CLINICAL STUDY PROTOCOL

TITLE PAGE

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**
Protocol Number:	BGB-A317-212
Phase:	2
Investigational Product(s):	Tislelizumab (BGB-A317), lenvatinib (a generic drug)
Proposed Indication(s):	Advanced Solid Tumors
Sponsor:	**BeiGene (Shanghai) Co., Ltd.** [redacted]
Sponsor Medical Monitor:	[redacted] Work Telephone: [redacted] Email: [redacted]
Original Protocol	27 November 2020
Protocol Amendment 1.0	01 November 2021
Protocol Amendment 2.0	03 November 2022

FINAL PROTOCOL APPROVAL SHEET

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

BeiGene, Ltd., Approval:

[redacted]

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-212

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd

Investigational Product(s): Tislelizumab (BGB-A317) and lenvatinib (a generic drug)

Title of Study: 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

Protocol Identifier: BGB-A317-212

Phase of Development: 2

Number of Patients: Approximately 70 patients in total

Part 1 (Safety run-in stage): 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 each of 5 prespecified tumor type cohorts. Three cohorts were closed prior to planned enrollment.

Study Centers: Approximately 14 centers in China

Study Objectives:

Part 1 (Safety run-in)

Primary:

- To assess the safety and determine the recommended Phase 2 dose (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)

Primary:

- To assess the overall response rate (ORR) of tislelizumab (IV, 400 mg Q6W) in combination with lenvatinib in patients with selected advanced solid tumors

Secondary:

- 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

Exploratory:

- To explore potential biomarkers that may correlate with clinical responses/resistance to tislelizumab in combination with lenvatinib
- To characterize the pharmacokinetics (PK) and immunogenicity of tislelizumab when given in combination with lenvatinib

Study Endpoints:

Part 1 (Safety run-in)

Primary:

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

Part 2 (Expansion)

Primary:

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

Secondary:

- 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

Exploratory:

- Potential biomarkers including but not limited to PD-L1 expression, TMB/DNA mutation/ microsatellite instability (MSI), blood tumor mutational burden (bTMB)/DNA mutation/MSI, and the association of biomarkers with disease status, response/resistance to tislelizumab in combination with lenvatinib
- Serum concentrations of tislelizumab and the incidence of ADA

Study Design

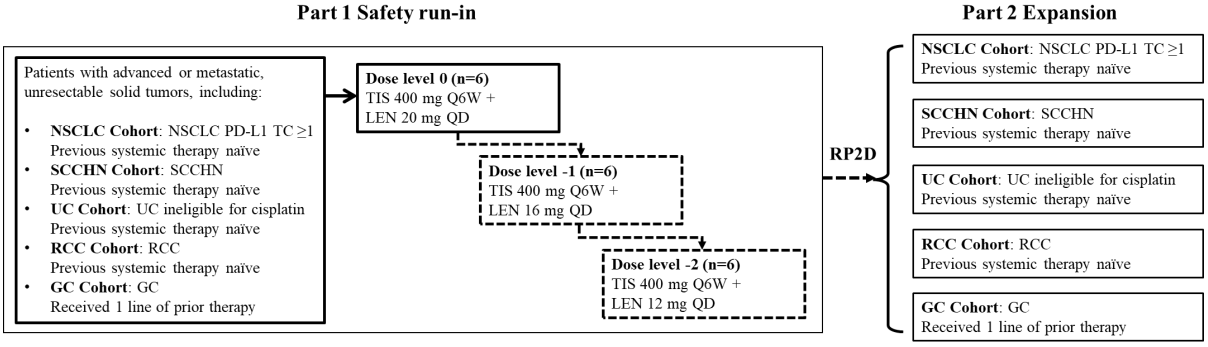
This is an open-label, multicenter, Phase 2 study to evaluate the safety and preliminary anticancer activity of tislelizumab in combination with lenvatinib in Chinese patients with locally advanced or metastatic tumors including programmed cell death ligand-1 (PD-L1) positive non-small cell lung cancer (NSCLC), squamous cell carcinoma of head and neck (SCCHN), urothelial cancer (UC), renal cell carcinoma (RCC), and gastric cancer (GC). Lenvatinib (Lenvatinib Mesilate Capsules, brand name JIELIEN® [hereafter referred to as "lenvatinib"]), which will be used in this study, is a generic drug to the lenvatinib capsules (Lenvatinib Mesilate Capsules, brand name Lenvima® [hereafter referred to as "Lenvima"]). This study includes 2 parts, Part 1 as safety run-in stage and Part 2 as expansion stage to assess the efficacy and safety of tislelizumab in combination with lenvatinib.

Six patients will receive lenvatinib 20 mg orally once daily as starting dose, administered 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 Safety Monitoring Committee (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 the total patient number including Part 1 and Part 2 will be approximately 30 at RP2D in the cohort of each tumor type. There will be a total of 5 cohorts in the study as NSCLC, SCCHN, UC, RCC, and GC,

respectively. 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). Patients will receive the study drug(s) until occurrence of progressive disease (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 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 NCI-CTCAE Version 5.0.

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.

Part 1

Tislelizumab will be administered at 400 mg Q6W for this study (including Part 1 and Part 2). For the drug combined with tislelizumab, lenvatinib will begin at dose of 20 mg QD.

Lower dose levels of lenvatinib initiated from 20 mg QD will be explored as necessary depending on observed safety profile. Lenvatinib dose will begin with Dose level 0: lenvatinib at 20 mg/day orally and tislelizumab 400 mg Q6W, IV will be administrated to patients with selected solid tumors on a 42-day treatment cycle. Dose de-escalation of lenvatinib includes Dose level -1: lenvatinib 16 mg/day orally and tislelizumab 400 mg Q6W, IV, and Dose level -2: lenvatinib 12 mg/day orally and tislelizumab 400 mg Q6W, IV. Once the dose has been reduced, re-escalation is not allowed.

Six patients will be enrolled for lenvatinib (20 mg QD) in combination with tislelizumab (IV, 400 mg Q6W). An SMC will be established to review the safety data collected from patients in Part 1 of the study first 28 days after starting tislelizumab (intravenously, 400 mg once per 6 weeks) in combination with lenvatinib. Based on these data, the SMC will recommend whether a dose modification of lenvatinib is needed, or whether the next part of the study can be initiated. The decision about establishing the RP2D is made by the sponsor.

If 0 or 1 in 6 patients experience a DLT at dose level of 20 mg QD lenvatinib combined with tislelizumab (IV, 400 mg Q6W) in select tumor type, then patients could be enrolled at this dose level subsequently for Part 2.

If 2 or more in 6 patients experience a DLT at dose level of 20 mg QD lenvatinib combined with tislelizumab (IV, 400 mg Q6W), 6 more patients would be enrolled at a next lower dose level, with dose reduction of lenvatinib from 20 mg to 16 mg QD or from 16 mg to 12 mg QD in combination with 400 mg tislelizumab Q6W.

If 2 or more in 6 patients experience a DLT at Dose level of 12 mg QD lenvatinib in combination with tislelizumab (IV, 400 mg Q6W), enrollment of patients will stop.

In the safety run-in period, safety information including but not limited to the DLTs, all treatment-emergent adverse event (TEAEs), laboratory abnormalities, and/or pharmacology data of first 28 day from first 6 evaluable patients will be reviewed by SMC. Recruitment will be on hold until the data have been reviewed.

A DLT is defined as 1 of the following toxicities occurring during the DLT assessment window (first 28 study days) and considered by the investigator to be related to 1 or more study drugs.

Hematologic:

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia
- ≥ Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 7 days
- ≥ Grade 4 anemia

Nonhematologic:

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days after optimal supportive care is initiated
- ≥ Grade 2 thromboembolic event

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 amylase or lipase elevation without clinical symptoms indicative of acute pancreatitis
- Grade 3 hypertension that returns to baseline or ≤ Grade 1 with appropriate supportive treatment

For safety run-in, patients who received <67% of scheduled tislelizumab and/or < 75% of scheduled lenvatinib during the DLT assessment window for any reason other than a DLT will be replaced.

All patients enrolled in the safety run-in period will be assessed for DLTs during the DLT assessment window. Once they complete the DLT assessment, each subject still receiving study treatment will continue with the same dosage. Tumor assessments will be continued as scheduled.

Part 2

Part 2 of the study will begin once the recommended dose is confirmed by the sponsor. Approximately 30 patients at RP2D will be enrolled in each cohort in parallel.

Each cohort will be evaluated independently for study endpoints and may be closed due to lack of preliminary anticancer activity or other reasons.

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. Computed tomography or magnetic resonance imaging (CT/MRI) scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days before Cycle 1/ Day 1), at all tumor assessment timepoints, and as clinically indicated. Patients with squamous cell carcinoma of the head and neck must also have head and neck scans performed.

MRI may be used instead of CT for head, neck, abdomen, and pelvis; however, the chest must be assessed using CT. Chest disease should not be followed using chest x-ray.

Imaging of the brain (preferably MRI) at baseline is required for all screened patients with the diagnosis of NSCLC. It also should be performed for patients with solid tumors other than NSCLC if clinically indicated. For patients with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment timepoints.

The tumor assessment schedule should not be affected by interruptions in study treatment. If a patient discontinues study treatment due to the reasons other than disease progression or death, tumor assessments will continue to be performed as scheduled 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.

Duration of Patient Participation:

Patients will receive study drug(s) until PD, unacceptable toxicity, death, or another discontinuation criterion is met.

Study Population:

- NSCLC Cohort: Patients with advanced NSCLC who have no prior systemic anti-tumor therapy for advanced disease, and whose tumor expressed PD-L1 status as tumor cell (TC) ≥ 1% by the Ventana SP263 assay, without EGFR mutation and/or known ALK gene translocation.
- SCCHN Cohort: Patients with recurrent or metastatic (R/M) SCCHN who have no prior systemic anti-tumor therapy for advanced disease. Patients who have a primary tumor site of nasopharynx (any histology) are not eligible.
- UC Cohort: Patients with locally advanced or metastatic UC who are cisplatin-ineligible and have no prior systemic anti-tumor therapy for advanced disease.
- RCC Cohort: Patients with advanced RCC with clear cell as predominant component and have no prior systemic anti-tumor therapy for advanced disease.
- GC Cohort: Patients with advanced gastric cancer/gastroesophageal junction adenocarcinoma (GC/GEJC) and have 1 line of prior systemic anti-tumor therapy for advanced disease.

Key Eligibility Criteria:

Inclusion:

1. Histologically and/or cytologically confirmed solid tumor types such as one of following: NSCLC, SCCHN, UC, RCC or GC. For patients with tumor types other than GC, should receive no prior systemic anti-cancer therapy for advanced disease. For GC cohort, patients should have had 1-line previous systemic treatment for advanced disease.
   - NSCLC Cohort: Advanced/metastatic NSCLC without EGFR mutation and/or known ALK gene translocation, and whose tumor expressed PD-L1 status as TC ≥ 1% confirmed by central laboratory utilizing Ventana SP263 assay. For non-squamous NSCLC patients without documented EGFR status, a tissue-based EGFR mutation assessment is required before enrollment.

     Note: Treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is acceptable if therapy was completed ≥ 6 months before the diagnosis of advanced or metastatic disease.
   - SCCHN Cohort: Recurrent or metastatic (R/M) SCCHN, primary tumor locations need to be oropharynx, oral cavity, hypopharynx, or larynx. Patients who have a primary tumor site of nasopharynx (any histology) are not eligible.

     Note: Systemic therapy as part of multimodal treatment for locally advanced disease is acceptable if it was completed ≥ 6 months before diagnosis of recurrent/metastatic disease. Metastatic means M1 per American Joint Committee on Cancer (AJCC), Eighth Edition.
   - UC Cohort: Advanced/unresectable (inoperable) or metastatic UC, including renal pelvis, ureters, bladder, or urethra. In order to be enrolled, the patient has to be cisplatin-ineligible, defined as meeting any of the following criteria:
     - Creatinine clearance (calculated by Cockcroft-Gault formula or measured) < 60 mL/min but >30 mL/min

     Note: Patients with a creatinine clearance (calculated or measured) < 30 mL/min or on dialysis are excluded from the study.
     - CTCAE, grade 2 or above audiometric hearing loss
     - CTCAE, grade 2 or above peripheral neuropathy

     Note: For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for UC, a recurrence-free interval > 12 months since the last treatment administration is required. Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks before the initiation of study treatment. Low-dose chemotherapy (eg., low dose cisplatin, cisplatin+5FU, mytomycin+5FU, or cisplatin+paclitaxel) given concurrent with radiation to the primary tumor site is not considered as systemic therapy.
   - RCC Cohort: Advanced/metastatic RCC with clear cell as predominantly component or have recurrent disease.

     Note: Prior neoadjuvant/adjuvant therapy of targeted agents to VEGF/VEGFR or mTOR is acceptable if it was completed > 12 months before recurrence.
   - GC Cohort: Confirmed diagnosis of GC or GEJC, which has been treated with 1 prior line of therapy for advanced disease. Patients need to have documented disease progression during/after previous first-line treatment. The disease progression needs to be confirmed by radiographic scan such as computed tomography (CT).

Note: Prior neoadjuvant or adjuvant therapy in which the interval between the completion of treatment and the occurrence of recurrence or metastatic disease was < 6 months will be counted as one line of treatment for advanced disease. External beam radiation therapy as neoadjuvant/adjuvant is acceptable, internal radioactive implant treatment is not allowed.

- Any standard chemotherapy regimen recommended by local guideline as first-line treatment is allowed. As first-line treatment, the chemotherapy should be received at least one cycle by patient. The substitution of drug(s) for the drug(s) with the same mechanism of action due to any reason other than disease progression is not considered a new line of therapy and is allowed. However, if a new component, dissimilar to any of the original components, is added to the regimen, the new combination is considered a new regimen which is not eligible. Prior intraperitoneal chemotherapy is allowed if completed at least 4 weeks before the initiation of study treatment.
- Patients with HER2 (+) must receive first-line anti-HER2 systemic therapy (anti-HER2 plus chemotherapy recommended by local guideline) and had documentation of disease progression during/after first-line anti-HER2 treatment. Patients with unknown status must have their HER2 status determined locally.

2. Tumor tissue (approximately 10 unstained slides) for central laboratory assessment of PD-L1 status for the NSCLC cohort during the screening period, and for retrospective analysis of other exploratory biomarkers related to response and resistance for NSCLC, SCCHN, UC and GC cohorts in a BeiGene designated central or test laboratory.
   - For cohorts of NSCLC, SCCHN, UC and GC, a fresh biopsy is mandatory in the absence of archival tumor tissues.
   - Submission of < 10 unstained slides is not a protocol deviation. If patients cannot provide 10 unstained slides, patients may be enrolled after confirmation with the sponsor.
   - For non-squamous NSCLC patients who could not provide EGFR documentation and complete EGFR test locally, 10 slides will be required additionally for central laboratory assessment of EGFR mutation.

   Note: In case of submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. For biopsy-derived samples, tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.
3. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤ 150/90 mmHg at screening, and no change in antihypertensive medications within 1 week before the Cycle 1 Day 1.

Exclusion:

1. For the NSCLC cohort, active leptomeningeal disease or uncontrolled, untreated brain metastasis will be excluded.
   - Patients with a history of treated and, at the time of screening, stable central nervous system metastases are eligible, provided they meet all of the following:
     - Brain imaging at screening shows no evidence of interim progression, clinically stable for at least 2 weeks and, have no evidence of new brain metastases
     - Have measurable disease and/or evaluable disease outside of the central nervous system
     - No ongoing requirement for corticosteroids as therapy for central nervous system disease; anticonvulsants at a stable dose are allowed

- No stereotactic radiation or whole-brain radiation ≤ 14 days before the first dose of study drug(s)

For other cohorts than NSCLC, known leptomeningeal disease or brain metastasis will be excluded.

2. Any of the following cardiovascular risk factors:
   a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug(s)
   b. Pulmonary embolism ≤ 28 days before the first dose of study drug(s)
   c. Acute myocardial infarction ≤ 6 months before the first dose of study drug(s)
   d. Heart failure meeting New York Heart Association Classification III or IV (Appendix 7) ≤ 6 months before the first dose of study drug(s)
   e. Ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug(s)
   f. Cerebrovascular accident ≤ 6 months before the first dose of study drug(s)
   g. QTcF interval (QT interval corrected for heart rate by Fridericia's formula [Appendix 8]) > 450 msec
   h. Cardiac left ventricular ejection fraction (LVEF) out of the institutional normal range as determined by multiplegated acquisition (MUGA) scan or echocardiogram. The same modality used at baseline must be applied for subsequent evaluations.
   i. Syncope or seizure ≤ 28 days before the first dose of study drug(s)
3. Patients having >1+ proteinuria on urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria. Patients with urine protein ≥1 g/24-hour will be ineligible
4. Have clinically significant bleeding (such as CTCAE ≥ Grade 2) within 21 days before first dose

Investigational Product, Dose, and Mode of Administration:

In both Part 1 and Part 2, tislelizumab 400 mg will be administered intravenously on Day 1 of each 42-day cycle.

In Part 1, lenvatinib will be initially administered at the dose of 20 mg orally, once daily.

In Part 2, lenvatinib will be taken at the RP2D from Part 1.

Reference Therapy, Dose, and Mode of Administration:

Not applicable

Statistical Methods:

Analysis Set

- The Safety Analysis Set (SAF) 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 (EAS) 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

1) received ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab administration during the DLT assessment window, remained on study during the DLT observation period, and had sufficient safety evaluation OR
2) experienced a DLT within the DLT observation period.

The detailed calculation of scheduled dose intensity of tislelizumab/lenvatinib is documented in the *Safety Monitoring Committee Operating Procedure* and *statistical analysis plan (SAP)* of this study.

- 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 tislelizumab and have a baseline and at least 1 postbaseline ADA result.

Efficacy Analysis

Primary and/or secondary efficacy endpoints will be based on investigators' tumor assessments per RECIST Version 1.1 (if applicable) and will be defined as follows:

- ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR).
- Duration of response is defined as the time from the first confirmed objective response until the first documentation of progression or death, whichever comes first.
- DCR is defined as the proportion of patients with best overall response, as defined in Appendix 11, of a CR, PR, or stable disease.
- 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.
- OS is defined as the time from the date of the first dose of study drugs to death due to any cause.

The efficacy endpoints will be summarized by cohort.

ORR assessed by the investigator and its 95% CI will be summarized by cohort based on the Safety Analysis Set and the Evaluable Analysis Set.

PFS will be estimated using the Kaplan-Meier method. The median PFS and the cumulative probability of PFS at-specific time points, if estimable, will be calculated and presented with 2-sided 95% CIs. PFS censoring rule will follow United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA, 2018).

DOR will be analyzed using methods similar to those described for PFS in the responders.

DCR will be analyzed using methods similar to those described for ORR based on the SAF and EAS.

Waterfall plots of maximum tumor shrinkage per patient will be presented.

OS will be analyzed in the SAF 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.

Safety Analysis

Safety will be assessed by monitoring and recording of AEs and laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE Version 5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA)

system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Extent of exposure to study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure, cumulative total dose received per patient, dose intensity (mg/day) and relative dose intensity (%).

The number (and percentage) of patients with dose reductions, dose delays, treatment interruptions, and study drug discontinuation will be summarized for each study drug.

The AE verbatim descriptions (as recorded by the investigator on the electronic case report form [eCRF]) will be classified into standardized medical terminology using the MedDRA®. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days after discontinuation of study drug(s), or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside the above mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE Version 5.0 within a system organ class and preferred term, even if the patient experienced ≥ 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, ≥ Grade 3 TEAEs, immune-mediated AEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, treatment interruption, or dose delay will be summarized.

Safety data will be summarized using the Safety Analysis Set by cohort and in overall study population except for analysis of DLT which is only applicable to patients in DLT evaluable set.

PK Analysis

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.

Sample Size Consideration

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 each of 5 prespecified tumor type cohorts

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.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BGB-A317	tislelizumab
BE	bioequivalence
bTMB	blood tumor mutational burden
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End-of-Treatment (Visit)
FDG	fluorine-18 [F-18] fluorodeoxyglucose
GC	gastric cancer
GCP	Good Clinical Practice
GEJC	gastroesophageal junction adenocarcinoma
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IV	intravenous
LVEF	left ventricular ejection fraction

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
MUGA	multiplegated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NMPA	(China) National Medical Product Administration
NSCLC	non-small cell lung cancer
ORR	overall response rate
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate by Fridericia's formula
PR	partial response
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of head and neck
SMC	Safety Monitoring Committee
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
T_{max}	time to maximum plasma concentration
UC	urothelial cancer
ULN	upper limit of normal

1. INTRODUCTION AND RATIONALES

1.1. Introduction

Combination therapy with a small molecule inhibitor of the vascular endothelial cell growth factor receptor (VEGFR) pathway may improve the clinical efficacy of immunotherapies and promote effective inhibition of angiogenesis in the tumor region which can suppress the growth of tumor cells and reduce the incidence of metastasis. The combination of immunotherapies and anti-angiogenic agents has been shown nonclinically to generate more potent antitumor effects (Khan et al, 2018) and has shown benefit in various therapeutic settings (Georganaki et al, 2018).

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4-variant monoclonal antibody against programmed cell death protein-1 (PD-1) under clinical development for the treatment for of multiple human malignancies. Tislelizumab is approved for the treatment of patients for the following indications in China:

- for use in combination with paclitaxel plus carboplatin or paclitaxel for injection (albumin-bound) plus carboplatin as first-line treatment in patients with unresectable, locally advanced, or metastatic squamous non-small cell lung cancer (NSCLC)
- for use in combination with pemetrexed and platinum chemotherapy as first-line treatment in patients with unresectable, locally advanced, or metastatic non-squamous NSCLC with no *EGFR* genomic tumor aberrations negative and *ALK* genomic tumor negative
- for use as monotherapy for the treatment of adult patients with locally advanced or metastatic non squamous NSCLC, with *EGFR* genomic tumor aberrations negative and *ALK* genomic tumor negative, that has progressed after or did not tolerate prior platinum-based chemotherapy and of adult patients with locally advanced or metastatic squamous NSCLC, with *EGFR* and *ALK* negative or unknown, that has progressed after or did not tolerate prior platinum-based chemotherapy
- for use in treatment of patients with locally advanced or metastatic esophageal squamous cell carcinoma who have disease progression following or are intolerant to first-line standard chemotherapy
- for use in combination with gemcitabine and cisplatin as first-line treatment in patients with recurrent or metastatic nasopharyngeal cancer

In addition, tislelizumab is conditionally approved in China for the following based on data from pivotal clinical studies.

- for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma who have received at least 2 lines of systemic chemotherapy regimens
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression whose disease progressed during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

- for the treatment pf patients with hepatocellular carcinoma who have been previously treated with at least one systemic therapy
- for the treatment of adult patients with advanced unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors: patients with advanced colorectal cancer (CRC) who had been treated with fluoropyrimidine, oxaliplatin, and irinotecan; and patients with other advanced solid tumors who develop disease progression after prior treatment and who have no satisfactory alternative treatment options.

Lenvatinib (Lenvatinib Mesilate Capsules, brand name JIELIEN® [hereafter referred to as "lenvatinib"]) is a generic drug to the lenvatinib capsules (Lenvatinib Mesilate Capsules, brand name Lenvima® [hereafter referred to as "Lenvima"]). As a receptor tyrosine kinase (RTK) inhibitor that inhibits VEGFR1-3; fibroblast growth factor receptor (FGFR) 1, FGFR 2, FGFR 3, FGFR 4; platelet-derived growth factor receptor (PDGFR) alpha, KIT, and RET, Lenvima has been approved in the United State (US) for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, in combination with everolimus for patients with advanced renal cell carcinoma following 1 prior antiangiogenic therapy, for the first-line treatment of patients with unresectable hepatocellular carcinoma, and in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. It is approved in China for the first-line treatment of patients with unresectable hepatocellular carcinoma.

NSCLC, squamous cell carcinoma of head and neck (SCCHN), urothelial cancer (UC), renal cell carcinoma (RCC), and gastric cancer (GC) are selected tumor types which are intended to be investigated under the combination treatment of lenvatinib plus tislelizumab in this study.

1.2. Lenvatinib

1.2.1. Pharmacology

RTK are essential components of signal transduction pathways that mediate cell-to-cell communication (Hubbard and Miller, 2007). They are a subclass of cell-surface growth-factor receptors with an intrinsic, ligand-controlled tyrosine-kinase activity. These single-pass transmembrane receptors, which bind polypeptide ligands - mainly growth factors - play key roles in processes such as cellular growth, differentiation, metabolism, and motility. In cancer, constitutive and aberrant activations of components of those pathways result in increased proliferation, survival, and metastasis. Therefore, these signaling pathways became prime targets for cancer therapy.

A preclinical study with human thyroid cancer models (Tohyama et al, 2014) shown the half-maximal inhibitory concentration (IC50) values of Lenvima for its targets are shown following: IC50 for VEGFR1, VEGFR2, VEGFR3, RET proto-oncogenes (RET), FGFR 1, FGFR 2, FGFR 3, FGFR 4, platelet-derived growth factor receptor (PDGFR) alpha and KIT proto-oncogenes (KIT) is 4.7 nmol/L, 3.0 nmol/L, 2.3 nmol/L, 6.4 nmol/L, 61 nmol/L, 27 nmol/L, 52 nmol/L, 43 nmol/L, 29 nmol/L and 85 nmol/L, respectively.

In preclinical studies, Lenvima showed inhibitory activities dose-dependently in VEGFR2-driven phosphorylation, tube formation and proliferation in human vascular endothelial cells (human umbilical vein endothelial cell – HUVEC) induced by VEGF. In in vivo studies where human cancer cells were transplanted in immune deficient mouse models, Lenvima also demonstrated high anticancer effect in a wide variety of cancers. In addition, safety results in nonclinical studies showed Lenvima to be well tolerated within the therapeutic range.

In vitro binding of Lenvima to human plasma proteins ranged from 98% to 99% (0.3-30 μg/mL). The contributions of albumin, α1-acid glycoprotein, and γ-globulin to the human plasma protein binding of Lenvima were estimated to be 93.2%, 6.1%, and 0.7%, respectively. In vitro, the Lenvima blood-to-plasma concentration ratio ranged from 0.59 to 0.61 (0.1-10 μg/mL) (LENVIMA (lenvatinib) [prescribing information], 2020; EMA assessment report for lenvatinib, 2015).

1.2.2. Clinical Experience

Use of Lenvima 24 mg QD for the treatment of differentiated thyroid cancer has been approved by the United States (US) Food and Drug Administration (FDA). The once daily combination of 18 mg Lenvima and 5 mg everolimus for patients with advanced renal cell carcinoma following 1 prior anti-angiogenic therapy was approved by the US FDA. Once daily Lenvima 12 mg (body weight ≥60 kg) or 8 mg (body weight <60 kg) QD orally as monotherapy has been approved by US FDA and China National Medical Product Administration (NMPA) for patients with unresectable hepatocellular carcinoma. In addition, Lenvima 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously (IV) every 3 weeks or 400 mg every 6 weeks has been approved by US FDA for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy (Keytruda (pembrolizumab) [prescribing information], 2020).

The pharmacokinetics and safety of lenvatinib has been studied in a study named “a single-center, open-label, randomized, single-dose, 2 cycle, 2 sequence, cross-over design study to evaluate the bioequivalence of lenvatinib and Lenvima in healthy subjects under fasting/after the meal status” (hereafter referred to as the “bioequivalence [BE] study”). The BE study was carried out with the Lenvatinib Mesilate Capsules (JIELIEN, dosage form: 4 mg] produced by Simcere Co., Ltd. and Lenvatinib Mesilate Capsules (Lenvima, dosage form: 4 mg] produced by Patheon Inc.

The results of the BE study suggested equivalency in in vivo metabolic processes of lenvatinib and Lenvima. Please refer to the lenvatinib Investigator’s Brochure for more detailed information (Simcere Investigator’s Brochure, 2021).

1.2.2.1. Clinical Pharmacology

The clinical BE study showed that concentration-time curves are similar between lenvatinib and Lenvima. The geometric mean ratio and 90% CI of the major pharmacokinetic (PK) parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) of lenvatinib were within the acceptable range (0.8 to 1.25), indicating that lenvatinib is bioequivalent to Lenvima. Administration with a high-fat meal did not change bioavailability of lenvatinib but delayed the median time to peak plasma concentration (T_{max}) from 2.25 hours to 4.5 hours (Simcere Investigator’s Brochure, 2021).

In patients with solid tumors administered single and multiple doses of Lenvima QD, the maximum observed Lenvima plasma concentration (C_{max}) and the AUC increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index varying between 0.96 (20 mg) and 1.54 (6.4 mg). At clinically relevant doses (≥12 mg QD), mean accumulation ratios of Lenvima ranged between 0.96 and 1.28. Plasma Lenvima concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of Lenvima was approximately 28 hours (LENVIMA (lenvatinib) [prescribing information], 2020).

1.2.2.2. Clinical Efficacy and Safety

The BE study assessed the safety of lenvatinib and compared it with that of Lenvima in healthy subjects. A total of 64 healthy subjects received a single dose, 4 mg of study drug (32 subjects in the lenvatinib group and 32 in the Lenvima group) under the fasting status. The study results showed that both drugs were safe and well tolerated. The overall incidence of treatment-emergent adverse event (TEAE) in the lenvatinib group and Lenvima group was 6.3% and 18.8%, respectively. All reported TEAEs were mild and none of them would lead to dose modification or dose delay. No death or serious adverse event (SAE) was reported throughout the study (Simcere Investigator's Brochure, 2021).

Lenvima has been approved for multiple advanced malignancies. Clinical data from the indications of RCC, NSCLC, SCCHN, UC, and GC are listed below. Refer to the prescribing information for detailed information of other approved indications regarding clinical efficacy (LENVIMA (lenvatinib) [prescribing information], 2020).

1.2.2.2.1. Lenvima in Renal Cell Carcinoma

The efficacy was evaluated in a multicenter, randomized (1:1:1) study (Study 205: NCT01136733), in which 153 patients with advanced or metastatic renal cell carcinoma who have previously received anti-angiogenic therapy received Lenvima 18 mg orally once daily with everolimus 5 mg orally once daily, Lenvima 24 mg orally once daily, or everolimus 10 mg orally once daily.

Of the 101 patients randomized to the Lenvima + everolimus combination arm, or to the everolimus monotherapy arm, the treatment effect of the combination on progression-free survival (PFS) was supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24, 0.75) compared with the everolimus arm. Median PFS was 14.6 months (95% CI: 5.9, 20.1) in the combination arm versus 5.5 months (95% CI: 3.5, 7.1) in the everolimus arm.

The clinical efficacy and safety of Lenvima in combination with pembrolizumab was explored in the phase 3 Keynote-581 study (CLEAR: NCT02811861). In this study, 1069 patients with advanced renal cell carcinoma and no previous systemic therapy were randomly assigned (1:1:1) to receive Lenvima (20 mg orally once daily) plus pembrolizumab (200 mg intravenously once every 3 weeks), Lenvima (18 mg orally once daily) plus everolimus (5 mg orally once daily), or sunitinib (50 mg orally once daily, alternating 4 weeks receiving treatment and 2 weeks without treatment). The combination therapy was associated with significantly prolonged PFS and overall survival (OS) than sunitinib. Grade 3 or higher TEAEs were reported in 82.4% of the patients who received Lenvima plus pembrolizumab, compared to 71.8% of those who received sunitinib. The most frequent Grade 3 or higher TEAEs occurring in the population receiving

Lenvima plus pembrolizumab included hypertension (27.6%), diarrhea (9.7%), and weight decrease (8.0%) (Motzer et al, 2021).

1.2.2.2.2. Lenvima in Non-Small Cell Lung Cancer

The clinical safety and efficacy of Lenvima in combination with pembrolizumab was evaluated in the Phase 3 LEAP-007 study (NCT03829332). In this study, 623 patients with PD-L1-positive, treatment-naïve NSCLC were randomly assigned (1:1) to receive pembrolizumab (200 mg intravenously once every 3 weeks) in combination with Lenvima (20 mg orally once daily) or placebo. The pembrolizumab plus Lenvima arm showed significantly prolonged PFS with an observed HR of 0.78 (95% CI: 0.64, 0.95) compared with the pembrolizumab plus placebo arm. Median PFS was 6.6 months (95% CI: 6.1, 8.2) in the pembrolizumab plus Lenvima arm versus 4.2 months (95% CI:4.1, 6.2) in the pembrolizumab plus placebo arm. The overall response rate (ORR) was higher in the pembrolizumab plus Lenvima arm (40.5%, 95% CI: 34.9%, 46.2%) versus 27.7% (95% CI: 22.8%, 33.0%) in the pembrolizumab plus placebo arm. Median OS was 14.1 months in the pembrolizumab plus Lenvima arm versus 16.4 months in the pembrolizumab plus placebo arm. Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 57.9% of patients in the pembrolizumab plus Lenvima arm and in 24.4% of the pembrolizumab plus placebo arm. The most frequent TRAEs occurring in the population receiving pembrolizumab plus Lenvima included hypertension (36.2%), hypothyroidism (36.2%), proteinuria (28.8%), and diarrhoea (27.8%). (Csoszi et al, 2021).

1.2.2.2.3. Lenvima in Squamous Cell Carcinoma of Head and Neck

In a Phase 1B/2 study (NCT02501096) of pembrolizumab plus Lenvima performed in patients with selected advanced solid tumors, 22 patients with advanced SCCHN were enrolled who had previously received several prior lines of systemic therapies (Taylor et al, 2020). ORR was reported as 46% (95% CI: 24.4% to 67.8%), and median PFS was 4.7 (95% CI: 4.0 to 9.8) months. Among a total of 137 patients with the selected solid tumor, TRAEs were reported in 97% (133/137) of patients, in which Grade 3 to 4 TRAEs were reported in 67% (92/137) of patients. The most common TRAEs were fatigue (58%), diarrhoea (52%), hypertension (47%), and hypothyroidism (42%).

1.2.2.2.4. Lenvima in Urothelial Cancer

The efficacy and safety of Lenvima in combination with pembrolizumab as first-line treatment was explored in the Phase 3 LEAP-011 study (NCT03898180), which is a randomized (1:1), double-blind study. In LEAP-011, 441 patients were enrolled in total, randomly assigned to receive pembrolizumab (200 mg intravenously once every 3 weeks) in combination with Lenvima (20 mg orally once daily) or placebo. Median PFS was 4.2 months (95% CI: 3.8, 5.9) in the pembrolizumab plus Lenvima arm versus 4.0 months (95% CI: 2.7, 5.4) in the pembrolizumab plus placebo arm, with an observed HR of 0.91 (95% CI: 0.71, 1.16). Median OS was 11.2 months (95% CI: 7.4, 14.9) in the pembrolizumab plus Lenvima arm versus 13.8 months (95% CI: 9.8, 18.8) in the pembrolizumab plus placebo arm. ORR was 31.2% in pembrolizumab plus Lenvima arm versus 26.5% in the pembrolizumab plus placebo arm. Grade 3 or higher TRAEs occurred in 50.0% of patients in the pembrolizumab plus Lenvima arm and 27.9% of patients in the pembrolizumab plus placebo arm. The most frequent TRAEs occurring in the population receiving pembrolizumab plus Lenvima included proteinuria

(37.8%), hypothyroidism (36.5%), hypertension (34.9%) and diarrhoea (20.7%). (Yohann et al, 2022).

1.2.2.2.5. Lenvima in Gastric Cancer

A Phase 2 study of Lenvima plus pembrolizumab as first- and second-line treatment was performed in 29 Japanese patients with advanced gastric cancer (EPOC1706, NCT03609359) (Kawazoe et al, 2020). Median PFS was 7.1 months (95% CI: 5.4, 13.7), and the safety profile was acceptable. ORR was reported as 69% (95% CI: 49%, 85%) in the overall population, in which ORR was reported as 40% in patients whose tumor PD-L1 status Combined Positive Score (CPS) was < 1, and 84% in those whose PD-L1 status CPS was ≥ 1. Grade 3 TRAEs occurred in 14 patients (48%); the most common Grade 3 TRAEs were hypertension (in 11 patients [38%]), proteinuria (5 patients [17%]), and platelet count decrease (2 patients [7%]). No Grade 4 TRAE, serious TRAE, or treatment-related death occurred.

1.3. Tislelizumab

1.3.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1. Tislelizumab binds to the extracellular domain (ECD) of human PD-1 with high specificity and affinity (dissociation constant [K_D] = 0.15 nM), as demonstrated by receptor binding assays based on surface plasmon resonance. Tislelizumab competitively blocks the binding of both PD-L1 and PD-L2, thus inhibiting PD-1-mediated negative signaling in T cells. In addition, tislelizumab has no effector functions mediated through Fc gamma receptors (Zhang et al, 2018). Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models.

Refer to the tislelizumab (BGB-A317) Investigator's Brochure (BeiGene Investigator's Brochure, 2021)for detailed information regarding pharmacology studies.

1.3.2. Clinical Experience

1.3.2.1. Safety

The overall safety experience with tislelizumab, as a monotherapy or in combination with other therapeutics, is based on experience in 2694 patients treated as of the cutoff date 20 May 2021. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of adverse events (AEs) to tislelizumab dose level. The safety profile for single-agent tislelizumab is similar to that observed with other PD-1 inhibitors.

Refer to the tislelizumab (BGB-A317) Investigator's Brochure (BeiGene Investigator's Brochure, 2021)for more detailed information.

1.3.2.1.1. Pooled Safety Assessment of Monotherapy Studies

There were 1992 patients treated in the 7 pooled solid tumor monotherapy studies. The patients in the solid tumor group of pooled monotherapy studies had a median treatment exposure duration of 4.07 months (range: 0.10 to 41.46) and median study follow-up duration of 11.53 months (range: 0.07 to 58.91). The median age of the patients was 60 years and 72.1%

were male. These patients had a median of 1.0 prior systemic anticancer therapy regimens (range: 0 to 12) and their most common tumor types were NSCLC (639 of 1992 patients, 32.1%), esophageal squamous cell carcinoma (15.9%), hepatocellular carcinoma (15.9%), urothelial bladder cancer (5.7%), and CRC (5.2%).

1.3.2.1.2. Treatment-Emergent Adverse Events

Of the 1992 patients in the solid tumor group of monotherapy studies, 1922 patients (96.5%) experienced ≥ 1 TEAE and 1391 patients (69.8%) experienced ≥ 1 TEAE considered treatment related. TEAEs ≥ Grade 3 in severity were experienced by 847 of 1992 patients (42.5%) and 269 patients (13.5%) experienced a ≥ Grade 3 TEAE considered treatment related. Serious TEAEs were reported in 706 patients (35.4%) and 209 patients (10.5%) experienced ≥ 1 serious TEAE considered treatment related. A total of 141 patients (7.1%) experienced a TEAE leading to death.

The most commonly occurring TEAEs were anaemia (502 of 1992 patients, 25.2%), aspartate aminotransferase (AST) increased (18.0%), alanine aminotransferase (ALT) increased (16.7%), decreased appetite (16.5%), and cough (15.1%).

The most commonly occurring ≥ Grade 3 TEAEs were anaemia (87 of 1992 patients, 4.4%), pneumonia (4.3%), AST increased (2.3%), hyponatraemia (2.1%), gamma-glutamyltransferase increased (1.7%), and hypertension (1.7%).

1.3.2.1.3. Treatment-Emergent Adverse Events Assessed as Related to Treatment

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 1391 (69.8%) experienced ≥ 1 treatment-related TEAE. The most commonly occurring treatment-related TEAEs were AST increased (250 of 1992 patients, 12.6%), ALT increased (12.1%), hypothyroidism (9.9%), anaemia (9.3%), and rash (8.0%).

269 (13.5%) experienced ≥ 1 tislelizumab-related TEAE of ≥ Grade 3 severity. The most commonly occurring ≥ Grade 3 TEAEs were AST increased (25 of 1992 patients, 1.3%), ALT increased (1.0%), and anaemia (1.0%). All other events occurred in < 1% of patients.

1.3.2.1.4. Treatment-Emergent Serious Adverse Events

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 706 (35.4%) experienced ≥ 1 treatment-emergent SAE. The most commonly occurring SAEs were pneumonia (95 of 1992 patients, 4.8%), pneumonitis (1.7%), dysphagia (1.2%), pleural effusion (1.0%), and pyrexia (1.0%).

209 (10.5%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most commonly occurring treatment-related SAE was pneumonitis (31 of 1992 patients, 1.6%). All other events occurred in less than 1% of patients.

1.3.2.1.5. Immune-Mediated Adverse Events

The majority of monotherapy studies pooled have undergone an adjudication process for identifying immune-mediated adverse events (imAEs). Only adjudicated imAEs are presented in this section. Of the 1912 patients in the adjudicated solid tumor group of pooled monotherapy studies, 286 patients (15.0%) experienced ≥ 1 imAE of any grade. The most commonly

occurring imAEs of any grade were hypothyroidism (115 of 1912 patients, 6.0%), pneumonitis (2.1%), immune-mediated lung disease (0.7%), rash (0.7%), ALT increased (0.6%), and hyperthyroidism (0.6%). The categories of imAEs experienced by ≥ 1% of patients were immune-mediated hypothyroidism (118 of 1912 patients, 6.2%), immune-mediated pneumonitis (3.7%), immune-mediated hepatitis (1.8%), and immune-mediated skin adverse reaction (1.3%).

73 patients (3.8%) experienced ≥ 1 imAE that was ≥ Grade 3 in severity. The most commonly occurring ≥ Grade 3 imAEs were pneumonitis (15 of 1912 patients, 0.8%), interstitial lung disease (0.4%), ALT increased (0.3%), AST increased (0.3%), and hepatitis (0.3%).

1.3.2.1.6. Infusion-Related Reactions

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 58 patients (2.9%) experienced ≥ 1 infusion-related reaction (IRR) of any grade. The most commonly occurring IRRs were "infusion-related reaction" (28 of 1992 patients, 1.4%), pyrexia (0.9%), rash (0.3%), hypotension (0.2%), nausea (0.2%), and pruritus (0.2%).

5 patients (0.3%) experienced ≥ Grade 3 IRRs. The most common ≥ Grade 3 IRRs was "infusion-related reaction" (2 of 1992 patients, 0.1%). All other ≥ Grade 3 IRRs occurred in single patients.

1.3.2.1.7. Fatal Adverse Events

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 163 patients (8.2%) died ≤ 30 days after their last dose of tislelizumab. The causes of death for these patients were adverse events (54 of 1992 patients, 2.7%), disease under study (2.6%), disease progression (2.5%), and "other" (0.4%). A total of 1230 patients (61.7%) died > 30 days after their last dose of tislelizumab. The causes of death for these patients were disease under study (664 of 1992 patients, 33.3%), disease progression (22.7%), "other" (4.5%), adverse events (1.1%), and "missing" (0.1%).

141 patients (7.1%) experienced ≥ 1 TEAE leading to death. The most commonly occurring TEAEs leading to death were "death" (16 of 1992 patients, 0.8%), pneumonia (0.7%), multiple organ dysfunction syndrome (0.6%), general physical health deterioration (0.5%), hepatic failure (0.5%), and respiratory failure (0.5%).

20 patients (1.0%) experienced ≥ 1 tislelizumab-related TEAE leading to death. The most commonly occurring tislelizumab-related TEAEs leading to death were pneumonia (3 of 1992 patients, 0.2%), "death" (0.1%), hepatic failure (0.1%), multiple organ dysfunction syndrome (0.1%), and pneumonitis (0.1%). All other events occurred in single patients.

1.3.2.2. Clinical Pharmacology

The PK of tislelizumab was characterized in 126 patients with solid tumors in the Phase 1 studies BGB-A317_Study_001 and BGB-A317-102 using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, or 10 mg/kg once every 2 weeks and 2.0 mg/kg, 5.0 mg/kg, or 200 mg once every 3 weeks (106 patients in BGB-A317_Study_001, 20 patients in Study BGB-A317-102). The drug exposure (C_{max} and AUC) increased in a dose-proportional manner from 0.5 mg/kg to 10 mg/kg, following first dose administration. Preliminary PK data from 27 patients administered 1 dose of 200 mg once every 3 weeks showed that tislelizumab

concentrations are between the range of concentrations observed from patients administered 2 mg/kg and 5 mg/kg doses.

The PK of tislelizumab was best characterized using a 3-compartmental model with linear clearance mechanism. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume of distribution (V_c), and peripheral volumes 2 and 3 (V_2 and V_3, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal $t_{1/2}$ was estimated to be approximately 23.8 days. The accumulation ratios were estimated to be 2.14 and 2.49 for AUC_{ss} and minimum serum concentration at steady state ($C_{min,ss}$), respectively. Steady state is expected to be reached in approximately 12 weeks.

1.3.2.3. Efficacy

Efficacy data of two Phase 1/2 monotherapy studies in advanced solid tumors, BGB-A317_Study_001 and BGB-A317-102, are summarized below.

1.3.2.3.1. Study BGB-A317_Study_001

BGB-A317_Study_001 was a 2-stage study. Phase 1A consisted of a dose-escalation and dose finding component, and Phase 1B investigated efficacy and safety in select tumor types. Responses were assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.

Of the 451 patients treated with tislelizumab in the study, best overall responses of complete response (CR) were reported in 6 patients (1.3%) and of partial response (PR) in 54 patients (12.0%). The resulting overall clinical response rate (CR + PR) was 13.3%. Additionally, there were 141 patients (31.3%) with a best overall response of stable disease.

Of 451 patients in the Safety Analysis Set, 156 patients in total were enrolled into GC, NSCLC, SCCHN, UBC, and RCC cohorts. The key efficacy data is summarized in Table 1. Please refer to Study BGB-A317_Study_001 (Desai et al, 2020) for more information regarding clinical efficacy.

Table 1: Summary of Tumor Response in Study BGB-A317_Study_001 (Safety Analysis Set)

	GC (N = 54)	NSCLC (N = 49)	SCCHN (N = 20)	UC (N = 17)	RCC (N = 16)
ORR (CR, PR)					
% (95% CI)	13.0 (5.37, 24.90)	12.2 (4.63, 24.77)	15.0 (3.21, 37.89)	29.4 (10.31, 55.96)	31.3 (11.02, 58.66)

Data cutoff: May 2019
Abbreviations: CR, complete response; GC, gastric cancer; SCCHN, squamous cell carcinoma of head and neck; NSCLC, non-small cell lung cancer; ORR, overall response rate; PR, partial response; RCC, renal cell carcinoma; UC, urothelial carcinoma.

1.3.2.3.2. Study BGB-A317-102

Study BGB-A317-102 is a 2-phase (Shen et al, 2020), nonrandomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Responses were assessed by the investigator per the RECIST v1.1 criteria.

Overall, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set. There was 1 patient (0.4%) with a CR reported. A total of 44 patients (17.7%) had a confirmed PR. The resulting overall clinical response rate was 18.1%. Additionally, there were 91 patients (36.5%) with a best overall response of SD.

Of 249 patients in the efficacy evaluable set, 84 patients in total were enrolled into GC, NSCLC, UC and RCC cohorts. The key efficacy was summarized in Table 2. Please refer to study BGB-A317-102 (Shen et al, 2020) for more information regarding clinical efficacy.

Table 2: Summary of Tumor Response in Study BGB-A317-102 (Safety Analysis Set)

	NSCLC (N = 56)	**GC (N = 24)**	**RCC (N= 21)**	**UC (N =22)**
ORR (CR, PR)				
%, (n/N) (Exact 95% CI)	18% (10/56) (8.9, 30.4)	17% (4/24) (4.7, 37.4)	10% (2/21) (1.2, 30.4)	14% (3/22) (2.9, 34.9)
DCR (CR, PR, SD)				
% (Exact 95% CI)	55% (41.5, 68.7)	29% (12.6, 51.1)	52% (29.8, 74.3)	41% (20.7, 63.6)
CBR (CR, PR, durable SD)*				
% (Exact 95% CI)	52% (38.0, 65.3)	25% (9.8, 46.7)	52% (29.8, 74.3)	27% (10.7, 50.2)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; GC, gastric cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PR, partial response; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma.
*OR (objective response) is based on the confirmed CR or PR according to RECIST v1.1. Durable SD is defined as SD duration ≥ 16 weeks.

1.4. Study Rationale

1.4.1. Rationale for the Dosing Regimen

1.4.1.1. Lenvatinib Starting Dose

The starting dose of 20 mg lenvatinib once daily in combination with tislelizumab has been selected. Lenvima 20 mg orally once daily in combination with pembrolizumab 200 mg IV every 3 weeks or 400 mg every 6 weeks has been approved by US FDA for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy (Keytruda (pembrolizumab) [prescribing information], 2020). In a Phase 1B/2 study of pembrolizumab in combination with Lenvima in

selected advanced solid tumors, Lenvima 20mg daily dose was identified as the MTD and recommended Phase 2 dose (RP2D) for combination of pembrolizumab (Taylor et al, 2020). Two dose-limiting toxicity (DLTs) (Grade 3 arthralgia and grade 3 fatigue) were reported in the initial combination cohort of Lenvima 24mg and pembrolizumab. No DLT was then observed in the subsequent de-escalation cohort of Lenvima 20mg. Therefore, 20mg of Lenvima was confirmed as MTD and RP2D for combination with pembrolizumab. Of 137 total patients across several tumor types, Lenvima dose reduction and/or interruption occurred in 85% patients, however 13% patients discontinued from the treatment of Lenvima; in addition, there were 45% and 15% of the total patients, respectively, who had pembrolizumab dose interruption and discontinuation. From the clinical data as outlined in Section 1.3.2.1 , tislelizumab has demonstrated a similar safety profile as other PD-1 antibodies including pembrolizumab. As shown in Table 3, the published safety data of immune mediated AEs of special interest indicates a similar safety profile of tislelizumab as pembrolizumab. Please refer to tislelizumab IB (BeiGene Investigator's Brochure, 2021) and prescribing information of pembrolizumab (Keytruda (pembrolizumab) [prescribing information], 2020) for details. Bioequivalence studies of lenvatinib suggested equivalency in in vivo metabolic processes of lenvatinib and Lenvima. Please refer to the lenvatinib Investigator's Brochure for more detailed information (Simcere Investigator's Brochure, 2021).

Table 3: Immune-Mediated AEs of Special Interest of Tislelizumab and Pembrolizumab

	Immune-mediated Adverse Events							
	Tislelizumab monotherapy in Solid Tumors (N = 1912)		**Pembrolizumab monotherapy in various Tumors (N = 2799)**					
Categories Preferred Term	**Any Grade n (%)**	**Grade ≥ 3 n (%)**	**Any Grade n (%)**	**Grade 1 (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5 (%)**
Immune-mediated hypothyroidism	118 (6.2)	1 (0.1)	237(8.5)		(6.2)	(0.1)		
Immune-mediated hyperthyroidism	12 (0.6)	1 (0.1)	17(3.4)		(0.8)	0.1		
Immune-mediated hepatitis	34 (1.8)	19 (1.0)	19 (0.7)		(0.1)	(0.4)	(<0.1)	
Immune-mediated pneumonitis	70 (3.7)	28 (1.5)	94 (3.4)	(0.8)	(1.3)	(0.9)	(0.3)	(0.1)
Immune-mediated myositis/rhabdomyolysis	14 (0.7)	5 (0.3)	(<1)					
Immune-mediated nephritis and renal dysfunction	6 (0.3)	2 (0.1)	9(0.3)		(0.1)	(0.1)	(<0.1)	
Immune-mediated colitis	17 (0.9)	6 (0.3)	48(1.7)		(0.4)	(1.1)	(<0.1)	

Source data: Tislelizumab IB v9.0, Table 17; Pembrolizumab prescribing information, Section 5.

Safety profile of the combination treatment of Lenvima plus pembrolizumab has been fully assessed in the Phase 1B/2 study of pembrolizumab in combination with Lenvima in selected advanced solid tumors (Taylor et al, 2020). The overall safety profile of the combination is acceptable. Based on available data, it is reasonable to select the starting dose of lenvatinib 20mg once daily in this study for NSCLC, SCCHN, UC, GC and RCC cohorts.

1.4.1.2. Tislelizumab

The clinical fixed dose of 200 mg intravenously once every 3 weeks was the approved tislelizumab dose in multiple indications.

For this study, alternate dose regimen 400 mg once every 6 weeks is selected by matching dose and exposure (AUC) with the exposure of 200 mg once every 3 weeks regimen. Exposure-response (E-R) assessments of available clinical data from Studies including BGB-A317_Study_001, BGB-A317-102, and BGB-A317-203 suggest no clinically significant relationships between tislelizumab exposure and efficacy (ORR) or safety across tumor types, and the 400 mg once every 6 weeks regimen is not expected to be clinically different from the 200 mg once every 3 weeks in terms of safety or efficacy outcomes. The expected peak concentration of 400 mg once every 6 weeks regimen compared with the 200 mg once every 3 weeks is well covered by the available safety data at the dose of 10 mg/kg every 2 weeks (Study BGB-A317_Study_001). Additionally, alternative 6-weekly dose administration is expected to increase patient compliance and offer additional convenience for care providers. Recently, the approval of the use of extended dosing regimen has also been reported for other PD-1 inhibitors such as nivolumab (240 mg Q2W and 480 mg Q4W) and pembrolizumab (200 mg Q3W and 400 mg Q6W), demonstrating the feasibility and utility of this approach (Long et al, 2018; Opdivo (nivolumab), 2018; Lala et al, 2018; Kenilworth, NJ, 2019; Press Release, 2019; Scot E, 2019; Peter H, 2019).

The potential drug-drug interaction between tislelizumab and lenvatinib is considered to be low; details can be found in Section 6.5.

1.4.2. Rationale for Combination of Tislelizumab and Lenvatinib in the Treatment of Advanced Solid Tumors

Tislelizumab as an anti-PD-1 antibody has shown efficacy and well tolerated safety in several types of tumors in clinical studies. In the select tumor types of NSCLC, SCCHN, UC, RCC and GC, the clinical antitumor activities have been observed in the Phase 1 and 2 studies. Tislelizumab has also been approved by China healthy authority for patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression whose disease has progressed during, following, or within 12 months of platinum-containing chemotherapy. The rationale for individual tumor types has been described in the below sections.

Lenvima as a kinase inhibitor has shown efficacy in several types of tumors. As monotherapy, Lenvima has demonstrated preliminary antitumor activities in NSCLC and RCC from published phase 1 or 2 studies. In addition, Lenvima has been approved in advanced RCC following one prior anti-angiogenic therapy as combination therapy with everolimus.

Combining an immunotherapeutic PD-1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the antitumor efficacy observed with either

agent alone. In addition, selected tyrosine kinase inhibitors have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, thereby increasing the frequency and function of effector immune elements while decreasing the number and function of immune suppressor cells.

1.4.3. Rationale for Tumor Type(s)

1.4.3.1. Non-Small Cell Lung Cancer

Worldwide, lung cancer has been the most common malignancy in the past few decades and the leading cause of cancer related death by far. In 2012, it was estimated that a total of 1.8 million new cases were diagnosed, accounting for 12.9% of all new cancer diagnoses (Wong et al, 2017). Likewise, lung cancer is also the most common cancer and the leading cause of cancer death in China; about 782,000 new cases of lung cancer were diagnosed in 2014 (Chen et al, 2015). According to statistics from the National Office on Tumor Cure and Prevention, about 626,000 people die of lung cancer each year in China (Chen et al, 2018).

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers (PDQ Adult Treatment Editorial Board, 2017). It includes 2 major pathological types: non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other subtypes) and squamous cell (epidermoid) carcinoma (NCCN Guidelines Version 4, 2019).

The KEYNOTE-042 study (Mok et al, 2019) demonstrated that single-agent pembrolizumab in the first-line setting significantly improved overall survival (OS) compared with platinum-based chemotherapy for patients with locally advanced or metastatic NSCLC, with PD-L1 expression of 1% or more (by 22C3 assay), but without EGFR mutation or ALK rearrangement. Pembrolizumab was approved in US and China for the first line treatment of patients with NSCLC expressing PD-L1 (TPS $\geq$ 1%) with no EGFR or ALK genomic tumor aberrations. Although pembrolizumab has been approved in PD-L1 positive NSCLC, in the exploratory analysis, clinical benefit of pembrolizumab in the subset population who had TPS 1-49% PD-L1 expressed tumor has not been demonstrated to be significantly prolonged over the standard of care chemotherapy (OS was 13.4 months in pembrolizumab versus 12.1 months in chemotherapy). It indicates that there is a need for a more robust effective and tolerable treatment for PD-L1 positive NSCLC.

Tislelizumab as an anti-PD-1 antibody showed antitumor activity in NSCLC in BGB-A317-001 and BGB-A317-102 studies (Desai et al, 2020; Shen et al, 2020). In those 2 studies, 49 patients (mostly Caucasian) and 56 Chinese patients with advanced NSCLC were evaluable for assessment respectively. ORR was reported as 12.2% and 18%, respectively. The additional two Phase 3 studies have also demonstrated superior efficacy for tislelizumab in combination with chemotherapy versus the backbone chemotherapy in squamous NSCLC and non-squamous NSCLC respectively. Overall, tislelizumab has shown clinical activity in NSCLC that is comparable to that of other marketed PD-1 antibodies globally.

In a Phase 1B/2 study (Taylor et al, 2020) of pembrolizumab plus Lenvima performed in patients with selected advanced solid tumor, 21 patients with advanced NSCLC were enrolled, of whom 52% has been treated with PD-1/L1 Abs previously. The ORR was reported as 33% (95% CI: 14.6 to 57.0), and median PFS was 5.9 months (95% CI: 2.3 to 13.8). Overall, it is expected that tislelizumab in combination with lenvatinib as one of chemo-free regimens would derive

additional clinical benefit in PD-L1 positive NSCLC versus the current standard of care. The combination treatment would be a potentially more effective and tolerable chemo-free regimen based on the assessment of mechanism of action (MoA) synergistic effects and available clinical data. While the Phase 3 LEAP-007 study (NCT03829332), which investigated the clinical safety and efficacy of pembrolizumab in combination with Lenvima or placebo in first-line NSCLC patients, showed a PFS benefit, no OS benefit was observed in the intent-to-treat (ITT) population. The median OS was 14.1 months in the pembrolizumab plus Lenvima arm versus 16.4 months in the pembrolizumab plus placebo arm. Based on results published at the European Society for Medical Oncology Immuno-Oncology (ESMO IO) Congress 2021 (Csoszi et al, 2021), the enrollment of the NSCLC cohort to Study BGB-A317-212 was suspended after 5 patients had enrolled.

1.4.3.2. Squamous Cell Carcinoma of Head and Neck

Squamous cell carcinoma of head and neck (SCCHN) is the 9th most common malignancy diagnosed world-wide accounts for 834,860 new patients and 8th in China (Bray et al, 2018). It was estimated that 64,000 new Chinese with SCCHN except nasopharynx cancer diagnosed in 2014 (Chen et al, 2018). First-line treatment of cetuximab plus chemotherapy with platinum and 5-fluorouracil is still the standard of care in China, which provides median overall survival of about 10 months (Vermorken et al, 2008).

PD-1 antibody monotherapy in SCCHN has shown efficacy and manageable safety in several studies. KEYNOTE-048 is a Phase 3 study (Burtness et al, 2019) conducted in patients with recurrent or metastatic squamous cell carcinoma of the head and neck, to evaluate pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy as first-line treatment. In this study for patients received pembrolizumab monotherapy, median overall survival was 14.9 months in groups whose tumor PD-L1 CPS ≥ 20 and 12.3 months in groups whose PD-L1 CPS ≥1; ORR was reported as 23% in groups whose PD-L1 CPS ≥20 and 19% in PD-L1 CPS ≥1 group. The study also demonstrated a statistically significant improvement in OS for the patients with PD-L1 CPS ≥1 randomized to pembrolizumab as a single agent compared to those randomized to cetuximab in combination with chemotherapy. Additionally, it was observed that there was no significant difference in OS between pembrolizumab single agent arm and the control arm in total population.

Tislelizumab as an anti-PD-1 antibody showed anti-cancer activity in SCCHN in a Phase 1A/1B clinical study (Desai et al, 2020). In this study, 20 patients with previously treated SCCHN were enrolled to receive tislelizumab single agent. ORR for this population was 15%, with an ORR of 20% and 8.3% for PD-L1 positive and PD-L1 negative patients, respectively.

PD-1 antibody in combination with Lenvima has shown efficacy and manageable safety in SCCHN. In a Phase 1B/2 study (Taylor et al, 2020) of pembrolizumab plus Lenvima performed in patients with selected advanced solid tumors, 22 patients with advanced SCCHN were enrolled who have received several prior lines of systemic therapies previously. ORR was reported as 46% (95% CI: 24.4 to 67.8), and median PFS was 4.7 (95% CI: 4.0 to 9.8) months. Tislelizumab in combination with lenvatinib is expected to show clinical benefit with a tolerable safety profile. For patients with SCCHN, a population with comparatively poor Eastern Cooperative Oncology Group (ECOG) performance and nutritional status, a chemo-free regimen could provide a more tolerable and efficient alternative to chemotherapy-based treatment.

1.4.3.3. Urothelial Carcinoma

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is an aggressive malignancy and the most common cancer of the urinary system. More than 90% of urothelial carcinoma originates in the bladder, while 8% may also originate at the renal pelvis and 2% in ureter or urethra. The epidemiology data found worldwide and in China are similar. It was estimated that there were 424,082 new cases and 148,270 deaths from bladder cancer in men and 125,311 new cases and 51,652 deaths in women worldwide in 2018 (Bray et al, 2018). In China, bladder cancer is the sixth most common cancer in men and the thirteenth in women, with approximately 80,500 new cancer cases (62,100 men and 18,400 women) and 32,900 deaths (25,100 men and 7800 women) in China in 2015 (Chen et al, 2016). Of all locally advanced or metastatic UC patients, approximately 46.6% received platinum-based chemotherapy as first line treatment. Only 20.5% of patients received cisplatin-based chemotherapy based on baseline disease characteristics (Sonpavde et al, 2014). OS was 13 to 15 months for patients who received GC (gemcitabine and cisplatin) as first-line treatment (Kaufman et al, 2000; Maase et al, 2000); while 26.1% of patients received gemcitabine and carboplatin with an inferior OS of only 9.3 months (Santis et al, 2012).

Tislelizumab as an anti-PD-1 antibody showed anti-cancer activity in urothelial cancer in 2 multi-cohort Phase 1/2 clinical studies (Desai et al, 2020; Shen et al, 2020). In those studies, 22 Chinese patients and a population of 17 mostly Caucasian patients with advanced urothelial cancer were enrolled respectively to receive tislelizumab. The ORR was 14% and 29.4% respectively for Chinese patients and for Caucasian dominant population. Additionally, tislelizumab has been approved by China authority for patients with previously treated advanced or metastatic urothelial carcinoma with PD-L1 high expression based on a single arm Phase 2 study (CTR20170071). In the study median PFS was 2.1 months (95% CI: 2.0-2.46) and median OS was 9.8 months (95% CI: 7.5-13.5). Overall response rate was reported as 23.1% in 104 patients who were evaluable for efficacy assessment (Ye et al, 2019).

In a Phase 1B/2 study (Taylor et al, 2020), pembrolizumab plus Lenvima was explored in patients with several selected advanced solid tumors, of which 20 patients with advanced urothelial carcinoma who had progressed after several lines of approved anti-cancer therapies enrolled. In urothelial carcinoma, anti-cancer activity of pembrolizumab in combination with Lenvima has demonstrated as an ORR was 25% (95% CI: 8.7 to 49.1), median PFS was 5.4 months (95% CI: 1.3 to NE) which is similar with that of gemcitabine and carboplatin (median PFS: 5.8 months) as first-line treatment in patients who are cisplatin ineligible as reported in EORTC Study 30986 (Santis et al, 2012).

Based on the available information, it is estimated that tislelizumab, which has a similar clinical activity as pembrolizumab, in combination with lenvatinib, which is a generic drug to Lenvima, could provide a similar efficacy as that reported from gemcitabine and carboplatin chemotherapy in first-line treatment setting for UC patients who are ineligible for cisplatin treatment. This chemo-free regimen would provide an additional option for this group of population for whom it is expected to have a relatively poor survival prognosis when compared to cisplatin eligible population. However, in the Phase 3 LEAP-011 Study (NCT03898180) of pembrolizumab in combination with Lenvima or placebo in patients with first-line UC, the resulting data showed no OS benefit in the ITT population. The median OS was 11.8 months in the pembrolizumab plus Lenvima arm versus 12.9 months in the pembrolizumab plus placebo arm. This result was

published at the American Society of Clinical Oncology Genitourinary (ASCO GU) Symposium in 2022 (Yohann et al, 2022). Therefore, the enrollment of the UC cohort to Study BGB-A317-212 was suspended.

1.4.3.4. Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the seventh most common cancer in men and the ninth most common cancer in women. Worldwide, there are an estimated 209,000 newly diagnosed cases of RCC and an estimated 102,000 deaths per year (Escudier et al, 2014). It is estimated that in 2015, 66,800 new RCC cases were diagnosed, and 23,400 deaths occurred in China (Chen et al, 2016). Approximately 90% of renal tumors are RCC and approximately 80% of these are of clear cell histology.

In a Phase 2 study (Atkins et al, 2020), 159 patients with advanced or metastatic RCC who had no previous treatment were enrolled to receive nivolumab monotherapy as first-line treatment. Of all 123 treatment-naïve ccRCC (clear cell RCC) patients, median PFS was 8.3 months (95% CI, 5.5-10.9) in all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk population, and median PFS in IMDC favorable and intermediate/poor population was 19.3 months (95% CI, 8.1-NA) and 5.5 months (95% CI, 3.9-9.1) respectively. ORR was reported as 31.7% (39/123) in overall population. KEYNOTE-427, a Phase 2 study evaluated pembrolizumab monotherapy as first-line treatment in patients with advanced RCC. This study showed that ORR in cohort A of 110 ccRCC patients as 36.4% (40/110) [95% CI, 27.4-46.1], median PFS was 7.1 months (95% CI, 5.6-11.0), and median OS did not reach (McDermott et al, 2020).

Tislelizumab as an anti-PD-1 antibody has shown efficacy and well tolerated safety in several types of tumor in multi-cohort Phase 1/2 studies (Desai et al, 2020; Shen et al, 2020). 21 Chinese patients and 16 mostly Caucasian patients with previously treated advanced renal cell carcinoma were enrolled to receive tislelizumab monotherapy. The ORR was reported as 10% and 31.3% respectively. These results demonstrated as an anti-PD-1 antibody, tislelizumab monotherapy is an effective agent in advanced renal cell carcinoma.

Lenvima monotherapy also showed encouraging efficacy in advanced renal cell carcinoma as second line treatment in a Phase 2 study (Motzer et al, 2015). This is a randomized, Phase 2, multicenter, open-label study enrolling patients with advanced clear-cell RCC who had received treatment with a VEGF-targeted therapy. In this study, patients who were randomized to receive Lenvima had median PFS of 7.4 months (95% CI, 5.6–10.2), median OS of 18.4 months (95% CI, 13.3–NE), and ORR of 27% (14/25, [95% CI, 16–41]).

In a Phase 1B/2 study, pembrolizumab 200mg IV Q3W plus Lenvima oral 20mg/day was explored in patients with several selected advanced solid tumors, of which 30 patients with advanced renal cell carcinoma with predominantly clear cell who had progressed after several lines of approved anti-cancer therapies were enrolled. Among patients in RCC cohort, pembrolizumab in combination with Lenvima has demonstrated an ORR of 70% (21/30; 95% CI, 50.6 to 85.3) and median PFS of 19.8 months (95% CI: 9.9-24.1) (Taylor et al, 2020). The CLEAR study published in 2021 confirmed the anti-tumor efficacy of this combination therapy in the first-line setting (Motzer et al, 2021).

Based on these results, we assume that tislelizumab monotherapy could provide similar efficacy as nivolumab or pembrolizumab and the combination treatment could have synergic effects in patients with advanced RCC.

1.4.3.5. Gastric Cancer

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer mortality worldwide (Globocan 2018d, 2020). Almost 1 million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total) according to the World Health Organization's Globocan 2012 database (Ferlay et al, 2015). There were 456,124 new diagnosed cases of stomach cancer and 390,182 deaths in China in 2018 (Globocan 2018d, 2020). Stomach cancer is the second highest incidences and mortality in China. Patients with newly diagnosed inoperable locally advanced or metastatic disease generally receive chemotherapy regimens containing platinum and fluoropyrimidine (Smyth et al, 2016; NCCN, 2017).

Patients with advanced GC who failed first line standard treatment represent a population with a great unmet medical need. In the second-line setting, the treatment options are still limited, including cytotoxic chemotherapy with docetaxel, paclitaxel, or irinotecan and the VEGFR2 monoclonal antibody ramucirumab based therapy, which is given as either monotherapy or in combination with paclitaxel. The prognosis remains poor, with the median overall survival being approximately 8 to 10 months.

In the second-line setting, the anti-VEGFR-2 antibody, ramucirumab, is an option since it has shown a survival benefit when added to chemotherapy compared with chemotherapy alone or as monotherapy compared with placebo (Fuchs et al, 2014; Wilke et al, 2014). In the third-line or above setting, apatinib, as monotherapy, is the only approved VEGFR-TKI in China. More recently, immunotherapy with anti-PD-1 antibodies pembrolizumab and nivolumab has resulted in durable remissions for a subset of patients (Le et al, 2016; Muro et al, 2016). Pembrolizumab has been approved by the FDA for the treatment of patients with PD-L1–positive recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have received 2 or more lines of chemotherapy (Keytruda (pembrolizumab) [prescribing information], 2020). Nivolumab has been approved by NMPA for the treatment of patients with recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have received 2 or more lines of systemic treatment.

Tislelizumab as an anti-PD-1 antibody has shown efficacy and well tolerated safety in several types of tumors in multi-cohort Phase 1/2 studies (Desai et al, 2020; Shen et al, 2020). In those studies, 52 and 24 patients with advanced gastric cancer were respectively enrolled into two studies, in which ORR was reported as 13.5% and 17% respectively and the median overall survival was reported as 4.7 months (95% CI, 2.4-NE) in the China study.

A Phase 2 study of Lenvima plus pembrolizumab as first and second line treatment was performed in 29 Japanese patients with advanced gastric cancer (EPOC1706) (Kawazoe et al, 2020). Median PFS was 7.1 months (95% CI: 5.4-13.7), median OS was not reached, and safety profile was acceptable. ORR was reported as 69% (95% CI: 49-85) in overall population, in which ORR as reported as 40% in patients whose tumor PD-L1 status CPS<1, and 84% in PD-L1 status CPS ≥ 1.

Based on the promising results from this Phase 2 study and available results from tislelizumab Phase 1/2 studies, it is expected tislelizumab in combination with lenvatinib would provide an efficient treatment option for this study population, for whom overall survival tends to be less than 12 months.

Since nivolumab plus mFOLFOX (oxaliplatin, folinic acid, and 5-fluorouracil)/XELOX (oxaliplatin and capecitabine) was approved by the US FDA and the China NMPA in 2021 and sintilimab plus XELOX was approved by the NMPA in 2022 for first-line GC/gastroesophageal junction adenocarcinoma (GEJC), a combination of anti-PD-1 agents with chemotherapy is widely used in this population. The population of patients with PD-1-naïve second-line GC has significantly decreased due to the changes regarding first-line standard of care; thus, the enrollment of the GC cohort to Study BGB-A317-212 was suspended after 3 patients had been enrolled.

1.4.4. Rationale for Biomarker Strategy

A number of biomarkers have been identified that correspond with response to immunotherapy for patients with NSCLC, SCCHN, UC, RCC, and GC.

PD-L1 expression has been demonstrated to be positively correlated with response to anti-PD-1 therapy across tumor types (Cristescu et al, 2018). For NSCLC, the expression of PD-L1 is positively correlated with response to anti-PD(L)-1 monotherapy (Keynote-042, IMpower-110). The correlation between PD-L1 and response to anti-PD(L)-1 in combination with mTKI has not been conclusive from limited data reported (MRTX-500, Keynote-146, COSMIC021). Thus, the correlation of PD-L1 with response needs further exploration. For SCCHN, PD-L1 expression is positively correlated with response to anti-PD-1 monotherapy (Keynote-048, Checkmate-141). One pilot study investigating the role of PD-L1 in predicting response to anti-PD-1 in combination with mTKI fail to come to a clear conclusion due to the high prevalence of PD-L1 positive patients (82% PD-L1+) in this study. Thus, the correlation of PD-L1 with response needs further exploration. For UC, clinical results (1st line setting/maintenance) demonstrate that PD-L1 expression is positively correlated with response to anti-PD-L1therapy (IMvigor-130, JAVELIN). There are several clinical studies investigating anti-PD(L)-1 plus mTKI in UC ongoing, however, biomarker data in this context has not been extensively reported. Consequently, the correlation of PD-L1 with response needs further exploration (Xu et al, 2019; Kawazoe et al, 2020; Fukuoka et al, 2020). For RCC, clinical results demonstrate that patients can benefit from anti-PD-1 in combination with mTKI regardless of PD-L1 expression (Keynote-426, Checkmate-9ER). For GC, the expression of PD-L1 is positively correlated with response to anti-PD-1 monotherapy (Keynote-061, Keynote-062). Additionally, 3 pilot studies have demonstrated the trend of patients who express PD-L1 benefiting from anti-PD-1 plus mTKI, compared to those negative for PD-L1 expression. This indicates that PD-L1 may be a potential biomarker predicting response to anti-PD(L)-1 in combination with mTKI in GC.

Tumor mutational burden (TMB) works as the surrogate marker for neo-antigen prediction and has been reported to positively correlate with response to anti-PD(L)-1, and serves as an independent biomarker from PD-L1, indicating that its combination with PD-L1 may lead to predictive synergy (Fumet et al, 2020; Cristescu et al, 2018).There have been limited data reported so far regarding the clear role of TMB in predicting response to anti-PD(L)-1 in combination with mTKI in NSCLC, SCCHN, UC and GC. Consequently, the role of TMB

requires further exploration. Blood TMB (bTMB), demonstrated good correlation with TMB if assessed with large panels, which has been explored due to its non-invasiveness feature, and has been reported to predict clinical benefit with anti-PD(L)-1 therapy in several clinical studies (POPLAR, OAK, MYSTIC studies, etc.) (Gandara et al, 2018). Apart from TMB, microsatellite instability (MSI), and DNA mutation can also be explored from the TMB detection panel, thus their role in predicting response/resistance can also be investigated.

Consequently, in the NSCLC, SCCHN, UC and GC cohorts, PD-L1, TMB/DNA mutation/MSI, bTMB/DNA mutation/MSI can be explored in tumor or blood samples to identify their potential predictive value, as well as resistance mechanisms in patients who receive tislelizumab in combination with lenvatinib.

1.5. Benefit-Risk Assessment

More than 1000 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. The safety profile is consistent with known class effects of anti-PD-1 antibodies including pembrolizumab and included mostly mild/moderate AEs. Very few Grade 3 or Grade 4 imAEs have been observed, which are generally reversible and manageable with study drug interruption and/or steroid treatment. Monotherapy of anti PD-1 antibodies including tislelizumab or Lenvima monotherapy has shown anti-tumor activity from available data in selected tumor types of interest. Synergic effects of the combination of PD-1 antibody with lenvatinib is expected based on pre-clinical studies.

The safety profile of the combination regimen of pembrolizumab plus Lenvima has been fully assessed in the published two phase 2 studies in solid tumors. MTD and RP2D of the combination therapy is established, and overall safety profile is tolerable and acceptable. See Section 1.4.1.1. In addition, the combination treatment is approved in the US for not MSI-H or dMMR patients with previously pretreated advanced endometrial carcinoma. Tislelizumab presents a similar safety profile as pembrolizumab and lenvatinib shows equivalency in in vivo metabolic characteristic to Lenvima. Therefore, it is expected that the combination of tislelizumab plus lenvatinib would be tolerable for the patients with select tumor types of interest.

In the phase 2 studies, pembrolizumab in combination with Lenvima showed promising results in selected, heavily treated solid tumors. Tislelizumab monotherapy as an anti PD-1 antibody presents similar efficacy as pembrolizumab based on available data. While the current standard of care in the select tumor types provides a moderate antitumor activity, however there is still an unmet medical need for an alternative treatment option for those patients who require a more tolerable and effective treatment. There is supportive evidence showing that 2 different mechanism of actions drugs combination would provide a synergistic clinical efficacy but still presents a tolerable safety profile. In consideration of unmet medical needs and expectation for effective chemo-free treatment for select tumor types, it is thought that tislelizumab in combination with lenvatinib would provide a favorable benefit risk profile for those patients.

Tislelizumab 400 mg Q6W could provide a convenient choice of administration. It is expected that safety and efficacy are similar with tislelizumab 200 mg Q3W based on the results from Exposure-response (E-R) assessments of available clinical data. Also, the higher C_{max} of 400 mg Q6W regimen compared with the 200 mg Q3W is well covered by the available safety data at

higher doses (up to 10 mg/kg Q2W doses were used in Study BGB-A317_Study_001). See Section 1.4.1.2. A Phase 3 study sponsored by BeiGene is ongoing to evaluate tislelizumab 400 mg Q6W in adjuvant therapy setting in resectable stage II and IIIA NSCLC (NCT 04379635).

A Safety Monitoring Committee (SMC) will be established consisting of the sponsor's clinical, safety, and medical team representatives (eg, medical monitor, Clinical Pharmacology and Drug Safety) and investigators. SMC will assess the preliminary safety of lenvatinib in combination with tislelizumab and recommend the RP2D of lenvatinib in combination with tislelizumab based on the available data in this study.

1.6. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints for Part 1 (Safety run-in)

Objectives	Endpoints
Primary	
To assess the safety and determine the RP2D of lenvatinib (20 mg or other dose QD) in combination with tislelizumab (intravenous [IV], 400 mg Q6W) in patients with advanced solid tumors	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, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined DLT criteria.

2.2. Study Objectives and Endpoints for Part 2 (Expansion)

Objectives	Endpoints
Primary	
To assess the ORR of tislelizumab (IV, 400 mg Q6W) in combination with lenvatinib at RP2D in patients with selected advanced solid tumors	ORR, as assessed using RECIST Version 1.1 (as described in Section 10.2) by investigator
Secondary	
To evaluate the preliminary anticancer activity of tislelizumab (IV, 400 mg Q6W) in combination with lenvatinib	PFS, DOR, and DCR, as assessed using RECIST Version 1.1 (as described in Section 10.2) by investigator and OS
To characterize the safety of tislelizumab (IV, 400 mg Q6W) in combination with lenvatinib	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
Exploratory	
To explore potential biomarkers that may correlate with clinical responses/resistance to tislelizumab in combination with lenvatinib	Potential biomarkers including but not limited to PD-L1 expression, TMB/DNA mutation/ microsatellite instability (MSI), bTMB/DNA mutation/MSI, and the association of biomarkers with disease status, response/resistance to tislelizumab in combination with lenvatinib
To characterize the PK and immunogenicity of tislelizumab when given in combination with lenvatinib	Serum concentrations of tislelizumab and the incidence of ADA

3. STUDY DESIGN

3.1. Summary of Study Design

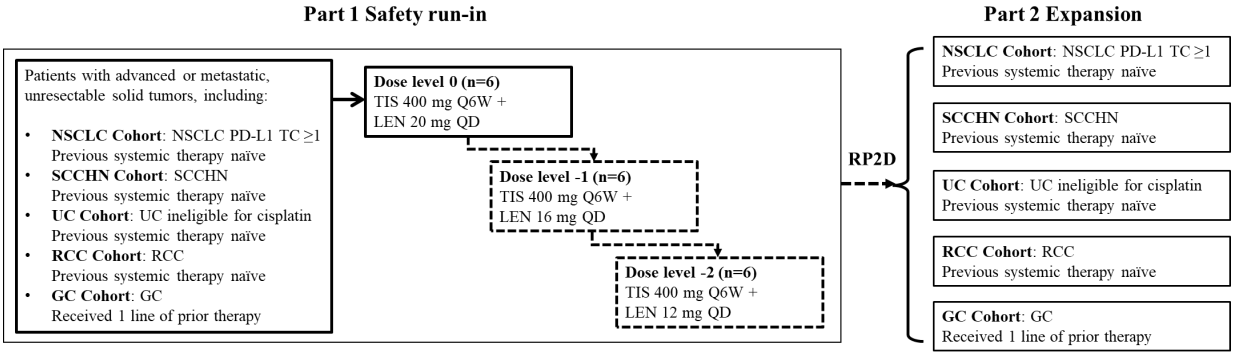
This is an open-label, multicenter, Phase 2 study to evaluate the safety and preliminary anticancer activity of tislelizumab in combination with lenvatinib in Chinese patients with locally advanced or metastatic tumors including PD-L1-positive NSCLC, SCCHN, UC, RCC, and GC. This study includes 2 parts, 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. 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). 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 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 NCI-CTCAE Version 5.0. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting.

Study procedures and assessments are further detailed in Section 7 and Section 8, respectively, and the Schedule of Assessments can be found in Appendix 1. Specific details are described in the following sections.

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.

3.2. Duration of Study

The sponsor reserves the right to suspend or prematurely close the enrollment or to prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. For the definition of end of study for individual patients or the entire protocol, please refer to Section 7.6 and Section 7.7, respectively.

After the end of study for patients who are still receiving study drug(s), lenvatinib will not be provided further; however, tislelizumab may continue to be provided for patients by enrolling into a long-term extension study.

3.3. Study Design of Part 1

3.3.1. Starting Dose and Dose De-Escalation Approach

Up to protocol development period, there is no safety data on lenvatinib in combination with tislelizumab 400 mg Q6W in Chinese patients with locally advanced or metastatic tumors, considering patient's safety, a safety run-in part for combination dosages of lenvatinib and tislelizumab will be performed. Patients in this part will have one of the following tumors: non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, renal cell carcinoma, or gastric cancer.

Tislelizumab will be administered at 400 mg Q6W for this study (including Part 1 and Part 2). For the drug combined with tislelizumab, lenvatinib will begin at dose of 20 mg QD. The rationale of starting doses of lenvatinib as combination treatment was summarized in Section 1.4.1.1.

Lower dose levels of lenvatinib initiated from 20 mg QD will be explored as necessary depending on observed safety profile. lenvatinib dose will begin with Dose level 0: lenvatinib at 20mg/day orally and tislelizumab 400 mg Q6W, IV will be administrated to patients with selected solid tumors on a 42-day treatment cycle. Dose de-escalation of lenvatinib includes Dose level -1: lenvatinib 16 mg/day orally and tislelizumab 400 mg Q6W, IV and Dose level -2: lenvatinib 12 mg/day orally and tislelizumab 400 mg Q6W, IV. Once the dose has been reduced, re-escalation is not allowed.

Six patients will be enrolled for lenvatinib (20 mg QD) in combination with tislelizumab (IV, 400 mg Q6W). An SMC will be established to review the safety data collected from patients in Part 1 of the study first 28 days after starting tislelizumab (intravenously, 400 mg once per 6 weeks) in combination with lenvatinib. Based on these data, the SMC will recommend whether a dose modification of lenvatinib is needed, or whether the next part of the study can be initiated. The decision about establishing the RP2D is made by the sponsor.

3.3.2. Rules for Dose De-Escalation

If 0 or 1 in 6 patients experience a DLT at dose level of 20 mg QD lenvatinib combined with tislelizumab (IV, 400 mg Q6W) in select tumor type, then patients could be enrolled at this dose level subsequently for Part 2.

If 2 or more in 6 patients experience a DLT at dose level of 20 mg QD lenvatinib combined with tislelizumab (IV, 400 mg Q6W), 6 more patients would be enrolled at a next lower dose level,

with dose reduction of lenvatinib from 20 mg QD to 16 mg QD or from 16 mg QD to 12 mg QD in combination with 400 mg tislelizumab Q6W.

If 2 or more in 6 patients experience a DLT at Dose level of 12 mg QD lenvatinib in combination with tislelizumab (IV, 400 mg Q6W), enrollment of patients will stop.

In the safety run-in period, safety information including but not limited to the DLTs, all TEAEs, laboratory abnormalities, and/or pharmacology data of first 28 days from first 6 evaluable patients at each dose level will be reviewed by SMC. Recruitment will be on hold until the data have been reviewed.

3.3.3. Assessment of Dose-Limiting Toxicity

For initial dose-finding recommendations, AEs will be assessed per the DLT criteria below (Section 3.3.4) during the 28-day DLT assessment window, which starts with the first day of study drug administration.

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.

Patients will be considered not evaluable for DLTs if they 1) did not receive ≥ 75% of scheduled lenvatinib or ≥ 67% (approximately two-thirds) of scheduled dose intensity of tislelizumab administration during the DLT assessment window, OR 2) received supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). Patients who are not DLT-evaluable must be replaced, if needed.

The detailed calculation of scheduled dose intensity of tislelizumab/ lenvatinib is documented in the *Safety Monitoring Committee Operating Procedure* and *statistical analysis plan (SAP)* of this study.

Clinically important or persistent AEs that are not part of the DLT criteria (Section 3.3.4) may also be considered a DLT following review by the sponsor in consultation with the investigators. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late immune-mediated AE [imAE]) for a given dose level may be considered regarding subsequent decisions.

Any patient who experiences a DLT may be withdrawn from treatment or may continue at a lower dose level or take one of study drugs following discussion with and approval by the medical monitor.

3.3.4. Dose-Limiting Toxicity Definition

All toxicities or AEs will be graded according to the NCI-CTCAE Version 5.0. A DLT is defined as 1 of the following toxicities occurring during the DLT assessment window (first 28 study days) and considered by the investigator to be related to 1 or more study drugs.

Hematologic:

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia
- ≥ Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 7 days
- ≥ Grade 4 anemia

Nonhematologic:

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days after optimal supportive care is initiated
- ≥ Grade 2 any thromboembolic event

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 amylase or lipase elevation without clinical symptoms indicative of acute pancreatitis
- Grade 3 hypertension that returns to baseline or ≤ Grade 1 with appropriate supportive treatment

For safety run-in, patients who received <67% of scheduled tislelizumab and/or < 75% of scheduled lenvatinib during the DLT assessment window for any reason other than a DLT will be replaced. All patients enrolled in safety run-in period will be assessed for DLTs during the DLT assessment window. Once they complete the DLT assessment, each subject still receiving study treatment will continue with the same dosage. Tumor assessments will be continued as scheduled.

3.4. Study Design of Part 2

Part 2 of the study will begin once the recommended dose is confirmed by the sponsor. 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 at RP2D will be enrolled per cohort in parallel.

Each cohort will be evaluated independently for study endpoints and may be closed due to lack of preliminary anticancer activity or other reasons.

NSCLC Cohort: Patients with advanced NSCLC who have no prior systemic anti-tumor therapy for advanced disease, and whose tumor expressed PD-L1 status as tumor cell (TC) ≥ 1% by the Ventana SP263 assay, without EGFR mutation and/or known ALK gene translocation.

SCCHN Cohort: Patients with recurrent or metastatic (R/M) SCCHN who have no prior systemic anti-tumor therapy for advanced disease. Patients have a primary tumor site of nasopharynx (any histology) are not eligible.

UC Cohort: Patients with locally advanced or metastatic UC who are cisplatin-ineligible and have no prior systemic anti-tumor therapy for advanced disease.

RCC Cohort: Patients with advanced RCC with clear cell as predominantly component and have no prior systemic anti-tumor therapy for advanced disease.

GC Cohort: Patients with advanced GC/GEJC and have 1 line of prior systemic anti-tumor therapy for advanced disease.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. No eligibility waivers will be granted.

4.1. Inclusion Criteria

Each patient must meet all the following inclusion criteria to be considered eligible for participation in this study:

1. Signed informed consent form (ICF) and able to comply with study requirements
2. Age ≥ 18 years (or the legal age of consent)
3. Histologically and/or cytologically confirmed solid tumor types such as one of following: NSCLC, SCCHN, UC, RCC or GC/ GEJC. For patients with tumor types other than GC/GEJC, should receive no prior systemic anti-cancer therapy for advanced disease. For GC/GEJC cohort, patients should have had 1-line previous systemic treatment for advanced disease.

   - NSCLC Cohort: Advanced/metastatic NSCLC without EGFR mutation and/or known ALK gene translocation, and whose tumor expressed PD-L1 status as TC ≥ 1% confirmed by central laboratory utilizing Ventana SP263 assay. For non-squamous NSCLC patients without documented EGFR status, a tissue-based EGFR mutation assessment is required before enrollment.

     Note: Treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is acceptable if therapy was completed ≥ 6 months before the diagnosis of advanced or metastatic disease.

   - SCCHN Cohort: Recurrent or metastatic (R/M) SCCHN, primary tumor locations need to be oropharynx, oral cavity, hypopharynx, or larynx. Patients who have a primary tumor site of nasopharynx (any histology) are not eligible.

     Note: Systemic therapy as part of multimodal treatment for locally advanced disease is acceptable if it was completed ≥ 6 months before diagnosis of recurrent/metastatic disease. Metastatic means M1 per American Joint Committee on Cancer (AJCC) Eighth Edition (Amin et al, 2017).

   - UC Cohort: Advanced/unresectable (inoperable) or metastatic UC, including renal pelvis, ureters, bladder, or urethra. In order to be enrolled, the patient has to be cisplatin-ineligible, defined as meeting any of the following criteria (Galsky et al, 2011):

     - Creatinine clearance (calculated by Cockcroft-Gault formula or measured) < 60 mL/min but >30 mL/min

       Note: Patients with a creatinine clearance (calculated or measured) < 30 mL/min or on dialysis are excluded from the study.

     - CTCAE, grade 2 or above audiometric hearing loss
     - CTCAE, grade 2 or above peripheral neuropathy

Note: For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for UC, a recurrence-free interval > 12 months since the last treatment administration is required. Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks before the initiation of study treatment. Low-dose chemotherapy (eg., low dose cisplatin, cisplatin+5FU, mytomycin+5FU, or cisplatin+paclitaxel) given concurrent with radiation to the primary tumor site is not considered as systemic therapy.

- RCC Cohort: Advanced/metastatic RCC with clear cell as predominantly component or have recurrent disease.

  Note: Prior neoadjuvant/adjuvant therapy of targeted agents to VEGF/VEGFR or mTOR is acceptable if it was completed > 12 months before recurrence.

- GC Cohort: Confirmed diagnosis of GC or GEJC, which has been treated with 1 prior line of therapy for advanced disease. Patients need to have documented disease progression during/after previous first-line treatment. The disease progression needs to be confirmed by radiographic scan such as computed tomography (CT).

  Note: Prior neoadjuvant or adjuvant therapy in which the interval between the completion of treatment and the occurrence of recurrence or metastatic disease was < 6 months will be counted as one line of treatment for advanced disease. External beam radiation therapy as neoadjuvant/adjuvant is acceptable, internal radioactive implant treatment is not allowed.

  - Any standard chemotherapy regimen recommended by local guideline as first-line treatment is allowed. As first-line treatment, the chemotherapy should be received at least one cycle by patient. The substitution of drug(s) for the drug(s) with the same mechanism of action due to any reason other than disease progression is not considered a new line of therapy and is allowed. However, if a new component, dissimilar to any of the original components, is added to the regimen, the new combination is considered a new regimen which is not eligible. Prior intraperitoneal chemotherapy is allowed if completed at least 4 weeks before the initiation of study treatment.
  - Patients with HER2 (+) must receive first-line anti-HER2 systemic therapy (anti-HER2 plus chemotherapy recommended by local guideline) and had documentation of disease progression during/after first-line anti-HER2 treatment. Patients with unknown status must have their HER2 status determined locally.

4. At least 1 measurable lesion per RECIST Version 1.1

   - A lesion in an area subjected to prior locoregional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since the start of therapy as defined by RECIST Version 1.1

5. Tumor tissue (approximately 10 unstained slides) for central laboratory assessment of PD-L1 status for the NSCLC cohort during the screening period, and for retrospective analysis of other exploratory biomarkers related to response and resistance for NSCLC, SCCHN, UC, and GC cohorts in a BeiGene designated central or special laboratory.
   - For cohorts of NSCLC, SCCHN, UC, and GC, a fresh biopsy is mandatory in the absence of archival tumor tissues.
   - Submission of < 10 unstained slides is not a protocol deviation. If patients cannot provide 10 unstained slides, patients may be enrolled after confirmation with the sponsor.
   - For non-squamous NSCLC patients who could not provide EGFR documentation and complete EGFR test locally, 10 slides will be required additionally for central laboratory assessment of EGFR mutation.

   Note: In case of submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. For biopsy-derived samples, tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.
6. ECOG Performance Status ≤ 1
7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤ 150/90 mmHg at screening, and no change in antihypertensive medications within 1 week before the Cycle 1 Day 1.
8. Adequate organ function as indicated by the following laboratory values ≤ 7 days before the first dose of study drugs
   a. Absolute neutrophil count ≥ 1.5 x 10^9/L
   b. Platelet count ≥ 100 x 10^9/L
   c. Hemoglobin ≥ 90 g/L, without blood transfusion or growth factor support ≥ 14 days before sample collection
   d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2 by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (Appendix 9)
   e. Serum total bilirubin ≤ 1.5 x ULN (less than 3 x ULN for patients with Gilbert syndrome)
   f. AST and ALT ≤ 2.5 x ULN or < 5 x ULN if hepatic metastases are present
   g. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤ 1.5.
9. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 120 days after the last dose of study drug(s), and have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drug(s) (Appendix 6).

10. Nonsterile males must be willing to use highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug(s) (Appendix 6).
    - A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    - Males with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this study:

1. For the NSCLC cohort, active leptomeningeal disease or uncontrolled, untreated brain metastasis will be excluded.

   Patients with a history of treated and, at the time of screening, stable central nervous system metastases are eligible, provided they meet all the following:

   - Brain imaging at screening shows no evidence of interim progression, clinically stable for at least 2 weeks and, have no evidence of new brain metastases
   - Have measurable disease and/or evaluable disease outside of the central nervous system
   - No ongoing requirement for corticosteroids as therapy for central nervous system disease; anticonvulsants at a stable dose are allowed
   - No stereotactic radiation or whole-brain radiation ≤ 14 days before the first dose of study drug(s)

   For other cohorts than NSCLC, patients with known leptomeningeal disease or brain metastasis will be excluded.
2. Prior therapy with lenvatinib or an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways
3. Active autoimmune diseases or history of autoimmune diseases that may relapse, with the following exceptions:
   a. Controlled Type 1 diabetes
   b. Hypothyroidism (provided it is managed with hormone-replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
4. Any active malignancy ≤ 2 years before the first dose of study drug(s) except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, or carcinoma in situ of the cervix or breast)

5. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s), with the following exceptions:
   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
6. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including but not limited to pulmonary fibrosis, acute lung diseases, etc.
7. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before the first dose of study drug(s)
8. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention).

   Note: Patients with symptomatic pleural effusion are excluded unless the patient undergoes a therapeutic thoracentesis or has had pleurodesis (more than 2 weeks prior) and has subsequently stable effusions.
9. Severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy before the first dose of study drug(s).
   a. Severe infections within 4 weeks before first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
   b. Received therapeutic oral or IV antibiotics within 2 weeks before first dose
   c. Antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
10. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) at screening
    - Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before the first dose of study drug(s).
11. Patients with active hepatitis C.
    - Patients with a negative HCV antibody test result at screening or a positive HCV antibody test result followed by a negative HCV RNA test result at screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before the first dose of study drug(s).

12. Known history of HIV infection
13. Any major surgical procedure ≤ 28 days before the first dose of study drug(s). Patients must have recovered adequately from the toxicity and/or complications from the intervention before the first dose of study drug(s).
14. Immunodeficiency, allogeneic stem cell transplantation, or organ transplantation
15. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug(s)
    b. Pulmonary embolism ≤ 28 days before the first dose of study drug(s)
    c. Acute myocardial infarction ≤ 6 months before the first dose of study drug(s)
    d. Heart failure meeting New York Heart Association Classification III or IV (Appendix 7) ≤ 6 months before the first dose of study drug(s)
    e. Ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug(s)
    f. Cerebrovascular accident ≤ 6 months before the first dose of study drug(s)
    g. QTcF interval (QT interval corrected for heart rate by Fridericia's formula [Appendix 8]) > 450 msec
    h. Cardiac left ventricular ejection fraction (LVEF) out of the institutional normal range as determined by multiplegated acquisition (MUGA) scan or echocardiogram. The same modality used at baseline must be applied for subsequent evaluations.
    i. Syncope or seizure ≤ 28 days before the first dose of study drug(s)
16. History of severe hypersensitivity reactions to other monoclonal antibodies
17. Serious nonhealing wound, ulcer, or bone fracture
18. Chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin), or investigational therapy ≤ 14 days or 5 half-lives (whichever is shorter) before the first dose of study drug(s). Also, palliative radiation treatment or other locoregional therapies within 14 days before the first dose of study drug.
19. Any Chinese herbal or Chinese patent medicine with anticancer activity approved by the NMPA (regardless of the type of cancer) used ≤ 14 days before the first dose of study drug(s)
20. Toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
21. Live vaccine ≤ 28 days before the first dose of study drug(s)
    - Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
22. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug(s), or will affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.

23. Concurrent participation in another therapeutic clinical study
    - Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.
24. Women who are pregnant or are breastfeeding
25. Inability to swallow capsules or disease/procedure significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
    - Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed (assuming no drug interaction potential).
26. Patients having >1+ proteinuria on urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria. Patients with urine protein ≥1 g/24-hour will be ineligible
27. Have clinically significant bleeding (such as CTCAE ≥ Grade 2) within 21 days before first dose

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Lenvatinib

Management (ie, handling, storage, administration, and disposal) of lenvatinib will be in accordance with relevant local guidelines, prescribing information/summary of product characteristics.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, USP type I), containing a total of 100 mg antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be stored at refrigerated conditions (2-8°C) and protected from light as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the tislelizumab IB (BeiGene Investigator's Brochure, 2021) for other details regarding tislelizumab.

5.2. Dosage, Administration, and Compliance

Treatment with study drug(s) on Day 1 of Cycle 1 must begin within 2 business days after receiving the confirmation of a patient's enrollment (Section 7.2). Treatment modifications (eg, dose delay/holds) will be based on specific laboratory and AE criteria, as described in Section 5.4. Guidelines for study treatment modification, delay or discontinuation as well as management of imAEs or infusion-related reactions are provided in Section 9.7 and Appendix 10.

Accurate records of all study drug(s) received, dispensed, returned, and disposed should be maintained in the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug management, drug preparation, storage, and administration.

5.2.1. Part 1

Planned dose level(s) for lenvatinib and tislelizumab are presented in Table 4.

Table 4: Planned Dose Levels for Lenvatinib and Tislelizumab

Study drug(s)	Dose
Lenvatinib	20 mg QD, oral (Dose level 0) 16 mg QD, oral (Dose level -1) 12 mg QD, oral (Dose level -2)
Tislelizumab	400 mg every 6 weeks, IV

This Part will review the safety profiles of the dosage of lenvatinib as 20 mg QD or other dose in combination with tislelizumab (intravenous [IV], at dose of 400 mg Q6W) in patients with selected types of solid tumor.

5.2.1.1. Tislelizumab

Tislelizumab 400 mg will be administered on Day 1 of each 42-day cycle (once every 6 weeks) by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding, 0.2- or 0.22-micron in-line or add-on filter.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 2 hours afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least 1 hour monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion of tislelizumab (Cycle 1, Day 1) will be delivered over 90 minutes; the second infusion may be administered over 60 minutes if 90 minutes are tolerated; and for the following infusions, at least 30 minutes is required if 60 minutes infusion is tolerated, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug. Study treatment with tislelizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 9.7.3 and Section 9.7.1.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.2.1.2. Lenvatinib

Starting on Day 1 of each Cycle, lenvatinib 20 mg will be administered orally once a day at approximately the same time each day. Patients will be instructed to swallow the capsules whole, in quick succession, with water. Lenvatinib can be administered with or without food. A dose of lenvatinib should be skipped if it is not taken within 12 hours of the scheduled time. An extra dose of lenvatinib should not be taken to make up for a missed dose. If vomiting occurs during treatment, no re-dosing of the patient is allowed before the next scheduled dose.

On Day 1 of each cycle lenvatinib will be administered at least 1 hour after completion of tislelizumab administration.

Compliance will be assessed by the investigator and/or study personnel at each patient visit along with information provided by the patient and documented accordingly. The investigator and/or

study personnel will keep accurate records of the quantities of capsules dispensed and used by each patient. This information must be captured in the source document at the end of each cycle.

5.2.2. Part 2

Patients enrolled in Part 2 will receive the study drug of the confirmed RP2D dose of lenvatinib in Part 1 and tislelizumab until occurrence of PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

5.3. Overdose

Any incorrect administration of study drug(s) or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or lenvatinib (defined as any dose > 20 mg) should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an incorrect administration or overdose of study drug(s) will be recorded on the AE electronic case report form (eCRF). Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 9.6.2. Supportive care measures should be administered as appropriate.

5.4. Dose Delay or Modification

A dose delay due to the reason other than tolerability is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond visit window). A dose interruption is an interruption of an infusion. Treatment cycles will be counted continuously regardless of dose delays.

Every effort should be made to administer the study drug(s) according to the planned dosage and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

5.4.1. Dose Delay or Modification for Tislelizumab

There will be no dose reduction for tislelizumab in this study.

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after the last dose of tislelizumab. If the administration of study drug can resume within ≤ 21 days, it should be administered in the current cycle. If tislelizumab needs to be withheld for > 21 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle. If the patient is unable to resume tislelizumab within 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from tislelizumab treatment. If the patient is unable to resume tislelizumab ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

Dose modification related to imAEs and infusion-related reactions are described in Section 9.7.3 and Section 9.7.1, respectively.

5.4.2. Dose Delay or Modification for Lenvatinib

Lenvatinib dose modification for patients who experience lenvatinib related adverse events of special interest should be in accordance with the guidelines provided in Table 5 and Table 6, while other related AEs which are not outlined in Table 5, dose modification for lenvatinib should follow guidelines provided in Table 6. Once the dose has been reduced, it should not be increased later. Any dose reduction below 4 mg/day must be discussed with the sponsor. If the administration of lenvatinib is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose.

For management of AE of lenvatinib of special interest, the instructions are summarized in Section 9.8.1. It is recommended to discuss with the medical monitors if the investigators propose to manage the AEs with otherwise strategy which is not outlined in Table 5, Table 6 and Section 9.8.1. Dose reductions of lenvatinib in Part 2 occur in succession starting at the confirmed dose identified in safety run-in.

For toxicity that is suspected of related to both tislelizumab and lenvatinib, the investigators should follow the recommendation referring to both instructions (Section 5.4.1 and Section 5.4.2) for dose delay and modification until the causality to individual agent is clearly identified. Lenvatinib may be resumed at the same dose if AE is assessed as not related to lenvatinib later.

Table 5: Recommended Dosage Modifications for Lenvatinib Related Adverse Events of Special Interest

Adverse Reaction	Severity	Dosage Modifications for Lenvatinib
Hypertension	Grade 3	Withhold for Grade 3 that persists despite optimal antihypertensive therapy. Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	Permanently discontinue.
Cardiac Dysfunction	Grade 3	Withhold until improves to Grade 0 to 1 or baseline. Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	Permanently discontinue.
Arterial Thromboembolic Event	Any Grade	Permanently discontinue.
Hepatotoxicity	Grade 3 or 4	Withhold until improves to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	Withhold until improves to Grade 0 to 1 or baseline. Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria	2 g or greater proteinuria in 24 hours	Withhold until less than or equal to 2 grams of proteinuria per 24 hours. Resume at a reduced dose. Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation	Any Grade	Permanently discontinue.
Fistula Formation	Grade 3 or 4	Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	Withhold until improves to less than or equal to 480 ms or baseline. Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	Withhold until fully resolved. Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.

Table 6: Dose Modifications for Lenvatinib Treatment-Related Toxicity

Lenvatinib Treatment-Related Toxicity[a,b]	During Therapy	**Adjusted Dose[f]**
Grade 1, Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] and Grade 3[g]		
First occurrence	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one dose level[b]
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one more dose level
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one more dose level
Grade 4[e,g]: Discontinue lenvatinib permanently		

a. An interruption of lenvatinib treatment for more than 21 days (due to lenvatinib treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed.
b. Excluding alopecia. Initiate optimal medical management for nausea, vomiting, hypothyroidism, hypertension and/or diarrhea before any lenvatinib interruption or dose reduction. For treatment-related hypertension, refer to Management of Hypertension (Section 9.8.1) for dose modification guidelines.
c. Applicable only to Grade 2 toxicities judged by subject and/or physician to be intolerable.
d. Obese patients with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These patients will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal BMI (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
f. Refer to Table 7 for adjusted dose.
g. For asymptomatic Grade ≥3 elevations of amylase and lipase, the sponsor's medical monitor should be consulted to obtain permission to continue treatment.

Table 7: Dose Reduction Recommendations for Lenvatinib

Initial Lenvatinib Dose (mg, QD)	Adjusted Dose To Be Administered (mg, QD)			
	Reduction 1	**Reduction 2**	**Reduction 3**	**Reduction 4**
20	16	12	8	4
16	12	8	4	
12	8	4		

QD = once daily.

General guidelines for holding periods of lenvatinib due to procedures:

For minor procedures, lenvatinib should be stopped 2 days before the procedure and restarted 2 days after, once there is evidence of adequate healing and no risk of bleeding. Needle biopsies (fine needle aspirations and core needle aspirations) are usually considered minor procedures.

For major procedures, lenvatinib should be stopped 1 week (5 half-lives) before the procedure and then restarted once there is clear wound healing and no risk of bleeding, but at least 1 week after the procedure. It is up to the investigator to determine if it is a major or minor procedure. Usually, a major procedure implies general anesthesia.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

All prior therapy, dates of administration, best response, and date of progression for all patients will be collected at study entry and entered into the eCRF.

Note: For patients without prior systemic anti-cancer therapy, planned neoadjuvant chemotherapy (to debulk the tumor before surgical intervention) plus postoperative adjuvant chemotherapy is considered 1 regimen.

For GC patient who has had previous first-line therapy, if the treatment is interrupted for surgery or radiotherapy or any other reason than disease progression and then continues with an unchanged schedule and components, that treatment is considered as 1 regimen despite the interruption.

6.2. Permitted Concomitant Medications/Procedures

The potential for drug-drug interaction between the study drug tislelizumab and small-molecule drug products is very low because tislelizumab is a therapeutic monoclonal antibody. Because tislelizumab is expected to be degraded into amino acids and recycled into other proteins, it is unlikely to have an effect on drug-metabolizing enzymes or transporters.

Unless noted otherwise, most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest are allowed.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before the first dose of study drug(s) and 30 days after the last dose of study drug(s) will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with lenvatinib or tislelizumab may be continued during the study.

Bisphosphonates and RANKL inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a nonmalignant indication.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) lenvatinib or tislelizumab.

Prophylactic antiemetic, granulocyte colony stimulating factors, granulocyte macrophage colony stimulating factors, platelet simulating factors or erythropoietin are permitted as clinically indicated.

6.2.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 10 and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatment (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

6.2.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at screening, must initiate treatment 2 weeks before the first dose and continue until 6 months after the last dose of tislelizumab. Patients should continue effective antiviral treatment during the study to decrease potential viral reactivation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease guideline because they lack resistance with long-term use (Terrault et al, 2016; AASLD/IDSA HCV Guidance Panel, 2015). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the investigator. However, interferon-based therapy for hepatitis B is not permitted on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before enrollment and continue treatment during the study and for 6 months after study drug tislelizumab discontinuation.

6.2.3. Radiation Therapy

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline if the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST Version 1.1
- The case is discussed with the medical monitor, and he/she agrees that the conditions required to receive palliative radiation are met

In addition, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per the investigator's discretion. The medical monitor should be informed of the on-study radiotherapy. These patients should have a tumor assessment of the lesion(s) before receiving the radiation therapy to rule out progression of disease.

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study or as otherwise noted:

- Any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents (including Chinese herbal medicine and Chinese patent medicines for the treatment of cancer regardless of cancer type), ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of study drug(s) and during the study. Chinese herbal and Chinese patent medicines with anticancer activity are defined as medication with approval by the NMPA (or other Country) for use as anticancer treatment (regardless of the type of cancer).
- Medications that prolong QT interval during study treatment with lenvatinib.

  Note: please refer to Appendix 12 for more details of known risk of QT Prolongation/Torsades de Pointes
- Live vaccines ≤ 28 days before the first dose of tislelizumab and ≤ 60 days following the last dose of tislelizumab.
- Immunosuppressive agents (except to treat a drug-related AE) during study treatment with tislelizumab.
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment during study treatment with tislelizumab.

  Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.
- Patients should not abuse alcohol or other drugs.
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin) ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of study drug(s) and during the study. Patients must notify the investigator of all herbal remedies used during the study.
- Radiation therapy, except for palliative radiation therapy described in Section 6.1.

6.4. Medications to Be Used with Caution

The use of potentially hepatotoxic drugs in patients with impaired hepatic function is allowed but should be carefully monitored.

With the exception of diagnostic biopsy of tumor tissue or placement of a venous access device, the investigator should discuss with the sponsor medical monitor any patient who requires surgery during the study.

Earlier studies have shown that Lenvima exposure is neither affected by food intake (Shumaker et al, 2014a) or coadministration of cytochrome P450 (CYP)3A4 inhibitors and inducers (Shumaker et al, 2015; Shumaker et al, 2014b).

Lenvima has been reported to prolong the QT/QTc interval. Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Please refer to Appendix 12 for a list of medications or substances to be avoided or used with caution during treatment with lenvatinib.

6.5. Drug-drug Interaction

6.5.1. Drug-drug Interaction between Tislelizumab and Lenvatinib

The potential drug-drug interaction between tislelizumab and lenvatinib is expected to be low.

Both drugs have different disposition pathways and are not overlapping. Tislelizumab is given by IV infusion has no impact on the oral absorption of lenvatinib. Like most therapeutic proteins, tislelizumab is eliminated from the body via non-specific proteolytic catabolism and target mediated elimination pathways, have no effect on drug-metabolizing enzyme, such as CYP3A4 enzyme that are responsible for the metabolism of lenvatinib and vice versa. Tislelizumab is unrelated to the pro-inflammatory cytokines, has no potential DDI interactions for drugs, like lenvatinib, are substrate of CYP/transporter (FDA, 2020).

6.5.2. Drug-drug Interaction between Lenvatinib and Other Drugs

Nonclinical studies identified that Lenvima is mainly metabolized by CYP3A4 enzyme and it's the substrate of P-glycoprotein (P-gp) and breast cancer resistance protein. However, the clinical drug-drug interaction study showed that co-administration of Lenvima with CYP3A4/P-glycoprotein inhibitors/inducer is not of a clinical concern (details can be found in Appendix 13).

7. STUDY PERIODS, VISITS, OR PROCEDURES

7.1. Screening Period

Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s). A patient who agrees to participate in this study will sign the ICF before undergoing any study-specific screening assessment. Refer to Section 8.1 for instructions regarding screening assessments.

7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.2. Demographics

Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with ICH guidance (ICH E5 1998, ICH E17 2017) adopted by the European Medicines Agency (EMA) and the US FDA, to understand whether race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well as any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

7.2. Enrollment

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation (ICH) E6.

The sponsor’s medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

7.3. Treatment Period

Patients will be treated as described in Section 5.2.

Patients may continue to receive study drug(s) beyond the initial investigator-assessed PD, as defined by RECIST Version 1.1 provided that the patient has investigator-assessed clinical benefit and is tolerating study drug(s). Refer to Section 7.6 and Section 8.3 for additional considerations regarding treatment continuation and withdrawal.

7.4. End-of-Treatment Visit

The End-of-Treatment (Visit) (EOT) Visit is conducted ≤ 7 days after the investigator determines that the patient must permanently discontinue all study drugs. If routine laboratory tests (eg, hematology, clinical chemistry) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of study drugs, the EOT Visit may also be used as the Safety Follow-up Visit.

See Appendix 1 for assessments to be performed for the EOT Visit.

7.5. Follow-up Periods

7.5.1. Safety Follow-up Period

Patients who permanently discontinue all study drugs will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted within 30 days [± 7 days] after the last dose of study drugs or before the initiation of new anticancer therapy, whichever occurs first. The Safety Follow-up Visit may coincide with the EOT Visit (see Section 7.4) but cannot occur before the EOT Visit. In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not patients started a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 9.6.

See Appendix 1 for assessments to be performed at the Safety Follow-up Visit.

7.5.2. Efficacy Follow-up Period

Patients who discontinue study drug(s) for reasons other than PD (eg, toxicity) or death will continue to undergo tumor assessments following the original plan until the patient experiences PD, starts new anticancer therapy, is lost to follow-up, withdraws consent or until patient death or study terminates, whichever occurs first. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact the patients by telephone to determine their disease status.

7.5.3. Survival Follow-up Period

After discontinuation of study treatment, patients will be followed for survival and further anticancer therapy information via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT or Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor. If both EOT and safety follow up visits are missed, the first survival follow-up visit should be calculated based on the date PI decided to End Treatment. Please use an "Equal Interval" calculation to estimate the next survival follow up visit/contact for the subject.

7.5.4. Lost to Follow-up

If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information. It may be possible to obtain the information from other contacts, such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

7.6. Discontinuation From Study Treatment or From the Study

7.6.1. Patient Discontinuation From Study Treatment (End of Treatment for an Individual Patient)

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment at any time. Patients who discontinue study treatment for reasons other than PD should be followed for assessments of preliminary anticancer activity (Section 8.3) and safety (Section 8.2), if possible.

The primary reason for discontinuation from study treatment should be documented on the appropriate eCRF. Patients may discontinue study treatment for reasons including but not limited to the following:

- PD
- AE
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents (including Chinese herbal medicine and Chinese patent medicines) for the treatment of cancer regardless of cancer type)
- Patient noncompliance
  Study site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug

accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

If tislelizumab or lenvatinib is discontinued permanently for reasons other than disease progression, the other drug could be continued as originally scheduled.

If the decision is made to continue lenvatinib monotherapy beyond initial progression, it should be confirmed with the sponsor and the patient will continue to be treated and monitored according to the schedule in Appendix 1. Lenvatinib monotherapy must be discontinued permanently upon documentation of further progression, either symptomatic or radiographic.

The guidance for tislelizumab use beyond the first disease progression is provided in Section 8.3.

7.6.2. Patient Discontinuation From the Study (End of Study for an Individual Patient)

Patients may discontinue from the study for reasons that include but are not limited to the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up

7.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow up. Alternatively, the end of study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for an EOT Visit and Safety Follow-up Visit as described in Section 7.4 and Section 7.5.1.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

After the end of study for the patients who are still receiving study drug(s), lenvatinib will not be provided afterwards, while tislelizumab may be continued for patients by enrolling into a long-term extension study.

8. STUDY ASSESSMENTS

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety throughout the study. All assessments must be performed and documented in the medical record for each patient.

Where applicable, dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

8.1. Screening Assessments

Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s) (refer to Appendix 1 for details). Patients who agree to participate will sign the ICF before undergoing any study-specific screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit are described in this section. For the description of assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 8.2), Tumor and Response Evaluations (Section 8.3), PK and ADA Assessments (Section 8.4) and Biomarkers (Section 8.5) sections.

Rescreening under limited conditions may be allowed after consultation with BeiGene (eg, when a patient's laboratory result narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD). Rescreening is allowed only once.

8.1.1. Pulmonary Function Tests

Patients who are suspected of having or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing that may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study.

For patients with NSCLC, pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the screening period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 60% of age- and sex-adjusted predicted performance levels (Pellegrino et al, 2005), the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study.

8.2. Safety Assessments

8.2.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes.

Height should only be measured and recorded during screening. Weight will be measured before study drug administration in every cycle.

8.2.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE Version 5.0 and recorded in the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs in the eCRF. Refer to Section 9.3 regarding AE definitions and reporting and follow-up requirements.

8.2.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 4) will be assessed during the study.

8.2.4. Laboratory Safety Tests

Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 3 per the timepoints shown in Appendix 1.

If clinical chemistry, hematology, urinalysis, and coagulation at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 3 days before study drug administration.

The following tests will also be conducted in this study at timepoints shown in Appendix 1.

- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the first dose of study drug(s). Furthermore, a negative urine pregnancy test must be completed and recorded before administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- Thyroid function testing (ie, thyroid stimulating hormone, free triiodothyronine [T3], and free thyroxine [T4])
- Hepatitis serology and viral load (refer to Section 8.2.7)

8.2.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and creatine kinase-muscle/brain (CK-MB) are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 10 for guidelines for management of suspected immune-mediated myocarditis, respectively). Serum troponins may be substituted per local guidelines if used consistently throughout the study. If CK and CK-MB at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 3 days before study drug administration.

8.2.5. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

When coinciding with blood draws (eg, performed within 30 minutes of each other), ECG assessment should be performed prior to blood draws. The patient should rest in a semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc.) before each ECG collection. If the ECG is not performed ≤ 3 days before the first dose of study drug(s), the test should be repeated and reviewed before study drug administration on Day 1 of Cycle 1. After Day 1 of Cycle 1, ECGs will be collected on Day 1 of each cycle and as clinically needed.

During the screening period, 3 consecutive 12-lead ECGs will be performed within 10 minutes for each interval to determine the mean QTcF interval (see Appendix 8). At other timepoints, a single 12-lead ECG will be performed for determination. Repeated 12-lead ECG will be performed if clinically indicated (see Appendix 1).

8.2.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE Version 5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 9.6.

8.2.7. Hepatitis B and C Testing

Testing will be performed by the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody). In the case of active HBV, the test will be followed by viral load assessment (HBV DNA).

Patients who have detectable HBV DNA at screening will perform the respective viral load test every 2 cycles starting at Cycle 3.

8.3. Tumor and Response Evaluations

Tumor imaging must be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 9 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks, then every 12 weeks (± 7 days) after 54 weeks based on RECIST Version 1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule.

Screening assessments and each subsequent tumor assessment must include CT scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc).

Patients with squamous cell carcinoma of the head and neck must also have head and neck scans performed. MRI may be used instead of CT for head, neck, abdomen, and pelvis; however, the chest must be assessed using CT. Chest disease should not be followed using chest x-ray.

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients with the diagnosis of NSCLC. It also should be performed for patients with solid tumors other than NSCLC if clinically indicated. Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s). For patients with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment timepoints.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron-emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.

- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans or when clinically indicated (eg. a CR is suspected in target lesion or when progression in bone is suspected), Tc-99m or PET bone scans should be repeated.
- For patients other than SCCHN, CT scans of the neck or extremities should be performed at screening, only if clinically indicated, and should be followed throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST Version 1.1 may be used.

Response will be assessed by the investigator using RECIST Version 1.1 (see Appendix 11). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment timepoint; confirmation 4 to 6 weeks after the first response is strongly recommended.

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to an apparent increase of existing tumor masses or appearance of new tumor lesions. Also, some patients may benefit from additional immune therapies despite evidence of PD. The following criteria must be met to treat patients with suspected pseudoprogression or confirmed evidence of PD:

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that they may be forgoing treatment that has shown benefit by continuing treatment beyond progression.
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed to with the medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

The tumor assessment schedule should not be affected by interruptions in study treatment. If a patient discontinues study treatment due to the reasons other than disease progression or death, tumor assessments will continue to be performed as scheduled until the patient begins a subsequent anticancer treatment, experiences disease progression, is lost to follow-up, withdraws consent, death, or until study terminates, whichever occurs first.

8.4. Pharmacokinetic Assessment and Antidrug Antibody Testing

Blood sampling for PK will be collected at the timepoints specified in the Schedule of Assessments (Appendix 2). Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (see Appendix 2). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al, 2008; Worobec and Rosenberg, 2004a; Worobec and Rosenberg, 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints.

The following assessments will be performed at a bioanalysis laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay
- PK assays: serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay

Shipping, storage, and handling of samples for the assessment of PK and ADA assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples to the central laboratory.

8.5. Biomarkers

Shipping, storage, and handling of blood as well as archival tumor and/or fresh tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Appendix 1A) for sample collection timepoints.

Archival tumor tissues (approximately 10 freshly cut unstained FFPE slides) need to be sent for central laboratory assessment of PD-L1 for the NSCLC cohort during the screening period, and for retrospective analysis of other exploratory biomarkers related to response and resistance for the NSCLC, SCCHN, UC and GC cohorts in a BeiGene-designated central or special laboratory. These exploratory biomarkers include but are not limited to PD-L1 expression in SCCHN, UC and GC cohorts, TMB/DNA mutation/MSI for patients in NSCLC, SCCHN, UC and GC cohorts. Submission of < 10 unstained slides is not a protocol deviation. For non-squamous NSCLC patients who could not provide EGFR documentation and complete EGFR test locally, 10 slides will be required additionally for central laboratory assessment of EGFR mutation.

A fresh tumor biopsy at a tumor lesion is mandatory for NSCLC, SCCHN, UC and GC cohorts if there are no available archival tumor samples during the screening period. Written patient consent is required for fresh tumor biopsies.

For fresh biopsies, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Blood samples will be obtained for the evaluation of exploratory biomarkers including, but not limited to bTMB/DNA mutation/MSI for patients in NSCLC, SCCHN, UC and GC cohorts, which will be collected at baseline (required), at the time of first confirmed tumor response (optional), and at the time of progressive disease (optional) (approximately 10 mL for each timepoint). Written patient consent is required for blood sample collections.

8.6. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment tislelizumab administration (Day 1) of each cycle should be performed before study treatment infusion/dose unless otherwise noted. Laboratory results must be reviewed before dosing.

Day 1 of Cycle 1 is defined as the day when initial infusion of tislelizumab administration or first lenvatinib dosage, which occur first. Study treatment of tislelizumab may be administered ± 3 days from the scheduled Day 1 of each cycle due to administrative reasons. On Day1 of each cycle, lenvatinib will be administered at least 1 hour after completion of tislelizumab administration.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 6 weeks from Day 1 of Cycle 1.

8.7. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/focused physical examination; ECOG Performance Status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and clinical chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected PD, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

9. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

9.1. Risks Associated With study drugs

9.1.1. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. imAEs are presented in Section 9.7.3.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 10.

9.1.2. Risks Associated With Lenvatinib

Lenvatinib is a kinase inhibitor that inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). It inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors; PDGFRα, KIT, and RET.

Lenvatinib may cause side effects like other kinase inhibitors, including: Hypertension, Cardiac Dysfunction, Arterial Thromboembolic Events, Hepatotoxicity, Renal Failure or Impairment, Proteinuria, Diarrhea, etc.

9.2. General Plan to Manage Safety Concerns

9.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from lenvatinib (both Lenvima and the generic drug) were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before the first dose of study drug(s) are excluded from the study. Patients with contraindications for lenvatinib treatment are also excluded from the study (see Section 4.2 for the full list of exclusion criteria).

9.2.2. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF and reported to the sponsor or designee immediately (ie, no more than 24 hours after learning of the event).

9.2.3. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE Version 5.0.

All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 8), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, tislelizumab will be administered only after clinical laboratory results have been reviewed. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

Investigators are instructed to report all AEs (includes pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 9.7.

9.3. Adverse Events

9.3.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug(s) administration even though the condition might have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug(s) or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

9.3.2. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI-CTCAE Version 5.0.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas, seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.6.2.

9.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug(s) and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug(s) should be considered and investigated. The investigator should consult the tislelizumab and lenvatinib Investigator's Brochure in the determination of his/her assessment (Simcere Investigator's Brochure, 2021; BeiGene Investigator's Brochure, 2021).

There may be situations when an SAE has occurred and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related" based on all information available at the time of reporting. An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug(s) (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug(s)
- Biological plausibility
- An AE should be considered "related" to study drug(s) if any of the following criteria are met; otherwise, the event should be assessed as "not related":
  - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
  - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
  - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

9.3.4. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

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. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the timeframes outlined in Section 9.6.2.

9.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to treatment interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

9.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it was more severe.
- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered to be SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

9.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the tislelizumab and lenvatinib Investigator's Brochure (Simcere Investigator's Brochure, 2021; BeiGene Investigator's Brochure, 2021).

9.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

9.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study drug(s), only SAEs should be reported.

After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug(s) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 8. For the follow-up period for AEs, see Section 9.3.4. For the definition of TEAEs, see Section 10.3.2.

Table 8: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Cohorts

Event Type	Record new or worsening events that occur during this period	
	Begin	End
SAEs[a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 9.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose of tislelizumab (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
[a] 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.

9.6.2. Reporting Serious Adverse Events

9.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 9.

Table 9: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial report	Documentation method	Timeframe for sending follow-up report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE report form

Abbreviations: SAE, serious adverse event.

9.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 9.6.2.1. The SAE report will always be completed as thoroughly as possible, including all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 9.3.3.

The sponsor will provide contact information for SAE receipt.

9.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 9.5) will be submitted to all applicable regulatory authorities and investigators for tislelizumab and lenvatinib studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

9.6.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

9.6.4. Progressive Disease

PD, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to PD should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to PD, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to PD should be recorded and reported.

9.6.5. Deaths

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an AE (eg, "death," "death of unknown cause," or "death unexplained").

9.6.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drug(s) or within 120 days after the last dose of study drugs, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug(s) should be recorded and reported as an SAE.

9.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information documents:

- Tislelizumab Investigator's Brochure, (BeiGene Investigator's Brochure, 2021)
- Lenvatinib Investigator's Brochure, (Simcere Investigator's Brochure, 2021)

9.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune related (see Section 9.7.3) should be classified as imAEs and identified as such in the eCRF AE page. Not all tislelizumab studies include a section in the eCRF AE page where imAEs are clearly identified. Therefore, all studies will rely on the company list of Potential imAEs to identify all cases in each study to be further assessed as immune-mediated AEs by the sponsor, in addition to those imAEs reported by the investigator via the AE CRF page.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 10.

An extensive list of potential imAEs appears in Table 11. All conditions similar to those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 10.

9.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Individual signs and symptoms of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

9.7. Management of Adverse Events of Special Interest for Tislelizumab

As a routine precaution, following completion of study drug(s) administration, patients must be monitored for a period afterward in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

The management for infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined in the following subsections.

9.7.1. Managing Infusion-Related Reactions

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) are provided in Table 10.

Table 10: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE grade	Treatment modification for <<tislelizumab or other infused drug>>
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text following this table. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug treatment.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug treatment. Hospitalization is recommended.

Abbreviations: NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions and premedication must be administered. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, the infusion should be discontinued and the patient should be withdrawn from tislelizumab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and, if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and the patient should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

9.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) (Soar et al, 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction, the infusion must be stopped immediately and the patient discontinued from the study treatment. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm; and are often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The patient should then be placed on monitor immediately and an Intensive Care Unit should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drug infusion. Alternative treatments for fever (ie, paracetamol) may be administered to the patient at the discretion of the investigator.

9.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, PD, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, the AE required the use of systemic steroids, other

immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 11. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune related.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al, 2017; Brahmer et al, 2018) and common immune-mediated toxicities are detailed in Appendix 10. For any AEs not included in Appendix 10, please refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al, 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 11: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism (eg, fatigue, weakness, weight gain); insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis; meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommendations for managing imAEs are detailed in Appendix 10.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade after restart of study drug should permanently discontinue treatment.

9.7.4. Renal Function Abnormalities

Patients with moderate renal dysfunction (estimated GFR > 30 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 by CKD-EPI equation) may be enrolled into the study. For patients with baseline renal insufficiency, the following algorithm is proposed for the use of steroid treatment in the management of imAEs:

- If the serum creatinine is normal at baseline, please see Section 9.7.3 and refer to Appendix 10 for the diagnosis and management of patients with abnormal renal laboratory values.
- If the serum creatinine is Grade 1 at baseline and the increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with study drug(s), refer to Appendix 10 for the diagnosis and management of patients with abnormal renal laboratory values. Check the estimated GFR using Appendix 9 and the estimated GFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by ≥ 50% from the baseline value OR the estimated GFR falls below 20 mL/min/1.73 m^2.
- If the serum creatinine is Grade 2 at baseline and the increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with study drug(s), refer to Appendix 10 for the diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the medical monitor.

9.8. Management of Adverse Events of Special Interest for Lenvatinib

9.8.1. The AE management guidance for risks for lenvatinib

9.8.1.1. Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that patients enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments a minimum of 1 hour apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive patients, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments a minimum of 1 hour apart. For those patients already on antihypertensive medication, treatment modification may be necessary if hypertension persists. For patients with hypertension and proteinuria, appropriate therapy, eg, angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist, is preferred (Kilfoy et al, 2009).

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the treatment period, patients with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 or more frequently as clinical indicated until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on repeat measurements after 1 hour:

1. Continue lenvatinib and institute antihypertensive therapy for patients not already receiving antihypertensive medication
2. For those patients already on antihypertensive medication, dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.
3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted. It should be restarted at one lower dose level as specified in Table 7 only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at an additional dose reduction as specified in Table 7 only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at a third dose reduction as specified in Table 7 only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue study drug

9.8.1.2. Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Assessments (Appendix 1). Guidelines for assessment and management of proteinuria:

1. Grading will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 5, "Recommended Dosage Modifications for lenvatinib Related Adverse Events of Special Interest"
2. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation is required in the following situations:
   - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
   - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is 2+, 3+, or 4+
3. Urine dipstick testing for patients with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months.

Grading of proteinuria should be performed according to CTCAE v5.0 but will be based on the 24-hour urine collection for total protein result, if a 24-hour urine was performed at that timepoint.

For patients with lenvatinib-related toxicity, the dose reduction and/or interruption instructions provided in Table 5 and Table 6 of the study protocol should be followed.

9.8.1.3. Management of Hepatotoxicity

Regular monitoring of liver function tests (eg, ALT, AST, bilirubin levels) should be conducted as detailed in the Schedule of Assessments (Appendix 1) and as clinically indicated. If signs occur indicating a decrease in liver function by 1 grade or more from baseline, the instructions contained in Table 5 of the protocol should be followed, "Recommended Dosage Modifications for lenvatinib Related Adverse Events of Special Interest". Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

9.8.1.4. Management of Thromboembolic Events

Patients should be advised to pay attention to the symptoms suggestive of venous thromboembolic events, which include acute onset of dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, redness and warmth to touch or tenderness. In case any of these signs or symptoms appear, patients should be instructed to report such signs and symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 5 of the protocol should be followed, "Recommended Dosage Modifications for Lenvatinib Related Adverse Events of Special Interest". Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

9.8.1.5. Management of Posterior Reversible Encephalopathy Syndrome (PRES)

In clinical studies with Lenvima, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of Lenvima-treated patients (LENVIMA (lenvatinib) [prescribing information], 2020). PRES is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In patients with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation may be required per instructions included in Table 5.

9.8.1.6. Management of hypocalcemia

Serum calcium should be monitored regularly per the Schedule of Assessments (Appendix 1). Hypocalcemia should be treated per institutional guidelines (eg, using, as appropriate, calcium, magnesium, and Vitamin D supplementation) until resolution.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

As described in the study objectives, this study is designed to establish the safety and tolerability, and preliminary anticancer activities of tislelizumab in combination with lenvatinib in patients with advanced solid tumors as assessed in multiple expansion cohorts.

The statistical analyses will be performed by the sponsor or designee after the data collection is completed and the database is locked and released. In general, data will be summarized by cohort, unless otherwise specified.

Details of the statistical analyses will be included in a separate SAP.

10.1. Statistical Analysis

The following descriptive statistics will be used to summarize the study data on the basis of their nature unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of non-missing observations, median, minimum and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time to event variables

10.1.1. Analysis Sets

The Safety Analysis Set (SAF) 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 (EAS) 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 detailed calculation of scheduled dose intensity of tislelizumab/ lenvatinib is documented in the *Safety Monitoring Committee Operating Procedure* and *statistical analysis plan* of this study.

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.

10.1.2. Patient Disposition

The number of patients treated, discontinued from study drug(s) and/or the study, and those with important/critical protocol deviations will be counted. The primary reason for study drug(s) and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (alive, dead, withdrew consent, or lost to follow-up) as of the data cutoff date will be summarized using the data from the eCRF.

Important/critical protocol deviations will be summarized and listed by category.

10.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the Safety Analysis Set. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, time since advanced/metastatic disease diagnosis, etc. Categorical variables include gender, ECOG Performance Status, region/country, race, prior systemic therapies received, stage of disease, metastatic site, etc. Other disease-specific parameters might be summarized in the relevant cohort as appropriate.

10.1.4. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study drug(s). Concomitant medications will be defined as medications that 1) started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or 2) started on or after the date of the first dose of study drug(s) up to 30 days after the patient's last dose (as of the Safety Follow-up Visit).

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. A listing of prior and concomitant medications will be provided.

10.2. Efficacy Analyses

Efficacy Analyses will be provided by subgroups as appropriate, such as PD-L1 subgroups, etc. Per-patient listings may be generated with limited patients for analysis.

Primary and/or secondary efficacy endpoints will be based on investigators' tumor assessments per RECIST Version 1.1 (if applicable) and will be defined as follows:

- ORR is defined as the proportion of patients who had confirmed CR or PR.
- Duration of response is defined as the time from the first confirmed objective response until the first documentation of progression or death, whichever comes first.
- DCR is defined as the proportion of patients with best overall response, as defined in Appendix 11,of a CR, PR, or stable disease.
- 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.

- OS is defined as the time from the date of the first dose of study drugs to death due to any cause.

General statistical considerations of efficacy analysis will be demonstrated in the following sections.

More details will be provided in the SAP.

10.2.1. Primary Efficacy Analysis

ORR assessed by the investigator and its 95% CI will be summarized by cohort based on the Safety Analysis Set and the Evaluable Analysis Set.

10.2.2. Secondary Efficacy Analysis

PFS, duration of response, DCR, and OS will be summarized by cohort and in overall study population.

PFS will be estimated using the Kaplan-Meier method. The median PFS and the cumulative probability of PFS at specific timepoints, if estimable, will be calculated and presented with 2-sided 95% CIs. PFS censoring rule will follow United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA, 2018).

Duration of response will be analyzed using methods similar to those described for PFS in the responders.

DCR will be analyzed using methods similar to those described for ORR based on the SAF and EAS.

Waterfall plots of maximum tumor shrinkage per patient will be presented.

OS will be analyzed in the SAF 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.

10.3. Safety Analyses

Safety will be assessed by monitoring and recording of AEs and laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE Version 5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized in the Safety Analysis Set by cohort and in overall study population except for analysis of DLT which is only applicable to patients in DLT Evaluable Set.

10.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity.

The number (and percentage) of patients with dose reductions, dose delays, treatment interruptions, and study drug discontinuation will be summarized for each study drug. Reasons for dose modifications and discontinuation will be summarized as well.

Patient data listings will be provided for all dosing records.

10.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA lower level term, preferred term, and primary system organ class.

DLTs will be summarized for the safety run-in stage.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days after discontinuation of study drug(s), or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside the above mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE Version 5.0 within a system organ class and preferred term, even if the patient experienced ≥ 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, ≥ Grade 3 TEAEs, immune-mediated AEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, treatment interruption, or dose delay will be summarized.

10.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for

categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by maximum postbaseline change.

Laboratory parameters that are graded by NCI-CTCAE Version 5.0 or higher will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, and sodium) will be summarized separately.

10.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, and body temperature) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

10.3.5. Pulmonary Function Test

Pulmonary function test results will be listed by patient and by visit if available.

10.4. 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.

10.5. 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.

10.6. Other Exploratory Analyses

Potential biomarkers including but not limited to PD-L1 expression, TMB/DNA mutation/ microsatellite instability (MSI), bTMB/DNA mutation/MSI, and the association of biomarkers with disease status, response/resistance to tislelizumab in combination with lenvatinib.

10.7. Sample Size Consideration

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 each of 5 prespecified tumor type cohorts

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.

11. STUDY COMMITTEES

11.1. Safety Monitoring Committee

An SMC will be established and include both the sponsor (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate) and investigators. The SMC will review and evaluate the safety information including but not limited to DLTs, all TEAEs, and laboratory abnormalities when the first 6 evaluable patients administered lenvatinib at each dose level in combination with tislelizumab (400 mg, IV, Q6W) have completed the first 28 days of treatment. The SMC will make recommendations on safety management (including resumption of enrollment, or de-escalation of lenvatinib dose to the next level, or termination of enrollment) and will recommend the RP2D for Part 2. The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

12.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries in the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

12.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

13.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

13.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

13.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), patient drug dispensation records, and returned or destroyed study drug(s). Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

14. ETHICS/PROTECTION OF HUMAN PATIENTS

14.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the International Council for Harmonisation E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the requirements of the International Council for Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

14.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

14.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

14.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

14.4. Patient and Data Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- full dates of birth;
- contact information (such as phone numbers or home or email addresses);

- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms [except in China], or on product dispensing logs provided to the sponsor, etc.).

Investigator and site must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by sponsor for sharing and transfers of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal or medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the tislelizumab Investigator's Brochure (BeiGene Investigator's Brochure, 2021) and lenvatinib Investigator's Brochure (Simcere Investigator's Brochure, 2021), this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the

disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study that includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

14.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Collection and Management Responsibilities

15.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

15.1.2. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

15.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out with due consideration to data protection and medical confidentiality.

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by lower level term, preferred term, and primary system organ class. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

15.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include but not be limited to documents such as the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements including but not limited to the following: archival at an off-site facility or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by your IRB/IEC.

15.3. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

15.4. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

15.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the study master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend or prematurely close the enrollment or to prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to: safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

15.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 15.4

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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17. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	**Screening[a]**	**Treatment cycles**								**Safety follow-up[c]**	**Survival follow-up[d]**
		Cycle 1 (42 days)				**Cycle 2-Cycle 3 (every 42 days)**		**≥ Cycle 4 (every 42 days)**	**EOT Visit[b]**		
Visit day	**-28 to -1**	**1[u]**	**8**	**15**	**29**	**1**	**22**	**1**	**0 to 7 days**	**30 days after last dose**	**Every 3 months**
Visit window			**±2**	**± 2**	**± 2**	**± 3**	**±3**	**±3**		**± 7**	± 14
Informed consent	X										
Inclusion/exclusion criteria	X										
Demographics/medical history/disease history	X										
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	
Height	X										
Weight	X	X				X		X	X	X	
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X		X	X	X	X	X	
12-lead ECG[g]	X	X				X		X		X	
Adverse events[h]	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant procedures	X	X	X	X	X	X	X	X	X	X	
Hematology[i]	X[i]	X		X	X	X[i]	X	X	X[b]	X	
Clinical chemistry[i]	X[i]	X	X	X	X	X[i]	X	X	X[b]	X	

Assessment	**Screening[a]**	**Treatment cycles**								**Safety follow-up[c]**	**Survival follow-up[d]**
		Cycle 1 (42 days)				**Cycle 2-Cycle 3 (every 42 days)**		**≥ Cycle 4 (every 42 days)**	**EOT Visit[b]**		
Visit day	**-28 to -1**	**1[u]**	**8**	**15**	29	**1**	**22**	**1**	**0 to 7 days**	**30 days after last dose**	**Every 3 months**
Visit window			**±2**	**± 2**	**± 2**	**± 3**	**±3**	**±3**		**± 7**	± 14
CK and CK-MB[j]	X	X		X	X	X	X	X	X[b]	X	
Coagulation parameters[i]	X[i]	X	X	X	X	X	X	X	X[b]	X	
Urinalysis[i]	X[i]	X	X	X	X	X	X	X		X	
Pregnancy test[k]	X	X				X		X		X	
Thyroid function[l]	X[l]	X				X		X		X	
HBV/HCV tests[m]	X		As clinically indicated [m]								
Pulmonary function tests[n]	X		As clinically indicated [n]								
Pharmacokinetics		See Appendix 2									
Anti-tislelizumab antibodies		See Appendix 2									
Blood biomarkers[o]		X	At the time of confirmed response and PD								
Tumor assessment[p]	X		Every 9 weeks (± 7 days) from Cycle 1 Day 1, for the first 54 weeks, then every 12 weeks (± 7 days)						X [b]		X
Archival or fresh tumor tissue[q]	X		See Appendix 1A								
Tislelizumab administration[r]		X				X		X			
Lenvatinib administration[s]		Daily									
LVEF examination[t]	X		As clinically indicated						X		
Survival status											X

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment (Visit); FEV1, forced expiratory volume; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; imAE, immune-mediated AE; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; LVEF = left ventricular ejection fraction, MUGA = multiplegated acquisition.

Note: Timepoints containing numbers represent timepoints with special considerations for that respective assessment.

[a] Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests unless otherwise indicated. The ICF signature alone does not define the start of the screening period, but the first study-related assessment date is to be used for the date of the Screening Visit.

[b] The EOT Visit is conducted ≤ 7 days after the investigator determines that the patient must permanently discontinue tislelizumab and lenvatinib. If routine laboratory tests (eg, hematology, clinical chemistry) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of study drugs, the EOT Visit may also be used as the Safety Follow-up Visit.

[c] Patients who permanently discontinue all study drugs will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted within 30 days [± 7 days] after the last dose of study drugs or before the initiation of new anticancer therapy, whichever occurs first. The Safety Follow-up Visit may coincide with the EOT Visit (see Section 7.4) but cannot occur before the EOT Visit. In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, is associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not patients started a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

[d] Survival Follow-Up Period: information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the EOT/Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

[e] Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion of tislelizumab, and if clinically indicated, during and 30 minutes after each tislelizumab infusion. Vital signs should also be recorded before administration of lenvatinib; recorded values may be used for post-tislelizumab assessment if vital signs are collected within 30 minutes after tislelizumab infusion.

[f] A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems at screening. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed.

[g] When coinciding with blood draws (eg, performed within 30 minutes of each other), ECG assessment should be performed prior to blood draws. The patient should rest in semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection. If the ECG is not performed ≤ 3 days before the first dose of study drug(s), the test should be repeated and reviewed before study drug administration on Day 1 of Cycle 1. After Day 1 of Cycle 1, ECGs will be collected on Day 1 of each cycle and as

clinically needed. During the screening period, 3 consecutive 12-lead ECGs will be performed within 10 minutes for each interval to determine the mean QTcF interval. At other timepoints, a single 12-lead ECG will be performed for determination. Repeated 12-lead ECG will be performed if clinically indicated.

[h] The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed but before the administration of study drug(s), only SAEs should be reported. After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after the last dose of study drug(s) (including tislelizumab and/or lenvatinib) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious and nonserious) should be reported for tislelizumab until 90 days after the last dose of tislelizumab regardless of whether the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

[i] Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 3. If clinical chemistry, hematology, urinalysis, and coagulation at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 3 days before study drug administration. Clinical chemistry, coagulation, and urinalysis (data collected as specified in Appendix 3) will be performed for Days 1, 8, 15 and 29 of Cycle 1 and then Day 1 and Day 22 for Cycle 2 and Cycle 3, then on Day 1 of each subsequent cycle. Hematology (data collected as specified in Appendix 3) will be performed for Days 1, 15 and 29 of Cycle 1 and then Day 1 and Day 22 for Cycle 2 and Cycle 3, then on Day 1 of each subsequent cycle. Refer to Section 9.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[j] CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. If CK and CK-MB at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 3 days before study drug administration.

[k] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the first dose of study drug(s). A negative urine pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[l] Analysis of free T3, free T4, and thyroid stimulating hormone will be performed by the local study site laboratory. If the thyroid function test at screening is not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, the test should be repeated and reviewed before study drug administration. Thyroid function tests will be performed at Day 1 of each subsequent cycle and at the Safety Follow-up Visit.

[m] Testing will be performed by a local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA), which will be assessed only when HBsAg or HCV antibody is positive, respectively. Patients who have detectable HBV DNA at screening will perform the respective viral load test every 2 cycles starting at Cycle 3 (ie, Day 1 of Cycles 3, 5, 7, etc) and the EOT Visit.

[n] For patients with tumor type other than lung cancer who are suspected of having or known to have serious/severe respiratory conditions, or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing that may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study. For patients with lung cancer, pulmonary function testing including spirometry and assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the screening period to assist the determination of suitability for the study. Respective test results need to be submitted to the sponsor. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, FEV1 < 60% or DLCO (if performed) < 60% of age- and sex-adjusted predicted performance levels, the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study.

[o] Blood samples will be collected for all patients at baseline (required), at the time of first confirmed tumor response (optional), and at the time of PD (optional). Approximately 10 mL for each timepoint. Written patient consent is required for blood sample collections.

[p] Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 9 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks, then every 12 weeks (± 7 days), based on RECIST Version 1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans). Patients with squamous cell carcinoma of the head and neck must also have head and neck scans performed. MRI may be used instead of CT for head, neck, abdomen, and pelvis; however, the chest must be assessed using CT. Chest disease should not be followed using chest x-ray. If a patient discontinues study treatment due to the reasons other than disease progression or death, tumor assessments will continue to be performed as scheduled until the patient begins a subsequent anticancer treatment, experiences disease progression, is lost to follow-up, withdraws consent or until patient death or study terminates, whichever occurs first. See Section 8.3 for more information.

[q] Archival tumor tissue (if available) must be sent to the central laboratory for PD-L1 assessment for the NSCLC cohort during the screening period and for retrospective analysis of exploratory biomarkers for NSCLC, SCCHN, UC and GC cohorts. If archival tumor tissues are not available during the screening period, a fresh tumor biopsy is mandatory for the NSCLC, SCCHN, UC and GC cohort. Written patient consent is required for fresh tumor biopsies. For fresh biopsy, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

[r] Tislelizumab will be given intravenously on Day 1 of each 42-day cycle (once every 6 weeks) (see Section 5.2 for details).

[s] Lenvatinib will be self-administered orally once daily (see Section 5.2 for details).

[t] During the study, MUGA scans or echocardiograms will be performed to assess LVEF at screening, EOT visit, and if clinically indicates assessed by investigator.

[u] Cycle 1 Day 1 (C1D1) is defined as the day when initial infusion of tislelizumab administration or first dose of lenvatinib, whichever happens earlier. Study treatment of tislelizumab may be administered ± 3 days from the scheduled Day 1 of each cycle due to administrative reasons. On Day1 of each cycle, lenvatinib will be administered at least 1 hour after completion of tislelizumab administration.

APPENDIX 1A. DOSE ESCALATION BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response.

Biomarker assessment	**Screening**	**Cycle 1**				**Patients with confirmed PR or CR**	**Patients with confirmed PD (End-of-treatment visit)**
Visit day	**-28 to ~ -1**	**1**	**2**	**8**	**15**		**0 to 7 days**
Peripheral blood (≈ 10 mL)[a]		X				X (+ 14 days of confirmation)	X
Archival or fresh tumor tissue[b]	X						

[a] Blood samples will be collected for all patients at baseline (required), at the time of first confirmed tumor response (optional), and at the time of PD (optional). Approximately 10 mL for each timepoint. Written patient consent is required for blood sample collections.

[b] Archival tumor tissue (if available) must be sent to the central laboratory for PD-L1 assessment for the NSCLC cohort during the screening period and for retrospective analysis of exploratory biomarkers for NSCLC, SCCHN, UC and GC cohorts. If archival tumor tissues are not available during the screening period, a fresh tumor biopsy is mandatory for the NSCLC, SCCHN, UC and GC cohort. Written patient consent is required for fresh tumor biopsies. For fresh biopsy, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

APPENDIX 2. PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE FOR TISLELIZUMAB

Study Visit	Timepoint	PK[a]	ADA[b]
Cycle 1, Day 1	Predose (within 60 min before start of infusion)	X	X
	Within 30 min after end of infusion	X	
Cycle 2, Day 1	Predose (within 60 min before start of infusion)	X	X
Cycle 3, Day 1	Predose (within 60 min before start of infusion)	X	X
	Within 30 min after end of infusion	X	
Cycle 5, Day 1	Predose (within 60 min before start of infusion)	X	X
Cycle 9, Day 1	Predose (within 60 min before start of infusion)	X	X
EOT/Safety Follow-up	EOT Visit or Safety Follow-up Visit (30 days ± 7 days after last dose)	X	X

Abbreviations: EOT, end of treatment; min, minutes; ADA, antidrug antibody

Note: Sample collection must be from opposite arm of that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for pharmacokinetic and antidrug antibody should be from a different site. Window: within 30 minutes after end of infusion for postdose samples and within 60 minutes before start of infusion for predose samples unless otherwise specified.

[a] Procedures for collection of PK samples are described in the laboratory manual. For tislelizumab, predose (within 60 minutes before starting infusion) samples are required to be collected on Day 1 of Cycles 1, 2, 3, 5 and 9. A postdose (within 30 minutes after completing tislelizumab infusion) sample is required to be collected on Day 1 of Cycles 1 and 3. An additional PK sample is required to be collected at the Safety Follow-up. If tislelizumab is permanently discontinued, scheduled PK sampling is no longer required except safety follow-up. Should a patient present with DLT event or any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.

[b] Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 3, 5, and 9 and at the mandatory Safety Follow-up Visit. If tislelizumab is permanently discontinued, scheduled ADA sampling is no longer required except safety follow-up. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/ECs.

APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Category	Parameters
Clinical chemistry	Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin, direct bilirubin, blood urea nitrogen or urea, amylase, lipase, potassium, sodium, total calcium[a], creatinine, Glucose, lactate dehydrogenase, total protein, creatine kinase[b], CK-MB[b], magnesium
Hematology	Red blood cell count, hematocrit, hemoglobin, platelet count, white blood cell count, lymphocyte count, neutrophil count
Coagulation	Prothrombin time, partial thromboplastin time or activated partial thromboplastin time, international normalized ratio
Urinalysis	Glucose, protein, blood, ketones, 24-hour protein[c], random urine protein to creatinine ratio
Thyroid function	Thyroid stimulating hormone, free T3, free T4
Others	HCV Ab, HCV RNA[d], HBsAg, HBsAb, HBcAb, HBV DNA[d], urine pregnancy test[e], serum pregnancy test[e]

Abbreviations: C1D1, Cycle 1 Day 1; CK-MB, creatine kinase-muscle/brain; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

[a.] Total calcium values will be corrected for patients with hypoproteinemia.

[b.] All patients will have creatine kinase and CK-MB testing at screening, and to be repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the End-of-Treatment/Safety Follow-up visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 8.2.4 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[c.] 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.

[d.] Refer to footnote m in Appendix 1 for detailed requirement.

[e.] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the first dose of study drug(s). A negative urine pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken et al, 1982. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 5. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease. Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barré syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome
Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Koyanagi-Harada disease

APPENDIX 6. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group, 2020). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral, injectable, or implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile male is one for azoospermia has been demonstrated in a semen sample examination as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug(s), and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 mIU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group, 2020.

APPENDIX 7. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin et al, 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 8. FRIDERICIA'S FORMULA FOR CORRECTING QT INTERVALS

Prolongation of the QT interval reflects abnormalities in cardiac repolarization and is a risk factor for various cardiovascular events including ventricular arrhythmias, heart failure, coronary artery disease, and death in various populations. Assessment of the QT interval requires correction for the heart rate in order to enable comparisons with standard reference values. Fridericia's formula is one of the most widely used method for correcting QT intervals (Fridericia, 1920). The formula is as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

QT is the QT interval measured from the start of QRS wave to the end of T wave (not including U wave).

RR is the RR interval, which could be calculated as 60 divided by heart rate (beats per minute).

APPENDIX 9. CHRONIC KIDNEY DISEASE-EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 2009) and the Modification of Diet in Renal Disease Study (MDRD) study equation. The National Kidney Disease Education Program calculators rely on creatinine determinations that are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

The CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) reported in mg/dL. This equation is recommended when estimated GFR values above 60 mL/min/1.73 m^2 are desired.

$$GFR = 141 \times \min (S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

APPENDIX 10. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-mediated AE (imAE) are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the AE?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-mediated Adverse Events

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

Recommended Diagnostic Tests in the Management of Possible Immune-mediated Adverse Events

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-Mediated Adverse Events

- Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required.
- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF]).
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3 or 4.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Colitis/Diarrhea	**1** Mild symptoms: ≤ 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. • If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myocarditis[a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multiplegated acquisition scan; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

APPENDIX 11. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al, 2009.

Definitions

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in ≥ 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no > 5 mm.
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no > 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all nonmeasurable.

Bone lesions:

- Bone scan, positron-emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT

or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm by 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, because CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease (PD).

Response Criteria

Evaluation of Target Lesions

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- Partial response (PR): ≥ a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive disease (PD): ≥ a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
- When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of stable disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of stable disease or PR of target disease will therefore be extremely rare.
- When the patient has only nonmeasurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorine-18 [F-18] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Timepoint Response

- It is assumed that at each protocol specified timepoint, a response assessment occurs. The following table provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline:

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- When patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	SD (Non-CR/non-PD)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; SD, stable disease.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

Best response determination in studies where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In trials where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial-specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of stable disease, measurements must have met the stable disease criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 12. MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING TREATMENT WITH LENVATINIB

MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING TREATMENT WITH LENVATINIB

The text below was obtained from the followings https://crediblemeds.org/ and http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Bold font indicates medications or substances that might be relatively commonly used.

Italic font indicates medications for indications that are exclusionary for the current study or would likely result in discontinuation from study treatment with lenvatinib for management of a concurrent illness.

MEDICATIONS THAT SHOULD BE AVOIDED

Drugs With a Known Risk of QT Prolongation/Torsades de Pointes

Amiodarone, anagrelide, *arsenic trioxide*, astemizole (off United States [US] market), **azithromycin**, bepridil (off US market), chloroquine, **chlorpromazine**, cilostazol, **ciprofloxacin**, cisapride (off US market), **citalopram**, **clarithromycin**, cocaine, disopyramide, dofetilide, domperidone (not on US market), donepezil, dronedarone, **droperidol**, **erythromycin**, **escitalopram**, flecainide, fluconazole, gatifloxacin (off US market), grepafloxacin (not on US market), halofantrine (not on US market), haloperidol, ibogaine (not on US market), ibutilide, levofloxacin, levomepromazine / methotrimeprazine (not on US market), levomethadyl (off US market), levosulpiride (not on US market), mesoridazine (off US market), **methadone**, moxifloxacin, **ondansetron**, *oxaliplatin*, *pentamidine*, pimozide, probucol (off US market), procainamide, propofol, quinidine, roxithromycin (not on US market), sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), sultopride (non on US market), terfenadine (off US market), terlipressin (not on US market), terodiline (not on US market), thioridazine, *vandetanib*.

CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS

Substrates with Narrow Therapeutic Index for CYP3A4

Astemizole, terfenadine, cisapride, pimozide, quinidine, benazepril, or ergot alkaloids (ergotamine, dihydroergotamine)

APPENDIX 13. CLINICAL STUDIES EVALUATING DRUG–DRUG INTERACTIONS WITH LENVIMA

Nonclinical studies identify CYP3A4 as a potentially important Cytochrome P450 isozyme responsible for metabolism of Lenvima. Clinical studies were conducted to test these findings.

Simultaneous CYP3A4/P-glycoprotein (P-gp) inhibition by ketoconazole slightly (15% to 19%) increases systemic exposure to Lenvima (Shumaker et al, 2015). Since no change was observed in half-life, T_{max}, or lag time (tlag), the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of change is small, co-administration of Lenvima with CYP3A4/P-gp inhibitors is not of clinical concern.

The influence of P-gp inhibition on Lenvima PK has been investigated. P-gp inhibition was accomplished by co-administering a single dose of rifampin with a single dose of Lenvima. Preliminary results suggest P-gp inhibition increases systemic exposure to Lenvima 26% to 32%. Thus, co-administration of Lenvima with P-gp inhibitors only causes a small increase in Lenvima exposure.

The influence of simultaneous P-gp and CYP3A4 induction on Lenvima PK has been investigated. Examination of simultaneous P-gp and CYP3A4 induction on Lenvima PK was accomplished by administering rifampin QD for 21 days (Shumaker et al, 2014a). A single dose of Lenvima was coadministered with the 15th dose of rifampin. Based on preliminary data, simultaneous P-gp and CYP3A4 induction minimally altered Lenvima exposure as mean C_{max} increased about 8% while AUC decreased about 7%. Coadministration of Lenvima with CYP3A4/P-gp inducers is not of clinical concern.

BGB-A317-212
PROTOCOL AMENDMENT 2.0
SUMMARY OF CHANGES

Study 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

BeiGene, Ltd., has updated the BGB-A317-212 protocol from Protocol Amendment 1.0 (01 November 2021) to Protocol Amendment 2.0 (03 November 2022). The primary purposes for this amendment are as follows:

- to terminate three cohorts (NSCLC, UC, and GC)
- to update Section 1 based on the latest Tislelizumab Investigator Brochure
- to decommission the treatment eligibility review process
- to update patient and data confidentiality language
- to update demographic language

In addition, editorial and format changes have been made throughout to enhance clarity and readability.

Key changes made from Protocol Amendment 1.0 to Protocol Amendment 2.0 are summarized in the table below.

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Cover Page, Headers, Final Protocol Approval Sheet	• Changed protocol edition and dates • Changed sponsor medical monitor	To update the protocol edition To update the contact information of the sponsor medical monitor	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Throughout the protocol	• Revised the cohort names from "Cohort A/B/C/D/E" to "**NSCLC/SCCHN/UC/RCC/GC Cohort,**" respectively	To define the cohort more clearly and to correspond to the termination of 3 cohorts (NSCLC, UC, and GC cohorts) in Part 2	N	N/A
Synopsis	• Revised the number of study centers from "Approximately 20 centers" to "**Approximately 14 centers**" • The synopsis was updated as appropriate to reflect changes made throughout the protocol	To update the number of study centers in China To be consistent with full protocol text	N	N/A
Section 1.1 Introduction **Section 1.3.2 Clinical Experience** **Section 1.4.1 Rationale for the Dosing Regimen**	• Updated the approved indications for tislelizumab in China • Updated the clinical safety data of tislelizumab • Updated the approved dose for tislelizumab • Updated efficacy data from BGB-A317_Study_001	To update the clinical data of tislelizumab to align with Tislelizumab Investigator Brochure Version 9.0 and Tislelizumab United States Prescribing Information	N	N/A
Section 1.2.2.2. Clinical Efficacy and Safety	• Deleted the wording ~~"Administration with a high-fat meal did not change safety results significantly"~~	To align with Lenvima (lenvatinib) Investigator's Brochure	N	N/A
Section 1.2.2.2. Clinical Efficacy and Safety	• Added the clinical efficacy and safety data of Lenvima for NSCLC, SCCHN, UC, and GC patients	To strengthen the rationale for the selection of tumor types in this study and the	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 1.2.2.2.2 Lenvima in Non-Small Cell Lung Cancer **Section 1.2.2.2.3 Lenvima in Squamous Cell Carcinoma of Head and Neck** **Section 1.2.2.2.4 Lenvima in Urothelial Cancer** **Section 1.2.2.2.5 Lenvima in Gastric Cancer**		termination of three cohorts (NSCLC, UC, and GC) in Part 2		
Section 1.4.1.1 Lenvatinib Starting Dose	• Added wording about the approved dose for Lenvima in combination with pembrolizumab	To strengthen the rationale for the starting dose of lenvatinib	N	N/A
Section 1.4.3.1 Non-Small Cell Lung Cancer **Section 1.4.3.3 Urothelial Carcinoma** **Section 1.4.3.5 Gastric Cancer**	• Added the latest study results (LEAP-007 study and LEAP-011 study) and the changes of first-line SoC for patients with GC in China	To strengthen the rationale for the termination of three cohorts (NSCLC, UC, and GC) in Part 2	N	N/A
Section 2.2 Study Objectives and	• Deleted specific tumor type information in the ORR and biomarker analysis	To increase the flexibility of ORR and biomarker analysis and to correspond	Y	Potential impact on study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Endpoints for Part 2 (Expansion)	• Deleted wording ~~"time-pairing"~~ in the exploratory objectives and endpoints	to the termination of 3 cohorts (NSCLC, UC, and GC) in Part 2 To increase the flexibility of post-dose PK sample analysis		
Section 3.1 Summary of Study Design **Section 3.4 Study Design of Part 2**	• Added wording **"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)"**	To correspond to the termination of 3 cohorts (NSCLC, UC, and GC) in Part 2	Y	Potential impact on study conduct
Figure 1 Study Schema	• Added the wording about specific tumor types	To clarify the tumor types included in this study	N	N/A
Section 3.2 Duration of Study	• Added wording about enrollment closure, study discontinuation, and the continuation of providing study drug(s)	To clarify the sponsor's right to close enrollment or discontinue the study	N	N/A
Section 4 Study Population	• Revised wording "The sponsor will not grant any eligibility waivers" to "**No eligibility waivers will be granted.**"	To correspond to the discontinuation of eligibility review by the sponsor's medical monitor prior to enrollment	N	N/A
Section 4.1 Inclusion Criteria	• Deleted wording "~~primary~~" in the note of the SCCHN cohort	To clarify the inclusion criteria of SCCHN patients	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	• Added clarification of the term "metastatic" in the note of the SCCHN cohort			
Section 5.2 Dosage, Administration, and Compliance	• Deleted wording ~~"medical monitor or designee's"~~	To correspond to the discontinuation of eligibility review by the sponsor's medical monitor prior to enrollment	N	N/A
Section 7.1.2 Demographics	• Added content regarding demographic factors and the justifying collection of race/ethnicity data	To update per sponsor's current process	N	N/A
Section 7.2 Enrollment	• Removed Treatment Eligibility Form language • Added wording that sponsor verification of patient eligibility will be managed by source data verification in accordance with ICH E6	To discontinue Treatment Eligibility review conducted by medical monitors prior to patient enrollment To update per sponsor's current process	Y	Potential impact on study management with no expected impact on patient safety
Section 8.2.4 Laboratory Safety Tests **Appendix 1 Schedule of Assessments**	• Added wording "urinalysis"	To clarify the clinical practice of urinalysis	N	N/A
Section 8.2.4.1 Cardiac Enzyme Monitoring	• Added wording about the performance of CK and CK-MB	To clarify the clinical practice of CK and CK-MB	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 1 Schedule of Assessments	during the screening period and result review while on study			
Section 8.2.5 Electrocardiograms **Appendix 1 Schedule of Assessments**	• Revised the frequency of 12-lead ECGs during the study	To increase the flexibility of 12-lead ECGs in clinical practice	N	N/A
Section 8.3 Tumor and Response Evaluations	• Added wording **"confirmation 4 to 6 weeks after the first response is strongly recommended"**	To clarify the recommended timeslot for the tumor response confirmation	N	N/A
Section 10.2.1 Primary Efficacy Analysis	• Revised the ORR analysis method	To increase the flexibility of efficacy analysis	N	N/A
Section 10.3.2 Adverse Events	• Updated the imAE definition	To be consistent with the new AE definition for tislelizumab	N	N/A
Section 10.6 Other Exploratory Analyses	• Deleted tumor type information in the biomarker analysis	To correspond to the termination of three cohorts (NSCLC, UC, and GC) in Part 2	Y	Potential impact on study conduct
Section 10.7 Sample Size Consideration	• Revised the number of patients from "Approximately 150" to **"Approximately 70"** • Added wording **"Three cohorts were closed prior to planned enrollment due to emerging data**	To correspond to the termination of three cohorts (NSCLC, UC, and GC) in Part 2	Y	Potential impact on study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	(NSCLC and UC cohorts) and changes to first-line standard of care (GC cohort). In the SCCHN and RCC cohorts, approximately"			
Section 14.4 Patient and Data Confidentiality	• Updated the confidentiality language	To update per sponsor's current legal language	N	N/A
Section 15.5 Study and Study Center Closure	• Added wording "**or to prematurely close**"	To increase the flexibility of enrollment closure	N	N/A
Appendix 2 Pharmacokinetic and Immunogenicity Sampling Schedule for Tislelizumab	• Added wording **"EOT Visit or Safety Follow-up Visit"**	To clarify the timepoint of EOT/Safety Follow-up	N	N/A
Appendix 3 Clinical Laboratory Assessments	• Revised wording "and" to **"or"** in footnote c	To increase the flexibility of routine urinalysis	N	N/A
Appendix 6 Contraception Guidelines and Definitions of "Women of Childbearing Potential, "No Childbearing Potential"	• Revised the postmenopausal follicle-stimulating hormone concentration from "> 30 IU/mL" to **"> 30 mIU/mL"**	To update the definition of postmenopausal to align with Clinical Trials Facilitation Group guideline	N	N/A

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; ECG, electrocardiogram; EOT, End-of-Treatment (Visit); GC, gastric cancer; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; imAE, immune-mediated adverse event; N, no; N/A, not applicable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PK, pharmacokinetic(s); RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of head and neck; SoC, standard of care; UC, urothelial cancer; Y, yes.