CLINICAL STUDY PROTOCOL

Title of Study Protocol:	A Phase 2 Study to Evaluate the Safety, Tolerability, and Preliminary Antitumor Activity of Sitravatinib plus Tislelizumab or Sitravatinib plus Tislelizumab in Combination with Nab-Paclitaxel in Patients with Locally Recurrent or Metastatic Triple Negative Breast Cancer (TNBC)
Protocol Number	BGB-900-2001-IIT
Phase of Development:	Phase 2
Investigational Product(s):	Sitravatinib (BGB-9468) and tislelizumab (BGB-A317)
Disease of Interest:	Triple negative breast cancer
Sponsor:	Fudan University Shanghai Cancer Center Department of Breast Surgery, 270 Dong'an Road, Shanghai 200032 P.R. China
Study Director:	Zhimin Shao, M.D. +86 13611709888 Email: zhimingshao@yahoo.com
Version No.:	Version 1.5/Dec. 24, 2022

INVESTIGATOR SIGNATURE PAGE

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I confirm that I have read the protocol, I understand it, and I will work in accordance with the protocol. I will also work in compliance with the ethical rules that have their origin in the *Declaration of Helsinki* and that are consistent with the "Good Clinical Practice" and the applicable laws and regulations.

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

Investigator Name: _____

Investigator Position: _____

Signature of Investigator: _____

Date: _____

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SYNOPSIS

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Protocol Number:	BGB-900-2001-IIT
Phase of Development:	Phase 2
Number of Patients:	Approximately 96 patients are planned to be enrolled
Study Center(s):	Department of Breast Surgery, Fudan University Shanghai Cancer Center

Objectives:

Primary objectives:

- To comprehensively evaluate the preliminary antitumor activity, safety, and tolerability of 100 mg sitravatinib plus tislelizumab based on the investigator-assessed overall response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and percentage of subjects experiencing grade ≥ 3 treatment-related adverse events (TRAEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0;
- To evaluate the preliminary antitumor activity of 70 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel based on the ORR assessed by investigators according to RECIST v1.1;

Secondary objectives:

- To evaluate the preliminary antitumor activity of 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel based on the duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) assessed by investigators according to RECIST v1.1;
- To assess the 1-year overall survival (OS) rates of patients receiving 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel;
- To evaluate the safety and tolerability of 70 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel according to NCI-CTCAE v5.0;
- To evaluate the safety and tolerability of 100 mg sitravatinib plus tislelizumab according to NCI-CTCAE v5.0 (excluding grade ≥ 3 TRAEs).

Exploratory objective:

- To explore potential biomarkers of efficacy, resistance, and/or progressive disease (PD) in tumor tissues.

Study Endpoints:

Primary Endpoints:

- Objective response rates (ORRs) of the three cohorts determined by the investigator according to RECIST v1.1:

  Cohort 1: ORR of 70 mg sitravatinib plus tislelizumab

  Cohort 2: ORR of 100mg sitravatinib plus tislelizumab

  Cohort 3: ORR of 70 mg of sitravatinib plus tislelizumab in combination with nab-paclitaxel

  - ORR: It is defined as the proportion of patients who achieve either complete response (CR) or partial response (PR) as the best overall response (BOR);
- The percentage of subjects in Cohort 2 (100 mg sitravatinib plus tislelizumab) that experience grade ≥ 3 TRAEs, as assessed by the investigator according to NCI-CTCAE v5.0.

Secondary Endpoints

- The DOR, DRC, and PFS of 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel, respectively, assessed by the investigator according to RECIST v1.1:
  - DOR: It is defined as the time from the first documented objective response to the recurrence or death from any cause (whichever occurs first);
  - DCR: It is defined as the proportion of patients with BOR being CR, PR, or stable disease (SD);
  - PFS: It is defined as the time from the first dose of the investigational products to the date of the first objectively documented progressive disease (PD) or death from any cause (whichever occurs first);
- The percentage of subjects that experience the OS event (within 1 year) after receiving 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel, respectively, as assessed by the investigator according to RECIST v1.1:
  - OS is defined as the time from the date of the first dose of the investigational products to the date of death from any cause. The 1-year survival rate (percentage of subjects alive at 1 year) will be estimated based on the OS data
- The safety and tolerability of 70 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel assessed based on the incidence, nature, and severity of AEs and serious AEs (SAEs) determined by NCI-CTCAE v5.0, the patient-reported outcomes (PROs) collected by using the EORTC QLQ-C30 (v3) Quality of Life Questionnaire, clinical laboratory abnormalities, relevant physical examinations, ECGs, vital signs, and the percentage of subjects who discontinue study treatment due to AEs;

  The safety and tolerability of 100 mg sitravatinib plus tislelizumab assessed based on the incidence, nature, and severity of AEs and serious AEs (SAEs) except for grade ≥ 3 TRAEs as determined according to NCI-CTCAE v5.0, the patient-reported outcomes (PROs) collected by using the EORTC QLQ-C30 (v3) Quality of Life Questionnaire,

clinical laboratory abnormalities, relevant physical examinations, ECGs, vital signs, and the percentage of subjects who discontinue study treatment due to AEs;

Exploratory Endpoints:

- The potential biomarkers associated with efficacy, resistance, and/or progressive disease (PD), including expression of programmed cell death protein ligand-1 (PD-L1), tumor-infiltrating lymphocytes (TILs), and forkhead box protein C1(FOXC1) in archival and/or fresh tumor tissues obtained prior to treatment, radiomics analysis, immune-related cytokines and peripheral blood cell classification, ctDNA testing, gene expression profiling (GEP), genetic/tissue mutation testing, single-cell sequencing, proteomics, and metabolomics.

Subject Population

Patients with locally recurrent or metastatic TNBC after receiving ≤ 3 prior lines of therapy.

Key Inclusion Criteria

Adult female patients (aged ≥ 18 years at the time of voluntarily signing the informed consent form) with histologically and radiographically confirmed locally recurrent or metastatic breast cancer of the TNBC (negative for ER, PR, HER2) type as clarified by histopathology. For all patients, the Eastern Cooperative Oncology Group (ECOG) performance status score is required to be ≤ 1, with adequate organ performance.

Investigational Products, Dose, and Mode of Administration:

Cohort A and Cohort B:

Sitravatinib: 70/100 mg, once daily (QD), administered orally (PO) for 21 consecutive days as a dosing cycle. Sitravatinib will be administered in combination with 200 mg tislelizumab which will be administered by intravenous (IV) injection, once every 3 weeks (Q3W), on the first day of each 21-day dosing cycle.

Cohort C:

Sitravatinib: 70 mg, once daily (QD), administered orally (PO) for 21 consecutive days as a dosing cycle. Sitravatinib will be administered in combination with 200 mg tislelizumab which will be administered by intravenous (IV) injection, once every 3 weeks (Q3W), on the first day of each 21-day dosing cycle. Nab-paclitaxel at 100 mg/m^2 will be administered via IV on Day 1 and Day 8 of each 3-week treatment cycle.

Study Design

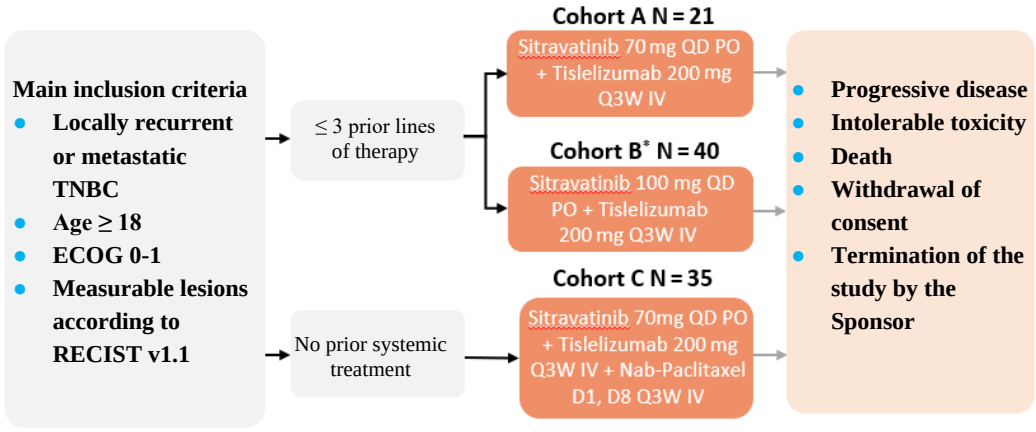
This is an open-label, single-center, and phase 2 clinical study in patients with locally recurrent or metastatic TNBC after receiving ≤ 3 prior lines of therapy. All patients will be treated with the investigational products during the treatment period until the development of PD, intolerable toxicity, death, withdrawal of consent, or termination of the study by the sponsor. There are 3 cohorts in the study:

Cohort A: Sitravatinib 70 mg QD PO plus 200 mg tislelizumab Q3W IV;

Cohort B: Sitravatinib 100 mg QD PO plus 200 mg tislelizumab Q3W IV;

Cohort C: Sitravatinib 70 mg QD PO plus 200 mg tislelizumab Q3W IV in combination with nab-paclitaxel 100 mg/m^2 D1, D8 Q3W IV;

Study Schema



*The enrollment into Cohort B shall start after that into Cohort A is completed

Abbreviations: TNBC = triple negative breast cancer; ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death protein-1; PD-L1 = programmed cell death protein ligand-1; QD = once daily; PO = oral administration; Q3W = once every 3 weeks; IV = intravenous injection; Sitra = sitravatinib; Tisle = tislelizumab;

Cohort A will follow the Simon's two-stage design to test the superiority of the combination therapy under study relative to the historical control. Of the first 12 patients in the efficacy analysis set of Cohort A, if the number of subjects with confirmed post-treatment response is 0, enrollment into Cohort A will be terminated, and the patients who have been enrolled in Cohort A will continue treatment with the investigational products and complete subsequent assessments until withdrawal. Otherwise, the Cohort A study will continue until 21 patients are enrolled.

Cohort C will follow the Simon's two-stage design to test the superiority of the combination therapy under study relative to the historical control. Of the first 18 patients in the efficacy analysis set of Cohort C, if the number of subjects with confirmed post-treatment response is ≤ 9, enrollment into Cohort C will be terminated, and the patients who have been enrolled in Cohort C will continue treatment with the investigational products and complete subsequent assessments until withdrawal. Otherwise, the Cohort C study will continue until 35 patients are enrolled.

If a patient drops out before the first assessment and could not be included in the efficacy analysis set, the dropout shall be supplemented.

Study Assessments:

The study assessment form is shown in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study.

Baseline Assessment

- Medical history: First diagnosis, hormone receptor status and HER-2 receptor status, tumor size, lymph node metastasis, previous treatment history of breast cancer, and menstrual status. Pre-existing conditions and concomitant medications, vital signs, ECOG score, and general physical examination.
- Laboratory tests: Hematology, urinalysis, liver and kidney function tests, and endogenous creatinine clearance test shall be performed within 1 week before

enrollment. Tumor marker examination, ECG, etc. shall be performed within 2 weeks before enrollment.

- Tumor assessment: Baseline assessment shall be performed within 4 weeks before the start of treatment and as close to the treatment start time as possible. Chest CT and abdominal MRI are recommended for imaging examination, and the same examination method shall be performed in subsequent follow-ups and assessments of the same lesion. Bone scans and head CT or MRI may be performed when they are considered necessary by the clinician as baseline examinations for tumors. The efficacy will be evaluated using RECIST 1.1 criteria, including measurable and non-measurable lesions, target and non-target lesions, and objective response criteria for tumors (complete response, partial response, stability, and progressive disease).

Assessments during the Treatment Period

- Clinical assessment: The vital signs, ECOG scores, and general physical examinations will be performed for the patients before each course of treatment.
- Laboratory tests: The hematology and liver and kidney function tests must be performed before each course of treatment, and the next course of treatment can only be carried out after all the toxicities have resolved to < grade 1.
- Efficacy assessment: The radiological assessment of tumor response shall be performed once approximately every 6 weeks (± 7 days). The efficacy will be evaluated using RECIST 1.1 criteria, including measurable and non-measurable lesions, target and non-target lesions, and objective response criteria for tumors (complete response, partial response, stability, and progressive disease).

Safety Assessment

- Adverse reactions will be assessed at each visit window as defined in Appendix 1 based on clinical and laboratory results and in reference to the common toxicity criteria specified in NCI-CTCAE v5.0.

Study Period

Enrollment of all patients is planned to be completed within 2.5 years, giving an estimated overall study duration of 3.5 years.

Statistical Methods

Analysis Sets:

- The safety set (SS) will include all the patients who have received at least 1 dose of any investigational product (any drug in the combination therapies).
- For Cohort A/Cohort C: The efficacy evaluable analysis set includes all the patients who have received at least 1 dose of any investigational product with measurable lesions at baseline (according to RECIST v1.1) and have at least 1 evaluable post-baseline tumor assessment (the patients who withdraw or die due to progressive disease prior to the first post-treatment tumor assessment shall also be included).
- For Cohort B: The efficacy evaluable analysis set includes all the patients who have received at least 1 dose of any investigational product with measurable lesions at baseline (according to RECIST v1.1) and have at least 1 evaluable post-baseline tumor assessment (the patients who withdraw due to ≥ grade 3 TRAEs, experience progressive disease, or die before the first post-treatment tumor assessment shall also be included).

Main Analyses:

In the efficacy analysis set, the investigator will evaluate the ORR hypothesis testing based on the efficacy analysis set according to RECIST v1.1, which will serve as the primary efficacy analysis.

For Cohort A:

In patients with locally recurrent or metastatic TNBC, an ORR of 25% is assumed for the sitravatinib plus tislelizumab regimen under study to indicate an improvement of clinical significance. The estimated historical rate of tislelizumab monotherapy in a similar population is 8%. The null hypothesis and alternative hypothesis are given as follows:

H_0: ORR ≤ 8%

Ha: ORR > 8%

In Cohort A, the superiority of the sitravatinib plus tislelizumab regimen over the historical control will be tested using the Simon's two-stage (Simon, 1989) design based on the efficacy analysis set of Cohort A. An interim efficacy analysis will be performed when 12 patients are enrolled. If there is no subject achieving confirmed response among the first 12 patients in stage 1, stage 2 will not be initiated. If the number of subjects achieving response is ≥ 1, stage 2 will be continued until 21 patients are enrolled in total. If the total number of subjects achieving response in stage 1 and stage 2 is > 3, it can be considered that the ORR of the sitravatinib plus tislelizumab regimen is superior to 8%.

For Cohort B:

The efficacy and toxicity of the sitravatinib plus tislelizumab regimen will be monitored simultaneously following a Bayesian optimal phase II (BOP2) design based on the efficacy analysis set of Cohort B (Zhou, Lee & Yuan, 2017). The study will be conducted with ORR as the efficacy endpoint and ≥ grade 3 TRAEs defined according to NCI-CTCAE 5.0 as the toxicity endpoint.

H_0: $p_{eff} \leq 0.08$ or $p_{tox} \geq 0.57$

Ha: $p_{eff} > 0.08$ and $p_{tox} < 0.57$

The investigational product is unacceptable as it is inefficient or intolerable in case of $p_{eff} \leq 0.08$ or $p_{tox} \geq 0.57$. The design parameters are optimized to maximize the probability of making correct decisions at 82% when the treatment is safe and effective and to control the probability of making incorrect decisions at less than 10% in case of ineffective or intolerable treatment.

The following decision table of the Bayesian optimal stopping boundary can be obtained.

Table 1: Bayesian optimal interim stopping boundary and the final margin

Number of patients treated	Termination of enrollment if the number of subjects with response is ≤	or the number of subjects with toxicity is ≥
20	1	13
40	3	23

The above interim test criteria are non-enforceable (e.g., if the treatment is considered beneficial to the patient group in combination with other conditions, the criteria can be ignored to continue the enrollment. The investigator may decide at any time whether to continue the trial based on a comprehensive assessment of the efficacy and safety).

For Cohort C:

In patients with locally recurrent or metastatic TNBC, an ORR of 65% is assumed for the sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen under study to indicate an improvement of clinical significance. The estimated historical ORR of nab-paclitaxel monotherapy in a similar population is 46%. The null hypothesis and alternative hypothesis are given as follows:

$$H_0: ORR \leq 46\%$$

$$Ha: ORR > 46\%$$

The superiority of the sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen over the historical control will be tested using the Simon's two-stage (Simon, 1989) design based on the efficacy analysis set of Cohort C. An interim efficacy analysis will be performed when 18 patients are enrolled. If the number of subjects achieving confirmed response is ≤ 9 among the first 18 patients in stage 1, stage 2 will not be initiated. If the number of subjects achieving response is > 9, stage 2 will be continued until 35 patients are enrolled in total. If the total number of subjects achieving response in stage 1 and stage 2 is > 19, it can be considered that the ORR of the sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen is superior to 46%.

The number and proportion of patients with ORR (CR or PR) in Cohort A, Cohort B, and Cohort C will be summarized, respectively, according to the criteria of NCI-CTCAE v5.0 and RECIST v1.1. In Cohort B, ≥ grade 3 TRAEs will be summarized. The proportion of ≥ grade 3 TRAEs and ORR as well as their two-sided Clopper-Pearson 95% confidence intervals (CIs) will be estimated. For Cohort A and Cohort C, the patients who withdraw early due to progressive disease (PD) or death and thus have no post-baseline tumor assessment performed will be considered as non-responders. For Cohort B, the patients who withdraw early due to ≥ grade 3 TRAEs, progressive disease (PD), or death and thus have no post-baseline tumor assessment performed will be considered as non-responders.

Secondary Efficacy Analyses:

The following analyses will be performed for the patients with locally advanced and metastatic TNBC in Cohort A, Cohort B, and Cohort C according to RECIST v1.1:

Duration of response (DOR): It is defined as the interval from the first recorded objective response (CR or PR) to the time of progressive disease (PD) (according to RECIST v1.1) as assessed by the investigator or death from any cause (whichever occurs first). The analysis of DOR will only include the responders. DOR and the corresponding quantiles (including medians) will be estimated using the Kaplan-Meier (KM) method. If possible, the generalized Brookmeyer and Crowley method will be used to establish the two-sided 95% CI for medians (Brookmeyer and Crowley, 1982). The DOR censoring rules will follow the FDA's Industry Guideline: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

Disease control rate (DCR): It is defined as the proportion of patients with BOR being CR, PR, and SD according to RECIST v1.1. The analysis of DCR will be performed based on the efficacy analysis set. The two-sided Clopper-Pearson 95% CI of DCR will be established to assess the precision of point estimates.

Progression-free survival (PFS): It is defined as the interval from the date of the first dose of the investigational products to the date of the first development of PD (assessed by the investigator according to RECIST v1.1) or death, whichever occurs first. The analysis of PFS will be performed based on the efficacy analysis set. The curve of KM estimates of PFS over time will be plotted. PFSs and corresponding quantiles (including medians) will be estimated using the KM method. If possible, the generalized Brookmeyer and Crowley method will be used to establish the two-sided 95% CI for medians (Brookmeyer and Crowley, 1982). PFS time point estimate, defined as the percentage of patients in the analysis set who still survive without progressive diseases developed throughout the specified time points (i.e., 3, 6, or 12 months), will be calculated using the KM method, and the corresponding 95% CI will be established using the Greenwood's formula (Greenwood, 1926). The PFS censoring rules will follow the FDA's Industry Guideline: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

1-year OS rate: The overall survival (OS) is defined as the time from the date of the first dose of the investigational products to the date of death from any cause. The analysis of OS will be performed based on the efficacy analysis set. The 1-year OS rate will be estimated in the efficacy analysis set using the KM method (Section 9.2.2) and the corresponding two-sided 95% CI will be calculated using the Greenwood's formula (Greenwood, 1926). The curve of KM estimates of OS over time will be plotted.

Secondary Safety Analyses:

The following analyses will be performed separately for the patients with locally recurrent or metastatic TNBC in Cohort A, Cohort B, and Cohort C. The safety will be determined by the reporting of AEs and laboratory test values (hematology, clinical chemistry, coagulation, and urinalysis). The results of vital signs, physical examinations, and ECG measurements will also be used to for safety characterization. The severity of AEs will be graded according to NCI-CTCAE v5.0. Patient-reported outcomes (PROs) will be collected using the EORTC QLQ-C30 (v3) Quality of Life Questionnaire. The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics will be performed for laboratory parameters and vital signs (e.g., n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and their changes from baseline will be calculated.

The number and proportion of patients that experience ≥ grade 3 TRAEs will also be summarized according to the NCI-CTCAE v5.0 for Cohort A/Cohort C, respectively, based on the efficacy analysis set. The proportion of ≥ grade 3 TRAEs and the two-sided Clopper-Pearson 95% CI will be estimated.

In addition, the number and percentage of patients who discontinue the study due to AEs according to NCI-CTCAE v5.0 will be summarized based on the efficacy analysis set, and the two-sided Clopper-Pearson 95% CI will be estimated for Cohort B.

Exploratory Analysis:

Biomarkers will be summarized using descriptive statistics. The relationship between the biomarkers and DOR, PFS, and OS will be explored using the KM method, log-rank test, and/or Cox proportional hazards model; the relationship between the biomarkers and ORR, PD, and DRC will be explored using the logistic regression and/or rate differences.

Sample Size Consideration

The study is aimed to enroll approximately 96 patients. Patients who drop out before the first assessment and thus cannot be included in the efficacy analysis set will be supplemented, and additional 4 to 6 patients may be required.

For Cohort A, a total of 21 patients will receive combination therapy. Based on the Simon's two-stage design, the power of test is approximately 80% to demonstrate the presence of a statistically significant difference between the ORR of the sitravatinib plus tislelizumab regimen under study (assumed as approximately 25%) and the historical ORR of tislelizumab monotherapy being 8% (one-sided α level of 0.1). Among the first 12 patients in the efficacy analysis set, if no subject show confirmed post-treatment response, the study will be terminated. Otherwise, the study will continue. If > 3 responders are observed among all 21 patients in the efficacy analysis set, a statistical superiority of this combination therapy over the historical control of 8% under the set conditions will be declared.

For Cohort B, a total of 40 patients will receive combination therapy. The historical ORR of tislelizumab monotherapy is estimated to be 8% and the historical rate of ≥ grade 3 TRAEs is estimated to be 57%. Assuming that the ORR of the sitravatinib plus tislelizumab regimen to be tested is 25% and the incidence of ≥ grade 3 TRAEs is 47%, 40 patients can show an approximately 82% power to demonstrate that the combination therapy is significantly superior to the historical control (i.e., tislelizumab monotherapy) under the one-sided test level of α = 0.1, based on the Bayesian optimal phase II (BOP2) design, with the efficacy and toxicity of the combination therapy monitored.

For Cohort C, a total of 35 patients will receive combination therapy. Based on the Simon's two-stage design, the power of test is approximately 80% to demonstrate the presence of a statistically significant difference between the ORR of the 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen under study (assumed as approximately 65%) and the historical ORR of nab-paclitaxel monotherapy being 46% (one-sided α level of 0.1). Among the first 18 patients in the efficacy analysis set, if ≤ 9 subjects show confirmed post-treatment response, the study will be terminated. Otherwise, the study will continue. If > 19 responders are observed among all 35 patients in the efficacy analysis set, a statistical superiority of this combination therapy over the historical control of 46% under the set conditions will be declared. Based on the data results from 35 patients in the previous phase, the investigator may consider expanding Cohort C to up to 50 subjects if the efficacy is achieved as expected.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma or serum concentration-time curve
BOR	Best overall response
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase cardiac muscle isoenzyme (CK-MB)
CR	Complete response
CRF	Case report form
CT	Computed tomography
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
EOT	End of treatment
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
G/GEJ	Gastric/gastroesophageal junction carcinoma
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Epidermal growth factor receptor 2
HR	Hormone receptor
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
INR	International normalized ratio

Abbreviation	Definition
irAE	Immune-related adverse event
IRB	Institutional Review Board
LFT	Liver function test
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death protein ligand-1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SOC	System organ class
sVEGFR-2	Soluble vascular endothelial growth factor receptor-2
TEAE	Treatment-emergent adverse event
TFT	Thyroid function test
TIL	Tumor-infiltrating lymphocyte
TNBC	Triple negative breast cancer
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VEGFR	Vascular epidermal growth factor receptor

1. INTRODUCTION AND RATIONALE

1.1. Background Information on Triple Negative Breast Cancer

Triple negative breast cancer (TNBC) is defined as breast cancer that lacks expression of estrogen receptors (ERs) and progesterone receptors (PRs) and dose not express human epidermal growth factor receptor-2 (HER2) (Dent et al., 2007). TNBC accounts for approximately 15% of newly diagnosed breast cancer cases in China. The clinical course of locally recurrent or metastatic TNBC is more aggressive than other subtypes of breast cancer. Locally recurrent or metastatic TNBC has a higher frequency of progression, a shorter progression-free survival (PFS), and worse overall survival (OS). At present, there is still a lack of effective treatment options for locally recurrent or metastatic TNBC, and chemotherapy remains the main systemic treatment. However, the efficacy of conventional chemotherapy regimens is poor in the treatment of locally recurrent or metastatic TNBC (Kassam et al., 2009). It has been reported that the median OS for patients with locally recurrent or metastatic TNBC is only 9–12 months when treated with traditional chemotherapy regimens (Dent et al., 2007; Kassam et al., 2009).

The discovery of immune checkpoints that regulate immune activation and the successful development of their monoclonal antibodies have ushered in a new era in the treatment of solid tumors and hematologic malignancies (Wei et al., 2018). Hormone receptor (HR)-positive breast cancer is the most common subtype of breast cancer, which belongs to the subtype of immunologically "cold" tumors with fewer tumor-infiltrating lymphocytes (TILs) and a lower tumor mutation burden. HER2-positive tumors respond well to HER2-targeted therapy, which is mediated in part by the mechanism of action of immune response. TNBC is considered to be the most immunogenic subtype of breast cancer among all subtypes, and it is the primary target in current clinical trials of immune checkpoint inhibitors (Esteva et al., 2019).

Study Keynote119 is a phase 3 clinical trial that compares pembrolizumab monotherapy with single-agent chemotherapy for the treatment of metastatic TNBC. The results of this study were first reported at the 2019 ESMO Congress and showed that the primary endpoint was not achieved with pembrolizumab monotherapy for metastatic TNBC and that there was no significant increase in OS in both PDL1-positive/negative populations. Moreover, there was no significant increase in ORR in both PD-L1-positive/negative populations. In fact, multiple studies have demonstrated no significant clinical benefit of immunological monotherapies in patients with locally recurrent or metastatic TNBC (Planes-Laine et al., 2019). The immunotherapy for TNBC shall proceed in combination with other drugs to realize the purpose of improving survival. At present, the treatment regimen of chemotherapy is mainly considered to be used in combination for breast cancer. Study IMpassion130 is a

phase 3 clinical trial that compares the atezolizumab plus nab-paclitaxel regimen with nab-paclitaxel for the treatment of metastatic TNBC. The results showed that, compared with treatment with nab-paclitaxel, the regimen of atezolizumab plus nab-paclitaxel achieved the primary study endpoint; the PFS in PD-L1 positive/negative populations was significantly increased, and the OS in PD-L1 positive population was also significantly increased (Schmid et al., 2018). Based on the results of this study, the regimen of atezolizumab plus nab-paclitaxel was approved by the FDA for the treatment of PD-L1-positive metastatic TNBC. In 2020, ASCO reported the study data from Keynote 355, a phase 3 clinical trial that compares the pembrolizumab plus chemotherapy regimen with chemotherapy for the treatment of locally recurrent or metastatic TNBC. The results showed that, compared to chemotherapy, the pembrolizumab plus chemotherapy regimen significantly prolonged the PFS of patients with PD-L1 positive (CPS ≥ 1 and CPS ≥ 10) locally advanced or metastatic TNBC. Based on the results of Keynote 355, in Nov. 2021, the US Food and Drug Administration accelerated the approval of pembrolizumab plus chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic triple negative breast cancer (TNBC) with confirmed expression of PD-L1 (CPS ≥ 10) based on an FDA-approved assay method.

Although some new progress has been made in the field of immunotherapy plus chemotherapy for TNBC treatment, the efficacy and safety of immunotherapy in combination with RTK inhibitors/chemotherapy for locally recurrent or metastatic TNBC are still worth exploring.

1.2. Sitravatinib — An Inhibitor of Receptor Tyrosine Kinases

The receptor tyrosine kinase (RTK) is an important part of the signaling transduction pathway that mediates intercellular communication (Hubbard and Miller, 2007). They are subtypes of cell surface growth factor receptors, of which the tyrosine kinase activity is controlled by endogenous ligands. These single-channel transmembrane receptors, which bind to polypeptide ligands (mainly growth factors), play a key role in cell growth, differentiation, metabolism, and movement. When these pathways are abnormally activated, the proliferation, survival, and metastasis of cancer cells will be enlivened. Therefore, these signaling pathways are considered the main targets for cancer treatment. Sitravatinib is a bioavailable oral RTK inhibitor with potential antitumor activity.

Sitravatinib is a potent inhibitor of a variety of RTKs including Axl, MER, MET, KIT, FLT3, RET, VEGFR1, VEGFR2, VEGFR3, PDGFRα, DDR2, TRKA, and TRKB. Among various cancers, sitravatinib targets oncogenic driver genes that promote the development and progression of cancer. In addition, the targets of sitravatinib are also expressed in a variety of immune cells, and these targets can

promote the formation of a tumor microenvironment (TME) that has an inhibitory effect on antitumor immunity. In addition, sitravatinib can also block VEGFR- and KIT-mediated immunomodulatory effects to further regulate TME and enhance the antitumor activity. Preclinical data of sitravatinib indicate that it can increase PD-L1 expression in tumor cells *in vitro* and *in vivo*. Preliminary studies in a homogenous mouse tumor model have also shown that sitravatinib promotes the proliferation of $CD4^+/CD8^+$ T lymphocytes throughout the body/in the spleen, increases the $CD4^+/CD8^+$ ratio, and reduces the number of myeloid-derived suppressor cells (MDSC) throughout the body. Therefore, the theoretical rationale is provided for the treatment with sitravatinib in combination with PD-1 checkpoint inhibitors.

1.2.1. Pharmacology

Sitravatinib has been proven to be a potent enzyme inhibitor of closely associated recombinant human RTK subtypes with IC_{50} values ranging from 0.5–76 nmol/L. Sitravatinib has shown potent activity in the RTK target-dependent cell assays, with IC_{50} values being < 10 to 181 nmol/L. Consistent with the antitumor and anti-angiogenic mechanisms of action, the antitumor efficacy of sitravatinib has been demonstrated in extensive human tumor xenograft models. In addition, the combination therapy with sitravatinib significantly boosted the activity of anti-PD-1 therapy in the CT26 homogenous mouse tumor model.

In vitro studies have demonstrated that sitravatinib is a highly permeable compound. The metabolism of sitravatinib is more extensive in dogs than in mice, rats, and human *in vitro*.

In vitro hERG results showed an IC_{50} of potassium current being 0.6 μM (0.38 μg/mL). At the recommended phase 2 dose (RP2D, 150 mg), the measured mean steady-state plasma concentration (corrected for free fraction) of patients was approximately 290-fold lower than the hERG IC_{50} concentration. No cardiovascular adverse reactions or effects on the QTc interval were observed at doses up to 4 mg/kg (mean plasma concentration within 6 hours being 0.072 μg/mL) in dogs. A slight increase in blood pressure was observed in the cardiovascular test in dogs.

A functional observational battery and respiratory assessment in rats showed no sitravatinib-related effects at doses up to 25 mg/kg.

For more nonclinical study details, please refer to the Sitravatinib Investigator's Brochure (IB) v8.1 (Aug. 23, 2021).

1.2.2. Toxicology

In the repeated-dose toxicity study in dogs, the body weight and food consumption were significantly decreased, but the target organs were not identified. Oral administration of sitravatinib (up to 3 mg/kg/day, QD) for 28 consecutive days in Beagle dogs resulted in intolerance of the animals as well as marked weight loss and anorexia, with one female dog requiring veterinary intervention and termination of treatment due to an overall condition deterioration. Based on the severity of the test article-related toxicity at 3 mg/kg/day, the no observed adverse effect level (NOAEL) was defined as 1 mg/kg/day.

Target organs associated with vascular endothelial growth factor (VEGF) identified in rats included adrenal glands, duodenal Brunner's gland, femurs, sternum (bone and bone marrow), spleen, lymph nodes, thymi, ovaries, kidneys (glomerulopathy, renal tubular necrosis, increased basophilic tubules), pancreas, and tongue. Except for the kidney and pancreas, the effects on the other organs were completely or partially recovered. Oral administration of sitravatinib (up to 25 mg/kg/day, QD) in Crl:CD (SD) rats resulted in intolerance of the animals, adverse clinical observations and vital signs, changes in body weight and food consumption, death, and premature termination of the trial. Based on the severity of the test article-related toxicity at 25 mg/kg/day and deaths that occurred in animals dosed at ≥ 10 mg/kg/day (although there was a decrease), the NOAEL for sitravatinib was defined as 2.5 mg/kg/day.

The mutagenicity and clastogenic effect of sitravatinib were assessed in a standard series of the "Good Laboratory Practice (GLP)" genotoxicity battery studies (Ames, chromosome aberration assay, and *in vivo* rat micronucleus assay), and the results were negative.

Additional details about the toxicology of sitravatinib are provided in Sitravatinib IB v8.1 (Aug. 23, 2021).

1.2.3. Clinical Pharmacology

Study 516-001 evaluated the single-dose and repeated-dose pharmacokinetics (PK) of sitravatinib alone. The blood samples for PK analysis were collected within 168 hours after a single dose and within 24 hours after each repeated dose. Plasma concentrations were determined using a validated and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method. The PK of sitravatinib was assessed using a non-compartmental model.

The median time to peak sitravatinib concentration was approximately 3–9 hours after a single dose. Exposure parameters (maximum plasma concentration [C_{max}] and area under the plasma or serum concentration-time curve [AUC]) were approximately proportional to the single dose (up to a maximum of 200 mg). The median elimination

half-life after oral administration was approximately 43–58 hours. Steady-state PK was achieved within an average of 11 to 15 days. Drug accumulation was observed after repeated-dose administration, with C_{max} of 1.6–4.2 folds and mean AUC_{0-24} of 2.0–5.1 folds. The maximum tolerated dose (MTD) and RP2D were determined to be 150 mg; the geometric means for steady-state C_{avg}, C_{max}, and AUC_{0-24} at this dose were 90.3 ng/mL, 114 ng/mL, and 2204 ng·h/mL, respectively. The plasma concentrations at dose levels of 120 mg and 150 mg overlapped.

The pharmacodynamic evaluation of sitravatinib is still ongoing; however, the initial analysis showed that the VEGF-A, soluble vascular endothelial growth factor receptor 2 (sVEGFR-2), and soluble MET extracellular segment (sMET) levels in the plasma samples of patients were regulated in a concentration-dependent manner. The predicted (95% CI) mean percentages of changes from baseline in the regulated biomarker exposures were approximately as follows: VEGF-A (up-regulated by 300%), sVEGFR-2 (down-regulated by 50%), and sMET (up-regulated by 35%), consistent with the inhibitory effects of VEGFR and MET. In Study MRTX-500, the mean C_{trough} at a dose level of 120 mg QD on Day 15 of Cycle 1 was 62.4 ng/mL. Based on these plasma exposure levels of sitravatinib, the biomarker levels are expected to be close to the optimal regulation.

For more details on the clinical pharmacology of sitravatinib, please refer to Sitravatinib IB v8.1 (Aug. 23, 2021).

1.2.4. Clinical experience of sitravatinib

The clinical trials evaluating the efficacy of sitravatinib alone, sitravatinib in combination with nivolumab, and sitravatinib in combination with tislelizumab are ongoing. For more details on sitravatinib and ongoing studies, please refer to Sitravatinib IB v8.1 (Aug. 23, 2021).

1.2.4.1. Study 516-001

Study 516-001 is an ongoing, multicenter, phase 1/1b study to evaluate the safety, PK, metabolism, PD, and clinical activity of sitravatinib in patients with advanced malignant solid tumors. In this study, it is determined that the 200 mg dose is greater than the MTD, and the evaluation is continued with sitravatinib monotherapy at 150 mg QD as RP2D. The phase 1b extension part includes patients with solid tumors with specific histological types of tumors and/or molecular markers. As of Jun. 26, 2019, among the 186 patients with available safety data, 183 (98%) had experienced at least one treatment-emergent AE, and 167 (90%) had experienced treatment-related AEs. Treatment-related AEs that were observed in ≥ 10% of patients are presented in Table 1.

Grade 3–5 treatment-related AEs that were observed in ≥ 5% of patients included hypertension (19%), diarrhea (10%), fatigue (7%), lipase increased (5%), and palmoplantar redness, swelling, and pain (5%).

Grade 4 treatment-related AEs were observed in 3 patients, including lipase increased in 2 patients (1%) and febrile neutropenia in 1 patient (1%). 1 patient (1%) experienced a grade 5 treatment-related AE of cardiac arrest.

Table 1. Treatment-emergent and treatment-related adverse events (≥ 10%) in Study 516-001 by preferred term

Adverse event term	Incidence (N = 186)
Diarrhea	92 (50%)
Fatigue	78 (42%)
Hypertension	73 (39%)
Nausea	53 (29%)
Decreased appetite	50 (27%)
Vomiting	44 (24%)
Palmar-plantar erythrodysesthesia syndrome	37 (20%)
Alanine aminotransferase increased	34 (18%)
Aspartate aminotransferase increased	34 (18%)
Hypothyroidism	31 (17%)
Stomatitis	27 (15%)
Dysphonia	26 (14%)
Weight decreased	26 (14%)
Abdominal pain	22 (12%)
Rash	21 (11%)
Constipation	20 (11%)
Dry mouth	20 (11%)
Lipase increased	18 (10%)
Proteinuria	18 (10%)

Serious adverse events: Of the 186 patients with available safety data, 73 (39%) experienced at least one treatment-emergent serious adverse event (SAE). Treatment-related SAEs were observed in 28 patients (15%), including 6 cases (3%) of diarrhea, respective 5 cases (3%) of nausea and vomiting, 4 cases (2%) of fatigue, 3 cases (2%) of hypertension, and respective 2 cases (1%) of headache, pancreatitis, and pulmonary embolism.

As of Jun. 26, 2019, 90 deaths were reported in this study with the primary causes being the disease under study (n = 61), unknown (n = 17), sepsis (n = 5), respiratory failure (n = 3), as well as aspiration pneumonia, cerebrovascular accident, cardiac arrest, and gastrointestinal hemorrhage (n = 1 each).

As of Apr. 18, 2018, 105 patients with advanced solid tumors had been enrolled in the phase 1b cohort, including 29 patients enrolled in the clinical study of clear cell renal cell carcinoma (RCC) after a failure of previous anti-angiogenic therapy. In the other 6 patients, confirmed PR was observed in 4 patients with long-term stability for 24 weeks and above (Pant et al., 2018).

1.2.4.2. Study MRTX-500

Study MRTX-500 is an open-label and parallel phase 2 study to evaluate sitravatinib in combination with nivolumab (a PD-1 inhibitor) in locally advanced unresectable or metastatic non-squamous NSCLC patients who have experienced progressive disease during/after previous immune checkpoint inhibitor treatment or after platinum-based doublet chemotherapy. This study began with a run-in period evaluation of sitravatinib at 120 mg/day in combination with nivolumab at 240 mg/2 weeks via intravenous infusion. The first 6 evaluable patients failed to report the dose-limiting toxicity (DLT) as defined in the protocol after treatment. Based on the preliminary evaluation of long-term tolerability from Study 516-001 (Mirati 2018b) and data from Study MRTX-500, it was decided by Mirati to conduct sitravatinib evaluation only at 120 mg as when the drug was used in combination with other drugs, the plasma exposure at this dose level was sufficient to achieve the required inhibition of VEGF and TAM receptors for antitumor efficacy. Therefore, the 120 mg dose level was selected as RP2D.

As of Jun. 26, 2019, the data from 135 patients with advanced or metastatic non-small cell lung cancer (NSCLC) (63 males/72 females; median age of 66 years, ranging from 37 to 89 years) had been entered into the clinical trial database. Patient enrollment was performed for both cohorts. Specifically, 107 patients were enrolled in the CIT-treated cohort and 22 patients were enrolled in the CIT treatment-naïve cohort. 6 patients have been enrolled in the PK pharmaceutical preparation substudy. Currently, enrollment is still ongoing.

As of Jun. 26, 2019, among 135 patients with safety data available, 131 (97%) had experienced at least 1 treatment-emergent AE, 126 (93%) had experienced treatment-related AEs, 125 (93%) had experienced sitravatinib-related AEs, and 91 (67%) had experienced nivolumab-related AEs. The treatment-related AEs that were observed in ≥ 10% of the patients are presented in Table 2.

Grade ≥ 3 treatment-related AEs that were observed in ≥ 5% of patients included hypertension (17%), diarrhea (11%), and fatigue (7%). 4 patients experienced grade 4 treatment-related AEs, including gastric ulcer perforation, hypertensive crisis, lipase increased, and lymphocyte count decreased (1 patient each, 1%). 2 patients (2%) experienced the grade 5 treatment-related AE of cardiac arrest.

Table 2. Treatment-emergent and treatment-related adverse events by preferred term in Study MRTX-500 (≥ 10%)

Adverse event term	Incidence (N = 135)
Diarrhea	66 (49%)
Fatigue	58 (43%)
Nausea	49 (36%)
Decreased appetite	45 (33%)
Weight decreased	40 (30%)
Hypertension	38 (28%)
Vomiting	33 (24%)
Hypothyroidism	29 (22%)
Dysphonia	24 (18%)
Aspartate aminotransferase increased	22 (16%)
Palmar-plantar erythrodysesthesia syndrome	22 (16%)
Stomatitis	22 (16%)
Alanine aminotransferase increased	20 (15%)
Dehydration	15 (11%)
Dry mouth	13 (10%)
Taste disorder	13 (10%)

Serious adverse events: Of the 135 patients with safety data available, 60 (44%) had experienced at least one treatment-emergent SAE. Treatment-related SAEs were observed in 31 patients (23%), among which 5 patients (4%) experienced diarrhea, 2 patients (2%) experienced cardiac arrest, deep vein thrombosis, hypertension, pancreatitis, non-infectious pneumonia, and each of 1 patient (1%) experienced adrenalitis, anemia, heart failure, colitis, confusion state, dehydration, ejection fraction decreased, embolism, fatigue, gastric ulcer perforation, gastritis, hypertensive crisis, hyponatremia, hypothyroidism, hypoxia, myocarditis, nausea, palmar-plantar erythrodysesthesia syndrome, pericardial effusion, pneumonitis, posterior reversible encephalopathy syndrome, pulmonary embolism, syncope, and vomiting.

As of the data cutoff date of Aug. 27, 2018, the data of 78 patients (35 males/43 females; median age of 65.7 years, ranging from 37 to 89 years) with advanced or metastatic non-small cell lung cancer were entered in the clinical trials database. 70 of

these patients had received CIT while 8 patients did not. 56 patients had at least 1 imaging scanning result that allowed for efficacy evaluation. The median number of prior lines of therapy was second-line. Of the 56 evaluable patients, 45 showed confirmed tumor shrinkage; 18 patients showed tumor shrinkage of more than 30%; 16 patients achieved PR or CR (including 9 patients with confirmed PR or CR; 2 patients with unconfirmed PR or CR are still in the trial and waiting for confirmation; 5 patients showed unconfirmed PR or CR that cannot be identified); 26 patients, including 8 responders, were still on treatment at the data cutoff date (Leal et al., 2018).

1.2.4.3. Study BGB-900-103

BGB-900-103 was an open-label, multicenter, phase 1b study to evaluate the sitravatinib plus tislelizumab regimen in patients with advanced or metastatic tumors including non-squamous NSCLC, RCC, or epithelial ovarian cancer. The primary objective was to evaluate the safety of sitravatinib plus tislelizumab. Secondary objectives included the evaluation of the preliminary antitumor activity and PK of sitravatinib plus tislelizumab in patients with selected tumor types. This study included the following 9 cohorts and all the patients were administered with sitravatinib at 120 mg/day in combination with an intravenous infusion of tislelizumab at 200 mg/3 weeks.

- Cohort A: Refractory/resistant metastatic non-squamous NSCLC after treatment with anti-PD-1/PD-L1 antibodies
- Cohort B: Anti-PD-1/PD-L1 antibody treatment-naïve metastatic non-squamous NSCLC.
- Cohort C: Refractory/resistant metastatic or advanced RCC after treatment with anti-PD-1/PD-L1 antibodies.
- Cohort D (China only): Metastatic or advanced RCC without any prior systemic treatment.
- Cohort E: Anti-PD-1/PD-L1 antibody treatment-naïve, recurrent, and platinum-resistant epithelial ovarian cancer.
- Cohort F: Metastatic squamous NSCLC treated with anti-PD-1/PD-L1 antibodies.
- Cohort G: Refractory/resistant unresectable or metastatic melanoma after treatment with anti-PD-1/PD-L1 antibodies.
- Cohort H: PD-L1 positive, locally advanced, or metastatic non-squamous NSCLC without any prior systemic treatment.

- Cohort I: PD-L1 positive, locally advanced, or metastatic squamous NSCLC without any prior systemic treatment.

As of Jun. 26, 2019, among the 48 patients with safety data available, the most common treatment-related AEs were hypertension (35%), alanine aminotransferase increased (25%), aspartate aminotransferase increased (23%), diarrhea (23%), nausea (21%), fatigue (17%), decreased appetite (15%), palmar-plantar erythrodysesthesia syndrome (15%), vomiting (15%), proteinuria (13%), weight decreased (13%), rash (10%), and transaminases increased (10%). 11 patients (23%) reported treatment-related SAEs, including 3 cases (6%) of transaminases increased and 1 case (2%) each of allergic reaction, bacteremia, heart failure, diarrhea, electrocardiogram QT prolonged, headache, hypertension, immune-mediated enterocolitis, immune-mediated hepatitis, intestinal obstruction, myalgia, non-cardiac chest pain, respiratory failure, and troponin I increased. As of Jun. 26, 2019, there were 3 deaths in this study, all of which were caused by the disease under study.

Preliminary efficacy

As of Jul. 17, 2019, the median progression-free survival was 18 weeks (range: 12.29–not achieved) and the median duration of response was not achieved for the patients in Cohort E in Study BGB-900-103. Of the 17 patients currently evaluable for efficacy, 4 (23.5%) showed confirmed response and 8 (47%) showed confirmed stable disease.

1.2.4.4. Study BGB-900-104

BGB-900-104 was an open-label, multicenter, phase 2 study to evaluate the use of sitravatinib monotherapy and sitravatinib plus tislelizumab in patients with advanced or metastatic HCC or G/GEJ. The primary objectives were to evaluate the safety of sitravatinib monotherapy and sitravatinib plus tislelizumab and to determine the RP2Ds of sitravatinib monotherapy (phase 1 dose escalation study started with a daily dose of 80 mg) and sitravatinib plus tislelizumab (administered via intravenous infusion at 200 mg/3 weeks). Secondary objectives included the evaluation of the preliminary antitumor activity and PK of sitravatinib monotherapy or sitravatinib plus tislelizumab. The phase 2 study consisted of 4 cohorts as follows:

- Cohort A: Anti-PD-1/PD-L1 antibody treatment-naïve HCC, monotherapy.
- Cohort B: Anti-PD-1/PD-L1 antibody treatment-naïve HCC, combination therapy.
- Cohort C: Refractory/resistant HCC after treatment with anti-PD-1/PD-L1 antibodies, combination therapy.

- Cohort D: Anti-PD-1/PD-L1 antibody treatment-naïve G/GEJ, combination therapy.

As of Jun. 26, 2019, of the 4 patients with safety data available, 1 patient receiving sitravatinib plus tislelizumab had not reported any AE to date. Of the 3 patients with available safety data for sitravatinib monotherapy, 3 patients (100%) had experienced sitravatinib-related AEs. The reported sitravatinib-related AEs included hypertension (3 patients, 100%), alanine aminotransferase increased, aspartate aminotransferase increased, palmar-plantar erythrodysesthesia syndrome (2 patients each, 67%), anemia, blood bilirubin increased, decreased appetite, diarrhea, neutrophil count decreased, platelet count decreased, stomatitis, and white cell count decreased (1 patient each, 33%). All patients reported grade 3 treatment-related events, including hypertension (100%). No grade 5 treatment-related events were reported. No serious treatment-related adverse events were reported. No deaths were reported in this study.

1.2.5. Rationale for dose selection of sitravatinib

The dose escalation study 516-001 in patients with advanced malignant solid tumors showed that the maximum tolerated dose of sitravatinib free base capsule administered once daily (QD) was 150 mg. The *in vivo* exposure (AUC and C_{max}) of sitravatinib increased dose-proportionally within the range of 10 mg QD to 200 mg QD. Based on the observation of long-term tolerability in patients receiving 120 mg or 150 mg QD in Study 516-001 and the experience in patients receiving 120 mg QD in combination with nivolumab in Study MRTX-500, 120 mg QD was ultimately selected as RP2D for the sitravatinib free base capsule. The PK data in previous studies indicated a high inter-individual variability (40%–70%) in sitravatinib *in vivo* exposure. In Study BGB-900-103 and Study BGB-900-104, the *in vivo* exposures of sitravatinib in the 80 mg and 120 mg dose groups were highly overlapped, which was consistent with the results from preliminary population pharmacokinetic simulations. Preliminary population pharmacokinetic analyses showed that the PK profiles of sitravatinib were independent of race and tumor type and the patients with TNBC were expected to have similar PK profiles. The preliminarily established exposure-effect model suggested that the *in vivo* exposure of sitravatinib had no apparent relationship with the objective response rate (ORR) and AE but only a weak relationship with the disease control rate (DCR) within the dose range of 80 mg QD to 120 mg QD.

In the currently ongoing Study BGB-900-104, no dose-limiting toxicity (DLT) was observed in the dose escalation phase I trial with a single dose of 80 mg QD and 120 mg QD of sitravatinib free base capsule monotherapy; the sitravatinib free base capsule monotherapy at 120 mg QD has been selected as the recommended phase 2 dose (RP2D) by the Safety Monitoring Committee and relevant cohort studies will be

conducted in the dose expansion phase II trial; no DLT was observed when the sitravatinib free base capsule at 80 mg QD was administered in combination with tislelizumab, and the incidence of DLT was 1/6 when the sitravatinib free base capsule at 120 mg QD was administered in combination with tislelizumab in patients with liver cancer and gastric cancer. The sitravatinib free base capsule at 120 mg QD has been selected as the RP2D when used in combination with tislelizumab by the Safety Monitoring Committee, and relevant combination treatment cohort studies will be conducted in the dose expansion phase II trial.

In order to optimize product characteristics and production efficiency, it is proposed to develop a sitravatinib malate capsule formulation as an alternative to the free base capsule formulation for pivotal clinical studies and future commercial production. Based on an open-label, double-crossover study in healthy subjects on the relative bioavailability of sitravatinib free base capsules and malate capsules, it is considered that a single dose of 100 mg sitravatinib malate capsule and 120 mg sitravatinib free base capsule administered orally under a fasted state have highly consistent pharmacokinetic profiles and comparable exposures. Therefore, the doses of sitravatinib malate capsule equivalent to the sitravatinib free base capsule at 80 mg QD and 120 mg QD are 70 mg QD and 100 mg QD, respectively.

In summary, the pharmacokinetic and pharmacodynamic analyses indicate that the sitravatinib malate capsule at 70 mg QD may have similar clinical efficacy and safety as 100 mg QD. In view of the relevant clinical study results of the sitravatinib free base capsule at present, it is intended in this study to simultaneously investigate the efficacy and safety of the sitravatinib malate capsule at the dose levels of 70 mg QD and 100 mg QD in combination with tislelizumab in patients with TNBC.

1.3. PD-1 Blocker Tislelizumab

The immune checkpoint-inhibitory receptor PD-1 is mainly expressed in activated T-cells, including $CD8^+$ cytotoxic T-lymphocytes and $CD4^+$ helper T-lymphocytes (Bersanelli and Buti, 2017; Topalian et al., 2012). It is generally believed that PD-1 regulates the key inhibitory signaling in T cells by binding to its ligands, thereby inhibiting antitumor immunity and promoting tumor progression. The PD-1 signaling cascade can down-regulate T cell receptors and attenuate T cell proliferation and functional activities, leading to T cell failure. In the tumor microenvironment, PD-1 expression in tumor-infiltrating lymphocytes is significantly up-regulated in the presence of cytokines such as IFN-γ and IFN-α, while the expression of PD-1 ligands (PD-L1) is significantly increased in tumor cells and tumor-associated immune cells. In addition, many types of solid tumors, including but not limited to melanoma, squamous cell carcinoma, uveal melanoma, NSCLC, head and neck squamous cell carcinoma, triple negative breast cancer, renal cell carcinoma, bladder carcinoma, and

ovarian carcinoma, have increased PD-1 expression levels in tumor-infiltrating lymphocytes and increased PD-L1 expression levels in tumors and/or tumor-associated stromal cells (Gong et al., 2011; Jin and Yoon, 2016; Liu et al., 2017; McDaniel et al., 2016; Patel and Kurzrock, 2015; Saito et al., 2013; Van Der Kraak et al., 2016). Several anti-PD-1 drugs have been approved for the treatment of a variety of cancers. Therefore, PD-1 is a mature target for cancer immunotherapy.

1.3.1. Pharmacology

Tislelizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody against PD-1 and is currently under clinical development for the treatment of a variety of human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1, with high specificity and affinity (dissociation constant [KD] = 0.15 nM). It competitively blocks the binding of PD-L1 and programmed cell death protein ligand 2 (PD-L2), thus inhibiting PD-1-mediated negative signaling transduction in T cells. In an *in vitro* cell-based assay, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and pre-activated peripheral mononuclear cells. Furthermore, the antitumor activity of tislelizumab has been demonstrated in xenograft models constructed by co-injection of PBMC and human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunodeficient mice.

The *in vitro* assays have revealed that the IgG4 antibody has very low binding affinity to the gamma fragment crystallizable region (Fc) receptor IIIA (FCγRIIIA) and complement 1q (a subunit of complement 1), suggesting either low or no antibody-dependent or complement-dependent cytotoxicity in humans (Labrijn et al., 2009).

For additional nonclinical study details of tislelizumab, please refer to Tislelizumab IB v9.0 (Oct. 20, 2021).

1.3.2. Toxicology

The toxicity and safety profiles of tislelizumab were studied in single-dose toxicology studies in mice and monkeys and in a 13-week repeated-dose toxicity study in monkeys. Tissue cross-reactivity was assessed in normal frozen tissues taken from humans and monkeys. The cytokine release effects were also assessed using fresh human whole blood cells. Pivotal toxicology studies were conducted in accordance with GLP requirements. The dose range of the single-dose regimen was 10 times the expected human dose to the highest human dose and that of the repeated-dose regimen was 3 times the highest human dose. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in human or monkey tissues, nor was any effect on cytokine release observed in human whole-blood assay. In the toxicokinetic profiling study, it was found that the systemic exposure increased in a dose-proportional manner without any significant drug accumulation or sex difference. Immunogenicity was observed, while neither immunotoxicity nor notable effects on systemic exposures were observed. The NOAEL of tislelizumab in the 13-week monkey toxicity study was defined as 30 mg/kg. The safety profiles of tislelizumab have been well studied to support the current Study BGB-900-104.

For additional details on the toxicology of tislelizumab, please refer to Tislelizumab IB v9.0 (Oct. 20, 2021).

1.3.3. Clinical Pharmacology

In the phase 1 studies BGB-A317_Study_001 and BGB-A317-102, interim PK was analyzed by non-compartmental methods using the serum concentration data of patients administered at 0.5, 2.0, 5.0, or 10 mg/kg (once every 2 weeks), 2.0 mg/kg, 5.0 mg/kg, or 200 mg/kg (once every 3 weeks) (parts 1, 2, and 3 of phase 1a and phase 1b of Study BGB-A317_Study_001), and 200 mg (once every 3 weeks) (phase 1 of Study BGB-A317-102). Following a single dose and at a steady state, C_{max} and AUC increased in a near dose-proportional manner from 0.5 mg/kg to 10 mg/kg. PK data at 200 mg (once every 3 weeks) (part 3 of phase 1a and Study BGB-A317-102) showed that the concentration of tislelizumab was between those observed after administration at 2 mg/kg and 5 mg/kg.

Preliminary analysis of population PK based on a three-compartment model with first-order elimination showed a systemic clearance (CL) of 0.164 L/day for tislelizumab, typical estimates of central volume of distribution (Vc) and peripheral volume of distribution (V2, V3) of 2.92 L, 0.928 L, and 1.39 L, respectively, and a half-life ($t_{1/2}$) of approximately 25.5 days. Race, sex, and body weight were not significantly correlated factors for the CL of tislelizumab, which supported a fixed dose across races.

1.3.4. Clinical experience of tislelizumab

As of May 20, 2019, there were 22 ongoing tislelizumab studies for solid tumors and hematological malignancies treated with monotherapy and combination therapy. Data obtained from 5 monotherapy studies on solid tumors (BGB-A317_Study_001, BGB-A317-102, BGB-A317-204, BGB-A317-208, and BGB-A317-209) and combination therapy studies (BGB-A317-205 and BGB-A317-206) are summarized below.

For additional details on the efficacy and safety of tislelizumab and ongoing studies, please refer to Tislelizumab IB v9.0 (Oct. 20, 2021).

1.3.4.1. Monotherapy studies (data cutoff May 20, 2019)

Preliminary safety

As of May 20, 2019, the treatment-related AEs with an incidence ≥ 10% in 1,137 patients with solid tumors with safety data available included anemia (20%), aspartate aminotransferase increased (16%), fatigue (16%), decreased appetite (16%), nausea (14%), alanine aminotransferase increased (14%), constipation (13%), fever (12%), diarrhea (12%), rash (11%), cough (11%), vomiting (10%), abdominal pain (10%), weight decreased (10%), and blood bilirubin increased (10%). Specifically, 494 patients (43%) experienced at least one grade ≥ 3 TEAE. The most frequent grade ≥ 3 TEAEs were anemia (n = 58, 5.1%), AST increased (n = 35, 3%), infectious pneumonia (n = 32, 3%), ascites (n = 24, 2%), and gamma-glutamyltransferase increased (n = 23, 2%). 141 patients (12%) experienced at least one grade ≥ 3 TEAE assessed as related to tislelizumab. The only grade ≥ 3 TEAEs with an incidence of ≥ 1% (≥ 13 patients) were AST increased (n = 19, 3%) and ALT increased (n = 15, 1%). Analysis on patients who experienced at least one grade ≥ 3 irAE showed that 106 patients (9%) had experienced such events. The most common irAEs of severity grade ≥ 3 were AST increased (n = 21, 2%), gamma-glutamyltransferase increased (n = 17, 2%), ALT increased (n = 16, 1%), and pneumonitis (n = 7, 1%). As of May 20, 2019, there were totally 619 deaths in this study, and the major causes included the disease under study (n = 561), adverse events (n = 23), unknown causes (n = 2), and others (n = 32).

Preliminary efficacy

As of May 20, 2019, the results of monotherapy studies with efficacy data available are as follows:

- BGB-A317_Study_001: A total of 451 patients were treated in this study and 441 patients were included in the efficacy analysis set. In all the disease cohorts, 5 patients (1.1%) achieved CR and 55 patients (12.5%) achieved confirmed PR. The final overall clinical response rate was 13.6%. The overall response rate for each disease cohort is listed in Table 54. In addition, 142 patients (32.2%) achieved stable disease (SD) as the best overall response, and 199 patients (45.1%) achieved PD as the best overall response.
- BGB-A317-102: Of the 300 patients treated, 249 were included in the efficacy evaluable analysis set. In all the disease cohorts and study phases, 1 patient (0.4%) achieved CR. A total of 44 patients (17.7%) achieved confirmed PR. The final overall clinical response rate was 18.1%. In

addition, 91 patients (36.5%) achieved SD as the best overall response. A total of 113 patients (45.4%) in this study achieved PD as the best response.

- BGB-A317-204: Of the 101 patients with evaluable efficacy, 10 (9.9%) achieved CR and 15 (14.9%) achieved confirmed PR. The final overall clinical response rate was 24.8%. In addition, 14 patients (13.9%) achieved SD as the best overall response.

1.3.4.2. Study BGB-A317-205 (data cutoff May 20, 2019)

Study BGB-A317-205 was a multi-cohort phase 2 study of tislelizumab in combination with standard chemotherapy as the first-line treatment for Chinese patients. Three cohorts of esophageal squamous cell carcinoma (ESCC), gastric adenocarcinoma, and gastroesophageal junction adenocarcinoma (GAC/GEJ adenocarcinoma) were enrolled simultaneously. The primary objective of this study was to evaluate the safety and tolerability of tislelizumab in combination with standard chemotherapy. Secondary objectives included the preliminary efficacy of this combination regimen for the treatment of such patients. In addition, PK and immunogenicity will be assessed.

Overall, of the 30 patients (median age: 60.5 years) who participated in Study BGB-A317-205, 83.3% were male and 100% were Asian (Chinese). The prior lines of therapy (LoT) against cancer included LoT = 0 (83.3%), LoT = 1 (3.3%), LoT = 2 (10.0%), and LoT = 3 or above (3.3%). The median duration of treatment exposure was 6.58 months (range: 0.7–18.9) and the median duration of study follow-up was 13.47 months (range: 0.1–19.2). As of May 20, 2019, of the 30 patients treated, 14 (46.7%) were still in the study, 7 (23.3%) were still on the treatment of tislelizumab, and 7 (23.4%) were being followed up.

Preliminary safety

In Study BGB-A317-205, a total of 30 safety subjects were evaluated by the investigator, and it was found that 22 patients (73.3%) experienced at least 1 TEAE related to tislelizumab treatment and 10 patients (33.3%) experienced grade ≥ 3 tislelizumab treatment-related TEAEs. The most common TEAEs with an incidence of ≥ 10% included anemia (n = 18, 60%), decreased appetite (n = 17, 57%), nausea (n = 16, 53%), fatigue (n = 15, 50%), leukopenia (n = 13, 43%), vomiting (n = 13, 43%), decreased neutrophil count (n = 12, 40%), decreased platelet count (n = 12, 40%), hypoalbuminemia (n = 10, 33%), pyrexia (n = 9, 30%), aspartate aminotransferase increased (n = 10, 33%), weight decreased (n = 10, 33%), alanine aminotransferase increased (n = 9, 30%), blood bilirubin increased (n = 9, 30%), white blood cell count decreased (n = 9, 30%), cough (n = 8, 27%), neutropenia (n = 8, 27%), diarrhea (n = 7, 23%), thrombocytopenia (n = 7, 23%), hyponatremia (n = 7, 23%), hypokalemia (n

= 6, 20%), hypoproteinemia (n = 6, 20%), body weight gain (n = 6, 20%), dizziness (n = 6, 20%), hypoesthesia (n = 6, 20%), hyperglycemia (n = 5, 16.7%), rash (n = 5, 16.7%), proteinuria (n = 5, 16.7%), palmar-plantar erythrodysesthesia syndrome (n = 4, 13%), pruritus (n = 4, 13%), hyperuricemia (n = 4, 13%), constipation (n = 4, 13%), dysphagia (n = 4, 13%), hyperbilirubinemia (n = 4, 13%), blood alkaline phosphatase increased (n = 3, 10%), gamma-glutamyltransferase increased (n = 3, 10%), free triiodothyronine increased (n = 3, 10%), gastroesophageal reflux disease (n = 3, 10%), fatigue (n = 3, 10%), peripheral edema (n = 3, 10%), hypochloremia (n = 3, 10%), leukocytosis (n = 3, 10%), pneumonitis (n = 3, 10%), expectoration (n = 3, 10%), and upper respiratory tract infection (n = 3, 10%). The most frequent grade ≥ 3 TEAEs were vomiting (n = 5, 16.7%), hyponatremia (n = 4, 13.3%), dysphagia (n = 3, 10.0%), as well as AST increased, weight decreased, decreased appetite, hypokalemia, anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, and pulmonary infection (n = 2 [6.7%] for each). 10 patients (33.3%) had at least one grade ≥ 3 TEAE that was assessed to be related to tislelizumab. Among the related TEAEs with an incidence of ≥ 5% (≥ 2 patients), only AST increased was ≥ grade 3 (n = 2, 6.7%). All other events were observed in 1 patient (3.3%) each. Of the overall 30 patients treated in Study BGB-A317-205, 23 (76.7%) experienced at least 1 potential irAE. The most common potential irAE was ALT increased (n = 5, 16.7%; grade ≥ 3 events were observed in 1 patient) and AST increased (n = 4, 13.3%; grade ≥ 3 events were observed in 2 patients). Of the 23 patients with potential irAEs, 11 (36.7% in total) experienced potential grade ≥ 3 irAEs. As of May 20, 2019, 1 patient (3.3%) died due to an AE.

Preliminary efficacy

As of May 20, 2019, the median duration of treatment exposure for patients in Study BGB-A317-205 was 6.58 months (range: 0.7–18.9) and the median duration of study follow-up was 13.47 months (range: 0.1–19.2). Of the 13 patients currently with available efficacy data, 7 (54%) showed confirmed response and 3 (23%) showed confirmed stable disease.

1.3.4.3. Study BGB-A317-206 (data cutoff May 20, 2019)

Study BGB-A317-206 was a multi-cohort phase 2 study of tislelizumab in combination with standard chemotherapy as the first-line therapy in Chinese patients with locally advanced or metastatic lung cancer. The primary objective of this study was to evaluate the antitumor activity of tislelizumab in combination with platinum-based chemotherapy doublet in this population. The secondary objectives were to evaluate the safety and tolerability of tislelizumab in combination with platinum-based chemotherapy doublet. In addition, the PK and immunogenicity are being evaluated. The patients were enrolled into one of the 4 cohorts based on the

pathological/histological diagnosis of their primary diseases. These 4 cohorts included a non-squamous non-small cell lung cancer (NSCLC) cohort, two squamous NSCLC cohorts, and a small cell lung cancer (SCLC) cohort. There was a safety run-in period and a dose expansion period in this study.

Overall, of the 54 patients (median age: 61.0 years) who participated in Study BGB-A317-206, 74.1% were male and 100% were Asian (Chinese). The prior lines of therapy (LoT) against cancer included LoT = 0 (98.1%) and LoT = 1 (1.9%). The median duration of treatment exposure was 8.82 months (range: 0.7–20.9) and the median duration of study follow-up was 15.69 months (range: 0.7–20.9). As of May 20, 2019, of the 54 patients treated, 35 (64.8%) were still in the study, 12 (22.2%) were still on the treatment of tislelizumab, and 23 (42.6%) were being followed up.

Preliminary safety

In Study BGB-A317-206, a total of 54 safety subjects were evaluated by the investigator, and it was found that 46 patients (85.2%) experienced at least 1 TEAE related to tislelizumab treatment, and 7 patients (13%) experienced grade ≥ 3 TEAEs. The most common TEAEs with an incidence of ≥ 10% were anemia (n = 44, 82%), neutrophil count decreased (n = 40, 74%), white blood cell count decreased (n = 40, 74%), platelet count decreased (n = 24, 44%), alanine aminotransferase increased (n = 22, 41%), aspartate aminotransferase increased (n = 22, 41%), decreased appetite (n = 22, 41%), nausea (n = 21, 39%), fatigue (n = 20, 37%), vomiting (n = 15, 28%), thrombocytopenia (n = 14, 26%), alopecia (n = 13, 24%), constipation (n = 12, 22%), pyrexia (n = 11, 20%), cough (n = 10, 19%), rash (n = 8, 15%), dizziness (n = 8, 15%), hypothyroidism (n = 8, 15%), leukopenia (n = 8, 15%), neutropenia (n = 8, 15%), hyponatremia (n = 8, 15%), insomnia (n = 7, 13%), hypoalbuminemia (n = 6, 11%), hypokalemia (n = 6, 11%), hypoferremia (n = 6, 11%), weight decreased (n = 6, 11%), and pneumonitis (n = 6, 11%). Specifically, 43 patients (79.6%) experienced at least one grade ≥ 3 TEAE. The most common grade ≥ 3 TEAEs were neutrophil count decreased (n = 26, 48.1%), anemia (n = 10, 18.5%), white blood cell count decreased (n = 8, 14.8%), platelet count decreased (n = 7, 13.0%), thrombocytopenia (n = 6, 11.1%), neutropenia (n = 4, 7.4%), ALT increased and hyponatremia (n = 3, 5.6%), as well as bone marrow failure, full blood count decreased, and hyperglycemia (n = 2, 3.7%). Of the overall 54 patients treated in Study BGB-A317-206, 31 (57.4%) experienced at least 1 potential irAE. The most common potential irAEs were hypothyroidism (n= 7, 13.0%), as well as ALT increased and AST increased (n = 6, 11.1%). Of the 31 patients with potential irAEs, 3 (5.6% in total) experienced potential grade ≥ 3 irAEs. As of May 20, 2019, 1 patient (1.9%) died due to an AE.

Preliminary efficacy

As of May 20, 2019, the median duration of treatment exposure for patients in Study BGB-A317-206 was 8.82 months (range: 0.7–20.9) and the median duration of study follow-up was 15.69 months (range: 0.7–20.9). Of the 54 patients currently with available efficacy data, 36 (67%) showed confirmed response and 13 (24%) showed confirmed stable disease.

1.3.5. Rationale for dose selection of tislelizumab

The PK, safety, and efficacy data obtained from the first-in-human trial BGB-A317_Study_001, along with data from other clinical studies, were comprehensively analyzed to determine the recommended dose for a pivotal study of tislelizumab. A fixed dose of 200 mg (once every 3 weeks) via intravenous (IV) administration was selected for further assessment. The MTD was not determined and only 1 DLT was reported in the first-in-human trial.

The incidences of treatment-related AEs and SAEs observed in patients dosed at 2 mg/kg (once every 2 weeks) and 5 mg/kg (once every 3 weeks) were comparable, suggesting there was no clear dose dependence between the regimens. The ORR was confirmed to be 10%–15% in patients receiving tislelizumab at 2 mg/kg and 5 mg/kg once every 2 weeks, compared to 15%–38% in patients receiving tislelizumab at 2 mg/kg and 5 mg/kg once every 3 weeks.

Based on the PK data from phase 1a Study BGB-A317_Study_001, the CL of tislelizumab was independent of body weight, race, and gender, with the serum exposure observed after administration at a dose level of 200 mg between those observed at 2 mg/kg and 5 mg/kg (with comparable safety and efficacy within the dose range). No unexpected treatment-related AEs were observed in the 200 mg fixed-dose cohort (BGB-A317_Study_001, phase 1a, part 3), compared with the body weight-based cohort.

Of the patients with evaluable solid tumors (n = 67) who were treated at a dose of 200 mg once every 3 weeks, 43 patients (64%) achieved confirmed response and 16 patients (24%) achieved confirmed stable disease. Therefore, the clinical efficacy of tislelizumab 200 mg administered once every 3 weeks is expected to be achieved with controlled and tolerated safety.

When tislelizumab is administered in combination with sitravatinib, the recommended initial dose is 200 mg once every 3 weeks.

1.4. Rationale for tislelizumab plus sitravatinib and tislelizumab plus sitravatinib in combination with chemotherapy for the treatment of locally recurrent or metastatic triple negative breast cancer

Monoclonal antibodies against PD-1 or PD-L1 immune checkpoints can block the protein from binding to ligands and enhance the immune response against cancer cells. These drugs have been proven to be useful in the treatment of various types of cancer, including skin melanoma, non-small cell lung cancer, renal cancer, bladder cancer, head and neck cancer, and Hodgkin's lymphoma. TNBC is considered to be the most immunogenic subtype of breast cancer among all subtypes, and it is the primary target in current clinical trials of immune checkpoint inhibitors. The immunotherapy for TNBC shall proceed in combination with other drugs to realize the purpose of improving survival (Planes-Laine et al., 2019). Preliminary data have confirmed that chemotherapy in combination with immunotherapy can significantly improve the survival of patients with TNBC (Schmid et al., 2018). So far, no data from large phase 3 studies have been published regarding the treatment of locally recurrent or metastatic TNBC with immunotherapy plus TKI/ immunotherapy plus TKI in combination with chemotherapy. The combination of a PD-1 checkpoint inhibitor for immunotherapy and another agent with both immunomodulatory and antitumor properties can enhance the antitumor efficacy of both drugs. The best clinical efficacy and good tolerability of tyrosine kinase inhibitors (TKIs) provide the basis for TKI treatment of cancer. Furthermore, selective TKIs have been proven to modulate the immunogenic status of tumors, improving tumor perfusion by reducing intratumoral pressure and modulating subsets of immune cells, thereby increasing the efficacy of immune elements while reducing the number and alleviating the function of immunosuppressive cells.

Tumor therapy, including the treatment of TNBC, is faced with selective challenges; mutations in a single cancer cell represent the continuous evolution of primary cancer. Almost all malignant tumors eventually develop resistance to anticancer therapies. The same is true in the case of immune checkpoint blockers, where most treated patients with an initial effective response eventually develop acquired resistance that helps cancer cells adapt to the environment and survive immune attacks, thus bringing a treatment challenge to be overcome (Syn et al., 2017). Therefore, there is an urgent need to explore therapeutic strategies to overcome endogenous/acquired resistance to checkpoint inhibitors.

Stravatinib plus tislelizumab may have a stronger antitumor activity, as sitravatinib may strengthen several links in the cancer immune cycle thereby enhancing the efficacy of tislelizumab. First, the antitumor activity of sitravatinib promotes the release of tumor antigens. Second, its inhibitory effect on the mitotic kinase receptors

VEGFR-2 and KIT results in a reduction of regulatory T cells (Tregs) and MDSCs, thereby promoting the expansion and migration of cytotoxic T cells against tumor cells and infiltrating tumor tissues. Third, sitravatinib reverses the TAM receptor-mediated immunosuppressive effect in the tumor microenvironment by inhibiting MERTK, increases the M2-polarized macrophage count from M1, and releases interleukin (IL)-12, IL-6, and tumor necrosis factors (TNFs). These downstream effects promote $CD8^+$ T cell activation and, through inhibition of AXL, terminate the toll-like receptor-dependent inflammatory response in dendritic cells, thereby facilitating antigen presentation. In addition, for patients with immune checkpoint treatment resistance, drug combination therapy targeting the molecular and cellular mechanisms of immune checkpoint treatment resistance is a reasonable method to improve their prognosis. The key molecular and cellular pathways of receptor tyrosine kinases are closely related to checkpoint inhibitor resistance, indicating that sitravatinib plus tislelizumab is a reasonable option for patients with immune checkpoint treatment resistance.

Paclitaxel drugs may enhance the antitumor activity of tislelizumab. The antitumor activity of paclitaxel drugs can promote the release of tumor antigens. Tumor antigens are recognized by antigen-presenting cells (APC) and presented to T cells with antitumor activity, which can promote T cell activation. Compared with the common solvent-based paclitaxel, nab-paclitaxel may have better antitumor efficacy, mainly because of the stronger permeability and local enrichment ability at tumor lesions of nab-paclitaxel. In addition, compared with the traditional solvent-based paclitaxel, hormone pretreatment is not involved in the use of nab-paclitaxel, which can avoid the influence of hormone use on the efficacy of immunotherapy, which indicates that nab-paclitaxel plus tislelizumab in combination with sitravatinib may be a reasonable option.

1.5. Benefit-Risk Assessment

The combination therapy with small molecule inhibitors involved in the VEGFR pathway may increase the clinical efficacy of immunotherapy and overcome resistance to checkpoint inhibitor therapy (see Section 1.2.4.2). The needs of patients for new treatment regimens and/or alternatives to previous immunotherapies are far from satisfaction. Based on the existing data of tislelizumab and sitravatinib as well as the data of other PD-1 or PD-L1 inhibitors and other small molecule inhibitors involved in the VEGFR pathway, tislelizumab plus sitravatinib has a stronger antitumor activity and controlled safety.

More than 300 patients have been treated with sitravatinib monotherapy and combination therapy. The clinical safety data from nonclinical toxicology studies as well as phase 1/1b and phase 2 studies suggest that sitravatinib-related AEs are

similar to those observed with other small molecule inhibitors in the VEGFR pathway. For further discussion of sitravatinib safety, please refer to Sitravatinib IB v8.1 (Aug. 23, 2021).

More than 1,000 patients have been treated with tislelizumab monotherapy and combination therapy at clinically relevant doses (≥ 2 mg/kg). The safety profiles are consistent with the known effects of anti-PD-1 antibodies and includes mostly mild/moderate AEs. Grade 3 or 4 irAEs are rarely observed and can be reversed and controlled by interruption of the interventional product and/or steroid therapy. For further discussion of the safety of tislelizumab, please refer to Tislelizumab IB v9.0 (Oct. 20, 2021).

Considering the clinical benefits of sitravatinib plus tislelizumab/sitravatinib plus tislelizumab in combination with nab-paclitaxel therapy in patients with locally recurrent or metastatic TNBC as well as the unmet needs of Chinese patients with locally recurrent or metastatic TNBC, especially those who are refractory/resistant to anti-PD1/PD-L1 antibodies, based on available treatment data, the benefit/risk assessment result of treatment with sitravatinib plus tislelizumab/sitravatinib plus tislelizumab in combination with nab-paclitaxel is considered favorable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary objectives

- To comprehensively evaluate the preliminary antitumor activity, safety, and tolerability of 100 mg sitravatinib plus tislelizumab based on the investigator-assessed overall response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and percentage of subjects that experience grade ≥ 3 treatment-related adverse events (TRAEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0;
- To evaluate the preliminary antitumor activity of 70 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel based on the ORR assessed by the investigator according to RECIST v1.1;

2.1.2. Secondary objectives

- To evaluate the preliminary antitumor activity of 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel based on the DOR, DCR, and PFS assessed by the investigator according to RECIST v1.1;
- To evaluate the 1-year OS rates of patients receiving 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel, respectively, according to RECIST v1.1;
- To evaluate the safety and tolerability of 70 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel according to NCI-CTCAE v5.0;
- To evaluate the safety and tolerability of 100 mg sitravatinib plus tislelizumab according to NCI-CTCAE v5.0 (excluding grade ≥ 3 TRAEs);

2.1.3. Exploratory objective:

- To explore potential biomarkers of efficacy, resistance, and/or progressive disease (PD) in tumor tissues.

2.2. Study Endpoints

2.2.1. Primary endpoints

- The ORR of 100 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel and the percentage of subjects that experience grade ≥ 3 TRAEs as determined by the investigator according to RECIST v1.1 and NCI-CTCAE v5.0;
  - ORR: It is defined as the proportion of patients who achieve either complete response (CR) or partial response (PR) as the best overall response (BOR);
- The ORR of 70 mg sitravatinib plus tislelizumab as assessed by the investigator according to RECIST v1.1;

2.2.2. Secondary endpoints

- The DOR, DRC, and PFS of 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel, respectively, assessed by the investigator according to RECIST v1.1:
  - DOR: It is defined as the time from the first documented objective response to the recurrence or death from any cause (whichever occurs first);
  - DCR: It is defined as the proportion of patients with BOR being CR, PR, or stable disease (SD);
  - PFS: It is defined as the time from the first dose of the investigational products to the date of the first objectively documented progressive disease (PD) or death from any cause (whichever occurs first);
- The percentage of subjects that experience the OS event (within 1 year) after receiving 70 mg sitravatinib plus tislelizumab, 100 mg sitravatinib plus tislelizumab, and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel, respectively, as assessed by the investigator according to RECIST v1.1:
  - OS is defined as the time from the date of the first dose of the investigational products to the date of death from any cause. The 1-year survival rate (percentage of subjects alive at 1 year) will be estimated based on the OS data

- The safety and tolerability of 70 mg sitravatinib plus tislelizumab and 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel assessed based on the incidence, nature, and severity of AEs and SAEs determined according to NCI-CTCAE v5.0, clinical laboratory abnormalities, relevant physical examinations, ECGs, vital signs, and the percentage of subjects who discontinue study treatment due to AEs;
- The safety and tolerability of 100 mg sitravatinib plus tislelizumab assessed based on the incidence, nature, and severity of AEs and SAEs except for grade ≥ 3 TRAEs as determined according to NCI-CTCAE v5.0; clinical laboratory abnormalities, relevant physical examinations, ECGs, vital signs, and the percentage of subjects who discontinue study treatment due to AEs;

2.2.3. Exploratory endpoints:

- The potential biomarkers associated with efficacy, resistance, and/or PD, including expression of PD-L1, TILs, and FOXC1 in archival and/or fresh tumor tissues obtained prior to treatment, radiomics analysis, immune-related cytokines and peripheral blood cell classification, ctDNA testing, GEP, genetic/tissue mutation testing, single-cell sequencing, proteomics, and metabolomics.

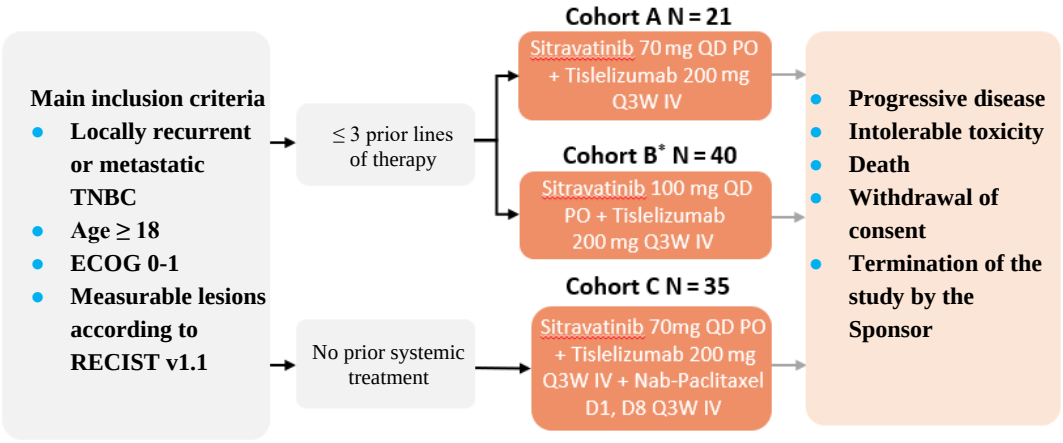
3. STUDY DESIGN

3.1. Overview of Study Design

This is an open-label, single-center, and phase 2 clinical study in patients with locally recurrent or metastatic TNBC after receiving ≤ 3 prior lines of therapy. All patients will be treated with the investigational products during the treatment period until the development of PD, intolerable toxicity, death, withdrawal of consent, or termination of the study by the sponsor. There are 3 cohorts in the study:

- **Cohort A (70 mg group):** Sitravatinib 70 mg QD PO plus 200 mg tislelizumab Q3W IV;
- **Cohort B (100 mg group):** Sitravatinib 100 mg QD PO plus 200 mg tislelizumab Q3W IV;
- Cohort C: Sitravatinib 70 mg QD PO plus 200 mg tislelizumab Q3W IV in combination with nab-paclitaxel 100 mg/m^2 D1, D8 Q3W IV;

Figure 1: Study schema



*The enrollment into Cohort B shall start after that into Cohort A is completed

Abbreviations: TNBC = triple negative breast cancer; ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death protein-1; PD-L1 = programmed cell death protein ligand-1; QD = once daily; PO = oral administration; Q3W = once every 3 weeks; IV = intravenous injection; Sitra = sitravatinib; Tisle = tislelizumab;

Cohort A will follow the Simon's two-stage design to test the superiority of the combination therapy under study relative to the historical control. Of the first 12 patients in the efficacy analysis set of Cohort A, if the number of patients with confirmed response is 0, enrollment into Cohort A will be terminated, and the patients who have been enrolled in Cohort A will continue treatment with the investigational product and complete subsequent assessments until withdrawal. Otherwise, the Cohort A study will continue until 21 patients are enrolled.

Cohort C will follow the Simon's two-stage design to test the superiority of the combination therapy under study relative to the historical control. Of the first 18 patients in the efficacy analysis set of Cohort C, if the number of patients with confirmed post-treatment response is ≤ 9, enrollment into Cohort C will be terminated, and the patients who have been enrolled in Cohort C will continue treatment with the investigational product and complete subsequent assessments until withdrawal. Otherwise, the Cohort C study will continue until 35 patients are enrolled.

If a patient drops out before the first assessment and could not be included in the efficacy analysis set, the dropout shall be supplemented.

3.2. Screening Period

Screening assessments will be completed within 28 days prior to the first dose of the investigational products. Patients who agree to participate in this study will sign the ICF prior to undergoing any screening procedure. Patients who are suspected or known to have severe respiratory conditions or exhibit significant respiratory symptoms unrelated to underlying cancer should undergo a pulmonary function test (refer to Appendix 1 for details). Patients who previously failed to meet some eligibility criteria (e.g., patients who happened to fail to meet the laboratory criteria due to remediable reasons other than rapidly deteriorating conditions or PD) may undergo repeated screening assessments within the original screening window upon the investigator's assessment; the investigator should determine the eligibility of patients according to the most recent screening assessment results. Additional details are provided in Section 7.1.

3.3. Treatment Period

After completion of all screening activities, eligible patients as confirmed by the investigator will be enrolled to receive treatment with sitravatinib plus tislelizumab. All patients will be treated with the investigational products during the treatment period until the development of PD, intolerable toxicity, death, withdrawal of consent, or termination of study by the sponsor. Patients who are medically stable at the end of the treatment period as assessed by the investigator will receive appropriate maintenance treatment and undergo survival follow-up. See the procedures for each outpatient visit in Appendix 1.

3.4. End-of-Treatment Visit and Safety Follow-up Calls

Patients who discontinue treatment for any reason should return to the study center for the end-of-treatment (EOT) visit within 30 days of the last dose of the investigational products, or before the initiation of a new anticancer treatment (whichever occurs first). If routine laboratory tests (e.g., hematology, clinical chemistry) have been conducted within 7 days before the EOT visit, these tests are not required to be repeated. If the previous tumor assessment is conducted within 6 weeks before the EOT visit, the assessment at the EOT visit is not required to be repeated. If the investigational products are initially interrupted due to an AE and then permanently discontinued, the EOT visit may be postponed, but no later than the allowable time limit for dose delay + 7 days.

The assessments required for the EOT visit are presented in Appendix 1.

Telephone contacts with patients should be completed 60 and 90 days (± 14 days) after the last dose of tislelizumab to assess irAEs and the safety of co-medication, regardless of the initiation of a new anticancer therapy. If patients report a suspected

irAE 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 8.6.

Tumor assessment for patients who discontinue study treatment prior to PD is described in Section 7.4.

3.5. Survival Follow-up

Survival follow-up and further anticancer treatment will be conducted in patients who discontinue study treatment via telephone follow-up, patient medical records, and/or clinic visit once approximately every 3 months (± 14 days) after the EOT visit, until death, loss to follow-up, withdrawal of consent, or termination of study by the sponsor.

3.6. Discontinuation from Study Treatment or Study

3.6.1. Patient discontinuation from study treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue any patient from the study treatment at any time. If possible, patients who discontinue study treatment for reasons other than PD should be followed up to assess the antitumor activity (Section 7.4), safety (Section 7.3), and survival (Section 3.5).

The primary reason for discontinuation from the study treatment should be documented on the appropriate case report form (CRF). Patients may discontinue study treatment for reasons which include but are not limited to, the following:

- Withdrawal of consent
- Pregnancy
- Any medical condition that the sponsor determines may jeopardize the patient's safety if she continues to receive study treatment
- Use of any other antitumor therapy (i.e., chemotherapy, hormone therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicines and traditional Chinese medicinal products] for the treatment of cancer)
- Patient non-compliance with the treatment regimen
- Progressive disease

3.6.2. Patient discontinuation from study (end of study for an individual patient)

Patients may discontinue study participation for reasons which include but are not limited to, the following:

- Withdrawal of consent
- Death
- Loss to follow-up
- Patients have completed all study assessments
- The sponsor terminates the study

3.7. End of Study

The end of this study is defined as the date of the last patient last visit (LPLV) or the date when the last data point necessary for the statistical analysis or safety follow-up of the last patient is collected, whichever is later.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may 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
- The overall enrollment of patients is unsatisfactory with an excessively slow recruitment process
- Poor protocol adherence

The sponsor will inform the study funder of the decision (if any) to terminate the study. It is necessary for patients who prematurely discontinue treatment to undergo the EOT visit as soon as possible.

In order to fully consider and protect the interests of patients, the sponsor will be responsible for informing the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the early termination of the study.

The investigational products will not be available for further use upon the end of the study. If the study is early terminated but the investigator assesses that patients can still benefit from the investigational products, application for continuation of medication may be submitted to the study funder for a total duration of up to 2 years.

4. STUDY POPULATION

Specific eligibility criteria for the patient screening are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waiver.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Able to provide a written ICF, and can understand and comply with the requirements and schedule of assessments of the study
2. Females aged ≥ 18 years old (or the legal age of commitment within the study occurrence jurisdiction) on the day the ICF is signed
3. Able to provide archival tumor tissues (formalin-fixed paraffin-embedded tumor tissue wax blocks [FFPE] or unstained slides)

   Note: If archival tumor tissues are not available or insufficient, a fresh biopsy is recommended. Patients who are unable to provide archival tumor tissues or biopsy samples but meet the other inclusion criteria are also eligible for this study.

   - Tumor tissues should be collected via a core needle or aspiration biopsy.
   - Tumor tissues from a fine-needle aspiration biopsy will not be accepted.
4. Patients with locally recurrent or metastatic TNBC as confirmed by histology and assessed by imaging according to the eighth edition of the tumor-node-metastasis (TNM) staging system for breast cancer published by the American Joint Committee on Cancer (AJCC). Histologically confirmed TNBC is defined as:

   - Tumors with ≤ 1% of ER expression by immunohistochemical (IHC) staining
   - Tumors with ≤ 1% of PR expression by IHC staining
   - Her2/neu ratio ≤ 1.8 by fluorescence in situ hybridization (FISH) or $0/1^{+}$ by IHC
5. Prior ≤ 3-line systemic therapies (Cohort A and Cohort B)

   - Naïve to anti-PD-1/PD-L1 antibodies: failure in/intolerance to/ineligibility for standard chemotherapies (including anthracyclines, paclitaxel, platinum-based agents, vinorelbine, capecitabine, and

gemcitabine) with no other prior immunotherapies (including but not limited to anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40, and anti-CD137); the number of prior chemotherapy lines is ≤ 3;

- Refractory/resistant to anti-PD-1/PD-L1 antibodies: one prior anti-PD-1/PD-L1 therapy; candidate for anti-PD-1/PD-L1 therapy either as the second-line therapy after the failure of standard chemotherapy or as the first-line therapy; TNBC with radiographic progression as determined by RECIST v1.1 during or after anti-PD-1/PD-L1 treatment; refractory to anti-PD-1/PD-L1 antibodies is defined as development of radiographic progression during or after anti-PD-1/PD-L1 treatment, PD as the best response achieved with anti-PD-1/PD-L1 therapy, or SD ≤ 6 weeks (+ 2 weeks according to the imaging assessment schedule is acceptable); resistant to anti-PD-1/PD-L1 antibodies is defined as CR or PR as the best response achieved with anti-PD-1/PD-L1 therapy, or SD lasting for > 6 weeks (+ 2 weeks according to the imaging assessment schedule is acceptable)

6. Patients refractory/resistant to anti-PD-1/PD-L1 antibodies with no previous toxicity associated with anti-PD-1/PD-L1 therapy, which is defined as follows:

   - Grade ≥ 3 anti-PD-1/PD-L1-related AEs
   - Grade ≥ 2 anti-PD-1/PD-L1-related irAEs, except for AEs that were resolved or well-controlled after interruption of anti-PD-1/PD-L1 antibodies or steroid treatment (excluding previous colitis, encephalitis, myocarditis, hepatitis, uveitis, and pneumonitis)
   - Anti-PD-1/PD-L1-related central nervous system (CNS) or ocular AEs of any grade

   Note: Patients with previous endocrine AEs are allowed to be enrolled if they can remain stable and asymptomatic under appropriate replacement therapy

7. No prior systemic therapy for locally recurrent or metastatic breast cancer (Cohort C), with the time to recurrence from prior (new) adjunctive drug therapy meeting the following requirements:

   - A time interval of ≥ 6 months between the end of (new) adjunctive treatment with paclitaxel drugs and the occurrence of recurrence/metastasis

- A time interval of ≥ 6 months between the end of (new) adjunctive treatment with anti-angiogenic drugs and the occurrence of recurrence/metastasis
- A time interval of ≥ 6 months between the end of (new) adjunctive treatment with immunotherapy drugs and the occurrence of recurrence/metastasis

8. ECOG performance status of ≤ 1 (Appendix 3)
9. Adequate organ performance (≤ 7 days prior to the first dose of the investigational products) as indicated by the following laboratory test values:
    a. Patients must receive no blood or platelet transfusion or growth factor support within ≤ 14 days before blood sample collection at screening, and must have:
        i. ANC ≥ 1.5×10^9/L
        ii. Platelets ≥ 75×10^9/L
        iii. Hemoglobin ≥ 90 g/L
    b. Serum creatinine ≤ 1.5 × upper limit of normal (ULN)
    c. AST and ALT ≤ 2.5 × ULN (≤ 5 ULN if liver metastasis is present)
    d. Total serum bilirubin ≤ 1.5 × ULN
    e. International normalized ratio (INR) ≤ 1.5 or prothrombin time ≤ 1.5 × ULN
    f. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN
    g. Serum albumin ≥ 30 g/L
10. No radiotherapy, endocrine therapy, molecular targeted therapy, or surgery within 3 weeks before the initiation of the study, and recovery from acute toxic reactions caused by prior treatment (surgical wounds [if any] are completely healed); no peripheral neuropathy or grade I peripheral neurotoxicity;
11. Females of childbearing potential must agree to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of the investigational products (Appendix 5), and have a negative serum pregnancy test ≤ 7 days prior to the first dose of the investigational products

4.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for inclusion:

1. Presence of active leptomeningeal disease or poorly controlled brain metastases. Stable imaging results, i.e., no progression for at least 4 weeks as confirmed by repeat imaging examinations, for patients with previously treated brain metastases (note: repeat imaging examinations should be performed during the screening period).
2. Active autoimmune diseases or history of autoimmune diseases that may recur (Appendix 4)

   Note: Patients with the following diseases are not excluded and may proceed to further screening:

   a. Well-controlled type I diabetes mellitus
   b. Hypothyroidism (provided it can be managed with hormone replacement therapy only)
   c. Well-controlled celiac disease
   d. Skin diseases not requiring systemic therapies (e.g., vitiligo, psoriasis, and alopecia)
   e. Any other diseases that are not expected to recur without external triggers
3. Any active malignancy ≤ 2 years prior to the first dose of the investigational products, except for specific cancer under investigation in this study and any previously radically treated cancer with local recurrence (e.g., resected basal or squamous cell skin cancer, in-situ carcinoma of the cervix, or breast cancer in situ)
4. Any medical conditions requiring systemic therapies with corticosteroids (prednisone or equivalent > 10 mg/day) or other immunosuppressive agents ≤ 14 days prior to the first dose of the investigational products

   Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

   a. Adrenal replacement steroids (prednisone or equivalent ≤ 10 mg/day)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroids with minimal systemic absorption

c. Short course (≤ 7 days) of corticosteroid used prophylactically (e.g., contrast dye allergy) or for the treatment of a non-autoimmune condition (e.g., delayed-type hypersensitivity reaction caused by contact allergen)

5. Presence of uncontrolled diabetes mellitus, grade ≥ 3 hypoalbuminemia, or grade > 1 abnormal laboratory tests involving blood potassium, sodium, or calcium despite standard drug treatment ≤ 14 days prior to the first dose of the investigational products
6. A history of interstitial lung disease, pneumonitis, or uncontrolled lung diseases, including pulmonary fibrosis, acute lung disorders, etc.
7. Severe chronic or active infections (including tuberculosis infection, etc.) requiring systemic antibacterial, antifungal, or antiviral therapies within 14 days prior to the first dose of the investigational products (note: patients with viral hepatitis receiving antiviral therapy are considered acceptable)
8. Active psychiatric disorders (schizophrenia, severe depressive disorder, bipolar affective disorder, etc.). Depression on antidepressants is not an exclusion criterion
9. Known history of human immunodeficiency virus (HIV) infection
10. Patients with treatment-naive chronic hepatitis B, or chronic hepatitis B virus (HBV) carriers (HBV DNA > 500 IU/mL), or active hepatitis C virus (HCV) carriers with detectable HCV RNA. Note: Inactive hepatitis B surface antigen (HBsAg) carriers and patients with active HBV infection with sustained anti-HBV suppression (HBV DNA < 500 IU/mL) can be enrolled.
11. Any major surgery requiring general anesthesia ≤ 28 days prior to the first dose of the investigational products
12. Prior allogeneic stem cell transplantation or organ transplant
13. Any of the following cardiovascular criteria

    a. Cardiac chest pain ≤ 28 days prior to the first dose of the investigational products, defined as moderate pain that limits instrumental activities of daily living

    b. Symptomatic pulmonary embolism ≤ 28 days prior to the first dose of the investigational products

c. Any history of acute myocardial infarction ≤ 6 months prior to the first dose of the investigational products

d. Any history of cardiac failure meeting New York Heart Association (NYHA) classification III or IV (6) ≤ 6 months prior to the first dose of the investigational products

e. Any event of ventricular arrhythmia (grade ≥ 2) ≤ 6 months prior to the first dose of the investigational products

f. Any history of cerebrovascular accident ≤ 6 months prior to the first dose of the investigational products

g. Corrected QT interval (QTc) (corrected by Fridericia's method) > 450 ms

Note: If the QTc interval of the initial ECG is > 450 ms, subsequent ECGs will be performed to exclude the result

h. Left ventricular ejection fraction (LVEF) assessed by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO) ≤ lower limit of normal (LLN). The same method must be used in the baseline assessment and subsequent assessments

i. Any episode of syncope or epileptic seizure ≤ 28 days prior to the first dose of the investigational products

14. Poorly controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)

15. Hypersensitivity to tislelizumab or sitravatinib, any component of the formulations, or any component of the drug containers

16. Hemorrhage, thrombotic disease, or use of anticoagulants (e.g., warfarin) or similar drugs requiring therapeutic INR monitoring within 6 months prior to the first dose of the investigational products

17. Systemic chemotherapy within 28 days prior to the first dose of the investigational products or immunotherapy (e.g., interleukin, interferon, thymosin, etc.), hormone therapy, targeted therapy, or any investigational therapy within 14 days or 5 half-lives (whichever is shorter) prior to the first dose of the investigational products

18. Use of any Chinese herbal medicine or traditional Chinese medicinal product with anticancer activity (regardless of the type of cancer) approved by China's National Medical Products Administration (NMPA) within 14 days prior to the first dose of the investigational products

19. No recovery to baseline level or stability in the toxicity resulting from prior anticancer treatment, except for AEs not considered as a safety risk (e.g., alopecia, neuropathy, and specific laboratory abnormalities).

20. Inoculation with live vaccines ≤ 28 days prior to the first dose of the investigational products

    Note: Seasonal influenza vaccines are generally non-live vaccines and are thus allowed. Intranasal influenza vaccines are live vaccines and are thus prohibited

21. Underlying disease conditions (including laboratory abnormalities) or alcohol/drug abuse or dependence that are not conducive to the administration of the investigational products, will affect the interpretation of toxicity of the investigational products and AEs or will result in inadequate or reduced compliance with the study

22. Concurrent participation in another clinical study, unless such study is an observational (non-interventional) clinical study or the patient is in the follow-up period of an interventional study

23. Inability to swallow capsules or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, total gastrectomy or small intestinal resection, bariatric surgery, inflammatory bowel disease, or incomplete or complete intestinal obstruction

24. Uncontrollable pleural effusion or pericardial effusion, or seroperitoneum requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention, excluding exfoliative cytology of the exudate) within 7 days prior to the first dose of the investigational products

25. Pregnant or lactating females

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Sitravatinib

Sitravatinib is available in 35 mg and 50 mg capsules.

Sitravatinib drug product is packaged in 75-mL high-density polyethylene bottles for oral solid medicines with a polypropylene child-resistant combination cap system. A 30 capsules/bottle packaging specification is used for both strengths of capsules. The provided bottles should be labeled for specific patient use, and the content of the label will comply with all applicable local regulatory requirements.

The bottles containing sitravatinib must be stored in the pharmacy of the study center under ambient conditions (15–30 °C).

Refer to the pharmacy manual for details regarding administration, accountability, and disposal. Additional details about sitravatinib are provided in Sitravatinib IB v8.1 (Aug. 23, 2021).

5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody that is formulated for IV injection in a single-use vial (20R glass, *United States Pharmacopoeia* [USP] type I) containing a total of 100 mg antibody in 10 mL of isotonic solution. Tislelizumab is aseptically filled in single-use vials and then sealed with Flurotec-coated butyl rubber stoppers and aluminum caps. Each vial is packaged in a carton.

The content of the label will comply with all applicable local regulatory requirements.

This investigational product must be stored under refrigeration conditions (2–8 °C) and away from light according to instructions on the label.

Refer to the pharmacy manual for details regarding IV administration, accountability, and disposal. Additional details about tislelizumab are provided in Tislelizumab IB v9.0 (Oct. 20, 2021).

5.1.3 Treatment with nab-paclitaxel

Nab-paclitaxel will be provided by the pharmacy of each center as prescribed by a physician. Management of these products (including labeling, handling, storage, management, and disposal) will be in accordance with the relevant local guidelines and/or instructions for use. For further details, please refer to the instructions for use provided by manufacturers for their respective chemotherapy agents. Each drug product must be stored under the temperature condition specified on the corresponding label.

5.2. Dosage and Administration

When sitravatinib and tislelizumab are scheduled for administration on the same day, the administration of sitravatinib should be earlier than the tislelizumab infusion.

5.2.1. Sitravatinib

Sitravatinib will be administered at 100 mg QD PO or 70 mg QD PO based on treatment group for 21 consecutive days as a dosing cycle.

The guidelines below should be followed for the administration of sitravatinib:

- Morning administration is preferred.
- The capsules should be taken under fasting conditions, at least 2 hours after the previous meal and 1 hour before the next meal. If administered once daily, the capsules should be taken in the morning, e.g., at least 1 hour before breakfast or lunch.
- The capsules should be administered with at least 200 mL (1 cup) of water.
- Patients should be instructed to swallow the whole capsule instead of chewing it.
- In case of vomiting after administration, the dose of sitravatinib should not be supplemented.
- If a patient forgets to take sitravatinib for more than 12 hours, she should skip this dose and resume taking the medicine the next day.

5.2.2. Tislelizumab

Tislelizumab (200 mg) will be administered on day 1 of each 21-day cycle (every 3 weeks). Tislelizumab will be administered via intravenous infusion through an IV line containing sterile, non-pyrogenic, and low-protein solution for injection with a 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for drug preparation and administration are provided in the pharmacy manual.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 1, Day 1) will be delivered in no less than 60 minutes; if this is well tolerated, then the subsequent infusions may be administered in no less than 30 minutes, which is the shortest time period permissible for infusion.

Tislelizumab should not be concurrently administered with any other drugs (see Section 6).

5.2.3. Nab-paclitaxel

The dose level of nab-paclitaxel is 100 mg/m^2 in this study. The drug will be administered intravenously on Day 1 and Day 8 of each 21-day cycle (the duration of infusion should be no less than 30 min).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 7.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

5.3. Compliance and Accountability

Compliance will be assessed at each patient visit by the investigator and/or study staff based on the information provided by patients. Patients enrolled in the study will be provided with patient diaries. Patients will be responsible for the maintenance of their own patient diaries and the recording of the number of sitravatinib capsules taken and the number of missing doses (if any). The study center staff who are responsible for drug accountability will record the number of dispensed drugs and the number of received drugs after each cycle visit. The patient diaries and pharmacist's medication records will be assessed by the investigator/study staff at each visit.

The investigational products required for completing this study (sitravatinib and tislelizumab) will be provided by BeiGene. The study center will acknowledge receipt of the investigational products. Any damaged shipments will be replaced.

Accurate records of all received, distributed, recalled, and handled investigational products will be reflected in the study center's drug inventory record form. Refer to the pharmacy manual for details regarding the management of the investigational products.

5.4. Overdose

5.4.1. Sitravatinib

Any overdose or maladministration of sitravatinib should be recorded in the patient's medical record and corresponding CRF. AEs related to an overdose or maladministration of this investigational product will also be recorded in the CRF. Any overdose- or maladministration-related SAE should be reported according to the SAE reporting procedures as described in Section 8.6.2.1 within 24 hours upon learning. Supportive care measures should be taken as appropriate.

5.4.2. Tislelizumab

Any overdose (defined as a dosage of ≥ 600 mg within 24 hours) or maladministration of tislelizumab should be recorded in the patient's medical record and corresponding CRF. AEs related to an overdose or maladministration of this investigational product will also be recorded in the CRF. As described in Section 8.6.2.1, any overdose- or maladministration-related SAE should be reported according to the SAE reporting procedures within 24 hours upon learning. Supportive care measures should be taken as appropriate.

5.4.3. Nab-paclitaxel

An overdose occurs when the dose specified in this protocol exceeds 20% of the total target dose, which should be recorded in the patient's medical record and corresponding eCRF. AEs related to an overdose or maladministration of this investigational product will also be recorded in the eCRF. As described in Section 8.6.2, any overdose- or maladministration-related SAE should be reported according to the SAE reporting procedures within 24 hours upon learning. Supportive care measures should be taken as appropriate.

5.5. Dose Modification and Delay

5.5.1. Dose modification

In this study, the dose of tislelizumab will not be reduced. Dose reductions of sitravatinib are listed in Table 1. Once the dose is reduced, re-increase of the dose, though generally not recommended, may be considered as appropriate according to the specific situation. If sitravatinib administration is interrupted due to reasons other than toxicity, this investigational product can be resumed at the same dose. Section 8.8 introduces the criteria for dose modification as well as recommendations and guidelines for the treatment of some sitravatinib-related toxicities.

Table 1: Dose reductions of sitravatinib

Starting dose	70 mg, QD	100 mg, QD
Dose level-1	50 mg, QD	70 mg, QD
Dose level-2	35 mg, QD	50 mg, QD[a]

[a.] The dose may be reduced to below 50 mg QD only after discussion with the investigator and careful consideration.

If one investigational product is interrupted or discontinued, it is at the discretion of the investigator to continue the use of another investigational product.

The required chemotherapy dose will be calculated using baseline body weight. Dose modification is required if the change in a patient's body weight is ≥ 10% from

baseline (the body weight newly recorded will be the new baseline body weight). There is no need for chemotherapy dose modification in patients with a body weight change of < 10%. In this study, the dose of nab-paclitaxel may be adjusted to 75 mg/m^2. Once the dose is reduced, re-increase of the dose, though generally not recommended, may be considered as appropriate according to the specific situation.

5.5.2. Dose Delay

The investigational products should be administered according to the planned dose and time schedule to the greatest extent. In the event of significant toxicity, doses may be delayed and/or reduced according to the guidelines provided. Reasons for dose modification or delay, the supportive measures taken, and the outcome will be documented in the patient's medical record and CRF.

Patients can temporarily suspend study treatment if they experience investigational product-related toxicity that requires treatment discontinuation. When the last doses of the investigational products have been administered respectively, patients should be retreated with the investigational products as soon as possible after AEs resolve to baseline or grade 1 (whichever is less severe) (re-dosing is required within 4 weeks for sitravatinib and within 12 weeks for tislelizumab). Sitravatinib should be resumed at a decreased dose level as shown in Table 1. If sitravatinib administration is interrupted due to reasons other than toxicity, this investigational product can be resumed at the same dose. If a patient experiences an AE that is considered to be related to chemotherapy, drug administration may be interrupted. When the last doses of the investigational products have been administered respectively, patients should be retreated with the investigational products as soon as possible after AEs resolve to baseline or grade 1 (whichever is less severe) (re-dosing is required within 3 weeks for the chemotherapy). If the patient is unable to resume medication within the allowable time limit after the last dose, she should be discontinued from receiving the investigational products.

The following dose delays or treatment interruptions are allowable:

- Sitravatinib may be continuously interrupted for up to 28 days. If treatment with sitravatinib is delayed for ≥ 14 days, consideration should be given to resuming treatment at a reduced dose. If interruption of a drug is planned for ≥ 28 days, the principal investigator should be informed before the patient permanently discontinues the investigational product.
- Tislelizumab may be delayed or interrupted for up to 12 weeks. Tislelizumab should be administered (on the same day as sitravatinib, if applicable) if dosing is delayed for ≤ 10 days before a planned dosing cycle (e.g., Cycle 3, Day 1), and all assessments should be made against the original cycle (i.e.,

Cycle 3). If dosing is delayed for more than 10 days, the patient should skip the administration of tislelizumab and proceed to tislelizumab administration on the first day of the next planned cycle (i.e., Cycle 4, Day 1).

No change will be made to the tumor assessment schedule even if the investigational products are delayed.

If the patient is unable to resume medication within the allowable time limit after the last dose, she should be discontinued from receiving the investigational products.

Tislelizumab-related irAEs and dose modification protocol for infusion-related reactions are presented in Appendix 7 and Section 8.7, respectively.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Concomitant Therapy

6.1.1. Permitted concomitant medications/procedures

The investigator may use most concomitant medications and therapies in line with the local standard of care as appropriate to provide supportive care (e.g., antiemetics, antidiarrheals) and protect the patient's interests.

The use of proton pump inhibitors and H_2 antagonists should be avoided (but not excluded) during the administration of the investigational products. Antacids should be preferred over proton pump inhibitors or H_2 antagonists. Antacids should be avoided 4 hours before and 2 hours after clinical investigational treatment.

Systemic corticosteroids given for the control of irAEs must be tapered gradually (see Appendix 7) and be reduced to non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next administration of the investigational products. The short-term use of steroids as prophylactic treatment (e.g., for patients with contrast allergies to diagnostic imaging contrast dyes) will be permitted.

Patients with active hepatitis B defined as either detectable HBsAg or HBV DNA at baseline must initiate antiviral treatment 2 weeks prior to the first dose of the investigational products and continue at least 6 months after the last dose of the investigational products. 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 (AASLD) guidelines because they lack resistance due to long-term use (Panel, 2015; Terrault et al., 2016). The investigator may use other antiviral agents as per local guidelines. Management of antiviral therapy is at the discretion of the investigator; however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.

Palliative (local) radiotherapy is permitted for pain control or prevention of fractures at bone disease sites present at baseline. Lesions receiving palliative radiotherapy should not be target lesions as defined by RECIST v1.1. The investigators should discuss relevant cases and confirm that the patients meet the criteria for palliative radiotherapy before they receive the treatment. In addition, palliative radiotherapy or other local ablation therapy for other non-target lesions is permitted if clinical necessity is determined at the investigator’s discretion. These patients should undergo a tumor assessment on the lesions before receiving radiotherapy, if possible, to exclude PD.

6.1.2. Prohibited concomitant medications/procedures

The following medications are prohibited during the study:

- Any adjunctive antitumor therapy (i.e., chemotherapy, hormone therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicines and traditional Chinese medicinal products] for the treatment of cancer). Chinese herbal medicines and traditional Chinese medicinal products with anticancer activity approved by the NMPA for anticancer treatment (regardless of the type of cancer)
- Live vaccines inoculated within 28 days prior to the first dose of the investigational products and 60 days following the last dose of the investigational products.
- Anticoagulants (e.g., warfarin) or similar drugs requiring therapeutic INR monitoring.

6.1.3. Restricted concomitant medications/procedures

The following medications are restricted during the study:

- Immunosuppressants (except for therapeutic agents associated with AEs).
- Systemic corticosteroids > 10 mg/day (prednisone or equivalent), except for those used to treat or control a drug-related AE (determined as per protocol) or for short-term use as prophylactic treatment.
- Patients should avoid alcohol completely and should avoid other addictive drugs during the study.
- The use of potentially hepatotoxic drugs in patients with impaired hepatic function should be closely monitored.
- Radiotherapy, except for the palliative radiotherapy mentioned in Section 6.1.1.
- The use of herbal medicines is not recommended during study treatment. Patients must inform the investigator of all herbal medicines used during the study.
- Opiates and other medications required for palliative care are permitted. Patients must inform the investigator of all concomitant medications used during the study.

6.2. Potential Interactions Between Investigational Products and Concomitant Medications

Sitravatinib is not considered a compound that tends to be inhibited by drug-drug interactions (DDI), as its metabolism involves a variety of enzymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4.

Based on the results of the *in vitro* CYP inhibition/induction assay indicating high plasma protein binding and potency less than 0.1 μM, sitravatinib is considered to have a low risk for DDI induction at the expected clinical dose and exposure level.

According to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 guideline, it is recommended to avoid drugs that may prolong the QT/QTc interval or cause torsade de pointes. Please refer to Appendix 9 for the list of drugs and substances that should be avoided or used with caution during treatment with sitravatinib.

Sitravatinib in combination with tislelizumab is unlikely to result in clinically relevant DDI based on absorption, metabolism, elimination, or protein binding. Tislelizumab is a monoclonal antibody drug (mAb) and is intravenously administered, whereas sitravatinib is a small molecule drug administered orally. Similar to most therapeutic proteins, tislelizumab is not expected to be metabolized by CYP or other drug metabolizing enzymes and is unlikely to influence CYP or other metabolizing enzymes in terms of inhibition or induction.

Paclitaxel is metabolized by cytochromes CYP2C8 and CYP3A4. Cautions are required when nab-paclitaxel is used in combination with known CYP2C8 and CYP3A4 inhibitors.

7. STUDY ASSESSMENTS AND PROCEDURES

Appendix 1 provides an overview of study-specific assessments and procedures as well as allowable time windows. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the patient's medical record.

Unless an acceptable time window is specified, all assessments will be performed on the specified visit day. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment unless otherwise noted. Laboratory results are required to be reviewed prior to administration. Drug administration can be initiated only when clinical assessments and local laboratory test values (which must be obtained prior to any administration) have been reviewed and judged as acceptable as per the protocol.

If the timing of a protocol-mandated study visit coincides with holidays, weekends, or other events, the visit should be rescheduled on the nearest feasible date, with subsequent visits conducted according to the original schedule calculated from Cycle 1 Day 1.

7.1. Screening Period

Screening assessments will be completed within 28 days prior to the first dose of the investigational products. Patients who agree to participate in this study will sign the ICF prior to undergoing any screening procedure. The screening procedure starts from Day 1 of the screening period. Patients who are suspected or known to have severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer must undergo a pulmonary function test (refer to Appendix 1 for details). Screening assessments may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

Unless otherwise specified, results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of the investigational products can be used for the purposes of screening rather than repeating such tests.

This section describes only the procedures to be conducted during the screening visit. For the description of other assessments that are conducted during screening as well as throughout the study, refer to safety assessment (Section 7.3) and tumor and response assessments (Section 7.4).

Rescreening can be conducted under specific conditions (for example, patients fail to meet the laboratory criteria but have results close to the laboratory criteria, which are not caused by rapidly deteriorating disease or PD and can be corrected) after careful evaluation by the investigator. However, rescreening is allowed only once.

7.1.1. Demographics and medical history

Demographic data will include sex, date of birth (or age), and race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer; reproductive status (i.e., of childbearing potential or no childbearing potential); history of alcohol use and tobacco use (i.e., former or current or never); and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic drugs, and nutritional supplements) given within 30 days prior to the first dose of the investigational products.

Cancer history involves assessments of prior surgery, prior radiotherapy, and prior drug therapy, including drug start and discontinuation dates, best response, and reason for discontinuation. Information on radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Females of childbearing potential and contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 5 for contraception guidelines and definitions of "females of childbearing potential" and "females with no childbearing potential"

7.1.3. Informed consent form and screening records

A written ICF for voluntary participation in the study must be obtained from the patients before any study-specific procedures are performed. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study center.

Prior to the first dose of the investigational products, all screening assessments must be completed and reviewed to confirm that the patients meet all eligibility criteria. The investigator will document screening information in the CRF to learn details about all screened patients and to confirm the eligibility or document the reasons for screening failure (as applicable).

7.1.4. Pulmonary function tests

Patients who are suspected or known to have severe respiratory disorder or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function tests, which may include but not limited to spirometry and

assessment of pulmonary diffusion capacity at screening to assist in the determination of suitability for inclusion in this study.

7.2. Enrollment

The investigator will assess the eligibility of each patient. All screening procedure results and relevant medical history must be available before the eligibility is determined. The patients meet all inclusion criteria can be enrolled, and those meeting any one of exclusion criteria shall not be enrolled. No eligibility waiver will be granted.

7.3. Safety Assessment

7.3.1. Vital signs

Vital signs include body temperature (°C), pulse rate, and blood pressures (systolic and diastolic) measured 10 minutes after resting.

7.3.2. Physical examination

During the screening visit, a complete physical examination will be conducted, including assessments of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. Any abnormality identified at screening will be graded according to NCI-CTCAE v5.0 and recorded on the CRF with appropriate disease/condition terms.

At subsequent visits (or as clinically indicated), symptom-directed and limited physical examinations will be performed. Changes from baseline will be recorded. New or worsened clinically significant abnormalities will be recorded as AEs on the AE CRF. Refer to Section 8.3 for AE definitions and reporting and follow-up requirements.

7.3.3. Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix 3) will be assessed during the study.

7.3.4. Laboratory safety tests

Assessments on hematology, clinical chemistry, coagulation, and urinalysis results obtained by the local laboratory will be conducted, of which certain items will be collected as specified in Appendix 1.

If laboratory tests required for screening are not completed within 7 days prior to the administration of the investigational products on Cycle 1 Day 1, these tests (hematology, clinical chemistry, and urinalysis) should be repeated before the administration of the investigational products, and the results should be reviewed. In

the study, hematology and clinical chemistry tests specified in Appendix 2 should be performed once a week for the first 2 cycles. All patients in this study should undergo hematology, clinical chemistry, and urinalysis tests at the beginning of each cycle and at the EOT visit. After Cycle 1, laboratory safety tests should be performed within 48 hours prior to the administration of the investigational products, and the results should be reviewed. For creatine kinase (CK) and creatine kinase-myocardial isoenzyme (CK-MB) tests as well as coagulation test, refer to Appendix 2.

The investigator may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decision.

Additionally, the following tests will be performed in this study:

- A urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed within 7 days prior to the administration of the investigational products, and the result documented should be negative. During the treatment, a urine or serum pregnancy test will be conducted prior to the administration of the investigational products every 3 treatment cycles and at the EOT visit. If the result of the urine pregnancy test is positive or suspected, a serum pregnancy test must be performed. A pregnancy test (urine or blood) must be completed prior to the administration of the investigational products every 3 treatment cycles and at the EOT visit, and the results documented should be negative.
- A thyroid function test (TFT) (thyroid-stimulating hormone [TSH], free T3, and free T4) will be performed at screening, every 3 cycles thereafter (i.e., Day 1 of Cycles 4, 7, 10, etc.), and at the EOT visit. Repeating this test is not required at the EOT visit if it is ≤ 63 days since the last test.
- All patients treated with tislelizumab will be tested for CK and CK-MB as part of clinical chemistry (see Appendix 2). Troponin I and/or troponin T tests may be performed if the CK-MB test is not available at local study centers. If tislelizumab has been permanently discontinued, CK and CK-MB tests will no longer be required. Patients with a history of heart disease who receive sitravatinib monotherapy (patients in Cohort A or those have discontinued tislelizumab) may undergo CK and CK-MB tests as clinically indicated.

7.3.5. Hepatitis B and C tests

The tests will be performed by local study centers at screening and will include HBV/HCV serology test (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

Patients who are positive for HBV DNA at screening will be tested for viral load once every 4 cycles and at the EOT visit.

7.3.6. Electrocardiogram

To achieve the purpose of safety monitoring, 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 study file at the study center.

When an ECG examination coincides with blood drawing, the ECG should be performed before blood sample collection. Patients should rest in lateral or supine position for at least 10 minutes before each ECG examination (see Appendix 1).

7.3.7. Multiple gated acquisition scan and echocardiography

Cardiac function will be assessed at screening and every 12 weeks thereafter (during the treatment). Assessment by MUGA scanning is preferred for the purpose of the study. ECHO assessment can be used instead if necessary. The method used for each patient should be consistent throughout the study.

7.3.8. Adverse event

AEs will be graded and recorded according to NCI-CTCAE v5.0 (NCI-CTCAE 2017) throughout the study. Characterization of toxicities will describe severity, duration, and time to onset of event.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.4. Tumor and Response Assessments

A tumor imaging examination should be performed within 28 days before the start of treatment and as close to the treatment start time as possible. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of the investigational products can be used for screening rather than repeating the standard-of-care tests. The radiological assessment of tumor response will be performed once approximately every 6 weeks (± 7 days).

Screening assessment and each subsequent assessment must include a chest computed tomography (CT) scan (oral/intravenous contrast agent, unless contraindicated) and an abdomen magnetic resonance imaging (MRI). Bone scans and head CT or MRI may be performed when they are considered necessary by the clinician as baseline examinations for tumors. Throughout the study, the same imaging procedures as those used to evaluate lesions during screening are required (e.g., the same contrast plan is required for CT scan). All known lesions must be documented at screening and reassessed at subsequent tumor assessments.

- If clinically indicated, brain imaging (MRI or CT) should be performed at the time of patient screening (≤ 28 days prior to signing the ICF).
- If a patient is known to have a contraindication to CT contrast agent or develops a contraindication during the study, a non-contrast CT of chest plus a contrast-enhanced MRI of abdomen (if possible) should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99 m [TC-99 m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening but not seen on subsequent CT or MRI scans or if clinically indicated, TC-99 m or PET bone scans should be performed when CR in target lesion is suspected or when PD in bone is suspected.
- CT scans of neck or limbs should also be performed if clinically necessary throughout the study and if the evidence of metastatic disease in these sites is available at screening. The assessment methods for other target lesions and non-target lesions based on RECIST v1.1 may be used at the discretion of the investigator.

Tumor response will be assessed using RECIST v1.1 (see Appendix 8). If possible, the assessment should be performed by the same assessor to ensure the consistency between visits. After the first documentation of tumor 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 time point.

For immunotherapy (e.g., tislelizumab), a pseudo-progression may occur due to immune-cell infiltration and other mechanisms, which can result in a significant increase in the size of existing tumors or the emergence of new tumor lesions. Therefore, if the investigator suspects that the radiologically detected PD is a pseudo-progression, the patient may continue to take tislelizumab until the PD is confirmed by subsequent repeat imaging at least 4 weeks later but no more than 6 to 8 weeks after the initial recording date of the PD. The following criteria must be met in order to treat patients with suspected pseudo-progression:

- Absence of clinical symptoms and signs of PD (including clinically significant worsening laboratory values)
- Stable ECOG performance status of ≤ 1

- Absence of rapid PD or of progressive tumor at critical anatomical sites (e.g., cord compression) that requires urgent alternative medical intervention.
- The investigator must obtain the written ICFs signed by patients for treatment following radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue the investigational products following the investigator-assessed progression must be agreed by the investigator and documented in the study records. Another informed consent from patients is required in this case.

Patients who have discontinued the study treatment prematurely for reasons other than PD (e.g., toxicity) will continue to undergo the originally scheduled tumor assessments until initiation of other anticancer treatment, development of PD, withdrawal of consent, loss to follow-up, death, or study termination, whichever occurs first.

Tumor assessments should be performed as scheduled, regardless of whether the study treatment is ongoing or discontinued.

7.5. Visit Windows

All visits must occur on the scheduled days (± 3 days), unless otherwise noted (see Appendix 1). Unless an acceptable time window is specified, all assessments will be performed on the specified visit day. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to administration.

If the timing of a protocol-mandated study visit coincides with holidays, weekends, or other events, the visit should be rescheduled on the nearest feasible date (see Appendix 1 for the visit window), with subsequent visits conducted according to the planned schedule every 3 weeks from Cycle 1 Day 1.

7.6. Unscheduled Visits

Unscheduled visits may be performed at any time as required by the patient or the investigator, including vital signs/focused physical examination, ECOG performance status, AE review, concomitant medications and procedure review, imaging assessments, physical examination of liver, spleen, and lymph nodes, disease-related constitutional symptoms, and hematology and chemical laboratory assessments. The date and reason for an unscheduled visit must be recorded in the source document.

If an unscheduled visit is necessary to assess toxicity or for suspected PD, diagnostic tests may be performed based on the investigator's assessment as appropriate.

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated with Sitravatinib and Tislelizumab

For treatment of solid tumors, sitravatinib and tislelizumab are investigational products in the stage of clinical development currently. Patient safety data for sitravatinib and tislelizumab are limited, and their complete safety profiles have not been characterized yet. The following recommendations are based on results from non-clinical and clinical studies of sitravatinib or tislelizumab and published data of other molecules in the same biological category.

PD-1/PD-L1 signaling pathway is involved in the mechanism of peripheral immune tolerance; therefore, such therapy may increase the risk of irAE, specifically the induction or enhancement of autoimmune conditions. Common AEs in anti-PD-1 treatment are presented in Section 8.7.

Guidelines for the management of more specific potential AEs arising from the treatment with sitravatinib or with anticancer drugs of the same category are shown in Section 8.8.

Although most irAEs observed in the treatment with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential serious complications. Recommended handling procedures for suspected irAEs are detailed in Appendix 7.

8.2. Risks Associated with Nab-Paclitaxel

For TNBC patients receiving nab-paclitaxel, common TRAEs include anemia, constipation, headache, neutrophils reduced, leukopenia, ALT increased, peripheral neurotoxicity, etc.; grade 3 or above TRAEs include neutrophils reduced, leukopenia, ALT increased, AST increased, gamma-glutamyltransferase increased, etc.

8.3. General Management Plan for Safety Concerns

8.3.1. Eligibility criteria

Eligibility criteria are intended to protect the safety of patients enrolled in this study. Results of non-clinical toxicological studies and clinical data of sitravatinib and tislelizumab, as well as non-clinical/clinical data of other RTK inhibitors and PD-L1/PD-1 inhibitors are taken into account in the development of the criteria. Specifically, patients with active autoimmune diseases occurring in the study or with a history of recurrent autoimmune diseases, patients who have received allogeneic

stem cell or organ transplants, and patients who have received live vaccines within 28 days before the first dose will be excluded from this study (see Section 4.2).

8.3.2. Safety monitoring plan

Safety will be evaluated in this study by monitoring all AEs, and AEs will be defined and graded according to NCI-CTCAE v5.0. The patient's safety (including laboratory test values) will be evaluated as per the schedule in Appendix 1. Moreover, clinical laboratory results must be reviewed before the start of each cycle.

In this study, all enrolled patients will undergo clinical assessments and standard laboratory tests before and at regular intervals during their participation in this study. Safety assessment will consist of medical interviews, recording of AEs, physical examinations, laboratory tests (hematology, chemistry, etc.), and other assessments. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All AEs occurring during the study and 30 days after the last dose of study treatment or before the initiation of other anticancer therapy (AEs occurring since the first dose of the investigational products and SAEs occurring since the signing of ICF) will be recorded, whichever occurs first. At the end-of-treatment, ongoing AEs related to the study treatment will be followed until the events have achieved complete response to baseline or grade ≤ 1, the events are assessed as stable by the investigator, the patient is lost to follow up, the patient withdraws the consent, or it has been determined that study treatment or participation is not the cause of the AEs.

irAEs within 90 days after the last dose of tislelizumab will be recorded, regardless of whether the patient starts a new anticancer therapy or not. Drug-related SAEs will continuously be recorded by the investigator after treatment discontinuation until death, withdrawal of consent, or loss to follow up (whichever occurs first).

The investigator is required to report all AEs (including pregnancy-related AEs) during the safety reporting period.

The potential safety concerns anticipated in this study, as well as measures intended to avoid or minimize toxicities, are outlined in the following sections.

8.4. Adverse event

8.4.1. Definition and reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including increase in severity, increase in frequency, extended duration, and/or being accompanied by a significantly worse outcome
- New conditions detected or diagnosed after investigational product administration, even though they may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either an investigational product or a concomitant 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 records (e.g., hospital progress notes, laboratory reports, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding the AE or SAE in the CRF.

8.4.2. Assessment of severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. All AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not applicable to the 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; mild, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to the AE

Note: The terms "severity" and "seriousness" are not synonymous. Severity is a measure of intensity (for example, 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 requirements and serves as the guide

for defining the obligation from the sponsor to report to applicable regulatory authorities in terms of regulatory system.

8.4.3. Assessment of causality

The investigator is obligated to evaluate the relationship between the investigational products and the occurrence of each AE or SAE using the 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 investigational products should be considered and investigated. The investigator should refer to the IBs of sitravatinib and tislelizumab in the determination of his/her assessment.

A case in which an SAE has occurred but the information provided by the investigator in the initial report is little may occur. However, it is very important that the investigator should assess and record the causality for each SAE, since the causality assessment is one of the criteria used to determine whether to report to the regulatory authorities. The investigator may change his/her original assessment conclusion of causality in light of follow-up information, and revise the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related". An AE is considered related if "a reasonable possibility" that an AE is caused by the investigational product (i.e., the possible causality is indicated by facts, evidence, or parameters) is present. A number of factors should be considered in making this assessment, including:

Temporal relationship of the AE to the drug administration of study treatment/study procedure

Whether an alternative etiology has been identified

Mechanism of action of the investigational product

Biological plausibility

An AE should be considered "related" to the investigational product if any of the following criteria are met, otherwise the event should be assessed as not related:

There is clear evidence to suggest the causality, and other possible contributing factors can be ruled out

There is evidence to suggest the causality, and the influence of other factors is unlikely

There is some evidence to suggest the causality (e.g., the AE occurred within a reasonable time after administration of the investigational product). However, a

potential alternative cause may be present (e.g., the subject's clinical conditions and other concomitant AEs).

8.4.4. Follow-up of adverse events

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

All AEs and SAEs documented at a previous visit/contact and designated as unresolved should be followed at subsequent visits/contacts.

All AEs and SAEs will be followed until they are resolved, the conditions stabilize or are considered chronic, the AEs or SAEs are otherwise explained, the patient is lost to follow-up, or the patient withdraws the consent. The investigator will ensure that the follow-up covers any supplemental investigations as indicated to elucidate the nature and/or causality of the AEs or SAEs. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The investigator should perform or arrange others to perform the supplemental measurements and/or assessments according to AEs to elucidate the nature and/or causality of the AE or SAE as fully as possible. If a patient dies during participation in the study or during a recognized follow-up period, the post-mortem report (including histopathological results) should be archived.

8.4.5. Laboratory abnormalities

Laboratory abnormalities (e.g., serum chemistry, full blood count, coagulation, or urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. These include clinically significant laboratory abnormalities or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinical significance will be judged by the investigator. In general, these laboratory abnormalities or other abnormal assessments:

Are associated with clinical signs or symptoms, or

Require active medical intervention, or

Lead to drug interruption or discontinuation, or

Require close observation, more frequent follow-up assessment, or

Require further diagnostic investigation.

Grade ≥ 3 abnormalities detected in liver function test (LFT) (ALT, AST, or total bilirubin) are required to be reported to the sponsor within 24 hours upon notification

according to the SAE reporting procedures. The LFT should be repeated as per the schedule in Appendix 7.

8.5. Definition of Serious Adverse Event

An SAE is any adverse medical event that, at any dose:

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongs hospitalization

  Note: In general, hospitalization signifies that the patient is admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observations and/or treatments that are not 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 ADL. This definition is not intended to include events of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere or prevent ADL, but do not constitute a substantial disruption

- Results in congenital anomaly or birth defect
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The followings are NOT considered as SAEs:

- Hospitalization for elective treatment of a pre-existing condition that has not worsened from baseline.
- Hospitalization for social/convenience considerations.
- Scheduled therapy for the target disease of the study, including hospitalizations due to transfusion support or convenience.

8.6. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any serious adverse reaction that is unexpected (i.e., not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the IB.

8.7. Timing, Frequency, and Method of Recording Adverse Events and Serious Adverse Events

8.7.1. Adverse event reporting period

After the ICF has been signed and prior to the administration of the investigational products, only SAEs should be reported.

After initiation of the investigational products, all AEs and SAEs, regardless of relationship to the investigational products, will be reported until either 30 days after the last dose of investigational products or initiation of a new anticancer therapy, whichever occurs first. irAEs (serious or non-serious) should be recorded until 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy or not.

The investigator should report all SAEs that are assessed as related to the investigational products, even after treatment termination.

8.7.2. Proactive inquiry of adverse events

The investigator or designee will learn 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?"

8.7.3. Progressive disease

In this study population, the term "progressive disease" (including fatal PD) that is expected and measured as an efficacy endpoint should not be reported as an AE term. Instead, symptoms, signs, or clinical sequelae that result from PD should be reported as the AE term(s).

For instance, a patient develops pleural effusion resulting from PD of metastasis to lungs. The event term should be reported as "pleural effusion" instead of PD. If a patient experiences a fatal multi-organ failure due to PD, the term "multi-organ

failure" should be reported as the SAE with death as outcome instead of reporting "fatal PD" or "death due to PD".

8.7.4. Death

Death is usually considered as an outcome rather than an event. If the only information available is death and death of unknown cause, the death can be reported as an event, e.g., "death", "death of unknown cause", or "death unexplained".

8.7.5. Pregnancy

If a female patient or the partner of a male patient becomes pregnant while the study therapy is given or within 120 days after the last dose of tislelizumab/sitravatinib, a pregnancy report form is required to be completed to facilitate the follow-up of outcome. Generally, the follow-up should be no longer than 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

An abortion, whether accidental, therapeutic, or voluntary, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the investigational products should be recorded and reported as an SAE.

8.7.6. Expedited reporting to health authorities, investigators, institutional review boards and independent ethics committees, and BeiGene

As the sponsor of this clinical trial, the investigator will promptly assess all SAEs based on cumulative experience in the investigational products to identify and expeditiously report new safety findings to appropriate regulatory authorities, IRB, and IEC according to applicable regulatory requirements.

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

- Sitravatinib IB v8.1 (Aug. 23, 2021) and Tislelizumab IB v9.0 (Oct. 20, 2021)

Additionally, the sponsor should report all SAEs and pregnancy events that meet the protocol-specified collection requirements to BeiGene within 24 hours upon learning about the SAEs and pregnancy events.

8.7.7. Assessing and recording immune-related adverse events

Since anti-PD-1 therapy may cause autoimmune disorders, AEs considered immune-related by the investigator (see Section 8.7.3) should be classified as irAEs and identified as irAEs in the CRF until 90 days after the last dose of tislelizumab.

The investigator should refer to the guidance on diagnostic evaluation and management of irAEs which are commonly seen with immune checkpoint inhibitors, as shown in Appendix 7.

An extensive list of potential irAEs is presented in Table 4. Based on a similar diagnostic process to that of reactions that are presented in more detail in Appendix 7, all conditions similar to those listed should be assessed to determine whether they are irAEs.

8.8. Management of Adverse Events of Special Interest of Tislelizumab

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 1 hour in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, if the infusion is well-tolerated in the first two cycles, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions, and irAEs according to the NCI-CTCAE criteria are outlined below.

8.8.1. Infusion-related reactions

The symptoms of infusion-related reactions include pyrexia, chills, 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, and cardiogenic shock. Patients will be closely monitored for such reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medications, including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen, must be given to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions caused by tislelizumab are provided in Table 3.

Table 2: Treatment modifications for symptoms of infusion-related reactions caused by tislelizumab

NCI-CTCAE grading	Treatment modifications of tislelizumab
Grade 1 — mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	The infusion rate is decreased by 50%. Any worsening is closely monitored. Medications are given as needed. Subsequent infusions should be given after premedication and at the decreased infusion rate.

NCI-CTCAE grading	Treatment modifications of tislelizumab
Grade 2 — moderate Therapy or infusion interruption indicated and symptomatic treatment be instituted immediately (e.g., antihistamines, NSAID, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Infusions are stopped. Infusions may be resumed at 50% of the previous rate once infusion-related reactions have been resolved or decreased to grade 1 in severity. Any worsening is closely monitored. Appropriate medications should be given as described below. Subsequent infusions should be given after premedication and at the decreased infusion rate.
Grade 3 — severe Persisted (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Infusions are stopped immediately. Appropriate medications should be given as described below. The patient should withdraw from the treatment with the investigational products.
Grade 4 — life threatening Life-threatening consequences; urgent intervention indicated.	Infusions are stopped immediately. Appropriate medications should be given as described below. The patient should withdraw from the treatment with the investigational products. Hospitalization is recommended

Abbreviations: h = hour; IV = intravenous injection; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug.

Once the infusion rate of tislelizumab has been decreased by 50% or suspended due to an infusion-related reaction, the subsequent infusions must be given with premedication and at a low rate. If the patient develops an infusion-related reaction (grade ≥ 2) for the second time at a low infusion rate, the infusion should be stopped, and the patient should discontinue tislelizumab.

Infusion reaction at NCI-CTCAE grade 1 or 2: Appropriate medications should be given as per the type of the reaction. These include but not limited to antihistamines (e.g., diphenhydramine or equivalent), antipyretics (e.g., acetaminophen or equivalent), and if indicated, oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, the patient should receive oral premedication with antihistamines (e.g., diphenhydramine or equivalent) and antipyretics (e.g., acetaminophen or equivalent), and should be closely monitored for clinical signs or symptoms of infusion reactions.

Infusion reaction at NCI-CTCAE grade 3 or 4: Appropriate medications should be given immediately as per type and severity of the reaction. These include but not limited to oral or IV antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.8.2. 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 from the Working Group of the Resuscitation Council (UK). The patient should be notified to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and 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 infusion must be immediately stopped and the patient should discontinue the study.

The patient will be injected with epinephrine and infused with dexamethasone if hypersensitivity reaction is observed, then a monitor will be connected immediately, and ICU should be alerted for possible transfer if necessary.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (i.e., 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of investigational product infusion. Alternative treatments for pyrexia (i.e., acetaminophen) may be given to patients at the discretion of the investigator.

8.8.3. Immune-related adverse events

Although sitravatinib may have immune-stimulating effects, no autoimmune AEs have been reported in any clinical trial, including the combination with nivolumab, and such AEs are not regarded as class effects of the drug. However, when sitravatinib is administered in combination with PD-1 inhibitors, it should be noted that sitravatinib may exacerbate or promote the occurrence of these AEs.

irAEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (e.g., combination drugs, infectious disease, PD, metabolism, toxin, or other neoplastic causes) with appropriate diagnostic tests which may include but not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, systemic steroids, other immunosuppressants, or endocrine therapy are required for the AE, and the occurrence of AE is consistent with the result of an immune-mediated mechanism of action, the irAE indicator in the eCRF AE page should be checked. In the most common case, irAEs and non-specific irAEs caused by tislelizumab may

have clinically relevant toxicities that possibly overlap with those of sitravatinib-related mild to moderate AEs (e.g., rash and colitis). The time to onset may help to distinguish AEs resulting from autoimmune effects and those resulting from non-specific toxicities.

A list of potential irAEs is shown in Table 4. When the patients who receive tislelizumab experience the conditions similar to those listed, it should assess and determine whether they are immune-related.

Recommendation for diagnostic assessment and management of irAEs is based on the latest ESMO and ASCO guidelines (Brahmer et al., 2018; Haanen et al., 2018), and common immune-related toxicities are detailed in Appendix 7. For any AEs not listed in Appendix 7, please refer to the latest ASCO Clinical Practice Guideline (Brahmer et al., 2018) for further guidance on diagnostic assessment and management of immune-related toxicities.

Table 3: Immune-related adverse events

Body system involved	Events
Skin (mild-common)	Pruritus or maculopapular rash; vitiligo
Skin (moderate)	Blistering or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare):	Full-thickness necrolysis/Stevens Johnson syndrome
Gastrointestinal	Colitis (including diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) increase; bowel perforation
Endocrine	Thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, e.g., fatigue, weakness, and weight increased; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	Localized pneumonia/diffuse alveolitis
Eye	Episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	Arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis; meningoencephalitis; myositis
Hematology	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 irAEs are detailed in Appendix 7.

In the event of an irAE during study treatment, sitravatinib and tislelizumab should be interrupted until the event stabilizes to grade ≤ 1. If a sitravatinib-related toxicity is not relieved to grade ≤ 1 within 4 weeks or a tislelizumab-related toxicity is not relieved to grade ≤ 1 within 12 weeks, the investigational product should be discontinued upon consultation with the sponsor. Treatments should be permanently discontinued in patients who experience any recurrent event of the same or greater severity.

8.9. Guidelines for Management of Sitravatinib-Specific Adverse Events

8.9.1. Treatment of sitravatinib-related non-hematological toxicity

A grade ≥ 3 non-hematological toxicity considered to be sitravatinib-related should be managed with interruption of sitravatinib (at a reduced dose or not) until the toxicity is resolved to grade ≤ 1 or baseline value. The treatment can be resumed at the same dose if the toxicity is well controlled with conventional supportive care (e.g., antiemetics, antidiarrheals, or electrolyte supplements); otherwise, the treatment can be resumed at a reduced dose, as shown in Table 5. This method is also applicable to manage a relapse of toxicity. Permanent discontinuation of study treatment should be considered if the treatment is interrupted for ≥ 28 days.

Table 4: Sitravatinib dose modification — non-hematological drug-related toxicity

Toxicity	Treatment delay	Dose modification
Grade 1	Implementation is based on the investigator's and the patient's discretion	
Grade 2 — asymptomatic	Implementation is based on the investigator's and the patient's discretion	
Grade 2 — symptomatic	Implementation is based on the investigator's and the patient's discretion	Decrease to the next lower dose level is recommended
Grade 3 or 4	Treatment is interrupted until the toxicity returns to grade ≤ 1 or baseline level	The treatment is resumed at a dose lower than the toxicity-induced dose by one or more level(s). Exceptions are presented in the footnote[a]

[a] Patients may resume the treatment at the same dose in the following cases:

- Grade 3 nausea, vomiting, or diarrhea that are managed with supportive care and persist for ≤ 72 hours

- Grade 3 or 4 electrolyte abnormality that is not clinically complicated and relieves spontaneously or with conventional medical treatment within 72 hours
- Grade 3 fatigue that persists for ≤ 8 days
- Grade 3 or 4 amylase or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis.

8.9.2. Management of sitravatinib-related hematological toxicity

Hematological toxicity is not a common cause of treatment interruption or discontinuation of sitravatinib. If grade ≥ 3 hematological events are observed and considered causally related to sitravatinib, the initial management method should be treatment interruption. In addition, the dose of sitravatinib should be reduced as appropriate in the following cases:

- Grade 3 or 4 neutropenia with pyrexia
- Grade 4 neutropenia persisting for > 7 days
- Any persistent grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant hemorrhage

8.9.3. Guidelines for dose modification for sitravatinib-specific adverse events

For increased blood pressure and hepatic transaminase that are unlikely to be immune-mediated, the guidelines for dose modification are shown in Table 6 and Table 7. The guidelines for management of Hy's Law cases are also provided below. The guidelines for management of sitravatinib-specific AEs are described as follows.

Table 5: Sitravatinib dose modification for increased blood pressure

Toxicity	Dose interruption	Dose modification
Grade 1 or 2 hypertension	Implementation is based on the investigator's discretion	
Grade 3 hypertension without clinically significant increase in blood pressure, as defined below	Investigator's discretion. Anti-hypertensives described in Section 8.8.4 are considered	
Grade 3 hypertension, with clinically significant increase in blood pressure, is defined as either an increase of ≥ 30 mmHg in systolic blood pressure to ≥ 180 mmHg or increase of ≥ 20 mmHg in diastolic blood pressure to ≥ 110 mmHg, which is confirmed by repeated test after at least 5 minutes	Treatment is interrupted until the toxicity returns to grade ≤ 2 or baseline level	Investigator's discretion

Toxicity	Dose interruption	Dose modification
Grade 4 hypertension	Treatment with sitravatinib is discontinued	Treatment with sitravatinib is discontinued

Abbreviation: BP = blood pressure

In cases where transaminase increased is not immune-mediated, the treatment should be conducted at the discretion of the investigator based on the clinical factors taken into account. The recommended sitravatinib dose modification is presented in Table 7.

Table 6: Sitravatinib dose modification for hepatic transaminase increased

Toxicity	Dose interruption	Dose modification
Grade 1 (> ULN to 3.0 × ULN1, if baseline level is normal; 1.5 to 3.0 × baseline value, if baseline level is abnormal)	Implementation is based on the investigator's and the patient's discretion	
Grade 2 (> 3.0 to 5.0 × ULN, if baseline level is normal; > 3.0 to 5.0 × baseline value, if baseline level is abnormal)	Not required	The dose is reduced by 1 dose level
Grade 3 or 4 (> 5.0 × ULN, if baseline level is normal; > 5.0 × baseline value, if baseline level is abnormal)	Treatment is interrupted until the toxicity returns to grade ≤ 1 or baseline level	The dose is reduced by 1 dose level if the toxicity recovers within 22 days. Treatment with sitravatinib is discontinued if the toxicity does not recover within 22 days.

Abbreviation: ULN = upper limit of normal.

Management of Hy's Law cases

In the event that a patient develops concurrent increase in AST and/or ALT ≥ 3 × ULN, bilirubin ≥ 2 × ULN but without concurrent increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN), which is not attributable to liver metastases or biliary obstruction, sitravatinib and tislelizumab should be permanently discontinued and steroids should be given.

8.9.4. Hypertension

It has been reported that sitravatinib can induce hypertension, including grade 3 hypertension events. Considering the treatment for patients with grade 3 hypertension and without clinically significant increase in blood pressure, dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine (see Table 6) can be considered if antihypertensive treatment is required. In case of grade 3 hypertension with clinically significant increase in blood pressure, it is recommended to interrupt sitravatinib until blood pressure is controlled. The treatment with sitravatinib may be

resumed at the same or a lower dose at the discretion of the investigator. If serious hypertension recurs, the investigator can change the medical management of the patient, reduce the dose of sitravatinib, or discontinue the study treatment as appropriate. In the event of grade 4 hypertension, sitravatinib should be permanently discontinued (see Table 6).

8.9.5. Palmar-plantar erythrodysaesthesia

DLT: palmar-plantar erythrodysesthesia (PPE) has been reported in phase I study of sitravatinib. Measures that can be taken to manage PPE include: avoid exposure of hands and feet to hot water or to other sources of heat during dish washing or bathing; avoid activities that cause unnecessary force or friction (tenderness) on the hands or feet; avoid contacting with harsh chemicals such as cleaning products; avoid using tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers; wear loose fitting, well-ventilated shoes and clothes. Treatments may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications (such as corticosteroid creams). In more severe cases, dose interruption or reduction is required.

8.9.6. Diarrhea/colitis

Diarrhea has been reported in the treatment with sitravatinib, but the mechanism remains unclear, as with other small molecule RTK inhibitors. Patients should be informed that diarrhea is a possible side effect and advised to take loperamide or similar drugs if diarrhea occurs. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt the treatment, but the treatment can be restarted once diarrhea is controlled. The investigator should also assess whether diarrhea may be attributable to the irAE of colitis.

In the event of abdominal pain or blood in abdominal mucus or stool or peritoneum, the possibility of immune-mediated colitis should be strongly suspected, as these features are not usually observed in sitravatinib-related diarrhea. Typically, diarrhea observed in the treatment with sitravatinib will be improved within a few days after study treatment interruption, and the patient can be closely observed, which may help determine the most likely causality.

8.9.7. Hemorrhagic events

No risk of hemorrhagic events with sitravatinib has been reported; however, hemorrhagic events have been reported with inhibitors of VEGFR. Patients with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and interruption of treatment is recommended for patients developing clinically significant hemorrhage.

8.9.8. Thrombotic events

Though thrombotic events (e.g., pulmonary embolism) have been reported with sitravatinib and with inhibitors of VEGFR, the risk of such events due to sitravatinib is unknown. Precautions should be taken for patients who have recently developed clinically significant thrombotic events, and the treatment should be discontinued in the event of clinically significant thromboembolic complications such as acute myocardial infarction or serious pulmonary embolism.

8.9.9. Non-immune-mediated thyroid dysfunction

Hypothyroidism and TSH elevation have been reported in patients taking sitravatinib. Patients diagnosed with hypothyroidism should receive the hormone replacement therapy and may continue the treatment with sitravatinib at the investigator's discretion.

8.9.10. Decreased left ventricular ejection fraction

Decreased LVEF has been reported with sitravatinib. In addition, during the study, decreases of LVEF to < 50% were observed in patients undergoing scheduled MUGA scan or ECHO. Interruption and/or dose reduction of sitravatinib should be performed in the event of LVEF decrease < 50% but > 20% from baseline. Discontinuation should be considered for patients in an urgent need of hospitalization for treatment of congestive heart failure (CHF).

8.9.11. Proteinuria

Although the risk of proteinuria due to sitravatinib is unknown, other inhibitors of the VEGFR pathway have been reported to induce proteinuria. Patients who develop ≥ 2+ proteinuria should undergo 24-hour urine collection to assess the urine protein; the treatment with sitravatinib should be discontinued in the presence of ≥ 2 g of proteinuria/24 hours and may be resumed when the protein level decreases to < 2 g/24 hours. Patients who develop nephrotic syndrome should withdraw from the treatment with sitravatinib.

9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1. Statistical analyses

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released.

Unless otherwise stated, the trial data will be summarized by nature using the following descriptive statistics:

- Continuous variables: number of non-missing observations, mean, SD, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of non-missing observations (N), median, minimum, and maximum. Kaplan-Meier (KM) event rates for specific time-to-event variables may also be provided.

9.1.1. Analysis set

- The safety set (SS) will include all the patients who have received at least 1 dose of any investigational product (any drug in the combination therapies).
- For Cohort A/C: The efficacy evaluable analysis set includes all the patients who have received at least 1 dose of any investigational product with measurable lesions at baseline (according to RECIST v1.1) and have at least 1 evaluable post-baseline tumor assessment (the patients who withdraw or die due to progressive disease prior to the first post-treatment tumor assessment shall also be included).
- For Cohort B: The efficacy evaluable analysis set includes all the patients who have received at least 1 dose of any investigational product with measurable lesions at baseline (according to RECIST v1.1) and have at least 1 evaluable post-baseline tumor assessment (the patients who withdraw due to ≥ grade 3 TRAEs, experience progressive disease, or die before the first post-treatment tumor assessment shall also be included).

9.1.2. Patient disposition

The number of patients treated, the number of patients who discontinue the investigational products and/or study, and the number of patients with important protocol deviations will be counted. The primary reasons for investigational product discontinuation will be summarized according to the category in the CRF. The end-of-

study status (alive, dead, withdrawing the consent, or lost to follow-up) at the data cut-off date will be summarized using the data from the CRF.

Important protocol deviations will be summarized and listed by category.

9.1.3. Demographic and other baseline characteristics

Demographic and other baseline characteristics of the safety analysis set will be summarized using descriptive statistics. Continuous variables include age, body weight, vital signs, time since the initial cancer diagnosis, and time since the advanced/metastatic disease diagnosis; categorical variables include number of systemic therapies before the study, sex, ECOG, country, ethnicity, and metastatic site.

9.1.4. Prior and concomitant medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications are defined as medications that stopped before the first dose of the investigational products. Concomitant medications are defined as medications that (1) started before the first dose of the investigational products and were continuing at the time of the first dose of the investigational products, or (2) started on or after the date of the first dose of the investigational products up to 30 days after the patient's last dose. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, i.e., associated with irAEs or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy and Safety Analyses

9.2.1. Main analyses

In the efficacy analysis set, the investigator will evaluate the ORR hypothesis testing based on the efficacy analysis set according to RECIST v1.1, which will serve as the primary efficacy analysis.

In patients with locally advanced or recurrent TNBC, an ORR of 25% is assumed for the sitravatinib plus tislelizumab regimen under study to indicate an improvement of clinical significance. The estimated historical rate of tislelizumab monotherapy in a similar population is 8%. The null hypothesis and alternative hypothesis are given as follows:

H_0: ORR ≤ 8%

Ha: ORR > 8%

For Cohort A:

In Cohort A, the superiority of the sitravatinib plus tislelizumab regimen over the historical control will be tested using the Simon's two-stage (Simon, 1989) design based on the efficacy analysis set of Cohort A. An interim efficacy analysis will be performed when 12 patients are enrolled. If there is no subject achieving confirmed response among the first 12 patients in stage 1, stage 2 will not be initiated. If the number of subjects achieving response is ≥ 1, stage 2 will be continued until 21 patients are enrolled in total. If the total number of subjects achieving response in stage 1 and stage 2 is > 3, it can be considered that the ORR of the sitravatinib plus tislelizumab regimen is superior to 8%.

For Cohort B:

The efficacy and toxicity of the sitravatinib plus tislelizumab regimen will be monitored simultaneously following a Bayesian optimal phase II (BOP2) (Zhou et al., 2017) design based on the efficacy analysis set of Cohort B (Zhou, Lee & Yuan, 2017). n indicates the sample size for interim analysis, and N indicates the maximum sample size. Y_{eff} and Y_{tox} indicate efficacy (confirmed ORR) and toxicity endpoints (grade ≥ 3 TRAE), respectively, $Y_{eff} = 1$ and $Y_{tox} = 1$ indicate the patient's efficacy and toxicity event, respectively. Assuming that the joint distribution of (Y_{eff}, Y_{tox}) follows a multinomial distribution, there are four possible results: $(Y_1, Y_2) = (1.1), (1.0), (0.1)$, and $(0,0)$. $\mathbf{p} = (P_{11}, P_{10}, P_{01}, P_{00})$ indicates the probability of observing these four results, with $p_{eff} = Pr(Y_{eff} = 1)$, $p_{tox} = Pr(Y_{tox} = 1)$, and $p_{efftox} = Pr(Y_{eff} = 1, Y_{tox} = 1)$.

H_0: $p_{eff} \leq 0.08$ or $p_{tox} \geq 0.57$

Ha: $p_{eff} > 0.08$ and $p_{tox} < 0.57$

The investigational product is unacceptable as it is inefficient or intolerable in case of $p_{eff} \leq 0.08$ or $p_{tox} \geq 0.57$. Therefore, in the course of the study, if any one of the following criteria is met, the drug will be considered ineffective or intolerable, and the enrollment will be stopped:

$$Pr\left(p_{eff} > 0.08 \middle| Interim\ data\right) < \lambda\left(\frac{n}{N}\right)^{\alpha} = 36\%,$$

Or

$$Pr(p_{tox} < 0.57 | Interim\ data) < \lambda\left(\frac{n}{N}\right)^{\alpha} = 36\%,$$

Where, λ = 0.6 and α = 0.74 are the optimized design parameters to achieve the probability of 82% of the maximized correct decision-making when the treatment is safe and effective (i.e., $p_{eff} = 0.25$, $p_{tox} = 0.47$, and $p_{efftox} = 0.12$, assuming that ORR and grade ≥ 3 TRAE rate are two independent variables), while to control the probability of incorrect decision-making at < 10% when the treatment is ineffective or intolerable (i.e., $p_{eff} = 0.08$, $p_{tox} = 0.57$, and $p_{efftox} = 0.05$, assuming that ORR and grade ≥ 3 TRAE rate are two independent variables). During the optimization of design parameters, $\mathbf{p}$ will be set to follow the Dirichlet prior $Dir(0.05,0.03,0.52,0.4)$ with a prior effective sample size of 1 (equivalent to an expected ORR of 0.08 for this patient and an expected grade ≥ 3 TRAE rate of 0.57), and at the same time the prior estimates of p_{eff} and p_{tox} will be ensured to be consistent with the thresholds specified above. In the interim analysis decision, in order to incorporate the historical information already available before the trial, an informative prior $Dir(0.05,0.05,0.45,0.45)$ will be applied to $\mathbf{p}$ when the above decision rules are calculated (equivalent to an expected ORR of 0.10 and an expected rate of ≥ grade 3 TRAEs of 0.50 for this patient). The following decision table of the Bayesian optimal stopping boundary is thus obtained.

Table 1: Bayesian optimal interim stopping boundary and the final margin

Number of patients treated	Termination of enrollment if the number of subjects with response is ≤	or the number of subjects with toxicity is ≥
20	1	13
40	3	23

According to Table 1, the analysis will be performed when the number of enrolled patients reaches at least 20 and 40 separately. In the first 20 patients in the efficacy analysis set, if the number of patients with a confirmed response is less than or equal to 1 or the number of patients with ≥ grade 3 TRAE is greater than or equal to 13, it is advised to stop enrollment. Otherwise, the study will continue. When the number of patients in the efficacy analysis set reaches 40, if the number of patients with a confirmed response is greater than 3 and the number of patients with ≥ grade 3 TRAE is less than 23, the investigational product is considered acceptable. Otherwise, the investigational product is considered unacceptable. The above interim test criteria are non-enforceable (e.g., if the treatment is considered beneficial to the patient group in combination with other conditions, the criteria can be ignored to continue the enrollment). The investigator may decide at any time whether to continue the trial based on a comprehensive assessment of the efficacy and safety).

For Cohort C:

In patients with locally recurrent or metastatic TNBC, an ORR of 65% is assumed for the sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen under study to indicate an improvement of clinical significance. The estimated historical ORR of nab-paclitaxel monotherapy in a similar population is 46%. The null hypothesis and alternative hypothesis are given as follows:

H0: ORR ≤ 46%

Ha: ORR > 46%

The superiority of the sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen over the historical control will be tested using the Simon's two-stage (Simon, 1989) design based on the efficacy analysis set of Cohort C. An interim efficacy analysis will be performed when 18 patients are enrolled. If the number of subjects achieving confirmed response is ≤ 9 among the first 18 patients in stage 1, stage 2 will not be initiated. If the number of subjects achieving response is > 9, stage 2 will be continued until 35 patients are enrolled in total. If the total number of subjects achieving response in stage 1 and stage 2 is > 19, it can be considered that the ORR of the sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen is superior to 46%.

The number and proportion of patients with ORR (CR or PR) in Cohort A, Cohort B, and Cohort C will be summarized separately according to the criteria of NCI-CTCAE v5.0 and RECIST v1.1. In Cohort B, the number and proportion of patients with ≥ grade 3 TRAEs and ORR (CR or PR) will be summarized. The proportion of ≥ grade 3 TRAEs and ORR as well as their two-sided Clopper-Pearson 95% confidence intervals (CIs) will be estimated. For Cohort A and Cohort C, the patients who withdraw early due to progressive disease (PD) or death and thus have no post-baseline tumor assessment performed will be considered as non-responders. For Cohort B, the patients who withdraw early due to ≥ grade 3 TRAEs, progressive disease (PD), or death and thus have no post-baseline tumor assessment performed will be considered as non-responders.

9.2.2. Secondary efficacy analyses

The following analyses will be performed for the patients with locally advanced or metastatic TNBC in Cohort A, Cohort B, and Cohort C according to RECIST v1.1:

Duration of response (DOR): It is defined as the interval from the first recorded objective response (CR or PR) to the time of progressive disease (PD) (according to RECIST v1.1) as assessed by the investigator or death from any cause (whichever occurs first). The analysis of DOR will only include the responders. DOR and the

corresponding quantiles (including medians) will be estimated using the Kaplan-Meier (KM) method. If possible, the generalized Brookmeyer and Crowley method will be used to establish the two-sided 95% CI for medians (Brookmeyer and Crowley, 1982). The DOR censoring rules will follow the FDA's Industry Guideline: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

Disease control rate (DCR): It is defined as the proportion of patients with BOR being CR, PR, and SD according to RECIST v1.1. The analysis of DCR will be performed based on the efficacy analysis set. The two-sided Clopper-Pearson 95% CI of DCR will be established to assess the precision of point estimates.

Progression-free survival (PFS): It is defined as the interval from the date of the first dose of the investigational products to the date of the first development of PD (assessed by the investigator according to RECIST v1.1) or death, whichever occurs first. The analysis of PFS will be performed based on the efficacy analysis set. The curve of KM estimates of PFS over time will be plotted. PFSs and corresponding quantiles (including medians) will be estimated using the KM method. If possible, the generalized Brookmeyer and Crowley method will be used to establish the two-sided 95% CI for medians (Brookmeyer and Crowley, 1982). PFS time point estimate, defined as the percentage of patients in the analysis set who still survive without progressive diseases developed throughout the specified time points (i.e., 3, 6, or 12 months), will be calculated using the KM method, and the corresponding 95% CI will be established using the Greenwood's formula (Greenwood, 1926). The PFS censoring rules will follow the FDA's Industry Guideline: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

1-year OS rate: The overall survival (OS) is defined as the time from the date of the first dose of the investigational products to the date of death from any cause. The analysis of OS will be performed based on the efficacy analysis set. The 1-year OS will be estimated in the efficacy analysis set using the above KM method (Section 9.2.2) and the corresponding two-sided 95% CI will be calculated using Greenwood's formula (Greenwood, 1926). The curve of KM estimates of OS over time will be plotted.

9.2.3. Secondary safety analyses

The following analyses will be performed separately for the patients with locally recurrent and metastatic TNBC in Cohort A, Cohort B, and Cohort C. The safety will be determined by the reporting of AEs and laboratory test values (hematology, clinical chemistry, coagulation, and urinalysis). The results of vital signs, physical examinations, and ECG measurements will also be used to for safety characterization. The severity of AEs will be graded according to NCI-CTCAE v5.0. The incidence of

TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics will be performed for laboratory parameters and vital signs (e.g., n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and their changes from baseline will be calculated.

The number and proportion of patients with ≥ grade 3 TRAEs will also be summarized according to the NCI-CTCAE v5.0 based on the efficacy analysis set for Cohort A. The proportion of ≥ grade 3 TRAEs and the two-sided Clopper-Pearson 95% CI will be estimated.

In addition, the number and percentage of patients who discontinue the study due to AEs according to NCI-CTCAE v5.0 will be summarized based on the efficacy analysis set, and the two-sided Clopper-Pearson 95% CI will be estimated for Cohort B.

9.2.4. Exposure

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

The number (percentage) of patients who experience dose reduction, dose interruption, dose delay, and discontinuation of the investigational products due to AEs will be summarized for each investigational product. The frequency of dose modification and discontinuation will be summarized by category.

All dosing records and calculated summary statistics will be provided in a patient data listing.

9.2.5. Adverse event

The verbatim descriptions of AEs (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (version 18.1 or higher) lowest level term, preferred term, and primary system organ class (SOC).

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 investigational products until up to 30 days following study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. The TEAE classification applies to irAEs recorded within 90 days after the last dose of tislelizumab, regardless of whether the patient has initiated a new anticancer therapy. The summary table only includes AEs that are treatment-emergent. 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 according to SOC and preferred term. A patient will be counted only once by the highest severity grade according to NCI-CTCAE v 5.0 under an SOC and preferred term, even if the patient experienced multiple TEAEs under a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized based on the relationship between TEAE and the investigational products. TEAEs include those events considered by the investigator to be related to the study treatment or with missing assessment of the causality. SAEs, deaths, TEAEs with ≥ grade 3 in severity, irAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, interruption, dose reduction, or dose delay will be summarized.

9.2.6. Laboratory analysis

Clinical laboratory (e.g., hematology, clinical chemistry, urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this study protocol. Descriptive summary statistics will be performed for laboratory parameters (e.g., n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables), and their changes from baseline will be calculated. Laboratory test values will be summarized through visits and worst post-baseline visits.

Laboratory parameters will be graded by NCI-CTCAE v5.0 or higher and summarized. In the summary of laboratory parameters graded by NCI-CTCAE, parameters (e.g., glucose, potassium, and sodium) graded as high and low levels will be summarized separately.

9.2.7. Vital signs

Specific vital signs, such as blood pressure and body temperature, will be summarized and listed. Changes from baseline will be listed for each parameter.

9.3. Exploratory Analysis

Biomarkers will be summarized using descriptive statistics. The relationship between the biomarkers and DOR, PFS, and OS will be explored using the KM method, log-rank test, and/or Cox proportional hazards model; the relationship between the biomarkers and ORR, PD, and DRC will be explored using the logistic regression and/or rate differences.

9.4. Sample Size Calculation

A total of 96 patients are expected to be enrolled in this study. Patients who drop out before the first assessment and thus cannot be included in the efficacy analysis set will be supplemented, and additional 4 to 6 patients may be required.

For Cohort A, a total of 21 patients will receive combination therapy. Based on the Simon's two-stage design, the power of test is approximately 80% to demonstrate the presence of a statistically significant difference between the ORR of the sitravatinib plus tislelizumab regimen under study (assumed as approximately 25%) and the historical ORR of tislelizumab monotherapy being 8% (one-sided α level of 0.1). Among the first 12 patients in the efficacy analysis set, if no subject show confirmed post-treatment response, the study will be terminated. Otherwise, the study will continue. If > 3 responders are observed among all 21 patients in the efficacy analysis set, a statistical superiority of this combination therapy over the historical control of 8% under the set conditions will be declared.

For Cohort B, a total of 40 patients will receive combination therapy. The historical ORR of tislelizumab monotherapy is estimated to be 8% and the historical rate of ≥ grade 3 TRAEs is estimated to be 57%. Assuming that the ORR of the sitravatinib plus tislelizumab regimen to be tested is 25% and the incidence of ≥ grade 3 TRAEs is 47%, 40 patients can show an approximately 82% power to demonstrate that the combination therapy is significantly superior to the historical control (i.e., tislelizumab monotherapy) under the one-sided test level of $\alpha = 0.1$, based on the Bayesian optimal phase II (BOP2) design, with the efficacy and toxicity of the combination therapy monitored.

For Cohort C, a total of 35 patients will receive combination therapy. Based on the Simon's two-stage design, the power of test is approximately 80% to demonstrate the presence of a statistically significant difference between the ORR of the 70 mg sitravatinib plus tislelizumab in combination with nab-paclitaxel regimen under study (assumed as approximately 65%) and the historical ORR of nab-paclitaxel monotherapy being 46% (one-sided α level of 0.1). Among the first 18 patients in the efficacy analysis set, if ≤ 9 subjects show confirmed post-treatment response, the study will be terminated. Otherwise, the study will continue. If > 19 responders are observed among all 35 patients in the efficacy analysis set, a statistical superiority of this combination therapy over the historical control of 46% under the set conditions will be declared. For Cohort C, the investigators may consider enrolling up to 50 patients if efficacy is favorable based on the results of prior data.

10. ACCESS TO SOURCE DATA/DOCUMENTS

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

10.1. Access to Information for Monitoring

According to the ICH GCP guidelines, the Study Director has direct access to the source documentation to validate the data recorded in the CRFs for consistency.

The Study Director or its designee is responsible for routine review of the CRFs 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. All investigators agree to cooperate with the Study Director to ensure that any problems detected during monitoring visits are resolved.

10.2. Access to Information for Auditing or Inspections

The investigators should be aware that upon receiving official notice, the original records related to the study should be prepared and made available to the appropriate qualified personnel or their designees, or inspectors from the health department. Verification of the data in the case report form must be directly checked against the original records.

11. QUALITY ASSURANCE AND QUALITY CONTROL

11.1. Regulatory Authority Approval

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

11.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, regulatory agencies may 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 any findings and relevant issues.

11.3. Drug Accountability Record

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

12. ETHICS/PROTECTION OF HUMAN PATIENTS

12.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with laws and regulations of the country in which the study is conducted, so as to afford greater protection to the individual. This study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

12.2. 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 to the IRB/IEC by the principal investigator and 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.

The investigators are 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 are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by the IRB/IEC, and archived in the study center's study file.

12.2.1. Protocol amendment

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities and to the IRB/IEC for review according to local requirements, and if applicable, a revised sample ICF can be submitted together in accordance with local requirements. Written approval documents must be obtained by the sponsor from the competent authorities (as locally required),

IRB/IEC, and study center before implementation of any changes, except changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only.

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

12.3. Informed Consent

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his/her participation in the study. The medical history or clinical records for each patient shall document the informed consent process and that written informed consent should be 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 ICFs 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 medical history or clinical records for each patient shall document the informed consent process and that written informed consent should be 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 study center file and must be available for verification by the Study Director at any time.

12.4. Patient and Data Confidentiality

The sponsor maintains confidentiality and privacy standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This approach ensures that patients' names are not included in any data that are transmitted to any sponsor location.

Patient medical information obtained during this study is confidential and may be disclosed only 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.

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.

13. DATA MANAGEMENT RESPONSIBILITIES

13.1. Study Records Retention

The investigators 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 one of the following categories: 1) investigator's study file, and/or 2) patient clinical source documents.

The investigator's study file will contain the study protocol/amendments, CRFs and query forms, IRB/IEC and governmental approval, ICF, 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 CRFs) will include patient hospital/clinic records, physician's and nurse's notes, original laboratory reports, X-ray, pathology, consultant letters, screening and enrollment log, etc.

Following end 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 (e.g., 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 (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigators must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigators must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The minimum retention time will meet the strictest standard applicable to that study center, as dictated by any institutional requirements or local laws or regulations, or sponsor's standards/procedures; otherwise, the retention period will default to 5 years.

13.2. Protocol Deviations

The investigators are 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.

The investigators are to document and explain any deviations from the approved study protocol. The investigators must immediately report any major deviations that might impact subject safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14. STUDY AND STUDY CENTER CLOSURE

Upon end of the study, the investigators will conduct the following activities as appropriate:

- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for all unused investigational products
- Review of study records for completeness

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

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16. APPENDIX

Appendix 1 Assessment Schedule

Assessment item	**Screening[1]**	**Treatment period**				**EOT visit[4]**	**Safety follow-up call[5]**	**Survival follow-up[6]**
		Cycles 1–2			**Cycle 3 and subsequent cycles**			
Days (window)	**Day -28 to Day -1**	**1[2]**	**8 (± 1)[3]**	**15 (± 2)[3]**	**1 (± 3)**	**Within 30 days of the last dose of the investigational products**	**60 days and 90 days (± 14 days) after the last dose of tislelizumab**	**Approximately every 3 months (± 14 days)**
Informed consent[1]	x							
Eligibility criteria	x							
Demographic/medical history/prior medications	x							
Height	x							
Vital signs/body weight[7]	x	x	x	x	x	x		
Physical examination[8]	x					x		
ECOG performance status	x	x			x	x		
12-lead ECG[9]	x	x			x	x		
AEs[10]	x	x	x	x	x	x	x	
Concomitant medications[11]	x	x	x	x	x	x	x	
Hematology[12]	x	x[12]			x	x[12]		
Clinical chemistry[12]	x	x[12]	x[12]	x[12]	x	x[12]		

Assessment item	**Screening[1]**	**Treatment period**				**EOT visit[4]**	**Safety follow-up call[5]**	**Survival follow-up[6]**
		Cycles 1–2			**Cycle 3 and subsequent cycles**			
Days (window)	**Day -28 to Day -1**	**1[2]**	**8 (± 1)[3]**	**15 (± 2)[3]**	**1 (± 3)**	**Within 30 days of the last dose of the investigational products**	**60 days and 90 days (± 14 days) after the last dose of tislelizumab**	**Approximately every 3 months (± 14 days)**
Coagulation parameters[12]	x	As clinically indicated						
Urinalysis[12]	x	x[12]	x[12]	x[12]	x	x[12]		
Pregnancy test[13]	x				x[13]	x		
Thyroid function[14]	x	Cycles 4, 7, 10 and every 3 cycles thereafter						
HBV/HCV test[15]	x	As clinically indicated						
Tumor assessment[16]	x	Every 6 weeks (± 7 days)						
Fresh/archival tumor tissues[17]	x							
Pulmonary function testing[18]	As clinically indicated							
Sitravatinib administration[19]		per day						
Tislelizumab administration[20]		x			x			
Survival status[6]								x
MUGA/echocardiography[21]	x	As clinically indicated						

Abbreviations: AE = adverse event; CR = complete response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CRF = electronic case report form; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MUGA = multiple gated acquisition scan; PD = progressive disease; PR = partial response; SAE = serious adverse event; X = to be performed.

Note: When sitravatinib and tislelizumab are scheduled for administration on the same day, the daily administration of sitravatinib should be earlier than the tislelizumab infusion.

1. In the screening period, the patient must sign the written informed consent before performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the first dose of the investigational products may be used for the purposes of screening and assessment rather than repeating the same tests.
2. All assessments for Cycle 2 Day 1 can be performed within a window of ± 3 days.
3. In Cycles 1–2, all patients will return to the study center on Days 8 and 15 for assessment.
4. EOT visits are conducted within 30 days of the last dose of investigational products or before the initiation of a new anticancer therapy, whichever occurs first. If routine laboratory tests (e.g., hematology, clinical chemistry) have been conducted within 7 days before the EOT visit, these tests are not required to be repeated. If a tumor assessment has been conducted within 6 weeks before the EOT visit, the assessment is not required to be repeated. If the investigational products are initially interrupted due to an AE and then permanently discontinued, the EOT visit may be postponed, but not later than the allowable time limit (+ 7 days) for dose delay.
5. Safety follow-up call. Telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, e.g., irAE-related or subsequent anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. Safety follow-up calls are not required for patients receiving sitravatinib monotherapy.
6. After the EOT visit, survival follow-up information will be collected via telephone calls (for phase 2 dose expansion phase only), patient medical records, and/or clinic visits approximately every 3 months (± 14 days) until death, loss to follow-up, withdrawal of informed consent, or study termination by the sponsor. All patients will be followed up by the study center for survival status and subsequent anticancer therapy information unless the patient requests to withdraw from follow-up.

7. Vital signs collected in the study will include measurements of body temperature, pulse, and blood pressures (systolic and diastolic) of the patient after resting for 10 minutes. The vital signs should be recorded within 60 minutes before tislelizumab administration, during tislelizumab infusion, and 30 minutes post-dose. For subsequent infusions, vital signs should be recorded within 60 minutes pre-dose, and if clinically indicated, during and 30 minutes after the infusion. Vital signs should be recorded before sitravatinib administration. If vital signs are collected within 60 minutes before tislelizumab infusion, the recorded values can be used for the pre-assessment of tislelizumab.
8. Physical examination should be performed during the screening period and at EOT follow-up to assess 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal and 7) neurological systems.
9. 12-lead ECG: ECG should be performed during the screening period, on Cycle 1 Day 1, at the beginning of each subsequent cycle, at EOT visits, and at other times when clinically indicated. Patients should rest for at least 10 minutes prior to each ECG. If an ECG is performed within 3 days prior to the first dose of the investigational products and within 3 days prior to the EOT visit, it is not required to be repeated on Day 1 of Cycle 1 and at the EOT visit.
10. AE will be graded and recorded according to NCI-CTCAE v5.0 throughout the study.
11. All concomitant medications received within 30 days before the first dose of the investigational products and 30 days after the last dose of the investigational products should be recorded.
12. Hematology, clinical chemistry, coagulation, and urinalysis (Appendix 2): If laboratory tests at screening are not performed within 7 days prior to the administration of investigational products on Cycle 1 Day 1, these tests (hematology, clinical chemistry, and urinalysis) should be repeated and reviewed before the administration of investigational products. In the study, hematology and clinical chemistry tests specified in Appendix 2 should be performed once a week for the first two cycles. For all patients, hematology, clinical chemistry, and urinalysis should be performed at the beginning of each cycle and at the EOT visit. After Cycle 1, laboratory safety tests should be performed and reviewed within 48 hours prior to the administration of investigational products. See Appendix 2 for CK, CK-MB, and coagulation tests.
13. A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the administration of investigational products. During the treatment, a urine or serum pregnancy test will be conducted prior to the administration of the investigational products every 3 treatment cycles and at the EOT visit. If the result of the urine pregnancy test is positive or suspected, a serum pregnancy test must be performed. A pregnancy test (urine or blood test) must be completed and documented as negative prior to the administration of investigational products every 3 treatment cycles and at the EOT visit.

14. Thyroid function tests, including FT3, FT4, and TSH, will be performed during the screening period and every 3 cycles thereafter (i.e., Day 1 of Cycles 4, 7, 10, etc.) and at the EOT visit. Repeating this test is not required at the EOT visit if it is ≤ 63 days since the last test.
15. HBV/HCV test: A test will be performed by a local study center during the screening period and will include HBV/HCV serology test (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Patients must be tested during the screening period. In addition, patients who are HBV DNA positive at screening will be tested for the appropriate viral load every 4 cycles starting from Cycle 5 (i.e., Day 1 of Cycles 5, 9, 13, etc.) and at the EOT visit.
16. Tumor imaging: Radiological images from standard collections prior to obtaining written informed consent and within 28 days before the administration of investigational products may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head may be required during the screening period based on clinical judgment; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient. The investigators must review the X-ray results before next cycle of drug administration. Tumor imaging will be performed within 28 days prior to Cycle 1 Day 1 and approximately every 6 weeks ± 7 days during the study period. The investigators may perform additional scans or more frequent assessments if clinically indicated. Patients who discontinue study treatment for reasons other than PD (e.g., toxicity) will continue scheduled tumor assessments until PD, withdrawal of consent, death, or study termination, whichever occurs first. Patients who continue tislelizumab treatment after PD confirmed by imaging will be monitored with follow-up scans before tislelizumab is discontinued and 6 to 8 weeks after the initial diagnosis of PD confirmed by imaging.
17. Archival tumor tissue will be collected if samples are available, and fresh tissue biopsies may be performed if archival samples are not provided.
18. Pulmonary function test: Patients who are suspected or known to have serious respiratory system disorders or exhibit significant respiratory symptoms unrelated to underlying cancer will undergo pulmonary function testing, which may include but is not limited to spirometry and assessment of diffusion capacity during the screening period to assist the determination of suitability for this study.
19. Sitravatinib is administered orally once daily before meals (capsules should be taken under fasting conditions, at least 2 hours after the previous meal and 1 hour before the next meal. If administered once daily, the capsule should be taken in the morning, e.g., at least 1 hour before breakfast or lunch).
20. Tislelizumab is administered after sitravatinib administration on Day 1 of each cycle.
21. MUGA/echocardiography: Assessment by multiple gated acquisition (MUGA) scanning is preferred for the purpose of the study. Echocardiographic assessment can be used instead if necessary.

Appendix 2 Clinical Laboratory Assessments

Clinical chemistry	Hematology	Coagulation[a]	Urinalysis
Alkaline phosphatase	Hematocrit	Prothrombin time or INR	Glucose
Alanine aminotransferase	Hemoglobin	aPTT	Protein
Aspartate aminotransferase	Platelet count		Hematology
Albumin	WBC count		Ketone
Total bilirubin Direct bilirubin	Lymphocyte count Neutrophil count		24-hour protein[b]
Blood urea nitrogen or urea			
Potassium			
Sodium Corrected calcium[c]			
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
CK[d] CK-MB[d,e]			

Abbreviations: aPTT = activated partial thromboplastin time; CK = creatine kinase; CK-MB = creatine kinase isoenzyme; INR = international normalized ratio; WBC = white blood cell.

a. A coagulation test will be required during the screening period, after which it will be performed when clinically indicated.

b. In urinalysis, if urine protein is ≥ 2+ by dipstick, then a total protein test will be performed for 24-hour urine sample, or a total protein and creatinine test will be

performed for a random urine sample to determine the urine protein/creatinine ratio.

c. If a corrected calcium test is not available at the local laboratory, a total calcium test can be performed instead.

d. Creatine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB) tests will be performed for patients receiving tislelizumab. CK, an enzyme produced by the cardiac muscle, and CK-MB tests will be performed on Day 1 of each dosing cycle (if CK-MB monitoring is not available, troponin I and/or troponin T will be tested instead) to confirm that none of the drugs are causing damage to the patient's heart. If tislelizumab has been permanently discontinued, CK and CK-MB tests will no longer be required. Patients with a history of heart disease who receive sitravatinib monotherapy (patients in Cohort A or those have discontinued tislelizumab) may undergo CK and CK-MB tests as clinically indicated.

e. If CK-MB is not tested, troponin I and/or troponin T will be assessed.

Additionally, the following tests will be performed in this study:

- A **serum pregnancy test** (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the administration of investigational products. During the treatment, a **urine or serum pregnancy test** will be conducted prior to the administration of investigational products every 3 treatment cycles and at the EOT visit. If the result of the urine pregnancy test is positive or suspected, a serum pregnancy test must be performed. A pregnancy test (urine or blood test) must be completed and documented as negative prior to the administration of investigational products every 3 treatment cycles and at the EOT visit.
- **Thyroid function tests** (thyroid-stimulating hormone [TSH], free T3, and free T4) will be performed during the screening period and every three cycles thereafter (i.e., Day 1 of Cycles 4, 7, 10, etc.) and at the EOT visit (see Section 7.3.5 for details). TFTs are not required at the EOT visit if the time since the last test is ≤ 63 days.

Appendix 3 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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. Incapable of self-care. Totally confined to bed or chair
5	Death

See the document for details (Oken et al 1982) Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 4 Pre-existing Immune Deficiencies or Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune diseases.

Please contact the principal investigator for any uncertainty regarding the exclusion criteria for immune deficiencies/autoimmune diseases.

Acute disseminated encephalomyelitis	Addison's 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	Bechet's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Allergic granulomatous angiitis	Crohn’s disease
Dermatomyositis	Autonomic imbalance
Acquired epidermolysis bullosa	Pemphigoid gestationis
Giant cell arteritis	Goodpasture's syndrome
Granulomatous angiitis	Graves' disease
Guillain-Barré syndrome	Hashimoto's disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki's disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren's ulcer

Scleroderma	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord's thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodusa
Polyarthritis	Autoimmune polyendocrinopathy syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren's syndrome
Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada syndrome

Appendix 5 Contraception Guidelines and Definitions of "Women of Childbearing Potential" and "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. These methods include the following:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progesterone-containing only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone release system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner, provided that partner is the sole sexual partner of the woman of childbearing potential participating in the trial and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of receiving study treatment).
  - **Note:** It should only be used as a contraceptive method when complete abstinence is consistent with the patient's daily and willing lifestyle. Periodic abstinence (such as calendar contraception, ovulation contraception, contraceptive rhythm method, post-ovulation method), claimed abstinence during study treatment exposure, and voluntary abstinence are all unacceptable contraceptive methods.

Barrier contraception (including male and female condoms with or without spermicide) is not a highly effective method of contraception. If used, this method must be combined with a highly effective contraceptive method listed above.

Definition of "women of childbearing potential" and "no childbearing potential"

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

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

- Surgically sterile (i.e., through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined by:
  - ≥ 55 years of age with natural menopause for ≥ 12 months or
  - < 55 years of age with natural menopause for ≥ 12 months and with follicle-stimulating hormone concentration > 30 IU/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 (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials.

Appendix 6 New York Heart Association (NYHA) Functional Classification

Class	Symptoms
I	Presence of cardiac disease, with no symptoms, and no limitation of physical activity, e.g. shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (e.g., mild shortness of breath and/or angina). Slight limitation during ordinary activity.
III	Marked limitation of physical activity due to cardiac disease symptoms, even less than ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Symptoms of heart failure at rest. Mostly confined to bed.

Adapted from Dolgin M, ed. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*.9th ed.
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 7 Immune-Related Adverse Event Evaluation and Management

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

Criteria used to diagnose irAEs 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 irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- 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 irAE field associated with the AE in the eCRF should be checked.

Recommended diagnostic tests in the management of possible immune-related AEs

Immune-related Toxicity	**Diagnostic Evaluation Guideline**
Thyroid disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual field and consider measuring pituitary endocrine hormone levels in blood samples. 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 imaging 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.
Neurotoxicity	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 test, including the following: FBC, UEC, LFT, CRP, TFT, stool microscopy and culture, viral PCR, Clostridium difficile toxin, and cryptosporidia (drug-resistant bacteria). In case of abdominal discomfort, consider imaging, e.g., X-ray and 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.

Recommended diagnostic tests in the management of possible immune-related AEs

Immune-related Toxicity	**Diagnostic Evaluation Guideline**
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (e.g., daily if Grade 3–4; every 2–3 days if Grade 2, until recovering). Review medications (e.g., statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology and hepatitis E PCR, and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, e.g., ultrasound scan for metastases or thromboembolism. Consult with a hepatologist. Liver biopsy is advised.
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 nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, and consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Review 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, CK, ESR, CRP, and troponin tests should be included, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and 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 muscle 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 cystolic 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-related adverse events

- Immune-related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention may be required as appropriate.
- Immune-related AEs should improve promptly after administration of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the Study Director.
- For some Grade 3 toxicities that resolve quickly, resumption of the investigational products may be considered if there is evidence of a clinical response to study treatment, after consultation with the Study Director.
- Steroid dosages in the table below are for oral or intravenous (IV) (methyl) prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider the use of steroid-sparing agents (e.g., 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 Judgment)**	**Management of Investigational Products**
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.
	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 co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone at 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
Hypophysitis	**1–2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone at 0.5–1 mg/kg/day for patients with hypophysitis. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3–4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3–4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV of methylprednisolone at 1 mg/kg for patients with headache/visual disturbance due to hypophysitis. 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 hypophysitis until resolved/improved to Grade 2 or less. 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 dyspnea	Commence antibiotics if infection suspected. Add oral prednisolone at 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider pneumocystosis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: e.g., blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone at ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
	3–4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone at 2–4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab at 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, e.g., blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurotoxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone at 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	Initiate treatment with oral prednisolone or IV methylprednisolone at 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.
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 stool, or nausea, or nocturnal episodes	Oral prednisolone at 0.5 mg/kg/day (non-enteric 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone at 1–2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, e.g., blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab at 5 mg/kg if no perforation, sepsis, tuberculosis, hepatitis, NYHA grade 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 Director.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reaction	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritation and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%–30% of BSA	Avoid skin irritation and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once daily or potent cream twice daily) ± 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 irritation and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgment: For moderate symptoms: oral prednisolone at 0.5–1 mg/kg/day for 3 days then taper over 2–4 weeks. For severe symptoms: IV methylprednisolone at 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 Director.
	4 Skin exfoliation > 30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone at 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 Judgment)	Management of Investigational Products
Hepatitis	**1** ALT or AST > ULN to 3 × ULN	Check LFTs within 1 week; 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 × ULN	Recheck LFTs every 48–72 hours: For persistent ALT/AST elevation: consider oral prednisolone at 0.5–1 mg/kg/day for 3 days then taper over 2–4 weeks. For rising ALT/AST: start oral prednisolone at 1 mg/kg/day and taper over 2–4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgment.	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 × ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone at 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone at 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; Treatment may be resumed only after discussion with the Study Director.
	4 ALT or AST > 20 × ULN	Initiate IV methylprednisolone 2 at 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 IV methylprednisolone. • If on IV, add mycophenolate mofetil (MMF) at 500–1000 mg twice a day • If worse on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
Nephritis	**1** Creatinine 1.5 × baseline or > ULN to 1.5 × ULN	Repeat creatinine weekly. If symptoms worsen, manage as per the criteria below.	Continue study treatment.
	2 Creatinine > 1.5–3 × baseline or > 1.5–3 × ULN	Ensure hydration and review creatinine in 48–72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with a nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone at 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 investigational products and resolved/improved to baseline grade: Restart investigational products (prednisolone tapered to < 10 mg).
	3 Creatinine > 3 × baseline or > 3–6 × ULN	Hospitalize patient for monitoring and fluid balance recovery; repeat creatinine every 24 hours; consult a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone at 1–2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If investigational products suspected: Discontinue study treatment.
	4 Creatinine > 6 × ULN	As per Grade 3, patient should be hospitalized where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
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 guidelines.	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 the patient's hyperglycemia symptoms are resolved, and blood glucose is stabilized at baseline or Grade 0–1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and local institute for emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye exam/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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone at 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 Director.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone at 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 IV (methyl)prednisolone at 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 Director.
	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	Manage according to local guidelines.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Manage according to local guidelines. 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
	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 at 0.5–1 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 Director.
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.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone at 1–2 mg/kg/day. Convert to oral prednisolone when symptoms improved 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 IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myoditis/ 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 × ULN or the symptoms worse, initiate oral prednisolone at 0.5–1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0–1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Management of Investigational Products
	3–4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone at 1 mg/kg. Consider bolus IV (methyl)prednisolone at 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	Hold study treatment until improved to Grade 0–1. Discontinue if any evidence of myocardial involvement
Myocarditis	**1** Asymptomatic but abnormal CK-MB, abnormal cardiac troponin, or intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1–2 mg/kg/day. Treat cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone at 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	Hold study treatment until complete recovery or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved
	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-myocardial isoenzyme; INR = international normalized ratio; IV = intravenous injection; LFT = liver function test; MMF = mycophenolate mofetil; 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.

Appendix 8 Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, Version 1.1

The text below was obtained from the following reference: Eisenhauer et al 2009.

Definition

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 (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable 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 at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (if lesions are 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 greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter □ 10 and < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, are considered as non-measurable.

Bone lesions:

- Bone scan, 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 non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) 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 non-cystic 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. Study 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 scan. 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 two 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, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 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 non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological 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.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target 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 non-target lesions involving the same organ as a single item on the electronic case record form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Guidelines for assessment of measurable disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline assessments 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 exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and > 10 mm diameter as assessed using calipers (e.g., 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 exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since 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 greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., 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 complete response 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 complete response. 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 (PSA) 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 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 (e.g., 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 PD.

Response criteria

Evaluation of target lesions

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive disease (PD): At least 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 at least 5 mm.
- Stable disease (SD): 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 forms may therefore 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, SD, 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 (e.g., 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 case report form. 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 non-reproducible, 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 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 non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- PD: Equivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target lesion, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), 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 non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase of 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 non-measurable 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, the detection of new lesions should be taken seriously. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., 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 complete response. 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 study 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 ordered which 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 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 lesion 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 on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The BOR is the best response recorded from the start of the study 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 BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "BOR".

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of CR or PR is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD 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 SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluable	No	PR
PR	Non-PD or not all evaluated	No	PR
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 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 "0" on the CRF.

In trials where confirmation of response is required, repeated "NE" time point 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 time point 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 study therapy.

Conditions that define "early progression, early death, and inevaluability" are study 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 complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm complete response. 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 (e.g., very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Confirmatory measurement/duration of response

Confirmation

In non-randomized 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, i.e., in randomized trials (phase 2 or 3) or studies where stable disease or progression is the primary endpoint, 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 studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study 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 progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response 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 trials, from the 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 two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline assessment. 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 9 Medications or Substances to Be Avoided or Used with Caution During Treatment with Sitravatinib

The text below was obtained from: https://crediblemeds.org/ and https://drug-interactions.medicine.iu.edu/Main-Table.aspx.

Bold font indicates drugs or substances that may be relatively commonly used.

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

MEDICATIONS THAT SHOULD BE AVOIDED

Drugs with a known risk of prolonged QT interval/torsades de pointes

Amiodarone, anagrelide, *arsenic trioxide*, astemizole (off US market), **azithromycin**, bepridil (off US market), chloroquine, **chlorpromazine**, cilostazol, **ciprofloxacin**, cisapride (off US market), **citalopram**, **clarithromycin**, cocaine, disopyramide, dofetilide, domperidone (off US market), donepezil, dronedarone, **droperidol**, **erythromycin**, **escitalopram**, flecainide, fluconazole, gatifloxacin (off US market), grepafloxacin (off US market), halofantrine (off US market), haloperidol, ibogaine (off US market), ibutilide, levofloxacin, levomepromazine/methotrimeprazine (off US market), levomethadyl (off US market), levosulpiride (off US market), mesoridazine (off US market), **methadone**, moxifloxacin, **ondansetron**, *oxaliplatin*, *pentamidine*, pimozide, probucol (off US market), procainamide, propofol, quinidine, roxithromycin (off US market), sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (off US market), sultopride (off US market), terfenadine (off US market), terlipressin (off US market), terodiline (off US market), thioridazine, *vandetanib*.

CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS

Sensitive substrates and substrates with narrow therapeutic index for P-gp and BCRP transporters

Enzyme	
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran elexilate, **digoxin**, *everolimus*, **fexofenadine**, *imatinib*, *lapatinib*, *maraviroc*, *nilotinib*, posaconazole, ranolazine, saxagliptin, sirolimus, **sitagliptin**, talinolol, tolvaptan, *topotecan*.
BCRP	Methotrexate, *mitoxantrone*, *imatinib*, *irinotecan*, *lapatinib*, **rosuvastatin**, sulfasalazine, topotecan.

CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS (CONTINUED)

Sensitive substrates and substrates with narrow therapeutic index for the indicated CYP enzymes

Enzyme	
CYP2B6	Bupropion.
CYP2C8	Repaglinide.
CYP2D6	Atomoxetine, desipramine, **dextromethorphan**, eliglustat, nebivolol, **nortriptyline**, perphenazine, tolterodine, venlafaxine.
CYP3A	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, *darunavir*, *dasatinib*, dronedarone, ebastine, eletriptan, eplerenone, *everolimus*, **felodipine**, ibrutinib, *indinavir*, lomitapide, **lovastatin**, lurasidone, *maraviroc*, **midazolam**, naloxone, nisoldipine, quetiapine, *saquinavir*, sildenafil, **simvastatin**, sirolimus, tacrolimus, ticagrelor, *tipranavir*, tolvaptan, triazolam, vardenafil.

Drugs with a conditional risk of torsades de pointes

Amantadine, amisulpride (off US market), amitriptyline, amphotericin B, *atazanavir*, bendroflumethiazide (off US market), chloral hydrate, **diphenhydramine**, doxepin, **esomeprazole**, **famotidine**, **fluoxetine**, fluvoxamine, **furosemide**, galantamine, garenoxacin (off US market), **hydrochlorothiazide**, hydroxychloroquine, hydroxyzine, indapamide, itraconazole, ivabradine, ketoconazole, **lansoprazole**, **loperamide**, **metoclopramide**, metolazone, metronidazole, *nelfinavir*, olanzapine, **omeprazole**, **pantoprazole**, **paroxetine**, piperacillin/tazobactam, posaconazole, propafenone, quetiapine, quinine sulfate, ranolazine, **sertraline**, solifenacin, *telaprevir*, torasemide, trazodone, voriconazole, ziprasidone.