CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2 Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Sitravatinib as Monotherapy and in Combination With Tislelizumab in Patients With Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma or Gastric/Gastroesophageal Junction Cancer
Protocol Identifier:	BGB-900-104
Phase:	1/2
Investigational Products:	Sitravatinib (MGCD516) and Tislelizumab (BGB-A317)
Indication:	Advanced Solid Tumors
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, California 94403 USA BeiGene, Ltd. c/o BeiGene AUS Pty Ltd 1C/528 Compton Road Stretton Queensland 4116, Australia BeiGene (Beijing) Co., Ltd. No. 30 Science Park Road Zhong-Guan-Cun Life Science Park Changping District Beijing, China 102206 P.R. China
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol:	05 July 2018
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Amendment 4.0:	28 April 2020

FINAL PROTOCOL APPROVAL SHEET

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

BeiGene, Ltd., Approval:

[redacted]

28 April 2020

Date

Sponsor Medical Monitor

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-900-104

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor:	BeiGene, Ltd.
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Protocol Identifier:	BGB-900-104
Phase of Development:	Phase 1/2
Number of Patients:	Approximately 18 to 36 DLT evaluable patients enrolled in Phase 1 and approximately 80 patients enrolled in Phase 2
Study Centers:	Approximately 20 centers in Asia Pacific including Australia and China

Study Objectives:

Phase 1:

Primary:

- To assess the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab
- To confirm the recommended Phase 2 dose (RP2D) for sitravatinib as monotherapy and in combination with tislelizumab

Secondary:

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

Exploratory:

- To explore potential biomarkers in association with efficacy, resistance, and/or progressive disease (PD) in tumor tissue and in peripheral whole blood
- To explore potential pharmacodynamic biomarkers for sitravatinib as monotherapy and in combination with tislelizumab
- To assess PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To explore the effect of pharmacogenetic (PGx) polymorphisms on PK of sitravatinib

Phase 2:

Primary:

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

Secondary:

- To assess the preliminary antitumor activity as indicated by duration of response (DOR),

disease control rate (DCR), and progression-free survival (PFS) per RECIST v1.1 as monotherapy and in combination with tislelizumab

- To characterize the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab
- To characterize the PK profile of sitravatinib

Exploratory:

- To assess potential biomarkers in association with efficacy, resistance, and/or PD in tumor tissue and in peripheral whole blood
- To explore potential pharmacodynamic biomarkers for sitravatinib as monotherapy and in combination with tislelizumab
- To assess PK and immunogenicity to tislelizumab when given in combination with sitravatinib
- To assess overall survival (OS)
- To explore the effect of pharmacogenetic (PGx) polymorphisms on PK of sitravatinib

Study Endpoints:

Phase 1 (Dose Escalation):

Primary Endpoints:

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

Secondary Endpoints:

- Plasma concentrations and the derived PK parameters of sitravatinib if data permit:
  - Single dose: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma or serum concentration-time curve from time zero to the last measurable time point ($AUC_{(0-t)}$), clearance after oral administration (CL/F)
  - Repeating dose: C_{max}, trough concentration at steady state (C_{τ}), T_{max}, area under the plasma concentration-time curve from time zero to 24 hours postdose at steady state ($AUC_{(0-\tau)}$), CL/F, accumulation ratio (Ro)
- Efficacy evaluations by investigators: ORR, DOR, DCR, and PFS based on RECIST v1.1

Exploratory Endpoints:

- Potential biomarkers, including, but not limited to, programmed cell death protein ligand-1 (PD-L1) expression, immune cell profiling, tumor mutation load, and gene expression profiling in archival and/or fresh tumor tissue and blood (or blood derivatives) obtained before, during, or after treatment or at PD; and the association with disease status and/or the response to sitravatinib as monotherapy or in combination with tislelizumab
- Changes of potential pharmacodynamic biomarkers in response to sitravatinib as monotherapy and in combination with tislelizumab, such as, but not limited to, soluble vascular endothelial growth factor receptor 2 (sVEGFR-2) and immune cell subpopulations in peripheral blood
- Serum concentrations of tislelizumab and anti-tislelizumab antibodies
- Effect of genetic polymorphisms of hepatic metabolizing enzymes and transporters, including, but not limited to, CYP1A2, 2D6, and 2C8 on the PK of sitravatinib

Phase 2 (Dose Expansion):

Primary Endpoint:

- Efficacy evaluations by investigators: ORR based on RECIST v1.1

Secondary Endpoints:

- Efficacy evaluations by investigators: DOR, DCR, and PFS based on RECIST v1.1
- Safety and tolerability will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE v5.0, relevant physical examination, ECGs, and laboratory assessments as needed
- PK: plasma concentrations of sitravatinib predose and postdose at steady state

Exploratory Endpoints:

- Potential biomarkers, including, but not limited to, PD-L1 expression, immune cell profiling, tumor mutation load, and gene expression profiling in archival and/or fresh tumor tissue and blood (or blood derives) obtained before, during, or after treatment or at PD; and the association with disease status and/or response to sitravatinib as monotherapy or in combination with tislelizumab
- Changes of potential pharmacodynamic biomarkers in response to sitravatinib as monotherapy and in combination with tislelizumab, such as, but not limited to, sVEGFR-2 and immune cell subpopulations in peripheral blood
- Serum concentrations of tislelizumab and anti-tislelizumab antibodies
- OS is defined as the time from date of first dose of study drug(s) to date of death due to any cause
- Effect of genetic polymorphisms of hepatic metabolizing enzymes and transporters, including, but not limited to, CYP1A2, 2D6, and 2C8 on the PK of sitravatinib

Study Population

Patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC or G/GEJ cancer.

Key Eligibility Criteria

Adult patients (≥ 18 years of age at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed HCC or G/GEJ cancer. All patients are also required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1, and adequate organ function.

Investigational Products, Dose, and Mode of Administration:

Phase 1 (dose escalation): Sitravatinib capsules will be administered orally, once daily, in a continuous regimen in 21-day cycles. The starting dose for sitravatinib in escalation evaluation will be 80 mg once daily. Depending on safety observations, the sitravatinib dose in the subsequent cohort of patients may be escalated to 120 mg once daily. Sitravatinib will be administered either as monotherapy or in combination with 200 mg tislelizumab, which will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Phase 2 (dose expansion): The recommended dose level of sitravatinib will be administered orally, once daily, in a continuous regimen in 21-day cycles. Sitravatinib will be administered either as monotherapy or in combination with 200 mg tislelizumab, which will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Study Design

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

or study termination by sponsor.

This study consists of the following phases:

Phase 1 (Dose escalation for sitravatinib as monotherapy and in combination with tislelizumab):

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

The combination dose escalation of sitravatinib (80 mg once daily and 120 mg once daily; modified 3 + 3 design) with tislelizumab (200 mg once every 3 weeks, in both cohorts) will be evaluated in patients with unresectable locally advanced or metastatic HCC or G/GEJ cancer. The combination dose escalation may start simultaneously with the monotherapy cohort as the dose regimen for all cohorts are considered safe based on the totality of available clinical data. There is no interaction anticipated between sitravatinib and tislelizumab to influence respective PK profiles. If the combination dose of 80 mg sitravatinib and 200 mg tislelizumab has been declared tolerable, the dose of sitravatinib will be escalated to 120 mg and tislelizumab will remain fixed at 200 mg. Approximately 12 to 24 DLT evaluable patients will be treated.

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

Phase 2 (**Dose expansion for sitravatinib as monotherapy and in combination with tislelizumab**): Approximately 20 patients will be enrolled in each cohort. There will be a total of 4 cohorts in the study.

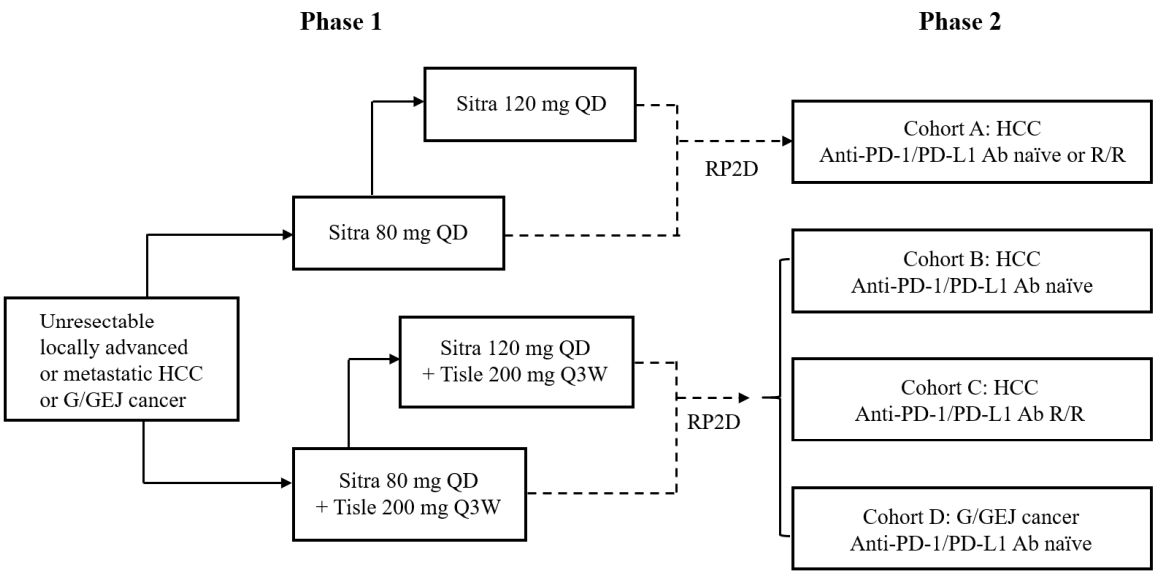
Sitravatinib monotherapy

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

Sitravatinib in combination with tislelizumab

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

Study Schema



Abbreviations: Ab, antibody; G/GEJ, gastric/gastroesophageal junction, HCC, hepatocellular carcinoma; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; PK, pharmacokinetic; QD, once a day; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose; R/R, refractory or resistant; Sitra, sitravatinib; SMC, Safety Monitoring Committee; Tisle, tislelizumab.

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

Study Assessments

A table of study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study.

Assessment of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose of study drug(s). For dose escalation decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for dose escalation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving monotherapy who do not receive ≥ 75% of scheduled sitravatinib during the DLT assessment window, unless they experience a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled sitravatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window, unless they experience a DLT.

Definition of DLT

A DLT is defined as any of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to sitravatinib and/or tislelizumab.

Hematologic

- Grade 4 neutropenia lasting > 3 days

- ≥ Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia
- ≥ Grade 4 anemia

Non-Hematologic

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not improve to ≤ Grade 2 within 3 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 hypertension that improves to < 160/100 mmHg, within 7 days of optimal supportive care
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)

Tumor Assessments

Radiological assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) in the first year, then every 9 weeks (± 7 days) thereafter.

Tumor response will be assessed by investigators based on RECIST v1.1.

The decision to continue study drug(s) beyond investigator-assessed progression must be agreed with the medical monitor and documented in the study records. In such cases, patients are also required to be reconsented.

Statistical Methods

This study is designed to verify the dose and to establish the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab and to assess the preliminary antitumor activity in selected tumor types. No formal hypothesis testing is planned. Descriptive statistical analyses will be performed for all patients in the Safety Analysis Set. The safety and efficacy (eg, ORR, DOR, DCR, PFS, and OS) data will be presented by phase and by cohort.

Analysis Sets

- The Safety Analysis Set includes all patients who received at least 1 dose of any study drug(s) (any component for the combination therapy). Patients from either Phase 1 or 2 are eligible for inclusion in the Safety Analysis Set.
- The Efficacy Evaluable Analysis Set includes patients who received at least 1 dose of any study drug with measurable disease at baseline per RECIST v1.1 who had at least 1 evaluable postbaseline tumor assessment unless treatment was discontinued due to clinical progression or death before tumor assessment. Patients from either Phase 1 or 2 are eligible for inclusion in the Efficacy Evaluable Analysis Set.
- DLT Evaluable Analysis Set for sitravatinib monotherapy includes patients who received at least 75% of the assigned total dose of sitravatinib for the DLT assessment window and had sufficient safety evaluation. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Phase 1 are eligible for inclusion in the DLT Evaluable Analysis Set of sitravatinib monotherapy.
- DLT Evaluable Analysis Set for sitravatinib and tislelizumab combination includes patients who received at least 75% of the assigned total dose of sitravatinib and ≥ 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment window. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Phase 1 are eligible for inclusion in the DLT Evaluable Analysis Set of sitravatinib and tislelizumab combination therapy.
- The PK Analysis Set includes patients who contributed at least 1 quantifiable post-baseline PK sample. Patients from either Phase 1 or 2 are eligible for inclusion in the PK Analysis Set.
- The ADA Evaluable Analysis Set includes all patients who received at least 1 dose of tislelizumab and for whom both baseline ADA and at least 1 post-baseline ADA results are available. Patients from either Phase 1 or 2 are eligible for inclusion in the ADA Evaluable Analysis Set.

Safety Analysis:

Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to the CTCAE v5.0. The incidence of DLT events and treatment-emergent adverse events (TEAEs) will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs. Safety analyses will be conducted in the Safety Analysis Set.

DLT Analysis:

DLTs during the DLT assessment window will be used to determine the dose and schedule of sitravatinib as monotherapy or in combination with tislelizumab. The DLT events will be summarized descriptively by monotherapy and combination dosing level in the DLT Evaluable Analysis Set in dose escalation stage.

PK Analyses:

Blood samples for PK analysis of sitravatinib and tislelizumab will be collected at specified time points. The actual collection date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points upon sponsor approval to ensure thorough PK monitoring.

All patients enrolled for Phase 1 will provide serial PK samples, and plasma concentrations of sitravatinib from these patients will be analyzed using noncompartmental analysis to calculate specified PK parameters. For all other sparse samples for sitravatinib, tislelizumab and anti-tislelizumab antibody, summary statistics will be provided.

Efficacy Analysis:

The efficacy endpoints (ie, ORR, DOR, PFS, and DCR) will be assessed by investigators using RECIST v1.1 and will be summarized to evaluate the antitumor activities of sitravatinib as monotherapy or in combination with tislelizumab.

- ORR is defined as the proportion of patients who had complete response (CR) or partial response (PR) assessed by investigator using RECIST v1.1. ORR, and its 95% confidence interval (CI) will be summarized.
- DOR is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier).
- DCR is defined as the proportion of patients with best overall response (BOR) of CR, PR and SD (stable disease).
- PFS is defined as the time from the date of the first dose of study drug(s) to the date of the first documentation of PD assessed by investigator using RECIST v1.1 or death, whichever occurs first.
- OS is defined as the time from date of first dose of study drug(s) to date of death due to any cause.

Descriptive statistics will be used to summarize the efficacy analysis. Exact 95% CI will be calculated for the rate variables (ORR and DCR).

Time-to-event variables DOR, PFS, and OS will be estimated using the Kaplan-Meier (KM) method and be plotted over time. Median DOR, PFS, and OS, if possible to estimate, will be presented in each arm, along with their 2-sided 95% CIs.

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

The Efficacy Analysis Set will be the primary analysis set for efficacy analysis.

Details of statistical analyses will be described in detail in the Statistical Analysis Plan (SAP).

Sample Size Considerations:

The study plans to enroll approximately 98 to 116 patients.

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

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CR	complete response
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
G/GEJ cancer	gastric/gastroesophageal junction cancer
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
irAE	immune-related adverse event

Abbreviation	Definition
IRB	Institutional Review Board
LFT	liver function testing
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PGx	pharmacogenetic
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
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VEGFR	vascular endothelial growth factor receptor

1. INTRODUCTION AND RATIONALES

1.1. Background Information on Advanced Solid Tumors

1.1.1. Hepatocellular Carcinoma

Liver cancer was the sixth most common type of cancer in 2012, with 782,000 new cases worldwide, the fifth most common cancer in men (554,000 cases, 7.5% of the total number of 7,410,400) and the ninth in women (228,000 cases, 3.4% of the total number of 6,657,500). It was also the second most common cause of cancer-related mortality worldwide, according to the World Health Organization's GLOBOCAN 2012 database, responsible for an estimated 746,000 deaths in 2012 (Ferlay et al 2015). In 2015, there was an estimated 466,100 new liver cancer cases and 422,100 liver cancer deaths in China (Chen et al 2016), accounting for approximately 50% of the total number of cases and deaths worldwide (Torre et al 2015). In 2018, it is estimated that there will be 2215 newly diagnosed liver cancer cases in Australia, and 2088 deaths from liver cancer (AIHW 2017). Hepatocellular carcinoma (HCC) accounts for 80% to 90% of primary liver cancer.

A variety of risk factors are known to cause HCC. These include infection with hepatitis viruses, aflatoxin B, tobacco, vinyl chloride, heavy alcohol intake, nonalcoholic fatty liver disease, hemochromatosis, and diabetes. Together, hepatitis B virus (HBV) and hepatitis C virus (HCV) account for 80% to 90% of all HCC cases worldwide (Bosch et al 2005). Chronic HBV infection is the dominant risk factor for the disease in most areas of Asia, with the exception of Japan (El-Serag 2012), while chronic infection with HCV is the leading cause of HCC in Western countries and in Japan (Choo et al 2016).

So far, there are only 2 first-line systemic treatments for advanced unresectable HCC approved by US Food and Drug Administration (FDA): sorafenib and lenvatinib. Regorafenib has also been approved by FDA as the second line of systemic treatment (Bruix et al 2017). However, sorafenib is difficult for patients to tolerate. The most common side effects include hypertension, hemorrhage, hand-foot skin reaction, diarrhea, sensory neuropathy, weight loss, rash, alopecia, anorexia, and pain in abdomen (NEXAVAR prescribing information). Even though lenvatinib shows noninferiority to sorafenib, it still has no decrease of adverse events (AEs) rate (Kudo et al 2018). Nivolumab is the only programmed cell death protein-1 (PD-1) inhibitor approved in US as second-line systemic treatment for advanced HCC after treatment with sorafenib (OPDIVO prescribing information; El-Khoueiry et al 2017). There were one-third of patients developing progressive disease (PD) in nivolumab CheckMate040 trial (El-Khoueiry et al 2017). Oxaliplatin in FOLFOX4 chemotherapy is approved in China for unresectable HCC (Chinese hepatocellular carcinoma guideline 2017), but more frequent hematological toxicity has been observed, including neutropenia, leukopenia, and thrombocytopenia, with especially higher rates in old patients (Qin et al 2014; Goldberg et al 2006).

Due to the unmet medical needs for HCC patients, tolerability issues with currently approved treatment options, and the lack of new monotherapy treatment options, combination therapy is becoming a major topic in clinical cancer research. Recently 3 studies showed combination therapy to have promising activity in HCC. The lenvatinib and pembrolizumab combination treatment for unresectable HCC (NCT03006926) showed an objective response rate (ORR) including unconfirmed patients of 42.3% in 26 evaluable patients (1/26 complete response [CR],

10/26 partial response [PR]) (Ikeda et al 2018). The other combination in HCC, atezolizumab and bevacizumab (NCT02715531), presents 65% ORR by independent review facility assessment in 23 evaluable patients (1/23 CR, 14/23 PR). The median progression-free survival (PFS) and overall survival (OS) have not been reached. The 6-month PFS is 65%. The 6-month OS is 86% (Stein et al 2018). No patients developed PD in either of the 2 studies above when the data were reported. SHR1210 combination treatment with apatinib showed similar results. Of the 16 evaluable HCC patients, the ORR was 43.8% (Xu et al 2018). Although the results are promising and suggestive of synergistic effects, anti PD-1/programmed cell death protein ligand-1 (PD-L1) and multiple kinase inhibitor combination therapy are still under investigation.

Despite these recent advances in the treatment of HCC, most patients will not show a major durable response to approved systemic treatments, including check point inhibition. Progression of disease during or after these treatments is common, and little is currently known about optimal management of such resistance. Treatment options after prior immunotherapy in HCC remain a significant unmet medical need.

1.1.2. Gastric/Gastroesophageal Junction Cancer

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer mortality worldwide. Almost 1 million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total) according to World Health Organization's GLOBOCAN 2012 database (Ferlay et al 2015). There were 679,100 new diagnosed cases of GC and 498,000 deaths in China in 2015 (Chen et al 2016). In 2018, it is estimated that there will be 2332 newly diagnosed GC cases in Australia, and 1078 deaths from GC (AIHW 2017).

Patients with newly diagnosed inoperable locally advanced or metastatic disease generally receive chemotherapy regimens containing platinum and fluoropyrimidine (Smyth et al 2016; NCCN 2017). The duration of first-line chemotherapy typically does not exceed 6 months because of PD or due to the toxicities of chemotherapy (Cunningham et al 2008; Van Cutsem et al 2006; Hess et al 2016).

In the second-line setting, the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) antibody ramucirumab is an option since it has shown a survival benefit comparable with chemotherapy (Fuchs et al 2014; Wilke et al 2014). Apatinib, as monotherapy, is the only approved treatment in China. However, according to these study results, monotherapy driven by tyrosine kinase inhibitors (TKIs) could not significantly improve patients' survival (Zhang et al 2017). More recently, immunotherapy with anti-PD-1 antibodies pembrolizumab and nivolumab has resulted in durable remissions for a subset of patients (Le et al 2016; Muro et al 2016). Pembrolizumab (Keytruda) has been approved by FDA for the treatment of patients with PD-L1–positive recurrent or advanced gastric or GEJ adenocarcinoma who have received 2 or more lines of chemotherapy (pembrolizumab label 2014).

In preclinical models, simultaneous blockade of PD-1 and VEGFR-2 enhanced T cell recruitment, activated local immune status, and induced synergistic antitumor effects (Yasuda et al 2013). More recent clinical study showed preliminary efficacy results in GC patients treated with ramucirumab plus pembrolizumab from a multicohort Phase 1a/b study (NCT02443324). For the cohort of ≥ second-line systemic therapy, the ORR was 7% (0/41 CR, 3/41 PR). The disease control rate (DCR) was 51%. The median PFS was 2.6 months. The median OS was 6.2 months. For the cohort of first line, the ORR was 14% (0/28 CR, 4/28 PR), The DCR was

64%. The median PFS was 5.6 months. The median OS was not reached when the data was reported. (Chau et al 2018, Bendell and Calvo 2018).

So far, specific application strategies for the combination of anti-PD-1/PD-L1 and TKIs need further exploration.

1.2. Sitravatinib as a Receptor Tyrosine Kinase Inhibitor

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

Sitravatinib is an orally bioavailable RTK inhibitor with potential antineoplastic activity. It is a potent inhibitor of multiple RTKs including Axl, MER, MET, KIT, FLT3, RET, VEGFR1, VEGFR2, VEGFR3, PDGFRα, DDR2, TRKA, and TRKB. Sitravatinib targets are genetically altered in a variety of cancers and act as oncogenic drivers, promoting cancer development and progression. In addition to targeting genetically altered oncogenic drivers, sitravatinib targets are expressed in a number of immune cell types and promote an immunosuppressive tumor microenvironment (TME), providing rationale for combining with PD-1 checkpoint inhibitor therapy. Simultaneously to the immunostimulatory effects, sitravatinib may further condition the TME in favor of antitumor activity by its immunomodulatory effects mediated through VEGFR and KIT inhibition. Preclinical data with sitravatinib indicate that it can increase expression of PD-L1 on tumor cells in vitro and in vivo. Pilot studies in syngeneic mouse tumor models also suggest that sitravatinib increases the proliferation and fraction of systemic/spleen CD4 + and CD8 + T lymphocytes and reduces the number of systemic myeloid-derived suppressor cells (MDSCs).

1.2.1. Pharmacology

Sitravatinib was demonstrated to be a potent inhibitor of the catalytic activity of a subset of closely related recombinant human RTKs with IC_{50} values ranging from 0.5 to 76 nmol/L. Sitravatinib showed potent activity in RTK-target dependent cell-based assays with IC_{50} values ranging from < 10 to 181 nmol/L. Consistent with this antitumor and antiangiogenic mechanism of action, sitravatinib demonstrated antitumor efficacy over a broad spectrum of human tumor xenograft models. In addition, concurrent treatment with sitravatinib greatly enhanced the activity of anti-PD-1 therapy in the CT26 syngeneic mouse tumor model.

In vitro studies demonstrated that sitravatinib is classified as a highly permeable compound. Sitravatinib was more extensively metabolized in dogs than in mice, rats, and humans in vitro.

In vitro results from the hERG assay demonstrate an IC50 of 0.6 µM (0.38 µg/mL) on the potassium current. At the recommended Phase 2 dose (RP2D) of 150 mg, the mean steady state plasma concentrations (adjusted for free fraction) observed in patients are approximately 290-fold lower than the hERG IC_{50} concentration. There were no adverse effects on the

cardiovascular system, including no effect on the QTc interval, when sitravatinib was administered to dogs at doses up to 4 mg/kg (mean 6-hour concentration of 0.072 µg/mL). Minor increases in blood pressures were observed during the dog cardiovascular study.

Assessment of the neurological functional observation battery and respiratory evaluations in rats did not reveal any sitravatinib-related effects at doses up to 25 mg/kg.

Please refer to the Sitravatinib Investigator's Brochure additional details regarding nonclinical studies of sitravatinib.

1.2.2. Toxicology

In repeat-dose toxicity studies in the dog, no target organs were identified, despite overt decreases in body weight and food consumption. Daily oral administration of sitravatinib to beagle dogs for up to 28 days at a dose level of 3 mg/kg/day was not tolerated and resulted in marked body weight loss and anorexia, with 1 female requiring veterinary intervention and treatment discontinuation because of general debilitation. Based on the severity of test article-related toxicity at 3 mg/kg/day, the no-observed-adverse-effect level (NOAEL) of sitravatinib is 1 mg/kg/day.

In the rat, vascular endothelial growth factor (VEGF)-related target organs were identified, including the adrenal gland, Brunner's glands in the duodenum, femur, and sternum (bone and bone marrow), spleen, lymph nodes, thymus, ovary, kidney (glomerulopathy, tubule necrosis, increased basophilic tubules), pancreas, and tongue. All effects, except those in the kidney and pancreas, either recovered or showed partial recovery. Daily oral administration of sitravatinib to Crl:CD (SD) rats at a dose level of 25 mg/kg/day was not tolerated and resulted in adverse clinical observations, changes in body weight and food consumption, mortality, and early termination. Based on the severity of the sitravatinib-related toxicity at 25 mg/kg/day and mortality (though reduced) in animals given ≥ 10 mg/kg/day, the NOAEL is 2.5 mg/kg/day.

Sitravatinib was evaluated in a standard battery of Good Laboratory Practice (GLP) genotoxicity studies (Ames, chromosome aberrations and in vivo rat micronucleus assays) and was considered negative for mutagenicity and clastogenicity.

Refer to the Sitravatinib Investigator's Brochure for more detailed information on the toxicology of sitravatinib.

1.2.3. Clinical Pharmacology

The pharmacokinetics (PK) profile of single-agent sitravatinib has been evaluated in Study 516-001 after single and repeated dose administration. Plasma samples for PK analyses were collected over a 168-hour period following single dose administration and over a 24-hour period following repeated dose administration. Plasma drug concentrations were determined using a validated, sensitive, liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The PK of sitravatinib was evaluated using non-compartmental analysis methods.

After single dose administration, sitravatinib reaches peak concentration in a median time of approximately 3 to 8 hours. Exposure parameters (maximum concentration [C_{max}] and area under the plasma or serum concentration-time curve [AUC]) are approximately dose proportional with single doses up to 200 mg. The median elimination half-life varies between approximately 42 and 58 hours after oral administration. The steady state PK is reached in a mean time of 11 to

15 days. Drug accumulation was observed after multiple dose administration and ranged from 1.8- to 3.5-fold for C_{max} and 2.0- to 4.7-fold for AUC_{0-24}. The 150 mg dose was determined to be the maximum tolerated dose (MTD) and RP2D; it results in a steady state geometric mean (C_{avg}), C_{max} and AUC_{0-24} of 91.0 ng/mL, 114 ng/mL and 2183 ng·h/mL, respectively. Plasma concentrations are overlapping for 120 mg and 150 mg dose levels.

Pharmacodynamic assessments of sitravatinib are ongoing; however, preliminary analysis shows a concentration dependent modulation of VEGF-A, soluble vascular endothelial growth factor receptor 2 (sVEGFR-2), and soluble MET ectodomain (sMET) levels in patients' plasma samples. The mean prediction (95% confidence interval [CI]) percent change from baseline in biomarker modulation with exposure, approached: VEGF-A (300% increase), sVEGFR-2 (50% decrease) and sMET (35% increase), consistent with VEGFR and MET inhibition. Mean C_{trough} at Cycle 1, Day 15 for the 120 mg QD dose level in study MRTX-500 is 68.0 ng/mL. At these sitravatinib plasma exposure levels, near optimal modulation of biomarker levels is expected.

Refer to the Sitravatinib Investigator's Brochure for more detailed information on clinical pharmacology of sitravatinib.

1.2.4. Clinical Experience With Sitravatinib

Sitravatinib monotherapy and sitravatinib in combination with nivolumab are being evaluated in ongoing studies. Please refer to the Sitravatinib Investigator's Brochure and Sitravatinib Development Safety Update Report (DSUR) for more detailed information on sitravatinib and the currently ongoing studies

1.2.4.1. Study 516-001

Study 516-001 is a multicenter Phase 1/1b study evaluating the safety, PK, metabolism, PD, and clinical activity of sitravatinib in patients with advanced solid tumor malignancies. The study determined the 200-mg dose exceeded the MTD and continued to evaluate 150 mg once daily as the RP2D for monotherapy. The Phase 1b expansion included patients having tumors with selected histological diagnoses and/or molecular markers of solid tumors. As of 26 June 2019, among the 186 patients with available safety data, 183 patients (98%) had experienced at least one TEAE, and 167 patients (90%) had experienced treatment-related AEs. Treatment-related AEs reported in ≥ 10% of patients are provided in Table 1 .

Treatment-related Grade 3-5 AEs reported in ≥ 5% of patients were hypertension (19%), diarrhea (10%), fatigue (7%), lipase increased (5%), and palmar-plantar erythrodysesthesia (5%). Treatment-related Grade 4 AEs were reported in 3 patients and included lipase increased in 2 patients (1%) and febrile neutropenia in 1 patient (1%). A treatment-related Grade 5 AE of cardiac arrest was reported in 1 patient (1%).

Table 1 Summary of Treatment-Emergent, Treatment-Related Adverse Events (≥ 10%) by Preferred Term for Study 516-001

Adverse Event Term	Frequency (N=186)
Diarrhoea	92 (50%)
Fatigue	78 (42%)

Adverse Event Term	Frequency (N=186)
Hypertension	73 (39%)
Nausea	53 (29%)
Decreased appetite	50 (27%)
Vomiting	44 (24%)
Palmar-plantar erythrodysaesthesia 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: Among the 186 patients with available safety data, 73 patients (39%) had experienced at least one treatment-emergent SAE. Treatment-related SAEs were reported in 28 patients (15%) and included diarrhea in 6 patients (3%), nausea and vomiting in 5 patients each (3%), fatigue in 4 patients (2%), hypertension in 3 patients (2%), and headache, pancreatitis, and pulmonary embolism in 2 patients each (1%).

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

1.2.4.2. Study MRTX-500

Study MRTX-500 is an open-label, parallel Phase 2 evaluation of sitravatinib in the combination with the PD-1 inhibitor nivolumab, in patients with locally advanced, unresectable or metastatic non-squamous non-small cell lung carcinoma (NSCLC) who have experienced PD either on or after prior treatment with a checkpoint inhibitor therapy or after treatment with a platinum-based doublet chemotherapy. The study began with a lead-in evaluation of sitravatinib 120 mg once daily in combination with nivolumab administered by intravenous infusion, 240 mg every 2 weeks. No protocol defined dose-limiting toxicities (DLTs) were reported in the first 6 evaluable patients treated. Based on preliminary long-term tolerability assessments from Study 516-001 (Mirati 2018) and data from MRTX-500, Mirati decided to evaluate only the

120-mg dose of sitravatinib as this dose level should be adequate to achieve plasma exposure required for inhibition of VEGF and TAM receptors necessary to achieve antitumor efficacy in the combination setting. The 120-mg dose level was selected as the RP2D.

As of 26 June 2019, patient data were entered in the clinical trial database for 135 patients (63 men/72 women; median age: 66 years; range 37 to 89 years) with advanced or metastatic NSCLC. All cohorts have enrolled patients, with 107 patients in the CIT-experienced cohorts and 22 patients in the CIT-naïve cohorts. Six patients have enrolled into the PK drug formulation substudy. Enrollment is ongoing.

As of 26 June 2019, among the 135 patients with available safety data, 131 patients (97%) had experienced at least one treatment-emergent AE; 126 patients (93%) had experienced treatment-related AEs; 125 patients (93%) had experienced sitravatinib-related AEs; and 91 patients (67%) had experienced nivolumab-related AEs. Treatment-related AEs were reported in ≥ 10% of patients provided in Table 2.

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

Table 2 Summary of Treatment-Emergent, Treatment-Related Adverse Events (≥ 10%) by Preferred Term for Study MRTX-500

Adverse Event Term	Frequency (N=135)
Diarrhoea	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 erythrodysaesthesia syndrome	22 (16%)
Stomatitis	22 (16%)
Alanine aminotransferase increased	20 (15%)
Dehydration	15 (11%)
Dry mouth	13 (10%)
Dysgeusia	13 (10%)

Serious Adverse Events: Among the 135 patients with available safety data, 60 patients (44%) experienced at least one treatment-emergent SAE. Treatment-related SAEs were reported in 31 patients (23%) and included diarrhea in 5 patients (4%); cardiac arrest, deep vein thrombosis, hypertension, pancreatitis, and pneumonitis in 2 patients (2%); and adrenalitis, anemia, cardiac failure, colitis, confusional 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 in 1 patient each (1%).

As of 26 June 2019, 57 deaths were reported in this study, with the primary causes of death being the disease under study (n=43), unknown (n=4), pneumonia (n=4), ischemic colitis (n=2), and aspiration, cardiac arrest, bronchopleural-cutaneous fistula hemorrhage, and pulmonary embolism (n=1 each).

1.2.5. Rationale for Selection of Sitravatinib Dose

Available nonclinical and safety and PK data from ongoing studies were analyzed to determine the recommended dose of sitravatinib. Nonclinical toxicology studies as well as clinical safety data from the Phase 1/1b and Phase 2 studies suggest that AEs associated with sitravatinib are similar to those observed with other small molecule inhibitors of the VEGFR pathway.

In Study 516-001, 150 mg once daily was recommended as the RP2D for monotherapy. Based on a recent evaluation of the sitravatinib clinical program, it is recommended that the starting dose be lowered to 120 mg orally once daily (Mirati 2018).

In Study MRTX-500, NSCLC patients received sitravatinib 120 mg once daily in combination with nivolumab. As recently reported (Mirati 2018), 45 patients have been enrolled in this ongoing study as of March 2018 and most AEs reported by investigators were Grade 1 or 2. The 120-mg dose of sitravatinib is expected to achieve plasma exposure required for inhibition of VEGFR and TAM receptors necessary to achieve antitumor efficacy in the combination setting.

Based on the available data described above, 120 mg once daily is considered safe and is the recommended dose in NSCLC patients. Since sitravatinib monotherapy and sitravatinib in combination with tislelizumab are being tested for the first time in GC and HCC patients in this study, 80 mg once daily is selected as the starting dose.

1.3. Tislelizumab as a PD-1 Blocker

Immune check point-inhibitory receptor, PD-1 is mainly expressed in activated T cells including CD8 + cytotoxic T-lymphocytes and CD4 + T-helper lymphocytes (Topalian et al 2012, Bersanelli and Buti 2017). It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor and attenuate T cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes, while the expression of PD-1 ligand, PD-L1, is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as IFN-γ and IFN-α in the tumor microenvironment. Furthermore, the increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor

and tumor-associated stromal cells is observed in many types of solid human 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 cancer, and ovarian cancer (Jin and Yoon 2016, ONO 2017, Patel and Kurzrock 2015, Van Der Kraak et al 2016, McDaniel 2016, Gong et al 2011, Liu et al 2017, Saito et al 2013). Several anti-PD-1 agents have been approved for the treatment of several cancers. Thus, PD-1 is an established target for cancer immunotherapy.

1.3.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [KD]=0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and preactivated, primary peripheral blood mononuclear cells. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were coinjected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to gamma fragment crystallizable region (Fc) receptor IIIA (FcγRIIIA) and complement 1q, a subunit of complement 1, by in vitro assays, suggesting either low or no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009).

Please refer to the Tislelizumab Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

1.3.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and monkeys and in a 13-week, repeat-dose toxicology study in monkeys. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood cells. The pivotal toxicology studies were conducted following GLP regulations. The single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. 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 either human or monkey tissues, nor was any effect on cytokine release observed in human whole-blood assay. The toxicokinetics profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was

considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study of BGB-900-104.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.3.3. Clinical Pharmacology

In the Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim PK analysis (data cutoff date 28 August 2017) was conducted using noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, or 10 mg/kg once every 2 weeks, and 2.0 mg/kg, 5.0 mg/kg, or 200 mg once every 3 weeks (Phase 1a Parts 1, 2, and 3, and Phase 1b in Study BGB-A317_Study_001) and patients who received doses of 200 mg once every 3 weeks in Phase 1 of Study BGB-A317-102 (n = 19). C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration and at steady state. Preliminary PK data from 27 patients who were administered 200 mg once every 3 weeks (Phase 1a, Part 3 and Study BGB-A317-102) showed tislelizumab concentrations between the range of concentrations observed for patients who were administered 2 mg/kg and 5 mg/kg doses.

Preliminary population PK analysis using a 2-compartment model with first-order elimination shows a systemic clearance (CL) of tislelizumab of 0.173 L/day, volume of distribution (V_d) in the central and peripheral compartments of 2.89 and 1.76 L, respectively, and half-life ($t_{1/2}$) was approximately 19 days. Race, gender, and body weight were not significant covariates on the CL of tislelizumab, which supports fixed-dosing across different ethnic groups.

1.3.4. Clinical Experience With Tislelizumab

As of 20 May 2019, there are 22 ongoing studies with tislelizumab with over 1705 patients treated. Of these, 13 studies have preliminary data available in the Tislelizumab Investigator's Brochure: 7 monotherapy studies, 2 chemotherapy combination therapy studies, and 4 investigational agent combination therapy studies.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the safety and efficacy data of tislelizumab when given as monotherapy or in combination with chemotherapy.

1.3.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy. Overall, there were 1273 patients in the Pooled Monotherapy studies: 1137 patients treated in 5 solid tumor studies and 136 patients treated in 2 hematologic malignancies studies. Of the 1273 enrolled, 544 patients (42.7%) remained on study as of 20 May 2019; 272 patients (21.4%) were still receiving tislelizumab treatment.

1.3.4.1.1. Pooled Demographics and Baseline Characteristics

Table 3 shows the demographics and baseline characteristics for the patients treated in the Pooled Monotherapy studies.

Table 3 Demographics, Baseline Characteristics, Treatment Exposure Duration, and Study Follow-up Duration in Pooled Monotherapy Studies (Safety Analysis Set)

Measure	Overall
	N = 1273
Age (years)	
Median	59.0
Min, Max	18, 90
Sex, n (%)	
Male	852 (66.9)
Female	421 (33.1)
Race, n (%)	
Asian	807 (63.4)
Black	11 (0.9)
White	405 (31.8)
Missing	2 (0.2)
Other	48 (3.8)
Prior systemic anticancer therapy regimens [a]	
Median	1.0
Min, Max	0, 12
Prior systemic anticancer therapy regimens (grouped)[a], n (%)	
0	271 (21.3)
1	413 (32.4)
2	265 (20.8)
≥3	324 (25.5)
Study treatment exposure duration (months)	
Median	3.58
Min, Max	0.1, 43.6
Study follow-up duration (months)	
Median	8.34
Min, Max	0.1, 47.5

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cutoff 20 May 2019.
[a] Only systemic therapies were selected.

Overall, the 1273 patients in the pooled monotherapy analysis had a median treatment exposure duration of 3.58 months (range: 0.1 to 43.6) and median study follow-up duration of 8.34 months (range: 0.1 to 47.5). Overall, the total pooled monotherapy population had a median age of 59 years and was 66.9% male.

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

Of the 1273 total patients treated in the Pooled Monotherapy studies, 846 (66.5%) experienced at least one treatment-related TEAE. The most commonly occurring TEAEs assessed as related to tislelizumab were aspartate aminotransferase increased (128 patients, 10.1%), alanine aminotransferase increased (123 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (96 patients, 7.5%), and pyrexia (94 patients, 7.4%).

Of the 1273 total patients treated in the Pooled Monotherapy studies, 162 (12.7%) experienced at least one ≥ Grade 3 TEAE assessed as related to tislelizumab. The only ≥ Grade 3 TEAEs that occurred in ≥ 1% (≥ 12 patients) in the total study population were aspartate aminotransferase increased (19 patients, 1.5%) and alanine aminotransferase increased (15 patients, 1.2%).

1.3.4.1.3. Treatment-Emergent Serious Adverse Events

Of the 1273 total patients treated in the Pooled Monotherapy studies, 424 (33.3%) experienced at least one treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs were pneumonia (35 patients, 2.7%), pyrexia (22 patients, 1.7%), and ascites (17 patients, 1.3%).

1.3.4.1.4. Special Categories of Immune-Related Adverse Events

Immune-related AEs are of special interest in tislelizumab studies because treatment with anti-PD-1 therapy can cause autoimmune disorders. As AEs of special interest, irAEs are monitored and captured consistently and rapidly.

Immune-related AEs are consistent with an immune-related mechanism or immune-related component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-related AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an irAE that spans a window of days to several months.

All irAEs presented here are assessed as related to study drug by the investigator and categorized by the BeiGene Safety/Pharmacovigilance team. Certain irAEs have multiple Medical Dictionary for Regulatory Activities (MedDRA) terms associated with the same category. Special categories have been created to group patients experiencing these events.

All irAEs that occurred in ≥ 1% in the total Pooled Monotherapy studies are shown in Table 4.

Table 4 Immune-Related Adverse Events of Any Grade Occurring in ≥ 1% in Pooled Monotherapy Studies (Safety Analysis Set)

Categories Preferred Term	Total (N = 1273)	
	Any Grade n (%) [a]	Grade ≥ 3 n (%) [a]
Patients with at least one potential immune-related AE [a]	602 (47.3)	121 (9.5)
Immune-related skin adverse reaction	242 (19.0)	11 (0.9)
Rash	97 (7.6)	4 (0.3)
Pruritus	78 (6.1)	0
Pruritus generalised	29 (2.3)	0
Rash maculo-papular	24 (1.9)	1 (0.1)
Immune-related hepatitis	233 (18.3)	51 (4.0)
Aspartate aminotransferase increased	129 (10.1)	21 (1.6)
Alanine aminotransferase increased	124 (9.7)	16 (1.3)
Blood bilirubin increased	74 (5.8)	4 (0.3)
Gamma-glutamyltransferase increased	45 (3.5)	17 (1.3)
Bilirubin conjugated increased	40 (3.1)	3 (0.2)
Immune-related endocrinopathies	187 (14.7)	7 (0.5)
Hypothyroidism	113 (8.9)	0
Hyperthyroidism	47 (3.7)	1 (0.1)
Hyperglycaemia	17 (1.3)	4 (0.3)
Immune-related colitis	75 (5.9)	10 (0.8)
Diarrhoea	66 (5.2)	5 (0.4)
Immune-related pneumonitis	50 (3.9)	30 (2.4)
Pneumonitis	22 (1.7)	9 (0.7)
Lung infection	13 (1.0)	8 (0.6)
Immune-related myositis/rhabdomyolysis/cardiomyopathy	39 (3.1)	7 (0.5)
Blood creatine phosphokinase increased	30 (2.4)	4 (0.3)
Immune-related nephritis and renal dysfunction	33 (2.6)	6 (0.5)
Blood creatinine increased	25 (2.0)	2 (0.2)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: AE, adverse event; N, total number of patients treated; n, number of patients within each category; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, system organ class.

Note: All AEs are coded using MedDRA and graded according to NCI CTCAE v4.03. Maximum CTCAE grade was selected per patient under each PT. Potential immune-related AE is identified based on a predefined list of AEs and assessed as treatment-related by investigators.
Sorted in descending order of the number of patients in SOC and PT in Any Grade under Total column.
Data cutoff 20 May 2019.
[a] Percentages are based on the total population.

Of the 1273 total patients for the Pooled Monotherapy studies, 602 (47.3%) experienced at least one irAE of any grade. The most commonly occurring irAEs of any grade were aspartate aminotransferase increased (129 patients, 10.1%), alanine aminotransferase increased (124 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (97 patients, 7.6%), and pruritus (78 patients, 6.1%). Analysis of the total patients with at least one irAE that also was ≥ Grade 3 in severity showed that 121 patients (9.5%) experienced such events. The most commonly occurring irAEs ≥ Grade 3 in severity were aspartate aminotransferase increased (21 patients, 1.6%), gamma-glutamyltransferase increased (17 patients, 1.3%), alanine aminotransferase increased (16 patients, 1.3%), pneumonitis and pneumonia (9 patients each, 0.7%).

1.3.4.1.5. Infusion-Related Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon. Of the 1273 total patients in the Pooled Monotherapy studies, 97 (7.6%) experienced at least one infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade that occurred in the total pooled analysis were pyrexia (50 patients, 3.9%), infusion-related reactions (28 patients, 2.2%), and pruritus (11 patients, 0.9%). There were 6 patients who reported a total of 7 ≥ Grade 3 infusion-related reactions in the Pooled Monotherapy studies (events of back pain, hypotension, infusion-related reaction, musculoskeletal chest pain, pyrexia, and rash).

1.3.4.1.6. Fatal Adverse Events

Treatment-emergent fatal AEs that occurred in the Pooled Monotherapy studies are shown in Table 5.

Table 5 Treatment-Emergent Fatal Adverse Events Regardless of Causality in Pooled Monotherapy Studies (Safety Analysis Set)

Category	Overall (N = 1273) n (%)
All deaths at data cutoff	641 (50.4)
Death ≤ 30 days after last dose	105 (8.2)
Primary cause of death	
Adverse event	21 (1.6)
Concurrent illness	0
Disease under study	22 (1.7)
Indeterminate	0

Category	Overall (N = 1273) n (%)
Progressive disease	52 (4.1)
Other	10 (0.8)
Death > 30 days after last dose	536 (42.1)
Primary cause of death	
Adverse event	14 (1.1)
Concurrent illness	0
Disease under study	95 (7.5)
Indeterminate	3 (0.2)
Progressive disease	399 (31.3)
Other	24 (1.9)
Missing	1 (0.1)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cutoff 20 May 2019.

Table 5 shows a total of 105 patients (8.2% of the total population) died ≤ 30 days after the last study drug dose in the Pooled Monotherapy studies as of 20 May 2019. Of these 105 patients, there were 21 patients (1.6% of the total population) who had an AE with a fatal outcome ≤ 30 days after the last study drug dose. Of the 536 patients (42.1% of the total population) who died > 30 days after the last study drug dose, 14 patients (1.1% of the total population) died as a result of an AE.

1.3.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 2 of the ongoing monotherapy studies in solid tumors, BGB-A317_Study_001 and BGB-A317-102, which are summarized below (data cutoff 20 May 2019).

1.3.4.2.1. Study BGB-A317_Study_001

BGB-A317_Study_001 is a 2-stage study. Phase 1a consists of a dose escalation and dose-finding component, Phase 1b investigates efficacy and safety in select tumor types.

Responses were assessed by the investigator per the RECIST v1.1 criteria. There were 451 patients treated in the study and 441 patients were included in the efficacy evaluable set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable postbaseline tumor assessment.

Across all disease cohorts, there were 5 patients (1.1%) with a CR. A total of 55 patients (12.5%) had a confirmed PR. The resulting overall clinical response rate was 13.6%. Additionally, there were 142 patients (32.2%) with a best overall response of stable disease (SD). A total of 199 patients (45.1%) had a best response of PD in this study.

1.3.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a two-phase, non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 is an indication expansion study.

Responses were assessed by the investigator per the RECIST v1.1 criteria.

Overall, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable postbaseline tumor assessment.

The tumor responses in the Efficacy Evaluable Analysis Set of Study BGB-A317-102 across all disease cohorts and study phases was 1 patient (0.4%) with a CR and 44 patients (17.7%) with confirmed PR. The resulting overall clinical response rate was 18.1%. Additionally, there were 91 patients (36.5%) with a best overall response of SD. A total of 113 patients (45.4%) had a best response of PD in this study.

1.3.5. Rationale for Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of 200 mg intravenously (IV) once every 3 weeks was selected for further evaluation. The MTD was not identified and only 1 DLT was reported in the first-in-human study.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 3 weeks.

According to PK data from BGB-A317_Study_001, Phase 1a, the CL of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the observed serum exposure of a 200-mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

No unexpected treatment-related AEs occurred in the 200-mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of SD, and 6 patients (46%) had a BOR of PD. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.

Tislelizumab 200 mg once every 3 weeks is the recommended initial dose for combination with sitravatinib.

1.4. Rationale for Combination of Sitravatinib and Tislelizumab in the Treatment of Advanced Solid Tumors

Cancer cells face selective pressures while being treated and mutations occurring in individual cancer cells represent continuous evolution of the original cancer. Almost all malignancies develop resistance to anticancer therapies eventually. This is also the case for checkpoint blockade agents where acquired resistance occurs in a large portion of treated patients who achieved an initial meaningful response. This phenomenon of acquired resistance helps cancer cells adapt to the environment and survive immune attacks and is a reminder of therapeutic challenges that need to be overcome (Syn et al 2017).

Combining an immunotherapeutic PD-1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone. The use of TKIs to treat cancer is well established based on robust clinical efficacy achieved with well tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected TKIs have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, thereby increasing the frequency and function of effector immune elements while decreasing the number and function of immune suppressor cells.

Monoclonal antibodies that target either PD-1 or PD-L1, checkpoint inhibitors, can block binding and boost the immune response against cancer cells. These drugs have been shown to be helpful in treating several types of cancer, including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. Cancer cells in most nonresponders to single-agent checkpoint inhibitors escape through innate mechanisms that allow the cancer cells to grow and survive. As a result, disease progresses at a rate consistent with the natural history. However, unlike intrinsic resistance, late relapses are now emerging in patients with prior clinical benefit after longer follow-up of clinical trials, suggesting the emergence of acquired resistance (Jenkins et al 2018). Strategies to improve the clinical efficacy of checkpoint inhibitors by overcoming innate or acquired resistance are needed.

Together, sitravatinib and tislelizumab may elicit greater antitumor activity, as sitravatinib is predicted to enhance several steps in the cancer immunity cycle that may augment the efficacy of tislelizumab. First, the antitumor activity of sitravatinib may promote the release of tumor antigens. Second, inhibition of the split kinase receptors VEGFR-2 and KIT may decrease the number of regulatory T cells (Tregs) and MDSCs, thus promoting the expansion and migration of antitumor cytotoxic T cells and their infiltration into tumor tissue. Third, sitravatinib may reverse the immunosuppressive effects within the tumor microenvironment that are mediated by the TAM receptors through inhibition of MERTK, resulting in an increased number of M1 versus M2-polarized macrophages and release of interleukin (IL)-12, IL-6, and tumor necrosis factor (TNF). These downstream effects enhance CD8 + T cell activation, and through the inhibition of AXL, promote increased antigen presentation through termination of the Toll-like receptor dependent inflammatory response in dendritic cells.

Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy is a rational approach to improving outcomes in patients. In summary, selective RTKs inhibit key molecular and cellular pathways strongly implicated in

checkpoint inhibitor resistance and therefore represent reasonable strategies to enhance or restore antitumor immunity when combined with anti-PD-1 or anti-PD-L1 monoclonal antibodies.

1.5. Benefit-Risk Assessment

Sitravatinib is being evaluated as monotherapy in the ongoing study 516-001 (NCT02219711). In a cohort for clear cell renal cell carcinoma, sitravatinib showed clinical activity with 4 confirmed PRs in a heavily pretreated patient population (n=20), suggesting that sitravatinib may be able to overcome resistance to prior antiangiogenic therapy with VEGF pathway inhibitors.

Combination therapy with a small molecule inhibitor of the VEGFR pathway may improve the clinical efficacy of immunotherapies and overcome resistance to checkpoint inhibitor therapy (refer to Section 1.2.4.2). For patients with HCC and GC, combination therapy may improve the clinical efficacy of single-agent immunotherapies (Section 1.1.1 and Section 1.1.2). Access to new treatment options and/or treatment options after prior immunotherapy remain a significant unmet medical need. Based on available tislelizumab and sitravatinib data and the publication from other PD-1 or PD-L1 inhibitors and other small molecule inhibitors of the VEGFR pathway, the combination of sitravatinib and tislelizumab may elicit greater antitumor activity and have a manageable safety profile. However, the risk benefit for this combination has not yet been established.

More than 100 patients have been treated with sitravatinib monotherapy and in combination. Nonclinical toxicology studies as well as clinical safety data from the Phase 1/1b and Phase 2 studies suggest that AEs associated with sitravatinib are similar to those observed with other small molecule inhibitors of the VEGFR pathway. For further discussion on the safety profile of sitravatinib, please refer to the Sitravatinib Investigator's Brochure.

More than 1000 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. The safety profile is consistent with known class effects of anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3 or Grade 4 irAEs have been observed, which are generally reversible and manageable with study drug interruption and/or steroid treatment. For further discussion on the safety profile of tislelizumab, please refer to the Tislelizumab Investigator's Brochure.

A SMC will be established and will monitor the preliminary safety and activity data for sitravatinib monotherapy and in combination with tislelizumab in this study. The SMC will be tasked with reviewing all available safety, tolerability, PK, and exploratory data and make recommendations on safety management.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives for Phase 1 (Dose Escalation)

2.1.1. Primary Objectives

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

2.1.2. Secondary Objectives

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

2.1.3. Exploratory Objectives

- To explore potential biomarkers in association with efficacy, resistance, and/or PD in tumor tissue and in peripheral whole blood
- To explore potential pharmacodynamic biomarkers for sitravatinib as monotherapy and in combination with tislelizumab
- To assess PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To explore the effect of pharmacogenetic (PGx) polymorphisms on PK of sitravatinib

2.2. Study Objectives for Phase 2 (Dose Expansion)

2.2.1. Primary Objective

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

2.2.2. Secondary Objectives

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

2.2.3. Exploratory Objectives

- To assess potential biomarkers in association with efficacy, resistance, and/or PD in tumor tissue and in peripheral whole blood
- To explore potential pharmacodynamic biomarkers for sitravatinib as monotherapy and in combination with tislelizumab
- To assess PK and immunogenicity to tislelizumab when given in combination with sitravatinib
- To assess overall survival (OS)
- To explore the effect of pharmacogenetic (PGx) polymorphisms on PK of sitravatinib

2.3. Study Endpoints for Phase 1 (Dose Escalation)

2.3.1. Primary Endpoints

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

2.3.2. Secondary Endpoints

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

2.3.3. Exploratory Endpoints

- Potential biomarkers, including, but not limited to, programmed cell death protein ligand-1 (PD-L1) expression, immune cell profiling, tumor mutation load, and gene expression profiling in archival and/or fresh tumor tissue and blood (or blood derivatives) obtained before, during, or after treatment or at PD; and the association with disease status and/or the response to sitravatinib as monotherapy or in combination with tislelizumab
- Changes of potential pharmacodynamic biomarkers in response to sitravatinib as monotherapy and in combination with tislelizumab, such as, but not limited to, soluble vascular endothelial growth factor receptor 2 (sVEGFR-2) and immune cell subpopulations in peripheral blood
- Serum concentrations of tislelizumab and anti-tislelizumab antibodies
- Effect of genetic polymorphisms of hepatic metabolizing enzymes and transporters, including, but not limited to, CYP1A2, 2D6, and 2C8 on the PK of sitravatinib

2.4. Study Endpoints for Phase 2 (Dose Expansion)

2.4.1. Primary Endpoint

- Efficacy evaluations by investigators: ORR based on RECIST v1.1

2.4.2. Secondary Endpoints

- Efficacy evaluations by investigators: DOR, DCR, and PFS based on RECIST v1.1
- Safety and tolerability will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE v5.0, relevant physical examination, ECGs, and laboratory assessments as needed
- PK: plasma concentrations of sitravatinib predose and postdose at steady state

2.4.3. Exploratory Endpoints

- Potential biomarkers, including, but not limited to, PD-L1expression, immune cell profiling, tumor mutation load, and gene expression profiling in archival and/or fresh tumor tissue and blood (or blood derives) obtained before, during, or after treatment or at PD; and the association with disease status and/or response to sitravatinib as monotherapy or in combination with tislelizumab
- Changes of potential pharmacodynamic biomarkers in response to sitravatinib as monotherapy and in combination with tislelizumab, such as, but not limited to, sVEGFR-2 and immune cell subpopulations in peripheral blood
- Serum concentrations of tislelizumab and anti-tislelizumab antibodies
- OS is defined as the time from date of first dose of study drug(s) to date of death due to any cause
- Effect of genetic polymorphisms of hepatic metabolizing enzymes and transporters, including, but not limited to, CYP1A2, 2D6, and 2C8 on the PK of sitravatinib

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter Phase 1/2 clinical study for patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC or G/GEJ cancer. All patients will receive study treatment(s) until PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor. There will be approximately 20 centers in Asia Pacific including Australia and China.

This study consists of 2 phases.

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

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

The combination dose escalation of sitravatinib (80 mg once daily and 120 mg once daily; modified 3 + 3 design) with tislelizumab (200 mg once every 3 weeks, in both cohorts) will be evaluated in patients with unresectable locally advanced or metastatic HCC or G/GEJ cancer. The combination dose escalation may start simultaneously with the monotherapy cohort as the dose regimen for all cohorts are considered safe based on the totality of available clinical data. There is no interaction anticipated between sitravatinib and tislelizumab to influence respective PK profiles. If the combination dose of 80 mg sitravatinib and 200 mg tislelizumab has been declared tolerable, the dose of sitravatinib will be escalated to 120 mg and tislelizumab will remain fixed at 200 mg. Approximately 12 to 24 DLT evaluable patients will be treated.

DLT Observation Period and the Modified 3 + 3 Scheme

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

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

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

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

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

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

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

Approximately 20 patients will be enrolled in each cohort. There will be a total of 4 cohorts in the study (Figure 1).

Sitravatinib monotherapy

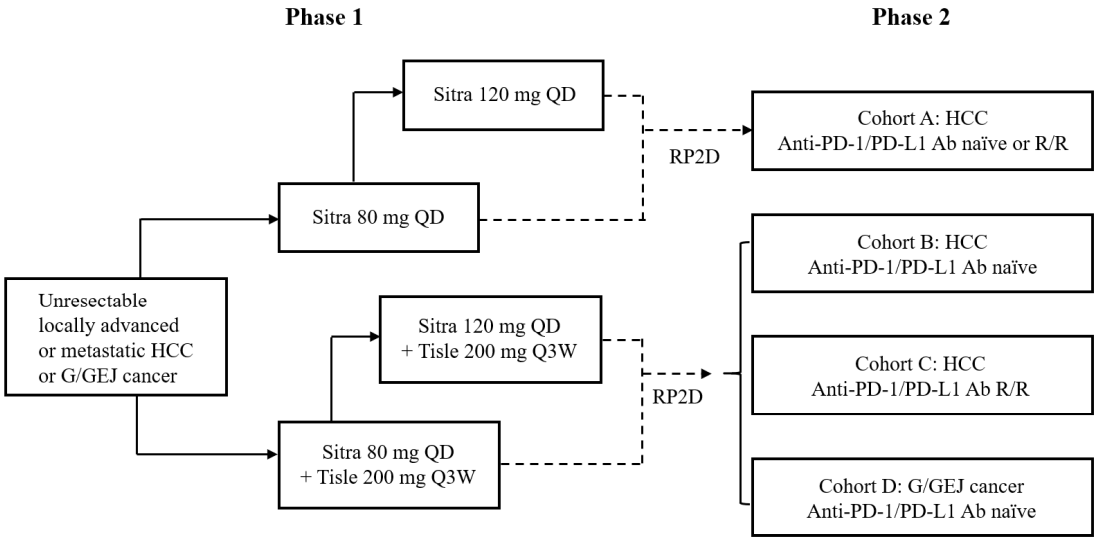
- Cohort A: Anti-PD-1/PD-L1 antibody naïve or refractory/resistant HCC

Sitravatinib in combination with tislelizumab

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

Sitravatinib will be administered orally, once daily continuously, tislelizumab will be administered sequentially starting on Cycle 1 Day 1 and every 21 days (ie, once every 3 weeks) thereafter. The study drug(s) will be administered until they meet a discontinuation criterion.

Figure 1: Study Schema



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

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose of study drug(s). Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure. Patients who are suspected or known to have serious respiratory concurrent condition or exhibit significant respiratory symptoms unrelated to underlying cancer will have a pulmonary function test (refer to Appendix 1 for details). Repeating screening assessments within the original screening window is allowed if the patient did not previously meet certain eligibility criteria (eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD) after consultation with the medical monitor; the investigator is to assess patient eligibility according to the latest screening assessment results. Refer to Section 7.1 for additional details.

3.3. Treatment Period

After completing all screening activities, patients confirmed to be eligible by the sponsor or designee will be enrolled to receive either sitravatinib monotherapy or sitravatinib in combination with tislelizumab. The patients will be enrolled according to their tumor type and by prior anti-PD-1/PD-L1 treatment. All patients will receive study drug(s) until occurrence of PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

Study procedures of each clinic visit are outlined in Appendix 1 and Appendix 2.

On days with PK assessments, study drug(s) should be administered in the clinic in accordance with the schedule for the PK samples. Assessments should be obtained before study drug(s) administration unless stated otherwise in Appendix 1 and Appendix 2 and should be performed in order of least invasive to most invasive assessment. All safety-related assessments must be reviewed and dose modifications, if necessary, must be made by the investigator or subinvestigator before study drug(s) administration.

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

Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit within 30 days after last dose of the study drug(s) or before initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) were performed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the study drug(s) were initially interrupted due to AEs and then permanently discontinued, the EOT Visit may occur later, but no later than the permitted time of dose delay plus 7 days.

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

Telephone contact with patients should be conducted to assess irAEs and concomitant medications (if appropriate; eg, if associated with an irAE or is a new 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. If patient reports 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.

Patients who discontinue study treatment prior to PD will have their tumors assessed as outlined in Section 7.4.

3.5. Survival Follow-up

In Phase 2 (dose expansion), patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

3.6. Discontinuation From Study Treatment or From the Study

3.6.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. Patients who discontinue study treatment for reasons other than PD, should be followed for assessments of antitumor activity (Section 7.4), safety (Section 7.3) and survival (Section 3.5), if possible.

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

- Patient withdrawal of consent
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer)
- Patient noncompliance
- PD

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

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

- Patient withdrawal of consent
- Death
- Lost to follow up
- Patients have completed all study assessments
- Sponsor termination of study

3.7. End of Study

The end of study is defined as the date when the last patient's last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is collected for the last patient, whichever occurs 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
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit.

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

The sponsor has the right to close a site at any time. The decision will be notified to the site in advance. Reasons for closing a site may include, but are not limited, to the following:

- Excessively slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with Good Clinical Practice (GCP), applicable laws, and regulations
- Study activity is completed (ie, all patients have completed and all obligations have been fulfilled)

3.8. Dose-Limiting Toxicities

3.8.1. Assessment of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose of study drug(s). For dose escalation decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for dose escalation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving monotherapy who do not receive ≥ 75% of scheduled sitravatinib during the DLT assessment window, unless they experience a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled sitravatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window, unless they experience a DLT.

3.8.2. Definition of Dose-Limiting Toxicity

A DLT is defined as any of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to sitravatinib and/or tislelizumab.

Hematologic

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

Non-Hematologic

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not improve to ≤ Grade 2 within 3 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 hypertension that improves to < 160/100 mmHg, within 7 days of optimal supportive care
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)

All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed with input from other functional representatives as appropriate. On the basis of a review of these data and in consultation with the investigators, a determination will be made regarding dose confirmation decisions and/or safety management.

SMC will be established and includes both the sponsor and investigators. The SMC will review all available safety, efficacy, PK, and exploratory data. Additional dose levels may be evaluated if needed. For the sitravatinib combination therapy, RP2Ds for each tumor type will be recommended by SMC based on 6 to 12 DLT evaluable patients respectively.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

4.1.1. Inclusion Criteria for All Patients

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

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place)
3. To provide archival tumor tissue (formalin-fixed paraffin-embedded [FFPE] block with tumor tissue or unstained slides)

   Note: If archival tumor tissue is not available or of sufficient quantity, a fresh biopsy is recommended. Patients who cannot provide archival tumor tissue or biopsy samples are eligible for the study if other enrollment criteria are satisfied.

   - Tumor tissue needs to originate from core or punch biopsy.
   - Tumor tissue from fine-needle aspiration is not acceptable.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 (Appendix 4)
5. Adequate organ function as indicated by the following laboratory values ≤ 7 days before the first dose of study drug(s):
   a. Patients must not have required a blood or platelet transfusion or growth factor support ≤ 14 days before sample collection at Screening for the following
      i. ANC ≥ 1.5 x 109/L
      ii. Platelets ≥ 75 x 109/L
      iii. Hemoglobin ≥ 90 g/L
   b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN), or estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 9)
   c. AST and ALT ≤ 3 x ULN for patients with G/GEJ cancer. AST and ALT ≤ 5 x ULN for patients with HCC
   d. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome), total bilirubin < 5 x ULN for patients with HCC and cirrhosis
   e. International normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 x ULN
   f. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
   g. Serum albumin ≥ 30 g/L

6. Females of childbearing potential must be willing to use a highly effective method of birth control (Appendix 7) for the duration of the study, and ≥ 120 days after the last dose of study drug(s), and have a negative serum pregnancy test ≤ 7 days of first dose of study drug(s)
7. Nonsterile males must be willing to use a highly effective method of birth control (Appendix 7) for the duration of the study and for ≥ 120 days after the last dose of study drug(s)

4.1.2. Phase 1 Inclusion Criteria

8. Failed current standard-of-care treatment, or standard-of-care treatment is considered not appropriate at present

For HCC patients

9. Histologically or cytologically confirmed, unresectable, locally advanced, or metastatic HCC

   Note: Fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma histology is excluded
10. Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease (Appendix 13) that is not amenable to or has progressed after loco-regional therapy and is not amenable to a curative treatment approach
11. Child-Pugh A classification for liver function (Appendix 5) assessed within 7 days of first dose of study drug(s)
12. No tumor thrombus involving main trunk of portal vein or inferior vena cava
13. No loco-regional therapy to the liver (ie, transarterial chemoembolization [TACE], transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 28 days before the first dose of study drug(s)
14. No prior history of ≥ Grade 2 hepatic encephalopathy before the first dose of study drug(s)
15. No clinical evidence of portal hypertension with bleeding esophageal or gastric varices within 6 months before the first dose of study drug(s)

For G/GEJ cancer patients

16. Histologically or cytologically proven adenocarcinoma of the stomach or gastroesophageal junction, inoperable locally advanced or with metastatic disease
17. No history of gastrointestinal (GI) perforation and/or fistulae within 6 months before the first dose of study drug(s)
18. No clinically significant GI bleeding within 3 months before the first dose of study drug(s)
19. No clinically significant bowel obstruction
20. No complete gastric resection
21. No weight loss ≥ 20% of total body weight within 2 months before the first dose of study drug(s)

4.1.3. Phase 2 Inclusion Criteria

22. At least 1 measurable lesion as defined by RECIST v1.1

    Note: Selected target lesion(s) must meet 1 of 2 criteria: 1) not previously treated with local therapy or 2) within the field of prior local therapy but with documented subsequent progression as per RECIST v1.1

Cohorts A, B, and C: HCC

23. Histologically or cytologically confirmed unresectable locally advanced or metastatic HCC

    Note: Fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma histology is excluded

24. Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease (Appendix 13) that is not amenable to or has progressed after loco-regional therapy and is not amenable to a curative treatment approach
25. Child-Pugh A classification for liver function (Appendix 5) assessed within 7 days of first dose of study drug(s)
26. No tumor thrombus involving main trunk of portal vein or inferior vena cava
27. No loco-regional therapy to the liver (ie, transarterial chemoembolization [TACE], transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 28 days before the first dose of study drug(s)
28. No prior history of ≥ Grade 2 hepatic encephalopathy before the first dose of study drug(s)
29. No clinical evidence of portal hypertension with bleeding esophageal or gastric varices within 6 months before the first dose of study drug(s)

Cohort A: Anti-PD-1/PD-L1 Antibody Naïve or Refractory/Resistant HCC

30. Failed current standard-of-care treatment, or standard-of-care treatment is considered not appropriate at present
31. Received ≤ 2 lines of systemic treatment

Cohort B: Anti-PD-1/PD-L1 Antibody Naïve HCC

32. Failed current standard-of-care treatment, or standard-of-care treatment is considered not appropriate at present
33. No other prior immunotherapies, including but not limited to, anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40, and anti-CD137
34. Received ≤ 2 lines of systemic treatment

Cohort C: Anti-PD-1/PD-L1 Antibody Refractory/Resistant (R/R) HCC

35. Received ≤ 2 lines of systemic treatment
36. Radiographic progression per RECIST v1.1 on or after anti-PD-1/PD-L1 therapy as the most recent treatment for unresectable locally advanced or metastatic HCC

- Anti-PD-1/PD-L1 antibody refractory is defined as radiographic progression on or after anti-PD-1/PD-L1 therapy with best response to anti-PD-1/PD-L1 of PD or SD for ≤ 6 weeks (+ 2 weeks permitted for radiographic scheduling)
- Anti-PD-1/PD-L1 antibody resistant is defined as best response to anti-PD-1/PD-L1 therapy of CR or PR or SD lasting for > 6 weeks (+ 2 weeks permitted for radiographic scheduling)

37. No other prior immunotherapies, including but not limited to, anti-CTLA-4, anti-OX40, and anti-CD137
38. No unacceptable toxicity from prior anti-PD-1/PD-L1 treatment, defined as:
    - ≥ Grade 3 AE related to anti-PD-1/PD-L1 treatment
    - ≥ Grade 2 irAE associated with anti-PD-1/PD-L1 unless the AE resolved or was well controlled by withholding anti-PD-1/PD-L1 and/or treatment with steroids, with the exception of prior colitis, encephalitis, myocarditis, hepatitis, uveitis, and pneumonitis, which are exclusionary
    - Central nervous system (CNS) or ocular AE of any grade related to anti-PD-1/PD-L1

    Note: Patients with a prior endocrine AE are allowed if they are stably maintained on appropriate replacement therapy and are asymptomatic

Cohort D: Anti-PD-1/PD-L1 Antibody Naïve G/GEJ Cancer

39. Failed current standard-of-care treatment, or standard-of-care treatment is considered not appropriate at present
40. Histologically or cytologically proven adenocarcinoma of the stomach or gastroesophageal junction, inoperable locally advanced or with metastatic disease
41. Radiographic progression per RECIST v1.1 on or after systemic treatment for unresectable locally advanced or metastatic G/GEJ cancer
42. No prior immunotherapies, including but not limited to, anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40, and anti-CD137
43. No history of gastrointestinal (GI) perforation and/or fistulae within 6 months before the first dose of study drug(s)
44. No clinically significant GI bleeding within 3 months before the first dose of study drug(s)
45. No clinically significant bowel obstruction
46. No complete gastric resection
47. No weight loss ≥ 20% of total body weight within 2 months before the first dose of study drug(s)

4.2. Exclusion Criteria for all Patients

Patients who meet any of the following criteria are not eligible to enroll:

1. Active leptomeningeal disease or uncontrolled brain metastasis. Patients with equivocal findings or with confirmed brain metastases are eligible for enrollment provided that they are asymptomatic and radiologically stable without the need for therapy such as radiation, surgery or corticosteroid therapy to control symptoms from brain metastases for ≥ 28 days before first dose of study drug(s).
2. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 6)

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

   a. Controlled Type I diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
3. Any active malignancy ≤ 2 years before the first dose of study drug(s) except for specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)
4. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s)

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

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
5. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or calcium despite standard medical management, or ≥ Grade 3 hypoalbuminemia ≤ 14 days before the first dose of study drug(s)
6. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases, etc
7. Severe chronic or active infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days prior to first dose of study drug(s). **Note**: antiviral therapy is permitted for patients with viral hepatitis
8. Known history of human immunodeficiency virus (HIV) infection
9. Untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV DNA > 500 IU/mL or active HCV carriers with detectable HCV RNA. Note: Inactive

hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL) can be enrolled

10. Any major surgical procedure requiring general anesthesia ≤ 28 days before the first dose of study drug(s)
11. Prior allogeneic stem cell transplantation or organ transplantation
12. Any of the following cardiovascular criteria
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug(s)
    b. Symptomatic pulmonary embolism ≤ 28 days before the first dose of study drug(s)
    c. Any history of acute myocardial infarction ≤ 6 months before the first dose of study drug(s)
    d. Any history of heart failure meeting New York Heart Association Classification (NYHA) III or IV (Appendix 8) ≤ 6 months before the first dose of study drug(s)
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug(s)
    f. Any history of cerebrovascular accident ≤ 6 months before the first dose of study drug(s)
    g. QT corrected (QTc) interval (corrected by Fridericia's method) > 450 msec
    Note: If QTc interval is > 450 msec on initial ECG, a follow up ECG will be performed to exclude result
    h. Current left ventricular ejection fraction (LVEF) < institutional LLN as assessed by echocardiography (ECHO). The same modality used at baseline must be applied for subsequent evaluations
    i. Any episode of syncope or seizure ≤ 28 days before the first dose of study drug(s)
13. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
14. Hypersensitivity to tislelizumab or sitravatinib, to any ingredient in the formulation, or to any component of the container
15. Bleeding or thrombotic disorders or use of anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring within 6 months before the first dose of study drug(s)
16. Any systemic chemotherapy within 28 days of the first dose of study drug(s) or immunotherapy (eg, interleukin, interferon, thymoxin, etc.), hormone therapy, targeted therapy, or any investigational therapies within 14 days or 5 half-lives (whichever is shorter) of first dose of study drugs
17. Any Chinese herbal or Chinese patent medicine with anticancer activity approved by the China National Medical Product Administration (NMPA) (regardless of the type of cancer) used within 14 days before the first administration of study drug(s)
18. Toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
19. Administration of live vaccine ≤ 28 days before the first dose of study drug(s)

Note: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed

20. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug(s) or affect the explanation of drug toxicity or AEs or result in insufficient or might impair compliance with study conduct
21. Concurrent participation in another clinical study, unless it is an observation (non-interventional) clinical study or during the follow-up period of an interventional study. Prior randomization in a tislelizumab study regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out
22. Inability to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the complete stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
23. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention; cytological confirmation of any effusion permitted) within 7 days before first dose of study drug(s)
24. Pregnant or breastfeeding woman

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Sitravatinib

Sitravatinib will be provided as 10 mg and 40 mg unit dose strength capsules.

Sitravatinib drug product is packaged in 30-count, high-density polyethylene (HDPE), opaque white, round 60 cc bottles. A tamper proof heat induction seal and a child resistant closure are used. The provided bottles may be labeled for specific patient use and given to the patient if the capsule count is the needed number. The contents of the label will be in accordance with all applicable local regulatory requirements.

The bottles of sitravatinib must be stored in labeled carton at refrigerated conditions (2ºC to 8ºC) in the study site Pharmacy. Once dispensed to patients, the bottles will be removed from the carton and can be stored at room temperature as specified on the label.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to the Sitravatinib Investigator's Brochure for other details regarding sitravatinib.

5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box. The contents of the label will be in accordance with all applicable local regulatory requirements.

Tislelizumab must be stored at temperatures between 2ºC and 8ºC and protected from light as specified on the label.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.2. Dosage and Administration

On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib should precede tislelizumab infusion.

5.2.1. Sitravatinib

In Phase 1, sitravatinib capsules will be administered orally, once daily, in a continuous regimen in 21-day cycles. The starting dose for sitravatinib in escalation evaluation will be 80 mg once daily. Depending on safety observations, the sitravatinib dose in the subsequent cohort of patients may be escalated to 120 mg once daily.

In Phase 2, SMC will confirm RP2D of the monotherapy and combination treatment dosing of sitravatinib, which can be withheld for up to approximately 28 days consecutively.

The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken in the fasted state, at least 2 hours after the previous meal and 1 hour before the next meal. For once daily dosing, capsules should be taken during the morning hours, for instance, at least 1 hour before breakfast or lunch.
- Capsules should be taken with at least 200 mL (1 cup) of water.
- Patients should swallow the capsules whole and not chew them.
- If vomiting occurs after dosing, sitravatinib doses should not be replaced.
- If a patient forgets to take sitravatinib for more than 12 hours, he/she should skip the dose and resume taking the drug the next day.

5.2.2. Tislelizumab

Tislelizumab (200 mg) will be administered on Day 1 of each 21-day cycle (once every 3 weeks). Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product 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 afterward 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 over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

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 10.

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

5.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or appropriately delegated study personnel at each patient visit and information provided by the patient. Patients enrolled in the study will be provided with patient diaries. The patient is responsible for maintaining the patient diary and will record the number of capsules of sitravatinib taken and if any were missed. The site personnel responsible for drug accountability will record the quantity of drug dispensed and quantity of drug received after the cycle visit. The patient diaries and the pharmacist record of drug will be assessed by the investigator/study personnel at each visit.

The study drugs required for completion of this study (sitravatinib and tislelizumab) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of study drugs. Any damaged shipments will be replaced.

Accurate records of all study drugs received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug(s) management.

5.4. Overdose

5.4.1. Sitravatinib

Any overdose or incorrect administration of sitravatinib should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.4.2. Tislelizumab

Any overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or incorrect administration of tislelizumab should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.5. Modification and Dose Delay

5.5.1. Dose Modification

There will be no dose reductions for tislelizumab in this study. Dose reductions for sitravatinib are presented in Table 6. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis. If the administration of sitravatinib is interrupted for reasons other than toxicity, then treatment with the study drug(s) may be resumed at the same dose. Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to sitravatinib are presented in Section 8.8.

Table 6: Sitravatinib Dose Reductions

Starting Dose	80 mg once daily	120 mg once daily
Dose Level -1	60 mg once daily	80 mg once daily
Dose Level -2	40 mg once daily	60 mg once daily[a]

[a] Dose reduction below 60 mg once daily may be undertaken after discussion with the sponsor.

If one study drug is interrupted or discontinued, administration of the other study drug may continue at the discretion of the investigator.

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor.

5.5.2. Dose Delay

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

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to study drugs and requires a dose to be withheld. Patients should resume study drugs as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 4 weeks for sitravatinib or 12 weeks for tislelizumab after last dose of the respective study drug. Sitravatinib should be resumed at a reduced dose level as outlined in Table 6. If the administration of sitravatinib is interrupted for reasons other than toxicity, then treatment with the study drug(s) may be resumed at the same dose.

The following dose delays or interruptions will be permitted:

- Sitravatinib can be interrupted for up to approximately 28 consecutive days. If treatment with sitravatinib is delayed for ≥ 14 days, then resumption at a reduced dose should be considered. If drug is planned to be interrupted ≥ 28 days, the medical monitor should be contacted before permanent patient discontinuation from the study drug.
- Tislelizumab can be delayed or interrupted for up to 12 weeks. If a dose is delayed for ≤ 10 days for a planned dosing cycle (eg, Cycle 3, Day 1), tislelizumab should be administered (on the same day with sitravatinib, if applicable) and all assessments should be conducted according to the original cycle (ie, Cycle 3). If the delay is > 10 days, the patient should skip the tislelizumab, and tislelizumab will be administered on Day 1 of the next planned cycle (ie, Cycle 4, Day 1).

The tumor assessment schedule will not be altered even if the administration of study drug(s) is delayed.

If the patient is unable to resume sitravatinib or tislelizumab within the permitted timeframe after the last dose of study drug(s), then the patient should be discontinued from the study drug(s).

Dose modification related to irAEs and infusion-related reactions for tislelizumab are described in Appendix 10 and Section 8.7, respectively.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Concomitant Therapy

6.1.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary in keeping with the local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals) and in a patient's interest are allowed.

Proton pump inhibitors and H_2 antagonists should be avoided during treatment on study but are not exclusionary. Switching from use of proton pump inhibitors or H_2 antagonists to use of antacids is preferred. Use of antacids should be avoided 4 hours before and 2 hours after administration of investigational study treatment.

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

Patients with active hepatitis B, defined as either detectable HBsAg or HBV DNA at baseline, must initiate treatment 2 weeks prior to first dose of study drug(s) and continue until 6 months after the last dose of study drug(s). Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel, 2015). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the Investigator; however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.

Palliative (limited-field) radiation therapy is permitted for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline. The lesion being considered for palliative radiation should not be a target lesion for RECIST v1.1. The case should be discussed with the medical monitor; the therapy will be used if the medical monitor agrees that the conditions required to receive palliative radiation are met. Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should undergo a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out PD.

6.1.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicine] for the treatment of cancer) is not allowed. Chinese herbal and Chinese patent medicines with anticancer activity are defined as

medication with approval by the China NMPA for use as anticancer treatment (regardless of the type of cancer).

- Live vaccines within 28 days before first dose of study drug(s) and 60 days following the last dose of study drug(s).
- Anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring.

6.1.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should avoid alcohol completely and should avoid other addictive drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.1.1.
- Herbal remedies are not recommended for use during the study treatment. Patients must notify the investigators of all herbal remedies used during the study.
- Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

6.2. Potential Interactions Between the Study Drugs and Concomitant Medications

Sitravatinib was not considered as a high-risk compound as a victim drug-drug interaction (DDI) because multiple enzymes, including CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4, are involved in its metabolism.

Based on the in vitro CYP inhibition/induction assay results, high plasma protein binding and less than 0.1 μM potency, sitravatinib perpetrator risk at projected clinical dose and exposure levels are considered to be low.

Per the International Council for Harmonisation (ICH) E14 guidance, it is recommended to avoid medications with potential to prolong QT/QTc or cause torsades de pointes. Please refer to Appendix 12 for a list of medications or substances to be avoided or used with caution during treatment with sitravatinib.

Potential Interaction Between Sitravatinib and Tislelizumab

Sitravatinib administered in combination with tislelizumab is unlikely to result in clinically relevant drug-drug interactions based on absorption, metabolism, elimination, or protein binding. Tislelizumab is a monoclonal antibody and is administered intravenously, whereas sitravatinib is a small molecule therapeutic administered orally. Like most therapeutic proteins, tislelizumab is not expected to be metabolized by CYP or other drug-metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

7. STUDY ASSESSMENTS AND PROCEDURES

The study-specific assessments and procedures with allowed time windows are outlined in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment 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 dosing. Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date, with subsequent visits conducted according to the planned schedule every 3 weeks from Cycle 1 Day 1.

7.1. Screening

Screening evaluations will be performed within 28 days prior to the first dose of study drug(s). Patients who agree to participate will sign the ICF prior to undergoing any screening procedure. The Screening period begins on the first day a screening procedure is conducted. Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the Screening period; the investigator is to assess patient eligibility according to the latest screening assessment results.

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

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during Screening, as well as throughout the study, refer to Safety Assessments (Section 7.3), Tumor and Response Evaluations (Section 7.4), and Biomarkers (Section 7.7) sections. The PK sampling schedule is shown in Appendix 2.

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

7.1.1. Demographics and Medical History

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

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before the first dose of study drug.

Cancer history will include an assessment of prior surgery, prior radiotherapy, and prior drug therapy, including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.

Archival tumor tissues (if available) will be collected for biomarker analysis. In addition to archival tumor tissues, a fresh tumor biopsy at baseline is recommended. Refer to Section 7.7 for details.

7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 7 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential"

7.1.3. Informed Consent and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study drug(s). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.4. Pulmonary Function Tests

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

7.2. Enrollment

The investigator will assess, and the sponsor or designee will confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet and send it to the medical monitor or designee to approve the enrollment. Study site personnel should ensure that a medical monitor's confirmation has been received before the study drug(s) administration.

7.3. Safety Assessments

7.3.1. Vital Signs

Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) after resting for 10 minutes.

7.3.2. Physical Examinations

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

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

7.3.3. Eastern Cooperative Oncology Group Performance Status

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

7.3.4. Laboratory Safety Test

Local laboratory assessments of hematology, clinical chemistry, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 1.

If laboratory tests at Screening are not performed within 7 days before administration of study drug(s) on Cycle 1 Day 1, these tests (hematology, clinical chemistry, and urinalysis) should be repeated and reviewed before study drug(s) administration. In Phase 1, hematology and clinical chemistry, as specified in Appendix 3, should be performed weekly for the first 2 cycles. For all patients in Phase 1 and Phase 2, 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 the results should be reviewed within 48 hours before study drug(s) administration. For creatine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB) tests and coagulation tests, refer to Appendix 3.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decision.

In addition, the following tests will be conducted in this study:

- 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 first administration of study drug(s). Urine or serum pregnancy tests will be performed during treatment before study drug(s) administration at each cycle and the EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug(s) at each cycle.
- Thyroid function tests (TFTs) (thyroid-stimulating hormone [TSH], free T3, free T4) will be performed at Screening, every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc) and the EOT Visit. The test does not need to be repeated at the EOT Visit within 63 days after last test.

- CK and CK-MB testing will be performed for all patients receiving tislelizumab as part of clinical chemistry (see Appendix 3). Troponin I and/or T may be performed if the local laboratory does not provide CK-MB analysis. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients with a history of cardiological disease receiving sitravatinib monotherapy, either in Cohort A or after discontinuation of tislelizumab, may receive CK and CK-MB testing if clinically indicated.

7.3.5. Hepatitis B and C Testing

Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (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 have detectable HBV DNA at Screening will receive a viral load test every 4 cycles and at the EOT Visit.

7.3.6. Electrocardiograms

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

When coinciding with blood draws, ECG assessment should be performed prior to blood draws. Patients should rest in semirecumbent supine position for at least 10 minutes prior to ECG collection (refer to Appendix 1).

7.3.7. Multigated Acquisition Scans or Echocardiograms

Evaluations of cardiac function will be performed at Screening and every 12 weeks during treatment. For study purposes, evaluation by multigated acquisition (MUGA) scan is preferred. Evaluation by echocardiogram is an acceptable alternative if necessary. The method used for individual patients should be consistent throughout study participation.

7.3.8. Adverse Events

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

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

7.4. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to the first dose of study drug(s). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) in the first year and thereafter approximately every 9 weeks (± 7 days).

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

The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (eg, the same contrast protocol for CT scans). All known sites of disease must be documented at Screening and reassessed at each subsequent tumor evaluation.

- Imaging of the brain (MRI or CT) at baseline (≤ 28 days of informed consent) should be performed at Screening if clinically indicated.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed 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-99m [TC-99m]) or PET should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans afterwards, or clinically indicated, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at Screening.
- At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Tumor response will be assessed using RECIST v1.1 (refer to Appendix 11). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After the first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment time point.

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic PD is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with tislelizumab until PD is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 6 to 8 weeks from the date of initial documentation of PD). The following criteria must be met in order to treat patients with suspected pseudoprogression:

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

- Absence of rapid PD or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond initial radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer

The decision to continue study drug(s) beyond investigator-assessed progression must be agreed with the medical monitor and documented in the study records. In such cases, patients are also required to be reconsented.

Patients who discontinue study treatment early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences PD, withdraws consent, is lost to follow-up, death, or until the study terminates, whichever occurs first.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

7.5. Pharmacokinetic Assessment

The PK concentrations will be determined using plasma (sitravatinib) or serum (tislelizumab) samples collected at specified time points within a reasonable variation window (refer to Appendix 1 and Appendix 2). The actual collection date and time of each sample collection will be recorded on the source document and eCRF.

In the event of a DLT or significant toxicity, it is recommended that an unscheduled PK blood sample be drawn as soon as possible.

Shipping, storage, and handling of samples will be managed through a central laboratory. Analysis of samples will be performed using specific validated bioanalytical methods. Full details on sample collection, processing, storage, and shipment will be provided in the Study Laboratory Manual.

7.6. Antidrug Antibody Testing

The anti-tislelizumab antibody concentrations will be determined using serum samples collected at specified time points within a reasonable variation window (refer to Appendix 1 and Appendix 2). Shipping, storage, and processing of samples will be managed through a central laboratory.

7.7. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

Archival/biopsy tumor tissue (FFPE with tumor tissue or approximately 15 unstained slides) will be sent to central laboratory for biomarker analysis, including but not limited to immunohistochemistry assay of PD-L1 status, tumor infiltrating lymphocytes, and tumor mutation load. Submission of < 15 unstained slides is not a protocol deviation.

For all patients, in addition to archival tumor tissue, a fresh biopsy of a tumor lesion within 28 days before Cycle 1 Day 1 and/or after 2 cycles of treatment (Cycle 3 Day 1) is recommended to obtain tumor samples for evaluating pharmacodynamic effects. For patients with confirmed PD during the study, an optional biopsy is recommended for exploration of the resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient informed consent is required before obtaining fresh tumor biopsies.

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

Blood samples will be collected at specified time points as described in the schedule of assessments to be used for the evaluation of pharmacodynamic biomarkers and exploratory biomarkers, including but not limited to cytokines, plasma proteins, immune cell populations, and circulating tumor DNA (ctDNA).

7.8. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment 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 dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Cycle 1 Day 1.

7.9. Unscheduled Visits

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Sitravatinib and Tislelizumab

Sitravatinib and tislelizumab are investigational agents that are currently in clinical development. Limited safety data for sitravatinib and tislelizumab in patients are available, and the full safety profiles have not been characterized. The following recommendations are based on results from nonclinical and clinical studies of sitravatinib or tislelizumab and published data on other molecules within the same biologic classes.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.

The guidelines for management of potential AEs more specific to treatment with sitravatinib or agents in the same class of cancer treatment are presented in Section 8.8.

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

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies of sitravatinib and tislelizumab, clinical data with sitravatinib and tislelizumab, as well as the nonclinical/clinical data from other RTK inhibitors and PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation, and patients who have received a live vaccine within 28 days before the first dose of study drug(s) are excluded from the study (see Section 4.2).

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (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.

Serum samples will be drawn for determination of antidrug antibody (ADA) to tislelizumab in patients for both Phase 1 and Phase 2 portions of the study. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2).

All AEs will be recorded during the study (AE from the time of the first dose of study drug(s) and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. At the EOT, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-related AEs will be recorded until up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

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

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

8.3.2. Assessment of Severity

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

Toxicities that are not specified in 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; minimal, 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 AE

Note: The terms "severe" and "serious" 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 definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

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

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending 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 there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified

- Mechanism of action of the study drug
- Biological plausibility

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Following Adverse Events

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

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

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

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

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

- are associated with clinical signs or symptoms, or

- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

Abnormalities in liver function tests (ALT, AST, total bilirubin) that are Grade 3 or higher need to be reported to the sponsor within 24 hours of occurrence via SAE reporting process as described in Section 8.6.2.1. Repeat liver function testing (LFT) should be performed according to the schedule in Appendix 10.

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

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

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

The following are NOT considered to be SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, 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 Investigator's Brochure.

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

8.6.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug(s) or initiation of new anticancer therapy, whichever occurs first. Immune-related AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab, regardless of if the patient starts a new anticancer therapy.

The investigator should report any SAEs that are assessed as related to study drug treatment, at any time after treatment discontinuation.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 7.

Table 7: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 h of first knowledge of the SAE	SAE form	As expeditiously as possible	SAE report	Email or fax SAE form

Abbreviations: h, hours; SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE, and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1 and Section 8.6.2.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for sitravatinib and tislelizumab studies.

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

8.6.3. Eliciting Adverse Events

The investigator or designee will ask 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?

8.6.4. Progressive Disease

PD, which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to PD should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to PD, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to PD should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

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

8.6.6. Pregnancies

If a female patient or the partner of a male patient receiving investigational therapy becomes pregnant within 120 days after the last dose of tislelizumab or sitravatinib, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow up will be no longer than 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Sitravatinib Investigator's Brochure and Tislelizumab Investigator's Brochure

8.6.8. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 8.7.3) should be classified as irAEs and identified as such in the eCRF AE page until 90 days after the last dose of tislelizumab.

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

An extensive list of potential irAEs appears in Table 9. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 10.

8.7. Management of Adverse Events of Special Interest of Tislelizumab

As a routine precaution, after infusion of tislelizumab on Cycle 1 and Cycle 2 Day 1, patients must be monitored for at least 1 hour afterward 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 management of infusion-related reactions, severe hypersensitivity reactions and irAEs according to the NCI-CTCAE criteria are outlined below.

8.7.1. Infusion-Related Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to tislelizumab is provided in Table 8.

Table 8: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Tislelizumab

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

Abbreviations: h, hours; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

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

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

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

oral or intravenous antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.7.2. Severe Hypersensitivity Reactions and Flu-like Symptoms

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

In the event of a systemic anaphylactic/anaphylactoid reaction (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 discontinued from the study.

The patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and ICU should be alerted for possible transfer if needed.

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

8.7.3. Immune-Related Adverse Events

While sitravatinib may have immunostimulatory effects, autoimmune AEs have not been reported in clinical trials, including to date in combination with nivolumab, nor are they recognized as class effects for this agent. However, the potential for sitravatinib to exacerbate or promote these AEs when administered in combination with a PD-1 inhibitor should be noted.

Immune-related AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, PD, metabolic, toxin, or other neoplastic causes) with appropriate diagnostic tests which may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out; the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the irAE indicator in the eCRF AE page should be checked. A clinically relevant overlap in toxicity may arise between an irAE attributed to tislelizumab and the nonspecific, most often mild to moderate AE (eg, rash and colitis) observed with sitravatinib. The time to onset may be helpful in distinguishing an AE that may be attributed to autoimmune effects versus nonspecific toxicity.

A list of potential irAEs is shown below in Table 9. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-related.

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

Table 9: Immune-Related Adverse Events

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

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

Recommendations for managing irAEs are detailed in Appendix 10.

In the event of an immune-related AE during study treatment, administration of sitravatinib and tislelizumab should be interrupted until the event stabilizes to ≤ Grade 1. If a toxicity does not resolve to ≤ Grade 1 within 4 weeks for sitravatinib or 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of the any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

8.8. Management of Sitravatinib-Specific Adverse Events

8.8.1. Management of Non-Hematological Toxicities of Sitravatinib

Patients experiencing symptomatic Grade 2 non-hematological sitravatinib-related adverse events are recommended to have a dose reduction to the next lower dose level at the discretion of

the investigator, per the reduction schedule (Table 10). Dose reductions are expected to improve treatment tolerability.

Non-hematological toxicities ≥ Grade 3 and considered to be related to sitravatinib treatment should be managed with sitravatinib interruption, until resolution of toxicity to ≤ Grade 1 or to baseline value. In the case of Grade 3 or 4 electrolyte abnormalities that are not clinically complicated and resolve spontaneously or with conventional medical treatment within 72 hours, or Grade 3 asymptomatic amylase or lipase elevation treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose as outlined in Table 10. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

Table 10: Sitravatinib Dose Modifications – Non-Hematological Drug-Related Toxicities

Toxicity	Drug Interruption	Dose Modification
Grade 1	May be implemented based on investigator and patient discretion	
Grade 2 - Asymptomatic	May be implemented based on investigator and patient discretion	
Grade 2 - Symptomatic	May be implemented based on investigator and patient discretion	Recommend dose reduction to next lower dose level
Grade 3 or 4	Hold until ≤ Grade 1 or return to baseline	Resume at dose one or more levels below that inducing the toxicity. Exceptions presented in footnotes

Notes:
[a] Management of specific adverse events (eg, hypertension) for sitravatinib are presented in sections below.
[b] Patients may resume at the same dose in the following cases:
- Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours
- Grade 3 amylase or lipase elevation that is not associated with symptoms or the clinical manifestations of pancreatitis

8.8.2. Management of Hematological Toxicities of Sitravatinib

Hematological toxicities are not a frequent cause of treatment interruption or discontinuation of sitravatinib treatment. Observed ≥ Grade 3 hematological events that are considered to be causally related to sitravatinib should initially be managed using treatment interruption. In addition, dose reduction at the discretion of sitravatinib should be implemented in the following cases:

- Grade 3 or 4 febrile neutropenia
- Grade 4 neutropenia persisting for > 7 days
- Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with clinically significant bleeding

8.8.3. Dose Modification Guidelines for Sitravatinib-Specific AEs

Dose modification guidelines for increased blood pressure and increased hepatic transaminase not likely to be immune-mediated are presented in Table 11 and Table 12 below. Guidance for

management of Hy's Law cases is also provided below. Additional management guidelines for sitravatinib-specific AEs are also described below.

Table 11: Sitravatinib Dose Modification for Increased Blood Pressure

Toxicity	Drug Interruption	Dose Modification
Grade 1 or 2 hypertension	May be implemented based on investigator and patient discretion	
Grade 3 hypertension without clinically significant increases in BP as defined below	Investigator discretion. Consider antihypertensives per Section 8.8.4	
Grade 3 hypertension with clinically significant increases in BP *defined as* either an increase of ≥ 30 mmHg in systolic BP to ≥ 180 mmHg *or* increase of ≥ 20 mmHg in diastolic BP to ≥ 110 mmHg, confirmed with repeated testing after at least 5 minutes	Hold until ≤ Grade 2 or return to baseline	Investigator discretion
Grade 4 hypertension	Discontinue sitravatinib	Discontinue sitravatinib

Abbreviation: BP, blood pressure.

For cases where transaminase increases are not likely to be immune-mediated, treatment management decisions should be made per investigator discretion in consideration of clinical factors. Recommended treatment modifications for sitravatinib are provided in Table 12.

Table 12: Sitravatinib Dose Modification for Increased Hepatic Transaminase

Toxicity	Drug Interruption	Dose Modification
Grade 1 (> ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal)	May be implemented based on investigator and patient discretion	
Grade 2 (> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x baseline if baseline was abnormal)	Not required	Decrease by 1 dose level
Grade 3 or 4 (> 5.0 x ULN if baseline was normal; > 5.0 x baseline if baseline was abnormal)	Hold until ≤ Grade 1 or return to baseline	If resolution occurs within 22 days, decrease by 1 dose level. If no resolution within 22 days, discontinue sitravatinib.

Abbreviation: ULN, upper limit of normal.

Management of Hy's Law Cases

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

8.8.4. Hypertension

Hypertension, including Grade 3 events, has been reported with sitravatinib. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine may be considered if antihypertensive therapy is required and should be considered for patients with Grade 3 hypertension without clinically significant increases in blood pressure (BP) (see Table 11). In cases of Grade 3 hypertension with clinically significant increases in blood pressure, temporary suspension of sitravatinib dosing is recommended until blood pressure is controlled. Treatment with sitravatinib may resume at the same or a lower dose at the discretion of the investigator. If significant hypertension recurs, options include change in medical management of the patient, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the investigator. In the event of Grade 4 hypertension, sitravatinib should be permanently discontinued (see Table 11).

8.8.5. Palmar-Plantar Erythrodysesthesia

Palmar plantar erythrodysesthesia (PPE) has been reported as a DLT in the Phase 1 study of sitravatinib. Measures that can be taken to manage PPE include avoidance of exposure of hands and feet to hot water when washing dishes or bathing, or to other sources of heat, avoidance of activities that cause unnecessary force or friction (rubbing) on the hands or feet, avoiding contact with harsh chemicals such as cleaning products, use of tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers, and wearing of loose-fitting, well-ventilated shoes and clothes. Treatment may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams. In more severe cases, dose interruption and reduction may be warranted.

8.8.6. Diarrhea/Colitis

Diarrhea has been reported with sitravatinib treatment, though the mechanism remains unclear, as with other small molecule RTK inhibitors. Patients should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled. Investigators should also evaluate whether diarrhea may be attributable to the irAE of colitis.

The presence of abdominal pain, mucus, or blood in the stool or peritoneal signs should raise the index of suspicion for immune-mediated colitis, as these features are generally not observed with sitravatinib treatment-associated diarrhea. The diarrhea observed with sitravatinib generally improves within several days of interrupting study medication, with close observation may help establish the most likely causality.

8.8.7. Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib is unknown; however, such events have been reported with inhibitors of VEGFR. Patients with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and suspension of treatment is recommended for patients developing clinically significant bleeding.

8.8.8. Thrombotic Events

Though thrombotic events (eg, pulmonary embolism) have been reported with sitravatinib and with inhibitors of VEGFR, the risk of such events with sitravatinib is unknown. Precautions should be taken in patients with recent, clinically significant thrombotic events, and treatment should be discontinued in patients who develop clinically significant thromboembolic complications such as acute myocardial infarction or severe pulmonary embolism.

8.8.9. Thyroid Dysfunction Other Than Immune-Mediated

Hypothyroidism and increases in TSH have been reported in patients taking sitravatinib. Patients diagnosed with hypothyroidism should be treated with hormone replacement therapy and may continue treatment with sitravatinib at the Investigator's discretion.

8.8.10. Decreased Left Ventricular Ejection Fraction

Decreased LVEF has been reported with sitravatinib. In addition, decreases of LVEF to < 50% on-study were observed in patients undergoing scheduled multigated acquisition (MUGA) scans or echocardiograms. The dose of sitravatinib should be interrupted and/or reduced in patients with an ejection fraction < 50% and > 20% below baseline. Discontinuation should be considered for patients requiring acute hospitalization for treatment of congestive heart failure (CHF).

8.8.11. Proteinuria

Although the risk with sitravatinib is unknown, proteinuria has been described with other inhibitors of the VEGFR pathway. Patients who develop ≥ 2 + proteinuria should undergo 24-hour urine collection for assessment of urine protein; treatment with sitravatinib should be discontinued in the presence of ≥ 2 g of proteinuria/24 hours and may restart when protein levels decrease to less than 2 g/24 hours. Patients who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

In general, data from Phase 1 part will be summarized by dose level and schedule, while data from Phase 2 part will be summarized by cohort, unless otherwise specified.

9.1. Statistical Analysis

9.1.1. Analysis Sets

- The Safety Analysis Set includes all patients who received at least 1 dose of any study drug (any component for the combination therapy). Patients from either Phase 1 or 2 are eligible for inclusion in the Safety Analysis Set.
- The Efficacy Evaluable Analysis Set includes all patients who received at least 1 dose of any study drug with measurable disease at baseline per RECIST v1.1 and who had at least 1 evaluable postbaseline tumor assessment unless treatment was discontinued due to clinical progression or death before tumor assessment. Patients from Phase 1 or 2 are eligible for inclusion in the Efficacy Evaluable Analysis Set.
- DLT Evaluable Analysis Set for sitravatinib monotherapy includes patients who received at least 75% of the assigned total dose of sitravatinib for the DLT assessment window and had sufficient safety evaluation. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Phase 1 are eligible for inclusion in the DLT Evaluable Analysis Set of sitravatinib monotherapy.
- DLT Evaluable Analysis Set for sitravatinib and tislelizumab combination includes patients who received at least 75% of the assigned total dose of sitravatinib and ≥ 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment window. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Phase 1 are eligible for inclusion in the DLT evaluable analysis set of sitravatinib and tislelizumab combination therapy.
- The PK Analysis Set includes patients who contributed at least 1 quantifiable post-baseline PK sample. Patients from either Phase 1 or 2 are eligible for inclusion in the PK Analysis Set.
- The ADA Evaluable Analysis Set includes all patients who received at least 1 dose of tislelizumab and for whom both baseline ADA and at least 1 post-baseline ADA results are available. Patients from either Phase 1 or 2 are eligible for inclusion in the ADA Evaluable Analysis Set.

9.1.2. Patient Disposition

The number of patients treated, discontinued from study drug(s) and/or study, and those with major protocol deviations will be counted. The primary reason for study drug(s) discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, dead,

withdrew consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Major protocol deviations will be summarized and listed by each 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, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include prior number of systemic treatment, gender, ECOG, country, race, and metastatic site.

9.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization 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 will be defined as medications that stopped before the day of first dose of study drug(s). Concomitant medications will be defined as medications that 1) started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or 2) started on or after the date of the first dose of study drug(s) up to 30 days after the patient's last dose. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, eg, associated with an irAE 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 Analyses

The efficacy endpoints (ie, ORR, DOR, PFS, and DCR) will be assessed by investigators using RECIST v1.1 and will be summarized to evaluate the antitumor activities of sitravatinib as monotherapy or in combination with tislelizumab.

Details of statistical analyses will be described in detail in the SAP.

Objective Response Rate (ORR)

The number and proportion of patients who achieve objective tumor response (CR or PR) according to RECIST v1.1 will be summarized. The ORR will be estimated along with Clopper Pearson 2-sided 95% confidence interval (CI).

Analyses for ORR will be presented by tumor expansion cohort.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with BOR of CR, PR, and SD in accordance with RECIST v1.1 criteria. DCR will be reported with the 95% CI.

Progression-Free Survival (PFS)

PFS is defined as the time from the date of first dose of study drug(s) to the date of the first documentation of PD as assessed by the investigator using RECIST v1.1 or death, whichever

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

Duration of Response (DOR)

DOR for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier). DOR analysis will only include responders. Censoring rule for DOR will follow PFS censoring rule.

Kaplan-Meier curve will be used to estimate median time and 95% CI for DOR. The censoring rule for PFS and DOR will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2007).

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

Analyses for DCR, PFS, and DOR will be presented by tumor expansion cohort.

Overall Survival (OS)

OS is defined as the time from date of first dose of study drug(s) to date of death due to any cause. Patients who remained alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of data cutoff or the last date the patient was known to be alive. Kaplan-Meier curve will be used to estimate OS at different time points.

9.3. Safety Analyses

Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECGs findings will also be used in determining the safety profile. The severity of AEs will be graded according to the CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables), and changes from baseline will be determined for laboratory parameters and vital signs. Safety analyses will be conducted in the Safety Analysis Set.

9.3.1. Extent of Exposure

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

The number (percentage) of patients requiring dose reduction, interruption, dose delay, and drug discontinuation due to AEs will be summarized for each study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category.

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

9.3.2. Adverse Events

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA (v18.1 or higher) by lower-level term, preferred term, and primary SOC.

DLT will be summarized at each dose cohort in Phase 1.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days following study drug(s) discontinuation or initiation of new anticancer therapy, whichever occurs first. TEAE classification also applies to irAEs recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v.5.0 within an SOC and preferred term, even if the patient experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, irAE, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3. Laboratory Analyses

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

Laboratory parameters that are graded by NCI-CTCAE v5.0 or higher will be summarized by NCI-CTCAE grade. Parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Specific vital signs, eg, blood pressure and temperature, will be summarized and listed. The change from baseline will also be presented.

9.3.5. Dose-Limiting Toxicity Analysis

DLTs during the DLT assessment window will be used to determine the dose and schedule of sitravatinib as monotherapy or in combination with tislelizumab. The DLT events will be

summarized descriptively by monotherapy and combination dosing level in the DLT Evaluable Analysis Set in dose escalation stage.

9.4. Pharmacokinetic Analysis

Blood samples for PK analysis of sitravatinib and tislelizumab will be collected at specified time points (Appendix 2). The actual collection date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points upon sponsor approval to ensure thorough PK monitoring.

For the PK analysis set that contributed serial plasma samples for sitravatinib on Cycle 1 Day 1 and Day 21, plasma concentration-time data of each patient will be tabulated and graphically presented on linear and semilogarithmic scales. Plots of sitravatinib concentration-time data will be presented for Cycle 1 Day 1 (after single dose) and Day 21 (at steady state). Pharmacokinetic parameters will be determined using standard noncompartmental method. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided. The final analysis of PK parameters will be calculated based on actual sample collection time, rather than scheduled times. The parameters will be summarized with descriptive statistics (eg, N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] % associated to the geometric mean).

PK parameters will include, but are not limited to, the following as allowed by data:

C_{max} (μg/mL)	Observed maximum plasma concentration during a sample interval.
C_{τ} (μg/mL)	Observed trough concentration at steady state.
T_{max} (hr)	Observed time to maximum plasma concentration during a sampling interval.
λz (hr^{-1})	Elimination rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination (C_{max} excluded).
$t_{1/2}$ (h)	Terminal elimination half-life, determined from the quotient 0.693/λz.
$AUC_{(0-t)}$ (μg.h/mL)	Area under the plasma concentration-time curve from time zero to the last measurable time point calculated by log-linear trapezoidal summation.
$AUC_{(0-\tau)}$ (μg.h/mL)	Area under the plasma concentration-time curve from time zero to 24 h postdose at steady state; calculated by log-linear trapezoidal summation.
CL/F (L/hr)	Apparent clearance after oral administration.
Ro	Observed accumulation ratio determined by $AUC_{(0-\tau),ss}$ /$AUC_{(0-24),\ Day1}$.

The sitravatinib and tislelizumab concentration data collected sparsely at predose and around T_{max} will be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

Additional PK, including population PK analyses, may be conducted as appropriate, and the results of such analysis may be reported separately from the CSR.

9.5. Immunogenicity Analyses

Samples to assess anti-tislelizumab antibodies will be collected. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADA. The incidence of positive ADA and neutralizing ADA will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

9.6. Other Exploratory Analyses

Summary statistics will be provided for pharmacodynamic biomarkers, including, but not limited to, plasma protein, cytokine, and immune cell subtypes in blood. An exploratory analysis on a potential correlation of these pharmacodynamic markers with PK parameters, safety, and antitumor activity will be performed as appropriate.

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug(s) response, such as efficacy and treatment resistance.

For potential PGx analysis of genes that may affect the PK of sitravatinib, a blood sample for DNA isolation will be collected from patients predose on Cycle 1 Day 1. If needed, these samples will be analyzed together with PGx samples from other studies to assess the impact of genetic polymorphisms on the PK of sitravatinib, and these results may be reported separately.

9.7. Sample Size Consideration

The study plans to enroll approximately 98 to 116 patients.

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

Estimates of the 95% CI of the observed ORR for several potential outcomes using the sample size of 20 patients are provided in Table 13.

Table 13: Estimates of 95% CI of ORR With 20 Patients

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

Abbreviations: CI, confidence interval; ORR, objective response rate.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

An SMC will be established consisting of the sponsor's clinical, safety, and medical team representatives (eg, medical monitor, Clinical Pharmacology, and Drug Safety) and investigators. All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed with input from other functional representatives as appropriate. On the basis of a review of these data and in consultation with the investigators, a determination will be made regarding dose and/or safety management.

10.2. Communication

Sponsor plans to have regular communications with all study sites (study investigators and coordinators) regarding:

- Study enrollment status
- Decisions on dose escalation
- Any significant safety findings
- Considerations for protocol amendments

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

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

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. A patient diary will be provided to each patient to record the sitravatinib dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be returned to the site personnel for review by the investigator/study personnel on a regular basis.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

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

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

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

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

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

13.4. Patient and Data Confidentiality

The sponsor will maintain 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 set transmitted to any sponsor location.

Patient medical information obtained by 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.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, the China NMPA, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the IND, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

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

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

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

14.1.2. Data Management/Coding

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

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

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

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

AEs will be coded using the MedDRA v18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA v18.1 or higher.

14.2. Study Records Retention

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

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

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

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

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

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

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

14.3. Protocol Deviations

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

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

14.4. Publication and Data Sharing Policy

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2018)

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

14.5. Study and Study Center Closure

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

- Return of all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study or suspend enrollment either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

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

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

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

14.6. Information Disclosure and Inventions

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

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

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

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.4

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment Period				EOT Visit[4]	Safety Follow-up Phone Call[5]	Survival Follow-up[6]
		Cycle 1 and 2			Cycle 3 and Subsequent Cycles			
Days (window)	**-28 to -1**	**1[2]**	**8 (±1)[3]**	**15 (±2)[3]**	**1(±3)**	**Within 30 Days After Last Dose of Study Drug(s)**	**60 and 90 (± 14) Days After Last Dose of Tislelizumab**	**Approximately Every 3 Months (± 14 days) (Phase 2)**
Informed consent[1]	x							
Inclusion/exclusion criteria	x							
Demographics/medical history/prior medications	x							
Child-Pugh classification score[7]	x (-7 to -1)							
Height	x							
Vital signs/weight[8]	x	x	x	x	x	x		
Complete physical examination[9]	x					x		
Limited physical examination[9]		x	x	x	x			
ECOG Performance Status	x	x			x	x		
12-Lead ECG[10]	x	x			x	x		

Assessment	Screening[1]	Treatment Period				EOT Visit[4]	Safety Follow-up Phone Call[5]	Survival Follow-up[6]
		Cycle 1 and 2			Cycle 3 and Subsequent Cycles			
Days (window)	**-28 to -1**	**1[2]**	**8 (±1)[3]**	**15 (±2)[3]**	**1(±3)**	**Within 30 Days After Last Dose of Study Drug(s)**	**60 and 90 (± 14) Days After Last Dose of Tislelizumab**	**Approximately Every 3 Months (± 14 days) (Phase 2)**
AEs[11]	x	x	x	x	x	x	x	
Concomitant medications[12]	x	x	x	x	x	x	x	
Hematology[13]	x	x[13]	x[13]	x[13]	x	x[13]		
Clinical chemistry[13]	x	x[13]	x[13]	x[13]	x	x[13]		
Coagulation parameters[13]	x	As clinically indicated						
Urinalysis[13]	x	x[13]			x	x[13]		
AFP (for HCC patients only)[14]	x	x[14]			x	x[14]		
Pregnancy test[15]	x	x[15]			x	x		
Thyroid function[16]	x	Cycles 4, 7, 10, and every 3 cycles thereafter						
HBV/HCV tests[17]	x	As clinically indicated						
Tumor assessment[18]	x	In the first year, every 6 weeks (± 7 days) every 9 weeks (± 7 days) thereafter						

Assessment	Screening[1]	Treatment Period				EOT Visit[4]	Safety Follow-up Phone Call[5]	Survival Follow-up[6]
		Cycle 1 and 2			Cycle 3 and Subsequent Cycles			
Days (window)	**-28 to -1**	**1[2]**	**8 (±1)[3]**	**15 (±2)[3]**	**1(±3)**	**Within 30 Days After Last Dose of Study Drug(s)**	**60 and 90 (± 14) Days After Last Dose of Tislelizumab**	**Approximately Every 3 Months (± 14 days) (Phase 2)**
Archival tumor tissue[19]	x							
Fresh tumor tissue (optional)[20]	x				x C3D1 only			
Pulmonary function test[21]	As clinically indicated							
Sitravatinib administration[22]		Daily						
Tislelizumab administration[23]		x			x			
Patient diary		x	x	x	x	x		
Survival status[6]								x
MUGA/echo-cardiogram[24]	x	Every 12 weeks (± 7 days)						
PK sampling for sitravatinib[25]		See Appendix 2						
PK sampling for tislelizumab[25]								
ADA sampling for tislelizumab[25]								
PGx[25]								

Assessment	Screening[1]	Treatment Period				EOT Visit[4]	Safety Follow-up Phone Call[5]	Survival Follow-up[6]
		Cycle 1 and 2			Cycle 3 and Subsequent Cycles			
Days (window)	**-28 to -1**	**1[2]**	**8 (±1)[3]**	**15 (±2)[3]**	**1(±3)**	**Within 30 Days After Last Dose of Study Drug(s)**	**60 and 90 (± 14) Days After Last Dose of Tislelizumab**	**Approximately Every 3 Months (± 14 days) (Phase 2)**
Pharmacodynamic biomarker[26]	x	C1D1, C2D1 and C3D1 (within 30 min before dosing of sitravatinib)						
ctDNA[26]	x	Confirmed PR or CR (± 14 days) or PD at EOT (± 14 days)						

Abbreviations: ADA, antidrug antibody, AE, adverse event; AFP, alpha fetoprotein; CR, complete response; ctDNA, circulating tumor DNA; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; 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, multigated acquisition; PD, progressive disease; PGx, pharmacogenetic; PK, pharmacokinetic; PR, partial response; SAE, serious adverse event; x, to be performed.
Note: On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib should precede tislelizumab infusion.

1. **During Screening**, written informed consent must be signed before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests.
2. All assessments on Cycle 2 Day 1 may be performed within a time window of ± 3 days.
3. **In Cycle 1 and Cycle 2**, only patients in Phase 1 will return to study sites for assessments on Days 8 and 15.
4. **The EOT Visit** is conducted within 30 days after last dose of the study drug(s) or before initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) have been performed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the study drug (s) were initially interrupted due to AEs and then permanently discontinued, the EOT Visit may occur later, but no later than the permitted time of dose delay plus 7 days.
5. **The Safety Follow-up Phone calls**. Telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a subsequent 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. Safety Follow-up Phone Call is not required for patients with sitravatinib monotherapy.
6. **Survival follow-up** information will be collected via telephone calls only in Phase 2 (dose expansion), patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
7. **Child-Pugh classification** for liver function (Appendix 5) is required to be assessed for HCC patients only within 7 days before the first dose of study drug(s).
8. **Vital signs** collected on study include temperature, pulse, and blood pressure (systolic and diastolic) after patient resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before; during; and within 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and within 30 minutes after the infusion. Vital signs should

also be recorded prior to administration of sitravatinib; recorded values may be used for pre-tislelizumab assessment if vital signs are collected within 60 minutes before tislelizumab infusion.

9. **Complete physical examination** including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems is required to be performed at Screening and EOT Visit. Limited physical examination: At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed.
10. **12-Lead ECG**: The ECG should be performed during Screening, C1D1, at the beginning of every subsequent cycle, EOT Visit, and as clinically indicated at other time points. Patients should be resting for at least 10 minutes before each ECG collection. If ECG has been performed within 3 days before first dose of study drug(s) and EOT Visit, the test does not need to be repeated on C1D1 and the EOT Visit.
11. **AEs** will be graded and recorded throughout the study according to NCI-CTCAE, v5.0.
12. **All concomitant medications** received within 30 days before the first dose of study drug(s) and 30 days after the last dose of study treatment should be recorded.
13. **Hematology, clinical chemistry, coagulation and urinalysis** (Appendix 3): If laboratory tests at Screening are not performed within 7 days before administration of study drug on Cycle 1 Day 1, these tests (hematology, clinical chemistry and urinalysis) should be repeated and reviewed before study drug administration. In Phase 1, hematology and clinical chemistry, as specified in Appendix 3, should be performed weekly for the first 2 cycles. For all patients in Phase 1 and Phase 2, hematology, clinical chemistry and urinalysis should be performed at the beginning of each cycle and the EOT Visit. After Cycle 1, laboratory safety tests should be performed, and the results should be reviewed within 48 hours before study drug(s) administration. For CK and CK-MB tests and coagulation tests, refer to Appendix 3.
14. **If AFP** test has been performed at Screening and within 21 days before EOT Visit, the test does not need to be repeated on C1D1 and the EOT Visit.
15. **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 before administration of study drug(s). Urine or serum pregnancy tests will be performed during treatment before study drug(s) administration at each cycle and EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug(s) at each cycle.
16. **TFTs** by analysis of FT3, FT4, and TSH will be performed at Screening, every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc) and EOT Visit. The test does not need to be repeated at the EOT Visit within 63 days after last test.
17. **HBV/HCV tests:** Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Testing at Screening is mandatory for patients. Additionally, for patients who have detectable HBV DNA at Screening, the respective viral load test will be performed every 4 cycles starting at Cycle 5 (ie, Day 1 of Cycles 5, 9, 13, etc), and EOT Visit.
18. **Tumor imaging:** Radiological images captured as standard of care before obtaining written informed consent and within 28 days before the first dose of study drug(s) may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented. At Screening, an MRI (or CT scan if MRI is contraindicated or not readily available) of the head may be required based on clinical judgement; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient.
    The investigator must review radiograph results before dosing at the next cycle. During the study, tumor imaging will be performed within 28 days prior to C1D1 and while on study approximately every 6 weeks ± 7 days in the first 12 months and approximately every 9 weeks ± 7 days thereafter. The investigator may perform additional scans or more frequent assessments if clinically indicated. Patients who discontinue study treatment early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first. Patients who continue tislelizumab treatment beyond radiographic PD will be monitored with a follow-up scan no more than 6 to 8 weeks beyond the initial diagnosis of radiographic PD before discontinuation of tislelizumab.
19. **Archival tumor tissue** (FFPE blocks or approximately 15 unstained FFPE slides) will be collected; if archival samples are not available, a fresh biopsy is recommended.

20. **Fresh biopsy**: In addition to archive tumor tissue, a fresh biopsy of a tumor lesion within 28 days before Cycle 1 Day 1 and/or after 2 cycles of treatment (approximately Cycle 3 Day 1) is recommended to obtain tumor samples for the evaluation of pharmacodynamic effects. An optional biopsy will also be taken from patients who have confirmed PD during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, post treatment biopsy should be ideally taken from the same tumor lesion as the screening biopsy. Written informed consent is required before obtaining fresh tumor biopsies.
21. **Pulmonary function test:** Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study.
22. **Sitravatinib administration** orally once daily without food (capsules should be taken in the fasted state, at least 2 hours after the previous meal and 1 hour before the next meal. For once daily dosing, capsules should be taken during the morning hours, for instance, at least 1 hour before breakfast or lunch.).
23. **Tislelizumab administration** (not for patients in sitravatinib monotherapy arm) on Day 1 of every cycle after sitravatinib administration.
24. MUGA/Echocardiogram: Evaluations of cardiac function will be performed at Screening and every 12 weeks (± 7 days). For study purposes, evaluation by MUGA scan is preferred. Evaluation by echocardiogram is an acceptable alternative if necessary. The method used for individual patients should be consistent throughout study participation.
25. See Appendix 2 for **PK sampling for sitravatinib, PK sampling for tislelizumab, ADA sampling for tislelizumab, and blood sampling for PGx analysis** while on study treatment.
26. **Blood sampling for biomarker analysis**: Peripheral blood samples will be collected for biomarker assessments, including, but not limited to cytokines, immune cell subpopulation, plasma protein and ctDNA. Approximately 15 mL of peripheral blood samples will be collected at Screening and on Day 1 (within 30 min before dosing of sitravatinib) of Cycles 1, 2, and 3. For the patients who have confirmed CR/PR or PD (at EOT Visit) as assessed by the investigator, additional blood samples (approximately 10 mL) will be collected at each time. Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual.

APPENDIX 2. SCHEDULE OF PK ASSESSMENTS

	Collection Time and Allowable Window	PK-Sitra[c]		PK-Tisle[d]	ADA-Tisle[e]	PGx[f]
		Phase 1	Phase 2	Phase 1 and Phase 2		
C1D1, C1D21	Predose - 30 min	x	x (C1D1 only)	x (C1D1 only, Pre-tisle-dose [-30 min])	x (C1D1 only, Pre-tisle-dose [-30 min])	x (C1D1 only)
	0.5 h ± 10 min	x		x (C1D1 only, Post-tisle infusion + 30min)		
	1 h ± 10 min	x				
	2 h ± 15 min	x				
	4 h ± 20 min	x				
	6 h ± 20 min	x	x (C1D1 only)			
	8 h ± 30 min	x				
	10 h ± 1 h	x				
	12 h ± 2 h[b]	x				
C1D2, C2D1	24h ± 2 h (Pre-C1D2 dose and Pre-C2D1 dose)[b]	x				
C2D1	Predose - 30 min		x	x (Pre-tisle-dose [-30 min])	x (Pre-tisle-dose [-30 min])	
	6 h ± 20 min		x			
C5D1	Predose - 30 min		x	x (Pre-tisle-dose [-30 min])	x (Pre-tisle-dose [-30 min])	
	0.5 h			x (Post-tisle infusion + 30min)		

	Collection Time and Allowable Window	PK-Sitra[c]		PK-Tisle[d]	ADA-Tisle[e]	PGx[f]
		Phase 1	Phase 2	Phase 1 and Phase 2		
	6 h ± 20 min		x			
C9D1, C17D1[a]	Predose - 30 min			x (Pre-tisle-dose [-30 min])	x (Pre-tisle-dose [-30 min])	
EOT	Within 30 Days After Last Dose of Study Drug(s)			x	x	

Abbreviations: ADA, antidrug antibody; irAE, immune-related adverse event; PGx, pharmacogenetic PK; pharmacokinetic; Sitra, sitravatinib; Tisle, tislelizumab; x, to be performed

a. Samples for tislelizumab PK and ADA will be collected if these cycles are achieved in this study.
b. Postdose samples for sitravatinib at 12 h and 24 h are optional and depend on site feasibility.
c. **PK sampling for sitravatinib**: Serial PK samples will be collected from all patients per cohort after single dose (C1D1) and at steady state (C1D21) in Phase 1. For patients enrolled in Phase 2 samples at predose (within 30 min before administration of sitravatinib) and 6 hours post dose will be collected on Day 1 of Cycles 1, 2, and 5. In the following situations additional PK sample may be collected: when a DLT event or SAE occurs, when a dose reduction happens, or when hepatic impairment status proceeds from mild to moderate in HCC patient cohorts.
d. **PK sampling for tislelizumab**: In Phase 1 and Phase 2, predose (within 30 min before starting tislelizumab infusion) samples should be collected on Day 1 of Cycles 1, 2, 5, 9, and 17 (if achieved); two postdose (within 30 min after the end of tislelizumab infusion) samples should be collected at C1D1 and C5D1; and an additional blood PK sample should be collected at the EOT Visit (See Appendix 1). Should a patient present with DLT event or ≥ Grade 3 or above irAE, additional blood PK samples may be taken to determine the serum concentration of tislelizumab.
e. **ADA sampling for tislelizumab**: In Phase 1 and Phase 2, samples should be collected before start of Day 1 tislelizumab infusion of Cycles 1, 2, 5, 9 and 17 (if achieved) and at the EOT Visit (See Appendix 1). All samples should be drawn at the same time as blood collection for predose PK samples.
f. **PGx**: A blood sample for DNA isolation will be collected from patients predose on C1D1.

APPENDIX 3. 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		Blood
Albumin	WBC count		Ketones
Total bilirubin	Lymphocyte count		24-hour protein[b]
Direct bilirubin	Neutrophil count		
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 cardiac muscle isoenzyme; INR, International Normalized Ratio; WBC, white blood cell.

a. Coagulation tests are required at Screening, and subsequently as clinically indicated.
b. On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein or a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.
c. If testing for corrected calcium is not feasible at the local laboratory, total calcium may be performed instead.
d. Patients receiving tislelizumab will receive CK and CK-MB testing. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients with a history of cardiological disease receiving sitravatinib monotherapy, either in Cohort A or after discontinuation of tislelizumab, may receive CK and CK-MB testing if clinically indicated.
e. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

In addition, the following tests will be conducted in this study:

- **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 administration of study drug(s). **Urine or serum pregnancy tests** will be performed during treatment before study drug(s) administration at each cycle and the EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug(s) at each cycle
- **Thyroid function tests** (thyroid-stimulating hormone [TSH], free T3, free T4) will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and EOT Visit (see Section 7.3.4 for details). TFT is not required at the EOT Visit if ≤ 63 days have passed since the last test.

APPENDIX 4. ECOG PERFORMANCE STATUS

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

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 5. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows:

- Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-37.
- Pugh RNH, Murray-Lyon IN, Dawson DL, et al. Transection of the esophagus for bleeding esophageal varices. Brit J Surgery. 1973;60:646-64.
- Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med. 1966;274(9):473-81.

Child-Pugh classification is either Grade A (mild: score 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: from 10 to 15 points) and is determined by both clinical and biochemical parameters (as shown below).

Clinical/Biochemical Parameter	Score (Anomaly Severity)		
	1	2	3
Hepatic encephalopathy (NCI-CTCAE grade)[a]	0[b]	1[c] or 2[d]	3[e] or 4[f]
Ascites (presence and severity)	None	Mild	Moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prolonged prothrombin time (seconds) or INR[g]	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

Abbreviations: INR, international normalized ratio; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

a. Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.
b. Grade 0: Consciousness, personality, neurological examination, and electrocardiogram are all normal.
c. Grade 1: Restlessness, sleep disorders, irritability/anxiety, hand tremor, writing disorders, 5CPS waves.
d. Grade 2: Lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.
e. Grade 3: Drowsiness, coma, orientation disorder, over-reflection, stiff/slow wave.
f. Grade 4: Cannot wake up from coma, no independent personality/behavior, irrational, slow 2-3CPS Delta activity.
g. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-637.

APPENDIX 6. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison'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	Behcet's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn's disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture's syndrome
Granulomatosis with polyangiitis	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
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord's thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodusa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter's syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren's syndrome
Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 7. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)
  - **Note:** Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR

- < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal 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 8. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

Adapted from Dolgin M, ed. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed.

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

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

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) Study equation. NKDEP's calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

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

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

where:

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

κ is 0.7 for females and 0.9 for males,

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

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

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

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

The online calculator for CKD-EPI can be found on the National Institute of Diabetes and Digestive and Kidney Diseases webpage (https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators)

Classification of Renal Impairment Using FDA Guidance for Industry

The renal impairment classification scale provided in the guidance document considers eGFR and Estimated Creatinine Clearance (CLcr). It allows for the fact that equations to calculate eGFR are evolving. In this study, eGFR will be calculated using the CKD-EPI equation.

Classification of Renal Function Based on Estimated GFR or Estimated Creatinine Clearance			
Stage	**Description**	**eGFR (mL/min/1.73m^2)**	**CLcr (mL/min)**
1	Control (Normal) GFR	≥ 90	≥ 90
2	Mild Decrease in GFR	60-89	60-89
3	Moderate Decrease in GFR	30-59	30-59
4	Severe Decrease in GFR	15-29	15-29
5	End Stage Renal Disease	< 15 not on dialysis or requiring dialysis	< 15 not on dialysis or requiring dialysis

APPENDIX 10. 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 judgement (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, PD, 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 PD 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 Adverse Events

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

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

- An irAEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	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 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation 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 breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (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.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the medical monitor.
	4 Life-threatening symptoms	If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN - 3 X ULN if baseline was normal; 1.5 - 3 X baseline if baseline was abnormal	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST > 3 - 5 X ULN if baseline was normal; > 3 - 5 X baseline if baseline was abnormal	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST > 5 - 20 X ULN if baseline was normal; > 5 - 20 X baseline if baseline was abnormal	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the medical monitor.
	4 ALT or AST > 20 X ULN if baseline was normal; > 20 X baseline if baseline was abnormal	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone • If on intravenous, add mycophenolate mofetil (MMF) 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		replacement therapy is available.	
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9- 13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9- 27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
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.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3	Admit to hospital for urgent	Hold study treatment;

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Abdominal pain, nausea, and vomiting	management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	reintroduce only after discussion with the medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms 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 intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		steroids and treat as Grade 2	
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and1-2 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, 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.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion	Initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or antithymocyte globulin	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 cardiac muscle isoenzyme; INR, international normalized ratio; LFT, liver function testing; 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 11. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

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

DEFINITIONS

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

Note: Lesions are either measurable or 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 1 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 (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no 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 to < 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, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all 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. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, 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 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, 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 case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, 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 (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following 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 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 (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and 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. (Note: the appearance of 1 or more new lesions is also considered progression).
- 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 complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report 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 (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline

become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially 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: Unequivocal progression (as detailed below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 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 disease, 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 1 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 3 trials when it is not a criterion of trial entry to have measurable disease. The

same general concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in 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: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).

Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to 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, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or 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 trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on trial 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 site of disease confirmed by CT, this is

PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drugs 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 trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "BOR".

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all 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 inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
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 "zero" on the eCRF.

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 trial therapy.

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDGPET 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 FDGPET 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 FDGPET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If 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 nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or 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 until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

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

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

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

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

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

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

MEDICATIONS THAT SHOULD BE AVOIDED

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

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

CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS

Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP Transporters

Enzyme	
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, **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**, naloxegol, nisoldipine, quetiapine, *saquinavir*, sildenafil, **simvastatin**, sirolimus, tacrolimus, ticagrelor, *tipranavir*, tolvaptan, triazolam, vardenafil.

Drugs with Conditional Risk of Torsades de Pointes

Amantadine, amisulpride (not on US market), amitriptyline, amphotericin B, *atazanavir*, bendroflumethiazide / bendrofluazide (not on US market), chloral hydrate, **diphenhydramine**, doxepin, **esomeprazole**, **famotidine**, **fluoxetine**, fluvoxamine**, furosemide / frusemide**, galantamine, garenoxacin (not on 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*, torsemide / torasemide, trazodone, voriconazole, ziprasidone.

APPENDIX 13. BARCELONA CLINIC LIVER CANCER (BCLC) STAGING CLASSIFICATION

The Barcelona Clinic Liver Cancer (BCLC) system has been widely validated and is the most commonly used staging system for HCC. It determines cancer stage and patient prognosis based on tumor burden, severity of liver disease, and the patient's ECOG Performance Status.

The staging according to the BCLC classification assigns prognoses based on clinical and tumor parameters and is summarized as follows:

BCLC Stage[a, b]				
Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Single nodule <2 cm Carcinoma in situ Child–Pugh A, ECOG PS 0	Single or 3 nodules <3 cm Child–Pugh A-B, ECOG PS 0	Multinodular, Child–Pugh A-B, ECOG PS 0	Portal invasion, Extrahepatic spread, Child–Pugh A-B, ECOG PS 1-2	Child–Pugh C ECOG PS 3-4

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

a. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology. 2016;150:835-53.
b. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.