CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 2, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sitravatinib in Combination With Tislelizumab in Patients With Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma That Progressed on or After Anti-PD-(L)1 Antibody Therapy
Protocol Identifier:	BGB-A317-Sitravatinib-203
Phase:	2
Investigational Medicinal Product(s):	Sitravatinib (BGB-9468), tislelizumab (BGB-A317), docetaxel, and irinotecan
Indication:	Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, Third Floor San Mateo, California 94404, USA
Sponsor Medical Monitor:	[redacted]
Original Protocol Version 0.0:	19 April 2022
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Protocol Amendment 2.0:	10 July 2023

Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sitravatinib in Combination With Tislelizumab in Patients With Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma That Progressed on or After Anti-PD-(L)1 Antibody Therapy

BeiGene, Ltd., Approval:

See electronic signature	*See electronic signature*
Sponsor Medical Monitor	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sitravatinib in Combination With Tislelizumab in Patients With Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma That Progressed on or After Anti-PD-(L)1 Antibody Therapy

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This protocol is a confidential communication of BeiGene, Ltd., and its affiliates. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its affiliates.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Medicinal Product(s): Sitravatinib (also known as BGB-9468), tislelizumab (also known as BGB-A317), docetaxel, and irinotecan

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Protocol Identifier: BGB-A317-Sitravatinib-203

Phase of Development: 2

Number of Patients: Approximately 100

Study Centers: Approximately 25 centers in Mainland China

Study Objectives and Endpoints:

Primary:

Objective	Endpoint
To assess the overall response rate (ORR) by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 in the Intention-to-Treat (ITT) Population between Arm A (sitravatinib plus tislelizumab) and Arm C (investigator-chosen chemotherapy)	ORR as assessed by the investigator, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1, in Arms A and C in the ITT Analysis Set

Secondary:

Objectives	Endpoints
To evaluate the duration of response (DOR) as assessed by the investigator per RECIST v1.1 in Arm A and Arm C	DOR as assessed by the investigator, defined as the time from the first confirmed objective response until the first documentation of disease progression or death, whichever comes first, in Arms A and C in the ITT Analysis Set
To assess the efficacy between Arm A and Arm C through overall survival (OS)	OS, defined as the time from the date of randomization until the date of death from any cause, in Arms A and C in the ITT Analysis Set
To assess the efficacy between Arm A and Arm C through disease control rate (DCR), clinical benefit rate (CBR), and progression-free survival (PFS) as assessed by the investigator per RECIST v1.1	DCR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or stable disease, in Arms A and C in the ITT Analysis Set CBR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease ≥ 24 weeks), in Arms A and C in the ITT Analysis Set

Objectives	Endpoints
	PFS as assessed by the investigator, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in Arms A and C in the ITT Analysis Set
To assess the efficacy of Arm A and Arm B (sitravatinib monotherapy) through ORR, DOR, DCR, CBR, and PFS as assessed by the investigator per RECIST v1.1	ORR as assessed by the investigator, defined as the proportion of patients with a confirmed CR or PR per RECIST v1.1, in Arms A and B in the ITT Analysis Set DOR as assessed by the investigator, defined as the time from the first confirmed objective response until the first documentation of disease progression or death, whichever comes first, in Arms A and B in the ITT Analysis Set DCR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or stable disease, in Arms A and B in the ITT Analysis Set CBR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease ≥ 24 weeks), in Arms A and B in the ITT Analysis Set PFS as assessed by the investigator, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in Arms A and B in the ITT Analysis Set
To assess the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab	Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute-Common Terminology Criteria for Adverse Events NCI-CTCAE v5.0; vital signs; and clinical laboratory test results in the Safety Analysis Set

Exploratory:

Objectives	Endpoints
To assess the OS between Arm A and Arm B	OS, defined as the time from the date of randomization until the date of death from any cause, in Arms A and B in the ITT Analysis Set
To perform a sample-based tumor assessment by independent review committee (IRC) in Arms A, B, and C	ORR as assessed by the IRC, defined as the proportion of patients with a confirmed CR or PR per RECIST v1.1, in part of patients in Arms A, B, and C

Objectives	Endpoints
To explore potential biomarkers that may correlate with clinical responses/resistance to sitravatinib plus tislelizumab or sitravatinib monotherapy versus chemotherapy	Potential biomarkers including but not limited to PD-L1 expression, tumor mutational burden (TMB)/DNA mutation/microsatellite instability (MSI), blood tumor mutational burden (bTMB)/circulating tumor DNA (ctDNA) monitoring/DNA mutation/MSI, gene expression profile (GEP), and tumor-infiltrated immune cells as well as the associations of biomarkers with disease status and response/resistance to sitravatinib plus tislelizumab or sitravatinib monotherapy versus chemotherapy
To characterize the pharmacokinetics of sitravatinib and its metabolite M10	Plasma concentrations of sitravatinib and its metabolite M10 at specified timepoints
To characterize the pharmacokinetics and immunogenicity of tislelizumab	Serum concentrations of tislelizumab and the incidence of antidrug antibodies (ADAs)
To assess health-related quality of life (HRQoL)	HRQoL is defined as the assessment of changes in patient-reported outcomes (PRO) of esophageal squamous cell carcinoma (ESCC)-related symptoms and function from baseline

Study Design:

This is an open-label, randomized, multicenter, Phase 2 study to investigate the efficacy and safety of sitravatinib in combination with tislelizumab given as a second- or third-line treatment in patients with locally advanced unresectable or metastatic ESCC whose disease progressed after prior platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy, with the anti-PD-(L)1 antibody administered in combination with or sequentially following the platinum-based chemotherapy.

The study will be conducted at approximately 25 centers in Mainland China. Approximately 100 patients with locally advanced unresectable or metastatic ESCC whose disease progressed on or after platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy will be randomized to receive either sitravatinib plus tislelizumab (Arm A), sitravatinib monotherapy (Arm B), or investigator-chosen chemotherapy (ICC) (Arm C). Patients must have received ≤ 2 lines of prior systemic therapy for locally advanced unresectable or metastatic disease. Other prior immunotherapeutic agents specifically targeting T-cell costimulation or checkpoint pathways (eg, anti-TIGIT antibody) are allowed if it was administered in combination with an anti-PD-(L)1 antibody. The choice of chemotherapy must be determined before randomization at the investigator's discretion, either docetaxel or irinotecan. Randomization will be stratified by programmed cell death protein ligand-1 (PD-L1) expression status (assessed by the Ventana PD-L1 [SP263] assay: Tumor Area Positivity [TAP] score ≥ 10% versus TAP score < 10%) in a 2:1:2 ratio to receive 1 of treatment regimens:

- Arm A: Sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Sitravatinib 100 mg orally once daily
- Arm C: Docetaxel 75 mg/m^2 intravenously on Day 1 of every 21-day cycle **OR** irinotecan 125 mg/m^2 intravenously on Days 1 and 8 of every 21-day cycle

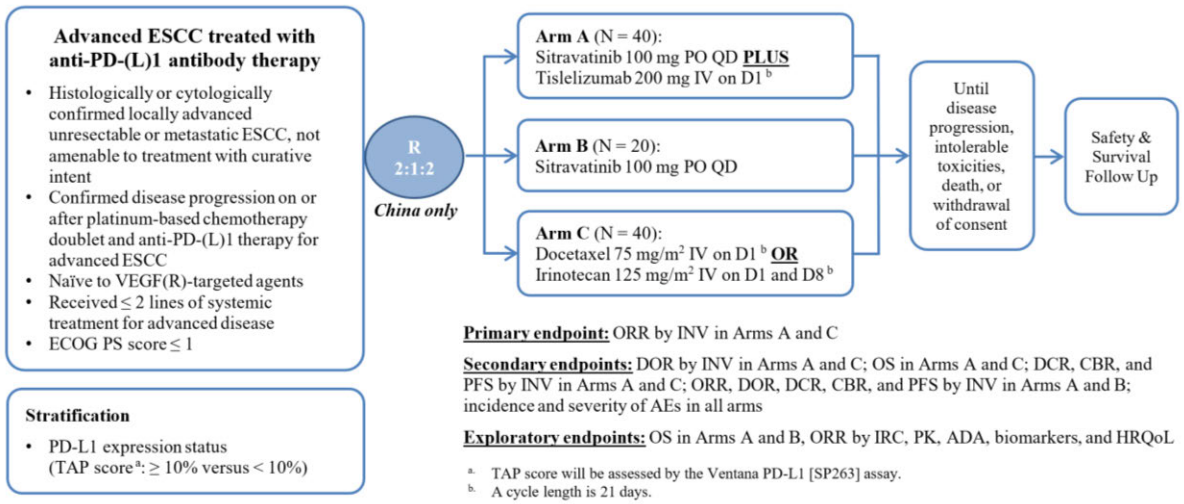
Switching of chemotherapeutic agent or cross-over between treatment arms will not be allowed during the study.

Efficacy and safety will be assessed between Arm A and Arm C, while efficacy between Arm A and Arm B will only be assessed for efficacy contribution analysis of tislelizumab in the combination treatment.

Study treatment will be administered until disease progression as assessed by the investigator per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met, whichever occurs first.

HRQoL will be assessed via 2 validated PRO instruments: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC Quality of Life Questionnaire-Oesophageal Cancer Module (EORTC QLQ-OES18).

Study Schema:



Abbreviations: CBR, clinical benefit rate; D, Day; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; INV, investigator; IRC, Independent Review Committee; IV, intravenously; N, number of patients; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-(L)1, programmed cell death protein (ligand)-1; PFS, progression-free survival; PK, pharmacokinetic(s); PO, orally; QD, once daily; R, randomization ratio; TAP, Tumor Area Positivity; VEGF(R), vascular endothelial growth factor (receptor).

Study Assessments:

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

The baseline tumor imaging will be performed ≤ 28 days before randomization. During the study treatment period, evaluation of tumor response by the investigator per RECIST v1.1 will be performed every 6 weeks from Day 1 of Cycle 1 for the first 55 weeks and then every 9 weeks thereafter.

After initiation of study treatment, all AEs and serious adverse events (SAEs), regardless of relationship to study treatment, will be reported until either 30 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be recorded until 90 days after the last dose of tislelizumab, regardless of initiation of new anticancer therapy. SAEs considered related to the study treatment that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

Duration of Patient Participation:

Duration of patient participation will vary by patient. Each patient's visit course will include:

- **Screening period** will be ≤ 28 days before randomization

- **Treatment period** will start on the first day of study drug administration and end on the last dose of study drug administration when the patient is discontinued from the study treatment for any reason.
- **End-of-Treatment (EOT) Visit:** Patient who permanently discontinues the study treatment (ie, sitravatinib and tislelizumab in Arm A, sitravatinib in Arm B, or ICC in Arm C) for any reason will be asked to return to the clinic for an EOT Visit, which is required to be conducted within 30 (± 7) days after the last dose of study treatment (unless otherwise specified) or before the initiation of subsequent anticancer therapy, whichever occurs first. If the decision to end the study treatment is made ≥ 23 days after the last dose of any component of the study treatment, the EOT Visit may occur later, but no later than 7 days after the decision.
- **Safety follow-up for immune-mediated adverse events (imAEs) period:** Patients who discontinue tislelizumab in Arm A will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE) at 60 (± 14) and 90 (± 14) days after the last dose of tislelizumab, regardless of whether they start a subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
- **Survival follow-up period**: Survival follow up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit or as directed by the sponsor until death, loss to follow up, withdrawal of consent, or study termination by the sponsor. All patients will be followed up for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow up.

Study Population:

Approximately 100 patients in Mainland China with locally advanced unresectable or metastatic ESCC that progressed after prior platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy, with the anti-PD-(L)1 antibody administered in combination with or sequentially following the platinum-based chemotherapy.

Key Eligibility Criteria:

Adult patients with histologically or cytologically confirmed locally advanced unresectable or metastatic ESCC that is not amenable to treatment with curative intent and progressed after prior systemic therapy are eligible. Prior treatment must include a platinum-based chemotherapy doublet and anti-PD-(L)1 antibody, with the anti-PD-(L)1 therapy administered in combination with or sequentially following the platinum-based chemotherapy. Other prior immunotherapeutic agents specifically targeting T-cell costimulation or checkpoint pathways (eg, anti-TIGIT antibody) are allowed if it was administered in combination with an anti-PD-(L)1 antibody. Patients must have received ≤ 2 lines of prior systemic therapy for locally advanced unresectable or metastatic ESCC; have ≥ 1 measurable lesion per RECIST v1.1 ≤ 28 days before randomization; and have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of ≤ 1. Archived or fresh tumor samples should be obtained from each patient for assessment of PD-L1 expression status by the Ventana PD-L1 (SP263) assay in the central lab during screening period.

Investigational Product, Dose, and Mode of Administration:

Arm A:

Sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks

Arm B:

Sitravatinib 100 mg orally once daily

Reference Therapy, Dose, and Mode of Administration:

Arm C:

Single-agent chemotherapy as determined before randomization at the investigator's discretion:

Docetaxel 75 mg/m^2 intravenously on Day 1 of every 21-day cycle **OR**
irinotecan 125 mg/m^2 intravenously on Days 1 and 8 of every 21-day cycle

Statistical Methods:

Primary analysis:

The primary analysis of ORR as assessed by the investigator is descriptive and exploratory; no formal testing is designed.

The crude odds ratio and risk difference of ORR, along with their exact 95% CIs will be calculated between Arms A and C. The ORR rate and its Clopper Pearson 95% CI will be calculated for each arm.

The primary analysis for ORR as assessed by the investigator will be conducted ≥ 4 months (approximately 3 tumor assessments) after the enrollment of the last patient.

Analysis sets:

- The ITT Analysis Set includes all patients randomly assigned to a treatment arm. Patients' data will be analyzed according to their randomized treatment arm. This will be the primary analysis population for all efficacy analysis.
- The Safety Analysis Set includes all patients who received at least 1 dose of any component of study treatment; it will be the population for the safety analyses.
- The Sitravatinib PK Analysis Set includes all patients who receive ≥ 1 dose of sitravatinib per the protocol and for whom any quantifiable postbaseline PK data for sitravatinib are available.
- The M10 PK Analysis Set includes all patients who receive ≥ 1 dose of sitravatinib per the protocol and for whom any quantifiable postbaseline PK data for M10 are available.
- The Tislelizumab PK Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab per the protocol and for whom any quantifiable postbaseline PK data for tislelizumab are available.
- The ADA Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab and for whom both baseline and ≥ 1 postbaseline ADA result are available.

Sample size considerations:

This exploratory study is not powered for the hypothesis testing between treatment arms but rather to obtain preliminary efficacy and safety data for sitravatinib in combination with tislelizumab and sitravatinib monotherapy for patients with locally advanced unresectable or metastatic ESCC that progressed on or after anti-PD-(L)1 antibody therapy. This study will enroll approximately 100 patients into 3 arms, with approximately 40, 20, and 40 patients in Arms A, B, and C, respectively. The efficacy of tislelizumab in combination with sitravatinib versus chemotherapy will be demonstrated by descriptive analysis of ORR, PFS, OS, DCR, CBR, and DOR as assessed by the investigator in the assessment between Arms A and C. The contribution of adding tislelizumab to sitravatinib monotherapy will be demonstrated by similarly descriptive analysis in the assessment of Arms A and B. With a sample size of 40 patients in Arm A (sitravatinib in combination with tislelizumab), the binomial probabilities of detecting ≥ 1 treatment-emergent adverse event (TEAE) with a frequency of 5% and 1% are approximately 0.87 and 0.33, respectively.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-9468	sitravatinib
BGB-A317	tislelizumab
BOR	best overall response
BP	blood pressure
BSA	body surface area
bTMB	blood tumor mutational burden
CPI	checkpoint inhibitor
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
EC	esophageal cancer
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EOT	End-of-Treatment
ESCC	esophageal squamous cell carcinoma
FDG	fluorodeoxyglucose
G/GEJ	gastric/gastroesophageal junction
GCP	good clinical practice
GEP	gene expression profile
HBV	hepatitis B virus
HCC	hepatocellular cancer

Abbreviation	Definition
HCV	hepatitis C virus
HR	hazard ratio
ICC	investigator-chosen chemotherapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IMP	investigational medicinal product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	interactive response technology
ITT	Intent-to-Treat (Analysis Set)
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD-L1	programmed cell death protein ligand-1
PD-(L)1	programmed cell death protein (ligand)-1
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RTK	receptor tyrosine kinase
SAE	serious adverse event
TAP	Tumor Area Positivity
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TMB	tumor mutational burden
TME	tumor microenvironment
ULN	upper limit of normal
V	Version

1. INTRODUCTION

1.1. Background Information on Advanced Esophageal Squamous Cell Carcinoma

Esophageal cancer (EC) is the eighth most common cancer in terms of incidence and the sixth most common cause of cancer-related death worldwide, with 604,100 new cases and 544,076 deaths observed in 2020 (GLOBOCAN 2020a). Eastern Asia exhibits the highest regional incidence for both men and women among the globe, which reflects on a large disease burden in China (GLOBOCAN 2020b). In China, EC is the sixth most common cancer and the fourth most common cause of cancer-related deaths. It was estimated that > 324,422 new EC cases were diagnosed and approximately 301,135 deaths occurred in China in 2020, accounting for 53.7% of the incidence and 55.3% of the mortality of global cases (GLOBOCAN 2020c).

Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma are the two main histologic types of EC. Because of differences in tumor localization and comorbidities, response to molecularly targeted therapy, and prognosis, ESCC and esophageal adenocarcinoma are usually considered as two distinct diseases that require different therapeutic strategies (Arnold et al 2015; Siewert and Ott 2007; Cancer Genome Atlas Research Network et al 2017; Salem et al 2018). ESCC is the dominant histological subtype of EC worldwide, accounting for approximately 90% of EC cases (Abnet et al 2018). Regions of high incidence include Eastern to Central Asia, along the Rift Valley in East Africa, and into South Africa. ESCC is more common in the elderly (aged ≥ 60 years) and has a mean male to female ratio of 3:1 (Lagergren et al 2017). The main risk factors include tobacco, alcohol, ingestion of hot liquid, and poor nutritional status (Tran et al 2005; Engel et al 2003).

Advanced ESCC is a rapidly progressing and symptomatic disease with poor clinical outcomes. The 5-year survival rate is only 5.2% for patients with distant metastases (SEER 2022).

1.2. Current Treatment of Advanced Esophageal Squamous Cell Carcinoma and Unmet Clinical Needs

International treatment guidelines are consistent in the approach to the treatment of ESCC, and the management is dependent on the characteristics of the patient (including PS and overall health status) and those of the tumor, mainly the Tumor Node Metastasis (TNM) stage (NCCN 2022; Muro et al 2019; Lordick et al 2016).

In newly diagnosed ESCC, neoadjuvant chemoradiation in combination with surgery is recommended for patients with localized resectable tumors, and definitive chemoradiation therapy is recommended for patients who decline surgery, are poor surgical candidates, or have locally advanced unresectable tumors. However, more than 30% of patients with ESCC are diagnosed at an advanced or metastatic stage (Abraham et al 2020) and are ineligible for curative interventions. Moreover, in one-third to one-half of patients treated with curative intent, the disease progressed, with approximately 5% to 20% of disease progression or death occurring within 6 months of the curative treatment (Shapiro et al 2015; Conroy et al 2014; Crosby et al 2017). Ultimately, most patients with ESCC will require palliative systemic treatment.

Patients with advanced ESCC (metastatic, unresectable, or recurrent after curative treatment) are recommended to receive first-line palliative chemotherapy (Lordick et al 2016). Platinum-based chemotherapy doublets, which include either platinum agents (cisplatin, oxaliplatin, or carboplatin) plus fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) or taxanes (paclitaxel or docetaxel) are recommended (NCCN 2022; Lordick et al 2016; Muro et al 2019). First-line palliation has an overall response rate (ORR) of 30% to 58% and a median overall survival (OS) of 10.0 to 13.2 months (Kato et al 2020; Liu et al 2016; Lee et al 2015).

Immune checkpoint inhibitors (CPIs) targeting the PD-(L)1 pathway have revolutionized the therapeutic landscape of advanced ESCC in recent years. Multiple multicenter, randomized Phase 3 studies have demonstrated that anti-PD-1 antibodies in combination with chemotherapy (cisplatin plus 5-FU or paclitaxel) as the first-line systemic treatment significantly prolongs the OS in patients with ESCC compared with chemotherapy alone (cisplatin plus 5-FU or paclitaxel) (Sun et al 2021; Luo et al 2021). Based on the positive readout of Keynote-590, pembrolizumab in combination with chemotherapy was approved in China in September 2021 for the treatment of locally advanced unresectable or metastatic EC in the first-line treatment setting (National Medical Products Administration [NMPA] Acceptance No.: JXSS2000051). In December 2021, another PD-1 inhibitor, camrelizumab was also approved by the NMPA to be used in combination with chemotherapy as the first-line treatment of ESCC (NMPA Acceptance No.: CXSS2100031) based on the results of ESCORT-1st. In addition to Keynote-590 and ESCORT-1st, multiple studies including Checkmate-648 (Doki et al 2022), ORIENT-15, and JUPITOR-06 demonstrate positive results for anti-PD-(L)1 antibodies in combination with chemotherapy as the first-line treatment for ESCC, which likely brings alternative options of anti-PD-(L)1 antibodies to the treatment setting in the near future. As the first chemotherapy-free regimen that had positive readout, nivolumab in combination with ipilimumab as the first-line treatment was superior than chemotherapy alone in prolonging survival in patient with ESCC regardless of programmed cell death protein ligand-1 (PD-L1) expression status (Doki et al 2022), which adds another PD-(L)1-based treatment option for the population. Furthermore, several Phase 3 studies including RATIONALE-306, HLX10-007-EC301, SKYSCRAPER-08, and GEMSTONE-304 are ongoing, which are all anti-PD-(L)1 antibodies (with or without an anti-TIGIT antibody) in combination with chemotherapy as first-line ESCC treatment setting.

Second-line or subsequent therapy for ESCC are dependent on patients' physical performance status and the prior therapy received. For patients whose disease progressed on the first-line chemotherapy, clinical benefits of anti-PD-(L)1 antibody monotherapy outweigh those of chemotherapy, which is demonstrated by prolonging patients' OS with a significantly more tolerable safety profile. Pembrolizumab monotherapy was approved for the treatment of recurrent locally advanced or metastatic ESCC that expresses PD-L1 (Combined Positive Score [CPS] ≥ 10) and progressed after ≥ 1 prior line of systemic therapy by the United States Food and Drug Administration (US FDA) in 2019 (Keytruda USPI 2020; Kojima et al 2020) and by the NMPA in 2020. Based on the results of ESCORT, camrelizumab monotherapy was approved by the NMPA in June 2020 for patients with advanced ESCC whose disease progressed after first-line chemotherapy or who were intolerant to the first-line chemotherapy, regardless of the PD-L1 expression status of ESCC (Huang et al 2020). Although nivolumab has not yet been approved by the NMPA, Chinese Society of Clinical Oncology (CSCO) guideline lists

nivolumab as a second-line treatment option for similar population based on efficacy results from ATTRACTION-3 (Kato et al 2019; CSCO 2021).

PD-(L)1 antibody in combination with chemotherapy as the first-line therapy and PD-(L)1 antibody monotherapy as the second-line therapy have become standard of care for patients with advanced ESCC. Even without epidemiological data to support, it is expected that CPI resistance in ESCC will inevitably develop in a large number of patients. Treatment options for ESCC are limited after exhausting platinum-based or fluoropyrimidine-based doublet chemotherapy and checkpoint therapy. Several single-agent chemotherapeutic regimens have been recommended by guidelines for treating ESCC after prior CPI failure, including docetaxel, paclitaxel, or irinotecan (NCCN 2022). Although the efficacy of single-agent chemotherapy after prior CPI treatment remains unclear for patients with ESCC, these therapeutic agents generally display poor OS outcomes (typically < 6 months) after prior chemotherapy failure (Shirakawa et al 2014; Mizota et al 2011; Song and Zhang 2014; Burkart et al 2007) (Table 1) and are associated with significant toxicity, which results in substantial morbidity and mortality with frequent dose interruptions, delays, or reductions.

- Docetaxel is associated with Grade 3 or 4 neutropenia (32.6% to 48.8%), febrile neutropenia (6.1% to 20.9%), and anaemia (2.3% to 9.1%), as well as Grade 3 or 4 anorexia (3.0% to 4.7%) and pneumonia (4.5%) (Shirakawa et al 2014; Mizota et al 2011).
- Paclitaxel is associated with Grade 3 or 4 neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), fatigue (9.4%), constipation (7.5%), pneumonia (7.5%), and sensory neuropathy (5.7%). Sensory neuropathy of any grade is observed in 81.1% of patients treated with paclitaxel and is often debilitating (Kato et al 2011).
- Irinotecan often results in neutropenia (21.4%), anaemia (28.6%), and diarrhoea (21.4%) (Burkart et al 2007).

Table 1: Second-Line Chemotherapy for Esophageal Squamous Cell Carcinoma

Agent	Study design and patient population	Sample size by histology (n)	Regimen	Median OS (mo)	Median PFS (mo)
Paclitaxel (Shirakawa et al 2014)	Retrospective study in Japanese patients	ESCC (n = 31)	100 mg/m^2 weekly for 6 weeks followed by a 1-week rest	6.1	2.5
Paclitaxel (Mizota et al 2011)	Retrospective study in Japanese patients	ESCC (n = 35) EAC (n = 3)	80 to 100 mg/m^2 Days 1, 8, and 15 for a 28-day treatment cycle	7.2 [a]	3.5 [a]
Paclitaxel (Ilson et al 2007)	Multicenter, collaborative study in US patients	ESCC (n = 32) EAC (n = 63)	80 mg/m^2 weekly	9.0 [a]	3.1 [a]

Agent	Study design and patient population	Sample size by histology (n)	Regimen	Median OS (mo)	Median PFS (mo)
Docetaxel (Shirakawa et al 2014)	Retrospective study in Japanese patients	ESCC (n = 132)	70 mg/m^2 Q3W	5.5	2.3
Docetaxel (Mizota et al 2011)	Retrospective study in Japanese patients	ESCC (n = 84) EAC (n = 2)	60 to 70 mg/m^2 Q3W	6.1 [a]	2.1 [a]
Docetaxel (Song and Zhang 2014)	Retrospective study in Chinese patients	ESCC (n = 41)	Not specified	5.2	3.2
Docetaxel (Albertsson et al 2007)	Prospective study in Scandinavian patients	ESCC (n = 39) EAC (n = 13)	Docetaxel alone: 100 mg/m^2 Q3W	NA [b]	NA [b]
Irinotecan (Burkart et al 2007)	Single-arm, Phase 2 study in German patients	ESCC (n = 7) EAC (n = 7)	100 mg/m^2 weekly x 3 every 4 weeks	5 [a]	2 [a]

Abbreviations: CR, complete response; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; mo, month(s); NA, not available; OS, overall survival; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; US, United States.

[a] Combined ESCC and EAC histology (and first- and second-line combined, Ilson et al 2007)

[b] Study I: CR, 5%; PR, 26%

Overall, clinical benefits of the single-agent chemotherapy regimens as second- or third-line options for patients with advanced ESCC after treatment failure with a prior anti-PD-(L)1 antibody and chemotherapy are diminished by modest treatment effect with significant toxicities such as myelosuppression and neuropathy (docetaxel, paclitaxel, and irinotecan) as well as diarrhoea (irinotecan). Dismal prognosis for patients with previously treated, locally advanced unresectable or metastatic ESCC highlights the large unmet medical need for novel therapies with survival benefit and better safety and tolerability profile.

1.3. Background Information on Sitravatinib

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 that bind polypeptide ligands (mainly growth factors) play key roles in processes such as cell 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 (also known as BGB-9468) 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), thus providing a rationale for combining with PD-1 CPI therapy. Along with the immunostimulatory effects, the immunomodulatory effects of sitravatinib mediated through VEGFR and KIT inhibition may further condition the TME in favor of antitumor activity. Preclinical data for sitravatinib indicate that it can increase PD-L1 expression in 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).

1.3.1. 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, sitravatinib is a substrate of P-glycoprotein (P-gp) but is not a substrate of breast cancer resistance protein (BCRP), Organic Anion Transporter (OAT) 1 or 3, Organic Cation Transporter (OCT) 2, Organic Transporting Polypeptide (OATP) 1B1 or 1B3, or Multi-Antimicrobial Extrusion Protein (MATE) 1 or 2K. Sitravatinib inhibited the efflux transporters P-gp and BCRP, and Bile Salt Export Pump (BSEP) mediated transport with IC_{50} values of 0.838 μM, 1.51 μM, and 5.06 μM, respectively. Sitravatinib demonstrated direct inhibition of cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, with IC_{50} values of 2.9 μM, 11 μM, 10 μM, 1.9 μM, 11 μM, and 0.81 μM, respectively.

Sitravatinib was more extensively metabolized in dogs than in mice, rats, and humans in vitro. In vitro results from the hERG assay demonstrate an IC_{50} of 0.6 μM (0.38 μg/mL) on the potassium current, which is approximately 227-fold higher than the mean free C_{max} at steady-state (0.00265 μM) in patients, suggesting a low risk for QTc prolongation. In vivo results demonstrated that there were no adverse effects on the cardiovascular system in telemetered dogs, including no effect on the QTc interval, when sitravatinib was administered as a single-dose to dogs at doses up to 4 mg/kg (mean 6-hour concentration of 0.072 μg/mL). Minor increases in vascular pressures were observed during the dog cardiovascular study.

Assessment of the neurological functional observation battery and respiratory evaluations (tidal volume, respiration rate, and minute volume) did not reveal any sitravatinib-related effects at doses up to 25 mg/kg in rats (Day 1 mean C_{max} = 4.9 μg/mL).

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

1.3.2. Toxicology

In the 4-week repeated-dose toxicology study in beagle dogs, sitravatinib was tolerated at doses up to 3 mg/kg/day, the highest dose tested (Study TX-MGCD516-006). No unscheduled deaths occurred in the study; however, 1 dog in the 3 mg/kg/day group was taken off dosing on Day 8 due to decreased body weight, emesis, loose feces, and dehydration. The remaining dogs in this dose group also exhibited decreased body weight and food consumption throughout the remainder of the dosing period. Upon necropsy, there were no treatment-related gross findings, clinical pathology changes, or microscopic findings attributed to sitravatinib at any dose level. Given the marked loss of body weight and decreased food consumption at 3 mg/kg/day, the no-observed-adverse-effect level (NOAEL) was considered 1 mg/kg/day.

In the 13-week repeated-dose study in dogs (Study TX-MGCD516-014), sitravatinib was tolerated at doses up to 2 mg/kg/day, the highest dose tested. There were no test article-related unscheduled deaths and no adverse sitravatinib-related ophthalmic or clinical pathology parameter changes. Target organ effects were limited to necrotizing vascular/perivascular inflammation in the serosa of the oviduct and uterus of the 2 mg/kg/day group females. These reproductive organ effects in females were not present after the 4-week recovery period, demonstrating complete reversal of these effects. Based on the adverse effects in the reproductive organs of female dogs given 2 mg/kg/day of sitravatinib, the NOAEL was considered to be 2 mg/kg/day in males and 0.6 mg/kg/day in females.

In rats, VEGF-related target organs were identified, including the adrenal gland, Brunner's glands in the duodenum, lymphoid tissues, ovary, kidney (increased basophilic tubules), liver, pancreas, tongue, bone, and teeth. All effects, except those in the kidney, bile duct, and pancreas, either recovered or showed partial recovery. Daily oral administration of sitravatinib to Crl:CD (Sprague Dawley) 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 was determined as 2.5 mg/kg/day.

Administration of sitravatinib in the 4-week repeated-dose rat study (TX-MGCD516-007) led to early deaths at 10 and 25 mg/kg/day. The cause of death and morbidity at these dose levels consisted of adrenal hemorrhage and necrosis. Based on the severity of the sitravatinib-related toxicity at ≥ 10 mg/kg/day, the NOAEL was 2.5 mg/kg/day.

Sitravatinib was evaluated in a standard battery of Good Laboratory Practice 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.

1.3.3. Clinical Pharmacology

The pharmacokinetics (PK) profile of single-agent treatment with the sitravatinib free-base formulation has been evaluated in Study 516-001 after single- and repeated-dose administration in patients with advanced solid tumor malignancies. Plasma samples for PK analyses were collected over a 168-hour period following single-dose administration (Lead-In Period) and over a 24-hour period following repeated-dose administration. Plasma drug concentrations were determined using a validated, sensitive, liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay. The PK of sitravatinib was evaluated using noncompartmental analysis methods.

After single-dose administration, sitravatinib reached peak concentration in a median time (t_{max}) of approximately 3.02 to 8.87 hours. Exposure parameters (maximum concentration [C_{max}] and area under the concentration-time curve [AUC]) were approximately dose proportional with single doses up to 200 mg. The arithmetic mean elimination half-life ranged from 42.1 to 51.5 hours. After multiple oral administration, steady-state appeared to have been reached by Day 8 and C_{max} and AUC_{τ} accumulation ratios at steady-state ranged from 1.82 to 6.89 and 2.13 to 8.34, respectively.

Sitravatinib underwent multiple biotransformation reactions following single oral administration to healthy male volunteers, with metabolism mediated via oxidation, and oxidative O- and N-dealkylation, as well as secondary sulfation, demethylation, dehydrogenation, deamination, and reduction. Sitravatinib was the most abundant circulating component in human plasma, accounting for > 56% of the total drug-related exposure. M10 was the only major metabolite, accounting for approximately 19% of the total drug-related exposure. M10 was evaluated in nonclinical studies, and the data suggested M10 was pharmacologically active against sitravatinib RTK targets.

Pharmacodynamic assessments of sitravatinib are ongoing; however, preliminary analysis shows a concentration-dependent modulation of VEGF-A, soluble VEGF-R2, and soluble MET ectodomain (sMET) levels in patients' plasma samples. The mean prediction (95% CI) percent change from baseline in biomarker modulation with exposure was as follows: 300% increase for VEGFA, 50% decrease for sVEGFR-R2, and 35% increase for sMET, consistent with VEGFR and MET inhibition. Mean C_{trough} at Day 15 of Cycle 1, for the 120 mg of sitravatinib free-base formulation once a day dose level in Study MRTX-500 was 62.4 ng/mL. At these sitravatinib plasma exposure levels, near-optimal modulation of biomarker levels are expected.

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

1.3.4. Clinical Experience With Sitravatinib

Sitravatinib monotherapy and sitravatinib in combination with nivolumab or tislelizumab (also known as BGB-A317; an anti-PD-1 monoclonal antibody) are being evaluated in ongoing studies. Please refer to the Sitravatinib Investigator's Brochure for more detailed information on sitravatinib and the currently ongoing studies.

1.3.4.1. Safety

Across the sitravatinib development program, a total of 1546 subjects/patients have received ≥ 1 dose of any study treatment with sitravatinib, including 215 patients in 8 pharmacokinetic studies of sitravatinib and 1331 patients with advanced/metastatic solid malignancies in 9 clinical studies. Of the 1279 patients with solid malignancies included in the safety analysis of sitravatinib, 220 patients have received treatment with sitravatinib as a single agent, an estimated 723 patients have received sitravatinib in combination with nivolumab, 20 patients have received sitravatinib in combination with nivolumab and ipilimumab, 16 patients have received sitravatinib in combination with pembrolizumab and enfortumab, and 300 patients have received sitravatinib in combination with the PD-1 inhibitor tislelizumab.

1.3.4.1.1. Safety Assessment of Monotherapy Study

Study 516-001 is a multicenter Phase 1/1b first-in-human clinical study evaluating the safety, PK, metabolism, pharmacodynamics, and clinical activity of single-agent sitravatinib in patients with advanced solid tumor malignancies. The study determined that the 200 mg dose exceeded the maximum tolerated dose (MTD) and 150 mg once daily was initially considered the viable Phase 1b starting dose, which was subsequently decreased to 120 mg once daily based on the ongoing assessment of tolerability. The Phase 1b expansion included patients having tumors with selected histological diagnoses (renal cell carcinoma and castrate-resistant prostate cancer) or with histological diagnosis and/or tumor molecular markers (genetic alterations in sitravatinib RTK targets, or loss of function mutations in CBL, the negative regulators of AXL, MET, and PDGFR/KIT signaling). As of 17 November 2022, among the 193 patients with available safety data, 190 patients (98%) had experienced ≥ 1 adverse event (AE) regardless of causality, and 174 patients (90%) had experienced ≥ 1 treatment-related AE. Treatment-related AEs reported in ≥ 10% of patients are provided in Table 2.

Treatment-related Grade 3 events reported in ≥ 5% of patients were hypertension (21%), diarrhoea (10%), fatigue (7%), and palmar-plantar erythrodysaesthesia syndrome (6%). Treatment-related Grade 4 events were reported in 3 patients and included lipase increased in 2 patients and febrile neutropenia in 1 patient.

Table 2: Summary of Treatment-Related, Treatment-Emergent Adverse Events (≥ 10% of Patients) by Preferred Term for Study 516-001

Adverse event Preferred Term, n (%)	**Patients (N = 193), n (%)**
Any treatment-related TEAE	174 (90.2)
Diarrhoea	98 (50.8)
Fatigue	83 (43.0)
Hypertension	78 (40.4)
Nausea	58 (30.1)
Decreased appetite	51 (26.4)
Vomiting	46 (23.8)

Adverse event Preferred Term, n (%)	Patients (N = 193), n (%)
Palmar-plantar erythrodysaesthesia syndrome	39 (20.2)
Aspartate aminotransferase increased	36 (18.7)
Alanine aminotransferase increased	35 (18.1)
Hypothyroidism	33 (17.1)
Stomatitis	28 (14.5)
Weight decreased	28 (14.5)
Dysphonia	27 (14.0)
Abdominal pain	22 (11.4)
Constipation	22 (11.4)
Proteinuria	22 (11.4)
Dry mouth	21 (10.9)
Rash	21 (10.9)
Dizziness	20 (10.4)

Abbreviation: TEAE, treatment emergent adverse event.

Serious Adverse Events: Overall, 79 patients (41%) have experienced ≥ 1 serious adverse event (SAE), regardless of causality, and treatment-related SAEs were reported in 30 patients (16%). Treatment-related SAEs reported in ≥ 2 patients (≥ 1%) included diarrhoea in 6 patients (3%), nausea and vomiting in 5 patients each (3%), fatigue in 4 patients (2%), hypertension in 3 patients (2%), and headache, left ventricular dysfunction, pancreatitis, and pulmonary embolism in 2 patients each (1%). A treatment-related Grade 5 SAR of cardiac arrest was reported in 1 patient.

Treatment Discontinuation and Deaths: Of the 193 treated patients, 189 patients (98%) have discontinued receiving study treatment, in most cases due to objective disease progression (90 patients [47%]), AE (31 patients [16%]), or patient withdrawal (31 patients [16%]). A total of 164 patients (85%) have discontinued the study, with the primary reasons being death (112 [58%]) and withdrawal by patient (35 [18%]).

1.3.4.1.2. Safety Assessment of Combination Study

MRTX-500: Sitravatinib in Combination With Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer

Study MRTX-500 is an open-label, parallel group Phase 2 evaluation of sitravatinib in the combination with nivolumab in patients with locally advanced, unresectable or metastatic nonsquamous non-small cell lung cancer (NSCLC). Patients who have experienced progressive disease on or after treatment with a CPI (CIT-experienced) as well as those who have experienced progressive disease after treatment with platinum-based doublet chemotherapy (CIT-naive) are enrolled. The sitravatinib treatment arm began with a lead-in evaluation of sitravatinib 120 mg once daily in combination with nivolumab administered by intravenous

infusion, 240 mg once every 2 weeks or 480 mg once every 4 weeks. No protocol-defined dose-limiting toxicities (DLTs) were reported in the first 6 evaluable patients treated with the sitravatinib free base at the starting dose of 120 mg once daily in combination with nivolumab. Based on the experience of patients enrolled into this study and in Study 516-001 (Mirati 2018), 120 mg once daily was selected as the Phase 2 dose of sitravatinib in combination with nivolumab at 240 mg once every 2 weeks or 480 mg once every 4 weeks.

As of 26 June 2022, among the 156 patients (excludes the PK substudies) with available safety data, 155 patients (99%) had experienced ≥ 1 AE regardless of causality; 146 patients (94%) had experienced treatment-related AEs; 145 patients (93%) had experienced sitravatinib-related AEs; and 115 patients (74%) had experienced nivolumab-related AEs. Treatment-related AEs reported in ≥ 10% of patients are provided in Table 3.

Sitravatinib-related Grade ≥ 3 events were reported in 86 patients (55%). Sitravatinib-related Grade 3 AEs were reported for 78 patients (50%), and the most common events (in > 5% of patients) by Preferred Term were hypertension (17%), diarrhoea (12%), and fatigue and weight decreased (5% each). Nivolumab-related Grade ≥3 events were reported for 39 patients (25%). Nivolumab-related Grade 3 events were reported for 35 patients (22%); only the event of diarrhoea occurred in > 5% of patients (8 patients, 5%).

Treatment-related Grade 4 events were reported for 7 patients (5%) overall, including 7 patients (5%) with sitravatinib-related Grade 4 events and 4 patients (3%) with nivolumab-related Grade 4 events. Grade 4 events related to sitravatinib included lipase increased, lymphocyte count decreased, acute kidney injury, hyperuricemia, pneumonitis, bacillus bacteraemia, duodenal ulcer, gastric ulcer perforation, hypertensive crisis, and haemorrhagic shock (in 1 patient each). Grade 4 events related to nivolumab included lipase increased, lymphocyte count decreased, pneumonitis, duodenal ulcer, and haemorrhagic shock (in 1 patient each). The Grade 4 events of haemorrhagic shock, duodenal ulcer, and bacillus bacteraemia occurred in the same patient.

Table 3: Summary of Treatment-Related, Treatment-Emergent Adverse Events (≥ 10% of Patients) by Preferred Term for Study MRTX-500

Adverse event Preferred Term, n (%)	Patients (N = 156)		
	Sitravatinib related	Nivolumab related	Any treatment related
Any treatment-related TEAE	145 (92.9)	115 (73.7)	146 (93.6)
Diarrhoea	82 (52.6)	38 (24.4)	85 (54.5)
Fatigue	66 (42.3)	45 (28.8)	72 (46.2)
Nausea	62 (39.7)	23 (14.7)	62 (39.7)
Decreased appetite	54 (34.6)	20 (12.8)	54 (34.6)
Weight decreased	44 (28.2)	15 (9.6)	44 (28.2)
Hypertension	46 (29.5)	2 (1.3)	46 (29.5)
Vomiting	41 (26.3)	18 (11.5)	41 (26.3)

Adverse event Preferred Term, n (%)	Patients (N = 156)		
	Sitravatinib related	Nivolumab related	Any treatment related
Hypothyroidism	15 (9.6)	36 (23.1)	40 (25.6)
Dysphonia	31 (19.9)	3 (1.9)	31 (19.9)
Palmar-plantar erythrodysaesthesia syndrome	27 (17.3)	1 (0.6)	27 (17.3)
Aspartate aminotransferase increased	25 (16.0)	17 (10.9)	26 (16.7)
Stomatitis	23 (14.7)	5 (3.2)	24 (15.4)
Alanine aminotransferase increased	23 (14.7)	17 (10.9)	23 (14.7)
Dry mouth	16 (10.3)	5 (3.2)	17 (10.9)
Dysgeusia	17 (10.9)	3 (1.9)	17 (10.9)
Dehydration	15 (9.6)	6 (3.8)	16 (10.3)
Proteinuria	15 (9.6)	4 (2.6)	16 (10.3)

Abbreviation: TEAE, treatment emergent adverse event.
Note: The order of adverse events is descending by incidence of "any treatment related" adverse events.

Serious Adverse Events: Among the 156 patients receiving study treatment, 79 patients (51%) experienced ≥ 1 SAE, regardless of causality. Treatment-related SAEs were reported in 42 patients (27%) overall, including sitravatinib-related SAEs in 34 patients (22%) and nivolumab-related SAEs in 19 patients (12%). Sitravatinib-related SAEs occurring in > 2 patients included diarrhoea (7 patients [5%]), pulmonary embolism (4 patients [3%]), and deep vein thrombosis (2 patients [1%]). Nivolumab-related SAEs occurring in ≥ 2 patients included diarrhoea and pneumonitis (3 patients [2%] each), as well as colitis, pancreatitis, and hypoxia (in 2 patients [1%] each). Treatment-related Grade 5 AEs were reported for 1 patient (1%) overall and included cardiac arrest (related to sitravatinib).

Treatment Discontinuation and Deaths: On the sitravatinib treatment arms, all patients have discontinued treatment with sitravatinib and nivolumab, except for 3 patients who enrolled in the continuation protocol, Study 516-014. Among these sitravatinib treatment patients, most patients had discontinued treatment due to objective disease progression (49%) or an AE (24%). On the sitravatinib treatment arms, a total of 141 patients have died, with the primary cause of death being the primary disease under study (120 of 141 patients [85%]). One death was attributed to study treatment toxicity (Grade 5 event of cardiac arrest related to sitravatinib).

BGB-900-103: Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors

Study BGB-900-103 is an open-label, multicenter, Phase 1b study sponsored by BeiGene, Ltd (BeiGene). The study is designed to evaluate sitravatinib in combination with tislelizumab in patients with advanced or metastatic malignancies, including squamous and nonsquamous NSCLC, renal cell cancer (RCC), or epithelial ovarian cancer. Patients receive sitravatinib 120 mg orally once a day in combination with tislelizumab 200 mg intravenously once every

3 weeks. Refer to the Sitravatinib Investigator's Brochure for an overview of the study design, study status, and study population.

As of 26 June 2022, all 216 patients who received study treatment experienced at least 1 AE regardless of causality. A total of 211 patients (98%) experienced treatment-related AEs overall, including 204 patients (94%) experiencing sitravatinib-related AEs and 165 patients (76%) experiencing tislelizumab-related AEs. Treatment-related AEs reported in ≥ 10% of patients overall are presented in Table 4.

Treatment-related Grade 3 events were reported in 96 patients (44%), and those reported in ≥ 5 patients were hypertension (35 patients [16%]), alanine aminotransferase (ALT) increased (11 patients [5%]), diarrhoea (8 patients [4%]), and palmar-plantar erythrodysaesthesia syndrome (7 patients [3%]), and fatigue, stomatitis, malaise, and hypokalaemia (in 5 patients [2%] each).

Treatment-related Grade 4 events were reported for 7 patients (3%), and treatment-related Grade 5 AEs were reported for 5 patients (death [2 patients, 1%]), and cardiac failure (respiratory failure), ischaemic stroke, and multiple organ dysfunction syndrome (1 patient [1%] each).

Table 4: Summary of Treatment-Related, Treatment-Emergent Adverse Events (≥ 10% of Patients) by Preferred Term for Study BGB-900-103

Adverse event Preferred Term, n (%)	Patients (N = 216)		
	Sitravatinib related	Tislelizumab related	Any treatment related
Any treatment-related AE	204 (94.4)	165 (76.4)	211 (97.7)
Diarrhoea	96 (44.4)	36 (16.7)	101 (46.8)
Alanine aminotransferase increased	84 (38.9)	65 (30.1)	96 (44.4)
Aspartate aminotransferase increased	83 (38.4)	65 (30.1)	92 (42.6)
Hypertension	76 (35.2)	7 (3.2)	77 (35.6)
Hypothyroidism	14 (6.5)	64 (29.6)	66 (30.6)
Palmar-plantar erythrodysaesthesia syndrome	62 (28.7)	4 (1.9)	62 (28.7)
Decreased appetite	56 (25.9)	14 (6.5)	57 (26.4)
Nausea	52 (24.1)	15 (6.9)	54 (25.0)
Vomiting	40 (18.5)	5 (2.3)	41 (19.0)
Weight decreased	41 (19.0)	9 (4.2)	41 (19.0)
Proteinuria	40 (18.5)	7 (3.2)	40 (18.5)
Blood creatine phosphokinase increased	23 (10.6)	30 (13.9)	39 (18.1)
Fatigue	32 (14.8)	12 (5.6)	35 (16.2)
Rash	25 (11.6)	21 (9.7)	35 (16.2)
Dysphonia	27 (12.5)	4 (1.9)	29 (13.4)

Adverse event Preferred Term, n (%)	Patients (N = 216)		
	Sitravatinib related	Tislelizumab related	Any treatment related
Blood creatine phosphokinase MB increased	23 (10.6)	14 (6.5)	26 (12.0)
Blood lactate dehydrogenase increased	21 (9.7)	19 (8.8)	26 (12.0)
Stomatitis	23 (10.6)	1 (0.5)	24 (11.1)
Blood bilirubin increased	23 (10.6)	10 (4.6)	23 (10.6)
Blood thyroid stimulating hormone increased	4 (1.9)	23 (10.6)	23 (10.6)
Platelet count decreased	19 (8.8)	17 (7.9)	22 (10.2)

Abbreviation: AE, adverse event.
Note: The order of adverse events is descending by incidence of "any treatment related" adverse events.

Serious Adverse Events: Among the 216 patients with available safety data, 119 patients (55%) experienced ≥ 1 SAE, regardless of causality. Treatment-related SAEs were reported in 70 patients (32%), and included diarrhoea in 8 patients (4%), pneumonia in 5 patients (2%) hepatic function abnormal in 4 patients (2%), and hypertension and immune-mediated lung disease in 3 patients each (1%). All other treatment-related SAEs occurred in ≤ 2 patients overall.

Treatment Discontinuation and Deaths: Of the 216 patients receiving study treatment, 201 patients (93%) have discontinued sitravatinib and 199 patients (92%) have discontinued tislelizumab treatment. The most common reasons for discontinuation from sitravatinib were progressive disease (125 patients [58%]), an AE (49 patients [23%]), and withdrawal by patient (18 patients [8%]). The most common reasons for discontinuation from tislelizumab were progressive disease (138 patients [64%]), an AE (32 patients [15%]), and withdrawal by patient (21 patients [10%]). A total of 143 deaths have been reported, and the primary cause of death was progressive disease (118 of 143 patients [83%]).

BGB-900-104: Sitravatinib Alone and in Combination With Tislelizumab in Patients With Hepatocellular Cancer or Gastric/Gastroesophageal Junction Cancer

Study BGB-900-104 is an open-label, multicenter, Phase 1/2 study sponsored by BeiGene. The study is designed to evaluate single-agent sitravatinib and sitravatinib in combination with tislelizumab in patients with advanced or metastatic hepatocellular cancer (HCC) or gastric/gastroesophageal junction (G/GEJ) cancer. The primary objective is to evaluate the safety of sitravatinib as monotherapy and in combination with tislelizumab and to determine the RP2D of sitravatinib as monotherapy and when administered in combination with tislelizumab 200 mg intravenously once every 3 weeks in the Phase 1 dose-escalation phase starting with a dose of 80 mg once a day. Secondary objectives include the assessment of the preliminary antitumor activity of sitravatinib administered either as a single agent or in combination with tislelizumab and PK. Refer to the Sitravatinib Investigator's Brochure for an overview of the study design, study status, and study population.

As of 26 June 2022, 108 of the 111 treated patients (97%) experienced ≥ 1 AE, regardless of causality. Sitravatinib-related AEs were reported in all patients receiving sitravatinib

monotherapy and in 75 patients (89%) receiving sitravatinib in combination with tislelizumab. Tislelizumab-related AEs were reported in 69 patients (82%) receiving sitravatinib in combination with tislelizumab. Treatment-related AEs reported in ≥ 25% of either treatment group are presented in Table 5.

Treatment-related Grade 3 events were reported in 14 patients (52%) in the sitravatinib monotherapy group and in 31 patients (37%) within the combination group.

Treatment-related Grade 3 events by Preferred Term reported in > 2 patients in the sitravatinib monotherapy group were hypertension (4 patients [15%]), palmar-plantar erythrodysaesthesia syndrome (3 patients [11%]), and diarrhoea, ALT increased, and aspartate aminotransferase (AST) increased (2 patients each [7%]). Hypertension, palmar-plantar erythrodysaesthesia syndrome, and platelet count decreased (5 patients [6%] each); gamma-glutamyltransferase increased and proteinuria (in 4 patients [5%] each); and diarrhoea, blood creatine phosphokinase increased, abdominal pain upper, anaemia, and rash (2 patients [2%] each) were reported in the combination group.

Treatment-related Grade 4 events were reported for 2 patients (hypokalaemia and haemoptysis in 1 patient [1%] each), and treatment-related Grade 5 events were reported for 5 patients (death [3 patients, 4%], and hepatic encephalopathy and respiratory failure [1 patient each, 1%]); all occurred in the combination group.

Table 5: Summary of Treatment-Related, Treatment-Emergent Adverse Events (≥ 25% of Patients) by Preferred Term for Study BGB-900-104

Adverse event Preferred Term, n (%)	Patients (N)	
	Sitravatinib monotherapy (N = 27)	Sitravatinib + tislelizumab (N = 84)
Any treatment-related AE [a]	27 (100.0)	75 (89.3)
Proteinuria[b]	14 (51.9)	38 (45.2)
Aspartate aminotransferase increased	13 (48.1)	35 (41.7)
Alanine aminotransferase increased	13 (48.1)	34 (40.5)
Palmar-plantar erythrodysaesthesia syndrome	19 (70.4)	30 (35.7)
Hypertension	7 (25.9)	28 (33.3)
Diarrhoea	16 (59.3)	25 (29.8)
Platelet count decreased	12 (44.4)	21 (25.0)

Abbreviation: AE = adverse event.
[a] Includes all treatment-related adverse events (sitravatinib and tislelizumab combined).
[b] Two Preferred Terms, proteinuria and albuminuria, were combined into one term as "Proteinuria."

Serious Adverse Events: SAEs were reported for 41 patients (37%) overall, regardless of causality. Sitravatinib-related SAEs were reported for 23 patients (21%), and tislelizumab-related SAEs were reported for 14 patients (17%). Sitravatinib-related SAEs in ≥ 2 patients included death (3 patients [4%]), hemoptysis and hepatic encephalopathy (2 patients each [2%]) in the combination group. Tislelizumab-related SAEs in ≥ 2 patients included death in 2 patients (2%).

Treatment Discontinuation and Deaths: Among the 111 patients treated with sitravatinib, 105 patients (95%) have discontinued sitravatinib treatment, in most cases due to progressive disease (64 patients [58%]), withdrawal by patient (21 patients [19%]), or an AE (10 patients [9%]). Among the 84 patients treated with tislelizumab, 80 patients (95%) have discontinued tislelizumab treatment, in most cases due to progressive disease (48 patients [57%]), withdrawal by patient (16 patients [19%]), or an AE (7 patients [8%]). A total of 58 deaths were reported for this study; 44 of 58 deaths (76%) were due to progressive disease.

1.3.4.2. Efficacy

1.3.4.2.1. Efficacy Assessment of Sitravatinib Monotherapy

Efficacy results are available from the Phase 1/1b Study 516-001 (Werner et al 2017). In this Phase 1b dose expansion study, sitravatinib was evaluated in different patient populations:

- Tumors harboring genetic alterations resulting in dysregulation of sitravatinib's RTK targets:
  - NSCLC with activating genetic alteration in *RET*, *KDR*, *PDGFRA*, *KIT*, *NTRK*, *DDR2*, *MET*, *AXL,* or with loss of function mutation with *CBL*
  - Any solid tumor malignancy with genetic alteration of sitravatinib RTK targets or *CBL*
- Metastatic renal cell carcinoma (mRCC) refractory to VEGF pathway inhibitors (simultaneously targeting MET and VEGFR)
- Castration resistant prostate cancer (CRPC) with bone metastases

As of 18 April 2018, 29 patients were enrolled in the Phase 1b mRCC study, after failure of prior anti-angiogenic therapy. Sitravatinib monotherapy showed 20% confirmed ORR among 20 evaluable patients. Prolonged stable disease for at least 24 weeks was observed in 6 additional patients.

As of 04 September 2018, 16 patients were enrolled in the Phase 1b CBL loss of function cohort. Among 8 clinical activity evaluable patients (received ≥ 1 cycle of sitravatinib for more than 80% of assigned total dose and ≥ 1 on-study disease assessment), sitravatinib monotherapy demonstrated antitumor activity in 2 patients (1 patient with NSCLC and 1 patient with melanoma).

1.3.4.2.2. Efficacy Assessment of Sitravatinib in Combination With PD-1 Blocking Agent

MRTX-500: Sitravatinib in Combination With Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer

Early signs of clinical activity from the Phase 2 MRTX-500 study have been observed in patients with nonsquamous NSCLC, whose disease has progressed following prior anti-PD-(L)1 therapy. As of the cutoff date of 01 June 2021, the median OS was 14.9 months (95% CI: 9.3 to 21.1 months) in patients with nonsquamous NSCLC who had clinical benefit from prior CPI therapy and received the sitravatinib plus nivolumab as second- or third-line treatment in the study (N = 68) (Leal et al 2021). Among the 68 patients, the ORR was 18% (12 responders of

68 patients) including 2 complete responses (CRs) (3%) and 10 partial responses (PRs) (15%), with a median duration of response (DOR) of 12.8 months; the median progression-free survival (PFS) was 5.7 months (95% CI: 4.9 to 7.6 months) (Leal et al 2021). The combination of sitravatinib with nivolumab is a rational approach to restore or enhance the clinical activity of treatment with a CPI in patients with immunotherapy resistant NSCLC.

BGB-900-103: Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors

Study BGB-900-103 is an open-label, multicenter, nonrandomized, multicohort, Phase 1b study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of sitravatinib in combination with tislelizumab in patients with advanced solid tumors (NCT03666143).

Cohort A and Cohort F of the study enrolled patients with nonsquamous and squamous metastatic NSCLC, respectively, with the disease refractory/resistant to anti-PD-(L)1 therapy. From December 2018 to June 2020, a total of 47 patients with NSCLC, nonsquamous (n = 24) and squamous (n = 23), were enrolled. As of the data cutoff date of 13 October 2020, the confirmed ORR was 13.6% and the disease control rate (DCR) was 86.4%. The median DOR was 6.90 months (95% CI: 3.06 months to not evaluable [NE]). The median PFS was 5.2 months (95% CI: 4.1 to 5.9 months). As of the data cutoff date, the median OS was 10.1 months (95% CI: 6.1 to 18.1 months), with a median follow-up duration of 12.4 months. The OS data were not mature (Gao et al 2021).

As of 29 March 2021, 63 patients with platinum-resistant ovarian cancer were enrolled to Cohort E. Fifty-nine patients were included in the Efficacy Evaluable Population. The confirmed ORR was 28.8% and the DCR was 79.7%. The median DOR was 5.6 months (95% CI: 2.8 to 22.3 months). The median PFS was 4.1 months (95% CI: 3.5 to 5.1 months). The median OS was 11.8 months (95% CI: 6.7 to 17.2 months), with a median follow-up duration of 8.9 months. However, the OS data were immature. When tumor samples were deemed as PD-L1 positive at a cut-off of ≥ 1% on tumor cells (TC) or ≥ 10% on immune cells (IC), no clear associations were observed between PD-L1 expression and ORR, PFS, or OS in the Efficacy Evaluable Population (Goh et al 2021).

Cohort G of the study enrolled 25 patients with anti-PD-(L)1 antibody refractory/resistant unresectable or metastatic melanoma and all enrolled patients were included in the Efficacy Evaluable Population. As of 29 March 2021, the confirmed ORR was 36.0% and the DCR was 88.0%. The median DOR was still NE (95% CI: 2.8% to 22.3%). The median PFS was 6.7 months (95% CI: 4.1 months to NE). With a median follow-up duration of 10.1 months, the median OS was not yet mature (Cui et al 2021).

In total, 220 patients with NSCLC were screened and 122 patients were enrolled in the study between 03 January 2019 and 10 February 2021. Of these 122 patients (the total NSCLC population), 115 patients were included in the five cohorts, with each cohort including 22 to 24 patients (Cohort A: n = 24; Cohort B: n = 22; Cohort F: n = 23; Cohort H: n = 22; Cohort I: n = 24) (Zhao et al 2023).

Median follow-up was 10.9 months (range: 0.4 to 30.6 months). Treatment-related adverse events (TRAEs) occurred in 98.4% of the patients, with ≥ Grade 3 TRAEs occurring in 51.6% of

patients. TRAEs led to discontinuation of either drug in 23.0% of the patients. The ORRs for the 5 cohorts were the following:

- Cohort A: 2 of 23 patients (8.7% [95% CI: 1.1% to 28.0%])
- Cohort B: 5 of 21 patients (23.8% [95% CI: 8.2% to 47.2%])
- Cohort F: 4 of 22 patients (18.2% [95% CI: 5.2% to 40.3%])
- Cohort H: 12 of 21 patients (57.1% [95% CI: 34.0% to 78.2%])
- Cohort I: 7 of 23 patients (30.4% [95% CI: 13.2% to 52.9%])

Median DOR was not reached in Cohort A and ranged from 6.9 to 17.9 months across other cohorts. Disease control was achieved in 78.3% to 90.9% of the patients. Median PFS ranged from 4.2 months (Cohort A) to 11.1 months (Cohort H) (Zhao et al 2023).

BGB-900-104: Sitravatinib Alone and in Combination With Tislelizumab in Patients With Hepatocellular Cancer or Gastric/Gastroesophageal Junction Cancer

Study BGB-900-104 is an open-label, multicenter, Phase 1/2 study to evaluate the safety and preliminary antitumor activity of sitravatinib in combination with tislelizumab in patients with advanced or metastatic HCC or G/GEJ cancer (NCT03941873). As of 12 July 2021, 43 patients with HCC and 24 patients with G/GEJ cancer were enrolled. In patients with HCC, the confirmed ORR was 10.0% and the DCR was 85%. The median DOR was 5.4 months (95% CI: 4.1 to 5.7 months). The median PFS was 4.8 months (95% CI: 3.2 to 6.9 months). With a median study follow-up of 8.6 months, the median OS was NE (95% CI: 8.6 months to NE). In patients with G/GEJ cancer, the confirmed ORR was 12.5% and the DCR was 66.7%. The median DOR was NE (95% CI: 3.5 months to NE). The median PFS was 3.4 months (95% CI: 2.0 months to NE). With a median study follow-up of 5.2 months, the median OS was NE (95% CI: 4.7 months to NE) (Zhang et al 2022; Chen et al 2022).

1.4. Background Information on Tislelizumab

Tislelizumab is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against programmed cell death protein-1 (PD-1) under clinical development for the treatment of several human malignancies. Tislelizumab is being investigated either as monotherapy or in combination with other therapies.

PD-1 is mainly expressed in activated T cells, including cluster of differentiation (CD)8^+ cytotoxic T lymphocytes and $CD4^+$ T-helper lymphocytes (McDermott and Atkins 2013). The PD-1 signaling cascade negatively regulates the T cell and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly upregulated on tumor-infiltrating lymphocytes, while the expression of PD-1 ligand (PD-L1) is significantly increased on tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as interferon-gamma (IFN-γ) and interferon-alpha in the TME (Riley 2009), which is observed in many types of human solid tumors. This body of evidence provides the basis for cancer immunotherapeutic intervention via the approach of antagonizing PD-1.

Refer to the most recent edition of the Tislelizumab Investigator's Brochure for additional background on tislelizumab.

1.4.1. Prior Clinical Experience With Tislelizumab

As of 20 July 2022, 18 studies with tislelizumab are ongoing, and 7 studies have been completed (Tislelizumab Investigator's Brochure). Of the 18 ongoing studies, 10 studies have data available: 5 monotherapy studies and 5 chemotherapy combination therapy studies.

For more detailed information on the safety and efficacy of tislelizumab when given as monotherapy or in combination with chemotherapy, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.4.1.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of monotherapy studies was conducted to provide a comprehensive safety assessment separate from combination therapy. Data from patients with solid tumors were analyzed separately from patients with hematologic malignancies.

As of 20 July 2022, data are available from 1992 patients treated in 7 pooled solid tumor monotherapy studies (Tislelizumab Investigator's Brochure). The median treatment exposure duration was 4.07 months (range: 0.10 to 55.46 months), and the median study follow-up duration was 11.65 months (range: 0.07 to 58.91 months). The median age of the patients was 60 years, and 72.1% were male.

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 1925 patients (96.6%) experienced ≥ 1 treatment-emergent adverse event (TEAE). The most commonly occurring (≥ 15%) TEAEs by Preferred Term were anaemia (25.3%) AST increased (18.4%), ALT increased (17.1%), decreased appetite (16.7%), and cough (15.3%). Of the 1992 patients, 712 patients (35.7%) experienced ≥ 1 treatment-emergent SAE. The most commonly occurring SAEs were pneumonia (4.8%), pneumonitis (1.4%), dysphagia (1.2%), pyrexia (1.1%), and pleural effusion (1.0%).

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 55 patients (2.8%) experienced ≥ 1 infusion-related reactions of any grade.

Most monotherapy studies pooled have undergone an adjudication processing for identifying imAE (see Tislelizumab Investigator's Brochure). Of the 1912 patients in the adjudicated solid tumor group of pooled monotherapy studies, 312 patients (16.3%) experienced ≥ 1 immune-mediated adverse event (imAE) of any grade. The most commonly occurring imAEs of any grade were hypothyroidism (6.3%), pneumonitis (2.1%), hyperthyroidism (0.9%), rash (0.9%), ALT increased (0.7%), and immune-mediated lung disease (0.7%). The categories of imAEs experienced by ≥ 1% of patients were immune-mediated hypothyroidism (6.6%), immune-mediated pneumonitis (3.8%), immune-mediated hepatitis (1.9%), immune-mediated skin adverse reaction (1.8%), and immune-mediated colitis (1.0%).

For more detailed information on the safety of tislelizumab when given as monotherapy or in combination with chemotherapy, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.4.1.2. Efficacy Assessment of Tislelizumab

Efficacy data from Studies BGB-A317-102, BGB-A317-205, and BGB-A317-302 that enrolled patients with ESCC are summarized below.

1.4.1.2.1. BGB-A317-102

Study BGB-A317-102 is a Phase 1/2 study investigating the safety, tolerability, PK, and preliminary antitumor activities of tislelizumab 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. The efficacy endpoints include ORR, DCR, and clinical benefit rate as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1.

There were 300 patients treated in the study and all treated patients were included in the Safety Analysis Set (Shen et al 2020). Of the 26 patients in the ESCC cohort, no patients (0%) had a CR. A total of 2 patients (8.0%) had a confirmed PR. Additionally, 7 patients (27%) had a best overall response (BOR) of stable disease. A total of 13 patients (50%) had a BOR of progressive disease in this cohort, and the assessment for 4 patients (15%) was unknown.

1.4.1.2.2. BGB-A317-205

Study BGB-A317-205 is a Phase 2, multicohort study to investigate the safety, PK, and preliminary antitumor activity of tislelizumab in combination with chemotherapy as first-line treatment in adults with inoperable, locally advanced or metastatic esophageal, gastric, or gastroesophageal junction carcinoma. The efficacy endpoints include ORR and DCR as assessed by the investigator per RECIST v1.1.

There were 30 patients treated in the study and all treated patients were included in the Safety Analysis Set (Xu et al 2020). Of the 15 patients in the ESCC cohort, no patients (0.0%) had a CR. A total of 7 patients (46.7%) had a confirmed PR. Additionally, 5 patients (33.3%) had a BOR of stable disease. Three patients (20.0%) did not have a postbaseline tumor assessment.

1.4.1.2.3. BGB-A317-302

Study BGB-A317-302 is a Phase 3, randomized, open-label, multicohort study to compare the efficacy and safety of tislelizumab versus investigator-chosen chemotherapy (ICC) (paclitaxel, docetaxel, or irinotecan) in patients with unresectable recurrent locally advanced or metastatic ESCC after prior systemic therapy. The efficacy endpoints include OS, PFS, ORR, and DOR as assessed by the investigator per RECIST v1.1.

A total of 512 patients were randomized in a 1:1 ratio to receive tislelizumab or ICC (256 patients each), and all of those patients were included in the Intent-to-Treat (ITT) Analysis Set (Shen et al 2021). As of the data cutoff date of 01 December 2020, the median duration of follow-up was 8.49 months in the Tislelizumab Arm and 5.80 months in the ICC Arm. Tislelizumab monotherapy demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of OS versus ICC with a stratified hazard ratio (HR) of 0.70. The median OS was 8.6 months (95% CI: 7.5 to 10.4 months) in the Tislelizumab Arm and 6.3 months (95% CI: 5.3 to 7.0 months) in the ICC Arm. A statistically significant and clinically meaningful OS benefit was also observed in patients with PD-L1 score ≥ 10% with a stratified HR of 0.54; the median OS improvement was 3.5 months (10.3 months in the Tislelizumab Arm versus 6.8 months in the ICC Arm). Treatment with tislelizumab resulted in a clinically relevant increase in the ORR (20.3% versus 9.8%) and more durable response (median DOR: 7.1 months versus 4.0 months) compared with ICC in the ITT Analysis Set.

For more detailed information on the efficacy of tislelizumab when given as monotherapy in patients with ESCC, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.5. Study Rationales

1.5.1. Rationale for Sitravatinib in Combination of Tislelizumab in the Treatment of Advanced Esophageal Squamous Cell Carcinoma After Checkpoint Inhibitor Failure

1.5.1.1. Rationale for Sitravatinib Monotherapy or in Combination With Tislelizumab in the Treatment of Advanced Esophageal Squamous Cell Carcinoma

The activity of tislelizumab in ESCC has been demonstrated in Studies BGB-A317-102 and BGB-A317-302 as monotherapy and in BGB-A317-205 in combination with chemotherapy, for patients treated in the second-line and first-line setting, respectively (Section 1.4.1.2).

Although anti-PD-1 therapy have made unprecedented success in prolonging ESCC patients' survival, many patients with advanced ESCC are still unresponsive or refractory to these therapies. Combination therapy with other novel agents represents one inevitable trend of cancer immunotherapy. These combination therapies are justified on the ground that the combination of 2 different therapies integrates different immunological and biological mechanisms for enhancing the antitumor activity. Moreover, clinical studies suggest that targeted therapy plays a role in enhancing certain links in cancer-immunity cycle (eg, tumor antigenicity and activation/transport/infiltration of T cells), which exerts synergistic and enhancing effects on immunotherapy. For example, sunitinib, targeting the mitogen-activated protein kinase (MAPK) and vascular endothelial growth factor (VEGF), not only has a direct impact on tumor cell growth and tumor angiogenesis, but also on tumor antigenicity and intratumoral T-cell infiltration. Antitumor activity of RTK inhibitor and PD-1 antibody combination works beyond direct cytostatic effects on tumor cells, which provides a scientific base for evaluating the clinical benefits of the combination treatment.

In addition to modifying tumor TME which enhances effect of immunotherapy, RTK inhibitor itself also has potential antineoplastic activity. The activity of sitravatinib monotherapy has been examined in Study 516-001, a Phase 1/1b study (NCT02219711) enrolling patients with different solid tumor types, and Study BGB-900-104, a BeiGene-sponsored Phase 1/2 study enrolling patients with HCC and G/GEJ cancer.

Multiple Phase 1 or 2 clinical studies, either initiated by the sponsor or investigator, are ongoing to investigate the antitumor activity of RTK inhibitor monotherapy or RTK inhibitor and PD-1 antibody combination in patients with ESCC. Available data have shown promising antitumor activity (Table 6), which indirectly support sitravatinib monotherapy or in combination with tislelizumab that may provide clinical benefit in patients with ESCC:

- Study CAP-02 is single-arm, Phase 2 study in China to investigate the efficacy and safety of camrelizumab in combination with apatinib (a selective inhibitor of VEGFR2) as second-line treatment after prior chemotherapy failure for patients with advanced ESCC (Meng et al 2022). As of 20 June 2021, 52 patients with ESCC after failure of first-line chemotherapy were enrolled. The confirmed ORR was 34.6%

(18 of 52 patients) (95% CI: 22.0% to 49.1%) and the DCR was 78.8% (95% CI: 65.3% to 88.9%). Among the 52 enrolled patients, 4 patients (8.0%) had a BOR of complete response (CR). The median OS and median PFS was 15.8 months (95% CI: 8.4 to 16.2 months) and 6.8 months (95% CI: 3.8 to 10.4 months), respectively. No clear association between PD-L1 expression level and clinical response was observed.

- Study ALOT-EC3 is a prospective and observational study in the real-world setting to explore the efficacy of various kinds of anti-PD-1 antibody in combination with anlotinib in second- and later-lines treatment of ESCC. Anlotinib is a RTK inhibitor that targets VEGFR 1, 2, and 3; FGFR 1 to 4; PDGFR α and β; RET; and c-KIT. As of 01 September 2021, in a total of 40 patients, 27 patients who received camrelizumab, 10 patients who received sintilimab, and 3 patients who received other brands of anti-PD-1 antibody were included in the analysis. The DCR was 87.5% (35 of 40 patients) and 12 patients (30.8%) had a BOR of CR or PR. The data of OS and PFS were not mature as of 01 September 2021 due to the short follow-up period (Hong et al 2022).
- Study NCT03603756 is an investigator-initiated Phase 2 study to investigate camrelizumab and apatinib in combination with chemotherapy (liposomal paclitaxel and nedaplatin) in patients with ESCC as first-line treatment. The preliminary data were encouraging: 80% of patients had a confirmed response and 96.7% of patients had their disease under control. The median OS and PFS were 19.4 months and 6.9 months, respectively (Zhang et al 2020).
- Study ALTER-1102 is a randomized, placebo-controlled, double-blind Phase 2 study in China in patients with advanced ESCC whose disease was previously treated with chemotherapy. A total of 165 patients were enrolled and randomized to receive anlotinib monotherapy or placebo (Huang et al 2021). During a median follow-up of 11.8 months, the ORR was almost doubled numerically in the anlotinib group compared with the placebo group (7.3% versus 3.6%; $p = 0.498$). The DCR was significantly higher in the anlotinib group than that in the placebo group (64% versus 18%; $p < 0.001$), with a higher proportion of patients achieving stable disease in the anlotinib group (57% versus 15%). The PFS was almost doubled in the anlotinib group (3.02 months versus 1.41 months, HR = 0.46 [0.32 to 0.66]; $p < 0.001$). However, prolonged OS was not observed with anlotinib monotherapy (6.11 months versus 7.20 months, HR = 1.18 [0.79 to 1.75]; $p = 0.426$).
- Study ESO-Shanghai 11 is an investigator-initiated, single-arm, Phase 2 study in China to investigate the efficacy of apatinib as a second- and later-line treatment in patients with ESCC (Chu et al 2021). The ORR was 7.5% and the DCR was 65%. Median PFS was 3.8 months and OS was 5.8 months.

Based on the positive readouts of Studies CAP-02 and NCT03603756, camrelizumab in combination with apatinib as well as camrelizumab and apatinib in combination with chemotherapy (liposomal paclitaxel and nedaplatin) have been recommended by CSCO as the Level III recommendation for patients with ESCC as second-line and first-line treatment options, respectively (CSCO 2021). In addition, anlotinib monotherapy and apatinib monotherapy have been recommended by CSCO as the Level II and Level III recommendation, respectively, for

patients with ESCC as a second-line treatment option, based on the findings from Studies ALTER-1102 and ESO-Shanghai 11 (CSCO 2021).

Table 6: Summary of Studies Evaluating Inhibitor of Receptor Tyrosine Kinase With or Without PD-1 for Esophageal Squamous Cell Carcinoma

Study	Study phase	Region	Treatment setting	Treatment regimen (n)	ORR (%)	DCR (%)	mOS (mo) HR (95% CI)	mPFS (mo) HR (95% CI)	DOR (mo)
ALTER-1102 (Huang et al 2021)	Phase 2	China	2L, after chemotherapy failure	Anlotinib (110) versus placebo (55)	7.3% versus 3.6%	64% versus 18%	6.11 versus 7.20 HR = 1.18 (0.79 to 1.75)	3.02 versus 1.41 HR = 0.46 (0.32 to 0.66)	5.8 in the Anlotinib Arm
ESO-Shanghai 11 (Chu et al 2021)	Phase 2, IIT	China	2L/2L+, after chemotherapy failure	Apatinib (40)	7.5%	65.0%	5.8	3.8	Not reported
CAP-02 (Meng et al 2022)	Phase 2, IIT	China	2L, after chemotherapy failure	Camrelizumab + apatinib (52)	34.6%	78.8%	15.8 (8.4 to 16.2)	6.8	Not reached (3.1 to not reached)
ALOT-EC3 (Hong et al 2022)	Prospective, observational	China	2L/2L+, after chemotherapy failure	Anlotinib + PD-1 (40) (Camre = 27, Sinti = 10, Other = 3)	30.0%	87.5%	Not reported	Not reported	Not reported
NCT03603756 (Zhang et al 2020)	Phase 2, IIT	China	1L	Camrelizumab + liposomal paclitaxel + nedaplatin + apatinib (30)	80%	96.7%	19.4	6.9	9.8

Abbreviations: Camre, camrelizumab; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; IIT, investigator-initiated trial; L, line; m, median; mo, month; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival; Sinti, sintilimab.

1.5.1.2. Rationale for Sitravatinib Monotherapy or in Combination With Tislelizumab in the Treatment of Tumors After Checkpoint Inhibitor Failure

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 treatment with 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 the therapeutic challenges that need to be overcome (Syn et al 2017). One of the mechanisms is an immunosuppressive TME. It includes a collection of various cell types that have switched sides and protect the cancer cells from immune system attacks. Various RTKs have been implicated in creating and maintaining an immunosuppressive TME.

Combining an immunotherapeutic PD-1 CPI with an RTK inhibitor that has both immunomodulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone. By targeting the specific RTK receptors, an immunosuppressive TME is converted to an immune-supportive TME, which makes the cancers more likely to respond to CPI treatment. The use of RTK blocking agents to treat cancer is well established based on robust clinical efficacy achieved with well-tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected targeted therapies 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.

As a potent spectrum-selective RTK inhibitor, sitravatinib inhibits several closely related RTKs, including members of the TAM family (TYRO3, AXL, and MER), as well as VEGFR2 and KIT. This inhibition weakens the cancer's defenses in the TME. 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 TME 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 IL-12, IL-6, and tumor necrosis factor. 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.

Treatment options after prior immunotherapy in patients with advanced solid tumors remain a significant unmet medical need. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to CPI therapy is a rational approach to improving outcomes in patients. Targeting RTKs has been shown to stimulate the immune system and cause synergistic effects that stimulate tumor shrinkage. Although there is no direct evidence supporting the activity of sitravatinib in combination with tislelizumab in ESCC after prior CPI failure, several studies have demonstrated encouraging efficacy results of this new combination therapy in patients with NSCLC:

- Phase 1b Study BGB-900-103 demonstrated promising anticancer activity for the combination treatment of sitravatinib with tislelizumab in patients with NSCLC. As of 13 October 2020, 24 patients with nonsquamous NSCLC and 23 patients with squamous NSCLC whose disease progressed on prior anti-PD-(L)1 therapy were enrolled. Among all the 47 patients, 6 patients (12.8%) had a confirmed ORR (95% CI: 5.17% to 27.35%), and 6 patients (13.6%) achieved a PR. The median DOR was 6.90 months (95% CI: 3.06 months to NE). The median OS and PFS were 10.09 months (95% CI: 6.05 to 18.14 months) and 5.19 months (95% CI: 4.07 to 5.85 months), respectively. A clear association between PD-L1 expression status and clinical response was not identified (Gao et al 2021).
- Phase 2 Study MRTX-500 demonstrated encouraging preliminary OS data with sitravatinib in combination with nivolumab in patients with NSCLC that progressed on or after CPI. As of June 2021, in the subset of patients with prior clinical benefit who received the combination in the second- or third-line treatment setting, the confirmed ORR was 18% which included 2 CRs (3%) and 10 PRs (15%). The median OS was 14.9 months (95% CI: 9.3 to 21.1 months) and the median DOR was 12.8 months. The 1- and 2-year OS rates were 56% and 32%, respectively (Leal et al 2021).

Two global Phase 3 studies, SAPPHIRE (NCT03906071) and BGB-A317-Sitravatinib-301, which evaluate sitravatinib in combination with nivolumab or tislelizumab in patients with NSCLC whose disease progressed on or after CPI therapy, are ongoing.

In summary, selective RTKs inhibit key molecular and cellular pathways strongly implicated in CPI resistance and therefore represent reasonable strategies to enhance or restore antitumor immunity when combined with anti-PD-(L)1 monoclonal antibodies. It has been established that the TME of ESCC is dominant with exhausted T and NK cells, regulatory T cells (Tregs), alternatively activated macrophages, tolerogenic dendritic cells, and MDSCs (Zheng et al 2020; Dinh et al 2021; Chen et al 2021), suggesting ESCC is a potential tumor type where combination therapy of immunotherapy and RTK inhibitors would have synergistic effect. Therefore, tislelizumab, which belongs to the same class of PD-1 blocking antibodies, may elicit comparable antitumor activity when combined with sitravatinib for patients with ESCC.

1.5.2. Rationale for Dose Selection

1.5.2.1. 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 that are associated with sitravatinib are similar to those observed with other small-molecule inhibitors of the VEGFR pathway.

Sitravatinib administered at 150 mg once a day was originally determined to be the MTD and RP2D in Study 516-001. Based on the long-term tolerability observed in patients who were enrolled in Study 516-001 and treated with 120 mg or 150 mg once a day, as well as the experience of patients who were enrolled in Study MRTX-500 and treated with 120 mg once a day in combination with nivolumab, 120 mg once a day was selected as the RP2D using the

sitravatinib free base capsule formulation. The 120-mg-once-a-day dose level is predicted to be adequate to achieve the plasma exposure required for inhibition of VEGF and TAM receptors necessary to attain antitumor efficacy with the combination therapy.

In Studies BGB-900-103 and BGB-900-104, the RP2D of sitravatinib in combination with tislelizumab was further evaluated in patients with advanced or metastatic malignancies, including squamous and nonsquamous NSCLC, platinum-resistant ovarian cancer, HCC, or G/GEJ cancer. As of 26 June 2021, a total of 327 patients were enrolled in the 2 studies, and the tolerability that was observed in these patients further supported the previously established RP2D of sitravatinib free base at 120 mg, either as monotherapy or in combination with tislelizumab, across tumor types. Based on the preliminary population PK analysis with the limited data of 77 patients, race and tumor type were not significant covariants on the PK profile of sitravatinib.

With the purpose of optimizing product characteristics and manufacturing efficiency, a 100 mg sitravatinib malate salt capsule formulation was developed and compared with 120 mg of the free base formulation. In Study 516-006, the inferential statistical analysis showed that the ratio and 90% CI of the geometric least squares means of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were within the bioequivalence range of 80% to 125%, demonstrating that the 120 mg sitravatinib free base and 100 mg malate capsule formulations produce exposures that are equivalent. In Study BGB-Sitravatinib-101, the relative bioavailability between the malate formulation manufactured by BeiGene and the free-base formulation was assessed in healthy volunteers. The results showed that the exposures (geometric means of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) after a single dose of 100-mg malate formulation were numerically lower than those observed with the 120-mg free-base formulation, with a difference of approximately 12%. This difference was not expected to be clinically meaningful as the PK exposures for the 120-mg free-base formulation were more varied and contained that of the 100-mg malate salt formulation.

Based on the available data described above, 100 mg once daily of sitravatinib malate salt capsule formulation is considered safe and is the recommended dose in patients with ESCC.

1.5.2.2. Rationale for Selection of Tislelizumab Dose

The dosage of 200 mg intravenously once every 3 weeks was selected based on safety, efficacy, and PK assessments in the first-in-human Study BGB-A317_Study_001. A wide range of dosages were investigated in this study, including 2 mg/kg or 5 mg/kg on schedules of once every 2 weeks or once every 3 weeks. For the once every 3 weeks schedule, a fixed dose of 200 mg was also investigated, and was ultimately selected for the following reasons:

- All dosages tested, including 200 mg once every 3 weeks, were tolerated. The MTD was not reached with dosages up to 10 mg/kg once every 2 weeks. The observed serum concentration after 200 mg dosing was within the range seen after 2 mg/kg and 5 mg/kg dosing.
- Preliminary clinical activity was observed at this dosage.
- Exposure-response relationships were flat for ORR and safety endpoints across a variety of tumor types (data from Studies BGB-A317_Study_001, BGB-A317-102, and BGB-A317-203). In addition, no clinically significant covariates were identified in population PK analysis.

- Compared with doses based on patient weight, a fixed dose simplifies dose administration and reduces the chance of medical errors.
- Compared with a once-every-2-weeks schedule, a once-every-3-weeks schedule allows for more convenient integration with common chemotherapeutic regimens and increases patient convenience.

In summary, the observed clinical benefits with a manageable safety profile in patients with advanced tumors supports tislelizumab 200 mg intravenously once every 3 weeks. The efficacy and safety of tislelizumab at the proposed dose have been subsequently studied in clinical studies, including patients with ESCC.

1.5.3. Rationale for Docetaxel and Irinotecan as the Comparators

There is no global consensus on standard of care for patients with ESCC who were previously treated with anti-PD-(L)1 antibody. Chemotherapy is typically administered, while the choice of agent differs by geography and is often tailored to the patient's needs. Generally, a single-agent regimen of docetaxel, paclitaxel, or irinotecan is preferable to combination chemotherapy for safety considerations (NCCN 2022).

Although these agents were widely used, there are no demonstrated clinically significant differences in response rates, PFS, or OS between them. In China, irinotecan is often chosen for second-line treatment of ESCC, while taxanes is widely used (approximately 70%) for first-line treatment in Chinese patients.

This study is designed to allow the choice of chemotherapy, based on the investigators' discretion, to represent the actual medical practice. Inclusion of both docetaxel and paclitaxel as ICC options are less clinically relevant because cross-resistance has been observed between the 2 agents. Therefore, docetaxel and irinotecan are selected as the comparators in the study. This design complies with international guidelines and provides flexibility to accommodate differences in treatment management between hospitals and physicians and the potential influence of patient characteristics on the treatment choice. In addition, the choice of comparator in the study is not expected to influence the survival outcome in the population, which is supported by studies showing similar results across the 2 agents chosen for the comparator arms (Shirakawa et al 2014; Mizota et al 2011; Song and Zhang 2014; Albertsson et al 2007; Burkart et al 2007) (Table 1).

1.5.4. Biomarker Strategy Rationale

Biomarker analyses will be performed to explore the association of biomarkers with patient prognosis, response, and potential resistance to sitravatinib in combination with tislelizumab. The planned biomarker analyses include but are not limited to PD-L1 expression status, tumor mutational burden (TMB)/DNA mutation/microsatellite instability (MSI), blood tumor mutational burden (bTMB)/circulating tumor DNA (ctDNA) monitoring/DNA mutation/MSI, gene expression profile (GEP), and tumor-infiltrated immune cells.

PD-L1 is expressed in tumor cells and tumor infiltrating immune cells, and its expression level was shown to correlate with clinical efficacy of tislelizumab treatment in Study RATIONALE-302, in which a larger magnitude median OS improvement was observed in patients with PD-L1 score ≥ 10% compared with investigator-chosen standard chemotherapy

(Shen et al 2021). In the present study, PD-L1 expression status will be assessed centrally by the Ventana PD-L1 (SP263) assay and its predictive role will be analyzed in patients treated with sitravatinib plus tislelizumab.

Highly mutated tumors can produce many neoantigens and these may increase T-cell reactivity. For this reason, high TMB may be associated with improved response to treatment with immune checkpoint blockade, including anti-PD-1 agents. Study KEYNOTE-158 demonstrated that, irrespective of tumor type, higher ORR with pembrolizumab treatment was observed in TMB-high patients (≥ 10 mutations per megabase) compared with that in TMB-low patients (29% versus 6%) (Marabelle et al 2020). MSI-H tumors are characterized by lymphocytic infiltration, somatic hypermutation, and increased neoantigen formation, rendering the tumor susceptible to immunotherapy as well (Dudley et al 2016). Therefore, TMB level, MSI status, along with any specific genetic alterations, merit further exploration for the association with clinical outcomes to sitravatinib in combination with tislelizumab. When assessed with large panels, good correlations between bTMB and TMB have been observed. In several clinical studies, bTMB has been explored as a potential predictive biomarker because the sample collection procedure is less invasive. Moreover, results from Studies POPLAR, OAK, and MYSTIC suggested that bTMB could predict clinical benefit with anti-PD-(L)1 therapy. Circulating tumor DNA (ctDNA) monitoring can be derived from bTMB panel. It has been shown that the baseline and dynamics during treatment of ctDNA monitoring could predict response/resistance to immunotherapies (Study GO30140). In summary, the role of TMB/MSI/DNA mutation and bTMB/ctDNA monitoring/MSI/DNA mutation in predicting response/resistance to sitravatinib in combination with tislelizumab will be explored.

Tumor-infiltrating lymphocyte abundance and location, along with immune-mediated gene expression profile, are associated with responses to immunotherapies including anti-PD-1 antibodies in different cancers (Cristescu et al 2018; Jiang et al 2018; Vilain et al 2017). Therefore, the relationship between clinical response to tislelizumab and tumor-infiltrating lymphocytes and/or GEP will be studied to explore potential predictive biomarkers.

Consequently, PD-L1, TMB/MSI/DNA mutation, bTMB/ctDNA monitoring/MSI/DNA mutation, GEP, and tumor-infiltrated immune cells can be explored in tumor or blood samples to identify their potential predictive value, as well as resistance mechanisms in patients who receive tislelizumab plus sitravatinib.

1.6. Benefit-Risk Assessment

Currently, patients with locally advanced unresectable or metastatic ESCC represent a patient population with a high unmet medical need. No standard of care has been established as second- or later-line treatment for patients with ESCC whose disease progressed on or after CPI treatment. Single cytostatic agents have been used for decades with modest treatment effect and significant toxicities.

Immunotherapy with CPIs has demonstrated responses in patients with advanced ESCC. Combination of CPI and a small-molecule inhibitor targeting the VEGFR pathway may improve the clinical efficacy of immunotherapies and overcome resistance to CPI therapy. Based on available data of sitravatinib and tislelizumab and available literatures of other PD-(L)1 inhibitors and other small-molecule inhibitors targeting the VEGFR pathway, the combination of

sitravatinib and tislelizumab may elicit greater antitumor activity with a manageable safety profile.

In all, 1546 patients have been treated with sitravatinib either as monotherapy or in combination with other drugs. Safety data from 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 targeting the VEGFR pathway. For further discussion on safety profile of sitravatinib, refer to the most recent edition of the Sitravatinib Investigator's Brochure.

A total of 2173 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) (Tislelizumab Investigator's Brochure). The safety profile is largely consistent with the known class effects of anti-PD-1 antibodies and includes mostly mild or moderate AEs. Grade 3 to 4 imAEs have been observed and they have been generally reversible and manageable with study treatment interruption and/or steroid treatment. Fatal imAEs were rare. For further discussion on safety profile of tislelizumab, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

As shown in Appendix 1, this study includes a comprehensive plan to monitor patient safety. The subsequent safety data will be continuously analyzed by the sponsor's study team and in consultation with the investigator(s) as needed. Refer to Section 7.4 and Section 8 for information regarding additional safeguards and considerations related to potential risk.

Given the unmet medical need and limited treatment options in this indication, the benefit-risk assessment for this study is considered favorable. To assess the potential benefit and safety of sitravatinib in combination with tislelizumab over single-agent chemotherapy, a randomized study will be conducted.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints

Table 7: Primary Objectives and Endpoints

Objective	Endpoint
To assess the overall response rate (ORR) by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 in the Intention-to-Treat (ITT) Population between Arm A (sitravatinib plus tislelizumab) and Arm C (investigator-chosen chemotherapy)	ORR as assessed by the investigator, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1, in Arms A and C in the ITT Analysis Set

Table 8: Secondary Objectives and Endpoints

Objectives	Endpoints
To evaluate the duration of response (DOR) as assessed by the investigator per RECIST v1.1 in Arm A and Arm C	DOR as assessed by the investigator, defined as the time from the first confirmed objective response until the first documentation of disease progression or death, whichever comes first, in Arms A and C in the ITT Analysis Set
To assess the efficacy between Arm A and Arm C through overall survival (OS)	OS, defined as the time from the date of randomization until the date of death from any cause, in Arms A and C in the ITT Analysis Set
To assess the efficacy between Arm A and Arm C through disease control rate (DCR), clinical benefit rate (CBR), and progression-free survival (PFS) as assessed by the investigator per RECIST v1.1	DCR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or stable disease, in Arms A and C in the ITT Analysis Set CBR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease ≥ 24 weeks), in Arms A and C in the ITT Analysis Set PFS as assessed by the investigator, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in Arms A and C in the ITT Analysis Set
To assess the efficacy of Arm A and Arm B (sitravatinib monotherapy) through ORR, DOR, DCR, CBR, and PFS as assessed by the investigator per RECIST v1.1	ORR as assessed by the investigator, defined as the proportion of patients with a confirmed CR or PR per RECIST v1.1, in Arms A and B in the ITT Analysis Set DOR as assessed by the investigator, defined as the time from the first confirmed objective response until the first documentation of disease progression or death, whichever comes first, in Arms A and B in the ITT Analysis Set

Objectives	Endpoints
	DCR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or stable disease, in Arms A and B in the ITT Analysis Set CBR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease ≥ 24 weeks), in Arms A and B in the ITT Analysis Set PFS as assessed by the investigator, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in Arms A and B in the ITT Analysis Set
To assess the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab	Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute-Common Terminology Criteria for Adverse Events NCI-CTCAE v5.0; vital signs; and clinical laboratory test results in the Safety Analysis Set

Table 9: Exploratory Objectives and Endpoints

Objectives	Endpoints
To assess the OS between Arm A and Arm B	OS, defined as the time from the date of randomization until the date of death from any cause, in Arms A and B in the ITT Analysis Set
To perform a sample-based tumor assessment by independent review committee (IRC) in Arms A, B, and C	ORR as assessed by the IRC, defined as the proportion of patients with a confirmed CR or PR per RECIST v1.1, in part of patients in Arms A, B, and C
To explore potential biomarkers that may correlate with clinical responses/resistance to sitravatinib plus tislelizumab or sitravatinib monotherapy versus chemotherapy	Potential biomarkers including but not limited to PD-L1 expression, tumor mutational burden (TMB)/DNA mutation/microsatellite instability (MSI), blood tumor mutational burden (bTMB)/circulating tumor DNA (ctDNA) monitoring/DNA mutation/MSI, gene expression profile (GEP), and tumor-infiltrated immune cells as well as the associations of biomarkers with disease status and response/resistance to sitravatinib plus tislelizumab or sitravatinib monotherapy versus chemotherapy
To characterize the pharmacokinetics of sitravatinib and its metabolite M10	Plasma concentrations of sitravatinib and its metabolite M10 at specified timepoints
To characterize the pharmacokinetics and immunogenicity of tislelizumab	Serum concentrations of tislelizumab and the incidence of ADAs

Objectives	Endpoints
To assess health-related quality of life (HRQoL)	HRQoL is defined as the assessment of changes in patient-reported outcomes (PRO) of esophageal squamous cell carcinoma (ESCC)-related symptoms and function from baseline

2.2. Definition of Primary Estimand

The primary scientific question of interest is:
Will sitravatinib in combination with tislelizumab given as a second- or third-line treatment increase the ORR over chemotherapy in patients with locally advanced unresectable or metastatic ESCC whose disease progressed on or after platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy, before the patients receive any new anticancer therapy or before disease progression?

The primary estimand is described by the following attributes:

1. Treatment of interest:
   The experimental treatment is sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks. The study control treatment for comparison is docetaxel 75 mg/m^2 intravenously on Day 1 of every 21-day cycle or irinotecan 125 mg/m^2 intravenously on Days 1 and 8 of every 21-day cycle.
2. Population:
   Patients with locally advanced unresectable or metastatic ESCC whose disease progressed after prior platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy, with the anti-PD-(L)1 antibody administered in combination with or sequentially following the platinum-based chemotherapy.
3. Primary variable:
   The primary variable is ORR, as assessed by the investigator, which is defined as the proportion of patients with a confirmed CR or PR before disease progression per RECIST v1.1.
4. Handling of remaining intercurrent events:
   - New anticancer therapy started before disease progression: patients starting any new anticancer therapy without achieving a confirmed CR or PR before will be considered as nonresponders (composite strategy).
   - Discontinuation of treatment before disease progression: response assessment after discontinuation of treatment will be counted and used for analysis (treatment policy strategy).
5. Population-level summary:
   The ORR difference between the sitravatinib plus tislelizumab arm and the ICC arm measured by crude odds ratio and risk difference.

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, randomized, multicenter, Phase 2 study to investigate the efficacy and safety of sitravatinib in combination with tislelizumab given as a second- or third-line treatment in patients with locally advanced unresectable or metastatic ESCC whose disease progressed after prior systemic chemotherapy, which is platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy, with the anti-PD-(L)1 antibody administered in combination with or sequentially following the platinum-based chemotherapy.

The study will be conducted at approximately 25 centers in Mainland China. Approximately 100 patients with locally advanced unresectable or metastatic ESCC whose disease progressed on or after platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy will be randomized to receive either sitravatinib plus tislelizumab (Arm A), sitravatinib monotherapy (Arm B), or ICC (Arm C). Patients must have received ≤ 2 lines of prior systemic therapy for locally advanced unresectable or metastatic disease. Other prior immunotherapeutic agents specifically targeting T-cell costimulation or checkpoint pathways (eg, anti-TIGIT antibody) are allowed if it was administered in combination with an anti-PD-(L)1 antibody. The choice of chemotherapy must be determined before randomization at the investigator's discretion, either docetaxel or irinotecan. Randomization will be stratified by PD-L1 expression status (assessed by the Ventana PD-L1 [SP263] assay: Tumor Area Positivity [TAP] score ≥ 10% versus TAP score < 10%) in a 2:1:2 ratio to receive 1 of treatment regimens:

- Arm A: Sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Sitravatinib 100 mg orally once daily
- Arm C: Docetaxel 75 mg/m^2 intravenously on Day 1 of every 21-day cycle **OR** irinotecan 125 mg/m^2 intravenously on Days 1 and 8 of every 21-day cycle

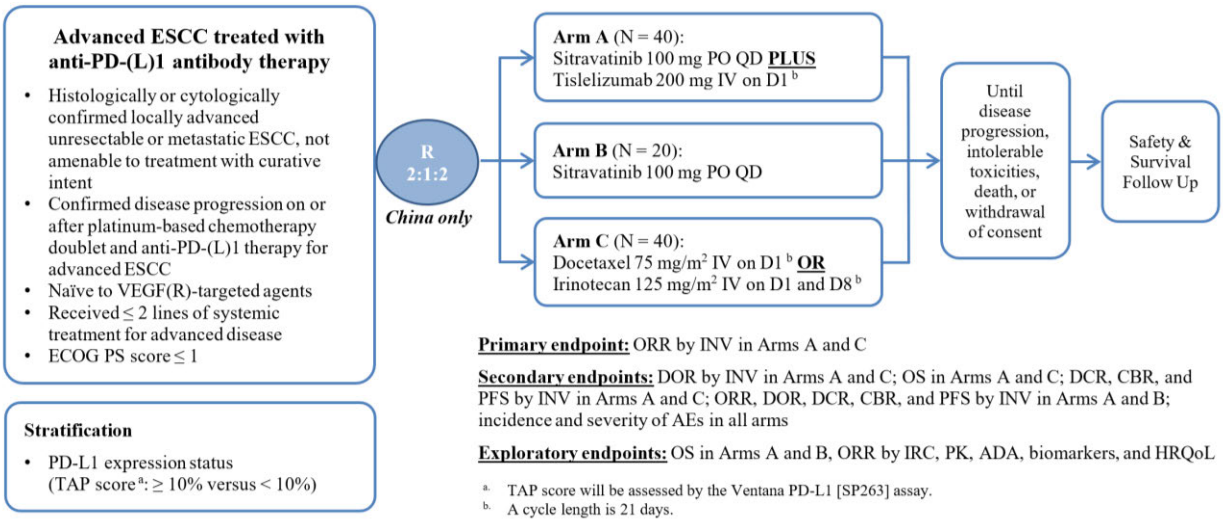
Switching of chemotherapeutic agent or cross-over between treatment arms will not be allowed during the study.

Efficacy and safety will be assessed between Arm A and Arm C, while efficacy between Arm A and Arm B will only be assessed for efficacy contribution analysis of tislelizumab in the combination treatment.

Study treatment will be administered until disease progression as assessed by the investigator per RECIST v1.1 (see Section 7.5), unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met, whichever occurs first (see Section 3.4).

HRQoL will be assessed via 2 validated patient-reported outcome (PRO) instruments: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC Quality of Life Questionnaire-Oesophageal Cancer Module (EORTC QLQ-OES18). The study design schematic is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: CBR, clinical benefit rate; D, Day; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; INV, investigator; IRC, Independent Review Committee; IV, intravenously; N, number of patients; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-(L)1, programmed cell death protein (ligand)-1; PFS, progression-free survival; PK, pharmacokinetic(s); PO, orally; QD, once daily; R, randomization ratio; TAP, Tumor Area Positivity; VEGF(R), vascular endothelial growth factor (receptor).

For all study procedures, see Section 7, Appendix 1, and Appendix 2.

3.2. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization (see Appendix 1). Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedure. Patients who are suspected of having concurrent obstruction as clinically indicated will take an esophagography/endoscopy test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results. For rescreening requirements, see Section 7.1.

3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 2:1:2 ratio to receive either sitravatinib plus tislelizumab (Arm A), sitravatinib monotherapy (Arm B), or ICC (Arm C). Randomization will be stratified by PD-L1 expression status (assessed by the Ventana PD-L1 [SP263] assay: TAP score ≥ 10% versus TAP score < 10%).

Patients will receive open-label treatment with one of the following:

- Arm A: Sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Sitravatinib 100 mg orally once daily

- Arm C: Docetaxel 75 mg/m^2 intravenously on Day 1 of every 21-day cycle **OR** irinotecan 125 mg/m^2 intravenously on Days 1 and 8 of every 21-day cycle

Switching of chemotherapeutic agent or cross-over between treatment arms will not be allowed during the study.

Administration of study treatment will continue until progressive disease as assessed by the investigator per RECIST v1.1 (see Section 7.5), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (whichever occurs first; see Section 3.4).

In select cases, patients in Arm A who are in ongoing treatment of sitravatinib plus tislelizumab may continue study treatment beyond the initial investigator-assessed RECIST v1.1-defined disease progression provided that the patient has investigator-assessed clinical benefit and is tolerating study treatment.

The following criteria must be met to treat patients after initial evidence of radiological disease progression:

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

Radiological assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 55 weeks, then every 9 weeks (± 7 days) thereafter based on RECIST v1.1. Tumor response will be assessed by the investigator. See Section 7.5 for details.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per National Cancer Institute-Common Terminology Criteria for Adverse Events NCI-CTCAE v5.0 and laboratory results. Vital signs, physical examinations, ECOG PS change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

3.4. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 3.7), 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 that include but are not limited to the following:

- Disease progression
- AE
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent systemic anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine and Chinese (or other Country) patent medicines] for the treatment of cancer)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study treatment compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

Patients who discontinue study treatment before disease progression will continue to undergo tumor assessments as outlined in Section 7.5.

3.5. End of Treatment

The End-of-Treatment (EOT) Visit is conducted when the investigator determines that the study treatment (ie, sitravatinib and tislelizumab in Arm A, sitravatinib in Arm B, or ICC in Arm C) will no longer be used or the patient withdraws from treatment. Patients will be asked to return to the clinic for an EOT Visit to occur 30 days (± 7 days) after the last dose of any component of the study treatment, or before the initiation of a new anticancer treatment, whichever occurs first. See Appendix 1 for assessments to be performed at the EOT Visit. If the decision to end the study treatment is made ≥ 23 days after the last dose of any component of the study treatment, the EOT Visit may occur later, but no later than 7 days after the decision.

3.6. Safety Follow-up for Immune-Mediated Adverse Events

Patients who discontinue tislelizumab in Arm A will be asked to return to the clinic or will be contacted by telephone to assess imAEs and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy). These contacts should be made at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

3.7. Survival Follow-up

Patients will be followed for survival and for information on subsequent anticancer therapy after discontinuation of study treatment. This follow-up will be conducted via telephone calls, patient medical records review, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or the end of the study (see Section 3.9).

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

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

- Patient withdrawal of consent
- Noncompliance
- AE
- Start of a new anticancer treatment
- Disease progression
- Death
- Loss to follow-up

3.9. End of Study

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

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early 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
- A rollover study becomes available

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 the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

At the end of the study, any patient who, in the opinion of the investigator, continues to benefit from tislelizumab and/or sitravatinib will be offered the option to continue treatment in a company-sponsored rollover study until the IMP(s) are commercially available in the country of the patient's residence.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2.

4.1. Inclusion Criteria

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

1. Patient must sign a written ICF and 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. Histologically or cytologically confirmed locally advanced unresectable or metastatic ESCC, not amenable to treatment with curative intent
4. Documented radiographic progression per RECIST v1.1 during or after platinum-based chemotherapy doublet and anti-PD-(L)1 therapy for locally advanced unresectable or metastatic ESCC. The anti-PD-(L)1 therapy could be administered in combination with or sequentially following the platinum-based chemotherapy. Patients must have received ≤ 2 lines of prior systemic therapy for locally advanced unresectable or metastatic disease.
    a. Other prior immunotherapeutic agents specifically targeting T-cell costimulation or checkpoint pathways (eg, anti-TIGIT antibody) are allowed if it was administered in combination with an anti-PD-(L)1 antibody. Patients whose disease progressed on or after anti-PD-(L)1 antibody plus anti-CTLA4 antibody as first-line systemic therapy followed by a platinum-based chemotherapy doublet are also allowed.
    b. Systemic treatment that had been administered as part of adjuvant/neoadjuvant therapy will be considered as a prior line of systemic treatment for the advanced disease if it was completed ≤ 6 months (180 days) before the diagnosis of locally advanced unresectable or metastatic disease.
    c. For locally advanced unresectable ESCC, systemic treatment that had been administered as part of a curatively intended multimodal therapy will be considered as a prior line of systemic treatment to the advanced disease if it was completed ≤ 6 months (180 days) before the disease progression. If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course should be counted as 1 line of therapy.
    d. The substitution of drug(s) for the drug(s) with the same mechanism of action due to any reason other than disease progression is not considered a separate line of therapy. When a new component, which is dissimilar to any of the original components, is added to the regimen, the new combination is considered a new regimen and is considered as a separate line of therapy.
5. At least 1 measurable lesion as defined per RECIST v1.1 as determined by local site investigator/radiology assessment ≤ 28 days before randomization
   Note: Lesions that had been previously irradiated were considered evaluable provided

that there was evidence of disease progression following the completion of radiation therapy.

6. ECOG PS score ≤ 1
7. Adequate organ function as indicated by the following laboratory values as indicated by the laboratory tests performed ≤ 7 days before randomization:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
      i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
      ii. Platelets ≥ 100 x 10^9/L
      iii. Hemoglobin ≥ 90 g/L
   b. Estimated glomerular filtration rate ≥ 45 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 9)
   c. Urine protein < 2+ by urine dipstick. If urine protein is ≥ 2+ by dipstick, then total protein from a 24-hour urine sample should be < 1 g/24 hours.
   d. Serum total bilirubin ≤ 1 x upper limit of normal (ULN) (total bilirubin must be < 2 x ULN for patients with Gilbert syndrome)
   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. AST and ALT ≤ 2.5 x ULN or < 5 x ULN if hepatic metastases are present. If AST and/or ALT > 1.5 x ULN, alkaline phosphatase (ALP) should be ≤ 2.5 x ULN.
8. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 180 days after the last dose of any component of study treatment. They must also have a negative urine or serum pregnancy test result ≤ 7 days before randomization. See Appendix 10.
9. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 180 days after the last dose of study treatment
   - A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
   - Males with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.
   - A nonsterile male with a partner of non-childbearing potential may not be required to use highly effective method of birth control.
10. Availability of tumor tissue (archival tumor tissues as formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 freshly cut unstained slides) that is of good quality and acceptable sample type for central laboratory assessment of PD-L1 expression status during the screening period and for retrospective evaluation of other exploratory biomarker analysis. A fresh biopsy is mandatory in the absence of archival tumor tissues. See Section 7.7.1 for details. PD-L1 expression status must be available before randomization. Patients with PD-L1 expression status of unevaluable is not eligible for the study.

Note: Patients may be permitted to be enrolled on a case-by-case basis after discussion with the sponsor's medical monitor if < 15 unstained slides are provided.

4.2. Exclusion Criteria

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

1. Have any contraindication for receiving treatment with both docetaxel and irinotecan
2. COVID-19 antigen or PCR positive by a certified laboratory during screening period
3. Patients with tumor located around important vascular structures as shown by imaging or the investigator determines that the tumor is likely to invade important blood vessels and may cause fatal bleeding (ie, radiologic evidence of tumors invading or abutting major blood vessels)
4. Patients with tumor that invades into organs located adjacent to the esophageal disease site (eg, aorta or respiratory tract) or recurrence in a previously irradiated area in the esophagus/thorax that has an increased risk of fistula during the study treatment period as assessed by the investigator
5. History of gastrointestinal perforation and/or fistula or aorto-esophageal fistula, and/or patients with ≥ CTCAE 5.0 Grade 2 esophageal obstruction/stenosis.
6. Have received prior anticancer agents that have same mechanism of action as sitravatinib (eg, RTK inhibitor with a similar target profile or VEGF- or VEGFR-targeted monoclonal antibodies)
7. Active leptomeningeal disease or uncontrolled, untreated brain metastasis
   Note: Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all the following criteria:
   a. Brain imaging at screening shows no evidence of interim progression, and there is no evidence of new brain metastases
   b. Patient clinically stable for ≥ 2 weeks
   c. Have measurable and/or evaluable disease outside the CNS
   d. No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days before randomization; anticonvulsants at a stable dose are allowed
   e. No stereotactic radiation or whole-brain radiation ≤ 14 days before randomization
8. Active autoimmune diseases or history of autoimmune diseases (Appendix 6) that may relapse

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

a. Controlled type 1 diabetes
b. Hypothyroidism (provided that it is managed with hormone replacement therapy only)
c. Celiac disease controlled by diet alone
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

9. Any malignancy ≤ 2 years before randomization except for the 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)

10. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

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

11. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management, or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization

12. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention)

13. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, or acute lung diseases.

14. Infection (including tuberculosis infection, etc) requiring systemic (oral or intravenous) antibacterial, antifungal, or antiviral therapy ≤ 14 days before randomization

Note: Antiviral therapy is permitted for patients with chronic infection with hepatitis B virus (HBV), or infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV). Patients receiving prophylactic antibiotics (eg, for prevention of urinary tract infection, chronic obstructive pulmonary disease, or for dental extraction) are eligible.

15. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA ≥ 2000 IU/mL at screening

Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 2000 IU/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines (see also Section 6.2.1.2). Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization.

16. Patients with active hepatitis C

Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. For treatment guidance, see

Section 6.2.1.3. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization.

17. Untreated HIV infection, if known. Patients with known HIV infection are eligible if the following criteria are met:
    a. Stable on antiretroviral therapy for ≥ 4 weeks before randomization
    b. Patient agrees to adhere to antiretroviral therapy per World Health Organization (WHO) guidelines
    c. No documented multidrug resistance that would prevent effective antiretroviral therapy
    d. Viral load of < 400 copies per mL at screening
    e. $CD4^+$ T-cell count ≥ 350 cells/μL at screening
    f. No history of an AIDS-defining opportunistic infection ≤ 12 months before randomization unless eligibility is agreed to by the medical monitor after consultation
    g. If prophylactic antimicrobial drugs are indicated, patients may still be eligible upon agreement with the medical monitor

Note: Patients with unknown HIV status is not required to complete HIV test at screening.

18. Any major surgical procedure or any esophageal surgery including a dilation procedure ≤ 28 days before randomization. Patients must have recovered adequately from the toxicity and/or complications from the intervention before randomization.
19. Prior allogeneic stem cell transplantation or organ transplantation
20. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living (ADL), ≤ 28 days before randomization
    b. Pulmonary embolism ≤ 28 days before randomization
    c. Deep vein thrombosis ≤ 6 months before randomization
    d. Any history of acute myocardial infarction ≤ 6 months before randomization
    e. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 7) ≤ 6 months before randomization
    f. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
    g. Any history of cerebrovascular accident ≤ 6 months before randomization
       QT interval corrected by Fridericia's method (QTcF) > 470 msec
       Note: If a patient has QTcF interval > 470 msec on an initial ECG, 3 consecutive ECGs will be performed several minutes apart to determine the mean QTcF interval.
    h. Uncontrolled hypertension (defined as systolic blood pressure (BP) > 150 mmHg and/or diastolic BP > 100 mmHg) that cannot be managed by standard antihypertension medications ≤ 28 days before randomization
    i. Cardiac left ventricular ejection fraction (LVEF) < 50% or lower limit of the institution's normal range as assessed by echocardiography or multigated acquisition (MUGA). The method used at screening is required to be used throughout the study.
    j. Any episode of syncope or seizure ≤ 28 days before randomization

21. A history of severe hypersensitivity reactions to sitravatinib, tislelizumab, docetaxel, and irinotecan, to any ingredient in the formulation, or to any component of the container.
22. Has received any of the following treatment:
    a. Any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies ≤ 14 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study treatment
    b. Patients with a history of esophagus/thoracic tumor radiotherapy within 6 months before randomization and/or with a history of radiotherapy in areas other than esophagus/thoracic tumor, any palliative radiation treatment, or other local regional therapies ≤ 14 days before the first dose of study treatment
    c. Any Chinese herbal medicine or Chinese patent medicines used to control cancer ≤ 14 days before randomization
23. Patients with 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)
24. Was administered a live vaccine ≤ 28 days before randomization.

Note: Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

25. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study treatment, will affect the explanation of drug toxicity or AEs, or will result in insufficient or impaired compliance with study conduct
26. Women who are pregnant or are breastfeeding.
27. Concurrent participation in another therapeutic clinical study.

Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

28. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
29. Patients who use anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring.
30. Within 3 months before randomization, patients with active bleeding disorder or any bleeding events ≥ Grade 3, unhealed wounds, gastrointestinal ulcers, or fractures

Note: Gastrointestinal ulcers include any esophageal ulcer, gastric ulcer, or intestinal ulcer.

31. Unacceptable toxicity on prior anti-PD-(L)1 treatment and/or other immune-oncology agents, defined as follows:

a. ≥ Grade 3 AE related to anti-PD-(L)1 treatment and/or other immune-oncology agents that did not respond to standard therapy and warranted treatment discontinuation

b. ≥ Grade 2 imAE associated with anti-PD-(L)1 treatment and/or other immune-oncology agents unless the AE resolved or was well controlled by withholding the anti-PD-(L)1 treatment and/or treatment with steroids, with the exception of prior colitis, encephalitis, myocarditis, hepatitis, pancreatitis, and pneumonitis, which are exclusionary

c. CNS or ocular AE of any grade related to anti-PD-(L)1 treatment and/or other immune-oncology agents

Note: Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

32. Patients with spinal cord compression due to metastatic disease not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that the disease has been clinically stable for > 2 weeks before randomization

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Sitravatinib

Sitravatinib will be provided as 35-mg and 50-mg unit dose strength capsules. Sitravatinib drug product is packaged in 30-count, high-density polyethylene, opaque white, round 75-cc bottles. A tamper-proof heat-induction seal and a child-resistant closure are used.

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

The study drug must be kept at the temperature and light conditions specified on the label and in the pharmacy manual. Refer to the pharmacy manual for details regarding administration, accountability, and disposal. Refer to the Sitravatinib Investigator's Brochure for other details regarding sitravatinib.

5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous infusion 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 a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap. Each vial is packaged into a single-carton box.

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

The study drug must be kept at the temperature and light conditions specified on the label and in the pharmacy manual. Refer to the pharmacy manual for details regarding reconstitution, intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.3. Docetaxel and Irinotecan

Management (eg, handling, storage, administration, and disposal) of docetaxel and irinotecan will be in accordance with relevant local guidelines and/or prescribing information. The actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

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

All study drugs must be kept at the temperature condition specified on the labels. For further details, see the manufacturer's prescribing information for each chemotherapy agent.

5.2. Dosage, Administration, and Compliance

Dosing schedules for arms, specified by individual arm, are provided in Table 10. The first dose of study treatment is to be administered ≤ 2 business days after randomization. The day of the first dose of study treatment will be documented as Day 1 of Cycle 1. All patients will be monitored continuously for AEs. Treatment modification (ie, dose delay, reduction, or

interruption) or discontinuation will be based on specific laboratory and AE criteria, as described in Section 5.5.

Table 10: Selection and Timing of Dose for Each Patient

Study drug	Dose	Frequency of administration	Route of administration	Duration of treatment
Arm A				
Sitravatinib	100 mg	Once a day	Oral	See Section 3.3
AND Tislelizumab [a]	200 mg	Day 1 of a 21-day cycle	Intravenous	See Section 3.3
Arm B				
Sitravatinib	100 mg	Once a day	Oral	See Section 3.3
Arm C				
Docetaxel	75 mg/m^2	Day 1 of a 21-day cycle	Intravenous	See Section 3.3
OR Irinotecan	125 mg/ m^2	Days 1 and 8 of a 21-day cycle	Intravenous	See Section 3.3

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

5.2.1. Sitravatinib

Sitravatinib capsules will be administered orally, once a day continuously for a total daily dose of 100 mg. The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken with a low-fat meal (Appendix 14) or on an empty stomach (defined as ≥ 2-hour fast before each dose and no food for ≥ 1 hour after each dose).
- Capsules should be taken with ≥ 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, the patient should skip the dose and resume taking the drug the next day.

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

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, storage, and administration are provided in the pharmacy manual.

The delivery period of the initial infusion (Day 1 of Cycle 1) will be ≥ 60 minutes; if this is well tolerated, then the delivery period of subsequent infusions may be shortened to ≥ 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).

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

5.2.3. Docetaxel

Docetaxel will be administered on Day 1, given every 21 days after all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.2. The initial treatment of docetaxel should be administered within 2 business days of randomization. Docetaxel should be administered at a dose of 75 mg/m^2 by intravenous infusion over 60 minutes according to manufacturer standards. Doses lower than 75 mg/m^2 are allowed if considered appropriate for any given patient. The first dose of docetaxel is dependent upon the patient's baseline body surface area (BSA). Subsequent doses of docetaxel must be recalculated if the change of body weight (increase or decrease) is ≥ 10% from baseline. Docetaxel doses do not need to be modified for any body weight change of < 10%. Calculating the chemotherapy doses by actual body weight is acceptable.

Before each administration of docetaxel, liver function tests (LFTs) and blood counts should be reviewed. Docetaxel should not be given if bilirubin > 1 x ULN or if AST and/or ALT > 1.5 x ULN concomitant with ALP > 2.5 x ULN. Docetaxel should not be given if neutrophil counts are < 1500 cells/mm^3.

Premedication might be recommended before infusion of docetaxel according to the manufacturer's instructions and local standards. To alleviate the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, premedication of oral corticosteroids, such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days should be given starting from the day before infusion of docetaxel. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. All medications will be documented on the appropriate eCRF.

For all treatment in subsequent cycles, the treatment interval should be 21 to 24 days (3-day window). If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc), the subsequent dosing visit should be scheduled as clinically appropriate.

Patients will be monitored continuously for AEs and will be instructed to notify their physician for new AEs, such as worsening of pre-existing conditions, or AEs that cause any change in performance status or ADL. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of docetaxel therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

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

5.2.4. Irinotecan

Irinotecan will be administered on Days 1 and 8, given every 21 days after all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.2. The initial treatment of irinotecan should be administered within 2 business days of randomization. Irinotecan should be administered at a dose of 125 mg/m^2 by intravenous infusion over 90 minutes or according to manufacturer standards. The first dose of irinotecan is dependent upon the patient's baseline BSA. Subsequent doses of irinotecan must be recalculated if the change of body weight (increase or decrease) is ≥ 10% from baseline. Irinotecan doses do not need to be modified for any body weight change of < 10%. Calculating the chemotherapy doses by actual body weight is acceptable. Alternate doses/schedules of irinotecan according to local standards of care may be used as long as the 21-day cycle length (or multiples of that) are maintained.

Premedication is recommended before infusion of irinotecan according to the manufacturer's instructions and local standards. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. To reduce the incidence and severity of fluid loss, premedication may include atropine and antiemetic agents, such as dexamethasone 10 mg along with another antiemetic agent (eg, ondansetron) on the day of irinotecan administered. All medications will be documented on the appropriate eCRF.

For all treatment in subsequent cycles, the treatment interval should be 21 to 24 days (3-day window). If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc), the subsequent dosing visit should be scheduled as clinically appropriate.

Patients will be monitored continuously for AEs and will be instructed to notify their physician for new AEs, such as worsening of pre-existing conditions, or AEs that cause any change in performance status or ADL. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of irinotecan therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

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

5.3. Overdose

5.3.1. 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.

5.3.2. Tislelizumab

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug 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 must be reported ≤ 24 hours after awareness via the SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.3.3. Docetaxel

There is no known antidote for docetaxel injection overdosage. In case of overdose, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdose include bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic granulocyte colony-stimulating factor as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken as clinically indicated.

5.3.4. Irinotecan

There is no known antidote for irinotecan injection overdosage. In case of overdose, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdose include bone marrow suppression and diarrhoea. Appropriate symptomatic measures should be taken as clinically indicated.

5.4. Investigational Medicinal Product Accountability

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

Accurate records of all IMPs received, dispensed, returned, and disposed of should be recorded on the site's Drug Inventory Log. Refer to the pharmacy manual for details of IMP management.

5.5. Dose Modification

Dose modification is defined as any of the following: dose reduction, dose delay, missed doses, and dose interruption. A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion or oral administration.

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

The dose modification guidelines in this section are not intended to be a substitute for clinical judgment. Investigators may delay or reduce doses for other reasons (eg, AEs or laboratory findings) as appropriate.

5.5.1. Dose Modification for Sitravatinib

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 ≤ 28 days for sitravatinib after the last dose of sitravatinib. Sitravatinib should be resumed at a reduced dose level (Table 11). In the setting of a Grade 3 or Grade 4 AE, treatment with study drug can be resumed to patients only after investigator consultation with the sponsor. 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.

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 the drug is planned to be interrupted for > 28 days, the medical monitor should be contacted before the patient permanently discontinues from the study drug.

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

Dose reduction levels for sitravatinib are presented in Table 11. Once the dose has been reduced, re-escalation is not recommended.

Table 11: Dose Reductions for Sitravatinib

Study drug/Dose level	Starting dose	Dose level -1	Dose level -2
Sitravatinib	100 mg	70 mg	50 mg [a]

[a] Dose reduction below 50 mg once daily may be undertaken after discussion with the sponsor.

Based on the known toxicity profiles of sitravatinib and tislelizumab, certain AEs are likely to be associated with one drug versus the other. For example, treatment-emergent hypertension or proteinuria are likely to be associated with sitravatinib rather than tislelizumab; similarly, imAEs are likely to be associated with tislelizumab rather than sitravatinib. However, some drug-related AEs, such as diarrhoea and elevated LFTs, are overlapping. Therefore, it is crucial to fully evaluate each AE to confirm the etiology or exclude other causes in order to determine the proper management of the adverse reaction and action regarding study treatment. The management guidelines for sitravatinib-specific AEs and tislelizumab-related AEs of special interest are provided in detail in Section 8.7 and Section 8.8, respectively.

For patients in Arm A receiving sitravatinib plus tislelizumab, sitravatinib administration may continue if tislelizumab is delayed or discontinued.

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 Modification for Tislelizumab

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

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is suspected to be related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and ≤ 12 weeks after the last dose of tislelizumab. Treatment intervals may be increased due to toxicity according to the dose modification guidelines. Cycle numbers will be counted based on the dosing of tislelizumab. For example, if the dosing of tislelizumab is

delayed for 14 days, the next cycle can resume after an additional 21 days (ie, Day 35). Sitravatinib could be given continuously, unless interruption or discontinuation criteria are met. If the patient is unable to resume tislelizumab ≤ 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment. If the patient is not able to resume tislelizumab ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

For patients in Arm A receiving sitravatinib plus tislelizumab, sitravatinib can be continued as monotherapy at the discretion of the investigator if the unacceptable AE is potentially attributed to anti-PD-1 therapy and clearly is not attributed to sitravatinib. Tislelizumab treatment may be continued when sitravatinib treatment is interrupted; however, tislelizumab should not be used as monotherapy after permanent discontinuation of sitravatinib due to limited anticancer effect of rechallenging PD-(L)1 monotherapy after progression on PD-(L)1 inhibitor or PD-(L)1-inhibitor-based therapy.

Specific treatment modifications to manage tislelizumab-related toxicities, such as imAEs and infusion-related reactions, are described in Section 8.8 and Appendix 8.

AEs (both nonserious and serious) associated with tislelizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment is critical to reduce complications. Tislelizumab must be withheld for severe or life-threatening AEs. See Appendix 8 for supportive care guidelines, including use of corticosteroids.

5.5.3. Dose Modification for Investigator-Chosen Chemotherapy

Dose modifications for chemotherapy should be performed per applicable local prescribing information and per local practice according to the investigator's clinical judgment. Recommended dose modifications for key chemotherapy toxicities are outlined in this section. These serve as guidelines and do not replace investigator judgment and applicable local label recommendations if more stringent.

Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by ≥ 10% from baseline (or the new reference body weight). Chemotherapy does not need to be modified for any body weight change of < 10%. Calculating the chemotherapy doses by actual body weight is acceptable. If reassessment of baseline weight is needed, the latest baseline weight is always to be used to calculate percent change in weight for all subsequent doses. The Mosteller formula is recommended for BSA calculation:

$$\text{BSA } (m^2) = \sqrt{\frac{hight\ (cm) \times weight\ (kg)}{3600}} \textbf{ OR } \text{BSA } (m^2) = \sqrt{\frac{hight\ (in) \times weight\ (lbs)}{3131}}$$

Study treatment-related toxicities must be resolved to baseline level or Grade 1 (whichever is more severe) before administering the next dose, except for alopecia, ≤ Grade 2 fatigue, or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study treatment. A maximum of 2 dose reductions for each chemotherapeutic agent are permitted.

Dose reduction levels for ICC are presented in Table 12. Guidances for dose reductions of docetaxel and irinotecan for specific AEs are provided in Table 13 and Table 14, respectively.

Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. If additional reductions are required, that chemotherapeutic agent must be discontinued.

Table 12: Dose Reductions for Investigator-Chosen Chemotherapy

Study drug/Dose level	Starting dose	Dose level -1 [a]	Dose level -2 [b]
Docetaxel	75 mg/m^2	60 mg/m^2	45 mg/m^2
Irinotecan	125 mg/m^2	100 mg/m^2	75 mg/m^2

[a] 20% decrease from the starting dose.
[b] 25% decrease from the starting dose.

Table 13: Docetaxel Dose Modifications for Specific Adverse Events

Docetaxel dose	Adverse event
75 mg/m^2	Starting Dose: Administer only if neutrophil count is > 1500 cell/mm^3
60 mg/m^2	• Febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥ 1500 cells/mm^3) • Platelet count < 100,000 cells/mm^3 (after recovering to a platelet count of ≥ 100,000 cells/mm^3) • Severe or cumulative cutaneous reactions
45 mg/m^2	• Second episode febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥ 1500 cells/mm^3)
Permanently discontinue docetaxel	After any of the following toxicities: • Severe hypersensitivity reactions • Peripheral neuropathy > Grade 3 • Severe or cumulative cutaneous reactions that continue at a dose of 45 mg/m^2 without recovery • Febrile neutropenia or neutrophils < 500 cells/mm^3 without recovery • Platelet count < 100,000 cells/mm^3 without recovery • Total bilirubin > 1 x ULN without recovery • Serum transaminase (AST, ALT) levels > 1.5 x ULN concurrent with serum ALP levels > 2.5 x ULN without recovery

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Table 14: Irinotecan Dose Modifications for Specific Adverse Events

Irinotecan dose	Adverse event
125 mg/m^2	Starting dose: Administer only if neutrophil count is > 1500 cell/mm^3
100 mg/m^2	Reduction from the starting dose for any of the following toxicities • Grade 3 neutropenia (neutrophils 500 cells/mm^3 to 999 cells/mm^3)

Irinotecan dose	Adverse event
	• Grade 3 diarrhoea (7 to 9 stools/day over pretreatment status)—hold dose until resolved to ≤ Grade 2 then restart at 100 mg/m^2 • Other Grade 2 or 3 non-hematologic toxicities except alopecia, anorexia, asthenia
75 mg/m^2	After any of the following toxicities: • Neutropenic fever: Omit dose until resolved, restart at 75 mg/m^2 • Grade 4 neutropenia (neutrophils < 500 cells/mm^3): Hold dose until neutrophil count is ≤ Grade 2 then restart at 75 mg/m^2 • Grade 4 diarrhoea (≥ 10 stools/day over pretreatment status): Hold dose until recovery to ≤ Grade 2 then restart at 75 mg/m^2 • Other Grade 4 nonhematologic toxicities except alopecia, anorexia, and asthenia: Omit dose until resolved to ≤ Grade 2 then restart at 75 mg/m^2

If ICC-related toxicities warrant a dosing delay, chemotherapy administration may restart as soon as is feasible. For example, chemotherapy administration can occur during an unscheduled visit. If recovery of ICC-related toxicity is not achieved ≤ 21 days after the scheduled day of the course, the patient will discontinue the chemotherapy. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date.

If the patient is unable to resume chemotherapy treatment ≤ 6 weeks after the last dose of chemotherapy, then the patient should be discontinued from treatment. If the patient is not able to resume chemotherapy ≤ 6 weeks after the last dose because of unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

Switching of chemotherapeutic agent will not be allowed during the study.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

All prior systemic anticancer therapy, dates of administration, best response, and date of progression for ESCC will be collected at study entry.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care for supportive care (eg, antiemetics, antidiarrheals) are allowed.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient ≤ 30 days before the first dose of study treatment will be recorded.

Opiates and other medications required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

6.2.1.1. Systemic Corticosteroids

Systemic corticosteroids given for the control of imAEs must be tapered gradually (see Appendix 8) and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. Use of steroids to manage chemotherapy-induced nausea and vomiting is permitted. The short-term use of steroids as prophylactic treatment (eg, in patients with allergies to diagnostic imaging contrast dyes) is permitted.

6.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 2000 IU/mL at screening, must initiate treatment > 2 weeks before randomization, and continue until 6 months after the last dose of study drug(s). The patients would not be eligible unless HBV DNA decreases to < 2000 IU/mL. If the patients are treated and eligible, patients should continue effective antiviral treatment during the study to decrease potential viral reactivation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel 2015). The investigator may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 2000 IU/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before enrollment. Once initiated, antiviral treatment should continue until 6 months after the last dose of study treatment or as permitted by local guidance.

6.2.1.3. Hepatitis C Treatment

Patients with detectable HCV RNA who are receiving treatment at screening must meet the criterion of negative HCV RNA to be eligible. If the patients are treated and eligible, they will remain on continuous, effective antiviral therapy during the study. Patients given antiviral therapy must not enroll until > 2 weeks after the initiation of such therapy. Investigators can consider treatment with sofosbuvir alone or in combination with other antivirals following the AASLD guideline or the local guidelines as appropriate. However, interferon-based therapy for HCV is not permitted on study.

6.2.1.4. Radiation Therapy

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

- Repeated imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation have been met

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

6.2.2. Prohibited Concomitant Medications/Procedures

Prohibited concomitant medications/procedures during the study, specified by treatment component, are provided in Table 15. Patients must notify the investigator of all herbal remedies used during the study.

Table 15: Prohibited Concomitant Medications/Procedures by Treatment Component

Component of study treatment	Prohibited concomitant medications/procedures
Any component of study treatment	• Less than 28 days before randomization: Live vaccines • During screening and through the EOT Visit: Any concurrent systemic anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents • During screening and through the EOT Visit: Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China NMPA for use as anticancer treatment (regardless of cancer type)
Sitravatinib	• During sitravatinib treatment: Anticoagulants, such as warfarin or similar agents, requiring therapeutic INR monitoring

Tislelizumab	• During tislelizumab treatment and ≤ 60 days after the last dose of tislelizumab: Live vaccines • During tislelizumab treatment: Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin)

Abbreviations: EOT, end of treatment; INR, international normalized ratio; NMPA, National Medical Products Administration

6.2.3. Restricted Concomitant Medications/Procedures

Restricted concomitant medications/procedures during the study, specified by treatment component, are provided in Table 16.

Table 16: Restricted Concomitant Medications/Procedures by Treatment Component

Component of study treatment	Restricted concomitant medications/procedures
Any component of study treatment	• Patients should not abuse alcohol or other 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 6.2.1.4
Sitravatinib	• During sitravatinib treatment: Medications have potential interactions with sitravatinib (See Section 6.3 and Appendix 11)
Tislelizumab	• During tislelizumab treatment: Immunosuppressive agents (except to treat a drug-related AE) • During tislelizumab treatment: 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
Docetaxel/irinotecan	• During chemotherapy: Medications have potential interactions with docetaxel or irinotecan (See Section 6.3 and Appendix 11)

Abbreviation: AE, adverse event.

6.3. Potential Interactions Between the Study Treatment and Concomitant Medications

Potential Interaction of Sitravatinib With Cytochrome P450 Enzyme Inhibitors/Substrates

Sitravatinib is not considered a high-risk compound as a victim of drug-drug interaction because multiple enzymes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, are involved in its metabolism.

In vitro, sitravatinib showed direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (Section 1.3.1). Concomitant medications that are sensitive substrates or substrates with a narrow therapeutic index for these CYP enzymes (examples listed in Appendix 11) should be used with caution during sitravatinib treatment.

Sitravatinib With Medications That Prolong QT/QTc

Per the International Council for Harmonisation (ICH) E14 guidance, it is recommended to use with caution for medications with a potential to prolong QT/QTc or cause torsades de pointes (examples listed in Appendix 11).

Potential Interaction of Sitravatinib With Transporter Modulators/Substrates

Sitravatinib was identified to be a substrate of P-gp and an inhibitor of both P-gp and BCRP (Section 1.3.1). Inhibitors of P-gp (eg, clarithromycin, itraconazole, propafenone, quinidine, ranolazine, ritonavir, and verapamil) may increase sitravatinib exposure while inducers of P-gp (eg, rifampin) may decrease sitravatinib exposure. Caution should therefore be taken when administering sitravatinib to patients taking medications that inhibit or induce P-gp. Concomitant medications that are sensitive substrates or substrates with narrow therapeutic indices for P-gp and/or BCRP transporters (examples listed in Appendix 11) should be used with caution during sitravatinib treatment.

Potential Interaction of Sitravatinib With 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 therapy administered orally. Like most therapeutic proteins, tislelizumab is not expected to be metabolized by CYP or other drug-metabolizing enzymes and is unlikely to affect CYPs or other metabolizing enzymes in terms of inhibition or induction.

Potential Interaction of Docetaxel With Cytochrome P450 3A4 Inhibitors/Inducers/ Substrates

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided unless there are no therapeutic alternatives. Do not administer strong CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine, or St. John's wort) in patients treated by docetaxel unless there are no therapeutic alternatives. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided (examples listed in Appendix 11).

Potential Interaction of Irinotecan With Cytochrome P450 3A4 Inhibitors/Inducers/ Substrates

Irinotecan and its bioactive metabolite SN-38 are metabolized by CYP3A4 and UGT1A1. The metabolism of irinotecan could be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4 and/or UGT1A1.

Do not administer strong CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine, or St. John's wort) with irinotecan unless there are no therapeutic alternatives. Do not administer

strong CYP3A4 inhibitors (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, or voriconazole) and UGT1A1 inhibitors (eg, atazanavir, gemfibrozil, or indinavir) or both CYP3A4 and UGT1A1 inhibitors (such as ketoconazole) in patients treated by irinotecan unless there are no therapeutic alternatives.

7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments is provided 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.

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

7.1. Screening

Screening evaluations will be performed ≤ 28 days before randomization. Patients who agree to participate will sign the ICF before undergoing any screening procedure. The screening period begins on the date the ICF is signed. Screening evaluations may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

For descriptions of other assessments conducted during screening, see Section 7.4 for safety assessments, Section 7.5 for tumor and response evaluations, and Section 7.7 for biomarker evaluations. The PK sampling schedule is shown in Appendix 2.

Rescreening under limited conditions may be allowed after consultation with the sponsor. For example, rescreening may be considered when a patient narrowly misses a laboratory criterion that is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once. Rescreened patients must provide new informed consent, as described in Section 7.1.1; a new patient number will be assigned as described in Section 7.1.2. Any new result will override the previous one (ie, the most recent result before randomization) and is the value by which study inclusion will be assessed, as it represents the patient's most current clinical state.

7.1.1. Informed Consent and Screening Log

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

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

7.1.2. Patient Numbering

After obtaining informed consent, study site personnel will access the interactive response technology (IRT) system to assign a unique patient number to a potential study participant.

Patients who are rescreened (see Section 7.1) will be assigned a new patient number. Screening numbers that are assigned to the same patient within the IRT system will be linked.

7.1.3. Demographic Data and Medical History

Demographic data will include the age or year of birth, sex, self-reported race/ethnicity, etc.

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

If appropriate, clinically significant disease should be graded according to NCI-CTCAE v5.0 and recorded in the medical history page of eCRF.

Cancer history will include pathologic diagnosis, stage at screening, tumor location, location of metastatic disease at study baseline, an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed before study entry may be collected for review by the investigator.

7.1.4. Women of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 10 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential".

7.2. Enrollment

7.2.1. Confirmation of Eligibility

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

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with ICH Good Clinical Practice (GCP) Guidelines (ICH E6).

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

7.2.2. Enrollment/Randomization

Site personnel will access the IRT system to randomly assign the patient to a treatment arm and to assign study treatment. Study treatment must commence ≤ 2 business days after randomization/treatment assignment.

Patient randomization will be stratified by PD-L1 expression status (assessed by the Ventana PD-L1 [SP263] assay: TAP score ≥ 10% versus TAP score < 10%). The choice of chemotherapy

regimen must be decided before randomization, and interchanging chemotherapy regimen is not permitted during the study period.

Once enrolled in the IRT, patients that have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for patient randomization:

- Patient number
- Year of birth
- PD-L1 expression status (assessed by the Ventana PD-L1 [SP263] assay: TAP score ≥ 10% versus TAP score < 10%)

7.3. Dispensation of Study Treatment

Sitravatinib, tislelizumab, and chemotherapy agents will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessments

7.4.1. Vital Signs

See Appendix 1 for vital signs collected and the timing of their collection.

7.4.2. Physical Examinations

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

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements (Appendix 1).

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Local and/or central laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function will be conducted as described in Appendix 1. Specific assessments to be performed are listed in Appendix 3.

If laboratory tests at screening are not performed ≤ 7 days before the first dose of study treatment, these tests should be repeated and reviewed before administration of study treatment. After Cycle 1, results are to be reviewed within 48 hours before study treatment administration.

Laboratory tests of hematology and serum chemistry as specified in Appendix 3 should be performed weekly for the first 3 cycles, at the beginning of each subsequent cycle, and at the

EOT Visit. Laboratory tests of coagulation parameters and urinalysis as specified in Appendix 3 should be performed at the beginning of each cycle and at the EOT Visit. Laboratory tests of thyroid function will be performed every 3 cycles and at the EOT Visit.

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.

7.4.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune CPIs, serum creatine kinase (CK) and CK cardiac isoenzyme (CK-MB) is monitored in all tislelizumab studies to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 8 for guidelines for management of suspected immune-mediated myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.4.5. Electrocardiograms

A 12-lead/15-lead/18-lead ECG is required during screening, at the beginning of each cycle, at the EOT Visit, and as clinically indicated at other time points (Appendix 1).

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

When coinciding with blood sample collection at the same timepoint, ECG assessment should be performed either before blood sample collection or ≥ 30 minutes after the blood sample collection. Patients should rest for ≥ 10 minutes before ECG collection. If a patient has QTcF interval > 450 msec for males or > 470 msec for females on an initial ECG, 3 consecutive ECGs will be performed several minutes apart to determine the mean QTcF interval.

7.4.6. Echocardiogram

Cardiac function will be evaluated at screening and every 12 weeks thereafter (Appendix 1). Evaluations by echocardiogram is preferred but evaluations by MUGA scan are acceptable, if necessary. The method used to assess cardiac function at screening is required to be used throughout the study.

7.4.7. Adverse Events

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

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

7.4.8. Hepatitis B and C Testing

Viral hepatitis B and C serologic markers and viral load (if applicable) will be tested by a central laboratory and/or the local laboratory. HBV testing will include hepatitis B surface antibody (HBsAb), HBsAg, and hepatitis B core antibody (HBcAb). In addition, HBV DNA will be

quantified in patients positive for HBsAg. For patients who have positive test results of HCV antibody, a test to quantify HCV RNA will be required.

Additional viral load assessment after screening is described in Appendix 1.

7.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests (only applicable if the same radiographic procedure will be used throughout the study). During the study treatment period, evaluation of tumor response by the investigator per RECIST v1.1 will be performed every 6 weeks (± 7 days) from Day 1 of Cycle 1 for the first 55 weeks and then every 9 weeks (± 7 days) thereafter (Appendix 1). If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule.

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

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

- MRI scan of brain at baseline is required for patients who are suspected to have CNS metastases. Screening evaluations will be performed ≤ 28 days before randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (technetium-99m) 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, technetium-99m or PET bone scans should be repeated when a CR is suspected in the target lesion or when progression in bone is suspected.
  - If bone metastases are visualized on the bone scan or PET scan at screening, a confirmatory CT/MRI scan should be performed. If the metastases are confirmed by CT/MRI, then evaluation by CT/MRI should be given preference for subsequent assessments. If the metastases are not confirmed by CT/MRI, then the use of bone scan or CT/MRI for subsequent assessments is at the investigator's discretion.

  - If an increase in the uptake of existing lesions is seen on a bone scan, or the appearance of new osteoblastic bone lesions is seen on an x-ray, CT, or MRI, this should not automatically be considered evidence of progression in an otherwise stable or responding subject. It may in fact be indicative of response to therapy.
  - New areas of uptake seen on a bone scan should not automatically result in diagnosis of progressive disease but should be correlated with other available imaging (eg, CT, MRI, or x-ray).
- CT scans of the neck or extremities should be performed at screening only if clinically indicated and should be repeated throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessing target lesions and nontarget lesions per RECIST v1.1 may be used. However, CT or MRI should be given preference for assessment of target lesions.

Tumor response will be assessed by the investigator using RECIST v1.1 (see Appendix 5). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits. At the sponsor's discretion, response assessment imaging may be collected during the study for the purpose of independent central review.

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

Once progressive disease has been assessed by the investigator, an additional confirmatory assessment is recommended if there is any reason to doubt the first assessment (eg, scan quality, suspected pseudoprogression). This confirmatory assessment should occur approximately 4 to 8 weeks after the first investigator assessment of progressive disease. Study treatment of sitravatinib plus tislelizumab is permitted to continue after the initial investigator assessment of progressive disease, provided that the criteria for treatment beyond disease progression in Section 3.3 are met.

At the investigator's discretion, patients may continue their assigned treatment in Arm A after progressive disease has been confirmed by the investigator per RECIST v1.1. To continue treatment, the criteria for treatment beyond disease progression in Section 3.3 must be met.

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

Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow-up, dies, 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. That is, assessments should not be adjusted for delays in cycles.

7.6. Pharmacokinetic and Antidrug Antibody Testing

The PK concentrations will be determined using plasma (sitravatinib and its metabolite M10) or serum (tislelizumab) samples collected at specified time points within a reasonable variation window (see Appendix 1 and Appendix 2). Sitravatinib PK samples will be sparsely collected from patients who receive sitravatinib (Arms A and B) and used for determining the concentrations of both sitravatinib and M10. PK and ADA samples for tislelizumab will be sparsely collected from patients who receive tislelizumab (Arm A). An additional sitravatinib PK blood sample may be drawn before a daily sitravatinib dose at a clinic visit ≥ 1 week after a dose modification of sitravatinib, or as soon as possible after a SAE. If deemed necessary, samples may be used for characterization of other sitravatinib metabolites. The actual time of each sample collection will be recorded on the source document and eCRF.

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (see Appendix 1 and Appendix 2). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Rosenberg and Worobec 2004a; Rosenberg and Worobec 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program.

The following assessments will be performed at a bioanalysis laboratory:

- ADA assay: ADA serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay
- Tislelizumab PK assay: serum samples for tislelizumab will be assayed for concentrations with use of a validated immunoassay
- Sitravatinib PK assay: plasma samples for sitravatinib will be assayed for concentrations of sitravatinib with use of a validated LC-MS/MS method
- M10 PK assay: plasma samples for sitravatinib will be assayed for M10 concentrations using a validated method

Shipping, storage, and handling of samples for the assessment of sitravatinib PK, M10 PK, tislelizumab PK, and tislelizumab ADA assays will be managed through a central laboratory. Refer to the laboratory manual for instructions.

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.

7.7.1. Tissue Biomarkers

See Appendix 1 for the tissue biomarker sample collection schedule.

Separate written patient consent is required for optional tumor tissue collection.

Archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) need to be sent for central laboratory assessment of PD-L1 expression status during the screening period

and for retrospective analysis of other exploratory biomarkers related to response and resistance for all patients in a sponsor-designated central/test laboratory. Patients may be permitted to be enrolled on a case-by-case basis after discussion with the sponsor's medical monitor if < 15 unstained slides are provided. These exploratory biomarkers also include, but not be limited to, TMB/DNA mutation/MSI, GEP, and tumor-infiltrated immune cells.

A fresh biopsy is mandatory in the absence of archival tumor tissues. Acceptable fresh biopsy 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, lavage samples, and bone/bone marrow aspirates are not acceptable.

In addition to baseline tumor tissues, fresh biopsies from an accessible tumor site(s) at the time of confirmed progressive disease are recommended to explore response or resistance mechanisms. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy.

7.7.2. Blood Biomarkers

See Appendix 1 for the blood biomarker sample collection schedule.

Separate written patient consent is required for optional blood sample collections.

Approximately 10 ml of peripheral blood samples will be collected at baseline (pre-dose, on Day 1 of Cycle 1, required). For patients who have confirmed CR/PR and progressive disease as assessed by the investigator, additional blood samples (approximately 10 ml, optional) will be collected at each timepoint.

Blood-based biomarkers will consist of bTMB/ctDNA monitoring/MSI/DNA mutation profile. Analyses may examine the association between these biomarkers and clinically relevant outcomes including response, resistance, and prognosis.

7.8. Patient-Reported Outcomes

HRQoL measured via PRO endpoints of global health status (GHS), physical function, and fatigue; and dysphagia, reflux, eating, and pain measured via PRO instruments of the EORTC-QLQ-C30 (Appendix 12) and EORTC-QLQ-OES18 (Appendix 13), respectively. Patients will be asked to complete the questionnaires during on-study clinic visits according to the schedule before any clinical activities (including blood draws or imaging scans) are performed or any health-related discussion. The study clinic visit schedules are in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.9. Visit Windows

All visits must occur within ± 3 days of 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 before study treatment administration

unless otherwise noted. Laboratory results should also be reviewed before study treatment administration.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1).

A cycle is defined as every 21 days. For patients in Arms A and C, subsequent visits should be conducted according to a new 21-day schedule based on the date of the patient's last infusion of tislelizumab or ICC, respectively. For patients in Arm B and patients in Arm A who continue sitravatinib monotherapy, subsequent visits should be conducted according to the fixed 21-day schedule from Day 1 of Cycle 1 (Arm B) or the start of sitravatinib monotherapy (Arm A), no matter if sitravatinib is interrupted or not.

7.10. 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 PS; AE review; review of concomitant medications and procedures; radiographic assessments; physical examination of liver, spleen, and lymph nodes; review of 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 suspected disease progression, then diagnostic tests may be performed based on the investigator assessment, and the results of diagnostic tests and images 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 Study Treatment

8.1.1. Risks Associated With Sitravatinib

The most notable AEs for sitravatinib included diarrhoea, fatigue, palmar-plantar erythrodysesthesia syndrome, and hypertension. The majority of AEs were mild to moderate in severity and manageable. The guidelines for management of potential AEs specific to treatment with sitravatinib or agents in the same class of cancer treatment are presented in Section 8.7.

8.1.2. Risks Associated With Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.8.2.

An imAE may occur at any time during or after treatment. Often, the etiology of imAEs is not clear, and other causes should be ruled out. This may require diagnostic testing and consultation with a specialist. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 8.

8.1.3. Risks Associated With Investigator-Chosen Chemotherapy

Most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhoea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Most frequent Grade 3 or 4 AEs are neutropenia, anemia, leukopenia, infection, and thrombocytopenia. Treatment-related mortality will increase if patients have abnormal liver function. Severe hypersensitivity, including very rare fatal anaphylaxis, has also been reported in patients despite receiving dexamethasone premedication.
Common adverse reactions of irinotecan observed in single-agent therapy clinical studies are nausea, vomiting, abdominal pain, diarrhoea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia. Most frequent Grade 3 or 4 AEs are diarrhoea, nausea, vomiting, leukopenia, neutropenia, abdominal pain, and asthenia. Early and late forms of diarrhoea can occur. Early diarrhoea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhoea can be life-threatening and should be treated promptly with loperamide. Monitor patients with diarrhoea and give fluid and electrolytes as needed. If patients develop ileus, fever, or severe neutropenia, they should receive antibiotic therapy, per institution-specific guidelines.

If severe diarrhoea and myelosuppression occur, irinotecan should be interrupted and either discontinued or dose reduced for subsequent cycles to subsequent doses.

Patients should be tested locally for the UGT1A1*28 allele as outlined in the prescribing information or according to local guidelines to determine if modifications to the starting dose are needed.

Refer to the most recent, locally approved prescribing information for information on the risks associated with docetaxel and irinotecan.

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 and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-(L)1 inhibitors, were considered. Specifically, patients at risk for developing study-emergent active autoimmune diseases or who have a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before randomization are excluded from the study. Patients with contraindications for sitravatinib, tislelizumab, or ICC are also excluded from the study (see Section 4.2 for the full list of exclusion criteria). Patients must be eligible for ≥ 1 of the 2 chosen chemotherapy agents in the study.

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 (except as noted in Section 8.6.4). All enrolled patients will be evaluated clinically and with standard laboratory tests at intervals described in Appendix 1. Safety evaluations will consist of medical interviews, physical examinations, laboratory measurements (hematology, chemistry, etc), imaging, consultations (as needed), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, study treatment will only be administered after clinical laboratory results have been reviewed. Administration of study treatment at study sites 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).

Serum samples will be drawn for determination of ADAs to tislelizumab in patients randomly assigned to Arm A.

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 Section 8.7 for sitravatinib-specific AEs and Section 8.8 for tislelizumab-related AEs of special interest.

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 treatment or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, or duration, and/or an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study treatment administration, even though the condition 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 treatment 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 must be blinded or redacted on the copies of the medical records before submission to the sponsor.

8.3.2. Assessment of Severity

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

Toxicities that are not specified in NCI-CTCAE v5.0 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 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 (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the

regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study treatment 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 administration of study treatment should be considered and investigated. The investigator should consult the Tislelizumab Investigator's Brochure, Sitravatinib Investigator's Brochure, and prescribing information for individual chemotherapy drugs in making his/her assessment.

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

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

- Temporal relationship of the AE to the administration of study treatment or study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study treatment
- Biological plausibility
- An AE should be considered "related" to study treatment 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 treatment). 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. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide the sponsor with further information 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 consultations with other health care professionals.

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE page of eCRF. Clinically associated events can be reported as a single event (eg, simultaneous occurrence of anemia, thrombocytopenia, and leukopenia may be reported as myelosuppression). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L (or mmol/L) should be recorded as "hyperkalemia."

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

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose, meet any of the following criteria:

- Results in death
- Is life-threatening
  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it 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 department 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, diarrhoea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator or by the sponsor 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 Recording Period

After informed consent has been signed but before the administration of the study treatment, only SAEs should be reported.

After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until either 30 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be recorded until 90 days after the last dose of tislelizumab, regardless of initiation of new anticancer therapy. SAEs considered related to the study treatment that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 17. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 17: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs (not treatment related)	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Treatment-related SAEs	Signing of informed consent	Patient death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
Nonserious AEs other than those due to PD	First dose of study treatment	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study treatment	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

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

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 (≤ 24 hours after determination) to the sponsor or designee as described in Table 18.

Table 18: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial/follow-up report [a]	Documentation method	Reporting method
All SAEs	≤ 24 hours after first knowledge of the SAE	SAE report	Electronic submission of SAE form to portal [b]

Abbreviation: SAE, serious adverse event.

[a] Report follow-up information that is clinically relevant and pertains to the SAE, which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to each study drug. Follow-up information will also be reported as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.

[b] SAE reports should be submitted to the sponsor safety database electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

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 or 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 event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he or she must not 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 report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a 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 tislelizumab studies.

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

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Disease Progression

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

8.6.5. Deaths

Death is an outcome and not usually considered an event. When a patient dies, if the only information available is death and the cause of death is unknown, then the death is reported as an AE, eg, “death NOS.” In all other cases, death is captured as an outcome.

8.6.6. Pregnancies

If a female patient or the female partner of a male patient becomes pregnant while the patient is receiving investigational therapy or ≤ 180 days after the last dose of study treatment, a pregnancy report form must be submitted to the sponsor. The pregnancy report must follow the same prompt reporting guidelines described in Section 8.6.2.1. The outcome of the pregnancy, including any premature termination of the pregnancy must also be reported to the sponsor.

While pregnancy itself is not considered an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly or birth defect in a child born to a patient exposed to the study treatment should be recorded and reported as an SAE.

Patients who become pregnant must immediately discontinue treatment (see Section 3.4). For patients who are no longer pregnant, resumption of treatment may be discussed with the medical monitor.

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 treatment 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 RSI documents:

- Sitravatinib Investigator's Brochure
- Tislelizumab Investigator's Brochure
- Local prescribing information for docetaxel
- Local prescribing information for irinotecan

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Treatment with anti-PD-1 therapy can cause autoimmune disorders. All AEs considered by the investigator to be immune mediated (see Section 8.8.2) should be classified as imAEs and identified as such on the AE page of eCRF.

8.6.9. Recording Infusion-Related Reactions

The signs and symptoms of an infusion-related reaction should be recorded as the adverse terms for those individual signs and symptoms. Each individual sign and symptom of an infusion reaction should be recorded as a separate AE in the eCRF and identified as an infusion-related reaction as the event term, and graded as such with the respective sign or symptom. In assessing whether an AE is infusion related, note that the symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock.

8.7. Sitravatinib-Specific Adverse Events

8.7.1. Non-Hematological Toxicities of Sitravatinib

Patients experiencing symptomatic Grade 2 non-hematological sitravatinib-related AEs are recommended to have a dose reduction to the next lower dose level at the discretion of the investigator and patient, per the reduction schedule (Table 19). 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 elevations in the absence of other clinical evidence of pancreatitis, treatment may be resumed at the same dose at the investigator's discretion; if not, treatment may be resumed at a reduced dose as outlined in Table 19. Sitravatinib should be interrupted for any grade pancreatitis, and the patient should be managed according to the standard of care. After resolution of pancreatitis, sitravatinib resumption is at the discretion of the investigator; if pancreatitis is assessed as related to sitravatinib treatment and treatment is resumed, a dose reduction is recommended. Recurrence of the toxicity may be managed

similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

Table 19: Sitravatinib Dose Modifications – Non-Hematological Drug-Related Toxicities

Toxicity [a]	Treatment delay	Dose modification
Grade 1	May be implemented based on investigator's and patient's discretion	
Grade 2 - Asymptomatic	May be implemented based on investigator's and patient's discretion	
Grade 2 - Symptomatic	May be implemented based on investigator's and patient's discretion	Recommend dose reduction to next lower dose level
Grade 3 or 4 [b]	Hold until ≤ Grade 1 or return to baseline	Resume at ≥ 1 dose levels below that inducing the toxicity. Exceptions presented in footnote b.

[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 the symptoms or the clinical manifestations of pancreatitis.

8.7.2. 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 of sitravatinib at the discretion of the investigator should be implemented in the following cases:

- Grade 3 or 4 febrile neutropenia
- Grade 4 neutropenia persisting for ≥ 8 days
- Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding

8.7.3. Dose Modification Guidelines for Sitravatinib-Specific Adverse Events

Dose modification guidelines for increased BP are presented in Table 20.

For cases where transaminase increases are not likely to be immune-mediated, treatment management decisions should be made per the investigator discretion in consideration of clinical factors. Recommended treatment modifications for sitravatinib are provided in Table 21.

Guidance for the management of Hy's Law cases is presented in Section 8.7.3.1.

Table 20: 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 8.7.4	
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

Abbreviations: BP, blood pressure; Hg, mercury.

Table 21: Sitravatinib Dose Modification for Increased Hepatic Transaminases

Toxicity	Drug interruption	Dose modification
Grade 1	May be implemented based on investigator and patient discretion	
Grade 2	May be implemented based on investigator and patient discretion	Decrease by 1 dose level
Grade 3 or 4	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.

Table 22: Sitravatinib Dose Modification for Palmar-Plantar Erythrodysesthesia Syndrome

Toxicity[a]	Treatment Delay	Dose Modification
Grade 1	Not required	Not required
Grade 2	Based on investigator discretion	Dose reduction to the next lower level
Grade 3	Hold until ≤ Grade 1 or return to baseline	Resume at dose one or more levels below that inducing the toxicity

[a] For any event of Palmar-Plantar Erythrodysesthesia syndrome, regardless of severity, patients are to be counseled on measures to mitigate the effects of PPE, including avoidance of exposure of hands and feet to hot water, other sources of heat, activities that cause unnecessary force or friction (rubbing), chemicals (eg, cleaning products) and wearing well-ventilated shoes or clothing. Treatment may include topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams.

8.7.3.1. Management of Hy's Law Cases

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

8.7.4. Hypertension

Hypertension, including Grade 4 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 BP (see Table 20). In cases of Grade 3 hypertension with clinically significant increases in BP, temporary suspension of sitravatinib dosing is recommended until BP 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 20).

8.7.5. Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome has been reported as a DLT in the Phase 1 study of sitravatinib. Measures that can be taken to manage 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; avoiding 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 (see Table 22).

8.7.6. Diarrhoea

Diarrhoea has been reported with sitravatinib treatment, though the mechanism remains unclear, as with other small-molecule RTK inhibitors. Patients should be counseled that diarrhoea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhoea develops. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhoea is controlled. Investigators should also evaluate whether diarrhoea may be attributable to the imAE 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-associated diarrhoea. The diarrhoea observed with sitravatinib generally improves within several days of interrupting study medication, and close observation may help establish the most likely causality.

8.7.7. 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 interruption of treatment is recommended for patients developing clinically significant bleeding.

8.7.8. Thrombotic Events

Arterial and venous thrombotic events have been observed with sitravatinib and other inhibitors of the VEGFR pathway. The majority of thrombotic events observed with sitravatinib have been venous thrombotic events. The occurrence of thrombotic events with sitravatinib is being monitored for further characterization. Precautions should be taken in patients with recent, clinically significant thrombotic events, and treatment should be permanently discontinued in patients who develop clinically significant thromboembolic complications such as acute myocardial infarction or severe pulmonary embolism.

8.7.9. Thyroid Dysfunction Other Than Immune-Mediated

Hypothyroidism and increases in thyroid-stimulating hormones have been reported in patients taking sitravatinib. Thyroid stimulating hormone level should be monitored during treatment with sitravatinib. Patients diagnosed with hypothyroidism should be treated with thyroid replacement therapy and may continue treatment with sitravatinib at the investigator's discretion.

8.7.10. 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 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.

8.7.11. 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 grams of proteinuria/24 hours and may restart when protein levels decrease to less than 2 grams/24 hours. Patients who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

8.7.12. Gastrointestinal Perforation/Fistula

Gastrointestinal perforation has been reported with inhibitors of VEGFR as an infrequent event (Kim et al 2020). The risk of gastrointestinal perforation with sitravatinib has not been fully characterized. However, such events have been reported with sitravatinib, and a potential exists for such events to be observed with increased frequency in patients with ESCC.

Sitravatinib and tislelizumab should be interrupted if gastrointestinal perforation is suspected and discontinued when it is confirmed.

For more details on the detection and management of gastrointestinal perforation/fistula, please refer to Appendix 15.

8.8. Tislelizumab-Related Adverse Events of Special Interest

Infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE v5.0 criteria are outlined below.

8.8.1. Infusion-Related Reactions and Hypersensitivity Reactions

Patients should be closely monitored during and after study treatment administration for infusion-related reactions and hypersensitivity reactions. See Section 5.2.2 for the monitoring periods required. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

See Appendix 8 for management of infusion-related reactions and hypersensitivity reactions as well as treatment modifications.

8.8.2. Immune-Mediated Adverse Events

In this study, imAEs are of special interest. Potential imAEs are listed in Table 23 below. All AEs similar to those listed in the table should be evaluated in patients receiving tislelizumab to determine whether the AE is immune mediated. The investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic causes, toxins, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data (see Appendix 8). If alternative causes have been ruled out and the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy, and it is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

Recommendations for managing imAEs are detailed in Appendix 8.

Table 23: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin (mild)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; sweet syndrome
Skin (severe)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhoea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; 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

Body system affected	Events
Eye	episcleritis; conjunctivitis; iritis/uveitis
Musculoskeletal	arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis; Guillain-Barre syndrome; meningitis; meningoradiculitis; meningoencephalitis; neuropathy

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

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.2.2, patients will be randomly assigned to treatment arms using the IRT system for this study by permuted block stratified randomization.

9.1.2. Analysis Sets

The ITT Analysis Set includes all patients randomly assigned to a treatment arm. Patients' data will be analyzed according to their randomized treatment arm. This will be the primary analysis population for all efficacy analysis.

The Safety Analysis Set includes all patients who receive at least 1 dose of any component of study treatment; it will be the population for the safety analyses.

The Sitravatinib PK Analysis Set includes all patients who receive ≥ 1 dose of sitravatinib per the protocol and for whom any quantifiable postbaseline PK data for sitravatinib are available.

The M10 PK Analysis Set includes all patients who receive ≥ 1 dose of sitravatinib per the protocol and for whom any quantifiable postbaseline PK data for M10 are available.

The Tislelizumab PK Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab per the protocol and for whom any quantifiable postbaseline PK data for tislelizumab are available.

The ADA Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab and for whom both baseline and ≥ 1 postbaseline ADA result are available.

9.1.3. Patient Disposition

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

Important protocol deviations will be summarized and listed by each category.

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT Analysis Set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since locally advanced unresectable or metastatic disease diagnosis, etc. Categorical variables include sex, ECOG PS, race, TNM Classification of

Malignant Tumor staging, alcohol consumption, tobacco use, primary tumor location (ie, cervical, upper, middle, and lower), previous treatment, and metastatic site, etc.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report for this protocol. Prior medications will be defined as medications that stopped before the day of first dose of study treatment. Concomitant medications will be defined as medications that 1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or 2) started on or after the date of the first dose of study treatment up to 30 days after the patient's last dose (as of the EOT Visit). In addition, telephone contact with patients in Arm A should be conducted to assess imAEs and concomitant medications (ie, those associated with an imAE or any new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab regardless of whether the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

9.2.1. Primary Efficacy Analysis

9.2.1.1. Primary Estimand

The primary estimand is defined in Section 2.2.

9.2.1.2. Primary Analysis for Primary Estimand

The primary analysis of ORR as assessed by the investigator is descriptive and exploratory; no formal testing is designed.

The crude odds ratio and risk difference of ORR, along with their exact 95% CIs (Thomas 1971; Chan and Zhang 1999) will be calculated between Arms A and C. The ORR rate and its Clopper-Pearson 95% CI will be calculated for each arm.

The primary analysis for ORR as assessed by the investigator will be conducted ≥ 4 months (approximately 3 tumor assessments) after the enrollment of the last patient.

9.2.1.3. Handling of Missing Values Not Related to Intercurrent Event

Patients without any postbaseline response assessment (for any reason) will be considered nonresponders.

9.2.1.4. Sensitivity and Supplementary Analyses for Primary Endpoint/Estimand

Sensitivity analyses and supplementary analyses may be considered and will be detailed in the SAP.

9.2.2. Secondary Efficacy Analysis

DOR as assessed by the investigator is defined as the time from the first confirmed objective response until the first documented disease progression or death date, whichever occurred first. Only patients who have achieved objective responses will be included in the analysis of DOR. Kaplan-Meier methodology will be used to estimate median or other quartiles of DOR along with its 95% CI by using Brookmeyer and Crowley method for Arms A and C. Event-free rate at selected timepoints will be estimated with 95% CI estimated using Greenwood formula. No assessment of DOR between Arm A and C will be performed as it would be based on non-randomized subgroups.

OS is defined as the time from randomization date to death from any cause. For patients who are not reported as having died at the time of analysis, OS will be censored at the date the patients were last known to be alive. Kaplan-Meier methodology will be used to estimate median or other quartiles of OS along with its 95% CI by using Brookmeyer and Crowley method for Arms A and C. Kaplan-Meier curves will be constructed to provide a visual description of the OS distribution. Event-free rate at selected timepoints (eg, 6 months and 12 months) will be estimated with 95% CI estimated using Greenwood formula. The HR of OS between Arms A and C will be estimated using a stratified Cox regression model with PD-L1 expression status (assessed by the Ventana PD-L1 [SP263] assay: TAP score ≥ 10% versus TAP score < 10%) as strata. The 95% CI for the HR will be provided. Unstratified analysis will also be presented.

PFS assessed by the investigator is defined as the time from the randomization date to disease progression or death, whichever occurs first. The PFS censoring rule will follow US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA 2018). Similar methodology used to evaluate OS between Arms A and C will be applied to the analysis of PFS for the assessment between Arms A and C.

DCR as assessed by the investigator is defined as proportion of patients with PR or CR or a stable disease per RECIST v1.1. Similar methodology used to evaluate ORR between Arms A and C in the primary analysis will be applied to the analysis of DCR for the assessment between Arms A and C.

CBR as assessed by the investigator is defined as proportion of number of patients with PR or CR or a durable stable disease per RECIST v1.1. Similar methodology used to evaluate ORR between Arms A and C in the primary analysis will be applied to the analysis of CBR for the assessment between Arms A and C.

ORR, DCR, and CBR as assessed by the investigator with its Clopper-Pearson 95% CI will be calculated for Arms A and B. Kaplan-Meier methodology will be used to estimate median or other quartiles of DOR and PFS along with its 95% CI by using Brookmeyer and Crowley method for Arms A and B. Event-free rate at selected timepoints will be estimated with 95% CI estimated using Greenwood formula.

9.2.3. Exploratory Efficacy Analysis

OS between Arms A and B will be analyzed using the same methodology as OS between Arms A and C in the secondary efficacy analysis.

ORR assessed by the Independent Review Committee (IRC) and its Clopper Pearson 95% CI will be calculated for each arm.

9.3. Safety Analyses

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 (milligrams), 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

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

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class (SOC) and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 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 treatment. Treatment-related TEAEs include those events considered by the investigator to be related to a study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs ≥ Grade 3, infusion-related reactions, imAEs, 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, serum 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 provided. 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 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

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

9.3.5. Pulmonary Function Test

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

9.4. Pharmacokinetic Analysis

The sitravatinib, M10, and tislelizumab concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK assessments, including population PK analyses, may be conducted as appropriate, and the results of such analyses may be reported separately from the clinical study report.

9.5. Immunogenicity Analyses

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

9.6. Other Exploratory Analyses

Exploratory biomarkers may also be assessed. Analyses may examine the association between relevant biomarkers and clinically relevant outcomes including patient prognosis, response, and resistance.

HRQoL will be assessed via changes in PRO key endpoints' scores from baseline.

9.7. Sample Size Consideration

This exploratory study is not powered for the hypothesis testing between treatment arms but rather to obtain preliminary efficacy and safety data for sitravatinib in combination with tislelizumab and sitravatinib monotherapy for patients with locally advanced unresectable or metastatic ESCC that progressed on or after anti-PD-(L)1 antibody therapy. This study will enroll approximately 100 patients into 3 arms, with approximately 40, 20, and 40 patients in Arms A, B, and C, respectively. The efficacy of tislelizumab in combination with sitravatinib

versus chemotherapy will be demonstrated by descriptive analysis of ORR, PFS, OS, DCR, CBR, and DOR as assessed by the investigator in the assessment between Arms A and C. The contribution of adding tislelizumab to sitravatinib monotherapy will be demonstrated by similarly descriptive analysis in the assessment of Arms A and B. With a sample size of 40 patients in Arm A (sitravatinib plus tislelizumab), the binomial probabilities of detecting ≥ 1 TEAE with a frequency of 5% and 1% are approximately 0.87 and 0.33, respectively.

9.8. Interim Analyses

No formal interim analyses will be conducted; administrative interim analysis is allowed. Summaries of efficacy and safety data may be generated to inform subsequent clinical development planning or to address emergent safety concerns.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Review Committee

An IRC will be established to perform an independent review of all scheduled radiological images and relevant unscheduled images to determine response and disease progression based on RECIST v1.1. During the study, sites will submit specific radiographic image files to the centralized data review facility on an ongoing basis or at the sponsor's request. A sample-based tumor assessment by the IRC will be used for exploratory analyses in this study.

All decisions made during the performance of the study will be based on the local investigator's assessment of radiographic images, clinical status, and relevant examination of the patients. Detailed rules and guidelines for radiographic imaging and tumor assessments by the IRC are outlined separately in the Imaging Manual and IRC Charter.

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 can 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 (ICH E6), 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 the sponsor 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 the representatives of a regulatory agency or representatives of the sponsor with 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 the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements. Alternatively, the sponsor will 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 performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

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

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 acknowledging 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 the sponsor's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

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

All drug supplies and associated documentation will be reviewed periodically and verified by the study monitor over the course of the study. A patient diary will be provided to each patient in Arms A and B to record the sitravatinib dose taken each day. Any missed doses with explanations should be recorded in the diary. The diary should be returned to the site personnel for review and will be reviewed by the investigator or 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 guidelines for GCP (ICH E6) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the Definitions and Standards for Expedited Reporting (ICH E2A).

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

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and the 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

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

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

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 before participation in the study.

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

Patients must reconsent 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 investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH GCP Guideline (ICH E6), as implemented locally. Such laws may be more stringent than the requirements in this protocol.

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

- names or initials (full or partial);
- *full* dates of birth;
- contact information (such as phone numbers or home or email addresses);
- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or

- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

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

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

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

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

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

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

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

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

Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and

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

13.5. Financial Disclosure

Investigators (including any subinvestigators and coinvestigators) are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators, and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with the sponsor 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 Entry in the Electronic Case Report Form

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

14.1.2. Data Collection

Data required by the protocol will be entered into an EDC system.

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

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

14.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by the sponsor 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.

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

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA by the lowest-level term, Preferred Term, and primary SOC. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. Data Integrity and In-House Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC system. Although the study is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3. 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 ≥ 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 and query forms, IRB/IEC and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include 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 logs, etc.

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

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

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers away from 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 away from the site.

Subject to patient consent, or as otherwise allowed under applicable law, biological samples at the conclusion of this study may be retained for ≤ 10 years or as allowed by your IRB/IEC, whichever is shorter.

14.4. 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 that they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

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

14.5. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the 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 the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. 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 for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.6. 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
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

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

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

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

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

14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to the following:

- 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 IRB/IEC 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 14.5

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening [a]	Treatment cycles				EOT Visit [b]	Safety follow-up for imAEs [c]	Survival follow-up [d]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) days after last dose**	**60 (± 14) and 90 (± 14) days after last dose of tislelizumab**	**Every 3 months (± 14 days)**
Informed consent [a]	X							
Inclusion/exclusion criteria	X							
Randomization [e]	X							
Demographics/medical history/prior medications [f]	X							
Vital signs/ height and weight [g]	X	x	x	x	x	x		
Physical examination [h]	X	x			x	x		
ECOG PS	X	x			x	x		
12-lead/15-lead/18-lead ECG [i]	X	x			x	x		
Adverse events [j]	X	x	x [k]	x [k]	x	x	x	x
Concomitant medications [l]	X	x	x [k]	x [k]	x	x	x	
Hematology [m]	X	x	x	x	x	x		
Serum chemistry [m]	X	x	x	x	x	x		

Assessment	Screening [a]	Treatment cycles				EOT Visit [b]	Safety follow-up for imAEs [c]	Survival follow-up [d]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) days after last dose**	**60 (± 14) and 90 (± 14) days after last dose of tislelizumab**	**Every 3 months (± 14 days)**
Coagulation parameters [m]	X	x	As clinically indicated		x	x		
Urinalysis [m]	X	x	As clinically indicated		x	x		
Pregnancy test [n]	X	x			x	x		
Thyroid function [o]	X	Every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc)				x		
HBV/HCV tests [p]	X	As clinically indicated						
COVID-19 testing [q]	X							
Esophagography/ Endoscopy	As clinically indicated in patients with obstruction							
Echocardiogram (preferred) or MUGA [r]	X	Every 12 weeks (± 7 days)						
PK sampling for sitravatinib and M10 (Arms A and B) [s]		Predose: Day 1 of Cycles 1, 2, and 5 Postdose: Day 1 of Cycles 1, 2, and 5						
PK sampling for tislelizumab (Arm A) [t]		Predose: Day 1 of Cycles 1, 2, 5, 9, and 17 Postdose: Day 1 of Cycles 1 and 5				x [u]		

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Assessment	Screening [a]	Treatment cycles				EOT Visit [b]	Safety follow-up for imAEs [c]	Survival follow-up [d]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) days after last dose**	**60 (± 14) and 90 (± 14) days after last dose of tislelizumab**	**Every 3 months (± 14 days)**
ADA sampling for tislelizumab (Arm A) [u]		Predose: Day 1 of Cycles 1, 2, 5, 9, and 17				x [u]		
Blood biomarkers [v]		Predose: Day 1 of Cycle 1	At time of response and at time of confirmed PD					
Tumor assessment [w]	X	Every 6 weeks (± 7 days) from Cycle 1 Day 1, for the first 55 weeks, and every 9 weeks (± 7 days) thereafter				x		x
PRO [x]		X (Cycle 1 Day 1). Then every 6 weeks (± 7 days) for the first 55 weeks (at Weeks 7, 13, 19, 25, 31, 37, 43, 49, and 55), and every 9 weeks (± 7 days) thereafter until EOT						
Archival tumor tissue or fresh tumor tissue [y]	X	At time of confirmed PD						
Tislelizumab administration (Arm A) [z]		x			x			
Sitravatinib administration (Arms A and B) [aa]		Daily						
Docetaxel administration (Arm C) [bb]		x			x			

Assessment	Screening [a]	Treatment cycles				EOT Visit [b]	Safety follow-up for imAEs [c]	Survival follow-up [d]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) days after last dose**	**60 (± 14) and 90 (± 14) days after last dose of tislelizumab**	**Every 3 months (± 14 days)**
Irinotecan administration (Arm C) [bb]		x	X		x			
Patient diary [cc]		x	X	x	x	x		
Survival status								x

Abbreviations: ADA, antidrug antibodies; AE, adverse event; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; COVID-19, coronavirus disease; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-OES18, EORTC Quality of Life Questionnaire-Oesophageal Cancer Module; EOT, End-of-Treatment; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICC, investigator-chosen chemotherapy; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IRT, interactive response technology; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PD, progressive disease; PD-L1, programmed cell death protein ligand-1; PET, positron emission tomography; PK, pharmacokinetic(s); PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TSH, thyroid stimulating hormone; v, version.

[a] Written informed consent is required before performing any study-specific tests or procedures. Screening evaluations must be completed ≤ 28 days before randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days of randomization may be used for screening assessments rather than repeating such tests.

[b] Patient who permanently discontinue the study treatment (ie, sitravatinib and tislelizumab in Arm A, sitravatinib in Arm B, or ICC in Arm C) for any reason will be asked to return to the clinic for an EOT Visit, which is required to be conducted 30 (± 7) days after the last dose of study treatment (unless otherwise specified) or before the initiation of subsequent anticancer therapy, whichever occurs first. If routine laboratory tests (eg, hematology and serum chemistry) were completed ≤ 7 days before the EOT Visit, the tests do not need to be repeated. A tumor assessment is not required at the EOT Visit provided that ≤ 6 weeks have passed since the last assessment. Patients who discontinue study treatment before disease progression will need to undergo tumor assessment as outlined in Section 7.5. If the decision to end the study treatment is made ≥ 23 days after the last dose of any component of the study treatment, the EOT Visit may occur later, but no later than 7 days after the decision.

[c] Patients who discontinue tislelizumab in Arm A will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE) at 60 (± 14) and 90 (± 14) days after the last dose of tislelizumab, regardless of whether they start a

subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

[d] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed up for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

[e] Patients will be randomized into either the sitravatinib plus tislelizumab (Arm A), or sitravatinib monotherapy (Arm B), or ICC (docetaxel or irinotecan, Arm C) via IRT. All patients are required to receive the study treatment ≤ 2 business days after randomization.

[f] Includes age or year of birth, sex, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history.

[g] Vital signs include temperature, pulse rate, respiratory rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected while the patient is in a seated position after resting for 10 minutes. For tislelizumab treatment, the patient's vital signs must be recorded ≤ 60 minutes before, during, and ≤ 30 minutes after the first infusion of tislelizumab. For subsequent infusions of tislelizumab, vital signs will be collected ≤ 60 minutes before infusion and, if clinically indicated, during and/or ≤ 30 minutes after the infusion. Vital signs should also be recorded before the administration of sitravatinib; recorded values may be used for pre-tislelizumab assessment if vital signs are collected ≤ 60 minutes before tislelizumab infusion. Patients randomized to receive ICC (Arm C) will follow the same procedure as receiving tislelizumab infusion. Patients who receive ICC will also be monitored for anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension. Patients who receive irinotecan will be monitor for diarrhoea and provided fluid and electrolytes supplementation as clinically indicated.
Height should only be measured and recorded during screening. Weight will be measured before study treatment administration in every cycle.

[h] A complete physical examination is required at Screening Visit while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.4.2). For patients who receive tislelizumab, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, an appropriate specialist will be consulted for further management guidance.

[i] The ECG recordings will be obtained during screening, at the beginning of each cycle, the EOT Visit, and as clinically indicated at other time points. Patients should be resting for ≥ 10 minutes before each ECG collection. When coinciding with blood sample collection at the same timepoint, ECG assessment should be performed either before blood sample collection or ≥ 30 minutes after the blood sample collection. If a patient has QTcF interval > 450 msec for males or > 470 msec for females on an initial ECG, 3 consecutive ECGs will be performed several minutes apart to determine the mean QTcF interval. If an ECG has been performed ≤ 3 days before the first study treatment or before the EOT Visit, the test does not need to be repeated on Cycle 1 Day 1 or the EOT Visit, respectively.

[j] The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but before the first administration of study treatment, only SAEs should be recorded. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, except AEs clearly due to disease progression (see Section 8.6.4), will be reported until either 30 days after last dose of study treatment or initiation of new anticancer therapy, whichever occurs first (see Section 8.6.1). The imAEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. SAEs considered related to the study treatment that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

[k] Review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15.

[l] All medications used by the patient ≤ 30 days before the first dose of study treatment (Section 7.1.3) and ≤ 30 days after the last dose of study treatment (Section 9.1.5) should be recorded.

[m] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3. If the laboratory tests at screening are not performed ≤ 7 days before the first dose of study treatment, these tests should be repeated

and reviewed before administration of study treatment. Hematology and serum chemistry (including liver function tests, data collected as specified in Appendix 3) will be performed weekly for the first 3 cycles, then at the beginning of each subsequent cycle and the EOT Visit. If CK−MB fractionation is not available, assess troponin I and/or troponin T instead. Coagulation test and urinalysis will be performed at screening, then at the beginning of each treatment cycle, at the EOT Visit, and as clinically indicated. Urine protein by dipstick must be < 2+ within 7 days before the first study treatment. Patients that have ≥ 2+ proteinuria on urine dipstick at baseline should undergo a 24-hour urine collection and must demonstrate < 1g of protein in 24 hours. After Cycle 1, the above-mentioned tests are to be performed and the results are to be reviewed ≤ 48 hours before study treatment administration. For patients in Arm C (treated with irinotecan), these tests should be performed every CXD8 from C4D8 as clinically indicated according to investigator decision.

[n] Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented with a negative result ≤ 7 days before randomization. Urine pregnancy tests will be performed at each visit before dosing, and at the EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[o] Analysis of FT3, FT4, and TSH will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at screening, every 3 cycles from Cycle 1 Day 1 (ie, Day 1 of Cycles 4, 7, 10, etc), and at the EOT Visit.

[p] Testing will be performed by a central laboratory or the local laboratory at screening and will consist of HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). HBV DNA or HCV RNA will be assessed in patients who test positive for HBsAg or HCV antibody, respectively. Patients who have detectable HBV DNA or HCV RNA at screening will undergo the respective viral load test every 4 cycles (ie, Day 1 of Cycles 5, 9, 13, etc).

[q] COVID-19 testing should be performed by a certified local laboratory, which may be located at the study site. Testing may alternatively be performed at a certified offsite laboratory, clinic, or hospital, with the agreement of the investigator.

[r] Evaluations of cardiac function will be performed at screening and every 12 weeks (± 7 days) thereafter. Evaluations by echocardiogram is preferred but evaluations by MUGA scan are acceptable, if necessary. The method used to assess cardiac function at screening is required to be used throughout the study.

[s] PK samples for sitravatinib and M10 will be collected from patients in Arms A and B. PK samples for tislelizumab will be collected from patients in Arm A. Procedures for collection of PK samples are described in the laboratory manual. See Appendix 2 for schedule of PK sampling for sitravatinib, M10, and tislelizumab.

[t] Blood samples for PK and ADA sampling of tislelizumab should be obtained 30 ± 7 days after the last dose of tislelizumab.

[u] All blood samples used to test for anti-tislelizumab antibodies should be drawn from patients in Arm A at the same time as blood collection for predose PK samples. See Appendix 2 for schedule of ADA sampling. These tests are required when allowed by local regulations/IRBs/IECs.

[v] Blood samples for biomarker analysis (approximately 10 mL for each timepoint) will be collected for all patients at baseline (predose on Cycle 1 Day 1, required), at the time of first tumor response (predose on Day 1 of the following cycle, optional), and at the time of progressive disease (optional). Collection at all 3 timepoints is preferred. Separate written patient consent is required for optional blood sample collections. Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual. See Section 7.7 for additional details.

[w] Radiological images captured as standard of care before obtaining written informed consent and ≤ 28 days before randomization may be used rather than repeating tests. MRI scan of brain at baseline is required for patients who are suspected to have CNS metastases. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening is required to be used throughout the study (eg, the same imaging protocol for CT or MRI). Bone scan or PET is required if clinically indicated. During the study treatment period, evaluations of tumor response by the investigator per RECIST v1.1 will be performed every 6 weeks (± 7 days) from Day 1 of Cycle 1 for the first 55 weeks and then every 9 weeks (± 7 days) thereafter. After the first documentation of response (CR or PR), confirmation of tumor response should occur ≥ 4 weeks after the first response or at the next scheduled assessment timepoint.
Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. That is, assessments should not be adjusted for possible delays in cycles. Tumor assessment should continue until study treatment discontinuation. Patients who discontinue study

treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow-up, or dies, or until the study terminates, whichever occurs first. See also Section 7.5.

[x] EORTC-QLQ-C30 and EORTC QLQ-OES18 are to be completed at baseline (Cycle 1 Day 1), every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 55 weeks (at Weeks 7, 13, 19, 25, 31, 37, 43, 49, and 55), and then at 9-week intervals (± 7 days) thereafter until EOT. If the disease evaluation does not coincide with a clinic visit for a patient, the assessment of PRO should be completed at the clinic visit closest to the disease evaluation for that patient. Questionnaires will be completed before any clinical activities or health-related discussions during on-study site visits.

[y] Archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) must be sent to the central laboratory for PD-L1 expression status detection during the screening period and to a sponsor designated central/test laboratory for retrospective analysis of exploratory biomarkers. If archival tumor tissues are not available during the screening period, a fresh tumor biopsy is mandatory. Optional fresh biopsies in patients who have confirmed progressive disease will be collected from accessible tumor sites. Separate written patient consent is required for optional tumor tissue collection. See Section 7.7 for additional details.

[z] For patients randomized to Arm A, tislelizumab will be administered by intravenous infusion once every 3 weeks beginning with the first dose on Day 1 of Cycle 1. The delivery period of the initial infusion (Day 1 of Cycle 1) will be ≥ 60 minutes. If this is well tolerated, the delivery period of subsequent infusions can be shortened to ≥ 30 minutes. Patients must be monitored for ≥ 60 minutes after the infusion is complete on Day 1 of Cycle 1. For Cycle 2 onward, patients must be monitored for ≥ 30 minutes after the infusion.
Note: Tislelizumab must not be concurrently infused with any other drug.

[aa] For patients randomized to Arms A and B, sitravatinib capsules should be taken with a low-fat meal (Appendix 14) or on empty stomach (defined as ≥ 2-hours fast before each dose and no food for ≥ 1 hour after each dose). Taking the sitravatinib capsules in the morning is preferred.

[bb] Patients may receive premedications before the initiation of chemotherapy according to the routine standard of care. Docetaxel should be administered at a dose of 75 mg/m^2 intravenously over 60 minutes on Day 1 of each 21-day cycle (once every 3 weeks). Doses lower than 75 mg/m^2 are allowed if considered appropriate for any given patient. If irinotecan is chosen, it should be administered at a dose of 125 mg/m^2 intravenously over 90 minutes on Days 1 and 8 of each 21-day cycle (once every 3 weeks). For all treatment in subsequent cycles, the treatment interval should be 21 to 24 days (3-day window). If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc.), the subsequent dosing visit should be scheduled as clinically appropriate.

[cc] A patient diary will be provided to each patient in the Arms A and B to record the sitravatinib dose taken each day. Any missed doses with explanations should be recorded in the diary. The diary should be returned to the site personnel for review and will be reviewed by the investigator or/study personnel on a regular basis.

APPENDIX 2. SCHEDULE OF ASSESSMENT OF PHARMACOKINETIC AND ANTIDRUG ANTIBODY

Sitravatinib and M10 PK (For Patients in Arms A and B):

	Day 1 of Cycles 1, 2, and 5	
Collection time and allowable window [a, b]	Predose of sitravatinib (≤ 60 minutes before administration)	Postdose of sitravatinib (6 hours [± 20 minutes] after administration)
Sparse PK sampling	X	X

Abbreviations: IEC, Independent Ethics Committee; IRB, Institutional Review Board; PK, pharmacokinetic(s).

[a] The PK samples for sitravatinib and M10 will only be collected from the patients who received sitravatinib treatment (Arms A and B).

[b] An additional PK blood sample may be drawn before a daily sitravatinib dose (trough sample) at any of the following events: 1) as soon as an occurrence of a serious adverse event, 2) at a clinic visit that is conducted ≥ 1 week following after a dose modification of sitravatinib. These tests are required when it is allowed by local regulations/IRBs/IECs.

Tislelizumab PK and ADA (Only for Patients in Arm A)

	Day 1 of Cycles 1, 2, 5, 9, and 17 (if achieved)		EOT Visit
Collection time and allowable window [a]	Predose of tislelizumab (≤ 60 minutes before the start of infusion)	Postdose of tislelizumab (≤ 30 minutes after the end of infusion)	30 ± 7 days after last dose of tislelizumab
Sparse PK sampling [b]	X	X (Day 1 of Cycles 1 and 5 only)	X
ADA sampling [c]	X		X

Abbreviations: ADA, antidrug antibodies; EOT, End-of-Treatment; imAE, immune-mediated adverse event; PK, pharmacokinetic(s).

[a] The PK and ADA samples for tislelizumab will only be collected from the patients who received tislelizumab treatment (Arm A).

[b] Should a patient present with any ≥ Grade 3 imAE, an additional blood sample for PK may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.

[c] All blood samples used to test for anti-tislelizumab antibodies should be drawn at the same time as blood collection for predose PK samples.

APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Serum chemistry	Hematology	Coagulation	Urinalysis	Thyroid function
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium [a] Creatinine Glucose Lactate dehydrogenase Total protein Creatine kinase [b] CK-MB [b]	Hematocrit Hemoglobin Platelet counts WBC count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Glucose Protein Blood 24-hour protein [c]	Free triiodothyronine Free thyroxine Thyroid stimulating hormone

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; WBC, white blood cell.

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

[b] All patients will have creatine kinase and CK-MB testing at screening, and to be repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the End-of-Treatment Visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[c] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein.

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP 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

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

APPENDIX 5. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES VERSION 1.1

Source: Eisenhauer et al 2009.

Definitions

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

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

Measurable Disease

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

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical exam (when superficial)

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.

Nonmeasurable Disease

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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.
- The concept of cystic metastases also applies to metastatic lesions with a necrotic component. Hence, measurable lesions with a necrotic component may be selected as target lesions. However, if non-necrotic lesions are present, these are preferred for selection as target lesions.

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. A maximum of 2 measurable lymph nodes, inclusive of all lymphatic chains involved, may be chosen as target lesions (ie, the lymphatic system is considered one organ). Target lesions should be selected based on size (lesions with the longest diameter), how representative they are of all involved organs, and whether they 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 perpendicular dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal, but the axial plane is recommended for measurements). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm by 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

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

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and

these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). If a nontarget lymph node normalizes (< 10 mm in short axis) after baseline, the respective evaluation should be "absent."

Guidelines for Evaluation of Measurable Disease

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

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

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: Target lesion measurements should be performed in the axial plane. 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). If there is a change from CT to MRI or the reverse, target lesions should continue to be measured provided the imaging parameters do not render measurements incomparable.
- 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 studies where recurrence after complete response (CR) or surgical resection is an endpoint.

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

Response Criteria

Evaluation of Target Lesions

- CR: Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- 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: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Both PR and PD: If the change in sum of diameters is consistent with both PR and PD at a tumor assessment visit, PD should take precedence.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target

nodal lesions recorded in a separate section where, to qualify for CR, each node must achieve a short axis <10 mm. For PR, stable disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

Evaluation of Nontarget Lesions

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

- CR: Disappearance of all nontarget lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of 1 or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of stable disease or PR in target disease, the overall tumor burden has increased sufficiently to

merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of stable disease or PR of target disease will therefore be extremely rare.

- When the patient has only nonmeasurable disease: This circumstance arises in some phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or it may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; 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 study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered evidence of PD even if he or 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 fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response
- It is assumed that at each protocol specified timepoint, a response assessment occurs. The following table provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline:

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

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

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

Nontarget Lesions	New Lesions	Overall Response
Any	Yes	PD

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

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study treatment until the end of treatment considering 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 nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized studies 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 studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

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

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

In studies where confirmation of response is required, repeated "not evaluable (NE)" timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression

even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

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

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

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

Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized studies 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 studies. However, in all other circumstances, ie, in randomized studies (Phase 2 or 3) or studies 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 study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

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.

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

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

Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Koyangai-Harada disease

APPENDIX 7. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

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

APPENDIX 8. INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS AND IMMUNE-MEDIATED ADVERSE EVENTS: EVALUATION AND MANAGEMENT

Management of Infusion-Related Reactions and Hypersensitivity Reactions

Management and treatment modifications for symptoms of infusion-related reactions associated with study treatment administration are provided in the table below.

If a hypersensitivity reaction occurs, the patient must be managed according to the best available medical practice, as described in the 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.

Treatment Modifications for Symptoms of Infusion-Related or Hypersensitivity Reactions Associated with Study Treatment Administration

NCI-CTCAE grade	Treatment modification for study treatment
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening signs or symptoms. Medical management as needed. Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, corticosteroids, and/or intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Closely monitor for worsening signs or symptoms. Appropriate 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 observation or clinical management.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study 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 treatment. Hospitalization is recommended.

Abbreviation: NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event.

If the infusion rate of study treatment has been decreased by 50% or suspended due to an infusion-related reaction, this decreased rate must be maintained for all subsequent infusions and be administered 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.

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

National Cancer Institute-Common Terminology Criteria for Adverse Event (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), an antipyretic (eg, paracetamol), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In subsequent cycles, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine) and an antipyretic (eg, paracetamol), and should be closely monitored for clinical signs and symptoms of an infusion reaction.

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

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

The patient will be administered epinephrine injection and dexamethasone infusion if severe hypersensitivity reaction is observed. The patient should be closely monitored, and ICU should be alerted for possible transfer as indicated.

Evaluation of Immune-Mediated Adverse Events

The recommendations below for the diagnosis and management of any immune-mediated adverse event (imAE) are intended as 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.

The recommendations for diagnostic evaluation and management of imAEs are based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017; Brahmer et al 2018). For any adverse events (AEs) not included in the tables below, refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

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

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

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

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

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

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

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

Management of Immune-Mediated Adverse Events

Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required. Immune-mediated AEs should improve promptly after introduction of immunosuppressive

therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.

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

For some Grade 3 toxicities that resolve quickly, rechallenge with study treatment may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.

Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF]). Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Management of Immune-Mediated Adverse Events

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

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

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

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

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
Colitis/ diarrhoea	**1** Mild symptoms: ≤ 4 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: ≥ 7 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,	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	4 Life-threatening symptoms	vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	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.
	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.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	2 ALT or AST >3 x to 5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST > 5 x to 20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment.
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. • If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study treatment, 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 treatment and resolved/improved to baseline grade: Restart study treatment if tapered to < 10 mg prednisolone.

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

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	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.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	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 improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.
Myocarditis [a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of	
	3 Severe symptoms with mild exertion		

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study treatment management
	4 Life-threatening	cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune related, permanently discontinue study treatment in patients with moderate or severe symptoms.

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

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

APPENDIX 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION EQUATION

In adults, the most widely used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2009) and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) 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.

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

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

where:

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

κ is 0.7 for females and 0.9 for males,

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

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

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

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

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

APPENDIX 10. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control (Clinical Trials Facilitation and Coordination Group [CTFG] 2020). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable

Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.

- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.

  - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility.

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)

Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study treatment, 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 used in combination with one of the highly effective forms of birth control listed above.

Definitions of "Women of Childbearing Potential" AND "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 (FSH) concentration > 30 mIU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

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

Adapted from Clinical Trials Facilitation and Coordination Group [CTFG] 2020.

APPENDIX 11. MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING TREATMENT WITH STUDY DRUGS

Examples of Drugs With a Known Risk of Torsades de Pointes

Aclarubicin (only on non-US market)	Disopyramide	lbutilide	Procainamide
Amiodarone	Dofetilide	Levofloxacin	Propofol
Anagrelide	Domperidone (Only on Non US Market)	Levomepromazine (methotrimeprazine) (only on non-US market)	Quinidine
Arsenic trioxide	Donepezil	Levomethadyl acetate (removed from US market)	Roxithromycin (only on non-US market)
Astemizole (removed from US market)	Dronedarone	Levosulpiride (only on non-US market)	Sertindole (only on non-US market)
Azithromycin	Droperidol	Meglumine antimoniate (only on non-US market)	Sevoflurane
Bepridil	Erythromycin	Mesoridazine (removed from US market)	Sotalol
Cesium Chloride	Escitalopram	Methadone	Sparfloxacin (removed from US market)
Chloroquine	Flecainide	Mobocertinib	Sulpiride (only on non-US market)
Chlorpromazine	Fluconazole	Moxifloxacin	Sultopride (only on non-US market)
Chlorprothixene (only on non-US market)	Gatifloxacin (removed from US market)	Nifekalant (only on non-US market)	Terfenadine (removed from US market)
Cilostazol	Grepafloxacin (removed from US market)	Ondansetron	Terlipressin (only on non-US market)
Ciprofloxacin	Halofantrine (only on non-US market)	Oxaliplatin	Terodiline (only on non-US market)
Cisapride (removed from US market)	Haloperidol	Papaverine HCI (intra coronary)	Thioridazine
Citalopram	Hydroquinidine (dihydroquinidine) (only on non-US market)	Pentamidine	Vandetanib

Clarithromycin	Hydroxychloroquine	Pimozide	
Cocaine	Ibogaine (only on non-US market)	Probucol (removed from US market)	

Adapted from CredibleMeds 2022; for the most current information, access the website: www.CredibleMeds.org.

Examples of Sensitive Substrates and Substrates With Narrow Therapeutic Index for P-gp and BCRP Transporters

Transporter	Substrates
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, and topotecan
BCRP	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan

Abbreviations: BCRP, breast cancer resistance protein; P-gp, P-glycoprotein.

Examples of Sensitive Substrates and Substrates With Narrow Therapeutic Index for the Indicated Cytochrome P450 Enzymes

Enzyme	Substrates
CYP2C8	Repaglinide
CYP2C9	Celecoxib
CYP2C19	S-mephenytoin and omeprazole
CYP2D6	Atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, and 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, and vardenafil

Abbreviation: CYP, cytochrome P450.

Examples of Inhibitors of Cytochrome P450 3A4 or P-gp

Strong CYP3A4 inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, tipranavir/ritonavir, troleandomycin, and voriconazole
Moderate CYP3A4 inhibitors	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil
P-gp inhibitors	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, and verapamil

Abbreviations: CYP, cytochrome P450; P-gp, P-glycoprotein.

APPENDIX 12. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE CORE CANCER (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊⌋⌊⌋⌊⌋
Your birthdate (Day, Month, Year): ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋
Today's date (Day, Month, Year): 31 ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 13. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE-OESOPHAGUS CANCER MODULE (EORTC QLQ-OES18)

ENGLISH

EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Could you eat solid food?	1	2	3	4
32.	Could you eat liquidised or soft food?	1	2	3	4
33.	Could you drink liquids?	1	2	3	4
34.	Have you had trouble with swallowing your saliva?	1	2	3	4
35.	Have you choked when swallowing?	1	2	3	4
36.	Have you had trouble enjoying your meals?	1	2	3	4
37.	Have you felt full up too quickly?	1	2	3	4
38.	Have you had trouble with eating?	1	2	3	4
39.	Have you had trouble with eating in front of other people?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Did food and drink taste different from usual?	1	2	3	4
42	Have you had trouble with coughing?	1	2	3	4
43.	Have you had trouble with talking?	1	2	3	4
44.	Have you had acid indigestion or heartburn?	1	2	3	4
45.	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46.	Have you had pain when you eat?	1	2	3	4
47.	Have you had pain in your chest?	1	2	3	4
48.	Have you had pain in your stomach?	1	2	3	4

APPENDIX 14. DEFINITION OF HIGH-FAT AND LOW-FAT MEALS

The definitions of high-fat and low-fat meals:

Meal Type	Total kcal	Fat		
		kcal	Grams	Percent
High-fat	800~1000	500~600	55~65	≥ 50%
Low-fat	400~500	100~125	11~14	25%

Composition of a high-fat meal:

Total Calories (kcal)	800~1000
Calories from Protein (kcal)	150
Calories from Carbohydrates (kcal)	250
Calories from Fat (kcal)	500~600
Percent Calories from Fat (%)	≥ 50%
An example of a High-Fat Breakfast 1*	• Two fried eggs (approximately 100 g) • 100 g of deep-fried dough stick • 100 g of ham sausage • 240 mL of whole milk
An example of a High-Fat Breakfast 2*	• Two eggs fried in butter (eggs 100 g, butter 15 g) • Two strips of bacon (50 g) • Two slices of toast with butter (butter 20 g, toast 30 g × 2) • 113 g of hash brown potatoes • 240 mL of whole milk

*50% of calories are derived from fat. Substitutions can be made to this meal if the content, volume, and viscosity are maintained.

Composition of a low-fat meal:

Total Calories (kcal)	400~500
Calories from Fat (kcal)	100~125
Fat (g)	11~14
Percent Calories from Fat (%)	25%
An example of a Low-Fat Breakfast 1*	• One boiled egg (approximately 50 g) • 100 g of steamed buns • 30 g of oatmeal or cornflakes

	• 240 mL of skim milk
An example of a Low-Fat Breakfast 2*	• 240 mL of milk (1% fat) • One boiled egg (approximately 50 g) • 30 g of oatmeal or cornflakes (can be made with 240 mL of 1% fat milk)

*25% of calories are derived from fat. Substitutions can be made to this meal if the content, volume, and viscosity are maintained.

Sources:

a. US FDA. Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs−Clinical Pharmacology Considerations, 2022.
b. CDE. Technical Guidelines for Food Impact Research in the Process of New Drug Development, 2021.

APPENDIX 15. THE DETECTION AND MANAGEMENT OF GASTROINTESTINAL PERFORATION/FISTULA

It is preferred to use a combination of thoracic imaging studies and endoscopy (both flexible bronchoscopy and upper endoscopy, if possible) for diagnosis (Kim et al 2020). Esophagography is performed preferentially with barium, given its favorable physiological profile compared to gastrograffin. The contrast-enhanced esophagogram demonstrates the defect in approximately 70% of patients with trachea-esophageal fistula (TOF).

The management of TOF requires a prompt multidisciplinary approach, including interventional pulmonology, gastroenterology, and thoracic surgery (Kim et al 2020).The general principle of preoperative management is to treat complications arising from the anatomic deformity, while addressing modifiable risk factors of fistula formation. Acid-suppressive therapy with H2-receptor antagonists or proton-pump inhibitors should be used to decrease the acidity and the volume of gastric acid. Patient positioning with head of bed elevated to ≥ 45°, strict limitation of oral intake, and frequent oral suctioning are used in conjunction with pharmacological therapy. Operative management could be considered if possible. Minimally invasive endoscopic procedures including stenting are typically preferred in patients with malignant TOF to improve nutritional status while preventing further complications. The main endoscopic technique to manage TOF is esophageal and/or airway stenting with the goal to seal the fistula and prevent the spillover to the respiratory tract.