CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	**A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TISLELIZUMAB IN COMBINATION WITH FRUQUINTINIB IN PATIENTS WITH SELECTED SOLID TUMORS**
Protocol Number:	BGB-A317-fruquintinib-201
Phase:	2
Investigational Product(s):	Tislelizumab (BGB-A317), fruquintinib
Proposed Indication(s):	Advanced Solid Tumors
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, California 94403 USA
Sponsor Medical Monitor:	[redacted], MD Telephone: [redacted] Email: [redacted]
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FINAL PROTOCOL APPROVAL SHEET

A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TISLELIZUMAB IN COMBINATION WITH FRUQUINTINIB IN PATIENTS WITH SELECTED SOLID TUMORS

BeiGene, Ltd., Approval:

[redacted] MD
Sponsor Medical Monitor

[redacted]
Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TISLELIZUMAB IN COMBINATION WITH FRUQUINTINIB IN PATIENTS WITH SELECTED SOLID TUMORS

Protocol Identifier: BGB-A317-fruquintinib-201

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Products: tislelizumab (BGB-A317); fruquintinib
Title of Study: A multicenter, open-label Phase 2 study to evaluate the efficacy and safety of tislelizumab in combination with fruquintinib in patients with selected solid tumors
Protocol Identifier: BGB-A317-fruquintinib-201
Phase of Development: 2
Number of Patients: Approximately 90 patients
Study Centers: Approximately 8 centers

Study Objectives:

Part 1

Primary:

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

Part 2

Primary:

- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1

Secondary:

- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the progression-free survival (PFS) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the disease control rate (DCR) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the clinical benefit rate (CBR) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the duration of response (DOR) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib in patients with selected solid tumors as measured by overall survival (OS)
- To assess the safety of tislelizumab in combination with fruquintinib

Exploratory:

- To characterize the immunogenicity of tislelizumab and its time-pairing pharmacokinetic (PK) when given in combination with fruquintinib
- To assess the PK of fruquintinib when given in combination with tislelizumab
- To explore potential biomarkers that may correlate with clinical responses/resistance to tislelizumab in combination with fruquintinib

Study Endpoints:

Part 1

Primary:

- Safety and tolerability will be assessed throughout the study by monitoring adverse events (AEs) characterized by type, frequency, severity per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, timing, seriousness, and relationship to study drug(s); and other safety assessments
- The RP2D of fruquintinib in combination with tislelizumab

Part 2

Primary:

- ORR – defined as the proportion of patients whose best overall response is complete response (CR) or partial response (PR) as assessed by investigator per RECIST v1.1

Secondary:

- PFS – defined as the time from the date of first dose to the date of the first determination of an objectively documented tumor progression as assessed by investigator per RECIST v1.1, or death, whichever occurs first
- DCR – defined as the proportion of patients whose best overall response is CR, PR, or stable disease (SD) as assessed by investigator per RECIST v1.1
- CBR – defined as the proportion of patients whose best overall response is CR, PR, or durable SD as assessed by investigator per RECIST v1.1
- DOR – defined as the time from the first occurrence of documented objective response to the time of progression as assessed by investigator per RECIST v1.1 or death from any cause, whichever occurs first
- OS – defined as the time from the date of first dose to the date of death due to any cause
- AEs characterized by type, frequency, severity per NCI-CTCAE v5.0, timing, seriousness, and relationship to study drug(s); and other safety assessments

Exploratory:

- Incidence of anti-tislelizumab antibodies (ADA) and its time-paring serum concentrations of tislelizumab
- Plasma concentrations and derived PK parameters of fruquintinib as data permit

- Potential biomarkers including but not limited to programmed cell death protein ligand-1 (PD-L1) expression, tumor mutational burden (TMB) and DNA mutation/blood tumor mutational burden (bTMB) and DNA mutation, gene expression profile (GEP) in the gastric cancer (GC), microsatellite stable (MSS) colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) cohorts, Epstein-Barr virus (EBV) in the GC cohort, MSS/microsatellite instable (MSI) status in the GC cohort, and the association of biomarkers with disease status, response/resistance to tislelizumab in combination with fruquintinib

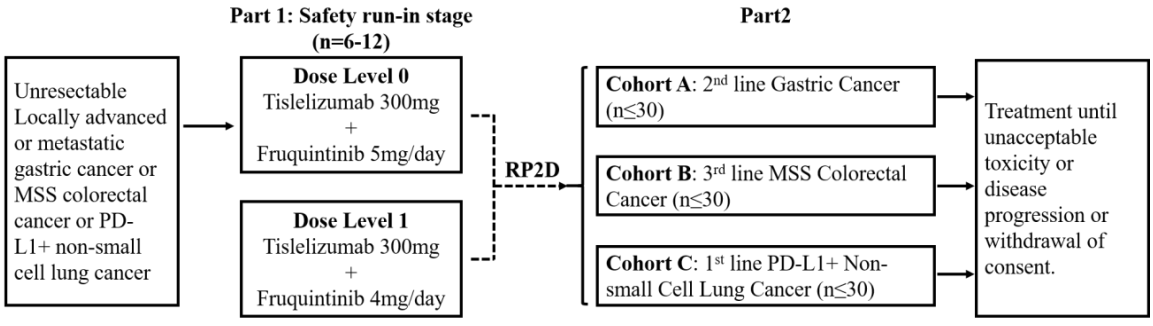
Study Design:

This is an open label, multicenter, Phase 2 study designed to assess the efficacy and safety of tislelizumab in combination with fruquintinib in patients with advanced or metastatic, unresectable GC, MSS CRC and PD-L1 positive (defined as TC≥1% by SP263 IHC) NSCLC. The study will be conducted in 2 parts.

Part 1 of the study will be the safety run-in stage during which the first 6 patients will be enrolled and assessed for dose-limiting toxicities (DLTs) during the 28-day DLT observation period. Study drug administration will begin at the full dose of fruquintinib (5 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) in combination with tislelizumab (300 mg once every 4 weeks). A lower dose level of fruquintinib (4 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) will be explored as necessary depending on observed toxicity. The determination of DLTs will be made by the investigator and sponsor after safety data has been reviewed. Only DLTs during the first 28 days of treatment will be assessed. The Safety Monitoring Committee (SMC) will evaluate the safety and tolerability of the combination therapy and will review the safety information including, but not limited to DLTs, all treatment-emergent adverse events (TEAEs), and laboratory abnormalities when the first 6 DLT-evaluable patients have completed their first 28 days of treatment or when ≥ 2 DLTs at the tested dose level occur. The SMC will make recommendations on safety management, including resumption of enrollment, de-escalation of fruquintinib to one lower dose level, or termination of enrollment. The final decision will be made by sponsor. Once sponsor has determined that the combination therapy could proceed, the current dose will be confirmed as the RP2D and enrollment for Part 2 will begin at RP2D. Patients enrolled in Part 1 at RP2D will be counted towards Part 2 by the diagnosis of the tumor types; up to approximately 30 patients per cohort will be enrolled at RP2D.

Tislelizumab and fruquintinib will be administered until disease progression, intolerable toxicity, death, withdrawal of consent or until the study terminates.

The study design schema is as follows:



Study Assessments:

In Part 1, DLT will be assessed per the DLT criteria below during the 28-day DLT assessment window, which begins on the first day of the administration of study drugs.

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

Hematologic:

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

Nonhematologic:

- Any ≥ Grade 4 toxicity
- Any Grade 3 toxicity that does not resolve to baseline or ≤ Grade 1 within 7 days after optimal supportive care is initiated

Note: The following nonhematologic AEs will not be considered DLTs:

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

Tumor assessments will be performed by the investigator using RECIST v1.1 criteria (Eisenhauer et al 2009). Tumor imaging (computed tomography [CT] with oral/intravenous [IV] contrast, unless contraindicated, or magnetic resonance imaging [MRI]) must be performed within 28 days prior to enrollment. On-study tumor assessments will occur every 8 weeks (±7 days) during the first 56 weeks and every 12 weeks (±7 days) thereafter until disease progression. If a patient discontinues study treatment due to any reasons other than disease progression, tumor assessments will continue to be performed as scheduled until disease progression, loss to follow up, initiation of subsequent therapy, withdrawal of consent, death, or until the study terminates, whichever occurs first.

Patients will be evaluated for any AEs and serious adverse events (SAEs) during the study (AEs will be collected from the time of the first dose and SAEs from the time of signing the informed consent) and occurring up to 30 days after the last dose of study drugs (all severity grades, per NCI-CTCAE v5.0) or until initiation of new anticancer therapy, whichever occurs first, and for immune-mediated adverse events (imAEs) occurring from the time of the first dose of tislelizumab and up to 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death or loss to follow-up, whichever occurs first. All study drug-related SAEs will be followed until they resolve , the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE, whichever occurs first.

Duration of Patient Participation:

Duration of study participation will vary by patient, depending on the duration of treatment and treatment outcomes. Each patient treatment course will include:

- Screening up to 28 days
- Treatment until disease progression (or other reason for discontinuation before progression)
  - In select cases, patients may continue treatment beyond disease progression.
- End of Treatment (EOT) Visit: ≤ 7 days after the investigator determines that the patient must permanently discontinue all study drugs.
- Safety Follow-up Visit: up to 30 days after the last dose of study drug
- Survival Follow-up Visits: every 3 months until death (or other reason before death)

Study Population: Patients with histologically or cytologically confirmed advanced or metastatic, unresectable GC, MSS CRC and PD-L1 positive (defined as TC≥1% by SP263 IHC) NSCLC.

Key Eligibility Criteria:

Eligible patients in both part 1 and part 2 must have at least 1 measurable lesion as defined per RECIST v1.1; have an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate organ function; and available archival tissue (or baseline tumor biopsy is required). Patients should have no prior therapies targeting CTLA-4, PD-1, PD-L1 or PD-L2, or any antibody or drug targeting T-cell costimulation or checkpoint pathway, and no prior treatment with a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor or anti-VEGFR antibody (eg, ramucirumab). The indication-specific inclusion criteria are as follows:

GC

- Histological or cytological documentation of adenocarcinoma of gastric or esophagogastric junction. All other histological types are excluded.
- Progression during or after prior first-line therapy containing any platinum/ fluoropyrimidine doublet (combination with anti-HER2 antibody is mandatory if tumor HER2 is documented positive). If relapse or metastasis occur during the adjuvant/neoadjuvant treatment containing platinum/fluoropyrimidine or within 6 months after the completion of the above treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first line systemic chemotherapy for progressive disease (PD).

MSS CRC

- Histological or cytological documentation of adenocarcinoma of the colon or rectum. All other histological types are excluded.
- Patients must have failed 2 lines of standard chemotherapies, including fluoropyrimidine, oxaliplatin, or irinotecan. Failed chemotherapies are defined as the occurrence of PD or intolerable toxicities during the treatment or after the last dose.
- Notes: a) Each line of treatment for advanced disease until PD includes one or more chemotherapy drugs used for ≥ 1 cycles; b) Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occur during the adjuvant/neoadjuvant treatment period for patients with nonmetastatic or metastatic disease who have received curative surgery or

within 6 months after the completion of the above treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first line systemic chemotherapy for PD; c) Patients could be enrolled once they have failed fluoropyrimidine, oxaliplatin and irinotecan based regimen as first line treatment.

- For RAS wild type tumor, must have received anti-VEGF and/or EGFR antibody treatment. For RAS mutation or RAS status unknown, must have received anti-VEGF antibody treatment.
- Tumor tissues were identified as MSS by polymerase chain reaction (PCR) by a central laboratory.

NSCLC

- Histologically or cytologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) NSCLC.
- Have had no prior systemic therapy for advanced or metastatic NSCLC. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a disease-free interval of at least 6 months from the last dose of chemotherapy and/or radiotherapy prior to first dose.
- Patients with documented EGFR mutation or known ALK gene translocation (both must be tissue-based test) will be excluded. For non-squamous patients with unknown EGFR status, archival or fresh tumor tissues are required for EGFR mutation assessment in central/local laboratory prior to enrollment and only those with wild type EGFR will be enrolled.
- Tumor tissues were identified as PD-L1 positive defined as TC≥1% by SP263 IHC by a central laboratory.

Investigational Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 300 mg intravenously on Day 1 of every 4−week cycle.

In part 1, fruquintinib administration will begin at a dose of 5 mg once daily orally for 3 weeks on followed by 1 week off for every 4−week cycle in safety run-in stage. A lower dose level of fruquintinib (4 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) will be explored as necessary depending on observed toxicity. In part 2, fruquinitinib will be administrated at RP2D.

Reference Therapy, Dose, and Mode of Administration:

Not applicable

Statistical Methods:

Analysis Set

- The Safety Analysis Set (SAS) includes all patients who received ≥ 1 dose of study drug(s). This will be the analysis set for the safety and efficacy analyses.
- The Evaluable Analysis Set (EAS) includes all patients who received ≥ 1 dose of study drug(s), have evaluable disease at baseline, and have ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment.

- The DLT Evaluable Analysis Set includes all patients who received at least 85% of the assigned total dose of fruquintinib and at least 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment period. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Part 1 are eligible for inclusion in the DLT Evaluable Analysis Set. This will be the analysis set for the DLT analyses.
- The PK Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have ≥ 1 quantifiable postbaseline PK data.
- The Antidrug Antibody (ADA) Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have a baseline and at least 1 postbaseline ADA result.

Primary Efficacy Analysis

The ORR is defined as the proportion of patients who had confirmed CR or PR as determined by the investigator using RECIST v1.1 in the Safety Analysis Set. ORR will be summarized for descriptive purposes in SAS. A two-sided Clopper-Pearson 95% CI of ORR will be constructed. ORR will be summarized based on patients from the RP2D dose level in overall and by tumor types. Additional summaries will be based on all dose levels in overall and by tumor types if necessary.

Best overall response (BOR) is defined as the best response recorded from the start of study drug(s) until data cut or start of new anticancer therapy. Patients with no postbaseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented. BOR will be summarized based on patients from the RP2D dose level in overall and by tumor types. Additional summaries will be based on all dose levels in overall and by tumor types if necessary.

Outcomes in the Evaluable Analysis Set will be evaluated as a sensitivity analysis.

Secondary Efficacy Analysis

PFS assessed by the investigators per RECIST v1.1 will be estimated using the Kaplan-Meier method in the Safety Analysis Set. The Kaplan-Meier estimates of PFS will be plotted over time. PFS at selected time points will be estimated with its 95% CI using Greenwood's formula. The corresponding quantiles (including the median), if estimable, will also be estimated using Kaplan-Meier method. A two-sided 95% CIs of median, if estimable, will be constructed using the generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). PFS censoring rule will follow the United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018). PFS will be summarized based on patients from RP2D dose level in overall and by tumor types. Additional summaries will be based on dose levels in overall and by tumor types if necessary.

DCR and CBR, assessed by the investigator per RECIST v1.1, will be summarized in a similar way as ORR.

DOR and OS will be analyzed similarly as PFS. Only patients who have achieved an objective response will be included in the analysis of DOR.

DLT analysis

DLTs during the DLT assessment period will be used to determine safety and tolerability of tislelizumab in combination of fruquintinib. The DLT events will be summarized descriptively in the DLT Evaluable Analysis Set.

Safety Analysis

Safety will be determined by the reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and electrocardiogram findings will also be used in determining the safety profile. The severity of AEs will be graded

according to NCI-CTCAE v5.0. Descriptive summary statistics will be used to analyze all safety data in the Safety Analysis Set. Safety analysis will be based on the summary of overall and by dose level. Additional safety analyses will also be summarized based on tumor types if necessary.

Pharmacokinetics Analysis

Blood samples will be collected for tislelizumab PK evaluation at postdose and trough (C_{trough}). The serum concentration data of tislelizumab will be tabulated and summarized by visit/cycle at which these samples are collected. For fruquintinib, serial PK blood samples will be collected for part 1 and sparse samples will be collected for part 2. Plasma fruquintinib concentration data will be summarized using descriptive statistics, C-T profiles, and other plots as appropriate. The corresponding PK parameters of fruquintinib will be calculated as data permit.

Immunogenicity Analysis

The immunogenicity results for tislelizumab will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients.

Sample Size

Approximately 30 patients are expected to be enrolled in each tumor type cohort at RP2D. There will be 3 cohorts based on selected solid tumors. Approximately 6 to 12 DLT evaluable patients will be enrolled in Part 1. Patients enrolled in Part 1 at RP2D will be counted towards Part 2 by the diagnosis of tumor types. Approximately 96 patients will be enrolled at maximum.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	tislelizumab
bTMB	blood tumor mutational burden
CRC	colorectal cancer
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End-of-Treatment (Visit)
GC	gastric cancer
GCP	Good Clinical Practice
GEP	gene expression profile
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
RP2D	recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VEGFR	vascular endothelial growth factor receptor

1. INTRODUCTION AND RATIONALES

1.1. Introduction

Combination therapy with a small molecule inhibitor of the vascular endothelial cell growth factor receptor (VEGFR) pathway may improve the clinical efficacy of immunotherapies and promote effective inhibition of angiogenesis in the tumor region which can suppress the growth of tumor cells and reduce the incidence of metastasis. The combination of immunotherapies and anti-angiogenic agents has been shown nonclinically to generate more potent antitumor effects (Khan and Kerbel 2018) and has shown benefit in various therapeutic settings (Georganaki et al 2018). For patients with advanced or metastatic, unresectable gastric cancer (GC), microsatellite stable (MSS) colorectal cancer (CRC) or non-small cell lung cancer (NSCLC), combination therapy may improve the clinical efficacy of single-agent immunotherapies. Based on this, tislelizumab in combination with fruquintinib will be evaluated in patients with advanced or metastatic GC, MSS CRC or NSCLC.

Fruquintinib is a potent, oral VEGFR tyrosine kinase inhibitor (TKI) with good kinase selectivity approved for the treatment of metastatic colorectal cancer in patients who have failed at least 2 prior systemic antineoplastic therapies in China. Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4-variant monoclonal antibody against programmed cell death protein-1 (PD-1). Tislelizumab is approved for the treatment of patients for the following indications in China:

- with relapsed or refractory classical Hodgkin lymphoma who have received at least 2 lines of systemic chemotherapy regimens
- with locally advanced or metastatic urothelial carcinoma with programmed cell death ligand-1 (PD-L1) high expression whose disease has progressed during, following, or within 12 months of platinum-containing chemotherapy

1.2. Fruquintinib

1.2.1. Pharmacology

Fruquintinib primarily targets the VEGFR family, VEGFR 1, 2 and 3 with 50% inhibitory concentration（IC_{50}) of 33 nM, 35 nM, and 0.5 nM, respectively. In multiple human tumor xenograft models in Nu/Nu mice, fruquintinib demonstrated a dose dependent anti-tumor activity accompanied by strong anti-angiogenesis effect in tumor tissues. In all tested tumor models fruquintinib showed statistically significant tumor growth inhibition at doses as low as 2 mg/kg/day.

Refer to the fruquintinib Investigator's Brochure for detailed information regarding pharmacology studies

1.2.2. Toxicology

No deaths occurred at single doses of 2000 mg/kg and 1000 mg/kg for rats and dogs, respectively. In repeated dose toxicity studies up to 9 months, there was a general trend for increased toxicity associated with increased duration of treatment. The main target organs were liver, kidney, adrenal gland, immune system (thymus, spleen, and lymph nodes), gastrointestinal system, bone marrow (sternum) and femur. The toxic responses were reversible after discontinuation of drug treatment.

- Safety Pharmacology: No adverse effects were observed in dog cardiovascular and respiratory systems at 0.34 mg/kg and in central nervous system at10 mg/kg.
- Reproductive and development toxicology: In the fertility and early embryonic development/implantation study, the no observed adverse effect level (NOAEL) for fertility in both male and female rats was 3 mg/kg and 0.5 mg/kg, respectively. The NOAEL for early embryonic development was 0.15 mg/kg. In the embryo-fetal development study, the NOAEL for both maternal effects and embryo-fetal development was 0.1 and 0.025 mg/kg in rats.
- Genetic toxicology: No genetic toxicity was found in either the bacterial reverse mutation test or the micronucleus test in mice. In the chromosome aberration test, fruquintinib, at 36.0 μg/mL, induced a significant increase in aberrant cells with structural chromosome aberrations in Chinese Hamster Lung cells, but this is not observed in other treated groups.

Refer to the fruquintinib Investigator's Brochure for detailed information regarding toxicology studies.

1.2.3. Clinical Pharmacology

The pharmacokinetics of fruquintinib were evaluated in patients with advanced malignant solid tumors (2009-013-00CH1). Following a single oral dose of 1, 2, 4, 5 or 6 mg of fruquintinib, clearance was found to be low. The half-life ($t_{1/2}$) was > 35 hours, therefore, a once daily dose regimen is suitable. Both the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) increased proportionally within dose levels of 1 to 6 mg. The steady state was reached following 14 days of consecutive once daily dosing and the AUC on Day 14 was 3-fold higher than on Day 1. The 4-week continuous dosing regimen was compared with 3 weeks of continuous dosing (once daily) with either 5 mg or 6 mg of fruquintinib, followed by a 1-week break (3 weeks on/1 week off). The pharmacokinetic (PK) results showed that fruquintinib profiles were similar between the two dosing regimens on the same dosing days (Days 1 and 14). Tumor types had little effect on the pharmacokinetic characteristics of fruquintinib.

In the food effect study conducted in healthy male volunteers, C_{max} from the fed condition group reduced 17% (geometric mean ratio 82.9%, 90% CI: 76.7% to 89.5%) compared to fasted condition group, and the AUC is comparable (geometric mean ratio 97.2%, 90% CI: 94.0% to 100.4%).

1.2.4. Prior Clinical Experience of Fruquintinib

As of 03 September 2019, there were 5 ongoing studies with fruquintinib. An additional 11 clinical studies have been completed, 7 in patients with cancer and 4 in healthy volunteers.

Refer to the fruquintinib Investigator's Brochure for more detailed information on fruquintinib safety and efficacy data when given as monotherapy or in combination with chemotherapy or other agents.

1.2.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 4 completed, double-blind, placebo-controlled monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy. In each study, patients randomized to fruquintinib treatment received 5 mg once daily, 3 weeks on/1 week off in a 4-week cycle. A total of 739 patients received at least 1 dose of fruquintinib in the pooled analysis of monotherapy studies.

1.2.4.1.1. Treatment-Emergent Adverse Events

Of the 739 patients in the pooled analysis of monotherapy studies, 729 (98.6%) patients reported treatment-emergent adverse events (TEAEs) and 711 (96.2%) patients reported treatment-related TEAEs. TEAEs ≥ Grade 3 were reported by 443 (59.9%) patients. The most commonly reported TEAEs ≥ Grade 3 (≥ 5.0% patients) were hypertension (19.9%) and palmar-plantar erythrodysesthesia (PPE) syndrome (10.7%). TEAEs ≥ Grade 3 reported by 363 (49.1%) patients were considered to be treatment-related by the investigator.

1.2.4.1.2. Treatment-Emergent Serious Adverse Events

Of the 739 patients in the pooled analysis of monotherapy studies, 169 (22.9%) patients reported serious adverse events (SAEs). The most common SAEs (≥ 1.0% patients) by Preferred Term included infectious pneumonia (24 [3.2 %] patients), intestinal obstruction (17 [2.3%] patients), pleural effusion (9 [1.2%] patients), death (10 [1.4%] patients), hepatic function abnormal (8 [1.1%] patients), and gastrointestinal haemorrhage (8 [1.1%] patients). One hundred twelve (15.2%) patients reported treatment-related SAEs; 41 (5.5%) patients had a fatal SAE.

1.2.4.1.3. Adverse Events of Special Interest

In the pooled analysis of monotherapy studies, the most frequently reported adverse events of special interest (AESIs) (> 10% of patients) were dermatological toxicity (59.7%), hypertension (49.7%), thyroid dysfunction (46.3%), proteinuria (40.6%), hepatic function abnormal (38.4%), hemorrhages (36.1%), and infections (31.9%). AESIs ≥ Grade 3 (> 5% of patients) included hypertension (22.1%), dermatological toxicity (11.1%), infections (7.3%), and hepatic function abnormal (6.5%).

1.2.4.1.4. Fatal Adverse Events

A total of 44 (6.0%) patients had TEAEs leading to death. Refer to the fruquintinib Investigator's Brochure for more detailed information on fruquintinib safety.

1.2.4.2. Efficacy Assessment of Fruquintinib

As of 03 September 2019, the available efficacy data from the Phase 1 study in solid tumors (2009-013-00CH1) and Phase 1b study in patients with CRC (2012-013-00CH3) showed promising clinical activity of fruquintinib including durable partial response (PR) and stable disease (SD) observed in the majority of the heavily pretreated patients with advanced cancer, particularly in patients with CRC, GC, and NSCLC. The results from the Phase 3 study in patients with CRC (FRESCO, 2013-013-00CH1) met its primary efficacy endpoint of OS and showed fruquintinib significantly improved the overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and disease control rate (DCR) as compared to placebo. A total of 416 patients were randomized to receive fruquintinib (5 mg once daily) or placebo in a 2:1 ratio, 3 weeks on/1 week off in a 4-week cycle. As the primary endpoint, the OS was significantly improved in the fruquintinib group compared with the placebo group (9.3 months versus 6.6 months; HR = 0.65; $p < 0.001$). The secondary endpoints of PFS (3.7 months versus 1.8 months; HR = 0.26; $p < 0.001$), ORR (4.7% versus 0.0%; $p = 0.01$) and DCR (62.2% versus 12.3%; $p < 0.001$), were also significantly increased in the fruquintinib group compared with placebo. Fruquintinib was granted approval by the China National Medical Product Administration (NMPA) based on results of the FRESCO study.

Promising efficacy results were also observed in the Phase 1b/2 study of fruquintinib in combination with paclitaxel as second-line therapy in patients with GC (2014-013-00CH3), 34 patients were enrolled and treated: 3, 3 and 28 patients in the fruquintinib 2 mg, 3 mg and 4 mg plus paclitaxel groups, respectively. The overall ORR and DCR were 27.3% (9/33 patients) and 63.6% (21/33 patients), respectively. The median PFS and median OS at the recommended Phase 2 dose (RP2D) (fruquintinib 4 mg + paclitaxel) were 4.0 and 7.8 months, respectively.

Another Phase 3 study of fruquintinib was completed in patients with non-squamous NSCLC who had failed second-line standard chemotherapy (2015-013-00CH1): there was no significant difference between the fruquintinib group and the placebo group in the primary efficacy endpoint (OS). However, fruquintinib significantly prolonged the PFS compared to placebo with a HR of 0.34 (95% CI: 0.279, 0.425) with $p < 0.001$ (stratified log-rank test). Statistically significant benefits were also obtained with fruquintinib in ORR and DCR.

1.3. Tislelizumab

1.3.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1. Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In addition, tislelizumab has no effector functions mediated through Fc gamma receptors (Zhang et al 2018). Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models

Please refer to the tislelizumab (BGB-A317) Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

1.3.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys.

No apparent toxicity was noted in single dose or 13-week repeat-dose monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay and human peripheral blood mononuclear cell assay. The toxicokinetic profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study, BGB-A317-fruquintinib-201.

Please refer to the tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.3.3. Clinical Pharmacology

Population PK analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who received doses ranging from 0.5 to 10 mg/kg once every 2 or 3 weeks. The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume (V_c), and peripheral volumes (V_2, V_3), were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), V_c (16.7%), V_2 (56.6%), and V_3 (94.2%). Consistent with other therapeutic IgG monoclonal antibodies, the volume of distribution at steady state (V_{ss}) was 5.238 L and the terminal half-life is approximately 25.5 days. (Deng et al 2012; Dirks and Meibohm 2010; Keizer et al 2010; Ryman and Meibohm 2017).

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) Performance Status, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show statistically significant impact on the PK of tislelizumab. Although tumor size, albumin, and tumor type were significant covariates on CL, while body weight, sex, and tumor type were significant covariates on V_c, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. Population PK analysis supports flat-dosing across different ethnic groups.

1.3.4. Prior Clinical Experience of Tislelizumab

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

Refer to the tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on tislelizumab safety and efficacy data when given as monotherapy or in combination with chemotherapy.

1.3.4.1. Pooled Safety Assessment of Monotherapy Studies

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

Refer to the tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

1.3.4.1.1. Treatment-Emergent Adverse Events

Of the 1273 total patients treated in the Pooled Monotherapy studies, 1210 (95.1%) experienced at least 1 TEAE and 846 (66.5%) experienced at least one treatment-related TEAE. TEAEs ≥ Grade 3 were reported by 548 (43.0%) patients. The most commonly occurring ≥ Grade 3 TEAEs were anaemia (64 patients, 5.0%), aspartate transaminase (AST) increased, pneumonia (35 patients each, 2.7%), and ascites (25 patients, 2.0%). All other events occurred in under 2.0% of the total Pooled Monotherapy population. A total of 163 (12.8%) patients experienced at least 1 ≥ Grade 3 TEAE assessed as related to tislelizumab.

1.3.4.1.2. Treatment-Emergent Serious Adverse Events

Of the 1273 total patients treated in the Pooled Monotherapy studies, 424 (33.3%) experienced at least 1 treatment-emergent serious adverse event (SAE). The most commonly occurring treatment-emergent SAEs were pneumonia (35 patients, 2.7%), pyrexia (22 patients, 1.7%), and ascites (17 patients, 1.3%).

1.3.4.1.3. Immune-Mediated Adverse Events

Anti-PD1 therapies are known to cause immune-mediated adverse events (imAEs) in some patients and therefore have been defined as adverse events of special interest (AESI) in tislelizumab clinical studies.

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

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

Immune-mediated AEs of hepatitis, pneumonitis, colitis, endocrinopathies, myocarditis, and serious skin adverse reactions have been identified as risks for tislelizumab. Refer to the tislelizumab (BGB-A317) Investigator's Brochure for more detailed information.

1.3.4.1.4. Infusion-Related Reactions

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

1.3.4.1.5. Fatal Adverse Events

A total of 68 patients (5.3%) had TEAEs leading to death. Refer to tislelizumab (BGB-A317) Investigator's Brochure Edition 7, Section 5.2.1.9) for a summary of the treatment-emergent fatal AEs that occurred in the Pooled Monotherapy studies.

1.3.4.2. Efficacy Assessment of Tislelizumab

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

1.3.4.2.1. Study BGB-A317_Study_001

Study BGB-A317 Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation (0.5 to 10 mg/kg) and dose-finding component with 3 parts (2 and 5 mg/kg given either once every 2 or 3 weeks, and a fixed dose of 200 mg given once every 3 weeks) to establish the maximum tolerated dose, if any, a RP2D, and followed by a Phase 1b component to investigate efficacy in select tumor types at the RP2D to further evaluate safety and tolerability of tislelizumab. Indication specific cohorts included esophageal cancer, GC, CRC, and NSCLC.

Responses were assessed by the Investigator per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.

There were 451 patients treated in the study and 441 patients were included in the Efficacy Evaluable Analysis Set. The analysis set included all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable post-baseline tumor assessment. This set included 52 patients in the gastric cancer cohort, 21 patients in the colorectal cohort and 46 patients in the NSCLC cohort.

Across all disease cohorts, there were 5 patients (1.1%) with a complete response (CR). A total of 55 patients (12.5%) had a confirmed PR. The resulting overall clinical response rate was 13.65%. Additionally, there were 142 patients (32.2%) with a best overall response of SD. A total of 199 patients (45.1%) had a best response of progressive disease (PD) in this study.

Of the 52 patients in the GC cohort, 7 patients (13.5%) had a confirmed PR. Additionally, there were 9 patients (17.3%) with a best overall response of SD. A total of 31 patients (59.6%) had a best response of PD in this cohort, and the assessment for 5 patients (9.6%) was missing. Of the 21 patients in the CRC cohort, 3 (14.3%) had a confirmed PR and 7 patients (33.3%) had a best overall response of PD. Two patients (9.5%) had missing assessments. Of the 46 patients in the NSCLC cohort, 6 patients (13%) had a confirmed PR. Additionally, there were 23 patients (50%) with a best overall response of SD. A total of 13 patients (28.3%) had a best response of PD in this cohort, and the assessment for 4 patients (8.7%) was missing.

1.3.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 evaluates the activity and safety of tislelizumab at its recommended Phase 2 dose of 200 mg given once every 3 weeks in indication specific expansion cohorts.

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

Overall, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable post-baseline tumor assessment. In Phase 2, this set included 12 patients in the GC cohort, 16 patients in the CRC cohort, 18 patients in the PD-L1 positive NSCLC cohort and 24 patients in the PD-L1 negative NSCLC cohort.

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

The tumor responses in the efficacy evaluable analysis set of Study BGB-A317-102 in the GC cohort (12 patients) was 3 patients (25.0%) had a confirmed PR. Additionally, there were 2 patients (16.7%) with a best overall response of SD. A total of 7 patients (58.3%) had a best response of PD in this cohort. In the CRC cohort (16 patients), 3 patients (18.8%) had a confirmed PR; 5 patients (31.3%) had a best overall response of SD, and 8 patients (50.0%) had a best response of PD. In the PD-L1 positive NSCLC cohort (18 patients), 2 patients (11.1%) had a confirmed PR; 7 patients (38.9%) had a best overall response of SD, and 9 patients (50.0%) had a best response of PD. In the PD-L1 negative NSCLC cohort (24 patients), 5 patients (20.8%) had a confirmed PR; 11 patients (45.8%) had a best overall response of SD, and 8 patients (33.3%) had a best response of PD.

1.4. Study Rationale

Numerous clinical studies are underway in a variety of indications (eg, renal cell carcinoma, NSCLC, CRC, gastrointestinal malignancies, melanoma, breast cancer, and urothelial carcinoma) to evaluate the combination of immunotherapies and anti-angiogenics.

Promising antitumor results have been reported in GC, MSS CRC and NSCLC (e.g. EPOC1603, EPOC1706, E7080-A001-111) with this combination therapies demonstrating a manageable safety profile consistent with individual monotherapy profiles (Fukuoka et al 2020). Refer to Section 1.4.3 for tumor type rationales. Additionally, since 2019, a number of similar combinations have been approved for a variety of indications demonstrating the therapeutic potential of immunotherapy and anti-angiogenic combinations. These include pembrolizumab plus axitinib for patients with advanced renal cell carcinoma (KEYNOTE-426, NCT02853331); pembrolizumab and lenvatinib for patients with advanced endometrial cancer (KEYNOTE-146, NCT02501096); and atezolizumab and bevacizumab for patients with unresectable or metastatic hepatocellular carcinoma (IMbrave150, NCT03434379).

Based on the available clinical data from the combination of immunotherapy and anti-angiogenics, demonstrating promising antitumor effect compared with the therapeutic effect of a single agent alone, the combination of tislelizumab and fruquintinib may provide a tolerable, effective treatment option for the patients with GC, MSS CRC or NSCLC.

1.4.1. Rationale for the Starting Dose

The full dose of fruquintinib (5 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) in combination with tislelizumab (300 mg once every 4 weeks) were selected as the starting doses for this study due to the well-established safety profiles of fruquintinib and tislelizumab, the non-overlapping mechanisms of action, and the desire to treat patients at doses shown to be effective in previous studies. Starting treatment with the full dose of each agent in an immunotherapy plus a TKI combination therapy is consistent with other trials. Axitinib, like fruquintinib, targets VEGFR 1, 2, 3 in addition to other pathways and has been evaluated in combination with an immunotherapy (pembrolizumab) for advanced renal cell carcinoma (RCC). The Phase 1b enrolled 52 patients (11 in dose-finding phase, 41 in dose-expansion phase) and treatment was initiated with the full dose of both agents (Atkins et al 2018). No unexpected toxicities were observed. Three dose-limiting toxicities were reported in the 11 patients treated during the dose-finding phase: 1 patient had a transient ischemic attack and 2 patients were only able to complete less than 75% of the planned axitinib dose because of treatment-related toxicity. The maximum tolerated dose of this regimen was estimated to be the full doses of each agent; overall, patients received almost the full protocol-planned doses of both drugs. 32 (62%) patients had their axitinib dose reduced (ie, to <5 mg twice per day for two consecutive doses) because of axitinib-related toxicities. Overall, 25 (48%) patients discontinued axitinib because of adverse events (n = 16) and disease progression (n = 9); 24 (46%) patients discontinued pembrolizumab early because of adverse events (n = 12) and disease progression (n = 12). Unprecedented antitumor activity and tolerability of this combination treatment led to breakthrough status designation from the U.S. Food and Drug Administration (FDA); subsequent FDA approval of this combination at full dosages for each agent for RCC was based on data from the Phase 3 KEYNOTE-426 study.

1.4.1.1. Tislelizumab

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. Tislelizumab has a wide safety margin (the dose ranged from 0.5 mg/kg to 10 mg/kg every 2 weeks in Study BGBA317_Study_001) with no maximum tolerated dose identified in Study BGB-A317_Study_001. The flat dose of 200 mg intravenously once every 3 weeks was selected for further evaluation.

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

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

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

The observed clinical activity in patients with advanced tumors, coupled with a manageable safety profile and supportive data, support the proposed tislelizumab dose of 200 mg intravenously once every 3 weeks as the recommended dose for pivotal studies. This dose regimen has been approved for treating patients with classical Hodgkin lymphoma and urothelial bladder cancer. The dosage of 200 mg Q3W was also used in other pivotal studies under the development, for more information please refer to the tislelizumab (BGB-A317) Investigator's Brochure.

The alternate regimen of 300 mg once every 4 weeks is selected by matching dosing and exposure (AUC) with the exposure of 200 mg once every 3 weeks regimen. Exposure-response (E-R) assessment of available clinical data from studies including BGB-A317_Study_001, BGB-A317-102, and BGB-A317-203 suggest no clinically significant relationships observed between tislelizumab exposure and efficacy (ORR) or safety across tumor types. Thus, 300 mg once every 4 weeks regimen is not expected to be clinically different from the 200 mg once every 3 weeks in terms of safety or efficacy outcomes. The higher maximum concentrations (C_{max}) of 300 mg once every 4 weeks regimen compared with the 200 mg once every 3 weeks is well covered by the available safety data at higher doses (up to 10 mg/kg once every 2 weeks were used in Study BGB-A317_Study_001). Moreover, the alternative 4-weekly dose administration is expected to increase patient compliance when in combination with fruquintinib and offer additional convenience for care providers.

1.4.1.2. Fruquintinib

The dose and mode of administration of fruquintinib (5mg, once daily, 3 weeks on /1 week off) determined for this study were based on the safety and efficacy results of the Phase 1 study (2009-013-00CH1) and Phase 1b study for the treatment of advanced colorectal cancer (2012-013-00CH3). As described in Section 1.2.3, PK data from Study 2009-013-00CH1 demonstrated that fruquintinib profiles were similar for the 2 dosing regimens (4-week continuous dosing and 3 weeks on/1 week off) on the same dosing days.

Study 2012-013-00CH3, a Phase 1b, randomized, open-label study, compared 2 different dosing regimens of fruquintinib as third-line or above therapy for advanced colorectal cancer. Patients were randomized to fruquintinib "4 mg once daily continuous regimen" (Group A) or "5 mg once daily 3 weeks on /1 week off regimen" (Group B). The efficacy under Group B was similar to the regimen of Group A even though the total amount of drug administration was slightly lower in Group B. The analysis of duration of treatment showed the average duration of treatment in Group B was longer than that in Group A, indicating better tolerance to the "5 mg once daily 3 weeks on/1 week off" regimen and the potential to prolong the treatment and impede disease progression. Therefore, "5 mg once daily 3 weeks on/1 week off" was confirmed as the recommended dosage for Phase 2/3 studies. The drug-drug interaction potential between tislelizumab and fruquintinib is considered to be low (refer to Section 6.5 for details), so no starting dose adjustment is needed for either drugs.

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

Immunotherapy has recently emerged as a novel strategy for treating different types of solid tumors, with promising results. However, a large proportion of patients do not respond to such approaches, and initial responders sooner or later develop resistance. One of the possible reasons for treatment failure with PD-1 blockade for advanced cancers is immune suppression through the immune checkpoints other than the PD-1/PD-L1 axis that regulate lymphocyte activation or through the immunosuppressive cells, including forkhead box P3 $(Foxp3)^{+}CD25^{+}$ regulatory T cells (T regs) and tumor-associated macrophages (TAMs) (Fukuoka et al 2020). VEGF-A, well-characterized for its major role in tumor vessel growth (neoangiogenesis), was recently identified as a key factor in tumor-induced immunosuppression. In particular, VEGF-A fosters the proliferation of immunosuppressive cells, limits T-cell recruitment into tumors, and promotes T-cell exhaustion (Lapeyre-Prost et al 2017).

As abnormal and augmented tumor vessels often occur in cancerogenesis, anti-angiogenic drugs have already demonstrated their effectiveness both in preclinical and in clinical settings. Although these VEGF pathway inhibitors can improve survival in many cancer types, some tumors have little or no beneficial effect from such therapies. Mechanisms related to the resistance to anti-VEGF/VEGFR therapy are not completely known. However, it is known that in anti-angiogenic therapy resistance often involves the activation of signaling pathways other than the VEGF pathway. Intra-tumor hypoxia and the related infiltration of immunosuppressive cells may also play a significant role in angiogenic relapse and drug resistance (Itatani et al 2018; Zarrin et al 2017).

Combining immunotherapy of anti-PD-L1 with anti-angiogenic therapy had reciprocal beneficial effects: anti-angiogenic drugs blocked the negative immune signals by increasing the ratio of anti-/pro-tumor immune cells and decreasing immune checkpoints expression, while immunotherapy restored immune-supportive microenvironment and promotes vascular normalization increasing lymphocyte infiltration and activation (Huang et al 2013).

1.4.3. Rationale for Tumor Type(s)

1.4.3.1. Gastric Cancer

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality worldwide (Globocan 2018d). Almost 1 million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total) according to the World Health Organization's Globocan 2012 database (Ferlay et al 2015). There were 456,124 new diagnosed cases of stomach cancer and 390,182 deaths in China in 2018 (Globocan 2018a). Stomach cancer is the second highest incidences and mortality in China. In Korea, stomach cancer had the 4th highest incidences (5127 new diagnosed cases) and 3rd highest mortality (3660 deaths) of cancers in 2018 (Globocan 2018c).

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

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

In preclinical models, the simultaneous blockade of PD-1 and VEGFR-2 enhanced T-cell recruitment, activated local immune status, and induced synergistic antitumor effects (Yasuda et al 2013). Recent preliminary efficacy results in patients with GC treated with lenvatinib plus pembrolizumab from a Phase 2 study (NCT03609359) were promising. In 29 patients, enrolled in the first-line or second-line setting, the ORR was 69% (1 CR, 19 PR) (Kawazoe et al 2020). The DCR was 100%. The median PFS was 7.1 months. The median OS had not been reached when the data was reported. In a Phase 1b trial, 25 patients with advanced GC received treatment with regorafenib plus nivolumab. Objective tumor response was observed in 11 patients (44%). Median progression-free survival was 5.6 months. Median OS was 12.3 months (Fukuoka et al 2020).

Specific application strategies for the combination of anti-PD-1/PD-L1 and VEGFR need further exploration.

1.4.3.2. Colorectal Cancer

Colorectal cancer is the third most diagnosed cancer and the second leading cause of cancer death worldwide, in both males and females(Globacan 2018b). It is the sixth most diagnosed cancer and the fifth leading cause of cancer death in China and Korea (Globocan 2018a; Globocan 2018c). In China, the age-standardized incidence and mortality rate of CRC has increased by about 1.9% per year for incidence and about 0.9% per year for mortality rate from 2000 to 2014 (Zheng et al 2018). In 2017, CRC was responsible for 1.79% of the total deaths in China (Yin et al 2019).

Although surgery is currently the primary course of treatment, it is ineffective in cases where the cancer has metastasized. The mainstay of first-line therapy for advanced CRC is combination chemotherapy plus an anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) antibody, depending on the tumor characteristics (NCCN 2020). However, most patients progress within 1 year (Chau and Cunningham 2009). Patients with CRC who do not benefit from first line therapy are often treated with second line chemotherapy. Beyond second line, targeted therapy such as regorafenib or fruquintinib have been shown to prolong survival in Chinese patient with mCRC compared with placebo in Phase 3 studies (Grothey et al 2013; Li et al 2018). Recently, immune checkpoint inhibitors have demonstrated impressive activity in patients with CRC and other solid tumors that are microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR). Nivolumab and pembrolizumab are currently approved by the FDA for patients with MSI-H/dMMR metastatic CRC (Morse et al 2020). However, the PD-1 blockade is particularly ineffective in patients with microsatellite stable (MSS) or mismatch repair (MMR)–proficient colorectal cancer which makes up the majority (95%) of mCRC patients (Ali et al 2018). This can be explained by the lower antigenicity due to the presence of fewer neoantigens, regardless of tumor mutation burden, resulting in fewer infiltrating CD8+ T cells in general and fewer strongly positive for PD-1 (Morse et al 2020). Recently, several strategies to turn a “cold” CRC tumor into an immunoreactive “hot” tumor were being tested in clinical trials. In a Phase 1b trial, 25 patients with advanced CRC received treatment with regorafenib plus nivolumab. Objective tumor response was observed in 9 patients (36%). After the exclusion of 1 patient with MSI-high CRC, the ORR was 33.3% in patients with MSS CRC. Median progression-free survival was 7.9 months (Fukuoka et al 2020).

The combination of anti-PD-1/PD-L1 and VEGFR warrants further evaluation as a treatment paradigm for patients with MSS colorectal cancer.

1.4.3.3. Non-Small Cell Lung Cancer

Lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer deaths worldwide (Bray et al 2018). NSCLC represents 80-85% of lung primary malignancies (PDQ Adult Treatment Editorial Board 2017). NSCLC is most often diagnosed at a metastatic stage, where 5-year survival rate ranges between 0 and 5% using traditional chemotherapy-based strategies (Goldstraw et al 2016). The success in immune checkpoint therapy in recent years has revolutionized traditional cancer treatment in NSCLC. In the first-line setting, KEYNOTE-042 demonstrated that single-agent pembrolizumab significantly improved overall survival (OS)

compared with platinum-based chemotherapy with advanced NSCLC, PD-L1 expression of 1% or more, but without EGFR mutation or ALK rearrangement (Mok et al 2019). Based on these results, the FDA approved pembrolizumab as a single agent for the first-line treatment of patients with advanced NSCLC whose tumors express PD-L1 (tumor proportion score, TPS ≥ 1%) with no EGFR or ALK genomic tumor aberrations. However, the use of pembrolizumab monotherapy in the less than <50% TPS score subset remains controversial as a specific look at the TPS score 1–49% versus 50% + subsets suggests that greatest benefit is noted in the group of high PD-L1 expressors and best might be preserved for patients who are not good candidates for chemotherapy (Mok et al 2019). The benefit of pembrolizumab used in the frontline setting in combination with chemotherapy versus chemotherapy alone has also been demonstrated in Phase 3 studies. Based on the positive results of KEYNOTE-189 (Gandhi et al 2018) and KEYNOTE-407 (Paz-Ares et al 2018), FDA has approved pembrolizumab combined with platinum-doublet chemotherapy in first-line NSCLC with squamous and non-squamous histology regardless of PD-L1 expression. Recently, two Phase 3 studies of tislelizumab plus platinum-doublet chemotherapy as first-line treatment in locally advanced and metastatic non-squamous and squamous NSCLC are ongoing (BGB-A317-304 and BGB-A317-307). Both studies have already announced positive result of PFS as primary endpoint. In Study BGB-A317-304, the addition of tislelizumab resulted in significantly improved PFS (9.7 months vs 7.6 months; P=0.0044, HR=0.645 [95% CI: 0.462, 0.902]) as well as higher ORR and longer DoR than observed with chemotherapy alone in patients with advanced non-squamous NSCLC. In Study BGB-A317-307, median PFS was 7.6 months (95% CI: 6.0, 9.8) and 7.6 months (95% CI: 5.8, 11.0) with tislelizumab combined with either paclitaxel and carboplatin or nab-paclitaxel and carboplatin, respectively, both of which were significantly longer than the median PFS (5.5 months [95% CI:4.2, 5.7]) with paclitaxel and carboplatin alone in patients with advanced squamous NSCLC.

PD1 blockade treatment is a new standard of first line treatment for PD-L1 positive NSCLC. However, a large proportion of patients do not respond to such treatment with an ORR of about 27% (Mok et al 2019). For patients with low tumor PD-L1 expression who can tolerate chemotherapy, PD-1 blockade plus chemotherapy was considered as the optimal approach, but at the cost of chemotherapy related toxicities. Despite the recent advances with anti-PD-1 therapy, most patients with advanced NSCLC have incurable diseases; more effective treatment options with better tolerability profile are needed, as first-line treatment for PD-L1 positive advanced NSCLC. Immunotherapy plus antiangiogenesis agents have been evaluated in some Phase 1and 2 studies. In a Phase 1b/2 study (E7080-A001-111), Lenvatinib plus pembrolizumab demonstrated a manageable safety profile and promising antitumor activity in patients with selected solid tumor types, including NSCLC. 21 NSCLC patients were enrolled. Most patients (86%) received at least 1 prior systemic therapy, 52% of the patients received prior an-PD(L)1 treatment before enrollment. ORR for patients with NSCLC were 33% (95% CI, 14.6% to 57.0%). The median DOR was 10.9 months (95% CI, 2.4 months to NE), and the median PFS was 5.9 months (95% CI, 2.3 to 13.8 months) (Taylor et al 2020).

1.4.4. Rationale for Biomarker Strategy

A number of biomarkers have been identified that correspond with a response to immunotherapy for patients with GC, MSS CRC or NSCLC.

PD-L1 expression has been demonstrated to be positively correlated with response to anti-PD-1 therapy across tumor types (Cristescu et al 2018). For GC, the expression of PD-L1 is positively correlated with response to anti-PD-1 monotherapy (Keynote-061, Keynote-062). Additionally, 2 pilot studies have demonstrated the trend of patients who express PD-L1 benefiting from anti-PD(L)-1 plus VEGFR-TKI, compared to those negative for PD-L1 expression (Jianming et al 2019; Fukuoka et al 2020). This indicates that PD-L1 may be a potential biomarker predicting response to anti-PD(L)-1 in combination with VEGFR-TKI in GC. For MSS CRC, clear correlation between PD-L1 expression and response to anti-PD(L)-1 has not been reported. One pilot study has demonstrated the negative correlation between PD-L1 expression and response to anti-PD(L)-1 in combination with VEGFR-TKI (Fukuoka et al 2020). Due to the limited number of patients, the role of PD-L1 expression in predicting response to anti-PD(L)-1 in combination with VEGFR-TKI warrants further exploration. For NSCLC, the expression of PD-L1 is positively correlated with response to anti-PD(L)-1 monotherapy (KEYNOTE-042, IMpower-110). The correlation between PD-L1 and response to anti-PD(L)-1 in combination with VEGFR-TKI therapies has not been conclusive from limited data reported (MRTX-500, Keynote-146, COSMIC021). Thus, the correlation of PD-L1 with response needs further exploration.

Tumor mutational burden (TMB) works as the surrogate marker for neo-antigen prediction and has been reported to positively correlate with the response to anti-PD(L)-1, and serves as an independent biomarker from PD-L1, indicating that its combination with PD-L1 may lead to predictive synergy (Fumet et al 2020; Cristescu et al 2018). For GC, the positive correlation between TMB and anti-PD(L)-1 monotherapy has been reported; however, pilot studies investigating the role of TMB in predicting response to anti-PD(L)-1 in combination with VEGFR-TKI have shown conflicting results in a limited number of patients. Thus, the correlation of TMB with response needs to be explored in larger cohorts (Jianming et al 2019; Fukuoka et al 2020). For CRC, 1 pilot study has shown the trend of patients with high TMB benefiting from anti-PD(L)-1 in combination with VEGFR-TKI, compared to those with low TMB. Due to the limited number of patients evaluated, this trend requires further verification (Fukuoka et al 2020). For NSCLC, one pilot study demonstrates that there is a trend of patients with higher TMB benefiting from anti-PD(L)-1 in combination with VEGFR-TKI, and this also requires further exploration in larger cohorts (WCLC 2019, NCT02954991). Blood TMB (bTMB), demonstrated good correlation with TMB if assessed with large panels, which has been explored due to its non-invasiveness feature, and has been reported to predict clinical benefit with anti-PD(L)-1 therapy in several clinical trials (POPLAR, OAK, MYSTIC trials, etc.) (Gandara et al 2018). Apart from tumor mutational burden, DNA mutation can also be explored from the TMB detection panel, thus its role in predicting response/resistance can also be investigated.

Gene expression profile (GEP) panels have been designed to investigate immune features (tumor immunogenicity, interferon gamma signature, immune cell population abundance, etc.), and tumor features (epithelial-mesenchymal transition, angiogenesis, hypoxia, cell adhesion, etc.). Interferon gamma signature has been shown to be positively correlated with response to anti-

PD(L)-1 monotherapy across tumor types (Cristescu et al 2018). Results related to GEP have not been reported in anti-PD(L)-1 plus VEGFR-TKI studies in patients with GC, MSS CRC or NSCLC yet, however, publications or presentations in hepatocellular carcinoma (GO30140 trial, ASCO 2020), melanoma (NCT03086174, ASCO 2020), and RCC have reported the association of GEP panels (selected genes) with response to anti-PD(L)-1 in combination with anti-VEGF/VEGFR-TKI (McDermott et al 2018; Wallin et al 2016), implying GEP panels may play a potential role in predicting response to anti-PD(L)-1 plus VEGFR-TKI in patients with GC, MSS CRC and NSCLC. Apart from its potential predictive value, GEP panels can be designed to explore underlying resistance mechanism like immunosuppressive cytokines and cells to guide potential combination strategies (Fumet et al 2020; Cristescu et al 2018).

Consequently, in the GC, MSS CRC and NSCLC cohorts, PD-L1, TMB and DNA mutation/bTMB and DNA mutation, and GEP can be explored in tumor or blood samples to identify their potential predictive value, as well as resistance mechanisms in patients who receive tislelizumab in combination with fruquintinib. Epstein-Barr virus (EBV) and MSS/MSI status（TMB panel can report the MSS/MSI status) in the GC cohort will be explored since EBV+/MSI-H GC patients were reported sensitive to anti-PD(L)-1 monotherapy (Figueroa-Protti et al 2019).

1.5. Benefit-Risk Assessment

Patients with advanced or metastatic, unresectable GC, MSS CRC who failed standard chemotherapies represent a population with a great unmet medical need. More effective treatment options with better tolerability profile are needed, as first-line treatment for PD-L1 positive advanced NSCLC. The combination of immunotherapies with VEGFR inhibitors may improve response rates and duration of response with immunotherapies. Recent clinical studies have demonstrated the synergistic effect of anti-angiogenics and immune checkpoint inhibitors in solid tumors, including MSS CRC, GC and NSCLC.

Data from the Phase 1b EPOC1603 trial of regorafenib plus nivolumab demonstrated objective tumor response in patients with advanced GC (44%) and in patients with MSS CRC (33. 3%) (Fukuoka et al 2020). Similarly, promising antitumor activity was observed in the Phase 2 EPOC1706 trial of pembrolizumab plus lenvatinib in patients with advanced GC with 20 (69%) of 29 patients having an objective response (Kawazoe et al 2020). In Phase 1b/2 E7080-A001-111 study, lenvatinib plus pembrolizumab demonstrated promising antitumor activity in advanced NSCLC, although around half of the patients received prior anti-PD(L)1 treatment.

More than 1273 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) with additional patients treated in combination studies. The safety profile is largely consistent with that of other anti-PD-1 antibodies and included mostly mild/moderate AEs. Grade 3 and Grade 4 imAEs have been observed and have been generally reversible and manageable with study drug interruption and/or steroid treatment. The programmed cell death protein ligand-1 (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 9.6.3. Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 9. For further information on the safety profile of tislelizumab, please refer to the tislelizumab (BGB-A317) Investigator's Brochure.

For fruquintinib, as of 03 September 2019, 7 clinical trials in patients with cancer had been completed and 5 clinical studies were ongoing. Important identified risks for fruquintinib included hemorrhage, hepatic function abnormal (including blood bilirubin increased, transaminase increased), infection, and hypertension. The AESIs included hemorrhages, hepatic function abnormal, infections, hypertension, dermatological toxicity, proteinuria, thyroid dysfunction, embolic and thrombotic events, arterial and venous, and gastrointestinal perforation/fistula. AE management guidelines are presented in Section 9.7. For further information on the safety profile of fruquintinib, please refer the fruquintinib Investigator's Brochure.

The potential drug-drug interaction between tislelizumab, a monoclonal antibody, and fruquintinib, a small molecule drug product, is expected to be very low. The tolerability of anti-PD-1 therapy and TKI combination has been demonstrated in other combination trials (eg, lenvatinib plus pembrolizumab in patients with advanced endometrial cancer [Makker et al 2019] and avelumab plus axitinib in patients with advanced hepatocellular carcinoma [Kudo et al 2019]). The toxicity profile of each therapy appeared consistent with their monotherapy profiles; thus, no severe overlapping toxicity is expected with fruquintinib in combination with tislelizumab.

To mitigate risk, the study will include a safety run-in (Part 1) during which the recommended Phase 2 dose (RP2D) of fruquintinib in combination with tislelizumab will be assessed by the Safety Monitoring Committee (SMC) before enrollment into Part 2 can proceed. Given the unmet medical need, the expected tolerability of the combination, the antitumor activity of tislelizumab and fruquintinib in GC, CRC and NSCLC, and potential for synergy with the combination as seen with other similar combination trials, the benefit-risk profile based on available tislelizumab and fruquintinib data, is considered favorable. In order to assess the potential benefit and safety of tislelizumab in combination with fruquintinib, an open-label study will be conducted.

1.6. Study Conduct

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives for Part 1

2.1.1. Primary Objective(s)

- To assess the safety and tolerability of tislelizumab in combination with fruquintinib
- To confirm the RP2D of fruquintinib in combination with tislelizumab

2.2. Study Objectives for Part 2

2.2.1. Primary Objective(s)

- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by investigator in patients with selected solid tumors as measured by the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1

2.2.2. Secondary Objectives

- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the progression free survival (PFS) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the disease control rate (DCR) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the clinical benefit rate (CBR) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the duration of response (DOR) per RECIST v1.1
- To assess the efficacy of tislelizumab in combination with fruquintinib as in patients with selected solid tumors as measured by overall survival (OS)
- To assess the safety of tislelizumab in combination with fruquintinib

2.2.3. Exploratory Objectives

- To characterize the immunogenicity of tislelizumab and its time-pairing PK when given in combination with fruquintinib
- To assess the PK of fruquintinib when given in combination with tislelizumab
- To explore potential biomarkers that may correlate with clinical response/resistance to tislelizumab in combination with fruquintinib

2.3. Study Endpoints for Part 1

2.3.1. Primary Endpoint

- Safety and tolerability will be assessed throughout the study by monitoring adverse events (AEs) characterized by type, frequency, severity per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, timing, seriousness, and relationship to study drug(s); and other safety assessments
- RP2D of fruquintinib in combination with tislelizumab

2.4. Study Endpoints for Part 2

2.4.1. Primary Endpoint

- ORR – defined as the proportion of patients whose best overall response is complete response (CR) or partial response (PR) as assessed by investigator per RECIST v1.1

2.4.2. Secondary Endpoints

- PFS – defined as the time from the date of first dose to the date of the first determination of an objectively documented tumor progression as assessed by investigator per RECIST v1.1, or death, whichever occurs first
- DCR – defined as the as the proportion of patients whose best overall response is CR, PR, or stable disease (SD) as assessed by investigator per RECIST v1.1
- CBR – defined as the as the proportion of patients whose best overall response is CR, PR, or durable SD as assessed by investigator per RECIST v1.1
- DOR – defined as the time from the first occurrence of documented objective response to the time of progression as assessed by investigator per RECIST v1.1 or death from any cause, whichever occurs first
- OS - defined as the time from the date of first dose to the date of death due to any cause
- AEs characterized by type, frequency, severity (as graded by the NCI-CTCAE v5.0), timing, seriousness, and relationship to study drug(s); and other safety assessments

2.4.3. Exploratory Endpoint

- Incidence of anti-tislelizumab antibodies (ADA), and its time-pairing serum concentration of tislelizumab
- Plasma concentrations and derived PK parameters of fruquintinib as data permit
- Potential biomarkers including but not limited to programmed cell death protein ligand-1 (PD-L1) expression, tumor mutational burden (TMB) and DNA mutation/blood tumor mutational burden (bTMB) and DNA mutation, gene expression profile (GEP) in the GC, MSS CRC and NSCLC cohorts, Epstein-Barr virus (EBV) in the GC cohort, microsatellite stable (MSS)/microsatellite instable (MSI) status in the GC cohort, and the association of biomarkers with disease status, response/resistance to tislelizumab in combination with fruquintinib

3. STUDY DESIGN

This is an open label, multicenter, Phase 2 study designed to assess the efficacy and safety of tislelizumab in combination with fruquintinib in patients with advanced or metastatic, unresectable GC, MSS CRC and PD-L1 positive (defined as TC≥1% by SP263 IHC) NSCLC. The study will be conducted in 2 parts.

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, approximately 90 patients (approximately 30 patients per each indication) will be enrolled and receive tislelizumab plus fruquintinib treatment at RP2D.

Part 1 of the study will be the safety run-in stage during which the first 6 patients will be enrolled and assessed for DLTs during the 28-day DLT observation period. Study drug administration will begin at the full dose of fruquintinib (5 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) in combination with tislelizumab (300 mg once every 4 weeks) based on the well-established safety profiles of tislelizumab and fruquintinib, the non-overlapping mechanisms of action, and the desire to treat patients at doses shown to be effective in previous studies. A lower dose level of fruquintinib (4 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) will be explored as necessary depending on observed toxicity. Refer to Section 3.1 and Section 3.2 for assessment of DLT guidance and DLT definitions, respectively. The determination of the DLT will be made jointly by the investigator and sponsor after safety data has been reviewed. Only DLTs during the first 28 days of treatment will be assessed. Once they complete the DLT assessment, each subject still receiving study treatment will continue with the same dosage.

- If 0-1 of 6 patients experience a DLT, the study may proceed at the current dose of both drugs.
- If 2 or more patients experience a DLT, then, following consultation with the SMC, the study will proceed with enrollment in the next defined lower dose (Dose Level -1), an additional 6 patients will be enrolled, and the 28-day DLT observation period will be repeated.
- If 2 or more patients experience a DLT in Dose Level -1, enrollment in the study will cease.

The SMC will evaluate the safety and tolerability of the combination therapy when the first 6 DLT-evaluable patients have completed the first 28 days of treatment or when ≥ 2 DLTs at the tested dose level occur. Safety information including but not limited to the DLTs, all TEAEs, and laboratory abnormalities will be reviewed by the SMC. The SMC will make recommendations on safety management, including resumption of enrollment, de-escalation of fruquintinib to one lower dose level, or termination of enrollment. The final decision will be made by sponsor. Once the sponsor has determined that the combination therapy could proceed, the current dose will be confirmed as the RP2D, and enrollment for Part 2 will begin at RP2D. Patients enrolled in Part 1 at RP2D will be counted towards Part 2 by the diagnosis of the tumor types; up to approximately 30 patients per cohort will be enrolled at RP2D.

Tumor assessments will be performed by the investigator using RECIST v1.1 criteria (Eisenhauer et al 2009). Tumor imaging (computed tomography [CT] with oral/IV contrast, unless contraindicated, or magnetic resonance imaging [MRI]) must be performed within 28 days prior to enrollment. On-study tumor assessments will occur every 8 weeks (±7 days) during the first 56 weeks and every 12 weeks (±7 days) thereafter until PD. If a patient discontinues study treatment due to any reasons other than PD, tumor assessments will continue to be performed as scheduled until disease progression, loss to follow up, initiation of subsequent therapy, withdrawal of consent, death, or until the study terminates, whichever occurs first.

All patients will be closely monitored for AEs throughout the study and for up to 30 days after the last dose of study drug(s). AEs will be graded according to the NCI-CTCAE v5.0. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting.

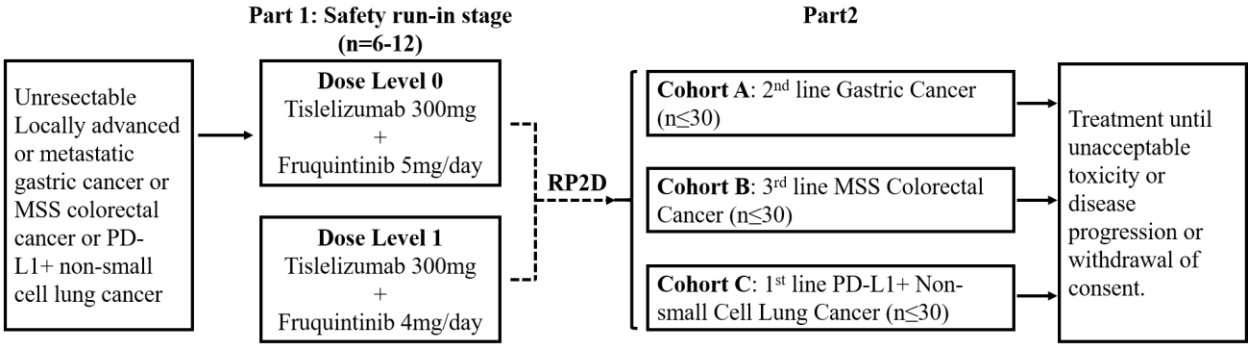
PK analysis will be performed for fruquintinib and tislelizumab. Biomarker analysis will include, but is not limited to tumor mutation burden, cytokine analysis, tumor-infiltrating lymphocytes assessment, and gene expression profiling (Section 8.5).

Tislelizumab and fruquintinib will be administered until PD, intolerable toxicity, death, withdrawal of consent, or until the study terminates. Patients may continue to receive tislelizumab and fruquintinib or either of the study drugs beyond the initial investigator-assessed PD, as defined by RECIST v1.1, provided that the patient has investigator-assessed clinical benefit and is tolerating study drug(s). For patients in the CRC cohort, tislelizumab monotherapy will not be permitted. Refer to Section 7.6 and Section 8.3 for additional considerations regarding treatment continuation and withdrawal. Patients who, at time of progression, have an ongoing AE that leads to treatment discontinuation and has completed the scheduled Safety Follow-up Visit will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a new anticancer therapy. If a patient discontinues study drug(s) due to reasons other than PD or death, tumor assessments should continue to be performed following the scheduled assessment plan until the start of new anticancer therapy, PD, death, lost to follow-up, or withdrawal of consent for efficacy follow-up (Section 7.5.2).

Patients who have discontinued study drug(s) should return to the site for an End-of-Treatment (EOT) Visit within ≤ 7 days as detailed in Section 7.4. After the EOT Visit, patients will have scheduled follow-up visits for safety and, if applicable, for efficacy per the Schedule of Assessments (Appendix 1).

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

Figure 1: Study Schema



Abbreviations: DLT, dose limiting toxicity; RP2D, recommended Phase 2 dose; SMC, Safety Monitoring Committee.
Notes: The first 6 patients will be enrolled and assessed for DLTs during the 28-day DLT observation period. Dosing will begin at Dose Level 0. Dose Level -1 will be explored as necessary depending on observed toxicity. The SMC will evaluate the safety and tolerability of the combination therapy when the first 6 DLT-evaluable patients have completed the DLT observation period or when ≥ 2 DLTs at the tested level occur. Enrollment for Part 2 will begin once the sponsor has determined that the combination could proceed and confirmed the RP2D of fruquintinib in combination with tislelizumab.

- Tislelizumab will be administered intravenously on Day 1 of every 4-week cycle.
- Fruquintinib will be administered daily, orally with 3 weeks on followed by 1 week off for every 4-week cycle.

3.1. Assessment of Dose-Limiting Toxicity

DLTs will be assessed per the DLT criteria below (Section 3.2) during the 28-day DLT assessment window, which begins on the first day of the administration of the study drugs. Patients will be considered evaluable for DLTs if they 1) received ≥ 85% of scheduled fruquintinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab administration during the DLT assessment window and/or 2) experienced a DLT.

Patients will be considered not evaluable for DLTs if during the DLT assessment window they 1) were withdrawn from the study, 2) did not receive ≥ 85% of scheduled fruquintinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab drug administration, 3) received prophylactic supportive care that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition), OR 4) have taken a strong inhibitor or inducer of enzyme CYP3A4 (Appendix 10) as the exposure to fruquintinib may be impacted. Patients who are not DLT-evaluable must be replaced, if needed.

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

3.2. Dose-Limiting Toxicity Definition

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

Hematologic:

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

Nonhematologic:

- Any ≥ Grade 4 toxicity
- Any Grade 3 toxicity that does not resolve to baseline or ≤ Grade 1 within 7 days after optimal supportive care is initiated

Note: The following nonhematologic AEs will not be considered DLTs:

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

4. STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Signed informed consent form (ICF) and able to comply with study requirements.
2. Age ≥ 18 years (or the legal age of consent).
3. At least 1 measurable lesion as defined by RECIST v1.1.

   Note: Selected target lesion(s) must meet one of these criteria: 1) not previously treated with local therapy or 2) within the field of prior local therapy but with subsequent progression as per RECIST v1.1.
4. Tumor tissue (archival tumor tissues as formalin-fixed paraffin-embedded blocks or approximately 15 unstained slides) for central laboratory assessment of MSS status (MSI test) for the CRC patients, PD-L1 status for the NSCLC patients, for central/local laboratory assessment of EGFR status for the non-squamous NSCLC patients with no EGFR documentation during the screening period, and for retrospective analysis of other exploratory biomarkers related to response and resistance for the CRC, GC and NSCLC patients in a BeiGene designated central or test laboratory.

   - A fresh biopsy is mandatory in the absence of archival tumor tissues.
   - For the CRC patients, approximately 2 mL peripheral whole blood will be collected for MSI test control during the screening period.
   - Submission of < 15 unstained slides is not a protocol deviation. If patients cannot provide 15 unstained slides, patients may be enrolled after confirmation with the sponsor.

   Note:

   Written informed consent is required prior to obtaining fresh tumor biopsies and blood samples. Biopsy tumor tissue must be obtained from a core or punch biopsy. Tumor tissue from a fine-needle aspiration is not acceptable.
5. In case of submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 (Appendix 4).

6. Adequate organ function as indicated by the following laboratory values ≤ 7 days before the first dose of study drug(s).
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 90 g/L, without blood transfusion or growth factor support ≥ 14 days before sample collection
    d. AST and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN for patients with liver metastases
    e. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
    f. Urine protein is ≤1+ by dipstick or 24-hour urine protein is < 1.0g/24-h
        - Patients with > 1+ proteinuria on urinalysis must undergo a 24-hour urine collection.
    g. Serum creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (Appendix 5)
    h. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless patient is receiving anticoagulant therapy and PT values are within the intended therapeutic range of the anticoagulant
7. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 120 days after the last dose of study drug(s), and have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drug(s) (Appendix 6).
8. Nonsterile males must be willing to use highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug(s) (Appendix 6).
    - A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    - Males with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.
9. Patients enrolled in part 1 and part 2 should be histologically or cytologically diagnosed with one of the following indications and meet the indication specific inclusion criteria.
    a. Gastric Cancer
        i. Histologically or cytologically confirmed, advanced or metastatic, unresectable adenocarcinoma of gastric or esophagogastric junction. All other histological types are excluded.
        ii. Progression during or after prior first-line therapy containing any platinum/fluoropyrimidine doublet (combination with anti-HER2 antibody is mandatory if tumor HER2 is documented positive). If relapse or metastasis occur during the adjuvant/neoadjuvant treatment containing platinum/fluoropyrimidine or within 6 months after the completion of the

above treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first line systemic chemotherapy for PD.

b. MSS CRC

i. Histologically or cytologically confirmed, advanced or metastatic, unresectable adenocarcinoma of the colon or rectum. All other histological types are excluded.

ii. Patients must have failed 2 lines of standard chemotherapies, including fluoropyrimidine, oxaliplatin, or irinotecan. Failed chemotherapies are defined as the occurrence of PD or intolerable toxicities during the treatment or after the last dose.

- Notes: a) Each line of treatment for advanced disease until PD includes one or more chemo drugs used for ≥ 1 cycle; b) Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occur during the adjuvant/neoadjuvant treatment period for patients with nonmetastatic or metastatic disease who have received curative surgery or within 6 months after the completion of the above treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first line systemic chemotherapy for PD; c) Patients could be enrolled once they have failed fluoropyrimidine, oxaliplatin and irinotecan based regimen as first line treatment.

iii. Patients with RAS wild type tumor must have received anti-VEGF and/or EGFR antibody treatment. Patients with RAS mutation or RAS status unknown must have received anti-VEGF antibody treatment.

iv. Tumor tissues were identified as microsatellite stable (MSS) by polymerase chain reaction (PCR) by a central laboratory.

c. NSCLC

i. Histologically or cytologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) NSCLC.

ii. Have had no prior systemic therapy for advanced or metastatic NSCLC. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a disease-free interval of at least 6 months from the last dose of chemotherapy and/or radiotherapy prior to first dose.

iii. Patients with documented EGFR mutation or known ALK gene translocation (both must be tissue-based test) will be excluded. For non-squamous patients with unknown EGFR status, archival or fresh tumor tissues are required for EGFR mutation assessment in central/local laboratory prior to enrollment and only those with wild type EGFR will be enrolled.

iv. Tumor tissues were identified as PD-L1 positive defined as TC≥1% by SP263 IHC by a central laboratory.

4.2. Exclusion Criteria

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

1. Has at screening any central nervous system metastasis and/or leptomeningeal disease.
2. Prior therapy targeting CTLA-4, PD-1, PD-L1 or programmed cell death protein ligand-2 (PD-L2) or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.
3. Prior treatment with VEGFR-TKI or anti-VEGFR antibody (eg, ramucirumab).
4. Received more than 1 line of systemic treatment for advanced or metastatic, unresectable adenocarcinoma of gastric or esophagogastric junction, or more than 2 lines of systemic treatment for advanced or metastatic, unresectable adenocarcinoma of the colon or rectum.
5. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 7), with the following exceptions:
    a. Controlled Type 1 diabetes
    b. Hypothyroidism (provided it is managed with hormone-replacement therapy only)
    c. Controlled celiac disease
    d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
    e. Any other disease that is not expected to recur in the absence of external triggering factors
6. Any active malignancy ≤ 2 years before the first dose of study drug(s) except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
7. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s), with the following exceptions:
    a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    b. Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
    c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
8. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including but not limited to pulmonary fibrosis, acute lung diseases, etc.
9. Clinically significant pericardial effusion.
10. Clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or abdominal tapping for drainage within 2 weeks prior to the first dose of study drug(s).
11. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before the first dose of study drug(s).

12. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy (not including antiviral therapy for hepatitis) ≤ 14 days prior to the first dose of study drug(s).
13. Untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) or active hepatitis C at screening.
    - Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before the first dose of study drug(s).
    - Patients with a negative hepatitis C virus (HCV) antibody test at Screening or positive HCV antibody test followed by a negative HCV RNA test at Screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody.
14. Known history of HIV infection
15. Any major surgical procedure ≤ 28 days before the first dose of study drug(s). Patients must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study drug(s).
16. Prior allogeneic stem cell transplantation or organ transplantation.
17. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug(s)
    b. Pulmonary embolism ≤ 6 months before the first dose of study drug(s)
    c. Acute myocardial infarction ≤ 6 months before the first dose of study drug(s)
    d. Heart failure meeting New York Heart Association Classification III or IV (Appendix 8) ≤ 6 months before the first dose of study drug(s)
    e. Ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug(s)
    f. Cerebrovascular accident ≤ 6 months before the first dose of study drug(s)
    g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications, defined as: systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg ≤ 28 days before the first dose of study drug(s)
    h. Syncope or seizure ≤ 28 days before the first dose of study drug(s)
18. Patients with active gastrointestinal and duodenal ulcers, ulcerative colitis, and other gastrointestinal disease or unresectable tumors with active bleeding, or other conditions that the investigator determines to possibly cause gastrointestinal bleeding, perforation and other conditions; or prior gastrointestinal perforation or gastrointestinal fistula that has not recovered after surgical treatment.
19. Evidence of tendency or medical history of bleeding (such as melena, hematemesis, hemoptysis, fresh in stool, etc.) within 2 months before first dose of study drug(s).

20. High risk of bleeding at screening due to tumor invasion into major vessels, such as pulmonary artery, the superior vena cava, or the inferior vena cava, as determined by investigators.
21. Have a medical history arterial thrombus or deep vein thrombosis within 6 months prior to the first drug administration; or experienced a stroke event and/or transient ischemic attack within 12 months; patients with implanted intravenous infusion pump or catheter related thrombosis or superficial vein thrombosis, except for patients with stable thrombus after routine anticoagulant therapy.
22. Known allergy to any of the components of tislelizumab or fruquintinib preparations including tartrazine (E102) and sunset yellow (E110) or have any previous history of severe hypersensitivity reactions to other monoclonal antibodies.
23. Chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin), or investigational therapy ≤ 28 days or 5 half-lives (whichever is shorter, but ≥ 14 days) before the first dose of study drug(s). Also, palliative radiation treatment or other locoregional therapies within 14 days prior to the first dose of study drug.
24. Use of strong inducers or inhibitors of CYP3A4 within 2 weeks or 5 times half-lives whichever is longer before the first dose of study drugs(Appendix 10)
25. Concomitant medications with a known risk of causing QT prolongation and/or Torsades de Pointes (Appendix 11)
26. Any Chinese herbal or Chinese patent medicine with anticancer activity approved by the NMPA (regardless of the type of cancer) used ≤ 14 days before the first dose of study drug(s).
27. 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).
28. Live vaccine ≤ 28 days before the first dose of study drug(s).
    - Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
29. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug(s), or will affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
30. Inability to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the complete small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
31. Prior randomization in a tislelizumab study regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out.

32. Concurrent participation in another therapeutic clinical study.
    - Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.
33. Women who are pregnant or are breastfeeding.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a sterile glass vial 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 condition as specified on the label.

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

5.1.2. Fruquintinib

Fruquintinib is presented as 2 capsule strengths (1 mg and 5 mg). The 1 mg capsule is presented as a No. 3 hard gelatin capsule containing 52 mg of a blended white to off-white powder that is composed of fruquintinib drug substance, microcrystalline cellulose, starch, and talc. The 5 mg capsule is presented as a No. 1 hard gelatin capsule containing 260 mg of the same blended powder as the 1 mg capsule.

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

The study drug must be kept at the temperature condition as specified on the label.

For further details, see the manufacturer's prescribing information for fruquintinib.

5.2. Dosage, Administration, and Compliance

Treatment with study drug(s) on Day 1 of Cycle 1 must begin within 2 business days after a patient's enrollment (Section 7.2). Treatment modifications (eg, dose delay/holds) will be based on specific laboratory and AE criteria, as described in Section 5.4. Guidelines for study treatment modification, delay, or discontinuation as well as management of imAEs or infusion-related reactions are provided in Section 9.6, Section 9.7, and Appendix 9.

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

Table 1: Selection and Timing of Dose for Each Patient

Study Drug	Dose	Frequency of Administration	Route of Administration
Tislelizumab	300 mg	Every 4 weeks	Intravenous
Fruquintinib	5 mg or 4 mg	3 weeks on/1 week off	Oral

Note: Fruquintinib starting dose will depend on which part of the study the patient is enrolled and if the RP2D has been determined.

5.2.1. Tislelizumab

Tislelizumab 300 mg will be administered on Day 1 of each 28-day cycle (once every 4 weeks).

Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

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

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 9.5.8 and Appendix 9.

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

5.2.2. Fruquintinib

Fruquintinib will be self-administered orally once daily for 21 days, followed by 7 days off in 28-day cycles with or without food. The capsules should be swallowed with a glass of water. On days when fruquintinib and tislelizumab dosing are both scheduled, the daily dose of fruquintinib should precede tislelizumab infusion.

In Part 1, the staring dose is 5 mg once daily. Depending on safety observations, the fruquintinib dose may be de-escalated to 4 mg once daily. The sponsor will confirm the RP2D of the combination treatment. In Part 2, fruquintinib will be administered at the RP2D.

An adequate supply of fruquintinib will be dispensed to patients on Day 1 of each new cycle (once every 4 weeks). Patients should record the date and time of drug administration and amount in the patient diary. Each time study drug is dispensed, compliance will be evaluated and reinforced. Treatment compliance will also be monitored by drug accountability and recorded in

the patient's medical record and electronic case report form (eCRF). If the number of capsules returned does not agree with the expected number, the patient should be counseled, and proper dosing reinforced.

The following guidelines should be followed for fruquintinib administration:

- Fruquintinib may be taken either in the fasting state or after meals.
- Capsules should be taken with 100 to 200 mL (1 cup) of water at approximately the same time each day.
- Patients should swallow the capsules whole and not chew them.
- If vomiting occurs after dosing, fruquintinib doses should not be replaced.
- If a dose is missed, the missed dose can be taken within a 12-hour window of the time the patient typically takes the dose. A double dose should not be administered to make up for missed individual doses.

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of fruquintinib therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.4.2 and Section 9.7.

5.3. Overdose

Any incorrect administration of study drug(s) or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or fruquintinib (defined as any dose greater than 5 mg daily dose) should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an incorrect administration or overdose of study drug(s) will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 9.5.2. In the event of overdose, further study drug administration should be held, and the patient should be observed closely for signs of toxicities. Appropriate supportive care measures should be provided if clinically indicated. Sites must contact the medical monitor prior to the patient resuming fruquintinib treatment.

5.4. Dose Delay or Modification

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

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

5.4.1. Dose Delay or Modification for Tislelizumab

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

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab or fruquintinib and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after the last dose of tislelizumab. If the administration of study drug can resume within ≤ 14 days, it should be administered in the current cycle. If tislelizumab needs to be withheld for > 14 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle. If the patient is unable to resume tislelizumab within 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from tislelizumab treatment. If the patient is unable to resume tislelizumab ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

5.4.2. Dose Delay or Modification for Fruquintinib

Should drug-related AEs occur, the severity of AEs will be graded according to the NCI CTCAE v5.0. Reasons for dose modifications or delays, the supportive measures taken, and the outcome should be documented in the patient's chart and recorded in the eCRF.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment can be continued at the same dose.
- To recover from acute toxicity, unless otherwise indicated, the treatment can be delayed for up to 14 days. If a treatment delay longer than 14 days is required, treatment should be discontinued. Continuation/resumption of fruquintinib treatment after an interruption of more than 14 days must be discussed with the medical monitor.
- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.

Treatment cycles will be counted continuously, regardless of dose delay.

The dose can be adjusted at any time due to the intolerable toxicity (**Error! Reference source not found.**). Once reduced, the dose cannot be re-escalated to the previous level.

- If the patient's original dose is 5 mg once daily, up to 2 dose reductions are permitted: one reduction from 5 mg once daily to 4 mg once daily, and if not tolerated, then a second reduction from 4mg once daily to 3 mg once daily.
- If the patient's original dose is 4 mg once daily, only 1 dose reduction is permitted: a reduction from 4mg once daily to 3 mg once daily.

Table 2: Fruquintinib Dose Reductions

Dose Level	Dose	Dose
Dose Level 0 (original dose)	5 mg once daily	4 mg once daily
Dose Level -1 (1st dose reduction)	4 mg once daily	3 mg once daily
Dose Level -2 (2nd dose reduction)	3 mg once daily	Not available

Dose reduction guidelines for haematologic and non-haematologic toxicities, other than guidance for important identified risks (palmar-plantar erythrodysesthesia [PPE], proteinuria, hypertension, decreased platelet count, hemorrhage, and liver function impairment in Table 8), are provided below (Table 3). Treatment should be held until AE/toxicity resolves or improves to ≤ Grade 1. If a patient has a Grade 3 toxicity that is expected to be manageable and reversible with a dose reduction, treatment should be held until toxicity resolves to ≤ Grade 1. Patients with Grade 3 non-haematologic toxicity not described below that does not resolve to ≤ Grade 1 within 14 days should permanently discontinue fruquintinib unless approval to continue is obtained in writing from the sponsor.

Table 3: Dose Modification Recommendations for Hematologic and Non-Hematologic Toxicity

AE Grade	Action
Grade 1 or 2[a]	None
Grade 3[b]	Interrupt the dose until the toxicity resolved to ≤ Grade 1 or baseline level within 14 days, then reduce the dose to a lower dose level
Grade 4	Discontinue treatment permanently

a. Should any arterial thrombosis occur, fruquintinib should be terminated.
b. Including Grade 3 diarrhea and stomatitis, etc. that are ineffectively treated by drug therapies, but excluding Grade 3 menstrual cycle extension.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

All prior therapy, dates of administration, best response, and date of progression for patient's cancer type will be collected at study entry and entered into the eCRF.

6.2. Permitted Concomitant Medications/Procedures

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

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before the first dose of study drug(s) and 30 days after the last dose of study drug(s) will be recorded.

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

Patients who use oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy may continue their use if indicated.

Prophylactic use of anticoagulation for the maintenance of patency of permanent indwelling central venous access devices or for patients at high risk of venous thromboembolism is permitted during study treatment. If patients are receiving anti-coagulation, they should be very closely monitored for potential hemorrhage.

The investigator should closely monitor patients receiving anti-platelet and/or anti-thrombotic drugs during study drug treatment and make a timely decision on whether to continue or stop such drugs in patients that report ≥ Grade 2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance.

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

Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 9 and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatment (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Hepatitis B Treatment

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

Radiation Therapy

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

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

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

6.3. Prohibited Concomitant Medications/Procedures

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

- Any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents (including Chinese [or other Country] herbal medicine and Chinese [or other Country] patent medicines for the treatment of cancer is not allowed. Chinese [or other Country] herbal and Chinese [or other Country] patent medicines with anticancer activity are defined as medication with approval by the NMPA (or other Country) for use as anticancer treatment (regardless of the type of cancer).
- Live vaccines ≤ 28 days before the first dose of study drug(s) and ≤ 60 days following the last dose of tislelizumab.
- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should not abuse alcohol or other drugs.

- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin) ≤ 28 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of study drug(s) and during the study. Patients must notify the investigator of all herbal remedies used during the study.
- Radiation therapy, except for palliative radiation therapy described in Section 6.2.
- Concomitant use of medications that have a known risk of causing QT prolongation and/or torsades de pointes (see Appendix 11 or refer to http://www.crediblemeds.org)

6.4. Medications to Be Used With Caution

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

Medications that are strong inhibitor or strong inducer of CYP3A should not be administered concomitantly with fruquintinib (See Appendix 10 for detailed information) unless investigator consider it necessary. Fruquintinib is metabolized through CYP3A so strong inhibitor or strong inducer of enzyme CYP 3A4 may significantly influence the metabolism of fruquintinib.

Fruquintinib showed inhibition of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporter in the in vitro studies, so drugs which are sensitive substrates, and substrates with narrow therapeutic index for P-gp and BCRP transporters should be avoided if possible (see Appendix 10). If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the P-gp or BCRP substrate medication.

Fruquintinib shows pH-dependent solubility (ie, solubility at pH 6.0–6.5 < solubility at pH 1–2) and is less well absorbed as gastrointestinal pH increases. Patients should avoid using proton pump inhibitors (eg, esomeprazole, lansoprazole, pantoprazole) during the study. If concomitant use of an acid-reducing agent is unavoidable, H2-antagonist (eg, famotidine, ranitidine, nizatidine) may be used but should be administered approximately 10 hours before or 2 hours after fruquintinib dosing. Antacid may be used, but the antacid dose should be administered at least 2 hours before or 2 hours after fruquintinib dosing.

6.5. Potential Interactions Between Tislelizumab and Fruquintinib

The potential for drug-drug interaction between tislelizumab and fruquintinib is expected to be low based on the metabolism of the drugs and their respective AE profiles. Tislelizumab is a therapeutic monoclonal antibody and is not expected to be metabolized by liver cytochrome P450 (CYP) or other drug-metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction. Even though fruquintinib was mainly metabolized via CYP enzymes, the possibility of tislelizumab interfering with this metabolism pathway is low.

7. STUDY PERIODS, VISITS, OR PROCEDURES

7.1. Screening Period

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

7.1.1. Informed Consent and Screening Log

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

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

7.2. Enrollment

All screening results and relevant medical history must be available before eligibility can be determined. The investigator must confirm that all eligibility criteria are met. The study site personnel will complete the Eligibility Authorization Packet, which must be signed by the investigator or a subinvestigator. The medical monitor or designee will review and approve if appropriate. No eligibility waivers will be granted. The study site personnel must ensure that confirmation of eligibility by the medical monitor has been received before the patient receives the first dose of study drug(s).

7.3. Treatment Period

Patients will be treated as described in Section 5.2.

Patients may continue to receive study drug(s) beyond the initial investigator-assessed PD, as defined by RECIST v1.1, provided that the patient has investigator-assessed clinical benefit and is tolerating study drug(s). Refer to Section 7.6 and Section 8.3 for additional considerations regarding treatment continuation and withdrawal.

7.4. End-of-Treatment Visit

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

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

7.5. Follow-up Periods

7.5.1. Safety Follow-up Period

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

All AEs, including SAEs, will be collected as described in Section 9.5.

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

7.5.2. Efficacy Follow-up Period

Patients who discontinue study drug(s) for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences PD, starts new anticancer therapy, or for any other reason listed in Section 7.6.2, whichever occurs first.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact the patients by telephone to determine their disease status.

7.5.3. Survival Follow-up Period

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

7.5.4. Lost to Follow-up

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

7.6. Discontinuation From Study Treatment or From the Study

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

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

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

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

If tislelizumab or fruquintinib is discontinued permanently for reasons other than disease progression, the other drug could be continued per the study protocol.

If the decision is made to continue fruquintinib monotherapy treatment beyond initial progression, the patient will remain on the trial and will continue to be treated and monitored according to the schedule in Appendix 1. Fruquintinib monotherapy treatment must be discontinued permanently upon documentation of further progression, either symptomatic or radiographic.

For patients with CRC, if fruquintinib is permanently discontinued, tislelizumab must be discontinued. Tislelizumab monotherapy is not allowed in the CRC cohort.

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

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

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

7.7. End of Study

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

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

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

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

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

In the opinion of the investigator, any patient who continues to derive clinical benefit at the end of study and remains eligible for continued treatment with tislelizumab or tislelizumab plus fruquintinib or fruquintinib alone will be offered the option to continue treatment either by enrolling into a long-term extension study after signing the respective informed consent form or by additional supply.

8. STUDY ASSESSMENTS

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.

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

8.1. Screening Assessments

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

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

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

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

8.1.1. Pulmonary Function Tests

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

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

Tests may be repeated as clinically indicated while on study.

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

8.2. Safety Assessments

8.2.1. Vital Signs

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

8.2.2. Physical Examinations

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

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs in the eCRF. Refer to Section 9.2 regarding AE definitions, reporting, and follow-up requirements.

8.2.3. Eastern Cooperative Oncology Group Performance Status

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

8.2.4. Laboratory Safety Tests

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

If clinical chemistry, hematology, coagulation , and urinalysis at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration.

For central laboratory assessments, details regarding sample collection and shipment will be provided in a separate laboratory manual.

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

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

8.2.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and CK cardiac isoenzyme (CK-MB) are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 9 for guidelines for management of suspected immune-mediated myocarditis, respectively). Serum troponins may be substituted per local guidelines if used consistently throughout the study. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients who continue to receive fruquintinib monotherapy may receive CK and CK-MB testing if clinically indicated.

8.2.5. Electrocardiograms

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

All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws). The patient should rest in a semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation) before each ECG collection.

8.2.6. 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 9.5.

8.2.7. Hepatitis B and C Testing

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

Patients who have detectable HBV DNA at screening will perform the viral load test every 4 cycles starting at Cycle 5.

8.3. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 8 weeks (± 7 days), from Day 1 of Cycle 1, for the first 56 weeks, then every 12 weeks (± 7 days) thereafter based on RECIST v1.1 (Appendix 12). If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule.

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

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

- Imaging of the brain (MRI or CT) at baseline is required for all screened NSCLC patients.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron-emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a complete response (CR) is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should be performed at screening, only if clinically indicated, and should be followed throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST Version 1.1 may be used.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 12). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

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

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

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

A patient who discontinues study drug(s) early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a new anticancer therapy, experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Tumor assessments must be performed on schedule regardless of whether study treatment has been administered or withheld. That is, they should not be adjusted for delays in cycles.

8.4. Pharmacokinetic Assessment and Antidrug Antibody Testing

Blood sampling for the PK of tislelizumab and fruquintinib will be collected at the timepoints specified in the Schedule of PK Assessments (Appendix 2).

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

The following assessments will be performed at a bioanalysis laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay
- PK assays: serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay and the plasma concentration of fruquintinib will be assayed using the validated LC-MS/MS method by request from the sponsor.

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

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

8.5. Biomarkers

Instructions for the processing, storage, and shipping of samples will be provided in the study laboratory manual. Refer to the Schedule of Assessments (Appendix 1) for sample collection timepoints.

Archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 freshly cut unstained FFPE slides) need to be sent for central laboratory assessment of MSS status (MSI test) for the CRC patients, PD-L1 status for the NSCLC patients, for central/local laboratory assessment of EGFR status for the non-squamous NSCLC patients with no EGFR documentation during the screening period, and for retrospective analysis of other exploratory biomarkers related to response and resistance for all patients in a BeiGene-designated central or test laboratory. These exploratory biomarkers include but are not limited to PD-L1, TMB/DNA mutation, and GEP for all enrolled patients, and EBV, MSS/MSI status (TMB panel can report the MSS/MSI status) for the GC patients. Submission of < 15 unstained slides is not a protocol deviation.

A fresh tumor biopsy at a tumor lesion is mandatory if there are no available archival tumor samples during the screening period. Optional fresh biopsies in patients who have confirmed PD will also be collected in the three cohorts during the study from accessible tumor sites. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

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

Approximately 2 mL of peripheral whole blood will be required for collection to work as the MSI test control during the screening period for CRC patients. Blood samples will be obtained for the evaluation of exploratory biomarkers including, but not limited to bTMB/DNA mutation for all enrolled patients, which will be collected 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) (approximately 10 mL for each timepoint). Written patient consent is required for blood sample collections.

8.6. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 4 weeks from Day 1 of Cycle 1.

8.7. Unscheduled Visits

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

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

9. SAFETY MONITORING AND REPORTING

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

9.1. General Plan to Manage Safety Concerns

9.1.1. 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 and fruquintinib, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors and anti-VEGFR TKIs, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before the first dose of study drug(s) are excluded from the study. Patients with contraindications for fruquintinib treatment are also excluded from the study (see Section 4.2 for the full list of exclusion criteria).

9.1.2. Abnormal Liver Function Tests

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

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

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

9.1.3. 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.

All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 4), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, study drug(s) will be administered only after clinical laboratory results have been reviewed. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.1.1).

Serum samples will be drawn for determination of ADAs to tislelizumab in patients.

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

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 9.6.

9.2. Adverse Events

9.2.1. Definitions and Reporting

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

Examples of AEs include:

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

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

9.2.2. Assessment of Severity

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

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas, seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.5.2.

9.2.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug(s) and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug(s) should be considered and investigated. The investigator should consult the tislelizumab (BGB-A317) and the fruquintinib Investigator's Brochure in the determination of 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 transmission of the SAE report to the sponsor because the causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

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

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug(s)
- Biological plausibility

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

9.2.4. Follow-up of Adverse Events

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

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

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

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the timeframes outlined in Section 9.5.2.

9.2.5. Laboratory Test Abnormalities

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

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

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

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

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

9.3. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered to be SAEs:

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

9.4. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the tislelizumab (BGB-A317) and the fruquintinib Investigator's Brochure.

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

9.5.1. Adverse Event Recording Period

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

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

AEs and SAEs should be recorded according to the details in Table 4. For the follow-up period for AEs, see Section 9.2.4. For the definition of treatment-emergent adverse events (TEAEs), see Section 10.3.3.

Table 4: Guidance for Duration of Recording New or Worsening Adverse Events

Event Type	Record new or worsening events that occur during this period	
	Begin	End
SAEs[a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 9.5.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

9.5.2. Reporting Serious Adverse Events

9.5.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial/Follow-up*[1] report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	Electronic submission of SAE Form to safety portal*[2]

Abbreviations: IMP, investigational medical product, SAE, serious adverse event.
*[1]. Report follow-up information clinically relevant and pertaining to the SAE which includes but 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 IMP. 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.

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

9.5.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 9.5.2.1. The SAE report will always be completed as thoroughly as possible, including all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

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

The investigator must always provide an assessment of causality for each SAE as described in Section 9.2.3.

The sponsor will provide contact information for SAE receipt.

9.5.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

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

All suspected unexpected serious adverse reactions (as defined in Section 9.4) will be submitted to all applicable regulatory authorities and investigators for tislelizumab and fruquintinib studies.

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

9.5.3. Eliciting Adverse Events

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

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

9.5.4. Progressive Disease

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

9.5.5. Deaths

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

9.5.6. Recording Pregnancies

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

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

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

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

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

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

- tislelizumab (BGB-A317) Investigator's Brochure
- fruquintinib Investigator's Brochure

9.5.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune related (see Section 9.6.3) should be classified as imAEs and identified as such in the eCRF AE page.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 9.

An extensive list of potential imAEs appears in Table 7. All conditions similar to those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 9.

9.5.9. Recording Infusion-Related Reactions

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

9.6. Management of Adverse Events of Special Interest for Tislelizumab

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

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

9.6.1. Managing Infusion-Related Reactions

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

Treatment modifications for symptoms of infusion-related reactions due to tislelizumab are provided in Table 6.

Table 6: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Tislelizumab

NCI-CTCAE grade	Treatment modification for tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text following this table. Subsequent infusions should be given after premedication and at the reduced infusion rate.

NCI-CTCAE grade	Treatment modification for tislelizumab
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug treatment.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug treatment. Hospitalization is recommended.

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

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

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

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

9.6.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

9.6.3. Immune-Mediated Adverse Events

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

A list of potential imAEs is shown below in Table 7. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune related.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 9. For any AEs not included in Appendix 9, please refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 7: Examples of Immune-Mediated Adverse Events

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

Body system affected	Events
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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

Recommendations for managing imAEs are detailed in Appendix 9.

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

9.7. Management of Adverse Events of Special Interest for Fruquintinib

The AE management guidance for important identified risks for fruquintinib are provided below. (Table 8).

Table 8: Management of Adverse Events Related to Fruquintinib

AE Grading Standard	Dose Adjustment	Treatment Suggestions
Palmar-Plantar Erythrodysethesia		
Grade 1: numb, paresthesia, dysesthesia, erythema, painless edema, desquamation, thicken skin and hand and foot discomfort which does not affect the normal activities; without any pain	None.	Active supportive treatment can be adopted to relieve the symptoms; for example, moisturizing skin cream, lotion, or hydrophilic urea ointment can be used.
Grade 2: erythema with pain accompanied by hand and foot swelling and /or discomfort, which affects normal activities	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment at the same dose level.	Active supportive treatment can be adopted to relieve the symptoms; for example, moisturizing skin cream, lotion, or hydrophilic urea ointment can be used.
Grade 3: wet desquamation, ulcer, blister or severe hand and foot pain or severe discomfort, which affects work or normal activities.	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Active supportive treatment can be adopted to relieve the symptoms; Should the same AE occur for 3 times or still occurs after 2 times of dose reduction, the drug should be terminated.
Proteinuria[a]		
Grade 1: Proteinuria 1+ by urinalysis; 24-hour urine protein quantitation < 1.0 g	None	Follow up at scheduled study visits.
Grade 2: Proteinuria 2+ by the urinalysis;	None	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.

AE Grading Standard	Dose Adjustment	Treatment Suggestions
24-hour urine protein quantitation is between 1.0 to < 2.0 g		
Grade 2: Proteinuria 2+ or above by urinalysis; 24-hour urine protein quantitation is between 2.0 to < 3.5 g (excluding 3.5 g)	• Hold treatment. If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 3: 24-hour urine protein quantitation ≥ 3.5 g	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide supportive treatment and increase the frequency of urine monitor to once or twice a week; consult nephrologist if necessary. Should the same AE occur for 3 times or still occurs after 2 times of dose reduction, the drug should be terminated.
Hypertension		
Grade 1: prehypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None.	Follow up as planned schedule
Grade 2: SBP 140-159 mmHg or DBP of 90-99 mmHg; or DBP symptomatic increase > 20 mmHg	None.	Treatment objective: lower the blood pressure to < 140/90 mm Hg (or < 130/80 mm Hg in patients with chronic renal disease and/or diabetes). Refer to Appendix 15.
Grade 3: SBP ≥ 160 mmHg or DBP ≥ 100mmHg; or more than one drug or more intensive therapy are used	• If BP > 160/100 mmHg lasts for > 7 days after initiation of anti-hypertensive treatment or modification of current anti-hypertensive treatment, treatment should be held. • If hypertension resolves to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Treatment objective: lower the blood pressure to < 140/90 mmHg (or < 130/80 mm Hg in patients with chronic renal disease and/or diabetes). Refer to Appendix 15.
Grade 4: Life threatening (eg, malignant hypertension, temporary or permanent neurological deficits and hypertensive crisis)	Permanently discontinue study treatment.	Emergent medical treatment.
Decreased Platelet Count		
Grade1: Platelet count < LLN - 75,000/ mm3;	None	Perform follow up visit as scheduled.

AE Grading Standard	Dose Adjustment	Treatment Suggestions
< LLN - 75.0 $\times 10^9$/L		
Grade 2: Platelet count < 75,000-50,000/mm^3; < 75.0 - 50.0 $\times 10^9$/L	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 7 days, resume treatment at the same dose level.	Hematology test should be monitored every 2-3 days; active treatment for platelet elevation is recommended.
	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Hematology test should be monitored every 2-3 days; active treatment for platelet elevation is recommended.
Grade 3: Platelet count < 50,000 - 25,000/mm^3; < 50.0 - 25.0 $\times$ 10^9/L	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Hematology test should be monitored every 2-3 days; active treatment (platelet transfusion) to elevate the platelet count is recommended. Hematology examination should be performed once every week in the follow up visit.
Grade 4: Platelet count < 25,000/mm^3; < 25.0 $\times$ 10^9/L	Permanently discontinue study treatment.	Hematology test should be performed once daily until the AE recovers to Grade 2 or a lower grade; platelet transfusion or other active treatment should be provided
Hemorrhage at Any Site		
Grade 1	None	Perform follow up visit as scheduled.
Grade 2	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide active treatment[c]
Grade 3 or above[b]	Permanently discontinue study treatment.	Emergent medical intervention[c]
Abnormal Liver Function[d]		
Grade 1	None.	Follow up per planned schedule.
Grade 2 or 3 (Liver function is abnormal but the biochemical criteria for Hy's Law[e] are not met)	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 14 days, resume treatment with a dose reduction to the next lower dose level.	Provide supportive care and increase the frequency of liver function monitoring to 1-2 times a week.

AE Grading Standard	Dose Adjustment	Treatment Suggestions
Grade 2 or 3 (Liver function is abnormal and the biochemical criteria for Hy's Law[e] are met)	The study drug should be terminated immediately.	Provide supportive care and increase the frequency of liver function monitoring to 2-3 times a week. Urgent medical intervention indicated.
Grade 4	The study drug should be terminated.	Urgent medical intervention indicated.

a. If protein ≥ 2+ on urinalysis during the study, a 24-hour urine test should be conducted within 1 week, and dose modification will be done by the result of 24-hour urine protein quantitation.
b. Refer to Appendix 14 for clinical management of severe or serious hemorrhage.
c. The investigator should closely monitor patients receiving anti-platelet and/or anti-thrombotic drugs during study drug treatment and make a timely decision on whether to continue or stop such drugs in patients that report ≥ Grade 2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance (See Section 6.2).
d. Including increasing of ALT, AST, and total bilirubin, whether or not the biochemical criteria for Hy's Law have been met.
e. Hy's Law is an increase in serum AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, and no other reason can be found to explain the biochemical changes, for example, new or worsening hepatobiliary metastases, elevated serum alkaline phosphatase indicating cholestasis, viral hepatitis, another suspect drug, or any other specific cause of severe hepatocellular injury. The elevation in transaminases must precede or be coincident with (ie, on the same day as) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. See Appendix 13 for additional information regarding Hy's Law.

10. 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).

10.1. Statistical Analysis

10.1.1. General Consideration

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including N, mean, standard deviation, median, minimum, and maximum values. Geometric mean and geometric coefficient of variation (CV) % will be included for PK parameters, where applicable. Coefficient of variation will not be presented for change-from-baseline results.

All derivations, statistical analyses, summaries, and listings will be generated using SAS Version 9.2 or higher. Graphics may be prepared using the same versions of SAS, or with SigmaPlot 12.5, or higher.

10.1.2. Analysis Sets

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

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

The DLT Evaluable Analysis Set includes all patients who received at least 85% of the assigned total dose of fruquintinib and at least 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment period. Additionally, patients who had a DLT event will also be considered evaluable. Only patients from Part 1 are eligible for inclusion in the DLT Evaluable Analysis Set. This will be the analysis set for the DLT analyses.

The PK Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have ≥ 1 quantifiable postbaseline PK data.

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

10.1.3. Patient Disposition

The number of patients that were treated, were discontinued from study drug(s) and/or the study, and were recorded with important protocol deviations will be counted in SAS. The primary reason for study drug(s) and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (alive, dead, withdrew consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF. Patient disposition will be summarized overall and by tumor types.

Important protocol deviations will be summarized and listed by category.

10.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Analysis Set using descriptive statistics.

Baseline patient characteristics will include a summary of the following:

- Patient demographic
- Baseline disease characteristics
- Prior anticancer therapies

Continuous variables include age, weight, height, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis. Categorical variables include gender, ECOG, Performance Status, race, TNM staging, number of prior system therapies received, and tumor type. Demographic and baseline characteristics will be summarized overall and by tumor types.

Other patient characteristics will be summarized as deemed appropriate.

10.1.5. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study drug(s). Concomitant medications will be defined as medications that 1) started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or 2) started on or after the date of the first dose of study drug(s) up to 30 days after the patient's last dose (as of the Safety Follow-up Visit). In addition, concomitant medication associated with an imAE or that is a new anticancer therapy at 60 and 90 days after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy, may also be included as part of the analysis where applicable. Any steroid use will be also included in the analysis where applicable. Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. Prior and concomitant medication will be summarized overall and by tumor types. A listing of prior and concomitant medications will be provided.

10.2. Efficacy Analyses

No formal hypothesis testing is planned in this trial.

10.2.1. Primary Efficacy Analysis

10.2.1.1. Overall Response Rate

The ORR is defined as the proportion of patients who had confirmed CR or PR as determined by the investigator using RECIST v1.1 in the Safety Analysis Set. ORR will be summarized for descriptive purposes in SAS. A two-sided Clopper-Pearson 95% CI of ORR will be constructed. ORR will be summarized based on patients from the RP2D dose level in overall and by tumor types. Additional summaries will be based on all dose levels in overall and by tumor types if necessary.

Best overall response (BOR) is defined as the best response recorded from the start of study drug(s) until data cut or start of new anti-cancer therapy. Patients with no postbaseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented. BOR will be summarized based on patients from the RP2D dose levels in overall and by tumor types. Additional summaries will be based on all dose level in overall and by tumor types if necessary.

Outcomes in the Evaluable Analysis Set will be evaluated as a sensitivity analysis.

10.2.2. Secondary Efficacy Analysis

10.2.2.1. Progression-free survival

PFS assessed by the investigators per RECIST v1.1 will be estimated using the Kaplan-Meier method in the Safety analysis set. The Kaplan-Meier estimates of PFS will be plotted over time. PFS at selected time points will be estimated with its 95% CI using Greenwood's formula. The corresponding quantiles (including the median), if estimable, will also be estimated using Kaplan-Meier method. Two-sided 95% CIs of median, if estimable, will be constructed with generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). PFS censoring rule will follow the US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018). PFS will be summarized based on patients from the RP2D dose level in overall and by tumor types. Additional summaries will be based on all dose levels in overall and by tumor types if necessary.

10.2.2.2. Disease control rate

DCR assessed by the investigator per RECIST v1.1 will be summarized in a similar way as ORR.

10.2.2.3. Clinical benefit rate

CBR assessed by the investigator per RECIST v1.1 will be summarized in a similar way as ORR.

10.2.2.4. Duration of response

DOR by the investigator per RECIST v1.1 will be similarly analyzed only in responders in Safety Analysis Set using the Kaplan-Meier method as described above. The statistical method applied to DOR is similar to the analysis described in Section 10.2.2.1.

10.2.2.5. Overall Survival

The OS is defined as the time from the date of first dose of study treatment until the date of death due to any cause. The statistical methods applied to OS is similar to the analysis described in Section 10.2.2.1.

10.3. Safety Analyses

Safety will be determined by the reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE v5.0. Descriptive summary statistics will be used to analyze all safety data in the Safety Analysis Set. Safety analysis will be based on the summary of overall and by dose level. Additional safety analyses will also be summarized based on tumor types if necessary.

10.3.1. Dose-Limiting Toxicity Analysis

DLTs during the DLT assessment period will be used to determine safety and tolerability of tislelizumab in combination with fruquintinib. The DLT events will be summarized descriptively in the DLT Evaluable Analysis Set.

10.3.2. Extent of Exposure

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

The number (percentage) of patients requiring treatment interruption, dose delay, dose reduction, or drug discontinuation because of AEs will be summarized for each study drug. Reasons for dose modifications will be summarized as well.

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

10.3.3. Adverse Events

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

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days following study drug(s) discontinuation or initiation of new anticancer therapy, whichever occurs first. The TEAE classification also applies to imAEs that are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a system organ class and preferred term, even if the patient experienced ≥ 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

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

10.3.4. Laboratory Analyses

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

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

10.3.5. Vital Signs

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

10.3.6. Pulmonary Function Test

Descriptive statistics for pulmonary function test result will be presented overall and by visit.

10.4. Pharmacokinetic Analyses

Blood samples will be collected for tislelizumab PK evaluation at postdose and trough (C_{trough}). The serum concentration data will be tabulated and summarized by the visit/cycle at which these samples are collected. For fruquintinib, serial PK samples will be collected for part 1 and sparse samples will be collected for part 2. Plasma fruquintinib concentration data will be summarized using descriptive statistics, C-T profiles, and other plots as appropriate. The corresponding PK parameters of fruquintinib will be calculated as data permit.

10.5. Immunogenicity Analyses

The immunogenicity results for tislelizumab will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients.

10.6. Other Exploratory Analyses

Potential biomarkers including but not limited to PD-L1 expression, TMB and DNA mutation/bTMB and DNA mutation, GEP in the GC, MSS-CRC and NSCLC cohorts, EBV in the GC cohort, MSS/MSI status in the GC cohort, and the association of biomarkers with disease status or response/resistance to tislelizumab in combination with fruquintinib may be explored.

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

10.7. Sample Size Consideration

Approximately 6 to 12 DLT evaluable patients will be enrolled at Part 1. Patients enrolled in Part 1 at RP2D will be counted towards Part 2 by the diagnosis of tumor types. Approximately 96 patients will be enrolled at maximum, and about 30 patients will be enrolled at RP2D per cohort to evaluate the preliminary efficacy, safety, and clinical pharmacokinetics.

The study plans to enroll approximately 90 patients at RP2D according to the business agreement:

- Cohort A: Gastric cancer (n = 30)
- Cohort B: Colorectal cancer (n = 30)
- Cohort C: Non-small cell lung cancer (n = 30)

No formal hypothesis testing is planned in this trial.

The 95% CIs when observing different numbers of responders among 30 patients in each cohort are presented in Table 9.

Table 9: 95% CI (%) When Observing Different Number of Responders in 30 Patients

Number of responders (ORR observed)	2 (6.7%)	3 (10.0%)	5 (16.7%)	6 (20.0%)	8 (26.7%)	9 (30.0%)
(95% CI) (%)	(0.82, 22.07)	(2.11, 26.53)	(5.64, 34.72)	(7.71, 38.57)	(12.28, 45.89)	(14.73, 49.40)

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; MSS, microsatellite stable; NSCLC, non-small cell lung cancer; ORR, overall response rate.
Notes: The historical response rate for the standard of care (SOC) in each cohort are the following:
ORR data of the SOC for 3rd line MSS CRC: fruquintinib (4.7%, Li et al 2018) / regorafenib (4%, Li et al 2015)
ORR data of the SOC for 2nd line GC: paclitaxel (16%) (Wilke et al 2014).
ORR data of the SOC for 1st line PD-L1+ NSCLC: pembrolizumab (27%) (Mok et al 2019)

10.8. Interim Analyses

Not applicable.

11. STUDY COMMITTEES

11.1. Safety Monitoring Committee

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

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

12.1. Access to Information for Monitoring

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

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

12.2. Access to Information for Auditing or Inspections

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

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1. Regulatory Authority Approval

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

13.2. Quality Assurance

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

13.3. Study Site Inspections

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

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

13.4. Drug Accountability

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

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

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

14. ETHICS/PROTECTION OF HUMAN PATIENTS

14.1. Ethical Standard

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

14.2. Institutional Review Board/Independent Ethics Committee

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

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

14.2.1. Protocol Amendments

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

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

14.3. Informed Consent

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

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

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

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

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

14.4. Patient and Data Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient 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 the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy 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.

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

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the tislelizumab (BGB-A317) and fruquintinib Investigator's Brochures, this protocol, eCRFs, the Investigational New Drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

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

14.5. Financial Disclosure

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

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Collection and Management Responsibilities

15.1.1. Data Entry in the Electronic Case Report Form

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

15.1.2. Data Collection

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

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

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

15.1.3. Data Management/Coding

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

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

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

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

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

15.2. Study Records Retention

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

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

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

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

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

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

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

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

15.3. Protocol Deviations

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

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

15.4. Study Report and Publications

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. 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 2016).

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

15.5. Study and Study Center Closure

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

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulations
- 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 IEC/IRB promptly and provide the reason for the suspension or termination.

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

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

15.6. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

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17. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening[a]	**Treatment cycles**				**Safety follow-up**[c]	**Survival follow-up**[d]
		Cycle 1-2 (28 days)		**≥ Cycle 3 (every 28 days)**	**EOT Visit**[b]		
Visit day	**-28 to -1**	**1**	**15**	**1**	**0 to 7 days**	**+ 30 days (visit)**	**Every 3 months**
Visit window		**± 3**	**± 3**	**± 3**		**± 7**	
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographics/medical history/disease history	X						
Vital signs/height and weight[e]	X	X[e]	X	X[e]	X	X	
Physical examination[f]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
12-lead ECG[g]	X	As clinically indicated				X	
Adverse events[h]	X	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X	
Prior and concomitant procedures	X	X	X	X	X	X	
Hematology[i]	X[i]	X	X	X[i]	X[b]	X	
Clinical chemistry[i]	X[i]	X	X	X[i]	X[b]	X	
CK and CK-MB[j]	X	X	X	X	X[b]	X	
Coagulation parameters[i]	X[i]	X	X	X[i]	X[b]	X	
Urinalysis[i]	X[i]	X	X	X		X	
Pregnancy test[k]	X	X		X		X	

	Screening[a]	Treatment cycles				Safety follow-up[c]	Survival follow-up[d]
		Cycle 1-2 (28 days)		≥ Cycle 3 (every 28 days)	EOT Visit[b]		
Visit day	**-28 to -1**	**1**	**15**	**1**	**0 to 7 days**	**+ 30 days (visit)**	**Every 3 months**
Visit window		**± 3**	**± 3**	**± 3**		**± 7**	
Thyroid function[l]	X			Cycles 4, 7, and every 3 cycles		X	
HBV/HCV tests[m]	X[m]	As clinically indicated[m]					
Pulmonary function tests[n]	X[n]	As clinically indicated					
Pharmacokinetics		See Appendix 2					
Anti-tislelizumab antibodies		See Appendix 2					
Blood biomarkers[o]	X	At baseline, time of response, and time of confirmed PD[o]					
Tumor assessment[p]	X	Every 8 weeks (± 7 days) from Cycle 1 Day 1 for the first 56 weeks, then every 12 weeks (± 7 days) thereafter			X[b]		X
Archival or fresh tumor tissue[q]	X	At time of confirmed PD					
Tislelizumab administration[r]		X		X			
Fruquintinib administration[s]		3 weeks on/1 week off					
Survival status							X

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CRC, colorectal cancer; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment (Visit); GC, gastric cancer; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; imAE, immune-mediated AE; MRI, magnetic resonance imaging; MSI, microsatellite instability; MSS, microsatellite stable; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TFTs, thyroid function tests; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.
Note: Timepoints containing numbers represent timepoints with special considerations for that respective assessment.

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

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

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

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

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

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

g. All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws). The patient should rest in semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.

h. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed but before the administration of study drug(s), only SAEs should be reported. After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after the last dose of study drug(s) (including tislelizumab and fruquintinib) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious and nonserious) should be reported for tislelizumab treatment until 90 days after the last dose of tislelizumab regardless of whether the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

i. Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 3. If clinical chemistry, hematology, coagulation, and urinalysis at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration. Hematology, clinical chemistry, coagulation, and urinalysis(data collected as specified in Appendix 3) will be performed biweekly for the first two cycles and then at the beginning of each subsequent cycle. Refer to Section 9.2.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

j. CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients who continue to receive fruquintinib monotherapy may receive CK and CK-MB testing if clinically indicated.

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

l. TFTs by analysis of FT3, FT4, and TSH will be performed at screening, every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc) and Safety Follow Up Visit. If FT3 or FT4 is not available, TT3 or TT4 should be tested instead.

m. Testing will be performed by the local or central laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA), which will be assessed only when HBsAg or HCV antibody is positive, respectively. Additionally, for patients who have detectable HBV DNA at screening, the respective viral load test will be performed every 4 cycles starting at Cycle 5 (ie, Day 1 of Cycles 5, 9, 13, etc) and the EOT Visit.

n. Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all NSCLC patients during the screening period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 60% of age- and sex-adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study. GC or CRC patients who are suspected of having or known to have serious/severe respiratory conditions, or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing that may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study.

o. Approximately 2 mL peripheral whole blood must be sent to the central laboratory for MSI test control during the screening period in the CRC patients. Additionally, blood samples 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 PD (optional). Approximately 10 mL for each timepoint. Written patient consent is required for blood sample collections.

p. Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 8 weeks (± 7 days), from Day 1 of Cycle 1, for the first 56 weeks, then every 12 weeks (± 7 days) thereafter, based on RECIST v1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. Imaging of the brain (MRI or CT) at baseline is required for all screened NSCLC patients.
All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).
Patients 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, death, or until the study terminates, whichever occurs first. See Section 8.3 for more information.

q. Archival tumor tissues (if available) must be sent to the central laboratory for MSS status detection (MSI test) for the CRC patients, PD-L1 status for the NSCLC patients and EGFR status (central/local laboratory) for the non-squamous NSCLC patients with no EGFR documentation during the screening period and for retrospective analysis of exploratory biomarkers for all enrolled patients. 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 PD in both cohorts will be collected during the study from accessible tumor sites. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.
For fresh biopsy, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for

cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

r. Tislelizumab will be given intravenously on Day 1 of each 28-day cycle (once every 4 weeks) (see Section 5.2.1 for details).

s. Fruquintinib will be self-administered orally once daily with 3 weeks on/1 week off (see Section 5.2.2 for details).

APPENDIX 2. SCHEDULE OF PK AND ADA ASSESSMENTS

	Collection Time and Allowable Window	Part 1: PK-Fruquintinib[a]	Part 2: PK-Fruquintinib[b]	Part 1+Part 2: PK-Tislelizumab[c]	Part 1+Part 2 ADA-Tislelizumab[d]
C1D1	Predose - 60 min	x	x	x (Pre-tisle-dose [-60 min])	x (Pre-tisle-dose [-60 min])
	Postdose + 30 min			x (Post-tisle infusion + 30 min)	
	1 h ± 10 min	x			
	2 h ± 15 min	x	x		
	4 h ±30 min	x			
	6 h ±30 min	x			
	8 h ± 60 min	x			
C1D15 (optional)	Predose - 60 min	x	x		
C2D1	Predose - 60 min	x	x	x (Pre-tisle-dose [-60 min])	x (Pre-tisle-dose [-60 min])
C2D15 (optional)	Predose - 60 min	x	x		
C4D1	Predose - 60 min	x	x	x (Pre-tisle-dose [-60 min])	x (Pre-tisle-dose [-60 min])
	Postdose + 30 min			x (Post-tisle infusion + 30min)	
C7D1	Predose - 60 min	x	x	x (Pre-tisle-dose [-60 min])	x (Pre-tisle-dose [-60 min])
C13D1	Predose - 60 min	x	x	x (Pre-tisle-dose [-60 min])	x (Pre-tisle-dose [-60 min])
SFU	Within 30 days after last dose of study drug(s)			x	x

Abbreviations: ADA, antidrug antibody; C, cycle; D, day; DLT, dose limiting toxicity; EC, ethics committee; IRB, institutional review board; min, minutes; PK, pharmacokinetics; SFU, safety follow-up; tisle, tislelizumab.

[a.] Procedures for collection of PK samples are described in the Laboratory Manual. PK samples for fruquintinib will be collected from all patients in Part 1 at predose (within 60 minutes before dosing), 1 (± 10 min), 2 (± 15 min), 4 (±30 min), 6 (± 30 min), and 8 hours (± 60 min) after dosing on Cycle 1 Day 1; predose (within 60

minutes before dosing) on Day 1 of Cycle 2, 4, 7, 13, and on Day 15 of Cycle 1 and 2 (optional) per site feasibility. If a patient is present with DLT event or any SAE, an additional blood PK sample may be taken to determine the plasma concentration of fruquintinib. These PK samples will be measured only if any safety issues occur and is requested from sponsor. If fruquintinib is permanently discontinued, the scheduled PK sampling of fruquintinib is no longer required.

[b.] Procedures for collection of PK samples are described in the Laboratory Manual. PK samples for fruquintinib will be collected from all patients in Part 2 at predose (within 60 minutes before dosing) on Day 1 of Cycle 1, 2, 4, 7, 13, and on Day 15 of Cycle 1 and 2 (optional); and 2 h (± 15 min) after dosing on Cycle 1 Day 1 per site feasibility. If a patient is present with DLT event or any SAE, an additional blood PK sample may be taken to determine the plasma concentration of fruquintinib. If fruquintinib is permanently discontinued, the scheduled PK sampling of fruquintinib is no longer required.

[c.] Procedures for collection of PK samples are described in the Laboratory Manual. For tislelizumab, predose (within 60 minutes before starting infusion) samples are required to be collected on Day 1 of Cycles 1, 2, 4, 7, and 13. A postdose (within 30 minutes after completing tislelizumab infusion) sample is required to be collected on Day 1 of Cycles 1 and 4. An additional PK sample is required to be collected at the Safety Follow-up. If tislelizumab is permanently discontinued, scheduled PK sampling is no longer required except for Safety Follow-up Visit. Should a patient present with DLT event or any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.

[d.] Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 4, 7, and 13 and at the mandatory Safety Follow-up Visit. If tislelizumab is permanently discontinued, ADA sampling is no longer required except for Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/ECs.

APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Clinical chemistry	Hematology	Coagulation	Urinalysis
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]	Red blood cell count Hematocrit Hemoglobin Platelet count White blood cell count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Glucose Protein Blood Ketones 24-hour protein[c] Random urine protein to creatinine ratio

Abbreviations: CK-MB, creatine kinase-muscle/brain.

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

[b] All patients will have creatine kinase and CK-MB testing at screening, and to be repeated at all scheduled visits during the first 2 treatment cycles, all predose assessments from Cycle 3 onwards, and at the End-of-Treatment/Safety Follow-up visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 8.2.4 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

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

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

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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. CHRONIC KIDNEY DISEASE-EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

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

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

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

where:

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

κ is 0.7 for females and 0.9 for males,

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

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

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

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

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

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

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). These methods include the following:

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

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

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

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

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

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

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

Adapted from Clinical Trials Facilitation Group 2014.

APPENDIX 7. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

APPENDIX 8. 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 9. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

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

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

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

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

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

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

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

Treatment of Immune-Mediated Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, 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 10. MEDICATIONS TO BE USED WITH CAUTION DURING TREATMENT WITH FRUQUINTINIB

Restricted drugs during the study are as follows:

Strong inhibitors and strong inducers of CYP3A4. Note, the list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin, erythromycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone, idelalisib
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir,
Grapefruit juice[a,b]
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), apalutamide, enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
For a more complete list, please refer to the Flockhart Table: http://medicine.iupui.edu/clinpharm/ddis/main-table

a. Super-concentrated grapefruit juice
b. During the study, patients should not consume large amounts of grapefruit or lime (or products that include these fruits, such as grapefruit juice, Seville oranges, and orange jam). No more than one cup (120 mL) of grapefruit juice, half a grapefruit, or a spoon full (15 g) of orange jam should be consumed each day.

Medications to be used with caution during the study are as follows:

Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP Transporters P-gp: aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan.

BCRP: methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.

APPENDIX 11. MEDICATIONS THAT HAVE A KNOWN RISK OF CAUSING QT PROLONGATION AND/OR TORSADES DE POINTES

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

Source: www.crediblemeds.org

APPENDIX 12. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al 2009.

Definitions

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

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

Measurable Disease

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

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

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

Nonmeasurable Disease

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

Nontarget Lesions

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

Guidelines for Evaluation of Measurable Disease

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

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

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

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

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following 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 trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease (PD).

Response Criteria

Evaluation of Target Lesions

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

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

Evaluation of Nontarget Lesions

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

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

New Lesions

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

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

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

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

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

Timepoint Response

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

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

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

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

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

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

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

Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

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

Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary

endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

APPENDIX 13. CLINICAL EVALUATION OF POSSIBLE DRUG-INDUCED LIVER INJURY (DILI)

If ALT or AST is elevated to higher than 3 x ULN **and** bilirubin is elevated to higher than 2 x ULN, fruquintinib treatment should be discontinued immediately, and supportive treatment should be given. This combination of lab abnormalities meets the biochemical criteria for Hy's law, which is associated with a markedly increased possibility of severe drug-induced liver injury (DILI), and may progress to liver transplantation or death (FDA Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation. FDA, 2009).

If the biochemical criteria for Hy's law are met, fruquintinib should be immediately discontinued, and patients need to be very closely monitored (bilirubin, ALP, AST, and ALT measured 2 to 3 times weekly until the results return to baseline or normal), and other causes of liver injury evaluated (eg, new or worsening hepatobiliary metastases; non-malignant biliary obstruction; viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis; preexisting or acute liver disease; ischemic liver injury; right-sided congestive heart failure; new or worsening liver metastases; or concomitant medication that could cause the observed injury). Consultation with a gastroenterologist or hepatologist should be considered.

Recommended Data Collection for Suspected DILI

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data. Data should be recorded on eCRFs where possible, and supplemented by investigator reporting as text in the clinical database:

- Medical history of the patient
  - Detailed history of current symptoms, diagnosis of complications and medical history
  - Previous medical history (viral hepatitis, alcoholic hepatitis, autoimmune disease, biliary tract disease and cardiovascular disease, etc.)
  - History of concomitant medication (including over-the-counter and prescription drugs, herbal medicine and dietary supplements), alcohol consumption, recreational drugs and special diet
  - History of exposure to potentially hepatotoxic chemicals
- Complete the following laboratory tests:
  - Hematology
  - Clinical biochemistry: ALT, AST, bilirubin (including total bilirubin and direct bilirubin), ALP, albumin, PTT or INR, amylase, fasting blood glucose, cholesterol and triglycerides
  - Other Serum Tests: Hepatitis A (Anti-IgM and Anti-IgG), hepatitis B (HbsAg, Anti-HBs and HBV DNA), hepatitis C (Anti-HCV, and HCV RNA test is required for any patient with positive test result), hepatitis D (Anti-IgM and Anti - IgG), hepatitis E (Anti-HEV and Anti-HEV IgM).

- Complete appropriate auxiliary examination:
  - Patients with confirmed elevation of ALT/AST combined with TBili are required to receive abdominal ultrasonography or other clinically applicable imaging examination within 48 hours (to exclude biliary tract, pancreatic, or intrahepatic causes, such as new or worsening hepatobiliary metastases or biliary calculi) and obtain the liver imaging result as soon as possible. If an alternative cause (such as biliary tract, pancreatic, or intrahepatic causes) of abnormal hepatic results cannot be confirmed by imaging, paracentesis is recommended for pathological examination after obtaining consent of the patient;
  - If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure);

Long-term follow-up: Perform close monitoring on the patient through repetitive tests of ALT, AST and bilirubin (including total bilirubin and direct bilirubin) two to three times weekly until the laboratory ALT and/or AST abnormality becomes stable or recovers, and then proceed according to the protocol.

APPENDIX 14. CLINICAL MANAGEMENT OF SEVERE OR SERIOUS HEMORRHAGIC EVENTS

If hemorrhagic events are evaluated as severe (CTCAE ≥ Grade 3) or SAEs, fruquintinib treatment should be discontinued or interrupted immediately, and appropriate treatment measures initiated to control bleeding (eg transfusion, radiologic, endoscopic, or elective operative intervention as indicated). When the patient is not well enough to tolerate an invasive procedure or operation, best supportive care is given (see Section 9.7). Patients need to be very closely monitored, both clinically (continuously), and by relevant laboratory testing (INR, aPTT, platelet count, hemoglobin) every 2 to 3 days until the results return to baseline or normal). During the initial assessment, a focused history and physical examination, with collection of vital signs and laboratory evaluation and imaging evaluation should be obtained, aimed at determining the time of onset, location, severity of bleeding, and whether bleeding is ongoing. Clinicians should be mindful of comorbidities and concomitant treatments (eg, anti-platelet therapy and/or thrombocytopenia, or liver disease) that could also contribute to bleeding and manage them as appropriate. Consultation with other department clinicians should be considered when necessary.

The investigator should closely monitor patients receiving anti-platelet and/or anti-thrombotic drugs during study drug treatment and make a timely decision on whether to continue or stop such drugs in patients that report ≥ Grade 2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance.

See Figure 2 below for guidance on the management of severe or serious hemorrhage at any site.

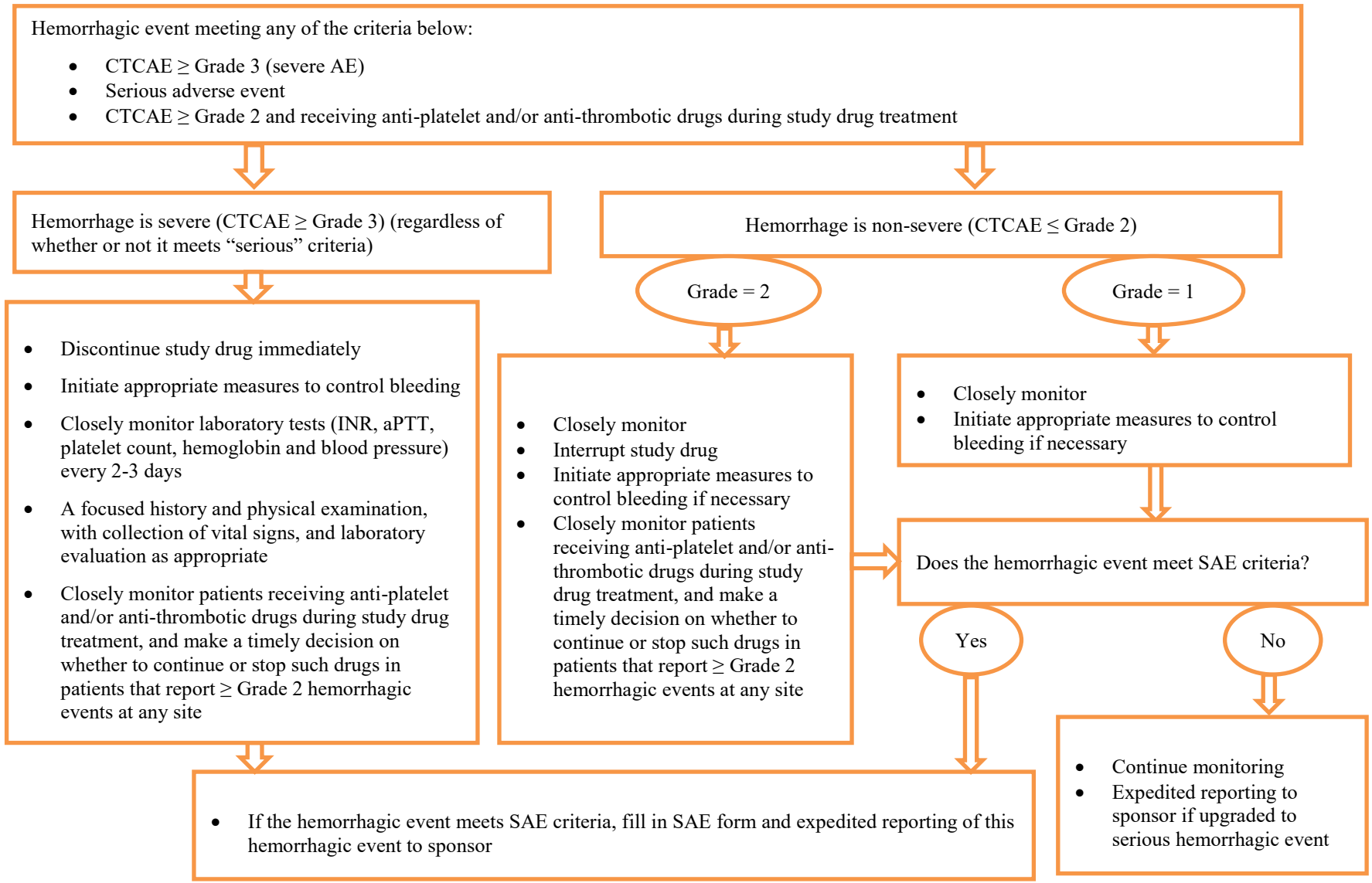
Recommended Data Collection for Severe or Serious Hemorrhagic Events:

The investigator is recommended to obtain the following information, so as to further evaluate and follow up and complete the clinical data. Data should be recorded on SAE/AESI report form where possible, and supplemented by Bleeding Event Follow-Up Questionnaire:

- Medical history of the patient
  - Detailed history of current symptoms, diagnosis of complications and medical history
  - Previous medical history
  - History of concomitant medication
    - Vitamin K antagonists (eg, warfarin)
    - NSAIDs (eg, aspirin)
    - Anti-platelet drugs (eg, clopidogrel/glycoprotein GPIIb/IIIa inhibitors/dipyridamole)
    - Other anticoagulants (eg, heparin/thrombolytics/SSRIs)
    - Food and herbal supplements with anticoagulant property
    - Immunosuppressants
    - Alcohol consumption
    - Recreational drugs and special diet

  - Family history of bleeding events
- Complete the following laboratory tests:
  - Hematology: hemoglobin, platelet, hematocrit, reticulocyte count
  - Clinical biochemistry: bleeding time, PTT, aPTT, INR
- Complete appropriate auxiliary examination:
  - Patients with confirmed bleeding are required to receive upper or lower GI endoscopy, bronchoscopy or other clinically applicable procedure or radiologic imaging within 48 hours, to confirm the site of bleeding.
  - If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure).

Figure 2: Severe or Serious Hemorrhagic Events Management Flow Chart



APPENDIX 15. MANAGEMENT OF HYPERTENSION IN PATIENTS RECEIVING FRUQUINTINIB

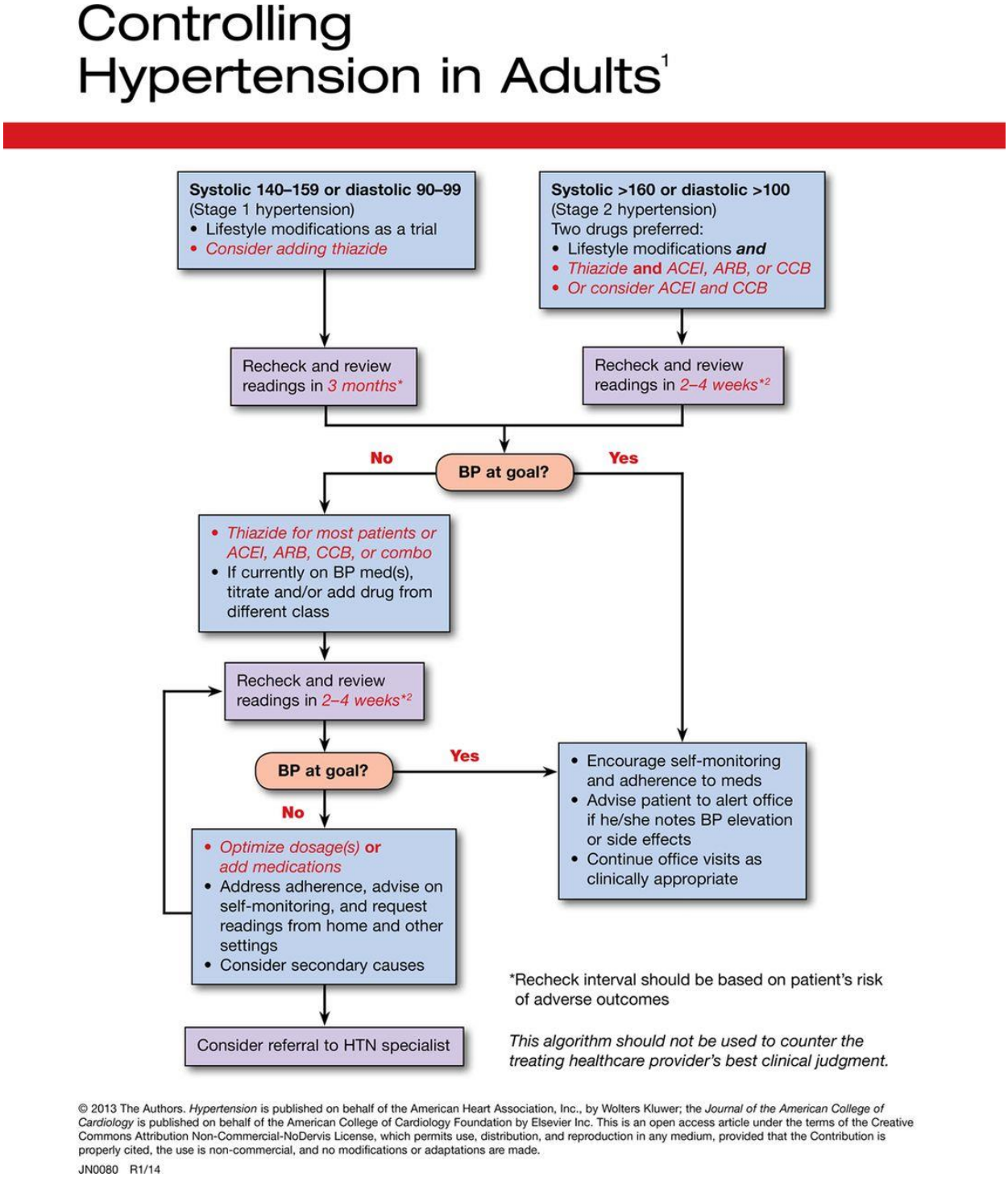
Hypertension is a common AE that has been reported in patients taking angiogenesis inhibitors (Izzedine 2009), including fruquintinib. Grade 3 AEs have been reported in 16% of patients treated with fruquintinib; no Grade 4 events have been reported to date. It appears that hypertension is a class-effect of VEGFR inhibitors (either antibodies or small molecules).

There is no standard therapy for angiogenesis inhibitor-induced hypertension because there have not been any published controlled clinical trials with specific agents. Therefore, one can take an approach based on the clinical characteristics of particular patients. Calcium channel blockers and angiotensin converting enzyme inhibitors (ACEI) are a reasonable first choice in most cases. For patients with proteinuria, chronic renal disease or metabolic disease, an ACE inhibitor or angiotensin II receptor blockers (ARB) may be preferred; for elderly patients, dihydropyridine calcium channel blockers may be preferred. In this appendix is a summary of the most recent American Heart Association (AHA)/American College of Cardiology (ACC) hypertension treatment guidelines. A cardiologist may be consulted if appropriate.

The objective of antihypertensive therapy in general is to control the blood pressure to a target level <140/90 mmHg. For high-risk populations, such as patients with chronic renal disease and/or diabetes, it may be appropriate to aim for a target blood pressure < 130/80 mmHg. Please see a summary of the most recent AHA/ACC hypertension treatment guidelines (Figure 3).

Figure 3: Schema from American Heart Association/ American College of Cardiology for Controlling Hypertension in Adults

Source: Go et al 2014.



Controlling Hypertension in Adults

The blood pressure (BP) goal for an individual is set by utilizing a combination of factors including scientific evidence, clinical judgment, and patient tolerance. For most people, the goal is <140 and <90;[3] however, lower targets may be appropriate for some populations such as African-Americans, the elderly, or patients with LV hypertrophy, systolic or diastolic LV dysfunction, diabetes mellitus or chronic kidney disease. Lifestyle modifications (LM) should be initiated in all patients with hypertension (HTN) and they should be assessed for target organ damage and existing cardiovascular disease. Self-monitoring[4] is encouraged for most patients throughout their care, and requesting and reviewing readings from home and community settings can help the provider assist the patient in achieving and maintaining good control. For patients with hypertension in combination with certain clinical conditions, specific medications should be considered first-line treatments.

Suggested Medications for Treatment of Hypertension in Presence of Certain Medical Conditions

- Coronary artery disease/Post MI: *BB, ACEI*
- Systolic heart failure: *ACEI or ARB, BB, ALDO ANTAG, thiazide*
- Diastolic heart failure: *ACEI or ARB, BB, thiazide*
- Diabetes: *ACEI or ARB, thiazide, BB, CCB*
- Kidney disease: *ACEI or ARB*
- Stroke or TIA: *thiazide, ACEI*

Lifestyle Modifications[3] (LM)

Modification	Recommendation	Approximate SBP Reduction (Range)**
Reduce weight	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5–20 mm Hg/10 kg
Adopt DASH*[5] eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Lower sodium intake[6]	a. Consume no more than 2,400 mg of sodium/day; b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with even greater reduction in BP; and c. Reduce intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not achieved	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons	2–4 mm Hg

* DASH, dietary approaches to stop hypertension
** The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals

Abbreviations

ACEI, angiotensin-converting-enzyme inhibitor; ALDO ANTAG, aldosterone antagonist; ARB, angiotensin II receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker; HTN, hypertension; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack

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