HUTCHMED

Clinical Study Protocol

AN OPEN-LABEL, PHASE 1b/2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF FRUQUINTINIB IN COMBINATION WITH TISLELIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

Short Title	A Phase 1b/2 Study of Fruquintinib in Combination with Tislelizumab in Advanced Solid Tumors
Investigational Product(s):	Fruquintinib (HMPL-013) and Tislelizumab (BGB-A317)
Protocol Number:	2020-013-00US3
Clinical Phase:	1b/2
Date of Issue:	06 December 2023
Amendment:	5
Version:	1
Sponsor:	HUTCHMED Limited Building 4, 720 Cailun Road, China (Shanghai) Pilot Free Trade Zone Shanghai, China, 201203 http://www.hutch-med.com
Regulatory Agency Identifier Number(s):	CCI [redacted]

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by ICH E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The principal investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	An Open-Label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of Fruquintinib in Combination with Tislelizumab in Patients with Advanced Solid Tumors
Protocol Number	2020-013-00US3
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Version	1

The design of this study as outlined by this protocol has been reviewed and approved by the sponsor's responsible personnel as indicated in the signature table below.

Name: PPD	**Title:** PPD HUTCHMED International Corp.
Signature: *See appended signature page*	**Date: [DD Month YYYY]**

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2020-013-00US3 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2)
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent, and updated consent in the event of new information or amendments, from all participants enrolled at my study site prior to initiating any study -specific procedures or administering investigational products to those participants
- To maintain records of each subject's participation and all data required by the protocol

Name:	**Title:**	**Institution:**
Signature:		**Date** *[DD Month YYYY]***:**

AMENDMENT SUMMARY

This Clinical Study Protocol 2020-013-00US3 Amendment 5 replaces Clinical Study Protocol 2020-013-00US3 Amendment 4. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary purpose of Amendment 5 is to provide notification of termination of this study upon the strategic evaluation of the clinical development of fruquintinib in the United States. This change is not based on any concern for patient safety or efficacy relative to fruquintinib and/or tislelizumab treatment. CCI [redacted] The major changes incorporated in Amendment 5 relative to Amendment 4 are summarized below. Editorial and formatting changes are not included in this summary. Summaries of prior amendments are available in Appendix 14.

Section Number	Summary of Change	Rationale for Change
Cover Page, Sponsor's Approval, Document History, and Header	Administrative updates were made to reflect Amendment 5.	Administrative updates were made to reflect Amendment 5.
Section 1.2 – Schedule of Events, Table 1; Section 6.1.4 – Treatment Period; Section 6.1.22 – Survival Follow-up Period; and Section 6.3 – Study Termination.	Language was added detailing the updated timeline for the last day to initiate a new treatment cycle, treatment discontinuation, end of treatment visit, and Safety Follow-up visit.	These updates were made to accommodate the process of study termination.
Section 1.2 – Schedule of Events, Table 2 and Section 6.1.19 – PK Assessments	Language was added to indicate termination of PK and immunogenicity sample collection after 31 December 2023.	This update was made to accommodate the process of study termination.

DOCUMENT HISTORY

Amendment	Version	Date of Issue
Original	1	12 Oct 2020
Amendment 1	1	16 Dec 2020
Amendment 2	1	01 Sep 2021
Amendment 3	1	07 Feb 2022
Amendment 4	1	02 Feb 2023

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-PD-1	anti-programmed cell death protein-1 antibody
anti-PD-L1	anti-programmed cell death protein-L1 checkpoint pathway
anti-VEGF	anti-vascular endothelial growth factor
aPTT	activated partial thromboplastin time
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the curve from time 0 extrapolated to infinite time
BCRP	breast cancer resistant protein
BOR	best overall response
BP	blood pressure
CAP	College of American Pathologists
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CK-MB	creatine kinase-MB
CI	confidence interval
CL	Clearance
C_{max}	maximum observed concentration
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CYP3A	cytochrome P450, family 3, subfamily A
CYP3A4	cytochrome P450, family 3, subfamily A4
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response

Abbreviation	Definition
EC	endometrial cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	endothelial growth factor receptor
ER	estrogen receptor
ER/PGR	estrogen receptor/progesterone receptor (abbreviated ER/PR in ASCO-CAP guidelines)
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GC	gastric cancer
GCP	Good Clinical Practice
GEP	gene expression profile
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
IC_{50}	inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
IEC	institutional ethics committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
INR	international normalized ratio
IO	immuno-oncology
IRB	institutional review board
IV	intravenous(ly)
IWRS	interactive web response system
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
M11	desmethylation product, HM5025423
MATE	multidrug and toxin extrusion
mBC	metastatic breast cancer
mCRC	metastatic colorectal cancer

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
MSI	microsatellite instability
MSS	microsatellite stable
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP1B	organic anion transporting polypeptide 1b
OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PGR	progesterone receptor (abbreviated PR in ASCO-CAP guidelines)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	oral
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PT	preferred term
Q3W	every 3 weeks
Q4W	every 4 weeks
QD	every day, once daily
QTcF	QT interval corrected by the method of Fridericia
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	System organ class
SOE	Schedule of Events

Abbreviation	Definition
SRC	safety review committee
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrated lymphocyte
TKI	tyrosine kinase inhibitor
TLF	tables, listings, and figures
TMB	tumor mutation burden
TMB-H	tumor mutation burden-high
TNBC	triple negative breast cancer
T_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
V_c	central volume
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

1 SYNOPSIS

Title	An Open-Label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of Fruquintinib in Combination with Tislelizumab in Patients with Advanced Solid Tumors
Short Title	A Phase 1b/2 Study of Fruquintinib in Combination with Tislelizumab in Advanced Solid Tumors
Protocol Number	2020-013-00US3
Phase	1b/2
Protocol Amendment 5	The primary purpose of the Amendment 5 is to provide notification of termination of this study upon the strategic evaluation of the clinical development of fruquintinib in the United States. This change is not based on any concern for patient safety or efficacy relative to fruquintinib and/or tislelizumab treatment. CCI [redacted]
Rationale	Angiogenesis is a critical step in the inception and development of malignant tumors. One of the major growth factors related to tumor angiogenesis is vascular endothelial cell growth factor (VEGF), which is secreted by tumors and activates the vascular endothelial growth factor receptor (VEGFR) signaling pathway leading to endothelial cell proliferation. Blocking of the VEGF/VEGFR signaling pathway can inhibit tumor angiogenesis and cut off the nutrients and oxygen supply to the tumor. Tumor immune surveillance is also key to detect, kill, and eliminate cancer cells. Key immune checkpoint molecules are the programmed cell death protein 1 (PD-1) and its ligand (PD-L1). When upregulated, the PD1/PD-L1 pathway protects cancer cells from immune surveillance. Thus, combination therapy with a small-molecule inhibitor of the VEGFR pathway may improve the clinical efficacy of PD-1/PD-L1 immunotherapies by promoting 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 preclinically to generate more potent anti-tumor effects than either agent alone and has shown benefit in various therapeutic settings. Fruquintinib is a small-molecule anti-tumor quinazoline class tyrosine kinase inhibitor (TKI) that selectively inhibits VEGF receptors 1, 2, and 3. Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4-variant monoclonal antibody against PD-1. In this study, fruquintinib in combination with tislelizumab will be evaluated in patients with locally advanced or metastatic solid tumors with expanded cohorts in triple negative breast cancer (TNBC), endometrial cancer (EC), and microsatellite stable (MSS) metastatic colorectal cancer (mCRC).
Target Population	Adult male and female patients ≥18 years of age with locally advanced or metastatic solid tumors. Part 1 (Safety Lead-in Phase): Patients with histologically or cytologically documented advanced or metastatic solid tumors of any type who have progressed on standard systemic therapy and for which no effective therapy or standard of care exists. Patients with TNBC in the Safety Lead-in must meet eligibility criteria defined in Cohorts A or B, and those with EC in the Safety Lead-in must meet eligibility criteria defined in Cohort C. Part 2 (Dose Expansion Phase): • Cohort A: TNBC (immuno-oncology [IO]-treated in the metastatic setting) • Cohort B: TNBC (IO-Naïve in the metastatic setting) • Cohort C: EC (IO Naïve) • Cohort D: MSS mCRC (IO Naïve)
Intervention	Part 1 (Safety Lead-in Phase):

	• Dose level 1: Fruquintinib 5 mg oral (PO) once daily (QD) 3 weeks on/ 1 week off + tislelizumab 300 mg intravenously (IV) every 4 weeks (Q4W) OR • Dose level -1: Fruquintinib 4 mg PO QD 3 weeks on/1 week off + tislelizumab 300 mg Q4W Part 2 (Dose Expansion Phase): Recommended Phase 2 dose (RP2D) from Part 1		
Objectives and Endpoints			
Part	**Tier**	**Objectives**	**Corresponding Endpoints**
Part 1: Safety Lead-in Phase	Primary	To assess the safety and tolerability of fruquintinib in combination with tislelizumab in patients with advanced solid tumors	AEs characterized by type, frequency, severity per NCI CTCAE v5.0, timing, seriousness, relationship to study drug(s), and discontinuation of study drug(s) due to AEs
		To confirm the RP2D of fruquintinib in combination with tislelizumab	RP2D
	Secondary	To evaluate the efficacy of fruquintinib in combination with tislelizumab per investigator assessment	ORR, PFS, DCR, CBR, DoR, and OS
		To characterize the PK profile of fruquintinib and metabolite M11 when combined with tislelizumab	Plasma concentrations of fruquintinib and M11
		To evaluate the PK and immunogenicity of fruquintinib in combination with tislelizumab	Serum concentrations of tislelizumab and incidence of ADA to tislelizumab
Part 2: Dose Expansion Phase	Primary	To evaluate the ORR assessed by the investigator in patients with advanced or metastatic TNBC, EC, or MSS mCRC when treated with fruquintinib in combination with tislelizumab	ORR per RECIST v1.1
	Secondary	To further evaluate efficacy of fruquintinib in combination with tislelizumab in patients with advanced or metastatic TNBC, EC, or MSS mCRC per investigator assessment	PFS, DCR, CBR, DoR, and OS
		To characterize the safety of fruquintinib in combination with tislelizumab	AEs characterized by type, frequency, severity per NCI CTCAE v5.0, timing, seriousness, relationship to study drug(s), and discontinuation of study drug(s) due to AEs.
		To assess the PK profile of fruquintinib and metabolite M11 when combined with tislelizumab	Plasma concentrations and derived PK parameters of fruquintinib and M11
		To characterize the PK and immunogenicity of fruquintinib when combined with tislelizumab	Serum concentrations of tislelizumab and incidence of ADA to tislelizumab
		To detect the expression of PD-L1, MSS/microsatellite instability status,	Changes from baseline in tumor markers, correlation with drug

		and other biomarkers in tumor tissues of patients, and to perform relevant efficacy analysis to provide reference for the determination of dominant population	exposure, and association with efficacy and safety parameters
	Exploratory	To explore potential biomarkers associated with anti-tumor effects of fruquintinib in combination with tislelizumab	Changes from baseline in biomarkers, correlation with drug exposure, and association with efficacy and safety parameters

Brief Summary: This is an open-label, multicenter, non-randomized, phase 1b/2 study to assess the safety and efficacy of fruquintinib in combination with tislelizumab in patients with locally advanced or metastatic solid tumors. This study will be conducted in 2 parts: a Safety Lead-in Phase (Part 1) and a Dose Expansion Phase (Part 2). The Safety Lead-in Phase will determine the RP2D. The RP2D will be administered to 4 cohorts of patients in the Dose Expansion Phase:

- Cohort A: TNBC (IO-Treated in the metastatic setting)
- Cohort B: TNBC (IO-Naïve in the metastatic setting)
- Cohort C: EC (IO Naïve)
- Cohort D: MSS mCRC (IO Naïve)

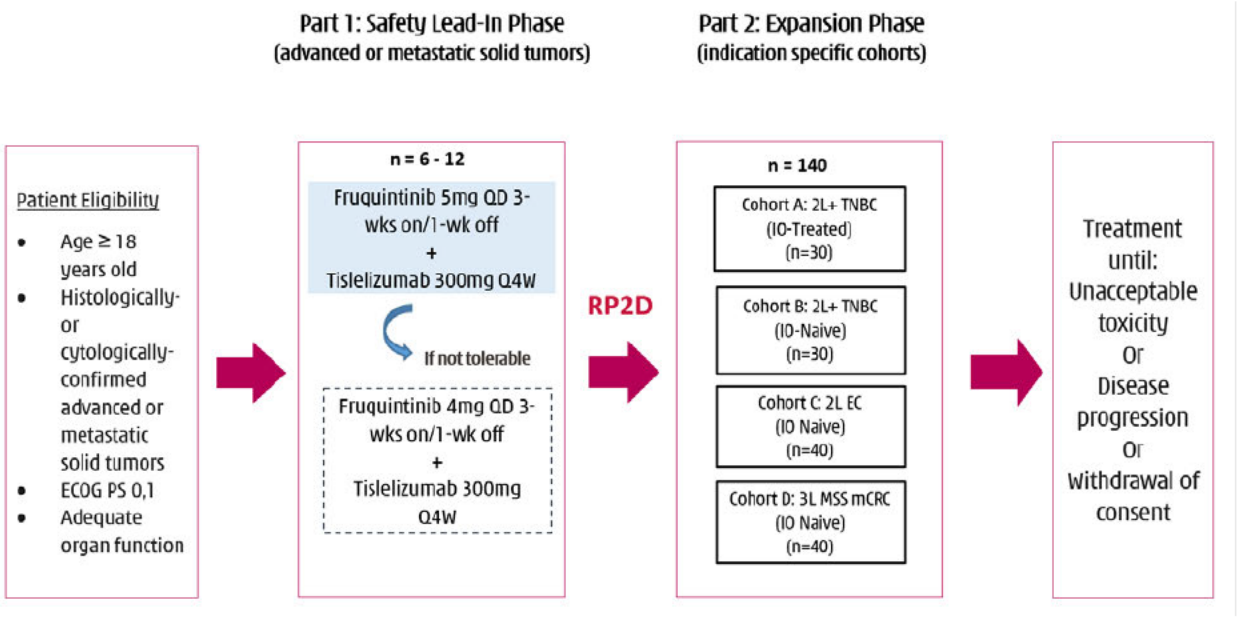
Condition/ Disease	Locally advanced or metastatic solid tumors
Study Duration	Approximately 30 months
Treatment Duration	28-day cycles
Health Measurement/ Observation	This study will determine the RP2D, as well as safety assessments including dose-limiting toxicities, treatment-emergent AEs, serious AEs, deaths, electrocardiograms, and clinical laboratory abnormalities. During the Dose Expansion Phase, patients will receive fruquintinib and tislelizumab at RP2D for 28 days in each cycle until progressive disease (PD), intolerable toxicity, death, withdrawal of consent, or until the study terminates. Patients may continue to receive fruquintinib and tislelizumab 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). 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 P140 D 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.
Visit Frequency	Cycle 1: every week (±1 day, except Day 1) Cycle 2: every 2 weeks (±1 day) Cycle 3 and onward: Day 1 (±3 days) End of Treatment: within 7 days (±3 days) after the last dose
Number of Participants	Part 1: approximately 6 to 12 patients will be enrolled Part 2: approximately 140 patients: 30 patients each in Cohorts A and B, 40 patients in Cohort C, and 40 patients in Cohort D Of note, based upon the strategic evaluation of the clinical development of fruquintinib, patient enrollment has been permanently discontinued for Cohorts A, B, and C in the Dose Expansion Phase, hence, the final actual total number of patients will reflect this strategic decision.
Data	Yes

Monitoring/ Other Committee	

1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Schematic



2L=second line; 3L=third line; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; IO=immune-oncology; mCRC=metastatic colorectal cancer; MSS=microsatellite stable; n=total number of patients; PS=performance status; QD=once daily; Q4W=every 4 weeks; RP2D=recommended Phase 2 dose; TNBC=triple negative breast cancer.

1.2 Schedule of Events

The schedule of events is presented in Table 1.

Table 1 Schedule of Events for Study 2020-013-00US3

Cycle/Period			C1				C2		C3+	EOT[w]	Safety Follow-up[x]	Survival Follow-up
Visit	**Screening**		**D1**	**D8**	**D15**	**D21**	**D1**	**D15**	**D1**	**≤7 Days After Last Dose**	**30 Days After EOT Visit**	**Every 8 Weeks After EOT Visit**
Visit Window (days)	**-28 to -1**	**-7 to -1**		**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**
Informed consent[a]	X											
PD-L1 expression confirmation[b]	X											
MSS/MSI status confirmation[c]	X											
Medical history, disease history[d]	X											
Demographics[e]	X											
Prior and concomitant medications and concomitant procedures[f]	X		X	X	X	X	X	X	X	X	X	
Comprehensive physical examination[g]	X		X									
Limited physical examination[h]				X	X	X	X		X	X	X	
Vital signs[i]	X		X	X	X	X	X	X	X	X	X	
ECOG performance status[i]		X	X				X		X	X	X	
Laboratory evaluations:		X										
Hematology[j]		X		X	X	X	X	X	X	X		
Blood chemistry[k]		X		X	X	X	X	X	X	X		
Blood amylase and lipase		X		X	X		X	X	X	X		
Fasting lipid panel[l]		X					X		X	X		
Coagulation indicators[m]		X		X	X	X	X	X	X	X		
Serum pregnancy test[n]		X									X	

Table 1 Schedule of Events for Study 2020-013-00US3

Cycle/Period			**C1**				**C2**		**C3+**	**EOT[w]**	**Safety Follow-up[x]**	**Survival Follow-up**
Visit	**Screening**		**D1**	**D8**	**D15**	**D21**	**D1**	**D15**	**D1**	**≤7 Days After Last Dose**	**30 Days After EOT Visit**	**Every 8 Weeks After EOT Visit**
Visit Window (days)	**-28 to -1**	**-7 to -1**		**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**
Urine pregnancy test[n]			X				X		X	X		
Thyroid function test[o]	X				X		X	X	X			
Urinalysis[p]		X				X	X		X			
Virological screening[q]	X								X	X		
PK assessments				Refer to Table 2								
Tislelizumab immunogenicity				Refer to Table 2								
12-Lead ECG[r]	X				X		X		X		X	
ECHO/MUGA scan	X		Every 12 weeks from C1D1 (±1 week) until progression of disease									
Tumor evaluation/imaging[s]	Screening and every 8 weeks (±1 week) from C1D1 until disease progression									X		
Fruquintinib drug administration			PO QD, Days 1 to 21 of each cycle									
Tislelizumab drug administration[t]			X				X		X			
AEs/SAEs[u]	X		X	X	X	X	X	X	X	X	X	
Overall survival[v]												X

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; C=cycle; CK=creatine kinase; CKMB=creatine kinase-MB; CrCl=creatinine clearance; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=end of treatment; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; INR=international normalized ratio; IV=intravenous; MSI=microsatellite instability; MSS=microsatellite stability stable; MUGA=multigated acquisition; PCR=polymerase chain reaction; PD=progressive disease; PD-L1=programmed death-ligand 1; PK=pharmacokinetics; PO=orally; QD=once daily; Q3W=every 3 weeks; Q4W=every 4 weeks; QTcF=QT interval corrected by the method of Fredericia; RNA=ribonucleic acid; RP2D=recommended Phase 2 dose; SAE=serious adverse event; SOP=standard operating procedure.

[a] Written informed consent must be obtained before any study-related examinations or procedures are performed. However, before informed consent is obtained, if the examinations for standard treatment are performed within 28 days before the planned C1D1, they can be used to replace the examinations during the screening period without repeating the examinations, except for examinations that need to be performed 7 days before the start of the study drug administration.

[b] PD-L1 expression as determined locally, for Cohorts A, B, and C. The results should be available in the source documents and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

[c] MSS/MSI status as determined locally, for Cohorts C and D only. The results should be available in the source documents and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

[d] Medical history and disease history data include significant clinical disease or symptom, surgical history, history of malignancy (including date of diagnosis, classification and prognosis evaluation of the study disease, and the treatment performed and the outcome; the tumor species and outcomes of any other previous malignancies), smoking history, history of alcohol consumption, history of drug abuse, and other medical-related history.

[e] Demographic information includes sex, race, and in some countries, year of birth.

[f] Concomitant medications include any prescription and over-the-counter medications started after signing of ICF. During the screening period, all drugs used for the patient within 28 days prior to the start of study drug should be recorded. In subsequent visits, the drugs used in the patient after the last record, as well as drugs 30 days after the last dose of study drug(s), should be recorded in eCRF. Subsequent new anti-tumor treatment regimens during the Safety and Survival Follow-up Periods will also be recorded.

[g] A comprehensive physical examination includes patient height, weight, and general condition, as well as an examination of the head, heart, chest (including the lungs), abdomen, extremities, skin, lymph nodes, nervous system, and additional areas/systems as clinically indicated.

[h] Limited physical examination includes vital signs and any change from baseline; any new abnormalities; examination of weight, thorax, abdomen; and additional areas/systems as clinically indicated. In order to assess changes from baseline and to evaluate for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, palpable masses, and appropriate examination to address any patient-reported symptoms.

[i] Assessments can be performed up to and including C1D1. Details for ECOG assessment can be found in Section 6.1.11 and for vital sign collection in Section 6.1.12.

[j] Hematology includes red blood cell count, hemoglobin, hematocrit, absolute reticulocyte count, white blood cell count and classifications (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), and platelet count. If abnormal or primitive immature cells are seen, they must also be recorded. Any additional routine blood tests during the study shall be arranged by the investigator as needed.

[k] Blood chemistry includes ALT, AST, alkaline phosphatase (ALP), bicarbonate, bilirubin/total bilirubin, lactic dehydrogenase, non-fasting total cholesterol, triglycerides, uric acid, total protein, albumin, blood urea nitrogen or urea, creatinine, CrCl rate, sodium, potassium, magnesium, chloride, corrected calcium (for patients with hypoproteinemia), phosphorus, blood glucose, creatine phosphokinase, and creatine kinase-MB (CK-MB). If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. 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 will be done as clinically indicated.

[l] Fasting lipid panel includes total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.

[m] Coagulation indicators include prothrombin time, aPTT, and INR.

[n] Female patients of childbearing potential (including those who have undergone tubal ligation) must undergo a serum pregnancy test ≤7 days before the first dose and record a negative result. If serum pregnancy test was drawn within 72 hours of C1D1, then urine pregnancy test is not required on C1D1. After enrollment, urine pregnancy test should be conducted on Day 1 of every treatment cycle starting from Cycle 1, and at the EOT visit. A serum pregnancy test should be performed at the Safety Follow-up Visit. If the result of urine pregnancy testing is equivocal, a serum test should be performed. Unscheduled testing via either method can be performed if there is an indication, however, any equivocal urine pregnancy tests should be repeated via serum pregnancy testing.

[o] Thyroid function tests include serum free tri-iodothyronine, serum free thyroxine, and thyroid stimulating hormone.

[p] Urinalysis includes urine pH, protein, glucose, blood and ketones; microscopic for white blood cell and red blood cell count. A 24-hour urine for quantitative protein must be collected from all patients with 1+ proteinuria.

[q] Testing will be performed by the local laboratory at screening and will include HBV/HCV serology (HBsAg 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 at the EOT visit.

[r] ECG indicators include PR interval, QRS interval, RR interval, QT/QTcF interval and heart rate. Unscheduled ECG or other cardiac examinations can be performed if clinically indicated. All ECGs should be done prior to dosing of study drugs.

[s] 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.

[t] Tislelizumab 300 mg IV will be administered on Day 1 of each 28-day cycle (once every 4 weeks). Every 3 weeks (Q3W) dosing of tislelizumab may be explored depending on the tolerability of the Q4W dosing schedule.

[u] After signing the informed consent form, all AEs including SAEs regardless of attribution will be collected until 30 days after the last dose of study drug or initiation of a new treatment therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered to be related to the study drug. 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.

[v] Following EOT, patients will be followed every 8 weeks (±14 days) via telephone or in manner that follows local site SOPs. 06 May 2024 will be the final day for survival follow up. Any patient who has not had contact with the site within 30 days of this date (and not previously reported as deceased or withdrawn consent for future follow-up) should have a final survival follow-up conducted via telephone or in a manner that follows local site SOPs.

[w] All patients on active treatment at the time of Amendment 5 are required to have an EOT visit. CCI [redacted] All EOT assessments described in the above table should be followed, including the final collection of patient drug diaries/final drug accountability review.

[x] All patients will be required to have a Safety Follow-up visit.

Table 2 Time and Events Schedule for Pharmacokinetics and Immunogenicity Assessments

Visit	Fruquintinib[a]	Tislelizumab	Immunogenicity (Anti-Tislelizumab Antibodies)
	PK Sample Time Point[b]	PK Sample Time Point[b]	
C1D1	Predose[c]	Pre-infusion[d]	Pre-infusion[d]
	2-4 h postdose	EOI[e]	
C1D8	Predose[c]	Any time during visit	-
C1D15	Predose[c]	Any time during visit	-
C1D21	Predose[c]	Any time during visit	-
	2-4 h postdose		
C2D1	Predose[c]	Pre-infusion[d]	Pre-infusion[d]
C4D1	Predose[c]	Pre-infusion[d]	Pre-infusion[d]
		EOI[e]	
C7D1	Predose[c]	Pre-infusion[d]	Pre-infusion[d]
C13D1	Predose[c]	Pre-infusion[d]	Pre-infusion[d]
EOT[f]	-	Any time during visit	Any time during visit

AE=adverse event; CxDx=Cycle X, Day X; h=hour; EOI=end of infusion; EOT=end of treatment; PK=pharmacokinetics.

Note: If at any time during an infusion day, should a patient present with any Grade ≥3 infusion-related AE, an additional blood PK sample must be taken to determine the serum concentration of tislelizumab. The actual time of PK sample, start time, and end time of infusion must be recorded.

[a] On days that both study drugs are administered, fruquintinib will be taken at the study site within 15 minutes before the start of infusion of tislelizumab.

[b] If dose delay occurs, then samples should be collected on the actual day of drug administration, not on the originally scheduled administration day. Additional samples can be obtained to help assess safety issues.

[c] Predose fruquintinib PK sample should be taken within 15 minutes prior to dosing.

[d] Pre-infusion PK and immunogenicity samples for tislelizumab should be collected within 60 minutes before starting tislelizumab infusion.

[e] End of infusion sample should be taken within 30 minutes after completing tislelizumab infusion.

[f] PK and immunogenicity samples should be collected according to the planned visit if the visit occurs prior to 31 December 2023. CCI [redacted]

2 INTRODUCTION

2.1 Study Rationale

Angiogenesis is a critical step in the inception and development of malignant tumors. Tumor cells growing rapidly in a state of hypoxia can secrete a variety of pro-angiogenic growth factors that stimulate endothelial cell proliferation leading to the formation of excessive new blood vessels around the tumor. These rapidly formed vasculatures are often coarsely packed and leaky, resulting in an exudation of tumors cells into the circulation initiating tumor metastasis. One of the major growth factors related to tumor angiogenesis is vascular endothelial cell growth factor (VEGF), which is secreted by tumors and activates the vascular endothelial growth factor receptor (VEGFR) signaling pathway leading to endothelial cell proliferation. Blocking of the VEGF/VEGFR signaling pathway can inhibit tumor angiogenesis and cut off the nutrients and oxygen supply to the tumor (Duda 2007).

Tumor immune surveillance is also key to detect, kill, and eliminate cancer cells. The programmed cell death protein-1 (PD-1) pathway plays a critical role in regulating the immune response. PD-1, an inhibitory immune checkpoint receptor expressed on activated T cells, B cells, natural killer cells, activated monocytes, dendritic cells, myeloid cells, and a subset of thymocytes (Pardoll 2012, Keir 2008) limits autoimmunity by regulating the activity of effector T cells in the periphery in response to an inflammatory stimulus (Pardoll 2012, Topalian 2012). Programmed death-ligand 1 (PD-L1), a PD-1 ligand, is an immunosuppressive signal that is upregulated in response to proinflammatory signals such as interferon-g (Keir 2008, Topalian 2012, Taube 2012). PD-L1 is expressed in multiple solid tumor including breast cancer, with expression relatively higher in triple negative breast cancer (TNBC) (Mittendorf 2014). The combination of immunotherapies and anti-angiogenic agents has been shown preclinically to generate more potent anti-tumor effects than either agent alone (Khan 2018) and has shown benefit in various therapeutic settings (Georganaki 2018). Thus, therapy with a small-molecule inhibitor of the VEGFR pathway may improve the clinical efficacy of PD-1/PD-L1 immunotherapies in tumors including TNBC by promoting inhibition of angiogenesis in the tumor region, which can suppress the growth of tumor cells and reduce the incidence of metastasis.

Fruquintinib, a potent, oral VEGFR tyrosine kinase inhibitor (TKI) with good kinase selectivity was approved for the treatment of metastatic colorectal cancer (mCRC) in patients who have failed at least 2 prior systemic antineoplastic therapies in China (FRESCO phase 3 study) (Li 2018). Safety and preliminary efficacy of fruquintinib have been demonstrated in metastatic breast cancer (mBC), including TNBC, in a phase 1 study conducted in China (Study 2009-013-00CH1) and in an ongoing phase 1/1b study conducted in the United States (US) (Study 2015-013-00US1). Expansion cohorts in TNBC and hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-mBC are currently enrolling. Fruquintinib is in clinical development for a number of other cancer indications, including gastric cancer (GC) and advanced non-small-cell lung cancer (NSCLC). A phase 3 study (FRESCO-2) of fruquintinib in combination with best supportive care is also ongoing in advanced colorectal cancer (CRC) patients in the US.

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G (IgG)4-variant monoclonal antibody against the immune checkpoint PD-1 that was approved in China for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma who received at

least 2 lines of systemic chemotherapy regimens and for the treatment of patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression whose disease progressed during or following or within 12 months of platinum-containing chemotherapy.

In this study, fruquintinib in combination with tislelizumab will be evaluated in patients with locally advanced or metastatic solid tumors with expanded cohorts in triple negative breast cancer (TNBC), endometrial cancer (EC), and microsatellite stable (MSS) mCRC.

2.2 Background

2.2.1 Target Indications and Populations

2.2.1.1 Triple Negative Breast Cancer

Triple negative breast cancer is characterized by a lack of expression of estrogen receptor (ER), progesterone receptor (PGR), and the HER2 (Ryu 2011). TNBC accounts for approximately 15% of breast cancers diagnosed worldwide with an estimated 1 million cases diagnosed annually. Patients diagnosed with TNBC have a worse prognosis compared to other types of breast cancer, with a 3-year overall survival (OS) rate of 14.7% (Leone 2019). Factors contributing to the poor prognosis are, in part, related to short disease-free survival and increased risk for lung, liver, and brain metastasis contributing to shortened OS. The combination of atezolizumab, a humanized engineered anti-programmed cell death protein-L1 checkpoint pathway (anti-PD-L1) monoclonal antibody, and nab-paclitaxel chemotherapy has been approved for the treatment of patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (Schmid 2018). However, treatment options following progression on the combination remain limited and prognosis remains poor. Thus, there is a high unmet need to investigate new therapies in patients with refractory TNBC and to explore potential mechanisms to overcome resistance to anti-PD-L1 therapy. Likewise, treatment options for TNBC patients whose tumors do not express PD-L1 are limited, and novel strategies to overcome potential intrinsic resistance to immunotherapy are also needed.

2.2.1.2 Endometrial Cancer

Endometrial cancer is the fourth most common cancer in women and the incidence is increasing with a lifetime risk of approximately 3% (Leslie 2012). There was an estimated 382,069 new cases and 89,929 deaths attributed to EC worldwide in 2018 (Zhang 2019). For patients with advanced EC and lymph node metastasis, the 5-year survival rate is less than 50%. For those with distant metastases, the survival rate falls to less than 20% (Ott 2017). Most ECs are identified at an early stage and are treated surgically with or without the addition of chemo- or radio-therapy. Common first-line treatment of advanced or recurrent EC consist of platinum-based chemotherapy regimens and may include biologics. Hormonal therapy (HT) can also be considered for those tumors that express hormone receptors, but few long-term responses are observed and generally result in relative short progression-free survival (Miller 2020). For a small number of patients whose tumors are microsatellite instability (MSI)-high (MSI-H) and mismatch repair deficient (dMMR), single-agent therapy with pembrolizumab is approved, but this represents only approximately 16% of recurrent EC tumors (Makker 2020). Considering the poor prognosis and increased incidence and mortality of endometrial cancer, there remains a high unmet need for effective therapies in advanced, metastatic, or recurrent ECs.

2.2.1.3 Colorectal Cancer

CRC is a major global health issue, with an estimated 1.9 million new cases and 935,000 deaths in 2020 worldwide (Bray 2020). The established initial and second-line systemic therapy for mCRC consists of fluoropyrimidine-, oxaliplatin-, and irinotecan-based cytotoxic chemotherapy (eg, FOLFOX: [5-Fluorouracil, leucovorin, and oxaliplatin] and FOLFIRI [5-fluorouracil, leucovorin, and irinotecan]). In addition, a biologic anti-vascular endothelial growth factor (anti-VEGF) therapy is typically given with chemotherapy (eg, bevacizumab), and if the tumor is RAS wild-type, an anti-endothelial growth factor receptor (EGFR) therapy (eg, cetuximab) is administered. When there is disease progression after the first 2 lines of chemotherapy, the established options are either regorafenib or TAS-102. There is no standard of care for patients who have progressed on chemotherapy, relevant biologics, and TAS-102 and/or regorafenib. Accordingly, there is an unmet medical need for new medications that are safe and effective in patients with refractory mCRC who have progressed on, or had intolerable toxicity from, available standard systemic therapies, and for whom no effective therapy or standard of care exists.

Immune checkpoint inhibitors have demonstrated activity in patients with CRC and other solid tumors that are MSI-H/dMMR, and nivolumab and pembrolizumab are currently approved by the Food and Drug Administration (FDA) for the 10% to 15% of patients with MSI-H/dMMR mCRC (Morse 2019). However, PD-1 blockade is particularly ineffective in patients with MSS or mismatch repair (MMR)–proficient CRC which makes up the majority (95%) of mCRC patients (Ali 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 2019). Recently, several strategies to turn a "cold" CRC tumor into an immunoreactive "hot" tumor were being tested in clinical trials, and a growing body of evidence supports the potentially synergistic effect of the combination of PD-L1 inhibitors and VEGFR TKIs in patients with MSS mCRC (Fukuoka 2020).

2.2.2 Description of Fruquintinib

Fruquintinib is a small-molecule anti-tumor quinazoline class tyrosine kinase inhibitor (TKI) that selectively inhibits vascular endothelial growth factor (VEGF) receptors 1, 2, and 3.

2.2.2.1 Fruquintinib Administration Regimen

Fruquintinib (HMPL-013) capsule 5 mg will be administered orally (PO) once daily (QD), 3 weeks on/1 week off (4-week cycles). Doses may be given either in the fasting state or after meals. If dose adjustment is required, 1-mg capsules will be used.

2.2.2.2 Fruquintinib Justification for Dosing Strategy

The optimal fruquintinib dose and dosing regimen were determined in 2 Chinese phase 1 studies, 2009-013-00CH1 and 2012-013-00CH3, as well as 1 US phase 1/1b study, 2015-013-00US1. During dose escalation, Study 2009-013-00CH1 investigated continuous daily doses of 1 mg, 2 mg, 4 mg, 5 mg, and 6 mg; in addition, 5 mg QD and 6 mg QD were studied on a regimen of 3 weeks on, 1 week off (4-week cycles). The maximum-tolerated dose (MTD)/recommended Phase 2 dose (RP2D) was 4 mg QD (continuous) or 5 mg QD (3 weeks on/1 week off).

In Study 2012-013-00CH3, the safety and tolerability of these 2 dosing regimens (4 mg QD continuously versus 5 mg QD, 3 weeks on/1 week off) were compared in patients with mCRC. The safety profile was better in the 5 mg QD (3 weeks on/1 week off) group than the 4 mg QD (continuous) group. In addition, there was accumulation of drug over time in the 4 mg QD (continuous) group. Thus, the 5 mg PO QD (3 weeks on/1 week off) dose and regimen was selected as the RP2D and the dosing regimen to be used in subsequent clinical development in China.

The RP2D and dosing regimen were tested in the phase 2 (2012-013-00CH1) and phase 3 (2013-013-00CH1 [FRESCO]) studies, which confirmed that the dose and dosing regimen were safe and effective in patients with refractory mCRC. The 5 mg PO QD (3 weeks on/1 week off) dose and regimen is the standard dose and dosing regimen in all other completed, ongoing, and planned studies in patients with advanced cancer.

In the US phase 1/1b study (2015-013-00US1), there were 2 dose cohorts in the dose escalation phase, 3 mg PO QD (n=7) and 5 mg PO QD (n=7). Fruquintinib was well tolerated in both dose cohorts. Therefore, 5 mg PO QD (3 weeks on/1 week off) was confirmed as the RP2D for global studies, as well.

2.2.3 Description of Tislelizumab

Tislelizumab (also known as BGB-A317) is a humanized, IgG4-variant monoclonal antibody against PD-1.

2.2.3.1 Tislelizumab Administration Regimen

Tislelizumab 300 mg will be administered intravenously on Day 1 of each 28-day cycle (once every 4 weeks). Every 3 weeks (Q3W) dosing of tislelizumab may be explored depending on the tolerability of the every 4 weeks (Q4W) dosing schedule.

2.2.3.2 Tislelizumab Justification for Dosing Strategy

The pharmacokinetics (PK), safety, and efficacy data obtained from the first-in-human 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 BGB-A317 Study_001), with no MTD identified in BGB-A317 Study_001. The flat dose of 200 mg intravenously once every 3 weeks was selected for further evaluation.

Rates of treatment-related adverse events (AEs) and serious AEs (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 show no relationship between exposure and treatment-emergent immune-mediated AEs (imAEs). Similarly, confirmed objective response rates (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 clearance (CL) of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the observed serum exposure of a 200 mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

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 best overall response (BOR) of partial response (PR), 4 patients (31%) had a BOR of stable disease (SD), and 5 patients (39%) had a BOR of progressive disease (PD). Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.

The observed clinical activity in patients with advanced tumors, coupled with a manageable safety profile and supportive data, supports 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 refer to the tislelizumab Investigator's Brochure (IB).

The alternative regimen of 300 mg once every 4 weeks is selected by matching dosing and exposure (area under the curve [AUC]) with the exposure of 200 mg once every 3 weeks regimen. Exposure-response assessment of available clinical data from studies including BGB-A317 Study_001, BGBA317-102, 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 observed 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 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.

2.2.4 Rationale for the Starting Combination Doses

The full dose of fruquintinib (5 mg daily, 3 weeks on followed by 1 week off, 4-week cycles) 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 studies. Axitinib, like fruquintinib, targets VEGFR 1, 2, and 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 study enrolled 52 patients (11 in dose-finding phase, 41 in Dose Expansion Phase), and treatment was initiated with the full dose of both agents. No unexpected toxicities were observed. Three dose-limiting toxicities (DLTs) 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. Thirty-two (62%) patients had their axitinib dose reduced (ie, to <5 mg twice per day for 2 consecutive doses) because of axitinib-related toxicities. Overall, 30 (58%) patients discontinued axitinib because of AEs (n=16) and disease progression (n=9); 27 (52%) patients discontinued pembrolizumab early

because of AEs (n=12) and disease progression (n=12). Unprecedented anti-tumor activity and tolerability of this combination treatment led to breakthrough status designation from the US 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 (Atkins 2018).

2.2.5 Supportive Nonclinical Data

2.2.5.1 Fruquintinib

2.2.5.1.1 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 IB for detailed information regarding pharmacology studies.

2.2.5.1.2 Toxicology

Fruquintinib has been evaluated in repeat-dose toxicology studies for up to 6 months (26 weeks) in rats and 9 months (39 weeks) in dogs. Other completed studies included single-dose studies, in vitro and in vivo genetic toxicology studies, a fertility and early embryonic development/implantation study in rats, and an embryo-fetal development study.

Key findings from the toxicology studies are summarized below:

- Safety pharmacology: No adverse effects were observed in dog cardiovascular and respiratory systems at the highest dose tested (0.34 mg/kg) and in the central nervous system at the highest dose tested (10 mg/kg).
- General toxicology: In single-dose toxicity studies in rats and dogs, no deaths occurred at a dose of up to 2000 mg/kg and 1000 mg/kg, respectively. In repeat-dose toxicity studies in rats (1 month and 6 months) and dogs (1 month and 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 (GI) system, bone marrow (sternum), and femur. The toxic responses were found to be reversible upon discontinuation of the drug treatment.
- 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 rats and female rats was found to be 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 in rats for both maternal effects and embryo-fetal development was found to be 0.1 mg/kg and 0.025 mg/kg, respectively.
- 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 (compared to the negative control) in the

percentages of aberrant cells with structural chromosome aberrations in Chinese hamster lung cells treated in vitro for 24 hours without S9 activation. There was no significant increase in the percentages of aberrant cells in other treated groups.

Refer to the fruquintinib IB for detailed information regarding toxicology studies.

2.2.5.1.3 Pharmacokinetics

Fruquintinib had good intrinsic membrane permeability and was not a substrate of efflux transporters (eg, P-glycoprotein [P-gp]). Following oral administration with [^{14}C]-fruquintinib in rat, it was found that fruquintinib was mainly distributed to metabolic and excretory organs.

Three major metabolites were observed in the incubation with liver microsomes of various species (human, mice, rats, dogs and monkeys). The most abundant metabolite of fruquintinib in human plasma was M11 (desmethylation product, HM5025423), and its production was mainly mediated by cytochrome P450, family 3, subfamily A4 (CYP3A4)/5.

Fruquintinib inhibited both P-gp and breast cancer resistance protein (BCRP) in a -dose dependent manner, with estimated IC_{50} values of 4.60 and 1.29 μM, respectively. No obvious inhibitory effects were observed on the following transporters: organic anion transporting polypeptide 1b1, 1b3 (OATP1B1, OATP1B3), organic anion transporter 1, 3 (OAT1, OAT3), organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), and multidrug and toxin extrusion 2-K (MATE2-K). Fruquintinib had no significant inhibitory effects on cytochrome P450s (CYPs) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 (IC_{50} >10 μM) and no inductive effects on CYPs 1A2, 2B6, and 3A4 at the test level of 10 μM. No significant time-dependent inhibition was observed for CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 at 10 μM.

The mass balance study in rats showed that roughly similar proportions (approximately 30%) of the drug were excreted in bile, urine and feces, respectively, after a single oral dose of [^{14}C]-fruquintinib.

Refer to the fruquintinib IB for detailed information regarding pharmacokinetics studies.

2.2.5.2 Tislelizumab

2.2.5.2.1 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 PDL-1 and programmed death 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 2018). Tislelizumab has demonstrated in vivo anti-tumor activity in several allogeneic xenograft models.

Refer to the tislelizumab IB for additional details regarding the pharmacology of tislelizumab.

2.2.5.2.2 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, 2020-013-00US3.

Refer to the tislelizumab IB for more detailed information on the toxicology of tislelizumab.

2.2.5.2.3 Pharmacokinetics

A pharmacokinetic (PK) study was conducted in cynomolgus monkey at single doses of 3, 10, or 30 mg/kg or at a repeat dose of 10 mg/kg weekly for 5 doses via intravenous infusion. The systemic exposure appeared to increase dose proportionally without gender difference or accumulation. After single-dose administration of 3, 10, or 30 mg/kg, the half-life ($t_{1/2}$) ranged from 74 to 183 hours, C_{max} ranged from 90 to 999 µg/mL, area under the curve $(AUC)_{0\text{-}1008h}$ ranged from 12,322 to 163,755 h*µg/mL, and volume of distribution (V_d) ranged from 22 to 52 mL/kg. The $t_{1/2}$ of tislelizumab in cynomolgus monkeys supported biweekly (every other week) dosing in the repeat-dose toxicology study.

Refer to the tislelizumab IB for additional details regarding pharmacokinetics of tislelizumab.

2.2.6 Supportive Clinical Data

2.2.6.1 Fruquintinib

2.2.6.1.1 Clinical Pharmacology and Pharmacokinetics

Single-dose and multiple-dose PK of fruquintinib have been characterized in Chinese and US patient populations and single-dose PK has been evaluated in healthy Chinese males.

In Chinese patients with cancer, plasma fruquintinib exposure increased proportionally over the single dose range tested from 1 mg to 6 mg (Study 2009-013-00CH1). Fruquintinib was rapidly absorbed with mean time to maximum concentration (T_{max}) ranging from 1.5 to 4.7 hours. Mean $t_{1/2}$ ranging from 35.2 to 48.5 hours was observed for fruquintinib. Following continuous dosing of fruquintinib 1, 2, 4, 5, or 6 mg QD, plasma fruquintinib concentration reached steady state by 14 days after dosing with exposure accumulating 3- to 4-fold at steady state compared to Day 1. Following dosing of fruquintinib at 5 mg QD and 6 mg QD at the 3 weeks on/1 week off schedule, plasma fruquintinib concentrations declined during the off week, as expected. Preliminary PK results from the US patient population (Study 2015-013-00US1) that received fruquintinib at 3 mg and 5 mg QD 3 weeks on/1 week off suggested that there were no meaningful differences in fruquintinib exposure between Chinese and US patients. Following

fruquintinib 5 mg QD 3 weeks on/1 week off, mean fruquintinib C_{max} and AUC_{tau} values on Day 21 were 326 ng/mL and 5969 h*ng/mL in Chinese patients (Study 2012-013-00CH3), respectively, compared with 385 ng/mL and 7530 h*ng/mL in US patients, respectively.

The effect of a high-fat high-calorie meal on the PK of fruquintinib 4 mg (4×1-mg capsules) was studied in healthy Chinese males (Study 2012-013-00CH2). Food delayed T_{max} of fruquintinib by 2.6 hours. A slight decrease in fruquintinib C_{max} by 17% was seen, although there was no observed effect on $AUC_{0-\infty}$.

Results from the mass balance study conducted in healthy Chinese patients (Study 2015-013-00CH2) indicated that 60.31% of total radioactivity was recovered in urine and 29.80% in feces. A total of 22 metabolites were identified in the plasma, urine, and feces samples. The M11 (N-desmethylation product) and M9 (carboxylic acid product) were the main metabolites; M11 accounted for 17.31%, and M9 accounted for 4.46% of the plasma exposure of total radioactivity. Only a small amount of unchanged fruquintinib was detected in urine, which accounted for 0.50% of the dose administered. The amount of fruquintinib in feces accounted for 5.34% of the dose administered.

M11 is a pharmacologically active metabolite found to inhibit VEGFR2 kinase activity and VEGF-induced VEGFR2 phosphorylation, with a potency approximately 2 to 10 times lower than that of fruquintinib. After multiple doses of fruquintinib 5 mg QD to patients for 21 days (Study 2015-013-00US1, preliminary data), M11 reached T_{max} after 1 hour. The mean (standard deviation) C_{max} and AUC_{0-24} values were 144 (56.2) ng/mL and 3080 (1250) h*ng/mL, respectively. M11 accumulated by 31.5-fold after multiple dosing. The mean (standard deviation) metabolite-to-parent ratio of M11 was 0.409 (0.135) at steady state. Overall, M11 is not expected to have a clinically meaningful contribution to the total pharmacological activity of fruquintinib at therapeutic exposure.

In Study 2015-013-00US1, preliminary PK data were comparable between the cancer populations in the US and China, suggesting no clinically meaningful effects of ethnicity on fruquintinib PK.

2.2.6.1.2 Clinical Safety

As of 03 September 2019, 7 clinical studies have been completed and 5 clinical studies (monotherapy and/or combination therapy) were ongoing in cancer patients. This included 3 phase 3 studies conducted in China: 1 completed monotherapy study in patients with mCRC, 1 completed monotherapy study in patients with advanced NSCLC, and 1 ongoing phase 3 study of fruquintinib in combination with paclitaxel in GC. There is 1 ongoing phase 1/1b study of fruquintinib being conducted in the US. In addition, 4 studies of fruquintinib have been completed in healthy volunteers.

A pooled analysis of 4 completed, double-blind, placebo-controlled monotherapy studies was conducted to provide a comprehensive safety assessment separate 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.

Refer to the current version of the fruquintinib IB for more detailed information on fruquintinib safety and efficacy data when given as monotherapy or in combination with chemotherapy or other agents.

2.2.6.1.2.1 Monotherapy Safety

Data presented in this section is from a pooled analysis of the 4 completed double-blinded, placebo-controlled studies, which include 739 patients on fruquintinib and 361 patients on placebo.

- *Adverse Events*: Of the 739 patients, 729 (98.6%) patients reported treatment-emergent AEs (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.
- *Serious Adverse Events*: The most common SAEs (≥1.0%) by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) included infectious pneumonia in 24 (3.2%) patients, intestinal obstruction in 17 (2.3%) patients, death in 10 (1.4%) patients, pleural effusion in 9 (1.2%) patients, hepatic function abnormal in 8 (1.1%) patients, and gastrointestinal hemorrhage in 8 (1.1%) patients. A total of 112 (15.2%) patients reported treatment-related SAEs; 41 (5.5%) patients had a fatal SAE.
- *Adverse Events of Special Interest*: The most frequently reported AEs of special interest (AESIs) (>10% of patients) in the fruquintinib group 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%). In the fruquintinib group, the AESIs of Grade ≥3 reported by >5% of patients included hypertension (22.1%), dermatological toxicity (11.1%), infections (7.3%), and hepatic function abnormal (6.5%).
- *Fatal Adverse Events*: A total of 44 (6.0%) patients had TEAEs leading to death.

2.2.6.1.2.2 Safety Analysis of Study 2015-013-00US1

This was a Phase 1/1b Dose Escalation/Dose Expansion Study in US Patients with Advanced Solid Tumors (Ongoing Study 2015-013-00US1).

As of the data cut-off date of 03 September 2019, 23 patients had been enrolled and received fruquintinib. Fourteen patients were enrolled in the dose escalation phase (7 patients at 3 mg QD, 7 patients at 5 mg QD, in 3 weeks on/1 week off [28-day] cycles). An additional 6 patients were enrolled in a planned expanded cohort of patients with advanced, refractory solid tumors at 5 mg QD 3 weeks on/1 week off regimen.

The RP2D determined in the dose escalation phase of US patients was 5 mg QD 3 weeks on/1 week off regimen, which is consistent with that of the approved drug label in China.

The AE profile of patients in Study 2015-013-00US1 was consistent with that of other clinical studies of fruquintinib. In the dose escalation phase, there was 1 DLT of Grade 4 hypertension at the 3-mg dose level that resolved after 2 days, and no DLTs were observed in the additional

3 patients at 3 mg or at the 5 mg 3 weeks on/1 week off regimen. All (100%) of the 23 patients reported TEAEs, among whom 22 (95.7%) patients reported treatment-related TEAEs. A total of 19 (82.6%) patients reported Grade ≥3 TEAEs, of whom 11 (47.8%) patients reported treatment-related Grade ≥3 TEAEs. The most frequently reported treatment-related TEAEs (≥20% of patients) by PT were Hypertension (43.5%), Proteinuria (34.8%), Decreased appetite (30.4%), Diarrhoea, Nausea, Dysphonia, Fatigue (26.1% each), and Constipation (21.7%). In the dose escalation phase, Grade ≥3 Hypertension was observed in 5 patients (35.7%) and was the only Grade ≥3 TEAE that occurred in ≥5% of patients.

Refer to the most recent version of the fruquintinib IB for additional details on clinical safety.

2.2.6.1.3 Clinical Efficacy

2.2.6.1.3.1 Monotherapy Efficacy

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 PR and SD, observed in the majority of the heavily pretreated patients with advanced cancer, particularly in patients with CRC, NSCLC, and GC.

The phase 3 study in patients with CRC (FRESCO, 2013-013-00CH1) met its primary efficacy endpoint of OS and showed that fruquintinib significantly improved the OS, progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) as compared to placebo. A total of 416 patients were randomized to receive fruquintinib (5 mg QD) 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; hazard ratio [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 for the treatment of patients with refractory mCRC by the China National Medical Products Administration (NMPA) based on the results of the FRESCO study.

One phase 3 study of fruquintinib was completed in patients with 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) (Lu 2020). However, fruquintinib significantly prolonged the PFS comparing to placebo with an HR of 0.34 (95% CI: 0.279, 0.425) with p <0.001 (stratified log-rank test). Statistically significant benefits were also shown with fruquintinib in ORR and DCR.

In the ongoing study 2015-013-00US1 of fruquintinib in patients with advanced solid tumors, 15 of 20 patients enrolled into the dose escalation phase and planned expanded cohort of 6 patients with advanced solid tumors were evaluable as of 03 September 2019. Two patients had a confirmed PR, 11 patients had confirmed SD, and 2 patients had PD. Of those patients, 3 patients had mBC (1 each of hormone receptor-positive/HER2-, hormone receptor-negative/HER2+ and TNBC). The patient with TNBC had SD.

2.2.6.1.3.2 Combination Therapy Efficacy

A phase 1b/2 study has been conducted to investigate the treatment of fruquintinib, in combination with paclitaxel, as second-line therapy in patients with GC (2014-013-00CH3). The results showed that the ORR and DCR were 27.3% (9/33) and 63.6% (21/33), respectively. The median PFS and median OS at the RP2D (fruquintinib 4 mg plus paclitaxel) were 4.0 months and 8.5 months, respectively.

The efficacy data in 1 ongoing study of fruquintinib in combination with gefitinib in patients with NSCLC (2016-013-00CH1) and in 1 ongoing study 2018-013-00CH3 of fruquintinib in combination with sintilimab in patients with advanced solid tumor were not available as of the data cutoff date (03 September 2019).

2.2.6.2 Tislelizumab

2.2.6.2.1 Clinical Pharmacology and Pharmacokinetics

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 CL mechanisms. No time-varying CL was observed in tislelizumab PK. The typical estimates of CL, central volume (V_c), and peripheral volumes (V2, V3) were 0.164 L/day and 2.92, 0.928, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), V_c (16.7%), V2 (56.6%), and V3 (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 2012, Dirks 2010, Keizer 2010, Ryman 2017).

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) performance status score, 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.

2.2.6.2.2 Clinical Safety

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 IB version 7, 13 September 2019: 7 monotherapy studies, 2 chemotherapy combination therapy studies, and 4 investigational agent combination therapy studies.

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separate 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 current tislelizumab IB for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

2.2.6.2.2.1 Monotherapy Safety

- *Adverse Events*: Of the 1273 total patients treated in the Pooled Monotherapy studies, 1210 patients (95.1%) experienced at least 1 TEAE and 846 patients (66.5%) experienced at least 1 treatment-related TEAE. TEAEs Grade ≥3 were reported by 548 patients (43.0%). The most commonly occurring Grade ≥3 TEAEs were anemia (64 patients, 5.0%), AST increased (35 patients, 2.7%), pneumonia (35 patients, 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.
- *Serious Adverse Events*: Of the 1273 total patients treated in the Pooled Monotherapy studies, 424 patients (33.3%) experienced at least 1 treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs were pneumonia (35 patients, 2.7%), pyrexia (22 patients, 1.7%), and ascites (17 patients, 1.3%).
- *Immune-Mediated Adverse Events*: Anti-programmed cell death protein-1 antibody(Anti-PD-1) therapies are known to cause imAEs in some patients and therefore have been defined as AESIs in tislelizumab clinical studies. Immune-mediated AEs (imAEs) are consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology that 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 HUTCHMED Limited (formerly known as Hutchison MediPharma Limited) Safety/Pharmacovigilance team. Certain imAEs have multiple 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 IB for more detailed information.
- *Infusion-Related Reactions*: Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are common. Of the 1273 total patients in the Pooled Monotherapy studies, 97 patients (7.6%) experienced at least 1 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).

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

2.2.6.2.3 Clinical Efficacy

Efficacy data are available from 2 of the ongoing monotherapy studies in solid tumors, BGB-A317_Study_001 and BGB-A317-102, as of 20 May 2019.

2.2.6.2.3.1 BGB-A317 Study_001

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 once either every 2 or every 3 weeks and a fixed dose of 200 mg given once every 3 weeks) to establish the maximum tolerated dose, if any, and an RP2D 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 includes all treated patients who had at least 1 measurable baseline target lesion and at least 1 evaluable post-baseline tumor assessment. This set included 52 patients in the GC cohort and 21 patients in the CRC 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 13.6%. Additionally, there were 142 patients (32.2%) with a BOR of SD. A total of 199 patients (45.1%) had a best response of 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 BOR 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 BOR of PD. Two patients (9.5%) had missing assessments.

2.2.6.2.3.2 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 RP2D of 200 mg given once every 3 weeks in indication-specific expansion cohorts in patients who had at least 1 measurable baseline target lesion and at least 1 evaluable post-baseline tumor assessment. This set includes 12 patients in the GC cohort and 16 patients in the CRC 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 BOR 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) were 3 patients (25.0%) who had a confirmed PR. Additionally, there were 2 patients (16.7%) with a BOR 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 BOR of SD, and 8 patients (50.0%) had a best response of PD.

Refer to the tislelizumab IB for more detailed information on tislelizumab efficacy data when given as monotherapy or in combination with chemotherapy.

2.2.7 Rationale for Fruquintinib and Tislelizumab in Combination

2.2.7.1 Triple Negative Breast Cancer

Triple negative breast cancer is more aggressive and has a worse prognosis compared to other types of breast cancer, with a median OS of 8 to 15 months (Liu 2020). Chemotherapy is the primary treatment for TNBC, but responses are short-lived. Treatment with immune checkpoint inhibitors (ICIs) has improved clinical outcomes in TNBC, and the use of immunotherapy in TNBC is supported by higher expression of PD-L1 in TNBC when compared to other breast cancer subtypes (Mittendorf 2014), a higher rate of tumor mutation burden (TMB) in high-grade tumors (although lower than that observed in other malignancies such as lung cancer and melanoma), and relatively higher tumor infiltrated lymphocyte (TIL) density in TNBC (Kandoth 2013). Several studies investigating anti-PD-L1 inhibitors as monotherapy in TNBC showed objective response rates of 5.2% to 18.5%, with higher response rates demonstrated in earlier lines of therapy. Based on the results of IMpassion130 study, the combination of atezolizumab, a humanized engineered anti-PD-L1 monoclonal antibody, and nab-paclitaxel chemotherapy was approved for the treatment of patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (Schmid 2018). However, treatment options for patients who progress on or who are not candidates for the combination remain limited, and prognosis remains poor. Thus, there is a high unmet need to investigate new therapies in patients with refractory TNBC and to explore potential mechanisms to overcome acquired or intrinsic resistance to anti-PD-L1 therapy. Although immunotherapy has emerged as an important treatment for a variety of cancers, including TNBC, a large proportion of patients do not respond to such treatment, and initial responders eventually develop resistance. One mechanism of resistance to immunotherapy is immune suppression through other immune checkpoints that regulate lymphocyte activation or through the immunosuppressive cells (Fukuoka 2020). There is increasing evidence that tumor angiogenesis is highly dependent on a suppressive tumor microenvironment, and VEGF-A was recently identified as a key factor in tumor-induced immunosuppression by facilitating the proliferation of immunosuppressive cells, limiting T-cell recruitment into tumors, and promoting T-cell exhaustion (Lapeyre-Prost 2017). Therefore, one strategy for targeting the tumor microenvironment is to inhibit angiogenesis while stimulating an effective immune response. The process of angiogenesis is promoted and influenced by inflammatory mediators such as cytokines and immune cells, which can affect the immune microenvironment. Anti-angiogenic agents can stimulate the immune system and act synergistically with ICIs to enhance anti-tumor response. The synergistic effect of anti-angiogenics and ICIs has been demonstrated by clinical benefit observed in multiple tumor types.

There is a growing body of evidence supporting the combination of anti-angiogenic agents and immunotherapy in TNBC. Despite the clinical activity observed with ICIs in TBNC, certain poorly immunogenic tumors such as breast cancer have intrinsically low-response rates to immunotherapy due to a paucity of tumor-infiltrating T lymphocytes and an abundance of immunosuppressive myeloid cell populations within the tumor microenvironment. Even for TNBC, which is more immune sensitive, the ORR of PD-1/PD-L1 blockade from early-phase monotherapy trials was low (Dirix 2018, Nanda 2016, Emens 2019). Therefore, there is an increased interest in identifying combination treatment strategies to improve the response rate and the efficacy of immunotherapy treatment (Emens 2017). The responsiveness of tumors to ICIs is dependent on multiple intrinsic and extrinsic factors. Notably, tumor vasculature is often morphologically abnormal and functionally impaired, resulting in reduced infiltration of immune effector cells into the tumor (Huang 2018). In addition, tumor blood vessels have impaired perfusion capacity, which creates increased intratumoral hypoxia that inhibits the activity of infiltrated cytotoxic T cells (Lanitis 2015). This process results in the accumulation of suppressive immune cells such as myeloid-derived suppressor cells and regulatory T-cells (Corzo 2010). The hypoxic tumor microenvironment also stimulates the secretion of several immunosuppressive cytokines (Facciabene 2011) and promotes the upregulation of PD-L1 on T cells (Barsoum 2014). Normalization of tumor vasculature has been proposed to reduce immunosuppression and synergize with cancer immunotherapy (Ali 2018).

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

There are several completed, ongoing, and planned studies of anti-angiogenic agents in combination with PD-L1 inhibitors in TNBC, including a phase 2 study of atezolizumab plus bevacizumab plus cobimetinib, a phase 2 study of SHR-1210 (an anti-PD-1 antibody) plus apatinib, and a phase 1/2 study of MEDI4738 plus bevacizumab plus olaparib, that support the investigation of the combination of fruquintinib and tislelizumab in TNBC, and promising anti-tumor activity has been seen with the combination. Preclinical studies with breast cancer models demonstrated that combining anti-PD-1 antibody and anti-VEGFR 2 therapy significantly improved responses to tumors (Li 2020). Results from the phase 2 study of SHR-1210 (or camrelizumab) in combination with apatinib in patients with advanced TNBC demonstrated a PFS of 3.7 months (Liu 2020). This stands in contrast to PFS of 1.9 months shown in the phase 1b KEYNOTE-012 with single-agent pembrolizumab (Nanda 2016). Patients who had a better response to the combination were found to have notable vascular remodeling and increase TILs when compared to poor responders. No correlation between PD-L1 expression and tumor response was observed (Li 2020). Taken together, these data suggest a synergistic activity with the combination of anti-angiogenic therapy and anti-PD-L1 antibodies and provide rationale for the combination in TNBC.

Based on the available clinical data from the combination of immunotherapy and anti-angiogenics, which demonstrate promising anti-tumor effect compared to the therapeutic effect of a single agent alone, the combination of fruquintinib and tislelizumab may provide a tolerable, effective treatment option for the patients with TNBC. This study will be aimed at investigating if the combination of fruquintinib with tislelizumab is safe and effective in TNBC and could give insight into overcoming potential resistance mechanisms to ICIs in these tumors.

2.2.7.2 Endometrial Cancer

Endometrial cancer, when diagnosed early, has a 5-year overall survival rate of 81%. The 5-year overall survival rate for stages IVa and IVb EC, however, is only 17% and 15%, respectively. Deaths associated with EC are increasing globally at a steady rate. Initial management of EC consists of surgery followed by radiation and/or cytotoxic chemotherapy. Recurrent disease is treated with cytotoxic, targeted, or hormonal therapy with or without radiotherapy. Despite these therapies, overall survival remains poor. EC cells possess the ability to downregulate immune response by activating PD-1 signaling. PD-1 and PD-L1 expression in ECs represent the highest expression among gynecologic cancers (Green 2020).

Multiple clinical studies with PD-1 inhibitors as monotherapy have demonstrated clinical efficacy in EC with ORRs between 26.7% and 53%. (Green 2020). The multi-tyrosine kinase inhibitor lenvatinib has been approved as monotherapy for iodine-refractory differentiated thyroid cancer and unresectable hepatocellular carcinoma. It has also been investigated in EC as second-line therapy in a phase 2 trial that demonstrated modest tumor activity with an ORR of 14.3% (Vergote 2020). There are ongoing studies to examine the efficacy of combinations of immunotherapies with differing mechanisms of action to overcome resistance mechanisms observed in monotherapy (Green 2020).

Recently, the combination of the multi-tyrosine kinase inhibitor lenvatinib in combination with the PD-1 inhibitor pembrolizumab was granted accelerated FDA approval in advanced EC. The KEYNOTE-146 was a phase 1b/2 study that evaluated this combination in patients with advanced tumors, including EC, and provided the basis for the approval. An analysis of 108 patients with EC showed the ORR was 38% with an ORR of 63.6% among those with MSI-H/dMMR tumors and 36.2% among those with microsatellite stable (MSS)/MMR proficient (pMMR) tumors. The overall DCR was 84.3%, including 80.9% among the MSI-H/dMMR population and 84.0% among those with MSS/pMMR tumors. ORR was similar regardless of PD-L1 expressions status (median follow-up of 18.7 months) (Vergote 2020). The confirmatory, phase 3 KEYNOTE-775(NCT03517449) randomized 827 patients and met its dual primary endpoints. With a median follow-up of 11.4 months, results demonstrated a median progression-free survival of 7.2 months vs 3.8 months (hazard ratio [HR]=0.56, $p<0.0001$) and median overall survival of 18.3 months vs 11.4 months (HR=0.63, $p<0.0001$) (Makker 2020). The KEYNOTE-775 study led to FDA approval of pembrolizumab in combination with lenvatinib in patients who had progressed on a platinum-based first-line chemotherapy.

2.2.7.3 Colorectal Cancer

The mainstay of first-line therapy for mCRC is combination chemotherapy plus an anti-VEGF or anti-EGFR antibody, depending on tumor characteristics. However, most patients progress within 1 year (Chau and Cunningham 2009). Patients with mCRC that progress on first-line therapy are often treated with second-line chemotherapy. Beyond the second line, targeted

therapy such as regorafenib or TAS-102 have been shown to prolong survival. However, the treatment benefit is short-lived. Recently, immune checkpoint inhibitors have demonstrated activity in patients with CRC and other solid tumors that are MSI-H/dMMR. Nivolumab and pembrolizumab are currently approved by the FDA for patients with MSI-H/dMMR mCRC (Morse 2019). However, PD-1 blockade is particularly ineffective in patients with MSS or MMR–proficient CRC, which makes up the majority (95%) of mCRC patients (Ali 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 2019). 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 exclusion of 1 patient with MSI-H mCRC, the ORR was 33.3% in patients with MSS mCRC. Median PFS was 7.9 months (Fukuoka 2020).

The combination of PD-1/PD-L1 and VEGFR inhibitors warrants further evaluation as a treatment paradigm for patients with mCRC.

2.2.8 Rationale for Biomarker Strategy

A number of biomarkers have been identified that correspond with response to immunotherapy for patients with TNBC, EC, or MSS mCRC. PD-L1 expression has been demonstrated to be positively correlated with response to anti-PD-1 therapy across tumor types (Cristescu 2018). For TNBC, the expression of PD-L1 is positively correlated with response to anti-PD-1 monotherapy. For EC, clear correlation between PD-L1 expression and response to anti-PD-1 has not been reported. However, there may be a correlation with MSS/MSI status for EC (Makker 2020). For MSS CRC, clear correlation between PD-L1 expression and response to anti-PD-L1 has not been reported. One pilot study has demonstrated the negative correlation between PD-L1 expression and response to anti-PD-L1 in combination with VEGFR-TKI (Fukuoka 2020). Due to the limited number of patients, the role of PD-L1 expression in predicting response to anti-PD-L1 in combination with VEGFR-TKI warrants further exploration. Hence, post-hoc biomarker studies will be performed in these tumors to evaluate signatures that may predict response to this combination.

TNBC is the most immunogenic breast cancer subtype, with high incidence of PD-L1 expression and abundant TILs. PD-L1 as a predictive biomarker of response to PD-1/PD-L1 blockade in TNBC has been recognized in several clinical trials. One representative is IMpassion130, in which a significant OS improvement was observed in PD-L1 positive patients by treatment with atezolizumab plus nab-paclitaxel compared to nab-paclitaxel chemotherapy. However, other TNBC studies (eg, KEYNOTE-086 [cohort A, pembrolizumab monotherapy in pretreated patients] and KEYNOTE-522 [pembrolizumab plus neoadjuvant chemotherapy]) demonstrated little or no difference in response according to PD-L1 status. Despite inconsistent results likely due to the different drugs, disease stages, prior treatments, PDL1 immunohistochemistry (IHC) assays, or all of these factors, PD-L1 is still an important and most widely studied biomarker in TNBC.

Accumulating evidence suggests that other biomarkers are predictive of response to ICIs, including MSI, MMR deficiency, and TMB. Microsatellite instability is the genetic hyper-mutability deriving from impaired deoxyribonucleic acid (DNA) MMR. High MSI is associated

with increased neoantigen production by tumors, greater immunogenicity, and stronger immune response. TMB is a measurement of the number of nonsynonymous mutations carried by tumor cells. Mutations lead to increased expression of neoantigens in the context of MHC class I antigens, enhancing the recognition of cancer cells by T cells. Based on the results from multiple KEYNOTE-series clinical trials, the FDA approved pembrolizumab for the treatment of any MSI-H or MMR-deficient unresectable or metastatic solid tumor and, recently, for any tumor mutation burden-high (TMB-H) solid tumors according to KEYNOTE-158. However, in breast cancer, limited data regarding the incidence of MSI-H, MMR-deficient, and TMB-H as well as the associations with the response to ICIs is available. Additionally, TILs have emerged as a predictive biomarker in response to ICI therapy. In the IMpassion-130 trial, CD8+TILs along with PD-L1 expression on immune cells have been associated with increased PFS and OS in patients treated with atezolizumab and nab-paclitaxel. This finding also suggests possible interactions among multiple factors in the immune microenvironment. In fact, evidence has been increasingly showing that combined biomarker strategies and incorporated multiple factors analysis could be more ideal approaches to enrich responders to PD-L1 blockade, although the optimal model has yet to be determined.

Taken together, these biomarker results mainly come from the clinical studies for anti-PD-L1 monotherapy or combination with chemotherapies in TNBC. Biomarker studies in this combination trial of fruquintinib and tislelizumab will retrospectively detect immune response biomarkers and explore whether there is a dominant population benefit from the combination treatment.

TMB works as the surrogate marker for neo-antigen prediction and has been reported to be positively correlated with response to anti-PD(L)-1, and serves as an independent biomarker from PD-L1, indicating that its combination with PD-L1 may lead to predictive synergy (Fumet 2020; Cristescu 2018). In 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 included, this trend needs further verification (Fukuoka 2020). Blood TMB, 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 2018).

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 (EMT, 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 2018). Results related to GEP have not been reported in anti-PD(L)-1 plus VEGFR-TKI studies in patients with MSS mCRC 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 2018; Wallin 2016), implying GEP panels may play a potential role in predicting response to anti-PD-(L)1 plus VEGFR-TKI in patients with MSS mCRC. 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 2020; Cristescu 2018).

Consequently, in the TNBC, EC and MSS mCRC cohorts, PD-L1, tumor mutational burden/blood-derived tumor mutational burden, and gene expression profiling 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. Further, MSS/MSI status in the EC cohort and CRC will be explored to determine if it correlates to response or sensitivity to anti-PD-1 therapy (Makker 2020).

2.3 Benefit:Risk Assessment

2.3.1.1 Risk Assessment

Appropriate exclusion criteria, monitoring, and dose modification guidance are included in the protocol to ensure the safety of patients enrolled in the clinical trial. Patients are excluded if they have signs, symptoms, or history that may put them at risk in the context of the identified and potential risks of fruquintinib. Section 7.5.3.2 provides detailed guidance on dose modifications for important identified risks including hepatic function impairment, hypertension, proteinuria, and hemorrhage. General dosing guidance to protect patients is included in Section 7.5. Thus, the identified and potential risks of treatment with fruquintinib and tislelizumab are appropriately mitigated by measures in the protocol (Table 3).

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Fruquintinib		
Important Identified Risk	Refer to the current fruquintinib IB for further details	
Hemorrhage	In patients receiving fruquintinib, the most frequent events on hemorrhage included gastrointestinal hemorrhage events, occult blood positive, epistaxis, hemoptysis and blood urine present. Fatal SAEs have been reported. Possible class effect: The risk of hemorrhages has been reported in most of the VEGFR inhibitors (eg, sorafenib, axitinib, regorafenib, sunitinib), including fatal cases.	AE observations Closely monitor hematology parameters, coagulation function parameters, urine and fecal occult blood.
Hepatic function abnormal (includes blood bilirubin increased, transaminase increase)	In patients receiving fruquintinib, the most frequent hepatic events included aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, hepatic function abnormal, and gamma glutamyl transferase increased. Fatal SAEs have been reported. Possible class effect: In some of VEGFR inhibitors (such as sorafenib, sunitinib, regorafenib), severe and fatal hepatotoxicity sometimes has been observed in the clinical trials.	AE observations Closely monitor hepatic function (ALT, AST, ALP, and bilirubin): once per week for Grade 2 events, twice per week for Grades 3-4 events.
Infection	In patients receiving fruquintinib, the most frequent events on infection included respiratory tract	AE observations

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	infection, urinary tract infection and pneumonia. Fatal SAEs have been reported. Possible class effect: In some of VEGFR inhibitors (such as sorafenib, regorafenib), infections were reported as one of the most common adverse reactions (≥20%). Fatal cases have been reported with regorafenib.	
Hypertension	In patients receiving fruquintinib, there have been no fatal events reported. Possible class effect: Mild to moderate hypertension has been observed in most VEGFR inhibitors (eg, sorafenib, regorafenib, axitinib, sunitinib).	AE observations Closely monitor blood pressure.
Identified Risk	Refer to the fruquintinib IB	
Dermatological toxicity (includes palmar-plantar erythrodysaesthesia [PPE] syndrome, rash, dermatitis)	In patients receiving fruquintinib, there have been no fatal events reported. The most frequent events included palmar-plantar erythrodysaesthesia syndrome, rash and dermatitis. Possible class effect: Hand-foot skin reactions and rash were common adverse reactions observed in Most of the VEGFR inhibitors (eg, sorafenib, regorafenib, axitinib, sunitinib).	AE observations
Proteinuria (includes protein urine present, albuminuria)	In patients receiving fruquintinib, there have been no fatal events reported. Possible class effect: Proteinuria has been observed in some VEGFR inhibitors (eg, sorafenib, regorafenib, axitinib, sunitinib) and VEGF inhibitors (bevacizumab).	AE observations Closely monitor urine routine parameters, 24-hour urine protein quantification, monitoring of blood urea, nitrogen, and creatinine.
Thyroid dysfunction (includes hypothyroidism, thyroid function test abnormal)	In patients receiving fruquintinib, 1 patient experienced fatal hyperthyroidism and thyroiditis subacute events. Possible class effect: Hypothyroidism and TSH decreased has been observed in some VEGFR inhibitors. Hyperthyroidism has been reported as an uncommon adverse reaction for sorafenib.	AE observations
Dysphonia	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Pharyngolaryngeal pain/discomfort	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Abdominal pain/discomfort	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Diarrhoea (includes frequent bowel movements)	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Decreased appetite	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Stomatitis	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Oral pain	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Proctalgia (anal pain)	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Weight decreased	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Platelet decreased	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations Closely monitor hematology parameters.
WBC decreased/neutrophil decreased	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations Closely monitor blood routine parameters.
Amylase increased	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Asthenia	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Musculoskeletal pain	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Back pain	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Arthralgia	In patients receiving fruquintinib, there have been no fatal events reported.	AE observations
Important Potential Risk	Refer to the fruquintinib IB, Section 6.5 and Table 57	
Gastrointestinal perforation	In patients receiving fruquintinib, there have been no fatal events reported. Possible class effect: The risk of severe and fatal gastrointestinal perforation has been observed in some VEGFR inhibitors (eg, regorafenib, axitinib, sunitinib).	AE observations
Arterial thrombosis	In patients receiving fruquintinib, there have been no fatal events reported. Possible class effect: In some of VEGFR inhibitors (such as sorafenib and axitinib), thromboembolic events were reported in some of the clinical trials. Axitinib includes fatal embolic event.	AE observations
RPLS	In patients receiving fruquintinib, there have been no fatal events reported. Possible class effect: In some of VEGFR inhibitors (such as sorafenib), RPLS was reported as an uncommon adverse reaction. Individual RPLS case	AE observations

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reports have been published with axitinib and regorafenib.	
Wound healing delayed	In patients receiving fruquintinib, there have been no fatal events reported. Possible class effect: Cases of impaired wound healing have been observed in VEGFR inhibitor sunitinib.	AE observations
Potential Risk	Refer to Fruquintinib IB	
LVEF decreased	In patients receiving fruquintinib, LVEF decreased including other related cardiac events have been reported. Possible class effect: Cases of LVEF decreased have been observed in VEGFR inhibitors.	AE observations
Other – Study Intervention, Tislelizumab		
Identified Risk	Refer to the tislelizumab IB	
Immune-mediated hepatitis	Immune-mediated hepatic events, defined as requiring use of corticosteroids and with no clear alternative etiology, can occur. Fatal cases have been reported.	Monitor patients for signs and symptoms of hepatic events; include liver enzyme monitoring. Corticosteroids can be administered at a dose of 0.5 to 2 mg/kg/day prednisolone equivalents for moderate (Grade 2) or greater liver enzyme elevations, with or without concomitant bilirubin elevations. Withhold tislelizumab for moderate (Grade 2) reactions, and permanently discontinue for recurrent severe (Grade 3) or life-threatening (Grade 4) hepatitis.
Immune-mediated pneumonitis	Immune-mediated pneumonitis, defined as requiring use of corticosteroids and with no clear alternative etiology, can occur. Fatal cases have been reported.	Monitor patients for signs and symptoms of pneumonitis; include diagnostic imaging as appropriate. Corticosteroids can be administered at a dose of 1 mg/kg/day prednisolone equivalents for moderate (Grade 2) pneumonitis and methylprednisolone 2 to 4 mg/kg/day for severe or life-threatening (Grade 3 or 4) pneumonitis. Withhold tislelizumab for moderate (Grade 2) reactions,

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		and permanently discontinue for severe or life-threatening (Grade 3 or 4) pneumonitis.
Immune-mediated colitis	Immune-mediated colitis and diarrhea, defined as requiring use of corticosteroids and with no clear alternative etiology, can occur.	Monitor patients for signs and symptoms of colitis or severe diarrhea. Withhold tislelizumab for moderate (Grade 2) or severe (Grade 3) diarrhea or colitis. Administer prednisolone at a dose of 0.5 to 2 mg/kg/day or equivalents. Permanently discontinue tislelizumab for recurrent severe (Grade 3) or life-threatening (Grade 4) colitis.
Immune-mediated endocrinopathies	Immune-mediated endocrinopathies, including thyroid disorders, diabetes mellitus, adrenal disorders, and hypophysitis, which may require anti-diabetic treatment or endocrine therapy, can occur.	Hypophysitis: Monitor patients for signs and symptoms of hypophysitis, including hypopituitarism and adrenal insufficiency. Prednisolone can be administered at a dose of 0.5 to 1 mg/kg/day prednisolone equivalents and hormone replacement as clinically indicated. Withhold tislelizumab for severe (Grade 3) cases when associated with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
		Type I diabetes mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold tislelizumab for severe (Grade 3) hyperglycemia until blood glucose has been stabilized and the patient is hyperglycemia symptom-free. Withhold or discontinue tislelizumab for life-threatening (Grade 4) hyperglycemia. Administer insulin as clinically indicated for Type I Diabetes.

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Thyroid disorders: Monitor patients for thyroid disorders and changes in thyroid function. Administer replacement hormones for hypothyroidism and thionamides/beta-blockers for hyperthyroidism as clinically indicated. Withhold or discontinue tislelizumab for severe (Grade 3) or life-threatening (Grade 4) hypothyroidism/hyperthyroidism.
		Other: Withhold tislelizumab for other severe (Grade 3) or life-threatening (Grade 4) endocrinopathies, and continue treatment only when symptoms have improved and endocrine deficiencies have been corrected.
Immune-mediated myocarditis	Immune-mediated myocarditis, defined as cardiac signs and symptoms with no clear alternative etiology, can occur.	Monitor for cardiac signs and symptoms periodically during treatment. Withhold treatment with tislelizumab for asymptomatic but significantly increased CK-MB or increased troponin OR signs and symptoms of possible myocarditis. Corticosteroids can be administered at a dose of 1 to 2 mg/kg/day prednisolone equivalents for moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4) myocarditis. Permanently discontinue treatment with tislelizumab for Grades 2 to 4 myocarditis.
Immune-mediated serious skin reactions	Immune-mediated serious skin reactions can occur.	Monitor patients for suspected severe skin reactions and exclude other causes. Corticosteroids can be administered at a dose of 0.5 to 2 mg/kg/day prednisolone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash.

Table 3 Risk Assessment (List of Risks as per Current IB [Edition 13.0])

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Withhold tislelizumab for severe (Grade 3) rash and permanently discontinue for life-threatening (Grade 4) rash.
	One case of fatal TEN was reported in a patient receiving tislelizumab in combination with zanubrutinib.	For signs or symptoms of SJS or TEN, withhold tislelizumab and refer the patient for specialized assessment and treatment. If SJS or TEN is confirmed, permanently discontinue tislelizumab.
Other immune-mediated adverse reactions	The following imAEs occurred in less than 1% of treated patients: encephalitis, rhabdomyolysis, myositis, nephritis, pancreatitis, and uveitis.	Monitor patients for signs and symptoms of other imAEs.
Infusion-related reactions	Symptoms of infusion-related reactions that may be observed include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Rare life-threatening reactions can occur.	Closely monitor patients for signs and symptoms during infusion.

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase, CK-MB=creatine kinase-MB; IB=Investigator's Brochure; imAE=immune-mediated adverse event; LVEF=left ventricular ejection fraction; PPE=palmar-plantar erythrodysesthesia; RPLS=reversible posterior leukoencephalopathy syndrome; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis; TSH=thyroid stimulating hormone; VEGFR=vascular endothelial growth factor receptor.

2.3.1.2 Benefit Assessment

Fruquintinib

Robust cumulative efficacy has been demonstrated for fruquintinib from the entire clinical program in China, including in patients with mCRC in the randomized, double-blind, placebo-controlled FRESCO trial, and in the US. Preliminary efficacy of fruquintinib has been demonstrated in mBC, including TNBC, in a phase 1 study conducted in China (Study 2009-013-00CH1) and in an ongoing phase 1/1b study conducted in the US (Study 2015-013-00US1). Expansion cohorts in TNBC and hormone-receptor positive, HER2-mBC are currently enrolling. A phase 3 study (FRESCO-2) of fruquintinib in combination with the best supportive care in advanced CRC patients has completed enrollment globally.

Tislelizumab

Preliminary data from ongoing phase 1 and phase 2 trials of single-agent tislelizumab suggest that there is anti-tumor activity across a variety of tumor types. Tislelizumab has also been shown to have anti-tumor activity in various solid tumors in ongoing phase 1 and phase 2 trials when combined with chemotherapy and poly-ADP ribose polymerase inhibitors. Across monotherapy and combination trials, anti-tumor activity has been seen.

2.3.1.3 Overall Benefit:Risk Conclusion

There remains an unmet need for patients with advanced TNBC, EC, and CRC. A growing body of evidence suggests that both fruquintinib and tislelizumab may potentially be efficacious in TNBC, EC, and CRC populations proposed in this trial.

Safety data from the completed and ongoing studies show that fruquintinib and tislelizumab were both well tolerated, with most of the AEs reported as Grade 1 to 2 (see current IB), and there have been no new or unexpected safety findings from the ongoing clinical trials to date.

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

Combining fruquintinib with tislelizumab may have synergistic effects where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall anti-tumor activity compared to that of each individual agent alone. Based on the preclinical toxicology data, the safety profile from clinical trials, the proposed safety management actions, the limited life expectancy of patients with advanced TNBC, EC, or CRC, the lack of effective alternative treatments, and efficacy seen in previous and ongoing clinical trials, the overall benefit-risk assessment supports the continued administration of fruquintinib and tislelizumab to patients with advanced cancer as an investigational treatment.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are summarized in Table 4.

Table 4 Objectives and Endpoints for Study 2020-013-00US3

Part	Tier	Objectives	Endpoints
Part 1: Safety Lead-in Phase	Primary	To assess the safety and tolerability of fruquintinib in combination with tislelizumab in patients with advanced solid tumors	AEs characterized by type, frequency, severity per NCI CTCAE v5.0, timing, seriousness, relationship to study drug(s), and discontinuation of study drug(s) due to AEs
		To confirm the RP2D of fruquintinib in combination with tislelizumab	RP2D
	Secondary	To evaluate the efficacy of fruquintinib in combination with tislelizumab per investigator assessment	ORR, PFS, DCR, CBR, DoR, and OS
		To characterize the PK profile of fruquintinib and metabolite M11 when combined with tislelizumab	Plasma concentrations of fruquintinib and M11
		To evaluate the PK and immunogenicity of fruquintinib in combination with tislelizumab	Serum concentrations of tislelizumab and incidence of ADA to tislelizumab
Part 2: Dose Expansion Phase	Primary	To evaluate the ORR assessed by the investigator in patients with advanced or metastatic TNBC, EC, or MSS mCRC when treated with fruquintinib in combination with tislelizumab	ORR per RECIST v1.1
	Secondary	To further evaluate efficacy of fruquintinib in combination with tislelizumab in patients with advanced or metastatic TNBC, EC, or MSS mCRC per investigator assessment	PFS, DCR, CBR, DoR, and OS
		To characterize the safety of fruquintinib in combination with tislelizumab	AEs characterized by type, frequency, severity per NCI CTCAE v5.0, timing, seriousness, relationship to study drug(s), and discontinuation of study drug(s) due to AEs.
		To assess the PK profile of fruquintinib and metabolite M11 when combined with tislelizumab	Plasma concentrations and derived PK parameters of fruquintinib and M11
		To characterize the PK and immunogenicity of fruquintinib when combined with tislelizumab	Serum concentrations of tislelizumab and incidence of ADA to tislelizumab
		To detect the expression of PD-L1 and MSS/MSI status and other biomarkers in tumor tissues of patients, and to perform relevant efficacy analysis to provide reference for the determination of dominant population	Changes from baseline in biomarkers, correlation with drug exposure, and association with efficacy and safety parameters

Table 4 Objectives and Endpoints for Study 2020-013-00US3

Part	Tier	Objectives	Endpoints
	Exploratory	To explore potential biomarkers associated with anti-tumor effects of fruquintinib in combination with tislelizumab	Changes from baseline in tumor markers, correlation with drug exposure, and association with efficacy and safety parameters

ADA=anti-drug antibody; AE=adverse event; CBR=clinical benefit rate; DCR=disease control rate; DoR=duration of response; EC=endometrial cancer; M11=desmethylation product, HM5025423; mCRC=metastatic colorectal cancer; MSI=microsatellite instability; MSS=microsatellite stable; NCI CTCAE=The National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression free survival; PK=pharmacokinetic; RECIST v1.1=response evaluation criteria in solid tumors version 1.1; RP2D=recommended Phase 2 dose; TNBC=triple negative breast cancer.

4 STUDY PLAN

Upon implementation of this protocol amendment, enrollment to expansion cohorts A (TNBC immuno-oncology [IO]-treated in the metastatic setting), B (TNBC IO-Naïve in the metastatic setting) and C (EC IO Naïve) in this study has been permanently discontinued based upon the strategic evaluation of the clinical development of fruquintinib in the United States with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to fruquintinib and/or tislelizumab treatment. Patients who are currently enrolled in these cohorts and are deriving benefit from treatment with fruquintinib and/or tislelizumab may continue to participate in the study as per protocol. There is no planned interruption in the supply of fruquintinib or tislelizumab to clinical trial sites with active patients.

4.1 Study Design

This is an open-label, multicenter, non-randomized, phase 1b/2 study to assess the safety and efficacy of fruquintinib in combination with tislelizumab in patients with advanced or metastatic solid tumors. This study will be conducted in 2 parts: a Safety Lead-in Phase (Part 1) and a Dose Expansion Phase (Part 2).

4.1.1 Part 1: Safety Lead-in Phase

Approximately 6 to 12 patients with histologically or cytologically documented advanced or metastatic solid tumors of any type who have progressed on standard systemic therapy and for which no effective therapy or standard of care exists will be enrolled and assessed for DLTs during the 28-day DLT observation period. Patients may be either immuno-oncology (IO) treated or naïve in the metastatic setting. Patients with TNBC in the Safety Lead-in must meet eligibility criteria defined in cohorts A or B, and those with EC in the Safety Lead-in must meet eligibility criteria defined in cohort C.

Part 1 of the study will begin by enrolling the first 6 patients and evaluating for DLTs during the 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 fruquintinib and tislelizumab, 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 4.1.3 and Section 4.1.4 for assessment of DLT guidance and DLT definitions, respectively. One dose reduction step is allowed for fruquintinib (refer to Figure 1 and Section 7.5.2). Only DLTs during the first cycle of treatment will be assessed.

- If 0 or 1 of 6 patients experiences 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 safety review committee (SRC), 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.

These criteria constitute the basis for RP2D determination, and the SRC must collectively determine the RP2D. Enrollment to Part 2 (expansion cohorts) will begin once the RP2D has been determined in Part 1 of the study.

The SRC will also review the data during Part 2 on an ongoing basis for safety.

4.1.2 Part 2: Dose Expansion Phase

Approximately 140 patients will be enrolled, including approximately 60 patients with TNBC (approximately 30 patients in each cohort [A and B]), and approximately 40 patients with EC in Cohort C, and approximately 40 patients with MSS mCRC in Cohort D. Patients will be enrolled to one of the following 4 cohorts. Of note, based upon the strategic evaluation of the clinical development of fruquintinib, patient enrollment has been permanently discontinued for Cohorts A, B, and C in the Dose Expansion Phase, hence, the final actual total number of patients will reflect this strategic decision.

- **Cohort A** (TNBC, immuno-oncology [IO]-treated in the metastatic setting):
  – Patients must have histologically or cytologically documented, advanced or metastatic TNBC as defined by American Society for Clinical Oncology (ASCO)-College of American Pathologists (CAP) guidelines. Up to 15 patients in cohort A can have ER or PGR low positive disease as defined by ASCO-CAP guidelines, if the treating physician considers the patient not eligible for adjuvant endocrine therapy. TNBC is defined as ER/PGR positivity of <1%, and ER/PGR low positive disease is defined by ER/PGR positivity of 1% to 10% (Allison 2020). (Note that the guidelines use PR as the abbreviation for progesterone receptor.)
  – Patients must have progressed on at least 1 line, but no more than 3 lines, of cytotoxic therapy in the locally advanced or metastatic setting. Patients must have also progressed on prior immunotherapy in the metastatic setting (Rakha 2014).
- **Cohort B** (TNBC, IO-Naïve in the metastatic setting):
  – Patients must have histologically or cytologically documented, locally advanced or metastatic TNBC as defined by ASCO-CAP guidelines. Up to 15 patients in cohort B can have ER or PGR low positive disease as defined by ASCO-CAP guidelines, if the treating physician considers the patient not eligible for adjuvant endocrine therapy. TNBC is defined as ER/PGR positivity of <1%, and ER/PGR low positive disease is defined by ER/PGR positivity of 1% to 10%. (Note that the guidelines use PR as the abbreviation for progesterone receptor.)
  – Patients must have progressed on at least 1 line, but no more than 3 lines, of cytotoxic therapy in the locally advanced or metastatic setting. Patients must not have received prior therapy with an ICI or other immunotherapy in the metastatic setting.
- **Cohort C** (EC, IO Naïve):
  – Patients must have histologically or cytologically documented, advanced or metastatic EC.
  – Patients must have progressed on 1 prior, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant setting and must not have received prior therapy with an ICI or other immunotherapy.

- **Cohort D** (MSS mCRC, IO Naïve):
  – Patients must have histologically or cytologically confirmed, advanced or metastatic, unresectable adenocarcinoma of the colon or rectum. All other histological types are excluded.
  – Patients must have failed 2 lines of standard chemotherapies, including fluorouracil, oxaliplatin, and 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 cycle; b) Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occur during the adjuvant/neoadjuvant treatment period 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.
  – Patients with RAS wild-type tumor must have received anti-VEGF and/or endothelial growth factor receptor (EGFR) antibody treatment. Patients with RAS mutation or RAS status unknown, must have received anti-VEGF antibody treatment.
  – Tumor tissue must have been assessed for MSS status prior to enrollment. The results should be available in the source documents and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

Local tumor assessments will be performed by the investigator using RECIST v1.1 criteria (Eisenhauer 2009). Tumor imaging (computed tomography [CT] with oral/intravenous contrast, unless contraindicated, or magnetic resonance imaging) must be performed within 28 days prior to enrollment. On-study tumor assessments will occur every 8 weeks (±7 days) 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 study termination, 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). Immune-mediated AEs (serious or nonserious) will be closely monitored until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Refer to Section 8 for additional and specific information regarding AE monitoring and reporting.

PK analysis will be performed for fruquintinib and tislelizumab (Section 6.1.19). Biomarker analysis will include but is not limited to TMB, cytokine analysis, tumor-infiltrating lymphocytes assessment, and gene expression profiling (Section 6.1.17). Fruquintinib and tislelizumab will be administered until PD, intolerable toxicity, death, withdrawal of consent, or study termination. Patients may continue to receive fruquintinib and tislelizumab or either of the study drugs beyond the initial investigator-assessed PD, as defined by RECIST v1.1, provided that the patients have investigator-assessed clinical benefit and are tolerating study drug(s). Refer to Section 6.2.1.1 and Section 6.2.1.2 for additional considerations regarding treatment discontinuation and withdrawal. Patients who, at time of progression, have an ongoing AE that leads to treatment discontinuation and who have 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 (Section 6.2).

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 6.1.20. After the EOT visit, patients will have scheduled follow-up visits for safety and, if applicable, for efficacy per the Schedule of Events (SOE) (Table 1).

Study conduct and interventions are further detailed in Section 6 and Section 7, respectively, the SOE can be found in Table 1, and the study schematic can be found in Section 1.1.

4.1.3 Assessment of Dose-Limiting Toxicity

For patients in the Safety Lead-in Phase (Part 1) described in Section 4.1.1 above, AEs will be assessed per the DLT criteria in Section 4.1.4 during the 28-day DLT assessment window, which starts with the first day of administration of 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 for a reason other than DLT, 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 an inducer of enzyme CYP3A (Appendix 4) 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.

4.1.4 Dose-Limiting Toxicity Definition

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

Hematologic:

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

Non-hematologic:

All Grade ≥3 non-hematologic toxicities will be considered DLTs with the following exceptions:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement, does not require hospitalization, AND resolves to Grade ≤1 within 7 days

- Grade 3 nausea/vomiting or diarrhea for <72 hours with adequate antiemetic and other supportive care
- Grade 3 fatigue for <1 week
- Grade ≥3 electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3 rash that returns to baseline or Grade ≤1 with appropriate supportive treatment within 7 days
- Grade ≥3 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 hypertension that returns to baseline or Grade ≤1 with appropriate supportive treatment within 7 days

4.2 Design Rationale

Refer to Sections 2.2.2, 2.2.3, and 2.2.4 for the justification of the starting combination doses.

5 POPULATION

5.1 Definitions

Patients officially enter the screening period after providing informed consent, either directly or via a legally authorized representative, where it is permitted by local law.

A consented patient who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment will be considered a screen failure. Screen failures may be rescreened once.

An enrolled patient is one who has been deemed eligible and has been assigned to a treatment cohort.

Inclusion/exclusion waivers will not be granted.

5.2 Inclusion Criteria

Patients may be enrolled in this study only if they satisfy all the following criteria:

1. Willing and able to provide informed consent signed by the study patient or legally acceptable representative, as specified by health authorities and institutional guidelines

2. Age of ≥18 years

3. Safety Lead-in: Must have histologically or cytologically documented advanced or metastatic solid tumors of any type who have progressed on standard systemic therapy and for which no effective therapy or standard of care exists. Patients with TNBC in the Safety Lead-in must meet eligibility criteria defined in cohorts A or B, and those with EC in the Safety Lead-in must meet eligibility criteria defined in cohort C.

   Cohorts A and B: Must have histologically or cytologically documented, advanced or metastatic TNBC as defined by ASCO-CAP guidelines (Allison 2020). Up to 15 patients in each cohort can have ER or PGR low positive disease as defined by ASCO-CAP guidelines, if the treating physician considers the patient not eligible for adjuvant endocrine therapy. TNBC is defined as ER/PGR positivity of <1%, and ER/PGR low positive disease is defined by ER/PGR positivity of 1% to 10% (Allison 2020). (Note that the guidelines use PR as the abbreviation for progesterone receptor.)

   Cohort C: Must have histologically or cytologically documented, advanced or metastatic endometrial carcinoma.

   Cohort D: Must have histologically or cytologically confirmed advanced or metastatic, unresectable adenocarcinoma of the colon or rectum. All other histological types are excluded.

4. Cohorts A and B: Must have progressed on at least 1 line, but no more than 3 lines, of cytotoxic therapy in the locally advanced or metastatic setting. For patients who have disease recurrence within 12 months of completion of adjuvant therapy, adjuvant chemotherapy will be considered first-line chemotherapy in the metastatic setting.
   a. Patients in cohort A must have received prior immunotherapy in the metastatic setting.

   b. Patients in cohort B must not have received prior therapy with an ICI or other immunotherapy in the metastatic setting.

   Cohort C: Patients must have progressed on 1 prior platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant setting and must not have received prior therapy with an ICI or other immunotherapy.

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

   Additional requirements:

   a. All patients must have received treatment with an anti-VEGF antibody (eg, bevacizumab, aflibercept, or ramucirumab);
   b. Patients with RAS wild-type tumors must have received an anti-EGFR antibody treatment (eg, cetuximab or panitumumab);
   c. Each line of treatment for advanced disease until PD includes 1 or more cytotoxic chemotherapy drugs used for ≥ 1 cycle;
   d. Previous adjuvant/neoadjuvant therapy is allowed. If relapse or metastasis occurred during the adjuvant/neoadjuvant treatment period or within 6 months after the completion of adjuvant treatment, that adjuvant/neoadjuvant therapy is considered as the failure of first-line systemic chemotherapy for PD.

5. Must have tumor tissue (fresh or archival tumor tissues as formalin-fixed paraffin-embedded blocks or approximately 15 unstained slides) collected for retrospective analysis of PD-L1 expression level, and/or MSS/MSI status, and other exploratory biomarkers related to response and resistance. Submission of <15 unstained slides is permitted, and patients may be enrolled after confirmation with the sponsor.

6. ECOG performance status of 0 or 1 (Appendix 2).

7. Expected survival of ≥12 weeks.

8. Have measurable disease as defined by RECIST v1.1. Tumors that were treated with radiotherapy are not considered measurable per RECIST v1.1 unless there has been documented progression of those lesions.

9. Adequate organ function indicated by the following laboratory values:

    a. Absolute neutrophil count of $\geq 1.5\times10^9$/L

    b. Platelet count of $\geq 100\times10^9$/L

    c. Hemoglobin ≥9 g/dL

    d. Serum total bilirubin ≤1.5× upper limit of normal (ULN) (total bilirubin must be <3× ULN for patients with documented Gilbert's syndrome)

    e. Patients without liver metastases must have ALT and AST ≤2.5× ULN; patients with liver metastases must have ALT and AST ≤5× ULN.

    f. Urine protein ≤1+ by dipstick or 24-hour urine protein <1 g/24 hours. Patients with 1+ proteinuria by dipstick must undergo 24-hour urine collection to assess urine protein level.

    g. Serum creatinine <1.5× ULN and creatinine clearance (CrCl) ≥60 mL/min per Cockcroft Gault- (Appendix 11)
    h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.5 ULN unless the patient is receiving anticoagulation therapy and INR and aPTT values are within the intended therapeutic range.

10. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement to use a highly effective form(s) of contraception that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 120 days after taking the last dose of study drug. Such methods include oral hormonal contraception (combined estrogen/progestogen or progestogen-only) associated with inhibition of ovulation together with a barrier method (eg, diaphragm, always containing a spermicide), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or sexual abstinence. Oral contraception should always be combined with an additional contraceptive method (ie, barrier method) because of a potential interaction with the study drug. The same criteria are applicable to male patients involved in this clinical trial if they have a partner of childbirth potential, and male patients must always use a condom. All female patients will be considered to have childbearing potential unless the said female patient has had natural menopause, induced artificial menopause, or undergone sterilization (hysterectomy and bilateral salpingo-oophorectomy).
11. PD-L1 status, as determined locally, must be documented for each patient in Cohorts A, B, and C, and MSS/MSI status must be documented for each patient in Cohorts C and D. The results should be available in the source documentation and be those used to make treatment decisions for the patient. A redacted copy of the local results should accompany the archival tumor samples submitted as part of the protocol.

5.3 Exclusion Criteria

Patients are not eligible for enrollment into this study if they have any of the following criteria:

1. Adverse events due to previous anti-tumor therapy have not recovered to ≤CTCAE Grade 1, except alopecia and peripheral neurotoxicity with ≤CTCAE Grade 2.
2. Other malignancies except for non-melanoma skin cancer, in situ cervical cancer, or bladder cancer (Tis and T1) that have been adequately treated during the 5 years prior to screening.
3. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of SD for 14 days or longer; patients requiring steroids within 4 weeks prior to start of study treatment are excluded.
4. Systemic anti-neoplastic therapies or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy, and immunotherapy.
5. Systemic small molecule-targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug.
6. Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug.
7. Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first dose of study drug.
8. Mean QT interval corrected by the method of Fridericia (QTcF) ≥480 ms.
9. EXCEPT for Safety Lead-in and Cohort A, patients who have previously received any anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, and anti-cytotoxic T lymphocyte-associated antigen-4 antibody (or any other antibody acting on T cell -co-stimulation or checkpoint pathways) in the metastatic setting are excluded.
10. Any condition that requires 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 (dose of ≤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).
11. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 9), 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.

12. Live vaccine ≤28 days before the first dose of study drug(s)

    a. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

13. Active infection requiring systemic antibacterial, antifungal, or antiviral therapy (not including antiviral therapy for hepatitis) for ≤14 days prior to the first dose of study drug(s) or a positive test for severe acute respiratory syndrome coronavirus 2 in the absence or presence of symptoms.

14. Active tuberculosis that is being treated with anti-tuberculosis therapy or that have received treatment with anti-tuberculosis therapy within 1 year before the first drug administration.

15. History or presence of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including but not limited to pulmonary fibrosis, acute lung diseases, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonia, severely impaired lung function, and other patients with conditions that may interfere with the detection and treatment of suspected drug-related pulmonary toxicity; radiation pneumonitis in the radiation therapy area is allowed.

16. 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.

    a. Patients with inactive hepatitis B surface antigen (HBsAg carriers who are treated and have stable HBV [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 antiviral therapy at screening should have been treated for >2 weeks before the first dose of study drug(s).

    b. Patients with a negative hepatitis C virus (HCV) antibody test at screening or a positive HCV antibody test followed by a negative HCV ribonucleic acid (RNA) test at screening are eligible. The HCV RNA test should be performed only for patients who tested positive for the HCV antibody.

17. Known history of human immunodeficiency virus (HIV) infection.

18. Major surgery within 60 days before the first drug administration. Patients must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study drug(s).

19. Patients who had any surgical or invasive therapy (except for puncture biopsy and venous catheterization) within 4 weeks before the first drug administration, or have unhealed wounds, ulcers, or fractures.

20. Prior allogeneic stem cell transplantation or organ transplantation.

21. Any of the following cardiovascular risk factors:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living (ADL), ≤28 days before the first dose of study drug(s).

b. Pulmonary embolism or venous thromboembolism ≤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 Function Classification III or IV (Appendix 12) ≤6 months before the first dose of study drug(s); left ventricular ejection fraction (LVEF) of <50%.

e. Ventricular arrhythmia Grade ≥2 in severity ≤6 months before the first dose of study drug(s).

f. Cerebrovascular accident ≤12 months before the first dose of study drug(s).

g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications, which is specified as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg. The patient must have blood pressures below both limits. Repeated assessments are permitted.

h. Syncope or seizure ≤28 days before the first dose of study drug(s).

22. 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.
23. Received strong inducers of cytochrome P450, family 3, subfamily A (CYP3A) taken within 2 weeks (or 5 times the t1/2 of the drug, whichever is longer) prior to the first study treatment.
24. Active gastrointestinal and duodenal ulcers, ulcerative colitis, and other gastrointestinal disease or unresectable tumors with active bleeding; 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.
25. History or presence of hemorrhage from any site (such as melena, hematemesis, hemoptysis, fresh in stool) within 2 months before the screening.
26. Tumor invasion of a large vascular structure (eg, pulmonary artery, the superior or inferior vena cava).
27. History of arterial thrombus or deep vein thrombosis within 6 months prior to the first drug administration; patients with implanted intravenous infusion pump or catheter -related thrombosis or superficial vein thrombosis, except for patients with stable thrombus after routine anticoagulant therapy.
28. Stroke event and/or transient ischemic attack within 12 months.
29. Women who are pregnant or lactating.
30. Patients with known allergy to any of the components of tislelizumab or fruquintinib preparations including tartrazine (E102) and sunset yellow (E110) or who have any previous history of severe allergy to monoclonal antibodies.
31. Patients must not have received prior treatment with a VEGFR tyrosine kinase inhibitor.

32. Except for Cohort D (MSS mCRC), patients must not have received prior treatment with a VEGFR antibody.

6 STUDY CONDUCT

6.1 Study Procedures

Enrollment is estimated to take approximately 20 months. Estimated study duration from open enrollment until completion of data analyses is approximately 30 months.

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.

The following procedures will be performed according to the schedule in Table 1.

6.1.1 Informed Consent

All patients must sign the informed consent form (ICF) prior to any study-related examinations or protocol procedures. Tumor assessments completed as standard of care prior to patient-signed ICFs, but within 28 days of first dose of study treatment, may be used as baseline scans.

All patients who sign the ICF are to be entered into the interactive web response system (IWRS). The system will generate a patient identification number, which will be assigned to the patient and will be used throughout the study.

6.1.2 Screening Period

The screening period begins at the signing of ICF. Screening evaluations will be performed according to the schedule and instructions set forth in Table 1. 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.

Rescreening may be allowed after consultation with the sponsor (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.

6.1.3 Enrollment

On day -2 to day 1, after verifying the patient's eligibility, the site will log into the IWRS and the patient will be enrolled by the system. The system will generate a serial number matching a bottle of investigational product in the site's inventory. The site will take the investigational product with the serial number assigned by IWRS from the inventory and dispense it to the patient. The first dose should be administered on cycle 1 day 1 within 2 business days after a patient's enrollment.

6.1.4 Treatment Period

Patients in the treatment phase will receive a combination dose based on dose level in Part 1 and the RP2D in Part 2. All patients will undergo continuous monitoring for safety and efficacy as described in Table 1. CCI [redacted]

6.1.5 Medical History

A complete medical history, including the patient's medical history, disease history, and prior therapies for disease prior to signing of the ICF, should be recorded at screening. Comorbidities that began prior to signing the ICF should be recorded and followed as medical history.

6.1.6 Tumor Diagnosis and Treatment History

Tumor diagnosis should include the date of primary diagnosis of disease and its type, disease stage, the date of first metastasis, type of previous treatment, start and end date/s, BOR, and date of PD.

The patient's history of radiation therapy, including the start and end date/s and the site of radiation, must be recorded. Surgical history, including operations and less-invasive diagnostic or therapeutic procedures (such as GI endoscopy and biopsy), the start and end date/s, name of each procedure, and operation site must also be recorded at screening and in the appropriate electronic case report form (eCRF).

6.1.7 Demographics

Demographic information includes sex and race, and in some countries, year of birth should be recorded at screening and in the applicable eCRF (as permitted by local regulations).

6.1.8 Concomitant Medication and Procedures

Concomitant medications and procedures should be assessed during the study according to the schedule of events in Table 1. Details of prohibited therapies, medications to be used with caution, permitted therapies, drug-drug interactions, and rescue therapies are available in Section 7.4.

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) should be recorded on the eCRF. After discontinuation of study treatment, subsequent new anti-tumor treatment regimens during the safety and survival follow-up periods should also be recorded.

6.1.9 Comprehensive Physical Examination

Comprehensive physical examinations should be assessed during the study according to the schedule of events in Table 1 and include patient height, weight, and general condition, as well as an examination of the head, heart, chest (including the lungs), abdomen, extremities, skin, lymph nodes, nervous system, and additional areas/systems as clinically indicated.

6.1.10 Limited Physical Examination

Limited physical examinations should be assessed during the study according to the schedule of events in Table 1 and include vital signs and any change from baseline; any new abnormalities; and examination of weight, thorax, abdomen, and additional areas/systems as clinically indicated. In order to assess changes from baseline and to evaluate for new abnormalities, the limited physical examination should assess for new or changed skin lesions, enlarged lymph nodes, palpable masses, and appropriate examination to address any patient-reported symptoms.

New or worsened clinically significant abnormalities should be recorded as AEs in the eCRF. Refer to Section 8 regarding AE and SAE definitions, reporting, and follow-up requirements.

6.1.11 Eastern Cooperative Oncology Group (ECOG) Performance Status

Patient performance status will be graded according to the ECOG performance status scale at study visits as indicated in Table 1. It is recommended that ECOG performance status scores be evaluated by the same investigator throughout the study. Details on the ECOG performance status assessment and grading scale are available in Appendix 2.

6.1.12 Vital Signs

Vital signs should be reviewed during the study according to the schedule of events in Table 1. Vital signs include blood pressure, heart rate, respiration rate, and temperature. For patients with a baseline history of hypertension or hypertension that develops on study, blood pressure should be monitored per institutional standard practice.

6.1.13 Laboratory Evaluations

6.1.13.1 Hematology

Hematology laboratory assessments should be performed during the study according to the schedule of events in Table 1 and include red blood cell count, hemoglobin, hematocrit, absolute reticulocyte count, white blood cell count and classifications (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), and platelet count. If abnormal or primitive immature cells are seen, they must also be recorded. Any additional routine blood tests during the study shall be arranged by the investigator as needed.

Note: If the neutrophil count is $\leq 1.0\times10^9$/L or the platelet count is $\leq 25\times10^9$/L, hematology assessments should be conducted per institutional standard practice.

6.1.13.2 Blood Chemistry

Blood chemistry laboratory assessments should be performed during the study according to the schedule of events in Table 1, and the panel includes ALT, AST, alkaline phosphatase (ALP), bicarbonate, bilirubin/total bilirubin, lactic dehydrogenase, non-fasting total cholesterol, triglycerides, uric acid, total protein, albumin, blood urea nitrogen or urea, creatinine, CrCl rate, sodium, potassium, magnesium, chloride, corrected calcium (for patients with hypoproteinemia), phosphorus, blood glucose, creatine phosphokinase, and creatine kinase-MB (CK-MB). If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. Serum troponins may be substituted per local guidelines if used consistently throughout the study. If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. Serum troponins may be substituted per local guidelines if used consistently throughout the study. If tislelizumab has been permanently discontinued, creatine kinase and CK-MB testing will be done as clinically indicated. **Note:** Blood chemistry tests for patients with ALT or AST increase by >3× ULN or increase by >2× baseline value should be performed per institutional standard practice.

Creatinine clearance rate (mL/min) should be calculated using the serum creatinine value according to the Cockcroft-Gault formula (see Appendix 11).

6.1.13.3 Blood Amylase and Lipase

Tests for blood amylase and lipase will be performed during the study according to the schedule of events in Table 1.

6.1.13.4 Fasting Lipid Panel

Fasting lipid panel, including total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides, will be performed during the study according to the schedule of events in Table 1.

6.1.13.5 Coagulation Indicators

Coagulation laboratory assessments should be performed during the study according to the schedule of events in Table 1. Coagulation tests include prothrombin time, activated partial thromboplastin time (aPTT), and INR.

6.1.13.6 Thyroid Function

Thyroid function tests should be performed during the study according to the schedule of events in Table 1 and include serum free tri-iodothyronine, serum free thyroxine, and thyroid stimulating hormone.

6.1.13.7 Urinalysis

Urinalysis should be performed during the study according to the schedule of events in Table 1 and includes urine pH, protein, glucose, blood, and ketones; microscopic for white blood cell and red blood cell count. On routine urinalysis, if urine protein is ≥1+ by dipstick, a 24-hour urine sample for total protein quantitation and a random urine sample for total protein and creatinine quantitation are to be obtained to determine the protein-to-creatinine ratio. For conversions between quantitative and qualitative results, see Appendix 8.

6.1.13.8 Pregnancy Test

Pregnancy testing for females of childbearing potential, including women who have had a tubal ligation, should be performed according to the schedule of events in Table 1. Serum pregnancy test must be performed ≤7 days before the first dose of study drug(s) and a negative result must be recorded. If serum pregnancy test was drawn within 72 hours of Cycle 1 Day 1 (C1D1), then urine pregnancy test is not required on C1D1. Furthermore, a negative urine pregnancy test must be completed and recorded before administration of study drug(s) according to the schedule of events in Table 1. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. Unscheduled testing via either method can be performed if there is an indication; however, any equivocal urine pregnancy tests should be repeated via serum pregnancy testing.

6.1.13.9 Virological Screening

Testing will be performed locally at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg and HCV antibody). In the case of active HBV or HCV infection (ie, HBsAg or HCV antibody is positive), these tests will be followed by viral load assessment (HBV DNA and HCV RNA). 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 at the EOT visit.

6.1.14 Electrocardiograms Monitoring

Single 12-lead electrocardiograms (ECG) will be collected in all patients using standardized equipment according to the schedule of events in Table 1.

ECG indicators include PR interval, QRS interval, RR interval, QT/QTcF interval, and heart rate. ECGs from standard equipment will be evaluated for safety by the principal investigator. Patients should reside in a quiet setting without distractions (eg, television, cell phones, and staff talking) at each scheduled time point for ECG measurements. Patients should rest in a supine position for at least 10 minutes before and 5 minutes after the scheduled time point and should refrain from talking or moving the arms or legs. Skin preparation should be optimal to obtain high-quality ECGs; if deemed appropriate, the chest should be shaved and prepared with light abrasion.

Unscheduled ECG or other cardiac examinations can be performed if clinically indicated. All ECGs should be done prior to dosing of study drugs.

6.1.15 Echocardiogram/Multigated Acquisition Scan

To evaluate the ejection fraction of patients, echocardiogram (preferred method) or multigated-acquisition scan will be performed during the study according to the schedule in Table 2. Assessment parameters include LVEF and general assessment of cardiac function. It is recommended to use the same assessment method throughout the study for each patient. Echocardiograms completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline assessment for LVEF.

6.1.16 Anti-Tislelizumab Antibody Test

Blood sampling will be collected at the time points specified in Table 2.

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab should be closely monitored. Validated screening and confirmatory assays will be employed to detect anti-drug antibodies (ADAs) at multiple time points throughout the study (see Table 2). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren 2008, Vergote 2020, Worobec 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 central laboratory:

- ADA assays: Serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay.

Shipping, storage, and handling of samples for the assessment of 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.

6.1.17 Tumor Sample Collection

Instructions for the processing, storage, and shipping of samples will be provided in the study laboratory manual. Refer to the schedule of events (Table 1) for sample collection time points.

A fresh tumor biopsy at a tumor lesion is mandatory if there are no available archival tumor samples during the screening period. 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.

6.1.17.1 Archived Tumor Sample

For all patients enrolled in the study, archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 freshly cut unstained FFPE slides) need to be sent for post hoc confirmation of PD-L1 (for Cohorts A, B, and C) expression and assessment of MSI/MSS status (for Cohorts C and D only), and assessment of exploratory markers including but not limited to TMB, cytokine analysis, tumor-infiltrating lymphocytes assessment, and gene expression profiling in a sponsor-designated central or test laboratory. Submission of <15 unstained slides is not a protocol deviation.

6.1.18 Tumor Evaluation/Imaging

Tumor assessments (local) are to be performed at study visits specified in Table 1.

All measurable and evaluable lesions should be assessed and documented using image-based evaluation. All patients are to be evaluated utilizing contrast-enhanced CT scan of the chest, abdomen, and pelvis, or other acceptable cross-sectional imaging per RECIST v1.1. Evaluations should include other areas of the body, as clinically indicated. Disease status will be assessed by the investigator or designated site staff using RECIST v1.1. The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each patient, unless medically contraindicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

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 patient medical record. 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.

6.1.19 Pharmacokinetics Assessments

Blood samples will be collected for analysis of fruquintinib and metabolite M11 plasma concentrations and tislelizumab serum concentration according to the PK schedule of events in Table 2. Serum samples will be collected for the analysis of antibodies to tislelizumab for ADA analysis according to Table 2. The actual dates and times of PK sampling should be recorded on the appropriate eCRF. In addition, the dates and times of fruquintinib dose administration and the date, start time, and end time of tislelizumab infusions must be recorded on the eCRF.

The following assessments will be performed at a central bioanalysis laboratory:

- PK assays: Serum samples will be assayed for tislelizumab concentration using a validated immunoassay, and the plasma concentration of fruquintinib and its metabolite M11 will be assayed using the validated liquid chromatography-tandem mass spectrometry method by request from the sponsor.

Shipping, storage, and handling of samples for assessment of PK will be managed through a central laboratory. A study-specific laboratory manual 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.

PK and immunogenicity samples should be collected according to the planned visit if the visit occurs prior to 31 December 2023. Sample collection per planned visit for visits occurring after 31 December 2023 should not be collected.

6.1.20 End of Treatment Visit

The EOT visit is conducted ≤7 days (±3 days) after the last dose when the investigator determines that the patient must permanently discontinue all study drugs. A tumor assessment is not required at the EOT visit if ≤6 weeks have passed since the last assessment.

See Table 1 for assessments to be performed for the EOT visit. If any laboratory assessments required for the EOT visit were completed ≤7 days before the EOT visit, these assessments do not need to be repeated.

6.1.21 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 30 days (±7 days) after the EOT visit.

In addition, telephone contact with patients should be conducted to assess imAEs (serious or nonserious) reported within 90 days after the last dose of tislelizumab regardless of whether or not the patient starts 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 8.

See Table 1 for assessments to be performed at the Safety Follow-up visit.

6.1.22 Survival Follow-up Period

Every 8 weeks (±14 days) after the EOT visit, the investigator or their designee should call the patients to collect information related to survival status and their use of other anticancer treatments, including drug name, dosage, and treatment start and end dates. Information related to radiotherapy received after disease progression is also needed, including radiotherapy location, radiation dose, start date, and end date.

Every effort should be made to obtain information on patients who discontinue study treatment but do not withdraw consent to continue participation in the study.

06 May 2024 will be the final day for survival follow-up. Any patient who has not had contact with the site within 30 days of this date (and not previously reported as deceased or withdrawn consent for future follow-up) should have a final survival follow-up conducted via telephone or in a manner that follows local site SOPs.

6.1.23 End of Study

The end of the study is defined as the last visit of the last patient in the study.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Subjects

6.2.1.1 Permanent Discontinuation of Treatment

The investigator has the right to discontinue a patient from the study for any condition that the investigator determines is in the best interest of the patient, any reasons of non-compliance (eg, missed doses and visits), or pregnancy.

Any patient who discontinues treatment should be encouraged to return to the study site for an EOT visit and Safety Follow-up visit outlined in Table 2, as long as the reason for permanent discontinuation is not withdrawal of consent. The primary reason for discontinuation must be recorded on the appropriate eCRF.

Subjects may be discontinued from treatment for any of the following reasons:

- Disease progression (according to RECIST v1.1). If the patient is experiencing a treatment benefit, in the opinion of the investigator, the patient may continue study treatment beyond radiographic progression until clinical progression. Determination of clinical progression is at the discretion of the investigator and may include both objective and subjective data. The continuation decision must be made by the investigator in consultation with the sponsor.

- Withdrawal of consent
- Intolerable toxicity
- Poor patient compliance
- Use of other anti-tumor treatment during the study
- Pregnancy
- Patient is lost to follow-up
- The investigator or sponsor determines it is in the best interest of the patient
- Study is terminated by the sponsor
- Death
- End of this study

Patients must be discontinued if they experience certain high-grade AEs, experience recurrent AEs, or experience AEs that warrant withdrawal of study treatment as determined by the principal investigator, as outlined in Section 7.5.

6.2.1.2 Withdrawal From Study

All study participants have the right to withdraw from the study at any time. During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.2.1.3 Replacement of Subjects

Patients who are not DLT evaluable in the Safety Lead-in cohort will be replaced to guarantee the protocol-required number of DLT evaluable patients to evaluate safety and tolerability.

6.2.1.4 Subjects Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts are to be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to be withdrawn from the study, and the withdrawal will be documented in the participant's medical record.

6.2.2 Stopping Rules

6.2.2.1 Part 1 (Safety Lead-in)

Dosing of individual patients will stop immediately in the event of the following:

- A DLT or DLT-equivalent (DLT that occurs outside the DLT assessment window) that does not return to baseline or Grade ≤1 within 21 days of onset
- A DLT or DLT-equivalent in the setting of a dose reduction that does not return to baseline or Grade ≤1 within 14 days of onset
- An immune-related AE (non-DLT) attributed to tislelizumab that does not return to baseline or Grade ≤1 within 12 weeks of onset

This study stage will end if the following condition is met:

- Excessive toxicity is present in dose level -1, defined as ≥2 patients experience a DLT.

6.2.2.2 Part 2 (Dose Expansion)

Safety data will be reviewed on an ongoing basis during study conduct. At a minimum of twice a year, study data will be reviewed by investigators to identify potential safety signals. Additional safety review meetings may be scheduled based upon concerns of the sponsor or investigators.

6.3 Study Termination

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

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Patients will be required to have a Safety Follow-up visit, as described in Section 6.1.21. The study will be terminated either 90 days after the last patient has received tislelizumab, or at the point at which all imAEs have resolved or are no longer being followed.

7 STUDY INTERVENTIONS

7.1 Description of Products

Investigational treatments used in this study are described in Table 5.

Table 5 Investigational Treatments Used in This Study

Product*	Section	Dose	Frequency	Route	Duration
Fruquintinib	7.1.1	5 mg, 4 mg, or 3 mg	Once daily 3 weeks on/ 1 week off	Oral	Until radiologically determined progressive disease per RECIST v 1.1, unacceptable toxicity, death, or withdrawal from study
Tislelizumab	7.1.2	300 mg	Once every 4 weeks	IV	Until radiologically determined progressive disease per RECIST v 1.1, unacceptable toxicity, death, or withdrawal from study

IV=intravenous; RECIST v 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.
*If either fruquintinib or tislelizumab is permanently discontinued due to toxicity, the other investigational treatment can be continued as a single agent, provided that the patients have investigator-assessed clinical benefit and are tolerating study drug.

7.1.1 Fruquintinib

7.1.1.1 Formulation, Packaging, Storage, and Handling

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. Additional information is available in the Pharmacy Manual.

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

All the investigational drugs should be sealed and stored in a secure, limited access area under appropriate conditions. The storage temperature should be between 10°C to 30°C. Investigational drugs should not be used beyond the expiration date provided by the manufacturer. The temperature monitoring log should be recorded and filed in the study binder.

For further details, refer to the fruquintinib IB.

7.1.1.2 Dosing and Administration

Treatment with study drug(s) on Day 1 of Cycle 1 must begin within 2 business days after a patient's enrollment (Section 6.1.3). Dose delay, interruption, or modification will be based on the specific laboratory and AE criteria, as described in Section 7.5. Guidelines for study treatment modification, delay, or discontinuation as well as management of imAEs or infusion-related reactions are provided in Section 8.4, Appendix 9 and Appendix 10.

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. Dosage, frequency of administration, and route of administration for both study drugs are described in Table 5.

Fruquintinib will be self-administered orally once daily for 3 weeks, followed by 1 week 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 Safety Lead-in Phase, the starting dose is 5 mg once daily on a 3 weeks on/1 week off schedule. Depending on safety observations, the fruquintinib dose may be de-escalated to 4 mg once daily on a 3 weeks on/1 week off schedule. If dose adjustment is required, four 1-mg fruquintinib capsules will be used to comprise the 4 mg dose. The SRC will confirm the RP2D of the combination treatment.

After completion of Part 1, in Part 2, the Dose Expansion Phase, patients will enroll within 2 cohorts to receive fruquintinib at the RP2D selected in Part 1 for 4-week cycles.

There is no predefined duration of treatment for each patient. It is intended that patients in both the Safety Lead-in and expansion phases will be treated until radiologically determined PD per RECIST v 1.1, unacceptable toxicity, death, or withdrawal from study.

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 the 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 eCRF. If the number of capsules returned does not agree with the expected number, the patient should be counseled and proper dosing should be 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 240 mL 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 7.5.

The administration time should be recorded accurately in the patient diary.

7.1.2 Tislelizumab

7.1.2.1 Formulation, Packaging, Storage, and Handling

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 under the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Refer to the IB for other details regarding tislelizumab.

7.1.2.2 Dosing and Administration

In Part 1 (Safety Lead-in Phase), tislelizumab 300 mg will be administered on Day 1 of each 28-day cycle (once every 4 weeks).

There is no predefined duration of treatment for each patient. It is intended that patients in both the Safety Lead-in and expansion phases will be treated until radiologically determined PD per RECIST v 1.1, unacceptable toxicity, death, or withdrawal from study.

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.

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. On the days of combination use of fruquintinib and tislelizumab, fruquintinib should be administered orally first before administering tislelizumab intravenously.

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.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 7.5.3 and Appendix 9.

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

The administration time should be recorded accurately.

7.2 Drug Accountability

7.2.1 Assignment/Disposal (Study Site)

All study drug required for this study will be provided by HUTCHMED Limited. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be recorded using the Drug Inventory Log.

Study drug will be disposed of at the study site according to the study site's institutional standard operating procedure or returned to HUTCHMED Limited or a HUTCHMED Limited-identified

entity with appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

7.2.2 Assignment/Return (Subject)

On Day -2 to Day 1, drug assignment will be performed. Patients will be provided with a pill diary and be instructed on how to account for each day's dose appropriately.

Patients should return all unused study drug and containers from the previous cycle on Day 1 (date of scheduled visits) of each subsequent cycle, and new study drug will be dispensed on the same day. Site staff should review the patient's pill diary and provide a new diary if necessary at the day 1 visit of each cycle.

If a dose adjustment is required (eg, decrease from 5 mg QD to 4 mg QD), the patient must return to the investigational site and return all unused study drug. The site staff must log into IWRS, adjust the dose, reassign the drug serial number, and dispense the new study drug dose (in 1mg capsules) to the patient.

7.3 Assessment and Verification of Compliance

The investigator is responsible for ensuring the patient's treatment compliance. The sponsor will provide supervision through on-site monitoring visits made by its representatives. The investigators should maintain complete and accurate records of drug dispensation and return. The dosing regimen and patient's actual dosing should be recorded in the original treatment records as well as the eCRF. At each treatment visit, the investigators or site staff should comprehensively assess the patient's treatment compliance according to the drug dispensing and return status at each visit and the actual dosing conditions, such as missed doses and overdosing reported by the patient. The patients must return all drug bottles and remaining capsules at the end of the study. The investigational sites must return all remaining supplies and drugs to the sponsor or provide evidence of destruction at the conclusion of the study.

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.

7.4 Prior and Concomitant Therapies

7.4.1 Prohibited Therapies

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

- Any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, and 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. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

- 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 7.4.3.
- Concomitant use of medications that have a known risk of causing QT prolongation and/or Torsades de Pointes (Appendix 13).

7.4.2 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 inducers of CYP3A should not be administered concomitantly with fruquintinib (see Appendix 4 for detailed information) unless the investigator considers it necessary. Fruquintinib is metabolized through CYP3A, so a strong inducer of enzyme CYP 3A4 may significantly influence the metabolism of fruquintinib.

Fruquintinib showed inhibition of P-gp and breast cancer resistance protein (BCRP) transporter in the in vitro studies, so drugs that are sensitive substrates, and substrates with narrow therapeutic index for P-gp and BCRP transporters should be avoided if possible (see Appendix 4). If these are used together, patients should be monitored more frequently for adverse reactions, and dose reduction of the P-gp or BCRP substrate medication should be considered.

7.4.3 Permitted Therapies

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, and red blood cell/platelet transfusions) and in a patient's interest are allowed.

Bisphosphonates and receptor activator of nuclear factor kappa-B ligand 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 anticoagulation, 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 who report Grade ≥2 hemorrhagic events at any site, based on an

individual assessment of the risk-benefit balance (see Appendix 6 for additional information on the clinical management of severe or serious hemorrhagic AEs).

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 or <2500 copies/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. 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 symptom control to other non-target 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. Fruquintinib treatment should be suspended during the radiation period and not resumed until at least 7 days after radiation only after meeting the following criteria:

- Radiation-related toxicities resolves to Grade ≤2
- No disease progression observed

7.4.4 Drug-Drug Interactions

Drug Interactions with Tislelizumab

Information about clinical drug interactions with tislelizumab is not available. The potential for drug-drug interaction between tislelizumab and small-molecule drug products, such as fruquintinib, is very low, given that tislelizumab is a therapeutic monoclonal antibody. Tislelizumab is a therapeutic monoclonal antibody and is not expected to be metabolized by liver 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.

Drug Interactions with Fruquintinib

Coadministration of fruquintinib with a strong CYP3A inducer reduced systemic exposure of fruquintinib by 65%. Therefore, medications that are strong inducers of CYP3A should not be administered concomitantly with fruquintinib.

7.4.5 Rescue Therapies

Not applicable.

7.5 Dose Delay, Interruption, or Modification

A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion of tislelizumab or of -self-administered dosing of fruquintinib during the three weeks it is scheduled to be received. 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.

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. The severity of AEs will be graded according to the NCI CTCAE v5.0, and the attribution of relatedness to the specific study drug should be noted.

- 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 1 grade and treated as Grade 1 toxicity for dose-modification purposes.
- Patients who develop arterial thromboembolic events should discontinue the study drug(s). If a patient suffers a venous thromboembolic event while still receiving the study drug(s), it may still be possible for him or her to remain on study treatment under close monitoring and dose modification of study drug(s).
- 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 with fruquintinib 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 or his or her designee. Guidance specific to tislelizumab temporary suspension is contained in Section 7.5.1.
- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If either fruquintinib or tislelizumab is permanently discontinued due to toxicity, the other investigational treatment can be continued as a single agent, provided that the patients have investigator-assessed clinical benefit and are tolerating study drug.

7.5.1 Dose Modification for Tislelizumab

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

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to fruquintinib or tislelizumab and requires a dose to be withheld. Guidance for management of tislelizumab administration in the presence of immune-mediated adverse events is located in Section 7.5.4. 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 ≤10 days, it should be administered in the current cycle. If tislelizumab needs to be withheld for >10 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.

7.5.2 Dose Modification for Fruquintinib

The dose can be reduced at any time due to the intolerable toxicity following the DLT observation window in the Safety Lead-in Phase (Table 6). 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: 1 reduction from 5 mg once daily to 4 mg once daily and, if not tolerated, a second reduction from 4 mg 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 4 mg once daily to 3 mg once daily.

Table 6 Fruquintinib Starting Dose Reductions

Dose Level	Dose	Reduced Dose
Dose Level 1* (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

*Doses are daily, on days 1 to 21 each 28-day cycle (3 weeks on/1 week off).

7.5.3 Fruquintinib Dose Modification Guidance

7.5.3.1 Fruquintinib Dose Modification Sequence for General Hematologic and Non-Hematologic Toxicity

Dose reduction guidelines for hematologic and non-hematologic toxicities, other than guidance for important identified risks (PPE, proteinuria, hypertension, decreased platelet count, hemorrhage, and liver function impairment) are provided in Table 7. Treatment should be held until AE/toxicity resolves or improves to Grade ≤1 or baseline level within 14 days. Patients with Grade 3 non-hematologic toxicity not described below that does not resolve to Grade ≤1 or

baseline level within 14 days should permanently discontinue the study drug unless approval to continue is obtained in writing from the sponsor.

Table 7 Fruquintinib Dose Modifications for Hematologic and Non-Hematologic Toxicity

NCI CTCAE v5.0 Toxicity Grading	Action
Grade 1 or 2[a]	None
Grade 3[b]	Interrupt the dose until the toxicity resolves 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, the treatment should be terminated.
b Including Grade 3 diarrhea and stomatitis that are ineffectively treated by drug therapies, but excluding Grade 3 menstrual cycle extension.

7.5.3.2 Fruquintinib Dose Modifications for Potential Risks and Important Identified Risks

The dose modification and treatment suggestions for potential risks are provided in Table 8 and for specific identified risks are provided in Table 9 (dermatologic toxicities), Table 10 (proteinuria), Table 11 (hypertension), Table 12 (decreased platelet count), Table 13 (hemorrhage at any site), and Table 14 (abnormal liver function).

Table 8 Fruquintinib Dose Modifications for Potential Risks

AE	Dose Adjustment
Gastrointestinal perforation	Study drug should be discontinued.
Arterial Thrombosis[a]	Study drug should be discontinued.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)[b]	If suspected as RPLS, the study drug should be discontinued.
Delayed Wound Healing	The general guidance for dose interruptions/reductions/discontinuations in response to AEs should be followed.

RPLS=Reversible Posterior Leukoencephalopathy Syndrome.
a The event term of arterial thrombosis encompasses the preferred terms (PT) of Aortic thrombosis, Cerebrovascular insufficiency, Embolism arterial, Peripheral embolism, Retinal artery occlusion, Subclavian artery thrombosis, and Transient ischemic attack.
b The signs and symptoms of RPLS include seizure, headache, altered mental status, visual impairment or cortical blindness with or without hypertension. The diagnosis of RPLS must be verified using brain magnetic resonance imaging (MRI).

Table 9 Fruquintinib Dose Modifications for Dermatological Toxicities

NCI CTCAE v5.0 Toxicity Grading	Dose Adjustment	Treatment Suggestions
Grade 1	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	• 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	• 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 occur after 2 times of dose reduction, the drug should be terminated.

AE=adverse event; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Table 10 Fruquintinib Dose Modifications for Proteinuria[a]

NCI CTCAE v5.0 Toxicity Grading	Dose Adjustment	Treatment Suggestions
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 urinalysis; 24-hour urine protein quantitation is between 1.0 to <2.0 g	None	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
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	• 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.

Table 10 Fruquintinib Dose Modifications for Proteinuria[a]

NCI CTCAE v5.0 Toxicity Grading	Dose Adjustment	Treatment Suggestions

AE=adverse event; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

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.

Table 11 Fruquintinib Dose Modifications for Hypertension

NCI CTCAE v5.0 Toxicity Grading	Dose Adjustment	Treatment Suggestions
Grade 1	None	Follow up as planned schedule.
Grade 2	None	Treatment objective: lower the blood pressure to <140/90 mmHg (or <130/80 mmHg in patients with chronic renal disease and/or diabetes). Refer to Appendix 7
Grade 3	• If BP >160/100mmHg 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 mmHg in patients with chronic renal disease and/or diabetes). Refer to Appendix 7
Grade 4	Permanently discontinue study treatment.	Emergent medical treatment.

AE=adverse event; BP=blood pressure; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Table 12 Fruquintinib Dose Modifications for Decreased Platelet Count

NCI CTCAE v5.0 Toxicity Grading	Dose Adjustment	Treatment Suggestions
Grade 1	None	Perform follow-up visit as scheduled.
Grade 2	• Hold treatment. • If the AE recovers to Grade 1 or baseline level within 7 days, resume treatment at the same dose level.	Platelet count should be performed 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.	Platelet count should be performed every 2-3 days; active treatment for platelet elevation is recommended.
Grade 3	• 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.	Platelet count should be performed every 2-3 days; active treatment (platelet transfusion) to elevate the platelet count is recommended. Platelet count should be performed once every week in the follow-up visit.
Grade 4	Permanently discontinue study treatment.	Platelet count 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.

AE=adverse event; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Table 13 Fruquintinib Dose Modifications for Hemorrhage at Any Site

NCI CTCAE v5.0 Toxicity Grading	Dose Adjustment	Treatment Suggestions
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.[b]
Grade 3 or above[a]	Permanently discontinue study treatment.	Emergent medical intervention.[b]

AE=adverse event; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

a Refer to Appendix 6 for clinical management of severe or serious hemorrhage.

b 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 who report Grade ≥2 hemorrhagic events at any site, based on an individual assessment of the risk-benefit balance.

Table 14 Fruquintinib Dose Modifications for Abnormal Liver Function

NCI CTCAE v5.0 Toxicity Grading[a]	Dose Adjustment	Treatment Suggestions
Grade 1	None.	Follow up per planned schedule.
Grade 2 or 3 (Liver function is abnormal but the biochemical criteria for Hy's Law[b] 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 testing to 1-2 times a week.
Grade 2 or 3 (Liver function is abnormal and the biochemical criteria for Hy's Law[b] are met)	The study drug should be terminated immediately.	Provide supportive care and increase the frequency of liver function testing to 2-3 times a week. Urgent medical intervention indicated.
Grade 4	The study drug should be terminated.	Urgent medical intervention indicated.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; ULN=upper limit of normal.

a Including increasing of ALT, AST, and total bilirubin, whether or not the biochemical criteria for Hy's Law have been met.

b 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 Section 8.2.2 for special reporting requirements and Appendix 5 for additional information regarding Hy's Law.

7.5.4 Dose Management for Tislelizumab

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).

Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
Thyroid disorders	1-2	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 tislelizumab or withhold in cases with systemic symptoms.
	3-4	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 tislelizumab; resume when resolved/improved to Grade 0-1.
Hypophysitis	1-2	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 tislelizumab.
	3-4	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 tislelizumab for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade ≤2. Discontinuation is usually not necessary.
Pneumonitis	1	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding tislelizumab until appearance improves and cause is determined.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
	2	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 tislelizumab. Re-treatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤10 mg/day. Discontinue tislelizumab if symptoms persist with corticosteroid treatment.
	3-4	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 tislelizumab.
Neurological toxicity	1	—	Continue tislelizumab.
	2	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold tislelizumab; resume when resolved/improved to Grade 0-1.
	3-4	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 tislelizumab.
Colitis/diarrhea	1	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for >14 days, manage as a Grade 2 event.	Continue tislelizumab.
	2	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 tislelizumab; resume when resolved/improved to baseline grade.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
	3	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 tislelizumab; re-treatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4		Discontinue tislelizumab.
Skin reactions	1	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue tislelizumab.
	2	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 tislelizumab.
	3	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 tislelizumab. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4	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 tislelizumab.
Hepatitis	1	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 tislelizumab if LFTs are unchanged or improving. Hold tislelizumab if LFTs are worsening until improvement is seen.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
	2	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 tislelizumab; resume when resolved/improved to baseline grade and prednisolone tapered to ≤10 mg.
	3	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 tislelizumab until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue tislelizumab.
	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	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue tislelizumab.
	2	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 tislelizumab. If not attributed to drug toxicity, restart tislelizumab. If attributed to study drug and resolved/improved to baseline grade: restart tislelizumab if tapered to <10 mg prednisolone.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
	3	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 tislelizumab until the cause is investigated. If study drug suspected: discontinue tislelizumab.
	4	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue tislelizumab.
Diabetes/ hyperglycemia	1	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue tislelizumab.
	2	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue tislelizumab or hold tislelizumab if hyperglycemia is worsening. Resume tislelizumab when blood glucose is stabilized at baseline or Grade 0-1.
	3	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold tislelizumab until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold tislelizumab until patient is hyperglycemia symptom-free and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular toxicity	1	Consider alternative causes and prescribe topical treatment as required.	Continue tislelizumab.
	2	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue tislelizumab or hold tislelizumab if symptoms worsen or if there are symptoms of visual disturbance.
	3	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold tislelizumab until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
	4	Initiate intravenous (methyl) prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue tislelizumab.
Pancreatitis	2	Monitor pancreatic enzymes.	Continue tislelizumab.
	3	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 tislelizumab; reintroduce only after discussion with the study medical monitor.
	4	Admit to hospital for emergency management and appropriate referral.	Discontinue tislelizumab.
Arthritis	1	Management per local guideline.	Continue tislelizumab.
	2	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue tislelizumab or, if symptoms continue to worsen, hold tislelizumab until symptoms improve to baseline or Grade 0-1.
	3	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 tislelizumab unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	1	Consider topical treatment or analgesia as per local guideline.	Continue tislelizumab.
	2	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 tislelizumab.
	3	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 tislelizumab until improved to Grade 0-1.
	4	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue tislelizumab.
Myositis/ rhabdomyolysis	1	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue tislelizumab.

Autoimmune Toxicity	NCI CTCAE v5.0 Toxicity Grading	Treatment Guidelines (Subject to Clinical Judgement)	Tislelizumab Management
	2	If CK is 3× ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold tislelizumab until improved to Grade 0-1.
	3-4	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 tislelizumab until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.
Myocarditis [a]	<2	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 tislelizumab. If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue tislelizumab 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	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 antithymocyte globulin.	
	3		
	4		

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 MB; ECG=electrocardiogram; INR=international normalized ratio; LFT=liver function test; MMF=mycophenolate mofetil; MUGA=multigated acquisition scan; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; 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.

8 SAFETY MONITORING

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.

Safety will be monitored through continuous reporting of AEs and SAEs, laboratory abnormalities, and incidence of patients experiencing dose modifications (including dose reductions and dose delays) and/or dose discontinuation of study drug (and reason for discontinuation).

Serum samples will be drawn for determination of ADAs to tislelizumab in patients. Investigators are instructed to report all AEs (including pregnancy-related AEs).

8.1 Definitions

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study patient temporally associated with the use of a study intervention, whether or not considered related to the intervention. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study intervention, whether or not considered related to the study intervention
- Any new disease or exacerbation of an existing disease (a worsening in the frequency or severity of a known condition). Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies)
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

8.1.2 Serious Adverse Event

An AE is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE. An event is considered “life-threatening” if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- An abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, or ectopic pregnancy) in a child born to a female patient or female partner of a male patient exposed to study drug
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following are NOT considered to be SAEs:

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

8.2 Adverse Event Reporting

8.2.1 Adverse Event Reporting Period

After signing the informed consent form, all AEs including SAEs regardless of attribution will be collected until 30 days after the last dose of study drug or initiation of a new treatment therapy, whichever is earlier. After this period, investigators should report only SAEs that are considered to be related to the study drug. 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.

8.2.2 Expedited Reporting

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events (both initial and follow-up) to the sponsor or its designee immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours after first learning of the event, regardless of relationship to study drug:

- SAEs (from informed consent to 30 days following the last dose of study drug or initiation of a new treatment of anti-tumor therapy, whichever is earlier)
- Abnormal hepatic function is defined as serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, regardless of seriousness.

  – For management of a hepatic function abnormal event, refer to Table 14. 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 ALP 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 5 for additional information regarding Hy's Law.

- CTCAE Grade ≥3 hemorrhagic event
  – When there is a Grade ≥3 hemorrhagic event per NCI CTCAE (version 5.0). The management of severe or serious hemorrhagic events will be conducted according to Appendix 6.
- Pregnancy

8.3 Definition of a 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 fruquintinib IB and the tislelizumab IB.

8.4 Definition of Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study for tislelizumab. 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 15. 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 2017, Brahmer 2018), and common immune-mediated toxicities are detailed in Appendix 9. For any AEs not included in Appendix 9, refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 15 Examples of Immune-Mediated Adverse Events

Body System Affected	Event
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

Table 15 Examples of Immune-Mediated Adverse Events

Body System Affected	Event
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism (eg, fatigue, weakness, weight gain); insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis; meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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.

8.5 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

8.6 Assessment of Severity

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the appropriate AE/SAE form.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of severity through clinical description by referring to the 5-grade determination standard in the NCI CTCAE v5.0. Use the guideline below for the assessment of severity when the observed or reported AE is not listed in the NCI CTCAE v5.0:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local, or noninvasive intervention indicated; limiting – age-appropriate instrumental ADL*

- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE

Note:

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.7 Causality Assessment

Investigators should use their knowledge of the patient, the circumstances surrounding the AE, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. To ensure consistency of causality assessments, investigators should apply the general guidelines provided as below:

- **Related:** There is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to, a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.
- **Not related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.8 Documenting Adverse Events

When an AE or SAE is recorded, the preferred medical terminology or concept should be used. Abbreviations and colloquialisms (eg, jargon or slang) should be avoided.

All AEs (including SAEs) should be recorded on the AE eCRF, and the check box for "Serious" should be ticked for entries that fit the criteria for SAEs. The investigator should also complete an SAE report and submit this to the sponsor or its designee within 24 hours of knowledge of the event.

Only 1 medical concept should be recorded in the event field on the eCRF.

8.8.1 Diagnosis versus Symptoms and Signs

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, hepatic failure should be recorded instead of jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.8.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause with the exception of severe or serious secondary events. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF if the dehydration is mild.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

8.8.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless the severity changes. If a persistent AE becomes more or less severe, it should be recorded again in a new eCRF entry.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the eCRF.

8.8.4 Abnormal Laboratory Values or Abnormal Vital Signs

Not every laboratory abnormality/abnormal vital sign qualifies as an AE. A laboratory test result/abnormal vital sign must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

Investigators are responsible for reviewing all laboratory findings and abnormal vital signs and determining whether or not each abnormality should be reported as an AE.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory

abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mmol/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

8.8.5 Preexisting Medical Conditions

A preexisting medical condition is one that is present at screening. Such conditions should be recorded on the eCRF as medical history. A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study (excluding deterioration of the study disease conditions). When such events are recorded on the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.8.6 Pregnancy

A female patient must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours of awareness to the sponsor (the reporting period for pregnancy continues up to 30 days after completion of the study drug). The investigator should counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until outcome of the pregnancy. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator.

Male patients must also be instructed to inform the investigator immediately if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. If such an event occurs, it should be reported as described above.

Pregnancy loss of any kind should always be classified as SAE (as the sponsor considers these medically significant), recorded on the eCRF, and expeditiously reported to sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

8.8.7 Worsening of Solid Tumor

Worsening and/or progression of the patient's solid tumor should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only. If there is any uncertainty about an AE being related only to the disease under study, it should be reported as an AE or SAE.

8.8.8 Death

All deaths that occur during the protocol-specified AE reporting period must have the underlying cause reported to the sponsor as an SAE with death listed as the outcome. Deaths due to the progression of disease must also be reported to the sponsor as an SAE. Death events that occur after 30 days following the last dose of study drug must be reported to the sponsor as an SAE

only if it is confirmed as related to study drug. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, record "Unknown cause death" on the eCRF, and the "unexplained/unknown death" should be reported expeditiously as an SAE. The SAE should be reported before the specific cause of death has been determined.

8.9 Duration of Follow-up for Adverse Events

The investigator will follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow-up, patient death, or end of study. Resolution of AEs and SAEs (with dates) should be documented on the appropriate eCRF and in the patient's medical record to facilitate source data verification. For SAEs, if, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the additional case details section of the eCRF.

For some SAEs, additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report) may be followed up by telephone, fax, email, and/or a monitoring visit.

All pregnancies that occur during the study should be followed until pregnancy outcome.

8.10 Overdose

For this study, any dose of fruquintinib greater than the 5 mg daily dose or tislelizumab equal or greater than 600 mg in a 24-hour period will be considered an overdose. No specific information is available on the treatment of overdose of fruquintinib or tislelizumab. 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 8.8. In the event of an overdose, further fruquintinib or tislelizumab administration should be held, and the patient should be observed closely for signs of toxicities. Appropriate supportive treatment should also be provided if clinically indicated. In the event of accidental or intentional overdose, the investigator or other site personnel should inform the sponsor's study representatives immediately, or no later than 24 hours. Sites must contact the medical monitor prior to the patient resuming fruquintinib treatment.

- An overdose with an associated AEs/SAEs should be recorded on the relevant AE/SAE eCRF and on the study drug eCRF.
- An overdose with no associated AEs/SAEs should only be reported on the study drug eCRF.

9 STATISTICAL ANALYSIS

9.1 Statistics and Analysis Method

All statistical analysis will be performed under the direction of the sponsor's personnel.

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP) document finalized prior to database lock.

The timing of analysis for each cohort may be different depending on completion of each cohort, and the final analysis of the study will be conducted at the time of analysis of the last cohort. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and PK measurements. Time to event variables will be summarized descriptively using Kaplan-Meier medians and quartiles. If less than 3 patients are enrolled to a particular cohort, no summary will be produced for the tumor type represented in that cohort. Patient data listings will be provided for all patients. Analyses will be performed using SAS® (version 9.1 or higher).

9.1.1 Statistical Hypothesis

No formal hypothesis testing is planned for this study. For efficacy endpoints, the study will provide the estimates and the associated 95% confidence interval (CI) for precision.

9.1.2 Sample Size Rationale

Approximately 146 to 152 patients are estimated to be enrolled in this study (approximately 6 to 12 patients in the dose escalation phase and approximately 140 patients in the Dose Expansion Phase). However, based upon the strategic evaluation of the clinical development of fruquintinib, patient enrollment has been permanently discontinued for Cohorts A, B, and C in the Dose Expansion Phase, hence, the final actual total number of patients will reflect this strategic decision.

9.1.2.1 Safety Lead-In Phase

Approximately 6 to 12 patients will be enrolled into this portion of the study. The total sample size will be determined by the incidence of DLTs in the Safety Lead-in Phase.

9.1.2.2 Dose Expansion Phase

Approximately 30 patients will be enrolled in each of the Cohorts A and B, approximately 40 patients in Cohort C, and approximately 40 patients in Cohort D in the Dose Expansion Phase of the study. Planned patient enrollment for each cohort can provide adequate precision for the estimate of ORR at a specific time point.

Table 16 shows the range of ORR and the corresponding 95% CIs for a sample size of 30 or 40 patients.

Table 16 Estimated ORR and 2-Sided 95% Confidence Intervals

Number of patients	Number of Responders	Estimated ORR	95% CI Lower Limit	95% CI Upper Limit
30	0	0.00	0.00	0.12
30	5	0.17	0.06	0.35
30	10	0.33	0.17	0.53
30	15	0.50	0.31	0.69
30	20	0.67	0.47	0.83
30	25	0.83	0.65	0.94
30	30	1.00	0.88	1.00
40	0	0.00	0.00	0.09
40	5	0.13	0.04	0.27
40	10	0.25	0.13	0.41
40	15	0.38	0.23	0.54
40	20	0.50	0.34	0.66
40	25	0.63	0.46	0.77
40	30	0.75	0.59	0.87
40	35	0.88	0.73	0.96
40	40	1.00	0.91	1.00

CI=confidence interval; ORR=objective response rate.
95% Clopper-Pearson interval for binomial distribution

However, based upon the strategic evaluation of the clinical development of fruquintinib, patient enrollment has been permanently discontinued for Cohorts A, B, and C in the Dose Expansion Phase, hence, the final actual total number of patients will reflect this strategic decision.

9.1.3 Analysis Sets

The following analysis sets are defined for the study:

- Safety analysis set: All enrolled patients who received at least 1 dose of fruquintinib or tislelizumab will be included in the safety analysis population. The safety evaluation will be performed based on the first dose of study treatment received by a patient. This is the primary population for safety and efficacy analyses.
- DLT evaluable analysis set: All patients enrolled in the Safety Lead-in portion of the study who are evaluable for DLT assessment. Patients will be considered DLT evaluable if he/she) has (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 not be considered DLT evaluable if during the DLT assessment window they (1) were withdrawn from the study for a reason other than DLT, (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 inducer of enzyme CYP3A (Appendix 4).

- Response evaluable analysis set: All patients who receive study treatment and have a baseline tumor assessment and at least 1 postbaseline assessment unless any clinical PD or death occurred before the first postbaseline assessment will be considered evaluable for anti-tumor efficacy endpoints.
- Anti-drug antibody analysis set: All patients who received at least 1 dose of study treatment and have a baseline and at least 1 postbaseline ADA result.
- Pharmacokinetic analysis set: All patients with at least 1 quantifiable plasma concentrations of fruquintinib and its metabolites combined with tislelizumab will be included in the pharmacokinetic analysis population.

9.2 Statistical Analyses

All summary tables, listings, and figures (TLFs) will be presented by cohort. Unless otherwise specified, for Cohort A and Cohort B, the TLFs will be presented overall, by cohort, and by category of ER/PGR positivity per ASCO-CAP guidelines (Allison 2020). TNBC will be defined as ER/PGR positivity of <1%, and ER/PGR low positive disease will be defined by ER/PGR positivity of 1% to 10%. (Note that the ASCO-CAP guidelines use PR as the abbreviation for progesterone receptor.)

9.2.1 Subject Disposition

The number and percentage of patients enrolled in the study, treated, and discontinued from study treatment(s) will be presented for the safety analysis set. The primary reason for treatment discontinuation will be summarized according to the categories in the eCRF. Patient disposition will be summarized overall and by cohorts.

Important protocol deviations will be summarized and listed by category.

9.2.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the safety analysis set using descriptive statistics.

A summary of baseline patient and disease characteristics, diagnosis, medical history, and prior therapies will be reported using descriptive statistics.

Other patient characteristics will be summarized as deemed appropriate.

Demographic and other baseline characteristics will be summarized overall and by cohorts.

9.2.3 Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study treatment(s). Concomitant medications will be defined as medications that 1) started before the first dose of study treatment(s) and were continuing at the time of the first dose of study treatment(s), or 2) started on or after the date of the first dose of study treatment(s) up to 30 days after the patient's last dose. Any steroid use will also be 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 cohorts. A listing of prior and concomitant medications will be provided.

9.2.4 Efficacy Analysis

No formal hypothesis testing is planned for this study.

9.2.4.1 Primary Efficacy Analysis

9.2.4.1.1 Objective Response Rate

The ORR is defined as the proportion of patients with a confirmed BOR of CR or PR as determined by the investigator using RECIST v1.1. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

The BOR is defined as the best response recorded from the start of study treatment until documented RECIST progression or the date of start of new anticancer therapy, whichever comes first.

The ORR and the corresponding 2-sided Clopper-Pearson 95% CI will be presented.

ORR will be summarized based on patients from the RP2D dose level overall and by cohorts. Additional summaries will be based on all dose levels overall and by cohorts if necessary.

As a sensitivity analysis, ORR will be presented for the response evaluable analysis set.

9.2.4.2 Secondary Efficacy Analysis

9.2.4.2.1 Progression-Free Survival

The PFS is defined as the time (months) from start of study treatment until the first radiographic documentation of objective progression as assessed by the investigator using RECIST v1.1, or death from any cause. Patients who have not objectively progressed or died by the date of the analysis cutoff or received any further anti-tumor therapy will be censored at the date of the last evaluable objective tumor assessment before the cutoff date or the anti-tumor therapy start date. Detailed censoring rules will be specified in the SAP.

The Kaplan-Meier (KM) method will be used to estimate PFS curves as well as PFS rates at various time points for patients in the safety analysis set. Median PFS (if estimable) will also be reported.

The PFS will be summarized based on patients from the RP2D dose level overall and by cohorts. Additional summaries will be based on dose levels overall and by cohorts if necessary.

9.2.4.2.2 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with a BOR of CR, PR, or SD as determined by the investigator using RECIST v1.1. The DCR and the corresponding 2-sided Clopper-Pearson 95% CI will be presented.

DCR will be summarized based on patients from the RP2D dose level overall and by cohorts. Additional summaries will be based on all dose levels overall and by cohorts if necessary.

9.2.4.2.3 Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of CR, PR, or durable SD as determined by the investigator using RECIST v1.1. The CBR and the corresponding 2-sided Clopper-Pearson 95% CI will be presented.

CBR will be summarized based on patients from the RP2D dose level overall and by cohorts. Additional summaries will be based on all dose levels overall and by cohorts if necessary.

9.2.4.2.4 Duration of Response

Duration of response (DoR) is defined as the time from the first occurrence of PR or CR, whichever comes first until disease progression or death. DoR will be summarized for responders using KM methodology.

DoR will be summarized based on patients from the RP2D dose level overall and by cohorts. Additional summaries will be based on all dose levels overall and by cohorts if necessary.

9.2.4.2.5 Overall Survival

Overall survival is defined as the time (months) from start of study treatment until the date of death due to any cause. The KM method will be used to estimate OS curves as well as OS rates at various time points. Median OS (if estimable) will also be reported.

OS will be summarized based on patients from the RP2D dose level overall and by cohorts. Additional summaries will be based on all dose levels overall and by cohorts if necessary.

9.2.5 Safety Analysis

The summary of the exposure to study treatment(s), AEs, AEs leading to drug modification or discontinuation including DLTs, changes in laboratory results, and changes in vital signs will be presented. The severity of all AEs will be graded according to NCI CTCAE v5.0, and the AE verbatim term will be coded by the MedDRA.

TEAEs are defined as AEs that started or worsened in severity on or after the first dose of study treatment and no later than 30 days after the date of the last study treatment administration. 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 number and frequency of patients experiencing AEs will be summarized according to system organ class (SOC) and preferred terms (PTs). If a patient reports a TEAE more than once within that SOC/PT, the AE with the highest severity will be used in the corresponding severity summaries.

The following safety summaries will be produced:

- Overview of AEs
- Summary of DLTs (Safety Lead-in portion)
- Summary of DLT-equivalent (DLTs that occur outside the DLT assessment window)
- Summary of TEAEs including severity and relationship to study drug
- Summary of imAEs including severity and relationship to study drug
- Summary of AESIs including severity and relationship to study drug

- Summary of serious TEAEs
- Summary of TEAEs leading to dose interruption, dose reduction, or termination of treatment

The above summaries will be repeated for TEAEs related to study treatment.

Drug exposure including number of cycles received, total duration of exposure, cumulative dose received (mg), dose intensity, and relative dose intensity of fruquintinib and tislelizumab will be summarized. The number and percentage of patients requiring dose interruption, dose delay, dose reduction, and treatment discontinuation because of AEs will be summarized for each study drug. Reasons for dose modifications will also be summarized.

For laboratory tests that are graded by NCI CTCAE v5.0, results will be summarized by grade. Treatment-emergent changes will be summarized by maximum postbaseline grade. A shift table summarizing shift from baseline of maximum postbaseline grade will be presented.

The changes in vital signs and ECOG performance status scores from baseline will be summarized. Changes in 12-lead electrocardiogram (for example, changes in QTcF) will be summarized.

9.3 Pharmacokinetics Analysis

Pharmacokinetic samples will be collected in this study. Evaluation of PK will be performed on the PK analysis set. Concentration data of fruquintinib, metabolite M11, and tislelizumab will be tabulated and summarized using descriptive statistics (number of patients, arithmetic mean with standard deviation, coefficient of variation, and geometric mean, median, minimum, and maximum) as appropriate.

Additional PK analyses, including population PK analyses and exploratory exposure-response (efficacy and safety endpoints) analyses, may be conducted as appropriate, and the results of such analysis may be reported separately from the clinical study report (CSR).

9.4 Immunogenicity Analysis

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

9.5 Other Exploratory Analyses

Distribution of PD-L1 expression will be examined in all patients. Other potential predictive markers including, but not limited to, TILs, MSS/MSI, TMB, cytokine expression, and gene signature profiling may be detected and analyzed.

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

Methodology for exploratory analyses will be described in the SAP. The biomarker data and analysis may be reported separately from the CSR.

9.6 Interim Analyses

Not applicable.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, consensus, and the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH Good Clinical Practice (GCP) Guidelines that have their origin in the Declaration of Helsinki, and applicable regulations and guidelines governing clinical study conduct.

10.2 Ethics Review

The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) must review the protocol and amendments, IB, ICF, study-relevant materials (such as advertisements for patient recruitment), and any other essential documents. IEC/IRB approval is to be obtained prior to the start of the study at the investigator site.

All amendments are to be reviewed and approved by the IEC/IRB and applicable regulatory authorities (as required) and documented. All SAEs and other significant safety findings should be reported to the sponsor, the IEC/IRB, and applicable regulatory authorities as required. During the study, protocol deviations that may increase a patient's risk should be reported to the IEC/IRB in a timely manner.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.3 Informed Consent

- Investigators or designees must obtain the signed ICF from patients prior to conducting any study-related procedures.
- The investigator or his/her representative will explain the nature of the study to the participant or to their legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- Patients must be informed that they may withdraw consent to participate in the study without any limitations. If the patient cannot sign the ICF, a legally acceptable representative of the patient must sign the ICF.
- If the patient and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the patient and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the patient and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations.
- Informed consent should be recorded on the eCRF.
- If the risk/benefit assessment changes after the safety analysis, the ICF needs to be reviewed and updated, and all updated information should be provided to patients (including patients who have already received the study drug).

10.4 Data Privacy

All information about the study drug (such as patent application, formulation, manufacturing process, and basic study information) is considered confidential as long as it is unpublished.

All information obtained in the study is considered confidential. The sponsor will open the information to investigational personnel and any other regulatory authority, when necessary. To ensure the completeness of the study analysis data, investigational personnel are accountable for providing all results and data to the sponsor.

Investigators must guarantee the privacy of patients by not disclosing patient-related information to third parties without authorization. eCRFs and other documents submitted to the sponsor should not contain the patient's name.

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- Patients are identified only by the unique identifier. Investigators may retain the identification forms, which include patient numbers, names, and addresses. ICFs and other documents should be documented properly and should not be given to the sponsor.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Disclosure

Final study results will be published on a public clinical study website according to applicable local guidelines and regulations.

10.6 Data Quality Assurance

- To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.
- All participant data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing the strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues, and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).

10.7 Biological Specimens and Data

For participants who provide informed consent agreeing to participate in future biomedical research, any unused samples for study-related research, as well as unused PK samples, may be stored for no longer than 15 years, or other period as per local requirements, after the final date of the database lock. After this storage period, any residual samples will be destroyed. The sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. The unused samples may be utilized for future biomedical research as permitted by local regulations.

The results of these future biomedical research analyses will not be shared with patients and will not be presented in the CSR.

If there are specific site or country requirements involving the pharmacogenomics analyses that the sponsor is unable to comply with, samples will not be collected at those sites.

All samples will be single/double-coded as defined by ICH Guideline E15.

11 OVERSIGHT

11.1 Independent Monitoring

No independent data monitoring is planned for this study. The sponsor will review study safety data on an annual basis, or more frequently, if safety concerns arise.

11.1.1 Safety Review Committee

Safety monitoring and evaluation of the dose escalation will be carried out by the SRC, which will be comprised of the sponsor's study team members (including, but not limited to, the medical monitor, safety monitor, and PK scientist) and the site principal investigators. Safety and PK data will be evaluated to determine whether it is safe to continue the assigned dosing combination for dose escalation, whether the dose should stay at the currently assigned dose level, or whether the dose should be de-escalated to the lower dose level. The SRC will be charged with determining the RP2D.

These criteria constitute the basis for RP2D determination, and the SRC must collectively determine the RP2D. Enrollment to Part 2 (expansion cohorts) will begin once the RP2D has been determined in Part 1 of the study.

The SRC will also review the data during Part 2 on an ongoing basis for safety.

11.2 Quality Control and Assurance

The clinical study will be executed and reported following GCPs, all applicable regulatory requirements, and applicable standard operating procedures, including quality control of documents.

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site. The sponsor and investigator will ensure that any individual or party who performs study-related duties or functions on behalf of the sponsor/investigator is qualified to perform the study-related duties or functions.

The overall procedures for quality assurance of clinical study data are described in the sponsor or designee's standard operational procedures. The planned quality assurance and quality control procedures for the study are described in the following sections.

11.2.1 Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, the sponsor's personnel (or designated CRO) will review the protocol and eCRF with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to GCP, and the progress of enrollment and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel, including the investigator, must be available to assist the field monitor during these visits.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The sponsor's monitoring standards require full verification of the informed consent, adherence to the inclusion/exclusion criteria, and documentation of

SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.2.2 Audits

Authorized representatives of the sponsor, a regulatory/competent authority, and/or an IRB/IEC representative may visit the site to perform audits or inspections, including source data verification. Should this occur, the investigator is responsible for the following:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection
- Documents patient to audit or inspection include but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB/IEC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

11.2.3 Records

11.2.3.1 Data Capture and Management

The term eCRF refers to the Case Report Forms within the electronic data capture (EDC) system. The EDC system is the database where pertinent study data are collected. For all patients, including screen failures, data will be collected on source documents first. The principal investigator is responsible for assuring that the data entered into eCRFs is complete and accurate and that entry and updates are performed in a timely manner. Data from ECG will be collected at the study sites, and the data will be transmitted to a designated CRO for centralized analysis, as well as for further processing and data reconciliation. Imaging data will be collected at the study sites, and a designated CRO will perform further processing, data reconciliation, and storage.

At all times, the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Patient source documents are the investigator's/physician's patient records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts.

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

11.2.3.2 Source Documentation

- The investigator/institution should maintain accurate source documents and study records for all patients that support the information entered in the eCRF.
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable and not obscure the original entry.
- All information recorded on eCRFs must be traceable to source documents in the patient's file. Any changes should be explained if necessary (eg, via an audit trail).

11.2.3.3 Records Retention

Records and documents, including signed ICFs, source documents, study drug documents, monitoring visit records, regulatory documents, and all other correspondence and documents pertaining to the conduct of this study must be retained by the investigator for at least 5 years after study completion, unless local regulations or institutional policies require a longer retention period.

If the documents cannot be stored properly at the investigational site, the documents can be transferred by the investigator and sponsor to an approved storage facility. The documents must be sealed for storage and easily found for review in the case of a regulatory authority audit. No records may be transferred to another location or party without written notification to the sponsor.

No records may be destroyed during the retention period following study completion or discontinuation without the written approval of the sponsor. Records must be destroyed in a manner that ensures confidentiality.

11.3 Study Termination or Study Site Closure

The sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study but has not enrolled any patient within a reasonable period of time.
- The investigator has violated any fundamental obligation in the study agreement, including, but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines.
- The total number of patients required for the study is enrolled earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the

reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

12 PUBLICATION POLICY

The study results may be published in scientific journals. The names of investigators who make an important contribution to the study implementation and management and personnel who make an important contribution to the study design, analysis, and interpretation (such as the sponsor's staff or consultants) will be listed in the publication. The sponsor will provide the article to investigators for review prior to publishing any study results. Investigators must obtain approval from the sponsor before contributing to any related articles or abstracts.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13 FINANCING AND INSURANCE

Financing and insurance information will be addressed in a separate agreement.

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