HUTCHMED

Clinical Study Protocol

An Open-Label Phase Ib/II Study of Surufatinib in Combination with Tislelizumab in Subjects With Advanced Solid Tumors

Short Title	Surufatinib in Combination With Tislelizumab in Advanced Solid Tumors
Investigational Product(s):	Surufatinib (HMPL-012) Tislelizumab (BGB-A317)
Protocol Number:	2020-012-GLOB1
Clinical Phase:	1b/2
Amendment:	5
Sponsor:	HUTCHMED Limited NO.4, Lane 720, Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
Regulatory Agency Identifier Number(s):	CCI [redacted] EudraCT number 2020-004163-12
Date of Issue:	29 November 2023

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by the International Council for Harmonisation (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 Ib/II Study of Surufatinib in Combination with Tislelizumab in Subjects With Advanced Solid Tumors
Protocol Number	2020-012-GLOB1
Amendment	5

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: [last name, first name] PPD	**Title:** PPD HUTCHMED International Corp.
Signature: *See appended signature page*	**Date:** [DD Mmm YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2020-012-GLOB1 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 GCP 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:**

DOCUMENT HISTORY

Amendment	**Date of Issue**
Original	30 September 2020
1	19 March 2021
2	10 October 2021
3	16 March 2022
4	30 November 2022

AMENDMENT SUMMARY

This Clinical Study Protocol 2020-012-GLOB1 Amendment 5 replaces Clinical Study Protocol 2020-012-GLOB1 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 the termination of this study based on the strategic reevaluation of the clinical development of surufatinib in the United States and Europe. This change is not based on any concern for patient safety or efficacy relative to surufatinib and/or tislelizumab treatment. CCI [redacted] The study will be terminated either 90 days after the last patient has received tislelizumab, or the point at which all immune-mediated adverse events (imAEs) have resolved or are no longer being followed, whichever occurs earlier.

The major changes incorporated in Amendment 5 relative to Amendment 4 are summarized below. Editorial and formatting changes are not included in this summary.

Details of changes made in prior amendments are summarized in Appendix 11.

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.
Synopsis, Section 1.2 – Schedule of Events, Table 1; Section 4.1.3 – Part 2 (Dose Expansion); Section 5.1 – Recruitment; Section 6.1.18 – Treatment Period; Section 6.1.20 – Efficacy Follow-up Period; Section 6.1.21 Survival Follow-up Period; Section 6.2.1.1 – Permanent Discontinuation of Treatment; 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.
Synopsis, Section 1.2 – Schedule of Events, Table 2; Section 6.1.16.1 – Sample Collection and Handling	Language was added to indicate termination of pharmacokinetic (PK) samples after Cycle 17.	These updates were made to accommodate the process of study termination.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin converting enzyme
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASPS	alveolar soft part sarcoma
AST	aspartate aminotransferase
ATC	anaplastic thyroid cancer
BCRP	breast cancer–resistant protein
BID	twice a day (bis in die)
BP	blood pressure
BRAF	B-Raf kinase
$BRAF^{V600E}$	B-Raf kinase V600E mutations
CxDx	Cycle x, Day x
CBR	clinical benefit rate
CD	compact disc
CL	clearance
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase myocardial band
CR	complete response
CRC	colorectal cancer
CRF	case report form (paper or electronic)
CRO	clinical research organization
CSF-1	colony-stimulating factor-1
CSF-1R	colony-stimulating factor-1 receptor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450, family 3, subfamily A
CYP3A4	cytochrome P450, family 3, subfamily A4
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response

Abbreviation	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
epNET	extrapancreatic neuroendocrine tumor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FcγR	Fc-gamma-receptor immunoglobulin
FGFR1	fibroblast growth factor receptor 1
GC	gastric cancer
GCP	Good Clinical Practice
GEP	gastroenteropancreatic
HBV	hepatitis b virus
HCV	hepatitis c virus
HIV	human immunodeficiency virus
HPF	high-power field
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
INR	international normalized ratio
IRB	Institutional Review Board
IP	investigational product
IV	intravenous(ly)
IWRS	interactive web response system
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
mCRC	metastatic colorectal cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NET	neuroendocrine tumor
NR	not reached
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction

Abbreviation	Definition
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
pNET	pancreatic neuroendocrine tumor
PO	oral(ly)
PR	partial response
PT	preferred term
QxW	every x weeks
QD	once daily
QTcF	QT interval corrected by the method of Fredericia
RAS	RAS oncoprotein
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	recommended phase 2 dose
SAE	serious adverse event
SANET-ep	advanced epNET
SANET-p	advanced pNET
SCLC	small-cell lung cancer
SD	stable disease
SRC	Safety Review Committee
SSA	somatostatin analog
STS	soft-tissue sarcoma
TAM	tumor-associated macrophage
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TTR	time to response
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma
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 Ib/II Study of Surufatinib in Combination With Tislelizumab in Subjects With Advanced Solid Tumors
Short Title	Surufatinib in Combination With Tislelizumab in Advanced Solid Tumors
Acronym	Not applicable
Phase	1b/2
Study Status as of Protocol Amendment 5	The primary purpose of Amendment 5 is to provide notification of termination of this study based on the strategic reevaluation of the clinical development of surufatinib in the United States and Europe. This change is not based on any concern for patient safety or efficacy relative to surufatinib and/or tislelizumab treatment. CCI [redacted]. The study will be terminated either 90 days after the last patient has received tislelizumab, or the point at which all immune-mediated adverse event (imAEs) have resolved or are no longer being followed, whichever occurs earlier.
Rationale	Surufatinib is a novel tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, as well as fibroblast growth factor receptor (FGFR) 1, which results in inhibition of angiogenesis. In addition, surufatinib inhibits signaling via colony-stimulating factor-1 receptor, which is thought to downregulate tumor-associated macrophages, thus promoting antitumor immunity. Tislelizumab is a humanized immunoglobulin G4 (IgG4)-variant anti-cell death protein 1 (PD-1) monoclonal antibody specifically engineered to minimize binding to Fc-gamma-receptor immunoglobulin (FcγR) on macrophages. In preclinical studies, binding to FcγR on macrophages has been shown to compromise the antitumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T-effector cells. Combining surufatinib with tislelizumab may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor activity compared to that of each individual agent alone.
Target Population	Male and female patients, ≥18 years of age, with evaluable or measurable (according to Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) advanced or metastatic solid tumors (colorectal cancer, neuroendocrine tumors, small-cell lung cancer, gastric cancer, soft tissue sarcoma, or anaplastic thyroid cancer) and Eastern Cooperative Oncology Group performance status of 0 or 1, who have progressed on or are intolerant of standard therapies.
Intervention	Surufatinib (HMPL-012) will be provided as 50-mg capsules. Tislelizumab 10 mg/mL will be provided as 100 mg/mL in 10 mL sterile, nonpyrogenic, and isotonic injectable solution for intravenous (IV) administration in a buffered formulation. The surufatinib will be administered with 240 mL (8 ounces) of water within 1 hour after breakfast. In Part 1 (dose escalation), surufatinib will be administered orally (PO) once daily (QD) at 250 mg or 300 mg with a 200-mg tislelizumab IV infusion every 3 weeks (Q3W). In Part 2, the indication-specific expansion portion of the study, patients will receive surufatinib at the recommended phase 2 dose (RP2D) (300 mg QD) selected in Part 1 with 200 mg tislelizumab IV, Q3W.

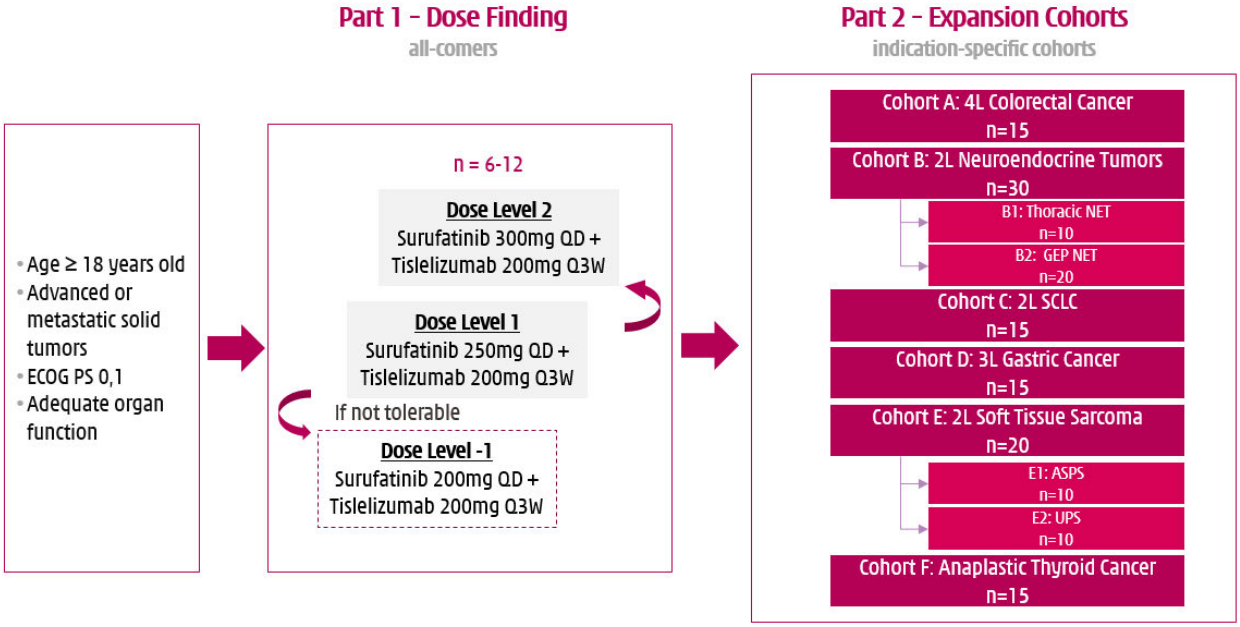
<table>
<tr><td>Description of Sites</td><td colspan="2">Part 1 will have approximately 4 to 6 sites for patient recruitment in the United States. Part 2 will include sites in the United States and Europe for patient recruitment.</td></tr>
<tr><td colspan="3">Objectives and Endpoints</td></tr>
<tr><td colspan="2"><u>Objectives</u>
Part 1 Primary:
To evaluate the safety and tolerability of surufatinib, thereby determining the RP2D and/or the maximum tolerated dose (MTD) of surufatinib in combination with tislelizumab
Part 2 Primary:
To evaluate the objective response rate (ORR) as assessed by the investigator in patients with advanced solid tumors when treated with surufatinib in combination with tislelizumab according to RECIST v1.1.</td><td><u>Corresponding Endpoints</u>
Part 1 Primary:
Safety including dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, ECGs, clinical laboratory abnormalities, and vital signs
Part 2 Primary:
ORR at 12 weeks</td></tr>
<tr><td colspan="2">Part 1 Secondary:
To evaluate the antitumor activity in patients with advanced solid tumors when treated with surufatinib in combination with tislelizumab according to RECIST v1.1
To characterize the pharmacokinetics (PK) and immunogenicity of tislelizumab and surufatinib in combination
Part 2 Secondary:
To evaluate further anticancer effects of surufatinib in combination with tislelizumab
To characterize the safety and tolerability of surufatinib in combination with tislelizumab
To characterize the PK and immunogenicity of tislelizumab and surufatinib in combination</td><td>Part 1 Secondary:
ORR, progression-free survival (PFS), disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR), time to response (TTR)
Concentrations of surufatinib in plasma and tislelizumab in serum
Incidence of antidrug antibodies (ADA) to tislelizumab
Part 2 Secondary:
PFS, DCR, CBR, DoR, TTR
Overall survival (OS); Cohorts A and F
Safety including TEAEs, SAEs, AEs leading to discontinuation, electrocardiograms (ECGs), clinical laboratory abnormalities, and study drug discontinuation due to AEs
Concentrations of surufatinib in plasma and tislelizumab in serum
Incidence of ADA to tislelizumab</td></tr>
<tr><td colspan="3">Brief Summary:
The purpose of this study is to evaluate the safety, tolerability, PK, and efficacy of surufatinib in combination with tislelizumab in participants with advanced solid tumors. Study details are outlined below.</td></tr>
<tr><td>Condition/Disease</td><td colspan="2">Advanced or metastatic solid tumors (colorectal cancer, neuroendocrine tumors, small-cell lung cancer, gastric cancer, soft tissue sarcoma, and anaplastic thyroid cancer)</td></tr>
</table>

Study Duration	Enrolled patients undergo a screening period of up to 28 days of the initial dose; patients may receive treatment for the treatment duration as described below. All patients will undergo an End of Treatment Visit within 37 days after the last dose and may undergo efficacy and survival follow-up every 12 weeks. As of Amendment 5, after the End of Treatment Visit, patients will be contacted by the sites to follow-up on any resolving or new immune-mediated adverse events for up to 90 days.
Treatment Duration	Each patient will be treated until disease progression, unacceptable toxicity, withdrawal of consent, new anticancer therapy, lost to follow-up, or death.
Health Measurement/Observation	Safety, including DLTs, TEAEs, SAEs, AEs leading to discontinuation, ECGs, clinical laboratory abnormalities, vital signs, and MTD and/or RP2D
Visit Frequency	Cycle 1: every week (Day 8 ±1 day and Day 15 ±1 days) Cycle 2: every 2 weeks (±1 day) Cycle 3 and onward: every 3 weeks (±3 days) Treatment Completion: 30±7 days after completion
Number of Participants	The total number of patients enrolled will depend on the number of dose escalations. The planned enrollment is approximately 122 patients. Part 1 – dose escalation: 6 to 12 patients Part 2 – dose expansion: 110 patients
Intervention Groups and Duration	Patients in both Part 1 and Part 2 will undergo screening period of up to 28 days and will receive treatment for the treatment duration as described above. All patients will undergo an End of Treatment Visit within 30 days after the last dose and may undergo efficacy and survival follow-up every 12 weeks. Part 1 (all cohorts): patients will receive oral surufatinib at a dose based on cohort level and intravenous tislelizumab at a 200-mg dose Part 2 (all cohorts): patients will receive oral surufatinib at the RP2D (300 mg QD) selected in Part 1 and intravenous tislelizumab at a 200-mg dose Dose modification is allowed for surufatinib no more than twice by 50 mg daily. No dose reductions for tislelizumab are permitted.
Data Monitoring/Other Committee	Yes Safety monitoring and evaluation of the dose escalation part will be carried out by Safety Review Committee, which will consist 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.

1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Design Schema



ASPS=alveolar soft part sarcoma; ECOG PS=Eastern Cooperative Oncology Group performance status; GEP=gastroenteropancreatic; L=line of therapy (e.g., 4L=fourth line of therapy); NET=neuroendocrine tumor; Q3W=every 3 weeks; QD=once daily; SCLC=small-cell lung cancer; UPS=undifferentiated pleomorphic sarcoma.

1.2 Schedule of Events

The schedule of events is presented in Table 1.

Table 1 Schedule of Events for Study 2020-012-GLOB1

Cycle/Period		Cycle 1			Cycle 2		Cycle 3+	EOT[20]	Efficacy Follow-up[21]	Survival Follow-up[18]
Visit	Screening	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Within 30 Days After Last Dose	Every 12 Weeks From EOT	Every 12 Weeks From PD
Visit window (days)	**-28 to -1**		**±1**	**±1**	**±1**	**±1**	**±3**	**±7**	**±14**	**±14**
Informed consent[1]	X									
Tumor sample for PD-L1 testing[2]	X									
Cohort F: Core needle biopsy[19]	X				X					
Medical history, disease history[3]	X									
Demographics[4]	X									
Prior and concomitant medications and concomitant procedures[5]	X	X		X	X	X	X	X		
Comprehensive physical exam[6]	X							X		
Limited physical exam[7]		X	X	X	X	X	X			
Height	X									
Weight	X	X	X	X	X	X	X	X		
ECOG performance status[8]	X	X			X		X	X		
Vital signs[9]	X	X	X	X	X	X	X	X		
Laboratory evaluations[10]										
Hematology	X[11]		X	X	X	X	X	X		
Blood chemistry	X[11]		X	X	X	X	X	X		
Blood amylase and lipase	X[11]		X	X	X	X	X	X		
Coagulation indicators	X[11]		X	X	X	X	X	X		
CK and CK-MB	X	X			X		X	X		
Thyroid test (FT3, FT4, TSH)	X[11]						Every 3 cycles starting from C4D1 (ie, C4D1, C7D1, C10D1)	X		
Serum pregnancy test	X[11]							X		

Table 1 Schedule of Events for Study 2020-012-GLOB1

Cycle/Period		Cycle 1			Cycle 2		Cycle 3+	EOT[20]	Efficacy Follow-up[21]	Survival Follow-up[18]
Visit	Screening	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Within 30 Days After Last Dose	Every 12 Weeks From EOT	Every 12 Weeks From PD
Visit window (days)	**-28 to -1**		**±1**	**±1**	**±1**	**±1**	**±3**	**±7**	**±14**	**±14**
Urine pregnancy test					X		X			
Urinalysis	X[11]				X		X	X		
Virological screening	X									
PK and ADA assessments		Refer to Table 2								
12-lead ECG[12]	X[11]			X	X	X	X	X		
ECHO/MUGA scan[13]	X				Every 12 weeks from C1D1 (±1 week)					
Tumor evaluation/imaging[14]	X		Q6W (±1 week) for the first 24 weeks from C1D1, then Q9W (±1 week) thereafter through EOT.						X[15]	
Surufatinib administration		QD, PO, based on dose escalation dose level in Part 1 and RP2D (300 mg) in Part 2								
Tislelizumab administration[16]		X			X		X			
AEs/SAEs[17]	X	X	X	X	X	X	X	X		
Overall survival[18]										X

ADA=antidrug antibody; AE=adverse event; CK=creatine kinase; CK-MB=creatine kinase myocardial band; CxDx=Cycle x, Day x; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FT3=serum free tri-iodothyronine; FT4=serum free thyroxine; ICF=informed consent form; imAE=immune-mediated adverse events; IV=intravenous; MUGA=multiple-gated acquisition; PD=progressive disease; PD-L1=programmed death-ligand 1; PO=orally; PK=pharmacokinetics; QD=once daily; QxW=every x weeks; RP2D=recommended phase 2 dose; SAE=serious adverse event; TSH=thyroid-stimulating hormone.

1. A written informed consent form should be obtained prior to any protocol-specific procedure or test. Procedural details for informed consent are available in Section 6.1.1.
2. Submit formalin-fixed, paraffin-embedded tumor sample or a minimum of 10 unstained slides for PD-L1 analysis for all patients enrolled in Part 2 of the study. Procedural details for archived tumor sample are available in Section 6.1.14.
3. Procedural details for medical history are available in Section 6.1.2. Tumor diagnosis and tumor treatment history are described in Section 6.1.3.
4. Procedural details for patient demographics, including baseline characteristics, are available in Section 6.1.4.
5. Procedural details for concomitant medications/treatments are available in Section 6.1.5.
6. Procedural details for comprehensive physical examination are available in Section 6.1.6.

7. Procedural details for limited physical examination are available in Section 6.1.7.
8. Procedural details for ECOG performance status are available in Section 6.1.8.
9. Procedural details for vital signs are available in Section 6.1.9.
10. Procedural details for laboratory evaluations are available in Section 6.1.10.
11. These tests should be completed within 7 days before the start of treatment; if completed more than 7 days before first dose, they must be repeated on C1D1 prior to dosing.
12. ECG is to be performed prior to dosing of study drugs and PK sample collection and ECHO assessments at each relevant visit. Other procedural details for 12-lead ECG are available in Section 6.1.11. Unscheduled ECG or other cardiac examinations can be performed if clinically indicated.
13. Procedural details for ECHO assessments are available in Section 6.1.12. MUGA scans are acceptable if ECHO cannot be performed.
14. Procedural details for tumor evaluation and imaging are available in Section 6.1.13.
15. Any patient who discontinues study treatment for any reason other than disease progression should be followed with tumor evaluation/imaging until progression is documented or until a new anticancer treatment is initiated.
16. Tislelizumab will be dosed on day 1 of every cycle starting at C1D1 (Q3W) as an IV infusion.
17. AEs will be collected from the signing of the ICF until 30 days after the last dose or initiation of new antitumor therapy, whichever occurs first. The relevant AEs will be followed up until they are recovered to the baseline status, already in a stable state as assessed by the investigator, or until the start of new antitumor therapy, loss to follow-up, death, withdrawal of informed consent, or end of study. SAEs are collected from the signing of the ICF until 30 days after the last dose or initiation of new antitumor therapy, and after this period, only SAEs related to the investigational drug are collected. In addition, telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate; ie, is associated with an imAE or is a new anticancer therapy) at 60 days and 90 days (±14 days) after the last dose of tislelizumab, regardless of whether or not patients started a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
18. All patients in dose expansion cohorts A and F may be followed for survival status every 12 weeks up to 2 years from last dose, until death, lost to follow-up, withdrawal of consent, or the end of the study. Survival information can be obtained via phone and/or clinical visits.
19. Cohort F: Mandatory core needle biopsies at screening, and on treatment (between C2D1 to C2D15). Procedural details for core needle biopsy are available in Section 6.1.14.1.
20. All patients on active treatment at the time of Amendment 5 are required to have an EOT visit. Treatment with surufatinib and tislelizumab should be discontinued on Day 28 of the last cycle 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. After the EOT visit, patients will be contacted by the sites to follow-up on any resolving or new immune-mediated adverse events for up to 90 days.
21. All patients on active treatment at the time of Amendment 5 will not be followed for efficacy after EOT.

Table 2 Time and Events Schedule for Pharmacokinetics and Immunogenicity Assessments

Visit	Surufatinib[1]	Tislelizumab	Immunogenicity (Anti-Tislelizumab Antibodies)
	PK Sample Time Point[2]	PK Sample Time Point[2]	
C1D1	Predose[3]	Preinfusion[4]	Preinfusion[4]
	2 to 4 hours postdose	EOI[5]	
C1D8	Predose[3]	Any time during visit	-
C1D15	Predose[3]	Any time during visit	-
	2 to 4 hours postdose		
C2D1	Predose[3]	Preinfusion[4]	Preinfusion[4]
C5D1	Predose[3]	Preinfusion[4]	Preinfusion[4]
		EOI[e]	
C9D1	Predose[3]	Preinfusion[4]	Preinfusion[4]
C17D1	Predose[3]	Preinfusion[4]	Preinfusion[4]

AE=adverse event; CxDx=Cycle X, Day X; hr=hours; EOI=end of infusion; EOT=end of treatment; PK=pharmacokinetic.

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

1 On days that both study drugs are administered, the surufatinib PK sample will be taken at the study site within 15 minutes before the start of the tislelizumab infusion.

2 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.

3 The predose surufatinib PK sample should be taken within 15 minutes prior to dosing.

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

5 EOI sample should be taken within 30 minutes after completing tislelizumab infusion.

6 Upon implementation of Protocol Amendment 5, EOT samples for Tislelizumab and Immunogenicity will no longer be required.

2 INTRODUCTION

2.1 Study Rationale

Recent development of novel classes of targeted therapeutics include 2 main types of targeted therapies, immune checkpoint inhibitors and small-molecule inhibitors, both of which have led to further development of personalized therapeutics in oncology.

One key immune checkpoint molecule is programmed cell death protein 1 (PD-1), which downregulate the magnitude of immune response and participate in peripheral tolerance. However, when upregulated, immune checkpoint signaling pathways such as PD-1/programmed death-ligand 1 (PD-L1), protect cancer cells from immune surveillance. Therefore, immune checkpoint molecules and their ligands are ideal anticancer treatment targets. It is known that anti-PD-1 and anti-PD-L1 antibodies upregulates Ras-Raf-MEK-ERK and PI3K-AKT signaling pathways in immune cells by blocking PD-1/PD-L1. As a result, anti-PD-1 or anti-PD-L1 treatments can restore T cells from an exhausted state and thus enhance tumor-killing activity.

Another important factor contributing to tumor growth is angiogenesis. As tumor cells require large amounts of oxygen and nutrients, they secrete proangiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor, and matrix metalloproteinase. As a result, the balance of proangiogenic factors and antiangiogenic factors is disturbed and multiple angiogenic pathways are activated. This abnormal angiogenesis leads to increased permeability of vessels, which allows tumor cells to leak into the circulation and leads to rapid tumor growth and metastasis.

There is increasing evidence that suggests the tumor microenvironment is closely related to the development and progression of cancer. Therefore, one effective strategy for inhibiting tumor growth is by targeting the tumor microenvironment via inhibition of angiogenesis while stimulating an immune response. The process of angiogenesis is influenced by inflammatory mediators such as cytokines and immune cells, which can affect the immune microenvironment. Antiangiogenic agents can stimulate the immune system and act synergistically with immune checkpoint inhibitors to enhance antitumor response.

Additionally, colony-stimulating factor-1 (CSF-1), a cell-surface tyrosine kinase inhibitor expressed by macrophages, promotes the infiltration and survival of immunosuppressive tumor-associated macrophages (TAMs) in the tumor microenvironment. High levels of TAMs in tumors are associated with poor prognostic outcomes. It has been proven that blocking CSF-1 receptors (CSF-1R) or blocking its kinase activity may reduce tumor burden. Consequently, by decreasing the immunosuppressive signals mediated by TAMs, some cells may upregulate PD-L1. Recent evidence suggests that targeting the CSF-1R pathway in combination with immune checkpoint inhibitors may activate an antitumor immune response more effectively.

Combining surufatinib with tislelizumab may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor activity compared to that of each individual agent alone.

2.2 Background

2.2.1 Target Indication and Population

CCI [redacted], enrollment to study 2020-012-GLOB1 was halted based upon the strategic evaluation of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. Currently enrolled patients who are deriving clinical benefit from treatment with surufatinib may continue to participate in the study as per the protocol. There is no planned interruption in the supply of surufatinib to clinical trial sites with active patients.

2.2.1.1 Colorectal Cancer

Colorectal cancer (CRC) is a major global health issue, with an estimated 1.8 million new cases and 881000 deaths in 2018 worldwide (Bray 2018). At the time of the design of this study, the established initial and second-line systemic therapy for metastatic CRC (mCRC) consisted 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-VEGF therapy was typically given with chemotherapy (eg, bevacizumab), and if the tumor is RAS oncoprotein (RAS) wild type, an anti-EGFR therapy (eg, cetuximab) was administered. In the small proportion of patients who are deficient mismatch repair/high levels of microsatellite instability in the metastatic setting (Koopman 2009), immunotherapy with nivolumab or pembrolizumab may be used (NCCN-CRC 2020, Morse 2020).

For patients who had disease progression after the first 2 lines of chemotherapy, the established options were either:

- Trifluridine/tipiracil (LONSURF®, TAS-102), an oral combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor (LONSURF USPI) or
- Regorafenib (STIVARGA®), a multikinase inhibitor with numerous in vitro targets that include vascular endothelial growth factor receptors (VEGFR) (STIVARGA USPI)

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. A recent estimation of the median overall survival (OS) for patients with mCRC, based on data from phase 3 clinical trials, observation studies, and registries, is 30 months (Grothey 2013, Mayer 2015). During this time, patients may receive several lines of therapy, with 1 or more "breaks." Both TAS-102 and regorafenib are approved in the third or greater (3+ line) line of therapy after progression on chemotherapy, and there are no approved treatments following progression on these agents. In this setting, the current options for patients with good performance status are to enter a clinical trial or to be rechallenged with prior chemotherapy (eg, 5-FU). Patients with poor performance status generally enter hospice care.

2.2.1.2 Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are rare tumors that arise from embryological neuroendocrine cells, and may produce polypeptide hormones. These tumors are broadly categorized into

well-differentiated, moderately differentiated, or poorly differentiated tumors (Sackstein 2018). Well-differentiated NETs that arise from the pancreas, which comprise approximately 10-11% of all NETs (Man 2018), are referred to as pancreatic neuroendocrine tumors (pNETs), whereas those arising from nonpancreatic tissues are referred to as extrapancreatic (ep)NET.

The prognosis of patients with NETs varies according to a number of different factors, such as location of primary and histological grade (Man 2018). The 5-year survival rate is 26.1% for patients with tumors of low grade versus 8.7% for those with undifferentiated high-grade tumors at diagnosis (Man 2018). The 5-year survival rate is 46.7% for patients with localized disease at diagnosis but 14.2% for those with distant metastasis (Man 2018).

A substantial proportion of patients with NETs are found to have either distant metastatic (22.0%) or regionally advanced disease (17.2%) at the time of diagnosis (Man 2018). This proportion is especially high for pNET patients (60.2%) (Halfdanarson 2008). Therefore, the majority of patients with pNET are not eligible for surgical resection, which is currently the best option for long-term survival.

Studies of the incidence of NETs based upon the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results database have consistently shown a marked increase in cases of NETs over the past 5 decades (Yao 2008, Dasari 2017, Sackstein 2018). The increased incidence of NETs was observed for all primary tumor sites, tumor stages, and tumor grades. Most of the growth is thought to be due to increased detection of early-stage tumors from improved techniques for detection (Hallet 2015).

Given the increasing incidence of NETs, the trend toward more advanced stage at diagnosis, and the poor prognosis, there is great need for effective treatment options to help improve survival of patients with regionally advanced or metastatic NETs.

Although approved therapies exist for the treatment of patients with locoregional advanced or metastatic NETs, they each have limitations. Treatment options for managing locoregional and metastatic NETs consist primarily of cytoreductive surgery and systemic antitumor therapy, including somatostatin analogs (SSAs), everolimus, sunitinib (limited to pNET only), lutetium 177-DOTATATE, interferon-alpha, and cytotoxic agents. However, because of the lack of clear efficacy of these available treatments, there is currently no evidence-based consensus supporting a specific sequence of regional versus systemic treatment regimen and no standardized treatment course for locoregional advanced or metastatic NETs (Shah 2018, NCCN-NET 2020).

Thus, there remains an unmet medical need for new medication that is safe and effective for patients with refractory NETs who have progressed through, or were intolerant of, the currently available systemic therapies.

2.2.1.3 Small-Cell Lung Cancer

Neuroendocrine tumors account for approximately 20% of lung cancers; approximately 14% are small-cell lung cancer (SCLC) (NCCN-SCLC 2020). In 2019, there were an estimated 29660 new cases in the United States (US) (Siegel 2019, NCCN-SCLC 2020). SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases (NCCN-SCLC 2020). Most patients with SCLC present with metastases. SCLC is highly sensitive to initial chemotherapy; however, most patients will succumb to disease recurrence.

Systemic therapy alone can palliate symptoms and prolong survival; however, long-term survival is uncommon (NCCN-SCLC 2020).

Platinum plus etoposide had been the standard treatment for patients with extensive stage SCLC; however, recently a randomized phase 3 trial demonstrated improved survival with the addition of atezolizumab (PD-L1 mAb) in combination with platinum and etoposide compared to chemotherapy alone. Median OS was significantly longer with the addition of atezolizumab than without, 12.3 months and 10.3 months, respectively (95% confidence interval [CI], 10.8-15.9 and 9.3-11.3, respectively) (Horn 2018). Given the short life expectancy despite approved therapies for the treatment of SCLC, there remains an unmet medical need for additional effective therapies.

2.2.1.4 Gastric Adenocarcinoma

Gastric cancer incidence and mortality have decreased in the US over the past several decades. However, gastric cancer ramines a major global health problem, with more than 1 million cases diagnoses in 2018, and causing more than 782000 deaths (NCCN-Gastric 2020).

First-line systemic therapy for patients with locally advanced or metastatic gastric cancer provides symptom palliation and improved survival. Preferred regimens included a fluoropyrimidine combined with a platinum agent (NCCN-Gastric 2020). Patients with HER2 over-expressing tumors should have trastuzumab added to their treatment regimen (Bang 2010). Second-line therapy should be tailored to patients' prior therapy and performance status. Options for second-line therapy include the biologic ramucirumab (VEGFR-2 mAb) alone or in combination with paclitaxel or additional cytotoxic chemotherapy (Fuchs 2014, Wilke 2014). Immunotherapy options include pembrolizumab in patients with MSI-H/dMMR tumors as second-line therapy or as third-line therapy for tumor-expressing PD-L1 >1% (NCCN-Gastric 2020). However, the landscape for immunotherapy in gastric adenocarcinoma treatment is evolving rapidly. Emerging data from the Checkmate 649 trial has reported an overall survival advantage for patients treated with nivolumab in combination with cytotoxic chemotherapy versus chemotherapy alone in the first-line treatment of patients with metastatic gastric cancer, esophageal junction cancer, or esophageal adenocarcinoma whose tumors express PD-L1 with a combined positive score ≥5 (BMS 2020).

Despite multiple therapies options available to patients with gastric cancer, the vast majority will succumb to their disease. Therefore, there remains an unmet need for additional effective therapies.

2.2.1.5 Soft Tissue Sarcoma

Soft tissue sarcomas (STS) are malignant tumors that arise from mesenchymal tissue with heterogeneous differentiation. International incidence rates range from 1.8 to 5 cases per 100000 individuals per year (Wibmer 2010). In the year 2019, there will be an estimated 12750 new cases and 5270 deaths from STS in the United States (American Cancer Society 2019). Soft tissue sarcomas are heterogeneous, with more than 100 different subtypes identified by the World Health Organization and are classified according to tissue of origin (Bleloch 2017).

For patients with incurable disease not amenable to locoregional therapies, first-line systemic treatment consists of cytotoxic chemotherapy. Doxorubicin has been considered the standard systemic therapy in the management of metastatic sarcomas for several years (Bramwell 2003, Verma 2008). Gemcitabine and docetaxel were found to have similar outcomes as doxorubicin

alone (Seddon 2017). Other drugs that may have clinical activity as single agents are ifosfamide and paclitaxel (depending on histology) (Lorigan 2007, Nielsen 1998, Maki 2007, Okuno 2003).

Since 2012, three drugs have been approved for the treatment of soft tissue sarcomas after failure of a first-line chemotherapy: pazopanib (VOTRIENT®) for all soft tissue sarcomas except adipocytic subtypes, eribulin for liposarcoma, and trabectedin for leiomyosarcoma and liposarcoma (van der Graaf 2012, Schoffski 2016, Patel 2019). Despite new agents, treatments for advanced STS remain palliative only and remains an unmet medical need.

Pazopanib is a multitargeted, oral, small molecule inhibitor of several tyrosine kinases including VEGFR 1, 2, and 3; platelet-derived growth factor receptor α and β; and fibroblast growth factor receptor-1 and -3 (VOTRIENT USPI). Pazopanib was approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of patients with soft tissue sarcomas, excluding adipocytic subtypes, who have received previous chemotherapy, based on results of the phase 3 randomized, double-blind PALETTE study (NCT00753688) that compared pazopanib to placebo in 369 patients (van der Graaf 2012). The median progression-free survival (PFS) was 4.6 months for patients who received pazopanib versus 1.6 months for patients who received placebo. However, the OS difference was not statistically significant.

Recently, checkpoint inhibitors have been studied in STSs with limited success in select subtypes. The SARC028 trial demonstrated single-agent activity of the PD-1 mAb pembrolizumab in undifferentiated pleomorphic sarcoma or dedifferentiated liposarcoma, with an objective response rate of 40% and 20%, respectively (Tawbi 2017). In Alliance trial A091401, limited efficacy of the single agent PD-1 mAb nivolumab was observed; however, the combination of nivolumab and ipilimumab (CTLA-4 mAb) demonstrated promising efficacy in sarcoma subtypes of undifferentiated pleomorphic sarcoma, leiomyosarcoma, myxofibrosarcoma, and angiosarcoma (D'Angelo 2018).

Based upon the premise that VEGF promotes an immunosuppressive microenvironment and contributes to immune checkpoint inhibitor resistance, a single-arm, phase 2 study of pembrolizumab in combination with the VEGFR kinase inhibitor axitinib reported encouraging activity in the subset of patients with alveolar soft part sarcoma (ASPS) with an overall response rate of 54.5% in 11 evaluable patients (Wilky 20199).

2.2.1.6 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is a highly aggressive cancer with a poor prognosis, having a median survival less than 6 months and 10-year survival rates less than 5% (Wendler 2016). Although ATC comprises less than 2% of thyroid cancers, it is estimated to be the cause of more than 50% of annual thyroid cancer-related mortality (Smallridge 2012).

The current standard treatment of ATC includes surgical debulking, external beam radiation therapy, and chemotherapy. However, due to its aggressive characteristics, surgery does not achieve satisfactory outcomes, and ATC acquires chemotherapy resistance easily. Treatments for ATC remain palliative, with cytotoxic chemotherapies generally recommended despite no improvement in survival (Ferrari 2020).

Recent studies have shown that 20% to 50% of ATCs harbor activating B-Raf kinase V600E mutations ($BRAF^{V600E}$), which has shown to be a molecular driver associated with ATC tumorigenesis. In a phase 2, open-label trial, 16 ATC patients with $BRAF^{V600E}$ mutations were

treated with a combination of a B-Raf kinase (BRAF) inhibitor (dabrafenib) and an MEK inhibitor (trametinib) (NCT02034110). Patients achieved an overall response rate of 69% (95% CI: 46.9, 86.6) and an estimated 12-month overall survival rate of 80% (Subbaiah 2018). This trial demonstrated that the combination of dabrafenib + trametinib has robust clinical activity in $BRAF^{V600E}$–mutant ATC; in 2018, the FDA approved the treatment combination for this patient population based on these results.

Despite recent advancements in treatment for $BRAF^{V600E}$-mutant patients, ATC remains a rare and aggressive disease. There remains a high unmet medical need for effective therapies of patients with BRAF wild-type ATC and patients with $BRAF^{V600E}$-mutant ATC following progression on dabrafenib + trametinib.

Investigation of the combination of tislelizumab and surufatinib are desirable based upon the following facts:

- PD-1 inhibitors combined with a VEGF tyrosine kinase inhibitor (lenvatinib) have demonstrated activity in ATC (Dierks 2021).
- ATCs are highly vascular tumors.
- ATCs are associated with enhanced levels of TAMs in the tumor microenvironment (Caillou 2011), which are thought to be a mechanism of resistance to immunotherapy alone.

2.2.2 Study Treatments

Study drug is defined as a single therapeutic agent (eg, surufatinib or tislelizumab). Study treatment is defined as a combination of therapeutic agents (eg, surufatinib in combination with tislelizumab).

2.2.2.1 Surufatinib

Surufatinib (also known as HMPL-012) is a novel tyrosine kinase inhibitor developed by HUTCHMED Limited that inhibits VEGFR 1, 2, and 3, as well as fibroblast growth factor receptor (FGFR) 1, which results in inhibition of angiogenesis. In addition, surufatinib inhibits signaling via CSF-1R, which is thought to down-regulate TAMs, thus promoting antitumor immunity.

2.2.2.2 Tislelizumab

Tislelizumab is a humanized immunoglobulin G4 (IgG4)-variant anti–PD-1 monoclonal antibody, developed by BeiGene, specifically engineered to minimize binding to Fc-gamma-receptor immunoglobulin (FcγR). In preclinical studies, binding to FcγR on macrophages has been shown to compromise the antitumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T-effector cells (Zhang 2018).

2.2.2.3 Justification of Dosing Strategy

Surufatinib Dosing Strategy

The optimal dose and dosing schedule for single agent surufatinib was determined in 2 phase 1 studies: 1 conducted in China and the other conducted in the US. A food effect study was also conducted to guide dosing in clinical trials.

In these early-phase studies, doses of 50 mg once daily (QD) to 350 mg QD as well as 125 mg twice a day (BID) and 150 mg BID were explored. None of the dose cohorts studied reached the maximum tolerated dose (MTD). However, drug exposure in the 350-mg QD group patients was no higher than that in the 300 mg QD group patients, therefore, increasing the dose was determined not likely to further increase the drug concentration in blood. Based on the clinical safety, efficacy, and pharmacokinetic (PK) data, the recommended phase 2 dose (RP2D) of surufatinib was determined to be 300 mg QD.

Surufatinib dosed at 300 mg QD has further demonstrated statistically significant and clinically meaningful efficacy in 2 completed phase 3 randomized, double-blind, placebo-controlled studies in patients with advanced epNET (SANET-ep) and patients with advanced pNET (SANET-p). Both studies were stopped early per Safety Review Committee (SRC) recommendation after meeting the primary endpoint at the interim analysis. For more information, please refer to the surufatinib Investigator's Brochure (IB).

In an open-label, phase 1 dose-escalation and dose-expansion study of surufatinib and toripalimab, a monoclonal humanized IgG4 PD-1 antibody (NCT03879057), surufatinib doses of 200 mg QD, 300 mg QD, and 250 mg QD were studied along with a fixed dose of toripalimab to determine the MTD and/or RP2D (Lu 2020).

The RP2D was determined to be surufatinib 250 mg daily plus toripalimab. One patient at 300 mg experienced dose-limiting toxicity of Grade 3 hyperthyroidism. Four of 8 evaluable patients at RP2D achieved partial response (PR), and the objective response rate (ORR) and disease control rate (DCR) were 50% and 100%, respectively. Additionally, there were no treatment-related fatal serious adverse events (SAEs).

Preliminary PK analysis showed surufatinib exposure at steady state increased dose proportionally, and individual PK profiles were comparable to those of surufatinib or toripalimab from previous monotherapy trials.

Surufatinib plus toripalimab was well tolerated with no unexpected safety signals observed, and showed encouraging antitumor activity in patients with advanced solid tumors (Lu 2020).

Overall, the collective safety, efficacy, PK, and exploratory exposure-response results from single-agent and combination studies support a starting dose of 250 mg QD. Alternate dose levels of 200 mg QD and 300 mg QD will allow for potential reduction or escalation based on safety and tolerability.

Tislelizumab Dosing Strategy

The clinical fixed dose of tislelizumab of 200 mg intravenously (IV), Q3W was selected based on comparable safety and efficacy profiles between 2 and 5 mg/kg in Study BGBA317_Study_001. Rates of treatment-related adverse events (AEs) and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg Q2W and Q3W were comparable, suggesting no clear dose dependence across the regimens. Additionally, PK data also show no relationship between exposure and treatment-emergent immune-mediated adverse events (imAEs).

ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg Q2W ranged between 10% and 15%, compared with a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg Q3W.

Clearance of tislelizumab was not dependent of body weight, and the observed serum exposure of a 200-mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses. Therefore,

clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg Q3W.

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. These findings support a 200 mg Q3W dose regimen for pivotal studies. Please refer to the tislelizumab IB for additional details.

In conclusion, the observed clinical activity in patients with advanced tumors coupled with a manageable safety profile and supportive data support the tislelizumab dose of 200 mg IV, Q3W as the recommended dose for pivotal studies, and this dose will be used for combination dosing in this study.

2.2.3 Supportive Nonclinical Data

Please refer to the surufatinib or tislelizumab IBs for additional details regarding nonclinical studies of surufatinib and tislelizumab, respectively.

2.2.3.1 Pharmacology

Surufatinib

Surufatinib mainly targets on VEGFR 1, 2, and 3, FGFR1, and CSF-1R. By using a [^{32}P-ATP] incorporation assay, the IC_{50} of surufatinib on VEGFR 1, 2, and 3 (also known as Flt1, KDR, and Flt4) were found to be 2 nM, 24 nM, and 1 nM, respectively. The IC_{50} on the kinase activity of FGFR1, 2, and 3 was determined to be 15 nM, 236 nM and 181 nM, respectively. The IC_{50} for CSF-1R (FMS) was 4 nM. In vitro assays demonstrated that surufatinib inhibited VEGFR activity and suppressed phosphorylation of VEGFR with an IC_{50} of 2 nM and blocked cell proliferation of VEGF-dependent human umbilical vein endothelial cell (HUVEC) and VEGF-induced HUVEC tube formation. In safety pharmacology studies, the results showed that surufatinib had a low risk on the cardiovascular, respiratory, and central nervous systems.

Tislelizumab

Tislelizumab (also known as BGBA317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against programmed cell death protein-1 (PD-1). Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D]=0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2, thus inhibiting PD-1-mediated negative signaling in T cells. Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models.

2.2.3.2 Toxicology

Surufatinib

In single-dose toxicology studies in rats and dogs, no mortality occurred up to the highest dose tested (2000 mg/kg), which indicated a good tolerability. Repeat-dose toxicology studies in rats and dogs identified target organs that included the hepatobiliary system, kidney, immune system, hematopoietic system, skeletal system, pancreas, adrenal glands, uterus, and corpus luteum. All effects were fully or partially reversible after a 4-week recovery period apart from effects on the

skeletal system (broken teeth). In a fertility and early embryonic development study in rats, female fertility was affected. In an embryo-fetal developmental study in rats, embryotoxic and teratogenic effects were observed, consisting of fetal external, visceral, and skeletal malformations. In an embryo-fetal study in rabbits, effects on embryo formation were observed resulting in retarded embryonic development. Surufatinib was not genotoxic based on a standard battery of in vitro and in vivo studies and was also not phototoxic in vivo.

Tislelizumab

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 no-observed-adverse-effect limit 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.

2.2.4 Supportive Clinical Data

2.2.4.1 Clinical Pharmacology and Pharmacokinetics

Surufatinib

In Chinese patients with cancer, surufatinib was absorbed rapidly, with the concentration reaching maximum level after 1.0 to 2.0 hours of dosing. Mean plasma half-life ranging from 14.9 hours to 20.2 hours was observed. Following multiple doses of surufatinib once daily (QD), the plasma surufatinib concentration reached steady state 14 days after dosing, with exposure accumulating 1.2- to 2.4-fold at steady state compared to Day 1 (2009-012-00CH1 and 2014-012-00CH1). Preliminary PK results from the US patient population (2015-012-00US1 [ongoing]) showed surufatinib exposure, in general, increased proportionally with an increasing dose from 50 mg to 400 mg QD. There were no meaningful differences in surufatinib exposure between Chinese and US patients (Kauh 2020).

A study for a single oral (PO) dose of surufatinib 250 mg under fasting or fed conditions indicated that the absorption extent of surufatinib was not affected by food intake, but the absorption rate was affected, as demonstrated by the significant difference in time to maximum concentration.

Tislelizumab

Population PK analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who received doses ranging from 0.5 to 10 mg/kg once every 2 or 3 weeks. The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume (V_c), and peripheral volumes (V_2, V_3) were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate interindividual

variability in CL (32.2%), V_c (16.7%), V_2 (56.6%), and V_3 (94.2%). Consistent with other therapeutic IgG monoclonal antibodies, the volume of distribution at steady state was 5.238 L and the terminal half-life was approximately 25.5 days (Deng 2012, Dirks 2010, Keizer 2010, Ryman 2017).

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) performance status, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show a 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.

2.2.4.2 Clinical Safety

Surufatinib

As of 11 February 2021, the safety database includes 792 patients who received at least 1 dose of surufatinib as monotherapy in completed or ongoing studies.

Of the 792 patients who received at least 1 dose of surufatinib as monotherapy, 781 patients (98.6%) experienced treatment-emergent adverse events (TEAEs) and 757 patients (95.6%) had at least 1 treatment-related TEAE. The most commonly reported treatment-related TEAEs included proteinuria, hypertension, diarrhoea, blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood thyroid stimulating hormone increased, hypertriglyceridaemia, and occult blood positive. A total of 568 patients (71.7%) reported TEAEs of Grade ≥3 and 509 patients (64.3%) had at least 1 treatment-related TEAE Grade ≥3. Additionally, approximately one-third of patients experienced an SAE. A total of 142 patients (17.9%) reported TEAEs leading to study drug discontinuation; 265 patients (33.5%) and 379 patients (47.9%) had TEAEs leading to dose reduction and dose interruption, respectively.

Please refer to the surufatinib IB for the most up to date safety information, and additional details regarding adverse events reported in ongoing and completed studies of surufatinib.

As of 11 February 2021, the safety database includes 163 patients who received surufatinib in combination with another therapeutic agent during completed or ongoing studies.

Of 163 patients who received at least 1 dose of surufatinib in a combination regimen, 158 patients (96.9%) experienced TEAEs and 153 patients (93.9%) had at least 1 treatment-related TEAE. A total of 76 patients (46.6%) reported TEAEs of Grade ≥3 and 58 patients (35.6%) had at least 1 treatment--related TEAE of Grade ≥3. A total of 64 patients (39.3%) reported TEAEs leading to dose interruption and 52 patients (31.9%) reported treatment-related TEAEs leading to dose interruption.

Tislelizumab

As of 20 May 2020, a pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separate from combination therapy. There were 1181 patients treated with monotherapy in 5 solid tumor studies.

Of the 1181 patients, 96.4% experienced at least 1 TEAE and 788 patients (66.7%) experienced at least 1 treatment-related TEAE. TEAEs ≥Grade 3 were reported by 552 patients (46.7%). One hundred sixty-seven patients (14.1%) experienced a ≥Grade 3 treatment-related TEAE. Serious TEAEs were reported in 415 patients (35.1%), while 107 patients (9.1%) experienced a serious treatment-related TEAE. Seventy-four patients (6.3%) died as a result of a TEAE.

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are common. Of 1181 patients, 45 (3.8%) experienced at least 1 infusion-related reaction of any grade. Please refer to the tislelizumab IB for the most up to date, and additional details regarding clinical safety in ongoing and completed studies of tislelizumab.

Immune-Mediated Adverse Events

Anti-PD-1 therapies are known to cause imAEs in some patients and therefore have been defined as AEs of special interest (AESI) in tislelizumab clinical studies, and as such, are being reported expeditiously and monitored closely.

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. imAEs 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.

imAEs of hepatitis, pneumonitis, colitis, endocrinopathies, myocarditis, diabetes, and serious skin adverse reactions have been identified as risks for tislelizumab.

Please refer to the tislelizumab IB for additional details regarding clinical safety in ongoing and completed studies of tislelizumab.

2.2.4.3 Clinical Efficacy

Surufatinib

Surufatinib has demonstrated statistically significant and clinically meaningful efficacy in 2 completed phase 3 randomized, double-blind, placebo-controlled studies in China in patients with advanced epNET (SANET-ep) and patients with advanced pNET (SANET-p) and has shown promising antitumor activity in the US (Study 2015-012-00US1). The SANET-ep study met its primary endpoint at the planned interim analysis, with significantly improved PFS in surufatinib--treated patients compared with placebo-treated patients (median PFS of 9.2 months in surufatinib--treated patients versus 3.8 months in placebo-treated patients; hazard ratio [HR] 0.334; $p<0.0001$). Similarly, surufatinib-treated patients in the SANET-p study showed a statistically significant improvement in PFS compared with placebo-treated patients (median PFS of 10.9 months in surufatinib-treated patients versus 3.7 months in placebo-treated patients; HR 0.491; $p=0.0011$). In addition to the primary PFS endpoint, SANET-ep and SANET-p demonstrated meaningful improvements in other important efficacy measures such as ORR, DCR, duration of response (DoR), and time to response (TTR).

In Study 2015-012-00US1, patients with biliary tract cancer, epNET, pNET, and STS were enrolled. Based on interim analysis for epNET and pNET cohorts, the PFS rate at 11 months for patients with epNETs (16 patients) was 51.1% (95% CI: 12.8, 80.3); and 57.4% (95% CI: 28.7, 78.2) for patients with pNETs (16 patients). The observed median PFS was 11.50 months (95% CI: 6.47, 11.50), and 15.18 months, (95% CI: 5.19, NR), for patients with epNETs and pNETs, respectively. An ORR of 6.3% was observed for patients with epNETs, and 18.8% for patients with pNETs. A disease control rate of 90.6% (95% CI: 75.0, 98.0) was observed for all NET patients (93.8% epNET; 87.5% pNET). All patients had previously received everolimus and/or sunitinib (Paulson 2021). Enrollment to the STS cohort is ongoing, and no analysis has been performed to date.

Tislelizumab

Efficacy data are available from 9 clinical studies, including 5 monotherapy and 4 combination studies. Preliminary antitumor activity has been observed across multiple tumor subtypes. Please refer to the tislelizumab IB for current details regarding efficacy of tislelizumab.

2.2.5 Benefit:Risk Assessment

2.2.5.1 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 surufatinib. Section 7.1.4 provides detailed guidance on dose modifications for AESI including liver function impairment, hypertension, proteinuria, and hemorrhage. General dosing guidance to protect patients is included in Section 6.2.2. Thus, the identified and potential risks of treatment with surufatinib and tislelizumab are appropriately mitigated by measures in the protocol. For the most up-to-date summary of potential risks and mitigation strategies, please refer the surufatinib and tislelizumab IBs, respectively.

2.2.5.2 Benefit Assessment

Surufatinib

Surufatinib has demonstrated statistically significant and clinically meaningful efficacy in 2 completed phase 3 randomized, double-blind, placebo-controlled studies in patients with advanced epNET (SANET-ep) and patients with advanced pNET (SANET-p). Additionally, data from the 2015-012-00US1 trial confirms that surufatinib also shows antitumor activity in a western patient population.

Tislelizumab

Preliminary data from ongoing phase 1 and phase 2 trials of single agent tislelizumab suggested that there is antitumor activity across a variety of tumor types. Tislelizumab has also been shown to have antitumor 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, antitumor activity has been seen in, but not limited to, cholangiocarcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, bladder cancer, and SCLC.

2.2.5.3 Overall Benefit:Risk Conclusion

There remains an unmet need for patients with advanced CRC, NETs, SCLC, gastric cancer, STS, and ATC. Evidence to date suggests that both surufatinib and tislelizumab may potentially be efficacious in the treatment of various cancers, including those in this proposed trial.

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

The potential drug-drug interaction between surufatinib, a small molecule drug product, and tislelizumab, a monoclonal antibody, is expected to be very low. The tolerability of tyrosine kinase inhibitor and anti-PD-1 therapy combination has been demonstrated in other combination trials (eg, lenvatinib plus pembrolizumab in patients with advanced endometrial cancer [Makker 2020] and avelumab plus axitinib in patients with advanced hepatocellular carcinoma [Kudo 2019]). The toxicity profile of each therapy appeared consistent with their monotherapy profiles; thus, no severe overlapping toxicity is expected with surufatinib in combination with tislelizumab.

Combining surufatinib with tislelizumab may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor 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 malignancies, the lack of effective alternative treatments, and the efficacy seen in previous and ongoing clinical trials, the overall benefit:risk assessment supports the continued administration of surufatinib and tislelizumab to patients with advanced cancer as an investigational treatment.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are summarized in Table 3.

Table 3 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	Part 1 To evaluate the safety and tolerability of surufatinib, thereby determining the RP2D and/or the MTD of surufatinib in combination with tislelizumab	Part 1 Safety, including DLTs, TEAEs, SAEs, AEs leading to discontinuation, ECGs, clinical laboratory abnormalities, and vital signs
	Part 2 To evaluate the ORR as assessed by the investigator in patients with advanced solid tumors when treated with surufatinib in combination with tislelizumab according to RECIST v1.1	Part 2 ORR at 12 weeks
Secondary	Part 1 • To evaluate the antitumor activity in patients with advanced solid tumors when treated with surufatinib in combination with tislelizumab according to RECIST v1.1 • To characterize the PK and immunogenicity of tislelizumab and surufatinib in combination	Part 1 • ORR, PFS, DCR, CBR, DoR, TTR • Concentrations of surufatinib in plasma and tislelizumab in serum • Incidence of ADA to tislelizumab
	Part 2 • To evaluate further anticancer effects of surufatinib in combination with tislelizumab • To characterize the safety and tolerability of surufatinib in combination with tislelizumab • To characterize the PK and immunogenicity of tislelizumab and surufatinib in combination	Part 2 • PFS, DCR, CBR, DoR, TTR • OS: Cohorts A and F • Safety, including TEAEs, SAEs, AEs leading to discontinuation, ECGs, clinical laboratory abnormalities, and study drug discontinuation due to AEs • Concentrations of surufatinib in plasma and tislelizumab in serum • Incidence of ADA to tislelizumab
Exploratory	Part 2 • To explore the distribution of PD-L1 expression and potential association between PD-L1 expression and tislelizumab treatment effect • Cohort F: To explore the influence of gene abnormalities on safety, and efficacy	Part 2 • PD-L1 expression • Cohort F: Changes from baseline in tumor markers, correlation with drug exposure, and association with efficacy and safety parameters

ADA=antidrug antibodies; AE=adverse event; CBR=clinical benefit rate; CRC=colorectal cancer; DCR=disease control rate; DLT=dose-limiting toxicity; DoR=duration of response; ECG=electrocardiogram; MTD=maximum tolerated dose; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PK=pharmacokinetic(s); RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; RP2D=recommended phase 2 dose; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TTR=time to response.

4 STUDY DESIGN

The study design schema is presented in Figure 1.

4.1 Overall Design

This open-label, phase 1b/2 study of surufatinib in combination with tislelizumab will evaluate the safety, tolerability, PK, and efficacy in patients with advanced solid tumors. The study consists of 2 parts: dose escalation (Part 1) and dose expansion (Part 2). Part 1 will be conducted to determine the RP2D and/or the MTD of surufatinib in combination with tislelizumab in patients with advanced or metastatic solid tumors who have progressed on or are intolerant of standard therapies. Part 2 will be an open-label, multicohort design to evaluate the antitumor activity of surufatinib in combination with tislelizumab in patients with specific types of advanced or metastatic solid tumors. Patients will receive the RP2D (300 mg surufatinib PO, QD + 200 mg tislelizumab, IV, Q3W) determined in Part 1 of this study.

4.1.1 Part 1 (Dose Escalation)

Patients with advanced or metastatic solid tumors of any kind who have progressed on or are intolerant of standard therapies will be enrolled into a dose-escalation phase using a 3+3 design. A total of 6 to 12 patients will be enrolled into this portion of the study.

2 dose levels will be evaluated during this phase of the study (Table 4).Dose level 1: 250 mg surufatinib, PO, QD + 200 mg tislelizumab, IV, Q3W

- Dose level 2: 300 mg surufatinib, PO, QD + 200 mg tislelizumab, IV, Q3W

A minimum of 3 patients will be enrolled at the starting dose (dose level 1).

- If no patients experience a dose-limiting toxicity (DLT) (Section 4.1.2), then the dose will be escalated to dose level 2.
- If one of the 3 patients at dose level 1 experiences a DLT, then 3 additional patients will be enrolled to dose level 1.
  - If one of 6 patients experience a DLT, then the dose will be escalated to dose level 2.
  - If two of 6 patients experience a DLT, then the dose will be deescalated to dose level -1, (200 mg surufatinib, PO, QD + 200 mg tislelizumab, IV, Q3W).
- If >33% of patients at any dose level experience a DLT, then the dose escalation will be halted.

Any patient who, in the opinion of the investigator, is deriving clinical benefit from the study treatment, may continue treatment beyond Cycle 1 until disease progression, unacceptable toxicity, withdrawal of consent, new anticancer therapy, lost to follow-up, or death.

Table 4 Dose Levels

Dose Level	Dosage	
	Surufatinib	**Tislelizumab**
-1	200 mg PO, QD	200 mg IV, Q3W
1	250 mg PO, QD	200 mg IV, Q3W
2	300 mg PO, QD	200 mg IV, Q3W

IV=intravenous; PO=orally; Q3W=every 3 weeks; QD=once daily.

4.1.2 Assessment of Dose-limiting Toxicities

If patients do not meet the below conditions, new patients will be enrolled as replacements to ensure there are at least 3 DLT-evaluable patients in each dose group.

AEs will be assessed per the DLT criteria shown below during the 21-day DLT assessment window, which begins on the first day of the administration of the study treatment. Patients will be considered evaluable for DLTs if they meet the following criteria:

- Received ≥85% of scheduled surufatinib and ≥67% (approximately two-thirds) of scheduled tislelizumab administration during the DLT assessment window and/or
- Experienced a DLT

Patients will be considered not evaluable for DLTs if any of the following occur during the DLT assessment window:

- They were withdrawn from the study.
- They did not receive ≥85% of scheduled surufatinib and ≥67% (approximately two-thirds) of scheduled tislelizumab drug administration.
- They received prophylactic supportive care that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition).
- They have taken a strong inhibitor or inducer of enzyme cytochrome P450, family 3, subfamily A4 (CYP3A4) (Appendix 3) as the exposure to surufatinib may be impacted. Patients who are not DLT evaluable will be replaced.

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.

According to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 evaluation criteria, the following AEs that occur within 21 days (DLT observation period) after the first drug administration of each cohort shall be defined as a DLT once they are determined by the investigator to be related to surufatinib and/or tislelizumab:

1. Nonhematologic toxicities
    a. Grade 3 or higher nonhematologic toxicity will be considered DLTs, except for the following conditions:
        i. Grade 3 fatigue lasting <7 days.
        ii. Grade 3 rash that returns to baseline or ≤Grade 1 with appropriate supportive treatment within 7 days.

iii. Grade 3 hypertension downgraded to ≤Grade 1 within 7 days with appropriate supportive therapy.
iv. Grade 3 endocrinopathy that is adequately controlled by hormonal replacement, does not require hospitalization, AND resolves to ≤Grade 1 within 7 days.
v. Grade 3 or higher amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis.
vi. Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
vii. Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.

1. Hematologic toxicities

b. Grade 3 or higher febrile neutropenia (neutrophil count $<1.0\times10^9$/L, accompanied with a single body temperature measurement of ≥38.3°C [101°F] or ≥38°C [100.4°F] persisting for 1 hour)
c. Grade 4 neutropenia lasting >7 days
d. Grade 4 thrombocytopenia lasting >7 days
e. Grade 3 thrombocytopenia accompanied with severe bleeding
f. Grade 4 anemia

Any life-threatening complication or abnormality not covered in the NCI CTCAE v5.0.

When counting abnormal laboratory results at the patient level, the most severe toxicity during study treatment will be chosen.

4.1.2.1 Recommended Phase 2 Dose and Maximum Tolerated Dose

As of 02 September 2021, all patients enrolled in the Part 1 dose escalation phase of this study completed the DLT assessment period. The SRC convened and determined the RP2D to be used for Part 2 dose expansion to be:

300 mg surufatinib, PO, QD + 200 mg tislelizumab, IV, Q3W

This determination was made based on review of the available cumulative safety data of all enrolled patients (n=12; dose level 1: 6, dose level 2: 6), and the observation of 2 DLTs (1 in each dose level). In dose level 1, one patient experienced a DLT of Grade 3 fatigue. In dose level 2, one patient experienced a DLT of Grade 3 dehydration.

MTD was not reached.

Overall treatment with the combination of surufatinib and tislelizumab was well tolerated across both dose levels.

4.1.3 Part 2 (Dose Expansion)

The dose -expansion portion of this study will enroll approximately 110 patients with various types of advanced or metastatic solid tumors across 8 cohorts (Table 5) to evaluate the antitumor activity of surufatinib in combination with tislelizumab. Patients will be enrolled to one of the cohorts

depending on their type of cancer. Each patient will be treated until disease progression, unacceptable toxicity, withdrawal of consent, new anticancer therapy, lost to follow-up, or death.

Any patient who, in the opinion of the investigator, is deriving clinical benefit from the study treatment, may continue treatment after discussion and approval from the sponsor.

CCI , enrollment to study 2020-012-GLOB1 was halted based upon the strategic evaluation of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor.

The number of patients enrolled in each cohort at the time of Protocol Amendment 4 are shown in Table 5.

At the time of Protocol Amendment 5, CCI The study will be terminated either 90 days after the last patient has received tislelizumab, or the point at which all imAEs have resolved or are no longer being followed, whichever occurs earlier.

Table 5 Dose Expansion Cohorts

Disease Cohort	Planned Number of Patients	Actual Number of Patients as of Amendment 4
Cohort A: CRC	15	15
Cohort B: NET		
Cohort B1: Thoracic NETs	10	10
Cohort B2: GEP NETs	20	20
Cohort C: SCLC	15	15
Cohort D: GC	15	3
Cohort E: STS		
Cohort E1: ASPS	10	0
Cohort E2: UPS	10	9
Cohort F: ATC	15	3

ASPS=alveolar soft part sarcoma; ATC=anaplastic thyroid cancer; CRC=colorectal cancer; GC=gastric cancer; GEP=gastroenteropancreatic; NET=neuroendocrine tumor; SCLC=small-cell lung cancer; STS=soft-tissue sarcoma; UPS=undifferentiated pleomorphic sarcoma.

Patients in Cohort A must have locally advanced or mCRC that is microsatellite stable and was previously treated with at least 3 prior lines of therapy.

Patients in Cohort B, with thoracic or gastroenteropancreatic (GEP) NET, must have progressive, locally advanced or metastatic, low-to-intermediate grade (Grade 1 or Grade 2), well-differentiated NETs that have progressed on at least 1 line of standard therapy.

Patients in Cohort C must have locally advanced or metastatic small-cell lung cancer (SCLC) that was previously progressed on first-line chemotherapy.

Patients in Cohort D must have microsatellite stable, PD-L1 ≥5%, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction, and previously been treated with at least 2 lines of standard therapy.

Patients in Cohort E, with ASPS or undifferentiated pleomorphic sarcoma (UPS), must have progressed on, or had discontinued due to intolerable toxicity to, at least 1 line of standard therapy or be unsuitable for standard frontline cytotoxic chemotherapy.

Patients in Cohort F must have locally advanced or metastatic ATC. Patients who have a BRAFV600E mutation must have previously been treated with 1 line of systemic therapy (not including radiation therapy) with a BRAF-targeted therapy.

4.2 Design Rationale

This open-label, dose-escalation, dose-expansion design was chosen to determine the RP2D and/or the MTD for the combination of surufatinib and tislelizumab in patients with solid tumors, and to explore the preliminary antitumor activity of the combination in various selected solid tumors.

While both surufatinib and tislelizumab have been studied extensively as single agents in various tumor types, they have not been studied in combination previously. It is hypothesized that the combination may improve response rates and duration of treatment, while maintaining a tolerable safety profile.

The dose escalation and expansion design allows for management of known and potential risks, while investigating the possible benefits (ie, antitumor activity) of the combination in various solid tumors. For further detail on the risk/benefit assessment, refer to Section 2.2.5.

5 POPULATION

5.1 Recruitment

To enroll 6–12 patients in Part 1, approximately 4-6 sites will be opened for patient recruitment.

To enroll approximately 110 patients into the 8 indication-specific cohorts in Part 2, sites in the US and Europe will be opened for patient recruitment.

CCI [redacted], enrollment to study 2020-012-GLOB1 was halted based upon the strategic evaluation of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor. This change was not based on any concern for patient safety or efficacy relative to surufatinib treatment. Currently enrolled patients who were deriving clinical benefit from treatment with surufatinib were able to continue to participate in the study as per the protocol.

At the time of Protocol Amendment 5, CCI [redacted] The study will be terminated either 90 days after the last patient has received tislelizumab, or the point at which all imAEs have resolved or are no longer being followed, whichever occurs earlier.

5.2 Definitions

Patients officially enter the screening period following provision of informed consent either directly or via a legally acceptable representative.

Patients who withdraw from the study after signing the informed consent form (ICF) and before enrollment will be considered screen failures. A screen failure is a consented patient who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to receiving treatment. Patients who failed the original screening may be screened again using their original patient identification number as assigned by interactive web response system (IWRS). A patient may only be rescreened once and is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

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

5.3 Inclusion Criteria

To be eligible for enrollment in this study, each individual must satisfy all of the following criteria:

1. Willing and able to provide informed consent signed by study patient or legally acceptable representative, as specified by health authorities and institutional guidelines
2. ≥18 years of age
3. Part 1: have evaluable lesions (according to Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1])
4. Part 2: have measurable lesions (according to RECIST v1.1)
5. Absolute neutrophil count (ANC) of $\geq 1.5\times10^9$/L, platelet count of $\geq 100\times10^9$/L, and hemoglobin ≥9 g/dL
6. Serum total bilirubin (TBIL) <1.5 times the upper limit of normal (ULN)
7. Proteinuria <2+ by urinalysis; if proteinuria ≥2+, proteinuria <1 g by 24-hour urinary protein test is required

8. Patients without liver metastases: must have alanine aminotransferase (ALT) and/or AST levels ≤2.5 times the ULN. Patients with liver metastases: must have ALT and AST levels ≤5 times the ULN
9. Creatinine clearance ≥60 mL/min, as calculated by the Cockcroft-Gault formula
10. International normalized ratio (INR) ≤1.5 × ULN and activated partial thromboplastin time (aPTT) ≤1.5 × ULN, unless the patient is currently receiving anticoagulants for prophylactic purposes.
11. Have a performance status of 0 or 1 on the ECOG scale
12. Female patients of childbearing potential and male patients with partners of childbearing potential: agree to use a highly effective form(s) of contraception that results in a low failure rate when used consistently and correctly. Additional details are described in Section 5.5.1.

Dose Escalation:

13. Histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type that has progressed on or are intolerant of standard therapies and for which no curative therapy exists.

Dose Expansion:

14. Histologically or cytologically documented, locally advanced or metastatic

    g. **Cohort A**: adenocarcinoma of the colon or rectum that is microsatellite stable. Patients must have progressed on or had discontinued due to intolerable toxicity to the following agents: fluoropyrimidine, oxaliplatin, irinotecan, an anti-VEGF targeted therapy, and if RAS wild-type and anti-epidermal growth factor receptor antibody therapy. Treatment progression is defined as disease progression during or within 3 months after the last dose of standard therapy. Prior therapy could have included adjuvant chemotherapy if a tumor had recurred within 6 months after the last administration of treatment.

    Note: Eligibility also requires knowledge of tumor RAS status (wild type or mutant) as reported by investigators.

    h. **Cohort B**: progressive, low, or intermediate grade (Grade 1 or Grade 2) NETs of thoracic (B1) or GEP (B2) origins. Patients must have radiological documentation of progression of disease in the last 6 months prior to the initiation of study treatment and must have progressed on at least 1 line of standard therapy for metastatic disease.
       i. For NETs originating from the thorax,
          A. Grade 1 is defined as <2 mitoses/10 high-power field (HPF) and no necrosis.
          B. Grade 2 is defined as 2-10/10 HPF and/or foci of necrosis.
       ii. For NETs originating from GEP,
          A. Grade 1 is defined as <2 mitoses/10 HPF and/or <3% Ki-67 index.
          B. Grade 2 is defined as 2-20/10 HPF and/or 3-20% Ki-67 index
       iii. If the mitotic ratio and Ki-67 index correspond to different grade, the higher grade is used to assign classification.

Patients who have functioning NETs and have been on a stable dose of an SSA for a minimum of 2 months prior to the first dose of study treatment for control of their secretory symptoms will be eligible.

Note: Prior therapy with a somatostatin analog is considered 1 line of therapy.

i. **Cohort C:** SCLC that has progressed on standard first line chemotherapy treatment.
j. **Cohort D:** Adenocarcinoma of the stomach or gastroesophageal junction and have progressed on at least 2 prior lines of therapy. Must be microsatellite stable and have tumor stain for PD-L1 by combined positive score ≥5%.
k. **Cohort E:** ASPS (E1) or UPS (E2). Patients must have radiological documentation of disease progression in the last 3 months prior to the initiation of study treatment and have progressed on, or had discontinued due to intolerable toxicity to, at least 1 line of standard therapy or be unsuitable for standard frontline cytotoxic chemotherapy.
l. **Cohort F:** Anaplastic thyroid cancer (a diagnosis that is noted to be consistent with anaplastic thyroid cancer is acceptable) that is considered not curable by resection. Patients with a $BRAF^{V600E}$ mutation must have previously been treated with 1 line of systemic therapy with a BRAF-targeted therapy. Prior cytotoxic chemotherapy and radiation for local disease control is not considered a prior line of therapy.

15. Patients in dose expansion: must be able to provide a minimum of 10 unstained slides for central confirmation of PD-L1 expression and microsatellite stability testing. In the event archived tumor samples are not available for testing, patients may opt for a core needle biopsy prior to beginning protocol therapy if medically feasible. Patients in Cohort F must also undergo core needle biopsy.

5.4 Exclusion Criteria

An individual is ineligible for this study if he or she meets any of the following criteria:

1. AEs due to previous antitumor therapy has not recovered to CTCAE ≤Grade 1, except alopecia and peripheral neurotoxicity with CTCAE ≤Grade 2
2. Part 2 patients with CRC (Cohort A), NETs (Cohort B), ASPS (Cohort E1), and ATC (Cohort F): previous treatment with anti-PD-1, anti-PD-L1/L2 antibodies, anti-cytotoxic T lymphocyte associated antigen-4 (CTLA-4) antibody, or any other antibody acting on T cell costimulatory or checkpoint pathway
   Note: Patients in the Part 1 and patients in Part 2 Cohorts C (SCLC), D (gastroesophageal junction or Gastric cancer), or E2 (UPS) may have received previous treatment with anti-PD-1, anti-PD-L1/L2 antibodies, CTLA-4 antibody, or any other antibody acting on T cell costimulatory or checkpoint pathway;
3. Previous treatment with surufatinib
4. Uncontrollable hypertension, defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg
5. Gastrointestinal disease or condition that investigators suspect may affect drug absorption, including, but not limited to, active gastric and duodenal ulcers, ulcerative colitis and other digestive disease, gastrointestinal tumor with active bleeding, or other gastrointestinal conditions that may cause bleeding or perforation by investigator's discretion

6. History or presence of a serious hemorrhage (>30 mL within 3 months), hemoptysis (>5 mL blood within 4 weeks), or life-threatening thromboembolic event within 6 months
7. Clinically significant cardiovascular disease, including but not limited to, acute myocardial infarction within 6 months prior to enrollment, severe/unstable angina pectoris or coronary artery bypass grafting, congestive heart failure according to the New York Heart Association classification ≥2, ventricular arrhythmias which need drug treatment, or left ventricular ejection fraction (LVEF) <50%
8. QT interval corrected by the method of Fredericia (QTcF) ≥480 milliseconds
9. Other malignant tumors within 5 years prior to screening (except cured basal-cell carcinoma or squamous carcinoma at skin and cervical carcinoma in situ)
10. Antitumor therapy received within 2 weeks or 5 half-lives, whichever is shorter, prior to the initiation of the investigational treatment, including, but not limited to, chemotherapy, radical radiotherapy, targeted therapy, immunotherapy, hepatic embolization, cryoablation, and radiofrequency ablation
11. Palliative radiotherapy for a bone metastasis lesion within 2 weeks prior to the initiation of the study treatment
12. Strong inducers or inhibitors of Cytochrome P450, family 3, subfamily A (CYP3A) taken within 2 weeks (or 5x half-lives, whichever is greater) prior to the first study treatment
13. Any clinically significant active infection, including, but not limited to, known human immunodeficiency virus (HIV) infection
14. Known history of active viral hepatitis. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with hepatitis c virus (HCV) infection who are currently on treatment are eligible if they have an undetectable HCV viral load. Patients with an unknown history of viral hepatitis must be screened for HBV with HBs antigen; HBc antibody and HBS antibody; and HBV-DNA, if indicated and for HCV with HCV antibody.
    a. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for >2 weeks before the first dose of study treatment.
    b. Patients with a negative HCV antibody test at Screening or positive HCV antibody test followed by a negative HCV RNA test at Screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody.
15. Brain metastases and/or leptomeningeal disease and/or spinal cord compression untreated with surgery and/or radiotherapy and without clinical imaging evidence of stable disease (SD) for 14 days or longer. Patients requiring steroids within 4 weeks prior to start of study treatment will be excluded.
16. Used corticosteroids (prednisone or other steroids with equivalent efficacy at a dose of >10 mg/day) or other immunosuppressants for systemic therapy within 2 weeks before the first drug administration. Nasal spray, inhaled, or other topical steroids are allowed (ie, ≤10 mg/day of prednisone or other glucocorticoids at an equivalent dose)
17. For patients with NETs: administration of SSAs in the absence of secretory symptoms discontinued at least 4 weeks before the first dose of study treatment;
18. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 8) 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

19. Any live or attenuated live vaccine within 4 weeks prior to first dosing or planned for the duration of the study

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

20. Major surgeries within 60 days prior to first dosing
21. Uncontrollable malignant pleural effusion, ascites, or pericardial effusion (defined as ineffectively controlled by diuresis or puncture drainage judged by investigators)
22. High risk of bleeding at screening due to tumor invasion into major vessels, such as pulmonary artery, the superior vena cava, or the inferior vena cava, as determined by investigators
23. Arterial thrombosis or thromboembolic events (including stroke and/or transient ischemic attack) within 12 months prior to first dosing
24. Patients with a history of deep venous thrombosis within 6 months prior to first dose, unless they have been on a stable dose of anticoagulation for at least 4 weeks prior to first dosing or have completed a planned course of anticoagulation
25. Tumor invasion of a large vascular structure (eg, pulmonary artery, the superior or inferior vena cava)
26. Clinically significant abnormal electrolyte abnormality as judged by investigators
27. Active severe infection or with an unexplained fever >38.3°C during screening or the first day of study treatment administration (at the discretion of the Investigator, patients with an infection that is controlled with appropriate therapy are eligible); refer to Appendix 10 for coronavirus disease 2019 (COVID-19) risk assessment
28. Active pulmonary tuberculosis and receiving anti-tuberculosis treatment or with anti-tuberculosis treatment within 1 year prior to first dosing
29. History of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonia, severe impairment of the lung function, etc. that may interfere with the detection and treatment of suspected drug-related lung toxicity, except radiation pneumonitis in the radiation treatment area
30. Female patients who are pregnant or breastfeeding
31. History of allergies to any ingredient of surufatinib or its capsule shell, including tartrazine (E102), tislelizumab, or to any mono-antibody
32. Any condition by which investigators judge patients not suitable to participate in this study.

5.5 Lifestyle Restrictions

5.5.1 Contraception

Female patients of childbearing potential and male patients with partners of childbearing potential are required 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 progestogen only hormonal contraception (combined oestrogen/progestogen should be avoided) or highly effective non-oral hormonal contraception (eg, Depo-Provera and Implanon) associated with inhibition of ovulation together with a barrier method (eg, diaphragm, always containing a spermicide), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or sexual abstinence in line with the preferred and usual lifestyle of the patients. Oral and non-oral hormonal contraception should always be combined with an additional contraceptive method (ie, barrier method) because of a potential interaction with the study drug. Male patients must always use a condom.

5.5.2 Pregnancy and Lactation

Women who are pregnant (ie, pregnancy test is positive before drug administration) or breastfeeding will be excluded from the study.

6 STUDY CONDUCT

6.1 Study Procedures

The following procedures will be performed according to the schedule in Table 1. All assessments must occur within ±3 days (±1 day during Cycle 1 and Cycle 2) from the scheduled date, unless otherwise noted.

6.1.1 Informed Consent

All patients must sign the ICF prior to any study-related examinations or protocol procedures. 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.

All patients who sign the ICF are to be entered into the 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 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.

6.1.3 Tumor Diagnosis and Treatment History

Tumor diagnosis should include the date of primary diagnosis of disease, tumor type, disease stage, date of first metastasis, type of previous treatment, start and end date/s of previous treatment, best overall response, and date of progressive disease (PD) if applicable. For patients in Part 2 with ATC, $BRAF^{V600E}$ mutation status should be recorded at screening if available.

6.1.4 Demographics

Demographic characteristics, including year of birth, sex, and ethnic group/race, should be recorded at screening and in the applicable case report form (CRF) (as permitted by local regulations).

6.1.5 Concomitant Medication and Procedures

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient. All concomitant medications taken within 28 days before the first dose must be recorded in the CRF, including the generic name of the drug and daily dose, the reason/s for using the medication, as well as the start and stop date/s of the medication.

6.1.6 Comprehensive Physical Examination

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.

6.1.7 Limited Physical Examination

Limited physical examination includes 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.

6.1.8 Eastern Cooperative Oncology Group Performance Status

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

6.1.9 Vital Signs

Vital signs include BP, heart rate, respiration rate, and temperature. For patients with a baseline history of hypertension or with hypertension that develops during the study, BP should be monitored per institutional standard practice.

For patients receiving antihypertensive medications who have either a baseline history of hypertension or new onset of hypertension during the study, blood pressure should be monitored per institutional standard practice.

6.1.10 Laboratory Evaluations

6.1.10.1 Hematology

Hematology assessments include red blood cell count, hemoglobin, hematocrit, platelet count, and white blood count with differential (absolute counts).

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

6.1.10.2 Blood Chemistry

The blood chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, TBIL, ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase, uric acid, total protein, lipase, amylase, and albumin.

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 (units, mL/min) should be calculated using the baseline serum creatinine (Scr) value according to the Cockcroft-Gault formula

- For males: creatinine clearance = [(140 - age) × weight (kg)] / [72 × Scr (mg/dL) × ideal body weight]
- For females: the same formula should be calculated and multiplied by 0.85.

6.1.10.3 Coagulation Indicators

Coagulation tests include prothrombin time, INR, and aPTT.

6.1.10.4 CK and CK-MB

Creatine kinase (CK) and creatine kinase myocardial band (CK-MB) levels will be evaluated at specified time points and when clinically indicated. If the CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients who continue to receive surufatinib monotherapy may receive CK and CK-MB testing if clinically indicated.

6.1.10.5 Thyroid Function

Thyroid function tests include serum free tri-iodothyronine (FT3), serum free thyroxine (FT4), and thyroid stimulating hormone (TSH).

6.1.10.6 Pregnancy Test

All female patients of childbearing potential must complete a serum pregnancy test at screening and within 30 days of the last dose (End of Treatment [EOT] Visit). A urine pregnancy test must be done prior to dosing on Day 1 of every cycle starting at Cycle 2. Serum pregnancy test should be repeated for women with suspected pregnancy. This is not applicable for postmenopausal female patients (ie, no menses for 12 months without an alternative medical cause), and the date of menopause should be recorded instead. Pregnancy testing and contraception are not required for women with documented permanent sterilization (eg, hysterectomy, bilateral salpingectomy and bilateral oophorectomy, or tubal ligation).

6.1.10.7 Urinalysis

Urinalysis parameters include urine pH, protein, glucose, and blood; microscopic for white and red blood cell count. A 24-hour urine sample for quantitative protein must be collected from all patients with ≥2+ proteinuria during screening. If urine protein is ≥2+ during the period of study treatment, a 24-hour urine sample for quantitative protein is to be collected within 1 week. For conversions between quantitative and qualitative results, please see Appendix 7.

6.1.10.8 Virological Screening

Virological screening includes HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb) and HCV (HCV antibody). If HBsAg or HBcAb is positive, HBV DNA is also required to be assayed by polymerase chain reaction (PCR) method; HBV DNA-negative patients can be enrolled, and their HBV DNA is required to be monitored every cycle. If HCV antibody is positive, HCV RNA is required to undergo PCR testing.

6.1.11 Electrocardiogram Monitoring

Single 12-lead electrocardiograms (ECG) will be collected in all patients using standardized equipment. 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 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.

6.1.12 Echocardiogram

An echocardiogram should be done at Screening and every 12 weeks thereafter through the EOT Visit. Assessment parameters include LVEF and general assessment of cardiac function. Multiple-gated acquisition scans are permitted if echocardiograms cannot be performed.

6.1.13 Tumor Evaluation/Imaging

Tumor evaluation of disease for all patients will be done during the screening period and then repeated as indicated in Table 1 until discontinuation criteria are met.

At screening, patients will have radiological assessments by cross-sectional imaging of the chest, abdomen, and pelvis (computed tomography [CT], magnetic resonance imaging [MRI], or a combination of CT/MRI) in order to identify lesions. In addition, other radiographic procedures (such as radionuclide bone scans), as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement. Assessments throughout the study should be made using the same modality as that used at screening. Tumor response will be evaluated locally by the investigator to support treatment decisions as well as the primary endpoint of antitumor activity. Tumor response will be evaluated per RECIST v1.1.

Investigators will assign target and non-target lesions in accordance with RECIST v1.1 guidelines at screening. These lesions will be followed locally throughout the study to determine continuation of treatment.

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.

CCI central imaging collection and storage for all patients will discontinued. Local tumor evaluation must be performed according to Table 1.

6.1.14 Archived Tumor Sample

A formalin-fixed, paraffin-embedded tumor sample or a minimum of 10 unstained slides will be requested for all patients enrolled in Part 2 of the study. These samples will be used for central confirmation of PD-L1 expression and microsatellite stability testing. In the event archived tumor samples are not available for testing, patients may opt for a core needle biopsy prior to beginning protocol therapy if medically feasible.

6.1.14.1 Core Needle Biopsy (Cohort F)

Patients in Cohort F must submit core needle tumor biopsies. A minimum of 3 cores should be collected both prior to starting treatment and on treatment (between and including C2D1 to C2D15), if clinically feasible. These samples will be used for central confirmation of diagnosis and exploratory biomarker analyses. Details regarding sample processing can be found in the study laboratory manual.

6.1.15 Patient Enrollment Process

On Day -2 to Day 1, after verifying the patient's eligibility, the site will log into the IWRS, and the patient will be assigned a serial number matching a bottle of investigational product (IP) in the site's inventory. The site will take the investigational product with the serial number assigned by IWRS from inventory and dispense it to the patient. The first dose should be administered on Cycle 1 Day 1.

6.1.16 Pharmacokinetics Evaluations

6.1.16.1 Sample Collection and Handling

Blood samples will be collected for analysis of surufatinib plasma concentration and tislelizumab serum concentration according to the PK schedule of events in Table 2. Serum samples will be collected for analysis antibodies to tislelizumab for antidrug antibody (ADA) analysis according to Table 2. The actual dates and times of PK and ADA sampling should be recorded in the appropriate CRF. Samples collected for PK and immunogenicity analyses may be used to evaluate safety or efficacy aspects that address concerns arising during or after the treatment period.

All reasonable measures must be taken to ensure accurate recording of information on study drug dosing in the CRF. For surufatinib, the actual date and time of the dose administered 1 day prior to and during each PK sampling day must be recorded. For tislelizumab, the actual start date and time of infusion, actual end date and time of infusion, infusion rate, infusion unit, as well as any action taken during the infusion (eg, interruption) for every infusion during each PK sampling day must be recorded.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided to the sites. Collection, handling, storage, and shipment of samples must be under the specified and, where applicable, controlled temperature conditions as indicated in the laboratory manual.

Upon implementation of Protocol Amendment 5, EOT PK samples for Tislelizumab and Immunogenicity will no longer be required (Table 2).

6.1.16.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of surufatinib using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Serum samples will be analyzed to determine concentrations of tislelizumab and ADA using a validated ELISA and ADA binding assay, respectively.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. If conducted, metabolite analysis will be reported outside of the clinical study report.

6.1.17 Screening Period

There is a 28-day screening period. Prior to any screening assessments, all patients must provide a signed ICF. Prior to inclusion in the study, the patients must undergo all appropriate screening procedures to check for eligibility.

6.1.18 Treatment Period

Patients in the treatment phase will receive a combination dose based on dose level in Part 1 and the RP2D (300 mg surufatinib PO, QD + 200 mg tislelizumab IV, Q3W) in Part 2. All patients in both parts will undergo continuous monitoring for safety and efficacy. CCI [redacted]

There is no predefined duration of treatment for each patient. Patients in both the dose escalation and expansion parts will be treated until radiologically determined PD per RECIST v1.1, unacceptable toxicity, withdrawal of consent, new anticancer therapy, lost to follow-up, or death. CCI [redacted]

6.1.19 End of Treatment Visit

Patients who have completed the study or have discontinued study treatment will be asked to return to the investigational site to receive safety examinations and assessments within 30 (±7) days after the last dose of study drug.

6.1.20 Efficacy Follow-up Period

If a patient discontinues for any reason other than PD, they will continue to be followed for efficacy until disease progression, withdrawal of consent, new anticancer therapy, lost to follow-up, or death.

As of Protocol Amendment 5, efficacy follow-up after the EOT will not be performed.

6.1.21 Survival Follow-up Period

All patients in expansion Cohorts A and F will be followed for survival status every 12 weeks (±14 days) for a maximum of 2 years from PD until death, lost to follow-up, withdrawal of consent, or end of study. Survival information can be obtained via phone, and information will be documented in the source documents and relevant CRFs.

6.1.22 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 Patients

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, reasons of noncompliance (eg, missed doses, visits), or pregnancy.

Any patient who discontinues treatment should be encouraged to return to the study site for an EOT Visit and Follow-up Visits outlined in Table 1 as long as the reason for permanent discontinuation is not withdrawal of consent. The primary reason for discontinuation must be recorded on the appropriate CRF.

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

1. 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.
2. Withdrawal of consent
3. Intolerable toxicity
4. Poor patient compliance
5. Use of other antitumor treatment during the study
6. Pregnancy
7. Patient is lost to follow-up
8. The investigator or sponsor determines it is in the best interest of the patient
9. Study is terminated by the sponsor
10. Death
11. End of the study

Patients must be discontinued if they experience certain high-grade AEs, experience recurrent AEs, or experience AEs that warrant discontinuation of study treatment as determined by the principal investigator, as outlined in Section 7.1.3.

Any patient who, in the opinion of the investigator, is deriving clinical benefit from the study treatment following disease progression, may continue treatment after discussion and approval from the sponsor, if all of the following criteria are met:Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values).

2. Stable ECOG performance status.
3. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites that requires urgent alternative medical intervention.
4. Investigators must inform patients that this practice is not considered standard in the treatment of cancer.

At the time of Protocol Amendment 5, the Sponsor has decided to terminate this study based on the strategic reevaluation of the clinical development of surufatinib in the United States and Europe. This change is not based on any concern for patient safety or efficacy relative to surufatinib and/or tislelizumab treatment. CCI [redacted] The study will be terminated either 90 days after the last patient has received tislelizumab, or the point at which all imAEs have resolved or are no longer being followed, whichever occurs earlier.

6.2.1.2 Withdrawal from Study

All patients 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. Every effort should be made to obtain information on patients who discontinue study treatment but who do not withdraw consent to continue participation in the study. 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 patient withdraws from the study, he or 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 Patients

Patients who are not DLT evaluable (Section 4.1.2) in a dose-escalation cohort will be replaced to guarantee the protocol required number of DLT-evaluable patients for dose escalation evaluations.

6.2.1.4 Patients Lost to Follow-up

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

Should the patient continue to be unreachable, he or she will be considered withdrawn from the study, and the withdrawal will be document in the patient's medical record.

6.2.2 Stopping Rules

6.2.2.1 Individual Patients

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) attributed to surufatinib that does not return to baseline or ≤Grade 1 within 21 days of onset
- A DLT or DLT equivalent attributed to surufatinib 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

6.2.2.2 Part 1 (Dose Escalation)

Dose escalation will be conducted in accordance with Section 4.1.1. This study stage will end if any of the following conditions are met:

- Excessive toxicity is present in dose level -1, defined as ≥2 patients experiencing a DLT
- Dose escalation may be discontinued before MTD is reached if pharmacokinetic evidence suggests dose-exposure relationship is maximized

Enrollment into Part 2 (indication-specific expansion cohorts) will begin once the MTD/RP2D has been determined in Part 1.

6.2.2.3 Part 2 (Dose Expansion)

Dosing of additional patients within an expansion cohort will be halted until applicable data can be reviewed by the sponsor and investigators if one of the following events occur:

- Three out of the first 6 patients experience a DLT or DLT-equivalent adverse event (within 42 days of Cycle 1, Day 1) that does not return to baseline or ≤Grade 1 within 21 days of onset
- Three out of the first 6 patients experience a DLT or DLT-equivalent adverse event (within 42 days of Cycle 1, Day 1) that does not return to baseline or ≤Grade 1 within 21 days of onset in the setting of a prior dose reduction

In addition, safety data will be reviewed on an ongoing basis during study conduct. At a minimum of twice a year, study data will be reviewed with 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, futility, etc. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

This study will be terminated by the Sponsor. CCI [redacted]. This change is not based on any concern for patient safety or efficacy relative to surufatinib and/or tislelizumab treatment. CCI [redacted] and have an EOT visit, as described in 6.1.19. After the EOT Visit, patients will be contacted by the sites to follow-up on any resolving or new imAEs for up to 90 days. The study will be terminated either 90 days after the last patient has received tislelizumab, or the point at which all imAEs have resolved or are no longer being followed, whichever occurs earlier.

The study will be stopped if stopping rules in Part 1 or Part 2 are met.

The study will be immediately suspended and no additional new patients will be dosed pending review and discussion of appropriate study data by the sponsor and investigators if 1 or more patients at any dose level experience death deemed to be related to protocol treatment by the investigator and/or medical monitor based upon close temporal relationship or other factors.

The study will not resume enrollment until all parties have agreed to the course of action and until the competent authorities and the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) have been notified in accordance with local regulations.

CCI [redacted].

7 STUDY INTERVENTIONS

7.1 Description of Products

Table 6 Investigational Treatments Used in This Study

Product	Section	Dose	Frequency	Route	Duration
Surufatinib (HMP-012)	7.1.1	200 mg 250 mg 300 mg	QD	PO	Until progressive disease, unacceptable toxicity, withdrawal of consent, new anticancer therapy, lost to follow-up, or death
Tislelizumab	7.1.2	200 mg	Q3W	IV	

IV=intravenous; PO=orally; QD=once daily; Q3W=every 3 weeks.

7.1.1 Surufatinib (HMP-012)

7.1.1.1 Formulation, Storage, Preparation, and Handling

Surufatinib comes as 50-mg capsules and should be stored and used according to the instructions on the label. Surufatinib capsules should not be used beyond the expiration date provided by the manufacturer.

7.1.1.2 Dosing and Administration

In Part 1, patients will receive surufatinib at a dose based on cohort level once daily by mouth. The dose is administered with 240 mL (8 ounces) of water within 1 hour after breakfast.

In Part 2, the indication-specific expansion portion of the study, patients will enroll within 8 disease cohorts to receive surufatinib at the RP2D (300 mg QD) dose selected in Part 1. The dose will be administered with 240 mL (8 ounces) of water within 1 hour after breakfast.

Patients should swallow the capsules whole and not chew them. If vomiting occurs after dosing, the surufatinib dose should not be replaced. If a dose is missed, a replacement dose can be taken if it is within 12 hours from the intended missed dose; otherwise, the patient should not make up the missed dose but resume schedule the following day. The missed dose should be reported to investigators and recorded in the CRF.

There is no predefined duration of treatment for each patient. Patients in both the dose escalation and expansion parts will be treated until radiologically determined PD per RECIST v1.1, unacceptable toxicity, or withdrawal of consent, new anticancer therapy, lost to follow-up, or death.

7.1.2 Tislelizumab

7.1.2.1 Formulation, Storage, Preparation and Handling

Tislelizumab (10 mg/mL) is presented as a sterile, nonpyrogenic, and isotonic injectable solution for IV administration in a buffered formulation. Each vial contains a total of 100 mg of tislelizumab in 10 mL buffered isotonic solution. The product should be stored in the carton box it came in at refrigerated conditions, and it is not to be frozen. Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic,

low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. Refer to the pharmacy manual for mixing instructions for intravenous injection and use.

7.1.2.2 Dosing and Administration

In Part 1, patients will receive tislelizumab 200 mg IV, and Q3W.

In Part 2, patients will enroll within 8 disease cohorts to receive tislelizumab 200 mg IV, and Q3W.

Tislelizumab is to be administered over 60 minutes in Cycle 1 and Cycle 2. Patients must remain on site for 1 hour after the infusion is complete. In Cycle 3 and beyond, tislelizumab can be administered over at least 30 minutes.

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. Refer to Appendix 9 for guidance regarding the management of adverse events associated with tislelizumab administration.

There is no predefined duration of treatment for each patient. Patients in both the dose escalation and expansion parts will be treated until radiologically determined PD per RECIST v1.1, unacceptable toxicity, or withdrawal of consent, new anticancer therapy, lost to follow-up or death.

7.1.3 Dose Modifications

The dose modification sequence by starting dose is shown in Table 7 for Part 1 and Table 8 for Part 2. If the patient is unable to tolerate surufatinib in either part, the dose will be reduced by 50 mg daily. A patient is allowed to have dose reductions of surufatinib no more than twice (ie, dose reductions of 50 mg from 300 mg QD to 250 mg QD and then to 200 mg QD).

No dose reductions for tislelizumab are permitted; however, dosing may be interrupted for up to 12 weeks if the patient is experiencing adverse reactions that, in the opinion of the investigator, are solely related to tislelizumab.

If a patient discontinues surufatinib or tislelizumab due to toxicity, they may continue receiving the other study drug (tislelizumab or surufatinib) alone if the investigator, in consultation with the medical monitor, believes the patient can still benefit from treatment. If 1 study drug is being held due to the toxicity, the patient may continue to receive the other study drug if, in the opinion of the investigator, the toxicity is solely related to only 1 of the study drugs.

The severity of AEs will be graded according to the NCI CTCAE v5.0. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded on the CRF.

- 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.
- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment will be continued at the same dose without reduction

or interruption. In addition, no dose reductions or interruptions will be required for anemia (nonhemolytic) because it can be satisfactorily managed.

- To recover from acute toxicity considered related to surufatinib, unless otherwise indicated, the treatment of surufatinib can be delayed for up to 21 days. If a treatment delay longer than 21 days is required, the patient should be discontinued from the study drug. Continuation or resumption of surufatinib treatment after an interruption of more than 21 days must be discussed with the medical monitor or designee.
- Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and 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 the study drug 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 tislelizumab treatment should be discontinued.
- Where several toxicities with different grades or severities occur at the same time, the dose modifications should be according to the highest grade observed.

Table 7 Dose Modification Sequence for Part 1

Dose	Surufatinib	Tislelizumab
Starting Dose	Refer to dose level	200 mg IV, Q3W
-1 dose	Reduce by 50 mg QD	
-2 dose	Reduce by 50 mg QD	

IV=intravenous; Q3W=every 3 weeks; QD=once daily.

Table 8 Dose Modification Sequence for Part 2

Dose	Surufatinib	Tislelizumab
Starting Dose	RP2D (300 mg QD)	200 mg IV, Q3W
-1 dose	Reduce by 50 mg QD	
-2 dose	Reduce by 50 mg QD	

IV=intravenous; Q3W=every 3 weeks; QD=once daily; RP2D=recommended phase 2 dose.

Dose reduction guidelines for hematologic and nonhematologic toxicities other than hypertension, proteinuria, liver function impairment, and hemorrhage are shown in Table 9. In principle, treatment of surufatinib should be held until the AE/toxicity resolves or improves to ≤Grade 1. If a patient has a ≥Grade 3 toxicity that is expected to be manageable and reversible with a dose reduction, treatment should be held until toxicity resolves or improves to ≤Grade 1. Patients with a ≥Grade 3 toxicity that does not resolve or improve to ≤Grade 1 within 21 days should permanently discontinue surufatinib.

Table 9 Dose Modification of Surufatinib for Hematologic and Nonhematologic Toxicity

NCI CTCAE Version 5.0 Toxicity Grading	Action
Grade 1 or Grade 2	None
Grade 3 or Grade 4[2]	
Expected manageable/reversible with dose reduction	Hold surufatinib[1]
Toxicity remains ≥Grade 3 >14 days	Discontinue surufatinib
Toxicity lasts ≤14 days and resolves to ≤Grade 1	Reduce 1 dose level
Recurrence of Grade 3 toxicity	Reduce 1 dose level or discontinue surufatinib[1]
Recurrence of Grade 4 toxicity	Discontinue surufatinib
Not expected manageable/irreversible with dose reduction	Discontinue surufatinib

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.
Note: Patients who experience gastrointestinal perforation should permanently discontinue study drug.
[1] Treatment should be withheld until toxicity resolves or improves to ≤Grade 1. For patients who cannot recover to ≤Grade 1 within 21 days, the study drug should be discontinued permanently.
[2] Patients with ≥Grade 3 heart failure or hemorrhage should permanently discontinue study drug.

7.1.4 Dose Modification of Surufatinib for Adverse Events of Special Interest

Dose modifications for the AESIs for surufatinib are provided in Table 10 (hepatic disorders), Table 11 (hypertension), Table 12 (proteinuria), and Table 13 (hemorrhage). AESIs of thyroid dysfunction and acute renal failure should also be monitored.

Table 10 Dose Modification of Surufatinib for Hepatic Disorders

Grade and Definition	Dose Adjustment	Suggested Actions
Grade 1: ALT >1 to 3×ULN or AST >1 to 3×ULN	None	Follow-up per planned schedule. Check total bilirubin.[1]
Grade 2: ALT >3 to 5×ULN or AST >3 to5×ULN	• If serum bilirubin >2×ULN, immediately hold surufatinib and tislelizumab and evaluate etiology[1] • If consistent with immune-mediated hepatitis, refer to Appendix 9 • Continue treatment if **NOT** consistent with immune-mediated hepatitis and serum bilirubin <2×ULN.	Provide supportive care and increase the frequency of liver function monitoring to 1 to 2 times a week, as clinically indicated.

Table 10 Dose Modification of Surufatinib for Hepatic Disorders

Grade and Definition	Dose Adjustment	Suggested Actions
Grade 3: ALT >5×ULN or AST >5×ULN	• If serum bilirubin >2×ULN, immediately hold surufatinib and tislelizumab and evaluate etiology[1] • If consistent with immune-mediated hepatitis, refer to Appendix 9 • If **NOT** consistent with immune -mediated hepatitis and serum bilirubin <2×ULN, hold surufatinib and tislelizumab ○ If transaminase elevation improves to ≤Grade 1 or baseline within 21 days, resume surufatinib treatment at one dose level lower and tislelizumab (no dose adjustment) once ○ If transaminase elevation does not improve to ≤Grade 1 or baseline within 21 days, discontinue surufatinib and tislelizumab	Provide supportive care and increase the frequency of liver function monitoring to twice a week, as clinically indicated; consult hepatic expert, if necessary.
Grade 4: ALT >20×ULN or AST >20×ULN	Discontinue surufatinib and tislelizumab.	Urgent medical intervention indicated.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

[1] If ALT or AST escalates to 3 times baseline level with bilirubin >2×ULN or the biochemical criteria for Hy's Law have been met, surufatinib should be discontinued immediately, and the event should be reported to the sponsor within 24 hours. See Appendix 4 for important additional information.

Table 11 Dose Modification of Surufatinib for Hypertension

Grade and Definition	Dose Modification	Suggested Actions
Grade 1: Prehypertension (systolic BP 120 mmHg to 139 mmHg or diastolic BP 80 mmHg to 89 mmHg)	None	None

Table 11 Dose Modification of Surufatinib for Hypertension

Grade and Definition	Dose Modification	Suggested Actions
Grade 2: Stage 1 hypertension (systolic BP 140 mmHg to 159 mmHg or diastolic BP 90 mmHg to 99 mmHg), medical intervention indicated, recurrent or persistent (≥24 hours), symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously within normal range, or monotherapy indicated	None	Treatment target: control blood pressure to below 140/90 mmHg. If patient has already received antihypertensive treatment at baseline, the dose should be increased or treatment changed. If patient did not receive treatment at baseline, monotherapy should be administered. Refer to relevant antihypertensive treatment guidelines for dose administration and modification and consult cardiologist if necessary.
Grade 3: Stage 2 hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg), medical intervention indicated, >1 drug or more intensive therapy than previously used indicated	If BP 160/100 mmHg lasts for >3 days after initiation of antihypertensive treatment or modification of current antihypertensive treatment, surufatinib treatment should be held. If hypertension resolves or improves to ≤Grade 1 within 21 days, surufatinib treatment can be restarted at a lower dose level.	Treatment target: control blood pressure below 140/90 mmHg. Initiate antihypertensive treatment, increase dose of current treatment, or add other treatments. For use and adjustment of antihypertensive treatment, refer to relevant treatment guidelines or consult cardiologist if necessary.
Grade 4: Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) or urgent intervention indicated	Discontinue surufatinib treatment.	Emergent medical intervention.

BP=blood pressure.

Table 12 Dose Modification of Surufatinib for Proteinuria

Grade and Definition	Dose Modification	Suggested Actions
Grade 1: 1+ proteinuria or urinary protein <1.0 g/24 hours	None.	Follow-up per planned schedule.
Grade 2: 2+ or 3+ proteinuria or urinary protein 1.0 g to 2.0 g /24 hours	None.	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 2: Proteinuria 2+ or 3+ or urinary protein 2.0 g to <3.5 g /24 hours	Hold surufatinib treatment and resume treatment at the same dose level if proteinuria resolves to ≤Grade 1 within 21 days.	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.

Table 12 Dose Modification of Surufatinib for Proteinuria

Grade and Definition	Dose Modification	Suggested Actions
Grade 3: Urinary protein ≥3.5 g/24 hours	Hold surufatinib. If test results resolve to ≤Grade 1 within 21 days, resume at a lower dose.	Provide supportive treatment and increase the frequency of urine monitor to once or twice a week; consult nephrologist if necessary.

AE=adverse event; CTCAE= Common Terminology Criteria for Adverse Events; QD=once daily

Note: If urine dipstick reveals proteinuria 2+, 24-hour urine collection should be performed for determination of total protein within 1 week. The CTCAE grade recorded for proteinuria should be determined by the 24-hour urine collection; however, the start date of the AE will be recorded as the first instant of proteinuria (ie, urine dipstick). If surufatinib dose has been reduced to 200 mg QD and a further dose reduction is required for recurrent proteinuria, keep the same daily dose of 200 mg QD of surufatinib for 3 consecutive weeks followed by a 1-week drug holiday, and repeat for each treatment cycle, (ie, 3 weeks on and 1 week off; every 4 weeks constitutes a treatment cycle). If proteinuria cannot resolve to ≤Grade 1 after a dose interruption of 21 days, continuation or resumption of surufatinib treatment should be discussed with the medical monitor. Surufatinib treatment should be discontinued if a patient develops nephrotic syndrome.

Table 13 Dose Modification of Surufatinib for Hemorrhage

Grade and Definition	Dose Modification	Suggested Actions
Grade 1	None	Follow-up per planned schedule.
Grade 2	Hold surufatinib treatment; resume at a lower dose if resolves to ≤Grade 1 within 21 days.	Active management.
≥Grade 3	Discontinue surufatinib.	Immediate medical intervention to identify and treat the source of bleeding.

Recommendations for managing imAEs are detailed in Appendix 9.

7.2 Treatment Assignment and Bias Minimization

7.2.1 Treatment Allocation

In Part 1, patients with locally advanced or metastatic solid tumors of any kind who have progressed on or are intolerant of standard therapies for which no curative therapy exists will be enrolled into a dose-escalation phase using a 3+3 design. A total of 6 to 12 patients will be enrolled into this portion of the study.

In Part 2, the dose-expansion portion of this study will enroll approximately 110 patients with various types of advanced or metastatic solid tumors across 8 cohorts (Table 5) to evaluate the antitumor activity of surufatinib in combination with tislelizumab as outlined in Section 4.1.3.

7.3 Assessment and Verification of Compliance

Site personnel will conduct capsule counts for surufatinib to estimate compliance and document on the CRF.

Doses of tislelizumab will be administered intravenously every 3 weeks during a patient visit; site personnel will document dose administration and document on the CRF.

7.4 Prior and Concomitant Therapies

7.4.1 Prohibited Therapies

Any therapy intended for the treatment of cancer (with the exceptions as noted in Section 7.4.2), whether currently marketed or experimental, is prohibited. This includes, but is not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy.

Prophylactic antiemetics, granulocyte colony-stimulating factors, granulocyte macrophage -colony stimulating factors, platelet simulating factors, or erythropoietin are not allowed during the DLT observation period in the dose-escalation phase.

The use of gastroduodenal mucosal protective agents, such as sucralfate, are allowed, but they must be taken at least 2 hours after the administration of surufatinib.

For patients with nonfunctioning NETs, concomitant use of SSAs is not permitted and must have been discontinued at least 4 weeks before administration of the first dose of study drug.

Concomitant use of medications that are known to cause QT prolongation and/ or Torsades des Pointes is not permitted. Consult the current list at http://www.qtdrugs.org/, which is updated continuously, for the most complete information.

Palliative radiation for symptom control is allowed provided it does not compromise tumor assessments of target lesions. However, surufatinib treatment should be suspended during the radiation period and resumed at least 7 days after radiation only after meeting the following criteria:

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

Live vaccines and immune-stimulant herbal medications are prohibited during treatment and for 60 days after last dose.

Systemic corticosteroids >10 mg daily (prednisone or equivalent) are prohibited except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.

7.4.2 Permitted Therapies

Patients who use hormonal therapy with gonadotropin releasing hormone agonists for prostate cancer, oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy should continue their use.

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 low-dose anticoagulation agents at study entry, the following guidance should be followed:

- Patients who are receiving warfarin or Coumadin-like products should have their INR monitored and maintained at the lower end of the therapeutic range (ie, close to 2.0 if the therapeutic range is 2.0 to 3.0).
- Patients who require low-molecular-weight heparin should receive the prophylactic dose and monitoring as specified by the appropriate product information label.

Patients who develop arterial thromboembolic events should discontinue the study treatment. If a patient suffers a venous thromboembolic event while still receiving study treatment, it may still be possible for him or her to receive study treatment under adequate monitoring and dose modification. The continuation decision must be made by the investigator in consultation with the sponsor.

Patients who have functioning NETs and who have been on a stable dose of an SSA for a minimum of 2 months prior to the first dose of study drug for control of their secretory symptoms will be permitted to enroll in the -dose expansion phase.

All supportive measures consistent with optimal patient care will be given throughout the study.

7.4.3 Drug-Drug Interactions

In vitro metabolism data indicate that CYP3A plays an important role in the metabolism of surufatinib. The potential effects of medications that can affect the PK of surufatinib via the CYP3A pathway have not been tested in the clinic. Therefore, medications that are strong inhibitors or inducers of CYP3A are prohibited and should not be administered concomitantly with surufatinib during the course of the study. Examples of these medications are listed in Appendix 3.

In vitro, surufatinib is shown to have the potential to inhibit CYP3A, P-glycoprotein (P-gp), and breast cancer–resistant protein (BCRP) (refer to the IB). Patients should avoid concomitant use of medications that are sensitive substrates of CYP3A, P-gp, or BCRP where possible. If used together, patients should be monitored more frequently for adverse reactions, and a dose reduction should be considered of the CYP3A, P-gp, or BCRP substrate medication. Examples of the medications that are sensitive substrates of CYP3A, P-gp, and BCRP are listed in Appendix 3.

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 surufatinib, is very low given tislelizumab is a therapeutic monoclonal antibody.

8 SAFETY MONITORING

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).

These safety evaluations will be performed from the time of ICF signature, throughout the treatment phase, and up to 90 days after the last study treatment administration. AEs and SAEs ongoing at the EOT will be followed until resolution. Any new SAE possibly related to study treatment and occurring any time after the EOT should be reported. The NCI CTCAE v5.0 will be used to classify the severity of all AEs and laboratory abnormalities.

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 in humans, 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), including 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, invasive screening procedures such as biopsies)
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Asymptomatic overdose will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of outcome.

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 it 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
- A congenital anomaly/birth defect

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.

8.1.3 Adverse Events of Special Interest

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

AESIs for surufatinib include hepatic disorder, proteinuria, hypertension, thyroid dysfunction, hemorrhage, and acute renal failure.

AESIs for tislelizumab include imAEs of hepatitis, pneumonitis, colitis, endocrinopathies, myocarditis, diabetes, and serious skin adverse reactions.

8.2 Adverse Event Reporting

8.2.1 Timeframe for Collection of Adverse Events

After signing the informed consent, all AEs and 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. Immune-mediated AEs and SAEs should be collected until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. Any SAEs that are considered to be related to either study drug by the investigator should be collected without regard to time elapsed since the last dose.

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 study. The investigator must report such events (both initial and follow-up) to the sponsor 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 the investigator's causality assessment:

- SAEs
- Abnormal liver function laboratory results
  - Serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, regardless of seriousness
  - Hy's Law: Increase in serum AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN and when 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 4 for additional information regarding Hy's Law
  - For management of hepatic function abnormal events, refer to Table 10.

- Hemorrhagic events
  - CTCAE ≥Grade 3 hemorrhagic event, regardless of seriousness.
  - For management for hemorrhagic events, refer to Table 13
  - The management of severe or serious hemorrhagic events will be conducted according to Appendix 5.

- Pregnancy

8.3 Eliciting Adverse Events

A consistent methodology of nondirective questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of nondirective questions include

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

8.4 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 CRF, 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. The following guideline should be used 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, and/or intervention not indicated
- Grade 2: "moderate;" minimal, local or noninvasive intervention indicated; and/or limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: severe or medically significant but not immediately life--threatening; hospitalization or prolongation of hospitalization indicated, disabling, and/or limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.
- Grade 4: life-threatening consequences and/or urgent intervention indicated
- Grade 5: Death related to AE

8.5 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 below:

- **Related:** An adverse event will be considered as "related" to the use of the IP if 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 rechallenge, 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:** An adverse event will be considered as "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event, or the presence of a more likely alternative explanation for the adverse event. Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. A causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.6 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 CRF, 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 designee within 24 hours of knowledge of the event.

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

8.6.1 Diagnosis Versus Symptoms and Signs

If known, a diagnosis should be recorded on the CRF 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 CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.6.2 Adverse Event 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 CRF 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 CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

8.6.3 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 CRF unless the severity changes. If a persistent AE becomes more or less severe, it should be recorded again in a new CRF 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 CRF separately.

8.6.4 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 for 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 CRF.

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 CRF. 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 CRF unless their severity, seriousness, or etiology changes.

8.6.5 Preexisting Medical Condition

A preexisting medical condition is one that is present at screening. Such conditions should be recorded on the CRF 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 CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.6.6 Pregnancy

A female patient must be instructed to stop taking the study treatment 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 treatment). 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 treatment 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 treatment. If such an event occurs, it should be reported as described above.

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

8.6.7 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.

8.6.8 Death

All deaths that occur during the 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. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, please record "Unknown cause death" on the CRF, 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.

8.6.9 Overdose

For this study, any dose of surufatinib >300 mg daily dose or tislelizumab ≥600 mg in a 24-hour period will be considered an overdose. No specific information is available on the treatment of overdose of surufatinib or tislelizumab. In the event of overdose, further surufatinib or tislelizumab administration should be withheld 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 sponsor study representatives immediately, or no later than 24 hours after becoming aware of the overdose.

- An overdose associated with AEs/SAEs should be recorded as the AE diagnosis/symptoms secondary to overdose on the relevant AE/SAE modules in the CRF and on the study drug CRF module.
- An intentional overdose should be reported as an AE, regardless of any associated signs or symptoms.
- An overdose with no associated signs or symptoms should only be reported on the study drug CRF module.

8.7 Duration of Safety Follow-up for Adverse Events

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

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 CRF 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 CRF.

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.

9 ANALYSIS

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), which will be finalized prior to the database lock.

The timing of analysis for each cohort may be different depending on the completion of each cohort, and the final analysis of the study will be conducted at the time of analysis of the last cohort. However, the accrued data from any cohort may be analyzed for internal decision-making purposes (for example, to provide information for a potential phase 3 study design).

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. Analyses will be performed using SAS® (Version 9.1 or higher). Unless otherwise stated, data will be summarized by dose level for Part 1 and by disease cohorts for Part 2 of the study.

9.1 Hypothesis

No formal hypothesis testing is planned for this study. For efficacy endpoints ORR, DCR, and CBR, the study will provide the estimates and the corresponding 2-sided Clopper-Pearson 95% CI for precision.

9.2 Population

9.2.1 Sample Size Rationale

The total number of patients enrolled will depend on the number of dose escalations and the need to characterize individual cohorts in the expansion phase further. The planned enrollment for this study is approximately 122 patients, including 6 to 12 patients in Part 1, and approximately 110 patients in Part 2.

CCI [redacted], further enrollment to this study was stopped and the planned number of patients in the impacted cohorts in Part 2 of the study were updated to reflect current enrollment numbers at the time enrollment was stopped (Table 5).

9.2.1.1 Part 1

To determine the recommended phase 2 dose (RP2D) and/or the MTD of surufatinib in combination with tislelizumab, a total of 6 to 12 patients will be enrolled into this portion of the study. The exact number will be determined by the number of DLTs across the 3 potential dose levels of surufatinib.

9.2.1.2 Part 2

The sample size selected for each cohort in Part 2 of the study can provide adequate precision for the estimated incidence rate of endpoint ORR.

Table 14 shows the range of observed ORR and the corresponding 2-sided 95% confidence intervals for cohorts of size 10, 15, and 20.

Table 14 Estimated ORR and 2-Sided 95% Confidence Intervals

Number of Patients	Number of Cases	Estimated Rate	95% CI Lower Limit	95% CI Upper Limit
10	0	0.00	0.00	0.31
	2	0.20	0.03	0.56
	4	0.40	0.12	0.74
	6	0.60	0.26	0.88
	8	0.80	0.44	0.97
	10	1.00	0.69	1.00
15	0	0.00	0.00	0.22
	3	0.20	0.04	0.48
	6	0.40	0.16	0.68
	9	0.60	0.32	0.84
	12	0.80	0.52	0.96
	15	1.00	0.78	1.00
20	0	0.00	0.00	0.17
	5	0.25	0.09	0.49
	10	0.50	0.27	0.73
	15	0.75	0.51	0.91
	20	1.00	0.83	1.00

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

9.2.2 Analysis Populations

The following analysis populations have been defined for the study:

- Safety analysis set: All enrolled patients who received at least 1 dose of surufatinib 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 Part 1 of the study who are evaluable for DLT assessment. A patient is DLT evaluable if he/she meets the following criteria:
  - received ≥85% of scheduled surufatinib and ≥67% (approximately two-thirds) of scheduled tislelizumab administration during the DLT assessment window and/or
  - experienced a DLT.

  Patients will be considered not evaluable for DLTs if during the DLT assessment window they

  - were withdrawn from the study,
  - did not receive ≥85% of scheduled surufatinib and ≥67% (approximately two-thirds) of scheduled tislelizumab drug administration,
  - received prophylactic supportive care that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition), OR

– have taken a strong inhibitor or inducer of enzyme CYP3A4 (Appendix 3).

- Response evaluable analysis set: All patients who receive study treatment and have a baseline tumor assessment and at least 1 post-baseline assessment, unless any clinical PD or death occurred before the first post-baseline assessment, will be considered evaluable for antitumor efficacy endpoints.
- Antidrug antibody (ADA) analysis set: All patients who received at least 1 dose of study treatment and have a baseline and at least 1 post-baseline ADA result.
- Pharmacokinetic analysis set: All patients with at least 1 quantifiable plasma concentrations of surufatinib combined with tislelizumab will be included in the pharmacokinetic analysis population.

9.3 Statistical Analysis

9.3.1 Patient Disposition

The number and percentage of patients that were enrolled in the study, treated, and discontinued from study drug(s) will be presented for all enrolled patients. The primary reason for treatment discontinuation will be summarized according to the categories in the CRF. Patient disposition will be summarized by dose level for Part 1 and by tumor types for Part 2.

Important protocol deviations will be summarized and listed by category.

9.3.2 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.

9.3.3 Prior and Concomitant Medications

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

9.3.4 Safety Analysis

The summary of the exposure to study drug(s), AEs, AEs leading to drug modification or discontinuation including DLTs, changes in laboratory results, and changes in vital signs, etc., 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 Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs are defined as AEs that started or worsened in severity on or after the first dose of study drug and no later than 30 days after the date of last study drug 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 (dose-escalation phase)
- Summary of DLT-equivalent (DLTs which 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 drug.

Drug exposure, including number of cycles received, total duration of exposure, cumulative dose received (mg), dose intensity, and relative dose intensity of surufatinib 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. The reasons for dose modifications will also be summarized.

For laboratory tests that are graded by NCI CTCAE v5.0 or higher, results will be summarized by grade for each visit during the treatment period. Treatment-emergent changes will be summarized by the maximum post-baseline grade. A shift-table summarizing shifts from baseline to maximum post-baseline 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.

9.3.5 Efficacy Analysis

No formal hypothesis testing is planned for this study.

9.3.5.1 Primary Efficacy Analysis

9.3.5.1.1 Objective Response Rate (ORR)

The ORR is defined as the proportion of patients with a confirmed best overall response (BOR) complete response (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 v1.1 progression or the start date of new anticancer therapy, whichever comes first.

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

ORR will be summarized by dose level for Part 1 and by tumor types for Part 2.

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

9.3.5.2 Secondary Efficacy Analysis

9.3.5.2.1 Progression-free Survival (PFS)

Progression-free survival is defined as the time (months) from the start of study treatment until the first radiographic documentation of objective progression as assessed by the investigator using RECIST v1.1 (Appendix 2), or death from any cause. Patients who have not objectively progressed or died by the date of the analysis cut-off or received any further antitumor therapy will be censored at the date of the last evaluable objective tumor assessment before the cut-off date or the antitumor therapy start date.

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) and 95% CI will also be reported. Detailed censoring rules will be included in the SAP.

PFS will be summarized by dose level for Part 1 and by tumor types for Part 2. Additional summaries may be based on all dose levels overall and by tumor types, if necessary.

9.3.5.2.2 Disease Control Rate (DCR)

Disease control rate is defined as the proportion of patients with a BOR of CR, PR, or SD lasting for at least 7 weeks as determined by the investigator using RECIST v1.1. The DCR and the corresponding 2--sided Clopper-Pearson 95% CI will be presented.

9.3.5.2.3 Clinical Benefit Rate (CBR)

Clinical benefit rate 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. Durable SD is SD for at least 6 months. The CBR and the corresponding 2-sided Clopper-Pearson 95% CI will be presented.

9.3.5.2.4 Duration of Response (DoR)

Duration of response 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. Censoring rules for DoR will be aligned with PFS.

9.3.5.2.5 Time to Response (TTR)

Time to response is defined as the time (months) from start of study treatment until the date of first occurrence of PR or CR. TTR will be summarized only for responders using KM methodology.

9.3.5.2.6 Overall Survival (OS)

Overall survival is defined as the time (months) from the 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) with 95% CI will also be reported. OS will be assessed in patients enrolled to the expansion Cohorts A (CRC) and F (ATC).

9.3.6 Pharmacokinetic Analysis

Evaluation on PK will be performed on the PK analysis set. Concentration data of surufatinib in plasma and tislelizumab in serum will be tabulated and summarized using descriptive statistics (number of patients [n]; arithmetic mean with standard deviation; coefficient of variation [CV%]; and geometric mean, median, minimum, and maximum) as appropriate.

9.3.7 Immunogenicity Analysis

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs to tislelizumab. The incidences of positive ADAs and neutralizing ADAs to tislelizumab will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

9.3.8 Other Exploratory Analyses

Distribution of PD-L1 expression will be examined in all patients. Potential association between PD-L1 expression and tislelizumab treatment effect will be explored. Other potential predictive markers will be assessed.

Methodology for exploratory analyses will be described in the SAP.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, consensus and ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP guidelines, and applicable regulations and guidelines governing clinical study conduct.

10.2 Ethics Review

The IEC/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 or 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 IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB
- Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC/IRB, 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 Data Privacy

All information about surufatinib and tislelizumab (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. HUTCHMED Limited 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. CRFs and other documents submitted to the sponsor should not contain the patient's name.

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.
- Patients are identified only by 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 patient must be informed that his or 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 patient, who will be required to give consent for their data to be used as described in the ICF.
- The patient must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

10.4 Disclosure

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

10.5 Data Quality Assurance

- To ensure the safety of patients 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 patient data relating to the study will be recorded on CRFs 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 physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, and responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be 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]).

10.6 Informed Consent

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

- Patients must be informed that their participation is voluntary. Patients or their legally acceptable 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 (HIPAA) requirements, where applicable, and the IEC/IRB 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 CRF.
- If the benefit:risk assessment changes after the safety analysis, the ICF needs to be reviewed and updated, and all updated information should be provided to patients or their legally acceptable representative (including patients who have already received the study drug).
- A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

11 OVERSIGHT

11.1 Safety Review Committee

Safety monitoring and evaluation of the dose escalation part will be carried out by the SRC, which will consist of the sponsor's study team members (including, but not limited to, the medical monitor, safety monitor, and PK scientist [as applicable]) and the site principal investigators. Safety data will be evaluated to determine whether it is safe to continue the assigned dosing combination for dose escalation, stay at the currently assigned dose level, or whether the dose should be de-escalated to the lower dose level. Pharmacokinetic data may also be reviewed if available. The SRC will be charged with determining the RP2D and/or MTD.The MTD will be defined as the maximum dose at which <33% of patients at a single dose level experience a DLT in the first cycle (Cycle 1, Days 1–21). The decision regarding the RP2D will take the following into consideration:The MTD, if reached

- Pharmacokinetic data may also be reviewed with or without associated safety and preliminary efficacy findings

These criteria constitute the basis for RP2D determination, and the SRC must collectively determine the RP2D.

The SRC may also review safety data during Part 2 of the study.

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 CRFs 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 CRFs, the adherence of the protocol to GCP, 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 CRF entries. The sponsor's monitoring standards require full verification of the informed consent form, adherence to the inclusion/exclusion criteria, and documentation of

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

11.2.2 Audits

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

- 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 subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IEC/IRB 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 CRF refers to 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 CRFs is complete, accurate, and that entry and updates are performed in a timely manner. Blood samples for PK and tumor samples for biomarker assessments will be collected by study sites and sent to the designated central laboratory for processing. 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 holding.

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 or 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 adequate and accurate source documents and study records for all patients that support the information entered in the CRF.
- 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 CRFs 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 are 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 staff or consultants from HUTCHMED Limited) will be listed in the publication. HUTCHMED Limited 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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