STATISTICAL ANALYSIS PLAN

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

Protocol Number:	2020-012-GLOB1
Name of Test Drug:	**Surufatinib (HMPL-012)** **Tislelizumab (BGB-A317)**
Phase:	1b/2
Sponsor Name:	HUTCHMED Limited No.4, Lane 720, Cailun Road, Zhangjiang Hi-tech Park, Shanghai, China Post Code: 201203
Analysis Plan Version	Version 2.0
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Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

APPROVAL SIGNATURES

AUTHOR:

PPD

Signature **Date**

PPD
Syneos Health

APPROVED BY:

PPD

Signature **Date**

PPD
HUTCHMED Limited

PPD

Signature **Date**

PPD
HUTCHMED Limited

PPD

Signature **Date**

PPD
HUTCHMED Limited

REVISION HISTORY

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ASPS	alveolar soft part sarcoma
ATC	anatomic therapeutic classification (WHO Drug Dictionnary)
ATC	anaplastic thyroid cancer
BLQ	below the lower limit of quantification
BMI	body mass index
BRAF	B-Raf kinase
$BRAF^{V600E}$	B-Raf kinase V600E mutations
CBR	clinical benefit rate
CFB	change from baseline
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450, family 3, subfamily A4
DBL	database lock
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	end of infusion
EOT	end of treatment
GC	gastric cancer
GCP	Good Clinical Practice
GEP	gastroenteropancreatic
ICF	inform consent form
ICH	International Council on Harmonization
imAE	immune-mediated AE

Abbreviation	Term
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
LLQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
MTD	maximum tolerated dose
NET	neuroendocrine tumor
OC	observed case
ORR	objective response rate
OS	Overall survival
PD	progressive disease
PD-L1	programmed death-Ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PO	oral(ly)
PR	partial response
PT	preferred term
QD	once daily
QxW	every x weeks
QTcF	QT interval corrected by the method of Fredericia
RAS	rat sarcoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCLC	small-cell lung cancer
SD	stable disease
SMQs	standardized MedDRA queries
SOC	system organ class
SRC	Safety Review Committee
STS	soft-tissue sarcoma
TEAE	treatment-emergent adverse event
TLF	table, listing, figure

Abbreviation	Term
TPR	timepoint response
TTR	time to response
UPS	undifferentiated pleomorphic sarcoma
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for study 2020-012-GLOB1. The SAP is based on Protocol amendment 5, dated 29 November 2023. Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

The analyses related to PK endpoints will be described in a separate analysis plan.

2. STUDY DETAILS

2.1. Study Objectives

Objectives	**Corresponding Endpoints**
Part 1 Primary: • To evaluate the safety and tolerability of surufatinib, thereby determining the recommended Phase 2 dose (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	**Part 1 Primary:** • Safety including dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, electrocardiograms (ECGs), clinical laboratory abnormalities, and vital signs **Part 2 Primary:** • ORR at 12 weeks
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 **Part 2 Exploratory:** • To explore the distribution of PD-L1 expression and potential association between PD-L1 expression and tislelizumab treatment effect	**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 (colorectal cancer) and F (anaplastic thyroid cancer) • 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 **Part 2 Exploratory:** • PD-L1 expression • Cohort F: Changes from baseline in tumor markers, correlation with drug exposure, and

• Cohort F: To explore the influence of gene abnormalities on safety, and efficacy	association with efficacy and safety parameters

2.2. Study 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 determined in Part 1 of this study.

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.

- Dose level 1: 250 mg surufatinib, oral (PO), once daily (QD) + 200 mg tislelizumab, intravenous (IV) every 3 weeks (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 DLT, then the dose will be escalated to dose level 2.
- If one of the 3 patients at dose level 1 experience 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).

- >33% of patients at any dose level experience a DLT, then the dose escalation will be halted.

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 (see Table 1) to evaluate the antitumor activity of surufatinib in combination with tislelizumab.

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 1 below.

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

Table 1 Dose Expansion Cohorts

Disease Cohort	PlannedNumber 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 metastatic CRC (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) neuroendocrine tumor (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 one 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 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 alveolar soft part sarcoma (ASPS) or undifferentiated pleomorphic sarcoma (UPS), must have progressed on at least 1 line of standard therapy or refused standard frontline cytotoxic chemotherapy.

Patients in Cohort F must have locally advanced or metastatic anaplastic thyroid cancer (ATC). Patients who have a $BRAF^{V600E}$ mutation must have previously been treated with 1 line of systemic therapy (not including radiation therapy) with a BRAF-targeted therapy.

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).

2.3. Determination of Sample Size

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 , 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 2).

Part 1

To determine the 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.

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

Table 2 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

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

3.1.1. Enrolled Set

The enrolled set includes all patients who signed ICF (inform consent form).

3.1.2. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least 1 dose of surufatinib or tislelizumab. 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.

3.1.3. DLT-Evaluable Analysis Set

All patients enrolled in Part 1 (dose escalation) 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

3.1.4. Response Evaluable Analysis Set

The response evaluable analysis set will include all patients who receive study treatment and have a baseline tumor assessment and at least one post-baseline assessment, unless any clinical progressive disease (PD) or death occurred before the first post-baseline assessment. Sensitivity analysis for efficacy endpoints ORR, DCR, CBR, DoR, and TTR will be conducted using this analysis set.

3.1.5. Pharmacokinetics (PK) Analysis Set

The pharmacokinetic analysis set include all patients with at least one quantifiable concentration of surufatinib or tislelizumab.

3.1.6. Antidrug Antibody (ADA) Analysis Set

The antidrug antibody analysis set include all patients who received at least one dose of tislelizumab and have a baseline and at least one post-baseline ADA result.

3.2. Protocol Deviations

Protocol deviations are recorded in the clinical trial management system as outlined in the latest version of the Protocol Deviation and Non-compliance Management Plan. Protocol deviations are categorized as major/minor before database lock.

Protocol deviations including deviations that are related to COVID-19 are recorded in the Clinical trial management system as outlined within the Protocol Deviation and Non-Compliance Plan.

4. ENDPOINTS

4.1. General Principles for Derived and Transformed Data

4.1.1. Reference Start Date and End Date and Study Day

Reference start date is defined as the first date when a non-zero dose of any study drug (surufatinib or tislelizumab, whichever occurs first) was administrated (first administration/dose date). Day 1 is the day of the first dose of study treatment in Cycle 1.

Study day will be calculated from the reference start date, and it will be used to show start/stop day of assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference start date, study day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date, study day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Reference end date is defined as the last date when a non-zero dose of any study drug was administered.

4.1.2. Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment prior to the first administration of any study drug (whichever occurs first), including scheduled and unscheduled visits, unless otherwise specified. For quantitative measurements,

- change from baseline (CFB) will be calculated as: CFB = assessment value at visit X – baseline value;
- percentage CFB (% CFB) will be calculated as % CFB = (assessment value at each visit X – baseline value)/baseline value × 100.

4.1.3. Treatment Period

Unless otherwise specified, the treatment period is defined as the period from first administration date of treatment to [30 days + 7 days protocol defined window] after last administration date on treatment. For safety data, only the assessments/events collected during the treatment period will be evaluated (except for related SAE and immune-mediated AE [imAE]).

The worst post-baseline is defined as the worst assessments/events during the treatment period including both scheduled and non-scheduled visit. The end of treatment (EOT) measurement is defined as the latest non-missing measurement taken during the treatment period.

CCI [redacted]

4.2. Exposure Endpoints

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 calculated as per algorithms included in Table 3.

Table 3 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Surufatinib	Tislelizumab
Dosing Schedule per Protocol	Part 1: 200 mg PO QD (4 capsules of 50-mg) 250 mg PO QD (5 capsules of 50-mg) 300 mg PO QD (6 capsules of 50-mg) Part 2: RP2D dose PO QD	200 mg IV Q3W of a 3-weeks cycle
Number of Cycles Treatment Received	Patients will be considered to have started a cycle if they have received at least one dose of study drug in the respective cycle.	
Duration of Exposure (days)	Last dose date of study drug – first dose date of study drug + 1.	Last dose date of study drug – first dose date of study drug + 21.
Cumulative Dose (mg)	Sum of the doses administered to a patient in the duration of exposure (mg)	
Dose intensity (mg/day)	Cumulative dose (mg) / (duration of exposure) [(mg/day)]	
Relative dose intensity (RDI) (%)	100 * [Dose intensity (mg/day) / (200 mg or 250 mg or 300 mg (mg/day)]	100 * [Dose intensity (mg/day) / (200 /21]
RDI Categories	< 50% 50 - < 70% 70 - < 90% 90 - < 110% ≥ 110%.	

PO = oral administration; QD = once daily; Q3W = every 3 weeks

Drug accountability data will be used to calculate the total dose administered (mg) for each cycle for surufatinib. The number of capsules taken for each dose level will be calculated as total capsules dispensed – total capsules returned in a cycle. The total dose administered (mg) in a cycle will be the sum of 50 mg capsules taken.

Dose Interruptions, Dose Reductions, and Dose Withdrawal

- Dose interruptions, dose reductions, and dose withdrawal are all based on the dose administration data, the associated reasons for each of them include categories: (1) AE, and (2) Other. Dose reduction is not allowed for Tislelizumab.
- Dose modifications of study drug include dose interruption and dose reduction.

  The following endpoints to reflect study drug adjustment will be derived.

Dosing modifications (including both dosing interruption and dose reduction): number of patients with any dosing modification, and categorized frequency of dosing modification (0, 1, 2, 3, 4, 5, 6, >6). This will be derived only for surufatinib.

Dosing interruption: number of patients with any dosing interruption and reasons for dosing interruption, and categorized frequency of dosing interruptions (0, 1, ≥2).

Dose reduction: number of patients with any dose reduction and reasons for dose reduction, and categorized frequency of dose reduction (0, 1, ≥2). This will be derived only for surufatinib.

4.3. Safety Endpoints

The primary endpoint for Part 1 dose escalation is safety.

The safety analysis set is used to evaluate the safety variables including AEs, clinical laboratory data, vital signs, single 12-lead ECG parameters, echocardiogram (ECHO)/ multiple-gated acquisition (MUGA) scan parameters, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, and death. The safety data during the treatment period will be evaluated, and the treatment period is defined as the duration from the date of the first study drug administration until [30 days + 7 days protocol defined window] after the last dose.

4.3.1. Dose Limiting Toxicities (DLTs)

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 drug.

Patients will be considered evaluable for DLTs if they meet the criteria (see criteria in section 3.1.3).

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 National Cancer Institute (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.

2. Hematologic toxicities

    a. 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)
    b. Grade 4 neutropenia lasting >7 days
    c. Grade 4 thrombocytopenia lasting >7 days
    d. Grade 3 thrombocytopenia accompanied with severe bleeding
    e. 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.

4.3.2. Adverse Events (AEs)

All AEs will be coded from verbatim text to preferred term (PTs) and grouped by system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. AEs will be collected from the time of signature of informed consent throughout the treatment period. AEs will be graded by investigator according to NCI CTCAE v5.0.

An AE is considered a TEAEs :

1) If the onset date is on after the start of study treatment (surufatinib or tislelizumab) or if the onset date is missing or
2) If the AE has an onset date before the start of study treatment but worsened in severity after the study drug administration until [30 days + 7 days protocol defined window] after the last dose of study treatment. After this period, treatment-related SAEs will also be considered as TEAEs.
3) The TEAEs 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.

Other AE variables include drug-related AEs, AEs leading to study drug modifications (i.e. dose interruption, dose reduction, or study drug withdrawal), AEs leading to death, and SAEs.

An AE is considered treatment-related in the summaries if it is assessed as related to any study drug by the investigator (surufatinib or tislelizumab) or if the assessment of relationship to study treatment is missing.

Severity of AEs is graded from Grade 1 to Grade 5 according to the NCI CTCAE v5.0. Missing severity grade is imputed as Grade 3.

COVID-19 related AEs will be identified based on recorded verbatum term and/or coded preferred term.

For AEs which are not on-going, duration of AE (days) is defined as AE end date – AE start date +1; for on-going AEs, the end date will be listed as 'Ongoing' and the duration of AE (days) will be approximated as '≥ date of last visit – AE start date +1'.

AEs of Special Interest (AESI) for surufatinib

AEs of special interest (AESI) will be identified based on the searching strategy listed in Appendix 3. AESIs will be extracted from MedDRA 27.0 by referring to the standardized queries in the table. The SMQ code only consider a 'narrow' scope, i.e. category A terms.

AESIs for surufatinib include drug related hepatic disorder, hypertension, haemorrhage, and acute renal failure.

Immune-mediated AEs (imAE) for tislelizumab

Immune-mediated AEs for tislelizumab will be identified based on the AE standardized MedDRA queries (SMQs) and are listed in Appendix 4.

4.3.3. Laboratory

Blood and urine samples for the determination of hematology, clinical chemistry, coagulation, thyroid function and urinalysis laboratory variables described in Table 4 will be measured.

Table 4 Laboratory Assessment

Laboratory Category	Laboratory tests
Hematology	red blood cell count (RBC), hemoglobin, hematocrit, platelet count, and white blood count with differential (absolute counts).
Chemistry	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
Coagulation	prothrombin time, INR, and aPTT
Thyroid function	serum free tri-iodothyronine (FT3), serum free thyroxine (FT4), and thyroid stimulating hormone (TSH).
Urinalysis	urine pH, protein, glucose, and blood; microscopic for white and red blood cell count

Change from baseline in laboratory test results to each assessment will be calculated.

The non-protocol specified tests (if any reported) will not be summarized; they will only be included in listings.

Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Clinical laboratory results will be graded according to CTCAE criteria, CTCAE v5.0 criteria (see Appendix 2). Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- Alanine aminotransferase (ALT) or/and aspartate aminotransferase (AST) >5 x ULN
- AST or/and ALT > 3× upper limit of normal (ULN) and ≤ 5×ULN
- Total bilirubin > 2×ULN
- Potential Drug-Induced Liver Injury (DILI): AST and/or ALT > 3×ULN and total bilirubin > 2×ULN
- Hy's Law criteria: AST and/or ALT > 3×ULN and total bilirubin > 2×ULN and ALP < 2× ULN.

Additionally, the minimum and maximum values for each patient over the entire treatment period for each hematology and chemistry laboratory parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

4.3.4. ECG

Electrocardiogram (ECG) parameters include heart rate, PR interval, RR interval, QT, QTcF and QRS intervals. Change from baseline to each post-baseline visit will be calculated and summarized by visit.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 5.

Additionally, the minimum and maximum values for each patient over the entire treatment period for each ECG parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 5 Potentially Clinically Significant Criteria for ECG

ECG Parameter (unit)	Criterion Value
Heart Rate (bpm)	>120
	<50
PR Interval (ms)	≥ 210
RR Interval (ms)	> 1200
	< 500
QRS Interval (ms)	≥ 120
	≤ 50
QT Interval (ms)	≥ 500
	≤ 300
QTcF (msec)	> 450
	> 480
	> 500
	≤ 300
	Increase from baseline > 30
	Increase from baseline > 60
	> 450 and increase from baseline > 30
	> 450 and increase from baseline > 60
	> 480 and increase from baseline > 30
	> 480 and increase from baseline > 60
	> 500 and increase from baseline > 30
	> 500 and increase from baseline > 60

4.3.5. Vital Signs

Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, heat rate, body temperature, weight, and height. Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 6.

Additionally, the minimum and maximum values for each patient over the entire treatment period for each vital sign parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 6 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion Value
SBP (mmHg), DBP (mmHg), Heart rate (bpm) Respiratory rate (breaths/min)	Increase from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 Decrease from baseline of > 0 - ≤ 20 > 20 - ≤ 40 > 40 (except for respiratory rate)
Weight (kg)	Percentage decrease from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20% Percentage increase from baseline of < 5% ≥ 5 – < 10% ≥ 10 - < 20% ≥ 20%

4.3.6. Performance Status

ECOG performance status is collected at screening and during the treatment period (i.e., Day 1 of each Cycle).

4.3.7. Echocardiogram

ECHOs will be done at Screening and every 12 weeks from C1D1 thereafter through the end of treatment visit. Assessment parameters include left ventricular ejection fraction (LVEF) and

overall interpretation of cardiac function. Multiple-gated acquisition scans (MUGAs) are permitted if ECHOs cannot be performed.

4.3.8. Physical Examination

A comprehensive physical examination (PE) at Screening and end of treatment visit, it includes general appearance, eyes, ears, nose and throat, head and neck, respiratory, cardiovascular, abdomen (gastrointestinal), skin, genitourinary system, lymph nodes, musculoskeletal, neurological assessments.

Limited physical examination at scheduled visits is a subset the comprehensive physical examination as deemed appropriate by the investigator.

Abnormal clinically significant findings in PE were to be reported as AEs (post-baseline) or MHs (screening).

These data will only be available in listings.

4.4. Efficacy Endpoints

4.4.1. Primary Endpoint

The primary endpoint of Part 2 is the ORR defined as the proportion of patients with a confirmed best overall response (BOR) of complete response (CR) or Partial Response (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 (see Table 7 for definition)

Table 7 Best Overall Response When Confirmation of CR and PR are Required

First TPR	Second TPR [a]	Best Overall Response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD

CR = Complete Response; NE = Not Evaluable; NA = Not Available; ORR = Objective Response Rate; PD = Progressive Disease; PR= Partial Response; SD = Stable Disease, TPR = Timepoint Response.

[a]The minimum interval for confirmation of CR and PR is 4 weeks.

[b] Best response will be SD if the first time point overall response is after 49 days (8 weeks from start of treatment and allowing a 7 day visit window) on study. Otherwise, the best response will be PD.

[c] Best response will be SD if the first time point overall response if after 49 days on study. Otherwise, the best response will be NE.

[d] Best response will be SD provided the criteria for PD have not been met from the first to second assessment.

* A best overall response of SD can only be made after the patient is on study for a minimum of 49 days (counted from Cycle 1 Day 1). If the patient is on study for less than 49 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

^ Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR.

For patients in the Safety Analysis set, who do not have any post-baseline tumor assessment (patients who died or progressed clinically prior to the first scheduled tumor assessment), the response category "NA" will be assigned for BOR of the patient.

ORR will be calculated using two different ways:

- Scenario #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with objective response being "Yes".
- Scenario #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with objective response being "Yes".

Both ways (confirmed and unconfirmed) of assigning BOR will be implemented.

4.4.2. Secondary Endpoints

4.4.2.1. 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, or death from any cause.

More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of

(i) disease progression as defined by RECIST Version 1.1 or death; or

(ii) withdrawal of consent; or

(iii) receiving subsequent anti-cancer therapy (not including radiotherapy and procedures), whichever is earlier.

Patients without report of PD or death from any cause at the time of analysis are censored as described in Table 8 below.

The PFS time will always be derived based on scan dates not tumor assessment dates. If PD is documented between scheduled visits, the actual date of documented progression will be used as an uncensored value in the analysis of PFS. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

- Date of progression is determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient is censored at the latest of the dates contributing to a particular overall visit assessment.

Table 8 Censoring Rules for PFS

Rule	Situation	Date of Progression or Censoring	Outcome
1	PD documented between schedule radiological assessment visits	Date of documented disease progression	Event
2	Death between scheduled radiological assessment visits Death before first documented PD Death after one missing radiological assessment visit	Date of death	Event
3	Documented PD directly following a missing radiological assessment visit, if having not had disease progression observed previously	Date of documented disease progression	Event
4	No baseline or post-baseline radiological assessments available	Date of start of study treatment	Censored
5	No death or PD by the time of data cut-off for final analysis (Alive without progressive disease, Lost to follow-up, withdrawal of consent)	Date of last adequate radiological assessment	Censored
6	Lost to follow-up or withdrawal of consent before PD or death	Date of last adequate radiological assessment	Censored
7	New anti-tumor therapy started prior to PD	Date of last adequate radiological assessment prior to or on date of initiation of new therapy visit	Censored
8	Death or PD occurred after two or more consecutive missed radiological assessment visits	Date of last adequate radiological assessment prior to missed visits	Censored

Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer therapy occur on the same day, will assume that the progression was documented first, e.g. outcome is progression and the date is the date of the assessment of progression

Note: Two consecutive scheduled tumor assessments is equal to 98 days (=2* [6 weeks *7+ 7 days]) since previous evaluable RECIST 1.1 or baseline assessment if there is no post baseline tumor assessment until 24 weeks and 140 days (=2* [9 weeks *7+ 7 days]) after.

4.4.2.2. 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.

4.4.2.3. 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.

4.4.2.4. Duration of Response

Duration of response (DoR) is defined as the time from the first occurrence of PR or CR by RECIST v1.1, until disease progression or death, whichever comes first.

Only those patients with objective responses of CR or PR will be included in this analysis.

Both the unconfirmed DoR based on the patients with unconfirmed CR/PR and the patients with confirmed DoR based on the confirmed CR/PR will be derived. For the confirmed DoR, the first date to observe the CR/PR will be as the response date for confirmed responder.

Censoring will follow the rules outlined for PFS in Table 8 of Section 4.4.2.1.

For those patients who do not have censored DoR, it is calculated as (date of death or PD or last assessment – date of first occurrence of CR or PR + 1)/30.4375.

4.4.2.5. Time to Response (TTR)

Time to response is defined as the time (months) from start of study treatment until the date of first documented objective response, either CR or PR (whichever status is recorded first), according to RECIST v1.1. It will be calculated for patients whose BOR is either CR or PR.

TTR is calculated as (date of first occurrence of CR or PR – date of start of study treatment + 1)/30.4375.

Date of CR/PR should use the latest tumor assessment date at the CR/PR visit.
Time to response will be based on tumor assessments up to PD, death or initiation of a further anti-tumor therapy, whichever occurs earlier.

Both the unconfirmed TTR based on the patients with unconfirmed CR/PR and the patients with confirmed TTR based on the confirmed CR/PR will be derived. For the confirmed TTR, the first date to observe the CR/PR will be used as the response date for confirmed responder.

4.4.2.6. Overall Survival (OS)

Overall survival will be performed for part 2 (Dose Expansion) on Cohort A (CRC) and Cohort F (ATC) only.

OS is defined as the time (months) from the start of study treatment until the date of death due to any cause.

That is, OS is calculated as (date of death or last known alive – date of start of study treatment + 1)/30.4375.

In the rare case, if year and month of death date are known but the day is unknown, day will be imputed as 15 if there are no visits or assessments after the 15th of the moth. For example, if a patient is reported to die on Dec2017, the death date will be imputed as 15 Dec2017 if there are no visits or assessments after 15Dec2017.

Patients with no event during the study will be censored at the date last known to be alive. OS will not be censored if a patient receives subsequent anticancer treatments after discontinuation of the study drugs.

Moreover, the last known alive date will be derived for patients not known to have died at the analysis cut-off date using the latest date (including complete date and partial date with Month and Year information) among the following data:

- All assessment dates (e.g. laboratory, vital signs assessments, ECG, ECOG, performance status assessment, tumor assessment dates etc.).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Adverse events start and end date.
- Date latest known alive collected during the survival follow-up.

4.5. Other Endpoints

4.5.1. Pharmacokinetic Endpoint

Blood samples will be collected for analysis of surufatinib plasma concentration and tislelizumab serum concentration according to the PK schedule of events in Table 9.

Table 9 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 post-dose	EOI[5]	
C1D8	Predose[3]	Any time during visit	-
C1D15	Predose[3]	Any time during visit	-

Table 9 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]	
	2 to 4 hours post-dose		
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]
EOT	-	Any time during visit	Any time during visit

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.

4.5.2. Immunogenicity

Serum samples will be collected for analysis antibodies to tislelizumab for antidrug antibody (ADA) analysis according to table above.

4.5.3. Other Exploratory Analyses

Exploratory analyses will be performed only for part 2 (Dose Expansion).

Distribution of PD-L1 expression
PD-L1 expression will be available at screening for all patients enrolled in Part 2. A summary table of PD-L1 expression on tumor cells at screening will be presented by cohort on the safety analysis set using following cut offs:

- ≥1%,
- ≥5%
- ≥10%.

5. ANALYSIS METHODS

5.1. General Principles

5.1.1. General Methodology

In general, all efficacy and safety will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size [n], mean, standard deviation, minimum, 25% percentile [Q1], median, 75% percentile [Q3], and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Time to event variable will be analyzed using the Kaplan-Meier method and summarized with median, 25% and 75% percentiles with their corresponding 95% confidence intervals (CI) which are calculated from a log-log transformation based on the method of Brookmeyer and Crowley (1982). Individual data will be presented in patient listings.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings.

All summary tables, listings, and figures (TLFs) will be presented by treatment groups as defined in Table 10.

Table 10 Treatment/Cohort Display in TLFs

Part of the study	Treatment Group	Treatment Description in Data Display
Part 1 - Dose Escalation	-1	Surufatinib 200 mg + Tislelizumab
	1	Surufatinib 250 mg + Tislelizumab
	2	Surufatinib 300 mg + Tislelizumab
Part of the study	Cohort group	Cohort Description in Data Display
Part 2 - Dose Expansion	1	Cohort A CRC
	2	Cohort B1 Thoracic NETs
	3	Cohort B2 GEP NETs
	4	Cohort C SCLC
	5	Cohort D GC
	6	Cohort E1 ASPS
	7	Cohort E2 UPS
	8	Cohort F ATC

For continuous data, unless otherwise specified, the mean, median, Q1, and Q3 will be presented with one more significant digits than the original values, and standard deviation will be reported with 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. The derived variables will be presented with one decimal place. Percentages will be reported with one decimal point; if the count is 0, no

percentage will be presented. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but ≥ 99.5% will be presented as ">99%." Any rounding will be done after all calculations are made.

5.1.2. Handling Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing — no missing imputation will be performed. Safety analyses will be conducted on the OC data only.

However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. The specific imputation rules are provided below, refer to Section 5.1.2.1 for the method of imputation of missing AE onset and stop date and Section 5.1.2.2 for the method of imputation of missing concomitant onset and stop dates. However, the imputed dates should not be shown in listings.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Unless otherwise specified, patients with missing data will be excluded only from analyses for which data are not available.

5.1.2.1. Adverse Events Start/End Date

AEs with onset/end dates that are partially/completely missing will be imputed as follows.

(i) AE start date:

- If the AE onset date is completely missing, the AE start date will be imputed as the reference start date (ie date of first treatment);
- If the AE onset date is partial missing, then
  - If both the year and the month are available and the year and the month are the corresponding year and month of the reference start date, then the AE start date will be imputed as the reference start date;
  - If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the reference start date, then the AE start date will be imputed as the 1st day of the month;
  - If only the year is available and the available year is the corresponding year of the reference start date, then the AE start date will be imputed as the reference start date;
  - If only the year is available, and the available year is not equal to the corresponding year of the reference start date, then the AE start date will be imputed as the January 1st of the year

(ii) AE end date will be imputed as below for the partial date only, the imputation rules only apply when the AE is not ongoing:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.

If the imputed AE end date is after the death date for patients known to be dead at end of study or cut off date, the date of the death will be used for AE end date. If the imputed AE end date is after the last known alive date for patients alive at the end of study or cut off date, the date of last known alive date will be used for AE end date.

For AE continuing at the cut-off date, the end date will not be imputed and instead will be reported as "ongoing".

5.1.2.2. Concomitant Medication/Procedure/Surgery Start/End Date

Concomitant Medication/Procedure/Surgery with onset/end dates that are partially/completely missing will be imputed as follows.

(i) start date:

- 1st day of the month will be used to impute the start date if only the day is missing
- January 1st will be used to impute the start date if both the day and month are missing
- If the date is completely missing, then the day before the reference start date will be imputed as the start date.

(ii) end date:

- Last day of the month will be used to impute the end date if only the day is missing
- December 31st of the year will be used to impute the end date if both the day and month are missing
- If the date is completely missing, assign 'continuing' status to the end date

If the imputed end date is after the death date or last known alive date, the date of the death or last known alive date will be imputed as the Concomitant medication/procedure/surgery end date.

5.1.2.3. Subsequent Anti-cancer Therapy Date

When a partial new anti-tumor therapy start date is reported, every effort will be made to identify the precedence relationship of starting date of new anti-tumor therapy relative to the reference end date. Below rules will be used:

- If the date is completely missing, new anti-tumor therapy date will be imputed as reference end date + 1;
- If only the day is missing, 15th day will be imputed as the new anti-tumor therapy date;

– If both the day and the month are missing, then July 1st will be imputed as the new anti-tumor therapy;

If the imputed date is earlier than reference end date, then it will be replaced with reference end date + 1, if the imputed date is later than the date of death or last known alive date, it will be replaced with the date of death or last known alive date.

5.1.2.4. Primary Diagnosis Date and Metastatic Disease Diagnosis Date

When a partial date of primary diagnosis or a partial date of first metastatic disease diagnosis is reported, the below imputation rules will be used:

– If the date is completely missing, no imputation will be conducted;

– If only the day is missing, 15th day will be assigned;

– If both the day and the month are missing, then July 1st will be assigned.

Check that the imputed date is not after or equal to the informed consent date.

5.1.3. Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug within each cycle defined as Day 1, to the dates that the scheduled visits occur. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 11. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patient's listings.

For windowed visits during the treatment cycles, if more than one visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used.

For the EOT, the last assessment in the window will be included in the summary.

For a patient who prematurely discontinues the study, the premature visit will be slotted accordingly. The window for EOT will be "last dose date of last cycle to last dose date of last cycle + [30 days + 7 days protocol defined window]".

Note that due to the database design all surufatinib cycles after cycle 25 will be stored as UNS. Thus for cycles 26+ the tislelizumab dosing information will be used. Additionally, if from cycle 26+ tislelizumab is not taken then the unscheduled visits will be sorted by date if surufatinib dosing and the cycle will be assigned sequentially.

Table 11 Visit Windowing

	Cycle 1			Cycle 2			Cycle 3	Cycle 4 and onwards	End of Treatment
Visit	**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D8**	**C2D15**	**C3D1**	**CXD1**	
Scheduled Day [a]	1	8	15	1	8	15	1	1	
ECOG	1			-1 to 1			-3 to 3	-3 to 3	Last dose date of last cycle to last dose date of last cycle + [30 days + 7 days protocol defined window]
Vital Sign	1	1 to 9	10 to 16	-1 to 1		2 to 16	-3 to 3	-3 to 3	
Hematology	-28 to 1	1 to 9	10 to 16	-1 to 1		2 to 16	-3 to 3	-3 to 3	
Clinical Chemistry	-28 to 1	1 to 9	10 to 16	-1 to 1		2 to 16	-3 to 3	-3 to 3	
Coagulation	-28 to 1	1 to 9	10 to 16	-1 to 1		2 to 16	-3 to 3	-3 to 3	
CK and C-MB	1			-1 to 1			-3 to 3	-3 to 3	
Thyroid function	-28 to 1							-3 to 3	
Urinalysis	-28 to 1			-1 to 1			-3 to 3	-3 to 3	
ECG	-28 to 1		1 to 16	-1 to 1		2 to 16	-3 to 3	-3 to 3	

[a] The scheduled day is relative to the Day 1 of each cycle.

5.1.4. Adjustment of Covariates

Not applicable

5.2. Analysis Methods

5.2.1. Patient Disposition

Summary of study disposition will be provided by dose level for Part 1 and by cohort for Part 2 for the following:

- Number of patients who signed the informed consent
- Number of screen failures
- Reason for screen failure
- Number of patients who did not receive study treatment
- Number of patients who received study treatment
- Patients still on study treatment
- Reason for study drug discontinuation for each study drug (adverse event, radiological disease progression, consent withdrawn and does not agree to future follow-up, patient decision and agrees to future follow-up, investigator decision, lost to follow-up, death, other)
- Number of patients going into efficacy follow-up
- Number and percentage of patients who discontinue the efficacy follow-up
- Reasons for discontinuation of the efficacy follow-up (death, lost to follow-up, withdrawal of consent, progressive disease, other, reasons are based on the reasons efficacy follow-up not conducted)

For Cohorts A and F (patients with PD) only:

- Number of patients going into survival follow-up
- Number and percentage of patients who discontinue the study
- Reason for discontinuation of the study (death, lost to follow-up and withdrawal of consent, reasons are based on the survival status)

A separate table will be presented to show the patients included in each analysis set and summary reasons for exclusion from an analysis set.
Patient's discontinuation status and inclusion in analysis sets will be also listed.

5.2.2. Protocol Deviations

Protocol deviations will be summarized descriptively for patients with at least one major protocol deviation by dose level and overall for Part 1 as well as by cohort and overall for Part 2.

A patient can have multiple important deviations and will be counted once per major/minor deviation.

COVID-19-related protocol deviations will be summarized descriptively by dose level and overall for Part 1 as well as by cohort and overall for Part 2.

In addition, all protocol deviations including deviations that are related to COVID-19 will be provided in a by-patient listing.

5.2.3. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be summarized by dose level and overall for Part 1 as well as by cohort and overall for Part 2 on the safety analysis set:

- Age (years) at screening, age groups (18-65, >65-75, >75 years and <65, ≥ 65 years),
- Gender, childbearing potential (female only)
- Race
- Ethnicity
- Region (United States, Europe)
- Country
- Baseline height (cm)
- Baseline weight (kg)
- Baseline BMI (kg/m^2) calculated as baseline weight (kg)/ [baseline height (m)]^2, BMI category (<18.5, ≥18.5 and <24, ≥24 kg/m^2)
- Baseline ECOG status.

5.2.4. Disease Characteristics

Oncology history will be summarized descriptively by dose level and overall for Part 1 as well as by cohort and overall for Part 2 for the safety analysis set for the following:

- Primary Diagnosis
    - Colorectal Cancer
    - Thoracic Neuroendocrine tumors
    - Gastroenteropancreatic Neuroendocrine tumors
    - Small-cell lung cancer
    - Gastric cancer
    - Soft tissue sarcoma (alveolar soft part sarcoma)
    - Soft tissue sarcoma (undifferentiated pleomorphic sarcoma)

- Other

- RAS Status (wild type, mutant, not applicable, unknown)
- BRAF Status (wild type, V600 E mutation, other)
- NET Functional Status (functional, non functional, not applicable, unknown)
- Time since first diagnosis of disease (months)
- Anatomical location of primary tumor
- Time since diagnosis of locally advanced/metastatic disease (months)
- Prior oncology treatments (prior anti-cancer medication, prior anti-cancer radiotherapy, prior anti-cancer procedures)

Time since first diagnosis of disease (months) = (date of first study treatment administration – date of first diagnosis of disease + 1)/30.4375

Time since metastatic disease (months) = (date of first study treatment administration – date of diagnosis of metastasis disease + 1)/30.4375

Prior oncology treatments including prior anti-cancer mediation, prior anti-cancer radiotherapy, prior anti-cancer procedure or surgery are summarized descriptively by dose level and overall for Part 1 as well as by cohort and overall for Part 2 for the safety analysis set.

5.2.5. Medical History

The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Medical history will be coded to SOC and PT using MedDRA version 27.0

The number and percentage of patients with any past medical/surgical history within each SOC and PT will be provided by dose level/cohort on the safety analysis set.

A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT).

Each summary will be ordered by descending order of incidence of SOC according to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

5.2.6. Prior and Subsequent Anti-cancer Therapy

Prior and subsequent anti-cancer therapy, including mediation, radiotherapy, and procedure or surgery, will be summarized descriptively by dose level/cohort and overall for the safety analysis set.

5.2.6.1. Prior and Subsequent Anti-cancer Medication

Prior anti-cancer medications are defined as those taken by the patient prior to the administration of study drug. Subsequent anti-cancer medications are defined as those taken by the patient after the discontinuation of the study drug.

Prior and subsequent anti-cancer medications will be coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e., ATC Level 2) and PT using the World Health Organization Drug Dictionary (WHO-DD) version March 2024.

The prior anti-cancer medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer medications will be summarized.

All prior and subsequent anti-cancer medications will be presented in patient listing.

5.2.6.2. Prior and Subsequent Anti-cancer Radiotherapy

Prior anti-cancer radiotherapy is defined as those taken by the patient prior to the administration of study drug.

Subsequent anti-cancer radiotherapy is defined as those taken by the patient after the discontinuation of the study drug.

The number and percentage of patients with at least one prior anti-cancer radiotherapy will be summarized.

All prior and subsequent anti-cancer radiotherapy will be presented in patient listing.

5.2.6.3. Prior and Subsequent Anti-cancer Procedure or Surgery

Prior anti-cancer procedure or surgery are defined as those taken by the patient prior to the administration of study drug. Subsequent anti-cancer procedure or surgery are defined as those taken by the patient after the discontinuation of the study drug.

Prior and subsequent anti-cancer procedure or surgery will be coded to SOC and PT using MedDRA (Medical Dictionary for Regulatory Activities) version 27.0

The prior anti-cancer procedure or surgery will be summarized by presenting the number and percentage of patients by PT and SOC. Patients taking the same medication multiple times will only be counted once for that PT or SOC.

Each summary will be ordered by descending order of incidence of SOC to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer procedure or surgery will be summarized.

All prior and subsequent anti-cancer procedure or surgery will be presented in a patient listing.

5.2.7. Prior and Concomitant Medications

Prior and concomitant medications (CMs) will be coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e. ATC Level 2) and PT using the WHO-DD version March 2024.

Medications taken and stopped prior to the first dose of study treatment are denoted "Prior". Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but no later than 37 days after the last dose are denoted "Concomitant".

Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

The prior medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the concomitant medications will be summarized.

All prior and concomitant medications will be presented in patient listing.

5.2.8. Concomitant Procedure

Medical or surgical procedures that started after first dose date but no later than 37 days after the last dose are denoted "Concomitant".

Concomitant medical or surgical procedures will be classified using the MedDRA version 27.0

The concomitant medical or surgical procedures will be summarized by presenting the number and percentage of patients by PT and SOC. Patients having the same medical or surgical procedure multiple times will only be counted once for that PT or SOC. Each summary will be ordered by descending order of incidence of SOC according to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

All concomitant medical or surgical procedures will be presented in patient listing.

5.2.9. Exposure of Study Treatment

Exposure of study treatment (duration of exposure, number of cycles of treatment received, cumulative dose, dose intensity and relative dose intensity for each study drug,) will be summarized by dose level and overall for Part 1 as well as by cohort and overall for Part 2.

Relative dose intensity will be also summarized using the following classifications:

- < 50%;
- 50 % - < 70% ;
- 70 % - < 90% ;
- 90 % - <110% ;
- >= 110 %

Number of cycles treatment received will be also summarized using the following classifications: (1, 2, 3, 4, 5, 6, >6)

The following summary for dose modification will be summarized separately for each drug (surufatinib and tislelizumab) by dose level, and overall for Part 1 as well as by cohort and overall for Part 2. Dose reduction/increase is not allowed with tislelizumab.

- Number of patients with any dose modification with surufatinib (including both drug interruption and dose reduction), and frequency of dose modification: 0, 1, 2, 3, 4, 5, 6, >6
- Number of patients with any drug interrupted with surufatinib or tislelizumab (number of patients experienced drug interruption and reasons for drug interruption, and frequency of drug interruptions: 0, 1, ≥ 2)
- Number of patients with any drug withdrawn with surufatinib or tislelizumab (number of patients experienced drug withdrawn and reasons for drug withdrawn)
- Number of patients with any dose reduced with surufatinib (Number of patients with any dose reduction and reasons for dose reduction; and frequency of dose reduction: 0, 1, ≥ 2.

5.2.10. Safety Analyses

Safety data during the treatment period will be summarized. Treatment period is defined as the duration from the date of the first study drug administration until 37 days after last dose. 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.

5.2.10.1. Dose-Limiting Toxicity (DLT)

Adverse events will be assessed by the DLT criteria during the 21-day assessment window, which begins on the day of the administration of study treatment.

All DLT analysis will be performed for the Part 1 dose escalation phase on the DLT evaluable analysis set. DLT analysis will be also done for the part 2 expansion phase on the safety analysis set.

The number of patients and percentage with DLTs or DLT-equivalent will be presented by dose level for part 1. Patients with DLTs or DLTs equivalent will be also summarized by SOC, PT, and highest CTCAE grade for each dose level.

The same analysis (DLT-equivalent only) will be provided for Part 2 on the safety analysis population.

DLTs or DLT-equivalent toxicities will also be presented in patient listings.

5.2.10.2. Adverse Events

An overall summary of the number and percentage of patients along with the number of adverse events for each dose level/cohort will be provided for the following categories of AEs:

Group	Summary Scope
All TEAEs	– CTCAE Grade ⩾3 AEs – Surufatinib-related AEs – Tislelizumab-related AEs – DLT – DLT-equivalent (DLTs which occur outside the DLT assessment window) – AEs Leading to Dose Reduction of Surufatinib – AEs Leading to Dose Interruption of Surufatinib – AEs Leading to Treatment Discontinuation of Surufatinib – AEs Leading to Dose Interruption of Tislelizumab – AEs Leading to Treatment Discontinuation of Tislelizumab – Surufatinib-related AEs Leading to Dose Reduction of Surufatinib – Surufatinib-related AEs Leading to Dose Interruption of Surufatinib – Surufatinib-related AEs Leading to Treatment Discontinuation of Surufatinib – Tislelizumab-related AEs Leading to Dose Interruption of Tislelizumab – Tislelizumab-related AEs Leading to Treatment Discontinuation of Tislelizumab – AEs Leading to Death
Serious TEAEs	– CTCAE Grade ⩾3 SAEs – Surufatinib-related SAEs – Tislelizumab-related SAEs – SAEs Leading to Dose Reduction of Surufatinib – SAEs Leading to Dose Interruption of Surufatinib

Group	Summary Scope
	– SAEs Leading to Treatment Discontinuation of Surufatinib – SAEs Leading to Dose Interruption of Tislelizumab – SAEs Leading to Treatment Discontinuation of Tislelizumab – Surufatinib-related SAEs Leading to Dose Reduction of Surufatinib – Surufatinib-related SAEs Leading to Dose Interruption of Surufatinib – Surufatinib-related SAEs Leading to Treatment Discontinuation of Surufatinib – Tislelizumab-related SAEs Leading to Dose Interruption of Tislelizumab – Tislelizumab-related SAEs Leading to Treatment Discontinuation of Tislelizumab – SAEs Leading to Death
Treatment-Emergent AESIs for Surufatinib	– CTCAE Grade ≥3 AESIs – Surufatinib -related AESIs – AESIs for Surufatinib Leading to Dose Reduction of Surufatinib – AESIs for Surufatinib Leading to Dose Interruption of Surufatinib – AESIs for Surufatinib Leading to Treatment Discontinuation of Surufatinib – AESIs for Surufatinib Leading to Dose Interruption of Tislelizumab – AESIs for Surufatinib Leading to Treatment Discontinuation of Tislelizumab – Surufatinib-related AESIs for Surufatinib Leading to Dose Reduction of Surufatinib

Group	Summary Scope
	– Surufatinib-related AESIs for Surufatinib Leading to Dose Interruption of Surufatinib – Surufatinib -related AESIs for Surufatinib Leading to Treatment Discontinuation of Surufatinib – AESIs for Surufatinib Leading to Death
Treatment-Emergent imAEs for Tislelizumab	– CTCAE Grade ≥3 imAEs – Treatment-related imAEs to Tislelizumab – imAEs for Tislelizumab Leading to Dose Reduction of Surufatinib – imAEs for Tislelizumab Leading to Dose Interruption of Surufatinib – imAEs for Tislelizumab Leading to Treatment Discontinuation of Surufatinib – imAEs for Tislelizumab Leading to Dose Interruption of Tislelizumab – imAEs for Tislelizumab Leading to Treatment Discontinuation of Tislelizumab – Tislelizumab-related imAEs for Tislelizumab Leading to Dose Interruption of Tislelizumab – Tislelizumab-related imAEs for Tislelizumab Leading to Treatment Discontinuation of Tislelizumab – imAEs for Tislelizumab Leading to Death
COVID-19-related TEAEs	- CTCAE Grade ≥ 3

The number and percent of patients experiencing a TEAE within each of the categories and sub-categories listed in Table above will be also summarized by SOC, PT, and highest CTCAE grade for each dose level/cohort. 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 summary will be sorted in descending order of frequency of SOC according to the sum of column. Within SOC, sort by descending frequency of PT according to the sum of column.

All AEs, including AEs that started prior to the study drug, will be presented in patient listings. In addition, separate listings of all SAEs, AESIs, imAEs, AEs leading to death, AEs leading to dose reduction, AEs leading to dose interruption, and AEs leading to study drug discontinuation will be provided.

5.2.10.3. Death

Number of deaths, primary cause of death and whether autopsy was performed are summarized descriptively for each dose level/cohort. Similarly, the deaths happening during the treatment period will also be tabulated.

Data for deaths will be provided as patient list in which the on-treatment death will be flagged.

5.2.10.4. Laboratory Evaluations

For hematology, clinical chemistry and coagulation labs, the observed values and change from baseline will be summarized by visit using descriptive statistics.

Toxicities for clinical labs will be characterized according to CTCAE, v5.0 (Appendix 2), and the frequency and percentage of patients with each CTCAE grade for each visit during the treatment period will be described. Moreover, any occurrence of Grade 3 or Grade 4 during the overall treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Summary tables will be also provided for abnormal hepatic laboratory values by dose level (for part 1) and by cohort (for part 2). Abnormal hepatic laboratory values are based on the pre-specified thresholds (section 4.3.3)

Listings of all laboratory data with normal reference ranges, and CTCAE grades (when possible) will be provided.

5.2.10.5. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline by visit.

A listing of all ECG data will be provided.

The criteria for potentially clinically significant findings are defined in Table 10.

The frequency and percentage of patients with any potentially clinically significant findings during the treatment period will be presented. The supportive data will be provided in patient data listings.

5.2.10.6. Vital Signs

For vital sign parameters (SBP, DBP, pulse rate, temperature, and weight) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 10) during the overall treatment period will be presented. A listing of all vital sign data will be provided.

Moreover, the minimum, and maximum, and their corresponding change from baseline vital sign values will be summarized descriptively overall treatment period.

5.2.10.7. Performance Status

The frequency and percentage of patients for each ECOG score level will be summarized by visit. Shift in grade from baseline to the maximum post-baseline score will be summarized.

A listing of ECOG score for all patients will be provided.

5.2.10.8. Echocardiogram

Descriptive statistics for ECHO/MUGA will be summarized by visit. A by-patient listing of ECHO/MUGA values at each time point will be presented.

5.2.10.9. Physical Examination

A listing of physical examination data for all patients will be provided.

5.2.11. Efficacy Analyses

No formal hypothesis testing is planned for this study.

5.2.11.1. Primary Efficacy Analyses

The number and percentage of patients in each category of derived BOR (CR, PR, Unconfirmed CR, Unconfirmed PR, SD, PD, or NE) will be summarized for the safety analysis set.

ORR and $ORR_{UNCONFIRMED}$ will be summarized by dose level for Part 1 and by cohort for Part 2.

The 95% CIs of ORR and $ORR_{UNCONFIRMED}$ will be calculated using the Clopper-Pearson exact binomial method for each dose level and cohort.

Overall objective responses and best overall responses are provided in listings by patients and visit.

5.2.11.2. Sensitivity Analysis for Efficacy Endpoint

As a sensitivity analysis, ORR, DCR, CBR, DoR, and TTR will be presented for the response evaluable analysis set.

5.2.11.3. Multiplicity Control

Not applicable.

5.2.11.4. Secondary Efficacy Analyses

Progression-Free Survival

PFS is defined in Table 10 and calculated as (date of death or radiographic PD or last assessment –start date of study treatment + 1)/30.4375.

The number and percent of patients who had PFS event (PD or death), the number and percent of patients censored, and reasons for censoring will be presented for each dose level (Part 1) and cohort (Part 2) for the safety analysis set.

Reasons for censoring include the following:

a. No baseline or post-baseline tumor assessments

b. Lost-to follow-up prior to progressive disease or death

c. New anti-tumor therapy started prior to PD or death

d. Death or PD occurred after two or more consecutive missed assessment

e. Withdrew consent prior to PD or death

f. Alive without disease progression at the data cut off date

Kaplan-Meier plots will be produced and the median, 25% and 75% percentile will be estimated using Kaplan-Meier method with their corresponding 95% CIs calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982).

In order to assess duration of follow-up for PFS, Kaplan Meier estimates will be calculated in the same way as in the analysis for primary PFS, while using different censoring rule which reverses censoring indicator of primary analysis of PFS instead, i.e. patients who progressed or died in PFS analysis will be censored at the date of PD (objective disease progression or death). Patients who are censored in PFS analysis will assigned as "event" with the same duration for PFS.

All PFS data will be provided in listings by patient.

DCR and CBR

DCR and CBR will be summarized by dose level for Part 1 and by cohort for Part 2.

The 95% CIs of DCR and CBR will be calculated using the Clopper-Pearson exact binomial method for each dose level and cohort.

DCR and CBR will be provided in listings by patients.

DoR and TTR

DoR and TTR will be summarized using Kaplan-Meier method. Both the unconfirmed and the confirmed DoR and TTR will be summarized. The median, 25% and 75% percentile will be estimated using Kaplan-Meier method with their corresponding 95% CI.

Censoring reasons for DoR will be the same as for PFS.

All confirmed and unconfirmed DoR and TTR data will be provided in listings by patient.

Overall Survival:

OS will be summarized using Kaplan-Meier method. Kaplan-Meier plot will be generated and median OS (if estimable) along with 95% CI and Q1 and Q3 percentiles will be calculated. Kaplan-Meier estimate with 95% CI at timepoints 6, 9, 12 months will be summarized.

OS will be assessed in patients enrolled to the expansion Cohort A (CRC) and Cohort F (ATC) only.

5.3. Other Analyses

5.3.1. Pharmacokinetic Analysis

Evaluation on PK will be performed on the PK population, which is defined as all subjects with at least one measurable concentration data point of surufatinib or tislelizumab.

Concentration data of surufatinib in plasma and tislelizumab in serum will be tabulated and summarized for each cycle at which PK are collected. Descriptive statistics will include number of patients [n], arithmetic mean, standard deviation, coefficient of variation [CV%], median, minimum, and maximum as appropriate.

For listing and presenting individual PK data, all concentrations will be presented in original units and to the same decimal place as reported by bioanalytical lab, e.g., ng/mL. The conventions presented in the table below will be used for the presentation of the descriptive statistics of PK concentrations.

Variable	**Summarized with:**
Minimum, Maximum	3 significant digits or based on actual measured values as needed
Mean (arithmetic), Median	3 significant digits
StdDev	3 significant digits
CV%	1 decimal point

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

5.3.1.1. Handling of Missing Concentration Data

Missing concentration data for all subjects who are administered scheduled study treatments is considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

5.3.1.2. Handling of Dose Reduction or Interruption

Any concentration data taken at or after the time of a dose reduced or interrupted of surufatinib, or a dose interrupted of tislelizumab will be listed with a flag but excluded from summary statistics.

5.3.1.3. Handling of below the lower limit of quantification (BLQ) Data

PK concentration summary, the following rules apply:

- For surufatinib, PK concentrations below the lower limit of quantification (BLQ) in predose samples on C1D1 will be set to zero; all other PK concentrations BLQ will be set to 0.5*LLOQ.
- For tislelizumab, all PK concentrations that are BLQ will be set to zero.
- When more than half (>50%) of the values at a single time point are BLQ, mean and median values will be reported as BLQ. Standard deviation and %CV will not be reported; maximum and minimum values will be reported as observed (i.e., minimal will be BLQ).

5.3.1.4. Handling of the Difference between the Scheduled (nominal time) and the Actual Sampling Times (actual time)

For all sampling times, the actual sampling times relative to dosing will be calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. Listing of PK sampling times will include planned nominal time of PK sample collection, allowed PK sampling window, actual time elapsed from the reference dose with the deviation from the nominal time, and measured concentrations of the drug. For surufatinib, the reference dose refers to the surufatinib dose administered prior to surufatinib PK sample collection. The dose administered on the day of PK visit may be used as the reference dose in case the date and time of the dose prior to surufatinib PK sample collection is not available (e.g. predose samples on Day 1 of Cycles 2, 5, 9, 17). For tislelizumab, reference dose will be the tislelizumab dose during the same cycle of tislelizumab PK sample collection or last tislelizumab dose for EOT samples.

The actual post-dose sampling times relative to dosing expressed in hours and rounded off to two decimal digits will be used. For the visit when no dose administration is scheduled (e.g. no tislelizumab administration on C1D8 and C1D15), the actual sampling times will be calculated as the difference between the actual clock time of sampling and the actual clock time of the most recent dose administered prior to the visit (e.g. C1D1). If the actual time of sampling is missing, it

will be reported as NR (not recorded) in the listing, and actual time elapsed from the reference dose will be reported as NC (not calculated).

5.3.2. Immunogenicity Analysis

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs to tislelizumab according to the following attributes and endpoints. ADA analysis set include all patients who received at least one dose of tislelizumab and that have one baseline ADA measurement and at least one post-baseline ADA measurement.

ADA attributes:

- **Treatment-boosted ADA** is defined as ADA positive at baseline that was boosted to a 4-fold or higher-level following drug administration.
- **Treatment-induced ADA** is defined as ADA negative at baseline and ADA positive post-baseline.
- **Transient ADA response** is defined as treatment-induced ADA detected only at 1 time point during treatment or follow-up, excluding last time point; or detected at 2 or more time points during treatment or follow-up, where the first and last positive samples are separated by less than 16 weeks and the last time point is negative.
- **Persistent ADA response** is defined as treatment-induced ADA detected at 2 or more time points during treatment or follow-up, where the first and last ADA positive samples are separated by 16 weeks or longer; or detected only in the last time point.
- **Neutralizing ADA** is defined as ADA that inhibits or reduces the pharmacological activity.

ADA response endpoints:

- ADA incidence (also known as treatment-emergent ADA) is defined as sum of treatment-induced and treatment-boosted ADA-positive patients as a proportion of the ADA evaluable population.
- ADA prevalence is defined as proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADA. 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. The results of this analysis may be reported separately from the CSR.

5.3.3. Other Exploratory Analyses

PD-L1 Expression:

The distribution of PD-L1 expression will be examined in all patients in Part 2.

The potential association between PD-L1 expression and tislelizumab treatment effect will be explored. Other potential predictive markers will be assessed.

The exploratory analysis may be reported separately from the CSR.

6. PLANNED ANALYSIS

6.1. Independent Data Monitoring Committee

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

6.2. Interim Analysis

There is no planned formal interim analysis. 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).

An unplanned interim analysis was conducted based on data cut off date of 30 November 2021 to review the safety and efficacy for the dose escalation Part 1 of the study only.

6.3. Final Analysis

The final analysis will be conducted after Database Lock (DBL) for this study.

7. CHANGE FROM THE PROTOCOL

There are no changes from the protocol-planned analyses.

REFERENCE

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982; 29-41.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

APPENDIX 1: STUDY SCHEDULE OF EVENTS

Cycle/Period		**Cycle 1**			**Cycle 2**		**Cycle 3+**	**EOT**	**Efficacy Follow-up**	**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		
Urine pregnancy test					X		X			
Urinalysis	X[11]				X		X	X		
Virological screening	X									
PK and ADA assessments		Refer to Table 9								
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

Footnotes for the Schedule of Events

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 of the protocol.
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 of the protocol.

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 of the protocol.
4. Procedural details for patient demographics, including baseline characteristics, are available in Section 6.1.4 of the protocol.
5. Procedural details for concomitant medications/treatments are available in Section 6.1.5 of the protocol.
6. Procedural details for comprehensive physical examination are available in Section 6.1.6 of the protocol.
7. Procedural details for limited physical examination are available in Section 6.1.7 of the protocol.
8. Procedural details for ECOG performance status are available in Section 6.1.8 of the protocol.
9. Procedural details for vital signs are available in Section 6.1.9 of the protocol.
10. Procedural details for laboratory evaluations are available in Section 6.1.10 of the protocol.
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 of the protocol. 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 of the protocol. MUGA scans are acceptable if ECHO cannot be performed.
14. Procedural details for tumor evaluation and imaging are available in Section 6.1.13 of the protocol.
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, or withdrawal of consent. 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 of the protocol.

APPENDIX 2: NCI CTCAE CRITERIA V5.0 FOR LABORATORY PARAMETERS

PARAMETER (SI Unit)	Hypo	Hyper	ATOXGR			
			Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/L)	Anemia	Hemoglobin increased	Increase in >0 - 2 g/dL Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Increase in >2 - 4 g/dL Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	Increase in >4 g/dL Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	~ ~
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm^3; <LLN - 75.0 × 10e9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 × 10e9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 × 10e9 /L	<25,000/mm^3; <25.0 × 10e9 /L
Leukocytes (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 × 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 × 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 × 10e9 /L	<1000/mm3; <1.0 × 10e9 /L
Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 × 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 × 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 × 10e9 /L	<500/mm3; <0.5 × 10e9 /L
Lymphocytes (10^9/L)	Lymphocyte count decreased	Lymphocyte count increased	<LLN - 800/mm3; <LLN - 0.8 × 10e9/L ~	<800 - 500/mm3; <0.8 - 0.5 × 10e9 /L >4000/mm3 - 20,000/mm3	<500 - 200/mm3; <0.5 - 0.2 × 10e9 /L >20,000/mm3	<200/mm3; <0.2 x 10e9 /L ~
Eosinophils (%)		Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-
Activated Partial Thromboplastin Time (s)		Activated partial thromboplastin time prolonged	>ULN - 1.5 × ULN	>1.5 - 2.5 × ULN	>2.5 × ULN; bleeding	~
International Normalized Ratio		INR increased	>1.2 - 1.5	>1.5 - 2.5	>2.5	~

PARAMETER (SI Unit)	Hypo	Hyper	ATOXGR			
			Grade 1	Grade 2	Grade 3	Grade 4
Albumin (g/L)	Hypoalbuminemia		<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	~
Glucose (mmol/L)	Hypoglycemia		<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Creatinine (umol/L)		Creatinine increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × baseline if baseline was abnormal; >1.5 - 3.0 × ULN if baseline was normal	>3.0 × baseline-6.0 × ULN if baseline was abnormal; >3.0 - 6.0 × ULN if baseline is normal	>6.0 × ULN
Creatine phosphokinase (IU/L)		CPK increased	>ULN - 2.5 × ULN	>2.5 × ULN- 5 × ULN	>5.0 X ULN - 10.0 x ULN	>10.0 × ULN
Alkaline Phosphatase (uKat/L)		Alkaline phosphatase increased	>ULN - 2.5 × ULN if baseline was normal; 2.0 - 2.5 × baseline if baseline was abnormal	>2.5 - 5.0 × ULN if baseline was normal; >2.5 - 5.0 × baseline if baseline was abnormal	>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 × ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate Aminotransferase (uKat/L)		Aspartate aminotransferase increased	>ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal	>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal	>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal	>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal
Alanine Aminotransferase (uKat/L)		Alanine aminotransferase increased	>ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal	>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal	>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal
		Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L

PARAMETER (SI Unit)	Hypo	Hyper	ATOXGR			
			Grade 1	Grade 2	Grade 3	Grade 4
Serum Calcium (mmol/L)	Hypocalcemia		<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Magnesium (mmol/L)		Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	~	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
	Hypomagnesemia		<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Potassium (mmol/L)		Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
	Hypokalemia		<LLN - 3.0 mmol/L	~	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium (mmol/L)		Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
	Hyponatremia		<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Urinary protein		Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0-<3.5g/24hrs	4+ proteinuria; urinary protein >= 3.5g/24hrs	~

APPENDIX 3: AESI CATEGORIES AND PREFERRED TERM

Categories and preferred terms for Surufatinib and Tislelizumab are listed below:

AESI term	Seraching strategy
Hepatic disorders	20000009 Cholestasis and jaundice of hepatic origin (SMQ) 20000013 Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) 20000010 Hepatitis, non-infectious (SMQ) 20000008 Liver related investigations, signs and symptoms (SMQ)
Hypertension	20000147 Hypertension (SMQ)
Haemorrhages	20000039 Haemorrhage terms (excl laboratory terms) (SMQ)
Acute renal failure	20000003 Acute renal failure (SMQ)

APPENDIX 4: IMAE FOR TISLELIZUMAB (PREFERRED TERM)

Treatment	Category	Preferred Term
Tislelizumab	Immune-mediated AEs	Immune-mediated adrenal insufficiency
Tislelizumab	Immune-mediated AEs	Immune-mediated adverse reaction
Tislelizumab	Immune-mediated AEs	Immune-mediated arthritis
Tislelizumab	Immune-mediated AEs	Immune-mediated cholangitis
Tislelizumab	Immune-mediated AEs	Immune-mediated cholestasis
Tislelizumab	Immune-mediated AEs	Immune-mediated cystitis
Tislelizumab	Immune-mediated AEs	Immune-mediated cytopenia
Tislelizumab	Immune-mediated AEs	Immune-mediated dermatitis
Tislelizumab	Immune-mediated AEs	Immune-mediated encephalitis
Tislelizumab	Immune-mediated AEs	Immune-mediated encephalopathy
Tislelizumab	Immune-mediated AEs	Immune-mediated endocrinopathy
Tislelizumab	Immune-mediated AEs	Immune-mediated enterocolitis
Tislelizumab	Immune-mediated AEs	Immune-mediated gastritis
Tislelizumab	Immune-mediated AEs	Immune-mediated hepatic disorder
Tislelizumab	Immune-mediated AEs	Immune-mediated hepatitis
Tislelizumab	Immune-mediated AEs	Immune-mediated hyperthyroidism
Tislelizumab	Immune-mediated AEs	Immune-mediated hypophysitis
Tislelizumab	Immune-mediated AEs	Immune-mediated hypothyroidism
Tislelizumab	Immune-mediated AEs	Immune-mediated lung disease
Tislelizumab	Immune-mediated AEs	Immune-mediated myocarditis
Tislelizumab	Immune-mediated AEs	Immune-mediated myositis
Tislelizumab	Immune-mediated AEs	Immune-mediated nephritis

Treatment	Category	Preferred Term
Tislelizumab	Immune-mediated AEs	Immune-mediated neurological disorder
Tislelizumab	Immune-mediated AEs	Immune-mediated neuropathy
Tislelizumab	Immune-mediated AEs	Immune-mediated oesophagitis
Tislelizumab	Immune-mediated AEs	Immune-mediated pancreatitis
Tislelizumab	Immune-mediated AEs	Immune-mediated renal disorder
Tislelizumab	Immune-mediated AEs	Immune-mediated thyroiditis
Tislelizumab	Immune-mediated AEs	Immune-mediated uveitis
Tislelizumab	Skin Adverse Reactions	Acute febrile neutrophilic dermatosis
Tislelizumab	Skin Adverse Reactions	Angioedema
Tislelizumab	Skin Adverse Reactions	Blister
Tislelizumab	Skin Adverse Reactions	Cutaneous vasculitis
Tislelizumab	Skin Adverse Reactions	Dermatitis
Tislelizumab	Skin Adverse Reactions	Dermatitis allergic
Tislelizumab	Skin Adverse Reactions	Dermatitis bullous
Tislelizumab	Skin Adverse Reactions	Dermatitis exfoliative
Tislelizumab	Skin Adverse Reactions	Dermatitis exfoliative generalised
Tislelizumab	Skin Adverse Reactions	Drug eruption
Tislelizumab	Skin Adverse Reactions	Eczema
Tislelizumab	Skin Adverse Reactions	Erythema multiforme
Tislelizumab	Skin Adverse Reactions	Fixed eruption
Tislelizumab	Skin Adverse Reactions	Idiopathic urticaria
Tislelizumab	Skin Adverse Reactions	Leukoderma
Tislelizumab	Skin Adverse Reactions	Mucocutaneous ulceration
Tislelizumab	Skin Adverse Reactions	Mucosal ulceration
Tislelizumab	Skin Adverse Reactions	Oculomucocutaneous syndrome

Treatment	Category	Preferred Term
Tislelizumab	Skin Adverse Reactions	Pruritus
Tislelizumab	Skin Adverse Reactions	Rash
Tislelizumab	Skin Adverse Reactions	Rash erythematous
Tislelizumab	Skin Adverse Reactions	Rash follicular
Tislelizumab	Skin Adverse Reactions	Rash macular
Tislelizumab	Skin Adverse Reactions	Rash maculo-papular
Tislelizumab	Skin Adverse Reactions	Rash papular
Tislelizumab	Skin Adverse Reactions	Rash pruritic
Tislelizumab	Skin Adverse Reactions	Rash pustular
Tislelizumab	Skin Adverse Reactions	Rash vesicular
Tislelizumab	Skin Adverse Reactions	Skin depigmentation
Tislelizumab	Skin Adverse Reactions	Skin exfoliation
Tislelizumab	Skin Adverse Reactions	Skin hypopigmentation
Tislelizumab	Skin Adverse Reactions	Skin necrosis
Tislelizumab	Skin Adverse Reactions	Stevens-Johnson syndrome
Tislelizumab	Skin Adverse Reactions	Toxic epidermal necrolysis
Tislelizumab	Skin Adverse Reactions	Urticaria
Tislelizumab	Skin Adverse Reactions	Urticaria papular
Tislelizumab	Skin Adverse Reactions	Urticaria vesiculosa
Tislelizumab	Skin Adverse Reactions	Vitiligo
Tislelizumab	Skin Adverse Reactions	Acute generalised exanthematous pustulosis
Tislelizumab	Skin Adverse Reactions	Urticarial vasculitis
Tislelizumab	Skin Adverse Reactions	Rash maculovesicular
Tislelizumab	Skin Adverse Reactions	Urticaria chronic
Tislelizumab	Skin Adverse Reactions	Mucocutaneous rash

Treatment	Category	Preferred Term
Tislelizumab	Skin Adverse Reactions	Toxic skin eruption
Tislelizumab	Skin Adverse Reactions	Dermatitis psoriasiform
Tislelizumab	Skin Adverse Reactions	Epidermal necrosis
Tislelizumab	Skin Adverse Reactions	Mucosal exfoliation
Tislelizumab	Skin Adverse Reactions	Exfoliative rash
Tislelizumab	Skin Adverse Reactions	Mucosal necrosis
Tislelizumab	Skin Adverse Reactions	Drug reaction with eosinophilia and systemic symptoms
Tislelizumab	Skin Adverse Reactions	Autoimmune dermatitis
Tislelizumab	Skin Adverse Reactions	Nodular rash
Tislelizumab	Diabetes	Diabetes mellitus
Tislelizumab	Diabetes	Diabetes mellitus inadequate control
Tislelizumab	Diabetes	Diabetes with hyperosmolarity
Tislelizumab	Diabetes	Diabetic hyperglycaemic coma
Tislelizumab	Diabetes	Diabetic hyperosmolar coma
Tislelizumab	Diabetes	Diabetic ketoacidosis
Tislelizumab	Diabetes	Diabetic ketoacidotic hyperglycaemic coma
Tislelizumab	Diabetes	Diabetic ketosis
Tislelizumab	Diabetes	Increased insulin requirement
Tislelizumab	Diabetes	Insulin resistant diabetes
Tislelizumab	Diabetes	Ketosis-prone diabetes mellitus
Tislelizumab	Diabetes	Pancreatogenous diabetes
Tislelizumab	Diabetes	Latent autoimmune diabetes in adults
Tislelizumab	Diabetes	Type 1 diabetes mellitus
Tislelizumab	Diabetes	Fulminant type 1 diabetes mellitus

HMP-2020-012-GLOB1-7015653-Statistical Analysis Plan V2.0 19September2024_to_Sign

Final Audit Report 2024-09-19

Created:	2024-09-19
By:	PPD
Status:	Signed
Transaction ID:	PPD

"HMP-2020-012-GLOB1-7015653-Statistical Analysis Plan V2.0 19September2024_to_Sign" History

Document created by PPD
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Challenge: The user completed the signing ceremony.

2024-09-19 - 1:17:09 PM GMT

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-09-19 - 1:18:30 PM GMT

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-09-19 - 1:19:16 PM GMT

Document e-signed by PPD

Signing reason: I am the approver

Signature Date: 2024-09-19 - 1:19:27 PM GMT - Time Source: server- IP address: PPD

Agreement completed.

2024-09-19 - 1:19:27 PM GMT