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STUDY TITLE:

A Phase 2 Study Evaluating Futibatinib (TAS 120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline.

STATISTICAL ANALYSIS PLAN
Version 1.0

APPROVAL PAGE

A Phase 2 Study Evaluating Futibatinib (TAS 120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma

Protocol TAS-120-203

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List of Abbreviations and definitions of terms

Abbreviation	Term
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Ccr	Calculated creatinine clearance
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements
iCPD	Confirmed progressive disease
IgG4	Immunoglobulin G4
IR	Incidence rate
iUPD	Unconfirmed progressive disease
I.V.	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MRI	Magnetic resonance imaging
ms	milliseconds
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events

NE	Not evaluable
NGS	Next generation sequencing
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
CCI	CCI
PO	Oral
CCI	CCI
PR	Partial response
PS	Performance status
PT	Preferred term
Q3W	Every 3 weeks
QD	Once daily
QTcF	Fridericia's corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SI	The International System of Units
SOC	System Organ Class
Tx	Treatment
UC	Urothelial carcinoma
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol TAS-120-203.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (I.V.) immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications.

Recently published data (Palakurthi et al. 2019) shows that fibroblast growth factor receptor (FGFR*)* inhibition and anti-PD-1 combination induced significant tumor regression and improved survival. For both erdafitinib monotherapy and combination treatments, tumor control was accompanied by tumor-intrinsic, FGFR pathway inhibition, increased T-cell infiltration, decreased regulatory T cells, and downregulation of PD-L1 expression on tumor cells. Finally, FGFR inhibition may also modulate the microenvironment in non-*FGFR3*-mutated tumors and lead to enhanced efficacy when combined with pembrolizumab in both wild-type and *FGFR3* mutated tumors (Siefker-Radtke et al. 2019).

Futibatinib is a novel and selective small molecule FGFR inhibitor, which is the first irreversible, covalent inhibitor of FGFR1–4 being tested in humans. Futibatinib selectively and irreversibly binds to FGFR to exert an inhibitory effect on the FGF/FGFR pathway. Preclinical studies have shown that futibatinib selectively inhibits the cell growth of human cancer cell lines bearing *FGFR* gene abnormalities; strong antitumor efficacy has been observed with futibatinib in nude mouse or nude rat xenograft models bearing tumors with *FGFR* gene abnormalities.

There is substantial evidence that the combination of a PD-1/PD-L1 inhibitor and an FGFR inhibitor may result in treatment benefit in this population. This Phase 2 study will assess the effect of pembrolizumab and futibatinib on patients with urothelial carcinoma (UC), including patients with *FGFR3* mutation / *FGFR1-4* fusion/rearrangement.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to assess the antitumor activity of the combination of futibatinib and pembrolizumab in patients with unresectable locally advanced or metastatic UC who are not candidate to receive a platinum-based treatment regimen as measured by objective response rate (ORR).

2.1.2. Secondary Objectives

- To evaluate disease control rate (DCR)
- To evaluate duration of response (DoR)
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To investigate the safety of futibatinib in combination with pembrolizumab

2.1.3. Exploratory Objectives

CCI [redacted]

CCI [redacted]

CCI [redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoint

- ORR, defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR)

2.2.2. Secondary Endpoints

- DCR, defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR
- DoR, defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
- PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first
- OS, defined as the time from the date of first dose to the death date
- Safety, based on reported adverse events (AEs) and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0

All the endpoints based on tumor response (ORR, DCR, DoR, PFS) will be calculated based on both Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and iRECIST criteria (Eisenhauer et al. 2009, Seymour et al. 2017).

2.2.3. Exploratory Endpoints

CCI [redacted]

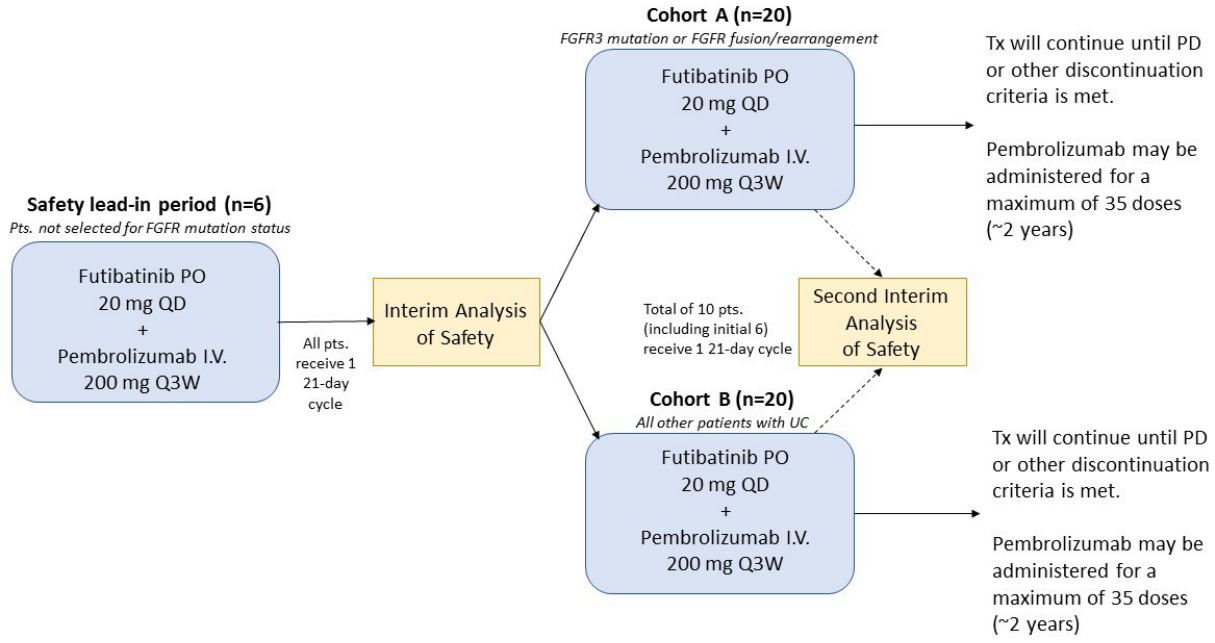
CCI [redacted]

CCI [redacted]

3. STUDY DESCRIPTION

3.1. Summary of Study Design

Study TAS-120-203 is an open-label, non-randomized, multicenter Phase 2 study evaluating the combination of futibatinib and pembrolizumab in patients with advanced or metastatic UC who are not candidates to receive a platinum-based treatment regimen. The design is briefly summarized in Figure 1.



Abbreviations: FGFR=fibroblast growth factor receptor; I.V.=intravenous; mg=milligrams; PD=progressive disease; PO=oral; QD=daily; Q3W=every 3 weeks; Tx=treatment.

Figure 1: Study design flow chart

A treatment cycle is defined as 21 days. All enrolled patients will receive the same treatment regimen:

- Futibatinib at an oral (PO) dose of 20 mg daily (QD); and
- Pembrolizumab at an intravenous (I.V.) dose of 200 mg every 3 weeks (Q3W).

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met; of note, pembrolizumab may be administered for a maximum of 35 doses or a maximum duration of 2 years, whichever is earlier.

The study will begin with a safety lead-in period. During this period, a total of 6 patients with advanced or metastatic urothelial carcinoma will be enrolled and treated for at least one 21-day cycle. Patients will be enrolled into this initial safety lead-in period without regard for *FGFR* alteration status.

After the first 6 patients have completed one cycle of treatment, the first safety analysis will occur. After confirmation of the safety of the combination, a total of 20 additional patients will be enrolled into each of the following 2 cohorts:

- Cohort A: Patients with UC and *FGFR3* mutation or *FGFR* fusion/rearrangement. Patients will be enrolled based on local results but tissue samples will be archived for retrospective confirmation at a central lab using next generation sequencing (NGS)
- Cohort B: All other patients with UC (including patients with other *FGFR* or non-*FGFR* aberrations and patients with wild-type [non-mutated] tumors)

A second safety analysis will occur after enrollment of a total of 10 patients (including the 6 patients from the safety lead-in), in order to confirm the safety profile of the combination before proceeding to the enrollment of the remaining patients in Cohorts A and B.

Please note: at each safety interim analysis, the combination of futibatinib and pembrolizumab will be considered intolerable if the incidence of unacceptable toxicity including dose-limiting toxicity (as defined in Section 5.2 "Definition of Dose-Limiting Toxicity" of the protocol) is ≥33%. If the combination is determined to be intolerable, the study may continue with a reduced dose of futibatinib (16 mg QD) if medically appropriate in the opinion of the investigator and Sponsor.

Of note, the 6 patients initially enrolled in the safety lead-in period will also be assigned to the respective cohort based on *FGFR* alteration, such that each cohort will contain a minimum of 20 and a maximum of 26 patients.

The detailed study schedule is shown in Table 1.

Table 1. Schedule of Events

Evaluations on Day 1 (D1) of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on Cycle 1D1 (C1D1). The End of Treatment (EOT) visit must be performed 0-7 days after a decision is made to discontinue study treatment (for patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed).

		Treatment Period (1 cycle =21 days)					Safety Follow-up			
		Cycle 1			Cycle ≥2					
Evaluation	**Screening (Within 28 days of 1st dose)**	**D1 (-1 day)**	**D8 (-1 day)**	**D15 (-1 day)**	**D1 (-1 day)**	**End of Cycle (±7days)**	**End of Treatment (+0-7 days)**	**30, 60, and 90 days after last dose (±3 days)**	**Survival Follow-up Period (every 12±2 weeks)**	**Notes**
Written informed consent	X									Written informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X									
Demographics/medical history	X									
Review of baseline signs and symptoms	X									
Prior & concomitant medications, AE assessments								►		Collect from the time main informed consent is signed through 90 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier.
Physical examination	X	X			X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X			X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and Weight	X	X			X		X	X		Height at screening only.
ECOG performance status	X	X			X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram		X			X		X	X		

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =21 days)					Safety Follow-up		Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1			Cycle ≥2					
		D1 (-1 day)	D8 (-1 day)	D15 (-1 day)	D1 (-1 day)	End of Cycle (±7days)	End of Treatment (+0-7 days)	30, 60, and 90 days after last dose (±3 days)		
Hematology	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X			X		X	X		
Chemistry (serum or plasma)	X	X	X	X	X		X	X		
Thyroid Function Tests	X	X			X					Every 6 weeks until discontinuation of pembrolizumab.
Pregnancy test	X						X			Serum pregnancy test required within 7 days prior to first dose for WOCBP. Additional testing (urine or serum) as required per local practice.
Ophthalmological examination	X			See Note						Examination to be performed by an ophthalmologist or qualified delegate. At screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits. In cases of retinal pigment epithelial detachment, events should be monitored at 2-3-week intervals.
CCI [redacted]				X						CCI [redacted]

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =21 days)					Safety Follow-up		Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1			Cycle ≥2					
		D1 (-1 day)	D8 (-1 day)	D15 (-1 day)	D1 (-1 day)	End of Cycle (±7days)	End of Treatment (+0-7 days)	30, 60, and 90 days after last dose (±3 days)		
Blood sample for CCI assessment		X			X		X			CCI [redacted]
Tumor tissue collection for CCI assessment	X				X					Mandatory tissue collection at baseline (archival or new tumor biopsy). Optional tumor biopsy to be performed at Day 1 of Cycle 2 only.
Tumor assessments (CT/MRI)	X					(X)	X	X	X	At baseline and the end of every 3 cycles (±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks before EOT) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).
Survival status									X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

3.2. Treatment Assignment and Blinding/Unblinding

After the patient's initial eligibility is established and informed consent has been obtained, futibatinib will be administered orally at a dose of 20 mg daily, and pembrolizumab will be administered as an I.V. infusion of 200 mg on Day 1 of each cycle (that is, every 3 weeks).

This is an open-label, non-randomized study. Blinding/unbinding is not applicable.

3.3. Determination of Sample Size

Approximately 20 patients will be enrolled in Cohort A. Sample size considerations are based on differentiating a historical control ORR per RECIST 1.1 of 35% or less, with a target ORR per RECIST 1.1 of 65%. Assuming the true ORR per RECIST 1.1 is 65%, the cohort has an approximate 80% power to reject the null hypothesis that the true ORR per RECIST 1.1 is ≤35%, considering a 2-sided alpha of 10%. With a sample size of 20, observing at least 12 responders will have a 90% confidence interval (CI) lower bound excluding 10% (ORR per RECIST 1.1 of 60% with 90% CI (39.4% - 78.3%)).

Approximately 20 patients will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR per RECIST 1.1 of 25% or less, with a target ORR per RECIST 1.1 of 50%. Assuming the true ORR per RECIST 1.1 is 50%, the cohort has an approximate 80% power to reject the null hypothesis that the true ORR per RECIST 1.1 is ≤25%, considering a 2-sided alpha of 10%. With a sample size of 20, observing at least 9 responders will have a 90% CI lower bound excluding 10% (ORR per RECIST 1.1 of 45% with 90% CI (25.9% - 65.3%)).

Note that the first 6 patients will be enrolled into the initial safety lead-in period without regard for *FGFR* alteration status. The 6 patients will also be assigned to Cohorts A or B based on *FGFR* alteration, such that each cohort will contain a minimum of 20 and a maximum of 26 patients.

4. STUDY PERIODS, TREATMENT REGIMENS, AND POPULATIONS FOR ANALYSIS

4.1. Study Periods for Analyses

Study periods are defined in Table 2.

Table 2. Definition of Study Periods for Analysis

Period	Definition
Baseline / Screening	From the day of Informed consent form (ICF) signature (up to 28 days before first dose) to the day and time of the first dose of study drug.
On-treatment	From the date of first dose of study drug through 30 days after the last dose of study drug. Unless otherwise specified, the on-treatment period will be the basis for the summaries of safety.

4.2. Treatment Groups/Cohorts

There are two cohorts in this study as described in Section 3.1. Patients in Cohort A must have an *FGFR3* mutation or *FGFR1-4* fusion/rearrangement. All other patients with UC (including patients with other *FGFR* or non-*FGFR* genetic aberrations and patients with wild-type [non-mutated] tumors) will be included in Cohort B.

4.3. Populations for Analysis

- **All Enrolled Population:** All patients enrolled in this study
- **All Treated Population/Full Analysis Set:** All patients in the All Enrolled Population who received at least one dose of study drug. Unless otherwise specified, the All Treated Population will be the basis for the summaries of efficacy and safety.
- CCI [redacted]

4.4. Timing of Analysis

The final analysis for the primary objective will be performed when all patients 1) discontinue study treatment, or 2) have at least 6 months follow-up.

5. STATISTICAL ANALYSIS

5.1. General Methods

All recorded data will be presented in listings.

The categorical data will be summarized using frequency counts and percentages of patients. The continuous data will be summarized using number of non-missing observation (n), mean, standard deviation, median, minimum and maximum unless otherwise specified.

Summary tables will be presented by cohort. Data listings will be presented with patient ID and cohort.

For concomitant medications/therapy and adverse events, the cycle number is determined based on their start/onset dates. For other collected data, the cycle number is determined based on their visit dates. These data include Lab test, Physical exam, Vital signs, Height and Weight, Ophthalmological exam, ECOG, ECG, Pregnancy test, Tumor biopsies, Scheduled tumor assessment.

When there are multiple laboratory records for a scheduled visit, the one closest to the target date will be used for analysis. If there are two or more records with the same time period to the target date, the record with the latest database entry date will be used for analysis.

Time to event distribution, PFS, OS, DoR, time to onset of adverse event of special interest (AESI) in a specific category, and time to resolution of AESI in a specific category, will be estimated using Kaplan–Meier techniques. The number of events and censorings will be reported. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed time points will be derived from the Kaplan-Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t). Confidence intervals for binomial proportions, ORR and DCR, will be derived using the Clopper–Pearson method.

All the analyses of efficacy, safety, and pharmacodynamics data for this study will be performed using SAS® statistical software package, Version 9.3 or a higher version.

5.2. Study Conduct

5.2.1. Accrual

The number of patients accrued will be summarized by country and investigational site on All Enrolled Population. A by-patient listing of accrual with cohort, first dosing date, country and investigational site will also be presented.

5.2.2. Protocol Deviations

Important protocol deviation (ICH E3 Q&A (R1)) is defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the subject's rights, safety or well-being. These include: Important ICF issues, inclusion/exclusion criteria not met, withdrawal criteria not followed; wrong treatment, incorrect dose/overdose based on protocol definitions, important deviations based on protocol design, and other important GCP deviations.

Important protocol deviations will be summarized by category and listed as well.

According to the FDA's guidance on conduct of clinical trials of medical products during COVID-19 pandemic, updated on March 27, 2020 (FDA, 2020), and the EMA's guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic, updated on April 28, 2020 (EMA, 2020), protocol deviations related to COVID-19 will be listed in the CSR.

5.3. Study Population

5.3.1. Patient Disposition

The number of patients in each study population (All Enrolled Population, All Treated Population, CCI) will be summarized by cohort. Patient disposition table will include number of patients treated at data cutoff, number of subjects with treatment ongoing at data cutoff, number of discontinued patients along with the reason for study discontinuation.

5.3.2. Demographic and Other Baseline Characteristics

The following baseline characteristics will be summarized by cohort. Listings will also be provided.

- Age
- Age category (< 65, ≥65)
- Sex (Male, Female)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino, Unknown)
- Race (American Indian/Alaska Native, Asian, Black/African American, Caucasian/White, Native Hawaiian/Other Pacific Islander, Other)
- Region (North America, Europe)
- ECOG PS (0, 1)
- Baseline height
- Baseline weight
- Location of Primary Tumor (Bladder, Upper Tract)
- Sub-type of Location of Primary Tumor (Basal-squamous, Luminal-papillary, Luminal-infiltrated, Luminal, Neuronal, Unknown)
- Any metastases (Yes, No)
- Prior surgery (Yes, No)
- Prior radiotherapy (Yes, No)
- Prior systemic anti-cancer therapy (Yes, No)
- Number of prior lines of systemic therapy
- *FGFR* Status

- *FGFR*1 Fusion, Rearrangement, or Translocation (Yes, No)
- *FGFR*2 Fusion, Rearrangement, or Translocation (Yes, No)
- *FGFR*3 Fusion, Rearrangement, or Translocation (Yes, No)
- *FGFR*3 mutation other than Fusion, Rearrangement, or Translocation (Yes, No)
- *FGFR*4 Fusion, Rearrangement, or Translocation (Yes, No)

All collected information for cancer diagnosis will be summarized and listed.

5.3.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, the most up-to-date version at the time of analysis). Medical history will be summarized by system organ class and preferred term for each cohort and for all patients and will be listed as well.

5.3.4. Prior/Concomitant Therapy

5.3.4.1. Prior Anticancer Therapy

Prior anticancer surgery and prior radiation therapy will be summarized for each cohort and for all patients based on All Treated Population. For prior surgery, the number and percentage of patients with at least one anticancer surgery for primary disease will be presented. The type of surgery will be summarized. The time from prior surgery to the first dosing date will be summarized. For prior radiation therapy, the number and percentage of patients with at least one radiation therapy for primary disease will be presented. The intention of radiotherapy, radiation therapy site location, duration of radiation therapy and time from end date of radiation therapy to first dosing date will be summarized.

For prior systemic anticancer therapy, the number and percentage of patients with at least one prior systemic anticancer therapy for primary disease will be presented. The treatment type and therapy type will be summarized. Patients' best response (CR, PR, SD, PD, and NE) to the therapy will be summarized. The duration of systemic anticancer therapy and time from end date of systemic anticancer therapy to first dosing date will be summarized. The reason for therapy discontinuation will also be summarized. The above analysis will be repeated for each treatment type (adjuvant therapies, neoadjuvant therapies, therapies for advanced/metastatic disease) in separate tables. The number of patients with prior systemic regimens will be summarized.

Prior anticancer therapy will be coded with World Health Organization (WHO) Drug Dictionary (most up-to-date version at the time of analysis) and will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) for each cohort and for all patients based on All Treated Population. Medications and therapies will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summarization if the patient has taken a medication more than once.

All collected information for prior surgery, prior-radiation therapy, and prior anticancer therapy will be listed.

5.3.4.2. Concomitant Medication and Therapy

Medications started prior to the first dose of study drug and continued into the treatment period are considered as concomitant medications and therapies. Medications taken on or after the first dose of study drug through 30 days after the last dose of study drug are considered as concomitant medications and therapies.

Concomitant medications will be coded with World Health Organization (WHO) Drug Dictionary (most up-to-date version at the time of analysis). Concomitant medications will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) for each cohort and for all patients based on All Treated Population. Medications will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summarization if the patient has taken a medication more than once. Agents and medications will be reported using the generic name. All concomitant medications will be listed.

In addition, the number and percentage of patients who received concomitant medications for management of hyperphosphatemia will be summarized by medication class and generic term for each cohort and for all patients. Total duration of medications (excluding overlaps) for management of hyperphosphatemia will be also summarized.

5.4. Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be performed for each cohort based on patients in All Treated Population.

5.4.1. Primary Efficacy Analyses

The primary endpoint is ORR per RECIST 1.1. The description of each efficacy endpoint is provided in Table 3. Tumor assessments will be performed as per Table 1. The evaluation of endpoints will be based on the Investigator or local radiologist.

Table 3. Efficacy Endpoint Definitions

Endpoint	Definition
ORR	The proportion of patients experiencing a best overall response of PR or CR
DCR	the proportion of patients experiencing a best overall response of SD, PR, or CR
DoR	The time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
PFS	The time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first
OS	The time from the date of first dose to the death date
Abbreviations: ORR=objective response rate; CR=complete response; PR=partial response; SD=stable disease; DCR=disease control rate; DoR=duration of response; OS=overall survival; PFS=progression-free survival	

ORR per RECIST 1.1 will be summarized by a binomial response rate for each cohort. ORR per RECIST 1.1 will be calculated based on the best overall response recorded from the start of treatment until progression disease or start of subsequent new anticancer treatment. The overall

response can be derived based on target lesion response, non-target lesion response and the emergence of new lesion for patients with measurable disease at baseline. Table 4 presents the rules to derive the overall response.

The best overall response, CR and PR, will be confirmed with at least 4 weeks intervals of two consecutive time points. A minimum of 6-week interval between initial treatment (first dosing date) and tumor measurement is required for SD. The confirmation rule of the best overall response per RECIST 1.1 is shown in Table 5.

The exact 2-sided 90% CI based on Clopper–Pearson methodology will be derived for ORR.

For Cohort A, the null hypothesis (ORR of 35%) will be rejected if at least 12 responders observed out of 20 patients.

For Cohort B, the null hypothesis (ORR of 25%) will be rejected if at least 9 responders observed out of 20 patients.

Table 4. Overall Response Assessment with Target/Non-target Lesion and New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 5. Confirmation Rules for Overall Response of PR and CR per RECIST 1.1

Earlier Response (to be confirmed)	Later Response (confirmation)	Confirmed Response
CR	CR	CR
CR	Not CR or missing	SD
PR	CR or PR	PR
PR	SD or PD or missing	SD
PR	SD and then PR (only one SD in between)	PR
SD	n/a – no confirmation needed	SD
PD	n/a – no confirmation needed	PD

5.4.2. Secondary Efficacy Analyses

The secondary efficacy endpoints are ORR per iRECIST, DCR per RECIST 1.1, DCR per iRECIST, DoR per RECIST 1.1, DoR per iRECIST, PFS per RECIST 1.1, PFS per iRECIST, and OS. The description of each efficacy endpoint is provided in Table 3. Tumor assessments will be performed as per Table 1. The evaluation of endpoints will be based on the Investigator or local radiologist.

ORR per RECIST 1.1, ORR per iRECIST, DCR per RECIST 1.1, and DCR per iRECIST will be calculated based on the best overall response. The exact 2-sided 95% CI based on Clopper–Pearson methodology will be derived for DCR. The 95% CI of ORR will also be calculated conventionally.

PFS per RECIST 1.1 and OS will be analyzed using Kaplan–Meier product-limit estimates for each cohort. Patients who are alive and progression-free as of the data cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. Median PFS per RECIST and OS will be presented with 2-sided 95% CI if estimable. The cumulative PFS and OS will be plotted over time by cohort. The censoring rule for PFS per RECIST and OS is in Table 6 and Table 8, respectively.

PFS per iRECIST will be analyzed using Kaplan–Meier product-limit estimates for each cohort. Patients who are alive and progression-free as of the data cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. Median PFS per iRECIST will be presented with 2-sided 95% CI if estimable. The cumulative PFS per iRECIST will be plotted over time by cohort.

- The event date to be used for PFS per iRECIST is the first date of iUPD at which iCPD is confirmed at the next assessment.
- If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that the iUPD date is not be used as the progression event date.
- If iCPD is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date is used as the progression event date in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol noncompliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer.
- The censoring rule for PFS per iRECIST is in Table 7, respectively.

DoR per RECIST 1.1 will be evaluated only in patients with objective response of CR or PR. DoR per RECIST 1.1 will be analyzed using Kaplan–Meier product-limit estimates for each cohort. Patients who are alive and progression-free as of the data cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. Median DoR per RECIST 1.1 will be presented with 2-sided 95% CI if estimable. The cumulative DoR per RECIST 1.1 will be plotted over time by cohort. The censoring rule for DoR per RECIST 1.1 is in Table 9.

DoR per iRECIST will be evaluated only in patients with objective response of CR or PR. DoR per iRECIST will be analyzed using Kaplan–Meier product-limit estimates for each cohort. Patients who are alive and progression-free as of the data cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. Median DoR per iRECIST will be presented with 2-sided 95% CI if estimable. The cumulative DoR per iRECIST will be plotted over time by cohort.

- The start date to be used for DoR per iRECIST is the first date of iCR or iPR for which the first evaluation is confirmed at the next assessment.
- The event date to be used for DoR per iRECIST is the first date of iUPD for which iCPD is confirmed at the next assessment.
- If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that the iUPD date is not be used as the progression event date.
- If iCPD is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date is used as the progression event date in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol noncompliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer.
- The censoring rule for DoR per iRECIST is in Table 10, respectively.

Table 6. Censoring Rules for Progression-Free Survival (PFS) per RECIST 1.1

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits	Date of the first assessment that determined PD	PFS event
2	Death during the study with no prior PD	Date of death	PFS event
3	Patients still on treatment without PD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
4	Treatment discontinuation for reasons other than PD or death, and no post baseline tumor assessments	Date of the first dose	Censored
5	Treatment discontinuation for reasons other than PD or death with post baseline tumor assessments	Date of the last tumor assessment	Censored
6	New anticancer treatment started	Date of the last tumor assessment before start of new treatment	Censored
7	Death or PD after two or more missed tumor assessments [c]	Date of the last tumor assessment before missed assessments	Censored
8	No baseline or unreadable baseline assessment but readable post baseline assessments	Date of the first dose	Censored

a. For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment.
b. This refers to patients who were still receiving study treatment at time of data cutoff.
c. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 77 days (= (21 [days/cycle] x 3 [cycles] + 7 [days]) x 2):
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD

Table 7. Censoring Rules for Progression-Free Survival (PFS) per iRECIST

No.	Situation	End Date	Outcome
1	Documented iCPD between scheduled visits	Date of the first assessment of iUPD for which iCPD is confirmed at the subsequent assessments.	PFS event
2	Death during the study with no prior iUPD and no prior iCPD	Date of death	PFS event
3	Death during the study with prior iUPD	Date of the first assessment of iUPD for which death is confirmed at the subsequent assessments.	PFS event
4	Patients still on treatment with no prior iUPD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
5	Patients still on treatment with prior iUPD as of data cut-off [a]	Date of the first assessment of iUPD for which the data cut-off occurred at the subsequent assessments.	PFS event
6	Treatment discontinuation with no prior iUPD	Date of the last tumor assessment	Censored
7	Treatment discontinuation with prior iUPD	Date of the first assessment of iUPD for which the treatment discontinuation occurred at the subsequent assessments.	PFS event
8	New anticancer treatment started with no prior iUPD	Date of the last tumor assessment before start of new treatment	Censored
9	New anticancer treatment started with prior iUPD	Date of the first assessment of iUPD for which the anticancer treatment started at the subsequent assessments.	PFS event
10	No post baseline tumor assessments	Date of the first dose	Censored
11	No baseline or unreadable baseline assessment but readable post baseline assessments	Date of the first dose	Censored

a. For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment.
b. This refers to patients who were still receiving study treatment at time of data cutoff.

Table 8. Censoring Rules for Overall Survival (OS)

Situation	End Date	Outcome
Death before cut-off	Date of death	OS event
Death after data cut-off	Date of data cut-off	Censored
Patient still alive at data cut-off	Date of data cut-off	Censored
Patient discontinued treatment due to any reason before data cut-off	Date last known to be alive	Censored

Table 9. Censoring Rules for Duration of Response (DoR) per RECIST 1.1

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits	Date of the first assessment that determined PD	DoR event
2	Death during the study with no prior PD	Date of death	DoR event
3	Patients still on treatment without PD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
4	Treatment discontinuation for reasons other than PD or death	Date of the last tumor assessment	Censored
5	New anticancer treatment started	Date of the last tumor assessment before start of new treatment	Censored
6	Death or PD after two or more missed tumor assessments [c]	Date of the last tumor assessment before missed assessments	Censored

a. For DoR, the date of last tumor assessment refers to the date of last adequate tumor assessment.
b. This refers to patients who were still receiving study treatment at time of data cutoff.
c. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 77 days (= (21 [days/cycle] x 3 [cycles] + 7 [days]) x 2):
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD

Table 10. Censoring Rules for Duration of Response (DoR) per iRECIST

No.	Situation	End Date	Outcome
1	Documented iCPD between scheduled visits	Date of the first assessment of iUPD for which iCPD is confirmed at the subsequent assessments.	DoR event
2	Death during the study with no prior iUPD and no prior iCPD	Date of death	DoR event
3	Death during the study with prior iUPD	Date of the first assessment of iUPD at which death is confirmed at the subsequent assessments.	DoR event
4	Patients still on treatment with no prior iUPD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
5	Patients still on treatment with prior iUPD as of data cut-off [a]	Date of the first assessment of iUPD for which the data cut-off occurred during the subsequent assessments.	DoR event
6	Treatment discontinuation with no prior iUPD	Date of the last tumor assessment	Censored
7	Treatment discontinuation with prior iUPD	Date of the first assessment of iUPD for which the treatment discontinuation occurred during the subsequent assessments.	DoR event
8	New anticancer treatment started with no prior iUPD	Date of the last tumor assessment before start of new treatment	Censored
9	New anticancer treatment started with prior iUPD	Date of the first assessment of iUPD for which the anticancer treatment started at the subsequent assessments.	DoR event

a. For DoR, the date of last tumor assessment refers to the date of last adequate tumor assessment.
b. This refers to patients who were still receiving study treatment at time of data cutoff.

5.5. Safety Analyses

Unless otherwise specified, all safety analyses will be performed based on All Treated Population. Tables and figures will be generated by cohort.

5.5.1. Extent of Exposure

5.5.1.1. Administration of Study Drug

The following parameters will be summarized by cohort and study drug:

- Duration of treatment
- Number of cycles treated
- Number of doses received
- Cumulative dose
- Relative dose intensity

Duration of treatment (days) will be calculated as: 1) calculate Date of last dose – Date of first dose + 1 for each treated cycle; 2) sum up across all treated cycles.

Cumulative dose is sum of the doses administered to a subject during the treatment period.

Relative dose intensity will be calculated as cumulative dose (dose received) divided by dose planned (taking the dosing cycle into consideration)

A by-patient listing of dosing of study drug and listing of batch number will be also provided.

5.5.1.2. Modification of Study Drug

The number and percentage of patients with at least one dose interruption along with reason for the interruptions will be summarized by cohort and study drug.

The number and percentage of subjects with at least one dose reduction and reason for the dose reduction will be summarized by cohort and study drug.

The number and percentage of subjects with at least one dose discontinuation and reason for the dose discontinuation will be summarized by cohort and study drug.

By-patient listings of dose interruption, dose reduction and dose discontinuation will be also provided.

5.5.2. Adverse Events

5.5.2.1. Deaths

On-treatment deaths and reasons for death will be summarized.

A by-patient listing of all deaths occurring during screening, on-treatment, or survival follow-up periods will be provided.

5.5.2.2. Adverse Events

AE is any untoward medical condition that occurs in patients while participating in this clinical study. Adverse events will be coded according to the MedDRA (the most up-to-date version at the time of analysis) terminology and the severity of the toxicities will be graded according to NCI CTCAE (Version 5.0), where applicable.

An on-treatment AE is defined as an AE that is starting or worsening at the time of or after the first dose of study drug administration and within 30 days after the last dose of study drug, and do not necessarily have a causal relationship to the use of the study drug. All AEs captured in the database will be listed; however, only on-treatment AEs will be summarized.

The following AE summary tables will be generated:

1) Summary of AEs with the number and percentage of patients reporting AEs, serious AEs, grade ≥ 3 AEs, AEs leading to study drug discontinuation, interruption and dose reduction, and AEs with outcome of deaths.

2) Summary of treatment-related AEs with the number and percentage of patients reporting AEs, serious AEs, grade ≥ 3 AEs, AEs leading to study drug discontinuation, interruption and dose reduction, and AEs with outcome of deaths.

3) Summary of AEs by worst CTCAE Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by System Organ Class (SOC) and Preferred Term (PT).

4) Summary of treatment-related AEs by worst CTCAE grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT.

5) Summary of AEs leading to death by SOC and PT.

6) Summary of the most common AEs (≥10% incidence) and median time to first AE by SOC and PT.

5.5.2.3. Adverse Events Leading to Discontinuation of Study Drug

AEs leading to discontinuation will be summarized:

- Summary of AEs leading to discontinuation of study drug by worst CTCAE Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of treatment-related AEs leading to discontinuation of study drug by worst CTCAE grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of AEs leading to discontinuation of study drug will also be provided.

5.5.2.4. Adverse Events Leading to Dose Modification of Study Drug

AEs leading to dose modification (including dose interruption and reduction) of study drug will be summarized:

- Summary of AEs leading to dose modification of study drug by worst CTCAE Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

- Summary of treatment-related AEs leading to dose modification of study drug by worst CTCAE grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of AEs leading to dose modification of study drug will also be provided.

5.5.2.5. Serious Adverse Events

Serious adverse event (SAE) will be summarized:

- Summary of SAEs by worst CTCAE Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of treatment-related SAEs by worst CTCAE Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of SAEs will also be provided.

5.5.2.6. Adverse Events of Special Interest

Incidence

AESI will be summarized:

- Summary of AESI with the number and percentage of patients reporting AESI, serious AESI, grade ≥ 3 AESI, AESI leading to study drug discontinuation, interruption and dose reduction, and AESI with outcome of deaths.
- Summary of AESI by worst CTCAE grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by category or subcategory / PT

A by-patient listing of AESI will also be provided.

Time to Onset

Time-to-onset of selected AESI (e.g. hyperphosphatemia) will be summarized for each category/subcategory of AESI.

- Time-to-onset of any grade AESI
- Time-to-onset of Grade ≥3 AESI

Time-to-onset analyses are restricted to treated patients with at least one specific event.

The derivation of time-to-onset of AESI is detailed in Section 6.4.

Time to Resolution

Time-to-resolution of selected AESI (e.g. hyperphosphatemia) will be summarized.

- Time-to-overall resolution of AESI
- Time-to-resolution of Grade ≥3 AESI (overall and until ≤ Grade 2)

The following summary statistics will be reported: percentage of subjects who experienced the specific events, percentage of subjects with resolution of the AESI (clustered), median, 1st quartile and 2nd quartile of time-to-resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

Time-to-resolution of Grade ≥3 AESI (e.g. hyperphosphatemia) will be graphically displayed using the Kaplan-Meier technique.

Time-to-resolution analyses are restricted to patients who experienced the specific events. Collapsing selected AE and derivation of time-to-resolution of AESI is detailed in Section 6.5.

5.5.2.7. Multiple Events

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs by SOC and PT
- A table showing the total number and rate (exposure adjusted) of occurrences for AESI by category / subcategory

The exposure adjusted incidence rate per X patient time is calculated as X×Y× (total number of unique AEs) / (total exposure time), where:

X = user-specified time factor, X= 1000 or 100

Y = 365.25 for years or Y = 30.4375 for months

For example, Incidence rate (IR) per 100 person-years of exposure (IR/100 P-Y) is calculated as 100 x 362.5 x (total number of unique AE count) / (total exposure time in days).

Unique instances of all AEs (that is, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (same PT) have been collapsed) will be summarized (0 event, 1 event, 2-3 events, ≥ 4 events) by PT. Unique instances of AESI will be summarized (0 event, 1 event, 2-3 events, ≥ 4 events) by category/subcategory.

Unique instances of all AEs will be listed.

The algorithm of collapsing selected AE records is detailed in Section 6.6.

5.5.3. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized using SI units. Laboratory measurements will be summarized for each parameter. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for clinical chemistry, hematology and coagulation parameters at each scheduled visit. Change from baseline will be summarized in a similar manner.

Laboratory test results will be graded by NCI CTCAE (Version 5.0). Shift tables will be presented for each laboratory parameter to display the shift from baseline grade to the worst post-baseline grade. Summary tables will be provided presenting the number and percentage of patients for each laboratory test by baseline grade and worst post-baseline grade. All post-baseline assessments (including unscheduled visits) will be used to determine the worst post-baseline grade. Time to maximum Grade 3/4 and time to resolution (return to grade <=2 or baseline grade or below) may be summarized as appropriate.

All clinical laboratory data will be presented in by-patient listings.

The laboratory tests of Hematology, Coagulation, Serum chemistry are listed in Table 11.

Table 11. Laboratory Tests

Assessment	Test Items
Hematology and Coagulation	Red blood cell count, Hemoglobin, Hematocrit, Platelet count, White blood cell count with differential (Absolute neutrophil count, Lymphocytes, Monocytes, Eosinophils, Basophils), Prothrombin time-international normalized ratio, Activated partial thromboplastin time, Fibrinogen
Chemistry (Serum or plasma)	AST, ALT, ALP, Total bilirubin, Direct bilirubin, Albumin, Lactate dehydrogenase, phosphate, Triglyceride, Total cholesterol, Creatinine, Urea or blood urea nitrogen, Sodium, Bicarbonate, Potassium, Chloride, Magnesium, Calcium (corrected value), Blood glucose, Creatinine clearance (if there is a measured value, use the measured value), estimated glomerular filtration rate

For a calculated creatinine clearance (Ccr) value, use the Cockcroft-Gault formula:

Male Ccr (mL/min) = weight (kg)×(140-age(years))/[72×serum creatinine (mg/dL)]

Female Ccr (mL/min) = male Ccr×0.85

6.5.3.1 Ophthalmological Examination

Ophthalmological examination will be performed at screening (within 28 days prior to futibatinib administration on Day 1 of Cycle 1), 4-6 weeks after starting treatment with futibatinib, and as indicated if symptoms or signs of mineral deposits. Ophthalmological examination encompasses external ocular examination, slit lamp biomicroscopy and dilated ophthalmoscopy. The results of each test will be summarized by scheduled time point. All ophthalmological examination results will be listed in by-patient listing.

5.5.4. Vital Signs

Vital sign measurements include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and body temperature. Each vital sign parameter will be summarized with descriptive statistics by scheduled time point. Change from baseline will be summarized in a similar manner.

Weight at each scheduled time point and change from baseline will be summarized with descriptive statistics by scheduled time point. Weight will be displayed in kilograms. Height, collected only at baseline, will be displayed in centimeters. Body temperature will be displayed in Celsius.

All vital sign data will be presented in by-patient listings.

5.5.5. Electrocardiograms

ECG measurements include HR, RR interval, QT interval, its Fridericia's correction, and proportion of clinically abnormal findings. QTcF (Fridericia's correction) is calculated as $QT/RR^{0.33}$. These ECG parameters will be summarized. Abnormal and abnormal plus clinically significant ECG findings will also be summarized.

All ECG data will be presented in by-patient listings.

5.5.6. Physical Examination

The physical examination will be performed during screening period, on day 1 of each cycle of treatment period, at the End of Treatment, and at safety follow-up.

The physical examination data will be presented in by-patient listing.

5.5.7. ECOG Performance Status

The ECOG performance status score will be obtained during screening period, on day 1 of each cycle of treatment period, at the End of Treatment, and at safety follow-up. The ECOG performance status scores and the grades from 0 to 5 are described in Table 12:

Table 12. Grade Categories of Eastern Cooperative Oncology Group Score

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care. Totally confined to bed or chair
5	Dead

The ECOG performance status score will be summarized with descriptive statistics by scheduled time point. A shift table will be presented to display the shift from baseline grade to the worst post-baseline grade.

5.5.8. Pregnancy Test

If the patient is female and of child bearing potential, a test will be performed during screening period and at the End of Treatment. Pregnancy test result will be presented in by-patient listing.

CCI CCI [redacted]

CCI CCI [redacted]

5.8. Interim Analyses

The first interim analysis of safety will be performed after the first 6 patients in the safety lead-in period have completed cycle 1 of treatment. The second interim analysis of safety will be performed after a total of 10 patients (including the initial 6 patients enrolled in the safety lead-in period) have completed cycle 1 of treatment.

Additional ad-hoc interim analysis for safety or efficacy may be performed as deemed as appropriate.

5.9. Other Analyses

Assessments were not completed or missed due to COVID-19 will be listed per visit.

6. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

6.1. Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study drug.

If the onset time of event or evaluation time or dosing time is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study drug
- Baseline evaluations (laboratory tests, ECOG performance status and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study drug (for ECG, assessments on the day of first dose of study drug will not be included in baseline evaluation)

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study drug will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

6.2. Post-Baseline Period

To allow differentiation as to which study period an Adverse Event occurred, three categories are defined based upon onset date. Adverse Events that had onset dates prior to the first dose of study drug are considered "prior". Adverse events with onset dates on or after the first dose of study drug and within 30 days following the last dose of study drug are considered "**on-treatment**" or equivalently "**treatment emergent**". Events with onset dates more than 30 days after the last dose of study drug are considered as "post-treatment". No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade. AE summary tables will be based on on-treatment AEs only. Adverse events with onset dates prior to the first dose of study drug as well as those after the last dose of study drug +30 days will be identified in the data listings.

6.3. AESI Definition and Conventions

The AESI consist of a list of preferred terms grouped by specific category (for example, pulmonary events, gastrointestinal events categories) and/or by subcategory (for example, diabetes). These categories and subcategories are defined based on MedDRA, and the list that is most current at the time of analysis will be used. Also, changes may be made to this list with each new version of MedDRA.

6.4. Time-to-Onset Definition

Time-to-onset of AESI (any grade) for a specific category (for example, pulmonary events, gastrointestinal events) is defined as the time between the day of the first dose of study drug and the onset date of the earliest AESI (of any grade) in this category.

Time-to-onset of AESI (Grade 3-5) for a specific category is defined similarly but restricted to Grade 3-5 AESI.

Time-to-onset of drug-related (Grade 3-5 or any grade) AESI for a specific category is defined similarly but restricted to drug-related AESI.

Time-to-onset for a specific subcategory is defined similarly but restricted to events in this subcategory.

6.5. Time-to-Resolution Definition

In order to derive the time-to-resolution, overlapping or contiguous AESI within a specific category will be collapsed into what will be termed "clustered" AESI. For example, if a subject (without pre-treatment AE) experienced an AE from 01 January to 05 January, another AE (with different PT but within same category) from 06 January to 11 January, and the same AE from 10 January to 12 January, these will be collapsed into one clustered AESI from 01 January (onset date) to 12 January (resolution date). Table 13 summarizes key derivation steps for each type of clustered select AEs.

Time-to-resolution of AESI (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all AESI clusters in this category experienced by patients. Events which worsened into Grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AESI is considered to be unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different AE events in the clustered AESI should at least have improved to the corresponding (that is, with same preferred term) baseline grade (or improve to lower grade). Time-to-resolution is defined only for subjects who experienced at least one AESI in the specific category.

The time-to-resolution of AESI (Grade 3-5) for a specific category is defined similarly with an onset date corresponding to a Grade 3-5 AESI.

Time-to-resolution of drug-related AESI (any grade or Grade 3-5) is defined similarly but restricted to drug-related AESI.

Time-to-resolution for a specific subcategory is defined similarly but restricted to events of this subcategory.

Table 13. Derivation of Clustered AESI

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment AESI from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AESI from the same category
Grade 3-5	Collapse any on-treatment AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 records (clusters with only Grade 1-2 should not be selected)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 record (clusters with only Grade 1-2 should not be selected)

Abbreviations: AE=adverse event; AESI=adverse event of special interest.

The algorithm for collapsing selected AE records is using the following conventions. For each patient and specified category, the corresponding AE records will be collapsed when:

- Multiple AE records have the same onset date.
- The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
- The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

6.6. Multiple Adverse Events

The algorithm for collapsing multiple records of select AE is using the following conventions. For each patient and specified category, the corresponding adverse event records will be collapsed when:

Multiple adverse event records have the same onset date.

The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).

The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

6.7. Other Data Handling Rules

Missing data will not be imputed in listings. The listings will only present the data recorded on the original CRF.

If an AE has a completely missing onset date, then the AE will be considered an on-treatment AE. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an adverse event or a medication has a partial missing start date or stop date, the following rules will be used to determine whether it is an on-treatment AE, or a prior or concomitant medication.

Table 14. Partial Date Imputation Rule for AE or Medication

Partial Missing Start or Stop Date	Derived Start Date	Imputed Stop Date
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month derived as January or same as first dose month if the year is same as the year of first dose.	Missing month imputed as December

A date with missing year will be considered as completely missing date, no imputation rule will be applied.
The rule in Table 14 is also used for determining the cycle of adverse event and concomitant medication. The derived date is used for determining AEs, the cycle of adverse event and concomitant medication.

For medical history, pre-study surgery, prior radiotherapy, and prior systemic anticancer therapies, a partial missing start date will be imputed as below:

- Missing year - no imputation, date left missing
- Missing day and month - January 1 will be assigned to the missing fields.
- Missing month only - Treat day as missing and replace both month and day with January 1.
- Missing day only - Assign the first day of the month to the missing day.

Note: additional rules for prior systemic anticancer therapies may apply as they pertain to checking for protocol violations

For medical history, pre-study surgery, prior radiotherapy, and prior systemic anticancer therapies,

a partially missing stop dates will be imputed as below:

- Missing year - no imputation, date left missing
- Month is missing and year is prior to year of first dose of study drug- impute 'December'.
- Month is missing and year is the same as the year of the first dose of study drug - impute same month as in first dose date of study drug.
- Day is missing - impute 'last day of that month'. If results in a date ≥ the date of the first dose of study drug impute day as the day prior to date of first dose of study drug.

7. REFERENCES

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8. CHANGES IN PLANNED ANALYSIS

There have been no changes to the initially planned analyses as of the finalization of this SAP.