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Official Title:	A randomized, open label, multicenter Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy
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Cover page of the integrated protocol

A randomized, open label, multicenter Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy

This protocol version is an integration of the following documents/sections:

- **Original protocol,** Version 1.0, dated 29 NOV 2017
- **Amendment no. 3** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 09 MAY 2019
- **Amendment no. 4** (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 12 NOV 2019

This document integrates the original protocol and all global amendments.

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol. This currently includes:

- **Amendment no. 1** (local amendment for UK only) dated 22 JAN 2018
- **Amendment no. 2** (local amendment for France only) dated 19 MAR 2018

1. Title page

A randomized, open label, multicenter Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy

Short title:	Phase 2/3 study of rogaratinib (BAY 1163877) vs chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma		
Acronym:	**FORT-1**		
Test drug:	BAY 1163877 / rogaratinib		
Study purpose:	Assess the efficacy and safety of rogaratinib compared to chemotherapy		
Clinical study phase:	Phase 2/3	Date:	12 NOV 2019
Registration:	EudraCT: 2016-004340-11	Version no.:	3.0
Sponsor's study no.:	17403		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		
Sponsor's medical expert:	PPD Bayer U.S. LLC 100 Bayer Blvd, PO Box 915 Whippany, NJ, 07981 USA Telephone no.: PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Role: Clinical Development Leader (CDL) PPD

Date: 13 Nov 2019

Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	A randomized, open label, multicenter, Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy
Short title	Phase 2/3 study of rogaratinib (BAY 1163877) vs chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma
Acronym	FORT-1
Clinical study phase	Phase 2/3
Study objectives	The original objectives of the study are provided below: Primary objective: • To demonstrate the superiority of rogaratinib over chemotherapy in terms of prolonging overall survival of urothelial carcinoma patients with FGFR positive tumors. Secondary objectives: • To evaluate additional efficacy including the following variables: o progression-free survival (PFS) o objective response rate (ORR) o disease control rate (DCR) o duration of response (DOR) • To evaluate the safety of rogaratinib (adverse events) Tertiary objectives: • Patient-reported outcome (PRO) • Evaluate biomarkers to investigate the drug (i.e. mode-of-action-related effect and/or safety) and/or the pathomechanism of the disease • Pharmacokinetics The objective for the **Phase 2** part of the study is to demonstrate the efficacy of rogaratinib over chemotherapy in terms of objective response rate of urothelial carcinoma patients with FGFR positive tumors. The Phase 3 part of the study will no longer be conducted, therefore OS will be considered an exploratory efficacy variable for the Phase 2.
Test drug	BAY 1163877
Name of active ingredient	Rogaratinib (BAY 1163877)
Dose(s)	600 mg twice daily (b.i.d.), continuously

Route of administration	oral	
Duration of treatment	Patients may continue on study treatment until any of the following events occur: • Radiological disease progression according to RECIST v.1.1 as assessed by independent central radiology review. o At the investigator's discretion, study treatment may continue beyond centrally confirmed radiological progression as defined by RECIST v.1.1 if the clinical condition of the patient is stable or the patient is improving symptomatically, and the investigator expects continued clinical benefit for the patient • Clinical progression • Unacceptable toxicity • Death • Withdrawal of consent • Withdrawal from the study treatment at the discretion of the investigator or designated associate(s)	
Comparator drugs	Taxane (docetaxel or paclitaxel)	Vinflunine
	The choice of the chemotherapy is at the discretion of the investigator, taking into consideration the status of the authorization or treatment guidelines in the given country.	
Name of active ingredient	Taxane (docetaxel or paclitaxel)	Vinflunine
Doses	Docetaxel 75 mg/ m² Paclitaxel 175 mg/ m² Every three weeks on D1 of the cycle	Vinflunine 320 mg/ m² Every three weeks on D1 of the cycle
Route of administration	intravenous infusion	intravenous infusion
Duration of treatment	See test drug above.	
Indication	Patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy	
Diagnosis and main criteria for inclusion /exclusion	Patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy **Main inclusion criteria:** • Existence of archival or fresh biopsy for FGFR testing. Mandatory FGFR testing of patients will be performed prior to start of screening. The timing of the FGFR test is at the discretion of the investigator. Investigators should ensure all patients will be eligible in terms of disease status and lines of treatment within this timeframe. • Male or female patients ≥ 18 years of age	

- Documented urothelial carcinoma (transitional cell carcinoma) including urinary bladder, renal pelvis, ureters, urethra meeting all of the following criteria
  - Histologically confirmed
    - Patients with mixed histologies are required to have a dominant transitional cell pattern.
  - Locally advanced (T4, any N; or any T, N 2−3) or metastatic disease (any T, any N and M1).
    Locally advanced bladder cancer must be unresectable i.e. invading the pelvic or abdominal wall (stage T4b) or presenting with bulky nodal disease (N2-3).
- ECOG Performance Status of 0 or 1
- Disease progression during or following treatment with at least one platinum-containing regimen (patients should have been treated for at least 2 cycles). In patients who received prior adjuvant/neoadjuvant platinum-containing chemotherapy, progression had to occur within 12 months of treatment.
- High FGFR1 or 3 mRNA expression levels in archival or fresh tumor biopsy specimen quantified as outlined in the lab manual
- At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) in contrast enhanced (unless contraindicated) CT or MRI

Main exclusion criteria:

- Previous or concurrent cancer except
  - cervical carcinoma in situ
  - treated basal-cell or squamous cell skin carcinoma
  - any cancer curatively treated > 3 years before randomization
  - Curatively treated incidental prostate cancer (T1/T2a)
- Ongoing or previous anti-cancer treatment within 4 weeks before randomization.
- More than two prior lines of systemic anti-cancer therapy for urothelial carcinoma given for advanced unresectable/metastatic disease.
- Ongoing or previous treatment with anti-FGFR directed therapies (e.g. receptor tyrosine kinase inhibitors including rogaratinib or FGFR-specific antibodies) or with taxanes or vinflunine
- Unresolved toxicity higher than National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v.4.03) Grade 1 attributed to any prior therapy/procedure excluding alopecia, anemia and/or hypothyroidism
- History or current condition of an uncontrolled cardiovascular disease including any of the following conditions:
  - Congestive heart failure (CHF) NYHA > Class 2
  - Unstable angina (symptoms of angina at rest) or new-onset angina

	(within last 3 months before randomization) o Myocardial infarction (MI) within past 6 months before randomization o Unstable cardiac arrhythmias requiring anti-arrhythmic therapy. Patients with arrhythmia under control with anti-arrhythmic therapy such as beta-blockers or digoxin are eligible. • Arterial or venous thrombotic events or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before randomization • Current evidence of endocrine alteration of calcium phosphate homeostasis (e.g. parathyroid disorder, history of parathyroidectomy, tumor lysis, tumoral calcinosis, paraneoplastic hypercalcemia) • Any hemorrhage / bleeding event ≥ CTCAE v.4.03 Grade 3 within 4 weeks before randomization • Current diagnosis of any retinal detachment, retinal pigment epithelial detachment (RPED), serous retinopathy or retinal vein occlusion For the complete list of inclusion and exclusion criteria, please refer to Sections 6.1 and 6.2 of this protocol.
Study design	Randomized, open-label, multicenter Phase 2/3 study. The study is composed of the following periods: • **Pre-treatment period,** including o **FGFR testing** The FGFR1&3 RNA in situ hybridization (RNA-ISH) test is used for the detection of FGFR1 and FGFR3 mRNA levels in formalin-fixed, paraffin-embedded (FFPE) tumor tissue from urothelial carcinoma patients. Mandatory FGFR testing will be performed prior to start of screening (signing of informed consent for study treatment eligibility). The timing of the FGFR test is at the discretion of the investigator. During the FGFR testing period, and after a positive FGFR test result was obtained, these samples are also tested for presence or absence of potential FGFR inhibitor resistance mutations in phosphoinositide 3-kinase catalytic subunit alpha isoform (PIK3CA) and/or in the human orthologues of rat sarcoma (RAS) encoding genes. The outcome of the mutation testing will not affect the study eligibility, it will be used for patient stratification. o **Screening** Only patients with FGFR positive tumors are eligible to continue to the screening which will be scheduled within 28 days before randomization. • **Treatment period**

Patients who meet all the eligibility criteria at screening will be randomized 1:1 using an Interactive Voice/Web Response System (IxRS) to receive either an oral regimen of continuous rogaratinib b.i.d. or chemotherapy (docetaxel, paclitaxel or vinflunine) administered through intravenous (i.v.) infusion every 3 weeks as a comparator drug (investigators choice). Randomization will be stratified by PIK3CA and/or RAS activating mutations (presence vs. absence), prior immunotherapy (yes vs. no), and modified 4-factor Bellmunt risk score (high vs. low).

- **Follow-up period,** including
  - **Active follow-up**

    Safety information is collected for all discontinued patients for at least 30 (up to +7) days after the last administration of study treatment, and both safety and efficacy information is collected for patients who discontinue study treatment without disease progression. Follow-up tumor evaluations will be performed (by CT or MRI) until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met.
  - **Long-term follow-up**

    Patients will be contacted (telephone contact is sufficient) every month (±7 days) to determine survival status and obtain information on subsequent systemic anti-cancer treatment until either data maturation for the final planned OS analysis is reached, death of the patient or any other criterion for withdrawal is met.

Phase 2/3 design

This study follows a Phase 2/3 design with interim analysis, meaning the patients recruited to the Phase 2 part of the study will automatically continue to the Phase 3 part without interruption if futility is not demonstrated at the 1st interim ORR analysis.

The Phase 2 part will end at the time of the cut-off for the 1st interim ORR analysis. To help structure the protocol flow, we present this Phase 2/3 study as one study protocol with two interim analyses, while the first interim indicates the end of the Phase 2 part, and the second and final analyses are considered the Phase 3 part including Phase 2 patients in the analyses.

The Phase 2 part of the study ends when the first approximately 116 confirmed FGFR positive patients with wild-type PIK3CA and RAS biomarkers have completed 4.5 months of treatment, at which time the analysis of Phase 2 part will be triggered. A DMC meeting will be scheduled to review the Phase 2 data. Decisions on trial termination, amendment or cessation of patient recruitment based on risk benefit assessments will be made after recommendations from the DMC have been assessed by the sponsor. In the meantime, the study will continue its routine recruitment until trial termination or recruitment cessation decisions are announced.

If the decision is made to continue the study at the end of Phase 2 period, the study moves on to Phase 3 part of the study. Randomization and treatment continue the same as the Phase 2 part of the study until 390

	deaths are seen in the PIK3CA and RAS WT patients. Before achieving the criteria for the first interim analysis, the study recruitment was put on hold after a recommendation of the study DMC. The sponsor decided to perform a full analysis and review of all study data and stopped the recruitment permanently. Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor.
Methodology	**Efficacy** For OS (original primary variable planned for the Phase 3 part), all patients who end study treatment for any reason (except death) will be contacted to assess survival until death, or any other criterion for withdrawal is met. The secondary efficacy endpoints (PFS, ORR, DCR, and DOR) will be assessed based on central radiological tumor evaluation. Tumor assessments will be performed by contrast-enhanced (unless contraindicated) computed tomography (CT) or magnetic resonance imaging (MRI) of chest/abdomen/pelvis at screening, every 6 weeks (± 7 days) starting from Cycle 1 Day 1 up to week 18, and thereafter, every 9 weeks (± 7 days). A minimum of at least 6 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment. In addition, brain and bone scans are required at screening. The brain and bone scans need to be repeated only if metastases or symptoms are present. Tumor scans are evaluated using RECIST v.1.1. All images need to be submitted continuously for independent central imaging review. The efficacy endpoint for the Phase 2 part of the study is ORR. OS data will be collected as an exploratory efficacy endpoint for the Phase 2. All patients who end study treatment for any reason (except death) will be contacted to assess survival until death, or any other criterion for withdrawal is met. **Safety** Safety and tolerability evaluations will be included in results of physical examinations, vital signs, 12-lead electrocardiogram (ECG) readings, adverse events, concomitant medications and laboratory tests. In addition, ophthalmological examinations will be performed. Each patient will be regularly monitored for potential adverse events and disease related signs and symptoms. AEs will be graded according to The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Laboratory toxicities will be graded according to CTCAE v.4.03 based on numerical laboratory values only. **Patient reported outcome (PRO)** Patient reported outcomes will be assessed using EORTC QLQ-C30 and EQ-5D-3L (at screening, on Day 1 of every cycle, at the EOT, and at the safety assessment visit of the active follow-up). **Pharmacokinetics** Plasma samples for measurement of rogaratinib (BAY 1163877) concentrations will be collected on Day 1 of Cycle 1, 2, 3, 4 and 5 at pre-dose (before supervised dose administration) and 1 (±0.5) hour post-dose.

	Main biomarker investigations For all patients to be enrolled, a biomarker analysis will be done before randomization on either a fresh or archival tumor biopsy sample to confirm high expression levels of fibroblast growth factor receptor (FGFR) mRNA using FGFR1&3 RNA *in situ* hybridization (RNA-ISH) test. The tumor biopsy sample will also be used to test for presence or absence of potential FGFR inhibitor resistance mutations in PIK3CA and/or RAS-encoding genes in FGFR-positive patients. The detection of activating mutations in PIK3CA and/or RAS-encoding genes will be conducted using commercially available assays.
Type of control	Active control: chemotherapy (docetaxel, paclitaxel or vinflunine). The choice of the chemotherapy is at the discretion of the investigator taking into consideration the status of the authorization or treatment guidelines in the given country.
Data Monitoring Committee	Yes
Number of patients	Although both PIK3CA and/or RAS mutant and wild type (WT) patients are recruited, this study is powered for the PIK3CA and RAS WT subgroup. Therefore, the recruitment will stop when approximately 450 PIK3CA and RAS WT patients who meet all selection criteria are randomly assigned in a 1:1 ratio, using IxRS, to one of the following treatment arms: • Rogaratinib, or • Chemotherapy Based on a current assumption that roughly 75% of all study population are PIK3CA and RAS WT patients, at the time when 450 WT patients are randomized, approximately a total of 600 patients (450 WT + 150 mutant patients) will be randomized in the all study population.
Primary variable	The primary efficacy variable of Phase 2 is ORR, and will be analyzed based on central review assessment. Overall survival (defined as the time from randomization until death from any cause) will be considered an exploratory efficacy variable for the Phase 2, since the Phase 3 part of the study will no longer be conducted.
Time point/frame of measurement for primary variable(s)	Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor. Originally planned analyses are given below as reference to the original design. Final OS analysis: at approx. 390 deaths in WT population (approx. 43 months after the start of randomization). In addition, two interim analyses are planned: • 1st interim ORR analysis (Phase 2 part): at approx. the first 116 confirmed FGFR positive patients with wild-type PIK3CA and RAS biomarkers complete 4.5 months of treatment

	• 2nd interim OS analysis (Phase 3 part): at approx. 195 deaths in PIK3CA and RAS WT patients (50% of 390 total death events in WT population, approx. 22 months after start of randomization)
Plan for statistical analysis	The formal statistical analyses will be both descriptive and inferential. Summaries will be provided for each of the treatment arms, rogaratinib and chemotherapy in both PIK3CA and RAS WT and all study population. In addition, descriptive summaries of population characteristics will be provided for the total study population. **Efficacy analyses** In Phase 3, the primary efficacy variable is overall survival (OS). OS data will be considered mature and the final OS analysis (i.e. primary completion) will be performed when approximately a total of 390 PIK3CA and RAS WT patients have died, in accordance with the power calculations specified for the full analysis set (FAS). For the primary efficacy variable of overall survival, a stratified log-rank test controlling type I error at a level of 0.025 (one-sided) will be conducted for the WT population first (step 1). A full alpha of 0.025 (one-sided) will be passed on to OS in all study population and some selected secondary endpoints (step 2), if and only if the null hypothesis of OS for WT population is rejected. Details on controlling family-wise type I error within step 2 for OS in all study population and selected secondary endpoints will be specified in the Statistical Analysis Plan (SAP). In addition, the hazard ratio (rogaratinib / chemotherapy) for OS and its 95% confidence interval will be calculated using the Cox model, stratified by the same factors used for randomization, for both PIK3CA and RAS WT and all study population (referred as "both populations" below). Kaplan-Meier (KM) estimates for OS and KM survival curves will also be presented for each treatment arm and both populations. The KM estimates at time points such as 3 months, 6 months etc. together with corresponding 95% confidence intervals as well as the differences of these estimates will also be calculated between the rogaratinib arm and the chemotherapy arm for both populations. The primary efficacy variable of Phase 2 is ORR, and will be analyzed based on central review assessment. Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor. Secondary efficacy variables include PFS, DCR and DOR based on central review assessments. Formal testing procedure with respect to PFS in WT and all study population will be specified in a separate Statistical Analysis Plan (SAP) document. Since the responders are not a randomized group, no statistical testing will be performed for DOR. Analysis of DOR will be descriptive in nature. **Safety analyses** Summary of adverse events (AEs) is considered a secondary objective for the study. Descriptive tables will be presented by treatment arm for both populations. AEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) terms (v.20.0 or later) and worst grade based on the National Cancer Institute (NCI) Common Terminology

	Criteria Adverse Event (CTCAE), version 4.03. For all events, the relationship to treatment and the severity of the event will be determined by the investigator and summarized by treatment for both populations. Further efficacy and safety analyses details will be outlined in Section 10 of this protocol and in the Statistical Analysis Plan (SAP).

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List of abbreviations

ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
AG	Joint stock company, *Aktiengesellschaft*
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AZD4547	Fibroblast growth factor receptor (FGFR) tyrosine kinase family inhibitor
b.i.d.	Twice daily, *bis in die*
BCRP	Breast cancer resistance protein
BP	Blood pressure
BSA	Body surface area
BSC	Best supportive care
BUN	Blood urea nitrogen
°C	Degree(s) Celsius
CA	California
CD8A	Cluster of differentiation 8A (T-cell surface glycoprotein)
CDL	Clinical Development Leader
CHF	Congestive heart failure
CI	Confidence interval
C_{max}	Maximal plasma concentration
cMet	Tyrosine-protein kinase Met
CMH	Cochran-Mantel-Haenszel
cMyc	v-Myc myelocytomatosis viral oncogene homolog
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organization
CSR	Central serous retinopathy
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
CxDx	Cycle x Day x
CYP	Cytochrome P450

CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
DCR	Disease control rate
DICOM	Digital Imaging and Communications in Medicine
dL	Deciliter
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
e.g.	For example, *exempli gratia*
eGFR	Estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D-3L	EuroQol Group's five dimensions questionnaire
ERK	Extracellular-signal-regulated kinase
eTMF	Electronic trial master file
EU	European Union
EudraCT	European Clinical Trials Database
°F	Degree(s) Fahrenheit
FACP	Fellow of the American College of Physicians
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
FFPE	Formalin-fixed, paraffin-embedded
FGF(R)	Fibroblast growth factor (receptor)
FIM	First-in-man
FRACP	Fellow of the Royal Australasian College of Physicians
FSH	Follicle stimulating hormone
FU	Follow-up
g	Gram
GC	Gemcitabine/cisplatin
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HCG	β-human chorionic gonadotropin
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous-cell carcinoma
HR	Hazard ratio
HRAS	Harvey rat sarcoma viral oncogene homolog

HRQoL	Health-related Quality of Life
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMS	Isotope dilution mass spectroscopy
i.e.	That is, *id est*
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INN	International Nonproprietary Names
INR	International normalized ratio
IR	Immediate release
IRC	Imaging review charter
IRB	Institutional Review Board
ISH	*In situ* hybridization
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous(ly)
IVRS	Interactive voice response system
IWRS	Interactive web response system
IxRS	Interactive voice/web response system
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
LAC	Lung adenocarcinoma
LDH	Lactic dehydrogenase
LLT	MedDRA lowest level term
LPLV	Last patient's last visit
LSF	Liquid service formulation
LSH	Life Science Data Hub
m	Meter
m^2	Square meter
MBBS	Bachelor of Medicine and Bachelor of Surgery
MD	Medical doctor
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
microRNA	Micro ribonucleic acid
min	Minute
mL	Milliliter
mm	Millimeter
mm^3	Cubic millimeter

MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
M&S	Modeling and simulation
mUC	Metastatic urothelial carcinoma
M-VAC	Methotrexate, vinblastine, adriamycin or doxorubicin, and cisplatin
NA	Not applicable
NCI	National Cancer Institute
ng	Nanogram
NJ	New Jersey
No.	Number
NOAC	Novel oral anticoagulant
NRAS	Neuroblastoma rat sarcoma oncogene
NSCLC	Non-small-cell lung carcinoma
NYHA	New York Heart Association
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
p53	Tumor suppressor
PD	Progressive disease
PD-1	Programmed death protein 1
PD-L1	Programmed death-ligand 1
pERK	Extracellular-signal-regulated kinase protein
PET	Positron emission tomography
P-gp	P-glycoprotein
PFS	Progression-free survival
pH	Hydrogen ion concentration
PhD	Doctor of Philosophy
PID	Patient identification number
PI/ICF	Patient information/informed consent form
PIK3CA	Phosphoinositide 3-kinase, catalytic subunit alpha isoform
PK	Pharmacokinetic(s)
p.o.	Orally, *per os*
PP	Polypropylene
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PS	Performance status
PSA	Prostate-specific antigen
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTT	Partial thromboplastin time
QA	Quality assurance
QLQ-C30	30 item Quality of Life Questionnaire
QoL	Quality of Life

QT	QT interval in ECG (time between the start of the Q wave and the end of the T wave)
QTc	Corrected QT interval
RAS	Rat sarcoma
RAVE	Data collection tool
RBC	Red blood cell (count)
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
ROS	Roll-over study
RoW	Rest of World
RPED	Retinal pigment epithelial detachment
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Steering Committee
SCR	Serum creatinine level
SD	Stable disease
SmPC	Summary of product characteristics
sqNSCLC	Squamous non-small-cell lung carcinoma
SSU	Smallest shippable unit
SUSAR	Suspected, unexpected, serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TC-99m	Technetium-99m
TEAE	Treatment-emergent adverse event
TM	Trade mark
TNM	Classification of Malignant Tumors (T = tumor, N = lymph node, M = metastasis)
TSH	Thyroid-stimulating hormone
UC	Urothelial carcinoma
ULN	Upper limit of normal
US / USA	United States / United States of America
USC	University of Southern California
VAS	Visual analog scale
WBC	White blood cell (count)
WOCBP	Women of childbearing potential
WT	Wild type

3. Introduction

In addition to the information provided below please also refer to the latest available version of the investigator's brochure (IB) for rogaratinib (BAY 1163877) and any additional data supplied by the sponsor.

3.1 Background

Bladder cancer is the ninth most common cancer worldwide with an estimated 439,000 new cases and approximately 165,000 death cases in 2012 (1); it is the sixth most common cancer in the United States with an estimated 77,000 new cases in 2016 (2). Approximately three times more men than women are diagnosed with bladder cancer; the majority of patients are > 65 years old.

Bladder cancer can be divided into non-muscle-invasive and muscle-invasive tumors. Approximately 90% of all muscle-invasive bladder cancers are urothelial (transitional) tumors which can occur in the bladder, renal pelvis, ureter and urethra.

Patients with locally advanced or metastatic urothelial carcinoma are not treatable with a curative intent. Standard-of-care systemic treatment for those who are fit enough to tolerate cisplatin includes cisplatin-containing combination chemotherapy, e.g. GC (gemcitabine/cisplatin) or M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) (3). Overall efficacy is similar between GC and M-VAC, but GC shows a better safety profile. Dose-dense M-VAC has a better toxicity profile and is more efficacious in terms of response rate and 2-year overall survival rate than conventional M-VAC. However, median overall survival is similar between the two regimens (4).

After relapse, no standard-of-care treatment exists. Most of the data are derived from uncontrolled trials and are variable depending on patient selection. Potential treatment options after failure of platinum-containing chemotherapy include single-agent chemotherapy (docetaxel, paclitaxel or vinflunine) (5-7). Gemcitabine has also shown good response rates, but most patients already receive this drug as part of their first-line therapy (8). For selected patients, combination chemotherapy can be considered. Recently, several PD-1 and PD-L1 inhibitors, including atezolizumab, pembrolizumab, nivolumab, durvalumab and avelumab have been approved by the FDA for treatment of relapsed patients.

Despite emerging new therapies the majority of patients will eventually progress and die from their disease. Thus there is a clear unmet medical need for the development of additional treatment options.

3.2 Rogaratinib

3.2.1 Mode of action

Rogaratinib (BAY 1163877) is an oral pan-FGFR inhibitor. It shows potent FGFR1, -2, -3 and -4 inhibition in biochemical assays that translates into strong inhibition of cellular downstream pERK resulting in inhibition of FGF2-stimulated tumor cell proliferation. Inhibition of cell proliferation by rogaratinib strongly correlates with expression of mRNA of FGFR isoforms as well as activation by somatic mutations. The high *in-vitro* potency and

mode of action translates into strong *in-vivo* efficacy in tumor models which have an activated FGFR signaling in non-small-cell lung cancer, small-cell lung cancer, bladder, head and neck as well as breast cancer. *In vivo* efficacy is correlated with effective inhibition of tumor FGFR phosphorylation and inhibition of FGFR downstream signaling as shown by pERK inhibition. Moreover, rogaratinib exhibits strong *in vivo* anti-tumor efficacy in monotherapy in FGFR mRNA overexpressing xenograft models with good tolerability. Efficacy in inhibition of tumor growth as well as the respective mode of action of inhibition of FGFR signalling such as phosphorylation of ERK1/2 was also strongly correlated with abundant expression levels of FGFR isoforms in tumor cells or tumor tissues. In addition, rogaratinib demonstrated additive activity with standard-of-care therapy in lung and urothelial carcinoma models.

Rationale for the quantification of mRNA levels of tumor FGFR1 and 3 as predictive biomarker

FGFR3 is the FGFR isoform which is most frequently overexpressed in urothelial carcinoma (overexpressed in up to 50% of all cases) (9, 10). In addition, FGFR3-activating mutations have been frequently observed in early stages of urothelial carcinoma and in advanced metastatic muscle invasive urothelial carcinoma with a lower prevalence (about 10%) (11). Data from a variety of clinical trials with FGFR inhibitors confirmed a high objective response rate (ORR > 30%) in urothelial carcinoma patients having a tumor with genetic (DNA) alterations in FGFR3-encoding gene (12, 13). However, clinical benefits from FGFR inhibitor treatment have also been reported in a urothelial carcinoma patient with high FGFR1 mRNA expression levels (14) and in a patient with high FGFR2 protein expression (15), although FGFR1 and FGFR2-positive UC tumors are more rare compared to FGFR3-positive tumors. In the Phase 1 Study 16443 (see Section 3.2.2), out of the > 120 tumor biopsies evaluated, 43 % were found to be positive for at least one FGFR isoform (FGFR1, or FGFR2 or FGFR3). Out of the FGFR-positive UC samples, prevalence of FGFR3 and FGFR1 mRNA-positivity was 92.4 % and 5.7 %, respectively, whereas isolated FGFR2-positivity could not be observed. It should be noted that this does not preclude future development of a test which is also able to identify the FGFR2 isoform, e.g. for different indication or to generate further data in urothelial carcinoma patients. However, as FGFR2 expression is considerably low in urothelial carcinoma patients, patient selection for Study 17403 will be based on FGFR1 and FGFR3 expression only. For the test device, FGFR1 and FGFR3 will be tested in parallel in one kit.

3.2.2 Clinical experience with rogaratinib

Details of the clinical experience with rogaratinib can be found in the latest available version of the investigator's brochure (IB) for rogaratinib, which contains comprehensive information on the study drug. The IB in its most current version is available in the study file.

Key risks of rogaratinib

Based on the cumulative evidence from the Phase 1 studies 16443 and 16958, the following clinical concepts are considered key risks of rogaratinib:

Retinal disorders

Retinal detachment was observed in association with the treatment with some tyrosine kinase inhibitors including AZD4547–a compound with pan-FGFR inhibitory activity. Therefore, ophthalmological examination was implemented at the baseline and during the course of the Phase 1 trial (Study 16443) to assess the potential effects of the compound on the retinal structure and function.

Details of retinal disorders that have occurred so far can be found in the latest available version of the IB for rogaratinib. Patients should be closely monitored for the risk of retinal disorders during the clinical trials.

Hyperphosphatemia and soft-tissue mineralization

Hyperphosphatemia is a pharmacodynamic effect of rogaratinib, driven by the inhibition of FGFR1 in the kidney and therefore is expected to occur in any patient treated with rogaratinib. Hyperphosphatemia is pathophysiologically linked to soft-tissue mineralization. Although no signs suggestive for soft-tissue mineralization were observed in patients treated with rogaratinib, soft-tissue mineralization is regarded to represent a potential risk of rogaratinib. Therefore, serum phosphate levels of patients treated with rogaratinib must be monitored to avoid a long-lasting hyperphosphatemia beyond the critical level defined as phosphate level ≥ 7 mg/dL (study-specific measures are described in Section 9.6.3.1). Elevation of serum phosphate level starts within few days after initiation of treatment with rogaratinib and may reach a critical level within 1 or 2 weeks.

Nail toxicity

Nail toxicity manifesting as nail dystrophy, onychomadesis, paronychia, and onycholysis were observed in patients treated with rogaratinib. Based on the currently available information the clinical course of nail toxicity can be summarized as follows:

The initial nail changes manifest as painless yellowish/brownish discoloration of the distal part of the nail, within 2-3 months after the start of the therapy with rogaratinib (800 mg b.i.d.). The nail changes progress and affect the structure and surface of the whole nail resulting in a symmetric (all fingers similarly affected) onychodystrophy. Painless onycholysis may follow on some fingers or toes. Nail bed, matrix and the tissue of finger/last phalanx do not seem to be affected. Nail bed inflammation or nail bed infection is regarded to be secondary to onychodystrophy and onycholysis. No SAEs related to nail disorders have been observed.

Please also refer to the latest available version of the investigator's brochure (IB) for rogaratinib.

3.3 Chemotherapy

Docetaxel

For docetaxel, the most common adverse reactions across all indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy,

dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. The most serious reactions include toxic deaths, hepatotoxicity, neutropenia, hypersensitivity, fluid retention, acute myeloid leukemia, cutaneous reactions, neurologic reactions, eye disorders, asthenia, alcohol intoxication (16). Additional information can be found in the SmPC.

Paclitaxel

Very common side effects for paclitaxel are neutropenia, anemia, leukopenia, peripheral neuropathy, nausea, diarrhea, vomiting, mucositis, alopecia, arthralgia, myalgia and hypersensitivity reaction (17). Additional information can be found in the SmPC.

Vinflunine

For vinflunine, the most common treatment-related adverse reactions reported in patients with transitional cell carcinoma of the urothelium were hematological disorders, mainly neutropenia and anemia; gastrointestinal disorders, especially constipation, anorexia, nausea, stomatitis/mucositis, vomiting, abdominal pain and diarrhea, and general disorders such as asthenia/fatigue (18). Additional information can be found in the SmPC.

3.4 Rationale of the study

The preliminary ORR of 24% as well as the toxicity profile observed for rogaratinib in Study 16443 in the urothelial carcinoma are considered favorable compared with other treatment options.

Single-agent taxanes and pemetrexed achieved response rates between 6% and 13% (reviewed in (19)). A Phase 3 trial comparing vinflunine to best supportive care (BSC) reported an ORR of 9% in the vinflunine treatment arm with a median PFS of 3 months for vinflunine (5).

More recently, the PD-L1-blocking antibody atezolizumab has shown an ORR of 15% in the total patient population regardless of PD-L1 expression with a median PFS of 2.7 months (20). Pembrolizumab, a PD-1 inhibitor, reached an ORR of 21% and a PFS of 2.1 months (21).

Additional PD-1 and PD-L1 inhibitors including nivolumab, durvalumab and avelumab have shown similar ORR results as atezolizumab and have recently been approved by the FDA for patients with locally advanced or metastatic urothelial carcinoma (mUC).

The encouraging results of Study 16443 support the continuation of the development of rogaratinib in urothelial carcinoma.

To this end, Study 17403 forms part of the sponsor's clinical development program for rogaratinib. It is intended to generate the pivotal data in support of rogaratinib's registration for the urothelial carcinoma indication in FGFR positive patients.

3.5 Benefit-risk assessment

The pre-clinical information on rogaratinib provides a sound rationale for its clinical activity in several tumor types including urothelial carcinoma. This is confirmed by preliminary

efficacy data from the Phase 1 Study 16443 indicating promising single agent anti-cancer activity of rogaratinib (ORR 24.0%) in patients with urothelial bladder cancer progressing after standard anti-cancer therapy, which is in line with the published data for other selective pan-FGFR inhibitors. The ORR is higher (30.6%) in patients with UC tumors without gain-of-function mutations in phosphatidylinositol-3-kinase catalytic subunit alpha gene (PIK3CA) or without gain-of-function mutations in genes coding for rat sarcoma (RAS) protein family. This data indicates that gain-of-function mutations in PIK3CA and RAS protein family may be responsible for resistance of UC tumors to treatment with pan-FGFR receptor inhibitors. Available data in this subgroup of patients is limited and it cannot be concluded that there is no treatment benefit with rogaratinib. The relevance of these mutations to the activity of standard chemotherapy is also unknown. Beyond UC, a promising anti-tumor efficacy was observed in patients with FGFR-positive head and neck cancer, sqNSCLC and adenoid cystic carcinoma.

The overall safety and tolerability profile of rogaratinib is manageable with risk monitoring and minimization activities reflected in the clinical trial protocols and the recommendations given in the current investigator's brochure. In addition, the results of the full review and analysis of FORT-1 data (cut-off date of 14 June 19) were also consistent with the known safety profile of rogaratinib.

Most frequent toxicities of rogaratinib such as blood phosphorus increased, diarrhea, nail toxicity and alopecia as well as frequent treatment emergent adverse events such as dry mouth, decreased appetite, fatigue, dysgeusia, dry skin, nausea, mucositis and arthralgia can be managed with supportive care in oncology.

The key risks associated with the use of rogaratinib are retinal disorders and soft tissue mineralization.

Retinal disorders consistent with retinal pigment epithelial detachment / central serous retinopathy (RPED/CSR) were observed in patients treated with rogaratinib. Mainly asymptomatic course and mild intensity (Grade 1, 2) of the rogaratinib associated RPED/CSR is in line with known benign nature of RPED/CSR. The risk of irreversible retinal damage is low and can be reduced by rogaratinib treatment withdrawal in case of symptomatic persistent or progressive retinal detachment. Regular ophthalmologic visits will be performed in patients participating in this trial.

Soft tissue mineralization was observed in toxicological studies with rogaratinib and other pan-FGFR inhibitors manifesting as ectopic calcification lesions in kidney, stomach, heart and blood vessels. During the course of the clinical testing of rogaratinib no events consistent with "soft tissue mineralization" were observed. The risk can be predicted and prevented by monitoring and control of phosphate levels in serum.

Risk monitoring and minimization activities reflected in the planned examinations are part of general medical practice and do not expose study participants to an undue risk or burden.

The randomized, controlled study design which includes single-agent chemotherapy, a standard of care treatment option used after failure of platinum-containing chemotherapy, ensures that patients in the control arm receive an active treatment.

Overall, the non-clinical and clinical data collected cumulatively for rogaratinib are considered to support a favorable benefit-risk profile of rogaratinib for use in this study for the planned patient population.

4. Study objectives

The original objectives of the study are provided below:

Primary objective:

- To demonstrate the superiority of rogaratinib over chemotherapy in terms of prolonging overall survival of urothelial carcinoma patients with FGFR positive tumors.

Secondary objectives:

- To evaluate additional efficacy including the following variables
  - progression-free survival (PFS)
  - objective response rate (ORR)
  - disease control rate (DCR)
  - duration of response (DOR)
- To evaluate the safety of rogaratinib (adverse events)

Tertiary objectives:

- Patient-reported outcome (PRO)
- Evaluate biomarkers to investigate the drug (i.e. mode-of-action-related effect and/or safety) and/or the pathomechanism of the disease
- Pharmacokinetics

The objective for the **Phase 2** part of the study is to demonstrate the efficacy of rogaratinib over chemotherapy in terms of objective response rate of urothelial carcinoma patients with FGFR positive tumors (see Section 10.5). The Phase 3 part of the study will no longer be conducted, therefore OS will be considered an exploratory efficacy variable for Phase 2.

The procedures and variables used to address the objectives are specified in Section 9.

5. Study design

5.1 Design overview

This is a randomized, open-label, multicenter Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.

The primary objective of this entire study 17403 is to compare rogaratinib (BAY 1163877) with chemotherapy (docetaxel, paclitaxel or vinflunine) in terms of prolonging the overall

survival (OS) of patients with FGFR positive urothelial carcinoma. The objective for the Phase 2 part of the study is to demonstrate the efficacy of rogaratinib over chemotherapy in terms of objective response rate (ORR) of urothelial carcinoma patients with FGFR positive tumors. For all study objectives, see Section 4.

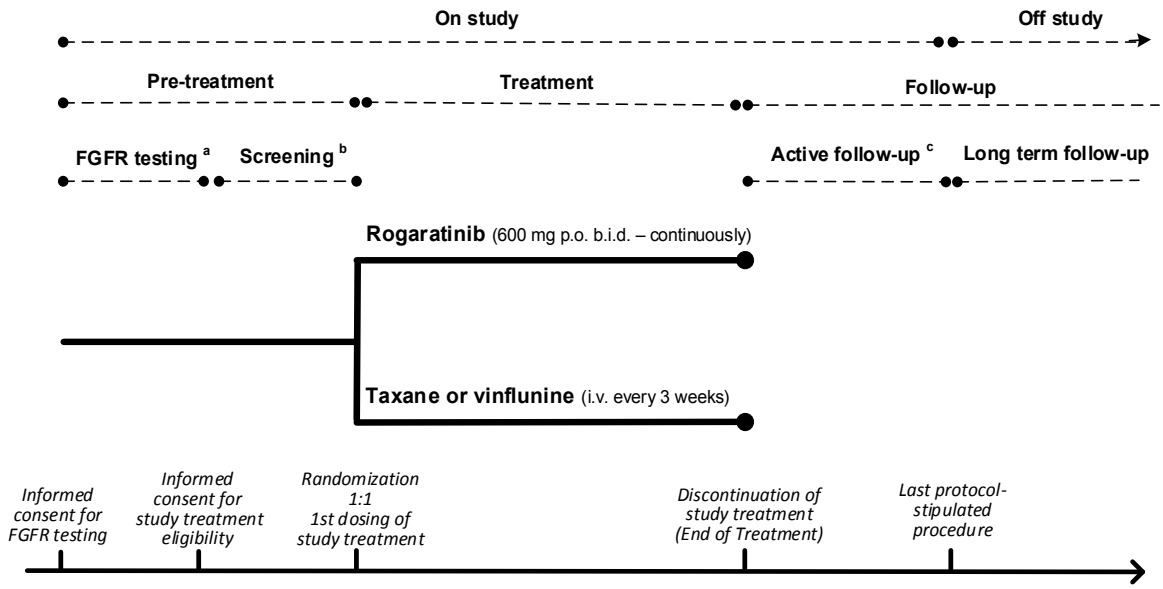
At randomization, patients will have locally advanced or metastatic urothelial carcinoma and have received at least one prior platinum-containing chemotherapy regimen. Only patients with FGFR1 or 3 positive tumors can be randomized into the study. Archival tumor tissue is adequate for testing of FGFR1 and 3 mRNA expression, which will be determined centrally using an RNA *in situ* hybridization (RNA-ISH) test (see Section 9.7.1).

The study will comprise the following periods:

1) **Pre-treatment period**, including **FGFR testing** and **screening**,
2) **Treatment period**, and
3) **Follow-up period**, including **active follow-up** and **long-term follow-up**.

Patients will be considered “on study” during the pre-treatment, treatment and active follow-up periods. During the long-term follow-up period the patients will be considered “off study” (i.e. no study-related procedures with the patient). An overview of the study design is presented in Figure 5–1.

Figure 5–1: Study 17403 – Design overview



b.i.d. = Twice daily, *bis in die*; FGFR = Fibroblast growth factor receptor; i.v. = intravenously; mg = Milligram; PIK3CA = Phosphoinositide 3-kinase, catalytic subunit alpha isoform; p.o. = Orally, *per os*; RAS = Rat sarcoma; mRNA = Messenger ribonucleic acid.

a: During FGFR testing period, patients will be tested for FGFR1 and 3 mRNA expression levels and, after a positive FGFR test result was obtained, these patients are also tested for presence or absence of potential FGFR inhibitor resistance mutations, PIK3CA and/or RAS. PIK3CA and/or RAS mutation status will not affect patient eligibility, but will be used for patient stratification.

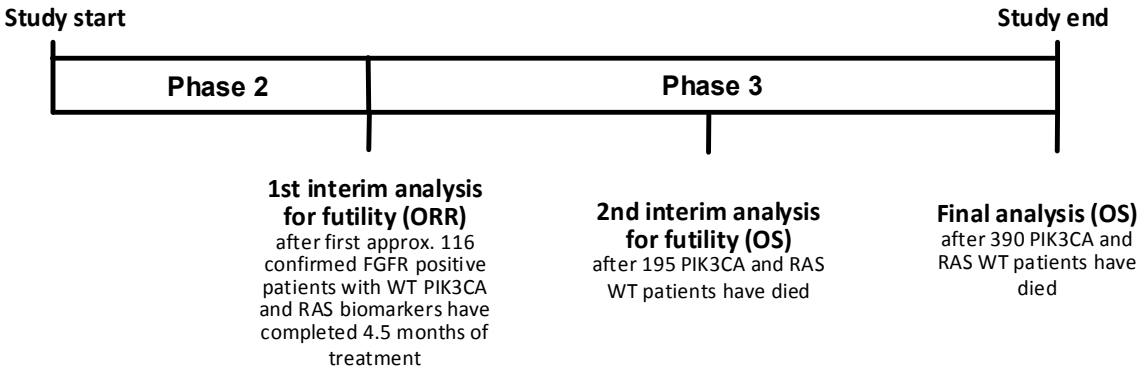
b: Only FGFR-positive patients (high expression of at least FGFR1 or 3) can enter screening.

c: Safety information is collected for all discontinued patients for at least 30 (up to +7) days after the last administration of study treatment, and both safety and efficacy information is collected for patients who discontinue study treatment without disease progression.

Phase 2/3 design

This study was originally designed to follow a Phase 2/3 design with interim analysis, meaning the patients recruited to the Phase 2 part of the study will automatically continue to the Phase 3 part without interruption if futility is not demonstrated at the 1st interim ORR analysis (see below and Section 10.5). An overview of the Ph2/3 study design is presented in Figure 5–2 below. The Phase 2 and 3 parts of the study follow the same screening, treatment and follow-up assessment schedule (Figure 5–1). The Phase 2 part will end at the time of the cut-off for the 1st interim ORR analysis. To help structure the protocol flow, we present this Phase 2/3 study as one study protocol with two interim analyses, while the first interim indicates the end of the Phase 2 part, and the second and final analyses are considered the Phase 3 part including Phase 2 patients in the analyses.

Figure 5–2: Overview of the original Phase 2/3 design



FGFR = Fibroblast growth factor receptor; ORR = Objective response rate; OS = Overall survival; PIK3CA = Phosphoinositide 3-kinase, catalytic subunit alpha isoform; RAS = Rat sarcoma; WT = Wild type.

Based on a current assumption that roughly 75% of all study population are PIK3CA and RAS WT patients, at the time when 450 WT patients are randomized, approximately a total of 600 patients (450 WT + 150 mutant patients) will be randomized in the all study population. The study will focus on randomizing 450 PIK3CA and RAS WT patients while leaving the number of PIK3CA and/or RAS mutant patients open to reflect the distributions in the study population.

The Phase 2 part of the study ends when the first approx. 116 confirmed FGFR positive patients with wild-type PIK3CA and RAS biomarkers have completed 4.5 months of treatment, at which time the analysis of Phase 2 part will be triggered. A DMC meeting will be scheduled to review the Phase 2 data. Decisions on trial termination, amendment or cessation of patient recruitment based on risk benefit assessments will be made after recommendations from the DMC have been assessed by the sponsor. In the meantime, the study will continue its routine recruitment until trial termination or recruitment cessation decisions are announced.

If the decision is made to continue the study at the end of Phase 2 period, the study moves on to Phase 3 part of the study. Randomization and treatment will continue the same as in the Phase 2 part of the study until 390 deaths are seen in the PIK3CA and RAS WT patients.

Before achieving the criteria for the first interim analysis, the study recruitment was put on hold after a recommendation of the study DMC. The sponsor decided to perform a full analysis and review of all study data and stop the recruitment permanently.

Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor.

5.2 Study periods

5.2.1 Pre-treatment period

FGFR testing

Before testing for FGFR1 and 3 mRNA expression levels, patients must sign a patient information/informed consent form (PI/ICF) (see Section 13.4.1), and meet all eligibility criteria for FGFR testing (see Section 6.1). Mandatory FGFR testing will be performed prior to start of screening (signing of informed consent for study treatment eligibility). The timing of the FGFR test is at the discretion of the investigator.

See more about FGFR testing in Section 9.7.1.

Only patients with FGFR-positive tumors (high expression of at least FGFR1 or 3) will be eligible to continue to the screening.

During the FGFR testing period, and after a positive FGFR test result was obtained, these samples are also tested for presence or absence of potential FGFR inhibitor resistance mutations, phosphoinositide 3-kinase catalytic subunit alpha isoform (PIK3CA) and/or in the human orthologues of rat sarcoma (RAS). PIK3CA and RAS testing is done in tumor DNA derived from archival biopsy specimen. The outcome of the mutation testing will not affect the study eligibility, it will be used for patient stratification. For more background information on the potential FGFR inhibitor resistance mutations, please refer to Section 5.4.

Screening

The screening period will start after the patient has signed the PI/ICF for study treatment eligibility (see Section 13.4.2). The screening for treatment eligibility will be scheduled within 28 days before randomization. Please refer to Table 9–1 for the detailed schedule for screening assessments.

5.2.2 Treatment period

All patients who meet the eligibility criteria will be randomized 1:1 into two treatment arms using an Interactive Voice/Web Response System (IxRS):

- Rogaratinib administered as oral (p.o.) 600 mg (3 x 200 mg) tablets twice daily (b.i.d.) continuously, or
- Chemotherapy as taxane (docetaxel or paclitaxel) or vinflunine administered through intravenous (i.v.) infusion every 3 weeks (on Day 1 of the cycle).

Randomization will be stratified by:

- PIK3CA and/or RAS activating mutations (presence vs. absence)
    - In cases when PIK3CA and/or RAS genetic testing results are not available before randomization, those patients with unknown mutation status prior to randomization will be grouped into the mutation “presence” strata in the randomization process.
- Prior immunotherapy (yes vs. no)

- Modified 4-factor Bellmunt risk score (high vs. low) (22)

The first administration of study drug should take place within 3 days of randomization.

The start of the treatment period is defined by the first administration of study treatment.

The planned length of a treatment cycle is 3 weeks (21 days) (see Sections 7.4.3.1 and 7.4.3.2 respectively for rogaratinib and chemotherapy dose modifications, which may lead to prolongation of the duration of a cycle).

Patients may continue on study treatment until any of the following events occur:

- Radiological disease progression according to RECIST v.1.1. At the investigator's discretion, study treatment may continue beyond radiological progression as defined by RECIST v.1.1 if the clinical condition of the patient is stable or the patient is improving symptomatically, and the investigator expects continued clinical benefit for the patient
- Clinical progression
- Unacceptable toxicity
- Death
- Withdrawal of consent
- Withdrawal from the study (see Section 6.4.1).

After discontinuation from study treatment, patients should be treated according to local practice. Please refer to Section 8.2 for post-study therapy.

The end-of-treatment (EOT) visit will be performed for all patients within 14 days after permanent discontinuation of study treatment.

5.2.3 Follow-up periods

5.2.3.1 Active follow-up

Safety information is collected for all discontinued patients for at least 30 (up to +7) days after the last administration of study treatment, and both safety and efficacy information is collected for patients who discontinue study treatment without disease progression. Follow-up tumor evaluations will be performed (by CT or MRI) until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met. During the active follow-up period, CT/MRI evaluations will be performed at the same intervals as during study treatment (every 6 weeks up to week 18, and thereafter, every 9 weeks) (see Table 9–1). Study drug-related toxicity/AE assessment will be followed up and patients will also be contacted for monthly survival assessment.

5.2.3.2 Long-term follow-up

Following completion of the active follow-up, patients will be contacted (telephone contact is sufficient) every month (±7 days) to determine survival status and obtain information on subsequent systemic anti-cancer treatment until either data maturation for the final planned OS analysis is reached, death of the patient or any other criterion for withdrawal is met. If a

patient is lost to follow-up, the site will try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local requirements. An additional contact attempt should be made at the time of each survival sweep.

Patients are considered "off-study" (i.e. no study-related procedures with the patient) while in long-term follow-up.

5.3 Primary variable

The primary efficacy variable of the Phase 3 of this study was overall survival. Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor.

The primary efficacy variable of Phase 2 is ORR, and will be analyzed based on central review assessment. OS will be considered an exploratory efficacy variable for the Phase 2 part.

See Section 9.4 for the full definition. See Section 10.3.1.1 for the planned statistical analyses of the primary variable.

For secondary efficacy variables, see Section 9.4.

Further variables are specified in Section 9.6 (safety variables), Section 9.5 (PK variables) and Section 9.7 (biomarker and PRO variables).

5.4 Justification of the design

Level of blinding: Due to the different dosing schedule, administration route and safety profile with the control drugs, an open-label study design is deemed justified. In addition, overall survival is the primary endpoint, an endpoint that is reliable and easy to measure, documented by date of death, thus bias is not a factor in this endpoint measurement.

Justification of rogaratinib dosage: in the Phase 1 Study 16443, no dose limiting toxicities (DLTs) were observed at doses ranging from 50 mg b.i.d. to 800 mg b.i.d. continuously in 3-week cycles. The highest evaluated dose of 800 mg b.i.d. was initially chosen as the recommended dose regimen for rogaratinib trials. Per DMC data review of 17403 study, the dose of 600 mg b.i.d., was recommended as the maximum starting dose of rogaratinib treatment. This dose regimen was accepted based on the following considerations:

- In the first-in-human study 16443 evaluating rogaratinib in the dose range from 50 mg b.i.d. to 800 mg b.i.d., exploratory rogaratinib plasma exposure to selected adverse events (fatigue, diarrhea and nausea) analysis did not show clear correlation. Additionally, exploratory rogaratinib plasma exposure-clinical response analysis also did not show clear correlation. Based on PK data in small number of patients treated at 600 mg BID (n=4) in Study 16443, a small difference of approximately 10% to 15% in rogaratinib plasma exposures was observed between 600mg b.i.d. and 800 mg b.i.d. dose levels. The range of rogaratinib plasma exposures after 600 mg b.i.d. and 800 mg b.i.d. are expected to largely overlap, although slightly lower at 600 mg b.i.d.

- Dose dependent changes in plasma phosphate concentration confirmed the mechanism of action related to inhibition of renal FGFR activity
- Clinical responses were observed in patients with urothelial bladder cancer and other tumor types with reduced dose regimen schedules.

In conclusion, the new dose schedule of rogaratinib 600 mg b.i.d is considered to be able to provide adequate exposure to the drug with favorable benefit-risk profile.

Choice of comparator: After relapse of first line chemotherapy, no standard of care treatment exists for patients with locally advanced or metastatic urothelial carcinoma. Most of the data are derived from uncontrolled trials and are variable depending on patient selection. Potential treatment options after failure of platinum containing chemotherapy include single agent chemotherapy (docetaxel, paclitaxel or vinflunine) (5-7). Gemcitabine has also shown good response rates, but most patients already receive this drug as part of their first line therapy (8). For selected patients combination chemotherapy can be considered. Recently immune checkpoint inhibitors targeting PD-L1 or PD-1, including atezolizumab, pembrolizumab, nivolumab, durvalumab and avelumab, have shown activity in relapsed urothelial carcinoma patients and have been approved by the FDA (20, 23).

Based on the current treatment paradigm and recommendations from US and European guidelines, single agent chemotherapy of either a taxane or vinflunine is chosen as the comparator for the proposed Phase 3 study. This ensures that study participants in the control arm will receive an active treatment. The doses are in line with current practice in the majority of the countries worldwide. To ensure suitable patients are given the opportunity of treatment with immune checkpoint inhibitors, where available, prior treatment with these agents will be allowed, but is not mandatory.

Patient selection: The FGFR1&3 RNA-ISH assay will be used to aid in the selection of cancer patients who may benefit from the pan-FGFR inhibitor (rogaratinib) therapy. In pre-clinical studies, only xenograft models with high expression levels of either FGFR1 or FGFR2 or FGFR3 demonstrated significant (> 50%) anti-tumor efficacy upon rogaratinib treatment. Preliminary data from Phase 1 Study 16443 confirms that a treatment benefit of having either a partial response or a long-lasting stable disease (SD) is observed in patients that have a high FGFR expression level. Therefore, having at least one FGFR isoform with a high FGFR expression level was selected as inclusion criterion for FGFR-positivity for this Study 17403. In Study 16443, out of > 120 UC biopsies, no single biopsy was found to be positive for FGFR2 only; 83 % were found positive for FGFR3 only, and 5.7 % were found positive for FGFR1 only. Instead, 11.3 % of samples were found to be positive for more than one FGFR isoform (FGFR1/2, FGFR1/3 and FGFR2/3). As either FGFR1 or FGFR3 was detected in all double-positive samples, the use of a FGFR2-specific probe would not lead to the identification of additional patients.

Randomization: Randomization will be stratified to ensure balance of the treatment groups with respect to the following important factors and to avoid any bias that may be associated with an imbalance.

Stratification factors are:

- PIK3CA and/or RAS activating mutations (presence *vs.* absence)

  Rationale: It has been recently published that activating mutations in PIK3CA and RAS genes (NRAS/KRAS/HRAS) are a resistance factor to FGFR inhibitors (24-26). Retrospective mutation analysis of urothelial carcinoma patients enrolled on rogaratinib in Study 16443 revealed that none of the 12 patients presenting with a partial response (PR) as best response according to RECIST v1.1, had an activating mutation in the aforementioned genes. In contrast, 7 out of 14 patients presenting with progressive disease (PD) as best response by rogaratinib-treatment, had an activating mutation in either PIK3CA and/or RAS-encoding genes. It is therefore planned to detect PIK3CA and RAS mutational status in tumor DNA after the FGFR testing in archival tumor biopsy specimen for stratification at randomization to ensure balance of the treatment groups with respect to these mutations. See additional details in Section 9.7.1.

- Prior immunotherapy (yes *vs.* no),

  Rationale: To ensure suitable patients are given the opportunity of prior treatment with the recently approved immune checkpoint inhibitors, stratification regarding use of prior immunotherapy is part of the study.

- Modified 4-factor Bellmunt risk score (high *vs.* low) (see Section 9.3.3)

  Rationale: Prognostic factors have been identified for both first and second line treatment of patients with urothelial carcinoma. For second line, the modified 4-factor Bellmunt risk score defines ECOG performance status, hemoglobin level, liver metastases and time from last systemic anti-cancer therapy dose as main prognostic factors for overall survival. Presence of liver metastases, ECOG PS $\geq$ 1, hemoglobin $<$ 10 g/dL and time from last systemic anti-cancer therapy dose $<$ 90 days are recognized as prognostic factors for predicting shorter overall survival (22).

For justification of the sample size, please refer to Section 10.4.

For justification of study procedures and measurements, see Section 9.8.

For strategies to limit the amount and impact of missing data, see Section 11.4.

5.5 End of study

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last patient for all centers in the respective country has occurred.

The end of the study as a whole will be reached when the last visit of the last patient has been achieved in all participating centers (EU and non-EU), or the primary completion event has been reached, whichever comes later.

LPLV is defined as the last patient's last active follow-up visit.

However, the LPLV date can also be reached based on the last patient stopping study treatment, switching to a roll-over study, a post-trial access program, or being switched to commercial drug supply with no cost to the patient.

If the trial is stopped but benefits are observed for patients, further treatment options may be discussed and agreed between the investigator, sponsor and the patients.

See also Sections 7.2 and 8.2 for further details on the roll-over study.

5.6 Primary completion

In the Phase 3 part, the primary completion for this study (i.e. corresponding to the final OS analysis) was planned when approximately 390 patients have died in the PIK3CA and RAS WT patient population.

Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor.

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

For post-study therapy, refer to Section 8.2.

6. Study population

Patient eligibility will be checked at two sequential time points:

1. At FGFR testing:
   - Mandatory FGFR testing of urothelial carcinoma patients will be performed **prior to start of screening** (signing of informed consent for study treatment eligibility). The timing of the FGFR test is at the discretion of the investigator.
   - Besides the basic criteria for FGFR testing specified below, any criterion as outlined under inclusion and exclusion criteria for screening already known to prohibit the patient's participation in the study should be considered. For "FGFR testing failure" see Section 6.4.1.1.
2. At screening:
   FGFR1 or 3-positive patients will be checked for study treatment eligibility using all further selection criteria specified below. For "screening failure" see Section 6.4.1.1.

6.1 Inclusion criteria

The following inclusion criteria must be met before randomization unless otherwise specified:

Inclusion criteria	***to be checked at***	
	FGFR testing	***Screening***
1. Ability to understand and signing of the written patient information/informed consent form (PI/ICF) for FGFR testing	●	
2. Existence of archival or fresh biopsy for FGFR testing. Mandatory FGFR testing of patients will be performed prior to start of screening (signing of informed consent for study treatment eligibility). The timing of the FGFR test is at the discretion of the investigator. Investigators should ensure all patients will be eligible in terms of disease status and lines of treatment.	●	
3. Male or female patients ≥ 18 years of age (at least age of legal maturity)	●	
4. Documented urothelial carcinoma (transitional cell carcinoma) including urinary bladder, renal pelvis, ureters, urethra, meeting all of the following criteria o Histologically confirmed ▪ Patients with mixed histologies are required to have a dominant transitional cell pattern. o Locally advanced (T4, any N; or any T, N 2−3) or metastatic disease (any T, any N and M1). Locally advanced bladder cancer must be unresectable i.e. invading the pelvic or abdominal wall (stage T4b) or presenting with bulky nodal disease (N2-3).	●	
5. ECOG Performance Status of 0 or 1	●	●
6. Disease progression during or following treatment with at least one platinum-containing regimen (patients should have been treated for at least 2 cycles). In patients who received prior adjuvant/neoadjuvant platinum-containing chemotherapy, progression had to occur within 12 months of treatment.		●

Inclusion criteria	***to be checked at***	
	FGFR testing	***Screening***
7. High FGFR1 or 3 mRNA expression levels in archival or fresh tumor biopsy specimen quantified as outlined in the lab manual.		●
8. Ability to understand and signing of the written PI/ICF for study treatment eligibility. Signed informed consent form must be available before any study-specific procedure for the respective study parts may begin.		●
9. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) in contrast enhanced (unless contraindicated) CT or MRI		●
10. Adequate laboratory and organ function: o Absolute neutrophil count (ANC) ≥ 1,500/mm^3 o Platelet count ≥ 100,000/mm^3 o Hemoglobin ≥ 9.0 g/dL (without transfusion or erythropoietin within 4 weeks before randomization) o Total bilirubin ≤ 1.5 times the upper limit of normal (ULN). Known Gilbert syndrome is allowed if total bilirubin is ≤ 3 x ULN. o Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer) o Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver and bone involvement of their cancer) o Lipase < 2 x ULN o Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to Modification of Diet in Renal Disease (MDRD) abbreviated formula. o International normalized ratio (INR) ≤ 1.5 × ULN, and partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 × ULN. Patients being treated with anticoagulant, e.g. warfarin or heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR is stable based on a pre-dose measurement as defined by the local standard of care.		●
11. Women of childbearing potential (WOCBP) and fertile men must agree to use adequate contraception when sexually active		●

Inclusion criteria	*to be checked at*	
	FGFR testing	*Screening*
from signing of the ICF for study treatment eligibility until at least 12 weeks after the last study drug administration of rogaratinib or vinflunine and until at least 6 months for docetaxel or paclitaxel. The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods include: o Combined (estrogen and progesterone containing: oral, intravaginal, transdermal) and progesterone-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation. o Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS). o Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success). o Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient). ▪ Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Male patients with a female partner of childbearing potential must use a condom and ensure that an additional form of contraception is also used during treatment and until 12 weeks after last study drug administration. Genetic consultation is recommended if the patient wishes to have children after ending the treatment with chemotherapy or rogaratinib. These treatments could affect male fertility; therefore fertility preservation (sperm conservation) should be considered before starting treatment with the study drug. Note: a woman is considered WOCBP, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a		

Inclusion criteria	***to be checked at***	
	FGFR testing	***Screening***
postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.		
12. Negative serum pregnancy test in women of childbearing potential (performed within 7 days before randomization). Negative results must be available prior to study drug administration.		●

6.2 Exclusion criteria

The following exclusion criteria must be met before randomization unless otherwise specified:

Exclusion criteria	***to be checked at***
	Screening
1. Previous or concurrent cancer except o cervical carcinoma *in situ* o treated basal-cell or squamous cell skin carcinoma o any cancer curatively treated > 3 years before randomization o curatively treated incidental prostate cancer (T1/T2a)	●

Exclusion criteria	***to be checked at Screening***
2. Active symptomatic or untreated brain metastases as determined by CT or MRI evaluation during screening and prior radiographic assessment. Patients with treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria: o evaluable or measurable disease outside the CNS o no metastases to midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm) o no history of intracranial or spinal cord hemorrhage o no evidence of significant vasogenic edema o anticonvulsants at stable dose are allowed o no stereotactic radiation, whole-brain radiation or neurosurgical resection within 12 weeks before the first study drug administration o radiographic demonstration of interim stability (i.e. no progression) between the completion of CNS-directed therapy and the screening radiographic study o screening CNS radiographic study ≥ 4 weeks since completion of radiotherapy or surgical resection. Also the patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for one month prior to and following screening radiographic studies).	●
3. Known human immunodeficiency virus (HIV) infection	●
4. Renal dialysis	●
5. Any malabsorption condition	●
6. Breast-feeding	●
7. Ongoing or previous treatment with anti-FGFR directed therapies (e.g. receptor tyrosine kinase inhibitors including rogaratinib or FGFR-specific antibodies) or with taxanes or vinflunine	●

Exclusion criteria	***to be checked at Screening***
8. More than two prior lines of systemic anti-cancer therapy for urothelial carcinoma given for advanced unresectable/metastatic disease	●
9. Ongoing or previous anti-cancer treatment within 4 weeks before randomization. o Patients who have received prior treatment with anti-CTLA-4 may be enrolled provided at least 5 half-lives (approximately 75 days) have elapsed before randomization. o Prior cancer vaccines and cellular immunotherapy are permitted. o Previous radiotherapy is acceptable under the following conditions: ▪ Therapeutic radiotherapy ≥ 3 weeks before the baseline tumor scan. ▪ Palliative radiotherapy for bone metastases or soft tissue lesions is allowed and should be completed >7 days prior to baseline tumor scan. ▪ Lesions at the site of previous radiotherapy should have evidence of progressive disease if this is the only site of disease. Anti-cancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity, including immunotherapy administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.	●
10. Use of strong inhibitors and inducers of CYP3A4 (see Appendix 16.1) should have been stopped 2 weeks before randomization.	●
11. Concomitant therapies that are known to increase serum calcium or phosphate levels and cannot be discontinued or switched to a different medication before randomization	●
12. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results	●
13. Major surgery, or significant trauma within 4 weeks before randomization (central line surgery is not considered major surgery)	●

Exclusion criteria	***to be checked at Screening***
14. Unresolved toxicity higher than National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v.4.03) Grade 1 attributed to any prior therapy/procedure excluding alopecia, anemia and/or hypothyroidism	●
15. History or current condition of an uncontrolled cardiovascular disease including any of the following conditions: o Congestive heart failure (CHF) NYHA > Class 2 o Unstable angina (symptoms of angina at rest) or new-onset angina (within last 3 months before randomization) o Myocardial infarction (MI) within past 6 months before randomization o Unstable cardiac arrhythmias requiring anti-arrhythmic therapy. Patients with arrhythmia under control with anti-arrhythmic therapy such as beta-blockers or digoxin are eligible	●
16. Arterial or venous thrombotic events or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before randomization	●
17. Current evidence of endocrine alteration of calcium phosphate homeostasis (e.g. parathyroid disorder, history of parathyroidectomy, tumor lysis, tumoral calcinosis, paraneoplastic hypercalcemia)	●
18. Current diagnosis of any retinal detachment, retinal pigment epithelial detachment (RPED), serous retinopathy or retinal vein occlusion	●
19. Active infection with hepatitis B or C, requiring treatment Note: prophylactic antiviral treatment against reactivation of chronic hepatitis B (e.g. entecavir) is allowed	●
20. Active infections (≥ CTCAE v.4.03 Grade 3)	●
21. Evidence or history of bleeding diathesis or coagulopathy	●
22. Any hemorrhage / bleeding event ≥ CTCAE v.4.03 Grade 3 within 4 weeks before randomization	●
23. Seizure disorder requiring therapy	●
24. Serious, non-healing wound, ulcer or bone fracture	●

Exclusion criteria	*to be checked at Screening*
25. Any condition that is unstable or could jeopardize the safety of the patient and his/her compliance in the study	●
26. Inability to swallow oral medications	●
27. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation	●
28. Previous assignment to study treatment during this study	●
29. Investigational drug treatment outside of this study during or within 4 weeks before randomization.	●
30. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)	●

6.3 Justification of selection criteria

The selection criteria are chosen to ensure that patients with specific risks for administration of the study drugs and/or patients with conditions which may have an impact on the aims of the study are excluded.

6.4 Withdrawal of patients from study

6.4.1 Withdrawal

6.4.1.1 Screening failure

Depending on the time point of withdrawal before randomization, a withdrawn patient is referred to as either “FGFR testing failure” or “screening failure” as specified below:

FGFR testing failure (pre-screening failures)

A patient with low FGFR 1 or 3 mRNA expression levels, quantified as outlined in the lab manual, **must not** be screened for study treatment eligibility but **needs to be withdrawn from the study** and is regarded as a “FGFR testing failure”. The “FGFR testing failure” will be registered in IxRS.

For data to be collected for FGFR testing failures, refer to Section 11.1 (data recorded during FGFR testing period)

Screening failure

Patients who have signed the pre-screening informed consent and have not completed the FGFR test and FGFR-positive patients who, for any reason (e.g. failure to meet the selection

criteria), terminate the study before randomization, are regarded as “screening failures”. The “screening failure” will be registered in IxRS.

For data to be collected for screening failures, refer to Section 11.1 (data recorded during screening).

6.4.1.2 Re-screening

Patients who have signed the pre-screening informed consent and have not completed the FGFR test could have the FGFR test done. **Re-testing for FGFR expression level after obtaining an initial negative result is not allowed.**

Re-starting the defined set of screening procedures to enable the “screening failure” patient’s participation at a later time point is **not** allowed.

Re-screening might be possible considering the following examples:

- The patient had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient’s initial attempt to participate have been changed (via protocol amendment).

Re-screening of patients is only allowed **once** after discussion with the sponsor’s designated medical representative and after approval by the sponsor. Sponsor’s approval of re-screening for a patient must be documented.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the informed consent form, even if it was not changed after the patient’s previous screening.

The screening failure will be registered in IxRS to close the patient identification number (PID), and re-screening will start again by signing a new informed consent form and being assigned a new PID via IxRS.

6.4.1.3 Withdrawal criteria

Withdrawal from study treatment

Patients *must* be withdrawn from the study treatment if any of the following occurs:

- Unacceptable toxicity.
  Any adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the investigator or his/her designated associate(s). Use of illicit drugs or other substances that may, in the opinion of the investigator or his/her designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results. For further details of toxicities leading to treatment discontinuation, please refer to Section 7.4.3 (dose modifications).

- Any grade of recurrent symptomatic pancreatitis.
- Grade 4 non-hematological toxicities in patients treated with rogaratinib.
    - For non-hematological toxicities in patients treated with chemotherapy, refer to the respective SmPC; the decision of dose modification or withdrawal is at the investigator's discretion.
- Grade 3 liver toxicity at the 2nd re-appearance, or grade 3 liver toxicity with AST or ALT > 8x ULN and concomitant rise in bilirubin (in case of negative risk-benefit assessment).
- Clinical progression and/or decline in ECOG PS that can be attributed to disease progression.
    - Symptomatic deterioration (i.e. uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression as determined by the investigator after integrated assessment of radiographic data and clinical status.
- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being.
- Start of a new anti-cancer regimen.
- Development of a malignancy other than urothelial carcinoma or excised non-melanoma skin cancer.
- Any decrease in visual acuity, ocular pain or discomfort, or symptomatic retinal disorders including retinal detachment / retinal pigment epithelial detachment / serous retinopathy / retinal vein occlusion classified analog to CTCAE v.4.03 as Grade 2 or higher. Based on the individual benefit risk assessment and after discussion with the sponsor, patient may interrupt treatment until recovery to at least Grade 1 and then treatment may be resumed at one dose level below. Patients with low visual acuity at baseline (best corrected visual acuity worse than 20/40 and up to 20/200) have to undergo individual clinical evaluation to determine the maintenance in the study, according to investigator's judgment and based on the individual benefit risk assessment.
- Newly diagnosed soft-tissue mineralization suspected to be caused by rogaratinib.
- Severe allergic reaction to study drugs (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- Substantial non-compliance with the requirements of the study.
- Interruption/delay in the administration of study treatment for > 24 days (due to toxicity) or for > 31 days (due to other reasons) from the next intended dose.

- Patients with a positive ß-human chorionic gonadotropin (HCG) test or any other sign consistent with pregnancy. Pregnancy will be reported via the Pregnancy Monitoring Form.
- Patient lost to follow-up.

Patients *may* be withdrawn from the study treatment if any of the following occurs:

- Documented radiological progression (according to RECIST 1.1 criteria) of urothelial carcinoma (local and/or central assessment), unless the patient may benefit from post-progression treatment according to the investigator's judgment. In case radiological progression is suspected by the investigator it is strongly recommended to wait for the confirmation of progressive disease by central review. The full responsibility for patient treatment will nevertheless always be with the treating physician.

  In the event of radiological progression as determined by RECIST (version 1.1) patients may continue to receive study treatment if identified as having continued clinical benefit. For example, a patient with radiological PD per RECIST as assessed by local assessment but improved clinical symptoms (clinical benefit defined as the absence of deterioration of ECOG performance status [e.g. ECOG should not deteriorate from baseline status: 0 to 2 or higher, from 1 to 3 or higher]) may be a patient identified as having continued clinical benefit from study treatment. Decisions about continuing study treatment will be made at the discretion of the investigator, based on the investigator's judgment about the patient's clinical status, and the sponsor should be informed. The reason for continuing treatment past progression needs to be recorded in patient file.
- At the specific request of the sponsor and in agreement with the investigator (e.g. obvious non-compliance, safety concerns).
- Development of any intercurrent illness or situation which, in the judgment of the investigator, may affect assessments of clinical status and study endpoints to a relevant degree.

For patients who withdraw consent to study, no further study-related procedures will be allowed. The patient will not suffer any disadvantage as a result. Any patient removed from the study will remain under medical supervision until discharge or transfer is medically acceptable. All patients will enter the active follow-up period upon discontinuation of the study treatment. Regardless of the reason for discontinuation, all patients will be followed for survival until death is documented, except for those who specifically withdraw consent to follow-up.

Withdrawal from active follow-up

Patients *must* be withdrawn from active follow-up if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.

- Radiologically confirmed PD is observed and/or clinical progression of urothelial carcinoma (local and/or central assessment).
- Start of subsequent systemic anti-cancer treatment.
- Development of a malignancy other than urothelial carcinoma
- Substantial non-compliance with the requirements of the study
- Withdrawal of consent to active follow-up visits
- If, in the investigator's opinion, continuation of the active follow-up visits would be harmful to the patient's well-being
- Patient lost to follow-up
- Death

Withdrawal from long-term follow-up

Patients *must* be withdrawn from long-term follow-up if any of the following occurs:

- Withdrawal of consent to long-term follow-up
- Patient lost to follow-up
- Death

Patients randomized but not treated

In the event a patient is randomized but never treated, an end-of-treatment electronic case report form (eCRF) should be filled out for the patient, stating the date of and reason for not treating the patient. Every effort should be made that the patient participates in the efficacy assessments of the active follow-up, and the long-term follow-up. No safety assessments are required.

Patients lost to follow-up

If a patient is lost to follow-up at any stage of the study, the site will try to contact the patient, the patient’s relatives, or another doctor treating the patient, unless prohibited by local requirements. All attempts to contact the patient or relatives should be documented.

6.4.1.4 General procedures

In all cases, the reason for withdrawal must be recorded in the eCRF and in the patient’s medical records. See Section 11.1 for data recoding.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature termination of the study).

6.4.2 Replacement

No replacement of randomized patients will be allowed during this study.

6.5 Patient identification

After a patient has signed the PI/ICF for FGFR testing, the patient identification number will be provided to the investigators through an Interactive Voice / Web Response System (IxRS). Patients will be identified by a 9-digit patient identification number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

When the patient is found to be eligible for study treatment, a randomization contact to IxRS will be performed and the patient will be given a unique randomization number. A patient can be randomized only once.

7. Treatments

7.1 Treatments to be administered

Patients who successfully complete the screening evaluations are eligible and will be randomized (using IxRS) to one of the two arms following a 1:1 ratio:

- the experimental arm: rogaratinib

  or

- the control arm: chemotherapy (docetaxel, paclitaxel or vinflunine)

The chemotherapy will be sourced centrally by the sponsor. The choice of the chemotherapy is at the discretion of the investigator taking into consideration the status of the authorization or treatment guidelines in the given country.

No other anti-cancer compounds and no placebo will be administered.

7.2 Identity of study treatment

In this study the term “test drug” refers to rogaratinib only. The terms “study drug” or “study treatment” refer to any of the two treatment regimens offered in this trial.

All study drugs centrally provided by the sponsor will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor’s agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs provided, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective

bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

In case patients are transferred to a roll-over study (ROS) or a post-trial access program, drug formulation and / or dosage might change compared to this study depending on the course of the clinical development.

In addition, the supply of commercially available non-Bayer drugs in a roll-over study or a post-trial access program will be at the discretion of the sponsor and can potentially change from central to local supply by the sponsor, to supply per prescription or any other available option.

7.2.1 Rogaratinib (test drug)

Rogaratinib (BAY 1163877) is packaged in a wide-necked, child-proof HDPE plastic bottle (90ml) with 56 dark red coated tablets per bottle. Rogaratinib should be stored in the original container not above 25ºC (77 ºF).

Details of the test drug rogaratinib are given in Table 7–1.

Table 7–1: Identity of test drug (IMP): rogaratinib (BAY 1163877)

Generic name / brand name / INN	Rogaratinib
Formulation	Tablet
Substance code number(s)	BAY 1163877 (BAY 1213802, hydrochloride of BAY 1163877)
Material	BAY 1163877 hydrochloride coated tablet 200mg
Galenical form / formulation / vehicle and reconstitution	IR (immediate release) tablets
Composition	Active ingredients: BAY 1163877 as hydrochloride Other ingredients: Cellulose microcrystalline (filler) Lactose monohydrate (filler) Crospovidone (disintegrant) Copovidone (binder) Magnesium stearate (lubricant) Silica colloidal anhydrous (glidant) Lacquer red (coating material)[a] [a](contains hypromellose, macrogol, titanium dioxide, ferric oxide red)
Strength (amount of drug per unit) or concentration	200 mg BAY 1163877 per tablet
Type of packaging and content	HDPE bottles with screw cap closure sealable to PP (4345 / 0202)
Marketing Authorization Holder	Not applicable

HDPE = High-density polyethylene; IMP = Investigational medicinal product; INN = International Nonproprietary Name; IR = Immediate release; mg = Milligram; PP = Polypropylene.

7.2.2 Chemotherapy (comparator drugs)

This study includes single-agent chemotherapy as a comparator.

The selection of the chemotherapy for the individual patient, either taxane (docetaxel or paclitaxel) or vinflunine, is at the discretion of the investigator taking into consideration the status of the authorization or treatment guidelines in the given country. The investigator's choice for the individual patient will be determined at the screening visit and recorded in IxRS.

The chemotherapy will be sourced centrally by the sponsor.

Docetaxel, paclitaxel or vinflunine will be prepared at the study centers in accordance with the product information and/or local standards and administered per local standards. The participating investigators are required to consult the SmPC/desk reference, which contains details regarding drug properties, formulation, handling, reconstitution, contraindications, precautions and administration. Additional considerations for the use of taxanes (docetaxel, paclitaxel) and vinflunine according to local guidelines should be followed.

7.3 Treatment assignment

The investigator or delegate will contact the IxRS to confirm whether patients have passed or failed the screening evaluations at the end of the screening period. Patients who successfully complete the screening evaluations are eligible and will be randomized following a 1:1 ratio to either the experimental arm (rogaratinib) or the control arm (chemotherapy; docetaxel, paclitaxel or vinflunine) using the IxRS.

The choice of the chemotherapy is at the discretion of the investigator taking into consideration the status of the authorization or treatment guidelines in the given country, and will be recorded in IxRS. The chemotherapy will be provided centrally by the sponsor.

Randomization will be stratified according to

- PIK3CA and/or RAS activating mutations (presence *vs.* absence)
- prior immunotherapy (yes *vs.* no)
- modified 4-factor Bellmunt risk score (high *vs.* low) (see Section 9.3.3)

The first administration of study drug should take place within 3 days of randomization.

To ensure random assignment, a computer-generated randomization list will be prepared by the sponsor and provided to an IxRS. Patients will be randomized using permuted-block randomization. The IxRS will assign each eligible patient to a treatment arm based on the randomization list and will assign a randomization number to the patient.

Confirmation of adequate level of FGFR overexpression will be obtained from the central lab. Confirmation of other inclusion and exclusion requirements will be obtained from the investigator. After confirmation of patient eligibility in IxRS, a patient may be randomized.

The IxRS procedure is described in detail in a separate IxRS instruction manual that will be maintained in the electronic trial master file (eTMF) and in each center's investigator site file.

7.4 Dosage and administration

7.4.1 Doses, dosing schedule and route of administration

Rogaratinib

Following randomization, rogaratinib (BAY 1163877) 600 mg (consisting of 3 tablets à 200 mg) will be taken orally (p.o.) twice a day (b.i.d.), on every day during a 21-day treatment cycle. It is important to take the tablets at the same times each day approximately 12 hours apart.

Special considerations/instructions for rogaratinib dosing:

Rogaratinib tablets should be taken with a glass of water (approximately 200 mL / 7 ounces). Tablets should be swallowed intact and not chewed. Rogaratinib tablets can be taken with or without food.

If a dose of rogaratinib is missed, the prescribed dose should be taken as soon as the patient remembers and up to 3 hours after the usual time. If this is not possible, missed doses should not be replaced and the patient should continue with the next dose as planned.

Chemotherapy

Following randomization, the assigned chemotherapy (monotherapy) will be given as intravenous (i.v.) infusion once every three weeks (on day 1 of a 21-day cycle). The cycle ends with the next infusion.

The most current version of the SmPC will be made available to the investigator and should be considered whenever necessary. In the comparator arm, patients should receive standard premedication for chemotherapy as per local standard-of-care and SmPC.

Docetaxel

The starting dose for docetaxel to be used is 75 mg/m² given as i.v. infusion.

All patients should be premedicated prior docetaxel administration in order to prevent severe hypersensitivity reactions (such as severe hypotension, bronchospasm general rash/erythema and fluid retention). Such premedication may consist of an oral corticosteroid, such as dexamethasone 16 mg per day for three days, starting 1 day prior to docetaxel administration, unless contraindicated. The appropriate premedication regimen may be determined by the investigator. Patients who have developed severe hypersensitivity reactions (such as severe hypotension, bronchospasm or generalized rash/erythema which require immediate discontinuation of docetaxel and appropriate therapy) should not be re-challenged with docetaxel.

See Section 7.4.3.2 for dose modification guidance.

Paclitaxel

The starting dose for paclitaxel to be used is 175 mg/m² given as i.v. infusion.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions (characterized by dyspnea and hypotension requirement treatment, angioedema and generalized urticaria). Such premedication may consist of dexamethasone 20 mg p.o. administered approximately 12 and 6 hours before paclitaxel, or for i.v. administration: 30 to 60 minutes before paclitaxel, diphenhydramine (or its equivalent) 50 mg i.v. 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) i.v. 30 to 60 minutes before paclitaxel. The appropriate premedication regimen may be determined by the investigator. Patients who have developed severe hypersensitivity reactions (such as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalized urticaria) should not be re-challenged with paclitaxel.

See Section 7.4.3.2 for dose modification guidance.

Vinflunine

The starting dose for vinflunine to be used is 320 mg/m² given as i.v. infusion.

In case of 'ECOG performance status (PS) of 1' or 'PS of 0 and prior pelvic irradiation', the treatment should be started at a dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

Dose recommendation in *elderly patients*:

In patients of at least 75 years and less than 80 years, dose of vinflunine to be given is 280 mg/m^2 every 3 weeks; in patients 80 years old and above, dose of vinflunine to be given is 250 mg/m^2 every 3 weeks.

Dose recommendation in *patients with renal impairment*:

Patients with moderate renal impairment (CrCl 40ml/min - <60 ml/min) the recommended dose of vinflunine is 280 mg/m^2 every 3 weeks. In patients with severe renal impairment (CrCl < 40 ml/min) the recommended dose of vinflunine is 250 mg/m^2 every 3 weeks.

Dose recommendation in *patients with hepatic impairment*:

The recommended dose of vinflunine is 250 mg/m² given once every 3 weeks in patients with mild liver impairment (Child-Pugh grade A) or in patients with a prothrombin time ≥60% ULN and 1.5xULN < bilirubin ≤ 3xULN and presenting at least one of the following criteria: transaminases > ULN and/or GGT > 5xULN.

7.4.2 Justification of selected doses

Please refer to Section 5.4.

7.4.3 Dose modifications

7.4.3.1 Dose modifications of rogaratinib

Doses of rogaratinib may be interrupted/delayed or reduced in case of clinically significant hematologic or other toxicities that are possibly, probably or definitely related to rogaratinib. Toxicities will be graded using CTCAE v.4.03. Dose modifications will follow pre-defined dose levels as indicated below.

Dose levels of rogaratinib are defined in Table 7–2.

Table 7–2: Dose levels of rogaratinib (BAY 1163877)

Level	Dose
0	600 mg b.i.d.
-1	400 mg b.i.d.

b.i.d = Twice daily, *bis in die*; mg = Milligram.

Dose modifications will be based on the highest grade of AE since last contact. If a patient experiences multiple toxicities, dose modification should be according to the toxicity with the highest grade.

- In case of multiple toxicities of the same grade, investigator should modify the dose using the most conservative approach, i.e. the lowest recommended dose.
- Patients in whom doses are interrupted due to toxicities should be followed up within 7 to 10 days to re-assess toxicities, if not specified otherwise.
- Patients requiring dose reduction of rogaratinib may have the dose re-escalated by one dose level, if they have been on a stable dose for 3 weeks or more without further toxicities requiring dose modification with the exception of dose reduction due to liver toxicities.
- Patients requiring a continuous dose interruption of rogaratinib due to toxicity > 24 days from the next intended dose or due to other reasons for > 31 days from the next intended dose will be withdrawn from the study treatment.
- If further dose reductions below level -1 are needed, per investigator´s risk benefit assessment, patients may continue at a 200 mg b.i.d. dose regimen after the approval of the sponsor, otherwise, patients will be discontinued from the study treatment.
- If a dose of rogaratinib is missed, the prescribed dose should be taken as soon as the patient remembers and up to 3 hours after the usual time. If this is not possible, missed doses should not be replaced and the patient should continue with the next dose as planned.

The cycle duration will consist of 21 days (delays will prolong the duration of a cycle).

Guidance for dose modifications of rogaratinib is presented in Table 7–3.

Table 7–3: Criteria for dose modification of rogaratinib due to toxicity (excluding hyperphosphatemia, liver toxicity, retinal disorders)

Grade [a]	Dose interruption/delay	Dose change
1 – 2	Treat as scheduled	No change
3	Interrupt/delay [b] until recovery to ≤ Grade 2	Decrease by 1 dose level
4	Discontinue study drug permanently	Discontinue study drug permanently

a: Excludes alopecia, nausea/vomiting and diarrhea if adequately controlled by antiemetic or antidiarrheal treatments, respectively.
b: If not recovered within 24 days, the test drug must be permanently discontinued.

7.4.3.1.1 Hyperphosphatemia

Dose modifications of rogaratinib for elevated serum phosphate levels (≥ 7 mg/dL) and management guidance for hyperphosphatemia are presented in Table 7–4.

Table 7–4: Dose modifications of rogaratinib and management for hyperphosphatemia

Serum phosphate	Countermeasures
Initial phosphate value is abnormally high, but less than 7 mg/dL	Continue rogaratinib at the same dose. Consider low phosphate diet [a] and / or initiate phosphate chelators.
≥ 7 mg/dL for two weeks despite phosphate lowering treatment	Hold rogaratinib and increase dose of phosphate chelators until recovery below 7 mg/dL. Re-start rogaratinib at the same dose level and continue phosphate chelators.
≥ 7 mg/dL despite optimal phosphate lowering treatments and two rogaratinib treatment interruptions on the same dose within four weeks	Hold rogaratinib and continue phosphate chelators until recovery below 7 mg/dL. Re-start rogaratinib, but at one dose level lower and continue phosphate chelators.
≥ 7 mg/dL despite optimal phosphate lowering treatments and two rogaratinib treatment interruptions within four weeks at 400 mg b.i.d.	Hold rogaratinib and continue phosphate chelators until recovery below 7 mg/dL. Re-start rogaratinib at 400 mg b.i.d. and continue phosphate chelators.

b.i.d. = Twice daily, *bis in die.*
a: Low phosphate diet can be considered if the patient's nutritional status is not affected.

In case phosphate binders are not tolerated, phosphate low diet should be considered.

For patients with elevated serum phosphate levels ≥ 7 mg/dL, serum phosphate level and standard single 12-lead ECG has to be checked weekly for ≥ 4 weeks until resolution (serum phosphate < 7 mg/dL).

In patients with hypocalcemia of CTCAE Grade ≥ 2, an additional 12-lead ECG has to be obtained on day of detection of hypocalcemia and should be repeated as clinically indicated.

7.4.3.1.2 Liver toxicity

Dose modifications of rogaratinib for liver toxicity are presented in Table 7–5. Liver toxicity refers to ALT and/or AST and/or bilirubin increases and/or hepatic failure considered possibly related to rogaratinib, and graded according to CTCAE v.4.03. Liver tests will be monitored throughout study treatment.

Table 7–5: Dose modifications of rogaratinib for liver toxicity

Toxicity	Modification schedule
Grade 1-2	No modifications. Treat as scheduled and check AST, ALT and bilirubin weekly for at least 4 weeks.
Grade 3 (except Grade 3 with ALT or AST > 8x ULN and a concomitant rise in bilirubin or hepatic failure)	Interrupt rogaratinib until recovery to ≤ Grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks [a].
1st reappearance	Interrupt rogaratinib until recovery to ≤ Grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks [a,d].
2nd reappearance	Withdraw patient from study treatment permanently [b]
Grade 3 with ALT or AST > 8x ULN and a concomitant rise in bilirubin (of any degree compared to previous bilirubin level) or hepatic failure (of any degree)	In case of a negative risk-benefit assessment, consider permanent discontinuation at the first occurrence [b,c] OR Interrupt rogaratinib until recovery to ≤ Grade 2 or baseline, then reduce 1 dose level and check AST, ALT and bilirubin weekly for at least 4 weeks [a].
1st reappearance	Withdraw patient from study treatment permanently [b]
AST/ALT > 3x ULN with concomitant bilirubin > 2x ULN (absence of another reason)	Withdraw patient from study treatment permanently [b]
Grade 4 [b]	Withdraw patient from study treatment permanently [b]

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

a: Dose will not be re-escalated to original dose after dose reduction for liver toxicity.
b: In case of discontinuation, check AST, ALT, and bilirubin weekly until recovery to baseline or stabilization.
c: Patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and / or AST.
d: If further dose reductions below level -1 are needed, per investigator´s risk benefit assessment, patients may continue at a 200 mg b.i.d. dose regimen after the approval of the sponsor, otherwise, patients will be discontinued from the study treatment.

Permanent discontinuation also applies to patients with 'AST/ALT > 8x ULN' or 'AST/ALT > 5x ULN for > 2 weeks' if no other reason is found for these elevations.

7.4.3.1.3 Retinal disorders

Patients who experience any decrease in visual acuity, ocular pain or discomfort, or any retinal disorders including retinal detachment / retinal pigment epithelial detachment / serous retinopathy / retinal vein occlusion have to undergo ophthalmologic examinations on Day 1 of every cycle.

Patients that experience any decrease in visual acuity, ocular pain or discomfort, or symptomatic retinal disorders including retinal detachment / retinal pigment epithelial detachment / serous retinopathy / retinal vein occlusion classified analog to CTCAE v.4.03 as Grade 2 or higher have to be permanently discontinued from study treatment. Based on the individual benefit risk assessment and after discussion with the sponsor, patient may interrupt treatment until recovery to at least Grade 1 and then treatment may be resumed at one dose level below. Patients with low visual acuity at baseline (best corrected visual acuity worse

than 20/40 and up to 20/200) have to undergo individual clinical evaluation to determine the maintenance in the study, according to investigator's judgment and based on the individual benefit risk assessment.

Monthly ophthalmological monitoring of the treatment associated retinal abnormality is recommended to be continued until resolution of the abnormality and to be documented in the source data for patients whose treatment was permanently discontinued.

7.4.3.2 Dose modifications of chemotherapy (comparator drugs)

Before each single administration of the chemotherapy the patient will be assessed for signs of hematologic and non-hematologic toxicity by clinical and laboratory investigations (see Section 9.1).

Findings will be graded according to CTCAE v.4.03 and it will be determined if the chemotherapy needs to be delayed or if the dose has to be modified. This decision will be clearly documented in the patient's records and the eCRF. Decision for dose delay and dose reduction will be based on local standard-of-care and/or SmPC.

Patients in whom doses are delayed due to toxicities should be followed up within 7 to 10 days to re-assess toxicities, if not specified otherwise.

Paclitaxel, docetaxel or vinflunine dose will be reduced for toxicities attributed to these drugs. Once dose reductions are made, re-escalation of doses is not permitted since dose reductions are permanent. Patients requiring a dose delay due to toxicity of > 24 days (or less if required in the dose modification section) from the next intended dose or due to other reasons for > 31 days from the next intended dose will be withdrawn from the study treatment.

The cycle duration will consist of 21 days, however any delay will prolong the duration of a cycle. The cycle ends with the next dose administration.

Specific dose modification guidance for paclitaxel, docetaxel or vinflunine is found in the subsections below. Additional considerations for the toxicity management including other measurement and dose modification according to local label and/or local guidelines should be followed by the investigators.

Specific dose modifications for vinflunine

In case of 'ECOG performance status (PS) of ≥ 1' or 'PS of 0 and prior pelvic irradiation', vinflunine treatment should be started at the dose of 280 mg/m^2. In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m^2 every 3 weeks for the subsequent cycles.

The recommended dose of vinflunine is 250 mg/m^2 given once every 3 weeks in patients with mild liver impairment (Child-Pugh grade A) or in patients with a Prothrombin time ≥60% ULN and 1.5xULN < bilirubin ≤ 3xULN and presenting at least one of the following criteria: transaminases > ULN and/or GGT > 5xULN.

In patients who initiate vinflunine at 280 mg/m^2 and who experience an AE requiring dose modification, the dose should be reduced to 250 mg/m^2 following the 1st occurrence and resolution, and discontinued following a 2nd occurrence. In patients who initiate vinflunine at

250 mg/m^2 and who experience an AE requiring dose modification, vinflunine should be discontinued.

Cases of posterior reversible encephalopathy syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain. Vinflunine should be discontinued in patients who develop neurological signs of PRES.

Guidance for dose delay of vinflunine due to toxicity is given in Table 7–6.

Table 7–6: Dose delay for subsequent cycles of vinflunine due to toxicity

Toxicity	Day 1 treatment administration
Neutropenia (ANC < 1,000/mm^3) or Thrombocytopenia (platelets < 100,000/mm^3)	- Delay until recovery (ANC ≥ 1,000/mm^3 and platelets ≥ 100,000/mm^3) and adjust the dose if necessary (see Table 7–7) - Discontinuation if recovery has not occurred within 2 weeks
Organ toxicity: moderate, severe or life-threatening	- Delay until recovery to mild toxicity or none, or to initial baseline status and adjust the dose if necessary (see Table 7–7) - Discontinuation if recovery has not occurred within 2 weeks
Cardiac ischemia in patients with prior history of myocardial infarction or angina pectoris	- Discontinuation

ANC = Absolute neutrophil count; mm^3 = Cubic millimeter.
Source: (18)

Specific dose adjustments for vinflunine due to toxicity are detailed below in Table 7–7.

Table 7–7: Vinflunine dose adjustments due to toxicity

Toxicity	Dose adjustment						
	Initial dose: vinflunine 320 mg/m²			Initial dose: vinflunine 280 mg/m² [c]		Initial dose: vinflunine 250 mg/m² [d]	
	1st event	2nd consecutive event	3rd consecutive event	1st event	2nd consecutive event	1st event	2nd consecutive event
Neutropenia Grade 4 (ANC < 500/mm³) > 7 days Febrile neutropenia (ANC < 1.000/mm³ and fever ≥ 38.5°C) Mucositis or constipation Grade 2 ≥ 5 days or Grade ≥ 3 any duration[a] Any other toxicity Grade ≥ 3 (severe or life-threatening) (except Grade 3 vomiting or nausea[b])	280 mg/m²	250 mg/m²	Permanent treatment discontinuation	250 mg/m²	Permanent treatment discontinuation	225 mg/m² [d]	Permanent treatment discontinuation

ANC = Absolute neutrophil count; °C = Degree(s) Celsius; CrCl = Creatinine clearance; CTCAE = Common Toxicity Criteria for Adverse Events; mg/m² = Milligrams per square meter; ml/min = Milliliters per minute.
a: CTCAE Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening".
b: CTCAE Grade 3 nausea is defined as no significant intake, requiring intravenous fluids. Grade 3 vomiting as ≥ 6 episodes in 24 hours over pretreatment; or need for intravenous fluids.
c: Starting dose of 280 mg/m² for patients with moderate renal impairment (40 ml/min ≤ CrCl ≤ 60 ml/min) and for elderly patients between ≥ 75 and < 80 years.
d: Starting dose of 250 mg/m² for patients with severe renal impairment (20 mL/min ≤ CrCl > 40 mL/min) and for elderly patients ≥ 80 years. Dose reduction to 225 mg/m² is allowed only in elderly patients ≥ 80 years and in patients with severe renal impairment because of a higher bioavailability of vinflunine in these patients.
Source: (18)

In patients with moderate renal impairment (40 ml/min ≤ CrCl ≤ 60 ml/min), the recommended dose of vinflunine is 280 mg/m² given once every 3 weeks. In patients with severe renal impairment (20 ml/min ≤ CrCl <40 ml/min), the recommended dose is 250 mg/m² given once every 3 weeks. For further cycles, the dose should be adjusted in the event of toxicities, as shown in Table 7–8.

The doses recommended in patients ≥ 75 years old are as follows:

- in patients at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 3 weeks.
- in patients 80 years old and beyond, the dose of vinflunine to be given is 250 mg/m² every 3 weeks.

For further cycles, the dose should be adjusted in the event of toxicities, as shown in Table 7–8.

Table 7–8: Vinflunine dose adjustments due to toxicity in renal impaired or elderly patients

Toxicity	Dose adjustment			
	Initial dose: vinflunine 280 mg/m^2		Initial dose: vinflunine 250 mg/m^2	
	1st event	2nd consecutive event	1st event	2nd consecutive event
Neutropenia Grade 4 (ANC < 500/mm^3) > 7 days Febrile neutropenia (ANC < 1.000/mm^3 and fever ≥ 38.5°C) Mucositis or constipation Grade 2 ≥ 5 days or Grade ≥ 3 any duration [a] Any other toxicity Grade ≥ 3 (severe or life-threatening) (except Grade 3 vomiting or nausea [b])	250 mg/m^2	Permanent treatment discontinuation	225 mg/m^2 [c]	Permanent treatment discontinuation

ANC = Absolute neutrophil count; °C = Degree(s) Celsius; CTCAE = Common Toxicity Criteria for Adverse Events; SmPC = Summary of Product Characteristics; mg/m^2 = Milligrams per square meter; ml/min = Milliliters per minute.
a: CTCAE Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as “moderate”, Grade 3 as “severe” and Grade 4 as “life-threatening”.
b: CTCAE Grade 3 nausea is defined as no significant intake, requiring intravenous fluids. Grade 3 vomiting as ≥ 6 episodes in 24 hours over pretreatment; or need for intravenous fluids.
c: Dose reduction to 225 mg/m^2 is allowed only in elderly patients and patients with renal impairment due to higher bioavailability of vinflunine as per SmPC.
Source: (18)

For further details refer to most current SmPC.

Specific dose modifications for paclitaxel

Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level ≥1500 cells/mm^3 and the platelet count is ≥100,000 /mm^3.

Patients who experience severe neutropenia (neutrophil count < 500 /mm^3 [corresponding to CTCAE Grade 4] for ≥ 7 days) or severe peripheral neuropathy (CTCAE Grade ≥ 3) should receive a dose reduction of 20 % for subsequent cycles. If further dose reduction is needed, treatment with paclitaxel should be discontinued.

Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. A dose reduction or withdrawal from treatment is at the discretion of the investigator after individually assessing the safety of each patient. Hypotension, hypertension, and bradycardia have been observed

during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment.

Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3-4 myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. Patients with severe hepatic impairment should not be treated with paclitaxel.

For further details refer to most current SmPC.

Specific dose modifications for docetaxel

In general, docetaxel should not be administered unless the neutrophil count is $\geq 1{,}500$ cells/mm^3.

In patients who experience either febrile neutropenia, neutrophil count < 500 cells/mm^3 (CTCAE Grade 4) for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy (CTCAE Grade ≥ 3) during docetaxel therapy, the dose of docetaxel should be reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Patients with hypersensitivity reactions:

If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalized rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Patients with hepatic impairment:

For patients with the following conditions, no dose reduction can be recommended as per SmPC and docetaxel should not be used unless strictly indicated:

- serum bilirubin > ULN and alkaline phosphatase > 6 x ULN
- serum bilirubin > ULN and ALT and AST > 3.5 x ULN and alkaline phosphatase > 6 x ULN
- ALT and AST > 3.5 x ULN and alkaline phosphatase > 6 x ULN

For further details refer to most current SmPC.

7.4.4 Treatment duration

Treatment with assigned study drug continues until any of the following events:

- Radiological disease progression according to RECIST v.1.1 as assessed by independent central radiology review.
    - At the investigator's discretion, study treatment may continue beyond centrally confirmed radiological progression as defined by RECIST v.1.1 if the clinical

condition of the patient is stable or the patient is improving symptomatically, and the investigator expects continued clinical benefit for the patient.

- Clinical progression
- Unacceptable toxicity
- Death
- Withdrawal of consent
- Withdrawal from the study treatment at the discretion of the investigator or designated associate(s)

For full list of withdrawal criteria refer to Section 6.4.1.3.

7.5 Blinding

Not applicable; this is an open-label study.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's electronic trial master file (eTMF); the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

The number of rogaratinib tablets dispensed and returned by the patients will be recorded on the eCRF and on the appropriated drug dispensing form. Reason(s) for dose interruption, reduction or omission will also be recorded on the eCRF.

For the chemotherapy (docetaxel, paclitaxel or vinflunine) the number of vials used will be recorded on the appropriate treatment dispensing form. Reasons for dose delay, reduction, or omission will be recorded in the source documents and on the eCRF.

All study drugs supplied by the sponsor will have a 2-panel standard label or booklet label affixed. One panel will be permanently attached to the smallest shippable unit (SSU), while the other panel will be a tear-off section that will be appended to the dispensing documentation.

Drug accountability on patient level must be done at every cycle on Day 1 visit, starting on Day 1 of Cycle 1. The monitor will review overall drug accountability and destruction per the site documentation.

7.7 Treatment compliance

Patient compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. Patients may be discontinued from the study treatment for non-compliance with follow-up visits or study treatment, at the discretion of the principal investigator or sponsor.

All reasons for non-compliance should be clearly documented in the patients' records and the eCRF.

Any discrepancies between actual and expected amount of returned study drug (rogaratinib) must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

The preparation and administration of the chemotherapy (docetaxel, paclitaxel or vinflunine) will be performed by appropriately trained personnel (e.g. site or pharmacy staff) that will ascertain and document that the patient receives all treatments as planned.

Each administration of the study drug must be recorded in the source documentation and the eCRF including every interruption/delay or reduction of the study treatment, regardless of the duration as well as reasons for dose interruption/delay, reduction, re-escalation (rogaratinib only) or omission.

Reasons for dose interruption / delay, reduction, re-escalation or omission will also be recorded in the source documents and in the eCRF.

An adequate record of receipt, distribution, and return/destruction of all study drugs must be kept in the form of a Drug Accountability Form.

8. Non-study therapy

8.1 Prior and concomitant therapy

Any medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. In general, patients should be closely monitored for side effects of all concomitant medications regardless of elimination path, especially those with narrow therapeutic indices, such as warfarin and digoxin.

Guidance on recording of prior and concomitant medications can be found in Section 11.1.

Excluded prior therapies are listed in Section 6.2 (Exclusion criteria).

Prohibited concomitant therapy

Both treatment arms

- Systemic anti-cancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy and hormonal therapy

- Bisphophonates and denosumab as supportive treatment started prior start of study treatment can be continued during the course of study, but newly start of treatment with denosumab or bisphophonates during the course of study drug treatment will not be allowed.
- Bone marrow transplant or stem cell rescue.
- Radiotherapy, except:
    - Concomitant palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
    - A short course of radiotherapy during study treatment due to a pathological fracture will be allowed after consultation with the sponsor, if the underlying bone lesion is not considered as a target lesion.
- Biotin-containing supplements (alternative names in over-the-counter drugs might be used, e.g. vitamin B7, vitamin H, coenzyme R) containing more than 30 µg daily dose should not be taken because of potential interference with laboratory tests (27).

Rogaratinib treatment arm only

- Rogaratinib is mainly metabolized by CYP3A4 and to a lesser extent by CYP2C9. Therefore,
    - Use of strong inhibitors and strong inducers of CYP3A4 (see Appendix 16.1) is not permitted for 2 weeks before the start of study treatment or during the study. Concomitant use of moderate and weak CYP3A4 inducers should be avoided as clinically significant decrease in plasma concentrations of rogaratinib cannot be ruled out.
    - Concomitant use of herbal preparations containing CYP3A4 inducers (e.g. St John's wort) are not permitted for 2 weeks before the start of study treatment or during the study.
    - Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.
- Therapies that are known to increase serum calcium or phosphate levels (i.e. antacids, phosphate-containing laxatives oral/rectal, potassium phosphate) are prohibited.

Chemotherapy arm only

- Drugs prohibited according to locally approved package inserts of paclitaxel, docetaxel and vinflunine are not permitted. The following information should be considered as a guidance based on package insert / summary of product characteristics:
    - The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is

concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Concomitant therapies that should be avoided

Rogaratinib treatment arm only

- Fluconazole is considered a moderate to strong inhibitor of CYP2C9 and should be avoided, if possible.
- Narrow therapeutic index drugs that are CYP3A4, P-gp and BCRP substrates (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be avoided, because drug interactions caused by irreversible inhibition of CYP3A4, P-gp and BCRP by rogaratinib cannot be ruled out.

Chemotherapy arm only

- Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.
- The concomitant use of vinflunine and potent CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole and grapefruit juice) or inducers (such as rifampicin and *Hypericum perforatum* (St John's wort) should be avoided since they may increase or decrease vinflunine and metabolite of vinflunine concentrations.

8.2 Post-study therapy

At the end of study treatment for the individual patient, further therapy is at the discretion of the investigator.

At the conclusion of the study, patients who demonstrate clinical benefit may be eligible to continue to receive study treatment. They may receive further treatment, assessments and/or be followed either via a post-trial access program, a roll-over study - subject to approval by the competent health authority and ethics committee - or through any other mechanism in accordance with local legal and compliance rules. This applies to patients on study treatment and in follow-up.

In the event a roll-over study is established, the present study will end when all patients have transitioned into the roll-over study or discontinued from this study for another reason (e.g. consent withdrawn, lost to follow-up, death). Until the transition to the roll-over study, patients will continue to follow all the procedures and visits required in the current version of the protocol.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Tabular schedule of evaluations is presented in Table 9–1.

Table 9–1: Tabular schedule of evaluations

Trial Periods	**Pre-treatment**			**Treatment**						**EOT**	**Follow-up**	
Visit Name	**FGFR testing**	**Screening**		**Cycle 1**			**Cycle 2**		**Cycle ≥ 3**	**EOT**	**Active FU**	**Long-term FU**
Visit Day[hh]				**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		**At least 30 days after last dose for safety assessments**[ii]	**Every month**
Time Window (Days)		Within 28 days before randomization	Within 7 days before randomization		+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	Within 14 days*	up to +7	+/- 7
Screening and enrollment												
Informed consent for FGFR testing[a]	X											
Informed consent for study treatment eligibility[a]		X										
Contact IxRS[b]	X	X		X			X		X	X		
Archival or fresh tissue for FGFR test and PIK3CA and RAS mutation test[c]	X											
Demographic data	X											
Documentation of urothelial carcinoma diagnosis	X											
Previous therapy for urothelial carcinoma[d]	X	X										
Medical history[d]		X										
Inclusion / exclusion criteria check[e]	X	X	X	X[x]								
ECOG	X		X	X			X		X	X	X	
Smoking history		X										
Bellmunt risk score			X									

Trial Periods	**Pre-treatment**			**Treatment**						**EOT**	**Follow-up**	
Visit Name	**FGFR testing**	**Screening**		**Cycle 1**			**Cycle 2**		**Cycle ≥ 3**	**EOT**	**Active FU**	**Long-term FU**
Visit Day[hh]				**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		**At least 30 days after last dose for safety assessments**[ii]	**Every month**
Time Window (Days)		Within 28 days before randomization	Within 7 days before randomization		+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	Within 14 days*	up to +7	+/- 7
Medication												
Randomization				X[y]								
Rogaratinib administration				continuously								
Chemotherapy administration				X			X		X			
Efficacy												
Tumor assessment (CT or MRI)[f]		X[g]		Every 6 weeks up to week 18 and thereafter every 9 weeks[z]						X[cc]	X[dd] applies only to patients who discontinued without progressive disease	
Brain (CT or MRI) and bone scan		X[h]										
Survival assessment											Monthly[ee] applies only to patients who discontinued without progressive disease	Monthly[ee]
Safety												
Physical examination[i]		X		X			X		X	X	X	
Ophthalmologic examination[j]		X					X[bb]		X[bb]	X		
Vital signs (BP, heart rate, body temperature), including weight[n] and height[o]			X	X	X	X	X	X	X	X	X	
Hematology[p]			X	X	X	X	X	X	X	X	X	
Coagulation panel[q]			X	X			X		X	X	X	
Biochemistry Full[r, s]			X	X			X		X	X	X	

Trial Periods	**Pre-treatment**			**Treatment**						**EOT**	**Follow-up**	
Visit Name	**FGFR testing**	**Screening**		**Cycle 1**			**Cycle 2**		**Cycle ≥ 3**	**EOT**	**Active FU**	**Long-term FU**
Visit Day[hh]				**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		**At least 30 days after last dose for safety assessments[ii]**	**Every month**
Time Window (Days)		Within 28 days before randomization	Within 7 days before randomization		+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	Within 14 days*	up to +7	+/- 7
Biochemistry Limited[r, t]					X	X		X				
Hormone panel (TSH, free T3, free T4)			X	X			X		X	X	X	
Urinalysis[u]			X	X	X		X			X		
eGFR (MDRD abbreviated formula)			X	X			X		X	X		
Pregnancy test (if applicable)[v]			X									
12-lead ECG[k]		X		X			X		X	X		
Toxicity / AE assessment[l]		continuously										
Concomitant medications[ff]		continuously										
Subsequent systemic anti-cancer treatment										X	X	X
Other												
Healthcare resource utilization[gg]		continuously										
PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L)[m]		X		X			X		X	X	X	
Pharmacokinetic sampling[aa]				X			X		X[aa]			
Blood sampling for plasma-based biomarker analyses[w]			X	X			X		X	X		

AE = Adverse event; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BP = Blood pressure; BUN = Blood urea nitrogen; CT = Computed tomography; CTCAE = Common Terminology Criteria Adverse Event; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = Electronic case report form; eGFR = Estimated glomerular filtration rate; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer 30 item Quality of Life

Questionnaire; EOT = End of treatment; EQ-5D-3L = EuroQol Group's five dimensions questionnaire; FGFR = Fibroblast growth factor receptor; FU = Follow-up; ICF = Informed consent form; INR = International normalized ratio; IxRS = Interactive Voice / Web Response System (IVRS/IWRS); LDH = Lactic dehydrogenase; MDRD = Modification of Diet in Renal Disease; MRI = Magnetic resonance imaging; PI/ICF = Patient information/informed consent form; PIK3CA = Phosphoinositide 3-kinase, catalytic subunit alpha isoform; PK = Pharmacokinetic(s); PRO = Patient-reported outcome; PT = Prothrombin time; PTT = Partial thromboplastin time; QTc = Corrected QT interval; RAS = Rat sarcoma; RECIST = Response Evaluation Criteria in Solid Tumors; RBC = Red blood cell count; SAE = Serious adverse event; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid-stimulating hormone; WBC = White blood cell count.

a. Routine procedures performed before informed consent can be used as screening data.

b. Contact IxRS (IVRS/IWRS) to record the following: - to register the patient who has signed the ICF for FGFR testing (a unique patient identifier will be assigned), - ICF for study treatment eligibility has been signed, - the patient is a FGFR test failure or screening failure (e.g. failed to meet the criteria during FGFR testing or the screening period), - for randomization, - on Day 1 of every treatment cycle so that the specific patient drug bottle/vial can be provided for dispensing purposes and also in case the patient has discontinued the study treatment (EOT) for any reason.

c. Archival tumor tissue should be used, fresh tissue should only be obtained when no archival tissue is available and when there is no additional risk for the patient in the investigator's judgment. Tissue will be used for central FGFR testing in all patients, and in addition for PIK3CA and RAS mutation testing in all FGFR-positive patients and for exploratory tumor-based biomarker analyses in randomized patients.

d. At FGFR testing, study disease characteristics are collected and prior therapies for the study indication including outcome are reviewed.

   At screening, study disease characteristics are updated if applicable; prior therapies for the study indication including outcome, medical history and non-study-indication-related medications are collected.

e. Limited inclusion criteria will be checked in patients before FGFR testing (see Section 6.1).

f. The radiological evaluation must include computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis with contrast media. Chest CT is strongly recommended and preferred versus chest MRI. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule. Note: all images need to be submitted continuously for independent central imaging review in digital format.

g. Pre-study contrast-enhanced CT/MRI (chest/abdomen/pelvis, and other areas of disease if applicable) may be acceptable as a baseline scan if done within 28 days before the first dose of study treatment and if evaluable by RECIST version 1.1.

h. A contrast enhanced (unless contraindicated) CT scan or MRI of the brain is required at screening to rule out brain metastases. Acquisition of both contrast enhanced (unless contraindicated) and unenhanced scans of the brain at baseline is strongly recommended. Further CT scan or MRI of the brain only need to be repeated if metastases or symptoms are present. Bone scan (Technetium-99m) must be performed at screening. All suspected sites of disease should be imaged. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, Technetium-99m bone scans should be repeated when complete response is identified in target disease or when progression in bone is suspected.

i. Full physical examination is done at screening and at the EOT visit. Brief physical examinations are mandatory on Day 1 of each cycle and at the safety assessment visit of the active follow-up.

j. Ophthalmologic examinations comprise previous eye history (at screening only), any ophthalmic symptoms, best corrected visual acuity, dilated indirect ophthalmoscopy with macular involvement assessment and optical coherence tomography including measurement of central retinal thickness. Examinations during treatment are to be conducted on Day 1 of every 2nd cycle, starting at Cycle 2 and at the EOT visit. Additionally, the investigator will ask the patient for changes in vision at each site visit. If change in vision is reported, an ophthalmological examination must be performed. In case of any findings, please refer to Section 9.6.3.6.

k. In each patient,12-lead ECG (supine position) is to be performed at screening, on Day 1 of Cycle 1, 2, 3, 4 and 5 at pre-dose (before supervised dose administration), and between 0.5 and 1.5 hours post-dose (for patients on the rogaratinib treatment arm, the ECGs can be performed together with required PK blood sampling). Beyond Cycle 5, 12-lead ECG is to be performed on Day 1 of every 3rd cycle (pre-dose) and at EOT (if not performed within 4 weeks). Triple 12-lead ECG (supine position) is to be

performed (pre-dose and post-dose) in case of QTc prolongation under treatment. Weekly 12-lead ECGs have to be performed in patients with an elevated phosphate level (≥ 7mg/dL) until resolution (phosphate level <7mg/dL). In patients with hypocalcemia (CTCAE Grade ≥ 2), an additional 12-lead ECG has to be obtained on day of detection of hypocalcemia and should be repeated as clinically indicated. See also Section 9.6.3.3.

l. All AEs identified after the patient has signed the PI/ICF for FGFR testing and until the patient ends the study (up to at least 30 days after the last administration of study treatment or end of active follow-up) must be fully documented in the source data. During FGFR testing period: AEs/SAEs related to the procedure of taking a fresh biopsy for FGFR testing corresponding AE/ SAE must be recorded. After the patient has signed the informed consent for study treatment eligibility any new finding or worsening of any ongoing medical history condition must be recorded as an AE/SAE up to at least 30 days after the last administration of study treatment. Thereafter, only AEs related to the study drugs have to be recorded until the end of active follow-up. However, at the investigator's discretion, SAEs may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

m. To be completed before the patient meets with a clinician and before any examination or test is performed on that day. Questionnaires are to be completed at screening, on Day 1 of every cycle, at the EOT visit and at the safety assessment visit of the active follow-up.

n. Weight is to be measured at screening (within 7 days before randomization) and on Day 1 of each cycle.

o. Height is to be measured only at screening (within 7 days before randomization).

p. Hematology panel: Hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.

q. Coagulation panel: PTT or activated PTT and PT-INR.

r. Including weekly evaluations of phosphate levels in patients with an elevated phosphate level ≥ 7 mg/dL.

s. Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine.

t. Limited biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, blood urea nitrogen (BUN) or urea, and creatinine.

u. Urine chemistry test is done at screening, on Cycle 1 Day 1 and Day 8, on Cycle 2 Day 1 and at the EOT. Microscopic examinations will be performed if clinically indicated.

v. Pregnancy test is to be repeated as frequently as required by local regulations.

w. The blood samples are intended for isolation of plasma to study tumor markers (genetic and non-genetic) circulating in blood. During the treatment cycles, plasma samples are to be collected before administration of study drugs.

x. Prior to randomization.

y. The first administration of study drug should take place within 3 days of randomization.

z. Tumor assessments (CT or MRI) are to be done according to RECIST v.1.1 (see Section 9.4.1) every 6 weeks (± 7 days) starting from Cycle 1 Day 1 up to week 18, and thereafter, every 9 weeks (± 7 days). A minimum of at least 6 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment.

aa. PK sampling in all rogaratinib-treated patients to be collected on Day 1 of Cycle 1, 2, 3, 4 and 5 at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose.

bb. During treatment (on Day 1 of every second cycle starting at Cycle 2) a time window of -7 days is allowed.

cc. Radiological tumor evaluation (within 14 days after last study treatment) (CT/MRI of chest, abdomen, and pelvis) using RECIST version 1.1. This is not necessary if the previous tumor evaluation was performed within 4 weeks (up to week 18) or within 7 weeks (beyond week 18).

dd. For patients who discontinue study treatment without disease progression, follow-up tumor evaluations will be performed (by CT or MRI) until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met. During the active follow-up period, CT/MRI evaluations will be performed at the same intervals as during study treatment period (every 6 weeks up to week 18, and thereafter, every 9 weeks).

ee. Survival sweeps (e.g. telephone calls to collect survival status information) are to be implemented for all ongoing patients to occur in the 2-week period after the data cut-off date is determined for the formal interim and primary completion analyses for overall survival.

ff. From signing of PI/ICF for study treatment eligibility up to 30 days after the last administration of study treatment, all concomitant medications (including start/stop dates, dose, frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as on the appropriate pages of the eCRF.

gg. Healthcare resource utilization information will be recorded once a patient has a hospitalization/healthcare visit, during the course of the study. Information on the start date, end date, ongoing status, location, scheduling status, main diagnosis at discharge, and number of working days missed must be recorded. Data will be analyzed on an *ad hoc* basis. See Section 9.7.3.

hh. It may be necessary to perform the procedures at unscheduled time points if deemed clinically necessary by the investigator.

ii. If the study treatment was permanently discontinued after dose interruption/delay of more than 30 days, the active follow-up visit should occur within 14 days of discontinuation. If the EOT and active follow-up visits will be scheduled at the same time, the visits can be combined.

* EOT visit will be performed within 14 days after permanent discontinuation of study treatment.

9.2 Visit description

9.2.1 Pre-treatment period

Routine procedures performed before informed consent can be used as screening data provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their disease may also be used prior to the informed consent date and time, if performed as part of the standard of practice.

9.2.1.1 FGFR testing

Mandatory FGFR testing of patients will be performed **prior to start of screening** (signing of informed consent for study treatment eligibility). The timing of the FGFR test is at the discretion of the investigator.

The following procedures will be performed prior to FGFR testing:

- Signed PI/ICF for FGFR testing (see Section 13.4.1).
- Contact IxRS to register patient (a unique patient identifier will be assigned).
- Check inclusion criteria for FGFR testing (see Section 6.1).
    - If a patient does not meet the selection criteria for FGFR testing, contact IxRS and confirm that the patient is a 'FGFR testing failure' and additionally provide the reason, if applicable in the eCRF.
- Documentation of demographics data, including year of birth, age, gender, race (as allowed by local regulation) and ethnicity (as allowed by local regulation).
- Obtain archival or fresh tumor tissue.
    - Only if no archival tumor tissue sample is available which has been handled and processed as described in the lab manual: perform a biopsy to obtain fresh tumor material. See more details in Section 9.7.1.
    - Tissue will be used for central FGFR testing in all patients, and in addition for PIK3CA and RAS mutation testing in all FGFR-positive patients, and for exploratory tumor-based biomarker analyses in randomized patients (see Section 9.7.1).
- Document study disease characteristics and review previous therapy for urothelial carcinoma including outcome (see Section 9.3.3).
- Check Eastern Cooperative Oncology Group performance status (ECOG PS) (see Section 9.6.3.5).
- Toxicity/AE assessment: during the FGFR testing period: AEs/SAEs related to the procedure of taking a fresh biopsy for FGFR testing (in case archival tumor tissue is not available) the corresponding AE and SAE have to be reported and must be fully documented in the source data. For all other events, these have to be fully documented in the source data and will be reported in the medical history only for those patients who have signed the PI/ICF for study treatment eligibility.

The following procedure will be performed after FGFR testing:

- For patients not meeting the eligibility criteria "high FGFR expression level" following confirmation by the central lab: record the patient in IxRS as a 'FGFR testing failure'.

9.2.1.2 Screening

After confirmation of high FGFR1 or 3 mRNA expression level has been received from central lab, the patient may enter the screening. Screening examinations for FGFR-positive patients will only be performed after having received the patient's written ICF for study treatment eligibility (see Section 13.4.2).

Note: Healthcare resource utilization information must be recorded once a patient has a hospitalization/healthcare visit (see Section 9.7.2).

The following screening procedures will be performed **within 28 days before randomization**:

- Signed PI/ICF for study treatment eligibility (see Section 13.4.2).
- Contact IxRS to confirm PI/ICF for study treatment eligibility has been signed and that the patient has started screening; select investigator's choice for the chemotherapy.
- PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L) (see Section 9.7.2).
    - Questionnaires are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- Check the inclusion and exclusion criteria for study treatment eligibility (see Section 6.1 for inclusion criteria and Section 6.2 for exclusion criteria).
- Update study disease characteristics (if applicable) and document previous therapy for urothelial carcinoma including outcome (see Section 9.3.3).
- Document relevant medical history (see Section 9.3.2) and non-study-indication-related medications (see Section 9.3.3).
- Document smoking history (see Section 9.3.3).
- Tumor assessment (CT or MRI) according to RECIST v.1.1 (see Section 9.4.1).
    - Pre-study contrast-enhanced CT/MRI (chest/abdomen/pelvis and other areas of disease if applicable) may be acceptable as a baseline scan if done within 28 days before the first dose of study treatment and if evaluable by RECIST version 1.1.
    - A contrast enhanced (unless contraindicated) CT scan or MRI of the brain is required at screening to rule out brain metastases. Acquisition of both contrast enhanced (unless contraindicated) and unenhanced scans of the brain at baseline is strongly recommended. Further CT scan or MRI of the brain only need to be repeated if metastases or symptoms are present.

- Bone scan (Technetium-99m) must be performed at screening. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, Technetium-99m bone scans should be repeated when complete response is identified in target disease or when progression in bone is suspected.
- Note: all images need to be submitted for independent central image review in digital format (for details see Section 9.4.1).

- Perform full physical examination (see Section 9.6.3.2).
  - Complete review of all organ systems, and full physical examination of (including but not limited to) general appearance, skin, head and neck, eyes, ears, nose, throat, heart, lungs, abdomen, musculoskeletal system, lymph nodes, genitourinary system, neurological system.
- Send patient for ophthalmological examination (see Section 9.6.3.6).
  - Ophthalmologic examinations comprise previous eye history (at screening only), any ophthalmic symptoms, best corrected visual acuity, dilated indirect ophthalmoscopy with macular involvement assessment and optical coherence tomography including measurement of central retinal thickness.
  - In case of any findings, please refer to Section 9.6.3.6.
- 12-lead ECG (see Section 9.6.3.3).
- Toxicity/AE assessment
  - Following signing of the PI/ICF for study treatment eligibility, any new finding or worsening of any ongoing medical history condition must be recorded as an AE and fully documented in both SOURCE DATA and eCRF (see Section 9.6.1.3)
- Record concomitant medication (see Section 8.1).

The following screening procedures will be performed **within 7 days before randomization**:

- Check the inclusion and exclusion criteria for study treatment eligibility (see Section 6.1 for inclusion criteria and Section 6.2 for exclusion criteria).
- ECOG PS (see Section 9.6.3.5).
- Measure vital signs, including blood pressure, heart rate and body temperature. Height and body weight will be measured and body surface area (BSA) will be derived (see Section 9.6.3.4).
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Coagulation panel: PTT or activated PTT and PT-INR (see Section 9.6.3.1).

- Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine. (See Section 9.6.3.1).
- Hormone panel: thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients (see Section 9.6.3.1).
- Urinalysis test (See Section 9.6.3.1), and if clinically indicated, microscopic examinations.
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Serum pregnancy test in women of childbearing potential. Negative serum pregnancy test must be documented before start of study treatment. Postmenopausal women who have not had periods for more than 1 year or surgically sterilized women will not be required to undergo a pregnancy test (this information should be recorded under medical history on the eCRF). See Sections 9.6.2 and 9.6.3.1.
    - Note: Pregnancy test to be repeated as frequently as required by local regulations.
- Blood sampling for plasma-based biomarker analyses.
    - Note: the blood samples are intended for isolation of plasma to study tumor markers (genetic and non-genetic) circulating in blood (see Section 9.7.1).
- Toxicity/AE assessment
    - Following signing of the PI/ICF for study treatment eligibility, any new finding or worsening of any ongoing medical history condition must be recorded as an AE and fully documented in both SOURCE DATA and eCRF (see Section 9.6.1.3).
- Review concomitant medications (see Section 8.1).
- Calculate and record Bellmunt risk score (high *vs.* low) (see Section 9.3.3 for guidance to calculate the score).
- Contact IxRS, if a patient does not meet study treatment eligibility criteria, and confirm that the patient is a 'screening failure' and additionally provide the reason, if applicable, in the eCRF.

9.2.2 Treatment period

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented, the patient will be randomly assigned to one of the following treatment arms: rogaratinib or chemotherapy, using IxRS. Rogaratinib will be administered continuously twice daily, and chemotherapy will be administered intravenously on Day 1 of each cycle, see Section 7.4.1 for dosing schedule.

For tumor assessments to be performed during the treatment period, see Section 9.2.2.7.

Healthcare resource utilization information must be recorded once a patient has a hospitalization/healthcare visit (see Section 9.7.2).

9.2.2.1 Day 1 of Cycle 1

The following procedures will be performed on C1D1 **before receiving study treatment** unless otherwise specified. Procedures that have been performed at screening within 3 days prior to start of study drug treatment do not need to be repeated on Cycle 1 Day 1 (with the exception of blood pressure, heart rate and body temperature). Eligibility must be confirmed and documented prior to randomizing the patient in IxRS.

- Contact IxRS to randomize the patient (see Section 7.3) and to dispense (rogaratinib) or apply (chemotherapy) medication based on derived BSA entered into IxRS, as applicable.
  The first administration of study drug should take place within 3 days of randomization. In case the study treatment will not start at the day of randomization, the date of the first dose needs to be entered into IxRS.
- PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L) (see Section 9.7.2).
  - Questionnaires are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- Review the inclusion and exclusion criteria for study treatment eligibility (see Section 6.1 for inclusion criteria and Section 6.2 for exclusion criteria).
  - If a patient does not meet criteria for study treatment eligibility and is not eligible for randomization then the patient must be registered as a 'screening failure' in IxRS and additionally provide the reason, if applicable, in the eCRF.
- AE/toxicity assessments (see Section 9.6.1.3).
- Ask the patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed.
  - In case of any findings, please refer to Section 9.6.3.6.
- Review of concomitant medications (see Section 8.1).
- ECOG PS (see Section 9.6.3.5).
- Perform brief physical examination (see Section 9.6.3.2).
  - Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality.
- Vital signs, including blood pressure, heart rate and body temperature. Body weight will be measured and BSA will be derived (see Section 9.6.3.4).
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Coagulation panel: PTT or activated PTT and PT-INR (see Section 9.6.3.1).

- Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine. (See Section 9.6.3.1).
    - Note: weekly evaluations of phosphate levels should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).
- Hormone panel: thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients (see Section 9.6.3.1).
- Urinalysis test (See Section 9.6.3.1), and if clinically indicated, microscopic examinations.
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- 12-lead ECG (see Section 9.6.3.3)
    - 12-lead ECG (supine position) is to be performed at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose (for patients on the rogaratinib treatment arm, the ECGs can be performed together with required PK blood sampling).
    - Note: Triple 12-lead ECG (supine position) is to be performed (pre-dose and post-dose) in case of QTc prolongation under treatment.
    - Note: weekly 12-lead ECGs to be performed for patients with an elevated phosphate level (≥ 7mg/dL) until resolution (phosphate level < 7 mg/dL). In patients with hypocalcemia (CTCAE Grade ≥ 2), an additional 12-lead ECG has to be obtained on day of detection of hypocalcemia and should be repeated as clinically indicated.
- PK sampling (pre- and post-dose) (see Section 9.5).
    - Note: sampling in all rogaratinib-treated patients to be collected on Day 1 of Cycle 1 at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose.
- Blood sampling (pre-dose) for plasma-based biomarker analyses.
    - Note: the blood samples are intended for isolation of plasma to study tumor markers (genetic and non-genetic) circulating in blood (see Section 9.7.1). During the treatment cycles, plasma samples are to be collected before administration of study drugs.
- Administration of chemotherapy (applicable to comparator arm only) (see Section 7.4).

9.2.2.2 Day 8 of Cycle 1

The following visit will be performed on C1D8 (± 3 days), laboratory procedures are allowed to be performed within 3 days prior to the visit unless otherwise specified:

- AE/toxicity assessments (see Section 9.6.1.3).
- Ask the patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed.
    - In case of any findings, please refer to Section 9.6.3.6.
- Review of concomitant medications (see Section 8.1).
- Vital signs, including blood pressure, heart rate and body temperature.
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Limited biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, blood urea nitrogen (BUN) or urea, and creatinine (see Section 9.6.3.1).
    - Note: weekly evaluations of phosphate levels and 12-lead ECG should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).
- Urinalysis test (See Section 9.6.3.1), and if clinically indicated, microscopic examinations.

For patients on the rogaratinib treatment arm, the procedures should be performed before receiving study treatment.

9.2.2.3 Day 15 of Cycle 1

The following visit will be performed on C1D15 (± 3 days), laboratory procedures are allowed to be performed within 3 days prior to the visit unless otherwise specified:

- AE/toxicity assessments (see Section 9.6.1.3).
- Ask the patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed.
    - In case of any findings, please refer to Section 9.6.3.6.
- Review of concomitant medications (see Section 8.1).
- Vital signs, including blood pressure, heart rate and body temperature (see Section 9.6.3.4).

- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Limited biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, blood urea nitrogen (BUN) or urea, and creatinine (see Section 9.6.3.1).
    - Note: weekly evaluations of phosphate levels and 12-lead ECG should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).

For patients on the rogaratinib treatment arm, the procedures should be performed before receiving study treatment.

9.2.2.4 Day 1 of Cycle 2

The following visit will be performed on Day 1 (± 3 days) of Cycle 2, laboratory procedures are allowed to be performed within 3 days prior to the visit **before receiving study treatment** unless otherwise specified:

- PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L) (see Section 9.7.2).
    - Questionnaires are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
    - PRO questionnaires are to be completed on Day 1 of each cycle.
- AE/toxicity assessments (see Section 9.6.1.3).
- Review of concomitant medications (see Section 8.1).
- ECOG PS (see Section 9.6.3.5).
- Perform brief physical examination (see Section 9.6.3.2).
    - Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality.
- Send patient for ophthalmological examination (see Section 9.6.3.6). Note: A time window of -7 days is allowed.
    - Ophthalmologic examinations comprise any ophthalmic symptoms, best corrected visual acuity, dilated indirect ophthalmoscopy with macular involvement assessment and optical coherence tomography including measurement of central retinal thickness.
    - Examinations during treatment are to be conducted on Day 1 (-7 days) of every 2nd cycle, starting at Cycle 2.
    - In case of any findings, please refer to Section 9.6.3.6.

- Vital signs, including blood pressure, heart rate and body temperature. Body weight will be measured and BSA will be derived (see Section 9.6.3.4).
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Coagulation panel: PTT or activated PTT and PT-INR (see Section 9.6.3.1).
- Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine. (See Section 9.6.3.1).
    - Note: weekly evaluations of phosphate levels and 12-lead ECG should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).
- Hormone panel: thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients (see Section 9.6.3.1).
- Urinalysis test (See Section 9.6.3.1), and if clinically indicated, microscopic examinations.
    - Note: from C2D1 onwards, urinalysis should be done only if clinically indicated.
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- 12-lead ECG (see Section 9.6.3.3)
    - 12-lead ECG (supine position) is to be performed at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose (for patients on the rogaratinib treatment arm, the ECGs can be performed together with required PK blood sampling).
    - Note: Triple 12-lead ECG (supine position) is to be performed (pre-dose and post-dose) in case of QTc prolongation under treatment.
    - Note: weekly 12-lead ECGs to be performed for patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL). In patients with hypocalcemia (CTCAE Grade ≥ 2), an additional 12-lead ECG has to be obtained on day of detection of hypocalcemia and should be repeated as clinically indicated.
- Contact IxRS on Day 1 of every treatment cycle to register the corresponding treatment cycle so that the specific patient drug bottle/vial can be provided for dispensing/applying purposes and also in case the patient has discontinued the study treatment for any reason.
- PK sampling (pre- and post-dose) (see Section 9.5).

- Note: sampling in all rogaratinib-treated patients to be collected on Day 1 of Cycle 2, 3, 4 and 5 at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose.

- Blood sampling (pre-dose) for plasma-based biomarker analyses.
  - Note: the blood samples are intended for isolation of plasma to study tumor markers (genetic and non-genetic) circulating in blood (see Section 9.7.1). During the treatment cycles, plasma samples are to be collected before administration of study drugs.
- Study drug accountability.
- Administration of chemotherapy (applicable to comparator arm only) (see Section 7.4).

9.2.2.5 Day 15 of Cycle 2

The following visit will be performed on Day 15 (± 3 days) of Cycle 2, laboratory procedures are allowed to be performed within 3 days prior to the visit unless otherwise specified:

- AE/toxicity assessments (see Section 9.6.1.3).
- Ask the patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed.
  - In case of any findings, please refer to Section 9.6.3.6.
- Review of concomitant medications (see Section 8.1).
- Vital signs, including blood pressure, heart rate and body temperature (see Section 9.6.3.4).
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Limited biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, blood urea nitrogen (BUN) or urea, and creatinine (see Section 9.6.3.1).
  - Note: weekly evaluations of phosphate levels and 12-lead ECG should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).

For patients on the rogaratinib treatment arm, the procedures should be performed before receiving study treatment.

9.2.2.6 Day 1 of Cycle ≥ 3

The following visit will be performed on Day 1 (± 3 days), laboratory procedures are allowed to be performed within 3 days prior to the visit of all subsequent cycles starting from Cycle 3 **before receiving study treatment** unless otherwise specified. From Cycle 3 onwards, visits are scheduled only for Day 1 of the treatment cycle.

- PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L) (see Section 9.7.2).
    - Questionnaires are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
    - PRO questionnaires are to be completed on Day 1 of each cycle.
- AE/toxicity assessments (see Section 9.6.1.3).
- Every 2nd cycle (Cycle 4, 6, 8…): Send patient for ophthalmological examination (see Section 9.6.3.6). Note: A time window of -7 days is allowed.
    - Ophthalmologic examinations comprise any ophthalmic symptoms, best corrected visual acuity, dilated indirect ophthalmoscopy with macular involvement assessment and optical coherence tomography including measurement of central retinal thickness.
    - In case of any findings, please refer to Section 9.6.3.6.
- Ask the patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed.
    - In case of any findings, please refer to Section 9.6.3.6.
- Review of concomitant medications (see Section 8.1).
- ECOG PS (see Section 9.6.3.5).
- Perform brief physical examination (see Section 9.6.3.2).
    - Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality.
- Vital signs, including blood pressure, heart rate and body temperature. Body weight will be measured and BSA will be derived. (See Section 9.6.3.4)
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Coagulation panel: PTT or activated PTT and PT-INR (see Section 9.6.3.1).
- Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine. (See Section 9.6.3.1).
    - Note: weekly evaluations of phosphates levels and 12-lead ECG should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).
- Hormone panel: thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients (see Section 9.6.3.1).

- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- 12-lead ECG (see Section 9.6.3.3)
    - 12-lead ECG (supine position) is to be performed on Day 1 of Cycles 3, 4 and 5 at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose (for patients on the rogaratinib treatment arm, the ECGs can be performed together with required PK blood sampling). Beyond Cycle 5, 12-lead ECG is to be performed on Day 1 of every 3rd cycle (pre-dose).
    - Note: Triple 12-lead ECG (supine position) is to be performed (pre-dose and post-dose) in case of QTc prolongation under treatment.
    - Note: weekly 12-lead ECGs to be performed for patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL). In patients with hypocalcemia (CTCAE Grade ≥ 2), an additional 12-lead ECG has to be obtained on day of detection of hypocalcemia and should be repeated as clinically indicated.
- Contact IxRS on Day 1 of every treatment cycle to register the corresponding treatment cycle so that the specific patient drug bottle/vial can be provided for dispensing/applying purposes and also in case the patient has discontinued the study treatment for any reason.
- PK sampling (pre- and post-dose) (see Section 9.5).
    - Note: sampling in all rogaratinib-treated patients to be collected on Day 1 of Cycle 2, 3, 4 and 5 at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose.
- Blood sampling (pre-dose) for plasma-based biomarker analyses.
    - Note: the blood samples are intended for isolation of plasma to study tumor markers (genetic and non-genetic) circulating in blood (see Section 9.7.1). During the treatment cycles, plasma samples are to be collected before administration of study drugs.
- Study drug accountability.
- Administration of chemotherapy (applicable to comparator arm only) (see Section 7.4).

9.2.2.7 Tumor assessments during treatment period

Scans (CT or MRI) for tumor assessments according to RECIST v.1.1 (see Section 9.4.1) are to be done every 6 weeks (± 7 days) starting from Cycle 1 Day 1 up to week 18, and thereafter, every 9 weeks (± 7 days) until the patient has permanently discontinued study treatment and has disease progression.

A minimum of at least 6 weeks from start of treatment is mandatory for the 1st “on treatment” tumor assessment in order to achieve a valid response of stable disease. In exceptional cases,

when it is deemed clinically necessary by the investigator due to safety reasons, an imaging scan at an earlier time point is allowed.

Note: all images need to be submitted for central image review in digital format (for details see Section 9.4.1).

9.2.2.8 End-of-treatment (EOT) visit

An end-of-treatment (EOT) visit will be performed within 14 days after permanent discontinuation of study treatment.

The following examinations will be done at the EOT visit:

- PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L) (see Section 9.7.2)
    - Questionnaires are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- Contact IxRS to register that the patient has discontinued study treatment for any reason.
- AE/toxicity assessments (see Section 9.6.1.3).
- Review of concomitant medications (see Section 8.1).
- Check ECOG PS (see Section 9.6.3.5).
- Perform full physical examination (see Section 9.6.3.2).
    - Complete review of all organ systems, and full physical examination of (including but not limited to) general appearance, skin, head and neck, eyes, ears, nose, throat, heart, lungs, abdomen, musculoskeletal system, lymph nodes, and if indicated by patient's history, the genitourinary system, gynecological organs, rectum.
- Send patient for ophthalmological examination (see Section 9.6.3.6).
    - Ophthalmologic examinations comprise any ophthalmic symptoms, best corrected visual acuity, dilated indirect ophthalmoscopy with macular involvement assessment and optical coherence tomography including measurement of central retinal thickness.
    - In case of any findings, please refer to Section 9.6.3.6.
- Vital signs, including blood pressure, heart rate and body temperature (see Section 9.6.3.4).
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Coagulation panel: PTT or activated PTT and PT-INR (see Section 9.6.3.1).

- Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine. (See Section 9.6.3.1).
    - Note: weekly evaluations of phosphate levels and 12-lead ECG should be done in patients with an elevated phosphate level ≥ 7 mg/dL.
- Hormone panel: thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients (see Section 9.6.3.1).
- Urinalysis test (See Section 9.6.3.1), and if clinically indicated, microscopic examinations.
- Blood sampling for plasma-based biomarker analyses.
    - Note: the blood samples are intended for isolation of plasma to study tumor markers (genetic and non-genetic) circulating in blood (see Section 9.7.1).
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4)
- 12-lead ECG (see Section 9.6.3.3)
    - Note: Triple 12-lead ECG (supine position) is to be performed (pre-dose and post-dose) in case of QTc prolongation under treatment.
    - Note: weekly 12-lead ECGs to be performed for patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).
- Tumor assessment (CT/MRI) according to RECIST v.1.1 (see Section 9.4.1).
    - Note: Radiological tumor evaluation should be done within 14 days after last study treatment. This is not necessary if the previous tumor evaluation was performed within 4 weeks (up to week 18) or within 7 weeks (beyond week 18).
    - Note: all images need to be submitted for central image review in digital format (for details see Section 9.4.1).
- Document information on subsequent systemic anti-cancer treatment (if applicable).

9.2.3 Follow-up periods

9.2.3.1 Active follow-up

Safety information is collected for all discontinued patients for at least 30 (up to +7) days after the last administration of study treatment, and both safety and efficacy information are collected for patients who discontinue study treatment without disease progression. If the EOT and safety follow-up visits will be scheduled at the same time, the visits can be combined.

The following assessments are to be done **for all patients** at least 30 (up to +7) days after the last administration of study treatment:

- PRO questionnaires (EORTC QLQ-C30 and EQ-5D-3L) (see Section 9.7.2).
    - Questionnaires are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- AE/toxicity assessments (see Section 9.6.1.3).
    - All AEs and SAEs identified from the PI/ICF up to at least 30 days after the last administration of study treatment must be documented in the source and reported on the eCRF. Thereafter, AEs related to the study drugs have to be reported and must be fully documented in the source data.
- Perform brief physical examination (see Section 9.6.3.2).
    - Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality.
- Ask the patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed.
    - In case of any findings, please refer to Section 9.6.3.6.
- Review of concomitant medications (see Section 8.1).
- Check ECOG PS (see Section 9.6.3.5).
- Vital signs, including blood pressure, heart rate and body temperature (see Section 9.6.3.4).
- Hematology panel: hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts. See Section 9.6.3.1.
- Coagulation panel: PTT or activated PTT and PT-INR (see Section 9.6.3.1).
- Full biochemistry panel: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine. (See Section 9.6.3.1).
    - Note: weekly evaluations of phosphate levels should be done in patients with an elevated phosphate level (≥ 7 mg/dL) until resolution (phosphate level < 7 mg/dL).
- Hormone panel: thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients (see Section 9.6.3.1).
- Document information on subsequent systemic anti-cancer treatment (if applicable).

- Healthcare resource utilization information must be recorded once a patient has a hospitalization/healthcare visit (see Section 9.7.2).

Additionally, the following assessments are to be done **for patients who discontinue study treatment for other reasons than disease progression** (in case disease progression is not confirmed by central review, it strongly recommended, that patients go into active follow-up for tumor assessments until central imaging has confirmed disease progression):

- Tumor assessment (CT or MRI) according to RECIST v.1.1 (see Section 9.4.1).
    - Note: During the active follow-up period, CT/MRI evaluations will be performed at the same intervals as during study treatment (every 6 weeks up to week 18, thereafter, every 9 weeks) (see Table 9–1).
    - Note: all images need to be submitted for central image review in digital format (for details see Section 9.4.1).
- Monthly survival assessment
    - Note: Survival sweeps (e.g. telephone calls to collect survival status information) are to be implemented for all ongoing patients to occur in the 2-week period after the data cut-off date is determined for the formal interim and primary completion analyses for overall survival.

9.2.3.2 Long-term follow-up

All patients in the long-term follow-up period will be contacted (telephone contact is sufficient) every month (±7 days) to determine survival status and obtain information on subsequent systemic anti-cancer treatment until either data maturation for the final planned OS analysis is reached, death of the patient or any other criterion for withdrawal is met. If a patient is lost to follow-up, the site will try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local requirements.

The information to be recorded at the long-term follow-up contacts:

- Monthly survival assessments
    - Note: Survival sweeps (e.g. telephone calls to collect survival status information) are to be implemented for all ongoing patients to occur in the 2-week period after the data cut-off date is determined for the formal interim and primary completion analyses for overall survival.
- Document information on subsequent systemic anti-cancer treatment (if applicable).

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

- Year of birth
- Age at Informed Consent (derived)
- Gender
- Race (as allowed by local regulation) and
- Ethnicity (as allowed by local regulation)

The demographic data are to be collected prior to FGFR testing.

Routine procedures performed before informed consent can be used as screening data.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent for study treatment eligibility
- Considered relevant for the patient's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

Baseline study disease characteristics to be collected **for all enrolled patients** during the FGFR test period:

- Urothelial carcinoma classification/diagnosis including
    - date of initial diagnosis
    - type of assessment
    - date of first progression / relapse
    - date of the most recent progression / relapse
    - histology
    - location of primary cancer
    - TNM classification of urothelial carcinoma at initial diagnosis and at study entry
        - At initial diagnosis: TNM classification according to the current AJCC edition at that time point
        - At study entry: TNM classification according to the AJCC 8th edition
    - grading at initial diagnosis
    - status of primary tumor at study entry

Prior systemic anti-cancer medication including outcome have to be reviewed and must be fully documented in the source data.

Further baseline study disease characteristics to be collected **for all FGFR-positive patients** enrolled for screening:

- PIK3CA and/or RAS activating mutations (presence vs. absence)
- Prior systemic anti-cancer medication including outcome.
- Liver metastases (yes / no)
- Prior anti-cancer therapy for urothelial carcinoma
    - Any prior medications, significant non-drug therapies and diagnostic procedures **for the study indication** will be collected, including:
        - Medications (any prior systemic anti-cancer therapy)
            - Trade name of medication
            - Dose of medication
            - Start date and end date
        - Surgery
            - Date of surgery
            - Type of surgery
        - Radiotherapy
            - Regimen
            - Location
            - Intent
            - Start date and end date
            - Cumulative dose
        - Local therapy
        - Diagnostic procedures
    - All **non-study-indication-related** medications taken within 2 weeks before randomization will be documented, including:
        - Trade name of medication
        - Reason for medication (indication)
        - Dose of medication
        - Start date and end date or if continuing at patient's last visit.
- Smoking history

Modified 4-factor Bellmunt risk score

Prognostic factors have been identified for both first and second line treatment of patients with urothelial carcinoma. For second line the modified 4-factor Bellmunt risk score defines ECOG performance status, hemoglobin level, liver metastases and time from last systemic anti-cancer therapy dose as main adverse prognostic factors for overall survival (22).

In this study, the modified 4-factor Bellmunt risk score (high *vs.* low) is used as one of the stratification factors for randomization.

The Bellmunt risk score for stratification is divided in 'high' and 'low' as follows:

- 'High' score: 3-4 points
- 'Low' score: 0-2 points.

Modified 4-factor Bellmunt risk score will be calculated based on the following parameters collected within 7 days before randomization:

- Hemoglobin level < 10 g/dL vs. ≥ 10 g/dL
- ECOG performance status 0 vs. 1 (see Section 9.6.3.5)
- Liver metastases absent vs. present
- Time from last systemic anti-cancer therapy dose (< 90 vs. ≥ 90 days)

The risk score is calculated by adding up the points for each parameter (0 or 1 for each). Guidance for calculating the score is given in Table 9–2.

Table 9–2: Guidance for calculating modified 4-factor Bellmunt risk score

Risk factor	High risk (1 point)	Low risk (0 points)
Hemoglobin level	< 10 g/dL	≥ 10 g/dL
ECOG performance status	1	0
Liver metastases	present	absent
Time from last systemic anti-cancer therapy dose	< 90 days	≥ 90 days

ECOG = Eastern Cooperative Oncology Group; g/dL = Grams per deciliter.

9.4 Efficacy

The original primary efficacy variable for the Phase 3 part of the study was overall survival.

The primary efficacy variable of Phase 2 is ORR, and will be analyzed based on central review assessment. Although OS is the primary variable originally planned for the Phase 3 part of this study, it is considered an exploratory efficacy variable for the Phase 2 part. The analysis will be performed when survival data is considered adequate for analysis by the sponsor.

OS is defined as the time (days) from randomization to death due to any cause. Patients alive at the date of data cut-off for analysis will be censored at the last date known to be alive. If a patient is lost to follow-up before any assessment after randomization, this patient will be censored at Day 1.

Secondary efficacy variables of the study are:

- Progression-free survival (PFS)
- Objective response rate (ORR)
- Disease-control rate (DCR)
- Duration of response (DOR)

The secondary efficacy endpoints (PFS, ORR, DCR, and DOR) will be assessed based on central radiological tumor evaluation.

PFS is defined as the time (days) from randomization to date of first observed disease progression (radiological or clinical assessment) or death due to any cause, if death occurs before progression is documented. The actual date that the tumor scan was performed will be used for this calculation. If a tumor assessment is performed over more than one day (e.g. scans for chest and abdomen done on different days for a same evaluation), the earliest date will be used for the calculation of PFS. For patients without documented radiological or clinical progression or death at the time of analysis, PFS will be censored at the last actual visit date of tumor evaluation.

For all patients, the best overall tumor response at each assessment will be determined locally by the investigator and centrally using the RECIST criteria (v1.1).

ORR is defined as the percentage of patients with complete response (CR) or partial response (PR). Patients for whom overall best response is not CR or PR, as well as patients without any post-baseline tumor assessment will be considered non-responders.

DCR is defined as the percentage of patients, whose overall best response was not progressive disease (i.e. CR, PR, SD or Non CR/Non PD). Tumor assessments with SD as response, that is performed prematurely after randomization of the patient (i.e. substantially earlier than the first planned radiological tumor assessment at 6 weeks), will not be taken into account.

DOR (for PR and CR) is defined as the time from the first documented objective response of PR or CR, whichever is noted earlier, to disease progression or death (if death occurs before progression is documented). DOR will be defined for responders only, i.e. patients with a CR or PR. The actual dates the tumor scans were performed will be used for this calculation. DOR for patients who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

9.4.1 Radiological tumor assessments

Tumor response will be measured using CT or MRI scans (with contrast unless contraindicated) and evaluated using RECIST v.1.1 (28) (see Appendix 16.2) to determine the secondary efficacy variables (progression-free survival [PFS], objective response rate [ORR], disease-control rate [DCR] and duration of response [DOR]). Radiological tumor assessments will be done locally, and in addition centrally to determine the secondary efficacy variables (see details below).

MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule. The first radiological tumor evaluation will be conducted

during screening within 28 days before randomization (see flow chart in Table 9–1). Scans (CT or MRI) for tumor assessments according to RECIST v.1.1 are to be done every 6 weeks (± 7 days) starting from Cycle 1 Day 1 up to week 18, and thereafter, every 9 weeks (± 7 days). A minimum of at least 6 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment in order to achieve a valid response of stable disease. In exceptional cases, when it is deemed clinically necessary by the investigator due to safety reasons, an imaging scan at an earlier time point is allowed.

For patients who discontinue study treatment without disease progression, follow-up tumor evaluations will be performed (by CT or MRI) until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met. During the active follow-up period, CT/MRI evaluations will be performed at the same intervals as during study treatment (every 6 weeks up to week 18, thereafter, every 9 weeks) (see Table 9–1).

The radiological evaluation at baseline must include CT or MRI of the chest, abdomen and pelvis with contrast media (unless contraindicated). At follow-up CT or MRI can be done exceptionally without use of contrast media if this is contraindicated (e.g. renal impaired patients). Chest CT is strongly recommended and preferred versus chest MRI. The same technique (e.g. slice thickness, field of view) and the same image method (CT or MRI) should be used within any given patient. All CT/MRI scans must meet the standard of care for imaging of lesions in the respective organ system(s). All suspected sites of disease will be imaged.

A contrast enhanced (unless contraindicated) CT scan or MRI of the brain is required at screening to rule out brain metastases. Acquisition of both contrast enhanced (unless contraindicated) and unenhanced scans of the brain at baseline is strongly recommended. An MRI scan of the brain is required to confirm or refute the diagnosis of central nervous system (CNS) metastasis at baseline in the event of an equivocal scan. Patients with definitely treated stable CNS metastases may be eligible for the study. Further CT scan or MRI of the brain is only to be repeated if metastases or symptoms are present.

The specific contrast media rules are provided in a separate imaging manual.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standard for a diagnostic CT scan, i.e. adequate radiation dose and i.v. contrast, if intended to be used for target lesion measurements.

Bone scans (Technetium-99m) should be performed at screening. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m bone scans should be repeated when complete response is identified in target disease or when progression in bone is suspected.

New lesions in PET or bone scan should be confirmed by CT or MRI.

All scans should be done with the identical modality (CT or MRI) and the identical technique (e.g., slice thickness, field of view) to those obtained at baseline.

Independent central image review

An ongoing central image review will be conducted for this study in order to determine the secondary efficacy variables (see Section 10.3.1.2). The blinded readers/adjudicator will be board certified, experienced and independent radiologists with broad expertise in oncology radiology and RECIST v.1.1 criteria. They will not have been involved in the clinical part of the study. In addition, investigators will determine treatment response according to RECIST v.1.1. Further details will be described in the Imaging Review Charter, IRC.

All image sets of the study, i.e. CT, MRI, bone scans and exceptionally FDG-PET (if needed for lesion confirmation) must be anonymized by the study sites and provided digitally as Digital Imaging and Communications in Medicine (DICOM) format after every imaging time point. The investigator must assure that all the images are of acceptable diagnostic quality.

Additional specific information on the handling (i.e. collection, shipment, tracking) of the images for the central image review will be provided in a separate imaging manual.

9.5 Pharmacokinetics / pharmacodynamics

Plasma samples for measurement of rogaratinib (BAY 1163877) concentrations (and metabolite(s) concentrations, if needed) will be collected from all rogaratinib-treated patients as follows:

- Day 1 of Cycle 1, 2, 3, 4 and 5:
    - at pre-dose (before supervised dose administration)
    - 1 (±0.5h) hour post-dose (between 0.5 and 1.5 after dose administration)

Oral administration of the morning dose of rogaratinib will be done under supervision of site staff on rogaratinib PK days.

Deviations from planned sampling time intervals will not be considered protocol deviations. The date and clock time of each sample as well as dates and times of the doses will be recorded in the eCRF as PK calculations will be based on the sampling times relative to dosing times. Missed samples do not need to be collected beyond Cycle 5. Samples may be collected irrespective of any dose modifications during the treatment cycle. No detailed dosing history is required before the pre-dose sample, but the dose that separates the pre- and post-dose sample needs to be taken under supervision and the time recorded. Data from this study will be pooled with data from other clinical trials for pharmacometric analysis.

Plasma concentrations of all analytes will be measured using a validated method. If required, other metabolites may be measured. Exploratory measurements of other moieties may be performed, if needed.

Details about the collection, processing, storage and shipment of samples will be provided in the laboratory manual.

Please refer to Section 10.3.3.1 for the analysis of the PK variables.

9.6 Safety

9.6.1 Adverse events

Investigators should refer to the Safety Information section of the current investigator's brochure (IB) of rogaratinib for the expected side effects. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

For the expected side effects of the comparator chemotherapy drugs (docetaxel, paclitaxel or vinflunine), please refer to the respective SmPCs.

Therapeutic monitoring should be performed following dose modification of study drugs in a manner consistent with the local clinical standard of care. In general, patients should be closely monitored for adverse drug reactions of all concomitant medications regardless of the path of drug elimination.

All concomitant medications must be recorded in the patient's source documentation as well as on the eCRF.

Patients must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. AEs should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or chemotherapy.

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for study treatment eligibility.

Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

New lesions or disease progression *per se* should not be regarded as AEs. Instead, the associated signs and symptoms should be recorded as AEs.

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, 12-lead ECG.

- Conditions that started before signing of informed consent for study treatment eligibility and for which no symptoms or treatment are present until signing of informed consent for study treatment eligibility are recorded as medical history (e.g. seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent for study treatment eligibility and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent for study treatment eligibility will be documented as adverse events. This includes intercurrent illnesses.

Definition of treatment-emergent adverse event (TEAE)

A treatment-emergent event is defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of study treatment.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
   - The admission is not associated with an AE
     (e.g. social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

   Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

All SAEs occurring must be handled via this process. All serious diagnoses, symptom(s), sign(s) or finding(s) that have a start date after signing the ICF for study treatment eligibility must be recorded as SAEs (see also Section 11.1). This also includes all serious events with a start date during screening period. A condition that was present before signing the PI/ICF and worsens after signing the PI/ICF for study treatment eligibility must also be recorded as an SAE if the serious criteria are met.

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of AEs should be documented using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03) (29).

The intensity of AEs is classified according to the following categories for events not listed in the CTCAE v.4.03 (e.g. soft-tissue mineralization):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL; instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

Causality should be assessed separately for each study treatment as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study drugs (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient’s pharmacodynamics should be considered.
- The assessment is not possible.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s).

Possible answers are “yes” or “no”.

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Drug delayed
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

All AEs identified after the patient has signed the PI/ICF for FGFR testing and until the patient ends the study (up to at least 30 days after the last administration of study treatment or end of active follow-up) must be fully documented in the source data. AEs are obtained by observation and as volunteered by the patients.

The following procedure applies after signing of the PI/ICF for FGFR testing:

- For patients with AE or SAE related to the procedure of taking a fresh biopsy for FGFR testing the corresponding AE and SAE have to be reported in the eCRF and must be fully documented in the source data.
- For all other events, these have to be fully documented in the source data and will be reported in the medical history only for those patients who have signed the PI/ICF for study treatment eligibility.

The following procedure applies after signing of the PI/ICF for study treatment eligibility.

- For screening failures, the investigator must record every SAE (see Section 11.1) and AE in the eCRF from the PI/ICF until date of screening failure.
- For patients eligible for treatment, all AEs and SAEs identified from the PI/ICF up to at least 30 days after the last administration of study treatment must be reported on the eCRF. Thereafter, AEs related to the study drugs have to be reported and must be fully documented in the source data.

After the end of the active follow-up phase there is no requirement to actively collect AEs (deaths will continue to be followed for efficacy purposes). An AE (irrespective of causal relationship) not completely resolved at the end of the pre-defined collection period must be followed up until resolution (chronicity, baseline grade or complete resolution) or until the investigator considers the event will not improve further. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

The investigator is responsible for grading and judging the causal relationship (see Section 9.6.1.2.3) of the recorded AEs.

AE documentation is event-based: All AEs that were ongoing at the end of treatment should be reviewed and updated up to at least 30 days after the last administration of study treatment. All new AEs that in the opinion of the investigator could be related to study treatment (information may be obtained via phone call), should also be collected and recorded up to at least 30 days after the last administration of study treatment.

All AEs should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If any patient should die within 30 days of treatment discontinuation, the investigator will inform the sponsor and record the cause of death in detail within 24 hours of awareness on an SAE form.

Documentation must be supported by an entry in the patient's file.

A laboratory test abnormality should only be reported as an AE if considered clinically relevant, e.g. causing the patient to withdraw from the study, causing dose modification of the study treatment, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

All of the following events are to be reported to the sponsor as SAEs following the reporting instructions detailed in this section (a copy of the pathology report should be sent, if available):

- **Acute myeloid leukemia (AML)** and **myelodysplastic syndrome (MDS)** occurring after chemotherapy for cancer.
- **Any new primary cancers** (or malignancy) during the course of the study (including skin cancers) regardless of relationship to study treatment.

  Once data regarding survival and remission status are no longer required by the protocol, only any new primary tumors regarded as related to study treatment should be reported.

Recurrent metastatic disease of the study indication should not be reported.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the Section 8 of the investigator's brochure (IB) for rogaratinib. For chemotherapy (paclitaxel, docetaxel, vinflunine), applicable SmPCs will be used.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Adverse events of special safety interest

Rogaratinib is an investigational drug and current knowledge of the AEs associated with this compound is limited. As with any new chemical entity, there is always potential for unexpected AEs, including hypersensitivity reactions.

Signs and symptoms suggestive for soft-tissue mineralization, and retinal disorders (classified analog to CTCAE v.4.03 as Grade ≥ 2) are defined as AEs of special interest (AESI). AESIs should be reported to the sponsor within 24 hours using a safety report form as outlined in Section 9.6.1.4 (Reporting of serious adverse events).

Soft-tissue mineralization

Clinical manifestation of soft-tissue mineralization caused by rogaratinib is expected to be similar to hyperphosphatemic familial tumoral calcinosis (congenital disease caused by loss-of function of FGF23-FGFR/Klotho signaling pathway). Therefore, any events consistent with ectopic calcification should be reported as AESI (e.g. MedDRA lowest level terms [LLTs] tissue calcification, metastatic calcification, calcification of muscles, intestinal calcification, cutaneous calcification).

Any patient with newly diagnosed soft-tissue mineralization suspected to be caused by rogaratinib should permanently discontinue the study treatment.

Retinal disorders (CTCAE Grade ≥ 2)

Any symptomatic retinal disorders including retinal detachment / retinal pigment epithelial detachment / serous retinopathy / retinal vein occlusion (classified analog to CTCAE v.4.03 as Grade ≥ 2) should be reported as AESI. The results of the ophthalmologic examination (Section 9.6.3.6) including any other abnormal ophthalmological findings should be reported in the source data and on a dedicated eCRF page.

Specific dose modification schemes for retinal disorders are defined in Section 7.4.3.1.3.

9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

Please refer to Section 9.6.3.1 for pregnancy testing.

9.6.3 Further safety

9.6.3.1 Laboratory evaluations

Safety laboratory analyses including urinalysis will be performed locally according to the schedule summarized in the tabular schedule of evaluations in Section 9.1.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE (see SAE definition in Section 9.6.1.1).

Clinical chemistry

Full clinical chemistry panel includes: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, glucose (fasting or non-fasting), AST, ALT, bilirubin (total and direct), ALP, total protein, albumin, lipase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine.

Limited clinical chemistry includes: sodium, potassium, chloride, magnesium, calcium (total or ionized), phosphate, blood urea nitrogen (BUN) or urea, and creatinine.

Phosphate levels should be evaluated weekly in patients with an elevated serum phosphate level (≥ 7 mg/dL) until resolution (serum phosphate < 7 mg/dL).

Hormone panel

The hormone panel includes thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) for all patients.

Hematology

Hematology panel includes: Hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.

Coagulation panel

Coagulation panel includes: PTT or activated PTT and PT-INR.

Estimated glomerular filtration rate (eGFR)

eGFR is to be determined during screening for study, on Day 1 of each cycle and at the EOT visit (see Table 9–1), and the value should be entered in the eCRF.

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated Glomerular filtration rate (GFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula. For the calculation, refer to Appendix 16.4.

Only patients with a baseline eGFR ≥30 mL/min/1.73 m2 are eligible to enter the study (see Section 6.1).

Urinalysis

The urine chemistry test includes: WBC, nitrite, pH, glucose, protein, ketones, bilirubin, urobilinogen, blood (RBC or hemoglobin).

Microscopic examinations will be performed if clinically indicated.

Pregnancy test

Serum pregnancy test will be performed at screening in women of childbearing potential. Negative serum pregnancy test must be documented before start of study treatment. Test to be repeated as frequently as required by local regulations. Postmenopausal women who have not had periods for more than 1 year or surgically sterilized women will not be required to undergo a pregnancy test (this information should be recorded under medical history on the eCRF).

Reporting of medical device failures

In Japanese study centers, the investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.6.3.2 Physical examinations

Physical examinations will be performed according to the schedule of evaluations in Table 9–1.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1), depending on criteria of relative timing (before or after signing the ICF for study treatment eligibility).

Full physical examination

A full physical examination will be done at screening and at the EOT visit.

Full physical examination includes review of all organ systems and examination of pertinent organ systems:

- General appearance
- Skin
- Eyes
- Ears, nose and throat
- Head and neck
- Lungs
- Heart
- Abdomen
- Lymph nodes
- Musculoskeletal system (including extremities and spine)
- Genitourinary system
- Neurological findings

Brief physical examination

Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality. Brief physical examinations are mandatory on Day 1 of each cycle and at the safety assessment visit of the active follow-up.

9.6.3.3 12-lead ECG

In each patient, 12-lead electrocardiogram (ECG) (supine position) readings will be performed at screening, on Day 1 of Cycle 1, 2, 3, 4 and 5 at pre-dose (before supervised dose administration) and between 0.5 and 1.5 hours post-dose (for patients on the rogaratinib treatment arm, the ECGs can be performed together with required PK blood sampling). Beyond Cycle 5, 12-lead ECG is to be performed on Day 1 of every 3rd cycle (pre- dose) and at EOT (if not performed within 4 weeks).

Triple 12-lead ECG (supine position) is to be performed (pre-dose and post-dose) in case of QTc prolongation under treatment. 12-lead ECG readings will be performed in triplicate (at least 1 minute apart with no more than 5 minutes in total for all three ECGs) after resting for at least 10 minutes in supine position. QTc prolongation should be followed with triple 12-lead ECG at the discretion of the investigator as clinically indicated.

Weekly 12-lead ECGs have to be performed in patients with an elevated serum phosphate level (≥ 7 mg/dL) until resolution (serum phosphate < 7 mg/dL).

In patients with hypocalcemia CTCAE Grade ≥ 2, an additional 12-lead ECG has to be obtained on day of detection of hypocalcemia and should be repeated as clinically indicated.

If patients develop significant conduction abnormalities during chemotherapy, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with chemotherapy. For details, please refer to the respective SmPC.

The overall interpretation of the 12-lead ECG (normal/abnormal, clinical relevance) and the 12-lead ECG diagnosis and data will be documented in the source documents and on the eCRF. This review should be completed by a qualified physician and signed and dated in the source at the time of review.

9.6.3.4 Vital signs (including height and body weight)

Vital signs, including systolic and diastolic blood pressure, heart rate and body temperature will be collected according to the tabular schedule of evaluations shown in Section 9.1.

Vital signs are to be measured by a member of the investigator's team.

Blood pressure has to be measured in a consistent manner throughout the study (preferably using a manual cuff at the same arm with the patient sitting for 5 min before the measurement). Any clinically relevant measurements or changes are to be reported as AEs (e.g. hypertension, tachycardia, bradycardia, etc.).

Height is measured in centimeters (cm) and obtained only at screening.

Body weight will be measured in kilograms (kg), measurement units 0.1 kg, and preferably be obtained without shoes. If clinically indicated (e.g. excessive weight loss), it is at the investigator's discretion to perform these measurements more frequently.

Additionally, body surface area (BSA) will be derived.

9.6.3.5 ECOG performance status

Patient's ability to manage activities of daily living will be appraised utilizing the performance status scale by Eastern Cooperative Oncology Group (ECOG). The patient's ECOG performance status (PS) will be estimated according to the schedule summarized in the study flow chart in Table 9–1. An ECOG PS score of 0 or 1 is required for study inclusion (see Section 6.1). Change of ECOG PS will be measured.

Grading definitions for ECOG performance status are given in Table 9–3 below.

Table 9–3: Definitions for ECOG PS grading

ECOG Grade	ECOG Status
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, e.g., 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.

ECOG PS = Eastern cooperative oncology group performance status.

9.6.3.6 Ophthalmological examination

An ophthalmologic examination will be performed by an ophthalmologist or an equivalent specialist at screening, during treatment (Day 1 [-7 days] of every second cycle) starting at Cycle 2 and at the EOT visit (see the tabular schedule of evaluations shown in Section 9.1). Additionally, the investigator will ask the patient for changes in vision at each site visit. If change in vision is reported, an ophthalmological examination must be performed.

As per ICH-GCP, at the principal investigator's discretion, a chosen optometrist or equivalent specialist who is licensed can perform the eye examinations as required by the study protocol.

The exam will include previous eye history (only at screening) and any ophthalmic symptoms, best corrected visual acuity, dilated indirect ophthalmoscopy with macular involvement assessment and optical coherence tomography (OCT) including measurement of central retinal thickness. The examination findings will be described in the source data and on the eCRF. Any findings qualifying as an adverse event will be recorded accordingly.

Patients who experience any retinal disorders including retinal detachment / RPED / serous retinopathy / retinal vein occlusion have to undergo ophthalmologic examinations on Day 1 of every cycle.

Ophthalmological monitoring of the treatment associated retinal abnormality is recommended to be continued until resolution of the abnormality and to be documented in the source data for patients whose treatment was permanently discontinued.

For dose modification of rogaratinib due to ophthalmological findings, see Section 7.4.3.1.3.

For reporting of AESI (retinal disorders Grade ≥ 2), see Section 9.6.1.6.

9.7 Other procedures and variables

9.7.1 Biomarker investigations

Only urothelial carcinoma patients with high FGFR1 or 3 mRNA expression levels will be eligible for study treatment. Therefore patients need to provide written PI/ICF for FGFR testing to be enrolled; archival tumor tissue is adequate for testing of FGFR1 and 3 mRNA expression.

Additional slides need to be provided for tumor DNA testing of mutations in PIK3CA and RAS-encoding genes, which have recently been identified as potential FGFR inhibitor resistance factors. Only FGFR positive patients will have the mutational testing as well. The outcome of the mutation testing will not affect the study eligibility.

If archival tissue is not available in sufficient quantity or quality for the FGFR1 and 3 RNA-ISH assay and/or for the PIK3CA and RAS mutation testing to be performed, then a new biopsy procedure would be necessary if the patient wants to pursue the option of entering the trial. This procedure would be performed at the discretion of the investigator and consent from the patient. The tumor material should be derived by a biopsy procedure associated with a non-significant risk, e.g. ultrasound-guided and will be limited to superficial lymph nodes, and other anatomical regions suited for non-invasive biopsy procedures. Fine needle aspirates would not be sufficient as a biopsy procedure for biomarker testing. No major organ should be biopsied, e.g. biopsy of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel are excluded.

The UC tumor tissue embedded into paraffin will be shipped to a central laboratory to confirm high expression levels of fibroblast growth factor receptor (FGFR) mRNA (see Section 6.1: Inclusion criteria) in all patients and in addition for testing the absence or presence of PIK3CA and/or RAS activating mutations in all FGFR-positive patients who have signed the PI/ICF for FGFR testing (see Section 5).

Method applied for patient selection in trial 17403

The FGFR1&3 RNA *in situ* hybridization (RNA-ISH) test is intended to be used for the detection of FGFR1and FGFR3 messenger RNAs (mRNAs) in formalin-fixed, paraffin-embedded (FFPE) tumor tissue from urothelial carcinoma patients. The FGFR1 and 3 RNA-ISH test will be used to aid in the selection of cancer patients who may benefit from the pan-FGFR inhibitor (rogaratinib) therapy. The RNA-ISH technology allows for the respective FGFR probe to bind to the target FGFR mRNA, and in combination with detection chemistry results in visualization of the FGFR mRNA signals. The signals are then quantitated by a trained pathologist using light microscopy. The final outcome can be used to assess the level of FGFR1 and 3 mRNA transcript overexpression. The analysis will be performed centrally.

In pre-clinical studies, only xenograft models with high expression levels of either FGFR1, or FGFR2 or FGFR3 demonstrated significant (> 50%) anti-tumor efficacy upon rogaratinib treatment. Preliminary data from Phase 1 study 16443 confirms that a treatment benefit of having either a partial response or a long-lasting stable disease (SD) is observed in patients

that have a high FGFR expression level. Therefore, having at least one FGFR isoform with a high expression level was selected as inclusion criterion for FGFR-positivity for this Study 17403.

Details about the collection, processing, storage and shipment of samples will be provided separately (laboratory manual).

PIK3CA and RAS mutation testing

The presence or absence of PIK3CA and/or RAS activating mutations is used as one of the stratification factors of the study and will be tested only in FGFR-positive patients who have signed the PI/ICF for FGFR testing. The detection of activating mutations in PIK3CA and/or RAS-encoding genes will be conducted by a central laboratory. Please refer to Section 5.1 for justification of the mutation testing.

Exploratory tumor-based biomarker analysis

For all randomized patients exploratory biomarker analyses will be performed from UC tumor specimen provided beyond the number of slides needed for FGFR1 and 3 testing and for the testing for PIK3CA and RAS mutations. This procedure is covered by the PI/ICF for FGFR testing.

These tumor tissue specimens may be used for the following purposes: (1) to evaluate mutations, copy numbers or gene rearrangements in FGFR encoding genes and in known oncogenes such as p53, PTEN, and cMyc in DNA extracted from tumor tissue specimens; (2) to analyze the gene expression of genes that may explain resistance or hyper-responsiveness to FGFR inhibitors, such as cMet, cMyc and FGF19 in RNA extracted from tumor tissue specimens; (3) to evaluate expression of non-coding tumor relevant RNAs, such as microRNAs; (4) to evaluate protein expression of immune markers, such as PD-L1 and CD8A in tumor specimen, e.g. by IHC.

Exploratory plasma-based biomarker analysis

All FGFR positive patients will be asked to provide blood samples for biomarker analyses, which will be obtained during regular study visits in which blood will be drawn for other scheduled but unrelated laboratory tests. The following procedures are covered by the PI/ICF for study treatment eligibility.

Genetic biomarkers from plasma:

These samples are intended for isolation of plasma to study tumor markers circulating in blood such as circulating tumor DNA (ctDNA) or circulating tumor RNA. Candidates of genes for the evaluation from ctDNA are RAS-encoding genes, PIK3CA, and cMet which have been described as contributors to acquired FGFR inhibitor resistance but also FGFR DNA alterations including but not limited to FGFR3 activating mutations and translocations to correlate with the respective FGFR DNA status detected in tumor specimen from the same patient. The types of analyses may comprise the identification of mutations or splice variants.

Furthermore, these plasma samples will serve as source for non-coding microRNA, as possible markers describing treatment response.

Non-genetic biomarkers from plasma:

Plasma samples will also be used to quantify the circulating levels of various proteins of interest, to attempt to identify a protein signature that correlates with drug response.

Plasma samples for the analyses of tumor biomarkers (genetic and non-genetic biomarkers) will be prepared from blood samples obtained at the following time points:

- At screening visit (within 7 days prior to randomization),
- on Day 1 (pre-dose) of each treatment cycle, and
- at the end-of-treatment (EOT) visit.

On treatment days, blood will be drawn for preparation of plasma samples prior to drug administration, if possible. In addition to the proteins and genes listed above, other biomarkers deemed relevant to this study will be measured if they will be identified as possible resistance mechanisms during the course of the study. Data from these additional biomarker analyses may also be correlated with measures of clinical efficacy.

9.7.2 Patient-reported outcomes (PRO)

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the EuroQol Group's EQ-5D-3L questionnaires will be used to collect patient-reported outcomes (PRO). The EORTC QLQ-C30 is a multidimensional validated cancer-specific quality of life questionnaire developed by the EORTC Study Group on QoL for use in international clinical trial settings. It includes five functional scales *(physical, role, emotional, social, and cognitive functioning),* 3 symptom scales *(fatigue, pain, and nausea and vomiting),* a global health status scale, and a number of single items assessing additional symptoms *(dyspnea, sleep disturbances, constipation, and diarrhea),* and perceived financial impact. The EORTC QLQ-C30 will be used to evaluate the total score, symptom scales / items and global health status of the patients.

The EQ-5D-3L is a generic, validated quality of life preference-based instrument to measure both utility and health status. It contains a descriptive system which measures 5 health dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The five health dimensions are summarized into a single score, the EQ-5D index score that ranges between 0 and 1 (0 representing the worst imaginable health state or death and 1 representing perfect health). The EQ-5D also contains a visual analog scale (EQ-visual analog scale [VAS]), which records the respondent's self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D-3L will be used to evaluate the index and VAS scores.

Data collection for both instruments would be completed at screening and on Day 1 of each cycle, at the EOT visit and at the safety assessment visit of the active follow-up.

9.7.3 Healthcare resource utilization

Healthcare resource utilization information will be recorded once a patient has a hospitalization/healthcare visit, during the course of the study. Information on the start date, end date, ongoing status, location, scheduling status, main diagnosis at discharge, and number of working days missed must be recorded. Data will be analyzed on an *ad hoc* basis.

9.8 Appropriateness of procedures / measurements

All efficacy and safety parameters, as well as the methods to measure them are standard variables / methods in clinical studies and/or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant. To ensure data can be compared between the treatment groups, all examinations (except blood sampling for PK analyses) will be the same in both treatment arms.

10. Statistical methods and determination of sample size

10.1 General considerations

Due to the stop of enrollment, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor. The analysis details of the Phase 3 as well as the transition from Phase 2 to Phase 3 are provided in the following sections as a reference to the original design.

Statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan.

To help structure the section, we present the statistical methods for this Phase 2/3 study as one study with two interim analyses, while the first interim indicates the end of the Phase 2 part, and the second and final analyses are considered the Phase 3 part including Phase 2 patients in the analyses.

Patients will be randomly assigned in a 1:1 ratio to one of the following treatment arms:

- Rogaratinib
- Chemotherapy (taxane or vinflunine)

More details on the treatments are provided in Section 7.

All patients enrolled to this study are expected to have FGFR positive testing results. Due to inter-evaluator variability in the scoring of FGFR test, a confirmation test could be done at the discretion of the sponsor to identify the FGFR positive patients which will be referred to as confirmed FGFR positive.

Although both PIK3CA and/or RAS mutant and WT patients are recruited, this study is powered for the PIK3CA and RAS WT subgroup. Therefore, the recruitment will stop when 450 PIK3CA and RAS WT patients are randomized. In the meanwhile, based on current assumption that about 75% of all study population are PIK3CA and RAS WT, roughly 600

patients in all study population (450 PIK3CA and RAS WT + 150 PIK3CA and/or RAS mutant) will be recruited to the study.

Randomization will be stratified by:

- PIK3CA and/or RAS activating mutations (presence vs. absence)
- Prior immunotherapy (yes vs. no)
- Modified 4-factor Bellmunt risk score (high vs. low) (see Section 9.3.3)

The following rule will be applied for WT and mutant subgroups to potentially remove some stratification factors from the subgroups to avoid over-stratification: if the smallest group within one stratification factor (other than activating mutation status) is less than 15% of all randomized patients in either subgroup (450 patients for WT, and the corresponding number of mutant patients for mutant subgroup), and all study population (with the exception of always including activating mutation status for all population), then this stratification factor will not be introduced into the model for the stratified statistical analysis of efficacy endpoints. As the majority of patients are anticipated to be randomized by the time of the planned formal interim analysis, this rule will be applied to both the 2nd interim analysis and final analysis of OS for consistency.

Data from patients who are transferred to a roll-over study may be pooled and analyzed together with the data from the study in which the patient was initially included. The results from these analyses will be reported separately.

10.2 Analysis sets

Full analysis set (FAS)

The primary population for the efficacy analysis is the Full analysis set (FAS) population (also considered the Intent-to-treat (ITT) analysis set), which is defined as all randomized patients. Patients will be analyzed as randomized, meaning even if a patient was randomized and received no drug or if randomized and received incorrect study drug at any time, these patients will still be analyzed for efficacy under FAS, as randomized. The FAS population is identical to the ITT population.

Safety analysis set (SAF)

The population for the safety analysis will be comprised of all patients who received at least one dose of study treatment (rogaratinib or chemotherapy). Patients will be analyzed as treated. Using a conservative approach, patients randomized to the chemotherapy arm will be analyzed under the rogaratinib arm if the patient received at least one dose of rogaratinib treatment, whereas patients randomized to the rogaratinib arm will still be analyzed under the rogaratinib arm regardless of receiving any chemotherapy. Only if a patient randomized to the rogaratinib arm received chemotherapy treatment only would the patient be analyzed under the chemotherapy arm. Note, given the study is designed as open-label and study drug between the two arms will be administered differently (i.e. oral versus intravenous) the possibility of a patient receiving incorrect treatment is unlikely.

In addition, in the rare case of early drop out without any post-baseline safety/visit information, the patient should be discussed at the Validity Review Meeting where a decision on inclusion into SAF set will be made.

10.3 Variables and planned statistical analyses

The formal statistical analyses will be both descriptive and inferential. Summaries will be provided for each of the treatment arms, rogaratinib and chemotherapy. In addition, descriptive summaries of population characteristics will be provided for the total study population.

Demographic and baseline characteristics, baseline cancer characteristics, medical history, prior anti-cancer therapies, concomitant medication, patient disposition will be summarized by treatment arm for the FAS population. For continuous measurements, the mean, standard deviation, range and median will be computed; for categorical values, the frequency and percent will be provided.

See Section 11.4 for handling of missing data.

10.3.1 Efficacy variables

10.3.1.1 Primary efficacy variable

Objective response rate (ORR) is the primary efficacy variable for the Phase 2 part. **ORR** will be compared between treatment arms using Fisher's exact test, based on independent central review assessments for both populations. Estimates and 95% confidence intervals will be computed for each treatment arm. The differences in ORR between the rogaratinib and chemotherapy arms and the corresponding 95% confidence intervals will also be calculated.

Overall survival was the primary efficacy variable (see Section 9.4 for definition) of the originally planned Phase 3 part. OS data will be considered mature and the final OS analysis (i.e. primary completion) will be performed when approximately a total of 390 PIK3CA and RAS WT patients have died, in accordance with the power calculations specified for the FAS. See Section 10.4 for additional details on sample size determination.

Due to the stop of enrollment, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor. The details below about step-wise hypothesis test and analysis of overall survival are provided as a reference to the original design.

For the primary efficacy variable of overall survival in the Phase 3 part, a stratified log-rank test controlling type I error at a level of 0.025 (one-sided) will be conducted for the WT population first (step 1). A full alpha of 0.025 (one-sided) will be passed on to OS in all study population and some selected secondary endpoints (step 2) if and only if the null hypothesis of OS for WT population is rejected. In case of failing to reject null hypothesis of OS for WT population, step 2) will not be tested. Details on controlling family-wise type I error within step 2) for OS in all study population and selected secondary endpoints will be specified in the Statistical Analysis Plan (SAP).

If the analysis in step 1) based on final OS data in WT population is positive, the efficacy of rogaratinib monotherapy in PIK3CA and RAS WT FGFR-positive locally advanced or metastatic urothelial bladder patients is considered established; Moreover, if the analysis in both step 1) and the OS in all study population part in step 2) are positive based on the testing details specified in SAP with the corresponding alpha level allocated for OS in all study population, the efficacy of rogaratinib mono therapy in all FGFR-positive locally advanced or metastatic urothelial bladder patients is considered established.

Therefore, to compare OS between the rogaratinib arm and the chemotherapy arm, the following hypothesis will be tested for the PIK3CA and RAS WT patients first and then all study population:

- H_0: hazard ratio (rogaratinib / chemotherapy) ≥ 1

  versus

- H_1: hazard ratio (rogaratinib / chemotherapy) < 1

The primary efficacy variable of OS in step 1) will be formally compared based on approximately 390 death events in the PIK3CA and RAS WT patients for WT population, using a stratified log-rank test, stratified by the stratification factors used for randomization, with consideration of the rule specified in Section 10.1. 390 death events plus the corresponding number of events occurred in the PIK3CA and/or RAS mutant patients during the same period of time will be included for the evaluation of the all study population in step 2) mentioned above, using the stratified log-rank test applying the same rule.

The primary stratified analysis for OS (and all other efficacy endpoints) will be based on stratification information as entered in IxRS for both step 1) and 2).

In addition to the stratified log-rank test, for the PIK3CA and RAS WT patients first and then all study population, the hazard ratio (rogaratinib / chemotherapy) for OS and its 95% confidence interval will be calculated using the Cox model, stratified by the same factors as stated above. Kaplan-Meier (KM) estimates for OS and KM survival curves will also be presented for each treatment arm. The KM estimates at time points such as 3 months, 6 months etc. together with corresponding 95% confidence intervals as well as the differences of these estimates will also be calculated between the rogaratinib arm and the chemotherapy arm, for both PIK3CA and RAS WT population and all study population (referred to as “both populations” below).

The sensitivity analysis will be performed by only including confirmed FGFR positive patients for WT population and all study population, respectively.

See Section 10.5 for additional details on the planned interim analysis of OS.

10.3.1.2 Secondary efficacy variables

Secondary efficacy variables including progression-free survival (PFS), disease control rate (DCR) and duration of response (DOR) (see Section 9.4 for definitions) will be analyzed based on final database.

Further analysis details with respect to PFS, DCR and DOR are summarized below.

For analyses of **PFS**, in both populations, the two treatment arms will be compared using a log-rank test stratified by three randomization stratification factors based on independent central review assessments. The hazard ratio (rogaratinib / chemotherapy) and 95% confidence interval will be provided. KM estimates and KM curves will also be presented for each treatment arm. The KM estimates at time points such as 2 months, 4 months etc. together with corresponding 95% confidence intervals as well as the differences of these estimates between the rogaratinib arm and the chemotherapy arm will also be calculated.

DCR will be analyzed similarly to ORR.

For both populations, summary statistics will be displayed for all best response categories: CR, PR, SD, Non CR/Non PD, PD by central radiographic imaging, and PD by clinical judgment. Frequency counts and percentages with exact 95% confidence intervals will be displayed.

Since the responders are not a randomized group, no statistical testing will be performed for **DOR**. Analysis of DOR will be descriptive in nature for both populations based on independent central review assessments. KM estimates and KM curves will be displayed for each treatment arm.

Analyses based on investigator's review assessments will also be performed for PFS, DCR and DOR as sensitivity analyses.

10.3.1.3 Subgroup analyses

For both populations, subgroup analyses for ORR, PFS and OS will be performed in a descriptive fashion if data are warranted. These may include, but may not be limited to, subgroups defined by demographics such as sex, race, ethnic group, geographic regions and age (calculated at the date of randomization using date of birth), baseline ECOG performance status, baseline cancer characteristics and stratification factors at randomization (such as prior immunotherapy-treated subgroup etc.). Descriptive statistics and hazard ratio estimates with 95% CI for OS and PFS will be provided at least within each category of the subgroup, provided there are sufficient numbers of events in total for the category within the subgroup across the treatment arms.

10.3.2 Safety variables

10.3.2.1 Adverse events (AEs)

Summary of adverse events is considered a secondary objective for this study. All AEs, whether considered drug-related or not, will be reported on the eCRF with start / stop dates, dates of any grade change, action taken, whether treatment was discontinued, any corrective measures taken, and outcome. For all events, the relationship to treatment and the severity of the event will be determined by the investigator. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terms (version 20.0 or later), and graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

For both populations, descriptive summary tables (frequency and percentage of patients, not of events) will be presented by treatment arm and MedDRA terms and NCI CTCAE v.4.03 worst grade for the following:

- Prevalence of AEs during screening
- Incidence rate of all treatment-emergent AEs (TEAEs)
- Incidence rate of treatment-emergent drug-related AEs
- Incidence rate of treatment-emergent serious AEs (SAEs)
- Incidence rate of serious treatment-emergent drug-related AEs
- Interval-specific and cumulative event rates for the more common AEs for treatment emergent adverse events

A treatment-emergent event is defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of study treatment.

10.3.2.2 Deaths and serious adverse events (SAEs)

The incidence of deaths in the study, and especially deaths up to within 30 days of last dose of study drug, will be summarized by treatment arm and cause of death for both populations. All deaths up to 30 days of last dose of study drug will be listed by patient with start and stop date of study treatment, date of death, and cause of death for both populations.

In addition to the above mentioned incidence table of all treatment-emergent SAEs, these events will be listed by patient with investigator AE term, start and stop date of study drug administration, start and stop date of AE, drug relationship, worst NCI CTCAE grade, action taken and outcome for both populations.

10.3.2.3 AEs leading to discontinuation of study treatment and/or withdrawal from the study and other significant AEs

The incidence of AEs leading to permanent discontinuation of study treatment and / or withdrawal from the study will be summarized by treatment arm for both populations, and be listed by patient with investigator AE term, start and stop date of study drug administration, start and stop date of AE, drug relationship, worst NCI CTCAE grade, action taken and outcome. In addition, incidence of AEs that caused dose reduction or interruption will be summarized separately by treatment arm for both populations.

10.3.2.4 Clinical laboratory evaluations

Frequency of laboratory abnormalities regarding hematology, clinical chemistry and clinical urinalysis will be tabulated by treatment arm for both populations. Worst grades for hematological and biochemical toxicities will be calculated according to CTCAE v.4.03 based on laboratory measurements, and will be summarized by treatment arm and NCI CTCAE v.4.03 category and worst grade for both populations. Frequency tables as well as tables with change in worst grade from baseline will be presented.

10.3.2.5 Other safety measures

For both populations and each treatment arm, vital signs (i.e. blood pressure, heart rate, body temperature) will be tabulated and summarized by visit for observed values and changes from baseline using descriptive statistics, as appropriate. 12-lead ECG data will also be summarized at baseline, by visit and end of treatment for observed values and changes from baseline using descriptive statistics, as data are available.

10.3.3 Other variables

All the variables listed in this section are considered tertiary variables.

10.3.3.1 Pharmacokinetic variables

The samples collected on Day 1 of Cycles 1 through 5 at pre-dose and between 0.5 and 1.5 hours post-dose will document a longitudinal exposure under steady state condition. The longitudinal exposure data will be used in exposure-response modelling of adverse events and clinical responses. Evaluation of the data described above will be presented in a separate report.

The details of the modeling analysis will be described in a separate Modelling and Simulation (M&S) Analysis Plan and the results may be reported in a separate M&S Report.

In the clinical study report, only plasma concentration data for all analytes will be listed.

10.3.3.2 Biomarker variables

Patients' biomarker status at baseline will be correlated with treatment effect in OS, PFS and response to explore which biological targets may be particularly important in defining the appropriate therapeutic population for the agent. Biomarker analyses and results will be provided in a separate report.

10.3.3.3 Patient-reported outcomes (PRO)

PRO data as measured by the EORTC QLQ-C30 and EQ-5D will be analyzed to assess differences in health-related Quality of Life (HRQoL) and health utility values between treatment arms based on time-adjusted Area Under the Curve (AUC) using all available data. The scoring of the PRO endpoints and handling of missing data will be detailed in the statistical analysis plan. Summary statistics will be presented for each of the PRO endpoints at each assessment time point and for change from baseline by treatment group for both populations.

Primary Analysis of PROs: If there is sufficient data, an analysis of covariance (ANCOVA) model will be used to compare the time-adjusted AUCs between the two treatment groups with covariates for baseline HRQoL score and the same stratification factors as used in the primary efficacy endpoint at the end of the study for both populations. Least-squares mean estimates; standard errors and 95% CIs will be estimated for each treatment group and for the treatment group difference for both populations. The treatment by covariate interactions will be explored in the ANCOVA models and the consistency of the treatment effect on HRQoL across different subsets defined by the covariates in the model will be assessed. In the event that the ANCOVA model assumptions (e.g., normality and homogenous variance of the error

terms, equality of slopes for different treatment regression lines) are not satisfied, the rank analysis of covariance may be used (30, 31).

Secondary Analyses of PROs: Sensitivity analysis using different imputation methods for imputing missing assessments may be performed. Additional exploratory analyses may be carried out using the linear mixed effect models to explore the effects of treatment, time and other covariates on the endpoints, assuming the missing data mechanism is missing at random.

10.4 Determination of sample size

Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3. As a reference, the following details provide the number of patients originally planned for the entire study:

The determination of sample size contains two aspects: Phase 2 and Phase 3 part of the study. The sample size for the Phase 2 part of the study (the first interim) is powered on ORR for FGFR positive PIK3CA and RAS WT population. The Phase 2 part of the study is designed to achieve 90% power to detect the difference in ORR between rogaratinib over chemotherapy in FGFR positive WT population with the assumption of 30% response rate in rogaratinib and 10% in chemotherapy. Assuming one-sided alpha of 0.1 for the Phase 2 part, power of 90%, and a randomization ratio of 1:1 between the rogaratinib and chemotherapy arms, a total of approximately 116 confirmed FGFR positive patients with wild-type PIK3CA and RAS biomarkers are required for the Phase 2 part, based on Fisher's exact test.

The sample size for the Phase 3 part of the study is powered on the primary efficacy variable of OS for PIK3CA and RAS WT population. The study is designed to have 90% power to detect an approximately 40% increase in median OS (i.e. a hazard ratio [HR] of 0.72, rogaratinib over chemotherapy) for the WT population. Assuming one-sided alpha of 0.025 for the Phase 3 part, power of 90%, and a randomization ratio of 1:1 between the rogaratinib and chemotherapy arms for the WT population, and one futility interim analysis of OS (paying a slight alpha penalty of 0.001), a total of 390 death events are required for the final OS analysis. If the futility stopping boundary for OS is not met at the interim analysis, the study will continue after the second interim for the study and the final OS analysis will be performed when approximately 390 death events are observed (see Table 10–1).

It is projected that 390 death events will have accumulated approximately 43 months after the start of randomization, assuming approximately 450 PIK3CA and RAS WT patients are randomized for two treatment arms combined at a rate of 20 patients per month after an initial 4-month ramp-up period for a 25-month long enrollment period, a dropout rate of 3%, exponentially distributed event times for OS, and 7 and 9.76 month median OS time for the chemotherapy and the rogaratinib arms, respectively. With the assumption that 75% of the patients in the all study population are PIK3CA and RAS WT, roughly 600 patients in all study population will be randomized in the two treatment arms combined.

East Software version 6.4 was used for determination of the sample size.

10.5 Planned interim analyses

A Data Monitoring Committee (DMC) will be instituted in order to ensure ongoing safety of study patients with respect to a risk/benefit assessment during periodic data review meetings, review results from the planned interim analysis and provide a formal recommendation for continuation/termination of the study and monitor study conduct to ensure the overall integrity of trial in maintained.

Before achieving the criteria for the first interim analysis, the study recruitment was put on hold after a recommendation of the study DMC. The sponsor decided to perform a full analysis and review of all study data and stopped the recruitment permanently.

Due to the stop of enrollment and full data analysis, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor.

The details of the two planned interim analyses are provided below as reference to original study design.

Two futility interim analyses were originally planned for this study.

The first one will be performed at the end of Phase 2 part when the first approximately 116 confirmed FGFR positive patients with wild-type PIK3CA and RAS biomarkers (58 patients each arm) complete 4.5 months of treatment. The study will continue with the Phase 3 part if the fisher's exact test for ORR based on central review assessments for the first approximately 116 WT patients yields a one-sided p-value less than 0.15. The second interim analysis (Phase 3 part) is planned when approximately 50% of the planned total number of required death events occurred in the WT subgroup (about 195 deaths in WT). The study continues if the observed HR for OS in WT subgroup is less than 0.96 (corresponding to greater than 4% improvement in OS for rogaratinib comparing to chemo), which is determined using O'Brien Fleming type boundary based on 195 death events. The actual stopping boundaries for the interim analysis will be calculated based on the actual number of events observed up to the database cutoff date used for the interim analysis.

Please note in both interim analyses, only WT subgroup will be analyzed and tested for futility. Analyses in all study population, as well as analyses with additional efficacy endpoints (such as DoR, PFS, etc. if data warrants) beyond the ones mentioned above as futility rules in both populations (defined earlier) will be performed and provided to DMC as supplemental information to assist decision making.

Recommendation for trial continuation will be guided by the monitoring boundaries at the formal interim analysis as well as safety evaluations from all data review meetings according to the DMC charter. All analyses to be presented to DMC to aid recommendations for trial continuation will be explicated in the DMC charter.

The DMC will be explicitly asked to give recommendations on the continuation or termination of the trial. Decisions on trial termination, amendment or cessation of patient recruitment based on risk benefit assessments will be made after recommendations from the DMC have been assessed by the sponsor.

The DMC is scheduled to receive the interim efficacy and safety data. Data which may compromise the integrity of the study (e.g., comparative data) will be analyzed and discussed only in the closed session of the DMC meetings. The closed session will be restricted to the DMC members and a non-voting and independent facilitator (a biostatistician from an independent statistical analysis center). Closed session minutes will be maintained by the DMC in confidence and will be provided to the sponsor only at completion of the trial. All data provided to the DMC and all deliberations of the DMC will be privileged and confidential. DMC members will sign Confidentiality Agreements prior to acceptance of participating on the DMC committee.

Table 10–1 summarizes the key elements for interim and final analysis based on the number of events assumed. The actual monitoring boundaries will depend on the actual number of events observed at the time of the interim analysis. Although we take a small alpha penalty of 0.001 for the first interim at the end of Phase 2, the nominal alpha for the final analysis remains the same, 0.025. East Software version 6.4 was used for determination of the study monitoring boundaries.

In case of early termination of the study at either interim due to futility, all the analyses specified (as appropriate) in Section 10.3 will be performed for the clinical study report including all data available at the time of study termination.

Table 10–1: Summary of planned interim and final analyses

	No. of patients / events	Endpoints	Go criteria for interim (success criteria for final)	Population
1st interim (Phase 2)	approximately 116 confirmed FGFR positive patients with wild-type PIK3CA and RAS biomarkers	ORR	One-sided p-value less than 0.15	WT only
2nd interim (Phase 3)	195 events in WT	OS	Observed HR < 0.96 (4% improvement)[a]	WT only
Final (Phase 3)	390 events in WT (and correspondent No. of events in all study population)	OS	One-sided p-value less than 0.025	Sequential 2 steps: WT first then all study population

FGFR = Fibroblast growth factor receptor; HR = Hazard ratio; No. = Number; ORR = Objective response rate; OS = Overall survival; PIK3CA = Phosphoinositide 3-kinase, catalytic subunit alpha isoform; RAS = Rat sarcoma; WT = Wild type.
a: Just an example based on 116 events in WT patient population at interim. The actual futility boundary will depend on the actual number of events observed at the time of the interim.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (LSH; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed

from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained. Study-specific RAVE training will be provided at the investigator's meetings, and a study-specific manual (eCRF completion guidelines) will be provided to all sites.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all patients enrolled in this study.

Limited data will be recorded for all patients in the FGFR testing period as described in Section 9.1. For patients not being eligible for randomization additional information is recorded: the reason for premature discontinuation and date of last visit.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the eCRF have source documentation available at the site.

Data recorded from FGFR testing failures (pre-screening failures)

At minimum, the following data should be recorded in the eCRF for patients who do not meet the eligibility criteria during pre-screening:

- Date of informed consent(s) that were signed (PI/ICF for FGFR testing)
- Subject (patient) identification

- Subject (patient) visit and visit date
- Inclusion criteria for FGFR testing met (yes / no)
- Demographic information (year of birth / age; sex; if applicable race / ethnicity)
- Tissue sampling (archival or fresh biopsy) for FGFR testing and PIK3CA and RAS mutation testing
- ECOG performance status
- Toxicity/AE assessment: during the FGFR testing period: AEs/SAEs related to the procedure of taking a fresh biopsy for FGFR testing (in case archival tumor tissue is not available) the corresponding AE and SAE have to be reported and must be fully documented in the source data
- End of FGFR testing period, primary reason for discontinuation
- Date of last visit

Data recorded from main screening failures

At minimum the following data should be recorded in the eCRF for patients who do not meet the eligibility criteria during screening:

- Date of informed consent that was signed (PI/ICF for study treatment eligibility)
- Inclusion/exclusion criteria for screening met (yes / no)
- ECOG PS
- Medical history (see Section 9.3.2)
- Reason for discontinuation and date of last visit

These data will be transferred to the respective database.

For patients who signed ICF for FGFR testing and who experienced an SAE related to the fresh biopsy procedure for FGFR testing, and for screening failures who had signed consent for study treatment eligibility and who experienced SAE, the following data should be collected in the eCRF in addition to the data specified above:

- All information related to the SAE such as:
  - The SAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page
  - Laboratory results related to SAE, if applicable

Data recorded of prior and concomitant medication

From signing of PI/ICF for study treatment eligibility up to 30 days after the last administration of study treatment, all concomitant medications (including start/stop dates, dose, frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as on the appropriate pages of the eCRF. At the EOT visit and during active and long term follow-up periods, any new systemic anti-cancer therapy has to be reported. With regards to other concomitant medications, only those that are administered to treat AEs related to study-specific procedures are mandatory to be reported during active follow-up. Administration of contrast media for protocol-specified radiological procedures (CT scan or MRI) does not need to be reported on the concomitant medication eCRF page, unless there is an AE related to the contrast medium injection (e.g. allergic reaction).

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.
- Site completes all the logistic and administration tasks required for efficient study conduct in a timely manner.

The monitors will be guided by the study team on expected monitoring visit frequency but these may increase/decrease dependent on the numbers of patients recruited at the site and outstanding tasks that need completing at each site.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory [FGFR test results]).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for analysis (i.e. locked database), the clinical database is planned to be re-opened for the inclusion of additional data e.g. pharmacokinetic data, biomarker data.

11.4 Missing data

In order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), every effort should be made to resolve incomplete or missing dates during the course of the study (i.e. edit checks, data cleaning / monitoring etc.). However, in rare circumstances, missing parts of either date of last contact or the date of death may occur where an imputation algorithm will be defined and stated in the Statistical Analysis Plan (SAP).

Missing or unevaluable tumor assessments (including a scheduled assessment that was not done and an incomplete assessment that does not result in an unambiguous tumor response according to RECIST v.1.1) will not be used in the calculation of derived efficacy variables related to tumor assessments unless a new lesion occurred or the lesions that were evaluated already showed progressive disease. No imputation will be performed for missing lesion assessment and tumor response. For example, if a patient misses a scan visit and PD is documented at the next available scan visit, the actual visit date of the first documented PD will be used to calculate PFS.

Further information related to the handling of missing parts of a tumor assessment date or last contact / death date for the derivation of efficacy endpoints, such as overall survival and progression free survival, will be detailed in the SAP.

For handling of missings in the QoL questionnaires, refer to the EORTC QLQ-C30 Scoring Manual (32) and the EuroQol EQ-5D User Guide (33), respectively.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where

the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- Strategic reasons (e.g. the clinical development of the drug is stopped).

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Sponsor's Medical Expert

Name: PPD
Address: Bayer U.S. LLC
100 Bayer Blvd, PO Box 915
Whippany, NJ, 07981 USA
Telephone no.: PPD
Email: PPD

Coordinating investigators

Name: PPD
Title: PPD
Address: PPD
USA
Telephone no.: PPD and PPD
Fax no.: PPD

Name: PPD
Title: PPD
Address: PPD
USA
Telephone no.: PPD
Fax no.: PPD

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the

protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

External data evaluation bodies

Data Monitoring Committee (DMC)

DMC will be instituted in order to ensure ongoing safety of study patients through a risk/benefit assessment during periodic data review meetings and to monitor study conduct to ensure that the overall integrity of the trial is maintained.

The DMC will include at least 3 members, including an independent statistician and oncologists. The DMC will operate independently of the sponsor and investigators. Data review meetings will be held periodically as per separate DMC charter. Enrollment to the study will continue throughout the scheduled meetings of the DMC.

The DMC will review the result of the scheduled interim analyses as described in Section 10.5, and determine whether to recommend stopping the study for futility per protocol criteria.

Decisions on trial termination, amendment, or cessation of patient recruitment based on risk/benefit assessment will be made after recommendations from the DMC have been assessed by the sponsor.

Steering Committee (SC)

A Steering Committee will support the sponsor during the conduct of the study in all aspects of safety and efficacy.

Central laboratory

PK and biomarker (FGFR expression, PIK3CA and RAS mutation and additional blood/tumor-based biomarker) tests will be performed centrally. Further details will be provided in the Laboratory Manual.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure

according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent

13.4.1 PI/ICF for FGFR testing

A patient information and informed consent form (PI/ICF) with brief study information on the study will be provided to patients with locally advanced or metastatic urothelial carcinoma who would like to participate in this study. A sample PI/ICF for the FGFR testing is provided as a separate document to this protocol.

The PI/ICF for the FGFR testing includes the general aspects of the study conduct, details on the tumor samples required to be taken to perform the FGFR testing in all patients, PIK3CA and RAS mutation testing in all FGFR-positive patients and exploratory biomarker analyses in randomized patients along with information on any trial risks from the fresh biopsy sampling (this applies only in case archival tumor sample is not available).

The patient has the right to ask the investigator to explain the study in detail and has the right to refuse his/her participation at any time without giving a reason.

13.4.2 PI/ICF for study treatment eligibility

A PI/ICF for study treatment eligibility will be provided to the patient who is confirmed to have FGFR1 or 3 positive urothelial carcinoma and still has interest to participate in this study, no longer than 28 days prior to randomization to study treatment.

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient / legal representative or proxy consenter (if the patient is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient / legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers end-of-study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the patient / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator / delegate will personally sign and date the form. The patient / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient's clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. Adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.
3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to patients / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient / legal representative or proxy consenter of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

13.4.3 PI/ICF for collection of data on pregnancy and birth

A PI/ICF for collection of data on pregnancy and birth will be used for fertile male patients whose female partner becomes pregnant. The PI/ICF will be signed by the male study patient and their pregnant female partner in case of pregnancy. The consent for the collection of data on pregnancy and birth in case a female study patient becomes pregnant is covered in the PI/ICF for study treatment eligibility.

13.4.4 PI/ICF on study updates

A PI/ICF on study updates may be used for update information (e.g. if new safety information is available) - for patients who are already participating in the study.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

The sponsor is interested in the publication of the results of every study it performs.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the eCRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient’s identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

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15. Protocol amendments

15.1 Amendment no.3

Amendment no.3 is a global amendment forming integrated protocol version 2.0, dated 09 MAY 2019.

Overall rationale for the amendment

The protocol was amended in response to issues brought up by DMC, Health Authorities, IRBs, and investigators at sites. These changes will allow for clarification of topics and enable better accrual at sites.

Changes to the protocol text

Changes to the protocol text are provided in a separate track-changes version.

High-level description of the changes and the affected sections are listed in the table below.

Section # and Name	Description of Change	Brief Rationale
2. Synopsis, 5.2.2 Treatment period, 5.4 Justification of the design, 6.4.1.3 Withdrawal criteria, 7.4.1 Doses, dosing schedule and route of administration, 7.4.3.1 Dose modifications of rogaratinib, 7.4.3.1.2 Liver toxicity	Maximum planned dose is reduced to 600 mg b.i.d. from 800 mg b.i.d. Dose levels and dose modifications are modified accordingly.	The maximum dose is reduced as per DMC recommendation for study 17403. The range of rogaratinib plasma exposures after 600 mg b.i.d. and 800 mg b.i.d. are expected to be similar however with an expected safer tolerability at 600 mg b.i.d.
2. Synopsis, 5.1 Design overview, 5.6 Primary completion 10.1 General considerations, 10.3.1.1 Primary efficacy variable, 10.3.1.2 Secondary efficacy variables, 10.4 Determination of sample size, 10.5 Planned interim analyses	Sample size for 2nd interim analysis and final analysis is updated. A sensitivity analysis is added for OS.	Due to inter-evaluator variability in the scoring of FGFR test, the sample size is changed in order to increase the study power.
2 Synopsis, 6.1 Inclusion criteria	The requirement of cytological confirmation of urothelial carcinoma is removed from the inclusion criteria. Applicable tumor classification is revised.	Cytological confirmation is not accepted in all countries to confirm tumor diagnosis and data may not be robust enough. Stage T4b is applicable only for bladder, but not applicable for renal, pelvis and ureters and uretha (only T4).

Section # and Name	Description of Change	Brief Rationale
6.1 Inclusion criteria	Additional wording is added in the contraception criterion.	Additional wording was requested by health authorities and ethics committees to align with the SmPC of the chemotherapy drugs.
6.2 Exclusion criteria	Exclusion criterion for active symptomatic or untreated brain metastases is modified: detailed clarification is added for patients with asymptomatic brain metastases. Time frame from completion of CNS directed therapy to first study drug intake is shortened to 12 weeks.	In order to provide detailed clarification considering patients with asymptomatic brain metastases to be included in this study and to give possibility to treat patients with stable and asymptomatic brain metastases earlier.
2 Synopsis, 6.2 Exclusion criteria	Exclusion criterion regarding more than two prior lines of systemic anti-cancer therapy for urothelial carcinoma is clarified.	Wording is added to further clarify that the two lines of prior systemic anticancer therapy is limited to advanced unresectable/metastatic disease.
6.2 Exclusion criteria	Immunotherapy is added to the definition of prior anti-cancer therapy.	To further clarify the criterion.
6.2 Exclusion criteria	An exception is added to exclusion criterion #19: prophylactic antiviral treatment of chronic hepatitis B (e.g. entecavir) is allowed.	Standard of care in several countries.
5.5 End of study, 7.2 Identity of study treatment, 8.2 Post-study therapy, 10.1 General considerations, 12. Premature termination of the study	Protocol is modified to introduce a roll-over study.	A roll-over study is introduced to allow a possibility to continue study treatment and/or follow-up in a separate study when this trial is stopped but benefits are observed for individual patients and/or follow up of patients is needed.
2 Synopsis, 7.1 Treatments to be administered, 7.2.2 Chemotherapy (comparator drugs), 7.3 Treatment assignment	Treatment guidelines in the given country are added to be considered when choosing the chemotherapy.	To allow treatment of patients randomized to the chemotherapy arm according to local guidance even though the drug is not approved in any indication in the respective country but used as standard of care defined by local guidance.

Section # and Name	Description of Change	Brief Rationale
7.2.2 Chemotherapy (comparator drugs), 7.4.3.2 Dose modifications of chemotherapy (comparator drugs)	Text is added to emphasize additional considerations for the use of taxanes (docetaxel, paclitaxel) and vinflunine according to local guidelines.	Local health authorities and ethic committees requested, that local guidelines should be followed for the use of the chemotherapy drugs.
9.7.1 Biomarker investigations	Wording is added to clarify that tumor material should be derived by a biopsy procedure associated with a non-significant risk and no major organ should be biopsied.	To clarify the tumor biopsy procedure for biomarker testing and to align with the wording provided by FDA.
5.2.2 Treatment period	Wording is added to clarify that in cases when PIK3CA and/or RAS genetic testing results are not available before randomization, those patients with unknown mutation status prior to randomization will be grouped into the mutation “presence” strata in the randomization process.	To clarify the stratification of PIK3CA/RAS unknown patients in the randomization process.
3.2.2 Clinical experience with rogaratinib, 3.5 Benefit-risk assessment, 7.4.3.1 Dose modifications of rogaratinib (Table 7-3), 7.4.3.1.1 Hyperphosphatemia, 9.1 Tabular schedule of evaluations, 9.2.1.2 Screening, 9.2.2.1 Day 1 of Cycle 1, 9.2.2.2 Day 8 of Cycle 1, 9.2.2.3 Day 15 of Cycle 1, 9.2.2.4 Day 1 of Cycle 2, 9.2.2.5 Day 15 of Cycle 2, 9.2.2.6 Day 1 of Cycle ≥ 3, 9.2.2.8 End-of-treatment (EOT) visit, 9.2.3.1 Active follow-up, 9.6.3.1 Laboratory evaluations, 9.6.3.3 12-lead ECG	Content relevant to dose modifications of rogaratinib and management for hyperphosphatemia is updated.	The management rules for hyperphosphatemia are modified to reflect the current benefit-risk profile of rogaratinib and to anticipate the “real life” use in the post-marketing setting.
8.1 Prior and concomitant therapy	Concomitant therapies are modified to allow continuation of bisphophonates and denosumab which has been started prior to start of study treatment but to prohibit start of treatment with these drugs during the study treatment.	Continuation of supportive treatment with denosumab and biphophonates should be allowed as concomitant therapy for patients with bone metastases if they have been started prior to study treatment as these are considred standard of care.

Section # and Name	Description of Change	Brief Rationale
8.1 Prior and concomitant therapy	An exception is added to prohibited concomitant radiotherapy: a short course of radiotherapy due to a pathological fracture is allowed if the underlying bone lesion is not considered as target lesion.	A short course of radiotherapy during study treatment due to pathological fracture is allowed as concomitant therapy, if medically needed for stabilization of the fracture.
8.1 Prior and concomitant therapy	Biotin-containing supplements containing more than 30 µg daily dose of biotin are added to prohibited concomitant medication.	Added as per FDA safety communication about potential interference between laboratory tests and drugs that contain > 30 µg daily dose of biotin.
9.1 Tabular schedule of evaluations, 9.2.2.6 Day 1 of Cycle ≥ 3, 9.6.3.3 12-lead ECG	Post-dose 12-lead ECG beyond cycle 5 is removed.	To lessen the burden for the patient. Evaluation of the relationship between PK and ECG results is only necessary up to Cycle 5, after which single ECGs only for safety reasons are sufficient.
6.4.1.3 Withdrawal criteria, 9.2.3.1 Active follow-up	Wording is added for PD confirmation read by independent central imaging review.	Clarification to explain the role of central PD confirmation review.
9.1 Tabular schedule of evaluations, 9.2.1.2 Screening, 9.4.1 Radiological tumor assessments.	Requirement of contrast enhanced (unless contraindicated) CT/MRI scans and strong recommendation of acquisition of both contrast enhanced and unenhanced scans for brain imaging at screening are added. Reference to Image Acquisition Guidelines is added.	Acquisition of contrast enhanced images is required and acquisition of both contrast enhanced and unenhanced brain images is strongly recommended considering MRI (or CT) of the brain is mandatory at screening to exclude active symptomatic or untreated brain metastases.
9.1 Tabular schedule of evaluations, 9.2.1.2 Screening, 9.2.2.1 Day 1 of Cycle 1, 9.2.2.4 Day 1 of Cycle 2, 9.2.2.6 Day 1 of Cycle ≥ 3, 9.2.2.8 End-of-Treatment (EOT) visit, 9.2.3.1 Active follow-up, 9.6.3.1 Laboratory evaluations	Hormones are moved from the full clinical chemistry panel to a separate hormone panel.	To be in alignment with the eCRF and the protocol standards.

Section # and Name	Description of Change	Brief Rationale
9.1 Tabular schedule of evaluations, 9.6.3.1 Laboratory evaluations	Urinalysis is changed from laboratory urinalysis to urine chemistry test, and for blood in urine it was made more flexible to measure RBC or hemoglobin.	The method for urinalysis is made more flexible as laboratory analysis of all parameters can not be done quantitatively in local laboratories in all countries.
9.1 Tabular schedule of evaluations	A footnote hh was added to clarify that procedures can be performed at unscheduled time points if deemed clinically necessary by the investigator.	To further clarify the opportunity to schedule any assessments or procedures at unscheduled timepoints outside the protocol time frames, to assess the safety of the patient if medically needed.
7.4.3.1.2 Liver toxicity	Wording is added to clarify that monitoring of liver function tests will be done throughout study treatment.	For further clarification.
9.6.1.6 Adverse events of special safety interest, 9.6.3.6 Ophthalmological examination, 9.6.3.3 12-lead ECG	Wording is modified to ensure that examination findings/ results will be documented in the source documents and in the eCRF.	For clarification and consistency.
6.4.1.3 Withdrawal criteria, 7.4.3.1.3 Retinal disorders	The definition of dose limiting toxicity for visual acuity decrease is clarified. Clinical evaluation of patients with low visual acuity at baseline to determine the maintenance in the study is added.	To take into account the visual acuity at baseline and allow investigators more flexibility to perform an individual benefit/risk assessment of patients at higher risk of developing retinal disorders.
2 Synopsis, 5.1 Design overview (Figure 5-1), 5.2.1 Pre-treatment period, 9.1 Tabular schedule of evaluations, 9.2.1.1 FGFR testing, 9.7.1 Biomarker investigations, 13.4.1 PI/ICF for FGFR testing	Relevent content is modified to clarify that PIK3CA and/or RAS activating mutations will be tested only in FGFR-positive patients.	Only an FGFR-positive patient can be enrolled on rogaratinib. If we would perform the PIK3CA/RAS mutation testing in parallel to the FGFR test, we would waste the FFPE slides needed for mutation testing from about 50 % of the screening population that is expected to be FGFR-negative. In times where more and more targeted therapies need any kind of pre-selection biomarker; we would limit the chance of these FGFR-negative patients to have a sufficient amount of FFPE slides available for other

Section # and Name	Description of Change	Brief Rationale
		experimental or standard therapies.
13.4.3 PI/ICF for collection of data on pregnancy and birth	Wording regarding PI/ICF for collection of data on pregnancy and birth is modified.	Wording is modified as PI/ICF for collection of data on pregnancy and birth is only used for fertile male patients and their female partner in case of pregnancy.
9.5 Pharmacokinetics / pharmacodynamics	It is further clarified that the morning dose of rogaratinib must be taken under supervision of site staff on rogaratinib PK days.	For further clarity.
3.2.2 Clinical experience with rogaratinib, 3.4 Rationale of the study, 3.5 Benefit-risk assessment	Detailed information about clinical studies with rogaratinib are deleted or updated based on the new IB.	Details about rogaratinib studies and clinical experience are omitted to avoid the need to amend the protocol each time when IB is updated. All details can be found from the most recent version of the IB for rogaratinib.
9.2.2.1 Day 1 of Cycle 1	Wording is modified to state that the procedures that have been performed at screening within 3 days prior to start of study drug treatment (rather than of randomization) do not need to be repeated on Cycle 1 Day 1 (with exception to blood pressure, heart rate and body temperature).	Amended to avoid inappropriately long time periods between screening safety assessments and start of study drug treatment.
9.2.2.7 Tumor assessments during treatment period, 9.4.1 Radiological tumor assessments	Wording is modified to clarify that in order to achieve a valid response of stable disease, a minimum of at least 6 weeks from start of treatment is mandatory for the 1st “on treatment” tumor assessment, and to allow an imaging scan at an earlier time point in exceptional cases when deemed clinically necessary by the investigator due to safety reasons.	To emphasize that a minimum of at least 6 weeks from start of treatment is required for the 1st “on treatment” tumor assessment in order to achieve a valid response of stable disease and to allow an imaging scan at an earlier time point if deemed clinically necessary due to safety reasons.

Section # and Name	Description of Change	Brief Rationale
Title page, Signature of the sponsor's medically responsible person, 13.1 Investigator(s) and other study personnel	Sponsor's medical expert and sponsor's medically responsible person are changed. The contact details of one of the coordinating investigators are updated.	Reorganization of sponsor's medical team. To provide up-to-date contact details.
16.4 Estimated glomerular filtration rate (eGFR) calculation	A website link is added to a GFR calculator.	To make the calculation of GFR easier for the sites.
2. Synopsis, 5.1 Design overview, 5.2.1 Pre-treatment period, 5.4 Justification of the design, 6. Study population, 6.1 Inclusion criteria, 6.4.1.1 Screening failure, 9.2.1.2 Screening, 9.7.1 Biomarker investigations	The references for RNAscope method and score for analysis of FGFR1 or 3 mRNA expression levels are removed.	To provide flexibility to adapt technology if necessary.
2. Synopsis, 9.7.1 Biomarker investigations	The reference to PCR method for PIK3CA/RAS analysis is removed.	To provide flexibility to adapt technology if necessary.
2. Synopsis, 5.1 Design overview, 10.4 Determination of sample size, 10.5 Planned interim analyses	Wording is added to clarify that approximately 116 confirmed FGFR positive patients are needed for first interim analysis.	Due to inter-evaluator variability in the scoring of FGFR test.
10.1 General considerations	A confirmation test may be performed to identify confirmed FGFR positive patients.	Due to inter-evaluator variability in the scoring of FGFR test.
10.5 Planned interim analyses	P-value criterion for interim analysis is increased from less than 0.1 to less than 0.15.	To re-power the study due to inter-evaluator variability.
10.5 Planned interim analyses	Wording is added to clarify that additional data may be provided to the DMC at all planned analysis points.	To provide a totality of information to the DMC to enable them to make decisions.
9.1 Tabular schedule of evaluations, 9.2.2.1 Day 1 of Cycle 1, 9.2.2.4 Day 1 of Cycle 2, 9.2.2.6 Day 1 of Cycle ≥ 3, 9.6.3.3 12-lead ECG	Wording is modified to clarify, that for patients on the rogaratinib treatment arm, the ECGs can be performed together with required PK blood sampling.	The previous wording referred to both treatment arms but this is not applicable to the chemotherapy arm as no PK samples are taken.

Section # and Name	Description of Change	Brief Rationale
9.2.2.2 Day 8 of Cycle 1, 9.2.2.3 Day 15 of Cycle 1, 9.2.2.5 Day 15 of Cycle 2	Wording is modified to clarify the timing of the assessments.	The previous wording referred to both treatment arms but this is not applicable to the chemotherapy arm as the chemotherapy treatment is not administred that day.
9.2.2.2 Day 8 of Cycle 1, 9.2.2.3 Day 15 of Cycle 1, 9.2.2.4 Day 1 of Cycle 2, 9.2.2.5 Day 15 of Cycle 2, 9.2.2.6 Day 1 of Cycle ≥ 3	Laboratory procedures are allowed to be performed within 3 days prior to the visit	To allow sites more flexibility.
9.1 Tabular schedule of evaluations, 9.2.3.1 Active follow-up	Wording was added to allow combination of EOT and Safety follow up visits	To allow sites more flexibility and prevent unnecessary burden to the patient.
11.1 Data recording	Wording is modified to clarify that data are recorded from pre-screening failures and main screening failures. Requirements of the data to be recorded to eCRF are reduced.	Simplification of the data to be recorded to eCRF.
2. Synopsis, 5.2.1 Pre-treatment period, 6. Study population, 6.1 Inclusion criteria, 9.1 Tabular schedule of evaluations, 9.2.1.1 FGFR testing	Time window for FGFR testing of patients prior to start of screening is removed. Inclusion criteria 2 and 3 were combined.	To relax inclusion criteria by allowing longer time from FGFR testing to start of screening.
7.4.3.1 Dose modifications of rogaratinib	Wording on the cycle duration is modified to state that cycle duration will be 21 days instead of 21 days of treatment with rogaratinib and delays but not interruptions will prolong the duration of a cycle.	To reflect the standard practice in oncology trials.
6.4.1.1 Screening failure, 6.4.1.2 Re-screening	Patients who have signed the pre-screening informed consent and have not completed the FGFR test are regarded as screening failures, but can be tested for FGFR expression.	Flexible timelines for FGFR tests were suggested per feasibility evaluation in order to increase the study recruitment.
10.3.1.3 Subgroup analyses	Details of geographic regions are removed.	The geographic regions will be detailed in SAP.
9.7.1 Biomarker investigations	FGFR DNA alterations were added in the list of examples for exploratory biomarker analysis.	To further clarify exploratory analysis.

In addition, editorial and administrative changes have been made throughout the document for clarity and consistency.

15.2 Amendment no.4

Amendment no.4 is a global amendment forming integrated protocol version 3.0, dated 12 NOV 2019.

Overall rationale for the amendment

The protocol was amended to reflect the decision of stopping the study enrollment at its Phase 2 and to add OS as exploratory efficacy variable to the Phase 2.

Changes to the protocol text

Changes to the protocol text are provided in a separate track-changes version.

High-level description of the changes and the affected sections are listed in the table below.

Section # and Name	Description of Change	Brief Rationale
Changes to the Study Conduct		
2. Synopsis 5.1 Design overview 5.6 Primary completion 10.1 General considerations 10.3.1.1 Primary efficacy variable 10.4 Determination of sample size 10.5 Planned interim analyses	Before achieving the criteria for the first interim analysis, the study recruitment was put on hold after a recommendation of the study DMC. The sponsor decided to stop the recruitment permanently and perform a full analysis and review of all study data. Due to the stop of enrollment, the study will not move forward to its Phase 3 and will remain as Phase 2. The study will remain open until the survival data is considered adequate for analysis by the sponsor. Clarifications are added to explain the above and to separate the plans for Phase 2 and Phase 3 more clearly, while details of originally planned study design and analyses are kept.	In the original design of the study, the Phase 2 part was expected to end at the time of the cut-off for the 1st interim analysis. However, the sponsor decided to perform an *ad hoc* full analysis and review of all study data and stop the study enrollment before the 1st interim analysis cut-off was reached. Therefore the study will not continue to Phase 3. The study will remain open as a Phase 2 study until the survival data is considered adequate for analysis by the sponsor.

Section # and Name	Description of Change	Brief Rationale
5.5 End of study, 7.2 Identity of study treatment 8.2 Post-study therapy	Added that patients can continue receiving rogaratinib treatment in a post-trial access program and LPLV can also be reached based on the last patient changing to a post-trial access program.	To offer additional flexibility.
Changes in planned analyses		
2. Synopsis 4. Study objectives 5.3 Primary variable 9.4 Efficacy 10.3.1.1 Primary efficacy variable 10.3.1.2 Secondary efficacy variables 10.3.1.3 Subgroup analyses 10.5 Planned interim analyses	The primary efficacy variable is updated as ORR for Phase 2 part and OS for Phase 3 part of the study. OS is considered an exploratory efficacy variable for the Phase 2 part and will be analyzed when the survival data is considered adequate for analysis by the sponsor. Minor modifications in text regarding secondary efficacy variables PFS, DCR and DOR are made accordingly.	Efficacy variables are updated as the study remains open as Phase 2 study.
10.3.3.3 Patient-reported outcomes (PRO)	Primary analysis of PROs will be done if there is sufficient data.	Due to stop of enrollment, the data may not be sufficient to conduct the analysis as originally planned.
Other changes		
1. Title page 13.1. Investigator(s) and other study personnel	The contact information of sponsor's medical expert is updated.	To provide up-to-date contact details.
3.2.2 Clinical experience with rogaratinib	Details of clinical experience with rogaratinib are deleted and the IB for rogaratinib is referred to for details.	Updated reference to the latest IB.
3.5 Benefit-risk assessment	Added that the results of the full review and analysis of FORT-1 data (cut-off date of 14 JUN 19) were also consistent with the known safety profile of rogaratinib.	To provide the latest information relevant to benefit-risk assessment.

In addition, editorial and administrative changes have been made throughout the document for clarity and consistency.

16. Appendices

16.1 CYP3A4 inhibitors and inducers

Table 16–1 below provides an overview of strong CYP3A4 inhibitors and inducers.

Table 16–1: Strong CYP3A4 inhibitors and inducers

Strong CYP3A4 inhibitors	Strong CYP3A4 inducers
boceprevir	carbamazepine
clarithromycin	enzalutamide
cobicistat	mitotane
conivaptan	phenytoin
danoprevir and ritonavir	rifampin
diltiazem	St. John's Wort
elvitegravir and ritonavir	
grapefruit juice	
idelalisib	
indinavir and ritonavir	
itraconazole	
ketoconazole	
lopinavir and ritonavir	
nefazodone	
nelfinavir	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	
posaconazole	
ritonavir	
saquinavir and ritonavir	
telaprevir	
tipranavir and ritonavir	
troleandomycin	
voriconazole	

CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4.
Source (34)

16.2 Response Evaluation Criteria in Solid Tumors (RECIST)

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (28). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v.1.1.

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v.1. 1. Rules described in the following for CT are equally valid for MRI.

Measurable disease

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

Chest X-ray will not be accepted in the study, Spiral-CT should be conducted.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in *short axis* when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Schwartz et al. in this special issue (35)). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Lytic bone lesions, with an identifiable soft-tissue component, evaluated by CT or MRI can be considered as measurable lesions if the soft-tissue component otherwise meets the definition of measurability
- Blastic bone lesions are non-measurable

Cystic lesions:

- Lesions that meet radiographic criteria for simple cysts should not be considered malignant lesions (neither measurable nor non-measurable)
- "Cystic lesions" thought to be cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. However, if non-cystic lesions are present in the same patients, these should be preferably selected for assessment

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area patiented to other loco-regional therapy, are usually not considered measurable. Previously treated lesions can only be selected as target lesions when they have progressed until baseline.

Target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved

organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes (with short axis ≥10 mm and < 15 mm) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Best Response: The best overall response is the best response recorded from the start of the study treatment until the end of treatment. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. While some non- target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all target lesions. Disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Non-CR/Non-PD (to be used for patients with non-target lesions only**)**: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, unequivocal progression (see comments below) of existing lesions represents progressive disease. (Note: the appearance of one or more new lesions is also considered progression).

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are

included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm.

To achieve unequivocal progression in patients with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

In the absence of measurable disease, the same general concepts apply here as noted above.

Table 16–2: Target and non-target lesion response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented at least once ≥6 weeks from baseline imaging
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease.
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Response duration

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

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

Stable disease duration

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

Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective.

Chest X-ray will not be accepted in the study, Spiral-CT should be conducted.

Computed tomography (CT)/ magnetic resonance imaging (MRI) - CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound – Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about the radiation exposure at CT, MRI may be used instead of CT in selected instances.

Tumor markers: tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

When effusions are known to be a potential adverse effect of treatment (e.g. angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

16.3 New York Heart Association (NYHA) classification

Table 16–3: New York Heart Association (NYHA) categories

Class	NYHA Functional Capacity
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

16.4 Estimated glomerular filtration rate (eGFR) calculation

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated Glomerular filtration rate (GFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula.

This equation of 4 variables (serum creatinine level [SCR], age, sex, and race) is recommended by the National Kidney Foundation for use in individuals 18 years or older.

The GFR calculator can be found at the following website (36):
http://www.kidney.org/professionals/kdoqi/gfr_calculator.

NOTE: This equation should be used only with those creatinine methods that have not been recalibrated to be traceable to isotope dilution mass spectroscopy (IDMS).

The above result should be multiplied by 1.212 for African-Americans and by 1.227 for Chinese (mainland China, Taiwan and Hong Kong). Due to the lack of confirmed information on Korean patients the results for these patients will not be multiplied by any factor (37).