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Official Title:	An international, multicenter, Phase 1b/2 study of rogaratinib (BAY1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma
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Cover page of the integrated protocol

An international, multicenter, Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma

This protocol version is an integration of the following documents/sections of 19131 Part A:

- **Amendment no. 5** (global amendment described in Section 15.5) forming integrated protocol Part A Version 6.0, dated 23 MAY 2023
- **Amendment no. 4** (global amendment described in Section 15.4) forming integrated protocol Part A Version 5.0, dated 09 NOV 2022
- **Amendment no. 3** (global amendment described in Section 15.3) forming integrated protocol Part A Version 4.0, dated 4 OCT 2021
- **Amendment no. 2** (global amendment described in Section 15.2) forming integrated protocol Part A Version 3.0, dated 10 FEB 2021
- **Amendment no. 1** (global amendment described in Section 15.1) forming integrated protocol Part A Version 2.0, dated 04 DEC 2018
- **Original protocol Part A,** Version 1.0, dated 04 DEC 2017

This document integrates the original protocol and all global amendments of 19131 Part A.

1. Title page

An international, multicenter, Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma

Short title: Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab in urothelial carcinoma

Note: Study 19131 originally comprised two separate parts: Phase 1b (Part A) and Phase 2 (Part B). The study parts differ in design, objectives, and treatment.

This part of the protocol is to be used for conducting Part A of the study only. Part B of the study will no longer be conducted.

Acronym:	**FORT-2**		
Test drug:	BAY 1163877 / rogaratinib / pan FGFR inhibitor		
Clinical study phase:	Part A: Phase 1b Part B: Phase 2	Date:	23 MAY 2023
Registration:	EudraCT: 2017-001483-38	Version no.:	6.0
Sponsor's study no.:	19131		
Sponsor:	Non-US: Bayer AG, D-51368 Leverkusen, Germany US: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, US		
Sponsor's medical expert:	PPD PPD PPD Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, US Telephone no.: PPD		

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

This is an electronically generated document that does not bear any sponsor signatures. The signature of the Sponsor's medically responsible person is filed in the TMF and available on request.

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

Note: Study 19131 originally comprised two separate parts: Phase 1b (Part A) and Phase 2 (Part B). The study parts differ in design, objectives, and treatment.

This part of the protocol is to be used for conducting Part A of the study only. Part B of the study will no longer be conducted.

Title	An international, multicenter, Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma
Short title	Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab in urothelial carcinoma
Acronym	FORT-2
Clinical study phase	Part A: Phase 1b
Study objectives	Primary objectives of Part A: • To determine the safety and tolerability of rogaratinib in combination with atezolizumab in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma • To determine the recommended Phase 2 dose (RP2D) of rogaratinib in combination with atezolizumab in this patient population. Secondary objective of Part A: • To assess the efficacy of the combination of rogaratinib and atezolizumab in this patient population. • To characterize the pharmacokinetics (PK) of rogaratinib in combination with atezolizumab in this patient population Exploratory objectives of Part A: • To assess new potential predictive or prognostic biomarkers and their association with tumor-related biomarkers, disease response, drug-resistance and patient outcome. • To evaluate further biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease. • To evaluate the combination of rogaratinib and atezolizumab with regard to patient-reported outcomes (PRO).
Test drug	Rogaratinib / BAY 1163877
Name of active ingredient	Rogaratinib
Dose	The RP2D will be determined in Part A of the study. Starting dose level of rogaratinib is 800 mg twice daily (b.i.d.), in continuous 21-day cycles. If suggested by safety findings, lower doses may be explored.

Route of administration	Oral
Duration of treatment	Patients will continue dosing until any of the following occurs: • Radiological disease progression according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) o At the investigator's discretion, study treatment may continue beyond radiological progression as defined by RECIST v1.1 (e.g. in case of suspected pseudoprogression) 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 • Consent withdrawal • Withdrawal from the study treatment at the discretion of the investigator or designated associate(s)
Combination drug	Atezolizumab
Name of active ingredient	Atezolizumab
Dose	1200 mg every 21 days
Route of administration	Intravenous (i.v.) infusion
Duration of treatment	See test drug above
Indication	FGFR-positive locally advanced or metastatic urothelial carcinoma
Diagnosis and main criteria for inclusion /exclusion	Patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible and have had no prior systemic treatment for locally advanced or metastatic disease. **Main inclusion criteria:** • Male or female patients ≥ 18 years of age (at least age of legal maturity) • Documented urothelial carcinoma (transitional cell carcinoma) including urinary bladder, renal pelvis, ureters, urethra, meeting all of the following criteria: o Histologically confirmed. o Patients with mixed histology are required to have a dominant transitional cell pattern. o Locally advanced (T4, any N; or any T, N2-3) or metastatic disease (any T, any N and M1). Note: 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). • High FGFR1 or 3 mRNA expression levels (RNAscope score of 3+ or 4+; measurement is part of this protocol) in archival or fresh tumor biopsy specimen

- At least 1 measurable lesion according to RECIST v1.1 in contrast enhanced (unless contraindicated) CT or MRI
- No prior systemic treatment for locally advanced or metastatic urothelial carcinoma. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting. Prior local intra-vesical chemotherapy or prior local immunotherapy (e.g. with Bacillus Calmette-Guérin [BCG]) is allowed if completed at least 4 weeks before first study drug administration.
- Ineligibility for cisplatin-based chemotherapy
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
- Adequate hematologic and end organ function
- Recovery to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v.4.03) Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug / procedure-related toxicity (patients with persistent alopecia, anemia [hemoglobin ≥ 9 g/dl], any grade peripheral neuropathy, impaired renal function [GFR > 30 mL/min/1.73 m^2], hearing loss and / or hypothyroidism that is adequately controlled by hormone replacement can be included)

Main exclusion criteria:

- Inability to swallow oral medications
- Any malabsorption condition
- Current diagnosis of any retinal disorders including retinal detachment, retinal pigment epithelial detachment (RPED), central serous retinopathy or retinal vein occlusion
- Previous or concurrent cancer except
  - cervical carcinoma *in situ*
  - treated basal-cell carcinoma or squamous cell skin cancer
  - localized prostate cancer treated with curative intent and known absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (T1/T2a, Gleason score ≤ 6 and PSA ≤ 10 ng/mL undergoing active surveillance and treatment-naïve)
  - any other cancer curatively treated > 3 years before the first study drug administration
- Ongoing or previous treatment with anti-FGFR directed therapies (e.g. receptor tyrosine kinase inhibitors including rogaratinib or FGFR-specific antibodies)
- Previous assignment to treatment during this study

	• Severe (CTCAE v.4.03 Grade ≥ 3) infections within 4 weeks before the first study drug administration, including but not limited to hospitalization for complication of infection, bacteremia, or severe pneumonia • History of autoimmune disease except: a) autoimmune-related hypothyroidism clinically stable on thyroid replacement hormone; b) controlled Type-I diabetes mellitus on a stable dose of insulin regimen • History or current condition of uncontrolled cardiovascular disease • Systolic/diastolic blood pressure ≤ 100/60 mmHg *and* concurrent heart rate ≥ 100/min • Renal failure requiring peritoneal dialysis or hemodialysis • Current evidence of endocrine alteration of calcium phosphate homeostasis (e.g. parathyroid disorder, history of parathyroidectomy, tumor lysis, tumoral calcinosis, paraneoplastic hypercalcemia) • Concomitant therapies that are known to increase serum calcium or phosphate levels and that cannot be discontinued or switched to a different medication before start of study treatment • Evidence or history of bleeding diathesis or coagulopathy • Any hemorrhage / bleeding event CTCAE v.4.03 ≥ Grade 3 within 4 weeks before the first study drug administration For the complete list of inclusion and exclusion criteria, please refer to Sections 6.1 and 6.2 of this protocol.
Study design	**<u>Part A study design</u>** Part A of the study is an open-label, single-arm, international, multicenter, Phase 1b study of rogaratinib in combination with atezolizumab. <u>*Dose selection:*</u> The dose selection part of the study 19131 will assess the safety and tolerability of the combination. The maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) for the combination will be determined using stepwise dose selection design based on a modified toxicity probability interval (mTPI) method (See Section 10.3.4.1). After dose selection, further patients (up to 50 in total for the whole Part A) will be enrolled to confirm the RP2D. The study is composed of the following study periods: • **Pre-treatment period**, including o **FGFR testing**

The mRNA expression of FGFR1 or 3 will be investigated using archival or fresh tumor biopsy specimen taken before the screening procedures are conducted. Only patients with locally advanced or metastatic urothelial carcinoma whose tumors are FGFR positive (RNAscope score of 3+ or 4+) will be included in the study.

- **Screening**

- **Treatment period**

Patients who meet all study inclusion and exclusion criteria will be eligible to start study treatment.

Patients will receive an oral, single dose of rogaratinib in the morning of Cycle 1 on Day 1, followed by single dose serial PK blood sampling for 8 hours and a second single dose of rogaratinib in the evening. Rogaratinib will be administered continuously twice daily on all 21 days in each cycle.

A fixed dose of 1200 mg atezolizumab will be administered through intravenous (i.v.) infusion on Day 1 of each 21-day cycle.

Patients will continue dosing of both study drugs until any of the following occurs:

- Radiological disease progression according to RECIST v1.1
  - At the investigator's discretion, study treatment may continue beyond radiological progression as defined by RECIST v1.1 (e.g. in case of suspected pseudoprogression) 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
- Consent withdrawal
- Withdrawal from the study treatment at the discretion of the investigator or designed associate(s).

- **Follow-up period**

After primary completion, follow-up information will not be collected after the safety assessment visit.

- **Active follow-up**

After permanent treatment discontinuation, a safety assessment visit must be scheduled for all patients at least 30 (+7) days after the last dose of study treatment. 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. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

Up to primary completion, for patients who permanently discontinue study treatment without radiological disease progression, drug-related AEs will continue to be collected and follow-up tumor evaluations will be performed (by CT or MRI with

	contrast unless contraindicated) until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal from study is met. o **Long-term follow-up** After completion of the active follow-up, patients will be followed up for survival status and start of subsequent systemic anti-cancer therapy approximately every 3 months (±14 days) until the end of the study (i.e. until last patient's last visit [LPLV]). In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated. Long-term follow-up will not be performed after primary completion.
Methodology	Part A (Phase 1b) of the study will evaluate safety, tolerability, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D), pharmacokinetics and efficacy of rogaratinib in combination with atezolizumab in FGFR-positive locally advanced or metastatic urothelial carcinoma. Doses for each study drug and the schedule of treatment are specified above in the study design. Primary and secondary variables will be assessed as specified below. **Safety** Safety and tolerability evaluations will include monitoring of all serious and non-serious adverse events, physical examinations, vital signs, ECOG performance status, electrocardiogram (ECG) readings, radiologic imaging, laboratory tests and concomitant medications. In addition, ophthalmological examinations will be performed regularly, according to the schedule of evaluations. Patient data will be analyzed for evidence of cumulative toxicity with repeated cycles of treatment. Each patient will be regularly assessed for potential adverse events, dose-limiting toxicities (DLTs) and disease related signs and symptoms. Adverse events will be reported using Medical Dictionary for Regulatory Activities (MedDRA) terms (version 20.0 or later) and their severity will be graded according to the NCI CTCAE version 4.03. **Determination of MTD** Stepwise dose selection design based on a modified toxicity probability interval (mTPI) method will be used to determine the MTD for the combination treatment. No decision is made before data of at least 4 patients are available on the first dose level and are evaluable for DLTs assessment. The sponsor in consultation with the investigators will decide how many additional patients need to be evaluable for DLTs on the same dose level before the next decision. The decision on the number of additional patients and on the next dose level will be based on the recommendations from the mTPI, clinical assessment, all available PK and safety data. The dose selection part will be finished after 20 patients are valid for the MTD assessment. The RP2D will be defined once sufficient data is

	available. The final decision about the RP2D will be made by the sponsor in consultation with the investigators. **Pharmacokinetics** Blood samples will be collected to measure rogaratinib pharmacokinetics in combination with atezolizumab. Pharmacokinetics of rogaratinib will be evaluated on Cycle 1 Day 1 after single dosing up to 8 hours post dose. In addition, blood (plasma) samples will be collected for exposure-response assessment on Day 1 of Cycles 2 to 5. For monitoring purposes of atezolizumab, blood (plasma) samples will be collected on Cycle 1 Day 1 at pre-dose, 1 (end of infusion [EOI]), 4 and 8 hours and on Cycle 1 Day 15 (approximately 336 hours post-dose). **Efficacy** Tumor assessments will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) (with contrast unless contraindicated), and patient survival will be followed up to determine the efficacy variables of this study: objective response rate (ORR), disease control rate (DCR), duration of response (DOR), best overall response (CR, PR, SD, Non CR/Non PD, PD), progression-free survival (PFS) and overall survival (OS). Tumor response will be evaluated using the RECIST v1.1. In addition, modified RECIST v1.1 for immune-based therapeutics (iRECIST) will be documented and used as supportive evidence for the detection of pseudoprogression and the determination of progressive disease for treatment decision. Tumor scans will be performed at screening (baseline), and then every 9 weeks (±7 days) starting from Cycle 1 Day 1 until radiological disease progression or end of the study. After primary completion, scans will be performed every 14 weeks (±14 days). A minimum of at least 9 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment. If the investigator considers radiographic changes secondary to drug-induced inflammation and not to tumor progression, the investigator may postpone a diagnosis of progressive disease until the next radiographic evaluation in the study. Radiological tumor assessments will be performed locally by investigators. To facilitate an independent evaluation of outcome in this study, tumor assessment imaging data will be collected, image quality controlled and stored for a potential central review of tumor evaluation by independent readers. The decision to perform the central review will be based on the outcome of the local efficacy assessments. Central review will not be used for treatment decisions. Up to primary completion, patients who discontinue the study treatment for any reason other than radiological PD will be followed for progression during active follow-up (which includes the safety follow-up period) until confirmed PD for this patient is observed. **Patient reported outcome (PRO)** Patient reported outcomes will be assessed using EORTC QLQ-C30 (at screening, on Day 1 of every cycle, at the EOT, and at the safety assessment visit of the active follow-up). After primary completion, PROs will not be required.
Type of control	Not applicable

Data Monitoring Committee	No
Number of patients	In Part A, approximately a total of 26-30 patients will be treated. Approximately 20 additional patients may be enrolled up to a total of 50 patients for the whole Part A.
Primary variables	• The incidence of DLTs will be used to determine the MTD and/or RP2D. • The incidence of treatment-emergent adverse events (TEAEs), treatment-emergent drug-related TEAEs, and treatment-emergent serious adverse events.
Time point/frame of measurement for primary variables	The incidence of DLTs will be determined in the first cycle. The incidence of TEAEs will be assessed for individual patients regularly in all cycles.
Plan for statistical analysis	For Part A (Phase 1b) of the study, all data will be listed and study summary tables will be provided where appropriate. Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. Where appropriate, summary statistics will be provided for the original data as well as for the changes versus baseline. Graphical illustrations will be provided where appropriate. Frequency tables will be provided for qualitative data. Time-to-event endpoints will be analyzed using Kaplan–Meier methodology. The dose selection will be performed using the modified toxicity probability interval method (mTPI). Due to the exploratory character of this study, no confirmatory analysis will be performed. All calculated p-values and confidence intervals are to be interpreted in the exploratory sense. The statistical evaluation will be performed by using the software package SAS (SAS Institute Inc., Cary, NC, USA) with the release to be specified in the statistical analysis plan. More detailed information of the planned statistical analyses can be found 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
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AZD4547	Fibroblast growth factor receptor (FGFR) tyrosine kinase family inhibitor
BAL	Bronchoscopic alveolar lavage
BC	Bladder cancer
BCG	Bacillus Calmette-Guérin
BCRP	Breast cancer resistance protein
b.i.d.	Twice daily, *bis in die*
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
°C	Degree(s) Celsius
C	Cycle
Ca x PO_4	Calcium-phosphorus product
CBC	Complete blood count
CD137	Cluster of differentiation 137 (inducible T-cell costimulatory receptor, member of the tumor necrosis factor receptor [TNFR] superfamily)
CD8A	Cluster of differentiation 8A (T-cell surface protein)
CHF	Congestive heart failure
CL/F	Apparent oral clearance
cm	Centimeter
C_{max}	Maximal plasma concentration
cMet	Tyrosine-protein kinase Met
cMyc	v-Myc myelocytomatosis viral oncogene homolog
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
CYP	Cytochrome P450

CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
D	Day
dB	Decibel(s)
DCR	Disease control rate
ddMVAC	Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin therapy
dL	Deciliter
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
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
EMA	European Medicines Agency
EOI	End of infusion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
ERK	Extracellular-signal-regulated kinase
EU	European Union
EudraCT	European Clinical Trials Database
°F	Degree(s) Fahrenheit
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FGF(R)	Fibroblast growth factor (receptor)
FiH	First-in-human
FSH	Follicle stimulating hormone
FU	Follow-up
g	Gram
GC	Gemcitabine plus cisplatin
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCG	β-human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HR	Heart rate

HRAS	Harvey rat sarcoma viral oncogene homolog
HRQoL	Health-related Quality of Life
IB	Investigator's brochure
IC	Tumor-infiltrating immune cell status
ICF	Informed consent form
ICH	International Council for Harmonization
iCPD	Confirmed progressive disease according to iRECIST
iCR	Confirmed response according to iRECIST
IDMS	Isotope dilution mass spectroscopy
i.e.	That is, *id est*
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
INN	International Nonproprietary Names
INR	International normalized ratio
iPR	Partial response according to iRECIST
IR	immediate release
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors modified for Immune-based therapeutics
iSD	Stable disease according to iRECIST
ISH	*In situ* hybridization
IUD	Intrauterine device
iUPD	Unconfirmed progressive disease according to iRECIST
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous(ly)
IxRS	Interactive voice/web response system
kg	Kilogram
L	Liter
LDH	Lactic dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantification
LLT	MedDRA lowest level term
LPFV	Last patient's first visit
LPLV	Last patient's last visit
LSH	Life Science Data Hub
MD	Medical doctor
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
MIBC	Muscle-invasive bladder cancer

microRNA	Micro ribonucleic acid
min	Minute(s)
mIU	Milli international unit
MIUC	Muscle-invasive urothelial carcinoma
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
mmol	Millimole
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MVAC	Methotrexate, vinblastine, doxorubicin, cisplatin
n	Number of patients
NC	North Carolina
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NE	Not evaluable
ng	Nanogram
NJ	New Jersey
NK	Natural killer (cells)
NLNT	New lesion – non-target
NLT	New lesion – target
NMIBC	Non-muscle-invasive bladder cancer
No.	Number
NSCLC	Non-small-cell lung carcinoma
NY	New York
NYHA	New York Heart Association
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
P	Probability value
p53	Tumor suppressor
PD	Progressive disease
PD-1	Programmed death protein 1
PD-L1	Programmed death-ligand 1
pERK	Phosphorylated extracellular-signal-regulated kinase
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
pH	Hydrogen ion concentration
PID	Patient identification number
PI/ICF	Patient information/informed consent form

PIK3C	Phosphoinositide 3-kinase, catalytic domain
PIK3CA	Phosphoinositide 3-kinase, catalytic subunit alpha isoform
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic(s) analysis set
PleurX	Drainage system
PP	Polypropylene
PR	Partial response
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	Quality of Life Questionnaire Core 30
QoL	Quality of Life
RAS	Rat sarcoma
RAVE	Data collection tool
RB	Retinoblastoma
RBC	Red blood cell (count)
RECIST	Response evaluation criteria in solid tumors
R_{end}	Last time point for apparent terminal rate constant, calculated from the last slope of a log-linear regression of the unweighted data considering the last concentration-time points >LLOQ (lower limit of quantification)
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RPED	Retinal pigment epithelial detachment
RR	Respiratory rate
R_{start}	First time point for apparent terminal rate constant, calculated from the last slope of a log-linear regression of the unweighted data considering the last concentration-time points >LLOQ (lower limit of quantification)
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
sCD25	Soluble cluster of differentiation 25 (soluble IL-2 receptor)
SCR	Serum creatinine level
SD	Stable disease
SIA	Systemic immune activation
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SOD	Sum of diameters
sqNSCLC	Squamous NSCLC
SUSAR	Suspected, unexpected, serious adverse reaction
t	Time

T3	Triiodothyronine
T4	Thyroxine
TC-99m	Technetium-99m
TCGA	The Cancer Genome Atlas
TEADR	Treatment-emergent drug-related adverse events
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TL	Target lesion
t_{last}	Time of last plasma concentration above LLOQ
TM	Trademark
t_{max}	Time to reach maximum drug concentration in plasma after single (first) dose
TNF	Tumor necrosis factor
TNM	Classification of Malignant Tumors (T = tumor, N = lymph node, M = metastasis)
TP53	Tumor protein p53
TSH	Thyroid-stimulating hormone
TURBT	Transurethral resection of bladder tumors
UBC	Urothelial bladder cancer
UC	Urothelial carcinoma
ULN	Upper limit of normal
UPM	Unit probability mass
US / USA	United States / United States of America
VAD	Ventricular assist device
V_Z/F	Apparent volume of distribution after extravascular administration
WBC	White blood cell (count)
WinNonlin	Pharmacokinetic software package
WOCBP	Woman of childbearing potential

Definitions of terms

Term	Definition
Pseudoprogression	An increase in the size of lesions, or the visualization of new lesions, followed by a response, which might be durable. Pseudoprogression phenomena might be observed during treatment with immunotherapeutic agents.
Study drug	The term “study drug” refers to any of protocol-stipulated drugs, i.e. rogaratinib or atezolizumab.
Study treatment	The term “study treatment” refers to all protocol-stipulated treatments, i.e. rogaratinib and atezolizumab.
Test drug	In this protocol the term “test drug” refers to rogaratinib only.

Combination drug	In this protocol the term “combination drug” refers to atezolizumab only.

3. Introduction

3.1 Study set up: Part A

Study 19131 is designed to evaluate safety, efficacy, RP2D and PK of rogaratinib in combination with atezolizumab in patients with untreated FGFR-positive urothelial carcinoma.

This part of the protocol is to be used for conducting Part A of the study only.

3.2 Background

Urothelial carcinoma

Bladder cancer (BC) is the most frequent among urothelial carcinomas (UC) that also include the less common UC arising from renal pelvis, ureters and urethra. It is the ninth most common cancer in the world, the sixth most common cancer in the United States and the second most common genitourinary tumor. It is a major cause of morbidity and mortality worldwide, causing approximately 429,000 new cases resulting in 165,000 deaths annually (1). An estimated 79,030 new cases of urinary bladder cancer (60,490 men and 18,540 women) will be diagnosed in the United States in 2017 with approximately 16,870 deaths (12,240 men and 4630 women) occurring during this same period (2). Approximately three times more men than women are diagnosed with bladder cancer; the majority of patients are > 65 years old. Approximately 4% of the patients have metastatic disease at the time of diagnosis (3). Additionally, about half of all patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal status. Local recurrences account for about 10% to 30% of relapse, whereas distant metastases are more common.

Over the past two decades, there has been no significant improvement in survival of BC with 5-year relative survival rates for locally advanced and metastatic disease of 33% and 5%, respectively (4). The majority (90%) of bladder cancers are composed of urothelial carcinoma (UBC [urothelial bladder cancer]). Seventy percent of the cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) with a favorable prognosis following transurethral resection and intravesical chemotherapy or immunotherapy with Bacillus Calmette-Guérin (BCG) (5). Nevertheless, approximately 40% of these patients will progress to muscle-invasive disease at five years depending on tumor pathological features (6). When considering the prognosis of muscle-invasive bladder cancer, even after optimal treatment with neoadjuvant chemotherapy and surgery, only 60% of these patients will be alive 5 years later due to distant recurrence (7). This aggressive biological behavior coupled with limited therapeutic options results in a median survival of 15 months for patients with metastatic disease (8). Therefore, there is an urgent need to improve outcomes with innovation or application of new treatments.

Traditionally, UBC is classified in 2 distinct types according to the grade. Low-grade tumors usually tend to recur locally with low risk of progression to invasive tumors. These tumors are characterized by oncogenic mutations in the fibroblast growth factor receptor 3 (FGFR, 70%), HRAS (30-40%) and PIK3C (10%) genes (9). In contrast, high grade invasive lesions harbor frequent loss of function alterations in TP53 and RB genes. In 2014, The Cancer Genome Atlas (TCGA) project provided advances in the landscape of genomic alterations within MIUC (10).

Fibroblast growth factors (FGF) and their corresponding receptor family (FGFR) drive crucial oncogenic signaling pathways including cell proliferation, survival and migration (11, 12). FGFRs are commonly altered in various human cancers including FGFR1 amplification in non-small cell lung cancer (e.g. sqNSCLC) (11, 12) and squamous cell carcinoma of the head and neck (SCCHN) (11, 12), or activating mutations of FGFR3 in bladder cancers (BC) (11, 12). These changes contribute to tumor cell growth, sustained angiogenesis, invasion and metastasis and resistance against other therapies.

Dysregulation of FGFRs has been identified in bladder cancers of all grades and stages. In NMIBC, activating point mutations of FGFR3 are common (70%). In MIBC, point mutations are less common (12-16%) but many tumors (> 40%) show upregulated expression of non-point mutated FGFR3 protein. Preclinical studies have confirmed FGFR3 as a relevant therapeutic target in bladder cancer; most cell lines show a cytostatic rather than cytotoxic response. Early results indicate responses to selective FGFR inhibitors in some bladder cancer patients. Rogaratinib is an oral pan-FGFR inhibitor that showed potent antitumor activity in preclinical models of FGFR mRNA overexpression tumors, including urothelial carcinoma, and promising clinical efficacy.

Treatment options

Cisplatin-based chemotherapy has been the standard of care in patients with newly diagnosed metastatic disease with an OS of approximately 15 months (8, 13). However, patients that are not eligible to be treated with cisplatin have poorer outcome with an OS of approximately 9 months with alternative treatment regimens based on carboplatin (13).

In the first-line setting, the selection of the chemotherapy regimen partially depends on the presence or absence of medical comorbidities, such as cardiac disease and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination chemotherapy alone has been reported only in good-risk patients, defined as those with good performance status, no visceral (i.e. liver, lung) or bone disease, and normal alkaline phosphatase or lactic dehydrogenase levels. Poor-risk patients, defined as those with poor performance status or visceral disease, have consistently shown very poor tolerance to multi-agent combination programs and few complete remissions, which are prerequisite for cure.

Gemcitabine plus cisplatin (GC) and dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (ddMVAC) are recommended first-line regimens for metastatic disease. A randomized Phase 3 trial comparing GC to MVAC confirmed, in a 5-year update analysis, that GC was not inferior to MVAC in term of overall survival (OS 13% vs 15.3%; PFS 9.8%

vs 11.3% respectively) (14). Another large randomized Phase 3 trial compared ddMVAC to standard MVAC (15, 16). At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. MVAC is inferior to ddMVAC in terms of toxicity and efficacy, and is inferior to GC in terms of toxicity; therefore, standard MVAC is no longer used.

The performance status of the patients is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. Alternative first-line regimens include carboplatin or taxane-based regimens or single agent chemotherapy. In patients with a glomerular filtration rate (GFR) less than 60mL/min, carboplatin may be substituted for cisplatin. A Phase 2/3 study assessed 2 carboplatin-containing regimens in medically unfit patients (PS 2). The objective response rate (ORR) was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However the response rates dropped to 26% and 20% respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR < 60mL/min) (13).

Carboplatin has been replaced in patients ineligible for cisplatin treatment in the first-line setting after the recent introduction of checkpoint inhibitors. Only limited data are available as to the value of carboplatin-containing chemotherapy in patients that failed prior treatment with checkpoint inhibitors. Retrospective analyses on small cohorts indicate that chemotherapy-naïve patients who receive chemotherapy after checkpoint inhibitor treatment maintain a high response rate to platinum (17). This treatment is however associated with considerable toxicity leaving a high unmet medical need. Approximately 20% of patients discontinue treatment due to adverse events. Myelotoxicity is very frequent with leucopenia Grade 3 or higher in more than a third of patients, sometimes coupled with febrile neutropenia.

Several new agents for the treatment of metastatic urothelial carcinoma are being investigated in clinical trials.

PD-1 and PD-L1 checkpoint inhibitors have garnered attention based on clinical trial data. The PD-L1 inhibitor atezolizumab (Tecentriq) and the PD-1 inhibitor nivolumab (Opdivo) received accelerated approval for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, regardless of PD-L1 expression level (18, 19). Recently, also the PD-1 inhibitor pembrolizumab (Keytruda) reported positive OS data versus standard of care chemotherapy in this indication (20). In addition, atezolizumab and pembrolizumab also received accelerated approval as a first-line treatment for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-based chemotherapy. More recently, based on tumor response rate and duration of response, FDA also granted accelerated approval to two newer PD-L1 inhibitors, avelumab (Bavencio) and durvalumab (Imfinzi) for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (21, 22).

Despite promising clinical data of checkpoint inhibitors, only a fraction of patients (approximately 25%) are responding to this treatment type. There is limited information about the optimal therapy for patients that progress on checkpoint inhibitor treatment.

Given the current treatment options, there is still a high unmet medical need for the treatment of UC.

It was previously published that FGFR3 expression is associated with a non-T-cell-inflamed tumor microenvironment (23), leading to a poorer response to inhibition of the PD-L1 axis. Our clinical data confirm that FGFR3 expression is inversely correlated with PD-L1 expression in urothelial bladder cancer (unpublished data). This represents the framework for testing the combination of rogaratinib and atezolizumab. The aim is to explore if rogaratinib, inhibiting FGFR, is able to induce a T-cell-inflamed phenotype, restoring sensitivity to PD-L1 inhibitors and improving their efficacy in urothelial carcinoma.

3.3 Rogaratinib

Rogaratinib (BAY 1163877) is a selective 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 such as non-small-cell lung cancer, small-cell lung cancer, urothelial carcinoma, head and neck cancer as well as breast cancer. *In-vivo* efficacy is correlated with effective inhibition of downstream signaling analyzed by pERK inhibition. Moreover, rogaratinib exhibits strong *in-vivo* anti-tumor efficacy in monotherapy in tumor xenograft models addicted to various FGFR alterations 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 bladder cancer 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) (24, 25). 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%) (26). 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 (27, 28). However, clinical benefits from FGFR inhibitor treatment have also been reported in a urothelial carcinoma patient with high FGFR1 mRNA expression levels (29) and in a patient with high FGFR2 protein expression (30), although FGFR1 and FGFR2-positive UC tumors are more rare compared to FGFR3-positive

tumors. In the FiH Study 16443 (see below), out of > 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, on the basis that FGFR2 expression is considerably low in urothelial carcinoma patients, patient selection for Study 19131 will be based on FGFR1 and FGFR3 expression only. For the test device, FGFR1 and FGFR3 will be tested in parallel in one kit.

Clinical experience with rogaratinib

Details of ongoing and completed studies 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

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 phosphate level ≥ 7 mg/dL beyond the critical level defined as calcium phosphate product higher than 70 mg^2/dL^2 (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.

Further details on other undesirable effects of rogaratinib as well as on clinical efficacy can be found in the latest available version of the IB of rogaratinib, which contains comprehensive information on the test drug.

3.4 Atezolizumab

Atezolizumab (Tecentriq) is a programmed death-ligand 1 (PD-L1) blocking antibody. PD-L1 is expressed by many cancer cells; PD-L1 and PD-L2 are ligands to programmed cell death protein 1 (PD-1) that is a cell surface receptor belonging to the immunoglobulin superfamily expressed on T cells, B cells, monocytes and natural killer (NK) cells when these cells are activated. Thus, the expression of PD-1 in a tumor is a marker of T-cell activation. Binding of PD-L1 to PD-1 receptor on T-cells results in suppression of T-cell migration, proliferation and function, as well as induction of suppressive regulatory T-cells. This PD-L1-PD-1 axis is used to regulate tolerance of "self" and thereby protect healthy tissues from autoimmune destruction. The cancer cells effectively utilize this regulation of peripheral tolerance to prevent T-cell mediated destruction of tumor cells by promoting the PD-L1-PD-1 axis. This understanding has led to the development of immune checkpoint inhibitors such as atezolizumab, nivolumab and pembrolizumab that inhibit the PD-L1-PD-1 axis and are approved for use in solid cancers.

Previous clinical studies with atezolizumab in urothelial carcinoma

The pivotal single-arm, multicenter, Phase 2 trial of atezolizumab (IMvigor210) in patients with locally advanced and metastatic urothelial cancer enrolled two cohorts of patients. In cohort 2, 310 patients previously treated with platinum-based chemotherapy received atezolizumab 1,200 mg intravenously every 3 weeks. The results of this large single arm Phase 2 study showed that atezolizumab induced durable anti-tumor responses in patients with advanced urothelial carcinoma whose tumors have progressed during or after treatment with platinum-based chemotherapy. Based on these results atezolizumab received accelerated FDA approval in May 2016 for the treatment of metastatic urothelial carcinoma in second-line after progression on platinum-based chemotherapy (19, 31).

Cohort 1 of IMvigor210 comprised patients who had not received previous treatment in the metastatic setting and were judged to be ineligible for cisplatin treatment. 123 patients were enrolled, of whom 119 received one or more doses of atezolizumab. At 17.2 months' median follow-up, the objective response rate was 23% and the complete response rate was 9%. Median response duration was not reached. Response occurred across all PD-L1 and poor prognostic factor subgroup. Median PFS was 2.7 months and median overall survival was 15.9 months. Tumor mutation load was associated with response. Treatment-related adverse events that occur in 10% or more of patients were fatigue (30%), diarrhea (12%), and pruritus (11%). One treatment-related death (sepsis) occurred. Nine (8%) patients had an adverse event leading to treatment discontinuation. Immune-mediated events occurred in 12% patients (18).

Details of ongoing and completed studies with atezolizumab can be found in the latest available version of the IB for atezolizumab. The IB in its most current version is available in the study file.

3.5 Rationale of the study

The Study 19131 is planned to evaluate the safety, tolerability, PK and efficacy of oral twice daily rogaratinib in combination with atezolizumab in patients with FGFR-positive locally

advanced or metastatic urothelial carcinoma who are cisplatin-ineligible and have had no prior systemic treatment for locally advanced or metastatic disease.

Urothelial cancer is a highly immunogenic tumor, in large part as a result of the relatively high level of mutations, which represent at least one of the mechanisms for the generation of tumor neo-antigens for the host immune system to recognize. PD-L1 overexpression in the tumor microenvironment and its binding to programmed death receptor-1 (PD-1) on tumor antigen-specific T cells is a mechanism for immune escape in urothelial cancer (32).

Dysregulation of FGFRs has been identified in bladder cancer as compared with normal bladder. Increased expression was associated with mutation, 85% of mutant tumors showed high level expression, overall 42% of tumors with no detectable mutation showed over-expression including many muscle invasive. This may represent a non-mutant subset of tumors in which FGFR3 signaling contributes to the transformed phenotype and which may benefit from FGFR-targeted therapy (33).

It was shown that FGFR3 expression is associated with a non-T-cell-inflamed phenotype in tumor tissue of patients with UBC (23). Expression analysis of PD-L1 in archival biopsy samples collected in Study 16443, showed that PD-L1 level is lower in patients with FGFR mRNA overexpression. A similar correlation was detected in patients with NSCLC using publically available TCGA data sets. It is assumed that a causal relationship between FGFR expression and T-cell exclusion leads to the observed findings and to a poorer response to inhibition of the PD-L1 axis by recently approved checkpoint inhibitors. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system.

Atezolizumab is a PD-L1 antibody that demonstrated durable responses in urothelial bladder cancer as first-line and second-line treatment for patients with locally advanced or metastatic urothelial carcinoma. It is assumed that patients with FGFR overexpression exhibit a poorer response to atezolizumab treatment based on the non-T-cell-inflamed phenotype. Therefore, it is hypothesized, that a combination of rogaratinib and atezolizumab can overcome this immune evasion improving immune-checkpoint inhibitor efficacy and disease response.

3.6 Benefit-risk assessment

The pre-clinical information on rogaratinib provides a sound rationale for its activity in several tumor models including urothelial carcinoma. This is confirmed by preliminary efficacy data from the Phase 1 Study 16443 showing signs of activity in advanced UBC with an ORR which compares favorably to existing therapies. During that trial, the overall safety profile was manageable with dose modifications; it was in line with what is expected and acceptable in the target population. Thus, the available data support the investigation of rogaratinib in advanced urothelial carcinoma.

Patients enrolled in Part A of study 19131 will receive rogaratinib at a starting dose of 800 mg b.i.d. that has been chosen for further clinical development concomitantly with the recommended dose of atezolizumab (1200 mg intravenous every 21 days). Due to distinctly different elimination pathways of rogaratinib and antibody atezolizumab, a pharmacokinetic drug interaction is unexpected.

Furthermore, the safety profiles of both drugs do not show relevant overlapping toxicities other than diarrhea and fatigue.

All patients will be followed closely for safety and efficacy; the planned examinations are part of general medical practice and do not expose study participants to an undue risk or burden.

Based on the above considerations, the benefit/risk ratio for study participation can be regarded as positive, and the study appears justified in the planned patient population.

4. Study objectives

The primary objectives of this Part A of the study are:

- To determine the safety and tolerability of rogaratinib in combination with atezolizumab in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma.
- To determine the recommended Phase 2 dose (RP2D) of rogaratinib in combination with atezolizumab in this patient population.

The secondary objectives of this Part A of the study are:

- To assess the efficacy of the combination of rogaratinib and atezolizumab in this patient population.
- To characterize the pharmacokinetics (PK) of rogaratinib in combination with atezolizumab in this patient population.

The exploratory objectives of this Part A of the study are:

- To assess new potential predictive or prognostic biomarkers and their association with tumor-related biomarkers, disease response, drug-resistance and patient outcome.
- To evaluate further biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease.
- To evaluate the combination of rogaratinib and atezolizumab with regard to patient-reported outcomes (PRO).

The procedures and variables used to address these objectives are specified in Sections 9, and 10.3, respectively.

5. Study design

5.1 Design overview

This study 19131 Part A is an open-label, single-arm, international, multicenter, Phase 1b study of rogaratinib in combination with atezolizumab in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma.

The primary objectives of this Phase 1b study (Part A) are to determine the safety, tolerability, RP2D and pharmacokinetics of rogaratinib in combination with atezolizumab in these patients. For all study objectives, see Section 4.

Before entering the screening, patients are to be tested for FGFR1 and 3 mRNA expression levels. Only patients with FGFR-positive tumors (RNAscope score of +3 or +4) can enter the study.

The study will comprise the following periods (see more in Section 5.2):

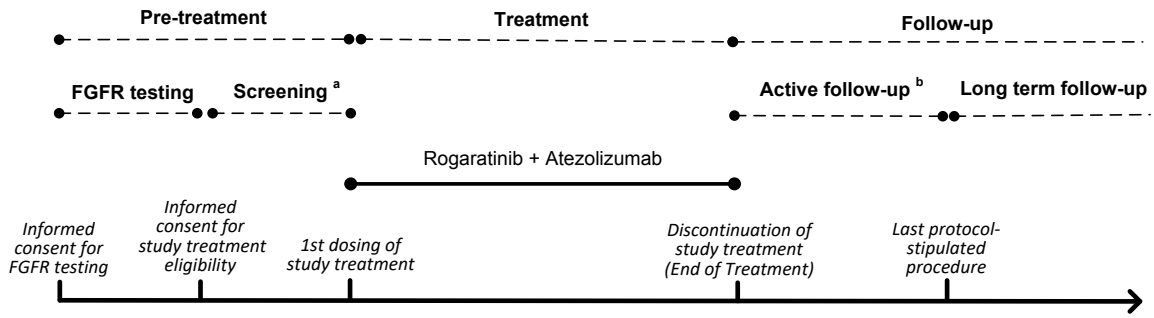
- **Pre-treatment period**, including **FGFR testing** and **screening**,
- **Treatment period**, and
- **Follow-up period, including active follow-up and long-term follow-up.**
    - After primary completion, follow-up information will not be collected after the safety assessment visit.

An overview of the study design is presented in Figure 5–1.

The study is conducted in patients who are cisplatin-ineligible and have had no prior systemic treatment for locally advanced or metastatic disease.

Patients will receive rogaratinib plus atezolizumab combination treatment.

Figure 5–1: Study 19131 Part A – Design overview



FGFR = Fibroblast growth factor receptor
a: Only FGFR positive patients can enter screening.
b: 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 radiological disease progression.

Dose selection

The dose selection part of the study 19131 will assess the safety and tolerability of the combination. The MTD will be determined by using stepwise dose selection design based on a modified toxicity probability interval (mTPI) method. Dose selection will stop after 20 valid patients are available and are evaluable for the MTD assessment. At the end of the DLT observation period of 20 patients the recommendations from the mTPI will be regarded as guidance and will be integrated with the clinical assessments of the available PK and safety data to determine the MTD. A total of approximately 26-30 evaluable patients will be enrolled to obtain additional safety data for confirming the MTD and determine the RP2D.

The mTPI provides a practical dose-finding scheme guided by the posterior inference for a simple Bayesian model. The maximum tolerated dose (MTD) is defined as the highest dose level that could be given so that the toxicity probability is below 30%. The starting dose of rogaratinib will be 800 mg b.i.d. Initially, at least 4 (4-6) patients will be enrolled. The next group of patients will be enrolled once the decision regarding the next dose level is made based on all available PK and safety data and the occurrence of DLTs (for details see Section 10.3.4). The decision about time of enrollment and the number of patients evaluable for DLTs on a dose level will be made by the sponsor in consultation with investigators during regularly held safety calls.

Safety will be regularly assessed during each cycle for potential adverse events, dose-limiting toxicities (DLTs) and disease-related sign and symptoms. Rogaratinib dosing will be interrupted/delayed or reduced in case of clinically significant toxicities. Atezolizumab dosing will not be adjusted, however dosing will be interrupted or delayed in case of clinically significant toxicity. For more detailed information on dose modifications see Section 7.4.3.

The mTPI method will recommend de-escalation, re-escalation or expansion of the current dose level on basis of the observed DLTs. The first dose finding action on a dose level will be performed after at least 4 patients are available on that dose level and are evaluable for DLTs. The possible dose finding actions (as specified in Table 10–1) are '**E**' =escalate to next higher

dose level (800 mg b.i.d. being the highest possible dose), '**S**'=stay at the current dose level, '**D**'=de-escalate to next lower dose level and '**DU**'= de-escalate to next lower dose level and exclude the current and higher dose levels from the further dose escalation due to unacceptably high toxicity (see Table 7–2 for rogaratinib dose levels). If the probability that a dose is above the MTD is greater than 95%, the dose will be declared as toxic and only lower doses will be given in subsequent cohorts. If the highest dose is reached, escalation ('E') leads to staying at that dose. At the lowest dose level de-escalation ('D') or de-escalation with unacceptable high toxicity ('DU') lead to stop of the study. Details are provided in Section 10.3.4.1

Intra-patient dose escalation is not permitted.

5.2 Study periods

5.2.1 Pre-treatment period

FGFR testing

Patients with urothelial carcinoma will be tested for mRNA expression levels of FGFR1 and 3 using archival or fresh tumor biopsy specimen. Before FGFR testing, patients must sign a patient information/informed consent form (PI/ICF) (see Section 13.4), and have to meet all eligibility criteria for FGFR testing (see Sections 6.1 and 6.2).

Only patients with FGFR-positive tumors (high expression [RNAscope score of 3+ or 4+] of FGFR1 and/or 3) will be eligible for the study and can continue to screening. See more about FGFR testing in Section 9.7.1.

Screening

The screening period for the study will start after the patient has signed the PI/ICF for study treatment eligibility (see Section 13.4). The screening will be scheduled within 28 days before start of study treatment. Please refer to Table 9–1 for the detailed schedule for screening assessments.

5.2.2 Treatment period

Patients who satisfy all selection criteria (see Sections 6.1 and 6.2) will be eligible to start study treatment.

The start of the treatment period is defined by the first administration of study treatment. Patients will receive rogaratinib plus atezolizumab combination treatment.

All details on dosing are provided in Section 7.4.1.

The length of a cycle is 3 weeks (21 days).

Patients will continue dosing of both study drugs until any of the discontinuation criteria specified in Section 7.4.4 occurs.

After discontinuation from study treatment, the 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

No further analysis is planned for this study after primary completion. After ending treatment, patients are no longer expected to continue the active follow-up after safety assessment visit and/or enter the long-term follow-up period.

Active follow-up

After permanent treatment discontinuation, a safety assessment visit must be scheduled for all patients at least 30 (up to +7) days after the last dose of study treatment. If the 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. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

Up to primary completion, for patients who permanently discontinue study treatment without radiological disease progression, drug-related AEs will continue to be collected and follow-up tumor evaluations will be performed (by CT or MRI with contrast unless contraindicated) until confirmed 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 every 9 weeks up to one year (from the previous scan date); after primary completion no tumor assessments will be performed (see Table 9–2).

Long-term follow-up

After completion of the active follow-up, all patients will be contacted (telephone contact by site is sufficient) to determine the survival status and subsequent systemic anti-cancer therapy approximately every 3 months (±14 days) until the end of the study (i.e. until last patient's last visit [LPLV]). 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. In addition, any AEs after the active follow-up visit qualifying as SAEs and AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated. Long-term follow-up will not be performed after primary completion.

5.3 Primary variable(s)

The primary variables of this Part A of the study are:

- Safety:
    - The incidence of DLTs will be used to determine the MTD and/or RP2D.
    - The incidence of treatment-emergent adverse events (TEAEs), drug-related TEAEs, and treatment-emergent serious adverse events.

See Section 10.3.4 for the planned statistical analyses of the safety variables.

5.4 Justification of the design

Level of blinding: The study is performed in a non-blinded design because this is considered adequate to meet the study objectives.

Justification of the patient selection: The FGFR1/3 RNAscope (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 either FGFR1 or FGFR2 or FGFR3 scores of 3+ or 4+ by RNAscope demonstrated significant (> 50%) anti-tumor efficacy upon rogaratinib treatment. Preliminary data from Phase 1 FiH 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 an RNAscope score of 3+ or 4+. Therefore, having at least one FGFR isoform with a score of at least 3+ was selected as inclusion criterion for FGFR-positivity for this Study 19131. 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, 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. For FGFR testing please see Section 9.7.1.

For justification of the drug dosages, see Section 7.4.2.

For justification of the sample size, see 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

The end of the study 19131 will be reached as soon as the last visit of the last patient (LPLV) has been reached in all centers in all participating countries (EU and non-EU).

LPLV is defined by the completion of the safety assessment visits determined by the last patient stopping study treatment, switching to a roll-over study, or any other form of continued study drug supply.

Decisions on trial termination can be made by the sponsor guided by strategic expectations for the study compounds after primary completion has been reached.

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 and other forms of continued study drug supply.

5.6 Primary completion

As safety is the primary objective of Part A, the primary completion event for Part A will be its LPLV or 9 months after LPFV, whichever occurs first.

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).

6. Study population

Eligible patients for this study will be patients with locally advanced or metastatic urothelial carcinoma, who are cisplatin-ineligible and have had no prior systemic treatment for locally advanced or metastatic disease.

Patient eligibility will be checked at two sequential time points:

1. At FGFR testing:
   - FGFR testing of patients will be performed at the investigators' discretion prior to start of screening (i.e. before signing of informed consent for study treatment eligibility).
   - 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. Investigators should ensure all patients will be eligible in terms of clinical condition, disease status and lines of treatment. For "FGFR testing failure" (those that are FGFR test negative and/or those that do not meet the inclusion/exclusion criteria) see Section 11.1.
2. At screening:
   - FGFR1 or 3 positive patients (RNAscope score of 3+ or 4+) will be checked for final eligibility using all further selection criteria specified below. For "screening failure" see Section 11.1.

6.1 Inclusion criteria

The following inclusion criteria are applicable for all patients:

Inclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
1. Male or female patients ≥ 18 years of age (at least age of legal maturity)	●	

Inclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
2. Ability to understand and signing of the written patient information/informed consent form (PI/ICF) for FGFR testing	●	
3. 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.		●
4. Existence of archival or fresh tumor biopsy specimen for FGFR1/3 mRNA expression testing • Patients who submit transurethral resection of bladder tumors (TURBT) specimens will be required to submit specimens containing muscle invasive component of the bladder tumor as verified by pathology review. If the TURBT specimens do not contain a muscle invasive component (i.e. T2 or greater), the specimens obtained at the time of cystectomy/nephroureterectomy or metastatic spread (i.e. sample from a metastatic lesion) will be required. • Patients who do not have archival tissue specimens meeting eligibility requirements may undergo a biopsy. The tumor material should be derived by a biopsy procedure associated with a non-significant risk (see Section 9.7.1).	●	
5. Documented urothelial carcinoma (transitional cell carcinoma) including urinary bladder, renal pelvis, ureters, urethra, meeting all of the following criteria: • Histologically confirmed • Patients with mixed histology are required to have a dominant transitional cell pattern. • Locally advanced (T4, any N; or any T, N2-3) or metastatic disease (any T, any N, and M1). Note: 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).	●	●
6. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) in contrast enhanced (unless contraindicated) CT or MRI. Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy before study enrollment and no other lesions are available for selection as target lesions. Patients with resected primary tumors who have documented metastases are eligible.	●	●
7. High FGFR1 or 3 mRNA expression levels (RNAscope score of 3+ or 4+; measurement is part of this protocol) in archival or fresh tumor biopsy specimen		●

Inclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
8. No prior systemic treatment for locally advanced or metastatic urothelial carcinoma. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting. Prior local intra-vesical chemotherapy or prior local immunotherapy (e.g. with Bacillus Calmette-Guérin [BCG]) is allowed if completed at least 4 weeks before the first study drug administration. Regionally available standard of care options must be considered for all patients.	●	
9. Ineligibility for cisplatin-based chemotherapy as defined by any one of the following criteria: • Impaired renal function (GFR > 30 but < 60 mL/min/1.73 m^2) according to the modification of diet in renal disease (MDRD) abbreviated formula • A hearing loss (measured by audiometry) of > 25 dB at two contiguous test frequencies in at least one ear • Grade ≥ 2 peripheral neuropathy (i.e. sensory alteration or paresthesia including tingling)	●	●
10. Recovery to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v.4.03) Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug / procedure-related toxicity (patients with persistent alopecia of any grade, anemia [hemoglobin ≥ 9 g/dL], any grade peripheral neuropathy, impaired renal function [GFR > 30 mL/min/1.73 m^2], hearing loss and/or hypothyroidism that is adequately controlled by hormone replacement can be included).		●
11. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1.	●	●

Inclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
12. Adequate bone marrow, liver and renal function as assessed by laboratory requirements conducted within 7 days of first study drug administration: • Absolute neutrophil count (ANC) ≥ 1,500/mm^3 (without granulocyte colony-stimulating factor support within 2 weeks before the first study drug administration) • Lymphocyte count ≥ 300/ mm^3 • Hemoglobin ≥ 9 g/dL (without transfusion or erythropoietin within 4 weeks before the first study drug administration) • Platelet count ≥ 100,000/mm^3 (without transfusion within 2 weeks before the first study drug administration) • Total bilirubin ≤ 1.5 × the upper limit of normal (ULN). Known Gilbert syndrome is allowed if total bilirubin is ≤ 3 x ULN. • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (≤ 5 times ULN for patients with liver involvement of their cancer) • Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 × ULN for patients with liver or bone involvement of their cancer) • Lipase and amylase ≤ 2 × ULN • Serum albumin ≥ 2.5 g/dL • Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to the modification of diet in renal disease (MDRD) abbreviated formula. • INR ≤ 1.5 × ULN and 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 and they are on a stable dose as defined by the local standard of care.		●
13. Negative serum pregnancy test in women of childbearing potential (performed within 7 days before the first treatment). Negative results must be available before the first study drug administration.		●

Inclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
14. Women of childbearing potential (WOCBP) and fertile men must agree to use adequate contraception when sexually active from signing of the ICF for study treatment eligibility until at least 5 months after the last atezolizumab administration or until at least one week after the last rogaratinib intake, whichever is later. 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: • Combined (estrogen and progesterone containing: oral, intravaginal, transdermal) and progesterone-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation. • Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success). • Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient). o 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 5 months after last atezolizumab administration or until at least one week after the last rogaratinib intake, whichever is later. 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 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.		●

6.2 Exclusion criteria

The following exclusion criteria are applicable for all patients:

Exclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
1. Previous or concurrent cancer except • cervical carcinoma *in situ* • treated basal-cell carcinoma or squamous cell skin cancer • localized prostate cancer treated with curative intent and known absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (T1/T2a, Gleason score ≤ 6, and PSA ≤ 10 ng/mL undergoing active surveillance and treatment-naïve) • any other cancer curatively treated > 3 years before the first study drug administration		●
2. Ongoing or previous treatment with anti-FGFR directed therapies (e.g. receptor tyrosine kinase inhibitors including rogaratinib or FGFR-specific antibodies).	●	
3. Previous assignment to treatment during this study	●	●
4. Investigational drug treatment outside of this study during or within 4 weeks before the first study drug administration.		●
5. 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: • evaluable or measurable disease outside the CNS • no metastases to midbrain, pons, medulla, cerebellum, or within 10mm of the optic apparatus (optic nerves and chiasm) • no history of intracranial or spinal cord hemorrhage • no evidence of significant vasogenic edema • no ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at stable dose are allowed • no stereotactic radiation, whole-brain radiation or neurosurgical resection within 4 weeks before the first study drug administration • radiographic demonstration of interim stability (i.e. no progression) between the completion of CNS-directed therapy and the screening radiographic study • Screening CNS radiographic study ≥ 4 weeks since completion of radiotherapy or surgical resection and ≥ 2 weeks since discontinuation of corticosteroids		●

Exclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
6. History or current condition of an uncontrolled cardiovascular disease including any of the following conditions: • Congestive heart failure (CHF) NYHA Class 2 or greater, unstable angina (symptoms of angina at rest) or • New-onset angina (within last 3 months before the first study drug administration) • Myocardial infarction (MI) within past 6 months before the first study drug administration • Unstable cardiac arrhythmias requiring anti-arrhythmic therapy. Patients with arrhythmia not requiring therapy or under control with anti-arrhythmic therapy such as beta-blockers or digoxin are eligible. • Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or known left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.		●
7. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis The following conditions are *no* reason for exclusion: • History of autoimmune-related hypothyroidism clinically stable on thyroid replacement hormone • Controlled Type-I diabetes mellitus on a stable dose of insulin regimen.		●
8. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g. PleurX) are allowed.		●
9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.		●
10. Known human immunodeficiency virus (HIV) infection		●

Exclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
11. Active hepatitis B virus (HBV; chronic or acute; defined as having a known positive hepatitis B surface antigen [HBsAg] test at the time of screening) or hepatitis C infection requiring treatment. • Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible if HBV DNA is negative. • Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.		●
12. Active tuberculosis (baseline chest X-ray and CT can be used for tuberculosis screening)		●
13. Clinically active infections (CTCAE v4.03 ≥ Grade 1) within 2 weeks before the first study drug administration		●
14. Severe (CTCAE v.4.03 Grade ≥ 3) infections within 4 weeks before the first study drug administration, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia		●
15. Treatment with therapeutic oral or i.v. antibiotics within 2 weeks before the first study drug administration. Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.		●
16. Seizure disorder requiring medication		●
17. History of organ allograft		●
18. Evidence or history of bleeding diathesis or coagulopathy		●
19. Any hemorrhage / bleeding event CTCAE v.4.03 ≥ Grade 3 within 4 weeks before the first study drug administration		●
20. Serious, non-healing wound, ulcer, or bone fracture		●
21. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation		●
22. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins		●
23. Inability to swallow oral tablets		●
24. Any malabsorption condition		●
25. Current diagnosis of any retinal disorders including retinal detachment, retinal pigment epithelial detachment (RPED), central serous retinopathy or retinal vein occlusion.		●

Exclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
26. Current evidence of endocrine alteration of calcium phosphate homeostasis (e.g. parathyroid disorder, history of parathyroidectomy, tumor lysis, tumoral calcinosis, paraneoplastic hypercalcemia).		●
27. Concomitant therapies that are known to increase serum calcium or phosphate levels (i.e. antacids, phosphate-containing laxatives oral/rectal, potassium phosphate) and that cannot be discontinued or switched to a different medication before the first study drug administration		●
28. Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study		●
29. Breast-feeding		●
30. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, TNF [CD137 agonist] and interleukin [IL]-2) within 6 weeks or five half-lives of the drug, whichever is shorter, before the first study drug administration.		●
31. Use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 (see Appendix 16.1) are not permitted for 2 weeks before the first study drug administration.		●
32. Treatment with systemic corticosteroids or other systemic immunosuppressant medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks before the first study drug administration, or anticipated requirement for systemic immunosuppressive medications during the trial. • Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the sponsor. • The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e. for adrenal insufficiency), and mineralocorticoids (e.g. fludrocortisone for adrenal insufficiency) is allowed.		●
33. Any administration of a live, attenuated, replication competent virus vaccine within 28 days before the study start or anticipation that such a live, attenuated, replication competent virus vaccine will be required during the study. Patients may receive inactivated vaccines.		●
34. Autologous bone marrow transplant or stem cell rescue within 4 months before the first study drug administration		●

Exclusion criteria	*to be checked at*	
	FGFR testing	**Screening**
35. Major surgery, open biopsy or significant traumatic injury within 4 weeks before the first study drug administration (central line surgery is not considered major surgery).		●
36. Renal failure requiring peritoneal dialysis or hemodialysis		●
37. Systolic/diastolic blood pressure ≤ 100/60 mmHg *and* concurrent heart rate ≥ 100/min		●
38. Clinically significant uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management)		●
39. Close affiliation with the investigational site; e.g. a close relative of the investigator or a dependent person (e.g. employee of or student at the investigational site)		●
40. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results		●

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 receiving study treatment, a withdrawn patient is referred to as either "FGFR testing failure" (those that are FGFR test negative and/or those that do not meet the inclusion/exclusion criteria for FGFR testing) or "screening failure" as specified below:

FGFR testing failure

A patient who was tested for FGFR mRNA expression level by FGFR1/3 RNAscope *in situ* hybridization assay and the test result for FGFR1 or 3 mRNA expression levels was not RNAscope score of 3+ or 4+ (measurement is part of this protocol) or fails to satisfy the selection criteria **must not** be screened for study treatment eligibility but **needs to be**

withdrawn from the study and is regarded a “FGFR testing failure”. The “FGFR testing failure” will be registered.

Re-testing is allowed if an unevaluable test result occurs.

See Section 11.1 for data to be collected for FGFR testing failures (those that are FGFR test negative and/or those that do not meet the inclusion/exclusion criteria for FGFR testing).

Screening failure

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before start of study treatment is regarded a “screening failure”.

See Section 11.1 for data to be collected for screening failures.

6.4.1.2 Re-screening

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 inclusion / exclusion criteria preventing the patient’s initial attempt to participate have been changed (via protocol amendment).

Re-screening of patients who have failed screening may only be allowed **once** after discussion with the sponsor’s designated medical representative and after approval by the sponsor. Sponsor 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 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.

6.4.1.3 Withdrawal criteria

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

- Consent withdrawal 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.

- Substantial non-compliance with study procedures
  - Patients requiring a dose interruption of rogaratinib due to toxicity > 21 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.
  - Off study drug (atezolizumab) longer than 42 days from the next intended dose
    - If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold > 42 days, atezolizumab may be restarted after sponsor approval.
    - If patients must be tapered off steroids used to treat adverse events, atezolizumab may be held for > 42 days. The acceptable length of interruption will depend on agreement between the investigator and the sponsor. (See also Section 7.4.3.3 for further details and specific recommendations).
  - Lost to follow-up
  - Use of another non-protocol anti-cancer therapy

- Unacceptable toxicity
  - If, in the investigator's opinion, continuation of study would be harmful to the patient's well-being.
  - Any toxicity requiring rogaratinib dose reductions below dose level -2.
  - Any toxicity requiring rogaratinib dose interruption longer than 21 days to resolve to Grade 1 or better.
  - Severe (Grade 3 or higher) allergic reactions such as exfoliative erythroderma, anaphylaxis, or vascular collapse.
  - Severe (Grade 3 or higher) infusion-related reactions.
  - Any other potential adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the investigator or his designated associate(s).
  - Any decrease in visual acuity, ocular pain or discomfort, or symptomatic retinal disorders including retinal detachment / retinal pigment epithelial detachment / central 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 judgement and based on the individual benefit risk

assessment.

- Liver toxicity with AST or ALT > 3 x ULN with concomitant bilirubin > 2 x ULN in the absence of an alternative explanation for these elevations.
- ≥ Grade 3 liver toxicity with ALT or AST > 5 x ULN and/or total bilirubin > 3 x ULN in the absence of an alternative explanation for these elevations.
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis.
- Any grade of recurrent symptomatic pancreatitis.
- Newly diagnosed soft tissue mineralization suspected to be caused by rogaratinib.
- Grade 4 non-hematological toxicity (laboratory abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator).
- Grade 3 or higher non hematologic toxicity atezolizumab-related and requiring treatment discontinuation (see also Section 7.4.3.3).
- Any Grade 2 or higher non hematologic toxicity atezolizumab-related not resolving at Grade 1 or better within 12 weeks despite symptomatic therapy

- Pregnancy as confirmed by a positive serum beta-HCG test. Pregnancy will be reported under the same timelines as a serious adverse event.
- At specific request of the sponsor.

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

- If the patient develops conditions which would have prevented his/her entry into the study according to the inclusion / exclusion criteria, he/she must be withdrawn immediately if safety is concerned; in other cases, the investigator will decide whether there is a conflict for the patient to continue.
- Development of a second malignancy that requires a different treatment. At investigator's discretion study treatment may continue if UC has a poorer prognosis as compared with the second malignancy of new onset.
- Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a relevant degree.
- Use of illicit drugs or other substances that may, in the opinion of the investigator or his designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- 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.

- Disease progression per RECIST v1.1. At discretion of the investigator, willing patients will be permitted to continue study treatment after radiologic progression according to RECIST v1.1 if all the following criteria are met:
  - Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator.
  - Absence of symptoms and signs indicating unequivocal progression of disease (including worsening of laboratory values [e.g. new or worsening hypercalcemia]).
  - No decline in ECOG performance status that can be attributed to disease progression.
  - Absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

In addition, treatment beyond progression should not delay an imminent intervention to prevent serious complications of disease progression (e.g. central nervous system [CNS] metastases).

Patients for whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continuing study treatment at the discretion of the investigator if they still meet the criteria above and in absence of unacceptable toxicity.

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.

After permanent treatment discontinuation, a safety assessment visit must be scheduled for all patients (refer to Section 5.2.3). After primary completion, follow-up information will not be collected after safety assessment visit.

Withdrawal from active follow-up

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

- Radiologically confirmed PD of urothelial carcinoma is observed (investigator assessment). (*Note: this applies only to the further efficacy assessments during the active follow-up period in patients who prematurely discontinued study treatment for reasons other than radiological disease progression*).
- Start of subsequent systemic anti-cancer treatment. (*Note: this applies only to the further efficacy assessments during the active follow-up period in patients who prematurely discontinued study treatment for reasons other than radiological disease progression*).
- 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.
- 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 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 and sites are expected to make at least 5 attempts to contact the patient over the course of 3 months. An additional contact attempt should be made at the time of the survival sweep.

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

Replacement of patients may occur in Part A in order to ensure the necessary number of evaluable patients for dose selection (at least 4 patients per tested dose level, a total of 20 evaluable patients). Patients who are not valid for efficacy assessment may be replaced, to ensure at least 26 valid patients for assessment of the RP2D. Patients may be replaced in the following circumstances:

Dose selection:

- Patients who discontinue or took less than 80% of the per protocol required total dose of either study drug (rogaratinib or atezolizumab) during the first cycle due to any reason

other than a DLT (note: protocol-defined dose reductions will not be considered incompliant).

Efficacy:

- Patients who took less than 80% of the per protocol required total dose of either study drug (rogaratinib or atezolizumab) during the first two cycles or patients without an efficacy assessment.

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.

The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center.

7. Treatments

7.1 Treatments to be administered

In Part A of the study, patients will receive a combination treatment of rogaratinib (a pan FGFR inhibitor) plus atezolizumab (a PD-L1 monoclonal antibody).

7.2 Identity of study treatment

In this protocol, the term “test drug” refers to rogaratinib only. The term “study drug” refers to any of protocol-stipulated drugs, i.e. rogaratinib or atezolizumab, and “study treatment” refers to the combination of rogaratinib and atezolizumab.

All study treatment 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, 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 batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor’s clinical supplies 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’s study file.

In case patients are transferred to a roll-over study or any other form of continued study drug supply with no cost to the patient, 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 any other form of continued study drug supply with no cost to the patient 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	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; PP = Polypropylene.

7.2.2 Atezolizumab – combination drug

The study drug atezolizumab serves as the combination drug in this study Part A. Atezolizumab received accelerated FDA and full EMA approval for the treatment of metastatic urothelial carcinoma who have been previously treated with a platinum-based chemotherapy or who are considered ineligible for cisplatin chemotherapy (18, 31). Atezolizumab will be sourced centrally by the sponsor. For full details on atezolizumab and

instructions for dilution, please refer to the current Summary of Product Characteristics (SmPC) or the investigator's brochure. (Note: the SmPC should only be referred to for the preparation instructions for atezolizumab. The IB should be the reference for all other information about atezolizumab).

Please also refer to atezolizumab label for guidance when prescribing with other medications.

Atezolizumab vials should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. They should not be frozen or shaken.

7.3 Treatment assignment

In Part A, all eligible patients will be assigned to receive the same combination treatment, rogaratinib plus atezolizumab.

7.4 Dosage and administration

7.4.1 Doses, dosing schedule and route of administration

7.4.1.1 Rogaratinib – test drug

Rogaratinib will be administered orally in a stepwise dose selection schedule shown in Table 7–2 until disease progression, unacceptable toxicity or consent withdrawal.

Patients will receive their initial dose of 800mg rogaratinib in the morning of Cycle 1 Day 1, followed by serial PK blood sampling for 8 hours and a second dose of 800mg rogaratinib in the evening. Rogaratinib will be administered continuously twice daily on all 21 days in each cycle.

Special considerations/instructions for rogaratinib

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.

It is important to take the medications at the same times each day approximately 12 hours apart. For the second dose of rogaratinib on C1D1, a time window of ± 3 hours is permitted. 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, the patient should miss the dose and continue with the next dose at the next prescribed interval.

Rogaratinib and atezolizumab will be dosed at the same time, starting first with the infusion and shortly after start (< 5 minutes) the intake of rogaratinib.

7.4.1.2 Atezolizumab – combination drug

A fixed dose of 1200 mg atezolizumab will be administered through intravenous (i.v.) infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity or consent withdrawal.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For more detailed information regarding administration, refer to the investigator's brochure.

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion in Cycle 1 is tolerated without infusion-associated adverse events, the second infusion in Cycle 2 may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all infusions in the subsequent cycles may be delivered over 30 (± 10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate and blood pressure) should be monitored 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No pre-medication will be allowed for the first dose of atezolizumab. Pre-medication may be administered for Cycles ≥ 2 at the discretion of the treating physician in case of previous infusion reaction. Pre-medication should be recorded in eCRF as concomitant medication.

For the management of infusion-related reactions see the specific section in Section 7.4.3.3.

Most common adverse reactions (≥ 20%) in patients with locally advanced or metastatic urothelial carcinoma were: fatigue, decreased appetite, nausea, urinary tract infection, constipation, diarrhea and pyrexia. Atezolizumab has been associated with risks such as the following: infusion-related reactions and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, myocarditis and meningoencephalitis. Immune-related adverse reactions (pneumonitis, hepatitis, colitis, endocrinopathies, other immune-related adverse reactions) requiring systemic corticosteroids or hormone replacement therapy occurred in < 20% patients. In addition, systemic immune activation (described below) is a potential risk associated with atezolizumab when given in combination with other immunomodulating agents.

Any overdose or incorrect administration of combination drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Guidelines for dose modification, treatment interruption or discontinuation and for the management of specific adverse events are provided in a specific section in Section 7.4.3.3.

7.4.2 Justification of selected doses

Rogaratinib: rogaratinib dose of 800 mg b.i.d. was chosen for further clinical development based on pharmacokinetic, biomarker, safety and anti-tumor activity in the Phase 1 dose escalation study 16443.

Atezolizumab: the approved dose of atezolizumab will be used in this study.

7.4.3 Dose modifications

7.4.3.1 Dose limiting toxicities (DLTs)

A DLT is defined as any of the following TEAEs occurring during Cycle 1 and regarded by the investigators and/or sponsor to be related to rogaratinib or atezolizumab. The CTCAE v 4.03 will be used to assess toxicities / adverse events.

Hematological

- Absolute neutrophil count (ANC) < 500/mm^3 for more than 7 days
- Febrile neutropenia (a disorder characterized by an ANC < 1,000/mm^3 and single temperature ≥ 38.3 °C or sustained temperature of ≥ 38.0 °C for more than 1 hour)
- Platelets < 25,000/mm^3
- Hemoglobin < 8.0 g/dL
- Grade 3 hemorrhage associated with thrombocytopenia of ≥ Grade 3

Non-hematological

- Any non-hematologic Grade 3 or higher toxicity except:
    - Grade 3 nausea, vomiting, and fatigue that resolve within 72 hours with or without supportive care.
    - Grade 3 diarrhea will be classified as DLTs if not resolved to Grade ≤ 2 or baseline following dose interruption of rogaratinib and/or withholding atezolizumab within 3 days with or without supportive care.
    - Laboratory abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator.
    - Grade 3 hypothyroidism
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis.
- Decrease of three lines or more in visual acuity scales, Grade 2 or higher ocular pain or discomfort, or symptomatic retinal disorders including retinal detachment, RPED, central serous retinopathy or retinal vein occlusions.
- Grade 2 with AST or ALT >3 x ULN and up to 5 x ULN or total bilirubin greater than 1.5 and up to 3 x ULN in absence of an alternative explanations for these elevations.
- Any toxicity not resolving within 21 days at ≤Grade 1 with or without supportive care.

Miscellaneous

- In case an unexpected drug-related toxicity is seen more frequently, this toxicity may be declared a DLT for the remainder of the study after thorough consultation between the investigator and the sponsor.
- Any rogaratinib-related toxicity that, at the discretion of the investigator, or his designated associate(s), is thought to warrant withholding the drug for more than 3 consecutive days.
- Such toxicities might be Grade 1 or Grade 2 toxicities which interfere with the activities of daily life (e.g. long-lasting fatigue, or anorexia), making a dose reduction necessary in order to ensure the patient's compliance.
- Inability to start Cycle 2 Day 1 due to clinically relevant toxicity.

For certain toxicities such as laboratory assessments without a clear clinical correlation (e.g. lipase increase without signs of a clinical pancreatitis) or in patients that violated the protocol, a discussion between the investigator and the sponsor may take place if that adverse event should be regarded as DLT necessitating dose reduction.

7.4.3.2 Dose modifications of rogaratinib

Dose of rogaratinib may be interrupted / delayed or reduced in case of clinically significant toxicities that are related to study drug therapy. The intensity of toxicities will be graded using the CTCAE v 4.03.

If a patient experiences a DLT during Cycle 1 (Days 1-21), the next dose of rogaratinib can be delayed for up to 21 days. This is permitted also in case of Grade 3 toxicities that are not defined as withdrawal criteria and that are persisting ≤ 7 days.

All patients who are re-treated following a DLT should undergo dose reduction of rogaratinib (see Table 7–2).

If the toxicity resolves within 21 days after the planned treatment date to ≤ Grade 1 re-starting rogaratinib at 1 dose level below the current dose can be considered (see Table 7–2). If such an improvement is not observed, the study treatment should be permanently discontinued.

Patients who experience a Grade 4 non-hematological toxicity, and any other toxicity defined as withdrawal criteria will be permanently withdrawn from the study treatment.

If a patient experiences clinically relevant toxicity after Cycle 1, the next dose of rogaratinib can be delayed for up to 21 days. This is permitted also in case of Grade 3 toxicities that are not defined as withdrawal criteria and that are persisting ≤ 7 days. If the toxicity resolves within 21 days after the planned treatment date to ≤ Grade 1 or baseline, reduction of the next dosing of rogaratinib by 1 dose level below the current dose (see Table 7–2) can be considered.

Patients requiring dose reduction to less than 400 mg b.i.d. should be permanently withdrawn from the study treatment.

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

Level	Dose
Starting level	800 mg b.i.d.
-1	600 mg b.i.d.
-2	400 mg b.i.d.

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

Dose modifications will be based on the highest intensity 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, with the exception of dose reduction due to liver toxicities, 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 and if toxicity has resolved to baseline.
- Patients requiring a dose interruption of rogaratinib due to toxicity > 21 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 -2 are needed, patients will be withdrawn 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 of treatment with rogaratinib (interruptions will not prolong the duration of a cycle).

Detailed dose adjustments for toxicities are described in Table 7–3. Patients who experience a Grade 4 toxicity must discontinue study drug permanently.

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

Grade [a]	Dose delay	Dose modification
1 – 2 [b]	Treat as scheduled	No change
3	Delay [c] until recovery to ≤ Grade 1	Decrease by 1 dose level [d]
4	Discontinue study treatment permanently	Discontinue study treatment permanently

a: Excludes alopecia, fatigue, nausea/vomiting if adequately controlled by antiemetic treatments. Laboratory abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator. In addition, specific dose modification rules for hyperphosphatemia, liver toxicity and retinal disorders are given in the following sections.
b: In case of Grade 2 diarrhea with no signs or symptoms of colitis and that does not resolve within 72 hours with or without supportive care, rogaratinib dosing has to be interrupted until resolution to Grade ≤ 1. No dose reduction is required.
c: If not recovered within 21 days, the study treatment will be permanently discontinued.
d: If dose reductions by more than 2 levels are required, the study treatment will be permanently discontinued.

7.4.3.2.1 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 chelators are not tolerated, low-phosphorus 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 the day of detection of hypocalcemia and should be repeated as clinically indicated.

7.4.3.2.2 Liver toxicity

Dose modifications of rogaratinib for liver toxicity are presented in Table 7–5 and have been adapted based on criteria established for liver toxicity due to atezolizumab concomitant administration. Immune-related hepatitis has been associated with the administration of atezolizumab. Refer to the latest available versions of rogaratinib and atezolizumab IBs for further details. Eligible patients must have adequate liver function, as manifested by measurement of hepatic transaminases and total bilirubin, and liver function will be monitored throughout study treatment. Liver toxicity refers to ALT and/or AST and/or bilirubin increases and graded according to CTCAE v.4.03.

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

Toxicity	Modification schedule
Hepatic event, Grade 1	No modifications. Treat as scheduled and check AST, ALT and bilirubin weekly for at least 4 weeks [a] or until values resolve to within normal limits
Hepatic event, Grade 2 with AST or ALT > 3 x ULN and up to 5 x ULN or total bilirubin greater than 1.5 and up to 3 x ULN in absence of an alternative explanation for these elevations	All events: No modification. Check AST, ALT and bilirubin level more frequently until return to baseline value Events of > 5 days' duration: 1. STOP rogaratinib 2. STOP atezolizumab 3. Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent 4. Check AST, ALT and bilirubin level weekly or more frequently till recovery to Grade 0-1 [a] 5. After recovery to Grade 0-1 re-start with rogaratinib -1 DL [b] and atezolizumab 6. Permanently discontinue atezolizumab and rogaratinib, and contact sponsor if event does not resolve to Grade 0-1 within 12 weeks
Hepatic event, Grade 3 with AST or ALT > 3 x ULN with concomitant bilirubin > 2 x ULN in absence of an alternative explanation for these elevations or with AST or AST > 5 x ULN and/or total bilirubin > 3 x ULN in absence of an alternative explanation for these elevations	Withdraw patient from study treatment permanently [a, c, d] and contact sponsor Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent If event does not improve within 48 hours after initiating corticosteroids, considering adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 months
Hepatic event, Grade 4	Withdraw patient from study treatment permanently [a, c]

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; DL = Dose level; ULN = Upper limit of normal.
a: In case of interruption/discontinuation, check AST, ALT, and bilirubin weekly or more frequently according to local standard of care, until recovery to Grade 0-1 or to baseline.
b: Dose will not be re-escalated to original dose after dose reduction for toxicity. If more than 2 dose level reductions are required, treatment will be permanently discontinued.
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 per investigator' judgment the Grade 3 hepatic event is unrelated to study treatment and reversible, the treatment may be restarted after resolution to Grade 0 or 1 or to baseline.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated liver function tests, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

7.4.3.2.3 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 (RPED) / central 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 / central 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 judgement 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.

7.4.3.3 Dose modifications of atezolizumab

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

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to study drug and requires a dose to be held.

If atezolizumab is held because of related adverse events for > 42 days beyond the next scheduled dosing, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 9.2.3.

If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold > 42 days, atezolizumab may be restarted with the approval of the sponsor.

If patients must be tapered off steroids used to treat adverse events, atezolizumab may be held for > 42 days. The acceptable length of interruption will depend on agreement between the investigator and the sponsor. During steroid taper and if toxicity has resolved to Grade ≤ 1, rogaratinib may continue as monotherapy.

Infusion-related reactions

Severe infusion reactions have occurred in patients in clinical trials of atezolizumab. Refer to the latest available version of atezolizumab IB for further details. Immediately interrupt infusion in patients with mild or moderate infusion-related reactions (Grade 1 and 2). Permanently discontinue atezolizumab in patients with Grade 3 or 4 infusion-related reactions.

The management of infusion-related reactions will be according to severity as follows:

In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be immediately interrupted at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes and then restart the infusion at half the rate been given at time of event onset. If tolerated at the reduced rate for 30 minutes, the infusion rate may then be increased to the original rate. If the symptoms recur, discontinue infusion of this dose.

In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment (e.g. oral or i.v. antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event. For the subsequent infusion, administer oral premedication with antihistamine and anti-pyretic and monitor closely for infusion-related reactions.

For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated (administer aggressive symptomatic treatment e.g. oral or i.v. antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

As per the IB withhold atezolizumab for any of the following:

- Grade 2 pneumonitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Grade 2 or 3 diarrhea or colitis
- Grade 2 or 3 hypophysitis
- Symptomatic adrenal insufficiency,
- Grade 3 or 4 hypothyroidism or hyperthyroidism

- Grade 3 or 4 hyperglycemia
- Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
- Grade 2 immune-mediated neuropathy, including facial paresis
- Grade 2 ocular inflammatory toxicity
- Grade 2 or 3 pancreatitis, or Grade 3 or 4 increases in amylase or lipase levels (greater than 2.0 times ULN)
- Grade 3 or 4 infection
- Grade 2 infusion-related reactions
- Grade 3 rash
- Grade 1 immune-mediated pericarditis
- Grade 2 immune-related nephritis
- Grade 2 or 3 immune-related myositis

Atezolizumab may be resumed in patients whose adverse reactions recover to Grade 0–1 (except for Grade 1 immune-mediated pericarditis).

Permanently discontinue atezolizumab for any of the following:

- Grade 3 or 4 pneumonitis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN in the absence of an alternative explanation for these elevations
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Grade 4 immune-mediated hypothyroidism or hyperthyroidism
- Any grade confirmed SJS or TEN
- Grade 3 or 4 immune-mediated neuropathy, including facial paresis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Grade 2–4 immune-mediated myelitis
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 or any grade of recurrent symptomatic pancreatitis
- Grade 2–4 immune-mediated myocarditis or immune-mediated pericardial disorders
- Grade 3 or 4 immune-related nephritis
- Grade 3 or 4 infusion-related reactions

- Grade 4 rash
- Grade 4 immune-related myositis

Management of specific adverse events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

The primary approach to Grade 1−2 immune-mediated adverse events is supportive and symptomatic care; for higher grade immune-mediated adverse events, oral or parenteral steroids are given, and either skipping a dose or stopping therapy is appropriate.

If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor. Recurrent Grade 2 immune-mediated adverse events may also mandate skipping a dose of atezolizumab or the use of steroids. Consideration for benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab.

Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events. However, resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

Management of immune-mediated AEs

For further details, please also refer to the latest version of the investigator's brochure of atezolizumab.

Immune-mediated pneumonitis or interstitial lung disease

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and with no clear alternate etiology, might occur during treatment with atezolizumab. Refer to the latest available version of atezolizumab IB for further details. It is

recommended to monitor patients for signs or symptoms of pneumonitis (dyspnea, cough, fatigue, hypoxia) with radiographic imaging.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant.

The management of immune-mediated pneumonitis will be according to the severity (Table 7–6).

Table 7–6: Management guidelines for pulmonary events, including pneumonitis

Event	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3 or 4
Pulmonary event	Continue atezolizumab and monitor closely Re-evaluate on serial imaging Consider patient referral to pulmonary specialist For recurrent events, treat as a Grade 3 or 4 event	Withhold atezolizumab until resolution Refer patient to pulmonary and infectious disease specialist and consider bronchoscopy or BAL with or without transbronchial biopsy Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent Resume atezolizumab if event resolves to ≤ Grade 1 within 12 weeks Permanently discontinue atezolizumab if event does not resolve to ≤ Grade 1 within 12 weeks and contact the sponsor [a, b, c, d] For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event	Permanently discontinue atezolizumab and contact sponsor [c] Oral or i.v. broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment Bronchoscopy or BAL with or without transbronchial biopsy is recommended Initiate treatment with 1−2 mg/kg/day i.v. methylprednisone If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

BAL = bronchoscopic alveolar lavage; CTCAE = Common Terminology Criteria for Adverse Events; i.v. = intravenous.

a: If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b: Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor.

c: Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

d: In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

Immune-mediated hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving atezolizumab treatment. Liver test abnormalities occurred in patients who received atezolizumab. Refer to the latest available version of atezolizumab IB for further details. For management of liver toxicity, refer to the Section 7.4.3.2.2 and Table 7–5.

Immune-mediated colitis or diarrhea

Immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving atezolizumab. Refer to the latest available version of atezolizumab IB for further details. It is recommended to monitor patients for signs and symptoms of diarrhea or colitis.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies including rogaratinib-related gastrointestinal toxicities. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, platelet count, or bandemia): perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Management of immune-related colitis will be according to its severity (Table 7–7).

Table 7–7: Management guidelines for immune-mediated gastrointestinal events (diarrhea or colitis)

Event	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3 or 4
Diarrhea or colitis	Continue atezolizumab. Initiate symptomatic treatment (oral fluids, loperamide, avoid high fiber/lactose diet). Endoscopy is recommended if symptoms persist for >7 days. Monitor closely.	Withhold atezolizumab Initiate symptomatic treatment. If strong clinical suspicion for immune-mediated colitis, start empiric i.v. steroids while waiting for definitive diagnosis. Patient referral to gastrointestinal specialist is recommended. For recurrent event or for events that persist >5 days, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. Resume atezolizumab if event resolves to ≤ Grade 1 within 12 weeks. [a,b] Permanently discontinue atezolizumab if event does not resolve to ≤ Grade 1 within 12 weeks and contact the sponsor. [a, b, c]	<u>Grade 3</u> Withhold atezolizumab Refer patients to gastrointestinal specialist for evaluation and confirmatory biopsy. Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. Resume atezolizumab if event resolves to ≤ Grade 1 within 12 weeks. [a,b] Permanently discontinue atezolizumab if event does not resolve to ≤ Grade 1 within 12 weeks and contact the sponsor. [a, b, c] <u>Grade 4</u> Permanently discontinue atezolizumab and contact sponsor. [c] Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

CTCAE = Common Terminology Criteria for Adverse Events; i.v. = intravenous.
a: If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
b: Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor.
c: Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

Immune-related endocrinopathies

Immune-related hypophysitis, thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving atezolizumab. Refer to the latest available version of atezolizumab IB for further details. Monitor patients for clinical signs and symptoms of endocrinopathies.

For management guidelines of endocrine events, see Table 7–8 below.

Table 7–8: Management guidelines for endocrine events

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	Withhold atezolizumab for up to 12 weeks after event onset [a]
	Refer patient to endocrinologist
	Perform brain MRI (pituitary protocol)
	Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day i.v. methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement
	Initiate hormone replacement if clinically indicated
	If event resolves to Grade 1 or better, resume atezolizumab [b]
	If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor [c]
	For recurrent hypophysitis, treat as a Grade 4 event
Hypophysitis (pan-hypopituitarism), Grade 4	Permanently discontinue atezolizumab and contact the sponsor [c]
	Refer patient to endocrinologist
	Perform brain MRI (pituitary protocol)
	Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day i.v. methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement
	Initiate hormone replacement if clinically indicated
Grade 1 hypothyroidism	Continue atezolizumab
	Initiate treatment with thyroid replacement hormone
	Monitor TSH weekly

Table 7–8: Management guidelines for endocrine events

Event	Management
Grade 2 hypothyroidism	Consider withholding atezolizumab Initiate treatment with thyroid replacement hormone Monitor TSH closely Consider patient referral to endocrinologist Resume atezolizumab when symptoms are controlled and thyroid function is improving
Grade 3 and 4 hypothyroidism	Withhold atezolizumab Initiate treatment with thyroid replacement hormone Monitor TSH closely Refer to an endocrinologist If patient develops myxedema (bradycardia, hypothermia and altered mental status), admit to hospital Resume atezolizumab when symptoms are controlled and thyroid function is improving In case of Grade 4 immune-mediated hypothyroidism, permanently discontinue atezolizumab and contact the sponsor [c]
Grade 1 hyperthyroidism	Consider patient referral to endocrinologist TSH ≥ 0.1 mIU/L and < 0.5 mIU/L: Continue atezolizumab Monitor TSH every 4 weeks TSH < 0.1 mIU/L: Follow guidelines for Grade 2 hyperthyroidism
Grade 2 hyperthyroidism	Consider withholding atezolizumab Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed Consider patient referral to endocrinologist Resume atezolizumab when symptoms are controlled and thyroid function is improving
Grade 3 and 4 hyperthyroidism	Withhold atezolizumab Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed Refer to endocrinologist Resume atezolizumab when symptoms are controlled and thyroid function is improving In case of Grade 4 immune-mediated hyperthyroidism, permanently discontinue atezolizumab and contact the sponsor [c]

Table 7–8: Management guidelines for endocrine events

Event	Management
Symptomatic adrenal insufficiency Grade 2-4	Withhold atezolizumab [a]
	Refer patient to endocrinologist
	Perform appropriate imaging
	Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement
	Resume atezolizumab if event resolves to Grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks [a, b]
	Permanently discontinue atezolizumab and contact sponsor if event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks [a, b, c]
Hyperglycemia, Grade 1 or 2	Continue atezolizumab
	Initiate treatment with insulin if needed
	Monitor for glucose control
Hyperglycemia, Grade 3 or 4	Withhold atezolizumab
	Initiate treatment with insulin
	Monitor for glucose control
	Resume atezolizumab when symptoms resolve and glucose levels are stable

i.v. = intravenous; mIU = Milli international unit; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.
a: If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
b: Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor.
c: Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions are an identified risk of atezolizumab. Severe cutaneous adverse reactions are a heterogeneous group of immunologically mediated drug eruptions frequently associated with drug use including immune checkpoint inhibitors as a class. Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalised exanthematous pustulosis, SJS, TEN, and drug rash with eosinophilia and systemic symptoms.

The management of severe cutaneous adverse reactions will be as follows:

- For suspected severe cutaneous adverse reactions, refer patients to a dermatologist for further diagnosis and management

- Withhold atezolizumab for patients with suspected SJS or TEN
- Withdraw atezolizumab permanently for any grade confirmed SJS or TEN
- Use caution when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions

For further details, refer to the latest version of the investigator's brochure of atezolizumab.

Other immune-related adverse reactions including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré, myocarditis, ocular inflammatory toxicity, pancreatitis, including increases in serum amylase and lipase levels, and myositis have occurred in patients treated with atezolizumab. For management guidelines of ocular toxicity, refer to Section 7.4.3.2.3.

Meningitis / encephalitis

Monitor patients for clinical signs and symptoms of meningitis or encephalitis.

Permanently discontinue atezolizumab for any grade of meningitis or encephalitis. Treat with i.v. steroids (1–2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once the patient has improved. When symptoms improve to ≤ Grade 1, taper steroids over ≥ 1 month.

Motor and sensory neuropathy

Monitor patients for symptoms of motor and sensory neuropathy. Management guidelines for neurologic disorders are presented in Table 7–9.

Table 7–9: Management guidelines for neurologic disorders

Event	Management
Immune-mediated neuropathy, Grade 1	Continue atezolizumab. Investigate etiology. Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Table 7–9: Management guidelines for neurologic disorders

Event	Management
Immune-mediated neuropathy, including facial paresis, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset. [a] Investigate etiology and refer patient to neurologist. Initiate treatment as per institutional guidelines. For general immune-mediated neuropathy: If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor. [c] For facial paresis: If event resolves fully, resume atezolizumab [b] If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	Permanently discontinue atezolizumab and contact the sponsor. [c] Refer patient to neurologist. Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	Permanently discontinue atezolizumab and contact the sponsor. Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or i.v. prednisone.
Immune-mediated myelitis, Grade 1	Continue atezolizumab unless symptoms worsen or do not improve. Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	Permanently discontinue atezolizumab and contact the sponsor. Investigate etiology and refer patient to a neurologist. Rule out infection. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	Permanently discontinue atezolizumab and contact the sponsor Refer patient to a neurologist. Initiate treatment as per institutional guidelines.

a Atezolizumab may be withheld for a longer time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The sponsor is available to advise as needed.

b If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The sponsor is available to advise as needed.

Infections

Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage occurred in patients receiving atezolizumab. Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold atezolizumab for ≥ Grade 3 infection.

Pancreatitis

Symptomatic pancreatitis without an alternative etiology occurred in clinical trials of atezolizumab. Monitor patients for signs and symptoms of acute pancreatitis.

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylases and lipase tests.

See Table 7–10 for management guidelines for pancreatic events, including pancreatitis.

Table 7–10: Management guidelines for pancreatic events, including pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2 1.5–2.0 × ULN	Continue atezolizumab. Monitor amylase and lipase weekly. For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 2 > 2.0–5.0 × ULN, Grade 3 or 4	Withhold atezolizumab. Refer patient to gastrointestinal specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with 1−2 mg/kg/day oral prednisone or equivalent. Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] Permanently discontinue atezolizumab and contact sponsor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] For recurrent events, permanently discontinue atezolizumab and contact sponsor. [c]
Immune-related pancreatitis, Grade 2 or 3	Withhold atezolizumab. Refer patient to gastrointestinal specialist. Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] Permanently discontinue atezolizumab and contact sponsor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] For recurrent events, permanently discontinue atezolizumab and contact sponsor. [c]

Table 7–10: Management guidelines for pancreatic events, including pancreatitis

Event	Management
Immune-related pancreatitis, Grade 4	Permanently discontinue atezolizumab and contact sponsor. [c] Refer patient to gastrointestinal specialist. Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ULN = upper limit of normal
a: If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
b: Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor.
c: Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

Immune-mediated cardiac events

Immune-mediated cardiac events include immune-mediated myocarditis and immune-mediated pericardial disorders.

Immune-mediated myocarditis

Immune-mediated myocarditis is an important identified risk associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g. patient may recall a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients suspected for possible myocarditis should be urgently evaluated with cardiac enzymes, ECG, chest X-ray, echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered for definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to guidelines in the Table 7–11.

Immune-mediated pericardial disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis. Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability. Patients should be evaluated for other

causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 7–11. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 7–11: Management guidelines for immune-mediated cardiac events

Event	Management
Immune-mediated myocarditis, Grades 2–4 and immune-mediated pericardial disorders, Grades 2–4	Permanently discontinue atezolizumab and contact sponsor. [c] Refer patient to cardiologist; initiate treatment as per institutional guidelines and, as needed, consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis as appropriate. Initiate treatment with 1–2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = Extracorporeal membrane oxygenation; i.v. = Intravenous(ly); VAD = Ventricular assist device.

Immune-related nephritis

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 7–12.

Table 7–12: Management guidelines for renal events

Event	Management
Renal event, Grade 1	Continue atezolizumab. Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset. [a] Refer patient to renal specialist. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact sponsor. [c]
Renal event, Grade 3 or 4	Permanently discontinue atezolizumab and contact sponsor. Refer patient to renal specialist and consider renal biopsy. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor.
b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

Immune-related myositis

Immune-related myositis is an important identified risk associated with the use of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine-kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle-biopsy. One etiology of myositis is immune-mediated, which is the current concern with atezolizumab.

Refer to Table 7–13 for detailed management guidelines of immune-mediated myositis.

Table 7–13: Management guidelines for immune-related myositis

Event	Management
Immune-related myositis, Grade 1	Continue atezolizumab Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines.
Immune-related myositis, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset [a] and contact sponsor. Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Consider treatment with corticosteroid equivalent to 1-2 mg/kg/day i.v. methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact sponsor. [c]
Immune-related myositis, Grade 3	Withhold atezolizumab for up to 1 weeks after event onset [a] and contact sponsor. Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day i.v. methylprednisolone or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisolone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact sponsor. [c] For recurrent events, treat as a Grade 4 event.
Immune-related myositis, Grade 4	Permanently discontinue atezolizumab and contact sponsor. [c] Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day i.v. methylprednisolone or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limiting mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

Table 7–13: Management guidelines for immune-related myositis

Event	Management
	If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

i.v. = intravenous
a: Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor.
b: If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
c: Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor.

Systemic immune activation

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents. SIA should be included in the differential diagnosis for patients who, in absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab.

Recommendations regarding early identification of SIA are provided below. In event of suspected SIA, the sponsor should be contacted immediately for additional guidance and study treatment should be interrupted. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

Early disease recognition is critical, and the clinician should consider SIA if, in absence of alternative etiologies, ≥ 2 of the following are present:

- Hypotension refractory to aggressive i.v. fluid challenge. May/can require vasopressin support
- Respiratory distress requiring aggressive supportive care. Supplemental oxygen, possible intubation.
- Fever greater than 38.5°C
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Unexplained laboratory abnormalities (change from baseline):
- Cytopenia (≥ Grade 2 in two or more lineage), significant transaminitis, coagulopathy, elevated creatinine.

Initial evaluation should include CBC with peripheral smear, PT, PTT, fibrinogen, D-dimer, ferritin, triglyceride, AST/ALT, total bilirubin, LDH, and a complete neurologic and abdominal examination (assess for hepatosplenomegaly).

If cytopenia (≥ 2 lineages and change from baseline) are present or ferritin is ≥ 3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy/aspirate (assess for evidence of hemophagocytosis)
- sCD25 (soluble IL-2 receptor)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus and herpes-simplex virus evaluation (evaluate for reactivated or active disease)

SIA is a clinical syndrome characterized by the following:

- Onset greater than 24 hours after exposure to drug, *and*
- Progressive clinical deterioration in an acutely ill patient (in absence of an alternate etiology), *and*
- Involving multiple organs (≥ 2), *and*
- Demonstrating specific laboratory abnormalities.

Diagnosis of SIA should only be made in patients who present with a constellation of clinical findings as outlined above and who fulfill the following established diagnostic criteria in the absence of an alternate etiology.

7.4.4 Treatment duration

Patients will continue dosing of both study drugs (rogaratinib and atezolizumab) until any of the following occurs:

- Radiological disease progression according to RECIST v1.1
    - At the investigator discretion, study treatment may continue beyond radiological progression as defined by RECIST v1.1 (e.g. in case of suspected pseudoprogression) 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
- Consent withdrawal
- 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 – Part A will be conducted in an open-label fashion.

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 study file; 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 drugs via the IxRS. The personnel will use the study drugs only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drugs 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.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned drug will be provided.

7.7 Treatment compliance

For treatment compliance oral administration of the morning dose of rogaratinib on Cycle 1 Days 1, 2, 8 and 15, and on Day 1 of subsequent cycles and every administration of atezolizumab will be done under supervision of site staff. This person will ascertain and document that the patient receives the treatment as planned. The information of each administration, such as dosing date, time and the administered dose, will be recorded in the eCRF. Patient compliance includes a willingness to comply with all aspects of the protocol, and to have blood collected for all safety and pharmacokinetic evaluations. Furthermore, patients need to agree with analysis of FGFR1/3 mRNA expression obtained from their own fresh or archival tumor tissue. Providing a fresh or archival tumor biopsy at FGFR testing is mandatory. Patients may be discontinued from the study for non-compliance with study procedures, at the discretion of the investigator or sponsor.

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

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.

The preparation and administration of atezolizumab will be performed by members of the investigator team during hospitalization and site visits.

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.

Every interruption/delay or reduction of the study treatment, regardless of the duration needs to be recorded.

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

8. Non-study therapy

8.1 Prior and concomitant therapy

All therapies specified as exclusion criteria (Section 6.2), except antibiotics, are also prohibited throughout the entire course of the study.

Therapeutic monitoring should be performed consistent with the local clinical standard of care following dose modification of study treatment. In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination.

All concomitant medications (including start / stop dates, total daily dose, and indication) must be recorded in the patient's source documentation and in the eCRF. Concomitant use of contrast media need not be recorded unless the patient experiences an AE and there is a reasonable possibility that the event might have been caused by exposure to contrast media.

Please refer also to atezolizumab label for guidance when prescribing with other medications.

Prohibited and discouraged concomitant therapy

Concomitant therapy with the following medication is **prohibited**:

- Concomitant use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 (listed in Appendix 16.1) are not permitted for 2 weeks prior to start of study treatment or during the study.
- Concomitant use of herbal preparations containing CYP3A4 inducers (e.g. St John's Wort) are not permitted during the study.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.
- 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 (34).
- Please refer atezolizumab package insert for guidance on prohibited concomitant medications.

Concomitant therapy with the following medication is **discouraged**:

- Patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.
- Initiation or increased dose of granulocyte colony-stimulating factors (e.g. granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) should be avoided. However use of granulocyte colony-stimulating factors is allowed for therapeutic intent at the discretion of the investigator and according to international guidelines and /or local standard of care.
- 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.
- Fluconazole is considered a moderate to strong inhibitor of CYP2C9 and should be avoided, if possible.

Permitted concomitant therapy

Concomitant therapy with the following medication is **allowed**:

- Supportive care for any underlying illness or for treatment-related toxicity (e.g. blood transfusion, platelet transfusion), if clinically indicated or at the investigator's discretion.
- All medication and therapies which are considered necessary for the patient's welfare, and which are not expected to interfere with the evaluation of the study drug, including antibiotics, may be given at the discretion of the investigator.
- Additional concomitant medications such as low dose heparin, gonadotropin releasing hormone agonist or antagonist, antihistamines and intravenous fluid supply, if clinically indicated
- Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists).
- Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunological effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the sponsor. If feasible, alternatives to corticosteroids should be considered. Pre-medication may be administered for Cycles ≥ 2 at the discretion of the treating physician after

consultation with the sponsor. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids and mineralocorticoids (e.g. fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

- Influenza vaccination should be given during influenza season only (approximately October to March in most regions). Patients must not receive live, attenuated influenza vaccine within 28 days prior to start of study treatment, during treatment, or within 90 days following the last dose of atezolizumab. Patients may receive inactivated vaccines.
- COVID-19 vaccines are allowed during study treatment. Vaccines based on mRNA technology are preferred, but also live, attenuated vaccines can be allowed if deemed appropriate for cancer patients.
- Patients taking narrow therapeutic index medications should be monitored proactively as per local standard of care.
- Antiemetic therapy is allowed.
- Bisphosphonates or denosumab with supplement of calcium and vitamin D.
- Treatment with “non-conventional therapies” (such as acupuncture), and vitamin / mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator (to be documented in the source notes and in the eCRF).
- Palliative radiotherapy for pain control (e.g. treatment of known bony metastases). Radiotherapy to target lesions is not allowed.

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 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 or any other form of continued study drug supply with no cost to the patient is established, the present study will end when all patients have transitioned into the roll-over study or any other form of continued study drug supply with no cost to the patient, 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

In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements.

9.1 Tabular schedule of evaluations

Tabular schedule of pre-treatment activities is presented in Table 9–1.

Tabular schedule of treatment and follow-up activities is presented in Table 9–2.

Table 9–1: Schedule of evaluations: Pre-treatment period (FGFR testing and screening)

Measures / actions	Pre-treatment		
	FGFR testing	Screening	
		Relative to first study drug administration	
		Within 28 days before*	Within 7 days before*
Signed informed consent	●[a1]	●[a2]	
Inclusion / exclusion criteria	●[b]	●	●
Tumor material for FGFR testing and additional biomarkers analyses (archival tissue sample or fresh biopsy)[c]	●		
Demographic data	●		
Complete medical / oncological history		●	
Baseline characteristics[d], including:			
Documentation of primary diagnosis (refractory, locally advanced or metastatic solid tumor) using complete pathological report	●		
Prior anti-cancer therapy[e]	●	●	
TNM classification (AJCC 8th edition)	●	●	
Existence of liver metastases (absence *vs.* presence)		●	
Existence of visceral metastases (absence *vs.* presence)		●	
Alcohol and smoking history/habits		●	
Karnofsky performance status		●	
Physical examinations		●	
Body height		●	
Body weight		●	
12-lead ECG[f]		●	
Vital signs (incl. body temperature, heart rate, RR, BP)		●	
ECOG performance status	●	●	
Ophthalmologic examination		●	
Chest X-ray[g]		●	
Blood / urine collection for safety laboratory tests[h]			●
Hormone panel (thyroid function tests [TSH, free T3 and free T4])			●
Calculation of eGFR (MDRD abbreviated formula)			●
Serum pregnancy test (in females with childbearing potential)			●
Blood sampling for plasma-based biomarker analyses[i]			●
Tumor assessment (CT / MRI scans)[j]		●	

Table 9–1: Schedule of evaluations: Pre-treatment period (FGFR testing and screening)

Measures / actions	Pre-treatment		
	FGFR testing	Screening	
		Relative to first study drug administration	
		Within 28 days before*	Within 7 days before*
Concomitant medication[k]		●	●
Toxicity / AE assessment[l]	●		●
PRO questionnaire (EORTC QLQ-C30)		●	

AE = Adverse event; AJCC = American Joint Committee on Cancer; BP = Blood pressure; CT = Computed tomography; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = Electronic case report form; eGFR = Estimated glomerular filtration rate; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer 30 item Quality of Life Questionnaire; FGFR = Fibroblast growth factor receptor; iRECIST = RECIST modified for immune-based therapeutics; MDRD = Modification of Diet in Renal Disease; MRI = Magnetic resonance imaging; PI/ICF = Patient information/informed consent form; PRO = Patient reported outcomes; RECIST = Response Evaluation Criteria In Solid Tumors; RR = Respiratory rate; SAE = Serious adverse event; T3 = Triiodothyronine; T4 = Thyroxine; TNM = Classification of malignant tumors (Tumor, lymph nodes, metastasis); TSH = Thyroid-stimulating hormone.

* Pre-study examinations may require hospitalization for 1-2 days.

a1: Informed consent for FGFR testing (including consent for exploratory biomarker analyses).

a2: Informed consent for study treatment eligibility must be signed before the 28-day screening phase.

b: Selected inclusion and exclusion criteria are to be checked prior to FGFR testing. See Sections 6.1 and 6.2.

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 and exploratory tumor-based biomarker analyses in all enrolled patients.

d: Refer to Section 9.3.3 for the baseline characteristics to be collected.

e: At FGFR testing, prior therapies for the study indication are collected. At screening, study disease characteristics and prior therapies for the study indication are updated if applicable, and non-study-indication-related medications collected.

f: At screening, ECG readings (in the supine position) should be performed in triplicate in close sequence and not more than 2 minutes apart.

g: The screening chest X-ray may be substituted with a chest X-ray that had been performed as part of the patient's previous routine care in the 3 months before start of study treatment.

h: Safety laboratory tests include clinical chemistry panel, hematology panel, coagulation panel, and urinalysis. Please refer to Section 9.6.3.1 for more detailed information of the tests to be collected.

i: The blood samples are intended for isolation of plasma to study tumor markers circulating in blood (see Section 9.7.1).

j: The radiological evaluation must include computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest, abdomen and pelvis with contrast media. A CT scan or MRI of the brain is required at screening to rule out brain metastases. Further CT scan or MRI of the brain only need to be repeated if metastases or symptoms are present. Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before start of study treatment and performed according to the Imaging Manual. Formal efficacy assessment will be done according to RECIST v1.1. iRECIST will be assessed as exploratory endpoint.

k: 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.

l: 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. Any new finding or worsening of any ongoing medical history condition after the patient has signed the informed consent for study treatment eligibility must be recorded as an AE/SAE.

Table 9–2: Schedule of evaluations: Treatment and follow-up periods

	Treatment									Follow-up[x]	
	Cycle 1 21 days				Cycle 2-4 21 days per cycle			Cycle ≥ 5 21 days per cycle	EOT Within 14 days after permanent discon-tinuation of treatment[v]	Active FU visit	Long-term FU (phone call)
Day (D)	D1	D2	D8	D15	D1[a]	D8	D15	D1		At least 30 days after last dose[v]	Every 3 months
Time window (days)			±1	±1	±2	±2	±2	±2		+7	±14
Safety											
Toxicities / AE assessment[b]	●	●	●	●	●	●	●	●	●	●[w]	
Physical examinations	●	●	●	●	●	●	●	●	●	●	
Body weight	●			●	●			●	●		
12-lead ECG[c]	●	●		●	●			●[c]	●[c]		
Vital signs (incl. body temperature, heart rate, RR, BP)[d]	●	●	●	●	●	●	●	●	●	●	
ECOG performance status	●	●	●	●	●	●	●	●	●		
Changes in vision[e]	●	●	●	●	●	●	●	●	●	●	
Ophthalmologic examination[f]					●			●	●		
Blood samples for safety laboratory tests[g]	●		●	●	●	●	●	●	●	●	
Hormone panel (thyroid function tests [TSH, free T3 and free T4])[h]	●				●			●	●		
Dipstick urinalysis[i]	●				●						

Table 9–2: Schedule of evaluations: Treatment and follow-up periods

	Treatment									**Follow-up[x]**	
	Cycle 1 21 days				**Cycle 2-4** 21 days per cycle			**Cycle ≥ 5** 21 days per cycle	**EOT** Within 14 days after permanent discon-tinuation of treatment[v]	**Active FU visit** At least 30 days after last dose[v]	**Long-term FU (phone call)** Every 3 months
Day (D)	**D1**	**D2**	**D8**	**D15**	**D1[a]**	**D8**	**D15**	**D1**			
Time window (days)			±1	±1	±2	±2	±2	±2		+7	±14
Calculation of eGFR (MDRD abbreviated formula)	•		•	•	•	•	•	•	•		
Urine pregnancy test (in females with childbearing potential)[j]	•				•						
Pharmacokinetics											
Blood samples for rogaratinib PK[k]	•→				•			•			
Blood samples for atezolizumab PK[l]	•→			•							
Medication											
Concomitant medication[m]	•	•	•	•	•	•	•	•	•	•	
Drug accountability[n]					•			•			
Dispense/return of rogaratinib and diary[n]	•				•			•	•		
Administration of rogaratinib[o]	Continuously twice daily until EOT										
Administration of atezolizumab	•				•			•			

Table 9–2: Schedule of evaluations: Treatment and follow-up periods

	Treatment									**Follow-up[x]**	
	Cycle 1 21 days				**Cycle 2-4** 21 days per cycle			**Cycle ≥ 5** 21 days per cycle	**EOT** Within 14 days after permanent discon-tinuation of treatment[v]	**Active FU visit** At least 30 days after last dose[v]	**Long-term FU (phone call)** Every 3 months
Day (D)	**D1**	**D2**	**D8**	**D15**	**D1[a]**	**D8**	**D15**	**D1**			
Time window (days)			±1	±1	±2	±2	±2	±2		+7	±14
Efficacy											
Tumor assessment (CT/MRI scans)[p]	Every 14 weeks (± 14 days)								●[q]	Every 14 weeks[r] applies only to patients who discontinued without progressive disease	
Others											
PRO questionnaire (EORTC QLQ-C30)[s]	●				●						
Blood sampling for plasma-based biomarker analyses[t]	●				●				●		
Additional tumor biopsy (optional)[u]	During Cycle 2 or later and/or at the time of radiological progression										
Subsequent systemic anti-cancer therapy										●	●
Survival status											●

Table 9–2: Schedule of evaluations: Treatment and follow-up periods

AE = Adverse event; AESI = Adverse event of special interest; BP = Blood pressure; CT = Computed tomography; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = Electronic case report form; eGFR = Estimated glomerular filtration rate; EOI = End of infusion; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer 30 item Quality of Life Questionnaire; EOT = End of treatment; FU = Follow-up; iRECIST = RECIST modified for immune-based therapeutics; MDRD = Modification of Diet in Renal Disease; MRI = Magnetic resonance imaging; PI/ICF = Patient information/informed consent form; PK = Pharmacokinetics; PRO = Patient reported outcomes; RECIST = Response Evaluation Criteria In Solid Tumors; RPED = Retinal pigment epithelial detachment; RR = Respiratory rate; SAE = Serious adverse event; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid-stimulating hormone; → = several samplings during the day.

a: Only in Cycle 2, time window should be +1.

b: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.

c: During the treatment period, ECGs are to be performed according to the following schedule: on Cycle 1 Day 1 before study drug administration and 2, 3, and 24 hours after the first dose (i.e. before Cycle 1 Day 2 morning dose), on Cycle 1 Day 15 before morning dose and 2 and 3 hours thereafter, on Cycle ≥ 2 Day 1 up to 1 hour after morning dose. See also Section 9.6.3.4. After primary completion, C ≥5 and EOT evaluations are optional and at the investigator's discretion.

d: Refer to Section 9.6.3.5 for specific instructions on vital signs measurements.

e: Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7).

f: Ophthalmologic examination will be performed on Day 1 of every 4th cycle, starting at Cycle 2. At the EOT visit, ophthalmologic examination will be done only in case the patient reports changes in vision. A time window of -7 days is allowed. Patients who experience any decrease in visual acuity, ocular pain or discomfort, or any retinal disorders including retinal detachment / RPED / central serous retinopathy / retinal vein occlusion have to undergo ophthalmologic examinations on Day 1 of every cycle. See Section 9.6.3.7 for more guidance on ophthalmological examinations, Section 7.4.3.2.3 for dose modification of rogaratinib in case of retinal disorders, and Section 9.6.1.6 for AESI reporting.

g: Safety laboratory tests include clinical chemistry panel, hematology panel and coagulation panel. Please refer to Section 9.6.3.1 for more detailed information of the tests to be collected. Safety laboratory tests can be collected up to 2 days prior to drug administration. In patients with an elevated serum phosphate levels (≥ 7 mg/dL) phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).

h: Hormone panel (thyroid function test) is to be performed on Cycle 1 Day 1 and thereafter on Day 1 of every 3rd cycle (i.e. Cycles 4, 7, 10, 13 etc.), prior to atezolizumab infusion. Hormone panel can be collected up to 2 days prior to drug administration. After primary completion, hormone panel (thyroid function test) should be done periodically, according to local standard of care.

i: Dipstick urinalysis can be collected up to 2 days prior to drug administration. Additional microscopic examinations will be performed if clinically indicated.

j: Urinary pregnancy tests will be performed on Day 1 of each cycle during treatment. Pregnancy test to be repeated as frequently as required by local regulations. A serum pregnancy test must be performed if the urine pregnancy test is positive. After primary completion, pregnancy tests will no longer be required if there are no active patients of child-bearing potential.

k: Rogaratinib PK samples will be collected on Cycle 1 Day 1 (Single dose PK): Pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose (to be taken before the evening dose of rogaratinib), and on Cycles 2 to 5, Day 1 (exposure-response modeling): pre-dose (before supervised dose administration), and 1 (± 0.5) hour post-dose.

l: For monitoring purposes of atezolizumab, blood (plasma) samples will be collected at the following time points: at Cycle 1 Day 1: pre-dose, 1 (EOI), 4 and 8

Table 9–2: Schedule of evaluations: Treatment and follow-up periods

hours post-dose; and at Cycle 1 Day 15: approximately 336 hours post-dose.

m: 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.

n: To have complete control over the distribution and use of the study drug, the drug accountability must be performed before new medication is handed out to the patient. Return of rogaratinib and diary at EOT visit.

o: Patients will receive their initial single-dose of 800 mg rogaratinib in the morning of Cycle 1 Day 1, followed by serial PK blood sampling for 8 hours and a second dose of 800 mg rogaratinib in the evening. Rogaratinib will be administered continuously twice daily on all 21 days in each cycle. Oral administration of the morning dose of rogaratinib on Cycle 1, Days 1, 2, 8 and 15, and on Day 1 of subsequent cycles will be done with a member of the site.

p: The radiological evaluation must include computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis with contrast media. Tumor assessments (CT or MRI) are to be done every 9 weeks (± 7 days) starting from Cycle 1 Day 1 until confirmed radiological disease progression or end of the study. After primary completion, scans will be performed every 14 weeks (±14 days). A minimum of at least 9 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment. Formal efficacy assessment will be done according to RECIST v1.1. iRECIST will be assessed as exploratory endpoint.

q: Radiological tumor evaluation (within 14 days after permanent discontinuation of 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).

r: For patients who discontinue study treatment without confirmed radiological 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 every 14 weeks ± 14 days (from the previous scan date).

s: Questionnaire is to be completed before the patient meets with a clinician and before any examination or test is performed on that day. Questionnaire is to be completed at screening and before primary completion on Day 1 of every cycle, at the EOT visit, and at the safety assessment visit of the active follow-up. After primary completion, questionnaire will not be done.

t: The blood samples are intended for isolation of plasma to study tumor markers circulating in blood (see Section 9.7.1). Until primary completion, during the treatment cycles, plasma samples are to be collected on Day 1 of each cycle before administration of study drugs, and at the EOT visit. After primary completion, blood sampling for plasma-based biomarker analyses will not be done except at the EOT visit.

u: An optional tumor biopsy is highly encouraged to be taken during Cycle 2 or later and/or at the time of disease progression or recurrence as per investigator's decision, if technically feasible (see Section 9.7.1).

v: 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.

w: 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. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated. 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.

x: After primary completion, follow-up information will not be collected after the safety assessment visit.

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 as part of the standard of practice at any time during the course of their disease prior to the informed consent date and time, may also be used.

9.2.1.1 FGFR testing

FGFR testing of patients will be performed at the investigator's discretion prior to start of screening (signing of informed consent for study treatment eligibility). Investigators should ensure all patients will be eligible in terms of clinical condition, disease status and lines of treatment.

The following procedures will be performed prior to FGFR testing:

- Signed PI/ICF for FGFR testing (including consent for exploratory biomarker analyses) (see Section 13.4.1).
- Register patient (a unique patient identifier will be assigned)
- Check inclusion and exclusion criteria for FGFR testing (see Section 6.1 for inclusion criteria and Section 6.2 for exclusion criteria).
    - If a patient does not meet the selection criteria for FGFR testing, register the patient as a 'FGFR testing failure' (those that are FGFR test negative and/or those that do not meet the inclusion/exclusion criteria for FGFR testing) 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 tissue for FGFR testing
    - Patients who submit TURBT specimens will be required to submit specimens containing muscle invasive component of the bladder tumor as verified by pathology review. If the TURBT specimens do not contain a muscle invasive component (i.e. T2 or greater), the specimens obtained at the time of cystectomy/nephroureterectomy or metastatic spread (i.e. sample from a metastatic lesion) will be required. An archival specimen, if available, should also be submitted.
    - 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. The tumor material should be derived by a biopsy procedure associated with a non-significant risk. See more details in Section 9.7.1.
    - Tissue will be used for central FGFR testing and exploratory tumor-based biomarker analyses in all enrolled patients (see Section 9.7.1).

- Document study disease characteristics (including TNM classification) 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 9.6.3.6)
- 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.

The following procedure will be performed after FGFR testing:

- For patients not meeting the eligibility criterion "high FGFR expression level" following confirmation by the central lab: record the patient as a 'FGFR testing failure' (those that are FGFR test negative and/or those that do not meet the inclusion/exclusion criteria for FGFR testing).

9.2.1.2 Screening

After confirmation of high FGFR1 or 3 mRNA expression level (RNA scope score of 3+ or 4+; measurement is part of this protocol) 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 PI/ICF for study treatment eligibility (Section 13.4.2). Note: Pre-study examinations may require hospitalization for 1-2 days.

The following screening procedures will be performed **within 28 days before first study drug administration**:

- Signed PI/ICF for study treatment eligibility (see Section 13.4.2)
- Register confirmation that PI/ICF for study treatment eligibility has been signed and that the patient has started screening.
- Check 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 the selection criteria for study treatment eligibility, register the patient as a 'screening failure' and additionally provide the reason, if applicable in the eCRF.
- PRO questionnaire (EORTC QLQ-C30) (see Section 9.7.2)
    - Questionnaire is to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- Update study disease characteristics (including TNM classification and existence of liver and visceral metastases), determine Karnofsky performance status (see Section 9.6.3.6),

and document previous therapy for urothelial carcinoma including outcome, and alcohol and smoking history/habits (see Section 9.3.3).

- Document medical history (see Section 9.3.2) and non-study-indication-related medications (see Section 9.3.3).
- Tumor assessment (CT or MRI) according to RECIST v1.1 and iRECIST (see Section 9.4).
    - Note: Screening assessment includes imaging of the brain.
- Send patient for ophthalmological examination (see Section 9.6.3.7)
    - In case of any findings, see Section 9.6.3.7.
- 12-lead ECG (see Section 9.6.3.4)
    - At screening, ECG readings (in the supine position) should be performed in triplicate in close sequence and not more than 2 minutes apart.
- Measure body height, weight. Additionally, BMI will be derived by the sponsor. See Section 9.6.3.3.
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- ECOG PS (see Section 9.6.3.6)
- Measure vital signs, including blood pressure, heart rate, respiratory rate and body temperature (see Section 9.6.3.5)
- Perform chest X-ray (see Section 9.6.3.8)
    - Note: the screening chest X-ray may be substituted with a chest X-ray that had been performed as part of the patient's previous routine care in the 3 months before start of study treatment.
- Record concomitant medications (see Section 8.1)
    - Note: 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.

The following screening procedures will be performed **within 7 days before first study drug administration**:

- Check 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 the selection criteria for study treatment eligibility, register the patient as a 'screening failure' and additionally provide the reason, if applicable in the eCRF.

- Collect blood/urine for safety laboratory tests including clinical chemistry, hematology and coagulation panels and urinalysis (see Section 9.6.3.1).
- Collect blood for hormone panel (thyroid function tests) (see Section 9.6.3.1).
- Blood sampling for plasma-based biomarker analyses.
  - Note: the blood samples are intended for isolation of plasma to study tumor markers circulating in blood (see Section 9.7.1).
- 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.
- 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).
  - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Record concomitant medications (see Section 8.1)
  - Note: 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.

9.2.2 Treatment period

For tumor assessments to be performed during the treatment period, see Section 9.2.2.4.

An optional tumor biopsy is highly encouraged to be taken during Cycle 2 or later and/or at the time of disease progression or recurrence as per investigator's decision, if technically feasible (see Section 9.7.1).

9.2.2.1 Cycle 1

Day 1 of Cycle 1

- PRO questionnaire (EORTC QLQ-C30) (see Section 9.7.2)
    - Questionnaire is to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5):
    - BP, HR and RR: 60 minutes before, every 15 (±5) minutes during, and 30 (±10) minutes after atezolizumab infusion.
    - Body temperature
- Measure body weight
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood/urine for safety laboratory tests including clinical chemistry, hematology and coagulation panels and urinalysis (see Section 9.6.3.1).
    - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Collect blood for hormone panel (thyroid function tests) (see Section 9.6.3.1).
    - Note: blood to be collected prior to atezolizumab administration.
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Urine pregnancy test in women of childbearing potential (see Sections 9.6.2 and 9.6.3.1).
    - Note: Pregnancy test to be repeated as frequently as required by local regulations. A serum pregnancy test must be performed if the urine pregnancy test is positive.
- 12-lead ECG (see Section 9.6.3.4)
    - Note: before and 2, 3 hours after morning dose
- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7)
- Review concomitant medications (see Section 8.1)
    - Note: 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.

- Blood (plasma) samples for PK assessments (see Section 9.5 for further guidance and time windows)
    - Rogaratinib PK:
        - Cycle 1 Day 1 (Single dose PK): pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose (to be taken before the evening dose of rogaratinib).
    - Atezolizumab PK:
        - pre-dose, and 1 (EOI), 4 and 8 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 circulating in blood (see Section 9.7.1). During the treatment cycles, plasma samples are to be collected before administration of study drugs.
- Dispense rogaratinib
- Rogaratinib administration orally (see Section 7.4)
    - Note: Oral administration of the morning dose of rogaratinib will be done with a member of the site.
- Atezolizumab administration i.v. (see Section 7.4)

Day 2 of Cycle 1

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5):
    - BP, HR and RR: before, and 1 and 2 hour(s) after morning dose
    - Body temperature
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- 12-lead ECG (see Section 9.6.3.4)
    - Note: 24 hours after first dose (i.e. before Cycle 1 Day 2 morning dose)
- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.

- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7)
- Review concomitant medications (see Section 8.1)
    - Note: 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.
- Rogaratinib administration orally (see Section 7.4)
    - Note: Oral administration of the morning dose of rogaratinib will be done with a member of the site.

Day 8 of Cycle 1

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs, including blood pressure, heart rate, respiratory rate and body temperature (see Section 9.6.3.5).
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).
    - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7)
- Review concomitant medications (see Section 8.1)
    - Note: 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.

- Rogaratinib administration orally (see Section 7.4)
    - Note: Oral administration of the morning dose of rogaratinib will be done with a member of the site.

Day 15 of Cycle 1

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5).
    - BP, HR and RR: before, and 1 and 2 hour(s) after morning dose.
    - Body temperature
- Measure body weight
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).
    - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- 12-lead ECG (see Section 9.6.3.4)
    - Note: before morning dose, and 2 and 3 hours thereafter
- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7)
- Review concomitant medications (see Section 8.1)
    - Note: 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.
- Blood (plasma) samples for PK assessments (see Section 9.5 for further guidance)
    - Atezolizumab PK:
        - Approximately 336 hours post-dose

- Rogaratinib administration orally (see Section 7.4)
    - Note: Oral administration of the morning dose of rogaratinib will be done with a member of the site.

9.2.2.2 Cycles 2 – 4

Day 1 of Cycle 2-4

- PRO questionnaire (EORTC QLQ-C30) (see Section 9.7.2)
    - Questionnaire is to be completed before the patient meets with a clinician and before any examination or test is performed on that day.
- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5):
    - BP, HR and RR: within 60 minutes before infusion and at the end of infusion
    - Body temperature
- Measure body weight
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood/urine for safety laboratory tests including clinical chemistry, hematology and coagulation panels and urinalysis (see Section 9.6.3.1).
    - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- On Cycle 4 only: collect blood for hormone panel (thyroid function tests) (see Section 9.6.3.1).
    - Note: blood to be collected prior to atezolizumab administration.
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Urine pregnancy test in women of childbearing potential (see Sections 9.6.2 and 9.6.3.1).
    - Note: Pregnancy test to be repeated as frequently as required by local regulations. A serum pregnancy test must be performed if the urine pregnancy test is positive.
- 12-lead ECG (see Section 9.6.3.4)
    - Note: up to 1 hour after morning dose
- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.

- Ask patient for changes in vision (at every visit of every cycle) and send patient (on Day 1 of every 2nd cycle, a time window of -7 days is allowed) for ophthalmological examination (see Section 9.6.3.7)
    - In case of any findings, see Section 9.6.3.7.
- Review concomitant medications (see Section 8.1)
    - Note: 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.
- Blood (plasma) samples for PK assessments (see Section 9.5 for further guidance)
    - Rogaratinib PK:
        - Cycles 2 to 5, Day 1 (for exposure-response modeling): pre-dose (before supervised dose administration), and 1 (± 0.5) hour 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 circulating in blood (see Section 9.7.1). During the treatment cycles, plasma samples are to be collected before administration of study drugs.
- Dispense rogaratinib
- Rogaratinib administration orally (see Section 7.4)
    - Note: Oral administration of the morning dose of rogaratinib will be done with a member of the site.
- Atezolizumab administration i.v. (see Section 7.4)
- Drug accountability

Day 8 of Cycle 2-4

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5).
    - BP, HR and RR: up to 1 hour after morning dose
    - Body temperature
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).

  - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Toxicity/AE assessment
  - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7)
- Review concomitant medications (see Section 8.1)
  - Note: 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.
- Rogaratinib administration orally (see Section 7.4)

Day 15 of Cycle 2-4

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5).
  - BP, HR and RR: Up to 1 hour after morning dose
  - Body temperature
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).
  - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Toxicity/AE assessment
  - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7)
- Review concomitant medications (see Section 8.1)

- Note: 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.

- Rogaratinib administration orally (see Section 7.4)

9.2.2.3 Cycles ≥ 5

Day 1 of Cycle ≥ 5

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs (see Section 9.6.3.5):
  - BP, HR and RR: within 60 minutes before infusion and at the end of the infusion
  - Body temperature
- Measure body weight
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).
  - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Every third cycle (Cycles 7, 10, 13 etc.): collect blood for hormone panel (thyroid function tests) (see Section 9.6.3.1). After primary completion, hormone panel (thyroid function tests) should be done periodically, according to local standard of care.
  - Note: blood to be collected prior to atezolizumab administration.
- Blood (plasma) samples for PK assessments (see Section 9.5 for further guidance)
  - Rogaratinib PK:
    - Cycle 5, Day 1 (for exposure-response modeling): pre-dose (before supervised dose administration), and 1 (± 0.5) hour post-dose.
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Urine pregnancy test in women of childbearing potential (see Sections 9.6.2 and 9.6.3.1).
  - Note: Pregnancy test to be repeated as frequently as required by local regulations. A serum pregnancy test must be performed if the urine pregnancy test is positive.
- Optional 12-lead ECG (see Section 9.6.3.4) (at the investigator's discretion)

- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision (at every visit of every cycle) and send patient (on Day 1 of every 4th cycle, a time window of -7 days is allowed) for ophthalmological examination (see Section 9.6.3.7)
    - In case of any findings, see Section 9.6.3.7.
- Review concomitant medications (see Section 8.1)
    - Note: 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.
- Dispense rogaratinib
- Rogaratinib administration orally (see Section 7.4)
    - Note: Oral administration of the morning dose of rogaratinib will be done with a member of the site.
- Atezolizumab administration i.v. (see Section 7.4)
- Drug accountability

9.2.2.4 Tumor assessments during treatment period

Scans (CT or MRI with contrast unless contraindicated) for tumor assessments according to RECIST v1.1 and iRECIST are to be done every 14 weeks (± 14 days) until radiological disease progression or end of the study. A minimum of at least 9 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment.

See Section 9.4 for further information on tumor assessments, and Appendix 16.2 for RECIST and iRECIST guidance.

9.2.2.5 End-of-treatment (EOT) visit

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

Note: If the study treatment was permanently discontinued after dose interruption/delay of more than 30 days, the active follow-up visit should also 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.

The following examinations will be done:

- ECOG PS (see Section 9.6.3.6)
- Measure vital signs, including blood pressure, heart rate, respiratory rate and body temperature (see Section 9.6.3.5).
- Measure body weight. Additionally, BMI will be derived by the sponsor. See Section 9.6.3.3.
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).
    - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Collect blood for hormone panel (thyroid function tests) (see Section 9.6.3.1). After primary completion, hormone panel (thyroid function test) should be done periodically, according to local standard of care.
- Blood sampling (pre-dose) for plasma-based biomarker analyses.
    - Note: the blood samples are intended for isolation of plasma to study tumor markers circulating in blood (see Section 9.7.1).
- Calculate eGFR according to MDRD abbreviated formula (see Appendix 16.4).
- Urine pregnancy test in women of childbearing potential (see Sections 9.6.2 and 9.6.3.1).
    - Note: Pregnancy test to be repeated as frequently as required by local regulations. A serum pregnancy test must be performed if the urine pregnancy test is positive.
- Optional 12-lead ECG (see Section 9.6.3.4) (at the investigator's discretion)
- Toxicity/AE assessment
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.
- Ask patient for changes in vision and send patient for ophthalmological examination in case the patient reports any changes in vision (see Section 9.6.3.7)
    - In case of any findings, see Section 9.6.3.7.
    - Note: 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.
- Tumor assessment (CT or MRI) according to RECIST v1.1 and iRECIST (see Section 9.4) (within 14 days after permanent discontinuation of 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).

- Review concomitant medications (see Section 8.1)
    - Note: 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.
- Return of rogaratinib and diary.

9.2.3 Follow-up periods

After primary completion, follow-up information will not be collected after the safety assessment visit.

9.2.3.1 Active follow-up

After permanent treatment discontinuation, a safety assessment visit must be scheduled for all patients at least 30 (up to +7) days after the last dose of study treatment. 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. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

The following examinations will be done **for all patients**:

- Measure vital signs, including blood pressure, heart rate, respiratory rate and body temperature (see Section 9.6.3.5).
- Perform physical examinations (see Section 9.6.3.2) including cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.
- Collect blood for safety laboratory tests including clinical chemistry, hematology and coagulation panels (see Section 9.6.3.1).
    - In patients with an elevated serum phosphate level (≥ 7 mg/dL), phosphate levels should be evaluated weekly until resolution (serum phosphate < 7 mg/dL).
- Toxicity/AE assessment.
    - Note: Chest X-ray should be done in case the patient shows symptoms of pulmonary toxicity.

- Ask patient for changes in vision. If change in vision is reported, an ophthalmological examination must be performed (see Section 9.6.3.7).
- Review of concomitant medications (see Section 8.1)
    - Note: 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.
- Document subsequent systemic anti-cancer therapy (if applicable)
- An optional tumor biopsy is highly encouraged to be taken during Cycle 2 or later and/or at the time of disease progression or recurrence as per investigator's decision, if technically feasible (see Section 9.7.1).

Additionally, up to primary completion, the following assessment is to be done **for patients who discontinue study treatment for reasons other than radiological disease progression:**

- Tumor assessment (CT or MRI) according to RECIST v1.1and iRECIST (see Section 9.4)
    - Note: During the active follow-up period, CT/MRI evaluations will be performed every 14 weeks ± 14 days (from the previous scan date) until disease progression and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met. No tumor assessments will be performed after primary completion.

9.2.3.2 Long-term follow-up

Long-term follow-up will not be performed after primary completion. All patients in the long-term follow-up period will be contacted (telephone contact by site is sufficient) every 3 months (±14 days) from completion of the active follow-up until the end of the study (i.e. until last patient's last visit [LPLV] (see Section 6.4.1.3)). 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. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

The information to be recorded at these contacts:

- Survival status
- Document subsequent systemic anti-cancer therapy (if applicable)

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

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

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** (i.e. all patients signing the PI/ICF for FGFR testing) during the FGFR testing period:

- Urothelial carcinoma diagnosis/classification including
    - date of initial diagnosis
    - type of assessment
    - date of the most recent progression / relapse
    - histology
    - location of primary cancer
    - TNM classification of urothelial carcinoma at study entry according to the AJCC 8th edition
    - grading at initial diagnosis

Prior systemic anti-cancer medications 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:

- Prior systemic anti-cancer medication.
- Liver metastases (absence *vs.* presence) and
- Visceral metastases (liver, bone, lung) (absence *vs.* presence)
- 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 4 weeks before start of study treatment 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.
- Review TNM classification (AJCC 8th edition)

- Karnofsky performance status (see Section 9.6.3.6)
- Alcohol and smoking habits/history

MSKCC categories and Bellmunt risk score

Prognostic factors have been identified for both first- and second-line treatment of patients with urothelial carcinoma. MSKCC established a prognostic model predicting overall survival in first-line urothelial carcinoma, which includes Karnofsky performance status (see Section 9.6.3.6) and visceral metastases as independent prognostic factors (35). For second-line the Bellmunt score defines ECOG performance status, hemoglobin level and liver metastases as main adverse prognostic factors for overall survival (36).

Bellmunt risk score will be derived by the sponsor based on the following parameters collected during screening assessments:

- Hemoglobin level < 10 g/dL *vs.* ≥ 10 g/dL
- ECOG PS 0 *vs.* ≥ 1
- Liver metastases absent *vs.* present

MSKCC categories will be derived by the sponsor based on the following parameters collected during screening assessments:

- Visceral metastases (liver, bone, lung) absent vs. present
- Karnofsky performance status ≥ 80% vs < 80 %

9.4 Efficacy

Patient survival will be followed up and tumor assessment will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) (with contrast unless contraindicated) to determine the efficacy variables of this study: objective response rate (ORR), disease control rate (DCR), duration of response (DOR), best overall response (CR, PR, SD, Non CR/Non PD, PD), progression-free survival (PFS) and overall survival (OS).

For definitions and analyses of the efficacy variables, please refer to Section 10.3.3.

Radiological tumor assessment

Radiological tumor assessments will be performed locally by investigators. All scan should be interpreted by the same radiologist/investigator during the study, where at all possible.

Tumor response will be measured using CT or MRI scans (with contrast unless contraindicated) and evaluated using RECIST v1.1 (37) (see Appendix 16.2) to determine the secondary efficacy variables (objective response rate [ORR], disease control rate [DCR] and duration of response [DOR], best overall response (CR, PR, SD, Non CR/Non PD, PD), and

progression-free survival [PFS]). According to RECIST v1.1, confirmation of PR and CR is not required considering the nature of the study and the protocol requirements.

In addition, modified RECIST v1.1 for immune-based therapeutics (iRECIST) will be documented as exploratory variables and used as supportive evidence for the detection of pseudoprogression and the determination of progressive disease for treatment decision (see (38) and Appendix 16.2).

To facilitate an independent evaluation of outcome in this study, tumor assessment imaging data will be collected, image quality controlled and stored for a potential central review of tumor evaluation by independent readers prior to the final efficacy analysis. The decision to perform the central review will be based on the outcome of the local efficacy assessments. Treatment decisions with immune-based therapeutics require assessment of the clinical presentation of patients that can only be performed by the investigator; therefore, central review will not be used for treatment decisions. Details will be outlined in the Image Review Charter. Images for tumor assessment, de-identified with respect to patient identification related privacy data (except study related subject identification number) will be collected for all patients enrolled at baseline and at all post-baseline evaluations and will be submitted for collection and image quality control to facilitate a potential central review. Specific information on image handling, imaging guidelines, instructions for image acquisition and image evaluation procedures will be outlined in the Imaging Manual for the study sites.

The first radiological tumor evaluation will be conducted during clinical screening within 28 days before start of study treatment (see Section 9.1). Tumor assessments are to be done every 9 weeks (± 7 days) starting from Cycle 1 Day 1 until radiological disease progression or end of the study. A minimum of at least 9 weeks from start of treatment is mandatory for the 1st "on treatment" tumor assessment.

For patients who discontinue study treatment without radiological 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 every 9 weeks (from the previous scan date). After 1 year of follow-up, CT scans may be scheduled approximately every 12 weeks. After primary completion, no tumor assessments will be done.

The radiological evaluation must include computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis with contrast media unless contraindicated. In case of contraindication to both, iodinated contrast agent for CT and gadolinium based contrast agent for MRI, evaluation should be performed with MRI (except chest region). 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.

At investigator's discretion, CT or MRI scan should be repeated at any time if progressive disease is suspected.

A CT (with contrast if not contraindicated) or MRI scan of the brain must be done at screening to exclude CNS metastasis. An MRI scan of the brain is required to confirm or

refute the diagnosis of CNS metastasis at baseline in the event of an equivocal scan. Patients with definitely treated stable CNS metastases may be eligible for the Study (see also Sections 6.1 and 6.2; inclusion/exclusion criteria).

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 clinically indicated. 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.

If radiographic changes are believed by the investigator to be secondary to drug induced inflammation and not to tumor progression (e.g. in case of suspected pseudoprogression), the investigator may postpone a diagnosis of progressive disease (PD) until the next radiographic evaluation in the study if all the following criteria are met:

- Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator.
- Absence of symptoms and signs indicating unequivocal progression of disease (including worsening of laboratory values [e.g. new or worsening hypercalcemia]).
- No decline in ECOG performance status that can be attributed to disease progression.
- Absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

Treatment beyond initial RECIST v1.1-defined progression is permitted only for patients who are clinically stable to continue on treatment until next imaging assessment (≥ 4 weeks later); this next imaging assessment should be no longer than 8 weeks later, to ensure that patients remain fit for salvage therapies. A longer time frame before the next assessment might be reasonable if no effective salvage therapies are available.

In addition, treatment beyond progression should not delay an imminent intervention to prevent serious complications of disease progression (e.g. central nervous system [CNS] metastases).

Patients for whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continuing study treatment at the discretion of the investigator if they still meet the criteria above and in absence of unacceptable toxicity.

9.5 Pharmacokinetics / pharmacodynamics

9.5.1 Drug measurements

Blood (plasma) samples for pharmacokinetic assessment of rogaratinib will be collected at the following time points:

- Cycle 1 Day 1 (Single dose PK): pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose (to be taken before the evening dose of rogaratinib).
- Cycles 2 to 5, Day 1 (for exposure-response modeling): pre-dose (before supervised dose administration), and 1 (± 0.5) hour post-dose.

For monitoring purposes of atezolizumab, blood (plasma) samples will be collected at the following time points:

- Cycle 1 Day 1: pre-dose, 1 (EOI), 4 and 8 hours post-dose.
- Cycle 1 Day 15: approximately 336 hours post-dose.

Whenever possible, all efforts should be made to adhere to the blood sampling schedule as given above. However, based on practical considerations, the following time range is provided: for planned time points ≤ 6 hours, PK samples should be collected within ± 15 minutes of the planned time, and for planned time points > 6 hours, PK samples should be collected within ±30 minutes. It is of importance that the actual date and time of blood sampling and related dosing date and time is documented in the eCRF and patient`s source document because PK calculations will be based on the actual sampling times relative to dosing times.

Sampling times outside these suggested intervals will be considered as “other deviations”. Cumulated substantial deviations of sampling times and/or consecutive, missing PK samples may lead to an insufficient (inadequate) description of the plasma concentration *vs.* time profiles of rogaratinib and thus affect the quality of the PK evaluation of the respective patient(s). In this case, these deviations should be classified as “important” and may lead as declared “validity findings” to the exclusion of the respective patient(s) from the PK analysis set.

When blood pressure measurement and PK sample collection are scheduled at the same time point, patient’s blood pressure will be measured before collection of the PK sample.

Plasma concentrations of rogaratinib and atezolizumab will be measured using a validated method. Instructions for sample collection, processing, storage and shipment will be described in a separate document (e.g. lab manual).

Exploratory monitoring of metabolites may also be performed in pooled plasma samples.

9.5.2 Non-compartmental pharmacokinetic evaluation

PK parameters will be calculated by non-compartmental analysis (NCA) according to current Bayer guidelines using Phoenix (WinNonlin) software. Details regarding the software version will be given in the clinical study report. Based on plasma concentration versus time results, the following parameters are planned to be calculated for rogaratinib:

Main PK parameters:

- **Cycle 1, Day 1 – single dose PK:** C_{max}, AUC(0-8)

Additional PK parameters:

- AUC(0-t_{last}), tmax and tlast on Cycle 1 Day 1

Other PK parameters (plasma):

- R_{start}, R_{end}, points terminal and %AUC(t_{last}-∞)

Additional parameters, e.g. apparent oral clearance (CL/F) and apparent volume of distribution after extravascular administration (V_Z/F), may be estimated, if appropriate.

Please refer to Section 10.3.5 for the analysis of the PK variables.

Pharmacokinetic evaluation – Population analysis

Pharmacokinetic data might be analyzed using nonlinear mixed effects models. Details of the model development and evaluation will be described in a separate Evaluation Plan and the results reported in a separate Evaluation Report.

Details on the collection, processing, storage, and shipment of PK samples will be provided in separate documents (e.g. sample handling sheets or lab manual).

9.6 Safety

Overview

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, defined and graded according to NCI CTCAE v.4.03. Patients will be assessed for safety (including laboratory values) according to the tabular schedule of evaluations (Section 9.1). Laboratory values must be reviewed prior of each infusion.

The safety outcome measures for this study are as follow:

- Incidence, nature and severity of AEs, graded according to NCI CTCAE v.4.03
- Change in vital signs, physical finding and clinical laboratory results

Safety assessments include:

- Physical examinations (see Section 9.6.3.2 for details)
- Vital signs (see Section 9.6.3.5 for details)
- Standard ECG variables (see Section 9.6.3.4 for details)
- Standard laboratory variables (see Section 9.6.3.1 for details)
- Ophthalmological examinations (see Section 9.6.3.7 for details)

Findings will be recorded as adverse events (AEs) or serious adverse events (SAEs) as applicable following main categorizations (see Section 9.6.1 for details):

- Treatment-emergent adverse events (TEAEs), drug-related TEAEs, and treatment-emergent serious adverse events

All serious adverse events and protocol-defined events of special interest (see Section 9.6.1.6) will be reported in an expedited fashion (see Section 9.6.1.4).

Each toxicity will be assessed as to whether it is dose limiting (see Section 7.4.1). The MTD and/or RP2D will be identified based on the incidence of DLTs during Cycle 1 in dose selection groups (for details see Section 10.3.4).

The investigator(s) and the sponsor or its representative will review regularly the safety data throughout the course of the study.

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 combination drug (atezolizumab), please refer to the investigator's brochure.

Therapeutic monitoring should be performed following dose selection or 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 other chemotherapy/treatment.

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, 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 are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent 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 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 rogaratinib intake or 90 days after the last atezolizumab administration.

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 PI/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 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).

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 treatments (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 separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- 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) must be fully documented in the source data. AEs are obtained by observation and as volunteered by the patients. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

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, only AEs related to the study drugs have to be recorded until the end of active follow-up. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

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 up to primary completion). 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. In addition, any AEs after the active follow-up visit qualifying as SAEs or AESIs of atezolizumab with an onset up to 90 days after last atezolizumab dosing that are reported to the sites need to be documented unless a new anti-cancer therapy has been initiated.

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 discontinuation of rogaratinib treatment or within 90 days of discontinuation of atezolizumab treatment, 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 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, should be reported as an AE.

"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)**
- **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 investigator's brochure (IB) for rogaratinib and atezolizumab.

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

Adverse events of special interest (AESIs) should be reported to the sponsor immediately within 24 hours using a safety report form as outlined in Section 9.6.1.4 (Reporting of serious adverse events).

Rogaratinib-specific AESIs

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):

- 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 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 / central 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 including any other abnormal ophthalmological findings should be reported in a dedicated eCRF page.

- Specific dose modification schemes for retinal disorders are defined in Section 7.4.3.2.3.

Atezolizumab-specific AESIs

The following adverse events are considered AESIs in this study and should be reported immediately, within 24 hours to the sponsor:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g. SJS, dermatitis bullous, TEN)

- Myelitis
- Facial paresis

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 will be performed locally according to the tabular schedule of evaluations shown 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).

Collection of blood for safety laboratory tests, including clinical chemistry, hematology and coagulation panels, can be performed within 2 days before administration of the study treatment.

Clinical chemistry

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

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 absolute counts of neutrophils, lymphocytes, monocytes, basophils, and eosinophils.

Coagulation panel

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

Urinalysis

The dipstick test includes: specific gravity, WBC, nitrite, pH, glucose, protein, ketones, bilirubin, urobilinogen, blood.

Additional microscopic examinations will be performed if clinically indicated.

After primary completion, urinalysis is no longer required

Estimated glomerular filtration rate (eGFR)

eGFR is to be determined according to the schedule summarized in the study flow chart in Section 9.1.

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 $\geq$ 30 mL/min/1.73 m^2 are eligible to enter the study (see Section 6.1).

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. After screening, a urine pregnancy test is used. The test (urine test) is to be repeated as frequently as required by local regulations. A serum pregnancy test must be performed if the urine pregnancy test is positive. 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). After primary completion, pregnancy tests are no longer required when there are no female patients of child-bearing potential.

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

The physical examination (by means of inspection, palpation and auscultation) will be performed according to the schedule of evaluations in Section 9.1 by a physician covering at least the organs of the cardiovascular, respiratory, and abdominal system, a complete review of body systems, neurological examination and assessment of skin status. Orientating tests of neurological function will be included.

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 PI/ICF for study treatment eligibility, respectively).

9.6.3.3 Body height, weight and BMI

Height is recorded only at screening.

Weight is recorded at screening, on Day 1 and Day 15 of Cycle 1 and thereafter on Day 1 of every cycle, and at the EOT visit.

Body mass index (BMI) will be derived by the sponsor (at the screening examination and at the end-of-treatment [EOT] visit).

9.6.3.4 12-lead ECG

Standard single 12-lead ECGs will be recorded in all patients according to the tabular schedule of evaluations shown in Section 9.1.

Standard single 12-lead ECG readings will be performed in the supine position as possible at the following time points (± 15 minutes):

- Screening
  - Note: at screening, ECG readings should be performed in triplicate in close sequence and not more than 2 minutes apart.
- Cycle 1, Day 1 and Day 2
  - Before and 2, 3 (Day 1) and 24 hours after first dose (i.e. before Cycle 1 Day 2 morning dose)
- Cycle 1, Day 15
  - Before morning dose, and 2 and 3 hours thereafter

- Cycle ≥ 2, Day 1; after primary completion, ECGs are optional and at the investigator's discretion
    - Up to 1 hour after morning dose
- EOT visit; after primary completion, ECGs are optional and at the investigator;s discretion

Beyond that schedule, weekly ECGs will be performed in patients with an elevated serum phosphate level (≥ 7 mg/dL) 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 the day of detection of hypocalcemia and should be repeated as clinically indicated.

9.6.3.5 Vital signs

Vital signs will include body temperature (axillary), respiratory rate (RR), heart rate and blood pressure (systolic and diastolic). Systolic and diastolic blood pressure and the heart rate will be obtained as duplicate measurements after 5 minutes supine or sitting position quiet rest. The vital sign assessments should be performed within the window of ±5 minutes from the planned time. Where the assessments coincide, the same resting period may be used for ECG and vital signs (ECG must be obtained before vital signs).

Blood pressure (BP) / heart rate (HR) profile will be measured as follows:

- Patient seated for at least 5 minutes before measurement with their arms bared and supported at heart level.
- At screening, duplicate measurements of BP must be done in both arms to see whether there is a difference in blood pressure readings between the patient's right and left arm. If one arm has higher blood pressure than the other, that arm should be used for further BP measurements (all further BP measurements must be done on the same arm whenever possible).
- Measurements (on the same arm) will be in duplicate and the mean value will be used for assessment. If the first two readings differ by more than 5 mmHg, additional two readings should be obtained and averaged.
- If a reduction of systolic BP below 90 mmHg or an increase in HR above 120 bpm is detected, the assessment has to be repeated after 2 hours.
- When blood pressure measurement and PK sample collection are scheduled at the same time point, patient's blood pressure will be measured before collection of PK sample.

RR, BP, HR and body temperature will be measured at the following time points (see also Section 9.1):

- Screening (one measurement within 28 days before start of treatment)
- Cycle 1 Day 1

  - BP, HR and RR: 60 minutes before, every 15 (±5) minutes during, and 30 (±10) minutes after atezolizumab infusion
  - Body temperature
- Cycle 1 Day 2
  - BP, HR and RR: Before, and 1 and 2 hour(s) after morning dose
  - Body temperature
- Cycle 1 Day 8
- Cycle 1 Day 15
  - BP, HR and RR: Before, and 1 and 2 hour(s) after morning dose
  - Body temperature
- Cycle ≥ 2 Day 1
  - BP, HR and RR: Within 60 minutes before infusion and at the end of the infusion
  - Body temperature
- Cycle 2-4, Day 8, Day 15
  - BP, HR and RR: Up to 1 hour after morning dose
  - Body temperature
- Cycle ≥ 5 Day 15
  - BP, HR and RR: Up to 1 hour after morning dose
  - Body temperature
- At EOT visit
- At the safety assessment visit of the active follow-up.

9.6.3.6 ECOG and Karnofsky 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 Section 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 for safety reasons.

Karnofsky performance status is used for determination of the MSKCC categories (see Section 9.3.3).

Grading definitions for both performance statuses are given in Table 9–3 below.

Table 9–3: Definitions for ECOG PS and Karnofsky PS grading

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	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
Normal activity with effort	80	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
Care for self. Unable to carry on normal activity or to do active work	70	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
Requires occasional assistance, but able to care for most of his needs	60	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
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death non-imminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Dead	0	5	Dead

ECOG PS = Eastern cooperative oncology group performance status; PS = performance status.
Source: (39)

9.6.3.7 Ophthalmological examination

Ophthalmological examination will be performed by an ophthalmologist or an equivalent specialist according to the tabular schedule of evaluations shown in Section 9.1.

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, slit lamp exam, tonometry, 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. Any findings qualifying as an adverse event will be recorded accordingly. 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.

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

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.

For dose modification of rogaratinib due to ophthalmological findings, see Section 7.4.3.2.3.

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

For additional details on management of atezolizumab-related ocular events see investigator's brochure for atezolizumab.

9.6.3.8 Chest X-ray

A chest X-ray should be performed (unless prohibited by local regulations) at screening to allow monitoring in case of suspected immune-related pneumonitis. The screening chest X-ray may be substituted with a chest X-ray that had been performed as part of the patient's previous routine care in the 3 months before start of study treatment. Any finding on a repeat chest X-ray that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded and monitored. Lesions identified on the baseline chest X-ray should also be evaluated by computed topography (CT) or magnetic resonance imaging (MRI) scan.

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.

If archival tissue is not available in sufficient quantity or quality for the FGFR1/3 RNAscope assays 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. Acceptable samples include excisional, incisional, punch, or forceps biopsies. 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 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).

Method applied for patient selection in trial 19131

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 FGFR1/3 RNA-ISH test (RNAscope technology by Advanced Cell Diagnostics) will be used to aid in the selection of cancer patients who may benefit from the pan-FGFR inhibitor (rogaratinib) therapy. The RNAscope technology allows for the respective FGFR probe to bind to the target FGFR mRNA, and in combination with RNAscope 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 according to the scoring scheme given in Table 9–4. The analysis will be performed centrally.

Table 9–4: FGFR1/3 RNA-ISH test (RNAscope® Assay): Preliminary stain intensity criteria

Stain Intensity Score	Stain Intensity Criteria
0	No staining or <1 dot per 10 cells
1	1-3 dots per cell
2	4-9 dots per cell. No or very few signal clusters.
3	10-15 dots per cell and less than 10% of signals in clusters
4	>15 dots per cell and more than 10% of signals in clusters

FGFR = Fibroblast growth factor receptor; ISH = *In situ* hybridization; RNA = Ribonucleic acid.

In pre-clinical studies, only xenograft models with either FGFR1, or FGFR2 or FGFR3 scores of 3+ or 4+ by RNAscope 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 an RNAscope score of 3+ or 4+. Therefore, having at least one FGFR isoform with a score of at least 3+ was selected as inclusion criterion for FGFR-positivity for this Study 19131.

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

Tumor-based biomarker analysis

For all enrolled patients, exploratory biomarker analyses will be performed from UC tumor specimens provided beyond the number of slides needed for FGFR1/3 testing. 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 known oncogenes such as p53, PTEN, RAS, PIK3CA 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 makers, such as PD-L1 and CD8A in tumor specimen, e.g. by IHC.

As per investigator's decision, and if technically feasible, biopsy during Cycle 2 or later and/or at the time of disease progression or recurrence is highly encouraged to be taken. This sample would allow generation of information about the identification of tumor biomarkers playing a role in therapy resistance. Note, however, that this is not considered to be mandatory by this study protocol.

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.

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. 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.

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 will be prepared from blood samples obtained according to the tabular schedule of evaluations shown in Section 9.1.

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.

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and / or literature data.

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) 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.

Data collection 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. After primary completion, questionnaire will not be done.

9.8 Appropriateness of procedures / measurements

All efficacy and safety variables, 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.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using the software package SAS (SAS Institute Inc., Cary, NC, USA); the version used will be specified in the statistical analysis plan.

All data will be listed, and study summary tables will be provided where appropriate. Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. Where appropriate, summary statistics will be provided for the original data as well as for the changes versus baseline. Graphical illustrations will be provided where appropriate. Frequency tables will be provided for qualitative data.

Due to the exploratory character of this Part A of the study, no confirmatory analysis will be performed. All calculated p-values and confidence intervals are to be interpreted in the exploratory sense.

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

Safety analysis set (SAF)

All patients who received at least 1 dose of study drug and have post-treatment safety data available will be included in the safety evaluation.

MTD analysis set

All patients who completed Cycle 1 and who took at least 80% of the required total dose (protocol-defined dose reductions will not be considered incompliant) of either study drug (rogaratinib or atezolizumab) during Cycle 1 or discontinued during Cycle 1 due to a DLT will be included in the MTD evaluation.

Efficacy analysis set

All patients who have received at least 1 dose of study drug and who have post-baseline efficacy data available will be included in the efficacy evaluation.

Pharmacokinetics (PK) analysis set (PKS)

All patients who have received at least 1 dose of study drug and with at least 1 valid concentration after first dosing and no important protocol deviations affecting the validity will be included in the PK evaluation.

10.3 Variables and planned statistical analyses

10.3.1 Disposition of patients

The number of patients enrolled and included in each analysis set will be tabulated by region, country and center. A summary table will also be presented for the number of patients enrolled and the number and percentage of patients in each of the defined analysis sets. The reasons for patients excluded from each of the analysis sets will also be tabulated. In addition, the number of patients who were enrolled, treated and discontinued will be summarized. Reasons for discontinuation of study treatment will be tabulated.

10.3.2 Demographic and other baseline characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) terms (v.20.0 or later).

10.3.3 Efficacy variables

All efficacy variables evaluated using the RECIST v1.1 (see Appendix 16.2) are linked to the secondary objective of the study Part A (see Section 4). All variables evaluated using the iRECIST v1.1 (see Appendix 16.2) are exploratory only.

Efficacy data will be summarized using descriptive statistics and will be graphically displayed if appropriate. The correlation between pharmacodynamic parameters and selected safety, efficacy, or PK parameters may be graphically displayed. Further statistical analyses may be conducted.

10.3.3.1 Secondary efficacy variable

The secondary efficacy variable is objective response rate.

Objective response rate (ORR) is defined as the percentage of patients whose best response is either a complete response (CR) or partial response (PR). Patients for whom best tumor response is not CR or PR, as well as patients without any efficacy assessment will be considered non-responders. According to RECIST v1.1, confirmation of PR and CR is not required considering the nature of the study and the protocol requirements.

10.3.3.2 Exploratory efficacy variables

Exploratory efficacy variables will include disease control rate (DCR) and duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

These variables are defined according to RECIST v1.1 as below:

Disease control rate (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 assignment to treatment of the patient (i.e. substantially earlier than the first planned radiological tumor assessment at 9 weeks), will not be taken into account.

Duration of response (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.

Progression-free survival (PFS) is defined as the time (days) from start of study treatment to date of first observed disease progression (investigator's 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 the 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.

Overall survival (OS) is defined as the time from start of study treatment 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 assignment to treatment, this patient will be censored at 1 day.

10.3.4 Safety variables

10.3.4.1 Determination of MTD

The objective of the dose selection phase is to determine the maximum tolerated dose (MTD) or confirm that the start dose level of rogaratinib (800 mg b.i.d.) is safe. The MTD is defined as the highest dose that can be given so that toxicity probability is below the target toxicity

P_T=30%. Estimation of the MTD will be based on the estimation of the observed dose dependent incidence rate of DLT in the first 21 days of dosing.

The modified toxicity probability interval (mTPI) design (40) will be applied to guide the dose selection decisions in the study. The equivalence interval of the toxicity probability for the MTD is set to [25%, 35%], in which any dose with a toxicity probability falling into this interval is considered as an estimate close to the true MTD. The dose selection part will be finished after 20 patients are evaluable for the MTD assessment. A beta-binomial Bayesian model with Beta(1,1) prior will be used to compute the posterior probabilities that the true rate of DLT is contained in each of the 3 toxicity intervals:

- [0, 25%] under-dosing (below the MTD)
- [25%, 35%] target dosing (close to the MTD)
- [35%, 100%] over-dosing (above the MTD)

The mTPI method calculates the unit probability mass (UPM) for above intervals with safety rules to stop due to excessive toxicity. In addition doses that are estimated to have excessive toxicity will be excluded from the trial.

The UPM for a given interval is defined as the probability of the interval divided by the length of the interval. Then an appropriate dose-finding action will be chosen based on the interval with the largest UPM. Specifically, if the UPM for the under-dosing interval is the largest, the dose is considered lower than the MTD and the recommendation is to escalate to the next higher dose or to stay on the dose level if current dose is the highest possible dose (800 mg b.i.d. being the highest possible dose) (letter **E** in Table 10–1); if the target dosing interval has the largest UPM, the mTPI design will recommend remaining at the current dose (letter **S** in Table 10–1); if the over-dosing interval has the largest UPM, the design will recommend de-escalating to the previous lower dose (letter **D** in Table 10–1). If the safety stopping rule is met, the toxicity of the current dose will be considered as unacceptable high and never be used again in the remainder of the trial (letters **DU** in Table 10–1). The safety rule is triggered if the posterior probability that the current dose is above the MTD is greater than 95%. All of these rules are summarized and precalculated in Table 10–1 below. No decision is made before data of at least 4 patients are available on the first dose level and are evaluable for DLTs. The sponsor in consultation with the investigators will decide how many additional patients need to be evaluable for DLTs on the same dose level before the next decision. See Table 7–2 for rogaratinib dose levels.

The decision on the number of additional patients and on the next dose level will be based on the recommendations from the mTPI, clinical assessment, all available PK and safety data.

The dose selection part will be finished after 20 patients are evaluable for DLT assessment and are available for the MTD determination. The RP2D will be defined once sufficient data is available. The final decision about the RP2D will be made by the sponsor in consultation with the investigators.

Table 10–1: Possible dose finding actions

Number of patients with observed DLTs	Number of patients treated at current dose																
	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
3	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
4	DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	S
5		DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S
6			DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
7				DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
8					DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S
9						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
10							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12									DU	DU	DU	DU	DU	DU	DU	DU	DU
13										DU	DU	DU	DU	DU	DU	DU	DU
14											DU	DU	DU	DU	DU	DU	DU
15												DU	DU	DU	DU	DU	DU
16													DU	DU	DU	DU	DU
17														DU	DU	DU	DU
18															DU	DU	DU
19																DU	DU
20																	DU

The column represents the number of patients treated at a given dose level in the trial. Each row represents the number of patients treated at the dose level and who have experienced dose-limiting toxicity (DLT) events. The letters in each cell provides the dose-assignment decision based on the data readout from the row and column numbers.
E: Escalate to the next higher dose (or stay if current dose is the highest possible dose)
S: Stay at the same dose
D: De-escalate to the previous lower dose (or stop if current dose is lowest possible dose)
DU: De-escalate to the previous lower dose and the current dose will never be used again.

10.3.4.2 Adverse events (AEs)

Individual listings of adverse events will be provided. Adverse events will be reported using MedDRA terms (v.20.0 or later) and graded according to NCI CTCAE v.4.03. The incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent drug-related adverse events (TEADRs), respectively, will be summarized in frequency tables using worst CTCAE v.4.03 grade. Frequency tables will also be provided for the changes of worst CTCAE v.4.03 grade after start of treatment versus baseline.

AEs will be considered to be treatment-emergent if they have started or worsened after first administration of study drug up to 30 days after the last dose of rogaratinib or 90 days after the last atezolizumab administration, whichever comes later.

10.3.4.3 Clinical laboratory evaluations

Laboratory data outside the reference range will be listed with abnormal values flagged. The incidence of laboratory data outside the reference range (low, high) will be summarized in frequency tables. The incidence of laboratory toxicities will be summarized by worst CTCAE v.4.03 grade. Frequency tables will be provided for the changes of worst CTCAE v.4.03 grade after start of treatment versus baseline.

10.3.4.4 Other safety measures

Quantitative data (vital signs, ECG) will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.

10.3.5 Pharmacokinetic variables

The concentration-times courses of rogaratinib in Cycle 1 will be tabulated by dose level. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration vs. time curves of all analytes (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted using both linear and semilogarithmic scale.

Pharmacokinetic characteristics (t_{max}, t_{last}, R_{start}, R_{end}, points terminal and %AUC [t_{last}-∞] excluded) will be summarized by the statistics mentioned above. T_{max} and t_{last} will be described utilizing minimum, maximum and median as well as frequency counts.

Concentration data from Cycle 2 to 5 as well as atezolizumab data will only be listed.

10.3.6 Biomarker variables

Biomarker data will be summarized using descriptive statistics and will be graphically displayed if appropriate. The correlation between biomarkers and selected safety, efficacy, or PK parameters may be graphically displayed. Further statistical analyses may be conducted.

10.3.7 Patient-reported outcomes (PRO)

PRO data as measured by the EORTC QLQ-C30 will be analyzed to assess differences in health-related Quality of Life (HRQoL) and health utility values using all available data. The scoring of the PRO endpoints and handling of missing data will be detailed in the statistical analysis plan.

PRO data will be summarized using descriptive statistics and will be graphically displayed if appropriate. Further statistical analyses may be conducted.

10.4 Determination of sample size

This Part A of the study is primarily a descriptive safety and tolerability Phase 1b trial.

No formal sample size calculation has been done for the dose selection part due to the exploratory nature of this Part A of the study. It is expected that up to 20 evaluable patients will be enrolled for safety and for the dose selection part. After 20 patients included in the dose selection, enrollment will continue up to a total of 26-30 patients at the most promising dose with regard to safety and efficacy to obtain additional data on safety, PK, and clinical activity.

A sample size of at least 26 evaluable patients at the MTD/RP2D will lead to a Bayesian posterior probability $P(\pi \leq 0.4 \mid data)$ of at least 91% with a power of at least 96% and a Bayesian posterior probability $P(\pi > 0.4 \mid data)$ of at least 92% and with 80% power assuming a true population proportion for the response rate of $\pi_u=0.6$ under the alternative hypothesis for the upper criteria and a population proportion of $\pi_l=0.15$ under the alternative hypothesis for the lower criteria.

In case that the highest dose of rogaratinib (800 mg b.i.d.) is well tolerated in combination with atezolizumab, it is expected that the minimum of 26-30 evaluable patients is included. Assuming a dropout rate of 15%, a total minimum sample size of approximately 30 patients at the MTD/RP2D is expected.

Based on tolerability, different rogaratinib starting doses may be explored in this study. And in addition to FGFR testing, tumor tissue will be tested for further potential predictors of response (e.g. PIK3CA mutations). If, for example, the most promising rogaratinib dose or patient subgroups are not clearly defined, approximately 20 additional patients may be enrolled up to a total of 50 patients to confirm signals in a larger sample size, when rogaratinib in combination with atezolizumab seems to be tolerated and early signs of clinical activity have been observed. This decision will be made by the Sponsor after consultation with the investigators.

All calculations were performed with SAS 9.4 using non-informative Jeffrey's priors.

10.5 Planned interim analyses

Safety data will be reviewed on an ongoing basis during dose selection. Additional analysis, as Bayesian dose-response and / or PK modeling of DLTs rates and CTCAE v.4.03 gradings may be performed after selected groups of patients in order to generate additional relevant information for the adaptive dose selection decisions. The sponsor together with all investigators will review all available data and make the final decision as to dose selection, de-escalation or group expansion during the adaptive dose selection part. This group of sponsor and investigators will also determine when to implement predefined stopping rules.

No formal interim analysis of the data collected during Part A is planned.

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.

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 treatment 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 has source documentation available at the site.

Data recorded during FGFR testing period

(Note: FGFR testing period will be considered as a pre-screening period and for the purpose of data collection it will be represented as Pre-Screening (FGFR testing) in the eCRF.)

At minimum, the following data should be recorded in the eCRF:

- Date of informed consent(s) that were signed (PI/ICF for FGFR testing)
- Subject (patient) identification
- Subject (patient) visit and visit date
- Inclusion/exclusion 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
- Urothelial carcinoma classification/diagnosis (see Section 9.3.3) including
    - date of initial diagnosis
    - type of assessment
    - date of the most recent progression / relapse,
    - histology
    - location of primary cancer
    - TNM classification of urothelial carcinoma at study entry according to the AJCC 8th edition
    - grading at initial diagnosis
- ECOG performance status (see Section 9.6.3.6)
- 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 during screening

In addition to the data listed above, the following data should be recorded in the eCRF:

- Date of informed consent that was signed (PI/ICF for study treatment eligibility)
- Inclusion/exclusion criteria for screening met (yes / no)
- Prior anti-cancer therapy for urothelial carcinoma and outcome (any prior medications, significant non-drug therapies and diagnostic procedures for the study indication) (see Section 9.3.3).
- Review TNM classification (AJCC 8th edition)
- ECOG PS (see Section 9.6.3.6)
- Karnofsky performance status (see Section 9.6.3.6)
- Liver metastases (absence vs. presence)
- Visceral metastases (liver, bone, lung) (absence vs. presence)
- Medical history (see Section 9.3.2)
- Alcohol and smoking habits/history
- Reason for discontinuation and date of last visit

These data will be transferred to the respective database.

For patients who signed PI/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. During active and long-term follow-up period, any new anti-cancer therapy (including systemic therapy, radiotherapy, surgery) has to be reported up to primary completion. 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/CRO'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.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- 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.

In the event of significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements. This includes the need for Remote Data Verification (RDV) which must only be used as a temporary measure where on-site monitoring visits are not possible and should focus on highest priority data (e.g. critical data). RDV and the mechanism used for this by the investigator site/country must be documented appropriately.

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. ECG, adjudication committees).

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

After its initial release for biometrical analysis, the clinical database is planned to be re-opened for the inclusion of the following 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.).

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF.

Missing data will not be replaced. Possible impact of missing values on the analysis will be discussed in the clinical study report.

Further details will be described in the SAP, if appropriate.

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 PPD
Address:	Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, US
Telephone no.:	PPD
Email:	PPD

Co-ordinating investigator(s)

Name:	Jonathan Rosenberg, MD
Title:	Doctor
Address:	Memorial Sloan Kettering Memorial Hospital 1275 York Avenue New York, NY 10065, 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

Central laboratory

PK and biomarker (FGFR expression and plasma/tumor based biomarker analysis) 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 subinvestigators) 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 test and exploratory biomarker analyses FGFR-positive tested 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 FGFR positive urothelial carcinoma and still has interest to participate in this study, no longer than 28 days prior to start of 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. For 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 female patients who become pregnant or for those fertile male patients whose female partner becomes pregnant. The PI/ICF will be signed by the female patient or the male patient and their pregnant female partner.

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, while 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.1

Amendment no.1 is a global amendment forming integrated protocol version 2.0, dated 04 DEC 2018.

Overall rationale for the amendment

The protocol was amended to address emerging safety data. In this regard, immune-related nephritis was added as new identified risk for atezolizumab and the management guideline of rogaratinib-induced hyperphosphatemia was updated.

The readability of the protocol was improved by reducing the introductory sections and inconsistencies were resolved in some parts of the protocol.

In addition, the option of transferring patients to a roll-over study was included.

The number of patients potentially included in the trial was changed.

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
7.4.3.3 Dose modifications of atezolizumab	Grade 2 immune-related nephritis is added as a criterion for withhold from atezolizumab treatment, and Grade 3 or 4 immune-related nephritis is added as a criterion for permanent discontinuation from atezolizumab treatment.	According to Atezolizumab IB, immune-related nephritis is identified as a new risk of for atezolizumab.

Section # and Name	Description of Change	Brief Rationale
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.
6.1 Inclusion criteria, 9.2.1.1 FGFR testing, 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 be consistent with other rogaratinib protocols.
2. Synopsis, 6.1 Inclusion criteria	Inclusion criterion 10 is modified for consistency.	For consistency with inclusion criterion 9 for cisplatin-ineligibility.
3.3 Rogaratinib, 6.4.1.3 Withdrawal criteria, 7.4.3.1 Dose limiting toxicities (DLTs), 7.4.3.2 Dose modifications of rogaratinib (Table 7–3), 7.4.3.2.1 Hyperphosphatemia, 9.1 Tabular schedule of evaluations (Table 9–2 footnote g), 9.2.2.1 Cycle 1, 9.2.2.2 Cycles 2 – 4, 9.2.2.3 Cycles ≥ 5, 9.2.2.5 End-of-treatment (EOT) visit, 9.2.3.1 Active follow-up, 9.6.3.1 Laboratory evaluations, 9.6.3.4 12-lead ECG	Content relevant to dose modifications of rogaratinib and management for hyperphosphatemia is updated. A formula to calculate calcium-phosphorus product (Ca x PO_4) is added in the protocol. The clinical chemistry panel is modified for calcium to only measure total calcium (instead of total or ionized) as total calcium is needed for the formula.	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. Serum phosphate will guide dose modifications of rogaratinib but Ca x PO_4 product will still be calculated for future data comparisons.
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.
8.1 Prior and concomitant therapy	It is clarified that all medication and therapies which are considered necessary for the patient’s welfare, and which are not expected to interfere with the evaluation of the study drug, including antibiotics, may be given at the discretion of the investigator.	For clarity and to emphasize antibiotics are not prohibited (except during the 14 days prior to start of study treatment).

Section # and Name	Description of Change	Brief Rationale
5.2.3 Follow-up periods, 9.1 Tabular schedule of evaluations (Table 9-2 footnote r), 9.2.3.1 Active follow-up, 9.4 Efficacy	It is clarified that during the active follow-up, tumor evaluations will be performed every 9 weeks from the previous scan date. The evaluation interval is increased to 12 weeks after one year.	For clarity and to provide a more relaxed schedule of assessment to the patient in order to reduce both hospital admissions and patient burden as well as renal toxicity due to contrast medium (i.e. patients starting active follow up have often chronic renal failure or contrast medium allergy or reported toxicity leading to treatment withdrawal).
9.1 Tabular schedule of evaluations (Table 9-2), 9.2.2 Treatment period, 9.2.3.1 Active follow-up, 9.7.1 Biomarker investigations	The timing of the optional tumor biopsy is modified to allow biopsy during Cycle 2 and/or at the time of disease progression.	To provide more flexibility in collecting tumor samples and to allow investigations in responding patients.
9.1 Tabular schedule of evaluations, 9.2.1.2 Screening, 9.2.2.1 Cycle 1, 9.2.2.2 Cycles 2 – 4, 9.2.2.3 Cycles ≥ 5, 9.2.2.5 End-of-treatment (EOT) visit, 9.6.3.1 Laboratory evaluations	Hormones are moved from the clinical chemistry panel to a separate hormone panel.	To be in alignment with the eCRF and the protocol standards, and to clarify the blood sampling schedule.
6.4.1.3 Withdrawal criteria	It is clarified that the patient being off study drug (atezolizumab) longer than 42 days beyond the next scheduled dosing is considered a substantial non-compliance with study procedures and the patient must be withdrawn from study treatment.	For consistency with Section 7.4.3.3 Dose modifications of atezolizumab.
9.6.3.4 12-lead ECG	A time window of ± 15 minutes is added for 12-lead ECG readings.	To allow flexibility for practical considerations.
6. Study population, 6.4.1.1 Screening failure, 9.2.1.1 FGFR testing	It is clarified that “FGFR testing failure” does not mean a failure of the FGFR test (i.e. the RNAscope assay), but a negative FGFR test result and/or not meeting the inclusion/exclusion criteria.	For further clarity.

Section # and Name	Description of Change	Brief Rationale
7.2.2 Atezolizumab – combination drug, 7.4.1.2 Atezolizumab – combination drug, 7.4.3.3 Dose modifications of atezolizumab, 9.6.1. Adverse events, 9.6.1.5 Expected adverse events	Prescribing information is deleted as a reference and Summary of Product Characteristics (SmPC) is used as reference only for the preparation instructions for atezolizumab.	SmPC should only be referred to for the preparation instructions for atezolizumab. The IB is the reference for all other information about atezolizumab.
7.4.1.1 Rogaratinib – test drug, 9.1 Tabular schedule of evaluations (Table 9-2, footnote o)	It is clarified that on C1D1 patients will receive 800 mg of rogaratinib in the morning (not only one tablet i.e. 400 mg), and the second dose of 800 mg in the evening.	For clarity (to avoid false interpretation of “single dose”).
7.4.1.1 Rogaratinib – test drug, 9.1 Tabular schedule of evaluations (Table 9-2, footnote k), 9.2.2.1 Cycle 1, 9.5.1 Drug measurements	A time window of ± 3 hours is added for the 2nd dose of rogaratinib on C1D1. Clarifications are included for PK sampling timepoints on C1D1 accordingly.	For flexibility for the 2nd dose for practical considerations.
7.4.3.2.2 Liver toxicity	Information on the incidence of liver toxicities in the rogaratinib FiH study was added.	To provide further data for investigators in this section.
9.5.1 Drug measurements	New best practice wording is included for handling of PK sampling times outside suggested time intervals and/or missing samples.	To clarify the sampling time points.
9.5.1 Drug measurements	It is clarified that the method used for measuring plasma concentrations of atezolizumab is also validated (not only the method for rogaratinib concentrations).	Missing information is added.
9.5.2 Non-compartmental pharmacokinetic evaluation	Additional PK parameter V_{ss}/F (apparent volume of distribution at steady state after extravascular administration) is changed to V_Z/F.	Parameter V_{ss} is a reliable PK parameter only for intravenous administration.
10.3.5 Pharmacokinetic variables	Statistical analyses of pharmacokinetic characteristics are further clarified.	To add clarity, in case there are more than one dose levels. Also, “other” PK parameters for technical documentation don’t need to be included in statistics anymore, as per internal guidance.

Section # and Name	Description of Change	Brief Rationale
16.2 Evaluation Criteria in Solid Tumors (RECIST and iRECIST)	Central confirmation of PD per iRECIST is deleted.	In Part A of the 19131 study there is no central review for treatment decisions.
3.3 Rogaratinib, 3.4 Atezolizumab	Detailed information about clinical studies of rogaratinib and atezolizumab are deleted.	Details about rogaratinib and atezolizumab studies and clinical experience are omitted to avoid the need to amend the protocol when IB is updated. All details can be found from the most recent version of the IB.
1.Title page, 13.1 Investigator(s) and other study personnel	Sponsor's medical expert's name and contact details are changed.	Reorganization of the medical team.
2. Synopsis, 5.1 Design overview, 10.4 Determination of sample size,	Sample size wording is clarified and modified to allow recruitment of up to 50 patients.	To allow the option to adjust the sample size based on emerging data.
6.4.2 Replacement	Wording regarding replacement for efficacy assessment was clarified	For further clarity.
6.4.1.3 Withdrawal criteria, 7.4.3.1. Dose limiting toxicities (DLTs), 7.4.3.2.3 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.
9.2.3.2 Long-term follow-up	It is clarified that all patients in the long-term follow-up period will be contacted every 3 months (±14 days) from completion of the active follow-up.	To clarify the beginning of the long-term follow-up as requested by the coordinating investigator.
9.6.3.1 Laboratory evaluations	RBC and hemoglobin are removed from urinalysis coverage.	Specification is not necessary as blood covers both RBC and hemoglobin
6.1 Inclusion criteria	It is added to #8 that regionally available standard of care options must be considered for all patients.	To exclude patients where standard of care options are more appropriate.
6.1 Inclusion criteria	The hearing loss criteria are revised to comply with CTCAE v 4.03.	For compliance with CTCAE v 4.03.

Section # and Name	Description of Change	Brief Rationale
6.1 Inclusion criteria	The time after last study drug administration, when male patients with a female partner of childbearing potential must use a condom and ensure that an additional form of contraception is also used, is changed from 12 weeks to 5 months.	For consistency within the inclusion criterion #14 and with Atezolizumab IB
6.2 Exclusion criteria	It is added that baseline chest X-ray and CT can be used for tuberculosis screening.	To clarify the determination of active tuberculosis.
6.4.1.3 Withdrawal criteria, 7.4.3.2.2 Liver toxicity	Criteria for liver toxicity are modified.	The liver toxicity criteria are changed to make the elevations consistent with the CTCAE grading.
9.2.2.1 Cycle 1, 9.6.3.5 Vital signs	The number of time points for monitoring the vital signs, including blood pressure, heart rate, respiratory rate and body temperature, on C1D15 are reduced.	Based on the schedule of study treatment (patients receive atezolizumab on Day 1 of every cycle, i.e. once every 3 weeks) no safety concerns are expected on C1D15 requiring intensive monitoring of vital signs (i.e. vital signs, including blood pressure, heart rate, respiratory rate and body temperature before and 0.5, 1, 2, 3, 4, 6 and 8 hours after morning dose).
7.4.1.2 Atezolizumab – combination drug, 9.2.2.1 Cycle 1, 9.2.2.2 Cycles 2 – 4, 9.2.2.3 Cycles ≥ 5 and 9.6.3.5 Vital signs	Body temperature measurement is separated from other vital signs blood pressure, heart rate and respiratory rate and scheduling is clarified and aligned with other parts of the protocol.	To ensure consistency in the frequency and timing of vital signs including HR, BP, RR and body temperature between the protocol sections and to allow flexibility for practical considerations.
2. Synopsis	Wording regarding rogaratinib dose was clarified.	To clarify that also lower doses of rogaratinib may be used.

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

15.2 Amendment no.2

Amendment no.2 is a global amendment forming integrated protocol version 3.0, dated 10 FEB 2021. This amendment is considered substantial based on the relevant criteria of the (EU) clinical trial legislation.

Overall rationale for the amendment

The protocol was amended to address emerging safety data. In this regard, immune-related myositis and severe cutaneous adverse reactions were added as new identified risks for atezolizumab and the respective management guidelines were added.

In addition, the option of continuing post-study therapy in any other form of continued study drug supply with no cost to the patient was included.

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
7.4.3.3 Dose modifications of atezolizumab	Suspected SJS and TEN are added as criteria to withhold atezolizumab treatment, and confirmed SJS and TEN are added as criteria for permanent discontinuation of atezolizumab treatment.	Severe cutaneous adverse reactions are identified as a new risk associated with the use of atezolizumab.
7.4.3.3 Dose modifications of atezolizumab	Grade 2 or 3 immune-related myositis is added as a criterion to withhold atezolizumab treatment, and Grade 4 immune-related myositis is added as a criterion for permanent discontinuation of atezolizumab treatment.	Immune-related myositis is identified as a new risk associated with the use of atezolizumab.
9. Procedures and variables	Alternate strategies for participant visits, assessments, medication distribution and monitoring are allowed in the event of a significant trial-continuity issue (e.g. caused by a pandemic).	To ensure trial-continuity in exceptional circumstances.

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion criteria, 8.1 Prior and concomitant therapy	COVID-19 vaccines are added as permitted prior and concomitant therapy. Vaccines based on mRNA technology are preferred, but also live, attenuated vaccines can be allowed if deemed appropriate for cancer patients. Live, attenuated, replication competent virus vaccines are not permitted.	To allow the use of COVID-19 vaccines during study treatment. Vaccines based on mRNA technology are considered safest for cancer patients.
6.1 Inclusion criteria	Duration of required contraception use after stopping rogaratinib is decreased based on the updated IB.	To take into account the possibility that a patient stops atezolizumab earlier than rogaratinib.
2. Synopsis, 6.2 Exclusion criteria, 6.4.1.3 Withdrawal criteria, 7.4.3.1 Dose limiting toxicities (DLTs), 7.4.3.2.3 Retinal disorders, 9.1 Tabular schedule of evaluations, 9.6.1.6 Adverse events of special safety interest, 9.6.3.7 Ophthalmological examination	Term “serous retinopathy” is updated to “central serous retinopathy”.	For consistency with IB.
8.1 Prior and concomitant therapy	Text is modified to clarify that antibiotics are permitted during the study.	For further clarity.
9.6.1.3 Assessments and documentation of adverse events	Clarification is added that only SAEs or AESIs of atezolizumab need to be reported until 90 days after the last atezolizumab administration (for rogaratinib 30 days).	For clarity and prevention of unnecessary reporting.
9.6.1.4 Reporting of serious adverse events	Regarding SAE reporting of AML and MDS, “occurring after chemotherapy for cancer’’ is removed.	Correction (not applicable).
7.4.3.2 Dose modifications of rogaratinib	Guidance for dose modification of Grade 3 toxicity (Table 7–3) is corrected to be consistent with the rest of the protocol. “Delay until recovery to ≤ Grade 1.”	Corrected to avoid inconsistency in the protocol.
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.

Section # and Name	Description of Change	Brief Rationale
9.6.3.1 Laboratory evaluations	Ca x PO4 product formula is removed.	Ca x PO4 product is no longer required to be calculated by sites.
9.1 Tabular schedule of evaluations	Urinalysis and hormone panel can be performed up to 2 days prior to drug administration.	To allow urinalysis and hormone panel the same time window as for safety laboratory tests.
5.5 End of study, 7.2 Identity of study treatment, 8.2 Post-study therapy	The option of continuing post-study therapy in any other form of continued study drug supply with no cost to the patient is included.	To offer more flexible possibilities to continue study treatment when this trial is stopped but benefits are observed for individual patients.
7.4.3.2.2 Liver toxicity, 7.4.3.3 Dose modifications of atezolizumab	Detailed numbers of AEs in clinical studies of rogaratinib and atezolizumab are deleted and references to IB are added.	To avoid the need to amend the protocol when IB is updated. Details can be found from the most recent version of the IB.
1. Title page, 13.1 Investigator(s) and other study personnel	The name and contact information of sponsor's medical expert are changed.	Personnel change.
Signature of the sponsor's medically responsible person	The signature of the Sponsor's medically responsible person is removed from the clinical study protocol.	Administrative change of Bayer process.

In addition, editorial changes have been made throughout the document.

15.3 Amendment no.3

Amendment no.3 is a global amendment forming integrated protocol version 4.0, dated 4 OCT 2021. This amendment is considered substantial based on the relevant criteria of the (EU) clinical trial legislation.

Overall rationale for the amendment

After primary completion, study procedures were reduced to decrease burden to patients and sites. The updated schedule of events is intended to mimic standard of care.

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
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods 9.2.2 Treatment period 9.2.2.3 Cycles ≥ 5 9.2.3.1 Active follow-up	After primary completion, Cycle ≥5 Day 15 evaluations and assessments were removed: Toxicities / AE assessment, physical examinations, vital signs, ECOG performance status, changes in vision, blood samples for safety laboratory tests, calculation of eGFR, concomitant medication	To relieve the burden on the patients remaining on treatment after study primary completion.
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods 9.2.2.3 Cycles ≥ 5 9.2.2.5 End-of-treatment (EOT) visit 9.6.3 Further safety	After primary completion, C ≥5 and EOT dipstick urinalysis was removed.	To relieve the burden on the patients remaining on treatment after study primary completion.
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods 9.2.2.3 Cycles ≥ 5 9.2.2.5 End-of-treatment (EOT) visit 9.6.3 Further safety	After primary completion, C ≥5 and EOT 12-lead ECG are considered optional and at the investigator's discretion	The primary completion safety data (as per cut date of July 2021) did not identify myocarditis or any other cardiac event as a safety signal. Optional ECG will give the flexibility for the investigators to use this resource as needed in addition to the management guidance provided on table 7-10.
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods Footnote f 9.2.2.3 Cycles ≥ 5 9.2.2.5 End-of-treatment (EOT) visit	After primary completion, the frequency of ophthalmologic examinations was reduced: The examination is performed on D1 of every 4th instead of every 2nd cycle, starting at C2. At the EOT visit, ophthalmologic examination is done only in case the patient reports changes in vision.	After primary completion, the patients that are currently in the study have been on treatment for at least 2 years, therefore, the chance of developing new ophthalmologic issues is small. In case of reported changes in vision, ophthalmological examinations will be performed.

Section # and Name	Description of Change	Brief Rationale
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods Footnote h 9.2.2.3 Cycles ≥ 5	After primary completion, hormone panel (thyroid function test) done periodically to reduce frequency of testing, according to local standard of care.	After primary completion, the testing frequency can be reduced and will be done according to local standard of care. The detection of asymptomatic thyroid function abnormality will rely on AE assessment at each visit. The investigators can order ad hoc TSH, T3 and T4 when hypothyroidism or hyperthyroidism is suspected based on symptomatic AE collection and decide the action to be taken for atezolizumab.
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods Footnote j 9.2.2 Treatment period 9.2.2.3 Cycles ≥ 5 9.2.2.5 End-of-treatment (EOT) visit 9.2.3 Follow-up periods 9.2.3.1 Active follow-up 9.6.3 Further safety	After primary completion, pregnancy tests no longer required if there are no active patients that are women of child-bearing potential.	After primary completion, pregnancy tests are no longer required because there are no female patients of child-bearing potential left in the study.
2. Synopsis 5.2.3 Follow-up periods 9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods 9.2.3.1 Active follow-up 9.2.2.4 Tumor assessments during treatment period 9.2.3 Follow-up periods	The interval for tumor assessments was prolonged from every 9 weeks to every 14 weeks during the treatment and active follow-up periods.	To relieve the burden on the patients remaining on treatment after study primary completion.

Section # and Name	Description of Change	Brief Rationale
2. Synopsis 9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods 9.2.2.3 Cycles ≥ 5 9.2.2.5 End-of-treatment (EOT) visit 9.2.3 Follow-up periods	After primary completion, the PRO questionnaire was removed from C4 onwards.	To relieve the burden on the patients remaining on treatment after study primary completion.
9. Procedures and variables Table 9.2 Schedule of evaluations: Treatment and follow-up periods Footnote t 9.2.2.3 Cycles ≥ 5 9.7.1 Biomarker investigations Plasma-based biomarker analysis 9.2.3 Follow-up periods 9.7.1 Biomarker investigations	After primary completion, blood sampling for plasma-based biomarker analyses are not done beyond C4 except at the EOT visit.	To relieve the burden on the patients remaining on treatment after study primary completion.
7.4.3.3 Dose modifications of atezolizumab	Management of Grade 1 and 2 atezolizumab infusion-related reactions was updated.	Alignment with updated atezolizumab IB.
10.3.5 Pharmacokinetic variables	The concentration-times courses of **only rogaratinib** in C1 is tabulated by dose level. Concentration data from C2-5 and all atezolizumab data is only listed.	Clarification
11.2 Monitoring	Remote data verification was allowed.	Introducing flexibility in case of trial conduct continuity issues. Modification request by BfArM.
1.Title page 13.1 Investigator(s) and other study personnel	Sponsor's medical expert's name was changed.	Reorganization of the medical team.
9.5.2 Non-compartmental pharmacokinetic evaluation	Update of software name.	Clarification

In addition, editorial changes have been made throughout the document.

15.4 Amendment no.4

Amendment no.4 is a global amendment forming integrated protocol version 5.0, dated 09 NOV 2022. This amendment is considered substantial based on the relevant criteria of the (EU) clinical trial legislation.

Overall rationale for the amendment

The protocol was amended to address emerging safety data: Immune-mediated pericardial disorders were added as new identified risk for atezolizumab and the respective management guidelines were added. Management guidelines for atezolizumab-specific adverse events were revised.

In addition, no further analysis is planned for this study after primary completion and the active and long-term follow-ups were concluded.

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
7.4.3.3 Dose modifications of atezolizumab	Management guidelines for immune-mediated pericardial disorders are added and grouped under immune-mediated cardiac events along with immune-mediated myocarditis.	Immune-mediated pericardial disorders are identified as a new risk associated with the use of atezolizumab.
7.4.3.3 Dose modifications of atezolizumab	Management guidelines for atezolizumab-specific adverse events are aligned with the IB.	To harmonize with the IB.
2. Synopsis, 5.1 Design overview, 5.2.3 Follow-up periods, 6.4.1.3 Withdrawal criteria, 9.2.3 Follow-up periods, 9.2.3.1 Active follow-up, 9.4 Efficacy, 9.6.1.3 Assessments and documentation of adverse events, 11.1 Data recording	After primary completion, follow-up data is no longer collected after the safety assessment visit in the active and long-term follow-ups.	Follow-up data is no longer needed.
5.5 End of study	LPLV definition is changed. Option for study termination by sponsor guided by strategic expectations for the study compounds after primary completion is added.	To give flexibility for strategic decisions of the sponsor.

In addition, editorial changes have been made throughout the document.

15.5 Amendment no.5

Amendment no.5 is a global amendment forming integrated protocol version 6.0, dated 23 MAY 2023. This amendment is considered substantial based on the relevant criteria of the (EU) clinical trial legislation.

Overall rationale for the amendment

The protocol was amended to address emerging safety data: immune-mediated myelitis and immune-mediated facial paresis were added as new identified risks for atezolizumab and the respective management guidelines were added. Management guidelines for atezolizumab-specific adverse events were revised.

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
7.4.3.3 Dose modifications of atezolizumab 9.6.1.6 Adverse events of special safety interest	Management guidelines for neurologic disorders, including immune-mediated myelitis and immune-mediated facial paresis, are added. Myelitis and facial paresis are added as atezolizumab-specific adverse events of special interests.	Immune-mediated myelitis and immune-mediated facial paresis are identified as a new risk associated with the use of atezolizumab.
7.4.3.3 Dose modifications of atezolizumab	Management guidelines for Grade 3 immune-mediated gastrointestinal events (diarrhea or colitis) and Grade 1 hyperthyroidism are updated.	Harmonization with the IB.
7.4.3.3 Dose modifications of atezolizumab	Grade 1 immune-mediated pericarditis is added in the list of reasons to withhold atezolizumab.	For consistency.
1.Title page 13.1 Investigator(s) and other study personnel	Sponsor's medical expert's name and contact information are changed.	Personnel change.

In addition, editorial changes have been made throughout the document.

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 (41)

16.2 Response Evaluation Criteria in Solid Tumors (RECIST and iRECIST)

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 (37) as well as the modified iRECIST guidelines for immune-based therapeutics as supportive data for efficacy and treatment decision. iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "i" (i.e. immune). Investigators should note the different

requirements for confirmatory scans as well as follow up for the two criteria. Further details can be found in the Imaging Manual.

RECIST

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 (42)). 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.

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 of 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 ≥ 9 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.

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.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For patients who show evidence of radiological PD by RECIST 1.1 the investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST for patient management). This decision by the investigator should be based on the patient's overall clinical condition and agreement.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

For any patient deemed **clinically unstable** the investigator should discontinue the study treatment.

If the investigator decides to continue treatment, the patient may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm or reject PD by iRECIST and to ensure that patients remain fit for salvage therapies.
Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" (SOD) will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target (NLT). The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target (NLNT).

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD at the immediate next visit, if ANY of the following occurs:

- Any of the factors that were assessed as being the basis for the initial iUPD show worsening
    - For target lesions that had shown SOD increase from nadir of at least 20% and ≥5 mm in total this is a further increase in the sum of diameters of ≥5 mm
    - For non-target lesions that had shown unequivocal growth worsening means any continued obvious growth in lesions overall tumor burden; this does not have to meet the “unequivocal” standard of RECIST 1.1 but as a guidance it should be approximately comparable with the definition for worsening of TL or NLT (i.e. SOD ≥5 mm)
    - For new lesions worsening is any of these:
        - An increase in the new lesions-target (NLT) sum of diameters by ≥5 mm
        - Obvious growth of new lesions-non-target (NLNT)
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) does not show any decrease beyond the initial PD threshold (by RECIST 1.1)

If progression is not confirmed, imaging should continue as originally planned (e.g., if scans were to be done at 9, 18, and 27 weeks, and a confirmatory scan was done at 13 weeks, then the next scans should be done at 18 weeks and 27 weeks) with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR or NE.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) does show a decrease beyond the initial PD threshold

The response is classified as iSD (decrease of SOD < 30 % from baseline and increase < 20% from nadir) or iPR (decrease of SOD ≥ 30% from baseline) compared to baseline, or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD per iRECIST is assessed by the investigator, patients will be discontinued from study treatment.

Note: If a patient has confirmed radiographic progression (iCPD) as defined above, but the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as originally planned and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudoprogression Resolves

After resolution of pseudoprogression and tumor shrinkage (i.e., achievement of iSD/iPR/iCR), the bar is reset again and iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudoprogression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any obvious further growth of non-target lesions, taken as a whole.

- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new lesions-target (NLT) show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified new lesions-non-target (NLNT) show further obvious growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging subsection above) is repeated.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the Imaging Manual and the iRECIST publication (38).

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 (43):
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 (44).