CLINICAL STUDY PROTOCOL

DZB-CS-201

Derazantinib

An open-label multi-cohort Phase 1b/2 study of derazantinib and atezolizumab in patients with urothelial cancer expressing activating molecular FGFR aberrations (FIDES-02)

Protocol Number/Version	DZB-CS-201 / Version 5.0
Compound	Derazantinib
Phase of development	1b/2
IND number	143805
EudraCT number	2019-000359-15
Date	8 March 2021
Project Physician	[redacted]
Clinical Pharmacologist	[redacted]
Project Statistician	[redacted]
Sponsor	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel, Switzerland

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DOCUMENT APPROVAL

The original version of this document has been electronically signed by the representatives of Basilea Pharmaceutica International Ltd identified on page 1, in compliance with the requirements of (US) 21 CFR Part 11 and other applicable national regulations regarding electronic records and electronic signatures.

Protocol synopsis

TITLE	An open-label multi-cohort Phase 1b/2 study of derazantinib and atezolizumab in patients with urothelial cancer expressing activating molecular FGFR aberrations (FIDES-02)
PROTOCOL NUMBER	DZB-CS-201 / Version 5.0
SPONSOR	Basilea Pharmaceutica International Ltd, Switzerland
STUDY PHASE	1b/2
INDICATION	Urothelial cancer
IND NUMBER	143805
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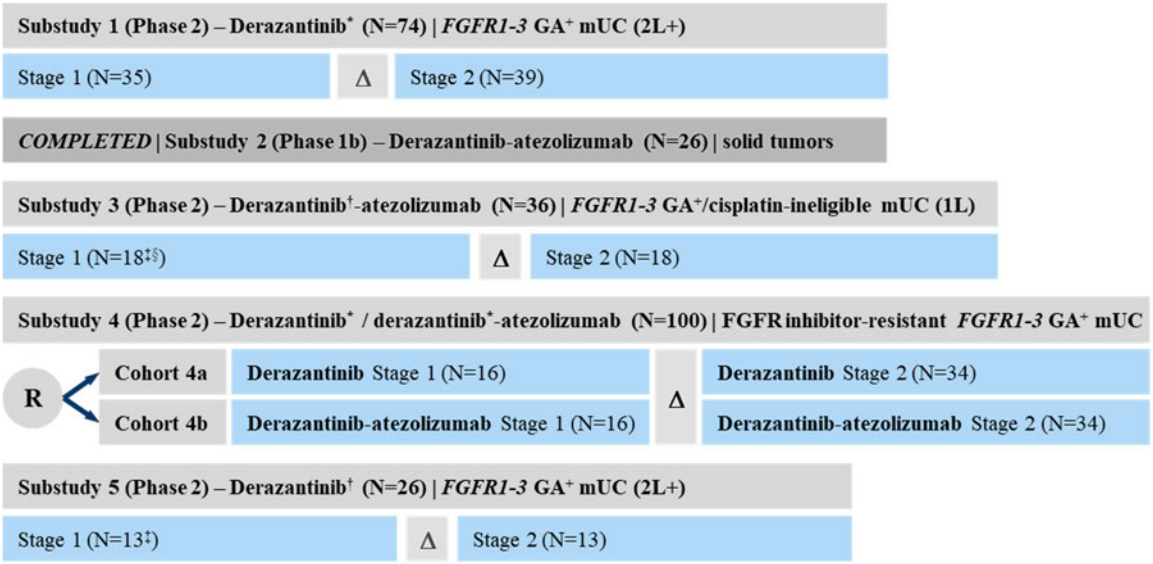
Overview of study design



Abbreviations: 1L: first-line treatment; 2+L: second-line or post-second line; Δ: decision for transition to Stage 2; FGFR: fibroblast growth factor receptor; GA: genetic aberration; mUC: locally advanced or metastatic and recurrent or progressing urothelial cancer; R: randomization.

* Derazantinib 300mg QD

† Derazantinib 200 mg BID

‡ Safety interim analysis after 10 patients

§ If derazantinib 200 mg BID is not assessed as safe and tolerable, the RP2D determined in Substudy 2 will be used.

STUDY DESIGN

This study is a multiple-cohort, multi-center Phase 1b/2 study. An overview of the study design is provided above. The efficacy of derazantinib or derazantinib-atezolizumab in combination is evaluated in substudies enrolling patients with genetic aberrations (GAs) in the fibroblast growth factor receptor (*FGFR*) genes of various clinical stages of disease progression and prior treatments.

Effective from Protocol Version 5.0, **Substudy 3** has been modified, and **Substudy 5** has been added. **Substudy 2** has been completed.

Patients with surgically unresectable or metastatic urothelial cancer (mUC) and *FGFR1*, *FGFR2*, or *FGFR3* mutations and rearrangements / fusions (for the purposes of this protocol hereafter referred to as *FGFR1–3* GAs) will be enrolled, and sample-size minimizing statistical designs with interim analyses for futility and efficacy will be used.

All prospective study participants must test positive for *FGFR1–3* GAs (see below). In **Substudy 4**, it is anticipated that positive *FGFR1–3* GA testing is available from the preceding FGFR inhibitor treatment.

The study comprises five open-label substudies:

- ***Substudy 1*:** Patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment. Patients in this substudy are to be treated with derazantinib 300 mg daily (QD) monotherapy.
- ***Substudy 2:*** As of Protocol Version 5.0, enrollment to this substudy was completed, with interim results described in Section 1.4.1.2.
- ***Substudy 3:*** As of Protocol Version 5.0, this substudy has been modified. First-line cisplatin-ineligible patients with mUC expressing *FGFR1–3* GAs are to be treated with derazantinib 200 mg twice daily (BID) and atezolizumab 1200 mg every 3 weeks (Q3W) in combination. If derazantinib 200 mg BID at the safety interim analysis (SIA) is not assessed as safe and tolerable, patients are to be treated with the RP2D determined in Substudy 2.
- ***Substudy 4*:** FGFR inhibitor-resistant patients with mUC expressing *FGFR1–3* GAs. Patients in this substudy are to be randomized (1:1) into two non-comparative cohorts: Cohort 4a patients will receive derazantinib 300 mg QD monotherapy, and Cohort 4b patients will receive derazantinib 300 mg QD and atezolizumab 1200 mg Q3W in combination.
- ***Substudy 5*:** Patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade, and have not received prior FGFR inhibiting treatment. Patients in this substudy are to be treated with derazantinib 200 mg BID monotherapy.

INVESTIGATIONAL PRODUCT(S)

Derazantinib, atezolizumab

TUMOR MOLECULAR TESTING DEVICE

Molecular eligibility for enrollment will be established by a positive test result for eligible *FGFR1-3* GAs (see Appendix 1). The molecular test is to be based on next generation sequencing (NGS) of either tumor tissue DNA and/or RNA, or plasma circulating-free DNA (cfDNA).

For patients with no access to local NGS testing, central testing will be performed in a laboratory in the USA designated by the Sponsor; this 'central testing' will be based on NGS testing of cfDNA from a liquid biopsy obtained at Pre-screening.

For potential prospective study participants without an available positive *FGFR1–3* GA test result, a Pre-screening visit (see below) is to be scheduled for liquid biopsy sampling.

Alternatively, an eligible, positive *FGFR1–3* GA test result obtained from local NGS testing ('local testing', the commissioning of which is the study site's responsibility) can be used to establish molecular eligibility; no Pre-screening visit is required. The commissioned NGS test for 'local testing' is to use standard protocols approved by the local IRB/IEC, Clinical Laboratory Improvement Amendments (CLIA), or other similar agency, or, where applicable, US FDA-approved kits. For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance; tests manufactured by health institutions and used only on their own patients are exempt from the Medical Devices Regulation requirements, and do not have to be CE-marked.

PRE-SCREENING VISIT AND INITIATION OF CLINICAL SCREENING

A Pre-screening visit is only required for prospective study participants under consideration for enrollment into Substudies 1, 3 or 5, and if no documented local NGS test result with an eligible *FGFR1–3* GA is available. If these patients have no access to local NGS testing, they are required to sign the Pre-screening Informed Consent Form (ICF) for molecular screening, and are not considered enrolled (i.e., patients are considered to be in pre-screening for the study) until receipt of a positive central molecular test result, and dated patient signature on the Study ICF. The Pre-screening visit for liquid biopsy sampling should be scheduled following assessment of objective documented progression after prior anti-cancer treatment (e.g., rather than during prior anti-cancer treatment) to optimize the likelihood of capturing cfDNA shedding reflective of disease progression.

No Pre-screening visit is required for patients with a known and eligible *FGFR1–3* GA status (see Appendix 1) from local NGS testing; these patients may directly initiate clinical screening procedures. **Substudy 4** patients also do not require a Pre-screening visit if their molecular eligibility is known from prior FGFR-inhibiting treatment (documentation of which should be made available at the Screening visit, otherwise a Pre-screening visit should be scheduled).

PLANNED NUMBER OF PATIENTS

The study plans to enroll up to 272 evaluable patients in total across all five substudies.

NUMBER OF CENTERS/LOCATIONS

Up to 100 study sites in Asia-Pacific, Europe, and North America.

OBJECTIVES (as applicable to active substudies)

Primary efficacy objective

- To evaluate the objective response rate (ORR) of derazantinib monotherapy (in Substudies 1 and 5, and Cohort 4a) and of derazantinib-atezolizumab in combination (in Substudy 3 and Cohort 4b) in patients with mUC expressing *FGFR1–3* GAs.

Primary safety objectives

- To confirm derazantinib 200 mg BID plus atezolizumab 1200 mg Q3W as a safe and tolerable regimen (Substudy 3).
- To confirm derazantinib 200 mg BID as a safe and tolerable dose regimen of derazantinib monotherapy (Substudy 5).

Secondary objectives

- To evaluate the efficacy of the study drugs as measured by disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS)
- To assess the safety and tolerability of the study drugs
- To characterize the PK profile of derazantinib 200 mg BID (and, if applicable, derazantinib metabolites) as monotherapy (Substudy 5) and in combination with atezolizumab (Substudy 3).
- To evaluate changes, and assess the minimally important difference, in health-related quality of life (HR-QoL) and symptom response from baseline by cohort, substudy and in the overall study population using the EORTC QLQ C30, FACT-Bl, EQ-5D (5L) visual analogue scale (VAS), and Health Transition Index/G-SET.

DOSE / ROUTE / REGIMEN (as applicable to active substudies)

In this study, a treatment cycle is 21 days in both monotherapy and combination cohorts.

Derazantinib is an investigational drug supplied as 100 mg immediate-release powder-filled capsules for oral administration. Atezolizumab is an approved medication supplied as 1200 mg/20 mL concentrate solution for intravenous (IV) infusion. The atezolizumab dose for all patients receiving the combination treatment will be 1200 mg Q3W.

In cohorts with a monotherapy regimen, unless a dose reduction is required to manage adverse events (AEs), the following doses of derazantinib are used:

- In **Substudy 1** and **Cohort 4a**, derazantinib 300 mg QD
- In **Substudy 5**, derazantinib200 mg BID

In cohorts with derazantinib-atezolizumab in combination, unless a dose reduction is required to manage AEs, the following doses of derazantinib are used:

- In **Substudy 3**, derazantinib 200 mg BID in combination with atezolizumab 1200 mg Q3W. If derazantinib 200 mg BID with atezolizumab 1200 mg Q3W is not assessed as safe and tolerable at the SIA, the full cohort of 36 patients will be enrolled and treated with the RP2D determined in Substudy 2
- In **Cohort 4b**, derazantinib 300 mg QD in combination with atezolizumab 1200 mg Q3W (as determined by Substudy 2)

KEY INCLUSION CRITERIA (as applicable to active substudies)

Inclusion criteria

(The full list of inclusion criteria is in Section 4.2 of the main protocol body)

1. Study Informed Consent Form signed by the patient indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study, prior to any study-related procedure.

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3. Histologically-confirmed transitional cell carcinoma of the urothelium of the upper or lower urinary tract.

4. Recurrent or progressing stage IV disease, or surgically unresectable, recurrent or progressing disease, as specified for each substudy:
   - **Substudy 1:** Patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment.
   - **Substudy 3:** First-line cisplatin-ineligible[1] patients with mUC expressing *FGFR1–3* GAs who have not received prior FGFR inhibiting treatment.
   - **Substudy 4:** Patients with FGFR inhibitor-resistant mUC expressing *FGFR1–3* GAs who have progressed on at least one standard regimen each of chemotherapy and immune-checkpoint blockade[2] and have received prior FGFR inhibiting treatment (excluding derazantinib)[3].
   - **Substudy 5:** Patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment.
5. An eligible *FGFR1–3* GA-positive test result for enrollment (see Appendix 1 and Section 3.1.1).
6. Measurable disease, as defined by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, documented within the 28 days prior to study drug administration.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1 or 2.
8. Adequate organ functions as indicated by Screening visit local laboratory values.
9. Men and women of childbearing potential must agree to avoid impregnating a partner or becoming pregnant, respectively, during the study, and for at least 5 months after the last dose of either investigational drug (see Inclusion criterion 9 in the main protocol body and Section 4.2 for full details).

KEY EXCLUSION CRITERIA (as applicable to active substudies)

(The full list of exclusion criteria is in Section 4.3. of the main protocol body)

1. Receipt of prior cancer treatment within specific interval periods (see Exclusion criterion 1 in the main protocol body).
2. For **Substudy 3** patients, prior treatment with anti-PD-1 or anti-PD-L1-therapeutic antibody, or PD-1/PD-L1 pathway-targeting agents.
3. Prior FGFR inhibiting treatment (except for **Substudy 4** patients).

[1] Cisplatin-ineligibility as defined by any one of the following criteria: 1) grade ≥ 2 peripheral neuropathy; 2) creatinine clearance (CL_{CR}) calculated by Cockcroft-Gault ≥ 30 mL/min but < 60 mL/min; 3) hearing impairment (measured by audiometry) of > 25 dB at two contiguous test frequencies in at least one ear; 4) comorbidity that forbids high-volume hydration.

[2] Prior treatment with combinations of immune-checkpoint blockade and FGFR inhibitor are not allowed; prior treatment with either sequential immune-checkpoint blockade and FGFR inhibitor treatment or combinations of FGFR inhibitor and chemotherapy are allowed.

[3] Patients assessed as having progressed upon prior treatment with FGFR inhibitors must have received FGFR inhibitor treatment for at least 12 weeks and have undergone at least one on treatment tumor imaging assessment.

4. For **Substudy 4** patients, prior treatment with FGFR inhibitor in combination with anti-PD-1 or anti-PD-L1 therapeutic antibody or PD-1/PD-L1 pathway-targeting agents.
5. Concurrent evidence of clinically significant corneal or retinal disorder likely to increase the risk of eye toxicity, including but not limited to bullous/band keratopathy, keratoconjunctivitis (unless keratoconjunctivitis sicca), corneal abrasion (unless related to trauma), inflammation/ulceration, confirmed by ophthalmological examination.
6. History of clinically significant cardiac disorders, including myocardial infarction or New York Heart Association Class II to IV congestive heart failure, within 6 months of the first dose of study drug, and/or concurrent and clinically significant abnormalities on electrocardiogram (ECG) at Screening, including QTcF > 450 ms for males or > 460 ms for females.

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10. Bellmunt score 3, or 2 if based on a combination of hemoglobin < 10 g/dL and presence of liver metastasis.
11. Any unresolved (at the time of Screening) clinically significant Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 toxicity (except for alopecia, grade 2 platinum-therapy related neuropathy, grade 2 anemia from previous anti-tumor treatment, grade 2 renal impairment per reduced CLCR by Cockcroft-Gault of 30–60 mL/min [which is generally accepted for this cancer population], and/or from medical/surgical procedures/interventions).
12. Known CNS metastases.
13. Lack of recovery from major (e.g., open abdominal) surgery after 4 weeks, or major elective surgery is planned during the foreseeable duration of the study.
14. Concurrent uncontrolled or active infection with human immunodeficiency virus (HIV; known HIV 1/2 antibodies positive).
15. Active hepatitis B or chronic hepatitis B without current antiviral therapy and an HBV DNA ≥ 100 IU/mL.
16. Active hepatitis C.
17. Active tuberculosis.
18. Severe bacterial, fungal, viral and/or parasitic infections on therapeutic oral or IV medication at the time of first dose of study drug administration

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MAIN STUDY ENDPOINTS (as applicable to active substudies)

Primary endpoints

The primary endpoint for efficacy is ORR, as measured by the proportion of patients with confirmed complete response (CR)[1] or partial response (PR)[2] by blinded independent central review (BICR).

[1] Evaluating target lesions, Complete Response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; further details Appendix 3 and Eisenhauer 2009.

[2] Evaluating target lesions, Partial Response (PR) is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; further details Appendix 3 and Eisenhauer 2009.

For the safety interim analysis in **Substudy 3**, the primary endpoint is the proportion of patients with DLTs during treatment with derazantinib 200 mg BID and atezolizumab 1200 mg Q3W in combination.

For the safety interim analysis in **Substudy 5**, the primary endpoint is the proportion of patients with DLTs during treatment with derazantinib 200 mg BID monotherapy.

Secondary endpoints
Efficacy, safety and pharmacokinetics of derazantinib will be measured overall and in prespecified subsets. The secondary endpoints for active substudies are provided in Section 3.2.2.

STATISTICAL ANALYSIS (as applicable to active substudies)
Key analysis populations

Safety / Intent-to-treat population: All patients with an eligible FGFR1–3 GA who received at least one dose of derazantinib or atezolizumab. Safety data will be summarized according to the treatment actually received.

Modified intent-to-treat (mITT) population: All patients who received at least one dose of derazantinib or atezolizumab, and have at least one post-baseline imaging assessment in accordance with RECIST 1.1, or documented clinical progression (every effort should be made to objectively assess radiographic progression). The mITT population will be used for all primary efficacy endpoint analyses.

Analysis of the primary efficacy endpoint
The primary efficacy endpoint will be ORR, defined as the achievement of confirmed CR or PR using RECIST 1.1, as assessed by BICR. Point estimates and 2-sided 95% confidence intervals (CIs) will be provided. The primary analysis will be performed on the mITT population and repeated on the per-protocol population.

Analysis of the primary safety endpoint (Substudies 3 and 5)
Safety interim analyses will be performed once up to 10 patients have been enrolled and full safety data are available in Substudies 3 and 5 to determine if the revised dosing regimen of derazantinib 200 mg BID either as monotherapy or in combination with atezolizumab is safe and tolerable. The safety evaluation will comprise updating a three-parameter cumulative Bayesian linear regression model (BLRM) with overdose control (EWOC) design with monotherapy and combination therapy for the incidence of DLTs to strictly manage the risk of excessive toxicity (see Section 8.3.5.1). The prior data will comprise the current number of DLTs observed at each derazantinib dose previously explored. With an acceptable target toxicity range for a dose defined as a probability of toxicity of 10% to 25% and an overdosing range of ≥25%, the posterior probability of overdosing will be updated over time. Data resulting in a posterior probability of overdosing for a dose in excess of 25% will be determined as unacceptable. This ensures a tolerable dose is chosen for subsequent evaluation of efficacy.

This process also involves regular dose decision meetings to review the updated cumulative model results as well as safety in individual patients. Safety and tolerability of both the monotherapy and the combination dose regimens, and restart of enrollment in Substudy 3 and 5 will be concluded by joint decisions taken by the IDMC, Investigators, and the Sponsor in reviewing the aggregate of DLT, AE and PK data from the first 10 patients each enrolled in Substudies 3 and 5.

Analysis of secondary endpoints

DCR will be summarized in the same way as the primary endpoint.

DOR, PFS and OS analyses will be performed using Kaplan-Meier (KM) methods. The analysis will be performed on the mITT population.

Sensitivity analyses within **Substudy 4** will be performed according to the stratification factor composite score and its variables.

ASSESSMENTS

Pharmacokinetics

Sparse derazantinib PK sampling: In the Sparse derazantinib PK sampling population, derazantinib plasma concentrations at each nominal time-point will be summarized by substudy and cohort using descriptive statistics.

Rich derazantinib PK sampling: All SIA patients in Substudies 3 and 5 will undergo Rich derazantinib PK sampling for measurement of plasma concentrations of derazantinib and relevant PK parameters. In the Rich derazantinib PK sampling population, PK parameters will be determined by non-compartmental analysis. The following parameters will be determined: C_{max}, t_{max}, $AUC_{0\text{-}12,}$, $AUC_{0\text{-}24}$, AUC_{last}. PK parameters from rich PK sampling will be summarized by Substudy and Cohort using descriptive statistics. Derazantinib plasma concentrations at each nominal time-point will be summarized by substudy and cohort using descriptive statistics.

In the atezolizumab PK population, atezolizumab and anti-drug antibodies (ADA) serum concentrations at each nominal time-point will be summarized by Substudy and Cohort using descriptive statistics.

Safety/tolerability

AE monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute CTCAE Version 5.0 (NCI CTCAE 5.0). AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), and grouped by System Organ Class and Preferred Term. Additional safety summaries will be provided for safety laboratory tests, vital signs, ECGs, physical examinations, ophthalmology examinations and ECOG PS.

Efficacy

Tumor response using RECIST 1.1 will be summarized by cohorts. Tumor response will be summarized using descriptive statistics and respective 95% confidence intervals. PFS, DOR, and OS will be summarized using KM analysis, including number and percentage of patients with events and of censored patients.

Biomarker analysis

The biomarker data will be summarized by treatment, using descriptive statistics. Exploratory analysis of the correlation between biomarkers and clinical efficacy endpoints may be performed.

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LIST OF ABBREVIATIONS

(i)CPD[1]	Confirmed progressive disease
(i)CR[1]	Complete response
(i)PR[1]	Partial response
(i)RECIST[1]	Response Evaluation Criteria In Solid Tumors
(i)SD[1]	Stable disease
(i)UPD[1]	Unconfirmed progressive disease
1L	First-line treatment
2+L	Second-line or post-second line treatment
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	AE of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AZB	Atezolizumab
BICR	Blinded independent central review
BLRM	Bayesian linear regression model
CI	Confidence interval
CL_{CR}	Creatinine clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRP	C-reactive protein
CRS	Cytokine-release syndrome
CSF1R	Colony-stimulating factor-1 receptor
CT	Computed tomography

[1] Where predicated by the letter '*i*', abbreviation refers to the equivalent acronym under RECIST adapted to account for the unique tumor response seen with immunotherapeutic drugs.

CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
cfDNA	Cell-free DNA
C*x*D*x*	Cycle (cycle number), Day (day number), e.g. C4D1 = Cycle 4, Day 1
CyTOF	Cytometry by time of flight
D0	Pretreatment phase
D1	Day 1
DCR	Disease control rate
DL	Dose Level
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
DZB	Derazantinib
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EU	European Union
EWB	Emotional well-being
EWOC	Escalation with overdose control
FACT-G	FACT General
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in-situ hybridization
FSH	Follicle stimulating hormone
fT3	Tri-iodothyronine
fT4	Thyroxine
FWB	Functional well-being
GA	Genetic aberration
GC	Gemcitabine/carboplatin

GCP	Good Clinical Practice
GEP	Gene-expression profile
GLP	Good Laboratory Practice
GPP3	Good Publication Practice
H_0	Null hypothesis
HA	Alternative hypothesis
HBV	Hepatitis B virus
hCG	Local serum pregnancy test
HCV	Hepatitis C virus
HIV	Human imunodeficiency virus
HR	Hazard ratios
HR-QoL	Health-related quality of life
IB	Investigator's Brochure
IC	Immune cell
IC_{50}	50% inhibition
iCCA	Intrahepatic cholangiocarcinoma
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IPCW	Inverse Probability of Censoring Weighted
IRB	Institutional Review Board
IRT	Interactive response technology
IRR	Immune-related reaction
ISF	Investigator Site File
ITT	Intent-to-treat
iUPD	Immunotherapy-treated unconfirmed progression
IV	Intravenous(ly)
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LFT	Liver function test
MAPK	MAP-Kinase

M-CAVI	Methotrexate/carboplatin/vinblastine
MedDRA	Medical Dictionary for Regulatory Activities
Mid-C2	Middle of Cycle2
mITT	Modified intent-to-treat
MMR-D	Mismatch repair-deficient
MRI	Magnetic resonance imaging
MSI-H	High-frequency microsatellite instability
MTD	Maximum tolerated dose
mUC	Locally advanced or metastatic and recurrent or progressing urothelial cancer
n	Number
NCI	National Cancer Institute
NCI CTCAE 5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NE	Not evaluable
NGS	Next-generation sequencing
OCT	Ocular coherence tomography
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD	Pharmacodynamics
PD-1	Programmed cell death receptor-1
PD-L1	Programmed death ligand-1
PDR	Pharmacodynamics Research Group
PDX	Patient-derived xenograft
PE	Polyethylene
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Prescribing Information
PK	Pharmacokinetic(s)
PO	Orally
POS	Positive (molecular status)
PopPK	Population PK

PP	Per protocol
PRO	Patient-reported outcome
PVC	Polyvinyl chloride
PWB	Physical well-being
Q3W	Every 3 weeks
QALY	Quality-adjusted life-year
QD	Once daily
QOD	Every other day
QTc	Corrected QT interval
QTcF	Difference between QTc corrected by Fridericia's formula
RNA	Ribonucleic acid
RNAseq	RNA sequencing
RP2D	Recommended Phase 2 dose
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SEER	Surveillance, Epidemiology, and End Results (Program)
SIA	Safety interim analysis
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
SWB	Social well-being
TAM	Tumor-associated macrophage
TEAE	Treatment-emergent adverse event
t_{max}	Time to peak (maximum) plasma concentration
TSH	Thyroid stimulating hormone
UC	Urothelial cancer
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analog scale

1 INTRODUCTION

1.1 Background on urothelial cancer

Urothelial cancer (UC) is the most common cancer of the urinary system worldwide, with UC of the bladder being the predominant histologic type and location. Although less common, UC may also originate in the renal pelvis, ureter, or urethra. It has been estimated that in 2019, there would be 80,470 new cases of bladder cancer and 17,670 deaths in the USA. Similar worldwide data estimate that there were 549,000 new cases and 199,922 deaths in 2018 (Bray 2018). The gender-specific estimates were 424,082 new cases and 148,270 deaths in men, and 125,311 new cases and 51,652 deaths in women (Bray 2018).

In a structured literature search, the crude incidence rate of UC reported for the USA, EU, and Japan was derived to be 25.7, 25.7 and 18.6 per 100,000 (83,662; 129,977; and 23,567 patients), respectively. The incidence of locally-advanced or metastatic UC was 3.8, 3.8 and 2.8 per 100,000 (12,494; 19,411 and 3,520 patients), respectively (Bharmal 2017).

Based on patients diagnosed with urothelial cancer since 1975 in the USA, the *Surveillance, Epidemiology, and End Results* (SEER) Program's Cancer Statistics Review 1975–2017 reported a 5.5% 5-year relative survival rate for patients diagnosed with primary metastatic UC (Howlader 2020). Poor prognostic factors for survival in patients with metastatic UC include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status < 80%, and visceral metastasis (i.e., lung, liver, or bone; Bajorin 1999). The presence of these unfavorable features was associated with a median survival of 4 months, compared with 18 months in patients without these features (Loehrer 1992).

Current choices for standard treatment of patients with locally-advanced or metastatic and recurrent or progressing UC (hereafter identified by the acronym mUC) are cisplatin-based chemotherapy, immune-checkpoint blockade, and combinations thereof. Specifically identified subgroups of mUC patients represent the indications investigated in this study. No targeted agents directed against oncogenic driver mutations have yet been fully approved in these indications.

1.1.1 Platinum-based chemotherapy in urothelial cancer

Prior to the advent of programmed cell death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) checkpoint inhibitors, systemic chemotherapy with cisplatin-based regimens was the standard of care (SoC), leading to median survival of around 1 year (von der Maas 2000, Sternberg 2001). However, for patients with platinum-refractory disease, median survival was only 6–9 months (Lorusso 1998, McCaffrey 1997, Papamichael 1997, Vaughn 2002).

Due to a variety of factors, including renal or hearing impairment, poor performance status, and neuropathies, 30% to 50% of patients with chemotherapy-naïve mUC are not candidates for cisplatin-based chemotherapy (Galsky 2011), and prior to the advent of therapeutic immune-checkpoint blockade, cisplatin-ineligibility limited treatment options to carboplatin-based regimes (Dash 2006, Galsky 2011, Bellmunt 2016).

Among the few randomized studies investigating how to best treat cisplatin-ineligible patients, a Phase 2/3 study compared two carboplatin-based chemotherapy regimens in mUC patients who were clinically considered ineligible ('unfit') for cisplatin chemotherapy as first-line treatment (De Santis 2009, De Santis 2011). Study participants received either gemcitabine/carboplatin (GCa) or methotrexate/carboplatin/vinblastine (M-CAVI). There were no significant differences in efficacy between the two treatment groups. The incidence of severe acute toxicities[1] was higher for those receiving M-CAVI. Patients treated with GCa attained an Objective Response Rate (ORR) of 36%. The median duration of treatment was 4 cycles and 14 weeks, respectively. The most common grade 3 to 4 toxicities with GCa were neutropenia (53%), febrile neutropenia (4%), thrombocytopenia (48%), and infection (12%), limiting the administration of the full six planned cycles to a minority of approximately one third of the platinum-ineligible population. The proportion of patients with severe acute toxicity-related death was 9% for patients treated with GCa. It is noted, however, that carboplatin is not a formally-approved drug for the treatment of cisplatin-ineligible patients.

1.1.2 Immune-checkpoint inhibiting agents in urothelial cancer

UC is a highly immunogenic tumor, partly as a result of the relatively high level of nonsynonymous mutations, which represents at least one mechanism for the generation of tumor neoantigens for the host immune system to recognize (Alexandrov 2013). PD-L1 overexpression in the tumor microenvironment and its binding to PD-1 on tumor antigen-specific T-cells is a mechanism for immune escape in UC. After decades of slow progress in drug development in UC, the advent of immune-checkpoint blockade has rapidly become an indispensable tool for its treatment. To date, atezolizumab, durvalumab, and avelumab (PD-L1 inhibitors), and pembrolizumab and nivolumab (PD-1 inhibitors), have been approved by the Food and Drug Administration (FDA) for mUC. In the post-platinum refractory setting, these five checkpoint blocking agents generated response rates between 15–21% (Balar 2017a, Balar 2017b and Suzman 2018, O'Donnell 2017, Sharma 2017, Powles 2017, Apolo 2017, Balar 2017), while ORR in the cisplatin-ineligible frontline setting was approximately 24% and 29% for atezolizumab and pembrolizumab, respectively.

In the two ongoing clinical studies, of atezolizumab (IMvigor130) and pembrolizumab (KEYNOTE-361), the Data Monitoring Committee (DMC) for each study performed an early review and found that patients in the monotherapy arms of both studies with PD-L1-low status had higher mortality compared with patients who received cisplatin- or carboplatin-based chemotherapy. The sponsors of both studies stopped enrolling patients whose tumors have PD-L1-low status to the atezolizumab or pembrolizumab monotherapy arms, in accordance with the DMCs' recommendations (Suzman 2018).

As a consequence, patients with mUC and PD-L1-low expression are without a standard and well-tolerated first-line treatment option beyond cytotoxic regimens which are often poorly tolerated in this indication (De Santis 2011).

[1] Severe acute toxicity was defined as death as a result of toxicity, renal toxicity (grade 3 to 4), febrile neutropenia (grade 3 to 4), hemorrhage/bleeding with thrombocytopenia (grade 4), or mucositis (grade 3 to 4).

1.2 FGFR inhibition in urothelial carcinoma

1.2.1 Current clinical evidence

Activation of the fibroblast growth factor receptor (FGFR) is a common oncogenic mechanism, occurring in a subset of nearly all common cancers (Babina 2017, Turner 2010). Genetic aberrations (GAs) in the *FGFR* genes in carcinomas result in receptor amplification, mutation, and generation of aberrant receptor fusions through translocation (Babina 2017, Turner 2010).

It is estimated that approximately 15-20% of patients with advanced/metastatic urothelial cancer have genomic *FGFR* aberrations (Necchi 2018, di Martino 2016, Helsten 2016). *FGFR3* mutations, and *FGFR1*, *FGFR2*, or *FGFR3* gene rearrangements and fusions (for the purposes of this protocol hereafter referred to as *FGFR1–3* GAs) are the most frequent *FGFR* GA among patients with UC and are found predominantly among patients whose tumors are allocated to the luminal subgroup (Choi 2017).

FGFR inhibitors have therefore been proposed for the treatment of patients whose tumors harbor *FGFR* GAs, and a number of FGFR inhibitors are currently under development in Phase 1–3 studies. Patients with mUC and *FGFR* GAs treated with FGFR inhibitors achieved an ORR ranging from 21–40% in uncontrolled clinical Phase 1/2 studies. The current evidence for FGFR-inhibiting treatment in mUC patients was generated with the following compounds:

- Erdafitinib (Balversa®) was granted an accelerated approval from the U.S. FDA in 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that have susceptible *FGFR3* or *FGFR2* genetic alterations and who progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (Balversa USPI) based on a Phase 2 study, reporting an ORR of 32% (N=87) ; of note, erdafitinib achieved an ORR of 59% (13 responses) in 22 UC patients unresponsive to immune-checkpoint blockade and an ORR of 35% (27 responses) in 77 UC patients without prior immune-checkpoint blockade (Loriot 2019).
- Infigratinib (BGJ398) achieved an ORR of 25% (N=67) in patients with confirmed *FGFR3* GAs (Pal 2018).
- Pemigatinib (INCB054828) is being investigated in an ongoing Phase 2 study of UC patients with fibroblast growth factor (*FGF*)/*FGFR* GAs (NCT02872714). Interim results from 61 patients with *FGFR3* mutations/fusions have demonstrated an ORR of 21% (Necchi 2018).
- Rogaratinib achieved an ORR of 24% (N=51) in patients with mRNA-ISH/NanoString confirmed *FGFR1/3* mRNA overexpression (Phase 1 expansion cohort) (Joerger 2018).

For derazantinib, preclinical data from a number of patient-derived xenograft mouse models in UC expressing *FGFR* mutations suggested a similar or superior efficacy with derazantinib in a direct comparison to erdafitinib using previously described equivalent dosing schedules (Perera 2017, Basilea data on file). In these experiments, similar or less body weight loss was observed with derazantinib.

Clinical anti-tumor activity with FGFR inhibitors was found in studies with patients identified by various methods (including but not limited to PCR, FM NGS™, RNAscope™/NanoString™) as carrying *FGFR* GAs, and applying differential definitions of the intended target population (mutations, fusions and ribonucleic acid [RNA] overexpression). In recent studies with erdafitinib (Loriot 2019), targeting mUC patients carrying *FGFR2/3* GAs has been shown to be a successful approach (Balversa USPI).

Based on a recent search in Foundation Medicine's FoundationInsight™ database of *FGFR1–3* GAs in 2,405 urothelial carcinoma test specimens, known or likely activating missense point mutations followed by rearrangements and copy number changes were found at a prevalence of approximately 18%, 4% and 3% of specimens, respectively. The frequency of known or likely activating FGFR3, FGFR2 and FGFR1 mutations and/or rearrangements/fusion eligible for this protocol is approximately 20%, 0.8% and 0.4%, respectively (Basilea data on file, Foundation Medicine Insight database, January 2019 – see Appendix 1). Due to the uncertainty around the oncogenic nature of *FGFR* amplification (Pearson 2016), *FGFR* amplifications are currently not included in the evaluation of derazantinib in patients with mUC expressing *FGFR1–3* GAs.

1.2.2 Derazantinib

Derazantinib is a spectrum-selective FGFR inhibitor with multi-kinase activity. In biochemical studies, derazantinib showed potent activity against both wild-type and variants of the FGFR kinases (*FGFR1–3*), and to a lesser extent against FGFR4, with inhibitor concentration values required for 50% inhibition (IC_{50}) in the low nM range. Less activity, but within 2–10 fold of FGFR2 activity, was observed for a number of other kinases relevant to anti-tumor treatment, i.e., VEGF-R2, PDGF-Rβ, KIT, RET, DDR2, colony-stimulating factor-1 receptor (CSF1R), and the Src family kinases (Hall 2016).

In an autophosphorylation assay, derazantinib inhibited autophosphorylation of *FGFR1* and *FGFR2* in a dose-dependent manner, suggesting that, in addition to inhibiting the active (phosphorylated) form of the kinase, derazantinib binds to the unphosphorylated or inactive form of the kinase and delays its activation. Across a large panel of cell-lines, IC_{50}s for inhibition of proliferation ranged from 0.1–10 µM, with the more sensitive lines being associated with high *FGFR* expression (1/2/3, or specific activating mutations). Preclinical studies demonstrated potent inhibition of tumor growth in FGFR pathway-activated models, including in *FGFR2*-driven (amplification/fusion/mutation) tumor xenografts grown subcutaneously in nude mice (Hall 2016). Furthermore, in a Phase I study, one derazantinib-treated evaluable UC patient with *FGFR2* and *FGF19* amplification achieved a partial response (PR) (Papadopoulos 2017).

Consequently, it is hypothesized that derazantinib may be a suitable treatment option for mUC patients expressing *FGFR1–3* GAs.

1.3 Combination of FGFR inhibition and immune-checkpoint blockade in urothelial carcinoma

Derazantinib is an investigational drug and is not yet registered in any indication globally. Atezolizumab (Tecentriq®) is a PD-L1 blocking antibody indicated (amongst others) for

the treatment of patients with locally surgically unresectable or metastatic UC, including those who were not eligible for frontline cisplatin-containing chemotherapy if their tumors express PD-L1 on more than 5% of tumor-infiltrating immune cells (ICs), as determined by an FDA-approved test[1], or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

Since pembrolizumab, the second drug approved for the treatment of specified mUC indications in the frontline setting, has received the same restriction of its indication for the frontline treatment of cisplatin-ineligible mUC patients whose tumors have PD-L1-low status, there is currently no strategic approach for mUC patients who express *FGFR* GAs and are considered cisplatin-ineligible in the frontline setting. Consequently, the availability of effective and tolerable treatment regimens for mUC patients with both *FGFR* GAs and PD-L1-low expression, which comprise approximately 20% of the frontline patient population, is limited. PD-L1-low expression together with expression of *FGFR* GAs is frequently seen in luminal-I-type tumors (Moreno 2020, Rosenberg 2020, Choi 2017, Siefker-Radtke 2018b, Loriot 2019). Interim results recently published from two ongoing Phase 2 studies using either rogaratinib and atezolizumab (Rosenberg 2020) or erdafitinib and cetrelimab (Moreno 2020) in combination demonstrated ORRs of 44% each in patients selected for *FGFR1/3* mRNA expression and specific *FGFR2/3* alterations, respectively, and unselected for PD-L1 expression.

The immunogenicity of UC is well documented (Babina 2017, Alexandrov 2013) and immune-checkpoint blockade has been demonstrated to generate long-term responses in several studies to date (Felsenstein 2018, Stenehjem 2018). However, recent research has identified an association between PD-L1-low expression and an increased probability of concurrent expression of *FGFR* GAs in UC patients (Choi 2017, Siefker-Radtke 2018b, Loriot 2019). In addition, redundancy in immunosuppressive pathways involves further mechanisms that could explain the observation that only certain subsets of UC patients respond to immune-checkpoint blockade; one example for such a pathway is the CSF1R interaction that leads to a phenotype switch of macrophages in the tumor microenvironment. A predominant M2-phenotype of tumor-associated macrophages (TAMs) has been shown to be associated with unfavorable patient outcomes, and to abolish susceptibility to therapeutic immune-checkpoint blockade (Rizvi 2018, Yang 2017, Hasita 2010). Conversely, it has been shown that CSF1R inhibition may bypass tumor-induced immunosuppression, restore T-cell activity, downregulate immunosuppressive macrophage activity and improve susceptibility to therapeutic immune checkpoint blockade using anti-PD-1/PD-L1 antibodies (Fleming 2018, Kim 2015, Ries 2014).

[1] For atezolizumab, a low PD-L1 expression level is less than 5% of immune cells staining positive for PD-L1 by immunohistochemistry. Information on FDA-approved tests for the determination of PD-L1 expression in locally-advanced or metastatic urothelial carcinoma or triple-negative breast cancer is available at: http://www fda.gov/CompanionDiagnostics.

In comparative kinase screens of known FGFR inhibitors, CSF1R kinase inhibition seems to be a unique characteristic of derazantinib (Basilea, data on file, 2019). Structural analyses suggest that conformations of FGFR- and CSF1R-structures are such that derazantinib can efficiently occupy the CSF1R kinase sub-pocket as well as the ATP-binding site of both FGFR and CSF1R (Basilea, data on file, 2019). Derazantinib reduced ligand-stimulated phospho-CSF1R in mouse macrophages in a concentration-dependent manner, with a maximum effect similar to the CSF1R inhibitor BLZ945 (Li 2019). In addition, studies found a frequent co-incidence of *FGFR* GAs (mainly *FGFR3* mutations) and low PD-L1 expression in UC patient samples (Choi 2017, Siefker-Radtke 2018b, Loriot 2019). These observations form the rationale to combine targeting FGFR-driven tumor cells with dual targeting of immunosuppressive stromal cells via CSF1R and PD-L1 to revert immune escape of tumor cells. Therefore, the administration of derazantinib in combination with atezolizumab may provide additional benefit, which is investigated in Substudies 2, 3 and 4 of this protocol.

1.4 Study rationale

1.4.1 Study design rationale

Several immune-checkpoint inhibitors, including atezolizumab (Balar 2017a, Rosenberg 2016), have already been approved for use in mUC, putting immune- inhibitors along-side standard platinum-based combination chemotherapy regimens (Felsenstein 2018). For patients with mUC expressing *FGFR* GAs, FGFR inhibitors are considered emerging treatment options in addition to standard chemotherapy regimens and immune-checkpoint inhibitors. Both preclinical and clinical data from derazantinib studies (Basilea, data on file, 2019, Papadopoulos 2017) and emerging clinical data from other studies with FGFR inhibitors (Joerger 2018, Pal 2018, Loriot 2019) have shown activity of FGFR inhibiting treatment in mUC patients. In addition, FGFR inhibitors in combination with anti-PD-(L)1 treatment have shown activity in patients with mUC, with ORRs of 44% for both rogaratinib in combination with atezolizumab (first-line cisplatin ineligible) and erdafitinib in combination with cetrelimab (second line or greater) (Rosenberg 2020; Moreno 2020).

Accordingly, this study is designed as a multiple cohort, multi-center Phase 1b/2 study to investigate the efficacy of derazantinib monotherapy or derazantinib-atezolizumab in combination in distinct populations of patients with either advanced solid tumors or upper/lower urinary tract mUC expressing any *FGFR* GAs. The study comprises the following five open-label substudies:

- ***Substudy 1:*** This substudy will enroll patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment. Patients in this substudy are to receive derazantinib 300 mg QD monotherapy, with the primary objective of assessing efficacy of this treatment regimen in this patient population (for substudy rationale see Section 1.4.1.1).
- ***Substudy 2:*** As of Protocol Version 5.0, enrollment to this substudy was completed, with interim results described in Section 1.4.1.2.

- ***Substudy 3:*** As of Protocol Version 5.0, this substudy has been modified. First-line cisplatin-ineligible patients with mUC expressing *FGFR1–3* GAs are to be treated with derazantinib 200 mg BID and atezolizumab 1200 mg Q3W in combination, with the co-primary objectives of assessing the safety and efficacy of this regimen in this patient population (for substudy rationale see Section 1.4.1.3). If derazantinib 200 mg BID at the safety interim analysis (SIA) is not assessed as safe and tolerable, patients are to be treated with the RP2D determined in Substudy 2 (see Section 1.4.1.2).
- ***Substudy 4:*** This substudy will enroll FGFR inhibitor-resistant patients with mUC expressing specific *FGFR1–3* GAs. Patients in this substudy are to be randomized (1:1) into two non-comparative cohorts: **Cohort 4a** patients will receive derazantinib 300 mg QD monotherapy, and **Cohort 4b** patients will receive derazantinib 300 mg QD and atezolizumab in combination. The primary objective of this substudy is to assess the efficacy of derazantinib monotherapy and derazantinib-atezolizumab in combination in this patient population (for substudy rationale see Section 1.4.1.4).
- ***Substudy 5:*** This substudy will enroll patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade, and have not received prior FGFR-inhibiting treatment. Patients in this substudy are to receive derazantinib 200 mg BID monotherapy, with the primary objective of assessing efficacy of this treatment regimen in this patient population (for substudy rationale see Section 1.4.1.5).

1.4.1.1 Rationale for Substudy 1

For derazantinib, preclinical data from a number of patient-derived xenograft mouse models in UC expressing *FGFR* mutations suggested a similar or superior efficacy with derazantinib in a direct comparison to erdafitinib using previously described equivalent dosing schedules (Perera 2017, Basilea data on file). In these experiments similar or less body weight loss was observed with derazantinib, suggesting a potential advantage in tolerability.

In clinical studies, patients with mUC and *FGFR* GAs treated with FGFR inhibitors achieved an ORR ranging from 21–40% in uncontrolled clinical trials (Joerger 2018, Necchi 2018, Pal 2018, Papadopoulos 2017, Loriot 2019). Additionally, in a subgroup of mUC patients expressing *FGFR* GAs and previously exposed to immune-checkpoint blockade, FGFR inhibition achieved a higher ORR of 59% (Loriot 2019). Of note, only one of these patients had an objective response to the prior immune-checkpoint blockade. While the range of activating *FGFR* GAs conferring oncogene addiction is still under investigation, there is evidence of activity of various FGFR inhibitors in mUC patients, and it appears that progression following immune-checkpoint blockade may comprise a patient subpopulation particularly susceptible to FGFR inhibitor treatment. The efficacy of derazantinib will be investigated in second-line or post second-line mUC patients expressing *FGFR1–3* GAs.

1.4.1.2 Rationale for Substudy 2 (including results)

Both derazantinib and atezolizumab have been studied in a substantial number of patients to understand their toxicity profile (see Section 1.4.3.2) (Papadopoulos 2017, Mazzaferro 2019, O'Donnell 2017, Balar 2017a, Rosenberg 2016). This substudy functions as a safety run-in cohort, with the aim of identifying the appropriate RP2D for the derazantinib-atezolizumab combination, before commencement of Substudy 3 and Substudy 4.

The sample size of approximately 12 patients per dose level has been based on recent contemporary studies with safety run-in cohorts for immune checkpoint blockade in combination with a tyrosine tyrosine kinase inhibitor in various solid tumors (Levy 2019,Bonomo 2018, Choueiri 2018, Atkins 2018).

Up to 24 evaluable patients will be included into two dose cohorts using a modified rolling-six design in order to characterize dose-limiting toxicities (DLTs) and the safety and tolerability profile of derazantinib when combined with atezolizumab, and identify potentially overlapping toxicities. The dose of atezolizumab will be 1200 mg (Q3W) while the starting dose of derazantinib will be 200 mg QD (Dose Level [DL] 1) which may be escalated to 300 mg (DL 2). Each dose-level will enroll up to 12 patients.

Results

The Intent-To-Treat (ITT) and Safety populations for the interim analysis of Substudy 2 comprised 26 patients, 14 in dose-level (DL) 1, and 12 in DL2. Across the two dose levels, 13 patients were enrolled in the maximum tolerated dose (MTD) cohorts to determine DLTs, seven in DL1 and six in DL2. To further assess safety and tolerability, 13 patients were additionally enrolled in the expansion cohorts, seven in DL1 and six in DL2. There were no DLTs assessed in either DL1 or DL2. The RP2D of derazantinib-atezolizumab in combination was determined to be 300 mg QD derazantinib plus 1200 mg atezolizumab Q3W.

The most commonly-reported AEs were fatigue/asthenia (31%), nausea (27%), and diarrhea (23%). Three patients (15%) had serious adverse drug reactions (ADRs), and six patients (23%) had ADRs of grade 3 or higher. Only one event of nephritis was reported as an immune-related AE. No ADRs leading to death were reported; the only AEs with a fatal outcome were two events of disease progression. 15% of patients experienced an AE that led to permanent discontinuation of study treatment. Overall, derazantinib-atezolizumab in combination was well tolerated without apparent differences in frequency and severity between both dose levels, and AEs were manageable for both dose levels (Abdul-Karim 2021, Basilea, data on file 2021).

1.4.1.3 Rationale for Substudy 3

The activity seen with erdafitinib in patients unresponsive to immune-checkpoint blockade generated the hypothesis that these patients may respond particularly well to FGFR inhibition, as PD-L1-low expression is frequently found in *FGFR* GAs expressing advanced urothelial cancers (Loriot 2019, Choi 2017, Siefker-Radtke 2018b). However, studies of both erdafitinib and rogaratinib in combination with immune-checkpoint

blockade also pursued an alternative hypothesis that immune-cell infiltration may be required for successful treatment resulting in target populations of mUC patients unselected for PD-L1 (Rosenberg 2020, Moreno 2020). The inhibiting effect of derazantinib on the CSF1R kinase (McSheehy 2019) regulating the phenotype of TAMs (Mantovani 2017, Ries 2014) may improve the immune-response to immune-check point inhibitors. Substudy 3 will therefore investigate whether first-line cisplatin-ineligible mUC patients derive a clinical benefit from derazantinib-atezolizumab in combination.

The dose regimen of derazantinib 300 mg QD plus atezolizumab 1200 mg Q3W was well tolerated and showed almost no increased toxicity over derazantinib monotherapy (see Section 1.4.1.2), suggesting that the benefit-risk may be further improved. Therefore, in line with the rationale for Substudy 5 (see Section 1.4.1.5), a higher dose of derazantinib (400 mg per day, given as 200 mg BID) will be explored.

1.4.1.4 Rationale for Substudy 4

Based on available literature of retrospective data and/or small cohorts of uncontrolled studies (Di Lorenzo 2015, Soga 2010), it is estimated that patients with mUC expressing *FGFR1–3* GAs treated with third or fourth-line single-agent chemotherapy and with progressive disease (PD) following platinum-containing chemotherapy, immune-checkpoint blockade, and/or FGFR inhibitor treatment, will attain an ORR of approximately 7% with single-agent chemotherapy regimens (e.g., taxanes or gemcitabine).

Acquired resistance to tyrosine kinase inhibitors, including FGFR inhibitors, remains an issue for patients receiving these targeted therapies, and several mechanisms of resistance to *FGFR*-directed therapy have been postulated (Chen 2011, Datta 2017, von der Maas 2000, Wang 2017). Current understanding of acquired resistance to FGFR-inhibiting treatment includes emergence of *de novo* or preexisting mutations conferring resistance at the drug binding site and activation of alternative pathways of receptor activation bypassing the FGFR-inhibiting effect, and has been clinically shown in patients with UC (Pal 2018).

There is some evidence that patients treated with FGFR inhibitors who experience progression may benefit from re-treatment with a different FGFR inhibitor (Meric-Bernstam 2018), and molecular modeling and *in vitro* studies have indicated that mutations leading to resistance to one FGFR inhibitor may be surmountable by treatment with a structurally distinct FGFR inhibitor (Goyal 2017), which is investigated by derazantinib monotherapy in Cohort 4a. Given the inhibiting effect of derazantinib on the CSF1R kinase (as described above), derazantinib may lead to an enhanced response to immune checkpoint inhibitors by dual targeting of the FGFR and CSF1R which may provide clinical benefit to this patient population, which is investigated in Cohort 4b.

The derazantinib dose in this substudy will be maintained at 300 mg QD since this substudy will enroll patients after at least three prior lines of treatment for mUC who are considered to benefit from the favorable benefit-risk profile of the current dose regimens.

1.4.1.5 Rationale for Substudy 5

Substudy 5 will include a similar target population as ongoing Substudy 1, however will explore a higher dose of derazantinib (400 mg per day, given as 200 mg BID) compared to the dose used in Substudy 1 (300 mg QD).

The rationale for exploring a higher dose of derazantinib is to assess whether a higher dose further improves the benefit-risk profile for derazantinib in patients with mUC and is based on observed safety and efficacy with derazantinib 300 mg QD in the ongoing current study, safety data with derazantinib 400 mg QD in the Phase 1 part of study ARQ 087-101, and new clinical pharmacology data. A dose regimen of 200 mg BID instead of 300 mg QD is anticipated to increase exposure and to enable a faster achievement of efficacious drug concentration levels in plasma and as such in tumor within a 1- or 2-week timeframe.

1.4.1.6 Rationale for molecular testing devices

Molecular eligibility for enrollment will be established by a positive test result for eligible *FGFR1-3* GAs (see Appendix 1). The molecular test is to be based on NGS of either tumor tissue DNA and/or RNA, or plasma circulating cell-free DNA (cfDNA).

Analysis of plasma cfDNA is an evolving technology that permits rapid and non-invasive genotyping of tumors. Plasma cfDNA is a subset of cell-free DNA that can be found in plasma, and represents genetic material from the primary tumor as well as metastases. cfDNA released by tumor cells undergoing apoptosis, necrosis, and in extracellular vesicles (exosomes) secreted from tumor cells is highly fragmented, ranging between 100 and 200 base pairs in size, and is rapidly cleared from the peripheral circulation with a short half-life (Sabari 2018, Diaz 2014). Plasma cfDNA harboring somatic mutations has been found to be highly specific for cancers, in some cancers (e.g., mUC) even highly prognostic (Vandekerkhove 2021), and has been proposed as a useful surrogate of tumor burden, intratumor heterogeneity, and response to therapy (Vandekerkhove 2021, Vandekerkhove 2019, Sabari 2018, Wyatt 2017, Pearson 2016, Diehl 2008).

Molecular testing of somatic mutations in ctDNA from liquid biopsies is feasible, with a short diagnostic turnaround time. It appears to be sufficiently sensitive to identify oncogenic driver DNA alterations present in matched metastatic tissue, which supports the utilization of plasma-derived DNA biomarkers to guide treatment eligibility for somatic *FGFR* GAs in this study.

Alternatively, and to account for the logistical constraints for some sites and patients, and the fact that in numerous investigational sites tissue remains the gold standard for molecular profiling of mUC (Vandekerkhove 2021), a local NGS testing using tissue DNA and/or RNA or plasma cfDNA will be accepted for patent enrollment. The NGS test commissioned at the study site's responsibility is to use standard protocols approved by the local IRB/IEC, Clinical Laboratory Improvement Amendments (CLIA), or other similar agency, or, where applicable, US FDA-approved kits. For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance; tests manufactured by health institutions and used only on their own patients are exempt from the Medical Devices Regulation requirements, and do not have to be CE-marked.

1.4.1.7 Rationale for pharmacodynamic research

Colony-stimulating factor 1 (CSF1)-mediated signaling via its receptor (CSF1R) is a key regulator of the proliferation, migration, survival, and differentiation of macrophages and their precursors (Stanley 2014). CSF1 is highly expressed by several tumors, and is associated with the presence of tumor-associated macrophages (TAMs) that closely resemble the M2-polarized functional phenotype. The presence of TAMs appears to be an adverse prognostic factor associated with poor survival in patients with solid tumors and hematological malignancies (Yang 2017). Targeting CSF1R signaling in TAMs may therefore be a promising therapeutic approach, by inhibiting tumor-promoting macrophages in the tumor microenvironment.

Derazantinib is a multikinase inhibitor that in addition to FGFR1–3 kinases also inhibits the CSF1R kinase. It has been shown in non-clinical studies that the CSF1R inhibitory effect of derazantinib on CSF1 stimulated mouse bone-marrow-derived macrophages is similar to known CSF1R inhibitors like pexidartinib and BLZ945 (Basilea data on file).

To investigate the pharmacodynamics (PD) of derazantinib, both as monotherapy and in combination with atezolizumab in patients with mUC, it is planned to investigate the role of CSF1R inhibition by derazantinib using a skin biopsy and blood sampling for monocyte subsets prior to the first dose of study drug at the Screening visit and on C2D1. Skin has been described as a surrogate tissue for PD dose selection, and as a sign of the anticipated mode of action reflective of changes in TAMs in paired tumor biopsies under CSF1R inhibiting treatment (Gomez-Roca 2019).

1.4.2 Rationale for patient reported outcomes

Patient-reported outcomes (PROs) provide an understanding of the impact a treatment has on a patient.

The EORTC QLQ-C30 is a validated instrument that has been widely used in assessing quality of life in patients with cancer. This instrument assesses global health status/quality of life, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms.

The FACT-Bl is a validated instrument that was developed for patients with bladder cancer and consists of the five subscales: physical well-being, functional well-being, emotional well-being, social well-being and an additional scale specific to bladder cancer.

The EQ-5D (5L) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years (QALYs). The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D also includes a graded (0 to 100) vertical visual analog scale (VAS) on which the patient rates his or her general state of health at the time of the assessment.

Health Transition Index/G-SET is a patient-rated change in health between two time periods using a five-point ordinal scale (single item) and will be used as an external anchor to determine the minimal important difference of the EQ-5D visual analogue scale, EORTC QLQ-C30 scales and FACT-Bl scales. It will be administered twice during the study.

1.4.3 Dose rationale

The cycle duration of derazantinib will be adapted from 4 weeks to 3 weeks continuous oral administration to match the cycle duration of the registered atezolizumab dosage of every 3 weeks (Q3W) and in order to harmonize study procedures and assessment intervals across all substudies and to reduce the likelihood of errors in dosing and deviations from prescribed protocol procedures.

1.4.3.1 Derazantinib

In clinical studies, the maximum tolerated dose of derazantinib monotherapy was assessed, and the RP2D was determined as continuous daily oral administration of 300 mg derazantinib (Papadopoulos 2017). In a Phase 2 study, derazantinib demonstrated encouraging anti-tumor activity and a manageable safety profile in patients with advanced, unresectable iCCA with *FGFR2* fusion who progressed after chemotherapy (Mazzaferro 2019).

Based on the data from completed and ongoing clinical studies with derazantinib, the most commonly reported drug-related adverse events (AEs) are transaminases elevations, fatigue /asthenia, gastrointestinal side effects (nausea, vomiting, diarrhea, constipation), xerostomia, hyperphosphatasemia, dysgeusia, decreased appetite, ocular side effects (xerophthalmia and blurred vision) and alopecia (see Section 7.1.1). Adverse events reported in derazantinib-treated patients have largely been mild to moderate in severity, and have infrequently required concomitant treatments (e.g., phosphate reducing agents) or study drug discontinuation.

New clinical pharmacology data from a food-effect study (Study DZB-CS-103) and from a mass balance study (Study DZB-CS-102) became available and simulations from a new two-compartment population PK model, which included data from these two new studies and from a previous clinical Phase 1 study (Study ARQ 087-101), was completed recently. The data from these analyses suggest that the half-life of derazantinib is in a range of 8 to 10 days compared to a previous assumption of only 5 days, and that the dose-exposure is linear across a dose range of 100 mg to 400 mg QD derazantinib.

The available safety data with derazantinib across the dose range of 100 mg to 400 mg QD together with the revised assumption on dose-linearity and half-life of derazantinib, support the exploration of a higher dose of 400 mg per day (given as 200 mg BID) as an additional option to assess whether the benefit to risk profile may be further improved in mUC patients (Derazantinib Investigator's Brochure [IB] - Edition 9.0, dated 29 January 2021).

1.4.3.2 Derazantinib in combination with atezolizumab

To date, the safety profiles of derazantinib (see Section 1.4.3.1) and atezolizumab have only been studied individually (Mazzaferro 2019, Petrylak 2018, Papadopoulos 2017, O'Donnell 2017, Balar 2017a, Herbst 2014).

In the first-in-human study of atezolizumab (formerly known as MPDL3280A), the PK for atezolizumab were shown to be consistent with those of typical immunoglobulins, with a mean terminal serum half-life of approximately 3 weeks. Dose-limiting toxicities were not reported, neither was a maximum tolerated dose (MTD) (Herbst 2014), indicating that atezolizumab was well tolerated up to a dose of 20 mg/kg body weight, including a flat 1200-mg dose, which was then used in further studies (Petrylak 2018).

For atezolizumab monotherapy, the incidence of SAEs in a pooled population from eight studies (N=3178) was 41.2%. The most common SAEs were pneumonia (3.1%), dyspnea (2.8%),pyrexia (2.5%), UTI (1.9%) and pleural effusion, pulmonary embolism, and sepsis (1.3%); urinary tract infections occurred more frequently in UC patients, while pneumonia was more common in lung cancer patients. In the overall population, Grade 3-4 AEs were reported by 46.5% of patients. The most common (>3% of patients) events were anaemia (5.0%), dyspnea (3.7%), fatigue (3.4%), hyponatremia (3.1%), and pneumonia (3.0%). In the overall pooled population, 7.1% of patients experienced an AE that led to withdrawal of study treatment. The most common AEs leading to withdrawal of study treatment were pneumonitis, pneumonia, death, sepsis, septic shock, dyspnea, and AST increased.

The results obtained from Substudy 2 confirmed the safety and tolerability of the novel derazantinib-atezolizumab combination (see Section 1.4.1.2) and the resulting RP2D allows combination of the full doses established for monotherapy treatment with either study treatment. In any cohort using the combination of derazantinib and atezolizumab, the clinical decision on continuation or withholding treatment within a combination setting will be based on current guidelines for immune checkpoint inhibitor treatment (Brahmer 2018).

1.5 Risk-benefit assessment

1.5.1 Derazantinib

Derazantinib is a potent FGFR inhibitor that shows strong anti-proliferative activity in cell lines harboring *FGFR2* alterations. In clinical trials in iCCA (Mazzaferro 2019, Papadopoulos 2017), derazantinib has been shown to be active with a manageable safety profile. In exploratory PDX studies of derazantinib and erdafitinib, the degree of anti-tumor activity and the level of toxicity appeared to be frequently similar, and with sometimes superior efficacy, to erdafitinib (Basilea data on file 2019). In clinical studies, patients with mUC and *FGFR* GAs treated with FGFR inhibitors achieved an ORR ranging from 21–40% in uncontrolled clinical trials (Joerger 2018, Necchi 2018, Pal 2018, Papadopoulos 2017, Loriot 2019). Additionally, in a subgroup of mUC patients expressing *FGFR* GAs and previously exposed to immune-checkpoint blockade, FGFR inhibition achieved a higher ORR of 59% (Loriot 2019). It is therefore expected that patients may derive a substantial benefit from derazantinib monotherapy.

In the event that derazantinib monotherapy does not meet the efficacy target, the proposed two-stage designs with interim analyses provide a reliable method for minimizing the number of patients enrolled to each study cohort and exposed to a potentially futile study drug.

Hyperphosphatemia, fatigue, ocular disorders, gastrointestinal disorders (constipation, diarrhea, nausea, vomiting, stomatitis, and dry mouth), transaminase elevations, hypertension, creatinine increased / renal disorders, hyponatremia, nail toxicity and alopecia are the most frequently reported adverse drug reactions (ADRs) with FGFR inhibitor treatments (Chae 2017, Katoh 2019, Balversa USPI, Pemazyre USPI, Abou-Alfa 2020, Loriot 2019), and are considered to be FGFR inhibitor class effects.

With regard to derazantinib, transaminase elevations is assessed as an important identified risk, and hyperphosphatemia, fatigue, ocular disorders, blood creatinine increased/renal disorders, hyponatremia, and nail toxicities are assessed as important potential risks. The following events are assessed as potential risks: gastrointestinal disorders, hypertension, alopecia[1], and QT prolongation[2].

As the safety data are accumulating and remain subject to final evaluation for ongoing studies with derazantinib, the Sponsor continues monitoring for the potential risks. In the current study, an Independent Data Monitoring Committee (IDMC) will assess safety data and provide recommendations to the Sponsor (see Section 3.5). Based on emerging information, the Sponsor will continue to evaluate safety data to characterize further potential risks and assess identified risks.

1.5.2 Derazantinib in combination with atezolizumab

Treatment with atezolizumab offers the potential for clinical benefit in patients with mUC. Atezolizumab is generally well tolerated, with reported AEs with potentially immune-related causes being consistent with an immunotherapeutic agent. These include rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, which have been observed in ongoing studies, and which to date have been monitorable and treatable. Detailed guidance on the management of immune-related AEs (see Section 7.1.1) is provided in the atezolizumab IB.

Both derazantinib and atezolizumab are generally well tolerated and treatment-related toxicities of both study drugs can be monitored and clinically managed. The results obtained from Substudy 2 confirmed the safety and tolerability of the novel derazantinib-atezolizumab combination (see Section 1.4.1.2) and the resulting RP2D allows combination of the full doses established for monotherapy with either drug.

It is expected that patients may derive a substantial benefit from a derazantinib-atezolizumab combination in Substudies 3 and 4 to balance any potentially increased toxicity from a combination of two drugs. In the event that the combination does not meet the efficacy targets, the proposed two-stage designs provide a reliable method to minimize the enrollment of patients to each study cohort and their exposure to a futile study drug.

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[1] Gastrointestinal disorders, and hypertension can be monitored and are clinically manageable, and the event alopecia has no significant impact on the physical condition of the patients.

[2] Based on available and centrally reviewed ECG data from study ARQ 087-101, QT prolongation is assessed as a non-important potential risk for derazantinib, because these data rule out a large effect (mean > 20 ms) on QTcF; there have been no SARs/arrhythmias reported as being consequent to QT prolongation, and the risk is mostly preventable with the routine risk minimization measures, which have been implemented (ECG triplicates for averaged QTcF within normal ranges prior to dosing, and monitoring of electrolyte abnormalities, concomitant medications, or other clinical factors, such as cardiac ischemia).

1.5.3 Pharmacodynamic research

Participation in the Pharmacodynamics Research (PDR) Group remains voluntary for patients. Similar PD evaluations have been performed in recently published study reports and have not reported an excess increase in AEs (e.g., Gomez-Roca 2019).

Patients willing to accept the extended schedule of assessments for the PD research, will sign a separate specific Informed Consent Form (ICF), which will detail the additional risks and benefits in relation to undergoing an extended schedule of study assessments.

1.5.4 Conclusion to risk-benefit assessment

Patients in clinical studies generally cannot expect to receive direct benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The available safety data for derazantinib (both at the current dose regimen of 300 mg QD and at the MTD of 400 mg QD, the latter being proposed to being explored as a revised dose regimen of 200 mg BID) do not indicate significant risks to study patients that require termination or modification of the ongoing derazantinib development program, and the safety profile for atezolizumab, which is a licensed medicine in UC, is well characterized. The proposed two-stage designs permit the minimization of patient accrual in case of study drug futility, and an IDMC will assess safety data and provide recommendations to the Sponsor.

The safety and tolerability profile of the novel combination treatment with derazantinib and atezolizumab has been assessed as clinically manageable in Substudy 2. No DLTs were observed, and no ADRs leading to death were reported; 15% of patients experienced an AE that led to permanent discontinuation of study treatment.

All substudies will include close safety monitoring through AE collection, and assessment of clinical safety laboratory tests, pregnancy testing, vital signs, centrally-read ECGs, physical examinations, ophthalmology examinations and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS).

The risk-benefit balance is therefore expected to be favorable in the intended mUC patient populations.

2 STUDY OBJECTIVES

Effective Protocol Version 5.0, only substudy objectives and hypotheses applicable to active substudies are included in this section.

2.1 Primary objectives and hypotheses

2.1.1 Primary efficacy objective

To evaluate the ORR of derazantinib monotherapy (in Substudies 1 and 5, and Cohort 4a) and of derazantinib-atezolizumab in combination (in Substudy 3 and Cohort 4b) in patients with mUC (i.e., surgically unresectable or metastatic UC) expressing *FGFR1–3* GAs.

- *Hypothesis of Substudy 1:* Patients with mUC expressing *FGFR1–3* GAs treated with derazantinib 300 mg QD will attain a clinically meaningful ORR (e.g., ~34%), which is superior to the estimated ORR of 21% attained with pemigatinib, which is the lowest ORR currently reported from studies with FGFR-inhibiting treatment of UC patients (Loriot 2019, Necchi 2018, Pal 2018).
- *Hypothesis of Substudy 3:* Patients with mUC expressing *FGFR1–3* GAs treated with derazantinib 200 mg BID in combination with atezolizumab 1200 mg Q3W will attain a clinically meaningful ORR (e.g., ~45%), which is superior to the estimated ORR of up to 25% obtained with treatments investigated/licensed for use this patient population (Pal 2018, Rosenberg 2016).
- *Hypothesis of Substudy 4:* Patients with mUC and disease progression after failure of prior FGFR inhibitor treatment treated with either derazantinib 300 mg QD or derazantinib 300 mg QD in combination with atezolizumab 1200 mg Q3W will attain a clinically meaningful ORR (e.g., ~20%), which is superior to the estimated ORR of up to 7% obtained with treatments (e.g., monotherapy taxanes in fourth-line or greater treatment) available for this patient population (Di Lorenzo 2015, Soga 2010).
- *Hypothesis of Substudy 5:* Patients with mUC expressing *FGFR1–3* GAs treated with derazantinib 200 mg BID will attain a clinically meaningful ORR (e.g., ~30%), which is superior to an ORR of 10%, which is acknowledged to be a benchmark whereby no further clinical investigation is warranted.

2.1.2 Primary safety objective of Substudy 3

To confirm derazantinib 200 mg BID with atezolizumab 1200 mg Q3W as a safe and tolerable dose regimen.

- *Hypothesis:* Derazantinib at a dose of 200 mg BID with atezolizumab 1200 mg Q3W is sufficiently well-tolerated to permit further clinical investigation.

2.1.3 Primary safety objective of Substudy 5

To confirm derazantinib 200 mg BID as a safe and tolerable dose regimen of derazantinib monotherapy.

- *Hypothesis:* Derazantinib at a dose of 200 mg BID is sufficiently well-tolerated to permit further clinical investigation.

2.2 Secondary objectives

- To evaluate the efficacy of the study drugs as measured by disease control rate (DCR), duration of response (DOR), PFS and overall survival (OS)
- To assess the safety and tolerability of the study drugs
- To characterize the PK profile of derazantinib 200 mg BID (and, if applicable, derazantinib metabolites) as monotherapy (Substudy 5) and in combination with atezolizumab (Substudy 3).

- To evaluate changes, and assess the minimally important difference, in health-related quality of life (HR-QoL) and symptom response from baseline by cohort, substudy and in the overall study population using the EORTC QLQ C30, FACT-Bl, EQ-5D (5L) visual analogue scale (VAS), and Health Transition Index/G-SET.

2.3 Exploratory objectives

2.3.1 Exploratory objectives specific to efficacy-estimating substudies

- To describe the type of *FGFR1–3* GAs in responders and non-responders
- To explore the concordance between molecular *FGFR* assessments from plasma-based and tissue-based NGS testing
- To explore the efficacy of derazantinib-atezolizumab in combination following documented disease progression in patients who previously received derazantinib monotherapy and crossed over to combination treatment (Substudy 4)
- To explore the efficacy of derazantinib-atezolizumab in combination by iRECIST (see Section 5.3.3.2.4) as measured by ORR, DCR, DOR and PFS
- To compare the efficacy of derazantinib with that of derazantinib-atezolizumab in combination to generate potential hypotheses for future comparative studies (Substudy 4)
- To explore the efficacy of derazantinib and of derazantinib-atezolizumab in combination by response-indicating molecular biomarkers, as measured by ORR, DCR, DOR, PFS and OS
- To explore the effect of derazantinib on CSF1R expressing cells in blood samples and skin biopsies
- To characterize utilities in patients treated with derazantinib or derazantinib-atezolizumab in combination using the EQ-5D (5L) for health economic modeling.

2.3.2 Exploratory PK objectives

- To explore the exposure of 300 mg QD derazantinib monotherapy (and, if applicable, derazantinib metabolites) and in combination with atezolizumab
- To explore the exposure of atezolizumab and anti-drug antibodies (ADA) directed against atezolizumab, in the context of atezolizumab combination with derazantinib

3 INVESTIGATIONAL PLAN

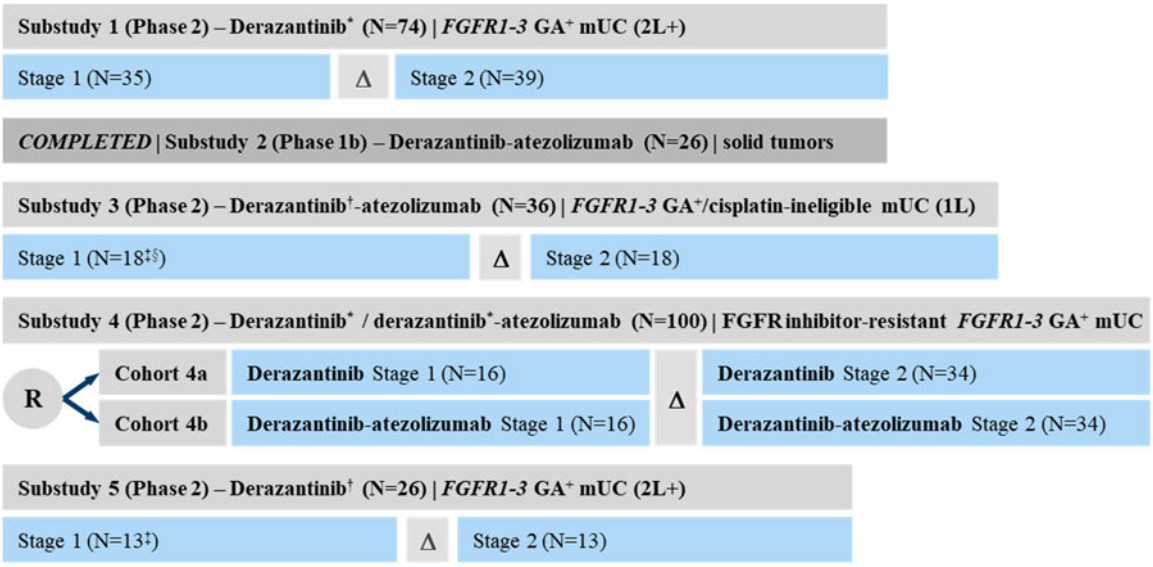
3.1 Overview of study design and study flow chart

This study is a multiple cohort, multi-center Phase 1b/2 study. An overview of the overall study design is provided in Figure 1. The efficacy of derazantinib or derazantinib-atezolizumab in combination is evaluated in cohorts addressing various clinical stages of disease progression and prior treatments.

Effective from Protocol Version 5.0, **Substudy 3** has been modified, and **Substudy 5** has been added. **Substudy 2** has been completed.

In all efficacy-estimating cohorts, sample-size minimizing statistical designs with interim analyses for futility and efficacy will be used.

Figure 1 Overview of study design



Abbreviations: 1L: first-line treatment; 2+L: second-line or post-second line; Δ: decision for transition to Part 2 / Stage 2; FGFR: fibroblast growth factor receptor; GA: genetic aberration; mUC: locally advanced or metastatic and recurrent or progressing urothelial cancer; R: randomization.

* Derazantinib 300mg QD

† Derazantinib 200 mg BID

‡ Safety interim analysis after 10 patients

§ If derazantinib 200 mg BID is not assessed as safe and tolerable, the RP2D determined in Substudy 2 will be used.

Only patients with mUC expressing *FGFR1–3* GAs will be enrolled (see Section 3.1.1).

As of Protocol Version 5.0, this study comprises five open-label substudies (of which four are ongoing; see Figure 1):

- ***Substudy 1:*** This substudy will enroll patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment. Patients in this

substudy are to receive derazantinib 300 mg QD monotherapy, with the primary objective of assessing of this treatment regimen treatment efficacy in this patient population.

- ***Substudy 2:*** As of Protocol Version 5.0, enrollment to this substudy was completed, with interim results described in Section 1.4.1.2.
- ***Substudy 3:*** As of Protocol Version 5.0, this substudy has been modified. First-line cisplatin-ineligible patients with mUC expressing *FGFR1–3* GAs are to be treated with derazantinib 200 mg BID and atezolizumab 1200 mg Q3W in combination, with the co-primary objectives of assessing the safety and efficacy of this regimen in this patient population. If derazantinib 200 mg BID at the SIA is not assessed as safe and tolerable, patients are to be treated with the RP2D determined in Substudy 2.
- ***Substudy 4:*** This substudy will enroll FGFR inhibitor-resistant patients with mUC expressing *FGFR1–3* GAs. Patients in this substudy are to be randomized (1:1) into two non-comparative groups: **Cohort 4a** patients will receive derazantinib 300 mg QD monotherapy, and **Cohort 4b** patients will receive derazantinib 300 mg QD and atezolizumab 1200 mg Q3W in combination. The primary objective of this substudy is to assess the efficacy of derazantinib monotherapy and derazantinib-atezolizumab in combination in this patient population.
- ***Substudy 5:*** This substudy will enroll patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR-inhibiting treatment. Patients in this substudy are to receive derazantinib 200 mg BID monotherapy, with the co-primary objectives of assessing the safety and efficacy of this treatment regimen in this patient population.

Patients enrolled in **Substudies 3, 4 and 5** have the option of participating in exploratory PD research to investigate the role of CSF1R inhibition by derazantinib. This will comprise a skin biopsy and blood sampling for monocyte subsets prior to the first dose of study drug (Screening Visit) and on C2D1 (see Section 5.3.5.3).

3.1.1 Molecular eligibility

Molecular eligibility for enrollment will be established by a positive test result for eligible *FGFR1-3* GAs (see Appendix 1). The molecular test is to be based on NGS of either tumor tissue DNA and/or RNA, or plasma cfDNA.

For patients with no access to local NGS testing, central testing will be performed in a laboratory in the USA designated by the Sponsor; this 'central testing' will be based on NGS testing of cfDNA from a liquid biopsy obtained at Pre-screening.

For potential prospective study participants without available positive *FGFR1–3* GA test result, a Pre-screening visit (see Section 3.1.2) is to be scheduled for liquid biopsy sampling.

Alternatively, an eligible, positive *FGFR1–3* GA test result obtained from local NGS testing ('local testing', the commissioning of which is the study site's responsibility) can

be used to establish molecular eligibility; no Pre-screening visit is required. The commissioned NGS test for 'local testing' is to use standard protocols approved by the local IRB/IEC, Clinical Laboratory Improvement Amendments (CLIA), or other similar agency, or, where applicable, US FDA-approved kits. For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance; tests manufactured by health institutions and used only on their own patients are exempt from the Medical Devices Regulation requirements, and do not have to be CE-marked.

3.1.2 Pre-screening

A Pre-screening visit is only required for prospective study participants under consideration for enrollment into Substudies 1, 3 or 5, and if no documented local NGS test result with an eligible *FGFR1–3* GA is available. If these patients have no access to local NGS testing, they are required to sign the Pre-screening Informed Consent Form (ICF) for molecular screening, and are not considered enrolled (i.e., patients are considered to be in pre-screening for the study) until receipt of a positive central molecular test result, and dated patient signature on the Study ICF. The Pre-screening visit for liquid biopsy sampling should be scheduled following assessment of objective documented progression after prior anti-cancer treatment (e.g., rather than during prior anti-cancer treatment) to optimize the likelihood of capturing cfDNA shedding reflective of disease progression.

No Pre-screening visit is required for patients with a known and eligible *FGFR1–3* GA status (see Appendix 1) from local NGS testing; these patients may directly initiate clinical screening procedures. **Substudy 4** patients also do not require a Pre-screening visit if their molecular eligibility is known from prior FGFR-inhibiting treatment (documentation of which should be made available at the Screening visit, otherwise a Pre-screening visit should be scheduled).

3.1.3 Screening

Clinical Screening procedures are required to confirm study-treatment eligibility (see Section 5.3.1). For the baseline study imaging assessment of measurable disease, RECIST 1.1 criteria apply (Appendix 2, Eisenhauer 2009).

Re-screening for molecular inclusion criteria is not permitted unless the tissue biopsy or liquid biopsy was not evaluable for technical reasons.

Under rare conditions and contingent upon Sponsor approval, patients may be given the possibility to be re-screened after initially failing screening.

3.1.4 Treatment period

Patients will be evaluated regularly during the treatment period as per the schedule of assessments shown in Table 1. If a patient visit deviates from the permitted protocol window, the next visit must be performed at the correct timing based on the date of Cycle 1 Day 1 (C1D1).

Blood samples for PK measurements of derazantinib and atezolizumab will be collected in accordance with the schedule set out in Table 1 and Section 5.3.4.1 (for derazantinib), and Section 5.3.4.2 (for atezolizumab).

Efficacy is to be evaluated by blinded independent central review (BICR) using RECIST 1.1 criteria every 9 weeks (±7 days) for the first 27 weeks, and every 12 weeks (±7 days) thereafter (see Section 5.3.3.2). Ideally, efficacy assessments are scheduled to permit treatment decision for D1 of the subsequent cycle.

Dose delays and/or reductions are permitted with derazantinib if a derazantinib-related toxicity is observed (see Section 6.1.1.5). No dose reductions are permitted with atezolizumab; however, dose delays are acceptable if an atezolizumab-related toxicity is observed (see Section 6.1.2.6). A related toxicity is defined as any toxicity considered related to derazantinib and/or atezolizumab, i.e., probably, or possibly related.

Substudies 3 and 5 will include a SIA for ADRs indicative of DLT (see Section 7.3.3) in the first 10 treated patients each. The process involves regular dose decision meetings (see Section 8.3.5.1). The schedule of AE assessments, including central ECGs and ophthalmological examinations, clinical safety laboratory blood sampling, and urinalysis has been expanded to a weekly schedule of assessments for the first two treatment cycles (see Table 1). Rich PK profiling will be performed for all patients during the safety run-in phase. The PK sampling schedule is provided in the Table 1.

In **Substudy 3**, if derazantinib 200 mg BID plus atezolizumab 1200 mg Q3W is considered a tolerable and safe at the safety interim analysis (endorsed by the IDMC), enrollment of Stage 1 will be completed for the efficacy interim analysis of patients. If the dose regimen is not tolerated, further enrollment will be revised and Stage 1 of Substudy 3 will enroll patients to be treated with the RP2D of derazantinib 300 mg QD plus atezolizumab 1200 mg Q3W, as determined in Substudy 2.

In **Substudy 5**, if derazantinib 200 mg BID is considered tolerable and safe at the interim analysis (endorsed by the IDMC), and also improves exposure as expected, enrollment of Stage 1 will be completed for the efficacy interim analysis of patients. If derazantinib 200mg BID is not considered tolerable and safe, other regimens may be investigated if needed following a protocol amendment.

3.1.5 End of Treatment / Safety Follow-up period

Patients will continue to receive study treatment until disease progression, patient withdrawal, lost to follow up, unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment; or until the substudy, cohort or the study is terminated by the Sponsor (see Section 4.4.4 for further details and reasons to stop receiving study treatment), whichever occurs first.

The End of Treatment visit will be conducted within 7 days after the administration of the last dose of study drug(s). Two Safety Follow-up visits will be conducted, 28 days (±3 days) and 90 days (±3 days) after the administration of the last dose of study drug(s). See Section 5.2.2.8 and Section 5.2.2.9 for further details.

Once patients have been discontinued from treatment with the initially assigned study drug, other treatment options will be at the discretion of the Investigator. All concomitant medications should continue to be recorded on the appropriate electronic case report form (eCRF) until last Safety Follow-up visit.

For further details on treatment and study discontinuation, see Section 4.4.4.

3.1.6 Optional post-discontinuation study treatment crossover (Cohort 4a)

Patients from **Cohort 4a** with PD (as assessed by BICR) will have the opportunity to receive treatment with derazantinib-atezolizumab in combination in a Crossover Phase. Crossover patients may initiate treatment with derazantinib-atezolizumab within 2 months of their last dose of derazantinib, regardless of the time of progression.

Crossover is optional and is at the discretion of the Investigator (with the Sponsor's and patient agreement).

3.1.6.1 Eligibility criteria for post-discontinuation study treatment crossover

Patients who permanently discontinue derazantinib due to an AE, withdraw consent, or for any reason other than PD, will not be eligible for crossover.

Patients who meet the following inclusion criteria are eligible for crossover:

1. Documented PD on derazantinib (as confirmed by BICR) as a participant of **Cohort 4a**
2. All ongoing AEs must have resolved to baseline or Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 (except alopecia and peripheral neuropathy)
3. No new central nervous system (CNS) metastases
4. ECOG PS of 0–2
5. Patient has not received any other systemic anti-cancer therapies after derazantinib administration during the treatment phase.
6. If required, completed palliative radiotherapy (30 Gy or less) ≥ 7 days before the first dose of crossover study treatment.
7. Patient has adequate organ function, as indicated by the laboratory values detailed in Section 4.2.

3.1.6.2 Assessments during post-discontinuation study treatment crossover

Once eligibility is confirmed, crossover patients will follow the same schedule of assessments as **Cohort 4b** patients (as detailed in Table 1), including atezolizumab PK and ADA sampling, but without further derazantinib PK sampling. In particular, safety-oriented assessments detailed in Section 5.3.2 need to be followed as specified.

Screening procedures need to be completed within 28 days of confirmed PD (or up to 42 days from last dose if recovering from an AE). Procedures and assessments completed at the time of withdrawal from the main study may be used for the start of the Crossover Phase of the study.

The tumor imaging used to determine PD can be used as the new baseline image for the Crossover Phase if this was obtained within the 28 days prior to receiving the first dose of derazantinib-atezolizumab combination.

Patients who crossover and then achieve a complete response (CR) per RECIST 1.1 criteria have the option to hold treatment with derazantinib and atezolizumab in combination while continuing in the study with the potential to resume treatment upon recurrence at the

discretion of the Investigator. Patients will receive the RP2D of derazantinib-atezolizumab unless their last dose of derazantinib was reduced according to dose modification prescribed by this protocol (see Section 6.1.1.5); derazantinib dose re-escalation in the crossover phase of this protocol is not permitted.

3.1.7 Survival Follow-up period

Patients who are permanently discontinued from study treatment for reasons other than death and consent withdrawal for further safety and survival follow-up, regardless of the reason, will enter the survival follow-up period (see Section 5.2.3).

Survival Follow-up (at least every 3 months ± 14 days from last dose of study drug) will start on the day of the last dose of either study drug and will continue until the study has completed (see Section 3.1.8) or other discontinuation criteria are met (see Section 4.4.4).

All subsequent anticancer therapies should continue to be recorded on the appropriate electronic case report form (eCRF) for the duration of the patient's survival follow up.

3.1.8 Beginning and end of the study

The study begins when the first patient signs any ICF.

The study ends when the last patient completes the last study-related phone-call or visit, discontinues from the study, or is lost to follow-up (i.e., the patient is unable to be contacted by the investigator).

In addition, the Sponsor may decide to terminate the study at any time (see Section 4.5.4).

For patients who continue to derive benefit (per Investigator assessment) from any of the study treatment regimens at the time of study closure, the Sponsor aims to provide continued individual access to study drug, either under a rollover study protocol, or in the context of compassionate use/named patient access, where applicable.

3.2 Endpoints

Effective Protocol Version 5.0, only endpoints applicable to active substudies are listed is this section.

3.2.1 Primary endpoints

3.2.1.1 Primary endpoint

- ORR, as measured by the proportion of patients with confirmed CR[1] or PR[2] by BICR.

[1] Evaluating target lesions, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; further details Appendix 3 and Eisenhauer 2009.

[2] Evaluating target lesions, PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; further details Appendix 3 and Eisenhauer 2009.

3.2.1.2 Primary safety endpoint (Substudies 3 and 5)

- For the safety interim analysis in **Substudy 3**, the primary endpoint is the proportion of patients with DLTs during treatment with derazantinib 200 mg BID and atezolizumab 1200 mg Q3W in combination.
- For the safety interim analysis in **Substudy 5**, the primary endpoint is the proportion of patients with DLTs during treatment with derazantinib 200 mg BID monotherapy.

Safety and tolerability of both the monotherapy and the combination dose regimens will be concluded by joint decisions taken by the IDMC, Investigators, and the Sponsor in reviewing the aggregate of DLT, AE and PK data from the first 10 patients enrolled in Substudy 3 and 5.

3.2.2 Secondary endpoints

- DCR, as measured by the proportion of patients with confirmed CR, PR or stable disease (SD)[1] by BICR
- DOR, as calculated from the first date of documented tumor response to disease progression by BICR
- Median PFS and PFS at 6 months, as determined by BICR and measured from time of first dose to time of objective tumor progression or death, and the proportion of patients alive and free of objective tumor progression 6 months after cohort assignment, respectively
- Median OS and OS at 6 months, as measured from time of first dose until time of death and the proportion of patients alive 6 months after cohort assignment, respectively
- Safety and tolerability of study drugs as measured by the frequency and severity of AEs, clinical laboratory parameters, vital signs, ECOG PS, physical examinations (including eye examinations), and ECG parameters over time, and graded by NCI CTCAE 5.0
- Derazantinib (and – if applicable –derazantinib metabolites) plasma concentrations, C_{max}, t_{max}, AUC_{0-12}, AUC_{0-24}, AUC_{last} assessed by measurements in blood samples during treatment as monotherapy (Substudy 5) or in combination (Substudy 3)
- Changes in HR-QoL and symptom response, measured by global, functional and symptom scores obtained from patient reported outcome instruments at baseline and over time (EORTC QLQ C30, FACT-Bl, EQ-5D [5L] VAS), and Health Transition Index/G-SET.

[1] Evaluating target lesions, SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease (PD, see following definition), taking as reference the smallest sum of diameters while on study. PD is defined as 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. (Note: the appearance of one or more new lesions is also considered progression).

3.2.3 Exploratory endpoints

3.2.3.1 Exploratory endpoints specific to efficacy-estimating substudies

- Responding and non-responding patients are to be analyzed by type of *FGFR1–3* GA.
- The proportion of patients with concordant molecular assessment from plasma-based and tissue-based testing measuring *FGFR* GAs in matched tumor-liquid biopsy samples obtained at baseline and during treatment will be described.
- The ORR, DCR, DOR, PFS and OS of patients treated with derazantinib-atezolizumab in combination will be evaluated for patients crossing over after documented disease progression on derazantinib monotherapy (Substudy 4).
- The ORR, DCR, DOR and PFS of patients treated with derazantinib-atezolizumab in combination will be evaluated by iRECIST (applicable to Substudies 3 and 4).
- In Substudy 4, the ORR, DCR, DOR, PFS and OS of patients treated with derazantinib will be compared to that of patients treated with derazantinib-atezolizumab in combination to generate potential hypotheses for future comparative studies.
- The ORR, DCR, DOR, PFS and OS of patients treated with derazantinib and derazantinib-atezolizumab in combination, respectively, will be evaluated by molecular profile, gene expression profile, and biomarkers.
- The proportion of patients with a specific reduction of immunosuppressive macrophages in skin biopsies or peripheral blood monocytes on derazantinib monotherapy and derazantinib-atezolizumab combination treatment.
- EQ-5D (5L) health status data will be used for obtaining utility measures for economic modeling. For the EQ-5D (5L), further scoring and analysis may be reported in a separate document.

3.2.3.2 Exploratory PK endpoints

- Derazantinib plasma concentrations, assessed by measurements in blood samples.
- Plasma concentrations of derazantinib metabolites (if applicable), assessed by measurements from blood samples.
- Atezolizumab serum concentrations, assessed by measurements from blood samples (Substudy 3, Cohort 4b, and Crossover).
- Serum ADA assayed from blood samples (Substudy 3, Cohort 4b and Crossover).
- Derazantinib plasma concentrations (C_{max}, t_{max}, AUC0-24, AUC_{last}), assessed by measurements from blood samples (applicable to Substudies with 300 mg QD).

3.3 Number of patients

The study plans to enroll up to 272 evaluable patients across all five substudies.

3.4 Study sites

Up to 100 study sites in Asia-Pacific, North America, and Europe.

3.5 Independent Data Monitoring Committee

An IDMC will be established by the Sponsor to evaluate accumulating safety data in patients enrolled in the study, to ensure their safety and wellbeing, and to provide recommendations to the clinical teams in charge of conducting the study.

For **Substudy 2**, the IDMC will be additionally responsible for determining the RP2D of derazantinib-atezolizumab in combination. This decision will be taken in an open session in which study Investigators and Sponsor representatives will be able to participate.

For **Substudy 3 and 5**, the IDMC will be additionally responsible for determining whether derazantinib 200 mg BID, either as monotherapy or in combination with atezolizumab, can be declared as tolerable regimens. This decision will be taken in an open session in which study Investigators and Sponsor representatives will be able to participate.

As detailed in the IDMC Charter, the IDMC will comprise experts in the field of oncology and biostatistics, who will be required to disclose their relevant financial interests to the Sponsor. None of the IDMC members may be involved in the conduct or reporting of any ongoing clinical study of which Basilea is the Sponsor.

4 STUDY POPULATION

Effective Protocol Version 5.0, only information applicable to active substudies is provided in this section.

4.1 Target populations

The target population is patients with surgically unresectable, metastatic, recurrent and/or progressing UC (i.e. mUC) expressing known and/or likely activating and/or oncogenic *FGFR1–3* GAs (see Appendix 1).

4.2 Inclusion criteria

Each patient must meet all of the following inclusion criteria (patients may repeat the screening procedures within the screening period after initially failing to meet the clinical inclusion criteria; rescreening for molecular inclusion criteria is not permitted unless the tissue biopsy or liquid biopsy was not evaluable for technical reasons):

1. Study ICF signed by the patient indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study, prior to any study-related procedure.
2. Male or female aged ≥ 18 years.
3. Histologically-confirmed transitional cell carcinoma of the urothelium of the upper or lower urinary tract
   Note: Minor components (< 50% overall) of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change, are acceptable.
4. Recurrent or progressing stage IV disease, or surgically unresectable, recurrent or progressing disease, as specified for each substudy:

- ***Substudy 1:*** Patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment.
- ***Substudy 3:*** First-line cisplatin-ineligible patients with mUC expressing *FGFR1–3* GAs, and have not received prior FGFR-inhibiting treatment.

  Cisplatin-ineligibility as defined by any one of the following criteria: 1) grade ≥ 2 peripheral neuropathy; 2) CL_{CR} calculated by Cockcroft-Gault >30 mL/min but < 60 mL/min; 3) hearing impairment (measured by audiometry) of > 25 dB at two contiguous test frequencies in at least one ear; 4) comorbidity that precludes high-volume hydration.
- ***Substudy 4:*** Patients with FGFR inhibitor-resistant, mUC expressing *FGFR1–3* GAs who have progressed on at least one standard regimen each of chemotherapy and immune-checkpoint blockade and have received FGFR inhibiting treatment (excluding derazantinib).

  Patients assessed as having progressed upon prior treatment with FGFR inhibitors must have received FGFR inhibitor treatment for at least 12 weeks and have undergone at least one on treatment tumor imaging assessment.

  Prior treatment with immune-checkpoint blockade and FGFR inhibitor in combination are not allowed; prior treatment with either sequential immune-checkpoint blockade and FGFR inhibitor treatment or combinations of FGFR inhibitor and chemotherapy are allowed.
- ***Substudy 5:*** Patients with mUC expressing *FGFR1–3* GAs who have progressed on at least one standard chemotherapy and/or immune-checkpoint blockade and have not received prior FGFR inhibiting treatment.

5. Eligible *FGFR1–3* GA-positive test result (see Appendix 1 and Section 3.1.1)
6. Measurable disease, as defined by the Investigator using RECIST 1.1 criteria, documented within the 28 days prior to study drug administration.
7. ECOG PS of 0, 1 or 2
8. Adequate organ functions as indicated by the following Screening visit local laboratory values:
   - Hemoglobin ≥ 9 g/dL
   - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   - Platelets ≥ 75×10^9/L
   - International normalized ratio (INR) 0.8 to upper limit of normal (ULN) or ≤ 3 for patients receiving anticoagulant therapy
   - Total bilirubin ≤ 2 × ULN
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN, or ≤ 5 × ULN for study patients with liver metastasis
   - Albumin ≥ 2.5 g/dL
   - CL_{CR} ≥ 30 mL/min (as calculated by the Cockcroft-Gault formula)

- For women of childbearing[1] potential only, negative serum human chorionic gonadotropin (hCG)[2]

9. Men and women of childbearing potential must agree to avoid impregnating a partner or becoming pregnant, respectively, during the study, and for at least 5 months after the last dose of either investigational drug.

   Male patients are considered not to be of child-producing potential if they have azoospermia (whether due to vasectomy or an underlying medical condition). Female patients are considered not to be of child-producing potential if they are:

   - postmenopausal[3], or
   - have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks prior to Screening, or
   - have a congenital or acquired condition that prevents childbearing.

   Male or female patients of child-producing potential must agree to comply with one of the following until at least 150 days after the last dose of derazantinib or atezolizumab:

   a) Abstinence from heterosexual activity[4]
   b) Using (or having their partner use) a highly effective method of contraception during heterosexual activity. Highly effective methods of contraception are[5]:
      - an intrauterine device
      - vasectomy of a female patient's male partner
      - a contraceptive rod implanted into the skin.
      - any combination of hormonal contraceptive and a barrier method (diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male condom or female condom)

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[1] Women who are defined as not being of childbearing potential are: any female who is postmenopausal (age ≥ 55 years with cessation of menses for 12 or more months, or less than 55 years but without spontaneous menses for at least 2 years, or less than 55 years with spontaneous menses during the last 1 year but currently amenorrhoeic, e.g., spontaneous or secondary to hysterectomy, AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels < 40 IU/L), or postmenopausal estradiol levels (< 5 ng/L) or according to the definition of "postmenopausal range" for the laboratory involved), or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

[2] Spurious positive serum beta-hCG values may be caused by the underlying urothelial cancer; plausibility of pregnancy should be established for women of childbearing potential with urothelial cancer and positive serum beta-hCG values.

[3] Postmenopausal is defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post -menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is not sufficient.

[4] Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if it is employed during the entire period of risk associated with the study treatment and if it is considered highly effective by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not highly effective methods of contraception.

[5] If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as a highly effective method of contraception for patients participating at sites in this country/region.

- combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral contraceptive pill [estrogen/progestin pill or progestin-only pill], contraceptive skin patch/implant, vaginal contraceptive ring, or subcutaneous contraceptive injection)

4.3 Exclusion criteria

Patients who meet **any** of the following criteria at Screening must not be enrolled in the study (patients may repeat the screening procedures within the screening period after initially failing to comply with exclusion criteria; rescreening for molecular inclusion criteria is not permitted unless the tissue biopsy or liquid biopsy was not evaluable for technical reasons):

Prior cancer treatment

1. Receipt of treatment before the first dose of study drug (Cycle 1 Day 1) within an interval shorter than the following, as applicable:
   - One chemotherapy or biological (e.g., antibody) cycle interval
   - Five half-lives of any small molecule investigational or licensed medicinal product
   - Two weeks, for any investigational medicinal product (IMP) with an unknown half-life
   - Four weeks of curative radiotherapy
   - Seven days of palliative radiotherapy
   - 12 months of neo-adjuvant or adjuvant chemotherapy or radiation (only applies to **Substudy 3**)
2. For **Substudy 3** patients, any prior treatment with anti-PD-1 or anti-PD-L1-therapeutic antibody, or PD-1/PD-L1 pathway-targeting agents
3. Prior FGFR inhibiting treatment (except **Substudy 4**).
4. For **Substudy 4** patients, prior treatment with FGFR inhibitor in combination with anti-PD-1 or anti-PD-L1 therapeutic antibody or PD-1/PD-L1 pathway-targeting agents.

Critical organ impairments

5. Concurrent evidence of clinically significant corneal or retinal disorder likely to increase the risk of eye toxicity, including but not limited to bullous/band keratopathy, keratoconjunctivitis (unless keratoconjunctivitis sicca), corneal abrasion (unless related to trauma), inflammation/ulceration, confirmed by ophthalmological examination.
6. History of clinically significant cardiac disorders:
   - Myocardial infarction, or New York Heart Association Class II to IV congestive heart failure, within 6 months of the first dose of study drug
   - Concurrent and clinically significant abnormalities on ECG at Screening, including QTcF > 450 ms for males or > 460 ms for females (mean values from triplicate ECGs; see Section 5.3.2.4)

7. Serum electrolyte abnormalities defined as follows:
   - Hyperphosphatemia: serum phosphate > institutional ULN
   - Hyperkalemia: serum potassium > institutional ULN
   - Hypokalemia: serum potassium < institutional LLN
   - Hypercalcemia: corrected serum calcium > 3.1 mmol/L (> 12.5 mg/dL)
   - Hypocalcemia: corrected serum calcium < 1.75 mmol/L (< 7.0 mg/dL)
   - Hypomagnesemia: < 0.4 mmol/L (< 0.9 mg/dL)
8. History of major thrombotic and clinically relevant bleeding event in the last 6 months before Screening which in the assessment of the Investigator puts the patient at high risk of bleeding during the study
9. Uncontrolled tumor-related hypercalcemia

Medical history

10. Bellmunt score 3, or 2 if based on a combination of hemoglobin < 10 g/dL and presence of liver metastasis.[1]
11. Any unresolved (at the time of Screening) clinically significant CTCAE grade ≥ 2 toxicity (except for alopecia, grade 2 platinum-therapy related neuropathy, grade 2 anemia from previous anti-tumor treatment, grade 2 renal impairment per reduced CLCR by Cockcroft-Gault of 30–60 mL/min [which is generally accepted for this cancer population], and/or medical/surgical procedures/interventions).
12. Known CNS metastases
13. Lack of recovery from major (e.g., open abdominal) surgery after 4 weeks, or major elective surgery is planned during the foreseeable duration of the study
14. Concurrent uncontrolled or active infection with human immunodeficiency virus (known HIV 1/2 antibodies positive)
15. Active hepatitis B or chronic hepatitis B without current antiviral therapy and an HBV DNA ≥ 100 IU/mL

    Note: Active hepatitis B is defined as a known positive hepatitis B surface antigen (HBsAg) result.
16. Active hepatitis C

    Note: Active hepatitis C is defined by a known positive Hep C antibody result and known quantitative hepatitis C virus (HCV) RNA results greater than the lower limits of detection of the assay.
17. Active tuberculosis
18. Severe bacterial, fungal, viral and/or parasitic infections on therapeutic oral or IV medication at the time of first dose of study drug administration
19. Significant gastrointestinal disorders that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of derazantinib (e.g., Crohn's

[1] Bellmunt scores (0–3) (Bellmunt 2010) are derived from three adverse risk factors (ECOG PS of ≥ 1, hemoglobin level < 10 g/dL, and presence of liver metastasis), and are based on the presence of zero, one, two, or three of the prognostic factors.

disease, ulcerative colitis, diarrhea, extensive gastric resection, functionally relevant gastrointestinal obstruction, or vomiting)

20. History of additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or *in situ* cervical cancer.
    Note: An incidental finding of prostate cancer (identified upon resection of the prostate) is acceptable, provided that the following criteria are met: Stage T2N0M0 or lower; Gleason score ≤ 6, and prostate-specific antigen below lower limit of normal by local laboratory.
21. Chronic leg ulcers, decubitus ulcers, or unhealed incisions.

General patient disposition

22. Known hypersensitivity or allergy any component of the derazantinib formulation.
23. Unable or unwilling to swallow the complete daily dose of study drug, or contraindicated to receive study drug.
24. Any other uncontrolled intercurrent illness that would unduly increase the risk of toxicity or limit compliance with study requirements, including but not limited to ongoing or active symptomatic infection, uncontrolled diabetes mellitus, or hepatic, renal, respiratory, or psychiatric illness.
25. A history or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition or disease that, in the opinion of the Investigator or the Sponsor if consulted, would pose a risk to the safety of the patient, or would interfere with the study evaluation, procedures, or completion.
26. Pregnant or breast feeding.

In addition, the following exclusion criteria related to atezolizumab are applicable **only** to patients to be enrolled into **Substudies 3 and 4**:

27. Treatment with systemic corticosteroids (except for steroidal replacement therapy) or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to first dose of study drug or anticipated requirement for systemic immunosuppressive medications during the study. Generally, inhaled, intranasal, intraocular, topical, and intra-articular joint injections are allowed.
28. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
29. History of allogeneic stem cell or solid organ transplantation.
30. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
31. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation

32. Hypersensitivity to atezolizumab or to any of the excipients
33. Patients requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents. (Exceptions include any patient on 10 mg or less of prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema)
34. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on Screening chest CT scan

4.4 Method of assignment to substudy and treatment

Patients will be assigned to a specific substudy based on the appropriate eligibility criteria.

For all substudies, a unique enrollment code will be assigned after written informed consent has been obtained, using the centralized Interactive Web Response System (IWRS). If a patient withdraws from participation in the study, his or her enrollment code will not be reused.

4.4.1 Substudy 1

All eligible patients will receive derazantinib 300 mg QD monotherapy. Treatment assignment is performed on C1D1, or as close as possible to the date on which treatment is to be administered.

4.4.2 Substudy 3

All eligible patients will receive derazantinib 200 mg BID and atezolizumab 1200 mg Q3W in combination. If derazantinib 200 mg BID at the safety interim analysis is not assessed as safe and tolerable, patients will be treated with the RP2D determined in Substudy 2 (i.e., derazantinib 300 mg QD and atezolizumab 1200 mg Q3W in combination). Treatment assignment is done on C1D1, or as close as possible to the date on which treatment is to be administered.

4.4.3 Substudy 4

Patients in **Substudy 4** are to be randomized (1:1) to receive study treatment with either derazantinib 300 mg QD monotherapy (**Cohort 4a**), or derazantinib 300 mg QD and atezolizumab 1200 mg Q3W in combination (**Cohort 4b**), based on a computer-generated randomization schedule via IWRS. Patients in Substudy 4 will be randomized on C1D1, or as close as possible to the date on which treatment is allocated. Randomization will be stratified for key prognostic factors according to the following algorithms:

- The presence of visceral metastasis, an ECOG PS of 2, or a preceding FGFR inhibitor treatment interval of less than 6 months (i.e., less than 24 full weeks) will be credited with one point, and patients will be stratified according to their composite score values of 0–1 versus 2–3 points.

4.4.4 Substudy 5

All eligible patients will receive derazantinib 200 mg BID monotherapy. Treatment assignment is performed on C1D1, or as close as possible to the date on which treatment is to be administered.

4.5 Discontinuation from the study treatment or study

4.5.1 Patient discontinuation from study treatment

Patients should be discontinued from study treatment at any time if they experience documented radiographic progression of disease. Patients will be permitted to remain on study treatment after RECIST 1.1 criteria for PD are met **only** if, in the opinion of the Investigator and with the agreement of the Medical Monitor, they continue to derive benefit from derazantinib or derazantinib-atezolizumab in combination.

In particular, for patients in **Cohort 4a**, every effort should be undertaken to obtain BICR confirmation on disease progression, in order to establish a baseline for a potential crossover.

Furthermore, patients should be discontinued from study treatment should any of the following occur:

- Any clinically unacceptable treatment-emergent toxicity occurring in patients treated with derazantinib monotherapy that persist despite optimal treatment or dose reduction
- Any clinically unacceptable treatment-emergent toxicity clearly attributable to derazantinib occurring in patients treated with derazantinib-atezolizumab in combination that persist despite optimal treatment or derazantinib dose reduction. In this instance derazantinib should be discontinued, whilst continuation of atezolizumab is at the discretion of the Investigator
- Any clinically unacceptable treatment-emergent toxicity clearly attributable to atezolizumab occurring in patients treated with derazantinib and atezolizumab in combination that require respective management, as detailed in Appendix 4
- Both study drugs (derazantinib and atezolizumab) should be discontinued for instances of overlapping toxicity (e.g., ophthalmological and/or hepatic adverse events) that cannot be clearly attributed to either drug
- Pregnancy (see Section 7.4.5)
- Patient decision to discontinue treatment and study visits
- Withdrawal of consent from treatment and study follow up calls
- Non-compliance with any part of the study, as assessed by the Investigator or Medical Monitor
- Investigator's decision after discussion with the Medical Monitor or designee
- Death

For all patients who discontinue derazantinib, AE monitoring must be continued for at least 28 days after the last dose of study drug (see Section 5.2.2.8); for patients discontinuing atezolizumab, AE monitoring must be continued for at least 90 days after the last dose (see Section 5.2.2.9).

For patients who fail to return for the End of Treatment visit and/or the Safety Follow-up visit(s), the Investigator must make every effort to contact the patient (by telephone or mail correspondence). The outcome of this contact must be documented by the Investigator and filed in the Investigator Site File (ISF). The reasons for discontinuation of treatment must be recorded in the eCRF.

4.5.2 Patient discontinuation from the study

Patients who discontinue from study treatment will be followed for survival until the end of the study criteria are met (see Section 3.1.8), either through direct contact with the patient or the patient's relatives, or collection of public records (e.g., death certificate) in accordance with local laws, unless they meet any of the following criteria:

- Withdrawal of consent for study treatment including safety and survival follow up
- Withdrawal of consent for long-term (survival) follow-up
- Lost to follow-up
- Death

4.5.3 Replacement of patients

Patients who are non-evaluable for efficacy (see Section 8.2.2) are to be replaced.

4.5.4 Study discontinuation

The Sponsor reserves the right to temporarily or permanently discontinue the cohort, substudy or study at any site or at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns (i.e. an identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health)
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice (GCP) guidelines, or other regulatory requirements by the Investigator(s)
- Request to discontinue the study by regulatory or health authority

The Sponsor and/or designee will promptly inform all Investigators and the appropriate regulatory authorities if the study is suspended or terminated for safety reasons. In the case of such a termination, the Investigator will notify the IRB or Independent Ethics Committee (IEC), as appropriate.

5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Effective Protocol Version 5.0, only assessments and procedures applicable to active substudies are provided in this section.

5.1 Summary of schedule of assessments

Study patients will be assessed in accordance with the items and schedules provided in Table 1. All applicable assessments must be documented in the eCRF for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to the start of each cycle; and study drug dosing should occur only if the clinical assessment and local clinical safety blood test values are acceptable.

Table 1 Schedule of assessments

	PSV	SV	Cycle 1			Cycle 2+			End of Treatment	Safety Follow-Up		Overall Survival Follow-Up
Assessment window	–	D −28 to D −1	D1	D8 (±3)	D15 (±3)	D1 (+3)[1]	D8[2] (±3)	D15[2] (±3)	≤ 7 days after last dose	28 days after last dose (±3)	90 days after last dose (±3)[3]	At least every 3 months from date of last dose (±14)
Substudy applicability	S1/S3/ S5	All	All	SIAP S3/S5	All	All	SIAP S3/S5	SIAP S3/S5	All	All	S3/S4	All
Informed Consent on Pre-screening ICF	X											
Molecular eligibility[4]	X											
Informed Consent on Study ICF		X										
Screening procedures[5]		X										
Physical examination		X	X			X			X	X	X	
ECOG PS		X	X	X	X	X	X	X	X	X	X	
Ophthalmological examination[6]		X				X			X			
ECG[7]		X	X	X	X	X	X	X	X	X	X	
Clinical safety laboratory blood samples[8]		X	X	X	X	X	X	X	X	X	X	
Urinalysis[9]		X	X			X			X			
Pregnancy test[10]		X	X			X			X	X	X	
Research liquid biopsy[11]		X				X			X			
Archival tumor tissue[12]		X										
Tumor imaging assessment [13]		X				X			X			
Treatment assignment/Randomization			X									
Study drug administration			X	X[14]	X[14]	X	X[14]	X[14]				
Study drug dispensing and/or accountability			X			X			X			
Derazantinib PK[15]			X	X	X	X	X	X		X		
Atezolizumab PK and ADA[16]			X			X				X		
AE assessments		X[17]	X	X	X	X[18]	X	X	X	X	X	
PRO assessments (not S2)[19]			X			X			X			
Concomitant medications/treatments		X	X	X	X	X	X	X	X	X	X	
Pharmacodynamic research (optional)[20]		X				X						
Survival contact[21]											X	X

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; C: cycle; D: day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PK: pharmacokinetics; PRO: patient reported outcome; PSV: Pre-screening visit; S[n]: Substudy [number]; SIAP: safety interim analysis patients; SV: Screening visit.

For footnotes, see next page.

1. Deviations from the visit schedule by +3 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. If a patient visit deviates from the permitted protocol window, the next visit must be performed at the correct timing based on the date of C1D1.
2. Only applicable to Cycle 2.
3. Applicable to all patients who received atezolizumab as part of their study treatment.
4. Applicable to **Substudies 1, 3 and 5** only (see Section 3.1.1).
5. Screening procedures (see Section 5.2.1.3) comprise assessment of eligibility criteria; medical history of cancer diagnosis and treatment; demographics, medical history, prior medications, baseline medical conditions, including weight and height; Bellmunt score assessment, tuberculosis blood test (e.g., interferon-γ release assay) if clinically indicated to rule out clinical suspicion of active tuberculosis; serology for human immunodeficiency virus, hepatitis B, and hepatitis C.
6. Patients will have complete ophthalmological examination, including optical coherence tomography (OCT), during Screening, the first four cycles (i.e., Day 1 [±7d] of Cycles 2–5) and the End of Treatment visit. A complete ophthalmological examination is to be repeated if new ocular symptoms occur or vision is impaired (see Section 5.3.2.3).
7. For all patients, a standard, triplicate, 12-lead ECG must be performed and read locally at all study visits; central reading of all ECG results will be performed (see Section 5.3.2.4). Note that the on-treatment ECGs (up to Cycle 4) should be performed as close as possible to the corresponding PK blood collection timepoint during those visits (see Footnote 16); if possible, ECG should be performed first, and then blood collected for PK within 5–10 minutes. Subsequently, ECGs will be performed pre-dose on Day 1 of every cycle, at End of Treatment and at Safety Follow-up.
8. Safety laboratory blood samples will be tested locally at all study visits . The results of these assessments must be reviewed prior to dosing (see Section 5.3.2.5).
9. Comprising specific gravity, pH, glucose, protein, ketones, and blood (see Section 5.3.2.6).
10. Women of child-bearing potential must have a negative local serum pregnancy test (hCG) at the SV and within 72 hours prior to dosing at C1D1. Subsequently, serum pregnancy testing will be performed prior to study drug dosing on Day 1 of every cycle, at the End of Treatment visit, and serum or urine pregnancy testing will be performed monthly for 150 days (5 months) following the last administration of study treatment. Monthly pregnancy testing after the end of treatment may be performed by the patient's local gynecologist to reduce the burden related to study visits at the site, but must be communicated to the study Investigator.
11. Research liquid biopsies are requested from all patients enrolled in **Substudies 1, 3, 4 and 5** at Screening and End of Treatment visits, and at the time point of the confirmatory CT scan (for complete response/partial response).

12. Archival tumor tissue (FFPE block; or a minimum of two H&E-stained slides plus at least 10 consecutive, unstained, 4 ± 1 µm thick sections, placed on positively charged slides) should be collected at the SV from **all enrolled patients** for biomarker assessment (including PD-L1 testing). If archival tumor tissue is not available, *de novo* biopsy may be performed but only if considered by the Investigator as safe and tolerable for the patient.

13. Tumor assessments performed as SoC prior to obtaining informed consent and within 28 days of the first dose of study treatment on C1D1 may be used rather than repeating tests. The first on-study tumor imaging assessments will be performed after 9 weeks on study, and will be repeated every 9 weeks (±7) from C1D1 (i.e., at C4D1, C7D1, C10D1) and every 12 weeks (±7) from C10D1 (i.e., at C14D1, C18D1, etc.) thereafter (with additional scans as clinically indicated and as per RECIST 1.1 criteria) until disease progression, death, or loss of follow-up. A tumor assessment should be performed at the End-of-Treatment visit only if the prior scan was not done within 4 weeks (28 days) prior to this visit, or if the prior scan did not show radiographic disease progression (see Sections 5.2.2.7 and 5.3.3.2). The same radiographic procedure as used at the SV must be used throughout the study for each patient to follow target lesions, and results must be reviewed by the Investigator before dosing at the next cycle. Imaging timing should be based on the first dose at C1D1, should follow calendar days, and should not be adjusted for delays in cycle starts.

14. For pre-dose PK blood sampling at C1D15 (**all substudies**), and C1D8, C2D8 and C2D15 (**safety interim analysis** patients in **Substudies 3 and 5**), administer derazantinib at the study site.

15. Derazantinib PK blood (plasma) sampling will be performed according to the following schedule:
    a. ***Rich PK profiling*** **- Applicable to safety interim analysis patients in Substudy 3 and 5 only**:
        - C1D1, prior to derazantinib dose, and 1 hour (± 5 minutes), 2hours (± 5 minutes), 4 hours (± 15 minutes), 8 hours (± 30 minutes), 10 hours (± 30 minutes), 12 hours (± 30 minutes; prior to the second dose administration), 24 hours after first derazantinib administration (i.e., 12 hours post second dose administration but within 1 hour prior to the third dose).
        - C1D8, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
        - C1D15, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
        - C2D1, prior to derazantinib (within 1 hour prior to the next dose), and 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 15 minutes), 8 hours (± 30 minutes), 10 hours (± 30 minutes), 12 hours (± 30 minutes; prior to the second dose administration), 24 hours after derazantinib administration (i.e., 12-hour post previous dose administration but within 1 hour prior to the next dose).
        - C2D8, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
        - C2D15, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration
        - C3D1, prior to derazantinib (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
        - C4D1, prior to derazantinib administration (within 1 hour prior to the next dose).
        - 28-day Safety Follow-up visit
    b. ***Sparse PK*** **–** Applicable to **all patients** (except safety interim analysis patients in Substudy 3 and 5; see rich PK sampling):
        - C1D1 and C1D15, prior to derazantinib (within 1 hour prior to next dose), and 6–8 hours after the study drug administration.

- C2D1, prior to derazantinib (within 1 hour prior to next dose)
- C3D1, prior to derazantinib (within 1 hour prior to next dose), and 6–8 hours after the study drug administration.
- C4D1, prior to derazantinib administration (within 1 hour prior to next dose)
- 28-day Safety Follow-up visit

16. For all patients in **Substudy 3** and **Cohort 4b and Crossover**, atezolizumab PK and ADA (serum) blood sampling will be performed according to the following schedule**:**
    - C1D1, prior to atezolizumab administration; and for PK only, 30 minutes after end of atezolizumab infusion
    - C2D1, C3D1, C4D1, prior to atezolizumab administration
    - C8D1, C12D1, C16D1, prior to atezolizumab administration
    - 28-day Safety follow-up visit
17. Non-serious and serious changes in or worsening of a patient's condition that occur between any informed consent and first study-drug administration, as well as any AEs in conjunction with tumor/liquid biopsies or imaging studies, will be captured in the eCRF (see Section 7.4.2).
18. AEs occurring between C1D1 and C1D21 in patients during the DLT observation period of **Substudy 3 and 5** will be assessed against the DLT definitions (outlined in Section 7.3.3) prior to study drug administration on C2D1. DLTs are also to be recorded in the eCRF.
19. PRO instruments should be self-administered at the study site before the patient sees the physician (i.e., at the start of the visit) and prior to the completion of other study assessments and the administration of study treatment (see Section 5.3.6).
20. (*Optional*) PD assessments in Substudy 3, 4 or 5 (i.e., blood sampling and skin biopsy) to be performed at screening, and on C2D1.
21. Survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries.

5.2 Study visits

5.2.1 Screening/enrollment period

5.2.1.1 Informed consent

Eligible patients may only be included in the study after providing written IEC/IRB-approved informed consent. Written informed consent must be obtained from each patient by the Investigator or designee prior to initiation of any study procedures (see Section 10.2 for details). A patient may only participate in the overall study once.

Patients who agree to participate in the study will sign the most recently approved ICF and will be provided with a copy of the document. Informed consent must be obtained within the 28 days prior to the first dose of study treatment on C1D1.

For patients in **Substudies 1, 3, or 5** with no documented local NGS test result with an eligible *FGFR1–3* GA, a separate Pre-screening ICF must first be signed by each prospective study participant to permit central testing for eligible *FGFR1–3* GAs.

For patients who are to be enrolled into the optional PDR of **Substudies 3, 4 and 5**, a separate specific PDR ICF providing consent for the additional study assessments applicable to this group must be signed.

5.2.1.2 Pre-screening visit

A Pre-screening visit is only required for prospective study participants under consideration for enrollment into **Substudies 1, 3 or 5**, if no documented local NGS test result with an eligible *FGFR1–3* GA (Appendix 1) is available at the Screening visit (see Section 3.1.1).

During the Pre-screening visit, a liquid biopsy blood sample for molecular central testing will be collected after written informed consent for pre-screening is obtained. The central testing will be performed in a laboratory in the USA designated by the Sponsor and will be based on NGS testing of cfDNA from a liquid biopsy obtained at Pre-screening visit. The liquid biopsy should be obtained following assessment of objective documented progression after prior anti-cancer treatment to optimize the likelihood of capturing cfDNA shedding reflective of disease progression. Liquid biopsy re-screening for molecular inclusion criteria is not permitted, unless the liquid biopsy was not evaluable for technical reasons.

For patients considered for enrollment into **Substudy 4**, a positive *FGFR1–3* GA test result from the prior FGFR inhibiting treatment is sufficient to initiate clinical screening procedures; documentation of the *FGFR1–3* GA-positive status should be made available at the Screening visit, otherwise a Pre-screening visit must be scheduled and confirmation by a positive central *FGFR1–3* GA test result should be sought.

5.2.1.3 Screening visit

The screening window for clinical screening procedures will be 28 days.

At the Screening visit, clinical eligibility of prospective study participants and baseline disease status will be assessed. Patients who fail to meet the eligibility criteria should not,

under any circumstances, be enrolled into the study and must be withdrawn from the study as a screen failure.

Patients who satisfy all of the inclusion criteria (see Section 4.2) and none of the exclusion criteria (see Section 4.3) may be enrolled in the study. After written informed consent is obtained, the following will be evaluated within 28 days prior to the first dose of study treatment and documented in the eCRF:

- Demographics/medical history/baseline medical conditions (see Sections 5.3.1.1 and 5.3.1.2)
- Medical history of cancer diagnosis and treatment (see Section 5.3.1.3)
- Record prior and concomitant medications (medications used within 30 days prior to Screening) (see Section 5.3.1.4)
- Physical examination, including height, weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Inclusion criterion 7 and Section 5.3.2.2)
- Bellmunt score (see Exclusion criterion 10)
- Complete ophthalmic examination, including OCT (see Exclusion criterion 5 and Section 5.3.2.3)
- Triplicate 12-lead ECG (see Exclusion criterion 6 and Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)

  Note: CL_{CR} should be calculated by the Cockcroft-Gault equation; prothrombin time, INR, and partial thromboplastin time are required at the Screening and End of Treatment visits.

- Tuberculosis blood test (e.g., interferon-γ release assay) if clinically indicated to rule out clinical suspicion of active tuberculosis (see Exclusion criterion 17)
- Serology for human immunodeficiency virus, hepatitis B, and hepatitis C (see Exclusion criteria 15 and 16)
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable (see Exclusion criterion 26, Section 5.3.2.7, and Section 7.1.3).
- Tumor measurement according to RECIST 1.1 (see Section 5.3.3.2 and Appendix 2)

  Note: Tumor assessments performed as SoC prior to obtaining informed consent and within 28 days of the first dose of study treatment on C1D1 may be used rather than repeating tests (if tumor assessment was performed after administration of the last dose of prior anti-tumor treatment).

- Research liquid biopsy (see Section 5.3.5.1)

- Archival tumor tissue for molecular biomarker assessments, including PD-L1 testing (FFPE block; or a minimum of two H&E-stained slides plus at least 10 consecutive, unstained, 4 ± 1 µm thick sections, placed on positively charged slides)

  Note: If archival tumor tissue is not available, de novo biopsy may be performed but only if considered by the Investigator as safe and tolerable for the patient.

- Skin biopsy and blood samples for monocyte subsets (optional for patients enrolled in **Substudies 3, 4, and 5** only; see Section 5.3.5.3).

Patients may repeat the clinical screening procedures within the screening period after initially failing to meet the clinical inclusion criteria. Under rare conditions and contingent upon Sponsor approval, patients may be given the possibility to be re-screened after initially failing screening.

5.2.2 Treatment period

Enrolled patients will be evaluated regularly, as indicated in Table 1. All visits are based on the date of the first dose at C1D1 regardless of drug holds. If a patient visit deviates from the protocol permitted window, the next visit must be done at the correct time based on the date of C1D1.

AEs and concomitant medications will be recorded on an ongoing basis during the treatment period, and at the selected time points as summarized in Table 1.

5.2.2.1 Cycle 1, Day 1 (all patients)

The following assessments will be made during this visit (all assessments except for AE assessment, post-dose 12-lead ECG, and post-dose PK blood collection [where applicable; see Section 5.3.4.1]) must be performed prior to the first dose):

- PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician) (see Section 5.3.6)
- Physical examination (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours after the first dose of study drug) (see Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)

  Note: 25-hydroxy vitamin D is required at C1D1, C3D1, C5D1, and the End of Treatment visit only. CRP is required at C1D1 only and thereafter if infection is suspected. TSH, fT3 and fT4 is required at C1D1 and subsequently every 4 cycles.

- Blood samples for derazantinib PK (see Section 5.3.4.1 for details of sampling schedule)
- Blood samples for atezolizumab PK and ADA (**Substudy 3, Cohort 4b and Crossover** only; see Section 5.3.4.2 for details of sampling schedule)

- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable, within 72 hours prior to dosing (see Section 5.3.2.7, and Section 7.1.3)
- Dispense and administer derazantinib capsules (see Section 6.1.1.1)
- Dispense and administer atezolizumab (if applicable) (see Section 6.1.2.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)

5.2.2.2 Cycle 1, Day 8 (±3 days) (SIA patients in Substudies 3 and 5)

The following assessments will be made during this visit:

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Blood samples for derazantinib PK (see Section 5.3.4.1 for details of sampling schedule)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours post-derazantinib dosing) (see Section 5.3.2.4)
- Record concomitant medications (see Section 5.3.2.9)
- Administer derazantinib capsules (see Section 6.1.1.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)

5.2.2.3 Cycle 1, Day 15 (±3 days) (all patients)

The following assessments will be made during this visit:

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Blood samples for derazantinib PK (see Section 5.3.4.1 for details of sampling schedule)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours post-derazantinib dosing) (see Section 5.3.2.4)
- Record concomitant medications (see Section 5.3.2.9)
- Administer derazantinib capsules (see Section 6.1.1.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)

5.2.2.4 Cycle 2+, Day 1 (+3 days) (all patients)

The following assessments will be made during this visit (all assessments except for AE assessment, post-dose 12-lead ECG, and post-dose PK blood collection [where applicable; see Section 5.3.4.1]) must be performed prior to study drug dosing):

- PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician) (see Section 5.3.6)
- Complete ophthalmological examination, including OCT, for the first four treatment cycles (i.e., Day 1 of Cycles 2–5), and if clinically indicated thereafter (see Section 5.3.2.3)
- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Triplicate 12-lead ECG (required on D1 of all cycles prior to dosing, or if clinically indicated; see Section 5.3.2.4)
  Note: On C3D1, ECGs should be performed pre-dose and approximately 6-8 hours post-dose.
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5).
  Note: Thyroid panel (Thyroid stimulating hormone [TSH], tri-iodothyronine [fT3], thyroxine [fT4]) are required every 4 cycles from C1D1; and 25-hydroxy vitamin D is required at C1D1, C3D1, C5D1 and the End of Treatment visit only.
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable, within 72 hours prior to dosing (see Section 5.3.2.7, and Section 7.1.3)
- Blood samples for derazantinib PK (See Section 5.3.4.1 for details of sampling schedule)
- Blood samples atezolizumab PK and ADA (**Substudy 3, Cohort 4b, and Crossover** only; see Section 5.3.4.2 for details of sampling schedule)
- Research liquid biopsy at the time point of the CT/MRI scan confirming response (see Section 5.3.5.1).
- Tumor imaging assessment, every 9 weeks from C1D1 (±7 days) for 27 weeks (i.e., prior to C4D1, C7D1, C10D1) then every 12 weeks (±7 days, i.e., at C14, C18, etc.) (see Section 5.3.3.2 and Appendix 2)
- Assess and record any DLTs (SIA patients in **Substudies 3** and **5** only) (see Section 7.3.3)
- Record concomitant medications (see Section 5.3.2.9)
- Dispense derazantinib capsules and perform drug accountability of returned drug (see Section 6.1.1.1 and Section 6.1.1.3).
  Note: To avoid unnecessary waste of study drug, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.
- Administer derazantinib capsules (see Section 6.1.1.1)
- Administer atezolizumab (if applicable) (see Section 6.1.2.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)

- Skin biopsy and blood samples for monocyte subsets on C2D1 only (optional for patients enrolled in **Substudies 3, 4, and 5** only; see Section 5.3.5.3)

5.2.2.5 Cycle 2, Day 8 (±3 days) (SIA patients in Substudies 3 and 5)

The following assessments will be made during this visit (all assessments except for AE assessment, post-dose 12-lead ECG, and post-dose PK blood collection [where applicable; see Section 5.3.4.1]) must be performed prior to study drug dosing):

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Blood samples for derazantinib PK (see Section 5.3.4.1 for details of sampling schedule)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours post-derazantinib dosing) (see Section 5.3.2.4)
- Record concomitant medications (see Section 5.3.2.9)
- Administer derazantinib capsules (see Section 6.1.1.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)

5.2.2.6 Cycle 2, Day 15 (±3 days) (SIA patients in Substudy 3 and 5)

The following assessments will be made during this visit (all assessments except for AE assessment, post-dose 12-lead ECG, and post-dose PK blood collection [where applicable; see Section 5.3.4.1]) must be performed prior to study drug dosing):

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Blood samples for derazantinib PK (see Section 5.3.4.1 for details of sampling schedule)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours post-derazantinib dosing) (see Section 5.3.2.4)
- ECOG PS (see Section 5.3.2.2)
- Record concomitant medications (see Section 5.3.2.9)
- Administer derazantinib capsules (see Section 6.1.1.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)

5.2.2.7 End of Treatment assessment (≤ 7 days after last dose) (all patients)

End of Treatment assessments are to be performed in patients who no longer receive study drug(s) (for any reason), and must take place within 7 days of the decision to permanently discontinue all study drug(s).

The following assessments will be performed during the End of Treatment visit:

- PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician) (see Section 5.3.6)
- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Complete ophthalmological examination, including OCT (see Section 5.3.2.3)
- Triplicate 12-lead ECG (Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)

  Note: 25-hydroxy vitamin D is required at C1D1, C3D1, C5D1, and the End of Treatment visit only.
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy testing
- Research liquid biopsy (see Section 5.3.5.1)
- Tumor imaging assessment, if the prior scan was not done within four weeks (28 days) prior to this visit or if the prior scan did not show radiographic disease progression (see Section 5.3.3.2 and Appendix 2). For patients who discontinue study treatment without documented radiologic disease progression, every effort should be made to perform radiologic imaging.
- Assess and record any AEs (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)
- Perform drug accountability of returned derazantinib (see Section 6.1.1.3)

5.2.2.8 Safety follow-up (28 days after last dose; ± 3 days)

All patients will be followed for a minimum of 28 days after the last dose of all study treatment. During the 28-day safety follow-up period, all AEs/SAEs and changes in concomitant medication should be reported.

Patients with unresolved study drug-related AEs (which occurred during the study treatment period or in the 28-day safety follow-up period; see Section 7.2.4 for the definition of a suspected AE) will be followed until, in the opinion of the Investigator, study drug-related toxicities have resolved to baseline, CTCAE grade 1, stabilized, or are deemed to be irreversible.

In addition, at the 28-day safety follow-up visit, the following assessments will be made:

- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Triplicate 12-lead ECG (Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)

- Serum or urine pregnancy testing (to be performed monthly until 150 days after the last administration of study drug) (see Section 5.3.2.7, and Section 7.1.3)
- Blood samples for derazantinib PK, if applicable (See Section 5.3.4.1 for details of applicable patients/ sampling schedule)
- Blood samples atezolizumab and ADA (**Substudy 3 Cohort 4b, and Crossover**; see Section 5.3.4.2 for details of applicable patients/ sampling schedule)

5.2.2.9 Safety follow-up (90 days after last dose; ± 3 days)

All patients who receive atezolizumab in **Substudy 3, Cohort 4b, and Crossover** will be followed for a minimum of 90 days after the last dose of all study treatment. During the 90-day safety follow-up period, all AEs/SAEs, changes in concomitant medication, and new anticancer treatment should be reported.

Patients with unresolved study drug-related AEs (which occurred during the study treatment period or in the 90-day safety follow-up period; see Section 7.2.4 for the definition of a suspected AE) will be followed until, in the opinion of the Investigator, study drug related toxicities have resolved to baseline, CTCAE Grade 1, stabilized, or are deemed to be irreversible.

In addition, at the 90-day safety follow-up visit, the following assessments will be made:

- Physical examination (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Triplicate 12-lead ECG (Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Serum or urine pregnancy testing (to be performed monthly until 150 days after the last administration of study drug) (see Section 5.3.2.7, and Section 7.1.3)

5.2.3 Survival follow-up period

5.2.3.1 Overall survival follow-up (at least every 3 months ± 14 days)

Survival follow-up will start the day of the last dose of study drug.

All patients and/or family will be contacted at 3-month intervals (±14 days) and record the patient status as *Alive* (date); *Dead* (date); *Alive, but withdrew consent for further follow up* (last date under consent); or Lost to Follow Up (date of last contact), and subsequent anticancer therapies.

Survival updates may be made more often than every 3 months if the patient is seen at the investigational site for other reasons and for study level survival sweep(s). The survival follow-up period will continue until the study has completed (see Section 4.5.4) or other discontinuation criteria are met (see Section 4.4.4).

Note: Survival follow-up can be done either over the telephone, or by collection of public records in accordance with local laws. For some patients the first survival contact may

occur at the time of the 90-day Safety-Follow-up visit (i.e. 90 days after the last dose had been administered).

Note: Pregnancy testing after 90 days (e.g., on Day 150) after the last dose of study drug may be performed at the patient's local gynecologist to reduce the burden related to study visits at the site, but must be communicated to the study Investigator.

5.3 Study procedures

5.3.1 Screening procedures

5.3.1.1 Medical history / baseline medical conditions

A full medical history, including relevant conditions, abnormalities, surgeries, diseases, or disorders, must be obtained at Screening and recorded in the eCRF. Medical history also includes any relevant worsening of a patient's condition which occurs after any informed consent, but prior to the start of first study-drug administration.

5.3.1.2 Demography

Demography should also be collected and recorded in the eCRF, including year of birth, gender, race (unless local regulations do not permit), and ethnicity (US patients).

5.3.1.3 Prior cancer history

Details regarding prior cancer history, current cancer diagnosis, tumor stage at the time of diagnosis and at Screening, and previous cancer-related surgical procedures, including type of the procedure and dates are also required.

Prior anti-cancer treatments must be recorded during Screening and documented for each patient in the eCRF, including:

- Previous anti-cancer agents received since the diagnosis of cancer (if relevant), including dates, duration and outcome of treatment.
- Previous radiation therapy received since the diagnosis of cancer, including anatomic site, dose and dates of treatment.

5.3.1.4 Prior and concomitant medications

All non-antineoplastic medications or significant non-drug therapies (including herbal medicines) taken within 30 days of the Screening visit must be documented for each patient in the eCRF.

5.3.2 Safety assessments

The Investigator will evaluate safety by AE monitoring (type, nature, severity, according to NCI CTCAE 5.0), physical examination (including vital signs), ophthalmological examination, ECG assessment, clinical safety blood tests, ECOG PS, and pregnancy testing.

These safety assessments must be performed at intervals indicated in the schedule of assessments (see Table 1). More frequent assessments may be performed at the Investigator's discretion, if medically indicated.

Safety data will also be reviewed by the Sponsor and by the IDMC (see Section 3.5).

5.3.2.1 Physical examination

The physical examination will include examination of general appearance, skin, nails, neck (including thyroid), eyes, nose, throat, cardiovascular system, thorax/lungs, abdomen, lymph nodes, extremities, and nervous system.

Additionally, the patient should undergo assessment of height (Screening visit only), weight, and vital signs (temperature [oral, axillary, or tympanic], blood pressure, respiration rate, and pulse).

Systolic and diastolic blood pressure must be obtained in the same position throughout a given visit, i.e., either sitting, semi-supine, or supine, as appropriate. Recordings are to be made after the patient has been in this position for at least 5 min.

Any clinically-significant physical change from baseline that occurs after first study-drug administration must be reported as an AE (see Section 7.4.3.1).

5.3.2.2 Eastern Cooperative Oncology Group performance status

ECOG PS will be assessed at all study visits.

Table 2 provides the scale to be used for these assessments.

Table 2 ECOG performance status

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

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

5.3.2.3 Complete ophthalmological examination

A complete ophthalmological examination, including OCT, should be performed by an ophthalmologist at the Screening visit, for the first four cycles (i.e., Day 1 [±7d] of Cycles 2–5), and at the End of Treatment visit. Thereafter, a complete ophthalmological examination is to be repeated if clinically indicated (e.g., new ocular symptoms occur or vision is impaired).

The complete ophthalmological examination may include the following:

- visual acuity
- tonometry
- anterior segment evaluation
- retinal evaluation, including OCT

For the individual patient, the same methods of assessment should be used throughout the study. Patients who develop ocular symptoms or changes in visual acuity while on the

study should be referred to the ophthalmologist for a complete ophthalmological examination.

5.3.2.4 Electrocardiogram (12-lead) triplicates

For all patients, a standard, triplicate, 12-lead ECG must be performed at all study visits using the pre-programmed device provided by the Sponsor.

ECGs must always be recorded after at least 5 minutes rest and while the patient is in a sitting, semi-supine, or supine position. Measurements should be separated by ~1 minute and be taken within a 5-minute time window. The on-treatment ECGs (up to Cycle 4) should be performed as close as possible to the corresponding PK blood collection timepoint during those visits (see Section 5.3.4.1); if possible, ECG should be measured first, and then blood collected for PK within 5–10 minutes.

ECGs must be assessed by the Investigator or their designee for any abnormalities, including prolongation of QTcF. The ECG printouts are to be signed and dated by the Investigator or their designee. Further instruction and training on handling the device and transmitting data will be provided to the study centers prior to study initiation.

All ECGs are to be transmitted to a central ECG laboratory for evaluation, including QTcF assessment. Any clinically-significant ECG change from baseline that occurs after first study drug administration must be reported as an AE (see Section 7.4.3).

5.3.2.5 Clinical safety laboratory blood tests

Blood samples for clinical safety laboratory testing should be performed locally at all study visits. For C1D1, clinical safety laboratory testing must be performed within 72 hours prior to study drug administration.

These assessments must be reviewed prior to dosing, and study drug administration should only occur if local laboratory test values are acceptable (i.e., CTCAE grade 2 or less), unless dose delays or modifications are clinically indicated (as assessed by the Investigator and agreed upon by Medical Monitor or designee; see Section 6.1.1.5).

Safety laboratory determinations will include hematology, blood chemistry, liver function tests, and coagulation tests. If clinically indicated, some or all of these tests may be repeated on other study days.

Clinical safety laboratory tests will comprise the following:

- ***Hematology:*** complete blood count including hemoglobin, hematocrit, absolute white blood cell count with 5-part differential, red blood cell count, and platelet count
- ***Blood chemistry:*** albumin, calcium, magnesium, chloride, C-reactive protein (CRP), creatinine, glucose, phosphate, potassium, amylase, lipase, total protein, sodium, thyroid panel (TSH, fT3, fT4), uric acid, and Vitamin D
  - CRP is required at C1D1 only and thereafter if infection is suspected;
  - CL_{CR}, as calculated by the Cockcroft-Gault equation (at the Screening Visit only);
  - TSH, fT3 and fT4 is required at C1D1 and subsequently every 4 cycles;

  - 25-hydroxy vitamin D is required at C1D1, C3D1, C5D1, and the End of Treatment visit only.

- ***Liver function tests:*** ALT, AST, Alkaline phosphatase (ALP), total and direct bilirubin, lactate dehydrogenase
- ***Coagulation tests:*** prothrombin time, INR, and partial thromboplastin time (at the Screening and End of Treatment visits, and if clinically indicated at any time during treatment)

Additional testing may be performed whenever clinically indicated at the discretion of the Investigator and if applicable in relation to the patient's medical history. All samples for a given study center must be analyzed by the same local laboratory throughout the study, as designated by the Investigator. The results are to be printed, signed and dated by the Investigator or their designee.

In the event of unexplained abnormal laboratory test values, the tests must be repeated immediately and followed-up until return to the normal range, stabilization, and/or until an adequate explanation of the abnormality has been determined. Abnormal laboratory results should not be recorded as an AE unless the abnormality is associated with a clinically-relevant condition (see Section 7.4.3.1.1).

5.3.2.6 Urinalysis

Urinalysis will be performed locally at the Screening visit, at C1D1 (within 72 hours prior to study drug administration), at D1 of all subsequent cycles, and at the End of Treatment visit.

Urinalysis should consist of specific gravity, pH, glucose, protein, ketones, and blood. If clinically indicated, some or all of these tests may be repeated on other study days.

5.3.2.7 Pregnancy testing

Women of child-bearing potential must have a negative hCG at Screening and within 72 hours prior to dosing at C1D1. Subsequently, serum pregnancy testing will be performed prior to study drug dosing on D1 of every cycle, at the End of Treatment visit, and serum or urine pregnancy testing will be performed monthly thereafter for 150 days following the last administration of study treatment.

Pregnancy testing after the end of treatment may be performed at the patient`s local gynecologist to reduce the burden related to study visits at the site, but must be communicated to the study Investigator.

The Investigator may conduct additional pregnancy tests (serum or urine) to confirm the absence of pregnancy at any time during the study. If a pregnancy test result is positive, study drug must be discontinued, the patient followed for safety, and the outcomes of the pregnancy assessed (see Section 7.4.5). Further details regarding the risk of pregnancy are provided in Section 7.1.3.

5.3.2.8 Adverse event monitoring

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in NCI CTCAE 5.0.

Please refer to Section 7 for details regarding AE collection and management.

5.3.2.9 Concomitant medications

Any medications or significant non-drug therapies (including herbal medicines) that are taken by or administered to the patient during the course of the study (until the safety follow-up visit at Day 28 for all patients, and Day 90 for patients receiving derazantinib-atezolizumab in combination) must be recorded in the eCRF including the dosage, frequency of administration, route of administration, therapeutic indication, and start/stop dates of use.

5.3.3 Efficacy assessments

5.3.3.1 Tumor imaging and assessment of disease

The process for image collection and transmission to the central imaging vendor is provided in the Imaging Charter. Tumor disease assessments should comprise the chest, abdomen, and pelvis. Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated, and for imaging in the brain.

A bone scan (BS) – alternatively, a whole-body MRI (WBMRI) - should also be performed at Screening only in patients with new symptoms (e.g., new persistently elevated ALP) to assess bone metastasis; screening of asymptomatic patients for clinically unapparent bone metastases is not supported by applicable guidelines (Witjes 2018) but may be done at the Investigator's discretion if local routine practice. Patients with positive BS/WBMRI at baseline will undergo further radiologic assessments of bone lesions performed at protocol-scheduled time points for tumor assessments and as per institutional practice. Lytic/mixed lesions with soft tissue component may be included in the evaluation of disease burden if it meets measurability criteria while blastic lesions are considered non-measurable, in accordance with RECIST 1.1.

The same imaging technique regarding modality and use of contrast should be used in a patient throughout the study.

Local site Investigator/radiology assessment based on RECIST 1.1 will be used to determine patient eligibility. All measurable and evaluable lesions should be assessed and documented by the site study team at the Screening visit.

All scheduled images for all study patients must be submitted to the central imaging vendor. Additional imaging (including other modalities) obtained at unscheduled time points to determine disease progression, as well as imaging obtained for other reasons, but which captures radiologic progression, must also be submitted to the central imaging vendor.

5.3.3.2 Tumor measurement and response evaluations

Tumor imaging assessments (CT/MRI of the chest, abdomen, and pelvis, plus a BS/WBMRI, if applicable) must be done at the time of the Screening visit. However, if an assessment has been performed for routine clinical management after administration of the last dose of any prior anti-tumor treatment, but prior to obtaining informed consent and within 28 days of first dose of study treatment on C1D1, then this may be used for Screening purposes; in such situations it is not necessary to repeat tests if the assessments are of sufficient diagnostic quality.

5.3.3.2.1 *Initial tumor imaging*

For initial tumor imaging at Screening, the site study team must review Screening images to confirm the patient has measurable disease per RECIST 1.1.

5.3.3.2.2 *On-treatment tumor imaging*

Study imaging assessments consist of CT/MRI of the chest, abdomen, and pelvis (plus a BS/WBMRI, if applicable). The first on-study tumor imaging assessments will be performed after 9 weeks on study, and will be repeated every 9 weeks from C1D1 (±7 days) (approximately every 3 cycles, i.e., at C4, C7, C10) or more frequently if clinically indicated. After 27 weeks (9 cycles), the assessment interval is every 12 weeks (±7 days, i.e. at C14, C18, etc.) for all patients. Imaging timing should be based on the first dose at C1D1, should follow calendar days, and should not be adjusted for delays in cycle starts.

Results of all on-treatment tumor imaging assessments must be reviewed by the Investigator before dosing at the next cycle.

5.3.3.2.3 *Post-treatment tumor imaging*

Patients who discontinue study treatment should have a tumor evaluation visit as soon as possible after the event (e.g., clinical deterioration; ± 4-week window). If a previous scan was obtained within 4 weeks prior to the End of Treatment Visit, then a scan is not mandatory. For patients who discontinue study treatment without documented radiologic disease progression, every effort should be made to perform radiologic imaging. For patients who discontinue study treatment due to documented PD, this is the final required tumor imaging.

5.3.3.2.4 *RECIST 1.1 and iRECIST*

The efficacy of derazantinib monotherapy treatment and derazantinib-atezolizumab in combination will be primarily measured by ORR evaluated by BICR using RECIST 1.1 (see Appendix 2).

In addition, an exploratory assessment will be performed using iRECIST criteria (Seymour 2017) in patients treated with derazantinib-atezolizumab in combination, including those patients undergoing crossover treatment (see Appendix 3 for comparison of RECIST 1.1 and iRECIST).

The iRECIST criteria is RECIST 1.1 adapted to account for the tumor response patterns seen with immunotherapeutic drugs. In patients undergoing combination treatment with derazantinib and atezolizumab, iRECIST will be used by the site Investigator / local

radiology review to assess tumor response and progression, and to make treatment decisions. These data will be collected in the clinical database. Treatment efficacy based on iRECIST as assessed by central imaging vendor review will be evaluated retrospectively.

The Investigator should make every attempt to perform the confirmation scan of CR or PR 4–5 weeks after the last scan was performed. The confirmation scan of iUPD should be performed 4–8 weeks after the last scan was performed, unless criteria for clinical stability are not met (see below).

5.3.3.2.5 *Management of immunotherapy-treated unconfirmed disease progression*

In patients treated with derazantinib-atezolizumab in combination[1] who have iUPD (i.e., initial evidence of radiological PD by RECIST 1.1 as verified by the central imaging vendor), it is at the discretion of the Investigator whether to continue a clinically stable patient (as defined below) on study treatment until repeat imaging is obtained. For patients with iUPD, confirmation is done on the basis of observing any of the following scenarios in clinically stable patients:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesions(s)

If progression is confirmed by a CT/MRI after 4–8 weeks, the patient should discontinue study treatment.

If progression is not confirmed and criteria of iCR, iPR, or iSD are met compared with baseline (i.e. a reduction in lesion diameter is shown compared to the iUPD assessment), then subsequent assessment are to be compared against the tumor diameter nadir values of iCR, iPR, or iSD. If iUPD occurs again (compared with nadir values of iCR, iPR, or iSD) then iUPD is again to be confirmed (by further growth) at the next assessment for iCPD to be assigned.

If no change in tumor size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudo-progression, to be identified (Seymour 2017). Patient management using iRECIST is detailed in Table 3.

This clinical judgment decision by the Investigator should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may continue to receive study treatment and tumor assessment should be repeated 4–8 weeks later in order to confirm iUPD by iRECIST per site assessment.

Clinical stability is defined as the following:

[1] Applicable to patients receiving derazantinib-atezolizumab in combination in Substudies 3 and 4, including patients in Cohorts 3a and 4a crossing over from derazantinib monotherapy after centrally confirmed radiographic PD per RECIST 1.1

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values, and
2) No decline in ECOG PS, and
3) Absence of rapid PD, and
4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Any patient deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per iRECIST, the Investigator should consider all target and non-target lesions, as well as any incremental new lesion(s).

Table 3 Imaging and treatment after first radiologic evidence of PD if iRECIST is followed

Imaging assessment	Clinically stable		Clinically unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First evidence of iUPD	Repeat imaging at 4–8 weeks to confirm PD (iCPD)	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	No repeat imaging	Discontinue
Repeat tumor imaging results in iCPD at the local site	No further repeat imaging	Withdraw from study treatment	Not applicable	
Repeat tumor imaging shows iSD, iPR or iCR by local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Not applicable	

Abbreviations: PD, progressive disease; iUPD, unconfirmed progressive disease; iCPD, confirmed progressive disease; iSD, stable disease; iPR, partial response; iCR, complete response; iRECIST, Response Evaluation Criteria In Solid Tumors (adapted to account for the unique tumor response seen with immunotherapeutic drugs).

5.3.4 Pharmacokinetic assessments

The collection, storage, and shipping of blood samples will be performed as described in the Laboratory Manual.

5.3.4.1 Pharmacokinetic assessments for derazantinib

Blood samples will be taken to determine the PK parameters of derazantinib. Exploratory assessments of metabolites of derazantinib may also be investigated from the same samples.

PK blood sampling for derazantinib will be performed according to a rich PK schedule or a sparse PK schedule.

5.3.4.1.1 *Overview of specific PK sampling requirements*

All patients, excluding SIA patients in Substudies 3 and 5, will undergo sparse PK sampling for measurement of derazantinib plasma concentrations. These samples may also be used for exploratory metabolite identification and/or quantification of metabolites.

All **SIA patients in Substudies 3 and 5** will undergo rich PK sampling for measurement of plasma concentrations of derazantinib and relevant PK parameters.

Additionally, in **Substudy 3, Cohort 4b and Crossover**, PK sampling of atezolizumab and ADAs will be performed.

5.3.4.1.2 *Rich PK profiling*

Rich PK profiling will be performed for all **SIA patients in Substudies 3 and 5**, and will be drawn in accordance with the following schedule[1]:

- C1D1, prior to derazantinib dose, and 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 15 minutes), 8 hours (± 30 minutes), 10 hours (± 30 minutes), 12 hours (± 30 minutes; prior to the second dose administration), 24 hours after first derazantinib administration (i.e., 12-hour post second dose administration but within 1 hour prior to the third dose).
- C1D8, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
- C1D15, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
- C2D1, prior to derazantinib (within 1 hour prior to the next dose), and 1 hour (± 5 minutes), 2 hours (± 5 minutes), 4 hours (± 15 minutes), 8 hours (± 30 minutes), 10 hours (± 30 minutes), 12 hours (± 30 minutes; prior to the second dose administration), 24 hours after derazantinib administration (i.e., 12-hour post previous dose administration but within 1 hour prior to the next dose).
- C2D8, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
- C2D15, pre-dose (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
- C3D1, prior to derazantinib (within 1 hour prior to the next dose), and 6–8 hours after derazantinib administration.
- C4D1, prior to derazantinib administration (within 1 hour prior to the next dose).
- 28-day Safety Follow-up visit

5.3.4.1.3 *Sparse PK sampling*

Sparse PK profiling will be performed for all patients (excluding SIA patients in Substudies 3 and 5), according to the following schedule:

[1] This schedule may be adapted to locally applicable clinical routine with the agreement of the Sponsor.

- C1D1 and C1D15, prior to derazantinib (within 1 hour prior to the next dose), and 6–8 hours after the study drug administration.
- C2D1, prior to derazantinib (within 1 hour prior to the next dose)
- C3D1, prior to derazantinib (within 1 hour prior to the next dose), and 6–8 hours after the study drug administration.
- C4D1, prior to derazantinib administration (within 1 hour prior to the next dose)
- 28-day Safety Follow-up visit

5.3.4.2 Assessments for pharmacokinetics and anti-therapeutic antibodies of atezolizumab

Blood samples for PK and ADA sampling in all patients in **Substudy 3** and **Cohort 4b** will be drawn in accordance with the following schedule:

- C1D1, prior to atezolizumab administration; and for PK only, 30 minutes after end of atezolizumab infusion
- C2D1, C3D1, C4D1, prior to atezolizumab administration
- C8D1, C12D1, C16D1, prior to atezolizumab administration
- 28-day Safety follow-up visit

5.3.5 Biomarker assessments

Archival (or *de novo,* if collected) tumor tissue and research liquid biopsy samples will be collected during this study to analyze a panel of biomarkers, including, but not limited to biomarkers representing MAPK (RAS/RAF/MEK/ERK), PI3K/AKT, and JAK/STAT pathways; indicating PI3K, PTEN, EGFR, MET and ERB3 signaling; demonstrating the phosphorylation status of phospho-S6, phospho-STAT, phospho-AKT, phospho-MEK, phospho-ERK.

In addition to these PD markers of target modulation, more generic markers of proliferation could be utilized to help confirm that significant inhibition of tumor proliferation has occurred. These include the proliferation index (Ki67), apoptosis levels (caspase activation), as measured by immunohistochemistry and also various measures of tumor vascularity. Anti-vascular effects may also be measured by immunohistochemistry to assess micro-vessel density and the endothelial markers CD34 and CD31.

Tumor and research liquid biopsy samples for biomarker assessments will be analyzed by the Sponsor or in specialized laboratories, as described in Section 5.3.5.2 and Section 5.3.5.1 below. Exceptions to the schedule of Biomarker assessments can be made according to the Sponsor's discretion.

5.3.5.1 Research liquid biopsy

Apart from diagnostic liquid biopsies for molecular eligibility, research liquid biopsies may comprise, but are not limited to, serum and plasma samples to analyze protein biomarkers, and cfDNA. The collection, processing, storage, and shipping of samples for the assessment of circulating biomarkers will be performed as described in the Laboratory Manual.

5.3.5.2 Archival tumor tissue

Archival tumor tissue should be collected from all patients enrolled with an *FGFR1–3* GA-positive test result. An FFPE block; or minimum of two H&E-stained slide plus at least 10 consecutive, unstained, 4 ± 1 µm thick sections, placed on positively charged slides, should be sent to the central laboratory for biomarker assessment, including PD-L1, as described in the Laboratory Manual.

If archival tumor tissue is not available, *de novo* biopsy may be performed but only if considered by the Investigator as safe and tolerable for the patient. For tumor tissue biopsy FFPE preservation, slide preparation and sample submission, see the Laboratory Manual.

5.3.5.3 Pharmacodynamic research (optional)

Patients enrolled into **Substudies 3, 4 and 5** have the option to participate in an exploratory PDR to investigate the role of CSF1R inhibition by derazantinib, comprising a skin biopsy and blood sampling for monocyte subsets prior to the first dose of study drug at the Screening visit and on C2D1. Up to 20 patients will be enrolled in this PDR Group.

The samples will be collected, processed and shipped as described in the Laboratory Manual.

5.3.5.4 Future biomedical research

The Sponsor will conduct Future Biomedical Research on specimens collected during this clinical study. This research may include genetic analyses (DNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes. Tissue/blood samples, plasma/serum samples, DNA isolates from samples available and processed during the study and not fully consumed for the described analyses may be stored and subsequently used for Future Biomedical Research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol as part of the main study, and will only be conducted on specimens from patients who have provided appropriate informed consent. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The goal is to use such information to develop safer, more effective drugs, and/or to ensure that patients receive the correct dose of the correct drug at the correct time.

The details of this Future Biomedical Research substudy are presented in Appendix 5. Additional informational material for IRBs/IECs and investigational site staff is provided in Appendix 5.

5.3.6 PRO assessments

Patient-reported outcomes will be measured using the EORTC QLQ C30, FACT-Bl, EQ-5D (5L), and Health Transition Index/G-SET instruments.

The EORTC QLQ-C30 was developed to assess the quality of life of cancer patients and is the most widely used cancer-specific HR-QoL instrument. It contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social),

three symptom scales (fatigue, nausea/vomiting, and pain), six single symptom items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) and global health and quality of life. The global health and quality of life items uses a 7-point scale scoring with anchors (1=very poor and 7=excellent); the other items are scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much).

The EORTC QLQ-C30 is the most frequently utilized and reported patient reported outcome measures in cancer clinical trials. The reliability, validity and practicality of these instruments have been reported (Aaronson 1993).

The FACT-Bl is instrument which was developed for patients with bladder cancer. It contains 40 items and consists of the five subscales: physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), social well-being (SWB) and an additional scale specific to bladder cancer. In addition, the PWB, FWB, EWB, and SWB subscales can be summed to form the FACTGeneral (FACT-G) score and the FACT-BL total score (FACT-G and the bladder cancer specific scale). The items are scored on a 4-point scale (0=not at all, 1=a little bit, 2= somewhat, 3=quite a bit, 4 = very much) (Karvinen 2007).

The EQ-5D (5L) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a five-point scale from 1 (no problem) to 5 (extreme problem). The EQ-5D also includes a graded (0 to 100) vertical VAS on which the patient rates his or her general state of health at the time of the assessment.

The Health Transition Index/G-SET is a single item and will be used as an external anchor to determine the minimal important difference of the EQ-5D visual analogue scale, EORTC QLQ-C30 scales and FACT-Bl scales. It will be administered twice during the study following the recent protocol by the EORTC Quality of Life Group (Musoro 2018) for evaluating the minimal important difference. The SET will be provided after 6 weeks (at C3D1) and 12 weeks (at C5D1). The SET is a patient-rated change in health between two time periods using a five point ordinal scale (1=much better now than six weeks ago; 2=somewhat better now than six weeks ago; 3=about the same as six weeks ago; 4=somewhat worse now than six weeks ago; 5=much worse now than six weeks ago, the recall period was adapted compared to the original item) (Ware 2002, Lloyd 2014).

The HR-QoL questionnaires will be provided to the patients to complete prior to being evaluated by the physician on D1 of every cycle, and at the End of Treatment visit.

Either a paper instrument or an electronic PRO data collection method may be used. The PRO instruments, translated as necessary into the local language, will be distributed by the Investigator's staff and completed by the patient. To ensure instrument validity, and to ensure that data standards meet Health Authority requirements, PRO instruments should be self-administered at the investigational site before the patient sees the physician (i.e., at the start of the visit) and prior to the completion of other study assessments and the

administration of study treatment. The questionnaire should be completed by the patient without assistance during their scheduled visit(s) at the clinic. Study site staff should review all instruments for completeness before the patient leaves the investigational site. The EQ-5D will always be completed by patients before completing the EORTC QLQ-C30, FACT-Bl, and the Health Transition Index/G-SET (only at visits after 6 and 12 weeks).

6 STUDY TREATMENTS

Derazantinib and atezolizumab are both considered to be IMPs in this study, and will be provided by the Sponsor. Detailed information related to IMP handling and storage is provided in the Pharmacy Manual.

As this is an open-label study, neither the patient, the Investigator / site staff, nor the Sponsor will be blinded to the treatment administered.

6.1 Investigational products

6.1.1 Derazantinib

Derazantinib is an investigational drug supplied as 100 mg powder-filled capsules for oral administration.

The Investigator must ensure that derazantinib capsules will be used only in accordance with the protocol.

6.1.1.1 Derazantinib administration

Derazantinib capsules will be administered by mouth. The schedules for the administration of derazantinib are shown in Section 6.1.3 and Table 6.

Derazantinib capsules should be administered at least 1 hour before, or at least 2 hours after, a meal. In the event of nausea or vomiting which is assessed as CTCAE grade ≥ 2, a light meal before subsequent derazantinib administration is allowed, to minimize the severity of the event.

6.1.1.2 Labeling and packaging

Derazantinib is supplied as capsules in white/opaque high-density polyethylene bottles with white/opaque polypropylene caps and labeled in the local languages as investigational agent, in accordance with local regulations and the Annex 13 Good Manufacturing Practice rules.

Labels must include the identity of the Sponsor and Investigator, patient number, protocol number, drug identification, storage conditions, content of study drug, and expiry date. Information on drug shipment including temperature logger and acknowledgement of receipt form to be completed by the receiver must also be included in the shipment.

6.1.1.3 Drug accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and acknowledge receipt in the IWRS system. A Packing Slip will be included with the shipment and must be completed upon receipt and returned as instructed on the form. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Log will be provided for derazantinib capsules. The log must be kept current and should contain the protocol number, the name and clinical site of the

Investigator, dates and quantities of drug received, patient's identification number to whom derazantinib capsules were dispensed, the date and quantity dispensed, and balance remaining, if from individual patient drug units, as well as the lot number, dose, and the initials of the dispenser. Drug accountability is performed to the capsule level.

To avoid unnecessary waste of derazantinib capsules, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.

At the end of the study or as directed, all study drugs, including unused, partially used, or empty containers, will be returned to the designee as instructed by the Sponsor. Derazantinib capsules will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of derazantinib capsules must be documented and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition Standard Operation Procedures (SOPs) or equivalent.

All derazantinib capsules inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

6.1.1.4 Shipping and storage conditions

The Sponsor will provide derazantinib capsules required for completion of this study. It will be shipped to the pharmacist/study personnel at the clinical sites during the study with orders being raised via the IWRS.

Drug supplies must be stored in a secure, limited access storage area.

The packaged drug product should be shipped and stored at controlled room temperature 20°C–25°C (68°F–77°F); allowable excursions are in the range of 15°C–30°C (59°F–86°F). Derazantinib capsules are stable when stored at controlled room temperature. Refer to the product label for specific storage conditions and handling requirements.

If storage conditions deviate from the above storage requirements, the Investigator will document the deviation and inform the study monitor within 24 hours of discovery of the deviation. The supplies should be held in quarantine and not dispensed until the deviation has been reviewed by the Sponsor's Quality Assurance or designee. If it is determined that the product is no longer suitable for use, the bottles must be reported as damaged in the IWRS and a resupply shipment will be made.

6.1.1.5 Dose modifications

In general, once the dose of derazantinib has been modified for a patient (as per Table 4), all subsequent cycles should be administered to that patient at the modified dose. The modified dose will be considered the maximum dose for all subsequent cycles for that patient.

When a drug-related toxicity is observed, dose delays and/or reductions in derazantinib administration are allowed. A drug-related toxicity is defined as any toxicity considered probably, or possibly related to derazantinib. If dose reduction is indicated, a patient should be assigned to the lower dose. Dose re-escalation is not permitted. In the event of a dose modification, the dose change(s) must be captured in the eCRF. If questions or considerations regarding dose modification arise or a specific dose modification is needed, the Sponsor's Medical Monitor or designee should be consulted.

Table 4 Derazantinib dose reduction schema

Current dose	Dose after reduction
2 capsules BID (400 mg daily)	3 capsules QD (300 mg daily)
3 capsules QD (300 mg daily)	2 capsules QD (200 mg daily)
2 capsules QD (200 mg daily)	1 capsule QD (100 mg daily)
1 capsule QD (100 mg daily)	1 capsule QOD (100 mg every other day)

Abbreviations: BID, twice a day; QD, once daily; QOD, every other day

For AEs of special interest (AESIs; see Section 7.2.6), including hyperphosphatemia and eye disorders, and any other AEs considered at least possibly derazantinib-related (see Section 7.1.1.2 for risks for derazantinib), Table 5 and Sections 6.1.1.5.1 to 6.1.1.5.3 provide specific guidance to manage these events through dose delays, reductions and/or discontinuations.

Table 5 Dose delays/reductions for drug-related toxicity

Hyperphosphatemia	
Serum phosphate level	**Action** (For serum phosphate ≥ 7.0 mg/dL, consider adding an oral phosphate binding/reducing agent until serum phosphate level returns to < 5.6 mg/dL)
< 7.0 mg/dL (< 2.26 mmol/L)	Continue derazantinib at current dose.
7.0 – 9.0 mg/dL (2.26 – 2.90 mmol/L)	Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL; the patient may restart derazantinib at the dose prior to hyperphosphatemia. If hyperphosphatemia lasts > 2 weeks, consider restarting at the next lower dose.
> 9.0 – 10.0 mg/dL (> 2.90 – 3.23 mmol/L)	Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL; the patient may restart at the next lower dose level.
> 10.0 mg/dL (> 3.23 mmol/L) or significant alteration from baseline renal function **or Grade 3 hypercalcemia**	Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL; the patient may restart at two dose levels lower, or permanently discontinue derazantinib (e.g., if considered life threatening event).
Central serious retinopathy / Retinal pigment epithelial detachment	
Grade	**Action**
Asymptomatic clinical or diagnostic observations only (Grade 1)	Withhold derazantinib until resolution. If the event resolves within 4 weeks, restart at the next lower dose level. If stable but not resolved for two consecutive eye examinations, restart at the next lower dose level.
Visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline (Grade 2)	Withhold derazantinib until resolution. If the event resolves within 4 weeks, the patient may restart at the next lower dose level.
Visual acuity worse than 20/40 or > 3 lines of decreased vision from baseline (Grade 3)	Withhold derazantinib until resolution. If the event resolves within 4 weeks, the patient may restart at two dose levels lower. If the event recurs, consider permanent discontinuation of derazantinib.
Visual acuity 20/200 or worse in affected eye (Grade 4)	Permanently discontinue derazantinib.
Other events	
CTCAE grade	**Action**
Grade 1 or 2	Continue derazantinib at current dose, unless dose delay/modification may be clinically indicated (as assessed by the Investigator and agreed upon by the Medical Monitor or designee).
Grade 3	Withhold derazantinib until recovery to Grade 1 or baseline; administer derazantinib at the next lower dose for subsequent dosing, unless further dose reduction is required.
Grade 4	Permanently discontinue derazantinib if the event is at least possibly related to derazantinib.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

6.1.1.5.1 *Hyperphosphatemia*

For all patients, it is recommended to restrict phosphate intake to 600–800 mg daily. As hyperphosphatemia is only defined by NCI CTCAE 5.0 with regards to escalating interventional measures (without specifications triggering these interventions) and not by laboratory values exceeding the upper limits of normal leading to specific interventions, Table 5 guides interventions for the management of hyperphosphatemia considered at least possibly related to derazantinib.

In alignment with interventions to ensure patient safety and for the purpose of this protocol, hyperphosphatemia is defined as:

Grade 1: > ULN to < 7.0 mg/dL (< 2.26 mmol/L)

Grade 2: Non-invasive intervention required (e.g., withhold drug or modify dose) or between 7.0 – 9.0 mg/dL (2.26 – 2.90 mmol/L)

Grade 3: Severe or medically significant, but not immediately life threatening or > 9.0 – 10.0 mg/dL (> 2.90 – 3.23 mmol/L)

Grade 4: Life-threatening consequences, urgent intervention indicated e.g., dialysis or > 10.0 mg/dL (> 3.23 mmol/L)

Patients who present with serum phosphate ≥ 7.0 mg/dL, adding an oral phosphate binding/reducing agent[1] until serum phosphate level returns to < 5.6 mg/dL should be considered, and patients should be instructed to adhere to a low-phosphate diet.

6.1.1.5.2 *Management of retinal adverse events*

A complete ophthalmological examination (see Section 5.3.2.3) should be performed by an ophthalmologist at the Screening visit, for the first four cycles (i.e., Day 1 of Cycles 2–5), and at the End of Treatment visit. Further complete ophthalmological examinations only need to be performed if clinically indicated. Table 5 provides specific guidance for the management of dose delays/reductions in the case of retinal adverse events possibly related to derazantinib.

6.1.1.5.3 *Management of QTc prolongation or other significant ECG abnormalities*

If significant QTc prolongation and/or significant ventricular arrhythmia is observed, i.e., a prolonged QTcF interval ≥ 501 ms on at least two separate ECGs (mean values from triplicate ECGs, consistent with a CTCAE grade 3 event), the patient must be monitored by the Investigator and hourly (triplicate) 12-lead ECG obtained until the mean QTcF has returned to ≤ 450 msec for males or to ≤ 460 msec for females. The clinical context and possible factors contributing to QTc prolongations such as electrolyte abnormalities (potassium, calcium or magnesium), concomitant medications, or other clinical factors such as cardiac ischemia must be carefully assessed, and any findings documented in the eCRF. The decision to continue treatment with derazantinib should be reviewed and supported by a cardiologist.

[1] Either calcium-containing (e.g., calcium carbonate and calcium acetate) or non-calcium-containing (e.g., sevelamer) phosphate binders, and/or phosphaturic agents, depending on serum calcium levels and in accordance with institutional guidelines, recommendations, and schedules.

Once QTc prolongation has resolved, and if a decision was made to continue treatment with derazantinib, patients may continue treatment at a lower dose with an ECG monitoring schedule defined by the cardiologist. Patients who experience a mean QTcF interval ≥ 501 ms on at least two ECGs at different timepoints after dose reduction will be discontinued from study.

All significant QTc prolongations or other relevant ECG abnormalities, will also be evaluated centrally.

6.1.1.6 Missed-dose management

A missed or vomited dose should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time. If the patient vomited the very first dose of derazantinib, the patient may be re-challenged at the Investigator's discretion.

6.1.1.7 Overdose

There is no specific guidance to be given at this time.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted. Any AE resulting from an overdose must be collected (see Section 7.5).

6.1.2 Atezolizumab

Atezolizumab is an approved medication supplied as 1200 mg/20 mL concentrate solution for IV infusion. Atezolizumab is an investigational drug for its use in combination with derazantinib.

6.1.2.1 Atezolizumab administration

Atezolizumab is for intravenous use. The infusions must not be administered as an intravenous push or bolus.

The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

The dosing schedule of atezolizumab in combination with derazantinib is shown in Section 6.1.3 and Table 6.

6.1.2.2 Labeling and packaging

Atezolizumab is supplied as 20 mL vials of concentrate for solution for infusion and labeled in the local languages as investigational agent, in accordance with local regulations and the Annex 13 Good Manufacturing Practice rules.

Labels must include the identity of the Sponsor and Investigator, patient number, protocol number, drug identification, storage conditions, content of study drug, and expiry date. Information on drug shipment including temperature logger and acknowledgement of receipt form to be completed by the receiver must also be included in the shipment.

6.1.2.3 Drug accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration

date, and acknowledge receipt in the IWRS system. A Packing Slip will be included with the shipment and must be completed upon receipt and returned as instructed on the form. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Log will be provided for atezolizumab. The log must be kept current and should contain the protocol number, the name and clinical site of the Investigator, dates and quantities of drug received, patient's identification number to whom atezolizumab was dispensed, the date dispensed, as well as the lot number, dose, and the initials of the dispenser.

At the end of the study or as directed, all study drugs, including unused, partially used, or empty containers, will be returned to the designee as instructed by the Sponsor. Atezolizumab will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return must be documented, and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition SOPs or equivalent.

All atezolizumab inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

6.1.2.4 Shipping and storage conditions

Ship and store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store the vial in the outer carton in order to protect from light.

6.1.2.5 Preparation and stability of study drug

Twenty mL of atezolizumab concentrate should be withdrawn from the vial and diluted into a 250 mL polyvinyl chloride (PVC), polyethylene (PE) or polyolefin infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, 1 mL of solution should contain approximately 4.4 mg of atezolizumab (1,200 mg/270 mL). The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately (see Section 6.3).

Parenteral medicinal products should be inspected visually for particulates and discoloration prior to administration. If particulates or discoloration are observed, the solution should not be used.

No incompatibilities have been observed between atezolizumab and intravenous bags with product-contacting surfaces of PVC, PE or polyolefin. In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

After dilution, chemical and physical in-use stability has been demonstrated for no more than 24 hours at 2 °C to 8 °C or 24 hours at ≤ 30 °C from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C).

6.1.2.6 Dose modifications

Dose modifications/reductions of atezolizumab are not permitted. Patients treated with derazantinib and atezolizumab in combination should be temporarily or permanently discontinued from atezolizumab and/or study treatment if any of the toxicities described in Appendix 4 occur, and are assessed by the Investigator as at least possibly atezolizumab-related.

If atezolizumab is discontinued per these guidelines, continuation of derazantinib is at the discretion of the Investigator (see Section 4.5.1).

6.1.2.7 Missed-dose management

If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

6.1.2.8 Overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted. Any AE resulting from an overdose must be collected (see Section 7.5).

6.1.3 Dosing schedule of study drugs

Effective Protocol Version 5.0, only dosing schedules applicable to active substudies are provided in this section.

Study drugs should be administered as shown in Table 6. There is no mandatory order for the administration of derazantinib and atezolizumab except on days of blood PK sampling, as specified elsewhere.

Table 6 Dosing schedule of study drugs by substudy

Substudy	Derazantinib (3-week cycle)	Atezolizumab (3-week cycle)
Substudy 1	300 mg QD	n/a
Substudy 3	200 mg BID	1200 mg Q3W
Substudy 4		
Cohort 4a	300 mg QD	n/a
Cohort 4b	300 mg QD	1200 mg Q3W
Substudy 5	200 mg BID	n/a

6.1.4 Duration of treatment

All patients will be treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study is terminated by the Sponsor, whichever occurs first.

Patients will be permitted to remain on study treatment after RECIST 1.1 criteria for PD are met (and are confirmed by BICR; see Section 4.5.1) if, in the opinion of the Investigator and with the agreement of the Medical Monitor, they continue to derive benefit from derazantinib or derazantinib-atezolizumab in combination.

For patients who continue to derive benefit (per Investigator assessment) from any of the study treatment regimens at the time of study closure, the Sponsor will provide continued individual access to study drug, either under a rollover study protocol, or in the context of compassionate use/named-patient access program, where applicable.

6.2 Treatment compliance

Interruptions from the protocol-specified treatment plan for greater than 6 weeks between study drug doses for non-drug-related or administrative reasons (see Section 6.1.1.5 and Section 6.1.2.6 for drug-related modifications) require consultation between the Investigator and the Sponsor, and written documentation of the collaborative decision on patient management.

6.2.1 Treatment compliance for derazantinib

Derazantinib will be self-administered by the patients outside the patient's visits. All doses given during the patient's visits with the Investigator will be administered under the supervision of clinical study personnel. The patients will be instructed to return all unused derazantinib at the next visit.

Compliance to the derazantinib regimen will be evaluated by counting unused capsules.

$$\% \text{ compliance} = \frac{\#\text{ of capsules dispensed} - \#\text{ of capsules returned}}{\#\text{ of capsules prescribed/ day}^{a} \times \#\text{ of days}^{b} \text{ in the dosing interval}} \times 100$$

[a] Number of capsules prescribed (i.e., 3 or as determined per the dose reduction guidelines for toxicity considered related to derazantinib and specified in the eCRF

[b] Number of days during that interval that the patient should have dosed (i.e., excluding any days that the patient was instructed to hold dosing due to an AE)

During the treatment period, if compliance is not between 80% and 120%, the patient will be counseled about the importance of adherence to the mandated regimen. If noncompliance in terms of dosing continues, the patient may have to be discontinued from the study treatment.

Administration of derazantinib capsules will be recorded in the 'Drug Accountability Log' and eCRF. Patients must return empty bottles and remaining capsules. Returned capsules must be recorded in the 'Drug Accountability Log', which is supplied to the site.

At each visit after the study treatment is initiated, the Investigator or designee must record the date, interval between visits, dose, and any dose changes/delays of study drug dispensed/administered. To avoid unnecessary waste of derazantinib capsules, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.

6.2.2 Treatment compliance for atezolizumab

Atezolizumab will be administered by site and/or institution staff in accordance with local SOPs and guidelines. The total volume of atezolizumab infused will be compared to the total volume prepared to determine compliance for each dose of atezolizumab administered.

6.3 Prior treatment

All non-antineoplastic medications or significant non-drug therapies (including herbal medicines) taken within 30 days of the Screening visit must be documented for each patient in the eCRF, including accurate start and stop dates of the regimens.

All surgical procedure history, prior chemotherapy (where allowed), and radiation therapy must be recorded on the appropriate eCRF. See Section 4.2, Inclusion criteria, and Section 4.3, Exclusion criteria for further details.

In **Substudy 3**, prior treatment with anti-PD-1 or anti-PD-L1-therapeutic antibody or pathway-targeting agents is not allowed.

Except for **Substudy 4**, prior treatment with FGFR inhibitor is not allowed. However, prior treatment with FGFR inhibitor in combination with anti-PD-1 or anti-PD-L1 therapeutic antibody or pathway-targeting agents is not allowed in Substudy 4. Prior treatment with either sequential immune-checkpoint blockade and FGFR inhibitor treatment or combinations of FGFR inhibitor and chemotherapy are allowed in Substudy 4. Patients assessed as having progressed upon prior treatment with FGFR inhibitors must have received FGFR inhibitor treatment for at least 12 weeks to be eligible for Substudy 4.

6.4 Concomitant treatments

Any medications or significant non-drug therapies (including herbal medicines) that are taken by or administered to the patient during the course of the study (until the safety follow-up visit at Day 28 for all patients, and Day 90 for patients receiving derazantinib-atezolizumab in combination) must be recorded in the eCRF including the dosage, frequency of administration, route of administration, therapeutic indication, and start/stop dates of use.

6.4.1 Permitted treatment

Palliative and supportive care for disease-related symptoms will be offered to all patients. In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions

- Erythropoietin Stimulating Agents (in accordance with ASCO, American Society of Hematology, or MEDICARE guidelines for the use of epoetin in patients with cancer and FDA alerts dated 09 March 2007, 08 November 2007, 12 March 2008, 31 July 2008, and 02 December 2008)
- Hematopoietic growth factors, including filgrastim (Neupogen®), or other granulocyte colony stimulating factors (in accordance with ASCO guidelines for the use of white blood cell growth factors (see http://jco.ascopubs.org/content/24/19/3187.full)
- Antiemetics may be administered according to standard practice
- Megestrol acetate (Megace®)
- Use of topical corticosteroids, topical and systemic antibiotics according to standard of care or institutional guidelines, and inhaled, intranasal, intraocular, topical, and intra-articular joint injections.
- Bisphosphonates and denosumab for bone metastases or hypercalcemia of malignancy
- Palliative radiotherapy for non-hepatic local pain (e.g., bone) control provided that, in the opinion of the Investigator, the patient does not meet the criteria for treatment discontinuation (i.e., clear progression of disease)

6.4.2 Prohibited treatment / Treatment to be avoided or used with caution

The following treatments are <u>not allowed</u> during the study:

- Any concurrent anti-cancer therapy including chemotherapy, radiotherapy, hormonal, targeted therapy, or immunotherapy
  - Palliative radiotherapy for local pain-control may be allowed, provided the patient does not meet criteria of progressive disease and treated lesions will not be included in the target/non-target lesion assessment
- Other investigational agents
- Immunosuppressive therapies, including systemic corticosteroids (except up to a 25 mg/day prednisone-equivalent dose or when used intermittently in an antiemetic regimen, or as premedication for imaging studies), unless indicated to treat immune-related AEs and atezolizumab is withheld.
- Immunomodulatory agents, including but not limited to interferons or interleukin-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.
- Live, attenuated vaccines within 28 days prior to enrollment.

The following treatments should be avoided, if possible, or used with caution during the study:

- Derazantinib may inhibit CYP1A2, CYP2C8, or CYP2D6 metabolism, hence co-administration of derazantinib with drugs known to be substrates of CYP1A2, CYP2C8, or CYP2D6 should be avoided or used with caution (see Appendix 7).
- Derazantinib may be a substrate and inhibitor of human P-glycoprotein (P-gp), therefore co-administration of derazantinib with drugs known to be P-gp substrates with narrow therapeutic index should be avoided or used with caution (Appendix 8).
- Drugs with known liver toxicity, e.g., clotrimazole, should be avoided or used with caution; if such drugs need to be administered, liver function tests should be done every 4–5 days during the drugs' co-administration.
- Drugs with the potential to prolong QT interval (see Appendix 9).
- Extended concomitant corticosteroid use at physiological doses (i.e., up to 10 mg/day prednisone equivalent).
- Influenza vaccinations (inactivated forms only) should be given during influenza season only (approximately October to March in the Northern hemisphere; April to September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccines (such as FluMist®) 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).

7 SAFETY

7.1 Warnings and precautions

7.1.1 Derazantinib

7.1.1.1 Treatment-emergent adverse events

In a completed Phase 1/2a study 119 patients were treated at doses of 25 mg every other day (QOD) to 425 mg QD. The MTD was determined as 400 mg QD, with no DLTs observed in 12 patients. The RP2D was determined at 300 mg QD with Grade 3 aspartate-aminotransferase elevations as the DLT at 250 mg and 425 mg QD. The current maximum administered dose is 425 mg QD.

Based on the data from all data available from completed and ongoing clinical studies, the derazantinib most commonly reported drug-related adverse events (AEs) are transaminases increased, fatigue /asthenia, gastrointestinal side effects (nausea, vomiting, diarrhea, constipation), xerostomia, hyperphosphatasemia, dysgeusia, decreased appetite, ocular side effects (xerophthalmia and blurred vision) and alopecia.

7.1.1.2 Identified and potential risks

In the literature, the most frequently reported AEs related to FGFR inhibitor class effects are hyperphosphatemia, fatigue, ocular disorders, gastrointestinal disorders (constipation, diarrhea, nausea, vomiting, stomatitis and dry mouth), transaminase elevation, hypertension, creatinine increase / renal disorders, hyponatremia, nail toxicity, and alopecia (Abou-Alfa 2020, Katoh 2019, Loriot 2019, Mazzaferro 2019, Chae 2017, Papadopoulos 2017).

Increased transaminases are assessed as an important identified risk related to derazantinib, requiring monitoring of transaminase levels with management through dose delays/reductions, as noted in the Reference Safety Information in Section 6 of the Investigator's Brochure.

Hyperphosphatemia, fatigue, ocular disorders, blood creatinine increased / renal disorders, hyponatremia, and nail toxicities are assessed as important potential risks for derazantinib based on the clinical toxicity profile of derazantinib (see Section 5.3.2 for safety measures to monitor and mitigate these risks during the study).

The following events are assessed as potential risks for derazantinib: gastrointestinal disorders, hypertension, alopecia, and QT prolongation.

7.1.2 Atezolizumab

The warnings and precautions for atezolizumab are listed in the atezolizumab IB, and in the USPI and EU SmPC for Tecentriq® (atezolizumab) (Tecentriq® USPI, Tecentriq® SmPC).

7.1.3 Contraception and pregnancy

Derazantinib may have adverse effects on a fetus *in utero*, and may have transient adverse effects on the composition of sperm.

There are no known reproductive risks to the female partner of a male patient receiving atezolizumab.

7.1.3.1 Contraception

Participants in this study must be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to be enrolled in the study, both male and female patients of child-producing potential must agree to the contraception requirements in Inclusion criterion 9b) (see Section 4.2), and must comply with these requirements from the day of first study medication, or for oral contraception from 14 days prior to the first study medication, throughout the study period, and until at least 150 days after administration of the last dose of study medication.

If there is any doubt that a patient of child-producing potential will reliably comply with the requirements for contraception, the patient should not be enrolled in the study.

7.1.3.2 Pregnancy testing

See Section 5.3.2.7 for details on pregnancy test requirements for this study.

See Section 7.4.5 for details of reporting and handling pregnancies.

7.1.3.3 Nursing mothers

As it is unknown whether derazantinib is excreted in human milk, because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment in this study (see Section 4.3).

7.2 Definitions

7.2.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigational patient administered a pharmaceutical product that does not necessarily have a causal relationship with study-drug treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Complications associated with scheduled procedures are considered AEs.

7.2.2 Serious adverse event

An SAE is any AE that meets one or more of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization, or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is classified by the Sponsor as an important medical event

Medical and scientific judgment should be exercised in deciding whether an AE should be considered an important medical event (and consequently an SAE). Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient, or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

It should be noted that:

- Death is considered an outcome of an AE. Whenever possible the underlying cause of death must be reported as the AE.
- A life-threatening SAE is any adverse experience that places the patient at risk of death at the time of its occurrence, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization is defined as any inpatient admission, even if for less than 24 h. For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit.

  The following hospitalizations, whether planned before or during the study, can be considered AEs but should not be considered SAEs:
  - Routine treatment or monitoring of UC, not associated with any deterioration in condition (e.g., hospitalizations related to study procedures, such as study-drug administration, PK assessments, etc.).
  - Elective or planned treatment, including surgical interventions, for UC if the plan for the respective intervention has been documented prior to first dose of study drug.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to UC and has not worsened.
  - Admission to a hospital or other institution for general care, not associated with any deterioration in condition.
- Treatment on an outpatient basis for an event which does not meet any of the above definitions of ‘serious’, and does not result in hospital admission, should not be considered as an SAE.

7.2.3 Unexpected adverse event or serious adverse event

An unexpected AE or SAE is one for which the nature or severity of the event is not consistent with the applicable reference safety information.

7.2.4 Suspected adverse event or serious adverse event

A suspected AE or SAE is defined as an AE or SAE that is probably or possibly related to the treatment with derazantinib and/or atezolizumab, or when the relationship is unknown.

7.2.5 Suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE considered by the Investigator or the Sponsor to be related to the study treatment and for which the nature or severity is not consistent with the applicable reference safety information (i.e., regardless of whether the nature or severity of an SAE has been previously observed/documented).

7.2.6 Adverse events of special interest

The following are considered AEs of special interest (AESIs) for the purposes of this study, based on the known safety profiles of derazantinib and atezolizumab:

- Hyperphosphatemia/blood phosphorus increased
- Hyponatremia
- Stomatitis
- Nail disorder
- Ocular/eye disorder
- Liver function tests abnormal (compared to baseline)
- Serum creatinine increase or renal failure
- Hypertension / cardiac disorders
- QT prolongation
- Immune-related AEs (see Section 4.5.1)

All AESI must be recorded in the eCRF. In addition, immune-related AESIs, which are CTCAE grade ≥ 2 or are serious, and all other AESIs which are CTCAE grade > 2 or are serious, must be reported to the Sponsor within 24 hours using the SAE/AESI form.

7.2.7 Treatment-emergent adverse events

Treatment-emergent AEs (TEAEs) are AEs not present prior to the start of study treatment, or AEs already present prior to the start of study treatment that worsen in either intensity or frequency following the treatment.

7.3 Evaluation of adverse events

7.3.1 Grading of Severity

The severity of AEs will be assessed according to NCI CTCAE 5.0.

Adverse events not included in NCI CTCAE 5.0 should be reported under “Other” within the appropriate category, and graded 1 to 5 according to the general grade definitions:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death

For AEs that can be described by NCI CTCAE 5.0, grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria and annotated accordingly.

7.3.2 Assessment of causality

The relationship between an AE and derazantinib and/or atezolizumab will be determined by the Investigator on the basis of their clinical judgment and following categories (see Appendix 10 for definitions):

- Not related
- Unlikely related
- Possibly related
- Probably related

7.3.3 Dose-limiting toxicities (applicable to Substudies 3 and 5)

All toxicities will be graded using NCI CTCAE 5.0. Toxicities judged by the Investigator to be unrelated to study drug administration (e.g., related to the underlying disease) are not considered DLTs. In contrast, the occurrence of any of the following toxicities during Cycle 1 (DLT period) will be considered a DLT, if judged by the Investigator to be possibly or probably related to study drug administration:

1. Grade 4 non-hematologic clinical toxicity (not laboratory).
2. Grade 4 hematologic toxicity lasting ≥14 days with optimal supportive care.
3. Grade 3 non-hematologic toxicity (not laboratory) or non-hepatic major organ AE lasting > 3 days despite optimal supportive care with the following exceptions:
   - Grade 3 nausea, vomiting, or diarrhea that resolves to grade <1 with or without supportive care prior to the next administration and/or with a light meal prior to derazantinib administration.
4. Any laboratory hepatic toxicity meeting Hy's law criteria for suspected severe drug-induced liver injury, defined as a rise in serum aminotransferases (AST or ALT) of > 3 × ULN and total bilirubin ≥ 2 × ULN, in the absence of any alternative reason (e.g., liver metastasis, another liver disease, or a concomitant drug).
5. Any grade 3 or 4 hepatic toxicity with the following exceptions:
   - For patients with grade 2 AST/ALT abnormality at baseline, an increase in the baseline abnormality to > 10 × baseline will be considered a DLT.
6. Any grade 3 non-hematologic or non-hepatic laboratory value if:
   - Medical intervention is required to treat the patient, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for > 3 days.
7. Febrile neutropenia at CTCAE grade 3 or 4:
   - CTCAE Grade 3 is defined as ANC <1.0 × 10^9/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour

- CTCAE Grade 4 is defined as ANC < 1.0 × 10^9/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

8. Thrombocytopenia < 25 × 10^9/L if associated with:
   - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
   - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.
9. Grade 5 toxicity (i.e., death).
10. Any immune-related CTCAE grade 2 or higher toxicities that require holding Cycle 2 of atezolizumab administration (**Substudy 3** only, see Section 6.1.2.6).
    Note that there should be a high level of suspicion that new symptoms are treatment related, in particular any new and early immune-related toxicity.

As dose modifications and dose titrations are not unusual with other FGFR-inhibitors, any ADRs which do not meet DLT criteria but which lead to temporary dose interruptions and/or dose reductions will contribute to the determination of the benefit-risk profile of the dose level, but will not be considered DLTs. Clinical management of ADRs is well established, and a dose reduction scheme is already provided in protocol Section 6.1.1.5.

7.4 Handling of safety information and collection periods

7.4.1 Responsibilities and procedures

The responsibility for the safety of an individual patient lies in all cases with the Investigator. This includes the timely review of all safety data obtained during the course of the study.

An Investigator must instruct their patients to report any AE and SAE they experience.

7.4.2 Handling of safety data during the pre-treatment period

Any relevant change in, or worsening of, a patient's condition occurring after any informed consent has been provided but prior to the start of first study-drug administration, is to be recorded in the eCRF as pre-dose medical history (see Section 5.3.1.1). However, in this period (between ICF and start of study medication), if an AE/SAE is assessed as related to the study procedure, the AE/SAE is to be reported accordingly in the eCRF as medical history and, in addition, SAE must also be reported to the Sponsor's safety representative, using the same procedures as for an SAE (see Section 7.4.3.2).

7.4.3 Handling of safety data during the treatment period and up to the last scheduled follow-up

From the start of first dosing up to and including the Safety Follow-Up visits 28 and – if applicable – 90 days after last study drug administration, respectively, any change in, or worsening of, a patient's condition must be collected and reported in the eCRF as an AE (see Section 7.4.3.1). Serious adverse events and AESIs must be additionally reported on the SAE/AESI report form (see Section 7.4.3.2).

7.4.3.1 Adverse event management

7.4.3.1.1 *Data collection*

All AEs directly observed (physical examination, laboratory test or other assessments), mentioned by the patient, or reported by the patient upon non-directive questioning, must be recorded on the AE pages of the eCRF.

All AEs must be recorded in the English language in the eCRF and should include the following information:

- Term. If possible, a diagnosis should be documented rather than signs and symptoms, using self-explanatory and concise medical terminology. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE or SAE, unless its outcome is death.
- Duration (start and end dates).
- Toxicity grade (CTCAE grade; see Section 7.3.1).
- Relationship to the study treatment (causality assessment; see Section 7.3.2).
- Action(s) taken with regards to study drugs (derazantinib and atezolizumab), or any suspected concomitant medication
- Additional treatments given for the event.
- Whether it is an SAE (seriousness assessment; see Section 7.2.2).
- Outcome.

Refer to the eCRF completion guidelines for further details on completing the AE/AESI/SAE in the eCRF.

In addition, the concomitant medications (with indication start and stop (if not ongoing) and Medical history should be updated as needed.

Abnormal laboratory results should not be recorded as an AE unless the abnormal result meets one or more of the following criteria:

- induces clinical signs or symptoms which require therapy or additional diagnostic evaluation
- requires dose modification derazantinib, or discontinuation of study participation
- is considered clinically significant

If a laboratory abnormality meets one of the above criteria, the clinical syndrome associated with laboratory abnormality is to be recorded, as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

AEs must also be reported in the source document with at least the nature of the event, the start and end date, the relationship to the study drugs (derazantinib and/or atezolizumab), treatment (if applicable), and outcome (in initial or follow up report).

7.4.3.1.2 *Follow-up*

Once an AE is detected, it must be proactively followed at each visit (or more frequently if necessary) for any changes in severity, relationship to the study drug, interventions required for treatment, and the event's outcome. Refer to the eCRF completion guidelines for further details on completing the AE/AESI/SAE in the eCRF.

All AEs must be followed-up until they have returned to baseline status or have stabilized, or until the scheduled Safety Follow-Up visit(s).

Unless the patient withdraws their consent, unresolved related AEs and both related and unrelated SAEs at the time of the Safety Follow-Up visit(s) will be followed until they have, in the opinion of the Investigator, resolved to baseline, CTCAE grade 1, stabilized, or are deemed to be irreversible (including death) and .

7.4.3.2 Serious adverse event and AESI reporting

7.4.3.2.1 *Investigators responsibility*

In addition to being reported and followed-up as AEs (see Section 7.4.3.1), SAEs and AESIs meeting expedited reporting criteria (see Section 7.2.6) must be reported to the Sponsor's safety representative listed below, within 24 h of awareness of the event.

In addition to SAE/AESI form completion, such reports might include detailed anonymized descriptions (e.g., discharge letter, autopsy report, etc.) and/or relevant data (e.g., ECG, laboratory tests, discharge summaries, postmortem results, etc.). If any questions or considerations regarding an SAE or AESI arise, the Sponsor's Medical Monitor or designee should be consulted.

Safety Vendor	**Sponsor's Medical Monitor**
[redacted]	[redacted]

The information provided in an SAE/AESI report should be as complete as possible, but contain a minimum of:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as serious or reportable AESI
- Patient identification and treatment (if applicable)
- Investigator's name and phone number (if applicable)
- Name of the suspect study drug and dates of administration
- Assessment of causality

If all information about the SAE or AESI is not yet known, the Investigator will be required to report any additional information within 24 hours as it becomes available.

The Investigators must in turn notify their governing IRB/IEC in line with local requirements. This activity may be delegated.

7.4.3.2.2 *Sponsor's responsibilities*

The Sponsor will ensure the reporting of SUSARs and any expeditable SAEs to regulatory Authorities, ECs/IRB in accordance with applicable laws.

In the event of a SUSAR, the Sponsor will ensure that Investigators active in Basilea-sponsored interventional studies with derazantinib are informed.

Expectedness of SAEs for regulatory expedited reporting will be assessed by the Sponsor against the applicable study drug Reference Safety Information (RSI).

For both derazantinib and atezolizumab the 'Reference Safety Information' Section in the relevant Investigator's Brochures (valid at the time of onset of the event) will serve as the RSI.

7.4.4 Handling of post-study safety data

After the Safety Follow-up visit(s), only study drug related SAEs and AESIs (see Section 7.2.6) should be collected and reported; however, these events should not be captured in the eCRF system.

New study drug related SAEs and AESIs that occur after the 28-day Safety Follow-up visit (or 90-day Safety Follow-up visit for atezolizumab-treated patients) will be followed until they have, in opinion of the Investigator, resolved to baseline, CTCAE grade 1, stabilized, or are deemed to be irreversible (including death).and if the patient withdraws their consent.

7.4.5 Reporting and handling of pregnancies

Female patients must inform the Investigator within 24 hours if they have experienced a ruptured condom, or any other concerns about possible reduction of contraceptive effectivity (i.e., forgotten pill or vomiting) during the study. In these cases, the patients must return to the study site as soon as possible, but not later than 24 hours after the Investigator is informed, for adequate medical measures and follow-up visits.

Female patients must inform the Investigator if they become pregnant during the study, or within 150 days after the last dose of study drug.

Study drug(s) must be discontinued immediately if a female patient becomes pregnant.

The Investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. The patient must be monitored until conclusion of the pregnancy and infants must be followed-up for at least 8 weeks after delivery. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE eCRF and in pregnancy and SAE form.

The Investigator must immediately notify the Sponsor's safety representative about any pregnancy by submitting a Pregnancy Report Form, in accordance with the requirements (timelines and contact details) of an SAE (see Section 7.4.3.2). In addition, pregnancy-related adverse outcomes must also be reported as AEs or SAEs (see Section 7.4.3.1). Note that an induced abortion which is not due to an AE does not constitute an SAE.

Male patients will be instructed through the information provided in the ICF to immediately inform the Investigator if their partner becomes pregnant during the study. A Pregnancy Report Form should be completed by the Investigator immediately (i.e., no more than 24 hours after learning of the pregnancy). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign the appropriate authorization to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Report Form with additional information on the course and outcome of the pregnancy.

An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

The Investigator must notify the local IEC/IRB about any pregnancies resulting in an adverse outcome, in accordance with applicable laws and regulations.

7.5 Adverse events associated with an overdose or error in drug administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied.

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm of the patient.

Any overdose or medication error (with or without AE) should be recorded in the eCRF.

All AEs associated with an overdose or medication error should be recorded on the eCRF (see Section 7.4.3.1). If the associated AE fulfils seriousness criteria, the event should be reported to the Sponsor immediately (see Section 7.4.3.2).

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Effective Protocol Version 5.0, only statistical considerations applicable to active substudies are provided in this section.

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

8.1 Sample size considerations by substudy

Simon's two-stage designs (Simon 1989) will be used for **Substudies 1 and 4**, and Fleming's two-stage designs (Fleming 1982) will be used for **Substudies 3 and 5**. At the time point of interim analysis and decision to transition from Stage 1 to 2, all data collected in Stage 1 patients will be used to inform the decision. Should the required number of events (i.e., responses) be reached prior to full enrollment to Stage 1, the time point for decision to transition from Stage 1 to Stage 2 may be taken before the stage is fully enrolled. If the required number of events (i.e., responses) is not reached at the time of full enrollment to Stage 1, further enrollment may be suspended to allow for all patients to be exposed to derazantinib or derazantinib-atezolizumab in combination for at least 3 months or until disease progression.

The use of such designs will limit the number of overall exposed patients to a maximum of approximately 98, should either derazantinib or derazantinib-atezolizumab in combination be ineffective in Stage 1 of all efficacy-estimating substudies, as compared to a maximum of 246 patients if derazantinib or derazantinib-atezolizumab are considered to be effective in all cohorts.

Assuming an overall incidence of approximately 20% qualifying *FGFR1–3* GAs (Helsten 2016), up to approximately 680 patients will be screened for *FGFR1–3* GAs, depending on the extent of preexisting molecular testing. Assuming that pre-treatment with an FGFR inhibitor was based on a known *FGFR* GA status, no repeated testing is anticipated for the approximately 100 patients enrolled in Substudy 4.

8.1.1 Substudy 1

The null hypothesis that the true ORR is $p_0 \leq 0.21$ will be tested against a one-sided alternative. In Stage 1, 35 evaluable patients will be enrolled. If 7 or fewer patients with an objective response are observed in Stage 1, the cohort will be stopped. If 8 or more patients with an objective response (defined as a CR or PR) are observed in these 35 patients, an additional 39 patients will be enrolled, for a total of 74 patients. The null hypothesis will be rejected if 22 or more responses are observed in these 74 patients. The one-sided Type I error rate is 0.0463, and the power is 0.8001 when the true ORR is $p_1 = 0.34$ and higher than the ORR of 32.2%, the highest reported value for an FGFR inhibiting treatment in mUC patients (Balversa USPI).

The ORR of 21% for the null hypothesis reflects the lower range of ORR seen in recent clinical studies of UC patients with FGFR GAs (Loriot 2019, Necchi 2018, Pal 2018).

8.1.2 Substudy 3

The Fleming's two-stage design sample size calculation is based on the assumption that first-line cisplatin-ineligible patients with advanced or metastatic mUC expressing *FGFR1–3* GAs treated with 200 mg BID derazantinib in combination with 1200 mg atezolizumab Q3W will attain a clinically meaningful ORR of approximately 45%, which is similar to that obtained with erdafitinib and cetrelimab (Moreno 2020), or rogaratinib and atezolizumab (Rosenberg 2020), in combination for this patient population, and is considered the benchmark by oncology experts. An ORR of 25% (estimated mean ORR with immune checkpoint-inhibiting monotherapy available for cisplatin-ineligible patients) is not considered sufficiently effective to warrant further clinical investigation.

Using a Fleming's two-stage design, a total sample size of 36 is required to test a null hypothesis of H□: $\pi \leq 0.25$ versus an alternative hypothesis of H_a: $\pi \geq 0.45$ with a one-sided target significance level of 0.05 and target power of 80%, where π is the true proportion of successes. This design results in an exact type 1 error rate of 0.046, an exact level of power of 81%, and an average sample size of 27 patients under H□ and 31 under H□. Table 7 summarizes the required samples sizes and required responses to either accept or reject H0.

Table 7 Summary of sample size and required responses of proposed two-stage Fleming design

	Sample size	Responders to accept H_0		Responders to reject H_0	
	N	n	%	n	%
Stage 1	18	4	22.2	10	55.6
Stage 2	36	13	36.1	14	38.9

8.1.3 Substudy 4, Cohorts 4a and 4b

For both cohorts within **Substudy 4**, the null hypothesis that the true ORR is $p_0 \leq 0.07$ will be tested against a one-sided alternative. In Stage 1 of each cohort, 16 evaluable patients will be enrolled. If 1 or fewer patients with an objective response are observed in these 16 patients, the cohort will be stopped. If 2 or more patients with an objective response are observed, an additional 34 patients will be enrolled for a total of 50. The null hypothesis will be rejected if seven or more responses are seen in these 50 patients. Type I error rate is 0.0448 and power is 0.8027 when true ORR is $p_1 = 0.20$.

The ORR of 7% for the null hypothesis reflects the ORR reported based on literature of retrospective data and/or small cohorts of uncontrolled studies (Di Lorenzo 2015, Soga 2010) for *FGFR1–3* GA expressing UC patients treated with third or fourth-line single-agent chemotherapy with prior progression following platinum-containing chemotherapy, immune-checkpoint blockade and/or FGFR inhibitor treatment.

8.1.4 Substudy 5

The Fleming's two-stage design sample size calculation is based on the assumption that patients with mUC expressing *FGFR1–3* GAs, after failure of prior platinum- or immune-checkpoint-inhibitor-containing treatment, treated with 200 mg BID derazantinib will attain a clinically meaningful ORR of approximately 30%. This is similar to that obtained with erdafitinib for this patient population, and considered the benchmark by oncology experts. An ORR of 10% is not considered sufficiently effective to warrant further clinical investigation.

Using a two-stage Fleming design, a total sample size of 26 is required to test a null hypothesis of H□: $\pi \leq 0.1$ versus an alternative hypothesis of H_a: $\pi \geq 0.3$ with a one-sided target significance level of 0.05 and target power of 80%, where π is the true proportion of successes. This design results in an exact type 1 error rate of 0.039, an exact level of power of 81.9%, an average sample number of 18 patients under H□ and of 21 under H□. Table 8 summarizes the required samples sizes and required responses to either accept or reject H_0.

Table 8 Summary of sample size and required responses of proposed two-stage Fleming design

	Sample size	Responders to accept H_0		Responders to reject H_0	
	N	N	%	n	%
Stage 1	13	1	7.7	5	38.5
Stage 2	26	5	19.2	6	23.1

8.2 Analysis populations

The following analysis populations are defined for this study:

8.2.1 Safety analysis population / Intent-to-treat population

The Safety / Intent-to-treat population consists of all patients with an eligible *FGFR1–3* GA who received at least one dose of derazantinib or atezolizumab. Safety data will be summarized according to the treatment actually received.

In the primary safety comparison, patients who crossover to derazantinib-atezolizumab combination are censored at time of crossover (i.e., AEs occurring during treatment with derazantinib-atezolizumab combination are excluded for Cohort 4a patients). An exploratory safety analysis will be conducted for the crossover population including all safety events starting from the date of the first dose of derazantinib-atezolizumab combination.

8.2.2 Modified intent-to-treat population

For all efficacy endpoint analyses, a mITT population will be used, comprising all patients who received at least one dose of derazantinib or atezolizumab, and have at least one post-baseline imaging assessment in accordance with RECIST 1.1, or documented clinical

progression (every effort should be made to objectively assess radiographic progression). Non-evaluable patients will be replaced.

8.2.3 Per-protocol population

The Per-protocol population will include all patients in the mITT population who have no major protocol deviations during the study. Protocol deviations will be identified prior to final analysis.

This analysis population will be used for secondary analysis of primary and secondary endpoints.

8.2.4 Pharmacokinetic analysis population

The PK analysis population consists of all patients who receive at least one dose of derazantinib and have at least one PK sample. Three sub-populations are defined, according to the analytes and sampling schedule:

- The Rich derazantinib PK profiling population (with PK parameter determination) consists of the patients enrolled in the rich sampling schedule (see Section 5.3.4.1.2) who receive at least 1 dose of study drug and have at least one PK sample.
- The Sparse derazantinib PK sampling population consists of the patients enrolled in the sparse sampling schedule (see Section 5.3.4.1) who receive at least 1 dose of study drug and have at least one PK sample.
- The atezolizumab PK population (see Section 5.3.4.2) consists of all patients who receive at least 1 dose of atezolizumab and have at least one PK sample.

8.3 Statistical and analytical methods

All endpoints will be summarized by substudy and cohort. All analyses will include summary statistics, including number and percentage for categorical variables, and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided 95% confidence intervals (CIs) will be provided where appropriate, except otherwise specified. Time-to-event analysis will be performed using Kaplan-Meier (KM) methods. Further detail will be provided in the study SAP.

All analyses will be carried out using SAS® version 9.3 or above (SAS Institute, Cary, North Carolina, USA).

8.3.1 Patient demographics, medical history, and other baseline characteristics

Demographics, medical history, and other baseline characteristics will be summarized for the safety/ITT, mITT and Per-protocol (PP) populations using descriptive statistics. No formal statistical comparisons will be performed.

Demographic, baseline characteristics, and medical history data for each patient will be provided in data listings.

8.3.2 Study treatment exposure and compliance

The dose, duration in days and compliance of study treatment(s) will be listed by patient and summarized through descriptive statistics by cohort in the Safety population.

8.3.3 Prior and concomitant treatments

Medications and significant non-drug therapies used prior to and after the start of the study drug will be listed by patient and summarized by Anatomical Therapeutic Chemical term and by cohort.

8.3.4 Efficacy analysis

All efficacy endpoints will be summarized by substudy and cohort.

All analyses will include summary statistics, including number of patients and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs based on the large sample assumption will be provided where appropriate.

Comparisons between cohorts of **Substudy 4** will be performed using descriptive statistics and for the purpose of hypothesis generation.

8.3.4.1 Primary endpoint

The primary endpoint in all substudies will be ORR, defined as the achievement of confirmed CR or PR using RECIST 1.1, as assessed by BICR. Point estimates and 2-sided 95% CIs will be provided. The primary analysis will be performed on the mITT population and repeated on the PP population.

Interim analyses for stage transition in the efficacy-estimating substudies will be performed when the number of patients specified below have been enrolled, have received at least one dose of study drug, and have at least had one post-baseline tumor imaging assessment, but no later than after the completion of Cycle 9 (i.e., have received approximately 27 weeks of treatment and had up to four post-baseline study imaging assessments). If the required number of responses per BICR specified for each cohort has not been observed at the time of enrollment of the last patient to Stage 1, enrollment may be suspended, or the cohort may be terminated due to apparent futility.

If the required number of responses per BICR specified for each cohort is reached earlier, interim analyses may be performed earlier.

The final analysis for ORR will be performed once all patients have been enrolled per cohort/substudy and have been followed for approximately up to 27 weeks of treatment (i.e., each patient had up to four post-baseline study imaging assessments). Patients without efficacy assessments are considered non-responders, and included in the analysis. Hypothesis testing (null hypothesis [H_0] versus alternative hypothesis [H_A]) will be performed at the interim and final analyses as per the below specified decision rules:

- **Substudy 1**

  H_0: $p \leq 0.21$ versus H_A: $p > 0.21$.

If there are five or fewer patients with a response (defined as a CR or PR) in the first 35 evaluable patients included in the interim analysis, the substudy will be stopped. If not, an additional 39 patients will be enrolled, for a total of 74 evaluable patients. The null hypothesis will be rejected if 22 or more responses are observed in these 74 patients.

- **Substudy 3**

  H_0: $p \leq 0.25$ versus H_A: $p > 0.45$.

  If there are four or fewer patients with a response (defined as a CR or PR) in the first 18 evaluable patients included in the interim analysis, the cohort will be stopped. If not, an additional 18 patients will be enrolled, for a total of 36 evaluable patients. The null hypothesis will be rejected if 14 or more responses are observed in these 36 patients (or if 10 or more responses are observed in the first 18 patients). Posterior estimates of the probability that the response rate exceeds 0.25 will also be calculated assuming a non-informative prior distribution.

- **Substudy 4**

  H_0: $p \leq 0.07$ versus H_A: $p > 0.07$.

  If there are one or zero patients with a response (defined as a CR or PR) in the first 16 evaluable patients included in the interim analysis in each of Cohort 4a and 4b, the cohort will be stopped. If not, an additional 34 patients will be enrolled, for a total of 50 evaluable patients. The null hypothesis will be rejected if seven or more responses are observed in these 50 patients.

- **Substudy 5**

  H_0: $p \leq 0.10$ versus H_A: $p > 0.30$.

  If there is one or fewer patient with a response (defined as a CR or PR) in the first 13 evaluable patients included in the interim analysis, the cohort will be stopped. If not, an additional 13 patients will be enrolled, for a total of 26 evaluable patients. The null hypothesis will be rejected if six or more responses are observed in these 26 patients (or if five or more responses are observed in the first 13 patients). Posterior estimates of the probability that the response rate exceeds 0.1 will also be calculated assuming a non-informative prior distribution.

8.3.4.2 Secondary efficacy endpoints

DCR will be summarized in the same way as the primary endpoint.

DOR, PFS and OS analyses will be performed using KM methods. The analysis will be performed on the mITT population and repeated on the PP population.

DoR will be calculated from the first date of documented tumor response (CR or PR) to the date of disease progression by BICR. If a patient is discontinued or is lost to follow-up with no documentation of PD, duration of response is defined as the time from the date of the first documentation of objective response to the date of the last tumor assessment as a censored value. If the patient dies with no documentation of PD, duration of response is defined as the time from the date of the first documentation of objective response to the

date of the last tumor assessment as a censored value. Patients who crossover to derazantinib-atezolizumab combination will be censored at time of crossover.

PFS will be calculated as the time from cohort assignment by IWRS until disease progression per RECIST 1.1, or death from any cause. Patients who discontinue treatment due to reasons other than disease progression by BICR or death will be censored in the PFS analyses at the date of their last tumor evaluation. Patients who progress or die after missing ≥ 2 consecutive scheduled tumor assessments will be censored at the date of the last tumor evaluation prior to progression or death. Patients who either have no baseline tumor evaluation or have no post baseline tumor evaluation will be censored at the date of the first dose. Patients who crossover to derazantinib-atezolizumab combination will be censored for the derazantinib analysis at the time of crossover. For patients crossing over from derazantinib to derazantinib-atezolizumab in combination and as an exploratory analysis, hazard ratios (HRs) for median OS time will be calculated using an Inverse Probability of Censoring Weighted (IPCW) modeling approach (Rimawi 2012).

OS time will be calculated from the date of cohort assignment by IWRS until death from any cause. Any patient without a date of death in the database at the time the survival analyses are performed will be censored at the time of their last study contact. For patients crossing over from derazantinib to derazantinib-atezolizumab in combination and as an exploratory analysis, HRs for median OS time will be calculated using an IPCW modeling approach (Rimawi 2012). Overall survival analysis may be repeated upon availability of long-term survival data.

Sensitivity analyses within Substudy 4 will be performed according to the stratification factor composite score and its variables.

8.3.5 Safety data analysis

Safety will be assessed through summaries of DLTs, AEs, safety laboratory evaluations, physical examinations, and vital signs. All safety analyses will be based on the Safety population. Analyses will be presented by substudy and cohort. The DLTs will be listed and summarized using descriptive statistics.

8.3.5.1 Dose-limiting toxicity (Substudies 3 and 5 only)

Safety interim analyses will be performed once 10 patients have been enrolled and full safety data are available to determine if the revised dosing regimen of 200 mg BID derazantinib either as monotherapy or in combination with atezolizumab is safe and tolerable.

The safety evaluation will comprise updating a three-parameter cumulative BLRM-EWOC design for the incidence of DLTs with monotherapy and combination therapy to strictly manage the risk of excessive toxicity (Neuenschwander 2008). For a derazantib dose d, let π_d denote the probability of DLT at dose d. If n subjects are evaluated at dose d, then the number of subjects, y, experiencing a DLT is assumed to follow a binomial distribution:

$$y \mid \pi_d \sim \text{Binomial}(n, \pi_d)$$

The relationship between monotherapy and combination derazantib doses, and DLT probabilities is modelled by the logistic curve;

$$\log(\pi_d/(1-\pi_d)) = \log(\alpha_i) + \beta \log(d/d^*), \qquad \alpha_1, \alpha_2, \beta > 0$$

Doses are rescaled as d/d* with reference dose d*= 600mg/day. The model parameters α_1, α_2 and β have the following interpretation:

- α_1 equals the odds of toxicity with monotherapy at the reference dose d*.
- α_2 equals the odds of toxicity with combination therapy at the reference dose d*.
- Doubling the dose results in an increase in odds of toxicity by a factor of 2^{β}.

The model parameters $\log(\alpha_1), \log(\alpha_2), \log(\beta)$ are given a weakly informative multivariate normal prior distribution, following (Neuenschwander 2014), with prior means (-1.386, -1.386, -0.781), prior standard deviations (5.472, 5.472, 0.973), and prior correlations of 0. This prior distribution ensures wide confidence intervals for toxicity probabilities at each dose.

With an acceptable target toxicity range for a dose defined as a probability of toxicity of 10% to <25% and an overdosing range of ≥25%, the posterior probability of overdosing will be updated over time. Data resulting in a posterior probability of overdosing for a dose in excess of 25% will be determined as unacceptable. This ensures a safe recommended dose is chosen for subsequent testing of anti-tumor efficacy. This process also involves regular dose decision meetings to review the updated cumulative model results as well as safety in individual patients.

Safety and tolerability of both the monotherapy and the combination dose regimens, and restart of enrollment in Substudies 3 and 5 will be concluded by joint decisions taken by the IDMC, Investigators, and the Sponsor in reviewing the aggregate of DLT, AE and PK data from the first 10 patients each enrolled in Substudies 3 and 5.

8.3.5.2 Other safety parameters

All AEs occurring during the study will be coded by standard MedDRA and grouped by System Organ Class and Preferred Term. Safety endpoints for AEs include the following: incidence of all TEAEs[1] and all serious AEs, AEs by severity, AEs by relationship to study drug, and discontinuation of patients from study therapy due to AEs and deaths.

Additional safety summaries will be provided for clinical laboratory tests, vital signs, ECGs, physical examinations, ophthalmology examinations, ECOG PS, and – if relevant – any drug exposure during pregnancy.

8.3.6 Pharmacokinetic analysis

In the Rich derazantinib PK sampling population, PK parameters will be determined by non-compartmental analysis. The following parameters will be determined: C_{max}, t_{max}, $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, AUC_{last}. PK parameters from rich PK sampling will be summarized by Substudy and Cohort using descriptive statistics. Derazantinib plasma concentrations at each nominal time-point will be summarized by substudy and cohort using descriptive statistics.

[1] Treatment emergent AEs (TEAE) are AEs not present prior to the start of study treatment, or AEs already present prior to the start of study treatment that worsen in either intensity or frequency following initiation of study drug treatment.

In the Sparse derazantinib PK sampling population, derazantinib plasma concentrations at each nominal time-point will be summarized by Substudy and Cohort using descriptive statistics.

In the atezolizumab PK population, atezolizumab and ADA serum concentrations at each nominal time-point will be summarized by Substudy and Cohort using descriptive statistics.

Population PK (PopPK) analyses may be performed with the possibility of pooling PK data from other clinical studies. Any PopPK analysis will be reported separately.

8.3.7 Pharmacodynamics analyses

Data from biomarker and other PD analyses will be summarized overall using descriptive statistics. Comparisons of clinical activity endpoints between biomarker defined groups may be performed.

8.3.8 PRO analysis

PRO scores from the EORTC QLQ-C30, FACT-Bl and EQ-5D instruments will be analyzed primarily using descriptive analysis.

The minimal important difference of the EQ-5D visual analogue scale, EORTC QLQ-C30 scales and FACT-Bl scales will be determined using the Health Transition Index/G-SET as an external anchor.

8.3.9 Crossover analysis

In the primary efficacy comparison, patients who crossover to derazantinib-atezolizumab combination are censored at time of crossover. Exploratory safety, PK/ADA, PRO and efficacy analyses will be conducted for the crossover population including all safety events, PK/ADA data, PRO data and RECIST 1.1 responses starting from the date of the first dose of derazantinib-atezolizumab combination.

8.3.10 Handling of missing data and discontinuations

Missing data will not be imputed. Patients whose clinical response is unknown or not reported will be treated as non-responders.

Reasons for discontinuation and the date of discontinuation from the study will be listed, and dates of first and last study drug provided as well as the duration of exposure to study drug and date. Summary tables will be provided by substudy and cohort.

9 STUDY ADMINISTRATION AND REGULATORY ASPECTS

9.1 Study records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

9.1.1 Investigator Site File

The ISF must contain all essential documents as required by International Council for Harmonization (ICH) E6 and applicable regulations, including the Investigators' Brochure, protocol and any subsequent amendments, eCRFs, Query Forms, documented IEC/IRB approvals, documented regulatory approvals, sample informed consent forms, drug records, staff curriculum vitae, and other appropriate documents/correspondence.

9.1.2 Case report forms

For each patient enrolled in the study via the IWRS, including patients who do not complete the study and patients for whom a eCRF is initiated during Screening but are not randomized, an eCRF must be completed and signed (manually or electronically) by the Investigator or authorized site staff. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

If the eCRF is to be the source document for certain data, this must be discussed and agreed with the Sponsor in advance, and clearly documented.

9.1.3 Patient source documents

Patient source documents used to record key efficacy/safety parameters, independent of the eCRFs, may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, original laboratory reports, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and patient screening and enrollment logs, patient's diary. Source documents are part of the study documents, and must be maintained and made available upon request for clinical monitoring visits, audits or inspections.

9.1.4 Document retention and archiving

The Investigator must keep all study documents on file for at least 15 years after completion or discontinuation of the study. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to applicable regulations.

These files must be made available for audits and inspection, upon reasonable request, to the authorized representative of the Sponsor, or to regulatory authorities.

Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the study documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

9.2 Sample retention

All biological samples taken will be stored for up to 5 years after completion or discontinuation of the study for future medical and/or scientific research projects related to derazantinib. All patients will be asked to provide informed consent for this purpose, authorizing the Sponsor to use their study information and samples for future research projects. If a patient withdraws consent to the use biological samples, the samples will be disposed or destroyed, and the action is documented. If samples have already been analyzed, the Sponsor is not obliged to destroy the results of this research.

After a maximum of 5 years, all stored samples will be returned to the study center or safely destroyed.

9.3 Clinical monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, the Sponsor will review the protocol, eCRFs and other study documentation with the Investigators and the site staff.

The Monitor must visit the Investigator and the study facilities on a regular basis throughout the study to verify adherence to GCP and the protocol and the completeness, consistency and accuracy of the data being entered into the eCRFs. The Monitor must also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must ensure that the monitor has direct access to all required study data (source documents) during the regular monitoring visits. This includes all patient records needed to verify the entries in the eCRFs.

The Investigator must cooperate with the Monitor to ensure that any protocol deviations or other issues detected in the course of monitoring visits are resolved.

Monitoring reports must be written after each monitoring visit, per site and per visit. These monitoring reports must be reviewed and approved by the respective supervisors of the Monitors.

Monitoring instructions are provided in the Monitoring Plan.

9.4 Audits and inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP, and regulatory requirements. These audits may also be conducted for quality assurance purposes to ensure that complete and accurate data are submitted, and that all AEs are being identified and reported in compliance with the protocol and applicable regulations. The study may also be inspected by regulatory authority inspectors, after appropriate notification.

In the event of an audit or an inspection, the Investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

9.5 Protocol amendments

Protocol amendments must be prepared by a representative of the Sponsor, and be reviewed and approved in accordance with the Sponsor's SOPs.

All protocol amendments must be submitted to the appropriate IEC/IRB for information and approval, in accordance with applicable laws and regulations, and to regulatory agencies if required.

Approval of a protocol amendment must be awaited before changes are implemented, with the exception of for changes necessary to eliminate an immediate hazard to study participants, or changes involving only logistical or administrative aspects of the study (e.g., changes to monitors, changes to telephone numbers).

9.6 Premature termination of the study

The Sponsor reserves the right to terminate the study at any time (see Section 4.5.4). An Investigator has the right to terminate his or her participation to the study at any time. Should either of these events occur, both parties will arrange the necessary procedures after review and consultation.

If the study is to be terminated early, the Sponsor and the Investigator must ensure that adequate consideration is given to the protection of the interests of all patients enrolled in the study.

9.7 Publication policy

The Sponsor is committed to registering this study in a publicly accessible clinical trial registry (e.g., www.clinicaltrials.gov), and will ensure that results of this study will be made available to the medical community consistent with the ICH GCP guidelines, the Sponsor's SOPs, applicable laws and regulations, and the Good Publication Practice (GPP3) guidelines (Battisti 2015).

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, submission of an abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing study results within 12 months after the last data become available, which may take up to several months after the last patient visit. The Sponsor will post a synopsis of study results for approved products on www.clinicaltrials.gov within 12 months after the last patient's last visit for the primary outcome, or within 12 months after the decision to discontinue development of derazantinib, or within 12 months of product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended if derazantinib is not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the clinical study report, subject to applicable confidentiality agreements.

When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol a Statistical Analysis Plan to facilitate peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so wishes, to post on its website the key sections of the protocol that are relevant to evaluating the study, specifically including those sections describing the study objectives and hypotheses, the inclusion and exclusion criteria, the study design and procedures, the efficacy and safety measures, the Statistical Analysis Plan, and any protocol amendments relating to those sections. The Sponsor reserves the right to redact proprietary information from these documents.

As this is a multicenter study, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an Investigator and his or her colleagues may publish their data independently. The limitations of single study site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit and related decisions in regard to publication of the results of this study will comply with the GPP3 guidelines (Battisti 2015).

The Sponsor retains the right to review all proposed abstracts, manuscripts, or presentations regarding this study 45 days prior to submission for publication/ presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

10 ETHICS AND GOOD CLINICAL PRACTICE

10.1 Good Clinical Practice

The study must be conducted in compliance with this protocol, ICH Guideline E6 and any relevant supplementary guidance on GCP and applicable laws and regulations.

This study will be conducted in accordance with the ethical principles having their origin in the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

All definitive non-clinical safety studies were conducted in accordance with Good Laboratory Practices regulations: OECD Principles of Good Laboratory Practice ENV/MC/CHEM (98)17 (revised in 1997).

10.2 Informed consent

Eligible patients may only be included in the study after providing written IEC/IRB-approved informed consent. Written informed consent must be obtained by the Investigator or designee from each patient prior to initiation of any study procedures.

It is the responsibility of the Investigator, or a person designated by the Investigator if acceptable by local regulations, to obtain prior written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential and identified risks of the study. It must also be explained to patients that they are completely free to refuse to enter the study, or to withdraw from the study at any time for any reason.

Written consent must be witnessed and countersigned by the Investigator or a qualified designee, as appropriate. In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and GCP as outlined in ICH Guideline E6 and other relevant guidelines, and the ethical principles having their origin in the Declaration of Helsinki.

Copies of signed consent forms must be given to the patient and the originals filed at the study site.

In the event that the patient is unable to read the consent document; an impartial witness must be present during the entire informed consent discussion. After the patient has verbally consented to participation in the study, the witness' signature must be obtained on the form to attest that the information in the consent form was accurately explained and understood.

The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment for derazantinib or atezolizumab, the consent form must be reviewed and updated. All patients currently enrolled in the study who have not yet completed the treatment or post-treatment phases must be given the new information and a copy of the revised form, and asked to give their consent to continuing in the study.

10.3 Patient confidentiality and data protection

The Investigator must ensure that patient anonymity is maintained, and that patients' identities are protected from unauthorized parties. This includes any electronic data generated during the study. In the eCRF, or other documents submitted to the Sponsor, patients must be identified only by an identification code, and not by name. The Investigator must keep a confidential patient identification code list, as described in Section 8.3.21 of ICH Guideline E6.

The Sponsor is responsible for ensuring compliance with all applicable data protection laws.

10.4 Independent Ethics Committees / Institutional Review Boards

This protocol and any accompanying material provided to the patient, including patient information sheets or descriptions of the study used to obtain informed consent, as well as any advertising material and information about any compensation provided to the patient, must be submitted to an IEC/IRB operating in compliance with ICH Guideline E6 and any relevant supplementary guidance on GCP, and with applicable laws and regulations. Approval from the IEC/IRB must be obtained and documented before starting the study.

Amendments made to the protocol after receipt of IEC/IRB approval must also be submitted to the IEC/IRB in accordance with local procedures and applicable laws and regulations.

11 PROTOCOL VERSION HISTORY

Date	Version	Summary of changes
27 March 2019	1.0	Submitted to the US FDA for review.
10 May 2019	2.0	Implemented FDA comments.
4 October 2019	3.0	Two changes initiated by the Sponsor, and changes in response to Health Authority requests made in the course of Clinical Trial Applications.
20 August 2020	4.0	Changes made to ensure consistency with the updated Investigator's Brochure, and changes pursuant to Investigator feedback.
8 March 2021	5.0	Changes made to adapt the design of substudies following the completion of Substudy 2 and interim results of Substudy 1. The design of Substudy 3 was modified, and a new substudy (Substudy 5) was added.

12 REFERENCES

(Aaronson 1993) Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993; 85: 365–376.

(Abdul-Karim 2021) Abdul-Karim RM, Chaudhry A, Patrikidou A, et al. Derazantinib in combination with atezolizumab in patients with solid tumors: Results from the dose-finding phase Ib substudy of FIDES-02. J Clin Oncol 39, 2021 (suppl 6; abstr 437).

(Abou-Alfa 2020) Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671–684.

(Alexandrov 2013) Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 500:415–421, 2013.

(Apolo 2017) Apolo AB, Ellerton JA, Infante JR, et al. Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): Pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. J Clin Oncol 35, 2017 (suppl; abstr 4528).

(Atkins 2018) Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol. 2018;19(3):405–415.

(Babina 2017) Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer. 2017 May;17(5):318–332.

(Bajorin 1999) Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol. 1999 Oct;17(10):3173–81.

(Balar 2017) Balar AV. Immune checkpoint blockade in metastatic urothelial cancer. J Clin Oncol 2017;19:2109–2112.

(Balar 2017a) Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017; 389:67–76.

(Balar 2017b) Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(11):1483–1492.

(Balversa USPI) http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/BALVERSA-pi.pdf

(Battisti 2015) Battisti WP, Wager E, Baltzer L, et al. Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med. 2015;163:461–464.

(Bellmunt 2010) Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010; 28(11):1850–1855.

(Bellmunt 2016) Bellmunt J, Mottet N, de Santis M. Urothelial carcinoma management in elderly or unfit patients. EJC Suppl. 2016;14(1):1–20.

(Bharmal 2017) Bharmal M, et al. Epidemiology of Locally Advanced or Metastatic Urothelial Cancer in the US, Europe and Japan. Value in Health, 2017. 20; 9: A419.

(Bonomo 2018) Bonomo P, Desideri I, Loi M, et al. Anti PD-L1 DUrvalumab combined with Cetuximab and RadiOtherapy in locally advanced squamous cell carcinoma of the head and neck: A phase I/II study (DUCRO). Clin Transl Radiat Oncol. 2018;9:42–47.

(Brahmer 2018) Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. 2018; 36:1714–1768.

(Bray 2018) Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.

(Chae 2017) Chae YK, Ranganath K, Hammerman PS, et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. Oncotarget, 2017, Vol. 8, (No. 9), 16052–16074.

(Chen 2011) Chen Y-F, Fu L-W. Mechanisms of acquired resistance to tyrosine kinase inhibitors. Acta Pharn Sin B. 2011;1:197–207.

(Choi 2017) Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014 Feb 10;25(2):152–65.

(Choueiri 2018) Choueiri TK, Larkin J, Oya M, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. Lancet Oncol. 2018;19(4):451–460.

(Dash 2006) Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107(3):506–513.

(Datta 2017) Datta J, Damodaran S, Parks H, et al. Akt activation mediates acquired resistance to fibroblast growth factor receptor inhibitor BGJ398. Mol Cancer Ther. 2017;16:614–24.

(De Santis 2009) De Santis M, Bellmunt J, Mead G, et al. Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy: Phase II—Results of EORTC Study 30986. J. Clin. Oncol. 2009; 27:5634–5639.

(De Santis 2011) De Santis M, Bellmunt J, Mead G, et al. Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy: Phase II—Results of EORTC Study 30986. J. Clin. Oncol. 2011;30:191–199.

(di Martino 2016) di Martino E, Tomlinson DC, Williams SV, et al. A place for precision medicine in bladder cancer: targeting the FGFRs. Future Oncol. 2016 Oct;12(19):2243–63.

(Di Lorenzo 2015) Di Lorenzo G, Buonerba C, Bellelli T et al. Third-line chemotherapy for metastatic urothelial cancer: a retrospective observational study. Medicine. 2015;94(51):e2297

(Diaz 2014) Diaz LA, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol. 2014;32(6):579–586.

(Diehl 2008) Diehl F, Schmidt K, Choti MA, et al. . Circulating mutant DNA to assess tumor dynamics. Nat Med . 2008;14(9):985–990.

(Eisenhauer 2009) Eisenhauer EA, P. TherasseP, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer 2009; 45:228–247.

(Felsenstein 2018) Felsenstein KM and Theodorescu D. Precision medicine for urothelial bladder cancer: update on tumour genomics and immunotherapy. Nat. Rev. Urol. 2018 Feb;15(2):92–111

(Fleming 1982) Fleming T. One-sample multiple testing procedure for phase II clincal trials. Biometrics. 1982;38:143–151

(Fleming 2018) Fleming V, Hu X, Weber R, et al. Targeting Myeloid-Derived Suppressor Cells to Bypass Tumor-Induced Immunosuppression. Front Immunol. 2018 Mar 2;9:398.

(Galsky 2011) Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol. 2011;29(17):2432–2438.

(Gomez-Roca 2019) Gomez-Roca CA, Italiano A., Le Tourneau C, et al. Phase I study of emactuzumab single agent or in combination with paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive M2-like macrophages. Ann. Oncol. 2019; 30:.1381–1392.

(Goyal 2017) Goyal L, Saha SK, Liu LY, et al. Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma. Cancer Discov. 2017;7(3): 252–263.

(Hall 2016) Hall TG, Yu Y, Eathiraj S, et al. Preclinical Activity of ARQ 087, a Novel Inhibitor Targeting FGFR Dysregulation. PLoS One. 2016 Sep 14;11(9):e0162594.

(Hasita 2010) Hasita H, Komohara Y, Okabe H, et al. Significance of alternatively activated macrophages in patients with intrahepatic cholangiocarcinoma. Cancer Sci. 2010 Aug;101(8):1913–9.

(Helsten 2016) Helsten T, Elkin S, Arthur E, et al. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. Clin Cancer Res. 2016 Jan 1;22(1):259–67.

(Herbst 2014) Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014; 515:563–567.

(Howlader 2020) Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

(Joerger 2018) Joerger M, Cassier P, Penel N, et al. Rogaratinib treatment of patients with advanced urothelial carcinomas prescreened for tumor FGFR mRNA expression. J Clin Oncol 36, 2018 (suppl 6S; abstr 494) (NCT01976741).

(Karvinen 2007) Karvinen KH, Courneya KS, North S, Venner P. Associations between exercise and quality of life in bladder cancer survivors: A population-based study. Cancer Epidemiol Biomarkers Prev. 2007 May;16(5):984–90.

(Katoh 2019) Katoh M. Fibroblast growth factor receptors as treatment targets in clinical oncology Nature Reviews Clinical Oncology. 2019;16(2):105–122.

(Kim 2015) Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration approvals. JAMA Intern Med 2015;175:1992–94.

(La Rosée 2015) La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Program 2015;1:190-6.

(La Rosée 2019) La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465-77.

(Levy 2019) Levy B, Paz-Ares L, Bennouna J, et al. Afatinib With Pembrolizumab for Treatment of Patients With Locally Advanced/Metastatic Squamous Cell Carcinoma of the Lung: The LUX-Lung IO/KEYNOTE 497 Study Protocol. Clin Lung Cancer. 2019;20:e407-e412.

(Li 2019) Li Z, Wu T, Zheng B, Chen L. Individualized precision treatment: Targeting TAM in HCC. Cancer Lett. 2019;458:86–91.

(Lloyd 2014) Lloyd H, Jenkinson C, Hadi M, et al. Patient reports of the outcomes of treatment: a structured review of approaches. Health and Quality of Life Outcomes 2014 12:5.

(Loehrer 1992) Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1992 Jul;10(7):1066–73.

(Loriot 2019) Loriot Y, Necchi A, Park SH, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2019;381:338-48.

(Lorusso 1998) Lorusso V, Pollera CF, Antimi M, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Eur J Cancer. 1998;34(8):1208–1212.

(Mantovani 2017) Mantovani A, Marchesi F, Malesci A, et al. Tumor-Associated Macrophages as Treatment Targets in Oncology. Nat Rev Clin Oncol. 2017 July; 14(7): 399–416.

(Mazzaferro 2019) Mazzaferro V, El-Rayes BF, Droz dit Busset M, et al. Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. Br J Cancer. 2019 Jan;120(2):165–171.

(McCaffrey 1997) McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol. 1997;15(5):1853–1857.

(McSheehy 2019) McSheehy P, Bachmann F, Forster-Gross , Marc Lecoultre, Mahmoud El Shemerly, Mila RocerNi, et al. Derazantinib (DZB): A dual FGFR/CSF1R-inhibitor active in PDX-models of urothelial cancer. Mol Cancer Ther. 2019;18(12 Suppl):LB-C12. doi:10.1158/1535-7163.TARG-19-LB-C12

(Meric-Bernstam 2018) Meric-Bernstam F, Arkenau H, Tran B, et al. Efficacy of TAS-120, an irreversible fibroblast growth factor receptor (FGFR) inhibitor, in cholangiocarcinoma patients with FGFR pathway alterations who were previously treated with chemotherapy and other FGFR inhibitors. Ann. Oncol. 2018; 29 (Supplement 5): v100–v110.

(Moreno 2020) Moreno V, Loriot Y, Valderrama,BP et al. Dose escalation results from phase Ib/II Norse study of erdafitinib + PD-1 inhibitor cetrelimab in patients with metastatic or locally advanced urothelial carcinoma and selected fibroblast growth factor receptor gene alterations. J Clin Oncol. 2020;38 (suppl 6):511. DOI: 10.1200/JCO.2020.38.6_suppl.511

(Musoro 2018) Musoro ZJ, Hamel J-F, Ediebah DE, et al. EORTC Quality of Life Group. 2018b. Establishing anchor-based minimally important differences (MID) with the EORTC quality of-life measures: a meta-analysis protocol. BMJ Open;8:e019117.

(Necchi 2018) Necchi A, Pouessel D, Leibowitz-Amit R, et al. Interim Results of fight-201, A phase 2, open-label, multicenter study of INCB054828 dosed intermittently in patients with metastatic or surgically unresectable urothelial carcinoma (UC) harboring fibroblast growth factor (FGF)/FGF receptor (FGFR) genetic alterations. Ann. Oncol. 2018;29 S(Supplement 8): mdy283.109

(Neuenschwander 2014) Neuenschwander B, Matano A, Tang Z et al (2014) A Bayesian Industry Approach to Phase I Combination Trials in Oncology. 1st Edition. Chapman and Hall Publishers.

(Neuenschwander 2008) Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Med Stat 2008;27(13):2420–2439.

(O'Donnell 2017) O'Donnell PH, Grivas P, Balar AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol. 2017;35(suppl;abstr 4502).

(Pal 2018) Pal SK, Rosenberg JE, Hoffman-Censits JH, et al. Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1–3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with FGFR3 Alterations. Cancer Discov. 2018 Jul;8(7):812–821.

(Papadopoulos 2017) Papadopoulos KP, El-Rayes BF, Tolcher AW, et al. A Phase 1 study of ARQ 087, an oral pan-FGFR inhibitor in patients with advanced solid tumours. Br J Cancer. 2017 Nov 21;117(11):1592–1599.

(Papamichael 1997) Papamichael D, Gallagher CJ, Oliver RT, et al. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. Br J Cancer. 1997;75(4):606–607.

(Pearson 2016) Pearson A, Smyth E, Babina IS, et al. High-Level Clonal FGFR Amplification and Response to FGFR Inhibition in a Translational Clinical Trial. Cancer Discov. 2016 Aug;6(8):838–851.

(Pemazyre USPI) https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213736s000lbl.pdf

(Perera 2017) Perera TPS, Jovcheva E, Mevellec L, et al. Discovery and Pharmacological Characterization of JNJ-42756493 (Erdafitinib), a Functionally Selective Small-Molecule FGFR Family Inhibitor. 2017, Mol Cancer Ther; 16(6); 1010–20.

(Petrylak 2018) Petrylak DP, Powles T, Bellmunt J, et al. Atezolizumab (MPDL3280A) Monotherapy for Patients With Metastatic Urothelial Cancer Long-term Outcomes From a Phase 1 Study. JAMA Oncol. 2018;4(4):537–544.

(Powles 2017) Powles T, O'Donnell PH, Massard C, et al. Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. JAMA Oncol. 2017 Sep 14;3(9):e172411.

(Ries 2014) Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell. 2014 Jun 16;25(6):846–59.

(Rimawi 2012) Rimawi M, Hilsenbeck SG. Making Sense of Clinical Trial Data: Is Inverse Probability of Censoring Weighted Analysis the Answer to Crossover Bias? J Clin Oncol 2012;30:453–458.

(Rizvi 2018) Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018 Feb;15(2):95–111.

(Rosenberg 2016) Rosenberg JE, Hoffman-Censits J, Powles T et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016; 387:1909–1920.

(Rosenberg 2020) Rosenberg JE, Gajate P, Morales-Barrera R et al. Safety and Preliminary Efficacy of Rogaratinib in combination with atezolizumab in a Phase Ib/II study of first-line treatment in cisplatin-ineligible patients with locally advanced or metastatic UC and FGFR mRNA overexpression. J Clin Oncol. 2020;38 (suppl 15):5014. DOI: 10.1200/JCO.2020.38.15_suppl.5014

(Sabari 2018) Sabari JK, Offin M, Stephens D et al. A Prospective Study of Circulating Tumor DNA to Guide Matched Targeted Therapy in Lung Cancers. J Natl Cancer Inst. 2018 Nov 28. doi: 10.1093/jnci/djy156. [Epub ahead of print] PMID: 30496436.

(Saka 2017) Saka H, Kitagawa C, Kogure Y, et al. Safety, tolerability and pharmacokinetics of the fibroblast growth factor receptor inhibitor AZD4547 in Japanese patients with advanced solid tumours: a Phase I study. Invest New Drugs. 2017 Aug;35(4):451–462.

(Schram 2015) Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

(Seymour 2017) Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017; 18: e143–52.

(Sharma 2017) Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017 Mar;18(3):312–322.

(Siefker-Radtke 2018a) Siefker-Radtke A, Curti B. Immunotherapy in metastatic urothelial carcinoma: focus on immune checkpoint inhibition. Nat Rev Urol. 2018 Feb;15(2):112–124.

(Siefker-Radtke 2018b) Siefker-Radtke AO, Necchi A, Rosenbaum E, et al. Efficacy of programmed death 1 (PD-1) and programmed death 1 ligand (PD-L1) inhibitors in patients with FGFR mutations and gene fusions: Results from a data analysis of an ongoing phase 2 study of erdafitinib (JNJ-42756493) in patients with advanced urothelial cancer. J. Clin. Oncol. 2018 36:6_suppl, 450–abstract 450.

(Simon 1989) Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials. 1989 Mar;10(1):1–10.

(Soga 2010) Soga N, Kise H, Arima K, et al. Third-line gemcitabine monotherapy for platinum-resistant advanced urothelial cancer. Int J Clin Oncol 2010; 15: 376–381.

(Stanley 2014) Stanley ER, Chitu V. CSF-1 receptor signaling in myeloid cells. Cold Spring Harb Perspect Biol 2014; 6(6). doi: 10.1101/cshperspect.a021857.

(Stenehjem 2018) Stenehjem D, Tran D, Nkrumah MA, Gupta S. PD1/PDL1 inhibitors for the treatment of advanced urothelial bladder cancer. OncoTargets Therapy 2018;11:5973–5989.

(Sternberg 2001) Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001;19(10):2638–2646.

(Suzman 2018) Suzman DL, Agrawal S, Ning YM, et al. FDA Approval Summary: Atezolizumab or Pembrolizumab for the Treatment of Patients with Advanced Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy. Oncologist. 2018 Dec 12. pii: theoncologist.2018-0084.

(Tecentriq® USPI) Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761034s000lbl.pdf

(Tecentriq® SmPC) Available at: https://www.medicines.org.uk/emc/product/8442/smpc

(Turner 2010) Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer. 2010 Feb;10(2):116–29.

(Vandekerkhove 2019) Vandekerkhove G, Struss WJ, Annala M et al. Circulating Tumor DNA Abundance and Potential Utility in De Novo Metastatic Prostate Cancer. Eur Urol. 2019 Jan 9; doi.org/10.1016/j.eururo.2018.12.042.

(Vandekerkhove 2021) Vandekerkhove G, Lavoie JM, Annala M et al. Plasma ctDNA is a tumor tissue surrogate and enables clinical-genomic stratification of metastatic bladder cancer. Nat Comm. 2021;12:184 | https://doi.org/10.1038/s41467-020-20493-6 | www.nature.com/naturecommunications

(Vaughn 2002) Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol. 2002;20(4):937–940.

(von der Maas 2000) von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000;18(17):3068–3077.

(Wang 2017) Wang L, Sustic T, Leite de Oliveira R, et al. A functional genetic screen identifies the phosphoinositide 3-kinase pathway as a determinant of resistance to fibroblast growth factor receptor inhibitors in FGFR mutant urothelial cell carcinoma. Eur Urol. 2017;71:858–62.

(Ware 2002) Ware, R. User's Manual for SF-36v2 Health Survey. 2nd Edition, Quality Metric Inc., Lincoln, 2002; 81–84.

(Witjes 2018) Witjes JA, Bruins M, Compérat E, et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. EAU Guidelines Office, Arnhem, The Netherlands. https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=panel.

(Wyatt 2017) Wyatt AW, Annala M, Aggarwal R et al. Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer. J Natl Cancer Inst. 2017;110(1):78–86.

(Yang 2017) Yang G, Shen W, Zhang Y, et al. Accumulation of myeloid-derived suppressor cells (MDSCs) induced by low levels of IL-6 correlates with poor prognosis in bladder cancer. Oncotarget. 2017 Jun 13;8(24):38378–38388.

13 APPENDICES

Appendix 1 Eligible FGFR genetic aberrations

Small variants in *FGFR1–3* (FGFR1–3^{mt})

Missense point mutations (substitutions), in-frame deletions and insertions, excluding inactivating variants in FGFR2 (H213Y, V248D, D530N, R759X, I642V, A648T).

Excluding small variants introducing a premature stop codon or reading frame shift upstream of the kinase domain.

- *FGFR1–3* small variants (insertions, deletions, substitutions) introducing a premature stop codon or a frame-shift downstream of the kinase domain *are eligible.*

***FGFR1–3* gene fusions and other rearrangements ('FGFR1–3^{fus}')**

- *FGFR1–3* gene fusions with breakpoints upstream or downstream of the kinase domain which are in-strand and in-frame with the partner gene
- *FGFR1–3* gene fusions with breakpoints upstream or downstream of the kinase domain likely to be a functional event but with insufficient data for stringency criteria and/or canonical orientation
- *FGFR1–3* gene rearrangements of any type (translocations, truncations, deletions, splice site variants) with breakpoints in introns and/or exons upstream or downstream of the kinase domain

Concurrent assumed activating and inactivating genetic aberrations

In the event that assumed activating (i.e., eligible) and inactivating genetic aberrations are detected in a patient sample and considering heterogeneity of tumor cell clonality, which cannot be resolved with cfDNA analysis from plasma, the resulting *FGFR1–3* GA status will be, for the purpose of this clinical study protocol, defined as molecularly eligible for considering conduct of clinical study screening procedures.

Appendix 2 Assessment of anti-tumor activity per RECIST v. 1.1

Assessment of tumor responses may be performed following the revised RECIST guidelines, version 1.1. Some of these definitions and criteria are highlighted below.

Measurability of tumor baseline

- CT with IV contrast and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.
- Standard imaging studies should be performed according to the imaging manual provided by the central imaging laboratory designated by the Sponsor.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

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).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Measurable 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 also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable

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 (nevi) or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of assessment

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. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin (nevi) nodules). For the case of skin (nevi) lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only patients with measurable disease at baseline should be included in the study.

Baseline documentation of 'target' and 'non-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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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 of the 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 of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes 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').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- *Complete Response:* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- *Partial Response:* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease:* 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. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease:* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. In this study, the minimum duration for SD is defined as 6 weeks.

Special notes on the assessment of target lesions

Lymph nodes. 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 CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each Response Criteria subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

(Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target 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:* Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *Progressive Disease:* Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on the assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' 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 the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Evaluation of new lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI of the brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it truly represents a new disease. If repeat scans confirm there is definitely a new lesion, then progression is to be declared using the date of the initial scan.

Evaluation of best overall 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.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. The table below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Time point response: Patients with target (+/– non-target) disease			
Target lesions	**Non-target lesions**	**New lesions**	**Overall Response**
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
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

The best overall response is determined once all the data for the patient are known.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in the size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the eCRF.

For patients with PR or CR, the Investigator should make every attempt to perform the confirmation scan 4 to 5 weeks after the last scan was performed. Radiographic disease progression must be confirmed by central radiology prior to treatment discontinuation if progression is seen on first or second post-treatment scan.

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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of tumor re-evaluation

In this study, tumor measurement will be conducted at baseline, and once every 9 weeks (every three cycles) for the first 27 weeks, and every 12 weeks (every four cycles) thereafter while the patient is on treatment or as clinically indicated until progression of disease, withdrawal of consent, or death. Tumor measurement will also be performed during the End of Treatment visit if it is not done within 28 days of the End of Treatment visit date or if prior scan did not show radiographic disease progression.

Baseline tumor assessments must be performed within 4 weeks (28 days) of the first dose of treatment.

All efforts must be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning methods, equipment, technique (including slice thickness and field of view), and the radiographic interpreter.

The radiological evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations must meet the SoC for imaging of lesions in the respective organ(s).

All target and non-target sites are evaluated at each time point of tumor assessment.

Confirmatory measurement/duration of response

Confirmation

Confirmation of PR and CR is required approximately 4–5 weeks after the initial scan showing PR or CR.

Duration of overall response

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria that are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

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). In this study, the minimum duration for SD is defined as 6 weeks.

Appendix 3 Comparison of RECIST 1.1 and iRECIST criteria

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Appendix 4 Management of atezolizumab-specific adverse events

Note: This appendix is a redacted version of the detailed guidance for the management of immune-related AEs, located in the atezolizumab IB (Edition 17), which should be consulted for further guidance.

Pulmonary events including pneumonitis	
Event	**Management**
Grade 1	Continue atezolizumab and monitor closely.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as a Grade 3 or 4 event.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Bronchoscopy or bronchoscopic alveolar lavage is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone, and consider adding an immunosuppressive agent if event does not improve within 48 hours after initiating corticosteroids. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Hepatic events	
Event	**Management**
Grade 1	Continue atezolizumab and monitor liver function tests (LFTs) until values resolve to normal or to baseline values.
Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events with a duration of > 5 days** • Withhold atezolizumab for up to 12 weeks after event onset. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.

Hepatic events	
Event	**Management**
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone, and consider adding an immunosuppressive agent if event does not improve within 48 hours after initiating corticosteroids. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Gastrointestinal events (diarrhea or colitis)	
Event	**Management**
Grade 1	• Continue atezolizumab and monitor closely. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone, and consider adding an immunosuppressive agent if event does not improve within 48 hours after initiating corticosteroids. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Endocrine Events	
Event	**Management**
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone, monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone, monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab, and monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold 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. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.
Symptomatic adrenal insufficiency, Grades 2-4	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab and monitor for glucose control. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab and monitor for glucose control. • Initiate treatment with insulin. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-	• Withhold atezolizumab for up to 12 weeks after event onset.

Endocrine Events	
Event	**Management**
hypopituitarism), Grade 2 or 3	• Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV 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. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

Ocular Events	
Event	**Management**
Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immuno-suppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immuno-suppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month.

Ocular Events	
Event	**Management**
Immune-mediated myocarditis	
Event	**Management**
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset and contact Medical Monitor. • Refer patient to cardiologist, initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to cardiologist, initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone 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.

Infusion-related reactions (IRR) and cytokine-release syndrome (CRS)	
Event	**Management**
Grade 1 (fever with or without constitutional symptoms)	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Infusion-related reactions (IRR) and cytokine-release syndrome (CRS)	
Event	**Management**
Grade 2 (fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen by nasal cannula or blow-by)	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 3 (fever with hypotension requiring a vasopressor [with or without vasopressin] and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or venture mask)	• Permanently discontinue atezolizumab and contact Medical Monitor. • Administer symptomatic treatment. For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 (fever with hypotension requiring multiple vasopressors [excluding Vasopressin] and/or hypoxia requiring oxygen by positive pressure [e.g., CPAP, BiPAP, intubation and mechanical ventilation])	• Permanently discontinue atezolizumab and contact Medical Monitor. • Administer symptomatic treatment. • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).

Infusion-related reactions (IRR) and cytokine-release syndrome (CRS)	
Event	**Management**
	• Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Pancreatic events including pancreatitis	
Event	**Management**
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5-2.0 × ULN:** • Continue atezolizumab and monitor amylase / lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0-5.0 × ULN:** • Treat as Grade 3.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset, and monitor amylase and lipase every other day. • Refer patient to GI specialist. • If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.

Pancreatic events including pancreatitis	
Event	**Management**
	• 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.

Dermatologic events	
Event	**Management**
Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 4	Permanently discontinue atezolizumab and contact Medical Monitor.

Neurologic Disorders	
Event	**Management**
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Investigate etiology. • Initiate treatment as per institutional guidelines. If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated	• Permanently discontinue atezolizumab and contact Medical Monitor.

Neurologic Disorders	
Event	**Management**
neuropathy, Grade 3 or 4	• Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1-2 mg/kg/day oral or IV prednisone.

Immune-mediated meningoencephalitis	
Event	**Management**
All grades	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone 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 $\geq$ 1 month.

Renal Events	
Event	**Management**
Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine, until values resolve to within normal limits or to baseline values.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • 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. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.

Renal Events	
Event	**Management**
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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.

Immune-Mediated Myositis	
Event	**Management**
Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset, and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV 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. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset, and contact Medical Monitor. • 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 IV 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 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, resume atezolizumab.

Immune-Mediated Myositis	
Event	**Management**
	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as Grade 4 event. Permanently discontinue atezolizumab and contact Medical Monitor.
Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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 IV 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 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.

Suspected hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS)	
Event	**Management**
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram 2015; La Rosée 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Appendix 5 Collection and Management of Specimens for Future Biomedical Research

Definitions

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Pharmacogenomics: The investigation of variations of DNA characteristics as related to drug/vaccine response.

Pharmacogenetics: A subset of pharmacogenomics; pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.

DNA: Deoxyribonucleic acid.

Future Biomedical Research Sample Collection

For the purposes of this appendix, the specimens collected in this study as outlined in Section 5.3.5.4 are considered to be the 'Future Biomedical Research Sample Collection', and will be used to study various causes for how patients may respond to a drug.

Scope of future biomedical research

Future biomedical research specimens will be stored to provide a resource for future studies conducted by the Sponsor focused on the study of biomarkers responsible for how a drug enters and is removed by the human body, how a drug works, other pathways a drug may interact with, or other aspects of disease. The specimens may be used for future assay development and/or drug development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance the understanding of how individuals respond to drugs and the understanding of human disease, and ultimately to improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor, or those working in partnership with, or at the direction of, the Sponsor.

Summary of procedures for future biomedical research

1. Patients for enrollment

All patients enrolled in Substudies 1, 3, 4 and 5 in clinical study DZB-CS-201 will be considered for enrollment in the Future Biomedical Research study.

2. Informed consent

Informed consent for specimens (i.e., DNA, protein, etc.) will be obtained during screening for protocol enrollment from all patients, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research is part of the study ICF and must be obtained before samples not fully consumed for the study analyses are subsequently used for Future Biomedical Research.

Informed consent for future biomedical research is to be handled in the same manner as other consents provided for the purposes of this study (see Section 10.2).

3. eCRF documentation for future biomedical research specimens

Documentation of patient consent for future biomedical research will be captured in the eCRF. Any specimens for which such an informed consent cannot be verified must be destroyed.

4. Future Biomedical Research Specimen Collections

Collection of specimens for future biomedical research will be performed as part of sample collection in accordance with study procedures.

Confidential subject information for future biomedical research

To optimize the research that can be conducted with future biomedical research specimens, it is critical to link patient clinical information with future test results, so that specific analyses can be conducted. Knowing patient characteristics like sex, age, medical history and treatment outcomes are critical to understanding the clinical context of analytical results.

All patient personal data collected for future biomedical research will be handled in accordance with the Sponsor's confidentiality and personal data standard operating procedures (SOPs), and in compliance with the EU General Data Protection Regulation (GDPR).

Biorepository specimen usage

Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or a third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will be contractually bound to comply with the Sponsor's personal data protection and confidentiality requirements, and with the GDPR. Any contracted third-party analyses will conform to the specific scope of analysis outlined in the Future Biomedical Research study. Future biomedical research specimens remaining with the third party after specific analysis is performed will continue to be protected by the contractual provisions and the requirement to comply with the GDPR.

Withdrawal from future biomedical research

Patients may withdraw their consent for future biomedical research at any time by contacting either the investigator or the Sponsor, and may have their specimens and all derivatives removed from the biorepository and destroyed. While any analyses in progress at the time of a request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research, no new analyses of a patient's specimens will be generated after a request for destruction is received.

Retention of specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 5 years from the end of the main study.

Data security

Databases containing specimen information and test results must be accessible only to the authorized Sponsor representatives and the designated study personnel and/or authorized collaborators. The Sponsor must ensure that database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

Reporting of future biomedical research data to patients

Information obtained from exploratory laboratory studies will not usually be reported to the patient, family, or physicians.

If any exploratory results are definitively associated with clinical significance for patients while the clinical study is ongoing, investigators will be contacted with information. After the clinical study has been completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Patients will not be identified in any published reports about this study or in any other scientific publication or presentation.

Risks versus benefits of future biomedical research

No additional risks to the patient from future biomedical research have been identified, as no additional specimens will be collected for future biomedical research after completion of this study (i.e., only leftover samples are being retained).

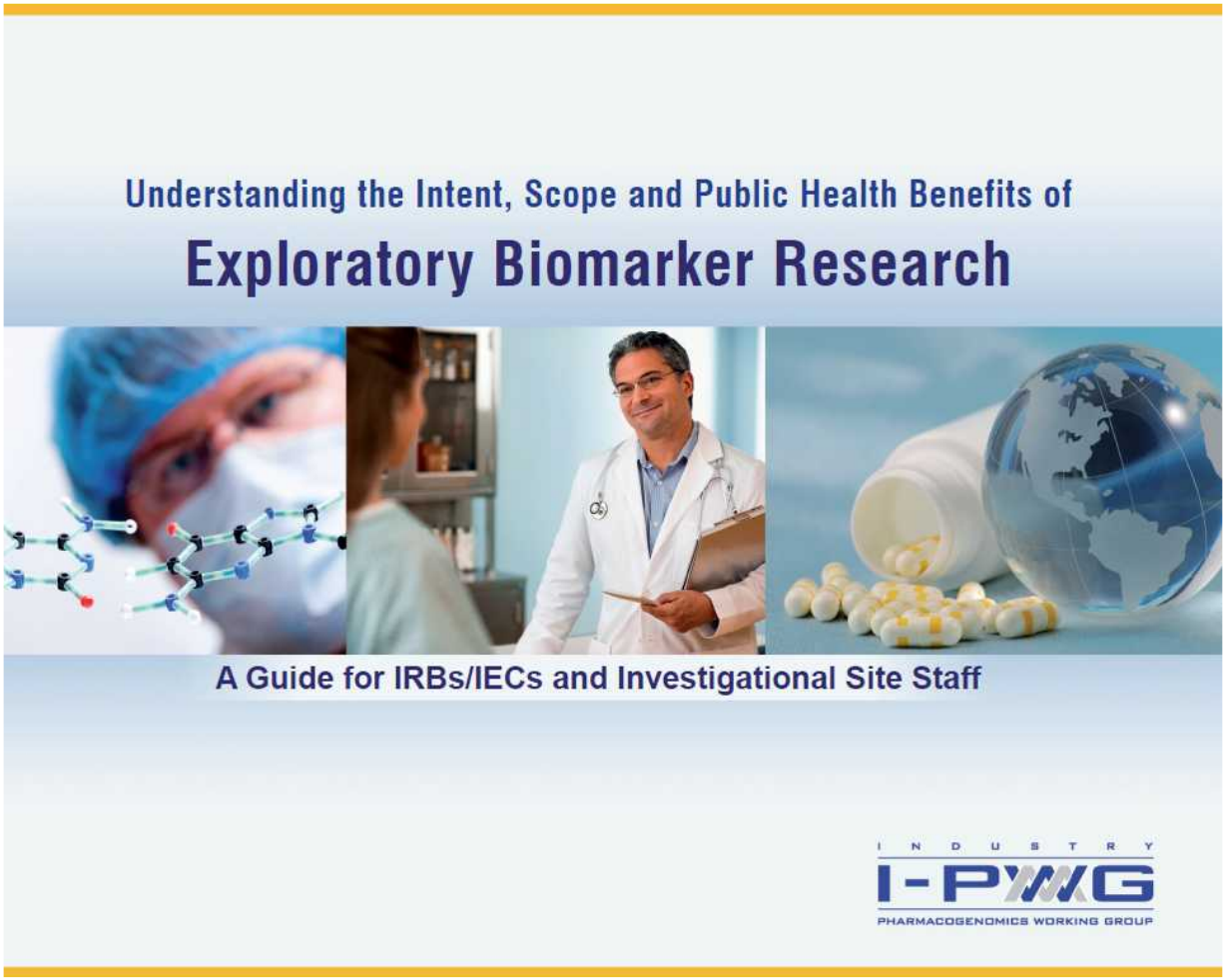
Questions

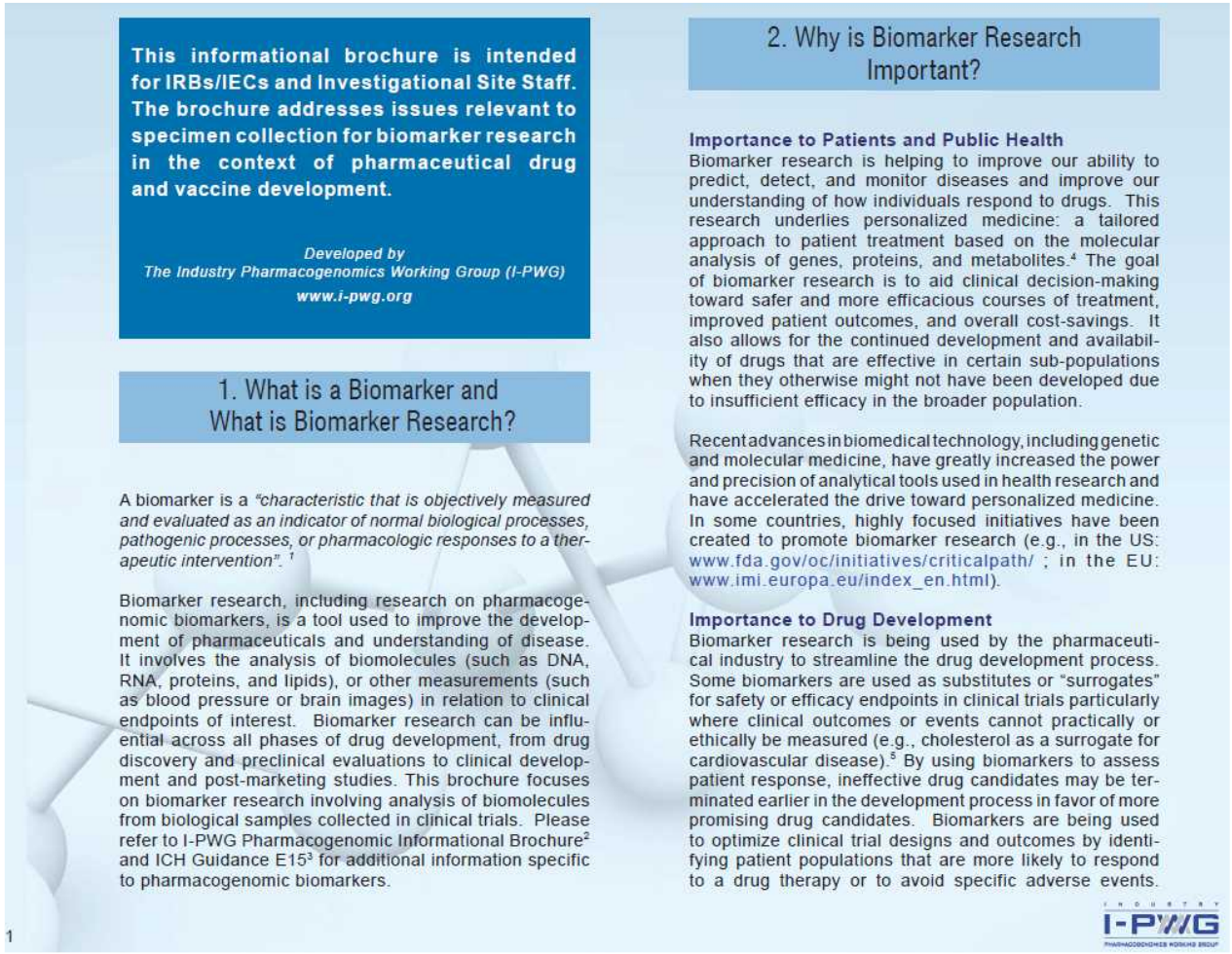
Any questions related to the future biomedical research should be emailed directly to medical.information@basilea.com.

Appendix 6 Understanding the intent, scope and public health benefits of exploratory biomarker research

Education Task Force, Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research, a Guide for IRBs/IECs & Investigational Site Staff. Published on I-PWG web site (www.i-pwg.org). December 2009.

Available at:
https://i-pwg.org/document-manager/publications/18-i-pwg-pharmacogenomics-informational-brochure/file


Understanding the Intent, Scope and Public Health Benefits of
Exploratory Biomarker Research
A Guide for IRBs/IECs and Investigational Site Staff
INDUSTRY
I-PWG
PHARMACOGENOMICS WORKING GROUP



This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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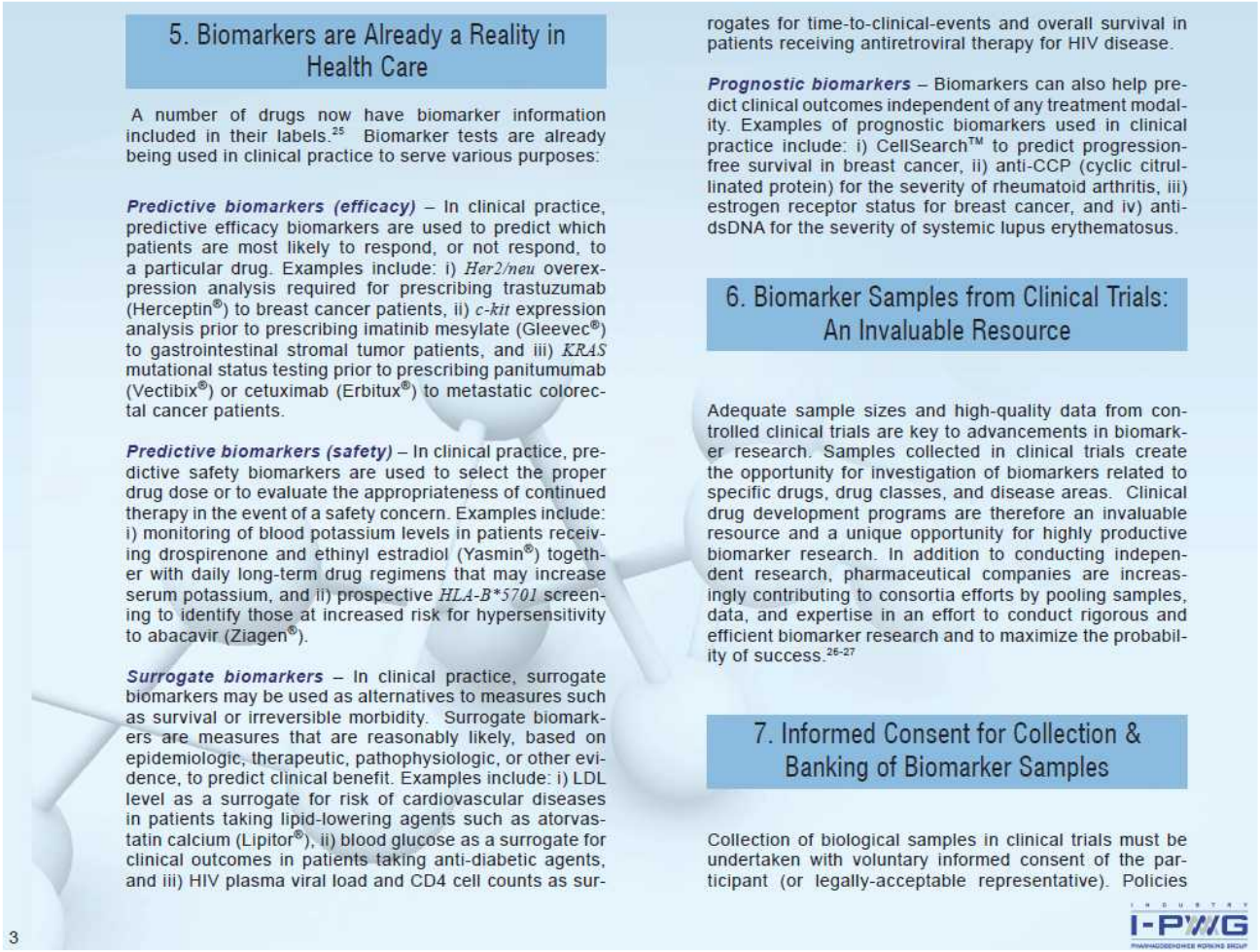

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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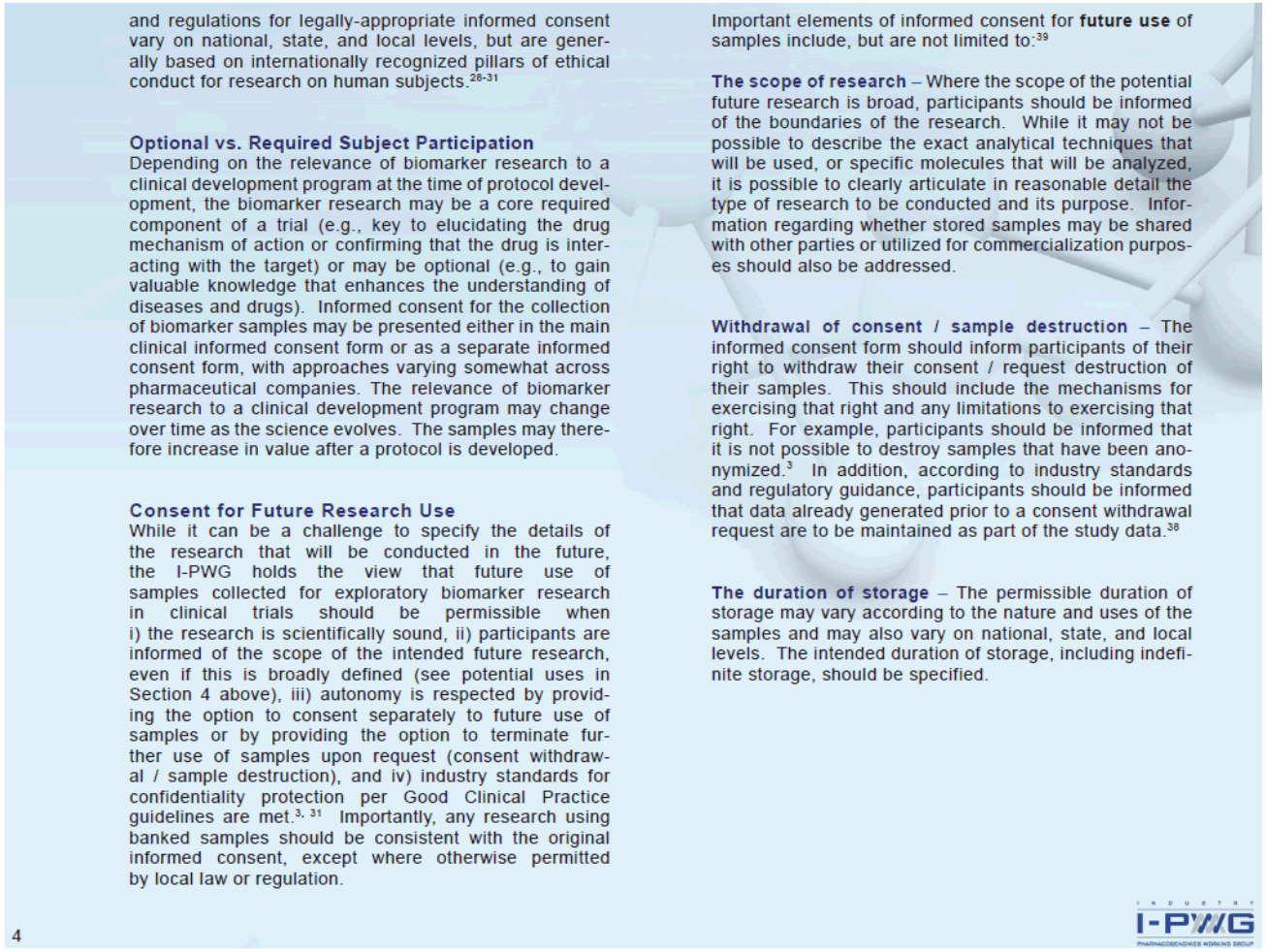

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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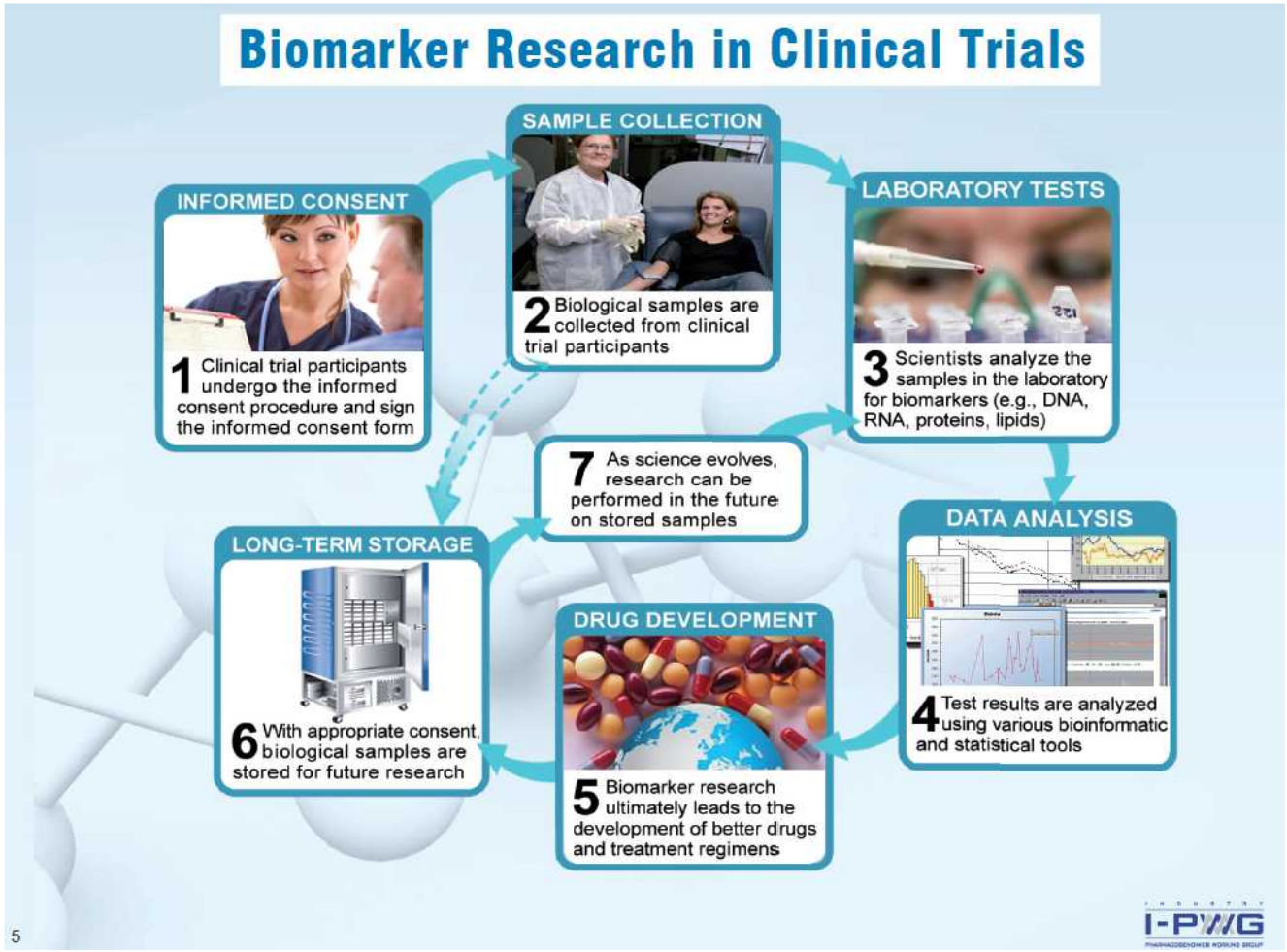
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
5
I-PWG

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"…provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: **www.i-pwg.org.**

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/ informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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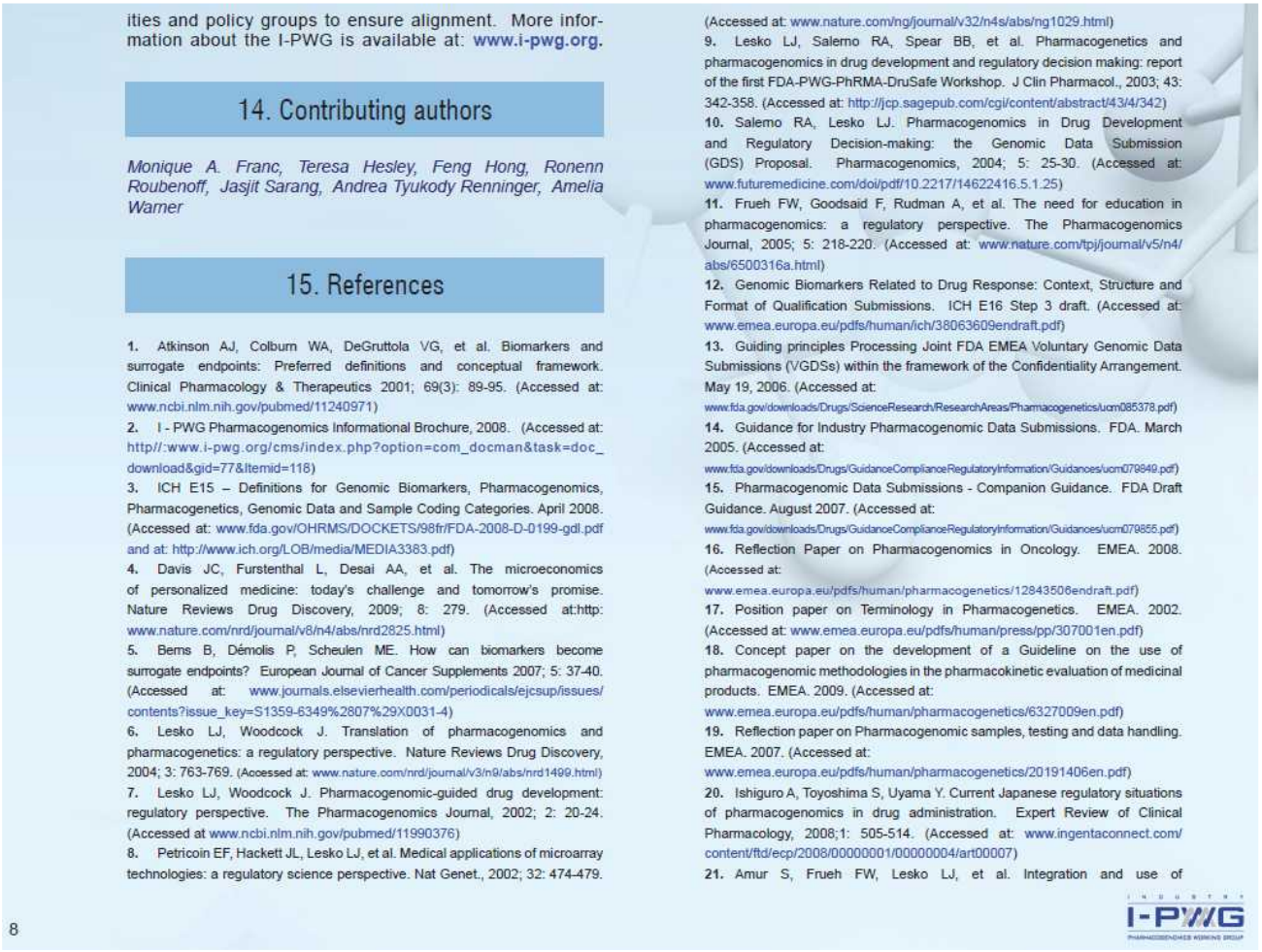

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/30700 1en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MEDIA482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)

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Appendix 7 Examples of in vivo substrates, inhibitors, and inducers for specific CYP enzymes

Inhibitors can be classified by their potency, such as:

- *Strong inhibitor* being one that causes at least a 5-fold increase in the plasma area under the curve (AUC) values, or more than 80% decrease in clearance.
- *Moderate inhibitor* being one that causes at least a 2-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- *Weak inhibitor* being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Selected inducers, inhibitors, and substrates of CYP2C8		
Substrates	**Inhibitors**	**Inducers**
• Amodiaquine (anti-malarial) • Cerivastatin (statin) • Paclitaxel (anti-tumoral) • Repaglinide (anti-diabetic) • Sorafenib (anti-tumoral) • Torsemide (diuretic)	**Strong**: • Gemfibrozil (lipid lowering) **Moderate** • trimethoprim (antibiotic) **Unspecified potency**: • glitazones (anti-diabetic) • montelukast (anti-asthmatic) • quercetin (antioxidant, supplement)	• rifampin (antibiotic)

Selected inducers, inhibitors, and substrates of CYP1A2		
Substrates	**Inhibitors**	**Inducers**

• many antidepressants
  ○ amitriptyline (tricyclic antidepressant)
  ○ clomipramine (tricyclic antidepressant)
  ○ imipramine (tricyclic antidepressant)
  ○ agomelatine
• some atypical antipsychotics
  ○ clozapine
  ○ olanzapine
• haloperidol (typical antipsychotic)
• caffeine (stimulant)
• ropivacaine (local anaesthetic)
• theophylline (xanthine, in respiratory diseases)
• zolmitriptan (serotonin receptor agonist)
	Strong:
	• ciprofloxacin (fluoroquinolone bactericidal)
	• many other fluoroquinolones (broad-spectrum antibiotics)
	• fluvoxamine (SSRI antidepressant)
	• verapamil (calcium channel blocker)
	Weak
	• cimetidine (H2-receptor antagonist)
	Unspecified potency:
	• amiodarone (antiarrhythmic agent)
	• interferon (antiviral, antiseptic, antioncogenic)
	• methoxsalen (in psoriasis)
	• mibefradil (calcium channel blocker)
	• **Some foods**
		• tobacco
		• **Some foods**
		  ○ broccoli
		  ○ brussels sprouts
		  ○ chargrilled meat
		  ○ cauliflower
		• insulin (in diabetes)
		• methylcholanthrene (carcinogen)
		• modafinil (eugeroic)
		• nafcillin (beta-lactam antibiotic)
		• beta-Naphthoflavone (chemopreventive)
		• omeprazole (proton pump inhibitor)

Selected inducers, inhibitors, and substrates of CYP1A2		
Substrates	**Inhibitors**	**Inducers**
• melatonin (antioxidant, sleep-inducer) • tamoxifen (SERM) • erlotinib (Tarceva, a tyrosine kinase inhibitor) • cyclobenzaprine (muscle relaxant, depressant) • estradiol (in hypoestrogenism) • fluvoxamine (SSRI antidepressant) • mexiletine (antiarrhythmic) • naproxen (NSAID) • ondansetron (5-HT3 antagonist) • phenacetin (analgesic) • paracetamol (analgesic, antipyretic) • propranolol (beta blocker) • riluzole (in amyotrophic lateral sclerosis) • tacrine (parasympathomimetic) • tizanidine (α-2 adrenergic agonist) • verapamil (calcium channel blocker) • warfarin (anticoagulant) • zileuton (in asthma)	○ grapefruit juice (its bitter flavanone naringenin) ○ cumin ○ turmeric	

Selected inducers, inhibitors, and substrates of CYP2D6		
Substrates **↑ = bioactivation by CYP2D6**	**Inhibitors**	**Inducers**

• All tricyclic antidepressants, e.g.
  ○ imipramine
  ○ amitriptyline
  ○ etc.
• Most SSRIs (antidepressant), e.g.
  ○ fluoxetine
  ○ paroxetine
  ○ fluvoxamine
• venlafaxine (SNRI antidepressant)
• mianserin (tetracyclic antidepressant)
• opioids
  ○ codeine↑ into morphine
  ○ tramadol↑
  ○ oxycodone
• antipsychotics, e.g.
  ○ haloperidol
  ○ risperidone
  ○ perphenazine
  ○ thioridazine
  ○ zuclopenthixol
  ○ iloperidone
  ○ aripiprazole
  ○ chlorpromazine
  ○ levomepromazine
  ○ remoxipride
• minaprine (RIMA antidepressant)
• tamoxifen↑ (SERM)
• beta-blockers
  ○ metoprolol
  ○ timolol
  ○ alprenolol
  ○ carvedilol
  ○ bufuralol
  ○ nebivolol
  ○ propranolol
• debrisoquine (antihypertensive)
• Class I antiarrhythmics
  ○ flecainide
  ○ propafenone
  ○ encainide
  ○ mexiletine
  ○ lidocaine
  ○ sparteine
	Strong:
	• SSRIs
	  ○ fluoxetine
	  ○ paroxetine
	• bupropion (non-SSRI antidepressant)
	• quinidine (class I antiarrhythmic agent)
	• cinacalcet (calcimimetic)
	• ritonavir (antiretroviral)
	Moderate
	• sertraline (SSRI)
	• duloxetine (SNRI)
	• terbinafine (antifungal)
	Weak:
	• buprenorphine (in opioid addiction)
	• amiodarone (antiarrhythmic)
	• cimetidine (H2-receptor antagonist)
	Unspecified potency:
	• antipsychotics
	  ○ haloperidol
	  ○ perphenazine
	  ○ thioridazine
	  ○ zuclopenthixol
	  ○ risperidone
	  ○ chlorpromazine
	• bicalutamide
	• hyperforin (St. John's Wort)
	• antihistamines (H1-receptor antagonists)
	  ○ Promethazine
	  ○ chlorphenamine
	  ○ diphenhydramine
	  ○ hydroxyzine
	  ○ tripelennamine
	• some SSRI antidepressants
	  ○ citalopram
	  ○ escitalopram
	• clemastine (antihistamine and anticholinergic)
	• celecoxib (NSAID)
	• clomipramine (tricyclic antidepressant)
	• cocaine (stimulant)
	• doxorubicin (chemotherapeutic)
		• dexamethasone (glucocorticoid)
		• rifampicin (bactericidal)
		Strong:
		• glutethimid

Selected inducers, inhibitors, and substrates of CYP2D6		
Substrates **↑ = bioactivation by CYP2D6**	**Inhibitors**	**Inducers**
• ondansetron (antiemetic) • donepezil (acetylcholinesterase inhibitor) • phenformin (antidiabetic) • tropisetron (5-HT3 receptor antagonist) • amphetamine (in ADHD, narcolepsy) • atomoxetine (in ADHD) • chlorphenamine (antihistamine) • dexfenfluramine (serotoninergic anorectic) • dextromethorphan (antitussive) into psychoactive dextrorphan • duloxetine (SNRI) • metoclopramide (dopamine antagonist) • Methoxyamphetamine • perhexiline (antianginal agent) • phenacetin (analgesic) • promethazine (antihistamine antiemetic)	• metoclopramide (antiemetic, prokinetic) • methadone (analgesic and anti-addictive) • moclobemide (antidepressant) • ranitidine (H2-receptor antagonist) • doxepin (tricyclic antidepressant, anxiolytic) • halofantrine (in malaria) • levomepromazine (antipsychotic) • mibefradil (calcium channel blocker) • midodrine (α_1 agonist) • ticlopidine (antiplatelet)	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix 8 Examples of *in vivo* substrates, inhibitors, and inducers of P-glycoprotein

Examples of *In Vivo* Substrates, Inhibitors, and Inducers of P-glycoprotein[1]			
Transporter	**Substrates**	**Inhibitors[1]**	**Inducers[2]**
P-gp (Gene *ABCB1*)	Aliskiren ambrisentan colchicine dabigatran etexilate digoxin everolimus fexofenadine imatinib lapatinib maraviroc, nilotinib posaconazole ranolazine saxagliptin sirolimus sitagliptin talinolol tolvaptan topotecan	Amiodarone azithromycin[3] captopril carvedilol clarithromycin conivaptan cyclosporine diltiazem dronedarone erythromycin[4] felodipine itraconazole ketoconazole[3] lopinavir and ritonavir quercetin[3] quinidine ranolazine ticagrelor verapamil	Avasimibe[5] carbamazepine[6] phenytoin rifampin St John's wort[7] tipranavir/ritonavir

Source: Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations
(http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

1 Not an exhaustive list. For an updated list, see the following link: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm

1 Inhibitors listed for P-gp are those that showed >25% increase in digoxin AUC or otherwise indicated if substrate is other than digoxin

2 Inducers listed for P-gp are those that showed >20% decrease in digoxin AUC or otherwise indicated if substrate is other than digoxin

3 Inhibitors listed are those that showed >25% increase in fexofenadine AUC

4 Inhibitors listed are those that showed >25% increase in talinolol AUC

5 Not a marketed drug

6 Inducers listed are those that showed >20% decrease in fexofenadine AUC

7 Herbal product

Appendix 9 Drugs with the potential to prolong QT and/or cause Torsades de Pointes

Known risk of Torsades de Pointes[24]

Generic name	Brand name	Generic name	Brand name
Aclarubicin	Aclacin and others	Ibogaine	None
Amiodarone	Cordarone and others	Ibutilide	Corvert
Anagrelide	Agrylin and others	Levofloxacin	Levaquin and others
Arsenic trioxide	Trisenox	Levomepromazine (methotrimeprazine)	Nosinan and others
Astemizole	Hismanal	Levomethadyl acetate	Orlaam
Azithromycin	Zithromax and others	Levosulpiride	Lesuride and others
Bepridil	Vascor	Mesoridazine	Serentil
Chloroquine	Aralen	Methadone	Dolophine and others
Chlorpromazine	Thorazine and others	Moxifloxacin	Avelox and others
Cilostazol	Pletal	Ondansetron	Zofran and others
Ciprofloxacin	Cipro and others	Oxaliplatin	Eloxatin
Cisapride	Propulsid	Papaverine HCl (Intra-coronary)	None
Citalopram	Celexa and others	Pentamidine	Pentam
Clarithromycin	Biaxin and others	Pimozide	Orap
Cocaine	Cocaine	Probucol	Lorelco
Disopyramide	Norpace	Procainamide	Pronestyl and others
Dofetilide	Tikosyn	Propofol	Diprivan and others
Domperidone	Motilium and others	Quinidine	Quinaglute and others
Donepezil	Aricept	Roxithromycin	Rulide and others
Dronedarone	Multaq	Sevoflurane	Ultane and others
Droperidol	Inapsine and others	Sotalol	Betapace and others
Erythromycin	E.E.S. and others	Sparfloxacin	Zagam
Escitalopram	Cipralex and others	Sulpiride	Dogmatil and others
Flecainide	Tambocor and others	Sultopride	Barnetil and others
Fluconazole	Diflucan and others	Terfenadine	Seldane
Gatifloxacin	Tequin	Terlipressin	Teripress and others
Grepafloxacin	Raxar	Terodiline	Micturin and others
Halofantrine	Halfan	Thioridazine	Mellaril and others
Haloperidol	Haldol and others	Vandetanib	Caprelsa

[24] Source: CredibleMeds® (https://www.crediblemeds.org).

Possible **risk of Torsades de Pointes[25]**

Generic name	Brand name	Generic name	Brand name
Abarelix	Plenaxis	Dexmedetomidine	Precedex and others
Alfuzosin	Uroxatral	Dextromethorphan/ Quinidine	Nuedexta
Apalutamide	Erleada	Dolasetron	Anzemet
Apomorphine	Apokyn and others	Efavirenz	Sustiva and others
Aripiprazole	Abilify and others	Eliglustat	Cerdelga
Artemether + Lumefantrine	Coartem	Encorafenib	Braftovi
Artenimol+piperaquine	Eurartesim	Epirubicin	Ellence and others
Asenapine	Saphris and others	Eribulin mesylate	Halaven
Atomoxetine	Strattera	Ezogabine (Retigabine)	Potiga and others
Bedaquiline	Sirturo	Felbamate	Felbatol
Bendamustine	Treanda and others	Fingolimod	Gilenya
Benperidol	Anquil and others	Fluorouracil (5-FU)	Adrucil and others
Betrixaban	Bevyxxa	Flupentixol	Depixol and others
Bortezomib	Velcade and others	Gemifloxacin	Factive
Bosutinib	Bosulif	Glasdegib	Daurismo
Buprenorphine	Butrans and others	Granisetron	Kytril and others
Cabozantinib	Cometriq	Hydrocodone - ER	Hysingla ER and others
Capecitabine	Xeloda	Iloperidone	Fanapt and others
Ceritinib	Zykadia	Imipramine (melipramine)	Tofranil
Clofazimine	Lamprene	Inotuzumab ozogamicin	Besponsa
Clomipramine	Anafranil	Isradipine	Dynacirc
Clotiapine	Entumine	Ketanserin	Sufrexal
Clozapine	Clozaril and others	Lacidipine	Lacipil and others
Crizotinib	Xalkori	Lapatinib	Tykerb and others
Cyamemazine (cyamepromazine)	Tercian	Lenvatinib	Lenvima
Dabrafenib	Tafinlar	Leuprolide	Lupron and others
Dasatinib	Sprycel	Lithium	Eskalith and others
Degarelix	Firmagon and others	Lopinavir and ritonavir	Kaletra and others
Delamanid	Deltyba	Maprotiline	Ludiomil and others
Desipramine	Pertofrane and others	Melperone	Bunil and others
Deutetrabenazine	Austedo	Memantine	Namenda XR and others

(Continued)

[25] Source: CredibleMeds® (https://www.crediblemeds.org).

Possible **risk of Torsades de Pointes (continued)[26]**

Generic name	Brand name	Generic name	Brand name
Midostaurin	Rydapt	Rilpivirine	Edurant and others
Mifepristone	Korlym and others	Risperidone	Risperdal
Mirabegron	Myrbetriq	Romidepsin	Istodax
Mirtazapine	Remeron	Saquinavir	Invirase(combo)
Moexipril/HCTZ	Uniretic and others	Sertindole	Serdolect and others
Necitumumab	Portrazza	Sorafenib	Nexavar
Nicardipine	Cardene	Sunitinib	Sutent
Nilotinib	Tasigna	Tacrolimus	Prograf and others
Norfloxacin	Noroxin and others	Tamoxifen	Nolvadex and others
Nortriptyline	Pamelor and others	Telavancin	Vibativ
Nusinersen	Spinraza	Telithromycin	Ketek
Ofloxacin	Floxin	Tetrabenazine	Nitoman and others
Osimertinib	Tagrisso	Tiapride	Tiapridal and others
Oxytocin	Pitocin and others	Tipiracil and Trifluridine	Lonsurf
Paliperidone	Invega and others	Tizanidine	Zanaflex and others
Palonosetron	Aloxi	Tolterodine	Detrol and others
Panobinostat	Farydak	Toremifene	Fareston
Pasireotide	Signifor	Tramadol	Crispin and others
Pazopanib	Votrient	Trimipramine	Surmontil and others
Perflutren lipid microspheres	Definity and others	Tropisetron	Navoban and others
Perphenazine	Trilafon and others	Valbenazine	Ingrezza
Pilsicainide	Sunrythm	Vardenafil	Levitra
Pimavanserin	Nuplazid	Vemurafenib	Zelboraf
Pipamperone	Dipiperon and others	Venlafaxine	Effexor and others
Primaquine phosphate	None	Vorinostat	Zolinza
Promethazine	Phenergan	Zotepine	Losizopilon and others
Prothipendyl	Dominal and others	Zuclopent(h)ixol	Cisordinol and others
Ribociclib	Kisqali		

[26] Source: CredibleMeds® (https://www.crediblemeds.org).

Conditional **risk of Torsades de Pointes**[27]			
Generic name	**Brand name**	**Generic name**	**Brand name**
Amantadine	Symmetrel and others	Ketoconazole	Nizoral and others
Amisulpride	Solian and others	Lansoprazole	Prevacid
Amitriptyline	Elavil and others	Loperamide	Imodium and many other OTC and Rx brands
Amphotericin B	Fungilin and others	Metoclopramide	Reglan and others
Amsacrine (acridinyl anisidide)	Amsidine	Metolazone	Zytanix and others
Atazanavir	Reyataz and others	Metronidazole	Flagyl and many others
Bendroflumethiazide or bendrofluazide	Aprinox and others	Nelfinavir	Viracept
Chloral hydrate	Aquachloral and others	Olanzapine	Zyprexa and others
Cimetidine	Tagamet and others	Omeprazole	Losec and others
Diphenhydramine	Benadryl and others	Pantoprazole	Protonix and others
Doxepin	Sinequan and others	Paroxetine	Paxil and others
Eperisone	Myonal and others	Piperacillin/Tazobactam	Tazosyn and Zosyn
Esomeprazole	Nexium and others	Posaconazole	Noxafil and others
Famotidine	Pepcid and others	Propafenone	Rythmol SR and others
Fluoxetine	Prozac and others	Quetiapine	Seroquel
Fluvoxamine	Faverin and others	Quinine sulfate	Qualaquin
Furosemide (frusemide)	Lasix and others	Ranolazine	Ranexa and others
Galantamine	Reminyl and others	Sertraline	Zoloft and others
Garenoxacin	Geninax	Solifenacin	Vesicare
Hydrochlorothiazide	Apo-Hydro and others	Telaprevir	Incivo and others
Hydroxychloroquine	Plaquenil and others	Torsemide (torasemide)	Demadex and others
Hydroxyzine	Atarax and others	Trazodone	Desyrel and others
Indapamide	Lozol and others	Voriconazole	VFend
Itraconazole	Sporanox and others	Ziprasidone	Geodon and others
Ivabradine	Procoralan and others		

[27] Source: CredibleMeds® (https://www.crediblemeds.org).

Appendix 10 Criteria for evaluating relationship between adverse events and study treatment

The relationship between an AE/SAE and derazantinib and/or atezolizumab will be determined by the Investigator on the basis of their clinical judgment and following definitions.

To align with the binary causality assessment required for clinical studies, based on the Investigator's evaluations, the cases will be categorized as:

- Unrelated: when evaluated as not related or unlikely related to derazantinib and/or atezolizumab.

  The AE does not follow a reasonable temporal sequence from study product administration, or can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
- Related: when evaluated as possibly or probably related to derazantinib and/or atezolizumab.

  The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concomitant diseases, concomitant medications).

  The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology, a known reaction to agent, or chemical group.

NOT RELATED

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias). If the drug was re-administered, it did not reappear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It is judged to be clearly and incontrovertibly due only to extraneous causes such as the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

UNLIKELY

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. If the drug was re-administered, it did not re-appear.

2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

POSSIBLE

This category is applicable to an AE that does not meet the criteria for 'not related' or 'unlikely', nor the criteria for 'probable'. An AE would be considered possible if, or when e.g.:

1. It follows a reasonable temporal sequence from administration of the drug (see also additional explanations above) or it follows a known pattern of the response to the suspected drug or drugs of the same substance class.
2. It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

Note: If an event neither follows a plausible temporal relationship nor a known pattern of response but there is no alternative explanation for the event, this will usually be judged a possibly related event.

PROBABLE

This category is applicable to an AE that is considered, with a high degree of certainty, to be related to the test drug. An AE event may be considered probable if it meets the following three criteria:

1. It follows a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is plausible. If the drug was interrupted or stopped the event did improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias.) If the drug was re-administered it did re-appear.
2. It follows a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

Regardless of the criteria mentioned above, reappearance of an event upon re-challenge must be regarded as strong evidence of probable relationship to test drug.

Appendix 11 Investigator's protocol signature page

BASILEA

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol / Version	DZB-CS-201 / 5.0	Basilea Product No:	Derazantinib
Protocol Title:	An open-label multi-cohort Phase 1b/2 study of derazantinib and atezolizumab in patients with urothelial cancer expressing activating molecular FGFR aberrations (FIDES-02)		
Basilea Pharmaceutica International Ltd			
Protocol date:	8 March 2021	Project Physician:	[redacted]
Name of Principal Investigator:			
Study site:			

I agree to the conditions relating to this study as set out in the above named Protocol and Study Procedures. I fully understand that any changes instituted by the Investigator(s) without previous discussion with the Sponsor's Project Clinician, Clinical Pharmacologist and Biostatistician (only if required) would constitute a protocol deviation, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well-being of the patients).

I agree to follow International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP), including the EU Clinical Trial Directive 2001/20/EC and specifically, obtain approval from the Independent Ethics Committee / Institutional Review Board prior to study start, allow direct access to source documents and agree to inspection by auditors from Basilea and regulatory authorities, as required by ICH GCP. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the above named protocol; if *any* other use is desired, *written permission* must be obtained from the Sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

To be signed by Principal Investigator (at minimum):

Please print names and dates next to the corresponding signatures

Signature	**Name**	**Date**
Principal Investigator		