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Statistical Analysis Plan for DZB-CS-201

Sponsor Name: Basilea Pharmaceutica International Ltd

Study 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)

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Table Of Contents

List of Abbreviations and Definition of Terms

Abbreviation or specialist term	Explanation
(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
ADA	Anti-drug antibodies
AE	Adverse event
AESI	AE of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
AZB	Atezolizumab
BLRM	Bayesian Logistic Regression Model
BICR	Blinded independent central review
CCG	Clinical change groups
CI	Confidence interval
CL_{CR}	Creatinine clearance
CLIA	Clinical Laboratory Improvement Amendments
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C*x*D*x*	Cycle (cycle number), Day (day number), e.g. C4D1 = Cycle 4, Day 1
DCR	Disease control rate
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
EWB	Emotional well-being
EWOC	Escalation with Overdose Control
FACT-G	FACT General
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
ft3	Tri-iodothyronine
ft4	Thyroxine
FWB	Functional well-being
GA	Genetic aberration
H_0	Null hypothesis
H_A	Alternative hypothesis
HR	Hazard ratios
HR-QoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

[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.

IEC	Independent Ethics Committee
IPCW	Inverse Probability of Censoring Weighted
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally important difference
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mUC	Locally advanced or metastatic and recurrent or progressing urothelial cancer
n	Number
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next-generation sequencing
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	Patient-reported outcome
PSV	Pre-screening visit
PT	Preferred term
PWB	Physical well-being
Q1	First quartile
Q3	Third quartile
Q3W	Every 3 weeks
QoL	Quality of life
QTc	Corrected QT interval
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SOP	Standard Operating Procedure
SV	Screening visit
SWB	Social well-being
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analog scale
WHO	World Health Organization

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 pelvic, 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).

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. At the time of protocol set up, no targeted agents directed against oncogenic driver mutations have yet been fully approved in these indications.

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, Suzman 2018, O'Donnell 2017, Sharma 2017, Powles 2017, Apolo 2017, Balar 2017c), 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).

1.3. FGFR Inhibition in Urothelial Carcinoma

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 carcinoma 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 2014).

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 NGS 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.

2. Study Objectives

2.1. Primary Objectives

2.1.1. Primary efficacy objectives

- 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 3and Cohort 4b) in patients with mUC expressing *FGFR1–3* GAs.

2.1.2. Primary safety objective for Substudy 3

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

2.1.3. Primary safety objective for Substudy 5

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

2.2. Secondary Objectives

- To evaluate the efficacy of the study drugs as measured by ORR (Substudy 2), 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 characterise 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 using the EORTC QLQ C30, FACT-BI, and 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 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 300mg 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

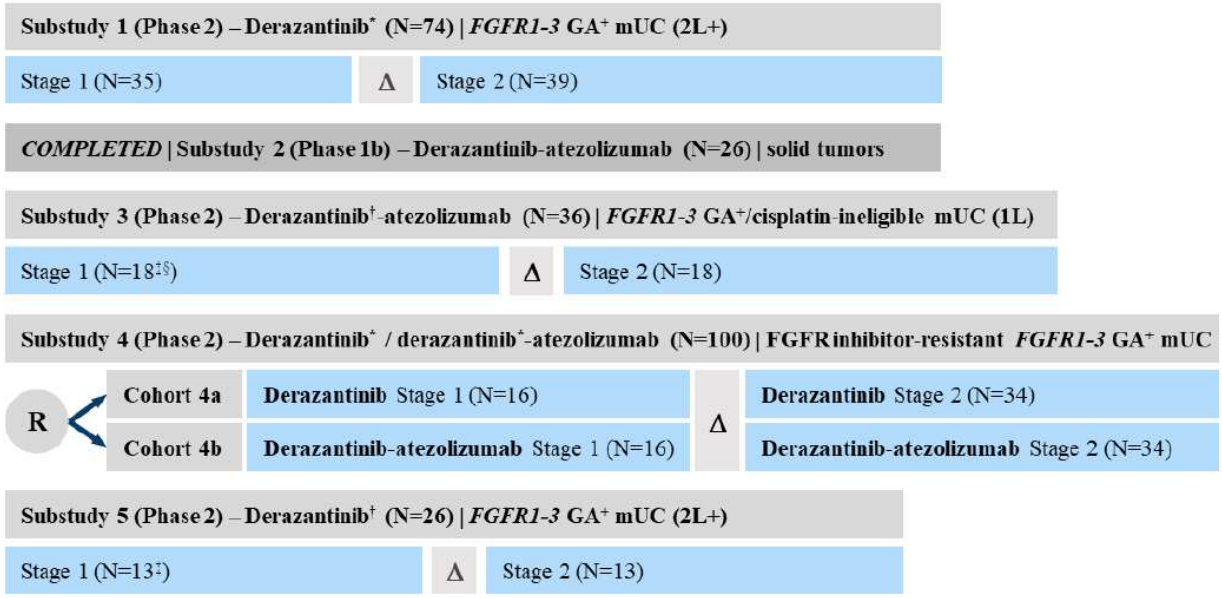
3. Study Design

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 in Substudy 2 will be used.

Only patients with mUC expressing FGFR1–3 GAs will be enrolled.

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

3.1. 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 300mg QC monotherapy, with the primary objective of assessing efficacy of this treatment regimen in this patient population. Randomization is not required.

Substudy 1 uses a Simon's two-stage design. In Stage 1, 35 evaluable patients will be enrolled. The decision to transition from Stage 1 to 2 will use all data collected in stage 1 to inform the decision and the decision will be taken according to the principles laid out in the IDMC charter. If 7 or fewer patients with an objective response (defined as a CR or PR) are observed in Stage 1, the cohort will be stopped. If 8 or more patients with an objective response 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.

Substudy 2

This substudy will enroll patients with any advanced solid tumor and any prior treatment (including FGFR inhibitor treatment), who have no standard treatment alternative. Patients in this substudy are to receive derazantinib-atezolizumab in combination, with the primary objective of identifying the appropriate recommended Phase 2 dose (RP2D) of the derazantinib-atezolizumab combination to be used in Cohort 3b and Cohort 4b. Assignment to a specific dose level and cohort will be controlled by the IWRS system.

This substudy is a safety run-in using a modified rolling-six design including up to 24 patients in two dose cohorts. If none or 1 of six patients in the dose-level 1 cohort (200 mg derazantinib QD plus 1,200 mg atezolizumab Q3W) experiences a DLT in Cycle 1, dose level 1 will be considered tolerable. The dose-level 1 will then be expanded by additional 6 patients (expansion cohort for dose level 1) to further characterize the safety and tolerability profile. In addition, the dose-level 2 cohort (300 mg derazantinib QD plus 1,200 mg atezolizumab Q3W) will start enrollment with an initial target sample size of 6 patients. If dose level 2 is considered tolerable, then dose level 2 will be expanded by additional 6 patients to further characterize the safety and tolerability profile of this dose level. The sample size may increase if there is a need to explore further intermediate dose levels.

The RP2D will be declared based on observed AEs by a joint decision taken by the IDMC, Investigators, and the Sponsor.

3.2. 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 3 uses a Fleming's two-stage design. A total sample size of 36 is required to test a null hypothesis of H_0: $\pi \leq 0.25$ versus an alternative hypothesis of H_a: $\pi \geq 0.45$, where π is the true proportion of successes. See Section 6.1.6.3 for details regarding the required sample size and required responses to either accept or reject H_0.

3.3. 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 300mg QC monotherapy, and Cohort 4b patients will receive derazantinib 300mg QC 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. Randomization will be based on a computer-generated randomization schedule via IWRS and will be stratified for key prognostic factors. 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.

Substudy 4 uses a Simon's two-stage design. In Stage 1, 16 evaluable patients will be enrolled for both cohorts. 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 patients. The null hypothesis will be rejected if 7 or more responses are seen in these 50 patients.

3.4. 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.

Substudy 5 uses a Fleming's two-stage design. A total sample size of 26 is required to test a null hypothesis of H_0: $\pi \leq 0.1$ versus an alternative hypothesis of H_a: $\pi \geq 0.3$, where π is the true proportion of successes. See Section 6.1.6.5 for details regarding the required sample size and required responses to either accept or reject H_0.

3.5. Subject crossover

Upon disease progression and at the Investigator's discretion, patients randomized to derazantinib monotherapy **Cohort 4a** may be offered to crossover to treatment with derazantinib-atezolizumab in combination.

Patients from Cohorts 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). The precise eligibility criteria for study treatment crossover are outlined in the associated study protocol.

4. Schedule of Assessments

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 ant bodies; 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.

	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

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).

5. Screening procedures 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.

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. 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.

9. Comprising specific gravity, pH, glucose, protein, ketones, and blood.

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. 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.
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 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.
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. Analysis Populations

The following patient populations (i.e., analysis sets) will be evaluated and used for presentation of the data:

5.1. Safety Population/ Intent-to-treat Population

The safety/intent-to-treat (ITT) 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).

5.2. Modified Intent-to-treat (mITT) 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) or death. Non-evaluable patients will be replaced.

5.3. Per-protocol (PP) Population

The PP population will include all patients in the mITT population who have no major protocol deviations which are determined to potentially impact efficacy analyses 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.

5.4. Maximum-tolerated Dose (MTD) Population (Substudy 2 only)

The MTD-determining population includes all patients enrolled in the MTD Part of each dose level who meet the following minimum criteria during the DLT period:

- received at least one dose of derazantinib and atezolizumab and has experienced a DLT;
- received ≥ 90% of the derazantinib and atezolizumab dose, respectively, in Cycle 1 and did not experience a DLT, have been observed for ≥ 21 days following the first dose, and have been evaluated for safety.

In the event that Cycle 1 exceeds 21 days, the period for patient's evaluability and DLT assessment will remain at 21 days.

Patients who do not meet these minimum evaluation requirements will be regarded as ineligible for the MTD-determining population. These patients will be included in the safety/ITT population but will be excluded from the calculation of DLT incidence and will be replaced by recruitment of additional patients.

Interim analyses for DLTs may be performed once at least five patients have been enrolled to a particular dose level, full DLT/safety data are available and a patient has not experienced a DLT, or when two DLTs have been observed in any number of patients enrolled in MTD Part of a particular dose level, whichever occurs first. Interim analyses are performed to determine if dose escalation is justified (or dose de-escalation is required) and if derazantinib in combination with atezolizumab is safe and tolerable.

5.5. Pharmacokinetic (PK) analysis population

The PK analysis population consists of all patients in the ITT population who have at least one PK sample result. 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 of the protocol) who receive at least 1 dose of study drug and have at least one PK sample result.
- The Sparse derazantinib PK sampling population consists of the patients enrolled in the sparse sampling schedule (see Section 5.3.4.1.3 of the protocol) who receive at least 1 dose of study drug and have at least one PK sample result.
- The atezolizumab PK population (see Section 5.3.4.2 of the protocol) consists of all patients who receive at least 1 dose of atezolizumab and have at least one PK sample result.

6. Statistical Methodology

6.1. Statistical and Analytical Issues

6.1.1. Statistical Methods

Tabulations will be produced for appropriate demographic, baseline, safety and efficacy parameters. Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category, where the denominator is the number of patients within the category at applicable time point (unless otherwise specified). Time-to-event data will be summarized using the Kaplan-Meier method.

By-patient data listings will be produced for data collected through the study (e.g., CRF, lab). All data listings that contain an evaluation date will contain a relative study day (Study Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. Baseline will be defined as the last evaluable/non-missing observation/assessment prior to the first dose of study drug on Cycle 1, Day 1.

Statistical analyses will be carried out by using SAS Version 9.4 or higher. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report.

Adverse events will be graded by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, and will be coded for summarization using the Medical Dictionary for Regulatory Activities (MedDRA® Version 22.0 or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2019 version or later).

6.1.2. Dose Level, Substudy, and Cohort Assignment

The definition of cohort and substudy in this study are detailed in Section 3. All analyses will be summarized by substudy and cohort (Substudies 1, 3, 4 and 5) or by dose level (Substudy 2)

6.1.3. Visit Windows

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window. Unless otherwise stated in the analysis sections below, unscheduled visits will be included in data listings only.

6.1.4. Handling of Dropouts and Missing Data

Unless indicated otherwise, summary statistics will be reported for observed data only and missing data will not be imputed. Patients whose clinical response is unknown or not reported will be treated as non-responders.

6.1.5. Pooling of Investigative Sites

As this is a Phase 1b/2 study, no by-site analyses are planned.

6.1.6. Determination of Sample Size

Simon's two-stage designs (Simon 1989) will be used for Substudies 1 and 4 and Fleming's two-stage designs 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 approximately 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.

6.1.6.1. Substudy 1

The null hypothesis that the true ORR is $p0 \leq 0.21$ 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 $p1 = 0.34$ 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 inhibitors (Loriot 2019, Necchi 2018, Pal 2018).

6.1.6.2. Substudy 2

This is a safety run-in using a modified rolling-six design including up to 24 patients in two dose cohorts. If none or 1 of six patients in the dose-level 1 cohort (200 mg derazantinib QD plus 1,200 mg atezolizumab Q3W) experiences a DLT in Cycle 1, dose level 1 will be considered tolerable. The dose-level 1 will then be expanded by additional 6 patients (expansion cohort for dose level 1) to further characterize the safety and tolerability profile. In addition, the dose-level 2 cohort (300 mg derazantinib QD plus 1,200 mg atezolizumab Q3W) will start enrollment with an initial target sample size of 6 patients. If dose level 2 is considered tolerable, then dose level 2 will be expanded by additional 6 patients to further characterize the safety and tolerability profile of this dose level. The sample size may increase if there is a need to explore further intermediate dose levels.

The RP2D will be determined by a joint decision taken by the IDMC, Investigators, and the Sponsor in reviewing the aggregate of DLT and AE data, and considering efficacy data.

6.1.6.3. 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_0: $\pi \leq 0.25$ 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_0 and 31 under H_1.

Table 2 summarizes the required samples sizes and required responses to either accept or reject H_0.

Table 2: Sample size and required responses of proposed two-stage Fleming design (Substudy 3)

	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

6.1.6.4. Substudy 4, Cohorts 4a and 4b

For both cohorts within Substudy 4, the null hypothesis that the true ORR is p0 ≤ 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 p1 = 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.

6.1.6.5. 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_0: $\pi \leq$ 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_0 and of 21 under H_1. Table 3 summarizes the required samples sizes and required responses to either accept or reject H0.

Table 3: Sample size and required responses of proposed two-stage Fleming design (Substudy 5)

	Sample size	Responders to accept H0		Responders to reject H0	
	N	n	%	n	%
Stage 1	13	1	7.7	5	38.5
Stage 2	26	5	19.2	6	23.1

6.2. Patient Characteristics

6.2.1. Patient Disposition

Patient disposition will be presented by substudy and cohort. In substudy 2 disposition will be presented by dose level. Tabulation will include the following:

- Number of patients screened
- Number (%) of patients dosed
- Number (%) in each patient population for analysis (including frequency of reasons excluded from PP population; distribution of major protocol deviations)
- Number (%) of patients who discontinued and reason(s) for discontinuation
- Number (%) of patients who completed the safety follow-up period (28 day and 90 day) and reasons for discontinuation
- Number (%) of patients who completed the survival follow-up period and reasons for discontinuation
- Treatment Phase and Study Duration

Patients excluded from the various analysis populations will be listed by substudy, cohort and dose level. Patients who discontinue will be listed by substudy, cohort and dose level with reason for discontinuation.

The number of patients by geographical region, country and site will be tabulated.

6.2.2. Protocol Deviations

Protocol deviations will be identified and categorized using the process outlined in the protocol deviation and non-compliance management plan. Review of protocol deviations for potential exclusion from analysis populations occurs at the monthly internal review meeting. The final decision will be made at the data review meeting with Basilea providing the final review and approval.

Major protocol deviations which are determined to potentially impact efficacy analyses will result in the removal of a patient from the PP population. For DZB-CS-201, the classification and categorization of protocol deviations per sponsor's definition are outlined in the Protocol Deviations Grading and Categorization Guidelines (Appendix 2 of the Protocol Deviation and Non-Compliance Management Plan) which is maintained in the collaborative workspace. The decision on which major protocol deviations warrant exclusion from the PP population will be determined prior to final analysis. Other deviations/scenarios may arise during the pre-lock data review that will be documented and reported.

Protocol deviations will be summarized for the safety/ITT population. The number and percentage of patients with a major deviation by type of deviation category will be presented by substudy and cohort (Substudies 1, 3,4 and 5) or by dose level (Substudy 2). In addition, all protocol deviations will be provided in a by-patient listing.

6.2.3. Background and Demographic Characteristics

Background and demographic characteristics will be summarized for the safety/ITT, mITT and PP populations. The following variables will be listed and summarized using both continuous and categorical descriptive statistics:

- Age
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- BMI (kg/m2) – calculated as weight (kg)/height $(m)^2$
- Child bearing potential
- Surgically Sterilized Status
- Menopausal Status
- ECOG at baseline

6.2.4. Smoking History

Smoking history data will be listed.

6.2.5. Tumor Molecular Status

For substudies 1, 3, 4 and 5, liquid and tissue tumor molecular status will be presented by substudy and cohort. For substudy 2, liquid and tissue tumor molecular status will be presented overall and by dose level. Tumor molecular status will be summarized for the safety/ITT population. The following variables will be summarized as categorical variables:

- Sample type (liquid/tissue)
- FGFR1 Status
- FGFR1 Gene Aberration Type
- FGFR2 Status
- FGFR2 Gene Aberration Type
- FGFR3 Status
- FGFR3 Gene Aberration Type
- Other FGFR
- Tissue PD-L1 Result
- Tissue PD-L1 Positive Result Category

- Expression results/range
- Score/cell type

6.2.6. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and concomitant procedures will be summarized for the safety/ITT population.

Study drug will be considered as any dose of either derazantinib or atezolizumab. The first dose date will be the first dose either derazantinib or atezolizumab was received and the last dose date will be last dose either derazantinib or atezolizumab was administered.

Prior medication will be defined as any medication taken and stopped prior to the first dose of study drug. Concomitant medication is defined as any medication ongoing at time of first dose of study drug or taken after the first dose of study drug. A concomitant procedure is defined as any procedure ongoing at time of first dose of study drug or occurring after the first dose of study drug.

Medications or procedures missing both start and stop dates, or having a start date prior to the first dose of study drug and missing the stop date, or having a stop date on or after the last dose of study drug and missing start date will be counted as concomitant.

For partial dates, the following approach will be taken:

- If the start day is missing but the start month and year are complete, a medication or procedure will be excluded as being concomitant only if the start month/year is before the month/year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start day and month are missing but the start year is complete, a medication or procedure will be excluded as concomitant only if the start year is before the year of study drug administration and if the stop date (either: full date, month and year if missing day, or year if missing month and day) is before study drug administration.

Prior and concomitant medications will be coded using the WHO Drug Dictionary (WHODRUG Global B3 Mar2019), and patient incidence will be tabulated by Anatomic Therapeutic Class (ATC) level 4 and preferred term (PT). Patients will be counted only once for each ATC or PT in the event that they have multiple records of the same ATC or PT in the database.

Concomitant procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or above and will be summarized by system organ class (SOC) and PT. Patients will be counted only once for each SOC or PT in the event that they have multiple records of the same SOC or PT in the database.

All prior and concomitant medications and procedures will be included in by-patient data listings.

6.2.7. Medical History (Non-Cancer Related)

Medical history will be summarized for the safety/ITT population. Medical history data will be summarized by SOC and PT per Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or above. Patients will be counted only once for each SOC or PT in the event that they have multiple records of the same SOC or PT in the database. All medical history data will be listed.

6.2.8. Cancer-Related Medical History

Cancer-related medical history will be summarized for the safety/ITT population. Descriptive statistics on cancer-related medical history characteristics will be presented for the following:

- Number of prior regimens of anti-cancer therapies related to study indication, and time since last anti-cancer related therapy calculated as date of first dose of study treatment – stop date of last anti-cancer related therapy. For each prior regimen of anti-cancer therapies (as well as last regimen), the following will be summarized: treatment setting, medication received, best treatment response, duration of response, time to progression, type of progression and reason therapy ended.
- Prior anti-cancer surgeries related to study indication. Anatomical location, Type of procedure, reason for procedure, presence of residual disease and time since last surgery will be summarized.
- Prior anti-cancer radiotherapy related to study indication. Anatomical location, total dose and time since last radiotherapy will be summarized.
- Time since first cancer diagnosis and time since most recent progression, calculated as the date of first dose of study treatment minus date of first diagnosis. If only month and year are provided, the day=15 will be assumed. If only year is provided, month=6 and day=30 will be assumed.
- Presence of Primary Tumor at Screening
- Tumor histology/Cytology at diagnosis/screening
- Anatomical location at diagnosis/screening
- Stage Classification at diagnosis/screening
- Histopathological Grade at diagnosis/screening
- TNM Staging at diagnosis/screening
- Metastatic location at diagnosis/screening
- Distant Metastasis at diagnosis/screening

The above will also be presented in data listings by substudy and patient.

6.2.9. Treatment Exposure and Compliance

Treatment exposure and compliance will be presented using the safety/ITT population.

Exposure to derazantinib and atezolizumab will be presented cumulatively. The number of cycles received and duration of treatment will be summarized using continuous statistics. The number of subjects with a dose reduction/interruption will be summarized as a categorical variable, including a summary of the reduced dose level achieved and the reasons for dose reduction/interruption. In addition, the total cumulative dose (mg) received will be summarized.

Dose intensity (%) will be summarised, defined as the percentage of the study drug a patient has taken compared to the amount of study drug the patient was originally planned to take at the time of their treatment allocation.

- $\%\ dose\ intensity = \frac{total\ cumulative\ dose\ received\ (mg)}{total\ cumulative\ dose\ planned\ (mg)} \times 100$

Derazantinib treatment compliance will be presented for each cycle and overall. Compliance will be calculated by counting unused capsules:

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

Compliance will also be summarized categorically, considering cut-offs of 80% and 120% for compliance.

Day 1 for each cycle will be identified using the Visit eCRF. The number of capsules prescribed per day will be 3 (except for substudy 2 dose level 1 where 2 capsules are planned) or as determined per the dose reduction guidelines for toxicity considered related to derazantinib and specified in the eCRF. Number of days during a dosing interval will be the number of dosing days in a cycle excluding any days that the patient was instructed to hold dosing due to an AE. The periods with missed dose for any other reason are not excluded when calculating compliance. Patients with discontinuation dates that fall within cycles will have their expected days adjusted in the compliance calculation for that cycle. For example, if a patient discontinues within Week 2 of Cycle 1, the number of days in the dosing interval will be calculated based of the date of the last dose within Week 2.

The total volume and total dose of atezolizumab administered will be presented cumulatively. The number of doses where atezolizumab is administered will be summarized using continuous descriptive statistics. Treatment compliance will be presented for each dose administered. Compliance will be determined by the total dose of atezolizumab received divided by the total planned dose.

6.3. Efficacy Analysis

All efficacy endpoints will be summarized by substudy and cohort. P-values and 95% CIs will be provided where appropriate. Comparisons between cohorts of substudy 4 will be performed using descriptive statistics and for the purposes of hypothesis generation only.

All efficacy analyses will be conducted using the mITT population. To evaluate sensitivity, the primary efficacy analyses (i.e. Section 6.3.1), will also be conducted using the PP population.

Assessments by Blinded Independent Central Review (BICR) consider two readers. Should there be disagreement between these two readers, an adjudicator decides which reader is correct. As such, all analyses which consider BICR assessments will be based upon the first reader by default, unless the second reader is selected following adjudication.

Per protocol inclusion criteria, only patients with measurable disease by RECIST version 1.1 criteria should be enrolled. If a patient without measurable disease is enrolled, the ITT principle requires including these patients in the analyses. Hence, analyses will be based on patients with either measurable or non-

measurable disease. For this purpose, non-CR/non-PD in patients with non-measurable disease will be considered equivalent to SD in patients with measurable disease, and the same rules will be applied.

Waterfall plots, spider plots and swimmer plots will be produced to accompany efficacy analyses.

6.3.1. Primary Efficacy Analysis

6.3.1.1. Objective Response Rate

The primary efficacy endpoint in all substudies will be objective response rate (ORR), defined as the achievement of confirmed CR or PR using RECIST 1.1 (Eisenhauer 2009) as assessed by BICR. Point estimates and exact 2-sided 95% CIs will be provided.

Classification of best confirmed response is done according to the following hierarchy and rules:

1. Complete Response (CR): requires two consecutive CR response assessments a minimum of four weeks apart
2. Partial Response (PR): requires two consecutive PR response assessments OR a PR response immediately followed by a CR response assessment (a minimum of four weeks apart)
3. Stable Disease (SD): requires only one SD response assessment (provided minimum criteria for SD duration met)
4. Non-CR/Non-PD (non-measurable disease patients only): requires only one Non-CR/Non-PD response assessment (provided minimum criteria for Non-CR/Non-PD duration met)
5. Progressive Disease (PD): requires only one PD response assessment

The minimum duration for SD and Non-CR/Non-PD is defined as 6 weeks, where the duration is calculated from the start of treatment until the criteria of SD is met.

The classification as per RECIST 1.1 (Eisenhauer 2009) is summarized in Table 4.

Table 4: Best overall response when confirmation of CR and PR required.

Overall response		BEST overall response
First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

As specified in RECIST 1.1, repeated 'NE' time point assessments complicate best response determination. Should a CR/PR be followed by a NE response and then a CR/PR, then confirmed response would be achieved (as an example PR-NE-PR will be considered as a confirmed response).

Note that iRECIST criteria (an adaptation of RECIST 1.1 to account for the tumor response patterns seen with immunotherapeutic drugs (Seymour 2017)) will also be considered in exploratory analyses.

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 specified below:

Substudy 1

H_0: $p \leq 0.21$ versus H_A: $p \geq 0.34$

If there are seven or fewer patients with an objective response (defined as a confirmed 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 with be rejected if 22 or more objective responses are observed in these 74 patients.

Substudy 3

H_0: $p \leq 0.25$ versus H_A: $p \geq 0.45$

If there are four or fewer patients with an objective response (defined as a confirmed 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 objective 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. A prior distribution Beta(1,1) will be used as a vague, non-informative prior, giving a uniform distribution with mean of 0.5 response rate with wide uncertainty. This will be multiplied by a likelihood with distribution Beta(a,b) where a is the number of responses and b is the number of non-responses, to obtain the posterior distribution from which the probability that the response rate exceeds 0.25 will be estimated. This analysis will only consider BICR assessed response within the mITT population.

Substudy 4

H_0: $p \leq 0.07$ versus H_A: $p \geq 0.20$

If there are one or zero patients with an objective response (defined as a confirmed 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 7 or more objective responses are observed in these 50 patients.

Comparisons between cohorts will be descriptively summarized by reporting the difference in point estimates between cohorts, with a 2-sided exact 95% CI for the difference and a p-value from a Fisher exact test.

Substudy 5

H_0: $p \leq 0.10$ versus H_A: $p \geq 0.30$

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. This analysis will only consider BICR assessed response within the mITT population.

6.3.2. Secondary Efficacy Variable(s)

6.3.2.1. Disease Control Rate (All Substudies)

Disease Control Rate (DCR) is defined as the proportion of patients achieving a confirmed CR or PR or stable disease (SD) (or Non-CR/Non-PD for patients with non-measurable disease) using RECIST 1.1 as assessed by BICR. Point estimates and exact 2-sided 95% CIs will be provided. Comparisons between cohorts of substudy 4 will be descriptively summarized by reporting the difference in point estimates between cohorts, with a 2-sided exact 95% CI for the difference and a p-value from a Fisher exact test.

6.3.2.2. Duration of Response (All Substudies)

Duration of Response (DOR) will be calculated from the first date of documented objective tumor response (confirmed CR or PR) to the date of disease progression as assessed by BICR or death. If a patient is discontinued or lost to follow-up with no documentation of PD, DOR is defined as the time from the date of first documented objective tumor response to the date of last tumor assessment as a censored value. PD or death post end of treatment will be censored at date of last tumor assessment as a censored value.

DoR will be derived only for patients who have the best overall response of CR or PR.

DOR will be analyzed using Kaplan-Meier methodology (Kaplan & Meier 1958). The median DOR will be presented along with the standard error and 2-sided 95% CI. If they are calculable, the 25th and 75th percentiles and the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented. The Kaplan-Meier survival curves will also be presented. For substudy 4 only comparisons between cohorts will be made by considering a hazard ratio, with associated 2-sided 95% confidence interval and p-value, from an unadjusted Cox proportional hazards model.

These analyses will be performed per cohort in substudies 1, 3, 4 and 5 and by dose level in substudy 2. The date of first dose, documented objective tumor response, disease progression, death, last tumor assessment, last contact and DOR days will be reported in a by-patient listing.

6.3.2.3. Progression-Free Survival (All Substudies)

Progression-Free Survival (PFS) will be calculated as the time from cohort assignment by IWRS until disease progression as assessed by BICR, or death from any cause, whichever comes first. Patients who either have no baseline tumor evaluation or have no post- baseline tumor evaluation will be censored at date of cohort assignment by IWRS. Patients without disease progression will be censored at the date of their last tumor evaluation. Patients who discontinue treatment due to reasons other than disease progression by BICR or death will be censored in the PFS analyses as the date of their last tumor evaluation prior to EOT. 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. Any deaths occurring after end of treatment are not taken into account as a PFS event. Patients who stopped treatment without PD will be censored at their last scan prior to end of treatment. For patients with missing end of treatment visit date, a +7 day window compared to the maximum of last dose date, last on treatment visit date will be applied to create a tentative end of treatment visit date and a cut-off for death occurring after this date. The rules for censoring PFS are summarized in the table below:

Table 5: Censoring scheme for PFS

Situation	Date of progression or censoring	Outcome
No baseline or post-baseline tumor assessments	Randomization / Cohort assignment	Censored
Progression documented between scheduled visits	Date of radiological assessment of measured lesions	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for reasons other than disease progression by BICR or death	Date of last radiological assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed tumor assessment or after end of treatment	Date of last radiological assessment of measured lesions prior to progression or death	Censored

Additional sensitivity analyses will be conducted which consider alternative censoring methods as outlined in FDA guidelines (FDA 2018, FDA 2015).

A first sensitivity analysis will consider the same analysis as outlined in Table 5, but also considering clinical progression as an event (either clinical or radiographic progression will be considered as an event, rather than just radiographic).

A second sensitivity analysis will include all post end of treatment assessments, such that subjects who die or progress after end of treatment will be considered as an event, with censoring at the earliest of last scan performed / new anti-cancer treatment. The censoring scheme for this analysis is outlined in Table 6.

Table 6: Censoring scheme for PFS - sensitivity analysis 2

Situation	Date of progression or censoring	Outcome
No baseline or post-baseline tumor assessments	Randomization / Cohort assignment	Censored
Progression documented between scheduled visits	Date of radiological assessment of measured lesions	Progressed
No progression	Date of last scan performed / new anti-cancer treatment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed tumor assessment or after end of treatment	Date of death or progression	Progressed

A third sensitivity analysis (Table 7) uses a conservative approach by assigning the date of discontinuation, or missed visit as an event date.

Table 7: Censoring scheme for PFS - sensitivity analysis 3

Situation	Date of progression or censoring	Outcome
No baseline or post-baseline tumor assessments	Randomization / Cohort assignment	Censored
Progression documented between scheduled visits	Date of radiological assessment of measured lesions	Progressed
No progression, treatment ongoing	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for reasons other than disease progression by BICR or death	Date of discontinuation	Progressed
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed tumor assessment or after end of treatment	Date of first missed visit	Progressed

PFS will be analyzed using Kaplan-Meier methodology (Kaplan & Meier 1958). The median duration of PFS will be presented along with the 2-sided 95% CI. If they are calculable, the 25th and 75th percentiles and

the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented. The Kaplan-Meier survival curves will also be presented. For substudy 4 comparison between cohorts will be made by considering a hazard ratio, with associated 2-sided 95% confidence interval and p-value, from an unadjusted Cox proportional hazards model.

The date of cohort assignment by IWRS, first dose, disease progression, death, last tumor assessment and PFS days will be reported in a by-patient listing.

6.3.2.4. Overall Survival (All Substudies)

Overall Survival (OS) 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. Crossover patients (Cohort 4a) will be censored at the time of crossover in the primary analysis of OS.

OS will be analyzed using Kaplan-Meier methodology (Kaplan & Meier 1958). The median duration of OS will be presented along with the standard error and 2-sided 95% CI. If they are calculable, the 25th and 75th percentiles and the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented. The Kaplan-Meier survival curves will also be presented. For substudy 4 comparisons between cohorts will be made by considering a hazard ratio, with associated 2-sided 95% confidence interval and p-value, from an unadjusted Cox proportional hazards model.

These analyses will be performed per cohort in substudies 1, 3, 4 and 5 and by dose level in substudy 2. The date of cohort assignment by IWRS, first dose, death, last study contact and OS days will be reported in a by-patient listing.

6.3.3. Exploratory Analysis

6.3.3.1. Time to progression

TTP will be calculated based on BICR assessment review from the first date of receiving study drug until radiographic disease progression.

The rules for censoring TTP are similar to PFS censoring. These are summarized in the table below:

Table 8: Censoring Scheme for TTP

Situation	Date of progression or censoring	Outcome
No baseline or post-baseline tumor assessments	Randomization / Cohort assignment	Censored
Progression documented between scheduled visits	Date of radiological assessment of measured lesions	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for reasons other than disease progression by BICR	Date of last radiological assessment of measured lesions	Censored

TTP will be analyzed using Kaplan-Meier methodology (Kaplan & Meier 1958). The median duration of TTP will be presented along with 2-sided 95% CI. If they are calculable, the 25th and 75th percentiles and the 2-sided 95% CIs around the percentiles will be presented. Kaplan-Meier estimates at 3, 6, 9 and 12 months will also be presented. The Kaplan-Meier survival curves will also be presented. For substudy 4 comparison

between cohorts will be made by considering a hazard ratio, with associated 2-sided 95% confidence interval and p-value, from an unadjusted Cox proportional hazards model.

6.3.3.2. Subgroup Analyses

Subgroup analyses (consisting of separate analyses within each subgroup) will be undertaken for all efficacy endpoints considering the following subgroups:

- FGFR1-3 mutation
- Other gene aberration types
- Upper tract urothelial cancer
- Lower tract urothelial cancer
- Stratification factor composite score (0-1 points) – substudy 4 only
- Stratification factor composite score (2-3 points) – substudy 4 only
- Stratification factor: Visceral metastasis – substudy 4 only
- Stratification factor: ECOG PS $\geq$2 – substudy 4 only
- Stratification factor: FGFR inhibitor internal of less than 6 months – substudy 4 only

6.3.3.3. iRECIST (Substudies 3 and 4)

Analyses of ORR, DCR, DOR and PFS will be repeated as outlined above evaluated by BICR using iRECIST criteria (Seymour 2017).

6.3.3.4. Crossover patients (Substudy 4)

There will be no specific analysis for crossover patients, due to low sample size. Crossover patients will not be included in summary tables/figures and their data will be listed only.

6.3.3.5. Investigator assessed response

In the primary analysis, tumor response will be based upon measurements evaluation by the BICR. However, an initial assessment of tumor response will be made by investigators at site. As an exploratory measure, analyses of BOR, DCR, DOR, PFS will be conducted considering investigator assessment only.

6.4. Safety Analysis (All substudies)

All safety analyses will be performed using the safety/ITT population, apart from in the analysis of DLTs in substudy 2 which will be performed using the MTD population (see Section 5.4). Analyses will be presented by substudy and cohort.

6.4.1. Adverse Events

Adverse events will be graded according to the NCI CTCAE Version 5.0, coded using the MedDRA coding system (version 22.0 or later), and displayed in tables and data listings by system organ class (SOC) and preferred term (PT). Dose-limiting toxicities (DLTs) are applicable to substudy 2, substudy 3 and substudy 5 only and are classified as the occurrence of any toxicity during Cycle 1 if judged by the investigator to be possibly or probably related to study drug administration from a pre-specified list in the protocol version 5 for substudies 3 and 5, and protocol version 4 for substudy 2.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE with the onset date as the date the event worsened. AEs will be reported (considered treatment-emergent) up to the end of the safety follow-up period.

Adverse events are summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given SOC or PT (i.e., the most related occurrence or the most intense occurrence). Missing relationship will be considered related to study drug.

An overall AE incidence summary table will be produced and will include:

- The number and percentage of patients reporting at least 1 treatment-emergent AE (TEAE)
- The number and percentage of patients reporting at least 1 serious TEAE (SAE)
- The number and percentage of patients reporting at least 1 related TEAE
- The number and percentage of patients reporting at least 1 related serious TEAE (SAE)
- The number and percentage of patients reporting at least 1 AE of Special Interest (AESI)
- The number and percentage of patients reporting at least 1 serious AESI
- The number and percentage of patients reporting at least 1 TEAE with toxicity grade of 3 or higher
- The number and percentage of patients reporting at least 1 related TEAE with toxicity grade of 3 or higher
- The number and percentage of patients reporting at least 1 TEAE classified as a DLT (Substudy 2, 3 and 5)
- The number and percentage of patients reporting a TEAE leading to a dose modification/interruption
- The number and percentage of patients reporting a TEAE leading to permanent discontinuation of study drug
- The number and percentage of patients with a TEAE leading to death

The overall AE incidence summary table described above will also include the number of events reported.

For all event types listed above in the overall AE incidence summary table, tabulations by SOC and PT will also be produced. Related TEAEs with toxicity grade of 3 or higher will also be summarised. These will be presented by SOC and PT, sorted by decreasing frequency.

No formal hypothesis-testing analysis of AE incidence rates will be performed. All AEs occurring on-study will be provided in data listings. By-patient listings also will be provided for the following: SAEs, DLTs (Substudy 2, 3 and 5), AEs leading to permanent discontinuation of study drug, and AEs leading to death.

6.4.2. BLRM analyses for 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 derazantinib dose d, let πd 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 derazantinib doses, and DLT probabilities is modelled by the logistic curve;

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

Doses are rescaled as d/d* with reference dose d*= 600mg/day. The model parameters $\alpha 1$, $\alpha 2$ and β have the following interpretation:

- $\alpha 1$ equals the odds of toxicity with monotherapy at the reference dose d*.
- $\alpha 2$ 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 2β.

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.

Safety interim analyses of dose-limiting toxicities in substudies 3 and 5 will be undertaken entirely by Basilea Pharmaceutica International Ltd.

6.4.3. Physical and Ophthalmological Examinations

Physical examinations will be performed at pre-screening, screening, at each cycle, end of treatment and safety follow-up visits (28 days and 90 days after last dose, as applicable), and symptom-driven examinations will be done as needed. Ophthalmological examinations will be performed during screening, the first four cycles (i.e. Day 1 of Cycles 2–5) and the End of Treatment visit. Physical examination and ophthalmological results will be listed.

6.4.4. Vital Signs

The actual value and change from baseline to each visit and at end of study will be descriptively summarized by visit/assessment for vital signs (i.e., systolic and diastolic blood pressure, heart rate, respiratory rate, temperature and body weight).

Height is measured at screening only. All vital sign data will be reported in a by-patient listing.

6.4.5. Electrocardiogram

The actual value and change from baseline to each visit and at end of study will be descriptively summarized by visit for ECG parameters (e.g., heart rate, RR interval, PR interval, QRS duration, QT interval, QTcF interval and QTcB interval). 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. Summary tables will consider the mean of the triplicate measurements at each visit as the single reported value.

A categorical analysis of QTcF interval and QTcB interval correction will also be presented, based on the number and percentage of patients meeting or exceeding specific thresholds for absolute QTcF/QTcB interval prolongation and change from baseline in QTcF/QTcB interval. In this analysis, the mean of the triplicate measurements will not be used; instead, the maximum at each timepoint will be considered.

For absolute QTcF/QTCB interval prolongation, the number and percentage of patients within the following thresholds will be summarized at each visit. The worst (largest) value will also be summarized.

- Interval ≤450 ms
- Interval >450 ms and ≤480 ms
- Interval >480 ms and ≤500 ms
- Interval >500 ms

The change from baseline in QTcF/QTcB interval to the worst (largest) post-baseline observation and at each study visit will also be summarized, considering the following thresholds:

- Interval increased from baseline ≤30 ms
- Interval increased from baseline >30ms and ≤60 ms
- Interval increased from baseline >60 ms

For the analysis of change from baseline, the mean of the triplicate measurements will be used for all visits. In the categorical analyses, the maximum of triplicate measurements will be used for post-baseline values.

These summary tables will be presented by timepoint, and for the maximum post baseline value.

All summary outputs for ECG will consider central ECG data.

All ECG data will be provided in a by-patient listing. Local ECG data will be listed only.

6.4.6. Laboratory Parameters

Baseline values and values at each visit for each laboratory parameter collected will be descriptively summarized.

Laboratory data will also be summarized using shift tables where appropriate. Each patient's continuous laboratory safety parameter values will be flagged as "low", "normal", "high" or "missing" relative to the normal ranges. Each patient's categorical laboratory safety parameter values will be flagged as "abnormal" or "normal". This categorical data will be summarized in shift tables comparing the minimum post-baseline value, maximum post-baseline value and all other relevant post-baseline visits with those at the baseline visit. Note that minimum post-baseline will only be displayed in the instances where there is a range with LLN>0.

In addition, CTCAE grade and hyperphosphatemia grade will be summarized. Shift tables of grade from baseline to maximum or minimum on-treatment as applicable will be produced. This analysis will also be produced considering cycle 1 only.

Laboratory results will be included in by-patient listings and will include CTCAE grade and hyperphosphatemia grade at each visit, as well as change from baseline at each visit.

Hy's law

Subjects who have elevated ALT, AST, and total bilirubin post baseline will be summarized descriptively as follows and Hy's law cases identified.

- ALT and AST: > 3x Upper Limit of Normal (ULN), > 5x ULN, > 10x ULN, > 20x ULN
- Total bilirubin >2x ULN
- ALT or AST: > 3x ULN and Total bilirubin >2x ULN

Plots of ALT and AST vs. Total bilirubin by module will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for total bilirubin. In each plot, peak total bilirubin x ULN will be on the vertical axis and peak ALT or AST x ULN will be on the horizontal axis.

6.4.7. Evaluation of Performance Status

ECOG performance status will be summarized in a shift table, which will summarise values at baseline, each visit and the maximum values during the study.

All ECOG performance assessments will be provided in a by-patient listing.

6.5. PK/PD Analysis

PK analyses are not the responsibility of [redacted] and details of planned analyses will be covered in a separate statistical analysis plan.

6.6. PRO Assessments (Substudies 1, 3, 4 and 5)

All PRO assessments analyses will be performed using the safety/ITT population and presented per substudy and cohort.

6.6.1. Establishing the Minimally Important Clinical Difference

For each assessment the minimally important difference (MID) in a score at C3D1 and C5D1 will be determined following the recent protocol by the EORTC Quality of Life Group (Musoro 2018). The Global Self Evaluated Transition (G-SET™) is a single item questionnaire administered twice during the study after 6 weeks (at C3D1) and 12 weeks (at C5D1). The questionnaire is a patient-rated change in health between two time periods using a five point ordinal scale (1 = much better now than 6 weeks ago; 2 = somewhat better now than 6 weeks ago, 3 = about the same as 6 weeks ago; 4 = somewhat worse now than 6 weeks ago; 5 = much worse now than 6 weeks ago).

Patients with complete data will be categorized into five mutually exclusive clinical change groups (CCG) reflecting the five possible levels of change. For each pair of timepoints (Change in summary score from baseline at C3D1 and Change in summary score from C3D1 at C5D1), a patient can thus belong to only one CCG category. Two methods for determining the MID will be explored:

1. **Mean Change Method**
   For a given mean absolute change in PRO assessment scale summary score: the MID for improvement is equal to the mean summary score of the 'small positive change' CCG (somewhat better now than 6 weeks ago) and the MID for deterioration is equal to the mean summary score of the 'small negative change' CCG (somewhat worse now than 6 weeks ago). The mean summary score of the 'small change' CCGs and that of the 'no change' CCG will be compared and reported. If the mean summary score for 'no change' CCG is similar to any of the two 'small change' CCGs, the estimated MID may be considered doubtful. No a priori rule will be established to determine if mean summary scores are sufficiently similar to determine MID to be doubtful.

2. **Linear Regression**
   For a given absolute change in PRO assessment scale summary score: the estimate of the numerical change in summary score that is associated with the transition between adjacent CCG categories will be determined using linear regression. Separate models will be fitted for improving and deteriorating scores based on the anchor. The outcome variable is the PRO assessment summary score, and the covariate is a binary anchor variable; coded as 'no change'=0 and 'small positive change'=1 for model on improvement (Other CCG categories are excluded from the linear regression model), and 'no change'=0 and 'small negative change'=1 for model on deterioration (Other CCG categories are excluded from the linear regression model. The resulting β's (i.e. slope parameters) correspond to the MIDs for improvement and deterioration respectively. No other covariates will be included in these models.

6.6.2. EQ-5D (5L)

The EQ-5D (5L) is a standardized instrument for use as a measure of health outcome. 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 (5L) 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.

The 5 questions will be summarized descriptively as categorical variables per substudy and cohort for all visits where the EQ-5D (5L) is collected. Each dimension and the VAS will be summarized as a continuous variable using descriptive statistics for the scores, change from baseline and percent change from baseline for all visits where the EQ-5D (5L) is collected. In addition, at C5D1, the change from C3D1 at C5D1 and the percentage change at C5D1 from C3D1 will also be reported. The minimally important change from baseline at C3D1 and change from C3D1 at C5D1 will be determined using the two methods detailed in Section 6.6.1. Missing scores will not be included in summary statistics and only subjects with both an observation at the specified visit and at baseline will be included in change from baseline summaries.

6.6.3. EORTC QLQ-C30

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 (PF), role (RF), emotional (EF), cognitive (CF) and social (SF)), 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 from 1 (very poor) to 7 (excellent). The other items are scored on a 4-point scale from 1 (not at all) to 4 (very much). A high score for a functional scale represents a high/healthy level of functioning. A high score for the global health status represents a high QoL. However, a high score for a symptom scale/item represents a high level of symptomatology/problems. The scoring method is outlined in Table 9 and the following paragraphs.

Table 9: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range	Version 3.0 Item numbers	Function scales
Global health Status /QoL	QL	2	6	29, 30	
Functional Scales					
Physical functioning	PF	5	3	1 to 5	F
Role functioning	RF	2	3	6,7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social function	SF	2	3	26, 27	F
Symptom scales/items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14,15	
Pain	PA	2	3	9, 19	
Dyspnea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

Raw score (RS) is calculated as the average of item score when at least half of the items are not missing. A linear transformation to 0–100 will then be applied to get the score (S) using the item range provided in Table 9.

For functional scales S = (1-(RS-1)/range) x 100

For symptom scales/items and global health status S = ((RS-1)/range) x 100

Each scale will be summarized at each visit as a continuous variable using descriptive statistics per substudy and cohort for the total scores, change from baseline and percent change from baseline for all visits where the EORTC QLQ-C30 is collected. In addition, at C5D1, the change from C3D1 at C5D1 and the percentage change at C5D1 from C3D1 will also be reported. For each of the functional scales, the minimally important change from baseline at C3D1 and change from C3D1 at C5D1 will be determined using the two methods detailed in Section 6.6.1.

6.6.4. FACT-BI

The FACT-BI is an 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 FACT-General (FACT-G) score and the

FACT-BI total score (FACT-G and the bladder cancer specific scale). The items are scored on a 5-point scale from 0 (not at all) to 4 (very much).

FACT-BI scores are derived by recording the answers in the item response column, performing reversals as indicated and then summing individual items to obtain a score. This is then multiplied by the number of items in the subscale and divided by the number of items answered, this produces the subscale score. A higher score indicates higher quality of life.

Table 10: Scoring FACT-BI (Version 4.0)

Subscale	Item Code	Reverse Item
Physical Well-Being (PWB)	GP1	Yes
	GP2	Yes
Score range: 0–28	GP3	Yes
	GP4	Yes
	GP5	Yes
	GP6	Yes
	GP7	Yes
Social/Family Well-Being (SWB)	GS1	No
	GS2	No
Score range: 0–28	GS3	No
	GS4	No
	GS5	No
	GS6	No
	GS7	No
Emotional Well-Being (EWB)	GE1	Yes
	GE2	No
Score range: 0–24	GE3	Yes
	GE4	Yes
	GE5	Yes
	GE6	Yes
Functional Well-Being (FWB)	GF1	No
	GF2	No
Score range: 0–28	GF3	No
	GF4	No
	GF5	No
	GF6	No
	GF7	No
Bladder Cancer Subscale	BL1	Yes
Score range: 0–48	C2	Yes
	C3	No
	BL2	Yes
	C5	Yes
	C6	No
	C7	No
	BL3	Yes
	BL4	No
	BL5	No
	C8	Yes
	C9	Yes

Each subscale, FACT-G and FACT-BI will be summarized as a continuous variable using descriptive statistics per substudy and cohort for the total scores, change from baseline and percent change from

baseline for all visits where the FACT-BI is collected. In addition, at C5D1, the change from C3D1 at C5D1 and the percentage change at C5D1 from C3D1 will also be reported. For each of the functional scales, the minimally important change from baseline at C3D1 and change from C3D1 at C5D1 will be determined using the two methods detailed in Section 6.6.1.

6.6.5. G-SET

G-SET is a patient-rated change in health between two time periods using a five-point ordinal scale. The response consists of a single question regarding health rating compared to 6 weeks previous. G-SET will be provided after 6 weeks (at Cycle 3 Day 1) and 12 weeks (at Cycle 5 Day 1). The responses at each time point will be summarised as a categorical variable. All G-SET data will be listed.

6.7. 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. Full details of the IDMC's roles and responsibilities are outlined in the IDMC charter.

6.8. Changes to Methods Planned in the Protocol

The planned Inverse Probability of Censoring Weighted (IPCW) modelling approach (Rimawi 2012) for crossover patients will not be undertaken due to low sample size of crossover patients.

7. Tables, Listings, And Figures

7.1. Programming Guidelines

Computer-generated output will adhere to the following specifications. The standard operating procedures (SOPs) of [redacted] will be followed in the creation and quality control of all tables, listings and figures.

7.1.1. Format of Output

Unless otherwise specified, all computer-generated output should be produced in landscape mode. Required margins: 3.36cm on top (the binding margin [or left for portrait output]), 2.11cm on right, 3.65cm on left, and 3.3cm on bottom. Courier New 8 pt font will be used for all outputs. All output should have the Sponsor name, protocol number, the type of delivery, and page number. Tables/listings/figures should be internally paginated in relation to total length (i.e., page number should appear sequentially as page n of N, where N is the total number of pages in the table). All output should have the following header at the top of the page:

Sponsor Name Protocol XXXXXXX	Confidential	Data Cut Off Date: ddmmmyyyy Page n of N

1. Output numeration will conform to International Conference on Harmonization (ICH) recommendations. When applicable, the final number will indicate the substudy the output applies to, e.g. 14.1.1.1 would indicate output for substudy 1 and 14.1.1.2 would indicate output for substudy 2. In this case, the study population should be identified immediately following the title in the format Substudy X – Analysis Population.
2. Column headings should be in initial upper-case characters.
3. For numeric variables, include “unit” in column or row headings where appropriate.
4. Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table.
5. If the categories are not ordered (e.g., race), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
6. An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
7. Listings should be sorted by substudy, cohort/dose level and patient numbers.
8. In a listing, display the patient number only once for the patient with multiple records. If a patient’s records run into multiple pages, display the patient number once for every page.

7.1.2. Format of Data

1. Unless otherwise specified for continuous variables, the estimated mean, median, Q1 and Q3 for a set of values should be printed out to 1 more significant digit than the individual units of measurement. Standard deviation will be printed out to 2 more significant digits than the individual units of measurement. The minimum and maximum should report the same significant digits as the original values.

2. Data in columns of a table should be formatted as follows:
    - Alphanumeric values are left-justified.
    - Whole numbers (e.g., counts) are right-justified.
    - Numbers containing fractional portions are decimal aligned.
3. Unless otherwise specified, percentage values should be printed with 1 digit to the right of the decimal point (e.g., 12.8%, 5.4%). Less-than signs "<0.1%" should be printed when values are >0.0 and <0.1% (not 0.0%).
4. Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A," with the footnote "N/A = not applicable," whichever is appropriate.
5. Dates should be printed in SAS DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
6. Time should be printed in SAS TIME5.format ("HH:MM": 17:30). Missing portions of time should be represented on patient listings as dashes (--:30). Times that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

7.2. Table of Contents for Tables, Listings and Figures

Tables, listings and figures shells are specified in a separate document.

8. References

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