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CLINICAL STUDY PROTOCOL

DZB-CS-202

Derazantinib

A Phase 1b/2 study of derazantinib as monotherapy and combination therapy with paclitaxel, ramucirumab or atezolizumab in patients with HER2-negative gastric adenocarcinoma harboring *FGFR* genetic aberrations (FIDES-03)

Protocol number / Version:	DZB-CS-202 / Version 5.0
Compound:	Derazantinib
Phase of development:	1b/2
IND number:	146726
EudraCT number:	2019-004505-27
Date:	21 May 2021
Project Physician:	[redacted]
Clinical Pharmacologist:	[redacted]
Project Statistician:	[redacted]
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487, PO Box, 4005 Basel, Switzerland

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Protocol synopsis

TITLE:	A Phase 1b/2 study of derazantinib as monotherapy and combination therapy with paclitaxel, ramucirumab or atezolizumab in patients with HER2-negative gastric adenocarcinoma harboring *FGFR* genetic aberrations (FIDES-03)
PROTOCOL NUMBER:	DZB-CS-202 / Version 5.0
SPONSOR:	Basilea Pharmaceutica International Ltd, Switzerland
STUDY PHASE:	1b/2
INDICATION:	Gastric cancer
IND NUMBER:	146726
EUDRACT NUMBER:	2019-004505-27
DATE:	21 May 2021

STUDY DESIGN

Design and investigational products

This study is an open-label, multiple-cohort, multicenter study of derazantinib – a potent and well tolerated fibroblast growth factor receptor (FGFR) inhibitor of tyrosine kinases of FGFR 1, 2, and 3 – as monotherapy and combination therapy with paclitaxel, ramucirumab, or atezolizumab in patients with human epidermal growth factor receptor 2 negative ($HER2^{neg}$) adenocarcinoma of the stomach or gastro-esophageal junction harboring *FGFR2* gene fusions or other rearrangements ('$FGFR2^{fus}$'), high-level *FGFR2* gene amplifications ('$FGFR2^{high\text{-}amp}$'; i.e., a quantitative correlate of > 10 *FGFR2* gene copy numbers called by the NGS algorithm of the central diagnostic test), or *FGFR1–3* mutations ('$FGFR1–3^{mt}$'). These gene abberations are collectively described in this protocol as '$FGFR^{fus/amp/mt}$'.

As of Protocol Version 5.0, this study has been modified to explore two dosing regimens of derazantinib: 300 mg once daily (QD) and 200 mg twice daily (BID).

The study comprises three substudies:

- **Substudy 1:** A Phase 2a study comprising two cohorts:
  - ***Cohort 1.1*** $FGFR2^{fus}$ / $FGFR2^{high\text{-}amp}$ patients to be treated with 300 mg QD derazantinib
  - ***Cohort 1.2*** $FGFR1–3^{mt}$ patients to be treated with 300 mg QD derazantinib
  - ***Cohort 1.3*** $FGFR^{fus/amp/mt}$ patients to be treated with 200 mg BID derazantinib
- **Substudy 2:** A Phase 1b/2 study of patients to be treated with derazantinib-paclitaxel-ramucirumab[1] in combination
- **Substudy 3:** A randomized controlled Phase 2b study comprising four cohorts:
  - ***Cohort 3.1*** Patients to be treated with derazantinib (test)
  - ***Cohort 3.2*** Patients to be treated with derazantinib-paclitaxel-ramucirumab[1] in combination (test)

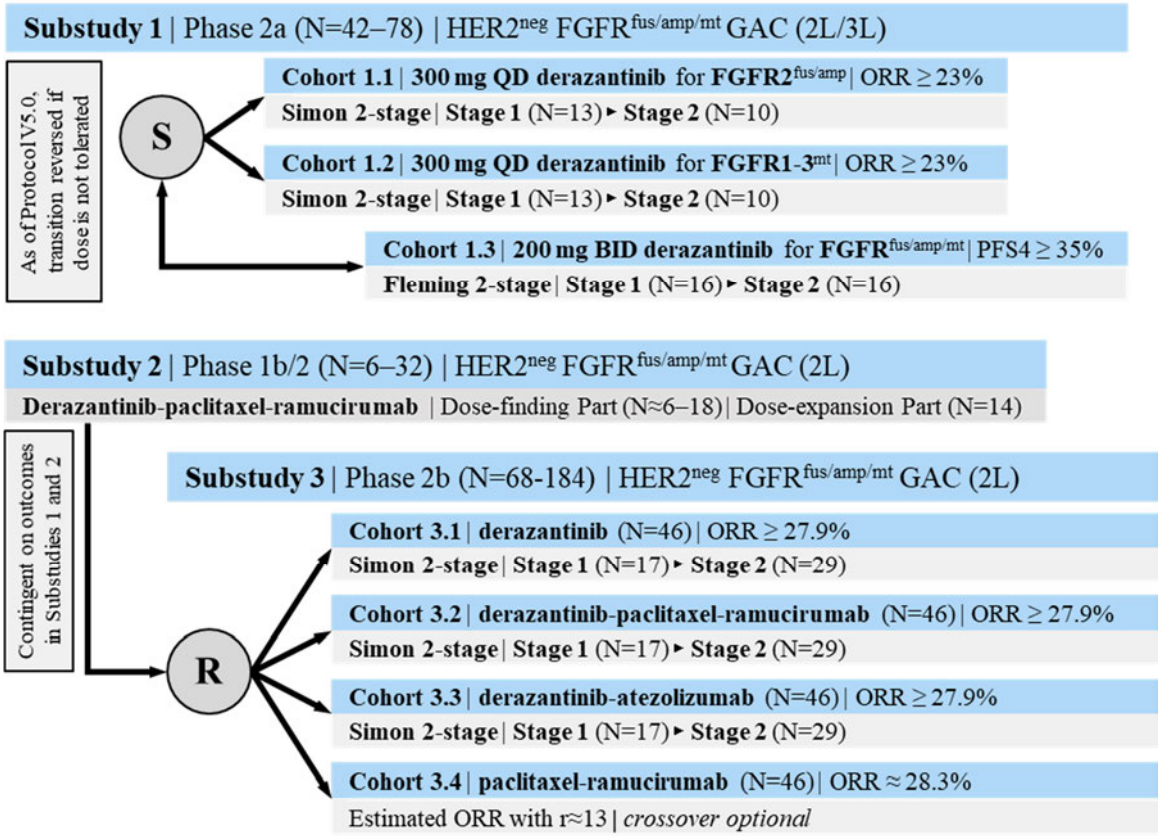
[1] A combination of either derazantinib-paclitaxel or derazantinib-ramucirumab may be explored if the combination of derazantinib-paclitaxel-ramucirumab exceeds the preset toxicity threshold of 33% dose-limiting toxicities (DLTs).

– ***Cohort 3.3*** Patients to be treated with derazantinib-atezolizumab in combination (test)

– ***Cohort 3.4*** Patients to be treated with paclitaxel-ramucirumab in combination (control)

An overview of the study design is provided in Figure 1.

Figure 1 Overview of study design



Abbreviations: 2L/3L, second/third-line; BID, twice daily; CR/PR, complete/partial response as per RECIST 1.1; $FGFR^{fus/amp/mt}$, tumor status with *FGFR2* gene fusion or rearrangement / amplification, or *FGFR1–3* mutation; $FGFR2^{fus}$, *FGFR2* fusion / rearrangement; $FGFR2^{high\text{-}amp}$, high-level *FGFR2* gene amplification; $FGFR1–3^{mt}$, *FGFR1–3* mutations; GAC, for either recurrent, locally advanced or metastatic gastric adenocarcinoma; $HER2^{neg}$, negative HER2 tumor status; ORR, objective response rate; p, probability (of response); pts, patients; QD, once daily; R, randomization; r_1/r_2, response(s) observed during stage 1 (r_1) and by the end of the cohort (r_2), respectively; S, stratification by genetic aberration.

Patient population

The study enrolls patients with either metastatic or recurrent locally-advanced *HER2*-negative ($HER2^{neg}$) adenocarcinoma of the stomach or gastro-esophageal junction (gastric adenocarcinoma [GAC]) inoperable at the time of screening, and radiologically-confirmed disease progression after one (Substudies 2 and 3) or one or two (Substudy 1) standard treatment regimens. The safety cohorts of Substudy 2 comprise GAC patients considered fit to tolerate the novel combination adding derazantinib to the second-line standard-of-care treatment paclitaxel-ramucirumab.

Tumor molecular testing for eligibility
Molecular eligibility for enrollment will be established by a positive test result for FGFR$^{fus/amp/mt}$. The molecular test is to be based on NGS of either tumor tissue DNA and/or RNA, or plasma cell-free DNA (cfDNA).

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

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

Substudy 1
As of Protocol Version 5.0, this substudy has been modified with the addition of *Cohort 1.3* targeting HER2^{neg} FGFR$^{fus/amp/mt}$ GAC, a population identical to that being investigated in ongoing *Cohorts 1.1* (FGFR2^{fus} or FGFR2$^{high\text{-}amp}$) and *1.2* (FGFR1–3^{mt}) combined to better address medical and operational aspects of study conduct. In *Cohort 1.3*, patients with either metastatic or recurrent locally advanced HER2^{neg} FGFR$^{fus/amp/mt}$ GAC, with radiologically confirmed disease progression after one or two standard treatment regimens are to be treated with derazantinib 200 mg BID. During enrollment into *Cohort 1.3*, enrollment into *Cohorts 1.1* and *1.2* is paused.

Substudy 2
This substudy comprises second-line patients with HER2^{neg} FGFR$^{fus/amp/mt}$ GAC and radiologically confirmed disease progression after one standard treatment regimen, who after Investigator assessment are considered fit (per multidisciplinary tumor board endorsement) to tolerate the novel combination of derazantinib-paclitaxel-ramucirumab and would otherwise be eligible for the second-line standard-of-care treatment paclitaxcel-ramucirumab.

Using a modified 3+3 dose-finding design for the Dose-finding Part followed by a Dose-expansion Part cohort of approximately 14 additional patients to reach 20 efficacy-evaluable patients dosed at the MTD, the Dose-finding Part will assess dose-limiting toxicities (DLTs) and safety to determine the MTD and subsequently the recommended Phase 2 dose (RP2D) of the triple combination of derazantinib-paclitaxel-ramucirumab. If the triple combination is not tolerated at the lowest dose level, a double combination of either derazantinib-paclitaxel or derazantinb-ramucirumab may be explored instead (see Section 3.1.7.2). The rationale for combining derazantinib and paclitaxel-ramucirumab is based on non-clinical data indicating a potential synergistic effect of derazantinib and paclitaxel, possibly linked to the anti-angiogenetic effects attributable to both study drugs.

Sites enrolling patients to both Substudy 1 and 2 will decide which substudy to allocate a prospective study participant to based on eligibility criteria, individual patient and disease status, prior antitumor treatment, and the number of available places on the treatment plan of Substudy 2.

Substudy 3

The design and statistical assumptions applicable to this substudy are contigent on findings from Substudies 1 and 2, and are currently under consideration. Prior to initiation of patient enrollment in this substudy, a protocol amendment may be submitted.

This substudy comprises four cohorts investigating the efficacy of derazantinib monotherapy, derazantinib-paclitaxel-ramucirumab, and derazantinib-atezolizumab, and comparing it to that of paclitaxel-ramucirumab as common control. Second-line patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC will be allocated by randomization following stratification by type of *FGFR* genetic aberration ($FGFR2^{fus}$ or $FGFR2^{high\text{-}amp}$ vs $FGFR1–3^{mt}$) and geographic region (Americas-Europe-Australia vs Asia). A Simon's two-stage design will be used in all test cohorts to investigate the primary objective.

The study rationale is based on non-clinical and clinical data supporting meaningful activity of FGFR inhibition (with and without concurrent paclitaxel administration) in GAC patients carrying *FGFR* genetic aberrations. Derazantinib, as a dual FGFR/CSF1R inhibitor, is hypothesized to bypass tumor-induced immunosuppression, restore T cell activity, downregulate immunosuppressive macrophage activity, and improve susceptibility to therapeutic immune checkpoint blockade using anti-PD-1/PD-L1 antibodies such as atezolizumab. The initiation of Substudy 3 is triggered by the availability of data considered sufficient and robust to support the rationale for monotherapy (*Cohort 3.1*), triple / double combination (*Cohort 3.2*), and the derazantinib-atezolizumab combination (*Cohort 3.3*). .

In *Cohort 3.4*, patients with progressive disease after treatment with paclitaxel-ramucirumab will have the option to crossover to treatment with derazantinib if no standard alternative treatment options are available.

INVESTIGATIONAL PRODUCT(S)

Derazantinib, paclitaxel, ramucirumab, atezolizumab

TUMOR MOLECULAR TESTING FOR ELIGIBILITY

Molecular eligibility for study enrollment will be established by a positive test result for $FGFR^{fus/amp/mt}$ using a next-generation sequencing (NGS) test of either tumor tissue DNA and/or RNA, or plasma cell-free deoxyribonucleic acid (cfDNA). For patients with no access to local NGS testing, central testing will be performed in a laboratory designated by the Sponsor; this "central testing" will be based on NGS testing of cfDNA from a liquid biopsy obtained at Pre-screening. The liquid biopsy is ideally to be obtained after assessment of objective documented progression after prior anti-cancer treatment. For Substudy 3, the scope of eligible *FGFR* genetic aberrations may be modified, taking into consideration any findings obtained from Substudy 1.

For molecular screening, patients are required to sign the study Informed Consent Form (ICF) and are not considered enrolled (i.e., patients are considered to be in pre-screening for the study) until receipt of a positive molecular test result, and second dated patient signature on the ICF.

CLINICAL SCREENING

Upon receipt of a positive test result and after obtaining a dated patient signature in a designated section of the study ICF acknowledging the positive test result and documenting the informed decision to participate in the study, clinical study procedures and any other study-related procedures may be conducted.

The screening window for clinical screening procedures will be 28 days and ensuring sufficient time has elapsed after prior anti-tumor treatment to eliminate interference with study treatment. Taking the required period between prior anti-tumor treatment and initiation of study treatment into consideration, the screening period is recommended to be kept as short as possible to limit the number of patients experiencing clinical deterioration due to their disease progression.

PLANNED NUMBER OF PATIENTS

The planned enrollment is approximately 314 evaluable patients across all three substudies.

NUMBER OF SITES/LOCATIONS

Approximately 85 study sites in the Americas, Europe, Australia, and Asia.

OBJECTIVES

Primary objectives

- ***Substudy 1***
  To evaluate the objective response rate (ORR; *Cohorts 1.1* and *1.2*) and 4-month progression-free survival rate (PFS4; *Cohort 1.3*) of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib monotherapy.
- ***Substudy 2***
  To determine the RP2D of derazantinib-paclitaxel-ramucirumab in combination in patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC.
- ***Substudy 3***
  To evaluate the ORR of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib, derazantinib-paclitaxel-ramucirumab, derazantinib-atezolizumab, or paclitaxel-ramucirumab.

Secondary objectives

- To evaluate the efficacy of the study drugs, as measured by ORR (in *Cohort 1.3* and Substudy 2), and by disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
- To compare the ORR, DCR, DOR, PFS, and OS of patients treated with derazantinib monotherapy, derazantinib-paclitaxel-ramucirumab, and derazantinib-atezolizumab each with that of patients treated with paclitaxel-ramucirumab (derived from data from Substudy 3).
- To characterize the PK profile of derazantinib 200 mg BID monotherapy (and, if applicable, derazantinib metabolites)
- To compare antitumor efficacy in patients treated with derazantinib monotherapy to that of patients treated with derazantinib-paclitaxel-ramucirumab, and derazantinib-atezolizumab as well as patients treated with derazantinib-paclitaxel-ramucirumab compared to that of patients treated with paclitaxel-ramucirumab, as measured by ORR, DCR, DOR, PFS, and OS, to investigate the contribution of derazantinib in combination treatment.
- To assess the safety and tolerability of the study drugs.
- To characterize the pharmacokinetic (PK) profile of derazantinib and paclitaxel when administered in combination.
- To evaluate changes, and assess the minimally important difference, in health-related quality of life (HR-QoL) and symptom response from baseline using the EQ-5D (5L) visual analogue scale (VAS), European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), EORTC Quality of Life Questionnaire-Stomach (QLQ-STO-22), and the Global Self Evaluated Transition (G-SET) / Health Transition Index (HTI).

STUDY DRUG / DOSE / ROUTE / REGIMEN

In Substudies 1 and 2, and in *Cohorts 3.1, 3.2* and *3.4*, a treatment cycle is 28 days.

In *Cohort 3.3*, a treatment cycle is 21 days.

Derazantinib is an investigational drug supplied as 100 mg immediate-release powder-filled capsules for oral administration. The initial dose for patients treated with derazantinib monotherapy in *Cohorts 1.1, 1.2,* and *3.1* will be 300 mg QD, the initial dose for patients treated with derazantinib monotherapy in *Cohort 1.3* will be 200 mg BID. In Substudy 2, the starting dose of derazantinib will be 200 mg QD in combination with ramucirumab and paclitaxel (see Section 3.1.7.2). In Substudy 3, the RP2D of the triple/double combination obtained from Substudy 2 and the RP2D of derazantinib-atezolizumab obtained from study DZB-CS-201 (FIDES-02, NCT04045613) will be used (details on clinical management of combinations are provided in Section 6.1.6). The adoption of the RP2D to be used in Substudy 3 is based on the joint decision of the respective study Independent Data Monitoring Committees (IDMCs) and Investigators in accordance with the IDMC Charter, and with the involvement of qualified Sponsor representatives (see Section 3.1.7.1).

Paclitaxel is an approved medication supplied as a non-aqueous 6 mg/mL solution in multidose vials for dilution with a suitable parenteral fluid prior to intravenous (IV) infusion. The target dose for all patients will be 80 mg/m^2 body-surface area (BSA), administered as a 1-hour IV infusion on D1, D8, and D15 of a 28-day cycle. In Substudy 2, various dose levels of paclitaxel may be investigated.

Ramucirumab is an approved medication supplied as a 10 mg/mL solution in either 10 mL or 50 mL vials. The target (and registered) dose for all patients will be 8 mg/kg body weight, administered as a 1-hour IV infusion on D1 and D15 of a 28-day cycle. In Substudy 2, various dose levels of ramucirumab may be investigated.

Atezolizumab is an approved medication supplied as 1200 mg/20 mL concentrate solution for IV infusion. The dose for all patients will be 1200 mg every 3 weeks (Q3W); with no dose reduction permitted.

KEY INCLUSION CRITERIA

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

1. Informed consent signed by the patient indicating that they understand the purpose of, and procedures required for, the study, and are willing to participate in the study, prior to any study-related procedure.
2. Male or female aged ≥ 18 years.
3. Histologically-confirmed adenocarcinoma of the gastro-esophageal junction or stomach. *Note: Every effort is requested to submit archival tumor tissue samples for correlative and confirmatory diagnostic and biomedical research.*
4. Negative HER2 status obtained from the most recent available tissue sample.
   Note: The HER2 status of GAC patients should be assessed using approved standard protocols, including, but not limited to FISH, chromogenic or silver in situ hybridization (CISH) or immunohistochemistry (IHC), in accordance with institutional standards. Patients with a HER2-positive (HER2^{pos}) status based on either HER2 amplification (by FISH or CISH) or, if FISH/CISH is unavailable, a HER2 IHC score of 3+, are not eligible and should not be tested molecularly for FGFR$^{fus/amp/mt}$ expression.

5. Inoperable[1] recurrent, locally-advanced adenocarcinoma or progressing stage IV adenocarcinoma of the gastro-esophageal junction or stomach, and prior antitumor treatment as specified for each Substudy:
   - **Substudy 1:** Patients with radiographically-documented disease progression after either standard first- or second-line treatment, and no approved treatment alternative.
   - **Substudy 2**: Patients with radiographically-documented disease progression after standard first-line treatment, and per Investigator assessment considered suitable to tolerate the treatment regimen.
   - **Substudy 3:** Patients with objective radiographically-documented disease progression:
     – During, or within 6 months after, administration of the last cycle of adjuvant / neoadjuvant / perioperative chemotherapy (platinum plus fluoropyrimidine with or without anthracycline and/or taxane and/or irinotecan) for locally advanced disease, or
     – During, or any time after, administration of the last cycle of first-line taxane-free chemotherapy (platinum plus fluoropyrimidine with or without anthracycline) for metastatic disease or locally advanced disease.

   Note: If the patient has received prior taxane, a 6-month taxane-free interval after the last administration of taxane-containing treatment needs to be respected.
6. Eligible *FGFR*$^{fus/amp/mt}$ positive test result (see Appendix 1 and Section 3.1.4).
7. Measurable disease as defined by the Investigator using Response Evaluation Criteria in Solid Tumors 1.1 criteria (RECIST 1.1)
8. ECOG PS 0 or 1.
9. Adequate organ functions, as indicated by Screening visit local laboratory values.
10. Men and women of childbearing potential must agree to avoid impregnating a partner or becoming pregnant, respectively, during the study, and for at least 150 days after the last dose of study drug.

KEY EXCLUSION CRITERIA

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

1. Receipt of prior cancer treatment within specific interval periods (see Section 4.3, Exclusion criterion 1).
2. For patients enrolled in Substudy 1, prior treatment with FGFR inhibitors.
3. For patients enrolled in Substudy 2 and 3, prior treatment with
   - Taxanes within 6 months prior to randomization
   - FGFR inhibitors or pathway-targeting agents
   - Anti-VEGF(R) therapeutic antibody or pathway-targeting agents.
4. For patients enrolled in Substudy 3, prior treatment with anti-programmed cell death receptor-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) therapeutic antibody or pathway-targeting agents.

[1] Patients are required to be staged as inoperable at the time of screening in order to avoid interference of any potentially planned surgery with RECIST requirements during the study.

5. Concurrent evidence of clinically significant corneal or retinal disorder likely to increase the risk of eye toxicity, including but not limited to bullous/band keratopathy, keratoconjunctivitis (unless keratoconjunctivitis sicca), corneal abrasion (unless related to trauma), inflammation/ulceration, confirmed by ophthalmological examination.
6. History of clinically significant cardiac disorders: New York Heart Association Class II to IV congestive heart failure, or any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months of the first dose of study drug; concurrent and clinically significant abnormalities on electrocardiogram [ECG] at Screening, including a QT interval corrected by Fridericia's formula [QTcF][1] > 450 ms for males or > 460 ms for females (mean values from triplicate ECGs; see Section 5.3.2.4).
7. Any unresolved (at the time of Screening) clinically-significant Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 toxicity (except for alopecia, Grade 2 platinum-therapy-related neuropathy, and Grade 2 anemia, from previous anti-tumor treatment and/or from medical/surgical procedures/interventions).
8. Known central nervous system (CNS) metastases.

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18. Pregnant or breast feeding.

Applicable to patients considered for enrollment in Substudy 2 or 3

19. Concurrent uncontrolled or active infection with human immunodeficiency virus (HIV; known HIV 1/2 antibodies positive).
20. Active hepatitis B or chronic hepatitis B without current antiviral therapy and HBV DNA ≥ 100 IU/mL.
    Note: Active hepatitis B is defined as a known positive hepatitis B surface antigen (HBsAg) result.
21. Active hepatitis C
    Note: Active hepatitis C is defined by a known positive hepatitis C antibody result and known quantitative hepatitis C virus (HCV) RNA results greater than the lower limits of detection of the assay.
22. Active tuberculosis.
23. Lack of recovery from major surgery after 4 weeks, or major elective surgery is planned during the foreseeable duration of the patient's participation in the study, or placement of a central venous access device within 7 days prior to randomization.
24. Uncontrolled arterial hypertension, with a systolic blood pressure ≥ 150 mm Hg or a diastolic blood pressure ≥ 90 mm Hg despite standard medical management.
25. History of gastrointestinal perforation and/or fistulae within 6 months prior to study entry.
26. History of clinically relevant bleeding disorders, vasculitis, or had a significant bleeding episode from the gastrointestinal tract within 3 months prior to study entry
    Note: Patients with a past gastrointestinal bleeding episode may be considered for enrollment if an upper gastrointestinal endoscopy performed after the bleeding event has demonstrated that the source of gastrointestinal bleed has been identified and the risk of re-bleeding is low.

[1] The averaged QTcF value from a triplicate set of ECGs will be taken for decision making (see Section 5.3.2.4).

27. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered 'significant') during the 3 months prior to randomization.
28. The patient is receiving therapeutic anticoagulation with warfarin, low-molecular weight heparin, or similar agents.
    Note: Patients receiving prophylactic anticoagulation therapy for cancer-associated thrombosis are eligible provided that the coagulation parameters defined in the inclusion criteria (international normalized ratio [INR] ≤ 1.5 and partial thromboplastin time [PTT/aPTT] ≤ 1.5 upper limit of normal [ULN] or prothrombin time [PT] ≤ 1.5 ULN, and PTT/aPTT ≤ 1.5 ULN) are met.
29. The patient is receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs, e.g., indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide). Acetylsalicylic acid (aspirin) is permitted at doses up to 325 mg/day.
30. Child-Pugh B or C liver cirrhosis, or a history of hepatic encephalopathy, hepatorenal syndrome, or clinically-meaningful ascites related to cirrhosis.

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Applicable only to patients considered for enrollment in Substudy 3.

32. Administration of a live, attenuated vaccine within 30 days prior to randomization.
33. Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to first dose of study drug or anticipated requirement for systemic immunosuppressive medications during the study; inhaled, intranasal, intraocular, topical, and intra-articular joint injections are allowed.
34. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
35. History of allogeneic stem cell or solid organ transplantation.

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38. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on Screening chest computed tomography (CT) scan

MAIN STUDY ENDPOINTS

Primary endpoints

In Substudy 1, for *Cohorts 1.1* and *1.2*, the primary endpoint is ORR, as measured by the proportion of patients with confirmed complete response (CR) or partial response (PR) by blinded independent central review (BICR) per RECIST 1.1. For *Cohort 1.3*, the primary endpoint is PFS4, as measured by the proportion of patients alive and free of disease progression by blinded independent central review (BICR) per RECIST 1.1 after the second on-study tumor assessment, i.e., approximately after 4 months of study treatment.

In Substudy 2, the primary endpoint is the RP2D of derazantinib-paclitaxel-ramucirumab in combination, estimated from safety and tolerability according to the aggregate of DLT criteria and adverse event (AE) data, and considering further PK and efficacy data of the combination. If the triple combination is not tolerated at the lowest dose level, the combination of derazantinib and paclitaxel or derazantinib and ramucirumab will be explored instead. In a joint decision, the IDMC, Investigators, and the Sponsor will determine the RP2D.

For all cohorts in Substudy 3, the primary endpoint is ORR, as measured by the proportion of patients with confirmed complete response (CR) or partial response (PR) by blinded independent central review (BICR) per RECIST 1.1. To determine the study population for Substudy 3, the outomes of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib in Substudy 1 are to be analyzed per cohort.

Secondary endpoints
Efficacy, safety and pharmacokinetics of derazantinib will be measured overall and in pre-specified subsets. Secondary endpoints are detailed in Sections 3.2.2.1, 3.2.2.2, and 3.2.2.3.

STATISTICAL ANALYSIS

Key analysis populations

Safety population
All patients who received at least one dose of study drug. Data will be summarized according to the treatment actually received. The Safety population will be used for secondary endpoint analyses and sensitivity analyses.

Intent-to-treat (ITT) population
All patients allocated and/or randomized to treatment, regardless of the administration of the study drug will be used for between-cohort efficacy analyses in Substudy 3, including pooled analyses of Substudy 1 and 3.

Modified ITT (mITT) population for single-arm non-comparison efficacy analyses
All patients who received at least one dose of study drug, 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 died from any cause. The mITT population will be used for all primary single-arm non-comparison efficacy analyses in Substudies 1, 2 and 3.

Analyses

Analysis of the primary endpoint of Cohorts 1.1 and 1.2, and Substudy 3 (ORR)
The primary efficacy endpoint of ORR is defined as the achievement of confirmed CR or PR using RECIST 1.1, as assessed by BICR. Point estimates and confidence intervals (CIs) will be provided. The primary analysis will be performed on the mITT population, and repeated on both the ITT and the Per-protocol (PP) population.

Analaysis of the primary endpoint of Cohort 1.3 (PFS4)
PFS4 will be the proportion of patients who are alive and have no disease progression at the second on-study tumor assessment at approximately 4 months from the first date of receiving study drug as assessed by survival status and response status using RECIST 1.1, as assessed by BICR. The 4-month analysis is intended to support the two-stage design, and PFS in general will a key secondary endpoint to determine the anti-cancer efficacy of derazantinib in the indication. The primary analysis for PFS4 will be performed on the subset of the mITT population who fulfilled the minimum exposure requirement (relative dose of > 0.50) until the second on-study tumor imaging assessment, or who experienced progression before the minimum exposure requirement.

Analysis of the primary endpoint of Substudy 2
Dose-limiting toxicities within the DLT interval (i.e., the first 28 days of the first treatment cycle) will be analyzed in the MTD Part population to determine whether derazantinib-paclitaxel-ramucirumab in combination is considered safe and tolerable (for details see Section 8.2.5 and 8.2.6). The MTD is defined as the highest dose level at which < 33% of patients experience a DLT.

If the triple combination is not tolerated at the lowest dose level, the double combination of derazantinib and paclitaxel or derazantinib and ramucirumab will be explored.

The Dose-finding Part is followed by enrollment of a Dose-expansion Part cohort of approximately 14 additional patients in order to reach 20 efficacy-evaluable patients dosed at the MTD.. The RP2D will be determined by a joint decision taken by the IDMC, Investigators, and the Sponsor after reviewing the aggregate of DLT and AE data, and considering further PK, efficacy, and PD data of the combination and potential toxicity-response modeling.

Analysis of secondary endpoints

Progression-free survival

Next to ORR as the primary endpoint, progression-free survival (PFS) is a key secondary endpoint, and is to be measured from patient enrollment to the first date of objectively measured radiographic progression by RECIST 1.1 (the recorded progression date [PD date]), or the date of death from any cause, whichever occurs first. Progression-free survival will be summarized using Kaplan-Meier methods and compared between groups using a log-rank test at a one-sided 5% alpha level (ITT and mITT poulations).

The censoring date for a patient with no documented progression before data cutoff or dropout is defined as the date of the last tumor assessment with no documented progression. Further sensitivity analyses will be specified in the Statistical Analysis Plan to assess the impact of the censoring rules applied.

Comparison of experimental treatment and common control

The comparisons of the efficacy of derazantinib, derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab with that of either derazantinib monotherapy or paclitaxel-ramucirumab, as measured by ORR and PFS, will be investigated. For the comparison between derazantinib and paclitaxel-ramucirumab for ORR and PFS, the ITT populations of the completely enrolled cohorts of Substudy 3 will be used, and completely enrolled cohorts of Substudy 1 and Substudy 3 will be combined for additional analyses. The comparisons of derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab in combination with that of either derazantinib monotherapy or paclitaxel-ramucirumab will be performed in the Substudy 3 ITT population.

Other secondary endpoints

Disease control rate (and ORR for Substudy 2) will be summarized in the same way as the primary endpoint. Duration of response (mITT population) and OS analyses (ITT population) will be performed using Kaplan-Meier methods. The analysis will be repeated on the PP population. Subgroup analyses within Substudies 1 and 3 will be performed according to the stratification factors.

ASSESSMENTS

Pharmacokinetics

Derazantinib (and any identified derazantinib metabolite) plasma concentrations will be measured in plasma samples. Concentrations at each nominal time point and all relevant PK parameters (maximum plasma concentration [C_{max}], time to peak [maximum] plasma concentration [t_{max}], area under the plasma concentration-time curve from 0 to 12 [$AUC_{0–12}$] and from 0 to 24 hours [$AUC_{0–24}$], AUC from time 0 to the last measurable concentration [AUC_{last}]) will be summarized using descriptive statistics.

In the paclitaxel-ramucirumab PK population, paclitaxel plasma concentrations and ramucirumab serum concentrations will be summarized at each nominal time point using descriptive statistics. Relevant PK parameters for paclitaxel (C_{max}, t_{max}, $AUC_{0–24}$, AUC_{last}, $t_{1/2}$, AUC_{inf}, T> 0.05) will be summarized using descriptive statistics.

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

Safety/tolerability
AE monitoring will be performed on an ongoing basis throughout the study, with severity graded according to the guidelines outlined in the CTCAE Version 5.0 (CTCAE 5.0). AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), and grouped by System Organ Class and Preferred Term. The incidence of treatment-emergent AEs (TEAEs) will be presented, including serious AEs (SAEs), AEs by severity, AEs by relationship to study drug, discontinuation of patients from study therapy due to AEs, and deaths. Additional safety summaries will be provided for safety laboratory tests, vital signs, ECGs, physical examinations, ophthalmology examinations, and ECOG PS.

Efficacy
Tumor response using RECIST 1.1 will be summarized by cohorts, and summarized using descriptive statistics and two-sided 90% CIs. Actual values and changes from baseline in tumor burden will be summarized by time point. PFS, DOR, and OS will be summarized using Kaplan-Meier analysis, including the number and percentage of patients with events, and the number of censored patients.

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

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(i)CPD[1]	Confirmed progressive disease
(i)CR[1]	Complete response
(i)PR[1]	Partial response
(i)RECIST[1]	Response Evaluation Criteria In Solid Tumors
(i)SD[1]	Stable disease
(i)UPD[1]	Unconfirmed progressive disease
ACRG	Asian Cancer Research Group
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	AE of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BICR	Blinded independent central review
BS	Bone scan
BSA	Body-surface area
Bx	Biopsy
cfDNA	Cell-free DNA
CI	Confidence interval
CIN	Chromosomal instability
CISH	Chromogenic or silver in situ hybridization
CL_{CR}	Creatinine clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRP	C-reactive protein
CSF1R	Colony-stimulating factor-1 receptor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA

[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.

C*x*D*x*	Cycle (cycle number), Day (day number), e.g. C4D1 = Cycle 4, Day 1
CYP	Cytochrome-P450
CyTOF	Cytometry by time of flight
D0	Pretreatment phase
DCR	Disease control rate
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
D*x*	Day (day number)
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMT	Epithelial-mesenchymal transition
EORTC	European Organization for Research and Treatment of Cancer
ERK	Extracellular signal-regulated kinase
ESMO	European Society of Medical Oncology
EU	European Union
FFPE	Formalin-fixed paraffin-embedded
FGFR	Fibroblast growth factor receptor
$FGFR^{fus/amp/mt}$	*FGFR2* gene fusion, rearrangement or amplification, or *FGFR1–3* mutation
$FGFR1–3^{mt}$	*FGFR1–3* mutation
$FGFR2^{fus}$	*FGFR2* gene fusion or rearrangement
$FGFR2^{high-amp}$	High-level *FGFR2* gene amplification
FISH	Fluorescence in-situ hybridization
FSH	Follicle stimulating hormone
fT3	Tri-iodothyronine
fT4	Thyroxine
GA	Genetic aberration
GAC	Gastric adenocarcinoma
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP3	Good Publication Practice

G-SET / HTI	Global Self Evaluated Transition / Health Transition Index
H0	Null hypothesis
HA	Alternative hypothesis
HBsAg	Hepatitis B surface antigen
hCG	Local serum pregnancy test
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
$HER2^{neg}$	*HER2*-negative
$HER2^{pos}$	*HER2*-positive
HIV	Human immunodeficiency virus
HR	Hazard ratios
HR-QoL	Health-related quality of life
IB	Investigator's Brochure
IC_{50}	50% inhibition
iCCA	Intrahepatic cholangiocarcinoma
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISF	Investigator Site File
ITT	Intent-to-treat
IV	Intravenous(ly)
JAK	Janus kinase
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
mITT	Modified intent-to-treat
MMR-D	Mismatch repair-deficient
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSS	Microsatellite stable
MTD	Maximum tolerated dose

mTOR	Mammalian target of rapamycin
n	Number
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NGS	Next-generation sequencing
OCT	Ocular coherence tomography
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death receptor-1
PDGFRβ	Platelet-derived growth factor receptor β
PD-L1	Programmed death ligand-1
PDX	Patient-derived xenograft
PE	Polyethylene
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Prescribing Information
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic(s)
PO	Orally
PopPK	Population PK
PP	Per protocol
PRO	Patient-reported outcome
PS	Performance status
PT	Prothrombin time
PTT/aPTT	Partial thromboplastin time
PVC	Polyvinyl chloride
Q*x*W	Every (number) weeks
QALY	Quality-adjusted life-year
QD	Once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-STO22	Quality of Life Questionnaire-Stomach
QOD	Every other day
QTc	Corrected QT interval
QTcF	Difference between QTc corrected by Fridericia's formula
RET	Rearranged during transfection
RNA	Ribonucleic acid
RNAseq	RNA sequencing

RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIAP	Safety interim analysis patients
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOP	Standard Operating Procedure
STAT	Signal transducer and activator of transcription
SUSAR	Suspected unexpected serious adverse reaction
SV	Screening visit
$t_{1/2}$	Elimination half-life
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent adverse event
t_{max}	Time to peak (maximum) plasma concentration
TP53	Tumor protein p53
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein-creatinine ratio
USA	United States of America
UTI	Urinary tract infection
VAS	Visual analog scale
VEGFR	Vascular endothelial growth factor receptor
WBMRI	Whole-body magnetic resonance imaging

1 INTRODUCTION

1.1 Gastric and gastro-esophageal adenocarcinoma

Gastric adenocarcinoma is the most common histological type (~95%) of all stomach malignancies and can originate from the fundus, corpus or antrum of the stomach. Gastro-esophageal adenocarcinomas originate from the cardia and gastro-esophageal junction region and are further anatomically classified by the Siewert-Stein classification (Siewert 1998). Gastric and gastro-esophageal adenocarcinomas (hereafter sub-summarized under 'gastric adenocarcinoma' and abbreviated as GAC) have two major histological phenotypes: the intestinal type with well-to-moderately-well-differentiated histology and the diffuse type with poorly differentiated histology (Ajani 2017, Lauren 1965). A World Health Organization (WHO) classification provides detailed descriptions of histological features and classifies GAC into tubular, papillary, mucinous, mixed and poorly cohesive carcinomas (Bosman 2010).

At the molecular level, The Cancer Genome Atlas (TCGA) has proposed four subtypes: 1) Epstein-Barr virus-positive (EBV^+) tumors; 2) microsatellite instability (MSI)-high tumors; 3) genomically stable tumors; and 4) tumors with chromosomal instability (CIN) (Bass 2014). Although different terminology and somewhat different groupings to the TCGA were used, the Asian Cancer Research Group (ACRG) subtyping generally (but not exactly) validated the TCGA findings and four subgroups: 1) tumors that are microsatellite stable (MSS) and have intact tumor protein p53 (TP53; $MSS/TP53^+$); 2) MSI-high; 3) MSS and expressing epithelial-mesenchymal transition signatures (EMT; MSS/EMT); and 4) MSS and have TP53 mutations ($MSS/TP53^-$). In addition, ACRG provided clinical information: patients with MSI-high or EBV-associated GAC had longer survival than those with the MSS/EMT subtype, and patterns of recurrence suggested that patients with MSS/EMT group tumors had higher rates of recurrence than the MSI-high group (63% versus 23%) and more frequently developed peritoneal metastases (Cristescu 2015). To date, these two classifications have some similarity and may guide novel target therapies to improve unsatisfactory outcomes, although neither has been validated as clinically relevant tools as of now.

1.2 Epidemiology and prognosis of gastric adenocarcinoma

In 2018, there were an estimated 1,033,700 new cases of GAC and 783,000 deaths from the disease worldwide (Bray 2018), making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death. Incidences are 2-fold higher in men than in women, with rates of 32.1 and 13.2 per 100,000 men and women, respectively, in Eastern Asia (eg, in Mongolia, Japan and the Republic of Korea [the country with the highest rates worldwide in both sexes]). The incidence in Northern America is generally low with rates of 5.6 and 2.8 per 100,000 men and women, respectively (Bray 2018). There is a notable difference across Europe with incidence rates lowest in Northern Europe (6.2 and 3.1 per 100,000 men and women, respectively) increasing to 8.2/3.7, 10.4/5.0 and 17.1/7.5 per 100,000 men and women in Western, Southern and Eastern Europe, respectively (Bray 2018).

While early stage GAC is associated with a 5-year survival rate of up to 95% (Crew 2006), advanced-stage GAC (which cannot be surgically treated) has a median survival of ~9–10 months (Ajani 2016). Despite improvements in endoscopic, surgical and systemic treatments the global 5-year survival rates remain unsatisfactory (~25–30%; Verdecchia 2007), with the exception of those in Japan and South Korea (> 50%; Torre 2016), a difference that can be attributed to early detection efforts in these Asian countries.

1.3 Systemic therapy of advanced-stage or metastatic gastric adenocarcinoma

Only patients with early stage disease and deemed medically fit are considered candidates for surgical procedures with curative intent. Patients with surgically unresectable GAC (or deemed unfit for surgery), and all patients with metastatic disease are candidates for conventional chemotherapy consisting of a platinum compound (with oxaliplatin preferred over cisplatin) and a fluoropyrimidine (oral or intravenous) (Ajani 2016, Smyth 2016a). Three-drug chemotherapeutic regimens and the use of epirubicin are discouraged (Ajani 2016, Elimova 2017, Smyth 2016a). Trastuzumab (an anti-human epidermal growth factor receptor 2 [HER2] antibody) is recommended with chemotherapy in the first-line setting for patients with $HER2^{pos}$ GAC (Bang 2010). From a scientific and medical perspective, ramucirumab (an anti-vascular endothelial growth factor receptor [VEGFR] 2 antibody) plus paclitaxel is recommended as a standard second-line treatment (Wilke 2014); single-agent ramucirumab may be used as a salvage treatment (Fuchs 2014). The cost-effectiveness of the combination of paclitaxel and ramucirumab has been questioned (Hall 2016a, Lam 2017, Saito 2017), which led to variable reimbursement decisions. For patients with *HER2*-negative ($HER2^{neg}$) metastatic GAC, the most widely recommended first-line regimen is fluoropyrimidine and platinum, and the most widely recommended second-line regimen is the combination of paclitaxel and ramucirumab. Per European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines for the treatment of gastric cancer, there is evidence and consensus for second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab (either as a single agent or in combination with paclitaxel) for patients who are of Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–1 (Ajani 2016, Smyth 2016a).

Given the propensity for tumors to develop resistance, the role of taxanes as a first-line treatment option is under debate, however, from a global perspective, taxanes are usually reserved for second-line treatment after failure of first-line treatment for metastatic disease or disease progression within 6 months of (neo)adjuvant or perioperative treatment (including radiotherapy in some regions). Given the sometimes preserved susceptibility of some tumors to repeated taxane-challenge, some Investigators have adopted the possibility to re-expose patients to taxane treatment under certain considerations and criteria for patient predisposition, even though this approach has not been systematically investigated (Ghosn 2016).

1.4 Molecular targets for targeted treatment of gastric adenocarcinoma

At the molecular level, four subtypes have been proposed by TCGA and ACRG (Cristescu 2015, Bass 2014). Of these subtypes, CIN (50% of all GACs) and MSS/TP53^{-} (36% of all GACs) tumors frequently harbor molecular aberrations in receptor tyrosine kinases (RTKs) and some of their signaling molecules are common in GACs (Bass 2014, Riquelme 2015, Elimova 2015, Ajani 2017). RTK amplifications are caused by chromosomal instability, whereby deoxyribonucleic acid (DNA) breaks lead to gene amplifications (Tanner 2005). Targeted therapies against these RTKs using either small-molecule inhibitors or antibodies have been extensively developed and tested in non-clinical and clinical trials. Although clinical outcomes for most have been disappointing (Ajani 2017), targeted therapies against HER2, VEGFR and related kinases have shown modest benefits (Bang 2010, Wilke 2014, Fuchs 2014, Li 2016). Interestingly, HER2 amplifications and fibroblast growth factor receptor 2 (FGFR2) gene rearrangement / amplification appear to be almost completely mutually exclusive as previously reported (Das 2014) and per a recent search in Foundation Medicine's FoundationInsight™ database (Basilea data on file, FoundationInsights™, 2020).

The RAINBOW trial was the landmark trial that established the role of ramucirumab, a monoclonal antibody inhibiting VEGFR2, as a valuable addition to second-line treatment for GAC patients. The RAINBOW trial, a double-blind, phase III, randomized trial, indicated that the addition of ramucirumab to paclitaxel resulted in a significant survival advantage when compared with paclitaxel monotherapy, with a median overall survival (OS) of 9.6 months ([95% confidence interval (CI): 8.5-10.8] versus 7.4 months [95%CI: 6.3-8.4], hazard ratio [HR] = 0.807 [95%CI: 0.678-0.962], p = 0.017); progression-free survival (PFS) of 4.4 months versus 2.9 months (HR = 0.635, p < 0.0001) and an objective response rate (ORR) of 28% versus 16% (p < 0.0001) (Wilke 2014). Combination therapy also resulted in an increased incidence of adverse events (AEs) including neutropenia (but not febrile neutropenia) and hypertension, but global quality of life scores were similar in both treatment arms, attesting to the tolerability of adding the anti-angiogenic agent (Wilke 2014).

1.5 FGFR inhibition in gastric adenocarcinoma

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

1.5.1 Current clinical evidence

Among several druggable molecular alterations found in GAC, amplification and/or overexpression of the *FGFR2* gene have elicited continued interest for target therapy of GAC (Van Cutsem 2017, Pearson 2016, Smyth 2016b, Lee 2016, Bang 2015). This is despite results from a recent randomized Phase 2 study that demonstrated that the monotherapy with an FGFR inhibitor (AZD4547) was not superior to paclitaxel with regard to progression-free survival of patients with any *FGFR2* amplification or polysomy (Van Cutsem 2017, Pearson 2016). Data from an accompanying translational research

effort, however, indicated that the strategy for patient stratification for AZD4547 treatment may not have been optimal (Pearson 2016). Using cell lines and patient-derived xenograft (PDX) models, the translational clinical study showed that only high-level *FGFR2* amplification (i.e., a ratio of *FGFR2* gene to chromosome-10 centromer signals > 5) initiates a distinct oncogene addiction phenotype, characterized by FGFR2-mediated transactivation of alternative receptor kinases and bringing phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signaling under FGFR control (Pearson 2016). Further independent studies using the selective covalent FGFR inhibitor TAS-120 and the antibody-dependent cellular cytotoxicity (ADCC)-enhanced, FGFR2b isoform-specific monoclonal antibody bemarituzumab (FPA144) reported clinical activity in patients with high-level *FGFR2* amplification (Kuboki 2017) and high FGFR2b expression (Catenacci 2017), respectively.

1.5.2 Derazantinib

Derazantinib is an FGFR1–3 inhibitor with potential activity against other kinases. In biochemical studies, derazantinib showed potent activity against both wild-type and variants of the FGFR kinases (*FGFR1–3*), with inhibitor concentration values required for 50% inhibition (IC_{50}) in the low nM range. Less activity, but within 2–10 fold of FGFR2 activity (IC_{50} of 5.2 nM), was observed for a number of other kinases relevant to anti-tumor treatment, i.e., VEGFR2, platelet-derived growth factor receptor β (PDGFRβ), KIT, rearranged during transfection (RET), colony-stimulating factor-1 receptor (CSF1R), and the Src family kinases (Hall 2016b).

With regard to the study treatment and drug combinations investigated in this study, it should be noted that derazantinib also has an IC_{50} of 31.7 nM for VEGFR2 (with a VEGFR2-to-FGFR2 ratio of 6) and an IC_{50} of 16.2 nM for CSF1R (with a CSF1R-to-FGFR2 ratio of 3). In addition, CSF1R kinase inhibition seems to be a unique characteristic of derazantinib among FGFR inhibitors (Basilea, data on file, 2019). Structural CSF1R kinase inhibition seems to be a unique characteristic of derazantinib among FGFR inhibitors (Basilea, data on file, 2019). Structural analyses suggest that conformations of FGFR and CSF1R-structures are such that derazantinib can efficiently occupy the CSF1R kinase sub-pocket as well as the adenosine triphosphate (ATP)-binding site of both FGFR and CSF1R (Basilea, data on file, 2019). Derazantinib reduced ligand-stimulated phospho-CSF1R in mouse macrophages in a concentration-dependent manner, with a maximum effect similar to the CSF1R inhibitor BLZ945 (Li 2019).

In an autophosphorylation assay, derazantinib inhibited autophosphorylation of FGFR1 and FGFR2 in a dose-dependent manner, suggesting that, in addition to inhibiting the active (phosphorylated) form of the kinase, derazantinib binds to the unphosphorylated or inactive form of the kinase and delays its activation. Across a large panel of 90 human tumor cell-lines, IC_{50}s for inhibition of proliferation ranged from 0.01–20 µM, with the more sensitive lines being associated with high FGFR expression (1/2/3) or specific activating mutations. Non-clinical studies demonstrated potent inhibition of tumor growth in FGFR pathway-activated models, including in FGFR-driven (amplification/fusion/mutation) tumor xenografts grown subcutaneously in nude mice (Hall 2016b, Basilea data on-file).

In PDX models, a similar distinct oncogene addiction phenotype, characterized by *FGFR2* gene fusions has been observed. Gastric cancer PDX models with *FGFR2* gene fusions showed a strong response to derazantinib characterized by regressions of more than 50%, which was consistent across all fusion-carrying models. PDX models as well as cell lines with *FGFR2* amplification also responded to some extent, and response seemed to be associated with concurrent gene expression, while no correlation between amplification and gene expression was noted, which was consistent with previous reports (Pearson 2016). Models with other *FGFR* genetic aberrations (including *FGFR1, 2* or *3* mutations) showed variable responses to treatment with derazantinib (Basilea data on file, 2019), sufficient to warrant clinical investigation.

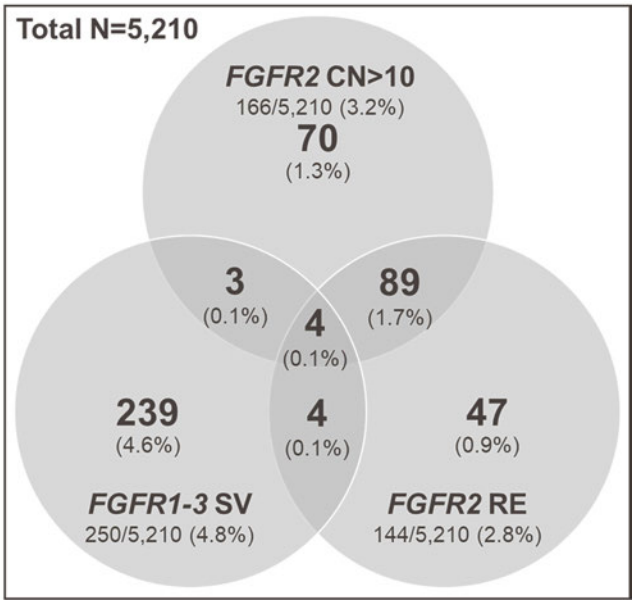
As outlined in Appendix 1, *FGFR2* gene fusions or other rearrangements with breakpoints up- or downstream of the kinase domain will include in-strand and in-frame fusions, as well as those rearrangements likely to be a functional event but with insufficient data for a fusion call by the NGS test algorithm. Also included will be *FGFR2* in-gene rearrangements (translocations, deletions, truncations, splice site variants) as well as nonsense variants C-terminal of the TK domain (exon 17 and downstream). For high-level *FGFR2* gene amplification, the quantitative correlate of > 10 *FGFR2* gene copy numbers called by the NGS algorithm of the central diagnostic test will be considered for enrollment to reflect the findings of translational clinical studies in gastric cancer specimens (Pearson 2016). For small variants in *FGFR1–3* ('FGFR1–3^{mt}'), missense point mutations (single base substitutions) other than known inactivating substitutions, in-frame deletions, and insertions, will be included. Patients with GAC harboring nonsense variants and frame shifts either in or upstream of the kinase domain will be excluded.

As shown in Figure 2, it is estimated that approximately 9% of patients with advanced or metastatic gastric cancer have an *FGFR2* gene fusion or rearrangement ('FGFR2^{fus}'), high-level *FGFR2* gene amplification ('FGFR2$^{high\text{-}amp}$'), and/or small variants (i.e., mutations) in either *FGFR1*, *2* or *3* (FGFR1–3^{mt}) annotated as functional genetic aberrations, hereafter collectively summarized as 'FGFR$^{fus/amp/mt}$' (Basilea data on file 2020, FoundationInsights™, January 2020, Pearson 2016, Helsten 2016, Das 2014, Su 2014, Liu 2014, Ahn 2016, Van Cutsem 2017). Some studies suggest an adverse prognostic impact of *FGFR2* signalling (Kim 2019, Ahn 2016), supporting a clinical role for therapeutic *FGFR* targeting. Based on a recent search in FoundationInsights™, known or likely functional *FGFR2* gene rearrangements, *FGFR2* copy number changes (more than 10 gene copies), or *FGFR1–3* mutations were found at a prevalence of approximately 2.8%, 3.2% and 4.6% of specimens, respectively (Basilea data on file, FoundationInsights™, 2020), among 5,210 largely advanced HER2^{neg} gastric cancer test specimens, supporting data found in various series reported in recent literature as indicated above.

Of note, a majority of cases harboring known or likely functional *FGFR2* gene fusions or rearrangements (93 of 144 cases, 65%) are reported to also harbor high-level *FGFR2* copy number changes (Figure 2), and for both genetic aberrations, non-clinical studies, including studies with derazantinib, have consistently reported susceptibility to FGFR-inhibiting treatment (McSheehy 2020, Chen 2019, Pearson 2016). Consequently, it is hypothesized

that derazantinib may be a suitable treatment option for advanced or metastatic patients with gastric and gastro-esophageal adenocarcinoma harboring *FGFR* genetic aberrations.

Figure 2 Frequency of *FGFR* genetic aberrations in HER2^{neg} gastric cancer



Abbreviations: CN, copy number; RE, fusion or rearrangement; SV, small variant.
Source: Basilea data on file, FoundationInsights™, January 2020.

1.5.3 Combination of derazantinib with either paclitaxel-ramucirumab or atezolizumab

Derazantinib is an investigational drug and is not yet registered in any indication globally.

Paclitaxel itself is not approved for the treatment of patients with GAC but is approved in combination with ramucirumab (Cyramza®) in patients with GAC whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy. In addition, both ESMO and NCCN guidelines consider paclitaxel-ramucirumab as a preferred treatment option for GAC patients whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy (Ajani 2016, Smyth 2016a). The anti-vascular effects and anti-angiogenesis effects of weekly administration of paclitaxel has been comprehensively reviewed (Bocci 2013) and with the approval of ramucirumab, the paradigm of anti-angiogenesis treatment with VEGFR2-blocking compounds has been recommended for the treatment of GAC patients in current EU and U.S. guidelines (Ajani 2016, Smyth 2016a). Of note, derazantinib may provide additional inhibition of VEGFR2 signaling based on its low IC_{50} of 31.7 nM for VEGFR2 (with a VEGFR2-to-FGFR2 ratio of 6), which may augment the treatment effect of the standard paclitaxel-ramucirumab regimen.

Clinical studies have suggested an adverse prognostic impact of FGFR2 signalling (Kim 2019, Ahn 2016). Non-clinical *in vivo* studies using patient-derived gastric cancer xenografts harboring *FGFR2* fusions or rearrangements have suggested a clearly

differential and superior efficacy of derazantinib over that of paclitaxel in these FGFR-driven tumors (McSheehy 2020). These findings support the clinical research approach of challenging paclitaxel as the mainstay of second-line treatment as proposed in Substudy 3, provided that the efficacy-estimating Substudy 1 provides a clinically meaningful efficacy signal in the biomarker-defined patient population.

The rationale for combining derazantinib with paclitaxel is further supported by the findings from non-clinical *in vivo* studies with SNU-16 gastric cancer cell line xenografts in mice, which is known to harbor both *FGFR2* fusions or rearrangements and high-level *FGFR2* amplification. These studies have shown that the combination of paclitaxel at the MTD with derazantinib at approximately half the MTD in a comparative study design clearly and consistently outperformed the efficacy of either drug as monotherapy, suggesting a potential synergistic effect of a paclitaxel-derazantinib combination treatment (Basilea, data on file 2020). The recommended phase 2 dose (RP2D) of the derazantinib-paclitaxel-ramucirumab combination will be established in Substudy 2.

Atezolizumab (Tecentriq®) is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma or metastatic non-small cell lung cancer. In the Phase 3 study DANTE (Al-Batran 2019), atezolizumab is currently being investigated as a perioperative treatment in combination with FLOT chemotherapy (fluorouracil-leucovorin, oxaliplatin and docetaxel) in GAC patients (NCT03421288). The role of adding immune-checkpoint blockade to the treatment armamentarium is currently the subject of extensive clinical research (Moehler 2020, Tabernero 2019).

With regard to derazantinib and from data obtained in comparative kinase screens of known FGFR inhibitors, CSF1R kinase inhibition seems to be a unique characteristic of derazantinib (Basilea, data on file, 2019). In the context of the putative role of CSF1R inhibition to bypass tumor-induced immunosuppression, restore T cell activity, downregulate immunosuppressive macrophage activity and improve susceptibility to therapeutic immune checkpoint blockade using anti-programmed cell death receptor-1 (PD-1)/PD-L1 antibodies (Fleming 2018, Kim 2015, Ries 2014), the dual targeting of immunosuppressive stromal cells via CSF1R and PD-L1 to revert immune escape of tumor cells plus the target therapy of FGFR-driven tumor cells form a rationale to explore the potential benefit of derazantinib-atezolizumab in combination, which is investigated in Substudy 3 under this protocol. Of note, derazantinib may provide clinically meaningful inhibition of CSF1R signaling based on both its low IC_{50} of 16.2 nM for CSF1R (with a CSF1R-to-FGFR2 ratio of 3) and the derazantinib-related reduction of phospho-CSF1R in a concentration-dependent manner observed *in vitro*, which are hypothesized to augment the treatment effect of the immune-checkpoint blockade recently indicated by results from the study KEYNOTE-062 (Tabernero 2019).

The dose for derazantinib-atezolizumab in combination is currently being established in an ongoing Phase 1b study DZB-CS-201 (FIDES-02, NCT04045613).

1.6 Study rationale

1.6.1 Study design rationale

Data from derazantinib studies using PDX models (Basilea, data on file, 2019), together with non-clinical and clinical data from other studies with FGFR inhibitors (Catenacci 2017, Kuboki 2017, Van Cutsem 2017, Pearson 2016), have indicated activity of FGFR inhibiting treatment in target patient populations enriched for FGFR-driven tumors. Combining the potentially beneficial impact of FGFR inhibition (using derazantinib) and dual targeting of immunosuppressive stromal cells via CSF1R (conferred by derazantinib) and PD-L1 (using atezolizumab), the study will also investigate whether the addition of derazantinib to atezolizumab results in a clinical benefit for GAC patients. This study design also takes into consideration that derazantinib may provide sufficient efficacy (McSheehy 2020) to replace a cytotoxic agent like paclitaxel in a patient population defined by FGFR-driven tumors.

Paclitaxel-ramucirumab is the recommended standard-of-care for GAC patients with disease progression after first-line treatment with fluoropyrimidine and a platinum compound. The standard therapy of paclitaxel-ramucirumab is considered a suitable treatment for GAC patients irrespective of the molecular characteristics of the underlying disease. The mode-of-action of both compounds is considered to target the general oncogenic characteristics of proliferation and angiogenesis. In select populations defined by a molecular marker with oncogenic potential that may not be sufficiently targeted by the mechanisms of standard treatment, the approach of using both alternative and additional treatments may provide better and additive, or even synergistic, benefits, This approach is supported by the superior non-clinical efficacy of derazantinib monotherapy over paclitaxel, as well as the activity in FGFR2-driven patient-derived xenografts, and the potential synergistic effect of the derazantinib-paclitaxel combination in a cell line xenograft harboring both *FGFR2* fusions and high-level *FGFR2* amplification. Taken together, this provides the rationale for attempting to provide a well-tolerated effective targeted single-agent treatment, and/or improving the performance of paclitaxel-ramucirumab in GAC patients carrying *FGFR* genetic aberrations.

Recent reports have indicated an anti-angiogenic effect of paclitaxel (Tonissi 2015, Fung 2014, Bocci 2013) in addition to the known anti-proliferative effect. The combination of the anti-angiogenic and anti-proliferative effects of paclitaxel with the growth-inhibiting and potentially additive anti-angiogenic effects of derazantinib may cause synergistic effects to better control disease progression in GAC patients (McSheehy 2020, Basilea data on file 2020).

Accordingly, this study is designed as a multiple cohort, multi-center Phase 1b/2 study to investigate the efficacy of derazantinib monotherapy or combination therapy with paclitaxel, ramucirumab or atezolizumab for the second-line treatment of GAC patients harboring an activating *FGFR* genetic aberration.

Based on findings that the coexistence of *HER2* amplification and *FGFR* genetic aberrations has been rarely found to date, the study will prescreen and enroll only patients with HER2^{neg} GAC, and will therefore not compete with potentially emerging HER2-directed treatment options.

The study comprises the following three open-label substudies:

- ***Substudy 1***: As of Protocol Version 5.0, this Substudy has been modified with the addition of *Cohort 1.3* targeting a population identical to that being investigated in ongoing *Cohorts 1.1* and *1.2*. GAC patients with specified *FGFR* genetic aberrations, after either first- or second-line treatment, and no approved treatment alternative are to be treated with derazantinib 200 mg BID in *Cohort 1.3*, with the aim of evaluating the safety, tolerability, and efficacy of derazantinib monotherapy in this patient population (for the rationale, see Section 1.6.3.1).
- ***Substudy 2:*** This Substudy will enroll GAC patients with specified *FGFR* genetic aberrations after standard first-line treatment, with the aim of evaluating the safety, tolerability, and efficacy of derazantinib-paclitaxel-ramucirumab in combination and determining the RP2D.
- ***Substudy 3***: This Substudy will enroll GAC patients with *FGFR* genetic aberrations indicative of response to derazantinib (per Substudy 1), with the aim of evaluating the efficacy of derazantinib, derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab in combination, and comparing their efficacy to that of paclitaxel-ramucirumab in this patient population.

1.6.2 Rationale for patient reported outcomes

Patient Reported Outcomes (PROs) provide an understanding of the impact a treatment has on a patient. For patients with GAC, it is imperative to balance survival benefit with health-related quality of life (HR-QoL) (Ajani 2017). In Phase 3 studies investigating chemotherapy with the addition of trastuzumab or ramucirumab, the addition of target therapy improved overall survival without compromising HR-QoL, as measured by validated HR-QoL questionnaires (Quality of Life Questionnaire-Core 30 [QLQ-C30] and EQ-5D) (Al-Batran 2016, Satoh 2014).

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

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a validated instrument that has been widely used in assessing quality of life in patients with cancer. This instrument assesses global health status/quality of life, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms. The EORTC Quality of Life Questionnaire-Stomach (QLQ-STO22) is a gastric cancer-specific module which has been developed to be used in combination with the EORTC QLQ-C30.

Global Self Evaluated Transition (G-SET) / Health Transition Index (HTI) is a patient-rated change in health between two time periods using a five-point ordinal scale (single item) and will be used as an external anchor to determine the minimal important difference of the EQ-5D visual analogue scale, EORTC QLQ-C30 scales and EORTC QLQ-STO22 scales. It will be administered twice during the study.

1.6.3 Dosage and cycle length

In Substudies 1 and 2 as well as *Cohorts 3.1, 3.2* and *3.4*, a treatment cycle is 28 days to follow the routine cycle interval of derazantinib and paclitaxel-ramucirumab in combination, respectively. In *Cohort 3.3*, owing to the treatment schedule of atezolizumab, a treatment cycle is 21 days.

1.6.3.1 Derazantinib dose

In a clinical Phase 1/2 study (ARQ 087-101), the maximum tolerated dose (MTD) of derazantinib monotherapy was declared as 400 mg once daily (QD), and the RP2D was determined as continuous oral administration of 300 mg derazantinib QD (Papadopoulos 2017). In the Phase 2 Part of this study, derazantinib demonstrated encouraging anti-tumor activity and a manageable safety profile in patients with advanced, unresectable intrahepatic cholangiocarcinoma (iCCA) with FGFR2 fusion who progressed after chemotherapy (Mazzaferro 2019).

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

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

The available safety data with derazantinib across the dose range of 100 mg to 400 mg QD, together with the revised assumption on dose-linearity and half-life of derazantinib, support the exploration of a higher dose of 400 mg per day (given as 200 mg BID) as an additional option to assess whether the benefit to risk profile may be further improved in GAC patients.

The primary endpoint of 4-month PFS rate in the Substudy 1.3 cohort will address the disease state of the emerging target population (predominant enrollment of third-line patients) and the acknowledged clinical objective of palliative disease stabilization with

prolonged progression-free intervals and moderate treatment-related toxicity rather than aggressive tumor shrinking regimens. Recent controlled phase 2 and 3 studies have demonstrated the clinical value of palliative third-line treatment of GAC patients using disease control rate and 4-month PFS rate as primary endpoints (Shitara 2018, Bando 2016).

1.6.3.2 Derazantinib dose in combination with paclitaxel-ramucirumab

To date, the safety profiles of derazantinib and paclitaxel-ramucirumab have only been studied individually (Mazzaferro 2019, Papadopoulos 2017, Van Cutsem 2017, Wilke 2014). The following safety-oriented considerations drive the dose-finding design to investigate the combination of standard paclitaxel-ramucirumab with derazantinib.

DLTs of paclitaxel are neutropenias with infections and severe acute hypersensitivity reactions across all dose levels routinely administered. Myelosuppression, neutropenia (with and without infections), anemia, thrombocytopenia, leukopenia, bleeding; minor hypersensitivity reactions (mainly flushing and rash); neurotoxicity (mainly peripheral neuropathy); nausea, vomiting and diarrhea; infections; mucosal inflammation; alopecia; arthralgia and myalgia are classified as very common side effects (Paclitaxel Ever Pharma SmPC). Taken together, the majority of anticipated side effects of pacalitaxel potentially overlapping with derazantinib, including diarrhea, vomiting, nausea, elevation in AST and bilirubin, can be managed by either supportive care measures or dose modifications routinely applied in the studied disease population (see Section 6.1.1.5 and 6.1.2.7).

In the Phase 1 study of ramucirumab, patients developed dose-limiting hypertension and deep venous thromboses at 16 mg/kg QW, and the next lower dose of 13 mg/kg QW was considered the MTD (Spratlin 2010). However, the recommended dose for single-agent ramucirumab was determined as 8 mg/kg Q2W, which was used in the REGARD trial, the pivotal Phase 3 study in patients with gastric or gastro-esophageal junction adenocarcinoma (Fuchs 2014). Hypertension, infusion-related reactions, impaired wound healing, hemorrhage, arterial thromboembolic events, gastrointestinal perforation and reversible posterior leukoencephalopathy syndrome are classified as AEs of special interest (AESIs) (Cyramza® USPI, Cyramza EPAR).

The Grade 3 or higher treatment-emergent toxicities seen most frequently with ramucirumab-paclitaxel (8 mg/kg ramucirumab as a 1-hour infusion on Day 1 (D1) and D15 plus 80 mg/m^2 paclitaxel as a 1-hour infusion on D1, D8, and D15 of a 28-day cycle) in the pivotal RAINBOW study (Wilke 2014) that could overlap with those seen with derazantinib in the combined analysis of data from studies ARQ 087-101 and DZB-CS-301 are hypertension (15% and 6%, seen for paclitaxel-ramucirumab and derazantinib, respectively), fatigue (12% and 7%) and diarrhea (4% and 2%). Patients with increased baseline values of bilirubin, AST and/or ALT had a statistically nonsignificant higher incidence of severe myelosuppression in studies with paclitaxel dosed at 135 mg/m^2 or higher. Derazantinib 300 mg QD administered to iCCA patients in studies ARQ 087-101 and DZB-CS-301 resulted in Grade 3 or higher transaminase elevations in 18.3% of patients, while none of these cases were assessed by the Sponsor as a drug-induced liver injury related to derazantinib.

To characterize the safety and tolerability profile of the triple combination of derazantinib-paclitaxel-ramucirumab in Substudy 2, a modified 3+3 dose-finding design with inclusion of an additional expansion cohort, with treatment of up to 20 patients at the MTD level will be used to assess potential overlapping and/or DLTs and determine the adequate dose for the evaluation of efficacy of the combination. The nominal doses of derazantinib 200 mg QD, 300 mg QD, and 200 mg BID will be tested for tolerability in combination with the standard dosing regimen 80 mg/m^2 paclitaxel and 8 mg/kg ramucirumab, the dosing regimen established and registered for the second-line treatment of gastric cancer patients (Wilke 2014, Cyramza® USPI, Cyramza EPAR). The starting dose of derazantinib will be 200 mg QD to account for both the potentially additive/synergistic effects of derazantinib added to paclitaxel, and a theoretical derazantinib-related CYP2C8 inhibition that may lead to a potentially increased paclitaxel exposure and increased frequency and severity of paclitaxel-related myelosuppression. Following the principles of modified 3+3 dose-finding design, individual dose de-escalation dose levels (DLs) may be explored in reaction to the nature and severity of emerging adverse drug reactions (ADRs).

1.6.3.3 Derazantinib in combination with atezolizumab

To date, the safety profiles of derazantinib and atezolizumab have only been studied individually (Mazzaferro 2019, Petrylak 2018, Papadopoulos 2017, O'Donnell 2017, Balar 2017, Herbst 2014). With regard to combination treatment adding derazantinib to standard-of-care treatment regimens, the safety profile of derazantinib is described in Section 1.6.3.2.

In the first-in-human study of atezolizumab (formerly known as MPDL3280A), the pharmacokinetics (PK) for atezolizumab were shown to be consistent with those of typical immunoglobulins, with a mean terminal serum half-life of approximately 3 weeks. Neither DLTs nor an MTD were reported (Herbst 2014), indicating that atezolizumab was well tolerated up to a dose of 20 mg/kg body weight, including a flat 1200-mg dose, which was then used in further studies (Petrylak 2018).

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

The results obtained from the Phase 1b cohort in the ongoing study DZB-CS-201 in patients with urothelial cancer confirmed the safety and tolerability of the novel derazantinib-atezolizumab combination, and the resulting RP2D allows combination of the full doses established for monotherapy treatment with either study treatment. Investigation

of the combination treatment in Substudy 3 is contingent on the determination of the RP2D by a joint decision of the Independent Data Monitoring Committee (IDMC), Investigators, and the Sponsor in that study, based on a review of the aggregate of DLT and AE data, and considering PK and efficacy data.

1.7 Risk-benefit assessment

1.7.1 Derazantinib

Derazantinib is a potent FGFR inhibitor that shows strong anti-proliferative activity in cell lines harboring *FGFR2* aberrations. In a clinical study in iCCA patients (Mazzaferro 2019, Papadopoulos 2017, Droz Dit Busset 2019), derazantinib was shown to be active in patients with *FGFR2* fusions, mutations and amplifications with a manageable safety profile. In exploratory gastric cancer PDX studies of derazantinib, a consistently strong anti-tumor activity was found, leading to complete responses in several animals, and a tolerable level of toxicity (McSheehy 2020).

The SHINE study of the FGFR inhibitor AZD4547 recently reported poor efficacy data for FGFR inhibition in a gastric cancer target population defined by *FGFR2* amplification and polysomy (Van Cutsem 2017). According to non-clinical data and a recent publication of the translational study using the same investigational compound (Basilea, data on file 2020, Pearson 2016), the definition of the target population may have been inadequate due to the inclusion of low-level *FGFR2* amplification and *FGFR2* polysomy (Van Cutsem 2017), which may explain the study results (Pearson 2016). The current protocol for study DZB-CS-202 therefore considers only prior clinical and non-clinical evidence supporting the functionality of high-level *FGFR2* amplification, and requires a more stringent definition of the putative target population. The inclusion of *FGFR1–3* mutations is exploratory based on the existing non-clinical data in models of gastrointestinal and urothelial tumors (McSheehy 2020, McSheehy 2019, Basilea data on file 2020).

Overall, it is expected that approximately 9% of GAC patients harbor a functional *FGFR* genetic aberration (Figure 2). Owing to the uncertainty of the predictive value of *FGFR1–3* mutations compared to the substantial non-clinical and clinical evidence for *FGFR2* rearrangements and high-level *FGFR2* amplification, respectively (McSheehy 2020, Chen 2019, Catenacci 2017, Kuboki 2017, Pearson 2016), the protocol will first aim to establish evidence of the predictive nature of *FGFR2* fusions, *FGFR2* amplifications, and *FGFR 1–3* mutations in Substudy 1, using a Fleming two-stage design that provides a reliable method for minimizing the number of patients exposed to potential futility of derazantinib monotherapy.

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

Hyperphosphatemia[1], fatigue, ocular disorders, blood creatinine increased / renal disorders, hyponatremia, and nail toxicities are assessed as important potential risks for derazantinib, based on the clinical toxicity profile of derazantinib. Safety measures to monitor and mitigate these risks during the study are outlined in Section 5.3.2.

The following events are assessed as potential risks for derazantinib: gastrointestinal disorders, hypertension, alopecia[1], and QT[2] prolongation. As the safety data are accumulating and remain subject to final evaluation for ongoing studies with derazantinib, the Sponsor continues monitoring for the potential risks. In the current study, an IDMC will assess safety data and provide recommendations to the Sponsor (see Section 3.5). Based on emerging information, the Sponsor will continue to evaluate safety data to characterize further potential risks and assess identified risks.

1.7.2 Derazantinib in combination with paclitaxel, ramucirumab and atezolizumab

1.7.2.1 Combination of derazantinib with paclitaxel-ramucirumab

Treatment with paclitaxel-ramucirumab offers patients an effective second-line standard-of-care treatment, however, the improvement compared with paclitaxel monotherapy, despite clear evidence of statistical significance from a well-designed clinical trial, may not be considered clinically meaningful according to the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS; Del Paggio 2017, Cherny 2015, Ellis 2014). Patients with GAC harboring potentially actionable molecular, oncogenic targets are still in need of treatment to improve the overall dismal outcome of GAC disease progression after standard first-line chemotherapy. Based on emerging non-clinical and clinical data, derazantinib could be a valuable addition to the treatment armamentarium of GAC patients harboring *FGFR* genetic aberrations (McSheehy 2020, Basilea data on file 2020). In a systematic clinical research approach carefully weighing potential benefits over risks, this study explores the addition of targeted FGFR inhibition to established and emerging standard treatments in a molecularly defined target population.

Paclitaxel-ramucirumab is a broadly used combination regimen with routinely applied, well-established supportive care measures to address AEs consistent with a chemotherapeutic agent (Paclitaxel Ever Pharma SmPC) and a biologic agent (Cyramza® USPI, Cyramza EPAR). Overall, the safety profile and emerging treatment-related toxicities of all three study drugs can be monitored and clinically managed.

In vitro data indicate that derazantinib might be an inhibitor of cytochrome-P450 (CYP) iso-enzymes 1A2, 2C8, and 2D6, and P-glycoprotein (P-gp, MDR1) efflux transporter. Paclitaxel is a known substrate for CYP2C8 (Paclitaxel Ever Pharma SmPC), and

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

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

derazantinib may therefore increase the plasma concentration of paclitaxel, potentially increasing the incidence of myelosuppression, the severity of myelosuppression or both. In contrast, inhibition of P-gp could increase the efficacy of paclitaxel through increased cellular penetration (Pires 2009), and/or increase the incidence or severity of, for example, liver toxicity and neurotoxicity, or both (Hubensack 2008). In addition, the potentially beneficial anti-angiogenic effect of VEGFR2 inhibition may also increase the incidence and severity of hypertension and hemorrhage, or both, as seen in previous studies combining paclitaxel and ramucirumab. No PK interactions are expected between a small molecule kinase inhibitor, such as derazantinib, and an antibody, such as ramucirumab. Prior to its use in Substudy 3, the PK of derazantinib, paclitaxel and ramucirumab in combination will be investigated in Substudy 2 together with the assessment of the tolerability, DLTs and the preliminary safety and efficacy profile of the combination of the three study drugs, using a modified 3+3 dose-finding design.

1.7.2.2 Combination of derazantinib with atezolizumab

Based on recently reported data from the KEYNOTE-062 study (Tabernero 2019), immune-checkpoint blockade offers the potential for clinical benefit in patients with GAC. Atezolizumab is generally well tolerated, with reported AEs with potentially immune-related causes being consistent with an immunotherapeutic agent. These include rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, which have been observed in ongoing studies, and which to date have been monitorable and treatable. Detailed guidance on the management of immune-related AEs (see Section 7.1.4) is available in the US Prescribing Information (PI), and the EU Summary of Product Characteristics (SmPC) for Tecentriq® (atezolizumab) (Tecentriq® USPI, Tecentriq® SmPC).

No PK interactions are expected between a small molecule kinase inhibitor such as derazantinib and an antibody, such as atezolizumab. The results obtained from the Phase 1b cohort in the ongoing study DZB-CS-201 (NCT04045613) in patients with advanced solid tumors confirmed the safety and tolerability of the novel derazantinib-atezolizumab combination, and the resulting RP2D allows combination of the full doses established for monotherapy with either drug.

1.7.2.3 Summary of risk-benefit assessment of combination treatment arms

Overall, there is consensus that GAC patients with disease progression after first-line standard treatment are in need of effective treatment alternatives with a clinically meaningful magnitude of clinical benefit. In a molecularly defined target population of GAC patients harboring functional *FGFR* genetic aberrations, this study aims to establish such benefit in accordance with safety measures and stopping rules in accordance with applicable guidelines. In the event that either derazantinib monotherapy or combinations with paclitaxel, ramucirumab or atezolizumab do not meet the efficacy targets explored in Substudy 3, the proposed two-stage designs provide a reliable method to minimize the enrollment of patients to each study cohort and their exposure to a futile study drug regimen.

1.7.3 Conclusion to risk-benefit assessment

Patients generally should not agree to participate in a clinical study with the understanding that they are assured of receiving direct benefit from treatment during participation, as early clinical studies are primarily designed to provide information about the safety and effectiveness of an investigational medicine.

The available safety data for derazantinib (both at the current dose regimen of 300 mg QD, and at the MTD of 400 mg QD, the latter being proposed to be explored as a revised dose regimen of 200 mg BID) do not indicate significant risks to study patients that require termination or modification of the ongoing derazantinib development program, and the safety profiles for paclitaxel, ramucirumab and atezolizumab, which are licensed medicines in several indications, are well characterized. The proposed two-stage designs permit the minimization of patient accrual in case of futility of study treatment, and an IDMC will reviewsafety data during the course of the study, and provide recommendations to the Sponsor.

The safety and tolerability profile of the novel combination treatment with 300 mg QD derazantinib and 1200 mg Q3W atezolizumab has been assessed as clinically manageable in Phase 1b cohort in the ongoing study DZB-CS-201 in patients with uretelial cancer. No DLTs were observed, and no ADRs leading to death were reported; 15% of patients experienced an AE that led to permanent discontinuation of study drug.

All substudies will include close safety monitoring through AE collection, and assessment of clinical safety laboratory tests, pregnancy testing, vital signs, electrocardiograms (ECGs), physical examinations, ophthalmology examinations and performance status.

The risk-benefit balance is therefore expected to be favorable in the intended GAC patient populations and across study cohorts.

2 STUDY OBJECTIVES

2.1 Primary objectives

2.1.1 Primary objective of Substudy 1 (*Cohorts 1.1 and 1.2*)

To evaluate the ORR of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib monotherapy.

2.1.2 Primary objective of Substudy 1 (*Cohort 1.3*)

To evaluate the PFS4 of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib monotherapy.

2.1.3 Primary objective of Substudy 2

To determine the RP2D of derazantinib-paclitaxel-ramucirumab in combination in patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC.

2.1.4 Primary objective of Substudy 3

To evaluate the ORR of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib, derazantinib-paclitaxel-ramucirumab, derazantinib-atezolizumab, or paclitaxel-ramucirumab.

2.2 Secondary objectives

2.2.1 Secondary objectives of Substudy 1

- To evaluate the efficacy of derazantinib, as measured by ORR (*Cohort 1.3*), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
- To assess the safety and tolerability of the study drugs
- To characterize the PK profile of derazantinib 200 mg BID monotherapy (and, if applicable, derazantinib metabolites)

2.2.2 Secondary objectives of Substudy 2

- To evaluate the efficacy of derazantinib-paclitaxel-ramucirumab in combination, as measured by ORR, DCR, DOR, PFS and OS
- To assess the safety and tolerability profile of derazantinib-paclitaxel-ramucirumab in combination
- To characterize the PK profile of derazantinib (and, if applicable, derazantinib metabolites) when administered in combination with paclitaxel-ramucirumab
- To characterize the PK of paclitaxel when administered in combination with derazantinib-ramucirumab.

2.2.3 Secondary objectives of Substudy 3

- To evaluate the efficacy of the study drugs, as measured by DCR, DOR, PFS, and OS
- To compare the ORR, DCR, DOR, PFS, and OS of patients treated with derazantinib monotherapy, derazantinib-paclitaxel-ramucirumab, and derazantinib-atezolizumab each with that of patients treated with paclitaxel-ramucirumab
- To compare the antitumor efficacy in patients treated with derazantinib monotherapy to that of patients treated with derazantinib-paclitaxel-ramucirumab, and derazantinib-atezolizumab, as well as patients treated with derazantinib-paclitaxel-ramucirumab compared to that of patients treated with paclitaxel-ramucirumab, as measured by ORR, DCR, DOR, PFS and OS, to investigate the contribution of derazantinib in combination treatment
- To assess the safety and tolerability of the study drugs
- To evaluate changes, and assess the minimally important difference, in HR-QoL and symptom response from baseline using the EQ-5D (5L) VAS, EORTC QLQ-C30, EORTC QLQ-STO-22, and the G-SET/HTI

2.3 Exploratory objectives

2.3.1 Exploratory objectives specific to efficacy-estimating Substudies

- To describe the type of $FGFR^{fus/amp/mt}$ genetic aberration in responders and non-responders
- To explore the efficacy of derazantinib-atezolizumab in combination by iRECIST (see Section 5.3.3.2.5) as measured by ORR, DCR, DOR and PFS
- To explore the concordance of liquid biopsy and tumor biopsy results
- To explore the molecular profile and gene expression profile of radiographic and metabolic responders versus non-responders by pre-treatment biopsy
- To explore molecular profile and gene expression profile changes indicative of radiographic response versus non-response by Cycle 1 liquid biopsy
- To describe emerging genetic markers of resistance in (non)-responders

2.3.2 Exploratory PK objectives

- To explore the exposure of derazantinib alone (and, if applicable, derazantinib metabolites) and in combination with paclitaxel-ramucirumab
- To explore the exposure of paclitaxel in combination with derazantinib-ramucirumab
- To explore the exposure of atezolizumab and ramucirumab, when administered in combination with derazantinib and derazantinib-paclitaxel, respectively
- To explore the emergence of anti-drug antibodies (ADA) directed against atezolizumab.

3 INVESTIGATIONAL PLAN

3.1 Overview of study design

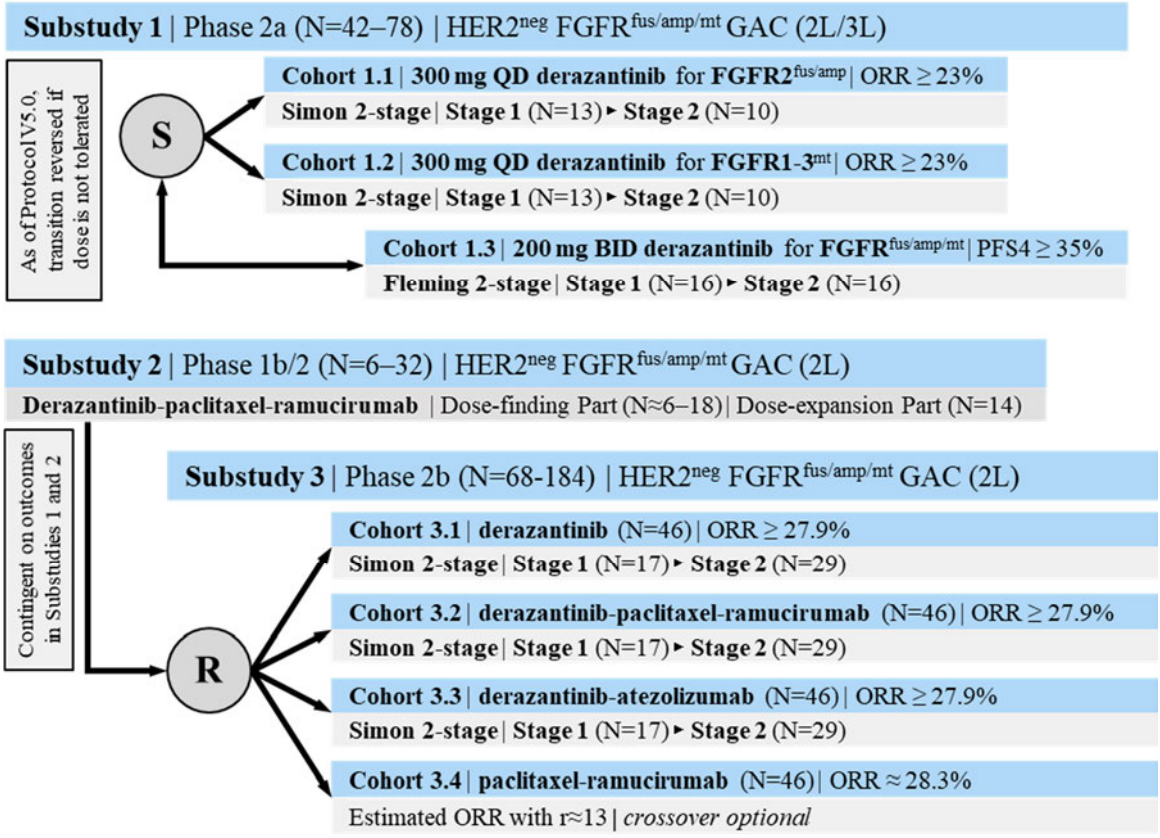
This study is an open-label, multiple-cohort, multi-center Phase 1b/2 study, comprising three substudies. An overview of the overall study design is provided in Figure 3.

Effective from Protocol Version 5.0, Substudies 1 and 2 have been modified.

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

Only patients with GAC expressing $FGFR^{fus/amp/mt}$ will be enrolled (see Section 3.1.1).

Figure 3 Overview of study design



Abbreviations: 2L/3L, second/third-line; BID, twice daily; CR/PR, complete/partial response as per RECIST 1.1; $FGFR^{fus/amp/mt}$, tumor status with *FGFR2* gene fusion or rearrangement / amplification, or *FGFR1–3* mutation; $FGFR2^{fus}$, *FGFR2* fusion / rearrangement; $FGFR2^{high\text{-}amp}$, high-level *FGFR2* gene amplification; $FGFR1–3^{mt}$, *FGFR1–3* mutations; GAC, for either recurrent, locally advanced or metastatic gastric adenocarcinoma; $HER2^{neg}$, negative HER2 tumor status; ORR, objective response rate; p, probability (of response); pts, patients; QD, once daily; R, randomization; r_1/r_2, response(s) observed during stage 1 (r_1) and by the end of the cohort (r_2), respectivelyS, stratification by genetic aberration.

3.1.1 Overview of Substudy 1

- As of Protocol Version 5.0, this substudy has been modified with the addition of *Cohort 1.3* targeting $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC, a population identical to that being investigated in ongoing *Cohorts 1.1* ($FGFR2^{fus}$ or $FGFR2^{high\text{-}amp}$) and *1.2* ($FGFR1–3^{mt}$) combined to better address medical and operational aspects of study conduct. In *Cohort 1.3*, patients with either metastatic or recurrent locally advanced $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC, with radiologically confirmed disease progression after one or two standard treatment regimens are to be treated with derazantinib 200 mg BID. During enrollment into *Cohort 1.3*, enrollment into *Cohorts 1.1* and *1.2* is paused.
- The primary objective of Substudy 1 is to assess the efficacy of derazantinib in patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC.
- As of Protocol Version 5.0, the primary endpoint of *Cohort 1.3* is the 4-month PFS rate

- If the new dose of 200 mg BID is not considered safe and tolerable, the initial *Cohorts 1.1* and *1.2* may be reopened for further enrollment.
- Up to 20 patients may be enrolled into *Cohort 1.3* in addition to the planned 32 patients, to further characterize efficacy and safety; enrollment may be restricted to patients with either $FGFR2^{fus/amp}$ or $FGFR1–3^{mt}$.
- The schedule of assessments for these patients is shown in Table 1.

3.1.2 Overview of Substudy 2

- This substudy comprises patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC with radiologically confirmed disease progression after first-line standard treatment, who, after Investigator assessment (and per multidisciplinary tumor board endorsement), are considered fit to tolerate the novel combination of derazantinib-paclitaxel-ramucirumab.
- Patients in this substudy are initially planned to receive derazantinib-paclitaxel-ramucirumab in combination; at the dose-finding stage, a decision may be taken to limit the study to investigate either derazantinib-paclitaxel or derazantinib-ramucirumab in combination.
- The primary objective of Substudy 2 is to determine the RP2D for the derazantinib-paclitaxel-ramucirumab (or derazantinib-paclitaxel/derazantinib-ramucirumab) combination, using a modified 3+3 dose-finding design.
- The schedule of assessments for these patients is shown in Table 2.

3.1.3 Overview of Substudy 3

The final design and statistical assumptions applicable to this substudy are contigent on findings from Substudies 1 and 2, and are currently under consideration. Prior to initiation of patient enrollment in this substudy, a protocol amendment will be submitted.

- The initiation of Substudy 3 is triggered by the availability of data considered sufficient and robust to support the rationale for monotherapy (*Cohort 3.1*), triple/double combination (*Cohort 3.2*) and derazantinib-atezolizumab combination (*Cohort 3.3*).
- This substudy comprises patients with either metastatic, or recurrent, locally advanced and inoperable, $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC, with radiologically confirmed disease progression after one standard treatment regimen.
- Patients will be allocated to one of four cohorts:
  - ***Cohort 3.1*** Patients randomized to be treated with derazantinib (test)
  - ***Cohort 3.2*** Patients randomized to be treated with derazantinib-paclitaxel-ramucirumab in combination (test)
  - ***Cohort 3.3*** Patients randomized to be treated with derazantinib-atezolizumab in combination (test)
  - ***Cohort 3.4*** Patients randomized to be treated with paclitaxel-ramucirumab in combination (control)

- Allocation to these cohorts is stratified by type of *FGFR* genetic aberration (FGFR2^{fus} or FGFR2$^{high\text{-}amp}$ vs FGFR1–3^{mt}) and geographic region (Americas-Europe-Australia vs Asia), and then randomized (1:1:1:1) between test and control cohorts.
- The primary objective of Substudy 3 is to assess the efficacy of derazantinib, derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab in combination, while controlling for the efficacy of paclitaxel-ramucirumab in this patient population is a secondary objective.
- The Schedule of Assessments for these patients is shown in Table 3 (*Cohorts 3.1, 3.2* and *3.4*) and Table (*Cohort 3.3*).

3.1.4 Molecular eligibility

Molecular eligibility for enrollment will be established by a positive test result for FGFR$^{fus/amp/mt}$. The molecular test is to be based on NGS of either tumor tissue DNA and/or RNA, or plasma cell-free DNA (cfDNA).

For patients with no access to local NGS testing, central testing will be performed in a laboratory designated by the Sponsor; this 'central testing' will be based on NGS testing of cfDNA from a liquid biopsy obtained at Pre-screening (see Section 3.1.2).

Alternatively, an eligible, positive FGFR$^{fus/amp/mt}$ test result obtained from local NGS testing ('local testing', the commissioning of which is the study site's responsibility) can be used to establish molecular eligibility; no Pre-screening visit is required. The commissioned NGS test for 'local testing' is to use standard protocols approved by the local IRB/IEC, Clinical Laboratory Improvement Amendments (CLIA), or other similar agency, or, where applicable, US FDA-approved kits. For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance; tests manufactured by health institutions and used only on their own patients are exempt from the Medical Devices Regulation requirements, and do not have to be CE-marked. For patients with a positive local test result, liquid biopsy samples for central confirmation of the FGFR status should be collected at the Screening visit, but the NGS test result from the central laboratory does not have an impact on the patient's eligibility.

3.1.5 Pre-screening

A Pre-screening visit is only required for prospective study participants if no documented local NGS test result with an eligible FGFR$^{fus/amp/mt}$ is available. If these patients have no access to local NGS testing, they are required to sign the Pre-screening Informed Consent Form (ICF) for molecular screening, and are not considered enrolled (i.e., patients are considered to be in pre-screening for the study) until receipt of a positive central molecular test result, and dated patient signature on the Study ICF. It is recommended to conduct the Pre-screening visit for liquid biopsy sampling following assessment of objective documented progression after prior anti-cancer treatment. However, in the interests of patients and to reduce off-treatment time between the last anti-cancer treatment and study treatment, liquid biopsy sampling might be performed at any time point after the last administration of anti-cancer therapy when disease progression is suspected.

No Pre-screening visit is required for patients with a known and FGFR$^{fus/amp/mt}$ status from local NGS testing; these patients may directly initiate clinical screening procedures.

3.1.6 Screening

Clinical Screening procedures are required to confirm study-treatment eligibility (see Section 5.2.3). For the baseline study imaging assessment of measurable disease, RECIST 1.1 criteria apply (Appendix 2, Eisenhauer 2009).

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

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

3.1.7 Treatment period

3.1.7.1 Efficacy-estimating substudies

In Substudies 1 and 2 and *Cohorts 3.1, 3.2* and *3.4*, a treatment cycle is defined as 28 days (Q4W). In *Cohort 3.3*, a treatment cycle is defined as 21 days (Q3W).

Substudy 1 *Cohort 1.3*, will include a safety interim assessment for ADRs indicative of DLT (see Section 7.3.3) in the first ten treated patients (the safety run-in phase**)**. The process involves regular dose decision meetings (see Section 8.3.5.1). The schedule of AE assessments, including ECGs and clinical safety laboratory blood sampling, has been expanded to a weekly schedule of assessments for the first two treatment cycles (see Table 1). Rich PK profiling will be performed for all patients during the safety run-in phase, to monitor exposure to derazantinib (and, if applicable, derazantinib metabolites), and to characterize the PK profile of derazantinib 200 mg BID as monotherapy to support safety and efficacy data. The PK sampling schedule is provided in Table 7.

- In Substudy 1, if derazantinib 200 mg BID is considered safe and tolerable at the safety interim analysis (endorsed by the IDMC), and also improves exposure as expected, enrollment of Stage 1 will be completed for the efficacy interim analysis of patients. If derazantinib 200mg BID is not considered safe and tolerable, *Cohorts 1.1* and *1.2* might be re-opened.
- In Substudy 2, following determination of the MTD for the derazantinib-paclitaxel-ramucirumab combination, an additional 14 patients will be enrolled for treatment at the MTD for this triple combination to assess efficacy and further investigate safety.
- In Substudy 3, treatment will consist of either:
  - Derazantinib, or
  - Derazantinib-paclitaxel-ramucirumab at the RP2D determined in Substudy 2, or
  - Derazantinib at the RP2D determined in study DZB-CS-201 plus atezolizumab 1200 mg Q3W, or
  - Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on D1, D8, D15 Q4W plus ramucirumab 8 mg/kg as a 1-hour infusion on D1 and D15 (Q4W)

Efficacy will be evaluated by blinded independent central review (BICR) using RECIST 1.1 criteria on C3D1 ±7 days, then every 8 weeks (±7 days) for the first 6 months, and every 12 weeks (±7 days) thereafter (see Section 5.3.3.2). Patients randomized to *Cohort 3.3* follow the same 8-week imaging assessment schedule; therefore scheduling of additional visits is required.

AEs will be assessed continuously and at every study visit. Dose delays and/or reductions are permitted with derazantinib if a derazantinib-related toxicity is observed (see Section 6.1.1.5). For paclitaxel (see Section 6.1.2.7) and ramucirumab (see Section 6.1.3.7), dose delays and/or reductions may be applied based upon the grade of toxicity experienced by the patient. For atezolizumab, no dose reductions are allowed, but dose delays are permitted if an atezolizumab-related toxicity is observed (see Section 6.1.4.6). A related toxicity is defined as any toxicity considered related to any study medication (or combination thereof), i.e., probably or possibly related.

In Substudy 3, HR-QoL and symptom response will be measured using the EQ-5D, EORTC QLQ-C30, EORTC QLQ-STO-22 and G-SET/HTI questionnaires. See Section 5.3.6 for a description of these HR-QoL instruments.

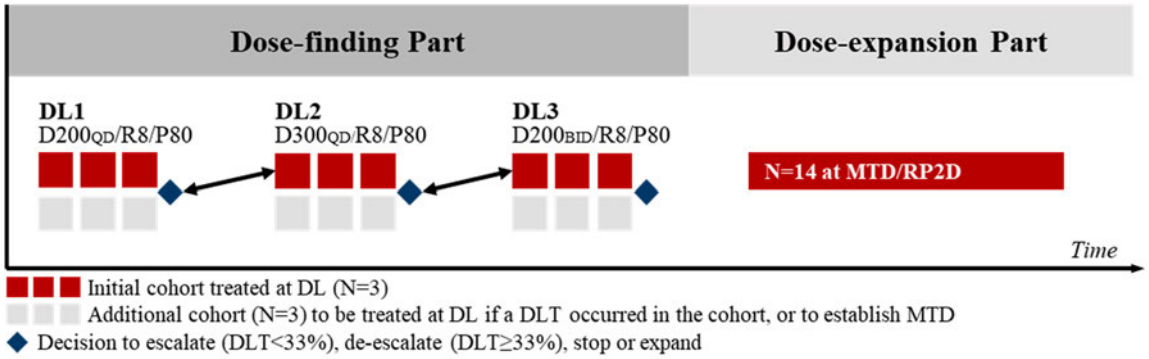
In Substudy 3, upon confirmed PD per RECIST 1.1, it is recommended that patients treated with paclitaxel-ramucirumab (in *Cohort 3.4*) are offered the option of crossing over to treatment with derazantinib (see Section 4.5.1 for details). However, crossing over remains at the Investigator's discretion.

3.1.7.2 Dose-finding Substudy 2

This substudy comprises an algorithm-based dose-finding design using the 3+3 design principles modified to allow concurrent enrollment of up to three patients to determine the MTD per assessment of ADRs indicative of DLTs (Figure 4). The MTD is defined as the highest dose level (DL) at which < 33% of patients experience a DLT. The DLT interval is defined as the first 28-day interval (i.e., Cycle 1) of study treatment. The target DLT threshold for the Dose-finding Part is set at 33%.

The Dose-finding Part is followed by enrollment of a Dose-expansion Part cohort of approximately 14 additional patients to reach 20 efficacy-evaluable patients dosed at the MTD.

Figure 4 Overview of Substudy 2



Abbreviations: DL, dose level; D, derazantinib [number gives dose in mg; BID, twice per day; qd, once per day]; MTD, maximum tolerated dose; P, paclitaxel [number gives dose in mg/m2]; R, ramucirumab [number gives dose in mg/kg]; RP2D, recommended Phase-2 dose.

Patients enrolled to the Dose-finding Part will be treated with increasing doses of derazantinib (planned DLs are 200 mg QD, 300 mg QD, 200 mg BID) and primarily fixed doses of 80 mg/m^2 paclitaxel and 8 mg/kg ramucirumab**.** If one patient experiences a DLT in any DL cohort among the first three enrolled and DLT-evaluable patients, the cohort will be expanded to six DLT-evaluable patients. The MTD is defined as the highest DL at which none or one of six participants (0% to 17%) experience a DLT (see Section 7.3.3 for DLT definition). The MTD is exceeded when at least two of three to six participants (≥ 33% to 67%) experience a DLT in any DL cohort. Declaration of the RP2D may follow the MTD declaration or may be modified considering review of the totality of available safety, efficacy, PK, PD data and potential toxicity-response modeling. Replacement of patients is described in Section 4.5.3.

If a patient experiences a DLT in Cycle 1, study therapy may be discontinued following discussion and agreement between the Sponsor and Investigator, or a dose modification (derazantinib), a dose delay (derazantinib and/or paclitaxel), or both may be implemented.

The triple combination may not be considered to be feasible if DL1 cannot be declared tolerable. The Sponsor may pursue a triple combination with reduced doses of paclitaxel and/or ramucirumab, or a two-drug combination of either derazantinib-paclitaxel or derazantinib-ramucirumab based on the available safety, PK and PD data, and potential toxicity-response modeling. Substudy 2 will be terminated if no combinations can be declared tolerable.

Investigation of the combination therapy in Substudy 3 is contingent on the determination of the RP2D by a joint decision of the IDMC, Investigators, and the Sponsor in Substudy 2, based on a review of the aggregate of DLT and AE data, and considering efficacy, PK, and PD data, and potential toxicity-response modeling.

3.1.8 End of Treatment / Safety Follow-up period

Patients will continue to receive study treatment until disease progression, patient withdrawal, lost to follow up, unacceptable toxicity, or until the Investigator's decision to

remove the patient from treatment; or until the Substudy, cohort or the study is terminated by the Sponsor, whichever occurs first.

In all substudies, once patients have been discontinued from treatment with the initially assigned study drug, other treatment options (including enrollment into the Crossover Phase for patients with confirmed disease progression after treatment with paclitaxel-ramucirumab; see Section 3.1.9) will be at the discretion of the Investigator. All subsequent therapies should continue to be recorded on the appropriate electronic case report form (eCRF) for the duration of the study.

For further details on treatment and study discontinuation, see Section 4.5.

3.1.8.1 End of Treatment visit

An End of Treatment visit will be conducted within 7 days after the decision to permanently discontinue treatment. At this time, patients who received treatment with paclitaxel-ramucirumab (*Cohort 3.4*) and who experienced disease progression may crossover to derazantinib treatment (at the discretion of the Investigator; see Section 3.1.9).

3.1.8.2 Safety Follow-up visit(s)

For all patients, Safety Follow-up visits will be conducted 28 days (±3 days) and 90 days (±3 days) after study treatment discontinuation. See Section 5.2.4.10 for further details.

3.1.9 Post-discontinuation study treatment crossover (*Cohort 3.4*)

Patients from *Cohort 3.4* with PD (as assessed by BICR) will have the opportunity to receive treatment with 300 mg derazantinib QD in a Crossover Phase. Crossover patients may initiate treatment with derazantinib within 2 months of their last dose of paclitaxel-ramucirumab, regardless of the time of progression.

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

3.1.9.1 Eligibility criteria for post-discontinuation study treatment crossover

Patients who withdraw consent, or discontinue paclitaxel-ramucirumab for any reason other than PD, or paclitaxel-ramucirumab-related toxicity, will not be eligible for crossover.

Patients who meet the following criteria are eligible for crossover:

- Documented PD on paclitaxel-ramucirumab as a participant of *Cohort 3.4* (PD to be confirmed by BICR)
- All ongoing AEs must have resolved to baseline or Common Terminology Criteria for Adverse Events (CTCAE) 5.0 Grade ≤ 1 (except alopecia and peripheral neuropathy)
- No new central nervous system (CNS) metastases
- ECOG PS of 0–2
- Patient has not received any other systemic anti-cancer therapies after paclitaxel-ramucirumab administration during the treatment phase.

- If required, completed palliative radiotherapy (30 Gy or less) ≥ 7 days before the first dose of crossover study treatment.
- Patient has adequate organ function, as indicated by the laboratory values detailed in Inclusion criterion 9.

3.1.9.2 Abbreviated screening procedures prior to study treatment crossover

The following procedures should be scheduled and performed after eligibility for post-discontinuation study treatment crossover is confirmed:

- Physical examination, including height, weight, and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Complete ophthalmic examination, including optical coherence tomography (OCT) (see Section 5.3.2.3)
- Triplicate 12-lead ECG (see Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable (see Inclusion criterion 10, Section 5.3.2.7, and Section 7.1.5
- Tumor imaging assessments, according to RECIST 1.1 (see Section 5.3.3.2 and Appendix 2)

  Note: Tumor assessments or ophthalmic examinations performed within 28 days of the first dose of crossover derazantinib treatment on C1D1 may be used rather than repeating tests.

3.1.9.3 Assessments during post-discontinuation study treatment crossover

Once eligibility is confirmed and abbreviated screening procedures have been completed, crossover patients will follow the same schedule of assessments as patients treated with derazantinib, as detailed in Table 3, but without derazantinib PK sampling. In particular, safety-oriented assessments detailed in Section 5.3.2 need to be followed as specified; dose modifications for derazantinib treatment are detailed in Section 6.1.1.5.

Screening procedures need to be completed within 28 days of confirmed PD (or up to 42 days from last dose if recovering from an AE). Procedures and assessments required under Section 3.1.9.2 and completed at the time of withdrawal from the main study may be used for the start of the Crossover Phase of the study. C1D1 of the Crossover Phase may occur within 2 months of their last dose of paclitaxel-ramucirumab, regardless of the time of progression.

The tumor imaging used to determine PD can be used as the new baseline image for the Crossover Phase if this was obtained within the 28 days prior to receiving the first dose of derazantinib (see Section 5.3.3.2.4).

3.1.10 Survival Follow-up period

Patients who are permanently discontinued from study treatment for reasons other than death, regardless of the reason, will enter the survival follow-up period (see Section 5.2.5).

Survival Follow-up (at least every 3 months ± 14 days from last dose of study drug) will start on the day of the last dose of study drug and will continue until the study has completed (see Section 3.1.11) or other discontinuation criteria are met (see Section 4.5).

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

3.1.11 Beginning and end of the study

The study begins when the first patient signs the ICF.

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

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

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

3.2 Endpoints

3.2.1 Primary endpoints

3.2.1.1 Primary endpoint in Substudy 1

3.2.1.1.1 *Cohorts 1.1 and 1.2*

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

3.2.1.1.2 *Cohort 1.3*

- PFS4, as measured by the proportion of patients alive and free of disease progression by survival status and BICR per RECIST 1.1 after approximately 4 months of study treatment.

3.2.1.2 Primary endpoint for Substudy 2

- The RP2D of derazantinib-paclitaxel-ramucirumab in combination, estimated from safety and tolerability according to the aggregate of DLT criteria and AE data, and considering further PK and efficacy data of the combination. The IDMC, Investigators and Sponsor will jointly determine the RP2D.

3.2.1.3 Primary endpoint in Substudy 3

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

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

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

3.2.2 Secondary endpoints

3.2.2.1 Secondary endpoints for Substudy 1

- PFS of patients treated with derazantinib, as measured from patient enrollment to PD date (see Section 8.3.5.2.1) by BICR
- ORR, as measured by the proportion of patients with confirmed CR or PR by BICR for *Cohort 1.3*
- DCR, as measured by the proportion of patients with confirmed CR, PR or stable disease (SD)[1] by BICR
- DOR, as calculated from the first date of documented tumor response to disease progression by BICR (or death if no documentation of PD is obtained)
- OS, as measured from patient enrollment to time of death
- Safety and tolerability of study drugs, as measured by the frequency and severity of AEs (graded by CTCAE version 5.0), clinical laboratory parameters, vital signs, ECOG PS, physical examinations (including eye examinations), and ECG parameters over time
- DLT in the first ten patients in *Substudy 1.3*
- Derazantinib (and, if applicable, derazantinib metabolites) plasma concentrations, C_{max}, t_{max}, $AUC_{0–12}$, $AUC_{0–24}$, AUClast assessed by measurements in blood samples

3.2.2.2 Secondary endpoints for Substudy 2

- ORR, as measured by the proportion of patients with confirmed CR or PR by BICR
- DCR, as measured by the proportion of patients with confirmed CR, PR or SD by BICR
- DOR, as calculated from the first date of documented tumor response to disease progression by BICR (or death if no documentation of PD is obtained)
- PFS of patients treated with derazantinib-paclitaxel-ramucirumab, as measured from patient enrollment to PD date by BICR
- OS, as measured from patient enrollment to time of death
- Safety and tolerability of study drugs, as measured by the frequency and severity of AEs (graded by CTCAE version 5.0), clinical laboratory parameters, vital signs, ECOG PS, physical examinations (including eye examinations), and ECG parameters over time
- Derazantinib (and – if applicable –derazantinib metabolites) plasma concentrations, C_{max}, t_{max}, AUC_{0-24}, AUC_{last}, assessed by measurements in blood samples

[1] Evaluating target lesions, SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD (see following definition), taking as reference the smallest sum of diameters while on study. PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Paclitaxel plasma concentrations, C_{max}, t_{max}, AUC_{0-24}, AUC_{last}, $t_{1/2}$, AUC_{inf}, T > 0.05 assessed by measurements in blood samples.

3.2.2.3 Secondary endpoints for Substudy 3

- ORR of patients treated with derazantinib, derazantinib-paclitaxel-ramucirumab, or derazantinib-atezolizumab, as measured by the proportion of patients with confirmed CR or PR by BICR, and for each treatment compared to that of paclitaxel-ramucirumab.
- PFS of patients treated with derazantinib, derazantinib-paclitaxel-ramucirumab, or derazantinib-atezolizumab, as measured from randomization to PD date by BICR, and for each treatment compared to that of paclitaxel-ramucirumab.
- DCR of patients treated with derazantinib, derazantinib-paclitaxel-ramucirumab, or derazantinib-atezolizumab, as measured by the proportion of patients with confirmed CR, PR or stable disease (SD)[1] by BICR, and for each treatment compared to that of paclitaxel-ramucirumab.
- DOR of patients treated with derazantinib, derazantinib-paclitaxel-ramucirumab, or derazantinib-atezolizumab, as calculated from the first date of documented tumor response to disease progression by BICR (or death if no documentation of PD is obtained), and for each treatment compared to that of paclitaxel-ramucirumab.
- OS of patients treated with derazantinib, derazantinib-paclitaxel-ramucirumab, or derazantinib-atezolizumab, as measured from patient enrollment to time of death, and for each treatment compared to that of paclitaxel-ramucirumab.
- ORR, DCR, DOR, PFS and OS of patients treated with derazantinib monotherapy compared to that of patients treated with derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab, as well as patients treated with derazantinib-paclitaxel-ramucirumab compared to that of patients treated with paclitaxel-ramucirumab, to investigate the contribution of derazantinib in combination treatment.
- Safety and tolerability of study drugs as measured by the frequency and severity of AEs (graded by CTCAE version 5.0), clinical laboratory parameters, vital signs, ECOG PS, physical examinations (including eye examinations), and ECG parameters over time.
- Changes in HR-QoL and symptom response, measured by global, functional and symptom scores obtained from patient reported outcome instruments (EQ-5D [5L] VAS, EORTC QLQ C30, EORTC QLQ-STO-22 and G-SET/HTI) at baseline and over time.

[1] Evaluating target lesions, SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD (see following definition), taking as reference the smallest sum of diameters while on study. PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

3.2.3 Exploratory endpoints

3.2.3.1 Exploratory endpoints specific to efficacy-estimating substudies

- Responding and non-responding patients are to be analyzed by type of FGFR genetic aberration.
- The proportion of patients with concordant molecular assessment from plasma-based and tissue-based testing measuring FGFR genetic aberrations in tumor-liquid biopsy samples obtained at baseline will be described.
- The ORR, DCR, DOR, PFS and OS of patients treated with derazantinib, derazantinib-paclitaxel-ramucirumab in combination, and derazantinib-atezolizumab in combination, respectively, will be evaluated by molecular profile, gene expression profile, and biomarkers.
- The ORR, DCR, DOR and PFS of patients treated with derazantinib-atezolizumab in combination per iRECIST.
- Changes in the molecular profile and emerging genetic markers of resistance in radiographic (non)responders (e.g., MAPK, PI3K/AKT, PTEN, JAK/STATwill be described .
- EQ-5D (5L) health status data will be used for obtaining utility measures for economic modeling. For the EQ-5D (5L), further scoring and analysis may be reported separately.

3.2.3.2 Exploratory PK endpoints

- Plasma concentrations of derazantinib (and, if applicable, derazantinib metabolites), assessed by measurements from blood samples obtained from patients entered into Substudies 1, 2 and 3.
- Plasma concentrations of paclitaxel, assessed by measurements from blood samples obtained from patients entered into Substudy 2

  Note: Based on PK data obtained during Substudy 2, the Sponsor may consider blood sampling for paclitaxel plasma concentrations in patients entered into Substudy 3.
- Serum concentrations of ramucirumab, assayed from blood samples obtained from patients entered into Substudies 2 and 3
- Serum concentrations and ADA for atezolizumab, assayed from blood samples obtained from patients entered into Substudy 3.

3.3 Number of patients

The study plans to enroll approximately 314 patients across all three substudies.

An evaluable patient for Substudies 1 and 3, and the Dose-expansion part of Substudy 2, is defined as a patient who qualifies for inclusion in the modified intent-to-treat (mITT) data analysis set (see Section 8.2.3). Non-evaluable patients will be replaced.

An evaluable patient in the Dose-escalation part of Substudy 2 is defined as a patient who qualifies for inclusion in the MTD analysis set (see Section 8.2.5). Non-evaluable patients will be replaced.

3.4 Study sites

Approximately 85 study sites in the Americas, Europe, Australia, and Asia.

3.5 Independent Data Monitoring Committee

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

The IDMC will assess safety data from all substudies and provide recommendations to the Sponsor after completing interim analyses of each cohort. For *Cohort 1.3*, the IDMC together with Investigators and the Sponsor will be responsible for determining whether derazantinib 200 mg BID as monotherapy can be declared a safe and tolerable regimen.

For Substudy 2, the IDMC together with Investigators and the Sponsor will be responsible for determining the RP2D of derazantinib-paclitaxel-ramucirumab in combination, to be administered to patients in Substudy 3. 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, and in accordance with the applicable regulations, 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 employees of the Sponsor, or involved in the conduct or reporting of study DZB-CS-202, or have a financial interest in the outcome of the study. In addition, no member of an IDMC of a clinical study with a different sponsor investigating gastric adenocarcinoma is eligible for membership of the DZB-CS-202 IDMC.

The conduct of the IDMC will be governed by the IDMC Charter.

4 STUDY POPULATION

4.1 Target population

The target population for Substudy1 is patients with either metastatic, or recurrent, locally advanced and inoperable, $HER2^{neg}$ GAC harboring either $FGFR2^{fus}$, $FGFR2^{high\text{-}amp}$, or $FGFR1–3^{mt}$, with radiologically confirmed disease progression after one or two standard treatment regimens, and no standard or approved treatment alternative.

The target population for Substudies 2 and 3 is patients with either metastatic or recurrent, locally advanced and inoperable, $HER2^{neg}$ GAC harboring either $FGFR2^{fus}$, $FGFR2^{high\text{-}amp}$, or $FGFR1–3^{mt}$, with radiologically confirmed disease progression after one standard treatment regimen.

4.2 Inclusion criteria

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

1. ICF signed by the patient indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study, prior to any study-related procedure.
2. Male or female aged ≥ 18 years.
3. Histologically-confirmed adenocarcinoma of the gastro-esophageal junction or stomach
   Note: Every effort is requested to submit archival tumor tissue samples[1] for correlative and confirmatory diagnostic and biomedical research.
4. Negative HER2 status obtained from the most recent available tissue sample[2]
   Note: The HER2 status of GAC patients should be assessed using approved standard protocols, including, but not limited to fluorescence in-situ hybridization (FISH), chromogenic or silver in situ hybridization (CISH) or immunohistochemistry (IHC), in accordance with institutional standards. Patients with a HER2 *positive (HER2^{pos}) status based on either HER2 amplification (by FISH or CISH) or, if FISH/CISH is unavailable, a HER2 IHC score of 3+, are not eligible and should not be tested molecularly for FGFR$^{fus/amp/mt}$ expression.*
5. Inoperable[3] recurrent, locally-advanced adenocarcinoma or progressing stage IV adenocarcinoma of the gastro-esophageal junction or stomach, and prior antitumor treatment as specified for each Substudy:
   - **Substudy 1:** Patients with radiographically-documented disease progression after either standard first- or second-line treatment, and no approved and/or tolerable treatment alternative (endorsed by multidisciplinary tumor board).
   - **Substudy 2**: Patients with radiographically-documented disease progression after standard first-line treatment, and per Investigator assessment considered suitable to tolerate the treatment regimen (endorsed by multidisciplinary tumor board).
   - **Substudy 3:** Patients with objective radiographically-documented disease progression:
     – During, or within 6 months after, administration of the last cycle of adjuvant / neoadjuvant / perioperative chemotherapy (platinum plus fluoropyrimidine with or without anthracycline and/or taxane and/or irinotecan) for locally advanced disease, or

       Note: If the patient has received prior taxane, a 6-month taxane-free interval after the last administration of taxane-containing treatment needs to be respected
     – During, or any time after, administration of the last cycle of first-line taxane-free chemotherapy (platinum plus fluoropyrimidine with or without anthracycline) for metastatic disease or locally advanced disease.

[1] If tumor tissue from an archival tumor block is available for analysis, the minimum requirements for slides prepared from such tumor blocks for central molecular testing are one H&E-stained slide plus at least 10 consecutive, unstained, 4 ± 1 µm thick sections placed on positively charged slides.

[2] Use of an FDA-approved test for the determination of the HER2 status is recommended in the USA.

[3] Patients are required to be staged as inoperable at the time of screening in order to avoid interference of any potentially planned surgery with RECIST requirements during the study.

6. Eligible FGFR$^{fus/amp/mt}$ positive test result(see Appendix 1 and Section 3.1.4).
   Note: The scope of eligible FGFR genetic aberrations for Substudy 3 may be modified and take into consideration findings obtained from Substudy 1.
7. Measurable disease as defined by the Investigator using RECIST 1.1 criteria
8. ECOG PS of 0 or 1
9. Adequate organ functions as indicated by the following Screening visit laboratory values:
   - Hemoglobin ≥ 9 g/dL
   - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
   - Platelets ≥ 100,000/μL
   - Serum sodium, corrected calcium, potassium, magnesium and phosphate within institutional normal ranges
   - International Normalized Ratio (INR) ≤ 1.5 or Prothrombin Time (PT) ≤ 1.5 upper limit of normal (ULN), and Partial Thromboplastin Time (PTT/aPTT) ≤ 1.5 ULN
   - Total bilirubin ≤ 2 × ULN
   - AST and ALT ≤ 3 × ULN, or ≤ 5 × ULN for study patients with liver metastasis
   - Albumin ≥ 2.5 g/dL
   - Creatinine clearance (CL_{CR}) ≥ 30 mL/min (as calculated by the Cockcroft-Gault formula)
   - Urinary protein ≤ 1+ on dipstick or ≤ 30mg/dL in routine urinalysis.
     Note: If urine dipstick or routine analysis indicates proteinuria ≥ 2+ or ≤ 30 mg/dL, then a 24-hour urine must be collected and must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study. Alternatively, a spot urine protein-creatinine ratio (UPCR) can be obtained on first morning urine sample, and must demonstrate a UPCR < 1 (or < 100 mg/mmol) to allow participation in the study.
   - For women of childbearing[1] potential only, negative serum human chorionic gonadotropin (hCG)[2]

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

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

10. Men and women of childbearing potential must agree to avoid impregnating a partner or becoming pregnant, respectively, during the study, and for at least 150 days after the last dose of either investigational drug.

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

    - are postmenopausal[1], or
    - have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to Screening, or
    - have a congenital or acquired condition that prevents childbearing.

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

    a) Abstinence from heterosexual activity[2]
    b) Using (or having their partner use) a highly effective method of contraception during heterosexual activity. Highly effective methods of contraception are[3]:
        - an intrauterine device
        - vasectomy of a female patient's male partner
        - a contraceptive rod implanted into the skin.
        - any combination of hormonal contraceptive and a barrier method (diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male condom or female condom)
        - combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral contraceptive pill [estrogen/progestin pill or progestin-only pill], contraceptive skin patch/implant, vaginal contraceptive ring, or subcutaneous contraceptive injection).

4.3 Exclusion criteria

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

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

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

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

Prior cancer treatment

1. Receipt of treatment before the first dose of study drug (Cycle 1 Day 1) within an interval shorter than the following, as applicable:
   - One chemotherapy or biological (e.g., antibody) cycle interval.
   - Five half-lives of any small molecule investigational or licensed medicinal product.
   - Two weeks, for any investigational medicinal product with an unknown half-life.
   - Four weeks of curative radiotherapy.
   - Seven days of palliative radiotherapy.
2. For patients enrolled in Substudy 1, prior treatment with FGFR inhibitors.
3. For patients enrolled in Substudy 2 and 3, prior treatment with:
   - Taxanes within 6 months prior to randomization
   - FGFR inhibitors or pathway-targeting agents
   - Anti-VEGF(R) therapeutic antibody or pathway-targeting agents.
4. For patients enrolled in Substudy 3, prior treatment with anti-programmed cell death receptor-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) therapeutic antibody or pathway-targeting agents.

Critical organ impairments

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

Medical history

7. Any unresolved (at the time of Screening) clinically significant CTCAE Grade ≥ 2 toxicity. (Exception: patients with alopecia, Grade ≤ 2 platinum-therapy related neuropathy, or Grade ≤ 2 anemia from previous anti-tumor treatment and/or from medical/surgical procedures/interventions, may be enrolled).
8. Known CNS metastases.
9. Severe bacterial, fungal, viral and/or parasitic infections on therapeutic oral or IV medication at the time of first dose of study drug administration.

10. Significant gastrointestinal disorders that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of derazantinib (e.g., Crohn's disease, ulcerative colitis, diarrhea, functionally relevant gastrointestinal obstruction, or vomiting).
11. History of additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or *in situ* cervical cancer.

    An incidental finding of prostate cancer (identified upon resection of the prostate) is acceptable, provided that the following criteria are met: Stage T2N0M0 or lower; Gleason score ≤ 6, and prostate-specific antigen below lower limit of normal by local laboratory.
12. Chronic leg ulcers, decubitus ulcers, or unhealed incisions.

General patient disposition

13. Known hypersensitivity or allergy to any component of the derazantinib, paclitaxel or ramucirumab formulation.
14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
15. Unable or unwilling to swallow the complete daily dose of derazantinib, or contraindicated to receive derazantinib, paclitaxel, ramucirumab and/or atezolizumab
16. Any other uncontrolled intercurrent illness that would unduly increase the risk of toxicity or limit compliance with study requirements, including but not limited to ongoing or active symptomatic infection, uncontrolled diabetes mellitus, or hepatic, renal, respiratory, or psychiatric illness.
17. A history or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition or disease that, in the opinion of the Investigator or the Sponsor if consulted, would pose a risk to the safety of the patient, or would interfere with the study evaluation, procedures, or completion.
18. Pregnant or breast feeding.

In addition, the following exclusion criteria are applicable <u>only</u> to patients to be enrolled into <u>Substudy 2 or Substudy 3</u>:

19. Concurrent uncontrolled or active infection with human immunodeficiency virus (HIV; known HIV 1/2 antibodies positive).
20. Active hepatitis or chronic hepatitis B without current antiviral therapy and an HBV DNA ≥ 100 IU/mL.

    <u>Note</u>: Active hepatitis B is defined as a known positive hepatitis B surface antigen (HBsAg) result.
21. Active hepatitis C

    <u>Note</u>: Active hepatitis C is defined by a known positive hepatitis C antibody result and known quantitative hepatitis C virus (HCV) RNA results greater than the lower limits of detection of the assay.
22. Active tuberculosis.

23. Lack of recovery from major (e.g., open abdominal) surgery after 4 weeks, or major elective surgery is planned during the foreseeable duration of the study, or placement of a central venous access device within 7 days prior to randomization.
24. Uncontrolled arterial hypertension, with a systolic blood pressure ≥ 150 mm Hg or a diastolic blood pressure ≥ 90 mm Hg despite standard medical management.
25. History of gastrointestinal perforation and/or fistulae within 6 months prior to randomization.
26. History of clinically relevant bleeding disorders, vasculitis, or had a significant bleeding episode from the gastrointestinal tract within 3 months prior to randomization.
27. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered 'significant') during the 3 months prior to randomization.
28. The patient is receiving therapeutic anticoagulation with warfarin, low-molecular weight heparin, or similar agents.

    Note: Patients receiving prophylactic, anticoagulation therapy for cancer-associated thrombosis are eligible provided that the coagulation parameters defined in the inclusion criteria (INR ≤ 1.5 and PTT/aPTT ≤ 1.5 ULN or PT ≤ 1.5 ULN, and PTT/aPTT ≤ 1.5 ULN) are met.
29. The patient is receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs, e.g., indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide). Acetylsalicylic acid (aspirin) is permitted at doses up to 325 mg/day.
30. Child-Pugh B or C liver cirrhosis, or a history of hepatic encephalopathy, hepatorenal syndrome, or clinically-meaningful ascites related to cirrhosis.
31. The patient has a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to randomization.

In addition, the following exclusion criteria are applicable <u>only</u> to patients to be enrolled into <u>Substudy 3</u>:

32. Administration of a live, attenuated vaccine within 30 days prior to randomization.
33. Treatment with systemic corticosteroids (except for steroidal replacement therapy) or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to first dose of study drug or anticipated requirement for systemic immunosuppressive medications during the study. Generally, inhaled, intranasal, intraocular, topical, and intra-articular joint injections are allowed.
34. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
35. History of allogeneic stem cell or solid organ transplantation.

36. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation.
37. Patients requiring systemic treatment within 3 months prior to randomization or a documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents. (Exceptions include any patient on 10 mg or less of prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema).
38. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on Screening chest CT scan.

4.4 Method of treatment assignment

For all substudies, a unique patient code will be assigned after written informed consent has been obtained, on entering the patient in Medidata RAVE EDC. If a patient withdraws from participation in the study, his or her patient code will not be reused.

4.4.1 Substudy 1

Patients in Substudy 1 are to be stratified by type of $FGFR^{fus/amp/mt}$ (see Section 3.1.1) to be allocated to *Cohort 1.1* ($FGFR2^{fus}$ / $FGFR2^{high\text{-}amp}$) and *Cohort 1.2* ($FGFR1–3^{mt}$)[1] and treated with derazantinib 300 mg QD monotherapy. As of Protocol Version 5.0, enrollment into *Cohorts 1.1* and *1.2* is paused, and eligible patients are enrolled into *Cohort 1.3*.

As of Protocol Version 5.0, patients with GAC harboring $FGFR^{fus/amp/mt}$ allocated to *Cohort 1.3* are to be treated with derazantinib 200 mg BID monotherapy

4.4.2 Substudy 2

All eligible patients in Substudy 2 will receive derazantinib-paclitaxel-ramucirumab in combination; treatment with either derazantinib-paclitaxel or derazantinib-ramucirumab may be considered if the triple combination is not tolerable. Assignment to a specific dose level and cohort will be controlled by the Medidata RAVE EDC system.

4.4.3 Substudy 3

Patients in Substudy 3 are to be stratified for type of $FGFR^{fus/amp/mt}$ and geographic region (see Section 3.1.3), and then randomized (1:1:1:1) to receive the following study treatment, based on a computer-generated randomization schedule via Medidata RAVE EDC:

- ***Cohort 3.1*:** Patients randomized to be treated with **derazantinib** (test)
- ***Cohort 3.2*:** Patients randomized to be treated with **derazantinib-paclitaxel-ramucirumab** (test)
- ***Cohort 3.3*:** Patients randomized to be treated with **derazantinib-atezolizumab** (test)
- ***Cohort 3.4*:** Patients randomized to be treated with **paclitaxel-ramucirumab** (control)

[1] Patients with $FGFR2^{fus}$ or $FGFR2^{high\text{-}amp}$ concurrent to any *FGFR1–3* mutation will be allocated to *Cohort 1.1*.

4.5 Discontinuation from the study treatment or the study

4.5.1 Patient discontinuation from study treatment

Patients must be discontinued from study treatment at any time if they meet any of the following criteria:

- Objective documented radiographic progression of disease per RECIST 1.1 (and/or iRECIST per Investigator discretion; see Section 5.3.3.2.4). Patients will be permitted to remain on study treatment after RECIST 1.1 criteria for PD are met **only** if, in the opinion of the Investigator and with the agreement of the Medical Monitor, they continue to derive benefit from study treatment.
- Documented clinical progression of disease.

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

- Any clinically unacceptable treatment-emergent toxicity occurring in patients treated with derazantinib monotherapy that persists despite optimal treatment or dose reduction.
- Any clinically unacceptable treatment-emergent toxicity clearly attributable to derazantinib, paclitaxel, ramucirumab, or atezolizumab alone or in combination that persists despite optimal supportive care treatment or dose reduction of the respective study drug or combination. In combinations, one study drug could be discontinued while continuation of the other study drug is at the discretion of the Investigator.
- Any severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions to paclitaxel should not be rechallenged with paclitaxel; patients who have developed severe hypersensitivity reactions to ramucirumab should not be rechallenged with ramucirumab (other study drugs may be continued).
- During combination treatment with derazantinib, paclitaxel, and/or ramucirumab, all study drugs should be discontinued for instances of overlapping Grade > 3 toxicity at least possibly study-drug-related (e.g., uncontrolled hypertension, fatigue, uncontrolled diarrhea, ophthalmological and/or hepatic AEs, including, but not limited to, AST increase) (see Section 6.1.6).
- Any clinically unacceptable treatment-emergent toxicities clearly attributable to atezolizumab occurring in patients treated with derazantinib-atezolizumab in combination in *Cohort 3.3* that require management, as detailed in Appendix 4.

  Note: In this instance atezolizumab should be discontinued, whilst continuation of derazantinib is at the discretion of the Investigator.
  Both study drugs (derazantinib and atezolizumab) should be discontinued for instances of overlapping toxicity (e.g., ophthalmological and/or hepatic AEs) that cannot be clearly attributed to either drug.

- Pregnancy (see Section 5.3.2.7).
- Patient decision to discontinue treatment and study visits.

- Withdrawal of consent for treatment and study follow-up calls (i.e., study discontinuation).
- Non-compliance with any part of the study, as assessed by the Investigator or Medical Monitor.
- Investigator's decision after discussion with the Medical Monitor or designee.
- Death.

For all patients who discontinue treatment, AE monitoring must be continued for at least 90 days after the last dose of study drug (see Section 5.3.2.7).

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

4.5.2 Patient discontinuation from the study

Patients who discontinue from study treatment will be followed for survival until the end of the study criteria are met (see Section 3.1.11), either through direct contact or collection of public records (e.g., death certificate) in accordance with local laws, unless they meet any of the following criteria:

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

4.5.3 Replacement of patients

4.5.3.1 Substudy 1

Patients who are non-evaluable for efficacy in Substudy 1 may be replaced. Patients non-evaluable for efficacy are those patients who received less than 50% of the planned derazantinib dose, or have no post-baseline imaging assessment in accordance with RECIST 1.1 without documentation of their disease and/or survival status.

4.5.3.2 Substudy 2

4.5.3.2.1 *Replacement of patients in the Dose-finding Part*

In Substudy 2, patients who received < 80% of the scheduled derazantinib, paclitaxel, or ramucirumab dose, respectively, in Cycle 1 (e.g., due to the vomiting of derazantinib tablets, or the discontinuation of paclitaxel and/or ramucirumab infusions) and who did not experience a DLT (see Section 7.3.3) will not be included in the assessment of the MTD for the particular dose level cohort, and will be replaced. However, patients who received < 80% of the scheduled derazantinib, paclitaxel, or ramucirumab dose, respectively, in Cycle 1 (e.g., due to the vomiting of derazantinib tablets within 2 hours, or the discontinuation of paclitaxel and/or ramucirumab infusions) will be taken into consideration for determination of the RP2D.

4.5.3.2.2 *Replacement of patients in the Dose-expansion Part*

Patients who are non-evaluable for efficacy in the Dose-expansion Part of Substudy 2 may be replaced. Patients non-evaluable for efficacy are those patients who received no doses of derazantinib, or have no post-baseline imaging assessment in accordance with RECIST 1.1 without documentation of their disease and/or survival status.

4.5.3.3 Substudy 3

Patients who are non-evaluable for efficacy in Substudy 3 may be replaced. Patients non-evaluable for efficacy are those patients who received no treatment, or have no post-baseline imaging assessment in accordance with RECIST 1.1 without documentation of their disease and/or survival status.

4.5.4 Study discontinuation

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

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

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

5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 Summary of schedule of assessments

Study patients will be assessed in accordance with the items and schedules provided in Table 1, Table 2, Table 3, and Table 4. All applicable assessments must be documented in the eCRF for each patient.

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

Table 1 Schedule of assessments for Substudy 1

Visit Name	**SV**		**Cycle 1** *(28-day cycle length)*			**Cycle 2+** *(28-day cycle length)*		**End of Treatment**	**Safety Follow-Up**	**Overall Survival Follow-Up**
Assessment window	–	**D −28 to −1**	**D1**	**D8 / D22 (±3d)**	**D15 (±3d**	**D1 (±3d)**	**D8[a] / D15[a] / D22[a] (±3d)**	**Within 7 days***	**28/90 days after last dose (±3d)**	**Every 3 months from date of last dose (±14d)**
Patients applicability		**All**	**All**	**SIAP**	**All**	**All**	**SIAP**	**All**	**All**	**All**
Informed Consent	X[b]	X[c]								
Tumor FGFR[fus/amp/mt] status (liquid biopsy)	X[b]									
Medical history		X								
Treatment allocation/randomization			X							
Physical examination (see Section 5.3.2.1)		X	X			X		X	X	
ECOG PS		X	X	X	X	X	X	X	X	
Ophthalmological examination (see Section 5.3.2.3)		X				X			X	
Triplicate ECG (see Section 5.3.2.4)		X	X	X	X	X	X	X	X	
Clinical safety laboratory blood samples[d]		X	X	X	X	X	X	X	X	
Urinalysis (see Section 5.3.2.6)		X	X			X		X		
Pregnancy test[e]		X	X			X		X	X	
Research liquid biopsy [f]		X				X		X		
Archival tumor tissue[g]		X								
Tumor imaging assessments		X[h]				X[i]		X[ij]		
Study drug administration			X	X[k]	X[k]	X[k]	X[k]			
Study drug dispensing and/or accountability			X			X		X		
Derazantinib PK[l]			X	X	X	X	X		X	
Prior and concomitant medications/treatments		X	X	X	X	X	X	X	X	

* EOT visit is to be within 7 days after the decision to permanently discontinue treatment.
Abbreviations: AE, adverse event; C, cycle; D, day; d, days; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, Not applicable; PK, pharmacokinetics; PRO, patient reported outcome; SIAP: safety interim analysis patients; SV, screening visit.
For footnotes see next page. Note: 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.

a. Only applicable to Cycle 2.

b. Only applicable to patients without a local positive $FGFR^{fus/amp/mt}$ result

c. Signature in a designated section of the study ICF acknowledging the positive $FGFR^{fus/amp/mt}$ test result and documenting the informed decision to participate in the study

d. Safety laboratory blood samples will be tested locally at all study visits. The results of these assessments must be reviewed prior to dosing.

e. 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, the 28-day Safety Follow-up visit and the 90-day Safety Follow-up visit. Monthly serum or urine pregnancy tests will subsequently be performed for 150 days following the last administration of study drug. Monthly pregnancy testing except the 28-day Safety Follow-up visit and the 90-day Follow-up visit 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.

f. A research liquid biopsy should be obtained at the Screening and End of Treatment visits, and at the time point of the confirmatory CT scan (for complete response/partial response), and/or the time point of clinical assessment of progression or the time point for the first CT scan documenting objective/confirmed radiographic progression.

g. Archival tumor tissue (FFPE block; or a minimum of two H&E-stained slipes plus at least 10 consecutive, unstained, 4 ± 1 μm thick sectons, placed on positively charged slides) should be collected at the SV from all enrolled patients for biomarker assessment.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.

h. Tumor assessments performed as standard of care (SoC) prior to obtaining informed consent and within 28 days of the first dose of study drug on C1D1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the SV.

i. Subsequent on-study tumor assessments are to be performed for all patients on C3D1 ±7 days and then every 8 weeks for 6 months (i.e., C5D1 and C7D1 ±7 days), and every 12 weeks (C10D1, C13D1, etc. ±7 days) thereafter (with additional scans as clinically indicated and as per RECIST 1.1 criteria) until disease progression, death, or loss of follow-up. 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.

j. A tumor assessment should be performed at the End-of-Treatment visit only if the prior scan was not done within 4 weeks (28 days) prior to this visit, or if the prior scan did not show radiographic disease progression (see Section 5.3.3.2.3.

k. For pre-dose PK blood sampling at C1D15, C2D1, C3D1, C4D1 (all patients), and C1D8, C1D22, C2D8, C2D15 and C2D22 (safety interim analysis patients), administer derazantinib at the study site.

l. Derazantinib PK blood (plasma) sampling will be performed according to the schedules outlined in Section 5.3.4.

m. Survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries.

Table 2 Schedule of assessments for Substudy 2

Visit Name	**SV**		**Cycle 1** *(28 days cycle length)*			**Cycle 2+** *(28 days cycle length)*			**End of Treatment**	**28-day Safety Follow-Up**	**Overall Survival Follow-Up**
Assessment window	–	**D −28 to −1**	**D1**	**D8 (±3d)**	**D15 (±3d)**	**D1 (±3d)**	**D8 (±3d)**	**D15 (±3d)**	**Within 7 days***	**28/90 days after last dose (±3d)**	**Every 3 months from date of last dose (±14d)**
Informed Consent	X[a]	X[b]									
Tumor FGFR$^{fus/amp/mt}$ status (liquid biopsy)	X[a]										
Medical history		X									
Treatment allocation/randomization			X								
Physical examination (see Section 5.3.2.1)		X	X			X			X	X	
ECOG PS		X	X	X	X	X	X	X	X	X	
Ophthalmological examination (see Section 5.3.2.3)		X				X				X	
Triplicate ECG (see Section 5.3.2.4)		X	X		X	X			X	X	
Clinical safety laboratory blood samples		X	X	X	X	X	X	X	X	X	
Urinalysis (see Section 5.3.2.6)		X	X	X	X	X	X	X	X		
Pregnancy test[c]		X	X			X			X	X	
Research liquid biopsy		X							X		
Archival tumor tissue[d]		X									
Tumor imaging assessments		X[e]				X[f]			X[g]		
Study drug administration			X	X	X	X	X	X			
Study drug dispensing and/or accountability			X			X			X		
Derazantinib/paclitaxel/ramucirumab PK[h] (see Section 5.3.4.3)			X	X	X	X				X	
AE assessments[i] (see Section 7.2)		X	X	X	X	X	X	X	X	X	
Prior and concomitant medications/treatments		X	X	X	X	X	X	X	X	X	
Survival contact[j]											X

* EOT visit is to be within 7 days after the decision to permanently discontinue treatment.
Abbreviations: AE, adverse event; C, cycle; D, day; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PK, pharmacokinetics; SV, screening visit.
For footnotes see next page. Note: 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, maintaining a minimum of at least 7 days between two paclitaxel administrations and at least 14 days between two ramucirumab administrations.

a. Only applicable to patient without a local positive FGFR$^{fus/amp/mt}$ result

b. Signature in a designated section of the study ICF acknowledging the positive FGFR$^{fus/amp/mt}$ test result and documenting the informed decision to participate in the study.

c. 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, the 28-day Safety Follow-up visit and the 90-day Follow-up visit. Monthly serum or urine pregnancy tests will subsequently be performed for 150 days following the last administration of study drug. Monthly pregnancy testing except the 28-day Safety Follow-up visit and the 90-day Follow-up visit 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.

d. Archival tumor tissue (FFPE block; or a minimum of two H&E-stained slipes plus at least 10 consecutive, unstained, 4 ± 1 µm thick sectons, placed on positively charged slides) should be collected at the SV from all enrolled patients for biomarker assessment.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.

e. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of the first dose of study drug on C1D1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the SV.

f. Subsequent on-study tumor assessments are to be performed for all patients on C3D1± 7 days and then every 8 weeks for 6 months (.i.e., C5D1 and C7D1 ± 7 days), and every 12 weeks (C10D1, C13D1 etc. ± 7 days) thereafter (with additional scans as clinically indicated and as per RECIST 1.1 criteria) until disease progression, death, or loss of follow-up. 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.

g. A tumor assessment should be performed at the End of Treatment visit only if the prior scan was not done within 4 weeks (28 days) prior to this visit, or if the prior scan did not show radiographic disease progression (see Section 5.3.3.2.3).

h. Blood (plasma or serum) sampling for derazantinib, paclitaxel and ramucirumab PK assessments will be performed shown in Section 5.3.4. No paclitaxel/ramucirumab PK assessment at 90-day Safety Follow-up visit.

i. AEs occurring between C1D1 and C1D28 in patients in the dose-limiting toxicity (DLT) Part of Substudy 2 will be assessed against the DLT definitions (outlined in Section 7.3.3) prior to study drug administration on C2D1. DLTs are also to be recorded in the electronic case report form.

j. Survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries.

Table 3 Schedule of assessments for Substudy 3 (except *Cohort 3.3*)

Visit Name	**SV**		**Cycle 1** *(28-day cycle length)*			**Cycle 2+** *(28-day cycle length)*			**End of Treatment**	**Safety Follow-Up**	**Overall Survival Follow-Up**
Patient applicablitiy	**All**		**All**	**P-R[a]**	**All**	**All**	**P-R[a]**		**All**		
Assessment window	**_**	**D −28 to −1**	**D1**	**D8 (±3d)**	**D15 (±3d)**	**D1 (±3d)**	**D8 (±3d)**	**D15 (±3d)**	**Within 7 days***	**28/90 days after last dose (±3d)**	**Every 3 months from date of last dose (±14d)**
Informed Consent	X[b]	X[c]									
Tumor FGFR[fus/amp/mt] status (liquid biopsy)	X[b]										
Medical history		X									
Treatment allocation/randomization			X								
Physical examination (see Section 5.3.2.1)		X	X	X	X	X	X	X	X	X	
ECOG PS		X	X	X	X	X	X	X	X	X	
Ophthalmological examination (see Section 5.3.2.3)		X				X				X	
Triplicate ECG (see Section 5.3.2.4)		X	X		X	X			X	X	
Clinical safety laboratory blood samples[d]		X	X	X[e]	X	X	X[e]	X[e]	X	X	
Urinalysis (see Section 5.3.2.6)		X	X	X	X	X	X	X	X		
Pregnancy test[f]		X	X			X			X	X	
Research liquid biopsy[g]		X					X		X		
Tumor imaging assessments		X[h]				X[i]			X[j]		
Study drug administration[k]			X	X	X	X	X	X			
Study drug dispensing and/or accountability			X			X			X		
Derazantinib[l] / Paclitaxel[m] PK			X		X	X					
Ramucirumab[n] PK			X		X	X				X	
AE assessments (see Section 7.2)		X	X	X	X	X	X	X	X	X	
PRO assessments (see Section 5.3.6)			X			X			X	X	
Prior and concomitant medications/treatments		X	X	X	X	X	X	X	X	X	
Survival contact[o]											X

* EOT visit is to be within 7 days after the decision to permanently discontinue treatment.
Abbreviations: AE, adverse event; C, cycle; D, day; d, days; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, Not applicable; P-R, patients treated with paclitaxel-ramucirumab in combination; PK, pharmacokinetics; PRO, patient reported outcome; SV, screening visit.
For footnotes see next page. Note: 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, maintaining a minimum of at least 7 days between two paclitaxel administrations and at least 14 days between two ramucirumab administrations.

a. Only applicable to ***Cohorts 3.2.*** and ***3.4*** in Substudy 3.

b. Only applicable to patient without a local positive $FGFR^{fus/amp/mt}$ result

c. Signature in a designated section of the study ICF acknowledging the positive $FGFR^{fus/amp/mt}$ test result and documenting the informed decision to participate in the study.

d. Safety laboratory blood samples at the Screening visit must include a tuberculosis blood test (e.g., interferon-gamma release assay) and serology for human immunodeficiency virus, chronic hepatitis B, or hepatitis C.

e. **Applicable to *Cohorts 3.2* and *3.4* only:** On D8 and D15 of all treatment cycles, patients should undergo safety laboratory blood sample testing within 1 day prior to paclitaxel-ramucirumab administration. The results of these assessments must be reviewed prior to dosing.

f. 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, the 28-day Safety Follow-up visit and the 90-day Follow-up visit. Monthly serum or urine pregnancy tests will subsequently be performed for 150 days following the last administration of study drug. Monthly pregnancy testing except the 28-day Safety Follow-up visit and the 90-day Safety Follow-up visit 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.

g. A research liquid biopsy should be obtained at the Screening and End of Treatment visits, and at the time point of the confirmatory CT scan (for complete response/partial response), and/or the time point of clinical assessment of progression or the time point for the first CT scan documenting objective/confirmed radiographic progression.

h. Tumor assessments performed as standard of care (SoC) prior to obtaining informed consent and within 28 days of the first dose of study drug on C1D1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the SV.

i. Subsequent on-study tumor assessments are to be performed for all patients on C3D1 ±7 days and then every 8 weeks for 6 months (i.e., C5D1 and C7D1 ±7 days), and every 12 weeks (C10D1, C13D1, etc. ±7 days) thereafter (with additional scans as clinically indicated and as per RECIST 1.1 criteria) until disease progression, death, or loss of follow-up. 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.

j. A tumor assessment should be performed at the End-of-Treatment visit only if the prior scan was not done within 4 weeks (28 days) prior to this visit, or if the prior scan did not show radiographic disease progression (see Section 5.3.3.2.3).

k. Derazantinib will be administered QD, ramucirumab on D1 and D15 of each cycle and paclitaxel on D1, D8 and D15 of each cycle, when applicable. Paclitaxel must not be started earlier than 60 minutes after completion of the ramucirumab infusion; the 1-hour observation period between administration of ramucirumab and paclitaxel is mandatory for the first two cycles, but may be omitted in Cycle 3 and beyond provided there has been no evidence of infusion-related reaction.

l. Applicable to patients treated with derazantinib (***Cohorts 3.1*** and ***3.2***). Blood (plasma) sampling for derazantinib PK assessments will be performed per schedule shown in Table 7, Table 9, and Table 10.

m. Applicable to patients treated with paclitaxel (***Cohort 3.2***). Blood (plasma) sampling for paclitaxel PK assessments will be performed per schedule shown in Section 5.3.4.5 Table 10.

n. Applicable to patients treated with ramucirumab (***Cohorts 3.2*** and ***3.4***). Blood (serum) sampling for ramucirumab PK assessments will be performed per schedule shown in Section 5.3.4.5 Table 10 and Section 5.3.4.7 Table 12. No ramucirumab PK assessment at 90-day Safety Follow-up visit.

o. Survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries.

Table 4 Schedule of assessments for *Cohort 3.3*

	SV		Cycle 1 *(21-day cycles)*		Cycle 2+ *(21-day cycles)*	End of Treatment	Safety Follow-Up	Overall Survival Follow-Up
Assessment window	–	D –28 to –1	D1	D15 (±3d)	D1 (±3d)	Within 7 days*	28/90 days after last dose (±3d)	At least every 3 months from date of last dose (±14d)
Informed Consent	X[a]	X[b]						
Tumor $FGFR^{fus/amp/mt}$ status (liquid biopsy)	X[a]							
Medical history		X						
Randomization			X					
Physical examination (see Section 5.3.2.1)		X	X	X	X	X	X	
ECOG PS		X	X	X	X	X	X	
Ophthalmological examination (see Section 5.3.2.3)		X			X		X	
Triplicate ECG (see Section 5.3.2.4)		X	X	X	X	X	X	
Clinical safety laboratory blood samples		X	X	X	X	X	X	
Urinalysis (see Section 5.3.2.6)		X	X	X	X	X		
Pregnancy test[c]		X	X		X	X	X	
Research liquid biopsy [d]		X			X	X		
Tumor imaging assessment		X[e]			X[f]	X[g]		
Study drug administration			X		X			
Study drug dispensing and/or accountability			X		X	X		
Derazantinib[h] PK (see Section 5.3.4.4)			X	X	X			
Atezolizumab[i] PK and ADA (see Section 5.3.4.6)			X		X		X	
AE assessments (see Section 7.2)		X	X	X	X	X	X	
PRO assessments (see Section 5.3.6)			X		X	X	X	
Prior and concomitant medications/treatments		X	X	X	X	X	X	
Survival contact[j]								X

* EOT visit is to be within 7 days after the decision to permanently discontinue treatment.
Abbreviations: AE, adverse event; C, cycle; D, day; d, days; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, Not applicable; PK, pharmacokinetics; PRO, patient reported outcome; SV, screening visit.
For footnotes see next page. Note: 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.

a. Only applicable to patient without a local positive $FGFR^{fus/amp/mt}$ result

b. Signature in a designated section of the study ICF acknowledging the positive $FGFR^{fus/amp/mt}$ test result and documenting the informed decision to participate in the study.

c. 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, the 28-day Safety Follow-up visit and the 90-day Follow-up visit. Monthly serum or urine pregnancy tests will subsequently be performed for 150 days following the last administration of study drug. Monthly serum or urine pregnancy testing except the 28-day Safety Follow-up visit and the 90-day Safety Follow-up visit 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.

d. A research liquid biopsy should be obtained at the Screening and End of Treatment visits, and at the time point of the confirmatory CT scan (for complete response/partial response, or if applicable confirmed progressive disease [iCPD]), and/or the time point of clinical assessment of progression or the time point for the first CT scan documenting objective/confirmed radiographic progression.

e. Tumor assessments performed as SoC prior to obtaining informed consent and within 28 days of the first dose of study drug on C1D1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the SV.

f. Subsequent on-study tumor assessments are to be performed on C3D15, then every 8 weeks (i.e. C6D8 and C9D1, ±7 days) for 6 months, and every 12 weeks (C13D1, C17D1, etc. ±7 days) thereafter (with additional scans as clinically indicated and as per RECIST 1.1 criteria) until disease progression, death, or loss of follow-up. 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.

g. A tumor assessment should be performed at the End-of-Treatment visit only if the prior scan was not done within 4 weeks (28 days) prior to this visit, or if the prior scan did not show radiographic disease progression (see Section 5.3.3.2.3).

h. Blood (plasma) sampling for derazantinib PK assessments will be performed per schedule shown in Section 5.3.4.6 Table 11.

i. Blood (serum) sampling for atezolizumab PK and ADA assessments will be performed per schedule shown in Section 5.3.4.6 Table 11 . No atezolizumab PK and ADA assessments at 90-day Safety Follow-up visit.

j. Survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries.

5.2 Study visits

5.2.1 Informed consent

For patients with no documented local NGS test result with an eligible FGFR$^{fus/amp/mt}$, the IEC/IRB approved ICF for pre-screening must first be signed by each prospective study participant to permit central testing for eligible FGFR$^{fus/amp/mt}$.

Written informed consent must be obtained from each patient by the Investigator or designee prior to initiation of any study procedures (see Section 10.2 for details). A patient may only participate in the overall study once.

For patients who received paclitaxel-ramucirumab in *Cohort 3.4* who are to be eligible for crossing over to derazantinib treatment (see Section 3.1.9), a separate specific Crossover Treatment ICF providing consent for the additional treatment and applicable extension of study-related procedures must be signed. The written informed consent acknowledges the specific benefit-risk profile of derazantinib treatment and the extension of study-related procedures aligned with *Cohort 3.1* (see Table 3).

Patients who agree to participate in the study will sign the most recently approved applicable ICF(s) and will be provided with a copy of the document(s). Informed consent must be obtained within the 28 days prior to the first dose of study treatment on Cycle 1, Day 1 (C1D1).

5.2.2 Pre-screening visit

A Pre-screening visit is only required for prospective study participants if no documented local NGS test result with an eligible FGFR$^{fus/amp/mt}$ is available at the Screening visit (see Section 3.1.4).

During the Pre-screening visit a liquid biopsy blood sample for molecular central testing will be collected after written informed consent for pre-screening is obtained. The central testing will be performed in a laboratory designated by the Sponsor and will be based on NGS testing of cfDNA from a liquid biopsy obtained at Pre-screening visit.

It is recommended to conduct the Pre-screening visit for liquid biopsy sampling following assessment of objective documented progression after prior anti-cancer treatment. However, in the interests of patients and to reduce off-treatment time between the last anti-cancer treatment and study treatment, liquid biopsy sampling might be performed at any time point after the last administration of anti-cancer therapy when disease progression is suspected. Liquid biopsy re-screening for molecular inclusion criteria is not permitted, unless the liquid biopsy was not evaluable for technical reasons.

5.2.3 Screening visit

The screening window for clinical screening procedures will be 28 days. Taking the required interval period between prior antitumor treatment and initiation of study treatment into consideration, the screening period is recommended to be kept as short as possible to limit the number of patients experiencing clinical deterioration due to their disease progression.

At the Screening visit, clinical eligibility of prospective study participants and baseline disease status will be assessed. Patients who satisfy all of the inclusion criteria (see Section 4.2) and none of the exclusion criteria (see Section 4.3) may be enrolled.

After written informed consent is obtained, the following will be evaluated within 28 days prior to the first dose of study treatment and documented in the eCRF:

- Demographics/medical history/baseline medical conditions (see Sections 5.3.1.2)
- Medical history of cancer diagnosis and treatment (see Section 5.3.1.3)
- Record prior and concomitant medications (medications used within 30 days prior to Screening) (see Section 5.3.1.4)
- Physical examination, including height, weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Complete ophthalmic examination, including optical coherence tomography (OCT) (see Section 5.3.2.3)
- Triplicate 12-lead ECG (see Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Research liquid biopsy
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable (see Inclusion criterion 10, Section 5.3.2.7, and Section 7.1.5
- Tumor imaging assessments, according to RECIST 1.1 (see Section 5.3.3.2 and Appendix 2)

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

- Archival tumor tissue for molecular biomarker assessments, including PD-L1 testing (FFPE block; or a minimum of two H&E-stained slides plus at least 10 consecutive, unstained, 4 ± 1 µm thick sections, placed on positively charged slides)
- AEs that occur following the full execution of the study ICF but prior to dosing, must be recorded in the medical history page of the eCRF. If the event is assessed as serious and related to the study procedure, the AE must be reported as an SAE as described in Section 7.2.2

Patients may repeat the screening procedures within the screening period after initially failing to meet the clinical inclusion criteria; rescreening for molecular inclusion criteria is not permitted unless the liquid biopsy was not evaluable for technical reasons. Under rare conditions and contingent on Sponsor approval, patients may be given the possibility to be re-screened after initially failing screening.

Patients who cannot be enrolled because they were planned for Substudy 2 but no slot was available should have the option to be enrolled into Substudy 1, either directly, or at a later stage when they progress under second-line treatment.

Patients who meet molecular inclusion criteria but with disease progression not confirmed at the screening CT are allowed to be clinically re-screened at the time PD is established.

5.2.4 Treatment period

All visits are based on the date of the first dose at C1D1 regardless of drug holds. If a patient visit deviates from the protocol permitted window, the next visit must be done at the correct time based on the date of C1D1. In Substudies 2, *Cohorts 3.2* and *3.4*, a minimum of at least 7 days needs to be maintained between two paclitaxel administrations and at least 14 days between two ramucirumab administrations.

Adverse events (see Section 7.2) and concomitant medications (see Section 6.4) will be recorded on an ongoing basis during the treatment period, and at the selected time points as summarized in Table 1, Table 2, Table 3, and Table 4.

5.2.4.1 Cycle 1, Day 1 (all patients)

Patients will be considered enrolled, i.e., allocated/randomized on C1D1, or as close as possible to the date on which treatment is allocated.

In all substudies, the following assessments will be made during this visit (all assessments except for AE assessment and post-dose PK blood collection [where applicable; see Section 5.3.4]) must be performed prior to the first dose):

- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Triplicate 12-lead ECG (performed pre-dose and 6-8 hours after the first dose of study drug) (see Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)

  Note: 25-hydroxy vitamin D is required at C1D1, C3D1, C5D1, and the End of Treatment visit only. CRP is required at C1D1 only and thereafter if infection is suspected. TSH, fT3 and fT4 is required at C1D1 and subsequently every 4 cycles
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable, within 72 hours prior to dosing (see Section 5.3.2.7, and Section 7.1.5)
- Blood samples for PK and ADA (see Section 5.3.4 for details of sampling schedule in each substudy)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)

Furthermore, the following assessments will be made during this visit in specific substudies only:

- **Substudy 1:**
  - Dispense and administer derazantinib (see Section 6.1.1.4)
- **Substudy 2:**
  - Dispense and administer derazantinib, paclitaxel, ramucirumab (see Sections 6.1.1.4, 6.1.2.6, and 6.1.3.6)
- **Substudy 3:**
  - PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician) (see Section 5.3.6)
  - Dispense and administer derazantinib, paclitaxel, ramucirumab and/or atezolizumab as applicable according to the patient's treatment allocation (see respective Sections 6.1.1.4, 6.1.2.6, 6.1.3.6 and/or 6.1.4.5)

5.2.4.2 Cycle 1, Day 8 and Day 22 (±3 days) – safety interim analysis patients in Substudy 1

The following assessments will be made during this visit:

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Blood samples for derazantinib PK (see Section 5.3.4.2 for details of sampling schedule)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours post-derazantinib dosing) (see Section 5.3.2.3)
- Record concomitant medications (see Section 5.3.2.9)
- Administer derazantinib capsules (see Section 6.1.1.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)

5.2.4.3 Cycle 1, Day 8 (±3 days) – paclitaxel-ramucirumab treatment cycles only

The following assessments will be made during this visit:

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Urinalysis (see Section 5.3.2.6)
- Blood samples for PK (see Section 5.3.4 for details of sampling schedule in each substudy)
- Administer paclitaxel (see Section 6.1.4.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)

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

The following assessments will be made during this visit:

- ECOG PS (see Section 5.3.2.2)
- Triplicate 12-lead ECG (see Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Urinalysis (see Section 5.3.2.6)
- Administer derazantinib capsules (if applicable) (see Section 6.1.1.1)Administer paclitaxel-ramucirumab (if applicable) (see Section 6.1.4.1)
- Blood samples for PK and ADA (see Section 5.3.4 for details of sampling schedule in each substudy)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)

5.2.4.5 Cycle 2+, Day 1 (± 3 days)

In all substudies, the following assessments will be made during this visit:

- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Complete ophthalmological examination, including OCT (for the first four treatment cycles [i.e., Day 1 of Cycles 2–5], and if clinically indicated thereafter; see Section 5.3.2.3)
- Triplicate 12-lead ECG (required on D1 of all cycles prior to dosing, or if clinically indicated; see Section 5.3.2.4).
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5).

  Note: Thyroid panel (Thyroid stimulating hormone [TSH], tri-iodothyronine [fT3], thyroxine [fT4]) are required every four cycles from C1D1; ; and 25-hydroxy vitamin D is required at C1D1, C3D1 and C5D1 and the End of Treatment visit only.
- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy test, if applicable, within 72 hours prior to dosing (see Section 5.3.2.7, and Section 7.1.5)
- Blood samples for PK and ADA (see Section 5.3.4 for details of sampling schedule in each substudy)
- Assess and record any DLTs (safety interim analysis patients in Substudy 1, Substudy 2 (Dose-finding Part) patients only) (see Section 7.3.3)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)
- If applicable, perform drug accountability of returned drug (see Section 6.1.1.3) and dispense derazantinib capsules (see Section 6.1.1.4)

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

- If applicable, dispense/administer study medication (see Sections 6.1.2.6, 6.1.3.6, 6.1.4.5, and 6.1.5 for derazantinib, paclitaxel, ramucirumab and atezolizumab, respectively) and perform drug accountability for any incompletely administered study drug (see respective Sections 6.1.2.3, 6.1.3.3, 6.1.4.3, and 6.1.5)
- Substudy 3 only: PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician; see Section 5.3.6)
- If applicable, tumor measurement and response evaluation until disease progression, death, or loss to follow-up (see Section 5.3.3.2 and Appendix 2).

Tumor imaging assessments are performed every 8 weeks (±7 days) for 6 months, and every 12 weeks (±7 days) (see Section 5.3.3.2 and Appendix 2).

Additionally, all patients should undergo a research liquid biopsy (see Section 5.3.5.1) at the time point of the CT scan (confirming response.

5.2.4.6 Cycle 2, Day 8, Day 15, and Day 22 (±3 days) – safety interim analysis patients in Substudy 1

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

- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Blood samples for derazantinib PK (see Section 5.3.4.2 for details of sampling schedule)
- Triplicate 12-lead ECGs (performed pre-dose and 6–8 hours post-derazantinib dosing) (see Section 5.3.2.4)
- Record concomitant medications (see Section 5.3.2.9)
- Administer derazantinib capsules (see Section 6.1.1.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8

5.2.4.7 Cycle 2+, Day 8 (±3 days) – paclitaxel treatment cycles only

The following assessments will be made during this visit:

- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Urinalysis (see Section 5.3.2.6)
- Dispense and administer paclitaxel (see Section 6.1.2.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)

5.2.4.8 Cycle 2+, Day 15 (±3days) – paclitaxel-ramucirumab treatment cycles only

The following assessments will be made during this visit:

- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Urinalysis (see Section 5.3.2.6)
- Dispense and administer paclitaxel-ramucirumab (see Section 6.1.2.1)
- Assess and record any AEs after study medication administration (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)

5.2.4.9 End of Treatment assessment (within 7 days after the decision to permanently discontinue all study drug) – all patients

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

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

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

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

- Urinalysis (see Section 5.3.2.6)
- Serum pregnancy testing (see Section 5.3.2.7 and Section 7.1.5)
- Research liquid biopsy (see Section 5.3.5.1)
- Tumor imaging assessment, if the prior scan was not done within four weeks (28 days) prior to this visit or if the prior scan did not show radiographic disease progression (see Section 5.3.3.2 and Appendix 2). For patients who discontinue study treatment without documented radiologic disease progression, every effort should be made to perform radiologic imaging.
- Assess and record any AEs (see Section 5.3.2.8)
- Record concomitant medications (see Section 5.3.2.9)
- Perform drug accountability of returned derazantinib (if applicable) (see Section 6.1.1.3)
- Substudy 3 only: PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician; see Section 5.3.6)

5.2.4.10 Safety follow-up (28 days / 90 days after last dose ± 3 days)

All patients will be followed for a minimum of 90 days after the last dose of all study treatment. During the 90-day safety follow-up period, all AEs/SAEs and changes in concomitant medication should be reported.

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

At the safety follow-up visits, the following assessments will be performed:

- Assess and record any AEs (see Section 5.3.2.8)
- Physical examination, including weight and vital signs (see Section 5.3.2.1)
- ECOG PS (see Section 5.3.2.2)
- Complete ophthalmological examination, including OCT (see Section 5.3.2.3)
- Triplicate 12-lead ECG (Section 5.3.2.4)
- Clinical safety laboratory blood tests (see requirements in Section 5.3.2.5)
- Serum pregnancy testing. Subsequently, serum or urine pregnancy testing should be performed monthly until 150 days after the last administration of study drug (see Section 5.3.2.7, and Section 7.1.5).
- Blood samples for PK and ADA (see Section 5.3.4)
- Concommitant medications (see Section 5.3.2.9)
- Substudy 3 only: PRO instruments (questionnaires should be completed by the patient prior to being evaluated by the physician; see Section 5.3.6)

5.2.5 Survival follow-up period

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

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

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

Survival updates may be made more often than every 3 months if the patient is seen at the investigational site for other reasons and for study level survival sweep(s). The survival follow-up period will continue until the study has completed (see Section 4.5.4) or other discontinuation criteria are met (see Section 4.5).

5.3 Study procedures

5.3.1 Screening procedures

5.3.1.1 Medical history / baseline medical conditions

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

5.3.1.2 Demography

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

5.3.1.3 Prior cancer history

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

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

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

5.3.1.4 Prior and concomitant medications

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

5.3.2 Safety assessments

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

These safety assessments must be performed at intervals indicated in the schedule of assessments (see Table 1, Table 2, Table 3, and Table 4). More frequent assessments may be performed at the Investigator's discretion, if medically indicated.

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

5.3.2.1 Physical examination, including vital signs

A complete physical examination of the major body systems should be performed at intervals indicated in the schedule of assessments (see Table 1, Table 2, Table 3, and Table 4).

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

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

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

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

5.3.2.2 Eastern Cooperative Oncology Group performance status

ECOG PS will be assessed at all study visits.

Table 5 provides the scale to be used for these assessments.

Table 5 ECOG performance status

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

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

5.3.2.3 Complete ophthalmological examination

A complete ophthalmological examination, including optical coherence tomography (OCT), should be performed by an ophthalmologist at the Screening visit, on D1 of the first four treatment cycles (i.e., Day 1 of Cycles 2–5)[1], at the 28-day Safety Follow-up visit, and at the 90-day Safety Follow-up visit. Note, the examination may be performed up to 8 days prior to the study visits. Thereafter, a complete ophthalmological examination is to be repeated if clinically indicated (e.g., new ocular symptoms occur, or vision is impaired).

[1] A more frequent schedule (i.e., every 3 months as of C5D1) may required in accordance with local regulations and where specified in a local ICF (e.g., for patients enrolled in France).

The complete ophthalmological examination include the following:

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

For the individual patient, the same methods of assessment should be used throughout the study. Patients who develop ocular symptoms or changes in visual acuity while on the study should be referred to the ophthalmologist for a complete ophthalmological examination.

5.3.2.4 Electrocardiogram (12-lead) triplicates

A standard, triplicate, 12-lead ECG should be performed at the intervals indicated in the schedule of assessments (see Table 1, Table 2, Table 3, and Table 4).

ECGs must always be recorded after at least 5 minutes rest and while the patient is in a supine or semi-supine position. Measurements should be separated by ~1 minute and be taken within a 5-minute time window.

In patients treated with derazantinib monotherapy in Substudies 1 and 3, on-treatment ECGs (up to Cycle 4) should be performed as close as possible to the corresponding PK blood collection time point during those visits (i.e., pre-dose and 6–8 hours after derazantinib administration; see Section 5.3.4.4); if possible, the ECG should be measured first, and then blood collected for PK within 5–10 minutes.

ECGs must be assessed by the Investigator or their designee for any abnormalities, including prolongation of QTcF; the three QTcF values obtained should be averaged for a mean QTcF value for decision making. The ECG printouts are to be signed and dated by the Investigator or their designee. Any clinically-significant ECG change from baseline that occurs after first study-drug administration must be reported as an AE (see Section 7.4.3).

5.3.2.5 Clinical safety laboratory blood tests

Blood samples for clinical safety laboratory testing should be performed locally at all study visits.

These assessments must be reviewed prior to dosing, and study drug administration after C1D1 should only occur if local laboratory test values are acceptable (i.e., CTCAE Grade 2 or less), unless dose delays or modifications are clinically indicated (as assessed by the Investigator and agreed upon by Medical Monitor or designee; see Section 6.1.1.5).

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

Clinical safety laboratory tests will comprise the following:

- ***Hematology:*** complete blood count including hemoglobin, hematocrit, absolute white blood cell count with 5-part differential, red blood cell count, and platelet count
- ***Blood chemistry:*** albumin, amylase, lipase, sodium, potassium, calcium, magnesium, chloride, phosphate, C-reactive protein (CRP), creatinine, glucose, and total protein
  - CRP is required at C1D1 and thereafter only if infection is suspected;
  - CL_{CR}, as calculated by the Cockcroft-Gault equation (at the Screening Visit only);
- ***Liver function tests:*** ALT, AST, alkaline phosphatase (ALP), total and direct bilirubin, lactate dehydrogenase
- ***Coagulation tests:*** prothrombin time, INR, and partial prothrombin time (at the Screening and End of Treatment visits, and if clinically indicated)
- ***Other tests:*** thyroid panel (TSH, fT3, fT4), and Vitamin D
  - TSH, fT3 and fT4 is required at C1D1 and subsequently every 4 cycles;
  - 25-hydroxy vitamin D is required at C1D1, C3D1, C5D1, and the End of Treatment visit only.

Furthermore, prospective Substudy 3 patients must undergo a tuberculosis blood test (e.g., interferon-gamma release assay) and serology for human immunodeficiency virus, chronic hepatitis B, or hepatitis C at the Screening visit.

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

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

5.3.2.6 Urinalysis

Urinalysis will be performed locally at the intervals indicated in the schedule of assessments (see Table 1, Table 2, Table 3, and Table 4).

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

5.3.2.7 Pregnancy testing

Women of child-bearing potential must have a negative hCG at Screening and within 72 hours prior to dosing at C1D1. Subsequently, serum pregnancy testing will be performed prior to study drug dosing on D1 of every cycle, at the End of Treatment visit, at the 28-day Safety Follow-up visit and at the 90-day Safety Follow-up visit. Monthly

serum or urine pregnancy tests must be performed for 150 days following the last administration of study treatment.

Monthly serum or urine pregnancy testing after the 28-day Safety Follow-up visit may be performed by the patient's local gynecologist (with the exception of the test to be performed at the 90-day Safety Follow-up visit) to reduce the burden related to study visits at the site, but must be communicated to the study Investigator.

The Investigator may conduct additional pregnancy tests (serum or urine) to confirm the absence of pregnancy at any time during the study. If a pregnancy test result is positive, study drug must be discontinued, the patient followed for safety, and the outcomes of the pregnancy assessed (see Section 7.4.5). Further details regarding the risk of pregnancy are provided in Section 7.1.5.

5.3.2.8 Adverse event monitoring

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

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

5.3.2.9 Concomitant medications

Concomitant medications during the course of the study (until the safety follow-up visit at Day 90 for all patients) must be recorded in the eCRF (see Section 6.4).

5.3.3 Efficacy assessments

5.3.3.1 Tumor imaging and assessment of disease

The process for image collection and transmission to the central imaging vendor is provided in the Imaging Charter. Tumor imaging assessments should comprise of CT (strongly preferred) or MRI of the chest, abdomen, and pelvis. MRI should primarily be used when CT is contraindicated.

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

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

5.3.3.2 Tumor measurement and response evaluations

5.3.3.2.1 *Baseline tumor imaging*

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

For initial tumor imaging of all patients at Screening, the site study team must review Screening images to confirm the patient has measurable disease per RECIST 1.1 (Appendix 3).

Local site Investigator/radiology assessment based on RECIST 1.1 will be used to determine patient eligibility. All measurable and evaluable lesions should be assessed and documented by the site study team at the Screening visit. Baseline imaging assessments must be submitted to the central imaging vendor and serve as baseline for subsequent central evaluations.

A bone scan (BS) – alternatively, a whole-body MRI (WBMRI) – should be performed at Screening only in patients with new symptoms (e.g., new persistently elevated ALP) to assess bone metastasis; screening of asymptomatic patients for clinically unapparent bone metastases is not supported by applicable guidelines (Ajani 2016, Smyth 2016a) but may be done at the Investigator's discretion if local routine practice. Patients with positive BS/WBMRI at baseline will undergo further radiologic assessments of bone lesions performed at protocol-scheduled time points for tumor assessments (see Section 5.3.3.2.2) and as per institutional practice. Lytic/mixed lesions with soft tissue component may be included in the evaluation of disease burden if it meets measurability criteria, while blastic lesions are considered non-measurable, in accordance with RECIST 1.1.

5.3.3.2.2 *On-treatment tumor imaging*

Study imaging assessments are identical to the imaging modalities used for baseline assessments. In general, and following common oncology practice, on-treatment tumor imaging assessments should be performed and evaluated prior to initiation of any new treatment cycle; results of all tumor imaging assessments must be reviewed by the Investigator before dosing at the next cycle to avoid treatment beyond objective radiographic disease progression. However, if necessary for administrative and organizational reasons, and in the absence of unequivocal signs of clinical worsening, it is acceptable to perform the on-treatment tumor imaging assessment after the start of a new treatment cycle, providing it is within 7 days of the start of the cycle.

Imaging timing should follow calendar days, and should not be adjusted for delays in cycle starts (i.e., the intervals indicated below should be followed throughout in all substudies irrespective of cycle intervals).

In all substudies, on-treatment tumor imaging is subject to BICR. In all substudies, the first on-study tumor imaging assessments will be performed on C3D1 ±7 days, and subsequently every 8 weeks (i.e., C5D1 and C7D1 ±7 days) for 6 months, then every 12 weeks (C10D1, C13D1 etc, ±7 days) thereafter (or more frequently if clinically indicated). New osseous uptake / lesions on BS/WBMRI in comparison to available prior BS/WBMRI will be assessed for progression per RECIST 1.1 (Appendix 3).

In *Cohort 3.3* and with regard to the 3-week cycle interval, the first on-study tumor assessments will be performed on C3D15, and subsequently every 8 weeks (i.e. C6D8 and C9D1, ±7 days) for 6 months, and then every 12 weeks (C13D1, C17D1 etc, ±7 days) thereafter (with additional scans as clinically indicated).

5.3.3.2.3 *Post-treatment tumor imaging*

Patients who discontinue study treatment should have a tumor imaging assessment as soon as possible, but no later than 28 days after the event. If a previous scan was obtained within 28 days prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory but recommended if the clinical situation indicates an altered disease status. For patients who discontinue study treatment due to documented PD, this is the final required tumor imaging for the study.

5.3.3.2.4 *Tumor imaging of patients after treatment crossover*

For patients enrolled in *Cohort 3.4*, the tumor imaging used to determine PD after paclitaxel-ramucirumab treatment can be used as the new baseline image for the Crossover Phase if this was obtained within the 28 days prior to receiving the first dose of derazantinib monotherapy.

Imaging timing should follow calendar days, and should not be adjusted for delays in cycle starts (i.e., the 8-/12-week intervals should be followed throughout in all substudies and irrespective of cycle intervals).

The first Crossover Phase tumor imaging assessments will be performed on C3D1 ±7 days, and subsequently every 8 weeks (i.e., C5D1 and C7D1 ±7 days) for 6 months, then every 12 weeks (C10D1, C13D1 etc ± 7 days) thereafter (or more frequently if clinically indicated). New osseous uptake / lesions on BS/WBMRI in comparison to available prior BS/WBMRI will be assessed for progression per RECIST 1.1 (Appendix 3).

5.3.3.2.5 *RECIST 1.1 and iRECIST*

Efficacy will be measured by ORR and PFS4, both evaluated by BICR using RECIST 1.1 (see Appendix 3).

In addition, in *Cohort 3.3* an exploratory assessment will be performed using iRECIST criteria (Seymour 2017) in patients treated with derazantinib-atezolizumab in combination (see Appendix 3 for comparison of RECIST 1.1 and iRECIST).

In patients undergoing combination treatment with derazantinib and atezolizumab, iRECIST will be used by the site Investigator / local radiology review to assess tumor response and progression, and to make treatment decisions. These data will be collected in the clinical database. Treatment efficacy based on iRECIST as assessed by central imaging vendor review will be evaluated retrospectively.

For all patients with CR or PR per RECIST 1.1, and for all patients of *Cohort 3.3* with immunotherapy-treated iUPD per iRECIST, the Investigator should make every attempt to perform the confirmation scan 4–8 weeks after the last scan was performed, unless criteria for clinical stability are not met (see below).

5.3.3.2.6 *Management of immunotherapy-treated unconfirmed disease progression*

For patients in *Cohort 3.3*, patient management using iRECIST is detailed in Table 6.

Table 6 Imaging and treatment after first radiologic evidence of PD if iRECIST is followed (for *Cohort 3.3* only)

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

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

Clinical stability is defined as the following:

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

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

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

5.3.4 Pharmacokinetic and immunogenicity assessments

The collection, storage, and shipping of blood samples will be performed as described in the Laboratory Manual and Flowchart, which will be provided to the study sites before study initiation.

The schedule of PK assessments may be adapted to locally applicable clinical routine with the agreement of the Sponsor.

5.3.4.1 Overview of specific PK sampling requirements

All patients, excluding safety interim assessment patients in Substudy 1 and patients in the dose-finding part of Substudy 2, will undergo sparse PK sampling for measurement of derazantinib plasma concentrations. These samples may also be used for exploratory metabolite identification and/or quantification of metabolites.

5.3.4.2 Assessments for rich pharmacokinetics for derazantinib monotherapy safety interim assessment patients in Substudy 1

All safety interim assessment patients in Substudy (first ten patients) will undergo rich PK sampling for measurement of plasma concentrations of derazantinib and relevant PK parameters in accordance with the schedule in Table 7. Omission of sample time points is allowed with Sponsor approval.

Table 7 Rich PK in Substudy 1 (first ten patients in *Cohorts 1.3*) with derazantinib 200 mg BID as monotherapy

Time points at visits	C1D1	C1D8/15/22	C2D1	C2D8/15/22	C3D1	C4D1
Within 1 h before the first or next dose.	■	■	■	■	■	■
1 h (± 5 min) after 1st dose	■		■			
2 h (± 5 min) after 1st dose	■		■			
4 h (± 15 min) after 1st dose	■		■			
6–8 h (±15 min) after 1st dose		■		■	■	
8 h (±30 min) after 1st dose	■		■			
10 h (±30 min) after 1st dose	■		■			
12 h (±30 min; prior to the 2nd dose) after 1st dose	■		■			
24 h after 1st dose (within 1 h before the next dose)	■		■			

■ derazantinib PK sampling.

5.3.4.3 Assessments for rich pharmacokinetics for derazantinib, paclitaxel, ramucirumab and (Substudy 2, Dose-finding Part)

Blood samples will be taken for all patients in the Dose-finding Part of Substudy 2 to characterize the PK of derazantinib and paclitaxel in plasma, and the PK of ramucirumab in serum. Exploratory assessments of metabolites of derazantinib, and routinely applied pre-medications may also be investigated from the same samples.

Blood samples in this patient group will be drawn in accordance with the schedule shown in Table 8. The sequence of study drug administration is derazantinib – ramucirumab – paclitaxel.

Table 8 Rich PK in the Dose-finding Part of Substudy 2 with derazantinib-paclitaxel-ramucirumab combination therapy

Time points at visits	C1D1	C1D8	C1D15	C2D1	C3D1	C4D1	SFU
Within 1 h before the first or next derazantinib dose; and at the SFU visits	■✱◆	■✱◆	■✱◆	■✱◆	■✱◆	■✱◆	◆
Within 5 min after the end of the ramucirumab infusion	■◆		■◆	■◆	■◆		
Within 5 min after the end of the paclitaxel infusion	■✱	■✱	■✱	■✱	■✱		
6 h (±15 min) after 1st derazantinib dose	■✱◆		■✱◆	■✱◆	■✱◆		
8 h (±30 min) after 1st derazantinib dose	■✱		■✱	■✱	■✱		
10 h (±30 min) after 1st derazantinib dose	■✱		■✱	■✱	■✱		
12 h (±30 min; prior to the 2nd dose) after 1st derazantinib dose	■✱		■✱	■✱	■✱		
24 h after derazantinib administration (within 1 h before the next derazantinib dose)	■✱◆	■✱	■✱◆	■✱◆	■✱◆		

■ derazantinib PK sampling; ✱ paclitaxel PK sampling; ◆ ramucirumab PK sampling.
SFU, 28-/90-day Safety Follow-up visits.

Timings provided in Table 8 are to be adhered to as closely as possible. Since infusion duration may vary (e.g., due to mild hypersensitivity reactions), exact documentation of the time of infusion start and infusion end, as well as blood sampling for PK, is mandatory. If the time point after derazantinib administration cannot be kept, priority is to be given to ensuring the exact PK sampling at the end of the paclitaxel and ramucirumab infusion, no later than within 5 minutes after the end of the infusion.

5.3.4.4 Assessments for sparse pharmacokinetics for derazantinib monotherapy (Cohorts 1.1, 1.2, 1.3, and 3.1)

Blood samples will be taken for all patients in *Cohorts 1.1, 1.2, 1.3,* and *3.1* to determine the PK parameters of derazantinib in plasma. Exploratory assessments of metabolites of derazantinib may also be investigated from the same samples. PK blood sampling will be performed according to the sparse PK schedule shown in Table 9.

Table 9 Sparse PK sampling in *Cohorts 1.1, 1.2, 1.3, and 3.1* with derazantinib monotherapy

Time points at visits	C1D1	C1D15	C2D1	C3D1	C4D1
Within 1 h before the first or next derazantinib dose.	■	■	■	■	■
6–8 h after derazantinib dose	■	■		■	

■ derazantinib PK sampling.

5.3.4.5 Assessments for sparse pharmacokinetics for derazantinib-paclitaxel-ramucirumab (Substudy 2, Dose-expansion Part, Cohort 3.2)

Blood samples will be taken for all patients in the Dose-expansion Part of Substudy 2 and *Cohort 3.2* to determine the PK parameters of derazantinib and paclitaxel in plasma, and PK parameters of ramucirumab in serum. Blood sampling will be performed according to the schedule shown in Table 10.

Table 10 Sparse PK sampling in *Cohort 3.2* with derazantinib-paclitaxel-ramucirumab combination therapy

Time points at visits	C1D1	C1D15	C2D1	C3D1	C4D1	SFU
Within 1 h before the first or next derazantinib dose; and at the SFU visits	■◆	■◆	■◆	■◆	■◆	◆
Within 1 h after end of paclitaxel infusion	■✱◆	■✱◆	■✱◆	■✱	■✱	
6–8 h after derazantinib	■	■		■		

■ derazantinib PK sampling; ✱ paclitaxel PK sampling ◆ ramucirumab PK sampling.
SFU, 28/90-day Safety Follow-up visits.

The sequence of study drug administration is derazantinib – ramucirumab – paclitaxel.

Timings provided in Table 10 are to be adhered to as closely as possible. Since infusion duration may vary (e.g., due to mild hypersensitivity reactions), exact documentation of the time of infusion start and infusion end as well as blood sampling for PK, is mandatory. If the timepoint after derazantinib administration cannot be kept, priority is to be given to ensuring the exact PK sampling at the end of the paclitaxel and ramucirumab infusion, no later than within 5 minutes after the end of the infusion.

5.3.4.6 Assessments for sparse pharmacokinetics for derazantinib-atezolizumab and anti-drug antibodies of atezolizumab (Cohort 3.3 only)

Blood samples will be taken for all patients in *Cohort 3.3* to determine the PK parameters of derazantinib in plasma, and PK parameters and ADA of atezolizumab in serum. Blood sampling will be performed according to the schedule shown in Table 11.

Table 11 Sparse PK and ADA sampling in *Cohort 3.3* with derazantinib-atezolizumab combination therapy

Time points at visits	C1D1	C1D15	C2D1	C3D1	C4D1	SFU
Within 1 h before the first or next derazantinib dose; and at the SFU visits	■●◉	■	■●◉	■●◉	■●◉	■●◉
6–8 h after derazantinib	■	■		■		

■ derazantinib PK sampling; ● atezolizumab PK sampling; ◉ atezolizumab ADA sampling.
SFU, 28-/90-day Safety Follow-up visits.

5.3.4.7 Assessments for sparse pharmacokinetics of ramucirumab (Cohort 3.4)

Blood samples will be taken for all patients in *Cohort 3.4* to determine the PK parameters of ramucirumab in serum. Blood sampling will be performed according to the schedule shown in Table 12.

Table 12 Sparse PK sampling in *Cohort 3.4* with paclitaxel-ramucirumab combination therapy

Time points at visits	C1D1	C2D1	C3D1	C4D1	SFU
Within 1 h before the ramucirumab infusion, and at the SFU visits	◆	◆	◆	◆	◆
Within 1 h after end of the ramucirumab infusion and at the SFU visits	◆	◆	◆	◆	

◆ ramucirumab PK sampling. SFU, 28-/90-day Safety Follow-up visits.

5.3.5 Biomarker assessments

Archival (or *de novo*, if collected) tumor tissue and research liquid biopsy samples will be collected during this study to analyze a panel of biomarkers, including, but not limited to biomarkers representing MAPK (RAS/RAF/MEK/ERK), PI3K/AKT, and JAK/STAT pathways; indicating PI3K, PTEN, epidermal growth factor receptor, MET and ERB3 signaling; demonstrating the phosphorylation status of phospho-S6, phospho-STAT, phospho-AKT, phospho-MEK, phospho-ERK, and RNA-expression of proteins activated by the MAPK-pathway such as SPRY2 and DUSP6, as well as the RNA-expression of the FGFR-1/2/3. Additional tumor and immune-related analyses may include, but not be limited to RNA sequencing (RNAseq) and cytometry by time of flight (CyTOF).

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

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

5.3.5.1 Reseach liquid biopsy

Liquid biopsies may comprise, but are not limited to, serum and plasma samples to analyze protein biomarkers and DNA. The collection, storage, and shipping of blood for the assessment of circulating biomarkers (e.g., proteins, cfDNA) will be performed as described in the Laboratory Manual and Flowchart.

All patients undergo liquid biopsies for future biomedical research (for cfDNA analysis) at Screening, at the time point of the confirmatory CT scan (for CR/PR, or if applicable iCPD), and/or either at the time point of clinical assessment of progression or the time point of the first CT scan documenting objective/confirmed radiographic progression, and, finally at the End of Treatment visit (see Section 5.3.5.3).

For each defined liquid biopsy time point, blood samples should be obtained following standard protocols, as outlined in the Laboratory Manual and Flowchart.

5.3.5.2 Archival tumor samples

For all patients with a positive test for $FGFR^{fus/amp/mt}$, every reasonable effort should be undertaken to collect available archived tumor samples to facilitate correlative and confirmatory diagnostic and biomedical research. An FFPE block; or minimum of two H&E-stained slides plus at least ten consecutive, unstained, 4 ± 1 µm thick sections, placed on positively-charged slides, should be sent to the central laboratory for biomarker assessment, including PD-L1, as described in the Laboratory Manual.

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

5.3.5.3 Future biomedical research

The Sponsor may conduct future biomedical research on specimens collected during this clinical study. This research may include genetic analyses (DNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes. Tissue/blood samples, plasma/serum samples, DNA isolates from samples available and processed during the study and not fully consumed for the described analyses may be stored and subsequently used for future biomedical research; further details are provided in the Laboratory Manual.

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

The details of this future biomedical research substudy are presented in Appendix 5. Additional informational material for IRBs/IECs and investigational site staff is provided in Appendix 6.

5.3.6 PRO assessments (Substudy 3 only)

Patient reported outcomes will be measured using the EQ-5D (5L), EORTC QLQ-C30 and EORTC QLQ-STO-22 instruments. HR-QoL and symptom response will be measured using the EQ-5D, EORTC QLQ-C30, EORTC QLQ-STO-22 and G-SET/HTI questionnaires. The HR-QoL questionnaires will be completed by the patient before the patient sees the physician (i.e., at the start of the visit) on D1 of every cycle. EQ5D should be completed first, followed by EORTC QLQ-C30, EORTC QLQ-STO-22, and G-SET/HTI.

The EQ-5D (5L) is a standardized instrument for use as a measure of health outcomes. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a five-point scale from 1 (no problem) to 5 (extreme problem).

The EQ-5D also includes a graded (0 to 100) vertical VAS on which the patient rates his or her general state of health at the time of the assessment (Herdman 2011).

The EORTC QLQ-C30 was developed to assess the quality of life of cancer patients and is the most widely used cancer-specific HR-QoL instrument. It contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), six single symptom items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) and global health and quality of life. The global health and quality of life items uses a 7-point scale scoring with anchors (1 = very poor and 7 = excellent); the other items are scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much).

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

The EORTC QLQ-STO-22 is a disease-specific questionnaire developed and validated to address measurements specific to gastric cancer. It is one of multiple disease-specific modules developed by the EORTC QLG (Quality of Life Group) designed for use in clinical studies, to be administered in addition to the QLQ-C30 to assess disease-specific treatment measurements. It contains 22 items with symptoms of dysphagia (4 items), pain or discomfort (3 items), upper gastrointestinal symptoms (3 items), eating restrictions (5 items), emotional (3 items), dry mouth, hair loss, and body image (Blazeby 2004).

The G-SET/HTI is a single item and will be used as an external anchor to determine the minimal important difference of the EQ-5D visual analogue scale, EORTC QLQ-C30 scales and EORTC QLQ-STO-22 scales. It will be administered twice during the study in line with the recent protocol by the EORTC Quality of Life Group (Musoro 2018) for evaluating the minimal important difference. The G-SET will be provided to participants in *Cohorts 3.1*, *3.2* and *3.4* after 8 weeks and 16 weeks, and to participants in *Cohort 3.3* after 6 weeks and 15 weeks. The G-SET is a patient-rated change in health between two time periods using a five point ordinal scale (1 = much better now than 8 weeks ago; 2 = somewhat better now than 8 weeks ago; 3 = about the same as eight weeks ago; 4 = somewhat worse now than 8 weeks ago; 5 = much worse now than eight weeks ago, the recall period was adapted compared to the original item) (Ware 2002, Lloyd 2014). For cohort 3.3, G-SET timepoints will be adapted accordingly.

The HR-QoL questionnaires will be provided to the patients to complete prior to being evaluated by the physician on Day 1 of every cycle, at the End of Treatment visit, and at the safety follow-up visits.

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

administration of study treatment. The questionnaire should be completed by the patient without assistance during their scheduled visit(s) at the clinic. Study site staff should review all instruments for completeness before the patient leaves the investigational site. The EQ-5D will always be completed by patients before completing the EORTC QLQ-C30, EORTC QLQ-STO22, and the G-SET/HTI (if applicable).

6 STUDY TREATMENTS

Derazantinib, paclitaxel, ramucirumab and atezolizumab are considered to be investigational medicinal products (IMPs) in this study, and will be provided by the Sponsor. Detailed information related to IMP handling and storage is provided in the Pharmacy Manual.

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

6.1 Investigational products

6.1.1 Derazantinib

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

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

6.1.1.1 Shipping and storage conditions

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

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

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

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

6.1.1.2 Labeling and packaging

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

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

6.1.1.3 Drug accountability

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

A Drug Accountability Log will be provided for derazantinib capsules. The log must be kept current and should contain the protocol number, the name and clinical site of the Investigator, dates and quantities of drug received, patient's identification number to whom derazantinib capsules were dispensed, the date and quantity dispensed, and balance remaining, if from individual patient drug units, as well as the lot number, dose, and the initials of the dispenser. Drug accountability is performed to the capsule level.

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

At the end of the study or as directed, all study drugs, including unused, partially used, or empty containers, will be destroyed locally and only returned to the designee as instructed by the Sponsor if the site cannot destroy locally. Derazantinib capsules will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of derazantinib capsules must be documented and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition Standard Operation Procedures (SOPs) or equivalent.

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

6.1.1.4 Derazantinib administration

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

When used in combination with paclitaxel and ramucirumab (see Section 6.1.6.2), derazantinib should be administered first, followed by ramucirumab and then paclitaxel. Paclitaxel must not be started earlier than 60 minutes after completion of the ramucirumab infusion; the 1-hour observation period between administration of ramucirumab and paclitaxel is mandatory for the first two cycles, but may be omitted in Cycle 3 and beyond provided there has been no evidence of infusion-related reaction.

6.1.1.5 Dose modifications

In general, once the dose of derazantinib has been modified for a patient, the modified dose will be considered the maximum dose for all subsequent cycles for that patient. The derazantinib dose reduction scheme is shown in Table 13.

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

Table 13 Derazantinib dose reduction scheme

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

Abbreviations: BID, twice a day; QD, once daily; QOD, every other day.
For AEs of special interest (AESIs; see Section 7.2.6), including transaminase elevations, hyperphosphatemia and eye disorders, and any other AEs considered at least possibly derazantinib-related (see Section 7.3.2 for risks for derazantinib), Table 14 and Sections 6.1.1.5.1 to 6.1.1.5.3 provide specific guidance to manage these events through dose delays, reductions and/or discontinuations. For patients with CTCAE grade 2 AST/ALT abnormality at baseline, an increase in the baseline abnormality to > 10 × baseline will be considered a DLT during the DLT observation periods in Substudies 1 and 2; see Section 7.3.3).

6.1.1.5.1 *Hyperphosphatemia*

For all patients, it is recommended to restrict phosphorus intake to 600–800 mg daily. As hyperphosphatemia is only defined by CTCAE 5.0 with regards to escalating interventional measures (without specifications triggering these interventions) and not by laboratory values exceeding the upper limits of normal leading to specific interventions, Table 14 guides interventions for the management of hyperphosphatemia considered at least possibly related to derazantinib.

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

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

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

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

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

Table 14 Dose delays/reductions for drug-related toxicity

HYPERPHOSPHATEMIA	
Serum phosphate level	**Action**
< 7.0 mg/dL (< 2.26 mmol/L)	Continue derazantinib at current dose.
7.0 – 9.0 mg/dL (2.26 – 2.90 mmol/L)	Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL*; the patient may restart derazantinib at the dose prior to hyperphosphatemia. If hyperphosphatemia lasts > 2 weeks, consider restarting at the next lower dose.
> 9.0 – 10.0 mg/dL (> 2.90 – 3.23 mmol/L)	Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL*; the patient may restart at the next lower dose level.
> 10.0 mg/dL (> 3.23 mmol/L) or significant alteration from baseline renal function or Grade 3 hypercalcemia	Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL*; the patient may restart at two dose levels lower, or permanently discontinue derazantinib (e.g., if considered life threatening event).
CENTRAL SERIOUS RETINOPATHY / RETINAL PIGMENT EPITHELIAL DETACHMENT	
Grade	**Action**
Asymptomatic clinical or diagnostic observations only (Grade 1)	Withhold derazantinib until resolution. If the event resolves within 4 weeks, restart at the next lower dose level. If stable but not resolved for two consecutive eye examinations, restart at the next lower dose level.
Visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline (Grade 2)	Withhold derazantinib until resolution. If the event resolves within 4 weeks, the patient may restart at the next lower dose level.
Visual acuity worse than 20/40 or > 3 lines of decreased vision from baseline (Grade 3)	Withhold derazantinib until resolution. If the event resolves within 4 weeks, the patient may restart at two dose levels lower. If the event recurs, consider permanent discontinuation of derazantinib.
Visual acuity 20/200 or worse in affected eye (Grade 4)	Permanently discontinue derazantinib.
OTHER EVENTS	
CTCAE grade	**Action**
Grade 1 or 2	Continue derazantinib at current dose, unless dose delay/modification may be clinically indicated (as assessed by the Investigator and agreed upon by the Medical Monitor or designee).
Grade 3 (see exception for AST/ALT elevations in Table 13)	Withhold derazantinib until recovery to Grade 1 or baseline; administer derazantinib at the next lower dose for subsequent dosing, unless further dose reduction is required.
Grade 4 (see exception for AST/ALT elevations in Table 13)	Permanently discontinue derazantinib if the event is at least possibly related to derazantinib.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.
* For serum phosphate ≥ 7.0 mg/dL, consider adding an oral phosphate binding/reducing agent until serum phosphate level returns to < 5.6 mg/dL.

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

6.1.1.5.2 *Management of retinal adverse events*

A complete ophthalmological examination (see Section 5.3.2.3) should be performed by an ophthalmologist at the Screening visit and for the first four cycles (i.e. D1 of C2-5). Further complete ophthalmological examinations only need to be performed if clinically indicated. Table 14 provides specific guidance for the management of dose delays/reductions in the case of retinal AEs possibly related to derazantinib.

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

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

Once QTc prolongation has resolved, and if a decision was made to continue treatment with derazantinib, patients may continue treatment at a lower dose level per Table 13 with an ECG monitoring schedule defined by the cardiologist.

Patients who experience a mean QTcF interval ≥ 501 ms on at least two ECGs at difference time points after dose reduction will be discontinued from study.

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

6.1.1.6 Missed-dose management

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

6.1.1.7 Overdose

There is no specific guidance to be given in regard to overdose of any study drug.

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

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

6.1.2 Paclitaxel

Paclitaxel is an approved medication supplied as a nonaqueous 6 mg/mL solution in multidose vials for dilution with a suitable parenteral fluid prior to IV infusion. Paclitaxel is an investigational drug for its use in combination with derazantinib. Its use as a weekly IV infusion as second-line treatment in GAC is supported by international guidelines (Ajani 2016, Smyth 2016a).

In general, preparation, administration and clinical management of paclitaxel and patients treated with paclitaxel should follow the description provided by the SmPC (Paclitaxel Ever Pharma SmPC). Topics most relevant to this protocol only are addressed below.

6.1.2.1 Shipping and storage conditions

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

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

Unopened vials of Paclitaxel Injection, USP are stable until the date indicated on the package when stored between 20° to 25°C (68° to 77°F), in the original package. Refer to the product label for specific storage conditions and handling requirements.

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

6.1.2.2 Labeling and packaging

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

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

6.1.2.3 Drug accountability

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

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

At the end of the study or as directed, all study drugs, including unused, partially used, or empty containers, will be destroyed locally, and only returned to the designee as instructed by the Sponsor if the site cannot destroy locally. Paclitaxel will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return must be documented, and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition SOPs or equivalent.

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

6.1.2.4 Preparation and stability of study drug

Paclitaxel must be diluted prior to infusion. Details of drug shipment, storage, and preparation are provided in the Pharmacy Manual. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-polyvinyl chloride (PVC) containing administration sets, such as those which are polyethylene-lined, should be used.

6.1.2.5 Paclitaxel premedication

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally (PO) administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to paclitaxel, and pantoprazole (40 mg) I.V. 30 to 60 minutes before paclitaxel.

6.1.2.6 Paclitaxel administration

Per recent publications and standard clinical practice, 80 mg/m² paclitaxel will be administered intravenously as a 1-hour infusion on days 1, 8, and 15 of a 28-day cycle (Ajani 2016, Smyth 2016a, Wilke 2014). Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

When used in combination with ramucirumab, paclitaxel must not be started earlier than 60 minutes after completion of the ramucirumab infusion; the 1-hour observation period between administration of ramucirumab and paclitaxel is mandatory for the first two cycles, but may be omitted in Cycle 3 and beyond provided there has been no evidence of infusion-related reaction.

6.1.2.7 Dose modifications

In this protocol, paclitaxel will be administered in combination with ramucirumab. Dose modification of the combination treatment are specified below (see Section 6.1.6.1).

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the DLT. Neutrophil nadirs usually occurr at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1.5×10^9/L. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level $> 1.5 \times 10^9$/L and platelets recover to a level $> 100 \times 10^9$/L.

Prior to D1, D8 and D15 of each administration of paclitaxel, hematology, urine protein (dipstick), liver, and renal function must be adequate (see Section 6.1.6.1), and all paclitaxel-related toxicities (except for alopecia) must have resolved to Grade < 2 or baseline. Pre-infusion laboratory data may not be older than 36 hours.

6.1.2.8 Missed-dose management

If a planned dose of paclitaxel is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain the D1, D8 and D15 28-day schedule.

6.1.2.9 Overdose

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis.

6.1.3 Ramucirumab

Ramucirumab is an approved medication supplied as a 10 mg/mL solution in single dose 10 mL or 50 mL vials for dilution with 0.9% sodium chloride prior to IV infusion. Ramucirumab is an investigational drug for its use in combination with derazantinib. It is approved for use as weekly IV infusion, either as a single agent or in combination with paclitaxel, as a second-line treatment in GAC.

In general, preparation, administration and clinical management of ramucirumab and patients treated with ramucirumab should follow the description provided by US PI and SmPC (Cyramza® USPI, Cyramza EPAR). Topics most relevant to this protocol only are addressed below.

6.1.3.1 Shipping and storage

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

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

Unopened vials of ramucirumab Injection, USP are stable for 3 years when stored between 2° to 8°C in the original package. The vial should not be frozen and should be protected

from light. Refer to the product label for specific storage conditions and handling requirements.

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

6.1.3.2 Labeling and packaging

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

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

6.1.3.3 Drug accountability

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

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

At the end of the study or as directed, all study drugs, including unused, partially used, or empty containers, will be destroyed locally, and only returned to the designee as instructed by the Sponsor if the site cannot destroy locally. Ramucirumab will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return must be documented, and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition SOPs or equivalent.

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

6.1.3.4 Preparation and stability

Ramucirumab must be diluted prior to infusion in 0.9% sodium chloride to a final volume of 250 mL. Dextrose solutions must not be used to dilute ramucirumab. Solutions of ramucirumab can be stored at ambient temperature (up to 25°C) for up to 4 hours and at 2°C to 8°C for up to 24 hours. Diluted solutions should be inspected visually for particulate matter and discolouration prior to administration.

6.1.3.5 Ramucirumab premedication

All patients should be premedicated prior to ramucirumab administration with an IV histamine-1 receptor antagonist (e.g., diphenhydramine hydrochloride or equivalent). Patients who have experienced a Grade 1 or 2 infusion-related reaction (IRR) should be premedicated with a histamine-1 antagonist, dexamethasone (or equivalent) and acetaminophen prior to infusion.

6.1.3.6 Ramucirumab administration

For GAC, the recommended dose of ramucirumab is 8 mg/kg every 2 weeks administered via an infusion pump over 60 minutes through a separate infusion line.

When used in combination with ramucirumab, paclitaxel must not be started earlier than 60 minutes after completion of the ramucirumab infusion; the 1-hour observation period between administration of ramucirumab and paclitaxel is mandatory for the first two cycles, but may be omitted in Cycle 3 and beyond provided there has been no evidence of infusion-related reaction.

6.1.3.7 Dose modifications

In this protocol, ramucirumab will be administered in combination with paclitaxel. Dose modification of the combination treatment are specified below (see Section 6.1.6.1).

Prior to D1 and D15 of each administration of ramucirumab, urine protein (dipstick), bone marrow, hepatic and renal function must be adequate (see Section 6.1.6.1), and all ramucirumab-related toxicities must have resolved to Grade < 2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria, for all three of which study drug discontinuation may be required; see Section 6.1.6.1). Pre-infusion laboratory data may not be older than 36 hours.

6.1.3.8 Missed dose management

If a planned dose of ramucirumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain the D1 and D15 28-day schedule.

6.1.3.9 Overdose

There are no data on overdose in humans. Ramucirumab was administered at doses up to 10 mg/kg every two weeks without reaching a maximum tolerated dose.

6.1.4 Atezolizumab

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

6.1.4.1 Shipping and storage conditions

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

Do not freeze.

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

6.1.4.2 Labeling and packaging

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

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

6.1.4.3 Drug accountability

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

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

At the end of the study or as directed, all study drugs, including unused, partially used, or empty containers, will be destroyed locally, and only returned to the designee as instructed by the Sponsor if the site cannot destroy locally. Atezolizumab will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return must be documented, and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition SOPs or equivalent.

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

6.1.4.4 Preparation and stability of study drug

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

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

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

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

If diluted atezolizumab infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion; or
- Under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for no more than 24 hours from time of preparation.

6.1.4.5 Atezolizumab administration

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

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

6.1.4.6 Dose modifications

In this protocol, atezolizumab will be administered in combination with derazantinib; the RP2D of the combination has been determined in study DZB-CS-201 (FIDES-02, NCT04045613). Dose modification of the combination treatment are specified below (see Section 6.1.6.3).

6.1.4.7 Missed-dose management

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

6.1.4.8 Overdose

There is no information on overdose with atezolizumab.

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

6.1.5 Dosing schedule

In Substudy 1, patients allocated to *Cohort 1.1* and *1.2* will receive oral derazantinib at a dose of 300 mg QD (three capsules of 100 mg each once per day); patients allocated to *Cohort 1.3* will receive oral derazantinib at a dose of 200 mg BID (two capsules of 100 mg each twice per day).

The dosing schedule for patients enrolled in Substudy 2 is described in Section 3.1.7.2 and Figure 4. Intermediate dose levels not described here may be investigated.

In Substudy 3, patients randomized to *Cohort 3.1* and *3.4* will receive 300 mg QD derazantinib and 80 mg/m^2 paclitaxel-ramucirumab, respectively. Patients randomized to *Cohort 3.2*, will use the RP2D of derazantinib-paclitaxel-ramucirumab in combination from Substudy 2. Patients randomized to *Cohort 3.3* will receive the RP2D determined in another clinical study investigating the RP2D of the derazantinib-atezolizumab combination (DZB-CS-201).

6.1.6 Dose modifications of combination treatments

6.1.6.1 Paclitaxel-ramucirumab combination (Substudy 3)

To assess the in-cycle paclitaxel-related toxicity or abnormal laboratory values, blood counts and serum chemistry will be repeated regularly (Table 3) and prior to paclitaxel-ramucirumab administration (see Table 15, Table 16 and/or Table 17), or more frequently if medically indicated.

In the case of paclitaxel-related toxicity or abnormal laboratory values (Table 17) on D8 or D15, paclitaxel will be skipped at that day. The start of the next cycle will be delayed until recovery to the values of Grade < 2 or baseline. If the start of a cycle is delayed due to toxicity, radiographic tumor assessment should not be delayed, but should be performed as per schedule until documentation of disease progression.

In the event that paclitaxel is delayed due to paclitaxel-related toxicities on D8 and/or D15 (Table 17), ramucirumab administrations should continue as scheduled until the next cycle has resumed. When the subsequent cycle of paclitaxel is initiated, administration of ramucirumab and paclitaxel will be resynchronized according to the study design described in this protocol (ie, the cycle will begin at D1 for both ramucirumab and paclitaxel, even if this requires ramucirumab to be administered on consecutive weeks). In case of discontinuation of paclitaxel for any reason, a new cycle will be started on D29 (D1 of the new cycle) with the administration of ramucirumab monotherapy, provided the criteria outlined in Table 16 are met.

Table 15 Criteria for paclitaxel treatment on D1 of Cycles 2+

Parameter	Value / Criterion
Absolute neutrophil count	$> 1.5 \times 10^9$ / L
Platelets	$> 100 \times 10^9$ / L
Serum Creatinine	< 1.5 × ULN or creatinine clearance >60 ml/min by Cockcroft
Bilirubin	< 1.5 × ULN
AST/ALT	≤ 3 × ULN for ALT/AST if no liver metastases, < 5 × ULN if liver metastases
Any other paclitaxel-related adverse event	CTCAE 5.0 Grade < 2 or baseline (except for alopecia)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; D, day; ULN, upper limit of normal.

Table 16 Criteria for ramucirumab treatment on D1 and D15 of each cycle

Parameter	Value / Criterion
Urine protein	Dipstick < 2+, UPCR < 2 (or <200 mg/mmol) or protein level < 2 g/24 h
Any other ramucirumab-related adverse event	CTCAE 5.0 Grade < 2 or baseline (except for hypertension, venous thromboembolic events, proteinuria, as detailed in Section 6.1.3.7)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; D, day.

In the case of ramucirumab-related toxicity on D15 (Table 16), ramucirumab will be delayed for one week and administered on D8 of the treatment cycle (with the second dose within the 28-day cycle administered on D15 of that cycle) provided that ramucirumab-related toxicities have resolved to Grade < 2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria, as detailed below). If toxicities have not resolved on D8, ramucirumab will be delayed for another week and administered on D15 according to the schedule described in this protocol. In both cases, paclitaxel (and derazantinib, if applicable) will continue according to the planned schedule.

Table 17 Criteria for paclitaxel treatment on D8 and D15 of each cycle

Parameter	Value / Criterion
Absolute neutrophil count	$> 1.0 \times 10^9$ / L
Platelets	$> 75 \times 10^9$ / L
Bilirubin	$< 1.5 \times$ ULN
AST/ALT	$\leq 3 \times$ ULN for ALT/AST if no liver metastases, $< 5 \times$ ULN if liver metastases
Any other paclitaxel-related adverse event	CTCAE 5.0 Grade < 2 or baseline (except for alopecia)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; D, day; ULN, upper limit of normal.

If one or more criteria outlined in Table 15, Table 16 and/or Table 17 are not met at the time of a planned treatment, the following general rules for the management of treatment delays and dose modifications apply for:

Paclitaxel

- *Drug-related AEs* – In the case of paclitaxel-related toxicity or abnormal laboratory values on D8 or D15 (Table 17), paclitaxel will be skipped at that day. No dose reductions of paclitaxel are allowed within a given cycle.
- *Dose modification* – The paclitaxel dose will be reduced by 10 mg/m^2 for the following cycle when Grade 4 hematological toxicity or Grade 3 paclitaxel-related non-hematological toxicity (except for alopecia) is observed. If the dose of paclitaxel is reduced because of potentially related AEs, subsequent dose increases are not permitted.
- *Discontinuation* – Paclitaxel will be permanently discontinued if dose reduction to less than 60 mg/m^2 would be required, or in case of any paclitaxel-related event that is deemed life-threatening, regardless of assigned toxicity grade.

Ramucirumab

- *Drug-related AEs* – In the case of ramucirumab-related toxicity on Day 15 (Table 16), paclitaxel will be administered according to the planned schedule but ramucirumab will be delayed for one week and administered on D22 of the treatment cycle, provided that ramucirumab-related toxicities have resolved to Grade < 2 or baseline (except for hypertension, venous thromboembolic events, or proteinuria, as detailed in Section 6.1.3.7).
- *Dose modification for non-life-threatening and reversible Grade 3 clinical AEs* – Dose modifications are permitted for ramucirumab in the setting of AEs considered to be at least possibly related to ramucirumab and that resolve to Grade < 2 or pretreatment baseline within one treatment cycle (approximately 28 days); if after re-administration a second and third instance of such an event occurs, ramucirumab should be subsequently re-administered at a dose of 6 mg/kg and 5 mg/kg, respectively.

- *Dose modification for Grade 4 AE deemed at least possibly related to ramucirumab* – Ramucirumab should be discontinued and only be considered for re-administration at the discretion of the Investigator in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities which resolve to Grade < 2 or pretreatment baseline within 1 treatment cycle (approximately 28 days); if after re-administration a second and third instance of such an event occurs, ramucirumab should be subsequently re-administered at a dose of 6 mg/kg and 5 mg/kg, respectively.
- *Patients with symptoms and laboratory abnormalities at baseline* – Patients who enter the study with symptoms or laboratory values equivalent to CTCAE Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the Investigator, and asymptomatic laboratory abnormalities (except for proteinuria; see below) should not result in dose interruptions, modifications, or discontinuation of study therapy unless determined by the Investigator to be clinically significant or life-threatening.
- *Skip drug* – If toxicities have not resolved on D22, ramucirumab will be skipped for that cycle and administered on D1 of the following cycle provided that ramucirumab-related toxicities have resolved to Grade < 2 or baseline.
- *Infusion-related reactions* – For Grade 1 or 2 IRRs, the infusion rate should be reduced by 50% with premedication administered (see Section 6.1.3.5). For Grade 3 or 4 IRRs, ramucirumab should be permanently and immediately discontinued. For severe hypertension, ramucirumab should be interrupted until the hypertension is controlled with medical management.
- *Proteinuria* – Patients should be monitored for the development of proteinuria during ramucirumab treatment. For urine protein levels ≥ 2 g/24 hours or UPCR ≥ 2 (≥ 200 mg/mmol), ramucirumab should be temporarily discontinued. Once the urine protein level returns to < 2 g/24 hours or UPCR returns to < 2 (or < 200 mg/mmol), treatment should be reinitiated at a reduced dose of 6 mg/kg every 2 weeks. A second dose reduction to 5 mg/kg is recommended if a urine protein levels ≥ 2 g/24 hours or UPCR ≥ 2 (≥ 200 mg/mmol) reoccurs. Ramucirumab must be permanently discontinued for a third occurrence of proteinuria ≥ 2 g/24 hours or UPCR ≥ 2 (≥ 200 mg/mmol).

  Permanently discontinue ramucirumab for urine protein levels > 3 g/24 hours or UPCR > 3 (or > 300 mg/mmol) **or** in cases of nephrotic syndrome.
- *Hypertension* – Ramucirumab should be permanently discontinued in cases of severe hypertension that cannot be controlled with antihypertensive therapy, for urine protein levels > 3 g/24 hours in cases of nephrotic syndrome, arterial thromboembolic events, gastrointestinal perforation, CTCAE Grade 3 or 4 bleeding events, spontaneous development of fistula or hepatic encephalopathy or hepatorenal syndrome.

- *Permanent discontinuation* – Ramucirumab should also be permanently discontinued in cases of severe arterial or venous thromboembolic events, gastrointestinal perforations, severe bleeding of CTCAE Grade 3 or 4 bleeding, spontaneous development of fistula and hepatic encephalopathy or hepatorenal syndrome, or in case of any ramucirumab-related event that is deemed life-threatening.
- *Surgery* – Ramucirumab should be temporarily discontinued prior to scheduled surgery until the wound is fully healed.

6.1.6.2 Derazantinib-paclitaxel-ramucirumab in combination (Substudy 3 only)

The management of derazantinib-paclitaxel-ramucirumab combination treatment during dose finding in Substudy 2 is detailed in Section 3.1.7.2.

To assess the in-cycle toxicity or abnormal laboratory values of paclitaxel, ramucirumab and derazantinib-related toxicity in Substudy 3, blood counts and serum chemistry will be repeated regularly (Table 3 and Table 4) and prior to D1 of study drug administrations (see Table 18 and Table 19), or more frequently if medically indicated.

Abnormal values and CTCAE toxicities exceeding the ranges in Table 18 and Table 19 are managed by dose modifications in relation to the cause of toxicity as described previously for the treatment with paclitaxel / ramucirumab (Section 6.1.6.1) and derazantinib (Section 6.1.1.5).

Table 18 Criteria for derazantinib-paclitaxel-ramucirumab combination treatment on D1 of Cycle 2+

Parameter	Value / Criterion
Serum phosphate	< 7.0 mg/dL (< 2.26 mmol/L)
Urine protein	Dipstick < 2+, UPCR <2 (or <200 mg/mmol) or protein level <2 g/24 h
Hemoglobin	≥ 8.0 g/dL
Absolute neutrophil count	≥ 1.5 × 10^9/L
Platelet count	≥ 100 × 10^9/L
Bilirubin	≤ 1.5 × ULN
AST/ALT	≤ 3 × ULN for ALT/AST if no liver metastases, < 5 × ULN if liver metastases
Any other study-drug–related adverse event	CTCAE 5.0 Grade < 2 or baseline (except for paclitaxel or derazantinib-related alopecia; and except for ramucirumab-related hypertension, venous thromboembolic events, and proteinuria, for all three of which study drug discontinuation may apply, as detailed in Section 6.1.3.7)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; D, day; ULN, upper limit of normal.

Table 19 Criteria for derazantinib-paclitaxel-ramucirumab combination treatment on D8 and/or D15 of each cycle

Parameter	Value / Criterion
Serum phosphate (**D15 only**)	< 7.0 mg/dL (< 2.26 mmol/L)
Urine protein (**D15 only**)	Dipstick < 2+, UPCR <2 (or < 200 mg/mmol) or protein level < 2 g/24 h
Absolute neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 75 \times 10^9$/L
Bilirubin	≤ 1.5 × ULN
AST/ALT	≤ 3 × ULN for ALT/AST if no liver metastases, < 5 × ULN if liver metastases
Any other adverse event	CTCAE 5.0 Grade < 2 or baseline (except for alopecia)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; D, day; ULN, upper limit of normal.

CTCAE Grade 4 toxicities that warrant permanent and immediate discontinuation of derazantinib are detailed in Table 13, the respective Grade 4 toxicities that warrant permanent and immediate discontinuation of paclitaxel and/or ramucirumab are detailed in the previsous section (see Section 6.1.6.1).

The following CTCAE Grade 4 toxicities **do not warrant permanent and immediate discontinuation** of derazantinib, paclitaxel or ramucirumab treatment:

- The first occurrence of derazantinib-related hyperphosphatemia > 9.0 mg/dl
- Grade 4 hematological toxicities
- The first occurrence of paclitaxel-related Grade 4 neutropenia or febrile neutropenia that have been controlled by supportive G-CSF administration and returned to Grade < 2 or baseline within 28 days

Note: The paclitaxel dose should be reduced by 10 mg/m^2 for the subsequent cycle.

In the event of discontinuation of any study drug for any reason, a new cycle will be started on D29 (D1 of the new cycle) with the administration of the remaining study drugs at the last dose level, provided the criteria outlined in Section 6.1.1.5 and/or Table 18 and Table 19 are met. In the event of toxicity clearly attributable to derazantinib during continued treatment and in particular outside of the DLT interval, the Investigator should consider early derazantinib dose modification measures to ensure that patients treated in this cohort are able to benefit from the proven activity of the paclitaxel-ramucirumab combination.

6.1.6.3 Derazantinib-atezolizumab in combination

Dose modifications/reductions of atezolizumab are not permitted.

Patients treated with derazantinib and atezolizumab in combination should be temporarily or permanently discontinued from atezolizumab and/or study treatment if any of the toxicities described in Appendix 4 occur, and are assessed by the Investigator as at least possibly related to atezolizumab.

CTCAE Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that have been controlled by hormone replacement.

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

6.1.7 Duration of treatment

All patients will be treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the Substudy, cohort or the study is terminated by the Sponsor, whichever occurs first. Patients will be permitted to remain on study treatment after RECIST 1.1 criteria for PD are met if, in the opinion of the Investigator and with the agreement of the Sponsor, they continue to derive benefit from derazantinib monotherapy, or derazantinib-paclitaxel-ramucirumab or derazantinib-atezolizumab in combination.

6.2 Treatment compliance

Interruptions from the protocol-specified treatment plan for greater than 6 weeks between study drug doses for non-drug-related or administrative reasons (see Section 6.1.1.5 and Section 6.1.4.6 for drug-related modifications) require consultation between the Investigator and the Sponsor, and written documentation of the collaborative decision on patient management.

6.2.1 Treatment compliance for derazantinib

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

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

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

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

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

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

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

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

6.2.2 Treatment compliance for paclitaxel-ramucirumab and atezolizumab

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

6.3 Prior treatment

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

All surgical procedure history, prior chemotherapy, and radiation therapy must be recorded on the appropriate eCRF.

See Section 4.2, Inclusion Criteria, and Section 4.3, Exclusion Criteria for further details.

6.4 Concomitant treatments

Any medications (including any anti-tumor medication and supportive care) or significant non-drug therapies (including herbal medicines) that are taken by or administered to the patient during the course of the study (until the safety follow-up visit at Day 90) must be recorded in the eCRF including the dosage, frequency of administration, route of administration, therapeutic indication, and start/stop dates of use.

6.4.1 Permitted treatment

Palliative and supportive care for disease-related symptoms will be offered to all patients as part of their routine clinical management. In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Erythropoietin Stimulating Agents (in accordance with American Society of Clinical Oncology [ASCO], American Society of Hematology, or MEDICARE guidelines for the use of epoetin in patients with cancer and US Food and Drug Administration alerts dated 09 March 2007, 08 November 2007, 12 March 2008, 31 July 2008, and 02 December 2008)
- Hematopoietic growth factors, including filgrastim (Neupogen®), or other granulocyte colony stimulating factors (in accordance with ASCO guidelines for the use of white blood cell growth factors (see http://jco.ascopubs.org/content/24/19/3187.full)
- Antiemetics may be administered according to standard practice, considerating potential drug-drug interactions (see Section 6.4.2 and Appendix 7)
- Megestrol acetate (Megace®)
- Use of topical corticosteroids, topical and systemic antibiotics according to standard of care or institutional guidelines
- Bisphosphonates and denosumab for bone metastases or hypercalcemia of malignancy
- Palliative radiotherapy for non-hepatic local pain (e.g., bone) control provided that, in the opinion of the Investigator, the patient does not meet the criteria for treatment discontinuation (i.e., clear progression of disease)

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

The following treatments are not allowed during the study:

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

- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.
- Patients must agree not to receive live, attenuated influenza vaccines (such as FluMist®) for 30 days prior to randomization (see Exclusion criterion 32), during treatment, or, for patients randomized to atezolizumab, within 5 months following the last dose of atezolizumab.

The following treatment in paclitaxel-treated patients (Substudy 2, *Cohort 3.2*, *Cohort 3.4*) is not allowed during the study:

- co-administration of drugs known to inhibit or induce either CYP2C8 or CYP3A4.

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

- Derazantinib may inhibit CYP1A2, CYP2C8, or CYP2D6 metabolism, hence co-administration of derazantinib with drugs known to be substrates of CYP1A2, CYP2C8, or CYP2D6 should be avoided or used with caution (see Appendix 7).
- Derazantinib may be a substrate and inhibitor of human P-glycoprotein (P-gp), therefore co-administration of derazantinib with drugs known to be P-gp substrates with narrow therapeutic index should be avoided or used with caution (Appendix 8).
- Drugs with known liver toxicity, e.g., clotrimazole, should be avoided or used with caution; if such drugs need to be administered, liver function tests should be done every 4–5 days during the drugs' co-administration.
- Drugs with the potential to prolong QT interval (see Appendix 9).
- Extended concomitant corticosteroid use at physiological doses (i.e., up to 10 mg/day prednisone equivalent).
- Influenza vaccinations (inactivated forms only) should be given during influenza season only (approximately October to March in the Northern hemisphere; April to September in the Southern Hemisphere).

7 SAFETY

7.1 Warnings and precautions

7.1.1 Derazantinib

7.1.1.1 Treatment-emergent adverse events

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

7.1.1.2 Identified and potential risks

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

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

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

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

7.1.2 Paclitaxel

The warnings and precautions for paclitaxel are listed in the EU SmPC for Paclitaxel (Paclitaxel Ever Pharma SmPC).

7.1.3 Ramucirumab

The warnings and precautions for ramucirumab are listed in the USPI and the EU EPAR for Cyramza® (ramucirumab) (Cyramza® USPI, Cyramza EPAR).

7.1.4 Atezolizumab

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

7.1.5 Contraception and pregnancy

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

Paclitaxel can cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while receiving paclitaxel, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

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

7.1.5.1 Contraception

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

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

7.1.5.2 Pregnancy testing

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

See Section 7.4.5 for details of reporting and handling pregnancies.

7.1.5.3 Nursing mothers

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

7.2 Definitions

7.2.1 Adverse event

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

AEs that occur following the full execution of the ICF but prior to dosing must be recorded in the medical history page of the eCRF. If the event is assessed as serious and related to the study procedure, the AE must be reported as an SAE as described in Section 7.2.2.

Adverse events, including SAEs, that occur after patients receive any anti-cancer therapy in the follow-up period, other than the study-defined treatments, will not be recorded as AEs or SAEs.

Complications associated with scheduled procedures are considered AEs.

7.2.2 Serious adverse event

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization, or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is classified as an important medical event or medically significant event

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

It should be noted that:

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

  The following hospitalizations, whether planned before or during the study, can be considered AEs but should not be considered SAEs:

  – Routine treatment or monitoring of GAC, not associated with any deterioration in condition (e.g., hospitalizations related to study procedures, such as study-drug administration, PK assessments, etc.).
  – Elective or planned treatment, including surgical interventions, both related and unrelated to GAC if the plan for the respective intervention has been documented prior to first dose of study drug.
  – Elective or pre-planned treatment for a pre-existing condition that is unrelated to GAC and has not worsened.
  – Admission to a hospital or other institution for general care, not associated with any deterioration in condition.

  Note: Prolongation of a scheduled hospitalization is considered an SAE.

- Treatment on an outpatient basis for an event which does not meet any of the above definitions of 'serious', and does not result in hospital admission, should not be considered an SAE.

7.2.3 Unexpected adverse event or serious adverse event

An unexpected AE or SAE is one for which the nature or severity of the event is not consistent with the applicable Reference Safety Information.

7.2.4 Suspected adverse event or serious adverse event

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

7.2.5 Suspected unexpected serious adverse reaction

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

7.2.6 Adverse events of special interest

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

- Hypersensitivity reactions
- Immune-related AEs
- Liver function tests abnormal (compared to baseline)
- Ocular/eye disorder
- Bone marrow suppression
- Serum creatinine increase or renal disorders
- Hyper-/hypotension / cardiac disorders (including QT prolongation)
- Neurotoxicity
- Hyperphosphatemia/blood phosphorus increased
- Hyponatremia
- Stomatitis
- Nail disorder
- Gastrointestinal disorders (e.g., nausea, vomiting, diarrhea)
- Gastrointestinal perforation
- Bleeding/hemorrhage (including gastrointestinal hemorrhage)
- Proteinuria

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

7.2.7 Further adverse event and serious adverse event definitions

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE/SAE.

Laboratory data are to be collected as stipulated in Section 7.4.3.1. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE or SAE unless its outcome is death.

7.2.8 Treatment-emergent adverse events

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

7.3 Evaluation of adverse events

7.3.1 Grading of severity

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

Adverse events not included in NCI CTCAE 5.0 should be reported under 'Other' within the appropriate category, and graded 1 to 5 according to the general grade definitions of mild, moderate, severe, life-threatening/disabling or death (CTCAE 5.0).

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

7.3.2 Assessment of causality

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

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

7.3.3 Dose-limiting toxicities

All toxicities will be graded using NCI CTCAE 5.0. Toxicities judged by the Investigator to be unrelated to study drug administration (e.g., related to the underlying disease) are not considered DLTs.

In contrast, the occurrence of any of the following toxicities during Cycle 1 (DLT period) will be considered a DLT, if judged by the Investigator to be possibly or probably related to study drug administration:

7.3.3.1 Any toxicities (hematologic or non-hematologic)

1. Resulting in death (Grade 5)

7.3.3.2 Hematologic toxicities

2. Febrile neutropenia ≥ Grade 3:
   - CTCAE Grade 3 is defined as ANC < 1.0×10^9/L with a single temperature of > 38.3 °C (101 °F) or a sustained temperature of ≥ 38 °C (100.4 °F) for more than one hour
   - CTCAE Grade 4 is defined as ANC < 1.0×10^9/L with a single temperature of > 38.3 °C (101 °F) or a sustained temperature of ≥ 38 °C (100.4 °F) for more than one hour, with life-threatening consequences and urgent intervention indicated.
3. Thrombocytopenia ≥ Grade 3 (< 50×10^9/L) if associated with:
   - A bleeding event, or
   - Requires platelet transfusion
4. Any other Grade 4 hematologic adverse drug reaction or laboratory abnormality, except for asymptomatic Grade 4 lymphocytopenia

7.3.3.3 Non-hematologic toxicities

5. Any Grade 4 non-hematologic adverse drug reaction or laboratory abnormality, except for asymptomatic Grade 4 elevations in alkaline phosphatase
6. Any Grade 3 non-hematologic adverse drug reaction lasting > 3 days despite optimal supportive care with the following exceptions:
   - Grade 3 nausea, vomiting, or diarrhea that improves to Grade 1 with or without supportive care and/or with a light meal prior to prior to the next derazantinib administration
   - Grade 3 fatigue, malaise or flu-like symptoms that improve to Grade ≤ 2 with or without supportive care prior to the next derazantinib administration
7. Any Grade 3 non-hematologic laboratory abnormality if:
   - The patient is symptomatic (and the abnormality is to be reported as an AE) and medical intervention is required to treat the patient, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for > 7 days.

   Note: Asymptomatic Grade 3 abnormalities which can be corrected through oral supplements and persist for ≤ 7 days are not considered a DLT.

8. For patients with Grade 2 AST/ALT abnormality at baseline, an increase in the baseline abnormality to > 10 × baseline will be considered a DLT.

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

7.4 Handling of safety information and collection periods

7.4.1 Responsibilities and procedures

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

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

7.4.2 Handling of safety data during the pre-treatment period

Any relevant change in, or worsening of, a patient's condition occurring after informed consent has been provided but prior to the start of first study-drug administration, is to be recorded in the eCRF as pre-dose medical history (see Section 5.3.1.1). However, in this period (between ICF and start of study medication) if an AE is assessed as related to the study procedure, the AE is to be reported accordingly, and if this event is considered to be serious (i.e., meets one or more of the criteria for an SAE in Section 7.2.2), this information must be reported to the Sponsor's safety representative, using the same procedures as for an SAE (see Section 7.4.3.2).

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

From the start of first dosing up to and including the Safety Follow-Up visit 90 days after last study drug administration, respectively, any change in, or worsening of, a patient's condition must be collected and reported in the eCRF as an AE (see Section 7.4.3.1). SAEs must be additionally reported and recorded on the SAE page of the eCRF (see Section 7.4.3.2).

After the follow-up period, only study-drug-related SAEs and AESIs must be collected and reported; these must also be followed until they have, in the opinion of the Investigator, resolved to baseline or CTCAE Grade 1, stabilized, or are deemed to be irreversible.

7.4.3.1 Adverse event management

7.4.3.1.1 *Data collection*

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

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

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

Refer to the eCRF completion guidelines for further details on completing the AE/SAE in the eCRF. In addition, the concomitant medications (with indication start and stop (if not ongoing) and Medical history should be updated as needed.

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

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

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

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

7.4.3.1.2 *Follow-up*

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

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

Unresolved study-drug-related AEs and study-drug-related and unrelated SAEs at the time of the Safety Follow-Up visit(s) must be followed up until they have, in opinion of the Investigator, resolved to baseline, CTCAE Grade 1, stabilized, or are deemed to be irreversible (including death), or until the patient withdraws their consent.

7.4.3.2 Serious adverse event and AESI reporting

7.4.3.2.1 *Investigator's responsibility*

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

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

Safety vendor	**Sponsor's Medical Monitor**
[redacted]	[redacted] Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel, Switzerland. [redacted]

The information provided in an SAE/AESI report should be as complete as possible, but must at a minimum include the following:

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

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

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

7.4.3.2.2 *Sponsor's responsibilities*

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

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

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

For derazantinib, and atezolizumab the Reference Safety Information Section in the relevant Investigator's Brochures (valid at the time of onset of the event) will serve as the RSI. For paclitaxel-ramucirumab in combination, the Cyramza® USPI and Cyramza® SmPC, respectively, are the RSI.

7.4.4 Handling of post-study safety data

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

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

7.4.5 Reporting and handling of pregnancies

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

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

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

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

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

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

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

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

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

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

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

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

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

8 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

8.1 Sample size considerations by substudy

Two-stage designs (Fleming 1982, Simon 1989) will be used in this study. At the time point of 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 will be suspended to allow for all patients to be exposed to study treatment 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 42 for Substudy 1 and 68 for Substudy 3, should study treatment be ineffective in Stage 1, as compared to a maximum of approximately 314 patients if derazantinib, derazantinib-atezolizumab and derazantinib-paclitaxel-ramucirumab are considered to be effective in all cohorts.

Assuming an overall incidence of approximately 9% patients with qualifying $FGFR^{fus/amp/mt}$ GAC (Van Cutsem 2017, Pearson 2016, Basilea data on file, FoundationInsights™, 2020), up to approximately 3,500 patients will be screened for $FGFR^{fus/amp/mt}$, depending on the extent of preexisting molecular testing.

The study design yields a type I error rate and power in relation to the anticipated true response rates for the respective cohorts as detailed in Sections 8.1.1 and 8.1.3.

8.1.1 Substudy 1

8.1.1.1 Cohorts 1.1 and 1.2

Simon's two-stage design will be used to test the null hypothesis that the true ORR is $p_0 \leq 0.05$ against a one-sided alternative. Hypothesis testing (null hypothesis [H_0] versus alternative hypothesis [H_A]) will be performed at the interim and final analyses. H_0 is $p \leq 0.05$ and is tested against H_A of $p > 0.05$.

In Stage 1, 13 evaluable patients will be enrolled. If no patients with an objective response (defined as a confirmed CR or PR) are observed in Stage 1, the cohort will be stopped. If 1 or more patients with an objective response are observed in these 13 patients, an additional 10 patients will be enrolled, for a total of 23 patients. The null hypothesis will be rejected if 4 or more objective responses are observed in these 23 patients (see Table 20). The Type I error rate is 0.0253 and power is 0.8037 when the alternative ORR is $p_A = 0.23$.

The ORR of 5% for the null hypothesis reflects Phase 3 data of ramucirumab, the only approved targeted antitumor drug used as monotherapy in second-line GAC patients (Fuchs 2014), which achieved an ORR of 3.4%. The ORR of 23% for the alternative hypothesis reflects ORRs seen in recent clinical studies of patients with GAC treated with paclitaxel (Van Cutsem 2017, Wilke 2014).

Table 20 Estimated type I and II errors (*Cohorts 1.1* and *1.2*)

Substudy/cohort	Type I error (α)	Power (1–β)	True response rate (p_A)
Cohorts 1.1 and *1.2*	0.0253	0.8037	0.23

8.1.1.2 Cohort 1.3

Fleming's two-stage design will be used to test the hypothesis that patients treated with derazantinib 200 mg BID will attain a clinically meaningful PFS4 of approximately 35%. This PFS4 is well above that obtained with trifluridine/tipiracil (Bando 2016, Shitara 2018) for a third-line patient population, and considered the benchmark by oncology experts.

Using a Fleming's two-stage design, a total sample size of 32 patients is required to test the null hypothesis H□ of $\pi \leq 0.15$ versus an alternative hypothesis H_a of $\pi \geq 0.35$ 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 0.04, an exact level of Power of 83%. Table 21 summarizes the required samples sizes and required responses to either accept or reject H□.

Up to 20 patients may be enrolled into *Cohort 1.3* in addition to the planned 32 patients, to further characterize efficacy and safety; enrollment may be restricted to patients with either $FGFR2^{fus/amp}$ or $FGFR1–3^{mt}$.

Table 21 Metrics of Fleming's two-stage design (*Cohort 1.3*)

	Sample size	Responders to accept H_0		Responders to reject H_0	
	N	N	%	n	%
Stage 1	16	2	12.5	7	43.8
Stage 2	32	8	25.0	9	28.1

8.1.2 Substudy 2

This substudy comprises an algorithm-based dose-finding design to determine the MTD per DLT assessment, followed by enrollment of an expansion cohort (N = 14) . If the triple combination is not tolerated, investigation of the two-drug regimens derazantinib-paclitaxel or derazantinib-ramucirumab may be considered.

Patients enrolled to the Dose-finding Part will follow a 3+3 dose-finding design, modified to allow for accrual of up to three patients concurrently per dose level (see Section 3.1.7.2)

Descriptive statistics will be used to analyze ORR within 20 patients treated at the MTD assuming that second-line HER2neg patients with GAC expressing FGFR GAs treated with derazantinib in combination with paclitaxel and/or ramucirumab will attain a clinically meaningful ORR of approximately 35%, which is similar to that obtained with paclitaxel and ramucirumab in combination for this patient population (Wilke 2014), and is considered the benchmark by oncology experts. Assuming 7/20 responders (CR or PR) would provide a 90% CI for ORR of 17.7 to 55.8.

Approximately 32 evaluable patients will be enrolled in Substudy 2.

The RP2D will be declared, based on all observed safety, efficacy, PK and PD data, and potential toxicity-response modeling, by a joint decision taken by the IDMC, Investigators, and the Sponsor.

8.1.3 Substudy 3

The design and statistical assumptions applicable to this substudy are contigent on findings from Susbtudies 1 and 2, and are currently under consideration. Prior to initiation of patient enrollment in this substudy, a protocol amendment may be submitted.

8.1.3.1 Cohort 3.1

For *Cohort 3.1, 3.2* and *3.3*, the null hypothesis that the true ORR is $p_0 \leq 0.125$ will be tested against a one-sided alternative H_A of $p > 0.125$. Hypothesis testing (null hypothesis [H_0] versus alternative hypothesis [H_A]) will be performed at the interim and final analyses.

In Stage 1, 17 evaluable patients will be enrolled. If 2 or fewer patients with an objective response are observed in these 17 patients, the cohort will be stopped. If 3 or more patients with an objective response are observed, an additional 29 patients will be enrolled for a total of 46 patients. The null hypothesis will be rejected if 10 or more objective responses are seen in these 46 patients (see Table 22).

The ORR of 12.5% for the null hypothesis reflects the lower bound of the 95% confidence interval (95% CI) of the ORR observed for patients with GAC treated with paclitaxel (Wilke 2014). The ORR of 27.9% for the alternative hypothesis reflects the ORR observed for patients with GAC treated with paclitaxel-ramucirumab (Wilke 2014).

Table 22 Estimated type I and II errors in efficacy-estimating cohorts in Substudy 3

Cohorts	Type I error (α)	Power (1–β)	True response rate (p_A)
Cohort 3.1, 3.2 and *3.3*	0.0464	0.8074	0.279

8.2 Analysis populations

The following analysis populations are defined for this study.

8.2.1 Safety population

The safety population comprises all patients who received at least one dose of study treatment (derazantinib, paclitaxel, ramucirumab or atezolizumab). Data will be summarized according to the treatment actually received.

In the primary safety comparison, patients who crossover to receive derazantinib after progression on the primarily assigned paclitaxel-ramucirumab treatment (in *Cohort 3.4*) are censored at time of crossover for the purpose of the primary substudy analyses.

8.2.2 Intent-to-treat population

The intent-to-treat (ITT) population comprises all patients enrolled for Substudy 1 or Substudy 2, or all patients randomized to treatment in Substudy 3, regardless of the administration of the study drug. The ITT population will be used for between-cohort efficacy analyses in Substudy 3, including pooled analyses of Substudy 1 and Substudy 3.

8.2.3 Modified intent-to-treat population

For single-arm non-comparison efficacy endpoint analyses in Substudies 1, 2 and 3, a modified intent-to-treat (mITT) population will be used, comprising all patients who received at least one dose of derazantinib, paclitaxel, derazantinib-paclitaxel-ramucirumab, or derazantinib-atezolizumab in combination, and have at least one post-baseline imaging assessment in accordance with RECIST 1.1, documented clinical progression (every effort should be made to objectively assess radiographic progression) or died from any cause. Non-evaluable patients will be replaced. Data will be summarized according to the treatment actually received.

8.2.4 Per-protocol population

The per-protocol population will include all patients in the mITT population who have no major protocol violations during the study. Protocol deviations will be identified prior to final analysis. This analysis population will be used for secondary analysis of primary and secondary endpoints.

8.2.5 MTD population (Substudy 2 only)

The MTD-determining population comprises all patients enrolled in the MTD Part of each dose level who meet the following minimum criteria during the first 28-day treatment cycle (Cycle 1):

- received at least one dose of derazantinib-paclitaxel-ramucirumab in combination and has experienced a DLT
- received ≥ 80% of the derazantinib-paclitaxel-ramucirumab dose, respectively, in Cycle 1 and, have been observed for ≥ 28 days following the first dose, and have been evaluated for safety

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 (see Section 4.5.3).

If one patient experiences a DLT in any DL cohort among the first three enrolled and evaluable patients, the cohort will be expanded to six evaluable patients. The MTD is defined as the highest DL at which none or one of six participants (0% to 17%) experience a DLT (see Section 7.3.3 for DLT definition of treatment-related AEs). The MTD is exceeded when at least two of three to six participants (≥ 33% to 67%) experience a DLT in any DL cohort. Replacement of patients is described in Section 4.5.3.

8.2.6 RP2D population (Substudy 2 only)

The RP2D will be declared by joint decision taken by the IDMC (see Section 3.5), Investigators, and the Sponsor, based on the RP2D population, consisting of the MTD population (see Section 8.2.5) and patients treated in the Expansion Part of any dose level with at least Cycle 1 treatment. A decision on the RP2D will account for the aggregate safety data review, including consideration of PK and preliminary efficacy data of the combination.

The final analysis of Substudy 2 will be performed when the last patient completes the last substudy-related phone-call or visit, discontinues from the substudy or is lost to follow-up (i.e., the patient is unable to be contacted by the Investigator).

8.2.7 Pharmacokinetic analysis population

The PK analysis population consists of all patients who receive at least one dose of derazantinib and have at least one PK sample. Sub-populations are defined, according to the analytes and sampling schedule (see Section 5.3.4):

- The rich derazantinib and paclitaxel PK profiling population (with PK parameter determination) consists of the patients enrolled in the rich sampling schedule (see Section 5.3.4.3) who receive at least 1 dose of study drug and have at least one PK sample.
- The sparse derazantinib PK sampling population consists of the patients enrolled in the sparse sampling schedule (see Section 5.3.4.4) who receive at least 1 dose of study drug and have at least one PK sample.
- The atezolizumab PK population (see Section 5.3.4.6) consists of all patients who receive at least 1 dose of atezolizumab and have at least one PK sample.
- The ramucirumab PK population consists of the patients enrolled in the sampling schedule (see Section 5.3.4.6) who receive at least 1 dose of study drug and have at least one PK sample.

8.3 Statistical and analytical methods

All endpoints will be summarized by substudy and cohort. All analyses will include summary statistics, including number and percentage for categorical variables, and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided 90% confidence intervals (CIs) will be provided where appropriate, except otherwise specified. Time-to-event analysis will be performed using Kaplan-Meier (KM) methods. Further detail will be provided in the study SAP.

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

8.3.1 Patient demographics, medical history, and other baseline characteristics

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

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

8.3.2 Study drug exposure and compliance

The dose, duration in days, and compliance with study drug will be listed by patient and summarized through descriptive statistics by cohort in the safety population.

8.3.3 Prior and concomitant treatments

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

8.3.4 Dose-limiting toxicity

In the MTD population, DLTs will be listed and summarized using descriptive statistics.

8.3.5 Efficacy analysis

8.3.5.1 Primary efficacy endpoint

8.3.5.1.1 *All except Substudy 1 Cohort 1.3*

The primary efficacy endpoint will be ORR, defined as the achievement of confirmed CR or PR using RECIST 1.1, as assessed by BICR. Point estimates and two-sided 90% CIs will be provided. The primary analysis will be performed on the mITT population and repeated on the PP population.

To determine the study population for Substudy 3, the outcomes of patients with $HER2^{neg}$ $FGFR^{fus/amp/mt}$ GAC treated with derazantinib in Substudy 1 are to be considered per molecular substype.

8.3.5.1.2 *Substudy 1 Cohort 1.3*

The primary efficacy endpoint will be progression-free survival at 4 months (PFS4) based on survival status or central radiology review per RECIST 1.1 (see Section 8.3.5.1 for details of PFS definition).PFS4 is measured as the proportion of patients alive and without disease progression with exposure not less than 50% of the planned dose, and a second post-baseline imaging assessment done approximately 4 months after treatment allocation.

A Fleming's two-stage design will be used, with approximately 16 patients in Stage 1, and an additional 16 patients if the study proceeds to Stage 2.The subset of the mITT population with a minimum exposure to at least 50% relative to the intended dose will be the primary analysis population.

8.3.5.1.3 *Operational aspects*

Interim analyses for stage transition in the efficacy-estimating substudies will be performed when the number of patients required for Stage 1 have been enrolled, have received at least one dose of study drug, and have at least had one post-baseline tumor imaging assessment, but no later than after the completion of Cycle 8 (in all cohorts except *Cohort 3.3*) and Cycle 11 (in *Cohort 3.3*), when patients have received approximately 32–33 weeks of treatment and had up to four post-baseline study imaging assessments.

If the required number of responses per BICR specified for each cohort has not been observed at the time of enrollment of the last patient to Stage 1, enrollment may be suspended, or the cohort may be terminated due to apparent futility. If the required number of responses per BICR specified for each cohort is reached earlier, both interim analyses may be performed and stage transition may occur earlier. Additional patients may be enrolled during the preparations required for a formal stage (e.g., completion of BICR) transition decision, if the overall benefit-risk profile can be considered favorable based on the known outcomes of patients enrolled at that time.

The final analysis will be performed once the required number of efficacy-evaluable patients have been enrolled into the cohort and have been followed for approximately up to 32–33 weeks of treatment (i.e., each patient had up to four post-baseline study imaging assessments). Patients without efficacy assessments are considered non-responders, and included in the analysis.

8.3.5.2 Secondary efficacy endpoints

8.3.5.2.1 *Progression-free survival and recorded progression date*

PFS is an important secondary endpoint for evaluating the efficacy of derazantinib, derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab. In the mITT population as the primary efficacy analysis population, PFS will be measured from the date of patient enrollment (i.e., treatment allocation / randomization of the patient) to first date of objectively measured radiographic progression by RECIST 1.1 or date of death from any cause (recorded progression date [PD date]). PFS will be summarized using KM methods (including median duration and PFS rates at 6 months) and compared between groups using a stratified log-rank test at a two-sided 5% alpha level.

The censoring date for a patient with no documented progression before data cutoff or dropout is defined as the date of the last tumor assessment with no documented progression.

For the PFS analysis, a patient who discontinues the study for undocumented clinical progression, change of cancer treatment, or decreasing performance status will be censored at the date of the last adequate tumor assessment. Further sensitivity analyses will be specified in the Statistical Analysis Plan to assess the impact of the censoring rules applied.

8.3.5.2.2 *Comparison of experimental treatment and common control*

Important secondary endpoints will be the comparison of the efficacy of derazantinib, derazantinib-paclitaxel-ramucirumab, and derazantinib-atezolizumab in combination, as measured by ORR and PFS with that of paclitaxel-ramucirumab, as well as the comparison of derazantinib with derazantinib-paclitaxel-ramucirumab and derazantinib-atezolizumab in combination, as measured by ORR, DCR, DOR, PFS, and OS, to understand the contribution of derazantinib to the combination treatment regimens.

For the comparison of derazantinib with that of paclitaxel-ramucirumab for ORR and PFS, the ITT population of the cohorts of Substudy 3 will be used, and completely enrolled cohorts of Substudy 1 and 3 will be combined for exploratory analyses.

The between-group comparisons of the ORR in each group will be performed using a Cochran-Mantel-Haenszel or Chi-square test at a one-sided 5% alpha level. The associated two-sided 90% confidence interval will be provided. PFS will be compared between groups using a stratified log-rank test at a one-sided 5% alpha level.

8.3.5.3 Additional secondary efficacy endpoints

DCR (and ORR for Substudy 1 *Cohort 1.3*) will be summarized in the same way as the primary endpoint. DOR, PFS and OS analyses will be performed using KM methods. The analysis will be performed on the mITT population (ITT for OS analysis) and repeated on the PP population.

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

OS will be calculated from the date of treatment allocation / randomization by Medidata RAVE EDC 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.

Sensitivity analyses within Substudies 1 and 3 will be performed according to the stratification factors and further potentially confounding prognostic factors.

8.3.6 Safety data analysis

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization.

8.3.6.1 Dose-limiting toxicity in Cohort 1.3

Safety interim analyses will be performed once up to ten patients have been enrolled and safety data for the 28-day DLT period are available to determine if the revised dosing regimen of 200 mg BID derazantinib 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 π_d denote the probability of DLT at dose d. If n subjects are evaluated at dose d, then the number of subjects, y, experiencing a DLT is assumed to follow a binomial distribution:

$$y \mid \pi\_d \sim \text{"Binomial"}(n,\pi\_d)$$

The relationship between monotherapy derazantinib doses, and DLT probabilities is modelled by the logistic curve:

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

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

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

The model parameters $\log(\alpha_1)$, $\log(\beta)$ are given a weakly informative multivariate normal prior distribution, following (Neuenschwander 2014), with prior means (−1.386, −0.781), prior standard deviations (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 will be assessed by a joint decision taken by the IDMC, Investigators, and the Sponsor in reviewing the aggregate of DLT, AE and PK data.

8.3.6.2 Other safety parameters

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

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

8.3.7 Pharmacokinetic analysis

In the rich derazantinib and paclitaxel PK population, PK parameters will be determined by non-compartmental analysis. The PK parameters determined from rich PK sampling will be summarized using descriptive statistics. Plasma concentrations at each nominal time point will be summarized using descriptive statistics.

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

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

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

In the ramucirumab PK population, ramucirumab serum concentrations at each nominal time point will be summarized overall, and by substudy and cohort using descriptive statistics.

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

8.3.8 Biomarker analysis

The biomarker data will be summarized overall using descriptive statistics. Comparisons of clinical activity endpoints between biomarker defined groups may be performed.

8.3.9 PRO analysis

PRO scores from the EQ-5D, EORTC QLQ-C30, and EORTC QLQ-STO-22 instruments will be analyzed primarily using descriptive analysis.

The minimal important difference of the EQ-5D visual analogue scale, EORTC QLQ-C30 scales and EORTC QLQ-STO-22 scales will be determined using the G-SET/HTI as an external anchor.

8.3.10 Handling of missing data and discontinuations

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

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

9 STUDY ADMINISTRATION AND REGULATORY ASPECTS

9.1 Study records

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

9.1.1 Investigator Site File

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

9.1.2 Case report forms

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

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

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

9.1.3 Patient source documents

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

9.1.4 Document retention and archiving

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

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

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

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

9.2 Sample retention

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

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

9.3 Clinical monitoring

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

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

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

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

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

Monitoring instructions are provided in the Monitoring Plan.

9.4 Audits and inspections

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

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

9.5 Protocol amendments

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

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

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

9.6 Premature termination of the study

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

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

9.7 Publication policy

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

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

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

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

As this is a multicenter study, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an Investigator and his or her colleagues may publish their data independently.

The limitations of single study site observations in a multicenter trial should always be described in such a manuscript.

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

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

10 ETHICS AND GOOD CLINICAL PRACTICE

10.1 Good Clinical Practice

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

10.2 Informed consent

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

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

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

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

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

The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment for derazantinib, atezolizumab, or paclitaxel, the consent form must be reviewed and updated. All patients currently enrolled in the study

who have not yet completed the treatment or post-treatment phases must be given the new information and a copy of the revised form, and asked to give their consent to continuing in the study.

10.3 Patient confidentiality and data protection

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

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

10.4 Independent Ethics Committees / Institutional Review Boards

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

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

11 PROTOCOL VERSION HISTORY

Date	Version	Summary of changes
14 November 2019	1.0	–
17 December 2019	2.0	Changes to address comments from the US FDA. Corrections and updates to ensure consistency throughout the protocol.
13 March 2020	3.0	Changes to address Health Authority comments.
7 April 2020	3.1	Correction of typographical errors.
3 July 2020	4.0	Changes made before study commencement to ensure consistency with the updated Investigator's Brochure, and pursuant to Investigator feedback.
21 May 2021	5.0	Modification of the designs of Substudies 1 and 2, implementation of a new dose regimen.

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13 APPENDICES

Appendix 1 Eligible *FGFR* genetic aberrations

<u>*FGFR2* gene fusions and other rearrangements ('FGFR2^{fus}')</u>

- *FGFR2* gene fusions with breakpoints upstream or downstream of the kinase domain which are in-strand and in-frame with the partner gene
- *FGFR2* gene fusions with breakpoints upstream or downstream of the kinase domain likely to be a functional event but with insufficient data for stringency criteria and/or canonical orientation
- *FGFR2* gene rearrangements of any type (translocations, truncations, deletions, splice site variants) with breakpoints in introns and/or exons upstream or downstream of the kinase domain
- *FGFR2* small variants (insertions, deletions, substitutions) introducing a premature stop codon or a frame-shift downstream of the kinase domain

<u>High-level *FGFR2* gene amplification (FGFR2$^{high\text{-}amp}$)</u>

The quantitative correlate of >10 *FGFR2* gene copy numbers called by the NGS algorithm of the central diagnostic test.

<u>Small variants in *FGFR1–3* (FGFR1–3^{mt})</u>

Missense point mutations (substitutions), in-frame deletions and insertions, excluding inactivating variants in FGFR2 (H213Y, V248D, D530N, R759X, I642V, A648T), and excluding small variants introducing a premature stop codon or reading frame shift upstream of the kinase domain.

FGFR1–3 small variants (insertions, deletions, substitutions) introducing a premature stop codon or a frame-shift downstream of the kinase domain are eligible.

<u>Concurrent assumed activating and inactivating genetic aberrations</u>

In the event that assumed activating (i.e., eligible) and inactivating genetic aberrations are detected in a patient sample and considering heterogeneity of tumor cell clonality, which cannot be resolved with ctDNA analysis from plasma, the resulting FGFR$^{fus/am/mt}$ status will be, for the purpose of this clinical study protocol, defined as molecularly eligible for considering conduct of clinical study screening procedures.

<u>FGFR2^{fus} or FGFR2$^{high\text{-}amp}$ concurrent to FGFR1–3^{mt}</u>

Patients with FGFR2^{fus} or FGFR2$^{high\text{-}amp}$ concurrent to any *FGFR1–3* mutation will be allocated to *Cohort 1.1*.

Appendix 2 Assessment of anti-tumor activity per RECIST v. 1.1

Assessment of tumor responses may be performed following the revised RECIST guidelines, version 1.1. Some of these definitions and criteria are highlighted below.

Measurability of tumor baseline

- CT with IV contrast and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.
- Standard imaging studies should be performed according to the Imaging Manual provided by the central imaging laboratory designated by the Sponsor.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows.

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin (nevi) or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions

Lesions that meet the criteria for radiographically-defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin (nevi) nodules). For the case of skin (nevi) lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only patients with measurable disease at baseline should be included in the study.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a *maximum* of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of the diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- *Complete Response:* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- *Partial Response:* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease:* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease:* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. In this study, the minimum duration for SD is defined as 6 weeks.

Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each Response Criteria subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

(Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- *Complete Response:* Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *Progressive Disease:* Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on the assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Evaluation of new lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI of the brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it truly represents a new disease. If repeat scans confirm there is definitely a new lesion, then progression is to be declared using the date of the initial scan.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the End of Treatment.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. The table below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Time point response: Patients with target (+/– non-target) disease			
Target lesions	**Non-target lesions**	**New lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

The best overall response is determined once all the data for the patient are known.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in the size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the eCRF.

For patients with PR or CR, the Investigator should make every attempt to perform the confirmation scan 4 to 5 weeks after the last scan was performed. Radiographic disease progression must be confirmed by central radiology prior to treatment discontinuation if progression is seen on first or second post-treatment scan.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of tumor re-evaluation

In this study, tumor measurement will be conducted at baseline. In all substudies, the first on-study tumor imaging assessments will be performed at C3D1 ±7 days, and subsequently every 8 weeks (i.e., C5D1 and C7D1 ±7 days) for 6 months, then every 12 weeks (C10D1, C13D1 etc., ±7 days) thereafter (or more frequently if clinically indicated), until progression of disease, withdrawal of consent, or death.

In *Cohort 3.3* and with regard to the 3-week cycle interval, the first on-study tumor assessments will be performed on C3D15, and subsequently every 8 weeks (i.e., C6D8 and C9D1, ±7 days) for 6 months, and then every 12 weeks (C13D1, C17D1 etc., ±7 days) thereafter (with additional scans as clinically indicated), until progression of disease, withdrawal of consent, or death.

Tumor measurement will also be performed during the End of Treatment visit if it is not done within 28 days of the End of Treatment visit date or if prior scan did not show radiographic disease progression.

Baseline tumor assessments must be performed within 4 weeks (28 days) of the first dose of treatment.

All efforts must be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning methods, equipment, technique (including slice thickness and field of view), and the radiographic interpreter.

The radiological evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations must meet the standard of care for imaging of lesions in the respective organ(s).

All target and non-target sites are evaluated at each time point of tumor assessment.

Confirmatory measurement / duration of response

Confirmation

Confirmation of PR and CR is required approximately 4–5 weeks after the initial scan showing PR or CR.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria that are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). In this study, the minimum duration for SD is defined as 6 weeks.

Appendix 3 Comparison of RECIST 1.1 and iRECIST criteria

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Appendix 4 Management of atezolizumab-specific adverse events

Note: This appendix is a redacted version of the detailed guidance for the management of immune-related AEs, located in the atezolizumab IB (Edition 17), which should be consulted for further guidance.

Pulmonary events including pneumonitis	
Event	**Management**
Grade 1	Continue atezolizumab and monitor closely.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as a Grade 3 or 4 event.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Bronchoscopy or bronchoscopic alveolar lavage is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone, and consider adding an immunosuppressive agent if event does not improve within 48 hours after initiating corticosteroids. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Hepatic events	
Event	**Management**
Grade 1	Continue atezolizumab and monitor liver function tests (LFTs) until values resolve to normal or to baseline values.
Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events with a duration of > 5 days** • Withhold atezolizumab for up to 12 weeks after event onset. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.

Hepatic events	
Event	**Management**
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone, and consider adding an immunosuppressive agent if event does not improve within 48 hours after initiating corticosteroids. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Gastrointestinal events (diarrhea or colitis)	
Event	**Management**
Grade 1	• Continue atezolizumab and monitor closely. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone, and consider adding an immunosuppressive agent if event does not improve within 48 hours after initiating corticosteroids. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Endocrine Events	
Event	**Management**
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone, monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone, monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab, and monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.
Symptomatic adrenal insufficiency, Grades 2-4	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab and monitor for glucose control. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab and monitor for glucose control. • Initiate treatment with insulin. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Endocrine Events	
Event	**Management**
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

Ocular Events	
Event	**Management**
Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immuno-suppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immuno-suppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month.

Ocular Events	
Event	**Management**
Immune-mediated myocarditis	
Event	**Management**
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset and contact Medical Monitor. • Refer patient to cardiologist, initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to cardiologist, initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Infusion-related reactions (IRR) and cytokine-release syndrome (CRS)	
Event	**Management**
Grade 1 (fever with or without constitutional symptoms)	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, c including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Infusion-related reactions (IRR) and cytokine-release syndrome (CRS)	
Event	**Management**
Grade 2 (fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen by nasal cannula or blow-by)	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • Administer symptomatic treatment. • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3 (fever with hypotension requiring a vasopressor [with or without vasopressin] and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or venture mask)	• Permanently discontinue atezolizumab and contact Medical Monitor. • Administer symptomatic treatment. For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

Infusion-related reactions (IRR) and cytokine-release syndrome (CRS)	
Event	**Management**
Grade 4 (fever with hypotension requiring multiple vasopressors [excluding Vasopressin] and/or hypoxia requiring oxygen by positive pressure [e.g., CPAP, BiPAP, intubation and mechanical ventilation])	• Permanently discontinue atezolizumab and contact Medical Monitor. • Administer symptomatic treatment. • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Pancreatic events including pancreatitis	
Event	**Management**
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5-2.0 × ULN:** • Continue atezolizumab and monitor amylase / lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0-5.0 × ULN:** • Treat as Grade 3.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset, and monitor amylase and lipase every other day. • Refer patient to GI specialist. • If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.

Pancreatic events including pancreatitis	
Event	**Management**
	• If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Dermatologic events	
Event	**Management**
Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 4	Permanently discontinue atezolizumab and contact Medical Monitor.

Severe Cutaneous Adverse Reactions (SCARs)[1]
Management
• For suspected SCARs, the patients should be referred to a dermatologist for further diagnosis and management • Atezolizumab should be withheld for patients with suspected Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) • Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN • Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Neurologic Disorders	
Event	**Management**
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Investigate etiology. • Initiate treatment as per institutional guidelines. If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1-2 mg/kg/day oral or IV prednisone.

[1] Severe Cutaneous Adverse Reactions (SCARs) are a heterogeneous group of immunologically-mediated drug eruptions. Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). SCARs are considered to be an identified risk for atezolizumab.

Immune-mediated meningoencephalitis	
Event	**Management**
All grades	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

Immune-Mediated Myositis	
Event	**Management**
Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset, and contact Medical Monitor. • Refer patient to rheumatologist or neurologist.

Immune-Mediated Myositis	
Event	**Management**
	• Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset, and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as Grade 4 event. Permanently discontinue atezolizumab and contact Medical Monitor.
Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month.

Suspected hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS)	
Event	**Management**
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015, Schram 2015, La Rosée 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Appendix 5 Collection and management of specimens for future biomedical research

Definitions

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Pharmacogenomics: The investigation of variations of DNA characteristics as related to drug/vaccine response.

Pharmacogenetics: A subset of pharmacogenomics; pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.

DNA: Deoxyribonucleic acid.

Future biomedical research sample collection

For the purposes of this appendix, the specimens collected in this study as outlined in Section 5.3.5.3 are considered to be the 'Future Biomedical Research Sample Collection', and will be used to study various causes for how patients may respond to a drug.

Scope of future biomedical research

Future biomedical research specimens will be stored to provide a resource for future studies conducted by the Sponsor focused on the study of biomarkers responsible for how a drug enters and is removed by the human body, how a drug works, other pathways a drug may interact with, or other aspects of disease. The specimens may be used for future assay development and/or drug development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance the understanding of how individuals respond to drugs and the understanding of human disease, and ultimately to improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor, or those working in partnership with, or at the direction of, the Sponsor.

Summary of procedures for future biomedical research

1. Patients for enrollment

All patients enrolled in clinical study DZB-CS-202 will be considered for enrollment in the future biomedical research study.

2. Informed consent

Informed consent for specimens (i.e., DNA, protein, etc.) will be obtained during screening for protocol enrollment from all patients, at a study visit by the Investigator or his or her designate. Informed consent for future biomedical research is part of the study ICF and must be obtained before samples not fully consumed for the study analyses are subsequently used for future biomedical research.

Informed consent for future biomedical research is to be handled in the same manner as other consents provided for the purposes of this study (see Section 10.2).

3. eCRF documentation for future biomedical research specimens

Documentation of patient consent for future biomedical research will be captured in the eCRF. Any specimens for which such an informed consent cannot be verified must be destroyed.

4. Future biomedical research specimen collections

Collection of specimens for future biomedical research will be performed as part of sample collection in accordance with study procedures. If additional blood specimens are collected specifically for future biomedical research, these should be obtained at a time when the patient is having blood drawn for other study purposes.

Confidential subject information for future biomedical research

To optimize the research that can be conducted with future biomedical research specimens, it is critical to link patient clinical information with future test results, so that pecific analyses can be conducted. Knowing patient characteristics like sex, age, medical history and treatment outcomes are critical to understanding the clinical context of analytical results.

All patient personal data collected for future biomedical research will be handled in accordance with the Sponsor's confidentiality and personal data standard operating procedures (SOPs), and in compliance with the EU General Data Protection Regulation (GDPR).

Biorepository specimen usage

Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or a third party (e.g., a university Investigator) designated by the Sponsor. The Investigator conducting the analysis will be contractually bound to comply with the Sponsor's personal data protection and confidentiality requirements, and with the GDPR. Any contracted third-party analyses will conform to the specific scope of analysis outlined in the future biomedical research study. Future biomedical research specimens remaining with the third party after specific analysis is performed will continue to be protected by the contractual provisions and the requirement to comply with the GDPR.

Withdrawal from future biomedical research

Patients may withdraw their consent for future biomedical research at any time by contacting either the Investigator or the Sponsor, and may have their specimens and all derivatives removed from the biorepository and destroyed. While any analyses in progress at the time of a request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research, no new analyses of a patient's speciments will be generated after a request for destruction is received.

Retention of specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 5 years from the end of the main study.

Data security

Databases containing specimen information and test results must be accessible only to the authorized Sponsor representatives and the designated study personnel and/or authorized collaborators. The Sponsor must ensure that database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

Reporting of future biomedical research data to patients

Information obtained from exploratory laboratory studies will not usually be reported to the patient, family, or physicians.

If any exploratory results are definitively associated with clinical significance for patients while the clinical study is ongoing, Investigators will be contacted with information. After the clinical study has been completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Patients will not be identified in any published reports about this study or in any other scientific publication or presentation.

Risks versus benefits of future biomedical research

No additional risks to the patient from future biomedical research have been identified, as no additional specimens will be collected for future biomedical research after completion of this study (i.e., only leftover samples are being retained).

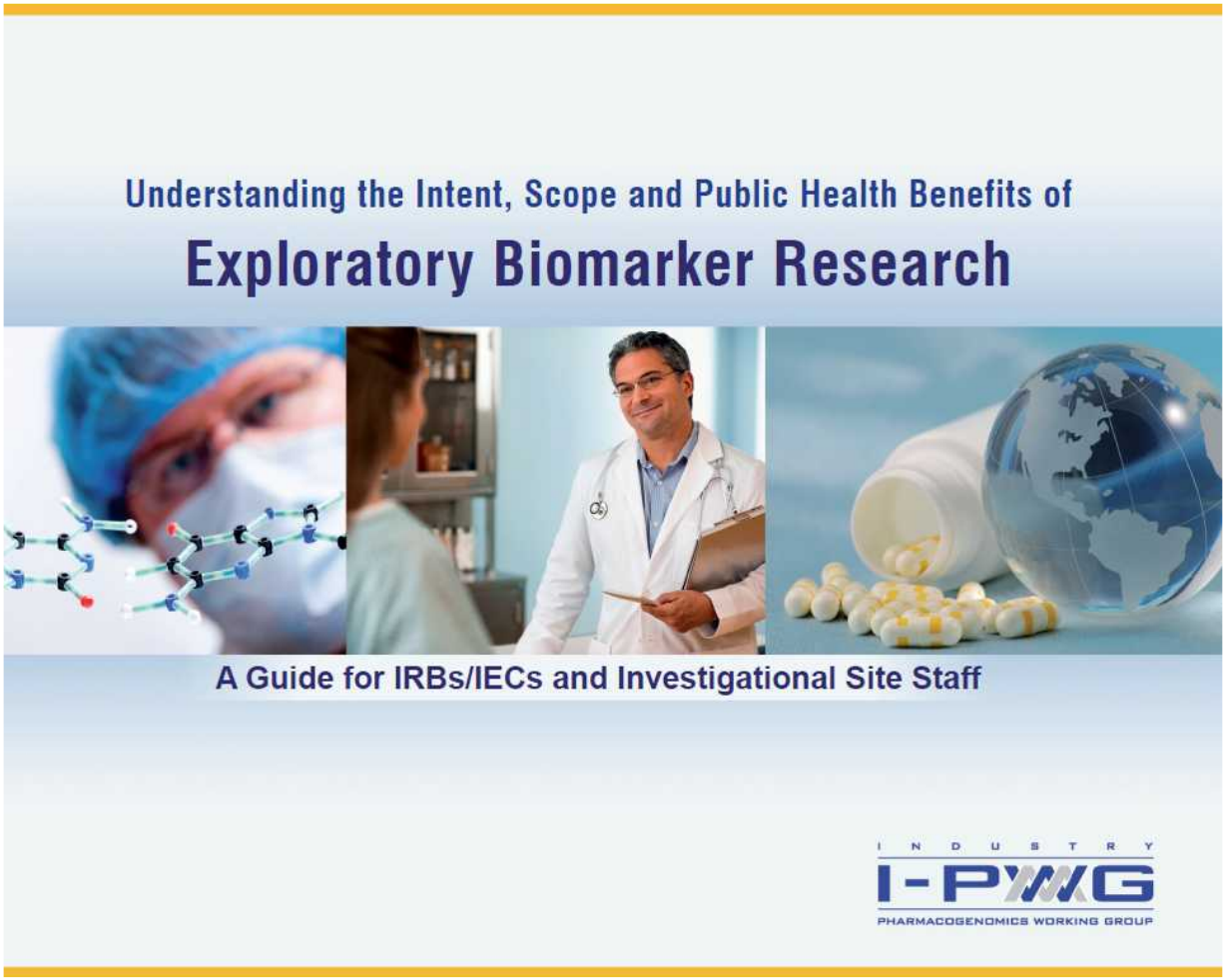
Questions

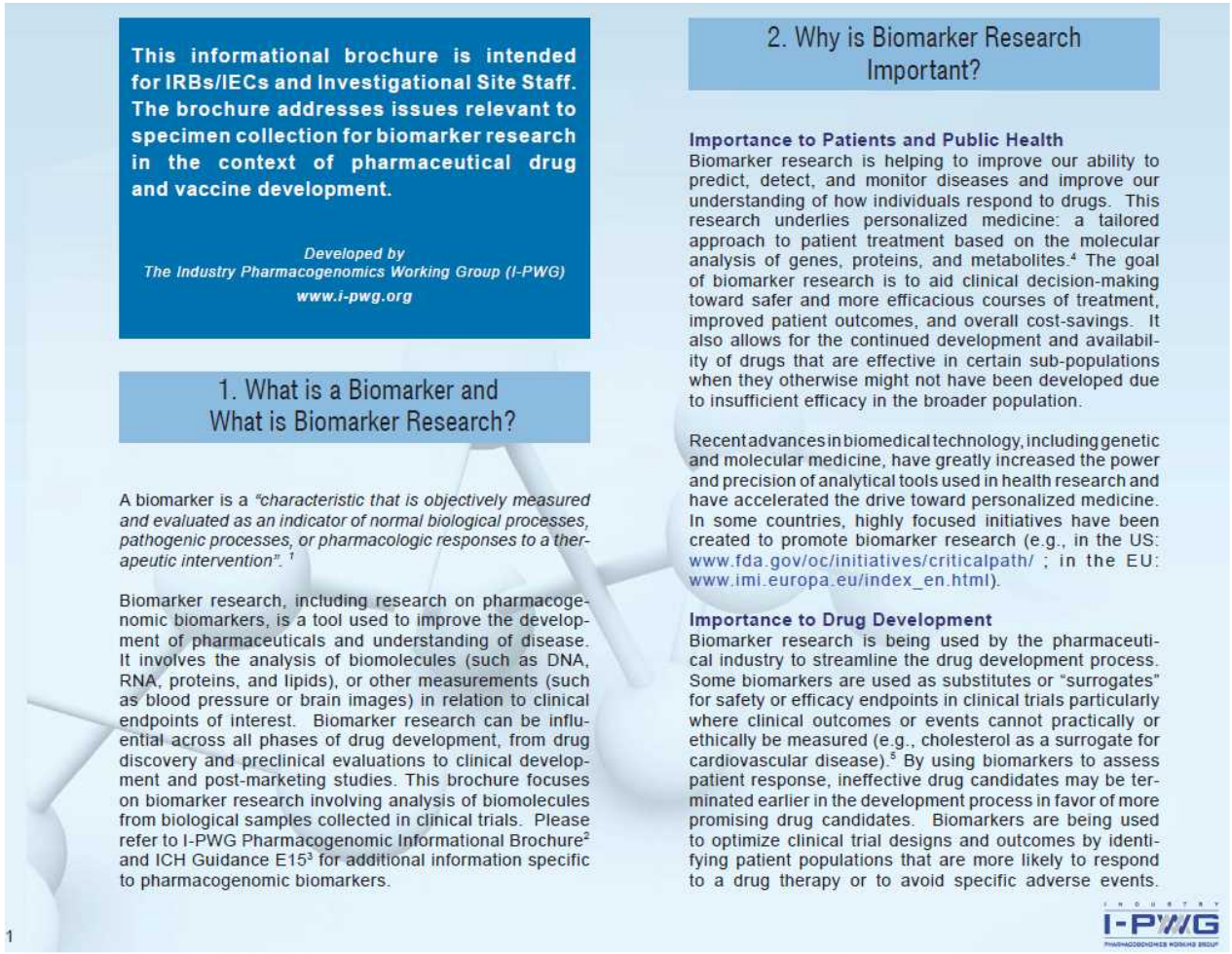
Any questions related to the future biomedical research should be emailed directly to medical.information@basilea.com.

Appendix 6 Understanding the intent, scope and public health benefits of exploratory biomarker research

Education Task Force, Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research, a Guide for IRBs/IECs & Investigational Site Staff. Published on the I-PWG web site (www.i-pwg.org). December 2009.

Available at:
https://i-pwg.org/document-manager/publications/18-i-pwg-pharmacogenomics-informational-brochure/file


Understanding the Intent, Scope and Public Health Benefits of
Exploratory Biomarker Research
A Guide for IRBs/IECs and Investigational Site Staff
INDUSTRY
I-PWG
PHARMACOGENOMICS WORKING GROUP



This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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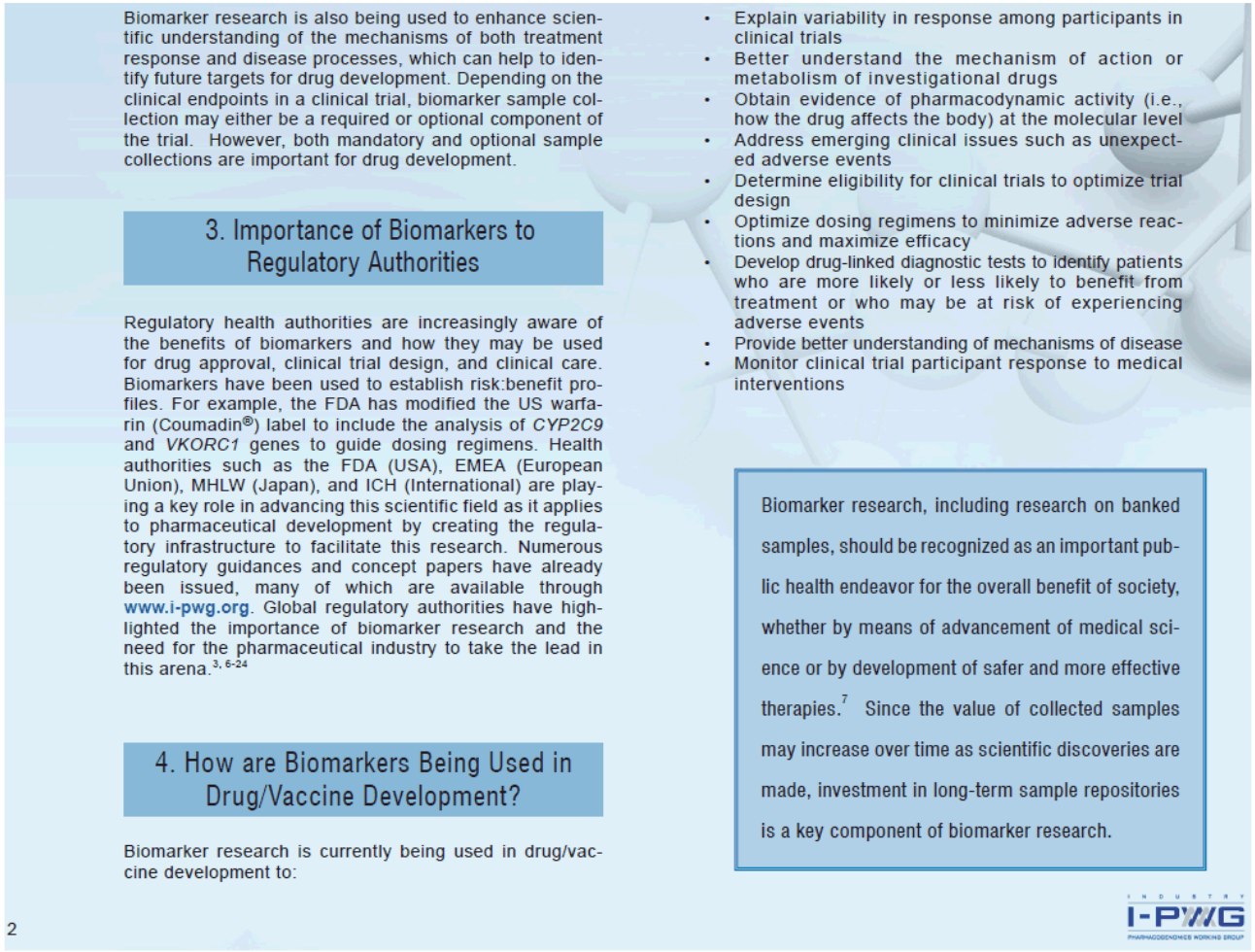

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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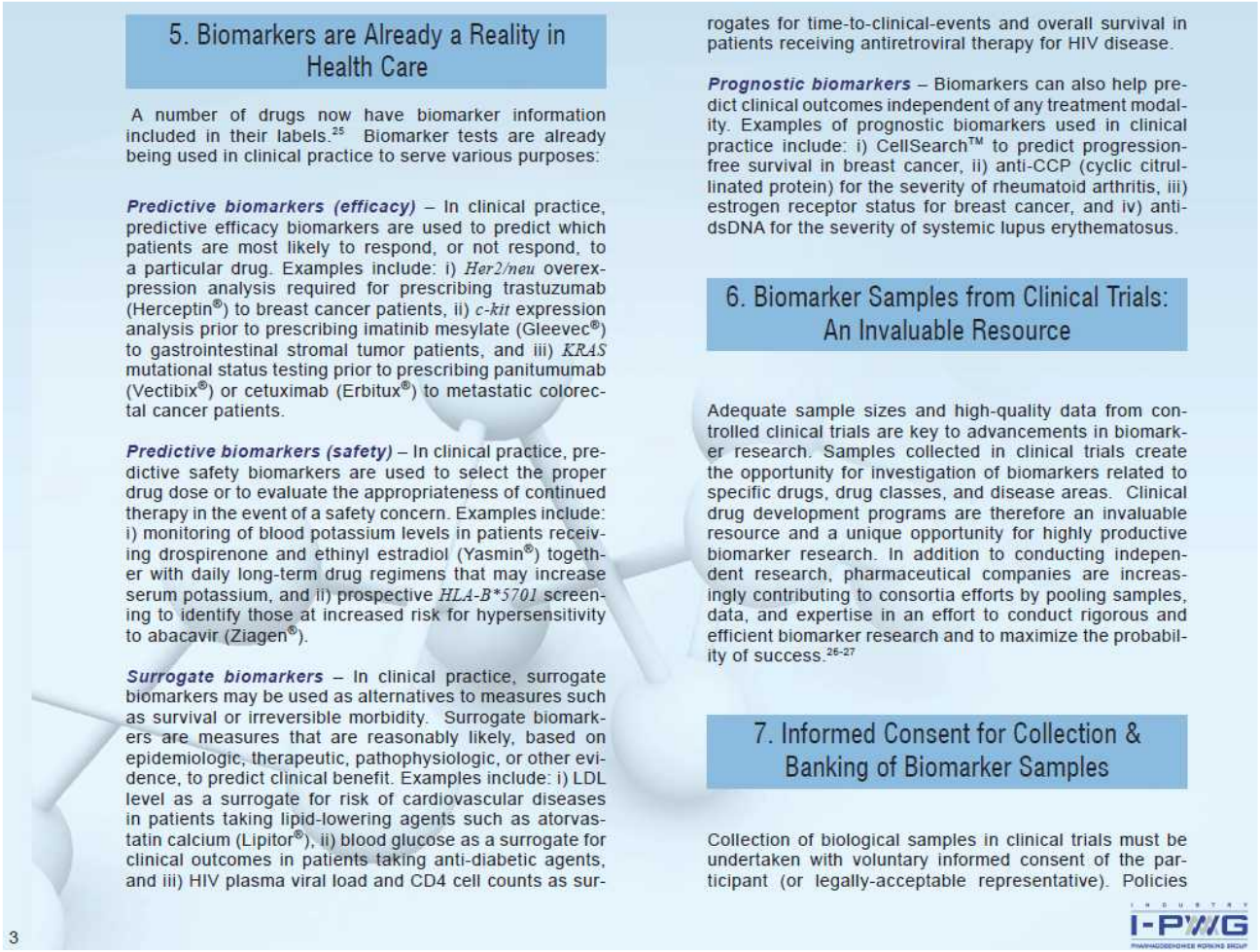

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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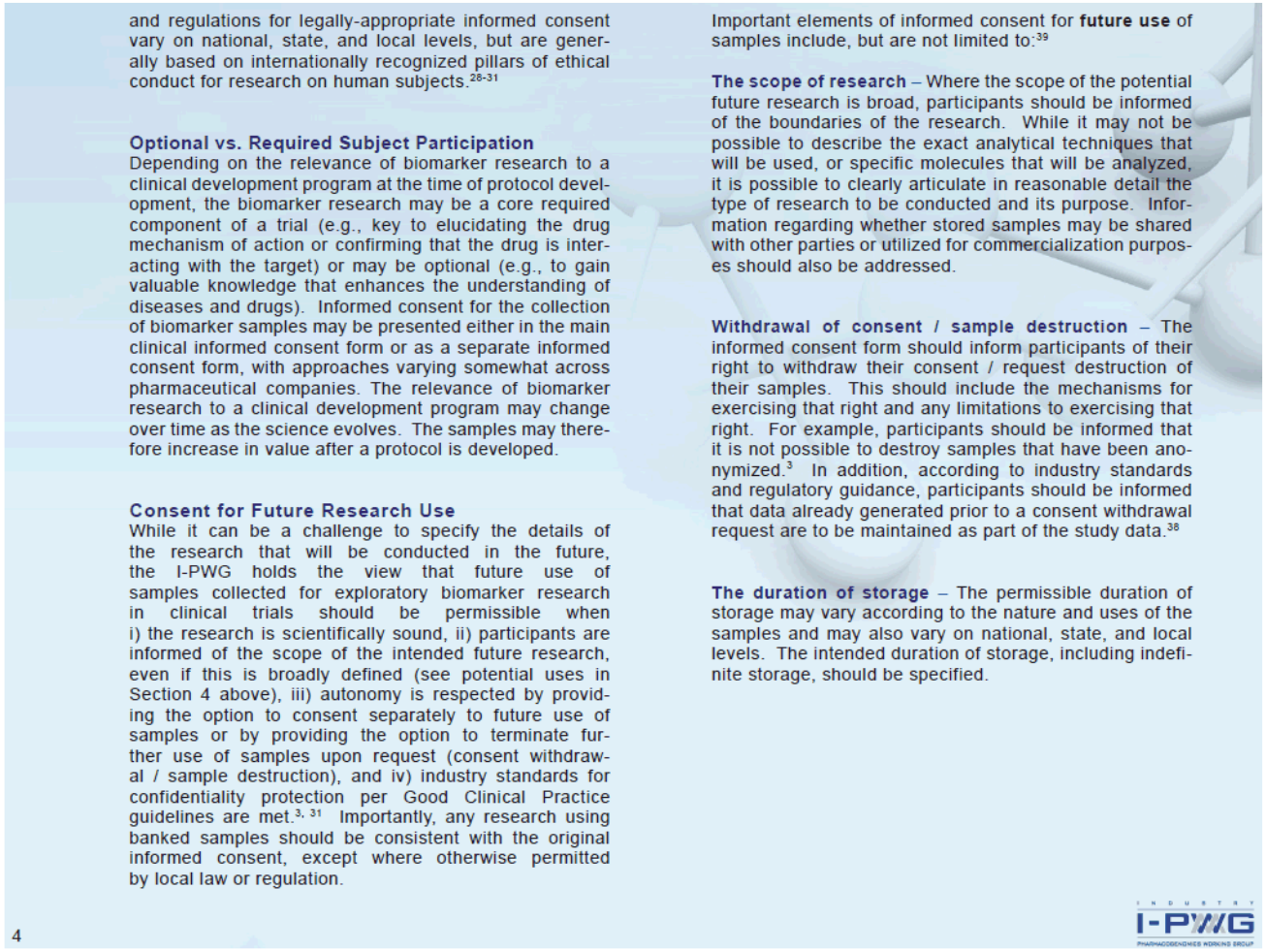

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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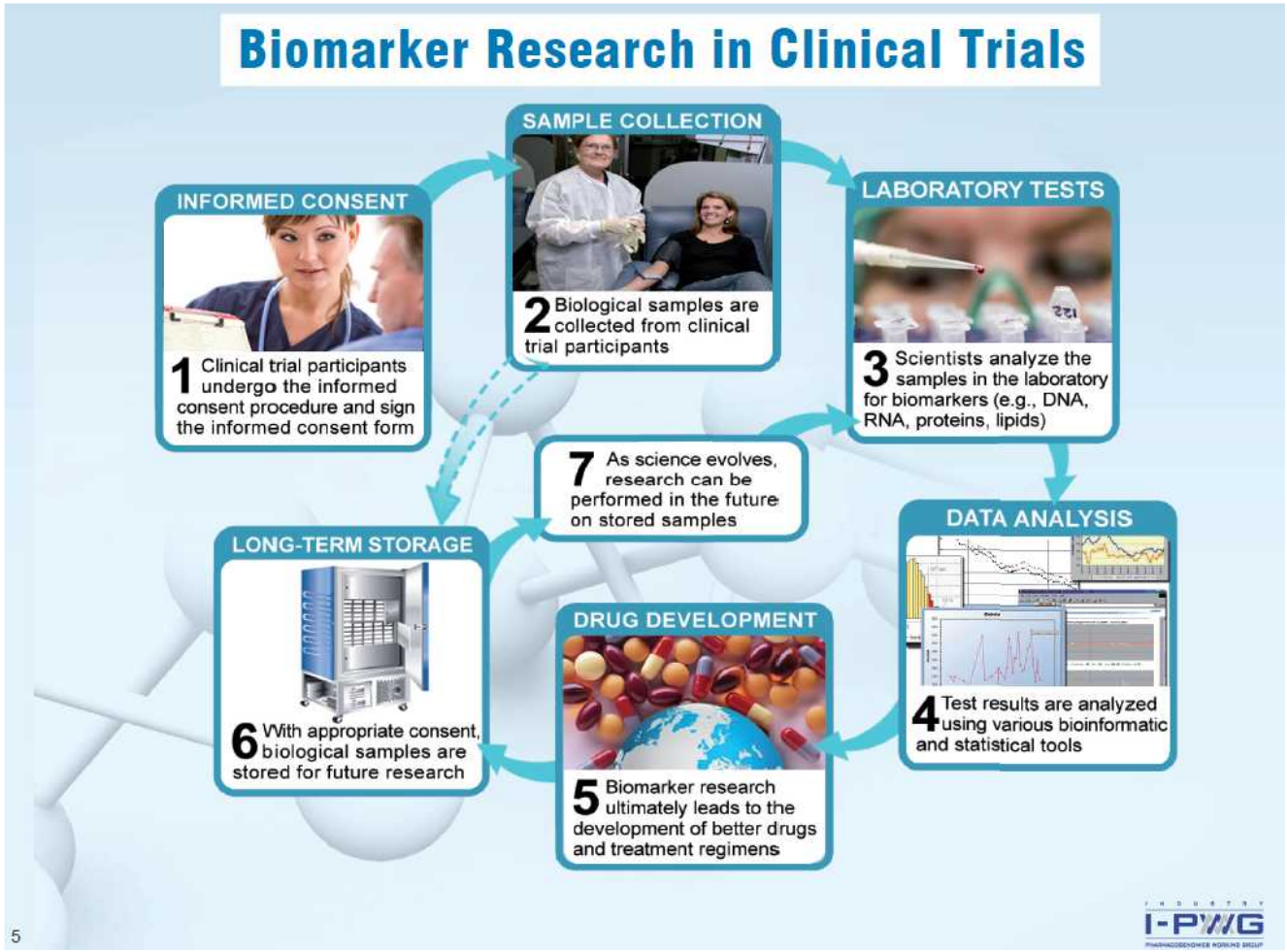
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
5
I-PWG

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

6

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"…provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: **www.i-pwg.org.**

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/ informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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Appendix 7 Examples of in vivo substrates, inhibitors, and inducers for specific CYP enzymes

A search was conducted in June–September 2019 to identify relevant substrates of CYP isoforms potentially inhibited by derazantinib which should be best avoided as co-medications.

Methodology to identify relevant substrates

Major interactions for typical inhibitors of the iso-enzymes of interest were searched in the interaction checker tool from drugs.com (https://www.drugs.com/drug_interactions.html), a free tool with good performance for DDI evaluation (Marcath 2018). The major interactions were selected and reviewed looking at the information in the 'Professional' tab. The drugs for which interaction is clearly assigned to the inhibition of the respective iso-enzyme are listed as substrates in the tables within this appendix; the drugs for which interaction is clearly assigned to other mechanisms (e.g., pharmacodynamic, other enzyme) are not listed in the tables. In cases of unclear assignment, the interaction was further evaluated by consultation of Stockley's Drug Interactions (Eighth edition (Baxter 2008), drug labels (e.g., EMA SPCs, USPIs), or reviews (e.g., EPARs).

Substrates for the specifc iso-enzyme listed in the University of Indiana Flockhart Table™ (https://drug-interactions.medicine.iu.edu/MainTable.aspx).were also checked.

Limitations and recommendations

Note that this list is not intended to be exhaustive. Interactions that are not present as 'major' in drugs.com (e.g. moderate interactions, interactions not captured in the tool) or in the Flockhart Table ™ are not listed.

To check for potential interactions, the combination of a drug with the reference inhibitors listed in the tables in drugs.com or in the labels can be checked for.

For additional information, consult a pharmacist or the Sponsor.

Identification and classification of inhibitors

Iso-enzyme inhibitors were identified as those listed as clinically relevant inhibitors by the FDA[1], or those that are given a specific classification in the Flockhart Table™. Note that this list is not exhaustive, and only provides examples of reference inhibitors.

Inhibitors can be classified by their potency:

- *Strong inhibitor*: causes at least a 5-fold increase in the plasma area under the curve (AUC) values, or more than 80% decrease in clearance.
- *Moderate inhibitor*: causes at least a 2-fold increase in the plasma AUC values, or
  50–80% decrease in clearance.
- *Weak inhibitor*: causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20–50% decrease in clearance.

[1] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-2

CYP1A2 relevant substrates and inhibitors

Substrates	Inhibitors
• Agomelatine [1] • Alosetron [1] • Aminophylline • Amitriptylline • Amoxapine • Caffeine • Clomipramine • Clozapine • Desipramine • Doluxetine • Doxepin • Haloperidol • Imipramine • Nortiptyline • Ondansetron • Oxtriphylline • Pirfenidone • Propranolol • Protriptyline • Ramelteon [1] • Tacrine • Tasimelteon • Theophylline • Tizanidine [1] • Trimipramine • Warfarin	**Strong** • Ciprofloxacin • Many other fluoroquinolones • Fluvoxamine [4] • Verapamil **Weak** • Cimetidine

[1] CONTRAINDICATED with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme.
[2] CONTRAINDICATED with an inhibitor of the iso-enzyme, with limited evidence that the interaction is mainly driven by this iso-enzyme.
[3] DOSE ADJUSTMENT advised with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme.
[4] Inhibitor with which search was conducted in www.drugs.com.

CYP2C8 relevant substrates and inhibitors

Substrates	Inhibitors
• Atorvastatin • Bexarotene • Cerivastatin • Fluvastatin • Loperamide • Lovastatin • Pioglitazone [3] • Pitavastatin • Pravastatin • Read yeast rice • Repaglinide [1] • Simvastatin [2] • Paclitaxel • Torsemide	**Strong** • Clopidogrel • Gemfibrozil [4] **Moderate** • Teriflunomide • Trimethoprim

[1] CONTRAINDICATED with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme.
[2] CONTRAINDICATED with an inhibitor of the iso-enzyme, with limited evidence that the interaction is mainly driven by this iso-enzyme.
[3] DOSE ADJUSTMENT advised with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme.
[4] Inhibitor with which search was conducted in www.drugs.com.

CYP2D6 relevant substrates and inhibitors

Substrates

- Alprenolol
- Amitriptyline
- Amoxapine
- Amphetamine
- Antipsychotics
- Aripiprazole [3]
- Atomoxetine [3]
- benzphetamine [3]
- brexpiprazole
- Bufuralol
- Carvedilol
- Chlorpromazine
- Clomipramine
- Codeine
- Debrisoquine
- Desipramine
- Desvenlafaxine
- Deutetrabenazine [3]
- Dextroamphetamine
- Dextromethorphan
- Dolasetron
- Donepezil
- Doxepin
- Duloxetine
- Eliglustat [1]
- Encainide
- Flecainide
- Fluoxetine
- Furazolidone [2]
- Granisetron
- Haloperidol
- Iloperidone [3]
- Imipramine
- Isocarboxazid [2]
- Levopromazine
- Methoxyamphetamine
- Metoclopramide
- Metoprolol
- Mexiletine
- Mianserin
- Nebivolol
- Nortryptiline
- Ondansetron
- Oxycodone
- Palonosetron
- Paroxetine [3]
- Perhexiline
- Perphenazine
- Pimozide [1]
- Promethazine
- Propafenone
- Propranolol
- Protriptyline
- Risperidone
- Selegiline [2]
- SSRIs
- Tamoxifen
- Tetrabenazine [3]
- Thioridazine [1]
- Timolol
- Tramadol
- Tricyclic anti-depressants
- Trimipramine
- Tropisetron
- Valbenazine [3]
- Vortioxetine [3]
- Zuclopenthixol

Inhibitors

Strong:
- Bupropion [4]
- Cinacalcet
- Fluoxetine
- Paroxetine [4]
- quinidine [4]

Moderate
- duloxertine
- erythromycin
- fluconazole
- rolapitant
- sertraline
- terbinafine
- verapamil

Weak:
- amiodarone
- cimetidine
- escitalopram

[1] CONTRAINDICATED with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme. [2] CONTRAINDICATED with an inhibitor of the iso-enzyme, with limited evidence that the interaction is mainly driven by this iso-enzyme.
[3] DOSE ADJUSTMENT advised with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme.
[4] Inhibitor with which search was conducted in www.drugs.com.
Underlined indicates caution is advised for an entire class, some of the individual drugs in the list are members of the classes; the use of class IA and III antiarrhythmics is not advised with quinidine but this is for pharmacodynamics reasons not specifically due to 2D6 inhibition.

Appendix 8 Examples of *in vivo* substrates, inhibitors, and inducers of P-glycoprotein

A search was conducted in June–September 2019 to identify relevant substrates of a transporter potentially inhibited by derazantinib and which should be best avoided as co-medications.

Methodology to identify relevant substrates

Major interactions for typical inhibitors of the transporter of interest were searched in the interaction checker tool from drugs.com (https://www.drugs.com/drug_interactions.html), a free tool with good performance for DDI evaluation (Marcath 2018). The major interactions were selected and reviewed looking at the information in the 'Professional' tab. The drugs for which interaction is clearly assigned to the inhibition of the respective transporter are listed as substrates in the tables within this appendix; the drugs for which interaction is clearly assigned to other mechanisms (e.g., pharmacodynamic, enzyme) are not listed in the tables. In cases of unclear assignment, the interaction was further evaluated by consultation of Stockley's Drug Interactions (Eighth edition (Baxter 2008), drug labels (e.g., EMA SPCs, USPIs), or reviews (e.g., EPARs).

Substrates for the specifc transporter listed in the October 2017 FDA *Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* are also listed.

Limitations and recommendations

Note that this list is not intended to be exhaustive. Interactions that are not present as 'major' in drugs.com (e.g., moderate interactions, interactions not captured in the tool) or in the October 2017 FDA guidance do not appear in the list.

To check for potential interactions for potential co-medications, the combination of the drug with the reference inhibitors listed in the tables in drugs.com or in the labels can be checked for.

For additional information, consult a pharmacist or the Sponsor.

Inhibitors

Iso-enzyme inhibitors were identified as those listed as clinically relevant inhibitors in the October 2017 FDA guidance.

Note that this list is not exhaustive, and only provides examples of reference inhibitors.

P-glycoprotein relevant substrates and inhibitors

Substrates	Inhibitors
• Aliskiren • Ambrisentan • Betrixaban • Colchicine [1] • Dabigatran etexilate • Digoxin [1] • Edoxaban [1] • Everolimus • Fexofenadine • Imatinib • Lapatinib • Lefamulin • Loperamide • Maroviroc • Nilotinib • Ranolazine • Saxagliptin • Sirolimus • Talazoparib [1] • Tolvaptan [1] • Topotecan	• Clarithromycin • Itraconazole • Quinidine • Verapamil [2]

[1] DOSE ADJUSTMENT advised with an inhibitor of the iso-enzyme, with evidence that the interaction is mainly driven by this iso-enzyme.
[2] Inhibitor with which search was conducted in www.drugs.com.

Appendix 9 Drugs with the potential to prolong QT and/or cause Torsades de Pointes

Known **risk of Torsades de Pointes**[1]

Generic name	Brand name	Generic name	Brand name
Aclarubicin	Aclacin and others	Ibogaine	None
Amiodarone	Cordarone and others	Ibutilide	Corvert
Anagrelide	Agrylin and others	Levofloxacin	Levaquin and others
Arsenic trioxide	Trisenox	Levomepromazine (methotrimeprazine)	Nosinan and others
Astemizole	Hismanal	Levomethadyl acetate	Orlaam
Azithromycin	Zithromax and others	Levosulpiride	Lesuride and others
Bepridil	Vascor	Mesoridazine	Serentil
Chloroquine	Aralen	Methadone	Dolophine and others
Chlorpromazine	Thorazine and others	Moxifloxacin	Avelox and others
Cilostazol	Pletal	Ondansetron	Zofran and others
Ciprofloxacin	Cipro and others	Oxaliplatin	Eloxatin
Cisapride	Propulsid	Papaverine HCl (Intra-coronary)	None
Citalopram	Celexa and others	Pentamidine	Pentam
Clarithromycin	Biaxin and others	Pimozide	Orap
Cocaine	Cocaine	Probucol	Lorelco
Disopyramide	Norpace	Procainamide	Pronestyl and others
Dofetilide	Tikosyn	Propofol	Diprivan and others
Domperidone	Motilium and others	Quinidine	Quinaglute and others
Donepezil	Aricept	Roxithromycin	Rulide and others
Dronedarone	Multaq	Sevoflurane	Ultane and others
Droperidol	Inapsine and others	Sotalol	Betapace and others
Erythromycin	E.E.S. and others	Sparfloxacin	Zagam
Escitalopram	Cipralex and others	Sulpiride	Dogmatil and others
Flecainide	Tambocor and others	Sultopride	Barnetil and others
Fluconazole	Diflucan and others	Terfenadine	Seldane
Gatifloxacin	Tequin	Terlipressin	Teripress and others
Grepafloxacin	Raxar	Terodiline	Micturin and others
Halofantrine	Halfan	Thioridazine	Mellaril and others
Haloperidol	Haldol and others	Vandetanib	Caprelsa

[1] Source: CredibleMeds® (https://www.crediblemeds.org).

Possible **risk of Torsades de Pointes**[1]

Generic name	Brand name	Generic name	Brand name
Abarelix	Plenaxis	Dexmedetomidine	Precedex and others
Alfuzosin	Uroxatral	Dextromethorphan/ Quinidine	Nuedexta
Apalutamide	Erleada	Dolasetron	Anzemet
Apomorphine	Apokyn and others	Efavirenz	Sustiva and others
Aripiprazole	Abilify and others	Eliglustat	Cerdelga
Artemether + Lumefantrine	Coartem	Encorafenib	Braftovi
Artenimol+piperaquine	Eurartesim	Epirubicin	Ellence and others
Asenapine	Saphris and others	Eribulin mesylate	Halaven
Atomoxetine	Strattera	Ezogabine (Retigabine)	Potiga and others
Bedaquiline	Sirturo	Felbamate	Felbatol
Bendamustine	Treanda and others	Fingolimod	Gilenya
Benperidol	Anquil and others	Fluorouracil (5-FU)	Adrucil and others
Betrixaban	Bevyxxa	Flupentixol	Depixol and others
Bortezomib	Velcade and others	Gemifloxacin	Factive
Bosutinib	Bosulif	Glasdegib	Daurismo
Buprenorphine	Butrans and others	Granisetron	Kytril and others
Cabozantinib	Cometriq	Hydrocodone - ER	Hysingla ER and others
Capecitabine	Xeloda	Iloperidone	Fanapt and others
Ceritinib	Zykadia	Imipramine (melipramine)	Tofranil
Clofazimine	Lamprene	Inotuzumab ozogamicin	Besponsa
Clomipramine	Anafranil	Isradipine	Dynacirc
Clotiapine	Entumine	Ketanserin	Sufrexal
Clozapine	Clozaril and others	Lacidipine	Lacipil and others
Crizotinib	Xalkori	Lapatinib	Tykerb and others
Cyamemazine (cyamepromazine)	Tercian	Lenvatinib	Lenvima
Dabrafenib	Tafinlar	Leuprolide	Lupron and others
Dasatinib	Sprycel	Lithium	Eskalith and others
Degarelix	Firmagon and others	Lopinavir and ritonavir	Kaletra and others
Delamanid	Deltyba	Maprotiline	Ludiomil and others
Desipramine	Pertofrane and others	Melperone	Bunil and others
Deutetrabenazine	Austedo	Memantine	Namenda XR and others

(Continued)

[1] Source: CredibleMeds® (https://www.crediblemeds.org).

Possible **risk of Torsades de Pointes (continued)**[1]

Generic name	Brand name	Generic name	Brand name
Midostaurin	Rydapt	Rilpivirine	Edurant and others
Mifepristone	Korlym and others	Risperidone	Risperdal
Mirabegron	Myrbetriq	Romidepsin	Istodax
Mirtazapine	Remeron	Saquinavir	Invirase(combo)
Moexipril/HCTZ	Uniretic and others	Sertindole	Serdolect and others
Necitumumab	Portrazza	Sorafenib	Nexavar
Nicardipine	Cardene	Sunitinib	Sutent
Nilotinib	Tasigna	Tacrolimus	Prograf and others
Norfloxacin	Noroxin and others	Tamoxifen	Nolvadex and others
Nortriptyline	Pamelor and others	Telavancin	Vibativ
Nusinersen	Spinraza	Telithromycin	Ketek
Ofloxacin	Floxin	Tetrabenazine	Nitoman and others
Osimertinib	Tagrisso	Tiapride	Tiapridal and others
Oxytocin	Pitocin and others	Tipiracil and Trifluridine	Lonsurf
Paliperidone	Invega and others	Tizanidine	Zanaflex and others
Palonosetron	Aloxi	Tolterodine	Detrol and others
Panobinostat	Farydak	Toremifene	Fareston
Pasireotide	Signifor	Tramadol	Crispin and others
Pazopanib	Votrient	Trimipramine	Surmontil and others
Perflutren lipid microspheres	Definity and others	Tropisetron	Navoban and others
Perphenazine	Trilafon and others	Valbenazine	Ingrezza
Pilsicainide	Sunrythm	Vardenafil	Levitra
Pimavanserin	Nuplazid	Vemurafenib	Zelboraf
Pipamperone	Dipiperon and others	Venlafaxine	Effexor and others
Primaquine phosphate	None	Vorinostat	Zolinza
Promethazine	Phenergan	Zotepine	Losizopilon and others
Prothipendyl	Dominal and others	Zuclopent(h)ixol	Cisordinol and others
Ribociclib	Kisqali		

[1] Source: CredibleMeds® (https://www.crediblemeds.org).

Conditional **risk of Torsades de Pointes**[1]

Generic name	Brand name	Generic name	Brand name
Amantadine	Symmetrel and others	Ketoconazole	Nizoral and others
Amisulpride	Solian and others	Lansoprazole	Prevacid
Amitriptyline	Elavil and others	Loperamide	Imodium and many other OTC and Rx brands
Amphotericin B	Fungilin and others	Metoclopramide	Reglan and others
Amsacrine (acridinyl anisidide)	Amsidine	Metolazone	Zytanix and others
Atazanavir	Reyataz and others	Metronidazole	Flagyl and many others
Bendroflumethiazide or bendrofluazide	Aprinox and others	Nelfinavir	Viracept
Chloral hydrate	Aquachloral and others	Olanzapine	Zyprexa and others
Cimetidine	Tagamet and others	Omeprazole	Losec and others
Diphenhydramine	Benadryl and others	Pantoprazole	Protonix and others
Doxepin	Sinequan and others	Paroxetine	Paxil and others
Eperisone	Myonal and others	Piperacillin/Tazobactam	Tazosyn and Zosyn
Esomeprazole	Nexium and others	Posaconazole	Noxafil and others
Famotidine	Pepcid and others	Propafenone	Rythmol SR and others
Fluoxetine	Prozac and others	Quetiapine	Seroquel
Fluvoxamine	Faverin and others	Quinine sulfate	Qualaquin
Furosemide (frusemide)	Lasix and others	Ranolazine	Ranexa and others
Galantamine	Reminyl and others	Sertraline	Zoloft and others
Garenoxacin	Geninax	Solifenacin	Vesicare
Hydrochlorothiazide	Apo-Hydro and others	Telaprevir	Incivo and others
Hydroxychloroquine	Plaquenil and others	Torsemide (torasemide)	Demadex and others
Hydroxyzine	Atarax and others	Trazodone	Desyrel and others
Indapamide	Lozol and others	Voriconazole	VFend
Itraconazole	Sporanox and others	Ziprasidone	Geodon and others
Ivabradine	Procoralan and others		

[1] Source: CredibleMeds® (https://www.crediblemeds.org).

Appendix 10 Criteria for evaluating relationship between adverse events and study drug

The relationship between an adverse event (AE)/serious AE (SAE) and derazantinib and/or atezolizumab and/or ramucirumab and/or paclitaxel will be determined by the Investigator on the basis of their clinical judgment and following definitions.

To align with the binary causality assessment required for clinical studies, based on the Investigator's evaluations, the cases will be categorized as:

- Unrelated: when evaluated as not related or unlikely related to derazantinib and/or atezolizumab and/or ramucirumab and/or paclitaxel.

  The AE does not follow a reasonable temporal sequence from study product administration, or can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
- Related: when evaluated as possibly or probably related to derazantinib and/or atezolizumab and/or ramucirumab and/or paclitaxel.

  The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concomitant diseases, concomitant medications).

  The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology, a known reaction to agent, or chemical group.

NOT RELATED

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias). If the drug was re-administered, it did not reappear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It is judged to be clearly and incontrovertibly due only to extraneous causes such as the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

UNLIKELY

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. If the drug was re-administered, it did not re-appear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

POSSIBLE

This category is applicable to an AE that does not meet the criteria for 'not related' or 'unlikely', nor the criteria for 'probable'. An AE would be considered possible if, or when e.g.:

1. It follows a reasonable temporal sequence from administration of the drug (see also additional explanations above) or it follows a known pattern of the response to the suspected drug or drugs of the same substance class.
2. It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

Note: If an event neither follows a plausible temporal relationship nor a known pattern of response but there is no alternative explanation for the event, this will usually be judged a possibly related event.

PROBABLE

This category is applicable to an AE that is considered, with a high degree of certainty, to be related to the test drug. An AE event may be considered probable if it meets the following three criteria:

1. It follows a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is plausible. If the drug was interrupted or stopped the event did improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias.) If the drug was re-administered, it did re-appear.
2. It follows a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

Regardless of the criteria mentioned above, reappearance of an event upon re-challenge must be regarded as strong evidence of probable relationship to test drug.

Appendix 11 Investigator's protocol signature page

BASILEA
INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol / Version	DZB-CS-202 / Version 5.0	Basilea Product No:	Derazantinib
Protocol Title:	A Phase 1b/2 study of derazantinib as monotherapy and combination therapy with paclitaxel, ramucirumab or atezolizumab in patients with HER2-negative gastric adenocarcinoma harboring *FGFR* genetic aberrations (FIDES-03)		
Basilea Pharmaceutica International Ltd			
Protocol date:	21 May 2021	Project Physician:	[redacted]
Name of Principal Investigator:			
Study site:			

I agree to the conditions relating to this study as set out in the above named Protocol and Study Procedures. I fully understand that any changes instituted by the Investigator(s) without previous discussion with the Sponsor's Project Clinician, Clinical Pharmacologist and Biostatistician (only if required) would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well-being of the patients).

I agree to follow International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP), including the EU Clinical Trial Directive 2001/20/EC and specifically, obtain approval from the Independent Ethics Committee / Institutional Review Board prior to study start, allow direct access to source documents and agree to inspection by auditors from Basilea and regulatory authorities, as required by ICH GCP. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the above named protocol; if *any* other use is desired, *written permission* must be obtained from the Sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

To be signed by Principal Investigator (at minimum):

Please print names and dates next to the corresponding signatures

Signature	**Name**	**Date**
	Principal Investigator	