Janssen Research & Development

Statistical Analysis Plan
Amendment 1

A Phase 1b-2 Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Various Regimens of Erdafitinib in Subjects with Metastatic or Locally Advanced Urothelial Cancer

Protocol 4275694BLC2002; Phase 1b-2
AMENDMENT 5

JNJ-42756493 (erdafitinib) and JNJ-63723283 (cetrelimab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

SAP Version	Issue Date	Revision
Original SAP	04JAN2021	NA
Amendment 1	10AUG2022	1. Expanded on the definitions of 'Treated Analysis Set' in Section 2.3.2.2 and 'Safety Analysis Set' in Section 2.3.3. 2. Clarified timing of the primary efficacy analysis and removed reference to IRRC in Section 5.2.1. 3. Added that the treated analysis set will be used (in addition to the response-evaluable analysis set) for the primary efficacy endpoint analysis (in Section 5.2.1 and 5.2.3.1) 4. Added 'Gastrointestinal Toxicity' to list of adverse events of clinical importance in Section 6.1.1.2 5. Additional subgroups added in Section 2.4

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic and Therapeutic Class
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPS	Combined Positive Score
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DoR	Duration of Response
DLT	Dose-Limiting Toxicity
DRC	Data Review Committee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
FGFR	Fibroblast Growth Factor Receptor
ICH	International Conference on Harmonization
IRRC	Independent Radiologic Review Committee
IWRS	Interactive Web Response System
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PDS	Protocol Deviation Specification
PD-L1	Programmed Death Ligand-1
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
PTH	Parathyroid Hormone
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SET	Study Evaluation Team
TEAE	Treatment-Emergent Adverse Event
TTR	Time to Response
ULN	Upper Limit of Normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This study is a Phase 1b-2 study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of various regimens of erdafitinib in subjects with metastatic or locally advanced urothelial cancer. The phase 1b aims to establish the recommended Phase 2 dose (RP2D) and to evaluate the safety for erdafitinib in combination with cetrelimab +/- platinum (cisplatin or carboplatin) chemotherapy. The Phase 2 aims to evaluate the safety and efficacy of the RP2D of erdafitinib + cetrelimab versus erdafitinib.

Erdafitinib is a selective and potent pan-fibroblast growth factor receptor (FGFR) kinase inhibitor with demonstrated clinical activity in subjects with metastatic or surgically unresectable urothelial cancer and other solid tumors with alterations in the FGFR pathway.

Cetrelimab is a fully human immunoglobulin G4 kappa monoclonal antibody that binds to PD-1 with high affinity and specificity, blocks binding to both PD-1 ligands – PD-L1 and PD-L2. It is currently being investigated for the treatment of advanced stage solid tumors.

Cisplatin is a chemotherapeutic agent that crosslinks with DNA to trigger apoptosis by interfering with mitosis and breakdown of DNA damage repair. Carboplatin is an alternate chemotherapeutic agent that inhibits the synthesis of RNA, DNA, and proteins in cells.

This SAP contains the details and methods to be used to perform the proposed safety, efficacy, pharmacokinetic (PK), and other secondary and exploratory endpoints analyses.

This SAP is based on the following study documents:

- Study Protocol, Amendment 5 (6 July 2022)
- Electronic Case Report Form (eCRF) (V9.0, 9 June 2020)

This SAP is in compliance with guidelines provided in the International Conference on Harmonization (ICH) Topic E9 Statistical Principles for Clinical Trials. In the event of future amendments to the protocol, this SAP may be modified as necessary to account for changes relevant to the statistical analysis.

1.1. Trial Objectives

The primary objective of the Phase 1b (dose escalation) portion of the study is to characterize the safety and tolerability of and to identify the recommended Phase 2 dose(s) (RP2D) and schedule for erdafitinib in combination with cetrelimab, and erdafitinib in combination with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy. The primary objective of the Phase 2 (dose expansion) portion of the study is to evaluate the safety and clinical activity of erdafitinib alone and in combination with cetrelimab in cisplatin-ineligible subjects with metastatic or locally advanced urothelial cancer (UC) with select FGFR gene alterations and no prior systemic therapy for metastatic disease. The secondary objectives of both phases of the study are to characterize the PK of erdafitinib and cetrelimab, and to assess the immunogenicity of cetrelimab. Additional secondary objectives of the Phase 2 portion include:

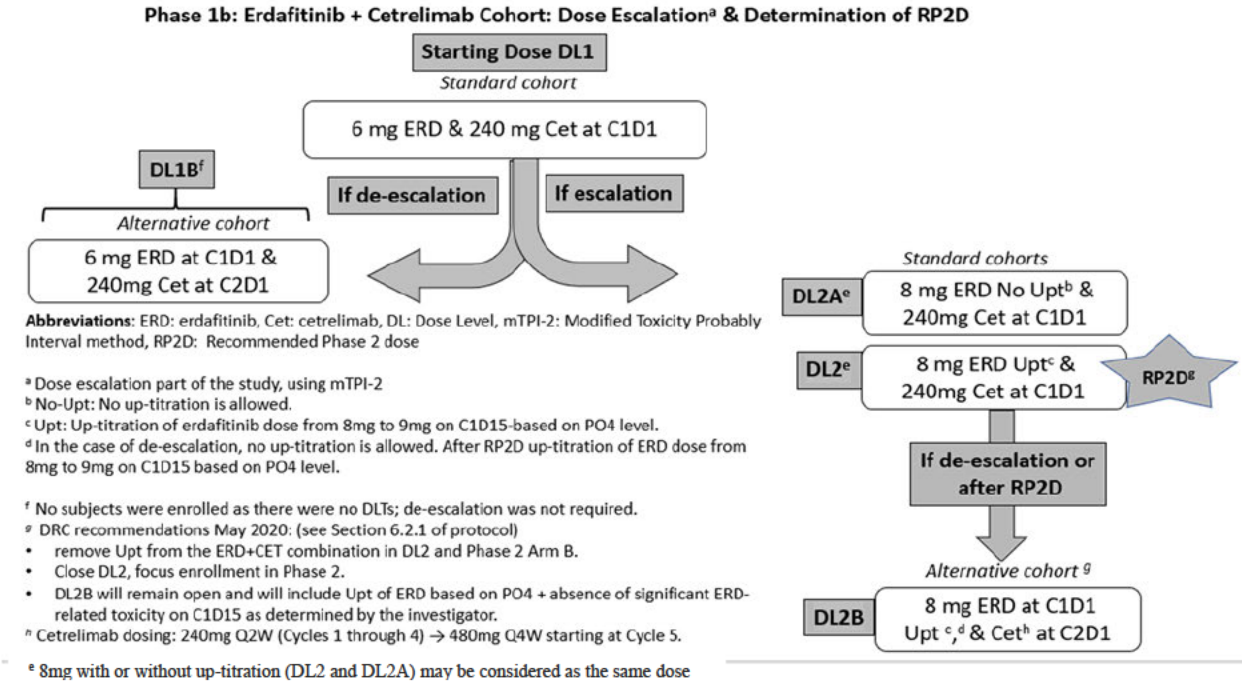
- To further assess safety at the RP2D of erdafitinib alone and in combination with cetrelimab
- To further to characterize the clinical activity of erdafitinib alone and in combination with cetrelimab

1.2. Trial Design

This is a 2-part, multicenter, open-label, Phase 1b-2 study of erdafitinib in combination with cetrelimab +/- platinum (cisplatin or carboplatin) chemotherapy (Phase 1b), followed by dose expansion of erdafitinib in combination with cetrelimab in subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations who are ineligible for cisplatin and have not received prior systemic therapy for metastatic disease (Phase 2). The details of the study design are described in Section 3 of the protocol.

The overview of the study is given in Figure 1, Figure 2 and Figure 3.

Figure 1: Overview of the Phase 1b: Erdafitinib + Cetrelimab Cohort



Abbreviations: ERD: erdafitinib, Cet: cetrelimab, DL: Dose Level, mTPI-2: Modified Toxicity Probably Interval method, RP2D: Recommended Phase 2 dose

[a] Dose escalation part of the study, using mTPI-2
[b] No-Upt: No up-titration is allowed.
[c] Upt: Up-titration of erdafitinib dose from 8mg to 9mg on C1D15-based on PO4 level.
[d] In the case of de-escalation, no up-titration is allowed. After RP2D up-titration of ERD dose from 8mg to 9mg on C1D15 based on PO4 level.

[f] No subjects were enrolled as there were no DLTs; de-escalation was not required.
[g] DRC recommendations May 2020: (see Section 6.2.1 of protocol)
- remove Upt from the ERD+CET combination in DL2 and Phase 2 Arm B.
- Close DL2, focus enrollment in Phase 2.
- DL2B will remain open and will include Upt of ERD based on PO4 + absence of significant ERD-related toxicity on C1D15 as determined by the investigator.

[h] Cetrelimab dosing: 240mg Q2W (Cycles 1 through 4) → 480mg Q4W starting at Cycle 5.

[e] 8mg with or without up-titration (DL2 and DL2A) may be considered as the same dose

Figure 2: Overview of the Phase 1b: Erdafitinib + Cetrelimab + Platinum Chemotherapy Cohort

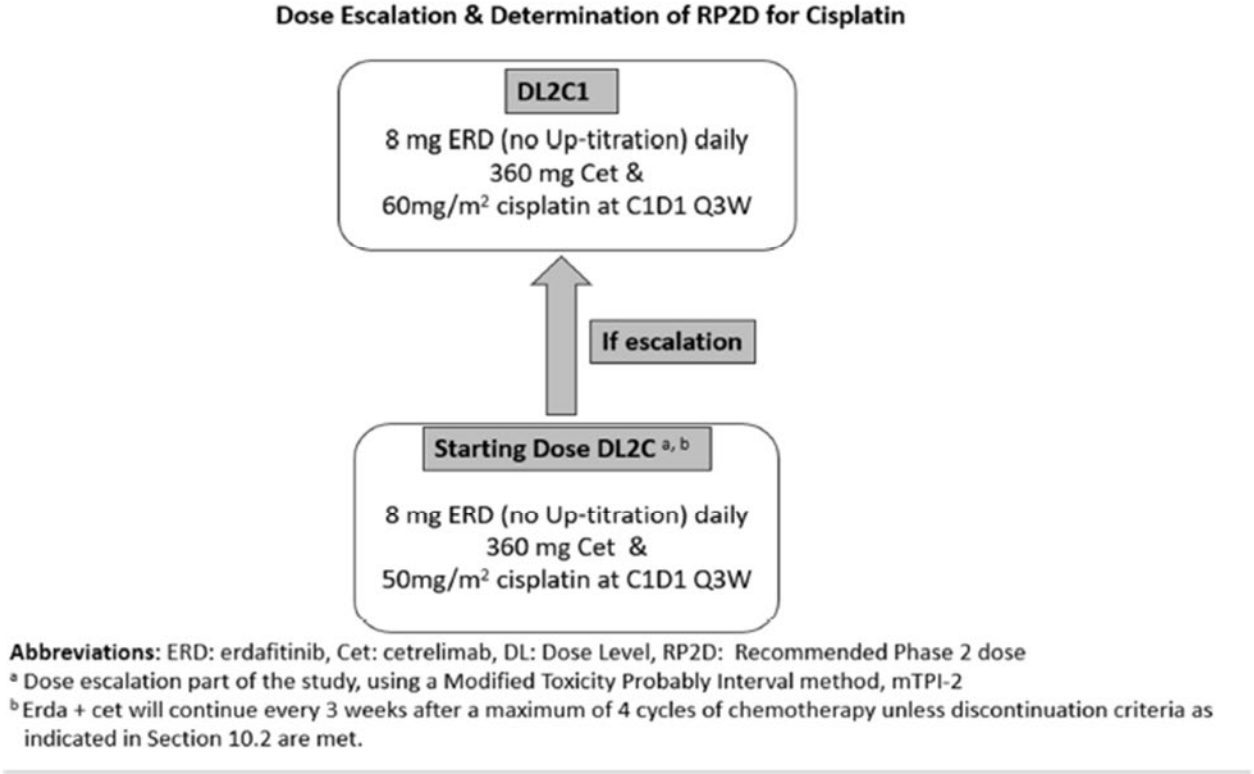
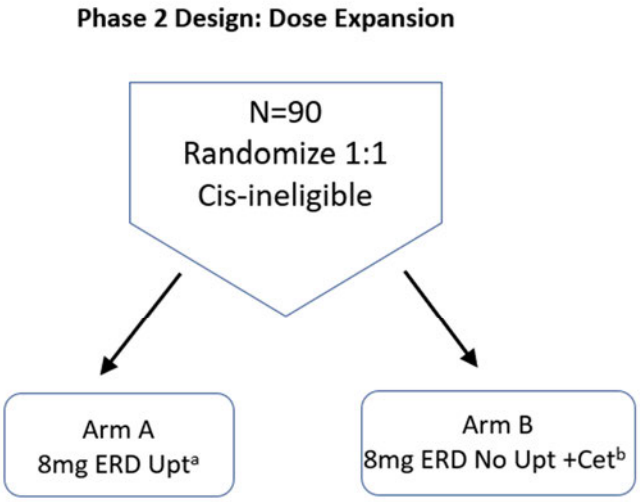


Figure 3: Overview of the Phase 2: Erdafitinib +/- Cetrelimab Cohort



Abbreviations: ERD: Erdafitinib, Cet: cetrelimab, RP2D: Recommended Phase 2 Dose
[a] Upt: Up-titration of erdafitinib dose from 8mg to 9mg on C1D15 based on PO4 level and absence of significant erdafitinib related toxicity on C1D15.
[b] Cetrelimab dosing: 240mg Q2W (Cycles 1 through 4) → 480mg Q4W starting at Cycle 5.

A Modified Toxicity Probability Interval (mTPI-2) method will be used by the Study Evaluation Team (SET) to guide dose escalation and RP2D recommendations in Phase 1b. A minimum of 6 subjects will be treated at a dose level or the next higher dose level before the dose level can be declared as the RP2D. A Data Review Committee (DRC) will be commissioned for Phase 2 of this study.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis in Phase 1b is that RP2D regimens of erdafitinib combined with cetrelimab +/- platinum chemotherapy can be identified for safe treatment of subjects with metastatic or locally advanced urothelial cancer with and without select FGFR gene alterations. No formal statistical hypotheses will be tested for the Phase 1b primary hypothesis.

In Phase 2, it is hypothesized that erdafitinib alone and in combination with cetrelimab are safe and have antitumor activity in cisplatin-ineligible subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations and no prior systemic therapy for metastatic disease.

1.4. Sample Size Justification

1.4.1. Sample Size for Phase 1b

The total number of subjects to be enrolled in Phase 1b will depend on the dose level at which DLT of the combination is met or the RP2D is determined. Once a dose level is open for enrollment, subjects will be entered in groups of 3 unless otherwise clinically indicated. Approximately 70 subjects will be enrolled in the Phase 1b, i.e., approximately 30 subjects will be enrolled in the erdafitinib + cetrelimab cohort and approximately 40 subjects will be enrolled in the erdafitinib + cetrelimab + platinum chemotherapy (cisplatin or carboplatin) cohort.

1.4.2. Sample Size for Phase 2

In Phase 2, approximately 90 subjects will be assigned randomly in a 1:1 ratio to receive either erdafitinib monotherapy treatment (Arm A) or erdafitinib and cetrelimab combination therapy (Arm B).

1) In the erdafitinib monotherapy arm (Arm A), objective response rate (ORR) will be estimated using a 95% confidence interval. Assuming a true ORR of 45%, a sample size of 45 subjects will result in a 95% confidence interval that excludes ORR less than or equal to 30%.

2) In the erdafitinib and cetrelimab combination therapy (Arm B), ORR will be estimated using a 95% confidence interval. Assuming a true ORR of 55%, a sample size of 45 subjects results in a 95% confidence interval that excludes ORR less or equal to 40%.

1.5. Randomization and Blinding

This is an open-label study. No blinding procedures will be applied.

In Phase 2, subjects will be randomly assigned in a 1:1 ratio to either erdafitinib monotherapy (Arm A) or in combination with cetrelimab (Arm B) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be stratified by ECOG PS (0-1 vs. 2). The interactive web response system (IWRS) will assign a unique treatment code, which dictates the treatment assignment for the subject.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Visit windowing will be based on phases:

Full Screening Phase: Begins within 28 days prior to the first dose of study medication.

Treatment Phase: Between the date of first dose of study medication and the date of the end of treatment visit. If the date of the end of treatment is not available, the date of last dose of study medication + 30 days will be used. The assessments performed during the 'End-of-Treatment Visit' will be included in this phase.

Follow-up Phase: After the last dose of study drug until death, withdrawal of consent or the end of the study.

2.2. Pooling Algorithm

The data from all study sites will be pooled together for analyses.

2.3. Analysis Sets

2.3.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all randomized subjects.

2.3.2. Efficacy Analysis Set

2.3.2.1. Response-Evaluable Analysis Set

The Response-Evaluable (RE) Analysis Set will include all subjects who satisfy the following:

- Received at least one dose of study drug
- Had a baseline and at least 1 adequate post-treatment disease evaluation or have had clinical signs and/or symptoms of disease progression or died prior to the first post-treatment disease evaluation in which case they will be considered non-responders. Adequate disease assessment is defined as having sufficient evidence to correctly indicate whether progression has occurred.

2.3.2.2. Treated Analysis Set

The Treated Analysis Set is defined as follows for each part of the study:

- All subjects who have received at least one dose of study drug in Phase 1b.
- All randomized subjects who have received at least one dose of study drug in Phase 2. The study drug assigned at randomization will be used for all efficacy analyses.

2.3.3. Safety Analysis Set

The Safety Analysis Set is defined as follows for each part of the study:

- All subjects who have received at least one dose of study drug in Phase 1b.
- All randomized subjects who have received at least one dose of study drug in Phase 2. The actual study drug received will be used for all safety analyses.

2.3.4. Pharmacokinetics Analysis Set

The Pharmacokinetics (PK) evaluable analysis set is defined as all subjects in the safety analysis set and have at least 1 valid blood sample drawn for PK analysis.

2.4. Definition of Subgroups

Subgroup analysis will be performed as necessary to assess the internal consistency of efficacy and/or safety. The table below lists the subgroups that will be used in the subgroup analyses as needed.

Subgroup	Definition
Region[1]	• North America (NA) • Europe (EU) • Rest-of-the-World (ROW)
Baseline ECOG performance status	• 0-1 • 2
Disease distribution (presence or absence of visceral metastases: lung, liver or bone)	• Presence • Absence
Bone metastasis	• Yes • No

Subgroup	Definition
Primary tumor location	• Lower tract - Bladder - Urethra - Prostate • Upper tract - Renal pelvis - Ureter
PD-L1 status	• Positive (Combined Positive Score (CPS) >=10) • Negative (CPS< 10)
Baseline creatinine clearance	• 30- 60 mL/min • >= 60 mL/min
Baseline hemoglobin level	• <10 g/dL • ≥ 10 g/dL
Maximum serum phosphate within first 3 months	• < 7 mg/dL • >= 7 mg/dL
FGFR alteration type	• Fusion • Mutation • Fusion and mutation
Gender	• Female • Male
Age Group	• < 65 years • >= 65 years • < 75 years >= 75 years
Race	• White • Non-White • Not reported

[1]North America (NA) includes USA and Canada; Europe (EU) includes Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom and any other countries belonging to geographical Europe. ROW includes Australia, China, India, Japan, South Korea, Taiwan, Thailand, Argentina, Brazil, Mexico, and any other countries not included in the NA or EU.

2.5. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration (for safety) or randomization date (for efficacy). All efficacy and safety assessments at all visits will be assigned a day relative to this date. A treated cycle for a specific drug is defined as a cycle in which the subject received any amount of the specific drug. The cycle number will be named according to the sequence of every 21-day cycle for study agent administration.

Assessments will be presented chronologically by study day or cycle day as described below:

- Reference date (Day 1) = randomization date (for efficacy data), or first dose date of study treatment (for safety data) for the Phase 2 portion of the study. In the Phase 1b portion, reference date (Day 1) is the first dose date.

- Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.
- Cycle Day = assessment date - date of the first day of the cycle +1.

2.6. Baseline Definition

Unless specified otherwise, the baseline value is defined as the last non-missing value collected before or on the date of administration of the first dose of study medication unless it is identifiable by time that the value is after the first dose. For subjects who have been randomized but not treated with any dose, randomization date will be used as the reference date for baseline value calculation.

2.7. Imputation Rules for Missing AE Date/Time of Onset/Resolution

In general, imputation of missing dates will be made for AE onset date, AE resolution date, date of death, start and end dates of prior, concomitant, and subsequent therapies, and date of initial diagnosis according to the following rules. Start date will be imputed before end date.

- If date is completely missing, no imputation will be made.
- If year is missing, no imputation will be made.
- If only year is present, but month and day are missing, then June 30th will be used.
- If only day is missing but year and month are available, then the 15th of the month will be used.

The above imputations will be modified by the following conditions and rules:

- For initial diagnosis if such imputed date is on or after the reference date, then reference date - 1 will be used.
- If such imputed date for prior therapies or initial diagnosis is on or after the reference date, then reference date - 1 will be used. If such imputed date for subsequent therapies is before or on date of last dose, then date of last dose +1 will be used.

The imputed start date for subsequent therapies will be adjusted sequentially using the following steps:

  - If the imputed start date is before the last dose date but in the same year and month, then the last dose date will be used.
  - If subsequent therapy end date is not missing and is before the imputed subsequent therapy start date, then the subsequent therapy end date will be used as the start date.

- If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the date the subject was last known to be alive + 1 will be used.
- The imputed AE start date will be adjusted sequentially using the following steps:
  - If the imputed date is in the same year and month as but day before the first dose date, then the first dose date will be used, or if the imputed date is in the same year and month as but day after the last dose date + 30 days, then the last dose date + 30 days will be used.

- If AE end date is not missing and the imputed AE start date is after the AE end date, then the AE end date will be used.
- If the imputed AE start date and is after date of death, then date of death will be used
- If the imputed AE start date is in the same month and year but after the 1st subsequent therapy start date, then 1st subsequent therapy start date will be used.

- If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.
- The AE imputation rule will be used for concomitant medications.

3. DATA REVIEW COMMITTEE

3.1. Data Review Committee

A Data Review Committee (DRC) will be commissioned to monitor data on an ongoing basis to ensure the safety of the subjects enrolled into Phase 2 of the study as well as ongoing data from Phase 1b. After each review, the DRC will make recommendations regarding the continuation of the study. The membership of the DRC will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. The DRC responsibilities, authorities and procedures will be documented in a separate DRC charter.

In addition to the periodic data reviews, an analysis of safety and efficacy (including an efficacy analysis by PD-L1 status) is planned when there are approximately 40 response-evaluable patients enrolled in Phase 2. The DRC will evaluate the results and subsequently make a recommendation on whether to stop the enrollment of PD-L1 positive patients or modify the study design.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Subject demographics and baseline disease characteristics will be summarized using descriptive statistics.

- Demographics and baseline characteristics: age, sex, race, ethnicity, geographic region, height (cm), weight (kg), systolic blood pressure/diastolic pressure (SBP/DBP (mmHg), body surface area (BSA (m^2)).
- Baseline disease characteristics: time from initial diagnosis to first dose, TNM Stage at initial diagnosis, type of histology, TNM classification of urinary bladder cancer at time of study entry, baseline Eastern Cooperative Oncology Group (ECOG) (0-1 versus 2), FGFR alteration type (mutation, fusion), baseline disease distribution (presence or absence of visceral metastases: lung, liver or bone), primary tumor location (lower tract [bladder, urethra or prostate] versus upper tract [renal pelvis, ureter]), hemoglobin level (<10 g/dL versus ≥10 g/dL), PD-L1 status (Positive versus Negative) and renal function (< 60 mL/min/1.73 m^2 versus >= 60 mL/min/1.73 m^2).

- FGFR (Specific alteration type)
  - Fusion: FGFR3:BAIAP2L1, FGFR2:BICC1, FGFR2:CASP7, FGFR3:TACC3v1, FGFR3:TACC3v3)
  - Mutation: FGFR3 S249C, R248C, G370C, Y373C
- Hematology: hemoglobin, platelet count, white blood cell (WBC) count, absolute neutrophil count (ANC).
- Chemistry: alanine aminotransferase (ALT), chloride, albumin, creatinine, creatinine clearance, alkaline phosphatase, magnesium, aspartate aminotransferase (AST), alpha-1-acid glycoprotein, bicarbonate, phosphate, blood glucose, potassium, blood urea nitrogen (BUN), sodium, total bilirubin, total protein, calcium, parathyroid hormone (PTH).

4.2. Disposition Information

The number of subjects in the following disposition categories will be summarized overall, by cohort (in Phase 1b) and by treatment group (in Phase 2).

Study Disposition

- Subjects who passed molecular screening
- Subjects who had full study screening
- Subjects who passed full study screening
- Subjects randomized
- Subjects completing the study
- Subjects who terminated study prematurely and the corresponding reasons

Treatment Disposition

- Subjects receiving study agent
- Subjects who discontinued study agent and the corresponding reasons for discontinuation

4.3. Treatment Compliance

Study agent compliance will be summarized descriptively based on the safety analysis set.

- For erdafitinib, study agent compliance will be calculated as follows:

  Study agent compliance (%) = (actual number of tablets taken/total number of tablets) x100%.

4.4. Extent of Exposure

The number and percentage of subjects who receive study agent (i.e., erdafitinib, erdafitinib/cetrelimab, erdafitinib/cetrelimab/chemotherapy) will be summarized by cohort or treatment group, as applicable. The administration of study agents will be presented, by medication administered within each cohort (Phase 1b) or treatment group (Phase 2) and will be described in terms of the total number of cycles administered, the median of cycles administered, dose intensity, dose modifications, dose interruptions, and relative dose intensity.

For daily dosing, treatment duration for the study will be calculated as date of last dose of study drug − date of first dose of study drug + 1. For non-daily dosing, if subjects died before end date of last cycle (incomplete last cycle), use death date – date of first dose of study drug + 1.

Descriptive statistics for treatment duration (N, mean, SD, median, and range [minimum, maximum], IQ range) will be presented by treatment group using the safety population.

Duration of treatment will be summarized in the following duration categories: [<6 weeks, 6-<12 weeks, 12-<18 weeks, 18-<24 weeks, 24-<30 weeks, 30-<36 weeks, 36-<42 weeks, 42-<48 weeks, and ≥48 weeks] by treatment group.

Total dosing days are defined as the total number of days that study agent (erdafitinib) has been administered to the subject (excluding days of study agent interruption).

Descriptive statistics will be presented for erdafitinib using the following parameters:

- Number of study agent administrations
- Cumulative total dose
- Dose intensity
- Relative dose intensity

The dose intensity of study agent is calculated as (sum of total daily dose during the treatment phase)/treatment duration.

Relative dose intensity is defined as cumulative total dose/planned total dose which is based on initial planned dose (taking into account up-titrations when they occur) displayed as percentages.

For cetrelimab and platinum chemotherapy, descriptive statistics for the following will be presented:

- Number of study agent administrations
- Cumulative total dose
- Mean cycle dose

- Relative dose intensity

The mean cycle dose is calculated as (sum of total dose during the treatment phase)/number of cycles.

For erdafitinib, cetrelimab and platinum chemotherapy the number (%) of subjects with a study agent modification will be summarized by treatment group. Reasons for study agent modifications will also be summarized.

A by-subject listing will present all the study agents that have been taken by the subject, which include cohort, treatment group, study day, cycle day, name of study agent and doses. Any dose modifications and the corresponding reasons will be presented accordingly.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Informed consent not signed
- Entered the study but did not satisfy I/E criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong study treatment or incorrect dose
- Received a disallowed concomitant treatment
- Developed AEs that met the criteria for discontinuing/interrupting study drug but not discontinued/interrupted
- Received erroneous test or procedure
- Visit schedule outside of the Protocol defined visit windows
- Others

A Protocol Deviation Specification (PDS) has been developed to provide more information about the major protocol deviations. Periodic meetings are required to investigate each potential protocol deviation.

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continued after the first dose of study agent.

The number and percentage of subjects taking concomitant medications from the first dose through the end of the treatment period will be tabulated by the Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and World Health Organization (WHO) drug generic term for each treatment group in the safety population. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication. A by-subject listing will also be presented for concomitant medication.

Prior medications will be summarized by treatment group and ATC terms.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Not applicable.

5.1.2. Data Handling Rules

Unless specified otherwise, missing values will not be imputed.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint for Phase 2 is ORR per RECIST version 1.1 as assessed by investigators. ORR is defined as the proportion of subjects who achieve confirmed complete response (CR) or confirmed partial response (PR). The primary efficacy analysis is planned with approximately 6 months of follow-up from last patient enrolled or sooner (if last patient discontinued prior to the 6-month follow-up). This will be the final analysis for the study. The primary efficacy analysis will be based on the response assessed by the investigators. Objective responses of CR or PR will be confirmed for this study per RECIST version 1.1.

Subjects will be considered as non-responders if they do not have CR or PR while on study, or do not have a baseline or post-baseline tumor assessment, or do not have adequate baseline tumor evaluation, or die, have progressive disease, or drop out for any reason or take subsequent therapy prior to reaching a CR or PR. Analysis of the primary efficacy endpoint will be based on the treated analysis set as well as the response-evaluable analysis set.

5.2.2. Estimand

Primary Trial Objective: To evaluate the efficacy of erdafitinib alone and in combination with cetrelimab in terms of objective response rate (ORR) as assessed by investigators in cisplatin-ineligible subjects with locally advanced urothelial cancer, with select FGFR gene alterations, and no prior systemic therapy for metastatic disease in Phase 2.

Study intervention:

- Erdafitinib
- Erdafitinib + cetrelimab

Population: Subjects with metastatic or locally advanced urothelial cancer harboring select FGFR gene alterations who have had no prior systemic therapy for metastatic disease and are ineligible for cisplatin.

Variable: Subject responder status per RECIST as assessed by investigators (responder – confirmed best overall response (BOR) of CR or PR; otherwise, non-responder).

Population-level summary: ORR, proportion of subjects with confirmed objective responses of CR or PR.

Intercurrent Event	Strategy for Addressing Intercurrent Events and Its Description
Treatment discontinuation	Treatment policy approach will be used, i.e., the value for the variable of interest will be used in the analysis regardless of subject's treatment disposition. For instance, if a subject discontinued study treatment but did not start subsequent anticancer therapy, the subject's responder status/tumor assessment will be used as if the subject is still on treatment regardless of the treatment discontinuation.
Subsequent anti-cancer therapy	While-on-treatment policy approach will be used, i.e., only the value for the variable of interest before the subsequent anticancer therapy will be used. For instance, if a subject started subsequent anticancer therapy, no matter if the subject discontinued treatment or not, the subject's responder status/tumor assessment after the subsequent anticancer therapy will not be used in the analysis.

5.2.3. Analysis Methods

The number of subjects who achieve CR or PR and the ORR along with the 95% Clopper-Pearson confidence intervals (CIs) will be reported.

5.2.3.1. Subgroup Analysis of ORR

A subgroup analysis of ORR will be conducted by PD-L1 status (positive vs. negative) as well as for the subgroups indicated in Section 2.4 as deemed necessary. The DRC will evaluate the results of the PD-L1 subgroup analysis and subsequently make a recommendation on whether to stop the

enrollment or modify the study design. For each subgroup, the observed ORR and a corresponding Clopper-Pearson 95% CI will be presented. The treated analysis set as well as the response-evaluable analysis set will be used for the ORR subgroup analysis.

5.3. Secondary Endpoints

The following will serve as additional measures of efficacy in Phase 2 only:

- Time to Response
- Duration of Response
- Progression-free survival
- Overall survival

5.3.1. Definition

- Time to Response (TTR) will be calculated from the date of randomization to the date of initial documentation of a response (CR or PR).
- Duration of Response (DoR) will be calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment date.
- Progression-free survival (PFS) is defined as the duration from the date of randomization until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever occurs first. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment date.
- Overall survival (OS) is measured from the date of randomization to the date of the subject's death. If a subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.

5.3.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the distributions of DoR, PFS and OS along with corresponding 95% confidence intervals for their medians and selected timepoints. TTR will be summarized descriptively.

TTR and DOR analyses will be based on responders only while PFS and OS analyses will be based on the treated analysis set. In addition, the analyses will be performed for the ITT population if needed.

6. SAFETY

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, electrocardiograms, physical examinations, clinical laboratory tests, ECOG performance status, ophthalmologic examinations, Amsler grid test, and other safety evaluations at specified time points as described in the Time and Events Schedule. Safety data will be analyzed using the safety analysis set.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of all AEs will be graded according to NCI-CTCAE Version 5.0.

6.1.1. Adverse Event Classifications

6.1.1.1. Treatment-Emergent Adverse Events

The treatment-emergent period is defined as the time from first dose date through 30 days after last dose date of erdafitinib/cisplatin/carboplatin and 100 days after last dose date of cetrelimab (whichever occurs later), or day before subsequent anti-cancer therapy, whichever occurs first. Treatment-emergent AEs (TEAEs) will meet at least one of the following conditions:

- All AEs that first occur in the TEAE period.
- All AEs present before first dose of the study drug but worsened in toxicity grade during the TEAE period.
- All AEs with missing start date but with end dates during the TEAE period.
- All AEs assessed to be related to the study drug.

Drug-related AEs are those assessed by investigator as being possible, probable or very likely related to study drug. To determine TEAE, partially missing AE start dates will be imputed according to the rules stated in Section 2.7.

Treatment-emergent AEs will be summarized by system organ class and preferred terms, by NCI toxicity grade, by relationship to study drug, and by action taken.

The severity of AEs will be graded on a scale of 1 to 5 according to the adult NCI Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0) where higher grades indicate events of higher severity.

For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by descending order of frequency.

Summary tables will be provided for treatment-emergent adverse events by cohort or treatment group:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent/termination of study participation
- AEs by severity, NCI-CTCAE toxicity grade
- AEs by relationship to study agent
- AEs leading to dose interruption/dose modification

In addition to the summary tables, listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study agent/termination of study participation

6.1.1.2. Adverse Events of Special Interest, Clinical Importance and Immune-Related Adverse Events

Adverse events of special interest include the MedDRA preferred terms for Central Serous Retinopathy (CSR).

Adverse events of clinical importance include all MedDRA preferred terms for the following customized queries:

- Skin Toxicity
- Nail Toxicity
- Eye Toxicity
- Hyperphosphatemia
- Gastrointestinal Toxicity

Adverse events of special interest, clinical importance, and immune-related adverse events will be summarized by preferred term and worst toxicity grade.

6.2. Deaths

Deaths will be displayed by actual treatment received. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent

A listing of subjects who died will be provided.

6.3. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set. If a subject has repeated laboratory values for a given time point, the one with the worst grade will be used.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points.

Shift tables will be provided summarizing the shift in laboratory values from baseline to the End-Of-Treatment visit with respect to abnormality criteria (low, normal, high).

Change from baseline to each scheduled time point will be summarized for chemistry and hematology by cohort or treatment group. Unscheduled laboratory test results will be listed and included in the laboratory shift tables.

Number and percentage of subjects with post-baseline clinically important laboratory values and/or markedly abnormal post-baseline values will be presented by cohort or treatment group.

The clinically important laboratory findings to be reported are described below:

- AST (U/L): ≥2x ULN
- ALT (U/L): ≥2x ULN
- Alkaline phosphatase (U/L): High (≥3xULN)
- Bilirubin (total) ≥2x ULN

Markedly abnormal laboratory findings to be reported are described below:

- AST (U/L) or ALT(U/L): ≥3x ULN
- AST(U/L) or ALT (U/L): ≥5x ULN
- Grade 4 NCI-CTCAE

Applicable laboratory results will be graded according to NCI-CTCAE version 5.0.

A listing for all subjects with clinically important laboratory values will be provided and a summary table of the number of such subjects will be provided by treatment group.

Descriptive statistics and change from baseline analyses of clinical laboratory results will be presented by treatment group.

Shift summaries from baseline laboratory value to the worst on-treatment US NCI-CTCAE, version 5.0 grade in chemistry and hematology tests with US NCI-CTCAE, version 5.0 will be presented.

6.3.1. Creatinine Clearance

Cockcroft-Gault Formula for Estimated Creatinine Clearance for Adults

$$eCR = \frac{(140 - Age(years)) \times Weight\ (kg) \times \{0.85\ if\ female\}}{72 \times Serum\ creatinine\ (mg/dL)}$$

for males, the factor is 1 instead of 0.85 or

$$eCR = \frac{(140 - Age(years)) \times Weight\ (kg) \times Constant}{Serum\ creatinine\ (\mu mol/L)}$$

Where Constant = 1.23 for men and 1.04 for women.

Reference: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation.

6.4. Vital Signs and Physical Examination Findings

Vital sign and physical examination summaries and reporting of screening will be based on the safety analysis set. Continuous vital sign parameters include weight, height, pulse, blood pressure (systolic and diastolic), heart rate, and temperature will be summarized by cohort or treatment group and scheduled visits.

6.5. Electrocardiogram

The ECG parameters that will be summarized over-time are heart rate, RR interval, QT interval, PR interval, QRS interval, QT interval, and QTc using the following correction methods: Fridericia's formula (QTcF). QTcF (Fridericia) will be used for assessment of QTc interval.

Fridericia's formula: QTcF (msec) = QT (msec) * (HR (bpm)/60)$^{1/3}$

Values outside the normal range will be flagged as follows.

Observed:

- Heart rate: L <50 bpm; H > 100 bpm
- RR interval: L < 600 ms; H > 1000 ms
- QT interval: H > 500 ms
- QTc interval: H > (450 ms for males, 470 ms for females); increase to > 500 ms

Change from baseline:

- QTc: 30-60 ms increase; increase > 60 ms

All treatment-emergent abnormal findings will be tabulated, displaying the number of subjects with abnormal findings after dosing. An abnormal finding is considered to be treatment emergent if it occurred during treatment and up to 30 days after the last dose of erdafitinib/cisplatin/carboplatin or up to 100 days after the last dose of cetrelimab, whichever occurs later.

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point based on safety population. No statistical testing will be performed. If more than 1 ECG

measurements are repeated at a visit, they will be averaged. The averaged value will be considered the 'Visit' ECG results.

Maximum QTc intervals and maximum changes from baseline will also be summarized similarly in a separate display.

The interpretation of the ECGs and percentage of subjects meeting the normality criteria will be summarized over time by treatment group and cohort.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Pharmacokinetic data will be listed for all subjects with available plasma erdafitinib or serum cetrelimab concentrations. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., missing information of dosing and sampling times). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

PK analyses will be performed on the Pharmacokinetics Analysis Set, which includes all randomized subjects who received at least 1 dose of erdafitinib and had at least 1 pharmacokinetic sample obtained posttreatment.

Descriptive statistics (N, mean, standard deviation, range, coefficient of variation (%CV), geometric mean, geometric coefficient of variation, and IQ range) will be used to summarize plasma/serum concentrations at each nominal sampling time point. Graphical exploration of data may be performed as deemed useful.

Plasma erdafitinib or serum cetrelimab concentrations below the Lower Limit of Quantification (LLOQ) will be imputed as zero in the summary statistics.

Plasma erdafitinib or serum cetrelimab concentrations below the lowest quantifiable limits will be imputed as ½ LLOQ for log-transformed data calculations.

All subjects and samples excluded from the analysis will be clearly documented and presented in a listing.

8. BIOMARKERS

Details of biomarker analysis will be presented in a separate plan and results will be presented in a separate report if needed.