Janssen Research & Development *

Clinical Protocol

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 42756493BLC2002; Phase 1b-2
AMENDMENT 5

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

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2017-001980-19

Status: Approved
Date: 11 July 2022
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-148605285, 8.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	08 Dec 2017
Amendment 1	22 Jan 2018
Amendment 2	30 May 2019
Amendment 3	26 Jun 2020
Amendment 4	08 Apr 2021
Amendment 5	06 July 2022

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (06 July 2022)

Overall Rationale for the Amendment: The overall reason for the amendment is to transfer all remaining subjects on study treatment to a new visit schedule with reduced data collection (Appendix 4) once the end of study data collection timepoint has been achieved. In addition, specifications for the primary efficacy analysis have been updated to align with the statistical analysis plan, and the priorities of the erdafitinib clinical development program.

Section Number and Name	Description of Change	Brief Rationale
Synopsis Time and Events Schedule 3.1.3 Schedule of Activities for All Ongoing Subjects After the End of Study Data Collection Timepoint (Protocol Amendment 5), Appendix 4 Table 1 12.3.1 All Adverse Events	A schedule of activities for all ongoing subjects after the end of study data collection timepoint has been added for subjects in Phase 1b and Phase 2.	To reduce the burden of study procedures not deemed necessary on remaining subjects after the end of study data collection.
6.2.3.6. Guidelines for Eye Toxicity Associated with Vision Changes 6.3.3. Cetrelimab Associated Toxicity Leading to Discontinuation of Study Treatment 8.CONCOMITANT THERAPY 9. STUDY EVALUATIONS 9.1.3. Treatment Phase 9.1.4. Follow-up Phase 9.2 Efficacy Evaluations 9.3 Pharmacokinetics and Immunogenicity 9.6 Safety Evaluations 10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/WITHDRAWAL FROM STUDY 12.3.1. Adverse Events 17.9.1 Study Completion/End of Study	Following approval of Amendment 5, the eCRF and clinical database will be closed. All SAE reporting and concomitant therapies associated with an SAE will occur through the Company Safety Repository. No Pk samples will be collected. An ad-hoc sample for immunogenicity may be collected if required.	To reduce the burden of study procedures not deemed necessary on remaining subjects after the end of study data collection.
Synopsis, 11.4 Efficacy Analyses (Phase 2 Only)	The primary efficacy analysis will occur within ~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.	Alignment with the Statistical Analysis Plan, which allows for longer follow-up for a more robust

Section Number and Name	Description of Change	Brief Rationale
	The IRRC review has been removed.	assessment of efficacy.
6.3.1 Retreatment Criteria for Cetrelimab 6.3.2. Dose Delay for Cetrelimab 6.3.3. Cetrelimab Associated Toxicities Leading to Discontinuation of Study Treatment	Added Grade ≤2 Hypothyroidism in the retreatment criteria of Table 15. Clarified Grade and definition of endocrinopathies leading to delay or discontinuation of cetrelimab.	To remove discrepancy of the definition between retreatment, delay and discontinuation of cetrelimab with respect to endocrinopathies.
6.3.4.2 Hepatic Adverse Events	The following text has been added: Subjects who have a predominant cholestatic pattern of liver injury (dominant increase in ALP relative to ALT /AST) should be further evaluated to exclude a diagnosis of treatment emergent sclerosing cholangitis. An evaluation may include ultrasound of liver, cholangiography and referral to gastroenterologist and/or a hepatologist.	Belgian health authority requirement for sclerosing cholangitis.
9.6.2. Clinical Laboratory Tests	Updated the footnote about fasting glucose results to: If fasting glucose results are available and meet the retreatment criteria, the HbA1c result does not need to be reviewed prior to dosing but should still be collected.	To clarify the meaning of the footnote.
Appendix 1 Table 1, Appendix 2 Table 1, Appendix 3 Table 1	The following changes are in reference to patients ongoing tumor assessment until Amendment 5 is approved: Disease evaluations have been changed so that after week 48 (± 3 days), then every 12 to 24 weeks (± 14 days) until disease progression. Labs prior to the D15 cetrelimab dose can be obtained up to 2 days prior.	To reduce the amount of study procedures for subjects who are on study for longer than 1 year.
10.1 Completion 12.3.1. All Adverse Events 17.9.1. Study Completion/End of Study	Definition of subject completion and end of study has been updated.	To reduce the burden of study procedures and data collection once the primary efficacy analysis data cutoff is achieved.
Throughout protocol	Minor corrections for clarification.	Clarifications

Amendment 4 (08 April 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to allow local prospective FGFR testing in addition to local historical testing (archived sample) to facilitate more rapid determination of molecular eligibility. Furthermore, the requirement for paired biopsies was removed. An adjustment to eligibility criteria relating to creatinine clearance (CrCl) was made to align Phase 1b and Phase 2 of the study for cisplatin-ineligibility and eligibility. In addition, other corrections and clarifications were made as detailed in the table below.

Section Number and Name	Description of Change	Brief Rationale
9.1.2. Screening Phase, Appendix 1 Table 1, Appendix 2 Table 1, Appendix 3 Table 1	Removal of reference to historical testing: Local ~~historical~~ test results	Clarification that local prospective FGFR testing as well as local historical testing is permitted and that biopsy samples may be archival or fresh tissue samples
	Subjects enrolling based on local ~~historical~~ testing must submit archival **or fresh** tumor tissue	
	Update relating to paired biopsies (for tables, text in Footnote "g"): **Paired biopsies at Screening and C2D1 are optional. The biopsy upon PD is also optional for all subjects.** ~~For subjects enrolling in the Phase 1b DL2B and Phase 2 Arm A cohorts, paired biopsies will be required (where local regulations permit and if the tumor is accessible) at Screening and C2D1 prior to erdafitinib administration (biopsy cohort).~~ High-risk areas of metastases such as brain, pancreas, and lung should not be considered as an accessible site for biopsy. Biopsies will be collected to aim to have a minimum of 15 evaluable biopsy pairs ~~(total from Phase 1b DL2B and Phase 2 Arm A cohorts)~~. ~~Exceptions may apply upon discussion between the investigator and medical monitor.~~	Removal of requirement of paired biopsies and clarification that, for cohorts other than Phase 1b DL2B cohort (which is now fully enrolled), paired biopsies are optional.
Synopsis (Subject population), 3.1. Overview of Study Design, 11.1.1. Sample Size - Phase 1b, Appendix 2 Section 3.1.1	Three ~~wild type~~ subjects **(either wild-type or with select FGFR gene alterations)** will be enrolled in the initial erdafitinib + cetrelimab + cisplatin dose level (50 mg/m^2). If the starting dose is safe, ~~3~~ **6** additional ~~wild type~~ subjects ~~and 3 additional subjects with select FGFR gene alterations~~ will be enrolled into the escalated dose of cisplatin (60 mg/m^2). **Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations**. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the maximum tolerated dose (MTD) for erdafitinib + cetrelimab + cisplatin. Three ~~wild type~~ subjects **(either wild-type or with select FGFR gene alterations)** will be enrolled in the initial erdafitinib + cetrelimab + carboplatin dose level (AUC4 mg/mL/min). If the starting dose is safe, ~~3~~ **6** additional ~~wild type~~ subjects ~~and 3 additional subjects with select FGFR gene alterations~~ will be enrolled into the escalated dose of carboplatin (AUC5 mg/mL/min). **Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations.** Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib + cetrelimab + carboplatin.	Clarification on FGFR status of subjects enrolled into the chemotherapy cohorts.
Appendix 1, Section 4.1, Appendix 2 Section 4.1,	Exception for Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: ~~approximately 6~~ **up to 3** subjects in each erdafitinib + cetrelimab + chemotherapy cohort **at each dose level** will be wild-type.	

Section Number and Name	Description of Change	Brief Rationale
Appendix 3 Section 4.1		
3.1.1. Phase 1b	Update to footnote e of Figure 1 from 9mg to 8mg	Correction of dose
Appendix 1 Section 4.1, Appendix 2 Sections 4.1 and 6.6.4, Appendix 3 Section 4.1	Creatine clearance (CrCl) at screening for subjects receiving platinum therapy amended: ~~to ≥30 instead of >50 mL/min~~: **≥30** ~~>50~~ mL/min **to receive carboplatin and ≥60 mL/min to receive cisplatin**	Aligned CrCl requirement for subjects receiving chemotherapy in Phase 1b with those of Phase 2
Appendix 2 Section 6.6.4	Rewording of text for clarity: In general, study drug**(s)** should be held for AEs ≥Grade 3 that are **not** attributable to erdafitinib, cetrelimab, platinum chemotherapy, or the disease under study. If the event resolves to Grade 1 or baseline within 4 weeks, **platinum chemotherapy and** erdafitinib may be reintroduced at one dose level lower. If the same toxicity does not recur or worsen within 4 weeks after re-starting ~~erdafitinib~~ **therapy**, then cetrelimab may be reintroduced at the same dose. Following re-introduction of ~~both~~ study drugs, if the same AE recurs at ≥Grade 3 or there is a second incidence of a ≥Grade 3 event that is not attributable to erdafitinib, cetrelimab, **platinum chemotherapy,** or the disease under study, ~~both~~ study drugs should be **permanently** discontinued.	Rewording of text for clarity.
1.5.2. Summary of Clinical Data	The outcome of the Data Review Committee (DRC) review of the first 20 subjects randomized to Phase 2 is provided at the end of Section 1.5.2. The DRC noted that identification and early treatment of immune-related adverse events (irAEs) are essential to limiting the duration and severity of these events. The section specifies the specific risk mitigation measures included in the protocol to manage the risk of irAEs.	Explanation regarding specific risk mitigation measures included in protocol.
1.7. Overall Rationale for the Study	In Section 1.7, under "Rationale for treatment in 1L mUC (Phase 2)", data from Study 42756493BLC2001 were provided that showed the efficacy of erdafitinib monotherapy in the subset of subjects with metastatic urothelial carcinoma (mUC) and select FGFR alterations and CCI [redacted]. Based on these data, it is anticipated that CCI [redacted] with select FGFR alterations CCI [redacted] The combination of erdafitinib + cetrelimab (Arm B) is designed to estimate CCI [redacted] Several observations are provided in this section, which point to the CCI [redacted] In addition, the use of randomization and its effect on reducing bias in the Phase 2 portion of the study is discussed. The withdrawal of durvalumab, another anti-PD1, is mentioned. The section concludes with stating that the effect of monotherapy check-point inhibitors in frontline urothelial carcinoma is limited to a smaller subset of patients, and additional treatment options are needed.	Justification for addition of Phase 2.

Section Number and Name	Description of Change	Brief Rationale
Tables 8, 9, 10, 13, and 14	In Table 8 (Guidelines for Management of Serum Phosphate Elevation), Grade 3 begin at 9.00 mg/dL (not >9.00 mg/dL). In Table 9 (Guidelines for the Management of Dry Mouth [Xerostomia]), Grade 3 management begins with "Hold study drug (for up to 28 days)" (removed the end phrase "discontinue if longer"). Added "orally" to medical management. In Table 10 (General Prophylaxis and Guidelines for the Management of Oral Mucositis), Grade 2 fifth bullet states ". . . then restart at 1 dose level below" ("below" was added). For symptom management, the last bullet now reads, ". . . and recommend appropriate anti-fungal or anti-viral agents" ("recommend" added). Abbreviations added to footnotes. In Table 13 (Guidelines for Management of Paronychia), in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, removed Grade 4. Also removed the definitions and column subheader now "Grade". In Table 14 (Guidelines for Management of Eye Toxicity), Grade 2, fourth management paragraph now reads, "If toxicity is [removed "Grade 2 and" here] reversible . . .". For Grade 3, first management sentence states, " . . . report an SAE and withhold erdafitinib." (Previously, stated "permanently discontinue erdafitinib".)	Updated guidance for specific toxicities associated with erdafitinib
6.3.1. Retreatment Criteria for Cetrelimab	Addition of footnote to Table 15: **If fasting glucose results are available and meet the retreatment criteria, the HbA1c result does not need to be reviewed prior to dosing, but should still be collected.**	Clarification for fasting glucose requirements
9.1.2. Screening Phase	The following text added: **If a biopsy is required to perform FGFR analysis, the ~~patient~~ subject must consent to this procedure utilizing the main study consent form.**	To provide clarification on consent for biopsy
9.1.2. Screening Phase	The following text was updated: Local~~ historical~~ test results (from tissue or blood) **or the Qiagen Therascreen FGFR RGQ RT-PCR test (from tissue)** performed at a CLIA-certified or regional equivalent laboratory ~~using the following methods~~ may be used to meet molecular eligibility.~~: local, direct digital counting methods, or the Qiagen Therascreen FGFR RGQ RT-PCR test.~~ **A ~~de-identified~~ copy of the test report documenting the FGFR result must be included in the ~~participant~~ subject records and a de-identified copy must also be submitted to the sponsor for confirmation of eligibility.**	To provide clarification on recording of local FGFR test results
9.1.2. Screening Phase	The following text added: **Concordance between local and central testing, where applicable, will be reviewed periodically by the sponsor.**	Added clarification that concordance between local and central testing will be reviewed.
9.2. Efficacy Evaluations	Rewording as follows: The site will send ~~all~~ radiographic scans for **all ~~patients~~ subjects randomized to Phase 2** to a central vendor for possible future independent assessment to confirm the response, if needed.	Clarified this text refers to subjects randomized to Phase 2.
9.3. Pharmaco-kinetics and Immuno-genicity	The following text added: **Post-dose blood samples should be drawn after both the drug infusion and the post-infusion flush have been completed.**	To ensure correct timing of post-infusion PK blood sample
9.5. Predictive and Exploratory Biomarkers	The following sentence was amended: Adjustments in the timing of biomarker collections may be made **or collections may be stopped** during the study based on emerging data.	To clarify that biomarker collection may be stopped once

Section Number and Name	Description of Change	Brief Rationale
		sufficient biopsies have been obtained.
9.6.2. Clinical Laboratory Tests	Alkaline phosphatase, fasting glucose, and HbA1c testing (additional explanation and detail was added for the glucose and HbA1c tests) were added to the Serum Chemistry Panel. "Total" was removed from amylase.	Addition of alkaline phosphatase, fasting glucose and HbA1c testing (at screening and as clinically indicated)
12.3.1. All Adverse Events	Update of language regarding AE collection: All AEs and special reporting situations, whether serious or non-serious, will be reported **starting** from the time a signed and dated Full-Study ICF is obtained until ~~100~~**30** days after the last dose of ~~study drug~~ **erdafitinib, and 100 days after the last dose of cetrelimab (whichever is longer)**. If the subject starts a subsequent systemic anticancer therapy, AE data collection will be limited to only Grade ≥2 immune-related AEs **(for ~~patients~~ subjects who received cetrelimab)** and **all** SAEs from the date the new anticancer therapy is initiated until **30 days after the last dose of erdafitinib or** 100 days after the last dose of cetrelimab**, whichever is longer (see table below)**. The chart in this section was updated accordingly.	Clarification around timing of AE collection.
Appendix 1 Table 1, Appendix 2 Table 1, Appendix 3 Table 1	Addition of the following for PO4, PTH, TSH, T3 and FT4: **May be obtained up to 2 days prior to Day 1 of each cycle: for exact assessments, see Section 9.6.2.**	Aligning with wording for chemistry parameters
Appendix 1, Section 4.1, Appendix 2 Section 4.1, Appendix 3 Section 4.1	Thyroid panel: **TSH,** T3 or Free T3 (FT3) and Free thyroxine (FT4)	TSH previously omitted from heading in error
Appendix 1 Table 2, Appendix 3 Table 2	Update to footnote: Pre-dose PK sample for erdafitinib and Pre-infusion PK and immunogenicity samples for cetrelimab may be collected up to ~~1 hour~~**30 minutes** before dosing, respectively.	To ensure consistency with Section 9.3.
Appendix 1 Table 2	Addition of footnote: **Cetrelimab PK is not required for alternative cohorts (alternative cohorts start cetrelimab on C2D1, e.g. DL2B).**	To provide clarification that cetrelimab PK is not required for alternative cohorts
Appendix 2 Table 2	Addition of Cetrelimab PK and Cetrelimab Immunogenicity assessments at End-of-Treatment and Follow-up timepoints	Corrections made to PK, immunogenicity and biomarker sample timings
Appendix 2 Table 2	Optional Tumor Biopsy for Biomarker Research assessments included in table for Full-study screening period, Treatment Cycle 2 Day 1, and End-of Treatment timepoint.	
Appendix 3, Table 2	Addition of Cetrelimab PK assessment at Treatment Cycle 1, Day 15	
Appendix 1 Table 1, Appendix 2 Table 1	CrCl ~~is to be performed only at Screening and~~ is calculated by the Cockcroft-Gault formula	Clarifications regarding timings of assessments
Appendix 2 Table 2	Clarifications for Cetrelimab PK for Treatment Cycle 1, Days 8 and 15 timepoints:	

Section Number and Name	Description of Change	Brief Rationale
	X **Any time during visit**	
Appendix 3, Table 1	Clarification that vital signs monitored pre-dose only for Arm A	
Appendix 2 Table 1	Addition of footnote: **Post-dose ECGs for subjects receiving platinum chemotherapy should be recorded as soon as possible upon completion of infusion on C2D1 and C4D1**	
11.1.2. Sample Size - Phase 2, 11.4. Efficacy Analyses (Phase 2 Only)	Added the following clarification: **approximately** 45 subjects results in a 95%	Text reworded for clarity
Synopsis (Statistical Methods), 11.4. Efficacy Analyses (Phase 2 Only)	Added the following clarification: **approximately** 90 **response-evaluable** subjects	
6.2.3.3. Guidelines for the Management of Dry Mouth and Stomatitis Table 9	Rewording as follows: ~~Saline peroxide~~ **salt**	
9.14. Follow-Up Phase	Rewording as follows: All subjects who enter the Follow-up Phase will have a follow-up visit every 12 weeks (± 7 days) after the last dose of study treatment to assess survival status and **assess** ~~start of~~ alternate anticancer therapy **data** until death, the subject withdraws consent, or the end of study, whichever occurs first as outlined in the cohort-specific Time and Events Schedule.	
Appendix 1 Section 6.1	Rewording as follows: ~~Both study drugs should be held for~~ **If a** ~~AEs~~ ≥Grade 3 AE **is** ~~that are~~ not attributable to **study treatment** (erdafitinib or cetrelimab~~, or chemotherapy~~**), or** the disease under study ~~(eg. immune-related, hyperphosphatemia, nail toxicity, stomatitis, CSR~~**), then all** ~~**both**~~ **study drugs should be held.**	
Appendix 2, Section 6.4.3	Addition of text: Routine primary prophylaxis **to treat immunosuppression** is not permitted for subjects	
Appendix 1, Section 4.1, Appendix 2 Section 4.1 and Appendix 3 Section 4.1	Rewording as follows: ~~Within normal institutional limits~~ **Below institutional ULN** within 14 days of treatment and prior to C1D1 (medical management allowed)	
Appendix 2, Table 1	**Treatment Cycle 3** [g] **Day 1 (±2)** | ~~**Day 8 (±2)**~~ | ~~**Day 15 (±2)**~~	Removal of columns as no study assessments performed at these timepoints
Appendix 1 Table 2,	Visit windows added to table header.	To add clarification on visit windows and to

Section Number and Name	Description of Change	Brief Rationale
Appendix 2 Table 2, Appendix 3 Table 2		align with Table 1 in each appendix.
Appendix 2, Section 3.1.1	Correction of cohorts: Erdafitinib + cetrelimab + cisplatin (DL2C~~,~~ **or** DL2C1~~, or DL2C2~~)	Typographical errors corrected
Amendment 3 summary of changes	2.1. Objectives and Endpoints for ~~Phase1b~~ **Phase 2** Note that in the Summary of Changes for Amendment 3, this was incorrectly noted in the subtitle for Section 2.1 Appendix 3 as Phase 1b rather than Phase 2. However, the subtitle in the body of the protocol is correct.	
Amendment 3 summary of changes	there are ~~110~~ **approximately 90** response-evaluable subjects. Note that in the Summary of Changes for Amendment 3, this was incorrectly noted as 110 rather than 90. However, the number in the body of the protocol is correct.	
Throughout protocol	Minor corrections to spelling and cross references, addition of new references to reference list, and removal of reference numbering.	

Amendment 3 26 Jun 2020

Overall Rationale for the Amendment: The overall reason for the amendment is to add a new cohort (erdafitinib + cetrelimab + platinum [cisplatin or carboplatin] chemotherapy) to the Phase 1b (Dose escalation) part of the study. As a result of adding this new cohort, the study title was revised and the layout of the protocol was reorganized to clarify inclusion/exclusion criteria, the Time and Events Schedule, toxicity management, and administrative changes for each cohort in respective appendices.

Section Number and Name	Description of Change	Brief Rationale
Protocol Title page; Synopsis (Title)	The title of the protocol was updated to "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".	To accommodate for the expanded scope of treatment cohorts within this Phase 1b/2 study.
Synopsis (Hypotheses); 2.2. Hypothesis for Phase 1b Erdafitinib + Cetrelimab + Platinum Chemotherapy (Appendix 2)	The hypothesis was amended to include the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.	To describe the study hypothesis for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.
2.1. Objectives and Endpoints for Phase1b (Appendix 2)	The primary objective of the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort was added to the study: "To characterize the safety and tolerability of erdafitinib in combination with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy, and to identify the recommended Phase 2 dose(s) (RP2D) and schedule for erdafitinib with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy".	To describe the primary objectives and endpoints for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.

Section Number and Name	Description of Change	Brief Rationale
	The primary endpoint for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort was added to the study: "Frequency and type of dose-limiting toxicity (DLT)".	
2.1. Objectives and Endpoints for Phase1b (Appendix 2)	The secondary objectives for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort of the study were added: • "To characterize the PK of erdafitinib in combination with cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy" • "To assess the immunogenicity of cetrelimab". The secondary endpoints for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort of the study were added : • "Concentration and PK parameters of erdafitinib, cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy" • "Detection of antibodies to cetrelimab and effects on serum cetrelimab levels".	To describe the secondary objectives and endpoints for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.
2.1. Objectives and Endpoints for Phase 1b (Appendix 2)	Exploratory objectives for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort were added to the study: • "To assess the CCI [redacted]" • "To evaluate changes in CCI [redacted]" • "To assess changes in CCI [redacted]" • "To explore biomarkers (DNA, RNA, and/or protein) in tissue and blood samples that could correlate with response or resistance to erdafitinib CCI [redacted]" • "To explore the relationships between PK, PD, AE profiles, and CCI [redacted]".	To describe the exploratory objectives for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.

Section Number and Name	Description of Change	Brief Rationale
2.1. Objectives and Endpoints for Phase1b (Appendix 1)	The primary objective of the Phase 1b erdafitinib + cetrelimab cohort was amended as follows: • ~~"To identify the RP2D and schedule of erdafitinib in combination with cetrelimab"~~ • **"To characterize the safety and tolerability of erdafitinib in combination with cetrelimab, and to identify the recommended Phase 2 dose(s) (RP2D) and schedule for erdafitinib".** The primary endpoints for the Phase 1b erdafitinib + cetrelimab cohort were amended as follows: • ~~"Incidence of DLT"~~ • ~~"Incidence of AEs"~~ • "**Frequency and type of dose-limiting toxicity (DLT)**".	To describe the change in the primary objectives and endpoints for the Phase 1b erdafitinib + cetrelimab cohort.
2.1. Objectives and Endpoints for Phase1b (Appendix 1)	The secondary endpoints for the Phase 1b erdafitinib + cetrelimab cohort were amended as follows: • ~~"Plasma erdafitinib and serum cetrelimab concentrations"~~ • ~~"Population PK parameters and metrics of systemic exposure of erdafitinib and cetrelimab"~~ • **"Concentration and PK parameters of erdafitinib and cetrelimab"** • "Detection of antibodies to cetrelimab and effects on serum cetrelimab levels".	To describe the change in the secondary endpoints for the Phase 1b erdafitinib + cetrelimab cohort.
2.1. Objectives and Endpoints for Phase1b (Appendix 3)	The primary objective of the Phase 2 erdafitinib +/- cetrelimab cohort was amended as follows: • "To evaluate the safety and clinical activity of erdafitinib alone and in combination with cetrelimab in ~~in first line mUC setting~~ **cisplatin-ineligible subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations and no prior systemic therapy for metastatic disease**".	To describe the change in the primary objectives for the Phase 2 erdafitinib + /-cetrelimab cohort.
2.1. Objectives and Endpoints for Phase1b (Appendix 3)	The following secondary endpoint for the Phase 2 erdafitinib +/- cetrelimab cohort was deleted: • ~~"Population PK parameters and metrics of systemic exposure of erdafitinib and cetrelimab".~~	To describe the change in the secondary endpoints for the Phase 2 erdafitinib +/- cetrelimab cohort.
Synopsis (Title)	A description of the mechanism of action for cisplatin and carboplatin that will be utilized in the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort was added below the study title.	To support the rationale for the addition of the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort into this study.
1. Introduction	Text added to describe the rationale for adding the platinum chemotherapy cohort to the study.	

Section Number and Name	Description of Change	Brief Rationale
1.6. Platinum Chemotherapy in Metastatic Urothelial Cancer	New section added to present safety, efficacy, PK and PD data regarding the use of cisplatin and carboplatin as standard of care agents in metastatic urothelial carcinoma.	
1.7. Overall Rationale for the Study	New subsection entitled "Rationale for addition of platinum [cisplatin or carboplatin] chemotherapy to erdafitinib and cetrelimab)" was added.	
1.8.2. Anticipated Benefits and Risks for Platinum Chemotherapy	New section added to describe the anticipated benefits and risks for platinum chemotherapy.	
3.2. Study Design and Starting Dose Rationale	New subsection entitled "Rationale for Combination of Erdafitinib, Cetrelimab, and Platinum Chemotherapy" was added. Rationale for the Subject Population was also updated.	
Synopsis (Overview of Study Design); 3.1. Overview of Study Design; 3.1.1. Phase 1b	The overview of the study design was updated and Figure 2 was created to describe the platinum chemotherapy cohort.	To provide an overview of dose escalation strategy for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.
Synopsis (Subject Population)	The description of the sample size was updated to: "**A total of approximately 160 subjects will be enrolled in this study. Thirty subjects are planned to be enrolled in the Phase 1b erdafitinib + cetrelimab cohort. Forty subjects are planned to be enrolled in the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort. Ninety subjects are planned to be enrolled in the Phase 2 erdafitinib +/1 cetrelimab cohort**". In addition, the subject population was defined as metastatic or locally advanced urothelial cancer.	To update the sample size and analysis of the Phase 1b and the Phase 2 cohort based upon the changes to the study objectives and endpoints as well as the addition of the Phase 1b erdafitinib+ cetrelimab + platinum chemotherapy cohort.
Synopsis (Statistical Methods)	The following updates were made to the Phase 2 statistical methods: "In Phase 2, approximately ~~120~~ **90** subjects will be assigned randomly in a 1:1 ratio to receive either erdafitinib monotherapy (Arm A) or erdafitinib and cetrelimab combination therapy (Arm B). With approximately ~~60~~ **45** subjects **on Arm A and assuming a true ORR of 45%**, ~~per arm,~~ the study is designed **such that the resulting 95% confidence interval for estimating ORR excludes those less or equal to** 30%**. Similarly, assuming a true ORR of 55% in Arm B, 45 subjects results in a 95% confidence interval that excludes ORR less or equal to 40%.** ~~to test the hypothesis null hypothesis (H_0) of: ORR ≤30% vs. the alternative hypothesis (H_a) of: ORR ≥45% in Arm A and H_0: ORR ≤30% vs. H_a: ORR ≥55% in Arm B. With 55 response-evaluable subjects per arm, this design has 80% and 97% power at a Type I error rate of 0.1 and 0.05 (1-sided) for Arm A and B, respectively. A futility analysis will be conducted by the DRC after approximately 40~~	

Section Number and Name	Description of Change	Brief Rationale
	~~response-evaluable subjects (refer to Statistical Analysis Plan for definition) have been obtained in Phase 2. enrolled and evaluated.~~ The objective response rate will be calculated with a ~~90~~ **95**% confidence interval by each arm in the treated population according to the RECIST 1.1 criteria **(Attachment 9)**".	
11.1.2. Sample Size - Phase 2	The following updates were made to the Phase 2 statistical methods: "In Phase 2, approximately ~~120~~ **90** subjects will be assigned randomly in a 1:1 ratio to receive either erdafitinib monotherapy (Arm A) or erdafitinib and cetrelimab combination therapy (Arm B). 1) In the erdafitinib monotherapy arm (Arm A), **ORR will be estimated using a 95% confidence interval. Assuming a true ORR of 45%, a sample size of 45 response evaluable subjects will result in a 95% confidence interval that excludes those less than or equal to 30%.** ~~the following hypothesis will be tested: H_0: ORR ≤30% vs. H_a: ORR ≥45%. With 55 response-evaluable subjects, this design has 80% power at a Type I error rate of 0.1 (1-sided) when the true ORR is 45% in the monotherapy arm~~. 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 response evaluable subjects result in a 95% confidence interval that excludes ORR less or equal to 40%."** ~~the following hypothesis will be tested: H_0: ORR ≤30% vs. H_a: ORR ≥55%. With 55 response-evaluable subjects, this design has 97% power at a Type I error rate of 0.05 (1-sided) when the true ORR is 55% in the combination arm.~~ ~~3) Accounting for a 10% drop-out rate, approximately 120 subjects will be enrolled".~~	
Synopsis (Statistical Methods); 11.4. Efficacy Analyses (Phase 2 only)	The trigger for the primary efficacy analysis was redefined as when there are 90 subjects. The final analysis will be performed after the end of the study.	
Synopsis (Subject Population and Statistical Methods); 3.1. Overview of Study Design; 3.1.2. Phase 2 (Figure 3);	The total number of subjects enrolled in each treatment cohort was updated.	

Section Number and Name	Description of Change	Brief Rationale
11.1.1. Sample Size - Phase 1b		
11.4. Efficacy Analyses (Phase 2 only)	The primary efficacy analysis was amended as follows: "The primary efficacy analysis is planned when ~~the last subject enrolled has a minimum of 6 months of follow-up and the final analysis will be performed after the End of the Study~~ **there are110 90 response-evaluable subjects. The final analysis will be performed after the end of the study**". The primary endpoint was amended as follows: • "Primary endpoint: ORR will be ~~calculated~~ **estimated** with a ~~90~~ 95% confidence interval. ~~Response will be assessed by investigators and may be assessed by an Independent Radiologic Review Committee (IRRC).~~**The primary efficacy analysis will be based on the response ~~will be~~ assessed by investigators.~~An~~ IRRC will also review responses for Phase 2. The IRRC assessment of response will be used for the reporting of the primary endpoint if the primary objective is achieved by using the investigators' assessments".**	
6.4. Administration of Platinum Chemotherapy (Cisplatin or Carboplatin) (Appendix 2)	Added subsections that provide a description of cisplatin, carboplatin, antiemetic therapy and supportive care guidelines for platinum chemotherapy, supportive care guidelines for chemotherapy, dose modification, dose delays, retreatment criteria, guidance for specific platinum chemotherapy toxicities, and platinum chemotherapy associated toxicities leading to discontinuation of study treatment.	To provide specific guidance to the site regarding the addition of the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.
8.1. Permitted Medications	A list of permitted antiemetics and a clarification regarding primary prophylaxis were added. The following sentence was amended: "**In general**, ~~G~~**g**rowth factor support **is permitted** for the management of treatment-emergent hematological toxicity as recommended according to National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer (NCCN/EORTC) guidelines. **Primary prophylaxis is not permitted for subjects who are under evaluation for DLTs"**.	
8.2. Prohibited Medications and Therapy	Table describing the prohibited concomitant medications and therapies was updated.	

Section Number and Name	Description of Change	Brief Rationale
14.1. Physical Description of Study Drug (s); 14.2. Packaging; 14.3. Labeling	Text regarding platinum (cisplatin or carboplatin) chemotherapy was added.	
Synopsis (Evaluations); 6.2.3.6. Guidelines for Eye Toxicity Associated with Vision Changes	Text updated to confirm that corneal or retinal abnormalities for subjects receiving erdafitinib are considered adverse events of special interest. These occurrences should be reported as adverse events or as serious adverse events if the severity is Grade 3 or higher and require enhanced reporting and data collection.	To provide guidance to the site staff regarding the potential adverse events associated with the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort. Also, to provide additional guidance to the sites regarding the reporting of adverse events.
6.5. Toxicity Due to One Study Drug and Continuation of Treatment	The following updates were made: "The dose modification guidelines described in Section 6.2, ~~and~~ Section 6.3, and **Section 6.4** are to be used throughout both phases of the study, **as applicable**. **If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity)**. The recommendation to discontinue study therapy may apply to ~~both~~ **all** study drugs".	
Attachment 4	Title and content of attachment updated to "Drugs Classified as Strong CYP3A4 Inhibitors, Moderate to Strong CYP3A4 Inducers, Moderate CYP2C9 Inhibitors, and Moderate CYP2C9 Inducers".	
Attachment 7	Statement regarding platinum chemotherapy was added. Template language regarding reporting of anticipated events and the Safety Assessment Committee was added.	
1.5.2. Summary of Clinical Data; 3.2. Study Design and Starting Dose Rationale	Incorporated text from the Investigator Brochure regarding alternate dosing regimens for cetrelimab.	Established safety data supports the rationale to change the dose regimen of the cetrelimab in the Phase 1b and the Phase 2 cohorts.
Synopsis (Overview of Study Design, Dosage and Administration); 3.1.1. Phase 1b (Figure 1); 3.1.2. Phase 2 (Figure 3); 3.1.1. Phase 1b (Appendix 1); 3.1.2. Phase 2 (Appendix 3); 6.1. Dose Combination for Erdafitinib +/- Cetrelimab Cohorts (Appendix 1, Appendix 3); 6.3. Administration of Cetrelimab	The text was amended to describe the change in the dosing regimen of cetrelimab from 240 mg Q2W (Cycles 1-4) to 480 mg Q4W (starting at Cycle 5) for all dose levels within the Phase 1b erdafitinib + cetrelimab cohort and the Phase 2 erdafitinib +/- cetrelimab cohort.	

Section Number and Name	Description of Change	Brief Rationale
6.3. Administration of Cetrelimab	To define the dose of cetrelimab as 360 mg IV Q3W in the erdafitinib + cetrelimab + platinum chemotherapy cohort.	
9.1.3. Treatment Phase	The following statement was amended: "The Treatment Phase will begin with the administration of the first dose of erdafitinib alone or in combination with cetrelimab **+/- platinum (cisplatin or carboplatin) chemotherapy** and will continue until disease progression or unacceptable toxicity (based on Investigator assessment) occurs".	Content updates to protocol text to increase the scope of the study to include the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.
9.5. Predictive and Exploratory Biomarkers	The following statement was amended: "To further elucidate the erdafitinib mechanism of action, the effect of erdafitinib**,** ~~or~~ the erdafitinib plus cetrelimab combination**, or the erdafitinib + cetrelimab + platinum chemotherapy combination** on tumor immune cell infiltrate ~~(~~and peripheral immune cells~~)~~ will be assessed".	
11.5. Pharmacokinetic Analyses; 11.8. PK/ PD Analyses; 16.1. Study-Specific Design Considerations	Text added regarding the platinum chemotherapy cohort.	
3.2. Study Design and Starting Dose Rationale	Updated the following subsections in regard to the potential interactions between platinum chemotherapy and cetrelimab: "Potential for PK-mediated drug-drug interaction" "Potential for PD-mediated drug-drug interaction (serum phosphate)".	To assess the impact of study drug(s) on safety, PK, and PD parameters due to the addition of the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.
9.3. PK and Immunogenicity; Time and Events Schedules (Appendix 1, Appendix 2, Appendix 3); PK, Immunogenicity, and Biomarker Sampling Tables (Appendix 1, Appendix 2, Appendix 3)	PK sampling times for the Phase 1b erdafitinib, cetrelimab, and the Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohorts were updated/added. The PK, immunogenicity, and biomarker sampling text were removed from the Time and Events Schedules and placed in cohort-specific appendix tables.	
9.4. Pharmacodynamic Evaluations	The following text was amended: "**Hypophosphatemia is a common adverse event of chemotherapy**. Phosphate levels will be evaluated throughout the study as a PD and safety biomarker ~~for erdafitinib~~. **Serum for the assessment of phosphate concentrations will be collected as outlined in the cohort-specific Time and Events Schedule**".	
Throughout the protocol	The following sections were moved from the main body of the protocol or included in a cohort-specific appendix: Time and Events Schedules Pharmacokinetic (PK), Immunogenicity, and Biomarker Samples Table	Revision to layout of the protocol text to describe each treatment cohort of the overall study in a cohort-specific appendix.

Section Number and Name	Description of Change	Brief Rationale
	Section 2.1. Objectives and Endpoints Section 2.2. Hypotheses Section 3.1.1 Phase 1b for Erdafitinib + Cetrelimab Cohort/ Phase 1b for Erdafitinib + Cetrelimab + Platinum (cisplatin or carboplatin) Chemotherapy Cohort Section 3.1.2 Phase 2 Erdafitinib +/- Cetrelimab Cohort Section 3.3 Dose-Limiting Toxicity Evaluation and Determination of RP2D Section 3.3.1. Definition of Dose-Limiting Toxicity for Phase 1b (Dose Escalation) Section 3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules Section 4. Subject Population Section 4.1. Inclusion Criteria Section 4.2. Exclusion Criteria Section 5. Treatment Allocation and Blinding Section 6. Dosage and Administration Section 6.1. Dose Combination for Erdafitinib + Cetrelimab Cohort/ Dose Combination for Erdafitinib + Cetrelimab + Platinum Chemotherapy Cohort/ Dose Combination for Erdafitinib +/- Cetrelimab Cohort Section 6.4. Administration of Platinum Chemotherapy (Cisplatin or Carboplatin) 6.4.1. Cisplatin 6.4.2. Carboplatin 6.4.3 Antiemetic Therapy and Supportive Care Guidelines for Platinum Chemotherapy 6.4.4. Dose Modification, Dose Delays, and Retreatment Criteria for Platinum Chemotherapy 6.4.5.Guidance for Specific Platinum Chemotherapy Toxicities 6.4.6. Platinum Chemotherapy Associated Toxicities Leading to Discontinuation of Study Treatment	
Time and Events Schedules (Appendix 1, Appendix 2, Appendix 3)	A separate Time and Events Schedule has been created for each of the 3 cohorts within this study.	To provide a separate cohort-specific Time and Events Schedule.
Tables for Pharmacokinetic, Immunogenicity, and Biomarker Samples (Appendix 1, Appendix 2, Appendix 3)	The PK, immunogenicity, and biomarker sampling text has been removed from the Time and Events Schedule. A cohort-specific table containing the sampling cycle days and times for PK, cetrelimab immunogenicity, and biomarker collection has been added to each appendix.	To provide a separate cohort-specific table containing the PK, immunogenicity, and biomarker sampling requirements.
1. Introduction	A description of the new layout of the protocol was added.	To provide the reader with an explanation regarding the reorganization of protocol text based on the main body of the protocol and cohort-specific text in the respective appendices.

Section Number and Name	Description of Change	Brief Rationale
4.1 Inclusion Criteria, 4.2 Exclusion Criteria	The inclusion and exclusion criteria have been updated (where applicable) to include the criteria for each of the 3 cohorts of the study. The criteria that is applicable to the respective cohort is indicated by bold text in Sections 4.1 and 4.2. The criteria that is not applicable to the respective cohort is indicated by greyed out text in Sections 4.1 and 4.2.	To provide the reader with an explanation as to how the inclusion and exclusion criteria were updated and reorganized to accommodate the 3 treatment cohorts within the study.
Synopsis (Overview of Study Design, Statistical Methods); 3.1.2. Phase 2; 11.1.2. Sample Size - Phase 2; 11.11. Futility Analysis for Phase 2	The description of the futility analysis was deleted.	A higher observed ORR in Phase 1b implies a low probability of stopping due to futility in Phase 2 and use of Simon's two-stage design not necessary. Therefore, conducting Phase 2 is considered more efficient without implementation of Simon's two-stage design which would involve a futility analysis.
11.1.2. Sample Size - Phase 2	The Simon two-stage design language was deleted.	
11.4. Efficacy Analyses (Phase 2 only)	The last paragraph in this section regarding the efficacy analyses of monotherapy and combination therapy was deleted.	
11.10. Data Review Committee	The following sentences were amended: "Additionally, **the DRC may review ongoing cumulative data from Phase 1b after the RP2D has been determined.** ~~The committee will review results of the planned futility analysis. After the review, the DRC will make recommendations regarding the continuation of the study.".~~	
Synopsis (Objectives, Endpoints, and Hypotheses); 2.1. Objectives and Endpoints	The primary objective for the Phase 2 part of the study was updated as follows: "To evaluate the safety and clinical activity of erdafitinib alone and in combination with cetrelimab in ~~in first line mUC setting~~ **cisplatin-ineligible subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations and no prior systemic therapy for metastatic disease".**	To better define the Phase 2 subject population.
Synopsis (Overview of Study Design); 1.7. Overall Rationale for the Study; 4.1. Inclusion criteria (Inclusion 6.2)	The definition of cisplatin-ineligibility was clarified.	
1.3. Erdafitinib; 1.8.1 Anticipated Benefits and Risks for Erdafitinib and Cetrelimab	Incorporated updated efficacy and safety data from Study 42756493BLC2001.	Incorporated updated data generated from other studies (including 42756493BLC2001) that support the objectives, endpoints, and subject populations in this study.
1.5.2. Summary of Clinical Data	Incorporated updated safety and efficacy data from the Phase 1b erdafitinib + cetrelimab cohort.	To comply with request from Belgian Health Authority.

Section Number and Name	Description of Change	Brief Rationale
1.5.2. Summary of Clinical Data; 1.8.1 Anticipated Benefits and Risks of Erdafitinib and Cetrelimab; 3.1.1. Phase 1b (Figure 1); 3.1.1. Phase 1b Erdafitinib + Cetrelimab cohort (Appendix 1)	Text added to confirm the dose of the RP2D as endorsed by the SET.	Confirms designation of the RP2D for the Phase 1b erdafitinib + cetrelimab cohort.
3.4. Study Evaluation Team; 16.1. Study-Specific Design Considerations; 3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules (Appendix 1); 6.1. Dose Combination for Erdafitinib + Cetrelimab Cohort (Appendix 1)	Text amended to describe the role of the SET and the DRC and the timing of the data review/analysis by the SET and the DRC.	The DRC assumes responsibility from the SET regarding the review of cumulative data once the RP2D of erdafitinib and cetrelimab has been determined.
1.5.2. Summary of Clinical Data; 3.1.1. Phase 1b (Figure 1); 3.1.2. Phase 2 (Figure 3); 6.2.1. Dose Up-titration Guidelines; 3.1.2. Phase 2: Erdafitinib +/- Cetrelimab Cohort (Appendix 3)	Reported the outcome of the DRC decision to change the erdafitinib titration guidelines for Phase 1b DL2B and Phase 2 Arm B.	The DRC recommended to remove the requirement for up-titration from the erdafitinib + cetrelimab combinations in order to mitigate the incidence of dose interruptions and reductions for erdafitinib.
3.1. Overview of Study Design	Table entitled “Molecular Eligibility Based Upon the Following FGFR Alterations” was added.	To provide clarity regarding molecular eligibility for the Phase 1b and Phase 2 parts of the study.
Synopsis (Subject Population); 3.1.1. Phase 1b for Erdafitinib + Cetrelimab + Platinum (cisplatin or carboplatin) Chemotherapy Cohorts (Appendix 2); 11.1.1. Sample Size - Phase 1b	Text regarding molecular eligibility was updated as follows: • Phase 1b erdafitinib + cetrelimab cohort and the Phase 2 erdafitinib +/- cetrelimab cohort: select FGFR gene alterations as described in Table 4 • Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: may be FGFR wild-type or express select FGFR gene alterations as described in Table 4 in tumor or blood. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations described in Table 4Table 4.	
Time and Events Schedules (Appendix	The following statement was added:	To allow remote consent for molecular eligibility screening.

Section Number and Name	Description of Change	Brief Rationale
1, Appendix 2, Appendix 3); 9.1.2. Screening Phase	"Consent for molecular screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation unless not permitted according to local guidance".	
6. Dosage and Administration (Appendix 1, Appendix 3)	The sequence of study drug administration was amended to: "On days that both drugs will be administered, the sequence of administration will be oral erdafitinib followed by the infusion of cetrelimab IV".	To define the sequence of administration of study drug(s) and to eliminate the time period between the administration of study drugs.
6.1. Dose Combination for Erdafitinib + Cetrelimab Cohort (Appendix 1)	Footnote "c" was amended to remove the time requirements between dosing of erdafitinib and cetrelimab.	
6.3. Administration of Cetrelimab	The following modification was added to the administration instructions of cetrelimab: "On days ~~on~~ **in** which both erdafitinib and cetrelimab will be administered, oral erdafitinib should be given ~~within 1 hour (±15 minutes)~~ before the start of cetrelimab IV infusion. **On days in which erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy will be administered, oral erdafitinib should be given** 4 ~~hours (±15 minutes)~~ **prior to cetrelimab, followed by** ~~the start of~~ **platinum (cisplatin or carboplatin) chemotherapy IV infusion.**~~, and cetrelimab is administered after chemotherapy".~~	
3.1. Overview of Study Design; Time and Events Schedules (Appendix 1, Appendix 3)	The following text was amended: "For subjects enrolling in the Phase 1b ~~Alternative Cohort~~ **DL2B** and Phase 2 Arm A **cohorts**, ~~at selected sites,~~ paired biopsies will be required **(where local regulations permit and if the tumor is accessible)** at Screening and C2D1 prior to erdafitinib administration (biopsy cohort). **High-risk areas of metastases such as brain, pancreas, and lung should not be considered as an accessible site for biopsy.** Biopsies will be collected to aim to have a minimum of 15 evaluable biopsy pairs (total from Phase 1b ~~Alternative Dosing~~ **DL2B** and Phase 2 Arm A **cohorts**). **Exceptions may apply upon discussion between the investigator and medical monitor.** ~~For patients outside of the biopsy cohort, biopsies may be performed where clinically feasible.".~~	To provide guidance to the sites regarding high-risk areas for biopsies.
9.5. Predictive and Exploratory Biomarkers	Text added to confirm that the sponsor cannot authorize performance of high-risk fresh biopsies to obtain tissue for retrospective central confirmation of FGFR status.	
9.6.11. Documentation of Hearing Loss; Time and Events Schedule (Appendix 3)	Text added to describe requirement for the documentation of hearing loss for subjects enrolled in the Phase 2 erdafitinib +/- cetrelimab cohort.	To describe the audiometry requirements for the sub population of the Phase 2 cohort.

Section Number and Name	Description of Change	Brief Rationale
5. Treatment Allocation and Blinding	Section modified to be cohort-specific.	To provide cohort-specific instructions to sites regarding treatment allocation and blinding.
Synopsis (Evaluations)	A reference to Attachment 9 was added.	Additional guidance provided to site with regard to assessing disease progression and the utilization of RECIST guidelines.
9.2.2. Treatment After Initial Disease Progression	The following paragraph was amended: "**If the site study team makes an initial assessment of disease progression, and if the subject is clinically stable, treatment with erdafitinib may be continued.** In the case of imaging-based progression (RECIST ~~-defined disease progression~~) subjects may continue to receive ~~erdafitinib and cetrelimab~~ **study** treatment**(s)** if the investigator and sponsor**'s** clinical team agree and if the subject is clinically stable as defined by the following criteria".	
9.2.2. Treatment After Initial Disease Progression	The following statement was modified: "If a subject is approved to continue treatment beyond initial RECIST defined disease progression**,** repeat **tumor** imaging must be performed **at least 4 weeks but no later than 6 weeks after the first tumor imaging indicating PD.** ~~repeat imaging must be performed within 4 weeks of the initial scan showing progression~~. **If repeat imaging meets the threshold for PD (≥20% increase in tumor burden [minimum 5mm] compared to extent of disease at the time of the first progression or unequivocal new lesion(s)** ~~evidence of a new lesion~~**, the subject will be discontinued from study treatment** ~~therapy~~. ~~If the repeat scan shows further progression of disease of >10% increase in tumor burden compared to the initial scan showing progression OR the patient has any new symptoms/worsening clinical status both study drugs must be permanently discontinued".~~	
Attachment 9	Added the RECIST guidelines (version 1.1).	
17.9.2. Study Termination	The following statement was added: "**The sponsor will ensure that subjects benefiting from study treatment(s) can continue to receive treatment(s) after the study has been terminated".**	To ensure treatment continuity for any subject receiving benefit from the study treatment.
Time and Events Schedules (Appendix 1, Appendix 2, Appendix 3)	Footnote/note added: "**CrCl is to be performed only at Screening and is calculated by the Cockcroft-Gault formula (Attachment 8)**".	To provide guidance to the site regarding the required method to calculate the estimated creatinine clearance.
Synopsis (Overview of Study Design)	The method for assessing renal function was changed. Utilizing the glomerular filtration rate was replaced by calculating creatinine clearance via the Cockcroft-Gault equation (Attachment 8).	
Attachment 8	Added the Cockcroft-Gault Formula.	
Time and Events Schedules (Appendix 1,	Footnote added: "**Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 10".**	Direction provided to site to manage study subjects during a national disaster.

Section Number and Name	Description of Change	Brief Rationale
Appendix 2, Appendix 3)		
7. Treatment Compliance	Text added for guidance on study conduct for enrolled subjects during a national disaster.	
Attachment 10	Added standard guidance regarding protocol requirements during the time of a national disaster.	
6.2.1. Dose Up-titration Guidelines; 6.2.3.1. Grading of Hyperphosphatemia and Nail Disorders; 6.2.3.2. Guidelines for the Management of Elevated Phosphate Levels	Serum phosphate values in the text and associated tables were updated.	To align with erdafitinib program standards.
6.2.3.3. Guidelines for Management of Dry Mouth and Stomatitis	Tables for Guidelines for the Management of Dry Mouth (Xerostomia) and General Prophylaxis and Guidelines for the Management of Oral Mucositis were updated.	
6.2.3.5. Guidelines for the Management of Nail Toxicity(Onycholysis, Onychodystrophy, and Paronychia)	Table for "General Prophylaxis & Guidelines for the Management of Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy)" was updated.	
8.3. Precautions for Concomitant Medications, Food, and Surgical Intervention	Text and table regarding the use of moderate inhibitors of CYP2C9 and strong CYP3A4 inducers were amended.	
9.6.7. Ophthalmic Examination	The following sentence was amended: "All images of the OCT scan must be stored in the subject's records**, and a redacted copy sent to the sponsor-selected central vendor for** possible future **independent** assessment".	
Attachment 5	Amsler grid replaced with new version.	
Throughout the protocol	NCI-CTCAE version 4.03 updated to version 5.0.	
12.1.3. Severity Criteria; 12.3.3. Disease-related Events or Outcomes Not Qualifying as Adverse Events or Serious Adverse Events; Attachment 7: Anticipated Events	Updated protocol template language replaced by existing protocol text.	To align with updated company protocol template language.
Throughout the protocol	Nomenclature revised to show: • "cohort": Phase 1b erdafitinib + cetrelimab ○ "regimen": Standard and Alternative ▪ "dose level": DL1, DL2, DL2A, etc. • "cohort": Phase 1b erdafitinib + cetrelimab + platinum chemotherapy	Clarification of existing text.

Section Number and Name	Description of Change	Brief Rationale
	○ "regimen": cisplatin or carboplatin ▪ "dose level": DL2C, DL2C1, etc. • "cohort": Phase 2 erdafitinib +/- cetrelimab ▪ "dose level": Arm A or Arm B.	
Throughout the protocol	"Time and Events Schedule" is replaced with "cohort-specific Time and Events Schedule".	
Throughout the protocol	Cycle duration was defined as: ○ 4 weeks (28 days) for the Phase 1b erdafitinib + cetrelimab cohort and the Phase 2 erdafitinib +/- cetrelimab cohort ○ 3 weeks (21 days) for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.	
Throughout the protocol	The phrase "selected FGFR alterations" was updated to "select FGFR alterations".	
Time and Events Schedules (Appendix 1, Appendix 2, Appendix 3)	The following note was amended as follows : • "Subjects enrolling based on local **historical** testing must submit archival tumor tissue and a blood sample for retrospective confirmation of FGFR status as soon as possible after enrollment".	
3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules (Appendix 1)	First sentence in paragraph updated to "The RP2D of the **erdafitinib/cetrelimab** combination will be determined after review of all available PK, PD, safety, and efficacy data from at least 6 subjects treated at the RP2D and the recommended dose by mTPI-2 design. Only 1 RP2D will be tested in Phase 2".	
Synopsis (Hypotheses)	The hypothesis for the Phase 2 (Dose Expansion) part of the study was amended as follows: "Erdafitinib alone and in combination with cetrelimab **is** ~~are~~ safe and ~~have~~ **has** anti-tumor activity in cisplatin-ineligible subjects with metastatic or locally advanced urothelial cancer with select~~ed~~ FGFR gene alterations and no prior systemic therapy for metastatic disease".	
1.3 Erdafitinib	The footnote for table entitled "Overall Summary of Treatment Emergent Adverse Events (TEAEs); Treated Subjects (Study 42756493-BLC2001)" was updated to include: "**(Study 42756493-BLC2001 CSR)**".	

Section Number and Name	Description of Change	Brief Rationale
1.5.2. Summary of Clinical Data	The following sentences were amended: "Clinical experience with cetrelimab in humans to date is based on preliminary data from the ongoing first-in-human (FIH) **monotherapy** study (Study 63723283LUC1001), a multicenter Phase 1/2 study in subjects with advanced solid tumor malignancies. ~~Part 1~~ **The Phase 1b** part of the study, initiated on 21 November 2016, consists of dose escalation cohorts and PK/pharmacodynamic (PD) cohorts. The highest doses administered to date are 800 mg once every 2 weeks(Q2W) and 480 mg once every 4 weeks (Q4W);~~ no maximum tolerated dose has been identified".~~	
1.5.2. Summary of Clinical Data	The following sentence was amended: "The purpose of dose expansion in ~~Part 2~~ **the Phase 2 part of the study** is to further characterize the safety and to assess the anti-tumor activity".	
1.7. Overall Rationale for the Study	The following sentence was deleted from this paragraph to ensure alignment with the title of this subsection (which pertains to first line subjects): "~~More recently, and beyond chemotherapy, several drugs including PD(L)-1 antibodies and erdafitinib have been approved in 2L mUC".~~	
1.8.1. Anticipated Benefits and Risks for Erdafitinib and Cetrelimab	The following sentence was amended: "Based on currently available clinical data **from erdafitinib and cetrelimab as monotherapies as well as preliminary data from this study Section 1.5.2,** the safety profiles for erdafitinib and cetrelimab are anticipated to ~~be~~ **remain** manageable".	
1.8.1. Anticipated Benefits and Risks for Erdafitinib and Cetrelimab	Text within the table entitled " Potential Risks and Mitigation Strategies Associated With Erdafitinib and Cetrelimab" was deleted to make table more concise.	
3.1. Overview of Study Design	The following modifications were made: "Subjects enrolled in **the Phase 1b erdafitinib + cetrelimab cohort** ~~Part 1~~ may have received any number of lines of prior therapy, **subjects enrolled in Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort will have had no prior systemic therapy for metastatic disease,** and subjects enrolled in ~~Part 2~~ **Phase 2** will have had no prior systemic therapy for metastatic disease and **will be** cis-ineligible (see the Inclusion Criteria 6.1 in Section 4.1)".	
3.1. Overview of Study Design	The following sentence was amended: **"All** subjects will **undergo** ~~be assessed for~~ molecular ~~e~~**eligibility** ~~**testing**~~ during Screening **to assess for select FGFR alterations (as defined in Table 4)** ~~**only** and those with tumors positive for the selected FGFR point mutations and translocations will be enrolled".~~	

Section Number and Name	Description of Change	Brief Rationale
3.1.2. Phase 2	Figure 3: Overview of the Phase 2: Erdafitinib +/- Cetrelimab Cohort was amended to change "PD-1" to "CET".	
3.2. Study Design and Starting Dose Rationale	The following paragraph was updated: "The recommended monotherapy dose for cetrelimab is based on clinical activity in the Phase 1 Study 63723283LUC1001. **One of** ~~T~~**the** identified RP2D regimen**s** of cetrelimab is a dose of 240 mg Q2W administered intravenously. The cetrelimab monotherapy RP2D regimen selection was based on an acceptable safety profile, similarity to other anti-PD-1 monoclonal antibodies, and preliminary evidence that target concentrations are achieved. **This regimen is being tested in the cohort combining erdafitinib and cetrelimab (Dose levels DL1, DL2, DL2A in Phase 1b and Arm B in Phase 2)".**	
3.2. Study Design and Starting Dose Rationale	The subject population was clarified as locally advanced or metastatic urothelial carcinoma.	
3.4. Study Evaluation Team	The composition of the SET is clarified as: "The SET will be chaired by the sponsor's Molecule Responsible Physician and membership will include the sponsor Study Responsible Physician, a sponsor clinical scientist, **a subset of** the study principal investigators, safety physician (sponsor's Safety Management Team chair), statistician, and clinical pharmacologist, along with additional sponsor staff, as appropriate".	
6.2.2. Dose Modification, Dose Delays, and Retreatment Criteria for Erdafitinib	The following sentence was deleted: ~~Dose cohort escalation / de-escalation rules for Phase 1b are described in Section 3.1.1 of the protocol.~~	
6.3.1. Retreatment Criteria for Cetrelimab	The following modification was made to the text regarding the retreatment criteria for cetrelimab: "**Chemistry and hematology should be assessed according to the Time and Events Schedule and laboratory** results and general physical status must be reviewed **prior to administration of cetrelimab**".	
6.3.2. Dose Delay for Cetrelimab	The following sentence was amended: "If cetrelimab administration is delayed beyond the allowed visit window ~~(Time and Events Schedule, Table 1)~~, then the dose will be considered a missed dose".	
6.3.3. Cetrelimab Associated Toxicities Leading to Discontinuation of Study Treatment	The term "study treatment" was replaced with "cetrelimab".	

Section Number and Name	Description of Change	Brief Rationale
6.3.4.12. Monitoring During and After Study Drug Administration	The following sentence was modified: "Subjects should be carefully observed during ~~study agent~~ **cetrelimab** infusions".	
8. Concomitant Therapy	Text was amended as follows: "~~In Phase 1b, a~~**A**ll therapies (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the eCRF. ~~For Phase 2, all therapies should be documented from the start of the study through Cycle 3; after the end of Cycle 3 only therapies used to treat an AE or SAE should be recorded".~~	
9.1.1. Overview	The following sentence was modified: "The study is divided into Screening, Treatment, and Follow-up Phases. The Time and Events Schedule ~~(Table 1 and Table 2)~~ **for each treatment cohort** summarize**s** the planned frequency and timing of all assessments applicable to this study".	
9.1.2. Screening Phase	Clarification made regarding: • molecular eligibility for FGFR status will be determined for all subjects • instructions regarding submission of biological samples added • requirements of a local laboratory regarding molecular eligibility assessment.	
9.3. PK and Immunogenicity	The following statement was amended: "Pharmacokinetic assessments will be performed for ~~both~~ erdafitinib~~, and~~ cetrelimab, **and platinum (cisplatin or carboplatin) chemotherapy cohort**. **Immunogenicity assessment will be performed for cetrelimab**".	
9.6.2. Clinical Laboratory Tests	The clinical laboratory tests were reorganized into categories and footnotes were removed as the schedule of laboratory requirements is described in the cohort-specific Time of Events Schedules.	
11.3. Analysis Population	Text added to describe the Phase 1b and Phase 2 parts of the study as dose escalation and dose expansion, respectively.	
11.4. Efficacy Analyses (Phase 2 only)	The following text was amended: "Primary endpoint: ORR will be ~~calculated~~ **estimated** with a ~~90~~ 95% confidence interval".	
Attachment 1	The column title was updated as follows: "Number of Subjects Treated **(at a Dose)".**	
1.8.1. Anticipated Benefits and Risks for Erdafitinib and Cetrelimab	Section title added to: "Anticipated Benefits and Risks **for Erdafitinib and Cetrelimab".**	Updated title of section for clarity.
3.2. Study Design and Starting Dose Rationale	Subsection title amended to: "Rationale for PK **and PD** Assessment".	

Section Number and Name	Description of Change	Brief Rationale
3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules	Section title amended to: "Determination of the **Phase 1b** RP2D Regimen and Alternative Dosing Schedules".	
6.2. Administration of Erdafitinib	Section title updated to: "**Administration of** Erdafitinib".	
6.3.1. Retreatment Criteria for Cetrelimab	The section title updated to: "Retreatment Criteria **for Cetrelimab**".	
6.3.2. Dose Delay for Cetrelimab	The section title updated to: "Dose Delay **for Cetrelimab**".	
6.3.3. Cetrelimab Associated Toxicities Leading to Discontinuation of Study Treatment	The section title updated to: "**Cetrelimab Associated** Toxicities Leading to Discontinuation of Study Treatment".	
Throughout the protocol	The term "patient" was changed to "subject".	Minor errors were noted.
1.2. FGFR Signaling; 1.3. Erdafitinib	The term "translocation" was changed to "fusion".	
4.2 Exclusion Criteria (Criterion 3 of Appendix 1, Appendix 2, Appendix 3)	"4.1" was updated to "3.1".	

Amendment 2 (30 May 2019)

The overall reason for the amendment: To amend the Part 2 study population to evaluate efficacy and safety of erdafitinib alone or in combination with cetrelimab in the first line cisplatin-ineligible metastatic urothelial carcinoma (mUC) setting. In addition, the amendment includes the lyophilized formulation for JNJ-63723283 (cetrelimab), addresses requests from health authorities, and addresses the feedback from the investigators on the eligibility criteria.

Where an actual text change is shown, this is indicated by bold text.

Applicable Section(s)	Description of Change(s)
Rationale: To amend Part 2 to evaluate efficacy and safety of single-agent erdafitinib alone or in combination with cetrelimab in the first line cisplatin-ineligible mUC setting.	
Synopsis (Objectives, Hypotheses; Overview of Study Design; Subject Population) 2.1 Objectives and Endpoints; 2.2 Hypothesis (Phase 2); 3.1 Overview of Study Design; 3.1.2 Phase 2	The Part 2 study population is being amended from previously treated to no prior systemic therapy for metastatic disease and cisplatin-ineligible. Figure 2 for the Phase 2 design has been updated.

Applicable Section(s)	Description of Change(s)
(Figure 2); 4.1 Inclusion Criteria (Criteria 6)	
3.2 Study Design and Starting Dose Rationale (Rationale for the Study Population)	The rationale for the subject population has been updated.
Synopsis (Statistical Methods); 3.1.1 Phase 1b 3.1.2 Phase 2; 11.1.2 Sample Size-Phase 2; 11.11 Futility Analysis for Phase 2	Revised statistical assumptions on sample size and futility analysis based on study design revisions. The upper limit number of expected subjects in the Phase 1b study has been increased from 25 to 30.
Synopsis (Objectives, Endpoints, and Hypotheses); 2.1 Objectives and Endpoints; 9.2.1 Efficacy Endpoints	Clarified that the ORR will be assessed by investigator assessment.
3.3.2 Determination of RP2D Regimen and Alternative Dosing Schedules	Text was added to permit exploration of alternative cohort DL2B to further characterize the safety of the combination if a standard dosing schedule is identified as the RP2D.
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 3.1.2 Phase 2; 5 Treatment Allocation	Stratification by ECOG PS (0-1 vs 2) has been added.
5 Treatment Allocation and Blinding	The stratification text for PD-1 expression was removed due to the updated study design.
Rationale: Incorporate health authority feedback for the country specific UK amendment: • To provide the definition of women of childbearing potential in the inclusion criteria to ensure appropriate management of contraception requirements and pregnancy testing. • To make the protocol consistent with the cetrelimab investigator's brochure information on the use of immunosuppressive agents at study entry and during the study. • To clarify exclusion for those with intolerance to protein-based therapies. • To include the final pregnancy test and other critical safety assessments 12 weeks after the last dose of study treatment.	
4.1 Inclusion Criteria Criterion 9	Text is added clarifying the definition of women of childbearing potential.
4.2 Exclusion Criteria Criterion 15	**Allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or immune-mediated thrombocytopenia or anemia), or to excipients of erdafitinib or cetrelimab (see the Investigator's Brochures for a list of excipients).**

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria Criterion 18	**Use of immunosuppressant agents, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, cyclosporine, azathioprine, and tumor necrosis factor α (TNF-α) blockers within 2 weeks before the planned first dose of study drug.**
8.2 Prohibited Medications and Therapy (Table 28)	The corticosteroids heading is changed to Immunosuppressive Agents and additional drugs are added to the table: methotrexate, cyclosporine, azathioprine, and TNF-α blockers.
Time and Events Tables1 and 2 (Follow-up visit column and new footnote); 9.1.4 Follow-up Phase; 9.6.4 Urine or Serum Beta-hCG Pregnancy Test	Physical examination, vital signs, and pregnancy testing to be performed at first follow-up visit (12 weeks after last dose).
Rationale: To enable collection of CCI [redacted]	
Time and Events Tables (footnotes j and k); 3.1 Overview of Study Design;	For subjects at selected sites in the Phase 1b Alternative Cohort and Phase 2, paired biopsies will be required at any time prior to erdafitinib (erdafitinib monotherapy arm) administration on Cycle 1 Day 1 and on Cycle 2 Day 1 (±3 days). Biopsies will be collected to aim to have a minimum of 15 evaluable biopsy pairs. Tumor biopsy to be taken within 2 weeks of documented disease progression.
9.5 Predictive and Exploratory Biomarkers	Addition of Phase 1b Alternative Cohort to paired biopsy assessments. Text mentioning adjustments to biomarker collections may occur based on emerging data.
Rationale: An independent radiology review committee (IRRC) has been added to ensure an unbiased and consistent evaluation of the study endpoints, if required.	
Synopsis; 11.4 Efficacy Analyses	Text describing assessment of the primary endpoint by an IRRC has been added.
Rationale: To remove unnecessarily restrictive eligibility criteria, to comply with health authority requests, and to align with other protocols across the erdafitinib program. • Creatinine clearance cutoff of >50 mL/min was used in first-in-human study of anti-PD-1 monotherapy (JNJ283) as precautionary measure. There is no evidence of acute renal toxicity with cetrelimab, consistent with other PD-1/PD-L1 antagonists. Furthermore, the study drugs are not excreted through the kidneys. Lowering creatinine clearance cutoffs will allow patients with mild renal impairment likely due to cancer and prior cancer treatments to receive treatment in the setting where options are limited. • Clarified exclusion criterion pertaining to patients with other malignancies. • Clarified that there is a lack of predictive value of history of macular/retinal medical history on the risk of occurrence of central serous retinopathy (CSR)/retinal pigment epithelial detachment (RPED) based on analysis of data from Phase 1 and 2 erdafitinib studies and evidence from the available literature. • CYP3A is important in metabolism of erdafitinib; however, the current data indicate that these interactions are not clinically relevant. At the time of protocol amendment 1, the final data quantifying the impact of CYP3A inhibitor on erdafitinib administration was not yet available. Meanwhile, results from Study EDI1007 now indicate that the exclusion of subjects using CYP3A inhibitors is not justified.	

Applicable Section(s)	Description of Change(s)
• Originally coagulation tests were included in the protocol for consistency with the FIH study (LUC1001). Based on the data generated from this study, there is no risk on clotting factors for the class of PD-1 and PD-L1. Furthermore, the evaluation of these factors is not in the prescribing information of approved therapies (eg, pembrolizumab)	
4.1 Inclusion Criteria (Criterion 2)	Histologic demonstration of transitional cell carcinoma of the urothelium. ~~Minor components (<50% overall) of v~~**V**ariant urothelial carcinoma histologies such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable.
4.1 Inclusion Criteria (Criterion 3)	To clarify inclusion of metastatic or locally advanced urothelial cancer and to align with other ongoing studies in the program: ~~Stage IV disease (m~~**M**etastatic or **locally advanced** ~~surgically unresectable, cT4b, N+, or M+~~ **urotherial** cancer.
4.1 Inclusion Criteria (Criterion 4)	Removal of text: Meet appropriate molecular eligibility criteria ~~(as determined by central laboratory screening)~~.
4.1 Inclusion Criteria (Criterion 5)	Criteria modified to enable assessment of response to therapy per RECIST 1.1 criteria at baseline.
4.1 Inclusion Criteria (Criterion 7)	Following text removed/changed: ECOG ~~performance status~~ PS grade of (see Attachment 3): 0, ~~or~~ 1, **or 2**.
4.1 Inclusion Criteria (Criterion 8)	Following changes made: ~~Clinical laboratory values~~ **Adequate organ function** at screening **defined as follows:** Renal function: Creatinine clearance (CrCl) ~~>50~~**≥40** mL/min/1.73 m^2 either directly measured via 24-hour urine collection or calculated using the Cockcroft-Gault formula Total bilirubin: ≤1.5 × ULN~~; subjects with Gilbert syndrome can enroll if conjugated bilirubin is within normal limits (≤1.5 x ULN~~ or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN ~~**INR or PT**~~ ~~≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants~~ ~~**Activated Partial Thromboplastin Time (aPTT)**~~ Removal of unnecessarily restrictive electrolyte results as an inclusion criterion.
4.2 Exclusion Criteria (Criterion 3)	Included language describing conditions of when neoadjuvant/adjuvant inhibitor therapy is allowed.
4.2 Exclusion Criteria (Criterion 4)	Removal of text: Active malignancies ~~(ie,~~ requiring concurrent therapy~~ requiring treatment change in the last 24 months)~~ other than urothelial cancer ~~(except skin cancers within the last 24 months that are considered completely cured)~~.
4.2 Exclusion Criteria (Criterion 8)	The exclusion criterion for Corrected QT interval was removed as it is redundant with inclusion criterion 8.

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria (Criterion 16)	Exclusion 16 was modified based on health authority recommendation to another study in the erdafitinib program (BLC3001) to remove baseline ocular conditions from the exclusion criteria.
4.2 Exclusion Criteria (Criterion 17)	Removal of exclusion criteria referring to CYP3A4 inhibitors.
4.2 Exclusion Criteria) (Criterion 22)	Removed/added text: Major surgery within 4 weeks of enrollment, or ~~will not have~~inadequate ~~recovered~~ **recovery** from the toxicity and/or complications from the intervention prior to starting therapy, ~~or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)~~
4.1 Inclusion Criterion 9; 4.2 Exclusion Criteria 15 and 18	See rationale for the UK country specific amendment for details.
Rationale: Updated guideline text on the rules of dose modifications until resolution of an AE, eye toxicities, and dry eye.	
6.1 Dose Combination Cohorts/Arms (note added to Table 7)	Text added describing guidance for management of toxicities associated with the study drugs and actions to be taken for both study drugs in the event of a ≥Grade 3 AE thought not attributable to erdafitinib, cetrelimab or the disease under study.
6.2.2 Dose Modification, Dose Delays, and Retreatment Criteria for Erdafitinib (Table 8)	Text added in Table 8 to clarify when and if actions should be taken for Grade 2 events, and what dose modification rules should be applied for resolution of an AE for Grade 2 and Grade 3 AEs. A footnote referring to Table 9 in the protocol has been added.
6.2.3.6 Guidelines for Eye Toxicity Associated with Vision Changes (Table 17)	The following sentence was added to Grade 1-3 toxicities: **Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 to 3-week intervals until resolution.** The following sentence was added to only Grade 2 toxicities: **Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the medical monitor.**
6.2.3.7 Guidelines for the Management of Dry Eye	Added ocular demulcents and removed hydrating/lubricating eye gels and ointments from the guidelines.
Rationale: Updates on background information.	
1.1 Urothelial Bladder Cancer	Updated text on the available regimens for urothelial bladder cancer.
1.2 FGFR Signaling	Additional information added about deregulation of FGFR signaling and FGFR alterations.
1.3 Erdafitinib	Addition of a short description of the JNJ-42756493BLC3001 THOR Study. IC_{50} values with respect to erdafitinib inhibition potency has been updated: < 1 to <~~1000~~ **130** nM in FGFR pathway-activated cancer cell lines

Applicable Section(s)	Description of Change(s)
1.3 Erdafitinib; 1.7 Anticipated Benefits and Risk	The efficacy and the safety results from the Study BLC2001 CSR were updated.
1.5.2 Summary of Clinical Data1.6 Overall Rational for the Study Design	Updates to clinical data from the newest version of the IB were added. Text describing the rationale for treatment in 1L mUC has been added.
1.7 Anticipated Benefits and Risk	Text describing the SET decision to endorse dose escalation to DL2 and an update on the FIH study 63723283LUC1001 has been added.
Rationale: Changes to Molecular Screening were implemented. Clarified that subjects may by-pass molecular screening on BLC2002 study if they have been previously molecular screened on another Janssen-sponsored protocol. Added that patients may meet molecular eligibility based on local next generation sequencing (NGS) test results to expedite enrolment. Added blood collection to molecular screening process to assess FGFR alteration status in circulating cell-free tumor DNA (ctDNA).	
Time and Events Tables; 9.1.2 Screening Phase	Addition of Molecular Eligibility Criteria to the Time and events tables. Text has been added in Section 9.1.2 to clarify processes during the Molecular Screening eligibility period (including text specific for Central Molecular Screening and FGFR analysis of tissue or blood by a local laboratory), and the full-study screening period.
Rationale: iRECIST criteria not yet fully validated.	
Tables and Events Tables and throughout the protocol	Reference to iRECIST removed throughout the protocol.
Rationale: To include information of the new lyophilized formulation.	
14.1 Physical Description of Study Drug(s)	This section was updated to include the description of a new lyophilized formulation of cetrelimab that may be used in the study.
Rationale: Errors/prior omissions, editorial issues, or changes for clarity/consistency were noted and corrected.	
Section 6.3 Administration of Cetrelimab; Throughout the protocol and Time and Events Tables 1 and 2	Replacement of JNJ-63723283 with cetrelimab and minor editorial changes. Corrected the window of erdafitinibadministration with cetrelimab for consistency across the document.
Time and Events Tables; 9.6.2 Clinical Laboratory tests (footnotes a, b, and c have been modified or updated)	Removal of bicarbonate and chloride measurements in the serum chemistry panel as unnecessary tests. Measurement of albumin, calcium, potassium and PTH have been added. C-reactive protein CRP was removed because it is a non-specific marker which is frequently elevated in UC patients.
Time and Events Tables; 9.6.2 Clinical Laboratory Tests	Coagulation assessments were removed. The following text has been added for clarification in the efficacy assessments:

Applicable Section(s)	Description of Change(s)
Time and Events Tables; 9.1.2 Screening Phase	**Disease assessments done within 35 days prior to C1D1 may be used as the Screening disease assessment.**
9.3 Pharmacokinetics and Immunogenicity	Corrected timing of PK assessments, biomarker and immunology assessments and merged these assessments with the Time and Events Tables.
3.1.1 Phase 1b	Phase 1b figure replaced with more decipherable figure.
3.1.1 Phase 1b 3.1.1 Phase 1b (Figure 1); 6.1 Dose Combination Cohorts/Arms	Clarified that 8mg with or without up-titration may be considered as the same dose level.
6.2.1 Dose Up-titration Guidelines	Added mmol/L values in brackets next to their corresponding serum phosphate concentrations (represented in mg/mL). Up-titration guidelines were updated for subjects with serum phosphate levels higher than 9.0 mg/dL to add that erdafitinib treatment will be withheld until it returns to less than 7.0 mg/dL while initiating treatment with a phosphate binder such as sevelamer.
Table of Events Tables; 6.3 Administration of Cetrelimab	Text was added to describe monitoring of vital signs during the 1st and subsequent infusions throughout the study
8. Concomitant Therapy	Text added to clarify that once a subject starts subsequent anticancer therapy, data collection of concomitant medications will be limited to ongoing or newly developed Grade ≥2 immune-related AEs considered related to erdafitinib.
8.2 Prohibited Medications (Table 28)	Medications known to increase serum levels of phosphate were removed from prohibited medications and added to the section with precautions for concomitantly administered medications (Table 29, Section 8.3).
8.3 Precautions for Concomitant Medications, Food, and Surgical Intervention; Attachment 4	Text in this section was updated to be consistent with CYP guidelines in the IB.
9.2 Efficacy Evaluations	Text explaining/clarifying the process for radiographic scans and CT scans at the sites has been added.
9.2.2 Treatment After initial Disease Progression	Clarification of assessments required following approval to continue treatment beyond RECIST progression.
9.6.6 Echocardiography or MUGA Scan	New section added.
9.6.7 Ophthalmic Examination	Clarification text added to mention when ophthalmic exams will be administered, what type will be administered, and by whom.
12.3.1 All Adverse Events	Clarified that once a subject starts subsequent anticancer therapy, collection of AE data will be limited to Grade ≥2 immune-related AEs and serious adverse events from the date the new anticancer therapy is initiated until 100 days after the last dose of study treatment. Grade 3 and higher AEs, if considered related to study drug, occurring more than 100 days after the last dose of study drug should also be reported.

Amendment 1 (22 January 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To clarify the dose escalation procedures in the Phase 1b part of the study and modify the dose-limiting toxicity criteria.

Applicable Section(s)	Description of Change(s)
Rationale: Additional text regarding the dose escalation procedures and a new Figure 1 have been introduced to enhance the clarity of Phase 1b part of the study. However, the planned procedures for this part have not changed.	
3.1.1 Phase 1b	Additional text has been added to clarify the dose escalation procedures. This includes for the case with 3 subjects treated at a dose level. Table 6 has been replaced with Figure 1.
Rationale: Removed a redundant criterion in the dose-limiting toxicity criterion: Since the use of immunosuppressing agents in excess of corticosteroids is mainly related to Grade 3 or higher immune toxicity as described in the management section of the protocol (Section 6.3.4), this is already included by the general Grade 3 toxicity rule of the DLT criteria.	
3.3.1 Definition of dose-Limiting Toxicity; Table 7 Dose-Limiting Toxicity Criteria	This criterion is removed: Immune-related toxicity requiring the use of therapies in excess of corticosteroids (eg, tumor necrosis factor inhibitors or mycophenolate mofetil)
Rationale: The introductory statement in Section 6.2.2 is expanded for further clarification. Section 6.2.2 is intended for toxicity management for erdafitinib. The table is intended as guidance for dose reduction based on observed toxicity and not for guiding dose escalation or de-escalation for dose cohorts in the Phase 1b of the study.	
6.2.2 Dose Modification, Dose Delays, and Retreatment Criteria for Erdafitinib	The introduction of this section is expanded: Treatment with erdafitinib should be discontinued or modified based on toxicity as described in Table 8 and the specific guidance below. **For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicities, specific management guidelines are provided in Sections 6.2.3.1 through 6.2.3.7. This guidance is only intended for toxicity management. Dose cohort escalation/de-escalation rules for Phase 1b are described in Section 3.1.1 of the protocol.**
Rationale: Clarifications have been made for dose reductions for management of hyperphosphatemia	
6.2.3.2 Guidelines for the Management of Elevated Phosphate Levels	7.0-9.0 mg/dL (2.3-2.9 mmol/L): A dose reduction will be implemented for persistent hyperphosphatemia (defined as serum phosphate ≥7 mg/dL for a period of 2 months) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances). >9.0-10 mg/dL (>2.9-3.2 mmol/L): A dose reduction will be implemented for persistent hyperphosphatemia (defined as serum phosphate ≥9 mg/dL for a period of 1 month) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances).
Rationale: The retreatment criteria for hemoglobin has been revised.	
6.3.1 Retreatment Criteria, Table 19	Hemoglobin ≥**8.0** g/dL with or without transfusion, erythropoietin, or both
Rationale: Laboratory criteria for Inclusion Criterion 8 is clarified with normal limits for conjugated bilirubin.	

Applicable Section(s)	Description of Change(s)
4.1 Inclusion Criteria (Criterion 8)	Total bilirubin ≤1.5 × ULN; subjects with Gilbert syndrome can enroll if conjugated bilirubin is within normal limits **(≤1.5 x ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN)**
Rationale: Contraception is clarified (Inclusion Criterion 9)	
4.1 Inclusion Criteria (Criterion 9)	For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 5 months after the last dose of study drug. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception
Rationale: The timing between dosing has been clarified.	
Table 2 (footnote c), Table 3 (footnote d), Table 4 (footnote d); 6.1 Dose Combination Cohorts/Arms, Table 8 (footnote c)	On days that both drugs will be administered, the sequence of administration will be oral erdafitinib ~~within~~ **at least** 1 hour ±15 min. **(ie, 45-75 min.)** before the start of infusion of JNJ-63723283 IV.
Rationale: Changes to clarify an exploratory biomarker objective because biopsies are collected in Phase 2 Arm, the statement only applies to erdafitinib (not the combination). Also, the planned cutoff of ≥ 1% for PD-L1 would not be considered PD-L1 high. Rather, the word "expressing" is more accurate.	
2.1 Objectives and Endpoints, Exploratory	To assess changes in CCI [redacted]
9.5 Predictive and Exploratory Biomarkers	PD-L1 expression level will be assessed via IHC in tumor tissue provided at screening. PD-L1 expression will be utilized as part of randomization criteria in Phase 2 to ensure equal distribution of PD-L1 ~~high~~ **positive** subjects between study arms.
Rationale: Minor changes for the pharmacokinetic assessments for Cycle 5 have been made, changing erdafitinib to JNJ-63723283. Also, in Table 4 (Phase 2), corrected the heading for JNJ-63723283 immunogenicity to be for Arm B only.	
Table 2, Table 3, Table 4 Pharmacokinetic, Immunogenicity & Biomarker Assessments	Cycle 5 Pre-dose **JNJ-63723283** Table 4 **JNJ-63723283 Immunogenicity** **Arm ~~A~~ B Only**
Rationale: Minor changes to laboratory tests have been made (Cycle 2 Day 1 sample was omitted by mistake; other tests have been added for electrolyte and thyroid function evaluation; parathyroid hormone [PTH] testing is added)	
Table 1 Time & Events Schedule; 9.6.2 Clinical Laboratory Tests	The chemistry Cycle 2 Day 1 sample is added to the table. TSH, T3, and free T4: Screening and every other Cycle (Day 1) Sodium, chloride, bicarbonate, and magnesium are specified to be taken at Screening, Cycle 2 Day 1, Cycle 3 Day 1 only; Serum phosphate and PTH will be tested on Cycle 1 Day 15, Cycle 2 Day 15, and Cycle 3 Day 15 only.

Applicable Section(s)	Description of Change(s)
Rationale: An assessment window is added for the disease imaging during the first 6 months.	
Table 1 Time & Events Schedule, Disease assessment and response evaluation	Every 6 weeks for 6 months **(±3 days**)
Rationale: The Safety Evaluation Team (SET) is now referred to as the Study Evaluation Team (SET) throughout the protocol, to be consistent with current Sponsor terminology.	
Synopsis; 3.4 Safety Evaluation Team	This is changed to **Study** Evaluation Team (SET).

SYNOPSIS

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

Erdafitinib (JNJ-42756493) is a selective and potent pan-fibroblast growth factor receptor (FGFR) kinase inhibitor with demonstrated clinical activity in subjects with alterations in the FGFR pathway.

Cetrelimab (JNJ-63723283) is a fully human immunoglobulin (Ig) G4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1) with high affinity and specificity, and blocks binding to both PD-1 ligands: programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2).

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.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Objectives	Endpoints
Phase 1b (Dose Escalation)	
Primary	
• 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	• Frequency and type of dose-limiting toxicity (DLT)
Phase 2 (Dose Expansion)	
Primary	
• 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	• Overall response rate (ORR) (partial response [PR] or better) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by investigator assessment • Incidence of adverse events (AEs)

Hypotheses

Phase 1b (Dose Escalation):

Erdafitinib + cetrelimab cohort: A RP2D(s) regimen of erdafitinib combined with cetrelimab can be identified for safe treatment of subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations.

Erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort: A RP2D(s) regimen of erdafitinib combined with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy can be identified for safe treatment of subjects with metastatic or locally advanced urothelial cancer with or without select FGFR gene alterations.

Phase 2 (**Dose Expansion**):

Erdafitinib +/- cetrelimab cohort: Erdafitinib alone and in combination with cetrelimab is safe and has anti-tumor 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.

OVERVIEW OF STUDY DESIGN

This is a 2-part, multicenter, open-label, Phase 1b-2 study of erdafitinib in combination with cetrelimab +/- platinum (cisplatin or carboplatin) chemotherapy, followed by dose expansion 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.

Dose escalation decisions in Phase 1b of the study will be made by the Study Evaluation Team (SET). The SET procedures are outlined in the SET charter. At least 3 subjects may be dosed at each dose level that will be explored. For all dose levels, a specified dose of oral once daily erdafitinib will be given; up-titration rules may not apply in specific dose levels, as decided by the SET, based on the totality of the safety data observed.

Phase 1b (Dose Escalation):
Erdafitinib + cetrelimab cohort: **(**APPENDIX 1: PHASE 1B ERDAFITINIB + CETRELIMAB**)**

Two dosing regimens may be explored: Standard Dose Levels (DL1, DL2 or DL2A) or Alternative Dose Levels (DL1B or DL2B).

Standard regimen (DL1, DL2, or DL2A)

Subjects with select FGFR alterations will be assigned to a starting dose level (Dose Level 1[DL1]) with oral erdafitinib (6 mg) and cetrelimab (240 mg) administered intravenously every 2 weeks (Q2W). Dose Level 2 (DL2) will receive erdafitinib (8 mg up-titrated to 9 mg once daily) and cetrelimab (240 mg) administered intravenously every 2 weeks at starting Cycle 1 Day 1 (C1D1). Dose Level 2A (DL2A) will receive erdafitinib (8 mg [no up-titration] once daily) and cetrelimab 240 mg administered intravenously every 2 weeks. At Cycle 5, the dose regimen for cetrelimab changes to 480 mg every 4 weeks (Q4W). In the Standard Dose Levels, the DLT period is one cycle (4 weeks/ 28 days).

Alternative regimen (DL1B and DL2B)

It is hypothesized that the sequential starting (starting with the FGFR inhibitor erdafitinib for 1 cycle of 4 weeks [28 days] prior to first administration of anti-PD-1 cetrelimab) might mitigate potential toxicities or lead to increased clinical benefit compared with concurrent administration. The Alternative Dose Level regime starts with a 4-week run-in of erdafitinib with subsequent concurrent dosing of erdafitinib and cetrelimab. Dose Level 1B (DL1B) will receive erdafitinib (6 mg) and cetrelimab 240 mg administered intravenously on Day 1 and Day 15 of a 4-week cycle. Dose Level 2B (DL2B) will receive erdafitinib (8 mg with up-titration to 9 mg after RP2D) and cetrelimab 240 mg administered intravenously on Day 1 and Day 15 of a 4-week cycle. At Cycle 5, the dose regimen for cetrelimab for all Alternative Dose Levels changes to 480 mg every 4 weeks. The Alternative Dose Levels will have a DLT period of 2 cycles (8 weeks). In these Alternative dose levels, the administration of cetrelimab is initiated on Cycle 2 Day 1 (C2D1), while the dose and schedule of erdafitinib is unchanged.

On 20 August 2019, the SET met to review data from DL2 (8 mg daily erdafitinib with up-titration + 240 mg cetrelimab every 2 weeks) and endorsed a RP2D of 8 mg erdafitinib orally once a day with up-titration to 9 mg based on C1D15 phosphate level and the dose of 240 mg cetrelimab IV Q2W.

On 12 May 2020, the Data Review Committee (DRC) made a recommendation to close Dose level 2 in Phase 1b and focus enrollment efforts into the Phase 2 part of the study. Therefore, DL2 will be closed. DL2B will remain open and will include up-titration of erdafitinib based on serum phosphate concentration from blood sample on Day 15 and the absence of significant erdafitinib-related toxicity on C1D15 as determined by the investigator.

Erdafitinib + cetrelimab + platinum chemotherapy cohort: (APPENDIX 2: PHASE 1B ERDAFITINIB+ CETRELIMAB + PLATINUM (CISPLATIN OR CARBOPLATIN) CHEMOTHERAPY**)**

Two new regimens will be explored where erdafitinib and cetrelimab will be combined with either cisplatin or carboplatin. In the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, the doses of erdafitinib (8 mg daily, no up-titration) and cetrelimab (360 mg every 3 weeks [Q3W]) are constant, while doses of cisplatin and carboplatin may be adjusted based on dose-limiting toxicity as described in the protocol and within the range of acceptable doses in the prescribing information (US prescribing information, EU SmPC, or equivalent for the region/country).

Erdafitinib + cetrelimab + cisplatin (erdafitinib + cetrelimab + cis) cohort:

First line subjects with or without select FGFR alterations will receive erdafitinib and cetrelimab in combination with cisplatin. The starting dose level of cisplatin will be 50 mg/m^2 administered intravenously on Day 1 of a 3-week cycle (DL2C). If the mTPI-2 criteria for escalation are met in DL2C, the dose of cisplatin will be increased to 60 mg/m^2 (DL2C1). The DLT period for dosing level DL2C and DL2C1 will be 2 cycles (6 weeks/42 days).

Erdafitinib + cetrelimab + carboplatin (erdafitinib + cetrelimab + carbo) cohort:

First line subjects with or without select FGFR alterations will receive erdafitinib and cetrelimab in combination with carboplatin. The starting dose of carboplatin (AUC4 mg/mL/min) administered intravenously on Day 1 of a 3-week cycle (DL2D). If the mTPI-2 criteria for escalation are met in DL2D, the dose of carboplatin will increase to AUC5 mg/mL/min with a maximum dose of 750 mg (DL2D1). The DLT period for dosing level DL2D and DL2D1 will be 2 cycles (6 weeks/42 days).

Phase 2 (Dose Expansion): (APPENDIX 3: PHASE 2 ERDAFITINIB +/ -CETRELIMAB)

Two dosing arms may be explored: Arm A and Arm B

Subjects who have not received prior systemic therapy for metastatic disease will be stratified by the Eastern Cooperative Oncology Group (ECOG) PS (0-1 versus 2) and assigned randomly (1:1 ratio) to either the erdafitinib monotherapy treatment at the starting oral dose of 8 mg (Arm A), or the combination treatment of erdafitinib and cetrelimab (Arm B). To further characterize safety and clinical activity of the erdafitinib and cetrelimab (Arm B) combination, the dose of erdafitinib and cetrelimab will be administered at 8 mg (no up-titration) and 240 mg Q2W, respectively for Cycles 1 through 4. At Cycle 5, the dosing regimen of cetrelimab is changed from 240 mg Q2W to 480 mg Q4W. Subjects in the Phase 2 dose expansion cohort of the study are cisplatin-ineligible. Cisplatin-ineligible subjects are defined as meeting at least one of the following criteria:

- Impaired renal function defined as calculated by Cockcroft-Gault (See Attachment 8) (Galsky 2011).
- Grade 2 or higher peripheral neuropathy per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0.)

- Grade 2 or higher hearing loss per NCI-CTCAE version 5.0.
- ECOG Performance Status 2.

On 12 May 2020, the DRC recommended to remove the requirement for up-titration of erdafitinib (to 9 mg daily [QD] dose) from Arm B of Phase 2 erdafitinib + cetrelimab combination based upon emerging safety data.

End of Study Data Collection Timepoint for all ongoing subjects in Phase 1b and Phase 2 (Protocol Amendment 5: APPENDIX 4**)**

Once the end of study data collection timepoint has been achieved, all subjects will transfer to a streamlined visit schedule to allow for more flexibility with study assessments and to continue to collect required safety information.

SUBJECT POPULATION

Approximately 160 subjects will be enrolled in this study. Thirty subjects are planned to be enrolled in the Phase 1b erdafitinib + cetrelimab cohort. Forty subjects are planned to be enrolled in the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort. Ninety subjects are planned to be enrolled in the Phase 2 erdafitinib +/- cetrelimab cohort.

Phase 1b (Dose Escalation):

Erdafitinib + cetrelimab cohort: Subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations as described in Table 4 with any number of prior lines of systemic therapy are eligible for enrollment in this part of the study. Subjects must have select FGFR gene alterations in tumor or blood. It is expected that 12-30 subjects will be enrolled in the erdafitinib + cetrelimab cohort. Subjects must be 18 years or older and have ECOG performance status (PS) Grade of 0-2.

Erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort:

First line subjects with metastatic or locally advanced urothelial cancer are eligible for enrollment in this part of the study. Subjects may be FGFR wild-type or express select FGFR gene alterations as described in Table 4 in tumor or blood. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations as described in Table 4. Three subjects (either wild-type or with select FGFR gene alterations) will be enrolled in the initial erdafitinib + cetrelimab + cisplatin dose level (50 mg/m^2). If the starting dose is safe, 6 additional subjects will be enrolled into the escalated dose of cisplatin (60 mg/m^2). Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the maximum tolerated dose (MTD) for erdafitinib + cetrelimab + cisplatin.

Three subjects (either wild-type or with select FGFR gene alterations) will be enrolled in the initial erdafitinib + cetrelimab + carboplatin dose level (AUC4 mg/mL/min). If the starting dose is safe, 6 additional subjects will be enrolled into the escalated dose of carboplatin (AUC5 mg/mL/min). Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib + cetrelimab + carboplatin.

In summary, it is expected that approximately 40 subjects will be enrolled in the platinum chemotherapy cohort. Subjects must be 18 years or older and have an ECOG PS Grade of 0-1 for cisplatin and 0-2 for carboplatin.

Phase 2 (Dose Expansion): Subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations as described in Table 4 who have had no prior systemic therapy for metastatic disease and are ineligible for cisplatin are eligible for enrollment in this part of the study. Subjects must

have select FGFR gene alterations in tumor or blood. Subjects must be 18 years or older and have ECOG PS Grade of 0-2. Approximately 90 subjects in the Phase 2 dose expansion part are expected to be enrolled.

DOSAGE AND ADMINISTRATION

Erdafitinib (6 mg, 8 mg with potential dose adjustments to 9 mg, depending on phosphate levels measured on C1D15) will be provided as tablets for oral administration and will be given once daily at approximately the same time of the day with or without food. When both drugs are administered on the same day, erdafitinib will be administered before cetrelimab (at doses of 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks). Cisplatin will be administered as IV every 3 weeks at 50 mg/m² or 60 mg/m² and carboplatin at AUC4 mg/mL/min or AUC5 mg/mL/min, every 3 weeks. All subjects will continue to receive study treatment until disease progression, unacceptable toxicity, or any other treatment discontinuation criteria are met.

Phase 1b (Dose Escalation):

Erdafitinib + cetrelimab cohort: erdafitinib (6 mg, 8 mg with the potential dose adjustments to 9 mg, depending on phosphate levels measured on C1D15) will be provided as tablets for oral administration and will be given once daily at approximately the same time of the day with or without food. Cetrelimab will be administered at doses of 240 mg every 2 weeks (Cycles 1-4) or 480 mg every 4 weeks (starting at Cycle 5). When both drugs are administered on the same day, erdafitinib will be administered before cetrelimab.

Erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort: erdafitinib (8 mg) will be given once daily at approximately the same time of the day with or without food. Cetrelimab and platinum chemotherapy intravenous infusions will be administered on Day 1 of a 3-week cycle. Erdafitinib oral dose will be given first, followed by cetrelimab and then platinum chemotherapy. A maximum of 4 cycles of platinum chemotherapy will be administered. If platinum chemotherapy is discontinued, the subject can continue to receive erdafitinib and cetrelimab.

Phase 2 (Dose Expansion):

Arm A: erdafitinib monotherapy (8 mg up-titrated to 9 mg) will be given once daily at approximately the same time of the day with or without food.

Arm B: erdafitinib 8 mg will be given once daily at approximately the same time of the day with or without food. Cetrelimab will be administered at doses of 240 mg every 2 weeks (Cycles 1-4) or 480 mg every 4 weeks (starting at Cycle 5). When both drugs are administered on the same day, erdafitinib will be administered before cetrelimab.

All subjects in Phase 1b and Phase 2 will continue to receive study treatment until disease progression, unacceptable toxicity, or any other treatment discontinuation criteria are met.

EVALUATIONS

The safety of erdafitinib + cetrelimab and erdafitinib + cetrelimab + platinum chemotherapy will be assessed based on medical review of safety parameters including but not limited to AEs, vital signs, physical examination, ECOG PS, laboratory tests, and electrocardiograms. Corneal or retinal abnormalities for subjects receiving erdafitinib will be considered as AEs of special interest. These occurrences should be reported as AEs or as serious AEs if the severity is a Grade 3 or higher and require enhanced reporting and data collection. Blood samples will be collected to assess the plasma pharmacokinetics (PK) of erdafitinib, platinum (cisplatin or carboplatin) chemotherapy and serum PK and immunogenicity of cetrelimab. Blood and tumor samples will also be assessed for biomarkers that could CCI [redacted]. The evaluation of response will be according to RECIST 1.1 (Attachment 9).

STATISTICAL METHODS

The number of subjects to be enrolled in Phase 1b will depend on the dose level at which the DLT criteria of the combination are met or the RP2D is determined. The total number of subjects to be treated in Phase 1b will be approximately 70. Among the 70 subjects, 30 are planned for the Phase 1b erdafitinib + cetrelimab cohort.

Approximately 40 subjects will be enrolled in the erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort. In Phase 2, approximately 90 subjects will be assigned randomly in a 1:1 ratio to receive either erdafitinib monotherapy (Arm A) or erdafitinib and cetrelimab combination therapy (Arm B). With approximately 45 subjects on Arm A and assuming a true ORR of 45%, the study is designed such that the resulting 95% confidence interval for estimating ORR excludes those less or equal to 30%. Similarly, assuming a true ORR of 55% in Arm B, approximately 45 subjects results in a 95% confidence interval that excludes ORR less or equal to 40%. The objective response rate will be calculated with a 95% confidence interval by each arm in the treated population according to the RECIST 1.1 criteria (Attachment 9). Safety data will be summarized descriptively.

The primary efficacy analysis is planned with ~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 investigators.

TIME AND EVENTS SCHEDULE

The Time and Events Schedule for the Phase 1b erdafitinib + cetrelimab cohort can be found in the Appendix 1 Table 1.

The Time and Events Schedule for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort can be found in Appendix 2 Table 1.

The Time and Events Schedule for the Phase 2 erdafitinib + cetrelimab +/- cohort of the study can be found in Appendix 3 Table 1.

The Time and Events Schedule for the Phase 1b and Phase 2 cohorts after the end of study data collection timepoint has been achieved can be found in APPENDIX 4 Table 1.

ABBREVIATIONS

ADL	Activities of daily living
AE	adverse event
AJCC	American joint committee on cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration curve
BSA	body surface area
BUN	Blood urea nitrogen
carbo	carboplatin
cet	cetrelimab
chemo	chemotherapy
CI	confidence interval
cis	cisplatin
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CR	complete response
CSR	central serous retinopathy
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCF	data clarification form
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug induced liver-injuries
DL	dose level
DLT	dose-limiting toxicity
DoR	duration of response
DRC	Data Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EMA	European Medicines Agency
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Cancer
erda	erdafitinib
EU	European union
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FIH	first-in-human
FLP	final lyophilized product
GCP	Good Clinical Practice
H_a	alternative hypothesis
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
H_0	null hypothesis
IB	Investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
INR	International normalization ratio

IPPI	Investigational Product Preparation Instructions
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction
IRRC	Independent Radiologic Review Committee
IV	intravenous
IWRS	interactive web response system
LFT	liver function test
MASCC	Multinational Association for Supportive Care in Cancer
MDSC	myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	modified toxicity probability interval
mUC	metastatic urothelial carcinoma
MUGA	multi-gated acquisition scan
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PD-1	programmed death receptor 1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PR	partial response
PRN	when needed
PS	performance status
PT	Prothrombin time
PTH	parathyroid hormone
PTT	Partial thromboplastin time
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QD	daily
QID	four times a day
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion
SAC	Safety assessment committee
SAE	serious adverse event
SD	stable disease
SET	study evaluation team
SIPPM	Site Investigational Product and Procedures Manual
SUSAR	suspected unexpected serious adverse reaction
TDAR	T-dependent antigen responses
TEAE	treatment-emergent adverse event

TID	three times a day
T_{max}	time to maximum serum concentration
TPN	total parenteral nutrition
Treg	regulatory T cells
TSH	Thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
USFDA	United States Food and Drug Administration
WFI	water for injection

1. INTRODUCTION

Erdafitinib (JNJ-42756493) 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.

JNJ-63723283 (cetrelimab) is a fully human immunoglobulin (Ig) G4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1) with high affinity and specificity, blocks binding to both PD-1 ligands: programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). Cetrelimab is currently being investigated for the treatment of advanced stage solid tumors in the ongoing Phase 1 study Protocol 63723283LUC1001 (EudraCT No. 2016-002017-22; NCT02908906).

Platinum-based chemotherapies and PD-1 therapies in eligible patients remain the mainstay of systemic therapy in metastatic or locally advanced urothelial cancer but they do not lead to adequate long-term outcomes. Various combination treatments including combination of platinum-based chemotherapy followed by PD-1 therapy, and CCI [redacted] are showing tolerable safety profiles. CCI [redacted]

The main body of this protocol will describe the overall conduct of this study, which will include the Phase 1b erdafitinib + cetrelimab, the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy dose escalation and dose expansion cohorts as well as the Phase 2 erdafitinib +/- cetrelimab dose expansion treatment arms. The appendices for each cohort will provide a granular level of information for each dose level/arm of the study. As the science evolves, new combinations of therapies may be added to this study.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Urothelial Bladder Cancer

Bladder cancer is the most common malignancy involving the urinary system. Urothelial (formerly called transitional cell) carcinoma is the predominant histologic type in the United States and Europe and the 4th most common cancer in males and 11th most common in females (Cancer Stat Facts 2017); (Cancer Genome 2014). Urothelial cancer can be subdivided into several subtypes based on their molecular signature. The Cancer Genome Atlas working group and others have reported that urothelial cancer can be classified, via gene expression signature, broadly into basal versus luminal subtypes (Cancer Genome 2014); (Choi 2014); (Damrauer 2014). Luminal 1 tumors, or luminal-papillary tumors, are reported to be enriched for FGFR3 mutations, and conversely lacking in immune marker expression and immune cell infiltrate (Choi 2017); (Siefker 2018). A study of 412 chemotherapy-naive, invasive, high-grade urothelial tumors

reported that 44% of luminal-papillary tumors have evidence of FGFR alterations and remain immunologically "cold" compared with the other subtypes (Robertson 2017); (Siefker 2018).

While therapy of bladder cancer in the early disease stages has significantly improved with the use of Transurethral Resection of Bladder Tumor, intravesical chemotherapy, or immunotherapy with Bacille Calmette-Guérin, once locally advanced or metastasized the overall survival (OS) dramatically decreases. Specifically, in the metastatic setting, OS is often limited with a 5-year survival of less than 15% with Stage IV disease (Cancer Stat Facts 2017). The introduction of cisplatin-containing chemotherapy regimens, specifically cisplatin-gemcitabine and the methotrexate, vinblastine, doxorubicin and cisplatin regimen (MVAC) significantly improved survival and are considered standard of care. Nevertheless, due to the high toxicity of cisplatin-containing regimens, nearly half of the patients are ineligible (Bajorin 1999); (Galsky 2011); (Yafi 2011) leading to very poor survival rates in this unfit patient population. For patients who are not eligible to receive cisplatin-based regimens, carboplatin-based regimens are the recommended first line option (EAU Guidelines 2017); (NCCN 2018). Overall response rates are 40% to 50% for cisplatin-based regimens and 30% to 40% for carboplatin-based regimens. Median survival is 14 to 15 months and 9 to 10 months in these groups, respectively. Once patients have failed front-line therapy, the options for further treatment are limited and outcomes dismal. Most widely used are single-agent chemotherapy such as docetaxel, paclitaxel or vinflunine, with response rate of approximately 10%. Until very recently, there were no approved available therapies for second line metastatic urothelial carcinoma (mUC). Five compounds targeting the PD-1/PD-L1 pathway have since received approvals in the US for use in patients who have received at least 1 prior line of therapy for metastatic urothelial carcinoma; however, with an objective response rate (ORR) ranging from approximately 15% to 20% and a median OS of approximately 8 to 10 months. Two of these compounds (atezolizumab and pembrolizumab) are also approved in the first line setting in patients with UC who are ineligible for cisplatin-based regimens. However, the use is restricted due to decreased survival associated with low expression of the PD-L1 (Tencentriq® 2016), (Keytruda® 2014). These compounds have only partially improved patients' outcomes and have not eliminated the need for novel treatments (De Maeseneer 2017). Due to the high unmet medical need, novel therapeutic options are required for the treatment of this challenging patient population.

1.2. FGFR Signaling

The family of FGFRs consists of 4 highly conserved transmembrane receptor tyrosine kinases, namely FGFR1 to 4 (Babina 2017). Together, these receptors are able to bind to over 20 different fibroblast growth factor ligands (Touat 2015). FGFR signaling has been shown to be enhanced by genetic alterations such as gene amplification, mutation, or gene fusions, thereby affecting various cellular mechanisms such as angiogenesis, anti-apoptosis, cell migration, and proliferation in various cancers. Several lines of evidence point to deregulation of FGFR signaling (eg, via FGFR mutation and gene fusion) being involved in bladder cancer pathogenesis (Babina 2017); (Dienstmann 2014); (Touat 2015).

In urothelial cancer, amplifications of FGFR 1 to 3 can be found in a subset of patients. More importantly, activating mutations of FGFR3 have been shown in 38-66% in noninvasive and

15-20% in invasive urothelial cancers (Knowles 2015); (Rodriguez-Vida 2015). Additionally, increased expression of FGFR1 and 3, independent of alterations of the FGFR gene have been reported in a significant proportion of urothelial cancer patients (Knowles 2015); (Rodriguez-Vida 2015) suggesting a therapeutic alternative for this patient population. The panel used for subject selection in erdafitinib studies was chosen based on the most frequently observed activating FGFR alterations in urothelial cancer (mutations in FGFR3, and FGFR2 and FGFR3 gene fusions). These include the most commonly observed FGFR3 mutations in bladder cancer: S249C, Y373C, R248C, and G370C mutations, which occur in the extracellular or transmembrane domains of the receptor leading to ligand-independent dimerization and constitutive activity (Dienstmann 2014). Of the selected fusion proteins, FGFR3:TACC3 fusions have the highest occurrence in bladder cancer (Rodriguez-Vida 2015). TACC3 fusions, along with the FGFR3:BAIAP2L1 fusion and FGFR2 fusion proteins FGFR2:CASP7 and FGFR2:BICC1, confer oncogenic potential via substitution of the C-terminal regulatory domain of FGFR with protein-protein interaction modules of the fusion partner, leading to ligand-independent dimerization and activation of FGFR (Babina 2017); (Katoh 2016); (Wu 2013).

1.3. Erdafitinib

Erdafitinib is a potent, oral pan-FGFR tyrosine kinase inhibitor with half maximal inhibitory concentration (IC_{50}) values in the low nanomolar range for all members of the FGFR family (FGFR1 to 4). It has demonstrated potent inhibition of cell proliferation with IC_{50} values ranging from <1 to <130 nM in FGFR pathway-activated cancer cell lines. Erdafitinib has been shown to have in vivo anti-tumor activity in various murine xenograft and patient-derived mouse models of FGFR-driven cancers including gastric, bladder, and others.

In humans, treatment with erdafitinib exhibited dose-related increase in maximum serum concentration (C_{max}) and area under the concentration curve (AUC) and time-independent pharmacokinetics (PK) within the dose range of 0.5 mg to 12 mg, both after single and multiple daily dosing. Median time to maximum serum concentration (T_{max}) observed ranged from 2 to 4 hours (erdafitinib as capsule). Erdafitinib is highly bound to plasma proteins such as α1-acid glycoprotein (α1-AGP). In patients, free fractions of erdafitinib in human plasma were small (average ~0.36%). In in vitro experiments, erdafitinib was shown to be a P-glycoprotein (P-gp) substrate and inhibitor.

Only unchanged erdafitinib was present in plasma with no circulating metabolites. The metabolites, mainly N- and O-dealkylated derivatives (M8 and M6, respectively), formed via CYP2C9 and CYP3A enzymes, are efficiently eliminated after their formation in the excreta (majority excreted in feces). Long terminal phase half-life of erdafitinib (>50 hours) in plasma was observed resulting in approximately 3- to 5-fold accumulation of C_{max} and AUC following multiple daily dosing.

The anti-tumor effect of erdafitinib was initially observed both in subjects with urothelial cancer with select FGFR alterations, as well as other solid tumors in the Phase 1 study (Study 42756493EDI1001). Activity and a dose were confirmed in the global Phase 2 trial (Study 42756493BLC2001).

Study 42756493BLC2001 is a global Phase 2 trial in subjects with select FGFR mutations and fusions with chemo-refractory and chemo-naïve advanced urothelial cancer who are ineligible for cisplatin. As of the clinical cutoff for the primary analysis on 15 March 2018, 210 subjects have been treated in this study: 33 subjects in the 10 mg intermittent dosing regimen, 78 subjects in the 6 mg daily regimen, and 99 subjects in the 8 mg daily regimen (selected dose regimen). Of the 99 subjects in the primary efficacy population in the 8 mg regimen, 87 (90%) subjects were chemo-refractory and 12 (10%) subjects were chemo-naïve. Confirmed ORR based on investigator assessment (complete response [CR] + partial response [PR]), was 40.4% in the 8 mg once daily regimen. For subjects in the 8 mg once daily regimen who were up-titrated to 9 mg, the ORR was 48.8% (Table 1). The overall summary of treatment-emergent events (TEAEs) from Study BLC2001 is presented in Table 2. The most frequently reported AEs in the 8 mg once daily regimen, most of which were Grade 1 or 2 in severity, were hyperphosphatemia (77%), stomatitis (58%), diarrhea (51%), and dry mouth (46%). Twenty-one subjects (21%) discontinued treatment due to AEs. The most common reason for discontinuation was general physical health deterioration. The frequency of reported AEs and discontinuations across all dose regimens combined was similar to that seen in the 8 mg once daily regimen.

Table 1: Best Overall Response – Investigator Assessment (8 mg QD) (Study 42756493-BLC2001)

	8 mg QD All	8 mg Daily Up-titrated to 9-mg Daily
Total number of subjects	99	41
Objective response rate (CR+PR)	40 (40.4%)	20 (48.8%)
95% CI	(30.7%, 50.1%)	(33.5%, 64.1%)
Disease control rate (CR+PR+SD)	79 (79.8%)	31 (75.6%)
95% CI	(71.9%, 87.7%)	(62.5%, 88.8%)
Best overall response		
Confirmed complete response (CR)	3 (3.0%)	2 (4.9%)
Confirmed partial response (PR)	37 (37.4%)	18 (43.9%)
Stable disease (SD)	39 (39.4%)	11 (26.8%)
Progressive disease (PD)	18 (18.2%)	10 (24.4%)
Inevaluable (NE)	2 (2.0%)	0

Abbreviations: CR= complete response; NE= not evaluable; PR= partial response; SD= stable disease

95% CI are 95% confidence interval calculated with normal approximation.

Table 2: Overall Summary of Treatment Emergent Adverse Events (TEAEs); Treated Subjects (Study 42756493-BLC2001)

	8 mg QD	6 mg QD	10 mg 7 on/7 off	Total
Total number of subjects	99	78	33	210
Any TEAEs	99 (100.0%)	78 (100.0%)	33 (100.0%)	210 (100.0%)
Drug-related	96 (97.0%)	69 (88.5%)	32 (97.0%)	197 (93.8%)
Grade 3-4 TEAEs	66 (66.7%)	51 (65.4%)	22 (66.7%)	139 (66.2%)
Drug-related	45 (45.5%)	22 (28.2%)	8 (24.2%)	75 (35.7%)
Serious TEAEs	39 (39.4%)	39 (50.0%)	14 (42.4%)	92 (43.8%)
Drug-related	9 (9.1%)	4 (5.1%)	1 (3.0%)	14 (6.7%)
Grade 3-4 serious TEAEs	33 (33.3%)	27 (34.6%)	13 (39.4%)	73 (34.8%)
TEAEs leading to dose reduction	55 (55.6%)	32 (41.0%)	13 (39.4%)	100 (47.6%)
Drug-related	55 (55.6%)	26 (33.3%)	12 (36.4%)	93 (44.3%)
TEAEs leading to dose interruption	70 (70.7%)	47 (60.3%)	16 (48.5%)	133 (63.3%)
Drug-related	61 (61.6%)	36 (46.2%)	13 (39.4%)	110 (52.4%)
TEAEs leading to treatment discontinuation	21 (21.2%)	18 (23.1%)	6 (18.2%)	45 (21.4%)
Drug-related	12 (12.1%)	6 (7.7%)	3 (9.1%)	21 (10.0%)
TEAEs leading to death	7 (7.1%)	15 (19.2%)	4 (12.1%)	26 (12.4%)
Drug-related	0	0	0	0

Subjects with > 1 records are counted only once at corresponding row levels.

Source: Attachment TSFAE01A (Study 42756493-BLC2001 CSR)

As of the clinical cutoff of 09 August 2019 (updated analysis), the median follow-up for 101 subjects treated in the erdafitinib 8 mg regimen in Study 42756493BLC2001 was ~24 months. The confirmed ORR by investigator assessment was 40%. The median duration of response (DoR) was 5.98 months. Thirty-one percent of responders had DoR≥1 year. The median PFS was 5.52 months. The median OS was 11.3 months. The 12 and 24-month survival rates were 49% and 31%, respectively. Median treatment duration was 5.4 months. The erdafitinib safety profile was consistent with the primary analysis. No new TEAEs were seen with longer follow-up. Central serious retinopathy (CSR) events occurred in 27% (27/101) of subjects; 85% (23/27) were Grade 1 or 2. Dosage was reduced in 13 subjects with CSR, interrupted in 8 subjects, and discontinued for 3 subjects. On the data cutoff date, 63% (17/27) CSR events had resolved; 6 of 10 of the ongoing CSR events were Grade 1. There were no treatment-related deaths.

A randomized, open-label, multicenter, global Phase 3 study (THOR study [JNJ-42756493BLC3001]) of erdafitinib versus standard of care is being conducted in subjects with advanced urothelial cancer and select FGFR aberrations who have progressed on or after 1 or 2 prior treatments, at least 1 of which includes an anti-PD(L)-1 agent (Cohort 1) or 1 prior treatment not containing anti-PD(L)-1 agent (Cohort 2).

For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Investigator's Brochure (IB) and IB Addenda for erdafitinib.

1.4. PD-1/PD-L1 Signaling

PD-1, a member of the B7 family of proteins, is a co-inhibitory immune checkpoint receptor that regulates adaptive T cell immunity. PD-1 is required for maintenance of peripheral tolerance during normal immune homeostasis, as well as for protection against excessive inflammation during acute immune responses. PD-1 is expressed on activated CD4+ and CD8+ T cells and acts to limit antigen-specific T cell activity through interaction with its ligands, PD-L1 and PD-L2. Cancer cells may often exploit the PD-1/PD-L1 pathway to escape immune surveillance. PD-L1 expressed on cancer cells initiate an immune-inhibitory signal through the PD-1 receptor on regulatory T cells (Tregs), leading to inhibition of T cell activation and proliferation, thereby negatively affecting the anti-cancer immune response, an essential mechanism of self-tolerance of the human body.

Clinical studies have shown that the PD-1/PD-L1 pathway is an attractive therapeutic target by reversing T cell exhaustion and boosting the anti-tumor immune response. In urothelial cancer, this approach was extensively explored with a variety of antibodies that blocked PD-1 and/or PD-L1, leading to the approval of several antibodies, such as atezolizumab and pembrolizumab, showing promising clinical activity (De Maeseneer 2017).

1.5. Cetrelimab

1.5.1. Summary of Nonclinical Data

In vitro assays with cetrelimab showed enhanced T cell function and reversed PD-1 mediated suppression of T cell receptor signaling by promoting nuclear factor of activated T cells (NFAT)-reporter transcriptional activity. These findings with cetrelimab were comparable to the observed activities for 2 anti-PD-1 monoclonal antibody analogues for nivolumab and pembrolizumab. In vivo, cetrelimab inhibited tumor growth in human PD-1 knock-in mice bearing MC38 murine colon carcinoma tumors and showed comparable anti-tumor efficacy to a nivolumab analogue.

Toxicology studies in cynomolgus monkeys indicate cetrelimab was well tolerated and the pivotal Good Laboratory Practice 5-week study demonstrated T-dependent antigen responses (TDAR). No cetrelimab -related effects were noted in the cardiovascular, respiratory, or central nervous system during the 5-week study. Primary cetrelimab -related findings noted in 4- and 5-week monkey studies at ≥10 mg/kg/wk included slight increases in blood monocyte counts and prothrombin times, and minor/transient decreases in absolute counts for blood CD3+T, CD3+/CD4+ T-helper, and CD3+/CD8+ T-cytotoxic lymphocytes, increases in the IgM and IgG secondary TDAR response to keyhole limpet hemocyanin antigen challenge, and minimally reduced thymic cellularity (decreased lymphocytes) that were considered not to be toxicologically significant. None of these findings were considered adverse and are anticipated to present low to no clinical risk in humans (eg, reduced thymic cellularity that was minimal in nature and was not associated with a correlative decrease in thymus weight or in thymus-to-body and thymus-to-brain ratios). In the 5-week study, the no-observed-adverse-effect-level was 100 mg/kg/wk (mean C_{max} 3,055.75 µg/mL and $AUC_{Day29-36}$ 12,658.15 µg day/mL following the dose on Day 29). Additionally, cetrelimab did not induce hemolysis in whole human blood and was compatible with

human serum at in vitro concentrations between 0.010 to 10 mg/mL, and the cetrelimab cytokine response in vitro in human blood was similar to other immune-modulatory compounds that have a low risk of cytokine release syndrome.

1.5.2. Summary of Clinical Data

Clinical experience with cetrelimab in humans to date is based on preliminary data from the ongoing first-in-human (FIH) monotherapy study (Study 63723283LUC1001), a multicenter Phase 1/2 study in subjects with advanced solid tumor malignancies. The Phase 1b part of the study, initiated on 21 November 2016, consists of dose escalation cohorts and PK/pharmacodynamic (PD) cohorts. The highest doses administered to date are 800 mg once every 2 weeks (Q2W) and 480 mg once every 4 weeks (Q4W); Part 1 has established a recommended Phase 2 dose (RP2D), which may be administered at either 240 mg (Q2W) or 480 mg (Q4W), based on interim safety, PK, and PD data. In the Phase 2 part of the study, initiated on 03 May 2017, this RP2D is being evaluated in selected solid tumor types including non-small cell lung cancer (NSCLC), melanoma, bladder cancer, renal cancer, small cell lung cancer, and gastric/esophageal cancer. The purpose of dose expansion in the Phase 2 part of the study is to further characterize the safety and to assess the anti-tumor activity.

In September 2017, additional interim safety, PK and PD data to support an alternate regimen (480 mg Q4W) with the same total dose as RP2D of 240 mg Q2W but given with a longer dosing interval was shown to enable flexibility of drug administration in various clinical settings. Selection of the RP2D of 240 mg Q2W and 480 mg Q4W was based on the following:

- No MTD has been identified with administration of doses up to 460 mg Q2W and 480 mg Q4W and doses were well tolerated.
- Cetrelimab demonstrated comparable preclinical in vivo tumor growth inhibition and comparable in vitro activity across various assays as the approved PD-1 inhibitors nivolumab and pembrolizumab. Therefore, similar clinical efficacious target concentrations would be expected for cetrelimab.
- Based on preliminary PK data, the median observed near-steady-state C_{min} for cetrelimab at 240 mg Q2W is 44.8 µg/mL (N=5, trough concentration before the fifth dose). This is comparable to the $C_{min,ss}$ reported for nivolumab (57 µg/mL [CDER Opdivo 2014, CMPH Opdivo 2017]) and pembrolizumab (23 µg/mL[CDER Keytruda® 2014, CMPH Pembrolizomab 2017]) at their approved doses (240 mg Q2W for nivolumab and 2 mg/kg or 200 mg Q3W for pembrolizumab).
- The median steady-state $C_{min,ss}$ for cetrelimab at 480 mg Q4W is expected to be approximately 42 µg/mL, based on an observed median C_{min} after first dose at 30 µg/mL and predicted accumulation ratio of ~1.4 based on preliminary PK modeling. The $C_{min,ss}$ from 240 mg Q2W and 480 mg Q2W is therefore expected to be comparable, and in range with other anti-PD-1 agents nivolumab and pembrolizumab at their approved clinical dose.
- Administration of cetrelimab resulted in saturation of PD-1 RO on circulating CD3+ T cells at all administered doses (80 to 480 mg) and dosing frequencies (Q2W and Q4W).

In addition, a relatively flat dose-response relationship has been demonstrated for 2 approved anti-PD-1 agents (nivolumab or pembrolizumab), suggesting a relatively broad therapeutic window (around 1 mg/kg to 10 mg/kg) for this mechanism of action where various doses and dosing regimens may lead to comparable clinical benefit/risk profile. The RP2D for cetrelimab, therefore, may be administered at either 240 mg Q2W or 480 mg Q4W, ie, same dose level with corresponding dosing frequencies that would result in the same total dose as 240 mg delivered every 2 weeks, while demonstrating acceptable safety as well as providing sufficient PK/PD coverage to ensure RO saturation throughout dosing interval. Investigation of additional dose levels and dosing frequencies (aside from 480 mg Q4W) may continue to be explored as alternative means to deliver the same RP2D (240 mg Q2W) (Investigator's Brochure for JNJ-63723283 2018).

Overall, the safety profile has been similar to that of other anti-PD1 agents (such as nivolumab and pembrolizumab), although a higher percentage of treatment-emergent infusion-related reactions (IRR) have been observed to date. The IRRs were reported for 24 (12.5%) treated subjects; majority were Grade 2 in severity, transient, and resolved with temporary interruption of the infusion and subjects received the full dose. The most frequently reported treatment-emergent IRRs were nausea, back pain, and dyspnea (4 subjects each) and pyrexia (3 subjects). Other events reported as IRRs in more than 1 subject included chills, erythema, rash, rash generalized, vomiting, flushing, and hypertension (based on 03 September 2018 data cut). Most subjects who were reported with IRRs received cetrelimab 240 mg Q2W, with the exception of 1 subject each who received cetrelimab 460 mg Q2W and 480 mg once every 4 weeks, and 2 subjects who received 800 mg Q2W.

In total, as of 03 September 2018, 192 subjects received at least 1 dose of cetrelimab, and of these, 156 subjects were evaluable for response. The ORR (CR+PR) was 15.4%, 2 (1.3%) subjects had a complete response and 22 (14.1%) had a partial response as assessed by the investigator.

As of the pharmacokinetic data cutoff date of 17 May 2018, the preliminary pharmacokinetic analysis included a total of 100 PK-evaluable subjects. Serum concentration data following the first dose of cetrelimab exhibited approximately linear PK. Maximum serum concentration (C_{max}), minimum serum concentration after the first dose (C_{min1}), and area under the curve for 1 dosing interval (AUC_{tau}) increased in an approximately dose-propartal manner from 80 to 800 mg. Interpatient variability was generally consistent with mAb therapeutics. Based on preliminary population PK modeling, the C_{min}, steady-state from 240 mg Q2W and 480 mg Q4W is comparable, and in range with other anti-PD-1 agents such as nivolumab or pembrolizumab at their respective approved clinical dose. In addition, PD-1 receptor occupancy on circulating CD3+ T cells was evaluated in 60 subjects and preliminary results indicated that post-dose saturation occurred throughout dosing interval at all dose levels (ranging from 80 mg to 800 mg) and all dosing frequencies (ranging from Q2W to Q4W).

The RP2D for cetrelimab, therefore, may be administered at either 240 mg Q2W or 480 mg Q4W, ie, same dose level with corresponding dosing frequencies that would result in the same total dose as 240 mg administered Q2W, while demonstrating acceptable safety as well as providing

sufficient PK/PD coverage to ensure RO saturation throughout dosing interval. Investigation of additional dose levels and dosing frequencies (aside from 480 mg Q4W) may continue to be explored as alternative means to deliver the same RP2D (240 mg Q2W) (Investigator's Brochure for JNJ-63723283 2018).

For the Phase 1b erdafitinib + cetrelimab cohort and Arm B in the Phase 2 part of the study, cetrelimab will be dosed at 240 mg Q2W for Cycles 1 through 4 and 480 mg Q4W starting at Cycle 5. For the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, cetrelimab will be dosed at 360 mg Q3W intravenously to align with the dosing frequency of platinum chemotherapy. CCI [redacted]

For the most comprehensive nonclinical and clinical information regarding cetrelimab, refer to the latest version of the Investigator's Brochure and Addenda for cetrelimab.

Erdafitinib in combination with Cetrelimab – Clinical Data from BLC2002

SET endorsement of RP2D

The SET for this study met in January 2019 to review data from DL1 (6 mg daily erdafitinib + 240 mg cetrelimab Q2W). No DLTs were noted, and the SET endorsed the dose escalation to the next dose level DL2A. On 17 May 2019, the SET met to review data from DL2A (8 mg daily erdafitinib with no up-titration + 240 mg cetrelimab Q2W). No DLTs were noted, and the dose level was cleared by the SET. Further, the SET endorsed the dose escalation to the next dose level DL2. On 20 August 2019, the SET met to review data from DL2 (8 mg daily erdafitinib with up-titration + 240 mg cetrelimab Q2W) and endorsed a RP2D of 8 mg erdafitinib orally once a day with up-titration to 9 mg based on C1D15 phosphate level and the dose of 240 mg cetrelimab IV Q2W.

Additional interim safety, PK and PD data to support an alternate regimen (480 mg Q4W) with the same RP2D of 240 mg Q2W of cetrelimab but given with a longer dosing interval enables flexibility of drug administration in various clinical settings. Thus, the dosing of cetrelimab at Cycle 5, is increased to 480 mg Q4W.

As of 08 January 2020, 17 subjects were enrolled in the dose escalation (Phase 1b) part of this ongoing study. All 17 subjects experienced an AE. Nine subjects (52.9%) experienced Grade ≥3 related AEs and 2 (11.8%) experienced serious adverse events (SAEs). Four (23.5%) subjects experienced AEs leading to discontinuation of study drug.

The most common (≥25%) AEs (any Grade) across all dose levels were stomatitis (70.6%), diarrhea (58.8%), dry mouth and hyperphosphatemia (52.9% each), dysgeusia (41.2%), dry skin (35.3%), alopecia, asthenia, and pyrexia (29.4% each). Ocular events including CSR are known class effects of inhibition of the mitogen-activated protein kinase pathway (Chae 2017; Rutkowski 2019). Three of 17 subjects across all doses experienced a CSR event. All events were Grade 2 that resolved to Grade 1 at the time of the data cutoff.

At the RP2D of 8 mg with an up-titration erdafitinib + cetrelimab (n=10), all subjects reported AEs. Six of 10 (60%) subjects experienced related Grade ≥3 AEs. Two of 10 (20%) experienced related serious related AEs. The most common AEs observed were similar to those across all doses. Two of 10 (20%) of the subjects reported a Grade 2 CSR event that had resolved to Grade 1 at the time of the data cutoff.

Forty-one percent of the subjects across all cohorts discontinued erdafitinib + cetrelimab. The majority (n=4) were in the initial dose cohort (6 mg erdafitinib + cetrelimab). The reasons for discontinuation were AE (n=1; urinary tract infection assessed as not related to study drugs), progressive disease (PD) (n=5), and death (n=1; colonic obstruction assessed as not related to study drugs). One subject treated at the RP2D discontinued due to PD.

The objective response rate was 50.0% and disease control rate (DCR) was 93.8% in response-evaluable subjects across all cohorts (n=16). In subjects treated at the RP2D (erdafitinib 8 mg with up-titration + cetrelimab 240 mg [n=9]), the objective response rate was 44.4% and DCR was 100%.

On 12 May 2020, the DRC discussed the requirement for up-titration from Arm B of Phase 2 erdafitinib + cetrelimab combination. Erdafitinib exposure data was reviewed and showed that the median dose intensity of DL2A (8 mg erdafitinib without up-titration + cetrelimab) was 6.14 mg/day, which was higher than the dose intensity of DL2 (8 mg erdafitinib with up-titration + cetrelimab, median 5.65 mg/day). It was postulated that subjects who were up-titrated were experiencing AEs such as stomatitis, which may have caused lengthy dose interruptions and more reductions as compared with non-up-titrated patients. Based on this, the DRC recommended to remove the requirement for up-titration from Phase 2 Arm B to further explore if 8 mg erdafitinib flat dosing could mitigate the incidence of dose reductions and interruptions due to AEs. The DRC also made a recommendation to close Dose level 2 in Phase 1b and focus enrollment efforts into the Phase 2 part of the study. Therefore, DL2 will be closed. DL2B will remain open and will include up-titration of erdafitinib based on serum phosphate concentration from blood sample on Day 15 and the absence of significant erdafitinib-related toxicity on C1D15 as determined by the investigator.

On 11 September 2020, the DRC convened for a scheduled review of the first 20 subjects randomized in the Phase 2 part of the study. The DRC recommendation was to continue the study as planned. Of particular note, the DRC reviewed a case of one subject death in Arm B due to pulmonary failure, which was assessed by the sponsor to be related to cetrelimab and not related to erdafitinib. The DRC noted that identification and early treatment of immune-related AEs (irAEs) are essential in limiting duration and severity. To manage the risk of irAEs, specific risk mitigation measures are included in the study protocol. Subjects with active autoimmune disease or a history of Grade 3 or higher toxicity effects from previous treatment with immunotherapy, are excluded from participating in the study. Management algorithms have been included to provide instructions for study drug interruption or dose delay (Section 6.3.2) and permanent discontinuation (Section 6.3.3) to minimize the risk of irAEs. Algorithms targeted to specific irAEs

such as pulmonary irAEs (Section 6.3.4.7) and gastrointestinal irAEs (Section 6.3.4.1) are also included.

1.6. Platinum Chemotherapy in Metastatic Urothelial Cancer

Platinum-based combination chemotherapy has been the standard of care in the first line treatment of metastatic urothelial carcinoma (mUC) (Bukhari 2017) as defined by current American Joint Committee on Cancer (AJCC) criteria. A cisplatin-based combination chemotherapy regimen is the preferred initial therapy for patients with mUC of the bladder and urinary tract who are cisplatin candidates. Depending on PD-L1 expression, or ineligibility to cisplatin-based treatment, atezolizumab and pembrolizumab are treatment options for some patients with metastatic urothelial cancer. Cisplatin-based combination chemotherapy results in superior survival when compared with single-agent cisplatin. A small proportion of patients with distant metastases in the nodes or lung may be cured by combination chemotherapy. However, cisplatin-related toxicity is a concern for many patients. In addition, not all patients with urothelial cancer are appropriate candidates for cisplatin therapy. For patients who are unable to receive cisplatin due to medical frailty or comorbidities, options include a carboplatin-based regimen (carboplatin plus gemcitabine, or carboplatin, gemcitabine, and paclitaxel), a non-platinum-based combination (eg, paclitaxel plus gemcitabine), immune checkpoint inhibitors, or for patients with select FGFR alterations, erdafitinib. For patients who are otherwise candidates for combination chemotherapy but are unable to receive cisplatin (eg, due to renal dysfunction, neuropathy, severe hearing loss, or heart failure), a combination of gemcitabine plus carboplatin is an alternative as the benefit of carboplatin-based therapy was demonstrated in European Organization for Research and Treatment of Cancer (EORTC) trial 30986 (Bellmunt 2020).

A meta-analysis of randomized controlled clinical trials compared chemotherapy regimens containing either cisplatin or carboplatin in combination with third generation antineoplastic agents including docetaxel, paclitaxel, and gemcitabine. Cisplatin-containing regimens were associated with a median survival of 9.1 months and a 1-year survival probability of 37%, while the carboplatin containing regimens were associated with a median survival of 8.4 months and a 1-year survival probability of 34%. The risk of death was higher with carboplatin compared with cisplatin, although the difference was not statistically significant (HR=1.07, 95 % CI: 0.99 – 1.15, p=.100). These data support the interchangeable use of carboplatin or cisplatin in combination with standard of care antineoplastic agents (Ardizzoni 2007).

The pharmacokinetics and pharmacodynamics of cisplatin and carboplatin have been extensively studied. Monoexponential decreases and plasma half-lives of about 0.5 hour are seen following 2-hour or 7-hour infusions of 100 mg/m^2 of cisplatin (Food and Drug Administration [FDA] label). Plasma levels of carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 mg/m^2 to 500 mg/m^2, with an initial plasma half-life (alpha) of 1.1 to 2 hours (n=6) and a post-distribution plasma half-life (beta) of 2.6 to 5.9 hours (n=6). Cisplatin and carboplatin are mainly eliminated via urine, and there is little evidence to date that either undergoes enzymatic biotransformation

Despite initial high response rates with conventional cisplatin-based chemotherapy regimens, 5-year survival is suboptimal at 5% to 20% and associated with cumulative toxicities with longer exposure. Targeted therapy and checkpoint inhibitors have established a definite role in mUC, however subjects often progress quickly and could benefit from the addition of platinum-based chemotherapy.

Combining platinum-based chemotherapy with a PD-1 therapy has been shown to improve progression-free survival in patients with metastatic urothelial cancer; however there still remains room for improvement. PD-1 agents alone have not shown adequate disease control without combining with chemotherapy. Although platinum-based chemotherapy remains a good option for patients, the cumulative toxicity of treatment with agents such as cisplatin or carboplatin can also prove difficult in managing a positive benefit/risk ratio.

1.7. Overall Rationale for the Study

Rationale for combining erdafitinib with cetrelimab

Several observations point to the potential for CCI [redacted]. These include the potential for CCI [redacted].

Urothelial carcinoma exhibits the third-highest mutation rate of all studied cancer types, behind NSCLC and melanoma (Alexandrov 2013). High tumor mutation burden is predicted to correlate with response to immunotherapies, due to the generation of neoantigens which may be recognized by the immune system. Recently, checkpoint inhibitors including atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab have been approved for treatment of advanced urothelial carcinoma, with observed response rates of ~13-30%. Despite these improvements, however, most patients fail to benefit from checkpoint inhibition.

The response to checkpoint inhibitors is largely dependent on an existing anti-tumor T cell response, including sufficient T cell infiltration in the tumor microenvironment (Harlin 2009). However, not all urothelial cancers exhibit high T cell infiltration. A report classified the microenvironment of urothelial carcinoma tumors as T-cell-inflamed versus non-T-cell-inflamed. FGFR mutations were significantly enriched in the non-T-cell-inflamed group, with no FGFR pathway alterations identified in T-cell-inflamed samples (Sweis 2016). Differential response to immunotherapies have been observed in urothelial carcinoma based on bladder cancer molecular subtype, and the underlying immune landscape of these subtypes. Urothelial cancer, like breast cancer, can be classified via gene expression signature into luminal and basal subtypes (luminal 1, 2, or basal 3, 4) (Cancer Genome 2014). Luminal 1 tumors are reported to be enriched for FGFR3 mutations, and lacking in immune marker expression and immune cell infiltrate (Choi 2017). The luminal 1 subtype showed the lowest response rate to the anti-PD-(L)1 inhibitors atezolizumab and nivolumab compared with other bladder cancer subtypes (Rosenberg 2016); (Sharma 2017). Analyses of atezolizumab Phase 2 data showed PD-L1 expression on tumor infiltrating immune

cells was more pronounced in the basal subtype compared with the luminal subtype, with response to atezolizumab lowest in the luminal 1 group (Rosenberg 2016).

CCI [redacted]. This is consistent with the preliminary observation that patients with CCI [redacted]

CCI [redacted] Some agents may affect the expression of checkpoint inhibitory molecules such as PD-L1 on tumor cells or sensitize the tumor to immune-mediated killing via alternate mechanisms. The BRAF inhibitor vemurafenib has been shown to increase expression of tumor antigens gp100 and MART1, increase tumor T cell infiltration, and decrease tumor secretion of immunosuppressive cytokines, and PD-L1 expression (Hughes 2016); (Vanneman 2012). In a preclinical model of breast cancer, treatment with the FGFR1 inhibitor PD173074 resulted in increased CD4+ and CD8+ T cell and decreased myeloid derived suppressor cell (MDSC) infiltration in tumors (Ye 2014). These data suggest CCI [redacted]

To inform the combination strategy of erdafitinib with a checkpoint inhibitor, the activity of erdafitinib alone or in combination with anti-PD-1 was assessed in a genetically engineered mouse model of lung cancer harboring mutations in FGFR and p53 ($FGFR2^{K660N}/p53^{R270H}$) (Palakurthi 2019). Vehicle control animals succumbed to disease after a median of 10.2 weeks, with anti-PD-1 treatment showing no benefit in this FGFR-mutant model (median survival of 9.7 weeks). Erdafitinib treated animals survived a median 13.4 weeks, while the combination of erdafitinib plus anti-PD-1 prolonged survival to a median of 19.7 weeks (n=8 animals per group; $p<0.0005$ for the combination versus control, and $p<0.004$ for the combination versus erdafitinib alone, log rank test). Treatment with erdafitinib alone led to increased infiltration of CD4+ and CD8+ T cells in tumor ($p=0.0233$, and $p=0.0008$ versus vehicle, respectively), with concomitant decreases in the expression of the cell exhaustion markers Tim-3 and Lag-3 on CD8+ T cells ($p=0.0171$ versus vehicle). A decrease in the number of Tregs (Foxp3+/CD25+) in tumors was also observed ($p=0.0191$ versus vehicle). CCI [redacted].

These results support the hypothesis that CCI [redacted] in this setting.

Rationale for addition of platinum (cisplatin or carboplatin) chemotherapy to erdafitinib and cetrelimab

Once diagnosed with metastatic disease, it is important for patients with urothelial cancer to initiate treatment without delay. The addition of platinum (cisplatin or carboplatin) chemotherapy to the erdafitinib/cetrelimab regimen presents a viable option for patients to treat metastatic disease immediately until targeted therapies and immunotherapies can demonstrate a response on their disease. It may also be less toxic as compared with multiple agent combination chemotherapy(ies).

Combining platinum (cisplatin or carboplatin) chemotherapy with targeted therapy and checkpoint inhibition may provide benefit to patients given the high response rate to chemotherapy in first line treatment, regardless of FGFR status. The addition of targeted therapy may deepen and lengthen that response.

Rationale for treatment in 1L mUC (Phase 2)

The management of metastatic urothelial cancer is driven by the global status of the patient including factors like ECOG PS Grade (0-1 versus 2), renal function (creatinine clearance [CrCl] ≥60ml/min/1.73 m^2 versus CrCl <60 ml/min/1.73 m^2) and presence of comorbidities (eg, hearing loss, cardiac dysfunction). Renal function for cisplatin-eligible patients is typically defined as CrCl ≥60mL/min/1.73 m^2 versus cisplatin-ineligible CrCl <60 ml/min/1.73 m^2 (Dogliotti 2007). Additionally, Grade 2 or higher hearing loss, ECOG PS of 2, or Grade 2 or higher peripheral neuropathy would also typically deem a patient ineligible for cisplatin (Galsky 2011). The global standard of care for both cis-eligible and cis-ineligible groups is combination chemotherapy. The standard of care for cisplatin-ineligible patients, includes combination chemotherapy of carboplatin and gemcitabine which has demonstrated an ORR of 39% for patients that have either ECOG 2 or CrCl <60 ml/min/1.73 m^2, 26% for patients with both factors and 20% when adding the risk factor of visceral metastasis. Median PFS for cisplatin-ineligible patients is approximately 3 months (Dogliotti 2007). Significant hematologic toxicity is observed with both gemcitabine/cisplatin and gemcitabine/carboplatin chemotherapy regimens; Grade 3-4 neutropenia occurs in 34-45% of patients (Dogliotti 2007). Additionally, the risk of nephrotoxicity makes these therapies undesirable in up to half of patients with mUC who have concurrent renal insufficiency (Rosenberg 2005).

Erdafitinib monotherapy demonstrated efficacy in a subset of mUC patients without prior systemic therapy treated in a separate Phase 2 Global Open-Label Study 42756493BLC2001 of the efficacy and the safety of erdafitinib in subjects with metastatic or surgically unresectable urothelial cancer with FGFR genomic alterations (Loriot 2019). In that study, 10 cisplatin-ineligible patients with urothelial cancer who had no prior lines of systemic therapy in the metastatic setting were enrolled. In these 10 patients, median progression-free survival was 9.82 months (95% confidence interval [CI]: 1.38, 15.90) and median overall survival was 18.14 months (95% CI: 8.74, not evaluable). This efficacy with erdafitinib is comparable with standard front-line chemotherapy combination treatments albeit with fewer hematologic toxicities. The median overall survival was 13.8 months (95% CI, 12.3, 15.8) with gemcitabine and cisplatin and 14.8 months (95% CI, 13.2, 16.8) with

MVAC (Von der Maase 2000). In another study, median survival was 15.1 months on HD-MVAC and 14.9 months on M-VAC (Sternberg 2006). With gemcitabine and carboplatin, a median OS of 9.3 months has been reported (DeSantis 2012). Among all mUC patients, irrespective of PD1 status, a median overall survival of 15·9 months (95% CI, 10.4, not estimable) with atezolizumab (Balar 2017) and a median OS of 11.5 months (95% CI, 10.0, 13.3) with pembrolizumab (Balar 2018) have been reported.

Based on the above data from BLC2001, cisplatin-ineligible patients with select FGFR alterations without prior systemic therapy are anticipated to have a beneficial effect from erdafitinib monotherapy. The combination of erdafitinib + cetrelimab (Arm B) is designed to estimate if and how much additive efficacy effect may be obtained with comparable or additional safety events. CCI [redacted].

Randomization in Phase 2 helps in reducing bias when interpreting the efficacy and safety data in each arm. Analyses of safety and efficacy will be performed by each arm when there are approximately 90 response-evaluable subjects randomized in Phase 2. In the interim, a Data Review Committee consisting of experts internal and external to Janssen will monitor Phase 2 data on an ongoing basis.

Pembrolizumab and atezolizumab received accelerated approval in the 1LmUC cisplatin-ineligible population-based on single arm studies. In the IMvigor 210 study the ORR was 23% with PFS 2.7 months. A similar ORR with pembrolizumab was observed in KEYNOTE-52 with a higher ORR in patients with higher PD-L1 expression. A recent review of ongoing 1L studies for both pembrolizumab and atezolizumab monotherapy indicated that pembrolizumab and atezolizumab may not work as well as chemotherapy in cisplatin-ineligible patients whose tumors have low expressions of PD-L1. As a result, the US FDA and European Medicines Agency (EMA) restricted the use of pembrolizumab and atezolizumab in first line setting for patients who are cisplatin-ineligible to patients whose tumors have high PD-L1 expression. Another anti-PD1, durvalumab, which had received an accelerated approval from the FDA, missed its primary end points in the confirmatory Phase 3 DANUBE trial in frontline urothelial cancer and had to be withdrawn from this indication.

Henceforth, the effect of monotherapy check-point inhibitors in frontline urothelial cancer is limited to a smaller subset of patients, and additional treatment options are needed. Currently there are a number of ongoing studies combining PD-L1 antibody therapy with chemotherapy, specifically gemcitabine and cisplatin, and also immunotherapy combination studies involving PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies in 1L mUC. New treatment options are needed in 1L mUC for the cisplatin-ineligible patient population with FGFR alterations.

1.8. Anticipated Benefits and Risks

Bladder cancer is the most common malignancy involving the urinary system with often limited OS in the metastatic setting. Despite the introduction of cisplatin-containing chemotherapy regimens, specifically cisplatin-gemcitabine and the MVAC regimen, nearly half of the subjects are ineligible leading to very poor survival rates in this unfit subject population due to high toxicity of cisplatin-containing regimens. Therefore, novel therapeutic options are required for the treatment of this subject population, specifically in the metastatic setting, representing an area of high unmet medical need.

1.8.1. Anticipated Benefits and Risks for Erdafitinib and Cetrelimab

Erdafitinib showed anti-tumor effect in subjects with urothelial cancer with select FGFR alterations. In the Phase 1 study (Study 42756493EDI1001, N=187), the anti-tumor effect of erdafitinib was observed in subjects with urothelial cancer with select FGFR alterations, as well as other solid tumors. For all subjects with relapsed/refractory urothelial cancer, the ORR across dose levels was 40.0% (12/30 subjects). At the 9 mg dose level, the ORR was 70.0% (7/10 subjects) for response-evaluable subjects with urothelial cancer who harbored select FGFR alterations. The global Phase 2 study (Study 42756493BLC2001) enrolled and treated subjects with select FGFR mutations and fusions with chemo-refractory and chemo-naïve advanced urothelial cancer who are ineligible for cisplatin (N= 210). The confirmed ORR by investigator assessment (CR+PR), 40.4% in the 8 mg once daily regimen. For subjects in the 8 mg once daily regimen whose dose was increased to 9 mg, the ORR was 48.4%. Response to erdafitinib was independent of age, sex, and baseline disease characteristics such as hemoglobin level or renal function. Subjects in the erdafitinib Phase 2 Study BLC2001 with a baseline CrCl less than 60 mL/min (n=41) who received 8 mg erdafitinib daily (QD) had an ORR of 39%. Eleven subjects received no prior lines of therapy. The ORR for this group of subjects receiving erdafitinib as their first line of therapy (N=11) was 36%, and the disease control rate (CR+PR+SD) was 82%.

Based on data from Study BLC2001 erdafitinib was approved by the United States Food and Drug Administration (USFDA) in April 2019 for use in adult patients with metastatic urothelial carcinoma which has susceptible FGFR3 or FGFR2 genetic alterations and have progressed during or following at least one line of prior platinum-containing chemotherapy.

As of the clinical cutoff of 09 August 2019, the median follow-up for 101 subjects treated in the erdafitinib 8 mg regimen in Study 42756493BLC2001 was ~24 months. The median DoR was 5.98 months. Thirty-one percent of responders had DoR ≥1 year. The median PFS was 5.52 months. The median OS was 11.3 months. The 12 and 24-month survival rates were 49% and 31%, respectively. Median treatment duration was 5.4 months.

As of 15 Jan 2019, in the FIH study 63723283LUC1001, 146 patients treated at the RP2D dose (240 mg Q2W) for cetrelimab were evaluable for response (Response evaluation criteria in solid tumors [RECIST] 1.1 per investigator assessment). More than half of this group was comprised of patients with advanced melanoma (n=50) and non-small cell lung cancer (NSCLC; n=30). Other tumor types enrolled to the study included high levels of microsatellite instability/deficient mismatch repair (MSI-H/dMMR) colorectal cancer (CRC) (n=41), gastric esophageal (10), small

cell lung (n=9), bladder (n=4) and renal (n=1). The ORR was 50% (80% confidence interval [CI] 33-67) in patients with PD-L1-high NSCLC (n=18) and 55% (80% CI 32-76) in patients with ≥1% PD-L1-positive melanoma (n=11), consistent with the ORRs observed in approved PD-L1 inhibitors (Rutkowski 2019). In both of those groups more than half of the response-evaluable subjects obtained clinical benefit (CR+PR+SD) for more than 6 months (67% and 73%, respectively). At the time of the data cut one of the bladder cancer patients was considered to have a response per the immune-related response criteria (Wolchok 2009), although was considered PD per RECIST 1.1.

Immune checkpoint inhibitors, such as anti-PD-1 monoclonal antibodies, target proteins that enhance the response of the immune system to tumor cells. By stimulating the endogenous immune system, however, there is the potential for adverse effects on other tissues by way of immune cell activation and inflammatory mechanisms. Treatment with anti-PD-1 monoclonal antibodies have been linked to irAEs which require close and more frequent monitoring, and early intervention such as administration of immunosuppressants. Immune-related endocrinopathies such as hypothyroidism and adrenal insufficiency may require endocrine replacement therapy. Other immune-related risks already identified with other PD-1 antibodies include gastrointestinal AEs such as colitis and diarrhea, pneumonitis, renal AEs such as nephritis and acute renal failure, hepatic AEs such as hepatitis and liver enzyme elevations, and dermatitis. The safety profile of currently approved anti-PD-1 antibodies (eg, atezolizumab and pembrolizumab), is manageable with most AEs being Grade 1 or Grade 2 in severity. Immune-related AEs typically resolve after systemic treatment with corticosteroids or discontinuation of study treatment.

In the FIH study 63723283LUC1001, treatment with cetrelimab showed overall similar toxicity profile when compared to already approved compounds targeting the PD-1/PD-L1 pathway. Treatment with erdafitinib in the Phase 1 (Study 42756493EDI1001) and a Phase 2 trial (Study 42756493BLC2001) was linked to hyperphosphatemia, diarrhea, dry mouth, asthenia, stomatitis, constipation, and decreased appetite as the most frequently reported AEs, most of which were Grade 1 or 2 in severity and treatment was well tolerated.

Based on currently available clinical data from erdafitinib and cetrelimab as monotherapies as well as preliminary data from this study in Section 1.5.2, the safety profiles for erdafitinib and cetrelimab are anticipated to remain manageable. Given the potentially complementary mechanisms of action of erdafitinib and cetrelimab (PD-1 inhibitor), it is hypothesized that this combination will provide increased efficacy relative to either agent alone in patients with urothelial cancer. As stated in Section 1.5.2 no DLTs were observed in any of the cohorts and the recommended Phase 2 dose (RP2D) was established as 8 mg erdafitinib orally once a day with up-titration to 9 mg based on C1D15 phosphate level + 240 mg cetrelimab IV Q2W.

After the RP2D was determined, the DRC met (ad hoc) at the request of the sponsor to review safety data as of 08 January 2020 with a particular focus on stomatitis at the RP2D. At that time stomatitis occurred in 70% of patients (7/10) at the RP2D which was higher than the frequency with erdafitinib monotherapy. The average time to onset was approximately 20 days which was sooner than that for erdafitinib monotherapy. The majority of patients experiencing mucositis at

the RP2D required dose interruption. The DRC concluded that additional data was required to further evaluate the benefit-risk profile of the RP2D.

The DRC reconvened on 12 May 2020. Based on emerging safety data, the DRC recommended to remove the requirement for up-titration from the RP2D of the erdafitinib + cetrelimab combination (See Section 1.5.2). It was postulated that subjects who were up-titrated may be experiencing more frequent or more severe AEs such as stomatitis, which may have contributed to dose interruptions and reductions as compared with non-up-titrated subjects. The DRC further concluded that the removal of up-titration may allow for better management of AEs and therefore increased dose intensity and adherence to study treatment. The DRC also made a recommendation to close the Phase 1b DL2 cohort to focus enrollment efforts into the Phase 2 part of the study. Dose Level 2B will remain open and include up-titration of erdafitinib based on phosphate and absence of significant erdafitinib-related toxicity on C1D15 as determined by the investigator.

This study will continue to monitor safety closely to ensure resolution of the anticipated erdafitinib and cetrelimab toxicities. These considerations strongly support the conduct of this study in an effort to improve the treatment outcomes for eligible subjects with urothelial cancer.

For this study, based on the mechanism of action, potential risks and mitigation strategies are outlined in Table 3 based on experience following administration of erdafitinib and cetrelimab.

Table 3: Potential Risks and Mitigation Strategies Associated With Erdafitinib and Cetrelimab

Potential Risk	Mitigation Strategies (Specific Guidance related to Potential Risk Locations)
Specific Erdafitinib Toxicities	
Elevated phosphate levels	Section 6.2.3.2.
Dry mouth and stomatitis	Section 6.2.3.3.
Dry skin and skin toxicity	Section 6.2.3.4.
Nail toxicity	Section 6.2.3.5.
Eye toxicity associated with vision changes	Section 6.2.3.6.
Dry eye	Section 6.2.3.7.
Specific Cetrelimab Toxicities	
Gastrointestinal AEs	Section 6.3.4.1.
Hepatic AEs	Section 6.3.4.2.
Endocrinopathies	Section 6.3.4.3.
Rash	Section 6.3.4.4.
Renal AEs	Section 6.3.4.5.
Neurological AEs	Section 6.3.4.6.
Pulmonary AEs	Section 6.3.4.7.
Uveitis and visual complaints	Section 6.3.4.8.
Lipase/amylase elevations	Section 6.3.4.9.
Infections	Section 6.3.4.10.
Infusion-related reactions	Section 6.3.4.11.

Abbreviations: AE = adverse event

1.8.2. Anticipated Benefits and Risks for Platinum Chemotherapy

The addition of platinum (cisplatin or carboplatin) chemotherapy is anticipated to affect both the efficacy and safety, and hence the benefit-risk profile of the study treatment in the Phase 1b

erdafitinib + cetrelimab + platinum chemotherapy cohort. In the first line patients with metastatic urothelial cancer, platinum-based chemotherapies are standard of care, and have AE profile consistent with 2 or more chemotherapeutic agents. Cisplatin-ineligible first line patients are treated with other chemotherapy combinations, some including carboplatin, or with approved PD1-inhibitors. In patients diagnosed with metastatic disease, the addition of platinum chemotherapy could provide a shorter time to response, to give time for targeted therapies and immunotherapies to demonstrate a response on their disease. A combination of cisplatin/carboplatin, cetrelimab and erdafitinib is anticipated to provide a comparable or better efficacy than platinum-based chemotherapy (combination of 2 chemotherapies) or PD-1 inhibitor monotherapy in first line setting.

Platinum chemotherapies (cisplatin or carboplatin) are known to have similar but varying frequency of AEs such as thrombocytopenia, leukopenia, anemia, vomiting, nausea, nephrotoxicity, neurotoxicity and ototoxicity, when used as monotherapies. Although erdafitinib, cetrelimab and platinum chemotherapies predominantly have non-overlapping toxicities, platinum chemotherapies are also associated with a number of electrolyte disorders, including hypophosphatemia (Oronsky 2017). Possible mechanisms of hypophosphatemia in platinum-treated patients include increased renal excretion due to tubular dysfunction, other electrolyte disorders (magnesium, calcium), deprivation due to cachexia, vomiting and diarrhea. The frequency of hypophosphatemia in advanced cancer patients can be high, with as many as 49.4% of patients experiencing phosphate levels <2.5 mg/dL and 22.9% of patients experiencing phosphate levels <2.0 mg/dL (Yoshida 2017). Erdafitinib, on the other hand, induces hyperphosphatemia. For erdafitinib, serum phosphate increase is a biomarker of target engagement as well as an expected AE. PD interactions are expected between erdafitinib and platinum chemotherapy, as both have opposite effect on serum phosphate. PD assessments will be characterized in this study to quantify the PD interaction between erdafitinib, cetrelimab, and platinum chemotherapies.

In conclusion, the benefit-risk balance with the addition platinum chemotherapies is anticipated to be favorable.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

The primary, secondary, and exploratory objectives and endpoints for the Phase 1b erdafitinib + cetrelimab cohort are described in Section 2.1 of Appendix 1.

The primary, secondary, and exploratory objectives and endpoints for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort are described in Section 2.1 of Appendix 2.

The primary, secondary, and exploratory objectives and endpoints for the Phase 2 erdafitinib +/- cetrelimab cohort of the study are described in Section 2.1 of Appendix 3.

2.2. Hypotheses

The hypothesis for the Phase 1b erdafitinib + cetrelimab cohort is described in Section 2.2 of Appendix 1.

The hypothesis for the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort is described in Section 2.2 of Appendix 2.

The hypothesis for the Phase 2 erdafitinib +/- cetrelimab cohort of the study is described in Section 2.2 of Appendix 3.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This study is an open-label, multicenter, Phase 1b-2 study to establish the RP2D for erdafitinib in combination with cetrelimab +/- platinum (cisplatin or carboplatin) chemotherapy, and the safety of erdafitinib in combination with cetrelimab and platinum chemotherapy in Phase 1b, and to evaluate the safety and efficacy of the RP2D of erdafitinib + cetrelimab versus erdafitinib in Phase 2, in subjects with advanced urothelial cancer with select FGFR gene alterations.

An overview of dose levels of the Phase 1b erdafitinib + cetrelimab cohort and Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort is described in Figure 1 and Figure 2, respectively. An overview of the Phase 2 dose expansion cohort is described in Figure 3.

Subjects enrolled in the Phase 1b erdafitinib + cetrelimab cohort may have received any number of lines of prior therapy, subjects enrolled in Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort will have had no prior systemic therapy for metastatic disease, and subjects enrolled in Phase 2 will have had no prior systemic therapy for metastatic disease and will be cis-ineligible (see the Inclusion Criteria 6.1 in Section 4.1). All subjects will undergo molecular testing during Screening to assess for select FGFR alterations (as defined in Table 4).

Table 4: Molecular Eligibility Based Upon the Following FGFR Alterations [a, b]

1 of the following fusions:			**1 of the following *FGFR3* gene mutations:**	
FGFR2-BICC1	FGFR2-CASP7	**OR**	R248C	S249C
FGFR3-TACC3	FGFR3-BAIAP2L1		G370C	Y373C

[a] Phase 1b erdafitinib + cetrelimab cohort and Phase 2 erdafitinib +/- cetrelimab cohort: tumors must have at least one gene fusion or gene mutation as defined above.

[b] Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: up to 3 subjects in each erdafitinib + cetrelimab + chemotherapy cohort at each dose level will be wild-type. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations as defined above. All other subjects must have at least one select FGFR alteration as defined above.

Tissue provided at Screening will be used to assess CCI [redacted] (exploratory). The study consists of 2 parts: Phase 1b, which is a dose escalation part to identify the safety and RP2Ds of erdafitinib + cetrelimab and erdafitinib

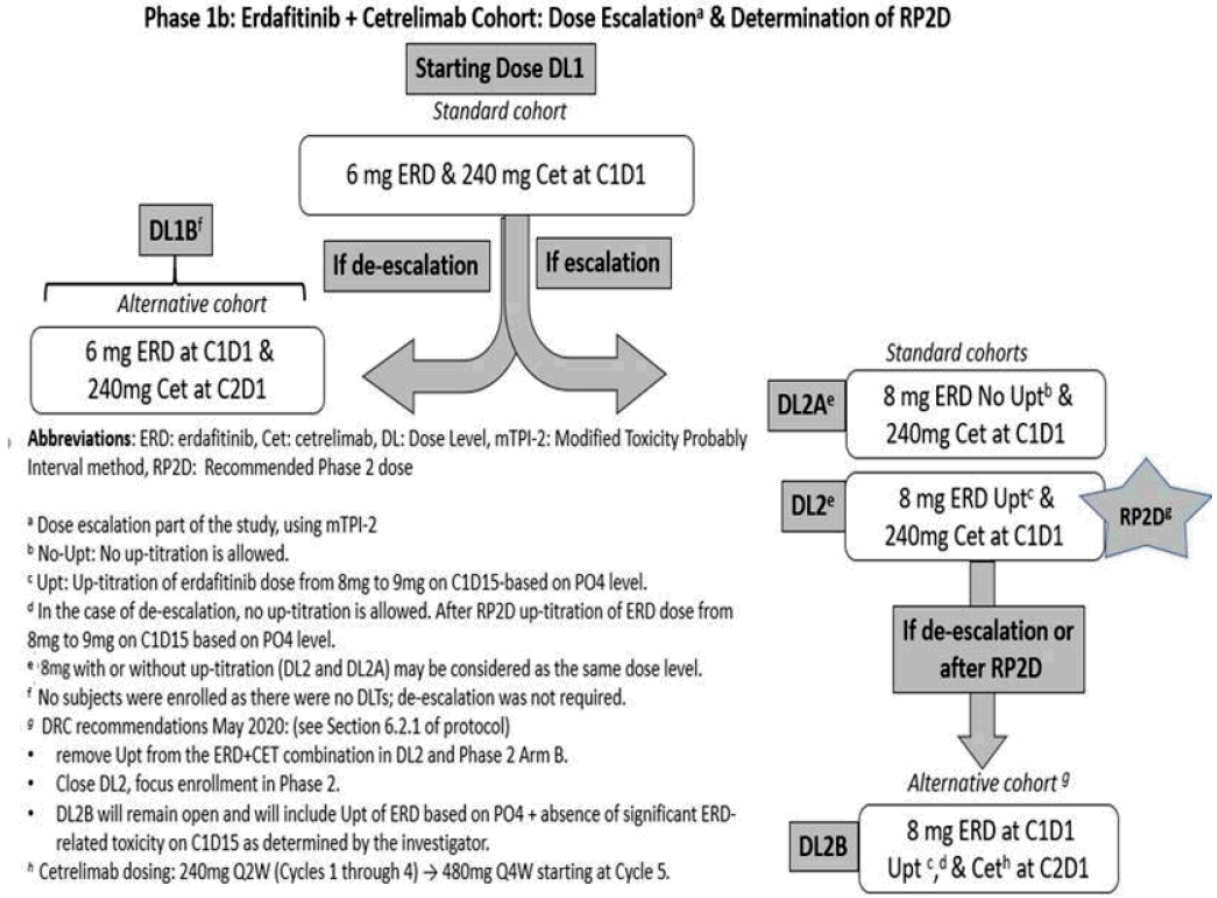
+ cetrelimab + platinum (cisplatin or carboplatin) chemotherapy, and Phase 2, which is a dose expansion part in which the erdafitinib monotherapy and the RP2D regimen of the erdafitinib + cetrelimab combination are evaluated to further characterize safety and clinical activity. In Phase 2, subjects will be randomized at a 1:1 ratio for treatment with erdafitinib monotherapy (Arm A) or with the erdafitinib + cetrelimab combination therapy (Arm B). Randomization will be stratified by ECOG PS (0-1 versus 2). A target of approximately 90 subjects will be enrolled in Phase 2, with the potential to enroll approximately 160 overall subjects in the study depending on the dose levels studied in Phase 1b.

Paired biopsies at Screening and C2D1 are optional. The biopsy upon PD is also optional for all subjects. High-risk areas of metastases such as brain, pancreas, and lung should not be considered as an accessible site for biopsy. Biopsies will be collected to aim to have a minimum of 15 evaluable biopsy pairs.

Subject participation will include: Screening Phase (detailed in Section 9.1.2), during which subject eligibility (including molecular eligibility) will be reviewed prior to administration of the first dose of erdafitinib in combination with cetrelimab, and platinum chemotherapy (where applicable); a Treatment Phase (detailed in Section 9.1.3) that will start at the first dose and continue until treatment is discontinued (as defined in Section 10.2); and a Follow-up Phase (detailed in Section 9.1.4). The end of the study is defined as the last study assessment for the last subject on study or if the sponsor terminates the study, whichever comes first (see Section 17.9).

3.1.1. Phase 1b

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



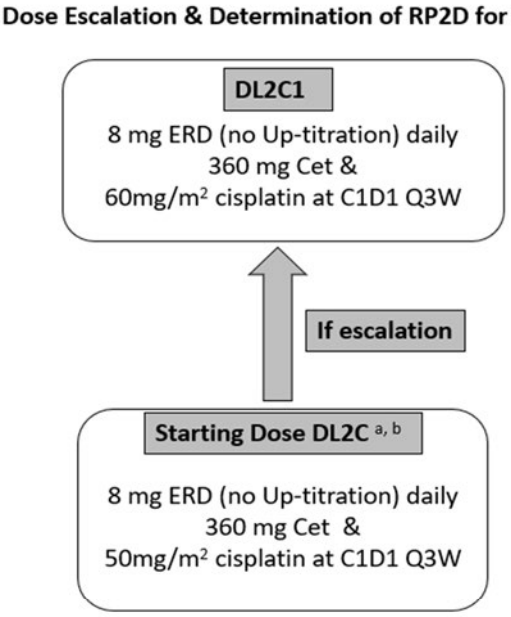
Abbreviations: ERD: erdafitinib, Cet: cetrelimab, DL: Dose Level, mTPI-2: Modified Toxicity Probably Interval method, RP2D: Recommended Phase 2 dose

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

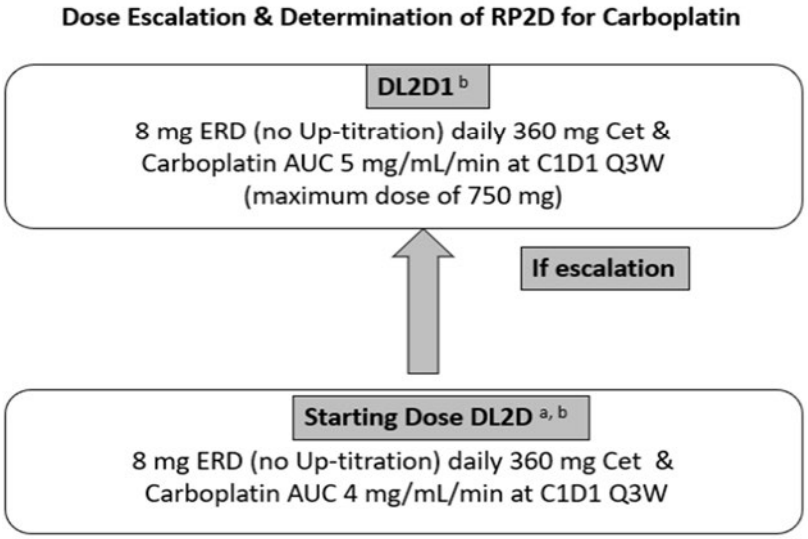
[h] Cetrelimab dosing: 240mg Q2W (Cycles 1 through 4) → 480mg Q4W starting at Cycle 5.

Refer to Section 3.1.1 of Appendix 1 for additional information regarding the study design of the Phase 1b erdafitinib + cetrelimab dose levels. Refer to Section 6.2.1 for a description of the erdafitinib dose titration guidelines.

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



Abbreviations: ERD: erdafitinib, Cet: cetrelimab, DL: Dose Level, RP2D: Recommended Phase 2 dose
[a] Dose escalation part of the study, using a Modified Toxicity Probably Interval method, mTPI-2
[b] Erda + cet will continue every 3 weeks after a maximum of 4 cycles of chemotherapy unless discontinuation criteria as indicated in Section 10.2 are met.

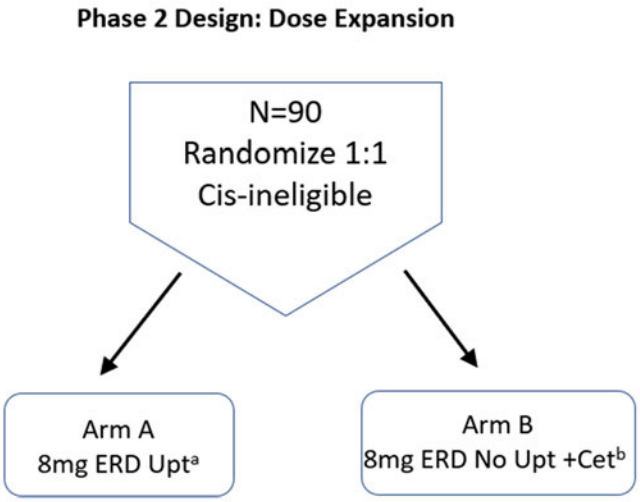


Abbreviations: ERD: erdafitinib, Cet: cetrelimab, DL: Dose Level, RP2D: Recommended Phase 2 dose
[a] Dose escalation part of the study, using a Modified Toxicity Probably Interval method, mTPI-2
[b] Erda + cet will continue every 3 weeks after a maximum of 4 cycles of chemotherapy unless discontinuation criteria as indicated in Section 10.2 are met.

Refer to Section 3.1.1 of Appendix 2 for additional information regarding the study design of the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort.

3.1.2. Phase 2

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.

Refer to Section 3.1.2 of Appendix 3 for additional information regarding the study design of the Phase 2 erdafitinib +/- cetrelimab (Dose expansion) cohort.

3.1.3. Schedule of Activities for All Ongoing Subjects After the End of Study Data Collection Timepoint (Protocol Amendment 5)

Following Amendment 5, once the end of study data collection timepoint has been achieved, subjects who continue to benefit from study treatment(s), as determined by their investigator, may continue to receive access to study treatment(s) on this study, with reduced data collection (see Section 17.9.1), either via a long-term extension roll-over study or any other post-trial access program, when permitted by local regulations. Provision may continue until the subject can commercially access study treatment(s) within the local healthcare system, until a decision is made not to pursue the studied indication, until the investigator decides it is in the best interest of the subject that study treatment(s) be discontinued, or until 2 years after local marketing authorization for is obtained for the studied indication, whichever comes first.

3.2. Study Design and Starting Dose Rationale

Rationale for Erdafitinib Dose and Regimen Selection

The recommended monotherapy dose for erdafitinib is based on clinical activity and safety data in the Phase 2 urothelial cancer study 42756493BLC2001 and subsequent PK/PD modeling.

Rationale for Cetrelimab Dose and Regimen Selection

CCI [redacted]

CCI

CCI

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CCI

Rationale for Combination of Erdafitinib and Cetrelimab

The study design is intended to test the hypothesis that the combination of erdafitinib with cetrelimab will lead to an improved anti-tumor effect with an overall favorable toxicity profile. As described in Section 1.8.1, these data indicate that erdafitinib monotherapy, as reported for other

CCI

The results of a study of an FGFR-mutant mouse model CCI

.

Rationale for Combination of Erdafitinib, Cetrelimab, and Platinum Chemotherapy

The addition of platinum (cisplatin or carboplatin) chemotherapy to the erdafitinib/cetrelimab regimen presents a viable option for patients to treat metastatic disease immediately until targeted therapies and immunotherapies can demonstrate a response on their disease.

Combining platinum chemotherapy with targeted therapy and checkpoint inhibition may provide benefit to patients given the high response rate to chemotherapy in first line treatment, regardless of FGFR status. The addition of targeted therapy may deepen and lengthen that response rate.

Rationale for the Subject Population

In this study, erdafitinib is approved by the USFDA for use in adult patients with locally advanced or metastatic urothelial carcinoma which has susceptible FGFR3 or FGFR2 genetic alterations and have progressed during or following at least one line of prior platinum-containing chemotherapy.

In the erdafitinib Phase 2 Study BLC2001, response to erdafitinib in patients with locally advanced or metastatic urothelial carcinoma was independent of age, sex, and baseline disease characteristics such as hemoglobin level or renal function. Response was also consistent regardless of the number of lines of prior systemic therapy; chemo-relapsed/refractory subjects with 1 or 2 or more lines of prior systemic therapy all responded to erdafitinib treatment. ORRs by investigator for subjects who received prior systemic therapy ranged from 36% to 60% and DCR by investigator ranging from 75% to 90% by number of prior systemic therapy lines. Subjects in Study BLC2001 with a baseline CrCl less than 60 mL/min (n=41) who received 8 mg erdafitinib QD had an ORR of 39%. Eleven subjects received erdafitinib as first line therapy in Study BLC2001. The ORR for this group of subjects was 36% (95% CI 7.9, 64.8), and the disease control rate (CR+PR+SD) was 82% (95% CI 59, 100). This supports the hypothesis that patients with FGFR alterations may benefit from first line treatment with erdafitinib. CCI [redacted]

Progress has been made in the clinical management of urothelial cancer by establishing comprehensive, multi-modality treatment regimens; however, the prognosis for advanced disease has not improved substantially. Cytotoxic chemotherapies as single agents or in combination with PD-1 have made advances for this patient population, however molecular profiling has established a definite role for therapy in a subset in mUC patients. In patients diagnosed with metastatic disease, the addition of platinum chemotherapy could provide a shorter time to response, to give time for targeted therapies and immunotherapies to demonstrate a response on their disease. There is an interest in determining if the combination of erdafitinib (targeted therapy), in combination with cetrelimab (PD-1) and cisplatin/carboplatin chemotherapy demonstrates clinical activity.

Rationale for Biomarker Collection

The biomarker assessments will evaluate the CCI [redacted] Based on data from single-agent studies, blood and tumor samples will be collected to explore biomarkers CCI [redacted]

Rationale for PK and PD Assessment

Potential for PK-mediated drug-drug interaction:

Due to the lack of common elimination pathways, no relevant PK interactions are expected between erdafitinib and cetrelimab. The PK assessments of both drugs will be characterized in this study to confirm the consistency of systemic exposure of the 2 compounds given in combination with those obtained following the single-agent administrations.

Since platinum-based chemotherapies are not eliminated by CYP enzymes but mainly via renal excretion, and are not perpetrators of CYP enzymes, the risk of enzyme-based drug-drug interaction (DDI) between erdafitinib and these platinum chemotherapy agents is low. Based on

in vitro studies, erdafitinib could be a potential inhibitor of OCT2 transporter (USPI). Since both cisplatin and carboplatin are substrates of OCT2, the potential transporter-based DDI between erdafitinib and these chemotherapy agents need to be characterized.

Interaction between platinum chemotherapy agents and cetrelimab is expected to be low given the different elimination pathway. Conversely, chemotherapy agents are not expected to affect cetrelimab clearance, which is mainly governed by protein catabolism pathways. Nevertheless, the PK of cisplatin and carboplatin, in addition to erdafitinib and cetrelimab, will be evaluated in this study, so that DDI, if any, between these drugs can be explored. As cisplatin and carboplatin are intended to be used in combination with erdafitinib and cetrelimab in this study, this evaluation is particularly important since platinum chemotherapy agents have narrow therapeutic range (FDA Guidance 2012).

Potential for PD-mediated drug-drug interaction (serum phosphate):

Due to the absence of cetrelimab effect on serum phosphate to date, no relevant PD interactions are expected between erdafitinib and cetrelimab. However, PD interactions are expected between erdafitinib and platinum (cisplatin or carboplatin) chemotherapies, as both have opposite effect on serum phosphate. PD assessments will be characterized in this study to quantify the PD interactions between erdafitinib, cetrelimab, and platinum chemotherapies.

Erdafitinib-induced hyperphosphatemia is a well characterized phenomenon. For erdafitinib, an increase in serum phosphate is a biomarker of target engagement as well as an expected AE. To avoid interference with the determination of the initial dose increase based on serum phosphate levels, it is recommended to avoid co-administration of serum phosphate level-altering agents with erdafitinib before the initial dose increase period (Days 14 to 21). So far, no effect of cetrelimab on serum phosphate has been observed. Platinum chemotherapies however lead to a number of electrolyte disorders, including hypophosphatemia (Oronsky 2017). Possible mechanisms of hypophosphatemia in platinum-treated patients include increased renal excretion due to tubular dysfunction, other electrolyte disorders (magnesium, calcium), deprivation due to cachexia, vomiting and diarrhea. The frequency of hypophosphatemia in advanced cancer patients can be high, with as many as 49.4% of patients experiencing phosphate levels <2.5 mg/dL and 22.9% of patients experiencing phosphate levels <2.0 mg/dL (Yoshida 2017).

3.3. Dose-Limiting Toxicity Evaluation and Determination of RP2D

For the Phase 1b erdafitinib + cetrelimab cohort, refer to Section 3.3 of Appendix 1. For the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, refer to Section 3.3 of Appendix 2.

3.3.1. Definition of Dose-Limiting Toxicity for Phase 1b (Dose Escalation)

For the Phase 1b erdafitinib + cetrelimab cohort, refer to Section 3.3.1 of Appendix 1. For the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, refer to Section 3.3.1 of Appendix 2.

3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules

For the Phase 1b erdafitinib + cetrelimab cohort, refer to Section 3.3.2 of Appendix 1. For the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, refer to Section 3.3.2 of Appendix 2.

3.4. Study Evaluation Team

Subject safety will be monitored throughout the Phase 1b part of the study by the SET established by the sponsor until the RP2D of erdafitinib and cetrelimab is determined. This committee will monitor all available treatment-emergent data (eg, PK, PD, safety) on an ongoing basis throughout the study to ensure the safety of subjects enrolled in this study.

The SET will be chaired by the sponsor's Molecule Responsible Physician and membership will include the sponsor Study Responsible Physician, a sponsor clinical scientist, a subset of the study principal investigators, safety physician (sponsor's Safety Management Team chair), statistician, and clinical pharmacologist, along with additional sponsor staff, as appropriate. The team will meet at regular frequency throughout study conduct. In addition, SET meetings may be conducted at any time during the study at the request of either the sponsor or investigator(s) to assess emerging safety signals. Documentation of meeting outcomes will be maintained by the sponsor. Decisions will be communicated to investigators and decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will also be promptly communicated to regulatory authorities as required.

Dose escalation decisions in Phase 1b of the study will be made by the SET. The schedule of dose escalation meetings will depend on the frequency of DLTs and if/when the MTD or maximum administered dose is determined or when an RP2D is determined. The SET can evaluate up-titrated and non-up-titrated subjects separately based on the totality of the emerging safety data. Cumulative safety data will be routinely assessed by the DRC after the RP2D of erdafitinib and cetrelimab is determined.

Prior to the determination of the RP2D of erdafitinib and cetrelimab, the SET may also decide on modifications in study conduct such as additional dose cohorts/dose levels if required or stop further enrollment into 1 or more of the cohorts/dose levels if treatment-emergent toxicity is determined to result in an unfavorable change in subject risk/benefit. Enrollment may be temporarily held, if needed, for the SET to evaluate the emerging data.

4. SUBJECT POPULATION

For the Phase 1b part of the study, refer to Section 4 of Appendix 1 or Section 4 of Appendix 2, as appropriate.

For the Phase 2 cohort of the study, refer to Section 4 of Appendix 3.

5. TREATMENT ALLOCATION AND BLINDING

For the Phase 1b part of the study, refer to Section 5 of Appendix 1 or Section 5 of Appendix 2, as appropriate.

For the Phase 2 cohort of the study, refer to Section 5 of Appendix 3.

6. DOSAGE AND ADMINISTRATION

For the Phase 1b part of the study, refer to Section 6 of Appendix 1 or Section 6 of Appendix 2, as appropriate.

For the Phase 2 cohort of the study, refer to Section 6 of Appendix 3.

6.1. Dose Combination Cohorts/Arms

For the Phase 1b part of the study, refer to Section 6.1 of Appendix 1 or Section 6.1 of Appendix 2, as appropriate.

For the Phase 2 cohort of the study, refer to Section 6.1 of Appendix 3.

6.2. Administration of Erdafitinib

Erdafitinib will be provided as tablets for oral administration. The study drug is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact and subjects should not attempt to dissolve them in water. Each dose should be taken at approximately the same time each day in the morning with or without food. Should an alternative dosing schedule be used in the study, subjects will be instructed to take their assigned dose of the study drug orally on that alternative dosing schedule.

The study drug will be dispensed at the first visit of each cycle. All study drug doses dispensed must be captured in the source documents, including the subject's diary card, and the electronic case report form (eCRF). Unused study drug in the issued bottles and empty bottles must be returned to the site at each study visit. Study drug must be returned to the site when a subject discontinues study treatment. Returned tablets cannot be re-issued in this study or outside the study (follow study drug accountability guidelines in the Site Investigational Product and Procedures Manual [SIPPM]).

If a dose is missed, it can be taken up to 6 hours after the scheduled time; the subject may return to the normal schedule the following day. If it has been more than 6 hours since the missed dose, then that dose should be skipped and the subject should continue treatment at the scheduled time the next day. Missed doses will not be replaced and the next dose will remain unchanged. If vomiting occurred with drug administration, no replacement dose will be taken and any such event that occurs up to 4 hours following dose administration must be recorded on the subject's diary card and the eCRF.

6.2.1. Dose Up-titration Guidelines

Based on emerging safety data, on 12 May 2020, the DRC recommended to remove the requirement for up-titration from the erdafitinib + cetrelimab combination in Arm B. The DRC also made a recommendation to close Dose level 2 in Phase 1b and focus enrollment efforts into the Phase 2 part of the study. Therefore, DL2 will be closed. DL2B will remain open and will include up-titration of erdafitinib based on serum phosphate concentration from a blood sample on Day 15 and the absence of significant erdafitinib-related toxicity on C1D15 as determined by the investigator.

Subjects assigned to Dose Level DL2 or DL2B in Phase 1b or Arm A and in Phase 2, will be assigned to the up-titrated dose level of erdafitinib based on serum phosphate concentration from a blood sample on Day 15 and the absence of significant erdafitinib-related toxicity on C1D15 as determined by the investigator. There is no up-titration in either of the erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort or Arm B of the Phase 2 erdafitinib +/- cetrelimab cohort.

- Subjects with serum phosphate levels higher than 9.00 mg/dL (>2.91 mmol/L) will withhold erdafitinib treatment, with at least weekly assessment of serum phosphate levels until it returns to less than 7.00 mg/dL (<2.25 mmol/L) while initiating treatment with a phosphate binder such as sevelamer (see Table 8 for detailed guidelines regarding further treatment).
- Subjects with serum phosphate levels between 7.00 to 8.99 mg/dL (2.25 mmol/L to 2.90 mmol/L) should increase the erdafitinib dose to 9 mg once daily, while concurrently initiating treatment with a phosphate binder such as sevelamer (see Table 8 for details).
- Subjects with serum phosphate level less than 7.00 mg/dL (<2.25 mmol/L) will increase the erdafitinib dose to 9 mg once daily without concomitant phosphate binder such as sevelamer.

6.2.2. Dose Modification, Dose Delays, and Retreatment Criteria for Erdafitinib

Treatment with erdafitinib should be discontinued or modified based on toxicity as described in Table 5 and the specific guidance below. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicities, specific management guidelines are provided in Sections 6.2.3.1 through Section 6.2.3.7. This guidance is only intended for toxicity management.

Table 5: Erdafitinib Dose Modification Rules Based on Toxicity [a]

Toxicity Grade	Action	Dose modification after resolution of AE
1	None	Continue same dose.
2	None or consider interruption if the toxicity is considered clinically significant	If interrupted, restart at same dose if toxicity is completely resolved to baseline or consider re-starting at 1 dose lower[b] if not completely resolved to baseline (but resolved to Grade 1).
3	Interrupt drug	Restart at 1 dose lower[b] if recovered to baseline (to Grade ≤1 or back to baseline for non-hematologic toxicity) within 28 days; restart at 2 doses lower[b] if not completely resolved to baseline (but resolved to Grade 1). Discontinue drug if unresolved for >28 days.
4	Interrupt drug	Discontinue.

Abbreviations: AE = adverse event

[a] For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity please follow specific recommendations in the management guidelines.

[b] Please refer to Table 6.

- Subjects with any Grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment where applicable.
- If erdafitinib is interrupted consecutively for 1 week or longer due to drug-related toxicity, the study drug may be reintroduced at either the same dose level or the first reduced dose level following recovery from the toxicity (Table 6). A second dose reduction may be implemented following a second occurrence of drug-related toxicity.
- If erdafitinib must be withheld for more than 28 days for a drug-related AE that fails to resolve to acceptable level (eg, Grade ≤1 non-hematologic toxicity or back to baseline), treatment with erdafitinib should be discontinued except when the subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of erdafitinib is in the best interest of the subject. Erdafitinib may be reintroduced at the same or a lower dose (Table 6) if the medical monitor is in agreement with the assessment.
- If erdafitinib was dose-reduced and the AE that was the reason for this dose reduction has completely resolved, the dose may be re-escalated to the next higher dose when the subject has been deriving benefit from treatment, and the investigator can demonstrate that dose re-escalation of erdafitinib is in the best interest of the subject and the medical monitor is in agreement with the assessment.
- In all cases of clinically significant impaired wound healing or imminent surgery or potential bleeding complications, it is recommended that dose administration be interrupted, appropriate clinical laboratory data (eg, coagulation) be carefully monitored, and supportive therapy administered, where applicable. Dose administration may be restarted when it is considered safe and at an appropriate dose, according to the investigator's assessment.

Dose modification rules are provided in Table 6.

Table 6: Dose Schedule and Dose Reductions for Erdafitinib

Category		No up-titration	With up-titration
		Dose	Dose
Starting dose	**6 mg**	**8 mg**	**8 mg**
Up-titration	None	None	9 mg
1st dose reduction	5 mg	6 mg	8 mg
2nd dose reduction	4 mg	5 mg	6 mg
3rd dose reduction	**stop**	4 mg	5 mg
4th dose reduction		**stop**	4 mg
5th dose reduction			**stop**

6.2.3. Guidance for Specific Erdafitinib Toxicities

Guidance related to specific erdafitinib toxicities is discussed in this section.

6.2.3.1. Grading of Hyperphosphatemia and Nail Disorders

Hyperphosphatemia and AEs related to nails will be graded as outlined in Table 7.

Table 7: Grading of Hyperphosphatemia and Nails Adverse Events

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nail Changes (onychodystrophy)		Nail discoloration, asymptomatic separation of the nail bed from the nail plate or nail loss	Nail/fingertips pain, symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	Severe nail fingertips pain, symptomatic separation of the nail bed from the nail plate or nail loss; significantly limiting instrumental ADL	Life-threatening consequences, urgent intervention indicated
Hyperphosphatemia	<5.50 mg/dl <1.75 mmol/L	5.50-6.99 mg/dl 1.75-2.24 mmol/L	7.00-8.99 mg/dl 2.25-2.90 mmol/L	9.00-10.00 mg/dl (2.91-3.20 mmol/L), or asymptomatic soft tissue calcification with any phosphate level	>10.00 mg/dl >3.20 mmol/L, or symptomatic soft tissue calcification with any phosphate level

ADL= activities of daily living

6.2.3.2. Guidelines for the Management of Elevated Phosphate Levels

Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 8.

Table 8: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom Management
<5.50 mg/dL (<1.75 mmol/L) (Grade 0)	Continue erdafitinib treatment.	None.
5.50-6.99 mg/dL (1.75-2.24 mmol/L) (Grade 1)	Continue erdafitinib treatment.	Restriction of phosphate intake to 600 – 800 mg/day.
7.00-8.99-mg/dL (2.25-2.90 mmol/L) (Grade 2)	Continue erdafitinib treatment. A dose reduction will be implemented for persistent[a] hyperphosphatemia (defined as serum phosphate ≥7.00 mg/dL for a period of 2 months) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances).	Restriction of phosphate intake to 600 – 800 mg/day. Start sevelamer 800 to 1,600 mg TID with food until phosphate level is <7.00 mg/dL.
9.00-10.00 mg/dL (2.91-3.20 mmol/L) (Grade 3)	Withhold [b] erdafitinib treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Restart treatment at the same dose level. A dose reduction will be implemented for persistent [a] hyperphosphatemia (defined as serum phosphate ≥9.00 mg/dL for a period of 1 month) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances).	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer up to 1,600 mg TID with food until serum phosphate level returns to <7.0 mg/dL.
>10.00 mg/dL (>3.20 mmol/L) (Grade 4)	Withhold [b] erdafitinib treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Restart treatment at the first reduced dose level. If persistent [a] hyperphosphatemia (≥10.00 mg/dL) for >2 weeks, erdafitinib should be discontinued permanently.	Medical management as clinically appropriate.
Significant alteration in baseline renal function or Grade 3 hypocalcemia	Erdafitinib should be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the sponsor's medical monitor agree that continuation of treatment is in the best interest of the subject, the drug may be restarted at 2 dose levels lower if appropriate. Follow other recommendations described above, Section 6.2.2.)	Medical management as clinically appropriate.

Abbreviations: TID = 3 times a day

Note: These are general guidelines that are based on emerging data and consensus experience of participating investigators or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If sevelamer hydrochloride (Renagel®) is not available, use of other phosphate binders (non-calcium containing) based on the local standard is recommended, including sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol®). These guidelines will be updated based on emerging data. Additional information on phosphorous in foods by class of food can also be found at www.permanente net/homepage/kaiser/pdf/42025.pdf. Additional information for phosphate management and diet can be found at the National Kidney Foundation website (http://www kidney.org/atoz/content/phosphorus.cfm)

a. Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value above the cutoff.

b. Study drug interruptions for hyperphosphatemia suggested to be 7 days in duration.

6.2.3.3. Guidelines for the Management of Dry Mouth and Stomatitis

Guidelines for the clinical management of dry mouth (xerostomia) and stomatitis are provided in Table 9 and Table 10, respectively.

Table 9: Guidelines for the Management of Dry Mouth (Xerostomia)

General Prophylaxis		
– Good oral hygiene. – Use a soft toothbrush. – Avoidance of spicy, acidic, hard, and hot food and beverages. – Use of mild-flavored toothpastes. – Use of salt and baking soda mouthwashes 3 or 4 times per day. – Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)		
Grade and Definition	**Study Drug Management**	**Medical Management**
Grade 1: symptomatic (eg, dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges PRN
Grade 2: moderate symptoms; oral intake alterations (eg, copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges PRN and Cevimiline 30 mg TID or Pilocarpine 5 mg TID
Grade 3: inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva less than 0.1 ml/min	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolved to Grade ≤1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Sorbitol lozenges PRN and Cevimiline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated

Abbreviations: PRN = when needed; TID = 3 times a day; TPN = total parenteral nutrition

Table 10: General Prophylaxis and Guidelines for the Management of Oral Mucositis

General Prophylaxis		
• Good oral hygiene • Use a soft toothbrush • Avoidance of spicy, acidic, hard, and hot food and beverages • Use of mild-flavored toothpastes • Avoidance of alcohol-based mouthwash • Use of salt and baking soda mouthwashes 3 or 4 times per day • Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)		
Guidelines for the Management of Oral Mucositis		
Grade	**Study Drug Management**	**Symptom Management**
Grade 1	Continue study drug at current dose.	• Continue general prophylaxis recommendations • Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. • Consider clotrimazole/nystatin if subjects are at risk of developing oral candidiasis.
Grade 2	• Consider holding study drug if the subject has other study drug-related concomitant Grade 2 AEs. • Hold study drug if the subject was already on symptom management (dexamethasone solution swish and spit and lidocaine 2-5% jelly or solution) for more than a week. • If the study drug is withheld, reassess in 1-2 weeks. • If this is the first occurrence of toxicity and resolves to ≤ Grade 1 or baseline within 2 weeks, restart at same dose. • If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below.	• Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. • Consider concomitant etiologies such as oral candidiasis, oral herpes and recommend appropriate anti-fungal or anti-viral agents.
Grade 3	• Hold study drug, with reassessments of clinical condition in 1-2 weeks. • When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	• Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. • Consider pain management strategies. • Consider IV hydration.
Grade 4	Discontinue study drug.	Evaluation and therapy as clinically indicated.
AE=adverse event; QID=four times a day.		

6.2.3.4. Guidelines for the Management of Dry Skin and Skin Toxicity

Guidelines for the management of dry skin are provided in Table 11.

- **General prophylaxis:**
  - Avoid unnecessary exposure to sunlight and excessive use of soap.
  - Avoid bathing in excess; use tepid rather than hot water.
  - Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
  - Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
  - Use broad spectrum sunscreen with a skin protection factor (SPF) ≥15.
  - Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
  - Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
  - For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

Table 11: Guidelines for Management of Dry Skin

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus.	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10 to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13-40% at night for areas with fissures.
Grade 3: Dry skin covering >30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL).	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to Grade ≤1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Use topical steroid ointment or cream* BID and zinc oxide 13-40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated.	Discontinue study drug.	Evaluation and therapy as clinically indicated.

Abbreviation: BID = twice a day
*Topical Steroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%

6.2.3.5. Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)

Guidelines for management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) are provided in Table 12. Guidelines for the management of paronychia are provided in Table 13.

Table 12: General Prophylaxis & Guidelines for Management of Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy)

General Prophylaxis		
• Good hygienic practices, keep fingers and toes clean • Keep nails trimmed but avoid aggressive manicuring • Use gloves for housecleaning and gardening to minimize damage and prevent infection • Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal • Wearing comfortable shoes (wide sized shoes with room for the toes)		
Guidelines for Management of Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy)		
Grade	**Study Drug Management**	**Symptom Management**
Grade 1	Continue study drug at current dose.	• Continue general prophylaxis recommendations • Over the counter nail strengthener OR poly-urea urethane nail lacquer (Nuvail) OR diethylene glycol monoethylether nail lacquer (Genadur) daily. • Use non- alcohol-containing moisturizing creams.
Grade 2	Consider holding study drug with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes > 2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below in consultation with the medical monitor.	• Manage as per Grade 1 • For signs of infection (periungual edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: ○ treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim BID) AND ○ topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) • Silver nitrate application weekly AND topical antibiotics AND vinegar soaks[a]
Grade 3	Hold study drug, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks.[a] For signs of infection (periungual edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.
Grade 4	Discontinue study drug.	Evaluation and therapy as clinically indicated.
[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B		

Table 13: Guidelines for Management of Paronychia

Grade	Study Drug Management	Symptom Management
Grade 1	Continue study drug at current dose.	Topical antibiotics AND vinegar soaks[a]
Grade 2	Continue study drug at current dose. Consider study drug holding if no improvement in 1 to 2 weeks. When resolves to Grade ≤1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor	Topical antibiotics AND vinegar soaks[a] AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) For signs of infection (periungual edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim) DS BID).
Grade 3	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to Grade ≤1 or base line, restart at 1dose level below in consultation with the medical monitor.	Vinegar soaks[a] AND consider nail avulsion For signs of infection (periungual edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim) DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation.

Abbreviations: ADL = activities of daily living; BID = twice daily; DS = double strength

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

6.2.3.6. Guidelines for Eye Toxicity Associated With Vision Changes

Following Amendment 5, after end of study data collection timepoint has been achieved, the eCRF will be closed and only eye events that meet criteria for SAE (eg, hospitalization) will be reported through the company safety repository.

Guidelines for eye toxicity associated with vision changes are provided in Table 14.

Corneal or retinal abnormalities for subjects receiving erdafitinib are considered AEs of special interest. If a subject experiences an event of confirmed new corneal or retinal abnormality while on study drug, these occurrences should be reported as AEs, or as SAEs if the severity is Grade 3 or higher. Any new and clinically significant symptoms, such as, but not limited to, blurred vision, partial or complete loss of vision, double vision, floaters or color spots or halos around light, change in color or night vision, photophobia, ocular pain or stinging sensation, or foreign body sensation should be further evaluated and managed per the guidelines below.

Amsler grid (illustrated in Attachment 5): For any positive Amsler grid test, the subject should be referred for a full ophthalmologic examination within 7 days. However, if the subject has an abnormal Amsler grid test and otherwise normal ophthalmologic exam at baseline (during Screening), a repeat ophthalmologic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler grid test at Screening, or the subject has developed new clinical symptoms.

Table 14: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only or abnormal Amsler grid test	Refer for an ophthalmologic examination. If an ophthalmologic exam cannot be performed within 7 days, withhold treatment of erdafitinib until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue erdafitinib therapy at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume erdafitinib therapy at the next lower dose level after consultation with the medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 to 3-week intervals until resolution. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the medical monitor.	Refer the subject for an ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Immediately withhold erdafitinib therapy. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold erdafitinib until signs and symptoms have resolved. Resume erdafitinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved, stabilized, or subject is lost to follow-up or withdraws consent (which ever happens first). If toxicity is reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume erdafitinib therapy at the next lower dose level after consultation with the medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 to 3-week intervals until resolution.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.

Grade and Definition	Study Drug Management	Medical Management
	Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the medical monitor.	
Grade 3: Severe or medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	If the toxicity is Grade 3, report as an SAE and withhold erdafitinib. If, however the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that re-starting drug is in the best interest of the subject, then erdafitinib therapy may be resumed at 2 dose levels lower if appropriate. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 to 3-week intervals until resolution. Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence consider permanent discontinuation.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with erdafitinib. Report as an SAE and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (which ever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.

Abbreviations: ADL = activities of daily living; CSR = central serous retinopathy; OCT = Optical Coherence Tomography; RPED = retinal pigment epithelial detachments; SAE=serious adverse event

6.2.3.7. Guidelines for the Management of Dry Eye

- **General considerations:** Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- **Prophylactic management:** Frequent use of artificial tear substitutes and ocular demulcents is strongly recommended.
- **Reactive management:**
  - Withhold erdafitinib for Grade 3 toxicity.
  - Artificial tear substitutes if not started, every 4 to 6 hours.
  - Ocular demulcents.
  - Severe treatment-related dry eye should be evaluated by an ophthalmologist.

6.3. Administration of Cetrelimab

In the Phase 1b erdafitinib + cetrelimab cohort and Arm B of Phase 2 (Cycles 1- 4) of the study, cetrelimab will be administered at 240 mg IV Q2W until 1 or more treatment discontinuation criteria are met. The dose of cetrelimab is increased to 480 mg IV Q4W starting at Cycle 5. In the

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, cetrelimab will be administered at 360 mg IV Q3W until 1 or more treatment discontinuation criteria are met.

The first infusion should be administered over 60 (±10) minutes. In the absence of infusion-related reactions, subsequent infusions may be administered intravenously over 30 (-5/+10) minutes. Study drug is to be administered under the supervision of site staff. For the first infusion, vital signs should be monitored before the start of the infusion, every 15 to 20 minutes during the infusion, at the end of infusion (EOI), and 2 hours (±15 min) after the end of infusion. After the completion of the first infusion, the subject may be discharged if considered clinically stable and all other study procedures have been completed. During subsequent infusions of cetrelimab, vital signs should be monitored pre-dose, once during infusion, and at the end of infusion. On days in which both erdafitinib and cetrelimab will be administered, oral erdafitinib should be given before the start of cetrelimab IV infusion. On days in which erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy will be administered, oral erdafitinib should be given prior to cetrelimab, followed by platinum (cisplatin or carboplatin) chemotherapy IV infusion. Refer to the Investigational Product Preparation Instructions (IPPI)/SIPPM for detailed instructions on drug preparation, storage, and administration.

6.3.1. Retreatment Criteria for Cetrelimab

Before each administration of study drug, the subject will be evaluated for possible toxicities that may have occurred since the previous dose. Chemistry and hematology should be assessed according to the Time and Events Schedule and laboratory results and general physical status must be reviewed prior to administration of cetrelimab. If immune-related toxicity has occurred, the criteria outlined in Section 6.3.4 must be followed for management. Treatment with cetrelimab may continue as long as the criteria for discontinuation of study drug as presented in Section 6.3.3 and Section 10.2 are not met. The criteria for retreatment are outlined Table 15.

Table 15: Retreatment Criteria for Cetrelimab

Adverse Event	Requirements before each study agent administration
ANC	≥1.0 x 10^9/L to be stable with or without growth factor support for 5 days
Platelet count	≥50.0 x 10^9/L with or without platelet transfusions, thrombopoietic cytokines, or both
Hemoglobin	≥8.0 g/dL with or without transfusion, erythropoietin, or both
Fasting glucose, if prompted by HbA1c	≤250 mg/dL (13.9 mmol/L)
Hyperthyroidism, Hypothyroidism	Grade ≤2
AST and ALT	≤3 x ULN (or ≤5 x ULN for subjects with tumor involvement in the liver)
Total bilirubin	≤1.5 x ULN
Rash	Grade ≤2
Other clinically significant toxicity	Recovery to Grade ≤1 or baseline

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HbA1c = hemoglobin A1c; ULN = upper limit of normal
If fasting glucose results are available and meet the retreatment criteria, the HbA1c result does not need to be reviewed prior to dosing, but should still be collected.

6.3.2. Dose Delay for Cetrelimab

CCI

[redacted]

The criteria for discontinuation of study treatment are described in Section 6.3.3 and Section 10.2.

6.3.3. Cetrelimab Associated Toxicities Leading to Discontinuation of Study Treatment

A subject must discontinue cetrelimab if:

- The investigator believes that for treatment-emergent toxicity it is in the best interest of the subject to discontinue study treatment
- Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones
- Grade 2 or 3 immune-related AEs (irAEs) that persist despite treatment modifications or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks

- A treatment-related AE does not resolve to Grade ≤1 within 12 weeks of the last dose of study drug unless otherwise agreed to by the sponsor medical monitor and the investigator based on evidence of clinical benefit
- Any non-hematological treatment-related event occurs a second time at Grade ≥3 severity
- Grade ≥3 (or recurrent Grade 2) pneumonitis
- Grade ≥3 nephritis with creatinine ≥3 xULN
- Grade ≥3 elevation of AST or ALT >5 xULN or total bilirubin >3 xULN
- For subjects with baseline Grade 2 elevation of AST or ALT due to liver metastasis, only Grade ≥3 elevations that are ≥50% of baseline for ≥7 days will require discontinuation of study treatment
- Liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increase ≥50% and lasts ≥1 week
- Grade ≥3 IRRs
- Immune-mediated encephalitis.

If a subject's cetrelimab is discontinued, this will not result in automatic withdrawal of the subject from the study. The subject may continue on the other study treatments(s). Following cetrelimab discontinuation, the subject should complete the End-of-Treatment Visit as described in Time and Events Schedule and Section 9.1.3. Once a subject discontinues treatment, the subject may not be retreated with the study drug.

Following Amendment 5 and after end of study data collection timepoint has been achieved, the eCRF will be closed and only SAEs must be reported through the company safety repository.

6.3.4. Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest

Therapy with immuno-oncology agents such as cetrelimab can lead to specific irAEs that differ in nature, severity and duration as compared to AEs caused by agents with a different mode of action. Early recognition and management of these irAEs may mitigate more severe/subsequent toxicity. However, differential diagnoses including non-inflammatory etiologies as well as the impact of the underlying malignant disease and/or concomitant medication should be evaluated according to standard medical practice.

Management algorithms have been developed to assist investigators in assessing and managing specific irAEs following administration of nivolumab (Knowles 2015); (Nivolumab 2016) and pembrolizumab (Keytruda® 2014); (Oken 1982). These guidelines are presented below and should be followed for cetrelimab. In addition to the management algorithms provided in following sections, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Ipilumumab 2015). These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune-related.

3. Symptomatic and topical therapy should be considered for low-Grade events.
4. Systemic corticosteroids should be considered for a persistent low-Grade event or for a severe event.
5. More potent immunosuppressants should be considered for events not responding to systemic corticosteroids (eg, anti-tumor necrosis factor agents or mycophenolate).

If delaying the dose is necessary to ameliorate a toxicity, follow the guidance in Section 6.3.2.

6.3.4.1. Gastrointestinal Adverse Events

Diarrhea and colitis have been observed in subjects receiving anti-PD-1 therapies. Early recognition and treatment of diarrhea and colitis are critical to their management (see Table 16). Subjects should be advised to seek immediate medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. In subjects with pre-existing diverticulosis and/or diverticulitis receiving concomitant medication with corticosteroids, nonsteroidal anti-inflammatory drugs, and opioid analgesics together with anti-PD-1 therapies, diverticular perforation has been observed.

Table 16: Management of Immune-Related Gastrointestinal Adverse Events

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2
Grade 2	**≤5 days:** Symptomatic treatment according to institutional standards **>5 days or recurrence:** 0.5–1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics; **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4 **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4	**Immediately:** 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy **Persistence >3 days or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 4 weeks
General	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory subjects; the lower bioavailability of oral corticosteroids needs to be considered. Clinical caution should be exercised, for subjects receiving concomitant medications of corticosteroids, nonsteroidal anti-inflammatory drugs, or opioid analgesics. In addition, monitor for signs and symptoms of potential perforation, especially in subjects with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

6.3.4.2. Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug induced liver-injuries (DILI) have been observed following treatment with anti-PD-1 therapies. Early recognition and treatment of elevated LFTs and DILI are critical to their management (see Table 17). Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to anti-PD-1 therapies.

Subjects who have a predominant cholestatic pattern of liver injury (dominant increase in ALP relative to ALT /AST) should be further evaluated to exclude a diagnosis of treatment emergent sclerosing cholangitis. An evaluation may include ultrasound of liver, cholangiography and referral to gastroenterologist and/or a hepatologist.

Table 17: Management of Immune-Related Hepatic Adverse Events

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1	Monitor LFTs as outlined in the protocol; **Worsening:** treat as Grade ≥2
Grade 2	Monitor every 3 days; **Returning to baseline:** resume per protocol monitoring **LFT elevation >5 days or worsening:** 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **LFT return to ≤Grade 1 or baseline:** taper steroids over at least 4 weeks; resume routine monitoring and resume study treatment per protocol
Grade 3-4	Monitor every ≤2 days; **Immediately:** 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist **Persistence >3 days or recurrence:** add mycophenolate mofetil 1g BID; if no response within ≤5 days consider other immunosuppressants per local guidelines **LFT return to Grade 2:** stop immunosuppressants **LFT return to ≤Grade 1:** taper steroids over at least 4 weeks

Abbreviations: BID = twice daily; LFT = liver function test

6.3.4.3. Endocrinopathies

Endocrinopathies have been observed following treatment with anti-PD-1 therapies. The events have typically been identified through either routine periodic monitoring of specific laboratory tests (eg, Thyroid Stimulating Hormone [TSH]) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. See Table 18 for management guidelines.

Table 18: Management of Immune-Related Endocrinopathies

For guidelines for delaying a dose, refer to Section 6.3.2.	
Asymptomatic TSH elevation	**TSH <0.5 xLLN** or **TSH >2 xULN** or **TSH >ULN in 2 subsequent measurements:** include free T4 assessment prior/after subsequent cycles of study treatment; consider endocrinology consultation
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary MRI scan. **With abnormal lab and pituitary scan:** 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics • In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

For guidelines for delaying a dose, refer to Section 6.3.2.	
	Clinical and laboratory improvement: taper steroids over at least 4 weeks; subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component **Without abnormal lab and pituitary scan but symptoms persist:** repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of propart to current illness)	Rule out sepsis **Immediately:** initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist **Adrenal crisis ruled out:** treat as symptomatic endocrinopathy
Type 1 diabetes mellitus (if new-onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	For T1DM or Grade 3-4 Hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

Abbreviations: LLN = lower limit of normal; MRI = magnetic resonance imaging; T1DM = Type 1 diabetes mellitus; ULN = upper limit of normal

6.3.4.4. Rash

Rash and pruritus were the most common skin irAEs observed following treatment with anti-PD-1 therapies. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate Grade. In some cases, rash and pruritus resolved without intervention. Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. A case of toxic epidermal necrolysis occurred in a subject receiving concomitant prophylaxis with trimethoprim/sulfamethoxazole, and it is possible that the initial rash was due to a sulfa-hypersensitivity reaction that was eventually augmented by anti-PD-1 therapies. This case highlights the possible importance of discontinuing other suspected drugs in the management of rash. See Table 19 for management guidelines.

Table 19: Management of Rash

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1-2	**Immediately:** Symptomatic therapy (eg, antihistamines, topical steroids) **Persistence ≤2 weeks or recurrence:** consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **Improvement to Grade ≤1:** taper steroids over at least 4 weeks **Worsening to Grade >2:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤ Grade 1:** taper steroids over at least 4 weeks
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

6.3.4.5. Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with anti-PD-1 therapies. Physicians should monitor creatinine regularly (see Table 20).

Table 20: Management of Renal Adverse Events

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1	Monitor creatinine weekly **Creatinine returns to baseline:** continue monitoring per protocol **Creatinine increases:** treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days **Immediately:** start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy **Improvement to Grade ≤1:** taper steroids over at least 4 weeks **Persistence >7 days or worsening:** treat as Grade 4
Grade 4	Monitor creatinine daily **Immediately:** consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to Grade ≤1:** taper steroids over at least 4 weeks
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids(eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

6.3.4.6. Neurological Adverse Events

Neurological AEs have been uncommonly observed following treatment with anti-PD-1 therapies. Neurological AEs can manifest as central abnormalities (eg, aseptic meningitis or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). The onset has been observed as early as after a single treatment. Early recognition and treatment of neurologic AEs is critical to their management (see Table 21). Subjects should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes.

Table 21: Management of Neurological Adverse Events

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1	Monitor per protocol **Worsening:** treat as ≥Grade 2
Grade 2	**Immediately:** treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent **Worsening:** treat as Grade 3-4.
Grade 3-4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics **Worsening or atypical presentation:** consider immunoglobulins IV (IVIG) or other immunosuppressive therapies according to institutional standards **Improvement to ≤ Grade 2:** taper steroids over at least 4 weeks
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

6.3.4.7. Pulmonary Adverse Events

Pulmonary AEs including radiographic changes (eg, focal ground glass opacities and patchy infiltrates) indicative of drug-related pneumonitis have been observed in subjects receiving anti-PD-1 therapies. These pulmonary AEs were either asymptomatic or associated with symptoms such as dyspnea, cough, or fever. The initial occurrence of pulmonary AEs may be as early as after a single dose of anti-PD-1 therapies or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management (see Table 22). Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms.

Table 22: Management of Pulmonary Adverse Events

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization **Immediately:** start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3-4 **Improvement to ≤ Grade 1 or baseline:** taper steroids over at least 4 weeks
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; **Persistence for 2 days or worsening:** add immunosuppression (eg, infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) **Improvement to ≤ Grade 2:** taper steroids over at least 6 weeks
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

6.3.4.8. Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause. Additional eye toxicity guidance is provided in Section 6.2.3.6. See Table 23 for management guidelines.

Table 23: Management of Uveitis and Visual Complaints

For guidelines for delaying a dose, refer to Section 6.3.2.	
Grade 1	Thorough eye examination
Grade 2	Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 3-4	Thorough eye examination Systemic corticosteroids

6.3.4.9. Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported in anti-PD-1 therapy studies in which systemic monitoring was used. Very few subjects reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values. The recommended management of anti-PD-1 therapy-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low-Grade levels over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

6.3.4.10. Infection

Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

6.3.4.11. Treatment of Anti-PD-1 Infusion-related Reactions

Since cetrelimab contains only human immunoglobulin protein sequences, it is less likely to induce a hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Management of IRRs is provided in Table 24.

All CTCAE Grade 3 or 4 IRRs should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met.

Table 24: Management of Infusion-Related Reactions

Management and Follow-up of Infusion-Related Reactions. For guidelines for delaying a dose, refer to Section 6.3.2	
Grade 1	No intervention indicated; remain at bedside and monitor subject until recovery from symptoms, Consider diphenhydramine 50 mg (or equivalent) and or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administration.
Grade 2	**Stop infusion**; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol 325 to 1000 mg (acetaminophen); consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms. **Restart infusion at 50% of initial rate:** if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. **Symptoms recur:** stop and discontinue further treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
Grade 3-4	**Stop infusion**; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their

	institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
General	**Prophylactic medications (after initial event)**: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations; if necessary, corticosteroids (recommended dose: up to 80 mg of IV methylprednisolone or equivalent) may be used. Appropriate resuscitation equipment should be available in the room and a physician readily available during the infusion of study drug.

6.3.4.12. Monitoring During and After Study Drug Administration

Subjects should be carefully observed during cetrelimab infusions. Trained study staff at the clinic should be prepared to intervene in case of any IRRs occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develops, then the infusion should be temporarily interrupted or slowed down. Guidelines outlined in Section 6.3.4.11 must be followed to manage IRRs.

Subjects should be monitored for at least 2 hours after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed. The investigator will determine the duration of safety monitoring for subsequent administrations.

6.4. Administration of Platinum Chemotherapy (Cisplatin or Carboplatin)

Refer to Section 6.4 of Appendix 2.

6.5. Toxicity Due to One Study Drug and Continuation of Treatment

The dose modification guidelines described in Section 6.2, Section 6.3, and Section 6.4.4 are to be used throughout both phases of the study, as applicable. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). The recommendation to discontinue study therapy may apply to all study drugs. However, in cases in which the investigator and the study sponsor agree that the observed drug-related AE leading to discontinuation was most probably related to 1 of the study drugs, continuation of therapy with the other study drug(s) is permitted after discussion with the medical monitor.

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of the amount of study drug dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study.

Subjects will receive instructions on compliance with study treatment at the Screening visit. A diary card will be given to the subject to record intake at home. On days when the subject visits the study center for dose administration or PK sampling, the investigator or designee will supervise

administration of the study drug and the exact time of administration will be recorded in the eCRF. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instruction to reeducate any subject who is not compliant with the study drug schedule.

If appropriate, site visits may be replaced with telephone visits during a national disaster, with site visits resuming as soon as possible thereafter. Please refer to Attachment 10 for additional guidance on study conduct for enrolled subjects during a national disaster.

8. CONCOMITANT THERAPY

Following Amendment 5, and after end of study data collection timepoint has been achieved, the eCRF will be closed and only concomitant therapies associated with an SAE must be reported through the company safety repository.

Therapies are to be recorded at the time of Screening (within 28 days prior to the first dose of study drug), throughout the study, and up to 100 days after the last dose of study drug in the appropriate section of the eCRF. Once a subject starts a subsequent systemic anticancer therapy, data collection will be limited to concomitant medications used to treat ongoing or newly developed Grade ≥2 immune-related AEs considered related to cetrelimab.

All therapies (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the eCRF. Caution should be exerted for subjects taking anticoagulant therapies. Frequent monitoring for international normalized ratio (INR) is allowed at the treating physician's discretion.

The sponsor must be notified in advance, or as soon as possible thereafter, of any instances where prohibited medications are administered.

8.1. Permitted Medications

Throughout the study, investigators may prescribe concomitant medications or treatments (including nutritional support, correction of metabolic disorders, optimal symptom control, and pain management) deemed necessary to provide adequate supportive care. Concurrent use of hormones for non-cancer related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Concomitant medications (eg, acetaminophen/paracetamol or diphenhydramine) deemed necessary by the investigator to provide adequate prophylaxis and management of IRRs are allowed. Refer to Section 6.3.4 for guidance on medications to manage immune-related toxicities.

In addition, the following medications may be administered during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.

  - Permitted antiemetics include: aprepitant, ondansetron, and dexamethasone
- Documented infectious complication should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- In general, growth factor support is permitted for the management of treatment-emergent hematological toxicity as recommended according to National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer (NCCN/EORTC 2018) guidelines. Primary prophylaxis is not permitted for subjects who are under evaluation for DLTs.
- Palliative radiotherapy: Localized radiotherapy for symptomatic control is permitted but should not include definitive radiation to target lesions.
- Chronic supportive therapies: Ongoing bisphosphonates and denosumab or other supportive therapies are permitted.

8.2. Prohibited Medications and Therapy

The following medications are prohibited during the study (Table 25). The sponsor must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered. Other anticancer treatments are not allowed in this study.

Table 25: Prohibited Concomitant Medications and Therapies[4]

Antineoplastic Therapy
• Cytotoxic chemotherapy (other than those under study in the appropriate cohort[s] of the study) • Biological therapy (including but not limited to: therapeutic antibodies and cytokines) • Radiation therapy[1] • Investigational agents
Immunotherapy
• Immunotherapy for any indication • Live, attenuated vaccines (including but not limited to the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, Bacillus Calmette-Guérin, and typhoid)[2].
Immunosuppressive Agents
• Systemic corticosteroids (>10 mg prednisone per day or equivalent for over 5 days) other than those given for IRRs, as described in Section 6.3.4 should be avoided.[3]   ○ Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest or for use as a premedication for chemotherapeutic agents specified in the protocol. • Methotrexate, cyclosporine, azathioprine, and TNF-α blockers.
Other
Colony-Stimulating Factors (CSFs): Routine primary prophylaxis is not permitted for subjects who are under evaluation for DLTs; For the use of CSFs after the DLT period ends, utilize (NCCN/EORTC 2018) guidelines.

Abbreviations: H1N1= Hemagglutinin Type 1 and Neuraminidase Type 1; IRRs= infusion-related reactions; TNF-α= tumor necrosis factor alpha

1. Palliative radiation therapy may be allowed after consultation and in agreement with the study sponsor.
2. Live, attenuated vaccines are prohibited 28 days prior to the first dose of study therapy and throughout study participation. Annual inactivated influenza vaccine is allowed.
3. Chronic (≥14 days) use of glucocorticoid for the clinical management of AEs is allowed. The use of physiologic doses of corticosteroids may be approved after consultation and in agreement with the study sponsor.
4. For further information regarding the interaction between cisplatin or carboplatin with other medicinal products (and other forms of interaction), please refer to the current approved label for cisplatin or carboplatin as applicable.

8.3. Precautions for Concomitant Medications, Food, and Surgical Intervention

The bioavailability and in consequence the safety as well as efficacy profile of the study drug may be altered when co-administered with medications or food listed in Table 26. Therefore, these medications should be avoided, or should be administered with caution concomitantly with study therapy. Guidance for surgical intervention is also provided in this table.

Based on in vitro data, erdafitinib is metabolized by cytochrome CYP2C9 and CYP3A4. A clinical drug-drug interaction study showed that on average, erdafitinib exposure (C_{max} and AUC) was increased 5% to 34% when co-administered with itraconazole (a strong inhibitor of CYP3A4) and 21% to 49% when co-administered with fluconazole (a moderate inhibitor of CYP2C9). For this reason, strong CYP3A4 and moderate CYP2C9 inhibitors should be used with caution (see Attachment 4). Consider alternative therapies that are not strong inhibitors of CYP3A4 or moderate inhibitors of CYP2C9 during treatment with erdafitinib. If co-administration of these drugs is unavoidable, monitor the subject closely for adverse reactions and consider dose modifications accordingly. If the strong inhibitor of CYP3A or moderate inhibitor of CYP2C9 is discontinued, the erdafitinib dose may be increased up to the maximum of 9 mg daily in the absence of drug-related toxicity.

The impact of moderate CYP2C9 inducers and strong CYP3A inducers (such as rifampin) on erdafitinib was not clinically studied. Co-administration of erdafitinib with these agents may significantly decrease erdafitinib exposure. Therefore, the concomitant use of these agents with erdafitinib should be avoided (see Attachment 4). Co-administration of erdafitinib with moderate CYP3A inducers may decrease erdafitinib exposure. Caution should be exercised for concomitant administration of erdafitinib and moderate inducers of CYP3A4 (see Attachment 4).

Erdafitinib was shown to inhibit, in in vitro experiments, human P-glycoprotein (P-gp) at the concentrations achieved at therapeutic doses in humans. If co-administration of erdafitinib with P-gp substrates is unavoidable, separate erdafitinib administration by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic index (https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf); in addition, drugs with a narrow therapeutic index should only be used when the benefit outweighs the potential risk.

Table 26: Concomitant Medications and Surgical Interventions to be Avoided or to be Used With Caution

Moderate CYP2C9 inducers and strong CYP3A inducers
• Co-administration of erdafitinib with these agents may significantly decrease erdafitinib exposure. Therefore, the concomitant use of these agents with erdafitinib should be avoided.
Moderate or strong CYP2C9 and CYP3A inhibitors, moderate CYP3A inducers
• Moderate or strong in vivo inhibitors of CYP3A and CYP2C9 enzymes should be used with caution[1] • Moderate in vivo inducers of CYP3A enzyme[1] should be used with caution
QT-Prolonging Agents
• Medications known to cause *Torsades de Pointes*[2]
P-gp Substrates
• P-gp substrates with narrow therapeutic index (eg, digoxin)
Medications Known to Increase Serum Levels of Phosphate
• Phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas & laxatives (oral/rectal)

Surgical Intervention
• Held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding

Abbreviations: P-gp = P-glycoprotein

1. For a listing of CYP3A and CYP2C9 inhibitors and inducers see Attachment 4.
2. For a listing of medications that cause QT prolongation see http://www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name.

9. STUDY EVALUATIONS

Following Amendment 5, and after end of study data collection timepoint has been achieved, the clinical database will be closed and only SAEs must be reported through the company safety repository.

9.1. Study Procedures

9.1.1. Overview

The study is divided into Screening, Treatment, and Follow-up Phases. The Time and Events Schedule for each treatment cohort summarizes the planned frequency and timing of all assessments applicable to this study. Clinical laboratory results (except PTH) must be available and reviewed by the investigator before study drug is administered. All planned assessments on dosing days should be completed prior to the start of the infusion unless otherwise indicated in the Time and Events Schedules. Treatment decisions will be based on local laboratory results.

Based on emerging data, adjustments to the planned schedule of assessments may be made by the sponsor in order to protect subject safety. These decisions will be documented in writing and appropriately communicated to participating investigators prior to implementation.

All planned assessments, including clinical laboratory tests (except PTH) must be completed and the results reviewed prior to the start of the infusion unless otherwise indicated in the Time and Events Schedules. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: electrocardiogram (ECG), vital signs, blood draw. Blood collections for biomarkers and PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. All blood samples must be taken from a vein contralateral to the arm into which cetrelimab is infused; alternatively, the sample may be taken from a central line.

The total maximum amount of blood to be drawn from each subject is estimated to be 17 mL at Screening. The majority of the blood samples will be collected during the first 4 cycles (ie, approximately 16 weeks). The approximate maximum blood volume drawn from each subject in this study during the first 4 cycles is in the range deemed acceptable for blood donation. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The Screening Phase will consist of a Molecular Eligibility Screening Period and a Full-Study Screening Period.

Molecular Eligibility Screening Period

The Molecular Eligibility Screening Period starts with the signing of a molecular eligibility informed consent form (ICF) and can occur at any time prior to administration of study drug (≥28 days prior to administration of the study drugs). Consent for molecular screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.

Subjects may by-pass the molecular Screening Phase of Study BLC2002 if they have already been molecularly screened for FGFR alterations by the central laboratory in the context of another Janssen-sponsored study.

Molecular eligibility will be determined for all subjects by the presence (or absence) of select FGFR mutations and fusions as described in Table 4.

During the Molecular Eligibility Screening Period, there are 2 approaches that may be used to determine FGFR status for this study, ie, central molecular screening or local test results:

1) **Central Molecular Screening (Submission of Tissue and Blood Samples Required*)**

FGFR analysis of tissue and blood by the central laboratory. Archival tumor tissue or a fresh biopsy sample and a blood sample will be sent to the central laboratories for testing. Blood and tissue samples do not need to be submitted concurrently; samples may be submitted as they become available during the Molecular Eligibility Screening Period. The central laboratory will evaluate subjects for molecular eligibility (where applicable) by analyzing tumor and blood specimens for the presence of select FGFR mutations and gene fusions. The sponsor or central laboratory/designee will communicate results of the molecular testing to the site. If a biopsy is required to perform FGFR analysis, the subject must consent to this procedure utilizing the main study consent form.

Subjects may enroll in the study if at least one sample (tissue or blood) results in identification of a study-eligible FGFR alteration, however if a subject enrolls based on blood testing, a tissue sample must be submitted for central confirmatory testing.

2) **Local report with evidence of a study-eligible FGFR mutation or fusion (or for Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort proof of FGFR testing, independent of FGFR status).** Local test results (from tissue or blood) or the Qiagen Therascreen FGFR RGQ RT-PCR test (from tissue) performed at a CLIA-certified or regional equivalent laboratory may be used to meet molecular eligibility. A copy of the test report documenting the FGFR result must be included in the subject records and a de-identified copy must also be submitted to the sponsor for confirmation of eligibility.

- If a subject is enrolled based on local testing, a tissue and blood sample must still be submitted at the time of enrollment for retrospective confirmation of FGFR status, diagnostic development, and biomarker research. If tissue specimens are not available for retrospective confirmation testing, the site should contact the sponsor prior to proceeding to full-study screening.

- The sponsor cannot authorize performance of high-risk fresh biopsies to obtain tissue for retrospective central confirmation of FGFR status.
- The results of retrospective central confirmation do not affect the subject's eligibility for the study. Results of retrospective confirmation studies will not be communicated to the site. Concordance between local and central testing, where applicable, will be reviewed periodically by the sponsor.

If a subject meets the molecular eligibility criteria (where applicable), he or she may continue study screening under the Full-Study ICF for determination of full-study eligibility.

Full-Study Screening Period

The Study Screening Period (for full-study eligibility) is within 28 days before the first dose of study medication with the exception of the screening disease assessments which may be done within 35 days prior to C1D1. Subjects must meet all the inclusion criteria and none of the exclusion criteria in Section 4. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. To reassess eligibility, retesting will take place during an unscheduled visit in the Screening Phase.

9.1.3. Treatment Phase

The Treatment Phase will begin with the administration of the first dose of erdafitinib alone or in combination with cetrelimab +/- platinum (cisplatin or carboplatin) chemotherapy and will continue until disease progression or unacceptable toxicity (based on investigator assessment) occurs. Subjects with PD per RECIST 1.1, but for whom the treating physician strongly believes that continuation of study treatment is in their best interest, may be allowed to continue on the study drug after consultation with the medical monitor (see Section 9.2.2). The subject may receive treatment until such time as the treating physician and the medical monitor agree that further continuation of treatment is no longer thought to benefit the subject. The subject must follow the procedure as outlined in the cohort-specific Time and Events Schedule as if he or she has not progressed.

Adverse events occurring any time after the subject signs the Full-Study ICF and up to 100 days after the last dose of study drug are to be recorded for all subjects (no AEs will be collected for subjects signing the molecular ICF only). Adverse event information will be graded using the NCI-CTCAE, version 5.0. See Section 12 for complete details on AE reporting. Concomitant medications used will also be recorded throughout this time period.

Throughout the Treatment Phase, the investigator will assess subject response to therapy using the RECIST 1.1 criteria (Attachment 9). Efficacy evaluations are described in Section 9.2. For subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging according to the imaging schedule in the cohort-specific Time and Events Schedule until the start of new anti-cancer treatment, disease progression, withdrawal of consent, death, or the end of the study, whichever occurs first.

End-of-Treatment Visit

The End-of-Treatment Visit will be performed after the last dose of study drug is administered and will include End-of-Treatment procedures as outlined the in the cohort-specific Time and Events Schedule. All subjects should have the End-of-Treatment Visit completed within 30 (+7) days after the last dose of study drug, and prior to the starting any subsequent cancer treatment, except for those who have withdrawn consent, died, or have been lost to follow-up.

Following amendment 5 and after end of study data collection timepoint has been achieved, the eCRF will be closed and only SAEs must be reported through the company safety repository.

Additional information on reporting of AEs can be found in Section 12.

9.1.4. Follow-Up Phase

All subjects who enter the Follow-up Phase will have a follow-up visit every 12 weeks (± 7 days) after the last dose of study treatment to assess survival status and assess alternate anticancer therapy data until death, the subject withdraws consent, or the end of study, whichever occurs first as outlined in the cohort-specific Time and Events Schedule. Assessments of survival status and alternate anticancer therapies must be recorded in the eCRF. If necessary, this visit can occur by telephone. At the first follow-up visit (12 weeks after the last dose), physical examination, vital signs, and pregnancy testing should be performed.

Following Amendment 5 and after end of study data collection timepoint has been achieved, the eCRF will be closed and subjects in Follow-Up will be considered to have completed the study.

9.2. Efficacy Evaluations

RECIST 1.1 will be applied by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy). After Screening, imaging will be performed during the study as indicated in the Time and Events Schedule. The site will send radiographic scans for all subjects randomized to Phase 2 to a central vendor for possible future independent assessment to confirm the response, if needed.

Computed tomography (CT) scans of the chest, abdomen, pelvis, and any other location where disease is present or suspected will be performed at Screening. During the study, disease response will be assessed using CT scans of the chest, abdomen, pelvis and any other locations of known disease. Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at Screening and at all subsequent response evaluations or in cases where use of CT scan is clinically contraindicated). For all other sites of disease, MRI studies do not replace the required chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

Imaging should not be delayed due to delays in cycle starts or extension of cycle intervals. After disease progression is documented, subjects will have an End-of-Treatment Visit and continue in the study for follow-up as outlined in Section 9.1.4. Identical methodology (CT scan or magnetic

resonance imaging [MRI]) should be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document disease status. Ultrasound, fluorine 18-fluorodeoxyglucose positron emission tomography, and plain X-rays are not acceptable methods of evaluating disease response in the absence of CT or MRI scans.

If symptomatic deterioration (based on global deterioration of health status) occurs without documentation of radiographic progression, then the clinical findings used to make this determination must be specified in the eCRF as "clinical disease progression" and documented in the source documents. Every effort should be made to document objective progression via radiographic confirmation even after discontinuation of treatment for symptomatic deterioration. Tumor response will be reported by the investigator in the eCRF.

Following Amendment 5 and after end of study data collection timepoint has been achieved, the eCRF will be closed and only SAEs must be reported through the company safety repository.

9.2.1. Efficacy Endpoints

Objective response rate according to RECIST 1.1 criteria by investigator assessment is the primary endpoint. Duration of response, TTR, PFS, and OS will serve as additional measures of efficacy.

The efficacy endpoints are defined below:

- Objective Response Rate (ORR) is defined as the proportion of subjects who achieve CR or PR, as assessed by the investigator.
- 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 PD (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.
- Time to Response (TTR) will be calculated from the date of randomization to the date of initial documentation of a response (CR or PR).
- Progression-free survival (PFS) is defined as the duration from the date of randomization until the date of first documented evidence of PD (or relapse for subjects who experience CR during the study) or death, whichever comes first. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- 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.

9.2.2. Treatment After Initial Disease Progression

If the site study team makes an initial assessment of disease progression, and if the subject is clinically stable, treatment with erdafitinib may be continued. In the case of imaging-based progression (RECIST 1.1) subjects may continue to receive study treatment(s) if the investigator and sponsor's clinical team agree and if the subject is clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating overt disease progression
- Stable ECOG PS Grade
- Absence of progressive tumor at critical anatomical sites (eg, spinal cord compression, new brain metastases) requiring urgent alternative medical intervention

If a subject is approved to continue treatment beyond initial RECIST defined disease progression, repeat tumor imaging must be performed at least 4 weeks but no later than 6 weeks after the first tumor imaging indicating PD. If repeat imaging meets the threshold for PD (≥20% increase in tumor burden [minimum 5 mm] compared to extent of disease at the time of first progression or unequivocal new lesion(s), the subject will be discontinued from study treatment.

9.3. Pharmacokinetics and Immunogenicity

Pharmacokinetic assessments will be performed for erdafitinib, cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy cohort. Immunogenicity assessment will be performed for cetrelimab.

Following amendment 5, and after end of study data collection timepoint has been achieved, no further PK samples of cetrelimab will be collected. An ad-hoc sample for immunogenicity and corresponding PK may be collected if required.

Samples for Erdafitinib PK:

Pre-dose and post-dose samples (3 mL per sample) will be collected for erdafitinib as outlined in the cohort-specific Time and Events Schedule. Post-dose blood samples should be drawn after both the drug infusion and the post-infusion flush have been completed. An additional 4 mL blood sample will be collected for determination of the FU (fraction of the unbound erdafitinib) and protein levels (total protein, albumin, and alpha-1-acid glycoprotein), as indicated in the cohort-specific Time and Events Schedule. Blood samples will be processed to obtain plasma for measurement of erdafitinib concentration by a validated analytical method under the direction of the sponsor. Acid glycoprotein and other proteins will also be measured. Plasma protein binding, if needed, will be determined by equilibrium dialysis. After dialysis, the buffer and plasma samples will be analyzed for erdafitinib content using a qualified liquid chromatography/mass spectrometry method by the sponsor's Bioanalytical Laboratory. Additional details are provided in the Laboratory Manual. The exact date and time of dosing must be recorded on the appropriate eCRF. The exact collection date and time of blood sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

Samples for both cetrelimab PK and anti-cetrelimab antibody determination:

Blood for the assessment of cetrelimab PK and anti-cetrelimab antibody and for immunogenicity assessment will be collected as outlined in the cohort-specific Time and Events Schedule.

All pre-infusion samples should be drawn within 30 minutes before infusion of cetrelimab. Pharmacokinetic samples are collected from the arm opposite from infusion site. If drug was administered via a central venous catheter, sample collection for PK should be from a different site. Post-dose blood samples should be drawn after both the drug infusion and the post-infusion

flush have been completed. Blood samples will be processed to obtain serum for measurement of cetrelimab concentration by a validated analytical method by the sponsor. Additional details are provided in the Laboratory Manual. The exact date and time of dosing (including start, and stop time of IV infusion, and volume infused) must be recorded on the appropriate eCRF. The exact collection date and time of blood sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

Samples for Platinum Chemotherapy PK:

Plasma PK sampling for cisplatin and carboplatin is outlined in Appendix 2 Table 2.

The exact date and time of dosing (including start, and stop time of IV infusion, and volume infused) must be recorded on the appropriate eCRF. The exact collection date and time of blood sampling must be recorded in the laboratory requisition form/source documentation and/or eCRF.

9.4. Pharmacodynamic Evaluations

For PD biomarker evaluation, serum phosphate levels will be monitored in subjects treated with the study drugs in the cohort-specific Time and Events Schedule. Hyperphosphatemia is a common FGFR inhibitor-induced toxicity due to renal tubular FGFR inhibition and, thus, it can serve as a PD marker of erdafitinib activity. Hypophosphatemia is a common AE of chemotherapy. Phosphate levels will be evaluated throughout the study as a PD and safety biomarker.

Serum for the assessment of phosphate concentrations will be collected as outlined in the cohort-specific Time and Events Schedule.

9.5. Predictive and Exploratory Biomarkers

Biomarkers will be analyzed in response to various parameters including but not limited to:

- Determination of CCI [redacted] or alternate methodology
- Assessment of changes in CCI [redacted] (Phase 2 [Arm A], and Phase 1b Alternate Dosing cohort)
- Status of CCI [redacted] via immunohistochemistry (IHC)
- Assessment of CCI [redacted] (Phase 2 [Arm A], and Phase 1b Alternate Dosing cohort). CCI [redacted] will be stained by IHC for expression of CCI [redacted]
- Profiling of CCI [redacted] via flow cytometry
- Assessment of CCI [redacted]
- Detection and quantification of circulating tumor DNA (ctDNA) from plasma to screen for CCI [redacted], and to monitor for the CCI [redacted].

Tissue for PD-L1, Immune Biomarkers, and Molecular Subtyping

Archival tissue will be collected at Screening to assess PD-L1 expression level and identify the molecular subtype of subject tumors.

PD-L1 expression level will be assessed via IHC in tumor tissue provided at Screening. Correlation of PD-L1 expression level with FGFR alteration status, and response to erdafitinib alone or in combination with cetrelimab will also be assessed.

Urothelial cancer can be classified, via molecular signature, into basal, luminal, and p53-like subtypes which may inform subject prognosis and response to treatment (Choi 2017). The molecular subtype of tissue samples collected at Screening will be determined by RNAseq analysis or alternate method. The correlation of bladder molecular subtype with FGFR alteration status, and response to erdafitinib alone or in combination with cetrelimab will be assessed.

CCI [redacted]

Fresh baseline, on treatment, and progression biopsies will be collected on study in Phase 2, Arm A, and the Phase 1b Alternate Dosing cohort, where clinically feasible (see the cohort-specific Time and Events Schedule). The sponsor cannot authorize performance of high-risk fresh biopsies to obtain tissue for retrospective central confirmation of FGFR status. CCI [redacted]

CCI [redacted]

Circulating Biomarkers

CCI [redacted]

CCI [redacted]

CCI [redacted]. Circulating tumor DNA are fragments of DNA shed in the bloodstream during cell turnover. In cancer, a fraction of the circulating DNA is made up from DNA shed by tumor cells. This ctDNA often harbors somatic alterations which are reflective of the original tumor. Circulating tumor DNA can be used to track response to treatment and the emergence of resistance by monitoring changes in target ctDNA levels over time. Samples collected prior to and during treatment will be screened for CCI [redacted].

Additional biomarkers (DNA, RNA, and protein) relevant to cancer may also be assessed in blood and tissue samples collected on study to better understand the CCI [redacted]. Adjustments in the timing of biomarker collections may be made or collections may be stopped during the study based on emerging data.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and emerging data and may be deferred if during or at the end of the study it becomes clear that the analysis will have no scientific value, or there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

9.6. Safety Evaluations

This study will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse event and SAE data will be reviewed internally on an ongoing basis to identify safety concerns by the study medical monitor. In addition, the sponsor's Safety Management Team will review the safety data routinely and will investigate specific safety queries. The Safety Management Team will review all SAEs.

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, ECOG PS, and other safety evaluations at specified time points as described in the Time and Events Schedules (see the cohort-specific Time and Events Schedule).

Following Amendment 5 and after end of study data collection timepoint has been achieved, the eCRF will be closed and only SAEs must be reported through the company safety repository.

Any clinically significant abnormalities or toxicities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint. For AEs such as skin/nail and mucosal toxicity, upon subject consent, photographs may be taken for assessment and monitoring of the toxicity.

9.6.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the signing of the Full-Study ICF up to

100 days after the last dose of study drug. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. Adverse events will be graded according the NCI-CTCAE, version 5.0. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.6.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected according to the cohort-specific Time and Events Schedule. More frequent clinical laboratory tests may be performed, as indicated by the overall clinical condition of the subject and for abnormalities that warrant more frequent monitoring.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Laboratory test results completed on C1D1 should be reviewed prior to dosing and subjects should continue to meet eligibility requirements per the Inclusion/Exclusion criteria.

The following tests will be performed (locally):

Hematology Panel

-hemoglobin
-platelet count
-white blood cell count and ANC only

Serum Chemistry Panel

-albumin
-sodium
-calcium
-alkaline phosphatase
-potassium
-creatinine
-magnesium
-AST, ALT
-total bilirubin
-lipase
-totalamylase
-HbA1c[a]
-glucose[b]

[a] If fasting glucose results are available and meet the retreatment criteria, the HbA1c result does not need to be reviewed prior to dosing but should still be collected.

[b] fasting glucose at screening and then only as clinically indicated.

Phosphate (PO_4)

Parathyroid hormone (PTH)

Thyroid Panel

-TSH
-FT4 (free thyroxine)
-T3 (Triiodothyronine)

Serology at Screening Only

- HIV antibody

- Hepatitis B virus surface antigen (HBsAg) and core (HBc) antibody: if positive, further testing of quantitative levels to rule out active infection is required.
- Hepatitis C virus (HCV) antibody: if positive, further testing quantitative levels to rule out active infection is required.

9.6.3. Renal Toxicity Evaluation

Creatinine or creatinine clearance will be determined per institutional standard.

9.6.4. Urine or Serum Beta-hCG Pregnancy Test

A highly sensitive serum pregnancy test (<5 IU/mL) (β-human chorionic gonadotropin [β-hCG] or urine pregnancy testing should be performed for women of childbearing potential. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. A pregnancy test should also be performed 12 weeks after the last dose (see the cohort-specific Time and Events Schedule).

9.6.5. Electrocardiogram

Screening 12-lead ECGs, to be used to determine subject eligibility, will be performed at the study-site. Post-dose ECGs will be collected according to the cohort-specific Time and Events Schedule.

The subject should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs. Triplicate ECGs should be performed with 5-minute intervals between each assessment. At least 1 printout of all 3 ECG traces should be produced and stored in the subject’s source documents. The 12-lead ECG recorder device used should have been recently serviced and calibrated. The following variables should be measured: heart rate, RR, QT, PR, QRS, QTc (Fridericia) intervals. QTcF will be used for assessment of QTc interval. The investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings).

9.6.6. Echocardiography or MUGA Scan

Echocardiograph (ECHO) or multi-gated acquisition scans (MUGA), if ECHO is not available, will be performed at Screening to establish baseline cardiac status. Further evaluations may be conducted if clinically indicated.

9.6.7. Ophthalmic Examination

All subjects will have an ophthalmological examination performed at Screening by an ophthalmologist, which should include assessment of visual acuity, fundoscopy (examination of both central and peripheral zones should be performed) and slit lamp biomicroscopy. An Optical Coherence Tomography (OCT) will also be performed at Screening. The Amsler grid test will also be administered by the treating physician or nurse at Screening. A follow-up examination should

be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment, or at regular intervals as deemed necessary by the screening ophthalmologist.

When CSR/Retinal Pigment Epithelial Detachments (RPED) is suspected, or fundoscopic retinal abnormalities are observed, as well as each time ocular AEs lead to the subject being referred to an ophthalmologist, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected renal vein occlusion (RVO). In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered. All images of the OCT scan must be stored in the subject's records, and a redacted copy sent to the sponsor-selected central vendor for possible future independent assessment.

Amsler grid testing will be administered by the treating physician or nurse according to the cohort-specific Time and Events Schedule. Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days. However, if the subject has an abnormal Amsler grid test at baseline (during Screening), then a repeat ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler grid test at Screening, or the subject has developed new clinical symptoms.

9.6.8. Vital Signs

Blood pressure (systolic and diastolic) and heart rate measurements will be assessed with a completely automated device consisting of an inflatable cuff and an oscillatory detection system according to the cohort-specific Time and Events Schedules. Temperature and respiratory rate will also be assessed. Clinically significant abnormalities should be reported as AEs.

9.6.9. Physical Examination

A full physical examination will be performed at Screening according to the Time and Events Schedule. Limited physical examinations of involved organs will be performed at subsequent visits as outlined in the cohort-specific Time and Events Schedule. Clinically significant abnormalities should be reported as AEs.

9.6.10. ECOG Performance Status

ECOG PS Grade will be determined at pre-specified timepoints listed in the cohort-specific Time and Events Schedule. ECOG scoring information is provided in Attachment 3.

9.6.11. Documentation of Hearing Loss

For subjects enrolled in the Phase 2 part of the study, documentation of Grade 2 or higher hearing loss is required for cis-ineligible subjects if hearing loss is the single reason for cis-ineligibility. Audiometry may be performed, or prior audiometry test results must be available for review. In subjects already using hearing aid, documentation of the use of a hearing aid is sufficient for this requirement. Audiometry tests that were performed prior to consent for the full-study was obtained is permitted to be collected as long as it is documented this procedure was performed as part of standard of care and not specifically for study purposes.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form/source documentation. Refer to the cohort-specific Time and Events Schedules for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

Following Amendment 5, once the end of study data collection timepoint has been reached, the eCRF will be closed and only SAEs must be reported through the company safety repository.

10.1. Completion

Prior to Protocol Amendment 5, a subject will be considered as having completed the study if he or she has died before the end of the study or has not been withdrawn from the study by the end of the study (see Section 10.2). Following Amendment 5, once the end of study data collection timepoint has been reached, subjects who continue to benefit from study treatment(s), as determined by their investigator, may continue to receive access to study treatment(s) on this study, with reduced data collection (see Section 17.9.1), either via a long term extension roll-over study or any other post-trial access program, when permitted by local regulations. Provision may continue until the subject can commercially access study treatment(s) within the local healthcare system, until a decision is made not to pursue the studied indication, until the investigator decides it is in the best interest of the subject that study treatment(s) be discontinued, or until 2 years after local marketing authorization for is obtained for the studied indication, whichever comes first.

Once the end of study data collection timepoint has been reached, subjects who have discontinued study treatment(s), and all ongoing subjects in the Follow-up Phase will be considered to have completed the study (see Section 17.9.1 for definition of end of study data collection).

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject who discontinued treatment will be followed up for recovery of AEs for subsequent therapies and survival.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
- The subject has met any of the criteria listed in Sections 6.2.2 or 6.3.3
- The subject becomes pregnant
- Disease progression

- Exception: if the investigator and medical monitor agree that continuation of treatment is in the best interest of the subject considering the terminal nature of the underlying disease, he/she may receive treatment until such time as the treating physician and the medical monitor agree that further continuation of treatment is no longer beneficial to the subject
- Unacceptable toxicity
- The subject refuses further treatment with the study drug
- The sponsor terminates the study
- Investigator decision approved by the sponsor

If a subject discontinues study treatment for any reason before the end of the Treatment Phase, an End-of-Treatment Visit should be completed, and posttreatment assessments should be obtained and scheduled assessments should be continued.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects may be replaced if 1 of the following criteria is met:

- The subject withdraws prior to the study drug administration.
- The subject is not evaluable for DLT (For the Phase 1b erdafitinib + cetrelimab cohort, refer to Section 3.3.1 of Appendix 1. For the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort, refer to Section 3.3.1 of Appendix 2.)

10.3. Withdrawal From the Use of Research Samples

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the Full-Study ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Sample Size Determination

This is a Phase 1b-2 study comprised of a Phase 1b dose escalation part and a Phase 2 dose expansion cohort. The sample size of each phase is calculated as described in Sections 11.1.1 and Section 11.1.2.

11.1.1. Sample Size - 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 are met or the RP2D is determined. Once a dose level is opened for enrollment, subjects will be entered in groups of 3 unless otherwise clinically indicated. A minimum of 6 subjects will be treated at a dose level or at the next higher level before the dose level can be declared as the RP2D. The expected number of subjects to be enrolled in the Phase 1b erdafitinib + cetrelimab cohort is 12 to 30.

A total of approximately 40 subjects will be enrolled in the Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort. Three subjects (either wild-type or with select FGFR gene alterations) will be enrolled in the initial erdafitinib + cetrelimab + cisplatin dose level (50 mg/m^2). If the starting dose is safe, 6 additional subjects will be enrolled into the escalated dose of cisplatin (60 mg/m^2). Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations as described in Table 4. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib + cetrelimab + cisplatin.

Three subjects (either wild-type or with select FGFR gene alterations) will be enrolled in the initial erdafitinib + cetrelimab + carboplatin dose level (AUC4 mg/mL/min). If the starting dose is safe, 6 additional subjects will be enrolled into the escalated dose of carboplatin (AUC5 mg/mL/min). Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib + cetrelimab + carboplatin.

11.1.2. Sample Size - 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), ORR will be estimated using a 95% confidence interval. Assuming a true ORR of 45%, a sample size of approximately 45 subjects will result in a 95% confidence interval that excludes those 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 approximately 45 subjects result in a 95% confidence interval that excludes ORR less or equal to 40%.

11.2. Dose Escalation (Phase 1b)

A Modified Toxicity Probability Interval method, mTPI-2, will guide the dose escalation and RP2D recommendation in Phase 1b. In the mTPI-2 method, a decision theoretical framework links the dose-finding decisions of "Stay", "De-escalation", and "Escalation" with the equivalence interval $(p_T - \varepsilon_1, p_T + \varepsilon_2)$, over-dosing interval(s), and under-dosing interval(s), respectively. In this study, we use $p_T = 0.33$ and $\varepsilon_1 = \varepsilon_2 = 0.05$, the equivalence interval is (0.28, 0.38). The interval, which has the largest posterior probability divided by the length of the interval, is selected as the winning interval and the dose-finding recommendation can be set correspondingly. At the end of Phase 1b, the estimated MTD is the dose with the smallest difference between the transformed posterior mean of p_d and p_T and among all the doses d. The detailed dose escalation guidelines for this study are outlined in and the SET charter. However, dose selection for the next cohort and the decision for RP2D are described in Section 3.3.

11.3. Analysis Populations

The analysis populations for the Phase 1b dose escalation part of the study are defined as the following:

- The Treated Population will consist of all subjects who receive at least 1 dose of study drug(s).
- DLT Evaluable Population: This set consists of all DLT evaluable subjects (defined in Section 3.3.1) among the treated population.

The analysis populations for the Phase 2 dose expansion part of the study are defined as the following:

- The Treated Population will consist of all subjects who receive at least 1 dose of study drug(s). The Treated Population will be used for all safety analyses and for efficacy analysis unless otherwise specified in the Statistical Analysis Plan.
- The PK/PD Population will consist of all subjects who received at least 1 dose of study dug(s) and have at least 1 during treatment sample collected to determine the concentration or PD biomarker response.

Subgroup analyses will be performed as appropriate, and details will be specified in the Statistical Analysis Plan.

11.4. Efficacy Analyses (Phase 2 Only)

The primary efficacy analysis is planned with ~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 investigators. After the end of study data collection timepoint has been achieved, no further efficacy data will be collected on the eCRF.

To explore the clinical activity of erdafitinib or erdafitinib in combination with cetrelimab in Phase 2, the following efficacy analyses will be performed by each arm in the treated population according to the RECIST 1.1 criteria:

- Primary endpoint: ORR will be estimated with a 95% confidence interval. The primary efficacy analysis will be based on the response assessed by investigators.
- Secondary endpoints: TTR will be summarized descriptively based on responders. The Kaplan-Meier method will be used to estimate the distribution of DoR based on responders. The distributions of PFS and OS will be summarized using similar Kaplan-Meier estimates.

11.5. Pharmacokinetic Analyses

Study drug concentration data will be listed by dose cohort/arm and summarized at each time point using descriptive statistics (arithmetic mean, standard deviation [SD], coefficient of variation, geometric mean, median, minimum, and maximum). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study agent, concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits, or early discontinuation from the study). The data from both phases of the studies will also be analyzed using population PK analysis via nonlinear mixed-effect modeling. Previously developed PK models may be used and updated as considered appropriate. Data may be combined with data from other studies to support a relevant structural population-based PK model. Available subject characteristics (demographics, laboratory variables, genotypes, etc.) may be tested as potential covariates affecting PK parameters. Individual PK parameters and metrics of exposure for erdafitinib, cetrelimab, and carboplatin/cisplatin will be summarized. Details of population PK analyses will be provided in a separate analysis plan and results will be described in a separate report, if such analyses are performed.

11.6. Immunogenicity Analyses

The incidence of antibodies to cetrelimab will be summarized for all subjects who receive a dose of cetrelimab and have appropriate samples for detection of antibodies to cetrelimab.

11.7. Pharmacodynamic Analyses, and Biomarker Analyses

CCI [redacted] over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in selected markers and clinical response will be explored.

Results of exploratory pharmacodynamic biomarker analyses may be presented in a separate report. Planned biomarker analyses may be deferred or canceled if emerging data show no likelihood of providing useful scientific information.

11.8. Pharmacokinetic/Pharmacodynamic Analyses

Model-derived exposure parameters of erdafitinib, cetrelimab, and platinum chemotherapy may be used to explore PK/PD correlation for key efficacy and safety parameters, including the influence of covariates, and inter-individual variability between exposure with relevant clinical or biomarker information using a population PK/PD approach. Details of these population PK/PD analyses will be provided in a separate analysis plan and results may be described in a separate report.

11.9. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to NCI-CTCAE, version 5.0 (see Table 7 for nail toxicity and hyperphosphatemia grading). All reported AEs with onset during the treatment period (ie, TEAEs and AEs that have worsened since baseline) will be included in the analysis.

Specifically, the following will be summarized:

- Incidence of DLT (Phase 1b)
- All AEs, including irAEs
- Grade 3 or higher AEs
- Serious AEs
- AEs leading to permanent discontinuation of treatment
- AEs leading to death

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline. Parameters with predefined toxicity grades will be summarized. Change from baseline to the worst Grade experienced by the subject during the study will be provided as shift tables.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst AE Grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of pulse/heart rate and blood pressure (systolic and diastolic), and change from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Frequency tabulations of the abnormalities will be made.

Electrocardiogram

The effects of erdafitinib and cetrelimab on ECGs (QT, QTc, PR, QRS, heart rate) will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values to allow detection of clinically relevant changes in individuals.

11.10. Data Review Committee

A DRC will be established to monitor data on an ongoing basis to ensure the safety of the subjects enrolled in Phase 2 of this study. Additionally, the DRC may review ongoing cumulative data from Phase 1b after the RP2D has been determined.

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.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrence. For some studies, subjects are not always able to provide valid verbal responses to open-ended questions. In these circumstances, the investigator will decide the appropriate method of reporting the AE.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the subject is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the subject is specifically not questioned.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the Full-Study ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union (EU) Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For erdafitinib and cetrelimab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

Adverse event severity is a clinical determination of the intensity of an AE. The severity assessment for an AE or SAE should be completed using the NCI-CTCAE, version 5.0. Any AE or SAE not listed in the NCI-CTCAE, version 5.0 will be graded according to the investigator clinical judgment by using the standard grades as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breast-feeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

For additional details on reporting a retinal abnormality, which is an AE of special interest, see Section 6.2.3.6.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported starting from the time a signed and dated Full-Study ICF is obtained until 30 days after the last dose of erdafitinib, and 100 days after the last dose of cetrelimab (whichever is longer). If the subject starts a subsequent systemic anticancer therapy, AE data collection will be limited to only Grade ≥2 immune-related AEs (for subjects who received cetrelimab) and all SAEs from the date the new anticancer therapy is initiated until 30 days after the last dose of erdafitinib or 100 days after the last dose of cetrelimab, whichever is longer (see table below). Grade 3 and higher AEs, if considered related to study drug, occurring more than 100 days after the last dose of study drug should also be reported. Resolution information after 100 days should be provided. Subjects who discontinue study drug due to drug-related toxicity will continue to be monitored for this toxicity until the toxicity resolves to baseline, stabilizes, or is deemed irreversible, the subject dies, or

subsequent therapy is started, whichever occurs first. Anticipated events will be recorded and reported as described in Attachment 7.

Following Amendment 5, once the end of study data collection timepoint has been achieved, all subjects will transition to the schedule of activities in APPENDIX 4. No further data will be collected on the eCRF. Subjects who are continuing to derive benefit from study treatment as assessed by their investigator may continue to receive study treatment(s); during this period, only serious adverse events will be monitored and entered into the Company safety repository.

Study Treatment	**Timing of AE collection**
Erdafitinib	All AEs collected until 30 days after the last dose; after this time period, Grade 3 and higher AEs related to study treatment*
Cetrelimab	All AEs collected until 100 days after the last dose; after this time period, Grade 3 and higher AEs related to study treatment*
Following subsequent systemic anticancer therapy	
Erdafitinib	All SAEs collected until 30 days after the last dose
Cetrelimab	Grade ≥2 immune-related AEs and all SAEs collected until 100 days after the last dose*

*After the end of study data collection date has occurred, only SAEs will be collected and entered into the Company safety repository.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Serious AEs, including those spontaneously reported to the investigator within 100 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual SAEs the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety

report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study-site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the

course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- A standard procedure for protocol therapy administration will not be reported as an SAE including hospitalization due to a longer than anticipated infusion time. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, PK, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

12.3.3. Disease-related Events or Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Progression of disease should not be considered nor should be reported as an AE (or SAE). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Section 12.1.1.).

12.3.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Erdafitinib will be supplied as 3 mg, 4 mg, and 5 mg tablets for oral use. It will be manufactured and provided under the responsibility of the sponsor. Refer to the erdafitinib IB for a list of excipients (Investigator's Brochure for JNJ-42756493 2018).

Cetrelimab can be supplied as a frozen liquid in vial or a lyophilized product in a vial.

Cetrelimab Frozen Liquid in Vial

The cetrelimab study material supplied for this study is a sterile, frozen liquid. Each vial of cetrelimab clinical study material contains 3 mL of a 10 mg/mL cetrelimab solution of cetrelimab. It will be manufactured and provided under the responsibility of the sponsor.

Cetrelimab Lyophilized

Cetrelimab is supplied as a single use, lyophilized product. The 90 mg cetrelimab final lyophilized product (FLP) has been designed to deliver 90 mg of a 30 mg/mL solution after reconstitution with 3 mL of water for injection (WFI). Additionally, a larger vialed 240 mg cetrelimab FLP has been designed to deliver 240 mg of a 30 mg/mL solution after reconstitution with 8 mL WFI.

Frozen and lyophilized drug products will be manufactured and provided under the responsibility of the sponsor. Refer to the cetrelimab IB for a list of excipients for both the frozen liquid and lyophilized drug products (Investigator's Brochure for JNJ-63723283 2018).

Cisplatin

Cisplatin will be sourced locally by the study-site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study-site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The study-site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

For further information regarding cisplatin refer to the current approved label.

Carboplatin

Carboplatin will be sourced locally by the study-site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study-site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The study-site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

For further information regarding cisplatin refer to the current approved label.

14.2. Packaging

The study drug will be packaged in kits. The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

Erdafitinib tablets for oral use in this study will be packaged in child-resistant packaging bottles. Each bottle will contain 30 tablets/bottle for each strength: 3 mg, 4 mg, and 5 mg.

Cetrelimab vials will not be dispensed in child-resistant packaging.

Cisplatin and carboplatin will be sourced locally and packaged according to local applicable laws and regulations.

No study drugs can be repacked without prior approval of the sponsor.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

Cisplatin and carboplatin will be sourced locally and labeled according to local applicable laws and regulations.

No study drugs can be relabeled without prior approval of the sponsor.

14.4. Preparation, Handling, and Storage

All study drugs must be stored as specified on the label.

Refer to the pharmacy manual/study-site investigational product manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. Study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study-site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study-site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study intervention must not be dispensed again, even

to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Investigator's Brochures
- IPPI/SIPPM
- Laboratory Manual
- RECIST 1.1 guidelines
- IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF (Molecular Eligibility and Full-Study)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. This is the first clinical evaluation of erdafitinib in combination with cetrelimab, as well as these study drugs in combination with platinum chemotherapy. As the benefits and risks in this study population are not fully known, this study will evaluate the safety and clinical activity of these combinations. In this study, 2 dosing schedules (concurrent and sequential dosing) may be explored to minimize the potential toxicities. Subjects will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. A SET or DRC will review evolving safety data from this study and other relevant studies. A discussion about the overall rationale for the study and the anticipated benefits and risks are provided in Sections 1.7 and 1.8, respectively. Based on the known data and the mechanism of action of both study drugs, there is adequate justification, including significant unmet clinical need, for evaluating these drugs in combination for the treatment of urothelial cancer in subjects who are eligible for this study.

Additionally, all subjects will undergo periodic disease assessments to monitor the underlying disease. The frequency of evaluations is similar to standard practice for patients outside of clinical trials and the overall risk is low. Subjects will have pre- and posttreatment tumor biopsies, where applicable. In general, these procedures are routinely performed during a subject's diagnostic work-up and follow-up care. Although biopsy collection is associated with risk, the complication rate for these procedures is low. The data obtained from this procedure will generate valuable scientific data on the pharmacodynamic effect of the combination of these study drugs in this study population. As with all clinical and pharmacology studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was

designed to collect the minimum number of blood samples that accurately and completely describe the pharmacology of the study drug. This minimizes the number of venipunctures and the total volume of blood collected from each subject during the study. The volume of blood to be drawn is considered to be customary and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study, based upon the standard of the American Red Cross (American Red Cross 2015).

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

After informed consent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PD biomarker, PK and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand erdafitinib, cetrelimab and co-medications in the protocol, and if applicable, to understand cancer, to understand differential drug responders, and to develop tests/assays related to erdafitinib, cetrelimab and co-medications in the protocol, if applicable. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Research Samples).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly

addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study-site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the

applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study-site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed ICF;

dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:
- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If an electronic source is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through electronic source may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of the study is defined as the last study assessment for the last subject on study or anytime the sponsor terminates the study, whichever comes first.

Prior to Protocol Amendment 5, the final data from the study-site was to be sent to the sponsor (or designee) after completion of the final subject visit at that study-site, in the time frame specified in the clinical trial agreement.

Following Amendment 5, the end of study data collection is defined as when the primary efficacy analysis clinical cutoff has been achieved. At that time, follow up of subjects will end and the eCRF will be closed. Subjects who are continuing to derive benefit from erdafitinib and/or cetrelimab treatment as assessed by their investigator may continue to receive erdafitinib and/or cetrelimab; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

17.9.2. Study Termination

The sponsor reserves the right to close the study-site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study-site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

The sponsor will ensure that subjects benefiting from study treatment(s) can continue to receive treatment(s) after the study has been terminated.

Reasons for the early closure of a study-site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study-site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding erdafitinib, cetrelimab, or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of erdafitinib and cetrelimab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study-site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will

be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: mTPI-2 Dose-finding Design

The mTPI-2 design is a new version of mTPI. The authors demonstrated that mTPI-2 has superior performance. The details can be found in the paper: Guo et al, (Guo 2017). The particular mTPI-2 used in the study (and) is as in the table below.

Number of Subjects with DLTs	Number of Subjects Treated (at a Dose)						
	3	4	5	6	7	8	9
0	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	**S**	**E**	**E**	**E**	**E**	**E**	**E**
2	**D**	**D**	**D**	**S**	**S**	**E**	**E**
3	**DU**	**DU**	**D**	**D**	**D**	**S**	**S**
4		**DU**	**DU**	**DU**	**D**	**D**	**D**
5			**DU**	**DU**	**DU**	**DU**	**D**
6				**DU**	**DU**	**DU**	**DU**
7					**DU**	**DU**	**DU**
8						**DU**	**DU**
9							**DU**

* **E**: Escalate to the next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **DU**: De-escalate to the previous lower dose and the current dose will never be used again in the study.

Attachment 2: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine subject eligibility for the study:

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Exclude	+	— *or* +	— *or* +
	—	—	+
Include	—	—	—
	—	+	+
	—	+	—

Centers for Disease Control and Prevention (US) (Interpretation of Hep B 2017).

Attachment 3: Eastern Cooperative Oncology Group Performance Status Grade

Grade	Eastern Cooperative Oncology Group Performance Status
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, eg, 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	Dead

Oken 1982

Attachment 4: Drugs Classified as Strong CYP3A4 Inhibitors, Moderate to Strong CYP3A4 Inducers, Moderate CYP2C9 Inhibitors, and Moderate CYP2C9 Inducers

Strong CYP3A4 Inhibitors

Boceprevir	Conivaptan
Clarithromycin	Indinavir
Grapefruit juice	Itraconazole
Lopinavir	Ketoconazole
Mibefradil	Ritonavir
Nefazodone	Nelfinavir
Posaconazole	Conivaptan
Saquinavir	Boceprevir
Telaprevir	Clarithromycin
Telithromycin	Erythromycin
Voriconazole	Troleandomycin
Fluconazole	

Strong Inhibitors: ≥5-fold increase in AUC or >80% decrease in CL.

Moderate to Strong CYP3A4 Inducers

Moderate CYP3A4 Inducers	
Bosentan	Efavirenz
Etravirine	Modafinil
Nafcillin	Lersivirine
Talviraline	Tipranavir
Lopinavir	
Strong CYP3A Inducers	
Avasimibe	Carbamazepine
Barbiturates eg, phenobarbital	Phenytoin
Rifabutin	Rifampin
St. John's wort	Mitotane
Enzalutamide	Apalutamide

Strong Inducers: ≥80% decrease in area under the curve (AUC). Moderate Inducers: 50% to 80% decrease in AUC.

Moderate CYP2C9 Inhibitors

Fluconazole	amiodarone
Miconazole	piperine
Oxandrolone	atacigual
tienilic acid	azapropazone
Bucolome	sulfaphenazole
Benzbromarone	

Moderate CYP2C9 Inducers

Carbamazepine	rifampin
Enzalutamide	aprepitant

Reference: University of Washington's Drug Interaction Database
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#4
Both these references may not be exhaustive and up-to-date at any given time. Please consult the product information of ongoing and new concomitant medications for the most accurate information on potential moderate to strong inhibitors or inducers of CYP3A4 and CYP2C9.

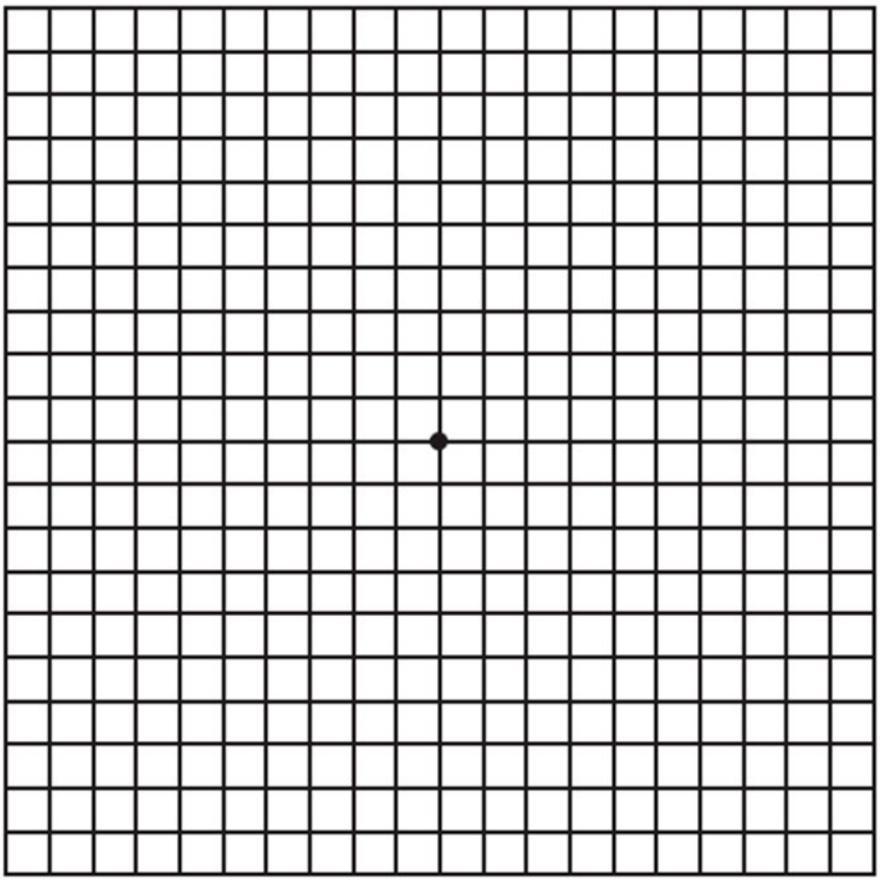
Attachment 5: Amsler Grid

Study Number: _____

Subject ID: _____

Date: _____

Examiner: _____



Attachment 6: The Stages of Heart Failure – New York Heart Association (NYHA) Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath) .
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Heart Failure Society of America The Stages of Heart Failure – NYHA Classification. Available at http://www.abouthf.org/questions_stages.html. Accessed October 6, 2008.

Attachment 7: Anticipated Events

Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study, the following events will be considered anticipated events:

- Cauda equina syndrome
- Haematuria
- Urinary incontinence
- Lymphedema
- Pathological fracture
- Spinal cord compression
- Urinary hesitation
- Ureteric obstruction
- Urine flow decreased
- Urinary retention
- Urinary tract obstruction
- Urinary tract stoma complication
- Urinary tract pain
- Urinary tract infection
- Urosepsis

Because this is the first study of the combination of cetrelimab and erdafitinib, other AEs cannot be anticipated. Platinum-based chemotherapies, cisplatin and carboplatin, are known to have similar but varying frequency of AEs such as thrombocytopenia, leukopenia, anemia, vomiting, nausea, nephrotoxicity, neurotoxicity and ototoxicity, when used as monotherapies, and increase in severity or frequency of such AEs in the cisplatin and carboplatin combination cohorts in this study cannot be anticipated.

Reporting of Anticipated Events

All AEs will be recorded in the electronic case report form (eCRF), regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 12.3.2. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) per applicable clinical trial legislation to Health Authorities and IRB/ECs (Note: Japan will not identify anticipated events for the health authorities). If an anticipated event is

considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

A SAC will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study treatment based on a review of the aggregate data by arm.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

Attachment 8: Cockcroft-Gault Formula for Estimated Creatinine Clearance (CrCl)

$$eCR = \frac{(140 - Age) \times Mass\ (kilograms) \times [0.85\ if\ female]}{72 \times Serum\ Creatinine\ (in\ mg/dL1)}$$

OR

$$eCcr = \frac{(140 - Age) \times Mass\ (kilograms) \times Constant}{Serum\ Creatinine\ (\ in\ \mu mol/L)}$$

Where Constant = 1.23 for men and 1.04 for women

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

Attachment 9: RECIST GUIDELINES

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The following information was extracted from Section 3, Section 4, and Appendix I of the New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009). Refer to the European Journal of Cancer article (2009;45(2):228-247) for the complete publication.

Measurability of tumor at baseline

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
- Lymph nodes to be considered pathologically enlarged and measurable. A lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness is recommended to be a maximum of 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

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 or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Specifications by methods of measurements

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 nodules). For the case of skin 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. See Appendix II for more details.

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. As is described in Appendix II, when CT scans have 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). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response (CR).

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

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. Measurable disease is defined by the presence of at least one measurable lesion

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.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

A sum of the diameters (longest for non-nodal lesions,) for all target lesions will be calculated and reported as the *baseline sum diameters*. The baseline sum 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) 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. 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 tumour response for target lesions.

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): 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 (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing non-target lesions. (*Note*: the appearance of one or more new lesions is also considered progression).

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 taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if posttreatment assessments are to be considered in determination of best overall response. 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.

Timepoint response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Best overall response: all timepoints

The *best overall response* is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 - Timepoint 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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable.

Table 2 - Timepoint Response: Patients with Non-Target Disease Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; NE = inevaluable.

[a] Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

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 as shown in Tables 1–2.

Conditions that define 'early progression, early death and inevaluability' are study-specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

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.

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 progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) 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 progressive disease).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Attachment 10: Guidance on Study Conduct During a National Disaster for Enrolled Subjects

It is recognized that a national disaster, eg, pandemic, may have an impact on the conduct of this clinical study. In alignment with the recent health authority guidances, the sponsor is providing guidance for study-related patient management in the event of disruption to the per protocol conduct of the study as outlined throughout the protocol. These measures are to be followed on a temporary basis. Once the national situation allows, the usual study conduct methods will resume. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of patients and site staff. If at any time a subject's safety is considered to be at risk, study drug will be discontinued, and study follow-up will be conducted, as outlined in the protocol. (Note: These measures do not apply to subjects who have not initiated study treatment.)

Scheduled visits for safety monitoring and other protocol required assessments that cannot be conducted in-person will be performed remotely/virtually (eg, telephone contact, telemedicine, remote nursing, remote administration of study drug), where feasible, or delayed until the time at which access is determined to be appropriate by the investigator and sponsor. Study assessments requiring investigator judgment, should be conducted by the investigator. At each contact, subjects will be interviewed to collect adverse events data and any changes to concomitant medications. Subjects will also be questioned regarding general health status to fulfill the physical examination requirement.

Flexibility for all protocol required assessments will be provided on a case by case basis, and with agreement between the sponsor and investigator. However, every effort should be made to adhere to protocol-specified assessments, including follow-up, if it is in the best interest of the subject. The sponsor will continue to monitor the conduct and progress of the clinical study and any changes (eg, delay or discontinuation in recruitment) will be communicated to the sites and health authorities.

Guidance specific to this protocol:

- Missed assessments or change to protocol assessments will be documented in the source documentation and in the eCRF. All study conduct performed outside of the protocol should be documented in the source documentation.

- If a site visit is not feasible, the investigator may discuss with the sponsor other mechanisms for the subject to receive study drug (eg, direct to patient shipment, obtain from another Investigative Site participating in the study). Any change in dispensing study drug must be documented in the source documentation and eCRF.

- Safety assessments may be conducted at a local facility after discussion with the sponsor.

- Critical laboratory tests, imaging or other diagnostic tests may be done at an authorized/certified (as legally required nationally) local laboratory or clinical facility. A copy of the laboratory report must be reviewed by the investigator and retained, along with the reference ranges, for the source documentation and provided with the eCRF.

- Consenting of subjects for full-study screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent. (Remote consenting for molecular eligibility screening is described in the main body of the protocol.)

APPENDIX 1: PHASE 1B ERDAFITINIB + CETRELIMAB

Appendix 1 Table 1: Time and Events Schedule – Phase 1b (Erdafitinib + Cetrelimab Cohort) (Up to and including Amendment 4)

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[f]		Treatment Cycle 2[f], 3[f]		All Other Cycles[f]		End of Treatment[a, f]	Follow-up Period[a, f]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[d]	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15[e, g] (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Screening Assessments											
Informed Consent (molecular and full-study)	Molecular Eligibility ICF to allow for assessment of FGFR status from archived tumor tissue, blood or local report. Full-Study ICF within 35 days prior to C1D1 to be used for subjects who meet molecular eligibility criteria. Must be signed before any study-related activity.[b]	X	X								
Eligibility Criteria	Details provided in Sections 4.1 and 4.2 of Appendix 1.		X								
Demography, and Medical History	Histology and cytology, staging, prior therapy, and response.		X								

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[f]		Treatment Cycle 2[f], 3[f]		All Other Cycles[f]		End of Treatment[a, f]	Follow-up Period[a, f]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[d]	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15[e, g] (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Molecular Eligibility Determination											
Local FGFR results (where applicable)[i]	Subjects may enroll based on local test results. • Subjects with local FGFR tissue or blood results must submit test report to the sponsor for central verification. • Subjects enrolling based on local testing must submit archival or fresh tumor tissue and a blood sample for retrospective confirmation of FGFR status as soon as possible after enrollment. The results of retrospective central confirmation do not affect the subject's eligibility for the study.	X									
Central Testing from Tissue and Blood[i]	Archival or fresh biopsy tumor tissue and a blood sample should be submitted for molecular eligibility screening. If fresh biopsy, the subject must sign the Full-Study ICF.	X									
Study Drug Administration											
Phase 1b											
Erdafitinib	See Sections 6.1 and 6.2.			Oral once daily							
Standard Regimen											
Cetrelimab infusion	See Sections 6.1 and 6.3.			X	X	X	X	X	X		

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[f]		Treatment Cycle 2[f], 3[f]		All Other Cycles[f]		End of Treatment[a, f]	Follow-up Period[a, f]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[d]	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15[e, g] (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Alternative Regimen											
Cetrelimab infusion	See Sections 6.1 and 6.3.					X	X	X	X		
Safety Assessments											
Vital Signs (temperature, blood pressure, pulse/heart rate, respiratory rate)	Monitor every 15-20 min during the 1st infusion; for monitoring during subsequent infusions see Section 6.3.		X	X	X	X	X	X	X	X	X[c]
Physical Examination (PE)	Complete PE including height and weight at Screening. Thereafter disease-directed PE. See Section 9.6.9.		X	X	X	X	X	X	X	X	X[c]
ECOG PS	See Attachment 3.		X	X		X		X		X	
12-lead ECG[j]	Results obtained within 60 days of C1D1 can be counted as screening assessment.		X			C2 only		C4 only		X	
Echocardiogram or MUGA	Results obtained within 6 months of C1D1 can be counted as screening assessment provided the subject has not experienced any cardiac event in the interim. Subsequent evaluations as clinically indicated.		X								
Amsler grid Test	To be performed by treating physician or nurse (or other appropriate study personnel).		X			X		X		X	
Ophthalmologic Exam	To be performed by an ophthalmologist See Section 9.6.7 for exact assessments.		X	As clinically indicated (eg, based on abnormal Amsler grid test, see Attachment 5)							
Laboratory Assessments (by the local laboratory)											

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[f]		Treatment Cycle 2[f], 3[f]		All Other Cycles[f]		End of Treatment[a, f]	Follow-up Period[a, f]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[d]	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15[e, g] (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Hematology	See Section 9.6.2; May be obtained up to 2 days prior to each cetrelimab dose.		X	X	X	X	X	X	X	X	
Chemistry[h]	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2.		X	X	X	X	X	X	X	X	
PO_4	May be obtained up to 2 days prior to each cetrelimab dose: for exact assessments, see Section 9.6.2. If appropriate, the decision to up-titrate erdafitinib will be based on C1D15 (±2 days) PO_4		X	X	X	X	X	X		X	
PTH	May be obtained up to 2 days prior to each cetrelimab dose: for exact assessments, see Section 9.6.2. After C6D1 PTH to be done every 3rd cycle. Results not required before dosing.		X		X	X		X		X	
TSH, T3, FT4	May be obtained up to 2 days prior to each cetrelimab dose: for exact assessments, see Section 9.6.2. T3 at Screening then only as clinically indicated.		X	Day 1 of every other cycle starting at C2D1							
Serology	See Section 9.6.2. Results obtained within 60 days of C1D1 are acceptable.		X								
Pregnancy test (pre-dose)	For women of childbearing potential, serum at Screening (β-hCG) - obtain ≤7 days of C1D1. Serum or urine thereafter. See Section 9.6.4.		X			X		X		X	X[c]

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[f]		Treatment Cycle 2[f], 3[f]		All Other Cycles[f]		End of Treatment[a, f]	Follow-up Period[a, f]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[d]	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15[e, g] (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Efficacy Assessments											
Disease assessment and response evaluation	Radiologic assessment by CT (preferred) or MRI of all disease sites (present and suspected) documented at Screening. The same methodology should be used throughout the study. Refer to Section 9.2. for details. Disease assessments done within 35 days prior to C1D1 may be used as the Screening disease assessment.		X	Every 6 weeks until week 48 (±3 days), then every 12 to 24 weeks (±14 days) until disease progression. The timing of disease assessments should be calculated from C1D1 and the schedule should be maintained regardless of cycle delays and/or study drug interruptions. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 9.1.3). Tumor response will be evaluated according to RECIST 1.1 criteria. (Seymour 2017). All unconfirmed PR/CR require confirmation of response as per RECIST 1.1.						
Ongoing Review											
Adverse Events	X - Continuous from signing of Full-Study ICF to up to 100 days after the last dose of study treatment or until the start of subsequent anticancer therapy. An AE should be monitored until it resolves to baseline, stabilizes, or is deemed irreversible, subject dies, or subsequent therapy is started, whichever occurs first.										
Concomitant medications	X - Continuous from signing of Full-Study ICF to up to 100 days after the last dose of study treatment or until the start of subsequent anticancer therapy, if earlier. See Section 8.										
Posttreatment Assessments											
Survival evaluation	Contact subject every 12 weeks (±7 days) after the last dose of study treatment by office visit, phone call or e-mail. See Section 9.1.4.										X
Subsequent anticancer therapy	Contact subject every 12 weeks (±7 days) after the last dose of study treatment by office visit, phone call or e-mail. See Section 9.1.4.										X

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; b-hCG= beta-human chorionic gonadotropin; C = cycle; CR= complete response; CT = computed tomography; ctDNA=circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI=end of infusion; FGFR= fibroblast growth factor receptor; FT4= free thyroxine; ICF = informed consent form; INR = international normalized ration; MRI = magnetic resonance imaging; MUGA= multi-gated acquisition scan; OCT = optical coherence tomography; PBMC=peripheral blood mononuclear cell; PD-L1 = programmed cell death ligand 1; PE = physical examination; PK = pharmacokinetics; PO_4 = phosphate; PR= partial response; PS = performance status; PT = prothrombin time; PTH=parathyroid hormone; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; T3= triiodothyronine; TCR=T cell antigen receptor; TSH= thyroid stimulating hormone

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[f]		Treatment Cycle 2[f], 3[f]		All Other Cycles[f]		End of Treatment[a, f]	Follow-up Period[a, f]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[d]	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15[e, g] (±2)	Within 30 Days (+7) of last dose	Every 12 weeks

[a] The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy. Follow-up visits will occur every 12 weeks (±7 days).

[b] For subjects signing a Full-Study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 35-day window starts with the first planned study-related procedure other than the tissue biopsy; however, AEs will need to be collected from the time of Full-Study ICF sign off.

[c] Physical examination, vital signs, and pregnancy testing at first follow-up visit (12 weeks after last dose).

[d] C1D1 must occur no more than 3 days after the Enrollment transaction in IWRS

[e] Subjects who discontinue cetrelimab but continue on erdafitinib do not need to come in for the Day 15 visit after Cycle 3.

[f] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 10.

[g] Subjects who continue cetrelimab dosing at Cycle 5 onward, do not need to come in for the Day 15 visit.

[h] CrCl is calculated by the Cockcroft-Gault formula (Attachment 8).

[i] Consent for molecular screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.

[j] Post-dose ECGs for subjects receiving erdafitinib monotherapy should be recorded 2 to 4 hours after the erdafitinib dose on C2D1 and, if possible, 2 to 4 hours after the erdafitinib dose on C4D1. Post-dose ECGs for subjects receiving erdafitinib and cetrelimab in combination should be recorded as soon as possible upon completion of infusion on C2D1 and C4D1. The End-of-Treatment ECG may be performed at any time during the End-of-Treatment Visit. Additional ECGs may be performed during the study as clinically indicated.

Appendix 1 Table 2: Pharmacokinetic, Immunogenicity, and Biomarker Samples for the Phase 1b (Erdafitinib + Cetrelimab Cohort) (Up to and Including Amendment 4)

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1		Treatment Cycle 2, 3		All Other Cycles		End of Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Standard Regimen [b]	Note: These samples should be drawn on the day study drug is administered.										
Erdafitinib PK [c]	Pre-dose erdafitinib [d] unless otherwise specified. See Section 9.3.			X	X	Pre-dose erdafitinib C2 & C3; 4h post erdafitinib C2D1 only [e]		Pre-dose erdafitinib C5; 4h post erdafitinib C5D1 only			
Erdafitinib Protein Binding Blood Sample	4 hrs Post-dose. See Section 9.3.					4h post erdafitinib C2D1					
Cetrelimab PK [c]	Pre-infusion [d] and EOI [f] unless otherwise specified. See Section 9.3.			X [g]	X [g]	X		C4D1 & C5D1		Any time during visit	At first follow-up visit, if possible
Cetrelimab Immunogenicity	Pre-infusion [d] See Section 9.3.			X	X	X		C4D1 & every other cycle starting at C5D1		Any time during visit	At first follow-up visit, if possible
CCI [redacted]	Pre-dose erdafitinib [d]			X	X	X	X				
CCI [redacted]	Pre-dose erdafitinib [d]			X	X	X	X			Any time during visit	
CCI [redacted]	Pre-dose erdafitinib [d]			X		C3D1		C5D1		Any time during visit	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1		Treatment Cycle 2, 3		All Other Cycles		End of Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Tumor tissue for PD-L1 testing and bladder cancer subtyping	Archival or fresh biopsy tissue must be available for biomarker analysis.	X									
Alternative Regimen [b]	Note: These samples should be drawn on the day study drug is administered.										
Erdafitinib PK [c]	Pre-dose erdafitinib [d] unless otherwise specified. See Section 9.3.			X	X	Pre-dose erdafitinib C2 & C3; 4h post erdafitinib C2D1 only [e]		Pre-dose erdafitinib C5; 4h post erdafitinib C5D1 only			
Erdafitinib Protein Binding Blood Sample	4 hrs Post-dose See Section 9.3.					4h post erdafitinib C2D1					
Cetrelimab PK [c]	Pre-infusion [d] and EOI [f] unless otherwise specified. See Section 9.3.			X	X	X		C4D1 & C5D1		Any time during visit	At first follow-up visit, if possible
Cetrelimab Immunogenicity	Pre-infusion [d] See Section 9.3.			X	X	X		C4D1 & every other cycle starting at C5D1		Any time during visit	At first follow-up visit, if possible
CCI [redacted]	Pre-dose erdafitinib [d]			X	X	X	X				
CCI [redacted]	Pre-dose erdafitinib [d]			X	X	X	X			Any time during visit	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1		Treatment Cycle 2, 3		All Other Cycles		End of Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Blood for ctDNA	Pre-dose erdafitinib [d]			X		C3D1		C5D1		Any time during visit	
Tumor Biopsy for Biomarker Research [h]	A tumor biopsy can be taken any time during a visit if a subject shows PD anytime throughout the study [i]		X			C2D1 (±3 days)				PD	
Tumor tissue for PD-L1 testing and bladder cancer subtyping	Archival or fresh biopsy tissue must be available for biomarker analysis.	X									

Abbreviations: ctDNA= circulating tumor DNA; EOI=end of infusion; FGFR= fibroblast growth factor receptor; PD= progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PBMC = peripheral blood mononuclear cells; TCR = T cell antigen receptor

[a] The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy. Follow-up visits will occur every 12 weeks (±7 days).
[b] The sampling schedule may be adjusted based on PK analysis output generated during the study or other safety concerns.
[c] 'Pre/post-dose' always refers to the dose of the compound for which PK samples are drawn. If dose delay occurs, then samples should be collected on the actual day of drug administration, not on the originally scheduled administration day.
[d] On the day in which both drugs are given, erdafitinib oral dose will be given before the start of cetrelimab IV infusion. Pre-dose PK sample for erdafitinib and Pre-infusion PK and immunogenicity samples for cetrelimab may be collected up to 30 minutes before dosing, respectively.
[e] Timepoint is relative to the dosing of erdafitinib. Erdafitinib PK samples may be collected during the cetrelimab infusion if necessary; however, the sample should be drawn from the contralateral arm (opposite the cetrelimab infusion site).
[f] As soon as possible after EOI.
[g] Cetrelimab PK is not required for alternative cohorts (alternative cohorts start cetrelimab on C2D1, e.g. DL2B).
[h] Paired biopsies at Screening and C2D1 are optional. The biopsy upon PD is also optional for all subjects. High-risk areas of metastases such as brain, pancreas, and lung should not be considered as an accessible site for biopsy. Biopsies will be collected to aim to have a minimum of 15 evaluable biopsy pairs.
[i] Tumor biopsy to be taken within 2 weeks of documented disease progression. Note: Additional samples may be collected at any time for assessment of AEs as clinically appropriate.

1. INTRODUCTION

Refer to Section 1 of the protocol for the introduction. The introduction includes a description of urothelial bladder cancer, FGFR signaling, erdafitinib, PD-1/PD-Li signaling, cetrelimab (summary of nonclinical data, summary of clinical data), platinum chemotherapy in metastatic urothelial cancer, overall rationale for the study, the anticipated benefits and risks for erdafitinib and cetrelimab, and the anticipated benefits and risks for platinum chemotherapy.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints for Phase 1b (Dose Escalation)

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of erdafitinib in combination with cetrelimab, and to identify the recommended Phase 2 dose(s) (RP2D) and schedule for erdafitinib	• Frequency and type of dose-limiting toxicity (DLT)
Secondary	
• To characterize the PK of erdafitinib and cetrelimab	• Concentration and PK parameters of erdafitinib and cetrelimab
• To assess the immunogenicity of cetrelimab	• Detection of antibodies to cetrelimab and effects on serum cetrelimab levels
Exploratory	
•To assess the CCI [redacted] •To evaluate CCI [redacted] •To assess changes in CCI [redacted] •To explore biomarkers (DNA, RNA, and/or protein) in tissue and blood samples that could CCI [redacted] •To explore the relationships between PK, PD, AE profiles, and CCI [redacted]	

2.2. Hypothesis for Phase 1b (Dose Escalation)

A RP2D(s) regimen of erdafitinib combined with cetrelimab can be identified for safe treatment of subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

Refer to Section 3.1 of the main body of the protocol.

3.1.1. Phase 1b for Erdafitinib + Cetrelimab Cohort

The Phase 1b erdafitinib + cetrelimab cohort represent the dose escalation part of the study. A Modified Toxicity Probability Interval method, mTPI-2, (Guo 2017) will be used by the Study Evaluation Team (SET, Section 3.4) to guide the dose escalation and RP2D(s) regimen recommendations (see Section 11.2, Attachment 1 and the SET charter). The expected number of subjects to be treated in the Phase 1b erdafitinib + cetrelimab cohort will range from 12 to 30.

Two dosing regimens may be explored: Standard Dose Levels (DL1, DL2 or DL2A) or Alternative Dose Levels (DL1B or DL2B) (Figure 1). Two dosing cohorts of erdafitinib may be explored, while cetrelimab IV dose will be fixed.

- Erdafitinib + cetrelimab Standard Dose Levels (DL1, DL2 or DL2A)

In the Standard Dose Levels, erdafitinib and cetrelimab starts concurrently from C1D1. The DLT evaluation period is 1 cycle (4 weeks [28 days]).

or

- Erdafitinib + cetrelimab Alternative Dose Levels (DL1B or DL2B)

In the Alternative Dose Levels, administration of erdafitinib starts on C1D1 but cetrelimab is initiated 1 cycle (28 days) later, on C2D1. A DLT period is 2 cycles (8 weeks). It is hypothesized that an initial erdafitinib monotherapy for 4 weeks may lead to improved tolerance of the subsequent concurrent dosing with a checkpoint inhibitor. The Alternative Dose Levels at the same dose is considered one dose level down from the Standard Cohort: DL1B for DL1 and DL2B for DL2/DL2A.

For the Phase 1b erdafitinib + cetrelimab cohort, cetrelimab will be dosed at 240 mg Q2W for Cycles 1 through 4 and 480 mg Q4W starting at Cycle 5. Refer to Figure 1 for an overview of the Phase 1b: erdafitinib + cetrelimab cohort.

The starting dose is DL1 (6 mg erdafitinib + 240 mg cetrelimab).

If based on the below rules, de-escalation is indicated from DL1, the one dose level down (DL1B) is started, and the Standard Dose Levels are abandoned. DL1B is the lowest dose cohort to be tested.

If based on the below rules, escalation is indicated from DL1, then DL2 and DL2A are started (with subjects being assigned to either cohort based on the pharmacodynamic up-titration rules).

If based on the below rules, de-escalation is indicated from DL2/DL2A, then DL2B is started.

The following rules for escalation/de-escalation apply throughout the Phase 1b part of the study:

- At least 3 subjects may be dosed in each dose level that will be explored.

- A staggered enrollment strategy will be applied to the first 3 subjects in a dose level. A minimal interval of 24 hours between a subject's first dose will be required.
- At least 3 subjects per dose level are required to complete the DLT evaluation period (1 cycle for the Standard Dose Levels and 2 cycles for the Alternative Dose Levels) or be discontinued for DLT before the SET can determine the dose and schedule for the next dose level.
- The SET will evaluate all available data including, but not limited to, PK, PD, safety, and preliminary anti-tumor activity, and will decide whether to escalate, stay at the current dose, or de-escalate the dose level based on the mTPI-2 guidelines outlined in Attachment 1. These are briefly explained for the case with 3 subjects treated at a dose level:
  - If *no subject in a dose level experiences a DLT*, dose escalation may proceed as guided by mTPI-2. The SET will confirm the dose level chosen for the next dose cohort.
  - If *1 out of 3 subjects in a dose level experiences DLT* during the DLT evaluation period, then the SET may decide to enroll additional subjects before determining the next dose level
  - If *2 out of 3 subjects in a dose level experience DLT* during the DLT evaluation period, dose de-escalation may proceed as guided by mTPI-2. The SET will confirm the dose level chosen for the next dose cohort.
  - If *3 out of 3 subjects in a dose level experience DLT* during the DLT evaluation period, dose de-escalation may proceed as guided by mTPI-2 and no further subjects will be dosed at this dose cohort in the study. The SET will confirm the dose level chosen for the next dose cohort.
- Dose escalation guided by the SET may continue until the RP2D is identified.

The identification of the RP2D will be based on the totality of data from all dose cohorts tested. Note: 8 mg with or without up-titration (DL2 and DL2A) may be considered as the same dose level.

- The SET can evaluate up-titrated and non-up-titrated subjects separately or combined based on the totality of the emerging safety data. The SET will also determine whether to modify or terminate dose cohorts, include additional dose cohorts, change doses or schedules of either drug, modify the study conduct if deemed necessary, and select the RP2D regimen for Phase 2 based on the emerging data (see Section 3.4).
- Intra-subject dose escalation is not allowed and subjects in Phase 1b will not be entered into Phase 2.

3.2. Study Design and Starting Dose Rationale

Refer to Section 3.2 of the main body of the protocol.

3.3. Dose-Limiting Toxicity Evaluation and Determination of RP2D

During Phase 1b, subjects will be entered in group at each dose level based on the mTPI-2 method (Guo 2017). After the last subject in each group (minimum of 3 DLT evaluable subjects) has completed the DLT observation period or developed a DLT, the SET will evaluate all available safety data and make the decision whether to escalate, stay at the current dose or de-escalate the

dose cohort with the second group of subjects treated, based on the guidelines outlined in and in the SET charter. Based on emerging clinical data, the SET might decide to include additional cohorts or terminate individual cohorts if deemed necessary. No intra-subject dose escalations will be allowed throughout this study.

3.3.1. Definition of Dose-Limiting Toxicity for Phase 1b (Dose Escalation)

Toxicities will be graded for severity according to the NCI-CTCAE, version 5.0. Only toxicities that occur during the DLT evaluation period will be used to define DLTs and for dose escalation decisions, but toxicities that occur during the entire treatment period will be recorded and considered in decisions regarding the RP2D.

The DLT evaluation period for Phase 1b is defined as 1 full cycle (4 weeks) of erdafitinib and cetrelimab from the start of the first erdafitinib dose. Therefore, in the Standard Dose Levels, the DLT period is defined as the first 4-week cycle, whereas in the Alternative Dose Levels, the DLT period is defined as the first 2 cycles (8 weeks).

If the subject receives more than 75% of any of the study drugs in the DLT evaluation period, the subject will be evaluable for DLT. If the subject received less than 75% of each assigned dose due to reasons other than toxicities (eg, disease progression, missed appointments, non-compliance, subject withdrawal), the subject may be replaced with a new subject. All available safety data from subjects will be taken into consideration by the SET. Dose-limiting toxicities are defined as any of the events listed in Appendix 1 Table 3.

Appendix 1 Table 3: Dose-Limiting Toxicity Criteria for Phase 1b: Erdafitinib + Cetrelimab Cohort

Criteria for Non-hematological Toxicity	
• Any Grade 3	**Exceptions**
	Asthenia, anorexia, fever, or constipation
	Fatigue that improves to Grade ≤2 in ≤ 7days
	Nausea lasting for ≤7 days responding to BSC [a]
	Vomiting and diarrhea that resolves in ≤ 3 days with BSC [a]
	Laboratory abnormalities that do not require hospitalization and are not felt to be clinically significant by the investigator
	Tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) that improves to Grade ≤ 2 in ≤ 7 days
	Elevation in AST or ALT for <7 days
• Any Grade 4	None
• Any Grade 5	None
• Elevation in AST or ALT >3x ULN meeting criteria for Hy's law [b]	

Criteria for Hematological Toxicity
Neutrophil count decreased: Grade 4 for >7 days
Febrile neutropenia: Grade ≥3 or 4
Platelet count decreased: Grade 3 with clinically significant bleeding or Grade 4
Any Grade 5 toxicity

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; ULN=upper limit of normal.

[a] Best supportive care (including electrolyte and hormone supplementation where clinically applicable) according to institutional standards or as outlined in Section 8.1.

[b] Concurrent elevation of bilirubin >2 times institutional ULN without initial evidence of cholestasis and no alternative etiology for AST/ALT elevation.

3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules

The RP2D of the erdafitinib + cetrelimab combination will be determined after review of all available PK, PD, safety, and efficacy data from at least 6 subjects treated at the RP2D and the recommended dose by mTPI-2 design. Only 1 RP2D will be tested in Phase 2.

The alternative dosing schedules, if explored, will be evaluated in a separate cohort distinct from dose escalation or dose expansion cohorts. The dose and schedule would be based on the totality of available data and decided by the SET or DRC.

The 4-week run-in of erdafitinib with subsequent concurrent dosing of erdafitinib and cetrelimab (eg alternative cohort DL2B) may be explored to further characterize the safety of the combination if the standard dosing schedule is identified as the RP2D. Subjects who meet appropriate molecular eligibility criteria at the time the RP2D is selected and who have had prior systemic treatment in the metastatic setting (ie, are not eligible for Phase 2) may be assigned 1:1 to the RP2D dose or the alternative cohort DL2B in consultation with the sponsor medical monitor if eligibility criteria are met. Subject safety will be monitored as indicated in Section 3.4. Cumulative safety evaluation will be performed after completion of Cycle 2 therapy for all subjects in each cohort (DL2B and RP2D).

3.4. Study Evaluation Team

Refer to Section 3.4 of the main body of the protocol.

4. SUBJECT POPULATION

Adult subjects age 18 years and older with metastatic or locally advanced urothelial cancer who meet the molecular eligibility and full-study eligibility are eligible for the study. Screening assessments will be performed as indicated in the Phase 1b erdafitinib + cetrelimab cohort Table and Events schedule (Appendix 1 Table 1). Molecular eligibility assessment may occur ≥28 days prior to administration of the study drugs.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the

investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. For a discussion of the statistical considerations of subject selection, refer to Section 11.1, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age.

2. Criterion modified per Amendment 2

   2.1 Histologic demonstration of transitional cell carcinoma of the urothelium. Variant urothelial carcinoma histologies such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable.

3. Criterion modified per Amendment 2

   3.1 Metastatic or locally advanced urothelial cancer (Stage IV disease per AJCC Staging Guidelines)

4. Criterion modified per Amendment 2

   4.1 Criterion modified per Amendment 3

   4.2 **Phase 1b erdafitinib + cetrelimab cohort** and Phase 2: Meet appropriate molecular eligibility criteria. Tumors must have at least one gene fusion or gene mutation as defined in Table 4.

   Exception for Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: up to 3 subjects in each erdafitinib + cetrelimab + chemotherapy cohort at each dose level will be wild-type. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations described in Table 4. All other subjects must have at least one select FGFR alteration as defined in Table 4.

5. Criterion modified per Amendment 2

   5.1 Must have measurable disease by radiological imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at baseline.

6. Criterion modified per Amendment 2
   6.1 Criterion modified per Amendment 3

   – 6.2 Prior systemic therapy for metastatic urothelial cancer:

   – **Phase 1b erdafitinib + cetrelimab cohort**:
     – Any number of lines of prior therapy
     – Renal function for subjects must have a creatinine clearance (CrCl) ≥30 mL/min as calculated by Cockcroft-Gault (Attachment 8)

   – Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:

- No prior systemic therapy for metastatic disease. **Note**: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting
- Renal function for subjects must have a creatinine clearance (CrCl) ≥30 mL/min to receive carboplatin and ≥60 mL/min to receive cisplatin as calculated by Cockcroft-Gault (Attachment 8)

- Phase 2:
  - No prior systemic therapy for metastatic disease. **Note**: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting.
  - Cisplatin-ineligible based on:
    - ECOG PS 0-1 AND at least one of the following criteria:
      - Renal function defined as creatinine clearance (CrCl) <60 mL/min as calculated by Cockcroft-Gault (Attachment 8) (Galsky 2011)
      - Grade 2 or higher peripheral neuropathy per NCI-CTCAE version 5.0.
      - Grade 2 or higher hearing loss per NCI-CTCAE version 5.0,
- **OR**
  - ECOG PS 2.

7. Criterion modified per Amendment 2

7.1 Criterion modified per Amendment 3

7.2 ECOG PS Grade of (see Attachment 3) as defined below:

Phase 1b erdafitinib + cetrelimab cohort: ECOG 0-2

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: ECOG 0-1 for cisplatin and ECOG 0-2 for carboplatin.

Phase 2: ECOG 0-2

8. Criterion modified per Amendment 1

8.1 Criterion modified per Amendment 2

8.2 Criterion modified per Amendment 3

8.3 Adequate organ function at Screening defined as follows:

- **Phase 1b erdafitinib + cetrelimab cohort** and Phase 2

Hematology	
Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks)	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
Platelets	$\geq 75 \times 10^9$/L
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L
Chemistry	
AST and ALT	≤2.5 × upper limit of normal (ULN) or

	≤5 × ULN for subjects with liver metastases
Creatinine clearance (mL/min)	Calculated using the Cockcroft-Gault formula (Attachment 8) **Phase 1b erdafitinib + cetrelimab cohort**: ≥30 mL/min Phase 2: ≥30 mL/min. If the subject is considered cisplatin-ineligible based on creatinine clearance then CrCl must also be <60 mL/min
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
Thyroid panel: TSH, T3 or Free T3 (FT3) and Free thyroxine (FT4)	All within normal range. If TSH is not within normal limits, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.
Phosphate	Below institutional ULN within 14 days of treatment and prior to C1D1 (medical management allowed)
Cardiovascular	
Left ventricular ejection fraction	Within normal institutional limits
Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal	

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort

Hematology	
Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks)	
Hemoglobin	≥9.0 g/dL (≥5.59 mmol/L) (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
Platelets	≥100×10^9/L
Absolute Neutrophil Count (ANC)	≥1.5×10^9/L
Chemistry	
AST and ALT	≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for subjects with liver metastases
Creatinine clearance (mL/min)	Calculated using the Cockcroft-Gault formula (Attachment 8) Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: ≥30 mL/min to receive carboplatin and ≥60 mL/min to receive cisplatin
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
Thyroid panel: TSH, T3 or Free T3 (FT3) and Free thyroxine (FT4)	All within normal range. If TSH is not within normal limits, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.
Phosphate	Below institutional ULN within 14 days of treatment and prior to C1D1 (medical management allowed)
Cardiovascular	
Left ventricular ejection fraction	Within normal institutional limits
Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal	

9. Criterion modified per Amendment 2

9.1 Criterion modified per Amendment 1.

9.2 Criterion modified per Amendment 3

9.3 **Phase 1b erdafitinib + cetrelimab cohort** and Phase 2**:**

Before the first dose of study drug:

Women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile as a result of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 5 months after the last dose of study drug. For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 5 months after the last dose of study drug. Contraception must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 5 months after the last dose of study drug.

Examples of highly effective methods include:

– user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner;
– user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and the combination of the study drugs have not been studied. Therefore, it is unknown whether the study drugs may reduce the efficacy of the contraceptive method.

– Sexual abstinence

(True sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of true sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-

ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception).

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:

Before the first dose of study drug:

Women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile as a result of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 6 months after the last dose of study drug. For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 6 months after the last dose of study drug. Contraception must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 6 months after the last dose of study drug.

Examples of highly effective methods include:

– user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner;

– user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and the combination of the study drugs have not been studied. Therefore, it is unknown whether the study drugs may reduce the efficacy of the contraceptive method.

– Sexual abstinence

(True sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of true sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception).

10. Women of childbearing potential must have a negative pregnancy test at Screening within ≤7 days of C1D1 (first dose of study drug) using a highly sensitive pregnancy test (serum β-human chorionic gonadotropin [β-hCG]); see Section 9.6.4).

11. Sign an informed consent form indicating that he or she understands the purpose of and procedures required for the study, and is willing and able to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

12. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to C1D1. For Phase 1b, subjects who have received the following prior anti-tumor therapy:
   - Received nitrosoureas and mitomycin C within 6 weeks.
2. Criterion modified per Amendment 3

   2.1 **Phase 1b erdafitinib + cetrelimab cohort**:

   - Chemotherapy within 3 weeks of C1D1.

   Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort and Phase 2:

   - Prior neoadjuvant/adjuvant chemotherapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation.
3. Criterion modified per Amendment 2

   3.1 Criterion modified per Amendment 3

   3.2 Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy. Prior neoadjuvant/adjuvant checkpoint inhibitor therapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation. PD-1 for non-muscle invasive bladder cancer is also allowed.
4. Criterion modified per Amendment 2

   4.1 Active malignancies requiring concurrent therapy other than urothelial cancer.
5. Symptomatic central nervous system metastases.
6. Prior FGFR inhibitor treatment.
7. Radiation therapy ≤30 days prior to planned C1D1.
8. Criterion modified per Amendment 2

   8.1 Criterion modified per Amendment 3

   8.2 History of uncontrolled cardiovascular disease including:

- Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V (Attachment 6) within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months.

9. Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.

10. Any of the following:

- Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection.
- Active autoimmune disease or a documented history of autoimmune disease that requires systemic steroids or immunosuppressive agents.

Note: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study. Subjects with a history of transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis) will not be excluded from the study.

- Grade 3 or higher toxicity effects from previous treatment with immunotherapy.
- Psychiatric conditions (eg, alcohol or drug abuse), dementia, or altered mental status.
- Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

11. Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.

12. Active or chronic hepatitis B or hepatitis C disease as determined by hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody (anti-HCV) positivity at Screening. If positive, further testing of quantitative levels to rule out active infection is required (see Attachment 2).

13. Criterion modified per Amendment 3

13.1 **Phase 1b erdafitinib + cetrelimab** and Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant, such as alopecia, skin discoloration, or Grade 1 hearing loss or neuropathy).

Phase 2: Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant such as alopecia, or skin discoloration).

14. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

15. Criterion modified per Amendment 2

15.1 Allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or immune-mediated thrombocytopenia or anemia), or to excipients of erdafitinib or cetrelimab (see the Investigator's Brochures for a list of excipients).

16. Criterion modified per Amendment 2

16.1 Current central serous retinopathy (CSR) or retinal pigment epithelial detachment (RPED) of any Grade.

17. Criterion deleted per Amendment 2

18. Criterion modified per Amendment 2

18.1 Use of immunosuppressant agents, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, cyclosporine, azathioprine, and tumor necrosis factor α (TNF-α) blockers, within 2 weeks before the planned first dose of study drug.

19. Vaccinated with a live attenuated vaccine within 28 days prior to the first dose of study drug and for 3 months after receiving the last dose of study drug. Annual inactivated influenza vaccine is permitted.

20. Criterion modified per Amendment 3

20.1 **Phase 1b erdafitinib + cetrelimab cohort** and Phase 2: Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 5 months after receiving the last dose of study drug.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after receiving the last dose of study drug.

21. Criterion modified per Amendment 3

21.1 **Phase 1b erdafitinib + cetrelimab cohort** and Phase 2: Plans to father a child while enrolled in this study or within 5 months after receiving the last dose of study drug.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Plans to father a child while enrolled in this study or within 6 months after receiving the last dose of study drug.

22. Criterion modified per Amendment 2

22.1 Major surgery within 4 weeks of enrollment, or inadequate recovery from the toxicity and/or complications from the intervention prior to starting therapy.

23. Criterion modified per Amendment 3

23.1 **Phase 1b erdafitinib + cetrelimab cohort** and Phase 2**:** not applicable.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: known sensitivity to any component of cisplatin or carboplatin.

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2 describes options for retesting. Section 17.4 describes the required documentation to support meeting the enrollment criteria.

5. TREATMENT ALLOCATION AND BLINDING

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

6. DOSAGE AND ADMINISTRATION

Phase 1b erdafitinib + cetrelimab cohort: On days that both drugs will be administered, the sequence of administration will be oral erdafitinib followed by the infusion of cetrelimab IV.

6.1. Dose Combination for Erdafitinib + Cetrelimab Cohort

Erdafitinib and cetrelimab (240 mg) will be administered either in the Standard (Cohort A) or Alternative (Cohort B) regimens. The dose of cetrelimab is increased to 480 mg every 4 weeks at Cycle 5.

The dose of study drug in each combination cohort/arm is shown in Appendix 1 Table 4.

Appendix 1 Table 4 : Erdafitinib and Cetrelimab Administration: Dose Levels

Phase	Dose Levels (DL) [a]	Erdafitinib (oral administration) [c]	Cetrelimab (IV infusion) [b, c]
1b	DL1[g]	6 mg once daily	240 mg Q2W starting at C1D1 480 mg Q4W starting at C5D1
1b	DL2[d, e, g]	8 mg up-titrated to 9 mg once daily	
1b	DL2A[d, g]	8 mg (no up-titration) once daily	
1b	DL1B[f, h]	6 mg once daily	240 mg Q2W starting at C2D1 480 mg Q4W starting at C5D1
1b	DL2B[h]	8 mg (up-titrated to 9 mg) once daily	

Note: For all dose levels, a fixed dose of cetrelimab will be administered.

[a] Additional dosing schedules may be explored if recommended by the SET or DRC and agreed upon by the sponsor.
[b] The cetrelimab dosing schedule can be adjusted if recommended by the SET or DRC and agreed upon by the sponsor.
[c] On days that both drugs will be administered, the sequence of administration will be oral erdafitinib followed by the infusion of cetrelimab IV.
[d] 8 mg with or without up-titration (DL2 and DL2A) may be considered as the same dose level.
[e] DL2 has been confirmed as the RP2D.
[f] No subjects were enrolled as there were no DLTs; de-escalation was not required.
[g] Phase 1b Standard Regimen.
[h] Phase 1b Alternate Regimen – a staggered dosing schedule applies. Erdafitinib dosing starts on C1D1, and cetrelimab dosing starts on C2D1.

If a subject permanently discontinues 1 of the study drugs, the subject may continue to receive the other study drug if investigator believes that the subject derives clinical benefit upon consultation with the sponsor's responsible medical monitor. Communication with the sponsor's responsible medical monitor including the final decision must be documented and retained in the sponsor's trial master file and in the investigator's study files.

If a ≥Grade 3 AE is not attributable to study treatment (erdafitinib or cetrelimab), or the disease under study, then all study drugs should be held. If the event resolves to Grade 1 or baseline within 4 weeks, erdafitinib may be reintroduced at one dose level lower. If the same toxicity does not recur or worsen within 4 weeks after re-starting erdafitinib, then cetrelimab may be reintroduced at the same dose. Following re-introduction of both study drugs, if the same AE recurs at ≥Grade 3 or there is a second incidence of a ≥Grade 3 event that is not attributable to erdafitinib, cetrelimab or the disease under study, both study drugs should be discontinued.

Guidance for the management of toxicity associated with erdafitinib or cetrelimab is provided in Sections 6.2 and 6.3, respectively.

For more information regarding the following sections, please refer to the main body of the protocol.	Page #
Section 6.2 Administration of Erdafitinib	Page 80
Section 6.3 Administration of Cetrelimab	Page 91
Section 6.4 Administration of Platinum Chemotherapy	Page 101

APPENDIX 2: PHASE 1B ERDAFITINIB+ CETRELIMAB + PLATINUM (CISPLATIN OR CARBOPLATIN) CHEMOTHERAPY

Appendix 2 Table 1: Time and Events Schedule – Phase 1b Erdafitinib+ Cetrelimab + Platinum Chemotherapy Cohort (Up to and Including Amendment 4)

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Screening Assessments																
Informed Consent (molecular and full-study)	Molecular Eligibility ICF to allow for assessment of FGFR status from archived tumor tissue, blood or local report. Full-Study ICF within 35 days prior to C1D1 to be used for subjects who meet molecular eligibility criteria. Must be signed before any study-related activity. [b]	X	X													
Eligibility Criteria	Details provided in Sections 4.1 and 4.2 of Appendix 2.		X													
Demography, and Medical History	Histology and cytology, staging, prior therapy, and response.		X													

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Molecular Eligibility Determination																
Local FGFR results (where applicable) [h]	Subjects may enroll based on local test results. • Subjects with local FGFR tissue or blood results must submit test report to the sponsor for central verification. • Subjects enrolling based on local testing must submit archival or fresh tumor tissue and a blood sample for retrospective confirmation of FGFR status as soon as possible after enrollment. The results of retrospective central confirmation do not affect the subject's eligibility for the study.	X														

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Central Testing from Tissue and Blood	Archival or fresh biopsy tumor tissue and a blood sample should be submitted for molecular eligibility screening. If fresh biopsy, the subject must sign the Full-Study ICF.	X														
Study Drug Administration																
Erdafitinib [d]	See Sections 6 and 6.2.			Oral once daily												
Cetrelimab infusion	See Sections 6.1 and 6.3.			X			X			X	X			X		
Chemotherapy infusion [f]	See Sections 6.4.1 and 6.4.2.			X			X			X	X					
Safety Assessments																
Vital Signs (temperature, blood pressure, pulse/heart rate, respiratory rate)	Monitor every 15-20 min during the 1st infusion; for monitoring during subsequent infusions see Section 6.3.		X	X	X	X	X	X	X	X	X			X	X	X [c]
Physical Examination (PE)	Complete PE including height and weight at Screening. Thereafter, disease-directed PE. See Section 9.6.9.		X	X			X			X	X			X	X	X [c]
ECOG PS	See Attachment 3.		X	X			X			X	X			X	X	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
12-lead ECG [i]	Results obtained within 60 days of C1D1 can be counted as screening assessment. Record post-dose ECGs, see Section 9.6.5 for exact timing. May be performed more often as clinically indicated.		X				X				X				X	
Echocardiogram or MUGA	Results obtained within 6 months of C1D1 can be counted as screening assessment provided the subject has not experienced any cardiac event in the interim. Subsequent evaluations as clinically indicated.		X													
Amsler grid Test	To be performed by treating physician or nurse (or other appropriate study personnel).		X				X			X	X			X	X	
Ophthalmologic Exam	To be performed by an ophthalmologist See Section 9.6.7 for exact assessments.		X		As clinically indicated (eg, based on abnormal Amsler grid test, see Attachment 5)											
Laboratory Assessments (by the local laboratory)																
Hematology	See Section 9.6.2; May be obtained up to 2 days prior to each cetrelimab dose.		X	X	X	X	X	X	X	X	X			X	X	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Chemistry	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2.		X	X	X	X	X	X	X	X	X			X	X	
Creatinine clearance calculation	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2. CrCl is calculated by the Cockcroft-Gault formula (Attachment 8).		X	X	X	X	X	X	X	X	X					
PO_4	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2.		X	X	X	X	X	X	X	X	X			X	X	
PTH	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2. After C6D1 PTH to be done every 3rd cycle. Results not required before dosing.		X			X	X			X	X			X	X	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
TSH, T3, FT4	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2. T3 at Screening then only as clinically indicated.		X	Day 1 of every other cycle starting at C2D1												
Serology	See Section 9.6.2. Results obtained within 60 days of C1D1 are acceptable.		X													
Pregnancy test (pre-dose)	For women of childbearing potential, serum at Screening (β-hCG) - obtain ≤7 days of C1D1. Serum or urine thereafter. See Section 9.6.4.		X				X			X	X			X	X	X [c]

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Efficacy Assessments																
Disease assessment and response evaluation	Radiologic assessment by CT (preferred) or MRI of all disease sites (present and suspected) documented at Screening. The same methodology should be used throughout the study. Refer to Section 9.2. for details. Disease assessments done within 35 days prior to C1D1 may be used as the Screening disease assessment.		X	Every 6 weeks until Week 48 (±3 days), then every 12 to 24 weeks (±14 days) until disease progression. The timing of disease assessments should be calculated from C1D1 and the schedule should be maintained regardless of cycle delays and/or study drug interruptions. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 9.1.3). Tumor response will be evaluated according to RECIST 1.1 criteria (Seymour 2017). All unconfirmed PR/CR require confirmation of response as per RECIST 1.1.											
Ongoing Review																
Adverse Events		X - Continuous from signing of Full-Study ICF to up to 100 days after the last dose of study treatment or until the start of subsequent anticancer therapy. An AE should be monitored until it resolves to baseline, stabilizes, or is deemed irreversible, subject dies, or subsequent therapy is started, whichever occurs first.														
Concomitant medications		X - Continuous from signing of Full-Study ICF to up to 100 days after the last dose of study treatment or until the start of subsequent anticancer therapy, if earlier. See Section 8.														
Posttreatment Assessments																
Survival evaluation		Contact subject every 12 weeks (±7 days) after the last dose of study treatment by office visit, phone call or e-mail. See Section 9.1.4.														X
Subsequent anticancer therapy		Contact subject every 12 weeks (±7 days) after the last dose of study treatment by office visit, phone call or e-mail. See Section 9.1.4.														X

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1[g]			Treatment Cycle 2 [g]			Treatment Cycle 3 [g]	Treatment Cycle 4 [g]			All Other Cycles [g]	End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1[e]	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; b-hCG= beta-human chorionic gonadotropin; C = cycle; CR= complete response; CT = computed tomography; ctDNA=circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI=end of infusion; FGFR= fibroblast growth factor receptor; FT4= free thyroxine; ICF = informed consent form; INR = international normalized ration; MRI = magnetic resonance imaging; MUGA= multi-gated acquisition scan; OCT = optical coherence tomography; PBMC=peripheral blood mononuclear cell; PD-L1 = programmed cell death ligand 1; PE = physical examination; PK = pharmacokinetics; PO_4 = phosphate; PR= partial response; PS = performance status; PT = prothrombin time; PTH=parathyroid hormone; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; T3= triiodothyronine; TCR=T cell antigen receptor; TSH= thyroid stimulating hormone

[a] The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy. Follow-up visits will occur every 12 weeks (±7 days).

[b] For subjects signing a Full-Study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 35-day window starts with the first planned study-related procedure other than the tissue biopsy; however, AEs will need to be collected from the time of Full-Study ICF sign off.

[c] Physical examination, vital signs, and pregnancy testing at first follow-up visit (12 weeks after last dose).

[d] On Day 1 of Cycles 1 through 4, erdafitinib oral dose will be given before the start of cetrelimab infusion, followed by platinum (cisplatin or carboplatin) chemotherapy. Pre-dose PK sample for erdafitinib to be taken within 30 mins before Pre-infusion PK (cetrelimab and platinum [cisplatin or carboplatin] chemotherapy), and immunogenicity samples for cetrelimab collected within 30 mins before cetrelimab infusion begins.

[e] C1D1 must occur no more than 3 days after the Enrollment transaction in IWRS.

[f] Cisplatin and carboplatin dosing will occur on Day 1 of each cycle for a maximum of 4 cycles.

[g] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 10.

[h] Consent for molecular screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.

[i] Post-dose ECGs for subjects receiving erdafitinib monotherapy should be recorded 2 to 4 hours after the erdafitinib dose on C2D1 and, if possible, 2 to 4 hours after the erdafitinib dose on C4D1. Post-dose ECGs for subjects receiving erdafitinib and cetrelimab in combination should be recorded as soon as possible upon completion of infusion on C2D1 and C4D1. Post-dose ECGs for subjects receiving platinum chemotherapy should be recorded as soon as possible upon completion of infusion on C2D1 and C4D1. The End-of-Treatment ECG may be performed at any time during the End-of-Treatment Visit. Additional ECGs may be performed during the study as clinically indicated.

Appendix 2 Table 2: Pharmacokinetic, Immunogenicity, and Biomarker Samples for the Phase 1b Erdafitinib+ Cetrelimab + Platinum Chemotherapy Cohort (Up to and Including Amendment 4)

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1			Treatment Cycle 2			Treatment Cycle 3	Treatment Cycle 4			All Other Cycles	End-of-Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Note: These samples should be drawn on the day study drug is administered.[b]																
Erdafitinib PK [c]	Pre-dose erdafitinib [e] unless otherwise specified. See Section 9.3.			X	X	X	Pre-dose and 4h post-dose			X				C5D1, pre-dose and 4h post erdafitinib dose		
Erdafitinib Protein Binding Blood Sample	4 h Post-dose See Section 9.3.						X									
Cetrelimab PK [c]	Pre-infusion [d] and EOI [f] unless otherwise specified; See footnote h for detailed sampling timepoints for cycles after Cycle 3; not all samples are taken on Day 1. See Section 9.3.			X	X Any time dur-ing visit	X Any time dur-ing visit	X			X	X [h]	X [h]	X [h]	X [h]	X Any time during visit	At first follow-up visit, if possible
Cetrelimab Immunogenicity	Pre-infusion [d] See Section 9.3.			X		X	X			X	X			Pre-infusion for C5. Then every other cycle after C5	X Any time during visit	At first follow-up visit, if possible
Cisplatin PK [i] (Cohort DL2C+ DL2C1)				X			X			X	X					
Carboplatin PK [j] (Cohort DL2D + DL2D1)				X			X			X	X					
CCI [redacted]	Pre-dose erdafitinib [d]			X	X	X	X									

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1			Treatment Cycle 2			Treatment Cycle 3	Treatment Cycle 4			All Other Cycles	End-of-Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Day 1 (±2)	Day 8 (±2)	Day 15 (±2)	Day 1 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
CCI [redacted]	Pre-dose erdafitinib [d]			X	X	X	X								Any time during visit	
CCI [redacted]	Pre-dose erdafitinib [d]			X			X			X				C5D1	Any time during visit	
Tumor tissue for PD-L1 testing and bladder cancer subtyping	Archival or fresh biopsy tissue must be available for biomarker analysis	X														
CCI [redacted] [g]			Optional				Optional								PD Optional	

Abbreviations: ctDNA= circulating tumor DNA; EOI=end of infusion; FGFR= fibroblast growth factor receptor; PD= progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PBMC = peripheral blood mononuclear cells; TCR = T cell antigen receptor

[a] The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy. Follow-up visits will occur every 12 weeks (±7 days).

[b] The sampling schedule may be adjusted based on PK analysis output generated during the study or other safety concerns.

[c] If dose delay occurs, then samples should be collected on the actual day of drug administration, not on the originally scheduled administration day.

[d] On Day 1 of Cycles 1 through 4, erdafitinib oral dose will be given before the start of cetrelimab infusion, followed by platinum (cisplatin or carboplatin) chemotherapy. Pre-dose PK sample for erdafitinib to be taken within 30 mins before Pre-infusion PK (cetrelimab and platinum-based [cisplatin or carboplatin] chemotherapy), and immunogenicity samples for cetrelimab collected within 30 mins before cetrelimab infusion begins.

[e] Timepoint is relative to the dosing of erdafitinib. erdafitinib PK samples may be collected during the cetrelimab infusion if necessary; however, the sample should be drawn from the contralateral arm (opposite the cetrelimab infusion site).

[f] As soon as possible after EOI.

[g] Optional paired biopsies will be collected in the Phase 1b erdafitinib + cetrelimab + platinum-based chemotherapy cohort. An additional optional biopsy will be collected upon PD.

[h] C4D1: Pre-infusion and EOI, C4D8: Post start of infusion, C4D15: Post start of infusion, and C5D1: Pre-infusion and EOI.

[i] For **Cisplatin**: PK samples are to be collected from the arm opposite from infusion site. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.
Cisplatin PK sample to be drawn at C1D1: Pre-infusion, EOI (within 5 min), 2h (±10 min), 4h (±10 min), and 8h (±10 min); C2D1 and C3D1: Pre-infusion; C4D1: Pre-infusion, EOI (within 5 min), 1.5h (±10 min), 2h (±10 min), 4h (±10 min), 8h (±10 min); and at any unscheduled visit(s). Sampling times are relative to the beginning of the infusion. Pre-infusion samples should be drawn within 30 minutes before the infusion begins. Cisplatin is planned to be infused over 1 to 2h. If infusion duration is 1.75 to 2h, then the 2h PK sample can be eliminated as EOI would cover this 2h timepoint.

[j] For **Carboplatin**: PK samples are to be collected from the arm opposite from infusion site. If drug was administered via a central venous catheter, sample collection for PK should be from a different site
Carboplatin PK sample to be drawn at C1D1: Pre-infusion, EOI (within 5 min), 1h (±10 minutes), 2h (±10 minutes), 4h (±10 minutes), and 8h (±10 minutes); C2D1 and C3D1: Pre-infusion; C4D1: Pre-infusion, EOI (within 5 min), 1h (±10 minutes), 2h (±10 minutes), 4h (±10 minutes), and 8h (±10 minutes); and at any unscheduled visit(s). Sampling times are relative to the beginning of the infusion. Pre-infusion samples should be drawn within 30 minutes before the infusion begins. Carboplatin is planned to be infused over 15 to 60 mins. If infusion duration is 45 to 60 min, then the 1h PK sample can be eliminated as EOI would cover this 1h timepoint.

1. INTRODUCTION

Refer to Section 1 of the protocol for the introduction. The introduction includes a description of urothelial bladder cancer, FGFR signaling, erdafitinib, PD-1/PD-Li signaling, cetrelimab (summary of nonclinical data, summary of clinical data), platinum chemotherapy in metastatic urothelial cancer, overall rationale for the study, the anticipated benefits and risks for erdafitinib and cetrelimab, and the anticipated benefits and risks for platinum chemotherapy.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints for Phase 1b (Dose Escalation)

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of erdafitinib in combination with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy, and to identify the recommended Phase 2 dose(s) (RP2D) and schedule for erdafitinib with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy	• Frequency and type of dose-limiting toxicity (DLT)
Secondary	
• To characterize the PK of erdafitinib in combination with cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy	• Concentration and PK parameters of erdafitinib, cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy
• To assess the immunogenicity of cetrelimab	• Detection of antibodies to cetrelimab and effects on serum cetrelimab levels
Exploratory	
• To assess the CCI • To evaluate changes in CCI • To assess changes in CCI • To explore biomarkers (DNA, RNA, and/or protein) in tissue and blood samples that could CCI • To explore the relationships between PK, PD, AE profiles, and CCI	

2.2. Hypothesis for Phase 1b (Dose Escalation)

A RP2D(s) regimen of erdafitinib combined with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy can be identified for safe treatment of subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

Refer to Section 3.1 of the main body of the protocol.

3.1.1. Phase 1b for Erdafitinib + Cetrelimab + Platinum (Cisplatin or Carboplatin) Chemotherapy Cohort

The Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort represents the dose escalation part of the study. A Modified Toxicity Probability Interval method, mTPI-2, (Guo 2017) will be used by the Study Evaluation Team (SET, Section 3.4) to guide the dose escalation and RP2D(s) regimen recommendations (see Section 11.2, Attachment 1 and the SET charter). The expected number of subjects to be treated in the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort is approximately 40. Three subjects (either wild-type or with select FGFR gene alterations) will be enrolled in the initial erdafitinib + cetrelimab + cisplatin dose level (50 mg/m^2). If the starting dose is safe, 6 additional subjects will be enrolled into the escalated dose of cisplatin (60 mg/m^2). Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations described in Table 4. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib + cetrelimab + cisplatin.

Three subjects (either wild-type or with select FGFR gene alterations) will be enrolled in the initial erdafitinib + cetrelimab + carboplatin dose level (AUC4 mg/mL/min). If the starting dose is safe, 6 additional subjects will be enrolled into the escalated dose of carboplatin (AUC5 mg/mL/min). Out of 6 subjects, up to 3 subjects can be wild-type and the other subjects should be with select FGFR gene alterations. Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib + cetrelimab + carboplatin.

An overview of dose levels of the Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort is described in Figure 2.The dose levels within the platinum chemotherapy cohort are:

Erdafitinib + cetrelimab + cisplatin (DL2C or DL2C1)

Erdafitinib, cetrelimab and cisplatin start concurrently on C1D1. A maximum of 4 cycles of cisplatin will be administered. The DLT period is 2 cycles (6 weeks).

and

Erdafitinib + cetrelimab + carboplatin (DL2D or DL2D1)

Erdafitinib, cetrelimab and carboplatin start concurrently on C1D1. A maximum of 4 cycles of carboplatin will be administered. The DLT period is 2 cycles (6 weeks).

Refer to Appendix 2 Table 4 for an overview of the Phase 1b: erdafitinib + cetrelimab + platinum chemotherapy dose levels.

Erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort:

The starting dose is 8 mg erdafitinib (no up-titration); 360 mg Q3W cetrelimab, and either 50 mg/m^2 Q3W for cisplatin (DL2C) or AUC 4mg/mL/min Q3W for carboplatin (DL2D).

If based on the rules below, dose escalation for cisplatin is DL2C to DL2C1.

If based on the rules below, dose escalation for carboplatin is DL2D to DL2D1.

The following rules for escalation apply for the Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort:

- At least 3 subjects may be dosed in each dose level that will be explored.
- A staggered enrollment strategy will be applied to the first 3 subjects in a dose level. A minimal interval of 24 hours between a subject's first dose will be required.
- At least 3 subjects per dose level are required to complete the DLT evaluation period or be discontinued for DLT before the SET can determine the dose and schedule for the next dose cohort.
- The SET will evaluate all available data including, but not limited to, PK, PD, safety, and preliminary anti-tumor activity, and will decide whether to escalate, stay at the current dose, or de-escalate the dose level based on the mTPI-2 guidelines outlined in Attachment 1. These are briefly explained for the case with 3 subjects treated at a specific dose of platinum (cisplatin or carboplatin) chemotherapy:
  - If *no subject at a specific dose level of platinum (cisplatin or carboplatin) chemotherapy experiences a DLT*, dose escalation may proceed. as guided by mTPI-2. The SET will confirm the dose level chosen for the next dose cohort.
  - If *1 out of 3 subjects at a specific dose level of platinum (cisplatin or carboplatin) chemotherapy experiences DLT* during the DLT evaluation period, then the SET may decide to enroll additional subjects before escalating the dose of platinum-based chemotherapy.
  - If *2 out of 3 subjects at a specific dose level of platinum (cisplatin or carboplatin) chemotherapy experience DLT* during the DLT evaluation period. The SET will confirm the dose level chosen for the next dose level.
  - If *3 out of 3 subjects at a specific dose level of platinum (cisplatin or carboplatin) chemotherapy experience DLT* during the DLT evaluation period. The SET will confirm the dose level chosen for the next dose cohort.
- Dose escalation guided by the SET may continue until the RP2D is identified.
- The identification of the RP2D will be based on the totality of data from all dose cohorts tested.
- The SET will determine whether to modify or terminate dose levels, include additional dose levels, change doses or schedules of either drug, modify the study conduct if deemed necessary, and select the RP2D regimen for Phase 2 based on the emerging data (see Section 3.4).
- Intra-subject dose escalation is not allowed and subjects in Phase 1b erdafitinib + cetrelimab + platinum chemotherapy dose levels will not be entered into Phase 2.

3.2. Study Design and Starting Dose Rationale

Refer to Section 3.2 of the main body of the protocol.

3.2.1. Rationale for the Combination of Erdafitinib, Cetrelimab, and Platinum (Cisplatin or Carboplatin) Chemotherapy

3.3. Dose-Limiting Toxicity Evaluation and Determination of RP2D

During Phase 1b, subjects will initially be enrolled into the starting dose of cisplatin or carboplatin (DL2C and DL2D) based on the mTPI-2 method. (Guo 2017) After the last subject in each group (minimum of 3 DLT evaluable subjects) has completed the DLT observation period or developed a DLT, the SET will evaluate all available safety data and make the decision whether to escalate, stay at the current dose or de-escalate the dose of platinum chemotherapy with the second group of subjects treated, based on the guidelines outlined in and in the SET charter. Based on emerging clinical data, the SET might decide to adjust the dose of cisplatin and/or carboplatin or terminate individual dose levels if deemed necessary. No intra-subject dose escalations will be allowed throughout this study.

3.3.1. Definition of Dose-Limiting Toxicity for Phase 1b (Dose Escalation)

Toxicities will be graded for severity according to the NCI-CTCAE, version 5.0. Only toxicities that occur during the DLT evaluation period will be used to define DLTs and for dose escalation decisions, but toxicities that occur during the entire treatment period will be recorded and considered in decisions regarding the RP2D.

The DLT evaluation period for the Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort is defined as 2 full cycles (6 weeks) of erdafitinib, cetrelimab, and platinum chemotherapy from the start of the first erdafitinib dose.

If the subject receives more than 75% of any of the study drugs in the DLT evaluation period, the subject will be evaluable for DLT. If the subject received less than 75% of each assigned dose due to reasons other than toxicities (eg, disease progression, missed appointments, non-compliance, subject withdrawal), the subject may be replaced with a new subject. All available safety data from subjects will be taken into consideration by the SET. Dose-limiting toxicities are defined as any of the events listed in Appendix 2 Table 3.

Appendix 2 Table 3: Dose-Limiting Toxicity Criteria for Phase 1b: Erdafitinib + Cetrelimab + Platinum Chemotherapy cohort

Criteria for Non-hematological Toxicity	
• Any Grade 3	**Exceptions**
	Asthenia, anorexia, fever, or constipation
	Fatigue that improves to Grade ≤2 in ≤ 7 days
	Nausea lasting for ≤7 days responding to BSC [a]
	Vomiting and diarrhea that resolves in ≤ 3 days with BSC [a]
	Laboratory abnormalities that do not require hospitalization and are not felt to be clinically significant by the investigator
	Tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) that improves to Grade ≤ 2 in ≤ 7 days
	Elevation in AST or ALT for <7 days
• Any Grade 4	None
• Any Grade 5	None
• Elevation in AST or ALT >3x ULN meeting criteria for Hy's law [b]	
Criteria for Hematological Toxicity	
Neutrophil count decreased: Grade 4 for >7 days	
Febrile neutropenia: Grade ≥3 or 4	
Platelet count decreased: Grade 3 with clinically significant bleeding or Grade 4	
Any Grade 5 toxicity	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; ULN=upper limit of normal.

[a] Best supportive care (including electrolyte and hormone supplementation where clinically applicable) according to institutional standards or as outlined in Section 8.1. Routine primary prophylaxis is not permitted for subjects who are under evaluation for DLTs; For the use of CSFs after the DLT period ends, utilize (NCCN/EORTC 2018) guidelines.

[b] Concurrent elevation of bilirubin >2 times institutional ULN without initial evidence of cholestasis and no alternative etiology for AST/ALT elevation.

3.3.2. Determination of the Phase 1b RP2D Regimen and Alternative Dosing Schedules

The RP2D of the erdafitinib/cetrelimab/platinum (cisplatin or carboplatin) chemotherapy combination will be determined after review of all available PK, PD, safety, and efficacy data from at least 6 subjects treated at the RP2D and the recommended dose by mTPI-2 design.

Alternative dosing strategies or schedules may be considered by the SET based on emerging data. The alternative dosing schedules, if explored, will be evaluated in a separate cohort distinct from dose escalation or dose expansion cohorts. The dose and schedule would be based on the totality of available data and decided by the SET.

Subjects who meet appropriate molecular eligibility criteria at the time the RP2D is selected and who have not had prior systemic treatment in the metastatic setting (ie, recurrence of tumor >12 months since last dose of chemotherapy for neo-adjuvant or adjuvant setting may be assigned 1:1 to the RP2D dose in consultation with the sponsor medical monitor if all other eligibility criteria are met.

Subject safety will be monitored as indicated in Section 3.4. Cumulative safety evaluation will be performed after completion of Cycle 2 therapy for all subjects in each dose level (DL2C, DL2C1, DL2D, and DL2D1).

3.4. Study Evaluation Team

Refer to Section 3.4 of the main body of the protocol.

4. SUBJECT POPULATION

Adult subjects age 18 years and older with metastatic or locally advanced urothelial cancer who meet the molecular eligibility and full-study eligibility are eligible for the study. Screening assessments will be performed as indicated in the Phase 1b erdafitinib + cetrelimab + platinum chemotherapy Table and Events schedule (Appendix 2 Table 1). Molecular eligibility assessment may occur ≥28 days prior to administration of the study drugs.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. For a discussion of the statistical considerations of subject selection, refer to Section 11.1, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age.

2. • Criterion modified per Amendment 2

   2.1 Histologic demonstration of transitional cell carcinoma of the urothelium. Variant urothelial carcinoma histologies such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable.

3. • Criterion modified per Amendment 2

   3.1 Metastatic or locally advanced urothelial cancer (Stage IV disease per AJCC Staging Guidelines)

4. • Criterion modified per Amendment 2
   • 4.1 Criterion modified per Amendment 3

   4.2 Phase 1b erdafitinib + cetrelimab cohort and Phase 2: Meet appropriate molecular eligibility criteria. Tumors must have at least one gene fusion or gene mutation as defined in Table 4.

   Exception for **Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort**: up to 3 subjects in each erdafitinib + cetrelimab + chemotherapy cohort at each dose level will be wild-type. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations

described in Table 4. All other subjects must have at least one select FGFR alteration as defined in Table 4.

5. Criterion modified per Amendment 2

5.1 Must have measurable disease by radiological imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at baseline.

6. Criterion modified per Amendment 2

6.1 Criterion modified per Amendment 3

6.2 Prior systemic therapy for metastatic urothelial cancer:

Phase 1b erdafitinib + cetrelimab cohort:

- Any number of lines of prior therapy

Renal function for subjects must have a creatinine clearance (CrCl) ≥30 mL/min as calculated by Cockcroft-Gault (Attachment 8)

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:

- No prior systemic therapy for metastatic disease. **Note**: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting
- Renal function for subjects must have a creatinine clearance (CrCl) ≥30 mL/min to receive carboplatin and ≥ 60 mL/min to receive cisplatin as calculated by Cockcroft-Gault (Attachment 8)

Phase 2:

- No prior systemic therapy for metastatic disease. **Note**: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting
- Cisplatin-ineligible based on:
  - ECOG PS 0-1 AND at least one of the following criteria:
- Renal function defined as creatinine clearance (CrCl) <60 mL/min as calculated by Cockcroft-Gault (Attachment 8) (Galsky 2011)
- Grade 2 or higher peripheral neuropathy per NCI-CTCAE version 5.0.
- Grade 2 or higher hearing loss per NCI-CTCAE version 5.0,

OR

- ECOG PS 2

7. Criterion modified per Amendment 2

7.1 Criterion modified per Amendment 3

7.2 ECOG PS Grade of (see Attachment 3) as defined below:

Phase 1b erdafitinib + cetrelimab cohort: ECOG 0-2

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: ECOG 0-1 for cisplatin and 0-2 for carboplatin.

Phase 2: ECOG 0-2

8. Criterion modified per Amendment 1

8.1 Criterion modified per Amendment 2

8.2 Criterion modified per Amendment 3

8.3 Adequate organ function at Screening defined as follows:

Phase 1b erdafitinib + cetrelimab cohort and Phase 2

Hematology	
Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks)	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
Platelets	$\geq 75\times10^9$/L
Absolute Neutrophil Count (ANC)	$\geq 1.5\times10^9$/L
Chemistry	
AST and ALT	≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for subjects with liver metastases
Creatinine clearance (mL/min)	Calculated using the Cockcroft-Gault formula (Attachment 8) Phase 1b erdafitinib + cetrelimab cohort: ≥30 mL/min Phase 2: ≥30 mL/min. If the subject is considered cisplatin-ineligible based on creatinine clearance then CrCl must also be <60 mL/min.
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
Thyroid panel: TSH, T3 or Free T3 (FT3) and Free thyroxine (FT4)	All within normal range. If TSH is not within normal limits, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.
Phosphate	Below institutional ULN within 14 days of treatment and prior to C1D1 (medical management allowed)
Cardiovascular	
Left ventricular ejection fraction	Within normal institutional limits
Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal	

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort

Hematology	
Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks)	
Hemoglobin	≥9.0 g/dL (≥5.59 mmol/L) (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
Platelets	≥100×10^9/L
Absolute Neutrophil Count (ANC)	≥1.5×10^9/L
Chemistry	
AST and ALT	≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for subjects with liver metastases
Creatinine clearance (mL/min)	Calculated using the Cockcroft-Gault formula (Attachment 8) **Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:** ≥30 mL/min to receive carboplatin and ≥60 mL/min to receive cisplatin.
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
Thyroid panel: TSH, T3 or Free T3 (FT3) and Free thyroxine (FT4)	All within normal range. If TSH is not within normal limits, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.
Phosphate	Below institutional ULN within 14 days of treatment and prior to C1D1 (medical management allowed)
Cardiovascular	
Left ventricular ejection fraction	Within normal institutional limits

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal

9. Criterion modified per Amendment 2

9.1 Criterion modified per Amendment 1.

9.2 Criterion modified per Amendment 3

9.3 Phase 1b erdafitinib + cetrelimab cohort and Phase 2:

Before the first dose of study drug:

Women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile as a result of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 5 months after the last dose of study drug. For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 5 months after the last dose of study drug. Contraception must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Women and men must agree not to donate eggs (ova,

oocytes) or sperm, respectively, during the study and for 5 months after the last dose of study drug.

Examples of highly effective methods include:

– user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner;

– user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and the combination of the study drugs have not been studied. Therefore, it is unknown whether the study drugs may reduce the efficacy of the contraceptive method.

– Sexual abstinence

(True sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of true sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception).

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:

Before the first dose of study drug:

Women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile as a result of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 6 months after the last dose of study drug. For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 6 months after the last dose of study drug. Contraception must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 6 months after the last dose of study drug.

Examples of highly effective methods include:

– user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner;

– user-dependent methods: combined (estrogen- and progestogen-containing)

hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and the combination of the study drugs have not been studied. Therefore, it is unknown whether the study drugs may reduce the efficacy of the contraceptive method.

– Sexual abstinence

(True sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of true sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception).

10. Women of childbearing potential must have a negative pregnancy test at Screening within ≤7 days of C1D1 (first dose of study drug) using a highly sensitive pregnancy test (serum β-human chorionic gonadotropin [β-hCG]); see Section 9.6.4).

11. Sign an informed consent form indicating that he or she understands the purpose of and procedures required for the study, and is willing and able to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

12. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to C1D1. For Phase 1b, subjects who have received the following prior anti-tumor therapy:

   - Received nitrosoureas and mitomycin C within 6 weeks.

2. Criterion modified per Amendment 3

   2.1 Phase 1b erdafitinib + cetrelimab cohort:

- Chemotherapy within 3 weeks of C1D1.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort and Phase 2**:**

- Prior neoadjuvant/adjuvant chemotherapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation.

3. Criterion modified per Amendment 2

   3.1 Criterion modified per Amendment 3

   3.2 Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy. Prior neoadjuvant/adjuvant checkpoint inhibitor therapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation. PD-1 for non-muscle invasive bladder cancer is also allowed.

4. Criterion modified per Amendment 2

   4.1 Active malignancies requiring concurrent therapy other than urothelial cancer.

5. Symptomatic central nervous system metastases.

6. Prior FGFR inhibitor treatment.

7. Radiation therapy ≤30 days prior to planned C1D1.

8. Criterion modified per Amendment 2

   8.1 Criterion modified per Amendment 3

   8.2 History of uncontrolled cardiovascular disease including:

   - Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V (Attachment 6) within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months.

9. Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.

10. Any of the following:

    - Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection.

- Active autoimmune disease or a documented history of autoimmune disease that requires systemic steroids or immunosuppressive agents.

Note: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study. Subjects with a history of transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis) will not be excluded from the study.

- Grade 3 or higher toxicity effects from previous treatment with immunotherapy.
- Psychiatric conditions (eg, alcohol or drug abuse), dementia, or altered mental status.
- Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

11. Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.

12. Active or chronic hepatitis B or hepatitis C disease as determined by hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody (anti-HCV) positivity at Screening. If positive, further testing of quantitative levels to rule out active infection is required (see Attachment 2).

13. Criterion modified per Amendment 3

13.1 Phase 1b erdafitinib + cetrelimab and **Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort**: Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant, such as alopecia, skin discoloration, or Grade 1 hearing loss or neuropathy).

Phase 2: Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant such as alopecia, or skin discoloration).

14. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

15. Criterion modified per Amendment 2

15.1 Allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or

immune-mediated thrombocytopenia or anemia), or to excipients of erdafitinib or cetrelimab (see the Investigator's Brochures for a list of excipients).

16. Criterion modified per Amendment 2

16.1 Current central serous retinopathy (CSR) or retinal pigment epithelial detachment (RPED) of any Grade.

17. Criterion deleted per Amendment 2

18. Criterion modified per Amendment 2

18.1 Use of immunosuppressant agents, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, cyclosporine, azathioprine, and tumor necrosis factor α (TNF-α) blockers, within 2 weeks before the planned first dose of study drug.

19. Vaccinated with a live attenuated vaccine within 28 days prior to the first dose of study drug and for 3 months after receiving the last dose of study drug. Annual inactivated influenza vaccine is permitted.

20. Criterion modified per Amendment 3

20.1 Phase 1b erdafitinib + cetrelimab cohort and Phase 2: Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 5 months after receiving the last dose of study drug.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after receiving the last dose of study drug.

21. Criterion modified per Amendment 3

21.1 Phase 1b erdafitinib + cetrelimab cohort and Phase 2: Plans to father a child while enrolled in this study or within 5 months after receiving the last dose of study drug.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Plans to father a child while enrolled in this study or within 6 months after receiving the last dose of study drug.

22. Criterion modified per Amendment 2

22.1 Major surgery within 4 weeks of enrollment, or inadequate recovery from the toxicity and/or complications from the intervention prior to starting therapy.

23. Criterion modified per Amendment 3

23.1 Phase 1b erdafitinib + cetrelimab cohort and Phase 2: not applicable.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: known sensitivity to any component of cisplatin or carboplatin.

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2 describes options for retesting. Section 17.4 describes the required documentation to support meeting the enrollment criteria.

5. TREATMENT ALLOCATION AND BLINDING

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

Subjects will be enrolled sequentially to a dose level after a discussion between the investigator and the sponsor.

6. DOSAGE AND ADMINISTRATION

Erdafitinib, along with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy infusions will be administered on the same day. Erdafitinib will be administered first, followed by cetrelimab and then platinum chemotherapy.

6.1. Dose Combination for Erdafitinib + Cetrelimab + Platinum Chemotherapy Cohort

Erdafitinib (8 mg oral without up-titration), cetrelimab (360 mg Q3W IV) and platinum chemotherapy will be administered at a starting dose of cisplatin 50 mg/m^2 Q3W IV in DL2C or carboplatin AUC 4 mg/mL/min Q3W IV in DL2D.

The dose levels for cisplatin and carboplatin are shown in Appendix 2 Table 4.

Appendix 2 Table 4: Erdafitinib, Cetrelimab, and Platinum Chemotherapy Administration: Dose Levels

Phase	Dosing Level [a, e]	Cisplatin or Carboplatin (IV infusion) [c, d]	Erdafitinib (oral administration) [c]	Cetrelimab (IV infusion) [b, c]
1b	DL2C	Cisplatin 50 mg/m^2 Q3W	8 mg (no up-titration) once daily	360 mg Q3W
1b	DL2C1	Cisplatin 60 mg/m^2 Q3W		
1b	DL2D	Carboplatin AUC 4 mg/mL/min Q3W (Not to Exceed 600 mg)		
1b	DL2D1	Carboplatin AUC 5 mg/mL/min Q3W (Not to Exceed 750 mg)		

[a] Additional dosing schedules may be explored if recommended by the SET and agreed upon by the sponsor.
[b] The cetrelimab dosing schedule can be adjusted if recommended by the SET and agreed upon by the sponsor.
[c] On days that all study drugs will be administered, the sequence of administration will be erdafitinib first, followed by cetrelimab and then platinum chemotherapy
[d] Erdafitinib + cetrelimab can continue every 3 weeks after a maximum of 4 cycles of platinum chemotherapy.
[e] See Section 3.1.1 of Appendix 2 for dose escalation.

6.2. Administration of Erdafitinib

Refer to Section 6.2 of the main body of the protocol.

6.3. Administration of Cetrelimab

Refer to Section 6.3 of the main body of the protocol.

6.4. Administration of Platinum Chemotherapy (Cisplatin or Carboplatin)

Standard chemotherapeutic agents will be prepared and administered as per the approved product label at the doses indicated below.

6.4.1. Cisplatin

The starting dose level for of cisplatin (DL2C) is 50 mg/m^2 IV Q3W. The dose level escalation rules for cisplatin are described in Section 3.1.1 of this appendix. Dosing with cisplatin should be immediately preceded and followed by hydration procedures. Supportive premedication and administration procedures for cisplatin are to align with the cisplatin label and local practice. A maximum of 4 cycles of cisplatin are to be administered to the subject. Erdafitinib and cetrelimab will continue after the subject receives 4 cycles of cisplatin.

6.4.2. Carboplatin

The starting dose level for carboplatin (DL2D) is AUC 4 mg/mL/min Q3W. The dose level escalation rules for carboplatin are described in Section 3.1.1 of this appendix. Supportive premedication and administration procedures for carboplatin are to align with the carboplatin label and local practice. A maximum of 4 cycles of carboplatin are to be administered to the subject. Erdafitinib and cetrelimab will continue after the subject receives 4 cycles of carboplatin.

Carboplatin dosing is calculated via the Calvert formula. Carboplatin dosing is not to exceed 600 mg for AUC4 dose level, and 750 mg for AUC5 dose level.

Calvert Formula:

Total Dose (mg) = (target AUC) x (CrCl + 25)

The estimated GFR used in the Calvert formula should not exceed 125 mL/min.

The maximum carboplatin dose (mg) = target AUC 4 (mg/min/mL) x (125 +25) = 4 x 150 mL/min is 600 mg.

The calculation of the creatinine clearance can be found in Attachment 8.

6.4.3. Antiemetic Therapy and Supportive Care Guidelines for Platinum Chemotherapy

Antiemetic therapy administered on days of platinum chemotherapy should follow Multinational Association for Supportive Care in Cancer (MASCC) guidelines (and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and aprepitant (or equivalent) as per the MASCC guidelines.

Routine primary prophylaxis to treat immunosuppression is not permitted for subjects who are under evaluation for DLTs. For the use of CSFs after the DLT period ends, utilize (NCCN/EORTC 2018) guidelines. However, subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

6.4.4. Dose Modification, Dose Delays, and Retreatment Criteria for Platinum Chemotherapy

Dose modifications must be based on the maximum toxicity experienced during a cycle. The investigator may attribute each toxicity event to platinum chemotherapy alone or to the combination of study drugs. Dose modification of the platinum chemotherapy agent and not the other agent(s) is appropriate if, in the opinion of the investigator, the toxicity is clearly related to platinum chemotherapy. If the toxicity is related to a combination of agents, all relevant agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications for that agent. See Section 6.2.2 for the dose modification, dose delay, and retreatment instruction for erdafitinib. See Section 6.3.1 and 6.3.2 for instructions regarding the retreatment and dose delay of cetrelimab, respectively.

If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Subjects can have a maximum of 2 dose modifications (if applicable) of platinum chemotherapy throughout the course of the study for toxicities. Subjects who require a 3rd dose modification to any particular component will have that agent discontinued.

Recommended dose modifications for platinum chemotherapy for hematologic and non-hematologic toxicity are described in Appendix 2 Table 5 and Appendix 2 Table 6, respectively. Appendix 2 Table 5 and Appendix 2 Table 6 serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Appendix 2 Table 5: **Recommended Dose Modifications for Platinum Chemotherapy: Hematological Toxicity**

		Cisplatin/Carboplatin	
Platelets (x10^3 cells/microliter)	**ANC (x10^3 cells/mm^3)**	**Dose modification (DM)**	
≥50 AND	≥0.5	DM 0	DM 0
≥50 AND	<0.5	DM -1	DM -1
<50 without bleeding AND	ANY	DM -1	DM -1
<50 with Grade ≥ 2 bleeding AND	ANY	DM -2	DM -2
ANY AND	<1.0 + fever ≥38.5°C (101°F)	DM -1	DM -1

Appendix 2 Table 6: Recommended Dose Modifications for Platinum Chemotherapy: Non-Hematological Toxicity

		Cisplatin	Carboplatin
Event	**CTC Grade**	**Dose modification (DM)**	
Nausea or vomiting	Grade 3 or 4	DM 0	DM 0
Diarrhea	Grade 3 or 4	DM -1	DM 0
Mucositis	Grade 3 or 4	DM 0	DM 0
Neurotoxicity	Grade 2	DM -2	DM 0
	Grade 3 or 4	Discontinue	DM -1
Transaminase elevation	Grade 3	DM -1	DM -1
	Grade 4	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3or 4	DM -1	DM -1

Appendix 2 Table 7 : Dose Modifications for Cisplatin and Carboplatin

Category	**Cisplatin**		**Carboplatin**	
Starting dose	50 mg/m^2	60 mg/m^2	AUC 4 mg/mL/min (maximum dose 600 mg)	AUC 5 mg/mL/min (maximum dose 750 mg)
1st dose modification	Stop cisplatin but continue erdafitinib+ cetrelimab	50 mg/m^2	Stop carboplatin but continue erdafitinib+ cetrelimab	AUC 4.5 mg/mL/min (maximum dose 675 mg)
2nd dose modification	N/A	Stop cisplatin but continue erdafitinib+ cetrelimab	N/A	Stop carboplatin but continue erdafitinib+ cetrelimab

Creatinine clearance (CrCl)

CrCl will be based on the original weight-based Cockcroft and Gault formula (Attachment 8). The subject's CrCl at Screening must be ≥30 mL/min to receive carboplatin and ≥60 mL/min to receive cisplatin prior to each cycle of platinum chemotherapy. Cisplatin may be delayed for up to 21 days (1 cycle) to allow the subject time to recover from the toxicity. If a subject's CrCl value has not returned to ≥30 mL/min within 42 days (2 cycles) after the previous dose, cisplatin must be discontinued.

In general, study drug(s) should be held for AEs ≥Grade 3 that are not attributable to erdafitinib, cetrelimab, platinum chemotherapy, or the disease under study. If the event resolves to Grade 1 or baseline within 4 weeks, platinum chemotherapy and erdafitinib may be reintroduced at one dose level lower. If the same toxicity does not recur or worsen within 4 weeks after re-starting therapy, then cetrelimab may be reintroduced at the same dose. Following re-introduction of study drugs, if the same AE recurs at ≥Grade 3 or there is a second incidence of a ≥Grade 3 event that is not attributable to erdafitinib, cetrelimab, platinum chemotherapy, or the disease under study, study drugs should be permanently discontinued.

For toxicity associated with platinum chemotherapy, the AE must resolve to Grade ≤1 or baseline prior to starting subsequent cycle. For individual subjects requiring a dose modification, treatment

for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the subject.

If a subject permanently discontinues 1 of the study drugs, the subject may continue to receive the other study drug(s) if investigator believes that the subject derives clinical benefit upon consultation with the sponsor's responsible medical monitor. Communication with the sponsor's responsible medical monitor including the final decision must be documented and retained in the sponsor's trial master file and in the investigator's study files.

6.4.5. Guidance for Specific Platinum Chemotherapy Toxicities

Cisplatin

The toxicity profile for cisplatin is described in the full prescribing information and labeling in the respective current US prescribing information, EU SmPC, or equivalent document for the specific region/country.

For subjects in DL2C, DL2C1 and DL2C2, cisplatin may produce cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. Serum creatinine, blood urea nitrogen (BUN), creatinine clearance, magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy and prior to each dose of cisplatin. Adequate renal function must be documented prior to receiving the next dose of cisplatin.

Audiometry will be performed for cis-ineligible ONLY if hearing loss is the single reason for cis-ineligibility. Audiometry will be performed as clinically indicated as ototoxicity is cumulative. Hearing loss during the study should be reported as an AE and graded according to CTCAE version 5.0.

Carboplatin

The toxicity profile for carboplatin is described in the full prescribing information and labeling in the respective current US prescribing information, EU SmPC, or equivalent document for the specific region/country.

For subjects in DL2D and DL2D1, bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also a DLT. Peripheral blood counts should be monitored frequently and, when appropriate, until recovery is achieved. Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy.

6.4.6. Platinum Chemotherapy Associated Toxicities Leading to Discontinuation of Study Treatment

The subject must discontinue platinum chemotherapy if:

- the subject experiences a Grade 3 or 4 unacceptable AE that does not resolve to Grade ≤ 1 within 7 days with medical management. Unacceptable AEs are described in Appendix 2 Table 8.

- the subject experiences any other intercurrent illness that prevents further administration of treatment, the subject must discontinue study treatment.

Appendix 2 Table 8: Unacceptable Adverse Events Leading to Discontinuation of Platinum Chemotherapy

Grade 4 Hematologic toxicities	Grade 3 Non- hematologic toxicities
Complete Blood Count: • leukopenia • thrombocytopenia • neutropenia • anemia	**Nephrotoxicity:** • elevation in BUN and creatinine • elevation in serum uric acid • decrease in CrCl
Serum electrolyte disturbances: • hypomagnesemia • hypocalcemia • hyponatremia • hypokalemia • hypophosphatemia	**Ototoxicity**: • tinnitus • bilateral hearing loss • dizziness
	Gastrointestinal: • nausea • vomiting

APPENDIX 3: PHASE 2 ERDAFITINIB +/ -CETRELIMAB COHORT

Appendix 3 Table 1: Time and Events Schedule – Phase 2 Erdafitinib +/- Cetrelimab Cohort (Up to and Including Amendment 4)

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
Screening Assessments											
Informed Consent (molecular and full-study)	Molecular Eligibility ICF to allow for assessment of FGFR status from archived tumor tissue, blood or local report. Full-Study ICF within 35 days prior to C1D1 to be used for subjects who meet molecular eligibility criteria. Must be signed before any study-related activity [b]	X	X								
Eligibility Criteria	Details provided in Sections 4.1 and 4.2 of Appendix 3.		X								
Demography, and Medical History	Histology and cytology, staging, prior therapy, and response.		X								
Molecular Eligibility Determination											
Local FGFR results (where applicable) [i]	Subjects may enroll based on local test results.	X									

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
	• Subjects with local FGFR tissue or blood must submit test report to the sponsor for central verification. • Subjects enrolling based on local testing must submit archival or fresh tumor tissue and a blood sample for retrospective confirmation of FGFR status as soon as possible after enrollment. The results of retrospective central confirmation do not affect the subject's eligibility for the study.										
Central Testing from Tissue and Blood [i]	Archival or fresh biopsy tumor tissue and a blood sample should be submitted	X									

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
	for molecular eligibility screening. If fresh biopsy, subject must sign the Full-Study ICF.										
Study Drug Administration [c]											
Erdafitinib	See Sections 6.1 and 6.2.			Oral once daily							
Cetrelimab infusion (Arm B only)	See Sections 6.1 and 6.3.			X [c]	X	X	X	X	X		
Safety Assessments											
Vital Signs (temperature, blood pressure, pulse/heart rate, respiratory rate)	Monitor every 15-20 min during the 1st infusion; for monitoring during subsequent infusions. See Section 6.3.		X	X [j]	X	X	X	X	X	X	X [d]
Physical Examination (PE)	Complete PE including height and weight at Screening. Thereafter disease-directed PE. See Section 9.6.9.		X	X	X	X	X	X	X	X	X [d]
ECOG PS	See Attachment 3.		X	X		X		X		X	
12-lead ECG [k]	Results obtained within 60 days of C1D1 can be counted as screening assessment. Record post-dose ECGs, See		X			C2 only		C4 only		X	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
	Section 9.6.5 for exact timing. May be performed more often as clinically indicated.										
Echocardiogram or MUGA	Results obtained within 6 months of C1D1 can be counted as screening assessment provided the subject has not experienced any cardiac event in the interim. Subsequent evaluations as clinically indicated.		X								
Amsler grid Test	To be performed by treating physician or nurse (or other appropriate study personnel).		X			X		X		X	
Ophthalmologic Exam	To be performed by an ophthalmologist. See Section 9.6.7 for exact assessments.		X	As clinically indicated (eg, based on abnormal Amsler grid test, see Attachment 5)							
Documentation of hearing loss (Grade 2 or higher) [1]	Hearing loss (where applicable) will be documented in the source for cisplatin-ineligible population and performed as		X								

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
	clinically indicated. See Section 9.6.11.										
Laboratory Assessments (by the local laboratory)											
Hematology	See Section 9.6.2; May be obtained up to 2 days prior to each cetrelimab dose.		X	X	X	X	X	X	X	X	
Chemistry [h]	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2.		X	X	X	X	X	X	X	X	
PO_4	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2.		X	X	X	X	X	X		X	
PTH	May be obtained up to 2 days prior to each cetrelimab dose; for exact assessments, see Section 9.6.2. After C6D1, PTH to be done every 3rd cycle. Results not required before dosing.		X		X	X		X		X	
TSH, T3, FT4	May be obtained up to 2 days prior to		X	Day 1 of every other cycle starting at C2D1							

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
	each cetrelimab dose; for exact assessments, see Section 9.6.2.T3 at Screening then only as clinically indicated.										
Serology	See Section 9.6.2. Results obtained within 60 days of C1D1 are acceptable.		X								
Pregnancy test (pre-dose)	For women of childbearing potential, serum at Screening (β-hCG) - obtain ≤7 days of C1D1. Serum or urine thereafter. See Section 9.6.4.		X			X		X		X	X [d]
Efficacy Assessments											
Disease assessment and response evaluation	Radiologic assessment by CT (preferred) or MRI of all disease sites (present and suspected) documented at Screening. The same methodology should be used throughout the study. Refer to		X	Every 6 weeks until Week 48 (±3 days), then every 12 to 24 weeks (±14 days) until disease progression. The timing of disease assessments should be calculated from C1D1 and the schedule should be maintained regardless of cycle delays and/or study drug interruptions. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 9.1.3). Tumor response will be evaluated according to RECIST 1.1 criteria (Seymour 2017). All unconfirmed PR/CR require confirmation of response as per RECIST 1.1.							

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks
	Section 9.2. for details. Disease assessments done within 35 days prior to C1D1 may be used as the Screening disease assessment.										
Ongoing Review											
Adverse Events	X - Continuous from signing of Full-Study ICF to up to 100 days after the last dose of study treatment or until the start of subsequent anticancer therapy. An AE should be monitored until it resolves to baseline, stabilizes, or is deemed irreversible, subject dies, or subsequent therapy is started, whichever occurs first.										
Concomitant medications	X - Continuous from signing of Full-Study ICF to up to 100 days after the last dose of study treatment or until the start of subsequent anticancer therapy, if earlier. See Section 8.										
Posttreatment Assessments											
Survival evaluation	Contact subject every 12 weeks (±7 days) after the last dose of study treatment by office visit, phone call or e-mail. See Section 9.1.4.										X
Subsequent anticancer therapy	Contact subject every 12 weeks (±7 days) after the last dose of study treatment by office visit, phone call or e-mail. See Section 9.1.4.										X

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; b-hCG= beta-human chorionic gonadotropin; C = cycle; CR= complete response; CT = computed tomography; ctDNA=circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI=end of infusion; FGFR= fibroblast growth factor receptor; FT4= free thyroxine; ICF = informed consent form; INR = international normalized ration; MRI = magnetic resonance imaging; MUGA= multi-gated acquisition scan; OCT = optical coherence tomography; PBMC=peripheral blood mononuclear cell; PD-L1 = programmed cell death ligand 1; PE = physical examination; PK = pharmacokinetics; PO_4 = phosphate; PR= partial response; PS = performance status; PT = prothrombin time; PTH=parathyroid hormone; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; T3= triiodothyronine; TCR=T cell antigen receptor; TSH= thyroid stimulating hormone

[a] The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy. Follow-up visits will occur every 12 weeks (±7 days).
[b] For subjects signing a Full-Study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 35-day window starts with the first planned study-related procedure other than the tissue biopsy; however, AEs will need to be collected from the time of Full-Study ICF sign off.
[c] Schedule for Phase 2 will be determined once RP2D from the Phase 1b erdafitinib + cetrelimab cohort has been identified.

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1 [g]		Treatment Cycle 2 [g], 3 [g]		All Other Cycles [g]		End-of-Treatment [a, g]	Follow-up Period [a, g]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2) [f]	Within 30 Days (+7) of last dose	Every 12 weeks

[d] Physical examination, vital signs, and pregnancy testing at first follow-up visit (12 weeks after last dose).
[e] C1D1 must occur no more than 3 days after the Randomization transaction in IWRS.
[f] Subjects on erdafitinib monotherapy (including subjects assigned to Arm A, as well as any subjects who permanently discontinue cetrelimab) do not need to complete the Day 15 visit after Cycle 3. After Cycle 4, subjects continuing on cetrelimab will switch to Q4W dosing and therefore do not need to complete the Day 15 visit procedures.
[g] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 10.
[h] CrCl is calculated by the Cockcroft-Gault formula (Attachment 8).
[i] Consent for molecular screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.
[j] Pre-dose only for Arm A.
[k] Post-dose ECGs for subjects receiving erdafitinib monotherapy should be recorded 2 to 4 hours after the erdafitinib dose on C2D1 and, if possible, 2 to 4 hours after the erdafitinib dose on C4D1. Post-dose ECGs for subjects receiving erdafitinib and cetrelimab in combination should be recorded as soon as possible upon completion of infusion on C2D1 and C4D1. The End-of-Treatment ECG may be performed at any time during the End-of-Treatment Visit. Additional ECGs may be performed during the study as clinically indicated.
[l] Audiometry tests that were performed prior to consent for the full-study was obtained is permitted to be collected as long as it is documented this procedure was performed as part of standard of care and not specifically for study purposes.

Appendix 3 Table 2: Pharmacokinetic, Immunogenicity, and Biomarker Samples for the Phase 2 Erdafitinib +/- Cetrelimab Cohort (Up to and Including Amendment 4)

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1		Treatment Cycle 2, 3		All Other Cycles		End of Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
Note: These samples should be drawn on the day study drug is administered.[b]											
Erdafitinib PK [c] (Both Arms)	Pre-dose erdafitinib [d] unless otherwise specified. See Section 9.3.			X	X	Pre-dose erdafitinib C2 & C3; 4h post erdafitinib C2D1 only [e]		Pre-dose erdafitinib C5; 4h post erdafitinib C5D1 only [e]			
Erdafitinib Protein Binding Blood Sample (Both Arms)	4 hrs Post-dose See Section 9.3.					C2D1					
Cetrelimab PK [c] (Arm B only)	Pre-infusion [d] and EOI [f] unless otherwise specified. See Section 9.3.			X	X	X		C4 & C5		Any time during visit	At first follow-up visit, if possible
Cetrelimab Immunogenicity (Arm B only)	Pre-infusion [d] See Section 9.3.			X	X	X		C4 and every other cycle starting at C5D1		Any time during visit	At first follow-up visit, if possible
[redacted]	A tumor biopsy can be taken at any time during a visit if a subject shows PD		X			C2D1 (±3 days)				PD	

Assessments/ Procedure	Notes	Molecular Eligibility Screening Period	Full-Study Screening Period	Treatment Cycle 1		Treatment Cycle 2, 3		All Other Cycles		End of Treatment [a]	Follow-up Period [a]
		≥28 days prior to C1D1	Within 28 days prior to C1D1	Day 1	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Day 1 (±2)	Day 15 (±2)	Within 30 Days (+7) of last dose	Every 12 weeks
	anytime throughout the study [h]										
CCI	Pre-dose erdafitinib [d]			X	X	X	X				
CCI	Pre-dose erdafitinib [d]			X	X	X	X			Any time during visit	
CCI	Pre-dose erdafitinib [d] unless otherwise specified.			X		C3D1		C5D1		Any time during visit	
CCI	Archival or fresh biopsy tissue must be available for biomarker analysis.	X									

Abbreviations: ctDNA= circulating tumor DNA; EOI=end of infusion; FGFR= fibroblast growth factor receptor; PD= progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PBMC = peripheral blood mononuclear cells; TCR = T cell antigen receptor

[a] The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy. Follow-up visits will occur every 12 weeks (±7 days).
[b] The sampling schedule may be adjusted based on PK analysis output generated during the study or other safety concerns.
[c] If dose delay occurs, then samples should be collected on the actual day of drug administration, not on the originally scheduled administration day.
[d] On the day in which both drugs are given, erdafitinib oral dose will be administered prior to cetrelimab IV infusion. Pre-dose PK sample for erdafitinib and Pre-infusion PK and immunogenicity samples for cetrelimab may be collected up to 30 minutes before dosing, respectively.
[e] Timepoint is relative to the dosing of erdafitinib. Erdafitinib PK samples may be collected during the cetrelimab infusion if necessary; however, the sample should be drawn from the contralateral arm (opposite the cetrelimab infusion site).
[f] As soon as possible after EOI.
[g] Paired biopsies at Screening and C2D1 are optional. The biopsy upon PD is also optional for all subjects. High-risk areas of metastases such as brain, pancreas, and lung should not be considered as an accessible site for biopsy. Biopsies will be collected to aim to have a minimum of 15 evaluable biopsy pairs.
[h] Tumor biopsy to be taken within 2 weeks of documented disease progression. Note: Additional samples may be collected at any time for assessment of AEs as clinically appropriate.

1. INTRODUCTION

Refer to Section 1 of the protocol for the introduction. The introduction includes a description of urothelial bladder cancer, FGFR signaling, erdafitinib, PD-1/PD-L1 signaling, cetrelimab (summary of nonclinical data, summary of clinical data), platinum chemotherapy in metastatic urothelial cancer, overall rationale for the study, the anticipated benefits and risks for erdafitinib and cetrelimab, and the anticipated benefits and risks for platinum chemotherapy.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints for Phase 2 (Dose Expansion)

Objectives	Endpoints
Primary	
• 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 with select FGFR gene alterations and no prior systemic therapy for metastatic disease	•Overall response rate (ORR) (partial response [PR] or better) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by investigator assessment • Incidence of adverse events (AEs)
Secondary	
• To characterize the PK of erdafitinib and cetrelimab	• Plasma erdafitinib and serum cetrelimab concentrations
• To assess the immunogenicity of cetrelimab	• Detection of antibodies to cetrelimab and effects on serum cetrelimab levels
• To further assess safety at the R2PD of erdafitinib alone and in combination with cetrelimab • To further characterize the clinical activity of erdafitinib alone and in combination with cetrelimab	• Incidence of AEs, serious adverse events (SAEs) and laboratory values • Duration of response (DoR) • Time to response (TTR) • Progression-free survival (PFS) • OS
Exploratory	
•To assess the expression of CCI [redacted] •To evaluate changes in CCI [redacted] •To assess changes in CCI [redacted] •To explore biomarkers (DNA, RNA, and/or protein) in tissue and blood samples that could CCI [redacted] •To explore the relationships between PK, PD, AE profiles, and CCI [redacted]	

2.2. Hypothesis

Erdafitinib alone and in combination with cetrelimab are safe and have anti-tumor 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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

Refer to Section 3.1 of the main body of the protocol.

3.1.1. Phase 1b

Not applicable to the Phase 2 erdafitinib +/- cetrelimab cohort.

3.1.2. Phase 2: Erdafitinib +/- Cetrelimab Cohort

An overview of the Phase 2 dose expansion cohort is described in Figure 3.

In Phase 2 (dose expansion), approximately 90 subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations based on molecular testing who meet the definition of cisplatin-ineligible and have not had prior systemic therapy for metastatic disease will be stratified by ECOG PS (0-1 versus 2) and then assigned randomly (1:1 ratio) to either the erdafitinib monotherapy treatment (Arm A), or the combination treatment of erdafitinib and cetrelimab (Arm B). To further characterize safety and clinical activity of the erdafitinib and cetrelimab (Arm B).

A DRC will be commissioned for Phase 2 of this study. Based on emerging safety data, on 12 May 2020, the DRC recommended to remove the requirement for up-titration from the erdafitinib + cetrelimab combination. The DRC also made a recommendation to close Dose level 2 in Phase 1b and focus enrollment efforts into the Phase 2 part of the study. Therefore, Arm B will no longer include up-titration for erdafitinib.

Refer to Section 11.10 of the main body of the protocol and the DRC charter for details regarding the composition and scope of the DRC.

Refer to Appendix 3 Table 3 for an overview of the Phase 2 dosing administration of erdafitinib and cetrelimab.

3.2. Study Design and Starting Dose Rationale

Refer to Section 3.2 of the main body of the protocol.

3.3. Dose-Limiting Toxicity Evaluation and Determination of RP2D

Not applicable to the Phase 2 erdafitinib +/- cetrelimab cohort.

3.4. Study Evaluation Team

Not applicable to the Phase 2 erdafitinib +/- cetrelimab cohort.

4. SUBJECT POPULATION

Adult subjects age 18 years and older with metastatic or locally advanced urothelial cancer who meet the molecular eligibility and full-study eligibility are eligible for the study. Screening

assessments will be performed as indicated in the Phase 2 erdafitinib +/- cetrelimab Time and Events Schedule Appendix 3 Table 1. Molecular eligibility assessment may occur ≥28 days prior to administration of the study drugs.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. For a discussion of the statistical considerations of subject selection, refer to Section 11.1, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age.

2. Criterion modified per Amendment 2

   2.1 Histologic demonstration of transitional cell carcinoma of the urothelium. Variant urothelial carcinoma histologies such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable.

3. Criterion modified per Amendment 2

   3.1 Metastatic or locally advanced urothelial cancer (Stage IV disease per AJCC Staging Guidelines)

4. Criterion modified per Amendment 2

   4.1 Criterion modified per Amendment 3

   4.2 Phase 1b erdafitinib + cetrelimab cohort and **Phase 2**: Meet appropriate molecular eligibility criteria. Tumors must have at least one gene fusion or gene mutation as defined in Table 4.

   Exception for Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: up to 3 subjects in each erdafitinib + cetrelimab + chemotherapy cohort at each dose level will be wild-type. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations described in Table 4. All other subjects must have at least one select FGFR alteration as defined in Table 4.

5. Criterion modified per Amendment 2

   5.1 Must have measurable disease by radiological imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at baseline.

6. Criterion modified per Amendment 2

   6.1 Criterion modified per Amendment 3

   –

   – 6.2 Prior systemic therapy for metastatic urothelial cancer:

   – Phase 1b erdafitinib + cetrelimab cohort:

- Any number of lines of prior therapy
- Renal function for subjects must have a creatinine clearance (CrCl) ≥30 mL/min as calculated by Cockcroft-Gault (Attachment 8)

- Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:
  - No prior systemic therapy for metastatic disease. **Note**: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting
  - Renal function for subjects must have a creatinine clearance (CrCl) ≥30 mL/min to receive carboplatin and ≥60 mL/min to receive cisplatin as calculated by Cockcroft-Gault (Attachment 8)

- **Phase 2:**
  - No prior systemic therapy for metastatic disease. **Note**: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting.
  - Cisplatin-ineligible based on:
    - ECOG PS 0-1 AND at least <u>one</u> of the following criteria:
  - Renal function defined as creatinine clearance (CrCl) <60 mL/min as calculated by Cockcroft-Gault (Attachment 8) (Galsky 2011)
  - Grade 2 or higher peripheral neuropathy per NCI-CTCAE version 5.0.
  - Grade 2 or higher hearing loss per NCI-CTCAE version 5.0,
- **OR**
  - ECOG PS 2

7. Criterion modified per Amendment 2

   7.1 Criterion modified per Amendment 3

   7.2 ECOG PS Grade of (see Attachment 3) as defined below:

   Phase 1b erdafitinib + cetrelimab cohort: ECOG 0-2

   Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: ECOG 0-1 for cisplatin and ECOG 0-2 for carboplatin.

   Phase 2: ECOG 0-2

8. Criterion modified per Amendment 1

   8.1 Criterion modified per Amendment 2

   8.2 Criterion modified per Amendment 3

   8.3 Adequate organ function at Screening defined as follows:

   - Phase 1b erdafitinib + cetrelimab cohort and **Phase 2**

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Hematology	
Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks)	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
Platelets	$\geq 75 \times 10^9$/L
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L
Chemistry	
AST and ALT	≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for subjects with liver metastases
Creatinine clearance (mL/min)	Calculated using the Cockcroft-Gault formula (Attachment 8) Phase 1b erdafitinib + cetrelimab cohort: ≥30 mL/min **Phase 2:** ≥30 mL/min. If the subject is considered cisplatin-ineligible based on creatinine clearance then CrCl must also be <60 mL/min.
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
Thyroid panel: TSH, T3 or Free T3 (FT3) and Free thyroxine (FT4)	All within normal range. If TSH is not within normal limits, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.
Phosphate	Below institutional ULN within 14 days of treatment and prior to C1D1 (medical management allowed)
Cardiovascular	
Left ventricular ejection fraction	Within normal institutional limits
Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal	

Phase 1b erdafitinib + cetrelimab + platinum (cisplatin or carboplatin) chemotherapy cohort

Hematology	
Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks)	
Hemoglobin	≥9.0 g/dL (≥5.59 mmol/L) (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
Platelets	$\geq 100 \times 10^9$/L
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L
Chemistry	
AST and ALT	≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for subjects with liver metastases
Creatinine clearance (mL/min)	Calculated using the Cockcroft-Gault formula (Attachment 8) Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: ≥30 mL/min to receive carboplatin and ≥60 mL/min to receive cisplatin
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
Thyroid panel: **TSH,** T3 or Free T3 (FT3) and Free thyroxine (FT4)	All within normal range. If TSH is not within normal limits, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.
Phosphate	Below institutional ULN within 14 days of treatment and prior to C1D1 (medical management allowed)
Cardiovascular	
Left ventricular ejection fraction	Within normal institutional limits

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; QTcF=QT corrected interval by the Fridericia's formula; ULN=upper limit of normal

9. Criterion modified per Amendment 2

9.1 Criterion modified per Amendment 1.

9.2 Criterion modified per Amendment 3

9.3 Phase 1b erdafitinib + cetrelimab cohort and **Phase 2:**

Before the first dose of study drug:

Women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile as a result of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 5 months after the last dose of study drug. For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 5 months after the last dose of study drug. Contraception must be consistent with local regulations

regarding the use of birth control methods for subjects participating in clinical trials. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 5 months after the last dose of study drug.

Examples of highly effective methods include:

– user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner;

– user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and the combination of the study drugs have not been studied. Therefore, it is unknown whether the study drugs may reduce the efficacy of the contraceptive method.

– Sexual abstinence

(True sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of true sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception).

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort:

Before the first dose of study drug:

Women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile as a result of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 6 months after the last dose of study drug. For men who are sexually active with women of childbearing potential: agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for 6 months after the last dose of study drug. Contraception must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 6 months after the last dose of study drug.

Examples of highly effective methods include:

– user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized

partner;

– user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered. It should be noted that interaction between hormonal contraception and the combination of the study drugs have not been studied. Therefore, it is unknown whether the study drugs may reduce the efficacy of the contraceptive method.

– Sexual abstinence

(True sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of true sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study drugs, and withdrawal are not acceptable methods of contraception).

10. Women of childbearing potential must have a negative pregnancy test at Screening within ≤7 days of C1D1 (first dose of study drug) using a highly sensitive pregnancy test (serum β-human chorionic gonadotropin [β-hCG]); see Section 9.6.4).

11. Sign an informed consent form indicating that he or she understands the purpose of and procedures required for the study, and is willing and able to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

12. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to C1D1. For Phase 1b, subjects who have received the following prior anti-tumor therapy:

   - Received nitrosoureas and mitomycin C within 6 weeks.

2. Criterion modified per Amendment 3

   2.1 Phase 1b erdafitinib + cetrelimab cohort:

   - Chemotherapy within 3 weeks of C1D1.

   Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort and **Phase 2**:

- Prior neoadjuvant/adjuvant chemotherapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation.

3. Criterion modified per Amendment 2

   3.1 Criterion modified per Amendment 3

   3.2 Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy. Prior neoadjuvant/adjuvant checkpoint inhibitor therapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation. PD-1 for non-muscle invasive bladder cancer is also allowed.

4. Criterion modified per Amendment 2

   4.1 Active malignancies requiring concurrent therapy other than urothelial cancer.

5. Symptomatic central nervous system metastases.

6. Prior FGFR inhibitor treatment.

7. Radiation therapy ≤30 days prior to planned C1D1.

8. Criterion modified per Amendment 2

   8.1 Criterion modified per Amendment 3

   8.2 History of uncontrolled cardiovascular disease including:

   - Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V (Attachment 6) within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months.

9. Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.

10. Any of the following:

    - Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection.
    - Active autoimmune disease or a documented history of autoimmune disease that requires systemic steroids or immunosuppressive agents.

    Note: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid

injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study. Subjects with a history of transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis) will not be excluded from the study.

- Grade 3 or higher toxicity effects from previous treatment with immunotherapy.
- Psychiatric conditions (eg, alcohol or drug abuse), dementia, or altered mental status.
- Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

11. Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.

12. Active or chronic hepatitis B or hepatitis C disease as determined by hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody (anti-HCV) positivity at Screening. If positive, further testing of quantitative levels to rule out active infection is required (see Attachment 2).

13. Criterion modified per Amendment 3

13.1 Phase 1b erdafitinib + cetrelimab and Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant, such as alopecia, skin discoloration, or Grade 1 hearing loss or neuropathy).

Phase 2: Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant such as alopecia, or skin discoloration).

14. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

15. Criterion modified per Amendment 2

15.1 Allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or immune-mediated thrombocytopenia or anemia), or to excipients of erdafitinib or cetrelimab (see the Investigator's Brochures for a list of excipients).

16. Criterion modified per Amendment 2

16.1 Current central serous retinopathy (CSR) or retinal pigment epithelial detachment (RPED) of any Grade.

17. Criterion deleted per Amendment 2

18. Criterion modified per Amendment 2

18.1 Use of immunosuppressant agents, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, cyclosporine, azathioprine, and tumor necrosis factor α (TNF-α) blockers, within 2 weeks before the planned first dose of study drug.

19. Vaccinated with a live attenuated vaccine within 28 days prior to the first dose of study drug and for 3 months after receiving the last dose of study drug. Annual inactivated influenza vaccine is permitted.

20. Criterion modified per Amendment 3

20.1 Phase 1b erdafitinib + cetrelimab cohort and **Phase 2:** Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 5 months after receiving the last dose of study drug.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after receiving the last dose of study drug.

21. Criterion modified per Amendment 3

21.1 Phase 1b erdafitinib + cetrelimab cohort and **Phase 2:** Plans to father a child while enrolled in this study or within 5 months after receiving the last dose of study drug.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: Plans to father a child while enrolled in this study or within 6 months after receiving the last dose of study drug.

22. Criterion modified per Amendment 2

22.1 Major surgery within 4 weeks of enrollment, or inadequate recovery from the toxicity and/or complications from the intervention prior to starting therapy.

23. Criterion modified per Amendment 3

23.1 Phase 1b erdafitinib + cetrelimab cohort and **Phase 2:** not applicable.

Phase 1b erdafitinib + cetrelimab + platinum chemotherapy cohort: known sensitivity to any component of cisplatin or carboplatin.

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2 describes options for retesting. Section 17.4 describes the required documentation to support meeting the enrollment criteria.

5. TREATMENT ALLOCATION AND BLINDING

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

In Phase 2, approximately 90 subjects will be enrolled and randomly assigned 1:1 to receive either erdafitinib or erdafitinib in combination with cetrelimab based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Randomization will be stratified by ECOG PS (0-1 versus 2). The interactive web response system (IWRS) will assign a unique treatment code, which dictates the treatment assignment for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and then give the relevant subject details to uniquely identify the subject.

6. DOSAGE AND ADMINISTRATION

On days that both drugs will be administered, the sequence of administration will be oral erdafitinib followed by the infusion of cetrelimab IV.

6.1. Dose Combination for Erdafitinib +/- Cetrelimab Arms

Arm A will be administered erdafitinib. Arm B will be administered erdafitinib + cetrelimab (240 mg) Q2W for Cycles 1 through 4. The dose of cetrelimab is increased to 480 mg Q4W starting at Cycle 5. The dose of study drug for each Arm of the Phase 2 portion of the study is shown in Appendix 3 Table 3.

Appendix 3 Table 3: Erdafitinib and Cetrelimab Administration: Dose Arms A and B

Phase	Dosing Arms	Erdafitinib (oral administration)	Cetrelimab (IV infusion)
2	Arm A	8 mg-up-titrated to 9 mg once daily	Not administered
2	Arm B	RP2D of Phase 1b 8 mg (no up-titration) once daily	240 mg Q2W- starting at Cycle 1 480 mg Q4W starting at Cycle 5

In Arm B, if a subject permanently discontinues 1 of the study drugs, the subject may continue to receive the other study drug if investigator believes that the subject derives clinical benefit upon consultation with the sponsor's responsible medical monitor. Communication with the sponsor's

responsible medical monitor including the final decision must be documented and retained in the sponsor's trial master file and in the investigator's study files.

If a ≥Grade 3 AE is not attributable to study treatment (erdafitinib or cetrelimab), or the disease under study, then all study drugs should be held. If the event resolves to Grade 1 or baseline within 4 weeks, erdafitinib may be reintroduced at one dose level lower. If the same toxicity does not recur or worsen within 4 weeks after re-starting erdafitinib, then cetrelimab may be reintroduced at the same dose. Following re-introduction of both study drugs, if the same AE recurs at ≥Grade 3 or there is a second incidence of a ≥Grade 3 event that is not attributable to erdafitinib, cetrelimab or the disease under study, both study drugs should be discontinued.

Guidance for the management of toxicity associated with erdafitinib or cetrelimab, is provided in Sections 6.2 and 6.3, respectively.

APPENDIX 4: SUGGESTED SCHEDULE OF ACTIVITIES FOR PHASE 1B AND PHASE 2 COHORTS FOLLOWING AMENDMENT 5

Appendix 4 Table 1: Schedule of Activities After End of Data Collection Timepoint (Protocol Amendment 5) – Phase 1b dose escalation, chemotherapy, and Phase 2 cohortsa,b,

Assessments/ Procedure	Notes	Cycle Xc	End-of-Treatment d, e,h
		Day 1 (±2)	Within 30 Days (+7) of last dose
Study Drug Administration			
Erdafitinib	See Sections 6.1 and 6.2.	Oral once daily	
Cetrelimab infusion (Arm B only)	See Sections 6.1 and 6.3.	X	
Safety Assessments			
Vital Signs (temperature, blood pressure, pulse/heart rate, respiratory rate)	See Section 6.3.	X	X
Physical Examination (PE)	Disease-directed PE. See Section 9.6.9.	X	X
Ophthalmologic Exam	To be performed by an ophthalmologist. See Section 9.6.7 for exact assessments.	As clinically indicated	
Adverse Events[f,g]		Continuous	
Concomitant Medications[g]		Continuous	
Laboratory Assessments (by local laboratory)			
Hematology	See Section 9.6.2; May be obtained up to 7 days prior to Day 1 of each dose.	X	X
Chemistry	May be obtained up to 7 days prior to Day 1 of each cycle; for exact assessments, see Section 9.6.2.	X	X
PO_4	May be obtained up to 7 days prior to Day 1 of each cycle; see Section 9.6.2.	X	X
TSH, T3, FT4	May be obtained up to 7 days prior to Day 1 of each cycle; see Section 9.6.2. T3 at Screening then only as clinically indicated.	X (subjects receiving cetrelimab)	X
PTH	Every 3rd cycle. May be obtained up to 7 days prior to Day 1 of each cycle; Results not required before dosing.	X (subjects receiving cetrelimab)	X
Pregnancy test (pre-dose)	Serum or urine, for women of childbearing potential. See Section 9.6.4.	X	X
Cetrelimab Immunogenicity	An ad-hoc sample for cetrelimab immunogenicity may be collected for purposes of safety evaluation if clinically indicated.		

Assessments/ Procedure	Notes	Cycle Xc	End-of-Treatment d, e,h
		Day 1 (±2)	Within 30 Days (+7) of last dose
Efficacy Assessments			
Disease assessment and response evaluation	Radiologic assessment by CT (preferred) or MRI of all disease sites (present and suspected) The same methodology should be used throughout the study. Refer to Section 9.2. for details.	To be performed at the discretion of the investigator based on routine treatment or as clinically indicated. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 9.1.3).	

Abbreviations: CT = computed tomography; FT4= free thyroxine; MRI = magnetic resonance imaging; PE = physical examination; PO_4 = phosphate; PTH=parathyroid hormone; T3= triiodothyronine; TSH= thyroid stimulating hormone

[a] Patients can transfer to this schedule of activities once the end of study data collection timepoint has been achieved.
[b]Phase 1b dose escalation cohort and Phase 2 subjects are on a 4-week cycle schedule. The Ph1b chemotherapy cohorts are on a 3-week cycle schedule.
[c]Cycle X -refers to the cycle upon which a subject transfers from the previous cohort to the new schedule.
[d]The End-of-Treatment Visit will occur within 30 days after the subject discontinues treatment for any reason. This assessment should be done prior to the subject starting a new therapy.
[e]Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 10
[f] Once a subject has transitioned to this schedule and has completed the follow-up visit, only required SAE data will be collected.
[g] Up to 30 days after the last dose if on erdafitinib alone, and 100 days after last dose of cetrelimab if receiving cetrelimab, whichever is longer.
[h] Refer to Section 10.1 for the definition of subject completion per Protocol Amendment 5.

INVESTIGATOR AGREEMENT

JNJ-42756493 (erdafitinib); JNJ-63723283 (Cetrelimab)
Clinical Protocol 42756493BLC2002 Amendment 5

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: 11June2022
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 11 July 2022