Janssen Research & Development *

Clinical Protocol

A Phase 3 Study of Erdafitinib Compared with Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations

Protocol 42756493BLC3001; Phase 3
AMENDMENT 6

JNJ-42756493 (erdafitinib)

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	29 Sep 2017
Amendment 1	26 Oct 2017
Amendment 2	01 May 2018
Amendment 3	18 Jan 2019
Amendment 4	29 Mar 2020
Amendment 5	25 March 2021
Amendment 6	20 January 2023

Amendments below are listed beginning with the most recent amendment.

Amendment 6 (20 January 2023)

The overall reason for the amendment: To add the Long-term Extension (LTE) Phase. The addition of the LTE Phase modifies the overall end of study definition. Study completion is distinct from end of study. Study completion is defined as the end-of-data-collection timepoint for both cohorts, which is defined as when the clinical cutoff ~~at~~ for the final analysis has been achieved. End of study is defined as when the last subject receives the last dose of study drug on the study.

Applicable Section(s)	Description of Change(s)
Rationale: To add the LTE Phase, which modifies the "study completion" and "end of study" definitions, as noted above.	
Synopsis (Overview of Study Design); Time and Events Schedule; 3.1. Overview of Study Design; 6.4. Continued Access to Study Drug after the End of Study Data Collection; Timepoint; 9.1.3. Treatment Phase; 9.1.4. Follow-Up Phase; 9.7.1. Adverse Events; 10.1. Completion; 17.9.1. Study Completion (ie, End of Data Collection Timepoint) and End of Study; Attachment 8	The LTE Phase was added to the protocol with Attachment 8, which includes a Time and Events Schedule. The LTE Phase is also mentioned in the synopsis and body of the protocol. Attachment 8 also adds that the Sponsor may decide to allow cross-over to erdafitinib at this time. The LTE Phase begins with the approval of Amendment 6 and with achievement of the clinical cut-off for the final analysis for each cohort. (For Cohort 1, the Sponsor will notify the investigators if the interim analysis will be considered the final analysis.) Upon initiation of the LTE Phase, the follow up of subjects will end and the eCRF will be closed. Subjects in the respective cohort who are continuing to derive benefit from study drug, as determined by their investigator may have continued access to study drug. This continued access to study drug could be either in the LTE Phase of this study, or, alternatively, subjects may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations.) During this LTE Phase (when study drug will be supplied by the Sponsor after the end of data collection timepoint), only serious adverse events will be reported to the Company safety repository. (In Adverse Event Section 9.7.1, the reader is also referred to the LTE Phase Attachment.) Clinical assessments will be conducted according to the standard of practice. New Section 6.4 was added to describe treatment with erdafitinib, chemotherapy, and pembrolizumab after the end of data collection time point.

Applicable Section(s)	Description of Change(s)
	Section 17.9.1 provides the modified study completion and end of study definitions. The study is considered completed at the time of the end-of-data-collection timepoint for both cohorts. The end-of-data-collection timepoint is defined as when the clinical cutoff at final analysis has been achieved. At that time, participation in the Follow-Up Phase will end and the data collection will conclude. The end of study is defined as when the last subject receives the last dose of study drug on the study. The Synopsis and Section 17.9.1, as well as the Time and Events Schedule (new Footnote "b"), clarify the end-of-data-collection timepoint. In Sections 10.1 and 17.9.1, the subject completion definition has been modified accordingly, ie, 1) died while on study or 2) not withdrawn by study completion (ie, by the end-of-data-collection timepoint). Section 3.1, Overview of Study Design, introduces the LTE Phase in the body of the protocol and a footnote was added to the study schema to note the LTE Phase. In this and other sections as applicable, the description of the Post-treatment Follow-up Phase end point was revised due to the addition of the LTE Phase (ie, "study completion" rather than "end of study" is used).
Rationale: Replaced comparator drug brand names with the corresponding generic compound names.	
1.2.1. Docetaxel; 1.2.2. Vinflunine; 1.3.1. Pembrolizumab; 14.1. Physical Description of Study Drug(s); 14.2. Packaging; References	Brand names "Taxotere", "Javlor", and "Keytruda" were replaced with respective generic names. Terminologies "SmPC" or "package inserts" were replaced with "locally available prescribing information". Removed summary of product characteristics/prescribing information of "Taxotere", "Javlor", and "Keytruda" from the list of references.
Rationale: To clarify the length of pembrolizumab treatment in Study KEYNOTE-045.	
1.3.1 Pembrolizumab	The following text was added for Study KEYNOTE-045: "Patients without disease progression could be treated with pembrolizumab up to 24 months."
Rationale: To correct the number of core items in the Functional Assessment of Cancer Therapy – Bladder Cancer (FACT-B1) assessment.	
9.5. Patient Reported Outcomes	The number of core items in FACT-B1 was corrected (ie, from 36 to 39 items).
Rationale: To align with the current protocol template.	
Attachment 6; Throughout the protocol	Updated Anticipated Event general information in Attachment 6; no change to the anticipated event terms. The term "country" was replaced with "country/territory".
Rationale: Minor clarifications and corrections were made.	
Throughout the protocol	Minor grammatical corrections and change to abbreviations made throughout.

Amendment 5 (25 March 2021)

The overall reason for the amendment:
The overall reason for this amendment is to revise the timing of the interim analyses for Cohort 1 and Cohort 2 to occur at a higher percentage of total events, ie, allow for more mature data. Also, the possible sample size re-estimation was removed and guidance on the futility boundary was provided.

Applicable Section(s)	Description of Change(s)
Rationale: The interim analysis for each cohort was revised to occur at a higher percentage of total events, to ensure that each interim analysis is conducted with more mature data. The sample size re-estimation for each cohort was removed to complete the study in a reasonable period of time. Also, guidance on the futility boundary was added to the interim analysis for each cohort.	
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; 3.1, Overview of Study Design; 11.2, Sample Size Determination; 11.3, Efficacy Analyses; 11.3.1, Primary Endpoint; 11.3.3, Subgroup Analyses; 11.3.4, Baseline Assessments; 11.8, Interim Analysis; 11.9, Independent Data Monitoring Committee	In the Synopsis (Overview of Study Design), the review of the interim analyses by the Independent Data Monitoring Committee (IDMC) was mentioned. Also, in the Synopsis (Statistical Methods), the stratification factors for comparison of the survival curves of OS between the treatment groups were listed. In Section 11.2, for both Cohort 1 and Cohort 2, the interim analysis is specified as an efficacy analysis and the percentage information fraction at which each interim analysis will occur was modified (Cohort 1 at approximately 65% and Cohort 2 at approximately 65%). The number of projected subjects enrolled per site was removed. In Section 11.3, for the comparison between the 2 treatment arms in each cohort, detail regarding the continuous and discrete variables was removed. The text regarding separate analysis of each cohort was moved to the end of this section. In Section 11.3.1, detail regarding the factors used in the Cox proportional hazards model for calculating the HR for erdafitinib related to the control was deleted. New Section 11.3.3 mentions the subgroup analyses for the primary and secondary efficacy endpoints with reference to the Statistical Analysis Plan (SAP) for further information. Due to this addition, former Section 11.3.3 is renumbered Section 11.3.4. In Section 11.8, the timing of the interim analyses was revised to occur when an approximately 65% information fraction is reached, ie, approximately 136 of 208 deaths in Cohort 1 and approximately 172 of 264 deaths in Cohort 2. The detail regarding the statistical software was deleted, as well as the detail regarding interim analysis plan (IAP). However, the significance level (ie, 0.05) to control the Type 1 error was added. Additional guidance for the stopping of each cohort due to futility was provided. Some editing of the main paragraph has occurred for better flow. In Section 11.9, text regarding IDMC recommendations at the time of the interim analysis pertaining to the sample size adjustment was deleted, as well as text regarding the communication of sample size recommendation. It was clarified that the IDMC will review the interim analysis results for both cohorts. The sentence regarding the safety review by the IDMC after the first 60 subjects in each cohort was moved from Section 11.8 to Section 11.9, and this sentence was expanded to add the safety reviews every 6 months thereafter.
Rationale: Clarified the liver enzyme (combined with alkaline phosphatase) inclusion criterion for Cohort 1 subjects at sites choosing docetaxel chemotherapy.	
4.1, Inclusion Criteria	Inclusion criterion 8.3 (now 8.4), the bullet for above mentioned criterion is as follows: "(For subjects in Cohort 1 at sites choosing docetaxel chemotherapy, both the ALT and AST values must be ≤1.5×ULN concomitant with alkaline phosphatase of ≤2.5×ULN)".
Rationale: Live vaccines are not a prohibited medication for patients receiving erdafitinib. The timeframe for avoidance of live vaccines was revised (ie, more restrictive) for vinflunine, docetaxel, or pembrolizumab.	

Applicable Section(s)	Description of Change(s)
8.2, Prohibited Medications	The prohibition for receipt of a live vaccine 3 months after the last dose of erdafitinib was removed. The timeframe for avoidance of a live vaccine for vinflunine and docetaxel was revised as follows: "Live vaccines within 30 days prior to the first dose and while participating in the study, [the prior phrase was added] and for 3 months following the last dose of study therapy." Also, examples of live vaccines were added. The timeframe for avoidance of a live vaccine for pembrolizumab was revised as follows: "Live vaccines within 30 days prior to the first dose and while participating in the study [this last phrase was added] and for 3 months following the last dose of study therapy." The examples of live vaccines previously in this location were deleted as they already appear in the above text for vinflunine and docetaxel.
Rationale: Clarified the start of the molecular eligibility assessment period when a biopsy is required. In addition, added that the sponsor must confirm eligibility based on local testing prior to entering full-study screening. Also, clarified in this section that the Sponsor must confirm eligibility based on local testing prior to entering full study screening.	
9.1.2, Screening Phase	Noted that the molecular eligibility assessment period begins with either the Molecular Eligibility Testing Informed Consent Form (ICF) or, if a biopsy is required, the Full-Study ICF. By Number (2) for the local report, added that the Sponsor must confirm eligibility based on local testing prior to entering full study screening.
Rationale: Added clarification that subjects on erdafitinib should follow the same visit schedule even when the drug is interrupted.	
9.1.3, Treatment Phase	In Section 9.1.3, the above clarification was added to the end of the first paragraph.
Rationale: Instruction for precaution with concomitant medications was updated, ie, the combination of erdafitinib with moderate CYP2C9 or strong CYP3A inducers should be avoided.	
8.3, Precautions for Concomitant Medications; Attachment 5	The above instruction was added to Section 8.3, along with additional information regarding erdafitinib and moderate CYP2C9 and strong CYP3A inducers. In Attachment 5, provided correction to the "Strong CYP3A4 Inhibitor" table, ie, Strong Inhibitors: ≥5-fold increase in AUC or ≥80 % (previously >80%) decrease in clearance.
Rationale: The prescribing information for pembrolizumab provides the most current information regarding dose modification.	
6.3.1, Pembrolizumab Dose Modifications	The reader is referred to the prescribing information for pembrolizumab and detailed instruction for dose modification was removed.
Rationale: Clarified the definition of superficial cancer in Inclusion Criterion 5	
4.1, Inclusion Criteria	Superficial cancer was clarified by adding additional description, ie, "(early disease/non-muscle invasive bladder cancer)" to Inclusion Criterion 5 (now 5.3). The criterion was also edited for further clarity.
Rationale: Update guidelines for management of paronychia.	

Applicable Section(s)	Description of Change(s)
6.1.2.5, Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia) Table 9	In accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, Grade 4 was removed from Table 9.
Rationale: Aligned wording in several sections with text common to oncology protocols.	
12.1.3, Severity Criteria; 12.3.2, Serious Adverse Events; 12.3.4, Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	In Section 12.1.3, the definitions of Grades 1 to 5 were added (the mild, moderate, and severe definitions were removed). Also, in Section 12.1.3, the NCI-CTCAE Version was corrected to 4.03 (was 4.0). The description of disease-related events (ie, disease progression) was moved from Section 12.3.2 to a new stand-alone Section 12.3.4, and the text aligned with wording for oncology protocols.
Rationale: Time Until Symptom Deterioration (subset of the FACT-B1) Patient Reported Outcome (PRO) assessment was added to more closely evaluate urinary symptoms.	
2.1.2, Endpoints; 11.6, Medical Resource Utilization and Patient Reported Outcomes Analyses	In Section 2.1.2, change from baseline in Time Until Symptom Deterioration (subset of the FACT-B1) was added as a secondary endpoint. In Section 11.6, the hypothesis was changed to "time to urinary symptom deterioration" (previously "meaningful symptom deterioration") will be delayed as measured by relevant items in the FACT-Bl.
Rationale: The description of some of the laboratory tests has been revised to reflect the Time and Events Schedule.	
9.1.1, Overview; 9.7.2, Clinical Laboratory Tests	In Section 9.7.2, the text was revised to reflect serum phosphate, calcium (or, if applicable, corrected calcium in the case of hypoalbuminemia), albumin, and serum parathyroid hormone testing per the Time and Events Schedule and to note that these tests are done for all subjects at screening, but only done for subjects in Arms 1A and 2A after screening. Also, these specific laboratory tests (ie, albumin, correct calcium, serum calcium, parathyroid hormone, phosphate) were removed from the list under "Serum Chemistry Panel". Updated the blood volume in Section 9.1.1.
Rationale: To provide more options for obtaining consent for molecular eligibility.	
Time and Event Schedule (footnote); Section 9.1.2, Screening Phase; 16.2.3, Informed Consent	Added that consent for molecular eligibility screening may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance. In Section 16.2.3, noted that informed consent for molecular eligibility may be obtained remotely.
Rationale: Clarified in the National Disaster attachment that usual study conduct resumes once the national situation allows and added guidance for consent during a national disaster.	

Applicable Section(s)	Description of Change(s)
Attachment 7, Guidance . . . During a National Disaster	Added text to the first paragraph to clarify that the measures in this appendix are temporary and that usual study conduct will resume once the national situation allows. The following text was added to clarify the consent process during a national disaster: Consenting of subjects for full study screening and for molecular eligibility screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent.
Rationale: To simplify sample collections during screening, it was clarified that serum phosphate, serum parathyroid hormone, and calcium and albumin collections, may be collected at Day -14 along with the hematology and chemistry panels. The collection window for all the clinical laboratory assessments was also provided. In addition, clarified when corrected calcium is required.	
Time and Events Schedule	For serum phosphate, serum parathyroid hormone, and calcium and albumin (under Chemistry) placed the "X" under the Day -14 column and removed from the Day -30 column (it is acknowledged that this is more restrictive, ie, these draws may no longer be collected between Day -30 to Day -14). The window for these assessments during the study was added to each row, ie, may be performed within 2 days prior to Day 1 and Day 14 of each cycle. The window for TSH and FT4 is within 2 days prior to Day 1. For the calcium [removed "corrected" prior to calcium] and albumin row, added a notation that corrected calcium is required for hypoalbuminemia.
Rationale: Clarified that no action on the part of the site is required for the "Tumor tissue for [programmed death-ligand 1] PD-(L)1 and biomarker testing" row on the Time and Event Schedule.	
Time and Events Schedule	For the "Tumor tissue for PD-(L)1 and biomarker testing" row that consists of 2 sub rows, the first row was deleted that pertained to collection at screening until 80 samples have been obtained from FGFR aberration negative subjects as this has already occurred. In the second row, the original text was replaced with text regarding no additional sample is required as PD-(L)1 and biomarker testing is assessed from the tumor tissue (archival or fresh biopsy) collected at prescreening. The "X" for this row remains unchanged but the text in parentheses regarding the fresh biopsy was deleted.
Rationale: In the Ethical Aspects section of the protocol, clarified which cohort required prior anti-PD-(L)1 agent use.	
16.1, Study-specific Design Considerations	In Section 16.1, clarified that Cohort 1 enrolls subjects with prior anti-PD-(L)1 agent use, and that Cohort 2 enrolls subjects without prior anti-PD-(L)1 agent use.
Rationale: Clarified the timing of disease assessments especially in relation to treatment interruptions.	
9.2, Efficacy Evaluations	Clarified the timing of disease assessments by noting that the date of randomization is the reference point regardless of interruptions to treatment.
Rationale: Clarified that the threshold for progressive disease	
9.2.2. Continuation of Treatment After Disease Progression	([added "eg"] eg, ≥20% increase in tumor burden compared to the nadir [previous baseline])
Rationale: For the timing of radiological assessments, clarified that the starting point is the date of randomization.	
Time and Event Schedule	Added that radiological assessments (every 6 weeks, etc.) are calculated from the date of randomization.

Applicable Section(s)	Description of Change(s)
Rationale: A minor correction was made to the guidelines for the management of elevated phosphate levels (Grade 3) and a clarification was made to the guidelines for the management of elevated phosphate levels (Grades 2 and 3).	
Table 4	For Grades 2 and 3 elevated phosphate levels (Symptom Management), expanded to include phosphate binders in general and added a notation regarding the information in the table footnotes regarding phosphate binders other than sevelamer. In addition, a small correction was added to the Grade 3 "Symptom Management" column that now reads " . . . until the serum phosphate level is [previously "returns to"] <7.00 mg/dL."
Rationale: Minor clarifications and corrections were made.	
Throughout the protocol; Synopsis (Hypotheses); Time and Events Schedule; 1.4.2, Erdafitinib; 2.1.1, Objectives; 2.1.2, Endpoints; 2.2, Hypothesis; 11.3.1, Primary Endpoint	The wording regarding prior treatments was clarified by adding "on or", ie, "must have progressed on or after 1 or 2 prior line(s)" for Cohort 1 throughout the protocol, except in the Objective section. Clarified the wording regarding randomization with the following change: Randomization to treatment will be within each ["within each" added and "by" removed] cohort. Section numbers were corrected throughout the protocol. In the Synopsis (under "Hypotheses") and Section 2.2, added "prior" to the hypotheses that now reads "following 1 or 2 prior line(s) of systemic therapy". In the Time and Event Schedule, the row related to FGFR testing was renamed "Local historical ["historical" added] FGFR test results for molecular eligibility. In Section 1.4.2, removed the reference citation for the Erdafitinib Investigator's Brochure (IB) and mention of addenda, which leaves the reader to refer to the most current version of the IB that includes addenda. In Sections 2.1.1 and 2.1.2, the objective and endpoint, respectively, related to actigraphy were removed. Actigraphy was removed with Amendment 4. In Section 11.3.1, "strata" added to clarify "pre-specified strata combining" to be implemented when there are too few OS events. The reference format was updated to the parenthetical style throughout.

Amendment 4 (29 Mar 2020)

The overall reason for the amendment: To allow subjects to meet appropriate molecular eligibility for the study by local historical test results for selected FGFR aberrations; ie, subjects can meet molecular eligibility criteria as determined by central laboratory screening as previously specified, or by local historical test results.

The rationale for and description of changes made during this protocol amendment are provided below. When changes are provided verbatim, deleted text is shown as strikethrough, and added text is shown as bold font.

Applicable Section(s)	Description of Change(s)
Rationale: To expedite enrollment, changes to Molecular Screening were implemented to determine a subject's eligibility by local historical test results for selected FGFR aberrations, not only by central laboratory testing, as required previously.	
Synopsis, Overview of Study Design; Time and Event Schedule; 3.1, Overview of Study Design, including Figure 1; 4, Subject Population; 4.1, Inclusion Criteria, Criterion 6; 9.1.2, Screening Phase	Specified that a subject's eligibility can also be determined by local historical test results for selected FGFR aberrations (ie, molecular eligibility can be confirmed using either central or local historical FGFR test results), and that if a subject is enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation of FGFR status, diagnostic development, and biomarker research. Details of acceptable testing methods and tissues suitable for FGFR testing were added. Details and rules for central testing and local historical testing were added.
Rationale: To clarify text for prior anti-PD-(L)1 treatment for Cohort 1, and to update text for Cohort 2.	
4.1, Inclusion Criteria, Criterion 5	Specified that, for Cohort 1, prior treatment with an anti-PD-(L)1 agent can be given as neo-adjuvant, adjuvant, or in metastatic line of treatment as frontline or maintenance therapy, and added details of the possible combinations. Text was revised as shown below for Cohort 2. Subjects who received neoadjuvant or adjuvant chemotherapy **or immunotherapy** and showed disease progression within 12 months of the last dose are considered to have received systemic therapy in the metastatic setting.
Rationale: To clarify that the criteria specified for Cohort 1 applies specifically to sites using docetaxel.	
4.2.2, Exclusion Criteria for Cohort 1 Subjects	Criterion 14 was amended to specify that it was applicable to participating sites using docetaxel.

Applicable Section(s)	Description of Change(s)
Rationale: To allow albumin to be used for calculating corrected calcium levels, and to allow evaluation of the relationship between calcium, phosphate, and parathyroid hormone, sampling timing for these analytes have been aligned.	
Time and Events Schedule, Clinical Laboratory Assessments; 9.8.2 (previous)/9.7.2 (current), Clinical Laboratory Tests	Additional timepoints for assessment of serum phosphate were added to the Time and Events Schedule, and parathyroid hormone was moved to a separate row. The timepoints for laboratory assessment of parathyroid hormone was revised. Laboratory assessments for corrected calcium and albumin were added to the Time and Events Schedule. The Serum Chemistry Panel was revised to add parathyroid hormone, albumin, and serum calcium; calcium was revised to corrected calcium. Specified that bicarbonate testing is only applicable if the test is locally available.
Rationale: To ensure consistency between the protocol and case report form (CRF) guidelines, harmonize rounding of phosphate values.	
6.1, Erdafitinib, Up-titration Guidelines; 6.1.2.1, Grading of Hyperphosphatemia, Table 3; 6.1.2.2, Guidelines for the Management of Elevated Phosphate Levels, Table 4	The values for grading of hyperphosphatemia have been revised throughout the protocol to include 2 decimals, for consistency with the CRF, and instructions for rounding the second decimal point were deleted. Toxicity grades (0 to 4) were added to Table 4.
Rationale: To delete sections describing actigraphy and its analysis, as enrollment in this exploratory substudy has been low, and the small sample size precludes meaningful analysis.	
Time and Events Schedule, Actigraphy sub-study; 9.6, Actigraphy (Selected Sites) (deleted); 9.6.1, Actigraphy-derived Endpoints and Analyses (deleted); 11.1, Subject Information; 11.7, Actigraphy Endpoints (deleted); 15, Study-Specific Materials	Information related to collecting and analyzing actigraphy was deleted.
Rationale: To improve adherence to and consistency in management of adverse events, as oral mucositis and nail toxicity were commonly observed adverse events in the study so far, and for consistency with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines.	
6.1.2.1, Grading of Hyperphosphatemia	Adverse events related to nails was deleted from Table 3 and from introductory text to Table 3.
6.1.2.3, Guidelines for the Management of Dry Mouth and Mucositis; Table 6, Guidelines for the Management of Oral Mucositis	Updated guidelines for general prophylaxis, as well as for management of oral mucositis were provided.
6.1.2.5, Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia), Table 8 and Table 9	Updated guidelines for management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) were provided in Table 8. Definitions of toxicity grade were deleted from Table 9.

Applicable Section(s)	Description of Change(s)
Rationale: To provide the latest available information on cytochrome P450 (CYP) inhibitors and inducers.	
8.2, Prohibited Medications; 8.3, Precautions for Concomitant Medications; Attachment 5, Drugs Classified as Strong or Moderate in Vivo Inhibitors and Inducers of CYP3A4/2C9 Enzymes	Updated information on CYP inhibitors and inducers was provided to align with currently available information and to revise "strong CYP2C9 inhibitor" to "moderate CYP2C9 inhibitor".
Rationale: To clarify instructions related to radiographic image assessments.	
9.2.1.2, Radiographic Images Assessment	Text was revised as shown below. Computed tomography (CT) scans of the chest, abdomen, pelvis, and any other location where disease is present will be performed at Screening**, and at each subsequent disease assessment visit**. ~~During the study, disease response will be assessed using CT scans of the 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 baseline 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.
Rationale: To add instructions to be followed during a national disaster.	
Time and Events Schedule, Footnote a (new); Attachment 7, Guidance on Study Conduct for Enrolled Subjects During a National Disaster (new)	A footnote was added to the Time and Events Schedule to refer to Attachment 7 for guidance on study conduct for enrolled subjects during a national disaster, and detailed instructions have been provided in Attachment 7.
Rationale: To revise minor errors or inconsistencies that were noted.	
Title page and footer	Updated confidentiality information was added.
Time and Events Schedule, Tumor tissue	Text was revised as shown below. Tumor tissue for **central** molecular screening
Time and Events Schedule, Radiological assessments	Text was revised as shown below. Every 6 weeks **(±7 days)** for 6 months, then every 12 weeks for the next 6 months (±7 days), then as clinically indicated.
Time and Events Schedule	A row for protein binding blood sample was added, for consistency with information provided in Section 9.3.
1.5, Overall Rationale for the Study	Text was revised as shown below. Despite the recent improvement in outcomes provided by compounds targeting the PD-1/PD-L1 pathway, all current treatment options still have relatively limited clinical activity as second-line therapy; and ~~there is~~ **at the time of initial protocol development,** no targeted therapy **was** approved for treating specific subsets of urothelial cancer subjects with FGFR alterations.

Applicable Section(s)	Description of Change(s)
4.1, Inclusion Criteria, Criterion 8c	Text was revised as shown below. Renal function: Creatinine clearance (CrCl) >30 mL/min/~~1.73 m^2~~ either directly measured via 24-hour urine collection or calculated using the Cockcroft-Gault formula (Attachment 2).
6.1.1, Dose Modifications and Dose Delays for Erdafitinib, Table 1	The title of Table 4 was revised as shown below. Erdafitinib Dose Modification Rules Based on **Erdafitinib-related** Toxicity
6.1.2.6, Guidelines for Eye Toxicity Associated With Vision Changes	Text was revised as shown below. If a subject experiences an event of confirmed new corneal or retinal abnormality while on study drug, the event should be reported as an adverse event ~~of special interest (if Grade 1 or 2)~~ or a serious adverse event (if Grade 3 or higher) as appropriate.
9.1.1, Overview	Text was revised as shown below. The number of samples and the blood volume will vary depending on the number of cycles of the study drug that the subject receives. The total maximum amount of blood to be drawn from each subject is estimated to be ~~27~~ **22** mL at screening, 266 mL over the course of the first 6 months (8 cycles) of treatment, 22 mL for every cycle thereafter, and 40 mL at the End-of-Treatment.
9.4, Predictive and Pharmacodynamic Biomarkers, Tissue for Immune Biomarkers and Molecular Subtyping); 9.4, Predictive and Pharmacodynamic Biomarkers, Circulating Biomarkers, Peripheral Immune Cell Profiling	Each of these sections, respectively, was revised as shown below. **At the time of protocol development,** it ~~is~~ **was** estimated that approximately 80 samples are needed to inform PD-L1 expression and bladder cancer subtype in FGFR aberration-negative subjects (see Section 11.5). T cell and Treg enumeration and T cell activation status will be assessed **at certain sites**.
9.5, Patient Reported Outcomes	Text was revised as shown below. Patients health-related quality of life, symptoms, functioning, and general well-being will be captured using 3 PRO measures: the FACT-Bl, PGIS, and the EQ-5D-5L. The PRO measures will be **collected** electronically**, if feasible** ~~(ePRO) collected~~, according to the Time and Events Schedule, to understand change over time and difference between treatment groups in each cohort.
9.8.5 (previous)/9.7.5 (current), Electrocardiogram	Text was revised as shown below. Triplicate ECGs should be performed with 5- **to 10-**minute intervals between each assessment.
9.8.6 (previous)/9.7.6 (current), Ophthalmologic Examination	Text was revised as shown below. All images of the OCT scan**s for enrolled subjects** must be stored in the subject's records and a redacted copy sent to the sponsor-selected central vendor for possible future independent assessment.
9.8.7 (previous)/9.7.7 (current), Vital Signs	Text was revised as shown below. Blood pressure (systolic and diastolic), heart rate, and ~~oral or tympanic~~ temperature will be assessed. Abnormalities will be recorded as AEs.

Applicable Section(s)	Description of Change(s)
16.1, Study-Specific Design Considerations	Text was revised as shown below. This is a Phase 3, multicenter, open-label randomized study to evaluate the efficacy and safety of erdafitinib, an oral pan-FGFR-inhibitor with pharmacodynamic adaptation of dose (starting dose of 8 mg once daily with potential up-titration to 9 mg once daily based on observed phosphate level on Study Day 14) compared to vinflunine, docetaxel or pembrolizumab in subjects with metastatic or surgically unresectable urothelial cancer with select FGFR genetic alterations who progressed on or after ~~one prior line of systemic therapy~~ **1 or 2 prior treatments (Cohort 1) or 1 prior treatment (Cohort 2)**.
Throughout the protocol	Minor errors and inconsistencies were revised, and grammatical, formatting, or spelling changes were made. Abbreviations and references were updated as needed.

Amendment 3 (18 January 2019)

The overall reason for the amendment: To address request from regulatory authorities and to expand the population eligible for cohort 1, in line with current standard of care.

Applicable Section(s)	Description of Change(s)
Rationale: To comply with health/regulatory authority requests.	
Synopsis; Time and Events Schedule; 2.1.1, Objectives; 2.1.2, Endpoints; 9.4 Predictive and Pharmacodynamic Biomarkers; 11.4, Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses	For subjects on erdafitinib (Arms 1A and 2A), added blood sample collection at Cycle 1 Day 14 (or later time point) for CYP2C9 genotyping and to allow exploration of the effect of CYP2C9 polymorphism on the pharmacokinetics (PK) of erdafitinib.
4.2, Exclusion Criteria, Criterion 6.1	Exclusion criterion 6.1 was modified based on health authority recommendation to remove baseline ocular conditions from exclusion criteria. The rationale pertains to 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 studies and evidence from the available literature.
6.1.2.6, Guidelines for Eye Toxicity Associated With Vision Changes (Table 10)	The following text was added under study drug management in Grade 1 to 3 of eye toxicity: **Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution.**

Applicable Section(s)	Description of Change(s)
Time and Events Schedule; 9.8.6, Ophthalmologic Examination	Tonometry was removed as an examination performed at screening, while slit lamp biomicroscopy was added, expanding on the scope of eye examination to be performed. The rationale pertains to a lack of value of tonometry in assessing the ocular toxicities associated with erdafitinib. Additionally, the wording "where available" was removed regarding Optical Coherence Tomography (OCT), making OCT a comprehensive part of the ophthalmological examination. Wording was added that a follow-up ophthalmologic examination may be performed at regular intervals as deemed necessary by the screening ophthalmologist. For consistency, a note at the screening time point for the ophthalmologic exam was added to read as such: **After 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.**
8.3, Precautions for Concomitant Medications	Added wording that the list of CYP3A4/2C9 inducers provided in Attachment 5 and in http://medicine.iupui.edu/CLINPHARM/ddis/main-table may not be exhaustive and up-to-date at any given time. The product information of ongoing and new concomitant medications should be consulted for the most accurate information on potential strong inducers of CYP3A4 and CYP2C9.
4.1, Inclusion Criteria, Criterion 9.1 and Criterion 11.2; 16.2.3, Informed Consent	Inclusion criterion 9.1 and informed consent section was modified to clarify that when signing the informed consent form, the subject understands the nature, significance, purpose of, procedures for, and consequences of the study and is willing to participate in the study. Inclusion criterion 11.2 was modified to add a definition for women of childbearing potential: **Fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.**
6.1.1, Dose Modifications and Dose Delays for Erdafitinib, Table 1	Added wording to specify the action for Grade 2 toxicities: **None, or consider interruption if the toxicity is considered clinically significant.** Revised the wording for Grade 2 toxicities for dose modification after resolution of AE: **If interrupted, restart at the same dose if toxicity is completely resolved to baseline or consider restarting at 1 dose lower if not completely resolved to baseline (but resolved to Grade 1).** Revised the wording for Grade 3 toxicities for dose modification after resolution of AE: **Restart at 1 dose lower if recovered to baseline (to Grade ≤1 or back to baseline for non-hematologic toxicity) within 28 days; restart at 2 doses lower if not completely resolved to baseline (but resolved to Grade 1) within 28 days.**
6.1.2.7, Guidelines for the Management of Dry Eye	Ocular demulcents were added as prophylactic management of dry eye. Ocular demulcents replaced hydrating/lubricating eye gels and ointments as reactive management of dry eye.

Applicable Section(s)	Description of Change(s)
10.2, Discontinuation of Study Treatment/Withdrawal From the Study	Revised the wording for discontinuation of study treatment by the investigator to read as: • The investigator believes that for safety reasons, tolerability reasons, or impairment of the subject's well-being (eg, due to AEs such as those described in Section 6) it is in the best interest of the subject to discontinue study treatment. Added the following wording for discontinuation of study treatment by the investigator: • The subject experiences an AE that, as described in Section 6, should result in discontinuation of study drug.
Rationale: To remove time restrictions in subjects who undergo a new biopsy for fibroblast growth factor receptor (FGFR) testing.	
Time and Events Schedule; 4, Subject Population	Text updated to specify that, for subjects undergoing a new tissue biopsy for molecular screening, the 30-day window will start with the first planned study-related procedure other than the tissue biopsy.
Rationale: To expand the subject population eligible for cohort 1 and to align with current standard of care following Food and Drug Administration (FDA) and European Medicines Agency (EMA) label restrictions of the patient population eligible for treatment with anti-PD-(L)1 at frontline to those with high PD-L1 status and common practice to administer a platinum-based treatment as standard of care as a second line treatment in this patient population.	
Synopsis; 2.1.1, Objectives; 2.2, Hypothesis; 3.1, Overview of Study Design; 4.1, Inclusion Criteria, Criterion 5.1	Revised inclusion criteria 5.1 to redefine subject population eligible for cohort 1 and cohort 2 to read as such: **Cohort 1: Prior treatment with an anti-PD-(L)1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment.** **Cohort 2: No prior treatment with an anti-PD-(L)1 agent; only 1 line of prior systemic treatment.** **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 therapy in the metastatic setting.** The study design and objectives were updated to indicate that efficacy of erdafitinib versus chemotherapy or pembrolizumab in subjects with advanced urothelial cancer harboring selected FGFR aberrations who have progressed 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 an anti-PD-(L)1 agent (cohort 2).
1.3, Immunotherapy	Added text about pembrolizumab and atezolizumab as FDA and EMA-approved medications for use in previously untreated subjects ineligible for cisplatin-containing chemotherapy, adding that the indication in this setting has been restricted to patients with high PD-L1 status and considerations regarding the standard of care for patients who receive a checkpoint inhibitor as frontline treatment.

Applicable Section(s)	Description of Change(s)
Rationale: To allow subjects with liver metastases and AST/ALT ≤5x institutional ULN to be included in the study.	
4.1, Inclusion Criteria, Criterion 8.2	Revised inclusion criterion 8.2 to allow subjects with liver metastases that have alanine aminotransferase and aspartate aminotransferase that are ≤5x the institutional upper limit of normal.
Rationale: To remove unnecessarily restrictive electrolyte result as inclusion criterion; no requirements for normal potassium are present in the comparators' labels and in the use of erdafitinib.	
4.1, Inclusion Criteria, Criterion 8.2	Revised inclusion criterion 8.2 to remove requirement to have potassium levels (electrolyte) within institutional normal limits.
Rationale: To allow subjects with low risk of progression from concurrent prostate cancer to enter the study.	
4.2, Exclusion Criteria, Criterion 2.2	Revised exclusion criterion 2.2 to allow subjects with localized prostate cancer with a Gleason score of 3+4 that have been treated more than **6 months** prior to the full study screening and are considered to **have a very low risk of recurrence.**
Rationale: To remove grade definition for neuropathy and hearing loss and remove diabetes as an exclusion criterion, as these are not contraindications to erdafitinib or comparator agents.	
4.2, Exclusion Criteria, Criterion 10.1	Revised exclusion criterion 10.1 to remove grade definitions for neuropathy, and hearing loss.
4.2, Exclusion Criteria, Criterion 13.2	Revised exclusion criterion 13.2 to remove poorly controlled diabetes (hemoglobin A1c >8) as an example of a condition that could prevent, limit, or cofound the protocol-specified assessments; instead, uncontrolled ongoing medical conditions was added.
Rationale: To remove medications known to increase serum levels of phosphate (add as precautionary medications) and medications known to increase the level of calcium as prohibited medications (no significant effect of calcium metabolism is observed with erdafitinib).	
8.2, Prohibited Medications; 8.3, Precautions for Concomitant Medications	Medications known to increase serum levels of calcium were removed as prohibited medications for subjects in Arms 1A and 2A for erdafitinib. Medications known to increase serum levels of phosphate were removed as prohibited medications and added to the section with precautions for concomitantly administered medications.
Rationale: To update blood volumes collected at each phase of the study.	
9.1.1, Overview	The blood volume to be collected at screening was revised to 27 mL, the blood volume to be collected over the course of the first 6 months was updated to 266 mL, and the blood volume to be collected for every cycle thereafter was updated to 22 mL.
Rationale: To allow subjects previously screened in the context of another study to by-pass the molecular screening phase of this study.	
9.1.2, Screening Phase	The following text was added: **Subjects may by-pass the molecular screening phase of BLC3001 if they have already been molecularly screened by the central laboratory in the context of another Janssen-sponsored study.**

Applicable Section(s)	Description of Change(s)
Rationale: To allow subject re-screening.	
9.1.2, Screening Phase	The following text was added: **Subjects will be allowed to be re-screened only once for eligibility (both molecular and full study eligibility) if the investigator has a valid reason (eg, true resolution of conditions previously meeting the exclusion criteria, availability of a different tumor tissue for FGFR testing, molecular internal quality control failure) to re-screen and after consultation with the medical monitor.**
Rationale: To clarify the requirement for monitoring of liver toxicity.	
9.8.2, Clinical Laboratory Tests	Added alkaline phosphatase test to the serum chemistry panel as it is required for subjects on docetaxel and helpful in all subjects to evaluate liver toxicity.
Rationale: Minor errors/prior omissions, editorial issues, or changes for clarity/consistency were noted and corrected.	
Time and Events Schedule; 9.8.2, Clinical Laboratory Tests	Clarified that serum phosphate and parathyroid hormone will be assessed for all subjects at screening, and at all other time points for Arms 1A and 2A only. Clarified that thyroid stimulating hormone (TSH) and free thyroxine 4 (FT4) will be assessed for all subjects at screening, and at all other time points, beginning at Cycle 2, for Arm 2B only.
Time and Events Schedule	Clarified that the urine or serum β-hCG pregnancy test will be assessed on Day 1 of every cycle from Cycle 2 during the treatment phase.
4.2, Exclusion Criteria, Criterion 9.1	Revised exclusion criterion 9.1 to exclude active infection with hepatitis B or C (within the past 6 months). Wording was updated to read as such: **Known active hepatitis B or C infection (unless polymerase chain reaction [(PCR]-negative [according to local laboratory range] on all available tests for the past 6 months)**
4.2, Exclusion Criteria, Criterion 14.2	Revised exclusion criterion 14.2 to clarify the most common cross-hypersensitivities to docetaxel as polysorbate and paclitaxel.
6.1, Erdafitinib	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**.
6.1, Erdafitinib	Added mmol/L values in brackets next to their corresponding serum phosphate concentrations (represented in mg/mL) and included rounding instructions.
6.1.2.1, Grading of Hyperphosphatemia and Nail Disorders (Table 3)	Added a ≥ symbol before the 2.9-3.2 mmol/L concentration under the Grade 3 column.
6.1.2.6, Guidelines for Eye Toxicity Associated With Vision Changes (Table 10)	For study management of Grade 2 toxicity, the following text was added: **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.**
9.1.2, Screening Phase	Added text that archival tumor tissue or a fresh biopsy sample will be sent to the central laboratory to be analyzed with an investigational device.
9.4, Predictive and Pharmacodynamic Biomarkers	Text has been updated to indicate that paired biopsies will be collected at disease progression, not end of treatment.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule; 9.6, Actigraphy (Selected Sites)	The text that subjects will be allocated in a 1:1 randomization was removed. Text was revised that a target of a total of approximately 200 subjects will be recruited (100 subjects in each cohort). Text regarding the Philips Actiwatch Spectrum actigraphy device was revised to indicate that it will be worn for 1 to 2 weeks within the screening period.
9.8.2, Clinical Laboratory Tests	Clarified that serum phosphate, parathyroid hormone, TSH, and FT4 will be tested for all subjects at screening.
9.8.5, Electrocardiogram	Text added that at least 1 printout of all 3 ECGs should be produced and stored in the subject's source documents.
9.8.6, Ophthalmologic Examination	Clarified that the Amsler grid test will be administered by the treating physician or nurse. Added that OCT should be performed when fundoscopic retinal abnormalities are observed, as well as each time ocular adverse events lead to a subject being referred to an ophthalmologist. The text recommending that color fundus photos or OCT images be obtained and stored in the subject's records for future reference was removed and replaced with the following: **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.**
9.8.8, Physical Examination	Clarified that subjects should have a repeated physical examination at Cycle 1 Day 1 prior to dosing if the previous one during screening occurred more than 7 days before first dosing.
9.8.9, ECOG Performance Status	Added that subjects should have a repeated ECOG assessment at Cycle 1 Day 1 prior to dosing if the previous one during screening occurred more than 7 days before first dosing.
11.4, Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses	The following text was removed: Relationships between plasma concentrations or metrics of systemic exposure and markers of pharmacological activities, efficacy or treatment-emergent adverse events could also be explored as data allow using population approaches (eg, non-linear mixed effects approaches).
12.3.3, Pregnancy	Text was updated that follow-up information regarding the outcome of pregnancy and any postnatal sequalae in the infant will be requested, not required.
Attachment 6: Anticipated Events	Hydronephrosis and oliguria were added to the list of anticipated events.
Throughout the protocol	Anti-PD(L)1 was revised to read as anti-PD-(L)1. Minor editorial, grammatical, spelling, or formatting changes were made.

Amendment 2 (1 May 2018)

The overall reason for the amendment: The overall reason for the amendment is to address feedback from health authorities.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the timing of pregnancy test at screening and the frequency of pregnancy tests during treatment until the end of systemic exposure.	
Time and Events Schedule and 9.7.4, Urine or Serum Beta-hCG Pregnancy Test	The protocol was revised to indicate that pregnancy test takes place 7 (not 14) days or fewer before first dose administration. Pregnancy testing specified to take place at the start of every 3-week cycle.
Rationale: Clarify the requirements for contraception in male subjects who are sexually active with women of childbearing potential.	
4.1, Inclusion Criteria, Criterion 11.1	Revised inclusion criterion 11.1 for men who are sexually active with women of childbearing potential: agrees to use a ~~barrier method of contraception (eg, c~~ondom with spermicidal foam/gel/film/cream/suppository~~)~~"
Rationale: To update wording to align with "Clinical Trial Facilitation Group" document for clarification of effective contraception.	
4.1, Inclusion Criteria, Criterion 11.1	Added the following wording to sexual abstinence "true abstinence when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.)"
Rationale: To manage the risk of hypothyroidism associated with pembrolizumab.	
Time and Events Schedule and 9.8.2, Clinical Laboratory Tests	The protocol was revised to indicate that thyroid stimulating hormone and free thyroxine 4 are tested at screening and then every other cycle during the study for Arm 2B only.
Rationale: To align with contraindications associated with vinflunine.	
4.1, Inclusion Criteria, Criterion 8.1	Revised inclusion criterion 8.1 to indicate that the allowed platelet count for subjects in Cohort 1 at sites choosing vinflunine chemotherapy is ≥100,000/mm^3.
Rationale: Current wording indicates that subjects with Gilbert's disease and any level of liver dysfunction are eligible.	
4.1, Inclusion Criteria, Criterion 8.1	Revised inclusion criterion 8.1 to clarify acceptable levels of bilirubin: ≤1.5xULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN.
Rationale: To cover infection risk associated with docetaxel/vinflunine.	
4.2.1, Exclusion Criteria for All Subjects, Criterion 13.1	Amended exclusion criterion 13.1 to "ongoing active infection requiring systemic therapy."
Rationale: To manage pulmonary toxicities associated with docetaxel.	
4.2.2, Exclusion Criteria for Cohort 1 Subjects, Criterion 14.1	Added wording to indicate that for sites using docetaxel, subjects with evidence of interstitial lung disease or active non-infectious pneumonitis are excluded.

Applicable Section(s)	Description of Change(s)
Rationale: To manage risk of cystoid macular edema associated with docetaxel.	
6.2.2, Docetaxel	Added the following wording for docetaxel as it relates to ocular toxicity: Cystoid macular edema has been reported in subjects treated with docetaxel. Subjects with impaired vision should undergo a prompt and complete ophthalmologic examination. In case cystoid macular edema is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.
Rationale: Recommendation from "Infectious Diseases Society of America Clinical Practice Guideline for Vaccination of the Immunocompromised Host, Clinical Infectious Diseases."	
8.2, Prohibited Medications	Added wording to indicate that live vaccines must be avoided for 3 months following the last dose of study therapy.
Rationale: To align with vinflunine Summary of Product Characteristics.	
8.2, Prohibited Medications	Added wording that strong inducers of CYP3A4 should be avoided for subjects receiving vinflunine.
Rationale: To manage risk of neurological toxicities associated with docetaxel and vinflunine.	
Time and Events Schedule and 9.8.8, Physical Examination	Indicated that a neurological examination is part of the physical examination.
Rationale: To align with results from clinical drug-drug interaction study.	
8.3, Precautions for Concomitant Medications	Amended to include updated precautions for concomitant medications.
Attachment 5, Drugs Classified as Moderate to Strong Inducers of CYP3A4/2C9 Enzymes	Deleted tables containing strong inhibitors for CYP3A4/2C9 enzymes
Rationale: To address feedback from health authorities and to align with the requirements of the prescribing information.	
4.1, Inclusion Criteria, Criterion 11.1	Revised the language for duration of breastfeeding restriction and for planning to become pregnant, to clarify that it extends for the same duration of contraception (during the study and for at least 6 months).
6.2.2.1, Docetaxel Dose Modifications, Table 12	Correction of typos in Table 12, Docetaxel Dose Modifications for Drug-related Adverse Events, Criteria for neutropenic fever and Neutropenia Grade 4 lasting more than 7 days: ("platelet" mention corrected to "neutrophils"). Treatment discontinuation option added to the second occurrence of neutropenic fever).
6.3, Pembrolizumab	Wording to clarify evaluation and management of immune-related adverse reactions was added.
6.3.1, Pembrolizumab Dose Modifications, Table 13	Footnote added: pembrolizumab should be permanently discontinued for recurrent Grade 3 adverse reactions. Added a statement to reference prescribing information in the case of dose modifications related to immune-related adverse reactions.

Applicable Section(s)	Description of Change(s)
Rationale: To address feedback from health authorities.	
Time and Events Schedule	Added collection of smoking history at screening.
Time and Events Schedule and 9.8.2, Clinical Laboratory Tests	Added serum sodium, chloride, bicarbonate, and magnesium to the chemistry labs scheduled during Cycle 1 Day 1 (baseline), Cycle 2 Day 1, and Cycle 3 Day 1 of the study.
6.1.2.2, Guidelines for the Management of Elevated Phosphate Levels, Table 4	Added clarification to the approach for dose reduction for persistent hyperphosphatemia defined as serum phosphate ≥7 mg/dL for a period of 2 months or serum phosphate ≥9 mg/dL for a period of 1 month and provided an example for clinically necessary: in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances.
Overview of Study Design, Dosage and Administration, 3.1, Overview of Study Design, Figure 1: Schematic Overview of the Study, 6.3 Pembrolizumab Dose modifications, 9.1.3, Treatment Phase	Removed all occurrences of the statement: "Subjects in the pembrolizumab arm will discontinue treatment at the completion of 2 years of pembrolizumab therapy."
12.3.1, All Adverse Events	Added wording to clarify that Japan will not identify anticipated events for the health authorities.
Attachment 6, Anticipated Events	Added statement that some countries will not identify anticipated events.
12.3.2, Serious Adverse Events	Added wording to clarify that progression of disease should not be considered an adverse event.
17.9.2, Study Termination	Possible reasons for study termination added: "in case of unacceptable risk, intolerable toxicity, or change in the benefit/risk profile."
6.2.1 Vinflunine	A statement regarding conservation of sperm was added.
8.3, Precautions for Concomitant Medications	The following wording was added: "…such as digoxin, dabigatran, and fexofenadine (https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf); in addition, drugs with a narrow therapeutic index should only be used where the benefit outweighs the potential risk."
11.2, Sample Size Determination	Added a statement that the average number of projected subjects per site is 2.3.
11.4 Pharmacokinetic and Pharmacokinetic/ Pharmacodynamic Analyses	The following was added: "Relationships between plasma concentrations or metrics of systemic exposure and markers of pharmacological activities, efficacy or treatment-emergent adverse events may also be explored as data allow using population approaches. Results of the analyses will be provided in a separate report."
Rationale: To align with pregnant partner informed consent form and allow appropriate safety follow-up for babies born to subjects and partners of male subjects.	
12.3.3, Pregnancy	Added wording to allow for follow-up information to be collected up to 12 months after the birth of a baby if a congenital anomaly or significant medical conditions is diagnosed at birth.

Applicable Section(s)	Description of Change(s)
Rationale: To include information on an optional actigraphy sub-study.	
Time and Events Schedule, 2.1.1, Objectives, 2.1.2 Endpoints, 9.6 Actigraphy (Selected Sites), 9.6.1 Actigraphy-derived Endpoints and Analyses, 11.1 Subject Information, 11.7 Actigraphy Endpoints, 15 Study-Specific Materials	Added information about actigraphy sub-study as well as corresponding objectives, endpoints, study-specific materials, and evaluable population.
Rationale: To clarify exceptions for active malignancies.	
4.2.1 Exclusion Criteria for all Subjects, Criterion 2.1	Exceptions to the active malignancies exclusion criteria were added, which include urothelial cancer, skin cancer treated within the last 24 months that is considered completely cured, localized prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance, and localized prostate cancer with a Gleason score of 3+4 that has been treated more than 12 months prior to full study screening and considered completely cured.
Rationale: Clarification added to exclusion criterion 6.1.	
4.2.1 Exclusion Criteria for All Subjects, Criterion 6.1	The following exclusion wording was added: "or lens conditions, such as untreated mature or hypermature senile cataract, affecting visual acuity that impair the ability to interpret the Amsler grid test."
Rationale: To clarify inclusion of metastatic or surgically unresectable urothelial cancer.	
4.1 Inclusion Criteria, Criterion 3.1	Updated inclusion criterion 3.1 to "Metastatic or surgically unresectable urothelial cancer."
Rationale: Minor errors were noted.	
Throughout protocol	Minor grammatical and formatting changes were made.

Amendment 1 (26 October 2017)

The overall reason for the amendment: The overall reason for the amendment is to clarify collection timepoints for biomarker samples and correct numbering of exclusion criteria. Deleted text is shown in strikethrough and added text in bold.

Applicable Section(s)	Description of Change(s)
Rationale: Clarify collection timepoints for biomarker samples.	
Time and Events Schedule	For collection of tumor tissue for PD-L1 and biomarker testing, added **Submit 1 archival sample as soon as possible after enrollment. If submitting fresh biopsy, collect prior to dosing on C1D1.**
9.4, Predictive and Pharmacodynamic Biomarkers	Optional paired biopsies will be collected pre-treatment (any time during the full screening period prior to dosing on Cycle 1 Day 1), on-treatment (~~on or around Cycle 2 Day 1~~ **on or within 2 weeks after Cycle 2 Day 1**), and at end of treatment (disease progression).

Applicable Section(s)	Description of Change(s)
Rationale: Correct formatting error.	
4.2.2, Exclusion Criteria for Cohort 1 Subjects	Renumber exclusion criterion to 14
4.2.3, Exclusion Criteria for Cohort 2 Subjects	Renumber exclusion criterion to 15
Rationale: Clarify timing and outcome of erdafitinib up-titration.	
3.2.3, Dosing Schedule for Erdafitinib	In the first paragraph: Treatment will be up-titrated to 9 mg, ~~or~~ maintained at 8 mg, **or withheld**, based on phosphate level measured on Cycle 1 Day 14…
6.1, Erdafitinib	In Up-titration Guidelines, Cycle 2 and 3 were deleted: On Day 14 of Cycles 1, ~~2, and 3~~, a blood sample will be drawn to determine serum phosphate concentration…
Rationale: Minor errors were noted	
Throughout protocol	Minor grammatical and formatting changes were made.

SYNOPSIS

A Phase 3 Study of Erdafitinib Compared with Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations

Erdafitinib (JNJ-42756493) is a selective and potent pan fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor with demonstrated clinical activity in subjects with solid tumors identified to have alterations in the FGFR pathway, including urothelial carcinoma.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Primary Objective

The primary objective of this study is to evaluate efficacy of erdafitinib versus chemotherapy or pembrolizumab in subjects with advanced urothelial cancer harboring selected FGFR aberrations who have progressed after 1 or 2 prior treatments, at least 1 of which includes an anti-programmed death-ligand 1(PD-[L]1) agent (cohort 1) or 1 prior treatment not containing an anti-PD-(L)1 agent (cohort 2).

The primary endpoint of overall survival will be evaluated in 2 cohorts:

- Cohort 1: erdafitinib versus chemotherapy (docetaxel or vinflunine) [subjects who have received prior anti-PD-(L)1 agent]
- Cohort 2: erdafitinib versus pembrolizumab [subjects who have not received prior anti-PD-(L)1 agent]

Secondary Objectives

- To evaluate progression-free survival (PFS) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the objective response rate (ORR) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the health-related quality of life (HRQOL) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the duration of response (DOR) for subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To characterize the safety profile of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the population pharmacokinetics of erdafitinib

Exploratory Objectives

- To evaluate DNA, RNA, or protein biomarkers in tissue and blood samples which potentially predict tumor response or resistance to erdafitinib, chemotherapy, or pembrolizumab
- To assess the expression of immune markers (eg, PD-[L]1) and determine molecular subtype in tumor samples
- To evaluate changes in peripheral blood immune cell types, levels, and activation status in response to erdafitinib, chemotherapy, or pembrolizumab
- To assess changes in tumor immune cell infiltrate and gene expression related to bladder cancer subtype, in response to erdafitinib in paired tumor biopsies
- To evaluate the relationship between erdafitinib exposure and efficacy and safety endpoints

- To evaluate the relationship between CYP2C9 polymorphism and pharmacokinetics (PK) of erdafitinib

Hypotheses

Cohort 1 hypothesis: Erdafitinib treatment prolongs overall survival (OS) in subjects with advanced urothelial cancer harboring selected FGFR aberrations following 1 or 2 prior line(s) of systemic therapy, with at least 1 line containing anti-PD-(L)1, compared with the OS of those treated with chemotherapy (docetaxel or vinflunine).

Cohort 2 hypothesis: Erdafitinib treatment prolongs overall survival (OS) in subjects with advanced urothelial cancer harboring selected FGFR aberrations following 1 prior line of systemic chemotherapy without anti-PD-(L)1, compared with the OS of those treated with pembrolizumab.

OVERVIEW OF STUDY DESIGN

This is a randomized, open label, multicenter, global phase 3 study of erdafitinib versus standard of care, consisting of chemotherapy (docetaxel or vinflunine) or anti-PD-(L)1 agent pembrolizumab, in subjects with advanced urothelial cancer and selected FGFR aberrations who have progressed on or after 1 or 2 prior treatments (cohort 1) or 1 prior treatment (cohort 2). Subjects will be assigned to Cohort 1 or Cohort 2 based upon prior treatment with an anti-PD-(L)1 agent. In Cohort 1, subjects who have received prior anti-PD-(L)1 will be randomized to erdafitinib versus chemotherapy (approximately 280 subjects). In Cohort 2, subjects who have not received prior anti-PD-(L)1 will be randomized to erdafitinib versus pembrolizumab (approximately 350 subjects). Cohort 1 and Cohort 2 will be assessed independently.

For each cohort, a review of the safety data will be performed by an Independent Data Monitoring Committee (IDMC) after at least 60 subjects have been enrolled in that cohort and every 6 months afterwards. The IDMC will also review efficacy and safety data for the predefined interim analysis.

The Screening Phase will start with molecular screening, which will be performed by a central laboratory or by review of local historical test results submitted to the sponsor for molecular eligibility assessment. Full study screening will occur after the completion of prior treatment and documentation of disease progression for subjects who meet the molecular screening criteria. The Treatment Phase will extend from randomization until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment. The post-treatment Follow-up Phase will extend from the End-of-Treatment Visit until the subject has died, withdraws consent, is lost to follow-up, or study completion for the respective cohort), whichever comes first.

Study completion and end of study are distinct timepoints. Study completion occurs at the end-of-data-collection timepoint for both cohorts, which is defined as when the clinical cutoff for the final analysis has been achieved. End of study is the time the last subject receives the last dose of study drug on the study.

The LTE Phase begins with the approval of Amendment 6 and with achievement of the clinical cut-off for the final analysis for each cohort. Upon initiation of the LTE Phase, participation in the Follow-Up Phase will end and study data collection will conclude in the clinical database; and only serious adverse events will be reported to the Company safety repository.

SUBJECT POPULATION

Subjects will be adults with histologic demonstration of Stage IV transitional cell carcinoma of the urothelium and documentation of disease progression. Subjects will have received 1 or 2 prior line(s) of systemic treatment (cohort 1) and 1 prior line of systemic treatment (cohort 2) for metastatic urothelial cancer and meet appropriate molecular eligibility criteria. ECOG performance status must be 0, 1, or 2, and bone marrow, liver, and renal function must be within protocol-specified limits.

DOSAGE AND ADMINISTRATION

Erdafitinib will be provided as tablets for oral administration. Subjects randomized to erdafitinib will be instructed to take erdafitinib orally, at a starting dose of 8 mg, once daily for 21 days on a 21-day cycle until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment. Each dose should be taken at approximately the same time each day, with or without food. Dose adjustments will be made based on Cycle 1 Day 14 serum phosphate levels.

Subjects randomized to chemotherapy will receive vinflunine 320 mg/m^2 as a 20-minute intravenous infusion once every 3 weeks or docetaxel 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. Treatment with either agent will be administered until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment. The choice of which chemotherapy regimen to use at each site will be determined by the investigator. Subjects randomized to immunotherapy will receive pembrolizumab 200 mg as a 30-minute intravenous infusion once every 3 weeks, until disease progression, intolerable toxicity, withdrawal of consent, or decision by the investigator to discontinue treatment.

EVALUATIONS

Assessment of responses for solid tumors will be performed according to RECIST (version 1.1) by investigators. Venous blood samples will be collected for determination of plasma concentrations of erdafitinib and alpha-1-acid glycoproteins, total protein, and fraction unbound, if required, at the time points specified in the Time and Events Schedule, for all subjects randomized to erdafitinib arms (Arm 1A and Arm 2A). Tissue collected on study will be used to assess the immune marker status and identify the molecular subtype of patient tumors. Germline DNA will be collected for subjects on erdafitinib for CYP2C9 genotyping. Patients' health-related quality of life symptoms, functioning, and general well-being will be captured using 3 PRO measures: the FACT-Bl, PGIS, and the EQ-5D-5L. Safety assessments will be based on medical review of adverse event (AE) reports and the results of vital sign measurements, electrocardiograms, physical examinations, clinical laboratory tests, ECOG performance status, ophthalmologic examinations, and other safety evaluations at specified time points as described in the Time and Events Schedule.

STATISTICAL METHODS

The primary endpoint is OS. The primary efficacy analysis will be based on the intent-to-treat (ITT) population that includes all randomized subjects in each cohort. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group within each cohort. The stratified log-rank test, with region (North America vs. European Union [EU] vs. rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2), and disease distribution (presence vs. absence of visceral metastases in lung, liver, or bone) as stratification factors, will be used to compare survival curves of OS between the 2 treatment arms in each cohort. There is one planned interim analysis for each cohort.

TIME AND EVENTS SCHEDULE

(For the Long-term Extension Phase Time and Events Schedule, please refer to Attachment 8)

Parameter	NOTES	Screening Phase			Treatment Phase[a] (21-day cycles)				Follow-Up Phase[a]
		Molecular Eligibility	Full Study Screening		Cycles 1, 2, 3		Cycle 4+	End of Treatment	
					Day 1	Day 14	Day 1		
Visit Window		N/A	-30 days	-14 days	C1: 0 days C2, C3: -2 to +2 days	-2 to +2 days	-2 to +2 days	30 (+7) days after last dose	every 12 weeks±7 days
Screening/Administrative: Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4. Check clinical status again before first dose of study medication. The End-of-Treatment Visit should occur before the start of any subsequent therapy, if such therapy starts within 30 days after last dose on study.									
Informed Consent (molecular and full study)	A molecular eligibility testing ICF may be used to allow for assessment of archived tumor tissue. A separate Full-Study ICF may be used for subjects who meet molecular eligibility criteria. Must be signed before any study-related activity.*	X	X						
Inclusion/exclusion criteria, medical history, and smoking history	Histological documentation of specific tumor type, prior anticancer therapy, reason for cisplatin ineligibility. Record demographic information.		X						
Tumor tissue for central molecular screening	Archival or fresh biopsy tumor tissue must be sent to central lab for molecular screening. If fresh biopsy, sign Full-Study ICF.	X							
Local historical FGFR test results for molecular eligibility	Local historical FGFR-positive test results (from tissue or blood) will be allowed (see guidelines in Section 9.1.2). If a subject is enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation of FGFR status, diagnostic development, and biomarker research.	X							
Tumor tissue for PD-(L)1 and biomarker testing	Note: No additional sample is required as PD-L1 and biomarker testing is assessed from the tumor tissue (archival or fresh biopsy) collected at prescreening.		X						
Study Drug Administration: Randomization will occur within 3 days prior to Cycle 1 Day 1. All information required for randomization purposes must be available at the time of randomization including: ECOG performance status score, FGFR alteration type (communicated by sponsor by time of randomization), disease distribution (presence or absence of visceral metastases: lung, liver, or bone) based upon baseline radiographic imaging performed during screening window, and prior anti-cancer treatment (whether prior anti-PD-(L)1 treatment has been received).									
Arm 1A and Arm 2A: Erdafitinib	Start with 8 mg, increase to 9 mg or maintain 8 mg based on C1D14 phosphate value (see guidelines in Section 6.1)				Once Daily				
Arm 1B: Chemotherapy	Vinflunine or Docetaxel				X		X		
Arm 2B: Immunotherapy	Pembrolizumab				X		X		

Parameter	NOTES	Screening Phase			Treatment Phase[a] (21-day cycles)				Follow-Up Phase[a]
		Molecular Eligibility	Full Study Screening		Cycles 1, 2, 3		Cycle 4+	End of Treatment	
					Day 1	Day 14	Day 1		
Visit Window		N/A	-30 days	-14 days	C1: 0 days C2, C3: -2 to +2 days	-2 to +2 days	-2 to +2 days	30 (+7) days after last dose	every 12 weeks±7 days
Safety Assessments									
Physical examination	At Screening, complete physical examination including neurological examination, height, and weight. During treatment, limited physical examination of affected organs, neurological examination and weight; record new abnormalities as AE.		X		X		X	X	
Vital signs	Check temperature, heart rate, systolic and diastolic blood pressure; record abnormalities as AE.		X		X		X	X	
ECOG performance status				X	X		X		
Urine or serum β-hCG pregnancy test	Sexually active women of childbearing potential only. Screening test within 7 days of first dose.			7 days	Day 1 of every cycle from Cycle 2			X	
Triplicate 12-lead ECG	Record postdose ECGs, see Section 9.7.5 for exact timing. May be performed more often as clinically indicated		X		C2D1		C4D1		
Ophthalmologic exam	To be performed by an ophthalmologist, for exact assessments see Section 9.7.6		X**						
Amsler Grid Test	To be performed by treating physician or nurse (as directed by specific site instructions). After screening, only Arms 1A and 2A.		X		X (C2, C3)		X	X	
Clinical Laboratory Assessments: Clinical laboratory test results (except parathyroid hormone) must be available in real time prior to dosing with study drug. Results of previous testing should be available for comparison as clinically necessary.									
Hematology	May be performed within 2 days prior to D1 of each cycle; for exact assessments see Section 9.7.2			X	X		X	X	
Chemistry	May be performed within 2 days prior to D1 of each cycle; for exact assessments see Section 9.7.2			X	X		X	X	
Chemistry	Serum phosphate for all subjects at screening. After screening, for Arms 1A and 2A only. May be performed within 2 days prior to D1 and D14; for exact assessments see Section 9.7.2.			X	X	X	X	X	
Chemistry	Serum parathyroid hormone for all subjects at screening. After screening, for Arms 1A and 2A only. May be performed within 2 days prior to D1 and D14; for exact assessments see Section 9.7.2.			X	X	X	C4, C5, C6, then every 3rd cycle thereafter	X	
Chemistry	Calcium and albumin for all subjects at screening. After screening, for Arms 1A and 2A only. For hypoalbuminemia, please provide corrected calcium. May be performed within 2 days prior to D1 and D14; for exact assessments see Section 9.7.2.			X	X	X	X	X	

Parameter	NOTES	Screening Phase			Treatment Phase[a] (21-day cycles)				Follow-Up Phase[a]
		Molecular Eligibility	Full Study Screening		Cycles 1, 2, 3		Cycle 4+	End of Treatment	
					Day 1	Day 14	Day 1		
Visit Window		N/A	-30 days	-14 days	C1: 0 days C2, C3: -2 to +2 days	-2 to +2 days	-2 to +2 days	30 (+7) days after last dose	every 12 weeks±7 days
Chemistry	TSH and FT4 for all subjects at screening. After screening, for Arm 2B only. May be performed within 2 days prior to D1.			X	Every other cycle from Cycle 2				
Efficacy and Other Assessments									
Radiological assessment	Identical methodology [CT, or MRI if site of disease not evaluable by CT] should be used for disease assessment at baseline and throughout the study whenever possible. Additional assessments may be performed, if clinically indicated.		X		Every 6 weeks (±7 days) for 6 months, then every 12 weeks for the next 6 months (±7 days) calculated from the date of randomization, then as clinically indicated. For subjects who discontinue study drug before disease progression, tumor assessments should continue as scheduled (see Section 9.1.3)				
FACT-BI, PGIS	PRO measures to be completed preferably before any other study procedures				X	X (C1 only)	X	X	
EQ-5D-5L	PRO measures to be completed preferably before any other study procedures. Continue in Follow-up until start of subsequent therapy.				X	X (C1 only)	X	X	X
Blood (plasma) for ctDNA	Collect sample predose				X (C1D1, C3D1)		X (C5D1)	X	
Blood for immune cell profiling (flow)	Collect sample predose. Collection may cease or time points modified based on emerging data.				X	X			
PBMCs for TCR sequencing	Collect sample predose. Collection may cease or time points modified based on emerging data.				X	X		X	
Tumor biopsy for biomarker research	Optional	Any time before first dose			C2D1 (+2 weeks)			X	
PK Blood Sample	Arms 1A and 2A only. Record dosing and PK collection times. See Section 9.3 for exact timing.				C1D14 anytime C2D1, predose and 2-4 hr postdose				
Protein binding blood sample	Arms 1A and 2A only.				C2D1, 2-4 hr postdose				
Blood Sample for CYP2C9 genotyping	Arms 1A and 2A only.				C1D14 (or later time point)				
Ongoing Subject Review									
Concomitant medications			X						
Adverse events[b]	Collected from the day full study ICF is signed until 30 days after last dose of study drug. If study drug is discontinued due to drug-related AE, AE should be monitored until it resolves to baseline,		X						X

Parameter	NOTES	Screening Phase			Treatment Phase[a] (21-day cycles)				Follow-Up Phase[a]
		Molecular Eligibility	Full Study Screening		Cycles 1, 2, 3		Cycle 4+	End of Treatment	
					Day 1	Day 14	Day 1		
Visit Window		**N/A**	**-30 days**	**-14 days**	**C1: 0 days C2, C3: -2 to +2 days**	**-2 to +2 days**	**-2 to +2 days**	**30 (+7) days after last dose**	**every 12 weeks±7 days**
	stabilizes, or is deemed irreversible, subject dies, or subsequent therapy is started, whichever occurs first.								
Survival status and subsequent anticancer therapy	May be assessed via telephone call. Survival status and start of alternate anticancer therapy will be monitored until death, withdrawal of consent, or study completion (ie,the end of data collection timepoint has been achieved for the respective cohort (See Section 17.9.1), whichever occurs first								X
Abbreviations to Time and Events Schedule: AE=adverse event; C=cycle; CT= computed tomography; ctDNA=circulating tumor DNA; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FGFR=fibroblast growth factor receptor; FT4=free thyroxine 4; hr=hour; ICF=informed consent form; MRI= magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; PRO=patient reported outcome; TCR=T cell receptor; TSH=thyroid stimulating hormone									

* Consent for molecular eligibility screening (but not full study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance. For subjects signing a new full-study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 30-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.

**After 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.

a. Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Attachment 7.

b. The LTE Phase begins with the approval of Amendment 6 and with achievement of the clinical cut-off for the final analysis for each cohort. (For Cohort 1, the Sponsor will notify the investigators if the interim analysis will be considered the final analysis.) Upon initiation of the LTE Phase, data collection will conclude. Subjects in the respective cohort who are continuing to derive benefit from study drug, as determined by their investigator may have continued access to study drug in the LTE Phase of this study. As an alternative to entering the LTE Phase, subjects may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. During this period (when study drug will be supplied on this study by the Sponsor after the end of data collection timepoint), only serious adverse events will be reported to the Company safety repository.

ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
α1-AGP	α1-acid glycoprotein
AUC	area under the curve
AUCu	area under the curve for unbound drug
BID	bis in die (two times each day)
BSC	best supportive care
CLIA	Clinical Laboratory Improvement Amendments
Cmax	maximal concentration
CR	complete response
CRF	case report form
CrCl	creatinine clearance
CSR	central serous retinopathy
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life – 5 Dimensions-5 Levels
EU	European Union
FACT-Bl	Functional Assessment of Cancer Therapy – Bladder Cancer
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FT4	free thyroxine 4
GCP	Good Clinical Practice
HR	hazard ratio
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
LTE	Long-term Extension [Phase]
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NK	natural killer
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PD-(L)1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein

PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PR	partial response
PRO	Patient-Reported Outcome
PGIS	Patient-Global Impression of Severity
QID	quater in die (four times each day)
RECIST	Response Evaluation Criteria in Solid Tumors
RGQ	Rotor-Gene Q
RNA	ribonucleic acid
RPED	retinal pigment epithelial detachment
RT-PCR	reverse transcription polymerase chain reaction
SMT	Safety Management Team
SUSAR	suspected unexpected serious adverse reaction
USP	United States Pharmacopeia
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TID	three times a day
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States

1. INTRODUCTION

Erdafitinib (JNJ-42756493) is a selective and potent pan fibroblast growth factor receptor (FGFR) inhibitor with demonstrated clinical activity in subjects with solid tumors identified to have alterations in the FGFR pathway, including urothelial carcinoma.

This Phase 3 study will evaluate single-agent erdafitinib versus established chemotherapy agents (docetaxel and vinflunine) and an anti-programmed death-ligand 1 (PD-[L]1) agent (pembrolizumab) in relapsed/refractory subjects with selected FGFR gene aberrations

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. Bladder Cancer

The worldwide age-standardized incidence rate of bladder cancer (per 100,000 person/years) is 9.0 for men and 2.2 for women (Ferlay 2013). Worldwide, the bladder cancer age-standardized mortality rate (per 100,000 person/years) was 3.2 for men versus 0.9 for women in 2012 (Ferlay 2013). Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments.

Half of the patients with muscle-invasive urothelial cancer relapse after radical cystectomy, depending on the pathological stage of the primary tumor and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to 15 percent of patients are already metastatic at diagnosis. Prognostic factors are crucial for assessing results and stratifying phase 3 studies. In a multivariate analysis, Karnofsky performance status of <80% and presence of visceral metastases are independent predictors of poor survival (Bajorin 1999).

1.2. Second-line Chemotherapy

Results of second-line treatment with chemotherapy from phase 2 studies are highly variable and depend on patient selection (Bellmunt 2014). Several agents have been tested in this setting as monotherapy or in combination (Yafi 2011). Response rates with monotherapy are lower than with combinations, but progression-free survival (PFS) has been short with both options. The only valid randomized phase 3 study in this patient population tested vinflunine and best supportive care (BSC) versus BSC alone (Bellmunt 2014). Based on the available evidence, taxanes and vinflunine are commonly recommended chemotherapy agents (NCCN 2017).

1.2.1. Docetaxel

Docetaxel, an analog of paclitaxel, is a taxane chemotherapeutic agent that received initial approval in the United States (US) in 1996 for the treatment of patients with advanced breast cancer who had failed front-line chemotherapy, and subsequently in a number of other malignancies. Docetaxel is not licensed for the treatment of patients with urothelial cancer, however it is commonly used in this setting based on the results of a phase 2 study conducted in patients (n 30) with advanced urothelial cancer who had failed 1 prior line of cisplatin-based treatment. Docetaxel was active as a single agent when administered at a dose of 100 mg/m^2 as a 1-hour infusion every 3 weeks (McCaffrey 1997). Four patients (13.3%) had a partial response (PR), with a duration of

response (DOR) from 3 to 8 months. Estimated median overall survival (OS) for all patients was 9 months. Myelosuppression was the major toxicity, with neutropenia, anemia, and thrombocytopenia frequently reported. Clinically significant nonhematologic toxicity was low.

For further information regarding docetaxel, refer to the locally available prescribing information for docetaxel.

1.2.2. Vinflunine

Vinflunine, a third-generation vinca alkaloid, provided promising results in phase 2 studies. A randomized Phase 3 study compared vinflunine plus BSC against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic urothelial carcinoma (Bellmunt 2009). The results showed an objective response rate (ORR) of 8.6%, a clinical benefit with a favorable safety profile and, most importantly, a survival benefit in favor of vinflunine, which was statistically significant in the eligible patient population (not in the intent-to-treat [ITT] population). Currently, vinflunine is the only approved second-line chemotherapy treatment and is approved in the EU.

For further information regarding vinflunine, refer to the locally available prescribing information.

1.3. Immunotherapy

Bacillus Calmette-Guérin (BCG) was approved by the US Food and Drug Administration (FDA) in 1990 as an immunotherapy agent for non-muscle invasive urothelial carcinoma. The effectiveness of BCG was an early sign that urothelial carcinoma is an immune-responsive tumor (Davarpanah 2017). More recently, checkpoint inhibitors are also promising in the treatment of urothelial carcinoma (Miller 2017). Atezolizumab (Tecentriq®), an anti-PD-(L)1 monoclonal antibody, received accelerated approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed during or after platinum-based chemotherapy or within 12 months of having received platinum-containing chemotherapy. In rapid succession, nivolumab (Opdivo,® anti-PD-(L)1 monoclonal antibody), durvalumab (Imfinzi,® anti-PD-(L)1 monoclonal antibody), and avelumab (Bavencio,® anti-PD-(L)1 monoclonal antibody) were all granted accelerated approval in the second-line setting. In Phase 2 or Phase 1b trials, overall response rates have ranged from 13.1% to 19.6%. Most recently, in May 2017, pembrolizumab (Keytruda,® anti-PD-(L)1 monoclonal antibody) was approved by the FDA for second-line treatment of locally advanced or metastatic urothelial carcinoma based on a phase 3 study. Pembrolizumab and atezolizumab also have been approved by the FDA and EMA for use in previously untreated patients ineligible for cisplatin-containing chemotherapy; however, the indication in this setting has subsequently been restricted to those patients whose tumor expresses PD-(L)1 with a Combined Positive Score ≥10 (pembrolizumab) or PD-(L)1 stained tumor-infiltrating immune cells covering ≥5% of the tumor area (atezolizumab). The restriction has reduced the previously untreated population eligible for treatment with a checkpoint inhibitor. For those patients who still receive single agent pembrolizumab or atezolizumab as frontline treatment, common clinical practice in second line is to administer platinum-based treatment as standard of care.

1.3.1. Pembrolizumab

In a multicenter, randomized, active-controlled Phase 3 study (KEYNOTE-045), patients with locally advanced or metastatic urothelial carcinoma and disease progression on or after platinum-containing chemotherapy were randomly assigned (1:1) to receive either pembrolizumab 200 mg every 3 weeks (n 270) or investigator's choice of a chemotherapy regimen (paclitaxel [n 84], docetaxel [n 84], or vinflunine [n 87]) every 3 weeks (n 255). Patients without disease progression could be treated with pembrolizumab up to 24 months. The median duration of exposure was 3.5 months for pembrolizumab and 1.5 months for chemotherapy. Objective response rate (ORR) was 21% for pembrolizumab and 11% for chemotherapy (p 0.002). Median overall survival (OS) was 10.3 months for the pembrolizumab group and 7.4 months for the chemotherapy group (HR 0.73; 95% CI: 0.59, 0.91, p 0.004). The study demonstrated statistically significant improvements in OS and ORR for patients assigned to pembrolizumab compared with chemotherapy. No statistically significant difference in progression-free survival (PFS) between the 2 treatment arms was observed. The most common adverse reactions (≥20%) included fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea.

For further information regarding pembrolizumab, refer to the locally available prescribing information for pembrolizumab.

1.4. Fibroblast Growth Factor Receptors and Erdafitinib

1.4.1. Fibroblast Growth Factor Receptors

Overexpression of fibroblast growth factor receptors (FGFRs), or aberrant regulation of their activity, has been implicated in many forms of human malignancies including urothelial carcinoma.

Fibroblast growth factor receptors are protein tyrosine kinases and consist of 4 members (FGFR1 to FGFR4). Upon binding to their natural ligand, FGF family members, FGFRs dimerize and autophosphorylate the tyrosine residue in the kinase domain activation loop to become fully activated. Activated FGFR further phosphorylate multiple signaling proteins bound to their intracellular portion, resulting in activation of Ras/mitogen-activated protein kinase (MAPK) and PI3-kinase/Akt signaling pathways. Other downstream signaling components of FGFRs include Src, and Rsk. The result is FGFR stimulation of cell growth, survival, migration, and differentiation depending on the cell type.

Fibroblast growth factor receptors are present in many types of normal and tumor cells and have been shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis. Overexpression of FGFRs, or aberrant regulation of their activity, has been implicated in many forms of human malignancies. Fibroblast growth factor receptor activating mutation, gene amplification, and translocation have been associated with neoplastic progression and tumor vascularization in multiple cancer types, including breast, lung, prostate, endometrial, gastric, and urothelial carcinoma. Therefore, targeting FGFRs in urothelial cancer

with a small molecule kinase inhibitor is an attractive strategy for the development of a novel cancer treatment.

1.4.2. Erdafitinib

Erdafitinib is an oral pan-FGFR tyrosine kinase inhibitor with 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 <1000 nM in FGFR pathway-activated cancer cell lines. Erdafitinib has been shown to have in vivo antitumor activity in mouse xenograft models of FGFR-driven gastric, bladder, and squamous non-small cell lung cancer (NSCLC) tumor models, and in patient-derived xenografts from squamous NSCLC, gastric, breast, and hepatocellular tumors.

In humans, erdafitinib exhibited dose-related increase in C_{max} and AUC and time-independent PK within the dose range of 0.5 mg to 12 mg, both after single and multiple daily dosing. Median t_{max} observed ranged from 2 to 4 hours (erdafitinib as capsule). Relative bioavailability was comparable under fed and fasted conditions. Erdafitinib is highly bound to plasma proteins such as α1-acid glycoprotein (α1-AGP). Free fractions of erdafitinib in human plasma were small (average~0.36%). Erdafitinib is a P-glycoprotein (P-gp) substrate.

An in vitro metabolism study in human liver microsomes and hepatocytes showed major involvement of CYP450 enzymes CYP2C9 and CYP3A4. Long terminal phase half-life of erdafitinib (>50 hours) in plasma was observed resulting in approximately 3-fold accumulation of C_{max} and AUC following multiple daily dosing.

In a recently completed phase 1 study (Study 42756493EDI1001, n 187), the antitumor effect of erdafitinib was observed in subjects with urothelial cancer with selected FGFR aberrations, as well as other solid tumors. For all subjects with relapsed/refractory urothelial cancer, ORR across dose levels was 40.0% (12/30 subjects). At the 9 mg dose level, ORR was 70.0% (7/10 subjects) for response-evaluable subjects with urothelial cancer who harbored selected FGFR aberrations. The most frequently reported adverse events (AEs) were hyperphosphatemia (65%), dry mouth (46%), asthenia (45%), stomatitis (39%), constipation (37%), and decreased appetite (34%). Thirteen subjects (7%) discontinued treatment due to AEs.

A global phase 2 study (Study 42756493BLC2001) is ongoing in subjects with relapsed/refractory advanced urothelial cancer with selected FGFR mutations and translocations. As of 09 June 2017, 173 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 62 subjects in the 8 mg daily regimen. The ORR, including confirmed and unconfirmed complete response (CR) and partial response (PR), was 39.7% in the 8 mg once daily regimen. For subjects in the 8 mg once daily group whose dose was increased to 9 mg, ORR was 50.0%. The most frequently reported AEs, most of which were Grade 1 or 2 in severity, were hyperphosphatemia (54.3%), diarrhea (49.7%), dry mouth (42.8%), stomatitis (42.2%) and decreased appetite (33.5%). Fourteen subjects (8%) discontinued treatment due to AEs.

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

1.5. Overall Rationale for the Study

Metastatic bladder cancer carries a dismal prognosis, with 5-year survival rate of only 5.0% (Howlader 2016). The mainstay of treatment is still limited to platinum-based chemotherapy in frontline, leading to a disappointing median OS of approximately 15 months. Second-line treatment with single-agent chemotherapy has a response rate of approximately 8% to 10% and OS of approximately 6 to 8 months. More recently, outcomes with compounds targeting the PD-1/PD-(L)1 pathway were reported in patients with disease progression on or after 1 prior line of treatment, with ORR of 15% to 20% and median overall survival of approximately 8 to 10 months. In randomized phase 3 studies, conflicting results were observed with pembrolizumab demonstrating significant improvement in overall survival against standard of care chemotherapy and atezolizumab failing to demonstrate an improvement in the same setting. Despite the recent improvement in outcomes provided by compounds targeting the PD-1/PD-(L)1 pathway, all current treatment options still have relatively limited clinical activity as second-line therapy; and at the time of initial protocol development, no targeted therapy was approved for treating specific subsets of urothelial cancer subjects with FGFR alterations.

The clinical data from phase 1 and 2 clinical studies demonstrate erdafitinib is active as a monotherapy in subjects with relapsed/refractory metastatic urothelial cancer with selected FGFR translocations and mutations.

Therefore, this phase 3 study aims to demonstrate superiority of single agent erdafitinib over established (chemotherapy) and emerging (anti PD-1/PD-[L]1 monoclonal antibodies) standard of care options in relapsed/refractory subjects with selected FGFR gene aberrations.

2. OBJECTIVE, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective of this study is to evaluate efficacy of erdafitinib versus chemotherapy or pembrolizumab in subjects with advanced urothelial cancer harboring selected FGFR aberrations who have progressed 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 an anti-PD-(L)1 agent (cohort 2).

The primary endpoint of OS will be evaluated in 2 cohorts:

- Cohort 1: erdafitinib versus chemotherapy (docetaxel or vinflunine) [subjects who have received prior anti-PD-(L)1 agent]
- Cohort 2: erdafitinib versus pembrolizumab [subjects who have not received prior anti-PD-(L)1 agent]

Secondary Objectives

- To evaluate progression-free survival (PFS) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the objective response rate (ORR) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the health-related quality of life (HRQOL) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the duration of response (DOR) for subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To characterize the safety profile of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
- To evaluate the population PK of erdafitinib

Exploratory Objectives

- To evaluate DNA, RNA, or protein biomarkers in tissue and blood samples which potentially predict tumor response or resistance to erdafitinib, chemotherapy, or pembrolizumab
- To assess the expression of immune markers (eg, PD-[L]1) and determine molecular subtype in tumor samples
- To evaluate changes in peripheral blood immune cell types, levels, and activation status in response to erdafitinib, chemotherapy, or pembrolizumab
- To assess changes in tumor immune cell infiltrate and gene expression related to bladder cancer subtype, in response to erdafitinib in paired tumor biopsies
- To evaluate the relationship between erdafitinib exposure and efficacy and safety endpoints
- To evaluate the relationship between CYP2C9 polymorphism and PK of erdafitinib

2.1.2. Endpoints

Primary Endpoint

The primary endpoint is overall survival (OS). Overall survival is measured from the date of randomization to the date of the subject's death. If the 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.

Secondary Endpoints

- PFS: duration in days from the date of randomization to the date of disease progression (assessed per RECIST v1.1 by the investigator) or relapse from CR or death, whichever is reported first. For subjects who do not have disease progression and are alive, as well as for subjects with unknown disease progression or unknown survival status as of the clinical cutoff date, PFS will be censored at the date of the last adequate disease assessment. If there is no postbaseline tumor assessment for a subject, PFS will be censored on the date of randomization. Refer to the Statistical Analysis Plan (SAP) for further details regarding

censoring rules. Adequate disease assessment is defined as having sufficient evidence to indicate correctly that progression has or has not occurred.

- ORR: the proportion of subjects who achieve complete response or partial response, as assessed per RECIST v1.1 by the investigator.
- Change from baseline in patient-reported health status and physical functioning scales of the Functional Assessment of Cancer Therapy Bladder Cancer (FACT-Bl), Time Until Symptom Deterioration (subset of FACT-Bl items), Patient-Global Impression of Severity (PGIS), and utility and visual analog scale of the European Quality of Life-5 Dimensions-5 Levels Questionnaire (EQ-5D-5L).
- DOR: for responders, duration in days from the date of initial documentation of a response to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. The censoring is similar to PFS.
- Safety: collection of adverse event, clinical laboratory values, electrocardiograms, vital signs, ophthalmologic evaluations, physical examinations.
- Oral clearance, area under the plasma concentration-time curve (and other parameters, as needed and as data permits) will be estimated using a population approach.

Exploratory Endpoint(s)

- PD-(L)1 expression level by immunohistochemistry (IHC), and bladder cancer subtype by RNA sequencing or other method(s) as appropriate
- Profile and activation status of peripheral immune cell subtypes by flow cytometry, T cell receptor (TCR) sequencing, or alternate method(s) as appropriate
- Tumor T cell infiltrate in paired biopsies by immunohistochemistry, and gene expression related to bladder cancer subtype by RNA sequencing or alternate method(s) as appropriate
- Use of models, such as Emax, to evaluate parameters describing the effect of erdafitinib exposure on clinical endpoints; for instance, erdafitinib concentration or metrics of exposure leading to 50% of the maximal effect
- Effect of CYP2C9 polymorphism on the PK of erdafitinib

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

Cohort 1 hypothesis: Erdafitinib treatment prolongs overall survival (OS) in subjects with advanced urothelial cancer harboring selected FGFR aberrations following 1 or 2 prior line(s) of systemic therapy, with at least 1 line containing anti-PD-(L)1, compared with the OS of those treated with chemotherapy (docetaxel or vinflunine).

Cohort 2 hypothesis: Erdafitinib treatment prolongs overall survival (OS) in subjects with advanced urothelial cancer harboring selected FGFR aberrations following 1 prior line of systemic chemotherapy without anti-PD-(L)1, compared with the OS of those treated with pembrolizumab.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, multicenter, global phase 3 study of erdafitinib versus standard of care, consisting of chemotherapy (docetaxel or vinflunine) or anti-PD-(L)1 agent pembrolizumab, in subjects with advanced urothelial cancer and selected FGFR aberrations who have progressed on or after 1 or 2 prior treatments (cohort 1) or 1 prior treatment (cohort 2). Subjects will be assigned to Cohort 1 or Cohort 2 based upon prior treatment with an anti-PD-(L)1 agent. In Cohort 1, subjects who have received prior anti-PD-(L)1 will be randomized to erdafitinib versus chemotherapy (approximately 280 subjects). In Cohort 2, subjects who have not received prior anti-PD-(L)1 will be randomized to erdafitinib versus pembrolizumab (approximately 350 subjects). Cohort 1 and Cohort 2 will be assessed independently.

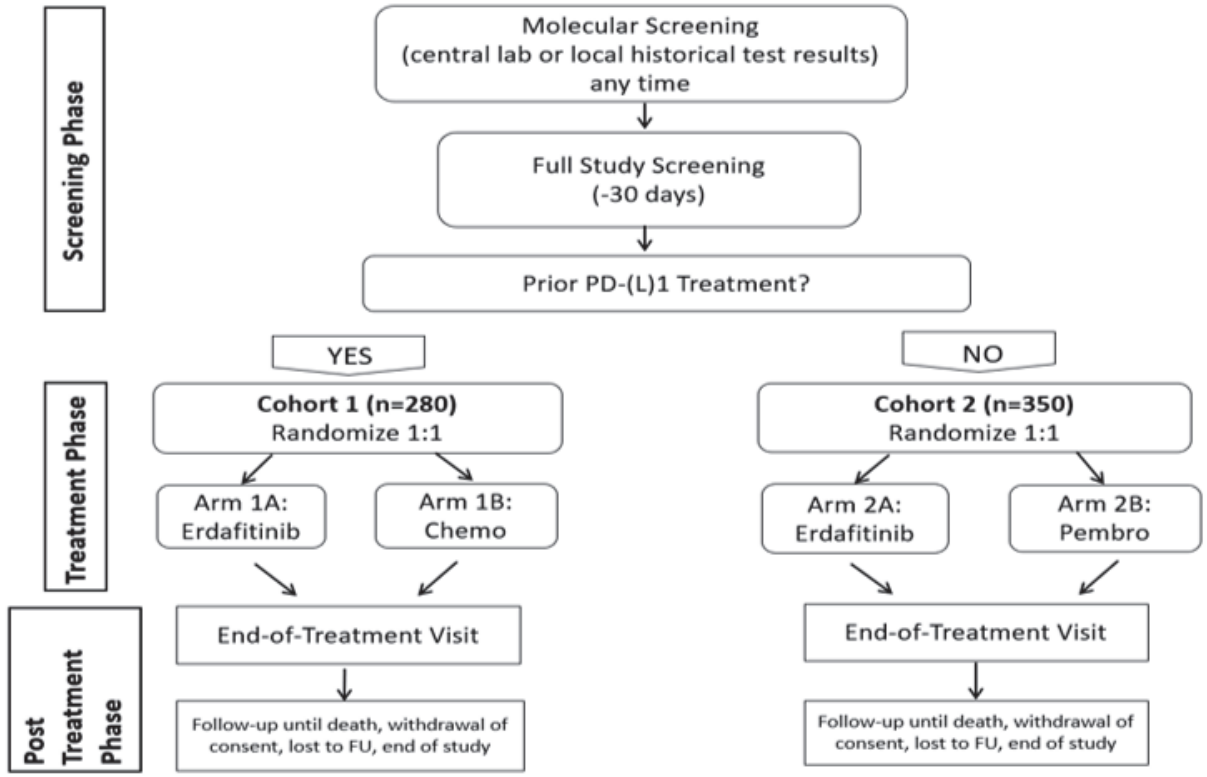
An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. Refer to Section 11.9 for details.

For each cohort, a review of the safety data will be performed by an IDMC after at least 60 subjects have been enrolled in that cohort and every 6 months afterwards. A review of one predefined interim analysis for each cohort will also be performed by the IDMC on both safety and efficacy data. Details are provided in Section 11.9.

The Screening Phase will start with molecular screening, which will be performed by a central laboratory or by review of local historical test results submitted to the sponsor for molecular eligibility assessment (see details in Section 9.1.2). Full study screening will occur after the completion of prior treatment and documentation of disease progression for subjects who meet the molecular screening criteria. The Treatment Phase will extend from randomization until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment. The post-treatment Follow-up Phase will extend from the End-of-Treatment Visit until the subject has died, withdraws consent, is lost to follow-up, or study completion (ie, the end of data collection timepoint has been achieved for the respective cohort discussed in Section 17.9.1), whichever comes first. Continued treatment with study drug after the end of data collection timepoint is discussed in Section 6.4.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Note: The Long-term Extension Phase is not included in the schematic (see Attachment 8).
Treatment until disease progression, intolerable toxicity, withdrawal of consent, or decision by investigator.

Subjects who meet all eligibility requirements will be entered into the study. Randomization to treatment will be within each cohort. In Cohort 1, subjects must have progressed on or after 1 or 2 prior line(s) of systemic treatment, with at least 1 line including anti-PD-(L)1 as monotherapy or as combination therapy, will be randomized 1:1 to erdafitinib (Arm 1A) or chemotherapy (vinflunine or docetaxel, Arm 1B). In Cohort 2, subjects must have progressed after one prior line of systemic treatment not containing anti-PD-(L)1 and will be randomized 1:1 to erdafitinib (Arm 2A) or pembrolizumab (Arm 2B). Stratified randomization will be implemented within each cohort with the following factors: region (North America vs European Union [EU] vs Rest of World), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases).

Subjects will be assessed for disease response by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST; v1.1) guidelines. Treatment with erdafitinib and pembrolizumab may continue beyond the initial demonstration of disease progression, according to criteria in Section 9.2.2.

The LTE Phase begins with the approval of Amendment 6 and with achievement of the clinical cut-off for the final analysis for each cohort. (For Cohort 1, the Sponsor will notify the investigators if the interim analysis will be considered the final analysis.) Upon initiation of the LTE Phase, the

follow up of subjects will end and study data collection will conclude in the clinical database. During this LTE Phase (when study drug will be supplied by the Sponsor after the data collection timepoint), only serious adverse events will be reported to the Company safety repository. Subjects in the respective cohort who are continuing to derive benefit from study drug, as determined by their investigator may have continued access to study drug in the LTE Phase of this study (Section 6.4). As an alternative to entering the LTE Phase, subjects may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. In the event of a decision by the Sponsor to allow cross-over to erdafitinib following the final analysis for each respective cohort, investigators will be notified. Detail regarding the LTE Phase is provided (including a Time and Events Schedule) in Attachment 8.

3.2. Study Design Rationale

3.2.1. Choice of Comparators

While platinum-based combination chemotherapy leads to high response rates in patients with advanced urothelial cancer of the bladder in the front-line setting, most patients will ultimately progress and optimal treatment in the second-line setting still needs to be determined. Factors such as advanced age and frailty, poor performance status, comorbidities, and rapidly progressive disease have rendered assessment of treatment options difficult.

There are no approved second-line chemotherapies for metastatic urothelial cancer in the US, while vinflunine is approved in the EU for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. Vinflunine has demonstrated survival benefit compared with BSC in a randomized phase 3 setting, but it has not been compared with other currently used agents such as taxanes.

National Comprehensive Cancer Care guidelines acknowledge that data on second-line systemic therapy for locally advanced or metastatic disease is highly variable, and that docetaxel is one of the available options (NCCN 2017). Although no labeled dosing guidelines are available for urothelial cancer, docetaxel is commonly administered at 75 mg/m^2 in other indications.

In recent years, several studies have investigated agents targeting the PD-(L)1 pathway in relapsed cancer patients. Pembrolizumab is the only PD-(L)1 agent that has shown a significant OS benefit compared with chemotherapy (vinflunine or taxanes) in a randomized phase 3 study and is approved by the FDA for second-line treatment of locally advanced or metastatic urothelial carcinoma.

Thus, the choice of vinflunine, the taxane docetaxel, and pembrolizumab as comparators to erdafitinib is supported by current treatment practice and international guidelines.

3.2.2. Two-cohort Design

With the approval and subsequent increased use of agents targeting the PD-(L)1 pathway in the front-line setting, 2 subgroups of relapsing patients are emerging: patients who have been treated with an anti-PD-(L)1 and patients who have not been exposed to an anti-PD-(L)1. Pembrolizumab has shown superior survival results over vinflunine or taxanes in the second-line setting. Moreover,

the above described results with chemotherapy and pembrolizumab were obtained in a population that was not preselected for the presence of FGFR gene aberrations. It is unclear whether the presence or absence of FGFR gene aberrations affects the response to chemotherapy or anti-PD-(L)1, and whether such an effect would differ according to the treatment received.

Urothelial cancer, like breast cancer, may be classified by gene expression signature into basal versus luminal subtypes. The 2 subtypes may be further subdivided into 3 to 5 classifications depending on which of several published gene signature algorithms are applied. Luminal tumors are generally sub-classified into 2 subgroups: (1) Luminal 1, Luminal Papillary, or Urobasal A; and (2) Luminal 2, Luminal Infiltrated, p53-like, or Genomically Unstable. The Basal subtype is sub-classified into: Squamous Cell Carcinoma Like, Urobasal B, and Infiltrated (Lund model); or Basal and Immune Undifferentiated, or Cluster III and Cluster IV for the Broad and TCGA models, respectively (TCGA 2014, Choi 2014, Damrauer 2014, Choi 2017, Seiler 2017, Lerner 2017). Bladder cancer subtype may inform patient prognosis and response to treatment, including response to neoadjuvant chemotherapy (Choi 2014, Seiler 2017). These subtypes may be enriched for specific mutations thought to contribute to their specific clinical features and biology (Choi 2017).

The Luminal 1 tumors are reported to be enriched for FGFR3 mutations, and lacking in immune marker expression and immune cell infiltrate (Choi 2017). Differential response to immunotherapy has been observed across bladder cancer subtypes, with the Luminal 1 subtype showing the lowest response rate to the anti-PD-(L)1 inhibitors atezolizumab and nivolumab compared with other bladder cancer subtypes (Rosenberg 2016, Sharma 2017).

Exploratory analyses of the atezolizumab phase 2 data show a clear differential response depending on the subtypes of urothelial cancer. PD-(L)1 expression on tumor infiltrating immune cells was more pronounced in the basal subtype (TCGA clusters III and IV) as compared to the luminal subtype (TCGA clusters I and II or Luminal 1 and Luminal 2). PD-(L)1 high expression was almost exclusively seen in the basal subtype. Response to atezolizumab was significantly higher in the Luminal 2 subtype as compared to the other subtypes, with lowest objective response rates in Luminal 1 and basal TCGA cluster II subtypes (Rosenberg 2016). FGFR-aberrations are most prevalent in the Luminal 1 subtype (TCGA 2014), the subtype with the poorest response to atezolizumab, which might point towards a lower response potential to anti-PD-(L)1 in tumors with FGFR-aberrations. This is consistent with our observation that subjects with FGFR-aberrations included in the ongoing Phase 2 study BLC2001 had a limited response rate (<5%) to prior anti-PD-(L)1 treatments compared with published response rates in first and second line for those compounds (15% to 20%).

It has also been postulated that resistance to chemotherapy is associated with FGFR-4 upregulation (Roidl 2009) or with activated FGFR-1 (Karajannis 2006). FGFR aberrations may therefore be associated with differential response to treatment with either chemotherapy or immunotherapy. Additionally, the 2 groups of patients who relapse following front-line treatment, ie, patients who have been previously treated with an anti-PD-(L)1 and patients who have not been exposed to an anti-PD-(L)1), could be different from each other, and response to second line treatment could

accordingly be different as well. Therefore, to adequately assess the specific role of FGFR alterations in these 2 groups, a design with 2 independent cohorts, one erdafitinib versus chemotherapy and one versus pembrolizumab, is warranted.

3.2.3. Dosing Schedule for Erdafitinib

Erdafitinib will be provided as a tablet for oral administration and subjects will be instructed to take 8 mg orally once daily for 21 days on a 21-day cycle, until disease progression, intolerable toxicity, withdrawal of consent, or decision by the investigator to discontinue treatment. Treatment will be up-titrated to 9 mg, maintained at 8 mg, or withheld, based on phosphate level measured on Cycle 1 Day 14, and taking into account observed toxicity to that day, as described in detail in Section 6.1.

The 8 mg starting dose was selected on the basis of pharmacokinetic (PK), pharmacodynamic and clinical data, which is summarized below.

Pharmacokinetics: At the 8 mg dose, based on PK simulations, the expected mean unbound C_{avg} plasma concentrations in subjects during the 28-day cycle period is 3.4 ng/mL. The mean unbound average plasma concentration of urothelial cancer subjects with clinical activity (partial responses) in the Phase 1 study was 2.5 ng/mL, which is also consistent with the preclinical target window. Antitumor activity is anticipated to correlate with preclinical AUC for unbound drug (AUCu), and at the 8 mg dose level, 90% of subjects will have unbound trough plasma concentrations and AUCu levels within the target window (0.6 to 2.4 ng/mL) by Day 3. Thus, 8 mg daily is predicted to generate continuously efficacious drug concentrations for the vast majority of subjects. The dosing regimen was further refined considering pharmacodynamic markers (see Clinical Activity section).

Pharmacodynamics: Hyperphosphatemia is a common drug-induced toxicity for anti-FGFR targeted agents due to renal tubular FGFR inhibition. This can serve as a pharmacodynamic marker of drug activity. In the Phase 1 study EDI1001, dose-dependent elevations in serum phosphate occurred in all subjects starting at 4 mg daily. Because this represents a target-mediated drug effect, the completed Phase 1 study could select a dose regimen that consistently induced manageable hyperphosphatemia but did not exceed a critical level requiring cessation of therapy. Data from the Phase 1 study indicates that a phosphate increase of at least 35% over baseline level may be associated with anti-tumor response. Therefore, a pharmacodynamic objective of 50% increase in phosphate level over baseline was considered to be appropriate. Given the median phosphate level of 3.6 mg/dL at baseline in the Phase 1 study, and of 3.3 mg/dL at baseline in the Phase 2 study (Interim Analysis 1 data) an increase of at least 50% for the majority of subjects would correspond to an absolute phosphate level of around 5.5 g/dL (which is also 35% over the phosphate upper limit of normal). Subjects achieving a phosphate level of less than 5.5mg/dL in the course of the first cycle dosing period would be considered to have had inadequate PD effect and would be candidates for dose escalation to 9 mg daily to achieve an optimum PD effect (phosphate above 5.5 mg/dL).

Clinical safety: The 8-mg daily dose is the continuous regimen that, based on modeling, would likely be well tolerated without significant treatment interruptions (approximately 10% to 15%

anticipated early interruptions) and for which the majority of subjects would tolerate the sustained dose of 8 mg once daily. Escalation on Day 15 of the first treatment cycle of daily dose from 8 mg once daily to 9 mg once daily in the subjects with both phosphate below 5.5 mg/dL (suboptimal pharmacodynamic effect), and without significant drug related toxicity (Grade ≥2 toxicity or Grade ≥1 central serious retinopathy or retinal pigment epithelial detachments) is unlikely to significantly change the overall tolerability profile.

Moreover, the observed safety of the 9-mg daily dose in the completed Phase 1 study did not raise concerns about prolonged hyperphosphatemia, and no soft-tissue calcification nor any electrolyte disturbance or endocrine abnormalities were reported. Similarly, in the ongoing Phase 2 study no such abnormalities were observed either. Therefore, a more insistent approach to up-titration can be adopted, allowing up-titration in subjects whose Day 14 phosphate is below 7 mg/dL without concurrent temporary use of phosphate binder treatment or Day 14 phosphate is 7-9 mg/dL with concurrent temporary use of phosphate binder treatment.

Clinical activity: Assessment of clinical activity at the 6-mg dose and in up-titrated subjects at IA1 is limited by the paucity of treated subjects, but 3 PR were observed in 14 subjects with phosphate level below 5.5 mg/dL and 4 PR in 7 subjects with phosphate level over 5.5 mg/dL, pointing to the potential importance of attaining full pharmacodynamic effect. Hence the aim is to bring a maximal number of subjects to the target phosphate of 7 to 9 mg/dL in order to attain maximal sustained inhibition of target, and thereby allow for potential optimization of efficacy, given the observed correlation thus far between clinical response and the pharmacodynamic effect on phosphate. Selective dose escalation to 9 mg for optimization of the pharmacodynamic effect is likely to increase the potential for clinical activity without significantly increasing dose interruptions or toxicity. The appropriateness of the proposed dosing regimen was supported by pharmacokinetic-pharmacodynamic simulations based on the modeling of phosphate levels: the proposed regimen was able to achieve the serum phosphate target level of 5.5 mg/dL in the majority of subjects, while reducing the number of unforeseen dose interruptions and dose adaptations.

3.2.4. Blinding, Control, Study Phase/Periods, Treatment Groups

Randomization will be used to minimize bias in the assignment of subjects to treatment groups within each cohort, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups within each cohort.

3.2.5. Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of erdafitinib and may help to identify population subgroups that respond differently to erdafitinib (or chemotherapy, or pembrolizumab). The goal of the biomarker analyses is to further understand the mechanism of action and potential erdafitinib-clinical response relationships.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

3.2.6. Patient Reported Outcomes Research

Patient-reported outcome (PRO) data complement data collected by other methods to support the clinical data and cost-effectiveness modeling as well as contributing to enhanced communication of value to patients, clinicians, regulators, and payers. Based on the clinical presentation of patients with bladder cancer and prior PRO research in bladder cancer clinical trials, the PRO endpoints of interest include scales from the FACT-Bl (physical well-being, functional well-being, bladder symptoms subscale), PGIS, and the EQ-5D-5L (utility value and visual analog scale). These PRO measures will be administered to test the hypothesis that treatment with erdafitinib maintains health-related quality of life as measured by time to symptom or functional deterioration by a prespecified meaningful change threshold. PRO data will be collected as outlined in the Time and Events Schedule to understand how the endpoints change over time, with treatment and with the clinical state of the subject.

4. SUBJECT POPULATION

Screening for molecular eligibility may be performed at any time prior to randomization; for details, see Section 9.1.2. Full study screening for molecular eligible subjects will be performed within 30 days before administration of the study drug. Separate informed consent forms (ICFs) may be used for molecular eligibility screening and full study screening. For subjects signing a new full-study ICF for the purpose of undergoing a new tissue biopsy for molecular screening, the 30-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.

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 must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, 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 (or the legal age of consent in the jurisdiction in which the study is taking place)

2. Histologic demonstration of transitional cell carcinoma of the urothelium. Minor components (<50% overall) of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable

3. Criterion amended per Amendment 2:
   3.1 Metastatic or surgically unresectable urothelial cancer

4. Documented progression of disease, defined as any progression that requires a change in treatment, prior to randomization

5. Criterion modified per Amendment 3:

   5.1 Criterion modified per Amendment 4:

   5.2. Criterion modified per Amendment 5:

   5.3 Cohort 1: Prior treatment with an anti-PD-(L)1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment. Prior treatment with an anti-PD-(L)1 agent could have been given as neo-adjuvant, adjuvant, or in metastatic line of treatment as frontline or maintenance therapy, as follows:

   - Together with chemotherapy or as maintenance therapy
   - Together with chemotherapy in metastatic setting
   - For superficial cancer (early disease/non-muscle invasive bladder cancer), OR in neo-adjuvant OR adjuvant setting. If these subjects did not relapse within a year of their last dose of anti-PD-(L)1, this will not be counted as a prior line of systemic treatment. These subjects will however still be eligible only for Cohort 1.

   Cohort 2: No prior treatment with an anti-PD-(L)1 agent; only 1 line of prior systemic treatment.

   Note: Subjects who received neoadjuvant or adjuvant chemotherapy or immunotherapy and showed disease progression within 12 months of the last dose are considered to have received systemic therapy in the metastatic setting.

6. Criterion modified per Amendment 4:

   6.1 Subjects must meet appropriate molecular eligibility criteria, as determined by central laboratory screening or by local historical test results (from tissue or blood) performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or regional equivalent laboratory using the following methods: local next-generation sequencing (NGS), direct digital counting methods, or the Qiagen Therascreen FGFR Rotor-Gene Q (RGQ) reverse transcription polymerase chain reaction (RT-PCR) test; see Section 9.1.2 for details.

   Tumors must have at least 1 of the following translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or 1 of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C.

7. ECOG performance status Grade 0, 1, or 2 (Attachment 1)

8. Criterion amended per Amendment 2:
   8.1 Criterion modified per Amendment 3:

8.2 Criterion modified per Amendment 4:
8.3 Criterion modified per Amendment 5:

8.4 Adequate bone marrow, liver, and renal function:

a. Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks):

Absolute neutrophil count (ANC) >1,500/mm^3

Platelet count >75,000/mm^3 (≥100,000/mm^3 for Cohort 1 subjects at sites choosing vinflunine chemotherapy)

Hemoglobin >8.0 g/dL (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)

b. Liver function:

Total bilirubin ≤1.5 x institutional upper limit of normal (ULN) OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN [≤1xULN for Cohort 1 subjects at sites choosing docetaxel chemotherapy]

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5x institutional ULN or ≤5x institutional ULN for subjects with liver metastases (For subjects in Cohort 1 at sites choosing docetaxel chemotherapy, both the ALT and AST values must be ≤1.5×ULN concomitant with alkaline phosphatase of ≤2.5×ULN)

c. Renal function: Creatinine clearance (CrCl) >30 mL/min either directly measured via 24-hour urine collection or calculated using the Cockcroft-Gault formula (Attachment 2).

d. Criterion deleted per amendment 3.

e. Phosphate: <ULN within 14 days of treatment and prior to Cycle 1 Day 1 (medical management allowed)

9. Criterion amended per Amendment 3:
9.1 Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the nature, significance, purpose of, procedures for, and consequences of the study and is willing to participate in the study.

10. A woman of childbearing potential who is sexually active must have a negative pregnancy test (β-human chorionic gonadotropin [βhCG]) at Screening (urine or serum).

11. Criterion amended per Amendment 2:
11.1 Criterion amended per Amendment 3:
11.2 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

For women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy):

- practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

  Examples of highly effective contraceptives include

  user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence: true abstinence when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.)

  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

- agrees to remain on a highly effective method of contraception during the study and for at least 6 months after the last dose of study drug
- agrees to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 6 months after the last dose of study drug
- not breastfeeding and not planning to become pregnant during the study and for at least 6 months after the last dose of study drug

For men who are sexually active with women of childbearing potential:

- agrees to use a condom with spermicidal foam/gel/film/cream/suppository
- agrees to not donate sperm during the study and for at least 6 months after the last dose of study drug
- not planning to father a child during the study or within 6 months after the last dose of study drug

4.2. Exclusion Criteria

4.2.1. Exclusion Criteria for All Subjects

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 randomization.

2. Criterion amended per Amendment 2:
   2.1 Criterion modified per Amendment 3:
   2.2 Active malignancies (ie, requiring treatment change in the last 24 months). The only allowed exceptions are:

   - urothelial cancer.
   - skin cancer treated within the last 24 months that is considered completely cured.
   - localized prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance).
   - localized prostate cancer with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence.

3. Symptomatic central nervous system metastases.

4. Received prior FGFR inhibitor treatment.

5. Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients

6. Criterion amended per Amendment 2:
   6.1 Criterion modified per Amendment 3.
   6.2 Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade.

7. History of uncontrolled cardiovascular disease including:

   a. unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V (Attachment 3) within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months.

   b. QTc prolongation as confirmed by triplicate assessment at screening (Fridericia; QTc >480 milliseconds).

   c. Pulmonary embolism or other venous thromboembolism (VTE) within the preceding 2 months.

8. Known active AIDS (human immunodeficiency virus (HIV) infection), unless the subject has been on a stable anti-retroviral therapy regimen for the last 6 months or more, has had no opportunistic infections in the last 6 months, and has CD4 count >350.

9. Criterion amended per Amendment 3:

9.1 Known active hepatitis B or C infection (unless polymerase chain reaction [PCR]-negative [according to local laboratory range] on all available tests for the past 6 months).

10. Criterion amended per Amendment 3:
10.1 Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, neuropathy, hearing loss).

11. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

12. Major surgery within 4 weeks before randomization.

13. Criterion amended per Amendment 2:
13.1 Criterion modified per Amendment 3:
13.2 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. Examples include ongoing active infection requiring systemic therapy and uncontrolled ongoing medical conditions.

4.2.2. Exclusion Criteria for Cohort 1 Subjects

In addition to the exclusion criteria listed above, any potential subject in Cohort 1 who meets the following criterion will be excluded from participating in the study:

14. Criterion amended per Amendment 2:
14.1 Criterion modified per Amendment 3:
14.2 Criterion modified per Amendment 4:

14.3 For those participating at sites using docetaxel: has a history of severe hypersensitivity reaction (eg, generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to either docetaxel or to other drugs formulated with polysorbate and paclitaxel. At sites using docetaxel, subjects with evidence of interstitial lung disease or active non-infectious pneumonitis are excluded.

4.2.3. Exclusion Criteria for Cohort 2 Subjects

In addition to the exclusion criteria listed above, any potential subject in Cohort 2 who meets any of the following criteria will be excluded from participating in the study:

15. Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. Subjects with vitiligo, diabetes Type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects who

require intermittent use of bronchodilators, inhaled steroids, or local steroid injections are not excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjøgren's syndrome will not be excluded from the study.

16. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

17. Evidence of interstitial lung disease or active non-infectious pneumonitis.

18. Active infection requiring systemic therapy.

19. Received a live virus vaccine within 30 days of first dose.

20. Known allergies, hypersensitivity, or intolerance to pembrolizumab or its excipients.

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 this 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

Treatment Allocation

Central randomization will be implemented in this study. Subjects will be assigned to Cohort 1 or Cohort 2 based upon prior treatment with anti-PD-(L)1 agent. Within each cohort, subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by region (North America vs EU vs rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2), and disease distribution (presence vs. absence of visceral metastases: lung, liver, or bone). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

6. DOSAGE AND ADMINISTRATION

6.1. Erdafitinib

Erdafitinib will be provided as tablets for oral administration. Subjects randomized to Arm 1A and Arm 2A will be instructed to take erdafitinib orally, at a starting dose of 8 mg, once daily for 21 days in a 21-day cycle until disease progression, intolerable toxicity, withdrawal of consent or

decision by the investigator to discontinue treatment. Each dose should be taken at approximately the same time each day, with or without food. 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, tablets must not be broken or chewed. Subjects should avoid consuming grapefruit or Seville oranges due to CYP450 3A4/5 inhibition.

Up-titration Guidelines

All subjects will start erdafitinib 8 mg once daily from Day 1 to Day 14 of Cycle 1. On Day 14 of Cycle 1, a blood sample will be drawn to determine serum phosphate concentration.

- 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 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 4 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 4 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. No concomitant treatment is required for these subjects.

If a dose is missed, then 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. 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 electronic case report form (eCRF).

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, and the 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 may not be re-issued in this study or outside the study (follow study drug accountability guidelines in the Site Investigational Product Manual).

6.1.1. Dose Modifications and Dose Delays for Erdafitinib

Treatment with erdafitinib should be discontinued or modified based on toxicity as described in Table 1. For eye, skin/nail, dry mouth/mucositis, and phosphate toxicity, specific recommendations in the management guidelines are provided in Section 6.1.2.

Table 1: Erdafitinib Dose Modification Rules Based on Erdafitinib-related Toxicity

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 restarting 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) within 28 days. Discontinue drug if unresolved for >28 days.
4	Interrupt drug	Discontinue.

[a] For eye, skin/nail, dry mouth/mucositis, and phosphate toxicity please follow specific recommendations in the management guidelines (Section 6.1.2).
[b] Please refer to Table 2.

- 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 (see dose reduction levels in Table 2). 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 adverse event 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 continued treatment with erdafitinib is in the best interest of the subject. Erdafitinib may be re-started at the same or a lower dose (Table 2) if the sponsor's medical monitor concurs with the assessment.
- If erdafitinib was dose-reduced and the adverse event that was the reason for this dose-reduction has completely resolved, the dose may be re-escalated to the next higher dose if the subject was 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 sponsor's medical monitor concurs 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 parameters) 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.

Table 2: Erdafitinib Dose Reduction Levels

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

6.1.2. Guidance for Specific Erdafitinib Toxicities

6.1.2.1. Grading of Hyperphosphatemia

Hyperphosphatemia will be graded as outlined in Table 3.

Table 3: Grading of Hyperphosphatemia

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hyperphosphatemia	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

6.1.2.2. Guidelines for the Management of Elevated Phosphate Levels

Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 4. Hyperphosphatemia should be graded according to Table 3.

Table 4: 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. Phosphate binders (eg, sevelamer 800 to 1,600 mg TID with food) until phosphate level is <7.00 mg/dL. (See information regarding phosphate binders other than sevelamer in the table footnote.)

Table 4: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom Management
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). Re start 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. Phosphate binders (eg, sevelamer up to 1,600 mg TID with food) until serum phosphate level is <7.00 mg/dL. (See information regarding phosphate binders other than sevelamer in the table footnote.)
>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). Re start 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 re started at 2 dose levels lower if appropriate. Follow other recommendations described above, Section 6.1.1.)	Medical management as clinically appropriate.

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

6.1.2.3. Guidelines for the Management of Dry Mouth and Mucositis

Guidelines for the clinical management of dry mouth (xerostomia) and mucositis are provided in Table 5 and Table 6, respectively.

- **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)

Table 5: Guidelines for Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug Management	Symptom 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 as needed
Grade 2: moderate symptoms; oral intake alterations (eg, copious water, other lubricants, diet limited to purees or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges as needed and Cevimiline 30 mg TID or Pilocarpine 5 mg TID, orally
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 as needed 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

Table 6: 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/territory 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/territory 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/territory 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.		

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

Guidelines for the management of dry skin are provided in Table 7.

- **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 7: Guidelines for Management of Dry Skin

Grade and Definition	Study Drug Management	Symptom 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
*Topical Steroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%		

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

Guidelines for management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) are provided in Table 8. Guidelines for the management of paronychia are provided in Table 9.

- **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)

Table 8: 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: o treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim BID) AND o 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.
BID=bis in die (two times each day).

Table 9: 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 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 one dose level below in consultation with the medical monitor.	Vinegar soaks[a] AND consider nail avulsion 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 [Bactrim] DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.

[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

6.1.2.6. Guidelines for Eye Toxicity Associated with Vision Changes

If a subject experiences an event of confirmed new corneal or retinal abnormality while on study drug, the event should be reported as an adverse event or a serious adverse event (if Grade 3 or higher) as appropriate. 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 4): 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 10: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug Management	Symptom 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 with erdafitinib until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue erdafitinib at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (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 at the next lower dose level after consultation with the sponsor's medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 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. 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 at the next lower dose level after consultation with the sponsor's medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 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 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 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 a serious adverse event and withhold erdafitinib. If 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 continuation of treatment is in the best interest of the subject, then drug may be resumed at 2 dose levels lower if appropriate. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2 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.

Table 10: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug Management	Symptom Management
Grade 4: Sight threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with erdafitinib. Report as a serious adverse event 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.
ADL Activities of Daily Living, OCT Optical Coherence Tomography		

6.1.2.7. 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

6.2. Vinflunine or Docetaxel

Subjects randomized to chemotherapy in Arm 1B will receive vinflunine 320 mg/m^2 as a 20-minute intravenous infusion once every 3 weeks or docetaxel 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. Treatment with either agent will be administered until disease progression, intolerable toxicity, withdrawal of consent or decision by the investigator to discontinue treatment. The choice of which chemotherapy regimen to use at each site will be determined by the investigator.

In cases where toxicity does not resolve to Grade 0-1 within 2 weeks after the last infusion of vinflunine or 4 weeks after the last infusion of docetaxel, study treatment should be discontinued after consultation with the sponsor. With investigator and sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 4 weeks may continue in the study only if asymptomatic and stable.

6.2.1. Vinflunine

Vinflunine, 320 mg/m^2, should be administered after all procedures and assessments for that day have been completed as outlined in the Time and Events Schedule. The body surface area (BSA) in m^2 should be calculated per local institutional practice. Consult the vinflunine summary of product characteristics for instructions on preparation and administration of the vinflunine infusion fluid and recommendations for co-medication (ie, laxatives and dietary measures including oral hydration are recommended from Day 1 to Day 7 after each vinflunine administration). Advice on

conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinflunine.

6.2.1.1. Vinflunine Dose Modifications

In case of WHO/ECOG performance status (PS) of ≥1 or PS of 0 and prior pelvic irradiation, vinflunine treatment should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

In subjects with moderate renal impairment (40 ml/min≤CrCl≤60 ml/min), the recommended dose is 280 mg/m² given once every 3 weeks. In subjects with severe renal impairment (20 mL/min≤CrCl<40 mL/min), the recommended dose is 250 mg/m² given once every 3 weeks.

The recommended dose of vinflunine is 250 mg/m² given once every 3 weeks in subjects with mild liver impairment (Child-Pugh Grade A) or in subjects with a prothrombin time ≥60% normal value and 1.5xULN<Bilirubin≤3xULN and presenting at least one of the following criteria: transaminases >ULN or gamma-glutamyltransferase >5xULN.

The recommended dose of vinflunine is 200 mg/m^2 given once every 3 weeks in patients with moderate liver impairment (Child-Pugh grade B) or in patients with a prothrombin time ≥50% normal value and bilirubin >3×ULN and transaminases >ULN and gamma-glutamyltransferase >ULN.

The doses recommended in subjects ≥75 years old are as follows:

- in subjects at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 3 weeks.
- in subjects 80 years old and beyond, the dose of vinflunine to be given is 250 mg/m² every 3 weeks.

In subjects who initiate vinflunine at 280 mg/m^2 and who experience an AE requiring dose modification, the dose should be reduced to 250 mg/m^2 following the first occurrence and resolution, and discontinued following a second occurrence. In subjects who initiate vinflunine at 250 mg/m^2 and who experience an AE requiring dose modification, the dose should be reduced to 225 mg/m^2 following the first occurrence and resolution, and discontinued following a second occurrence.

Cases of posterior reversible encephalopathy syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms are, as follows: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain. Vinflunine should be discontinued in subjects who develop neurological signs of PRES.

For all grades of neutropenia lasting ≤7 days, hold vinflunine administration until neutrophils recover to >1500 cells/mm^3. For thrombocytopenia Grades 1, 2, 3, hold vinflunine until platelets

recover to >100,000 cells/mm^3. For anemia Grades 1, 2, 3, hold vinflunine until resolution to Grade 1 or baseline. Specific dose modifications for subjects receiving vinflunine are recommended in Table 11. Dose modifications for vinflunine should also be considered according to local product labels.

Table 11: Vinflunine Dose Adjustments for Drug-related Adverse Events

Toxicity	Dose Adjustment				
	Initial Dose: Vinflunine 320 mg/m^2			Initial Dose: Vinflunine 280 mg/m^2	
	First Occurrence	Second Occurrence	Third Occurrence	First Occurrence	Second Occurrence
Neutropenia Grade 4 lasting >7 days (hold treatment until neutrophils >1500 cells/mm^3)	Vinflunine 280 mg/m^2	Vinflunine 250 mg/m^2	Discontinue treatment	Vinflunine 250 mg/m^2	Discontinue treatment
Thrombocytopenia Grade 4 (hold treatment until platelets >100,000 cells/mm^3)					
Anemia Grade 4 (hold treatment until Grade 1 or baseline)					
All other Grade 3 or 4 toxicities (hold treatment until Grade 1 or baseline)					
Neutropenic fever (Temperature ≥100.5°F and ANC≤1000/L)					
Mucositis or constipation Grade 2 ≥5 days or Grade ≥3 any duration [a]					
Cardiac ischemia in subjects with prior history of myocardial infarction or angina pectoris	Discontinue treatment	N/A	N/A	Discontinue treatment	N/A

[a.] NCI CTC Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening"

6.2.2. Docetaxel

Docetaxel, 75 mg/m^2, should be administered after all procedures and assessments for that day have been completed as outlined in the Time and Events Schedule. The body surface area (BSA) in m^2 should be calculated per local institutional practice. All subjects should be premedicated with oral corticosteroids, such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The appropriate premedication regimen may be determined by the investigator.

Cystoid macular edema has been reported in subjects treated with docetaxel. Subjects with impaired vision should undergo a prompt and complete ophthalmologic examination. In case cystoid macular edema is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.

Consult the docetaxel prescribing information for instructions on preparation and administration of the docetaxel infusion fluid, and recommendations for co-medication.

6.2.2.1. Docetaxel Dose Modifications

Docetaxel should not be given to subjects with bilirubin >1x ULN, or to subjects with AST or ALT >1.5 x ULN with concomitant alkaline phosphatase >2.5 x ULN. Subjects with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Docetaxel should also not be given to subjects with a neutrophil count of <1500 cells/mm^3.

Severe fluid retention has been reported following docetaxel therapy. Subjects should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention. Subjects with pre-existing effusions should be monitored closely from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures, eg, salt restriction, oral diuretic(s).

For all grades of neutropenia lasting ≤7 days, hold docetaxel until neutrophils recover to >1500 cells/mm^3. For thrombocytopenia Grades 1, 2, 3, hold docetaxel until platelets recover to >100,000 cells/mm^3. For anemia Grades 1, 2, 3, hold docetaxel until resolution to Grade 1 or baseline. Dose modifications for subjects receiving docetaxel are recommended below in Table 12. Dose modifications for docetaxel should also be considered according to local product labels.

Table 12: Docetaxel Dose Modifications for Drug-related Adverse Events

Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Peripheral Neuropathy				
Grade 1, 2		No	60 mg/m^2	N/A
Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic Fever (defined as T≥100.5°F and ANC≤1000/L) Neutropenia Grade 4 lasting more than 7 days				
	First occurrence	Hold treatment until neutrophils recover to ≥1500/L	Docetaxel: 60 mg/m^2	
	Second occurrence	Hold treatment until neutrophils recover to ≥1500/L	Docetaxel: 50 mg/m^2	Consider treatment discontinuation
	Third occurrence	Yes	N/A	Yes
Thrombocytopenia				
Grade 4	First occurrence	Hold treatment until platelets recover to >100,000 cells/mm^3	Docetaxel: 60 mg/m^2	Consider treatment discontinuation
	Second occurrence	Hold treatment until platelets recover to >100,000 cells/mm^3	Docetaxel: 50 mg/m^2	Consider treatment discontinuation
	Third occurrence	Yes	N/A	Yes
Anemia				
Grade 4	First occurrence	Hold treatment until resolution to Grade 1 or baseline	Docetaxel: 60 mg/m^2	Consider treatment discontinuation
	Second occurrence	Hold treatment until resolution to Grade 1 or baseline	Docetaxel: 50 mg/m^2	Consider treatment discontinuation
	Third occurrence	Yes	N/A	Yes
Non-hematologic toxicity or other hematologic toxicity not described above				
Grade 3, 4	First occurrence	Hold treatment until resolution to Grade 0-1 or baseline	Docetaxel: 60 mg/m^2	Consider treatment discontinuation
	Second occurrence	Hold treatment until resolution to Grade 0-1 or baseline	Docetaxel: 50 mg/m^2	Consider treatment discontinuation
	Third occurrence	Yes	N/A	Yes

6.3. Pembrolizumab

Subjects randomized to immunotherapy in Arm 2B will receive pembrolizumab 200 mg as a 30-minute intravenous infusion once every 3 weeks, until disease progression, intolerable toxicity, withdrawal of consent, or decision by the investigator to discontinue treatment. Pembrolizumab should be administered after all procedures and assessments for that day have been completed as outlined in the Time and Events Schedule. Most immune-related adverse reactions occurring during treatment with pembrolizumab are reversible and managed with interruptions of

pembrolizumab, administration of corticosteroids, and/or supportive care. Immune-related adverse reactions may also occur after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than 1 body system can occur simultaneously.

For suspected immune-related adverse reactions, adequate evaluation to confirm etiology or exclude other causes should be ensured. Please refer to the pembrolizumab prescribing information for specific instructions on how to assess and manage specific immune-related adverse reactions, including pneumonitis, colitis, hepatitis, endocrinopathy, cutaneous, and other adverse reactions.

Consult the pembrolizumab prescribing information for instructions on preparation and administration of the pembrolizumab infusion fluid.

6.3.1. Pembrolizumab Dose Modifications

For dose modifications for pembrolizumab and management of pembrolizumab related adverse events, please refer to the prescribing information.

6.4. Continued Access to Study Drug after the End of Data Collection Timepoint

Subjects may have continued access to study drug on this study in the LTE Phase. The continuation of study drug after the end of data collection timepoint (Section 17.9.1, Attachment 8) is as follows:

- Erdafitinib (Cohorts 1 and 2): Subjects in each cohort who are continuing to derive benefit from erdafitinib as determined by their investigator may continue to receive erdafitinib.

  Provision of erdafitinib may continue until the subject can commercially access study treatment within the local healthcare system, until the investigator decides it is in the best interest of the subject that erdafitinib be discontinued, or until 2 years after local marketing authorization is obtained for the studied indication, whichever comes first. Also, the Sponsor will not provide continued erdafitinib treatment if the final analysis for the respective cohort does not show superiority for erdafitinib treatment, unless the investigator determines that the subject is benefitting from erdafitinib and decides that treatment should be continued. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of the study drugs becomes available during the study or program.
- Pembrolizumab (Cohort 2): For subjects who are continuing to derive benefit from pembrolizumab, provision of pembrolizumab may continue until 2 years after the first dose of pembrolizumab (at start of study) or until the subject can commercially access pembrolizumab within the local healthcare system, whichever comes first.
- Chemotherapy (docetaxel and vinflunine, Cohort 1): Subjects who are continuing to derive benefit from chemotherapy will be switched to commercially supplied chemotherapy within the local healthcare system (outside of this study), at or shortly after the end of data collection timepoint. Provision of chemotherapy may continue in the LTE Phase of this study until the subject can commercially access chemotherapy within the local healthcare system.

After the end of data collection timepoint, only serious adverse events will be reported to the Company safety repository when study drug is supplied by the Sponsor.

Also, in the event of a decision by the Sponsor to allow cross-over to erdafitinib following the final analysis for each respective cohort, investigators will be notified (see Attachment 8 for more details).

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of the amount of study drug (erdafitinib, vinflunine, docetaxel, or pembrolizumab) 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. On PK sampling days, record the time of erdafitinib intake as accurately as possible. 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 CRF. 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.

8. CONCOMITANT THERAPY

Concomitant therapies are to be recorded at the time of screening (within 30 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the CRF.

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 CRF. Caution should be exerted for subjects taking anti-coagulant therapies (see Section 8.3). 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

Permitted medications are to be recorded at the time of screening (within 30 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the eCRF.

- Symptomatic treatment: Supportive care, such as antibiotics, analgesics, transfusions, diet, etc., and concomitant medications for the symptomatic treatment of related toxicities (Grade 1 to 4) may be administered according to the standard of care at the site, and the treating physician's discretion, as clinically indicated.
- Prophylactic medication: Appropriate prophylactic antiemetic regimens may be provided if required, in accordance with institutional practice and current European Society of Medical Oncology guidelines.

- Chronic supportive therapies: Ongoing bisphosphonates and denosumab or other supportive therapies are permitted.
- Palliative radiotherapy: Localized radiotherapy for symptomatic control is permitted, but should not include definitive radiation to target lesions.

8.2. Prohibited Medications

The following concomitant medications are prohibited during the study. The sponsor must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

- Concurrent investigational agents
- Concurrent antineoplastic agents or hormonal anticancer therapy
- For subjects in Arm 1B (both vinflunine and docetaxel):

  Strong inhibitors of the CYP3A4 enzymes. Strong inducers of CYP3A4 should be avoided for subjects receiving vinflunine (see Attachment 5 for strong or moderate CYP3A4 inhibitors and inducers).

  Live vaccines within 30 days prior to the first dose and while participating in the study, and for 3 months following the last dose of study therapy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine
- For subjects in Arm 1B (vinflunine only): QT/QTc prolonging drugs
- For subjects in Arm 2B (pembrolizumab):

  Live vaccines within 30 days prior to the first dose and while participating in the study and for 3 months following the last dose of study therapy.

  Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

8.3. Precautions for Concomitant Medications

The following precautions are advised for subjects in Arms 1A and 2A (erdafitinib):

- 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 5). 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 in the absence of drug-related toxicity.

The impact of moderate CYP2C9 inducers and strong CYP3A4 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 5). 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 5).

- Erdafitinib was shown to inhibit, in in vitro experiments, human P-glycoprotein (P-gp) at concentrations achieved at therapeutic doses in humans. If the compound is administered with drugs that are substrates of P-gp, there is the potential for observing increased concentrations of the substrate drug. Therefore, caution should be exercised for co-administered drugs that are P-gp substrates, such as digoxin, dabigatran, and fexofenadine (https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf); in addition, drugs with a narrow therapeutic index should only be used where the benefit outweighs the potential risk.
- For subjects taking erdafitinib: medications known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) thought to increase serum phosphate levels. Caution should be exercised considering the risk benefit ratio, and more frequent monitoring of phosphate levels during treatment with medications known to increase the serum level of phosphate put in place.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of safety, efficacy, PK, biomarker, and other measurements applicable to this study. Patient reported outcome questionnaires should be completed before any other assessments at each clinic visit.

The number of samples and the blood volume to be collected will vary depending on the number of cycles of the study drug that the subject receives. The maximum amount of blood to be drawn from each subject is estimated to be approximately 30 mL at screening, approximately 300 mL over the course of the first 6 months (8 cycles) of treatment, then approximately 455 mL if the subject remains on treatment for a period of 2 years, and approximately 45 mL at the End-of-Treatment. Unscheduled blood samples may be required for safety issues of individual subjects.

9.1.2. Screening Phase

The Screening Period will consist of a molecular eligibility screening period and a full study screening period. The molecular eligibility assessment period starts with obtaining consent using the Molecular Eligibility Testing Informed Consent Form (ICF) or, if a biopsy is required, the Full-Study ICF, and may occur at any time prior to randomization. Consent for molecular eligibility screening (but not full study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance. Archival

tumor tissue or a fresh biopsy sample will be sent to the central laboratory to be analyzed with an investigational device, even if local FGFR test results are available. Tissue suitable for FGFR testing must be taken from either a metastatic site or from a urothelial tract region or a lesion that is T2 or above. If a fresh biopsy is needed, the subject will sign the full study ICF.

Molecular eligibility can be confirmed using either central or local FGFR test results.

(1) Central Screening: the central laboratory will evaluate subjects for molecular eligibility by analyzing tumor specimens for the presence of selected FGFR gene mutations and translocations. The sponsor or central laboratory/designee will communicate results of the molecular eligibility testing to the site. If a subject meets the molecular eligibility criteria, he or she may continue study screening under the Full-Study ICF for determination of the full-study eligibility. Subjects may by-pass the molecular screening phase of BLC3001 if they have already been molecularly screened by the central laboratory in the context of another Janssen-sponsored study.

(2) Local report with evidence of a study-eligible FGFR mutation or translocation: local historical test results (from tissue or blood) performed at a CLIA-certified or regional equivalent laboratory using the following methods may be used to meet molecular eligibility: local NGS, direct digital counting methods, or the Qiagen Therascreen FGFR RGQ RT-PCR test. The Sponsor must confirm eligibility based on local testing prior to entering full study screening.

- If a subject is enrolled based on local historical testing, a tissue 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 central molecular screening, 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.

The Full Study Screening Period is 30 days before the first dose of study medication on Cycle 1 Day 1. Subjects must meet all of the inclusion and none of the exclusion criteria in Section 4. All information required for randomization purposes must be available at the time of randomization including: ECOG performance status, FGFR alteration type (translocation or mutation), disease distribution (presence or absence of visceral metastases in the lung, liver or bone) based upon baseline radiographic imaging performed during screening window, and prior therapy. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. To re-assess eligibility, retesting will take place during an unscheduled visit in the Screening Phase.

Subjects will be allowed to be re-screened only once for eligibility (both molecular and full study eligibility) if the investigator has a valid reason (eg, true resolution of conditions previously meeting the exclusion criteria, availability of a different tumor tissue for FGFR testing, molecular test internal quality control failure) to re-screen and after consultation with the medical monitor.

9.1.3. Treatment Phase

The Treatment Phase will begin with the administration of the first dose of erdafitinib, vinflunine, docetaxel, or pembrolizumab and will continue until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or study completion (ie, the end of data collection timepoint has been achieved for the respective cohort). However, treatment with study drug may continue after the end of the study data collection timepoint (see Section 6.4 and Attachment 8). Subjects assessed with progressive disease, but for whom the treating physician strongly believes that continuation of study treatment is in their best interest, may be allowed to continue treatment with erdafitinib or pembrolizumab after consultation with the medical monitor (please see guidelines in Section 9.2.2). The subject will continue to follow procedures as outlined in the Time and Events Schedule and receive treatment until such time as the treating physician and the medical monitor agree that further continuation of treatment is no longer providing benefit to the subject. Subjects on erdafitinib, should follow the same visit schedule even when the drug is interrupted.

Adverse events occurring any time after the subject signs the Full-Study ICF and up to 30 days after the last dose of study drug are to be recorded for all subjects (no adverse events will be collected for subjects signing the molecular ICF only). Adverse event information will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. See Section 12 for complete details on adverse event reporting. Concomitant medications used will also be recorded throughout this time period.

Throughout the Treatment Period, the investigator will assess response to therapy using RECIST Version 1.1. 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, until (1) the start of new anti-cancer treatment, (2) disease progression, (3) withdrawal of consent, (4) death, or (5) 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 in the Time and Events Schedule. All subjects should have the End-of-Treatment Visit completed 30 (+7) days after the last dose of study drug, or prior to the starting any subsequent cancer treatment, except for those who have withdrawn consent, died, or have been lost to follow up.

Additional information on reporting of adverse events is provided 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 End-of-Treatment Visit to assess survival status and start of subsequent anti-cancer therapy until death, withdrawal of consent, lost to follow-up, or study completion (ie, the end of data collection timepoint has been achieved for the respective cohort) whichever occurs first as outlined in the Time and Events Schedule. Subjects who do not want to continue in the Follow-up

Phase will be asked to complete and sign a withdrawal of consent form to specify if they agree to have survival data collected or not. Assessments of survival status and alternate anticancer therapies must be recorded in the eCRF. If necessary, this visit can occur by telephone.

9.2. Efficacy Evaluations

Disease assessments will be performed every 6 weeks for the first 6 months and then every 12 weeks for the next 6 months (±7-day window) using date of randomization as reference (regardless of interruptions in treatment), as outlined in the Time and Events Schedule. After the first year, assessments will be performed as clinically indicated. Assessment of responses for solid tumors will be performed according to RECIST (Version 1.1) by investigators. For subjects who discontinue study drug before disease progression, tumor assessments should continue as described in Section 9.1.3.

More frequent radiological assessments are allowed, if clinically indicated/desirable. Identical methodology (computed tomography [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 (FDG-PET), and plain x-rays are not acceptable methods of evaluating disease response in the absence of CT or MRI scans.

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

9.2.1. Evaluations

9.2.1.1. RECIST Assessment of Disease

RECIST 1.1 is an accepted methodology by regulatory authorities. 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 repeated during the study as indicated in the Time and Events Schedule.

9.2.1.2. Radiographic Images Assessment

Computed tomography (CT) scans of the chest, abdomen, pelvis, and any other location where disease is present will be performed at Screening, and at each subsequent disease assessment visit. 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 baseline and at all subsequent response evaluations or in cases where use of CT scan is clinically contraindicated). 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.

9.2.2. Continuation of Treatment After Disease Progression

If the site study team makes an initial assessment of disease progression, and if the subject is clinically stable, treatment with erdafitinib or pembrolizumab may be continued at the discretion of the investigator. Repeat tumor imaging at least 4 weeks after the first tumor imaging indicating progressive disease. If repeat imaging still meets the threshold for PD (eg, ≥20% increase in tumor burden compared to the nadir) but shows no clinically significant increase in tumor burden compared to the previous time point, treatment may be continued as per treatment calendar after consultation with the sponsor. If repeat imaging confirms progressive disease and clinically significant increase in tumor burden compared to the previous time point, subjects will be discontinued from study therapy.

9.3. Pharmacokinetics

Venous blood samples will be collected for determination of plasma concentrations of erdafitinib and alpha-1-acid glycoproteins, total protein, and fraction unbound, if required, at the time points specified in the Time and Events Schedule, for all subjects randomized to erdafitinib arms (Arm 1A and Arm 2A). On PK sampling day C1D14, for morning clinic visits, morning dosing should be withheld until after the PK sample has been obtained in the clinic. For afternoon clinic visits, subjects should take their dose as usual and a post-dose sample should be collected during the visit. On C2D1, the dose should be withheld; upon admission to the site, a PK sample (predose) will be collected and the erdafitinib dose can then be taken. The safety ECG will be recorded at approximately the time of maximal erdafitinib concentration (2-4 hour postdose, see Section 9.7.5) and a second sample will be obtained after the ECG recording. The time of dosing and the time of PK sample must be recorded accurately. If indicated by the emerging safety findings or if the scheduled PK samples are not collected due to treatment interruption, unscheduled blood samples may be collected. The total number of samples and blood volume will not be substantially increased without approval of ethics committees/institutional review boards. The Laboratory Manual provides further information regarding handling and shipment of blood/plasma samples.

9.3.1. Analytical Procedures

Blood samples will be processed to obtain plasma for measurement of erdafitinib concentration by a validated analytical method under the direction of the sponsor. AGP 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.

9.4. Predictive and Pharmacodynamic Biomarkers

Tissue will be collected in this study to determine both PD-(L)1 expression and the bladder cancer subtype of enrolled subjects, and correlation of these factors with FGFR status (presence of mutation or gene fusion) and response to erdafitinib, pembrolizumab, or chemotherapy.

To further elucidate the erdafitinib mechanism of action, the impact of erdafitinib on peripheral immune cells (and tumor immune cell infiltrate, where available) will be assessed. Erdafitinib was observed to increase tumor T cell infiltrate and clonal expansion in a genetically engineered mouse model of lung cancer harboring an FGFR2 mutation (unpublished data). Assessment of peripheral, and tumor immune cell infiltrate in this study, will determine whether these preclinical observations occur in subjects treated with erdafitinib, and whether changes in immune cell number, profile or activation status correlate with clinical response to erdafitinib.

Germline DNA will be collected for subjects on erdafitinib (see Time and Events Schedule) from a blood sample for the purpose of CYP2C9 genotyping to allow exploration of the effect of CYP2C9 polymorphism on the PK of erdafitinib.

Serum phosphate levels will be monitored in subjects treated with erdafitinib as a marker of target engagement. The Phase 1 Study 42756493EDI1001 demonstrated that phosphate levels are a robust pharmacodynamic biomarker, and that achieving target increases in serum phosphate may be associated with clinical response to erdafitinib.

Tissue for Immune Biomarkers and Molecular Subtyping

Tissue collected on study will be used to assess the immune marker status and identify the molecular subtype of subject tumors. Changes in the tumor in response to treatment with erdafitinib (or chemotherapy or pembrolizumab) will be assessed in subjects who provide optional pre- and post-treatment biopsies.

Tissue collected at screening will be used to:

- Assess the status of immune biomarkers, including but not limited to PD-L1 expression, via IHC
- Determine the molecular subtype of tumor samples by RNA sequencing analysis or alternate method.

Initially tissue for PD-L1 expression and subtyping will be collected from all subjects (FGFR-negative and FGFR-positive) during molecular eligibility testing. Once approximately 80 samples are received from FGFR aberration-negative subjects, collections will continue only for enrolled subjects (FGFR aberration-positive) for the remainder of the study. At the time of protocol development, it was estimated that approximately 80 samples are needed to inform PD-L1 expression and bladder cancer subtype in FGFR aberration-negative subjects (see Section 11.5).

The correlation of PD-L1 status and bladder molecular subtype with FGFR alteration status, and response to erdafitinib, chemotherapy, and pembrolizumab, will be assessed.

Optional paired biopsies will be collected pre-treatment (any time during the full screening period prior to dosing on Cycle 1 Day 1), on-treatment (on or within 2 weeks after Cycle 2 Day 1), and at disease progression. To understand if erdafitinib has an impact on tumor immune cell profile, pre- and post-treatment tissue samples will be stained by IHC for expression of immune cell markers including but not limited to CD3, CD4, CD8, FoxP3, CD68, and PD-L1.

Paired biopsies may also be utilized for bladder cancer subtype determination (via RNA sequencing or alternate method) to examine if treatment with erdafitinib (or chemotherapy or pembrolizumab) induces a change in gene expression related to bladder cancer molecular subtype.

Biopsies may also be screened for the presence of FGFR alterations and alterations in other genes to track FGFR status over the course of treatment and explore mechanisms of acquired resistance in response to treatment with erdafitinib (or chemotherapy or pembrolizumab). This may be accomplished via next-generation sequencing or alternate method.

Circulating Biomarkers

Blood samples for circulating biomarker should be collected predose at timepoints specified in the Time and Events Schedule. Collection of samples may cease or time points may be modified based on emerging data.

Peripheral Immune Cell Profiling

Profiling of peripheral immune cells and determination of activation status will be performed in blood samples collected on study, via flow cytometry. T cell and Treg enumeration and T cell activation status will be assessed at certain sites. Profiling of additional immune cell types, eg, natural killer cells (NK) and myeloid derived suppressor cells (MDSCs), may also be performed in blood. RNA sequencing, Nanostring, or alternate methodology may also be applied, where appropriate.

T cell receptor sequencing will be performed to assess changes in T cell receptor clonality induced by treatment with erdafitinib (or chemotherapy or pembrolizumab).

Circulating Tumor DNA

Blood for analysis of circulating tumor DNA (ctDNA) will be collected at multiple time points on study. Analysis of ctDNA offers the potential of a non-invasive method to identify subjects for molecularly-based targeted therapies, and to follow the emergence of response or resistance to treatment. 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. The aim is to identify alterations in FGFR and other genes in blood as markers of response or resistance to erdafitinib, and to determine whether blood could serve as a suitable alternative to tumor tissue for detection of FGFR alterations.

Circulating tumor DNA may 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 changes in the levels or types of genetic alterations observed over time, and to monitor for the emergence of potential markers of resistance to erdafitinib, pembrolizumab, or chemotherapy.

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 disease and mechanisms of response or resistance to the erdafitinib, pembrolizumab, or chemotherapy.

Adjustments in the timing of biomarker collections may be made during the study based on emerging data, however the number or volume of biomarker sampling will not increase.

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.

9.5. Patient Reported Outcomes

Patients health-related quality of life, symptoms, functioning, and general well-being will be captured using 3 PRO measures: the FACT-Bl, PGIS, and the EQ-5D-5L. The PRO measures will be collected electronically, if feasible, according to the Time and Events Schedule, to understand change over time and difference between treatment groups in each cohort. EQ-5D-5L will be collected in the Follow-up Phase until start of subsequent anti-cancer therapy.

The FACT-Bl consists of 39 core items, with 5-point Likert response scales, covering 5 primary domains: physical well-being, social/family well-being, emotional well-being, functional well-being and bladder symptom subscale. The answer scales range from “Not at all” to “very much”. The FACT-Bl will be used to support PRO hypothesis testing (see Section 11.6).

The PGIS is a single question regarding the patient report of disease severity: Considering all aspects of your bladder cancer symptoms right now would you say your bladder cancer symptoms are none, mild, moderate, severe, or very severe? The PGIS is an anchor question that will be used to establish the magnitude of meaningful change in this study.

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) (Herdman 2011). The scores for the 5 separate questions are categorical and are cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L asks respondents to select their response based on their current health (“today”) and takes less than 5 minutes to complete.

9.6. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects at the disease assessment visits. Protocol mandated procedures, tests, and encounters are excluded. The data collected will be used to conduct exploratory analyses that may be used to support the value story and cost-effectiveness modeling for market access. The data collected may include:

- Number and characteristic of diagnostic and therapeutic tests procedures (inpatient and outpatient)
- Number and duration of hospitalization (total length of stay [days]), including duration by each hospital unit (intensive care unit)
- Outpatient medical encounters (including physician, nurse practitioner or emergency room visits, tests and procedures)
- Please see eDC manual for more details.

9.7. Safety Evaluations

This study will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse event and serious adverse event 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 (SMT) will review the safety data routinely and will investigate specific safety queries. The SMT will review all serious adverse events.

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, clinical laboratory tests, ECOG performance status, ophthalmologic examinations, and other safety evaluations at specified time points as described in the Time and Events Schedule.

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 adverse events such as skin/nail and mucosal toxicity, upon subject consent, photographs may be taken for assessment and monitoring of the toxicity.

9.7.1. 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 time of a signed and dated Full-Study ICF until 30 days after the last dose of study drug. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Adverse events will be graded according to the NCI-CTCAE, Version 4.03. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. During the LTE Phase (Attachment 8), only serious adverse events will be reported to the Company safety repository, which will be conducted as specified in Section 12.3.2 using the appropriate serious adverse event reporting method.

9.7.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected according to the 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 adverse event section of the eCRF.

Laboratory test results completed on Cycle 1 Day 1 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 by the local laboratory:

Hematology Panel

-hemoglobin
-platelet count
-white blood cell (WBC) count and ANC only

Serum Chemistry Panel

-alanine aminotransferase (ALT)
-aspartate aminotransferase (AST)
-total bilirubin
-chloride
-bicarbonate; only applicable if the test is locally available
-creatinine
-potassium
-sodium
-magnesium
-alkaline phosphatase

Serum phosphate, serum parathyroid hormone, calcium (or, if applicable, corrected calcium in the case of hypoalbuminemia), and albumin will be tested for all subjects at screening.

For subjects in Arms 1A and 2A only:

- Serum phosphate, calcium (or, if applicable, corrected calcium in the case of hypoalbuminemia), and albumin is required on C1D1, C1D14, C2D1, C2D14, C3D1, C3D14 and then from Cycle 4 onwards, only on Day 1 and at the EOT visit.

Serum parathyroid hormone is required on C1D1, C1D14, C2D1, C2D14, C3D1, C3D14, C4D1, C5D1, C6D1 and then every third cycle thereafter on Day 1 and at the EOT visit.

Thyroid stimulating hormone and free thyroxine 4 will be tested for all subjects at screening, and every other cycle from Cycle 2 for subjects in Arm 2B only.

9.7.3. Renal Toxicity Evaluation

Creatinine or creatinine clearance will be determined per institutional standard.

9.7.4. Urine or Serum Beta-hCG Pregnancy Test

A urine or serum sample will be obtained for a pregnancy test (β-hCG) in sexually active female subjects of child-bearing potential at screening within 7 days of the first dose and at End-of-Treatment. Additional serum or urine pregnancy tests will be performed on Day 1 of every cycle, to establish the absence of pregnancy at any time during the subject's participation in the study.

9.7.5. Electrocardiogram

12-lead electrocardiograms (ECGs) will be performed at any time during the screening period. Postdose ECGs for subjects in Arm 1A and Arm 2A should be recorded 2 to 4 hours after the erdafitinib dose on Cycle 2 Day 1 and, if possible, 2 to 4 hours after the erdafitinib dose on Cycle 4 Day 1. Postdose ECGs for subjects in Arm 1B and Arm 2B should be recorded as soon as possible upon completion of infusion on Cycle 2 Day 1 and Cycle 4 Day 1. Additional ECGs may be performed during the study as clinically indicated.

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- to 10-minute intervals between each assessment. At least 1 printout of all 3 ECGs 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 (Fridericia) 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).

9.7.6. Ophthalmologic Examination

All subjects should have an ophthalmologic 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) should 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 central serous retinopathy (CSR)/retinal pigment epithelial detachment (RPED) is suspected, or fundoscopic retinal abnormalities are observed, as well as each time ocular adverse events 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 Retinal 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 scans for enrolled subjects 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 (Attachment 4) testing will be administered to all subjects at Screening and during the treatment phase only to subjects in Arm 1A and Arm 2A according to the 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 and otherwise normal ophthalmologic exam at baseline at baseline (during Screening), then 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.

9.7.7. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and temperature will be assessed. Abnormalities will be recorded as AEs.

9.7.8. Physical Examination

A full physical examination, including neurological examination, height, and weight will be performed at screening. Subjects should have a repeated physical examination at Cycle 1 Day 1 prior to dosing if the previous one during screening occurred more than 7 days before first dosing. Limited physical examinations of involved organs, neurological examination, and weight, will be performed at subsequent visits as listed in the Time and Events Schedule. New abnormalities will be recorded as AEs.

9.7.9. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status grade will be determined at pre-specified time points listed in the Time and Events Schedule. Subjects should have a repeated ECOG assessment at Cycle 1 Day 1 prior to dosing if the previous one during screening occurred more than 7 days before first dosing. The scoring information is provided in Attachment 1.

9.8. 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 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

10.1. Completion

A subject will be considered as having completed the study if he or she has died during the study or has not been withdrawn by study completion (ie, at the end of data collection timepoint).

10.2. Discontinuation of Study Treatment/Withdrawal From the Study

Discontinuation of Study Treatment

A subject who discontinues study treatment will continue to participate in the study for follow-up of survival status, subsequent anti-cancer therapy, EQ-5D-5L completion, and resolution of any ongoing drug-related AEs. For subjects who discontinue treatment before disease progression, every effort should be made to continue to monitor their disease status according to the Time and Events Schedule (see Section 9.1.3).

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons, tolerability reasons, or impairment of the subject's well-being (eg, due to AEs such as those described in Section 6) it is in the best interest of the subject to discontinue study treatment
- The subject experiences an AE that, as described in Section 6, should result in discontinuation of study drug
- The subject becomes pregnant; discontinuation of study treatment in this instance should be discussed with the medical monitor
- Progression of disease is assessed

  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 erdafitinib or pembrolizumab until such time as the treating physician and the medical monitor agree that further continuation of treatment is no longer beneficial to the subject.
- The subject refuses further treatment with the study drug
- The sponsor terminates the study
- Investigator decision approved by the sponsor

If a subject discontinues treatment, an End-of-Treatment Visit should be conducted 30 (+7) days of the subject's last dose of study drug. The primary reason for treatment discontinuation will be clearly documented in the subject's medical record and recorded in the eCRF. Once a subject discontinues treatment with the study drug, the subject will not be permitted to be retreated.

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 consent before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. In addition, subjects who withdraw consent must complete and sign a withdrawal of consent form to specify if they agree to have survival data collected or not. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects may be replaced only if the subject withdrew prior to the study drug administration.

10.3. Withdrawal from the Use of Research Samples

The subject may withdraw consent for use of samples for future 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. Subject Information

The analysis populations are defined as:

1. Intent-to-Treat (ITT) population: defined as all randomized subjects. Subjects in this population will be analyzed according to the treatment to which they are randomized.
2. Pharmacokinetic-evaluable population: defined as all randomized subjects who received at least 1 dose of erdafitinib and had at least 1 evaluable pharmacokinetic sample obtained posttreatment.
3. Biomarker population: defined as all randomized subjects with at least 1 biomaterial available and who have consented to participate in the study's biomarker evaluations.
4. Safety population: defined as all randomized subjects who received at least 1 dose of study drug. Safety data will be analyzed according to the actual treatment received.

The ITT population will be used to summarize the study population and characteristics, efficacy, PRO data, and health economic data; the safety population will be used to summarize the safety data, unless otherwise specified.

11.2. Sample Size Determination

Cohort 1 will enroll approximately 280 subjects (approximately 140 subjects to each arm). The data cutoff date for the final analysis will be when approximately 208 death events have occurred. Assuming 53% improvement in median OS of the erdafitinib arm over the chemotherapy arm (a hazard ratio [HR] of 0.65 for the erdafitinib relative to chemotherapy group, under the exponential distribution assumption), the study has at least 85% power to detect a HR of 0.65 at a statistical significance level of 5% (2-sided) with one interim analysis for efficacy at an approximately 65% information fraction (approximately 136 deaths) and a final analysis.

Cohort 2 will enroll approximately 350 subjects (approximately 175 subjects to each arm). The data cutoff date for the final analysis will be when approximately 264 death events have occurred. Assuming 46% improvement in median OS of the erdafitinib arm over the pembrolizumab arm (a hazard ratio of 0.69 for the erdafitinib relative to the pembrolizumab group, under the exponential distribution assumption), the study has at least 85% power to detect an HR of 0.69 at a statistical significance level of 5% (2-sided) with one interim analysis for efficacy at an approximately 65% information fraction (approximately 172 deaths) and a final analysis.

The randomization for both cohorts is stratified by the following factors: region (North America vs EU vs rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2) and the presence of visceral metastases (yes, no).

11.3. Efficacy Analyses

Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, quartiles, and ranges will be used. For discrete variables, frequency will be summarized. For time-to-event variables, Kaplan-Meier (KM) estimates will be provided, and a stratified log-rank test will be used. The type 1 error will be controlled at 5% (2-sided) only within each cohort. All tests will be conducted at a 2-sided alpha level of 0.05, and 95% confidence intervals (CI) will be provided, unless stated otherwise. Each cohort will be analyzed separately.

11.3.1. Primary Endpoint

The primary endpoint is OS. The primary efficacy analysis will be based on the ITT population that includes all randomized subjects in each cohort. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group within each cohort. The stratified log-rank test will be used to compare survival curves of OS between the 2 treatment arms. The stratification factors to be used in the analysis are as follows: region (North America vs EU vs rest of world), ECOG performance status (0 or 1 vs 2), and disease distribution (presence vs absence of visceral metastases: lung, liver, or bone). Pre-specified strata combining will be implemented when some strata have too few OS events, as specified in the SAP.

Additionally, the hazard ratio for erdafitinib relative to the control and its associated 95% CI will be calculated based on the Cox proportional hazards model.

11.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed in Section 2.1.2. PFS will be analyzed the same as OS. Kaplan-Meier method will be used to estimate the distribution of DOR. ORR will be analyzed by Cochran-Mantel-Haenszel chi-square test for randomized subjects with measurable disease at baseline. The analyses of the secondary efficacy endpoints will include all randomized subjects (ITT subjects) unless otherwise specified. The family-wise type 1 error will be strongly controlled at 5% (2-sided) for the secondary efficacy endpoints. Specific details will be provided in the SAP.

11.3.3. Subgroup Analyses

The primary efficacy and secondary efficacy endpoints will be analyzed by each subgroup. A list of subgroups and their definitions will be described in the SAP.

11.3.4. Baseline Assessments

All demographic and baseline characteristics will be summarized for the ITT population. The baseline value is defined as the value collected at the time closest to but prior to the randomization.

11.4. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

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

Population PK analysis of plasma concentration-time data of erdafitinib may be performed using nonlinear mixed-effect modeling. Previously developed PK models may be used and updated as considered appropriate. Relationships between plasma concentrations or metrics of systemic exposure and CYP2C9 polymorphism, markers of pharmacological activities, efficacy or treatment-emergent adverse events may also be explored as data allow using population approaches. Results of the analyses will be provided in a separate report.

11.5. Biomarker Analyses

PD-L1 high rate by immunohistochemistry in FGFR alteration-negative, molecular-screening non-qualified subjects, will be compared with PD-L1 high rate in FGFR alteration-positive subjects. At least 80 FGFR alteration-negative subjects will be tested for PD-L1 status in tumor tissue. All enrolled FGFR alteration-positive subjects will be tested for PD-L1 status. Assuming the PD-L1 high rate in FGFR alteration-negative subjects is 40% and the PD-L1 high rate in FGFR alteration-positive subjects is 15%, the estimated sample size will have at least 80% power to achieve a statistical significance level of 5% (2-sided).

Within each cohort, approximately 45 subjects in the erdafitinib arm and approximately 15 subjects in the comparator arm (a total of 60 subjects per cohort) represent the minimum number of subjects whose samples are anticipated to be tested via flow cytometry and TCR sequencing. Samples from approximately 45 subjects in the erdafitinib arm will produce a 2-sided 90% CI with a width equal to 0.25 when 50% of subjects in each erdafitinib arm achieve at least 20% relative change from baseline to post-baseline. Sample collections will continue until at least 45 subjects are enrolled in the erdafitinib arm of each cohort to support these analyses, or until collections are no longer needed, as data warrant.

Blood for ctDNA analysis will be collected from all subjects on study. Sample size calculations were performed to determine how many samples needed to be tested in order to observe the emergence of markers of resistance to erdafitinib treatment. For subjects treated with erdafitinib,

samples from approximately 145 subjects among responders and approximately 145 subjects among non-responders will be assayed by next-generation sequencing of ctDNA. This sample size produces a 2-sided 95% CI with a width equal to 0.15 when the acquired resistance (among responders) and intrinsic resistance (among non-responders) proportion in each group is 0.30. Samples not tested and samples collected from the comparator arms will be stored for future investigation into the mechanisms of resistance and comparison with prior findings.

For each of the biomarker samples sizes estimated above, the number of subjects for which samples are collected may be modified based on emerging data. Collections may continue, stop, or time points modified based on emerging data.

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

Changes in molecular markers (FGFR or other genes), bladder cancer subtype markers, immune cells or markers, and phosphate over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and clinical response will be explored.

11.6. Medical Resource Utilization and Patient Reported Outcomes Analyses

Medical resource utilization and Patient-reported Outcomes will be summarized descriptively by treatment group. Additional analyses may be conducted; details and results of any additional analyses will be presented in a separate report.

The hypothesis is that patient reported time to urinary symptom deterioration will be delayed as measured by relevant items in the FACT-Bl. Further, time to meaningful functional deterioration will be significantly longer as measured by the Physical Well-being Scale (FACT-Bl).

11.7. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided. Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Electrocardiograms

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT corrected according to Fridericia's formula (QTcF) (ICH E14 2005).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T wave morphology or the occurrence of U waves.

ECOG PS

ECOG scores will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

11.8. Interim Analysis

There is one planned interim analysis for each cohort. The interim analyses are planned after an approximately 65% information fraction (approximately 136 of 208 deaths) in Cohort 1 and (approximately 172 of 264 deaths) in Cohort 2 will have occurred. Both superiority and futility will be assessed for Cohort 1 and Cohort 2. The classical O'Brien-Fleming boundaries will be used for these assessments. The stopping boundaries will be implemented by Lan-DeMets spending function to control the Type 1 error at the 0.05 significance level overall for each cohort. The futility assessment for each cohort is not binding. Also, each cohort may be stopped when the HR is 1.0 or greater, taking into consideration the totality of the data. Specific details will be provided in the interim analysis plan (IAP).

Procedures will be in place to ensure that the results of the interim analysis do not influence the conduct of the study, investigators, or subjects.

11.9. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be commissioned for reviewing safety and efficacy data from this study. For each cohort, a review of the safety data will be performed after at least 60 subjects have been enrolled in that cohort and every 6 months thereafter. The IDMC will review the interim efficacy and safety analysis results for each cohort and will make recommendations regarding study continuation based on the pre-specified boundary and the guidance on futility as outlined in the IAP. The IDMC will consist of at least three medical experts in the relevant therapeutic area and at least one statistician. The details will be provided in a separate IDMC 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 adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

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

Unsolicited Adverse Events

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or noninvestigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 -noninvestigational) product, whether or not related to that medicinal (investigational or -noninvestigational) product. (Definition per International Council for 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 adverse events starting with the signing of the Full Study ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and 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 one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For erdafitinib, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For vinflunine, docetaxel, and pembrolizumab, the expectedness of an adverse event will be determined by whether or not it is listed in the corresponding package insert/summary of product characteristics.

Adverse Event Associated with the Use of the Drug

An adverse event 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 adverse event that is not related to the use of the drug.

Doubtful

An adverse event 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 adverse event 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 adverse event 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 adverse event 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 adverse event. The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE, Version 4.03. Any adverse event or serious adverse event not listed in the NCI-CTCAE, Version 4.03 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 adverse event.

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 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
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated Full-Study ICF (no adverse events will be collected for subjects signing the molecular ICF only) is obtained until 30 days after last dose of study drug. 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. Serious adverse events, including those spontaneously reported to the investigator within 30 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. Adverse events that occur between signing the ICF for assessment of molecular eligibility and before signing the full study eligibility screening ICF will not be collected.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 6. Some countries/territories require reporting of all adverse events to health authorities, eg, Japan will not identify anticipated events for the health authorities.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. 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 CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events 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 serious adverse events 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 serious adverse events 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 serious adverse events 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 a serious adverse event should be made by facsimile (fax).

All serious adverse events 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 a serious adverse event. 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 a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (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 CRF). 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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. (Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event).
- Administration of blood or platelet transfusion. (Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.)
- Procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling) (Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event).
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.

12.3.3. 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 serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study should be withdrawn from the study after consultation with the sponsor's medical monitor.

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 requested. Follow-up information may continue to be collected up to 12 months after the birth of a baby, if a congenital anomaly or significant medical condition is diagnosed at birth.

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

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

Progression of disease should not be considered nor should be reported an AE (or serious adverse event). 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 (see Section 12 Adverse Event Reporting).

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 a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event 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. Refer to the Investigator's Brochure for a list of excipients.

Vinflunine 250 mg (25 mg/mL) will be provided by the sponsor.

Docetaxel 80 mg (20 mg/mL) will be provided by the sponsor.

Pembrolizumab 100 mg (25 mg/mL) will be provided by the sponsor.

14.2. Packaging

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

Vinflunine 250 mg (25 mg/mL) will be packaged as 1 vial in a non-resistant carton.

Docetaxel 80 mg (20 mg/mL) will be packaged as 1 vial in a non-resistant carton.

Pembrolizumab 100 mg (25 mg/mL) will be packaged as 1 vial in a non-resistant carton.

14.3. Labeling

The study drugs must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Study-site personnel will instruct subjects on how to store study drugs for at-home use as indicated for this protocol. Subjects should be advised to keep all medications out of reach and sight of children.

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

14.4. Preparation, Handling, and Storage

Refer to the pharmacy manual/study site investigational product and procedures 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. For erdafitinib, the dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. For vinflunine, docetaxel, and pembrolizumab, the study drug administered to the subject must be documented on the drug accountability form. All 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, and study drug returned by the subject, 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, or used returned study drug for destruction, 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, vials, or infusion bags 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 drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. 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:

- Erdafitinib Investigator's Brochure
- Vinflunine SmPC
- Docetaxel Package Insert or SmPC
- Pembrolizumab Package Insert

- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- NCI-CTCAE Version 4.03
- PRO completion guidelines
- RECIST guidelines Version 1.1
- IVRS/IWRS Manual
- eDC Manual
- eSource Manual
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a Phase 3, multicenter, open-label randomized study to evaluate the efficacy and safety of erdafitinib, an oral pan-FGFR-inhibitor with pharmacodynamic adaptation of dose (starting dose of 8 mg once daily with potential up-titration to 9 mg once daily based on observed phosphate level on Study Day 14) compared to vinflunine, docetaxel or pembrolizumab in subjects with metastatic or surgically unresectable urothelial cancer with select FGFR genetic alterations 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 an anti-PD-(L)1 agent (Cohort 2).

The collective experience from both the Phase 1 and current ongoing global Phase 2 trials, suggest that the proposed regimen is likely to be well tolerated. Objective tumor response is reported with erdafitinib in this specific population; with ORR of 70.0% (7/10 subjects) for response-evaluable subjects with urothelial cancer in the 9 mg once daily regimen in the Study EDI1001 and ORR of 39.7%, including confirmed and unconfirmed CR and PR, in the 8 mg once daily regimen in Study BLC2001. For subjects in the 8 mg once daily group whose dose was increased to 9 mg, ORR was 50.0%.

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 adverse events of the study, and provide their consent voluntarily will be enrolled.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the trial, as outlined in the Time and Events Schedules.

The total blood volume to be collected is considered to be within the normal range allowed for this adult subject population over this time frame (North Shore LIJ 2014).

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- or /territory-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)
- Investigator's Brochure (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.

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 Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events 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 (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements indicating that he or she understands the nature, significance, purpose of, procedures for, and consequences of the study and is willing to participate in the study. 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.

Informed consent for molecular eligibility may be obtained remotely.

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 treating physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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.

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.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative] must be informed about the study as soon as possible and give consent to continue.

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/territories.

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, and PK 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, vinflunine, docetaxel, or pembrolizumab, to understand urothelial cancer, to understand differential drug responders, and to develop tests/assays related to erdafitinib, vinflunine, docetaxel, or pembrolizumab, and urothelial cancer. 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 Samples in Future Research.

16.2.6. Country/Territory Selection

This study will only be conducted in those countries/territories 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 CRF 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/territory, 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 informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; 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). Missing PRO data form will be recorded directly into the CRF and will be considered as source data. The minimum source documentation requirements for Section 4.1 and Section 4.2 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 the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. 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 CRF 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 CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, 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 CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF 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.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, 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 CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF 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 CRF 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 CRF 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

CRF 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.

17.9. Study Completion/Termination

17.9.1. Study Completion (ie, End of Data Collection Timepoint) and End of Study

Study Completion (ie, End of Data Collection Timepoint)

The **study is considered completed** at the time of the end-of-data-collection timepoint for both study cohorts. The-end-of-data-collection timepoint is defined as when the clinical cutoff at final analysis has been achieved. At that time, participation in the Follow-Up Phase and will end and the data collection will conclude. (For Cohort 1, the Sponsor will notify the investigators if the interim analysis will be considered the final analysis.)

The subject completion definition is provided in Section 10.1

End of Study

The **end of study** is defined as when the last subject receives the last dose of study drug on the study.

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, eg in case of unacceptable risk, intolerable toxicity, or change in the risk/benefit profile; this might include recurrence of adverse events of which character, severity, or frequency is new in comparison to the existing risk profile. Data derived from other clinical trials or toxicology studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study. 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.

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 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 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 exploratory 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 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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.

REFERENCES

Bajorin DF (1999), Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol. 1999;17(10):3173–3181.

Bellmunt J (2014), Orsola A, Leow JJ, et al on behalf of the ESMO Guidelines Working Group. ESMO Guidelines: Bladder cancer: ESMO Practice Guidelines for Diagnosis, Treatment, and Follow-up. Annals of Oncology. 2014;25(suppl 3):iii40-iii48.

Bellmunt J (2009), Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27(27):4454-4461.

Choi W (2017), Ochoa A, McConkey DJ, et al. Genetic alterations in the molecular subtypes of bladder cancer: Illustration in the Cancer Genome Atlas Dataset. Eur Urol. 2017;72(3):354-365.

Choi W (2014), Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014;25(2):152-165.

Damrauer JS (2014), Hoadley KA, Chism DD, et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. Proc Natl Acad Sci USA. 2014;111(8):3110-3115.

Davarpanah NN (2017), Yuno A, Trepel JB, Apolo AB. Immunotherapy: a new treatment paradigm in bladder cancer. Curr Opin Oncol. 2017;29(3):184-195. doi: 10.1097/CCO.0000000000000366.

Ferlay J (2013), Steliarova-Foucher E, Loret-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49:1374.

Herdman M (2011), Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-1736.

Howlader N (2016), Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2015). ICH Harmonized Tripartite Guideline E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. ICH 12 May 2005.

Karajannis MA (2006), Vincent L, Direnzo R, et al. Activation of FGFR1beta signaling pathway promotes survival, migration and resistance to chemotherapy in acute myeloid leukemia cells. Leukemia. 2006;20(6):979-986.

Lerner SP (2017), Robertson G, Kim J, et al. Comprehensive molecular characterization and analysis of muscle-invasive urothelial carcinomas. J Clin Oncol. 2017;35(15_suppl):4500-4500.

McCaffrey JA (1997), Hilton S, Mazumdar M, et al. Phase II Trial of Docetaxel in Patients with Advanced or Metastatic Transitional-Cell Carcinoma. J Clin Oncol. 1997;15:1853-1857.

Miller L (2017). The rapid uptake of immunotherapy in bladder cancer. Targeted Oncology June 16, 2017. http://www.targetedonc.com/publications/targeted-therapy-news/2017/june-2017/the-rapid-uptake-of-immunotherapy-in-bladder-cancer.

National Comprehensive Cancer Network (NCCN) Guidelines, Bladder Cancer Version 2.2017.

North Shore LIJ. Human subject protection program guidance document: Maximum blood draw limits. 2013.Available at: http://www.feinsteininstitute.org/wp-content/uploads/2013/02/Maximum-Blood-Draw-Limits.pdf. Accessed on 31 October 2014.

Roidl A (2009), Berger HJ, Kumar S, et al. Resistance to chemotherapy is associated with fibroblast growth factor receptor 4 up-regulation. Clin Cancer Res. 2009;15(6):2058-2066.

Rosenberg JE (2016), Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909-1920.

Seiler R (2017), Ashab HA, Erho N, et al. Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol. 2017; pii: S0302-2838(17)30251-8. doi: 10.1016/j.eururo.2017.03.030.

Sharma P (2017), Retz M, Siefer-Radke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18(3):312-322.

The Cancer Genome Atlas (TCGA) Research (2014). Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014;507(7492):315-322.

Yafi FA (2011), North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. Current Oncology. 2011;18(1):e25-e34.

Attachment 1: ECOG Performance Status

Grade	ECOG Performance Status Grade
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;596:649-655.

Attachment 2: Cockcroft-Gault Formula for Estimated Creatinine Clearance

$$eCR = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dL}^{l})}$$

OR

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

Where Constant = 1.23 for men and 1.04 for women

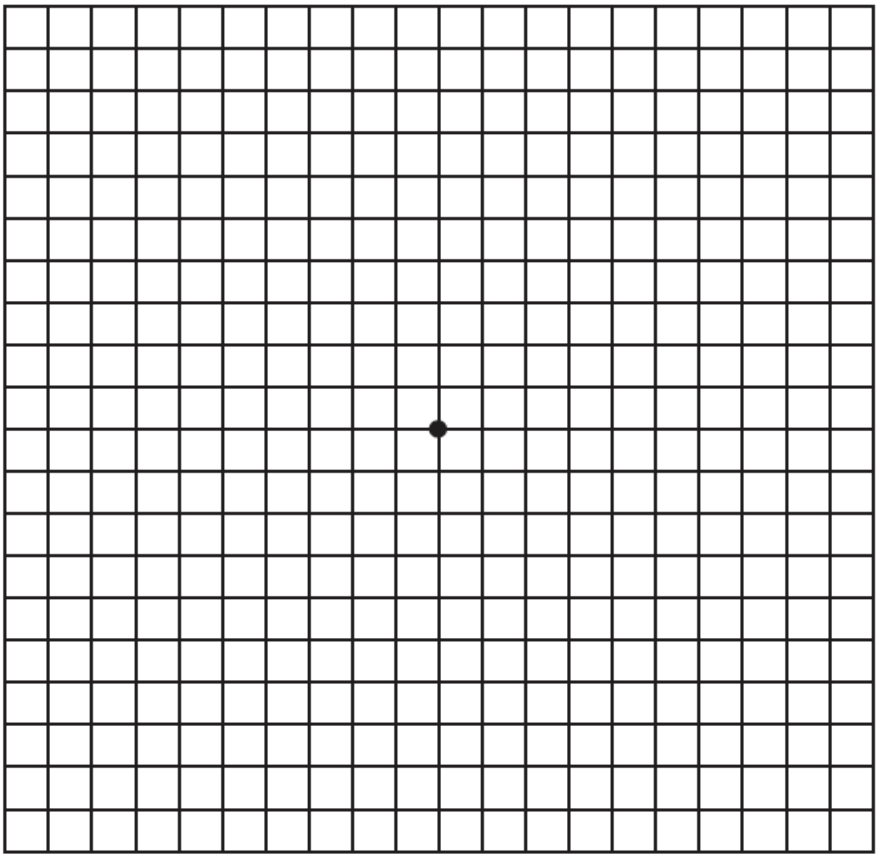
[l]http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

Attachment 3: 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 4: Amsler Grid



Attachment 5: Drugs Classified as Strong or Moderate in Vivo Inhibitors and Inducers of CYP3A4/2C9 Enzymes

Strong CYP3A4 Inhibitors

boceprevir	conivaptan
clarithromycin	indinavir
grapefruit juice	itraconazole
lopinavir	ketoconazole
mibefradil	ritonavir
nefazodone	nelfinavir
posaconazole	erythromycin
saquinavir	troleandomycin
telaprevir	
telithromycin	
voriconazole	
fluconazole	

Strong Inhibitors: ≥5 fold increase in AUC or ≥80% decrease in clearance.

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 6: Anticipated Events

Purpose

This appendix applies only to the reporting of anticipated events by the Sponsor to the US FDA, and US-based Investigators and IECs/IRBs, in accordance with the FDA's guidance. The intent is to minimize the submission of a multitude of uninformative IND safety reports to these recipients.

Definition of an Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs, independent of exposure to study treatment, as a consequence of (a) the underlying disease or condition under investigation, (b) characteristics of the study population (eg, age), or (c) the background treatment regimen.

Background

The FDA acknowledges that certain serious adverse events can be anticipated to occur commonly in the study population regardless of drug exposure. Although these anticipated serious adverse events may meet the definition of unexpected (ie, SUSARs), because they are not listed in the IB, they do not warrant expedited reporting as individual cases, or even in aggregate if the incidence is consistent with the expected background rates in the study population.

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
hydronephrosis
urine flow decreased, including oliguria
urinary retention
urinary tract obstruction
urinary tract stoma complication
urinary tract pain
urinary tract infection
urosepsis

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events.

To meet US safety reporting, the Sponsor's Safety Assessment Committee (SAC) will periodically perform aggregate analysis of anticipated events per the Anticipated Events Safety Monitoring Plan (ASMP) (see below). If an anticipated event is determined to occur more frequently in the experimental arm(s) of the study and there is a reasonable possibility that the anticipated event could be drug-related, the Sponsor will prepare an aggregate safety report for reporting of these events to FDA and US-based IRBs/ECs and Investigators.

Sponsor's Safety Assessment Committee (SAC)

The Sponsor's SAC is an established safety committee, independent of the study team, that performs reviews of prespecified anticipated events at an aggregate level. 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. The SAC will consider in its analysis all relevant drug development data, in addition to the clinical study data.

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 (ASMP).

Attachment 7: Guidance on Study Conduct for Enrolled Subjects During a National Disaster

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 subject 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 judgement 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 judgement, 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 case report form. 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 and for molecular eligibility screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent.

Attachment 8: Long-Term Extension Phase with Potential Cross-over to Erdafitinib

The purpose of the Long-term Extension (LTE) Phase is to provide continued study drug to subjects, while minimizing data collection burden. Subjects in the respective cohort who are continuing to derive benefit from study drug, as determined by their investigator may have continued access to study drug in the LTE Phase of this study (see Section 6.4). As an alternative to entering the LTE Phase, subjects may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. (Also, potential cross-over to erdafitinib treatment is discussed below under "Study Treatment Administration".)

The LTE Phase for a given cohort begins with the approval of Amendment 6 and with achievement of the final analysis for that cohort. (For Cohort 1, the Sponsor will notify the investigators if the interim analysis will be considered the final analysis.)

Upon initiation of the LTE Phase, participation in the Follow-Up Phase will end and study data collection will conclude in the clinical database. During this LTE (when study drug will be supplied by the Sponsor after the data collection timepoint), only serious adverse events will be reported to the Company safety repository, which will be conducted as specified in Section 12.3.2 using the appropriate serious adverse event reporting method. No analyses other than routine periodic safety review encompassing reported serious adverse events are planned for the LTE.

Criteria to Cross-over to Erdafitinib

Subjects entering the LTE Phase will continue to receive the study drug that they were receiving at the time of transition to LTE. However, the Sponsor may decide to allow cross-over to erdafitinib if superiority for erdafitinib for the primary objective of the respective cohort is achieved and based on the IDMC recommendations. Subjects are eligible to cross-over to erdafitinib up to 90 days after notification of cross-over. Subjects must meet the following criteria to be eligible to cross-over to erdafitinib:

1. Subjects are willing and able to provide written informed consent to cross-over to erdafitinib.
2. Phosphate level must be less than ULN within 14 days prior to the cross-over (medical management allowed)
3. No central serous retinopathy (CSR) or retinal pigment epithelial detachment.
4. Subjects must have received comparator drug in the study within 60 days prior to notification of cross-over.
5. Subjects must have progressed on or within 60 days after discontinuing comparator drug on the study. Alternatively, cross-over to erdafitinib may be permitted if assessed to be in the best interest of the subject due to suboptimal response to or toxicity of comparator therapy.
6. Subjects have not received any systemic anti-cancer therapy since discontinuing comparator drug in the study.

Additional criteria may be required by the Sponsor based on the IDMC recommendation.

Subjects who elect not to continue in the LTE Phase will be discontinued from the study within approximately 3 months from the initiation of the LTE Phase at the site.

Study Treatment Administration

Open-label study treatment

Study treatment (erdafitinib, chemotherapy, or pembrolizumab) may continue to be administered as described in Sections 6.1 (erdafitinib), 6.2 (vinflunine or docetaxel), 6.3 (pembrolizumab), and Section 6.4 (Continued Access to Study Drug after the End of Data Collection Timepoint) of the protocol.

In the event of a decision by the Sponsor to allow cross-over to erdafitinib following the final analysis for each respective cohort, investigators will be notified and provided with specific criteria for cross-over to erdafitinib.

Prohibitions and Restrictions

Refer to protocol Sections 8.2 and 8.3.

Study Procedures for the Long-term Extension

All subjects continuing in the LTE Phase will follow the schedule of procedures provided in the table further in this section.

Clinical assessments will be conducted according to the standard of practice. Serious adverse events will be reported to the Company safety repository as specified in the table on the following page. Specific safety assessments may be performed if required by local Health Authorities.

Assessment of Anticipated Events will cease at start of the LTE Phase.

Discontinuation Criteria for the Long-term Extension

Subjects continue on study drug as defined in Section 6.4.

The assessments and timing are specified in the Time and Events Schedule (Table 13) for the LTE Phase below.

Case Report Form Completion

No data will be collected in the eCRF during the LTE Phase. However, documentation of assessments performed should be done in the subject file/source notes.

Section 17.5 of the main protocol will remain in effect but follow the Time and Events Schedule and list of assessments in the table below.

Table 13: Time and Events Schedule (Long-term Extension)

Procedures	**Open-label Treatment**
	Continuing to Receive Erdafitinib, Chemotherapy, or Pembrolizumab
Informed Consent	
	Subjects must sign the updated informed consent prior to entering LTE Phase
Study Drug Dispensing	
Erdafitinib, chemotherapy, or pembrolizumab	Continuous. See Sections 6.1 (erdafitinib), 6.2 (vinflunine or docetaxel), 6.3 (pembrolizumab), and Section 6.4 (Continued Access to Study Drug after the End of Data Collection Timepoint).

Study drug accountability	Drug accountability will be done.
Safety	
Hematology and blood chemistry	Assessments for pembrolizumab, chemotherapy, and erdafitinib as per local prescribing information. (If erdafitinib is not approved in a country/territory, the Erdafitinib Investigator's Brochure will be utilized.) In addition, as clinically indicated.
Other safety assessments	Assessments for pembrolizumab, chemotherapy, and erdafitinib as per local prescribing information. (If erdafitinib is not approved in a country/territory, the Erdafitinib Investigator's Brochure will be utilized.) In addition, safety assessments as clinically indicated. Only serious adverse events will be reported to the Company safety repository; see Section 12.3.2 of protocol. Pregnancy reporting should continue as described in Section 12.3.3. No other safety data are collected.
Efficacy	
	Per local practice. No data is collected.

AE=adverse events; LTE=Long-Term Extension.

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 conduct of the study and the obligations of confidentiality.

Coordinating Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): PPD

Institution: Janssen Research and Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor; a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	23-Jan-2023 14:21:45 (GMT)	Document Approval