Janssen Research & Development

Statistical Analysis Plan

A Randomized Phase 2 Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Subjects Who Received Bacillus Calmette-Guérin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) and FGFR Mutations and Fusions

Protocol 42756493BLC2003

Original Protocol 24-September-2019
Amendment 1 05-November-2019
Amendment 2 26-March-2020
Amendment 3 26-October-2020
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Amendment 5 24-September-2021
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JNJ-42756493 (erdafitinib)

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

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AMENDMENT HISTORY

Version Number	Document Date	Author	Modification Details
1.0	04Nov2020	PPD	Initial draft
2.0	25Feb2021	PPD	**Includes information on additional IDMC delivery:** **Updates for Protocol amendment 4:** - Removes references to the DDI substudy in TSIDS-NEW01, TSIDS-ST02. **Corrects for errors:** - Remove Bladder cancer subtype section on TSIDEM-NEW01 (information not collected in this study).
2.1	28Apr2021	PPD	**Changed baseline definition:** includes observations "on or prior to" first dose rather than only "prior to" first dose.
2.2	30Oct2021	PPD	**Updated for PA #5:** changed AESI from "corneal and retinal abnormalities" to "Central Serous Retinopathy". Minor edits to formatting.
3.0	11Nov2022	PPD	**Updated for early enrollment termination and change in study's regulatory intent from registrational to non-registrational:** • Changed cohort sample sizes • Removed interim analyses • Removed hypothesis tests • Removed PRO analysis • Removed secondary objective to evaluate HRQoL • Updated Section 3 for ending of IDMC monitoring • Removed medical resources utilization summary

3.1	17Apr2023	PPD	• **Added language explaining enrollment termination in Section 1.2**
			• **Added final cohort sample sizes to Section 1.2 and 1.4**
			• **Updated definition of treatment phase to start on day of first dose of study drug to be consistent throughout document**
			• **Changed Cohort 2 CR rate timing to 8 weeks and 32 weeks**
			• **Removed all analyses other than descriptive reporting**
			• **Added a table of hazard ratio confidence intervals to Section 1.4**
			• **Added exploratory endpoints for Cohort 2 and Cohort 3**
			  • Cohort 2: DOR
			  • Cohort 3: DOR and BOR

Version Number	Document Date	Author	Modification Details

			• **Removed the following exploratory endpoints:**
			  ◦ Disease-specific survival
			  ◦ RFS by central histopathologic review
			  ◦ OS adjusted for crossover
			  ◦ Time to cystectomy
			  ◦ RFS by comparator
			  ◦ Concordance with central histopathologic review
			• **Removed Table 4, the summary of AE analyses to be performed**
			• **Removed TEAE reporting related to CYP3A inhibitor from Section 6.1.1**
			• **Removed the following from Safety section:**
			  ◦ Descriptive statistics for clinical laboratory tests
			  ◦ Change from baseline to each time point for clinical laboratory test results
			  ◦ Vital signs
			  ◦ Physical examination findings
			  ◦ ECG summaries
			  ◦ Ophthalmologic exams
			• **Removed details from PK section**

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BCG	Bacillus Calmette-Guérin
BOR	best overall response
C1D1	Cycle 1 Day 1
CFA	Confirmatory factor analysis
CI	confidence interval
CIS	carcinoma in situ
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
DOR	duration of response
DPS	Data Presentation Specifications
eCDF	Empirical Cumulative Distribution Function
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFA	Exploratory factor analysis
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
EU	European Union
eCRF	electronic case report form
EQ-5D-5L	EuroQol-5 Dimension 5-Level Instrument
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
GHS	Global Health Status
HR	hazard ratio
HRQoL	health-related quality of life
IAP	interim analysis plan
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IQ	interquartile
IR	intermediate risk
ITT	intent-to-treat
KM	Kaplan-Meier
LS	Least Squares
MCID	Minimum Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MMC	mitomycin C
NA	North America
NCI	National Cancer Institute
NMIBC	non-muscle invasive bladder cancer
OS	overall survival
PD	pharmacodynamic(s)
PD	progressive disease
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	principal investigator
PK	pharmacokinetic(s)

PP	per protocol
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QLQ-C30	Quality of Life Questionnaire Core-30 Items
RFS	recurrence-free survival
RFS2	recurrence-free survival on subsequent anticancer therapy
ROW	rest of the world
RS	Raw Score
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SD	stable disease
SOC	system organ class
SUSAR	sudden unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TTP	time to progression
TUR	transurethral resection
US NCI	United States National Cancer Institute
VAS	Visual Analogue Score
WBC	white blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

INTRODUCTION

The purpose of the statistical analysis plan (SAP) is to lay out key elements including definitions and statistical methods for the planned analyses for efficacy, safety, and other endpoints. The SAP was based upon the fifth amended version of the study protocol 42756493BLC2003<clinical_trial_id> (dated 24 September 2021) and further updated according to an internal decision to terminate the study's enrollment earlier than original planned at the study design.

1.1. Trial Objectives

1.1.1. Primary Objective (Cohort 1: Papillary disease only)

For Cohort 1, the primary objective of the study is to evaluate recurrence-free survival (RFS) in subjects treated with erdafitinib vs Investigator's Choice, for subjects with high-risk NMIBC who harbor FGFR mutations or fusions, and who recurred after BCG therapy.

1.1.2. Secondary Objectives

1.1.2.1. Secondary Objectives for Cohort 1

The secondary objectives for Cohort 1 are the following:

- To evaluate time to progression.
- To evaluate overall survival (OS).
- To evaluate RFS rate at 6 and 12 months.

1.1.2.2. Other Secondary Objectives for All Cohorts

The following secondary objectives will be evaluated for all cohorts:

- To evaluate erdafitinib PK.
- To evaluate safety and tolerability of erdafitinib.

1.1.3. Exploratory Objectives

1.1.3.1. Cohort 2 (Carcinoma in situ (CIS) with or without papillary disease)

The efficacy objectives for Cohort 2 are to evaluate the efficacy of erdafitinib based on the following:

- Complete response (CR) rate at 8 weeks.
- CR rate at 32 weeks
- Duration of response (DOR)

1.1.3.2. Cohort 3 (Intermediate-risk marker lesion)

The efficacy objective for Cohort 3 as an exploratory endpoint is to evaluate the efficacy of erdafitinib based on the following:

- CR rate
- Best overall response (BOR)
- DOR

1.2. Trial Design

This is an open-label, global, multicenter, randomized, Phase 2 study of the safety and efficacy of erdafitinib in subjects with NMIBC and FGFR mutations or fusions (see protocol Section 5.1).

Cohort 1 was planned to enroll approximately 240 subjects with high-risk NMIBC presenting as papillary tumor only, with disease recurrence after BCG therapy, and who either refuse or are not eligible for cystectomy The reason for not being eligible for cystectomy or for refusing cystectomy are entered into the electronic case report form (eCRF). Subjects are assigned randomly 2:1 to treatment with erdafitinib or the investigator's choice of either intravesical gemcitabine or intravesical mitomycin C (MMC)/hyperthermic MMC, respectively. Randomization is stratified by tumor stage (Ta vs T1) and type of prior BCG therapy (BCG-unresponsive vs BCG-experienced). BCG strain administered is also be documented in the eCRF. Subjects in the BCG-experienced strata are capped at approximately 50% of the total study population (See protocol Section 6.3). Investigators must choose between intravesical gemcitabine or intravesical MMC/hyperthermic MMC for each subject at screening, and the choice of the agent must take prior exposure into consideration. Subjects in Cohort 1 with locally confirmed high-risk recurrence on Investigator's Choice may cross over to treatment with erdafitinib. Molecular screening must start within 12 weeks after the last transurethral resection of bladder tumor (TURBT) done for high-risk recurrence if molecular testing is being done on post-BCG specimen. Peri-operative intravesical chemotherapy prior to study entry per local standard of care and prior immunotherapy (e.g., PD1 inhibitor, etc.) are allowed.

The enrollment of Cohort 1 was terminated in later 2022 due to poor accrual. At the enrollment termination, 73 subjects were randomized into the Cohort 1 according to the study design and they were treated and followed per protocol.

Cohort 2 and Cohort 3 are exploratory.

Cohort 2 was planned to enroll approximately 20 subjects with high-risk, BCG-unresponsive NMIBC presenting as CIS with or without concurrent papillary tumor, and who either refuse or are not eligible for cystectomy. The reason for not being eligible for cystectomy or for refusing cystectomy will be entered into the eCRF. All subjects enrolled in Cohort 2 will receive treatment with erdafitinib. Peri-operative intravesical chemotherapy prior to study entry per local standard of care and prior immunotherapy (e.g., PD1 inhibitor, etc.) are allowed. Additionally, subjects in

this cohort may receive chemotherapy as bridging therapy after adequate BCG therapy while being considered for trial.

Cohort 3 was planned to enroll approximately 20 subjects at select study sites and will include subjects with intermediate-risk NMIBC presenting as papillary disease only. All previous tumors for these subjects must be low grade (G1-G2), Ta, or T1, with no previous CIS. Furthermore, subjects must have a risk of progression less than 5% for 2 years, and the risk of recurrence must be greater than 50% as calculated using the European Organisation for Research and Treatment of Cancer (EORTC) risk calculator.[4] There are no predefined BCG or intravesical chemotherapy requirements for subjects enrolled in Cohort 3. All tumors must be removed except for a single, untouched 5 to 10 mm lesion. All subjects enrolled in Cohort 3 will receive treatment with erdafitinib.

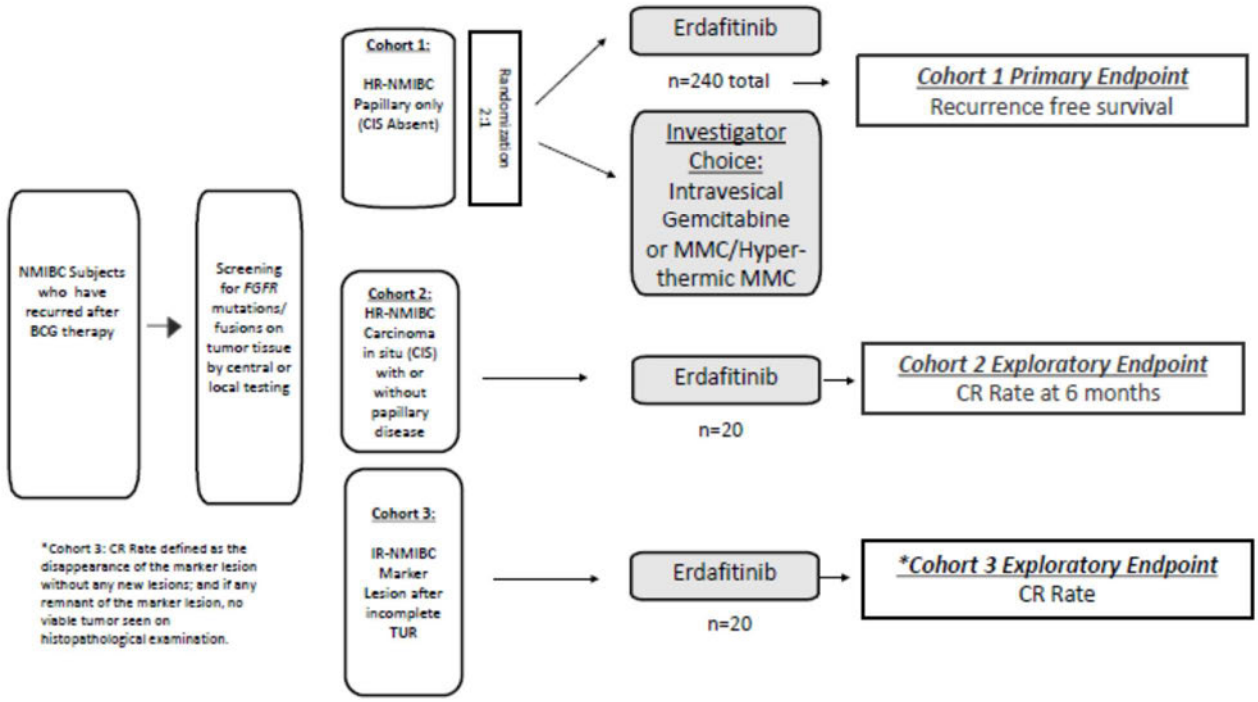
The enrollment of both exploratory cohorts was terminated in December 2022 as enrollment approached approximate target. At the enrollment termination, 16 subjects were enrolled into Cohort 2 and 18 subjects were enrolled into Cohort 3 according to the study design and they were treated and followed per protocol.

Molecular eligibility will be determined before screening for remaining eligibility criteria. The Treatment Phase will begin on Day 1 for subjects meeting all eligibility criteria. The Follow-up Phase includes a 30-day Safety Follow-up Visit, disease assessment follow-up, and survival follow-up. An Independent Data Monitoring Committee (IDMC) was commissioned for Cohort 1 and dissolved after the Cohort 1 termination of enrollment.

A diagram of the study design is provided in

Figure **1**. Details about the study design can be found in the study protocol.

Figure 1: Schematic Overview of the Study (original design prior to the termination of enrollment)



BCG= bacillus Calmette-Guérin; CIS=carcinoma in situ; CR=complete response; FGFR= fibroblast growth factor receptor; HR=high risk; IR=intermediate risk; MMC=mitomycin C; NMIBC=non-muscle-invasive bladder cancer; RFS=recurrence-free-survival; TUR=transurethral resection

1.3. Statistical Hypotheses for Trial Objectives

No hypothesis testing will be performed for Cohort 1, Cohort 2, or Cohort 3.

1.4. Sample Size Determination

Cohort 1 was planned to enroll approximately 240 subjects in a 2:1 randomization ratio. The primary efficacy analysis was planned to be performed when approximately 160 recurrence events were observed. This plan was based on the assumption of 67% improvement in the median RFS of the erdafitinib arm over the control arm, i.e., a hazard ratio (HR) of 0.60 for the erdafitinib arm relative to the control arm, improving the median RFS from 6 months to 10 months, 160 recurrence events would provide approximately 86% power to achieve a statistically significant difference between the treatment arms in RFS (2-sided alpha=0.05).

The termination of Cohort 1 enrollment resulted in a sample size of approximately 73 for the purpose of summarizing the data descriptively. With a total number of 73 subjects under the 2:1 randomization ratio, the 95% CIs for the possible hazard rations assumed to be observed at the end of the study are presented as follows:

Hazard Ratio Confidence Intervals

	Number of Events			
	20	30	40	50
Hazard Ratio				
0.4	(0.16, 1.01)	(0.19, 0.85)	(0.21, 0.77)	(0.22, 0.72)
0.5	(0.20, 1.27)	(0.23, 1.07)	(0.26, 0.96)	(0.28, 0.90)
0.6	(0.24, 1.52)	(0.28, 1.28)	(0.31, 1.16)	(0.33, 1.08)

Cohort 2 was planned to enroll approximately 20 subjects. As suggested by the International Bladder Cancer Group[1], a 40% CR rate at 6 months would be clinical meaningful. With 20 subjects, the cohort would have produced a 2-sided 95% CI of (16%, 64%) when the observed CR rate is 40%. The termination of enrollment resulted in a Cohort 2 sample size of 16.

Cohort 3 was planned to enroll approximately 20 subjects. A CR rate of 30% to 50% has been reported in most previous marker lesion studies[2] With 20 subjects, the lower bound of the 95% CIs would exclude 0 if the observed CR rate is at least 30%. The 95% CIs for different observed CR rates based on 20 subjects are as follows:

Observed rate	95% CI
30%	(7%, 53%)
40%	(16%, 64%)
50%	(26%, 74%)
60%	(36%, 84%)

The termination of enrollment resulted in a Cohort 3 sample size of 18.

1.5. Randomization and Blinding

This is an open-label study; neither the sponsor, investigators, nor subjects will be blinded to assigned treatment. Central randomization will be implemented in this study. In Cohort 1, subjects will be randomly assigned to 1 of 2 treatment groups in a 2:1 randomization ratio (erdafitinib: Investigator's Choice) 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 the type of resected papillary disease (Ta vs T1) and type of prior BCG therapy (BCG-unresponsive vs BCG-experienced). Subjects in the BCG-experienced strata will be capped at approximately 50% of the total study population. Investigators must indicate their Investigator's Choice selection for each subject during screening.

All subjects in Cohort 2 and Cohort 3 will be assigned to treatment with erdafitinib.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Visit windowing will be based on the following phases and cycles:

Screening Phase: The Full-Study Screening Phase includes the interval between signing the Main-study ICF and the day the subject is randomized (Cohort 1) or receives the first dose of study drug (Cohort 2 and Cohort 3). The full Screening Phase should not exceed 35 days. Assessments

that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. In specific, for Cohort 1, the Screening Phase is a period of 35 days before the subject is randomized. For Cohort 2 and 3, the Screening Phase is a period of 35 days before the subject receives the first dose of study drug.

Treatment Phase: The Treatment Phase will begin on Cycle 1 Day 1 following the first dose of study drug, and end at the date of end of treatment (EoT) visit. If the date of the end of treatment is not available, the date of last dose of study medication + 7 days will be used.

The Treatment Phase will be subdivided by cycles, based on the nominal treatment cycles as defined in protocol and recorded on the Case Report Form (CRF). A treatment cycle is defined as 28 days.

Follow-up Phase: After EoT until the study cutoff. The Follow-up Phase includes a 30-day (+ 7 days) Safety Follow-up Visit, disease assessment follow-up (every 24±2 weeks), and survival follow-up (every 12±2 weeks). Total subject involvement in the study is up to 4 years from the day of randomization (Cohort 1) or enrollment (Cohort 2 and Cohort 3).

Cycle-based analysis may be performed for safety parameters during the Treatment Phase up to date of last dose + 7 days or End-of-Treatment visit whichever comes later.

2.2. Pooling Algorithm for Analysis Centers

All participating study sites will be pooled together for analysis.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

2.3.1.1. Intent-to-Treat Analysis Set

In Cohort 1, the Intent-to-Treat (ITT) Analysis Set includes all randomized subjects. Subjects in this group will be primarily analyzed by the treatment to which they are assigned, regardless of the actual treatment received.

In Cohort 2 and 3, the ITT Analysis Set includes all treated subjects.

Primary efficacy analyses, secondary efficacy endpoints, and summary of subject disposition, demographics and baseline characteristics will be based on the ITT Analysis Set.

2.3.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 dose of study drug. This analysis set will be used for exposure and safety analyses. Safety data will be analyzed according to the actual treatment received.

2.3.3. PK Evaluable Analysis Set

The PK Evaluable Analysis Set includes all subjects who have received at least 1 dose of erdafitinib and had at least 1 PK sample obtained post-treatment.

The Erdafitinib plasma PK analysis set is defined as subjects (FGFR+):

- who have received at least 1 dose of study drug;
- who have at least one evaluable PK sample

A plasma PK sample is considered to be not evaluable if

- there are e.g., missing information of dosing and sampling times
- vomiting occurs within the first 2.5 hours following the last dose intake prior to the predose PK sample draw
- vomiting occurs within first 2.5 hours after Cycle 2 Day 1 dose
- the patient does not take study drug according to the originally assigned dose and assigned dose post up-titration for at least 5 consecutive days without interruption or dose modification prior to the PK sampling day
- For the predose PK sample, the draw occurs outside the 18-30 hours window after the last dose intake
- For the predose PK sample, the draw occurs after the next dose

A tissue or a urine erdafitinib PK sample is considered to be not evaluable if

- there are e.g., missing information of dosing and sampling times

2.4. Definition of Subgroups

Subgroup analyses will be performed as appropriate to evaluate the consistency in the selected efficacy and safety endpoints. Table 1 below provides the categorical variables for subgroup analysis.

Table 1 Categorical variables used for subgroup analyses

Subgroup	Definition	Analysis Type
Region	• North America (NA) • Europe (EU) • Rest-of-the-World (ROW)	E, S
Prior BCG Therapy	• Unresponsive • Experienced	E, S
Tumor Stage	• Ta • T1	E
Baseline ECOG Status	• 0 • 1	E
FGFR Alteration Type	• Mutations • Fusions	E
PD-L1 Status	• Positive • Negative	E

Subgroup	Definition	Analysis Type
Baseline Creatinine Clearance	• < 30 mL/min • 30 - <60 mL/min • ≥60 mL/min	E, S
Age Group	• <65 • ≥65	E, S
Gender	• Female • Male	E, S
Race	• White • Non-white	E, S

2.5. Study Day and Relative Day

A treatment cycle for a specific drug is defined as a cycle in which the subject received any amount of the specific drug. The cycle number will be named according to the sequence of every 28-day cycle for study drug administration.

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

The reference date is defined as the date of the initial study agent administration of any study agent. If the subject was not dosed, then the visit date should be used. If the visit date is not available, then the randomization date should be used. Otherwise reference date will be missing.

Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.

Cycle Day = assessment date – date of first day of the cycle + 1.

The full study screening period is 35 days before the randomization or first dose of the study drug on Cycle 1 Day 1. Randomization will occur within 3 days prior to Cycle 1 Day 1.

There is no “Day 0”.

2.6. Baseline

Baseline is defined as the last non-missing observation on or prior to the start of the first study drug administration. For subjects who have been randomized but not treated with any dose, randomization date will be used as the reference date for baseline value calculation. Change from baseline will be defined as the difference between post-baseline value and baseline value.

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

2.7.1. Methods of Handling Missing Data

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

2.7.2. Missing/Partial Dates

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

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

For initial diagnosis if such imputed date is on or after the reference date, then reference date – 1 will be used. If such imputed date for prior therapies or initial diagnosis is on or after the reference date, then reference date – 1 will be used. If such imputed date for subsequent therapies is before date of last dose, then date of last dose +1 will be used. The imputed start date for subsequent therapies will be adjusted sequentially using the following steps:

- If the imputed start date is before the last dose date but in the same year and month, then the last dose date will be used.
- If subsequent therapy end date is not missing and is before the imputed subsequent therapy start date, then the subsequent therapy end date will be used as the start date.
- If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date will be used. If the last known alive date is beyond the clinical cutoff date, use the clinical cutoff date.

The imputed AE start date will be adjusted sequentially using the following steps:

- If the imputed date is in the same year and month as but day before the first dose date, then the first dose date will be used, or if it is in the same year and month as but day after the last dose date + 30 days, then the last dose date + 30 days will be used.
- If AE end date is not missing and the imputed AE start date is after the AE end date, then the AE end date will be used.
- If the imputed AE start date and is after date of death, then date of death will be used
- If the imputed AE start date is in the same month and year but after the 1st subsequent therapy start date, then 1st subsequent therapy start date will be used.
- If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

The AE imputation rule will be used for concomitant medication.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Two interim analyses were originally planned. Due to the change in the conduct of the study, they will no longer be included.

An IDMC was commissioned for reviewing safety data at various intervals outlined in the IDMC Charter.

The IDMC monitored data to ensure the safety of the subjects enrolled in this study. The safety review focused on deaths, treatment discontinuations, serious adverse events, Grade ≥3 events, and events of special interest. Based on the results from these scheduled safety review meetings, the IDMC chair could have requested additional interim analyses and more frequent monitoring. All deaths, treatment discontinuations and serious adverse events were reviewed by the sponsor's medical monitor on an ongoing basis to identify safety concerns, and the IDMC was informed of any new potential signals.

The IDMC was composed of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. Refer to the IDMC charter for detailed procedures.

Prior to the termination of enrollment, an independent third-party Statistical Support Group (SSG) prepared the unblinded data packages, which included tables, listings and/or figures, and sent the packages to the IDMC for several safety review meetings. Due to the termination of enrollment in all cohorts of the study and since a recent IDMC found the safety of erdafitinib in BLC2003 consistent with the known safety profile of erdafitinib, no further monitoring by the IDMC will be conducted.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group and overall within each cohort.

4.1. Demographics and Baseline Characteristics

Subject demographics and baseline disease characteristics will be summarized using descriptive statistics, which include the following items:

- Demographics and baseline characteristics:
    - age, sex, race, ethnicity, geographic region, height (cm), weight (kg), systolic blood pressure/diastolic pressure (SBP/DBP) (mmHg)
- Baseline disease characteristics:
    - Baseline ECOG (0, 1)
    - Prior BCG therapy (unresponsive, experienced)
    - Tumor stage (Ta, T1)
    - FGFR alteration type

  - Specific Mutation (FGFR3 S249C, R248C, G370C, Y373C
  - Specific Gene Fusions (FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1)
  - PD-L1 status (Positive, Negative)
- Hematology: hemoglobin, platelet count, white blood cell (WBC) count, absolute neutrophil count (ANC)
- Comprehensive Metabolic: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, sodium, calcium, potassium, albumin, bicarbonate, alkaline phosphatase, magnesium
- 1,25-Dihydroxyvitamin D
- Phosphate (all subjects at screening; subjects receiving erdafitinib only after screening)
- Parathyroid hormone (PTH) (all subjects at screening; subjects receiving erdafitinib only after screening)

4.2. Disposition Information

All enrolled subjects will be summarized overall based on the following:

- Subjects completing the study
- Subjects who terminated study prematurely
- Reasons for termination of study
- Subjects who completed study drug
- Subjects who discontinued study drug
- Reasons for discontinuation of study drug
- Treatment disposition
- Screen Failures

4.3. Treatment Compliance

Study drug compliance will be summarized descriptively based on the Safety Analysis Set.

For subjects on erdafitinib (all cohorts), study drug compliance will be calculated as follows:

- Study drug compliance (%) = (actual dose taken/total dose prescribed) x100.

For subjects on comparator drugs (gemcitabine or MMC/hyperthermic MMC for Cohort 1), study drug compliance will be calculated as follows:

- Study drug compliance (%) = (actual number of intravesical infusions /total number of infusions prescribed) x100.

4.4. Extent of Exposure

The number and percentage of subjects who receive the study drug (the Safety Analysis Set) will be summarized by treatment group (erdafitinib vs Investigator's Choice) for Cohort 1, and for Cohorts 2 and 3. The administration of study drugs will be presented, by medication administered within each treatment group and will be described in terms of total number of cycles administered, the median of cycles administered, dose intensity, dose modifications, dose withholdings, and dose interruptions.

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

Descriptive statistics for treatment duration (N, mean, SD, median, and range [minimum, maximum]) will be presented by treatment group using the safety population. Subject-years of exposure are calculated as days of exposure/365.25. Subject-years will be presented by treatment group.

Duration of treatment will be summarized by treatment group. Subjects may be included in more than one category if they are administered different treatments, i.e. subjects assigned to Investigator's Choice that cross over to Erdafitinib. Subjects randomized but not dosed will be summarized in a separate line.

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

The number (%) of subjects with a dose adjustment will be summarized by treatment group and cycle. Reasons for dose adjustments will also be summarized.

Descriptive statistics will be presented for study drug (erdafitinib) using the following parameters:

- Number of study drug administrations
- Cumulative total dose
- Mean daily dose
- Relative dose intensity

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

Relative dose intensity is defined as cumulative total dose/planned total dose which is based on initial planned dose displayed as percentages.

A by-subject listing will present all the study drugs that have been taken by the subject, which include cohort, treatment group, study day, cycle day, name of study drug and doses. Any dose adjustment/withhold/delays and the reasons need to be presented accordingly.

4.5. Protocol Deviations

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

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

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

4.6. Prior and Concomitant Medications

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

The number and percentage of subjects taking concomitant medications from the first dose through the end of the on-treatment period (up to 30 days after the last dose of study drug) will be tabulated by the Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term for each treatment group in the safety population. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication. A by-subject listing will also be presented for concomitant medication.

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

Summaries of concomitant medications of special interest may be provided: CYP3A4 and CYP2C9 inhibitors and inducers, P-glycoprotein (P-gp) substrates, and 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).

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Because of the nature of the modified study, no hypothesis testing will be performed for Cohort 1, Cohort 2, or Cohort 3. Descriptive statistics will be used to summarize the study endpoints.

5.1.2. General Analysis Considerations

The cohorts will be analyzed separately. Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, interquartiles (IQs), and ranges will be used. For discrete variables, frequency will be summarized.

The comparisons between the 2 treatment groups in Cohort 1 will be performed using descriptive statistics.

Subjects who have crossed over from treatment with Investigator's Choice to treatment with Erdafitinib will have crossover status indicated in the listings. In the tables, subjects will be summarized based on the information collected prior to crossover. If a substantial number of subjects cross over, then a category for crossover subjects may be added to the tables.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Recurrence-free Survival

5.2.1.1. Definition

For Cohort 1, the primary endpoint is recurrence-free survival (RFS). RFS is defined as the time from randomization until the date of the reappearance of high-risk disease (high grade Ta, T1, or CIS), or death, whichever is reported first. At the cutoff date for analysis, subjects who are recurrence-free and alive or have unknown status will be censored at the last tumor assessment. In addition, subjects without any postbaseline disease assessment will be censored at the randomization. Subjects who withdrew consent from the study before RFS event will be censored at the last tumor assessment. Subjects who are lost to follow-up will be censored at the last tumor assessment before subjects are lost to follow-up. Subjects who start subsequent anticancer therapies without RFS event will be censored at the last disease assessment before the start of subsequent anticancer therapies.

Table 2: RFS Event and Censoring Method

Situation	Outcome	Date of Event or Censoring
Reappearance of high-risk disease (high grade Ta, T1, or CIS)	RFS event	Earliest date that indicates recurrence
Death*	RFS event	Date of death
No postbaseline disease assessment	Censored	Date of randomization
Other, such as: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent anticancer therapy prior to reappearance of high-risk disease or death	Censored	Date of last tumor assessment prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anticancer therapy, or cross over from comparator to erdafitinib

*Subjects who died after consent withdrawal will be censored at the date of consent withdrawal for RFS analysis

RFS is calculated in months as follows:

RFS = (date of RFS event or censoring – date of randomization + 1) / (365.25/12).

5.2.1.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population: all randomized subjects, with high-risk NMIBC who harbor FGFR mutations or fusions, and who recurred after BCG therapy.
- Variable: time to event, RFS.
- Intercurrent event:
  - Treatment discontinuation. Treatment policy approach is used, where the occurrence of the intercurrent event is irrelevant: the value of the event is used regardless of treatment discontinuation occurring.
  - Subsequent anticancer therapy. While on treatment strategy will be used, that is, RFS will be censored at the start date of anticancer therapy. Note that for subjects randomized to Investigator's Choice in Cohort 1, the treatment of erdafitinib after cross over is considered as use of subsequent therapy and the while on treatment strategy will be used.
- Population-level summary: Descriptive statistics.

5.2.1.3. Analysis Methods

The primary efficacy analysis on RFS will be based on the ITT population in Cohort 1. The Kaplan-Meier method will be used to estimate the distribution of overall RFS for each treatment group. The median RFS with 95% CI will be provided. In addition, the number and percentage of subjects who had an RFS event or were censored will be reported. The reasons for RFS censoring will be summarized accordingly. The Kaplan-Meier RFS curve will also be plotted by treatment group.

5.2.1.4. Subgroup Analyses

Subgroup analysis may be performed for the selected potential prognostic variables (as listed in Table 1) to assess the consistency and robustness of the treatment benefit for RFS if sufficient data are captured.

Subgroup analysis on selected secondary endpoints may be generated.

5.3. Secondary Efficacy Endpoints (Cohort 1)

5.3.1. Time to Progression (TTP)

5.3.1.1. Definition

For Cohort 1, time to progression (TTP) is defined as the time from the date of randomization until the date of first documented evidence of any of the following disease progression or death:

- Development of or increase in stage to lamina propria invasion (e.g., increase from Ta to T1)
- Development of or increase in stage to muscle-invasive disease (stage ≥T2)
- Development of or increase in stage to lymph node (N+) or distant metastasis (M1) disease (subject must have previously been diagnosed with N0 and/or M0 disease)
- Increase in tumor grade from low to high (including CIS)
- Death

At the cutoff date for analysis, subjects who are progression free and alive or have unknown status will be censored at the date of the last tumor assessment. Subjects who withdraw consent to study or are lost to follow-up will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the randomization.

Table 3: TTP Event and Censoring Method

Situation	Outcome	Date of Event or Censoring
Disease progression prior to start of subsequent anticancer therapy	TTP event	Earliest date that indicates disease progression
Death*	TTP event	Date of death
No postbaseline disease assessment	Censored	Date of randomization
Other, such as: • Withdrawal of consent to study participation • Lost to follow-up	Censored	Date of last tumor assessment prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anticancer therapy, or cross over from comparator to erdafitinib

*Subjects who died after consent withdrawal will be censored at the date of consent withdrawal for TTP analysis

5.3.1.2. Analysis Methods

. Descriptive statistics will be used to assess TTP of the two treatment groups for the ITT population in Cohort 1. The Kaplan-Meier TTP curve will be plotted by treatment group.

l be plotted by treatment group.

5.3.2. Overall Survival

5.3.2.1. Definition

For Cohort 1, overall survival (OS) is defined as the time from the date of randomization to the date of the subject's death resulting from any cause. Subjects who are alive or have unknown vital status will be censored at the date the subject was last known to be alive. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up.

5.3.2.2. Analysis Methods

OS will be analyzed using descriptive statistics for the ITT population in Cohort 1. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. The Kaplan-Meier OS curve will be plotted by treatment group.

5.3.3. RFS Rate

5.3.3.1. Definition

See Section 5.2.1 for RFS definition and analysis method. The RFS rate at 6 and 12 months with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group in Cohort 1.

5.3.3.2. Analysis Methods

The RFS rate will be calculated with its associated 2-sided 95% CIs.

5.3.4. RFS2

5.3.4.1. Definition

For Cohort 1, RFS2 is defined as the time from the date of randomization until the date of the reappearance of high-risk disease (high grade Ta, T1, or CIS) on the first subsequent non-surgical anticancer treatment, or death due to any cause, whichever is reported first. Subjects who are recurrence-free, or who have a recurrence event but do not receive subsequent anticancer therapy and who are alive or have unknown status will be censored at the last tumor assessment. Subjects who have a recurrence event and have received subsequent anticancer therapy, but do not have a recurrence event on the subsequent therapy and are alive or have unknown status will be censored at the last tumor assessment.

5.3.4.2. Analysis Methods

Descriptive statistics will be used to assess RFS2 for the two treatment groups. The Kaplan-Meier RFS2 curve will be plotted by treatment group.

5.4. Exploratory Efficacy Endpoints

5.4.1. All Cause RFS (Cohort 1)

5.4.1.1. Definition

All Cause RFS is defined as the time from randomization until the date of the reappearance of any of the following, whichever is reported first:

- Low- or high-grade Ta
- Low- or high-grade T1 or higher
- CIS
- N+
- M+
- Death

At the cutoff date for analysis, subjects who are recurrence-free and alive or have unknown status will be censored at the last tumor assessment. In addition, subjects without any postbaseline disease assessment will be censored at the randomization. Subjects who withdrew consent from the study before All Cause RFS event will be censored at the last tumor assessment. Subjects who are lost to follow-up will be censored at the last tumor assessment before subjects are lost to follow-up. Subjects who start subsequent anticancer therapies without All Cause RFS event will be censored at the last disease assessment before the start of subsequent anticancer therapies.

All Cause RFS is calculated in months as follows:

All Cause RFS = (date of event or censoring – date of randomization + 1) / (365.25/12).

5.4.1.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the distribution of All Cause RFS for each treatment group. The median All Cause RFS with 95% CI will be provided. In addition, the number and percentage of subjects who had an All Cause RFS event or were censored will be reported. The Kaplan-Meier All Cause RFS curve will also be plotted by treatment group.

5.4.2. Complete Response Rate at 8 weeks and 32 weeks (Cohort 2)

5.4.2.1. Definition

For Cohort 2, exploratory endpoints include complete response (CR) rate at 8 weeks and CR rate at 32 weeks. CR is defined as at least one of the following: 1) negative cystoscopy and negative (including atypical) urine cytology; or 2) positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology. Only CRs prior to the start of subsequent anticancer therapy will be considered for this endpoint. CR rate at 8 weeks is calculated as the number of patients who report a CR on or after 50 days following treatment start divided by the number of treated patients in Cohort 2. CR rate at 32 weeks is calculated as the number of patients who report a CR on or after 218 days following treatment start divided by the number of treated patients in Cohort 2.

5.4.2.2. Analysis Methods

The CR rate at 8 weeks and the CR rate at 32 weeks will be calculated with their associated 2-sided 95% CIs.

5.4.3. Duration of Response (Cohort 2)

5.4.3.1. Definition

Duration of response will be analyzed for subjects in Cohort 2 with a BOR of CR only and is defined as the interval between the date of initial documentation of a response and the first documented evidence of PD, recurrence, or death due to any cause. Subjects who are progression- and recurrence-free and alive or have unknown status will be censored at the last tumor assessment. Subjects who had disease progression or death event but started a subsequent anti-cancer therapy before disease progression or death event will be censored at the last disease assessment before the subsequent therapy.

5.4.3.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the median DOR with 95% CI.

5.4.4. Complete Response Rate (Cohort 3)

5.4.4.1. Definition

For Cohort 3, an exploratory endpoint is CR rate. CR is defined as the disappearance of the marker lesion without any new lesions; and if any remnant of the marker lesion, no viable tumor seen on histopathological examination. Only CRs prior to the start of subsequent anticancer therapy will be considered for this endpoint. The CR rate is calculated as the number of patients who report at least one CR divided by the number of treated patients.

5.4.4.2. Analysis Methods.

The CR rate will be calculated with its associated 2-sided 95% CIs.

5.4.5. Best Overall Response (Cohort 3)

5.4.5.1. Definition

For Cohort 3, the best overall response (BOR) is defined as the best response documented after start of study treatment. CR for Cohort 3 is defined above. A partial response (PR) for Cohort 3 is defined as marker lesion reduction by 50%. Stable disease (SD) for Cohort 3 is defined as marker lesion reduction by less than 50%. Progressive disease (PD) for Cohort 3 is defined as any marker lesion growth beyond baseline.

5.4.6. Duration of Response (Cohort 3)

5.4.6.1. Definition

Duration of response will be analyzed for subjects in Cohort 3 with a BOR of CR or PR and is defined as the interval between the date of initial documentation of a response and the first

documented evidence of PD, recurrence, or death due to any cause. Subjects who are progression- and recurrence-free and alive or have unknown status will be censored at the last tumor assessment. Subjects who had disease progression or death event but started a subsequent anti-cancer therapy before disease progression or death event will be censored at the last disease assessment before the subsequent therapy.

5.4.6.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the median DOR with 95% CI.

6. SAFETY

All safety analyses will be based on the Safety Analysis Set based on actual treatment received, unless otherwise specified.

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, 12-lead electrocardiogram (ECG), physical examinations, clinical laboratory tests, ophthalmologic examinations, and other safety evaluations at specified time points as described in the Schedule of Activities in protocol Section 1.3.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). These coded AE terms are referred to as preferred terms (PT); classification into System Organ Class (SOC) is a result of the coding process.

6.1.1. All Adverse Events

Treatment-emergent AEs (TEAEs) are defined as 1) those that first occur in TEAE period (defined as the time from first dose date through 30 days after last dose date, or day before subsequent anticancer therapy, whichever occurs first); 2) present before first dose, but worsened in toxicity grade during TEAE period; 3) had missing start date and its end date is during the TEAE period; 4) was a drug-related event. To determine TEAE, partially missing AE start dates will be imputed according to the rules stated in section 2.7.2.

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

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

For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by frequency in incidence (the highest to lowest incidence).

6.1.2. Anticipated/Unlisted (unexpected) Adverse Event

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). 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.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. Anticipated and unlisted (unexpected) AEs by SOC, PT and toxicity grade will be summarized by treatment group.

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 IB. For gemcitabine or MMC/hyperthermic MMC, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable package insert or summary of product characteristics.

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

- hematuria
- dysuria
- nocturia
- bladder perforation
- ureteric stenosis
- urinary incontinence
- urinary hesitation
- stranguria
- ureteric obstruction
- urine flow decreased
- urinary retention
- urinary tract obstruction
- urinary tract pain
- urinary tract infection
- urosepsis

6.1.3. Adverse Events of Special Interest and other safety observations

Central Serous Retinopathy for subjects receiving erdafitinib is considered an adverse event of special interest. These occurrences should be reported as an event of special interest (if Grade 1 or 2) and as serious adverse events if the severity is Grade 3 or higher.

Adverse events of interest will be summarized.

Other safety observations are defined as: Hyperphosphatemia (serum phosphate elevation), Nail Disorders such as Onycholysis/Onychodystrophy and Paronychia; dry mouth, mucositis, dry skin/skin toxicities and dry eye.

6.2. Deaths

A summary of all deaths, deaths within 60 days after treatment, and deaths during the treatment and up to 30 days after last dose will be provided, along with the primary cause of death. In particular, frequencies of deaths due to study treatment-related adverse events will also be reported. A death is study medication-related death if the primary cause is a drug related AE.

6.3. Clinical Laboratory Tests

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

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

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

Markedly abnormal laboratory findings to be reported are described below:

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

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

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

6.4. Electrocardiogram

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (e.g., changes in T wave morphology or the occurrence of U waves). Clinically relevant ECG abnormalities are defined as follows:

- Heart rate (bpm): Low < 50; High > 100
- RR Interval (msec): Low < 600; High > 1000
- QT Interval (msec): High > 500
- QTcF Interval (msec): High (Males) > 450; High (Females) > 470; Very High > 500

6.5. Eastern Cooperative Oncology Group (ECOG) Performance Status

Screening ECOG performance status will be summarized for each cohort.

6.6. Other Safety Parameters

Pregnancy testing results will be presented in a by-subject listing.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Erdafitinib pharmacokinetic data in different metrices (plasma, urine, and tissue) will be listed for all subjects with available erdafitinib concentrations. Concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, CV for mean, standard deviation, minimum, median, maximum, but handled as missing for the calculation of the geometric means and their CV.

If appropriate, descriptive statistics, including arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric CV, minimum and maximum, will be tabulated for erdafitinib PK concentrations and protein binding data by time point if provided.

8. BIOMARKERS

FGFR variant type will be summarized by treatment group. Primary and key secondary efficacy endpoints will be summarized with the subgroups of FGFR Alteration Type (mutations vs. fusions). A subgroup analysis on the specific variants may be performed if a large number of subjects possess the variant.

Results of exploratory 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.

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