Janssen Research & Development

Statistical Analysis Plan – Amendment 1

A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

Protocol 42756493BLC2001; Phase 2

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

SAP Version	Issue Date
Original SAP	04 June 2015
Amendment 1	29 September 2016

ABBREVIATIONS

AE(s)	adverse event (s)
AESI	adverse events of special interest
ALT	alanine aminotransferase
ALC	absolute lymphocyte counts
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BOR	best objective response
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CR	complete response
CRF	case report form
CMH	Cochran-Mantel-Haenszel
CT	computed tomography (scan)
CYP	cytochrome P450
DBP	diastolic blood pressure
DOR	duration of response
DRC	Data Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FGFR	fibroblast growth factor receptor
Hgb	hemoglobin
IA1	Interim Analysis 1
IA2	Interim Analysis 2
INR	international normalized ratio
IRRC	Independent Radiologic Review Committee
IWRS	Interactive Web Response System
JRD	Janssen Research & Development, LLC
LDH	lactic acid dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MUGA	multi-gated acquisition scan
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NED	no evidence of disease
ORR	overall response rate
OS	overall survival
PD	progressive disease
PE	primary Efficacy (analysis population)
PET	positron emission tomography

PFS	progression-free survival
PK	pharmacokinetics
PLT	Platelets
PR	partial response
PT	preferred term
PTH	parathyroid hormone
RECIST	Response Evaluation Criteria in Solid Tumors
RE	Response Evaluable (population)
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SMT	Safety Management Team
SOC	system organ class
TEAE	treatment-emergent adverse events
TTR	time to response
ULN	upper limit of normal
UNK	unknown
WBC	white blood cell (count)
WHO	World Health Organization

1. INTRODUCTION

This clinical study is a phase 2, two-arm multicenter, open-label study to determine the efficacy and the safety of two different dose regimens of a pan-FGFR tyrosine kinase inhibitor JNJ-42756493 in subjects with metastatic or surgically unresectable urothelial cancer with FGFR genomic alterations.

The purpose of the statistical analysis plan (SAP) is to lay out key elements including definitions and statistical methods for the planned analyses for the primary, secondary, exploratory, safety, and other endpoints.

1.1. Trial Objectives

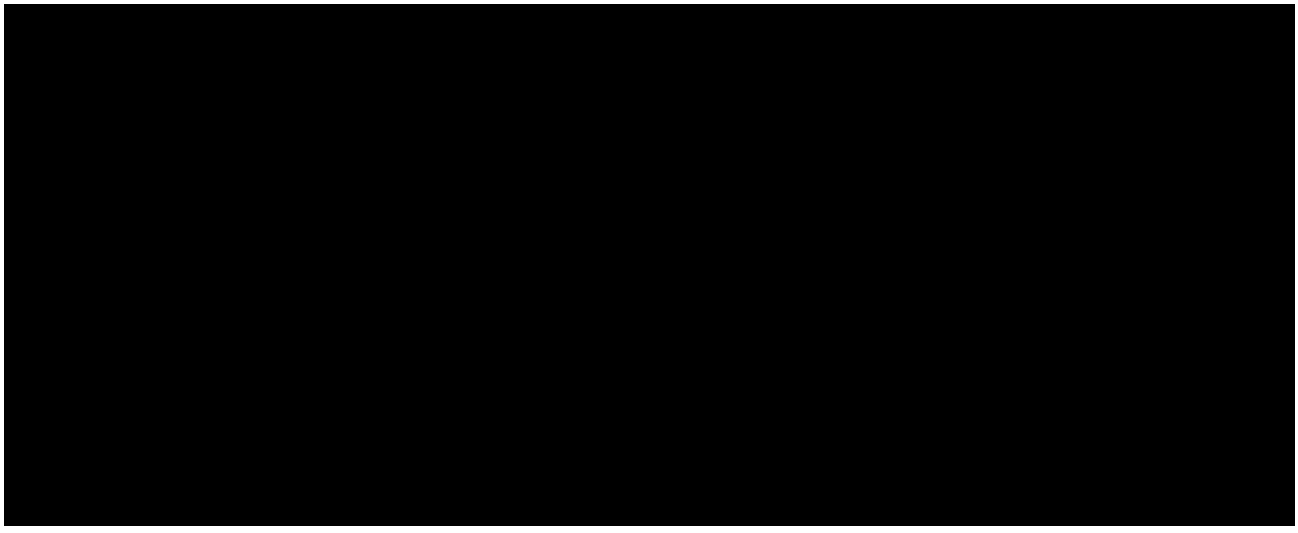
1.1.1 Primary Objective

The primary objective of the study is to evaluate the objective response (complete response [CR]+ partial response [PR]) rate of the selected dose regimen in subjects with metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations.

1.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the objective response rate of the selected dose regimen in chemo-refractory subjects
- To evaluate progression-free survival (PFS), duration of response, and overall survival of the selected dose regimen in all and chemo-refractory subjects
- To evaluate the response rate in biomarker-specific subgroups (translocations versus mutations) with the selected dose regimen
- To evaluate the objective response rate, PFS, duration of response, and overall survival of the other dose regimens tested
- To evaluat`e the safety and pharmacokinetics of JNJ-42756493 of all dose regimens



1.2. Trial Design

This is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of 2 different dose regimens (Regimen 1: 10 mg oral study drug once daily on an intermittent schedule [Days 1 through 7 and Days 15 through 21 of a 28-day cycle]; Regimen 2: 6 mg oral study drug once daily on a continuous schedule [Days 1 through 28 of a 28-day cycle]), and selection of a more favorable dose regimen for JNJ-42756493 in subjects with metastatic or surgically unresectable urothelial cancer with select FGFR genetic alterations. Based on analysis of data up to Interim Analysis 1 (IA1), the Data Review Committee (DRC) decided to terminate further enrollment to the intermittent schedule and select the continuous schedule with a starting dose of 8 mg and possible up-titration to 9 mg (Regimen 3) for further enrollment. It is expected that approximately 180 subjects with specified FGFR genetic alterations will be enrolled in the study, of which about 30 subjects will be treated with Regimen 1, about 50 subjects will be treated with Regimen 2, and approximately 100 subjects will be treated with Regimen 3. When approximately 88 subjects have been treated in Regimen 3, if less than 80 subjects are chemo-refractory, then enrollment of chemo-naïve subjects in Regimen 3 will be stopped but enrollment of chemo-refractory subjects will continue until at least 80 chemo-refractory subjects are treated in Regimen 3 or a total of approximately 100 subjects are treated with Regimen 3.

The study comprises a Screening Phase (molecular screening and full study screening), a Treatment Phase, and a post-treatment Follow-up Phase. Prior to IA1, subjects were randomized to 1 of 2 treatment regimens and stratified according to Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin level, FGFR alteration type, pretreatment status, and disease distribution. After IA1, subjects will be assigned to Regimen 2. Following implementation of Amendment 3, all new subjects will be assigned to Regimen 3.

Subjects will be assessed for disease response according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) guidelines. The end of study is defined as 12 months after last subject is enrolled or anytime the Sponsor terminates the study.

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 and ECOG performance status at specified time points as described in the protocol. Phosphate levels will be evaluated throughout the study as a pharmacodynamic marker for safety.

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1.4. Sample Size Justification

Sample size determination prior to IA1 is described in the Protocol Amendment 3, Attachment 9.

After IA1, it is expected that approximately 180 subjects with specified FGFR genetic alterations will be enrolled in the study. Of these, about 30 subjects will be treated with Regimen 1, about 50 subjects will be treated with Regimen 2, and approximately 100 subjects will be treated with Regimen 3. When approximately 88 subjects have been treated in Regimen 3, if less than 80 subjects are chemo-refractory, then enrollment of chemo-naïve subjects in Regimen 3 will be stopped but enrollment of chemo-refractory subjects will continue until at least 80 chemo-refractory subjects are treated in Regimen 3 or a total of approximately 100 subjects are treated with Regimen 3.

The number of subjects to be treated with Regimen 3 (at least 88) was based on sample size calculation using the following assumptions:

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After a total of about 88 subjects are treated at Regimen 3, enrollment will be stopped if at least 80 chemo-refractory subjects have been treated with Regimen 3. However, if the number of chemo-refractory subjects treated with Regimen 3 is less than 80, then the enrollment will change as follows:

1) Enrollment of chemo-naïve subjects will be stopped.

2) Enrollment of chemo-refractory subjects may continue until a total of 80 chemo-refractory subjects are treated.

Enrollment of at least 80 chemo-refractory subjects will provide at least 80% power to reject the null hypothesis within the chemo-refractory subgroup under the above assumptions.

1.5. Randomization

Before IA1, central randomization was implemented in this study. Subjects were randomly assigned to treatment Regimen 1 or 2 via a web-based and computer-generated randomization method. Subjects will be randomized to receive Regimen 1: 10 mg of oral study drug on Days 1 through 7 and Days 15 through 21 of a 28-day cycle; or Regimen 2: 6 mg of oral study drug on

Days 1 through 28 of a 28-day cycle. Randomization was covariate-adaptive randomization according to ECOG performance status (0-1 versus 2), hemoglobin level (<10 g/dL versus ≥10 g/dL), FGFR alteration type (translocation versus mutation), pretreatment status (chemo-refractory versus chemo-naive), and disease distribution (presence or absence of visceral metastases: lung, liver, and bone). The randomization would continue until a favorable dose regimen is selected or a maximum of 110 subjects was entered into the study, whichever comes first. The interactive web response system (IWRS) would assign a unique treatment code, which will dictate the treatment assignment for the subject.

After IA1, all subjects will be assigned to Regimen 2. After implementation of Amendment 3, all subjects will be assigned to Regimen 3.

1.6. Blinding Procedures

As this is an open-label study, blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Study Medication

Regimen 1: 10 mg of JNJ-42756493 taken orally each day on an intermittent dosing schedule of 7 days on and 7 days off of a 28-day cycle.

Regimen 2: 6 mg of JNJ-42756493 taken orally each day for 28 days of a 28-day cycle.

Regimen 3: 8 mg of JNJ-42756493 taken orally each day for 28 days of a 28-day cycle.

2.2. Analysis Sets

The analysis populations for this study are defined as the following:

- The Primary Efficacy (PE) analysis population will consist of all subjects who are assigned to Regimen 3 and treated by at least 1 dose of study drug.
- The Treated Population (TP) will consist of all subjects who receive at least 1 dose of study drug. All safety analyses will be performed using the Treated Population.
- The Response-Evaluable (RE) population will include all subjects who satisfy all of the following:
  - Met all eligibility criteria for the study;
  - Received at least 1 dose of study drug;
  - Had a baseline and at least 1 adequate post-treatment disease evaluation, have had clinical signs and/or symptoms of disease progression or died prior to the first post-treatment disease evaluation (these subjects will be considered non-responders). Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred.

- The efficacy analyses at IA1 will be performed using the RE population. The safety analyses at IA1 will be performed using the TP.
- The Pharmacokinetic/Pharmacodynamic Population will consist of all subjects who received at least 1 dose of JNJ-42756493 and had at least 1 sample collected during treatment to determine the drug concentration or pharmacodynamic biomarker response.

2.3. Baseline Definitions

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

2.4. Cycles

Nominal cycles as defined in protocol and recorded on the Case Report Form (CRF) will be used in the statistical analyses.

2.5. Visit Windows

Visit windowing will be based on phases and cycles:

Full Screening Phase: Begins at 30 days prior to the first dose of study medication.

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

The Treatment Phase will be subdivided by cycles, based on the nominal treatment cycles as recorded on the CRF.

Follow-up: After the end of treatment until the study cut off or the end of study.

Cycle-based analysis may be performed for safety parameters during the treatment phase. For the analysis of laboratory values based on grade by cycle, worst grade within each cycle will be used.

2.6. Study Day and Cycle Day

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

Reference date (Day 1) = first dose date of study medication. If a subject has not been treated, then randomization date will be used.

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

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

2.7. Missing and 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.

However, the above imputations will be modified by the following rules:

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

2.8. Treatment-Emergent Period

The treatment-emergent period is defined as the time from first dose date through 30 days after last dose date, or day before subsequent anticancer therapy, whichever occurs first.

2.9. Definition of Subgroups

Subgroup analysis will be performed for the selected variables to assess the internal consistency of efficacy and/or safety. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

Table 1 Subgroup Definition

Subgroup	Definition of Subgroup	Analysis Type
ECOG performance status	0-1, 2	E, S
Hemoglobin level	<10 g/dL, ≥10 g/dL	E, S
FGFR alteration type	translocation, mutation	E
Pretreatment status	chemo-refractory, chemo-naive	E, S
Disease distribution	presence or absence of visceral metastases: lung, liver, and bone	E
analysis type E= efficacy (PFS, OS, BOR, DOR) analysis type S= safety (adverse events)		

2.10. Exposure Related Definitions

Treatment duration for the study will be calculated as (date of last dose of study drug – date of first dose of study drug + 1).

The dose intensity is defined as the ratio of total dose taken and treatment duration. The relative dose intensity is defined as the ratio of total dose taken and total prescribed dose).

3. INTERIM ANALYSIS AND DATA REVIEW COMMITTEE

3.1. Data Review Committee

The DRC conducted a safety analysis and the interim analysis (IA1). The DRC will be conducting further safety analyses. Details of the composition of the DRC and their operational procedures will be specified in the DRC charter.

3.2. Safety Monitoring Team

Safety will be monitored by the sponsor's medical monitor or study responsible physician throughout the study. In addition, the sponsor's SMT, a multi-disciplinary team including an internal safety physician, will review the safety data and will investigate specific safety queries.

In addition, the SMT will review all serious adverse events. In the event a significant safety issue is identified, both the internal safety team and the responsible investigators will convene to discuss the safety data and to make a recommendation on the future conduct of the study. All decisions will be documented and will be distributed to investigators. The IRB or IEC will be notified if required.

3.3. Interim Analysis

There were 2 planned interim analyses (IA1 and IA2), which were to be performed for safety, futility, and dose regimen selection. Based on analysis of data up to IA1, the Data Review Committee (DRC) decided to terminate further enrollment to the intermittent schedule and select the continuous schedule with a starting dose of 8 mg and possible up-titration to 9 mg (Regimen 3) for further enrollment. The details of the planned IA1 can be found in Protocol Amendment 3 Attachment 9. This precludes the need for the planned IA2.

4. SUBJECT AND TREATMENT INFORMATION

4.1. Subject Disposition

Disposition information will be summarized for the treated population. Subject enrollment will be summarized by region, country, and investigator. The number of subjects undergoing, discontinuing and completing the study treatment as well as their reasons for treatment discontinuation will be summarized.

Descriptive statistics will be provided for time on study treatment and time on study.

4.2. Demographics and Baseline Characteristics

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

- Demographics and baseline characteristics: age, sex, race, ethnicity, geographic region, height (cm), weight (kg), systolic blood pressure/diastolic pressure (SBP/DBP (mmHg), body surface area (m^2)
- Baseline disease characteristics: time from initial diagnosis to first dose, time from progression/relapses since last line of treatment to first dose, TNM Stage at initial diagnosis, type of histology, TNM classification of urinary bladder cancer at time of study entry, baseline Eastern Cooperative Oncology Group (ECOG) (0-1 versus 2), pretreatment status (chemo-refractory, chemo-naïve) and other prior therapies, FGFR alteration type (mutation, translocation), hemoglobin level (<10 g/dL versus ≥10 g/dL).
- Hematology: hemoglobin, platelet count, white blood cell (WBC) count, ANC
- Chemistry: alanine aminotransferase (ALT), chloride, albumin, creatinine, creatinine clearance, alkaline phosphatase, magnesium, aspartate aminotransferase (AST), alpha-1-acid glycoprotein, bicarbonate, phosphate, blood glucose, potassium, blood urea nitrogen (BUN), sodium, total bilirubin, total protein, calcium, parathyroid hormone (PTH).

4.3. Prior and Concomitant Medications

For summarization purposes, medications will be coded to a generic term based on the World Health Organization (WHO) dictionary. Medications administered prior to the first dose of study medication will be considered prior medications. Concomitant therapies include those taken during Treatment Phase.

Incidence of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and drug generic term. Prior anticancer therapy will be summarized by type (e.g. radiotherapy, surgery, chemotherapy). Best response to last line of prior therapy will also be summarized. Number of prior lines of anticancer therapies will be summarized. Concomitant medications of special interest may be provided for strong CYP3A4/5 inhibitors/inducers and renagel. A comprehensive list of CYP450 isoenzymes and CYP3A4 inhibitors, inducers is provided in Attachment 4 of the protocol.

4.4. Protocol Deviations

Subjects with major protocol deviations will be listed by treatment regimen.

Protocol deviations will be based on clinical review, but not limited to, the following aspects: (1) treatment compliance, (2) patient safety, (3) efficacy assessment deviation, (4) eligibility criteria. Protocol deviations will be closely monitored during the execution of the study and the final set of protocol deviation criteria will be determined before database lock.

4.5. Extent of Exposure

Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for total number of cycles, treatment duration and dosing information for each treatment regimen.

The number and percentage of subjects with dose reduction, dose interruption, and dose re-escalation will be summarized. Subjects with dose modifications and reasons for dose modifications will be summarized. Total number of days with dose skipped, percentage of dose skipped and maximum duration of dose skip (days) will also be provided.

Details of exposure related definition is specified in Section 2.10.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Statistical inference on the primary endpoint will be tested at 0.025 one-sided level.

Efficacy for the secondary endpoint will be tested at one-sided 0.025 level for the chemo-refractory subgroup, after the primary endpoint has been declared significant.

5.1.2. Data Handling Rules

Unless specified otherwise, missing values will not be imputed.

5.1.3. General Analysis Considerations

In general, all interval estimation will be reported using 2-sided 95% confidence intervals (CIs).

Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, and ranges will be used. For categorical variables, number and percentage of subjects in each category will be summarized. For time-to-event variables, Kaplan-Meier estimates will be provided.

All statistical analyses will be performed using statistical analysis system (SAS®). Analyses of disposition, demographic, baseline disease characteristics, prior and concomitant therapy, treatment compliance and extent of exposure will be conducted on the treated population. No statistical testing is planned

Tumor response will be evaluated using the RECIST version 1.1. Response will be assessed by investigators and may be assessed by an Independent Radiologic Review Committee (IRRC). Independent Radiologic Review Committee assessment may not be performed if the investigator assessments indicate that the primary objective has not been met (IRRC assessment will not be performed for IA1 and IA2). If response is assessed by an IRRC, the IRRC assessment of response will be used for the primary and final analyses, and the response assessed by the investigators will be used for supportive analyses.

The primary analysis will be conducted 6 months after the enrollment of the last subject of the PE population. All efficacy endpoints will be analyzed at the same cutoff date of the primary analysis. Analysis of duration of response, PFS, and overall survival will be performed separately for all subjects and chemo-refractory subjects for the PE analysis population.

The final analysis will be performed 12 months after last subject is enrolled. All analyses on efficacy endpoints will be updated based on the treated population.

5.2. Primary Efficacy Endpoint

5.2.1. Best Objective Response (BOR)

A subject's best objective response is defined as the best (overall) objective response a subject achieved during the study in the order of Completer Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), where CR and PR are confirmed as per RECIST 1.1. Responders are subjects with BOR of CR or PR. Subjects without measurable disease at baseline or without post-baseline tumor assessment are considered non-responders.

5.2.2. Analysis Method

The primary analysis will be conducted 6 months after the enrollment of the last subject of the PE population. The primary efficacy analyses will be based on the PE analysis population. The

objective response rate is defined as the proportion of responders over the PE population. The response rate and its 95% 2-sided confidence interval will be calculated using normal approximation to the binomial distribution. The null hypothesis will be rejected if the low bound of 95% 2-sided confidence interval of the response rate is above 25%.

5.3. Secondary Endpoints

5.3.1. Best Objective Response in Chemo-refractory Subjects

Best objective response in chemo-refractory subjects will be analyzed using the same analysis methods as used for BOR for the primary endpoint (Section 5.2.2). Only chemo-refractory subjects in the PE population will be included in this analysis.

5.3.2. Progression-free Survival (PFS)

5.3.2.1. PFS

Progression-free survival is defined as the duration from the date of the first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death due to any cause, whichever occurs first, regardless of the use of subsequent anticancer therapy. Data from subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment. Subjects with no baseline or no post-baseline disease assessment will be censored at the date of first dose.

The analyses of PFS will be based on the PE population. The Kaplan-Meier method will be used to estimate the distribution of PFS. The median PFS and 95% CI will be provided. PFS rate with 95% CI at selected landmark points will be provided.

5.3.2.2. Sensitivity analysis of PFS

Sensitivity analysis may be performed for PFS as follows:

1) Use of subsequent anticancer therapy prior to documented PD, relapse or death . Two alternative censoring rules may be applied for subjects who start subsequent anticancer therapy prior to first documentation of disease progression or death due to any cause:
   a. subjects will be considered to have had a PFS event at the initiation of subsequent therapy.
   b. subjects will be censored at the last disease assessment showing no evident of PD before the use of subsequent anticancer therapy.
2) Disease assessment follow up: subjects will be censored at the last disease assessment if they progress or die after missing ≥2 planned disease assessment visits.

The reason for censoring will be summarized for PFS.

5.3.3. Overall Survival (OS)

Overall survival, measured from the date of first dose of study drug to the date of the subject's death from any cause. If the subject is alive or the vital status is unknown, the subject's data will be censored at the date the subject was last known to be alive.

The analyses of OS will be based on the PE population. Overall survival will be analyzed using the same analysis methods as used for PFS (Section 5.3.2.1).

5.3.4. Duration of Response (DOR)

Duration of response will be assessed for subjects with the best objective response 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 progressive disease (or relapse for subjects who experience CR during the study) or death due to any cause, regardless of the use of subsequent anticancer therapy. Subjects who are progression-free and alive will be censored at the time of their last disease assessment.

The analyses of DOR will be based on the PE population. Duration of response will be analyzed using the same analysis methods as used for PFS (Section 5.3.2.1).

5.3.5. Subgroup Analysis

Subgroup analyses for the best objective response rate will be conducted for each subgroup (Section 2.9) within the PE population and chemo-refractory population, respectively. Exact 95% confidence intervals will be calculated using normal approximation.

Subgroup analysis of time-to-event endpoints will be performed within the PE population and chemo-refractory population, respectively, using the analysis methods specified in Section 5.3.2.1.

5.3.6. Additional efficacy analysis

Additional efficacy analyses will be performed on BOR, PFS, OS, DOR by each other dose regimens and by combining subjects up-titrated to 8 mg QD with subjects assigned to Regimen 3, etc. These analyses will be performed in the treated population.

6. SAFETY

Safety will be analyzed using the incidence and severity of AEs, laboratory tests, electrocardiogram (ECG) measurements, vital signs, physical examination and ECOG performance status. Unless specified otherwise, all safety analyses will be based on the treated analysis set. Descriptive statistics will be reported for all safety data. Inferential statistics are not planned to be performed on safety data.

Unless otherwise stated, safety data will be summarized by treatment regimen as treated, by combining subjects up-titrated or switched to 8 mg QD with subjects assigned to Regimen 3.

6.1. Adverse Events

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

Table 2 Summary of Adverse Event Analyses to be Performed

Category	Analysis	Sorted By	Cut off	Drug-Related TEAE
General	Overall summary			✔
	TEAEs	SOC+ PT+ toxicity grade; PT+ toxicity grade	10%, 5%	✔
	Serious TEAEs	SOC+ PT + toxicity grade; PT+ toxicity grade	2%	✔
	Grade 3 or worse TEAE	PT+ toxicity grade	2%	✔
	TEAEs leading to treatment discontinuation	PT + toxicity grade		✔
	TEAEs leading to death	PT + toxicity grade		
	TEAEs leading to dose modification or interruption	PT + toxicity grade		
	AEs of clinical interest	PT + toxicity grade		
	Other safety observations (e.g. other malignancies, eye disorder)	PT + toxicity grade		
	Deaths within 30 days of last dose	Reason for death		
Subgroup	Overall summary			
	TEAEs	SOC+ PT+ toxicity grade		

6.1.1. All Adverse Events

Treatment-emergent AEs (TEAEs) are defined as 1) those that first occur in TEAE period (as defined in Section 2.8); 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. Drug-related AEs are those assessed by investigator as being possible, probable or very likely related to study drug. To determine TEAE, partially missing AE start dates will be imputed according to the rules stated in Section 2.7.

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

The severity of AEs will be graded on a scale of 1 to 5 according to the adult NCI Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0 or higher) 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).

For subjects using CYP3A inhibitor during treatment-emergent period, all TEAEs will be summarized by SOC, PT, maximum severity, any CYP3A inhibitor (Yes vs No), and strong CYP3A inhibitor (Yes vs No).

6.2. Adverse Events of Clinical Interest and other safety observations

Adverse events of interest may be included based on the following criteria:

- Liver events, eye toxicities, elevated phosphate levels, dry mouth, stomatitis, dry skin, skin toxicities, nail toxicities, events related to (delayed) wound healing.

Adverse events of interest will be summarized.

6.3. Deaths

A summary of 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.

6.4. Clinical Laboratory Tests

Laboratory data of hematology and serum chemistry up to 30 days after last dose or the end of treatment visit date, whichever is later, will be reported in SI units.

Laboratory results will be graded according to NCI-CTCAE version 4.03. Note that toxicity grading for creatinine increase will be based on the NCI CTC v4.03 criteria, but limited only to the part based on the upper limit of normal (ULN), the other part, that is based on change from baseline, will not be used for toxicity grading. Generic normal ranges will be applied whenever reference ranges are not available.

The following laboratory tests will be analyzed:

- Hematology: hemoglobin, platelet count, white blood cell (WBC) count, ANC
- Chemistry: alanine aminotransferase (ALT), chloride, albumin, creatinine clearance, alkaline phosphatase, magnesium, aspartate aminotransferase (AST), alpha-1-acid glycoprotein, bicarbonate, phosphate, blood glucose, potassium, blood urea nitrogen (BUN), sodium, total bilirubin, total protein, calcium, parathyroid hormone (PTH).

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each time point of assessment as well as for the changes from baseline to the last value. Parameters will be summarized by toxicity grade. Change from baseline to the worst grade during the treatment will be provided as shift tables for

selected parameters. In addition, treatment-emergent worsening in toxicity grade will be summarized for selected hematology and chemistry parameters.

Liver function abnormality by Hy's Law: For subjects with any elevated liver enzyme (AST or ALT) of >3xULN, ALP <2xULN, and associated with an increase in bilirubin (total) ≥2xULN, a listing for all subjects with all such records will be provided and a summary table of the number of such subjects will be provided by regimen.

6.4.1. Creatinine Clearance

Creatinine clearance (CrCl) is calculated using the Cockroft-Gault formula:

$$CrCl_{(est)} = \frac{(140 - age[yr])(lean\ body\ wt[kg])}{(72)(serum\ creatinine[mg/dL])} \times 0.85 (if\ female)$$

for males, the factor is 1 instead of 0.85

6.5. Electrocardiogram

Over-time summary statistics (mean, standard deviation, median and range) of vital signs will be provided. A separate summary will be produced for vital signs at baseline, maximum, change to maximum, last value, and change to last value. Clinical significance will be summarized.

The ECG parameters that will be summarized are heart rate, RR interval, QT interval, PR interval, QRS interval and QTc. The QTc will be computed using Fridericia's correction, i.e., QTcF = $/\sqrt[3]{RR}$. QTcF will be used for the assessment of QTc interval prolongation. QTcB = $QT/\sqrt{RR}$ will also be computed and used for exploratory analysis of QTc interval prolongation.

Values outside the normal range will be flagged as follows.

Observed:

Heart rate: L <50 bpm; H > 100 bpm

RR interval: L < 600 ms; H > 1000 ms

QT interval: H > 500 ms

QTc interval: H > (450 ms for males, 470 ms for females); increase to >500 ms

Change from baseline:

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

MUGA scans will be similarly summarized at screening.

All treatment-emergent abnormal findings will be tabulated, displaying the number of subjects with abnormal findings after dosing. An abnormal finding is considered to be treatment-emergent if it occurred during treatment and up to 30 days after the last dose.

6.6. Vital Signs and Physical Examination Findings

Over-time summary statistics (mean, standard deviation, median and range) of vital signs will be provided. A separate summary will be produced for vital signs at baseline, maximum, change to maximum, last value, and change to last value.

In addition, any significant vital sign changes will be tabulated. Specifically, Grade 2 or above hypertension according to NCI CTCAE version 4.0 or higher will be summarized.

In order to be included in the table, a subject must have both a baseline value and a value for the given post-baseline time point.

Abnormal physical examination findings will be summarized by body system.

6.7. Other Safety Measures

Frequencies of ECOG score will be reported over time. Descriptive statistics of change in ECOG scores from baseline will also be provided.

7. PHARMACOKINETICS

Details of PK analysis will be presented in a separate plan and results will be presented in a separate report.

8. BIOMARKERS

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

9. Symptom Measurement Questionnaire

The Symptom Measurement Questionnaire (SMQ) is a self-administered patient-reported outcome (PRO) instrument measuring symptoms experienced by patients with urothelial cancer. It consists of five items covering five different symptoms including pain, fatigue, cough, shortness of breath, and blood in urine. Responses to each of the five items are from 1 to 7 on a Likert scale. Each of the five items can be scored individually with a higher score indicating higher degree of symptom severity. An overall symptom score is generated by summing the score of the five items and dividing the total by five. If there are missing items, the total score is calculated by the sum of all completed items and dividing it by the number of completed items. A higher score indicates higher degree of symptoms severity.

The Global Impression of Change (Symptoms) is a single-item self-administered PRO to rate the change in health since the start of the trial. A 7-point response scale is used, with a lower score indicting greater improvement in subject's self-reported health.

The Global Impression of Change (Quality of Life) is a single-item self-administered PRO to rate the change in health-related quality of life (HRQoL) since the start of the trial. A 7-point

response scale is used, with a lower score indicting greater improvement in subject's self-reported HRQoL.

The change from baseline to each time point for the overall symptom score and each item will be summarized. The global impression of change (symptoms) and the global impression of change (Quality of Life) will be summarized by each time point. Number of observations, means, standard deviations, medians, and ranges will be given at each time point.