Statistical Analysis Plan

A randomized, multicenter, double-blind, placebo-controlled, Phase 3 study of the Bruton's Tyrosine Kinase inhibitor ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine, in the first line treatment of patients with metastatic pancreatic adenocarcinoma (Amendment 5)

PCYC-1137-CA

January 15, 2018

Version 1.0

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Statistical Analysis Plan Approval

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By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALC	Absolute Lymphocyte Counts
ANC	Absolute Neutrophil Counts
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30
EU	European Union
FDA	Food and Drug Administration
Hgb	Hemoglobin
DMC	Data Monitoring Committee
ITT	Intent-To- Treat
IV	Intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluable
NLR	Neutrophil/Lymphocyte Ratio
ORR	Overall Response Rate
OS	Overall Survival
PCYC	Pharmacyclics
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient Reported Outcome
PT	Preferred Term
QoL	Quality of life
SAP	Statistical Analysis Plan

SD	Stable Disease
SMQ	Standardized MedDRA query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
VTE	Venous Thromboembolic Events
UNK	Unknown
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol Amendment 5 and is to define key elements including variable definitions, and statistical methods for analysis of data in evaluation of efficacy and safety of the study PCYC-1137-CA. Analyses of biomarker and pharmacokinetics (PK) data will be addressed in separate documents. Throughout this SAP, "study treatment" and "study drug" are used interchangeably, both referred to as ibrutinib/placebo, nab-paclitaxel, and/or gemcitabine

Analysis methods specified in this document take precedence over those described in protocol should there be any difference. This SAP will be finalized before unblinding.

1.1 Study Design

This is a randomized, multicenter, double-blind placebo-controlled, Phase 3 study comparing ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine in the first-line treatment of subjects with metastatic pancreatic adenocarcinoma.

Safety Run-in Phase:

Six subjects will initially be recruited to receive open-label ibrutinib in combination with nab-paclitaxel and gemcitabine. The independent Data Monitoring Committee (DMC) will review data on the safety of ibrutinib combined with nab-paclitaxel and gemcitabine after the first 6 subjects have completed at least 28 days of follow-up after the initiation of combination therapy. Following DMC review and confirmation, the study may proceed to the Double-blind Randomized Phase.

Double-blind Randomized Phase:

The second phase of the study will be a randomized, double-blind comparison of ibrutinib in combination with nab-paclitaxel and gemcitabine *versus* placebo in combination with nab-paclitaxel and gemcitabine.

Approximately 420 subjects will be randomized between Arm A (ibrutinib in combination with nab-paclitaxel and gemcitabine) and Arm B (placebo in combination with nab-paclitaxel and gemcitabine). All subjects in Arm A and Arm B are to receive nab-paclitaxel (intravenous [IV]) 125 mg/m^2 and gemcitabine (IV) 1000 mg/m^2 given on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity. Unless otherwise indicated, all subjects in Arm A and Arm B per randomization are to receive oral ibrutinib 560 mg or matching placebo given orally once daily continuously starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. If nab-paclitaxel and/or gemcitabine or ibrutinib/placebo are discontinued

prior to disease progression, the remaining agents will be continued until unacceptable toxicity or disease progression.

1.2 Endpoints

1.2.1 Primary Endpoints

The primary endpoints are progression-free survival (PFS), as assessed by the investigator-based on RECIST 1.1 and overall survival (OS).

1.2.2 Secondary Endpoints

- Overall response rate (ORR): complete response (CR) + partial response (PR) per investigator assessment
- Carbohydrate antigen (CA) 19-9 (CA19-9) response: proportion of subjects with a decline of ≥ 60% from baseline
- Patient-reported outcome (PRO) by EORTC QLQ-C30: time until definitive deterioration (TUDD1) for global health status/quality-of-life (QoL) scale.
- Rate of venous thromboembolic events (VTE)
- Clinical benefit response (CBR) rate

1.2.3 Safety Assessments

- Safety and tolerability of the study treatment (ibrutinib/placebo, nab-paclitaxel, and/or gemcitabine)

1.2.4 Exploratory Endpoints

Exploratory endpoints to be included in the CSR are,

- CA19-9 response rate for a ≥ 20% reduction and a ≥ 90% reduction
- Disease control rate (DCR)
- Time to diminished pain (TDP)
- OS for the survival maintenance subgroup, *and*
- EORTC QLQ-C30 Global Health Status/QoL scale: time until definitive deterioration (TUDD2) (see Table 3 for endpoint definition).

In addition, baseline serum cytokine and C-reactive protein (CRP) biomarkers compared to PFS and OS will be explored.

1.3 Statistical Hypotheses

The statistical hypotheses for each of the primary endpoints (PFS or OS) can be written as follows:

H_0: $S_I(t) = S_C(t)$, for all $t > 0$, where $S_I(t)$, and $S_C(t)$ are survival functions for the experimental and control arms, respectively at all time points t:

vs.

H_1: $S_I(t) \neq S_C(t)$, for some $t > 0$

These hypotheses will be tested for the primary endpoints using a 2-sided stratified log-rank test at an α level specified in Section 1.6. The source of the stratification factors will be based on Interactive Web Response System (IWRS) data.

1.4 Sample Size Determination

The sample size calculation is based on a 2-sided family-wise Type I error rate (aka. family-wise error rate, FWER) of 0.05 for 2 primary endpoints, PFS and OS. The FWER is controlled at 0.05, with 0.007 allocated to the PFS endpoint and 0.043 allocated to the OS endpoint.

In this protocol amendment, a total of 424 subjects have been randomized with a 1:1 allocation to the 2 treatment arms. The calculations are based on the following assumptions using EAST software Version 6.3.1 and the actual enrollment rates.

For PFS:

- Median PFS is 5.5 months for the control arm (nab-paclitaxel and gemcitabine) (Von Hoff 2013).
- Target hazard ratio is 0.66 which corresponds to a 51% improvement in median PFS (eg, from 5.5 months to 8.33 months) for the ibrutinib + nab-paclitaxel + gemcitabine arm compared to the placebo + nab-paclitaxel + gemcitabine arm
- 2-sided $\alpha = 0.007$
- A total of 350 PFS events will provide approximately 88% power.

For OS:

- Median OS is 8.5 months for the control arm (nab-paclitaxel and gemcitabine) (Von Hoff 2013).
- Target hazard ratio is 0.735 which corresponds to approximately 36% improvement in median OS (e.g., from 8.5 months to 11.6 months) for the ibrutinib + nab-paclitaxel + gemcitabine arm compared to the placebo + nab-paclitaxel + gemcitabine arm

- 2-sided $\alpha = 0.043$
- A group sequential design with 1 interim analysis is planned when at least 250 deaths occur (approximately 71% of the deaths occur). The Lan-DeMets alpha spending function with O'Brien-Fleming boundary for efficacy will be used.
- A total of 353 OS events will provide approximately 80% power for the study.

1.5 Planned Analysis

1.5.1 Final Analysis PFS and OS Interim Analysis

The OS interim analysis strategy has been changed from Protocol Section 10.4.1. Conditions for conducting the OS interim analysis are described below.

At the time of the planned final PFS analysis (i.e., at least 350 PFS events as specified in the protocol), if the total number of OS events is ≥ 333 (i.e., $\geq 94\%$ of the OS information fraction) the PFS final analysis will be delayed until approximately 350 OS events have been reached. On the other hand, if the total number of the OS events is < 333 at the time of the final PFS analysis, the PFS final analysis will take place, and the OS interim analysis will only be conducted when the PFS endpoint is statistically significant. A Heybittle-Peto boundary with a 2-sided significance level of 0.0001 will be used for the OS interim analysis. Otherwise, a final OS analysis will be performed at approximately 350 events if the PFS endpoint is not statistically significant.

Secondary endpoints will be tested following a prespecified hierarchical order. If both PFS and OS endpoints are statistically significant, the secondary endpoints will be tested using a 2-sided alpha of 0.05. However, if only the OS endpoint (or PFS endpoint) is statistically significant, the secondary endpoints will be tested using a 2-sided alpha of 0.043 (or 0.007).

1.5.2 Final Analysis OS

The final analysis for the OS will be conducted after approximately 350–353 OS events are reached.

1.6 Testing Procedure and Level of Significance

The Type I error rate will be controlled for testing the primary and secondary endpoints. A 2-sided FWER of 0.05 will be used, with 0.007 allocated to the PFS hypothesis testing and 0.043 allocated to the OS hypothesis testing. The alpha level for the OS interim analysis will be based on a Heybittle-Peto boundary with a 2-sided significance level of 0.0001. The plan for conducting the interim and final OS analyses is specified in Section 1.5.1 and Section 1.5.2, respectively.

The secondary endpoint hypotheses will be tested sequentially with a 2-sided alpha level of 5% if both PFS and OS analyses show superiority. However, if only OS (or PFS) endpoint shows

superiority, the secondary endpoint hypotheses will be tested sequentially at an alpha level of 4.3% (or 0.7%).

The secondary endpoints will be ranked in the following hierarchical order. Statistical testing will follow this sequence.

1) ORR: CR + PR per investigator assessment
2) CA19-9 response: proportion of subjects with a decline of ≥ 60% from baseline
3) PRO by EORTC QLQ-C30: TUDD1 for global health status/QoL scale.
4) VTE rate
5) CBR rate

1.7 Blinding and Randomization Methods

1.7.1 Blinding Method

This is a double-blind study; the blinding method is described in the protocol (ie, Section 5.1 "Treatment Allocation and Blinding") and the DMC charter.

1.7.2 Randomization Method

Randomization will be implemented in this study using IWRS. The randomization of treatment assignment will be stratified by the following factors:

- Karnofsky Performance Status (KPS) 70-80 vs. 90-100
- Liver metastasis (present vs. absent)
- Age ≤ 65 years vs. > 65 years.

Subjects will be randomly assigned in a 1:1 ratio to the 2 treatment arms within each of 8 randomization strata using permuted block stratified randomization.

2 GENERAL ANALYSIS CONSIDERATION

The statistical analysis sections in this SAP are mainly for the Double-blind Randomized Phase. Subjects will be analyzed and summarized by treatment as randomized for all safety and efficacy endpoints. Safety run-in data will be summarized or listed separately from Phase 3 data and placed in an appendix of the clinical study report (CSR). They include tables for demographic, baseline characteristics and baseline disease characteristics; overview of treatment-emergent adverse events (TEAEs), all TEAEs by system organ class (SOC)/preferred term (PT), and maximum severity; and 1 efficacy listing (for best overall response, progression/death, and associated dates).

Unless otherwise specified, the baseline value is defined as the last non-missing valid value collected prior to the first administration of study treatment. For subjects who have been randomized but not treated, randomization date will be used as the reference date for baseline.

Subgroup analyses are mainly to demonstrate trend and assess internal consistency of any treatment benefit and/or safety signal. Forest plots of hazard ratios and associated confidence intervals will be provided to show the trend. Statistical tests will not be performed.

2.1 Analysis Sets

Intent-to-Treat Population

The intent-to-treat (ITT) population includes all subjects randomized into the study.

Safety Population

The safety population (SP) includes all subjects in the ITT population who received at least 1 dose of any study treatment (ibrutinib/placebo, nab-paclitaxel, and/or gemcitabine)

2.2 Definition of Subgroups

Analyses for the baseline subgroups (hereafter referred as “subgroup” or “subgroups”) will be performed for selected variables. The baseline subgroup variables (Table 1) and the cutoff values are subject to change if warranted to better represent the data.

Post-baseline outcome subgroups (hereafter referred as “post- baseline subgroup” or “post-baseline subgroups” as needed) are outcome variables and are exploratory in nature. Selected data will be summarized by these post- baseline subgroups (Table 2).

Table 1 Baseline Subgroups

Subgroup	Definition of Subgroup	Analysis Type
Age	≤ 65, > 65	B, E, S,
Gender	Male, Female	B, E, S,
Race	White, Non-White	B, E, S,
Geographic region	US, EU, Asia Pacific	B, E, S
Neutrophil/Lymphocyte Ratio (NLR)	≤ 4, > 4	E
KPS	70-80, 90-100	E,
Liver metastasis	Present, absent	E,
Renal function (creatinine clearance)	< 30, 30 - < 60, ≥ 60 mL/min	S
Hepatic function (NCI ODWG definition)	normal, mild, moderate, severe (or normal vs. non-normal as appropriate)	S

Analysis type: B=Demographics, Baseline Characteristics, Baseline Disease Characteristics; E = Efficacy (PFS and OS); KPS: Karnofsky Performance Status; NCI ODWG: NCI Organ Dysfunction Working Group Liver Function Classification (Ramanathan et al, 2008); S = Safety (Overview TEAE, TEAE by SOC/PT, Grade 3 or higher TEAE by SOC/PT).

Table 2 Post-Baseline Outcome Subgroups

Subgroup	Definition of Subgroup	Analysis Type
CYP3A inhibitor (for concomitant medications only)	Strong vs. other user	S
	Strong/moderate vs. other user	S
Survival Maintenance Subgroup	Subjects who are progression-free and alive at 6 months of treatment and who continue ibrutinib/placebo after having discontinued the 2 chemotherapies	Overall survival

Analysis type: S = Safety (Overview TEAE, TEAE by SOC/PT).

3 SUBJECT INFORMATION

3.1 Subject Disposition

The disposition tables will include the following summaries by treatment and overall.

- Analysis populations (all subjects)
- Enrollment by region, country and investigator (ITT population)
- Summary of randomization stratification per IWRS (ITT population)
- Study Treatment Disposition and Discontinuation (ITT population)
- Study Status, Duration of Treatment and Study Exit (ITT population).

The Kaplan-Meier estimates will be calculated to estimate the time on study using reversed censoring from the OS analysis.

3.2 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized with descriptive statistics for the ITT population by treatment arm.

3.3 Concomitant Medications

Medications will be coded to Anatomical Therapeutic Chemical (ATC) class and the preferred drug name (hereafter referred as “preferred name”) per World Health Organization (WHO) Drug dictionary.

Concomitant medications will be summarized by ATC class and preferred term for each treatment arm in the safety population. The summarization includes all the concomitant medications taken any time while on study treatment (ie, from the date of first dose through the date of last dose of the study treatment). Each subject will be counted once for each preferred term, and each ATC class. The following concomitant medications will be summarized separately. Details are in the mock-up tables.

- CYP3A inhibitors and inducers – This list requires a medical and pharmacology review, with finalization at the time of analysis
- Anticoagulants and antiplatelet agents will need medical review as above

3.4 Extent of Exposure to Study Treatment

Exposure to study treatment will be summarized by treatment arm for the safety population. Descriptive statistics will be provided for the following data for each of the 3 drugs unless otherwise specified: treatment duration (month), total number of doses received, total number of cycles received (for each chemotherapy), total cumulative dose administered for each drug, dose

intensity and relative dose intensity (%), and number (%) of subjects with dose reduction due to adverse events (AEs).

3.5 Subsequent Anti-Cancer Treatment

Subsequent anti-cancer treatment (including anti-cancer chemotherapy, anti-cancer radiation, and surgeries and procedures performed with therapeutic intent) will be summarized by treatment arm for the safety population. The ATC level will be specified in the mock-up table footnote.

4 ANALYSIS FOR ENDPOINTS

Analysis of endpoints will be conducted on the ITT population unless otherwise specified. For subgroup, sensitivity, and exploratory analyses, only the analyses that provide meaningful information will be presented for the CSR. The following 3 randomization stratification factors will be used for the stratified analysis/test: KPS (70-80 vs. 90-100), liver metastasis (present vs. absent), and age (≤ 65 years vs > 65 years). All stratified tests will be based on randomization stratification factors as recorded in the IWRS.

Table 3 Definitions and Analyses for Endpoints

Endpoint	Definition	Analysis Method
Primary Endpoints		
PFS assessed by investigator	Time from the date of randomization to the date of the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first, regardless of the use of subsequent anticancer therapy prior to documented PD or death.	Primary Analysis: Stratified log-rank test is the primary analysis comparing treatment differences. Stratified Cox regression model with Efron's tie handling method will be used to estimate HR and its associated 2-sided 95% CI. In addition, Kaplan-Meier estimates and median PFS with its associated 95% CI will be displayed. Subjects without an event will be censored at the last adequate tumor assessment date showing no evidence of progressive disease. Sensitivity Analysis: 1) Same analysis as the primary analysis except subjects who received subsequent anticancer therapy prior to documented progression or death will be censored at the date of the last adequate tumor assessment showing no evidence of progressive disease prior to or on the initiation of the new therapy. 2) Unstratified log-rank test, unstratified Cox regression model, confidence intervals using same censoring rule as for the primary analysis. Subgroup Analysis: Hazard ratio and its 95% CI from

Endpoint	Definition	Analysis Method
		unstratified Cox regression model for each subgroup.
OS	Time from the date of randomization to the date of death from any cause	Primary Analysis: Stratified log-rank test is the primary analysis comparing treatment differences. Stratified Cox regression model with Efron's tie handling method will be used to estimate HR and its associated 2-sided 95% CI. In addition, Kaplan-Meier estimates and median OS with its associated 95% CI will be displayed. Subjects who did not die will be censored at the last known alive date. Sensitivity Analysis: Unstratified log-rank test, unstratified Cox regression model and associated confidence intervals. Subgroup Analysis: Hazard ratio and its 95% CI from unstratified Cox regression model for each subgroup.
Secondary Endpoints:		
ORR	The proportion of subjects achieving a best overall response of CR or PR per investigator assessment per RECIST 1.1 at or prior to initiation of subsequent anticancer therapy	CMH chi-square test controlled for 3 stratification factors
CA19-9 response rate for ≥ 60% reduction	The proportion of subjects with at least a 60% decrease from baseline at or prior to initiation of subsequent anticancer therapy.	CMH chi-square test of response rate controlling for 3 stratification factors; Descriptive statistics of change and percentage change from baseline will be summarized by time.
EORTC QLQ-C30 Global Health Status/QoL scale: time until definitive deterioration (TUDD1)	TUDD1 was defined as the time interval between randomization and the first occurrence of a decrease in QLQ-C30 score ≥ 10 points without any further improvement in QoL score of ≥ 10 points or any further available QoL data due to	Stratified log-rank test. Descriptive statistics by time, Kaplan-Meier estimates

Endpoint	Definition	Analysis Method
	dropping out after the deterioration (Bonnetain et al, 2010).	
VTE	Proportion of subjects with TEAE VTE of any grade defined by SMQ terms as "embolic and thrombotic events, venous"	Chi-square test
CBR rate	Proportion of subjects who meet the "responder" criteria below prior to initiation of the subsequent anticancer therapy. Response was defined as achievement of a ≥50% reduction in MPAC visual analog scale which measures pain intensity **or** analgesic consumption, **or** a ≥ 20-point improvement from baseline in KPS sustained for a period of ≥ 4 consecutive weeks without showing any sustained worsening from baseline in any of the other parameters OR Subject was stable on all aforementioned parameters (pain and KPS), and also showed a marked, sustained weight gain (≥ 7% increase from baseline maintained for ≥ 4 weeks) not due to fluid accumulation (Burris et al, 1997)	CMH chi-square test controlled for 3 stratification factors; descriptive statistics for 4 categories (i.e., MPAC pain intensity reduction ≥ 50%, analgesic consumption reduction≥ 50%, KPS improvement ≥ 20 points, weight gain ≥ 7%)
Exploratory Endpoints		
CA19-9 response rate for ≥ 20% and ≥ 90% reductions	The proportions of subjects with at least a 20%, 90% decrease from baseline at or prior to initiation of subsequent anticancer therapy	CMH chi-square test controlling for 3 stratification factors Descriptive statistics of change and percentage change from baseline will be summarized by time.
DCR	Proportion of subjects achieving best response of CR, PR, or SD (≥ 8 weeks) per investigator assessment per RECIST 1.1 at or	CMH chi-square test controlled for 3 stratification factors

Endpoint	Definition	Analysis Method
	prior to initiation of subsequent anticancer therapy	
TDP	Time to the first 50% reduction from baseline in MPAC visual analog scale of pain intensity sustained for 4 weeks or longer on or prior to initiation of subsequent anticancer therapy.	Kaplan-Meier estimates, median TDP and its 2-sided 95% CI.
EORTC QLQ-C30 Global Health Status/QoL scale: time until definitive deterioration (TUDD2)	TUDD2 is defined as the time interval between randomization and the first occurrence of a decrease in QLQ-C30 score ≥ 10 points observed at all time points after the first deterioration or the subject dropped out after deterioration resulting in missing data (Anota et al, 2015).	Descriptive statistics by time, Kaplan-Meier estimates and hazard ratio

CBR: Clinical Benefit Response Rate; CMH: Cochran-Mantel-Haenszel; CI: confidence interval; CR: complete response; HR: estimate hazard ratio; KPS: Karnofsky Performance Status; MPAC: Memorial pain Assessment Card; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RECIST 1.1: Response Evaluation Criteria In Solid Tumors; SD: stable disease; TEAE: treatment-emergent adverse event; SMQ; standardized MedDRA (Medical Dictionary for Regulatory Activities) query; VTE: Venous thromboembolic event, DCR: disease control rate. TDP: time to diminished pain.

All primary and secondary endpoints will be analyzed for the ITT population.

5 SAFETY ASSESSMENTS

Safety data will be summarized by treatment. Table 4 summarizes the safety analyses to be carried out. Adverse events (AEs) will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the investigator according the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Events of special interest such as hemorrhagic events, major hemorrhage, and other safety observations such as hypertension, interstitial lung disease (ILD), severe cutaneous adverse reactions (SCAR), rash, cardiac arrhythmia excluding atrial fibrillation, and other malignancies will be included.

In general, the treatment-emergent period is defined as the period from the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent antineoplastic therapy, whichever comes first. Treatment-emergent adverse events are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment or events with a complete missing onset date but with a resolution date during the treatment phase.

All laboratory values will be converted to and reported as international standard (SI) units. In general, only data from the central laboratory will be summarized and analyzed. Laboratory parameters will be graded using the NCI CTCAE, Version 4.03. Unless otherwise specified, only baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis.

Table 4 Summary of Safety Assessments

Assessment Type	Definition	Analysis Methods
AE	TEAEs, SAEs, Grade 3 or higher TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, protocol- defined events of special interest and other safety observations	Descriptive summary statistics and/or listings
Laboratory Parameters	Worst post-baseline toxicity grade for CTCAE gradable hematology and chemistry. Abnormalities in creatinine clearance, uric acid, and liver function	Descriptive summary statistics and/or listings
Vital Signs and other Observations Related to Safety	Blood pressure, heart rate, new or worsened eye-related symptoms	Descriptive summary statistics and/or listings

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; TEAE: treatment-emergent adverse event

6 CHANGES IN PROTOCOL PLANNED ANALYSIS

Protocol Section 10.4.1 states the following:

"PFS final analysis and OS interim analysis will be carried out at the same time after at least 350 PFS events and 250 death events (approximately 71% of death events) are observed. To control the family-wise Type I error rate the fallback method as specified in the FDA Draft Guidance (Multiple Endpoints in Clinical Trials, 2017), will be used to test the two primary endpoints. A 2-sided family-wise Type I error rate (FWER) of 0.05 will be used with 0.007 allocated to the PFS hypothesis testing and 0.043 allocated to the OS hypothesis testing. Lan-DeMets alpha spending function with O'Brien-Fleming boundary for efficacy will be used to determine the Type I error rate for the interim and final OS analyses depending on whether an alpha of 0.043 or 0.05 is used."

However, the OS interim analysis strategy has been changed from Protocol Section 10.4.1. Conditions for conducting the OS interim analysis are outlined below:

1) If at the time of the planned final PFS analysis, (i.e., at least 350 PFS events as specified in the protocol) the total number of OS events is ≥ 333 (ie, ≥ 94% of the OS information fraction), the PFS final analysis will be delayed until the final OS events of approximately 350 have been reached.

2) If at the time of the planned final PFS analysis, the total number of the OS events is < 333, the PFS final analysis will take place.

    a. If the PFS endpoint at the final analysis is significant, the OS interim analysis will be conducted using the Heybittle-Peto boundary.

        i. The interim analysis boundary will be based on a fixed Heybittle-Peto boundary using a 2-sided significance level of 0.0001.

    b. If the PFS endpoint at the final analysis is not significant, the OS will be tested at the time of the final analysis when a total of ~350 OS events have occurred.

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