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Statistical Analysis Plan

A Multicenter, Open-Label, Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab in Previously Untreated Subjects with Follicular Lymphoma

PCYC-1125-CA

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Version 4.0

Revision History

Version Number	Date	Description
1.0	18Feb2014	Original version
2.0	11Feb2016	Version 2.0: Reason for changes • To be consistent with the protocol amendment 2.0 • To be consistent with the biometrics standard analytical methods
3.0	06Jul2017	Version 3.0: Reason for changes • Updated the latest protocol version and date referenced in the introduction section of SAP • Updated the language to clarify that PK and biomarker analysis are not within the scope of SAP • Analysis population: replaced 'study drug' by 'study treatment; removed the safety analysis population • Extent of exposure: updated the definition of average daily dose • Analysis of ORR: updated the 95% CI to exact binomial (Clopper-Pearson) method • In the PFS analysis, subjects who receive subsequent antineoplastic therapy before PD or death will not be censored at the last evaluable disease assessment prior to the start date of the new therapy • Updated the definition of hemorrhagic events and major hemorrhagic events (Section 5.1.2) • Added the following Safety Observations per team discussion: Interstitial Lung Disease (ILD), Severe Cutaneous Adverse Reaction (SCAR), Cardiac Arrhythmia Excluding A. Fib, and rash (Section 5.1.3) • T/B/NK data analysis (Section 5.2 in SAP v2.0) is out of the scope of SAP and is removed

4.0	26Oct2017	Amendment summary: This version applies the latest SAP template; structure and contents are updated to align with other studies. Below are the major changes made: 1. Removed the section for objectives of study and add a section for endpoints; removed the section for blinding and randomization method and refer to the protocol; simplified languages where appropriate

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
BSA	Body Surface Area
BTK	Bruton's Tyrosine Kinase
CI	confidence interval
CR	complete response.
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FL	follicular lymphoma
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PO	per os (oral), by mouth
PR	partial response
PT	preferred term
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse events
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) lays out key elements including definitions and statistical methods for analysis of data in evaluation of efficacy and safety for the PCYC-1125-CA study. Analyses of pharmacokinetics data and biomarkers will be addressed in separate documents.

1.1. Study Design

This is an open-label, phase 2 study designed to assess the efficacy and safety of ibrutinib combined with rituximab in previously untreated subjects with FL. The study will include approximately 80 subjects in two treatment arms.

In Arm 1 (n = 60), subjects will receive ibrutinib 560 mg PO (by mouth) continuously until disease progression or unacceptable toxicity. In addition, subjects will receive rituximab 375 mg/m^2 IV once weekly for 4 doses for the first 4 weeks of study treatment. Subjects in Arm 1 will have imaging efficacy assessments every 12 weeks for the first 8 assessments and then every 16 weeks thereafter.

In Arm 2 (n = 20), subjects will receive ibrutinib 560 mg PO continuously as a single agent for the first 8 weeks, then ibrutinib at 560 mg will continue concurrently with rituximab 375 mg/m^2 IV once weekly for 4 doses. Once treatment with rituximab is complete, subjects will continue to receive single-agent ibrutinib continuously until disease progression or unacceptable toxicity. Subjects in Arm 2 will have imaging efficacy assessments at the end of 8 weeks and then every 12 weeks thereafter for 8 assessments and then every 16 weeks thereafter. Subjects who progress prior to starting rituximab will be discontinued from the study. Rituximab will not be administered prior to the protocol-specified administration.

One of the purposes of Arm 2 is to identify biomarkers that predict sensitivity or resistance to ibrutinib. Based on phase 1 clinical data in FL it is predicted that approximately half of the subjects treated in this arm will show evidence of resistance to single-agent ibrutinib. By providing a lead-in time prior to the initiation of rituximab, pre- and post-progression biopsy samples can be collected to address markers of drug resistance. These objectives are exploratory and therefore the primary and secondary objectives related to clinical efficacy are paramount, but will be analyzed separately from Arm 1, since the treatment regimen in this arm is different.
For Arm 1, pre-treatment and post-progression tumor tissue biopsies are optional. For Arm 2, pre-treatment tumor tissue biopsy is required and post-progression tumor tissue biopsies are desired but optional. Tumor samples may be analyzed by gene expression profiling (GEP), whole exome sequencing (WES), or other methods.

Ibrutinib and rituximab are each referred to as a component of study treatment. Study drug and study treatment are interchangeable concepts throughout this document.

1.2. Endpoints

Primary Endpoints

Efficacy

The primary endpoint is ORR (Complete response [CR] + Partial Response [PR]) based on Cheson (2007) as assessed by the investigator.

Secondary Endpoints

Efficacy:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)

Safety:

- Frequency, severity, and relatedness of treatment-emergent adverse events (AEs)
- Frequency of treatment-emergent AEs requiring discontinuation of study drug or dose reductions

1.3. Statistical Hypotheses

The primary hypothesis of this study is that the ORR of ibrutinib and rituximab combination treatment in low grade FL subjects is equal to or lower than 53%.

The statistical hypotheses are as follows:

H_0: the ORR of ibrutinib and rituximab combination treatment in low grade FL subjects is equal to or lower than 53%

versus

H_1: the ORR of ibrutinib and rituximab combination treatment in low grade FL subjects is greater than 53%

These hypotheses will be tested using a 2-sided 95% confidence interval that will be calculated for ORR based on exact binomial distribution (Clopper-Pearson).

1.4. Sample Size Determination

Arm 1

The planned sample size for Arm 1 in this open-label, phase 2 study is 60. The hypotheses test of primary endpoint analysis for Arm 1 in this study assumes an underlying response rate of 53% for first-line rituximab treatment in subjects with low grade FL (Hainsworth 2002; Freedman 2009). Assuming a true response rate of 71%, a sample size of 60 eligible subjects provides greater than 80% power to reject the null hypothesis $H_0 \leq 53\%$ at 1-sided 2.5% significance level.

Arm 2

Twenty (20) subjects will be enrolled in Arm 2. One of the purposes of Arm 2 is to identify biomarkers that predict sensitivity or resistance to ibrutinib. Due to the exploratory nature of the study objective of Arm 2, the sample size was determined without a formal calculation. The sample size of 20 was determined since it was deemed an adequate number to implement exploratory evaluation of biomarker activities in relation to ibrutinib treatment.

1.5. Planned Analyses

The primary analysis for the clinical study report (CSR) will occur at least 1 year after the last subject enrolled in Arm 1 received the first dose of study treatment.

1.6. Testing Procedure and Level of Significance

The 2-sided significance level for the final analysis of primary endpoint (ORR) will be 0.05. Tests of secondary endpoints will be performed using the same significance level.

2. GENERAL ANALYSIS CONSIDERATION

Time to event or duration of event endpoints will be based on the actual event date (or censoring date) rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

In general, the baseline value is defined as the last valid measurement on or prior to the first dose of study treatment (ibrutinib/placebo, rituximab). For by-visit analysis, visit windows will be used to associate assessment with a scheduled visit and will be created in reference to the date of the first dose of study treatment to assign a visit number based on the assessment date.

2.1. Analysis Sets

All-treated population:

The subjects who are enrolled in the study and have received at least 1 dose of study treatment. Safety and efficacy analyses will be performed using the all-treated population.

Response-evaluable population:

The subjects in the all-treated population who have measurable disease at baseline and have at least 1 adequate post-treatment disease assessment by the investigator before the start of subsequent anti-cancer therapy.

2.2. Definition of Subgroups

There is no subgroup analysis planned.

3. SUBJECT INFORMATION

3.1. Subject Disposition

The number of subjects who enrolled and the number of subjects who received study treatment (subjects in the safety population) will be summarized by treatment arm.

Disposition information will be summarized for all-enrolled subjects. Subject enrollment will be summarized by investigator and by treatment arm. Study termination and treatment discontinuation will be summarized by the reason for discontinuation for each arm.

3.2. Demographics and Baseline Characteristics

Baseline characteristics and demographic information at baseline will be summarized with descriptive statistics by treatment arm.

3.3. Prior and Concomitant Medications

Medications will be coded to a generic name and an Anatomical Therapeutic Chemical (ATC) class per the World Health Organization (WHO) drug dictionary. Concomitant medications will be summarized by therapeutic class and preferred term and by treatment arm. Concomitant medications are defined as medications that were taken at any time on treatment (i.e. from the date of the first dose of study treatment through the date of the last dose of study treatment). The following concomitant medications will be summarized separately: growth factors, blood supportive products and immunoglobulin, CYP3A inhibitors/inducers, anticoagulants and/or antiplatelets.

3.4. Extent of Exposure to Study Treatment

Exposure to study treatment will be summarized by treatment arm. Descriptive statistics will be provided for treatment duration and dosing information (e.g. total cumulative dose administered, relative dose intensity, dose reduction due to adverse events) for all study treatments.

3.5. Previous Treatment History and Subsequent Antineoplastic Therapies

Previous treatment history and subsequent FL antineoplastic agents will be summarized separately.

4. EFFICACY AND SAFETY ANALYSES

4.1. Efficacy Analyses

Efficacy endpoints and analysis methods for the randomized treatment arms (Arms 1 and 2) are summarized in Table 1.

Table 1: Summary of Efficacy Analyses

Endpoint	Definition	Analysis Methods
Primary Endpoint		
ORR	Proportion of subjects achieving the best overall responses of CR or PR prior to initiation of the next line of antineoplastic therapy as assessed by investigator per the Cheson (2007) criteria.	Primary ORR and its 2-sided 95% CI will be calculated using the exact binomial distribution (Clopper-Pearson), based on the all treated population. Sensitivity analysis ORR will be performed using the response-evaluable population.
Secondary Endpoints		
PFS	Time from the date of the first dose of study treatment to confirmed PD or death from any cause, whichever occurred first, as assessed by investigator. For subjects without any baseline or post-baseline disease assessment, PFS will be censored on the date of the first study treatment dose.	Primary Kaplan-Meier method, based on the all treated population.

Endpoint	Definition	Analysis Methods
DOR	Time from the date of the first documented response (CR or PR) to the first documented evidence of PD or death from any cause. For subjects with no PD nor death at the time of analysis, DOR will be censored on the date of the last adequate post-baseline disease assessment, or on the date of the first occurrence of response (CR or PR) if there is no disease assessment afterwards.	Primary Analysis of DOR will be based on the subjects who have achieved a response (CR or PR) prior to initiation of the next line of anticancer therapy in the all-treated population. The median DOR and its 2-sided 95% CI will be obtained using the same method as described for PFS.
OS	Overall survival (OS) is defined as the time from the date of the first dose of study treatment to the date of death due to any cause. For subjects who are known to be alive or whose survival status is unknown at the time of analysis and/or study closure, OS data will be censored at the date last known alive. Subjects who withdraw consent prior to study closure will be censored on the date of the consent withdrawal.	Primary Based on the all-treated population. KM curves will be used to estimate the distribution of OS.

4.2. Safety Analyses

Safety data will be summarized by treatment arm. Table 2 summarizes the safety analyses to be performed for all treatment arms.

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 NCI-CTCAE v4.03.

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 v4.03.

Unless otherwise specified, only baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis. In general, the treatment-emergent period is defined as the period from the date of the first dose of study treatment (rituximab, ibrutinib/placebo) up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent antineoplastic therapy (including crossover ibrutinib), whichever comes first. The treatment-emergent period for crossover ibrutinib is defined as the period from the date of the first dose of ibrutinib after crossover up to 30 days after the date of the last dose of ibrutinib or the day before initiation of subsequent antineoplastic therapy, whichever comes first.

The treatment-emergent adverse events (TEAEs) are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment.

Table 2: Summary of Safety Analyses

Safety Assessment	**Definition**	**Analysis Methods**
Safety and tolerability	AE: TEAEs, SAEs, grade 3 or worse TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, protocol- defined events of special interest such as hemorrhagic events, major hemorrhage, and other safety observations such as hypertension, ILD, SCAR, rash, cardiac arrhythmia excluding atrial fibrillation), other malignancies Worst post-baseline toxicity grade for selected lab tests: Worst post-baseline toxicity grade, Hgb, creatinine clearance, abnormal uric acid, liver function abnormalities	Descriptive summary statistics and/or listings

Safety Assessment	Definition	Analysis Methods
	Vital signs, blood pressure, heart rate, temperature, respiratory rate, weight	

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ILD: interstitial lung disease; SAE; serious adverse event; SCAR: severe cutaneous adverse reaction; TEAE: treatment-emergent adverse event

5. MODIFICATION OF ANALYSIS TO THE PROTOCOL

Below is a major change made to the analyses described in the protocol:

- To be consistent with the biometrics standard method of PFS analysis, the censoring rule for PFS has been modified where the censor date for subjects without disease progression or death is based on the date of the last disease assessment, regardless of whether the given subject received alternative anticancer therapy. In the protocol, the censor date is based on the last disease assessment prior to the subsequent anti-cancer therapy.

6. REFERENCES

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