Statistical Analysis Plan

A Randomized Multicenter Study of Ibrutinib in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed/Refractory Multiple Myeloma

PCYC-1138-CA

June 26, 2018

Version 2.0

Statistical Analysis Plan Approval

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SAP Version:	2.0
Date:	26JUN2018

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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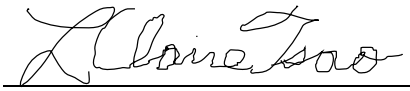 Claire Tsao, PhD Senior Director, Biostatistics	26Jun2018 Date (ddMMMyyyy)
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCB	Duration of Clinical Benefit
DOR	duration of overall response
Hgb	hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
NCI	National Cancer Institute
ORR	overall response rate
PCYC	Pharmacyclics
PD	progressive disease
PR	partial response
PT	preferred term
SAP	statistical analysis plan
TEAE	treatment-emergent adverse events

1 INTRODUCTION

The Study PCYC-1138-CA consisted of a Phase 1 and a Phase 2 part. After completion of the Phase 1 part, in which 11 subjects received study treatment, the sponsor decided to not pursue an indication for treatment of patients with multiple myeloma with ibrutinib and therefore terminate the study early. Thus, this statistical analysis plan (SAP) is to define only the key study elements for the Phase 1 part of the study including variable definitions, and statistical methods for analysis of data in evaluation of efficacy and safety. Analyses of pharmacokinetics data will be addressed in a separate document. Biomarker analysis will not be performed due to early termination of the study. Throughout this SAP, "study treatment" and "study drug" are used interchangeably.

Analysis methods specified in this document take precedence over those described in the study protocol should there be any difference.

1.1 Study Design – Phase 1

The Phase 1 part of the study was an open-label, international, multicenter dose-finding study of the ibrutinib, pomalidomide and dexamethasone combination in subjects with relapsed/refractory multiple myeloma (MM). Up to 18 patients were to be enrolled in order to determine the maximum therapeutic dose/maximum administered dose (MTD/MAD). In the dose finding portion of the study, up to 2 cohorts were to be explored (Table 1). The study followed a 3+3+3 dose escalation design. The MTD/MAD was defined as the highest dose level at which <33% (ie, ≤ 1 of 6 or ≤ 2 of 9) of subjects in a cohort experience a study treatment related dose limiting toxicity (DLT).

Table 1: Dosing Levels and Cohorts

Dose Level	Cohort	Ibrutinib[a]	Pomalidomide[b]	Dexamethasone[c]
-1	-1	420 mg once daily	4 mg	40 mg
1 (Starting Dose)	1	560 mg once daily	4 mg	40 mg
2	2	840 mg once daily	4 mg	40 mg

[a.] Ibrutinib was administered PO starting on Day 1 of Cycle 1, dosing was continuous thereafter (without interruption).

[b.] Pomalidomide was administered PO on Days 1 – 21 of a 28-day cycle.

[c.] Dexamethasone was administered PO once weekly. The dose was reduced to 20 mg weekly in those >75 years of age

1.2 Objective/Endpoints of Study – Phase 1

- **Primary Objective**
  - To determine the MTD)/ MAD of the ibrutinib, pomalidomide and dexamethasone combination.
  - To determine the safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory MM.
- **Secondary Endpoints**
  - Overall response rate (ORR): partial response (PR) or better, per the International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011)[1,2,3]
  - Duration of Response (DOR)
  - The clinical benefit rate (CBR) and its duration, defined as ≥ minimal response (MR) according to the IMWG response criteria
  - To evaluate the pharmacokinetics (PK) of ibrutinib and pomalidomide when given in combination with dexamethasone

1.3 Sample Size Determination

Phase 1: This was a standard 3+3+3 design to determine the MTD/MAD and toxicity profile of ibrutinib in combination with pomalidomide and dexamethasone. Dose escalation were to follow the 3+3+3 principle and up to 2 cohorts were to be explored. This study was not powered for comparison of treatment cohorts. Up to 18 subjects were to be enrolled into the Phase 1 part of the study.

1.4 Planned Analysis

- **Final Analysis**

The final analysis for the clinical study report will be conducted when all Phase 1 subjects have exited PCYC-1138-CA study. The sponsor decided not to perform the Phase 2 part of the study following a decision not to pursue an indication for multiple myeloma for ibrutinib.

2 GENERAL ANALYSIS CONSIDERATION

Subjects will be analyzed and summarized for safety and other selected endpoints.

2.1 Analysis Sets

- **Safety Population**

  The safety population include subjects who have received any dose of study treatment.

- **Response-Evaluable Population**

  The response-evaluable population is defined as subjects who are in safety population and provided at least one post-baseline response (or disease) assessment. All subjects in safety population received at least 1 post-baseline response assessment.

3 SUBJECT INFORMATION

3.1 Subject Disposition

The disposition tables will include the following summaries.

- Analysis population
- Study Treatment Disposition and Discontinuation
- Study Status, Duration of Treatment and Study Exit

Time on study is defined as the interval between the date of first dose and the date of last known to have been alive. The Kaplan-Meier method will be used to estimate the median time on study with subjects who died being censored at death date.

3.2 Demographics and Baseline Characteristics

Subject demographics, baseline characteristics and baseline disease characteristics will be summarized with descriptive statistics for the safety population.

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 drug dictionary. Listings will be provided to present the data.

Concomitant CYP3A inhibitors and inducers taken any time while on study treatment (i.e., from the date of first dose through the date of last dose of the study treatment) will be summarized by ATC class and preferred term (PT). Each subject will be counted once for each PT, and each ATC class.

3.4 Extent of Exposure to Study Treatment

Exposure to the 3 study drugs will be summarized 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) and number (%) of subjects with dose reduction due to adverse events (AEs).

4 ANALYSIS FOR ENDPOINTS

Analysis of secondary endpoints (Table 2) will be conducted on the safety population.

Table 2: Definitions and Analyses for Secondary Endpoints

Endpoint	Definition	Analysis Method
Secondary endpoints:		
Overall Response Rate (ORR)	The proportion of subjects achieving a best overall response of PR or better per investigator assessment per IMWG at or prior to initiation of subsequent anticancer therapy	ORR will be estimated and the corresponding 2-sided 95% exact binomial confidence interval will be calculated.
Duration of Response (DOR)	The time interval between the date of initial documentation of a response and the date of first documented evidence of PD, death, or date of censoring for the subjects not progressed/died. The censoring date is the last adequate tumor assessment date.	A listing will be provided.
Clinical Benefit Rate (CBR)	The proportion of subjects achieving a best overall response of MR or better per investigator assessment per IMWG at or prior to initiation of subsequent anticancer therapy	CBR will be estimated and the corresponding 2-sided 95% exact binomial confidence interval will be calculated.

Note: DOR; duration of response; PD: disease progression; PR: partial response; MR: minimal response; IMWG: International Myeloma Working Group.

5 SAFETY ASSESSMENTS

Safety data will be summarized for safety population unless otherwise indicated. Table 3 summarizes the safety analyses to be carried out. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs were graded by the investigator according the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. A listing will be provided to indicate dose-limiting toxicity (DLT).

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 anticancer therapy, whichever comes first. Treatment emergent AEs 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 v4.03.

Table 3: Summary of Safety Assessments

Assessment Type	Definition	Analysis Methods
AE	TEAEs, SAEs, non-serious TEAE, 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 and other safety observations	Descriptive summary statistics and/or listings
Lab	Worst post-baseline toxicity grade for selected 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	SBP, DBP, weight, heart rate, new or worsened eye-related symptoms	Descriptive summary statistics and/or listings
Dose Limiting Toxicity (DLT)	DLT	Listing

TEAE: treatment-emergent adverse event; SAE= serious adverse event; SBP: systolic blood pressure; DBP: diastolic blood pressure; CTCAE= Common Terminology Criteria for Adverse Events.

6 CHANGES IN PROTOCOL PLANNED ANALYSIS

The following modifications to the protocol "Statistical Methods and Analysis" section is made due to the decision by sponsor to terminate the study early.

1) Phase 2 part of the study was not initiated, therefore, the analysis for Phase 2 will not be performed.

2) Biomarker analysis will not be performed due to early termination of the study.

3) The secondary endpoint of the duration of clinical benefit response will not be performed due to the early termination of the study.

7 REFERENCES

1. Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. Leukemia 2008; 22(2):231-239.

2. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20(9):1467-1473.

3. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117(18): 4691-4695.