



Statistical Analysis Plan

An Open-label study of Ibrutinib in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma

PCYC-1139-CA

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Overall Response
Hgb	hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	median progression-free survival
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PCYC	Pharmacyclics
PD	progressive disease
PFS	progression-free survival
PR	partial response
PT	preferred term
SAP	statistical analysis plan
TEAE	treatment-emergent adverse events

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the protocol Amendment 4 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-1139-CA. Analyses of pharmacokinetics data will be addressed in a separate document. Biomarker analysis will not be performed for this study, as the Sponsor decided not to pursue the indication of multiple myeloma for ibrutinib. Throughout this SAP, “study treatment” and “study drug” are used interchangeably.

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

1.1 Study Design

The study is an open-label, international, multicenter study of ibrutinib in combination with bortezomib and dexamethasone in subjects with MM who have received 2 or 3 prior lines of therapy and have demonstrated disease progression following the completion of the last line of therapy.

Approximately 125 subjects were to be enrolled. Due to early termination of the study per sponsor’s decision, enrollment was closed at the time when 74 subjects received at least 1 dose of study drug. The decision to discontinue study was based on the consideration that MM may not be the disease area where ibrutinib can provide a significantly better therapeutic benefit for the majority of patients compared to other approved drugs currently on the market. Therefore, the sponsor decided to focus the future research and development efforts in other disease areas where we can provide more benefits to patients.

1.2 Endpoints

- **Primary Endpoint(s)**
 - The primary efficacy endpoint is median Progression Free survival (PFS) per the International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011)^{1,2,3} in subjects with relapsed or relapsed and refractory MM.
- **Secondary Endpoints**
 - Overall response rate (ORR): partial response (PR) or better, according to the IMWG response criteria per investigator assessment
 - PFS rates at landmark points are the percentages or probabilities of surviving and progression-free at the landmark time points.
 - Duration of Response (DOR)

- Overall Survival (OS)
- Time to Progression (TTP)
- **Exploratory Endpoint**
 - Time to subsequent anticancer therapies in subjects with relapsed or relapsed and refractory MM
- **Safety Assessments**
 - Safety and tolerability of ibrutinib in combination with bortezomib and dexamethasone

1.3 Statistical Hypotheses

The null hypothesis is the median PFS (mPFS) ≤ 8 months and the alternative hypothesis is mPFS ≥ 12 months. A 2-sided 95% confidence interval for the mPFS will be calculated to test the hypothesis.

1.4 Sample Size Determination

The sample size was originally estimated to be approximately 125 to achieve 80% power at a 1-sided 0.025 significance level to test the null hypothesis of mPFS ≤ 8 months vs ≥ 12 months under the alternative hypothesis, with the assumption that the PFS follows an exponential distribution. The 2-sided 95% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for mPFS will be calculated to test the hypotheses. An mPFS of 8.1 months was observed in the PANORAMA-1 Study where a similar patient population was treated with bortezomib and dexamethasone⁴. This hypothesis for mPFS with the revised enrollment to only include 2-3 prior lines of therapy without enrollment limitations for prior bortezomib exposure is further supported by recent data in the ENDEAVOR Study demonstrating similar outcome⁵. The sample size of approximately 125 subjects is determined by simulation method assuming that the PFS follows an exponential distribution and the mPFS is 12 months with ibrutinib in combination with bortezomib and dexamethasone. In addition, an enrollment period of 20 months with an average enrollment rate of 6 subjects per month, an exponential censoring process allowing approximately 6.5% censored observations, for example, due to non-progression related dropout, during the study duration prior to the analysis, and the time of primary analysis at 12 months after the last subject enrolled into the study were also assumed in the simulation. Under the above assumptions, approximately 83 PFS events would occur prior to the analysis.

1.5 Planned Analysis

- **Final Analysis**

The final analysis for the clinical study report was originally planned to include the data up to 12 months after the last subject enrolled or 83 PFS events occurred, whichever occurs earlier. However, after 74 subjects were enrolled and treated, the sponsor decided to terminate the study due to a decision to no longer pursue the indication. Therefore, the final analysis will be conducted when all subjects have exited PCYC-1139-CA study (study termination or subjects being rolled over to a long-term extension study, PCYC-1145-LT). The timing of the primary analysis will be approximately 18-20 months after the last subject enrolled. No interim analysis will be conducted.

2 GENERAL ANALYSIS CONSIDERATION

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

2.1 Analysis Sets

- **All-Treated Population**

The all-treated population include subjects who have received any dose of study treatment.

- **Response-Evaluable Population**

The response-evaluable population is defined as all-treated subjects who provided at least one post-baseline response (or disease) assessment.

- **Safety Population**

The safety population include subjects who have received any dose of study treatment which is the same as all-treated population.

2.2 Definition of Subgroups

Analyses for the baseline subgroups (hereafter referred as “subgroup” or “subgroups”) will be performed for the primary endpoint analysis to assess the internal consistency of any treatment benefit. The baseline subgroup variables (Table 1) and the cutoff values are subject to change if warranted to better represent the data.

Table 1: Baseline Subgroups

Subgroup	Definition of Subgroup	Analysis Type
Prior bortezomib exposure	Yes, No	Efficacy: Progression Free Survival
Number of prior line therapy	1, >= 2	Efficacy: Progression Free Survival

3 SUBJECT INFORMATION

3.1 Subject Disposition

The disposition tables will include the following summaries.

- Analysis population (all-treated subjects)
- Enrollment by region, country and investigator
- Study Treatment Disposition and Discontinuation
- Study Status, Duration of Treatment and Study Exit

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, baseline characteristics and baseline disease characteristics will be summarized with descriptive statistics for the all-treated 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.

Concomitant medications will be summarized by ATC class and preferred term (PT). The summarization includes all the concomitant medications 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). Each subject will be counted once for each PT, and each ATC class. The following concomitant medications will be summarized separately. Details are in the mock-up tables.

- CYP3A inhibitors and inducers
- Anticoagulants and antiplatelet agents
- Prophylaxis for infections

3.4 Extent of Exposure to Study Treatment

Exposure to study treatment will be summarized for the all-treated 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). Dexamethasone exposure will be analyzed in 2 separate modules (prior to

12May2017 vs. on/after 12May2017) per the protocol amendment 4 which decreased the frequency of dexamethasone dose regimen.

3.5 Subsequent Anti-Cancer Treatment

Subsequent anti-cancer treatment will be summarized for the all-treated population.

4 ANALYSIS FOR ENDPOINTS

Analysis of endpoints (Table 2) will be conducted on the all-treated population.

Table 2: Definitions and Analyses for Endpoints

Endpoint	Definition	Analysis Method
Primary Endpoints:		
PFS assessed by investigator	Progression free survival (PFS) is defined as the time from the date of first dose of study treatment to confirmed disease progression or death from any cause, whichever occurs first. The PFS will be assessed according to the IMWG response criteria.	<u>Primary Analysis:</u> Kaplan-Meier (KM) estimates, mPFS and its associated 95% confidence interval will be displayed. The 2-sided 95% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for mPFS will be calculated to test the hypotheses. The null hypothesis will be rejected if the lower bound of the confidence interval is greater than 8 months. <u>Subgroup Analysis:</u> KM estimates, mPFS and its associated 95% CI similar to those for the primary analysis will be calculated by Number of prior systemic therapies (1 vs ≥ 2 and prior bortezomib exposure (yes vs no)
Secondary endpoints:		
PFS Rates at landmark points	PFS rates at landmark points are the proportion of subjects without progression (i.e., KM estimates) at the landmark time points.	PFS at landmark time points (4, 8, 12, 16 months from date of first dose of study treatment) will be obtained by Kaplan-Meier method. The 95% CI for the landmark PFS rates will be provided using the log-log-transformed Greenwood variance estimate.
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	ORR will be estimated and the corresponding 2-sided 95% exact binomial confidence interval will be calculated.

Endpoint	Definition	Analysis Method
Overall Survival (OS)	anticancer therapy Time from date of first dose of study treatment to the date of death from any cause	Kaplan-Meier estimates, median OS (mOS) and its associated 95% confidence interval will be displayed.
Duration of Response (DOR)	The time interval between the date of initial documentation of a response (PR or better) 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.	Kaplan Meier estimates, median DOR and its associated 95% confidence interval will be displayed.
Time to Progression (TTP)	Time from date of first dose of study treatment to the date of first documented evidence of PD or date of censoring for the subjects not progressed. The censoring date is the last adequate tumor assessment date.	Kaplan Meier estimates, median TTP and its associated 95% confidence interval will be displayed.

Note: PR: partial response; IMWG: International Myeloma Working Group. The primary and secondary endpoints will be analyzed for the All-Treated population.

5 SAFETY ASSESSMENTS

Safety data will be summarized for all-treated 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 will be graded by the investigator according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

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, 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

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

6 CHANGES IN PROTOCOL PLANNED ANALYSIS

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

- 1) The interim analysis per Protocol Section 10.5.7 will not be performed.
- 2) Biomarker analysis will not be performed.
- 3) The study originally planned to have 125 subjects enrolled. Due to early termination of the study per sponsor’s decision, enrollment was closed and 74 subjects received at least 1 dose of study drug. The planned statistical power will not be met due to the decrease in sample size. Therefore, the final efficacy analysis will focus only on the primary endpoint, as well as PFS, OS and ORR. The exploratory analysis (time to subsequent anticancer therapies) will not be performed.
- 4) Safety analyses will be conducted on the all-treated population.

7 REFERENCES

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