Statistical Analysis Plan

TITLE: **A Multicenter Study of Ibrutinib and Lenalidomide in Combination with DA-EPOCH-R in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma**

PROTOCOL: **PCYC-1124-CA**

DATE: **29 September 2017**

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SUMMARY OF PLANNED ANALYSES

Endpoint	Definition	Analysis Method
Part 1:		
Primary Endpoints (for all subtypes of DLBCL):		
MTD	MTD and DLTs	Descriptive summaries and/or listings.
Safety and tolerability	TEAEs, SAEs, and other safety parameters	Descriptive summaries and/or listings.
Secondary Endpoint (for all subtypes of DLBCL):		
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.	ORR and its corresponding exact binomial 2-sided 90% CI, based on the all-treated population enrolled in Part 1. Analysis will be also conducted for ABC DLBCL subtype and for ABC and other non-GCB subtype, determined by GEP.
Part 2:		
Primary Endpoint:		
ORR	The same as above	Primary ORR and its 2-sided 90% CI will be calculated using the exact binomial distribution, based on the all-treated population at the RP2D with the ABC subtype of DLBCL, determined by GEP. Sensitivity • Based on the response-evaluable population at the RP2D with the ABC subtype of DLBCL, determined by GEP. • Based on the all-treated population at the RP2D with ABC and other non-GCB subtype, determined by GEP.
Secondary Endpoints:		
Efficacy:		
PFS	Time from the date of the first dose of study drug to confirmed PD or death from any cause, whichever occurred first.	Primary Kaplan-Meier method, based on the all-treated population at the RP2D with the ABC subtype of DLBCL, determined by GEP. Sensitivity

Endpoint	Definition	Analysis Method
		Based on the all-treated population at the RP2D with ABC and other non-GCB subtype, determined by GEP.
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 who have achieved an overall response but did not die or progress 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 at the RP2D with the ABC subtype of DLBCL, determined by GEP. The median DOR and its 2-sided 95% CI will be obtained using the same method described for PFS. Sensitivity Based on the all-treated population at the RP2D with ABC and other non-GCB subtype, determined by GEP.
OS	Overall survival (OS) is defined as the time from the date of the first dose of study drug to the date of death due to any cause. For subjects who are not known to have died at or prior to the database lock date, 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 at the RP2D with the ABC subtype of DLBCL, determined by GEP, KM curves will be used to estimate the distribution of OS. Sensitivity Based on the all-treated population at the RP2D with ABC and other non-GCB subtype, determined by GEP.
Safety:		
Safety and tolerability	TEAEs, SAEs, and other safety parameters	Descriptive summaries and/or listings.

ABC: Activated B-cell; CI: confidence interval; CR: complete response; DLBCL: diffused large B-cell lymphoma; ECOG PS: Easter Cooperative Oncology Group Performance Status; GCB: germinal center B cell-like; GEP: gene expression profile; KM: Kaplan-Meier; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RP2D: recommended phase 2 dose.

1 Introduction

This Phase 1/2b open-label, non-randomized U.S. multicenter study is designed to evaluate the safety and efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in the treatment of subjects with relapsed or refractory diffuse large B-cell Lymphoma.

This statistical analysis plan (SAP) describes the statistical methodology of efficacy and safety analyses for this study. This plan does not cover the pharmacokinetic (PK) or biomarker analyses, which will be performed and reported by the DMPK Department and Biomarker group of Pharmacyclics, respectively.

2 Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Part 1

Primary Objectives:

- To determine the maximum tolerated dose (MTD) of the combination of ibrutinib, lenalidomide and dose-adjusted (DA)-EPOCH-R in relapsed or refractory DLBCL.
- To determine the safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL.

Secondary Objectives:

- To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL subjects as assessed by the ORR.

2.1.2 Part 2

Primary Objectives:

- To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory ABC DLBCL subjects as assessed by overall response rate (ORR).

Secondary Objectives:

- To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory ABC DLBCL as assessed by progression-free survival (PFS), duration of response (DOR) and overall survival (OS).
- To determine the safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with ABC DLBCL.

Exploratory Objectives:

- To determine the pharmacokinetics (PK) of ibrutinib when dosed with lenalidomide in combination with DA-EPOCH-R
- To evaluate biomarkers of sensitivity or resistance to ibrutinib and lenalidomide in combination with DA-EPOCH-R

2.2 Endpoints

2.2.1 Part 1

Primary Endpoint: (for all subtypes of DLBCL)

- MTD
- Safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL

Secondary Endpoint: (for all subtypes of DLBCL)

- ORR

2.2.2 Part 2

Primary Endpoint:

- ORR including CR (complete response) and PR (partial response) in ABC DLBCL

Secondary Endpoints:

Efficacy:

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

Safety:

- Frequency, severity, and relatedness of AEs
- Frequency of AEs requiring discontinuation of study drug or dose reductions

Exploratory Endpoints:

- Plasma pharmacokinetics of ibrutinib
- Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib
- Frequency of tumor mutations (or other molecular markers) between pre- and post-treatment tissue that predict acquired resistance.
- Change in secreted protein levels (ie, chemokines, cytokines)
- Change in peripheral T/B/natural killer (NK) counts and immunophenotypical analysis

3 Study Methods

3.1 General Study Design and Plan

This is an open-label, non-randomized multicenter study conducted in 2 parts. In Parts 1 and 2, treatment will be administered in 3-week cycles (21 days each). In Part 1, a minimum of 3 and a maximum of 24 subjects with DLBCL will be enrolled into a standard 3+3 design to determine the MTD which will be used in Part 2. Approximately 26 subjects with relapsed or refractory de novo DLBCL non-GCB subtype will be enrolled in Part 2 and will receive

ibrutinib at a fixed dose of 560 mg and lenalidomide at the established MTD together with DA-EPOCH-R. If no MTD is identified, then subjects in Part 2 will be treated with the maximum administered doses (MAD), which is the treatment dose from Part 1 dose level 4.

3.2 Part 1 − Dose Escalation

The dose-escalation part of the study, Part 1, will determine the MTD of the combination of ibrutinib, lenalidomide and DA-EPOCH-R in subjects with DLBCL. Subjects will receive ibrutinib at a fixed dose of 560 mg (or 420 mg if there is toxicity associated with 560 mg) and lenalidomide at an escalating dose of 0, 15, 20 and 25 mg on Days 1-7 of each 21-day cycle. DA-EPOCH-R will be given at standard doses on Days 1-5 of each 21-day cycle.

The dose escalation will follow a 3+3 design with 3 subjects in each cohort. Cohort dose escalation will occur if the subject incidence of Dose-limiting toxicities (DLTs) during the first 22 days of study treatment is <33%. If one subject within the initial cohort of 3 subjects experiences a DLT, an additional 3 subjects may be enrolled at the same dose level. If the initial dose is safe and tolerable with no further DLTs, the next dose level examined will be dose level 2. Dose escalation will continue to dose level 4. The MTD will be defined as the highest dose level with an observed incidence of DLTs in <33% of the subjects enrolled in the cohort. If DLTs occur in <33% of subjects in dose level 4, then the MTD will not be identified and the dose level 4 dose will be the maximum administered doses (MAD).

In the event of toxicity associated with 560 mg of ibrutinib (DLTs during the first 22 days of study treatment is >33% in dose level 1), 420 mg of ibrutinib (dose level -1) may be used for the dose escalation cohorts if it is deemed safe in combination with DA-EPOCH-R. In this case, a maximum of 30 subjects may be enrolled in Part 1 (up to 6 subjects at the -1 level and 4 x 6 = 24 subjects at levels 1, 2, 3 and 4).

At the RP2D, at least 6 subjects will be treated at this level prior to start of Part 2.

A DLT is defined as an Adverse Event (AE) that occurs within the first 22 days (Cycle 1, Cycle 2 Day 1 predose) of dosing that meets the DLT definition (refer to the protocol Section 5.5.1), is clinically relevant, and is considered at least possibly related to ibrutinib and/or lenalidomide in the opinion of the investigator.

3.3 Part 2 − Expansion

Part 2 will enroll subjects with non-GCB DLBCL as identified by IHC. The primary objective is to determine the ORR of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with ABC DLBCL as analyzed by gene expression profiling (GEP).

The RP2D determined in Part 1 will be the dose for lenalidomide used for all subjects in Part 2. Subjects from Part 1 that received the RP2D of lenalidomide will be carried over to Part 2.

Depending on the number of subjects enrolled at the RP2D in Part 1 and the number of subjects with the ABC subtype that will be identified by GEP in Part 2, additional subjects will be enrolled to ensure 26 subjects with confirmed ABC DLBCL.

4 Sample Size

The planned sample size for Part 2 is at least 26 subjects with ABC subtype of DLBCL as determined by GEP. The primary efficacy analysis will be the comparison of the ORR within the ABC subtype to a historical control ORR of 60%. In subjects with relapsed and refractory DLBCL, EPOCH/EPOCH-R was observed to have a response rate of between 68-75% (Gutierrez 2000, Jermann 2004). Since the response rate is expected to be lower in the more aggressive ABC subtype, an ORR of 60% has been selected for the historic control value. A Part 2 sample size of 26 subjects will have 81% power to test the null hypothesis that ORR will be ≤60% versus the alternative hypothesis that ORR will be ≥85% at the 1-sided significance level α of 5% when the exact binomial test method is used.

5 General Considerations

5.1 Analysis Populations

The Part 1 analyses will be performed by dose cohort pooling all subtypes of DLBCL (e.g., GCB, ABC, PMBL, and unclassified). Part 2 analyses will be performed on the ABC subtype of DLBCL as determined by GEP, with sensitivity analyses for the efficacy endpoints performed using the non-GCB subtype of DLBCL as determined by IHC.

- **All treated population** will include subjects who have enrolled and received at least 1 dose of any of the study treatments. Efficacy and safety analyses will be performed for the all-treated population enrolled in Part 1, and separately for subjects dosed at the RP2D (MTD or MAD) from Part 1 and all subjects from Part 2.

- **Response-evaluable population** will include subjects who have enrolled, received at least 1 dose of any of the study treatments, and have measurable disease at baseline and have at least one adequate post treatment disease assessment by investigator before the start of subsequent anti-cancer therapy. This is the sensitivity analysis population for ORR at the RP2D.

5.2 Changes from the Protocol

Changes from the statistical section in the protocol are as follows:

1. 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. For those subjects who were dosed and had received a subsequent anti-cancer therapy, the reason for the new therapies and how the new therapy could impact the PFS outcome will be described.
2. Regarding the exploratory analyses for ORR, DOR, PFS and OS in the non-GCB subtype of DLBCL, the non-GCB subtype will be determined by GEP by combining

the ABC and unclassified categories. Only when the GEP subtype is missing, the subjects will be summarized into the category based on the IHC data. In case that there is any meaningful difference observed between the non-GCB subgroup determined by IHC and that by GEP, an exploratory analysis of ORR will be performed in the non-GCB subtype determined by IHC.

3. The protocol specified combined efficacy population is essentially the all-treated analysis population at the RP2D. The safety analysis population and the all-treated analysis population have the same definition. Consequently, the combined efficacy population and safety analysis population are removed and consolidated into the all-treated population for simplicity and clarity.
4. Response-evaluable population will be used for sensitivity analysis of only ORR at the RP2D.
5. PK is noted as an exploratory objective but a secondary endpoint in the protocol. PK will be considered an exploratory endpoint for the analysis to align with the protocol objectives.

6 Subject Information

6.1 Subject Disposition

Subject enrollment will be summarized by dose cohort in Phase 1b or by ABC/non-ABC subtype in Phase 2 for subjects treated at the RP2D. The disposition of all enrolled subjects will be summarized by study phase.

6.2 Demographic and Baseline Variables

Summary tables will present demographic information and baseline characteristics for subjects in the all-treated population.

Concordance is summarized for the all-treated population at the RP2D between the DLBCL subtypes determined by GEP test in the central lab and that by the IHC test in the local lab.

6.3 Prior and Concurrent Medications

All reported medications will be provided in listings for all subjects in the all-treated population. Prior medications and concomitant medications will be summarized separately.

Concomitant use of CYP3A inhibitors will be listed and summarized separately.

Subsequent anticancer therapies are anti-DLBCL treatments that started after discontinuation of study treatment (i.e. started after the last dose of study drug) and will be summarized by type (e.g. radiotherapy, systemic therapy, bone marrow or stem cell transplant).

6.4 Exposure to Study Drug

The treatment cycles each subject received will be summarized. Subjects with any dose interruption/reduction due to AE will be summarized. Also the cycle delay and its reasons will be summarized for all-treated population at the RP2D.

Summary tables for ibrutinib and lenalidomide will present the cumulative dose received, the number of doses received, the total amount of study drug received, relative dose intensity, subjects with at least 1 dose interruption/reduction due to adverse event.

7 Efficacy Analyses

7.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint in Part 1.

The primary endpoint at the RP2D is ORR (CR + PR) based on the Cheson (2007) criteria as assessed by the investigator. The primary analysis will be based on subjects in the all-treated population at the RP2D (see Section 5.1) with the ABC subtype of DLBCL. The ORR will be estimated according to the crude proportion of confirmed responders based on the best overall response. Subjects without any baseline or post-baseline measurements are considered non-responders. The 90% 2-sided exact confidence interval (CI) will be calculated for the ORR.

If the lower bound of the 2-sided 90% CI for ORR is greater than 60%, then the hypothesis that the ORR of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with relapsed or refractory DLBCL is equal to or lower than 60% will be rejected at the 1-sided α of 5% significance level.

7.2 Secondary Efficacy Endpoints

The Part 1 secondary efficacy endpoint is ORR (CR + PR) based on the Cheson (2007) criteria as assessed by the investigator. The ORR and its 2-sided 90% exact CI will be calculated by dose cohort and by DLBCL subtype, respectively, in the all-treated population. The all-treated population of each dose cohort will include all subtypes of DLBCL.

The secondary efficacy endpoints at the RP2D are duration of response (DOR), progression-free survival (PFS), and overall survival (OS), based on subjects in the all-treated population with the ABC subtype of DLBCL.

Progression free survival (PFS) is defined as the time from the date of the first study drug dose to confirmed disease progression or death from any cause, whichever occurs first. The median PFS will be obtained using the Kaplan-Meier method and its 95% CI will be calculated. PFS at landmark time points (e.g., 3, 6, 9, 12 months from the first study drug dose date) will also be obtained by Kaplan-Meier method. 95% CI for the landmark PFS rates will be calculated.

The DOR is defined as the interval between the date of the first documented response (CR, PR) and the date of the first documented evidence of progressive disease (PD) or death. DOR will be analyzed for the subjects who achieve an overall response prior to initiation of

the next line of anticancer therapy (i.e., responders). Subjects who have achieved an overall response but did not die or experience PD at the time of analysis will be censored at the date of the last response assessment. The median DOR and its 95% CI will be obtained using the same method described for PFS.

OS is defined as the time from the date of the first study drug dose until the date of death due to any cause. Subjects who are not known to have died at or prior to the database lock date will be censored at the date last known alive. The last known alive date will be derived from any visit/assessment dates including dosing, laboratory, AE, vital signs, etc. Subjects who are completely lost to follow-up for survival since receiving the first dose will be censored on the date of the first dose. Subjects who withdraw consent prior to study closure will be censored on the date of the consent withdrawal. A similar statistical analysis and estimation will be performed for OS as described for PFS.

7.3 Sensitivity Analysis

A sensitivity analysis of ORR for subjects dosed at the RP2D will be performed as assessed by investigators for subjects defined by the response-evaluable population.

A sensitivity analysis of the efficacy endpoints (i.e., ORR, PFS, DOR, and OS) will be performed for subjects dosed at the RP2D with the non-GCB subtype of DLBCL as determined by GEP. If the subtype cannot be determined by GEP, it will be determined by IHC.

8 Safety Analyses

Adverse events, changes in clinical laboratory results from baseline, a summary of vital signs and ECG values will be provided. All safety analyses will be based on the all-treated population (except for the DLT evaluation which will be based on the DLT population).

8.1 DLT Assessment

At the safety review meeting, DLTs will be assessed for the first 6 to 9 subjects in the DLT population. A listing of subjects for the DLT assessment will be provided.

8.2 Adverse Events

Adverse events collected in the CRF (verbatim terms) by investigators will be coded to a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of adverse events is assessed in the National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) Version 4.03.

8.2.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events will be summarized by system organ class and preferred terms and by NCI toxicity grade. The same summary will be provided for treatment-related AEs, AEs leading to treatment discontinuation, AEs leading to treatment discontinuation for

subjects who discontinued treatment due to AE, AEs leading to dose reduction and serious TEAEs. An adverse event overview on the incidences of all the above will be presented.

8.2.2 Adverse Events of Special Interest

8.2.2.1 Major Hemorrhage and All Hemorrhagic Events

Hemorrhagic events will be identified by hemorrhage Standardized MedDRA Query [SMQ] excluding laboratory terms and be tabulated. Major hemorrhage is a subset of hemorrhagic events which are grade ≥3 or serious or belong to central nervous system (CNS) hemorrhage/hematoma.

8.2.3 Other Safety Observations in AE Reporting

Summary of treatment-emergent leukostasis, infections, TLS, cytopenia, hypersensitivity, hepatic disorders, and atrial fibrillation will be based on the TEAE summary by SOC and preferred term.

Treatment emergent interstitial lung disease, rash, severe cutaneous adverse reactions, and cardiac arrhythmia (excluding atrial fibrillation) will be summarized by preferred terms based on SMQ term search and/or medical monitor and safety scientist review.

8.2.4 Other Malignancies

All new malignant tumors including solid tumors, skin malignancies, and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including long-term post-progression follow-up for OS. Other malignancies will be summarized similar to standard AE tables or listed.

8.2.5 Deaths

Treatment-emergent adverse events leading to death with be summarized.

8.3 Clinical Laboratory Tests

A summary of worst post-baseline toxicity grade will be provided. The events with Grade 3 and 4 as the worst post-baseline toxicity grade will be also provided.

9 References

Cheson B.D, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma, Journal of Clinical Oncology 2007; 25: 579-586.Efficacy Analyses