

Redacted Statistical Analysis Plan for Journal Use

A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Protocol PCYC-1130-CA

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LIST OF ABBREVIATION

Abbreviation	Definition
AE	adverse event
ALC	absolute lymphocyte counts
ANC	Absolute neutrophil counts
ATC	Anatomical Therapeutic Chemical
BOR	best overall response
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CRi	complete response with an incomplete marrow recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOL	duration of lymphocytosis
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EQ-5D	EuroQoL Five-Dimension.
FISH	fluorescence in situ hybridization
DMC	data monitoring committee
IGHV	immunoglobulin heavy-chain variable region
IRC	independent review committee
IRR	infusion related reaction
ITT	intent-to treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia Criteria
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
nPR	nodular partial response
ORR	overall response rate
OS	overall survival

Abbreviation	Definition
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetic
PR	partial response
PRO	patient reported outcome.
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SOC	system organ class
TEAE	treatment-emergent adverse events
WBC	white blood cell count
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-1130-CA study. Analyses of pharmacokinetics (PK) data and exploratory analyses for clonal evolution, disease-related mechanisms of resistance and the secreted protein analysis for obinutuzumab-related infusion reactions will be addressed in separate documents.

Throughout this SAP, “study treatment” and “study drug” are used interchangeably.

1.1. Study Design

This is a randomized, multicenter, open-label, Phase 3 study designed to evaluate the safety and efficacy of ibrutinib in combination with obinutuzumab, when compared to chlorambucil in combination with obinutuzumab, in subjects diagnosed with CLL or SLL, who are treatment-naïve but now require therapy.

Subject participation includes a Screening Phase, a Pre- Progressive Disease (Pre-PD) Phase, and a Follow-up Phase.

The Screening Phase is up to 30 days prior to randomization. The Pre-PD Phase extends from randomization until disease progression (PD), death, loss to follow up, or consent withdrawal, whichever occurs first. During this phase, subjects receive the study treatment once randomized and the response evaluations are scheduled every 4 cycles from the initial dose of study drug until Cycle 33, and then every 6 cycles until disease progression regardless of whether subject is on study treatment or has discontinued study treatment due to a reason other than PD. The Follow-up Phase begins once a subject has progressive disease and continues until death, loss to follow up, consent withdrawal, or study end, whichever occurs first.

The response and progression evaluations are performed in accordance with the IWCLL guidelines including recent clarifications (Hallek 2008, Hallek 2012, Hallek 2013, Cheson 2012, and IWCLL 2017). An independent review committee (IRC) was established to conduct progression and response assessment centrally. Criteria for response categories, as well as the process and convention of the IRC were prospectively detailed in the IRC charter.

An independent Data Monitoring Committee (DMC) is formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the DMC and detailed DMC procedures are provided in a separate charter. The DMC reviews the safety data periodically and provides recommendations according to the charter.

Study Dosage and Administration

Treatment Arm A: Ibrutinib PO and Obinutuzumab IV

Ibrutinib will be given orally at a dose of 420 mg daily (3 capsules) until disease progression or unacceptable toxicity.

Obinutuzumab will be administered intravenous at a fixed dose of 1000 mg over 6 cycles: given on Days 1+2 (100 mg on Day 1 and 900 mg on Day 2), Day 8 (1000 mg) and Day 15 (1000 mg) of Cycle 1 and on Day 1 (1000 mg) only of subsequent cycles, for up to 6 cycles.

Treatment Arm B: Chlorambucil PO and Obinutuzumab IV for Six 28-day Cycles

Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of each cycle, for up to 6 cycles.

Obinutuzumab will be administered the same as in arm A.

Upon IRC-confirmed progression, subjects in Arm B have the opportunity to receive ibrutinib monotherapy orally at a dose of 420 mg daily (3 capsules) continuously until determined otherwise by the investigator.

1.2. Endpoints

1.2.1. Primary Endpoint

- Progression free survival (PFS) by IRC

1.2.2. Secondary Endpoints

- PFS by IRC in high risk analysis set
- Rate of sustained hemoglobin improvement
- Rate of MRD-negative response
- ORR by IRC
- OS
- Rate of infusion related reactions
- Rate of sustained platelet improvement
- Rate of clinically meaningful improvement in EQ-5D-5L utility score

1.2.3. Safety Assessments

- Safety and tolerability of ibrutinib in combination with obinutuzumab compared with chlorambucil in combination with obinutuzumab

1.3. Statistical Hypotheses

The primary hypothesis of this study is that the experimental treatment ibrutinib + obinutuzumab compared with chlorambucil + obinutuzumab will significantly improve PFS in subjects diagnosed with CLL or SLL who are treatment-naive but now require active therapy.

The statistical hypotheses are as follows:

H_0 : The PFS distributions of experimental treatment group, $S_I(t)$, and the control group, $S_C(t)$, are equal at all time points t :

$$S_I(t) = S_C(t), \text{ for all } t > 0$$

versus

H_1 : The PFS distributions of experimental treatment group, $S_I(t)$, are different from the control group, $S_C(t)$, at at least one time point t :

$$S_I(t) \neq S_C(t), \text{ for some } t > 0$$

These hypotheses will be tested using a 2-sided stratified log-rank test at α level of 0.05.

1.4. Sample Size Determination

This study was powered for testing the primary hypothesis of this study.

The sample size is calculated based on the assumptions:

- Randomization ratio of 1:1
- Median PFS of 27 months for Arm B (chlorambucil in combination with obinutuzumab)
- Target hazard ratio of 0.55, which corresponds to median PFS of 49.1 months for Arm A (ibrutinib combined with obinutuzumab).

On this basis, 94 PFS events provide 80% power to achieve a statistical significance level of 5% (2-sided) under exponential distribution. With an estimated accrual rate of 18 subjects per month, approximately 212 eligible subjects were to be enrolled to observe 94 PFS events in about 36 months from the first subject randomized.

The sample size and power calculations were calculated using the software package, East (Cytel Software Corp, Cambridge, MA) version 6.3.

1.5. Planned Analysis

1.5.1. Interim Analysis

No interim analysis is performed in this study.

1.5.2. Primary Analysis

The primary analysis of PFS will be performed after approximately 94 confirmed progression/death events have occurred. The analysis of the secondary endpoints including OS will be performed at the time of PFS primary analysis.

1.5.3. Final Analysis

After the primary analysis of PFS, the Sponsor will continue to follow the subjects for approximately 4 years after the first subject was enrolled. When the study closed, a final analysis will be performed, and a CSR addendum will be drafted.

1.6. Testing Procedure and Level of Significance

To preserve the study wise type I error rate of 0.05, the primary and secondary endpoints will be tested based on a serial gatekeeping testing procedure at the two-sided significance level of 0.05 according to the hierarchical order as listed in 1.2.2.

1.7. Blinding and Randomization Methods

1.7.1. Blinding Method

In this open-label study, neither the subjects nor the investigators are blinded to treatment. However, access to efficacy data is controlled so that the Sponsor's staff overseeing the conduct of the study or analyzing/summarizing data do not have an aggregated efficacy summary by treatment arm prior to database lock. Details are described in the Minimizing Bias Document.

Assessment for progression and response assessment is performed centrally by the IRC. Members of the IRC are blinded to the study treatment. The IRC data flow and workflow are detailed in the IRC charter.

1.7.2. Randomization Method

Central randomization will be implemented in this study. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, subjects will be randomized based on the following stratification factors:

- ECOG 0-1 vs 2
- Cytogenetics - will be stratified into one of three categories
 1. del 17p
 2. del 11q without del 17p
 3. others (neither del 17p nor del 11q)

Subjects will be randomized in a 1:1 ratio to either Treatment Arm A or Treatment Arm B within each randomization stratum. This randomization scheme will be implemented within the Interactive Web Response System (IWRS).

2. GENERAL ANALYSIS CONSIDERATION

2.1. Analysis Sets

Intent-To-Treat (ITT) population: defined as all subjects who were randomized. Subjects will be grouped according to the treatment assigned at randomization. This population will be the primary population for the analyses of efficacy endpoints, disposition, demographics and baseline characteristics, baseline disease characteristics, subsequent anticancer therapy and patient-reported outcome data.

Safety population: defined as all subjects who received at least 1 dose of any one of the three study drugs (ibrutinib, chlorambucil, or obinutuzumab). Safety data will be analyzed as treated. The Safety Population will be used to summarize the safety (including dosing and concomitant medications) data.

High risk analysis set: defined as randomized subjects with del17p or TP53 mutation or del 11q at baseline per central lab results.

2.2. Definition of Subgroups

Subgroup analyses will be performed for the selected variables to assess the internal consistency of the treatment benefit.

3. SUBJECT INFORMATION

Subject information will be summarized descriptively. No inferential test will be performed.

3.1. Subject Disposition

Subject randomization will be summarized by region, country, site and by stratification factors. Subject disposition for each study treatment and for study participation will be tabulated. The overall duration of receiving any study treatment and time on study will be summarized correspondingly.

Time on study is defined in the same way as overall survival with reversed censoring, i.e., subjects who died will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

3.2. Demographics and Baseline Characteristics

Demographic information and baseline characteristics including but not limit to age, gender, race, histology type, time from initial diagnosis, staging, and potential prognostic factors will be summarized with descriptive statistics for ITT population by treatment arm and, in addition, by subgroups.

3.3. Prior and Concomitant Medications

Medications will be coded to preferred term and Anatomical Therapeutic Chemical (ATC) class according to World Health Organization (WHO) Drug dictionary.

Prior medications are defined as medications that started prior to the first dose date of study drug. 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 drug through the date of the last dose of study drug).

Concomitant medications will be summarized by therapeutic class and preferred term in the safety population. The following concomitant medications of special interest will be summarized separately: growth factors, blood supportive products and immunoglobulin, CYP3A inhibitors/inducers, anticoagulants and/or antiplatelet.

3.4. Extent of Exposure to Study Treatment

Exposure to ibrutinib, chlorambucil, obinutuzumab will be summarized separately for treatment duration and dosing information (e.g. total cumulative dose administered, relative dose intensity, ibrutinib or chlorambucil dose reduction due to adverse events).

3.5. Subsequent Antineoplastic Therapies

Subsequent CLL/SLL antineoplastic agents will be summarized by type of therapies.

4. ANALYSIS FOR ENDPOINTS

Analysis of endpoints will be conducted on the ITT population, unless otherwise specified. Table 1 summarizes the efficacy endpoints and analysis methods to be performed.

The following two randomization stratification factors will be used for the stratified analysis/test: ECOG performance status (0, 1 versus 2) and Cytogenetics (del 17p, del 11q without del 17p, others). To reflect the randomization process and maintain the integrity of randomization, all stratified tests will be based on randomization stratification factors as recorded in the IWRS.

For subgroup and exploratory analysis, only the analysis that provide meaningful information will be presented.

Table 1: Definitions and Analyses for Endpoints

Endpoint	Definition	Analysis Method
Primary Endpoint		
PFS assessed by IRC	Time from the date of randomization to the date of IRC-assessed disease progression or date of death from any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death.	<p><u>Primary</u> Treatment effect of ibrutinib plus obinutuzumab compared to chlorambucil plus obinutuzumab was tested with a log-rank test. The hazard ratio and its 95% CI based on a Cox regression model are calculated. PFS distribution is estimated by Kaplan-Meier method: median PFS and landmark estimates with 2-sided 95% CIs are to be provided for each treatment arm.</p> <p><u>Sensitivity</u> Analyzing PFS assessed by investigator using the same method as PFS assessed by IRC.</p> <p><u>Subgroup</u> Hazard ratio and its 95% CI based on unstratified Cox regression model for each subgroup.</p>
Secondary Endpoints		
PFS assessed by IRC in high risk analysis set	Defined the same as the primary endpoint.	Analyzed the same as primary endpoint in high risk analysis set
ORR assessed by IRC	The proportion of subjects achieving a best overall response of CR, CRi, nPR, or PR per IRC assessment at or prior to initiation of subsequent antineoplastic therapy.	Chi-square test.
Overall survival (OS)	Time from the date of randomization to the date of death from any cause. All deaths observed at the time of the analysis will be considered as events. For subjects who were not known to have died at the time of the analysis, OS data will be censored at date last known alive.	Analyzed the same as PFS primary analysis.
Rate of MRD-negative response	Proportion of subjects who achieved MRD-negative response defined as < 1 CLL cell per 10,000 leukocytes as assessed by flow cytometry of a bone marrow aspirate or peripheral blood sample per central laboratory.	Chi-square test for MRD-negative response rate by bone marrow

- Rate of infusion related reactions will be analyzed using a Chi-square method.
- Rate of sustained platelet improvement will be analyzed using a Chi-square method
- Rate of clinically meaningful improvement in EQ-5D-5L utility score will be analyzed using a Chi-square method

5. SAFETY ASSESSMENTS

Safety data will be summarized for the safety population. Table 2 summarizes the safety analyses to be performed.

Adverse events will be coded in accordance with the MedDRA. Severity of AEs will be graded by the investigator according to the NCI-CTCAE v4.03 for non-hematological AEs and IWCLL 2008 guidelines for hematologic toxicity.

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 (including the cross-over ibrutinib monotherapy for arm B subjects), whichever comes first.

The treatment-emergent adverse events (TEAE) are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment. Unless otherwise specified, only TEAEs will be included in the adverse event summaries.

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. Hematologic parameters including platelet counts, hemoglobin, and neutrophils will be assessed by the grading scale for hematologic toxicity in CLL studies in the IWCLL 2008 guidelines. All other gradable 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.

Table 2: 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. TEAEs within the first 9 months of study treatment and TEAEs in the crossover period	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	Blood pressure, 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. REFERENCES

Bhattacharya S, Fyfe G, Robert J, and Daniel J. Sargent. Role of sensitivity analyses in assessing progression-free survival in late-stage oncology trials. *J Clin Oncol.* 2009;27: 5958-5964

Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol* 2012; 23:2820-22.

Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008; 111:5446-5456.

Hallek M, Cheson BD, Catovsky D, et al. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. *Blood* 2012 (letter; published 4 June 2012). http://bloodjournal.hematologylibrary.org/content/111/12/5446/reply#bloodjournal_el_6920. Accessed 23 August 2012.

Hallek M, Cheson BD, Catovsky D, et al. E-Letter regarding "Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines": Clarification of iwCLL criteria for a partial response to therapy. *Blood* Nov 13 2013.

Hallek M. "Presentation and discussion of revised iwCLL guidelines for the approach to a CLL patient." XVII International Workshop on Chronic Lymphocytic Leukemia; 2017 May 12–15; New York, USA.

Stone AM, Bushnell W, Denne J, et al. Research outcomes and recommendations for the assessment of progression in cancer clinical trials from a PhRMA working group. *European Journal of Cancer* 2011; 47, 1763-1711

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials, *Biometrics* 1979; 35:549-556.

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.* 1998; 16:139-14