# PHARMACYCLICS LLC

# STATISTICAL ANALYSIS PLAN FOR CSR ADDENDUM

---

# A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE 3 STUDY OF THE BRUTON'S TYROSINE KINASE (BTK) INHIBITOR IBRUTINIB VERSUS OFATUMUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

---

## PCYC-1112-CA; PHASE 3

## IMBRUVICA® (IBRUTINIB; PCI-32765)

**NCT Number: NCT01578707**

| | |
|---|---|
| **Status:** | Approved |
| **Date:** | 25 April 2019 |
| **Prepared by:** | Pharmacyclics LLC |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| CI | confidence interval |
| CLL | chronic lymphocytic leukemia |
| CMH | Cochran-Mantel-Haenszel |
| CR | complete response |
| CRi | complete response with incomplete marrow recovery |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| del17p | deletion of the short arm of chromosome 17 |
| DMC | data monitoring committee |
| HR | hazard ratio |
| IRC | independent review committee |
| ITT | intent to treat |
| iwCLL | International Workshop on CLL |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| nPR | nodular partial response |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PR | partial response |
| SAE | Serious adverse events |
| SAP | statistical analysis plan |
| SLL | small lymphocytic lymphoma |
| TEAE | Treatment-emergent adverse events |

# 1. INTRODUCTION

Study PCYC-1112-CA (hereafter referred to as Study 1112) is a randomized, multicenter, open-label, comparator-controlled Phase 3 study of ibrutinib versus ofatumumab in subjects with previously treated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Study 1112 compared the efficacy and safety of orally administered ibrutinib 420 mg/day with that of ofatumumab administered intravenously at an initial dose of 300 mg followed by 2000 mg x 11 doses over a 24-week period. Randomization of subjects into both treatment arms was 1:1, and subjects received ibrutinib until progressive disease (PD) or unacceptable toxicity was observed, whichever occurred first. Two separate randomization schemes were generated for each geographic region (North America vs. Rest of World). Under each scheme, randomization was stratified using the following factors:

- Presence vs. absence of disease refractory to purine analog and anti-CD20 containing combination chemo-immunotherapy regimen.
- Presence vs. absence of deletion of the short arm of chromosome 17 (del17p), as defined by assay specification on pre-treatment fluorescence in situ hybridization or cytogenetics evaluation.

The primary endpoint was progression-free survival (PFS) as assessed by the independent review committee (IRC) per criteria from the 2008 International Workshop on CLL (iwCLL) with the clarification regarding treatment-related lymphocytosis (Hallek et al, 2013). Key secondary efficacy endpoints included overall survival (OS) and overall response rate (ORR) (based on the IRC assessment).

Initially, subjects treated with ofatumumab who had experienced PD as confirmed by an IRC were allowed to receive ibrutinib if deemed appropriate by the investigator following medical monitor approval. Based on the positive results from the interim analysis in December 2013, the data monitoring committee (DMC) recommended to allow the remaining subjects originally randomized to ofatumumab to be provided with access to ibrutinib therapy. In addition, the DMC recommended the interim analysis be the primary analysis for the study and the Clinical Study

Report (CSR) was completed on 25 March 2014. After the primary analysis, IRC evaluations were discontinued, while efficacy assessments by the investigators continued until study closure.

Subjects remaining on treatment at the time of study closure will have the option to be rolled over to a separate long-term extension study.

The final analysis will be based on the final data extract from 26 November 2018. This statistical analysis plan (SAP) is to describe the final analysis of data in evaluation of efficacy and safety of Study 1112.

## 2. GENERAL ANALYSIS CONSIDERATION

### 2.1. ITT Population

The Intent-to-Treat (ITT) population includes all randomized subjects. Subjects in this population will be analyzed according to the treatment to which they were randomized. The ITT population will be used for efficacy analyses and to produce subject disposition summaries.

### 2.2. Safety Population

All randomized subjects who received at least one dose of study drug will be included in the safety population. Subjects in the safety population will be analyzed according to the actual treatment received and will be used to summarize the safety (including dosing) data.

## 3. SUBJECT INFORMATION

### 3.1. Duration of Study Follow-up

Duration of follow-up on the study will be summarized by treatment arm and for the combined arms. Median duration will be obtained using Kaplan–Meier methodology with reverse censoring.

## 4. EFFICACY ANALYSES

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 two randomization stratification factors will be used for the stratified analysis/test.

Table 1: Definitions and Analyses for Endpoints

| **Endpoint** | **Definition** | **Analysis Method** |
|---|---|---|
| Progression-free survival (PFS) per investigator | Time from date of randomization to date of first documentation of PD per investigator response assessment or date of death due to any cause, whichever occurs first, regardless of the use of subsequent anticancer therapy including crossover prior to documented PD or death. Subjects who are alive and had not progressed will be censored at the date of last evidence of non-PD.<br>Subjects without a baseline assessment or adequate post baseline assessment will be censored at date of randomization. | Kaplan-Meier (KM) will be used to estimate median with its 95% confidence interval (CI) and selected landmark estimates (95% CI). The hazard ratio (HR) with its 95% CI, will be estimated by Cox regression model (with treatment as the only covariate) stratified by the two randomization stratification factors. KM curves and the forest plot of HRs for PFS in each subgroup will be provided. |
| Overall survival (OS) | Time from date of randomization to date of death from any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date when they were last known to be alive.<br>Subjects who received subsequent anti-neoplastic therapy will not be censored at next-line therapy, including ofatumumab subjects who received ibrutinib as subsequent therapy. | ITT analysis: The same methods used to analyze PFS will be used to analyze OS. |
| Overall response rate (ORR) per investigator | The proportion of subjects achieving a best overall response of CR, CRi, nPR, or PR per investigator assessment at or prior to initiation of subsequent anti-neoplastic therapy. | P-value is based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by the two randomization stratification factors. |
| Sustained hemoglobin improvement | Proportion of subjects with hemoglobin increase >= 20 g/L over baseline continuously for >=56 days without blood transfusions or growth factors. | Analysis for ITT and the subgroup with anemia at baseline (hemoglobin <= 110 g/L): Chi-square test. |
| Sustained platelet improvement | Proportion of subjects with platelet increase >= 50% over baseline continuously for >=56 days without blood transfusions or growth factors. | Analysis for ITT and the subgroup with thrombocytopenia at baseline (platelet <= 100 x $10^9$ /L): Chi-square test. |

## 5. SAFETY ASSESSMENTS

Safety data will be summarized for the safety population.

Adverse events will be coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the investigator according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 for non-hematological AEs and iwCLL 2008 guidelines for hematologic toxicity.

Treatment-emergent adverse events (TEAE) are all reported AEs from the first dose of the study drug, through the treatment phase and up to 30 days after the last dose of the study drug or initiation of subsequent anticancer therapy, whichever came first. TEAE SAEs, TEAE non-SAEs and TEAE leading to death will be summarized by treatment arm.