

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205552Orig2s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 205552

**Supplement #:**

**Drug Name:** Ibrutinib

**Indication(s):** Relapsed or refractory Chronic Lymphocytic Leukemia

**Applicant:** Pharmacyclics

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**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics V

**Statistical Reviewer:** Yun Wang, PhD

**Concurring Reviewers:** Lei Nie, PhD, Acting Team Leader  
Thomas Gwise, PhD, Deputy Division Director

**Medical Division:** Office of Hematology and Oncology Product

**Clinical Team:** Nicole Verdun, MD  
Angelo De Claro, MD

**Project Manager:** Diane Hanner, MPH

**Keywords:** Chronic Lymphocytic Leukemia, Overall Response Rate, Duration of Response;  
Single arm trial.

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## 1 EXECUTIVE SUMMARY

New drug application (NDA) 205552 submission was split into two separate submissions based on two different indications: original-1 submission for mantle cell lymphoma (MCL), and original-2 submission for chronic lymphocytic leukemia (CLL). FDA granted accelerated approval in November 2013 for MCL indication based on original-1 submission. This statistical review is for original-2 submission. In original-2 submission, the applicant seeks the approval of ibrutinib for treatment of relapsed or refractory CLL patients who received at least one prior regimen.

This NDA original-2 submission is based on two clinical studies (Study PCYC-1102-CA and Study PCYC-04753) in 149 subjects in which ibrutinib was evaluated as a single agent at different doses for the treatment of CLL patients. PCYC-1102-CA is a Phase 1b/2 study of ibrutinib at two dose levels (420 mg or 840 mg) in 133 subjects with treatment-naïve or relapsed/refractory CLL/Small Lymphocytic Lymphoma (SLL). This statistical review only considers 48 subjects with relapsed/refractory CLL treated at dose of 420 mg, the targeted dose and indication the applicant seeks the approval for, in the Study PCYC-1102-CA. Study PCYC-04753 enrolled 16 CLL patients into different doses and only provided preliminary efficacy results of ibrutinib. Therefore, Study PCYC-04753 was not included in this statistical review.

Study PCYC-1102-CA was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

In Study PCYC-1102-CA, the overall response rate (ORR) per independent review committee (IRC) assessments was 56.3% (95% CI [41.2%, 70.5%]) with median duration of response (DOR) not achieved yet (95% CI not evaluable).

The response data from Study PCYC-1102-CA demonstrated some clinically meaningful treatment effect of ibrutinib for relapsed and refractory CLL patients. Top line results from Study PCYC-1112-CA, an ongoing randomized, multicenter, and open-label Phase 3 study of the ibrutinib versus ofatumumab in patients with relapsed or refractory CLL/SLL, showed significant improvement in PFS for ibrutinib compared to ofatumumab, which provided more evidence of clinical benefit of ibrutinib for refractor/relapsed CLL patients.

## 2 INTRODUCTION

### 2.1 Overview

Ibrutinib is a selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of B-cell malignancies. By combining fast covalent binding to BTK with rapid in vivo elimination, ibrutinib provides a unique approach to improve selectivity for BTK in vivo relative to reversibly inhibited off-target kinases.

The proposed indication submitted in this NDA original-2 application is for the treatment of patients with relapsed/refractory CLL who have received at least one prior regimen.

Ofatumumab (Arzerra) is currently approved for treatment of patients with CLL based on an open-label, single-arm, multicenter study of 154 patients with relapsed or refractory CLL.

Patients with CLL refractory to fludarabine and alemtuzumab (n = 59) comprised the efficacy population. Overall response rate (complete response (CR), unconfirmed CR (CRu), and partial response) to ofatumumab for patients with CLL refractory to fludarabine and alemtuzumab was 42% (99% CI: 26%-60%), with duration of response of 6.5 months (95% CI: 5.8 – 8.3 months); There was no complete response.

Study PCYC-1102-CA was an open-label, nonrandomized, multi-center, Phase 1b/2 study of ibrutinib in subjects with treatment-naïve or relapsed/refractory CLL/SLL. Cohorts were defined by the disease population (treatment-naïve or relapsed/refractory) and by the ibrutinib dose level (420 mg or 840 mg). The primary efficacy endpoint is ORR per IRC using International Myeloma Working Group (IMWG) response criteria. The secondary efficacy endpoints are TTR, time to disease progression (TTP) and OS.

A total of 133 patients with CLL/SLL were enrolled between 20 May 2010 and 18 April 2012 from 8 sites in the US. The data cut-off date was 18 December 2012. Among the enrolled 133 patients, only 48 relapsed/refractory CLL patients treated with at least one dose of ibrutinib 420 mg were included in the efficacy analyses for CLL indication.

The original protocol for Study PCYC-1102-CA was dated 11 March 2010, and the latest version was Amendment 5 dated 14 June 2012.

Throughout this review, relapsed/refractory CLL patients received ibrutinib at dose of 420 mg daily are referred as “Relapsed/Refractory 420 mg” arm in the text, the tables/figures.

TABLE 1: LIST OF ALL STUDIES INCLUDED IN ANALYSIS

<b>Study</b>	<b>Phase and Design</b>	<b>Treatment Period</b>	<b>Follow-up Period</b>	<b># of Subjects per Arm</b>	<b>Enrollment period Geographic region</b>
<i>PCYC-1102-CA</i>	Phase 1b/2, open-label, nonrandomized, multi-center study designed to evaluate the efficacy and safety of ibrutinib monotherapy (420 mg or 840 mg daily) in subjects with treatment-naïve or relapsed/refractory CLL/SLL	Treatment until completion of planned treatment duration, progressive disease (PD), death, or any other reason listed in the protocol for mandatory withdrawal.	After treatment discontinuation, subjects were followed for PD quarterly until PD or start of further anti-CLL therapy, after that, patients will be followed quarterly for survival until death or study closure.	N=133	20 May 2010 – 18 April 2012 8 sites in the US

## 2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: <\\CDSESUB1\evsprod\NDA205552\205552.enx>

## 3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the Study PCYC-1102-CA.

### 3.1 Data and Analysis Quality

The overall response data for Study PCYC-1102-CA were derived and saved in analysis dataset “ADEFIRC”, “ADTTEIRC” for both IRC and investigator assessments. This NDA original-2 application provided source data for deriving overall response from individual disease assessments. The statistical reviewer can verify overall response per IRC for most patients in Study PCYC-1102-CA. However the statistical and clinical reviewers determined that:

- Three partial responses (PR) claimed by the applicant for patients 123-401, 217-109, 217-401 should be treated as non-responses due to lack of confirmation of the response.
- One PR claimed by the applicant for patient 217-112 should be treated as non-response due to undetectable tumor burden at baseline.

Therefore, the number of PR derived by the FDA reviewers was 4 less than those derived by the applicant. The responses derived by the FDA reviewers were used in this statistical review.

In addition, FDA reviewers determined that patient 032-108 with partial response progressed on January 10, 2012, instead of being censored on November 13, 2012 as the applicant claimed.

### 3.2 Evaluation of Efficacy

#### 3.2.1 Study Design and Endpoints

##### 3.2.1.1 Study Design

The Study PCYC-1102-CA is an open-label, nonrandomized, multi-center, Phase 1b/2 study of ibrutinib in subjects with treatment-naïve or relapsed/refractory CLL/SLL. The primary objective of the study was to determine the safety of a fixed-dose daily regimen of ibrutinib at 2 dose levels (420 mg and 840 mg) in subjects with CLL/SLL. Assessment of preliminary efficacy is one of the secondary objectives.

There were 6 treatment cohorts in Study PCYC-1102-CA (Table 2). The sponsor considered a sample size of 12 to 24 subjects per cohort was sufficient to define the safety profile and pharmacokinetic characteristics of the 2 fixed-dose regimens of ibrutinib. No interim analysis was planned for any cohort.

Reviewer’s comment: This statistical review for Study PCYC-1102-CA is based on data from CLL patients in cohort 1 and 4 only because that subset represents the targeted population and dose the Sponsor applied for approval in this submission.

TABLE 2: SUMMARY OF TREATMENT COHORTS IN STUDY PCYC-1102-CA

Cohort	Population	Ibrutinib Dose	Planned Sample Size
1	Relapsed/refractory	420 mg/day	24
2	Treatment-naïve ≥ 65 years	420 mg/day	24
3	Relapsed/refractory	840 mg/day	24
4	Relapsed/refractory high-risk	420 mg/day	24
5	Treatment-naïve ≥ 65 years	840 mg/day	12
6	Relapsed/refractory*	420 mg/day	16

\* Effects of fed-versus-fasted state.

[Source: Study PCYC-1102-CA CSR Pages 19 Table 1]

### 3.2.1.2 Efficacy Endpoints

Safety, as measured by the incidence, severity, and drug-relatedness of clinical adverse events, was the primary endpoint.

Overall response rate assessed by investigators was one of the secondary endpoints. ORR was defined as the percent of subjects who achieved either a partial response (PR) or complete response (CR), according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 guidelines.

Duration of response (DOR), measured from the time CR or PR was first recorded to the time when progressive disease was objectively documented, was one of the exploratory endpoints.

### 3.2.2 Statistical Methodologies

The overall response rate and the corresponding 95% exact confidence interval (CI) will be presented for CLL patients in cohort 1 and 4. Median duration of response and the corresponding 95% CI calculated using Kaplan-Meier method will be presented as well.

### 3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Study PCYC-1102-CA enrolled 133 subjects with naïve or relapsed/refractory CLL/SLL from 8 sites in US, 27 to cohort 1, 26 to cohort 2, 34 to cohort 3, 25 to cohort 4, 5 to cohort 5, 16 to cohort 6. Please refer to Table 2 for description of cohort 1- 6. Only 49 subjects with relapsed/refractory CLL enrolled into cohort 1 and 4 were considered in this statistical review. One of 49 subjects never received any dose of ibrutinib and was excluded from all treated population.

## Subject disposition

In Study PCYC-1102-CA, at the time of study cutoff of 18 December 2012, all 48 subjects discontinued study treatment. The most common reason for discontinuation was completion of specified study treatment plan (72.9%). The second most common reason for treatment discontinuation was disease progression (8.3%). Twenty nine out of 35 patients who completed study-specified treatment plan were enrolled into extension Study PCYC-1103-CA for continuing treatment with ibrutinib.

TABLE 3: SUBJECT DISPOSITION, RELAPSED/REFRACTORY CLL PATIENTS TREATED WITH 420MG

<b>Relapsed/refractory CLL 420 mg</b>	
	<b>N=48</b>
	<b>n (%)</b>
Subject discontinued study treatment	48 (100)
Primary reason for discontinuation	
Completion of study treatment plan	35 (72.9)
Disease progression	4 (8.3)
Adverse event	3 (6.3)
Subjects decision	3 (6.3)
Physician's decision	1 (2.1)
Patient not compliant	1 (2.1)
Withdrawal due to SCT	1 (2.1)

SCT: stem-cell transplant

[Source: Statistical reviewer's analysis]

### Subject demographics and baseline disease characteristics

Demographics and baseline characteristics for the 48 patients relapsed/ refractory CLL patients received 420 mg ibrutinib in Study PCYC-1102-CA are summarized in Table 4. Baseline disease characteristics are summarized in Table 5.

TABLE 4: DEMOGRAPHICS AND BASELINE CHARACTERISTICS, RELAPSED/REFRACTORY CLL PATIENTS TREATED WITH 420MG

<b>Relapsed/refractory CLL 420 mg</b>	
<b>N=48</b>	
Age (years)	
Mean (SD)	63.9 (11.0)
Median (Min, Max)	67.0 (37, 82)
Category, n (%)	
< 65	23 (47.9)
≥ 65	25 (52.1)
Sex, n (%)	
Male	34 (70.8)
Female	14 (29.2)
Race, n (%)	
White	45 (93.8)
Other	3 (6.2)
ECOG performance Status, n (%)	
0	18 (37.5)
1	30 (62.5)

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group

[Source: Statistical reviewer's analysis]

TABLE 5: BASELINE DISEASE CHARACTERISTICS, RELAPSED/REFRACTORY CLL PATIENTS TREATED WITH 420MG

<b>Relapsed/refractory CLL 420 mg</b>	
<b>N=48</b>	
Time from diagnosis to first dose (Months)	
Mean (SD)	95.7 (62.9)
Median (Min, Max)	80.1 (14.2, 283.0)
Tumor bulk (largest diameter), n (%)	
< 5 cm	26 (54.2)
≥ 5 cm	22 (45.8)
Rai stage at baseline	
0 – II	19 (39.6)
III – IV	27 (56.2)
Unknown	2 (4.2)
Prior number of regimens	
Mean (SD)	4.3 (2.7)
Median (Min, Max)	4.0 (1.0, 12.0)
Category, n (%)	
< 3	18 (37.5)
≥ 3	30 (62.5)
Del 17p	
Positive	18 (37.5)
Negative	28 (58.3)
Unknown	2 (4.2)

[Source: Statistical reviewer's analysis]

In Study PCYC-1102-CA, 1 patient had major eligibility criteria deviations defined in the study protocol.

## 3.2.4 Results and Conclusions

### 3.2.4.1 Results of overall response

The results of overall response per IRC for relapsed/ refractory CLL patients received 420 mg ibrutinib are summarized in Table 6. Overall response rate was 56.3%. Median duration of response was not reached yet.

TABLE 6: RESULTS OF ORR PER IRC, RELAPSED/REFRACTORY CLL PATIENTS TREATED WITH 420MG

	Relapsed/refractory CLL 420 mg N=48
Overall response rate (CR + PR), n (%)	27 (56.3)
Complete response (CR), n (%)	0 (0)
Partial Response (PR), n (%)	27 (56.3)
95% CI for ORR (%)	(41.2, 70.5)
Duration of response (DOR)	N=27
Number of subjects progressed or died, n (%)	4 (14.8)
Median DOR (Months)	NE

CI: confidence interval; NR: not evaluable.

[Source: Statistical reviewer's analysis]

#### Reviewer's comment:

- The number of PR derived by the FDA reviewers based on IRC assessments was 4 less than those derived by the applicant.
- FDA reviewers determined that patient 032-108 with partial response, progressed on January 10, 2012, instead of being censored on November 13, 2012 as the applicant claimed.

The results of overall response per investigator assessments for relapsed/ refractory CLL patients received 420 mg ibrutinib are summarized in Table 7. Overall response rate was 77.1%. Median duration of response was not reached yet.

TABLE 7: RESULTS OF ORR PER INVESTIGATOR ASSESSMENTS, RELAPSED/REFRACTORY CLL PATIENTS TREATED WITH 420MG

	<b>Relapsed/refractory CLL 420 mg N=48</b>
Overall response rate (CR + PR), n (%)	37 (77.1)
Complete response (CR), n (%)	0 (0)
Partial Response (PR), n (%)	37 (77.1)
95% CI for ORR (%)	(62.7, 88.0)
Duration of response (DOR)	N=37
Number of subjects progressed or died, n (%)	3 (8.1)
Median DOR (Months)	NE

CI: confidence interval; NR: not evaluable.

[Source: Statistical reviewer's analysis]

### 3.2.4.2 Analysis results for other efficacy endpoints

The analysis results of overall survival (OS) are summarized in Table 8 for relapsed/ refractory CLL patients received 420 mg ibrutinib in Study PCYC-1102-CA.

TABLE 8: SUMMARY OF OS ANALYSIS RESULTS, RELAPSED / REFRACTORY CLL PATIENTS TREATED WITH 420MG

Endpoints	Statistic	Relapsed/refractory CLL 420 mg N=48
OS (Months)		
	Number (%) of subjects censored	44 (91.7)
	Number of subjects died	4 (8.3)
	Median (95% CI)	NE

CI: confidence interval; NE: not evaluable; SD: standard deviation.

[Source: Statistical reviewer's analysis]

#### Reviewer's comment:

- Analysis results presented in Table 8 are exploratory because OS analysis is not interpretable in single-arm study.

### 3.2.4.3 Conclusions for efficacy

The Study PCYC-1102-CA demonstrated durable treatment benefit of ibrutinib for patients with relapsed and/or refractory chronic lymphocytic leukemia.

### 3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

### 3.4 Benefit-risk assessment

Because the pivotal study supporting this NDA original-2 application was a single-arm study, the benefit/risk can not be assessed based on comparative analyses. Whether the submission demonstrated an overall favorable risk-benefit profile on ibrutinib is deferred to the clinical team reviewing this submission.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Age, Race and Region

Table 9 summarizes the subgroup analyses of ORR by gender, age for the Study PCYC-1102-CA. The ORR results by subgroups are consistent with the ORR results for all patients.

TABLE 9: ORR PER IRC – SUBGROUP ANALYSES BY GENDER AND AGE, RELAPSED / REFRACTORY CLL PATIENTS TREATED WITH 420MG

<b>Subgroup</b>	<b>Relapsed/refractory CLL 420 mg</b>
	<b>N=48</b>
	<b>r/n (%)</b>
	<b>(95% CI (%))</b>
<hr/>	
Gender	
Male	19/34 (55.9) (37.9, 72.8)
Female	8/14 (57.1) (28.9, 82.3)
Age	
< 65 yrs	12/23 (52.2) (30.6, 73.2)
≥ 65 yrs	15/25 (60.0) (38.7, 78.9)

r: number of response, n: number of subjects in a subgroup  
[Source: Statistical reviewer's analysis]

#### Reviewer's comments:

- Most patients in Study PCYC-1102-CA were White, subgroup analyses of ORR by race were not performed.
- All patients in the Study PCYC-1102-CA were enrolled in United States; therefore results of ORR by region are not provided.

## 4.2 DEL17p status

Results of overall response in patients with del17p positive status are summarized in Table 10. Overall response rate for patients with positive del17p was 44.4%. Median duration of response was not reached yet.

TABLE 10: ORR PER IRC – SUBGROUP ANALYSES BY DEL17P POSITIVENESS RELAPSED / REFRACTORY CLL PATIENTS TREATED WITH 420MG

	Relapsed/refractory CLL 420 mg Del17p positive N=18
Overall response rate (CR + PR), n (%)	8 (44.4)
Complete response (CR), n (%)	0 (0)
Partial Response (PR), n (%)	8 (44.4)
95% CI for ORR (%)	(21.5, 69.2)
Duration of response (DOR)	8
Number of subjects progressed or died, n (%)	1 (12.5)
Median DOR (Months)	NE (12.0, NE)

CI: confidence interval; NR: not reached yet.

[Source: Statistical reviewer's analysis]

## **5 SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues**

Study PCYC-1102-CA was single-arm study, no comparative evaluation of treatment effect of ibrutinib can be performed within the trial.

### **5.2 Collective evidence**

Ibrutinib provided durable treatment effect for patients with relapsed or refractory chronic lymphocytic leukemia in Study PCYC-1102-CA.

### **5.3 Conclusions and Recommendations**

This NDA original-2 application was based on one pivotal multicenter Phase I studies (PCYC-1102-CA) to evaluate the treatment effect of ibrutinib for patients with relapsed/refractory CCL.

Study PCYC-1102-CA demonstrated durable overall response benefit of ibrutinib for relapsed or refractory chronic lymphocytic leukemia patients who received at least one prior regimen. However, because Study PCYC-1102-CA was a single-arm study, the treatment effects of ibrutinib can only be descriptively summarized and no comparative evaluation of treatment effect of ibrutinib can be performed within the trial. The final decision on the benefit-risk evaluation of ibrutinib is deferred to the clinical review team.

### **5.4 Labeling recommendations**

The reviewer does not have any comment for the labeling.

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/s/  
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YUN WANG  
01/31/2014

LEI NIE  
01/31/2014

THOMAS E GWISE  
01/31/2014

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 205552

**Applicant:** Pharmacyclics

**Stamp Date:** May 31, 2013

**Drug Name:** Ibrutinib

**NDA/BLA Type:** 505(b)(1)

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** \_\_\_\_ Yes \_\_\_\_

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	<b>X</b>			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<b>X</b>			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	<b>X</b>			
Appropriate references for novel statistical methodology (if present) are included.			<b>X</b>	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	<b>X</b>			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			<b>X</b>	This NDA is based on single-arm trials with ORR as the primary endpoints. Any subject dropped out without response will be treated as non-responders. No investigation of effect of dropouts on statistical analysis will be performed.

**Comment:**

**Yun Wang**

**August 6, 2013**

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Reviewing Statistician

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Date

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Supervisor/Team Leader

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Date

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YUN WANG  
08/14/2013

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