Survival adjusting for crossover: phase 3 study of ibrutinib *vs.* chlorambucil in older patients with untreated chronic lymphocytic leukemia/small lymphocytic lymphoma

Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is indicated by the US FDA for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and allows for treatment without chemotherapy. This broad approval, including treatment-naïve (TN) patients was based on the primary analysis from RESONATE-2 (PCYC-1115/1116), a randomized phase 3 trial of ibrutinib vs. chlorambucil in older patients with TN CLL/SLL (N=269).[1] Chlorambucil was the standard of care for older patients with TN CLL/SLL at the time of trial initiation (2013). The primary analysis with median follow up of 18.4 months demonstrated superiority of ibrutinib vs. chlorambucil for progression-free survival (primary endpoint; HR 0.16, 95% CI 0.09-0.28, *P*<0.001, median not reached *vs.*18.9 months), overall survival (OS; HR 0.16, 95% CI 0.05-0.56, *P*=0.0010, median not reached in both arms), overall response rate (86% *vs.* 35% *P*<0.001), and sustained improvements in hematologic variables (in patients with baseline anemia, 84% *vs.* 45% improved hemoglobin, *P*<0.001; in patients with baseline thrombocytopenia, 77% *vs.* 43% improved platelet count, *P*=0.005) in the intent-to-treat (ITT) population. The most common adverse events (≥20%) with ibrutinib were diarrhea, fatigue, cough, and nausea, and with chlorambucil were nausea, fatigue, neutropenia, anemia, and vomiting. At the time of the primary analysis, 20 patients had died (3 and 17 randomized to ibrutinib and chlorambucil, respectively) and 33 of 133 patients randomized to chlorambucil had crossed over to receive treatment with ibrutinib (extension study PCYC-1116) after progressive disease (PD). While PFS is not affected by crossover, the ITT OS analysis can be influenced by crossover, as OS reported for the chlorambucil arm reflects the mixed treatment effects of both chlorambucil and ibrutinib following crossover. The objective of this supplemental OS analysis was to assess OS (ITT) with longer follow up and estimate the treatment effect on OS adjusted for the impact of crossover by 2 commonly-used statistical methods. Results of this supplemental OS analysis continue to demonstrate a statistically significant survival benefit for single-agent ibrutinib over chlorambucil in older patients with treatment-naïve CLL/SLL. The study design for PCYC-1115 (*clinicaltrials.gov identifier*

Table 1. Baseline Patient and Disease Characteristics.

Characteristic	Ibrutinib (n=136)	Chlorambucil	
		Crossover to ibrutinib (n=54)	Non-crossover (n=79)
Median time since diagnosis, months (range)	30.5 (1-241)	35.0 (1-277)	20.9 (1-294)
Median age, years (range)	73 (65-89)	73 (65-84)	72 (65-90)
≥70 years, n (%)	6 (71)	41 (76)	52 (66)
ECOG performance status, n (%)			
0	60 (44)	23 (43)	31 (39)
1	65 (48)	26 (48)	41 (52)
2	11 (8)	5 (9)	7 (9)
Rai stage III or IV, n (%)	60 (44)	24 (44)	38 (48)
CIRS-G score, n (%)			
>6	42 (31)	18 (33)	26 (33)
≤6	79 (58)	29 (54)	46 (58)
Missing	15 (11)	7 (13)	7 (9)
CrCl <60 mL/min, n (%)	58 (44)	29 (54)	38 (48)
LDH >250 U/L, n (%)	39 (29)	15 (28)	16 (20)
Bulky disease, n (%)			
Yes (≥5 cm)	54 (40)	20 (37)	20 (25)
No (<5 cm)	80 (59)	33 (61)	57 (72)
Missing	2 (1)	1 (2)	2 (3)
β2-microglobulin, n (%)			
>3.5 mg/L	85 (63)	40 (74)	49 (62)
≤3.5 mg/L	41 (30)	11 (20)	22 (28)
Missing	10 (7)	3 (6)	8 (10)
Hemoglobin ≤11 g/dL, n (%)	51 (38)	23 (43)	32 (41)
Platelet count ≤100,000/mm^3, n (%)	35 (26)	11 (20)	17 (22)
Del11q, n (%)			
Yes	29 (21)	13 (24)	12 (15)
No	101 (74)	34 (63)	62 (78)
Missing/not reported	6 (4)	7 (13)	5 (6)

CIRS: Cumulative Illness Rating Scale for geriatrics; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase.

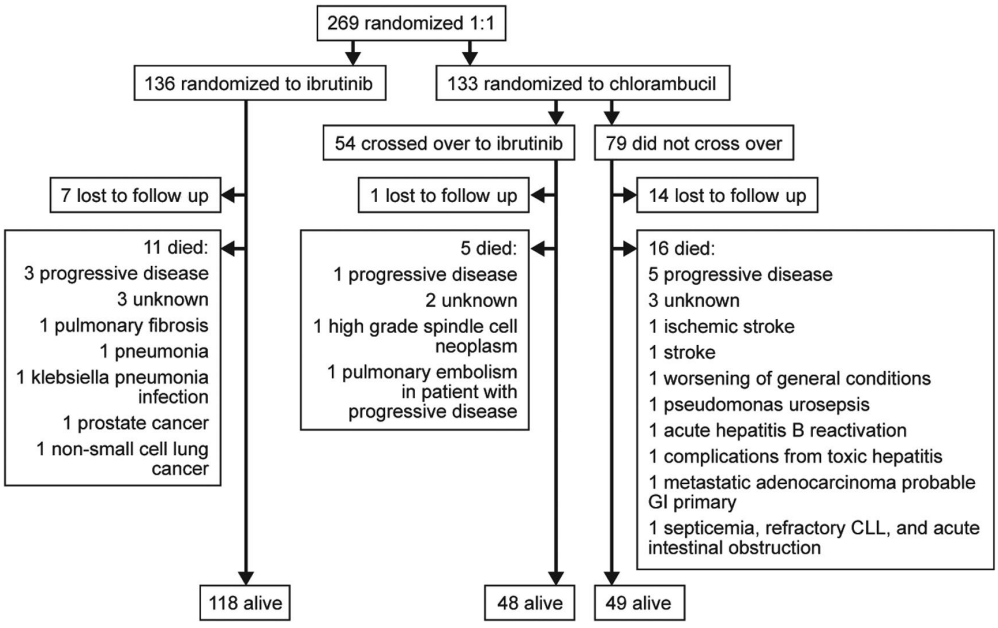

Figure 1. Patient disposition and causes of death.

01722487) has been previously described in detail.[1] Briefly, patients aged ≥65 years with TN CLL/SLL (excluding del17p) were randomized 1:1 to oral ibrutinib 420 mg once daily until PD or unacceptable toxicity, or chlorambucil 0.5 mg/kg (up to a maximum of 0.8 mg/kg) on days 1 and 15 of a 28-day cycle for up to 12 cycles. Patients could enroll in a separate extension study PCYC-1116 (*clinicaltrials.gov identifier 01724346*) after independent review committee-confirmed PD or at PCYC-1115 study closure for continuing treatment and follow up. All patients with an iwCLL indication for treatment after PD were offered second-line treatment with ibrutinib (crossover to ibrutinib arm) or could be treated with any other agent based on investigator's choice. As PCYC-1116 is ongoing, patients randomized to chlorambucil in PCYC-1115 continue to crossover to ibrutinib in PCYC-1116. Studies were approved by the institutional review board or independent ethics committee at each participating institution and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

In the ITT OS analysis, all randomized patients were analyzed according to initial treatment assignment regardless of subsequent anticancer therapy. To account for the effects of patient crossover, two OS sensitivity analyses were performed. In the first analysis, patients who crossed over from chlorambucil to ibrutinib treatment were excluded. Simple adjustment methods such as this, or censoring at the time of crossover may be prone to selection bias. As the patient population included in this study tends to survive long after progression, events before crossover are very limited. Thus, selection bias through censoring will be more prominent than when excluding crossover patients given the high rate of crossover and the roughly balanced baseline characteristics in this study for those who did and did not crossover (Table 1). In the second analysis, the rank-preserving structural failure time (RPSFT) model was used.[2,3] RPSFT is a randomization-based method for estimating counterfactual survival times, i.e., survival times that would have been observed had no crossover from chlorambucil to ibrutinib occurred. The RPSFT model was designed specifically in the context of randomized controlled trials (RCTs), relies on the assumption of balanced treatment arms, and is often used when available data are unlikely to capture all factors that predict both treatment changes and outcomes. This approach is therefore appropriate in situations where high rates of crossover occur and the crossover may be associated with prognostic factors. Therefore, RPSFT was selected over the Inverse Probability of Censoring Weighted (IPCW) model, which requires that data be available on all baseline and time-dependent prognostic factors for mortality that independently predict crossover, which is not generally the case in RCTs.

The ITT analysis and analysis excluding crossover patients were conducted based on a stratified log-rank test, with stratification by Eastern Cooperative Oncology Group performance status (ECOG PS; 0-1 *vs.* 2) and Rai stage (0-II *vs.* III-IV). The RPSFT analysis used a Cox model including treatment and baseline covariates (ECOG PS, Rai stage, age, sex, bulky disease, del11q, region, ethnicity, lactate dehydrogenase, β2-microglobuin, and creatinine clearance) to adjust for any imbalances between treatment arms and improve precision. *P* value is not reported for the RPSFT model, as it is based on projected data.

At a median follow up of 28.1 months (*vs.* 18.4 months in primary analysis), in 269 randomized patients, 215 (80%) remained on study, 22 (8%) were lost to follow up, and 32 (12%) had died (Figure 1). In the ITT analysis, OS for patients randomized to ibrutinib was significantly longer (Figure 2; HR 0.44, 95% CI 0.21-0.92, *P*=0.0243). At 24 months, the Kaplan-Meier estimates of OS were 95% and 84% for patients randomized to ibrutinib *vs.* chlorambucil, respectively. Of 133 patients randomized to chlorambucil, 54 patients (41%) had crossed over to ibrutinib with a median follow up time post-crossover of

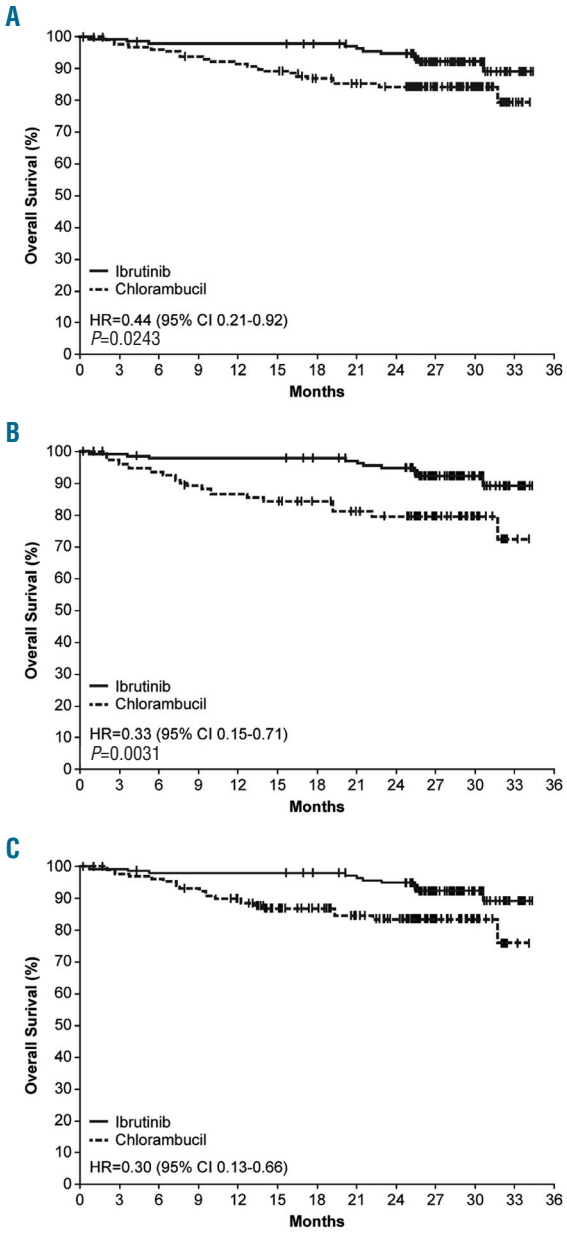

Figure 2. Kaplan-Meier curves of overall survival for (A) patients randomized to ibrutinib or chlorambucil (intent-to-treat population), (B) when excluding patients randomized to chlorambucil who crossed over to ibrutinib, and (C) by the rank-preserving structural failure time method.

12.5 months. Exposure to chlorambucil was similar, with a median of 6.6 and 7.1 months in patients who did and did not crossover, respectively. Baseline characteristics for the two study arms were generally balanced and have been previously reported.[1] Characteristics for patients randomized to chlorambucil who did or did not crossover to ibrutinib were similar (Table 1), though patients who crossed over to ibrutinib had a longer median time since diagnosis (35.0 *vs.* 20.9 months), were more often ≥70 years old (76% *vs.* 66%), and more often had creatinine clearance <60 mL/min (54% *vs.* 48%), lactate dehydrogenase >250 U/L (28% *vs.* 20%), β2-microglobuin >3.5 mg/L (74% *vs.* 62%), and del11q (24% *vs.* 15%) *vs.* patients who did not cross over to ibrutinib. After adjusting for crossover effects, the 2 sensitivity analyses showed more prominent OS benefit of ibrutinib than the ITT analysis: HR 0.33 (95% CI 0.15-0.71, *P*=0.0031) when excluding patients who crossed over from the OS analysis and HR 0.30 (95% CI 0.13-0.66) when using the RPSFT model (Figure 2). A key assumption in the RPSFT model is "common treatment effect of the active treatment," i.e., patients who crossed over to ibrutinib benefit equally to patients who were originally randomized to ibrutinib. This assumption was roughly held as survival with ibrutinib from randomization was not significantly longer (*P*=0.1446) than survival with ibrutinib following crossover.

In summary, with additional follow up, the ITT analysis for OS continued to demonstrate a significant advantage for single-agent ibrutinib over chlorambucil in older patients with TN CLL/SLL, despite frequent crossover from chlorambucil. Although chlorambucil is no longer considered standard of care for the treatment of CLL/SLL, it is notable that due to the effectiveness of ibrutinib in the majority of patients, median OS in the ibrutinib arm remains unestimable based on the small number of events. However, in terms of testing the relative OS benefit compared with chlorambucil, the analysis was preplanned with reasonable power. In both sensitivity analyses undertaken to adjust for the effects of crossover, results further indicate that treatment with single-agent ibrutinib was associated with statistically significant OS benefit compared with chlorambucil.

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