Ibrutinib versus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma: A Randomized, Open-Label Phase 3 Study

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INTRODUCTION

- The estimated incidence of chronic lymphocytic leukemia (CLL) is 4.2 cases per 100,000/year in the Western world[1] and <1 case per 100,000/year in China.[2]
- CLL is an incurable disease, and patients eventually relapse or become refractory to treatment.[3]
- Rituximab, an anti-CD20 monoclonal antibody, has shown modest overall response rates (6% to 35%) when used as monotherapy in relapsed CLL.[4-7]
- Ibrutinib, a potent covalent inhibitor of Bruton's tyrosine kinase, is approved in the US and Europe for the treatment of mantle cell lymphoma (in patients who have received ≥1 prior therapy), CLL/small lymphocytic lymphoma (SLL; including del[17p]), and Waldenström's macroglobulinemia.[8,9]
- To compare the efficacy and safety of ibrutinib with rituximab, we conducted a randomized, open-label, multicenter, phase 3 study of a predominantly Asian population of patients with relapsed/refractory CLL/SLL.

METHODS

- This randomized, open-label, multicenter, phase 3 study was conducted at 29 sites in China, Australia, Taiwan, and Malaysia.
- Key eligibility criteria included: ≥18 years with a diagnosis of active CLL/SLL that required treatment; received at least 1 prior therapy for CLL/SLL; and not considered appropriate candidates for purine analog-based therapy.
- Patients were randomly assigned 2:1 to receive 420 mg oral ibrutinib until disease progression (PD) or unacceptable toxicity or up to 6 cycles of intravenous rituximab.
- Rituximab was administered at 375 mg/m^2 on day 1 and 500 mg/m^2 on day 15 of cycle 1; 500 mg/m^2 on days 1 and 15 for cycle 2; and 500 mg/m^2 on day 1 of cycles 3 to 6.
- The primary endpoint was investigator-assessed progression-free survival (PFS); key secondary endpoints were overall response rate (ORR), overall survival (OS), and safety.
- Eligible patients in the rituximab arm who had confirmed PD by an independent physician were permitted to cross over to receive ibrutinib.
- An interim analysis using O'Brien-Fleming boundary for superiority was planned after approximately 45 PFS events.

RESULTS

- At the interim analysis, the independent data monitoring committee recommended early stopping of the study for efficacy; the clinical cutoff date was December 1, 2015.
- Here we present data from an updated analysis with longer follow-up (data cutoff date of April 14, 2016); results from the interim analysis and updated analysis were consistent.

Patients

- 160 eligible patients were randomized; 106 patients to the ibrutinib arm and 54 patients to the rituximab arm.
- At data cutoff, 72 (67.9%) patients in the ibrutinib arm, and no patients in the rituximab arm remained on treatment.
- The median duration of exposure was 16.4 months for ibrutinib and 4.6 months for rituximab.
- Patient demographics and characteristics were generally comparable between both treatment arms (**Table 1**).

Table 1. Demographics and Baseline Characteristics (ITT Population)

	Ibrutinib (n=106)	Rituximab (n=54)	Total (N=160)
Age			
Mean (SD)	63.6 (10.4)	63.6 (13.0)	63.6 (11.3)
Median	65	67	66
Range	(39, 87)	(21, 86)	(21, 87)
Sex, n (%)			
Female	29 (27.4)	18 (33.3)	47 (29.4)
Male	77 (72.6)	36 (66.7)	113 (70.6)
Race, n (%)			
Chinese	91 (85.8)	45 (83.3)	136 (85.0)
White	14 (13.2)	8 (14.8)	22 (13.8)
Asian, not Chinese	1 (0.9)	0	1 (0.6)
Other	0	1 (1.9)	1 (0.6)
Baseline Rai stage (CLL only), n (%)			
N	99	51	150
I	9 (9.1)	11 (21.6)	20 (13.3)
II	11 (11.1)	3 (5.9)	14 (9.3)
III	18 (18.2)	9 (17.6)	27 (18.0)
IV	61 (61.6)	28 (54.9)	89 (59.3)
Baseline Binet stage (CLL only), n (%)			
N	100	51	151
A	2 (2.0)	4 (7.8)	6 (4.0)
B	25 (25.0)	10 (19.6)	35 (23.2)
C	73 (73.0)	37 (72.5)	110 (72.8)
Prior purine analog therapy, n (%)			
Yes	69 (65.1)	42 (77.8)	111 (69.4)
No	37 (34.9)	12 (22.2)	49 (30.6)
Number of prior CLL/SLL therapies			
N	105	54	159
Category, n (%)			
1	55 (52.4)	23 (42.6)	78 (49.1)
2	24 (22.9)	11 (20.4)	35 (22.0)
≥3	26 (24.8)	20 (37.0)	46 (28.9)
ECOG performance status, n (%)			
0	54 (50.9)	23 (42.6)	77 (48.1)
1	52 (49.1)	31 (57.4)	83 (51.9)
Bulky disease, n (%)			
Yes (≥5cm)	42 (39.6)	28 (51.9)	70 (43.8)
No (<5cm)	64 (60.4)	26 (48.1)	90 (56.3)
Chromosome 11q deletion, n (%)			
Yes	22 (20.8)	12 (22.2)	34 (21.3)
No	84 (79.2)	42 (77.8)	126 (78.8)
Chromosome 17p deletion, n (%)			
Yes	23 (21.7)	13 (24.1)	36 (22.5)
No	83 (78.3)	41 (75.9)	124 (77.5)
IGVH status, n (%)			
Mutated	33 (31.1)	16 (29.6)	49 (30.6)
Unmutated	63 (59.4)	35 (64.8)	98 (61.3)
Unevaluable	10 (9.4)	3 (5.6)	13 (8.1)
Cytopenia at baseline[a], n (%)			
Yes	82 (77.4)	43 (79.6)	125 (78.1)
No	24 (22.6)	11 (20.4)	35 (21.9)

CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group; IGVH = immunoglobulin variable heavy-chain; ITT = intent-to-treat; SD = standard deviation; SLL = small lymphocytic lymphoma. [a]Cytopenia defined as platelet count ≤100,000/µL, Hgb ≤11 g/dL, or ANC ≤1500/µL.

Efficacy

- PFS was significantly improved for patients in the ibrutinib arm compared with the rituximab arm (HR=0.180, 95% CI: 0.105-0.308; p <0.0001; **Figure 1**).
  - Median PFS was not reached in the ibrutinib arm; median PFS for the rituximab arm was 8.3 months (range, 0-22.6).
  - At the 18-month landmark, the estimated PFS rate in the ibrutinib arm was 74.0% and 11.9% in the rituximab arm.
- Improvement in PFS in the ibrutinib arm compared with the rituximab arm was observed in all subgroups examined (**Figure 2**).

Figure 1. Progression-Free Survival (ITT Population)

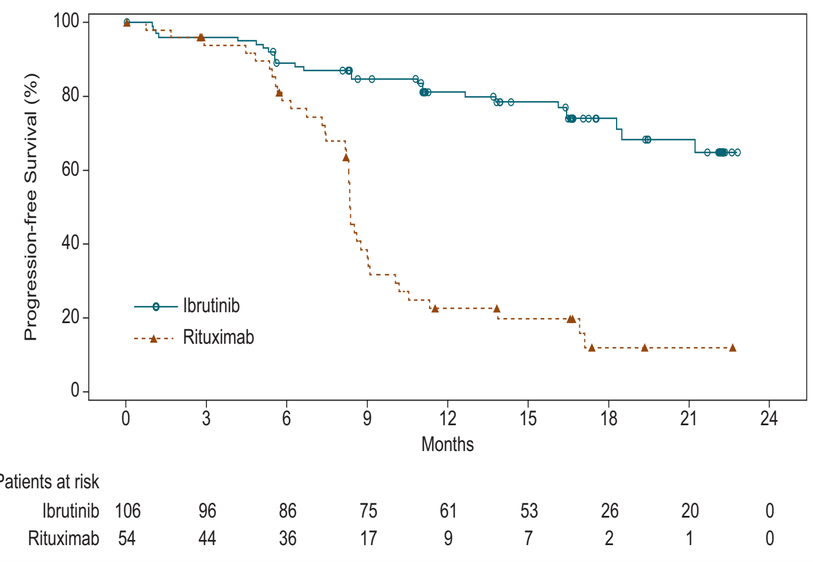
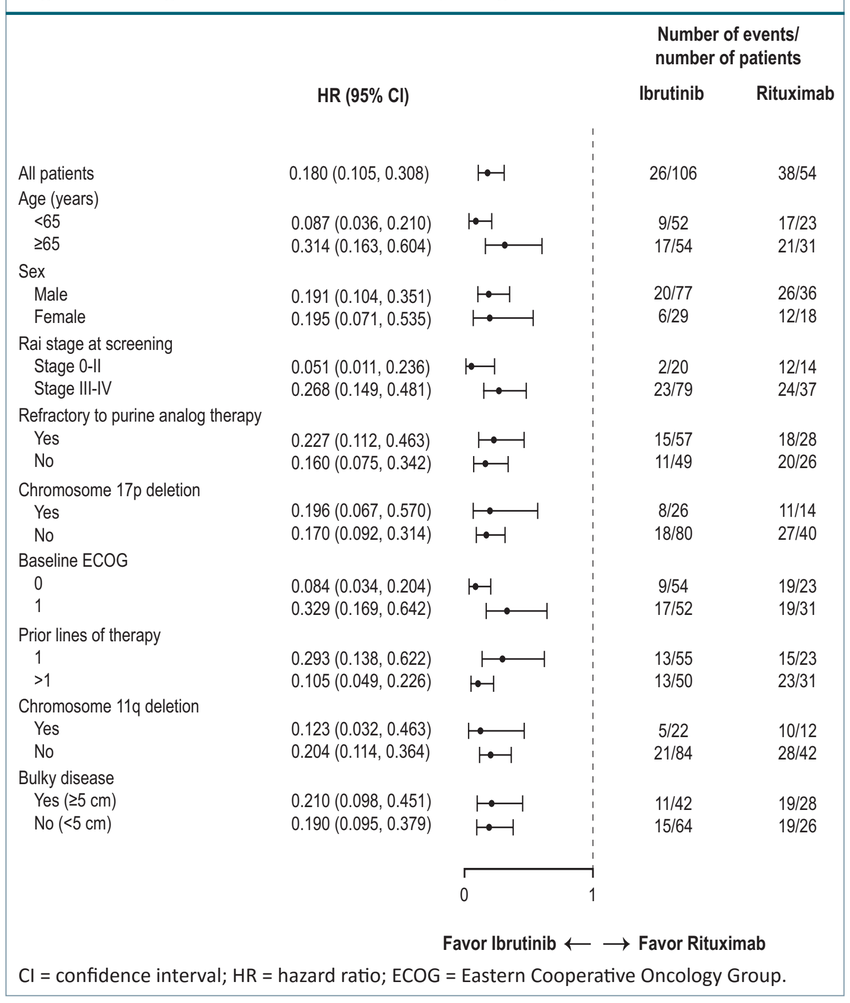


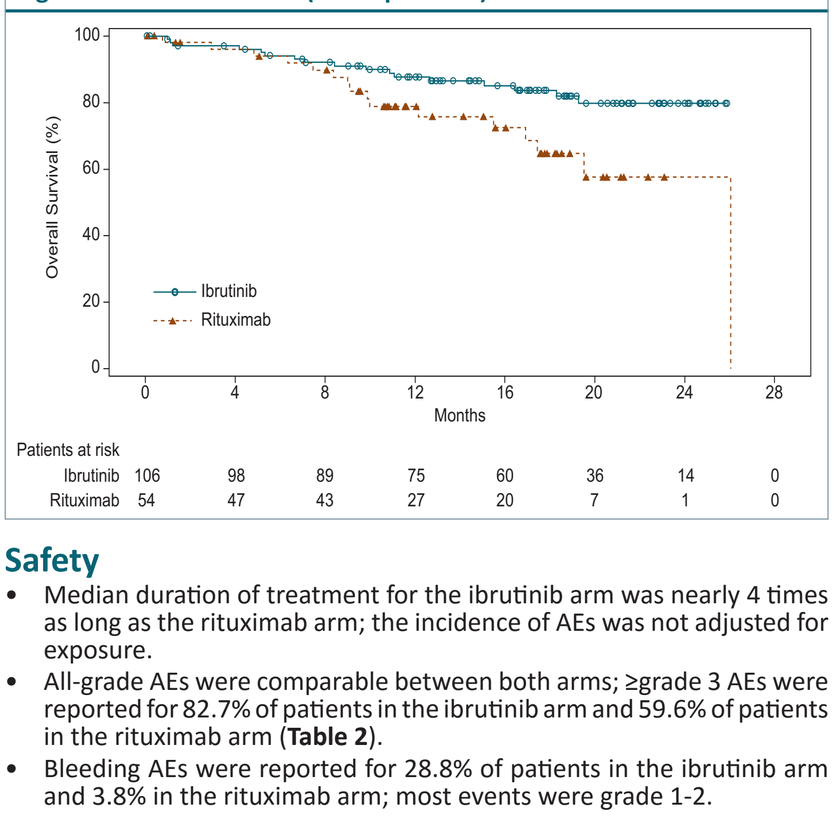
Figure 2. Progression-Free Survival by Subgroup



CI = confidence interval; HR = hazard ratio; ECOG = Eastern Cooperative Oncology Group.

- ORR (complete response [CR] + partial response [PR]) was significantly higher for the ibrutinib arm (53.8%) than for the rituximab arm (7.4%).
  - CR was achieved in 4 (3.8%) patients in the ibrutinib arm and 0 patients in the rituximab arm.
  - ORR including PR with lymphocytosis was significantly higher for the ibrutinib arm (67.9%) than for the rituximab arm (7.4%).
- At a median follow-up of 17.8 months (range, 0.1-26.1), an improvement in OS was observed in the ibrutinib arm compared with the rituximab arm (HR=0.446; 95% CI: 0.221-0.900; p=0.0206; **Figure 3**).
  - The estimated 24-month OS rate was 79.8% in the ibrutinib arm and 57.6% in the rituximab arm.
  - 20 (37.0%) patients in the rituximab arm crossed over to receive ibrutinib therapy after confirmed PD. As a result, OS was impacted by implementation of crossover.

Figure 3. Overall Survival (ITT Population)



Safety

- Median duration of treatment for the ibrutinib arm was nearly 4 times as long as the rituximab arm; the incidence of AEs was not adjusted for exposure.
- All-grade AEs were comparable between both arms; ≥grade 3 AEs were reported for 82.7% of patients in the ibrutinib arm and 59.6% of patients in the rituximab arm (**Table 2**).
- Bleeding AEs were reported for 28.8% of patients in the ibrutinib arm and 3.8% in the rituximab arm; most events were grade 1-2.

Table 2. Adverse Events Reported by ≥10% of Patients (Safety Population)

	Ibrutinib (n=104)		Rituximab (n=52)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
AE				
Diarrhea	35 (33.7)	4 (3.8)	3 (5.8)	0
Platelet count decreased	31 (29.8)	8 (7.7)	15 (28.8)	3 (5.8)
Neutrophil count decreased	28 (26.9)	19 (18.3)	21 (40.4)	13 (25.0)
Cough	26 (25.0)	1 (1.0)	4 (7.7)	0
Pyrexia	25 (24.0)	1 (1.0)	14 (26.9)	1 (1.9)
Neutropenia	24 (23.1)	17 (16.3)	11 (21.2)	10 (19.2)
Rash	24 (23.1)	0	3 (5.8)	0
Upper respiratory tract infection	23 (22.1)	7 (6.7)	6 (11.5)	1 (1.9)
Lung infection	21 (20.2)	17 (16.3)	6 (11.5)	5 (9.6)
Fatigue	20 (19.2)	0	6 (11.5)	0
Thrombocytopenia	17 (16.3)	5 (4.8)	3 (5.8)	0
Anemia	16 (15.4)	2 (1.9)	5 (9.6)	0
Hemoglobin decreased	15 (14.4)	0	6 (11.5)	0
Nasopharyngitis	15 (14.4)	0	0	0
Nausea	15 (14.4)	0	1 (1.9)	0
Constipation	13 (12.5)	0	0	0
Lymphocyte count increased	13 (12.5)	11 (10.6)	0	0
Leukocytosis	12 (11.5)	12 (11.5)	0	0
Mouth ulceration	12 (11.5)	0	2 (3.8)	0
Vertigo	11 (10.6)	0	0	0
White blood cell count decreased	6 (5.8)	2 (1.9)	9 (17.3)	3 (5.8)
Chills	1 (1.0)	0	9 (17.3)	0

AE = adverse event.

CONCLUSIONS

- This is the first study of ibrutinib in a predominantly Asian population of patients with CLL/SLL and the first study to compare ibrutinib with rituximab.
- Ibrutinib significantly improved PFS, ORR, and OS compared with rituximab.
- Ibrutinib displayed a manageable safety profile with no new or unexpected events reported.
- These data demonstrate the favorable benefit-risk profile of ibrutinib for the treatment of relapsed/refractory CLL/SLL in patients from the Asia-Pacific region.

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