Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study

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ABSTRACT

MABLE investigated the efficacy and safety of rituximab plus bendamustine or rituximab plus chlorambucil in fludarabine-ineligible patients with chronic lymphocytic leukemia. Patients received rituximab plus bendamustine or rituximab plus chlorambucil every four weeks for six cycles. Rituximab plus chlorambucil-treated patients without a complete response after Cycle 6 received chlorambucil monotherapy for at least six additional cycles or until complete response. The primary endpoint was complete response rate (confirmed by bone marrow biopsy) after Cycle 6 in first-line patients. Secondary endpoints included progression-free survival, overall survival, minimal residual disease, and safety. Overall, 357 patients were randomized (rituximab plus bendamustine, n=178; rituximab plus chlorambucil, n=179; intent-to-treat population), including 241 first-line patients (n=121 and n=120, respectively); 355 patients received treatment (n=177 and n=178, respectively; safety population). In first-line patients, complete response rate after Cycle 6 (rituximab plus bendamustine, 24%; rituximab plus chlorambucil, 9%; *P*=0.002) and median progression-free survival (rituximab plus bendamustine, 40 months; rituximab plus chlorambucil, 30 months; *P*=0.003) were higher with rituximab plus bendamustine than rituximab plus chlorambucil. Overall response rate and overall survival were not different. In first-line patients with a complete response, minimal residual disease-negativity was higher with rituximab plus bendamustine than rituximab plus chlorambucil (66% *vs.* 36%). Overall adverse event incidence was similar (rituximab plus bendamustine, 98%; rituximab plus chlorambucil, 97%). Rituximab plus bendamustine may be a valuable first-line option for fludarabine-ineligible patients with chronic lymphocytic leukemia. *clinicaltrials.gov identifier: 01056510*

Introduction

Rituximab plus fludarabine and cyclophosphamide (R-FC) is standard treatment for medically fit chronic lymphocytic leukemia (CLL) patients,[1,2] with high response rates in previously untreated patients (first-line; 1L) and treated patients (second-line; 2L).[3-5] However, many CLL patients are elderly and have comorbidities, making them ineligible for fludarabine-based treatment.[6] Chemotherapy options for these patients include bendamustine (B) and chlorambucil (Clb).

In treatment-naïve CLL patients, phase II studies showed promising efficacy with rituximab plus B (R-B)[7] or Clb (R-Clb),[8,9] while the phase III CLL11 study demonstrated improved efficacy with R-Clb and obinutuzumab plus Clb (G-Clb) *versus* Clb monotherapy.[10,11] G-Clb also increased progression-free survival (PFS) and complete response (CR) rates *versus* R-Clb,[10,11] although infusion-related reactions and neutropenia were more common; infection rates were not increased, however.[10] While a phase III study demonstrated superior efficacy in terms of CR and PFS with B *versus* Clb in treatment-naïve CLL,[12,13] the activity of R-B *versus* R-Clb has not been directly compared.

Herein, we present results from the randomized, open-label, multicenter, phase IIIb MABLE study, which aimed to investigate the efficacy and safety of R-B and R-Clb in fludarabine-ineligible CLL patients.

Methods

Study design

Patients received rituximab (intravenous 375 mg/m^2 Day [D] 1, Cycle [C] 1 and 500 mg/m^2 D1, C2-C6) plus B (intravenous 90 mg/m^2 [1L] or 70 mg/m^2 [2L] D1 and D2, C1-C6) or Clb (oral 10 mg/m^2 D1-D7, C1-C6) every four weeks for six cycles. R-Clb patients without CR after C6 received Clb monotherapy for ≤6 additional cycles or until CR. After treatment completion, patients were followed every three months for one year, then every six months until data cut-off. Treatment was discontinued if the patient had progressive disease.

MABLE was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws, and approved by institutional review boards and ethics committees at participating centers. All patients provided written informed consent.

Patients

Patients were aged ≥18 years, with confirmed CLL requiring treatment as per the International Workshop on CLL (iwCLL) criteria,[14] Binet stage B/C disease, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and investigator assessment of ineligibility for fludarabine-based treatment (*Online Supplementary Information*). Exclusion criteria included transformation to aggressive B-cell malignancy and previous malignancy within five years of enrollment (unless treated with curative intent). For full inclusion and exclusion criteria see the *Online Supplementary Information.*

During recruitment, the protocol was amended to permit inclusion of patients with progressive Binet stage A disease and to exclude 2L patients (due to slow recruitment). All 2L patients recruited before this amendment were included in the final analysis, as tumor response in this patient subpopulation was a secondary study endpoint; however, as the number of 2L patients enrolled was relatively small, there was insufficient power to show statistically significant differences between study treatments in this patient subpopulation.

Study endpoints

The primary endpoint was CR rate (confirmed by bone marrow [BM] biopsy) after C6 in 1L patients. Secondary endpoints included CR rate after C6 in 2L patients, PFS, overall survival (OS), time to next leukemic treatment, minimal residual disease (MRD), and safety. Response was assessed after C3 and C6 as per iwCLL 2008 guidelines.[14] Response was also assessed in the R-Clb arm at C12,

with treatment being discontinued for patients showing evidence of CR during C7-C12. Assessments are detailed in the *Online Supplementary Information.*

Safety

Adverse events (AEs) were monitored throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for AEs v4.0 and coded according to the Medical Dictionary for Regulatory Activities v17.0.

Statistical analysis

Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). The safety population included all randomized patients who received treatment.

For 1L patients, the between-arm difference in response rates was tested using a one-sided continuity-corrected χ^2 test. A two-sided continuity-corrected χ^2 test assessed between-arm differences in overall response rates (ORRs) and molecular responses. PFS and OS were summarized by Kaplan–Meier estimates and compared *via* the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as a covariate.

Results

Patients

The study was conducted between 23 February 2010 and 31 March 2014. Of the 357 patients in the ITT population, comprising 241 1L patients (R-B, n=121; R-Clb, n=120) and 116 2L patients (R-B, n=57; R-Clb, n=59), 355 received treatment (R-B, n=177; R-Clb, n=178). Ninety-five patients (27%) withdrew from treatment during the study (Figure 1).

Overall, 92/120 (76.7%) 1L patients treated with R-B and 97/120 (80.8%) 1L patients treated with R-Clb received six cycles of rituximab; 92 (76.7%) and 57 (47.5%) received six cycles of B and Clb, respectively. Twelve (10.0%) patients treated with R-Clb received 12 cycles of Clb. The median number of R, B and Clb doses was six for each. The median (interquartile range) dose of rituximab was 4780.5 mg (4222.5-5346.5) in 1L patients treated with R-B and 5028.5 mg (4546.0-5349.0) in 1L patients treated with R-Clb. In total, 6/121 (5.0%) patients treated with R-B and 2/120 (1.7%) patients treated with R-Clb had a reduction or delay in their treatment schedule due to treatment-emergent toxicities.

Baseline characteristics were balanced in the 1L population (Table 1; baseline characteristics for all patients are presented in *Online Supplementary Table S1*). Deletion of 17p was not an exclusion criterion due to a lack of efficacy data relating to 17p deletion for the treatment combinations used at the time of study design. Thus, 13 1L patients (R-B, 10; R-Clb, 3) with 17p deletion were included. Median follow-up was 23.5 months (R-B) and 23.3 months (R-Clb). Median age in 1L patients was 72 years in both treatment arms; the majority of patients were aged 65 years or more. The median number of comorbidities (active medical conditions) in 1L patients was three in both arms (Table 1); the most common comorbidities were vascular disorders and metabolism disorders affecting 49% and 37% of patients, respectively (*Online Supplementary Table S2*). The great majority of all patients in the study (including 2L patients) used concomitant medication during the study (R-B, 96%; R-Clb, 94%).

Table 1. Demographic characteristics for patients receiving 1L therapy.

	1L therapy	
	R-B **(N=121)**	**R-Clb** **(N=120)**
Age (years)		
Median (min, max)	72 (41, 86)	72 (38, 91)
≥65 years, n (%)	86 (71)	90 (75)
≥75 years, n (%)	45 (37)	44 (37)
Sex		
Male, n (%)	70 (58)	80 (67)
Female, n (%)	51 (42)	40 (33)
Active medical conditions, n		
Median (min, max)	3 (0, 12)	3 (0, 18)
Binet stage, n (%)		
A	6 (5)	8 (7)
B	73 (60)	66 (55)
C	37 (31)	43 (36)
Missing	5 (4)	3 (3)
ECOG PS, n (%)		
0	62 (51)	59 (49)
1	50 (41)	51 (43)
2	9 (7)	8 (7)
Missing	0	2 (2)
Body surface area, m²		
Mean (SD)	1.811 (0.2382)	1.807 (0.1706)
Min, max	1.30, 2.48	1.41, 2.29
IGVH mutational status, n (%)		
Mutated	41 (34)	46 (38)
Unmutated	73 (60)	59 (49)
Other[a]	3 (3)	8 (7)
Not tested	4 (3)	7 (6)
11q status, n (%)		
Heterozygous deletion	24 (20)	19 (16)
Normal	96 (79)	99 (83)
Not tested	1 (1)	2 (2)
17p status, n (%)		
Heterozygous deletion	10 (8)	3 (3)
Normal	110 (91)	114 (95)
Not tested	1 (1)	3 (3)
11q/17p deletion, n (%)		
Heterozygous deletion	32 (26)	22 (18)
Normal	88 (73)	96 (80)
Not tested	1 (1)	2 (2)
13q deletion (S25 or S319 probe)[b], n (%)		
Homozygous deletion	3 (3)	1 (1)
Two clones (one homozygote, one heterozygote)	15 (12)	6 (5)
Heterozygous deletion	42 (35)	5 (4)
Normal	61 (50)	60 (50)
Not tested	1 (1)	2 (2)
Trisomy 12, n (%)		
Trisomy	30 (25)	19 (16)
Normal	90 (74)	99 (83)
Not tested	1 (1)	2 (2)

[a]Other includes polyclonal and oligoclonal. [b]Deletion status according to at least one probe (NB, in the R-B group, one patient with two clones by S319 probe and heterozygous deletion by S25 probe is counted twice). 1L: first-line; ECOG PS: Eastern Cooperative Oncology Group performance status; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil; SD: standard deviation.

Colony-stimulating factors were taken more frequently by patients treated with R-B (111/178 [62.4%] vs. 71/179 [39.7%] for R-Clb). ECOG performance status scores were ≥1 in approximately half the study population. At baseline, 108/177 (61.0%), 56/177 (31.6%) and 4/177 (2.3%) patients treated with R-B, and 102/178 (57.3%), 60/178 (33.7%) and 3/178 (1.7%) patients treated with R-Clb had normal; abnormal, non-clinically significant; and abnormal clinically significant calculated creatinine clearance, respectively.

Efficacy

In 1L patients, the CR rate after C6 was higher with R-B versus R-Clb (24% [n=29/121] vs. 9% [n=11/120]; P=0.002; Table 2). Logistic regression analysis supported the R-B treatment effect after adjusting for baseline covariates (odds ratio 4.18, 95% CI 1.77-9.87; P=0.001). None of the covariates had a statistically significant impact on the CR rate.

ORRs (based on the investigator's assessment) at the end of rituximab treatment were similar for R-B and R-Clb (91% vs. 86%; P=0.304). The proportion of patients with stable disease (3% vs. 6%) and progressive disease (3% vs. 2%) at the end of treatment were also similar for R-B vs. R-Clb, respectively.

A statistically significant ten-month extension in median PFS was observed with R-B versus R-Clb (39.6 vs. 29.9 months; HR [adjusted for baseline Binet stage] 0.523, 95%
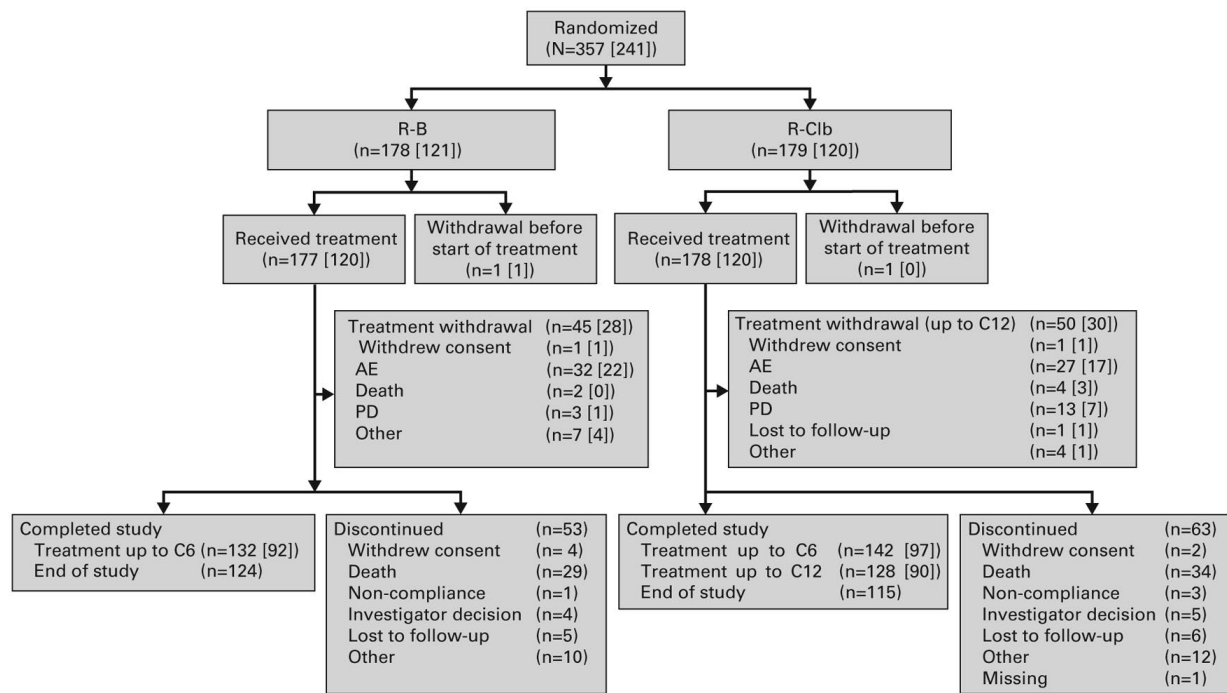

Figure 1. Patient disposition. Numbers in parentheses represent the number of patients from the 1L subpopulation. In total, 118 patients (33%) discontinued the study prematurely, due to death (R-B 16%; R-Clb 19%), patient lost to follow-up (3% per arm), investigator decision (R-B 2%; R-Clb 3%), patient withdrew consent (R-B 3%; R-Clb 2%), patient non-compliance (R-B 1%; R-Clb 2%), and 'other' reasons (R-B 6%; R-Clb 7%). Reason for withdrawal was not available for one patient (R-Clb). AE: adverse event; C: cycle; N: number of patients; PD: progressive disease; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil.

Table 2. CR and PRs at C6 in 1L patients.

Assessment	Analysis		R-B	R-Clb
CR confirmed by BM biopsy[a]	CR	N	121	120
		n (%)	29 (24)	11 (9)
		P-value[b]	0.002	
	Logistic regression[c]	N	113	103
		OR (95% CI)	4.18 (1.77-9.87)	
		P-value[d]	0.001	
PR based on the investigator's assessment	PR	N	121	120
		n (%)	60 (50)	79 (66)

[a]CRs confirmed by BM biopsy only were included. [b]P-value is based on a one-sided continuity corrected χ^2 test. [c]The following covariates were included in the logistic regression: Binet stage (A and B vs. C); IGVH mutational status (mutated vs. unmutated); 17p/11q deletion (heterozygote deletion vs. normal); ECOG PS (0 vs. ≥1). [d]P-value is based on the Wald test. BM: bone marrow; CI: confidence interval; CR: complete response; OR: odds ratio; PR: partial response; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil.

Table 3. MRD negativity at the confirmation-of-response visit[a] in 1L patients.

	R-B	R-Clb
Overall ITT population	(n=121)	(n=120)
MRD-negative patients, n (%)	49 (41)	16 (13)
Patients with CR	(n=29)	(n=11)
MRD-negative patients, n (%)	19 (66)	4 (36)
Patients with CR or PR based on the investigator's assessment[b]	(n=89)	(n=90)
MRD-negative patients, n (%)	47 (53)	16 (18)

[a]Performed 12 weeks after the end of C6 disease response assessment. [b]Includes patients with CR (with or without BM confirmation) or PR by investigator assessment. Negative MRD was defined as proportion of malignant B cells to white blood cells of $<10^{-4}$, as assessed by allele-specific oligonucleotide real-time quantitative polymerase chain reaction assay measured in BM aspirate (or PB if BM unavailable). MRD data were available for 45/50 patients with a CR based on the investigator's assessment (BM, n=42; PB, n=1; unknown=2) and 182/241 patients overall (BM, n=145; PB, n=32; unknown=5). CR: complete response; ITT: intent-to-treat; MRD: minimal residual disease; PR: partial response; RB: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil.

CI 0.339-0.806; *P*=0.003; Figure 2A); median OS was not significantly different (43.8 months *vs.* not reached; HR [adjusted for baseline Binet stage] 0.975, 95% CI 0.505-1.880; *P*=0.939; Figure 2B). During the study, 11/121 (9.1%) patients treated with R-B and 22/120 (18.3%) patients treated with R-Clb had a documented intake of any new leukemia treatment. Due to the low numbers, the median time to next leukemic treatment could not be calculated for either treatment arm (log-rank test for comparison between treatment arms: *P*=0.037).

MRD data were available for 45/50 patients (90%) who had a CR based on the investigator's assessment and 182/241 patients (76%) overall. BM aspirates were available for 42/45 patients (93%) and 145/182 patients (80%), respectively. MRD-negativity rates at the confirmation-of-response visit (ITT population) were higher for R-B than for R-Clb (41% *vs.* 13%; Table 3). In 1L patients with a CR after C6, MRD-negativity rates at the confirmation-of-response visit were higher in the R-B group than in the R-Clb group (66% *vs.* 36%). A similar pattern was seen in those with a CR or PR according to investigator's assessment (53% *vs.* 18%).

Efficacy results in 2L patients are presented in the *Online Supplementary Information.*

Safety

Safety results are presented for the pooled population (1L and 2L patients). AEs were similar between arms (R-B, 98%; R-Clb, 97%; Table 4). The most common AEs by System Organ Class (SOC) were 'blood and lymphatic system disorders' (R-B, 75%; R-Clb, 64%); the most commonly reported AE was neutropenia (R-B, 56%; R-Clb, 49%). AEs in the SOC 'skin and subcutaneous tissue disorders' were more frequent in the R-B *versus* R-Clb arm (36% *vs.* 23%), driven by a higher incidence of rash (16% *vs.* 5%).

Grade ≥3 AEs were higher with R-B (75%) than R-Clb (64%), mainly due to a higher incidence of serious AEs (SAEs) of the SOC 'infections and infestations'. The most common grade ≥3 AEs were of the SOC 'blood and lymphatic system disorders' (R-B, 56%; R-Clb, 47%). SAEs were experienced by 41% (R-B) and 32% (R-Clb) of patients, and were most frequently of the SOC 'infections and infestations' (R-B, 19%; R-Clb, 8%; Table 4).

Rituximab-related AEs were experienced by 81% (R-B) and 73% (R-Clb) of patients. B/Clb-related AEs were reported for 92% (R-B) and 80% (R-Clb) of patients. Drug-related AEs (rituximab, B, and Clb) were most commonly of the SOC 'blood and lymphatic system disorders'. AEs leading to rituximab discontinuation were experienced by 18% (R-B) and 11% (R-Clb) of patients. AEs leading to discontinuation of B or Clb were reported for 19% and 18% of patients, respectively. In 1L patients, AEs leading to treatment discontinuation were experienced by 22 R-B patients (18%) and 14 R-Clb patients (12%).

Overall, 65 patients died (R-B, n=30, 17%; R-Clb, n=35, 20%) due to CLL (R-B, n=14, 8%; R-Clb, n=20, 11%) and AEs (R-B, n=16, 9%; R-Clb, n=14, 8%). Cause of death was missing for one patient (R-Clb arm). AEs leading to death were infection (n=4 per arm), acute myeloid leukemia or myelodysplastic syndrome (n=1 per arm), other neoplasm (R-Clb, n=1), and other causes (R-B, n=11; R-Clb, n=8). Treatment-related AEs leading to death included thrombocytopenia, neutropenic sepsis and febrile neutropenia (n=1 each) in the 1L population and multi-organ failure, pneumonia, acute myeloid leukemia and sepsis (n=1 each) in the 2L population.

Discussion

R-FC is the standard 1L treatment for medically-fit patients with CLL. However, this regimen can cause significant myelosuppression and high rates of early and late infections, especially in elderly patients[15] who may have comorbidities and be considered ineligible for fludarabine-based treatment.[6] In MABLE, the efficacy and safety of R-B and R-Clb were investigated in fludarabine-ineligible CLL patients. B is an established treatment for CLL, and a previous phase III study of B *versus* Clb in treatment-naïve patients demonstrated improved CR rates and median PFS with B.[12,13] R combined with chemotherapeutic agents prolongs OS in previously untreated, medically fit CLL patients.[16,17] In unfit patients, survival was improved by the addition of G to Clb.[10]

Among 1L patients in MABLE, the rates of CR and of CR with MRD-negativity were higher for R-B than for R-Clb. ORRs were similar in the two arms. Whereas the CR rate in 1L R-Clb patients in MABLE (9%) was comparable with that in R-Clb patients in the phase III CLL11 study (7%),[10] the ORR for R-Clb-treated patients was higher in MABLE than in CLL11 (86% *vs.* 58%). Two explanations for this might be the different Clb doses used (MABLE, 10
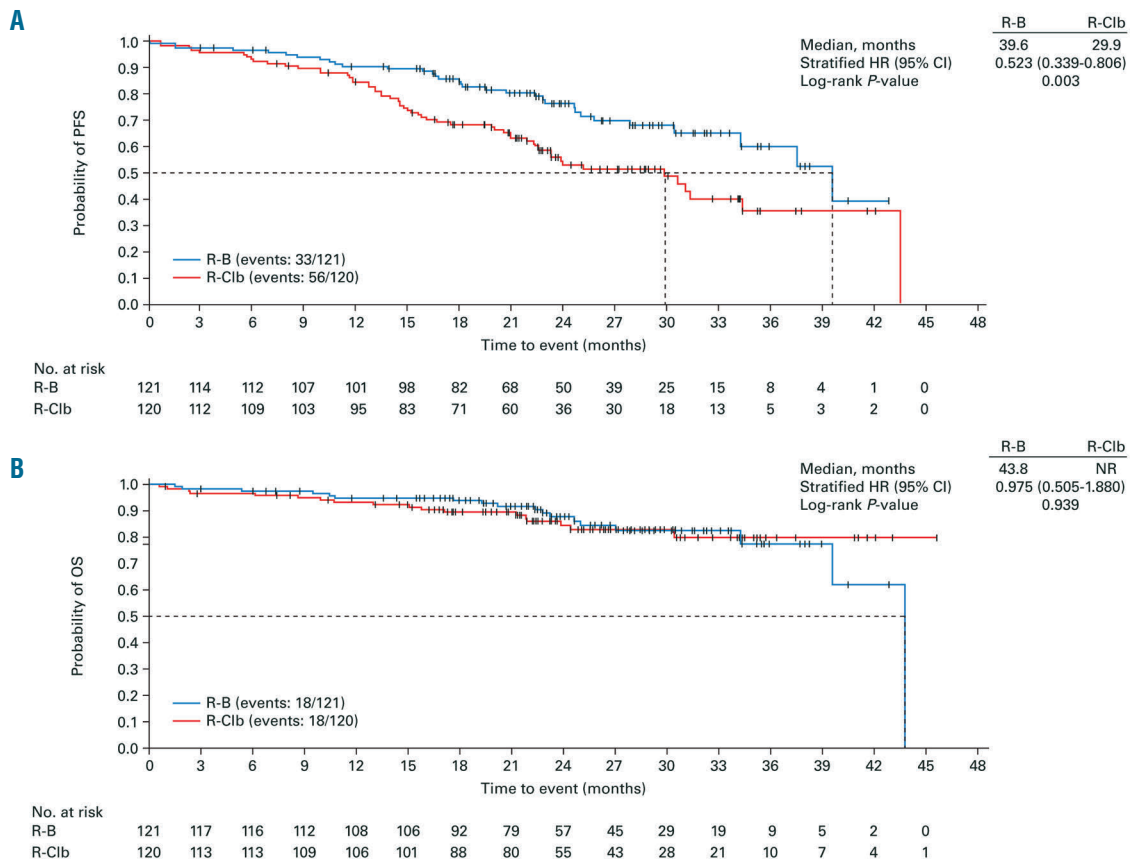
Figure 2. Efficacy in 1L patients. (A) PFS and (B) OS. CI: confidence interval; HR: hazard ratio; NR: not reached; OS: overall survival; PFS: progression-free survival; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil.

mg/m^2; CLL11, 0.5 mg/kg), which resulted in a higher median cumulative dose (MABLE, 720 mg; CLL11, 366-400 mg), and differences in the study populations, with patients in MABLE having fewer active comorbidities than those in CLL11 (medians of 3 and 5, respectively) and a better performance status.[10] Earlier phase II studies in elderly CLL patients treated 1L with R-Clb reported CR rates of 10-17% and ORRs of 82-84%.[8,9] The CLL2M trial, a phase II study of CLL patients treated 1L with R-B, at the same B dosage as the current study, reported a CR rate of 23% and an ORR of 88%.[7]

In 1L patients in the study reported herein, the median PFS of 39.6 months in the R-B arm was significantly longer (by 10 months) than the value in the R-Clb arm. This result is similar to the median PFS of 43.2 months achieved in fit CLL patients treated with R-B in the CLL10 study,[18] and is consistent with the findings of the CLL2M study, which enrolled fit and unfit 1L patients and reported a median event-free survival in R-B-treated patients of 33.9 months.[7] The CLL2M study did not select patients by fitness, but a substantial proportion could be considered unfit based on age, Binet stage, and renal impairment.[7] In MABLE, 33% of the 1L patients were Binet stage C and the median age was 72 years. The PFS result in the R-Clb arm in MABLE was almost twice as long as that in CLL11 (29.9 vs. 15.4 months),[11] however, as noted above, a direct comparison of these studies is limited by differences in Clb doses and patient fitness.

In MABLE, 1L patients with CR had higher MRD-negativity rates with R-B versus R-Clb, indicating a greater depth of response with R-B. Of note, MRD was assessed primarily in BM from patients with CR based on the investigator's assessment, whereas in CLL11 and previous phase II studies, MRD was measured in peripheral blood ([PB] or BM) from all patients.[7,8,10] One phase II study reported a MRD-negativity rate of 12.5% (2/16 patients) using BM aspirates from R-Clb-treated patients who achieved a CR/unconfirmed CR.[9]

Median OS was not significantly different between treatment arms in 1L patients in MABLE and was not reached in previous phase II studies of R-B and R-Clb,[7-9] or in the CLL11 and COMPLEMENT-1 studies.[11,19] At current follow-up reported for CLL11 and COMPLEMENT-1, no significant OS benefit was observed for G-Clb versus R-Clb or ofatumumab plus Clb (Ofa-Clb) versus Clb, respectively,[11,19] whereas a significant improvement was observed for G-Clb versus Clb alone.[10] Further observation is required to determine if there is an OS benefit with G-Clb versus R-Clb or Ofa-Clb versus Clb.

Safety profiles (for pooled 1L and 2L patients) were similar for R-Clb and R-B, with no new or clinically relevant safety signals, and events were as expected for CLL patients receiving immunochemotherapy.[7-9] Incidences of all-grade AEs, SAEs, and treatment-related AEs were similar across arms. Grade ≥3 AE incidence was slightly higher with R-B versus R-Clb, driven by a higher incidence of

Table 4. Summary of AEs (safety population).

Patients, n (%)	R-B (N=177)	R-Clb (N=178)
All-grade AEs	173 (98)	173 (97)
Grade ≥3 AEs	132 (75)	113 (64)
SAEs	73 (41)	56 (32)
Most common all-grade AEs[a]		
Blood and lymphatic system disorders	133 (75)	113 (64)
Neutropenia	99 (56)	88 (49)
Leukopenia	42 (24)	31 (17)
Anemia	41 (23)	27 (15)
Thrombocytopenia	37 (21)	44 (25)
Lymphopenia	30 (17)	21 (12)
Gastrointestinal disorders	99 (56)	90 (51)
Nausea	53 (30)	46 (26)
Diarrhea	30 (17)	22 (12)
Constipation	28 (16)	23 (13)
General disorders and administrative site conditions	93 (53)	87 (49)
Pyrexia	37 (21)	17 (10)
Asthenia	29 (16)	34 (19)
Skin and subcutaneous tissue disorders	63 (36)	40 (23)
Rash	29 (16)	9 (5)
Most common grade ≥3 AEs[b]		
Blood and lymphatic system disorders	99 (56)	84 (47)
Neutropenia	76 (43)	65 (37)
Leukopenia	29 (16)	15 (8)
Anemia	18 (10)	12 (7)
Lymphopenia	17 (10)	10 (6)
Thrombocytopenia	17 (10)	16 (9)
Febrile neutropenia	12 (7)	7 (4)
Most common SAEs[b]		
Infections and infestations	33 (19)	15 (8)
Pneumonia	8 (5)	2 (1)
Blood and lymphatic system disorders	25 (14)	15 (8)
Febrile neutropenia	11 (6)	7 (4)

[a]Preferred terms with incidence of ≥15% in either study arm. [b]Preferred terms with incidence of ≥5% in either study arm. Non-serious AEs were reported until 28 days after the end of the last treatment cycle. SAEs unrelated to study treatment were reported until six months after the end of treatment or until the start of new anti- chronic lymphocytic leukemia treatment. Treatment-related SAEs were to be reported indefinitely. AE: adverse event; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil; SAE: serious adverse event.

infections and infestations. Few patients in either arm discontinued therapy due to AEs. Treatment withdrawal due to AEs was reported for 18% of patients receiving 1L R-B and 12% receiving R-Clb.

As previously noted, the results of the CLL11 study show that, in unfit CLL patients, G-Clb was associated with higher response rates and longer PFS than R-Clb, with more frequent MRD eradication and an acceptable toxicity profile.[10] In addition, current guidelines, (European Society for Medical Oncology and National Comprehensive Cancer Network), recommend Clb in combination with an anti-CD20 antibody as standard 1L therapy in unfit CLL patients.[20,21] However, in MABLE and previous studies, R-B was associated with a good response rate and improved PFS compared with R-Clb. Currently, evidence to guide the choice between R-B and G-Clb in 1L unfit patients with CLL is limited, although a recent meta-analysis of PFS and OS results in five studies showed a trend towards better efficacy for G-Clb than R-B;[22] however, the difference was not significant despite a significant difference between G-Clb and other comparators such as R-Clb, Ofa-Clb, Clb, and fludarabine. A randomized trial comparing these combinations could resolve this question.

Some limitations of our study should be acknowledged. Since we relied only on investigator assessments of tumor response to evaluate efficacy, and did not include assessments by an independent review committee, this might have introduced a potential bias in the efficacy results. Comparison of our results with those of other studies in CLL patients is potentially complicated because the selection of patients based on fitness was based on a judgment made by the investigator that the patients were not eligible for fludarabine, according to a set of pre-defined crite-

ria that were based on the prescribing information for fludarabine at the time of study design; the Cumulative Illness Rating Scale scoring was not used. However, a recent randomized study comparing the efficacy of ibrutinib with Clb used an age cut-off of 65 years as the only criterion for selecting "older" patients, and did not carry out any assessment of comorbidities.[23]

Although the efficacy of immunochemotherapy combinations such as R-B, Ofa-Clb, and G-Clb in CLL have been shown,[7,11,19] obinutuzumab plus B (G-B) needs to be evaluated further, although it is likely that future clinical studies will focus more on the combination of anti-CD20 antibodies with novel agents such as ibrutinib, idelalisib, and venetoclax. Indeed, these agents have shown promising efficacy when combined with anti-CD20 monoclonal antibodies (including rituximab) in the relapsed/refractory CLL setting,[24-29] and are now being evaluated in 1L.[23] Furthermore, additional safety data for 1L B-cell receptor (BCR) signaling inhibitors are required. In March 2016, the US Food and Drug Administration alerted healthcare professionals about safety concerns with idelalisib when used in combination with rituximab or R-B in CLL and follicular lymphoma. This was related to a high rate of viral and fungal infections that led the sponsor to discontinue six trials.[30]

However, given the economic burden associated with new agents and the fact that BCR inhibitors are not yet available in many European countries, immunochemotherapy combinations are likely to continue to be valuable treatment options for 1L patients with CLL.[31]

In conclusion, in fludarabine-ineligible CLL patients, 1L R-B treatment significantly improved CR rates and median PFS *versus* R-Clb, and increased MRD-negativity rates, with no new safety signals reported. R-B may be a valuable 1L option for fludarabine-ineligible CLL patients and this combination continues to be widely used in clinical practice in Europe, reinforcing the interest of this large randomized study.

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