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Abstract 2744 Rituximab in Combination with Bendamustine or Chlorambucil for Treating Patients with Chronic Lymphocytic Leukemia: Interim Results of a Phase IIIb Study (MaBLe)

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The current standard of care for fit patients (pts) with chronic lymphocytic leukemia (CLL) is rituximab (R) in combination with fludarabine and cyclophosphamide; however, many pts with CLL are elderly and have comorbidities that render them ineligible for fludarabine treatment. Two common treatment options for fludarabine-ineligible pts are bendamustine (B) or chlorambucil (Clb). A further promising treatment option, following the success of the combination of R with fludarabine and cyclophosphamide, might be to combine B or Clb with R. The following study aims to assess the responses of pts to a combination of R and either B or Clb in first-line (1L) or second-line (2L) pts with CLL, with the primary objective being to compare the confirmed complete response (CR) rate (assessed according to Hallek *et al.*Blood 2008) after 6 cycles of treatment between the two treatment arms for the pooled 1L and 2L pts.

Pts (aged ≥ 18 years) who were ineligible for fludarabine treatment, as a result of age or a greater number of comorbidities, were randomized to either the R-B or R-Clb arm. Pts were 1L or 2L, where relapse had occurred no earlier than 12 months since their last dose of 1L treatment. Pts in the R-B arm were treated with six 28-day cycles of B (1L: 90 mg/m^2 Days 1 and 2; 2L: 70 mg/m^2 Days 1 and 2) with R administered on Day 1 of cycle 1 (375 mg/m^2) and cycles 2–6 (500 mg/m^2). Pts in the R-Clb arm received the same dose of R but in place of B they received Clb (10 mg/m^2Days 1–7, cycles 1–6), and those pts in the R-Clb arm that had not achieved a CR after 6 cycles continued to receive Clb monotherapy for up to 6 further cycles. Tumor assessments were made after cycles 3, 6 and 12 and then 3-monthly for at least a year.

Enrollment and randomization are ongoing and, at present, a total of 339 pts have been randomized between the two treatment arms, 126 of whom are included in this interim analysis with the remaining pts continuing on the study. Of these 126 pts, 58 were randomized into the R-B arm and 68 the R-Clb arm. Patient characteristics between the two treatment arms were well balanced (Table). The median age of pts was 74 years (75 years for the R-B arm and 73 years for the R-Clb arm) and the majority of pts were taking concomitant medication (57/58 pts [98%] in the R-B arm; 64/68 pts [94%] in the R-Clb arm). Compared with previous clinical trials in CLL where pts are usually younger and fitter, this patient population is closer in age and fitness to pts presenting in the clinic. A total of 85 pts were previously untreated, with the remaining 41 having received one line of previous treatment. 2L pts had received a median of 6 prior cycles of treatment. The safety population was made up of 124 pts (R-B: n = 57; R-Clb: n = 67) who had received at least one dose of the study medication; 104/124 pts completed all 6 cycles of rituximab treatment.

After 6 cycles of treatment, 14/58 pts (24%) in the R-B arm had a confirmed CR compared with 7/68 pts (10%) in the R-Clb arm (p = 0.033). For 1L pts the corresponding CR rates were 30% in the R-B arm vs 13% in the R-Clb arm (p = 0.054) and 2L pts exhibited CR rates of 11% in the R-B arm vs 4% in the R-Clb arm (p = 0.413). At the end of treatment, the overall response rate (ORR) was not different between the R-B and the R-Clb arms (88% and 81%, respectively [p = 0.404]). ORRs for 1L pts were 88% in the R-B arm vs 80% in the R-Clb arm and for 2L pts were 89% in the R-B arm vs 83% in the R-Clb arm.

Safety was similar between the two treatment arms with the most common adverse events (AEs) (any grade) being neutropenia (R-B: 42% vs R-Clb: 46%) followed by nausea (R-B: 26% vs R-Clb: 22%). The most common AE at ≥ grade 3 was neutropenia (R-B: 32% vs R-Clb: 34%). Serious AEs were experienced by 20 pts (35%) in the R-B arm and 23 pts (34%) in the R-Clb arm; the most frequent serious AE was pneumonia (R-B: 7% vs R-Clb: 2%). 5/57 pts (9%) in the R-B arm and 8/67 pts (12%) in the R-Clb arm withdrew from the study prematurely due to AEs.

R-B or R-Clb could provide useful treatment options for pts with CLL who are ineligible for the current fludarabine-containing standard of care. Interim results from this study have indicated that R-B shows a trend towards higher CR rates compared with R-Clb.

Table: Baseline patient characteristics

Characteristic	R-bendamustine (n = 58)	R-chlorambucil (n = 68)
Median age, years (range)	75 (49–87)	73 (44–91)
Sex, %	-	-
Male	60	65
Female	40	35
Binet stage, %	-	-
A	5	0
B	55	59
C	33	37
Not reported	7	4
17p/11q del, %	12	4
*IGVH*status, %	-	-
Mutated	41	52
Unmutated	53	38
Other	5	10
Line of treatment, %	-	-
1L	69	66
2L	31	34

Disclosures: Leblond: *Roche:* Advisory Board Other, Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Mundipharma:* Honoraria; *Janssen-Cilag:* Honoraria. **Off Label Use:** Rituximab in Combination with Bendamustine or Chlorambucil for Treating Patients with Chronic Lymphocytic Leukemia. **Rassam:** *Johnson and Johnson:* Unrestricted research grant Other; *ROCHE:* Honoraria; *BMS:* Honoraria. **Raposo:** *Roche:* Consultancy. **Oertel:** *Roche:* Employment, Equity Ownership.