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HIGH RATES OF UNDETECTABLE MINIMAL RESIDUAL DISEASE REMISSIONS WITH TIME-LIMITED BENDAMUSTINE, RITUXIMAB, AND VENETOCLAX (BR-VR) IN UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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INTRODUCTION

Background: Despite the efficacy of venetoclax (VEN) in frontline CLL, optimal combination regimens and duration of treatment remain unclear. We hypothesized that cytoreduction with bendamustine/rituximab (BR) induction followed by venetoclax/rituximab (VR) consolidation for a fixed 1-year duration would be associated with an increased rate of undetectable minimal residual disease (uMRD) compared to historical controls and a reduction in the risk of tumor lysis syndrome (TLS). Here we report updated data from a fully-enrolled ongoing phase 2 multicenter, US, single-arm, open-label study (NCT03609593) designed to assess the safety and efficacy of BR-VR in previously untreated CLL patients (pts).

METHODS

- Previously untreated CLL/SLL pts ≥ 18 years requiring therapy per iwCLL criteria initially received 3 cycles of bendamustine 50-90 mg/m2 daily for 2 days and rituximab 375 mg/m2 every 28 days for 3 cycles
- Following BR, VEN was initiated with a standard dose escalation from 20 mg to 400 mg daily over 5 weeks This was followed by 6 cycles of VR with rituximab given monthly and 5 cycles of VEN alone (12 cycles of VEN in total)
- Additional eligibility included:
- ECOG PS ≤ 2, hemoglobin ≥8g/dL, ANC ≥1000/mm3, and platelets ≥50,000/mm3
- Response was assessed by 2018 iwCLL criteria with uMRD testing by central flow cytometry at a level of <10-4 in peripheral blood (PB) and bone marrow (BM)
- The primary endpoint was objective response rate (ORR)
- Secondary endpoints included uMRD rate, time to uMRD, and adverse events (AEs) assessed by CTCAE v 5.0

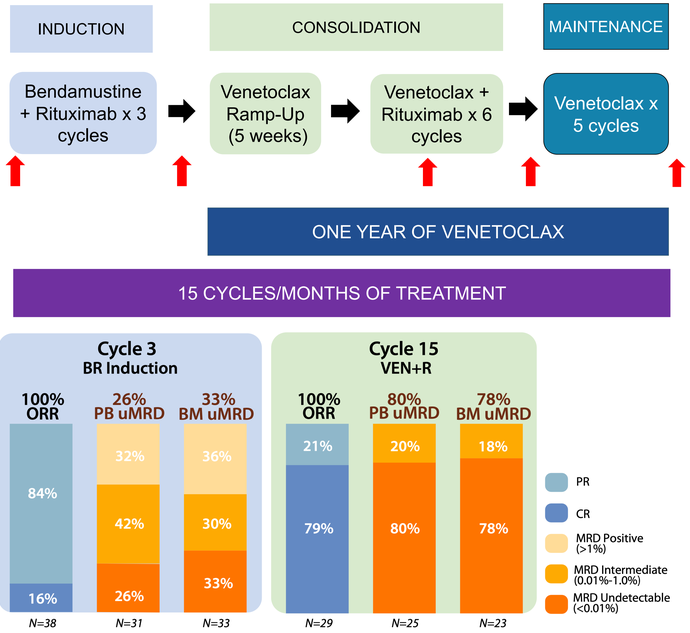
RESULTS

Results: As of data cutoff on 15 July 2023, 42 pts were accrued. Baseline demographics were as follows: male/female (29/13), median age 61.5 yrs (range 38-84). Baseline prognostic studies showed unmutated IGHV in 22 (52%) pts, TP53 aberrant (either del(17p) and/or TP53 mutation) in 2 (5%) pt, del(11q) in 3 (7%) pts, and complex karyotype in 11 (26%) pts. TLS risk among 24 evaluable pts at baseline was high (H) in 9 (21%), medium (M) in 22 (52%), and low (L) in 6 (26%).

At a median follow-up of 16.6 mo. (range, 3-40), 37 pts remain on study. Of 29 pts with at least 15 mo. follow-up (completing all therapy), the ORR was 100% (79% CR/CRi, 21% PR [due to small residual nodes]). 1 pt had radiographic progression of disease 15 mo. after completing therapy but remains on observation not having met iwCLL criteria for subsequent therapy. 3 pts died on study (2 due to COVID-19 and 1 developed newly metastatic squamous cell carcinoma and taken off study after achieving a CR post-VEN ramp-up). Bendamustine was administered at doses of 50 mg/m2 in 11%, 70 mg/m2 in 13%, and 90mg/m2 in 76% of pts. In 38 evaluable pts, response assessments after cytoreduction with BR demonstrated 16% of pts achieved CR/CRi and 84% achieved PR. For evaluable pts at 16 mo., uMRD (<0.01%) in the PB and BM was observed in 80% (20/25) and 78% (18/23) of pts, respectively. MRD was intermediate (0.01% - <1.0%) in 17% (4 patients) in BM (Figure 1 ORR and MRD). Median time to uMRD was 11 mo. (range 3-15) in PB and 10 mo. (range 2.6-15) in BM.

The most common treatment-emergent AEs during BR induction were (any grade/grade ≥3) anemia in 15/4 (36%/10%) pts, nausea in 9/0 (21%/0%), neutropenia in 12/8 (29%/19%), rash in 12/1 (29%/2%), constipation 7/0 (17%/0%), and infusion reactions in 7/1 (17%/2%). 2 pts (5%) developed febrile neutropenia during BR. Emergent AEs during VEN treatment included neutropenia in 21/13 (50%/31%), diarrhea in 18/0 (43%/0%) pts, leukopenia in 14/4 (24%/10%), and nausea in 11/0 (26%/0%).

TLS risk was substantially reduced after BR lead-in. Of 9 H-risk pts at baseline, 1 remained H-risk after BR; of 16 M-risk pts, 5 remained M-risk, with the remainder at L-risk (89% reduction in H-risk TLS).



CONCLUSIONS

BR-VR is a safe and well-tolerated regimen in untreated CLL pts. BR debulking substantially reduces TLS risk, and this sequential strategy achieves high rates of PB and BM uMRD across all prognostic risk groups.

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