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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Orelabrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (OFCG) for First-Line Treatment of Chronic Lymphocytic Leukemia: A Multicenter, Investigator-Initiated Study (cwCLL-001 Study)

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Background: A phase II trial has shown, first-line treatment with iFCG (ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab) led to a bone marrow (BM) undetectable minimal residual disease (uMRD) rate of 98% (44/45) as best response in treatment-naïve patients with chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL). But this study[1] does not include patients with unmutated immunoglobulin heavy–chain variable region gene (*IGHV*) and/or del(17p)/ *TP53* mutation, and ibrutinib was the first generation BTK (BTKi) which had relatively high off-target adverse effects (AEs). Our study has demonstrated the efficacy and safety of the second generation BTKi orelabrutinib in patients with relapsed/refractory CLL [2]. Therefore, we used orelabrutinib (O), and initiated the phase II OFCG trial in younger, fit patients with previously untreated CLL/SLL unrestricted by *IGHV* mutation status and del(17p)/ *TP53* aberrations (cwCLL-001 study, NCT05322733).
Methods: This is a multicenter, open-label, non-randomized phase II study for previously untreated patients with CLL/SLL without restriction by del(17p)/ *TP53* aberrations and/or *IGHV* mutation status. A 7-day lead-in period with single-agent oral orelabrutinib(150 mg daily)was given in all patients, followed by OFCG regimen which consisted of orelabrutinib, intravenous Obinutuzumab, fludarabine and cyclophosphamide for up to three 28-day cycles. MRD was detected by 8 multi-color flow cytometry (FCM) at 10^{-4} sensitivity and cloneSEQ using NGS (next generation sequencing) assay with a sensitivity of up to 10^{-6}. If the patients could achieve undetectable MRD in BM, they will discontinue FC and receive 3 cycles of OG (orelabrutinib and obinutuzumab). Otherwise, the patients will receive another 3 cycles of OFCG. Patients will discontinue obinutuzumab if they achieve BM uMRD after 6 cycles and continue six additional cycles of orelabrutinib; all other patients will receive six cycles of OG. Patients who achieved BM uMRD after 12 cycles discontinue all treatments, otherwise will continue orelabrutinib for up to additional 1 year (Fig. 1). The primary endpoint is the percentage of uMRD in BM after 6 cycles by FCM (at 10^{-4} sensitivity). The secondary endpoint is the percentage of uMRD in BM and peripheral blood (PB) at other key time points by FCM, best overall response rate (ORR), complete response rate (CRR), progression-free survival (PFS), 2- and 3-year PFS rate, duration of response (DOR), overall survival (OS), 3-year OS rate as well as safety. The percentage of uMRD by NGS is an exploratory endpoint.
Results: From 30 May 2022 to 30 Jun 2023, 25 patients were enrolled. Median age was 49 years old (range, 23-62). Unmutated IGHV, TP53 mutation/del(17p) and del(11q) were detected in 56.5% (13/23), 16.0% (4/25), and 24.0% (6/25) of patients, respectively. At data cut off (30 Jun 2023), 19 patients completed 3 cycles of OFCG and were evaluable. 75% (15/20, 1 patient who off study was assessed at the end of C2 cycle) of patients achieved PB uMRD and 57.9% (11/19) achieved BM uMRD by FCM, ORR and CR/CRi rate was 100% (18/18) and 38.9% (7/18) (Fig. 2). One patient died after cycle 3 due to COVID-19 infection. 16 patients completed 6 cycles, 14 of them were evaluable and achieved deeper response irrespective of different strategies during cycle 4 to 6, PB uMRD and BM uMRD was 100% (14/14) and 85.7% (12/14) by FCM, and the ORR and CRR was 100% (14/14) and 57.1% (8/14), respectively. In *IGHV* unmutated subgroup, ORR was 100% (10/10) with 50% (5/10) CRR, 87.5% (7/8) patients achieved BM uMRD by FCM after cycle 6. The results of MRD response by NGS assay will be presented in the formal report. 91.7% patients experienced at least one treatment emergent AE at the data cutoff. Most AEs were mild and

tolerable. The most frequent AEs (≥10% of any grade) were neutropenia, leukopenia and thrombocytopenia. No bleeding or cardiovascular AEs greater than grade 3 occurred in these patients. Overall, OFCG demonstrated a favorable safety profile.
Conclusion: This is the first clinical trial exploring the efficacy and safety of the second generation BTKi plus chemoimmunotherapy in patients with CLL. The OFCG regimen shows a rapid and deep molecular remission with a pleasant safety profile in the TN CLL patients including the ones with unfavorable factors.

References:

1. Jain N, et al., Leukemia. 2021 Dec;35(12):3421-3429.
2. Xu W, et al. Am J Hematol. 2023 Apr;98(4):571-579.

Disclosures No relevant conflicts of interest to declare.

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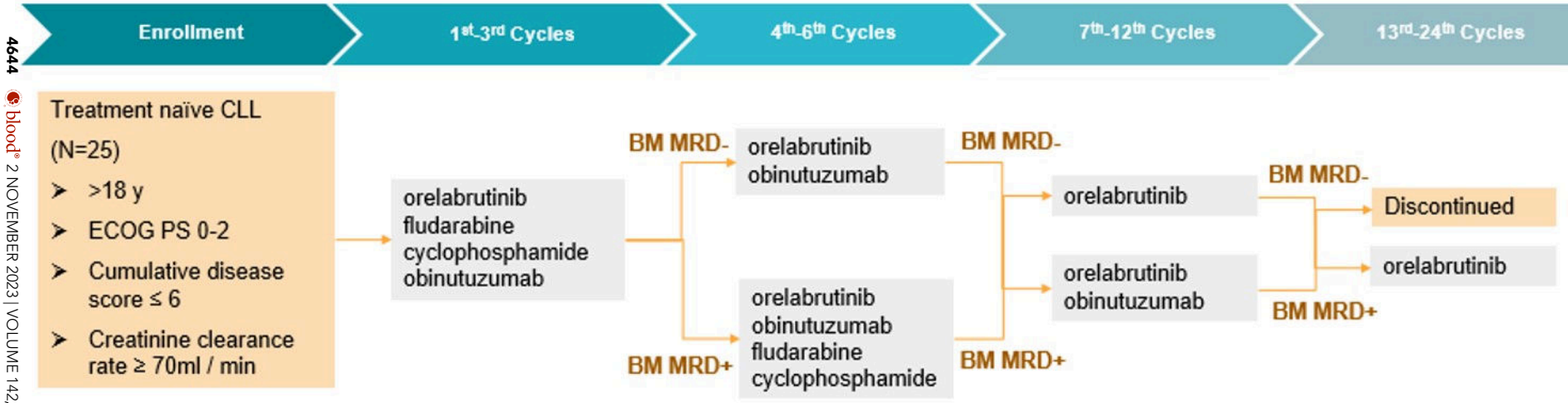

Fig. 1 OFCG study design

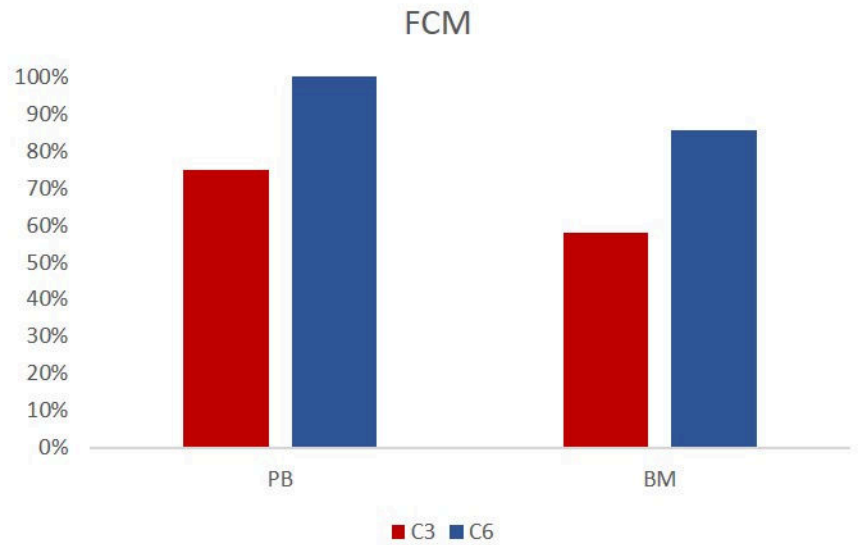

Fig. 2 MRD status in peripheral blood (PB) and bone marrow (BM) by flow cytometry (FCM) after cycle 3 (C3) and cycle 6 (C6)

Figure 1