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A Prospective, Single-Center, Single-Arm Clinical Trial of Zanubrutinib Monotherapy and ZFCG combined therapy was given sequentially for the Treatment of Primary Symptomatic CLL/SLL (Stop Trial)

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OBJECTIVES

- Our trial investigated a time-limited combination immunochemotherapy strategy in treatment-naïve CLL patients, aiming to deepen remission, achieve uMRD, and enable treatment cessation to enhance quality of life.

CONCLUSIONS

- The ZFCG regimen demonstrated high rates of CR with uMRD in treatment-naïve CLL patients after 4 cycles of combination therapy, accompanied by excellent uMRD rates in PB and BM. All patients who completed 16 cycles of therapy fulfilled the criteria for treatment cessation.
- With a median follow-up of nearly 1 year (max 20 months) post-treatment, 29 out of 30 patients maintained continuous CR with uMRD. However, longer follow-up is required to determine the durability of treatment-free remission. These preliminary findings from the Stop Trial indicate that ZFCG is an effective, time-limited treatment option for treatment-naïve CLL patients.

INTRODUCTION

- Although Bruton tyrosine kinase (BTK) inhibitor monotherapy yields an overall response rate (ORR) of 80–90% and prolongs survival in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1, 2, 3], its complete response (CR) rate remains suboptimal (<10%). Even after 7–8 years of continuous treatment, the CR rate only improves to around 30%[4]. More critically, achieving undetectable minimal residual disease (uMRD) is infrequent, compelling patients to undergo long-term BTK inhibitor therapy.

METHODS

- The regimen consisted of zanubrutinib (Z) monotherapy (160 mg twice daily) for 12 cycles, followed by four cycles of combination therapy with fludarabine (F, 25 mg/m² IV D1-3 cycles 13-16), cyclophosphamide (C, 250 mg/m² IV D1-3 cycles 13-16), and obinutuzumab (G, 1000 mg IV D0, 7, 14 cycle 13; 1000 mg IV D0 cycles 14-16) (ZFCG regimen).
- After cycle 16, response and MRD status in peripheral blood (PB) and bone marrow (BM) were assessed by four-color flow cytometry. Patients achieving CR/CRi with uMRD in both PB and BM could stop treatment; others could choose to continue or stop zanubrutinib monotherapy. (NCT05287984)

Abbreviations
EOT, End of Treatment; BM, bone marrow ; PB, Peripheral blood; FCM, flow immunophenotyping; uMRD, undetectable minimal residual disease.

RESULTS

- As of April 1, 2025, 59 pts initiated into this therapy. Thirty pts completed combination therapy; 3 withdrew (1 due to COVID-19 impact, 2 due to disease progression：one in zanubrutinib monotherapy phase, the other post the ZFCG phase).

EFFICACY

- All 59 patients received zanubrutinib monotherapy, with 41 progressing to the ZFCG phase.
- Among the 30 patients who completed 4 cycles of ZFCG and underwent efficacy assessment, after 12 cycles of zanubrutinib monotherapy alone, the CR rate was 13.3% (4/30), and only 1 patient (3.3%) achieved CR with uMRD in both PB and BM. After 2 cycles of ZFCG, 18 patients (60%) achieved both CR and CR with PB+BM uMRD.
- Upon completion of 4 cycles of ZFCG, the proportion of patients achieving CR and CR with PB+BM uMRD increased to 76.7% (23/30) and 73.3% (22/30), respectively.
- Additionally, with a median follow-up of nearly 1 year (max 20 months) post-treatment100% of patients (30/30) achieved PB uMRD, and 96.7% (29/30) achieved BM uMRD.
- All 30 patients met the criteria for treatment cessation after completing 16 cycles of therapy. With a maximum treatment-free interval of 20 months, 29 patients maintained CR with uMRD without treatment. However, 1 patient experienced disease progression, characterized by the reappearance of a pulmonary mass noted at diagnosis, 7 months post-cessation, although the BM remained in CR with uMRD at recurrence.

SAFETY

- During the ZFCG phase, the most common grade ≥3 adverse events (AEs) were thrombocytopenia (32.5%), neutropenia (27.5%), and leukopenia (25%). Grade ≥3 non-hematological AEs included lung infection (15%) and febrile neutropenia (5%).

Figure 1. Study design

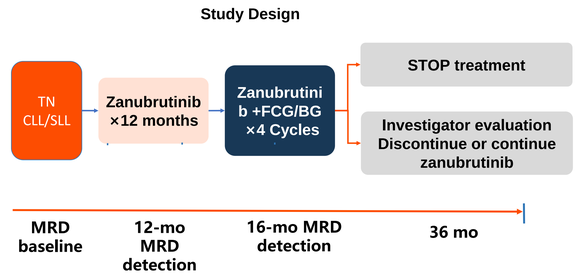
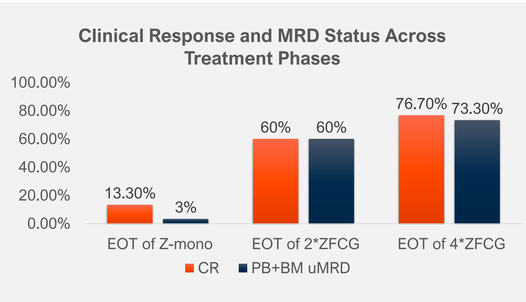


Table 1. Baseline characteristic

Baseline characteristic	N = 59
Age	
Median (range), years	58 (33-65)
Gender	
Male, n (%)	40 (67.8%)
CLL-IPI score	
High risk, n (%)	12 (20.3%)
Very high risk, n (%)	2 (3.4%)
IGHV umutated	23(38.3%)
Cytogenetic abnormalities	
TP53 deletion	1(1.7%)
ATM deletion	9(15.3%)
RB1 deletion	13(22.0%)
ATM deletion	9(20.3%)
TP53 mutation	2(3.4%)

Figure 2. Clinical Response and MRD Status Across Treatment Phases



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ABBREVIATIONS

EOT, END OF TREATMENT; BM, BONE MARROW ; PB, PERIPHERAL BLOOD; FCM, FLOW IMMUNOPHENOTYPING; UMRD, UNDETECTABLE MINIMAL RESIDUAL DISEASE.