# Orelabrutinib combined with bendamustine and obinutuzumab as the first-line treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma: a phase II multicenter exploratory study

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## BACKGROUND

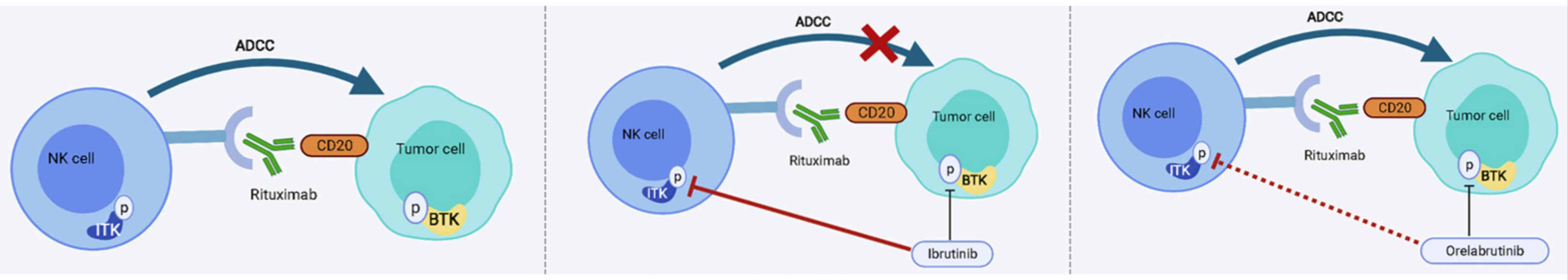
**Unmet needs in treatment of CLL/SLL**

- Targeted therapy with Bruton's tyrosine kinase inhibitors (BTKi) has emerged as a standardized treatment for patients with previously untreated or relapsed/refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).[1]
- However, due to given the increase in adverse events, high dropout rates and drug resistance with long-term continuous administration of BTKi, there was an increased focus on time-limited BTKi-based regimens and undetectable minimal residual disease (uMRD).[2-4]

**Rationale for combining orelabrutinib, bendamustine and obinutuzumab**

- BTKi plus bendamustine (B) and rituximab has been confirmed to be associated with promising activity for CLL/SLL through fixed-duration therapy.[5]
- Obinutuzumab (G) is a new generation anti-CD20 antibody with enhanced direct cell killing and antibody-dependent cellular cytotoxicity (ADCC) compared with rituximab.[6]
- Orelabrutinib is a novel BTKi with excellent target selectivity for B- cell lymphoma, [7] and has shown an encouraging anti-tumor activity and favorable safety profile in CLL/SLL.[8]
- Notably, orelabrutinib showed a significant higher complete response (CR) rate for CLL/SLL comparing to other BTKi within a short treatment period.[9]
- Orelabrutinib combined with anti-CD20 antibody rituximab could preserve natural killer- cell-mediated ADCC induced by rituximab and produces synergistic anti-tumor responses (**Figure 1**).[10]

**Figure 1. Synergistic effects of orelabrutinib and anti-CD20 antibody.**[10]




**Abbreviations:** ADCC, antibody-dependent cellular cytotoxicity; NK cell, natural killer cell; BTK, Bruton's tyrosine kinase; ITK, inducible T cell kinase; P, phosphorylated.

## OBJECTIVES

To investigate the new time-limited orelabrutinib combined with BG regimen in patients with CLL/SLL who are ineligible for intensive chemotherapy.

## METHOD

**Study design and patients**

- This study is a multicenter, single-arm, phase II trial (NCT05918276).
- Approximately 24 patients with histologically/pathologically confirmed CD20 positive CLL/SLL will be enrolled.

**Key eligibility**

- Aged 18-65 years with severe disease (non-CLL CIRS≥6) or >65 years;
- Histologically confirmed CLL/SLL as per IWCLL2008 criteria;
- CD20 positive
- ≥1 treatment indication;
- ECOG PS 0-2
- No prior systemic therapy

N=24

**Treatment schedule**

BG regimen (cycle 1-6)

Orelabrutinib (cycle 2-7)

0 1 2 4 6 7 13 19 25 (months)

evey 3-6 months

**BG regimen:**
B: C1 (70mg/m² d2,3); C2-C6 (90mg/m² d1,2);
G: C1 (100mg d1+900mg d2 or 1000mg d1; 1000mg d8,15); C2-C6 (1000mg d1).

**Orelabrutinib:**
oral 150 mg, once daily

Bone marrow MRD
Peripheral blood MRD
Efficacy evaluation

**Endpoints**

- The primary endpoint is CR/incomplete CR (CRi) with uMRD rate at the end of cycle 7. Taking the CR/CRi with uMRD rate as the primary endpoint would avoid the lack of stability (return to positivity within a short time) and inadequate assessment (residual lesions at other sites) by MRD negativity alone.

## RESULTs

As of July 2024, eight patients have been enrolled. The median age is 66 years (range: 53–70), with 62.5% male. ECOG PS scores were 0 in 75% of patients and 1 in 25%. Rai staging distribution was I–II in 37.5% and III–IV in 62.5% of patients. Bulky disease was present in one patient (12.5%), and mutated IGHV status was observed in 75% of cases(**Table1**).

Data showed a 100% CR/CRi & uMRD after 7 cycles combined treatment; CR/CRi with uMRD was achieved in 87.5% of cases, indicating potential clinical benefits （**Figure2**） .

Safety analysis revealed thrombocytopenia and neutropenia in seven patients, with adverse events ≥ Grade 3 occurring in 25% of cases, all reversible. No incidences of bleeding or atrial fibrillation were reported. One patient experienced Grade 3 pulmonary infection, now resolved（**Table2**）.

**Table 1. Patient Baseline Characteristics (N=8)**

| Baseline Characteristics | Value (N=8) |
|---|---|
| Age, median (range) | 66 (53-70) |
| Gender | |
| Male | 5 (62.5%) |
| Female | 3 (37.5%) |
| ECOG Performance Status | |
| 0 | 6 (75.0%) |
| 1 | 2 (25.0%) |
| Rai Stage | |
| I-II | 3 (37.5%) |
| III-IV | 5 (62.5%) |
| Bulky Disease (≥10 cm) | |
| No | 7 (87.5%) |
| Yes | 1 (12.5%) |
| Mutated IGHV | 6 (75.0%) |

**Figure 2. Treatment Response Assessment Following OBG Regimen**

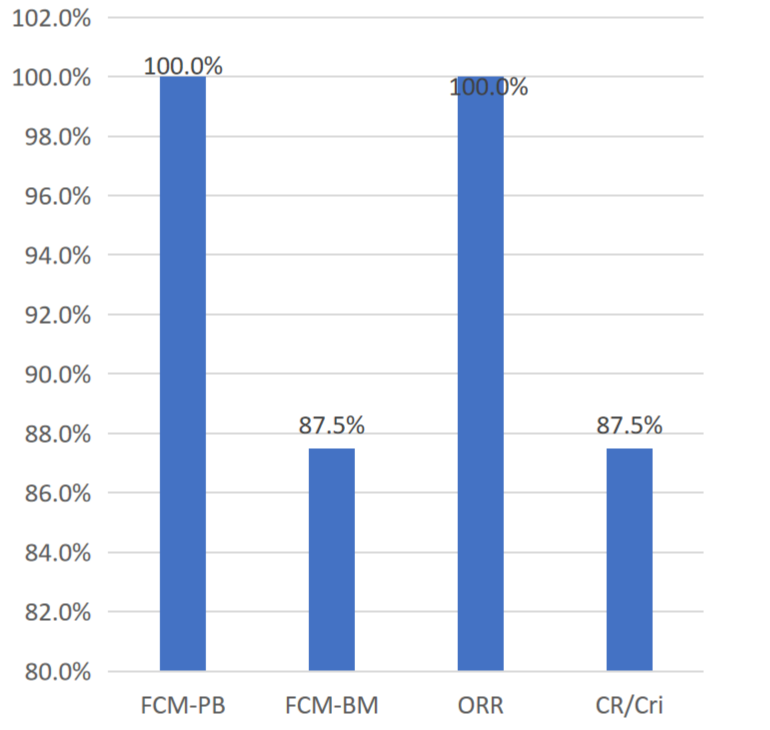



**Table 2.Post-treatment Safety Analysis of OBG Regimen**

| Adverse Event | Incidence (n=8) | Grade ≥3 Events | Outcome |
|---|---|---|---|
| Thrombocytopenia | 7 patients (87.5%) | 2 patients (25%) | All reversible |
| Neutropenia | 7 patients (87.5%) | 2 patients (25%) | All reversible |
| Pulmonary infection | 1 patient (12.5%) | Grade 3 | Resolved |
| Bleeding | 0 patients (0%) | - | - |
| Atrial fibrillation | 0 patients (0%) | - | - |

*CRi was defined as CR with incomplete recovery of bone marrow; #CRu was defined as CR/CRi with spleen size≤16 cm.

## CONCLUSION

- The OBG regimen demonstrates efficacy as a promising time-limited therapy and manageable adverse events in unfit CLL/SLL patients.

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