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

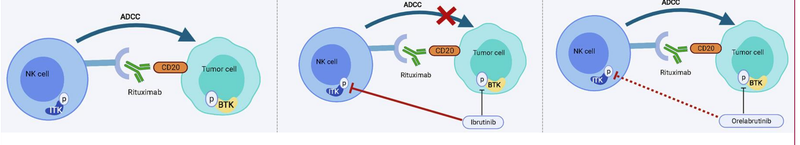
Unmet needs in treatment of CLL/SLL

- 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 inclusion/exclusion criteria are outlined in **Table 1**.

Table 1. Patients eligibility

Key inclusion criteria	Key exclusion criteria
• Aged 18-65 years with severe disease (non-CLL CIRS≥6) or >65 years; • Histologically/pathologically confirmed CLL/SLL as per IWCLL2008 criteria; • CD20 positive • At least one treatment indication; • ECOG PS 0-2 • No prior systemic therapy for CLL/SLL	• Known chromosome 17p deletion or TP53 mutations; • Active and uncontrolled autoimmune cells reduce disease; • Existing or prior Richter's syndrome; • Central nervous system involvement; • Received glucocorticoid therapy within 14 days before the first administration

Abbreviations: CIRS, Cumulative Illness Rating Scale score; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Treatment and assessment

- Eligible patients will receive the BG regimen for the first 28-day cycle, followed by five cycles of orelabrutinib plus BG regimen (cycle 2-6), and thereafter one cycle of orelabrutinib monotherapy (**Figure 2**).
- MRD was monitored by next-generation sequencing in bone marrow at baseline and cycle 7; in peripheral blood at baseline, 4/7-cycle, and 13/19/25-month.
- Efficacy evaluation will be performed at baseline, cycle 4, cycle 7 and every 3-6 months thereafter for response assessment by investigators per IWCLL2008 criteria;
- Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

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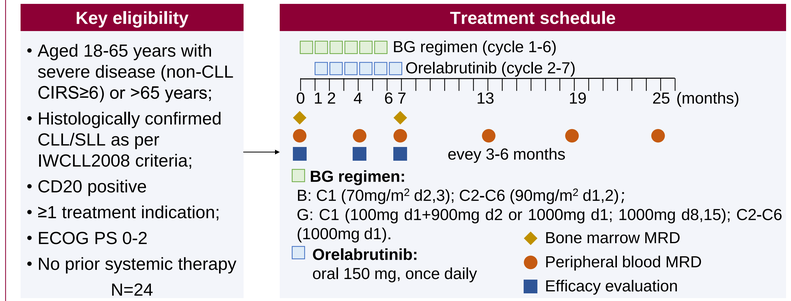
METHOD

Figure 2. Study design and treatment schedule.



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.
- Secondary and exploratory endpoints are outlined in **Table 2**.

Table 2. Study endpoints

Primary endpoint	CR/CRi with uMRD rate at the end of cycle 7*
Secondary endpoints	CR/unconfirmed CR (CRu) with uMRD rate#; Overall response rate; uMRD rate; Progression-free survival; Overall survival; Duration of response; Quality of life; Safety.
Exploratory endpoint	Dynamic monitoring of MRD in bone marrow and peripheral blood.

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

CONCLUSION

This study is a multicenter, single-arm, phase II trial designed to investigate the new time-limited regimen with orelabrutinib and BG in patients with CLL/SLL who are ineligible for intensive chemotherapy.

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