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623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL**Effectiveness and Safety of Orelabrutinib Combined with Rituximab As First-Line Treatment in Marginal Zone Lymphoma**

Jiada Xu¹, Lu-Ya Cheng², Yang Ke³, Yi-An Zhang², Li-Juan Cui⁴, Hui Xiao⁵, Yue-Xin Cheng⁶, Peng Liu, MD¹

¹Department of Hematology, Zhongshan Hospital, Fudan University, Shanghai, China

²Zhongshan Hospital, Fudan University, Shanghai, China

³Zhongshan Hospital Affiliated to Fudan University, Shanghai, China

⁴General Hospital of Ningxia Medical University, Ningxia, China

⁵Zhongnan Hospital of Wuhan University, Wuhan, China

⁶The First People's Hospital of Yancheng, Yancheng, China

Background: Marginal zone lymphoma (MZL) collectively is the third most common type of B-cell non-Hodgkin's lymphoma (NHL) worldwide, with an increased trend in incidence during the last two decades (Rossi D E *et al.*, *N Engl J Med.* 2022). The lack of predominant first-line systemic therapy and toxicities associated with current rituximab-based therapies have inspired the exploration of more optimal treatment strategies (Becnel MR *et al.*, *Br J Haematol.* 2019). Given the crucial role of bruton tyrosine kinase (BTK) in the B-cell receptor signaling pathway, BTK inhibitor has been proven to yield robust outcomes with improved tolerability in the development of NHL (Dhillon S *et al.*, *Drugs.* 2021; Xu W *et al.*, *Blood.* 2019; Song Y *et al.*, *Blood.* 2019). Orelabrutinib is a novel BTK inhibitor with high selectivity and has been approved in China for relapsed/refractory MZL recently (Dhillon S *et al.*, *Drugs.* 2021). Meanwhile, several clinical studies reported that orelabrutinib in combination with rituximab in NHL could preserve natural killer cell-mediated antibody-dependent cellular cytotoxicity induced by rituximab and enhance the clinical efficacy (Yu H *et al.*, *Mol Ther Oncolytics.* 2021; Qu C *et al.*, *Blood.* 2023). However, orelabrutinib plus rituximab as the first-line treatment for MZL remains largely understudied, thus, we conducted a retrospective study to evaluate its effectiveness and safety.

Methods: Between July 27, 2021 and March 18, 2023, 10 patients with MZL who received orelabrutinib (150 mg, qd, po) with rituximab (375 mg/m², iv, day 1 of each 28-day cycle) as first-line therapy were included in this retrospective study. After 6 cycles of treatment, patients underwent orelabrutinib monotherapy (150 mg, qd, po) as maintenance for a year. Dynamic dose adjustment was performed according to the patient's clinical status. Effectiveness was assessed by positron emission tomography/computed tomography-based 2014 Lugano criteria. The primary endpoint was the overall response rate (ORR); secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety.

Results: Ten patients (6 males; median age 63.5 years, range 45-76) were included in this study, 4 with extranodal MZL of mucosa-associated lymphoid tissue (40.0%), 2 with nodal MZL (20.0%), 1 with splenic MZL (10.0%), and 3 with unknown subtype (30%). Among a total of 10 patients, 3 (30%) achieved complete response (CR) and 6 (60%) attained partial response (PR) as their best response for an ORR of 90% (**Figure 1**). After a median follow-up of 13.0 months (range 7.8-24.7), the median PFS was not reached and a 6-month PFS rate was 100% (**Table 1**). OS could not be assessed due to there were no deaths occurred. As of the cut-off date (May 6, 2023), 8 patients received orelabrutinib maintenance treatment and the median duration of maintenance treatment was 9.6 months (range 3.0-17.8). The ORR was 75% (6/8) during maintenance treatment, while 1 patient had stable disease (SD) and 1 developed progressive disease (PD). In addition, abnormal hematology due to disease gradually recovered with the therapy within 4 months. No serious adverse events were observed. The off-target related AEs such as atrial fibrillation, diarrhea, and major hemorrhage were not reported.

Conclusion: This retrospective data suggests that orelabrutinib with rituximab has an encouraging anti-tumor activity in MZL, with a favorable safety profile. These results provide a potential first-line treatment strategy in MZL. Further verification in prospective clinical trials of clinical outcomes of orelabrutinib in first-line MZL is warranted in the future.

Disclosures No relevant conflicts of interest to declare.

OffLabel Disclosure: The indications for Orelabrutinib are as follows: relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), relapsed/refractory mantle cell lymphoma (MCL), and relapsed/refractory marginal zone lymphoma (MZL). The purpose of this abstract is to evaluate the efficacy of first-line treatment of MZL with orelabrutinib.

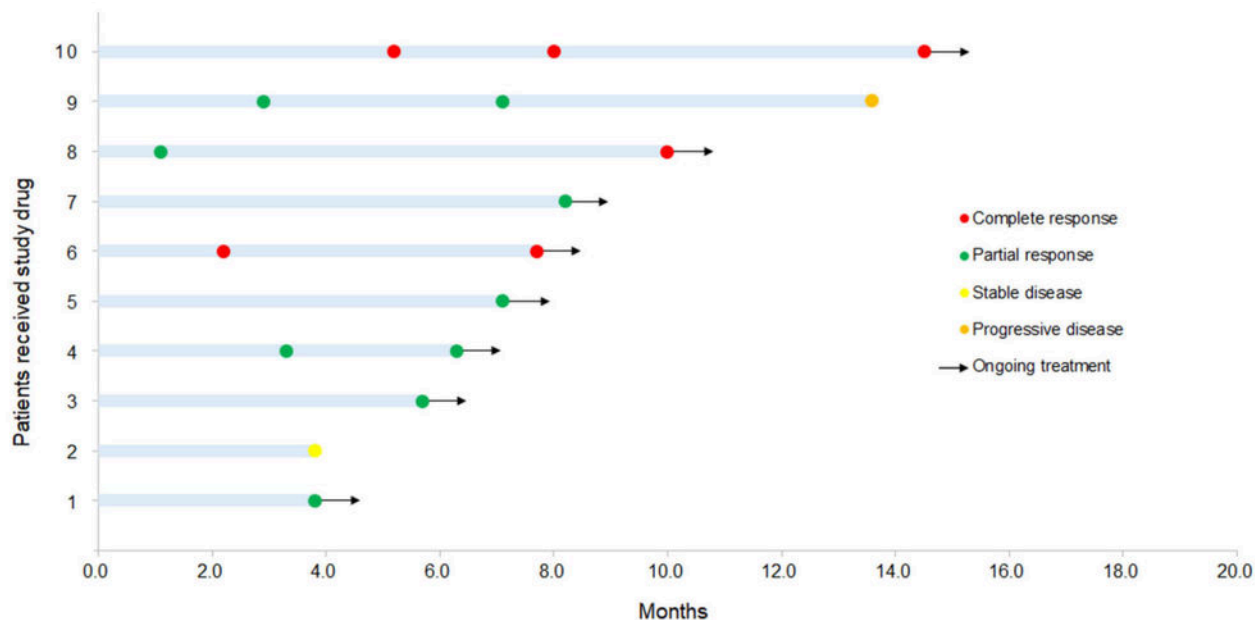


Figure 1 Swimmer plot

Table 1 Summary of best response data for combined therapy

| Variable | Total (n=10) |
|----------|--------------|
| ORR | 9 (90.0%) |
| CR | 3 (30.0%) |
| PR | 6 (60.0%) |
| SD | 1 (10.0%) |
| PD | 0 |

ORR, overall response rate, CR, complete response, PR, partial response, SD, stable disease, PD, progressive disease.

Figure 1

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