Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenström's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study

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Summary

Background Orelabrutinib is a novel, small molecule, selective irreversible Bruton tyrosine kinase inhibitor. The purpose of this study was to evaluate the efficacy and safety of orelabrutinib in patients with relapsed or refractory Waldenström's macroglobulinemia (R/R WM).

Methods This is a prospective, multicenter study of orelabrutinib in patients with WM who had at least one prior line of treatment. Orelabrutinib was administered orally at a daily dose of 150 mg until disease progression or unacceptable toxicity. The primary endpoint was major response rate (MRR) assessed by the Independent Review Committee (IRC) according to IWWM-6. This study is registered with ClinicalTrials.gov, NCT04440059. This trial was also registered on Center for Drug Evaluation (www.chinadrugtrials.org.cn) in March 2019, with a number of CTR20190036.

Findings Between August 2019 and December 2020, 66 R/R WM patients were assessed for eligibility. Forty-seven eligible patients were evaluated for efficacy at a median follow-up of 16.4 months (interquartile range: 12.5, 19.5). As assessed by IRC, the MRR was 80.9%, and the overall response rate was 89.4%. The median time to at least a minor response was 1.9 months. The PFS rates was 89.4% at 12 months. For patients with $MYD88^{L265P}/CXCR4^{NEG}$,

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$MYD88^{L265P}$/$CXCR4^{S338X}$, and $MYD88^{NEG}$/$CXCR4^{NEG}$ mutations, the MRRs were 84.6%, 100%, and 25.0%. Most adverse events were Grades 1 or 2 (91.0%). The common grade 3 or higher adverse events occurring were neutropenia (10.6%), thrombocytopenia (6.4%), and pneumonia (4.3%). Serious adverse events (SAE) occurred in 10 patients (21.3%). One treatment-related death was reported (hepatitis B reactivation).

Interpretation Orelabrutinib has shown good efficacy and manageable safety profiles in patients with R/R WM.

Funding InnoCare Pharma.

Keywords: Orelabrutinib; BTK; MYD88; CXCR4; Waldenström's Macroglobulinemia

Research in context

Evidence before this study

Despite recent advancement of the treatment for WM, Waldenström's macroglobulinemia is still incurable. MYD88 (L265P) mutation is highly prevalent in WM disease which is a driving mutation for the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase (BTK). Inhibition of BTK has revolutionized the treatment landscape for patients of WM. However, because of off-target activities, clinical uses of current approved BTK inhibitors remain compromised due to adverse events such as atrial fibrillation, bleeding, and diarrhoea. These adverse events lead to a substantial discontinuation rate observed in clinical studies of these BTK inhibitors. A new highly selective BTK inhibitor is warranted.

Orelabrutinib is a novel, highly selective small molecule inhibitor of BTK which is distinctive from other marketed BTK inhibitor drugs that are active against multiple kinases other than BTK. Orelabrutinib has been previously approved to treat patients with relapsed or refractory (R/R) mantle cell lymphoma and R/R chronic lymphocytic leukemia/small lymphocytic lymphoma. Here we report the efficacy and safety of orelabrutinib in patients with relapsed or refractory Waldenström's macroglobulinemia (R/R WM).

Added value of this study

Orelabrutinib induced deep remissions in R/R WM patients with a relatively short median follow-up. Due to its high selectivity for BTK, orelabrutinib also provides a differentiated safety profile. The incidence of the most concerning AEs in clinical treatment with BTK inhibitors are relatively low.

Implications of all the available evidence

Based on the high response rate and well tolerated safety profile, orelabrutinib could offer a novel treatment option for the treatment of B-cell malignancies such as Waldenström's macroglobulinemia.

Introduction

Waldenström's macroglobulinemia (WM), a rare B-cell lymphoma, is a lymphoplasmacytic lymphoma characterized primarily by bone marrow infiltration and IgM monoclonal gammopathy.[1] Typical therapies for WM include plasma exchange, systemic anticancer therapy (e.g., alkylating agents, nucleoside analogs, immunomodulators, proteasome inhibitors, anti-CD20 monoclonal antibodies), and hematopoietic stem cell transplantation.[2] Despite advances in therapy, WM remains incurable.

Mutations of *MYD88* and *CXCR4* are commonly involved in the development of WM.[3] MYD88 is an adaptor protein in the B-cell receptor (BCR) pathway that triggers downstream signaling including nuclear factor-κB activation. Approximately 90% to 95% of WM patients carry $MYD88^{L265P}$ mutation. This mutation is not only critical for diagnosis, but also has prognostic significance on WM. $CXCR4^{WHIM}$ somatic mutation, usually extending from amino acid position 308 to 352, has been essentially involved in both the clinical presentation and treatment outcomes of WM.[4] Among $CXCR4^{WHIM}$ somatic mutations, $CXCR4^{S338X}$ is the most common one.[5-7] The identification of *MYD88* and *CXCR4* mutations in WM has facilitated rational drug development, including the development of Bruton tyrosine kinase (BTK) inhibitors.

Ibrutinib and zanubrutinib are BTK inhibitors approved by the U.S. Food and Drug Administration for the treatment of patients with WM.[8,9] BTK inhibitor alone or in combination with rituximab are preferred treatment options recommended by the 10th International Workshops for Waldenström's macroglobulinemia (IWWM- 10).[10] Although effective, their off-target effects, usually associated with frequent toxicities such as atrial fibrillation, bleeding, and diarrhoea, lead to a substantial discontinuation rate observed in currently available studies of these BTK inhibitors.[11–13]

Orelabrutinib is a newly developed BTK inhibitor with high selectivity. It is highly potent against BTK (half maximal inhibitory concentration [IC_{50}], 1.6 nM) with notable

less off-target inhibition of other tyrosine kinases.[14] In a screening test of 456 kinases in vitro at a concentration of 1 μM, orelabrutinib had significant inhibition only on BTK (> 90%) (Supplementary Figure 1). Compared with other BTK inhibitors, orelabrutinib exhibited a high selectivity profile.[15] Orelabrutinib exhibited linear pharmacokinetic characteristics with dose-proportional increases in plasma exposure (Supplementary Figure 2). A near-complete BTK occupancy was achieved at a subtherapeutic dose of ≥ 50 mg/day and lasted for 24 h (Supplementary Figure 3).[14] In early clinical studies, orelabrutinib was efficacious and well tolerated in a variety of B-cell malignancies.[16,17] Orelabrutinib has been previously approved in China by the National Medical Products Administration to treat patients with relapsed or refractory (R/R) mantle cell lymphoma and R/R chronic lymphocytic leukemia/small lymphocytic lymphoma.[18] High kinase selectivity, persistent BTK target occupancy, potent anti-tumor activity, and the safety profile support orelabrutinib as an alternative treatment option for B-cell malignancies such as WM.

Here we report the data of a multicenter, open-label, prospective study to evaluate the efficacy and safety of orelabrutinib in patients with R/R WM.

Methods

Study design and participants

Males and females aged ≥ 18 years with R/R WM requiring treatment per criteria from the IWWM-7 were enrolled in China. Eligible patients were required to have adequate organ function and an absolute neutrophil count and platelet count of at least 0.75×10^9/L and 50×10^9/L, respectively. Patients were excluded if they had evidence of disease transformation or central nervous system involvement. Prior exposure to a BTK inhibitor or PI3K, Syk, and BCL-2 inhibitors was also excluded. Patients with uncontrolled or significant cardiovascular disease, including any class 3 or 4 congestive heart failure, unstable angina, or myocardial infarction within six months, or history of clinically relevant QTc prolongation or QTc interval at screening > 480 ms were excluded. Hepatitis B surface antigen positive subjects were excluded. Central institutional ethics committee approval was obtained at Peking Union Medical College Hospital (the approval number is HS2019004). All enrolled patients signed informed consent forms.

The study was conducted in accordance with China's Good Clinical Practice and the 2013 Declaration of Helsinki. The protocol was approved by the responsible ethics committee at each participating center. The protocol is included in the appendix.

Procedures

Patients received orelabrutinib 150 mg once daily until disease progression or unacceptable toxicity. Serum immunoglobulins and serum M protein were measured every cycle to cycle 12 and every three cycles thereafter. Radiological assessments were conducted at screening, every two cycles until cycle 6, every three cycles until cycle 26, and every six cycles thereafter. Bone marrow aspirates and biopsies were assessed at screening and for confirmation of a complete response (CR). Patients with hepatitis B virus (HBV) core antibody (HBcAb) positive at screening were recommended to receive prophylactic antiviral therapy and undergo HBV serological testing at least every three cycles. Patients with known human immunodeficiency virus (HIV) infection or hepatitis C virus (HCV) infection were excluded in this study.

Bone marrow specimens were collected at screening. $MYD88^{L265P}$ and $CXCR4^{S338X}$ mutations were assayed by real-time allele-specific polymerase chain reaction (AS-PCR) method in genomic DNA.[19]

Safety assessments including adverse events, laboratory tests, vital signs, and electrocardiogram were carried out at every cycle until cycle 12, and every three cycles thereafter. All adverse events within 28 days after the end of treatment were recorded. Treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Outcomes

The primary endpoint was major response rate (MRR; proportion of patients who achieved CR + very good partial response [VGPR] + partial response [PR]), as assessed by the Independent Review Committee (IRC) according to IWWM-6.[20] Secondary endpoints included assessments of efficacy, including MRR as assessed by investigator, overall response rate (ORR), duration of major response (time from the first major response to progressive disease [PD] or death), duration of response (DOR; time from the first response to PD or death), disease control rate (DCR; proportion of patients who achieved CR + VGPR + PR + minimal response [MR] + stable disease [SD]), progression-free survival (PFS), clinical benefit (including changes in serum IgM, hemoglobin, and extramedullary disease), time to major response (TTMR; time from first dose to at least PR), time to response (TTR; time from first dose to at least MR), and overall survival (OS), as well as safety. Exploratory endpoints included the effect of *MYD88* and *CXCR4* mutations on outcomes such as MRR, ORR, DCR, TTMR, PFS, and OS. Improvement in hemoglobin was defined as hemoglobin increase ≥ 2 g/dL compared with baseline for intention-to-treat (ITT) subjects or ≥ 11.5 g/dL for subjects with hemoglobin <11.5 g/dL at baseline.

Statistical analysis

A Simon two-stage design with a total of 44 patients with R/R WM provided 90% power to test the null hypothesis (MRR ≤ 30%) against the alternative

hypothesis (MRR ≥ 55%), with a two-sided significance level of 0.05.

The data cutoff for the analyses presented was Dec 2, 2021. All efficacy and safety endpoints were assessed based on ITT population in which all patients who received at least one dose of orelabrutinib were included. The primary endpoint was also analyzed based on Per-protocol set (PPS) which includes all patients who received at least one dose of orelabrutinib, had at least one valid post-baseline tumor assessment, had good compliance and had no major protocol deviations which might potentially impacts the efficacy results. For the primary endpoint MRR, descriptive statistics were used to calculate the number of major response subjects (CR, VGPR, PR) and their percentage among the numbers included in the efficacy evaluation, as well as the 95% confidence interval (CI) of the percentage using exact binomial test. The same analysis methods were applied to ORR and DCR. PFS was measured from the time of first dose of study drug to disease progression or death from any cause. OS was measured from the time of first dose of study drug to death from any cause. Time-to-event endpoints were estimated using the Kaplan-Meier method. The subgroup analyses of the primary endpoint were done using baseline demographic and clinical characteristics (sex, age [≤65 or >65 years, ≤75 or >75 years], ECOG [0 or ≥1], prognostic score at enrollment, prior lines of therapy, baseline $\beta 2$ microglobulin, platelets, hemoglobin and IgM levels, relapsed/refractory, and baseline extramedullary lesions). The subgroup analyses methods were the same as the main analysis of the primary endpoint. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Inc.). This study is registered with ClinicalTrials.gov, NCT04440059.

Role of the funding source

The sponsor of the study had a role in the study design, data collection, analysis, and interpretation. All authors had full access to the data, reviewed the manuscript, decided to submit for publication, and vouch for the accuracy and completeness of the data reported and for adherence to the protocol. The corresponding author, with the aid of a medical communications agency, had the final responsibility to submit for publication.

Results

Demographic and baseline characteristics

Between August 2019 and December 2020, 66 R/R WM patients from 15 hospitals in China were assessed for eligibility. Nineteen patients were excluded (did not meet all inclusion criteria or met exclusion criteria). Forty-seven patients were enrolled (Figure 1). The demographics and baseline characteristics are summarized in Table 1. The median age was 63 (range, 47 to 80) years, and the majority (85.1%) were male. All R/R WM patients had received at least one prior anti-cancer therapies including rituximab, purine analogue, proteasome inhibitor, immunomodulatory drugs (Supplementary Table 1). The most common indications on treatment initiation (≥10%) were B symptoms, anemia, thrombocytopenia (Supplementary Table 2). Most patients (83.0%) had multiple prognostic factors for intermediate- or high-risk disease according to the International Prognostic Scoring System (IPSS). All patients received at least one prior therapy (Supplementary Table 1), and the median number of prior regimens was one (range, 1 to 5). The median time from first-line therapy to the first dose of orelabrutinib was 28.1 months (range, 2.9 to 168.9). Baseline IgM was ≥ 40 g/L for 40.4% of patients and ≥ 70 g/L for 10.6% of patients, with a median of 30.3 g/L (range, 7.3 to 121.8 g/L). 72.3% of patients had a hemoglobin level ≤110 g/L, with a median of 102.0 g/L (range, 86 to 112.5 g/L).

Genotyping for tumor mutation status ($MYD88^{L265P}$ and $CXCR4^{S338X}$) was performed for all 47 patients. Thirty-nine patients (83.0%) had $MYD88^{L265P}$ mutation ($MYD88^{L265P}/CXCR4^{NEG}$), and four patients (8.5%) had both mutations ($MYD88^{L265P}/CXCR4^{S338X}$). The remaining four patients (8.5%) had neither mutation on $MYD88^{L265P}$ or $CXCR4^{S338X}$ ($MYD88^{NEG}/CXCR4^{NEG}$).

Efficacy evaluation

At the data cutoff, the median duration of follow-up was 16.4 months (interquartile range [IQR]: 12.5, 19.5). A decline in serum IgM levels from the baseline value (median 30.3 g/L) was observed, with a median reduction of 80.4% (IQR: −91.3, −62.3) (Figure 2A). Along with IgM reduction, hemoglobin levels were increased with time on treatment (Figure 2B). At baseline, 72.3% of patients had a hemoglobin level ≤ 110 g/L. A rapid increase in hemoglobin levels was observed at a median time of two cycles (IQR: 1 to 5). Improvement in hemoglobin levels from baseline (median 102.0 g/L) was found in 87.2% of patients, with a median maximal improvement of 33.0 g/L (IQR: 25.0, 61.0). 72.3% of patients had extramedullary disease which is defined as adenopathy (longest diameter >1.5 cm), splenomegaly (>13 cm), and hepatomegaly (>16 cm in the midclavicular line) at enrollment. The median sum of the product of perpendicular diameters (SPD) for target lymph nodes was 222.3 mm^2 compared with a baseline median SPD of 587.1 mm^2, with a maximal reduction from baseline of 61.0% (Supplementary Figure 4).

For the ITT population, the MRR was 80.9% (95% CI 66.7–90.9), including 21.3% of patients who achieved a best response of VGPR and 59.6% of patients who achieved PR, as assessed by IRC. Likewise, as assessed by investigator, 80.9% of patients had a VGPR (17.0%) or PR (63.8%) as the best response. The ORR was 89.4% (95% CI 76.9–96.5), with 97.9% of patients achieving disease control (Supplementary

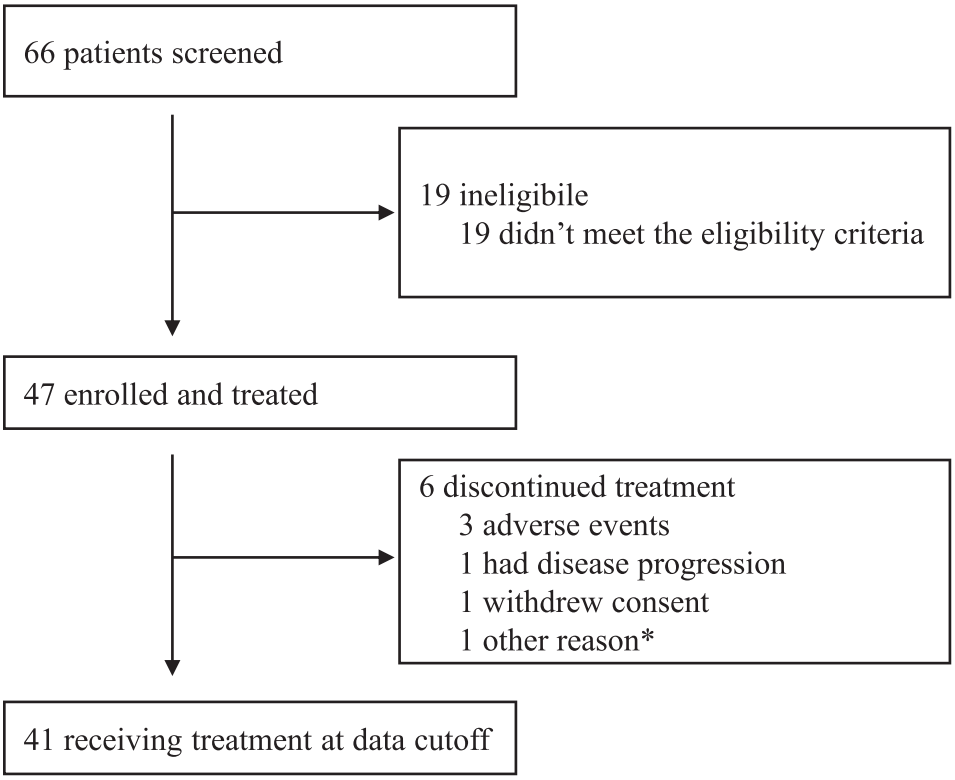

Figure 1. Trial profile.
* One patient discontinued treatment due to noncompliance.

Table 3 and Supplementary Figure 5). Overall response was reported in 37 (94.9%) of 39 *MYD88* ^{L265P}/*CXCR4*^{NEG} patients, 4 (100%) of 4 *MYD88*^{L265P}/*CXCR4*^{S338X} patients, and 1 (25%) of 4 *MYD88*^{NEG}/*CXCR4*^{NEG} patients. Major response was reported in 33 (84.6%) of 39 *MYD88* ^{L265P}/*CXCR4*^{NEG} patients, 4 (100%) of 4 *MYD88*^{L265P}/*CXCR4*^{S338X} patients, and 1 (25%) of 4 *MYD88*^{NEG}/*CXCR4*^{NEG} patients (Supplementary Table 4). The subgroup analysis showed consistent treatment effect across prespecified subgroups, including patients aged >65 years (94.7%) and >75 years (100%) and those who received more than one previous line of therapy (88.2%), were at medium to high risk according to IPSS (80.0% and 92.9%), and had relapsed disease (100%) (Figure 3). The primary endpoint analysis results based on the PPS are similar to those based on the ITT population. A total of 44 patients were included in PPS, and 3 patients were excluded from PPS due to poor compliance (2 patients) and lack of post-baseline tumor assessment (1 patient). Based on PPS, the MRR assessed by IRC was 81.8% (95% CI: 67.3%, 91.8%).

The median time to first documented overall response was 1.9 months, with an overall response rate at 12 months of 90.3% (95% CI 79.4–96.8). The median time to first documented major response was 2.0 months, with a major response rate at 12 months of 81.5% (95% CI 68.8–91.3). Median duration of major response has not yet been reached with a sustained MRR at 12 months of 91.6% (95% CI 76.0–97.2). Median duration of response has not yet been reached, with a sustained response rate at 12 months of 92.5% (95% CI 78.6–97.5). For patients with *MYD88*^{L265P} and *CXCR4*^{NEG} genotype, the median time to achieve major response was substantially the shortest (1.9 months), followed by those with genotypes *MYD88*^{L265P}/*CXCR4*^{S338X} (3.6 months) and *MYD88*^{NEG}/*CXCR4*^{NEG} (not achieved).

Four patients experienced disease progression. There were four deaths in this study: three patients (6.4%) had TEAEs with fatal outcomes (intracranial hemorrhage, retroperitoneal mass, and hepatitis B reactivation) and only hepatitis B reactivation was assessed as drug related. One patient died of a retroperitoneal mass (no biopsy was performed) 7 months after initiation of orelabrutinib. One patient died 28 days after the last dose of orelabrutinib (death reason unknown). The median PFS and OS were not yet been reached. The estimated PFS rates were 95.7% (95% CI 84.0–98.9) at six months and 89.4% (95% CI 76.3–95.4) at 12 months (Figure 4A). The estimated OS rates were 97.9% at six months and 93.6% at 12 months (Supplementary Figure 6). We also evaluated the impact of *MYD88* and *CXCR4* mutation status on PFS. As shown in Figure 4B, the 12-month estimated PFS rates were

Characteristic	*N*=47 (%)
Sex	
Male	40 (85.1%)
Female	7 (14.9%)
Median age, years (range)	63.0 (47.0, 80.0)
Age group, years	
<65	24(51.1%)
65–75	19 (40.4%)
>75	4 (8.5%)
ECOG Performance Status	
0	23 (48.9%)
1–2	24 (51.1%)
Extramedullary disease	
Any extramedullary disease	34 (72.3%)
Liver enlargement	4 (8.5%)
Spleen enlargement	11 (23.4%)
IgM	
≥ 40 g/L	19 (40.4%)
≥ 70 g/L	5 (10.6%)
Platelet ≤ 100×10^9	7 (14.9%)
Hgb ≤ 110 g/L	34 (72.3%)
β2 microglobulin >3 mg/L	32 (68.1%)
MYD88/CXCR4 genotype	
$MYD88^{L265P}/CXCR4^{NEG}$	39 (83.0%)
$MYD88^{L265P}/CXCR4^{S338X}$	4 (8.5%)
$MYD88^{NEG}/CXCR4^{NEG}$	4 (8.5%)
IPSS	
Low risk	8 (17.0%)
Intermediate risk	25 (53.2%)
High risk	14 (29.8%)
Median time from first line therapy to study treatment, months (range)	28.1 (2.5, 168.9)
Previous lines of therapy	
1	30 (63.8%)
>1	17 (36.2%)
Prior lines of therapy, median (range)	1 (1, 5)

***Table 1*: Demographics and baseline disease characteristics.**
ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; IgM: immunoglobulin M; IPSS: International Prognostic Scoring System.

92.3%, 75%, and 25% in patients with $MYD88^{L265P}/CXCR4^{NEG}$, $MYD88^{L265P}/CXCR4^{S338X}$, and $MYD88^{NEG}/CXCR4^{NEG}$ mutations, respectively.

Safety evaluation

Safety was evaluated in a total of 47 patients who received orelabrutinib treatment, among whom 43 patients (91.5%) received orelabrutinib treatment for more than one year. Three patients (6.4%) discontinued study treatment due to TEAEs (one each of intracranial hemorrhage, lung cancer, and hepatitis B reactivation). The median duration of exposure was 499 days (Q1, Q3: 341.0, 592.0), and the median relative dose exposure intensity was 100% (Q1, Q3: 99.4, 100). All 47 patients experienced at least one TEAE. Most TEAEs were Grades 1 or 2 (91.0%). The most frequently reported TEAEs (occurring in ≥10% of patients) included thrombocytopenia (27.7%), weight increased (25.5%), neutropenia (19.1%), influenza-like illness (14.9%), leukocytopenia, upper respiratory tract infection, and rash (12.8% each), and alanine aminotransferase increased, blood lactate dehydrogenase increased, and mouth ulceration (10.6% each). TEAEs by grade are summarized in Table 2. Grade 3 or higher TEAEs occurred in 19 patients (40.4%) and were most commonly (at least 2 patients) neutropenia (10.6%), leukocytopenia (6.4%), thrombocytopenia (6.4%), pneumonia (4.3%), and cataracts (4.3%). Serious adverse events occurred in 10 patients (21.3%). The serious adverse event occurring in at least two of the 47 patients was pneumonia (4.3%).

Atrial fibrillation, second primary malignancy, hemorrhage, hypertension, cytopenia, infections, and diarrhea are the most concerning AEs in clinical treatment with BTK inhibitors (Supplementary Table 5). There was no atrial fibrillation/flutter in this study, and only one patient (2.1%) reported lung cancer, which was assessed as unlikely related to orelabrutinib. A total of 15 patients (31.9%) experienced hemorrhage of any grade, and only one (2.1%) had a major hemorrhage event (defined as Grade 3 or higher, serious, or any grade central nervous system bleeding event): a cerebral hemorrhage (Grade 5), which was assessed as unlikely related to orelabrutinib (the patient had intracranial hemorrhage during plasmapheresis due to hyperviscosity). Only one patient (2.1%) reported hypertension, which was categorized as Grade 2. A total of 20 patients reported cytopenia, of which 11 (23.4%) were Grades 1 or 2; there were no serious events of cytopenia. Twenty patients (42.6%) reported at least one infection. Most infections were well controlled. Grade 3 or higher infections were reported in four patients (8.5%) (two with pneumonia, one with hepatitis B reactivation, and one with gastroenteritis). The patient with Grade 5 hepatitis B reactivation had a positive HBcAb test at baseline. Hepatitis B reactivation was associated with rising HBV DNA and increased bilirubin. Considering hepatitis B reactivation may occur after treatment with BTK inhibitors, patients with positive HBcAb at screening were suggested to receive prophylactic antiviral therapy, and HBV serological testing was performed at least every three cycles during study treatment.

Discussion

WM is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells and IgM monoclonal gammopathy. Identification of *MYD88* and *CXCR4* mutations has deepened the understanding of the signaling pathways in WM. *MYD88* gene mutation leads to the constitutive activation of downstream pathways involving BTK-mediated signaling.[21] The development of BTK inhibitors has changed

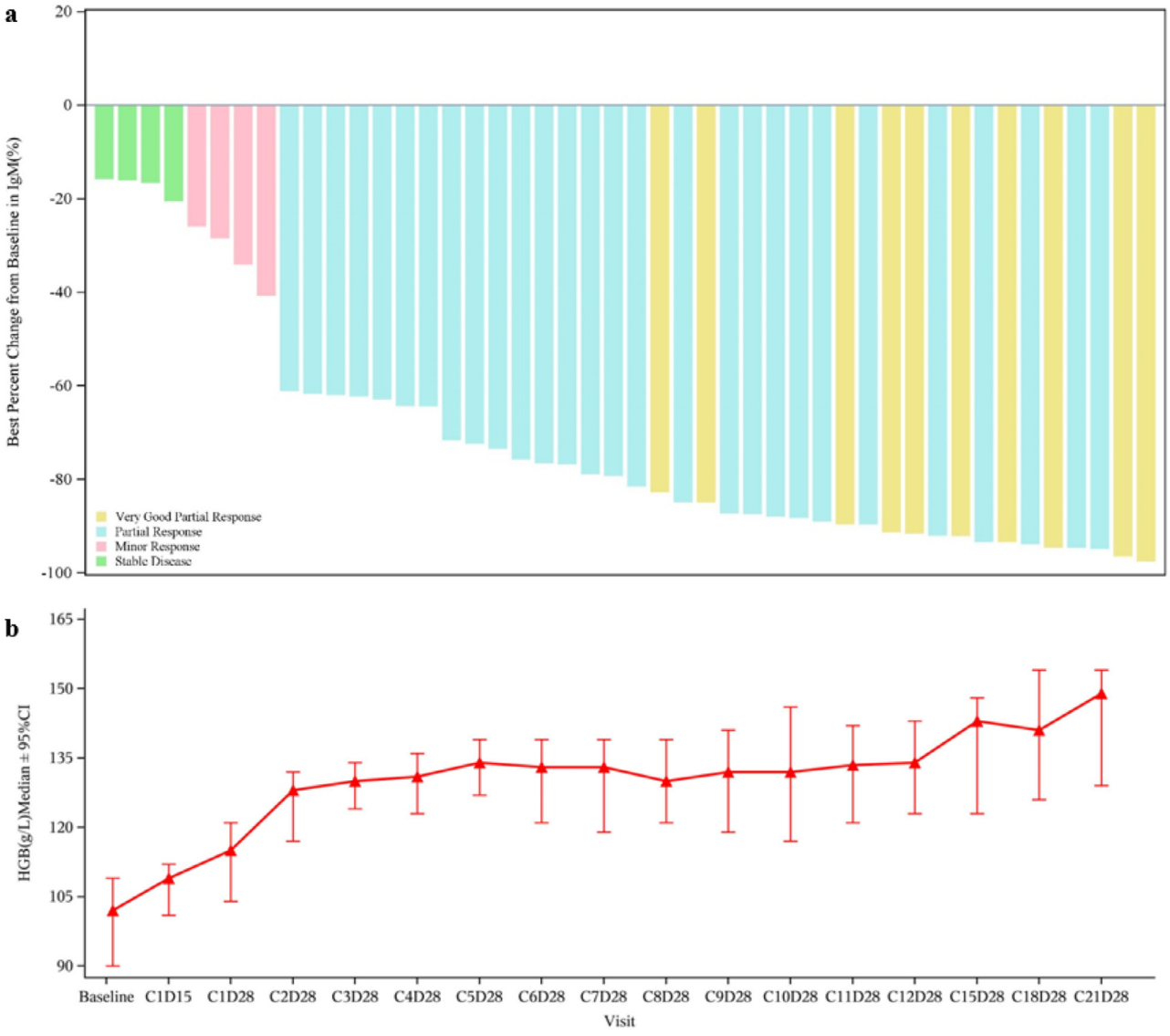

Figure 2. Waterfall plot of best percent change from baseline in IgM (a) and maximum improvement in hemoglobin concentration over time (b).

Hgb: hemoglobin; IgM: immunoglobulin M; Error bars denote 95% CI.

the treatment landscape of WM. However, because of target selectivity issues, clinical uses of BTK inhibitors are associated with toxicities due to off-target activities. In vitro orelabrutinib inhibited BTK from ligand binding to a significant level (>90%), distinctive from other marketed BTK inhibitor drugs that targeted multiple other tyrosine kinases (Supplementary Figure 1).[14,22,23] These results translate to a wide therapeutic window of orelabrutinib in which the drug can be safely used. Over 395 patients with B-cell malignancies have been treated with orelabrutinib. Due to its high selectivity for BTK and favorable safety profile, orelabrutinib is anticipated to provide a favorable option for the treatment of B-cell malignancies such as WM.

In this study, with a median follow-up of 16.4 months, orelabrutinib rapidly achieved deep and durable remissions in R/R WM patients. The median time from first-line therapy to study treatment was 28.1 months, and 83.0% of patients had intermediate- or high-risk disease according to IPSS. Substantially high MRRs and VGPRs were observed even with a relatively short follow-up period. Differences in baseline characteristics may limit the cross-study comparisons of BTK inhibitor efficacy in R/R WM patients, although generally comparable.[24–26] Most demographic and prognostic variables (e.g., median age, low hemoglobin (<100 g/L) and elevated IgM (≥40 g/L), proportion of IPSS scores, refractory disease, extramedullary disease)

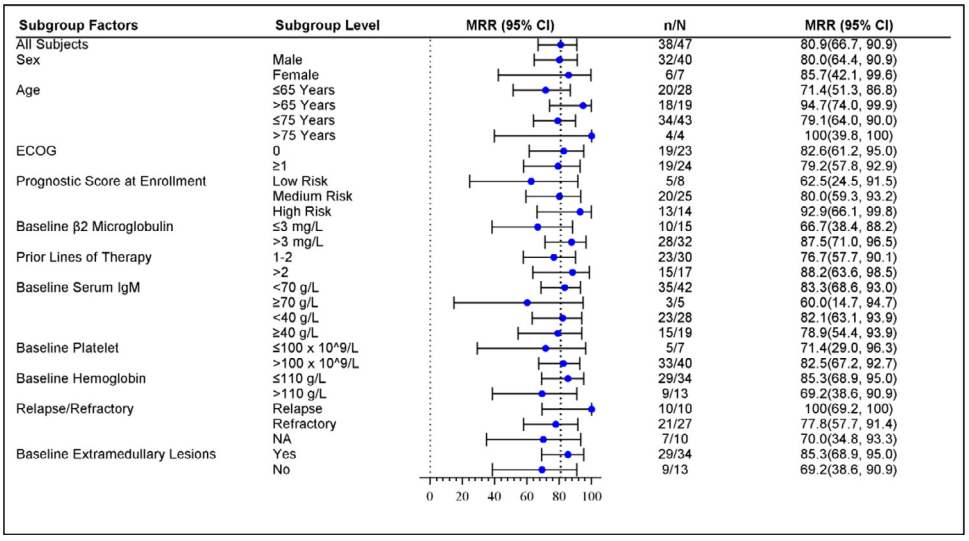

Figure 3. Subgroup analysis.
ECOG: Eastern Cooperative Oncology Group; IgM: immunoglobulin M; MRR: major response rate; NA: not available.

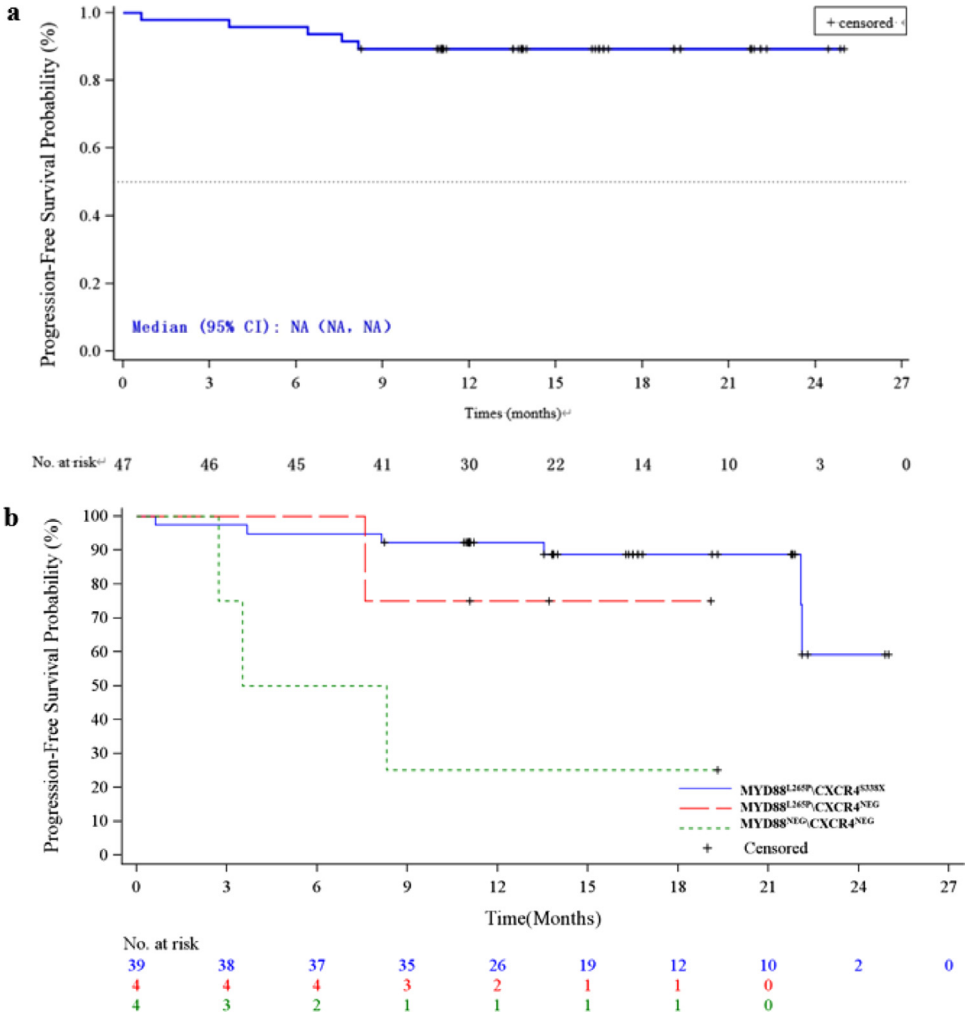

Figure 4. PFS Kaplan-Meier curve (ITT) (a) and PFS by genotype (b).
NA: not available.

Preferred Term	All Grades	Grade ≥3
TEAEs	**47 (100%)**	**19 (40.4%)**
Thrombocytopenia	13 (27.7%)	3 (6.4%)
Weight increased	12 (25·5%)	1 (2.1%)
Neutropenia	9 (19.1%)	5 (10.6%)
Influenza-like illness	7 (14.9%)	0
Rash	6 (12.8%)	0
Leukocytopenia	6 (12.8%)	3 (6.4%)
Upper respiratory tract infection	6 (12.8%)	0
Mouth ulceration	5 (10.6%)	0
Alanine aminotransferase increased	5 (10.6%)	0
Blood lactate dehydrogenase increased	5 (10.6%)	0
Cataracts	3 (6.4%)	2 (4.3%)
Pneumonia	2 (4.3%)	2 (4.3%)

***Table 2*: Summary of treatment-emergent adverse events.**
Data are in a total of 47 patients. TEAEs of all grades occurring in at least 10% of patients and grade 3 or higher TEAEs occurring in at least 2 patients are shown. Grade 3 or higher TEAEs that occurred in one (2.1%) patient each included weight increased, retroperitoneal mass, blood uric acid increased, hepatitis B reactivation, gastroenteritis, acute pancreatitis, headache, vertebrobasilar insufficiency, intracranial hemorrhage, hypokalaemia, hyponatraemia, age-related macular degeneration, angle closure glaucoma, hepatic function abnormal, lung neoplasm malignant, benign pancreatic neoplasm, anemia, and prostatomegaly.
TEAEs: treatment-emergent adverse events.

were similar to other BTK inhibitor studies. The MRR of orelabrutinib was 80.9% with a median follow-up of 16.4 months. A pivotal study of ibrutinib demonstrated a major response rate of 73%, with a VGPR of 15.8%, after a similar follow-up of 19 months.[25] The effect of acalabrutinib was also investigated in R/R WM; however, the VGPR rate was only 9%[26]. Tirabrutinib, which is also a covalent BTK inhibitor, has demonstrated a MRR of 88.9% in the 9 R/R WM patient cohort.[27] The MRR of zanubrutinib was reported to be 69.8% at a significantly longer follow-up (median 33 months).[28] The proportion of patients with a best response of VGPR or PR increased over time with orelabrutinib treatment, indicating further potential for better categorical response with longer follow-up duration (Supplementary Figure 7). Encouraging major responses were consistent across prespecified subgroups, including elderly patients aged >75 years and those who were at high risk according to IPSS.

It is noteworthy that rapid reductions of IgM and extramedullary disease were observed by a comparatively short median time to response (1.9 months). Of interest, the median times to response were 7.5 months for ibrutinib,[11] 4.6 months for acalabrutinib,[26] and 3 months for zanubrutinib.[28]

Different genotypes of *MYD88* and *CXCR4* have an impact on response to BTK inhibitors. Clinically meaningful response was observed for patients with $MYD88^{L265P}/CXCR4^{WT}$ and $MYD88^{L265P}/CXCR4^{S338X}$, which is similar to findings from studies of acalabrutinib and zanubrutinib in R/R WM.[26,28,29] However, these data should be interpreted with caution due to the small numbers of patients and limited follow-up time. In the current study, the mutation rate of $MYD88^{L265P}/CXCR4^{S338X}$ was relatively low compared with previously published results.[25] The discrepancy may be confounded by a low detection rate of *CXCR4* mutation (*s338x*) by AS-PCR compared to next-generation sequencing (NGS) for $CXCR4^{WHIM}$.

Orelabrutinib displayed a well tolerated safety profile, with a low discontinuation rate (6.4%) compared to ibrutinib's 9–29%.[30,31] The median duration of exposure and relative dose intensities were high. The adverse events observed in this study were consistent with the pooled safety analysis of orelabrutinib in other B-cell malignancies. No unexpected toxicities were observed. The most common adverse events were Grades 1-2 and did not require additional treatment. Events of cytopenia and infections (including upper respiratory infection, urinary tract infection, pneumonia, and nasopharyngitis) were expected as they are commonly reported from the same class of drugs and were mostly mild to moderate. The incidence of major bleeding in patients with WM treated with orelabrutinib (2.1%) was much lower than for those treated with ibrutinib (9%) and zanubrutinib (6%).[30] Substantially lower rates of diarrhea (6.4%) and hypertension (2.1%) were recorded for orelabrutinib compared with ibrutinib (32% and 16%, respectively) and zanubrutinib (21% and 11%, respectively). No treatment-emergent Grade 3 or higher diarrhea was observed. Atrial fibrillation/flutter was reported in 15% of patients receiving ibrutinib and 2% of patients receiving zanubrutinib. Grade 3 or higher atrial fibrillation was reported for 4% of patients treated with ibrutinib.[30] Recently, long-term study results of tirabrutinib have been update, of which 7% of WM patients experienced Grade 1-2 atrial fibrillation.[27] In this Phase 2 study, no atrial fibrillation/flutter was reported in R/R WM patients treated with orelabrutinib. A possible explanation may be elucidated by the fact that orelabrutinib only targeted BTK with > 90% inhibition as shown by KINOMEscan (Supplementary Figure 1) while other BTK inhibitors inhibited additional kinases including EGFR, TEC, and BMX.[14] Superior selectivity translates into an advantageous safety profile of orelabrutinib.

Single-arm study design is a limitation of this study which does not enable direct comparisons to existing treatment options with confounders adjustment. Randomized studies against standard treatments are warranted to further validate the clinical benefits of orelabrutinib in WM patients. The low detection rate of *CXCR4* mutation data is a further limitation of this analysis. The mutation rate found in this study was 8.5%, compared with 11.4%[28] and 34%[25] in previously published studies. This discrepancy may be because only

the $CXCR4^{S338X}$ mutation allele was detected by AS-PCR assay. NGS is needed for the detection of all of the *CXCR4* mutations, although S338X is the most prevalent loss-of-function mutation. In addition, median PFS and DOR are not reached and will need longer follow-up duration.

In summary, orelabrutinib monotherapy in R/R WM patients showed a deep and durable response with favorable safety, resulting from high target selectivity. These study results indicate that orelabrutinib has the potential to be a suitable therapeutic choice for patients with R/R WM.

Contributors

Dao-bin Zhou, Xin-xin Cao, Jie Jin, Cheng-cheng Fu, Shu-hua Yi, Wei-li Zhao, Zi-min Sun, Wei Yang, Deng-ju Li, Guo-hui Cui, Jian-da Hu, Ting Liu, Yong-ping Song, Bing Xu, Zun-min Zhu, Wei Xu, and Ming-zhi Zhang were principal investigators. Dao-bin Zhou, Xin-xin Cao, Ren-bin Zhao, and Ya-min Tian were responsible for manuscript development and editing, and approval of the final manuscript. Ya-min Tian and Bin Zhang collected and analyzed the data. Dao-bin Zhou, Xin-xin Cao and Ren-bin Zhao designed the study.

Data sharing statement

InnoCare Pharma. is committed to data transparency and will consider data sharing requests on a case -by-case basis. Summary trial information for study NCT04440059 is available online. This trial was also registered on Center for Drug Evaluation (www.chinadrugtrials.org.cn) in March 2019, with a number of CTR20190036. In addition, InnoCare Pharma will provide the study protocol, statistical analysis plan, and informed consent form, and post results on ClinicalTrials.gov as required.

Declaration of interests

DBZ, XXC, JJ, ZZF, SHY, WLZ, ZMS, WY, DJL, GHC, JDH, TL, YPS, BX, ZMZ, WX, and MZZ declare no competing interests. YMT, BZ, and RBZ are employees of InnoCare Pharma.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101682.

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