A Phase II Trial of the Bruton Tyrosine-Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Relapsed/Refractory Waldenström Macroglobulinemia

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ABSTRACT

Purpose: Although Bruton tyrosine kinase (BTK) inhibitors have demonstrated promising efficacy in patients with Waldenström macroglobulinemia (WM), data in Asian populations are scarce. This trial is the first to investigate the effect of a BTK inhibitor in Chinese patients with relapsed/refractory (R/R) WM.

Patients and Methods: Patients with R/R WM with at least one prior regimen were enrolled into this single-arm, multicenter, phase II study (NCT03332173) and received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was major response rate (MRR), as assessed by an independent review committee. Secondary endpoints included progression-free survival, overall response rate, duration of major response, and safety.

Results: Forty-four patients were enrolled. After a median follow-up of 33.0 (range, 3.2–36.5) months, MRR in all patients was 69.8%, with very good partial response or better in 32.6% of patients. All mutation groups benefited from zanubrutinib treatment (MRR in patients with *MYD88*^{L265P} mutation, 73%; MRR in patients with *MYD88* wild type mutation, 50%). A higher response rate was seen in the *MYD88*^{L265P}/*CXCR4*^{WT} population, compared with the other populations. Median progression-free survival and median duration of major response were not reached. The most frequently reported grade ≥3 treatment-emergent adverse events (AEs) were neutrophil count decreased (31.8%), and platelet count decreased and pneumonia (20.5% each). No case of atrial fibrillation/flutter occurred.

Conclusions: Zanubrutinib achieved a high rate of response that was durable and deep in patients with R/R WM across all subgroups, and potentially confers a positive benefit–risk profile for WM.

Introduction

Waldenström's macroglobulinemia (WM) is a generally indolent and relatively rare B-cell lymphoplasmacytic lymphoma, characterized by bone marrow infiltration with monoclonal IgM protein secretory lymphoplasmacytic cells. Bruton tyrosine kinase (BTK) is known to play an important role in the development of WM (1, 2). Two mutations are common and well investigated in WM, including activating mutation of myeloid differentiation primary response gene 88 gene (*MYD88*) and CXC-chemokine receptor 4 (*CXCR4;* refs. 3–7). The mutation of *MYD88* triggers downstream IRAK-and BTK-mediated NF-κB signaling and is seen in 90% of patients with WM (8, 9). The mutation of *CXCR4* has been seen in approximately 30% of cases and also leads to constitutive activation (10). Either or both of these mutations can be found in patients with WM and lead to different clinical pictures and outcomes.

Zanubrutinib is a next-generation BTK inhibitor, which, in preclinical studies, demonstrated greater selectivity for BTK versus other tyrosine kinases expressed in hepatocellular carcinoma (HCC)-family kinases and epidermal growth factor receptor (EGFR)-family kinases in biochemical assays. Zanubrutinib also showed favorable pharmacokinetic/pharmacodynamic properties (11). In a phase I clinical trial, zanubrutinib had complete and sustained 24-hour BTK occupancy in both peripheral blood mononuclear cells (PBMCs) and lymph node biopsies from patients treated with 160 mg twice daily (12). Zanubrutinib has also been associated with a high response rate in patients with WM, with many of the responses being durable. In a phase I/II study of patients with B-cell malignancies, 45% of 73 patients with WM achieved very good partial response (VGPR) or complete response (CR) and 82% achieved major response, after a median follow-up of

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Translational Relevance

Although our understanding of the pathophysiology of Waldenström macroglobulinemia (WM) and its treatment have improved in the past decade, it remains an incurable disease with substantial mortality. Bruton tyrosine kinase (BTK) inhibition has been shown to be an effective therapeutic strategy in WM, but *MYD88* wild-type (*MYD88*^{WT}) has been associated with poor outcomes when treated with ibrutinib, a first-generation BTK inhibitor. Zanubrutinib is a selective, next-generation BTK inhibitor that has demonstrated complete and persistent BTK occupancy in lymph node tissues and peripheral blood mononuclear cells (PBMCs) and presented favorable pharmacokinetic/pharmacodynamic properties. In this study, zanubrutinib demonstrated deep and high response in this difficult-to-treat population. *BIRC3-MALT1* fusion was detected for the first time in *MYD88*^{WT} WM, indicating a novel NF-κB activation mechanism and the involvement of NF-κB activation in BTK inhibitor primary resistance.

30.3 months. Additionally, the estimated 3-year progression-free survival (PFS) rate was 80.5%, and the overall survival rate was 84.8%. Treatment was generally well tolerated, with atrial fibrillation, major hemorrhage, and grade 3 diarrhea reported in 5%, 4%, and 3% of patients, respectively (13). The phase III ASPEN trial compared safety and efficacy of ibrutinib versus zanubrutinib in patients with WM. Although statistical significance was not reached at a median follow-up of 19.4 months, a higher VGPR rate was achieved by more patients on zanubrutinib than those on ibrutinib (28% vs. 19%). Zanubrutinib was also associated with a trend toward a better quality of response and less toxicity, particularly cardiovascular toxicity (14).

Given the scarce data, to generate more data on zanubrutinib in Asian WM populations, and to support its approval in WM, a phase II study was conducted in Chinese patients with relapsed/refractory (R/R) WM. At the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition in December 2020 (virtual meeting), we reported results that were assessed by the independent review committee (IRC), which had a median follow-up of 18.6 months (15). Here we report the efficacy results per investigator's assessment and safety data from the study after longer follow-up.

Patients and Methods

Study design and participants

This was a pivotal, single-arm, open-label, multicenter, phase II study of zanubrutinib in Chinese patients with R/R WM (NCT03332173; Supplementary Fig. S1). The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation guidelines. Institutional review boards (IRB) and independent ethics committees approved the protocol, and all patients provided written informed consent prior to taking part. Data were collected by the investigators and their research teams. All authors had full access to the data, and all were responsible for analyzing/interpreting the data.

Eligible patients had pathology confirmed R/R WM, were aged ≥18 years, had at least one prior line of a standard chemotherapy-containing regimen (with completion of at least two continuous treatment cycles), met at least one of the criteria for treatment per a consensus panel from the 7th IWWM (16), and had Eastern Cooperative Oncology Group (ECOG) performance status score between 0 and 2. Eligible patients were also required to have adequate baseline hematologic function (neutrophils ≥0.75 × 10^9/L, independent of growth factor support within 7 days of first dose of study drug; platelets ≥50 × 10^9/L, independent of growth factor support or transfusion within 7 days of first dose of study drug; hemoglobin ≥80 g/L, independent of erythropoietin support or transfusion within 7 days of first dose of study drug), adequate renal function (estimated creatinine clearance ≥30 mL/min), and adequate liver function (transaminase levels ≤3 times the upper limit of normal, total bilirubin ≤2 times the upper limit of normal). Patients were excluded if they had current central nervous system involvement, currently active clinically significant cardiac disease (e.g., uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification; ref. 17, or history of myocardial infarction within 6 months of screening), or histologic transformation to aggressive lymphoma; those requiring concurrent, strong CYP3A inhibitors/inducers were also excluded. Patients with a history of atrial fibrillation and those requiring concurrent antithrombotic medications (e.g., aspirin, anticoagulants) were allowed to participate. There were no requirements regarding *MYD88* or *CXCR4* mutations.

Procedures

Patients received zanubrutinib 160 mg orally twice daily until disease progression or unacceptable toxicity. Levels of quantitative IgM and M protein (by serum protein electrophoresis) in serum were measured at screening, every 4 weeks for the first 52 weeks, and every 12 weeks thereafter. If baseline quantitative IgM levels were unavailable, responses were assessed by changes in M protein levels. Contrast enhanced computed tomography (CT) scans for evaluation of extramedullary disease were performed at screening, every 12 weeks during the first 48 weeks of the study, and then every 24 weeks until disease progression. Tumor assessment was done by the investigator at the time of each CT scan after baseline. Bone marrow aspirate and biopsy were assessed at screening, every 24 weeks thereafter, for confirmation of a CR, and at other times as clinically indicated. Optional bone marrow aspiration was collected from patients with progressive disease (PD). Mutations in *MYD88* and *CXCR4* whole exons were assessed on baseline bone marrow aspirate without B-cell selection using a validated next-generation sequencing (NGS) panel with 1.5% sensitivity. Genetic variants including single-nucleotide variant (SNV), INDEL, copy-number variation (CNV) and gene fusion on 475 lymphoma-related genes were assessed by a validated NGS panel with 3% sensitivity in PD samples without B-cell enrichment. Quality-of-life was not assessed.

Evaluation of type, frequency, severity [graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03], and outcomes of adverse events (AEs) were assessed from a safety perspective. All treatment-emergent AEs (TEAEs) were summarized. TEAE was defined as an adverse event that had an onset or worsening in severity from baseline (pretreatment) on or after the date of the first dose of study drug up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurred first. Worsening of an event to grade 5 beyond 30 days after the last dose of study drug of a TEAE was also considered a TEAE (if it was prior to the start of a new anticancer therapy). AEs which were known to be associated with BTK inhibitors were predefined as AEs of interest and were identified in accordance with predefined Medical Dictionary for Regulatory Activities version 23.0 search criteria. AEs of interest included hemorrhage, major hemorrhage (defined as serious or grade

Table 1. Baseline demographics and disease characteristics of Chinese patients receiving zanubrutinib for R/R WM.

	Patients ($N = 44$)	*MYD88*^{L265P}/ *CXCR4*^{WT} ($N = 32$)	*MYD88*^{L265P}/ *CXCR4*^{WHIM} ($N = 5$)	*MYD88*^{L265P} ($N = 37$)	*MYD88*^{WT} [a] ($N = 7$)
Median age, years (range)	65 (41–83)	66 (41–83)	64 (55–70)	65 (41–83)	60 (52–66)
>65 years	19 (43.2)	16 (50.0)	2 (40.0)	18 (48.6)	1 (14.3)
Male, *n* (%)	27 (61.4)	21 (65.6)	2 (40.0)	23 (62.2)	4 (57.1)
ECOG performance status, *n* (%)					
≥1	26 (59.1)	16 (50.0)	4 (80.0)	20 (54.1)	6 (85.7)
Median weight, kg (range)	62.9 (46.0-89.0)	62.3 (46.5-89.0)	66.0 (46.0-78.0)	62.8 (46.0-89.0)	63.0 (48.0-75.0)
Median time since initial diagnosis of WM to first dose (years)	1.58	1.58	0.82	1.55	2.40
WM prognostic score, *n* (%)					
Low risk	11 (25.0)	7 (21.9)	1 (20.0)	8 (21.6)	3 (42.9)
Intermediate risk	13 (29.5)	8 (25.0)	3 (60.0)	11 (29.7)	2 (28.6)
High risk	20 (45.5)	17 (53.1)	1 (20.0)	18 (48.6)	2 (28.6)
Median number of prior systemic therapies, regimens (range)	2 (1–6)	2 (1–6)	2 (1–6)	2 (1–6)	3 (1–4)
Median baseline IgM, g/L (range)	30.85 (3.16–96.50)	32.20 (9.30–96.50)	29.00 (13.00–56.80)	31.30 (9.30–96.50)	23.50 (3.16–62.60)
Baseline IgM ≥40g/L, *n* (%)	19 (43.2)	14 (43.8)	2 (40.0)	16 (43.2)	3 (42.9)
Serum β2-microglobulin >3 mg/L, *n* (%)	34 (77.3)	26 (81.3)	3 (60.0)	29 (78.4)	5 (71.4)
Genotype, *n* (%)					
MYD88^{L265P}/*CXCR4*^{WT}	32 (72.7)	32 (100)	0	32 (86.5)	0
MYD88^{L265P}/*CXCR4*^{WHIM}	5 (11.4)	0	5 (100.0)	5 (13.5)	0
MYD88^{WT}	7 (15.9)	0	0	0	7 (100.0)
Peripheral blood cytopenias, *n* (%)					
Anemia (hemoglobin ≤110 g/L)	33 (75.0)	25 (78.1)	4 (80.0)	29 (78.4)	4 (57.1)
Thrombocytopenia (platelet count ≤100 × 10^9/L)	9 (20.5)	6 (18.8)	1 (20.0)	7 (18.9)	2 (28.6)
Neutropenia (ANC ≤1.5 × 10^9/L)	11 (25.0)	7 (21.9)	2 (40.0)	9 (24.3)	2 (28.6)
Extramedullary disease at baseline, *n* (%)	32 (72.7)	25 (78.1)	2 (40.0)	27 (73.0)	5 (71.4)
Percent bone marrow involvement[b], *n* (%)					
Lower bound ≥50%	17 (38.6)	15 (46.9)	1 (20.0)	16 (43.2)	1 (14.3)
Upper bound <50%	22 (50.0)	13 (40.6)	4 (80.0)	17 (45.9)	5 (71.4)
Other	5 (11.4)	4 (12.5)	0	4 (10.8)	1 (14.3)

Abbreviations: ANC, absolute neutrophil count; *CXCR4*, C-X-C motif chemokine receptor 4; IgM, immunoglobulin M; *MYD88*, myeloid differentiation primary response gene 88; WT, wild type; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome.
[a]Patients with *MYD88*^{WT} included one patient with *CXCR4*^{WHIM} and six patients with *CXCR4*^{WT}.
[b]The extent of bone marrow involvement by lymphoma was reported for some bone marrow biopsies as a range rather than a fixed percent. To accommodate those bone marrow biopsy results for which a percent range was reported, all patients were classified as to the extent of lymphomatous involvement in bone marrow into groups with a lower limit of the range ≥50%, the upper limit of the range <50%, or neither.

≥3 bleeding at any site, or central nervous system bleeding of any grade), atrial fibrillation/flutter, hypertension, second primary malignancies (including skin cancers), tumor lysis syndrome, infections (including opportunistic infections), neutropenia, thrombocytopenia, and anemia.

Study endpoints and statistical analysis

The safety analysis set included all patients with WM who received at least one zanubrutinib dose. The efficacy-evaluable set consisted of all patients in the safety analysis set with confirmed WM based on central pathologic review and with baseline IgM level ≥5 g/L. The primary endpoint for the study was the major response rate (MRR), defined as the proportion of patients who achieved best overall response of at least partial response (PR) as assessed by the IRC. The assessment was conducted according to modified criteria from the 6th IWWM. A decrease of 25% to 49% from baseline in serum IgM levels denoted a minor response (MR). A decrease of 50% to 89% and ≥90% in serum IgM levels, together with extramedullary disease improvement if existing at baseline, were PR and VGPR, respectively. Normalization of serum IgM level; no monoclonal IgM spike, BM disease involvement or extramedullary disease was required for CR (18, 19). In the R/R WM population, MRR in historical controls was assumed to be approximately 30%, based on results from trials that took place before the emergence of BTK inhibitors. MRR in this study was assumed to be 60%, which is deemed a clinically meaningful improvement; hence, the null and alternative hypotheses were set as H0: MRR = 30% and Ha: MRR >30%. A sample size of 40 patients was proposed based on the precision of an MRR estimate and the power of the comparison with the historical rate. Using a binomial exact test, the power was >0.969 with 40 patients to demonstrate statistical significance and superiority at a one-sided alpha of 0.025 as per the assumption outlined above. A two-sided Clopper–Pearson 95% confidence interval (CI) of MRR was constructed to assess the precision of the rate estimate. Concordance rate was calculated to show assessment consistency between the IRC and investigators.

Other efficacy and exploratory endpoints included overall response rate (minor response or better), PFS, duration of major response (DOMR), resolution of treatment precipitating symptoms, antilymphoma effect, overall survival (OS), and CR plus VGPR rates in

Table 2. Disease response in Chinese patients with R/R WM receiving zanubrutinib, as assessed by the investigator.

	Patients ($N = 43^a$)	*MYD88*^{L265P}/ *CXCR4*^{WT} ($N = 32$)	*MYD88*^{L265P}/ *CXCR4*^{WHIM} ($N = 5$)	*MYD88*^{L265P} ($N = 37$)	*MYD88*^{WT} ($N = 6$)^c
Best overall response, *n* (%)					
CR	0	0	0	0	0
VGPR	14 (32.6)	13 (40.6)	0	13 (35.1)	1 (16.7)
PR	16 (37.2)	11 (34.4)	3 (60.0)	14 (37.8)	2 (33.3)
MR	3 (7.0)	2 (6.3)	0	2 (5.4)	1 (16.7)
SD	2 (4.7)	1 (3.1)	1 (20.0)	2 (5.4)	0
PD	7 (16.3)	4 (12.5)	1 (20.0)	5 (13.5)	2 (33.3)
Discontinued study prior to first tumor assessment	1 (2.3)	1 (3.1)	0	1 (2.7)	0
CR + VGPR rate, *n* (%); (95% CI)^b	14 (32.6); (19.08–48.54)	13 (40.6); (23.70–59.36)	0;(0.00–52.18)	13 (35.1); (20.21–52.54)	1 (16.7);(0.42–64.12)
MRR (PR or better), *n* (%); (95% CI)^b	30 (69.8); (53.87–82.82)	24 (75.0); (56.60–88.54)	3 (60.0); (14.66–94.73)	27 (73.0); (55.88–86.21)	3 (50.0); (11.81–88.19)
Overall response rate (MR or better), *n* (%); (95% CI)^b	33 (76.7); (61.37–88.24)	26 (81.3); (63.56–92.79)	3 (60.0); (14.66–94.73)	29 (78.4); (61.79–90.17)	4 (66.7); (22.28–95.67)

Abbreviations: CI, confidence interval; CR, complete response; CXCR4, C-X-C motif chemokine receptor 4; MR, minor response; MRR, major response rate; MYD88, myeloid differentiation primary response gene 88; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild-type; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome.
[a]One patient was excluded from the efficacy analysis due to baseline IgM <5g/L.
[b]Calculated using the Clopper–Pearson method.
[c]Patients with *MYD88*^{WT} included one patient with *CXCR4*^{WHIM} and five patients with *CXCR4*^{WT}.

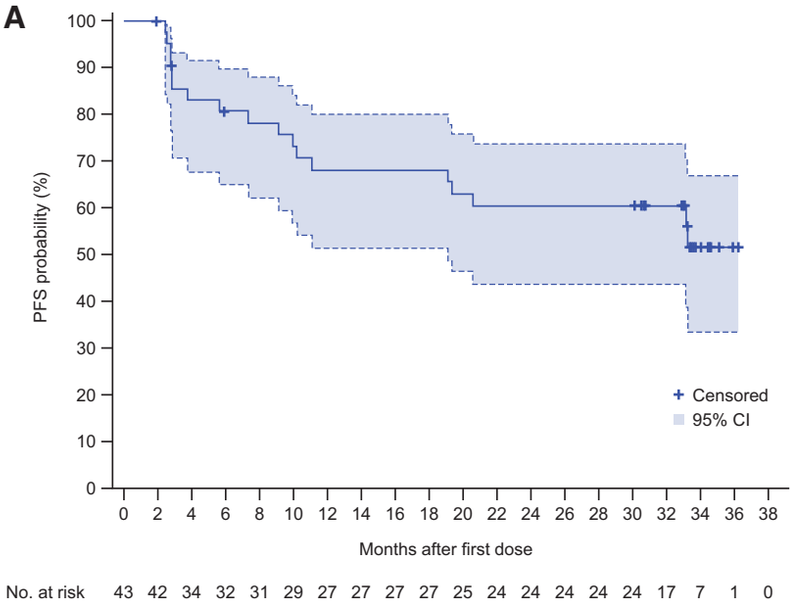
patients with *MYD88*^{L265P} WM. Time to response and response across subgroups were also examined. Response rates were summarized as the percentage of responders for each category (CR plus VGPR, major response, and overall response) with 95% CIs. PFS was measured from the time of first study drug dose to disease progression or death, whichever occurred first. DOMR was assessed as the time from first major response until disease progression or death, whichever happened first. Resolution of treatment precipitating symptoms was defined as absence of symptoms from a postbaseline timepoint onward during the study. Antilymphoma effect was specified as any reduction in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or splenomegaly by CT scan. OS was defined as time from first study drug dose until death from any cause. Patients not experiencing PD or death were censored on the day of their last disease assessment before subsequent anticancer therapy initiation for DOMR and PFS analysis. Median DOMR, PFS, and event-free rates at landmark timepoints were estimated using the Kaplan–Meier method. The 95% CIs for median DOMR and PFS were calculated using the method of Brookmeyer and Crowley, and the Greenwood's formula was used to determine the 95% CIs for event-free rates. Median follow-up times for PFS and DOMR were estimated using the reverse Kaplan–Meier method.

Biomarker analysis

For *MYD88* and *CXCR4* mutation detection, PCR-based amplification was used to enrich the whole exons of *MYD88* and *CXCR4* for NGS assessment. Mutations were identified using Torrent Variant Caller software and were annotated using ANNOVAR (RRID:SCR_012821). Germline mutations were filtered using dbSNP, 1,000 Genomes, ExAC, ESP6500 databases. Mutations with less than 1.5% variant allele frequency but with more than 500 high-quality sequence reads coverage are also reported. To explore resistance mechanisms to zanubrutinib, whole exons and partial introns of 475 lymphoma-related genes were captured by probe hybridization, and sequencing reads were processed and mapped to hg19 genome using Burrows–Wheeler Aligner. Functional mutations were filtered using OncoKB (RRID:SCR_014782) for downstream interpretation.

Results

The study was conducted at 11 centers in China. The first patient was dosed on August 31, 2017, and the last patient was enrolled and received the first dose of zanubrutinib on May 8, 2018. After the primary analysis, patients were gradually transferred to a long-term extension study as of October 2020. The last patient last visit in this phase II study occurred on January 11, 2021. A total of 44 patients were enrolled, and all received at least one dose of the study drug. Baseline characteristics are shown in **Table 1** (the mutation status and bone marrow involvement of each patient are listed in Supplementary Table S1; prior systemic therapies and best response to last systemic regimen are listed in Supplementary Table S2). Most patients (75%) were intermediate or high-risk [as per the International Prognostic Scoring System for Waldenström Macroglobulinemia (IPSSWM); ref. 20] and the median number of prior systemic therapies was two. The median time from diagnosis to study initiation was 1.58 (range, 0.3–11.1) years. Peripheral cytopenias were frequent at baseline: 33 (75.0%) patients had anemia (hemoglobin ≤110 g/L); 9 (20.5%) had thrombocytopenia (platelet count ≤100 × 10^9/L); and 11 (25.0%) had neutropenia (neutrophil count ≤1.5 × 10^9/L). *MYD88* wild type (*MYD88*^{WT}) patients made up approximately 16% of the population. Comparing patients with *MYD88*^{L265P} and *MYD88*^{WT}, the demographics and disease characteristics were generally comparable, except that there was a higher proportion of patients more than 65 years of age, of intermediate/high risk, and with a higher percent of bone marrow involvement at baseline in the *MYD88*^{L265P} subgroup, while there was a higher proportion of patients with ECOG ≥1 in the *MYD88*^{WT} subgroup, and the median number of prior systemic therapies was higher.



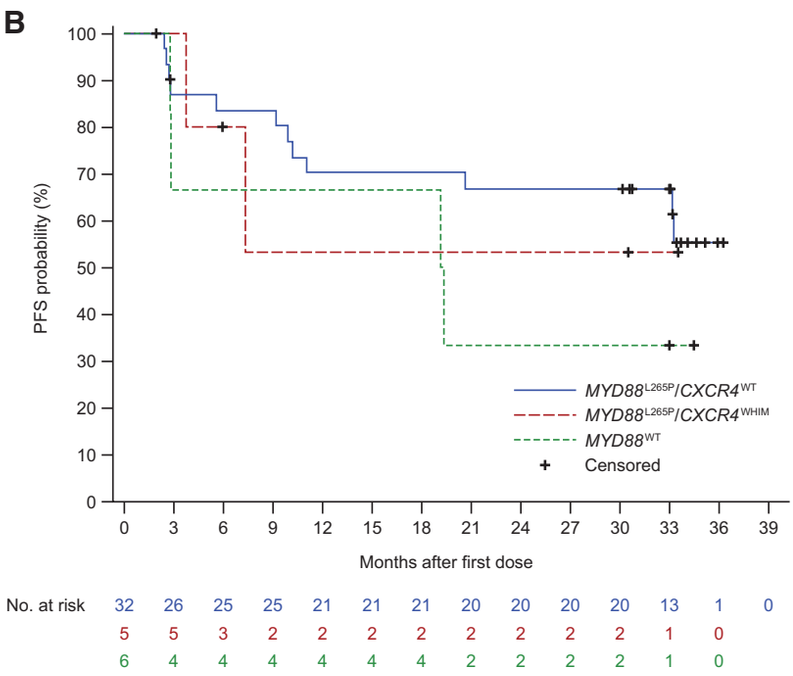


Figure 1.
Kaplan–Meier plots of survival in Chinese patients with R/R WM receiving zanubrutinib. **A,** PFS as assessed by the investigator. **B,** PFS by genotype as assessed by the investigator. (*Continued on the following page.*)

As of the data cutoff date (January 11, 2021), median follow-up was 33.0 months (range, 3.2–36.5 months). For the 43 patients evaluable for the efficacy analysis (one was excluded due to baseline IgM <5 g/L), MRR per investigator assessment was 69.8% ($n = 30$; **Table 2**), with VGPR achieved by 32.6% of patients ($n = 14$). The MRR was generally consistent across prespecified subgroups, including patients aged more than 65 years, those with baseline ECOG performance status of ≥1, those with low baseline hemoglobin (≤110 g/L), and those with extramedullary disease at baseline (Supplementary Fig. S2). Response was rapid, as evidenced by median times to major response or overall response being approximately 3 months (first on-study response assessment was to be conducted at week 12, as per protocol; Supplementary Table S3). For all patients, as of the data cutoff date, medians were not reached for PFS (**Fig. 1A**; **Fig. 1B** presents Kaplan–Meier plots of PFS per mutation), DOMR (**Fig. 1C**), and OS (**Fig. 1D**). The event-free rate for major responders was 75.1% at 24 months, and the 24-month OS rate was 87.8%. The 24-month PFS rate for all patients was 60.5%. For patients with $MYD88^{L265P}/CXCR4^{WT}$, $MYD88^{WT}$, and $MYD88^{L265P}/CXCR4^{WHIM}$, the rates were 66.9%, 33.3%, and 53.3%, respectively.

Thirty-six (83.7%) patients achieved resolution of one or more WM-related disease manifestations that were present at baseline and

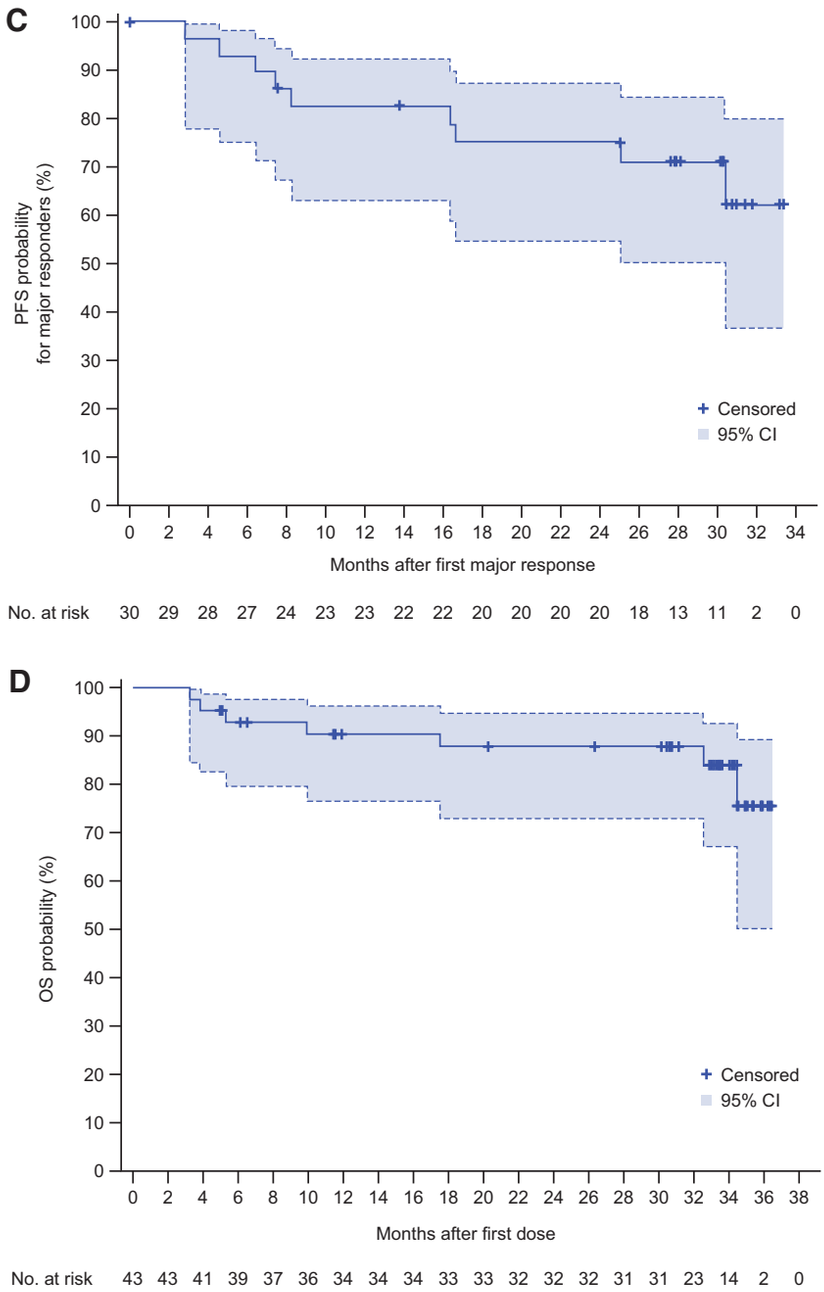


Figure 1.
(*Continued.*) **C,** PFS for major responders, as assessed by the investigator. **D,** CI, confidence interval; *CXCR4*, C-X-C motif chemokine receptor 4; *MYD88*, myeloid differentiation primary response gene 88; OS, overall survival; PFS, progression-free survival; R/R, relapsed refractory; WM, Waldenström macroglobulinemia; WT, wild-type; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome.

precipitated the need for treatment, most notably anemia, fatigue, hyperviscosity, and B symptoms. Thirty-six (83.7%) patients had an antilymphoma effect. Of these, 63.9% had a reduction in size of lymphadenopathy (the median maximum improvement from baseline was 73.4%), and 25.0% had a reduction in size of splenomegaly (the median maximum improvement from baseline was 80.0%).

The median baseline serum IgM level was 31.3 g/L (range, 9.3–96.5 g/L). The median maximal reduction from baseline in the level of serum IgM was 21.7 g/L (range, −13.5 to 61.2 g/L), and the median percentage reduction from baseline was 83.8%. Along with IgM reduction, hemoglobin concentration improved (Supplementary Fig. S3): the median maximal improvement from baseline was 31.0 g/L (range, -6.0 to 82.0 g/L), and the median percentage improvement was 32.2%.

As of the data cutoff date of January 11, 2021, the median duration of exposure was 934.0 days (range, 19–1104 days), and the median actual and relative dose intensities were 317.4 mg/day and 99.2%, respectively (see **Fig. 2** for a summary of patient disposition).

The most frequently reported TEAEs were neutrophil count decreased (59.1%), white blood cell count decreased (31.8%), upper respiratory tract infection, pneumonia and platelet count decreased (29.5% each), diarrhea (25.0%), weight increased (22.7%), and arthralgia (20.5%). Grade ≥3 AEs reported in ≥5% of patients included neutrophil count decreased (31.8%), platelet count decreased and pneumonia (20.5% each), white blood cell count decreased and hypertension (11.4% each), and anemia and upper respiratory tract infection (6.8% each; **Table 3**).

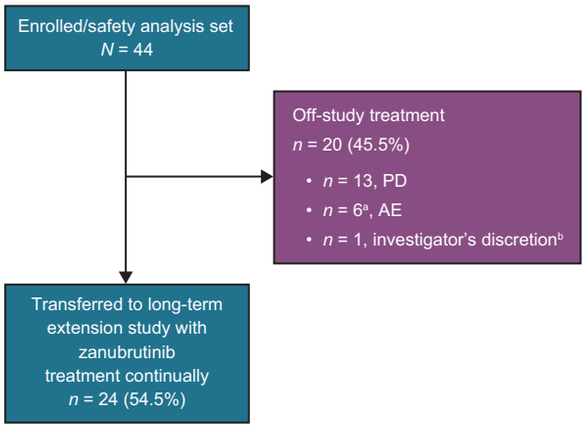


Figure 2.
Disposition of patients receiving zanubrutinib (median follow-up, 33.0 months). [a]One patient discontinued study treatment and subsequently died due to 'progression of WM' that was reported as an AE. [b]The patient achieved MR and was discontinued per the investigator's discretion. AE, adverse event; MR, minor response; WM, Waldenström macroglobulinemia; PD, progressive disease.

AEs of special interest with the highest prevalence included infections (79.5%), neutropenia (59.1%), hemorrhage (50.0%), thrombocytopenia (29.5%), hypertension (20.5%), and anemia (18.2%). The most frequently reported infections (all grades) were upper respiratory tract infection and pneumonia (29.5% each), and urinary tract infection (18.2%). Two (4.5%) patients had an infection that led to discontinuation of the study drug. The opportunistic infection incidence rate was 2.3% (one patient with pulmonary mycosis). Although neutropenia events were reported in 59.1% of patients, none of them were serious, grade 5, or febrile neutropenia. Ten patients received granulocyte colony-stimulating factor for the management of neutropenia, and no patient discontinued treatment due to neutropenia. Bleeding events, including minor events such as contusion and petechiae, were reported in 50.0% of patients. Almost all bleeding events were grade 1 or 2. Major hemorrhage was reported in two (4.5%) patients: one experienced grade 3 upper gastrointestinal hemorrhage, and the other had grade 3 ecchymosis and retinal hemorrhage. No cases of atrial fibrillation/flutter, skin cancer, or tumor lysis syndrome were reported (**Table 3**).

Serious AEs occurred in 25 (56.8%) patients. The most common (in at least two patients) were pneumonia [10 (22.7%) patients], upper respiratory tract infection [three (6.8%) patients], and skin infection and pleural effusion [two (4.5%) patients each].

AEs leading to treatment interruption occurred in 17 (38.6%) patients overall. According to the protocol, grade ≥3 treatment-related AEs necessitated immediate dose interruption rather than dose reduction, which may explain the high dose-interruption rate. AEs reported in two or more patients were pneumonia [six (13.6%) patients], platelet count decreased [three (6.8%) patients], and neutrophil count decreased and retinal hemorrhage [two (4.5%) patients each]. The median duration of treatment interruptions was 19.0 days (range, 3.5–50.0 days), including two patients who held treatment for procedure. Most initial treatment modifications occurred at or prior to cycle 6 (for five patients this happened at cycle 10 or later). Most patients resumed zanubrutinib after supportive treatment, with only two discontinuing after experiencing TEAEs that led to dose interruption. Dose reduction was allowed when an AE that had led to dose interruption recurred. Only one patient had dose reduction due to arthralgia. However, it was not a recurrent event. Dose reduction was based on the investigator's decision.

Table 3. Most common (≥10% in all patients) TEAEs (any grade) and AEs of special interest in Chinese patients with R/R WM receiving zanubrutinib.

	Patients (*N* = 44)	
TEAE by preferred term, *n* (%)	**All grade**	**Grade ≥3**
Neutrophil count decreased	26 (59.1)	14 (31.8)
White blood cell count decreased	14 (31.8)	5 (11.4)
Upper respiratory tract infection	13 (29.5)	3 (6.8)
Platelet count decreased	13 (29.5)	9 (20.5)
Pneumonia	13 (29.5)	9 (20.5)
Diarrhea	11 (25.0)	0
Weight increased	10 (22.7)	1 (2.3)
Arthralgia	9 (20.5)	1 (2.3)
Purpura	8 (18.2)	0
Urinary tract infection	8 (18.2)	1 (2.3)
Rash	8 (18.2)	0
Anemia	8 (18.2)	3 (6.8)
Hypertension	8 (18.2)	5 (11.4)
Decreased appetite	7 (15.9)	0
Cough	6 (13.6)	0
Hypoalbuminemia	6 (13.6)	0
Nasopharyngitis	6 (13.6)	0
Pyrexia	6 (13.6)	0
Hypokalemia	6 (13.6)	1 (2.3)
Hyperglycemia	5 (11.4)	1 (2.3)
Alanine aminotransferase increased	5 (11.4)	0
Aspartate aminotransferase increased	5 (11.4)	0
Chest discomfort	5 (11.4)	1 (2.3)
AESI category, *n* (%)	**Any grade**	**Grade ≥3**
Hemorrhage	22 (50.0)	2 (4.5)
Major hemorrhage	2 (4.5)	2 (4.5)
Hypertension	9 (20.5)	5 (11.4)
Infections	35 (79.5)	20 (45.5)
Opportunistic infections	1 (2.3)	1 (2.3)
Neutropenia	26 (59.1)	14 (31.8)
Anemia	8 (18.2)	3 (6.8)
Thrombocytopenia	13 (29.5)	9 (20.5)
Second primary malignancies	3 (6.8)	3 (6.8)
Skin cancer	0	0
Atrial fibrillation/flutter	0	0
Tumor lysis syndrome	0	0

Abbreviations: AEs, adverse events; AESI, adverse event of special interest; R/R, relapsed/refractory; TEAEs, treatment-emergent adverse events; WM, Waldenström macroglobulinemia.

In total, six (13.6%) patients experienced AEs that led to study drug discontinuation, including five (11.4%) patients who experienced TEAEs that led to study drug discontinuation. One patient discontinued treatment more than 30 days after the last dose of zanubrutinib due to "retinal hemorrhage"; this was not counted as a TEAE leading to study drug discontinuation. TEAEs in four of these patients were (one patient each) pneumonia, laryngeal cancer, WM (reported by the investigator as an AE due to unexpected rapid progression of WM and suspected transformation to aggressive lymphoma), and intracranial mass (MRI and cerebrospinal fluid confirmed WM involvement and disease progression); the fifth patient experienced both acute hepatitis B (grade 5) and multiple organ dysfunction syndrome (grade 5).

Seven (15.9%) patients died during the study: three due to disease progression, three due to AEs, and one due to severe pneumonia and

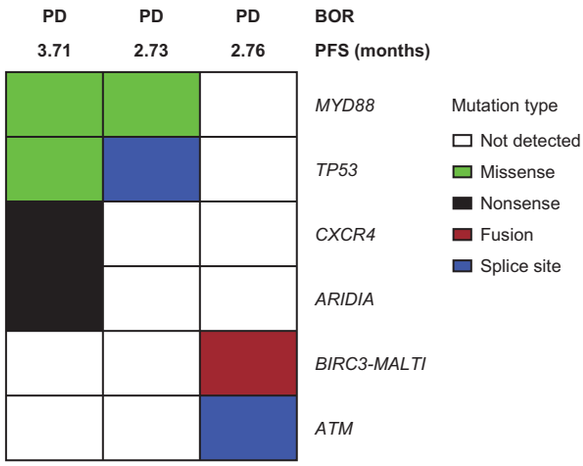


Figure 3.

Genetic variants in three progressive disease samples in Chinese patients with R/R WM. Abbreviations: BOR, best overall response; BOR, best overall response; *CXCR4*, C-X-C motif chemokine receptor 4; *MYD88*, myeloid differentiation primary response gene 88; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia; PD, progressive disease; PFS, progression-free survival.

respiratory failure (occurring 972 days after the last dose of zanubrutinib). Of the three patients who died as a result of AEs, two died within 30 days of receiving the last dose of study drug: one was due to acute hepatitis B and multiple organ dysfunction syndrome, both of which were related to study drug per investigator judgment; the other was recorded as "unknown reason" (the investigator concluded that the death was due to WM progression, which was reported as an AE, and accompanying respiratory failure that was unlikely to be related to the study drug). The third patient died due to progression of WM, which was reported as an AE by the investigator.

To study zanubrutinib resistance mechanisms, three disease-progression samples were sequenced. All three patients—one with *MYD88*^{WT} and two with *MYD88*^{L265P} mutations—failed to respond to zanubrutinib treatment and progressed within 4 months. An *ATM* splice site mutation and *BIRC3-MALT1* fusion were found in the *MYD88*^{WT} sample, and both *MYD88* mutant samples had *TP53* mutations, with one sample also having *CXCR4* and *ARID1A* mutations (**Fig. 3**).

Discussion

WM is characterized by the overproduction of IgM by malignant lymphoplasmacytic B cells. Although WM can remain asymptomatic for a long time, patients requiring therapy usually present with a myriad of clinical manifestations due to elevated or otherwise pathologic IgM. Recently, BTK inhibitor therapy has gained acceptance based on results from phase II and III studies of ibrutinib, which demonstrated compelling evidence of efficacy in patients with R/R WM (10, 21). Although it was generally well tolerated, ibrutinib monotherapy led to substantial toxicities, including diarrhea (38%), hemorrhage (28%), rash (21%), nausea (21%), musculoskeletal pain (21%), muscle spasms (19%), and fatigue (18%; ref. 22). Inhibition of off-target kinases such as EGFR, TEC, and IL2-inducible T-cell kinase (ITK), is thought to underlie many of the toxicities, including diarrhea, bleeding, and atrial fibrillation (12, 23–25). Acalabrutinib is a BTK inhibitor being investigated in R/R WM; however, the VGPR rate in the phase II study was only 9% (26). These results point to there being a need for a new BTK inhibitor that can demonstrate improved efficacy and tolerability in R/R WM.

Zanubrutinib is a novel, small-molecule inhibitor of BTK. In kinase inhibition and cell-based assays, it was more selective than ibrutinib for inhibition of BTK, exhibiting less off-target activity against EGFR, TEC, ITK, and other kinases; it is therefore predicted to have fewer and less severe toxicities such as hypertension, diarrhea, bleeding (23, 24), and atrial fibrillation (14). Compared with acalabrutinib (27), zanubrutinib achieved approximately tenfold higher exposure in human subjects and it has a longer half-life. These findings support the potential for zanubrutinib to have better efficacy and tolerance.

The current study is the first to evaluate the efficacy and safety of zanubrutinib with a focus on Asian patients with R/R WM, a population underrepresented in previous BTK inhibitor clinical trials. Baseline demographics were, in general, representative of patients with R/R WM. However, disease characteristics suggested the study population was composed of patients with R/R WM with a relatively poor prognosis. Patients had received a median of two prior anticancer regimens. The median time from the initial diagnosis to the first dose was relatively short at 1.58 years, and 45.5% of patients were classified as high risk as per the IPSSWM. Furthermore, 68.2% (30/44) of patients had best response to the last regimen of stable disease or PD (22.7% for PD). Patients also had a high percentage of peripheral blood cytopenias at baseline, (particularly anemia; 75.0%), a high proportion (72.7%) had extramedullary disease, nearly half (43.2%) had IgM ≥40 g/L, and over three-quarters had serum β2-microglobulin >3 mg/L. Further evidence that patients enrolled in this study had poor prognosis and aggressive disease, was the high rate of early disease progression or death. Nearly 40% of patients (7/18) who had disease progression or death as of the data cutoff date (January 11, 2021) had those events recorded either before or at the first tumor assessment.

Meaningful clinical benefit from zanubrutinib treatment was achieved in this study, despite the poor health of the patients enrolled. More than two-thirds (69.8%) of patients achieved a major response after a median follow-up of 33.0 months. Onset of response was rapid, as evidenced by the median times to overall and major response (both approximately 3 months) and in consideration of the fact that the first on-treatment response assessment was scheduled at week 12. Responses were durable, as demonstrated by the median of DOMR not being reached after a longer median follow-up of 33.0 months.

At the sixth IWWM, a new category of response, VGPR, defined as a ≥90% reduction in serum IgM with a reduction in the extent of extramedullary disease, was adopted. This addition recognized the predictive value of VGPR for PFS, and the distinction between VGPR (≥90% IgM reduction) and PR (≥50% but <90% IgM reduction) in relation to PFS (18). With chemoimmunotherapy in WM, patients with VGPR have PFS outcomes indistinguishable from CR (28). In this study, a high VGPR rate was reached (32.6%); in patients with *MYD88*^{L265P}, the VGPR rate was 35.1%. This is consistent with the trend seen in the ASPEN study (20% vs. 29% in patients with R/R WM on ibrutinib or zanubrutinib treatment, respectively; ref. 14). The VGPR rate was also higher than the 9% recorded in the acalabrutinib study (26).

In general, the benefits of zanubrutinib shown in this study are comparable with results in the phase III ASPEN trial, even though the target populations, study designs, and disease characteristics of enrolled patients differed between the two studies. Patients receiving zanubrutinib in both studies achieved deep and durable responses. This is consistent with a recent report that the pharmacokinetics of zanubrutinib were similar in Chinese and non-Chinese patients (29). The median actual and relative dose intensities were very high in the

present study, thus demonstrating that zanubrutinib has a tolerable and manageable safety profile. The AE profile was generally consistent with previous findings. Most patients experiencing dose interruption resumed treatment following supportive treatment; although five patients were reported by investigators as having AEs leading to treatment discontinuation, two of them were subsequently proved to have disease progression. Similarly, investigators eventually determined that two of the three patients who died due to AEs in fact had disease progression. AEs of special interest were defined based on the known and theoretical toxicity profile for the class of BTK inhibitors. Although hemorrhage was observed in 50.0% of patients, only two patients experienced major hemorrhage. In line with the experience of zanubrutinib to date, most AEs were mild or moderate cutaneous bruising or mucosal bleeding. Importantly, no atrial fibrillation/flutter AEs occurred. Five (11.4%) patients experienced the TEAE of grade ≥3 hypertension. Infections were relatively common; consistent with prior clinical experience with BTK inhibitors and the natural history of the underlying disease, most were mucosal infections involving the respiratory and urinary tracts. Even so, few patients (4.5%) discontinued zanubrutinib as the result of infection. Similarly, peripheral blood cytopenias (especially neutropenia) were expected and common given their high prevalence at baseline, but they were rarely serious and were effectively managed without significant compromise to study treatment.

Activating mutation L265P in *MYD88* is present in more than 90% of patients with WM and triggers prosurvival signals such as NF-κB, PI3K/AKT, MAPK, and STAT pathways through activating tyrosine-protein kinases including BTK, hematopoietic cell kinase, and spleen tyrosine kinase. The *CXCR4* mutation, the most common mutation in *MYD88* mutant WM, promotes sustained activation of AKT and ERK pathways (30) and is associated with an inferior response to ibrutinib (10). In the current study, the mutation rate of *MYD88* and *CXCR4* was relatively low compared with previously published results (10). This may be because use of bone marrow samples without CD19+ cell enrichment would have led to a lower frequency of the mutation allele in the sample, which may not have been detected by the NGS assay because of its limit of detection of 1.5%. Based on current genomic data, patients with $MYD88^{L265P}/CXCR4^{WT}$ benefited more from zanubrutinib treatment than patients with $MYD88^{L265P}/CXCR4^{WHIM}$ or $MYD88^{WT}$. The rates of VGPR, major response, and overall response for patients with $MYD88^{L265P}/CXCR4^{WT}$ were 40.6%, 75.0%, and 81.3%, respectively, and for patients with $MYD88^{WT}$ were 16.7%, 50.0%, and 66.7%; for patients with $MYD88^{L265P}/CXCR4^{WHIM}$ these rates were 0%, 60.0%, and 60.0%. Meanwhile three of six patients with $MYD88^{WT}$ achieved major response, which is higher than in the ibrutinib phase II study (10). *TP53* mutations are present in 2% to 3% of patients with WM (30) and associated with shorter OS with rituximab-based regimens or chemotherapy (31). Preclinical data show that ibrutinib reduces cell survival in both *TP53* wild type and mutant WM cells, but *TP53* mutant cells have less survival inhibition effect (31). This study detected *TP53* mutations in two out of three disease progression samples, and one had *CXCR4* mutation. The effect of *TP53* mutation on the response of BTK inhibitors in WM needs to be further evaluated in a larger patient population.

Mutations found in patients with $MYD88^{WT}$ WM are predicted to activate the NF-κB pathway, impart epigenetic dysregulation, and impair DNA damage repair. Most of the mutations are also present in aggressive B-cell lymphoma (32). *BIRC3-MALT1* fusion has been reported to activate the NF-κB pathway through inhibition of *BCL10* degradation and has been found in 15% to 40% of MALT lymphomas (33). The current study found *BIRC3-MALT1* fusion in a patient with $MYD88^{WT}$ WM who did not respond to zanubrutinib treatment, thereby uncovering a novel mechanism of NF-κB pathway activation in WM and indicating that activation of the NF-κB pathway in WM may be involved in BTK inhibitor primary resistance.

A limitation of the current study is the single-arm design, which makes efficacy and safety comparisons with other BTK inhibitors difficult. The ongoing phase III ASPEN study comparing zanubrutinib with ibrutinib in patients with WM has recently been published, thus allowing further direct comparison of these two BTK inhibitors (14). Another limitation of the study is the difference in prior therapy compared with other studies conducted outside China. Because rituximab has not been approved in WM in China so it can't be reimbursed, the affordability is a big issue. Seventy-five percent of patients in this study received anti-CD20 antibody, while the percentage was higher in studies implemented in the USA and Europe (ibrutinib study, 90%; ref. 10; acalabrutinib study, 88%; ref. 26). Finally, unsorted bone marrow was used for mutation analysis, and the NGS assay, which had a limit of detection of 1.5%, may not have been sensitive enough to detect low-frequency mutations: the mutation rate found in this study was 84% *MYD88* and 13.6% *CXCR4*, compared with 89% *MYD88* and 34% *CXCR4* in previously published studies (34).

Conclusions

In this study, zanubrutinib achieved high, deep, rapid, and durable responses in patients with R/R WM. Response differences were found in different mutations, the highest being in the $MYD88^{L265P}/CXCR4^{WT}$ population. Patients with $MYD88^{wt}$ mutation also benefited from zanubrutinib treatment. Along with the observed safety data, zanubrutinib has the potential to confer a favorable benefit–risk profile in patients with R/R WM. Additionally, as a selective BTK inhibitor, zanubrutinib offers the potential for improved efficacy and tolerability over existing treatment options.

Data Sharing

Additional data are provided in the data supplement available online. Individual participant data will not be shared prior to regulatory approval of zanubrutinib for the treatment of WM. Requests for copies of the protocol and statistical analysis plan will be considered: qiulg@ihcams.ac.cn

Authors' Disclosures

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Authors' Contributions

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formal analysis, methodology, writing–original draft, project administration, writing–review and editing. **J. Zhong:** Conceptualization, data curation, formal analysis, methodology, project administration, writing–review and editing. **Y. Yu:** Conceptualization, methodology, project administration, writing–review and editing. **B. Wu:** Conceptualization, formal analysis, methodology, project administration, writing–review and editing. **L. Qiu:** Data curation, writing–review and editing.

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