Adv Ther (2025) 42:2937–2949
https://doi.org/10.1007/s12325-025-03202-x

ORIGINAL RESEARCH

Indirect Comparisons of Efficacy of Zanubrutinib Versus Orelabrutinib in Patients with R/R MCL: An Extended Follow-up Analysis

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Received: October 30, 2024 / Accepted: April 8, 2025 / Published online: May 3, 2025

ABSTRACT

Introduction: Our previous study has suggested a favorable progression-free survival (PFS) with zanubrutinib over orelabrutinib in patients with relapsed or refractory mantle cell lymphoma (R/R MCL). Here, we conducted an updated analysis to indirectly compare the long-term efficacy between zanubrutinib and orelabrutinib in patients with R/R MCL.

Methods: Individual patient data from the zanubrutinib study were adjusted to match the patient population profile of the orelabrutinib study. An unanchored matching-adjusted indirect comparison (MAIC) was performed to adjust for effect modifiers and prognostic variables. The efficacy outcomes included investigator-assessed PFS, overall survival (OS), and overall response rate (ORR). Response evaluations were only computed tomography (CT)-based assessments in the orelabrutinib study, while positron emission tomography (PET)- and CT-based assessment were both performed in the zanubrutinib study. The comparison of PFS assessed by CT between zanubrutinib and orelabrutinib was the primary result.

Lijuan Deng and Yuqin Song contributed equally to this study.

Prior Presentation: Yuqin Song, et al. *Blood* 2023; 142 (Suppl 1): 1682 (https://doi.org/10.1182/blood-2023-181352).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-025-03202-x.

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***Results*:** After matching, the baseline characteristics were balanced between zanubrutinib and orelabrutinib, with an effective sample size of 70 in the zanubrutinib study. PFS assessed by CT was significantly longer in the zanubrutinib study vs. the orelabrutinib study (median PFS, not reached vs. 22.0 months; hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.34–0.86; $P=0.009$). With longer follow-up, OS continued to trend favorably for zanubrutinib, with OS rate at 24 months numerically higher (83.7% vs. 74.3%); no statistical difference was observed (HR 0.68, 95% CI 0.36–1.27; $P=0.223$). ORR was numerically higher in the zanubrutinib study (85.5% vs. 82.1%; odds ratio 1.28, 95% CI 0.56–2.94; $P=0.556$).
***Conclusion*:** MAIC results demonstrated that zanubrutinib had significantly longer PFS compared with orelabrutinib in the treatment of patients with R/R MCL.

Keywords: Zanubrutinib; Orelabrutinib; Matching-adjusted indirect comparison; Progression-free survival; Relapsed or refractory mantle cell lymphoma

Key Summary Points

Why carry out this study?

Mantle cell lymphoma (MCL) is a rare, aggressive, and incurable subtype of B cell non-Hodgkin lymphoma.

We carried out an updated analysis to compare the long-term efficacy between zanubrutinib and orelabrutinib in patients with R/R MCL.

What was learned from this study?

MAIC results indicated that zanubrutinib had significantly longer PFS when treating patients with R/R MCL in comparison to orelabrutinib.

With longer follow-up, OS continued to trend favorably for zanubrutinib, with OS rate at 24 months numerically higher than orelabrutinib (83.7% vs. 74.3%).

INTRODUCTION

Mantle cell lymphoma (MCL) is a rare, aggressive, and incurable subtype of B cell non-Hodgkin lymphoma that characterized by a relapsing clinical course and poor long-term outcome [1, 2]. Bruton's tyrosine kinase (BTK) inhibitors have greatly improved the outcomes of relapsed

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or refractory (R/R) MCL [3–5] and are among the most effective treatment therapies for patients with R/R MCL.

Ibrutinib, a first-generation BTK inhibitor, demonstrated favorable responses in patients with R/R MCL [3] but is associated with off-target toxicities, such as diarrhea, atrial fibrillation, bleeding, etc. [6, 7], which could limit its continuous use. The next-generation BTK inhibitors with less off-target effects include acalabrutinib, zanubrutinib, and orelabrutinib. Acalabrutinib was approved for the treatment of R/R MCL on the basis of a phase 2 study with 15.2 months follow-up [4]. The final results of the phase 2 study with median 38.1 months follow-up showed that overall response rate (ORR) was 81.5%, complete response (CR) rate was 47.6%, median progression-free survival (PFS) was 22.0 months, and median overall survival (OS) was 59.2 months [8]. Zanubrutinib, a highly selective, potent, next-generation BTK inhibitor, has demonstrated favorable safety [9, 10] and superior efficacy [9–11] over ibrutinib in two phase 3, randomized studies in Waldenström macroglobulinemia (ASPEN study) and R/R chronic lymphocytic leukemia/small lymphocytic lymphoma (ALPINE study). Zanubrutinib received accelerated approval for patients with MCL with at least one prior therapy in the USA on the basis of a phase 2 study (BGB-3111-206) with 18.4 months follow-up [5]. With long-term median follow-up of 35.3 months, the ORR was 83.7%, CR rate was 77.9%, median PFS was 33.0 months, and median OS was not reached (NR) [12]. Orelabrutinib, another novel next-generation BTK inhibitor, was approved in China for the treatment of patients with R/R MCL with at least one prior therapy. In the phase I/II study (ICP-CL-00102), with a median follow-up of 23.8 months, the ORR was 81.1%, CR rate was 27.4%, median PFS was 22.0 months, and median OS was NR [13].

All of the next-generation BTK inhibitors exhibited a favorable efficacy in patients with R/R MCL. The potential differences between these next-generation BTK inhibitors are of great interest for clinicians and might provide useful information for future research. However, no head-to-head study has compared the next-generation BTK inhibitors.

Zanubrutinib demonstrates a higher unbound trough half-maximal inhibitory value (IC_{50}) concentration ratio compared to orelabrutinib [14], a critical pharmacokinetic/pharmacodynamic determinant ensuring near-complete BTK inactivation throughout the dosing interval. This pharmacokinetic profile minimizes BTK signaling rebound by preventing target re-engagement during drug trough periods, a phenomenon not consistently observed with orelabrutinib. Whether these differences will lead to differences in clinical efficacy still needs further confirmation.

We previously conducted an indirect comparison to estimate the efficacy between zanubrutinib and orelabrutinib in the treatment of R/R MCL, and results suggested a higher CR rate and favorable PFS with zanubrutinib over orelabrutinib [15]. Here, we conducted an updated analysis to indirectly compare the long-term efficacy between zanubrutinib (median follow-up 35.3 months) and orelabrutinib (median follow-up 23.8 months) in patients with R/R MCL.

METHODS

Individual patient data from the zanubrutinib study (BGB-3111-206) were adjusted to match the patient population profile of the orelabrutinib study (ICP-CL-00102). As both trials were single-arm and were not linked through a common control arm, an unanchored matching-adjusted indirect comparison (MAIC) was performed to adjust for effect modifiers and prognostic variables. Ethics committee approval was not required for the study. For the zanubrutinib trial, the study was designed and monitored in accordance with sponsor procedures in compliance with the ethical principles of Good Clinical Practice, International Conference on Harmonization guidelines, the Declaration of Helsinki, and applicable local regulatory requirements. All patients provided written informed consent. The protocol, any amendments, and informed consent forms were reviewed and approved by the institutional review boards/independent ethics committees. For the orelabrutinib trial, all patients provided written informed consent [13].

Data Sources

BGB-3111-206

BGB-3111-206 is a multicenter, single-arm, phase II study (n = 86; ClinicalTrials.gov NCT03206970) conducted in China to evaluate the efficacy and safety of zanubrutinib in the treatment of patients with R/R MCL. Patients with R/R MCL received zanubrutinib (160 mg BID) until progressive disease (PD), unacceptable toxicity, death, or withdrawal of consent. Key eligibility criteria included central pathologically confirmed MCL with measurable disease (at least one but fewer than five prior lines of therapy), relapse or failure to achieve at least partial response (PR) to last regimen, age 18 to 75 years, and Eastern Cooperative Oncology performance status (ECOG PS) ≤ 2.

The primary endpoint was ORR assessed by the independent review committee (IRC). Secondary endpoints included investigator-assessed ORR, duration of response (DOR), and PFS. The exploratory endpoint was OS.

There are several publications on the BGB-3111-206 study [5, 12]. The publication which had the comparable median follow-up time of 35.3 months with the orelabrutinib study [12] was used as the source data of zanubrutinib. Patients in the BGB-3111-206 study are still followed up for long-term outcomes.

ICP-CL-00102

ICP-CL-00102 is a multicenter, phase I/II study (n = 106; ClinicalTrials.gov NCT03494179) comprising two stages to investigate the efficacy and safety of orelabrutinib in Chinese patients with R/R MCL. In the first stage, patients with R/R MCL were randomized to receive the orelabrutinib at 100 mg BID or 150 mg once daily. In the second stage, additional patients were enrolled to receive orelabrutinib 150 mg once daily. Key eligibility criteria were age 18–75 years, histopathological confirmed patients with MCL, ECOG PS of 0–2, 1–4 prior lines of therapy, and relapsed or failed to achieve response. The primary endpoint was ORR assessed by the IRC. Secondary endpoints were ORR assessed by investigator, DOR, PFS, and OS.

There is only one published report on the ICP-CL-00102 study, with a median follow-up time of 23.8 months [13], which was used as the aggregated data source for orelabrutinib.

The study design, key eligibility criteria, and endpoints were similar between the BGB-3111-206 study and ICP-CL-00102 study (Supplementary Table 1).

Efficacy Outcomes

Efficacy outcomes included investigator-assessed PFS, OS, and ORR. CR was not included and analyzed because there was no positron emission tomography (PET)-based assessment in the orelabrutinib study. The definitions of PFS, OS, and ORR were similar between the BGB-3111-206 study and ICP-CL-00102 study. PFS was defined as the time from starting treatment to the date of disease progression or death, whichever occurred first. OS was defined as the time from treatment to death. ORR was defined as the proportion of patients achieving either a PR or CR according to the Revised International Working Group Criteria for Malignant Lymphomas (the Lugano classification) [16].

Response evaluations as assessed by the investigator and IRC were based on PET scans and computed tomography (CT) with contrast in the BGB-3111-206 study. The response assessment was only based on CT in the ICP-CL-00102 study. We did not analyze the CR rate because of the lack of PET results in the orelabrutinib study, and PET is the 2014 Lugano recommendation to assess CR [17].

Since the different response evaluations would have an impact on PFS, we treated the comparison of PFS assessed by CT between zanubrutinib and orelabrutinib as the primary result while the comparison of PFS assessed by PET in the zanubrutinib study versus the PFS assessed by CT in the orelabrutinib study as a supplementary result.

Statistical Analysis Methods

An unanchored MAIC was conducted in patients with R/R MCL. MAIC is a propensity-score-weighting-based method to generate comparative effectiveness evidence when individual patient data (IPD) are available in one study and aggregate data in another [18]. In this analysis, the unanchored MAIC adjusts the mean of effect modifiers and prognostic factors in BGB-3111-206 to match those reported characteristics for ICP-CL-00102.

The first step when implementing an MAIC is to align the patient population of the trials to be compared. Patients across two trials were matched on available potential effect modifiers and prognostic variables, including sex, bulky disease, bone marrow involvement, disease stage, simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI), prior autologous stem cell transplantation (ASCT), and the number of prior lines of treatment. Age and ECOG PS were not included in the model because these two factors were already included in the sMIPI score. A matching model with age and ECOG PS included was also conducted as a sensitivity analysis. The baseline characteristics to be matched in MAIC were selected on the basis of the preliminary feasibility assessment and discussions with clinical experts. The weight of individual patients was calculated by the method of moments, following the published guidance from the National Institute for Health and Care Excellence Decision Support Unit [19]. The weighted efficacy outcomes of BGB-3111-206 were compared with those reported in ICP-CL-00102. The survival outcomes of ICP-CL-00103 were estimated from the pseudo-IPD generated from the digitized Kaplan–Meier curve and the at-risk table of ICP-CL-00102 [20]. The hazard ratio (HR) and the odds ratios (OR) with 95% confidence interval (CI) and *P* value of the outcomes between two trials were estimated by the weighted Cox model and logistic regression model, respectively.

RESULTS

Baseline Characteristics

Eighty-six patients from BGB-3111-206 and 106 patients from the ICP-CL-00102 study were included in this analysis (Supplementary Table 2). The baseline characteristics were generally balanced between zanubrutinib and orelabrutinib groups (all $P \geq 0.05$). However, patients in the zanubrutinib group had a higher percentage of at least two prior lines of therapy (70% vs. 55%) and lower percentage of prior ASCT (3% vs. 8%) compared with the orelabrutinib group. After matching, the baseline characteristics were well balanced between the two groups (all $P = 1$; Table 1), with an effective sample size (ESS) of 70 in the zanubrutinib group.

Efficacy Outcomes

PFS

With a median follow-up of 35.3 months in the zanubrutinib group and 23.8 months in the orelabrutinib group, the median PFS assessed by CT was NR in the zanubrutinib group before and after matching and it was 22.0 months in the orelabrutinib group. After matching, PFS assessed by CT was statistically significantly longer in the zanubrutinib group than in the orelabrutinib group (HR 0.54, 95% CI 0.34–0.86; $P = 0.009$) (Table 2, Fig. 1). Before matching, the original PFS assessed by CT was also significantly longer in the zanubrutinib group compared with orelabrutinib (HR 0.61, 95% CI 0.39–0.94; $P = 0.025$) (Table 2, Fig. 1). Patients in the zanubrutinib group had numerically higher PFS rates at months 12 and 24 than the patients in the orelabrutinib group (after matching: 80.1% vs. 65.1%; 67.3% vs. 46.5%) (Table 2).

As a supplementary analysis, we compared the PFS assessed by PET for zanubrutinib with the PFS assessed by CT for orelabrutinib and PFS was also significantly better in the zanubrutinib group than in the orelabrutinib group (after matching: median PFS, NR vs. 22.0 months; HR

Table 1 Baseline characteristics of zanubrutinib versus orelabrutinib before and after matching

Characteristics, %	ICP-CL-00102	BGB-3111-206			
	Orelabrutinib ($n = 106$)	Before matching		After matching	
		Zanubrutinib ($n = 86$)	*P*	Zanubrutinib (ESS = 70)	*P*
Male	79%	78%	0.96	79%	1
Bulky disease LD ≥ 5 cm	39%	45%	0.43	39%	1
Bone marrow involvement	41%	45%	0.60	41%	1
Stage III	21%	16%	0.55	21%	1
Stage IV	74%	74%	1	74%	1
Prior lines of treatment ≥ 2	55%	70%	0.05	55%	1
sMIPI high risk	12%	9%	0.83	12%	1
sMIPI intermediate risk	33%	34%	1	33%	1
Prior ASCT	8%	3%	0.37	8%	1

LD longest diameter, *sMIPI* simplified Mantle Cell Lymphoma International Prognostic Index, *ESS* effective sample size, *ASCT* autologous stem cell transplantation

0.63, 95% CI 0.40–0.99; $P = 0.044$) (Fig. 2). The 12- and 24- month PFS rates were also numerically higher in the zanubrutinib group compared with the orelabrutinib group (after matching: 78.6% vs. 65.1%; 62.2% vs. 46.5%). Though PET-based assessment was more sensitive than CT in detecting disease progression [21], disease progression can be identified earlier by PET than by CT, a statistically significant difference on PFS was still observed between zanubrutinib (PET-based) and orelabrutinib (CT-based).

OS

With the limited follow-up time, the median OS rates were both NR for zanubrutinib and orelabrutinib. Although no statistical significance was achieved, the OS trended favorably for zanubrutinib compared to orelabrutinib (after matching: HR 0.68, 95% CI 0.36–1.27; $P = 0.223$) (Table 2, Fig. 3). The 12- and 24-month OS rates were both numerically higher in the zanubrutinib group compared with the orelabrutinib group (after matching: 85.1% vs. 83.9%; 83.7% vs. 74.3%). The pre-matching OS results were consistent with the post-matching results (Table 2).

ORR

ORR was 83.7% and 85.5% in the zanubrutinib group before and after matching, respectively. And ORR was 82.1% in the orelabrutinib group. ORR was numerically higher in the zanubrutinib group compared with the orelabrutinib group before (OR 1.12, 95% CI 0.53–2.40; $P = 0.764$) and after matching (OR 1.28, 95% CI 0.56–2.94; $P = 0.556$) (Table 2).

Sensitivity Analysis

The sensitivity analysis results were consistent with the comparative findings. After matching, the ESS was 48 in the zanubrutinib group (Supplementary Table 3). PFS assessed by CT was significantly longer in the zanubrutinib group than in the orelabrutinib group (after matching: HR 0.59, 95% CI 0.36–0.97; $P = 0.038$) (Fig. 4). After matching, with longer follow-up, OS continued to trend favorably for zanubrutinib, with OS rates at 12 and 24 months numerically higher (84.7% vs. 83.9%; 82.0% vs. 74.3%); no statistical difference was observed

Table 2 The efficacy comparison between zanubrutinib and orelabrutinib before and after matching

Outcomes	Before matching			After matching		
	Zanubrutinib ($n = 86$)	Orelabrutinib ($n = 106$)	*P*	Zanubrutinib (ESS = 70)	Orelabrutinib ($n = 106$)	*P*
Median follow-up, months	35.3	23.8		–	–	
PFS						
Median PFS (95% CI), months	NR (26.4, NR)	22.0 (13.8, NR)		NR (27.7, NR)	22.0 (13.8, NR)	
HR (95% CI)	0.61 (0.39–0.94)		0.025	0.54 (0.34–0.86)		0.009
12-month PFS rate	77.5%	65.1%		80.1%	65.1%	
24-month PFS rate	63.9%	46.5%		67.3%	46.5%	
OS						
Median OS (95% CI), months	NR	NR		NR	NR	
HR (95% CI)	0.84 (0.46–1.51)		0.550	0.68 (0.36–1.27)		0.223
12-month OS rate	83.0%	83.9%		85.1%	83.9%	
24-month OS rate	80.4%	74.3%		83.7%	74.3%	
ORR	83.7%	82.1%		85.5%	82.1%	
OR (95% CI)	1.12 (0.53–2.40)		0.764	1.28 (0.56–2.94)		0.556

PFS progression free survival; *OS* overall survival; *ORR* overall response rate; *HR* hazard ratio; *OR* odds ratio; *NR* not reached; *ESS* effective sample size; *CI* confidence interval

between zanubrutinib and orelabrutinib (HR 0.75, 95% CI 0.37–1.51; $P = 0.421$). ORR was similar between the two groups (after matching: OR 0.92, 95% CI 0.38–2.20; $P = 0.850$).

DISCUSSION

In this analysis with extended follow-up, we further demonstrated the better efficacy of zanubrutinib over orelabrutinib in the treatment of R/R MCL with respect to the PFS. MCL is a relatively rare lymphoma subtype and accounts for between 2% and 6% of all patients diagnosed with non-Hodgkin lymphoma in China [22]. The goal of MCL treatment is to prolong disease remission while minimizing toxicity, making nonchemotherapeutic approaches with active agents attractive [23]. Recently, BTK inhibitors have become a mainstay of therapy for patients with R/R MCL, with several developed for this indication in China. Although next-generation BTK inhibitors zanubrutinib and orelabrutinib both showed benefits for patients with R/R MCL in China, and with recommendation in guidelines, a comparison between the two BTK inhibitors is lacking, and there is no consensus on the best treatment options in the second-line settings. In our previous study, with a median follow-up of 18.4 months in the zanubrutinib group and 16.4 months in the orelabrutinib group, median PFS was NR either and PFS was

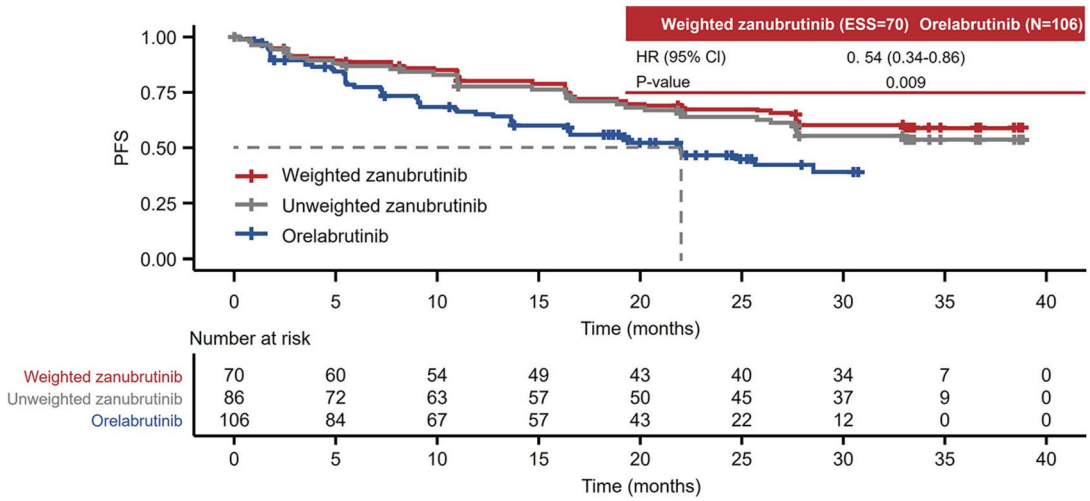

Fig. 1 PFS assessed by CT for zanubrutinib versus orelabrutinib. *PFS* progression-free survival, *ESS* effective sample size, *HR* hazard ratio, *CI* confidence interval

favorable for zanubrutinib over orelabrutinib [15]. In this study, with an extended median follow-up of 35.3 months in the zanubrutinib group and 23.8 months in the orelabrutinib group, PFS in the zanubrutinib group, regardless of CT or PET-based assessment, was significantly longer than in the orelabrutinib group (CT-based assessment). Based on the Lugano criteria, PET-based assessment is considered a driver in lymphoma response assessment rather than CT [17]. However, only CT-based assessment was performed in the orelabrutinib study. To make the analysis more comparable, the comparison of PFS assessed by CT was the primary result (HR 0.54, 95% CI 0.34–0.86; P= 0.009). Meanwhile, we also compared the PFS assessed by PET for zanubrutinib with the PFS assessed by CT for orelabrutinib as additional information. Though PET-based assessment was more sensitive to detect disease progression than CT [21], we still observed that PFS was statistically significantly longer in the zanubrutinib group (PET-based) than the orelabrutinib group (CT-based) (HR 0.63, 95% CI 0.40–0.99; P= 0.044). Tam et al. observed that zanubrutinib maintains a concentration above its IC_{50}, which is 0.71 nM at a daily dosage of 320 mg, regardless of whether it is administered once or twice daily. The concentration at the end of the dosing interval is seven times and two times the IC_{50} for these schedules, ensuring consistently higher levels over a 24-h period [14]. The IC_{50} value of orelabrutinib is 15 nM at a daily dosage of 150 mg. When targeting BTK, zanubrutinib's IC_{50} value is notably lower (0.71 vs. 15 nM) than that of orelabrutinib [24]. Clinically, achieving higher ratios of drug concentration to IC_{50} at doses that are well tolerated is anticipated to result in more prolonged inhibition of BTK [14]. Compared with orelabrutinib, zanubrutinib sustains a comparatively elevated ratio of unbound trough concentration to IC_{50}. This contributes to the continuous and complete deactivation of BTK within target tissues, allowing for the consistent replenishment of unbound BTK during the dosing period, which might account for the improved survival profile of zanubrutinib over orelabrutinib in this indirect comparison analysis. Since no head-to-head study has compared any two next-generation BTK inhibitors, our study suggests that regarding the efficacy difference between zanubrutinib and orelabrutinib, zanubrutinib had significantly better PFS than orelabrutinib in the treatment of patients with R/R MCL.

In this study, we also compared the OS between zanubrutinib and orelabrutinib. With the relatively short follow-up time, median OS was NR in both groups. As a result of the very limited number of OS events, the analysis of OS

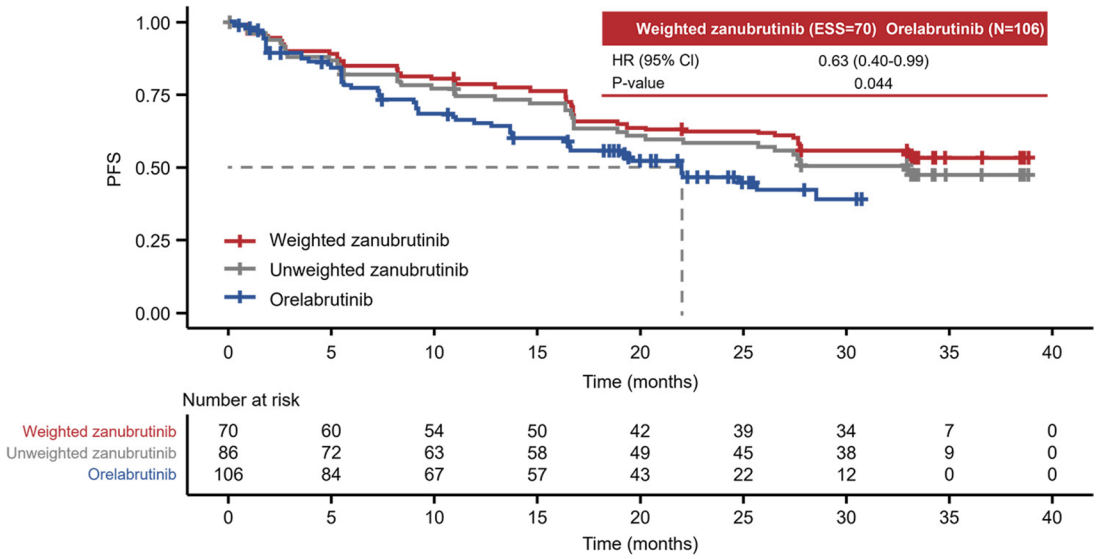

Fig. 2 PFS assessed by PET for zanubrutinib versus the PFS assessed by CT for orelabrutinib. *PFS* progression-free survival, *ESS* effective sample size, *HR* hazard ratio, *CI* confidence interval

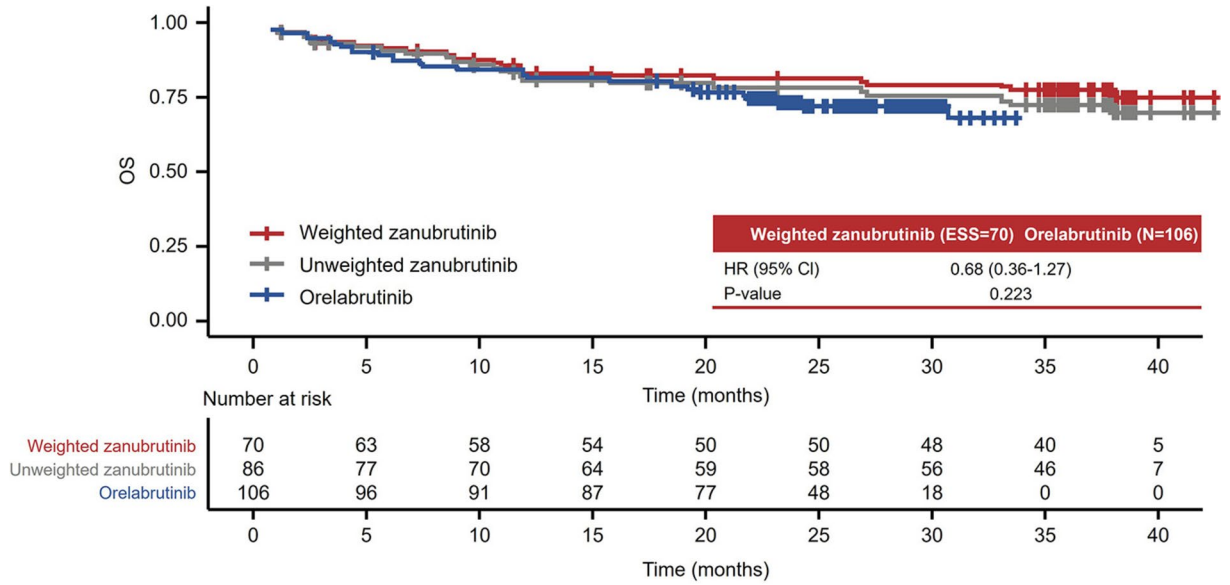

Fig. 3 OS of zanubrutinib versus orelabrutinib. *OS* overall survival, *ESS* effective sample size, *HR* hazard ratio, *CI* confidence interval

was not powered enough to detect a statistical meaningful difference between these two groups but there is a favorable trend on OS towards zanubrutinib over orelabrutinib (HR 0.68). What is more, the 24-month OS rate was also numerically higher in the zanubrutinib group than the orelabrutinib group (83.7% vs. 74.3%). The findings here might indicate a better OS on zanubrutinib; however, longer follow-up is warranted to determine any differences between the

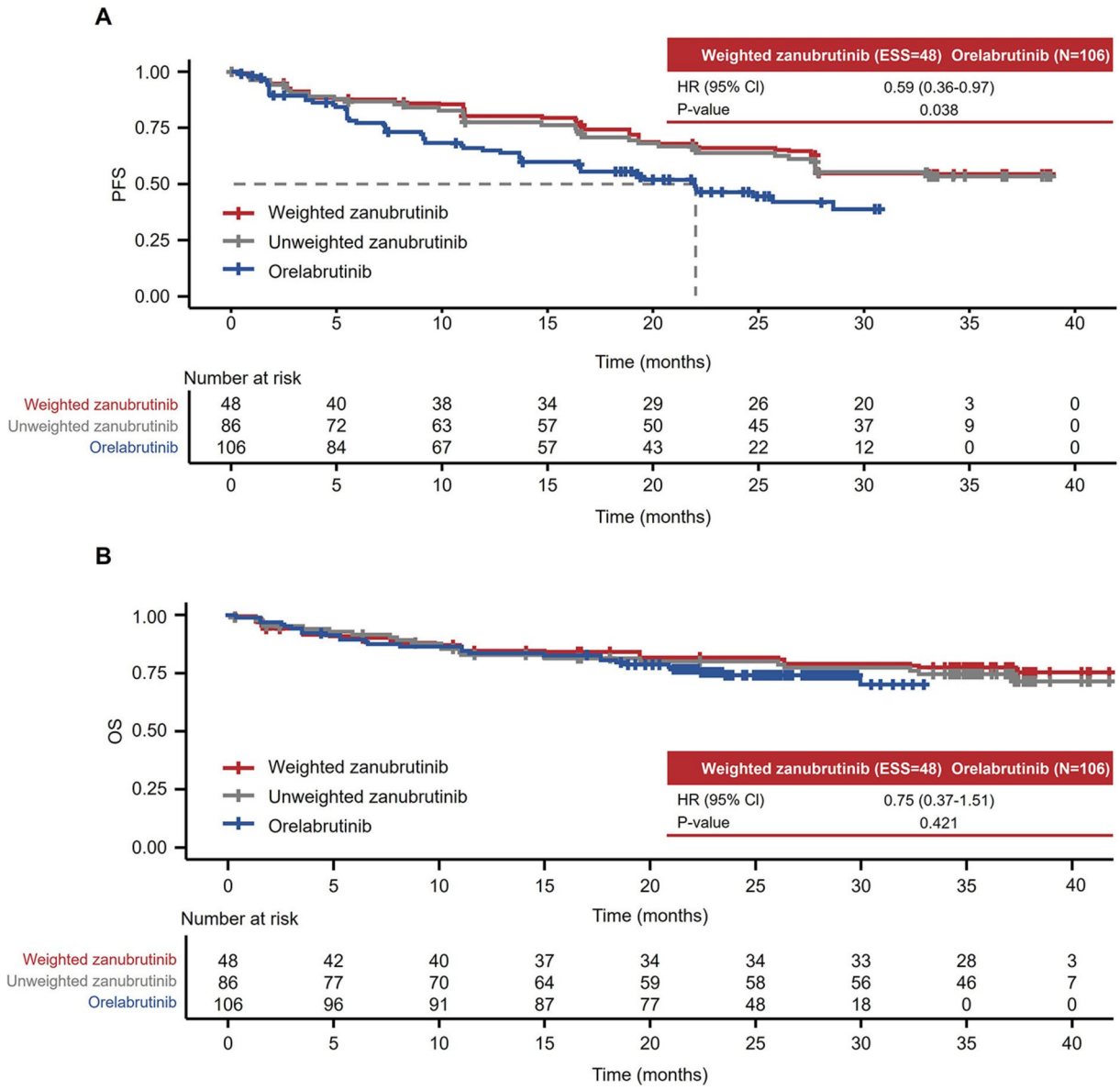

Fig. 4 Sensitivity analysis. **a** PFS assessed by CT for zanubrutinib versus orelabrutinib; **b** OS of zanubrutinib versus orelabrutinib. *PFS* progression-free survival, *OS* overall survival, *ESS* effective sample size, *HR* hazard ratio, *CI* confidence interval

zanubrutinib and orelabrutinib with respect to survival.

The MAIC analysis reduces the bias raised by the population difference between the two trials and thus makes the endpoints more comparable. The evidence generated by this post hoc analysis will be stronger than the naïve treatment comparison [15]. Before matching, the proportions of patients with age ≥ 65 years were similar between the zanubrutinib and orelabrutinib trials. The lower proportion of ASCT in the zanubrutinib study is consistent with the real-world treatment patterns for Chinese patients with MCL. A prior real-world study of 693 Chinese patients with MCL reported that only 11.5% (n = 80) underwent

ASCT consolidation, despite 69% of the cohort being younger than 65 years [25]. This utilization rate is markedly lower than in the USA or EU, reflecting region-specific clinical preferences in China. In addition, we acknowledge the differential proportions of primary refractory patients between the two trials (52% in the zanubrutinib vs. 30% in orelabrutinib). As shown in the zanubrutinib trial, subgroup analyses confirmed consistent efficacy regardless of refractory status: ORR was 82.2% (95% CI 67.9–92%) for refractory disease and 85.4% (95% CI 70.8–94.4%) for non-refractory disease [5]. Given this evidence, we did not identify refractory status as a factor in the primary analysis.

However, there are a few limitations. In this analysis, since both trials are single arm, the comparison was conducted through an unanchored MAIC analysis, which relies on the assumption that all prognostic factors and effect modifiers are identified and included in population matching. Despite all available prognostic factors and effect modifiers having been included, along with sensitivity analyses to reduce the bias and demonstrate the robustness, this assumption is still strong and cannot be verified. Potential violation of this assumption leads to bias. Furthermore, we did not analyze the safety in this study because of the potential differences in adverse events collection, reporting, follow-up time between studies, and limited sample size. Finally, in our study, post-treatment interventions, including stem cell transplantation, were not systematically captured as a result of variability in follow-up documentation across data sources. Future studies should investigate outcomes in patients bridging from BTKi to SCT, as this sequencing may influence long-term survival.

CONCLUSIONS

The MAIC results demonstrated that the efficacy of zanubrutinib was statistically significantly better than that of orelabrutinib in the treatment of patients with R/R MCL with respect to PFS. The findings of this study add further information for clinicians to use when choosing therapy for patients with R/R MCL.

Medical Writing/Editorial Assistance. Medical writing and editorial assistance, under the direction of the authors, was provided by Meiting Gao from BeiGene (Shanghai), China and Natasha Aggarwal from Indegene Private Limited, Bangalore, India, and was funded by BeiGene.

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Funding. No funding or sponsorship was received for this study. The journal's Rapid Service and Open Access Fees are funded by BeiGene.

Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. The authors Lijuan Deng, Yuqin Song, Keshu Zhou, Dengju Li, Jianda Hu, Dehui Zou, Sujun Gao, Haiyan Yang,

Huilai Zhang, Jie Ji, Wei Xu, Ru Feng, Jie Jin, Fangfang Lv, Cheng Fang, Sheng Xu, Jun Zhu have no conflicts of interest to disclose.

Ethical Approval. Ethics committee approval was not required for the study. For the zanubrutinib trial, the study was designed and monitored in accordance with sponsor procedures in compliance with the ethical principles of Good Clinical Practice, International Conference on Harmonization guidelines, the Declaration of Helsinki, and applicable local regulatory requirements. All patients provided written informed consent. The protocol, any amendments, and informed consent forms were reviewed and approved by the institutional review boards/independent ethics committees. For the orelabrutinib trial, all patients provided written informed consent [13].

REFERENCES

1. Hillmen P, Brown JR, Eichhorst BF, et al. ALPINE: zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Future Oncol. 2020;16:517–23.
2. Kumar A, Sha F, Toure A, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. Blood Cancer J. 2019;9:50.
3. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369:507–16.
4. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391:659–67.
5. Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. Clin Cancer Res. 2020;26:4216–24.
6. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102:1796–805.
7. Coutre SE, Byrd JC, Hillmen P, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. Blood Adv. 2019;3:1799–807.
8. Le Gouill S, Długosz-Danecka M, Rule S, et al. Final results and overall survival data from a phase II study of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma, including those with poor prognostic factors. Haematologica. 2024;109:343–50.
9. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023;388:319–32.
10. Dimopoulos MA, Opat S, D'Sa S, et al. Zanubrutinib versus ibrutinib in symptomatic Waldenström macroglobulinemia: final analysis from the randomized phase III ASPEN study. J Clin Oncol. 2023;41:5099–106.
11. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: interim analysis of a randomized phase III trial. J Clin Oncol. 2023;41:1035–45.
12. Song Y, Zhou K, Zou D, et al. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Blood. 2022;139:3148–58.
13. Deng L-J, Zhou K-S, Liu L-H, et al. Orelabrutinib for the treatment of relapsed or refractory MCL:

a phase 1/2, open-label, multicenter, single-arm study. Blood Adv. 2023;7:4349–57.

14. Tam CS, Ou YC, Trotman J, Opat S. Clinical pharmacology and PK/PD translation of the second-generation Bruton's tyrosine kinase inhibitor, zanubrutinib. Expert Rev Clin Pharmacol. 2021;14:1329–44.

15. Song Y, Zhou K, Yang S, et al. Indirect comparisons of efficacy of zanubrutinib versus orelabrutinib in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma or relapsed or refractory mantle cell lymphoma. Invest New Drugs. 2023;41:606–16.

16. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059–68.

17. Narang J, Bajpai S, Jarecha RR, et al. Comparison of CT and PET-based assessments per lugano criteria in FDG-avid lymphoma—a retrospective analysis of independent review assessments. Blood. 2019;134:5277.

18. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010;28:935–45.

19. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents). NICE Decision Support Unit; 2016. https://research-information.bris.ac.uk/ws/portalfiles/portal/94868463/Population_adjustment_TSD_FINAL.pdf. Accessed 27 Feb 2025.

20. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2021;21:111.

21. Albano D, Ferro P, Bosio G, et al. Diagnostic and clinical impact of staging 18F-FDG PET/CT in mantle-cell lymphoma: a two-center experience. Clin Lymphoma Myeloma Leuk. 2019;19:e457–64.

22. Yoon DH, Cao J, Chen T-Y, et al. Treatment of mantle cell lymphoma in Asia: a consensus paper from the Asian Lymphoma Study Group. J Hematol Oncol. 2020;13:21.

23. Maddocks K. Update on mantle cell lymphoma. Blood. 2018;132:1647–56.

24. Shadman M, Flinn IW, Levy MY, et al. Phase 2 study of zanubrutinib in BTK inhibitor-intolerant patients (Pts) with relapsed/refractory B-cell malignancies. Blood. 2021;138:1410.

25. Yang P, Cai Q-Q, Zhang W, et al. Real-world treatment and outcome patterns of patients with mantle cell lymphoma in China: a large, multicenter retrospective analysis. Cancer Med. 2023;12:13204–16.