Received: 1 August 2024 | Revised: 2 December 2024 | Accepted: 2 January 2025

DOI: 10.1002/ijc.35339

RESEARCH ARTICLE

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER | UICC

Pirtobrutinib in Chinese patients with relapsed or refractory B-cell malignancies: A single-arm, open-label, phase 2, multicenter trial

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Funding information
Eli Lilly and Company

Abstract

Pirtobrutinib, a highly selective, noncovalent (reversible) Bruton tyrosine kinase inhibitor (BTKi), demonstrated clinically meaningful antitumor responses in covalent BTKi pretreated mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in the global phase 1/2 BRUIN study. In this multicenter, open-label, phase 2 trial, we investigated the efficacy and safety of pirtobrutinib in Chinese patients with BTKi pretreated relapsed/refractory (R/R) MCL, CLL/SLL, or other B-cell malignancies. All patients received pirtobrutinib once daily in

Yanyan Liu and Ningjing Lin contributed equally to this study.

Efficacy data for the MCL cohort and safety data for the entire cohort as of April 10, 2023, have previously been presented at ASH 2023 and published in abstract form (Song et al. Blood 2023;142[suppl 1]:3636).

continuous 28-day cycles. The primary endpoint was the overall response rate (ORR). Efficacy was assessed in patients with MCL and CLL/SLL with prior BTKi treatment and safety in all enrolled patients who received at least one dose of pirtobrutinib. Among 35 patients with covalent BTKis (cBTKi) pretreated MCL, the ORR was 62.9% (95% CI: 44.9, 78.5), the median duration of response (DOR) was not reached, and the 12-month DOR rate was 59.7% (95% CI: 35.3, 77.5). Among 11 patients with cBTKi pretreated CLL/SLL, the ORR was 63.6% (95% CI: 30.8, 89.1), and the 12-month DOR rate was 83.3% (95% CI: 27.3, 97.5). The most common adverse events in the safety population ($n = 87$) were anemia (32.2%) and neutrophil count decreased (31.0%). Grade ≥3 hemorrhage occurred in 2.3% of patients and there were no cases of atrial fibrillation/flutter. Pirtobrutinib demonstrated clinically meaningful efficacy in Chinese patients with cBTKi pretreated R/R MCL, preliminary antitumor activity in Chinese patients with cBTKi pretreated R/R CLL/SLL and was generally well-tolerated with no new safety signals observed.

KEYWORDS
chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, noncovalent BTK inhibitor, pirtobrutinib

What's New?

Pirtobrutinib, a highly selective, noncovalent (reversible) Bruton tyrosine kinase inhibitor (BTKi), has shown promise in treating patients with B-cell malignancies following treatment with covalent BTKis. However, potential geographic and ethnic differences in patient response to pirtobrutinib remain to be clarified. This trial conducted in Chinese patients previously treated with covalent BTKi found that pirtobrutinib had clinically meaningful efficacy in relapsed/refractory mantle cell lymphoma and preliminary antitumor activity in chronic lymphocytic leukemia/small lymphocytic lymphoma and was generally well-tolerated. The results are consistent with those previously found in a global population and support pirtobrutinib as a promising treatment option for Chinese patients.

1 | INTRODUCTION

Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy with a poor prognosis and a heterogeneous clinical course, comprising 2.6%–6.3% of all lymphoma cases in China,[1,2] with an incidence of approximately 0.2–0.4 per 100,000 people per year.[3] Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), the most common adult leukemia, has a significantly higher incidence among Caucasians and is extremely low in Asians, including China, where the age-adjusted incidence rate is 0.2–0.8 per 100,000 people per year.[4,5]

Covalent Bruton tyrosine kinase inhibitors (cBTKis) have significantly changed the therapeutic landscape for B-cell malignancies, such as MCL and CLL/SLL.[6–12] However, treatment failure often occurs through the development of resistance or intolerance.[7,11,13–15] The prognosis for patients with relapsed/refractory (R/R) MCL or CLL/SLL who have progressed after cBTKi therapy is extremely poor.[11,12,14,16,17] Therefore, there remains an unmet need for effective and well-tolerated therapies for patients with MCL or CLL/SLL who develop disease progression or primary resistance to cBTKi treatment.[15]

Pirtobrutinib, a highly selective and noncovalent (reversible) BTKi, effectively inhibits both wild-type and C481-mutant BTK with low nM potency. Its favorable oral pharmacology allows for continuous BTK inhibition throughout the once-daily dosing period, irrespective of the intrinsic BTK turnover rate.[18–20] In contrast to cBTKis, pirtobrutinib appears to uniquely stabilize or maintain BTK by blocking access to upstream kinases and phosphorylation of Y551, potentially inhibiting scaffolding interactions that likely support kinase-independent BTK signaling.[18]

In the phase 1/2 BRUIN trial, a first-in-human, multicenter, open-label study, pirtobrutinib showed promising efficacy and a favorable safety profile in patients with B-cell malignancies who had previously been treated with a cBTKi.[20–22] These results demonstrate that pirtobrutinib can further extend the clinical benefit of BTK inhibition after failure of cBTKi treatment. Pirtobrutinib is approved by the US Food and Drug Administration for use in patients with R/R MCL after at least two lines of systemic therapy including a BTKi, and for patients with CLL/SLL after at least two lines of systemic therapy including a BTKi and BCL-2 inhibitor.[23] In the EU, pirtobrutinib has been approved for use in patients with R/R MCL previously treated with a BTKi.[24]

BRUIN study did not include patients from China, leaving a gap in understanding the potential geographic and ethnic differences in response to pirtobrutinib. To address this uncertainty and meet China's regulatory requirements, a phase 2 trial has been designed as a bridging study to the BRUIN study. This trial aims to evaluate the efficacy and safety of pirtobrutinib in Chinese B-cell malignancies patients, especially with MCL or CLL/SLL who have previously received cBTKi treatment and to determine consistency with the benefits observed in the global population of the BRUIN study.

2 | MATERIALS AND METHODS

This was a phase 2, open-label trial conducted at 19 centers in China. Patients aged ≥18 years with histologically confirmed B-cell malignancies were assigned to one of three cohorts based on tumor histology and prior treatment history. Cohort 1 comprised patients with a confirmed diagnosis of non-blastoid MCL and at least one site of radiographically assessable disease, with documentation of overexpression of cyclin D1 and/or t (11;14), who had received prior chemoimmunotherapy and progressed following a BTKi-containing regimen. Cohort 2 included patients diagnosed with CLL/SLL who had progressed on a prior BTKi-containing regimen. Cohort 3 included patients with a confirmed diagnosis of MCL, CLL/SLL, or other type of B-cell non-Hodgkin lymphoma (NHL) (including but not limited to diffuse large B-cell lymphoma, marginal zone lymphoma or Waldenström macroglobulinemia),[25] patients not otherwise eligible for Cohorts 1 and 2, and who had progressed on, or were intolerant to or unsuitable for, standard of care. Across all cohorts, eligible patients had an Eastern Cooperative Oncology Group performance status of 0–2; disease requiring treatment; adequate organ function; and had either progressed on or been intolerant of the most recent line of therapy or relapsed prior to enrolment.

Patients were excluded if they had known central nervous system involvement by systemic lymphoma or primary central nervous system lymphoma; experienced a major bleeding event or grade ≥3 arrhythmias during prior treatment with a BTKi; received stem cell transplantation or CD-19 chimeric antigen receptor-modified (CAR) T-cell therapy within 60 days prior to study treatment; received previous investigational agents or anticancer therapies, major surgery, or radiotherapy without an adequate wash out period prior to study treatment; required therapeutic anticoagulation with warfarin; or had significant cardiovascular disease. Full eligibility criteria are described in the Supplementary Material.

2.1 | Treatment and assessments

Patients received oral pirtobrutinib 200 mg once daily as monotherapy in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal. Patients with disease progression could continue treatment if deriving ongoing clinical benefit per the investigator's opinion.

Tumor assessments were performed at baseline, every 8 weeks (±7 days) for the first year, every 12 weeks (±2 weeks) for the second year, and every 6 months (±4 weeks) thereafter. Tumor response was assessed according to the Lugano Treatment Response Criteria 2014 for patients with MCL[26] and the International Workshop on CLL 2018 criteria for patients with CLL/SLL.[27]

Safety was continuously monitored throughout the trial and up to 28 days (±7 days) after the last dose of pirtobrutinib. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 5.0. The relatedness of AEs to treatment was determined by the investigator.

2.2 | Outcomes

The primary endpoint was the overall response rate (ORR) assessed by the independent review committee (IRC), defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) for MCL, or a CR, CR with incomplete bone marrow recovery (CRi), nodular PR, or PR for CLL/SLL. For CLL, an additional analysis was performed to assess the ORR including a PR with lymphocytosis (PR-L) (ORR with PR-L), as patients with CLL who achieve a PR-L are also considered responders.[28]

Secondary endpoints included IRC-assessed duration of response (DOR), defined as the time from the start date of the first response (PR or better) until progressive disease or death from any cause, whichever occurred first; progression-free survival (PFS), defined as the time from the first dose of pirtobrutinib to progressive disease or death from any cause, whichever occurred first; overall survival (OS), defined as time from the first dose of pirtobrutinib to the date of death from any cause; and safety, evaluated by the frequency and severity of AEs including AEs of special interest, defined as known AEs associated with the BTKi class.

2.3 | Statistical analysis

Eligible patients were planned to be enrolled into the three cohorts (at least 30 patients for Cohort 1, up to 30 patients for Cohort 2, and up to 50 patients for Cohort 3). Assuming an ORR of 50% (or higher) among patients in the BTKi pretreated population, enrolment of approximately 30 patients would provide a corresponding two-sided exact 95% confidence interval (CI) with a lower limit that exceeded 30%, which is considered a clinically meaningful improvement for patients with MCL or CLL/SLL who have failed prior cBTKi therapy.[29–32]

Efficacy was assessed in patients with MCL, or CLL/SLL treated with prior cBTKi and who had received at least one dose of study drug. The safety population included all enrolled patients who received at least one dose of pirtobrutinib. Subgroup analyses for ORR were conducted based on baseline characteristics.

Patient disposition, baseline demographic and clinical characteristics, best overall response, and safety data were summarized

descriptively. ORR was estimated with exact two-sided 95% CIs calculated using the Clopper–Pearson method. For time-to-event endpoints including DOR, PFS, and OS, the Kaplan–Meier method was used to estimate the survival curves and to generate median survival times, with 95% CIs and survival rates computed by Brookmeyer and Crowley, and Greenwood methods, respectively. Statistical analysis was performed using SAS software (version 9.4).

A data cutoff date of September 26th, 2023 was selected to ensure that all patients enrolled would be followed for at least 12 months from enrolment.

3 | RESULTS

3.1 | Patients

Between May 2021 and September 2022, 87 patients were enrolled (33 from Cohort 1, 11 from Cohort 2, and 43 from Cohort 3) and received treatment with pirtobrutinib, including 39 with MCL, 17 with CLL/SLL, and 31 with other types of NHL. Among these patients, 35 with MCL (28 with non-blastoid MCL confirmed by central pathology review) and 11 with CLL/SLL who had previously received cBTKi were included in the efficacy analysis (Figure 1).

Baseline characteristics are summarized in Table 1. Among the 35 patients with cBTKi-pretreated MCL, the median age was 66.0 years and the median number of prior lines of therapy was 3.0 (range 1.0–9.0): 97.1% had received chemotherapy, 88.6% had received an anti-CD20 antibody, and 28.6% an immunomodulatory drug (e.g., lenalidomide). A total of 88.6% of patients had discontinued prior cBTKi due to disease progression, and 68.6% had an intermediate/high-risk Simplified Prognostic Index for Advanced-stage Mantle Cell Lymphoma (sMIPI) score. Similar baseline demographics and disease characteristics were observed among the 28 patients with non-blastoid MCL who had received prior cBTKi treatment.

Among the 11 patients with cBTKi pretreated CLL/SLL, the median age was 64.0 years and the median number of prior lines of

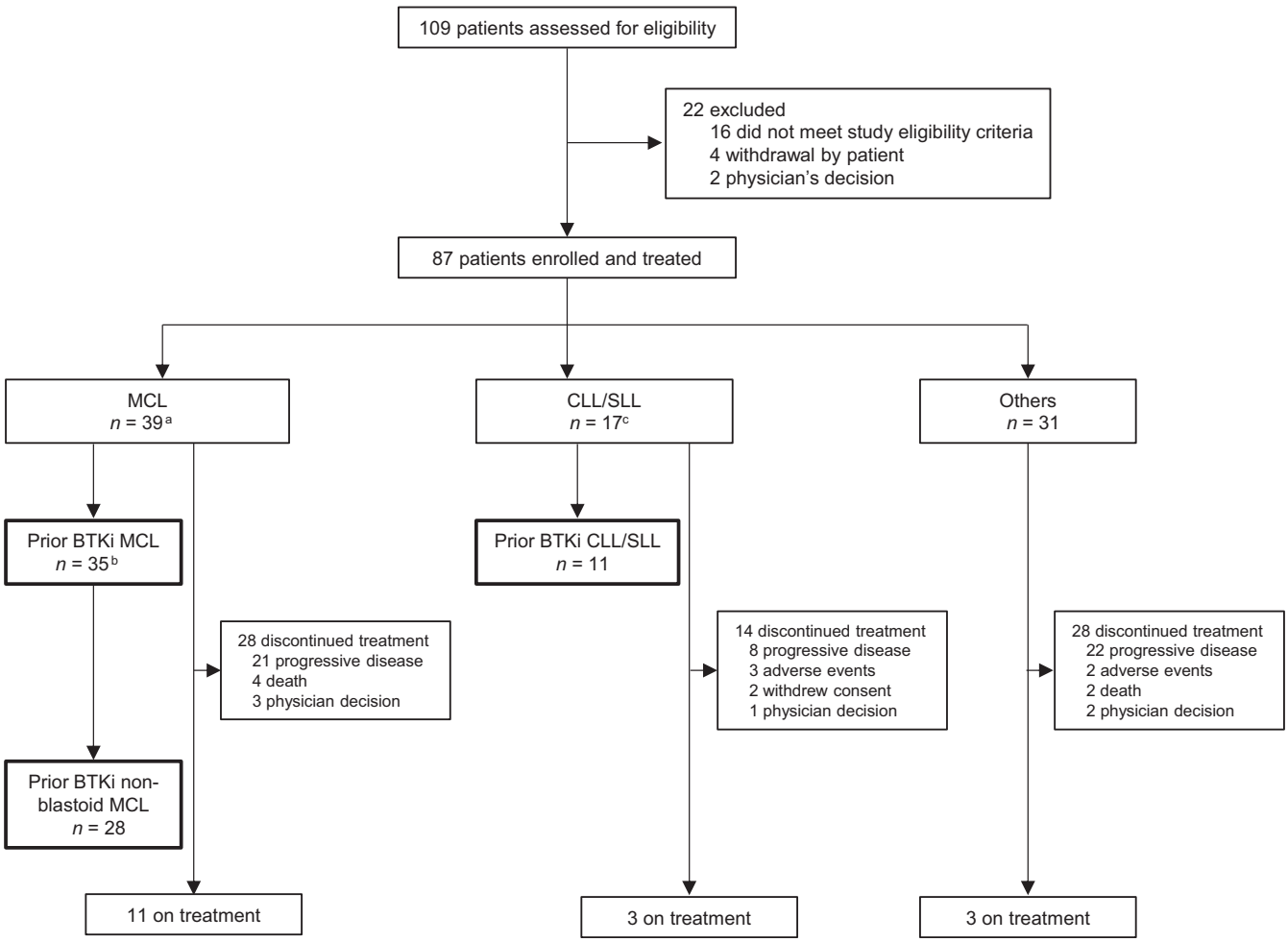

FIGURE 1 Analysis sets. [a]Includes four BTKi naïve MCL patients. [b]Includes two patients with blastoid MCL and five patients who were excluded due to central pathology indicated as blastoid MCL ($n = 2$), no adequate tumor sample was provided to the central lab ($n = 2$), or no measurable disease at baseline ($n = 1$). A total of 28 patients were centrally confirmed to have non-blastoid MCL and had measurable disease as assessed by the investigator. [c]Includes six BTKi naïve CLL/SLL patients. BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; *n*, number; SLL, small lymphocytic lymphoma.

TABLE 1 Baseline demographics and clinical characteristics.

	cBTKi pretreated MCL ($n = 35$)	cBTKi pretreated non-blastoid MCL ($n = 28$)	cBTKi pretreated CLL/SLL ($n = 11$)
Males, *n* (%)	23 (65.7)	18 (64.3)	7 (63.6)
Median age (range), years	66.0 (47–75)	66.5 (49–75)	64.0 (42–72)
Median time since initial diagnosis (range), months	56.3 (6.6–171.1)	62.1 (6.6–171.1)	80.2 (34.8–128.2)
ECOG PS, *n* (%)			
0	12 (34.3)	10 (35.7)	6 (54.5)
1	22 (62.9)	17 (60.7)	5 (45.5)
2	1 (2.9)	1 (3.6)	0 (0.0)
s-MIPI score, *n* (%)			
Low risk	11 (31.4)	9 (32.1)	–
Intermediate risk	12 (34.3)	8 (28.6)	–
High risk	12 (34.3)	11 (39.3)	–
Tumor bulk[a,b], *n* (%)			
<5 cm	26 (74.3)	22 (78.6)	6 (54.5)
≥5 cm	8 (22.9)	6 (21.4)	5 (45.5)
Unknown	1 (2.9)	0 (0.0)	0 (0.0)
Extranodal disease[a,c], *n* (%)			
Yes	19 (54.3)	15 (53.6)	6 (54.5)
No	15 (42.9)	13 (46.4)	5 (45.5)
Unknown	1 (2.9)	0 (0.0)	0 (0.0)
Bone marrow involvement[a], *n* (%)			
Yes	22 (62.9)	19 (67.9)	9 (81.8)
No	12 (34.3)	9 (32.1)	0 (0.0)
Unknown	1 (2.9)	0 (0.0)	2 (18.2)
Number of lines of prior systemic therapy, median (range)	3.0 (1.0–9.0)	3.0 (1.0–8.0)	2.0 (1.0–7.0)
Prior systemic therapy, *n* (%)			
BTKi	35 (100.0)	28 (100.0)	11 (100.0)
Chemotherapy	34 (97.1)	27 (96.4)	10 (90.9)
Anti-CD20 antibody	31 (88.6)	24 (85.7)	3 (27.3)
IMiD (lenalidomide)	10 (28.6)	9 (32.1)	1 (9.1)
Other systemic therapy	6 (17.1)	5 (17.9)	2 (18.2)
Proteasome inhibitor	5 (14.3)	2 (7.1)	0 (0.0)
PI3K inhibitor	3 (8.6)	2 (7.1)	1 (9.1)
Stem cell transplant	2 (5.7)	2 (7.1)	0 (0.0)
BCL2 inhibitor	2 (5.7)	0 (0.0)	3 (27.3)
CAR T-cell therapy	1 (2.9)	0 (0.0)	1 (9.1)
Reason for discontinuation from any prior BTKi, *n* (%)			
Progressive disease	31 (88.6)	24 (85.7)	9 (81.8)
Intolerance or other	4 (11.4)	4 (14.3)	2 (18.2)

Abbreviations: BCL2, B-cell lymphoma 2; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drugs; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma; s-MIPI, simplified Mantle Cell Lymphoma International Prognostic Index.

[a]Based on investigator assessment.

[b]Based on all target lesions.

[c]Based on locations of target and nontarget lesions.

TABLE 2 Efficacy endpoints.

	cBTKi pretreated MCL ($n = 35$)	cBTKi pretreated non-blastoid MCL ($n = 28$)	cBTKi pretreated CLL/SLL ($n = 11$)
ORR, % (95% CI)	62.9 (44.9, 78.5)	71.4 (51.3, 86.8)	63.6 (30.8, 89.1)
Best overall response, *n* (%)			
CR	4 (11.4)	4 (14.3)	2 (18.2)
CRi	–	–	0
nPR	–	–	0
PR	18 (51.4)	16 (57.1)	5 (45.5)
PR-L	–	–	1 (9.1)
SD	3 (8.6)	2 (7.1)	1 (9.1)
PD	6 (17.1)	4 (14.3)	1 (9.1)
NE	4 (11.4)	2 (7.1)	1 (9.1)
DOR			
Median, months (95% CI)	Not reached (4.8, –)	Not reached (4.8, –)	18.3 (1.9, –)
Median follow-up, months (IQR)	12.0 (9.0, 14.9)	11.9 (9.0, 12.0)	17.5 (6.5, –)
12 months rate, % (95% CI)	59.7 (35.3, 77.5)	60.8 (34.8, 79.1)	83.3 (27.3, 97.5)
PFS			
Median, months (95% CI)	6.8 (5.3, –)	9.4 (5.3, –)	18.3 (1.7, –)
Median follow-up, months (IQR)	13.7 (9.4, 16.8)	13.7 (10.9, 13.9)	19.3 (4.6, –)
12 months rate, % (95% CI)	44.1 (25.5, 61.3)	46.7 (26.1, 64.9)	77.1 (34.5, 93.9)
OS			
Median, months (95% CI)	15.5 (10.0, –)	15.5 (9.3, –)	24.3 (5.4, –)
Median follow-up, months (IQR)	16.0 (13.4, 24.8)	16.0 (13.8, 20.9)	23.5 (21.9, 25.4)
12 months rate, % (95% CI)	61.9 (43.6, 75.8)	60.7 (40.4, 76.0)	81.8 (44.7, 95.1)

Abbreviations: cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete bone marrow recovery; DOR, duration of response; IQR, interquartile range; MCL, mantle cell lymphoma; nPR, nodular partial response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma.

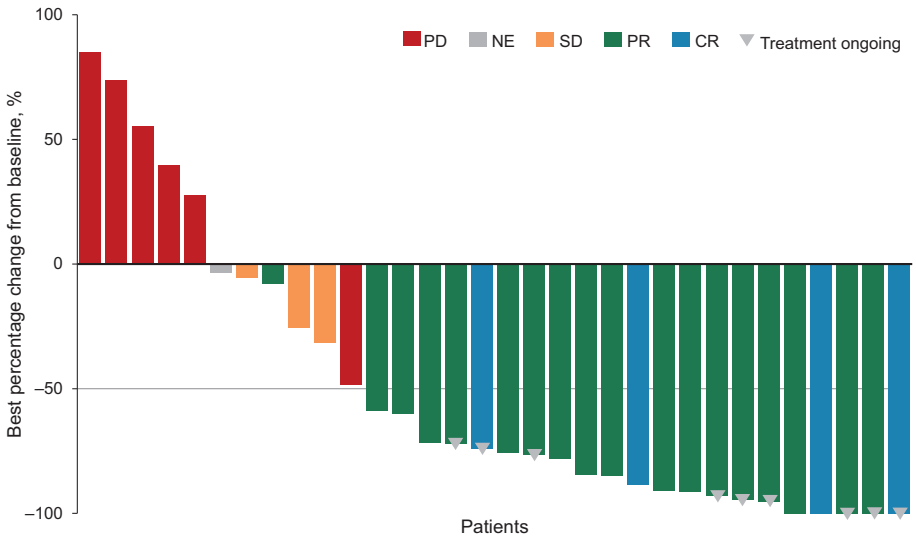

FIGURE 2 Waterfall plot showing the best change in tumor burden (covalent Bruton's tyrosine kinase inhibitor pretreated mantle cell lymphoma). CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

therapy was 2.0 (range 1.0–7.0): 90.9% had received chemotherapy, 27.3% had received an anti-CD20 antibody, and 27.3% had received a BCL2 inhibitor. A total of 81.8% of patients had discontinued prior cBTKi due to disease progression.

3.2 | Efficacy

Among the patients with cBTKi pretreated MCL ($n = 35$), the IRC-assessed ORR was 62.9% (95% CI: 44.9, 78.5), which included a CR in four patients (11.4%) and a PR in 18 patients (51.4%) (Table 2, Figure 2). The ORR was generally consistent across prespecified subgroups, regardless of demographics, number of prior lines of therapy, type of prior therapy, or disease risk as assessed by the sMIPI, or with bone marrow involvement at baseline (Figure S1). The median DOR was not reached at the cut-off date and, after a median follow-up of 12.0 months, the 12-month DOR rate was 59.7% (95% CI: 35.3, 77.5) (Table 2, Figure 3A). The median PFS after a median follow-up of 13.7 months was 6.8 months (95% CI: 5.3, not evaluable [NE]) and the 12-month PFS rate was 44.1% (95% CI: 25.5, 61.3) (Table 2, Figure 3B). The median OS after a median follow-up of 16.0 months, was 15.5 months (95% CI: 10.0, NE) and the 12-month OS rate was 61.9% (95% CI: 43.6, 75.8) (Table 2, Figure 3C).

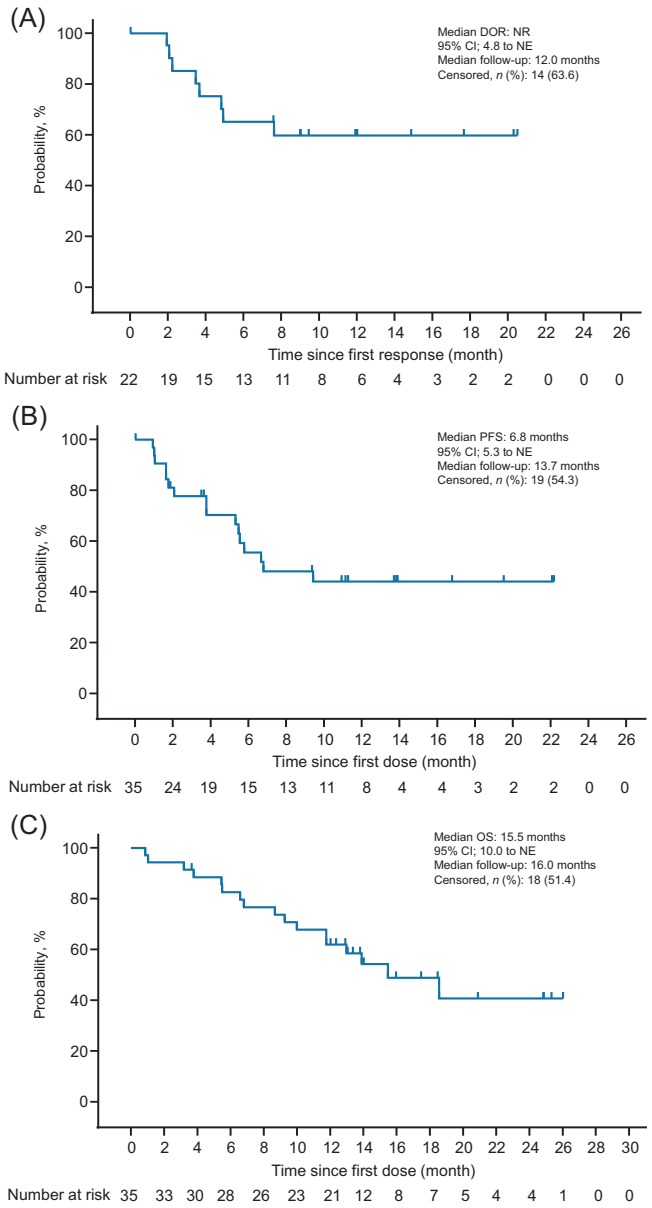

FIGURE 3 Duration of response (A), progression-free survival (B), and overall survival rates in patients with cBTKi pretreated MCL. Vertical check marks represent censoring. cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; DOR, duration of response; MCL, mantle cell lymphoma; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Anti-tumor activity among the patients with cBTKi-pretreated centrally confirmed non-blastoid MCL ($n = 28$) was similar to that in the wider MCL population. The ORR was 71.4% (95% CI: 51.3, 86.8). The 12-month DOR rate was 60.8% (95% CI: 34.8, 79.1), the median PFS was 9.4 months (95% CI: 5.3, NE), and the 12-month PFS rate was 46.7% (95% CI: 26.1, 64.9). The median OS was 15.5 months (95% CI: 9.3, NE), with a 12-month OS rate of 60.7% (95% CI: 40.4, 76.0) (Table 2).

For the patients with cBTKi pretreated CLL/SLL ($n = 11$), the ORR was 63.6% (95% CI: 30.8, 89.1) and the ORR with PR-L was 72.7% (95% CI: 39.0, 94.0). The median DOR was 18.3 (1.9, –), after a median follow-up of 17.5 months, the 12-month DOR rate was 83.3% (95% CI: 27.3, 97.5). The median PFS and OS were 18.3 months (95% CI: 1.7, NE) and 24.3 months (95% CI: 5.4, NE), respectively (Table 2).

The IRC-assessed ORR in patients with all MCL, CLL/SLL, and other NHL are summarized in Table S1.

3.3 | Safety

All enrolled patients received at least one dose of pirtobrutinib and were included in the safety population ($n = 87$). The median duration of treatment was 4.2 months (interquartile range [IQR] 1.8, 14.1) and the median relative dose intensity was 98.6% (IQR 91.2, 100.3). AEs leading to dose reductions and interruptions were observed in seven (8.0%) and 41 (47.1%) patients, respectively. Five (5.7%) patients discontinued treatment due to AEs, which were considered related to study treatment in three (3.4%) patients.

The most common AEs were anemia (28 [32.2%]), neutrophil count decreased (27 [31.0%]) and white blood cell count decreased (21 [24.1%]) (Table 3). The most frequent grade ≥3 AE and treatment-related AE was neutrophil count decreased (reported in 19 [21.8%] and 17 [19.5%] patients, respectively). Serious AEs (SAEs) were reported in 33.3% of patients, among which 13.8% were considered related to the study treatment and these were most commonly caused by infection events (5.7%).

AEs leading to death occurred in five (5.7%) patients, two of which were deemed related to study treatment by the investigator. One was a patient with follicular lymphoma with a large tumor burden who died due to acute tumor lysis syndrome, tumor necrosis, and

TABLE 3 Most common adverse events (occurring in ≥15% of patients; safety population, $n = 87$).

	Adverse events		Treatment-related adverse events	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Subjects with ≥1 AE	86 (98.9)	57 (65.5)	79 (90.8)	38 (43.7)
Anemia	28 (32.2)	7 (8.0)	23 (26.4)	4 (4.6)
Neutrophil count decreased	27 (31.0)	19 (21.8)	25 (28.7)	17 (19.5)
White blood cell count decreased	21 (24.1)	7 (8.0)	18 (20.7)	6 (6.9)
Blood bilirubin increased	20 (23.0)	2 (2.3)	16 (18.4)	1 (1.1)
Hypokalaemia	20 (23.0)	3 (3.4)	12 (13.8)	2 (2.3)
COVID-19	17 (19.5)	3 (3.4)	3 (3.4)	1 (1.1)
Hyperuricaemia	17 (19.5)	1 (1.1)	10 (11.5)	1 (1.1)
Hyperglycaemia	15 (17.2)	1 (1.1)	8 (9.2)	0
Platelet count decreased	15 (17.2)	7 (8.0)	11 (12.6)	4 (4.6)
Aspartate aminotransferase increased	14 (16.1)	2 (2.3)	12 (13.8)	2 (2.3)
Pyrexia	14 (16.1)	0	6 (6.9)	0
Adverse events of special interest[a]				
Infection	39 (44.8)	18 (20.7)[b]	22 (25.3)	6 (6.9)
COVID-19	17 (19.5)	3 (3.4)	3 (3.4)	1 (1.1)
COVID 19 pneumonia	2 (2.3)	2 (2.3)	0	0
Bleeding	17 (19.5)	2 (2.3)[c]	15 (17.2)	1 (1.1)
Hemorrhage	10 (11.5)	2 (2.3)	8 (9.2)	1 (1.1)
Neutropenia[d]	36 (41.4)	22 (25.3)	34 (39.1)	20 (23.0)
Anemia	28 (32.2)	7 (8.0)	23 (26.4)	4 (4.6)
Thrombocytopenia[e]	19 (21.8)	8 (9.2)	15 (17.2)	5 (5.7)
Hypertension	6 (6.9)	2 (2.3)	1 (1.1)	0
Atrial fibrillation/flutter	0	0	0	0

Abbreviations: AE, adverse event; *n*, number of patients.
[a]Composite term.
[b]Includes two (2.3%) grade 5 infections (one subject with COVID-19, and one subject with infection).
[c]Includes one (1.1%) grade 5 bleeding event (the subject with large tumor burden developed grade 5 tumor lysis syndrome, tumor necrosis and hemorrhage after one dose of pirtobrutinib).
[d]Includes neutropenia and neutrophil count decreased.
[e]Includes platelet count decreased and thrombocytopenia.

hemorrhage after one dose of pirtobrutinib. The other patient had MCL and died due to infection.

The analysis of AEs of special interests revealed that no cases of atrial fibrillation/flutter were observed. Grade ≥3 infections (excluding COVID-19 events) were reported in 13 (14.9%) patients, and the most common event was pneumonia (4.6%). Grade ≥3 hemorrhage and hypertension both occurred in 2.3% of patients. Only two patients had a dose reduction due to cytopenia and this reduction did not lead to discontinuation of pirtobrutinib in either patient. In addition, only one patient reduced dosage, and one patient discontinued treatment due to infection.

4 | DISCUSSION

In this phase 2 trial, pirtobrutinib demonstrated clinically meaningful efficacy in Chinese patients with MCL who were pretreated with a cBTKi. After a 12-month follow-up, among all patients with cBTKi-pretreated MCL, the IRC-assessed ORR was 62.9% (95% CI: 44.9, 78.5). These promising findings are consistent with those previously reported from the global phase 1/2 BRUIN study, in which the IRC-assessed ORR was 57.8% (95% CI: 46.9, 68.1) in patients with BTKi-treated R/R MCL.[22] Overall, our results suggest that pirtobrutinib is effective in Chinese patients with MCL who have failed prior cBTKi treatment and has the potential to extend the clinical benefit from BTK inhibition even after cBTKi treatment failure.[12,16,33]

All patients in this study were heavily pretreated and had experienced progression following prior cBTKi treatment. Despite this, 11.4% of the patients with MCL achieved a CR confirmed by PET-CT and showed no bone marrow involvement on biopsy samples at the CR timepoint or baseline. A similar response was observed consistently across most of the prespecified subgroups, even in some high-risk groups such as patients with sMIPI high risk or with bone marrow

involvement at baseline. The response to pirtobrutinib was also durable; the median DOR was not reached after a minimum of 12 months follow-up, and the 12-month DOR rate was 59.7%, consistent with findings from previous BRUIN study.[22] Furthermore, the 12-month OS rate was 61.9%, indicating that pirtobrutinib may provide a survival benefit, considering the median OS of <10 months reported in previous studies for patients with MCL who progressed after cBTKi treatment.[22,34–36]

The efficacy results of this study have important implications for the treatment of Chinese patients with MCL who are intolerant of, or resistant to, cBTKis, which is currently a setting with limited effective treatment options.[12,14,16,33] In China, CAR T-cell therapy has been investigated in patients with MCL.[37] Although this would expand the treatment options for MCL patients following cBTKi failure, CAR-T therapy might not be feasible for use in a broader population due to its high cost and logistics, and its utility is limited for rapidly progressing disease after BTKi failure, or for frail patients who cannot tolerate this approach.[7,15,38] Furthermore, CAR-T therapy is only available at experienced clinical centers.[7,15,38] Other investigational therapies such as bispecific antibodies and other non-covalent BTKis are currently under development, although as yet there are limited data for these in Chinese patients.[12,14]

In the present study, the IRC-assessed ORR in patients with CLL/SLL previously treated with a BTKi was 63.6% (95% CI: 30.8, 89.1), and a favorable median PFS of 18.3 months was also observed. Although only a limited number of patients with CLL/SLL were enrolled, this result supports the findings of the BRUIN study, in which pirtobrutinib also provided a clinical benefit in patients with BTKi pretreated CLL/SLL.[21]

The safety profile of pirtobrutinib in this Chinese patient population was consistent with that reported in the phase 1/2 BRUIN study, with no new safety signals observed for the BTKi drug class. Most AEs were mild to moderate in severity, with low rates of either discontinuation due to AEs or treatment-related SAEs. As expected in this heavily pretreated patient population, anemia and decreased neutrophil counts were commonly observed; however, the incidence of grade ≥3 events was similar to that reported for cBTKis, and all cases were effectively managed with dose interruption, supportive care, or both.[39–41] Only two patients had a dose reduction due to cytopenia and this reduction did not lead to discontinuation of pirtobrutinib in either patient. Atrial arrhythmias and bleeding are considered to have a potential association with BTKi treatment.[16,17] However, in the present study, there were no reports of atrial fibrillation/flutter, and only 2.3% of patients developed grade ≥3 hemorrhage. In addition, only one patient reduced dosage, and one patient discontinued treatment due to infection. The favorable safety profile of pirtobrutinib may be due to its highly selective and reversible profile.[16,33]

This study has several limitations. First, the single-arm trial design lacks a direct comparison of pirtobrutinib with other available therapies for R/R MCL. Additionally, this study had a limited sample size as it was designed as a bridging study of the BRUIN phase 1/2 study. Consequently, further evaluation of pirtobrutinib's safety profile in Chinese patients, particularly its long-term safety, is necessary in a larger patient population. Furthermore, the inclusion of only a small number of patients with CLL/SLL limits the conclusions that can be drawn for this population.

Despite these limitations, pirtobrutinib has demonstrated a favorable efficacy and safety profile in patients whose disease progressed during prior cBTKi treatment. Several ongoing randomized, global, phase 3 clinical trials are evaluating pirtobrutinib for the treatment of B-cell malignancies, including one in patients with pretreated BTKi-naïve MCL (NCT04662255), and four in patients with CLL or SLL (NCT05023980, NCT05254743, NCT04666038, and NCT04965493). These trials aim to provide robust data on pirtobrutinib' efficacy and safety across different patient populations, to build on the evidence garnered from single-arm trials to date.

5 | CONCLUSIONS

Pirtobrutinib demonstrated clinically meaningful efficacy in Chinese patients with MCL following progression on cBTKi therapy and resulted in longer survival times compared to historical data. Additionally, pirtobrutinib exhibited preliminary antitumor activity in Chinese patients with cBTKi pretreated R/R CLL/SLL. Pirtobrutinib was generally well tolerated, with no new safety signals observed in this Chinese population. The efficacy and safety profile in Chinese patients were consistent with those reported from the global phase 1/2 BRUIN study suggesting that pirtobrutinib is a promising treatment option for Chinese patients with MCL pretreated with a cBTKi.

AUTHOR CONTRIBUTIONS

Yanyan Liu: Writing – review and editing; investigation. **Ningjing Lin:** Investigation; writing – review and editing. **Shuhua Yi:** Investigation; writing – review and editing. **Huiqiang Huang:** Investigation; writing – review and editing. **Ye Guo:** Investigation; writing – review and editing. **Qingyuan Zhang:** Investigation; writing – review and editing. **Haiyan Yang:** Investigation; writing – review and editing. **Huilai Zhang:** Investigation; writing – review and editing. **Liling Zhang:** Investigation; writing – review and editing. **Ru Feng:** Investigation; writing – review and editing. **Yijiao Qian:** Conceptualization; investigation; writing – review and editing. **Jiankun Zhu:** Conceptualization; writing – review and editing; formal analysis; investigation; methodology. **Yuqin Song:** Conceptualization; investigation; writing – review and editing. **Jun Zhu:** Conceptualization; investigation; writing – review and editing; supervision.

ACKNOWLEDGMENTS

The authors thank Junjun Liu from Eli Lilly and Company for data interpretation, critical suggestions for improvement, and preparation of the first draft and final revision; Jake Burrell and Lyndsey Wood from Rude Health Consulting Limited for medical writing and editorial assistance (funded by Eli Lilly and Company).

FUNDING INFORMATION

This study was sponsored by Eli Lilly and Company. Eli Lilly and Company was involved in the study design and conduct; data collection, management, analyses, and interpretation of the data; preparation,

review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

YQ and JZ are employees of and shareholders in Eli Lilly and Company. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Eli Lilly and Company upon reasonable request. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The trial was conducted in accordance with the principles of international ethics guidelines, including the Declaration of Helsinki and applicable laws and regulations. Institutional review boards approved the protocol at each study site and all patients provided written informed consent before being included in the study. This study is registered at ClinicalTrials.gov (NCT04849416).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Liu Y, Lin N, Yi S, et al. Pirtobrutinib in Chinese patients with relapsed or refractory B-cell malignancies: A single-arm, open-label, phase 2, multicenter trial. *Int J Cancer*. 2025;156(11):2158-2168. doi:10.1002/ijc.35339