

Rocbrutinib in Covalent BTK Inhibitor Exposed Relapsed or Refractory Mantle Cell Lymphoma: a Phase 2, Open-label, Multicenter, Single-arm Study

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Abstract

Rocbrutinib is a fourth-generation Bruton's tyrosine kinase (BTK) inhibitor with a unique dual covalent/non-covalent binding mechanism. Its efficacy and safety were evaluated in covalent BTK inhibitor-pretreated patients with mantle cell lymphoma in this phase 2 pivotal study. Patients received rocbrutinib until disease progression or unacceptable toxicities. The primary endpoint was overall response rate (ORR) assessed by independent review committee (IRC). Among 62 enrolled subjects, median age was 61 years (range, 37-79), and median number of prior therapies was 3 (range, 1-10). The IRC-assessed ORR was 63.9% (95% CI, 50.6-75.8), including 23.0% with complete response; Median duration of response was 16.46 months (95% CI, 8.25-not reached). Adverse events were primarily grade 1-2 hematologic events. Grade $\geq$ 3 hemorrhage occurred in 3.2% of patients, and no atrial fibrillation/flutter cases were reported. Rocbrutinib achieved high response rate and durable response, with a favorable safety profile in this difficult-to-treat population. ClinicalTrials.gov registration: NCT05716087.

Introduction

Mantle cell lymphoma (MCL) is a relatively rare subtype of B-cell non-Hodgkin lymphoma (B-NHL) with heterogeneous clinical behaviors, which can be indolent to highly aggressive^[1]. In recent years, the overall prognosis of patients with MCL has dramatically improved due to the approval of novel drugs, especially the emergence of covalent Bruton tyrosine kinase inhibitors (cBTKi). The latter has been the standard of care in relapsed/refractory (R/R) population^[2-5] and also in the first-line setting^[6, 7]. Nevertheless, disease progression inevitably occurs during the treatment, and the long-term utility of cBTKi may also be compromised by treatment intolerance. There are very limited treatment options for these patients and the prognosis is poor. Salvage therapies such as bendamustine- or lenalidomide-based regimens yield low response rates of less than 30% with overall survival less than 12 months^[8, 9]. CD19-targeted chimeric antigen receptor (CAR) T-cell products have been approved for the treatment of R/R MCL patients after prior cBTKi therapy. They have demonstrated high response rate, durable response, and survival benefits, but its application is often limited by patient fitness, safety concerns, and practical feasibility^[10-12]. Non-covalent BTK inhibitors (ncBTKi) are developed to overcome the resistance of lymphoma cells to cBTKi and represent a novel targeted strategy, but there's room for efficacy improvement^[13]. Consequently, there remains unmet medical needs for developing more efficacious, broadly accessible, and well-tolerated therapies for MCL patients previously exposed to cBTKi.

Rocbrutinib is a novel, highly selective, fourth-generation BTKi capable of binding wild-type BTK covalently with an active warhead, C481 mutant BTK (C481S, C481F and C481R) non-covalently, and other non-C481 mutations such as kinase-dead mutation L528W, gatekeeper mutation T474I covalently^[14, 15]. It has sub-nanomolar potency, high kinase selectivity for BTK, and human pharmacokinetic exposure that supports continuous BTK inhibition under once daily dosing period. In

the first-in-human phase 1 study, rocbrutinib showed promising efficacy and favorable safety in multiple types of B cell non-Hodgkin lymphoma, including R/R MCL patients who have failed prior cBTKi treatment (ORR 70.6%, complete response (CR) rate 35.5%) [16-18].

The phase 2 ROCK-1 trial was initiated to further evaluate the efficacy and safety of rocbrutinib in Chinese patients with R/R MCL who have progressed after or intolerance to prior cBTKi therapy. Here, we report the primary efficacy and safety results.

Results

Patients

From May 17, 2023, to June 05, 2024, a total of 62 subjects were enrolled and received at least one dose of rocbrutinib at 150 mg once daily (QD). Among which, 61 patients were histologically confirmed as MCL by central laboratory review and included in the baseline and efficacy analyses. Baseline characteristics are summarized in Table 1. The median age was 61 years (range 37-79), and 73.8% were male. 19.7% of patients with blastoid or pleomorphic histology, 68.9% of patients with a Ki-67 proliferation index $\geq 30\%$, 62.2% of patients had an intermediate- or high-risk disease based on simplified MCL International Prognostic Index (sMIPI) score, and 29.5% of patients with at least one bulky disease ($\geq 5\text{cm}$ in longest diameter). At baseline, 55 patients (90.2%) had Ann Arbor stage IV disease and 52 (85.2%) patients with at least one extranodal disease. The median number of prior lines of therapy was 3 (range 1-10). 100% had been exposed to cBTKi, 95.1% to anti-CD20 antibody, 31.1% to immunomodulator, 9.8% to BCL-2 inhibitor, and 6.6% had received autologous stem cell transplant. Four patients (6.6%) discontinued their most recent previous cBTKi treatment due to unacceptable toxicity, among which 2 patients had no evidence of progression. The remaining 59 patients (96.7%) had disease progressed prior to study entry. The median number of prior cBTKi was 1 (range, 1-3), with 31.1% of patients receiving two or more prior cBTKi.

As of June 05, 2025, the median time on study treatment of all 62 enrolled patients was 5.5 months (range, 0.3-21.2) and the median relative dose intensity was 100.0% (range, 74.0-100.0). Treatment was discontinued in 45 (72.6%) patients, and reasons for treatment discontinuation included disease progression (n = 37), patient withdrawal (n = 5), death (n = 1), investigators' discretion (n = 1) and poor compliance (n = 1).

Table 1: Demographic and baseline disease characteristics

<i>Characteristics</i>	<i>N = 61</i>
<i>Age, years</i>	
Median (range)	61 (37-79)
≥ 65 years, n (%)	25 (41.0)
<i>Race, n (%)</i>	
Chinese	61 (100)
<i>ECOG performance status, n (%)</i>	
0	13 (21.3)
1-2	48 (78.7)
<i>sMIPI score, n (%)</i>	
Low (0-3)	23 (37.7)
Intermediate (4-5)	23 (37.7)
High (6-11)	15 (24.6)
<i>Bulky disease, n (%)</i>	
Yes (≥5cm tumor mass)	18 (29.5)
No	43 (70.5)
<i>Extranodal disease, n (%)</i>	
Yes	52 (85.2)
Bone marrow involvement	39 (63.9)
Gastrointestinal involvement	14 (23.0)
<i>Histology, n (%)</i>	
Classic	35 (57.4)
Blastoid	8 (13.1)
Pleomorphic	4 (6.6)
Not reported	14 (23.0)
<i>Number of lines of prior systemic therapy</i>	
Median (range)	3 (1-10)
1, n (%)	8 (13.1)
2, n (%)	19 (31.1)

3 or more, n (%)	34 (55.8)
Prior systemic therapies, n (%)	
cBTK inhibitor	61 (100)
Chemotherapy	58 (95.1)
Anti-CD20 antibody	58 (95.1)
Immunomodulator	19 (31.1)
BCL-2 inhibitor	6 (9.8)
Stem cell transplant (auto-SCT) or CAR-T	5 (8.2)
Type of prior BTK inhibitors	
Ibrutinib	25 (40.9)
Zanubrutinib	36 (59.0)
Orelabrutinib	15 (24.5)
Others	6 (9.8)
Number of prior BTK inhibitors	
Median (range)	1 (1-3)
1, n (%)	42 (68.9)
2, n (%)	17 (27.9)
3 or more, n (%)	2 (3.3)
Treatment duration of the most recent prior BTK inhibitor (months), median (range)	18.5 (0.1-67.4)
Relapsed/refractory to any prior BTK inhibitor, n (%) ^a	59 (96.7)
Discontinued the most recent prior BTK inhibitor due to intolerance/toxicity, n (%)	4 (6.6)
TP53-mutated (N=23) ^b	6 (26.1)

Abbreviations: BCL-2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T-Cell; ECOG PS, Eastern Cooperative Oncology Group performance status; sMIPI, simplified mantle-cell lymphoma International Prognostic Index.

^a defined as the demonstration of disease progression while on or after cessation of BTKi therapy, *irrespective of the reason for treatment discontinuation.*

^b Twenty-three patients had baseline sequencing data or archived results.

Efficacy

As of June 05, 2025, among the full analysis set (n = 61), the ORR as assessed by independent review committee (IRC) was 63.9% (95% CI, 50.6 to 75.8), including 23.0% (n = 14) with complete response and 41.0% (n = 25) with partial response (Table 2). Shrinking of target lesions was observed in 43 (76.8%) of 56 patients who had completed at least one post-treatment response assessment (Figure 1). The majority of responders achieved their response by the first efficacy assessment, the median time to response (TTR) was 1.84 months (range, 1.61-3.75). IRC-assessed responses were observed across different prespecified subgroups (Data Supplement [Figure S1]), including those with poor prognostic features, such as high-risk per sMIPI score (7 [46.7%] of 15 patients), bulky disease (9 [50.0%] of 18 patients), blastoid variant (4 [50.0%] of 8 patients), baseline Ki-67 level of 30% or higher (26 [61.9%] of 42 patients) and those who had received ≥ 3 prior lines of therapy (12 [54.5%] of 22 patients). The ORR to rocbrutinib was comparable between patients who have received more than one prior cBTKi (63.1%, 12/19) and the overall population (63.9%, 39/61). The concordance between IRC- and investigator-assessed overall response was 98.4%, with an investigator-assessed ORR of 62.3% and complete response of 26.2%. 2 patients tested positive for the presence of BTK C481S mutation at baseline, both have achieved response after rocbrutinib treatment.

Based on IRC's assessment, the estimated median duration of response (DOR) was 16.46 months (95% CI, 8.25 to not evaluable [NE]) after a median follow-up of 11.27 months (95% CI, 8.41 to 14.03) (Table 2, Figure 2A). The median progression free survival (PFS) after a median follow-up of 12.85 months (95% CI, 10.18 to 15.64) was 7.39 months (95% CI, 3.71 to 18.30) and the 12-month PFS rate was 45.7% (95% CI, 32.1 to 58.4) (Table 2, Figure 2B). The median DOR and PFS based on investigators' assessment was 13.70 months (95% CI, 5.55 to NE) and 5.52 months (95% CI, 3.71 to 12.68), respectively (Table 2, Data Supplement [Figure S2]). After a median follow-up of 17.02 months (95% CI, 14.78 to 18.46), the median overall survival (OS) was not reached (95% CI, 14.62 to NE) with 62.3% of patients alive and the estimated 18-month OS rate was 60.6% (95% CI, 46.1% to 72.4%) (Table 2, Figure 2C).

Table 2: Efficacy of rocbrutinib in patients with cBTKi pre-treated **MCL assessed by IRC and investigators**

<i>Efficacy parameters</i>	<i>IRC-assessed</i> (n = 61)	<i>Investigators-assessed</i> (n = 61)
ORR, % (95% CI)	63.9 (50.6 to 75.8)	62.3 (49.0 to 74.4)
BOR, n (%)		
Complete response	14 (23.0)	16 (26.2)
Partial response	25 (41.0)	22 (36.1)
Stable disease	4 (6.6)	7 (11.5)
Progressive disease	14 (23.0)	12 (19.7)
Not evaluable ^a	4 (6.6)	4 (6.6)
<i>DOR</i>		
Patients with a response, No.	39	38
Patients with censored data, n (%)	22 (56.4)	19 (50.0)
median DOR (95% CI), months	16.46 (8.25 to NR)	13.70 (5.55 to NR)
Median follow-up, months	11.27	12.71
<i>PFS</i>		
Patients with censored data, n (%)	27 (44.3)	22 (36.1)
median PFS (95% CI), months	7.39 (3.71 to 18.30)	5.52 (3.71 to 12.68)
Median follow-up, months	12.85	12.91
<i>OS</i>		
Patients with censored data, n (%)	38 (62.3)	
median OS (95% CI), months	NR (14.62 to NR)	
Median follow-up, months	17.02	

Note: Overall response and best response were determined according to the 2014 Lugano criteria.

Abbreviations: BOR, best overall response; cBTKi, covalent Bruton tyrosine kinase inhibitor; DOR, duration of response; IRC, independent review committee; MCL, mantle cell lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

^a Patients without at least one post-baseline tumor assessment.

Safety

All enrolled patients received at least one dose of rocbrutinib were included in the safety analysis (n=62). 96.8% of patients experienced at least one treatment-emergent adverse events (TEAEs). Common TEAEs (TEAEs with an incidence rate of 10% or higher) and adverse events of special interest (AESI) are respectively presented in Table 3 and Table 4. Common TEAEs of any grade were thrombocytopenia (43.5%), anemia (30.6%), neutropenia (29.0%), leukocytosis (24.2%), lymphocytosis (24.2%), increased blood creatinine (21.0%), hyperuricemia (21.0%), infectious pneumonia (19.4%), leukopenia(17.7%), hypoalbuminemia (17.7%), weight loss (16.1%), hypokalemia (16.1%), constipation (16.1%), hypercholesterolemia (14.5%), hypertriglyceridemia (12.9%), upper respiratory tract infection (12.9%), pulmonary inflammation (12.9%), lymphocytopenia (11.3%), blood bilirubin increased (11.3%), petechiae (11.3%), fever (11.3%), and the majority were grade 1 or 2 in severity. 36 out of 62 patients (58.1%) reported at least one grade 3 or higher TEAEs. Grade 3 or higher TEAEs with an incidence rate of 5% or higher were lymphocytosis (12.9%), anemia (11.3%), infectious pneumonia (11.3%), neutropenia (9.7%), thrombocytopenia (6.5%). There were no grade 5 TEAEs reported. Any grade and grade ≥ 3 lymphocytosis was reported as TEAEs in 15 (24.2%) and 8 (12.9%) of 62 patients, respectively, whereas none of them were accompanied by any symptoms.

AESIs commonly associated with BTK inhibitors were infrequent. Regardless of causality to study treatment, infections of any grade occurred in 32 (51.6%) patients, of which 15 (24.2%) were grade 3 or 4. The most common grade ≥ 3 infections were infectious pneumonia (12.9%). Median time to onset and duration of treatment-related infectious pneumonia was 4.7 months (range, 0.8-11.7) and 4.3 months (range, 0.5-9.9+), respectively. All types of bleeding of any grade occurred in 19 (30.6%) patients, the most frequent of which was grade 1 petechiae (11.3%), other bleeding events include grade 1 hematuria (8.1%), subcutaneous hemorrhage (6.5%) or grade 1-2 bruising (4.8%). 2 patients (3.2%) had major bleeding events (grade ≥ 3 hemorrhage), of which one patient experienced grade 4 gastrointestinal hemorrhage (considered as both disease- and treatment-related), another patient, with a long medical history of hypertension, experienced grade 4 intracranial hemorrhage (considered as unlikely related to the treatment). Other AESI, such as hypertension and QT corrected interval prolonged, each occurred in 6.5% of patients (n = 4), all were grade 1 or 2. There were no cases of atrial fibrillation or flutter, and no second primary malignancies was reported.

Serious AEs (SAEs) considered related to rocbrutinib were reported in 11 patients (17.7%), including infectious pneumonia (8.1%), viral pneumonia, urinary tract infection, upper respiratory tract infection, leukocytosis, abnormal liver function, creatinine increased, thrombocytopenia, acute kidney injury, gastrointestinal bleeding (1.6% each). 21 patients (33.9%) had dose interruption due to TEAEs, which were considered related to study treatment in 13 (21.0%) patients. TEAEs leading to dose reduction were observed in 2 patients (3.2%), including one case each of epistaxis and asthenia. No patient permanently discontinued rocbrutinib due to TEAEs, and no death was attributed to study treatment.

Table 3. Adverse events with an incidence rate of 10% or higher

Adverse Events	Safety Population (n = 62)			
	TEAEs, n (%)		TRAEs, n (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Thrombocytopenia	27 (43.5)	4 (6.5)	25 (40.3)	4 (6.5)
Anemia	19 (30.6)	7 (11.3)	15 (24.2)	6 (9.7)
Neutropenia	18 (29.0)	6 (9.7)	16 (25.8)	4 (6.5)
Leukocytosis	15 (24.2)	3 (4.8)	15 (24.2)	3 (4.8)
Lymphocytosis	15 (24.2)	8 (12.9)	15 (24.2)	8 (12.9)
Creatinine increased	13 (21.0)	1 (1.6)	10 (16.1)	0
Hyperuricemia	13 (21.0)	0	9 (14.5)	0
Infectious pneumonia	12 (19.4)	7 (11.3)	8 (12.9)	4 (6.5)
Leukopenia	11 (17.7)	3 (4.8)	9 (14.5)	1 (1.6)
Hypoalbuminemia	11 (17.7)	0	9 (14.5)	0
Weight loss	10 (16.1)	0	4 (6.5)	0
Hypokalemia	10 (16.1)	1 (1.6)	6 (9.7)	0
Constipation	10 (16.1)	0	3 (4.8)	0
Hypercholesterolemia	9 (14.5)	0	6 (9.7)	0
Hypertriglyceridemia	8 (12.9)	1 (1.6)	6 (9.7)	1 (1.6)
URTI	8 (12.9)	3 (4.8)	3 (4.8)	1 (1.6)
Pneumonitis	8 (12.9)	0	6 (9.7)	0
Lymphocytopenia	7 (11.3)	1 (1.6)	7 (11.3)	1 (1.6)
Blood bilirubin increased	7 (11.3)	0	7 (11.3)	0
Petechiae	7 (11.3)	0	7 (11.3)	0
Fever	7 (11.3)	0	2 (3.2)	0

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; URTI: upper respiratory tract infection.

Table 4. Adverse event of special interest (AESI) of rocbrutinib

AESI ^a	Safety Population (n = 62)			
	TEAE, n (%)		TRAE, n (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Thrombocytopenia	27 (43.5)	4 (6.5)	25 (40.3)	4 (6.5)
Anemia	19 (30.6)	7 (11.3)	15 (24.2)	6 (9.7)
Neutropenia	18 (29.0)	6 (9.7)	16 (25.8)	4 (6.5)
Infections (all types)	32 (51.6)	15 (24.2)	15 (24.2)	6 (9.7)
URTI ^b	14 (22.6)	3 (4.8)	4 (6.5)	1 (1.6)
Infectious pneumonia ^c	13 (21.0)	8 (12.9)	9 (14.5)	5 (8.1)
Bleeding (all types)	19 (30.6)	2 (3.2)	15 (24.2)	1 (1.6)
Petechiae	7 (11.3)	0	7 (11.3)	0
Bruising	3 (4.8)	0	3 (4.8)	0
Major hemorrhage ^d	2 (3.2%)	2 (3.2%)	1 (1.6)	1 (1.6)
Hypertension ^e	4 (6.5)	2 (3.2%)	1 (1.6)	1 (1.6)
QT corrected interval prolonged	4 (6.5)	0	4 (6.5)	0
Atrial fibrillation/flutter	0	0	0	0
Second Primary Malignancies	0	0	0	0

Abbreviations: AESI: Adverse event of special interest; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; URTI: upper respiratory tract infection.

^a AESI are those that were previously associated with cBTKi and are all composite preferred terms.

^b includes upper respiratory tract infections, sinusitis, nasopharyngitis, and pharyngotonsillitis.

^c includes infectious pneumonia, viral pneumonia

^d defined as any grade ≥3 bleeding at any site or central nervous system bleeding of any grade.

^e defined as hypertension or blood pressure increased

Discussion

In this pivotal phase 2 single-arm study, rocbrutinib demonstrated promising efficacy and manageable safety in heavily pretreated Chinese patients with MCL who had prior cBTKi treatment, a population

representing a high unmet medical need per current available treatment options. The non-covalent BTKi such as pirtobrutinib are establishing a new standard of care for cBTKi-resistant MCL, reporting ORR of 57.8% and a CR rate of 20.0% in the pivotal BRUIN study^[13]. After a 12-month follow-up of the last enrolled patients in ROCK-1 study, the ORR and median DOR assessed by IRC were 63.9% (95% CI, 50.6 to 75.8) and 16.46 months (95% CI, 8.25 to not reached), respectively. The promising response rates met the primary endpoint of this study and are consistent with those previously reported from the phase 1 study, in which the ORR was 70.6% in patients with BTKi pre-treated R/R MCL^[17]. In addition, no new safety signals were identified in this study compared to those with other BTK inhibitors, with low rates of treatment-related grade ≥ 3 bleeding (1.6%) and infection (9.7%), and no atrial fibrillation or flutter being observed. Based on the clinical data from ROCK-1 study, rocbrutinib will become a new benchmark for the treatment of this population and further consolidate the role of new generation BTK inhibitors in this disease area.

We provide the first evidence of the tolerability and efficacy of rocbrutinib monotherapy in patients with MCL in the post-BTK inhibitor treatment setting. The ORR of 63.9% (CR rate of 23.0%) and median DOR of 16.46 months, as assessed by IRC, were encouraging and showed favorable treatment benefit for the population^[9, 13, 19]. Overall baseline demographic and disease characteristics in this study were generally comparable to those in previous reported studies targeting patients with R/R MCL previously exposed to BTKi^[10-13, 19, 20]. The median age in this study was 61 years (range 37-79), and 41% patients with age ≥ 65 years, this was somewhat younger compared with that reported for the aforementioned studies (median age, 66-70 years in the pirtobrutinib study; 65 years in KTE-X19 study; 69 years in venetoclax study). This is consistent with previous reports^[21, 22] that the Chinese population were with younger age at disease onset. In the ROCK-1 study, we did not find significant age differences in patients' tolerance to rocbrutinib, and older population also achieved an encouraging response from the treatment. In this study, the median number of prior lines of therapies was 3 (range 1-10), which was consistent with that from previous studies^[13, 20]. The median number of prior cBTKi treatment was 1 (range, 1-3). Among which, zanubrutinib was the most frequently used cBTKi, accounting for 59.0% of patients (n = 36). Whereas, ibrutinib or acalabrutinib were commonly used prior cBTKi in pirtobrutinib study^[13]. Whether the type of prior cBTKi used could affect response rate to rocbrutinib remains unknown, as 31.1% of patients (n = 19) in this study have received two or more prior cBTKi therapy and their ORR was comparable with the overall population (63.1% versus 63.9%). According to previous report of pirtobrutinib^[13], the ORR to pirtobrutinib was similar in patients previously treated with zanubrutinib (n = 6; ORR, 50.0%) versus ibrutinib (n = 59; ORR, 59.3%), acalabrutinib (n = 31; ORR, 58.1%), however, the sample sizes across subgroups were small and their baseline characteristics may be imbalanced. In agreement with previous studies^[13, 19], patients who discontinued previous cBTKi treatment because of toxicity or other reasons (including unknown reasons, lack of response and other causes) had better efficacy outcomes than those discontinued due to disease progression. The majority of patients in this study had progressed disease at study entry, the response rate in patients who discontinued cBTKi due to disease progression was 51.2%, which was still higher than the protocol

prespecified target ORR of 50%. The activity of rocbrutinib in MCL with poor prognostic features, including those with blastoid histology and high Ki-67 levels, was also encouraging. However, one of the limitations of the subgroup analyses were the small sample size; for example, only 4 and 6 patients were with pleomorphic histology or TP53 mutation, so these data are not adequate to make a conclusion that patients with pleomorphic variant or TP53 mutation will have a lower possibility to achieve a response.

Although resistance mechanisms to cBTKi, such as most common mutations in BTK at the C481 position and in PLCG2, have been well characterized in chronic lymphocytic leukemia ^[23-25], the mechanisms of cBTK inhibitor resistance in MCL have not been extensively studied or well understood. BTK mutations are rarely observed in MCL, suggesting that resistance to cBTK inhibitors in this disease may be intrinsic or mediated through nongenetic mechanisms ^[26, 27]. The efficacy of rocbrutinib in MCL or other NHLs following cBTKi treatment may be attributable to its unique dual binding mechanism, sub-nanomolar potency, and favorable human pharmacokinetic exposure ^[15, 28-30]. As we know, both CAR T-cell therapy and ncBTKi have been approved and expanded treatment options in the setting of R/R MCL. The access of CAR T-cell therapy was limited due to excess toxicities, as well as the requirement of holding and bridging therapies ^[31-33]. While ncBTKi effectively target C481-mutant BTK, their activity against wild-type BTK is competitive and reversible. In contrast, the covalent binding ability of rocbrutinib to wild-type BTK may provide more sustained and profound suppression of tumor clones that remain dependent on wild-type BTK signaling, while its non-covalent binding ability could concurrently inhibit mutant or resistant clones. This dual blockade could potentially delay the emergence of resistance and deepen responses, translating into the high ORR and prolonged DOR observed in this study. It is noteworthy that 2 patients with BTK C481S mutation achieved response after treatment with rocbrutinib. As mentioned above, although BTK mutations may not serve as a primary resistance mechanism in MCL, this is nonetheless an encouraging observation. Other emerging therapies such as bispecific antibodies have shown high response rates in the R/R MCL patients with prior exposure of BTKi, but are still under clinical investigations ^[34].

Beyond efficacy, safety profile of rocbrutinib is favorable and the toxicities are manageable. It is critical for its continuous use in an elderly population and warrants its further clinical development, especially in combination with other standard regimens. No unexpected safety signal was reported in this study. The incidence rate of grade ≥ 3 events was comparable to that reported for other BTK inhibitors ^[2-5, 13]. Notably, in the present study, there was no report of atrial fibrillation or flutter, while it was reported as 1.6% to 3.7% (grade 3 or higher events) in studies with other BTK inhibitors ^[35-37]. The predominant bleeding events observed with rocbrutinib were grade 1 petechiae. The incidence of grade ≥ 3 hemorrhage was only 3.2% ^[2-5, 13]. In addition, the frequency of hypertension with any grade was low (6.5%), and the majority of events being grade 1 or 2. This improved safety likely stems from high selectivity of rocbrutinib for BTK, minimizing off-target inhibition of kinases such as IL2 inducible T cell kinase (ITK) and Tec family of tyrosine kinases (TEC) which are implicated in these toxicities. The predominant adverse events of rocbrutinib were manageable cytopenias and infections, which are expected in this heavily pretreated and elderly population, and comparable to other products in the same

class. Of note, rocbrutinib remained well tolerated despite the fact that all subjects had received prior cBTKi therapy, 31.1% of whom had received two or more prior cBTKi, and the median treatment duration of the most recent cBTKi was 18.4 months (maximum, 67.4 months). This is a relevant observation given that prolonged prior exposure to cBTKi may increase the risk of cumulative toxicities. We have noticed that creatinine levels increased during the treatment of rocbrutinib (21.0%), but no special intervention was needed, and the vast majority of events were grade 1 to 2 in severity. A possible mechanism of elevated creatinine is the inhibition of renal transporters by rocbrutinib. Pre-clinical study has shown rocbrutinib could inhibit the renal MATE-1 (multidrug and toxin extrusion protein 1) and MATE-2K (multidrug and toxin extrusion protein 2K) transporters, which could result in the inhibition of creatinine efflux. This kind of elevation of serum creatinine was reversible and didn't lead to renal function impairment. Similar observations have also been reported for other BTKi [36, 37]. In this study, the rate of dose reduction (3.2%) was low and no treatment discontinuations due to TEAEs were reported. This favorable safety profile is paramount for a drug intended for long-term administration in patient populations that is often elderly and frail, potentially enabling longer treatment duration and better preservation of quality of life.

The limitations of this study include its single-arm study design, which precludes direct comparison of efficacy and safety with other therapies, and its relatively small sample size. Also, the median duration of response and overall survival were still not mature. Though significant survival benefit had been observed, longer follow-up time is needed to further characterize the survival benefits and long-term safety profile of rocbrutinib. Furthermore, while promising activity was observed across patients with poor prognosis, the sample sizes within these subgroups were small and may be imbalanced/incomparable. Predictive or prognostic biomarkers for rocbrutinib, such as specific BTK mutation profiles or B-cell receptor signaling aberrations, have not yet been fully identified, highlighting an important area for future translational investigation. Despite the above-mentioned limitations, the baseline data are comparable to those of previously published studies and should be representative of the current real-world population. Additionally, the data of this study are consistent with those from phase I study of rocbrutinib [16, 17], lending robustness to our findings and conclusions.

In conclusion, ROCK-1 study demonstrates that rocbrutinib, as a fourth-generation BTKi, is a highly promising treatment for patients with R/R MCL previously treated with cBTKi. It has achieved high response rates, deep response and durable disease control, along with a favorable safety profile. For patients with cBTKi-exposed MCL, rocbrutinib offers new hope for effective and well-tolerated long-term disease management. The findings from this study strongly support further clinical development of rocbrutinib, and the ongoing phase 3 randomized trial comparing rocbrutinib with investigator's choice of approved cBTK inhibitors in R/R MCL (NCT07377578) will evaluate its potential use in earlier lines of therapy.

Methods

Study Design and Participants

The ROCK-1 trial (LP-168-CN201) is a single-arm, multicenter, open-label, phase 2 study conducted across 27 study centers in China. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the institutional review board at each center. All patients provided written informed consent. This trial is registered with ClinicalTrials.gov (identifier: NCT05716087).

Eligible patients were adults (≥ 18 years) with histologically confirmed diagnosis of MCL by central laboratory review who had progressed on or after prior cBTKi therapy (BTKi-intolerance also allowed) and had previously received anti-CD20 antibody based therapies unless contraindicated. Other key inclusion criteria included at least one measurable disease per Lugano 2014 criteria, an Eastern Cooperative Oncology Group performance status of 0-2, and adequate organ function. Key exclusion criteria were known disease involvement of the central nervous system (CNS), prior exposure to ncBTKi or BTK degrader, prior allogeneic hematopoietic stem cell transplantation, CAR-T treatment within 90 days, clinically significant cardiovascular disease, active bleeding, or a history of other malignancies within 2 years.

The study protocol or full eligibility criteria are described in the Supplementary Material.

Treatment and Study Procedures

Enrolled patients received oral rocbrutinib at 150 mg once daily (QD) continuously in 28-day cycles until disease progression or unacceptable toxicity or patients/physicians' decision to withdraw. Dose modifications were permitted for the management of adverse events (AEs) per protocol-defined guidelines. Disease assessments via computed tomography (CT) or positron emission tomography-CT (PET-CT) were performed at baseline, every 8 weeks for the first 8 cycles, and every 12 weeks thereafter. Bone marrow biopsy and gastrointestinal endoscopy (if clinically indicated) were performed at baseline and repeated upon demonstration of CR by imaging if involvement has been documented in baseline. Response was respectively assessed by independent review committee (IRC) and investigators, based on the Lugano 2014 lymphoma response criteria. Safety was continuously monitored throughout the study and up to 28 days after the last dose of study treatment. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The causality of AEs to study treatment was determined by the investigators.

Study Endpoints

The primary endpoint was overall response rate (ORR) assessed by IRC, defined as the proportion of patients achieving a complete response (CR) or partial response (PR) as their best response. Secondary endpoints included ORR assessed by investigators, duration of response (DOR) and progression-free survival (PFS) respectively assessed by IRC and investigators, overall survival (OS), and safety. DOR was defined as the time from the start date of the first documented response to the earlier date of progressive disease or death from any cause. PFS was measured from the first dose of study treatment

to the earlier documentation of progressive disease or death from any cause. OS was measured from first dose of study treatment to the date of death from any cause.

Safety endpoints included the incidence, severity, and attribution of treatment-emergent adverse events (TEAEs). Treatment-related adverse events (TRAEs) were defined as TEAEs that considered as definitely related, probably related or possibly related to rocbrutinib. Adverse events of special interest (AESIs) for BTK inhibitors were prespecified as cytopenias, infections, hemorrhage, gastrointestinal disorders, hepatic function abnormalities, cardiac arrhythmias (including atrial fibrillation/flutter), hypertension, and second primary malignancies, and were analyzed separately. The preferred term for AESI were grouped according to pre-specified rules defined in the statistical analysis plan (Supplementary Material).

Statistical Analysis

All analyses were conducted according to the statistical analysis plan (SAP) (Supplementary Material). The sample size of 62 patients was calculated based on a pre-specified target value design to differentiate between a null hypothesis ORR of 30% and an alternative hypothesis ORR of 50%, to provide approximately 85% power and one-sided alpha of 0.025. Ruling out a lower limit of 30% for ORR is considered clinically meaningful for patients with MCL who have discontinued prior cBTKi therapy, as ORRs of approximately 30% were reported in patients with cBTKi-exposed MCL from previous reports (salvage immunochemotherapies, 29-32%) [8, 9].

Descriptive statistics were used to present patient disposition, demographics, disease characteristics, overall response, and safety data. Efficacy analyses were primarily performed on the full analysis set (FAS), which included all enrolled patients who received at least one dose of rocbrutinib and the diagnosis of MCL was confirmed by central laboratory review. Safety analyses included all patients who received at least one dose of rocbrutinib. ORR and its two-sided 95% confidence interval (CI) based on the binomial distribution were calculated using the Clopper-Pearson method. Time-to-event endpoints (DOR, PFS, OS) were estimated using the Kaplan-Meier method. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Declarations

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Author contributions

Y. Song, Q. Cai, X. Tang, K. Zhou, L. Liu, Z. Peng, X. Yan, K. Ding, J. Shen, H. Wu, J. Cui, H. Zhou, J. Wu, H. Jing, M. Jiang, X. Sun, Y. Yang, K. Yu, W. Yang, Z. Li, Z. Jin, S. Yi, F. Li, G. Wu, X. Wei, G. Wang, Y. Wu, N. Lin, and J. Zhu treated and monitored the patients, and collected the data. F. Tan, Y. Shen, Y. Lou, X. Xiao and Y. Chen were involved in study design, data interpretation and manuscript preparation. Y. Song, N. Lin, and J. Zhu designed the study and revised the manuscript.

Competing interests

F. Tan, Y. Shen, Y. Lou, X. Xiao are employees of Guangzhou Lupeng Pharmaceutical Co., Ltd. Y. Chen is an employee of Newave Pharmaceutical Inc.. The remaining authors declare no competing interests.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022 Jul;36(7):1720-1748. doi: 10.1038/s41375-022-01620-2. Epub 2022 Jun 22. Erratum in: *Leukemia*. 2023 Sep;37(9):1944-1951.
2. Wang ML, Rule S, Martin P, et al. *Engl J Med*. 2013 Aug 8;369(6):507-16. doi: 10.1056/NEJMoa1306220. Epub 2013 Jun 19.
3. 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 Feb 17;391(10121):659-667.
4. Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2021 Jun 22;5(12):2577-2585.
5. Deng LJ, Zhou KS, Liu LH, et al. Orelabrutinib for the treatment of relapsed or refractory MCL: a phase 1/2, open-label, multicenter, single-arm study. *Blood Adv*. 2023 Aug 22;7(16):4349-4357.
6. Wang M, Salek D, Belada D, et al. ECHO investigators; ECHO Investigators. Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma. *J Clin Oncol*. 2025 Jul 10;43(20):2276-2284.
7. Dreyling M, Doorduijn J, Giné E, Jerkeman M, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. *Lancet*. 2024 May 25;403(10441):2293-2306.
8. Wang M, Schuster SJ, Phillips T, et al. Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004). *J Hematol Oncol*. 2017 Nov 2;10(1):171.
9. Cheah CY, Chihara D, Romaguera JE, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. *Ann Oncol*. 2015 Jun;26(6):1175-1179.

10. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2020 Apr 2;382(14):1331-1342.
11. Wang M, Siddiqi T, Gordon LI, et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study. *J Clin Oncol*. 2024 Apr 1;42(10):1146-1157.
12. Xie Y, Zhou KS, Li LF, et al. Phase 2 study of relmacabtagene autoleucel (CD19 CAR-T) for relapsed/refractory mantle cell lymphoma in Chinese adults. *Blood Adv*. 2026 Feb 24;10(4):1134-1144.
13. Wang ML, Jurczak W, Zinzani PL, et al. Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma. *J Clin Oncol*. 2023 Aug 20;41(24):3988-3997.
14. Jennifer A. Woyach, Danielle M. Brander, Boyu Hu, et al. LP-168 (Rocbrutinib), a Novel Covalent and Non-Covalent Next-Generation Inhibitor of Bruton's Tyrosine Kinase: Updates on the Phase 1 Trial and Initial Results of the CLL Gatekeeper Mutation Cohort. *Blood* 2024; 144 (Supplement 1): 4622.
15. Britten Gordon, Elizabeth Muhowski, Janani Ravikrishnan, et al. Targeting Covalent and Non-Covalent Btki-Resistant CLL Using the Dual Irreversible/Reversible 4 th Generation BTK Inhibitor LP-168. *Blood* 2023; 142 (Supplement 1): 416.
16. Yuqin Song, Qingqing Cai, Ming Jiang, et al. A Novel Dual Covalent and Non-Covalent Next Generation Inhibitor of Bruton's Tyrosine Kinase LP-168 in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma: Safety and Efficacy Results from a Phase 1 Study. *Blood* 2023; 142 (Supplement 1): 4400.
17. Yuqin Song, Qingqing Cai, Ming Jiang, et al. Safety and Efficacy Results from the Phase I Study of a Novel Dual Covalent and Non-Covalent Next Generation Inhibitor of Bruton's Tyrosine Kinase LP-168 in Patients with Relapsed/Refractory Mantle Cell Lymphoma. *Blood* 2023; 142 (Supplement 1): 3033.
18. Yuqin Song, Qingqing Cai, Keshu Zhou, et al. Efficacy and safety of rocbrutinib, a highly selective 4th-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory Mantle Cell Lymphoma (R/R MCL): Updated results from the phase 1 study. *Blood* 2025; 146 (Supplement 1): 3587.
19. Eyre TA, Walter HS, Iyengar S, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. *Haematologica*. 2019 Feb;104(2):e68-e71.
20. 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 Jun 1;156(11):2158-2168.
21. Sun J, Yang Q, Lu Z, et al. Distribution of lymphoid neoplasms in China: analysis of 4,638 cases according to the World Health Organization classification. *Am J Clin Pathol*. 2012 Sep;138(3):429-34.
22. Ping Yang, Shuozi Liu, Jing Wang, et al. Clinical Characteristics, Treatment and Outcome of Patients with Mantle Cell Lymphoma: A Large, Multicenter Retrospective Analysis in China, *Blood*, Volume

- 138, Supplement 1, 2021, Page 4522, ISSN 0006-4971.
23. Sharma S, Galanina N, Guo A, et al. Identification of a structurally novel BTK mutation that drives ibrutinib resistance in CLL. *Oncotarget*. 2016 Oct 18;7(42):68833-68841.
 24. Nawaratne V, Sondhi AK, Abdel-Wahab O, Taylor J. New means and challenges in the targeting of BTK. *Clin Cancer Res*. 2024; 30(11):2333-2341.
 25. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294.
 26. Justin Taylor. Big cells, bigger BTK resistance in mantle cell lymphoma. *Blood* 2025; 146 (21): 2500–2501.
 27. Rahal R, Frick M, Romero R, et al. Pharmacological and genomic profiling identifies NF-κB-targeted treatment strategies for mantle cell lymphoma. *Nat Med*. 2014 Jan;20(1):87-92.
 28. Britten Gordon, Lillian Cool, Elizabeth Muhowski, et al. Targeting BTKi-resistant CLL using the dual irreversible/reversible 4th generation BTK inhibitor rocbrutinib. *Blood* 2025; 146 (Supplement 1): 1532.
 29. Jennifer A. Woyach, Deborah M. Stephens, Danielle M Brander, et al. Initial Results of a Phase 1 Dose Escalation Study of LP-168, a Novel Covalent and Non-Covalent Next-Generation Inhibitor of Bruton's Tyrosine Kinase. *Blood* 2023; 142 (Supplement 1): 328.
 30. Yuqin Song, Qingqing Cai, Ming Jiang, et al. A Novel Dual Covalent and Non-Covalent Next Generation Inhibitor of Bruton's Tyrosine Kinase LP-168 in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma: Safety and Efficacy Results from a Phase 1 Study. *Blood* 2023; 142 (Supplement 1): 4400.
 31. O'Reilly MA, Sanderson R, Wilson W, et al. Brexucabtagene autoleucel for relapsed/refractory mantle cell lymphoma: Real-world outcomes in the United Kingdom. *Blood* 140 (Suppl1): 7519-7521, 2022.
 32. Ahmed N, Thiruvengadam SK, Hamadani M, et al. Real-world outcomes of brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma: a CIBMTR analysis. *Blood Adv*. 2025 Oct 28;9(20):5382-5396.
 33. O'Reilly MA, Wilson W, Burns D, Kuhn A, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in the United Kingdom: A real-world intention-to-treat analysis. *Hemasphere*. 2024 Jun 13;8(6):e87.
 34. Phillips TJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab in Relapsed/Refractory Mantle Cell Lymphoma: Results From a Phase I/II Study. *J Clin Oncol*. 2025 Jan 20;43(3):318-328.
 35. Ibrutinib [package insert]. San Francisco, CA, Pharmacyclics, 2023.
 36. Zanubrutinib [package insert]. San Mateo, CA, BeiGene USA Inc, 2024.
 37. JAYPIRCA (pirtobrutinib) [package insert]. Indianapolis, IN: Lilly USA, LLC: 2025.

Figures

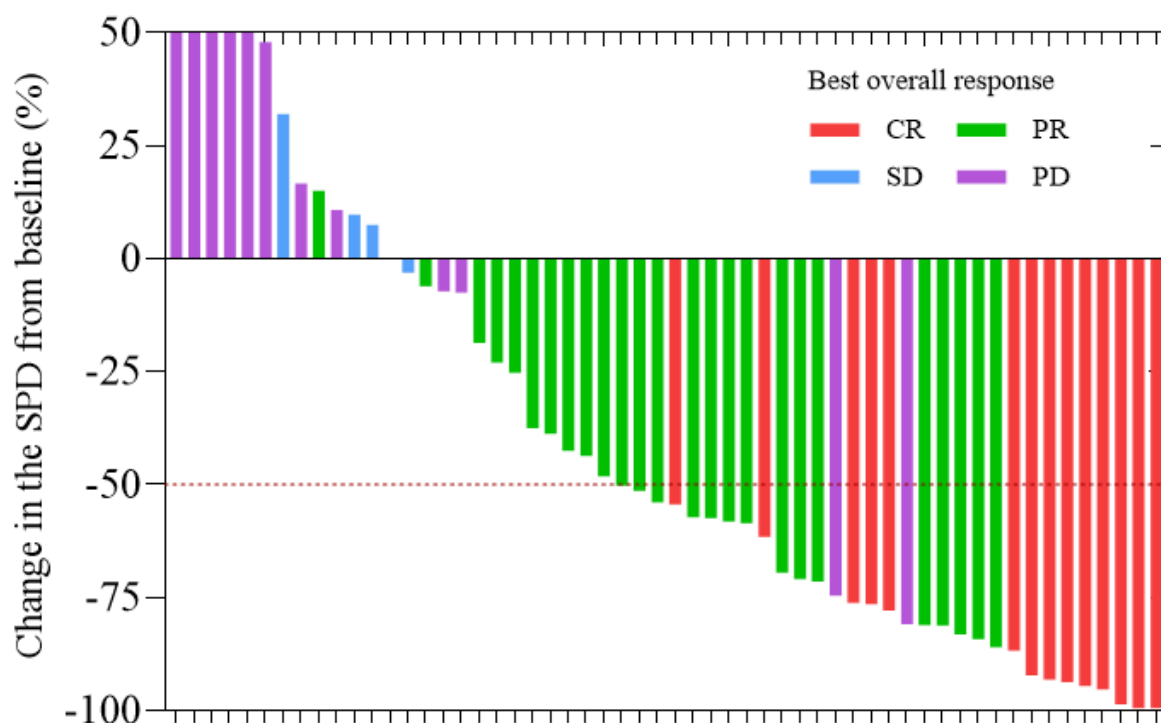


Figure 1

Best change in tumor burden from baseline assessed by IRC

Note: measured by changes in the sum of product of diameter (SPD) based on CT evaluation. Data for 5 patients are not shown in the waterfall plot because of study treatment discontinuation before the first response assessment, or clinical progression lack of adequate imaging evaluation.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SPD, sum of product of diameter.

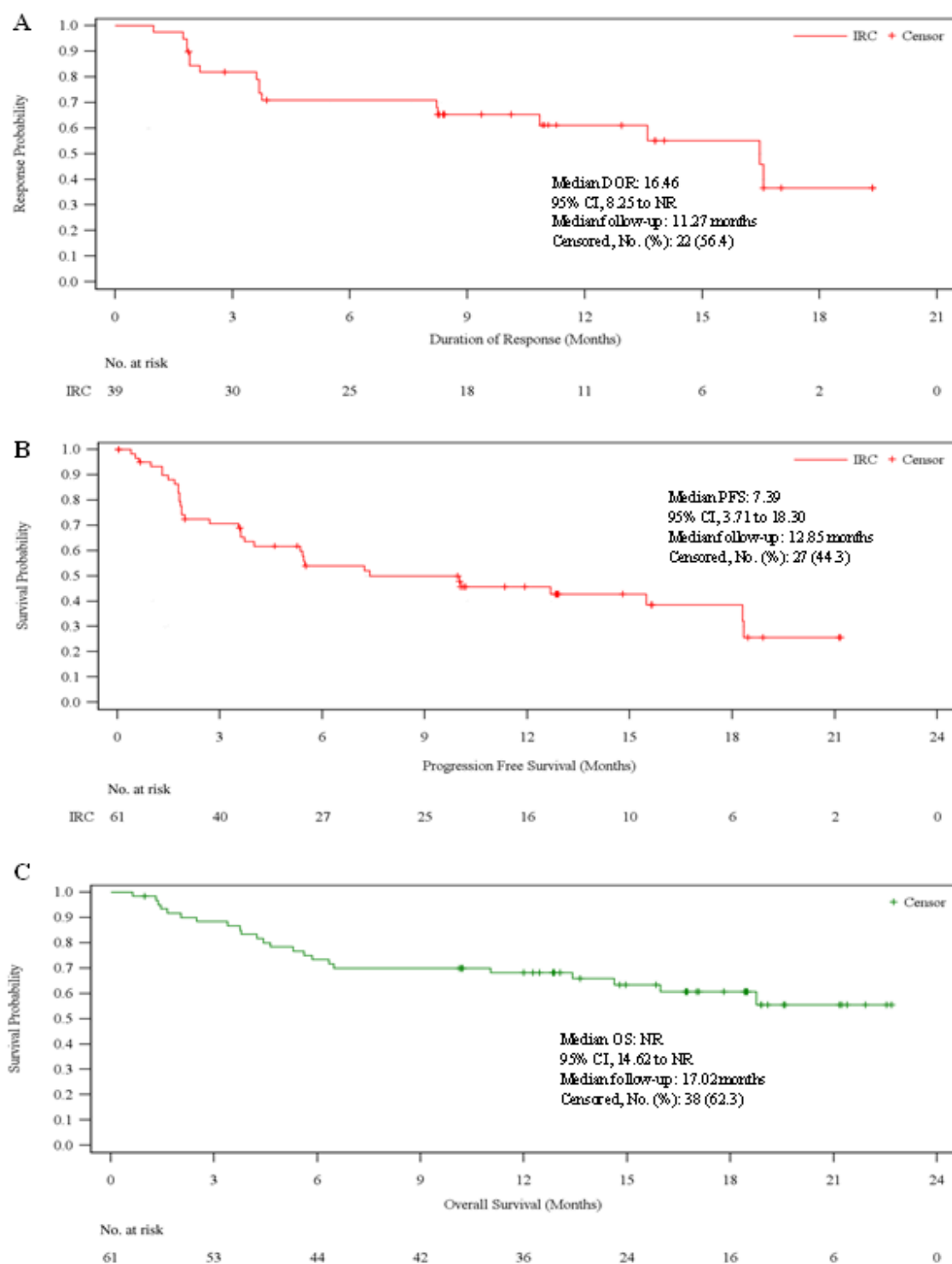


Figure 2

Kaplan-Meier curve of (A) IRC-assessed duration of response (DOR), (B) IRC-assessed progression-free survival (PFS), and (C) overall survival (OS) in patients with cBTKi pre-treated MCL treated with rocbutinib.

Supplementary Files

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