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Safety and efficacy of acalabrutinib plus bendamustine and rituximab in patients with treatment-naive or relapsed / refractory mantle cell lymphoma: phase Ib trial

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Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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ABSTRACT

This multicenter, open-label, phase 1b study (ACE-LY-106) assessed the safety and efficacy of acalabrutinib, bendamustine, and rituximab (ABR) in treatment-naive (TN) and relapsed or refractory (R/R) mantle cell lymphoma (MCL). Patients received acalabrutinib from cycle 1 until disease progression or treatment discontinuation, bendamustine on days 1 and 2 of each cycle for up to 6 cycles, and rituximab on day 1 of each cycle for 6 cycles, continuing every other cycle from cycle 8 for 12 additional doses (TN cohort). Eighteen patients enrolled in the TN and 20 in the R/R cohort. Median duration of exposure to acalabrutinib was 34.0 and 14.6 months in the TN and R/R cohorts, respectively. No new safety risks were identified, and most adverse events (AEs) were grades 1 or 2. Thirteen patients from the TN cohort (72.2%) and 17 patients from the R/R cohort (85.0%) reported grade 3–4 AEs, most commonly neutropenia (TN: 38.9%, R/R: 50.0%). AEs leading to death were pneumonitis (n=1, TN cohort), COVID-19, and cerebrospinal meningitis (n=1 each, R/R cohort). Overall response was 94.4% and 85.0% in the TN and R/R cohorts, respectively; complete response rates were 77.8% and 70.0%, respectively. After a median follow-up of 47.6 months, median progression-free survival (PFS) and overall survival (OS) were not reached in the TN cohort. After a median follow-up of 20.4 months, median PFS was 28.6 months and OS was not reached in the R/R cohort. Results indicate that ABR was safe and efficacious, supporting further study in patients with TN MCL.

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INTRODUCTION

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma (NHL), accounting for 5% to 10% of NHL cases.[1,2] Chemoimmunotherapy (CIT) with bendamustine plus rituximab (BR) is a treatment option for patients with treatment-naive (TN) or relapsed or refractory (R/R) MCL, particularly for patients older than 65 years of age who do not qualify for dose-intensified regimens.[1-3] According to real-world data, BR is the most commonly used frontline treatment for MCL, followed by R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high doses of cytarabine and methotrexate).[2] In a phase 3 study of TN MCL, the substitution of vincristine with bortezomib in the R-CHOP regimen (VR-CAP) significantly improved median overall survival (OS) in TN MCL compared with R-CHOP, albeit with an observed increase in hematologic toxicity.[4,5] Despite the availability of several frontline regimens, relapses and treatment-refractory disease remain common and additional therapy options for MCL are needed.[2,6] Effective targeted therapies for R/R MCL include Bruton tyrosine kinase (BTK) inhibitors, chimeric antigen receptor (CAR) T-cell therapies, immunomodulatory agents, and proteasome inhibitors.[1,7] BTK inhibitors have led to a paradigm shift in the treatment of MCL and have become standard treatments in the R/R MCL setting. Acalabrutinib (A) is a highly selective, second-generation, targeted, covalent BTK inhibitor approved for the treatment of patients with R/R MCL.[3,8,9] With the advent of these orally administered novel targeted agents for the treatment of relapsed or refractory MCL, many studies were initiated to explore the earlier use of BTK inhibitors

for patients with MCL in combination with the standard of care,[7] including this phase 1b study of acalabrutinib, bendamustine, and rituximab (ABR) in patients with R/R and TN MCL.

An earlier report of this multicenter, phase 1b study showed that treatment with ABR in patients with TN and R/R MCL is well tolerated and resulted in high response rates.[10] Here, we present the updated and final data on the safety and efficacy of ABR in patients after a median follow-up of 47.6 months for the TN cohort and 20.4 months for the R/R cohort.

METHODS

Study design and population

This represents part 1 of a multicenter, open-label, phase 1b trial designed to assess the safety and efficacy of ABR in TN and R/R patients with MCL (ACE-LY-106, NCT02717624). Full methods can be found in the Supplemental Information.

In this study, adults with a pathologically confirmed diagnosis of MCL were enrolled in the study in 2 cohorts: the TN MCL cohort and the R/R MCL cohort, which included patients with disease that had relapsed after or been refractory to ≥1 prior therapies. Patients with prior BTK inhibitor or BCL-2 inhibitor therapy or significant cardiovascular disease (detailed in Supplemental Information) were excluded from the study.

Study oversight

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. The study protocol was approved by the institutional review boards. All patients provided written informed consent. The data cutoff date for the analysis was June 15, 2022.

Treatment regimen

Patients received acalabrutinib 100 mg orally twice daily from day 1, cycle 1 until disease progression or treatment discontinuation (**Figure 1**). Bendamustine 90 mg/m^2 was administered as an intravenous infusion over 30 minutes on days 1 and 2 of each 28-day cycle for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on day 1 of each cycle for 6 cycles. Patients with TN MCL who achieved partial response (PR) or complete response (CR) continued receiving rituximab therapy every other cycle for up to 12 doses starting on cycle 8.

Endpoints and assessments

The primary objective of the study was to determine the safety of ABR as assessed by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious AEs (SAEs), dose-limiting toxicities (DLTs), or AEs leading to discontinuation of study treatment. A DLT review was performed to assess the toxicity of the combination regimen.

To evaluate the efficacy of ABR in patients with TN and R/R MCL, investigator-assessed overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS) were included as secondary endpoints.

Statistical analyses

Descriptive statistics were used to summarize baseline demographics and disease characteristics, study drug administration, efficacy, and safety outcomes.

ORR was summarized by number and percentage of patients, and its corresponding 95% confidence interval (CI) was calculated using an exact binomial test (Clopper-Pearson). Best ORR by Lugano criteria and by PET/CT alone were summarized by number and percentage of patients for each response category.

Kaplan-Meier (K-M) curves were used to estimate the distribution of DOR, PFS, and OS. The proportions of patients who were event-free or alive were estimated based on the K-M method, and corresponding 2-sided 95% CIs were calculated and presented for the median. The number of patients at risk was calculated and presented at selected timepoints of 6 months, 9 months, and every 3 months thereafter.

RESULTS

Patients and exposure

In total, 38 patients were enrolled from May 2016 through March 2017 at 15 sites across 3 countries (US, n=26; Poland, n=11; Italy, n=1). There were 18 patients in the TN cohort and 20 patients in the R/R cohort. **Table 1** shows demographics and baseline characteristics. Fifty-five percent of enrolled patients were ≥65 years of age, and 92% were classified as Ann Arbor stage IV.

In the R/R cohort, prior treatments included combinations of antineoplastic agents (45%); cyclophosphamide plus doxorubicin, prednisone, rituximab, and vincristine (45%); bendamustine plus rituximab (25%); cytarabine plus rituximab (15%); rituximab (15%); chlorambucil plus rituximab (5%); cisplatin plus cytarabine and dexamethasone (5%); cisplatin plus cytarabine, etoposide and methylprednisolone (5%); cytarabine (5%); enzalutamide (5%; used in a previous clinical trial for MCL); lenalidomide (5%); and ONC201 (5%).

At the time of data cutoff, the median follow-up was 47.6 months (range: 0.6–72.4) for the TN cohort and 20.4 months (range: 1.2–64.2) for the R/R cohort. Details of treatment exposure and disposition can be found in **Supplemental Information Table 1**.

Fourteen (77.8%) patients in the TN cohort and 10 (50.0%) in the R/R cohort completed the first 6 cycles of ABR and continued acalabrutinib. The most common reason for not

completing 6 cycles of ABR was AEs, followed by disease progression and withdrawal by investigator (**Supplemental Information Table 1**). One patient (6.7%) in the TN cohort discontinued acalabrutinib due to an AE (allergic reaction) before completing 6 cycles of BR. No DLTs were reported. Median duration of exposure to acalabrutinib was 34.0 months in the TN cohort versus 14.6 months in the R/R cohort.

After the final data cutoff date, 10 patients (6 patients in the TN cohort and 4 patients in the R/R cohort) who were still benefiting from treatment per the investigator's discretion continued to receive acalabrutinib in a post-trial access program. All other patients discontinued the study; among these patients, the most common cause of study discontinuation was death (**Table 2**). Considering individual medications, acalabrutinib was discontinued due to AEs in 6 patients (33.3%) in the TN cohort and 9 patients (45%) in the R/R cohort (**Supplemental Information Tables 2 and 3**). Acalabrutinib dose reductions due to AEs occurred in 4 (22.2%) and 2 (10.0%) patients in the TN and R/R cohorts, respectively. Bendamustine dose reductions due to AEs occurred in 6 (33.3%) and 5 (25.0%) patients in the TN and R/R cohorts, respectively.

Safety

The most common any-grade AEs for the TN cohort were nausea (n=14, 77.8%), fatigue (n=13, 72.2%), cough (n=11, 61.1%), and headache (n=11, 61.1%), and for the R/R cohort, neutropenia (n=11, 55%), upper respiratory infection (n=8, 40.0%), nausea (n=8, 40.0%), cough (n=8, 40.0%), and diarrhea (n=8, 40.0%) (**Table 3**). Most AEs were

grades 1 or 2. Grade 3 or 4 AEs were reported in 72.2% of patients in the TN cohort and 85.0% in the R/R cohort, most commonly neutropenia (TN: 38.9%, R/R: 50%).

SAEs of any grade were reported in 11 patients (61.1%) in the TN cohort and 13 patients (65.0%) in the R/R cohort. SAEs affecting ≥2 patients in the TN cohort were pneumonia (n=4, 22.2%), hypoxia, and pyrexia (n=2 each, 11.1%), while in the R/R cohort, pneumonia was reported in 3 patients (15.0%). There were no cases of atrial fibrillation, ventricular tachyarrhythmias, or tumor lysis syndrome in any of the cohorts. Events of clinical interest are detailed in **Table 3**.

In the TN cohort, 5 patients (27.8%) died (n=1, AE [pneumonitis, related to acalabrutinib]; n=4, unknown; T**able 2**, **Supplemental Information Table 4**). The ages of the 4 patients who died of unknown causes were 65, 79, 81, and 85 years, and the number of days from the last dose of study drug were 126, 60, 22, and 5, respectively. In the R/R cohort, 6 patients (30.0%) died (n=2, AE [n=1, COVID-19, unrelated to study medications; n=1, cerebrospinal meningitis, unrelated to study medications]; n=2, progressive disease (PD); n=2, unknown). Two patients (TN: n=1, R/R: n=1) listed under “unknown” had PD confirmed shortly (5 and 22 days, respectively) before their deaths. Of the 6 patients who died in the R/R cohort, 5 discontinued the study due to death and 1 initially discontinued due to withdrawal of consent and subsequently died due to PD (**Table 2**).

Efficacy

Investigator-assessed ORR by Lugano criteria was 94.4% (17/18 patients; 95% CI: 72.7, 99.9) in the TN cohort and 85.0% (17/20 patients; 95% CI: 62.1, 96.8) in the R/R cohort (**Figure 2**). CR rate by Lugano criteria was 77.8% (14/18 patients) in the TN cohort and 70.0% (14/20 patients) in the R/R cohort (**Figure 2**). CR rate by PET/CT alone was 88.9% (16/18 patients) in the TN cohort and 80.0% (16/20 patients) in the R/R cohort (**Supplemental Information Figure 1**).

Median DOR was not reached in the TN cohort and was 43.5 months in the R/R cohort. Maximum change in the sum of product diameters for each cohort is presented in **Figures 3A and 3B**.

In the TN cohort, with a median follow-up of 47.6 months (range: 0.6–72.4), median PFS and OS were not reached (**Figures 4A and 5A**). Estimated PFS rates at 12 and 36 months were 88.5% (95% CI: 61.4, 97.0) and 68.1% (95% CI: 39.2, 85.4), respectively (**Figure 4A**). Estimated OS rates at 12 and 36 months were 88.9% (95% CI: 62.4, 97.1) and 74.6% (95% CI: 45.0, 89.8), respectively (**Figure 5A**).

In the R/R cohort, with a median follow-up of 20.4 months (range: 1.2–64.2), median PFS and OS were 28.6 months (95% CI: 11.8, non-evaluable [NE]) and not reached (95% CI: 16.6, NE), respectively (**Figures 4B and 5B**). Estimated PFS rates at 12 and 36 months were 73.0% (95% CI: 46.7, 87.8) and 47.3% (95% CI: 22.6, 68.6), respectively (**Figure 4B**). Estimated OS rates at 12 and 36 months were 88.7% (95% CI: 61.4, 97.1) and 69.7% (95% CI: 41.5, 86.2), respectively (**Figure 5B**).

DISCUSSION

This phase 1b study demonstrates that treatment with triple-combination ABR was tolerable, with a toxicity profile consistent with the known profiles of single-agent acalabrutinib, bendamustine, and rituximab. Furthermore, ABR was shown to be effective in patients with TN MCL and R/R MCL.

Safety and tolerability are important considerations when selecting treatment for lymphoma. Various therapies are currently available for MCL, depending on age, fitness, baseline comorbidities, disease stage, and other factors,[1] and often involve CIT regimens, frequently bendamustine-based combinations.[2] Targeted agents, such as BTK inhibitors, are approved for R/R MCL and offer an oral option with an acceptable safety profile.[3] Ibrutinib, acalabrutinib, and zanubrutinib are BTK inhibitors that are being investigated for patients with TN MCL, both in combination with CIT and in chemotherapy-free approaches.[11-14] While no BTK inhibitor–based combination is currently approved for MCL, key insights have emerged from recent and ongoing clinical trials.

In a phase 1/1b study of rituximab, bendamustine, and ibrutinib in 48 patients with TN MCL or R/R NHL,[14] grade 3 or 4 toxicities predictably included lymphopenia (77%), neutropenia (33%), thrombocytopenia (19%), and rash (25%). The phase 3 SHINE trial[13] was a placebo-controlled trial of ibrutinib plus BR in older patients with TN MCL (N=523). At a median follow-up of 84.7 months, BR-ibrutinib demonstrated an

improvement in median PFS compared with BR-placebo (80.6 vs 52.9 months, respectively) with no OS benefit. The addition of ibrutinib was accompanied by additional toxicity, including higher incidences of pneumonia and atrial fibrillation during the maintenance period, as well as higher rates of discontinuations due to AEs and deaths when compared with the BR-placebo group. Grade 3 or 4 AEs in the SHINE study occurred in 81.5% of patients in the ibrutinib-treated group and 77.3% of patients in the placebo-treated group.[13]

Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK to reduce off-target effects seen with ibrutinib.[15] This difference was demonstrated in the phase 3 head-to-head comparison of acalabrutinib versus ibrutinib in patients with previously treated CLL.[16] Compared with ibrutinib, acalabrutinib-treated patients had fewer cardiovascular TEAEs and a lower incidence of hypertension (9.4% vs 23.2%, respectively), arthralgia (15.8% vs 22.8%), and diarrhea (34.6% vs 46.0%), but higher incidences of headache (34.6% vs 20.2%) and cough (28.9% vs 21.3%) were observed.[16] After a median follow-up of 40.9 months, all-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib- versus ibrutinib-treated patients (9.4% vs 16.0%, respectively; P=0.02). The number of patients discontinuing BTK inhibitor therapy due to TEAEs was also lower in the acalabrutinib arm versus ibrutinib (14.7% vs 21.3%, respectively).[16]

The greater specificity of acalabrutinib was the basis of the current study hypothesis, which confirmed that adding acalabrutinib to BR could produce durable remission

without new safety signals. This phase Ib study establishes the safety profile of ABR and, despite small sample sizes, it suggests high efficacy, with CR achieved by most patients in the TN and R/R cohorts (77.8% and 70%, respectively). The more frequent discontinuation of bendamustine in the R/R cohort, alongside its lymphodepleting nature, suggest that risk- or response-adapted strategies to tailor bendamustine utilization in R/R MCL should be explored.

In this study, limitations arise from the small sample size and the variability of underlying reasons for discontinuation during this period (PD in 2 patients). Of the 11 total deaths reported during the study, 6 were not attributable to a specific cause (though 2 of these patients had progressive disease confirmed shortly before their deaths). These factors hinder the interpretation of any observations regarding deaths and discontinuations.

The randomized, placebo-controlled, phase 3 ECHO trial (NCT02972840), based on these phase 1 data, seeks to demonstrate the PFS benefit of ABR versus placebo plus BR in older adults with newly diagnosed MCL.[17] An interim analysis from this trial demonstrated clinical benefit with ABR among these patients. This study, along with others testing first-line BTK inhibitors for MCL (TrAVeRse [NCT05951959], BOVen [NCT03824483], EA4181 [NCT04115631])[18-20] will provide key efficacy and safety data and may alter the treatment landscape for this challenging disease.

CONCLUSION

The safety profile of ABR is consistent with expectations for the individual agents in the combination regimen. ABR demonstrated high efficacy in patients with TN and R/R MCL. Nonetheless, the limited sample size presents a constraint in fully interpreting certain observations. The study findings support the further exploration of ABR in patients with TN MCL in the ongoing, placebo-controlled phase 3 ECHO trial, which aims to confirm the safety profile and efficacy of long-term ABR.

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TABLES

Table 1. Demographics and Baseline Characteristics

	TN Cohort (n=18)	R/R Cohort (n=20)	Total (N=38)
Age, median (range), y	66.0 (48–86)	65.0 (47–82)	65.5 (47–86)
Male, n (%)	11 (61.1)	13 (65.0)	24 (63.2)
ECOG PS ≤1, n (%)	18 (100.0)	19 (95.0)	37 (97.4)
Bulky lymph nodes, n (%)			
>5 cm	3 (16.7)	6 (30.0)	9 (23.7)
≥10 cm	1 (5.6)	2 (10.0)	3 (7.9)
Ann Arbor stage IV disease, n (%)	16 (88.9)	19 (95.0)	35 (92.1)
Simplified MIPI score, n (%)[a]			
Low risk (0–3)	7 (38.9)	4 (20.0)	11 (28.9)
Intermediate risk (4–5)	7 (38.9)	12 (60.0)	19 (50.0)
High risk (6–11)	2 (11.1)	3 (15.0)	5 (13.2)

Missing	2 (11.1)	1 (5.0)	3 (7.9)
Bone marrow involvement, n (%)	15 (83.3)	9 (45.0)	24 (63.2)
Blastoid MCL, n (%)	1 (5.6)	3 (15.0)	4 (10.5)

[a]Derived using the factors of age, ECOG PS, lactate dehydrogenase level, and white cell count at baseline, with score range depending on the range of these factors. ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma Prognostic Index; R/R, relapsed/refractory; TN, treatment-naive.

Table 2. Patient Disposition

Patients, n (%)	TN Cohort (n=18)	R/R Cohort (n=20)	Total (N=38)
Study completion (still on acalabrutinib)	6 (33.3)	4 (20.0)	10 (26.3)
Study Discontinuations			
Due to death[a]	5 (27.8)	5 (25.0)[b,c]	10 (26.3)
Due to disease progression	0	1 (5.0)[b]	1 (2.6)
Due to AE/SAE	1 (5.6)	2 (10.0)	3 (7.9)
Due to other/unknown[d]	4 (22.2)	2 (10.0)	6 (15.8)
Due to objective evidence of disease progression (eg, PET, CT)	1 (5.6)	4 (20.0)	5 (13.2)
Due to withdrawal of consent	0	2 (10.0)	2 (5.3)
Due to withdrawal by investigator	1 (5.6)	1 (5.0)	2 (5.3)
Due to AE/SAE	2 (11.0)	1 (5.0)	3 (7.9)
Due to other	3 (16.7)	3 (15)	6 (15.8)

[a]Including only patients who died prior to discontinuation from the study. [b]Among a total of 6 deaths in R/R cohort, 5 patients discontinued from study due to death and 1 patient died after discontinuation from the study due to withdrawal of consent. This patient was counted as discontinuing from the study due to “withdrawal of consent” rather than due to

“death.” [c]Among a total of 6 deaths in R/R cohort, 5 patients discontinued from study due to death and 1 patient died after discontinuation from the study due to withdrawal of consent. This patient was counted as discontinuing from the study due to “withdrawal of consent” rather than due to “death”. [d]More information on patients who died due to unknown causes can be found in the Supplemental Information. AE, adverse event; CT, computed tomography; PET, positron emission tomography; R/R, relapsed/refractory; SAE, serious adverse event; TN, treatment-naive.

Table 3. Treatment-emergent AEs Occurring in ≥30% of Patients and Events of Clinical Interest

	TN Cohort (n=18)		R/R Cohort (n=20)		Total (N=38)	
Most Common AEs, n (%)	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Nausea	14 (77.8)	0	8 (40.0)	0	22 (57.9)	0
Fatigue	13 (72.2)	0	7 (35.0)	1 (5.0)	20 (52.6)	1 (2.6)
Cough	11 (61.1)	0	8 (40.0)	0	19 (50.0)	0
Headache	11 (61.1)	0	4 (20.0)	0	15 (39.5)	0
Vomiting	10 (55.6)	0	6 (30.0)	0	16 (42.1)	0
Constipation	9 (50.0)	0	5 (25.0)	0	14 (36.8)	0
Diarrhea	9 (50.0)	0	8 (40.0)	3 (15.0)	17 (44.7)	3 (7.9)
Upper respiratory tract infection	8 (44.4)	0	8 (40.0)	0	16 (42.1)	0
Dizziness	7 (38.9)	0	4 (20.0)	1 (5.0)	11 (28.9)	1 (2.6)
Neutropenia	7 (38.9)	7 (38.9)	11 (55.0)	10 (50.0)	18 (47.4)	17 (44.7)
Pyrexia	7 (38.9)	0	3 (15.0)	0	10 (26.3)	0
Arthralgia	6 (33.3)	1 (5.6)	1 (5.0)	0	7 (18.4)	1 (2.6)
Rash	6 (33.3)	0	5 (25.0)	0	11 (28.9)	0
Events of Clinical Interest, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Cardiac events[a]	4 (22.2)	3 (16.7)	4 (20.0)	3 (15.0)	8 (21.1)	6 (15.8)
Hypertension	3 (16.7)	3 (16.7)	2 (10.0)	2 (10.0)	5 (13.2)	5 (13.2)

Neutropenia	10 (55.6)	8 (44.4)	13 (65.0)	12 (60.0)	23 (60.5)	20 (52.6)
Thrombocytopenia	2 (11.1)	2 (11.1)	4 (20.0)	3 (15.0)	6 (15.8)	5 (13.2)
Hemorrhage[a]	8 (44.4)	2 (11.1)	6 (30.0)	3 (15.0)	14 (36.8)	5 (13.2)
Major hemorrhage	2 (11.1)	2 (11.1)	3 (15.0)	3 (15.0)	5 (13.2)	5 (13.2)
Infections[a]	13 (72.2)	5 (27.8)	15 (75.0)	6 (30.0)	28 (73.7)	11 (28.9)
Interstitial lung disease/pneumonitis	3 (16.7)	1 (5.6)	2 (10.0)	0	5 (13.2)	1 (2.6)
Second primary malignancies	4 (22.2)	1 (5.6)	2 (10.0)	0	6 (15.8)	1 (2.6)
Second primary malignancies excluding skin cancers	2 (11.1)	1 (5.6)	1 (5.0)	0	3 (7.9)	1 (2.6)

[a]Detailed information on cardiac events, hemorrhage and infections is available in the Supplemental Information. AE, adverse event; R/R, relapsed/refractory; TN, treatment-naive.

FIGURE LEGENDS

Figure 1. Study design. [a]One cycle was 28 days. [b]Only for patients who achieved a response (PR or better). [c]Until disease progression or treatment discontinuation for any reason. BID, twice daily; IV, intravenously; MCL, mantle cell lymphoma; PO, orally; PR, partial response; R/R, relapsed/refractory; TN, treatment-naive.

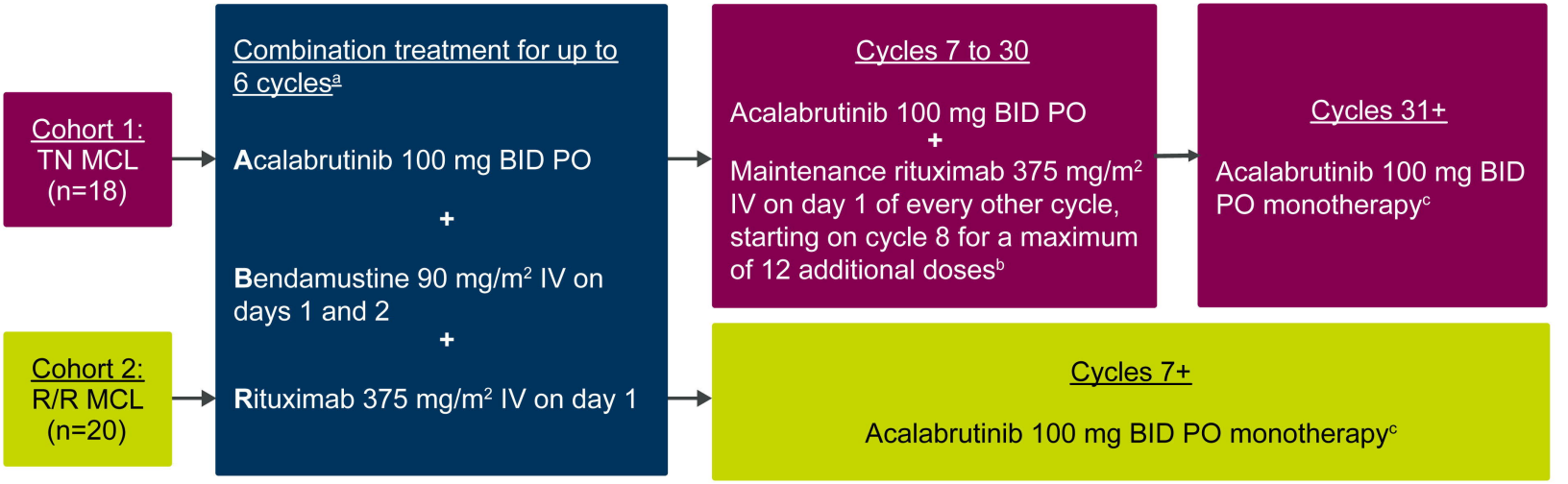
Figure 2. Investigator-assessed ORR by Lugano criteria. ORR is defined as achieving CR or PR. [a]95% exact binomial confidence interval. [b]Includes patients without any adequate post-baseline response assessment. CI, confidence interval; CR, complete response; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive.

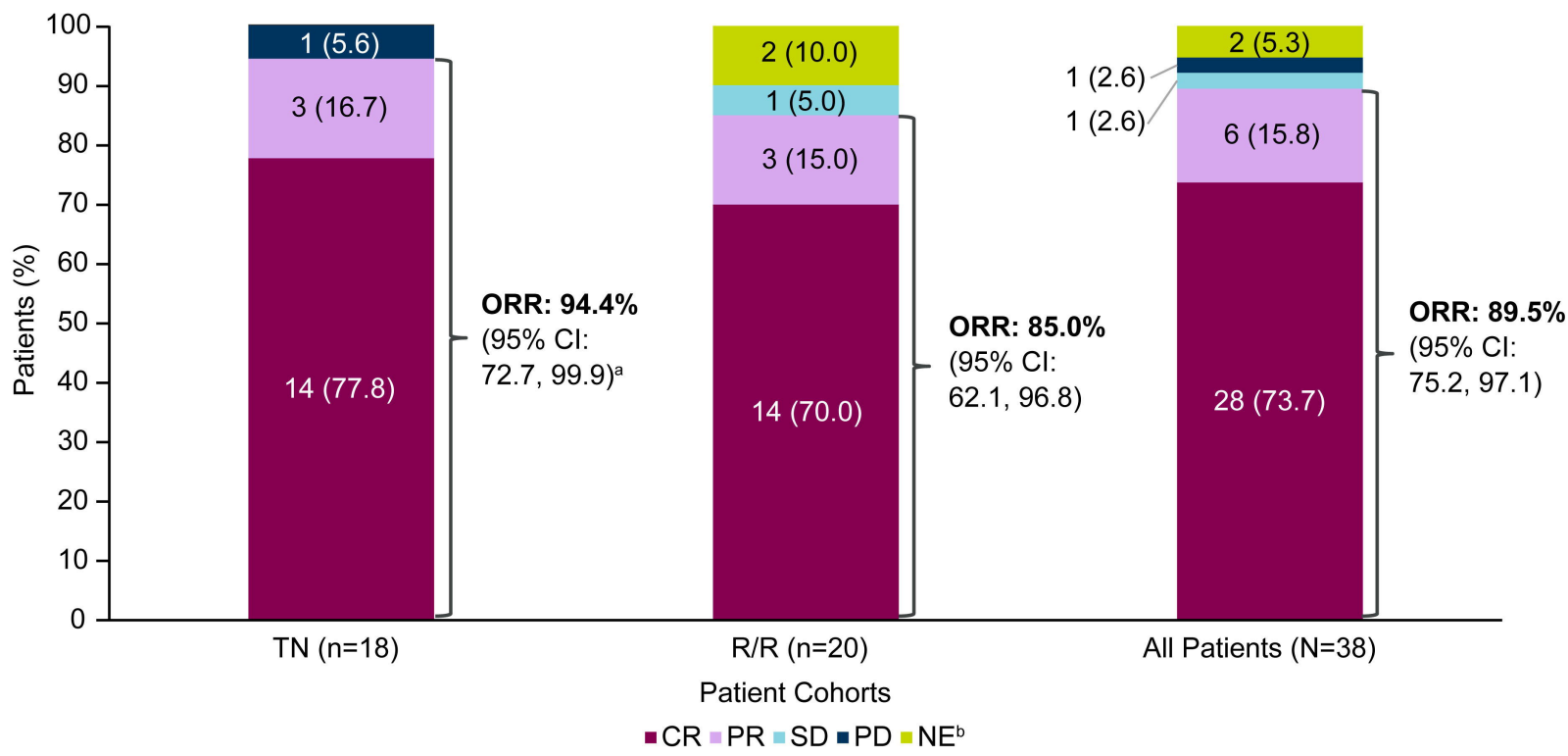
Figure 3. Maximum change from baseline in sum of product diameters for each patient cohort. (A) Change in SPD for the TN cohort is shown. (B) Change in SPD for the R/R cohort is shown. Results were based on best responses. One patient in the TN cohort (patient had PD) and 2 patients in the R/R cohort did not have post-baseline tumor measurements and were excluded from SPD analysis. CR, complete response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SPD, sum of product diameters; TN, treatment-naive.

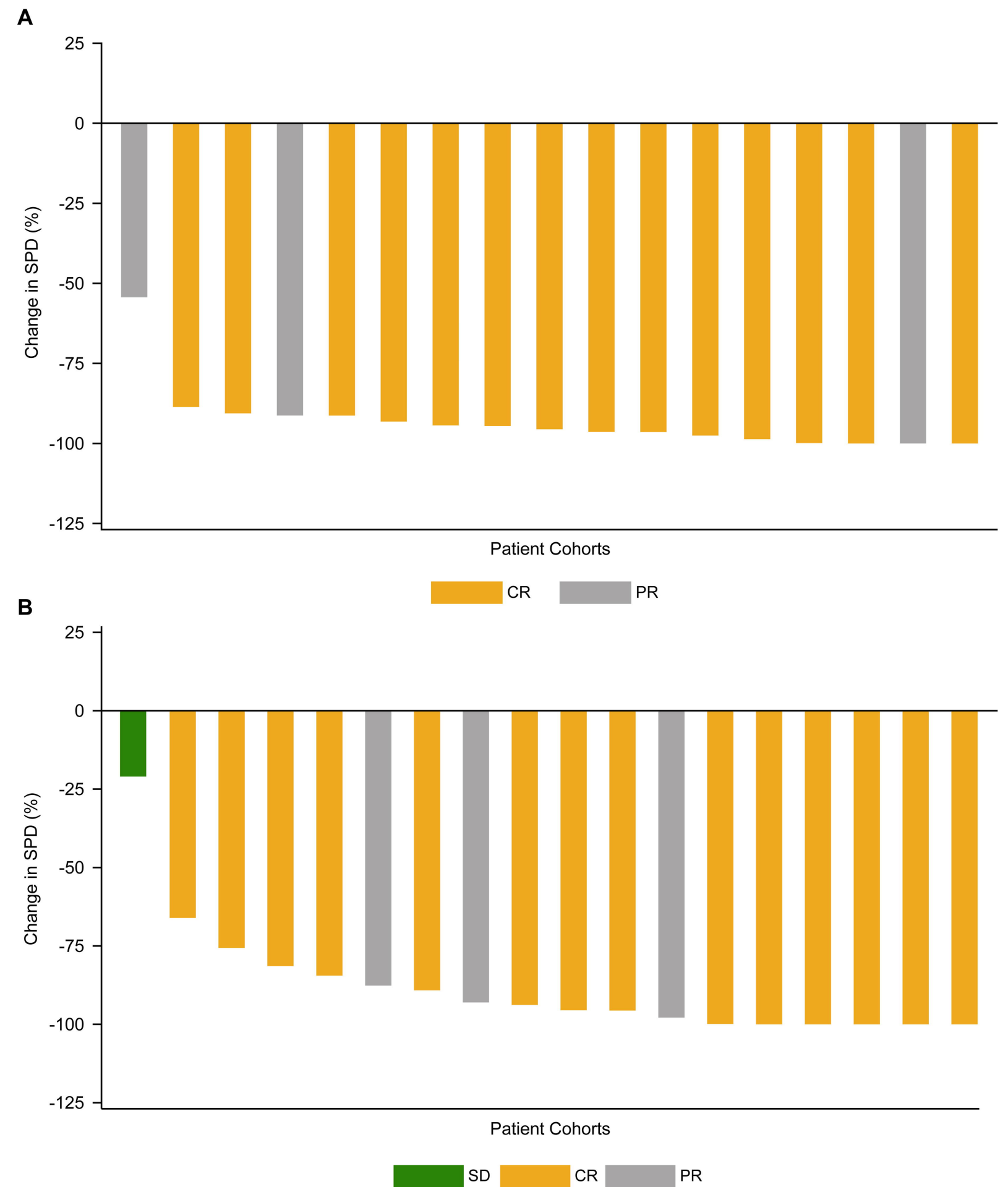
Figure 4. Progression-free survival for each patient cohort. (A) The Kaplan-Meier plot depicts PFS for the TN cohort. (B) The Kaplan-Meier plot for PFS for the R/R cohort

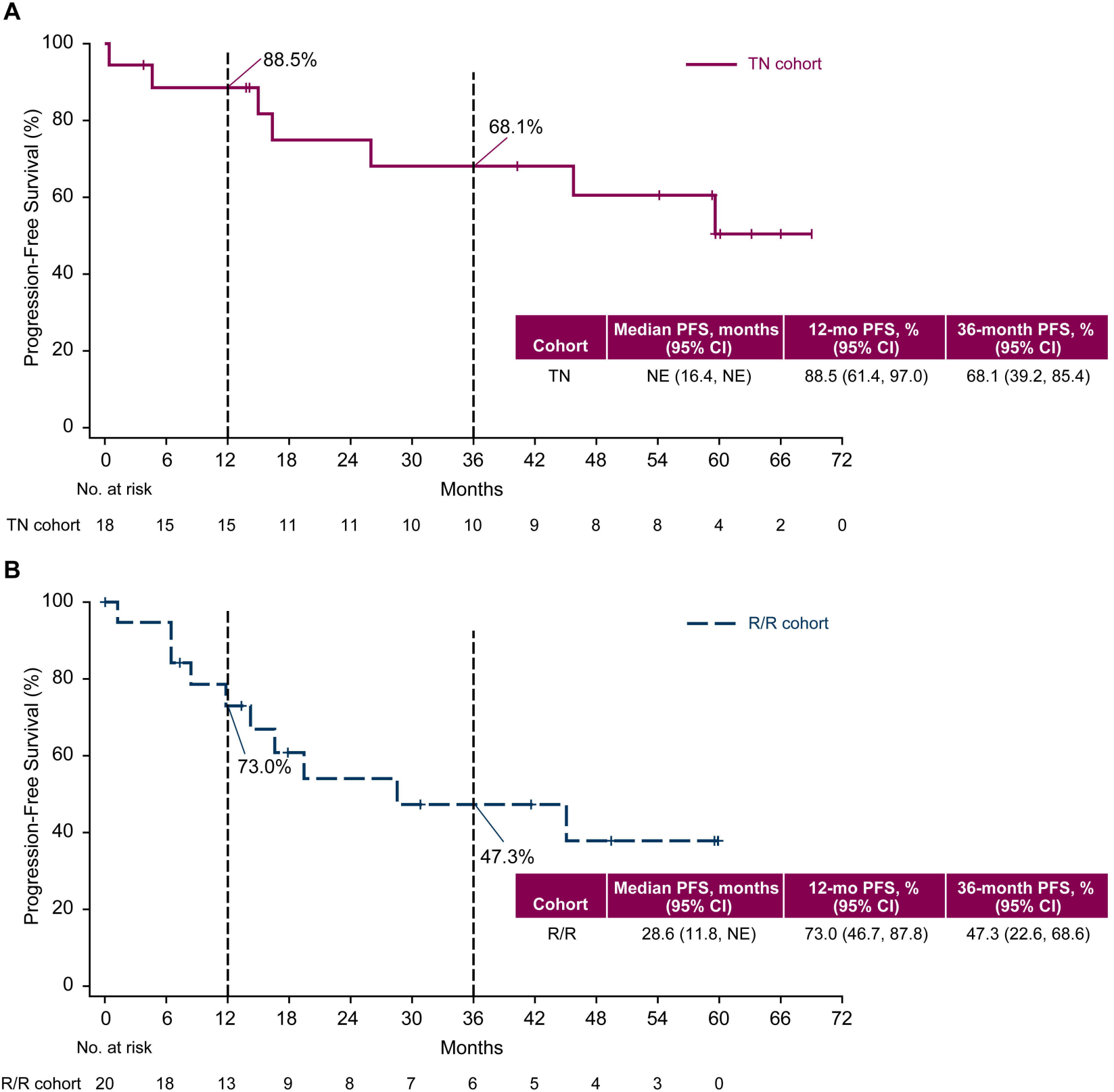
is shown. CI, confidence interval; NE, not estimable; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive.

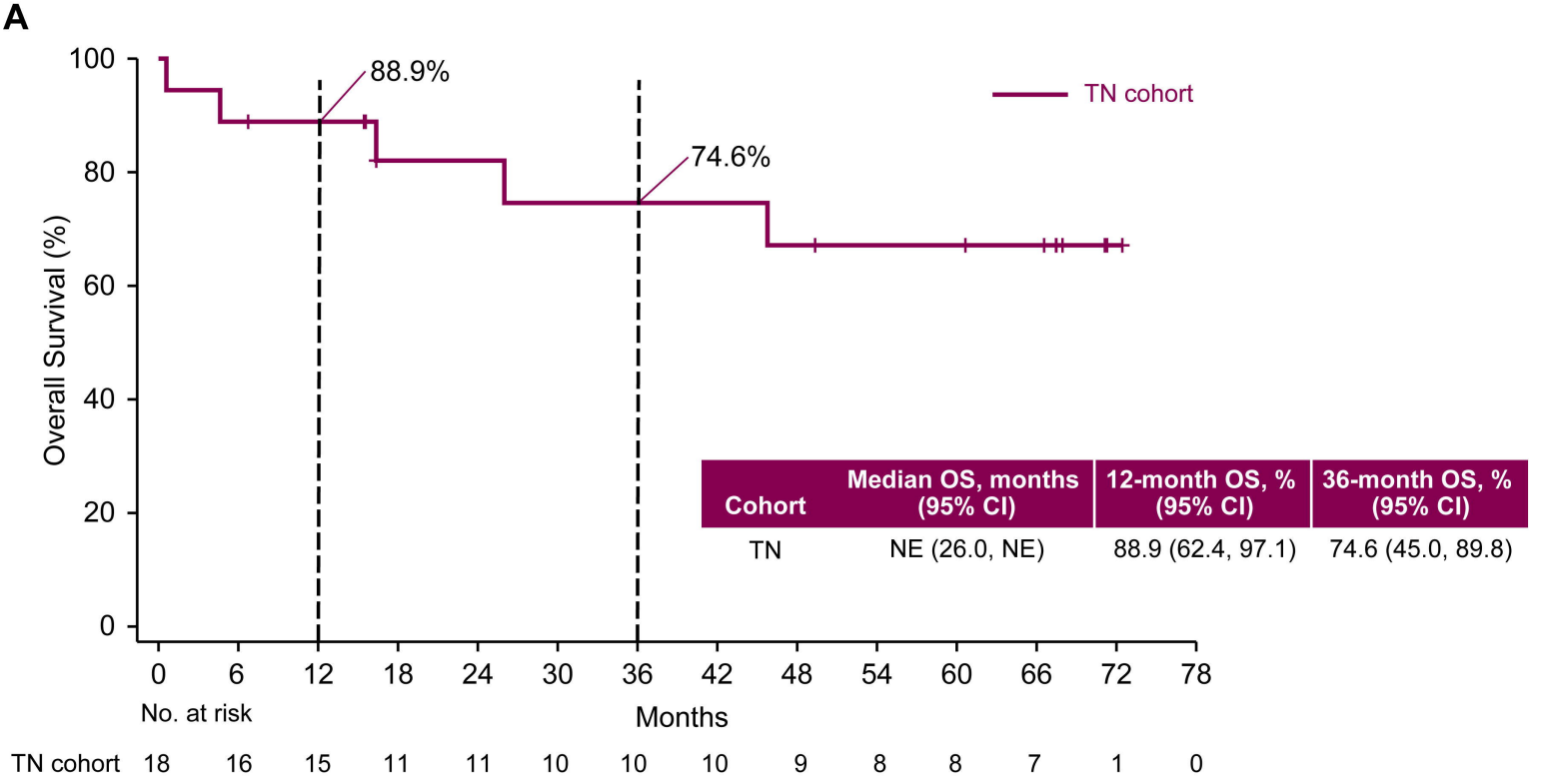
Figure 5. Overall survival for each patient cohort. (A) The Kaplan-Meier plot depicts OS for the TN cohort. (B) The Kaplan-Meier plot for OS in the R/R cohort is shown. CI, confidence interval; NE, not estimable; OS, overall survival; R/R, relapsed/refractory; TN, treatment-naive.


Cohort 1:
TN MCL
(n=18)
Cohort 2:
R/R MCL
(n=20)
Combination treatment for up to 6 cycles[a]
Acalabrutinib 100 mg BID PO
+
Bendamustine 90 mg/m2 IV on days 1 and 2
+
Rituximab 375 mg/m2 IV on day 1
Cycles 7 to 30
Acalabrutinib 100 mg BID PO
+
Maintenance rituximab 375 mg/m2 IV on day 1 of every other cycle, starting on cycle 8 for a maximum of 12 additional doses[b]
Cycles 31+
Acalabrutinib 100 mg BID PO monotherapy[c]
Cycles 7+
Acalabrutinib 100 mg BID PO monotherapy[c]

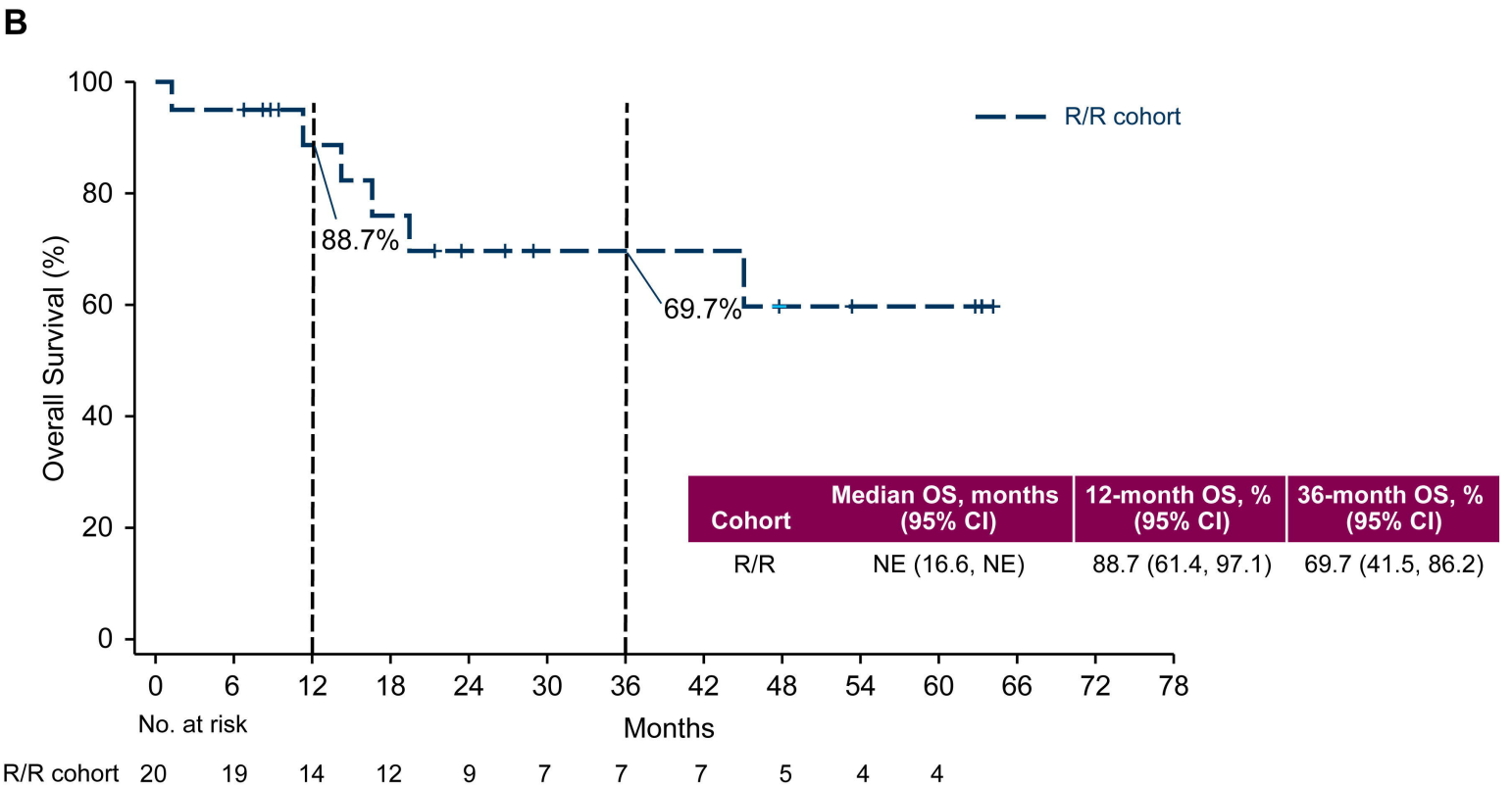

100
90
80
70
60
50
40
30
20
10
0
Patients (%)
1 (5.6)
3 (16.7)
14 (77.8)
ORR: 94.4%
(95% CI:
72.7, 99.9)[a]
2 (10.0)
1 (5.0)
3 (15.0)
14 (70.0)
ORR: 85.0%
(95% CI:
62.1, 96.8)
2 (5.3)
1 (2.6)
1 (2.6)
6 (15.8)
28 (73.7)
ORR: 89.5%
(95% CI:
75.2, 97.1)
TN (n=18)
R/R (n=20)
All Patients (N=38)
Patient Cohorts
CR
PR
SD
PD
NE[b]


A
25
0
-25
-50
-75
-100
-125
Change in SPD (%)
Patient Cohorts
CR
PR
B
25
0
-25
-50
-75
-100
-125
Change in SPD (%)
Patient Cohorts
SD
CR
PR


A
100
80
60
40
20
0
Progression-Free Survival (%)
88.5%
68.1%
TN cohort
Cohort | Median PFS, months (95% CI) | 12-mo PFS, % (95% CI) | 36-month PFS, % (95% CI)
TN | NE (16.4, NE) | 88.5 (61.4, 97.0) | 68.1 (39.2, 85.4)
0 6 12 18 24 30 36 42 48 54 60 66 72
Months
No. at risk
TN cohort 18 15 15 11 11 10 10 9 8 8 4 2 0
B
100
80
60
40
20
0
Progression-Free Survival (%)
73.0%
47.3%
R/R cohort
Cohort | Median PFS, months (95% CI) | 12-mo PFS, % (95% CI) | 36-month PFS, % (95% CI)
R/R | 28.6 (11.8, NE) | 73.0 (46.7, 87.8) | 47.3 (22.6, 68.6)
0 6 12 18 24 30 36 42 48 54 60 66 72
Months
No. at risk
R/R cohort 20 18 13 9 8 7 6 5 4 3 0



Cohort	Median OS, months (95% CI)	12-month OS, % (95% CI)	36-month OS, % (95% CI)
TN	NE (26.0, NE)	88.9 (62.4, 97.1)	74.6 (45.0, 89.8)



Cohort	Median OS, months (95% CI)	12-month OS, % (95% CI)	36-month OS, % (95% CI)
R/R	NE (16.6, NE)	88.7 (61.4, 97.1)	69.7 (41.5, 86.2)

Supplemental Information – Tables

Supplemental Table 1. Treatment Exposure and Disposition

Patients, n (%)	TN Cohort (n=18)	R/R Cohort (n=20)	Total (N=38)
Acalabrutinib Exposure			
Number of cycles[a] administered, median (range)	37.0 (1.0–79.0)	14.0 (1.0–69.0)	19.0 (1.0–79.0)
Discontinued acalabrutinib, n (%)	12 (66.7)	16 (80.0)	28 (73.7)
AE/SAE	6 (33.3)	9 (45.0)	15 (39.5)
Clinical or objective progression	2 (11.1)	5 (25.0)	7 (18.4)
Withdrawal by investigator	2 (11.1)	1 (5.0)	3 (7.9)
Other	2 (11.1)[b,c]	1 (5.0)[d]	3 (7.9)
Discontinued acalabrutinib before completion of 6 cycles of bendamustine and rituximab	1 (5.6)	0	1 (2.6)
Bendamustine Exposure			
Number of infusions administered, median (range)	12.0 (2.0–12.0)	11.5 (2.0–12.0)	12.0 (2.0–12.0)

Discontinued bendamustine, n (%)	3 (16.7)	6 (30.0)	9 (23.7)
Clinical or objective progression	1 (5.6)	1 (5.0)	2 (5.3)
AE/SAE	2 (11.1)	5 (25.0)	7 (18.4)
Completed study regimen	15 (83.3)	14 (70.0)	29 (76.3)
Rituximab Exposure			
Number of infusions administered, median (range)	16.0 (1.0–18.0)	6.0 (1.0–6.0)	6.0 (1.0–18.0)
Discontinued rituximab, n (%)	10 (55.6)	2 (10.0)	12 (31.6)
Clinical and objective progression	2 (11.1)	1 (5.0)	3 (7.9)
AE/SAE	6 (33.3)	1 (5.0)	7 (18.4)
Withdrawal by investigator	2 (11.1)	0	2 (5.3)
Completed study regimen	8 (44.4)	18 (90.0)	26 (68.4)

[a]28 days per cycle. [b]Per sponsor's request for final database lock. [c]Withdrawal of consent. [d]Deterioration of mental status.
AE, adverse event; R/R, relapsed/refractory; SAE, serious adverse event; TN, treatment-naive.

Supplemental Table 2. ABR Discontinuation by Treatment Period – TN Cohort (n=18)

Patients, n (%)	Acalabrutinib + Bendamustine + Rituximab Cycles 1–6			Acalabrutinib + Rituximab[a] Cycles 7–30		Acalabrutinib Monotherapy Cycles 31+	Entire Study Period		
	A	B	R	A	R	A	A	B	R
Ongoing treatment with drug	14 (77.8)	0	15 (83.3)	9 (50.0)	0	6 (33.3)	6 (33.3)	0	0
Completed treatment period	—	15 (83.3)	0	—	8 (44.4)	—	—	15 (83.3)	8 (44.4)
Discontinued treatment with drug	4 (22.2)	3 (16.7)	3 (16.7)	5 (27.8)	7 (38.9)	3 (16.7)	12 (66.7)	3 (16.7)	10 (55.6)

Reason for Discontinuation									
Clinical or objective disease progression	1 (5.6)	1 (5.6)	1 (5.6)	0	1 (5.6)	1 (5.6)	2 (11.1)	1 (5.6)	2 (11.1)
AE	2 (11.1)	2 (11.1)	1 (5.6)	4 (22.2)	5 (27.7)	0	6 (33.3)	2 (11.1)	6 (33.3)
Investigator's decision	1 (5.6)	0	1 (5.6)	1 (5.6)	1 (5.6)	0	2 (11.1)	0	2 (11.1)
Other	0	0	0	0	0	2 (11.1)[b]	2 (11.1)[b]	0	0

[a]Patients with response ≥PR received rituximab every other cycle, from cycles 8–30, for 12 doses. Continued rituximab was available only for the TN cohort.

[b]Other reasons for drug discontinuation were sponsor's request for final database lock (n=1) and poor clinical condition (n=1).

A, acalabrutinib; B, bendamustine; AE, adverse event; PR, partial response; R, rituximab; TN, treatment-naive.

Supplemental Table 3. ABR Discontinuation by Treatment Period – R/R Cohort (n=20)

Patients, n (%)	Acalabrutinib + Bendamustine + Rituximab Cycles 1–6			Acalabrutinib Monotherapy Cycles 7–30	Acalabrutinib Monotherapy Cycles 31+	Entire Study Period		
	A	B	R	A	A	A	B	R
Ongoing treatment with drug	18 (90.0)	0	0	7 (35.0)	4 (20.0)	4 (20.0)	0	0
Completed treatment period	—	14 (70.0)	18 (90.0)	—	—	—	14 (70.0)	18 (90.0)
Discontinued treatment with drug	2 (10.0)	6 (30.0)	2 (10.0)	11 (55.0)	3 (15.0)	16 (80.0)	6 (30.0)	2 (10.0)

Clinical or objective disease progression	1 (5.0)	1 (5.0)	1 (5.0)	3 (15.0)	1 (5.0)	5 (25.0)	1 (5.0)	1 (5.0)
AE	1 (5.0)	5 (25.0)	1 (5.0)	7 (35.0)	1 (5.0)	9 (45.0)	5 (25.0)	1 (5.0)
Investigator's decision	0	0	0	1 (5.0)	0	1 (5.0)	0	0
Other	0	0	0	0	1 (5.0)[a]	1 (5.0)[a]	0	0

[a]One patient discontinued acalabrutinib due to withdrawal of consent.

A, acalabrutinib; B, bendamustine; AE, adverse event; R, rituximab; R/R, relapsed/refractory.

Supplemental Table 4. Summary of Deaths in All Treated Patients

Patients, n (%)	TN Cohort (n=18)	R/R Cohort (n=20)	Total (N=38)
All deaths	5 (27.8)	6 (30.0)	11 (28.9)
Primary cause of death			
Adverse event	1 (5.6)	2 (10.0)	3 (7.9)
Disease progression	0	2 (10.0)	2 (5.3)
Unknown	4 (22.2)	2 (10.0)	6 (15.8)
Deaths within 30 days after last dose of study drug	3 (16.7)	3 (15.0)	6 (15.8)
Primary cause of death			
Adverse event	1 (5.6)	1 (5.0)	2 (5.3)
Unknown	2 (11.1)	2 (10.0)	4 (10.5)
Deaths more than 30 days after last dose of study drug	2 (11.1)	3 (15.0)	5 (13.2)
Primary cause of death			
Disease progression	0	2 (10.0)	2 (5.3)
Adverse event	0	1 (5.0)	1 (2.6)

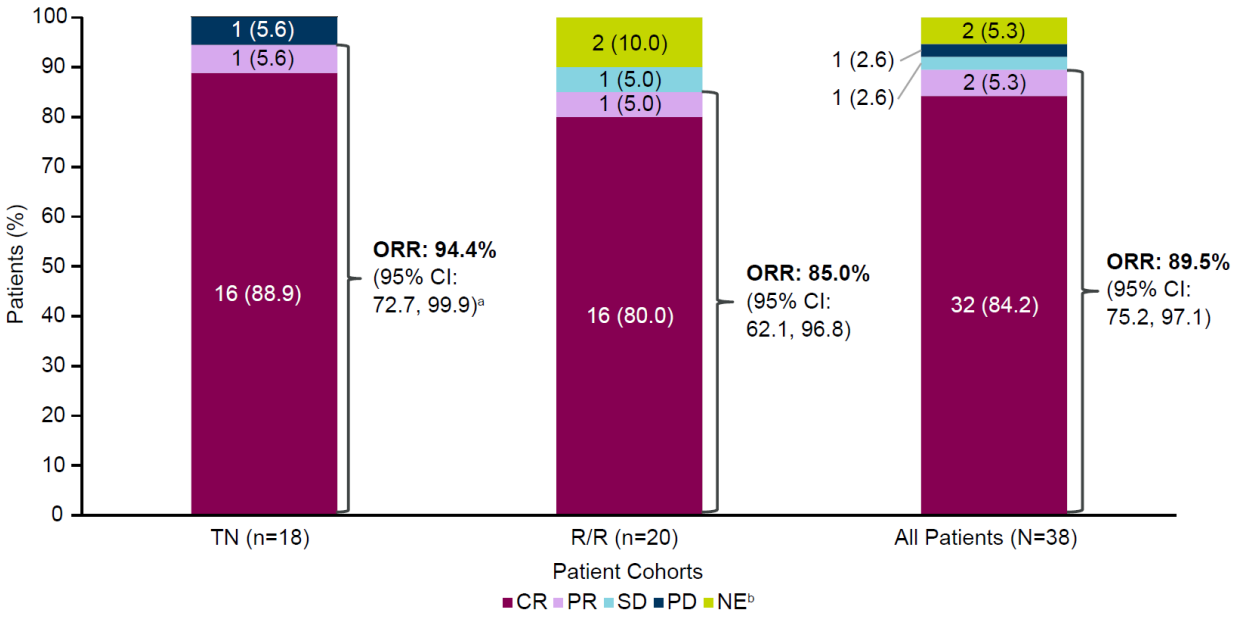
Unknown	2 (11.1)	0	2 (5.3)

All deaths in the whole study period are included, which includes patients who died during the main study period and those who died after discontinuing from the study drug(s) and during the survival follow-up period.

Supplemental Information – Figure

Supplemental Figure 1

Investigator-assessed ORR by PET/CT alone. ORR is defined as achieving CR or PR. [a]95% exact binomial confidence interval. [b]Includes patients without any adequate post-baseline response assessment. CI, confidence interval; CR, complete response; CT, computed tomography; NE, not estimable; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive.



Supplemental Information – Methods

Study design and population

This was part 1 of a multicenter, open-label, phase 1b trial designed to assess the safety and efficacy of acalabrutinib, bendamustine, and rituximab (ABR) in treatment-naive (TN) and relapsed/refractory (R/R) patients with mantle cell lymphoma (MCL) (ACE-LY-106, NCT02717624).

Adult patients (≥18 years) with a pathologically confirmed diagnosis of MCL with translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1 requiring treatment and an Eastern Cooperative Oncology Group performance status ≤2 were enrolled in the study in 2 cohorts. The TN MCL cohort included patients with MCL requiring treatment and for which no prior therapies had been received, and the R/R MCL cohort included patients with disease that had relapsed after or been refractory to ≥1 prior therapies. Patients who discontinued any prior treatment for MCL for tolerability reasons, and patients with a radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension) also could be enrolled in the R/R cohort.

Patients with prior Bruton tyrosine kinase (BTK) inhibitor or BCL-2 inhibitor therapy or significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any New York Heart Association class III–IV cardiac disease, or corrected QT interval >480

milliseconds) were excluded from the study. Patients with controlled, asymptomatic atrial fibrillation during screening were not excluded. Patients requiring systemic anticoagulation with warfarin or equivalent vitamin K antagonist, or any history of central nervous system lymphoma or leptomeningeal disease also were excluded from enrollment.

The enrollment target was a maximum of 36 to 48 patients, depending on dose-limiting toxicity (DLT)-driven dose finding. DLT was evaluated in the first 6 patients per cohort after completing 1 cycle. If fewer than 2 (33%) patients had DLTs, cohorts were expanded; if 2 or more patients had DLTs, acalabrutinib dosage would be reduced to 100 mg daily for all patients.

Study oversight

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. The study protocol was approved by the institutional review boards and all patients provided written informed consent. The data cutoff date for the analysis was June 15, 2022.

Treatment regimen

The treatment protocol is detailed in **Figure 1** of the main article. Patients received acalabrutinib 100 mg orally twice daily from day 1, cycle 1 until disease progression or intolerance. Bendamustine 90 mg/m^2 was administered as an intravenous infusion over

30 minutes on days 1 and 2 of each 28-day cycle for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on day 1 of each cycle for 6 cycles. Patients with TN MCL who achieved partial response (PR) or complete response (CR) continued rituximab therapy every other cycle for up to 12 doses starting on cycle 8.

Standard supportive care medications were permitted as per institutional standards (eg, antiemetics, antipyretics, antibiotics, transfusion of blood products). Prophylactic use of growth factors or administration in response to severe myelosuppression was permitted in accordance with American Society of Clinical Oncology guidelines.[1]

A DLT was defined as the occurrence of any of the study drug–related adverse events (AEs) including grade ≥3 nausea, vomiting, or diarrhea lasting >72 hours despite optimal antiemetic or antidiarrheal management; grade ≥3 neutropenia associated with fever or lasting ≥14 days despite adequate granulocyte colony-stimulating factor use; grade 3 or 4 thrombocytopenia that resulted in bleeding (exception was thrombocytopenia improvement to grade ≤2 or ≥80% of the baseline value by cycle 1 day 28 without a platelet transfusion); other grade ≥3 toxicities (with the exception of grade ≥3 laboratory abnormalities lasting <7 days that were not clinically significant and grade 3 or 4 leukopenia/lymphopenia); or dosing delay due to toxicity for >21 consecutive days.

For any DLT related to acalabrutinib, the dose of acalabrutinib was withheld until the toxicity was grade 1 or lower. Thereafter, acalabrutinib was resumed at one lower dose

level and the minimum dose of acalabrutinib was 100 mg orally per day. After the DLT review was cleared, dose modifications of acalabrutinib (detailed in the table below) occurred after drug-related toxicities for grade 4 neutropenia (absolute neutrophil count <500/μL) for >7 days, grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, and grade 3 or greater non-hematological toxicities.

Table: Acalabrutinib Dose Modifications for Study Intervention–Related Toxicities

<table>
<tr><th>Adverse reaction</th><th>Adverse reaction occurrence</th><th>Dose modification
(Starting dose = 100 mg approximately every 12 hours)</th></tr>
<tr><td rowspan="3">Grade 3 thrombocytopenia with bleeding

Grade 4 Thrombocytopenia

OR

Grade 4 neutropenia lasting longer than 7 days

Grade 3 or greater non-hematological toxicities</td><td>First and second</td><td>Interrupt acalabrutinib. Once toxicity has resolved to grade 1 or baseline, acalabrutinib may be resumed at 100 mg approximately every 12 hours.</td></tr>
<tr><td>Third</td><td>Interrupt acalabrutinib. Once toxicity has resolved to grade 1 or baseline, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily.</td></tr>
<tr><td>Fourth</td><td>Discontinue acalabrutinib.</td></tr>
</table>

Acalabrutinib was withheld for a maximum of 28 consecutive days from expected dose in the event of toxicity. Study treatment was discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.

Dosing adjustments for bendamustine were as follows: the starting dose of bendamustine was 90 mg/m^2. The lower dose level was 70 mg/m^2. If lower doses were required, treatment with bendamustine was discontinued. In case of grade ≥3 neutropenia or thrombocytopenia, or any other grade 4 hematologic toxicity, bendamustine was withheld until it improved to grade ≤2. Treatment was resumed at the lower dose level. In case of grade ≥3 drug-related non-hematologic toxicity, bendamustine was withheld until it improved to grade ≤1. Treatment was resumed at the lower dose level. For any toxicities not listed here, the bendamustine prescribing information was referred to after discussion with the medical monitor. Acalabrutinib treatment was continued when BR treatment was held or dose reduced for expected AEs associated with chemotherapy. Bendamustine was held for a maximum of 28 consecutive days from expected dose due to toxicity and study treatment was discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor. If a subject was unable to tolerate bendamustine, it was discontinued but treatment with rituximab was continued. Similarly, if intolerance to rituximab occurred during the initial 6 cycles, further treatment with rituximab was continued.

Endpoints and assessments

The primary endpoint of the study was safety of ABR. AEs were mapped using the Medical Dictionary for Regulatory Activities thesaurus terms and graded according to Common Terminology Criteria for Adverse Events version 4.03.

To evaluate the efficacy of ABR in patients with TN and R/R MCL, investigator-assessed overall response rate (ORR, defined as the proportion of patients achieving either a PR or a CR at any time during the treatment period), duration of response (DOR), and progression-free survival (PFS, defined as the time from first dose date to documented disease progression or death from any cause, whichever occurred first) were included as secondary endpoints. All endpoints were evaluated per the 2014 Lugano criteria for NHL, which requires positron emission tomography (PET)/computed tomography (CT) and bone marrow (BM) biopsy confirmation of CR.[2] ORR confirmed by PET/CT alone without BM biopsy was also calculated. Overall survival (OS) was also assessed.

Patients were evaluated by clinical examination and laboratory tests every cycle, and CT scans for tumor assessments on day 1 of cycles 3, 5, and 8 (±7 days) for both cohorts. For the TN cohort, CT scans were performed every 4 cycles (16 weeks; ±7 days) from cycles 8 to 48, then every 6 cycles thereafter. For the R/R cohort, CT scans were done every 3 cycles (12 weeks; ±7 days) through cycle 23 and then every 4 cycles (16 weeks; ±7 days) from cycles 27 to 47, then every 6 cycles thereafter. For both cohorts, PET/CT scans were performed on day 1 of cycle 3, and then only to confirm CR. Patients with confirmed CR were not required to undergo further PET/CT scans.

Statistical analyses

Descriptive statistics were used to summarize baseline demographics and disease characteristics, study drug administration, efficacy, and safety outcomes.

Safety was evaluated by analyzing the extent of exposure to the study drug, all AEs, serious AEs, non-serious AEs leading to study drug discontinuation, and study drug–related AEs. The frequency of AEs was summarized by system organ class and preferred terms according to the Medical Dictionary for Regulatory Activities, as well as per severity per Common Terminology Criteria for Adverse Events version 4.03. Only treatment-emergent AEs were included in the summarized analysis. For events with varying severity, the worst reported grade was used. Laboratory parameters were analyzed with shift tables and summaries of changes from baseline to worst post-treatment value. Figures of changes in laboratory parameters over time were generated for certain parameters. Changes from baseline in vital sign assessments were tabulated and summarized.

ORR was summarized by number and percentage of patients, and its corresponding 95% confidence interval (CI) was calculated using an exact binomial test (Clopper-Pearson). Best ORR by Lugano criteria and by PET/CT alone were summarized by number and percentage of patients for each response category (CR, PR, stable disease [SD], progressive disease [PD], non-evaluable [NE], and unknown). For patients achieving CR or PR, descriptive statistics were calculated for time to initial response and best response.

Kaplan-Meier (K-M) estimates of PFS, OS, and DOR in months and the corresponding 2-sided 95% CIs were calculated and presented for the median, with a K-M curve used

to estimate the distribution of PFS and OS. Sensitivity analyses were conducted by censoring patients who died due to COVID-19 infection, and the corresponding K-M plots were provided for PFS and OS. Only patients who achieved an objective response (CR or PR) were included in the analysis of DOR.

Supplemental Information – Results

Events of Clinical Interest

- **Cardiac events**
  - TN cohort: 4 patients (1 with aortic valve disease [grade 2]; 1 with cardiac failure [grade 3] and tachycardia [grade 1]; 1 with tachycardia [grade 3]; and 1 with pericardial effusion [grade 3])
  - R/R cohort: 4 patients (1 with tachycardia [grade 1]; 1 with unstable angina [grade 4]; 1 with angina pectoris [grade 3]; and 1 with acute coronary syndrome [grade 3])
- **Hemorrhage**
  - TN cohort: 8 patients (1 with hematuria [grade 2], alveolar hemorrhage [grade 4], and hematoma [grade 1]; 1 with ecchymosis [grade 1]; 1 with contusion [grade 1], hemarthrosis [grade 3], and ecchymosis [grade 1]; 1 with hematochezia, rectal hemorrhage, epistaxis, and petechiae [all grade 1]; 1 with gingival bleeding, rectal hemorrhage, contusion, and epistaxis [all grade 1]; and 1 with contusion [grade 1])
  - R/R cohort: 6 patients (1 with hemoptysis [grade 1]; 1 with contusion and hemoptysis [both grade 1]; 1 with increased tendency to bruise [grade 1] and subdural hematoma [grade 3]; 1 with intestinal hemorrhage [grade 3]; 1 with gastrointestinal hemorrhage [grade 3], contusion, and petechiae [both grade 1]; and 1 with contusion [grade 1])

- **Grade ≥3 infections**
  - TN cohort: 5 patients (1 with appendicitis [grade 3], pneumonia [grade 3], and sepsis [grade 4]; 2 with pneumonia [each grade 3]; 1 with cellulitis and perineal cellulitis [both grade 3]; and 1 with influenza and pneumonia Moraxella [both grade 3])
  - R/R cohort: 6 patients (1 with infection [grade 3] and COVID-19 [grade 5]; 1 with bronchitis [grade 3]; 1 with respiratory tract infection and pneumonia [both grade 3]; 1 with appendicitis [grade 3]; 1 with pneumonia [grade 3]; and 1 with otitis [grade 3])

Deaths due to other/unknown causes

A total of 6 patients died due to other/unknown causes. In the TN cohort, there were 4 patients: in one patient, PD was confirmed 5 days before death. One patient was hospitalized approximately 7 months before death due to a serious AE of grade 2 aortic valve disease mixed (reported as combined defect of aortic valve; moderate stenosis plus moderate defective closure), which was considered unrelated to study treatment. The patient was treated and discharged. One patient was previously hospitalized for stroke, but no cause was given on certificate of death. One patient had serious AEs of pneumonia, pericardial effusion, and atrial fibrillation within 6 months of death, which were considered unrelated to study treatment. In the R/R cohort, there were 2 patients: one patient died 22 days after PD was diagnosed. One patient had a nonserious event of pyoderma gangrenosum, which was considered ongoing at the time of death. The

patient previously had a grade 3 pyoderma gangrenosum considered related to acalabrutinib, for which treatment was received.

References

1. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33(28):3199-212.
2. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Plain Language Summary

Why was this study done?

Mantle cell lymphoma (MCL) is a rare B-cell malignancy (a cancer of the white blood cells) that affects mostly older adults and is usually treated with a combination of chemotherapy and immunotherapy. Chemoimmunotherapy treatment is often associated with severe side effects and additional safe and effective treatments are needed when patients no longer respond to treatment. This study, called ACE-LY-106, evaluated the safety and efficacy of a combination therapy option to treat patients with MCL who have either not received prior treatment or are no longer responding to treatment. This combination therapy included acalabrutinib, bendamustine, and rituximab. Bendamustine is a chemotherapy drug while acalabrutinib and rituximab block specific proteins on the cancer cells. Treatment with these drugs prevents the cancer cells from growing and spreading.

How were the data collected?

In this study, all participants who received treatment were seen by the medical team periodically and had blood tests and imaging studies to assess how their disease was responding to treatment (efficacy) and how well they were tolerating the treatment (safety).

What were the results?

With approximately 4 years of follow-up in patients who had not received prior treatment and 1.5 years of follow-up in patients whose cancer had returned or no longer responded to prior treatments, most patients achieved either a complete response or partial response after treatment with acalabrutinib, bendamustine, and rituximab. The

safety profile of the combination treatment was acceptable, with no new safety risks identified.

Why do the results matter to patients and physicians?

This study showed that combination therapy with acalabrutinib, bendamustine, and rituximab is a promising and highly effective treatment option for patients with MCL who had not received prior treatment or were no longer responding to treatment. These results support further study of this combination in patients with MCL.