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

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Abstract

This multicenter, open-label, phase Ib study (ACE-LY-106) assessed the safety and efficacy of acalabrutinib, bendamustine, and rituximab (ABR) in treatment-naïve (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 cohort 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 (AE) 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 AE, most commonly neutropenia (TN: 38.9%; R/R: 50.0%). AE 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.

Introduction

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma (NHL), accounting for 5-10% of NHL cases.[1,2] Chemoimmunotherapy (CIT) with bendamustine plus rituximab (BR) is a treatment option for patients with treatment-naïve (TN) or relapsed or refractory (R/R) MCL, particularly for patients >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 front-line 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 III 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 front-line 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 Ib study of acalabrutinib, bendamustine, and rituximab (ABR) in patients with R/R and TN MCL.

An earlier report of this multicenter, phase Ib 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 Ib trial designed to assess the safety and efficacy of ABR in TN and R/R patients with MCL (ACE-LY-106; clinicaltrials.gov identifier: NCT02717624). Full details of the methods used can be found in the *Online Supplementary Appendix*. 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 the *Online Supplementary Appendix*) were excluded from the study.

Ethical issues

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 (TEAE) or abnormalities of laboratory tests, serious AE (SAE), dose-limiting toxicities (DLT), or AE 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.

Overall response rate 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 dis-

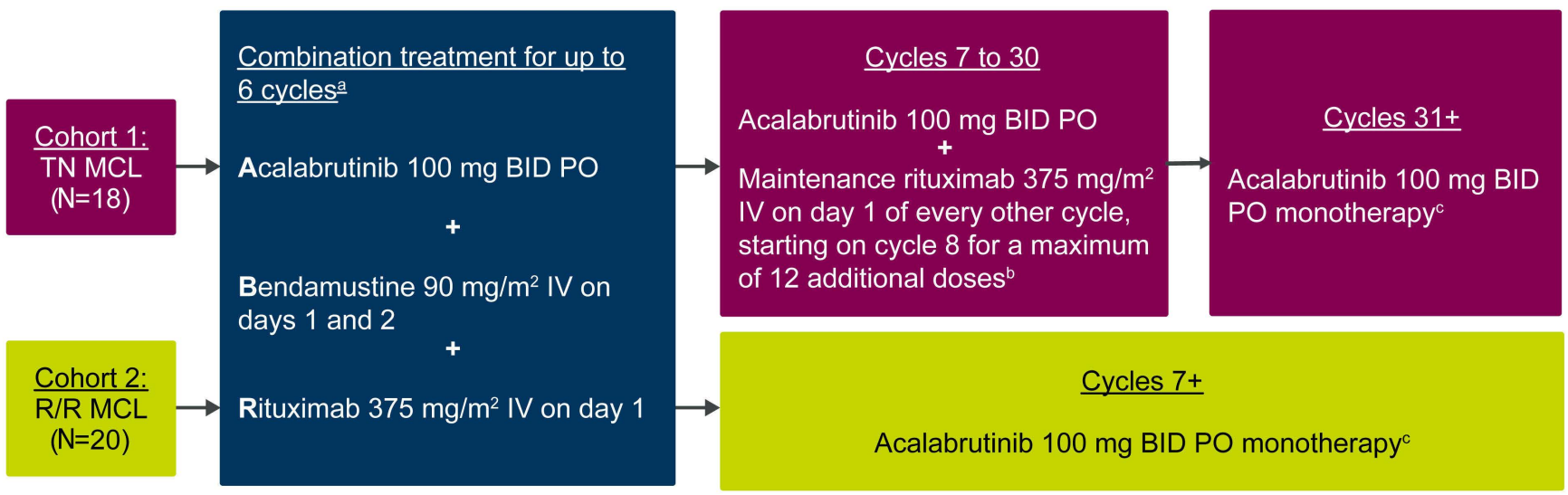

Figure 1. Study design. BID: twice daily; IV: intravenously; MCL: mantle cell lymphoma; PO: orally; PR: partial response; R/R: relapsed/refractory; TN: treatment-naïve. [a]One cycle was 28 days. [b]Only for patients who achieved a response (PR or better). [c]Until disease progression or treatment discontinuation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

tribution 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 two-sided 95% CI were calculated and presented for the median. The number of patients at risk was calculated and presented at selected timepoints of six months, nine months, and every three 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 *Online Supplementary Table S1*.

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 AE, followed by disease progression and withdrawal by investigator (*Online Supplementary Table S1*). One patient (6.7%) in the TN cohort discontinued acalabrutinib due to an AE (allergic reaction) before completing 6 cycles of BR. No DLT 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 AE in 6 patients (33.3%) in the TN cohort and 9 patients (45%) in the R/R cohort (*Online Supplementary Tables S2* and *S3*). Acalabrutinib dose reductions due to AE occurred in 4 (22.2%) and 2 (10.0%) patients in the TN and R/R cohorts, respectively. Bendamustine dose reductions due to AE occurred in 6 (33.3%) and 5 (25.0%) patients in the TN and R/R cohorts, respectively.

Safety

The most common any grade AE 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 AE were grades 1 or 2. Grade 3 or 4 AE were reported in 72.2% of patients in the

Table 1. Demographics and baseline characteristics.

Characteristic	TN cohort N=18	R/R cohort N=20	Total N=38
Age in years, median (range)	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)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; MCL: mantle cell lymphoma; MIPI: Mantle Cell Lymphoma Prognostic Index; R/R: relapsed/refractory; TN: treatment-naïve. [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.

Table 2. Patients' disposition.

	TN cohort N=18	R/R cohort N=20	Total N=38
Study completion (still on acalabrutinib), N (%)	6 (33.3)	4 (20.0)	10 (26.3)
Reasons for study discontinuations, N (%)			
Death[a]	5 (27.8)	5 (25.0)[b,c]	10 (26.3)
Disease progression	0	1 (5.0)[b]	1 (2.6)
AE/SAE	1 (5.6)	2 (10.0)	3 (7.9)
Other/unknown[d]	4 (22.2)	2 (10.0)	6 (15.8)
Objective evidence of disease progression (e.g., PET, CT)	1 (5.6)	4 (20.0)	5 (13.2)
Withdrawal of consent	0	2 (10.0)	2 (5.3)
Withdrawal by investigator	1 (5.6)	1 (5.0)	2 (5.3)
AE/SAE	2 (11.0)	1 (5.0)	3 (7.9)
Other	3 (16.7)	3 (15.0)	6 (15.8)

AE: adverse event; CT: computed tomography; PET: positron emission tomography; R/R: relapsed/refractory; SAE: serious adverse event; TN: treatment-naïve. [a]Including only patients who died prior to discontinuation from the study. [b]Among a total of 6 deaths in the R/R cohort, 5 patients discontinued from study due to death and one 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 the R/R cohort, 5 patients discontinued from study due to death and one 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 *Online Supplementary Appendix*.

Table 3. Treatment-emergent adverse events occurring in ≥30% of patients and events of clinical interest.

Adverse events	TN cohort N=18		R/R cohort N=20		Total N=38	
Most common AE, 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)

AE: adverse event; R/R: relapsed/refractory; TN: treatment-naïve. [a]Detailed information on cardiac events, hemorrhage and infections is available in the *Online Supplementary Appendix.*

TN cohort and 85.0% in the R/R cohort, most commonly neutropenia (TN: 38.9%; R/R: 50%).

Serious adverse events of any grade were reported in 11 patients (61.1%) in the TN cohort and 13 patients (65.0%) in the R/R cohort. SAE 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) (Table 2, *Online Supplementary Table S4*). The 4 patients who died of unknown causes were 65, 79, 81, and 85 years old, 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 one 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 (*Online Supplementary Figure S1*).

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 Figure 3A and B.

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 Ib study demonstrates that treatment with triple-combination ABR was tolerable, with a toxicity pro-

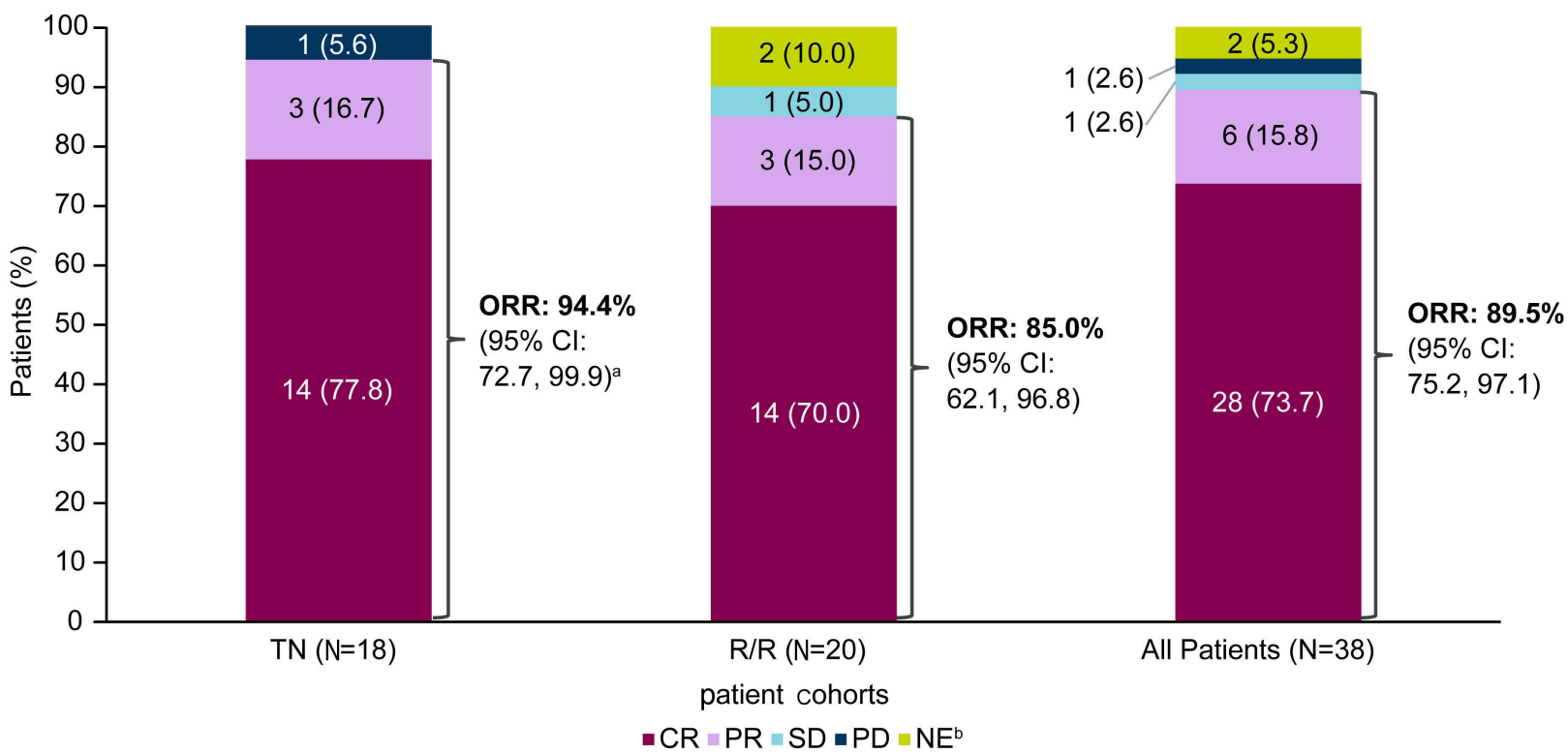

Figure 2. Investigator-assessed overall response rate by Lugano criteria. Overall response rate (ORR) is defined as achieving complete response (CR) or partial response (PR). [a]95% exact binomial confidence interval. [b]Includes patients without any adequate post-baseline response assessment. CI: Confidence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

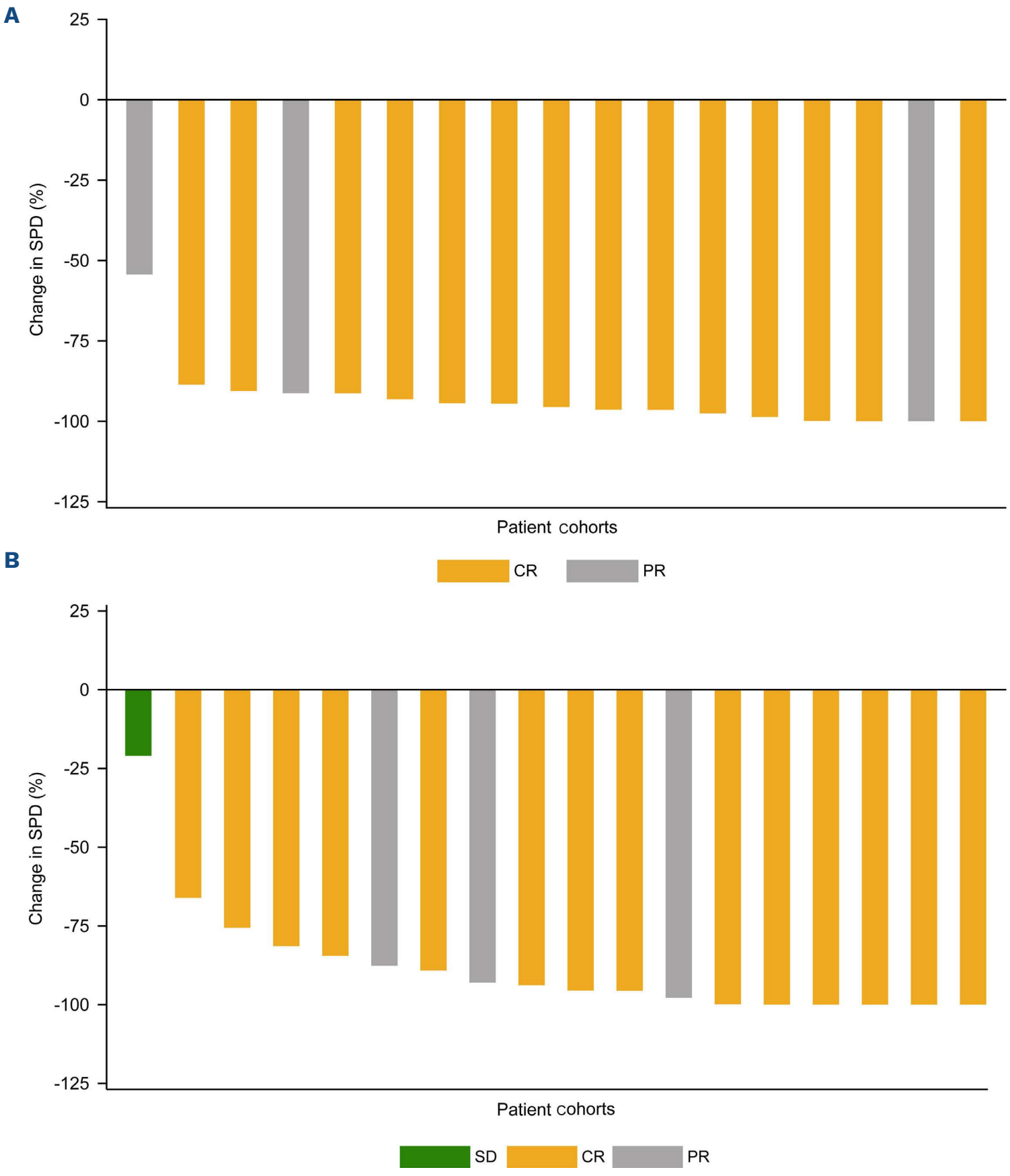

Figure 3. Maximum change from baseline in sum of product diameters for each patient cohort. (A) Change in sum of product diameters (SPD) for the treatment-naïve (TN) cohort is shown. (B) Change in SPD for the relapsed/refractory (R/R) cohort is shown. Results were based on best responses. One patient in the TN cohort (patient had progressive disease [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; PR: partial response; SD: stable disease.

file 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

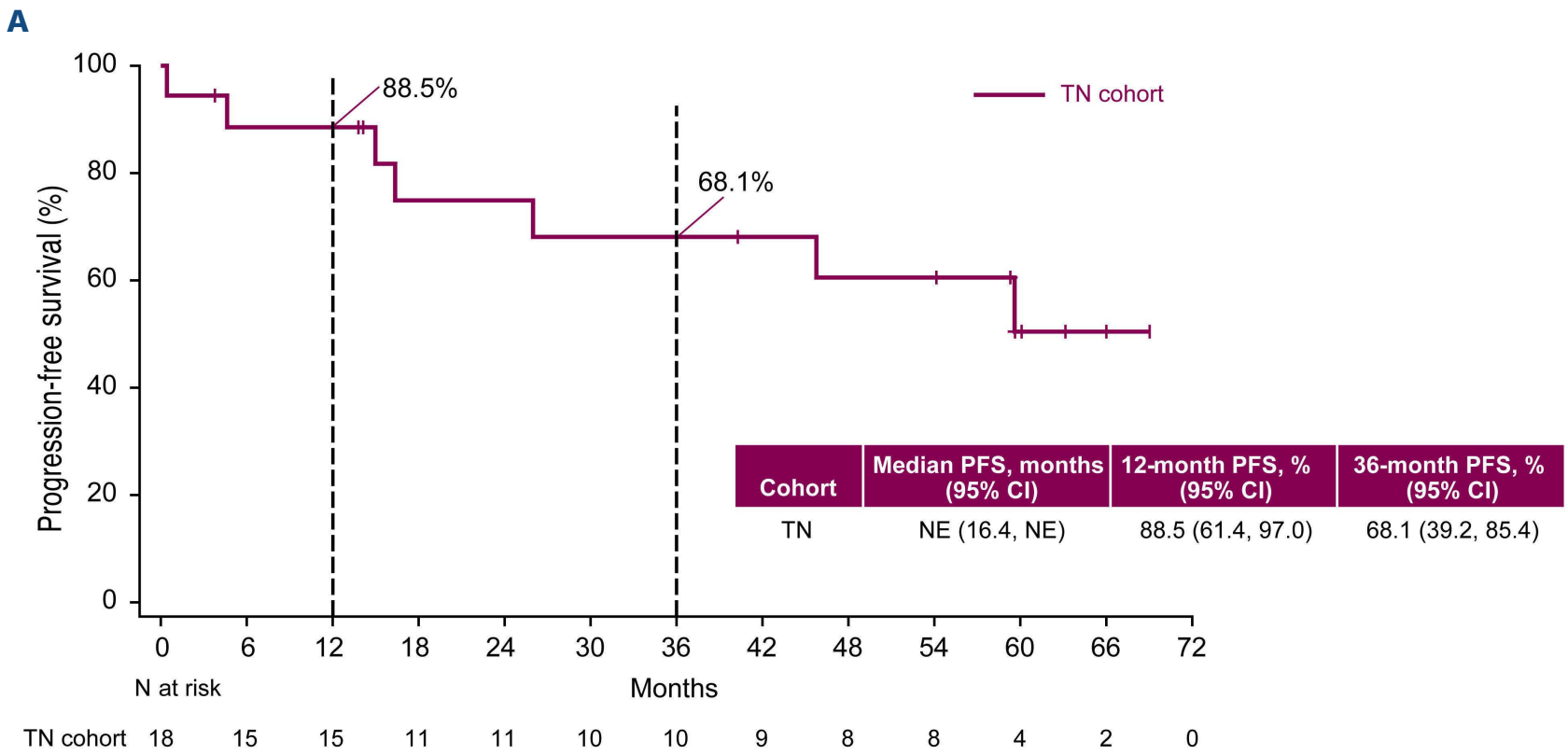

Figure 4. Progression-free survival for each patient cohort. (A) The Kaplan-Meier plot depicts progression-free survival (PFS) for the treatment-naïve (TN) cohort. (B) The Kaplan-Meier plot for PFS for the relapsed/refractory (R/R) cohort is shown. CI: Confidence Interval; NE: not estimable.

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 I/Ib 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 III 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 AE and deaths when compared with the BR-placebo group. Grade 3 or 4 AE 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

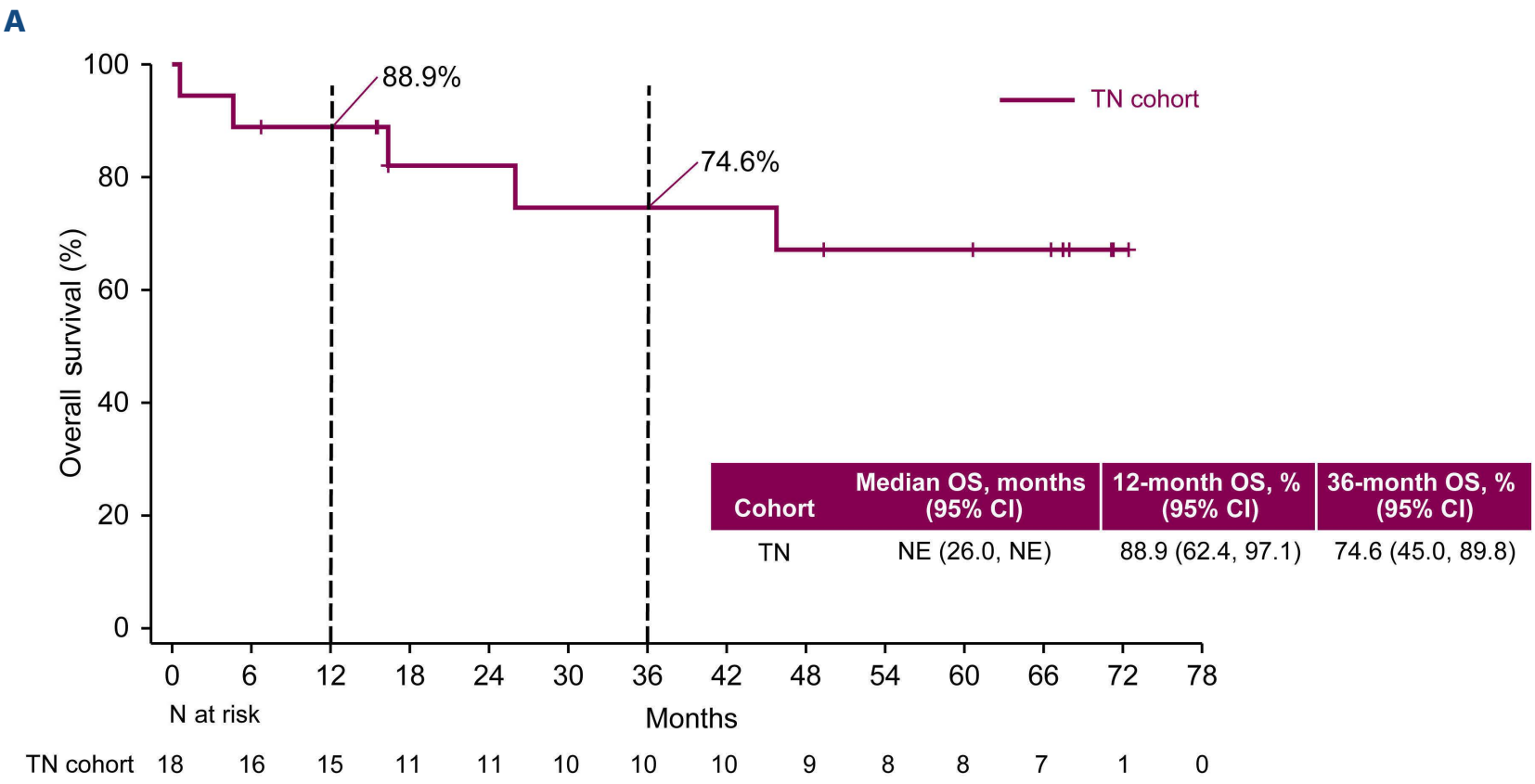

Figure 5. Overall survival for each patient cohort. (A) The Kaplan-Meier plot depicts overall survival (OS) for the treatment-naïve (TN) cohort. (B) The Kaplan-Meier plot for OS in the relapsed/refractory (R/R) cohort is shown. CI: Confidence Interval; NE: not estimable.

and selective inhibitor of BTK to reduce off-target effects seen with ibrutinib.[15] This difference was demonstrated in the phase III head-to-head comparison of acalabrutinib *versus* ibrutinib in patients with previously treated chronic lymphocytic leukemia.[16] Compared with ibrutinib, acalabrutinib-treated patients had fewer cardiovascular TEAE 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 TEAE was also lower in the acalabrutinib *versus* the ibrutinib arm (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 III ECHO trial (clinicaltrials.gov identifier: NCT02972840), based on these phase I 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 [clinicaltrials.gov identifier: NCT05951959], BOVen [clinicaltrials.gov identifier: NCT03824483], EA4181 [clinicaltrials.gov identifier: NCT04115631])[18-20] will provide key efficacy and safety data and may alter the treatment landscape for this challenging disease.

In 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 III ECHO trial, which aims to confirm the safety profile and efficacy of long-term ABR.

Disclosures

TP reports consultancy for AbbVie, ADCT, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Genmab, Genentech, Epizyme, Eli Lilly, Incyte, Janssen, Kite, MorphoSys, Pharmacyclics, Seattle Genetics, Regeneron, and Xencor, research funding from AbbVie, Bayer, Genentech, and Sobi, sits on the Scientific Committee of Genmab, Genentech, and Merck, and is a CDP Scholar in Clinical Research of the Leukemia & Lymphoma Society. MW reports consultancy for AbbVie, Acerta Pharma, ADC Therapeutics America, Amphista Therapeutics Ltd., AstraZeneca, Be Biopharma, BeiGene, BioInvent, Bristol Myers Squibb, Deciphera, DTRM Biopharma (Cayman) Ltd., Genentech, InnoCare, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Lilly, Merck, Miltenyi Biomedicine, Milken Institute, Oncternal, Parexel, Pepromene Bio, Pharmacyclics, and VelosBio, research funding from Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genmab, Genentech, Innocare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics, VelosBio, and Vincerx, and honoraria from AbbVie, Acerta Pharma, AstraZeneca, Bantam Pharmaceutical, BeiGene, BioInvent, Bristol Myers Squibb, CAHON, Catamount Medical Education, Dava Oncology, Eastern Virginia Medical School, Genmab, i3Health, IDEOlogy Health, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Medscape, Meeting Minds Experts, MD Education, MJH Life Sciences, Merck, Moffit Cancer Center, MSC National Research Institute of Oncology, NIH, Nurix, Oncology Specialty Group, OncLive, Pharmacyclics, Physicians Education Resources (PER), Practice Point Communications (PPC), Research to Practice, Scripps, Syneos Health, Studio ER Congressi, South African Clinical Hematology Society, and WebMD. TR reports research funding from Acerta, Roche, Janssen, AbbVie, Novartis, BioGene, AstraZeneca, Pharmacyclics, Pfizer, MorphoSys, UTX-TGR, GSK, and Bristol Myers Squibb, has received travel and accommodation expenses from Roche, Janssen, and AbbVie, honoraria from Sandoz, Novartis, Octapharma, BioGene, AstraZeneca, and Pharmacyclics, and consultancy from Sandoz, Takeda, and Momenta. KP reports consultancy from AbbVie, ADC, AstraZeneca, BeiGene, Bristol Myers Squibb, Caribou, Fate Therapeutics, Genentech, Epizyme, Eli Lilly, Janssen, Kite Pharma, Merck, Pfizer, Pharmacyclics, Sana Biotechnology, Seattle Genetics, and Xencor, and research funding from AbbVie, Adaptive, Adicet, AstraZeneca, Bristol Myers Squibb, Century Therapeutics, CRISPR Therapeutics, Epizyme, Eli Lilly, Fate Therapeutics, Genentech, Janssen, Kite Pharma, Pfizer, Pharmacyclics, and Xencor. SR is an employee and stock shareholder of AstraZeneca. C-CW is an employee and stock shareholder of AstraZeneca. WJ reports research funding from AstraZeneca, and sits on the Advisory Boards of AstraZeneca. SDS reports research funding from ADC Therapeutics, AstraZeneca, Ayala (spouse), Bayer, BeiGene, Bristol Myers Squibb (spouse), De Novo Biopharma, Enterome, Genentech, Ignyta (spouse), Incyte Corporation, Kymera Therapeutics, Merck Sharp and Dohme Corp., MorphoSys, Nanjing Pharmaceuticals Co. Ltd., and Viracta Therapeutics, and consultancy or Advisory Board for ADC Therapeutics, AstraZeneca, BeiGene, Karyopharm, Kite, Incyte, Numab Therapeutics AG, AbbVie, Coherus Biosciences (Advisory Board, spouse), and Genentech. None of the other authors have any conflicts of interest to disclose.

Contributions

CCW is responsible for study design, enrolled patients, and collected, assembled and analyzed the data. TR is a study investigator, enrolled patients, and collected and assembled the data. SS and KP are study investigators and enrolled

patients. SR collected and assembled the data. All authors prepared, reviewed and revised the manuscript, interpreted the data, and approved the final version of the manuscript for publication.

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Data-sharing statement

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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