ARTICLE - Non-Hodgkin Lymphoma

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

Tycel Phillips,[1] Michael Wang,[2] Tadeusz Robak,[3] David Gallinson,[4] Don Stevens,[5] Krish Patel,[6] Safaa Ramadan,[7] Chuan-Chuan Wun,[8] Wojciech Jurczak[9] and Stephen D. Smith[10]

[1]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [2]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [3]Copernicus Memorial Hospital, Medical University of Lodz, Lodz, Poland; [4]Summit Medical Group, Florham Park, NJ, USA; [5]Norton Cancer Institute, Louisville, KY, USA; [6]Swedish Cancer Institute, Seattle, WA, USA; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, South San Francisco, CA, USA; [9]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland and [10]University of Washington/Fred Hutchinson Cancer Center, Seattle, WA, USA

Correspondence: T. Phillips
tphillips@coh.org

Received: January 5, 2024.
Accepted: August 27, 2024.
Early view: September 5, 2024.

https://doi.org/10.3324/haematol.2023.284896

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)

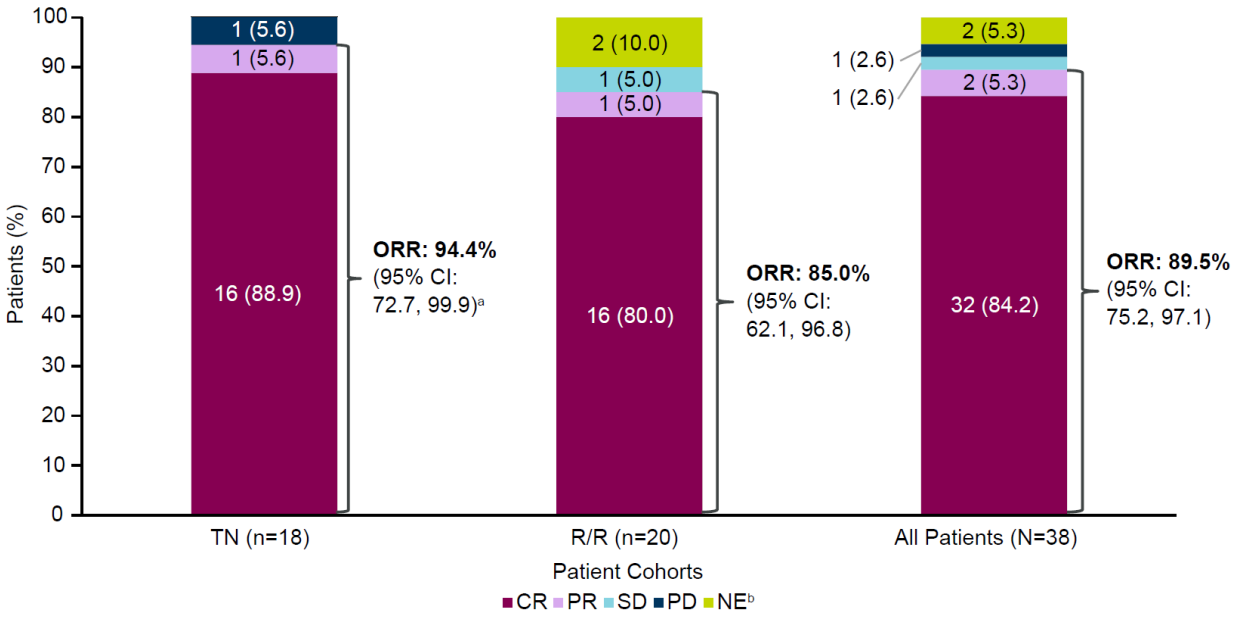
Unknown	2 (11.1)	0	2 (5.3)

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.