Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma

Michael Wang, MD[1]; David Salek, MD[2]; David Belada, MD[3]; Yuqin Song, MD[4]; Wojciech Jurczak, MD, PhD[5,6]; Brad S. Kahl, MD[7]; Jonas Paludo, MD[8]; Michael P. Chu, MD[9]; Iryna Kryachok, MD[10]; Laura Fogliatto, MD[11]; Chan Y. Cheah, DMSc[12,13]; Marta Morawska, MD, PhD[14,15]; Juan-Manuel Sancho, MD[16]; Yufu Li, MD[17]; Caterina Patti, MD[18]; Cecily Forsyth, MD[19]; Jingyang Zhang, PhD[20]; Robin Lesley, PhD[20]; Safaa Ramadan, MD, PhD[21]; Simon Rule, MD, PhD[21]; and Martin Dreyling, MD, PhD[22]; for the ECHO investigators

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ABSTRACT

PURPOSE The combination of the Bruton tyrosine kinase inhibitor ibrutinib with bendamustine-rituximab for first-line treatment of mantle cell lymphoma (MCL) prolonged progression-free survival (PFS), but without improvement in overall survival (OS), likely because of toxicity. Acalabrutinib was shown to be efficacious and less toxic than ibrutinib in a head-to-head trial in chronic lymphocytic leukemia and therefore might lead to better outcomes in MCL.

METHODS Patients 65 years and older with previously untreated MCL received acalabrutinib (100 mg twice daily) or placebo (until disease progression or unacceptable toxicity), plus six cycles of bendamustine (90 mg/m² once daily; days 1 and 2) and rituximab (375 mg/m² as a single dose; day 1) followed by rituximab maintenance in responding patients for 2 years. Crossover to acalabrutinib at disease progression was permitted. The primary end point was PFS per the independent review committee; overall response rate and OS were secondary end points.

RESULTS In total, 598 patients were randomly assigned, with 299 in each arm. At a median follow-up of 49.8 months using the reverse Kaplan-Meier method, the median PFS was 66.4 months in the acalabrutinib arm and 49.6 months in the placebo arm (hazard ratio [HR], 0.73 [95% CI, 0.57 to 0.94]; $P = .0160$). Benefit was seen across all subgroups, including those with high-risk features. Overall response/complete response rates were 91.0%/66.6% and 88.0%/53.5% in the acalabrutinib and placebo arms, respectively. OS was not significantly different (HR, 0.86 [95% CI, 0.65 to 1.13]; $P = .27$). Grade 3 or greater adverse events were reported in 88.9% and 88.2% in the acalabrutinib and placebo arms, respectively.

CONCLUSION The combination of acalabrutinib with bendamustine-rituximab significantly improved PFS. Clinical benefit of acalabrutinib with bendamustine-rituximab was achieved with manageable toxicity.

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INTRODUCTION

Mantle cell lymphoma (MCL) is an aggressive, incurable B-cell lymphoma.[1-3] Chemoimmunotherapy typically followed by autologous stem-cell transplant has been the standard of care in young, fit patients and produces high response rates and longer progression-free survival (PFS).[4,5] Dose-intensive therapies are not well tolerated by older or frailer patients because of toxicity; in these groups, regimens such as bendamustine-rituximab are standard of care.[5,6]

Bruton tyrosine kinase inhibitors (BTKis) have demonstrated benefit in relapsed/refractory MCL,[7-9] with favorable efficacy observed with use in earlier lines of therapy, including first-line in younger patients.[10-14] As a consequence, there has been interest in using these therapies in combinations in the first-line setting in older patients. The addition of the BTKi ibrutinib to bendamustine-rituximab for first-line treatment of MCL (SHINE) prolonged PFS, but with no improvement in overall survival (OS), likely because of increased deaths attributable to ibrutinib-related toxicity.[15]

Acalabrutinib is a second-generation covalent BTKi with greater specificity for BTK compared with ibrutinib.[16] In a prospective head-to-head comparison of ibrutinib and acalabrutinib in patients with chronic lymphocytic leukemia,

CONTEXT

Key Objective

Should acalabrutinib be added to bendamustine plus rituximab as frontline therapy in older patients with mantle cell lymphoma (MCL)?

Knowledge Generated

The addition of acalabrutinib to bendamustine plus rituximab significantly improved progression-free survival (PFS) compared with placebo and bendamustine plus rituximab in patients with previously untreated MCL, including those with high-risk features. Toxicity in both study arms was manageable.

Relevance *(J.W. Friedberg)*

These results directly led to approval by the US Food and Drug Administration for the combination of acalabrutinib, bendamustine, and rituximab for adults with previously untreated MCL ineligible for autologous stem cell transplantation. Future studies should determine optimal duration and sequencing of Bruton tyrosine kinase inhibition for patients with MCL and should define subsets of patients who no longer require chemotherapy treatment for this disease.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

acalabrutinib had superior safety, including reduced cardiovascular toxicities.[17] A phase Ib trial demonstrated that acalabrutinib with bendamustine-rituximab produced durable responses with a tolerable safety profile in patients with either untreated or relapsed/refractory MCL.[18]

Here, we present the results of the randomized, multicenter, double-blind, placebo-controlled, phase III ECHO trial (ClinicalTrials.gov identifier: NCT02972840) evaluating bendamustine-rituximab alone versus in combination with acalabrutinib in older patients with previously untreated MCL.

METHODS

Patients

Patients enrolled were 65 years or older with pathologically confirmed MCL requiring treatment, with no previous systemic anticancer therapy and with adequate organ function, radiologically measurable disease, and an Eastern Cooperative Oncology Group performance status of 2 or less. Excluded patients had a history of previous malignancy, were planned to receive stem-cell transplant, had evidence of CNS involvement, or had significant cardiovascular disease. Concurrent anticoagulation with warfarin or equivalent vitamin K antagonists or strong CYP3A inhibitors or inducers was not permitted.

Trial Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive acalabrutinib 100 mg twice daily or placebo. Treatment allocation was blinded to investigators and patients. Random assignment was stratified by geographic region (North America, Western Europe, other) and simplified MCL International Prognostic Index score (low [0-3], intermediate [4-5], or high risk [6-11]). All patients received bendamustine 90 mg/m^2 once daily on days 1 and 2 and rituximab 375 mg/m^2 as a single dose on day 1 for six cycles (28 days/cycle) as induction. Patients achieving partial or complete response received rituximab maintenance at a dose of 375 mg/m^2 as a single dose on day 1 of every even cycle from cycles eight through 30. Acalabrutinib or placebo was commenced with bendamustine-rituximab therapy and given continuously until disease progression or unacceptable toxicity. Patients receiving placebo were eligible to cross over to receive sponsor-provided acalabrutinib on disease progression.

Outcomes and Assessments

The primary end point was PFS assessed by an independent review committee. Secondary end points included overall response rate, OS, and safety. The interim efficacy and overall safety were monitored by an independent data monitoring committee (see the Data Supplement [online only] for the independent data monitoring committee listing).

Computed tomography was performed every 12 weeks for 96 weeks and every 24 weeks thereafter until disease progression. Positron emission tomography/computed tomography scans were performed at weeks 12 and 24 and thereafter only to confirm complete response. Bone marrow assessment and GI endoscopy were repeated to confirm complete response only if patients had bone marrow or GI involvement, respectively, at baseline. Response rate and PFS were assessed per Lugano classification.[19] Minimal residual disease (MRD) was assessed in peripheral blood every 24 weeks and at complete response or progressive

disease using the ClonoSEQ (Adaptive Biotechnologies) assay. Bone marrow was assessed for MRD at screening and complete response. Formalin-fixed paraffin-embedded (FFPE) analyses were conducted using a custom next-generation targeted sequencing panel (a modified version of the AZHeme600 panel[20]) which had a median average panel coverage of 1,394× (range, 332-5,413×). The variant allele frequency cutoff was ≥5% for FFPE. Germline variants of unknown significance were removed if present at a >0.05% population allele frequency in gnomAD. Sequencing artifacts were removed using a panel of normals. Adverse events were defined and graded per Common Terminology Criteria for Adverse Events version 4.03.

Trial Oversight

The study was conducted in accordance with the protocol, the International Council for Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practices, applicable local regulations, and the ethical principles of the Declaration of Helsinki. An Institutional Review Board and Independent Ethics Committee approved the protocol at each site. All patients provided written informed consent.

Statistical Analysis

A sample size of at least 546 patients was calculated to achieve an approximately 90% power to detect a hazard ratio (HR) of 0.67 in PFS, which, under model assumptions, translates to a 49% improvement in median PFS. PFS and OS were estimated using the Kaplan-Meier method and compared between arms using a stratified log-rank test. A stratified Cox regression model provided the estimated HR and two-sided 95% CIs. Median follow-up was also calculated using the Kaplan-Meier technique where the censoring indicator is reversed. Efficacy was evaluated in the full analysis set, defined as all randomly assigned patients. Safety was evaluated in the safety analysis set, defined as all patients who received at least one dose of study drug.

RESULTS

Patients and Treatment

From April 2017 to March 2023, 598 patients from 195 sites in 26 countries in North and South America, Europe, Asia, and Australia were randomly assigned to the acalabrutinib (n = 299) or placebo arms (n = 299) and were included in the full analysis set (Fig 1). In each arm, 297 patients received at least one dose of study treatment and were included in the safety analysis set. The median age was 71 years (range, 65-86). The arms were well balanced with respect to patient characteristics, including *TP53* mutation (Table 1).

At the data cutoff (February 15, 2024), the median time on study was 44.9 months (range, 0.03-81.3). In the acalabrutinib arm, 74.2% (n = 222) of patients completed induction treatment versus 75.3% (n = 225) in the placebo arm. Regarding maintenance therapy, 51.5% (n = 154) of patients completed rituximab maintenance per protocol in the acalabrutinib arm compared with 45.8% (n = 137) in the placebo arm. Overall, 202 patients (67.6%) discontinued acalabrutinib and 219 patients (73.2%) discontinued placebo, with the most common reasons being adverse events (43.1% and 31.4%, respectively) and PD (12.4% and 28.8%, respectively; Fig 1). The median duration of treatment was 28.6 months

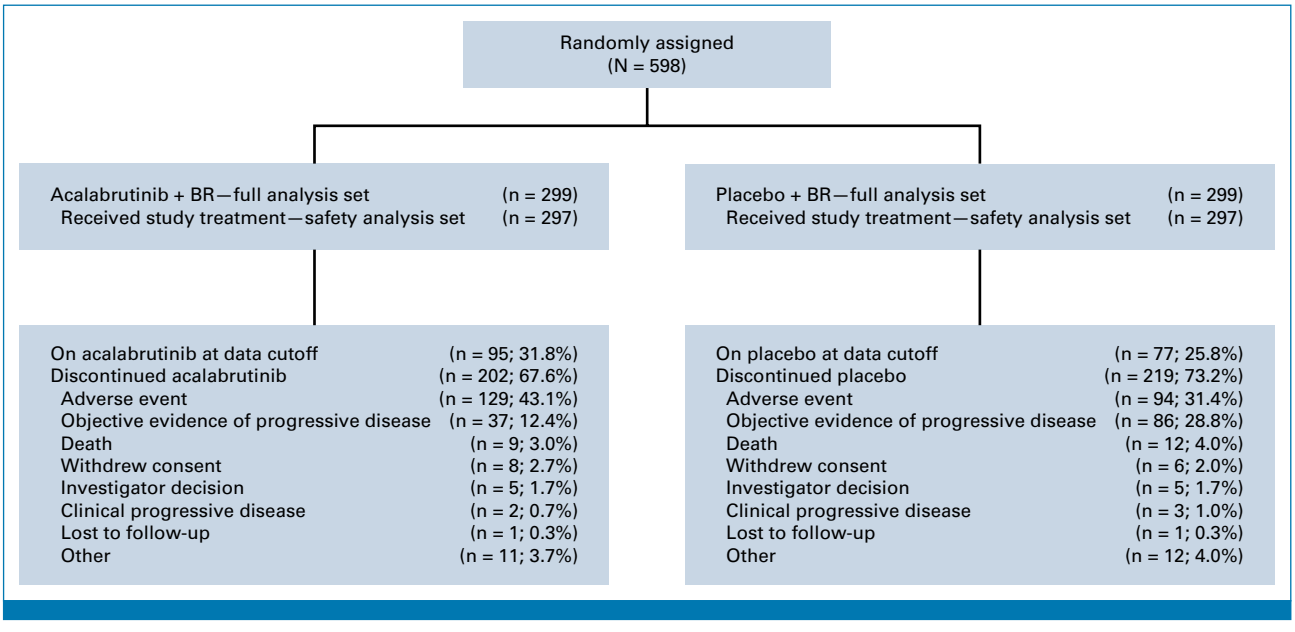

FIG 1. CONSORT diagram showing patient disposition. BR, bendamustine-rituximab.

TABLE 1. Demographics and Baseline Characteristics

Characteristic	Acalabrutinib + Bendamustine-Rituximab (n = 299)	Placebo + Bendamustine-Rituximab (n = 299)
Age, years, median (range)	71 (65-85)	71 (65-86)
≥70, No. (%)	176 (58.9)	182 (60.9)
≥75, No. (%)	84 (28.1)	77 (25.8)
Male, No. (%)	214 (71.6)	209 (69.9)
Race, No. (%)		
White	233 (77.9)	235 (78.6)
Asian	44 (14.7)	49 (16.4)
American Indian or Alaska Native	2 (0.7)	2 (0.7)
Black or African American	1 (0.3)	2 (0.7)
Multiple	5 (1.7)	0
Not reported	14 (4.7)	11 (3.7)
Time from diagnosis to random assignment, months, median (range)	1.7 (0-116.4)	1.5 (0.1-142.4)
ECOG PS score, No. (%)[a]		
0	156 (52.2)	140 (46.8)
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
3	0	2 (0.7)
Ann Arbor staging for lymphoma, No. (%)		
I	2 (0.7)	1 (0.3)
II	15 (5.0)	11 (3.7)
III	31 (10.4)	24 (8.0)
IV	251 (83.9)	263 (88.0)
Tumor bulk ≥5 cm, No. (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorphic histology, No. (%)	41 (13.7)	38 (12.7)
Simplified MCL International Prognostic Index score, No. (%)		
Low risk	99 (33.1)	101 (33.8)
Intermediate risk	128 (42.8)	125 (41.8)
High risk	72 (24.1)	73 (24.4)
Extranodal disease	264 (88.3)	277 (92.6)
TP53 status, No. (%)		
Mutated	22 (7.4)	29 (9.7)
Unmutated	97 (32.4)	83 (27.8)
Unknown	180 (60.2)	187 (62.5)
Ki-67 index, No. (%)		
<30%	133 (44.5)	126 (42.1)
≥30%	139 (46.5)	147 (49.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma.
[a]Two patients in each arm had missing ECOG PS score.

(range, 0.1-80.1) with acalabrutinib and 24.6 months (range, 0.03-76.4) with placebo, with a median relative dose intensity of 96.3% (range, 36.2%-108.2%) and 97.3% (range, 20.4%-122.1%), respectively. The median time on study after crossover was 12.0 months (range, 0.7-63.4). All subsequent anticancer therapies are outlined in Appendix Table A1, including 51 patients who crossed over to acalabrutinib within the trial.

Efficacy

In total, 110 (36.8%) patients in the acalabrutinib arm and 137 (45.8%) in the placebo arm either died or had PD. At a median follow-up of 49.8 months using the reverse Kaplan-Meier method, the median PFS assessed by the independent review committee was longer at 66.4 months (95% CI, 55.1 to not evaluable) in the acalabrutinib arm versus 49.6 months (95% CI, 36.0 to 64.1) in the placebo arm (stratified HR, 0.73 [95% CI, 0.57 to 0.94]; P = .0160; Fig 2A). The overall concordance rate with investigator-assessed PFS was 94.3% in the acalabrutinib arm and 95.7% in the placebo arm. Of the 137 PFS events in the placebo arm, 99 were PD per the independent review committee. Of these 99 progressors, 75 (75.8%) received at least one subsequent anticancer therapy, and among these 75, 68 (90.7%) received BTKis. PFS benefit with acalabrutinib was generally consistent across subgroups, including patients at high risk of poor outcomes (Fig 3). Following a prespecified analysis which censored for COVID-19 deaths, the median PFS was not reached in the acalabrutinib arm versus 61.6 months in the placebo arm (HR, 0.64 [95% CI, 0.48 to 0.84]; P = .0017; Fig 2B).

Overall response rates assessed by the independent review committee were 91.0% (95% CI, 87.3 to 93.8) in the acalabrutinib arm and 88.0% (95% CI, 83.9 to 91.3) in the placebo arm. In the acalabrutinib arm, 66.6% achieved complete response versus 53.5% in the placebo arm. The median duration of response was 63.5 months (95% CI, 52.5 to not evaluable) in the acalabrutinib arm and 53.8 months (95% CI, 37.6 to 66.1) in the placebo arm. Rates of MRD negativity (10^{-5}) at the end of six cycles of induction (24 weeks) were 70.7% (n = 188 of 266) and 67.9% (n = 171 of 252) in the acalabrutinib and placebo arms, respectively. Among patients who were MRD-negative at the end of induction, 6% (n = 11 of 188) in the acalabrutinib arm and 15% (n = 26 of 171) in the placebo arm converted to MRD-positive during the maintenance phase. Conversely, among patients who were MRD-positive at the end of induction (24 weeks), 37.5% (n = 3 of 8) in the acalabrutinib arm and 20% (n = 3 of 15) in the placebo arm converted to MRD-negative during the maintenance phase.

In total, 97 patients in the acalabrutinib arm and 106 patients in the placebo arm died. The cause of death was disease

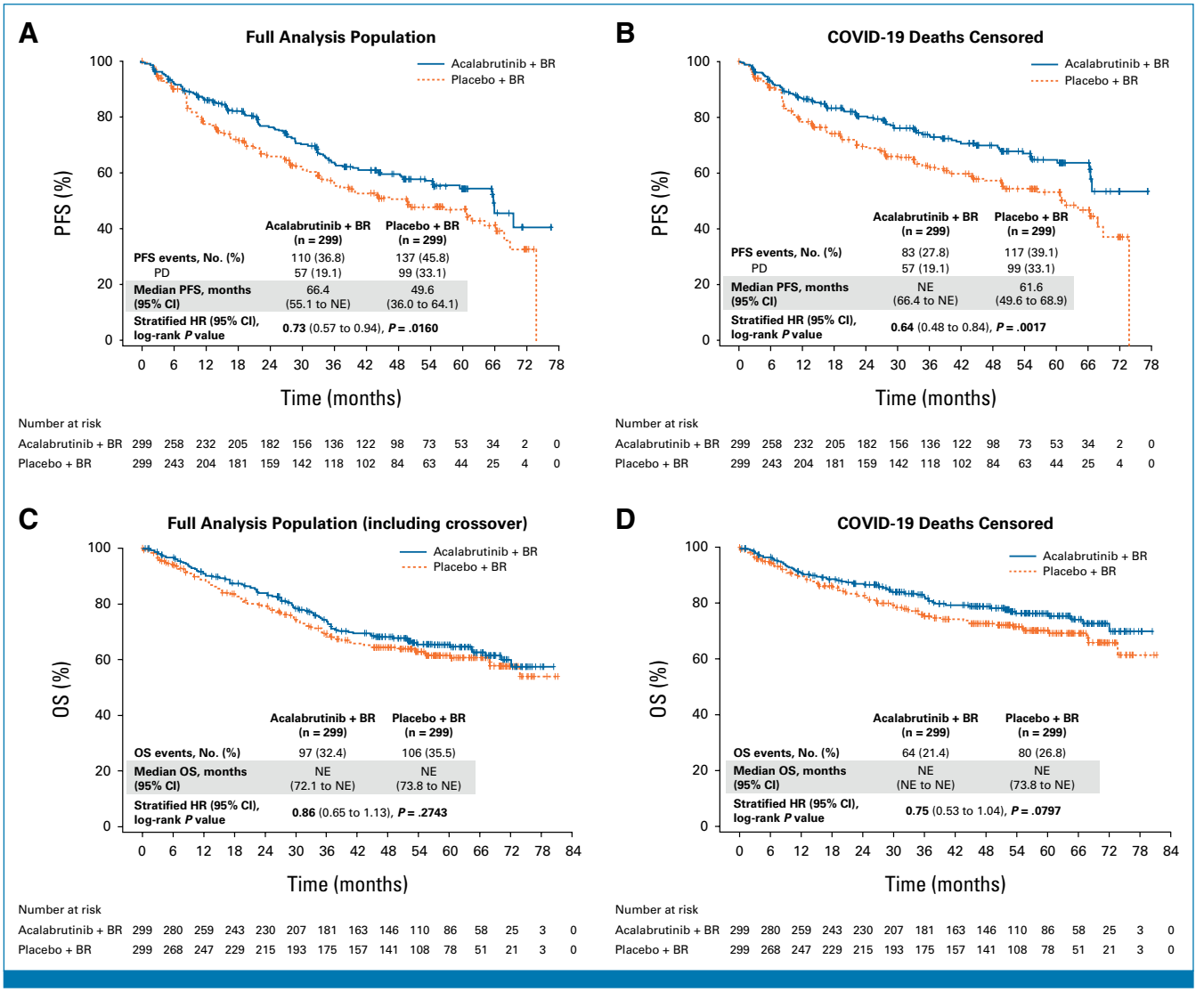

FIG 2. PFS and OS with and without COVID-19 deaths and PFS by acalabrutinib exposure. (A) PFS in the full analysis population. (B) PFS when COVID-19 deaths were censored. (C) OS in the full analysis population, including crossover. (D) OS when COVID-19 deaths were censored. Symbols in all panels indicate censored data. BR, bendamustine-rituximab; HR, hazard ratio; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

progression in 30 (10%) versus 43 (14.4%) and adverse events in 46 (15.4%) and 41 (13.7%) in the acalabrutinib and placebo arms, respectively (Table 2); 11 of the 43 deaths in the placebo arm because of disease progression occurred within the first 6 months of the study. Of the 106 deaths in the placebo arm, 38 occurred in patients who received a BTKi as a second-line therapy and 68 occurred in patients who did not receive a BTKi as a second-line therapy. Median OS was not reached in either arm (Fig 2C). OS was not different between arms (HR, 0.86 [95% CI, 0.65 to 1.13]; $P = .2743$). In the placebo arm, 51 patients crossed over to acalabrutinib after experiencing disease progression on placebo and an additional 25 patients switched to BTKi outside of the study. This trial was conducted during the COVID-19 pandemic; in total, 33 patients from the acalabrutinib arm and 26 patients from the placebo arm died as a consequence of COVID-19 disease. In a prespecified sensitivity analysis censoring for COVID-19 deaths, the difference in OS did not reach statistical significance (HR, 0.75 [95% CI, 0.53 to 1.04]; $P = .0797$; Fig 2D).

Safety

Comparing acalabrutinib versus placebo arms, the frequency of any-grade adverse events was 99.7% versus 99% and the frequency of grade 3 or greater adverse events was 88.9% versus 88.2% (Table 3). Grade 3 or greater serious adverse events occurred in 64.3% in the acalabrutinib arm versus 55.9% in the placebo arm, with adjustment for exposure attenuating observed differences (Appendix Table A2). The most common (occurring in >30%) adverse events with acalabrutinib and placebo, respectively, were nausea (42.8% and 37.7%), neutropenia (40.1% and 41.4%), diarrhea (37.4% and 27.9%), COVID-19 disease (30.6% and 20.9%),

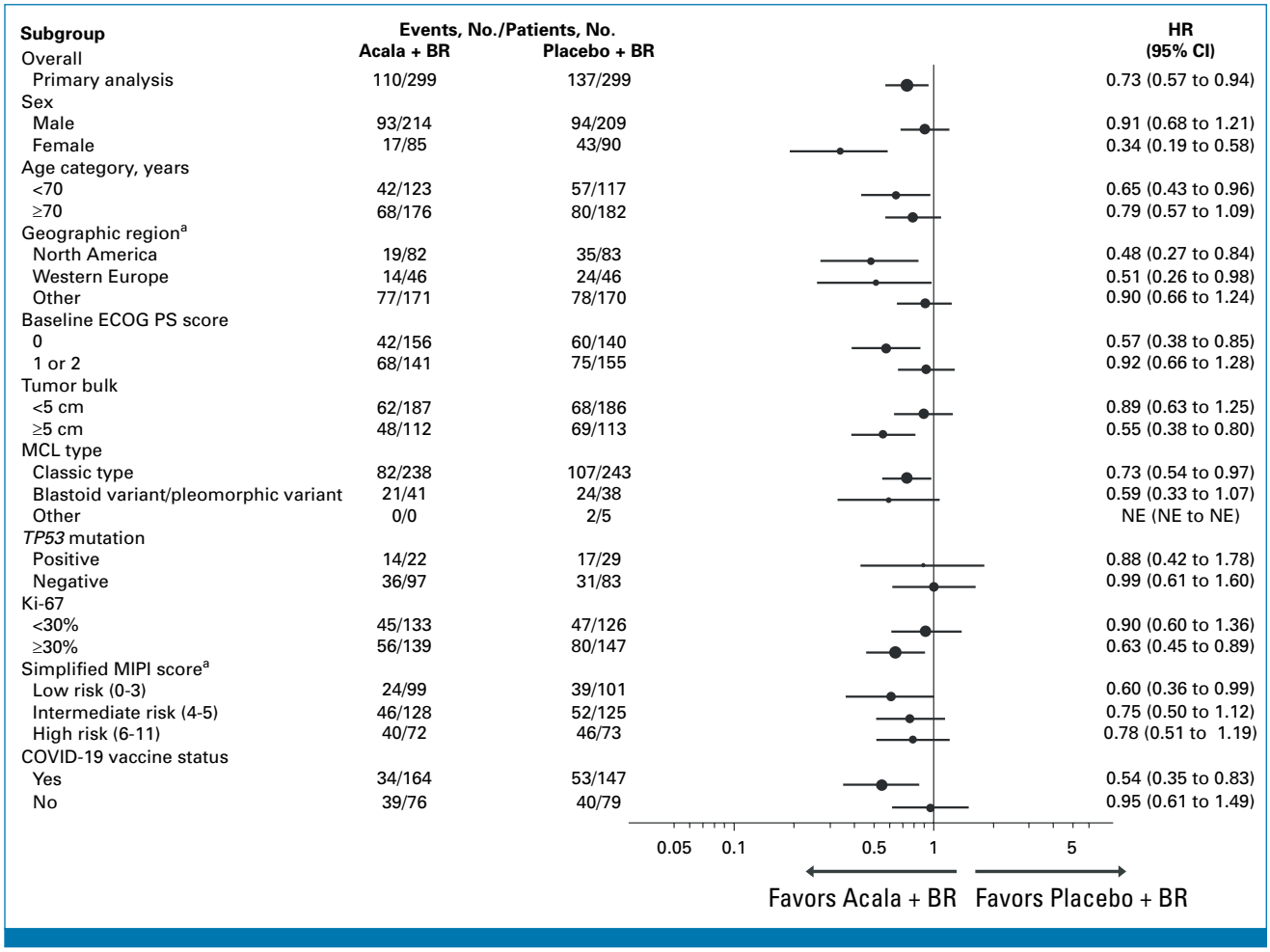

FIG 3. Subgroup analysis of PFS (full analysis population). Forest plot of subgroup analysis for PFS assessed by the independent review committee. [a]Per interactive voice/web response system record. BR, bendamustine-rituximab; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; PFS, progression-free survival.

and headache (30.3% and 14.1%). Incidence of adverse events during induction (0-6 cycles), maintenance (7-30 cycles), and monotherapy (30+ cycles) phases are presented in Appendix Tables A3 and A4.

Among events of clinical interest (acalabrutinib *v* placebo), atrial fibrillation/flutter was reported in 6.7% versus 4.4%, hypertension in 12.5% versus 16.2%, and infections in 78.1% versus 71.0% (Appendix Table A5). Grade ≥3 infections occurred in 41.1% of patients with acalabrutinib versus 34.0% with placebo; however, differences were attenuated when adjusted for treatment exposure (17.4 *v* 16.0 per 100 patient-years). COVID-19–related adverse events of any grade occurred in 40.7% in the acalabrutinib arm versus 29.6% in the placebo arm (Appendix Table A6). Grade 3 or greater COVID-19 events occurred in 20.2% versus 16.8%, and grade 5 COVID-19 events occurred in 9.4% versus 6.7%. COVID-19 adverse events resulting in treatment discontinuation occurred in 31 (10.4%) patients in the acalabrutinib arm and 19 (6.4%) patients in the placebo arm. Incidence of COVID-19 events, with and without adjustment for treatment exposure period, is presented in Appendix Table A6.

All other adverse events leading to discontinuation of acalabrutinib/placebo in one or more patients are presented in Appendix Table A7; COVID-19–related events were the most common adverse events leading to discontinuation of acalabrutinib/placebo. Adverse events with a fatal outcome within 30 days after the last dose were reported in 36 (12.1%) patients in the acalabrutinib arm and 30 (10.1%) patients in the placebo arm (Appendix Table A8). Among these fatal events, COVID-19 disease accounted for 24 (8.1%) patients in the acalabrutinib arm and 16 (5.4%) patients in the placebo arm. In addition, fatal adverse events occurring beyond 30 days after the last dose were reported in 10 (3.4%) patients in the acalabrutinib arm and eight (2.7%) patients in the placebo arm, with fatal COVID-19 events documented in four patients in each arm.

DISCUSSION

In this trial, the combination of acalabrutinib with bendamustine-rituximab resulted in a substantial and clinically meaningful improvement in PFS compared with placebo plus bendamustine-rituximab in older patients with

TABLE 2. Summary of Deaths (full analysis set)

Death	Acalabrutinib + Bendamustine-Rituximab (n = 299), No. (%)	Placebo + Bendamustine-Rituximab Including Crossover (n = 299), No. (%)
Total deaths	97 (32.4)	106 (35.5)
Because of disease progression	30 (10.0)	43 (14.4)
≤30 days after last dose because of adverse events	27 (9.0)	27 (9.0)
>30 days after last dose because of adverse events	19 (6.4)	14 (4.7)
Other[a]	14 (4.7)	16 (5.4)
Unknown	7 (2.3)	6 (2.0)

[a]Other includes fatal adverse events occurring >30 days after last study drug dose AND not considered treatment-related.

previously untreated MCL. Although numbers of patients in high-risk subgroups were small, there was no suggestion that these patients, particularly those with high-risk MCL International Prognostic Index (MIPI) or Ki-67 ≥ 30%, had inferior outcomes. OS was not significantly different; however, the majority (75.8%) of patients who progressed in the placebo arm ultimately received subsequent anticancer therapy (BTKis in 90.7%) at relapse either within or outside the trial. Notably, among patients in the placebo arm who died, the majority of them did not receive a BTKi. The clinical benefit of acalabrutinib plus bendamustine-rituximab was achieved without major excess toxicity. Higher adverse event rates in the acalabrutinib arm are likely due in part to the longer duration of acalabrutinib treatment versus placebo as adjusting incidence rates for exposure attenuated differences between arms. This trial was conducted during the COVID-19 pandemic. Grade 3 or greater COVID-19–related adverse events, including those leading to treatment discontinuation and death, were more frequent in the acalabrutinib arm. Despite the pandemic, the primary end point was met; moreover, when COVID-19–related deaths were censored, the PFS benefit remained significant. As chemotherapy-free combinations also have been reported to have good efficacy and tolerability,[21,22] other randomized trials will need to assess how acalabrutinib plus bendamustine-rituximab compares with those therapies.

Incorporating a highly active and relatively nontoxic agent such as a BTKi as first-line treatment has the potential to improve the standard of care and augment therapeutic approaches. The ECHO trial followed a similar approach to the SHINE trial, which evaluated the addition of ibrutinib to bendamustine-rituximab in older patients with untreated MCL. This combination resulted in superior median PFS (80.6 months, ibrutinib; 52.9 months, placebo; median follow-up, 84.7 months).[15] However, no OS difference was

TABLE 3. Summary of Adverse Events and Most Common Adverse Events

Adverse Event	Acalabrutinib + Bendamustine-Rituximab (n = 297), No. (%)	Placebo + Bendamustine-Rituximab (n = 297), No. (%)
Any treatment-emergent adverse event	296 (99.7)	294 (99.0)
Grade ≥3	264 (88.9)	262 (88.2)
Grade 5	36 (12.1)	30 (10.1)
Serious adverse events	205 (69.0)	184 (62.0)
Grade ≥3	191 (64.3)	166 (55.9)
Treatment-emergent adverse event leading to acalabrutinib/placebo discontinuation	127 (42.8)	92 (31.0)

Most Common Treatment-Emergent Adverse Events in ≥20% in Either Arm	Any Grade, No. (%)	Grade ≥3, No. (%)	Any Grade, No. (%)	Grade ≥3, No. (%)
Nausea	127 (42.8)	4 (1.3)	112 (37.7)	4 (1.3)
Neutropenia	119 (40.1)	105 (35.4)	123 (41.4)	110 (37.0)
Diarrhea	111 (37.4)	9 (3.0)	83 (27.9)	7 (2.4)
COVID-19 disease	91 (30.6)	26 (8.8)	62 (20.9)	21 (7.1)
Headache	90 (30.3)	4 (1.3)	42 (14.1)	2 (0.7)
Fatigue	87 (29.3)	8 (2.7)	72 (24.2)	11 (3.7)
Pyrexia	86 (29.0)	7 (2.4)	72 (24.2)	4 (1.3)
Cough	80 (26.9)	0	60 (20.2)	1 (0.3)
Vomiting	76 (25.6)	2 (0.7)	41 (13.8)	3 (1.0)
Constipation	73 (24.6)	3 (1.0)	75 (25.3)	1 (0.3)
Anemia	68 (22.9)	28 (9.4)	60 (20.2)	30 (10.1)
Rash	61 (20.5)	4 (1.3)	48 (16.2)	4 (1.3)
Infusion-related reaction	43 (14.5)	2 (0.7)	65 (21.9)	6 (2.0)

observed with ibrutinib (HR, 1.07 [95% CI, 0.81 to 1.40]), likely because of more deaths related to adverse events in the ibrutinib arm and the use of subsequent antilymphoma therapies.[15] In comparison, in the present study, the HR for OS was 0.86 (95% CI, 0.65 to 1.13; $P = .27$), with 97 deaths in the acalabrutinib arm and 106 deaths in the placebo arm, despite a shorter time on study (44.9 months) and frequent crossover. Using acalabrutinib in this approach maintains the PFS advantage while avoiding serious toxicity because of ibrutinib when combined with chemotherapy in older patients.[23]

The TRIANGLE study incorporated ibrutinib into standard first-line treatment in younger patients with MCL and demonstrated superior efficacy against the control arm without ibrutinib, establishing a new standard-of-care induction treatment and maintenance therapy.[14] Further analysis showed that this ibrutinib-containing regimen without autologous stem-cell transplantation (ASCT) was superior to the ASCT without ibrutinib, suggesting a possible end to the use of ASCT in patients with MCL.[24] In older patients, first-line BTKi use with rituximab has produced promising results.[25,26] Randomized studies comparing such approaches against standard chemoimmunotherapy in older patients are ongoing as well as the exploration of triplet approaches incorporating venetoclax.[22]

One of the concerns regarding first-line BTKi use has been the poor outcomes seen historically on relapse.[27,28] This is of less concern given newer evidence of BTKi use in earlier lines of therapy,[29] and novel therapies, such as noncovalent BTKis, BTK protein degraders, CAR-T therapies, and T-cell–engaging bispecific antibodies, retain substantial efficacy even after covalent BTKi therapy.[30-33]

In conclusion, acalabrutinib improved PFS when added to bendamustine-rituximab in patients 65 years or older with previously untreated MCL. OS was not significantly different although the majority of patients who experienced disease progression on placebo crossed over to treatment with a BTKi.

AFFILIATIONS

[1]Department of Lymphoma/Myeloma, MD Anderson Cancer Center, University of Texas, Houston, TX
[2]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic
[3]4th Department of Internal Medicine—Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic
[4]Key Laboratory of Carcinogenesis and Translational Research, Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China
[5]Pratia MCM Maków, Krakow, Poland
[6]Department of Clinical Oncology, MSC National Research Institute of Oncology, Krakow, Poland
[7]Washington University in St Louis, St Louis, MO
[8]Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN
[9]Department of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Canada
[10]Department of Oncohematology, National Cancer Institute, Kyiv, Ukraine
[11]Department of Clinical Hematology, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil
[12]Department of Haematology, Sir Charles Gairdner Hospital, Nedlands, Australia
[13]Medical School, University of Western Australia, Perth, Australia
[14]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland
[15]Hematology Department, St John's Cancer Center, Lublin, Poland
[16]Clinical Hematology Department, ICO-IJC-Hospital Germans Trias i Pujol, Badalona, Spain
[17]Department of Hematology, Henan Cancer Hospital, Zheng Zhou, China
[18]Oncohematology Unit, A.O.O.R. Villa Sofia Cervello, Palermo, Italy
[19]Central Coast Haematology, North Gosford, Australia
[20]AstraZeneca, South San Francisco, CA
[21]AstraZeneca, Cambridge, United Kingdom
[22]Medizinische Klinik III, Klinikum der Universitaet Munchen, Muenchen, Germany

CORRESPONDING AUTHOR

Michael Wang, MD; e-mail: miwang@mdanderson.org.

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AUTHOR CONTRIBUTIONS

Conception and design: Michael Wang, Wojciech Jurczak, Jingyang Zhang, Safaa Ramadan, Martin Dreyling
Provision of study materials or patients: Yuqin Song, Wojciech Jurczak, Brad S. Kahl, Jonas Paludo, Iryna Kryachok, Chan Y. Cheah, Juan-Manuel Sancho, Yufu Li, Caterina Patti, Martin Dreyling
Collection and assembly of data: David Salek, David Belada, Wojciech Jurczak, Brad S. Kahl, Michael P. Chu, Iryna Kryachok, Chan Y. Cheah, Marta Morawska, Juan-Manuel Sancho, Yufu Li, Caterina Patti, Jingyang Zhang, Robin Lesley, Safaa Ramadan, Simon Rule, Martin Dreyling
Data analysis and interpretation: David Belada, Yuqin Song, Wojciech Jurczak, Brad S. Kahl, Jonas Paludo, Michael P. Chu, Laura Fogliatto, Chan Y. Cheah, Juan-Manuel Sancho, Cecily Forsyth, Jingyang Zhang, Robin Lesley, Safaa Ramadan, Simon Rule, Martin Dreyling
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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A complete list of the ECHO trial investigators is provided in Appendix Table A9.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375-2390, 2016
2. Jain P, Wang ML: Mantle cell lymphoma in 2022—A comprehensive update on molecular pathogenesis, risk stratification, clinical approach, and current and novel treatments. Am J Hematol 97: 638-656, 2022
3. Silkenstedt E, Salles G, Campo E, et al: B-cell non-Hodgkin lymphomas. Lancet 403:1791-1807, 2024
4. Silkenstedt E, Dreyling M: To consolidate or not to consolidate: The role of autologous stem cell transplantation in MCL. Hematol ASH Educ Prog 1:42-47, 2024
5. Kumar A, Eyre TA, Lewis KL, et al: New directions for mantle cell lymphoma in 2022. Am Soc Clin Oncol Educ Book 42:1-15, 2022
6. Eyre TA, Bishton MJ, McCulloch R, et al: Diagnosis and management of mantle cell lymphoma: A British Society for Haematology guideline. Br J Haematol 204:108-126, 2024
7. Wang M, Rule S, Zinzani PL, et al: Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, multicentre, phase 2 trial. Lancet 391:659-667, 2018
8. Song Y, Zhou K, Zou D, et al: Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. Clin Cancer Res 26: 4216-4224, 2020
9. Wang ML, Rule S, Martin P, et al: Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 369:507-516, 2013
10. Minson A, Hamad N, Di Ciaccio P, et al: Death from mantle cell lymphoma limits sequential therapy, particularly after first relapse: Patterns of care and outcomes in a series from Australia and the United Kingdom. Br J Haematol 204:548-554, 2024
11. Jerkeman M, Ekberg S, Glimelius I, et al: Nationwide assessment of patient trajectories in mantle cell lymphoma: The Swedish MCLcomplete Project. Hemasphere 7:e928, 2023
12. Kumar A, Sha F, Toure A, et al: Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: Progressive shortening in response duration and survival after each relapse. Blood Cancer J 9:50, 2019
13. Dreyling M, Goy A, Hess G, et al: Long-term outcomes with ibrutinib treatment for patients with relapsed/refractory mantle cell lymphoma: A pooled analysis of 3 clinical trials with nearly 10 years of follow-up. Hemasphere 6:e712, 2022
14. Dreyling M, Doorduijn J, Giné E, et al: Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): A three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet 403:2293-2306, 2024
15. Wang ML, Jurczak W, Jerkeman M, et al: Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. N Engl J Med 386:2482-2494, 2022
16. Barf T, Covey T, Izumi R, et al: Acalabrutinib (ACP-196): A covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. J Pharmacol Exp Ther 363:240-252, 2017
17. Byrd JC, Hillmen P, Ghia P, et al: Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase 3 trial. J Clin Oncol 39:3441-3452, 2021
18. Phillips TJ, Wang M, Robak T, et al: Safety and efficacy of ABR in pts with TN or R/R MCL: Ph Ib trial. J Clin Oncol 41, 2023 (suppl 16; abstr 7546)
19. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32:3059-3068, 2014
20. Roschewski M, Patel MR, Reagan PM, et al: Phase I study of acalabrutinib plus danvatirsen (AZD9150) in relapsed/refractory diffuse large B-cell lymphoma including circulating tumor DNA biomarker assessment. Clin Cancer Res 29:3301-3312, 2023
21. Jain P, Ok Cy, Fetooh A, et al: Acalabrutinib with rituximab as first-line therapy for older patients with mantle cell lymphoma—A phase II clinical trial. Hematol Oncol 41:150-151, 2023
22. Wang ML, Robak TP, Maddocks KJ, et al: Acalabrutinib plus venetoclax and rituximab in treatment-naive mantle cell lymphoma: 2-year safety and efficacy analysis. Blood Adv 8:4539-4548, 2024
23. Younes A, Sehn LH, Johnson P, et al: Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. J Clin Oncol 37:1285-1295, 2019
24. Dreyling M, Doorduijn JK, Gine E, et al: Role of autologous stem cell transplantation in the context of ibrutinib-containing first-line treatment in younger patients with mantle cell lymphoma: Results from the randomized Triangle trial by the European MCL Network. Blood 144(suppl 1):240, 2024
25. Jain P, Zhao S, Lee HJ, et al: Ibrutinib with rituximab in first-line treatment of older patients with mantle cell lymphoma. J Clin Oncol 40:202-212, 2022
26. Giné E, de la Cruz F, Jiménez Ubieto A, et al: Ibrutinib in combination with rituximab for indolent clinical forms of mantle cell lymphoma (IMCL-2015): A multicenter, open-label, single-arm, phase II trial. J Clin Oncol 40:1196-1205, 2022
27. Martin P, Maddocks K, Leonard JP, et al: Postibrutinib outcomes in patients with mantle cell lymphoma. Blood 127:1559-1563, 2016
28. Cheah CY, Chihara D, Romaguera JE, et al: Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol 26:1175-1179, 2015
29. Tivey A, Shotton R, Eyre TA, et al: Ibrutinib as first-line therapy for mantle cell lymphoma: A multicenter, real-world UK study. Blood Adv 8:1209-1219, 2024
30. Wang ML, Jurczak W, Zinzani PL, et al: Pirtobrutinib in covalent Bruton tyrosine kinase inhibitor pretreated mantle-cell lymphoma. J Clin Oncol 41:3988-3997, 2023
31. Linton K, Collins G, Forconi F, et al: Latest results from an ongoing first-in-human phase 1A/B study of NX-5948, a selective Bruton's tyrosine kinase (BTK) degrader, in patients with relapsed/ refractory CLL and other B-cell malignancies. Hemasphere 8(suppl 1):120-121, 2024
32. Wang M, Munoz J, Goy A, et al: KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med 382:1331-1342, 2020
33. Phillips TJ, Dickinson M, Morschhauser F, et al: Glofitamab monotherapy induces high complete response rates in patients with heavily pretreated relapsed or refractory mantle cell lymphoma. Blood 140(suppl 1):178-180, 2022

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Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma

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Michael Wang
Honoraria: AstraZeneca, Kite, a Gilead company, Merck, Studio ER Congressi, MSC National Research Institute of Oncology, Research to Practice, Janssen, BeOne, Binacea, CAHON, Editorial Medica AWWE SA, East Virginia Medical School, Instituto Scientifico Romagnolo, Mayo Clinic, MJH Life Sciences, Pfizer, Physicans' Education Resource, Plexus, PromCon S.R.E, Medscape/WebMD, VJHemonc, Bristol Myers Squibb
Consulting or Advisory Role: AstraZeneca, Kite, a Gilead company, Innocare, Oncternal Therapeutics, Lilly, Boxer Capital, Galapagos NV, Genmab, Pfizer, PER, Janssen, Bristol Myers Squibb, Merck, Pepromene
Research Funding: AstraZeneca (Inst), Pharmacyclics (Inst), Kite, a Gilead company (Inst), Juno Therapeutics (Inst), Oncternal Therapeutics (Inst), Lilly (Inst), Innocare (Inst), Genmab (Inst), Genentech (Inst), Janssen (Inst), AbbVie (Inst), Bantam Pharmaceutical (Inst), BeOne (Inst), Nurix (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Celgene, Dava Oncology, Kite, a Gilead company, Physicans' Education Resource

David Salek
Honoraria: Swiss Biopharma
Consulting or Advisory Role: Roche/Genentech
Research Funding: AbbVie, AstraZeneca, BeiGene, Janssen/Pharmacyclics, Lilly, Merck, MorphoSys
Travel, Accommodations, Expenses: Gilead Sciences

David Belada
Consulting or Advisory Role: Roche, Gilead Sciences, Janssen-Cilag, Takeda, MorphoSys, Genmab, Dr Reddy's, Bristol Myers Squibb/Celgene
Research Funding: Roche (Inst), Gilead Sciences (Inst), Janssen-Cilag (Inst), Takeda (Inst), MorphoSys (Inst), Pharmacyclics (Inst), Dr Reddy's (Inst), Genmab (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Gilead Sciences, Takeda, Roche, AbbVie

Wojciech Jurczak
Consulting or Advisory Role: BeiGene, Lilly, AbbVie/Genentech, Takeda
Research Funding: Roche, Takeda, Janssen-Cilag, BeiGene, AstraZeneca, Lilly, AbbVie/Genentech

Brad S. Kahl
Consulting or Advisory Role: AbbVie, ADC Therapeutics, Genentech, Roche, AstraZeneca, BeiGene, Bristol Myers Squibb, Merck, Pfizer, Roche
Research Funding: Genentech (Inst), BeiGene (Inst), AstraZeneca (Inst)

Jonas Paludo
Consulting or Advisory Role: AbbVie (Inst), AstraZeneca (Inst)
Research Funding: Karyopharm Therapeutics (Inst), Biofourmis (Inst)

Michael P. Chu
Honoraria: Janssen Oncology, Gilead Sciences, Roche, Roche, AstraZeneca, Sanofi, Bristol Myers Squibb/Celgene
Research Funding: Janssen Oncology (Inst)
Travel, Accommodations, Expenses: Janssen, Bristol Myers Squibb/Celgene

Iryna Kryachok
Consulting or Advisory Role: Janssen, AstraZeneca, AbbVie, Takeda, Roche, Merck
Speakers' Bureau: AstraZeneca, AbbVie, Takeda, Roche
Research Funding: Janssen, Bayer, Karyopharm Therapeutics, MSD, Acerta Pharma, AbbVie, Debiopharm Group, Acerta Pharma, Merck, Bayer, InnoCarePharm, Chromos Pharma, Pharmacyclics
Expert Testimony: Takeda, Janssen, AstraZeneca, Takeda
Travel, Accommodations, Expenses: Takeda, MSD, AbbVie, Roche

Chan Y. Cheah
Honoraria: Roche/Genentech (Inst), Janssen-Cilag (Inst), TG Therapeutics, Loxo/Lilly, AstraZeneca (Inst), Gilead Sciences, BeiGene (Inst), Novartis, Menarini (Inst), Dizal Pharma (Inst), SOBI, crispr therapeutics
Consulting or Advisory Role: Janssen-Cilag, Roche/Genentech (Inst), Loxo/Lilly, Gilead Sciences, AstraZeneca, Kite, a Gilead company (Inst), Menarini (Inst), Dizal Pharma (Inst), BeiGene (Inst)
Research Funding: Roche/Genentech (Inst), Bristol Myers Squibb (Inst), AbbVie (Inst), Merck (Inst), Lilly (Inst)
Travel, Accommodations, Expenses: Roche, Lilly, BeiGene

Juan-Manuel Sancho
Honoraria: Roche, Gilead Sciences, Janssen, Incyte, Lilly, BMS, AbbVie, BeiGene
Consulting or Advisory Role: Roche, Gilead Sciences, Janssen, BeiGene, Incyte, Lilly, BMS, SOBI
Speakers' Bureau: Gilead Sciences, AbbVie, BeiGene
Travel, Accommodations, Expenses: Roche, AbbVie

Cecily Forsyth
Consulting or Advisory Role: Novartis, AstraZeneca, SOBI
Travel, Accommodations, Expenses: AbbVie, Novartis, Janssen

Jingyang Zhang
Employment: AstraZeneca, Day One Biopharmaceuticals
Stock and Other Ownership Interests: AstraZeneca

Robin Lesley
Employment: AstraZeneca
Stock and Other Ownership Interests: Amgen, AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Safaa Ramadan
Employment: AstraZeneca

Simon Rule
Employment: AstraZeneca
Stock and Other Ownership Interests: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Martin Dreyling
Honoraria: AstraZeneca, BeiGene, Kite/Gilead, Janssen, Lilly Foundation, Roche, BMS GmbH & Co. KG
Consulting or Advisory Role: Gilead Sciences, Janssen-Cilag, Novartis, Roche, Beigene, AbbVie/Genentech (Inst), Lilly Medical, Bristol Myers Squibb/Celgene, AstraZeneca, AvenCell, Genmab, Incyte, SOBI
Research Funding: Janssen-Cilag (Inst), Roche Pharma AG (Inst), AbbVie (Inst), Kite/Gilead (Inst), Lilly (Inst)
Travel, Accommodations, Expenses: Janssen-Cilag, Roche Pharma AG

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APPENDIX

TABLE A1. Subsequent Anticancer Therapy

Therapy	Acalabrutinib + Bendamustine-Rituximab (n = 299), No. (%)	Placebo + Bendamustine-Rituximab Including Crossover (n = 299), No. (%)
≥1 subsequent anticancer therapy	30 (10.0)	88 (29.4)
≥1 Bruton tyrosine kinase inhibitor as subsequent treatment[a]	13 (43.3)	76 (86.4)
Acalabrutinib	1 (3.3)	55 (62.5)
Ibrutinib	7 (23.3)	17 (19.3)
Nemtabrutinib	1 (3.3)	0
Pirtobrutinib	2 (6.7)	4 (4.5)
Zanubrutinib	2 (6.7)	5 (5.7)
All subsequent treatment regimens[b]		
BTKi[c]	13 (4.3)	76 (25.4)
Acalabrutinib	1 (0.3)	54 (18.1)
Ibrutinib	5 (1.7)	11 (3.7)
Ibrutinib/ixazomib (clinical trial)	0	2 (0.7)
Ibrutinib/obinutuzumab	0	1 (0.3)
Ibrutinib/pevonedistat (clinical trial)	0	1 (0.3)
Ibrutinib/R-methotrexate/Ara-C/dexamethasone	1 (0.3)	0
Ibrutinib/venetoclax	0	1 (0.3)
Nemtabrutinib	1 (0.3)	0
Pirtobrutinib	2 (0.7)	3 (1.0)
R-Acalabrutinib	0	1 (0.3)
R-Ibrutinib	1 (0.3)	0
R-Ibrutinib/venetoclax + IT	0	1 (0.3)
R-Pirtobrutinib	0	1 (0.3)
R-Zanubrutinib	0	1 (0.3)
Zanubrutinib	2 (0.7)	4 (1.3)
Chemotherapy-based[c]	12 (4.0)	29 (9.7)
ASCT	0	1 (0.3)
BEAM	1 (0.3)	0
Bendamustine	1 (0.3)	0
Bendamustine/cinobufagin	0	1 (0.3)
CHOEP	0	1 (0.3)
CHOP	2 (0.7)	4 (1.3)
COP	1 (0.3)	1 (0.3)
Cyclophosphamide	0	1 (0.3)
Cyclophosphamide/etoposide/procarbazine	0	1 (0.3)
DHAP	0	1 (0.3)
ESHAP	0	1 (0.3)
High-dose Ara-C	0	1 (0.3)

(continued in next column)

TABLE A1. Subsequent Anticancer Therapy (continued)

Therapy	Acalabrutinib + Bendamustine-Rituximab (n = 299), No. (%)	Placebo + Bendamustine-Rituximab Including Crossover (n = 299), No. (%)
High-dose methotrexate	0	1 (0.3)
Hyper-CVAD	0	1 (0.3)
ICE	0	1 (0.3)
Melphalan/fludarabine/cyclophosphamide	1 (0.3)	0
Methotrexate	1 (0.3)	0
Mini-R-CHOP	0	1 (0.3)
Nordic protocol	1 (0.3)	0
R-BAC	0	2 (0.7)
R-CEOP	0	1 (0.3)
R-CHOP	1 (0.3)	5 (1.7)
R-CHOP/R-Ara-C	1 (0.3)	3 (1.0)
R-CHOP/R-DHAOX	0	2 (0.7)
R-CY	1 (0.3)	0
R-DA-EPOCH/high-dose-Ara-C	1 (0.3)	0
R-DHAC	0	1 (0.3)
R-DHAOX	0	2 (0.7)
R-DHAP	1 (0.3)	1 (0.3)
R-FGIV	0	1 (0.3)
R-GEMOX	0	2 (0.7)
R-HD-CY/DEX	1 (0.3)	0
R-hyper-CVAD	0	1 (0.3)
R-Maxi-CHOP-RM	0	1 (0.3)
TECAM/ASCT	1 (0.3)	0
VCD	1 (0.3)	0
VR-CAP	1 (0.3)	3 (1.0)
Targeted/immune therapy[c]	12 (4.0)	17 (5.7)
BGB-11417 (clinical trial)	1 (0.3)	1 (0.3)
BRD	0	1 (0.3)
CAR-T	0	1 (0.3)
Epcoritamab (clinical trial)	0	1 (0.3)
FLU/CY/CAR-T	1 (0.3)	2 (0.7)
Glofitamab-obinutuzumab	0	1 (0.3)
Lenalidomide	1 (0.3)	4 (1.3)
Mosunetuzumab/polatuzumab vedotin (clinical trial)	0	1 (0.3)
Obinutuzumab	0	1 (0.3)
R-Lenalidomide	2 (0.7)	2 (0.7)
Rituximab	3 (1.0)	1 (0.3)
TQB3909 (clinical trial)	1 (0.3)	0
Umbralisib/ublituximab (clinical trial)	2 (0.7)	1 (0.3)

(continued on following page)

TABLE A1. Subsequent Anticancer Therapy (continued)

Therapy	Acalabrutinib + Bendamustine-Rituximab (n = 299), No. (%)	Placebo + Bendamustine-Rituximab Including Crossover (n = 299), No. (%)
Venetoclax	1 (0.3)	3 (1.0)
Zilovertamab vedotin (clinical trial)	1 (0.3)	0
Other	1 (0.3)	3 (1.0)
Chinese medicine (unknown active ingredients)	0	1 (0.3)
Radiotherapy	1 (0.3)	2 (0.7)

Abbreviations: Ara-C, cytarabine; ASCT, autologous stem-cell transplant; BAC, bendamustine + cytarabine; BEAM, carmustine + etoposide + cytarabine + melphalan; BRD, bendamustine + lenalidomide + dexamethasone; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; CEOP, cyclophosphamide + etoposide + vincristine + prednisone; CHOEP, cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; COP, cyclophosphamide + vincristine + prednisone; CVAD, cyclophosphamide + vincristine + doxorubicin + dexamethasone; CY, cyclophosphamide; DEX, dexamethasone; DHAOX, dexamethasone + high-dose cytarabine + oxaliplatin; DHAC, dexamethasone + high-dose cytarabine + carboplatin; DHAP, dexamethasone + high-dose cytarabine + cisplatin; EPOCH, etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin; ESHAP, etoposide + methylprednisolone + high-dose cytarabine + cisplatin; FGIV, filgrastim + gemcitabine + ifosfamide + vinorelbine; GEMOX, gemcitabine + oxaliplatin; ICE, ifosfamide + carboplatin + etoposide; R-, rituximab; IT, intrathecal therapy; Maxi-CHOP-RM, Nordic regimen with rituximab maintenance; TECAM, thiotepa + etoposide + cytarabine + cyclophosphamide + melphalan; VCD, bortezomib + cyclophosphamide + dexamethasone; VR-CAP, bortezomib + rituximab + cyclophosphamide + doxorubicin + prednisone.

[a]Proportion based on the number of patients with at least one subsequent treatment.

[b]Proportion based on all patients in the full analysis set.

[c]Individual patients could receive >1 therapy within the same therapeutic category.

TABLE A2. Exposure-Adjusted Incidence Rates of Overall Adverse Events

Incidence Rate per 100 Person-Years	Acalabrutinib + Bendamustine-Rituximab (n = 297)	Placebo + Bendamustine-Rituximab (n = 297)
Grade ≥3	83.3	106.8
Grade 5	4.2	4.0
Serious adverse events	40.0	36.3
Grade ≥3	32.6	29.3
Treatment-emergent adverse event leading to acalabrutinib/placebo discontinuation	15.5	12.4

NOTE. Exposure-adjusted incidence rate was defined as (total number of patients with an event × 100)/(total exposure time for all patients at risk in years in the main study period).

TABLE A3. Summary of Adverse Events by Treatment Period (cycles)

	0-6 Cycles		7-30 Cycles		31+ Cycles	
Category of Adverse Event	Acalabrutinib + Bendamustine-Rituximab (n = 297), No. (%)	Placebo + Bendamustine-Rituximab (n = 297), No. (%)	Acalabrutinib + Bendamustine-Rituximab (n = 259), No. (%)	Placebo + Bendamustine-Rituximab (n = 248), No. (%)	Acalabrutinib + Bendamustine-Rituximab (n = 158), No. (%)	Placebo + Bendamustine-Rituximab (n = 139), No. (%)
Any treatment-emergent adverse event	287 (96.6)	289 (97.3)	249 (96.1)	234 (94.4)	143 (90.5)	123 (88.5)
Grade ≥3	208 (70.0)	204 (68.7)	168 (64.9)	156 (62.9)	90 (57.0)	63 (45.3)
Grade 5	4 (1.3)	7 (2.4)	15 (5.8)	13 (5.2)	17 (10.8)	10 (7.2)
Serious adverse events	92 (31.0)	80 (26.9)	107 (41.3)	90 (36.3)	71 (44.9)	53 (38.1)
Grade ≥3	80 (26.9)	73 (24.6)	95 (36.7)	75 (30.2)	67 (42.4)	46 (33.1)
Treatment-emergent adverse event leading to acalabrutinib/placebo discontinuation	24 (8.1)	26 (8.8)	62 (23.9)	47 (19.0)	41 (25.9)	19 (13.7)

TABLE A4. Most Common Adverse Events by Treatment Period (cycles)

	0-6 Cycles				7-30 Cycles				31+ Cycles			
	Acalabrutinib + Bendamustine-Rituximab (n = 297)		Placebo + Bendamustine-Rituximab (n = 297)		Acalabrutinib + Bendamustine-Rituximab (n = 259)		Placebo + Bendamustine-Rituximab (n = 248)		Acalabrutinib + Bendamustine-Rituximab (n = 158)		Placebo + Bendamustine-Rituximab (n = 139)	
System Organ Class and Preferred Term	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)
Blood and lymphatic system disorders	144 (48.5)	100 (33.7)	128 (43.1)	97 (32.7)	102 (39.4)	70 (27.0)	104 (41.9)	78 (31.5)	28 (17.7)	20 (12.7)	20 (14.4)	12 (8.6)
Neutropenia	92 (31.0)	76 (25.6)	90 (30.3)	75 (25.3)	74 (28.6)	62 (23.9)	79 (31.9)	70 (28.2)	17 (10.8)	14 (8.9)	11 (7.9)	6 (4.3)
Anemia	48 (16.2)	17 (5.7)	39 (13.1)	18 (6.1)	28 (10.8)	8 (3.1)	25 (10.1)	8 (3.2)	7 (4.4)	4 (2.5)	11 (7.9)	7 (5.0)
Thrombocytopenia	31 (10.4)	16 (5.4)	32 (10.8)	15 (5.1)	11 (4.2)	3 (1.2)	4 (1.6)	1 (0.4)	3 (1.9)	1 (0.6)	0	0
Cardiac disorders	38 (12.8)	10 (3.4)	24 (8.1)	6 (2.0)	26 (10.0)	8 (3.1)	25 (10.1)	5 (2.0)	15 (9.5)	6 (3.8)	11 (7.9)	4 (2.9)
Ear and labyrinth disorders	14 (4.7)	1 (0.3)	7 (2.4)	0	12 (4.6)	2 (0.8)	8 (3.2)	0	8 (5.1)	0	4 (2.9)	0
Endocrine disorders	2 (0.7)	0	2 (0.7)	0	4 (1.5)	0	2 (0.8)	0	0	0	1 (0.7)	0
Eye disorders	35 (11.8)	0	22 (7.4)	0	29 (11.2)	3 (1.2)	25 (10.1)	2 (0.8)	13 (8.2)	1 (0.6)	13 (9.4)	5 (3.6)
GI disorders	192 (64.6)	16 (5.4)	192 (64.6)	19 (6.4)	113 (43.6)	17 (6.6)	79 (31.9)	11 (4.4)	48 (30.4)	4 (2.5)	32 (23.0)	2 (1.4)
Nausea	117 (39.4)	4 (1.3)	103 (34.7)	3 (1.0)	14 (5.4)	0	19 (7.7)	2 (0.8)	10 (6.3)	0	4 (2.9)	0
Diarrhea	72 (24.2)	2 (0.7)	60 (20.2)	6 (2.0)	51 (19.7)	6 (2.3)	27 (10.9)	1 (0.4)	20 (12.7)	1 (0.6)	7 (5.0)	0
Vomiting	63 (21.2)	1 (0.3)	33 (11.1)	3 (1.0)	22 (8.5)	0	10 (4.0)	0	6 (3.8)	1 (0.6)	0	0
Constipation	58 (19.5)	3 (1.0)	71 (23.9)	1 (0.3)	21 (8.1)	0	7 (2.8)	0	6 (3.8)	0	6 (4.3)	0
General disorders and administration site conditions	144 (48.5)	15 (5.1)	137 (46.1)	17 (5.7)	82 (31.7)	7 (2.7)	67 (27.0)	3 (1.2)	40 (25.3)	2 (1.3)	28 (20.1)	1 (0.7)
Fatigue	77 (25.9)	7 (2.4)	63 (21.2)	10 (3.4)	24 (9.3)	1 (0.4)	18 (7.3)	1 (0.4)	11 (7.0)	1 (0.6)	8 (5.8)	1 (0.7)
Pyrexia	59 (19.9)	6 (2.0)	54 (18.2)	4 (1.3)	28 (10.8)	1 (0.4)	21 (8.5)	0	7 (4.4)	0	5 (3.6)	0
Edema peripheral	24 (8.1)	0	31 (10.4)	0	20 (7.7)	1 (0.4)	16 (6.5)	0	7 (4.4)	0	2 (1.4)	0
Hepatobiliary disorders	6 (2.0)	3 (1.0)	6 (2.0)	1 (0.3)	5 (1.9)	2 (0.8)	6 (2.4)	3 (1.2)	2 (1.3)	2 (1.3)	0	0
Immune system disorders	13 (4.4)	3 (1.0)	8 (2.7)	1 (0.3)	13 (5.0)	0	3 (1.2)	0	2 (1.3)	0	4 (2.9)	1 (0.7)
Infections and infestations	111 (37.4)	24 (8.1)	114 (38.4)	31 (10.4)	176 (68.0)	54 (20.8)	130 (52.4)	37 (14.9)	112 (70.9)	32 (20.3)	85 (61.2)	23 (16.5)
Upper respiratory tract infection	23 (7.7)	1 (0.3)	23 (7.7)	0	31 (12.0)	0	15 (6.0)	0	12 (7.6)	0	18 (12.9)	0
Pneumonia	13 (4.4)	6 (2.0)	14 (4.7)	9 (3.0)	31 (12.0)	15 (5.8)	17 (6.9)	5 (2.0)	11 (7.0)	6 (3.8)	11 (7.9)	7 (5.0)
COVID-19 disease	1 (0.3)	0	3 (1.0)	2 (0.7)	38 (14.7)	13 (5.0)	22 (8.9)	5 (2.0)	57 (36.1)	5 (3.2)	42 (30.2)	9 (6.5)
COVID-19 pneumonia	0	0	1 (0.3)	1 (0.3)	19 (7.3)	6 (2.3)	16 (6.5)	12 (4.8)	29 (18.4)	19 (12.0)	21 (15.1)	8 (5.8)

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TABLE A4. Most Common Adverse Events by Treatment Period (cycles) (continued)

	0-6 Cycles				7-30 Cycles				31+ Cycles			
	Acalabrutinib + Bendamustine-Rituximab (n = 297)		Placebo + Bendamustine-Rituximab (n = 297)		Acalabrutinib + Bendamustine-Rituximab (n = 259)		Placebo + Bendamustine-Rituximab (n = 248)		Acalabrutinib + Bendamustine-Rituximab (n = 158)		Placebo + Bendamustine-Rituximab (n = 139)	
System Organ Class and Preferred Term	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)
Injury, poisoning, and procedural complications	75 (25.3)	3 (1.0)	85 (28.6)	7 (2.4)	57 (22.0)	5 (1.9)	35 (14.1)	3 (1.2)	23 (14.6)	5 (3.2)	14 (10.1)	3 (2.2)
Infusion-related reaction	40 (13.5)	1 (0.3)	63 (21.2)	6 (2.0)	2 (0.8)	0	3 (1.2)	0	1 (0.6)	1 (0.6)	1 (0.7)	0
Investigations	113 (38.0)	58 (19.5)	101 (34.0)	51 (17.2)	79 (30.5)	43 (16.6)	80 (32.3)	37 (14.9)	33 (20.9)	11 (7.0)	32 (23.0)	6 (4.3)
Neutrophil count decreased	39 (13.1)	29 (9.8)	39 (13.1)	24 (8.1)	38 (14.7)	29 (11.2)	23 (9.3)	12 (4.8)	7 (4.4)	5 (3.2)	5 (3.6)	2 (1.4)
WBC count decreased	32 (10.8)	17 (5.7)	25 (8.4)	7 (2.4)	28 (10.8)	18 (6.9)	19 (7.7)	8 (3.2)	5 (3.2)	4 (2.5)	4 (2.9)	2 (1.4)
Lymphocyte count decreased	21 (7.1)	18 (6.1)	25 (8.4)	24 (8.1)	9 (3.5)	7 (2.7)	25 (10.1)	20 (8.1)	3 (1.9)	3 (1.9)	6 (4.3)	3 (2.2)
Metabolism and nutrition disorders	107 (36.0)	25 (8.4)	100 (33.7)	25 (8.4)	58 (22.4)	11 (4.2)	58 (23.4)	12 (4.8)	25 (15.8)	8 (5.1)	19 (13.7)	3 (2.2)
Decreased appetite	33 (11.1)	0	35 (11.8)	1 (0.3)	13 (5.0)	0	3 (1.2)	0	1 (0.6)	0	2 (1.4)	0
Musculoskeletal and connective tissue disorders	88 (29.6)	6 (2.0)	66 (22.2)	4 (1.3)	81 (31.3)	7 (2.7)	67 (27.0)	3 (1.2)	35 (22.2)	4 (2.5)	32 (23.0)	4 (2.9)
Arthralgia	19 (6.4)	2 (0.7)	22 (7.4)	1 (0.3)	33 (12.7)	0	23 (9.3)	1 (0.4)	6 (3.8)	0	13 (9.4)	1 (0.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	10 (3.4)	2 (0.7)	7 (2.4)	1 (0.3)	36 (13.9)	12 (4.6)	29 (11.7)	13 (5.2)	31 (19.6)	7 (4.4)	21 (15.1)	7 (5.0)
Nervous system disorders	124 (41.8)	14 (4.7)	86 (29.0)	10 (3.4)	51 (19.7)	7 (2.7)	55 (22.2)	7 (2.8)	23 (14.6)	6 (3.8)	25 (18.0)	7 (5.0)
Headache	84 (28.3)	4 (1.3)	32 (10.8)	1 (0.3)	11 (4.2)	0	11 (4.4)	0	2 (1.3)	0	5 (3.6)	1 (0.7)
Dizziness	31 (10.4)	1 (0.3)	31 (10.4)	1 (0.3)	17 (6.6)	0	16 (6.5)	0	3 (1.9)	1 (0.6)	9 (6.5)	0
Product issues	1 (0.3)	0	0	0	0	0	2 (0.8)	0	0	0	0	0
Psychiatric disorders	35 (11.8)	0	24 (8.1)	3 (1.0)	17 (6.6)	1 (0.4)	13 (5.2)	0	8 (5.1)	1 (0.6)	5 (3.6)	0
Renal and urinary disorders	28 (9.4)	7 (2.4)	30 (10.1)	4 (1.3)	28 (10.8)	5 (1.9)	23 (9.3)	6 (2.4)	15 (9.5)	3 (1.9)	7 (5.0)	1 (0.7)
Reproductive system and breast disorders	9 (3.0)	0	9 (3.0)	1 (0.3)	21 (8.1)	2 (0.8)	16 (6.5)	0	9 (5.7)	1 (0.6)	2 (1.4)	0

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TABLE A4. Most Common Adverse Events by Treatment Period (cycles) (continued)

	0-6 Cycles				7-30 Cycles				31+ Cycles			
	Acalabrutinib + Bendamustine-Rituximab (n = 297)		Placebo + Bendamustine-Rituximab (n = 297)		Acalabrutinib + Bendamustine-Rituximab (n = 259)		Placebo + Bendamustine-Rituximab (n = 248)		Acalabrutinib + Bendamustine-Rituximab (n = 158)		Placebo + Bendamustine-Rituximab (n = 139)	
System Organ Class and Preferred Term	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)
Respiratory, thoracic, and mediastinal disorders	98 (33.0)	10 (3.4)	78 (26.3)	15 (5.1)	87 (33.6)	4 (1.5)	71 (28.6)	10 (4.0)	36 (22.8)	4 (2.5)	29 (20.9)	3 (2.2)
Cough	37 (12.5)	0	36 (12.1)	0	49 (18.9)	0	34 (13.7)	1 (0.4)	14 (8.9)	0	12 (8.6)	0
Dyspnea	30 (10.1)	2 (0.7)	17 (5.7)	7 (2.4)	15 (5.8)	0	8 (3.2)	0	6 (3.8)	1 (0.6)	5 (3.6)	0
Skin and subcutaneous tissue disorders	157 (52.9)	38 (12.8)	106 (35.7)	8 (2.7)	94 (36.3)	10 (3.9)	67 (27.0)	3 (1.2)	34 (21.5)	2 (1.3)	27 (19.4)	1 (0.7)
Rash	50 (16.8)	3 (1.0)	30 (10.1)	3 (1.0)	16 (6.2)	1 (0.4)	21 (8.5)	0	3 (1.9)	0	3 (2.2)	1 (0.7)
Maculopapular rash	40 (13.5)	20 (6.7)	14 (4.7)	2 (0.7)	7 (2.7)	1 (0.4)	7 (2.8)	0	4 (2.5)	0	3 (2.2)	0
Pruritus	32 (10.8)	2 (0.7)	25 (8.4)	0	19 (7.3)	0	18 (7.3)	2 (0.8)	3 (1.9)	0	4 (2.9)	0
Vascular disorders	55 (18.5)	9 (3.0)	52 (17.5)	14 (4.7)	49 (18.9)	11 (4.2)	44 (17.7)	17 (6.9)	21 (13.3)	6 (3.8)	17 (12.2)	3 (2.2)
Hypertension	12 (4.0)	4 (1.3)	16 (5.4)	9 (3.0)	20 (7.7)	8 (3.1)	30 (12.1)	15 (6.0)	12 (7.6)	6 (3.8)	6 (4.3)	2 (1.4)

TABLE A5. Events of Clinical Interest

	Acalabrutinib + Bendamustine-Rituximab (n = 297)		Placebo + Bendamustine-Rituximab (n = 297)	
Event Type	Any Grade, No. (%)	Grade ≥3, No. (%)	Any Grade, No. (%)	Grade ≥3, No. (%)
Cardiac events	71 (23.9)	23 (7.7)	55 (18.5)	18 (6.1)
Atrial fibrillation/flutter	20 (6.7)	12 (4.0)	13 (4.4)	5 (1.7)
Ventricular tachyarrhythmias	7 (2.4)[a]	0	7 (2.4)[b]	0
Neutropenia	163 (54.9)	149 (50.2)	166 (55.9)	138 (46.5)
Bleeding	84 (28.3)	6 (2.0)	51 (17.2)	10 (3.4)
Major bleeding	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Hypertension	37 (12.5)	17 (5.7)	48 (16.2)	25 (8.4)
Infections	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Interstitial lung disease/ pneumonitis	10 (3.4)	2 (0.7)	10 (3.4)	4 (1.3)
Second primary malignancies (excluding nonmelanoma skin)	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)

NOTE. Grouping of related preferred terms.
[a]Consists of ventricular arrhythmia (n = 2, grade 1), ventricular extrasystoles (n = 2, grade 1; n = 2, grade 2), and ventricular tachycardia (n = 1, grade 1).
[b]Consists of ventricular arrhythmia (n = 1, grade 1; n = 1, grade 2), ventricular extrasystoles (n = 3, grade 1; n = 1, grade 2), and ventricular tachycardia (n = 1, grade 2).

TABLE A6. Impact of COVID-19 Disease

		COVID-19–Related Adverse Events	
Category of Adverse Event		Acalabrutinib + Bendamustine-Rituximab (n = 297)	Placebo + Bendamustine-Rituximab (n = 297)
Any adverse event	Incidence rate, No. (%)	121 (40.7)	88 (29.6)
	Exposure-adjusted incidence rate per 100 person-years	0.162	0.129
Grade ≥3	Incidence rate, No. (%)	60 (20.2)	50 (16.8)
	Exposure-adjusted incidence rate per 100 person-years	0.073	0.069
Grade 5	Incidence rate, No. (%)	28 (9.4)	20 (6.7)
	Exposure-adjusted incidence rate per 100 person-years	0.033	0.026
Serious adverse events	Incidence rate, No. (%)	60 (20.2)	52 (17.5)
	Exposure-adjusted incidence rate per 100 person-years	0.073	0.071
Grade ≥3	Incidence rate, No. (%)	58 (19.5)	48 (16.2)
	Exposure-adjusted incidence rate per 100 person-years	0.070	0.066
Adverse event leading to acalabrutinib/placebo discontinuation	Incidence rate, No. (%)	31 (10.4)	19 (6.4)
	Exposure-adjusted incidence rate per 100 person-years	0.036	0.025

NOTE. Exposure-adjusted incidence rate was defined as (total number of patients with an event × 100)/(total exposure time for all patients at risk in years in the main study period).

TABLE A7. Adverse Events Leading to Discontinuation of Acalabrutinib/Placebo in >1 Patient

	Acalabrutinib + Bendamustine-Rituximab (n = 297)		Placebo + Bendamustine-Rituximab (n = 297)	
Adverse Event Type	Any Grade, No. (%)	Grade ≥3, No. (%)	Any Grade, No. (%)	Grade ≥3, No. (%)
COVID-19 disease	14 (4.7)	9 (3.0)	9 (3.0)	6 (2.0)
COVID-19 pneumonia	13 (4.4)	11 (3.7)	8 (2.7)	8 (2.7)
Neutropenia	12 (4.0)	11 (3.7)	10 (3.4)	9 (3.0)
Pneumonia	5 (1.7)	5 (1.7)	1 (0.3)	1 (0.3)
Hepatitis B reactivation	4 (1.3)	1 (0.3)	5 (1.7)	0
Pyrexia	2 (0.7)	0	1 (0.3)	1 (0.3)
Pneumonitis	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)
Atrial fibrillation	2 (0.7)	2 (0.7)	1 (0.3)	0
Anemia	2 (0.7)	2 (0.7)	0	0
Cellulitis	2 (0.7)	1 (0.3)	0	0
Cytomegalovirus infection	2 (0.7)	1 (0.3)	0	0
ALT increased	2 (0.7)	2 (0.7)	0	0
Colorectal adenocarcinoma	2 (0.7)	1 (0.3)	0	0
Headache	2 (0.7)	0	0	0
Sepsis	1 (0.3)	1 (0.3)	3 (1.0)	3 (1.0)
Myocardial infarction	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)
Thrombocytopenia	0	0	2 (0.7)	2 (0.7)
Fatigue	0	0	2 (0.7)	1 (0.3)
Hepatitis B DNA increased	0	0	2 (0.7)	0

TABLE A8. Adverse Events With Fatal Outcome

Adverse Event	Acalabrutinib + Bendamustine-Rituximab (n = 297), No. (%)	Placebo + Bendamustine-Rituximab (n = 297), No. (%)
Within 30 days after last dose	36 (12.1)	30 (10.1)
COVID-19 pneumonia	15 (5.1)	10 (3.4)
COVID-19 disease	8 (2.7)	6 (2.0)
Pneumonia	3 (1.0)	0
Clostridium difficile colitis	1 (0.3)	0
Dyspnea	1 (0.3)	0
Intestinal adenocarcinoma	1 (0.3)	0
Neuroendocrine carcinoma	1 (0.3)	0
Cytomegalovirus pneumonia	1 (0.3)	0
Pneumonitis	1 (0.3)	0
Postacute COVID-19 syndrome	1 (0.3)	0
Sepsis	1 (0.3)	2 (0.7)
Tumor lysis syndrome	1 (0.3)	1 (0.3)
Urosepsis	1 (0.3)	0
Aortic aneurysm rupture	0	1 (0.3)
Cardiac arrest	0	1 (0.3)
Cardiopulmonary failure	0	1 (0.3)
Gunshot wound	0	1 (0.3)
Malignant melanoma	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Pulmonary embolism	0	2 (0.7)
Respiratory failure	0	1 (0.3)
Road traffic accident	0	1 (0.3)
Transitional cell carcinoma	0	1 (0.3)
Beyond 30 days of last dose	10 (3.4)	8 (2.7)
COVID-19 disease	2 (0.7)	1 (0.3)
COVID-19 pneumonia	2 (0.7)	3 (1.0)
Sepsis	2 (0.7)	1 (0.3)
Cachexia	1 (0.3)	0
Cholangiocarcinoma	1 (0.3)	0
Meningitis	1 (0.3)	0
Septic shock	1 (0.3)	0
Febrile neutropenia	0	1 (0.3)
Interstitial lung disease	0	1 (0.3)
Multiple organ dysfunction syndrome	0	1 (0.3)

TABLE A9. ECHO Trial Investigators

Country	Investigators
Argentina	Nicolas Cazap, Maria Cecilia Foncuberta, Gonzalo Garate, Jarchum Gustavo, Miguel A Pavlovsky, Dardo Riveros
Australia	Ross Baker, Jason Butler, Paul Cannell, Chan Cheah, Tara Cochrane, Cecily Forsyth, Pratyush Giri, Amanda Johnston, Denise Lee, Hui-Peng Lee, Sally Mapp, Fernando Roncolato, Aung Thant, Patricia Walker, Nicole Wong Doo
Belgium	Hilde Demuynck, Fritz Offner, Vanessa Van Hende, Vibeke Vergote, Ka Lung Wu
Brazil	Carlos Chiattone, Sergio de Azevedo, Joao Samuel de Holanda Farias, Laura Fogliatto, Ana Fonseca, Nelson Hamerschlak, Nicolas Lazaretti, Vanderson Rocha, Jose Salvador Rodrigues de Oliveira, Marco Salvino, Rodrigo Santucci, Mariza Schaan, Phillip Scheinberg, Adriana Scheliga, Garles Miller Vieira
Canada	Neil Berinstein, Melina Boutin, Michael Chu, Mary-Margaret Keating, Ariah Schattner, Diego Villa Restrepo
China	Xinan Cen, Xin Du, Ru Feng, Sujun Gao, Haiwen Huang, Jie Ji, Jie Jin, Xiaoyan Ke, Dengju Li, Fei Li, Jianyong Li, Junmin Li, Yan Li, Yufu Li, Zhenyu Li, Li'e Lin, Tingbo Liu, Fangfang LV, Yuerong Shuang, Yuqin Song, Lan Sun, Xiuhua Sun, Zhao Wang, Huijing Wu, Yaming Xi, Ruixiang Xia, Hongwei Xue, Haiyan Yang, Shuhua Yi, Cheng Zhang, Huilai Zhang, Mingzhi Zhang, Qingyuan Zhang, Xielan Zhao, Hui Zhou
Czech Republic	David Belada, Roman Hajek, Pavel Jindra, Jiri Mayer, Jan Novak
France	Julie Abraham, Fontanet Bijou, Kamal Bouabdallah, Florence Cymbalista, Sophie de Guilbert, Vincent Delwail, Philippe Genet, Kamel Laribi, Philippe Rodon
Germany	Thomas Decker, Peter Dreger, Martin Dreyling, Georg Hess, Georg Lenz, Stephan Stilgenbauer, Dirk Tummes
Greece	Konstantinos Anargyrou, Meletios-Athanassios Dimopoulos, Eleni Kapsali, Eirini Katodritou, Despoina Kyriakou, Panayiotis Panayiotidis, Vasiliki Pappa, Niki Stavroyianni, Argiris Symeonidis
Hong Kong	Hoi Ching Cheng, Yok-Lam Kwong, Harold Lee, Ting Ying Ng, Raymond Wong
Hungary	Zita Borbenyi, Árpád Illés, Zsolt Lazar, Ágnes Nagy, Zsolt Nagy, Tamas Schneider
Israel	Irit Avivi, Ronit Gurion, Netanel Horowitz, Aaron Ronson
Italy	Luca Arcaini, Carola Boccomini, Paolo Ghia, Stefano Luminari, Caterina Patti, Caterina Plenteda, Armando Santoro, Vittorio Ruggero Zilioli, Pier Luigi Zinzani
Japan	Ilseung Choi, Daisuke Ennishi, Kentaro Fukushima, Satoshi Ichikawa, Takayuki Ishikawa, Koji Izutsu, Koji Kato, Dai Maruyama, Hirokazu Nagai, Shuichi Ota, Toko Saito, Rika Sakai, Ritsuro Suzuki, Hiro Tatetsu, Nobuhiko Uoshima, Takahiro Yano, Isao Yoshida
Republic of Korea	Ki-Seong Eom, Jin Seok Kim, Sang-A Kim, Seok Jin Kim, Jung-Hee Lee, Yeung Chul Mun, Sung Yong Oh, Sung Soo Yoon
Mexico	Elsa Veronica Avila Arreguin, Adriana Dominguez Andrade, David Gomez Almaguer, Maria Silvia Rivas Vera, Luis Solis Anaya
New Zealand	Leanne Berkahn, Samar Issa, Lucy Pemberton, David Simpson
Peru	Brady Beltran, Shirely Quintana, Jose Carlos Revilla, Ernesto Vargas
Poland	Sebastian Grosicki, Janusz Halka, Wieslaw Jedrzejczak, Wojciech Jurczak, Wanda Knopinska-Posluszny, Jacek Krzanowski, Ewa Lech-Maranda, Marta Morawska, Tadeusz Robak, Piotr Rzepecki, Tomasz Wróbel
Romania	Gabriela Borsaru, Tudor Eliade Ciuleanu, Catalin Danaila, Mihaela Lazaroiu
Russia	Julia Alexeeva, Valeriy Chistyakov, Georgy Manikhas, Natalia Mikhailova, Andrey Proydakov, Elena Mikhailovna Volodicheva, Sergey Voloshin
Spain	Mariana Bastos, Javier Briones, Raul Cordoba, Jose Gómez Codina, Eva Maria Gonzalez, Ana Marin, Carlos Panizo, Guillermo Rodriguez, Antonio Salar, Juan-Manuel Sancho, Jose A. García-Vela, Victor Jimenez Yuste
Taiwan	Chien-Yuan Chen, Chang-Fang Chiu, Liang-Tsai Hsiao, Ching-Yuan Kuo, Tung-Liang Lin
Ukraine	Iryna Kryachok, Tamila Lysa, Zvenyslava Maslyak, Larysa Nogaieva, Sergey Polenkov, Ganna Usenko
United States	Richie Agajanian, Bertrand Anz, Arvind Chaudhry, Alden Chiu, Jennifer Cultrera, James D'Olimpio, Kieron Dunleavy, Suzanne Fanning, Ian Flinn, Nashat Gabrail, David Gallinson, Alec Goldenberg, Andre Goy, Solomon Graf, Natalie Grover, Brian Hess, Marc Hoffman, Iris Isufi, Brad Kahl, Suman Kambhampati, Dean Kirkel, Guillermo Lazo Diaz, Moshe Levy, Delong Liu, Monica Mead, Jonas Paludo, Anjan Patel, Shachar Peles, Daniel Persky, Craig Portell, Allison Rosenthal, Dahlia Sano, Sonali Smith, Stephen Smith, Stephen Spurgeon, Don Stevens, Jason Tache, Michaela Tsai, Lauren Veltri, Michael Wang, Habte Yimer
Vietnam	Quoc Khanh Bach, Huyen Nga Do, Hung Vu Luu, Trong Khoa Mai, Nhu Hiep Pham, Thanh Tung Tran