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# Final phase 2 study results of acalabrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia

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**Key Points**

- Long-term phase 1/2 data demonstrate high response rates and sustained PFS with acalabrutinib in both TN and R/R CLL.
- Acalabrutinib was well tolerated; adverse event rates decreased over time with no new safety signals with long-term follow-up.

Acalabrutinib is a selective, covalent Bruton tyrosine kinase inhibitor approved for marketing in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). We report final, long-term phase 1/2 study results in 99 patients with treatment-naive (TN) and 134 with relapsed/refractory (R/R) CLL/SLL. At final data cutoff, 71% and 31% of patients in the TN and R/R cohorts, respectively, remained on acalabrutinib treatment (median follow-up of 73.7 and 52.6 months). Among the events of clinical interest (any grade) in the TN and R/R cohorts, atrial fibrillation was reported in 6.1% and 9.0%, hypertension in 29.3% and 23.1%, other malignancies (excluding nonmelanoma skin cancer) in 14.1% and 17.2%, and major bleeding in 8.1% and 8.2% of patients, respectively. The incidence of the most common adverse events decreased over time. Overall response rates were 97.0% and 94.8% in the TN and R/R cohorts, respectively, with similar response findings among patients with standard and high-risk genomic features. In the TN cohort, median progression-free survival (PFS) was not reached and the 72-month PFS rate was 86.7% (95% confidence interval [CI], 77.0-92.5). For the R/R cohort, median PFS was 66.1 months (range, 0.4-87.8) and the 72-month PFS rate was 45.1% (95% CI, 35.6-54.1). This final analysis extends the duration of benefit observed with acalabrutinib, demonstrates that no new safety signals are apparent with longer follow-up, and confirms the safety and tolerability of acalabrutinib monotherapy for patients with CLL/SLL. This trial was registered at www.clinicaltrials.gov as #NCT02029443.

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Data underlying the findings described in this article 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/.

The full-text version of this article contains a data supplement.

## Introduction

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is a low-grade B-cell malignancy with outcomes revolutionized by the introduction of targeted therapies directed at Bruton tyrosine kinase (BTK) and the B-cell lymphoma 2 (BCL2) protein.[1,2] Historically, patients were treated with chemoimmunotherapy (CIT) regimens that resulted in high response rates, but often with substantial toxicity, subsequent refractory disease, and mortality.[1,2] The first-generation covalent BTK inhibitor (BTKi), ibrutinib, proved highly effective.[3,4] However, safety and tolerability issues due in part to alternative-target effects, primarily atrial fibrillation, hypertension, gastrointestinal symptoms, myalgias/arthralgias, nail and hair changes, and sudden death, limit its ability to be used long term, which is necessary for maximal benefit.[5-12]

Second-generation covalent BTKis, including acalabrutinib and zanubrutinib, were introduced with improved BTK selectivity and pharmaceutical properties, with the assumption that reduced toxicity would be observed, thereby decreasing the rates of therapy discontinuation and improving patient outcomes.[13-15] ACE-CL-001 (ClinicalTrials.gov identifier: NCT02029443) was the first phase 1/2, open-label, multicenter study demonstrating efficacy and tolerability of acalabrutinib for patients with treatment-naive (TN) or relapsed/refractory (R/R) CLL/SLL.[13,16,17] Subsequently, acalabrutinib demonstrated a tolerable safety profile and durable efficacy in 2 complementary phase 3 trials (ELEVATE-TN and ASCEND) in CLL.[18,19] Based on these results, acalabrutinib was approved by the US Food and Drug Administration for patients with TN CLL/SLL as a single agent and in combination with obinutuzumab and for patients with R/R CLL/SLL as a single agent.[18-20] Subsequent analyses of the ELEVATE-TN and ASCEND studies, at ~6 and 4 years of follow-up, respectively, supported the continued efficacy and safety of acalabrutinib for TN and R/R CLL, respectively.[21,22] However, additional long-term follow-up data for acalabrutinib are needed. When initiating indefinite cancer therapy, the cumulative occurrence of adverse events (AEs), disease progression, treatment compliance, and potential long-term complications are all important considerations.

Initially accruing patients with R/R CLL in dose escalation, ACE-CL-001 was amended to treat all patients at the recommended phase 2 dose of 100 mg twice daily. Although ELEVATE-TN and ASCEND provided data for acalabrutinib's approval in CLL/SLL, ACE-CL-001 establishes that acalabrutinib can be utilized safely long term with continued efficacy. For the TN cohort, a previous analysis of ACE-CL-001 at a median follow-up (mFU) of 53 months demonstrated a 97% overall response rate (ORR; 90% partial response [PR]; 7% complete response [CR]) and a 48-month duration of response (DOR) of 97%, with only 6% discontinuing treatment due to AEs.[16] Favorable efficacy and safety were also reported for the R/R cohort.[13,17] With a median treatment duration of 41 months, 56% of patients remained on acalabrutinib, with a median progression-free survival (PFS) not reached in the overall population. The 2 most common reasons for treatment discontinuation were progressive disease (PD; 21%) and AEs (11%). Here, we report the final analysis of ACE-CL-001, with an mFU of 74 months (6.1 years) in the TN cohort and 53 months (4.4 years) in the R/R cohort, representing the longest-running study of single-agent acalabrutinib for CLL. In addition to the extended efficacy and safety results for ACE-CL-001, this report presents a Kaplan-Meier analysis of PFS by number of prior lines of therapy (LOT) in the R/R cohort, univariate and multivariate analyses of predictors of response, and long-term immunologic analyses of key immune effector cells and immunoglobulins over >6 years of follow-up in both cohorts.

## Methods

### Patients

Detailed study methodology of ACE-CL-001 has been reported previously.[13,16,17] Briefly, patients aged ≥18 years with a diagnosis of CLL/SLL who met ≥1 of the 2008 International Workshop on Chronic Lymphocytic Leukemia criteria[23] for treatment and had adequate organ function and an Eastern Cooperative Oncology Group performance status score of 0 to 2 were enrolled. Eligible patients with TN CLL/SLL had either declined CIT or had comorbidities that precluded treatment with CIT; patients with R/R CLL/SLL had received at least 1 prior treatment. Key exclusion criteria were significant cardiovascular disease (defined as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, any class III or IV cardiac disease per New York Heart Association functional classification, or left ventricular ejection fraction ≤40%); corrected QT interval ≥480 milliseconds; uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura; history of bleeding diathesis; and need for concomitant treatment with warfarin or equivalent vitamin K antagonists or proton pump inhibitor therapy.

### Evaluation and treatment

All patients were assessed by a central laboratory for interphase cytogenetics, including del(17p) and del(11q) status (local laboratory data were used if del(17)(p13.1) and del(11)(q22.1) status were unavailable); immunoglobulin heavy-chain variable region (IGHV) gene mutation status; mitogen-stimulated (Cytosine-phosphate-Guanine [GpG] oligodeoxynucleotides) karyotype; ZAP-70 methylation; and β2-microglobulin at screening. Complex karyotype was defined as having ≥3 chromosomal abnormalities on stimulated karyotyping. Patients with R/R CLL were successively enrolled in cohorts, receiving oral acalabrutinib 100, 175, 250, and 400 mg once daily and 200 mg twice daily in the dose-escalation (phase 1) portion and were switched to 100 mg twice daily and 200 mg daily in the dose-expansion (phase 2) portion of the study. Patients with TN CLL were enrolled in the phase 2 portion during which they were successively enrolled to cohorts of acalabrutinib at 100 mg twice daily or 200 mg daily. All patients were switched to 100 mg twice daily per protocol amendment in May 2015. All patients received acalabrutinib treatment in 28-day cycles until PD, unacceptable toxicity, or death.

### Study assessments

The primary study end point was safety, assessed via AEs, laboratory testing, and vital signs. AEs were coded according to the Medical Dictionary for Regulatory Activities (version 24) and graded according to the Common Terminology Criteria of the National Cancer Institute, version 4.03. Secondary end points included ORR (defined as CR, CR with incomplete bone marrow

recovery, PR, or PR with lymphocytosis [PRL]),[24] DOR, and PFS, as assessed by the investigator; event-free survival (EFS) was assessed as a post hoc analysis. PFS was defined as the time from the first dose to documented PD or death. DOR was defined as the time from the date of first response (PRL or better) to documented PD or death from any cause, whichever occurred first. EFS was defined as the time from the first dose to documented PD, death, initiation of new anti-CLL therapy, or treatment discontinuation due to an AE, whichever occurred first.

Response evaluations, including radiologic examination, were conducted at screening and at the end of cycles 2, 4, and 6; then every 6 cycles until cycle 36; and every 12 cycles thereafter. Response assessments were based on 2008 International Workshop on Chronic Lymphocytic Leukemia criteria including computed tomography scan assessment,[23] incorporating clarification for treatment-related lymphocytosis.[25] Patients who discontinued treatment without PD or death were censored at the last adequate assessment, and those who received a new anticancer therapy before PD or death were censored at the date of the last adequate assessment before receiving the new anticancer therapy.

T-cell, natural killer (NK) cell, and monocyte counts and serum immunoglobulin (immunoglobulin A [IgA], IgG, and IgM) levels were assessed and measured at baseline; before cycles 3, 10, and 16; then every 6 cycles until cycle 36; and every 12 cycles thereafter.

### Statistical analyses

All enrolled patients who received ≥1 dose of acalabrutinib were included in the safety analyses. The efficacy-evaluable population included all those who received ≥1 dose of study drug and had ≥1 response assessment. No formal tests of hypotheses were performed; descriptive statistics were used to summarize the results. *P* values <.05 were considered descriptive and not definitive due to the high number of exploratory tests performed, and analyses were not adjusted for multiplicity. PFS, DOR, and EFS were estimated using the Kaplan-Meier methodology; PFS and DOR data were censored at the last clinical evaluation for patients who discontinued treatment without documented PD or death. Wilcoxon signed-rank test was used to evaluate changes from baseline in immunoglobulin levels and immune cell counts. The data cutoff for the analysis was 15 July 2021.

Univariate and multivariate Cox regression models were used to estimate hazard ratios (HRs) and identify predictors of disease progression. The following baseline characteristics were included in the models: age (≥70 vs <70 years), CD8 cell count (normal [≥150 to ≤1000 per μL] vs abnormal), bulky disease (≥5 vs <5 cm), β2-microglobulin (>3.5 vs ≤3.5 mg/L), sex (male vs female), NK cell count (normal [≥78 to ≤620 per μL] vs abnormal), Rai stage (I/II vs III/IV), IGHV status (mutated vs unmutated), and del(17p) presence (yes vs no). In univariate analysis, HR (95% confidence interval [CI]) and *P* values were based on Cox proportional hazards analysis including each baseline characteristic in the model. In multivariate analysis, HR (95% CI) and *P* values were based on Cox proportional hazards analysis including all 9 baseline characteristics of interest in the model. A Cox proportional hazards analysis using backward elimination was performed for any significant covariate ($P < .05$).

**Table 1. Treatment duration and disposition**

| | TN n = 99 | R/R n = 134 |
|---|---|---|
| Patients on treatment at data cutoff | 70 (70.7) | 41 (30.6) |
| **Treatment discontinuations** | | |
| AEs* | 10 (10.1) | 20 (14.9) |
| PD | 6 (6.1) | 49 (36.6) |
| Physician decision | 5 (5.1) | 11 (8.2) |
| Death | 2 (2.0) | 6 (4.5) |
| Withdrawal of consent | 2 (2.0) | 4 (3.0) |
| Pregnancy | 1 (1.0) | 0 |
| Other | 5 (5.1) | 3 (2.2) |
| Median study duration, mo (range) | 73.7 (0.9-82.4) | 52.6 (0.6-88.8) |

Data are presented as n (%) unless otherwise specified.
*Data for treatment discontinuations due to AEs (disposition data) were captured from the treatment termination case report form; data for AEs leading to treatment discontinuation (safety analysis) were captured from the AE case report form.

All patients provided written informed consent. The independent ethics committee or the institutional review board at each participating site approved the study protocol, and the study was performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

## Results

### Patients

Patients with TN CLL were enrolled between 15 August 2014 and 10 December 2015, and patients with R/R CLL were enrolled between 30 January 2014 and 18 November 2015. A total of 99 patients with TN CLL (median age, 64 years) and 134 with R/R CLL (median age, 66 years) received ≥1 dose of acalabrutinib and were included in the analyses. Patient demographics and baseline characteristics for each cohort were described previously (supplemental Table 1).[16,17] Among patients with available samples in the TN and R/R cohorts, 10.2% (9/88) and 26.7% (31/116) had del(17p), 13.8% (9/65) and 28.1% (16/57) had *TP53* mutation, 12.1% (12/99) and 26.1% (35/134) had del(17p) and/or *TP53*%, and 62.0% (57/92) and 73.0% (81/111) had unmutated IGHV (uIGHV), respectively. In the R/R cohort, 2 patients received prior BCL2 inhibitor therapy; no patient received prior BTKi therapy.

At data cutoff, mFU was 73.7 months and 52.6 months in the TN and R/R cohorts, respectively, and 70.7% of patients with TN CLL and 30.6% of those with R/R CLL remained on therapy (Table 1). The primary reasons for treatment discontinuation were AEs (TN, 10.1%; R/R, 14.9%) and disease progression (TN, 6.1%; R/R, 36.6%). Treatment discontinuation due to disease progression included 5 patients with Richter transformation (TN, n = 1 [at study day 996]; R/R, n = 4 [at study days 50, 473, 644, and 989]).

### Safety

The median (range) treatment exposure was 73.7 (0.2-82.4) months in the TN cohort and 49.7 (0.2-88.8) months in the R/R cohort. Almost all patients (99.7%) experienced ≥1

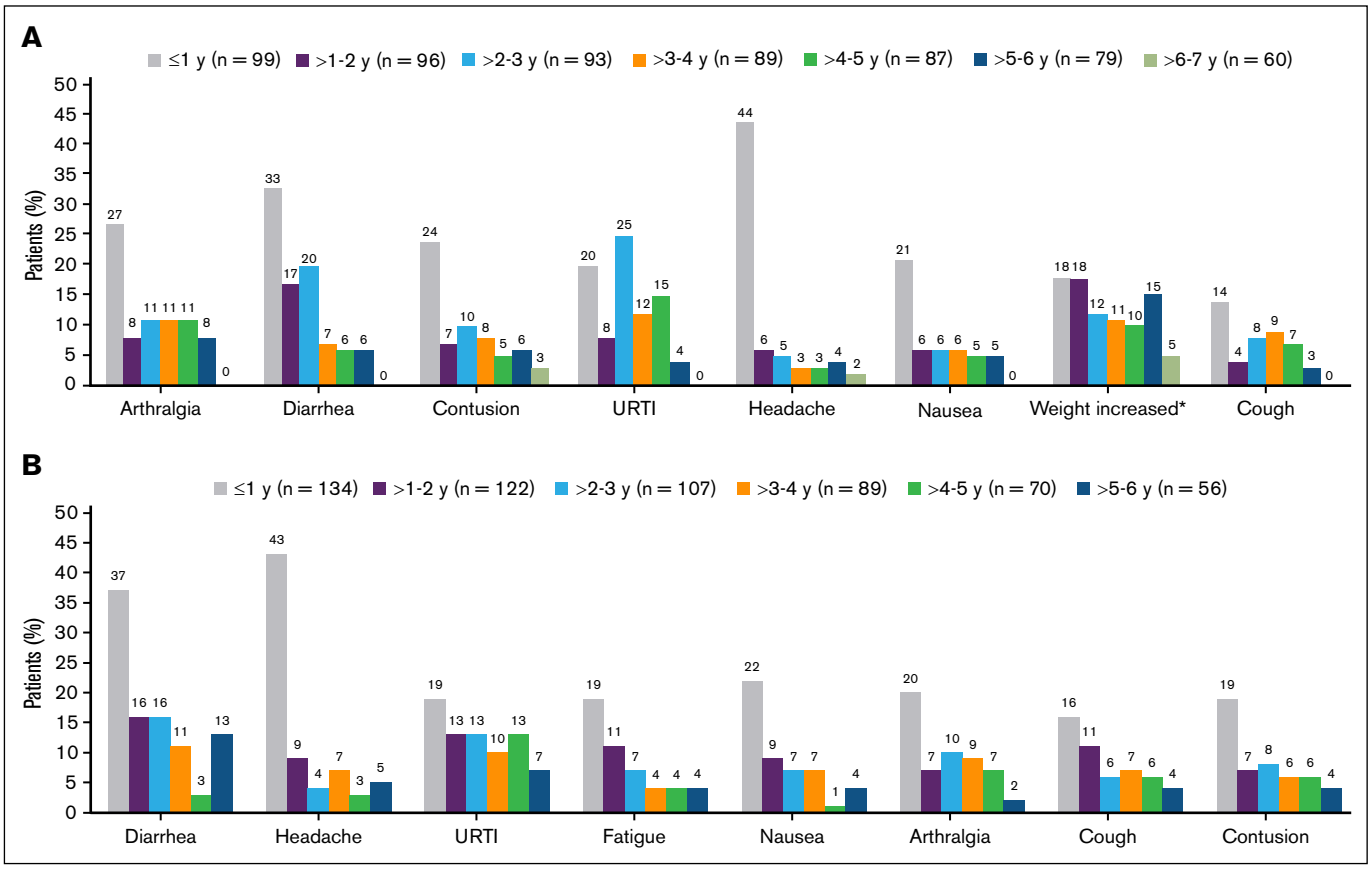


**Figure 1. Incidence of select TEAEs occurring in ≥30% of patients by yearly interval.** TN (A) and R/R (B) CLL cohorts are shown. A TEAE was counted only once in the interval in which the TEAE started. Although a patient could have been counted in multiple intervals, the ≥30% threshold for inclusion was based on the total number of unique patients with the specific event. *Weight increase was reported as a MedDRA term based on investigator assessment. Although reported as a TEAE, weight increase may not be associated with detrimental effects in this population of patients with CLL. MedDRA, Medical Dictionary for Regulatory Activities; URTI, upper respiratory tract infection.

treatment-emergent AEs (TEAEs) during the study, and most (71.1%) had grade ≥3 AEs. No unexpected late-term AEs were noted with extended follow-up.

In the TN cohort, the most common TEAEs (percent of any grade [percent of grade ≥3]) were arthralgia (55.6% [2.0%]), diarrhea (53.5% [6.1%]), contusion (50.5% [0%]), upper respiratory tract infection (49.5% [1.0%]), headache (48.5% [5.1%]), nausea (34.3% [4.0%]), increased weight (33.3% [8.1%]), and cough (32.3% [0%]) (supplemental Table 2). The incidence of the most common AEs decreased over time (Figure 1A; supplemental Figure 1A). Atrial fibrillation occurred as a total of 8 events in 6 patients (3 patients with grade ≥3 events) overall, with a consistently low incidence observed throughout the study period (1 event at ≤1 year, 1 at >1-2 years, 3 at >2-3 years, 1 at >3-4 years, 1 at >4-5 years, 1 at >5-6 years, and 0 at >6-7 years). The most common grade ≥3 TEAEs (occurring in ≥5% of patients) were hypertension (12.1%), weight increase (8.1%), pneumonia (8.1%), neutropenia (8.1%), diarrhea (6.1%), syncope (6.1%), and headache (5.1%). The only grade ≥3 TEAEs (n >2) with a ≥50% increase in cumulative incidence since the last data cutoff at 53 months of follow-up[16] were pneumonia (4.0% [prior update] vs 8.1%) and syncope (4.0% [prior update] vs 6.1%).[16]

In the R/R cohort, the most common TEAEs (percent any grade [percent grade ≥3]) included diarrhea (53.7% [5.2%]), headache (50.7% [0%]), upper respiratory tract infection (41.0% [0.7%]), fatigue (36.6% [3.0%]), nausea (35.1% [0.7%]), cough (35.1% [0%]), arthralgia (35.1% [0.7%]), and contusion (31.3% [0%]) (supplemental Table 3). The incidence of TEAEs generally decreased over time (Figure 1B; supplemental Figure 1B). The yearly occurrence of atrial fibrillation events (12 total events in 11 patients [4 patients with grade ≥3]) in this predominantly older cohort (57.5% were aged ≥65 years) was consistently low over time (1 event at ≤1 years, 4 at >1-2 years, 2 at >2-3 years, 1 at >3-4 years, 2 at >4-5 years, 2 at >5-6 years). The most common grade ≥3 TEAEs were neutropenia (15.7%), pneumonia (15.7%), hypertension (11.2%), anemia (7.5%), and syncope (6.0%). Since the last data cutoff (at mFU of 41 months),[17] few additional grade ≥3 TEAEs were reported and included pneumonia (6 patients), hypertension (5 patients), neutropenia (2 patients), dyspnea (2 patients), and anemia (1 patient).

Serious TEAEs were reported in 49.5% and 63.4% of patients in the TN and R/R cohorts, respectively (supplemental Tables 4 and 5). The most common serious TEAEs in the TN cohort were pneumonia (6.1%), squamous cell carcinoma of the skin (4.0%), and

**Table 2. Events of clinical interest**

| | TN, n = 99 | | R/R, n = 134 | |
|---|---|---|---|---|
| **ECIs** | **Any grade** | **Grade ≥3** | **Any grade** | **Grade ≥3** |
| **Cardiac events** | 32 (32.3) | 7 (7.1) | 47 (35.1) | 15 (11.2) |
| Atrial fibrillation | 6 (6.1) | 3 (3.0) | 12 (9.0) | 4 (3.0) |
| Ventricular tachyarrhythmias | 0 | 0 | 2 (1.5)* | 1 (0.7) |
| Anemia | 10 (10.1) | 3 (3.0) | 22 (16.4) | 10 (7.5) |
| **Leukopenia** | 9 (9.1) | 9 (9.1) | 27 (20.1) | 25 (18.7) |
| Neutropenia | 9 (9.1) | 9 (9.1) | 26 (19.4) | 25 (18.7) |
| Other leukopenia | 1 (1.0) | 1 (1.0) | 2 (1.5) | 1 (0.7) |
| Thrombocytopenia | 1 (1.0) | 1 (1.0) | 10 (7.5) | 8 (6.0) |
| **Hemorrhage** | 73 (73.7) | 7 (7.1) | 95 (70.9) | 8 (6.0) |
| Major hemorrhage | 8 (8.1) | 7 (7.1) | 11 (8.2) | 8 (6.0) |
| Hepatotoxicity | 4 (4.0) | 2 (2.0) | 4 (3.0) | 2 (1.5) |
| Hypertension† | 29 (29.3) | 13 (13.1) | 31 (23.1) | 15 (11.2) |
| Infections | 86 (86.9) | 19 (19.2) | 118 (88.1) | 44 (32.8) |
| Interstitial lung disease/pneumonitis | 3 (3.0) | 0 | 1 (0.7) | 0 |
| **Other malignancies** | 32 (32.3) | 7 (7.1) | 35 (26.1) | 13 (9.7) |
| Other malignancies, excluding nonmelanoma skin cancer | 14 (14.1) | 5 (5.1) | 23 (17.2) | 12 (9.0) |
| Tumor lysis syndrome | 0 | 0 | 1 (0.7) | 0 |

Data are presented as n (%).
ECIs, events of clinical interest; SMQ, Standardized Medical Dictionary for Regulatory Activities query.
*One patient experienced grade 4 ventricular fibrillation on study day 1322 that resolved (male with a history of moderate hypertension); 1 patient experienced grade 2 ventricular tachycardia on study day 1836 that resolved (male with a history of mild hypertension).
†ECI of hypertension includes all preferred terms per the search of SMQ Hypertension (narrow).

influenza (3.0%). COVID-19 (grade 3) was reported in 1 patient in the TN cohort. In the R/R cohort, most common serious TEAEs were pneumonia (14.2%), acute kidney injury (3.7%), and anemia, atrial fibrillation, diarrhea, and hypercalcemia (3.0% each). COVID-19 pneumonia and COVID-19 were reported in 3 (2.2%; 2 grade 3 and 1 grade 2) and 2 (1.5%; both grade 3) patients, respectively, in the R/R cohort.

Among the TN cohort patients, AEs led to treatment discontinuation in 11 patients: other malignancies (n = 4; 1 each of angiosarcoma, glioblastoma multiforme, prostate cancer, and small-cell lung cancer) and amyotrophic lateral sclerosis, cardiac failure, cerebral hemorrhage, gastric hemorrhage, noncardiac chest pain, sepsis, and urinary tract infection (n = 1 patient each). In the R/R cohort, AEs led to treatment discontinuation in 21 patients: pneumonia (n = 5); anemia, diarrhea, neutropenia, and thrombocytopenia (n = 2 each); and abdominal pain, atrial flutter, autoimmune hemolytic anemia, cardiac arrest, cardiac failure congestive, chronic myeloid leukemia, delirium, dyspnea, lung adenocarcinoma, lymphoedema, myelodysplastic syndrome, and peripheral neuropathy (n = 1 each).

No cases of sudden cardiac death (Medical Dictionary for Regulatory Activities term) were considered related to acalabrutinib in either cohort. All on-study deaths (n = 2) in the TN cohort were previously reported (1 patient due to multiple organ dysfunction in the setting of pneumonia and 1 patient due to cardiac failure during an ongoing lung infection and atrial fibrillation).[16] Thirteen (9.7%) on-study grade 5 AEs were reported in the R/R cohort, of which 3 occurred following the prior report[17] (1 each of cardiac arrest, cerebrovascular accident, and plasmablastic lymphoma). The patient with grade 5 cardiac arrest had a history of hypertension, rectal bleeding, and aortic aneurysm; cardiac arrest occurred 2 days after a grade 3 fall with a grade 3 spinal fracture and 2 days after the last dose of acalabrutinib. None of the fatal AEs was considered by the investigator to be treatment-related in the R/R cohort.

The most common events of clinical interest (percent any grade [percent grade ≥3]) in the TN and R/R cohorts were infections (86.9% [19.2%] and 88.1% [32.8%]), bleeding events (73.7% [7.1%] and 70.9% [6.0%]), cardiac events (32.3% [7.1%] and 35.1% [11.2%]), and other malignancies (32.3% [7.1%] and 26.1% [9.7%]), respectively (Table 2).

## Efficacy

At final data cutoff, the ORR (CR + CR with incomplete bone marrow recovery + PR + PRL) was 97.0% (TN) and 94.8% (R/R). The ORRs in the TN cohort among patients with high-risk features were 100% (9/9) for those with del(17p), 100% (9/9) for *TP53* mutation, 100% (57/57) for uIGHV, and 100% (12/12) for complex karyotype (Table 3). ORR rates in the R/R cohort were 87.1% (27/31; del(17p)), 81.3% (13/16; *TP53*), 90.1% (73/81; uIGHV), and 85.0% (17/20; complex karyotype). Median PFS was not reached in the TN cohort and was 66.1 months (range, 0.4-87.8) in the R/R cohort; 72-month PFS rates were 86.7% (95% CI, 77.0-92.5; Figure 2A-C) and 45.1% (95% CI, 35.6-54.1; Figure 2D-F), respectively. In the TN cohort, median PFS was 57 months (95% CI, 15.2-77.5) in the del(17p) subgroup vs not

**Table 3. Response outcomes (all-treated population)**

| Response | TN, n = 99 | R/R, n = 134 |
|---|---|---|
| ORR (CR + CRi + PR + PRL), % (95% CI*), n/N | 97.0 (91.4-99.4), 96/99 | 94.8 (89.5-97.9), 127/134 |
| ORR (CR + CRi + PR), % (95% CI*), n/N | 97.0 (91.4-99.4), 96/99 | 90.3 (84.0-94.7), 121/134 |
| **Best response, n (%)** | | |
| CR | 9 (9.1) | 5 (3.7) |
| CRi | 0 | 0 |
| PR | 87 (87.9) | 116 (86.6) |
| PRL | 0 | 6 (4.5) |
| SD | 1 (1.0) | 1 (0.7) |
| PD | 0 | 2 (1.5) |
| Unknown† | 2 (2.0) | 4 (3.0) |
| **ORR (CR + PR + PRL) by cytogenetic feature, % (95% CI*), n/N** | | |
| del(17p) | 100.0 (66.4-100.0), 9/9 | 87.1 (70.2-96.4), 27/31 |
| *TP53* mutation | 100.0 (66.4-100.0), 9/9 | 81.3 (54.4-96.0), 13/16 |
| del(11q)‡ | 100.0 (78.2-100.0), 15/15 | 87.0 (66.4-97.2), 20/23 |
| uIGHV | 100.0 (93.7-100.0), 57/57 | 90.1 (81.5-95.6), 73/81 |
| mIGHV | 91.4 (76.9-98.2), 32/35 | 86.7 (69.3-96.2), 26/30 |
| Complex karyotype (≥3 chromosomal abnormalities) | 100.0 (73.5-100.0), 12/12 | 85.0 (62.1-96.8), 17/20 |

CRi, CR with incomplete hematologic recovery; mIGHV, mutated IGHV region genes; SD, stable disease; uIGHV, unmutated IGHV region genes.
*95% exact binomial CI.
†Patients did not have on-treatment response assessments.
‡Included patients without del(17p) or who were missing del(17p) status.

reached (95% CI, not estimable [NE] to NE) for patients without del(17p) (Figure 2A). In the R/R cohort, the median PFS was 33.1 months (95% CI, 17.5-43.5) in the del(17p) subgroup vs not reached (95% CI, 71.8 to NE) in those without del(17p) (Figure 2D). In the TN cohort, the 72-month PFS rates were 84.7% and 91.1% in those with uIGHV and mutated IGHV (mIGHV), respectively (Figure 2B). For the R/R cohort, the corresponding rates were 37.3% and 60.0% (Figure 2E). Similar analyses for patients with *TP53* mutation were not performed due to the small sample size (TN, n = 9; R/R, n = 16). When analyzed by the number of prior LOTs, median PFS was not reached (1 prior LOT; n = 47), 60.6 months (2 prior LOTs; n = 23), and 44.0 months (>2 prior LOTs; n = 64); 48-month PFS rates were 78.9%, 63.3%, and 39.8% for 1, 2, and >2 prior LOTs, respectively (supplemental Figure 2).

Median EFS was 79.1 months (95% CI, 79.1 to NE) in the TN cohort and 53.8 months (95% CI, 44.1-66.1) in the R/R cohort; the 72-month EFS rates were 78.1% (95% CI, 68.0-85.3) and 37.4% (95% CI, 28.9-45.9), respectively (Figure 3). Reported EFS events in the TN cohort included treatment discontinuation due to AEs (n = 10/99 [10.1%]), PD (n = 9/99 [9.1%]), and new anti-CLL therapy (n = 3/99 [3.0%]); in the R/R cohort, these included treatment discontinuation due to AEs (n = 18/134 [13.4%]), death (n = 5/134 [3.7%]), PD (n = 54/134 [40.3%]), and new anti-CLL therapy (n = 3/134 [2.2%]).

Univariate and multivariate analyses were performed to identify baseline characteristics predictive of PD. In the TN cohort, among the baseline factors tested, the presence of del(17p) (vs without del(17p)) was the only factor associated with a significantly higher risk of PD (HR, 12.3; 95% CI, 3.02-49.7; $P = .0004$) in univariate analysis (supplemental Table 6). Multivariate analysis in the TN cohort was not feasible due to a low number of patients with PD (n = 9). For the R/R cohort, univariate analysis identified a lower risk of PD for patients with mIGHV vs uIGHV (HR, 0.41; 95% CI, 0.18-0.93; $P = .0321$) and a higher risk for those with vs without del(17p) (HR, 5.18; 95% CI, 2.84-9.43; $P < .0001$) (supplemental Table 7). In multivariate analysis in the R/R cohort, del(17p) was the only significant covariate to be included in the model using backward elimination; patients with del(17p) had a higher risk of PD vs those without del(17p) (HR, 4.40; 95% CI, 1.50-12.9; $P = .0071$).

### Immunologic studies

Changes in immune effector cell counts over time, including T cells (CD4 and CD8), NK cells, and monocytes, as well as in absolute lymphocyte counts are presented in supplemental Figure 3. Similar changes in cell counts were generally observed between the TN and R/R cohorts, with a steady decline through the first 60 weeks of acalabrutinib treatment followed by a plateau in cell counts for each cell type. An analysis of immunoglobulin levels also revealed similar general trends between the TN and R/R cohorts, with similar or increased levels of IgA and IgG and decreased levels of IgM (supplemental Figure 4).

## Discussion

Here, we report the final results of the phase 1/2 ACE-CL-001 study, providing long-term follow-up for patients with TN and R/R CLL treated with acalabrutinib monotherapy. At study

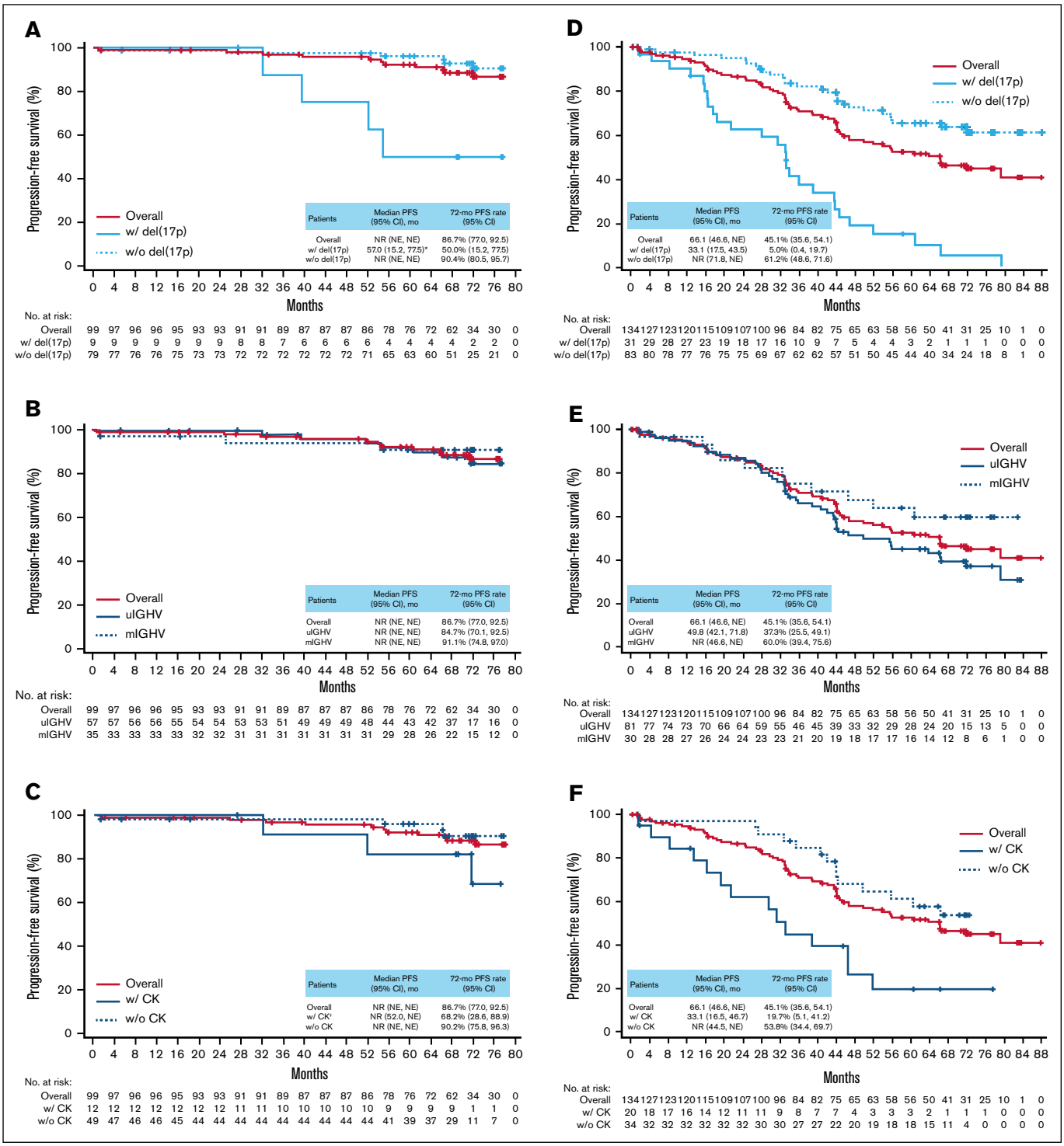


**Figure 2. Progression-free survival overall and by high-risk genomic features, including del(17p), IGHV, and complex karyotype.** TN (A-C) and R/R (D-F) CLL cohorts are shown. PFS was defined as the time from the date of the first dose to the date of the first PD or death due to any cause, whichever came first. Patients were not observed for PD, death, or start of new therapy after acalabrutinib discontinuation. *Large variation in estimate in TN del(17p) is due to limited sample size. †Of the 12 patients in the TN cohort with CK (≥3 chromosomal abnormalities), 5 also had del(17p). CK, complex karyotype; NR, not reached; w/ with; w/o, without.

completion, 71% of patients in the TN cohort and 31% in the R/R cohort remained on acalabrutinib. In the TN cohort, at an mFU of 73.7 months, the median PFS was not reached, and in the R/R cohort, the median PFS was 66.1 months at an mFU of 53 months. The differences in PFS were observed based on the presence of del(17p), but not complex karyotype or IGHV mutational status in

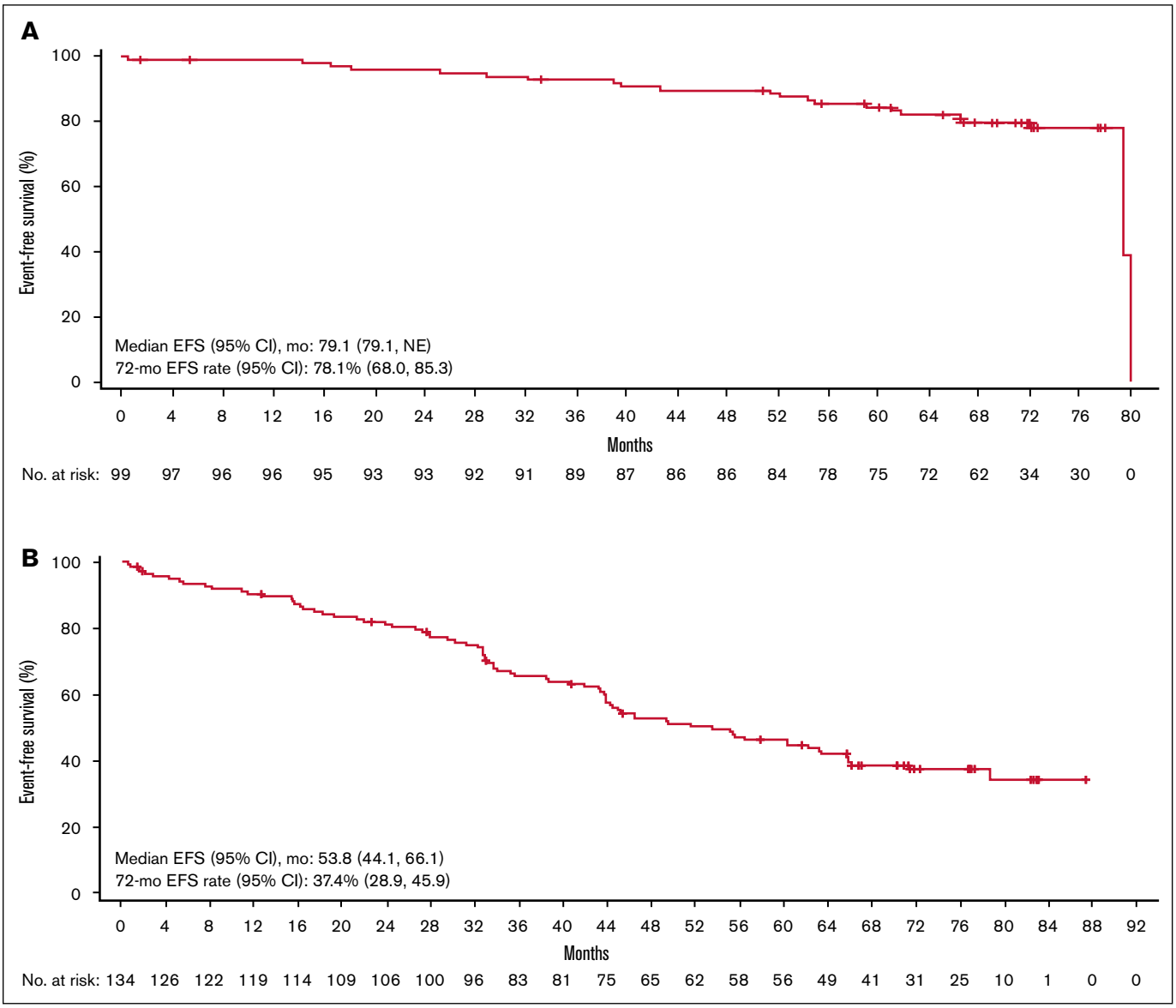


**Figure 3. Event-free survival.** TN (A)* and R/R (B) CLL cohorts are shown. EFS was calculated as the number of months from treatment start date to disease progression, death, start of new anticancer therapy, or treatment discontinuation due to an AE (whichever occurred first) before data cutoff. *The curve drops to 0 at 80 months because the last patient in the curve had an EFS event rather than being censored.

the TN cohort; in the RR cohort, differences in PFS were observed based on del(17p) and complex karyotype and not IGHV status.

The most common AEs were consistent with those reported in prior follow-up analyses of this study,[16,17] and no new AE signals were observed. The frequencies of atrial fibrillation and contusion/bleeding were lower than those reported in previous reports for ibrutinib,[3,4] whereas the rates of atrial fibrillation were comparable with those with zanubrutinib.[26] Notably, in this study, the rates of atrial fibrillation remained consistently low throughout the study. Overall, the most common AEs in both the TN and R/R cohorts generally diminished over time. In particular, hypertension did not increase over time in this study, which contrasts with that with ibrutinib and zanubrutinib, in which the frequency was sustained or continued to escalate with time.[4,26] The incidence of atrial fibrillation with ibrutinib was higher than that with acalabrutinib and persisted over time.[4]

Importantly, long-term findings from ACE-CL-001 offer further understanding of the impact of BTKis on cardiovascular outcomes. The phase 3 ELEVATE-RR study revealed improved tolerability and a lower frequency of hypertension and atrial fibrillation with acalabrutinib vs ibrutinib among patients with CLL.[27] These data help clarify the question of whether cardiovascular AEs are due to a BTKi class effect. Furthermore, the observation of sustained or increasing rates of hypertension over time with continuous ibrutinib or zanubrutinib treatment[4,26] can be concerning because end-organ effects associated with chronic hypertension are broad and can include the risk of heart disease, stroke, and renal dysfunction. This long-term follow-up study of acalabrutinib

provides support that hypertension does not increase over time, which potentially distinguishes it from newer second-generation BTKis.

The efficacy results from this final analysis are comparable with outcomes reported from studies of other BTKis, including ibrutinib[3,4] and zanubrutinib,[28] although any interpretations or conclusions based on cross-trial comparisons should be avoided. In the RESONATE-2 study, which included patients with TN CLL without del(17p), median PFS was not reached among those treated with ibrutinib (mFU, 88.5 months; 7-year PFS rate, 59%); ORR (including PRL) was 92%, and 13% progressed while on treatment with ibrutinib.[3] In the RESONATE study, among patients with R/R CLL receiving ibrutinib (mFU, 65.3 months), the cumulative ORR (including PRL) was 91%, the overall median PFS was 44.1 months, the cumulative ORR (including PRL) was 91%, and the median PFS by LOT was not reached for patients who received 1 prior LOT, and was 67.3, 44.1, 33.0, and 27.3 months among patients who received 2, 3, 4, or $\geq$5 prior LOTs, respectively.[4] In the ALPINE study (mFU, 29.6 months), among patients with R/R CLL who received a median of 1 prior LOT, zanubrutinib demonstrated a higher ORR (not including PRL) than ibrutinib (83.5% vs 74.2%); this benefit was observed across all prespecified subgroups, including high-risk populations with del(17p), *TP53* mutation, or both.[28] In our study, high response rates were observed among patients with high-risk features, especially in the TN cohort in which 100% ORR was achieved across subgroups. Notably, a minimal difference in 72-month PFS rates was observed in the TN cohort based on IGHV status, whereas the 72-month PFS rate in the R/R cohort was reduced among patients with uIGHV.

The field of CLL has advanced significantly since the initial development of ibrutinib; we now enter a second age of therapy selection based on physician and patient preference for time-limited vs continuous treatments, short- and long-term AEs, and, ultimately, patient outcomes. This early-phase study uniquely contributes to the field by providing long-term safety and efficacy data with acalabrutinib therapy. For patients with TN or R/R CLL, continuous acalabrutinib monotherapy demonstrated exceptional durability of response and an acceptable tolerability profile with long-term treatment. Although cross-comparison of trial outcomes can be problematic, PFS for patients with del(17p) and/or *TP53* mutation have been noted to be significantly shorter with a fixed-duration combination of venetoclax + obinutuzumab in TN CLL, prompting many to consider continuous BTKis as better options in this setting.[29] Notably, only 2 patients in the R/R cohort received prior targeted therapy (both receiving a BCL2 inhibitor). This minimal exposure to prior targeted therapy may affect the relevance of the R/R findings in today's clinical setting in which targeted agents are commonly used for initial therapy.

Although durable efficacy was demonstrated with acalabrutinib, acquired BTKi resistance can be a concern, most notably with mutations at BTK Cys481.[30,31] In a separate analysis, molecular profiling was performed at baseline and posttreatment for 41 patients (nonprogressed, n = 23; progressed, n = 18) in ACE-CL-001 to identify novel predictive markers of acquired acalabrutinib resistance.[30] Several known drivers of CLL were identified that correlated with disease progression while on acalabrutinib therapy (eg, *MYC*, *MCL-1*, and *LAG3*). However, only baseline expression of CD49d or CD79b (quantified by extracellular flow cytometry and gene expression profiling) was found to be predictive of PD.[30]

An analysis of CLL lymphocyte counts revealed a general decrease over time with acalabrutinib treatment.[27,32] However, the impact of BTKis can extend to non-CLL lymphocytes. Given acalabrutinib's different off-target specificities compared with those of ibrutinib,[33] a different impact upon T-cell and NK cell circulation may be expected. Whether the circulating cell count is representative of the tissue-residing populations is unclear and measuring the circulating pool may not be of value. Of potentially greater importance is the rate of infections, which diminished over time with acalabrutinib treatment, ostensibly due to improvements gained by removing the impairment of the CLL without the deleterious impact of chemotherapy.

In conclusion, this final analysis of the ACE-CL-001 study establishes the long-term efficacy of acalabrutinib in TN and R/R CLL/SLL with no new safety signals, including among patients at higher risk of relapse.

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## Authorship

Contribution: R.R.F., W.G.W., S.M.O., and J. C. Byrd designed the study; R.R.F., W.G.W., J.M.C., J.R.B., T.M., D.M.S., K.P., J.A.W., S.M.O., and J. C. Byrd performed study investigation; R.R.F., W.G.W., P.E.M.P., J.M.C., J.R.B., T.M., P.M., D.M.S., K.P., S.M.O., and J. C. Byrd provided patients or study materials; R.R.F., W.G.W., J.R.B., T.M., D.M.S., K.P., M.d.B., S.M.O., and J. C. Byrd were responsible for collection and assembly of data; R.R.F., W.G.W., M.d.B., S.M.O., and J. C. Byrd conducted data analysis; R.R.F., W.G.W., J.M.C., J.R.B., D.M.S., P.G., K.P., M.d.B., S.M.O., and J. C. Byrd interpreted data; R.R.F., W.G.W., J.M.C., J.R.B., T.M., P.M., D.M.S., P.G., K.P., M.d.B., and J. C. Byrd prepared the manuscript; and all authors participated in the critical review and revision of the manuscript and provided approval of the manuscript for submission.

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