CLL-186

# Interim Results From ASSURE: A Phase 3b Safety Study of Acalabrutinib in Patients With Chronic Lymphocytic Leukemia

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## Objective

- To report interim safety results from ASSURE (NCT04008706), an ongoing global, phase 3b safety study of acalabrutinib monotherapy in patients with CLL in a real-world clinical practice setting

## Conclusions

- The safety profile of acalabrutinib in patients with CLL was consistent with previous clinical studies
- Rates of infection were high but manageable with low mortality when COVID-19 deaths were excluded, and rates of cardiac events were low, with no new safety signals identified
- COVID-19 TEAEs, including fatalities and those leading to treatment discontinuation, were commonly observed, as study enrollment spanned the COVID-19 pandemic[1]

## Plain language summary

**Why was this study done?**
Chronic lymphocytic leukemia (or CLL) is a common type of blood cancer in adults. Acalabrutinib is a drug that inhibits a protein called Bruton tyrosine kinase, which plays a key role in the development of CLL. Acalabrutinib has been approved for the treatment of CLL based on findings from previous acalabrutinib clinical trials. The ASSURE trial was conducted to examine the side effects of acalabrutinib in a broader real-world population.

**How were the data collected?**
Adult patients with CLL were given acalabrutinib 100 mg twice daily for approximately 48 months (or longer if the patient was benefiting from the drug) and continuously monitored during this time. Patients were organized into groups according to their previous treatment for CLL (ie, no prior treatment, 1 or more prior treatments, or previous treatment with ibrutinib). This analysis was conducted before trial completion for an early (interim) analysis of the safety data at a median follow-up of 32 months.

**What were the results?**
Overall, safety was similar to previous acalabrutinib clinical trials. However, since the trial was conducted during the COVID-19 pandemic, COVID-19–related side effects including death were common. Rates of non–COVID-19 infection were high but manageable and rates of heart-related side effects were low. No new safety signals were reported.

**Why do the results matter to patients and physicians?**
The results confirm safety results from previous clinical trials and help to further characterize less common side effects and inform the management of common side effects when treating CLL in a real-world clinical setting.

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## Introduction

- Acalabrutinib is a second-generation Bruton tyrosine kinase inhibitor approved for patients with TN or R/R CLL[2-4]
- Efficacy and safety of acalabrutinib for TN or R/R CLL were previously confirmed in three phase 3 randomized clinical trials (ASCEND, ELEVATE-TN, ELEVATE-RR)[3-5]
- We report interim safety results from ASSURE (NCT04008706), an ongoing global, phase 3b safety study evaluating acalabrutinib monotherapy in patients with CLL in a real-world clinical practice setting

## Methods

### ASSURE: Multicenter, Open-label, Single-arm, Phase 3b Study




[a]1 cycle = 28 days.
[b]Or until disease progression, toxicity requiring discontinuation, withdrawal of consent, loss to follow-up, death, or study termination, whichever comes first.

## Results

### Patients and Disposition

- The first enrolled patient was dosed with acalabrutinib in October 2019 and the trial was fully enrolled in October 2021
- Patient disposition is shown in **Figure 1**
- Demographics and baseline characteristics are provided in **Table 1**
- Median follow-up duration was 32.2, 32.5, and 22.0 months in the TN, R/R, and ibrutinib-intolerant cohorts, respectively
- Median (range) relative dose intensity was 99% (9%–200%), 99% (63%–200%), and 97% (42%–119%), respectively
- Using Kaplan-Meier analysis, the estimated proportion of patients remaining on treatment at 30 months was 71%, 62%, and 45%, respectively (**Figure 2**)

### TEAEs Overall

- The most common TEAEs are shown in **Table 2**
- Overall, 261 (47%) patients had confirmed or suspected COVID-19 infection (TN, 43%; R/R, 55%; ibrutinib intolerant, 38%)
- Grade ≥3 TEAEs were reported in 57% of patients overall (TN, 54%; R/R, 63%; ibrutinib intolerant, 45%)
- Serious TEAEs were reported in 42% of patients overall (TN, 38%; R/R, 50%; ibrutinib intolerant, 25%), most commonly COVID-19 (12%), pneumonia (6%), and COVID-19 pneumonia (5%)
- TEAEs led to treatment discontinuation in 19% of patients (TN, 15%; R/R, 26%; ibrutinib intolerant, 18%) (**Supplemental Table 1**)
  - TEAEs associated with COVID-19 infection led to treatment discontinuation in 11% of patients

### Events of Clinical Interest

- Events of clinical interest are reported in **Table 3**; incidences of atrial fibrillation/flutter, hypertension, and major hemorrhage were low
  - Of patients who had an atrial fibrillation TEAE (n=26), one third (30.8%; n=8) had prior history of atrial fibrillation
  - Of patients with a hypertension TEAE (n=43), most had medical history of hypertension (79.1%; n=34)
  - The population of patients with vs without a hypertension TEAE was slightly older (age ≥65 years: 79% vs 68%), more commonly male (67% vs 61%), and more likely to have high baseline blood pressure (>140/90 mmHg) (30% vs 18%), chronic kidney disease (16% vs 7%), and diabetes (23% vs 19%)
- Second primary malignancies (excluding non-melanoma skin cancer) are detailed in **Supplemental Table 2**
- Details on Richter transformation and myeloid malignancies are provided in the **Supplemental Text**

### Deaths

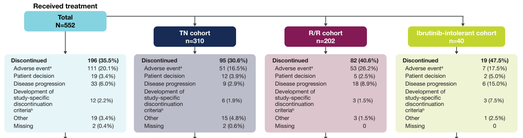
- Deaths were reported in 65 patients (12%) overall (TN, 7%; R/R, 19%; ibrutinib intolerant, 8%)
- 56 patients had grade 5 TEAEs during the treatment-emergent period
  - Most occurred in patients with confirmed/suspected COVID-19 (n=41), most commonly COVID-19 (n=20), COVID-19 pneumonia (n=9), pneumonia (n=2), and acute respiratory failure (n=2)
  - Grade 5 TEAEs in patients without confirmed/suspected COVID-19 (n=15) are reported in **Supplemental Table 3**

### Table 1. Patient Demographics and Baseline Characteristics

| | TN cohort n=310 | R/R cohort n=202 | Ibrutinib-intolerant cohort n=40 | Total N=552 |
|---|---|---|---|---|
| Age, median (range), years | 70.5 (41–90) | 68.0 (37–90) | 70.0 (27–88) | 69.5 (27–90) |
| Age group | | | | |
| <65 years | 85 (27.4) | 72 (35.6) | 15 (37.5) | 172 (31.2) |
| ≥65–<75 years | 126 (40.6) | 80 (39.6) | 11 (27.5) | 217 (39.3) |
| ≥75 years | 99 (31.9) | 50 (24.8) | 14 (35.0) | 163 (29.5) |
| Sex, male | 198 (63.9) | 121 (59.9) | 18 (45.0) | 337 (61.1) |
| ECOG PS[a] | | | | |
| 0 | 141 (45.5) | 86 (42.6) | 11 (28.2) | 238 (43.2) |
| 1 | 134 (43.2) | 88 (43.6) | 20 (51.3) | 242 (43.9) |
| 2 | 35 (11.3) | 28 (13.9) | 8 (20.5) | 71 (12.9) |
| Rai stage[b] | | | | |
| Lymphocytosis only (stage 0) | 40 (14.1) | 18 (9.5) | 5 (16.1) | 63 (12.5) |
| Lymphocytosis with lymphadenopathy (stage I) | 80 (28.3) | 51 (26.8) | 6 (19.4) | 137 (27.2) |
| Lymphocytosis with hepatomegaly or splenomegaly (stage II) | 64 (22.6) | 43 (22.6) | 8 (25.8) | 115 (22.8) |
| Lymphocytosis with anemia (stage III) | 42 (14.8) | 21 (11.1) | 2 (6.5) | 65 (12.9) |
| Lymphocytosis with thrombocytopenia (stage IV) | 45 (15.9) | 45 (23.7) | 8 (25.8) | 98 (19.4) |
| Genetic markers | | | | |
| del(17p) AND/OR mutated *TP53* | 37 (14.9) | 44 (26.2) | 7 (21.2) | 88 (19.6) |
| del(17p) | 23 (10.1) | 19 (11.8) | 4 (12.9) | 46 (11.0) |
| Mutated *TP53* | 24 (10.2) | 40 (24.7) | 5 (15.6) | 69 (16.1) |
| Unmutated IGHV | 183 (64.0) | 144 (73.1) | 21 (65.6) | 348 (67.6) |
| Number of previous therapies, median (range) | None | 1 (1–7) | 2 (1–4) | 1 (1–7) |
| Medical history of hypertension | 183 (59.0) | 100 (49.5) | 20 (50.0) | 303 (54.9) |
| Medical history of atrial fibrillation | 22 (7.1) | 20 (9.9) | 5 (12.5) | 47 (8.5) |

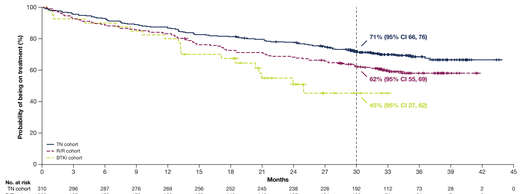
Data are n (%) unless otherwise specified. Percentages are based on total number of subjects with non-missing data.
[a]One patient in the ibrutinib-intolerant cohort had missing ECOG PS score.
[b]74 patients had missing (n=48) or unknown (n=26) Rai stage.

### Figure 1. Patient Disposition




[a]Data for treatment discontinuations due to adverse events (disposition data) were captured from the treatment termination case report form (vs the adverse event case report form for TEAEs leading to treatment discontinuation [safety data] reported in Supplemental Table 1, leading to minor numerical discrepancies).
[b]Six of these patients (TN, n=2; R/R, n=3; ibrutinib intolerant, n=1) were originally classified in the "Other" category by the investigator.

### Figure 2. Kaplan-Meier Plot of Time to Treatment Discontinuation




### Table 2. Most Common Treatment-Emergent Adverse Events (TEAEs; ≥15% [any grade] or ≥5% [grade ≥3] in any cohort)

| TEAEs (preferred terms), n (%) | TN cohort n=310 | | R/R cohort n=202 | | Ibrutinib-intolerant cohort n=40 | | Total N=552 | |
|---|---|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Headache | 129 (41.6) | 4 (1.3) | 77 (38.1) | 3 (1.5) | 28 (70.0) | 0 | 234 (42.4) | 7 (1.3) |
| COVID-19 | 120 (38.7) | 34 (11.0) | 92 (45.5) | 35 (17.3) | 14 (35.0) | 2 (5.0) | 226 (40.9) | 71 (12.9) |
| Diarrhea | 102 (32.9) | 4 (1.3) | 57 (28.2) | 2 (1.0) | 11 (27.5) | 1 (2.5) | 170 (30.8) | 7 (1.3) |
| Contusion | 82 (26.5) | 0 | 43 (21.3) | 0 | 9 (22.5) | 0 | 134 (24.3) | 0 |
| Arthralgia | 68 (21.9) | 4 (1.3) | 24 (11.9) | 2 (1.0) | 12 (30.0) | 0 | 104 (18.8) | 6 (1.1) |
| Nausea | 55 (17.7) | 1 (0.3) | 35 (17.3) | 0 | 8 (20.0) | 0 | 98 (17.8) | 1 (0.2) |
| Fatigue | 59 (19.0) | 2 (0.6) | 26 (12.9) | 5 (2.5) | 8 (20.0) | 1 (2.5) | 93 (16.8) | 8 (1.4) |
| Anemia | 36 (11.6) | 15 (4.8) | 33 (16.3) | 15 (7.4) | 7 (17.5) | 1 (2.5) | 76 (13.8) | 31 (5.6) |
| Constipation | 52 (16.8) | 2 (0.6) | 13 (6.4) | 0 | 2 (5.0) | 0 | 67 (12.1) | 2 (0.4) |
| Pneumonia | 30 (9.7) | 15 (4.8) | 28 (13.9) | 19 (9.4) | 6 (15.0) | 3 (7.5) | 64 (11.6) | 37 (6.7) |
| Vomiting | 27 (8.7) | 2 (0.6) | 16 (7.9) | 0 | 6 (15.0) | 0 | 49 (8.9) | 2 (0.4) |
| COVID-19 pneumonia | 10 (3.2) | 8 (2.6) | 23 (11.4) | 20 (9.9) | 1 (2.5) | 0 | 34 (6.2) | 28 (5.1) |
| Neutropenia | 14 (4.5) | 11 (3.5) | 19 (9.4) | 12 (5.9) | 1 (2.5) | 1 (2.5) | 34 (6.2) | 24 (4.3) |

### Table 3. Events of Clinical Interest

| Events of clinical interest,[a] n (%) | TN cohort n=310 | | R/R cohort n=202 | | Ibrutinib-intolerant cohort n=40 | | Total N=552 | |
|---|---|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Cardiac events | 60 (19.4) | 21 (6.8) | 31 (15.3) | 10 (5.0) | 9 (22.5) | 1 (2.5) | 100 (18.1) | 32 (5.8) |
| Atrial fibrillation/flutter | 20 (6.5) | 7 (2.3) | 4 (2.0) | 1 (0.5) | 2 (5.0) | 1 (2.5) | 26 (4.7) | 9 (1.6) |
| Ventricular arrhythmias[b] | 3 (1.0) | 0 | 0 | 0 | 1 (2.5) | 0 | 4 (0.7) | 0 |
| Hemorrhage | 156 (50.3) | 12 (3.9) | 95 (47.0) | 8 (4.0) | 19 (47.5) | 1 (2.5) | 270 (48.9) | 21 (3.8) |
| Major hemorrhage | 12 (3.9) | 12 (3.9) | 9 (4.5) | 8 (4.0) | 1 (2.5) | 1 (2.5) | 22 (4.0) | 21 (3.8) |
| Hypertension | 29 (9.4) | 10 (3.2) | 12 (5.9) | 7 (3.5) | 2 (5.0) | 1 (2.5) | 43 (7.8) | 18 (3.3) |
| Infections (including COVID-19) | 229 (73.9) | 76 (24.5) | 152 (75.2) | 81 (40.1) | 30 (75.0) | 8 (20.0) | 411 (74.5) | 165 (29.9) |
| Second primary malignancies excluding non-melanoma skin | 29 (9.4) | 16 (5.2) | 17 (8.4) | 7 (3.5) | 3 (7.5) | 2 (5.0) | 49 (8.9) | 25 (4.5) |

[a]Includes new-onset and worsening of existing condition.
[b]All ventricular arrhythmia events were ventricular extrasystoles.

**References**
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**Abbreviations**
BID, twice daily; CI, confidence interval; CLL, chronic lymphocytic leukemia; DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region genes; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MedDRA, Medical Dictionary for Regulatory Activities; MSSO, Maintenance and Support Services Organization; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TN, treatment-naive.

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