Poster CLL-354

Pooled Analysis of Cardiovascular Events from Clinical Trials Evaluating Acalabrutinib Monotherapy in Patients with Chronic Lymphocytic Leukemia (CLL)

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Objective

- A retrospective pooled analysis of data from all clinical studies of acalabrutinib (from phase 1 to 3) in CLL was conducted to further characterize cardiac and hypertension-related effects of acalabrutinib in patients with CLL

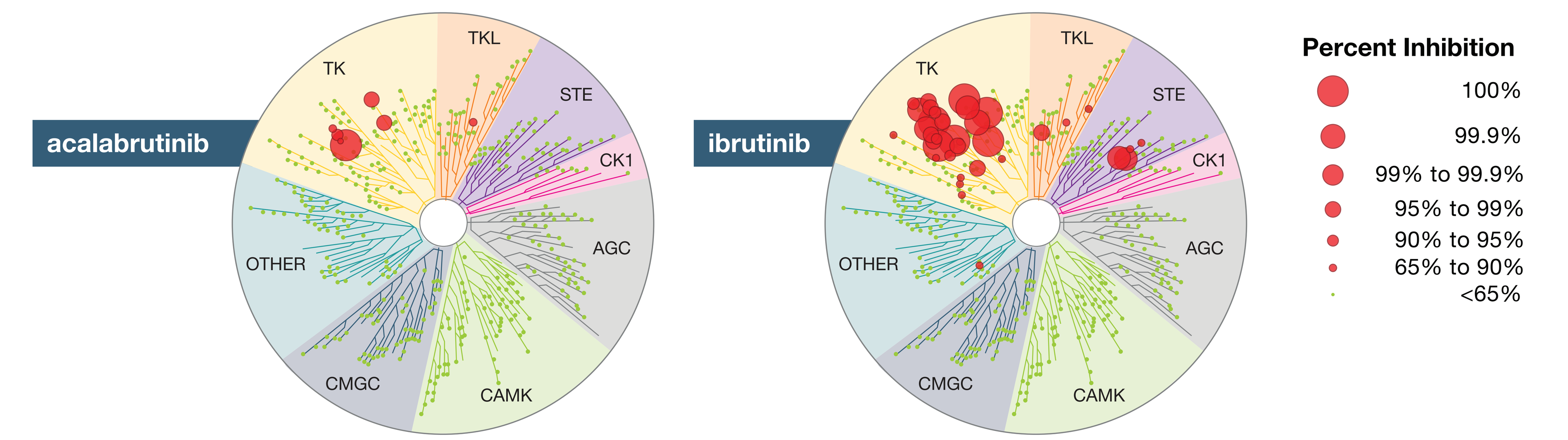
Conclusions

- In this analysis, cardiac AEs occurred in 17% of patients with CLL treated with acalabrutinib monotherapy and rarely resulted in acalabrutinib discontinuation; 91% of patients with cardiac AEs had pre-existing risk factors
 - The rate of cardiac AE onset was generally constant over time on study
 - 25% of grade ≥3 cardiac AEs were reported during the first 6 months on acalabrutinib
- Atrial fibrillation incidence with acalabrutinib was 4% with a median follow-up duration of 25.9 months; for comparison, the incidence of new onset atrial fibrillation was 6% after a median follow-up of 7.3 years in a CLL population with no prior history of atrial fibrillation[1]
- Overall, these data suggest a low risk of cardiac AEs with acalabrutinib in patients with CLL
- These findings are supported by the results of the phase 3, randomized ELEVATE-RR trial (ACE-CL-006; NCT02477696), which showed a statistically lower incidence of any-grade atrial fibrillation and hypertension with acalabrutinib versus ibrutinib in patients with previously treated CLL with del(17p) or del(11q)[2]

Introduction

- Cardiovascular (CV) toxicities have been associated with the first-generation Bruton tyrosine kinase inhibitor (BTKi) ibrutinib, potentially due to off-target kinase inhibition[3]
 - For example, findings from an analysis of 562 patients with lymphoid malignancies suggested an increased incidence of hypertension and atrial fibrillation with ibrutinib treatment, with rates of 78% and 13%, respectively, reported after a median follow-up of 30 months[4]
- The next-generation BTKi acalabrutinib has greater selectivity for BTK than ibrutinib *in vitro* (**Figure 1**),[5,6] which may result in an improved safety profile[3,6-8]
- This analysis characterized CV adverse events (AEs) in patients with chronic lymphocytic leukemia (CLL) who received acalabrutinib monotherapy in clinical trials

Figure 1. Kinome profiling using KINOMEscan at a single dose (1 μM)[9]


acalabrutinib
ibrutinib
TK
TKL
STE
CK1
AGC
CAMK
CMGC
OTHER
Percent Inhibition
100%
99.9%
99% to 99.9%
95% to 99%
90% to 95%
65% to 90%
<65%

Poster

Supplementary material

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Methods

- Data were included from a pooled population of patients treated with ≥1 dose of acalabrutinib monotherapy (N=762) (**Table 1**)
- Acalabrutinib was given orally at total daily doses of 100–400 mg and continued until progressive disease (PD) or toxicity
 - 78% of patients (n=596) received 100 mg twice daily (BID) dose only
 - 166 patients started on a different dose, of which 106 (14%) later switched to 100 mg BID
- Assessments:
 - Cardiac AEs (AEs categorized under the system organ class cardiac disorders)
 - Incidence, seriousness, severity, and relationship to acalabrutinib (per investigator assessment)
 - Time to onset and event duration
 - Event management and resolution (grade ≥3 cardiac AEs)
 - Incidence in first 6 months
 - Hypertension AEs (AEs categorized under the preferred term hypertension)
 - Incidence and time to onset
 - Cardiovascular and hypertension risk factors (based on patient medical histories)

Table 1. Pooled Studies

Study Name	Study Description	Number of Patients
ACE-CL-001 (NCT02029443)[6,10-12]	**Ph 1/2 study** of acalabrutinib in patients with CLL	301; TN/RR: 112/189
ACE-CL-007 (NCT02475681; **ELEVATE-TN**)[13a]	**Ph 3 study** of acalabrutinib ± O vs C+O in TN CLL	224; all TN
ACE-CL-309 (NCT02970318; **ASCEND**)[14]	**Ph 3 study** of acalabrutinib vs IdR or BR in RR CLL	189; all RR
15-H-0016 (NCT02337829)[15]	**Ph 2 study** of acalabrutinib in patients with RR or TN with del(17p) CLL	48; TN/RR: 16/32

BR, bendamustine plus rituximab; C, chlorambucil; IdR, idelalisib plus rituximab; O, obinutuzumab; Ph, phase; RR, relapsed/refractory; TN, treatment-naïve.
[a]Study has acalabrutinib monotherapy and combination therapy arms; only monotherapy patients were included.

Results

Patients, Exposure, and Disposition

- Patient demographics and baseline characteristics were similar between the total acalabrutinib population and the subgroup of patients with cardiac AEs (**Table 2**)
- Among all patients (N=762), median follow-up duration was 25.9 months (range, 0.0–58.5; n=761)
- Most patients (73%; n=553) remained on acalabrutinib at data cutoff
 - 208 patients (27%) discontinued acalabrutinib, most commonly due to PD (11%; n=82) or AEs (9%; n=70)
- 129 patients (17%) experienced cardiac AEs of any grade while on study; cardiac AEs led to acalabrutinib discontinuation in 7 patients (0.9%)
- 91% (n=117/129) of patients with cardiac AEs vs 80% (n=503/633) without cardiac AEs had ≥1 CV risk factor before starting acalabrutinib
 - The most prevalent CV risk factors (defined in Supplemental Methods) for patients with vs without cardiac AEs were hypertension (65% [n=84] vs 53% [n=333]), diabetes mellitus (19% [n=24] vs 12% [n=79]), hyperlipidemia (16% [n=21] vs 11% [n=67]), hypothyroidism (16% [n=21] vs 12% [n=73]), hypercholesterolemia (14% [n=18] vs 16% [n=104]), and atrial fibrillation (12% [n=16] vs 6% [n=40])

Table 2. Patient Demographics and Baseline Characteristics

Demographic/Baseline Characteristic	All Patients (N=762)	Patients With Cardiac Events (n=129)
Age, median (range), years	67.0 (32–89)	69.0 (42–84)
Male, n (%)	508 (67)	83 (64)
ECOG PS score ≤1, n (%)	707 (93)	122 (95)
Number of prior regimens, median (range)	1 (0–13)	1 (0–10)
Treatment-naïve disease, n (%)	352 (46)	58 (45)
Relapsed/refractory disease, n (%)	410 (54)	71 (55)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

- The most frequent any grade cardiac events were atrial fibrillation, palpitations, and tachycardia (**Table 3**)
- Among the 37 patients with grade ≥3 cardiac AEs, 18 (49%) were continuing acalabrutinib at data cutoff
 - 6 of the 37 patients (16%) discontinued acalabrutinib due to those grade ≥3 cardiac AEs (acute myocardial infarction [n=2], cardiac failure congestive [n=2], cardiac failure [n=1], cardiac tamponade [n=1])
 - 13 patients discontinued acalabrutinib due to other AEs (n=4), PD (n=5), death (n=3), and other reasons (n=1)

Results continued

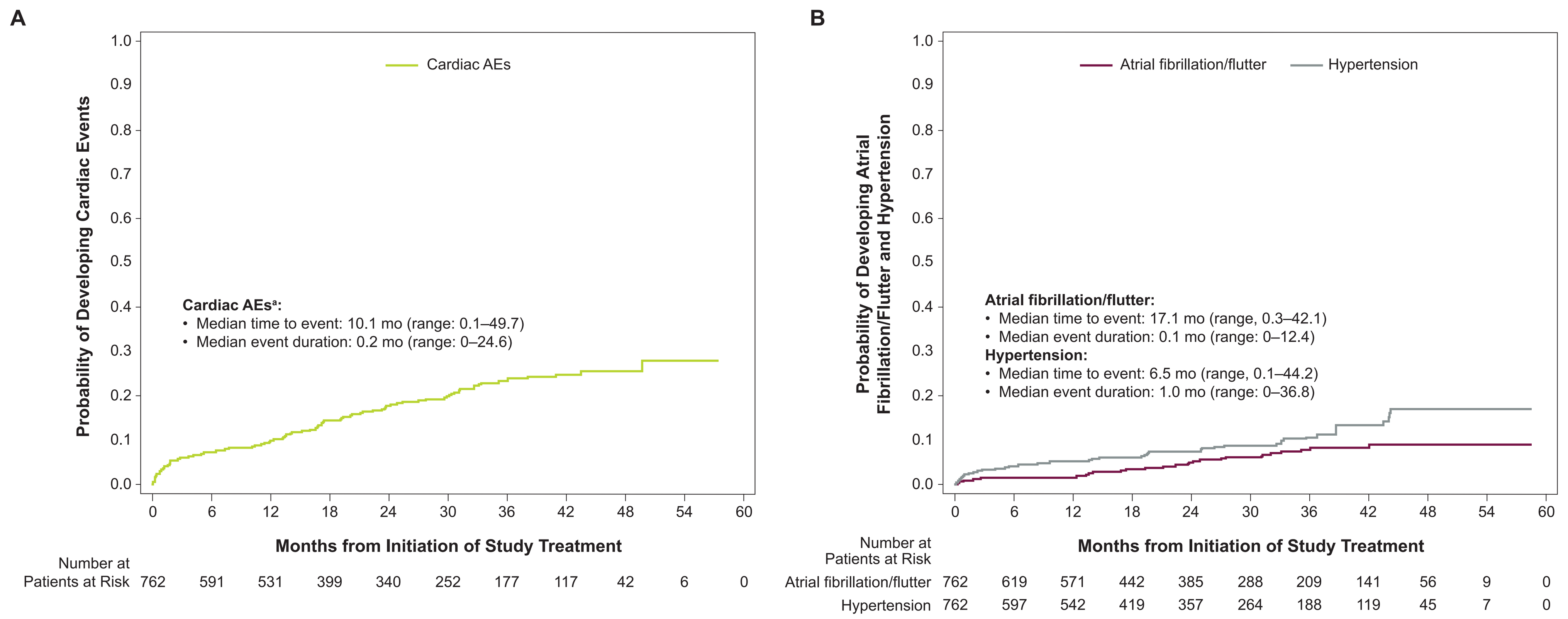
Table 3. Incidence of Cardiac Adverse Events

	All Patients (N=762)	
Event	Any Grade	Grade ≥3[c]
Any cardiac AE,[a] n (%),[b] [number of events]	129 (17), [199]	37 (5), [51]
Most common cardiac AEs (preferred terms; occurring in ≥4 patients), n (%), [number of events]		
Atrial fibrillation/flutter[d]	38 (5), [48]	11 (1), [12]
Atrial fibrillation	34 (4), [44]	10 (1), [11]
Atrial flutter	4 (0.5), [4]	1 (0.1), [1]
Palpitations	23 (3), [27]	0
Tachycardia	17[e] (2), [18]	0
Sinus tachycardia	11[e] (1), [13]	1 (0.1), [1]
Angina pectoris	10 (1), [11]	2 (0.3), [2]
Bradycardia	9 (1), [10]	2 (0.3), [2]
Cardiac failure	6 (0.8), [6]	3 (0.4), [3]
Acute myocardial infarction	5 (0.7), [6]	5 (0.7), [6]
Supraventricular tachycardia	4[e] (0.5), [4]	1 (0.1), [1]

[a]AEs categorized under the system organ class cardiac disorders.
[b]199 AEs were reported in 129 patients (17%). No events under the preferred terms "sudden death" or "sudden cardiac death" were reported.
[c]Other grade ≥3 AEs of interest included complete AV block (n=2; 0.3%), acute coronary syndrome (n=1; 0.1%), second-degree AV block (n=1; 0.1%), and ventricular fibrillation (n=1; 0.1%).
[d]Patients with "atrial fibrillation" or "atrial flutter" preferred terms combined. There was no overlap between patients with "atrial fibrillation" and "atrial flutter" events.
[e]One patient had both "tachycardia" and "sinus tachycardia" events. Another patient had both "sinus tachycardia" and "supraventricular tachycardia" events. A third patient had both "tachycardia" and "supraventricular tachycardia" events. All other reports of "tachycardia," "sinus tachycardia," and "supraventricular tachycardia" occurred in unique patients.
AE, adverse event; AV, atrioventricular.

- 51 grade ≥3 cardiac events were reported in 37 patients (grade 3=37; grade 4=12; grade 5=2)
 - Grade 5 events included acute myocardial infarction (patient had preexisting hypertension, type 2 diabetes mellitus, cardiovascular disorder, and chronic kidney disease) and congestive heart failure (patient had prior history of congestive cardiac failure, aortic stenosis, and atrial fibrillation)
 - 13 of the 51 events (in 9 patients) occurred in the first 6 months on acalabrutinib (**Supplemental Table 1**)
- Among the 51 grade ≥3 events:
 - 16 (31%) led to dose delay and 6 (12%) led to acalabrutinib discontinuation
 - 36 (71%) were managed with concomitant meds, and 43 (84%) resolved
 - Of the events that resolved, 15 were associated with dose delays, 4 resulted in drug withdrawal, and 24 had no associated dose modifications or changes
- Time to onset and duration of events are reported for cardiac events overall in **Figure 2A** and for atrial fibrillation/flutter and hypertension in **Figure 2B**
- Among 38 patients with atrial fibrillation/flutter, 7 (18%) had a prior history of arrhythmia/atrial fibrillation/flutter
- Among 67 patients with hypertension events, 43 (64%) had pre-existing hypertension
 - Other than pre-existing hypertension, the most common risk factors (incidence >5%) included hyperlipidemia (19% [n=13]), hypercholesterolemia (19% [n=13]), diabetes mellitus (10% [n=7]), coronary artery disease (9% [n=6]), chronic obstructive pulmonary disease (7% [n=5]), and coronary artery bypass (6% [n=4])

Figure 2. Time to Onset of (A) Cardiac Events[a] and (B) Atrial Fibrillation/Flutter and Hypertension


A
Cardiac AEs
Probability of Developing Cardiac Events
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Cardiac AEs[a]:
• Median time to event: 10.1 mo (range: 0.1–49.7)
• Median event duration: 0.2 mo (range: 0–24.6)
0 6 12 18 24 30 36 42 48 54 60
Months from Initiation of Study Treatment
Number at Patients at Risk 762 591 531 399 340 252 177 117 42 6 0
B
Atrial fibrillation/flutter
Hypertension
Probability of Developing Atrial Fibrillation/Flutter and Hypertension
Atrial fibrillation/flutter:
• Median time to event: 17.1 mo (range, 0.3–42.1)
• Median event duration: 0.1 mo (range: 0–12.4)
Hypertension:
• Median time to event: 6.5 mo (range, 0.1–44.2)
• Median event duration: 1.0 mo (range: 0–36.8)
0 6 12 18 24 30 36 42 48 54 60
Months from Initiation of Study Treatment
Number at Patients at Risk
Atrial fibrillation/flutter 762 619 571 442 385 288 209 141 56 9 0
Hypertension 762 597 542 419 357 264 188 119 45 7 0

[a]AEs categorized under the system organ class cardiac disorders.

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