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Letter to the Editor

Cumulative review of hypertension in patients with chronic lymphocytic leukemia treated with acalabrutinib

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Running head: Rates of hypertension with acalabrutinib for CLL

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Clinical Trial Information

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Data Sharing Statement

Data underlying the findings described in this manuscript 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/.

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Study investigator: AF, GF, KP

Enrolled patients: AF, GF, KP

Collection and assembly of data: YM, NB, VM

Data analysis: AF, YM, JR, NB, PM

Data interpretation: All authors

Manuscript preparation: All authors

Manuscript review and revisions: All authors

Final approval of manuscript: All authors

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a B-cell malignancy predominantly affecting older adults.[1,2] Comorbid cardiovascular disease in patients with CLL/SLL is correlated with higher mortality,[3] with hypertension among the most commonly occurring.[1]

Bruton tyrosine kinase (BTK) inhibitors have been associated with cardiovascular toxicities, including hypertension.[4] Acalabrutinib is a second-generation BTK inhibitor that has less off-target kinase inhibition than ibrutinib and zanubrutinib.[5] In the phase III ELEVATE-RR study, hypertension was less frequent with acalabrutinib (9.4%) versus ibrutinib (23.2%).[6] To more comprehensively compare hypertension rates with acalabrutinib versus other comparators, we performed a cumulative analysis of hypertension incidence and prevalence in patients with CLL/SLL in the acalabrutinib clinical trial database. We also analyzed hypertension prevalence before treatment initiation from claims data to provide a background hypertension rate from an untreated CLL/SLL population.

Patients with CLL/SLL who were treated with acalabrutinib with or without obinutuzumab and enrolled in 1 of 6 clinical trials within the acalabrutinib clinical database were included (phase I–II clinical trials: 15-H-0016, CL-001, CL-003; phase III clinical trials: ELEVATE-RR, ELEVATE-TN, ASCEND; **Supplemental Table 1**). All patients had CLL/SLL requiring treatment and had treatment-naive (TN) or relapsed/refractory (R/R) disease. Details regarding study populations and acalabrutinib dosing were previously published.[6-12] Because phase I–II clinical trials were included, acalabrutinib was administered at total daily doses ranging from 100–400 mg; most

patients in this analysis (>75%) received 100 mg twice daily. Treatment continued until progressive disease or toxicity. Comparator data included ibrutinib from ELEVATE-RR and other comparators, including obinutuzumab + chlorambucil from ELEVATE-TN and idelalisib + rituximab or bendamustine + rituximab from ASCEND; details on comparator dosing were also previously published.[6,11,12]

Data from patients with TN CLL/SLL from 3 fully adjudicated closed claims databases (Optum, MarketScan, IQVIA) were analyzed. The studies used in this analysis were conducted in accordance with the consensus ethical principles derived from international guidelines. Study protocols were approved by the institutional review boards. All patients provided written informed consent.

In the clinical database analysis, hypertension events and related preferred terms were defined using the “hypertension” narrow Standardized MedDRA Query per Medical Dictionary for Regulatory Activities (MedDRA) v25.1, which included new and worsening hypertension. New and worsening hypertension events were defined as treatment-emergent hypertension events among patients without and with past medical history (PMH) of hypertension, respectively. Hypertension prevalence was assessed at median treatment exposure, and exposure-adjusted incidence rate was measured in events/100 person-years per the following formula:

$$exposure\ adjusted\ incidence = \frac{N \times 100}{\sum_i t_i}$$

in which N is the number of events in the treatment arm, t_i is the duration of the treatment-emergent period (in years) for the patient i, and Σ_i is the sum across all patients in the treatment arm.

To provide a background prevalence, hypertension prevalence based on ICD-9 and ICD-10 codes was assessed in patients from the claims databases within 6 months prior to CLL/SLL treatment initiation.

In total, 1756 patients (TN CLL/SLL, n=660; R/R CLL/SLL, n=1096) from the clinical trial database were included; 947 (53.9%) received acalabrutinib monotherapy, 223 (12.7%) received acalabrutinib + obinutuzumab, 264 (15.0%) received ibrutinib as a comparator (from ELEVATE-RR), and 322 (18.3%) received other comparators (obinutuzumab + chlorambucil in ELEVATE-TN; idelalisib + rituximab or bendamustine + rituximab in ASCEND). Demographics and baseline characteristics were similar between treatment groups. PMH of hypertension was documented in 54.2% of patients treated with acalabrutinib monotherapy, 65.9% treated with acalabrutinib + obinutuzumab, 48.5% treated with ibrutinib, and 59.9% treated with other comparators (**Supplemental Table 2**).

Data from a total of 24,025 patients were analyzed from the claims databases, 9149 from Optum, 4058 from MarketScan, and 10,818 from IQVIA.

Hypertension prevalence among the 24,025 patients with TN CLL/SLL prior to treatment initiation included in the 3 claims databases ranged from 47.3–66.1% (**Figure 1A**). In the clinical trial data, hypertension prevalence during treatment was 59.6% in the 947 patients treated with acalabrutinib monotherapy (median treatment exposure: 47.3 months) and 70.0% in the 223 patients treated with acalabrutinib + obinutuzumab (median treatment exposure: 59.4 months) (**Figure 1B**).

Among the 1756 patients included in the clinical trial database, 270 (15.4%) experienced a treatment-emergent adverse event (new or worsening) of hypertension.

Among the 147 patients treated with acalabrutinib monotherapy who experienced hypertension, median age was 65 years, 66.0% were male, and 59.9% had hypertension at the time of acalabrutinib initiation (**Supplemental Table 3**).

The exposure-adjusted incidence rate of hypertension (any grade) was 4.205 in the 947 patients treated with acalabrutinib monotherapy, 3.926 in the 223 patients treated with acalabrutinib + obinutuzumab, 8.590 in the 264 patients treated with ibrutinib, and 4.788 in patients treated with other comparators (**Table 1**). A similar trend was observed for the exposure-adjusted incidence rate of grade ≥3 hypertension. The exposure-adjusted incidence rate of new-onset hypertension (any grade) was 3.718 in the 434 patients treated with acalabrutinib monotherapy, 2.620 in the 76 patients treated with acalabrutinib + obinutuzumab, 9.056 in the 136 patients treated with ibrutinib, and 4.746 in the 129 patients treated with other comparators (**Figure 2**). The exposure-adjusted incidence rate of new-onset grade ≥3 hypertension was low with acalabrutinib monotherapy (0.504) and acalabrutinib + obinutuzumab (0.291); the rate with ibrutinib was 2.145. In patients with a PMH of hypertension, the exposure-adjusted incidence rate of worsening hypertension was similar among most treatment groups, but was relatively higher with ibrutinib (**Figure 2**). Among patients with new-onset hypertension, 2.7% (n=4) treated with acalabrutinib monotherapy and 0 treated with acalabrutinib + obinutuzumab required new concomitant antihypertensives. Among patients with worsening hypertension, 6.8% (n=10) treated with acalabrutinib monotherapy and 5.1% (n=2) treated with acalabrutinib + obinutuzumab required new concomitant antihypertensives. No patients discontinued acalabrutinib treatment due to hypertension; 4 patients (2.7%) with worsening hypertension in the acalabrutinib

monotherapy group had their dose temporarily withheld, and 1 patient (2.6%) with worsening hypertension in the acalabrutinib + obinutuzumab group had their dose reduced.

The exposure-adjusted incidence rates of the most common hypertension preferred terms are provided in **Table 1**. In a subgroup analysis of patients from ELEVATE-RR, the exposure-adjusted incidence rate of any-grade hypertension in patients treated with acalabrutinib (3.053) was 2.8-fold lower than that reported in patients treated with ibrutinib (8.590) and similarly lower for grade ≥3 events (1.200 vs 3.146).

Based on our analysis of patients with CLL/SLL from large claims databases, hypertension is common, with hypertension prevalence prior to treatment initiation for CLL/SLL ranging from 47.3–66.1%. In patients treated with acalabrutinib from the clinical trial database, on-treatment hypertension prevalence was 59.6%. Similarly, previous clinical trial data analyses have shown that a number of patients with CLL/SLL develop new or worsening hypertension during an observation period regardless of treatment.[13] In the CLL12 study, a study of early intervention in patients with asymptomatic CLL, the event rate of new or worsening hypertension in patients assigned to the placebo arm was 8.3% at a median follow-up of 69.3 months.[13] In the ELEVATE-TN study, among patients with TN CLL treated with acalabrutinib monotherapy, 8.9% experienced hypertension at a median follow-up of 58.2 months.[14]

Our results suggest de novo hypertension (9.056) is more frequent than worsening hypertension (8.109) in patients treated with ibrutinib. These findings may have implications for clinical practice, as increased surveillance for de novo

hypertension development should be implemented in the management of patients receiving ibrutinib, particularly as hypertension management may differ based on whether the patient has pre-existing hypertension or develops de novo hypertension.[15]

Our results are consistent with previously reported safety data in patients treated with acalabrutinib. In an analysis of ELEVATE-RR, exposure-adjusted incidence rate (events per 100 person-months) of hypertension as a selected event of clinical interest (as defined by MedDRA v23.0) was 3 times higher with ibrutinib (1.2) than with acalabrutinib (0.4) for any-grade events and 4 times higher with ibrutinib (0.4) than with acalabrutinib (0.1) for grade ≥3 events.[16]

A limitation of this analysis is that the 6 clinical studies were not designed to detect differences in hypertension rates between treatment groups; therefore, no statistical comparisons were performed. The analysis was also not designed to provide statistically valid cross-trial comparisons. In addition, a small number of patients treated with acalabrutinib monotherapy did not receive the 100 mg twice-daily dosing because some included studies started before the dose was standardized. Another limitation is that the reporting of hypertension prevalence rates prior to treatment provided by claims databases is dependent on ICD-9 and ICD-10 codes used to define hypertension, and therefore may be influenced by possible cases of errors or omission in coding. However, the purpose of using these claims data was to provide a background rate of hypertension in patients with CLL/SLL prior to treatment initiation, not to provide comparisons with clinical trial data. Lastly, our analysis does not explore the mechanisms behind BTK inhibitor–induced hypertension, which are not well understood.

In summary, exposure-adjusted incidence rates of new or worsening hypertension in patients with CLL/SLL receiving treatment with acalabrutinib monotherapy and acalabrutinib + obinutuzumab in this analysis were low overall. Our analysis suggests that acalabrutinib monotherapy does not worsen pre-existing hypertension or increase the risk of new-onset hypertension in patients with CLL/SLL.

REFERENCES

1. Larsson K, Mattsson M, Ebrahim F, Glimelius I, Höglund M. High prevalence and incidence of cardiovascular disease in chronic lymphocytic leukaemia: a nationwide population-based study. Br J Haematol. 2020;190(4):e245-e248.
2. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021;96(12):1679-1705.
3. Rotbain EC, Niemann CU, Rostgaard K, da Cunha-Bang C, Hjalgrim H, Frederiksen H. Mapping comorbidity in chronic lymphocytic leukemia: impact of individual comorbidities on treatment, mortality, and causes of death. Leukemia. 2021;35(9):2570-2580.
4. Sestier M, Hillis C, Fraser G, Leong D. Bruton's tyrosine kinase inhibitors and cardiotoxicity: more than just atrial fibrillation. Curr Oncol Rep. 2021;23(10):113.
5. Podoll T, Pearson PG, Kaptein A, et al. Identification and characterization of ACP-5862, the major circulating active metabolite of acalabrutinib: both are potent and selective covalent Bruton tyrosine kinase inhibitors. J Pharmacol Exp Ther. 2023;384(1):173-186.
6. 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. 2021;39(31):3441-3452.
7. Sun CCL, Nierman PK, Kendall EK, et al. Clinical and biological implications of target occupancy in CLL treated with the BTK inhibitor acalabrutinib. Blood. 2020;136(1):93-105.

8. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):323-332.
9. Woyach JA, Blachly JS, Rogers KA, et al. Acalabrutinib plus obinutuzumab in treatment-naive and relapsed/refractory chronic lymphocytic leukemia. Cancer Discov. 2020;10(3):394-405.
10. Byrd JC, Woyach JA, Furman RR, et al. Acalabrutinib in treatment-naïve chronic lymphocytic leukemia. Blood. 2021;137(24):3327-3338.
11. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020;395(10232):1278-1291.
12. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2020;38(25):2849-2861.
13. Langerbeins P, Robrecht S, Nieper P, et al. Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): final results of the CLL12 trial [abstract 024]. Hematol Oncol. 2023;41(S2):56-58.
14. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: 5-year follow-up of ELEVATE-TN [abstract P666]. Hemasphere. 2022;6(S3):564-565.

15. Samples L, Voutsinas JM, Fakhri B, et al. Hypertension treatment in patients receiving ibrutinib: a multicenter retrospective study. Blood Adv. 2024;8(9):2085-2093.

16. Seymour JF, Byrd JC, Ghia P, et al. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. Blood. 2023;142(8):687-699.

Table 1. Exposure-adjusted incidence rates of “hypertension” SMQ (narrow) by preferred terms

	Acalabrutinib monotherapy (N=947)		Acalabrutinib + Obinutuzumab (N=223)		Ibrutinib[a] (N=264)		Comparators[b] (N=322)	
Hypertension, events/100 person-years	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
“Hypertension” SMQ (narrow)	4.205	1.659	3.926	1.208	8.590	3.146	4.788	2.210
Blood pressure increased	0.114	0.029	0	0	0.363	0.242	0	0
Blood pressure systolic increased	0	0	0	0	0.121	0	0	0
Essential hypertension	0.029	0.029	0	0	0	0	0	0
Hypertension	4.005	1.573	3.826	1.208	8.469	3.025	4.788	2.210
Hypertensive crisis	0.029	0	0.101	0	0	0	0	0
Hypertensive heart disease	0	0	0.101	0	0	0	0	0
Malignant hypertension	0.029	0.029	0	0	0	0	0	0

CLL, chronic lymphocytic leukemia; MedDRA, Medical Dictionary for Regulatory Activities; R/R, relapsed/refractory; SMQ, Standardized MedDRA Query.

[a]Patients with R/R CLL from ELEVATE-RR.

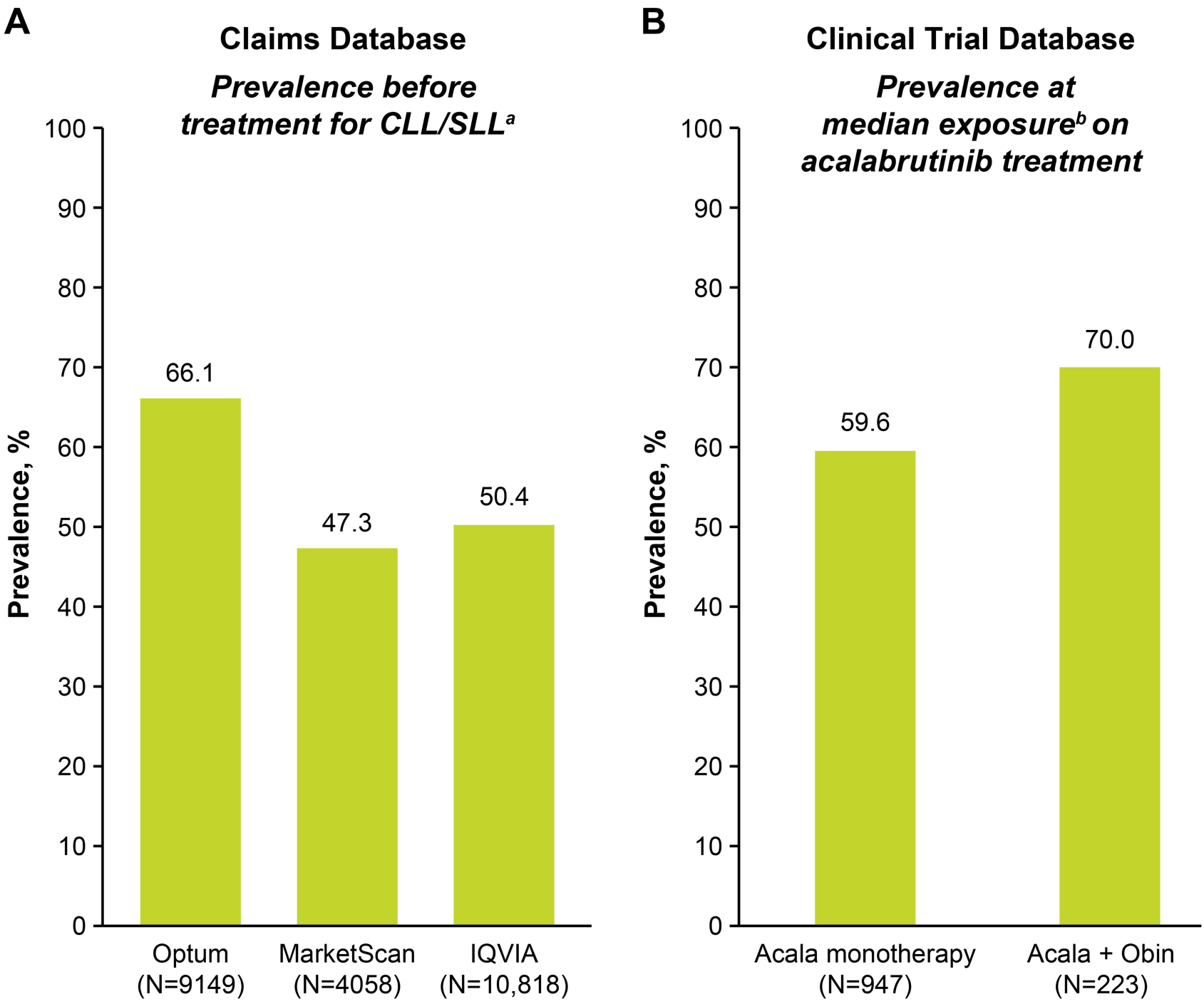
[b]Patients with CLL treated with obinutuzumab + chlorambucil (ELEVATE-TN), idelalisib + rituximab (ASCEND), or bendamustine + rituximab (ASCEND).

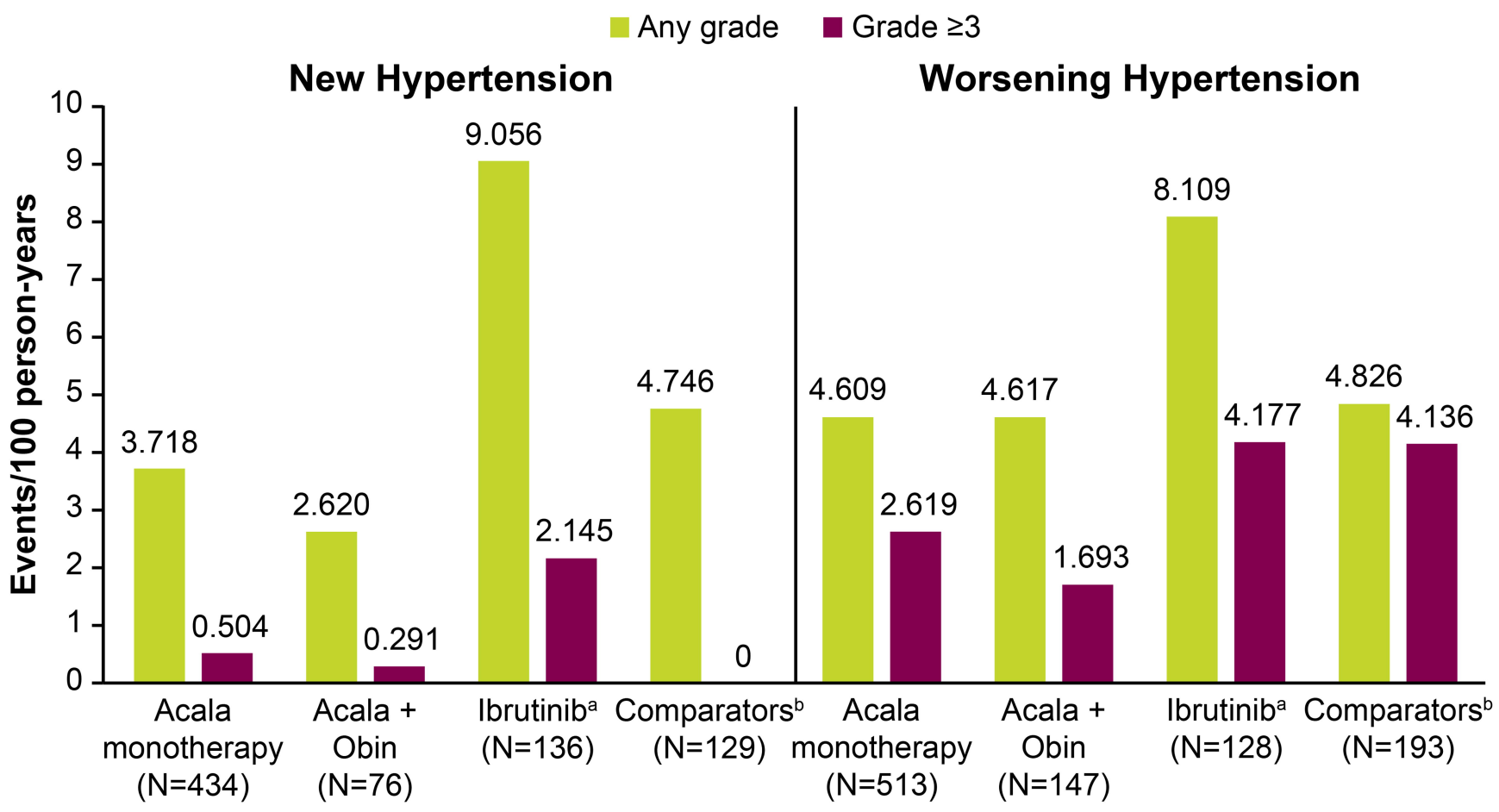
FIGURE LEGENDS

Figure 1. Hypertension prevalence in patients with CLL/SLL.

A: Prevalence of hypertension in patients before the start of CLL/SLL treatment in the claims database. B: Prevalence of hypertension in patients treated with acalabrutinib in the clinical trial database. Acala, acalabrutinib; CLL, chronic lymphocytic leukemia; Obin, obinutuzumab; SLL, small lymphocytic lymphoma. [a]Proportion of CLL/SLL patients with hypertension diagnosis who were within 6 months of initiating treatment for CLL/SLL. [b]Median treatment exposure of 47.3 months for acalabrutinib monotherapy and 59.4 months for acalabrutinib + obinutuzumab.

Figure 2. Exposure-adjusted incidence rate of new and worsening hypertension in patients with CLL/SLL according to treatment. Exposure-adjusted incidence rate of new and worsening hypertension in the subset of patients without and with prior history of hypertension, respectively. Acala, acalabrutinib; CLL, chronic lymphocytic leukemia; Obin, obinutuzumab; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma. [a]Patients with R/R CLL from ELEVATE-RR. [b]Patients with CLL treated with obinutuzumab + chlorambucil (ELEVATE-TN), idelalisib + rituximab (ASCEND), or bendamustine + rituximab (ASCEND).


A
Claims Database
Prevalence before treatment for CLL/SLL[a]
Prevalence, %
100
90
80
70
60
50
40
30
20
10
0
66.1
47.3
50.4
Optum (N=9149)
MarketScan (N=4058)
IQVIA (N=10,818)
B
Clinical Trial Database
Prevalence at median exposure[b] on acalabrutinib treatment
Prevalence, %
59.6
70.0
Acala monotherapy (N=947)
Acala + Obin (N=223)


Any grade
Grade ≥3
New Hypertension
Worsening Hypertension
Events/100 person-years
10
9
8
7
6
5
4
3
2
1
0
3.718
0.504
2.620
0.291
9.056
2.145
4.746
0
4.609
2.619
4.617
1.693
8.109
4.177
4.826
4.136
Acala monotherapy (N=434)
Acala + Obin (N=76)
Ibrutinib[a] (N=136)
Comparators[b] (N=129)
Acala monotherapy (N=513)
Acala + Obin (N=147)
Ibrutinib[a] (N=128)
Comparators[b] (N=193)

Supplemental Information

Supplemental Table 1. Study summaries

Study Name	Study Description	Treatments	Number of Patients
15-H-0016 (NCT02337829)	Phase II study in patients with R/R CLL/SLL or TN CLL/SLL with del(17p)	Acalabrutinib monotherapy	48 (TN, n=16; R/R, n=32)
ACE-CL-001 (NCT02029443)	Phase I–II study in patients with TN or R/R CLL/SLL	Acalabrutinib monotherapy	301 (TN, n=99; R/R, n=202)
ACE-CL-003 (NCT02296918)	Phase Ib study in patients with TN or R/R CLL/SLL	Acalabrutinib + obinutuzumab	45 (TN, n=19; R/R, n=26)
ACE-CL-006 (NCT02477696; ELEVATE-RR)	Phase III study in patients with R/R CLL	Acalabrutinib monotherapy vs ibrutinib	529 (R/R, n=529)
ACE-CL-007 (NCT02475681; ELEVATE-TN)	Phase III study in patients with TN CLL	Acalabrutinib monotherapy or acalabrutinib + obinutuzumab vs obinutuzumab + chlorambucil	526 (TN, n=526)
ACE-CL-309 (NCT02970318; ASCEND)	Phase III study in patients with R/R CLL	Acalabrutinib monotherapy vs idelalisib + rituximab or bendamustine + rituximab	307 (R/R, n=307)

CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naive.

Supplemental Table 2. Patient demographics and baseline characteristics

Characteristic	Acalabrutinib Monotherapy (N=947)	Acalabrutinib + Obinutuzumab (N=223)	Ibrutinib[a] (N=264)	Comparators[b] (N=322)
Age, median (range), y	67 (32–89)	69 (41–88)	65 (28–88)	69 (34–91)
P-value*	–	0.0024	0.5552	<0.0001
Male, n (%)	636 (67.2)	143 (64.1)	193 (73.1)	202 (62.7)
P-value*	–	0.3875	0.0660	0.1474
PMH of hypertension, n (%)[c]	513 (54.2)	147 (65.9)	128 (48.5)	193 (59.9)
P-value*	–	0.0015	0.1017	0.0720
Number of concomitant antihypertensive agents, n (%)				
1	154 (16.3)	43 (19.3)	53 (20.1)	51 (15.8)
P-value*	–	0.2781	0.1455	0.8585
2	106 (11.2)	40 (17.9)	37 (14.0)	42 (13.0)
P-value*	–	0.0061	0.2090	0.3716
3	54 (5.7)	19 (8.5)	13 (4.9)	24 (7.5)
P-value*	–	0.1175	0.6249	0.2584
>3	29 (3.1)	10 (4.5)	18 (6.8)	13 (4.0)
P-value*	–	0.2872	0.0052	0.3982
Body mass index, kg/m^2				
Mean (SD)	27.3 (5.0)	27.9 (5.4)	27.3 (4.9)	27.2 (4.9)
Median (range)	26.6 (15.8–48.9)	27.0 (18.1–50.5)	27.1 (17.8–54.5)	26.7 (15.6–46.3)
P-value*	–	0.3061	0.9984	0.9880

Body mass index category (kg/m^2), n (%)				
25 to <30 (overweight)	391 (41.3)	86 (38.6)	113 (42.8)	131 (40.7)
P-value*	–	0.4566	0.6588	0.8488
≥30 (obese)	223 (23.5)	62 (27.8)	64 (24.2)	81 (25.2)
P-value*	–	0.1830	0.8145	0.5594
Smoking status (yes), n/N (%)[d]	184/443 (41.5)	76/178 (42.7)	110/264 (41.7)	76/169 (45.0)
Former, n (%)	153 (34.5)	56 (31.5)	84 (31.8)	56 (33.1)
P-value*	–	0.0007	<.0001	0.6376
Current, n (%)	31 (7.0)	20 (11.2)	26 (9.8)	20 (11.8)
P-value*	–	0.0002	<0.0001	0.0204
Chronic kidney disease, n (%)[e]	67 (7.1)	12 (5.4)	19 (7.2)	18 (5.6)
P-value*	–	0.3645	0.9456	0.3572
Sleep apnea syndrome, n (%)	52 (5.5)	15 (6.7)	8 (3.0)	14 (4.3)
P-value*	–	0.4750	0.1033	0.4248
Diabetes mellitus[f]	177 (18.7)	58 (26.0)	50 (18.9)	64 (19.9)
P-value*	–	0.0141	0.9270	0.6395
Dyslipidemia[g]	264 (27.9)	86 (38.6)	64 (24.2)	94 (29.2)
P-value*	–	0.0017	0.2399	0.6506

CLL, chronic lymphocytic leukemia; MedDRA, Medical Dictionary for Regulatory Activities; PMH, past medical history; R/R, relapsed/refractory; SD, standard deviation; SMQ, Standardized MedDRA Query; y, years.

*Versus acalabrutinib monotherapy.

[a]Patients with R/R CLL from ELEVATE-RR.

[b]Patients with CLL treated with obinutuzumab + chlorambucil (ELEVATE-TN), idelalisib + rituximab (ASCEND), or bendamustine + rituximab (ASCEND).

[c]PMH of hypertension defined as MedDRA v25.1 (narrow) hypertension SMQ.

[d]Among patients whose smoking habits were collected.
[e]Aggregate term that includes the following terms: chronic kidney disease, dialysis, dialysis device insertion, glomerulonephritis chronic, hyperparathyroidism secondary, kidney fibrosis, and renal failure.
[f]Aggregate term that includes the following terms: blood glucose increased, diabetes mellitus, gestational diabetes, glucose tolerance impaired, glycosylated hemoglobin increased, hyperglycemia, impaired fasting glucose, insulin resistance, steroid diabetes, type 1 diabetes mellitus, type 2 diabetes mellitus, and type 3 diabetes mellitus.
[g]Aggregate term that includes the following terms: blood cholesterol increased, blood triglycerides increased, diabetic dyslipidemia, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, lipid metabolism disorder, lipids abnormal, lipoprotein (a) increased, metabolic syndrome, type IIa hyperlipidemia, type V hyperlipidemia.

Supplemental Table 3. Patient demographics and baseline characteristics in patients who experienced hypertension

Characteristic	Acalabrutinib Monotherapy (N=147)	Acalabrutinib + Obinutuzumab (N=39)	Ibrutinib[a] (N=71)	Comparators[b] (N=13)
Age, median (range), y	65 (44–85)	67 (44–88)	65 (49–83)	66 (43–84)
P-value*	–	0.5883	0.7832	0.7061
Male, n (%)	97 (66.0)	26 (66.7)	53 (74.6)	12 (92.3)
P-value*	–	0.9364	0.1958	0.0509
PMH of hypertension, n (%)[c]	88 (59.9)	30 (76.9)	33 (46.5)	7 (53.8)
P-value*	–	0.0492	0.0624	0.6720
Number of concomitant antihypertensive agents, n (%)				
1	29 (19.7)	10 (25.6)	26 (36.6)	5 (38.5)
P-value*	–	0.4200	0.0071	0.1135
2	18 (12.2)	9 (23.1)	14 (19.7)	3 (23.1)
P-value*	–	0.0878	0.1440	0.2676
3	10 (6.8)	5 (12.8)	4 (5.6)	2 (15.4)
P-value*	–	0.2198	0.7415	0.2602
>3	9 (6.1)	1 (2.6)	8 (11.3)	1 (7.7)
P-value*	–	0.3811	0.1843	0.8227
Body mass index, kg/m^2				
Mean (SD)	27.5 (4.8)	27.5 (4.1)	28.2 (5.7)	27.1 (4.8)

Median (range)	26.7 (15.8–45.0)	27.3 (18.7–36.4)	27.4 (19.3–54.5)	26.3 (19.6–35.0)
P-value*	–	1.0000	0.7197	0.9943
Body mass index category (kg/m^2), n (%)				
25 to <30 (overweight)	58 (39.5)	18 (46.2)	33 (46.5)	3 (23.1)
P-value*	–	0.4494	0.3244	0.2438
≥30 (obese)	40 (27.2)	9 (23.1)	19 (26.8)	4 (30.8)
P-value*	–	0.6024	0.9441	0.7830
Smoking status (yes), n (%)[d]	16/44 (36.4)	6/17 (35.3)	34/71 (47.9)	3/6 (50.0)
Former	15 (34.1)	6 (35.3)	28 (39.4)	2 (33.3)
P-value*	–	0.3635	<0.0001	0.5612
Current	1 (2.3)	0	6 (8.5)	1 (16.7)
P-value*	–	N/C	N/C	N/C
Chronic kidney disease, n (%)[e]	12 (8.2)	2 (5.1)	5 (7.0)	2 (15.4)
P-value*	–	0.5230	0.7724	0.3771
Sleep apnea syndrome, n (%)	9 (6.1)	7 (17.9)	4 (5.6)	0
P-value*	–	N/C	N/C	N/C
Diabetes mellitus[f]	17 (11.6)	15 (38.5)	10 (14.1)	1 (7.7)
P-value*	–	<0.0001	0.5966	0.6719
Dyslipidemia[g]	52 (35.4)	17 (43.6)	18 (25.4)	4 (30.8)
P-value*	–	0.3451	0.1375	0.7386

CLL, chronic lymphocytic leukemia; MedDRA, Medical Dictionary for Regulatory Activities; N/C, not calculated; PMH, past medical history; R/R, relapsed/refractory; SD, standard deviation; SMQ, Standardized MedDRA Query; y, years.

*Versus acalabrutinib monotherapy. *P*-values were not calculated when numbers were low.
[a]Patients with R/R CLL from ELEVATE-RR.
[b]Patients with CLL treated with obinutuzumab + chlorambucil (ELEVATE-TN), idelalisib + rituximab (ASCEND), or bendamustine + rituximab (ASCEND).
[c]PMH of hypertension defined as MedDRA v25.1 (narrow) hypertension SMQ.
[d]Among patients whose smoking habits were collected.
[e]Aggregate term that includes the following terms: chronic kidney disease, dialysis device insertion, glomerulonephritis chronic, kidney fibrosis, and renal failure.
[f]Aggregate term that includes the following terms: diabetes mellitus, glucose tolerance impaired, glycosylated hemoglobin increased, hyperglycemia, impaired fasting glucose, insulin resistance, type 1 diabetes mellitus, and type 2 diabetes mellitus.
[g]Aggregate term that includes the following terms: blood cholesterol increased, diabetic dyslipidemia, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia.