LEUCEMIA LINFATICA CRONICA, OGGI... ED OLTRE

Il profilo di tossicità: non può che giocare un ruolo nella scelta

SISTEMA SANITARIO REGIONALE
IRCCS ISTITUTI FISIOTERAPICI OSPITALIERI

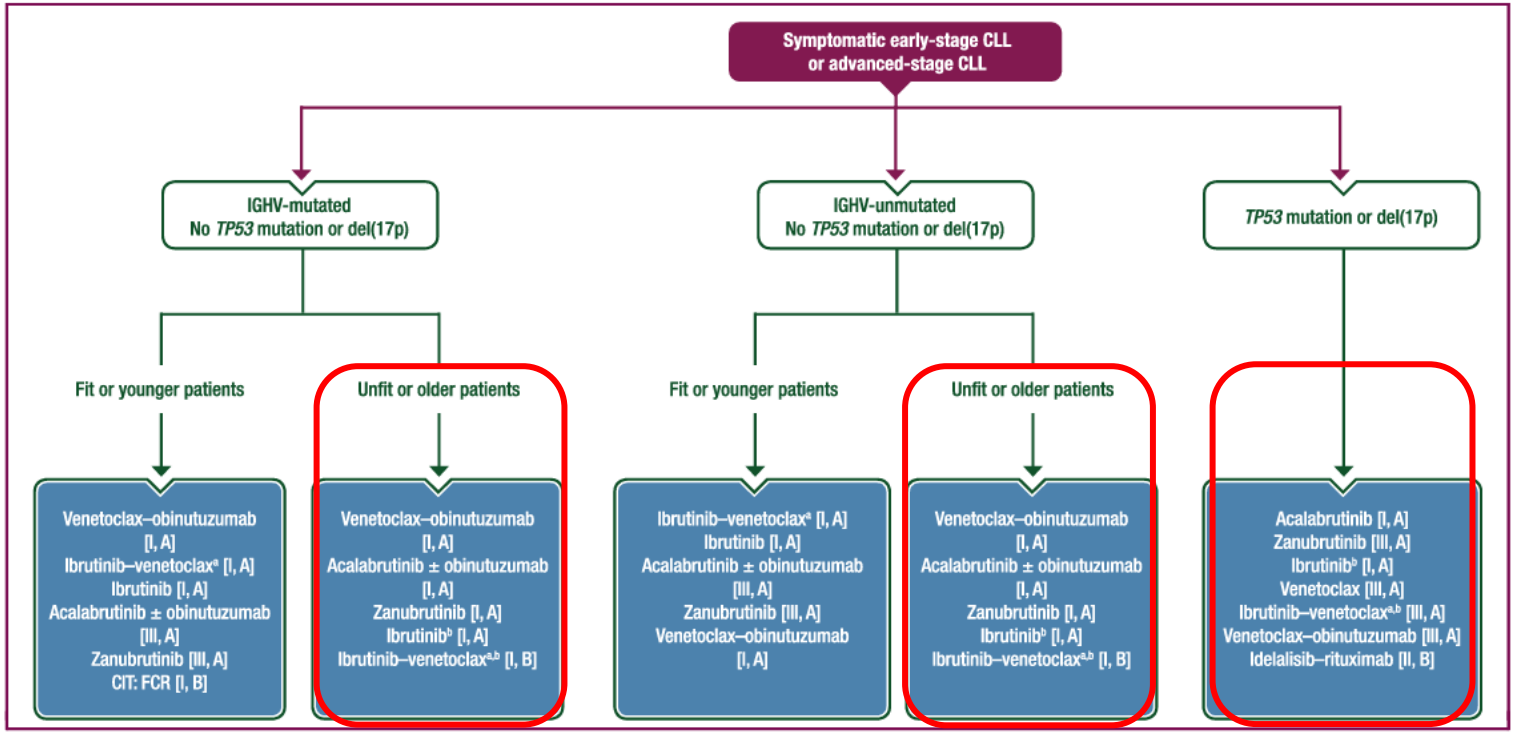
Paolo Falcucci
Ematologia
IRCCS Istituto Nazionale Tumori Regina Elena - Roma

IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA
ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Cagliari, Hotel Regina Margherita – 16 Ottobre 2024

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	-	-	-	-	-	-	x
AstraZeneca	-	-	-	-	-	-	x
Beigene	-	-	-	-	-	x	x
Janssen	-	-	-	-	-	-	x

ESMO clinical practice guideline interim update 2024



[b]Ibrutinib or ibrutinib–venetoclax should be considered carefully in older patients with cardiac comorbidities.

Eichhorst B et al. Ann Oncol 2024

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Acalabrutinib[f,g,*] ± obinutuzumab (category 1) • Venetoclax[f,h] + obinutuzumab (category 1) • Zanubrutinib[f,g,*] (category 1)	• Ibrutinib [f,g,i,*] (category 1) • Ibrutinib[f,g,*] + obinutuzumab (category 2B) • Ibrutinib[f,g,*] + rituximab[j] (category 2B) • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[k,l,m] • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[n] + anti-CD20 mAb[o,p] ▸ Obinutuzumab ± chlorambucil[q] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[o] (category 2B; category 3 for patients <65 y without significant comorbidities)

Covalent BTKi

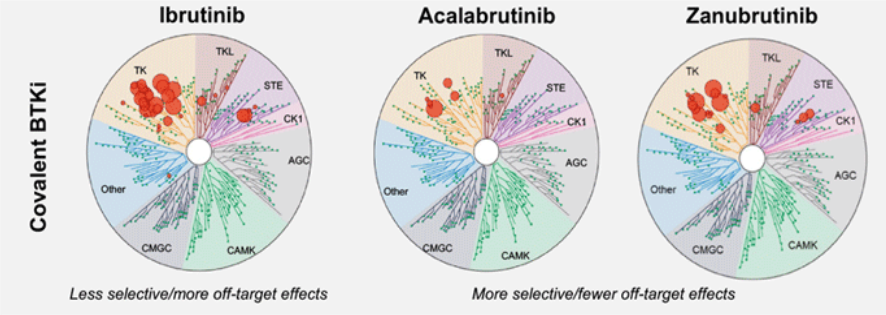
SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL With del(17p)/*TP53* Mutation
(alphabetical by category)

CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

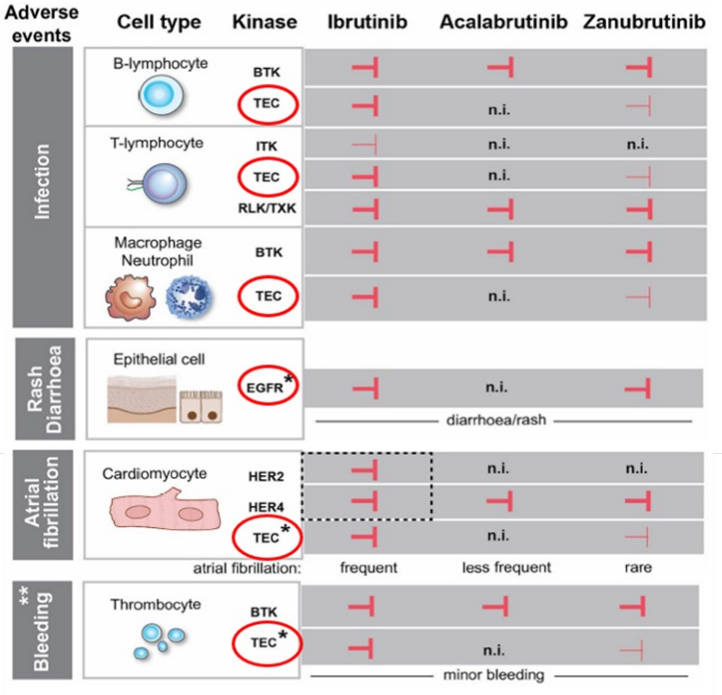
FIRST-LINE THERAPY[e]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Acalabrutinib[f,g,*] ± obinutuzumab • Venetoclax[f,h] + obinutuzumab • Zanubrutinib[f,g,*]	• Ibrutinib[f,g,i,*] • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ HDMP + anti-CD20 mAb[o] ▸ Obinutuzumab

Selectivity: kinome profiling of BTK Inhibitors using DiscoverX KINOMEscan

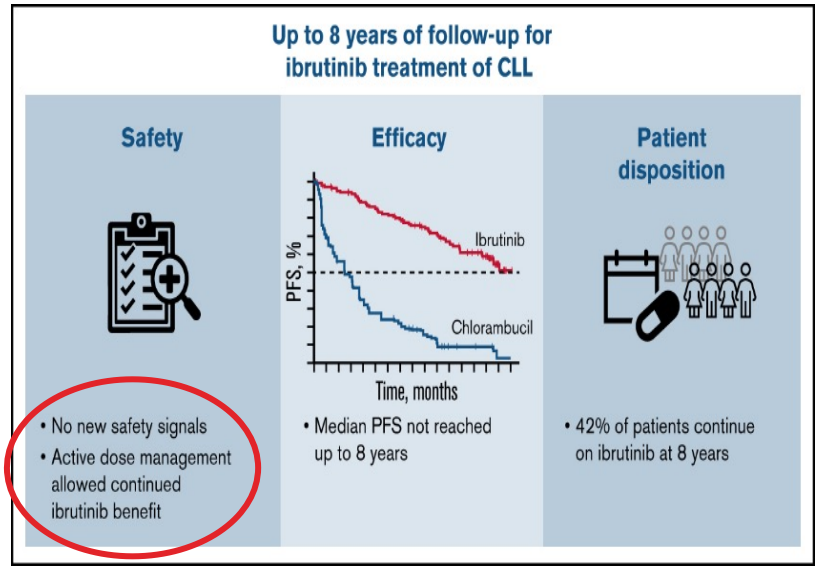


Less selective BTK inhibitors have more off-target effects, which contribute to more toxicity compared with more selective agents[2]



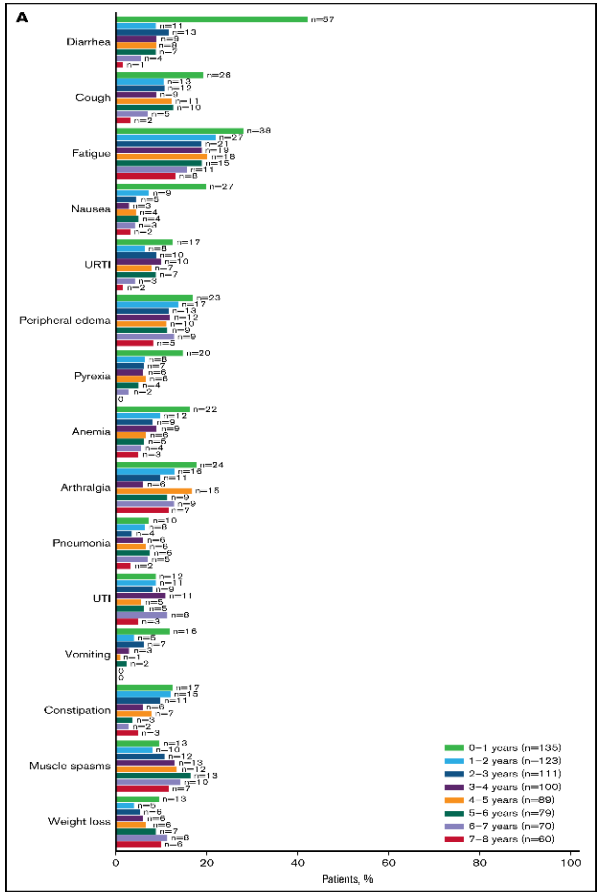
Estupinan et al. Frontiers in Cell and Dev Biology 2021
Herman et al. ClinCancer Res. 2017

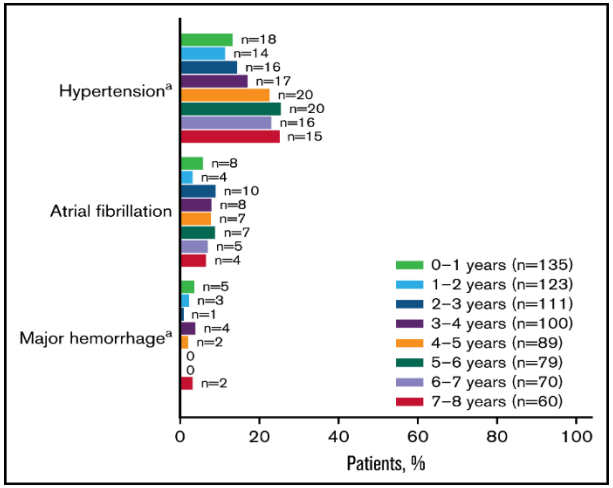
RESONATE-2: first-line Ibrutinib treatment for patients with chronic lymphocytic leukemia



	First line Ibrutinib (n=136)
Median duration of Ibrutinib treatment, (years) range	6.2 (0.06-8.1)
Continuing Ibrutinib on study, n (%)	57 (42)
Discontinued Ibrutinib, n (%)	
• AE	32 (24)
• PD	18 (13)
• Death	12 (9)
• Withdrawal by patients	9 (7)
• Investigatior decision	7 (5)

Barr PM et al. Up to 8-year follow-up from RESONATE-2. Blood Advances 2022; 6 (11): 3440-3450.





The most frequent **AEs** of any grade with Ibrutinib were:

- **diarrhea** (50%)
- **cough** (37%)
- **fatigue** (37%)

AEs of clinical interest:

- **hypertension:** prevalence rates (grades 1-3) were 25%, 23%, and 25% of patients in years 5-6, 6-7, and 7-8, respectively.
  Overall, grade 3 hypertension occurred in 17 (12%) patients

- **atrial fibrillation:** prevalence rates (grades 1-3) over time were 9%, 7%, and 7% of patients in years 5-6, 6-7, and 7-8, respectively.
  Overall, grade 3 atrial fibrillation occurred in 8 (6%) patients.

Barr PM et al. Up to 8-year follow-up from RESONATE-2. Blood Advances 2022; 6 (11): 3440-3450.

Presentation #636

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN

Jeff P. Sharman,[1] Miklos Egyed,[2] Wojciech Jurczak,[3] Alan Skarbnik,[4] Krish Patel,[5] Ian W. Flinn,[6] Manali Kamdar,[7] Talha Munir,[8] Renata Walewska,[9] Marie Hughes,[10] Laura Maria Fogliatto,[11] Yair Herishanu,[12] Versha Banerji,[13] George Follows,[14] Patricia Walker,[15] Karin Karlsson,[16] Paolo Ghia,[17] Ann Janssens,[18] Florence Cymbalista,[19] John C. Byrd,[20] Emmanuelle Ferrant,[21] Alessandra Ferrajoli,[22] William G. Wierda,[22] Veerendra Munugalavadla,[23] Catherine Wangui Wachira,[24] Chuan-Chuan Wun,[23] Jennifer A. Woyach[20]

[1]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR, USA; [2]Somogy County Mór Kaposi General Hospital, Kaposvár, Hungary; [3]Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; [4]Novant Health Cancer Institute, Charlotte, NC, USA; [5]Swedish Cancer Institute, Seattle, WA, USA; [6]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [7]University of Colorado Cancer Center, Aurora, CO, USA; [8]Haematology, Haematological Malignancy Diagnostic Service (HMDS), St. James's Institute of Oncology, Leeds, United Kingdom; [9]Cancer Care, University Hospitals Dorset, Bournemouth, United Kingdom; [10]Tauranga Hospital, Tauranga, New Zealand; [11]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [12]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [13]Departments of Internal Medicine, Biochemistry & Medical Genetics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba and CancerCare Manitoba, Winnipeg, Canada; [14]Department of Haematology, Addenbrooke's Hospital NHS Trust, Cambridge, United Kingdom; [15]Peninsula Health and Peninsula Private Hospital, Frankston, Melbourne, Australia; [16]Skåne University Hospital, Lund, Sweden; [17]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [18]University Hospitals Leuven, Leuven, Belgium; [19]Bobigny: Hématologie, CHU Avicennes, Bobigny, France; [20]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [21]Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service d'Hématologie Clinique, Pierre-Bénite, France; [22]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [23]AstraZeneca, South San Francisco, CA, USA; [24]AstraZeneca, New York, NY, USA

Presented at the American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023

ELEVATE-TN study design

TN CLL (N=535)

Key inclusion criteria

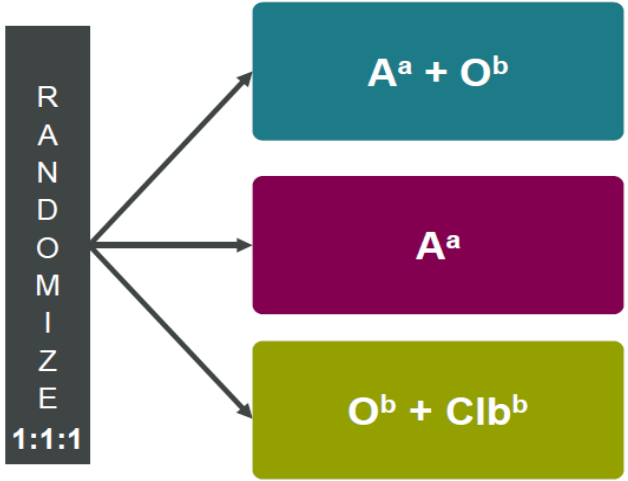
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.
[b]Treatments were fixed duration and administered for 6 cycles.

ELEVATE-TN: events of clinical interest for Acalabrutinib

6 year follow-up

Safety

	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	49 (27.5)	22 (12.4)	42 (23.5)	21 (11.7)
Atrial fibrillation	13 (7.3)	3 (1.7)	16 (8.9)	3 (1.7)
Bleeding	95 (53.4)	12 (6.7)	81 (45.3)	8 (4.5)
Major bleeding	16 (9.0)	12 (6.7)	10 (5.6)	8 (4.5)
Hypertension[a]	20 (11.2)	8 (4.5)	20 (11.2)	9 (5.0)
Infections	147 (82.6)	63 (35.4)	144 (80.4)	50 (27.9)
SPMs	36 (20.2)	18 (10.1)	35 (19.6)	9 (5.0)
SPMs excluding non-melanoma skin	24 (13.5)	13 (7.3)	22 (12.3)	7 (3.9)

Hypertension and AF was low also at 74.5 months of follow-up

SEQUOIA: study design

multicenter, multicohort, open-label, part-randomized phase III trial

PHASE 3

Study Identifier: BGB-3111-304, NCT03336333

Primary Endpoint: PFS by IRC in Cohort 1

Key Secondary Endpoints: Cohort 1: ORR, DOR, safety; Cohort 2: ORR, PFS, DOR; Cohort 3: ORR, PFS, DOR, rate of undetectable MRD at $<10^{-4}$ sensitivity; safety

KEY ELIGIBILITY CRITERIA

- Treatment-naïve CLL/SLL
- Met iwCLL criteria for treatment
- ≥65 years of age or <65 years of age and unsuitable for FCR treatment
- Measurable disease by CT/MRI
- No current or past history of Richter's transformation

STRATIFICATION FACTORS

- Age (<65 vs. ≥65 years)
- Binet stage (C vs. A or B)
- *IGHV* mutational status (mutated vs. unmutated)
- Geographic region (NA vs. EU vs. APAC)

del(17p) FISH test

TREATMENT

Cohort 1 without del(17p) → R 1:1
- Arm A: Zanubrutinib 160 mg PO BID until PD (n=241)
- Arm B: Bendamustine + Rituximab × 6 (n=238)

Cohort 2 with del(17p)
- Arm C: Zanubrutinib 160 mg PO BID until PD (n=111)[b]

Cohort 3 with del(17p)
- Arm D: Zanubrutinib 160 mg PO BID + venetoclax (n= ~80)

FOLLOW-UP

Safety and survival

Assessments

- Response assessments were conducted every 12 weeks from start of cycle 1 for 96 weeks and then every 24 weeks until PD
- CR/CRi confirmed via bone marrow biopsy
- AEs documented until PD or start of next CLL therapy

Statistical Analysis

- Efficacy endpoints analyzed using ITT analysis and the per-protocol analysis set
- Safety was assessed in all pts who received ≥1 dose of treatment

Tam CS et al. Lancet Oncol. 2022 Aug;23(8):1031-1043.
Munir T et al. Poster presented at EHA 2023; Abstract number: P639

Summary of EAIRs for select AEIs

cohorts 1 and 2 (any grade and grade ≥3)

SEQUOIA – extended mFU 44m

	Patients without del(17p)		Patients with del(17p)
	Arm A: Zanubrutinib (n=240)	Arm B: BR (n=227)	Arm C: Zanubrutinib (n=111)
Atrial fibrillation and flutter	0.13	0.08	0.15
Hemorrhage	2.02	0.40	2.73
Major hemorrhage	0.20	0.05	0.20
Hypertension	0.49	0.45	0.35

Exposure-adjusted incidence rates for hypertension were similar between arms and lower than previously reported.

Atrial fibrillation events remained low.

Zanubrutinib discontinuation rates in patients without and with del(17p) were 24.9% and 29.7%, respectively.

Zanubrutinib was well tolerated over this extended treatment period and aligned with the known profile of BTK inhibitors.

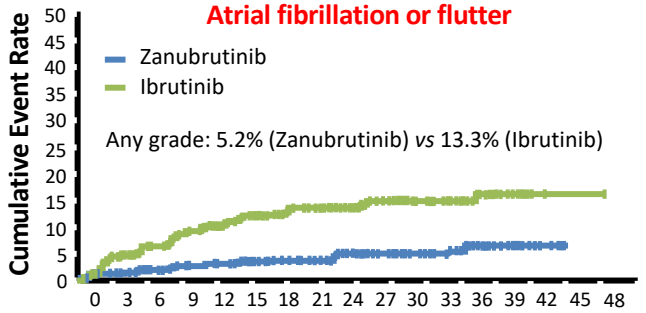
Tam CS et al. Lancet Oncol. 2022 Aug;23(8):1031-1043.
Munir T et al. Poster presented at EHA 2023; Abstract number: P639

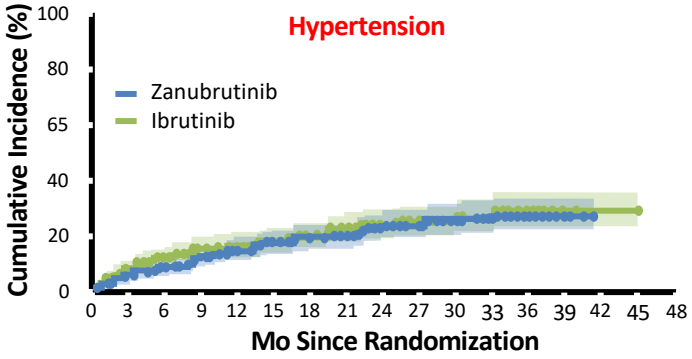
Second-generation covalent BTK inhibitors *vs* Ibrutinib

ALPINE: Zanubrutinib *vs* Ibrutinib in R/R CLL/SLL

Randomized phase III trial of **Zanubrutinib** *vs* **Ibrutinib** for patients with CLL relapsed or refractory to ≥1 previous line of treatment; no prior BTKi (N = 652)

extended mFU 39m	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)
Congestive cardiomyopathy	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)





Brown JR. et al, NEJM. 2023;388:319-332.
Brown JR et al. Oral Presentation at ASH 2023; abstract number 202.

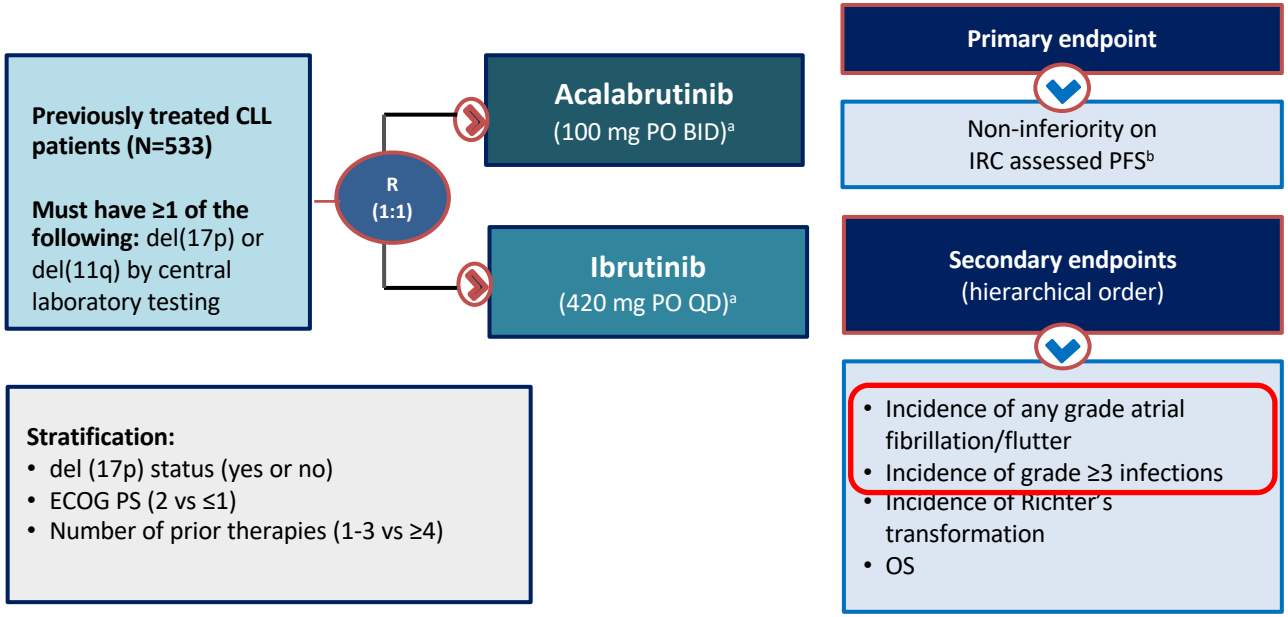
ALPINE – extended mFU 39m

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 related	145 (44.8)	56 (17.3)	105 (32.4)	38 (11.7)
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

- lower rate of grade ≥3 and serious AEs, fewer AEs leading to treatment discontinuation, and dose reduction.
- safer cardiac profile than Ibrutinib with significantly lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and no fatal cardiac events.

Brown JR. et al, NEJM. 2023;388:319-332.
Brown JR et al. Oral Presentation at ASH 2023; abstract number 202.

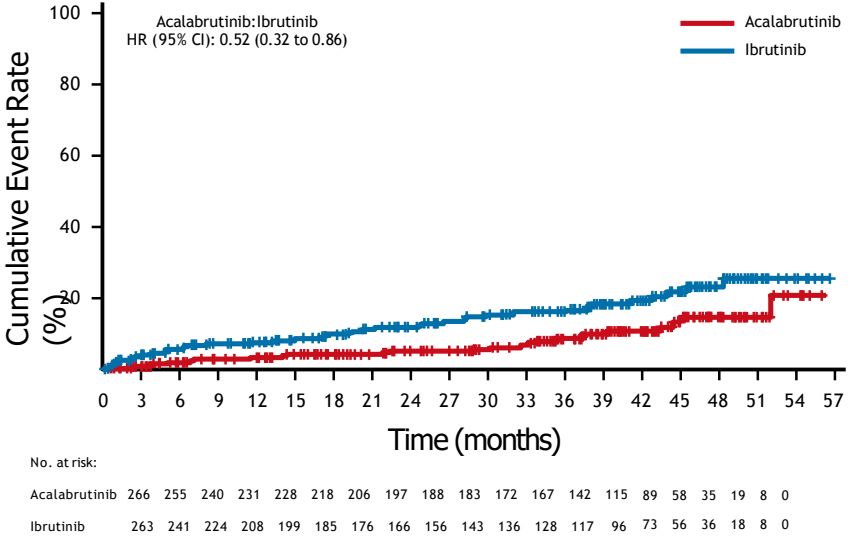
ELEVATE-RR: study design

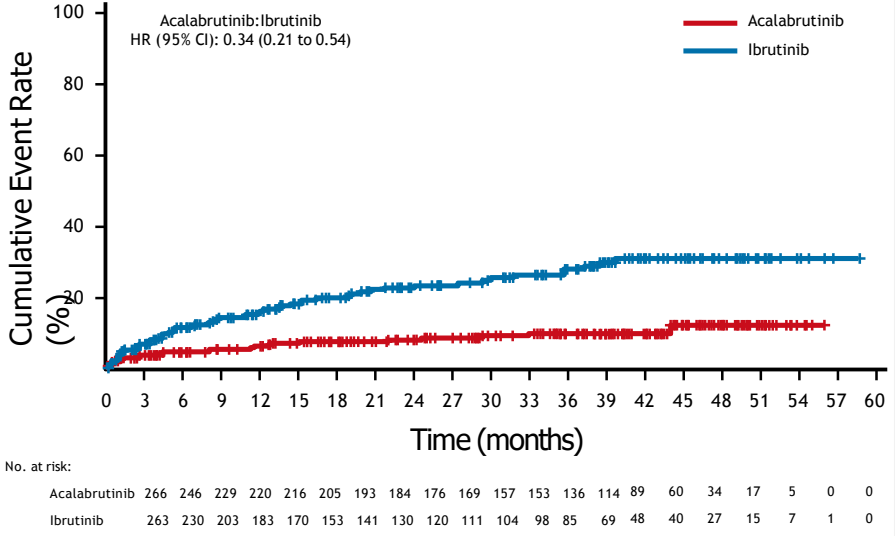


[a]Continued until disease progression or unacceptable toxicity. [b]Conducted after enrollment and accrual of ~250 IRC-assessed PFS events. BID = twice daily; CLL = chronic lymphocytic leukemia; ECOG PS = eastern cooperative oncology group performance status; IRC = independent review committee; OS = overall survival; PFS = progression-free survival; PO = orally; R = randomization; QD = once daily.

Byrd JC. ASCO 2021. Abstr 7500. Byrd JC. JCO. 2021;39:3441.7,5

ELEVATE-RR: cumulative incidence of any-grade atrial fibrillation and hypertension





ATRIAL FIBRILLATION

9.4% *vs* 16% (p=0.02)

48% lower cumulative AF risk with Acalabrutinib

HYPERTENSION

9.4% *vs* 23.2%

Byrd JC. ASCO 2021. Abstr 7500. Byrd JC. JCO. 2021;39:3441.7,5

ELEVATE-RR: additional endpoints

mFU 40.9m

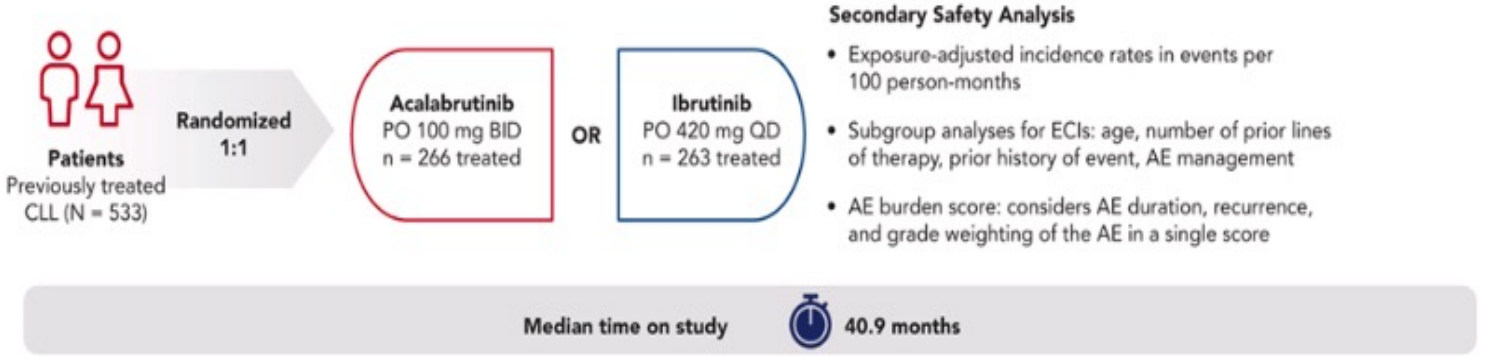
	Any grade		Grade ≥3	
Events, n (%)	**Acalabrutinib** (n=266)	**Ibrutinib** (n=263)	**Acalabrutinib** (n=266)	**Ibrutinib** (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation	**25 (9.4)**	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrythmias	0	3 (1.1)	0	1 (0.4)
Bleeding events	**101 (38.0)**	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension	**25 (9.4)**	**61 (23.2)**	11 (4.1)	24 (9.1)
Infections	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis	**7 (2.6)**	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Atrial fibrillation/flutter events of any grade were significantly lower with Acalabrutinib *vs* Ibrutinib (9.4% *vs* 16%; *P*=0.02)

Statistically significant reduction in any grade **atrial fibrillation** rates, Acalabrutinib was associated with a lower incidence of **bleeding events**, **hypertension**, and **ILD/pneumonitis**

Byrd JC. ASCO 2021. Abstr 7500. Byrd JC. JCO. 2021;39:3441.7,5

Detailed safety profile of Acalabrutinib *vs* Ibrutinib in previoulsy treated CLL in the ELEVATE-RR trial



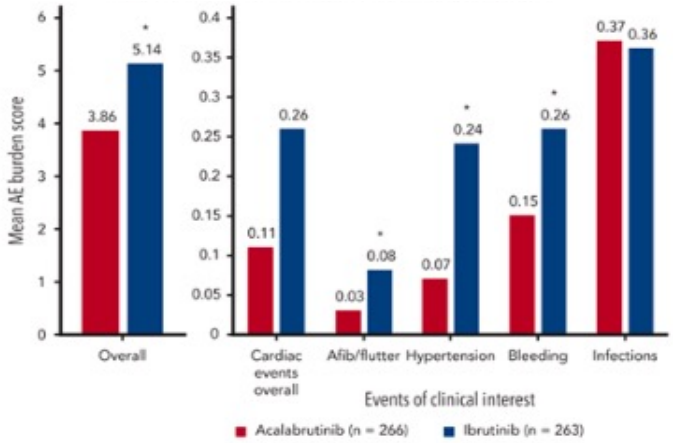
Seymour JF et al, Blood. 2023 Aug 24;142(8):687-699

Detailed safety profile of Acalabrutinib *vs* Ibrutinib in previoulsy treated CLL in the ELEVATE-RR trial

Exposure-adjusted Incidence

- Diarrhea, arthralgia, UTI, back pain, muscle spasms, and dyspepsia incidence rates were 1.5- to 4.1-fold higher with ibrutinib
- Headache and cough incidence rates were 1.6- and 1.2-fold higher, respectively, with acalabrutinib
- Afib/flutter, hypertension, and bleeding incidence rates were 1.6- to 2.8-fold higher with ibrutinib

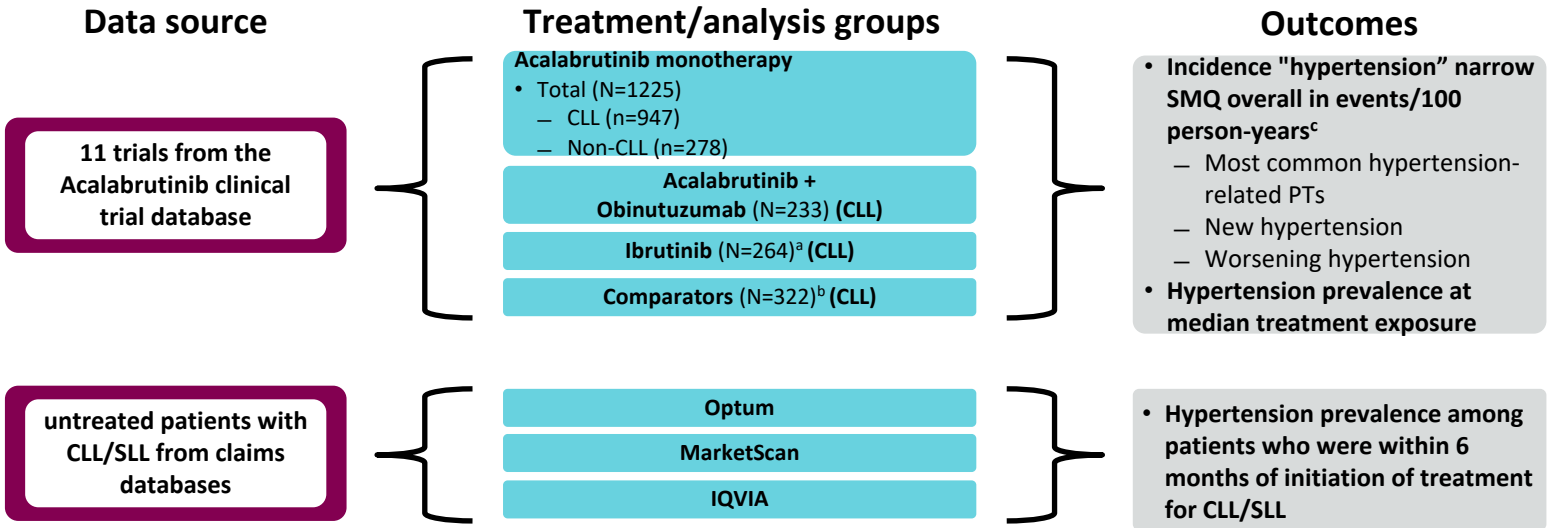
Event-based analyses and AE burden scores demonstrated higher AE burden overall and specifically for **atrial fibrillation**, **hypertension**, and **hemorrhage** with Ibrutinib *vs* Acalabrutinib



*Two-sided *P*-value < .05 without multiplicity adjustment based on Wilcoxon rank-sum test. *P*-value compares difference in overall distribution rather than mean score.

Seymour JF et al, Blood. 2023 Aug 24;142(8):687-699

Cumulative review of hypertension in patients with CLL and other hematologic malignancies treated with Acalabrutinib



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

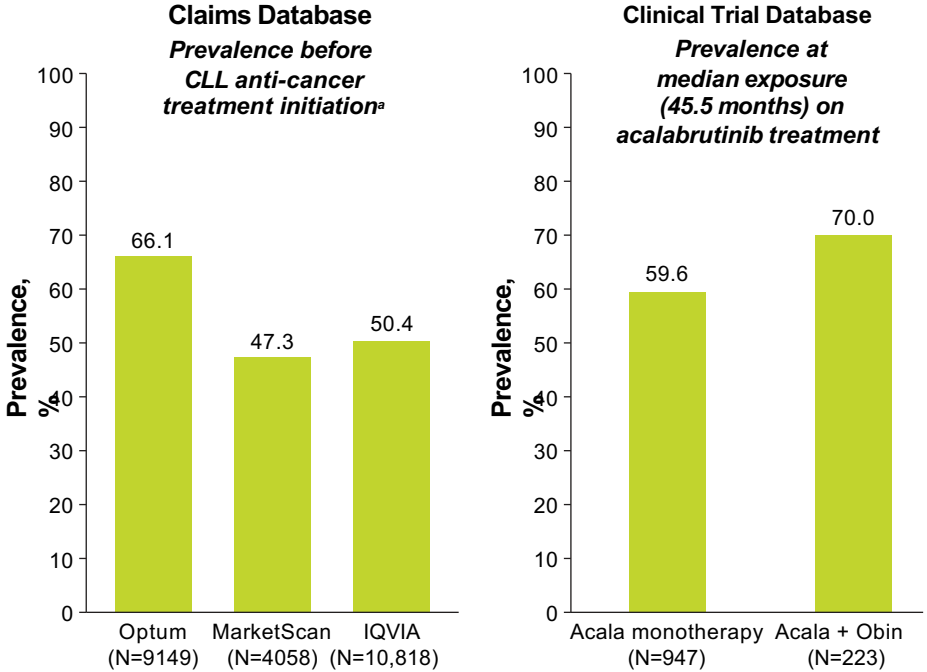
[b]Patients with CLL treated with Obinutuzumab plus Chlorambucil (ELEVATE-TN), Idelalisib plus Rituximab (ASCEND), or Bendamustine plus Rituximab (ASCEND)

[c]"Hypertension" narrow SMQ per MedDRA 25.1.

Ferrajoli A, et al. Poster presented at ASH; December 9-12, 2023; San Diego

Cumulative review of hypertension in patients with CLL and other hematologic malignancies treated with Acalabrutinib

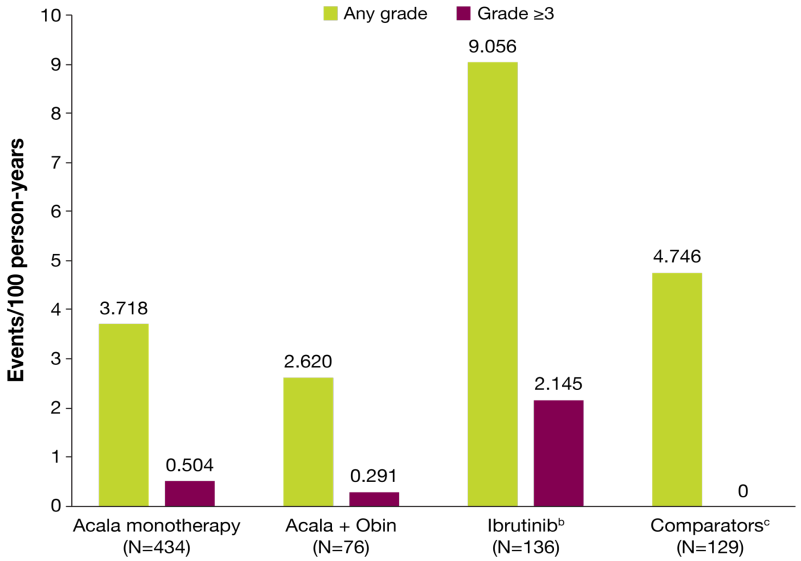
Figure 2. Comparative prevalence of hypertension in patients with CLL



- in the **claims database** analysis of patients with TN CLL prior to treatment initiation, prevalence of hypertension ranged from 47.3% to 66.1%

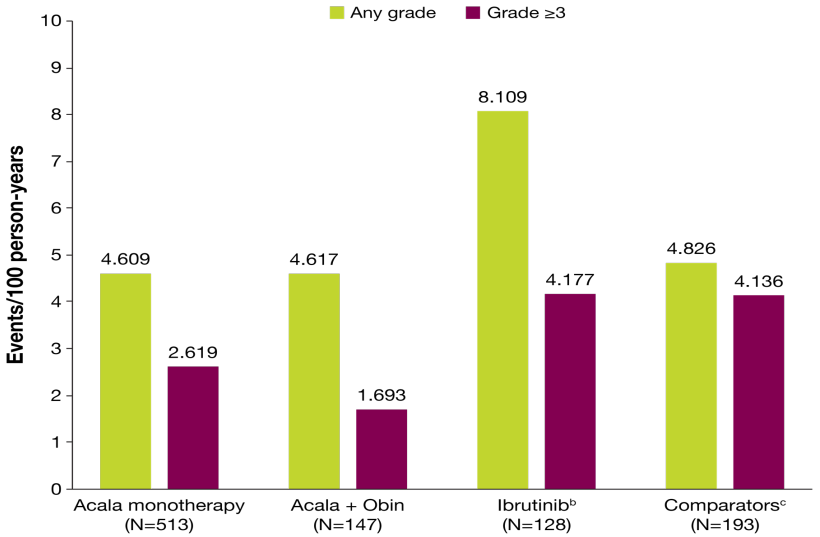
- in the **clinical trial database** of patients with CLL treated with Acalabrutinib monotherapy, hypertension prevalence was 59.6% at a median treatment exposure of 45.5 months

Exposure-adjusted incidence rate of **new hypertension** in patients with CLL



EAIR of **new hypertension** in patients with CLL treated with Acalabrutinib monotherapy was 3.718, which was lower than in the patients with CLL treated with Ibrutinib in ELEVATE-RR (9.056)

Exposure-adjusted incidence rate of **worsening hypertension** in patients with CLL



EAIR of **worsening hypertension** was relatively similar among Acalabrutinib monotherapy, Acalabrutinib +Obinutuzumab, and comparator groups, except Ibrutinib, which was relatively higher

Ferrajoli A, et al. Poster presented at ASH; December 9-12, 2023; San Diego

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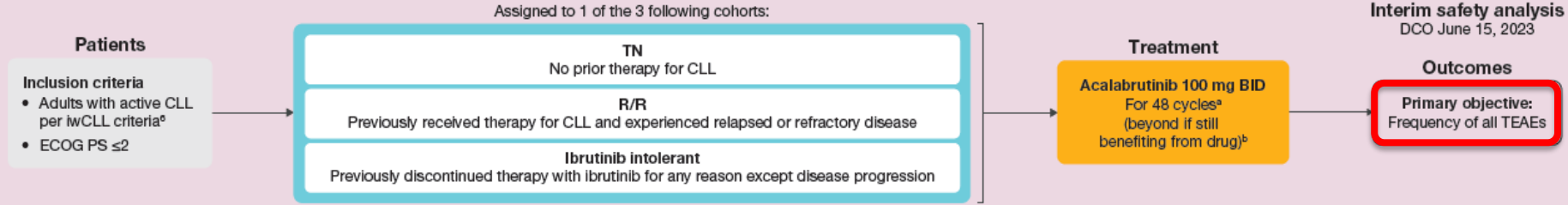
Interim Results From ASSURE: A Phase 3b Safety Study of Acalabrutinib in Patients With Chronic Lymphocytic Leukemia

Stephen Opat,[1] Farrukh T. Awan,[2] Laura Fogliatto,[3] Eugene Nikitin,[4] Joanna Czerwinski,[5] Rodrigo Santucci Alves da Silva,[6] Srinivas Jujjavarapu,[7] Olga Samoilova,[8] Caroline Dartigeas,[9] Hoa Tran,[10] Javier de la Serna,[11] Versha Banerji,[12] Laura Magnano Mayer,[13] Jason Hart,[14] Julia von Tresckow,[15] Christian B. Poulsen,[16] Ki Seong Eom,[17] Michele Merli,[18] Ellie John,[19] Jiefen Munley,[20] Shweta Hakre,[21] Richard Hermann,[21] Carsten U. Niemann[22]

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.

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

Presented at EHA Annual Meeting 2024; Madrid, Spain

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RWE confirm clinical trials data in term of TTD and AEs

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

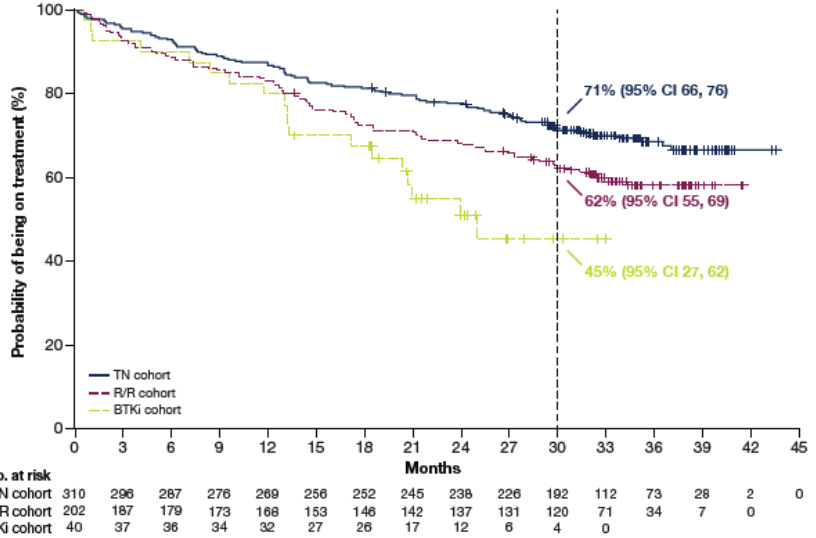

Table 3. Events of Clinical Interest

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.

Presented at EHA Annual Meeting 2024; Madrid, Spain

REGULAR ARTICLE

blood advances

Real-world comparative effectiveness of acalabrutinib and ibrutinib in patients with chronic lymphocytic leukemia

Lindsey E. Roeker,[1] Maral DerSarkissian,[2] Kellie Ryan,[3] Yan Chen,[2] Mei Sheng Duh,[2] Svea K. Wahlstrom,[4] Shweta Hakre,[5] Louise Yu,[2] Helen Guo,[2] and Anthony R. Mato[1]

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first comparative effectiveness study of Acalabrutinib and Ibrutinib in real-world patients with chronic lymphocytic leukemia

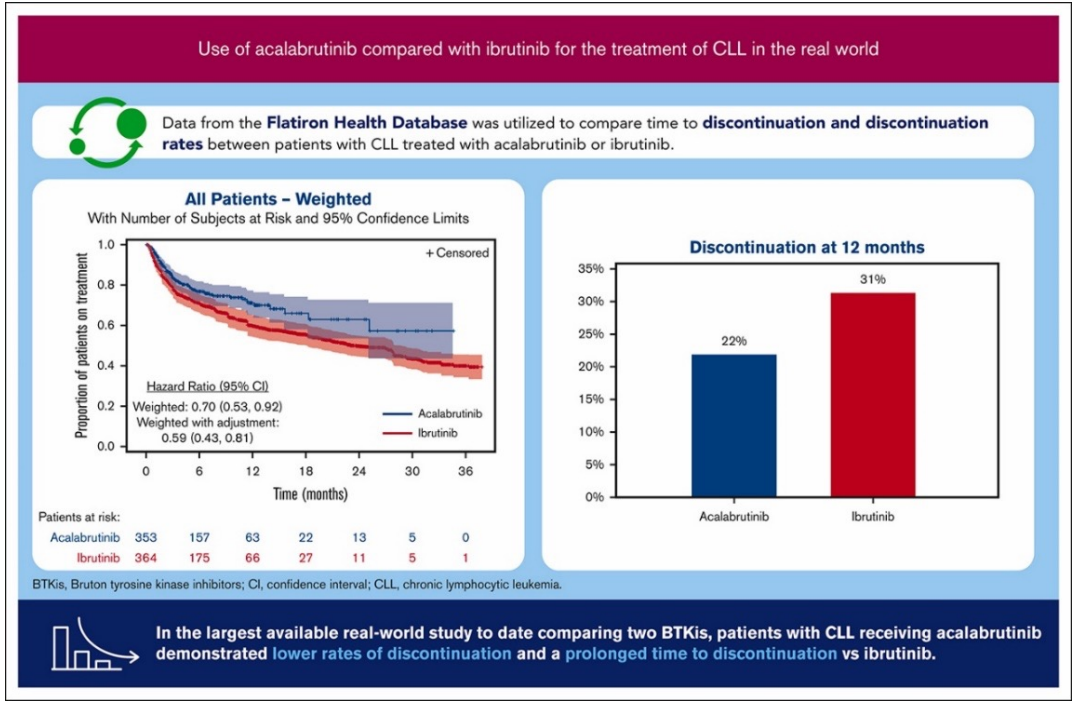
1. **Flatiron Cohort**
   Patients with physician-documented CLL and/or SLL diagnosis[1] or evidence in unstructured documents having been treated specifically for CLL/SLL in the Flatiron Health Database (data cut-off: February 28, 2021)
   N = 12,886
2. Initiation of alcabrutinib or ibrutinib in any line of therapy on or after January 1, 2018 (initiation of acalabrutinib or ibrutinib was defined as the index date)
   N = 2613 (20.3%)
3. Two or more clinic encounters[2] on different days in the Flatiron Health Database during the study period[3]
   N = 2613 (100%)
4. Aged 18 years or older at index date
   N = 2613 (100%)
5. Not enrolled in a clinical study or receiving an investigational drug during the study period
   N = 2571 (98.4%)
6. Did not receive concurrent antineoplastic treatment[4] for another malignancy[5] during the study period
   N = 2509 (97.6%)
7. **Cohort assignment[6]**

Acalabrutinib	**N = 353**	**(14.1%)**
1L	*N = 67*	
2L or later	*N = 286*	
Ibrutinib	**N = 2249**	**(89.6%)**
1L	*N = 1211*	
2L or later	*N = 1038*	

Lindsey E et al. Blood Adv. 2023 Aug 22;7(16):4291-4301

Acalabrutinib demonstrated statistically significant longer time to discontinuation than Ibrutinib

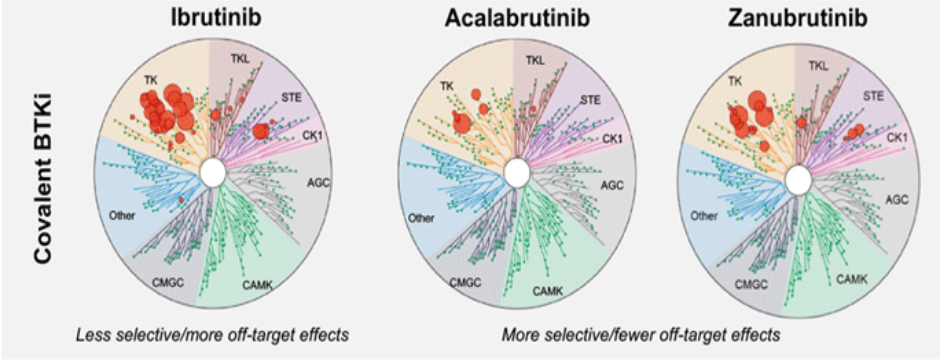
Flatiron Study - 2509 patients 2018-2021

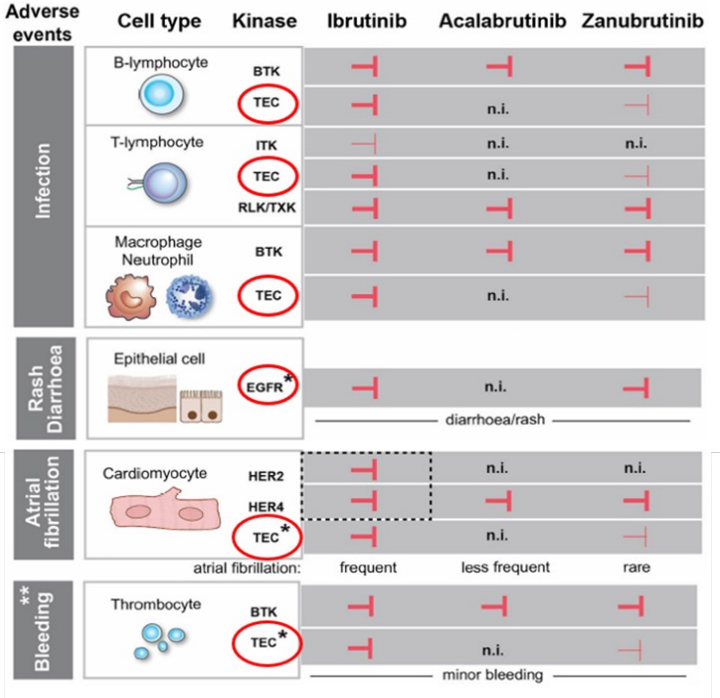


The **median** (95% CI) **TTD was not reached** (NR; 25.1, NR) **for the Acalabrutinib** cohort and was **23.4 months** (18.1, 28.7) **for the Ibrutinib** cohort.

The **discontinuation rate** at 12 months was **22% for the weighted Acalabrutinib** cohort vs **31% for the weighted Ibrutinib** cohort (P = .005).

Lindsey E et al. Blood Adv. 2023 Aug 22;7(16):4291-4301





second generation BTKi inhibitors: same efficacy less toxicity

Estupinan et al. Frontiers in Cell and Dev Biology 2021
Herman et al. ClinCancer Res. 2017