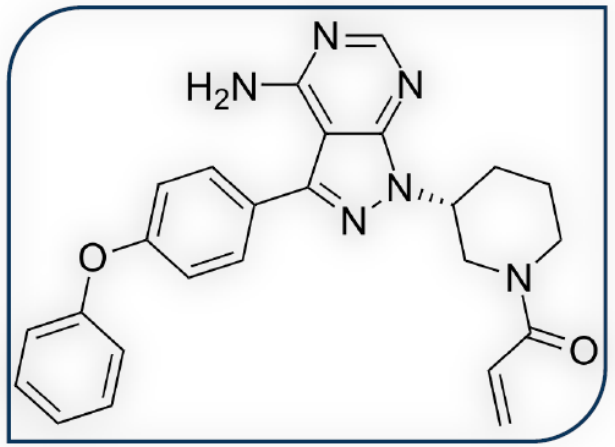
La safety cardiovascolare e il suo ruolo

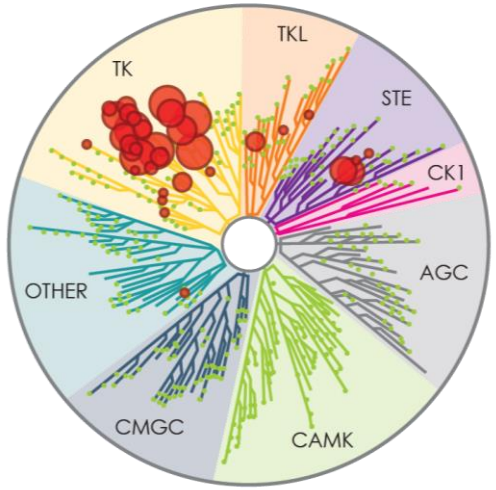
Marta Coscia
Università dell'Insubria e ASST Sette Laghi
Varese

DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X				X	X	
AstraZeneca					X	X	
Behring						X	
Beigene					X	X	
GSK	X		X			X	
Johnson&Jhonson	X				X	X	

The first in class BTKi ibrutinib





Ibrutinib is a targeted therapy that primarily binds irreversibly to Bruton's tyrosine kinase (BTK) but it **also shows off-target activity** against other kinases.

Ibrutinib also **inhibits other members of the TEC kinase family**

- ITK, TEC
- RLK, BMX

This **lack of complete selectivity is responsible of toxicities** and clinically relevant adverse events

- Inhibition of TEC e downstream Akt signalling is responsible of **arrhythmogenic effects** of BTKi
- Interaction with HER2 - a protein that supports cardiomyocyte homeostasis and efficient contractility - contibutes to **acute and chronic cardiomyocyte disfunction** potentially **culminating in heart failure**

Herman S, et al. Blood 2011; de Rooij M, et al. Blood 2012; Ponader S et al. Blood 2012

Clinically relevant AEs related to BTKis administered cointinuously

Cross trial comparison – incidence of clinically relavant AEs in phase 3 studies evaluating continuous BTKi in frontline treatment

	ELEVATE-TN[1] (Acala arm)	SEQUOIA ARM w/o del17p[2]	SEQUOIA with del17p[3]	RESONATE-2[4]
mFU	*6 years*	*5 years*	*5 years*	*5 years*
HTN any grade	**11.2%**	19.6%	18%	26%
HTN Grade ≥ 3	**5%**	12.1%	8%	9%
AF any grade	8.9%	7.1%	8%	16%
AF Grade ≥ 3	1.7%	1.4%	5%	5%
Bleeding any grade	45.3%	52.1%	60%	NA
Bleeding Grade > 3	4.5%	7.5%	6%	11%

1 Sharman, Jeff P et al. *Blood* 2025; 2 Shadman et al. *J Clin Oncol* 2025; 3 Tam et al. Poster EHA 2025; 4 Burger et al. *Leukemia* 2020

Clinically relevant AEs related to BTKis administered cointinuously

Cross trial comparison – incidence of clinically relavant AEs in phase 3 studies evaluating continuous BTKi in frontline treatment

	ELEVATE-TN[1] (Acala arm)	SEQUOIA ARM w/o del17p[2]	SEQUOIA with del17p[3]	RESONATE-2[4]
mFU	*6 years*	*5 years*	*5 years*	*5 years*
HTN any grade	**11.2%**	19.6%	18%	26%
HTN Grade ≥ 3	**5%**	12.1%	8%	9%
AF any grade	8.9%	7.1%	8%	16%
AF Grade ≥ 3	1.7%	1.4%	5%	5%
Bleeding any grade	45.3%	52.1%	60%	NA
Bleeding Grade > 3	4.5%	7.5%	6%	11%

1 Sharman, Jeff P et al. *Blood* 2025; 2 Shadman et al. *J Clin Oncol* 2025; 3 Tam et al. Poster EHA 2025; 4 Burger et al. *Leukemia* 2020

Clinically relevant AEs related to BTKis administered cointinuously

Cross trial comparison – incidence of clinically relavant AEs in phase 3 studies evaluating continuous BTKi in frontline treatment

	ELEVATE-TN[1] (Acala arm)	SEQUOIA ARM w/o del17p[2]	SEQUOIA with del17p[3]	RESONATE-2[4]
mFU	*6 years*	*5 years*	*5 years*	*5 years*
HTN any grade	11.2%	19.6%	18%	26%
HTN Grade ≥ 3	5%	12.1%	8%	9%
AF any grade	**8.9%**	**7.1%**	**8%**	16%
AF Grade ≥ 3	**1.7%**	**1.4%**	**5%**	5%
Bleeding any grade	45.3%	52.1%	60%	NA
Bleeding Grade > 3	4.5%	7.5%	6%	11%

1 Sharman, Jeff P et al. *Blood* 2025; 2 Shadman et al. *J Clin Oncol* 2025; 3 Tam et al. Poster EHA 2025; 4 Burger et al. *Leukemia* 2020

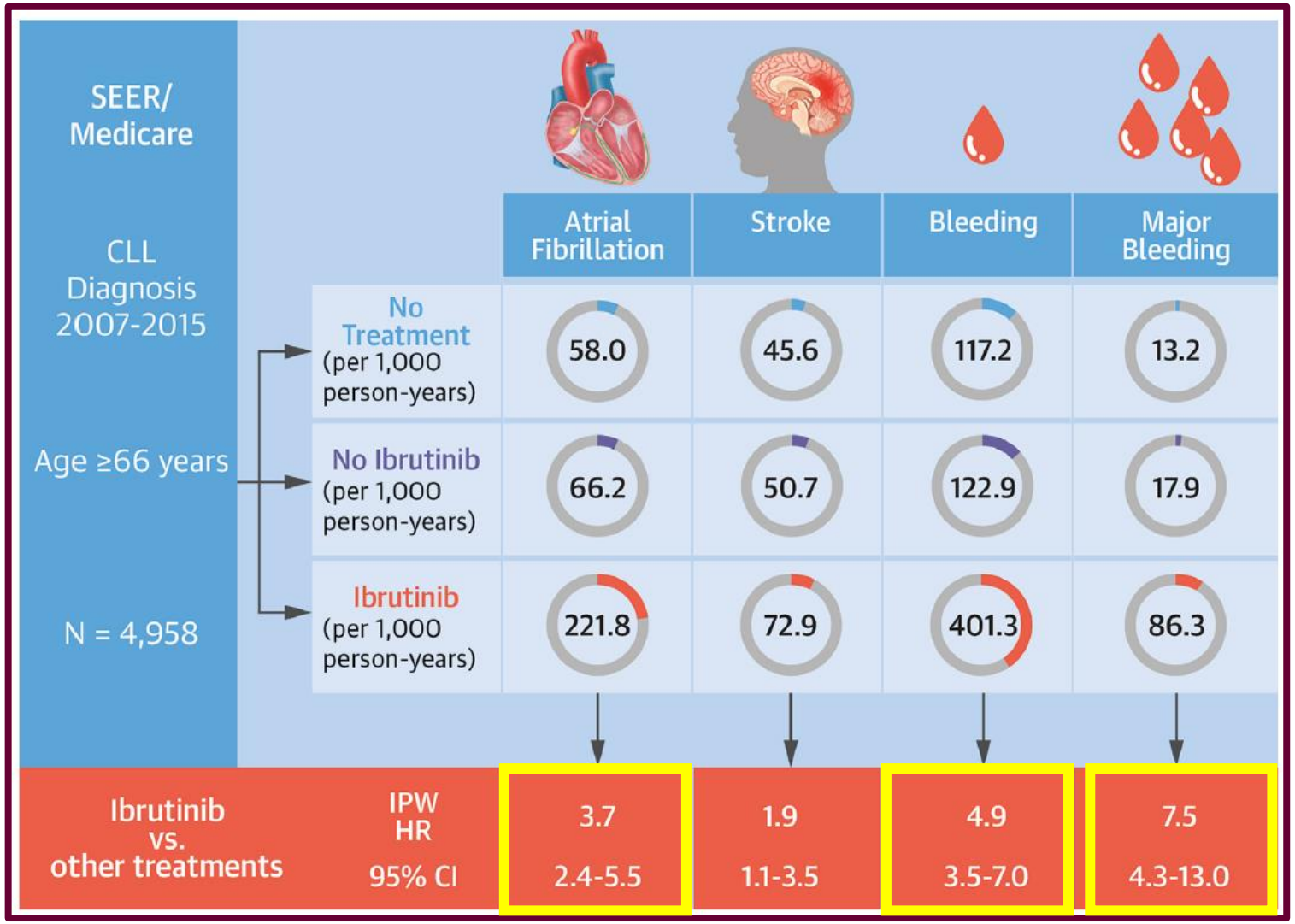
Clinically relevant AEs related to BTKis administered cointinuously

Cross trial comparison of clinically relavant AEs in phase 3 studies evaluating continuous BTKi in frontline treatment

	ELEVATE-TN[1] (Acala arm)	SEQUOIA ARM w/o del17p[2]	SEQUOIA with del17p[3]	RESONATE-2[4]
mFU	*6 years*	*5 years*	*5 years*	*5 years*
HTN any grade	11.2%	19.6%	18%	26%
HTN Grade ≥ 3	5%	12.1%	8%	9%
AF any grade	8.9%	7.1%	8%	16%
AF Grade ≥ 3	1.7%	1.4%	5%	5%
Bleeding any grade	45.3%	52.1%	60%	NA
Bleeding Grade > 3	**4.5%**	7.5%	6%	11%

1 Sharman, Jeff P et al. *Blood* 2025; 2 Shadman et al. *J Clin Oncol* 2025; 3 Tam et al. Poster EHA 2025; 4 Burger et al. *Leukemia* 2020

AEs in patients receiving Ibrutinib continuous treatment



Comparison of CLL patients treated with ibrutinib with those who were treated without ibrutinib in a linked SEER-Medicare database of 4958 patients.

3.036 (61.2%) were never treated, 1.623 (32.7%) were treated but not with ibrutinib, and 299 (6.0%) were treated with ibrutinib.

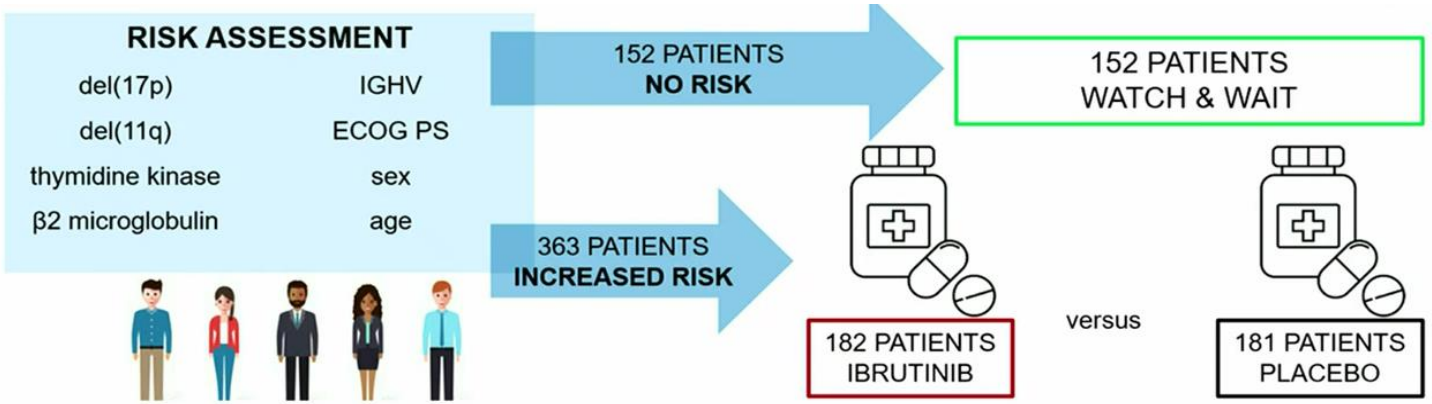
ibrutinib use was associated with an increased risk of AF, bleeding, and major bleeding, and associated with stroke and MI, albeit at borderline statistical meaningfulness.

IPW = inverse probability weighted; SEER = Surveillance, Epidemiology, and End Results program.

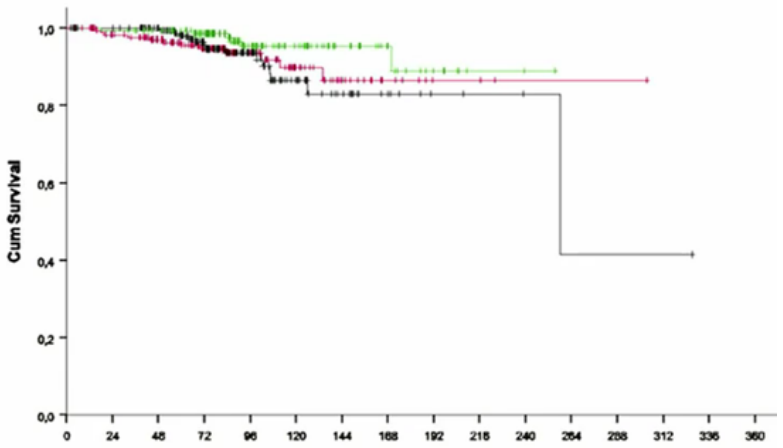
Diamond A et al., ACC CardioOncol. 2023

Ibrutinib versus placebo in TN early stage high risk CLL

Phase 3, double-blind, placebo-controlled CLL12 trial



OS



	Ibrutinib N=170	Placebo N=168
Max. CTC grade, N (%)		
CTC grades 1 – 5	136 (80)	88 (52.4)
CTC grade 5	4 (2.4)	1 (0.6)
Bleeding	62 (36.5)	25 (14.9)
Cardiac arrhythmias	38 (22.4)	16 (9.5)
Cardiac event other than arrhythmia	30 (17.6)	26 (15.5)
Diarrhea	69 (40.6)	48 (28.6)
Hypertensive disorders	33 (19.4)	14 (8.3)

	Ibrutinib N=182	Placebo N=181
All death cases, N (%)	12 (6.6)	14 (7.7)
Progressive CLL	1	1
Second malignancy	2	5
Infection	2	1
Intracranial bleeding	2	-
Cardiac decompensation / sudden death	2	1
Concomitant disease	-	1
Unknown	3	5

Langerbeins P et al. Blood 2022; Langerbeins P et al. EHA 2023.

Ibrutinib in old-old patients

IBRUTINIB IN PATIENTS ≥ 80 YEARS OLD: A MULTICENTER ITALIAN COHORT

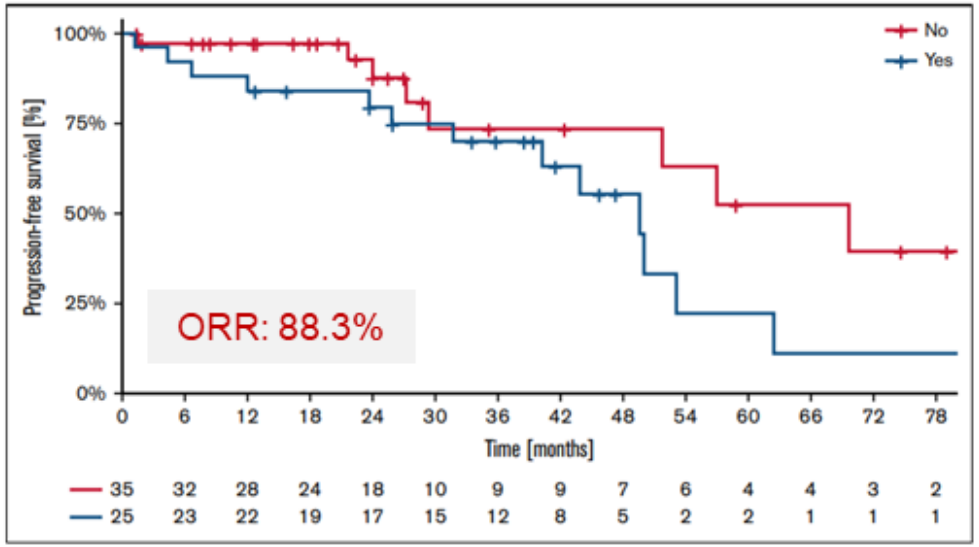
Multicenter, retrospective study.

60 consecutive patients with TN or R/R CLL, ≥80 years old

Median observation: 27 months

Concomitant cardioactive therapies, n (%)	
At least 1 cardioactive drug	44 (73.3)
>2 cardioactive drugs	18 (10.8)
Antihypertensive drugs	38 (63.3)
Anticoagulants	3 (5)
Lipid-lowering drugs	10 (16.7)
Antiplatelets drugs	21 (35)

PFS by treatment withholding

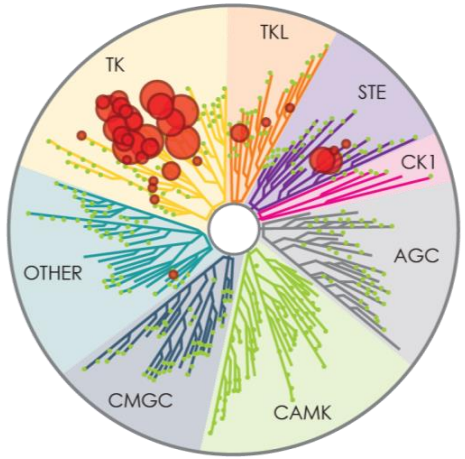


Median PFS 69.7 months in patients not experiencing temporary drug withholding (7-30 days) vs 49.7 months in patients who had drug interruptions (P = .079).

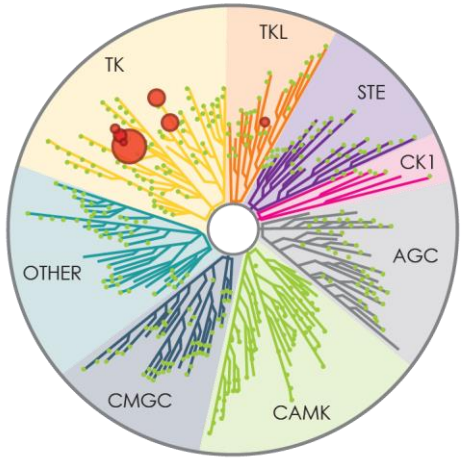
Handling AEs to keep patients on treatment is of crucial importance as therapy interruptions could negatively impact on PFS.

Reda et al. Blood Adv. 2023

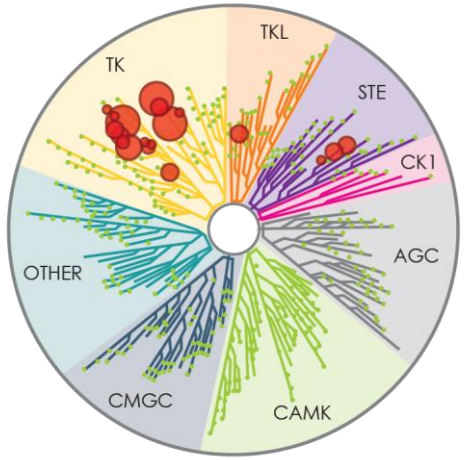
Second generation BTKis



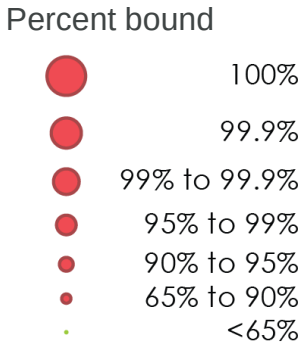
Ibrutinib



Acalabrutinib



Zanubrutinib



- Age-related changes in cardiac structure and function, underlying comorbidities and polypharmacy can exacerbate cardiovascular risk of CLL patients
- The selection of a BTKi agent with a higher target selectivity and a more favorable safety profile is a determinant aspect of treatment decision making

Munoz J et al., Ther Adv in Hematol 2022; Oliva S and Molica S, Eur J Haematol 2025

Safety profile of acalabrutinib vs ibrutinib in ELEVATE-RR

Phase 3
R/R High-Risk CLL
(N=533)

Acalabrutinib 100 mg BID

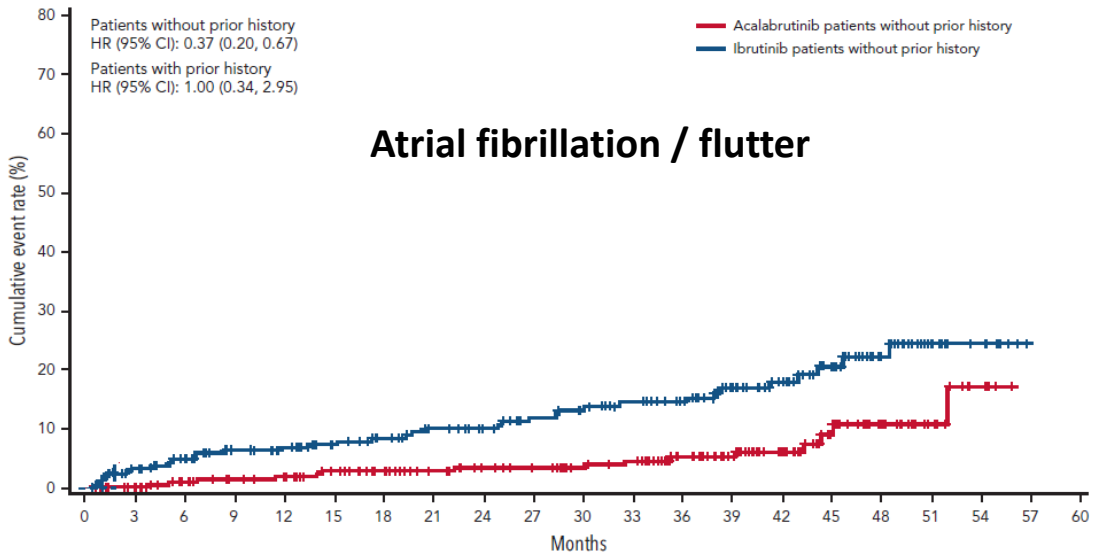
Ibrutinib 420 mg QD

SAFETY in favor of Acalabrutinib

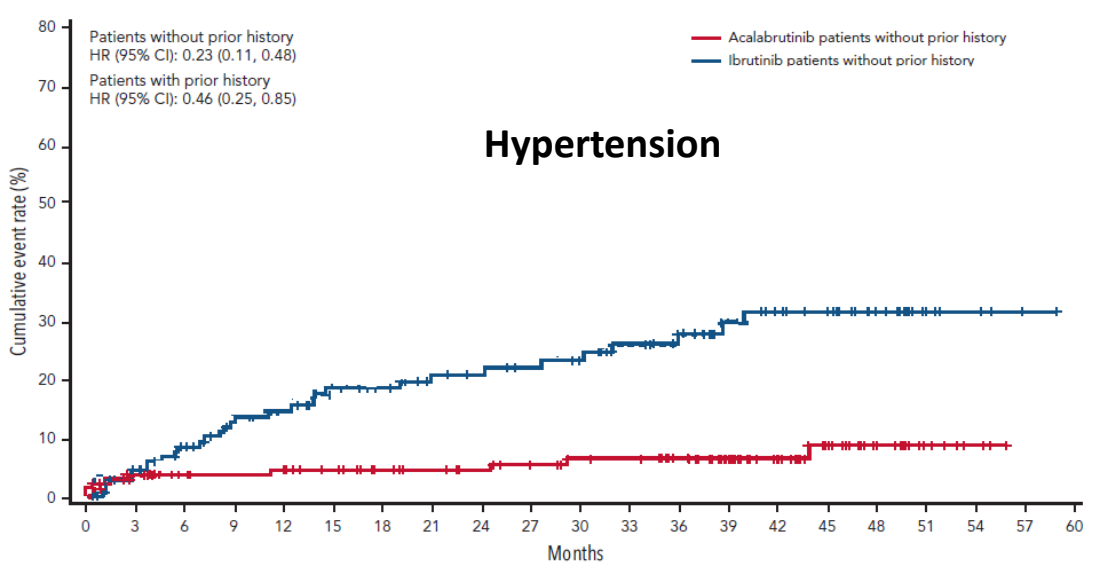
- Lower discontinuation rate
- Risk of new-onset atrial fibrillation/flutter and new-onset hypertension showed relative rate reductions of 63% and 77%, respectively, favoring acalabrutinib

Median follow-up 41 months

A



B



Patients without a prior history of cardiovascular pathologies have a lower risk of developing AF/HTN if treated with acalabrutinib rather than ibrutinib

Seymour JF et al. Blood 2023

Seymour JF et al. Blood 2023

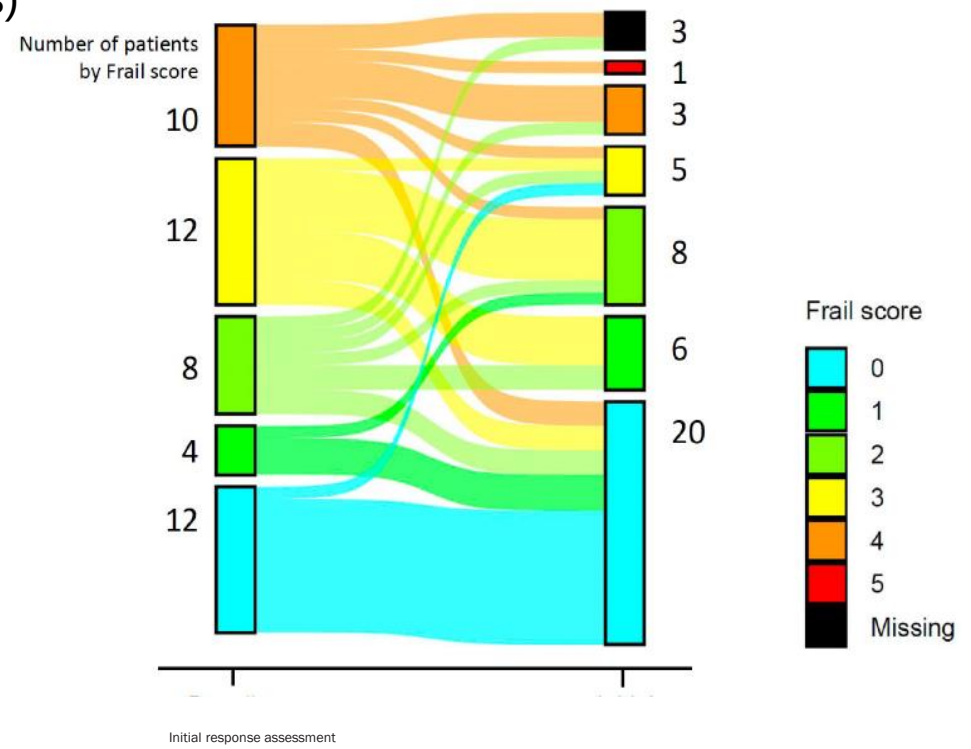
Acalabrutinib safety results: CLL-FRAIL

Adverse Events Summary (n=52) (median observation time 17.7 months)

Adverse Event, n (%)	All Grades	Grade ≥3
Any AE	**52 (100)**	**33 (63.5)**
COVID-19	19 (36.5)	3 (5.8)
Hematoma	19 (36.5)	0
Diarrhea	12 (23.1)	1 (1.9)
Anemia	9 (17.3)	6 (11.5)
Constipation	9 (17.3)	0
Headache	9 (17.3)	0
Fatigue	8 (15.4)	0
Edema	8 (15.4)	--
Contusion	7 (13.5)	0
Thrombocytopenia	6 (11.5)	1 (1.9)
Vertigo	6 (11.5)	0
Dehydration	6 (11.5)	1 (1.9)
Rash	6 (11.5)	2 (3.8)
Cardiac failure	**4 (7.7)**	**3 (5.8)**
Palpitations	4 (7.7)	0

Only frequent adverse events (≥10% of patients) and cardiac events are depicted

- Atrial fibrillation:
  - 2 cases (CTC G2 and G3)
  - 4% all grades – 1.8 grade ≥3
- 5 patients (9%) died
  - There was one deadly SAE termed suspicion of cardiac event, in a case of a 85-year old patient with sudden death at home and known cardiac comorbidities.



53% of pts had an improvement in their FRAIL scale scores (21% were considered frail at month 6, compared to 47% at screening)

Simon F, et al. Poster presentation, ASH Annual Meeting, 2024

Simon et al. *Blood* 4 Sep. 2025, doi:10.1182/blood.2025028550

Acalabrutinib safety results: pooled analysis of three phase 3 trials

› Clin Lymphoma Myeloma Leuk. 2025 Apr 30:S2152-2650(25)00150-8.
doi: 10.1016/j.clml.2025.04.018. Online ahead of print.

Cardiac Events in Three Phase 3 Randomized Trials Including Acalabrutinib in Chronic Lymphocytic Leukemia

Rupal O'Quinn [1], Anthony J Corry [2], Naghmana Bajwa [2], Suman Jannuru [3], Hong Chen [2], Paulo Miranda [2], Jennifer R Brown [4]

ELEVATE-TN		
acalabrutinib + Obin	acalabrutinib	Obin + Clb
(n=178)	(n=179)	(n=169)

ASCEND		
acalabrutinib	Idela + Ritux	Benda + Ritux
(n=154)	(n=118)	(n=35)

ELEVATE-RR	
acalabrutinib	Ibr
(n=266)	(n=263)

- **AF incidence among A-treated patients is similar to that of patients treated with the comparator**
- **HTN is not reported among the most frequent TEAEs.**

Exposure adjusted incidence rate of cardiac disorders

Table 2 Most Frequent (EAIR ≥0.03) and All Fatal Treatment-Emergent Cardiac Disorder PTs in Pooled Acalabrutinib Monotherapy and Pooled Comparator Groups

Cardiac Disorder PT	Number of Events (EAIR)					
	Acalabrutinib Pooled (n = 599)			Comparator Pooled (n = 585)		
	Any Grade	Grade ≥3	Fatal	Any Grade	Grade ≥3	Fatal
Any cardiac disorder PT	127 (0.55)	49 (0.21)	5 (0.02)	107 (0.95)	37 (0.33)	9 (0.08)
Atrial fibrillation	47 (0.20)	16 (0.07)	0	46 (0.41)	10 (0.09)	0
Palpitations	19 (0.08)	0	0	13 (0.12)	0	0
Cardiac failure	10 (0.04)	7 (0.03)	0	9 (0.08)	7 (0.06)	1 (0.01)
Tachycardia	10 (0.04)	0	0	9 (0.08)	0	0
Angina pectoris	13 (0.06)	4 (0.02)	0	6 (0.05)	2 (0.02)	0
Sinus tachycardia	2 (0.01)	0	0	6 (0.05)	0	0
Cardiac failure chronic	2 (0.01)	1 (0.00)	0	5 (0.04)	3 (0.03)	1 (0.01)
Myocardial ischemia	3 (0.01)	1 (0.00)	0	4 (0.04)	2 (0.02)	0
Acute myocardial infarction	3 (0.01)	3 (0.01)	0	3 (0.03)	2 (0.02)	0
Arrhythmia	4 (0.02)	1 (0.00)	0	3 (0.03)	0	0
Atrial flutter	3 (0.01)	1 (0.00)	0	3 (0.03)	2 (0.02)	0
Cardiac arrest	1 (0.00)	1 (0.00)	0	3 (0.03)	3 (0.03)	3 (0.03)
Coronary artery disease	1 (0.00)	1 (0.00)	0	3 (0.03)	2 (0.02)	0
Mitral valve incompetence	0	0	0	3 (0.03)	2 (0.02)	0
Myocardial infarction	3 (0.01)	3 (0.01)	1 (0.00)	3 (0.03)	3 (0.03)	1 (0.01)
Pericarditis	1 (0.00)	0	0	3 (0.03)	2 (0.02)	0
Sinus bradycardia	6 (0.03)	0	0	3 (0.03)	0	0
Cardiorespiratory arrest	2 (0.01)	2 (0.01)	2 (0.01)	0	0	0
Cardiopulmonary failure	1 (0.00)	1 (0.00)	1 (0.00)	2 (0.02)	2 (0.02)	2 (0.02)
Stress cardiomyopathy	1 (0.00)	1 (0.00)	1 (0.00)	0	0	0
Cardiac failure acute	0	0	0	1 (0.01)	1 (0.01)	1 (0.01)

EAIR = exposure-adjusted incidence rate; PT = preferred term.

O'Quinn R et al. *Clinical lymphoma, myeloma & leukemia* 2025

Safety profile of zanubrutinib vs ibrutinib in ALPINE

Phase 3
R/R CLL
(N=652)

Zanubrutinib
160 mg BID

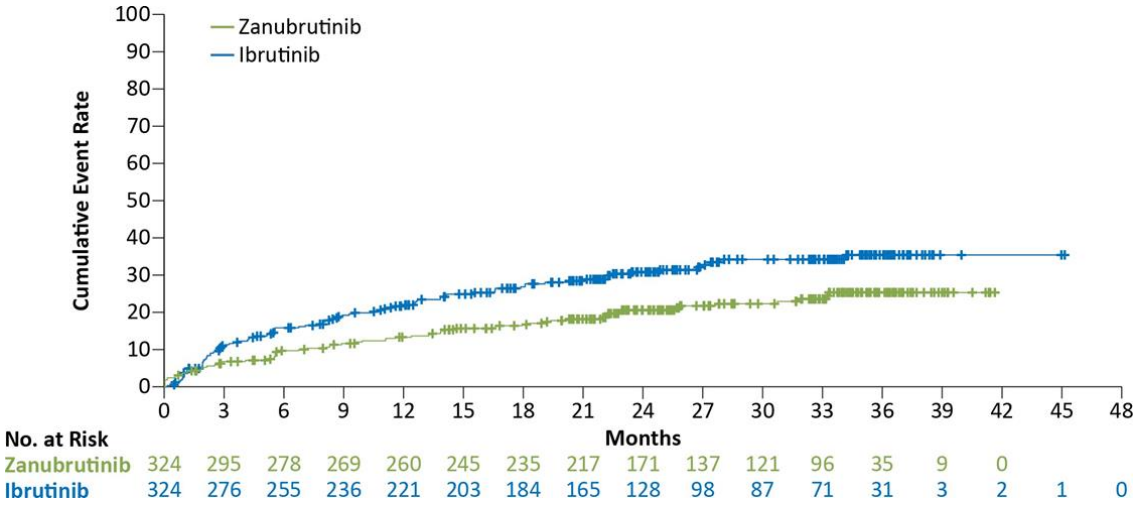
Ibrutinib 420
mg QD

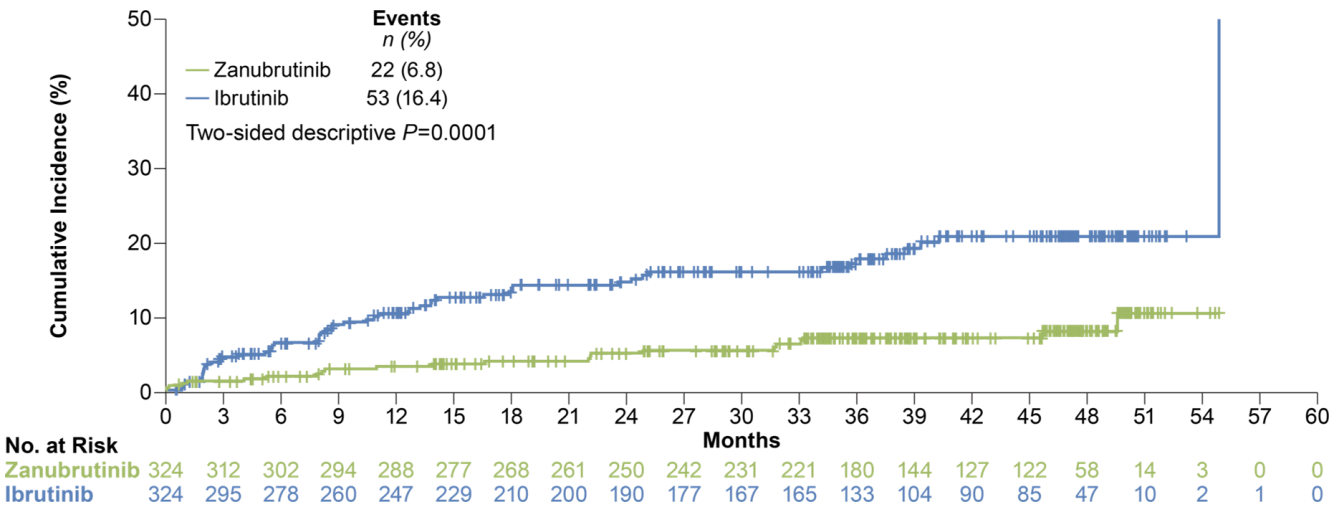
Median follow-up
42.5 months

SAFETY

<u>In favor of Zanubrutinib</u>

- Lower discontinuation rate
- Lower cumulative incidence of AF and cardiac disorders





Overall, **a lower incidence of cardiac disorders** was reported with zanubrutinib (21.3%) vs ibrutinib (29.6%)

A **lower incidence of atrial fibrillation** was reported with zanubrutinib (5.2%) vs ibrutinib (13.3%)

Brown J et al. N Engl J Med. 2023;388:319-332; Brown J et al. Oral Presentation Presented at ASH 2022. Brown, JR et al. Oral Presentation at ASH 2023

Safety profile of zanubrutinib vs ibrutinib in ALPINE

Phase 3
R/R CLL
(N=652)

Zanubrutinib
160 mg BID

Ibrutinib 420
mg QD

Median follow-up
42.5 months

SAFETY

In favor of Zanubrutinib

- Lower discontinuation rate (30-month discontinuation rate for AEs = 16%)
- Lower cumulative incidence o cardiac disorders and f AF

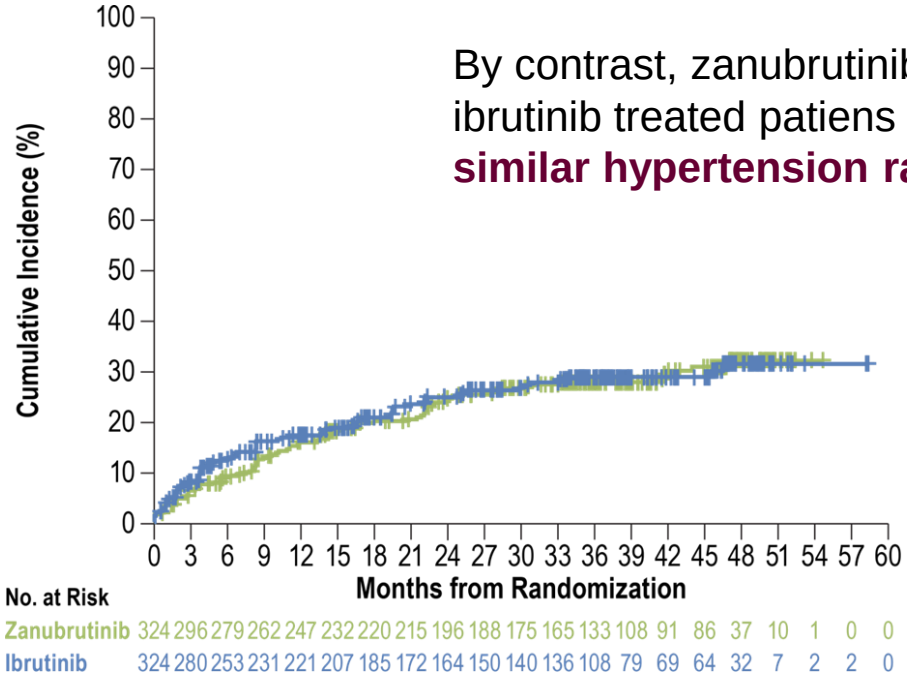
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)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

Serious cardiac adverse events were lower with zanubrutinib vs ibrutinib

Atrial fibrillation or flutter (3 vs 13)

Ventricular fibrillation (0 vs 2)

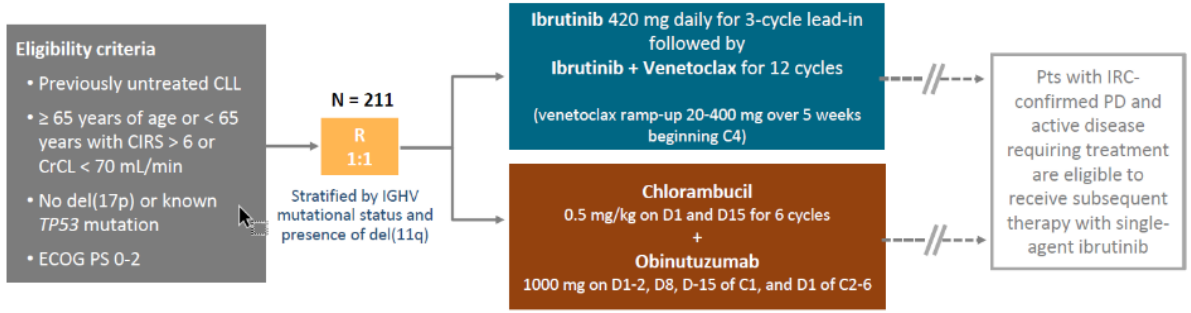
Fatal cardiac events:
Zanubrutinib, n=0 (0%)
Ibrutinib, n=6 (1.9%)

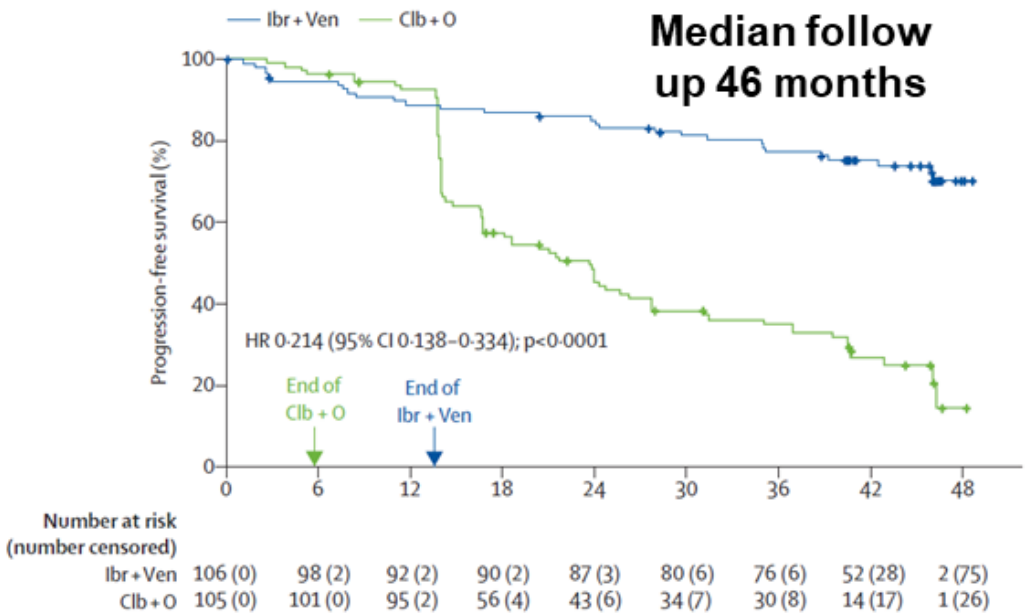


By contrast, zanubrutinib and ibrutinib treated patiens showed **similar hypertension rates**

Brown J et al. N Engl J Med. 2023; Brown J et al. Oral Presentation, ASH 2022; Brown, JR et al. Oral Presentation, ASH 2023

Fixed duration V+I in elderly or unfit CLL – GLOW study





Total number of deaths	Ibr+Ven (n = 106)		Clb+O (n = 105)	
	19		39	
Reasons for deaths	**On treatment**	**Post randomized treatment[a]**	**On treatment**	**Post randomized treatment[a]**
Infection related	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2[b]	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	**7**	**12**	**2**	**37**

Should the V+I combination be reserved to younger and more fit patients?

Kater AP et al. NEJM Evid 2022; Munir T et al. J Clin Oncol 2023; Niemann C et al. Lancet 2023

Fixed duration A+V±O: AMPLIFY safety results

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

Crossover *not built into protocol*

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:
1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

Table 2. Adverse Events and Selected Events of Clinical Interest (Safety Population).*

Adverse Events	Acalabrutinib–Venetoclax (N=291)		Acalabrutinib–Venetoclax–Obinutuzumab (N=284)		Chemoimmunotherapy (N=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
Events						
Selected events of clinical interest						
Any event of clinical interest	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac event						
Any	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation or flutter	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmia†	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage						
Any	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)

- **AEs leading to dose withholding or reduction** were similar across the 3 arms

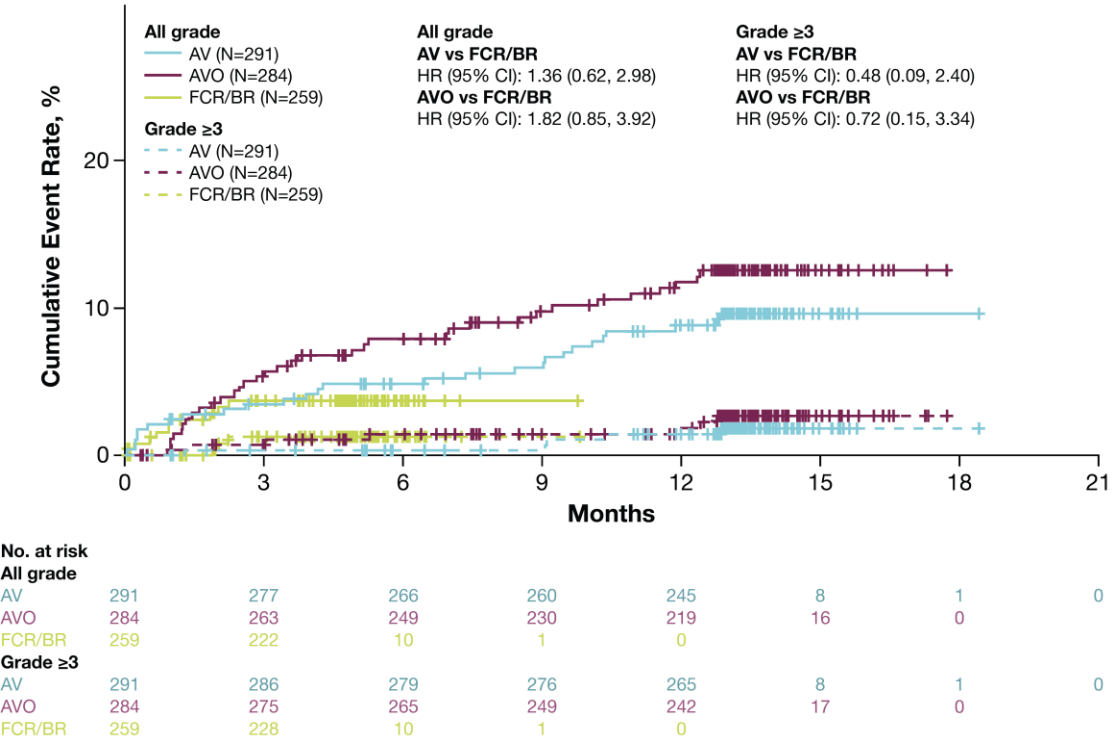
Table S10. AEs Leading to Dose Withholding or Reduction of Any Treatment by System Organ Class and Preferred Term (N>1 in Combined Treatment Arms) (Safety Population).

	AV (N=291)	AVO (N=284)	FCR/BR (N=259)
Any AE leading to dose withholding of any treatment*†	**145 (49.8)**	**184 (64.8)**	**81 (31.3)**
Cardiac disorders	1 (0.3)	3 (1.1)	1 (0.4)
Vascular disorders	4 (1.4)	0	1 (0.4)
Hematoma	2 (0.7)	0	0
Hypertension	2 (0.7)	0	0

- Only 2 cases of **hypertension** among 575 patients treated with either AV or AVO were listed among the AEs leading to dose withholding or reduction

Brown JR et al., N Engl J Med 2025

Fixed duration A+V: AMPLIFY safety post-hoc analysis



The incidence of cardiac events adjusted for exposure is similar among AV-AVO-FCR/BR arms

Table 1. Exposure-Adjusted Event Rates of ECIs

Events per 100 Person-Months	AV (N=291) Any Grade	AV (N=291) Grade ≥3	AVO (N=284) Any Grade	AVO (N=284) Grade ≥3	FCR/BR (N=259) Any Grade	FCR/BR (N=259) Grade ≥3
Any TEAE of clinical interest	25.275	11.706	36.098	18.895	57.791	38.123
Cardiac events	0.831	0.126	1.110	0.211	0.855	0.285
Atrial fibrillation	0.050	0.025	0.159	0.053	0.143	0.143
Ventricular tachyarrhythmias	0.050	0	0.079	0	0	0

The incidence of **any-grade cardiac events** was higher with AV (9.3%) and AVO (12.0%) vs FCR/BR (3.5%) (AV vs FCR/BR, P=0.0063, AVO vs FCR/BR, P=0.0003)

EAERs of **cardiac events** were similar across arms: 0.83 (AV), 1.11 (AVO) and 0.86 (FCR/BR)

Seymour et al. Poster iwCLL 2025

Conclusions

- Ibrutinib continuous treatments is burdened by a not negligible risk of clinically relevant and particularly cardiovascular AEs
- For patients with a high CV risk selecting treatment with the least CV risk is essential
- Second-generation BTKis are safer than ibrutinib, especially with respect to arrhythmias
- Acalabrutinib is also safer in terms of hypertension risk
- Time-limited Ibrutinib–venetoclax should be considered carefully in older patients with cardiac comorbidities
- Improving clinical trial designs, with thorough baseline cardiovascular risk assessment, will generate better data to guide the management of at-risk patients.