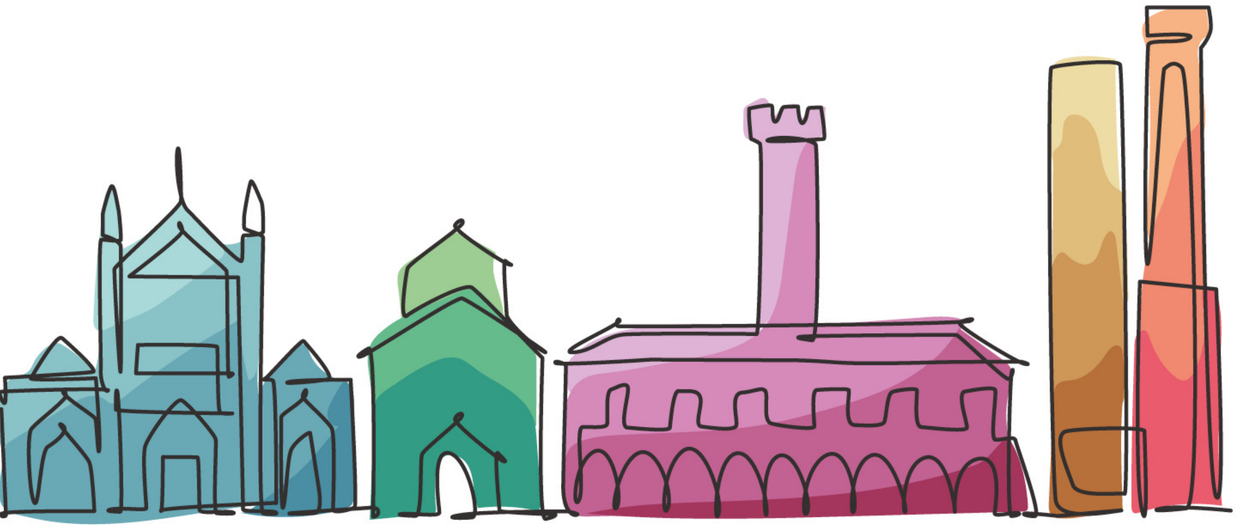
PRECEPTORSHIP



Un confronto sulla gestione delle malattie linfoproliferative al Sant'Orsola di Bologna

Bologna, NH DE LA GARE, 18 settembre 2025

LA LEUCEMIA LINFATICA CRONICA: MANAGEMENT ED APPROCCIO TERAPEUTICO DEI PAZIENTI IN PRIMA LINEA E DEI PAZIENTI RICADUTI/REFRATTARI

Beatrice Casadei,
IRCSS AOU Sant'Orsola

Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite-Gilead					x	x	
Novartis					x		
Celgene-BMS						x	
Abbvie					x	x	
Janssen					x	x	
Lilly					x		
Beigene						x	
Roche					x	x	
Incyte					x		
Takeda						x	

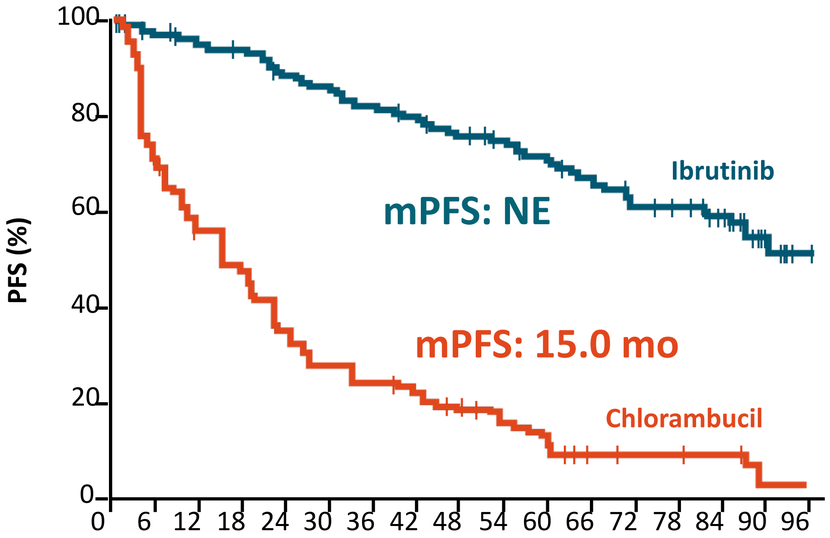
CLL frontline treatment

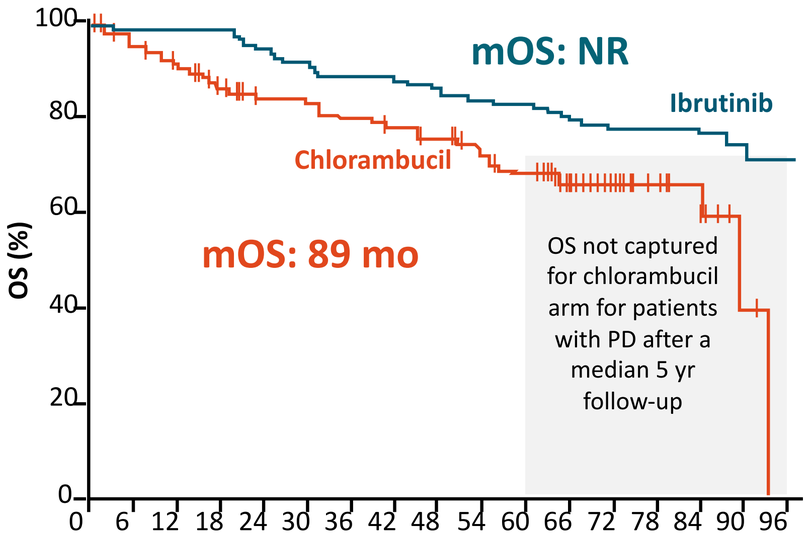
INDEFINITE THERAPY WITH BTKi

First-Generation cBTKi: Earlier Role as 1L Therapy for CLL

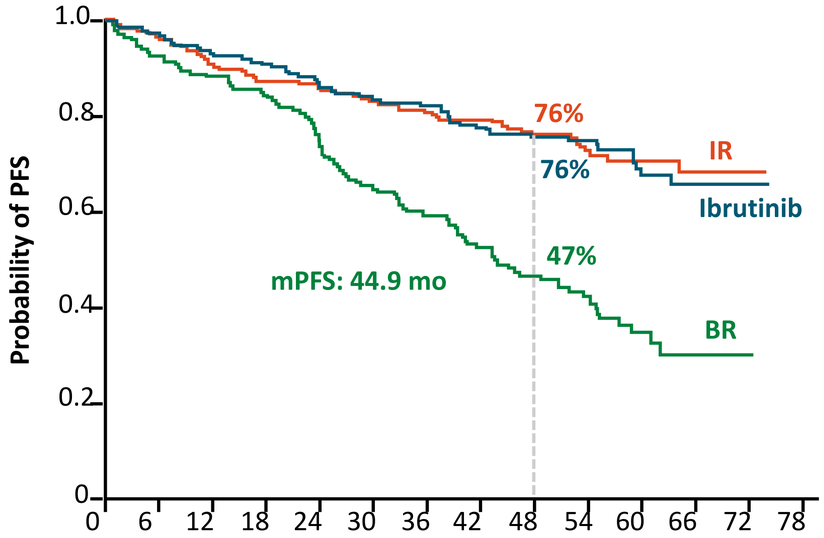
- Outcomes with ibrutinib alone or in combination with rituximab in CLL
  - Superior to chlorambucil in patients ≥65 yr in PFS and OS (RESONATE-2)
  - Superior to BR in patients ≥65 yr in PFS
  - Associated with a-fib, bleeding, bruising, hypertension, myalgias, arthralgias, and diarrhea
    - Treatment was discontinued in 41% of patients in the RESONATE-2 trial, mostly due to AEs

RESONATE-2 Trial: Overall[1,2]
(Patients aged ≥65 yr with untreated CLL)





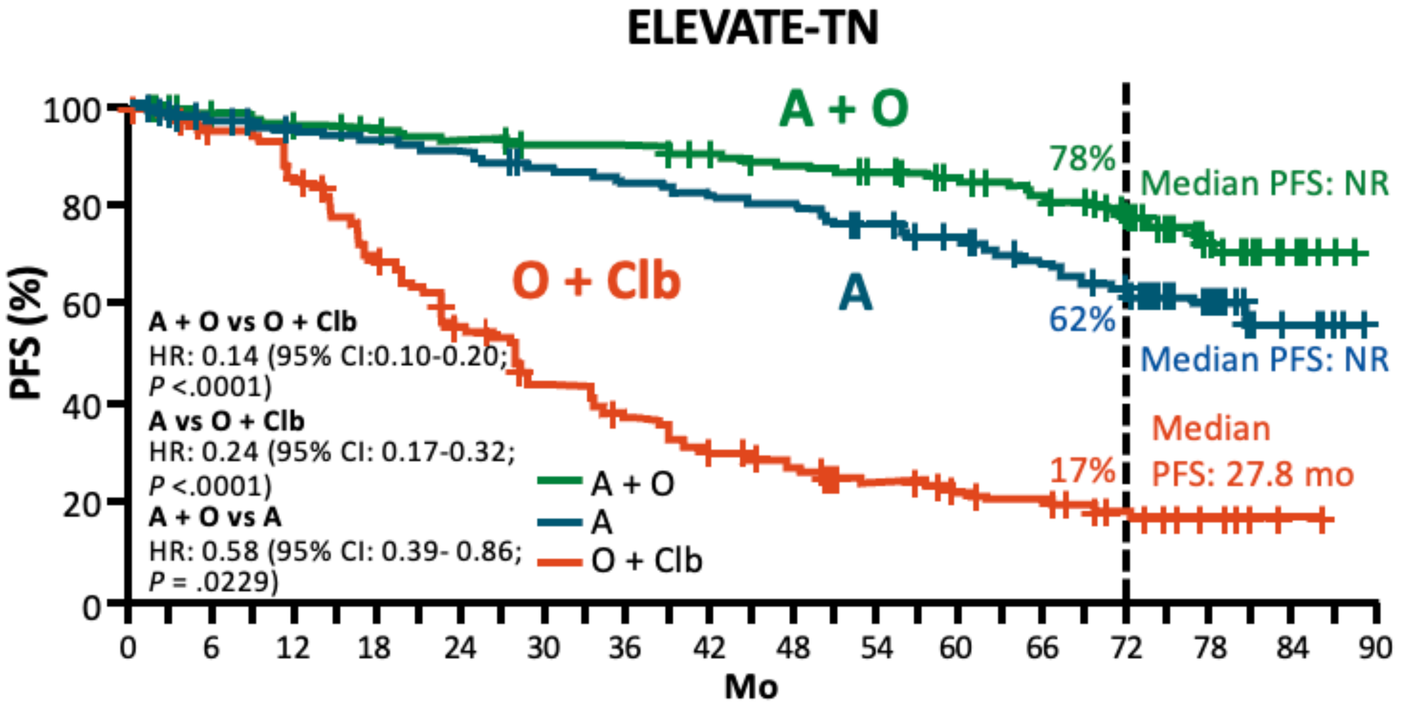
A041202 Trial: Overall[3]
(Patients aged ≥65 yr with untreated CLL)



1. Barr. Blood Adv. 2022;6:3440. 2. Burger. Leukemia. 2020;34:787. 3. Woyach. Blood. 2024;143:1616.

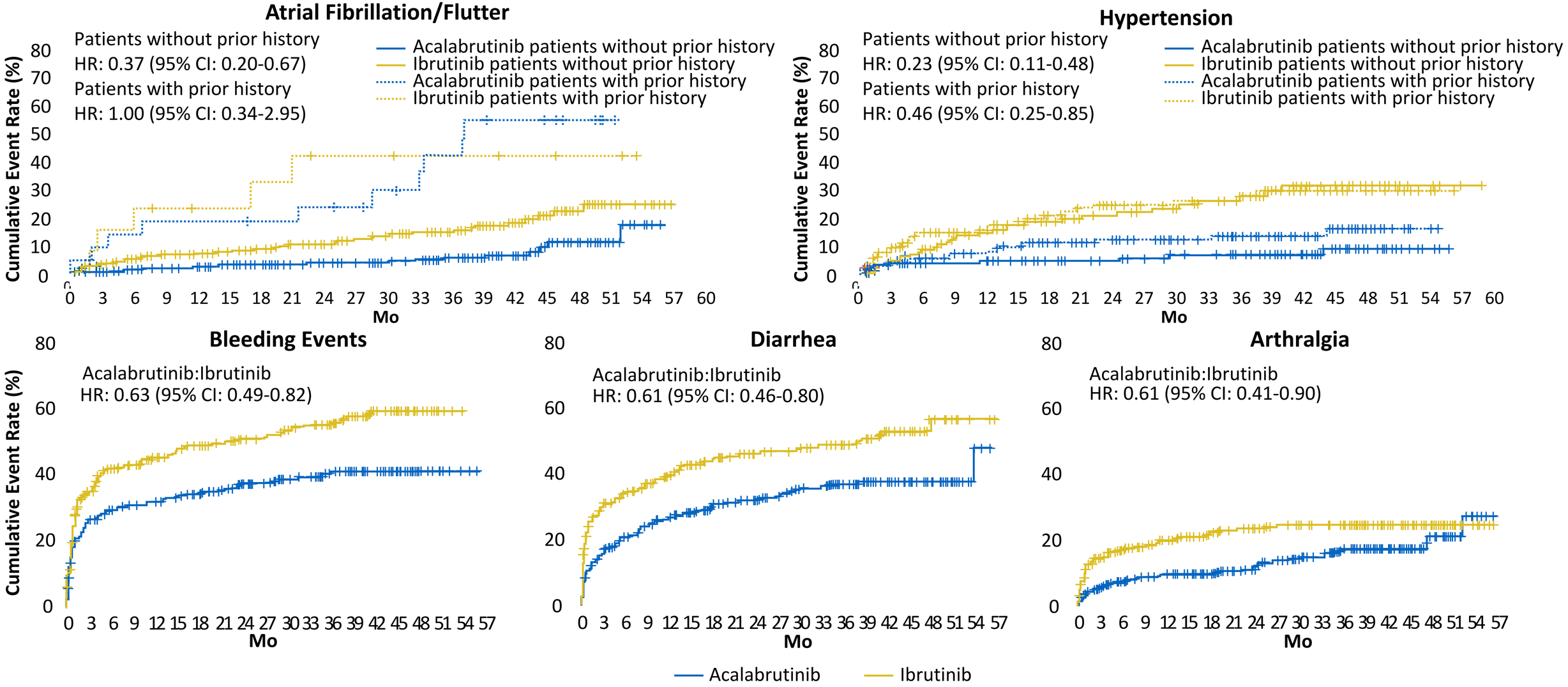
Next-Generation cBTKi Acalabrutinib: Fewer AEs and Superior to CIT

- Acalabrutinib ± obinutuzumab is superior to CIT in PFS
- Lower rates of atrial fibrillation, hypertension, serious bleeding
- Discontinuation due to AEs was approximately 10%



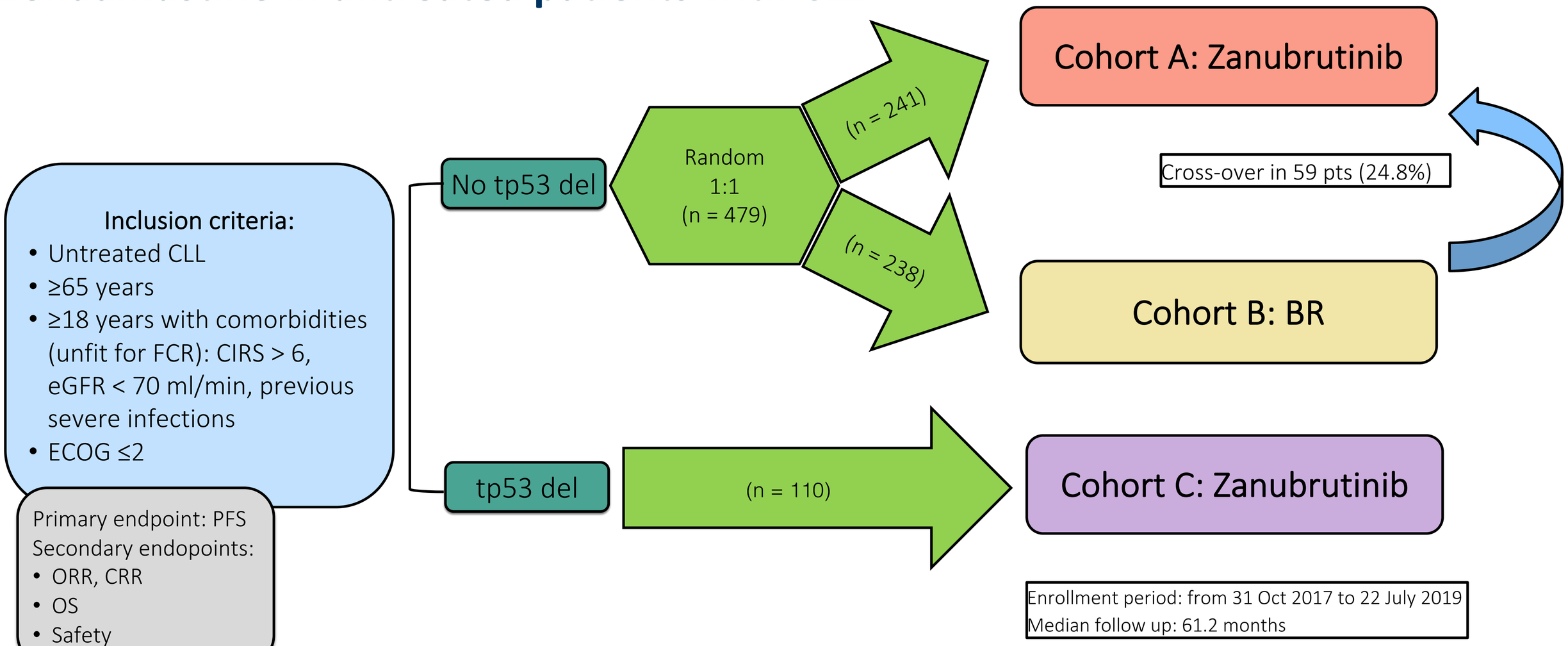
Sharman. ASH 2023. Abstr 636. Ramakrishnan. ASH 2023. Abstr 1902.

ELEVATE-RR: Cumulative Incidence of Any-Grade AEs of Special Interest



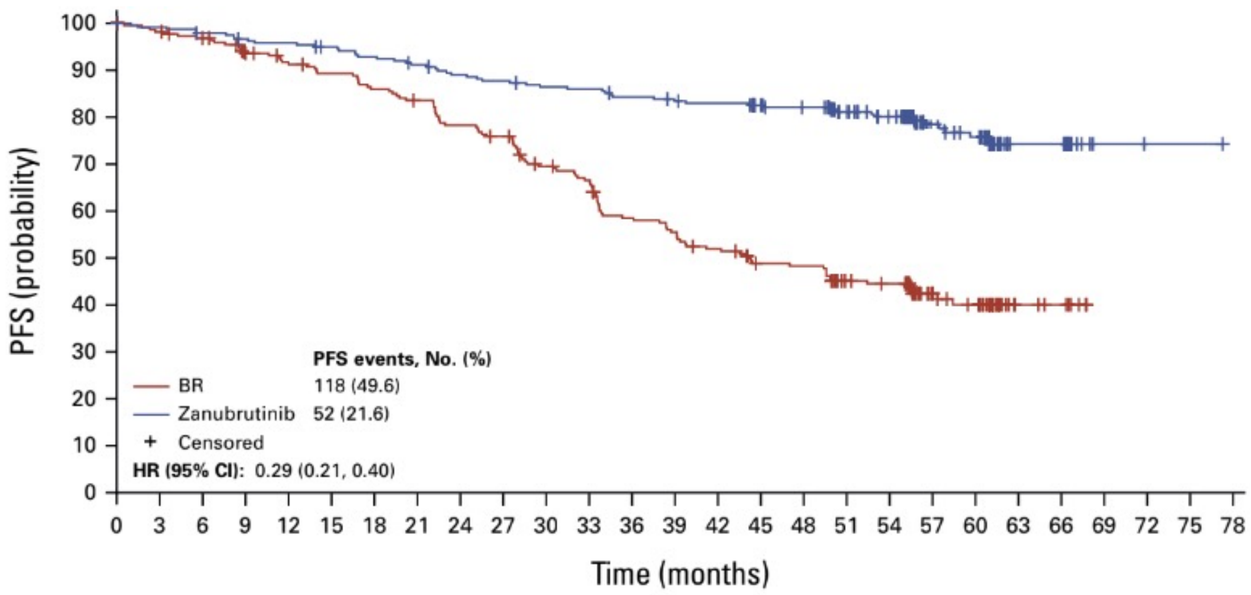
Byrd. JCO. 2021;39:3441. Hillmen. EHA 2021. Abstr S145.

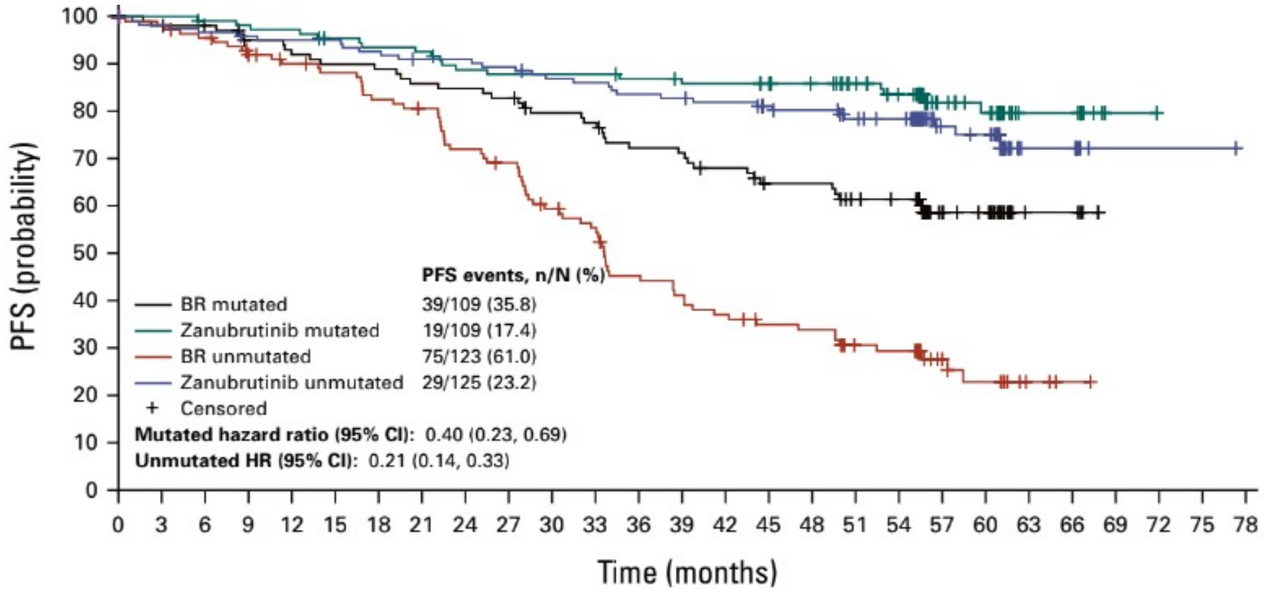
SEQUOIA: A phase 3 randomised study of Zanubrutinib vs Rituximab – Bendamustine in untreated patients with CLL



Tam CS, et al, Lancet Oncol. 2022;23(8):1031-1043.

SEQUOIA results: PFS choorts A-B (primary end point)

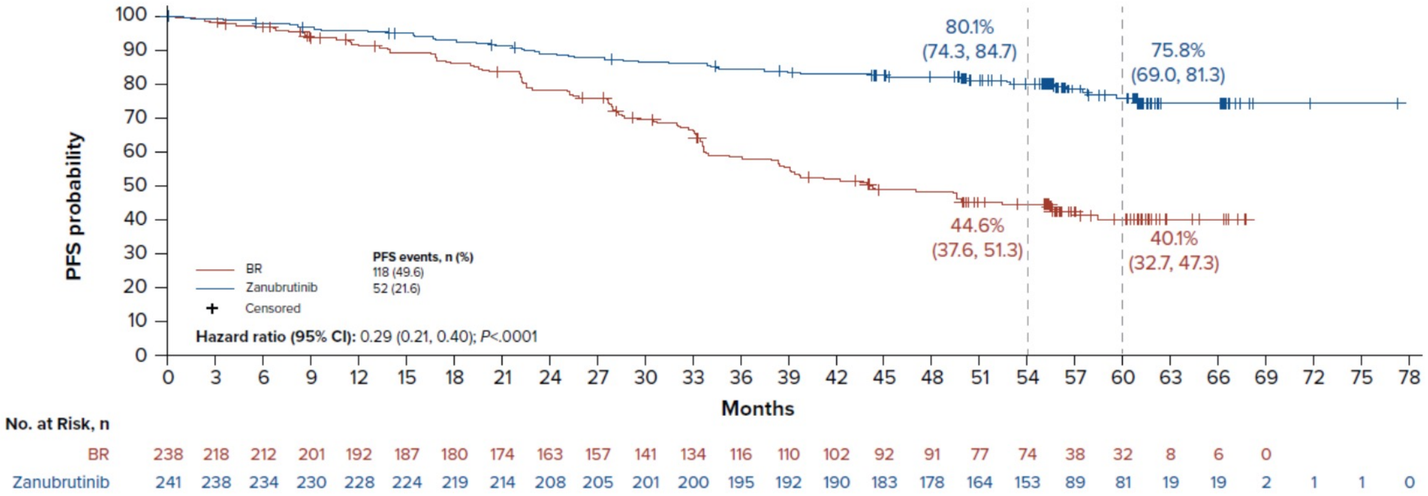




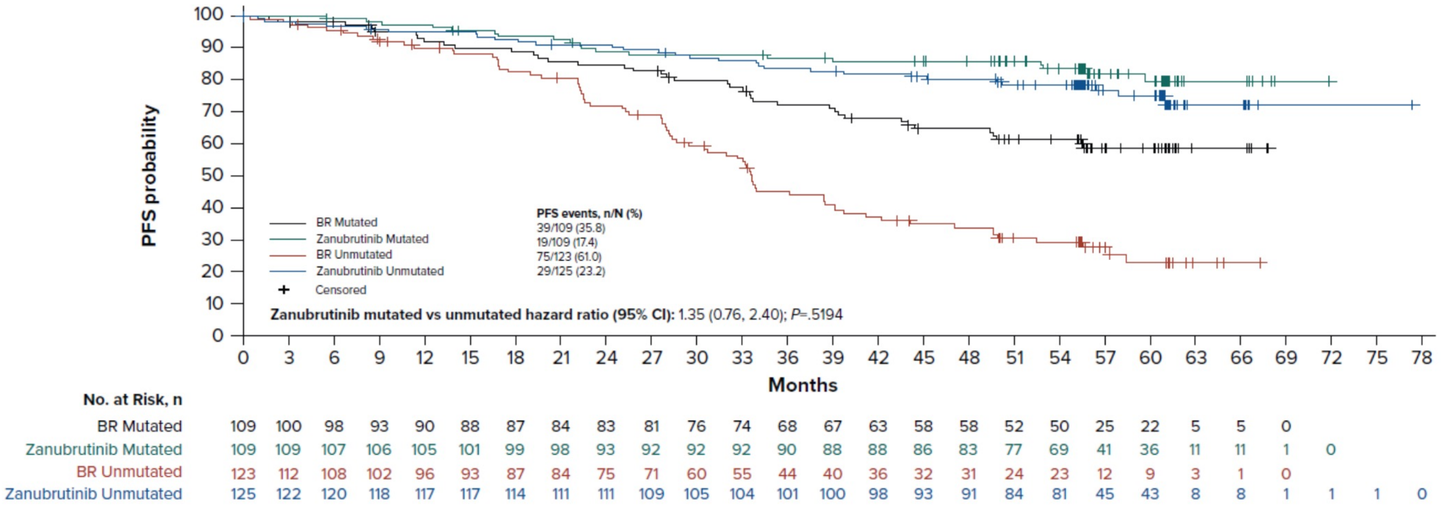
Median PFS: NR vs 44.1 months
5-years-PFS: 75.8% vs 40.1%
PFS was better in both IGHV mutated and unmutated patiens
COVID-adjusted 5-years-PFS: 78.7 vs 40.6%

Tam CS, et al, Lancet Oncol. 2022;23(8):1031-1043.

SEQUOIA: 5-year follow up



- Median PFS was not reached in patients who received zanubrutinib and was 44.1 months in patients who received BR
- Estimated 60-month PFS rates were 75.8% and 40.1% for zanubrutinib and BR, respectively



- ORR was 97.5% with zanu and 88.7% with BR
- CR/CRi rates were 20.7% with zanu and 23.5% with BR
- At this follow-up, 34 deaths occurred in each arm
  - Estimated 54-month OS rates were 87.7% and 86.0%
  - Estimated 60-month OS rates were 85.8% and 85.0% for zanu and BR

Shadman M, J Clin Oncol. 2025 Mar;43(7):780-787.

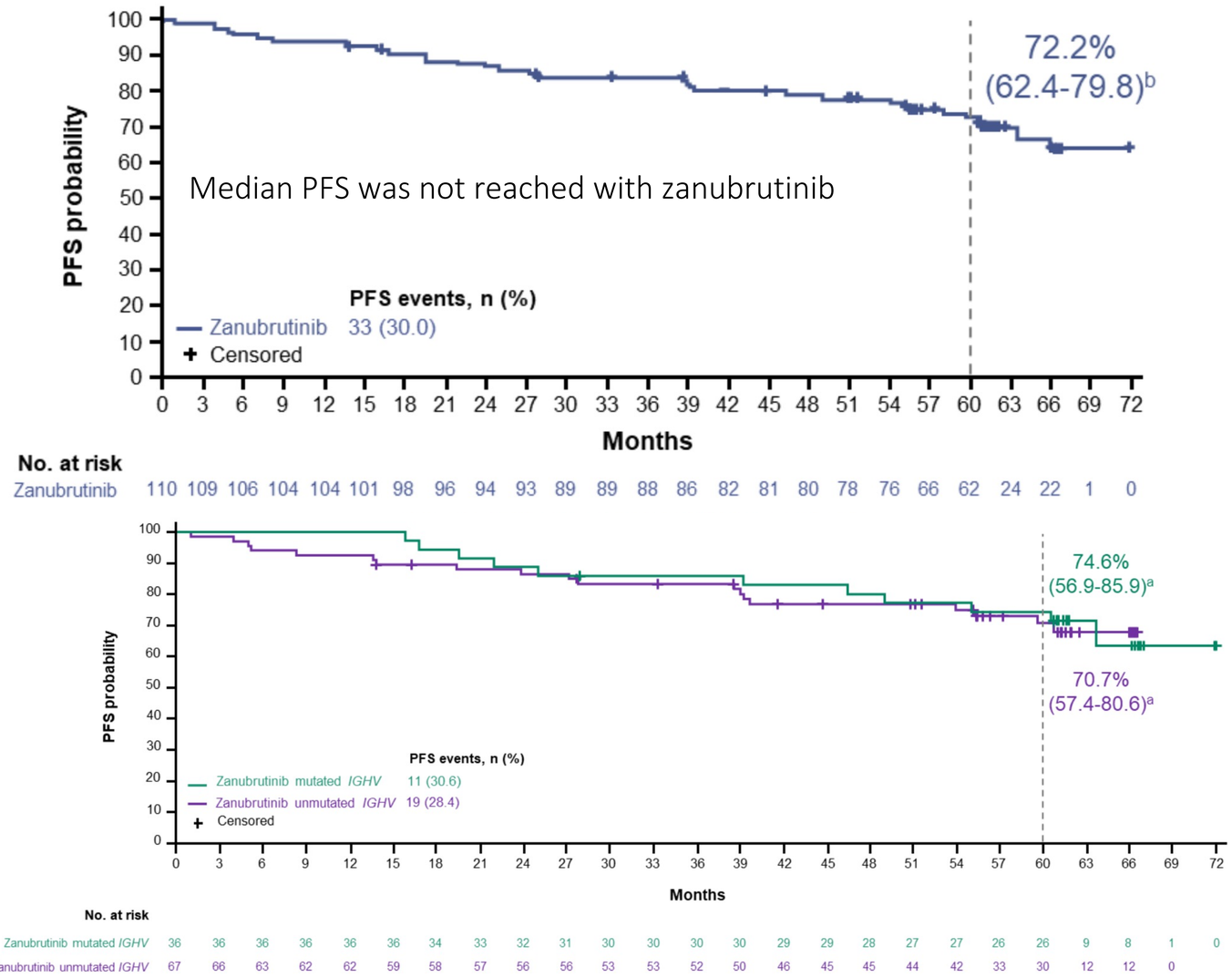
SEQUOIA: Arm C Baseline demographics and clinical characteristics

Baseline characteristics	All patients (N=111)
Age, median (range), years	71 (42-87)
≥65 years, n (%)	95 (85.6)
Male, n (%)	79 (71.2)
ECOG PS 0/1, n (%)	97 (87.3)
CLL, n (%)	100 (90.1)
SLL, n (%)	11 (9.9)
Binet stage C, n (%)[a]	37 (37.0)
Bulky disease, n (%)	
LDi ≥5 cm	44 (39.6)
LDi ≥10 cm	12 (10.8)

Baseline characteristics	All patients (N=111)
Median time from initial diagnosis, months	21.39
***TP53* mutated, n (%)**	47 (42.3)
del(17p), n (%)	110 (99.1)
del(17p) and *TP53* mutated, n (%)	47 (42.3)
IGHV mutated, n (%)	36 (32.4)
IGHV unmutated, n (%)	67 (60.4)
Complex karyotype, n (%)	
≥3 abnormalities	31 (27.9)
≥5 abnormalities	21 (18.9)

Shadman M, J Clin Oncol. 2025 Mar;43(7):780-787.

SEQUOIA Arm C: 5-year follow-up

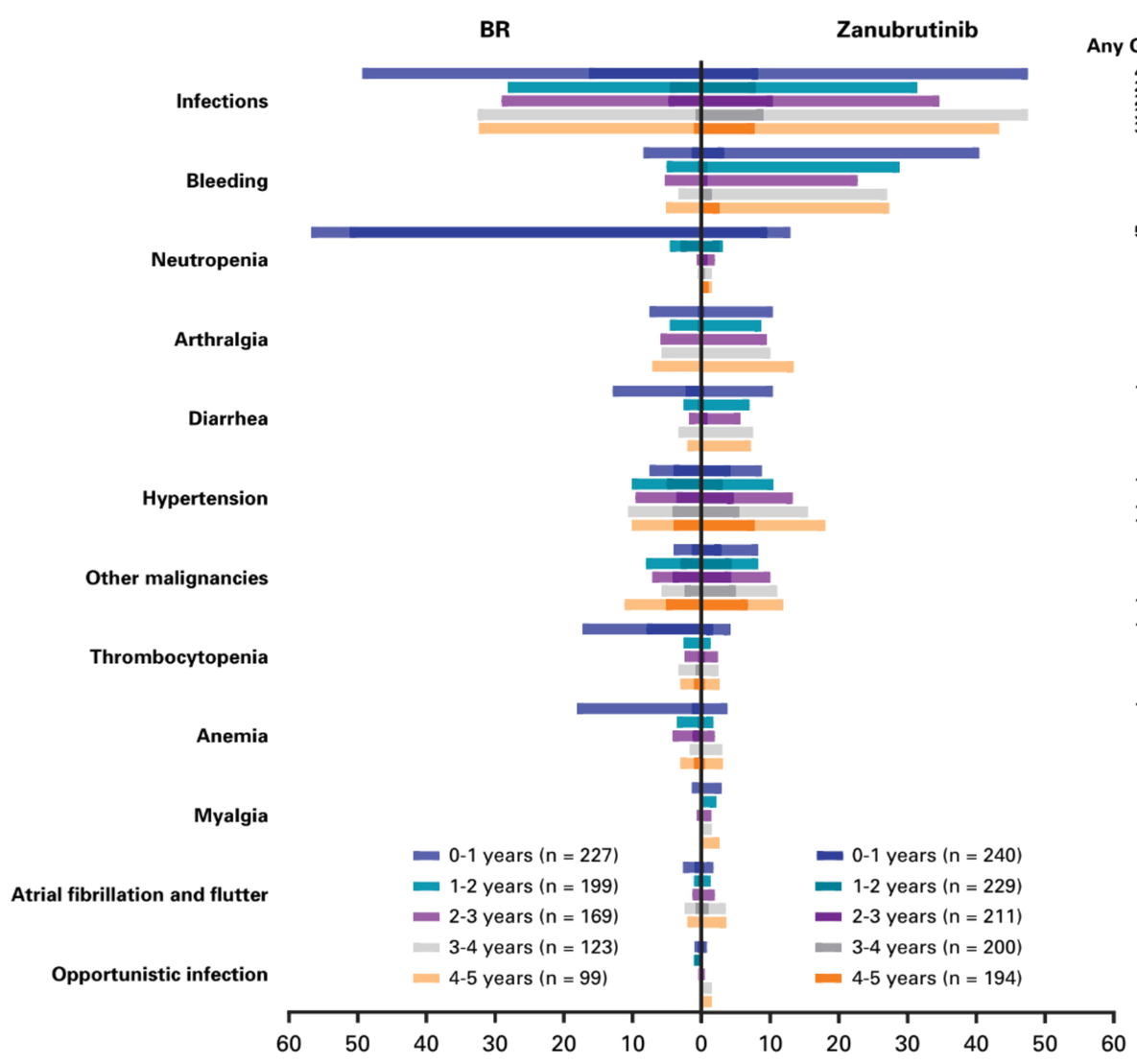


With a median follow-up of 5-years, zanubrutinib demonstrates durable efficacy in patients with del(17p).

The estimated 60-month PFS with zanubrutinib was 72.2%, similar to that observed in patients without del(17p)1 , highlighting that zanubrutinib overcomes the negative prognostic impact of del(17p)

Shadman M, J Clin Oncol. 2025 Mar;43(7):780-787.

SEQUOIA safety



	BR		Zanubrutinib	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Infections	49.3	16.3	47.5	8.3
	28.1	4.5	31.4	7.9
	29.0	4.7	34.6	10.4
	32.5	0.8	47.5	9.0
	32.3	1.0	43.3	7.7
Bleeding	8.4	1.3	40.4	3.3
	5.0	0.5	28.8	0.9
	5.3	0.0	22.7	0.9
	3.3	0.0	27.0	1.5
	5.1	0.0	27.3	2.6
Neutropenia	56.8	51.1	12.9	9.6
	4.5	3.0	3.1	2.6
	0.6	0.0	1.9	0.9
	0.0	0.0	1.5	0.5
	0.0	0.0	1.5	1.0
Arthralgia	7.5	0.4	10.4	0.4
	4.5	0.0	8.7	0.4
	5.9	0.0	9.5	0.0
	5.7	0.0	10.0	0.0
	7.1	0.0	13.4	0.0
Diarrhea	12.8	2.2	10.4	0.4
	2.5	0.0	7.0	0.4
	1.8	0.0	5.7	0.9
	3.3	0.0	7.5	0.0
	2.0	0.0	7.2	0.0
Hypertension	7.5	4.0	8.8	4.2
	10.1	5.0	10.5	3.1
	9.5	3.6	13.3	4.7
	10.6	4.1	15.5	5.5
	10.1	4.0	18.0	7.7
Other malignancies	4.0	1.3	8.3	2.9
	8.0	3.0	8.3	4.4
	7.1	4.1	10.0	4.3
	5.7	2.4	11.0	5.0
	11.1	5.1	11.9	6.7
Thrombocytopenia	17.2	7.9	4.2	1.7
	2.5	0.0	1.3	0.0
	2.4	0.0	2.4	0.5
	3.3	0.8	2.5	0.0
	3.0	1.0	2.6	0.5
Anemia	18.1	1.3	3.8	0.4
	3.5	0.0	1.7	0.4
	4.1	1.2	1.9	0.0
	1.6	0.0	3.0	0.0
	3.0	1.0	3.1	0.5
Myalgia	1.3	0.0	2.9	0.0
	0.0	0.0	2.2	0.0
	0.6	0.0	1.4	0.0
	0.0	0.0	1.5	0.0
	0.0	0.0	2.6	0.0
Atrial fibrillation and flutter	2.6	0.9	1.7	0.4
	1.0	0.5	1.3	0.0
	1.2	0.0	1.9	0.0
	2.4	0.8	3.5	1.0
	2.0	0.0	3.6	0.0
Opportunistic infection	0.9	0.4	0.8	0.4
	1.0	1.0	0.0	0.0
	0.0	0.0	0.5	0.0
	0.0	0.0	1.5	0.0
	0.0	0.0	1.5	0.0

SAE: 57% (gr≥3 50%) vs 57% (gr≥3 51%)
Infections: 80% (gr≥3 30%) vs 65% (gr≥3 22.5%)
Bleeding: 52% (gr≥3 7.5%) vs 13% (gr≥ 2%)
Hypertension: 20% (gr≥3 12%) vs 12% (gr≥3 6%)
COVID-19: 39% (gr≥3 9%) vs 12% (gr≥3 2%)
Pneumonia: 14% (gr≥3 6%) vs 11% (gr≥3 5%)

Neutropenia: 13% (gr≥3 10%) vs 46% (gr≥3 41%)
Anemia: 9% (gr≥3 1%) vs 21% (gr≥3 3%)
Thrombocytopenia: 6% (gr≥3 2%) vs 14% (gr≥3 7%)

Secondary malignancies: 24% vs 15%
Secondary skin cancer: 13% vs 9%

Tam CS, et al, Lancet Oncol. 2022;23(8):1031-1043.

Outcomes for PFS and OS for CLL frontline phase 3 trials with BTKi

Trial treatment no. of patients	Characteristics (median, if not indicated otherwise)		Estimate at month	PFS rate (%)				OS rate (%)			
				All patients	uIGHV	mIGHV	17p− and/or TP5 3mut	All patients	uIGHV	mIGHV	17p− and/or TP5 3mut
RESONATE-2 Ibr n = 136	FU: 60	Age: 73	36	82[a]	82[a]	83[a]		88[a]			
	CIRS >6: 31%		48	74[a]	75[a]	80[a]		86[a]			
	CrCl <60 mL/min: 44%		72	62[a]	62[a]	67[a]		77[a]			
ALLIANCE Ibr n = 182	FU: 55	Age: 71	36	82	82	84	78	89	89	86	83
		CrCl: 69	48	76	73	84	73	85	85	86	83
			72								
ELEVATE-TN Acala n = 179	FU: 75	Age: 70	36	84				92			
		CrCl: 75	48	78	77	81	76	88			
			72	62	60		56	76	76		72
SEQUOIA Zanu n = 241	FU: 44	Age: 70	36	84	82	87		91	89	93	
			48	79	72	86		88	85	93	
			72								

[a] Estimates from survival curve.

[b] Sole TP53 mutation; empty fields = data not available.

Acala, acalabrutinib; Age, age in years; CrCl, creatinine clearance in mL/min; FU, median follow-up time in months; Ibr, ibrutinib; n.a., not applicable as 17p− and TP53mut were excluded; Obi, obinutuzumab; R, rituximab; Ven, venetoclax; Zanu, zanubrutinib.

CLL frontline treatment

FIXED-DURATION VEN-BASED COMBINATIONS

A phase 3, open-label, multicenter, randomised study of Obinutuzumab-Venetoclax vs Obinutuzumab-Chlorambucil in untreated patients with CLL and coexisting medical conditions (CLL 14)

Inclusion criteria

- Untreated CLL
- ≥18 years
- Unfit due to coexisting conditions (CIRS >6 or eGFR <70 ml/min or both)
- Plt ≥30.000/mmc (≥10.000/mmc if BOM involvement)
- Hb ≥9 g/dl (unless BOM involvement)
- ANC ≥1.000/mmc
- No ECOG restrictions

Exclusion criteria

- Richter transformation
- CNS involvement
- eGFR < 30 ml/min
- Uncontrolled AIHA or ITP

Obinutuzumab-Venetoclax

Obinutuzumab-Chlorambucil

Enrollment period: from 7 Aug 2015 to 4 Aug 2016
Median follow up: 39.6 months

Response assesment:

- C4D1
- C7D1
- 3 months after tp completion

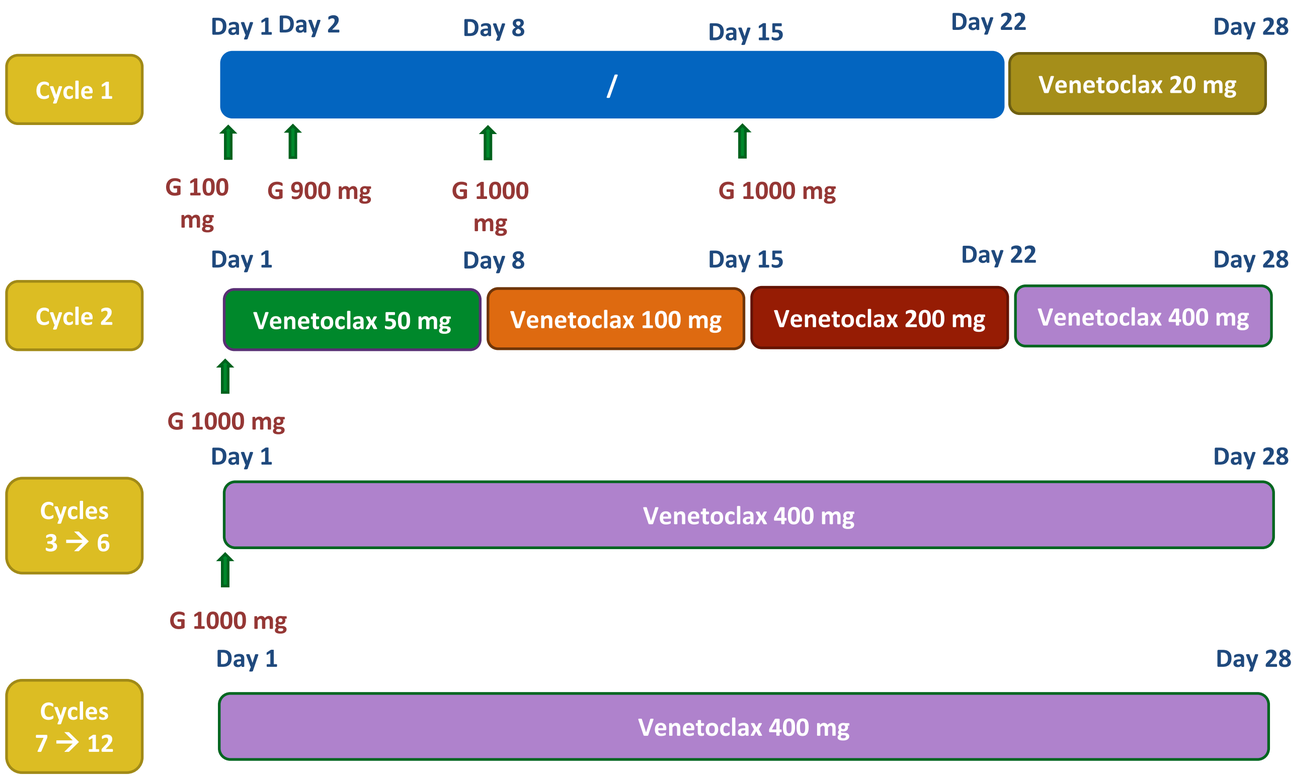
Primary endpoint: PFS
Secondary endopoints:

- ORR, CRR (at 3 months after tp completion);
- MRD in PB and BM (at 3 months after tp completion via ASO-PCR);
- DOR, EFS, TTNT, OS

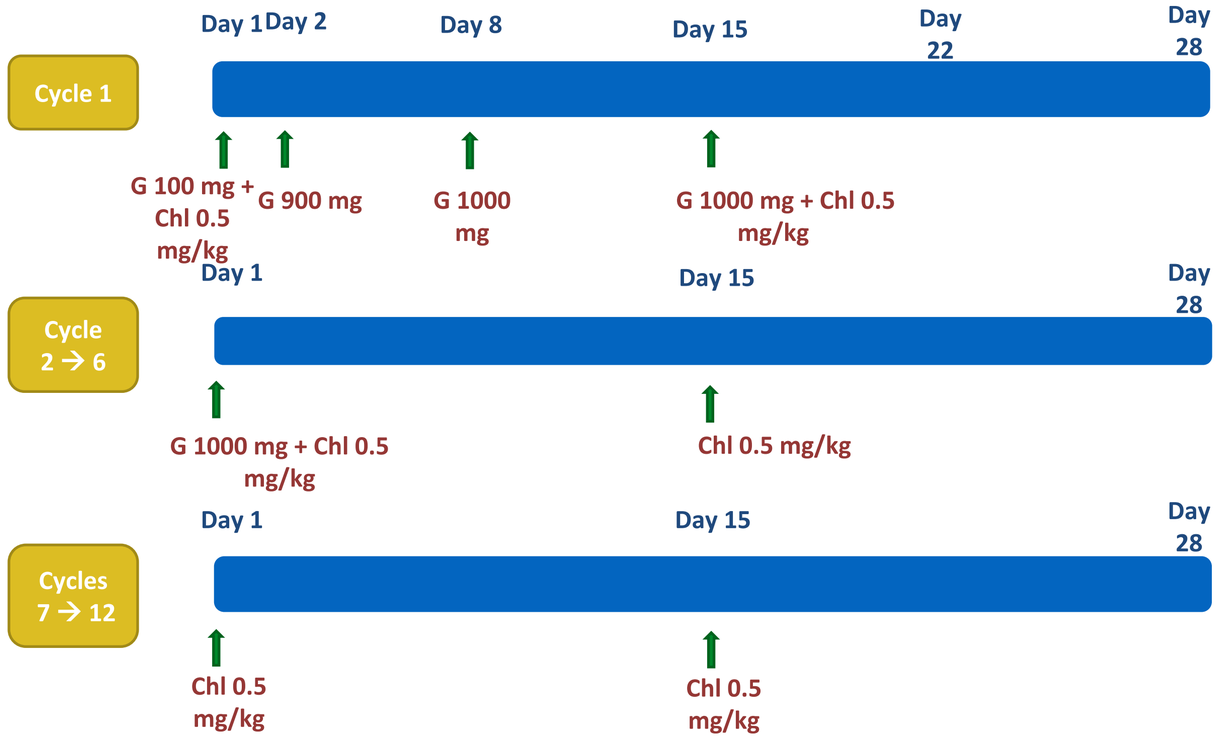
K. Fischer et al, N Engl J Med 2019;380:2225-2236

Treatment schedule CLL14

Obinutuzumab-Venetoclax



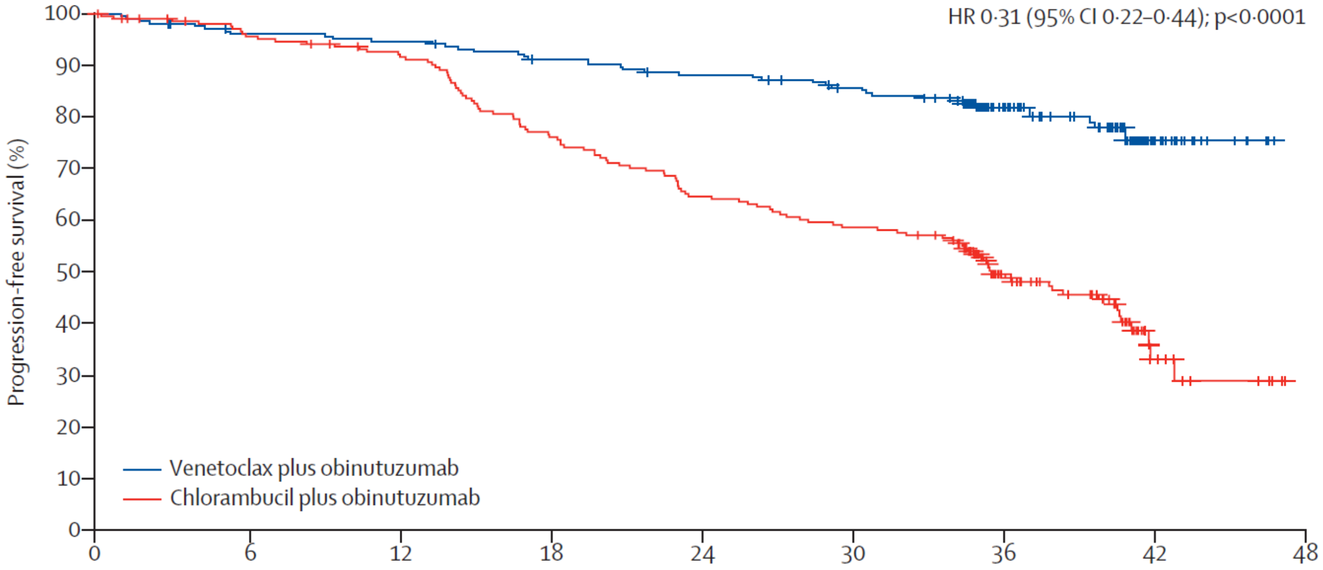
Obinutuzumab-Chlorambucil



K. Fischer et al, N Engl J Med 2019;380:2225-2236

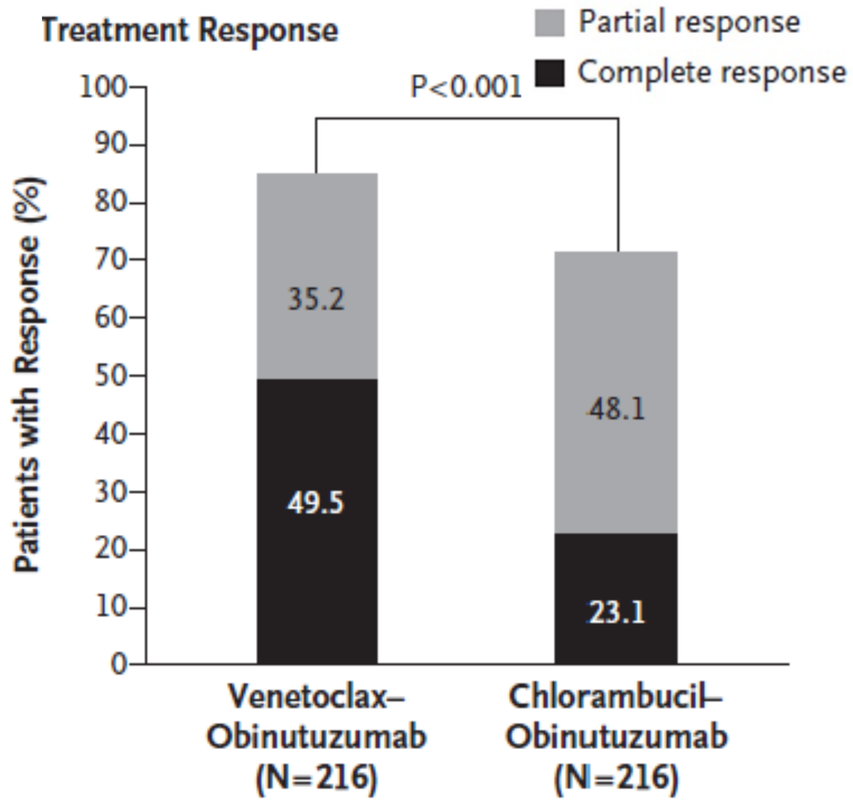
CLL14 results: PFS

Median follow up: 39.6 months
Median PFS: NR vs 35.6 months
3-years PFS: 81.9% vs 49.5%



Number at risk (number censored)									
Venetoclax plus obinutuzumab	216 (0)	195 (13)	192 (13)	183 (15)	176 (16)	167 (20)	97 (83)	23 (151)	0 (174)
Chlorambucil plus obinutuzumab	216 (0)	194 (13)	184 (16)	153 (16)	129 (16)	117 (16)	69 (48)	1 (93)	0 (103)

ORR: 84.7% (CR 49.5%) vs 71.2% (CR 23.1%)

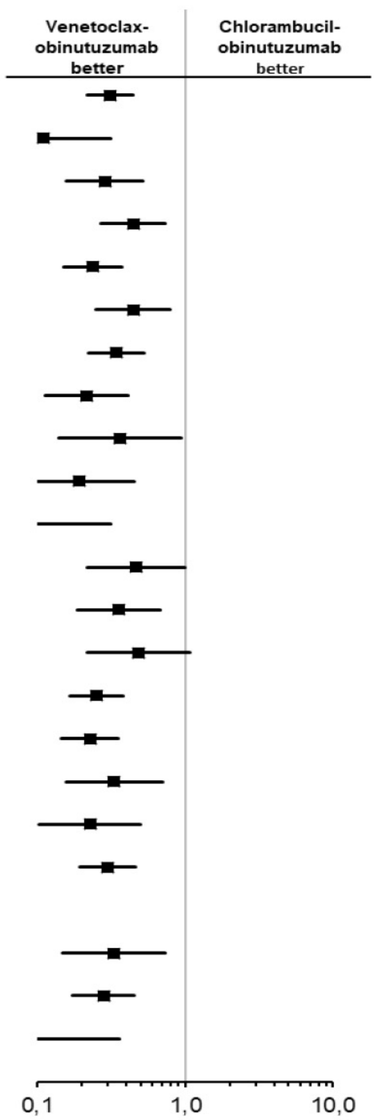


42 PFS events (21 due to PD, 9 of whom required II line therapy) vs 113 PFS events (102 due to PD)

K. Fischer et al, N Engl J Med 2019;380:2225-2236

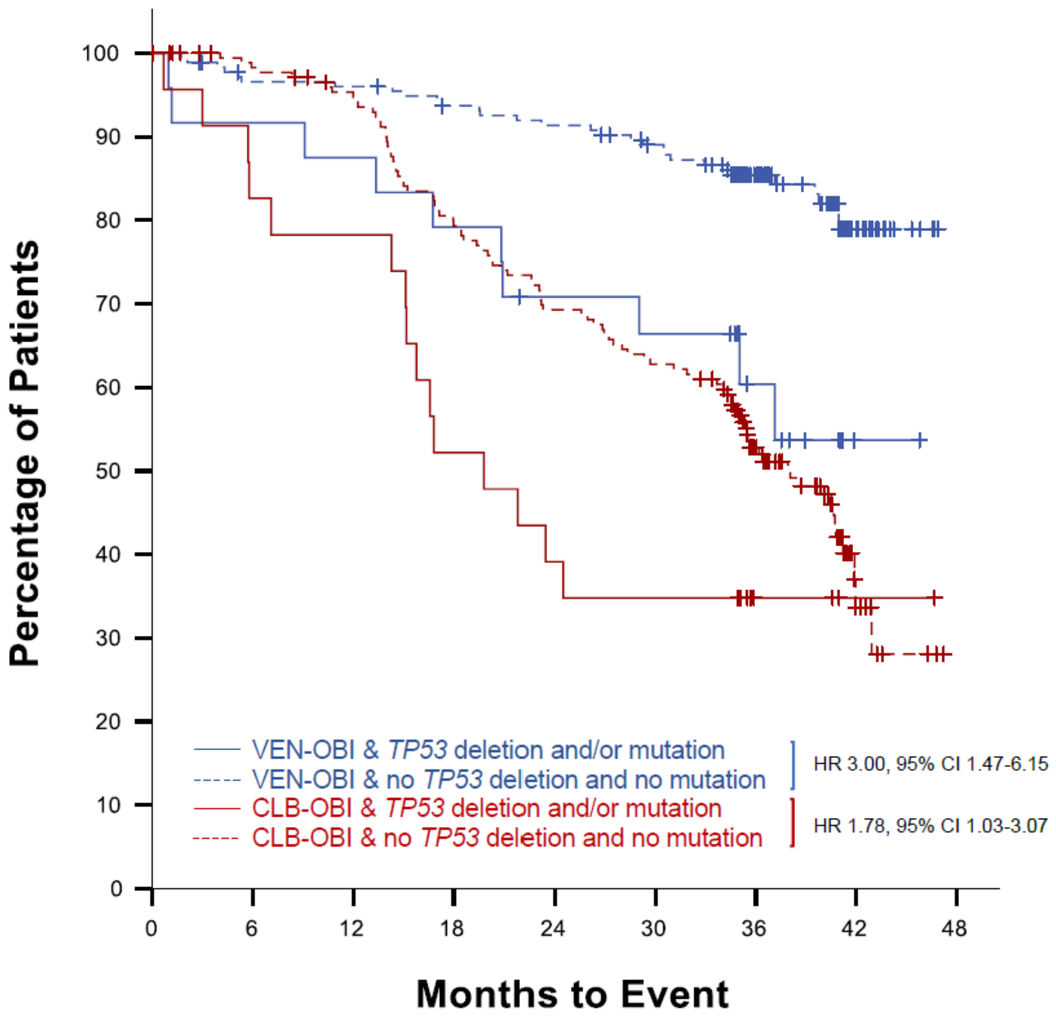
CLL14 results: PFS – Forest plot

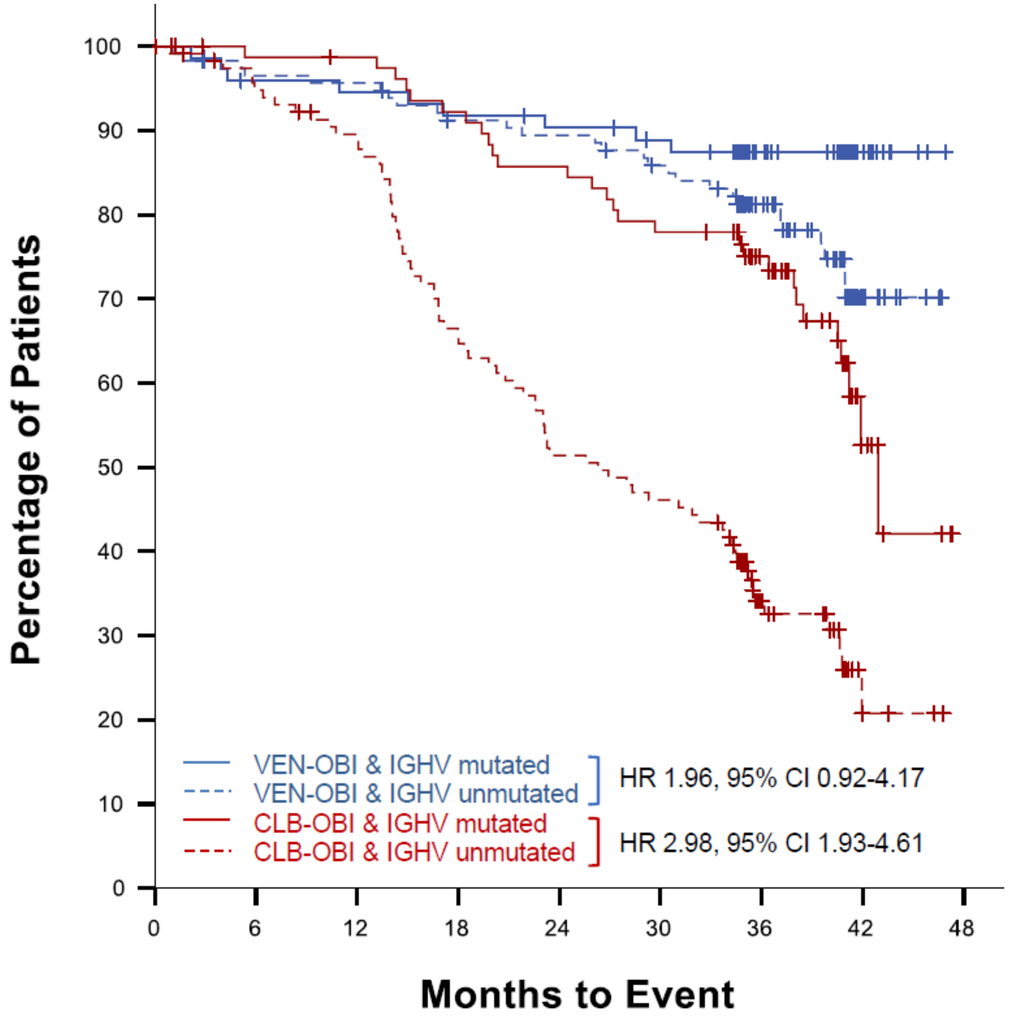
			Chlorambucil-obinutuzumab			Venetoclax-obinutuzumab						
Category	Subgroup	Total n	n	Events	PFS rate month 36 (%)	n	Events	PFS rate month 36 (%)	Hazard ratio	95% Wald CI	Interaction test	Venetoclax-obinutuzumab better / Chlorambucil-obinutuzumab better
All		**432**	**216**	**113**	**49.5**	**216**	**42**	**81.9**	**0.31**	**0.22-0.44**		
Binet stage at screening	A	90	44	26	43.7	46	4	93.4	0.11	0.04-0.32	0.060	
	B	156	80	41	51.2	76	15	82.6	0.29	0.16-0.52		
	C	186	92	46	51.4	94	23	75.1	0.44	0.27-0.73		
Age groups (years)	<75	282	138	76	46.9	144	25	85.0	0.24	0.15-0.37	0.107	
	≥75	150	78	37	53.9	72	17	75.4	0.44	0.25-0.79		
Gender	Male	289	143	71	50.3	146	30	79.9	0.34	0.22-0.53	0.261	
	Female	143	73	42	47.8	70	12	86.0	0.21	0.11-0.41		
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	10	23.1	17	8	48.5	0.36	0.14-0.94	0.141	
	del(11q)	74	38	24	35.2	36	7	85.3	0.19	0.08-0.45		
	Trisomy 12	76	40	22	40.4	36	2	96.2	0.07	0.02-0.31		
	No abnormalities	92	42	18	62.9	50	11	78.4	0.47	0.22-0.99		
	del(13q)	145	74	33	62.0	71	13	84.0	0.35	0.19-0.67		
TP53 deletion and/or mutation	Present	49	24	15	34.8	25	10	60.4	0.48	0.22-1.08	0.223	
	Not present	368	184	92	52.8	184	30	85.4	0.25	0.17-0.38		
IGHV mutational status	Unmutated	244	123	78	34.1	121	27	81.2	0.23	0.15-0.35	0.385	
	Mutated	159	83	28	75.0	76	9	87.4	0.33	0.16-0.70		
Complex karyotype	NCKT	333	167	80	56.0	166	29	84.6	0.30	0.20-0.46	0.390	
	CKT/HCKT	64	30	22	22.5	34	9	75.0	0.23	0.10-0.49		
CLL-IPI risk group	Low	36	19	3	88.9	17	0	100	NE	0.00-NE		
	Intermediate	102	55	24	60.7	47	8	86.7	0.328	0.15-0.73		
	High	230	118	66	45.9	112	23	81.8	0.280	0.17-0.45		
	Very high	19	8	8	0	11	4	62.3	0.042	0.01-0.36		



K. Fischer et al, N Engl J Med 2019;380:2225-2236

CLL14 PFS according to risk factor

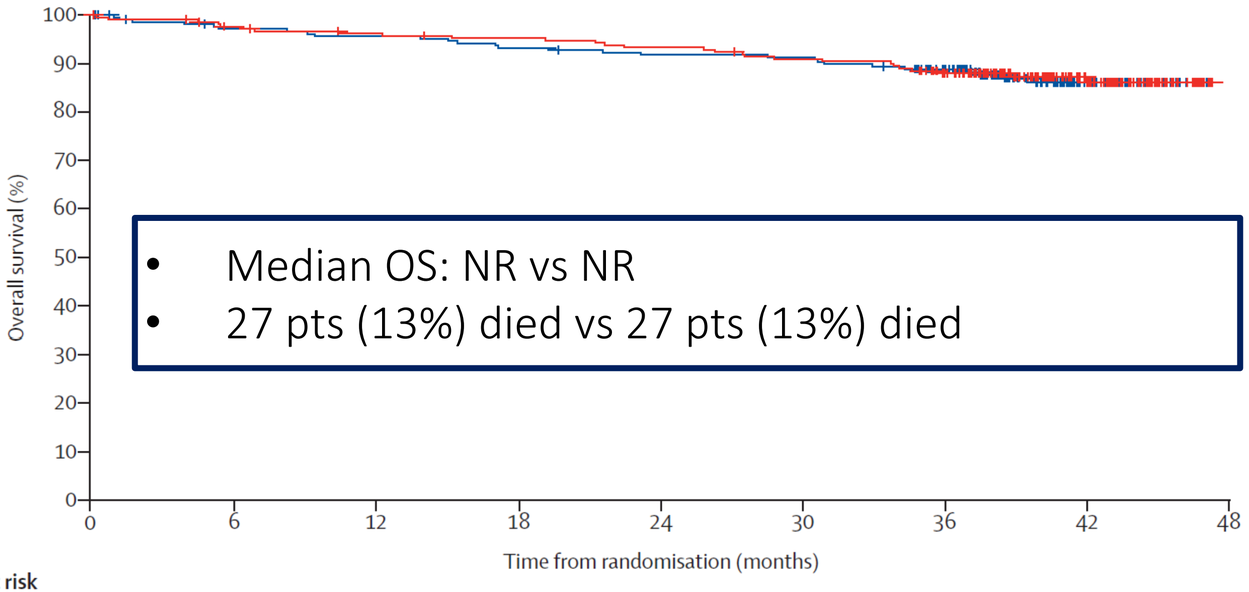




PFS is lower in pts with TP53m/del17p and IGHV unmutated

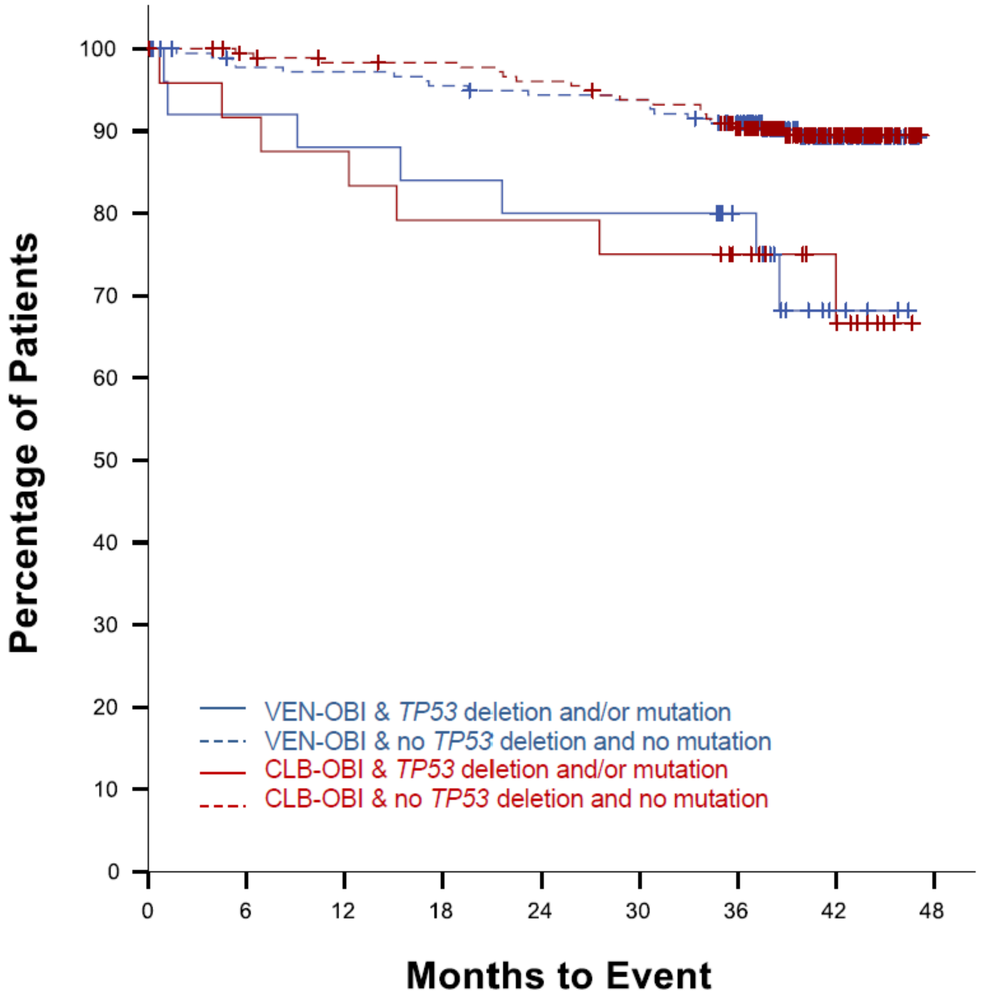
K. Fischer et al, N Engl J Med 2019;380:2225-2236

CLL14 results: OS



- Median OS: NR vs NR
- 27 pts (13%) died vs 27 pts (13%) died

Number at risk (number censored)									
Venetoclax plus obinutuzumab	216 (0)	201 (9)	198 (9)	193 (8)	189 (10)	188 (10)	169 (24)	65 (124)	0 (189)
Chlorambucil plus obinutuzumab	216 (0)	206 (5)	201 (7)	198 (8)	194 (8)	188 (9)	170 (21)	71 (118)	0 (189)



Most common cause of death was:

- AE: 19 pts (9%) and PD 5 pts (2%)

vs

- PD: 11 pts (5%) and AE 11 pts (5%)

K. Fischer et al, N Engl J Med 2019;380:2225-2236

CLL14 safety

Overall Incidence of Adverse Events (Any Grade)

- Venetoclax–Obinutuzumab: 94.3% of patients
- Chlorambucil–Obinutuzumab: 99.5% of patients

Treatment Discontinuation Due to AEs

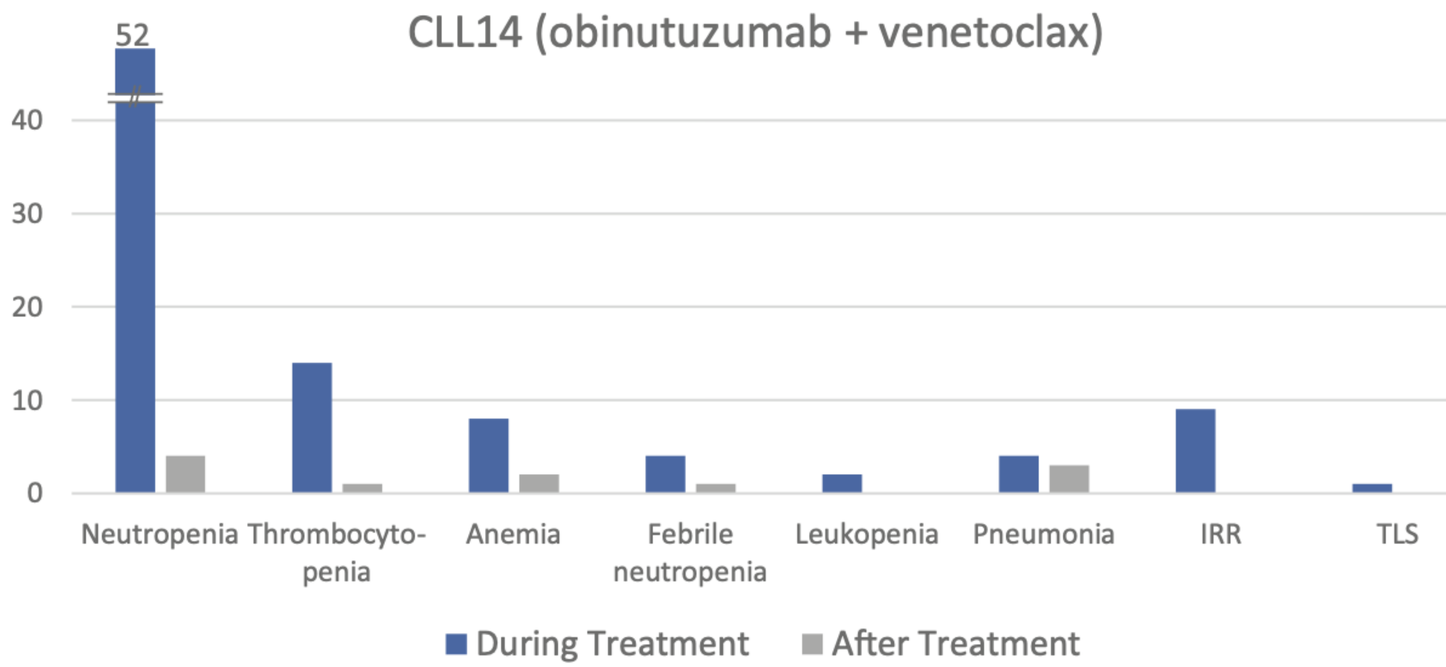
- Venetoclax–Obinutuzumab: 16.0%
- Chlorambucil–Obinutuzumab: 15.4%

Most Common Grade 3/4 Adverse Event

- Neutropenia (in both treatment groups)

Other G3-4 AEs

- Febrile neutropenia: 5.2% (obi-ven) vs 3.7% (obi-chl)
- Infections: 17.5% (obi-ven) vs 15% (obi-chl)

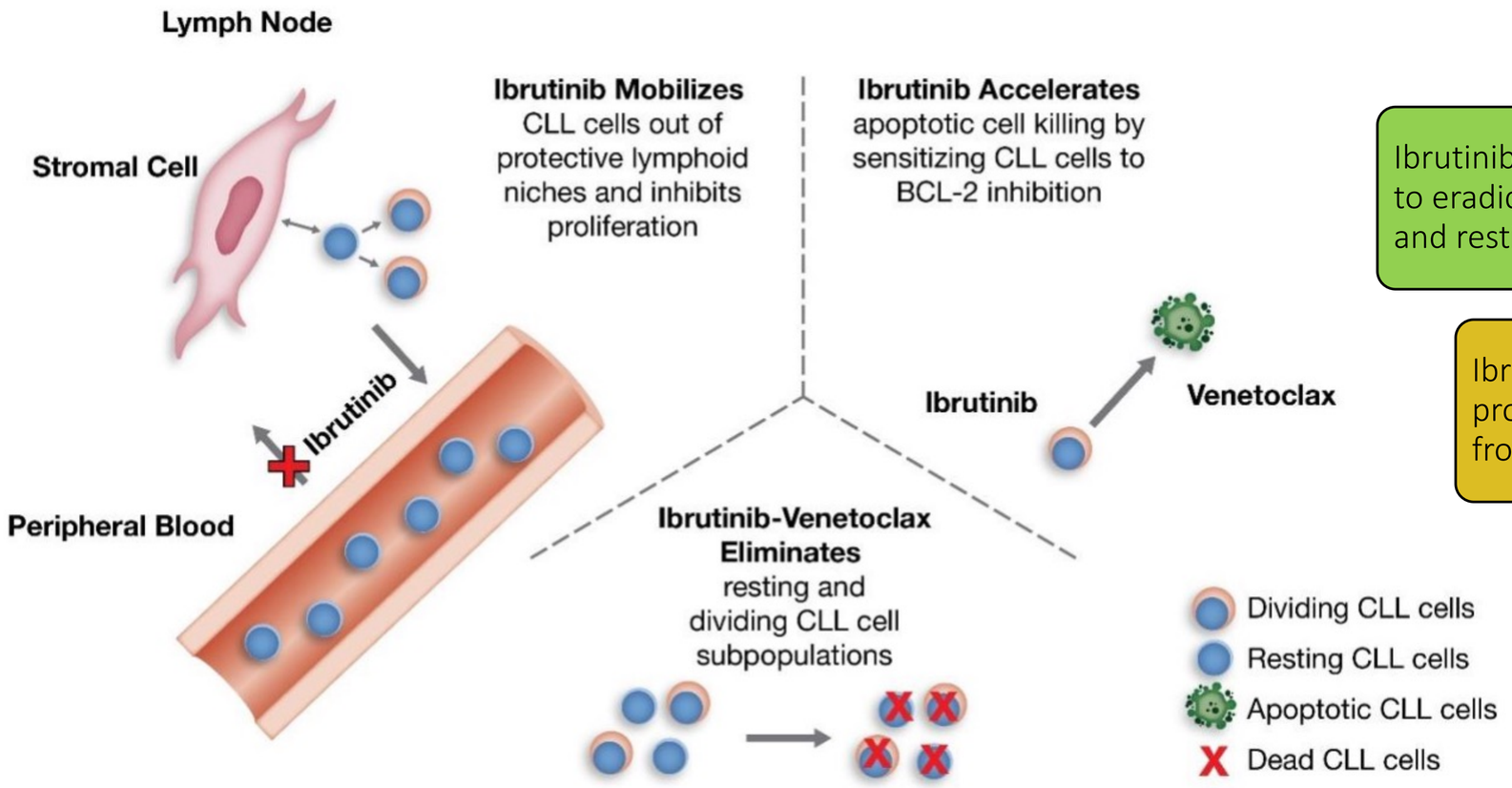


AE-related deaths: 19 (9%) vs 11 (5%)
Deaths occurring during tp: 4 (2%) vs 5 (2%)
Deaths possibly tp-related: 1 pt (sepsis) vs 2 pts (septic shock and metastatin skin K)
Most common cause of AE-related death: Infections and cardiac events vs Infections and neoplasm

Grade 3-4 AE: 150 (71%) vs 155 (72%)
Most common grade 3-4 AE:
Neutropenia: 112 (53%) vs 102 (48%)
Thrombocytopenia: 29 (13%) vs 35 (15%)
infusion-related reactions (IRRs) 17 (9%) vs 22 (11%)

K. Fischer et al, N Engl J Med 2019;380:2225-2236

Putative Mechanism of Action for Ibru-Ven combination in CLL



Ibrutinib and Venetoclax work synergistically to eradicate CLL by eliminating both dividing and resting leukemic subpopulations.

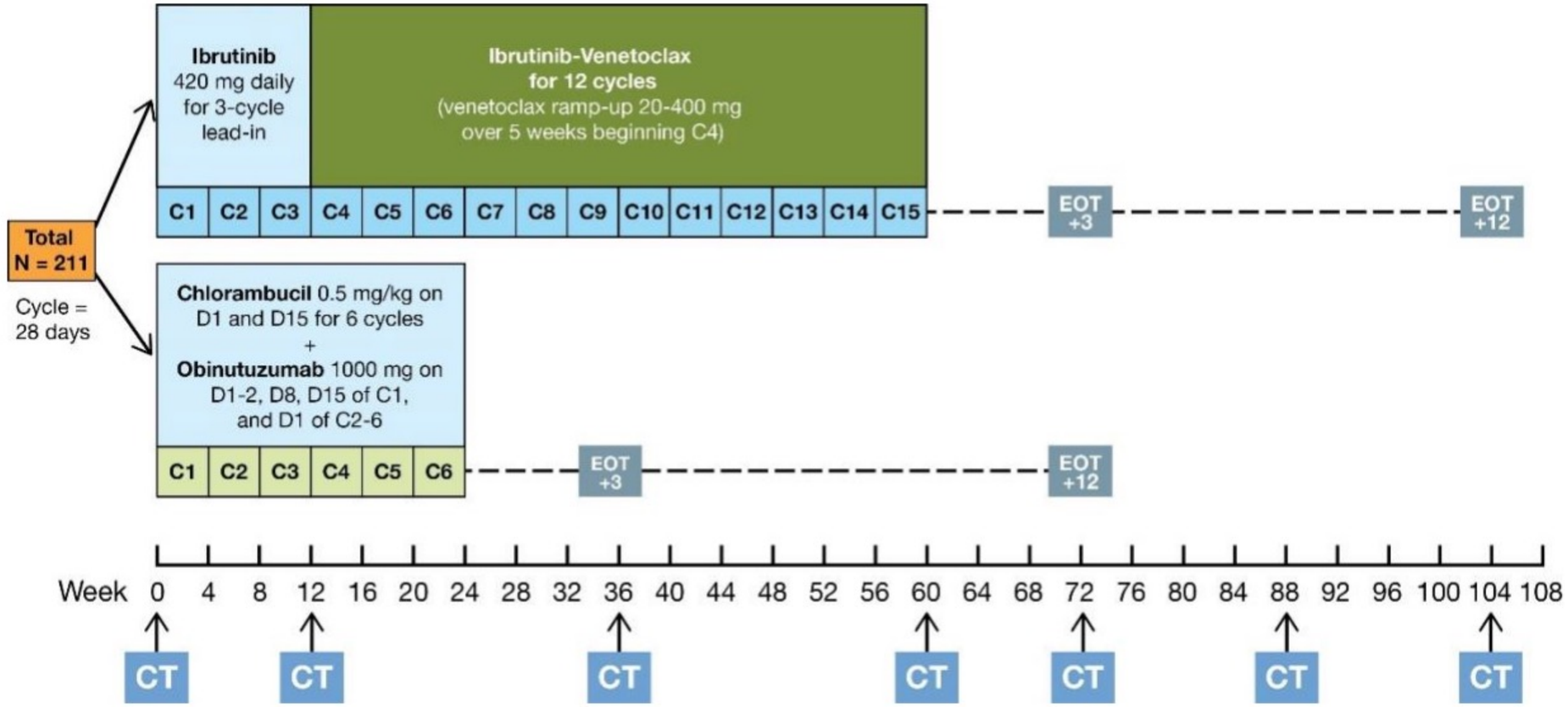
Ibrutinib effectively inhibits tumor cell proliferation, while mobilizing leukemic cells from protective lymphoid niches.

Ibrutinib increases the sensitivity of CLL cells to BCL-2 inhibition, thereby accelerating apoptotic cell killing by venetoclax.

Combining ibrutinib and venetoclax has the potential to induce deep responses with time-limited therapy, enabling treatment-free remissions for patients

A.P. Karter et al NEJM Evid. 2022 Jul;1(7):EVIDoa2200006

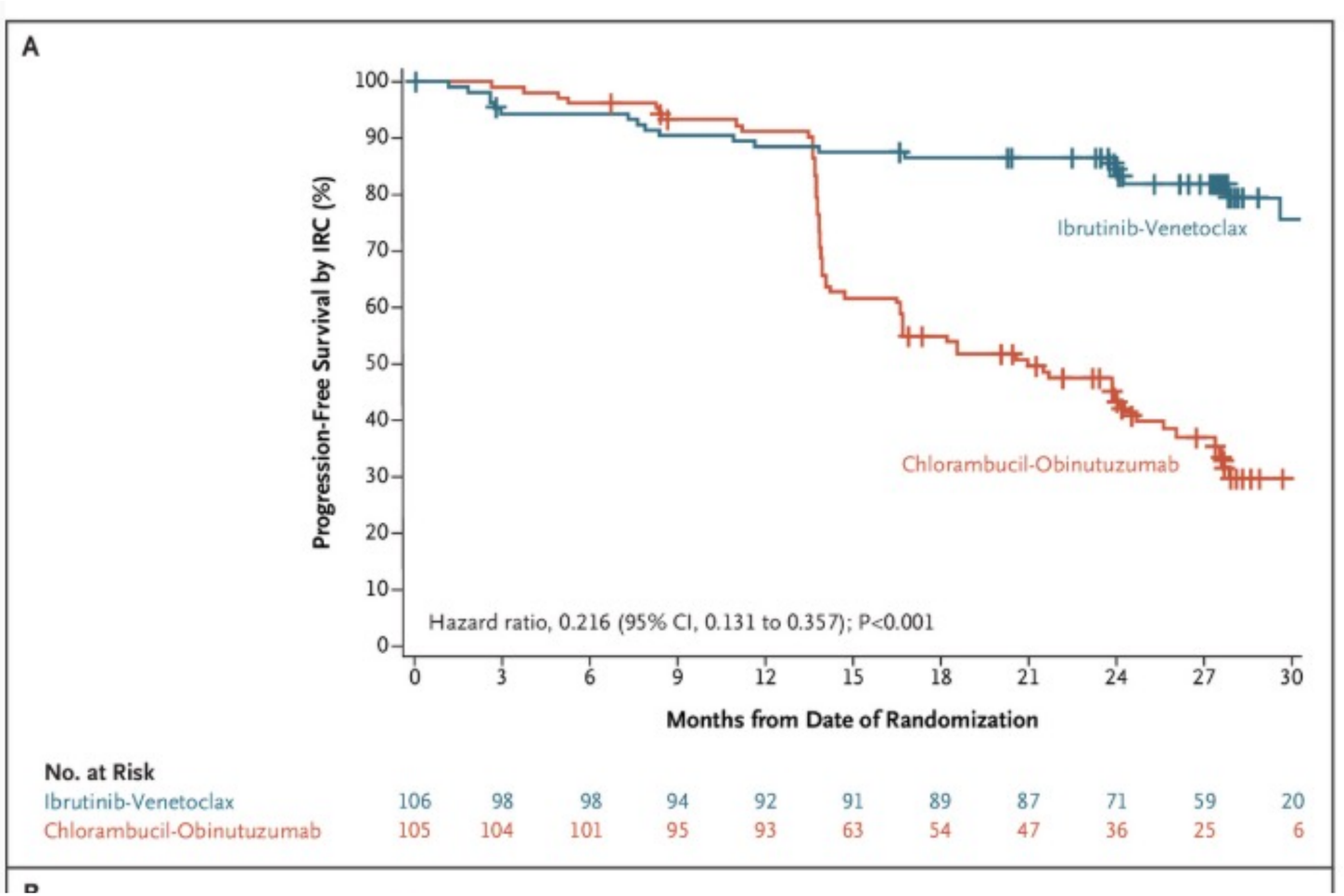
GLOW: a phase 3 trial evaluating the efficacy and safety of ibrutinib-venetoclax in older patients and/or those with comorbidities with previously untreated chronic lymphocytic leukemia (CLL)

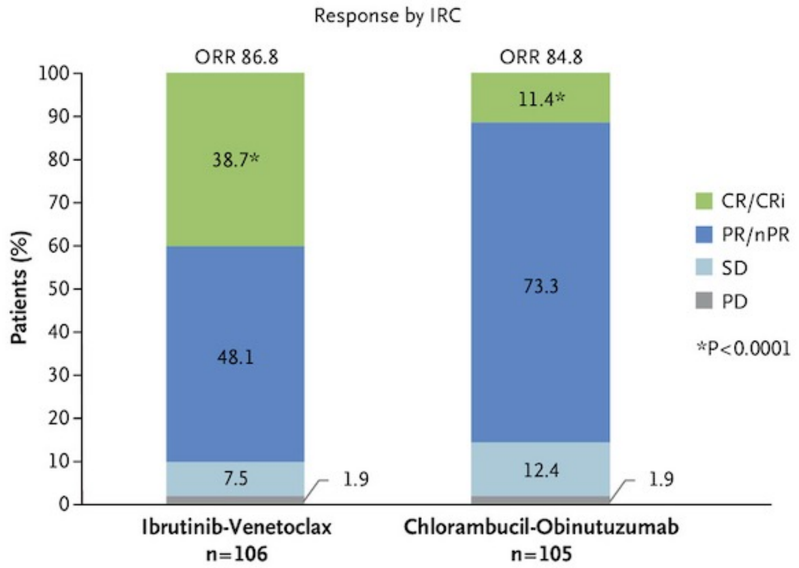


Progression-free survival (PFS) events were confirmed by CT scan and absolute lymphocyte count.

A.P. Karter et al NEJM Evid. 2022 Jul;1(7):EVIDoa2200006

GLOW efficacy outcomes

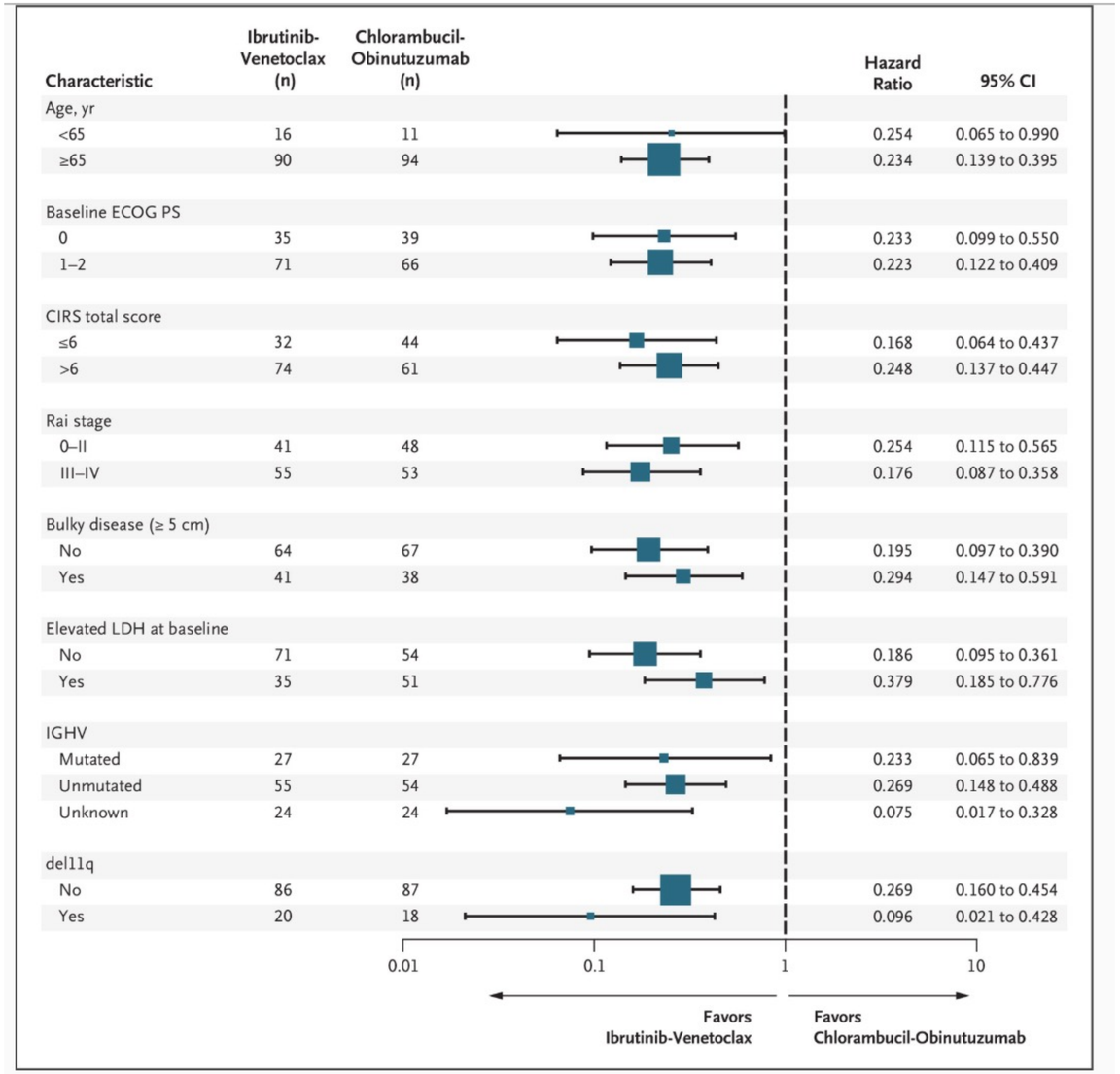




The ORR as assessed by IRC was similar between treatment arms (86.8% vs. 84.8%), with a higher proportion of CR in the Ibru-ven arm

A.P. Karter et al NEJM Evid. 2022 Jul;1(7):EVIDoa2200006

Subgroup Analysis of Independent Review Committee–Assessed PFS

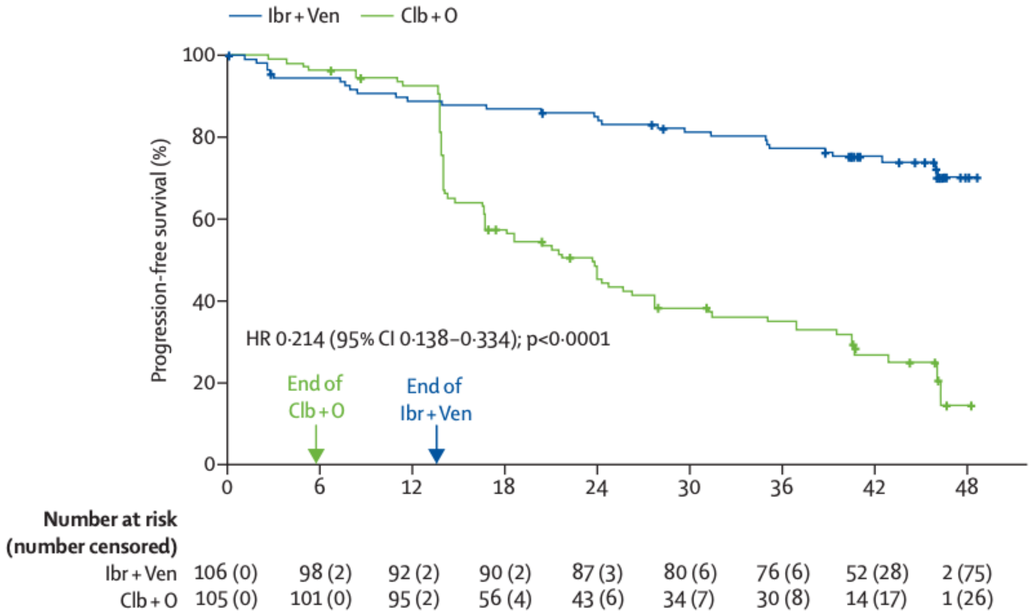


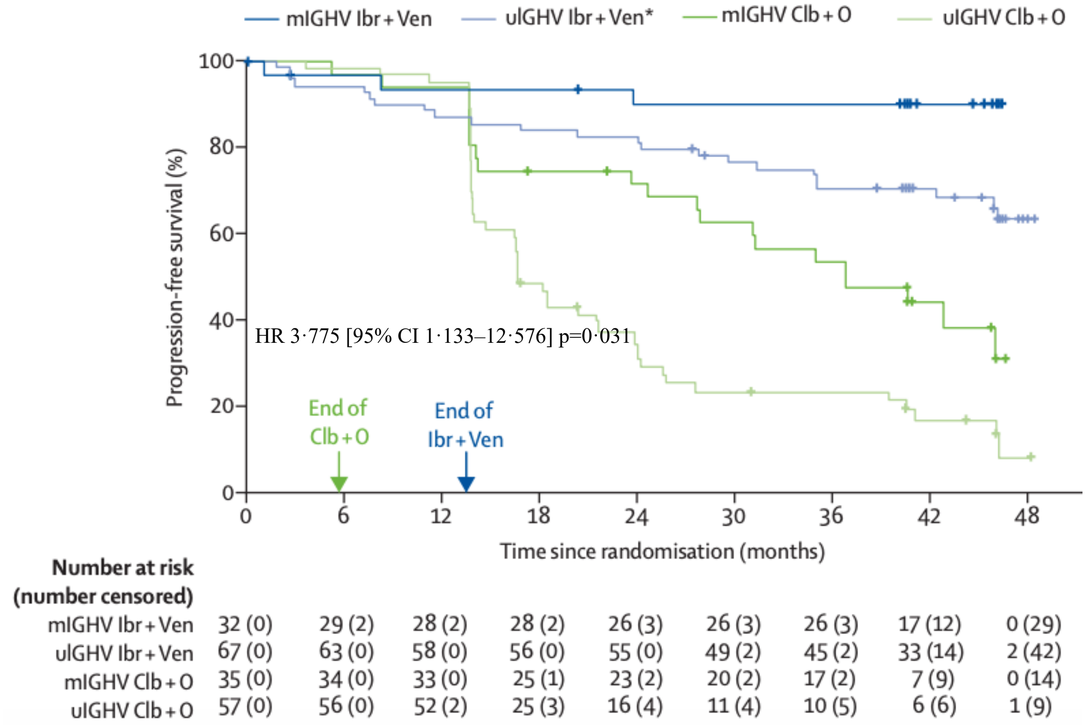
Characteristic	Ibrutinib-Venetoclax (n)	Chlorambucil-Obinutuzumab (n)	Hazard Ratio	95% CI
Age, yr				
<65	16	11	0.254	0.065 to 0.990
≥65	90	94	0.234	0.139 to 0.395
Baseline ECOG PS				
0	35	39	0.233	0.099 to 0.550
1–2	71	66	0.223	0.122 to 0.409
CIRS total score				
≤6	32	44	0.168	0.064 to 0.437
>6	74	61	0.248	0.137 to 0.447
Rai stage				
0–II	41	48	0.254	0.115 to 0.565
III–IV	55	53	0.176	0.087 to 0.358
Bulky disease (≥ 5 cm)				
No	64	67	0.195	0.097 to 0.390
Yes	41	38	0.294	0.147 to 0.591
Elevated LDH at baseline				
No	71	54	0.186	0.095 to 0.361
Yes	35	51	0.379	0.185 to 0.776
IGHV				
Mutated	27	27	0.233	0.065 to 0.839
Unmutated	55	54	0.269	0.148 to 0.488
Unknown	24	24	0.075	0.017 to 0.328
del11q				
No	86	87	0.269	0.160 to 0.454
Yes	20	18	0.096	0.021 to 0.428

A benefit in IRC-assessed PFS was shown in patients treated with ibrutinib-venetoclax across stratification factors (del(11q) status and IGHV mutational status), and in prespecified subgroups, including patients 65 years of age or older or with a CIRS score greater than 6

A.P. Karter et al NEJM Evid. 2022 Jul;1(7):EVIDoa2200006

GLOW 4-year follow-up: PFS



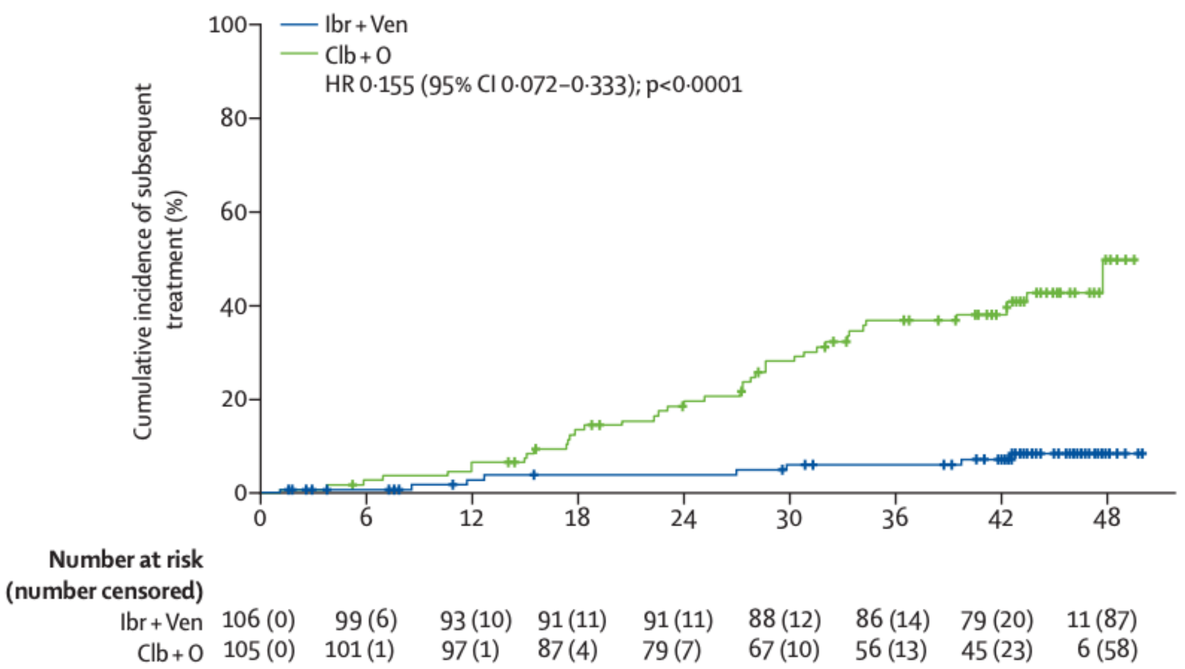


With a median follow-up of 46 months (IQR 43–47), independent review committee-assessed progressionfree survival remained superior for the ibrutinib– venetoclax group (29 events) compared with the chlorambucil–obinutuzumab group.

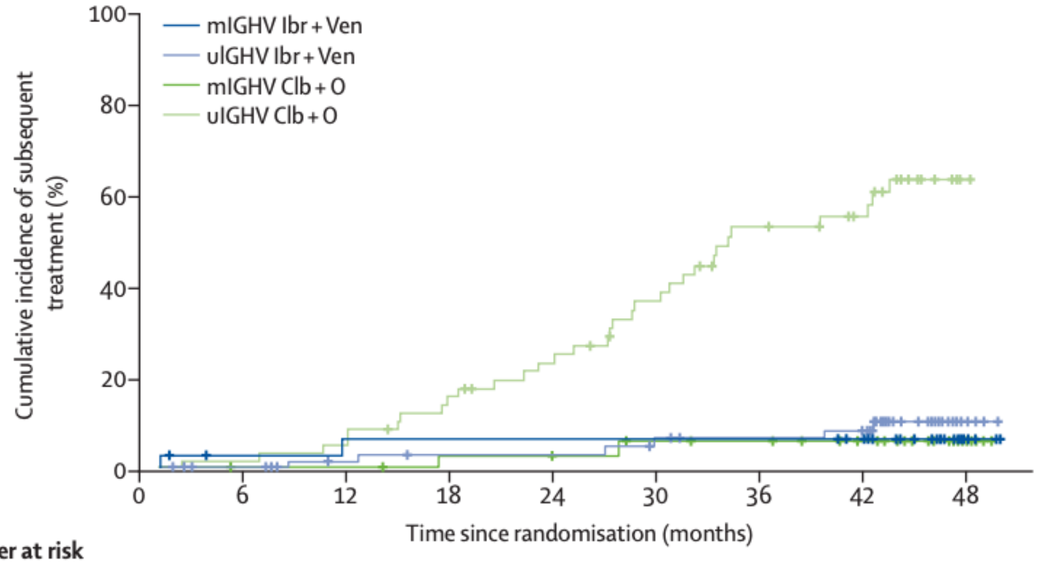
When assessing progression-free survival per IGHV mutation status, 42-month rates in the ibrutinib– venetoclax group were 69·8% (95% CI 57·2–79·4; 23 events) in patients with unmutated IGHV compared with 90·0% (72·0–96·7; three events) in patients with mutated IGHV

Niemann CU, et al. Lancet Oncol. 2023;24(12):1423-1433

GLOW 4-year follow-up: incidence of subsequent treatment



Number at risk (number censored)									
Ibr + Ven	106 (0)	99 (6)	93 (10)	91 (11)	91 (11)	88 (12)	86 (14)	79 (20)	11 (87)
Clb + O	105 (0)	101 (1)	97 (1)	87 (4)	79 (7)	67 (10)	56 (13)	45 (23)	6 (58)



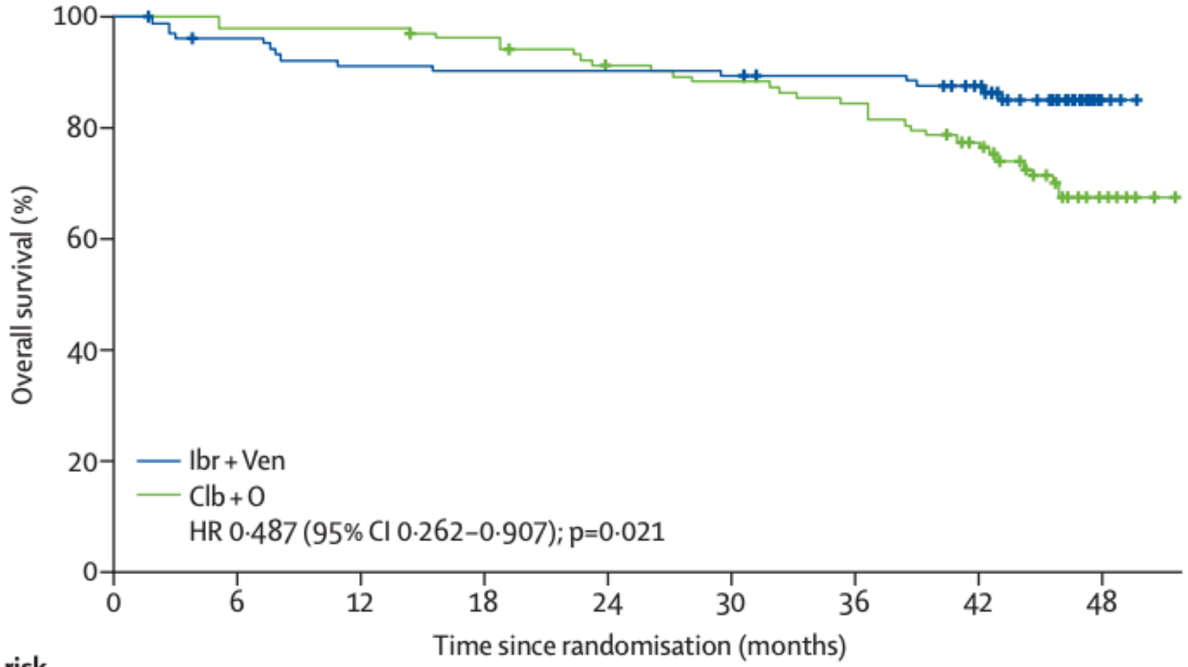
Number at risk (number censored)									
mIGHV Ibr + Ven	32 (0)	29 (2)	28 (2)	28 (2)	28 (2)	28 (2)	27 (3)	24 (6)	4 (26)
mIGHV Clb + O	35 (0)	34 (1)	34 (1)	32 (2)	31 (3)	29 (4)	28 (5)	22 (11)	5 (28)
uIGHV Ibr + Ven	67 (0)	64 (3)	59 (7)	57 (8)	57 (8)	54 (9)	53 (10)	51 (11)	7 (54)
uIGHV Clb + O	57 (0)	56 (0)	52 (0)	47 (1)	41 (3)	32 (5)	22 (7)	17 (11)	1 (24)

At the 46-month median follow-up, median time to next treatment was not reached in both treatment groups. Among patients receiving first-line ibrutinib–venetoclax, eight (8%) of 106 required second-line treatment, compared with 41 (39%) of 105 among the chlorambucil–obinutuzumab-treated patients.

Most patients in the ibrutinib–venetoclax group had not initiated subsequent therapy at 3·5 years, regardless of IGHV-mutation status (61 [91%] of 67 with unmutated IGHV and 30 [94%] of 32 with mutated IGHV who did not require the next line of therapy), whereas 25 (44%) of 57 patients with unmutated IGHV and 33 (94%) of 35 with mutated IGHV in the chlorambucil obinutuzumab group had not initiated subsequent therapy at 3·5 years.

Niemann CU, et al. Lancet Oncol. 2023;24(12):1423-1433

GLOW 4-year follow-up: OS



Number at risk (number censored)									
Ibr + Ven	106 (0)	100 (2)	95 (2)	94 (2)	94 (2)	93 (2)	91 (4)	83 (10)	12 (79)
Clb + O	105 (0)	103 (0)	103 (0)	100 (1)	93 (3)	90 (3)	86 (3)	74 (8)	15 (60)

At the 46-month median follow-up, the ibrutinib–venetoclax group demonstrated an overall survival advantage compared with the chlorambucil– obinutuzumab group.

The estimated 42-month overall survival rate was 87·5% (95% CI 79·4–92·5) for patients in the ibrutinib–venetoclax group and 77·6% (68·2–84·5) for patients in the chlorambucil– obinutuzumab group.

There were twice as many deaths in the chlorambucil–obinutuzumab group (30 [29%] of 105) than in the ibrutinib–venetoclax group (15 [14%] of 106; appendix pp 10, 19).

Niemann CU, et al. Lancet Oncol. 2023;24(12):1423-1433

FLAIR phase 3 study: ibru plus ven with MRD-driven duration of treatment

Fludarabine (oral) (24 mg/m^2/da x 5 days C1-C6)

Cyclophosphamide (oral) (150 mg/m^2/days x 5 days C1-C6)

Rituximab (375 mg mg/m^2 C1, 500 mg mg/m^2 C2-6)

CLL requiring therapy by IWCLL Criteria

Random 1:1 (n = 523)

(n = 260)

(n = 263)

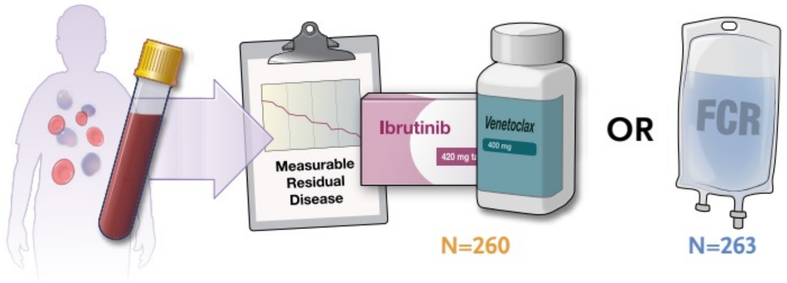
Primary end point comparing MRD-guided ibrutinib–venetoclax with FCR: PFS

I+V given for 2 to 6 years

Venetoclax 400 mg/day

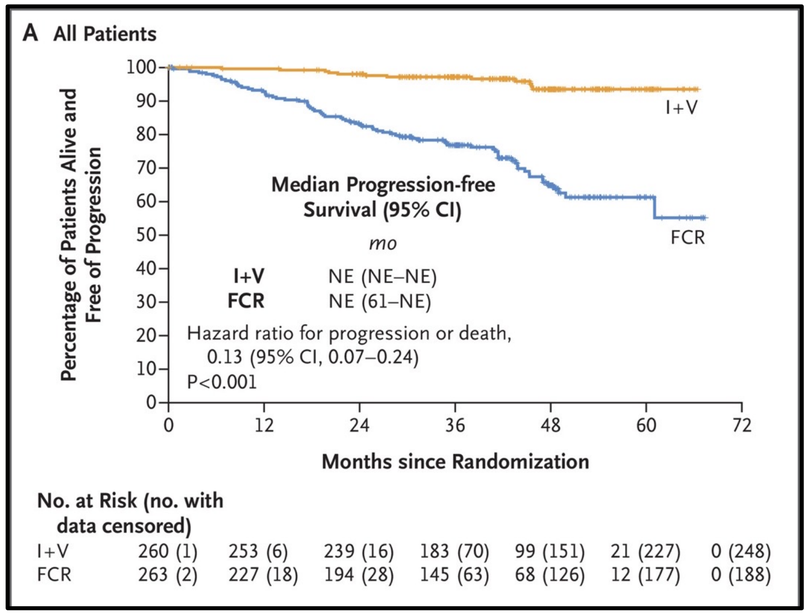
Ibrutinib 400 mg/day

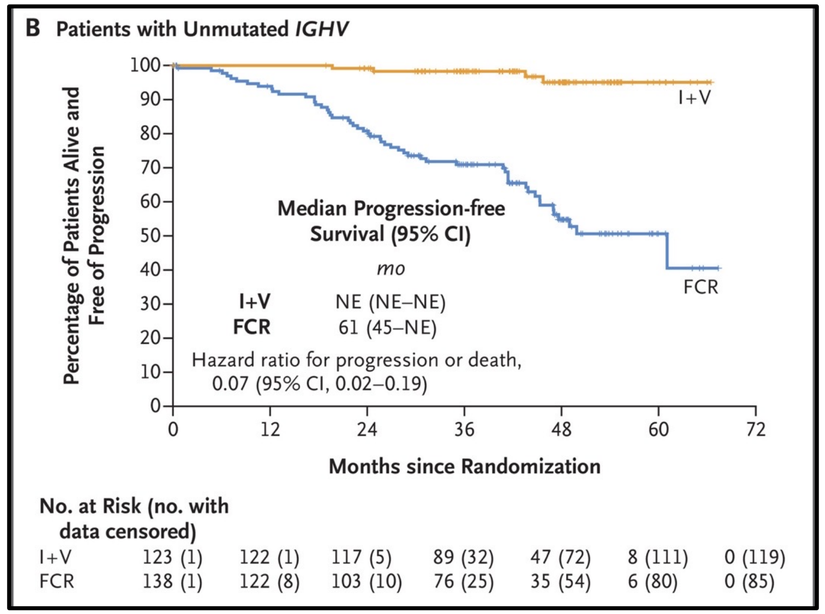
Duration of therapy: double time to MRD negativity

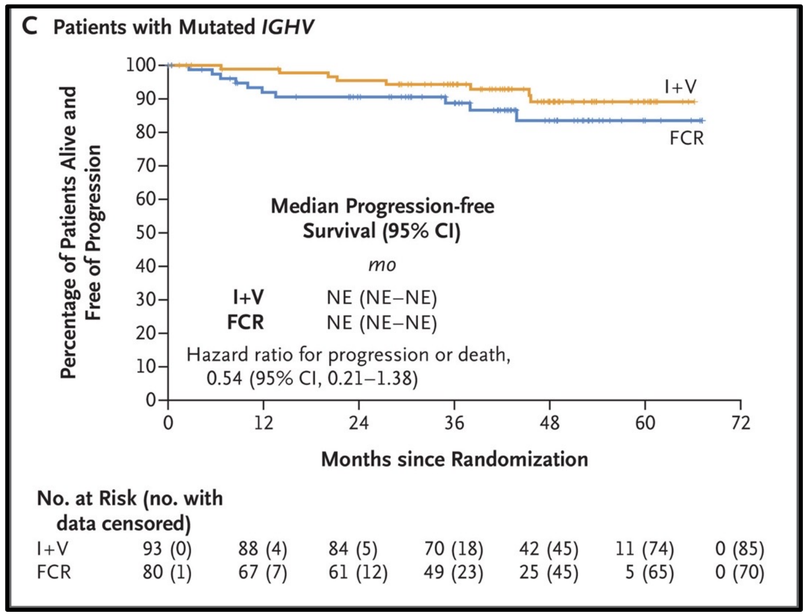


Munir T. et al N Engl J Med 2024;390:326-337

FLAIR PFS







Median follow-up: 43.7 months (about 3.6 years).

Events (progression or death):
- Ibrutinib–venetoclax group: 12 out of ~260 patients (4.6%)
- FCR group: 75 out of ~263 patients (28.5%)

Estimated 3-year progression-free survival (PFS):
- Ibrutinib–venetoclax: 97.2% (95% CI: 94.1–98.6)
- FCR: 76.8% (95% CI: 70.8–81.7)

Hazard Ratio (HR) for progression or death: 0.13
- Patients on ibrutinib–venetoclax had an 87% lower risk of progression or death compared to those on FCR.

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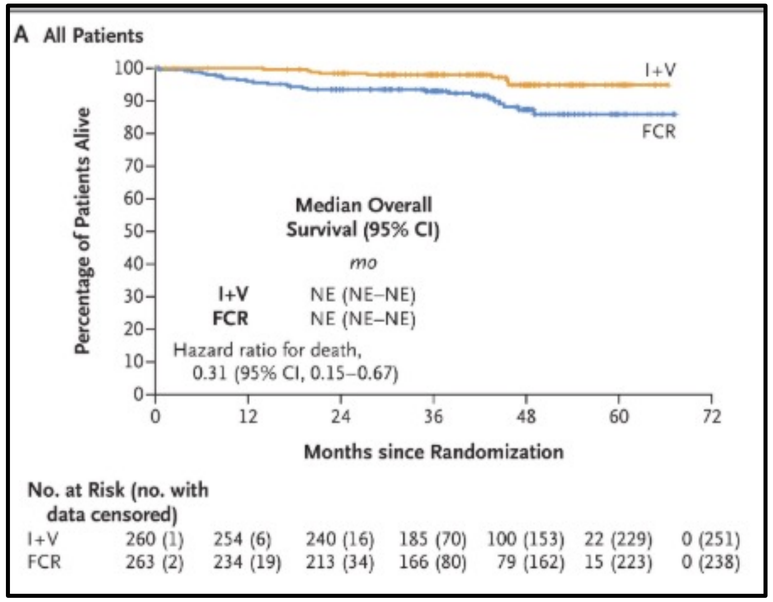
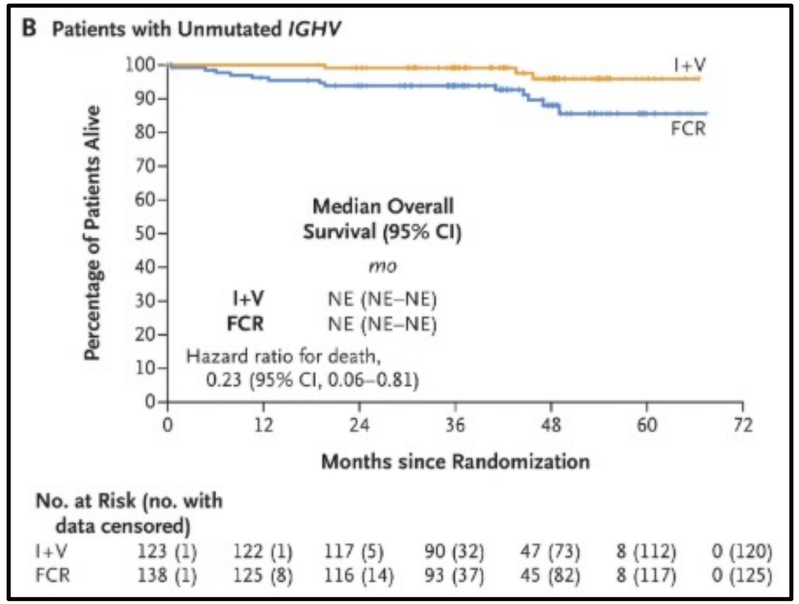
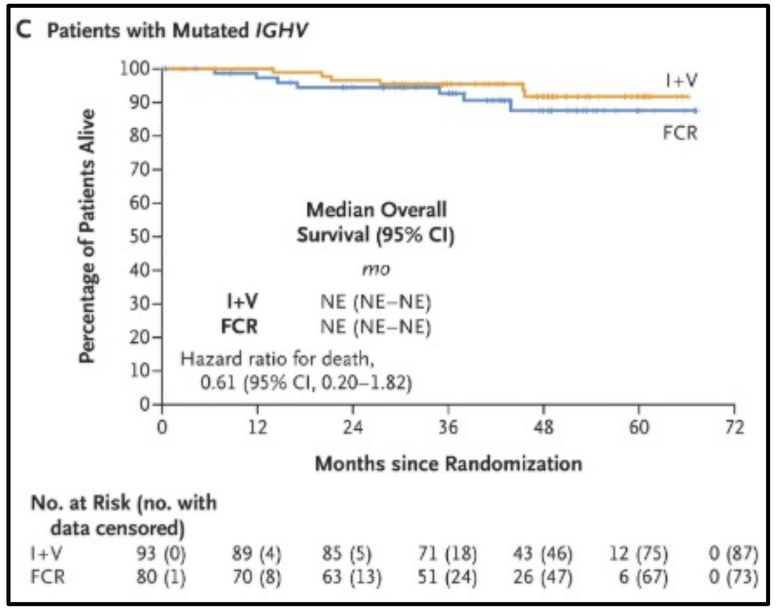
FLAIR OS







The hazard ratio for death (ibrutinib–venetoclax vs. FCR) was 0.31 (95% CI, 0.15 to 0.67). Results for overall survival appeared to **favor** ibrutinib–venetoclax as compared with FCR in patients with unmutated IGHV (hazard ratio for death, 0.23; 95% CI, 0.06 to 0.81) but not in those with mutated IGHV (hazard ratio, 0.61, 95% CI, 0.20 to 1.82). Subgroup analyses suggested benefit of ibrutinib–venetoclax with respect to overall survival across all subgroups except patients with mutated IGHV

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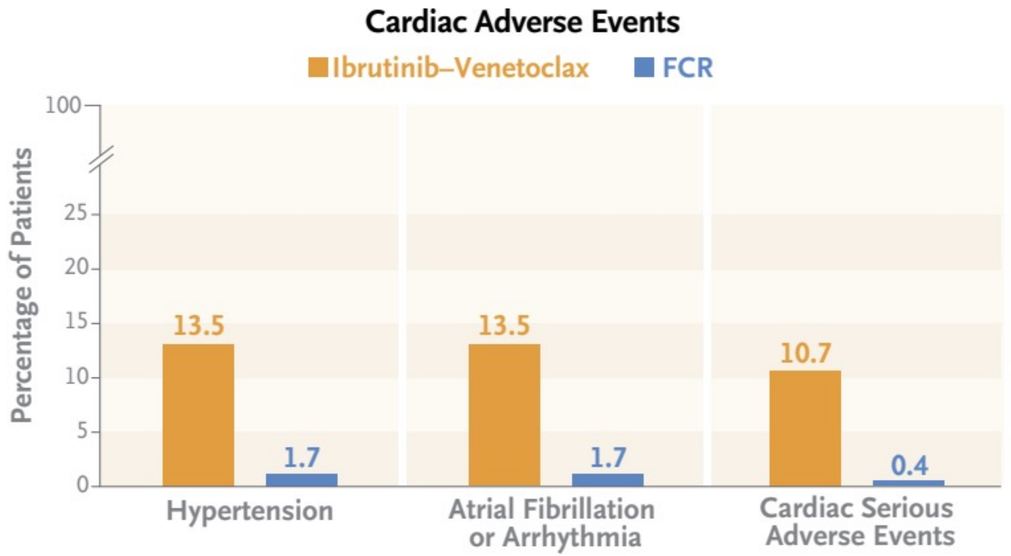
FLAIR safety

Table 2. Adverse Events, According to Maximum Grade, within 1 Year after Randomization (Safety Population).*

Adverse Event	Ibrutinib–Venetoclax (N=252)				FCR (N=239)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
	number of patients (percent)							
Acute kidney injury	0	0	0	0	4 (1.7)	3 (1.3)	0	0
Anemia	24 (9.5)	2 (0.8)	0	0	50 (20.9)	33 (13.8)	4 (1.7)	0
Atrial fibrillation or arrhythmia	10 (4.0)	2 (0.8)	0	0	4 (1.7)	0	0	0
Constipation	8 (3.2)	1 (0.4)	0	0	60 (25.1)	0	0	0
Cough	4 (1.6)	0	0	0	45 (18.8)	4 (1.7)	0	0
Diarrhea	58 (23.0)	2 (0.8)	0	0	46 (19.2)	6 (2.5)	0	0
Dyspnea	10 (4.0)	0	0	0	22 (9.2)	3 (1.3)	1 (0.4)	0
Fatigue	38 (15.1)	1 (0.4)	0	0	108 (45.2)	9 (3.8)	0	0
Febrile neutropenia	0	0	0	0	0	13 (5.4)	0	0
Fever	5 (2.0)	0	0	0	57 (23.8)	17 (7.1)	0	0
Headache	10 (4.0)	0	0	0	31 (13.0)	1 (0.4)	0	0
Hemolysis or hemolytic anemia	0	0	0	0	3 (1.3)	3 (1.3)	0	0
Hypertension	6 (2.4)	6 (2.4)	0	0	3 (1.3)	1 (0.4)	0	0
Infections and infestations, other	1 (0.4)	0	0	0	0	3 (1.3)	0	0
Infusion-related reaction	0	0	0	0	64 (26.8)	2 (0.8)	1 (0.4)	0
Lung infection	0	0	0	0	3 (1.3)	3 (1.3)	1 (0.4)	0
Lymphocyte count decreased	4 (1.6)	0	0	0	4 (1.7)	4 (1.7)	4 (1.7)	0
Nausea	43 (17.1)	3 (1.2)	0	0	138 (57.7)	1 (0.4)	0	0
Neutropenia	23 (9.1)	16 (6.3)	10 (4.0)	0	27 (11.3)	53 (22.2)	60 (25.1)	0
Other	24 (9.5)	7 (2.8)	0	0	26 (10.9)	7 (2.9)	0	1 (0.4)
Platelet count decreased	39 (15.5)	3 (1.2)	2 (0.8)	0	65 (27.2)	16 (6.7)	8 (3.3)	0
Rash	26 (10.3)	1 (0.4)	0	0	66 (27.6)	5 (2.1)	0	0
Sepsis	0	0	0	0	0	10 (4.2)	4 (1.7)	0
Skin infections	2 (0.8)	0	0	0	3 (1.3)	3 (1.3)	0	0
Taste alteration or loss of appetite	4 (1.6)	0	0	0	30 (12.6)	0	0	0
Upper respiratory infection	6 (2.4)	1 (0.4)	0	0	24 (10.0)	8 (3.3)	0	0
Vomiting	15 (6.0)	1 (0.4)	0	0	65 (27.2)	5 (2.1)	0	0

* The safety population included all the patients who had undergone randomization and received at least one treatment cycle. Shown are adverse events of any grade that occurred in at least 10% of the patients in either treatment group and adverse events of grade 3 or higher that occurred in at least 1% of the patients in either treatment group.

- Of 491 patients in the safety population, 450 (91.6%) reported at least one adverse event.
- The most common grade 3 to 5 adverse events occurring within 1 year after randomization were neutropenia (10.3% ibrutinib–venetoclax group vs 47.3% FCR group), anemia (in 0.8% vs 15.5%, respectively), and thrombocytopenia (in 2.0% vs 10.0%).
- Common adverse events of any grade were fatigue (15.5% in the ibrutinib–venetoclax group vs 49.0% in the FCR group) and neutropenia (19.4% vs 58.6%], respectively).
- A total of 15 grade 3 adverse events involving febrile neutropenia occurred in 13 patients (5.4%) in the FCR group; none occurred in the ibrutinib–venetoclax group
- Cardiac SAEs occured more often in the ibru-ven arm



Munir T. et al N Engl J Med 2024;390:326-337

Outcomes for PFS and OS for CLL frontline phase 3 trials

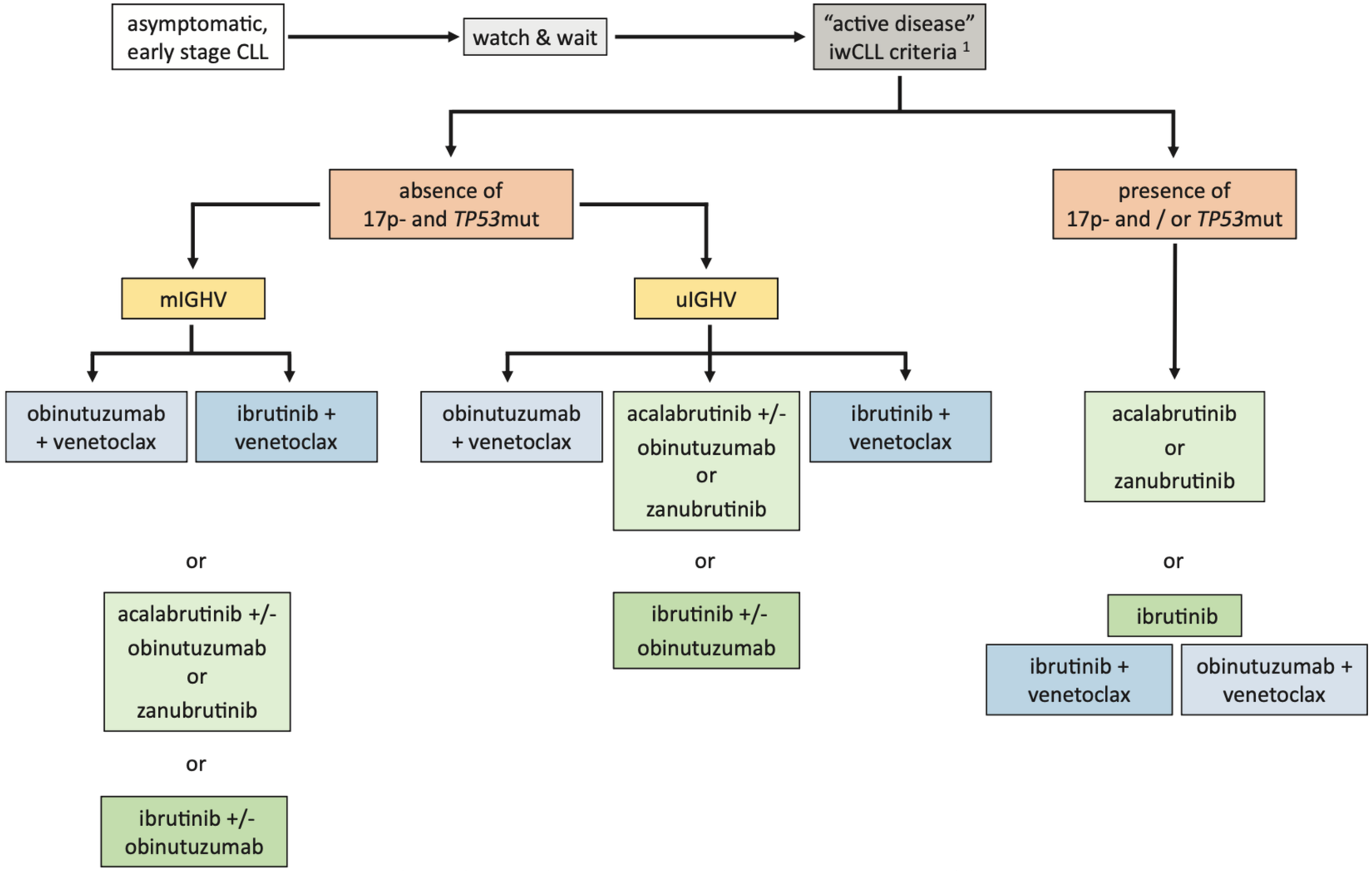
Trial treatment no. of patients	Characteristics (median, if not indicated otherwise)		Estimate at month	PFS rate (%)				OS rate (%)			
				All patients	uIGHV	mIGHV	17p− and/or TP5 3mut	All patients	uIGHV	mIGHV	17p− and/or TP5 3mut
CLL14 Obi-Ven n = 216	FU: 76	Age: 72	36	82	82	86	63	89	89	91	80
	CIRS: 9	CrCl: 65.2	48	74	69	85	54	85	83	89	72
			72	53	43	72	22	79	78	82	60
CLL13 Obi-Ven n = 229	FU: 51	Age: 62	36	89	84	94	n.a.	97	96	97	n.a.
	CIRS: 2	CrCl: 86.3	48	82	74	92	n.a.	95	94	97	n.a.
			72								
GLOW Ibr-Ven n = 106	FU: 57	Age: 71	36	79	72[a]	90[a]		90[a]			
	CIRS: 9	CrCl: 66.5	48	70	63[a]	90[a]		86[a]			
			72								
FLAIR Ibr-Ven n = 260	FU: 44	Age: 62	36	97				98	99	96	
		CrCl: 83	48	94				95			
			72								

[a] Estimates from survival curve.

[b] Sole TP53 mutation; empty fields = data not available.

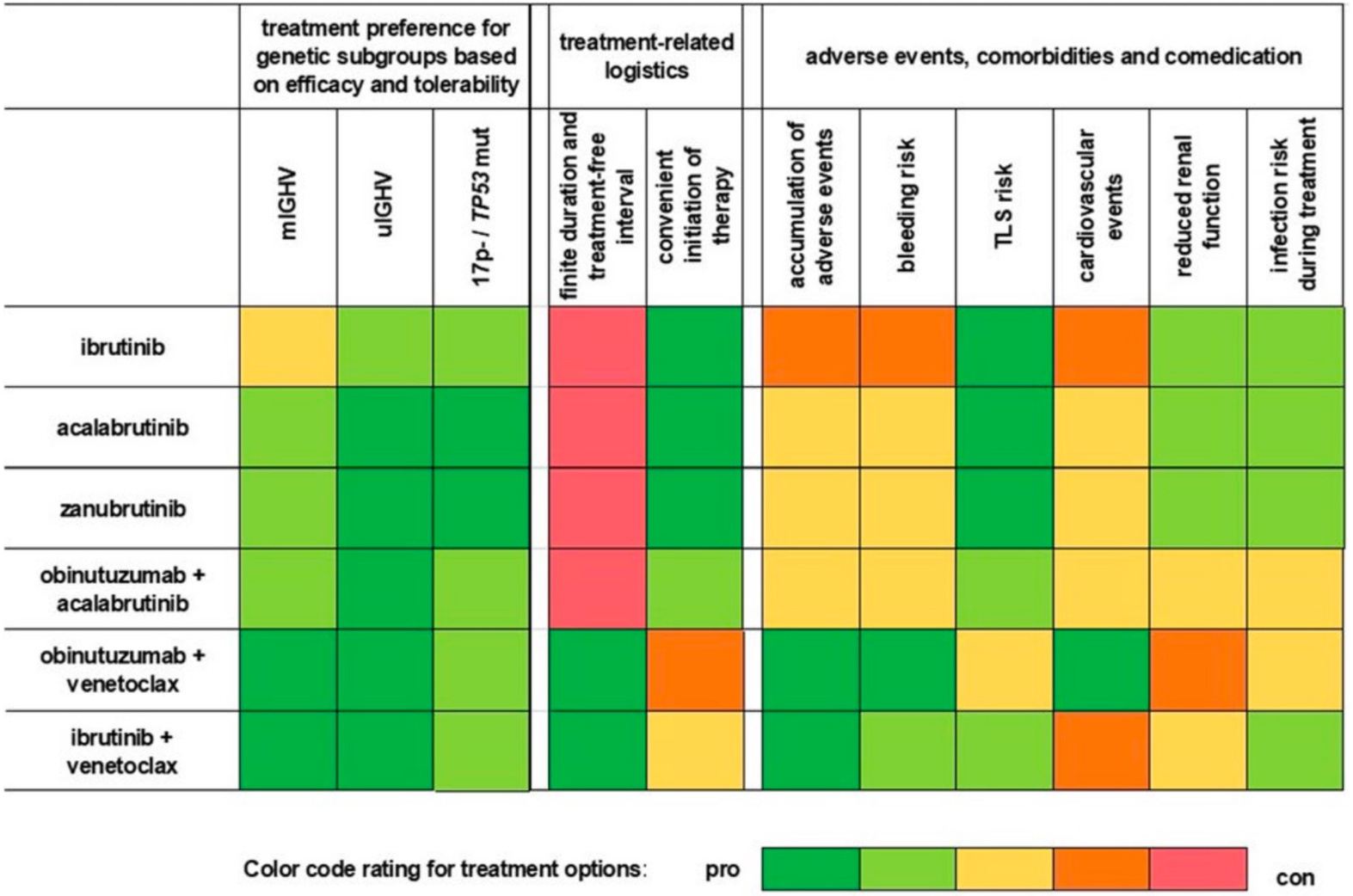
Acala, acalabrutinib; Age, age in years; CrCl, creatinine clearance in mL/min; FU, median follow-up time in months; Ibr, ibrutinib; n.a., not applicable as 17p− and TP53mut were excluded; Obi, obinutuzumab; R, rituximab; Ven, venetoclax; Zanu, zanubrutinib.

Suggested frontline treatment algorithm according to genetic CLL subgroups



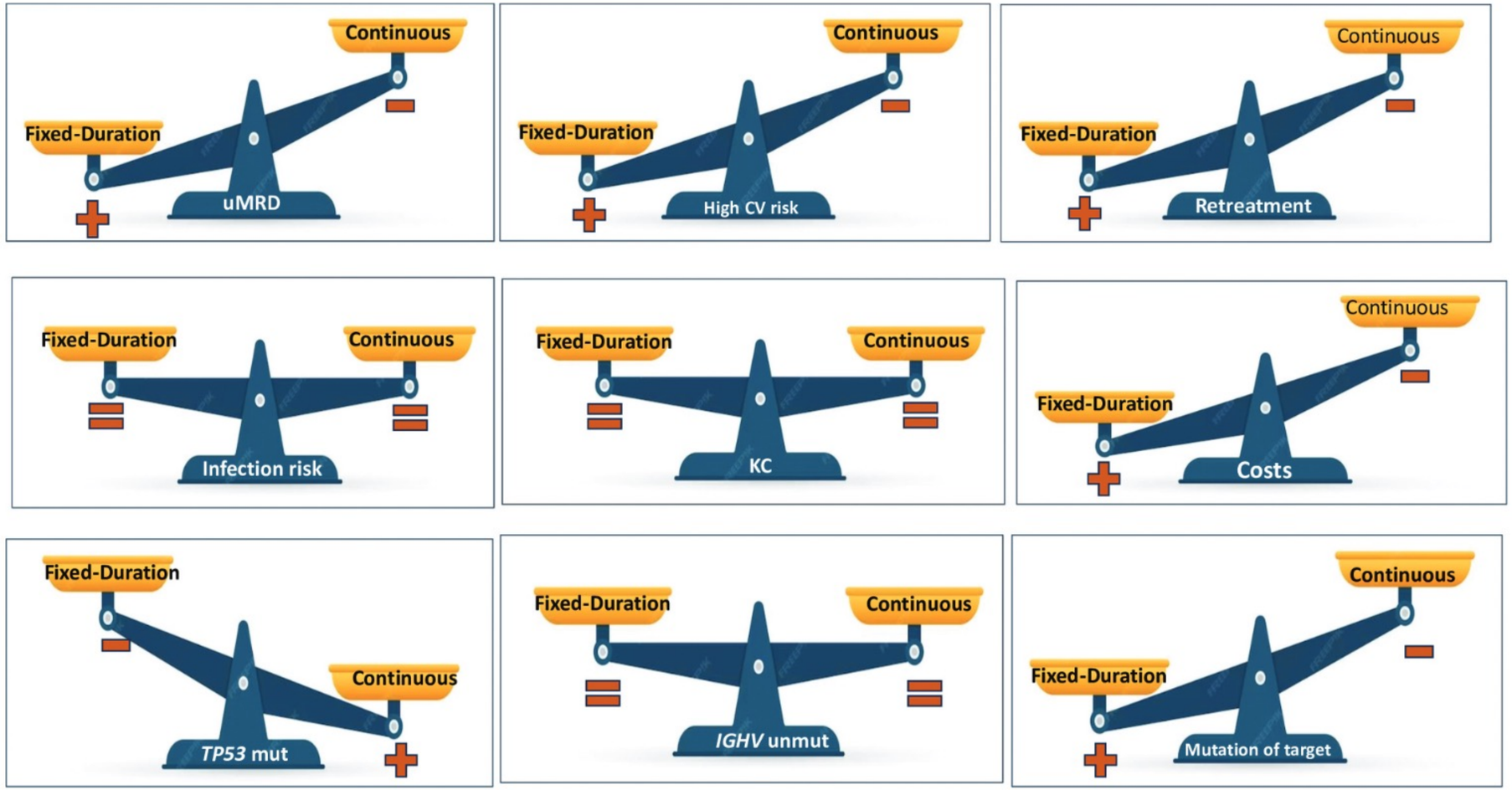
Tausch E et al, Hematology Am Soc Hematol Educ Program. 2024;2024(1):457-466.

Heat map of treatment options in frontline CLL



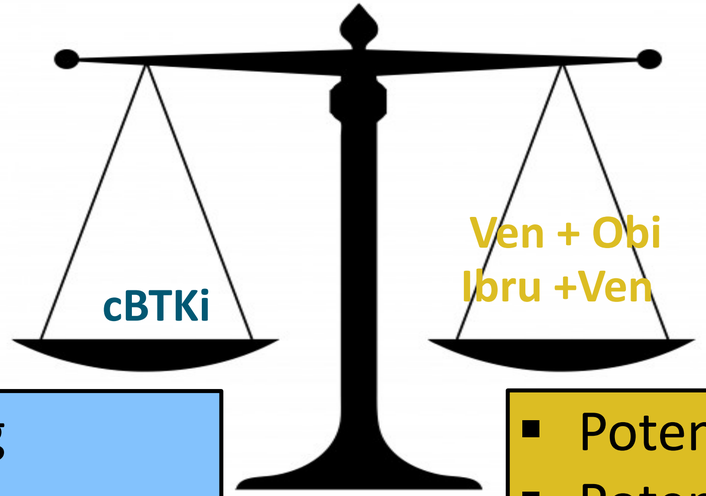
Tausch E et al, Hematology Am Soc Hematol Educ Program. 2024;2024(1):457-466.

Potential advantages and disadvantages of continuous versus fixed-durationtherapy



Molica, S. et al. Expert Review of Anticancer Therapy, 24(3–4), 101–106

Frontline cBTKi vs Ven based fixed duration therapies: Factors to Consider



- Requires continuous dosing
- More data in patients with del(17p)/*TP53* mutations
- Convenience (no infusions, TLS monitoring)
- Associated with cardiac and bleeding events

- Potential for 1 yr time-limited therapy
- Potential for cost saving if 1 yr of therapy is durable
- Requires ramp up period with TLS monitoring and prophylaxis
- No known cardiac or bleeding risks in obi-ven schedule

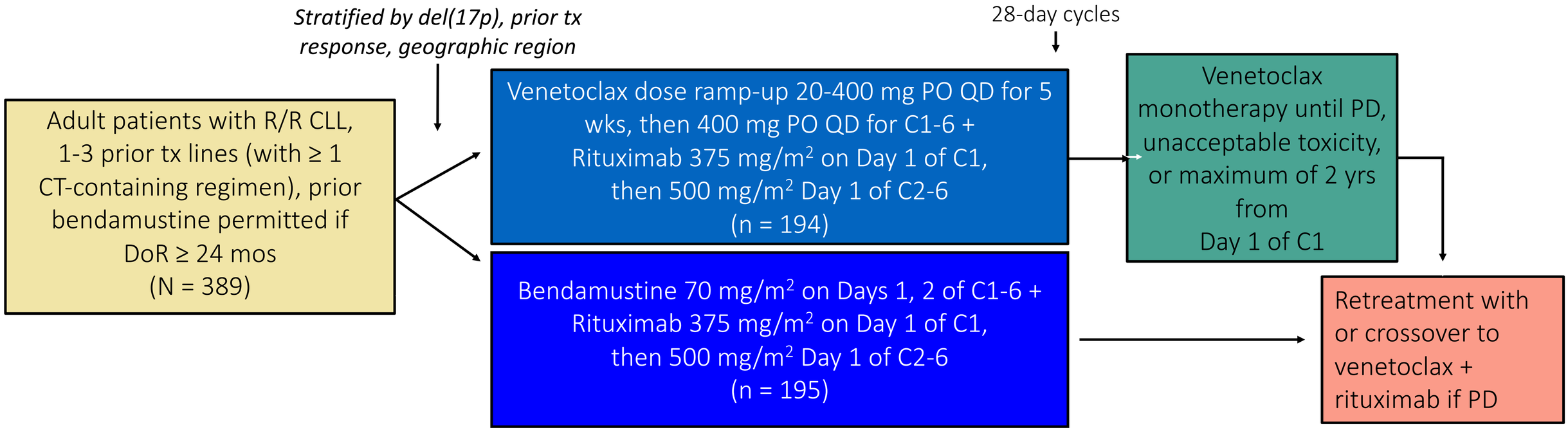
Brem. Blood Adv. 2022;6:1361. Molica. Int J Hematol Oncol. 2020;9:IJH31.

Relapsed/Refractory CLL

VENETOCLAX-BASED TREATMENTS

Venetoclax–Rituximab in R/R CLL: the MURANO trial

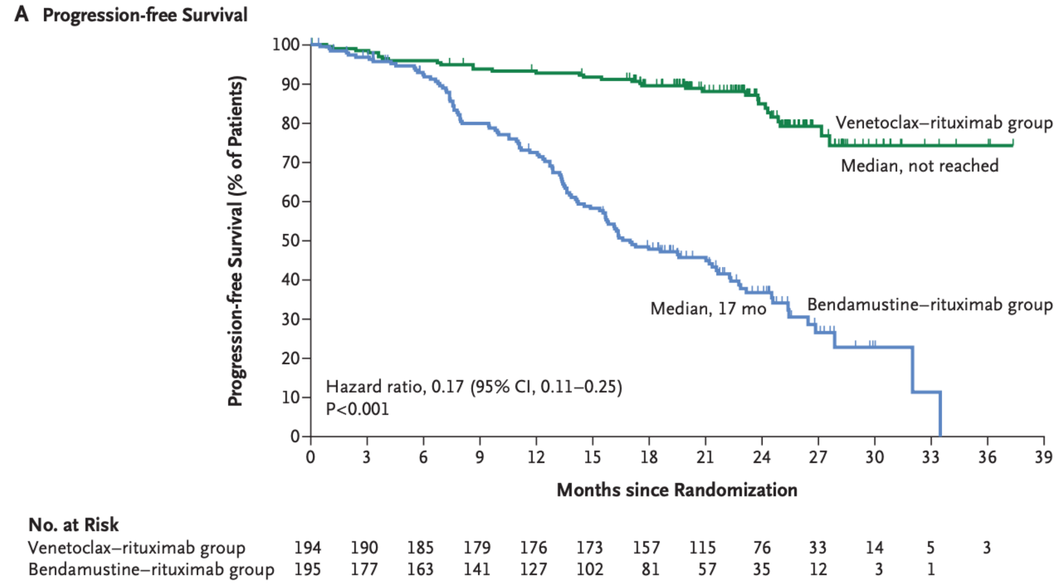
- Multicenter, randomized, open-label phase III trial; current analysis of outcomes after median follow-up of 59 mos

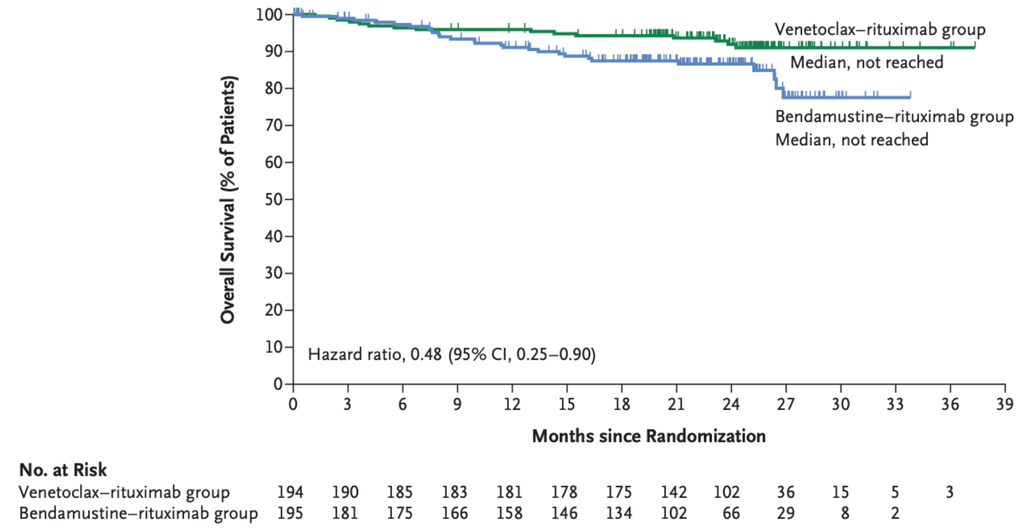


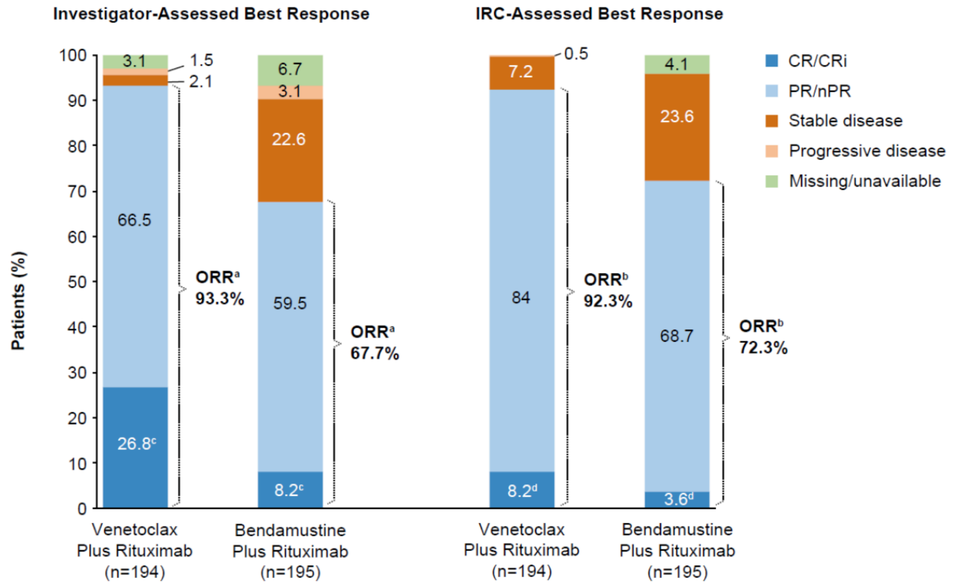
- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS, safety

JF Seymour, N Engl J Med 2018;378:1107-1120

MURANO trial: PFS and OS







- After a median follow-up period of 23.8 months, the median investigator assessed PFS was significantly longer in the venetoclax–rituximab group than in the bendamustine–rituximab group.
- The median PFS was not reached in the venetoclax–rituximab group and was 17 months in the bendamustine–rituximab group.
- The 2-year rate of investigator-assessed progression-free survival was 84.9% in the venetoclax–rituximab group and 36.3% in the bendamustine–rituximab group.
- The rate of OS was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group, with 24-month rates of 91.9% and 86.6%, respectively

JF Seymour, N Engl J Med 2018;378:1107-1120

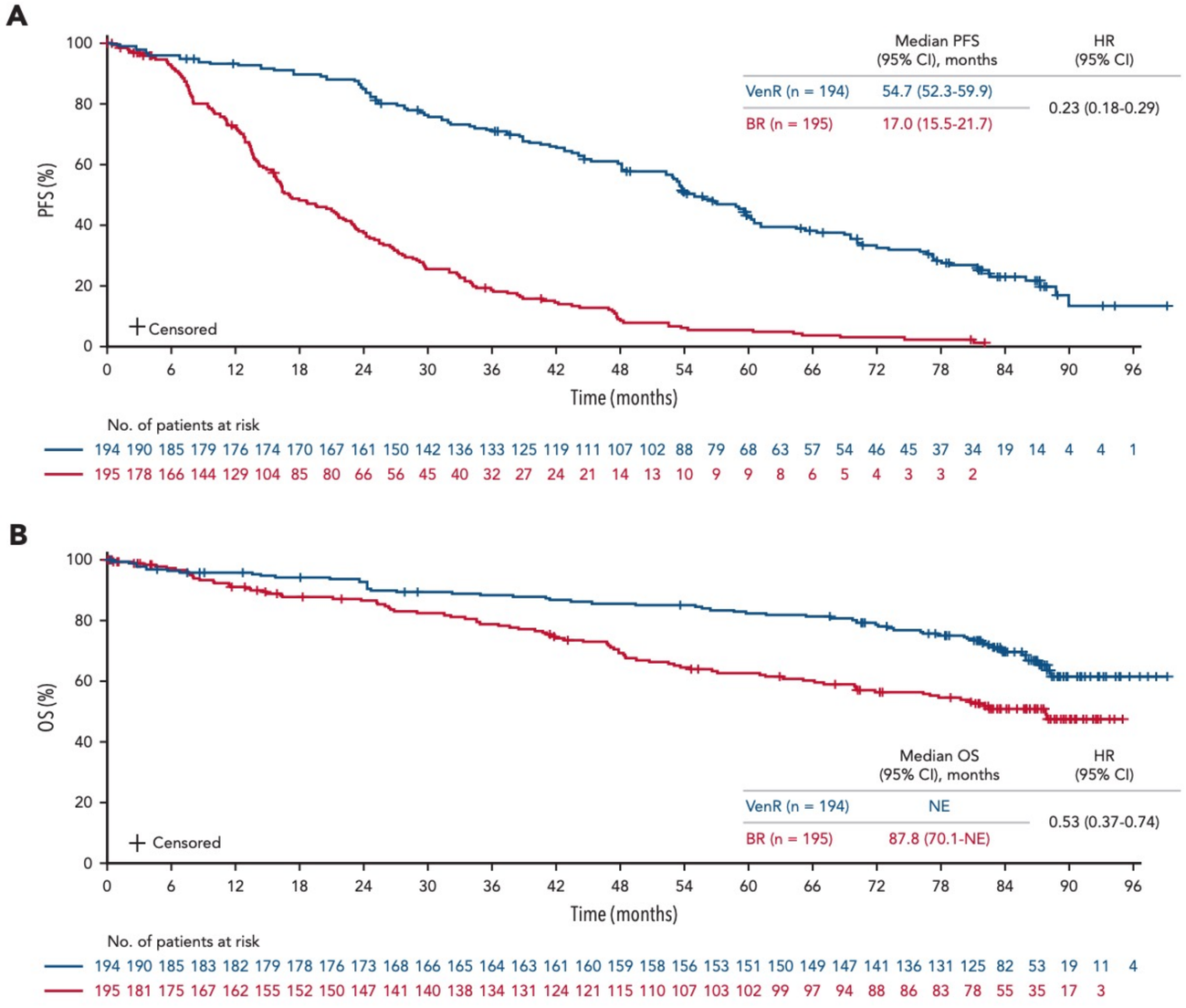
MURANO trail: safety

	Venetoclax + rituximab arm n=194		Bendamustine + rituximab arm n=188	
	Venetoclax	Rituximab	Bendamustine	Rituximab
Dose interruption				
Patients with ≥1 AE leading to dose interruption, n (%)	135 (69.6)	39 (20.1)	53 (28.2)	69 (36.7)
AE leading to dose interruption of any treatment in ≥5 patients in either arm, n (%)				
Neutropenia	84 (43.3)	25 (12.9)	22 (11.7)	23 (12.2)
Neutrophil count decreased	5 (2.6)	0	4 (2.1)	4 (2.1)
Thrombocytopenia	9 (4.9)	1 (0.5)	8 (4.3)	6 (3.2)
Pneumonia	8 (4.1)	1 (0.5)	3 (1.6)	3 (1.6)
Upper respiratory tract infection	7 (3.6)	1 (0.5)	4 (2.1)	4 (2.1)
Bronchitis	5 (2.6)	3 (1.6)	2 (1.1)	1 (0.5)
Infusion-related reaction	0	6 (3.1)	2 (1.1)	23 (12.6)
Diarrhea	9 (4.6)	0	0	0
Nausea	7 (3.6)	0	1 (0.5)	1 (0.5)
Dose reduction				
Patients with ≥1 AE leading to dose reduction, n (%)	27 (13.9)	2 (1.0)	26 (13.8)	2 (1.1)
AE leading to dose reduction of any treatment in ≥2 patients in either arm, n (%)				
Neutropenia	16 (8.2)	1 (0.5)	14 (7.4)	0
Febrile neutropenia	2 (1.0)	0	3 (1.6)	0
Thrombocytopenia	0	0	3 (1.6)	0
Anemia	1 (0.5)	0	2 (1.1)	0
Treatment discontinuation				
Patients with ≥1 AE leading to treatment discontinuation, n (%)	25 (12.9)	10 (5.2)	17 (9.0)	13 (6.9)

- Adverse events were more frequently reported in the venetoclax–rituximab group due to longer treatment duration.
- Neutropenia was the most common event, occurring more often with venetoclax (60.8% vs. 44.1%). Grade 3–4 adverse events were also higher (82.0% vs. 70.2%), especially severe neutropenia (57.7% vs. 38.8%).
- However, serious complications like febrile neutropenia and infections were less frequent with venetoclax.
- Neutropenia was the main cause of dose interruptions in this group.

JF Seymour, N Engl J Med 2018;378:1107-1120

The MURANO study: final analysis of VenR for patients with R/R CLL



- The median PFS with VenR was 54.7 vs 17.0 months with BR. The 7-year PFS rate with
- VenR was 23.0%; no BR-treated patients remained progression free at this time point.

- The median OS with VenR was not reached (NR) vs 87.8 months with BR. The 7-year OS rates with VenR were 69.6% vs 51.0% with BR.

- Patients with mutated TP53 and/or del(17p) had the poorest 7-year PFS rate at 5%. No patients with high GC were progression free at 7 years

At 85.7 months median follow-up, VenR shows superior outcomes vs. BR, with longer PFS, improved OS, and delayed TTNT

AP Karter, Blood (2025) 145 (23): 2733–2745.

Retreatment with Ven following a time-limited Ven-based regimen

- Multicenter, international retrospective study in patients with CLL
  - Treated with venetoclax-based regimen in any line of therapy → retreatment with a second venetoclax-based regimen
- Data collected from 15 medical centers (n = 30), CLL Collaborative Study of Real-World Evidence database (n = 5) and MURANO (n = 11)
  - Total (N = 46)
- ORR to venetoclax retreatment among 39 patients with available response date: 79.5%
  - Complete response: 33.3%
- Median time to venetoclax retreatment: 10 mo
- Median PFS among venetoclax retreated patients: 25 mo (95% CI: 17-42)

Thompson. Blood Adv. 2022;6:4553.

Relapsed/Refractory CLL

BTK INHIBITORS

ALPINE (Zanu vs Ibru): study design

Randomized, open-label phase III trial (median f/u: 29.6 mo)

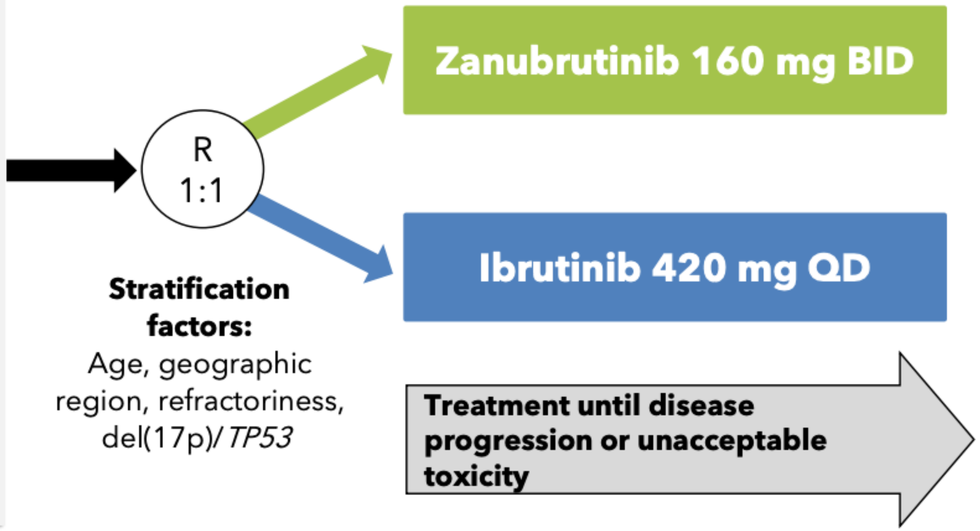
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



- Primary endpoint: noninferiority and superiority of investigator-assessed ORR
- Secondary endpoints: incidence of atrial fibrillation or flutter, PFS, DoR, OS, TTF, ≥ PR-L rate, PROs, safety

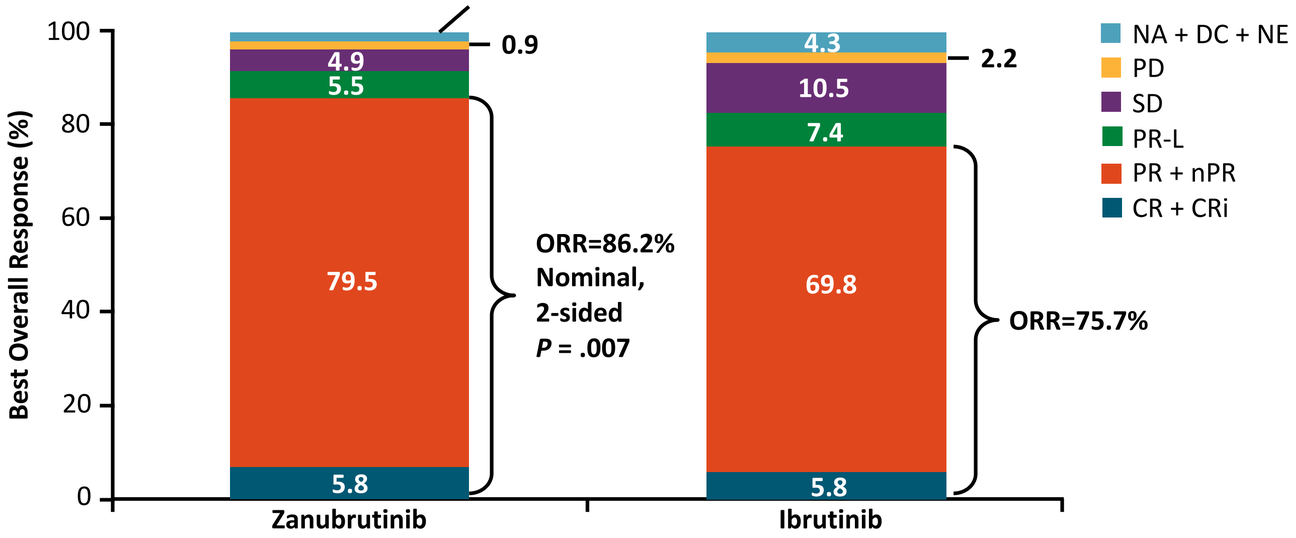
Brown JR. N Eng J Med. 2023; 388(4):319-332.

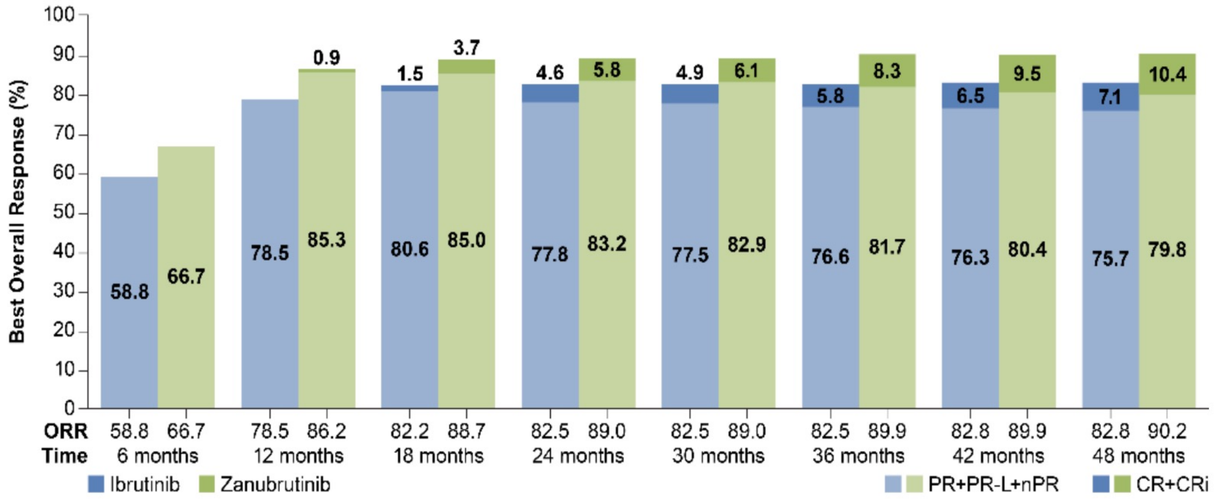
ALPINE: baseline characteristics

Characteristic	Zanubrutinib (n = 327)	Ibrutinib (n = 325)
Median age, yr (range) ▪ ≥65 yr, n (%)	67 (35-90) 201 (61.5)	68 (35-89) 200 (61.5)
Male sex, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Median prior lines of systemic therapy, n (range) ▪ >3 prior lines, n (%)	1 (1-6) 24 (7.3)	1 (1-12) 30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%) ▪ del(17p) with or without *TP53*^{mut} ▪ *TP53*^{mut} without del(17p)	75 (22.9) 45 (13.8) 30 (9.2)	75 (23.1) 50 (15.4) 25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
IGHV mutational status, n (%) ▪ Mutated ▪ Unmutated	 79 (24.2) 239 (73.1)	 70 (21.5) 239 (73.5)
Complex karyotype, n (%)*	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

Brown JR, .N Eng J Med. 2023; 388(4):319-332.

ALPINE: ORR



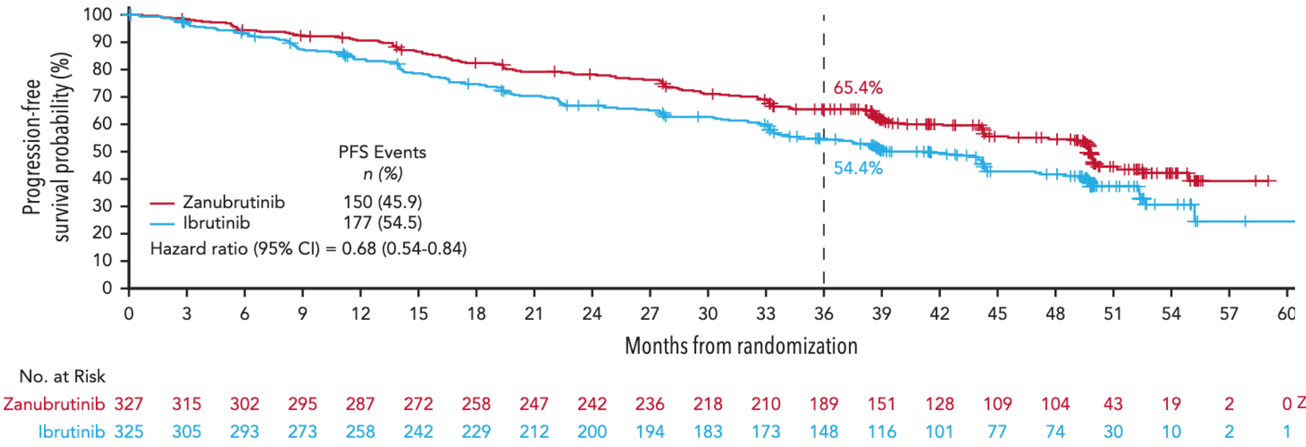


- A higher proportion of patients achieved CR/CRi with zanubrutinib than ibrutinib
- Complete Responses deepen over time in both arms

Brown J, .N Eng J Med. 2023; 388(4):319-332.

ALPINE: PFS

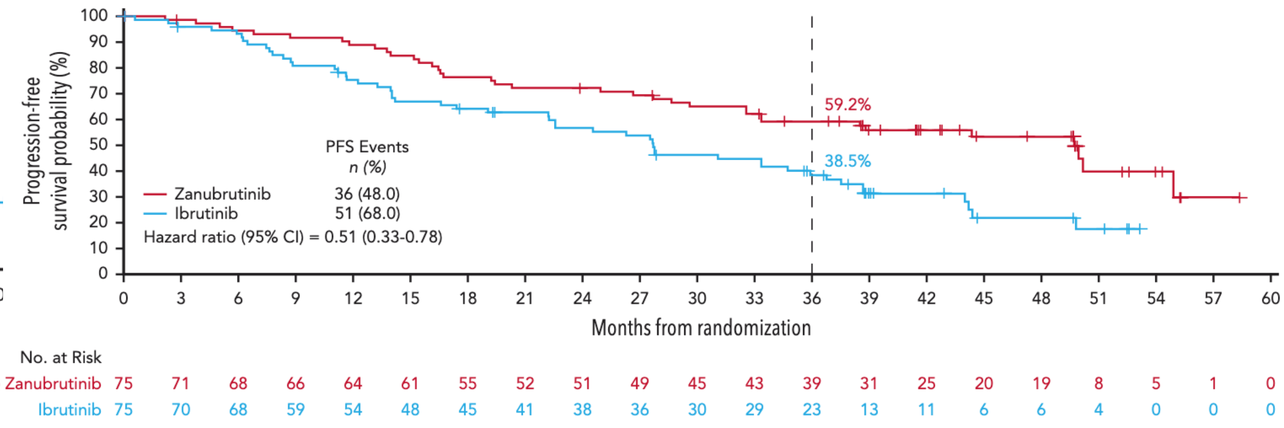
Patients in the overall population



No. at Risk

Zanubrutinib	327	315	302	295	287	272	258	247	242	236	218	210	189	151	128	109	104	43	19	2	0
Ibrutinib	325	305	293	273	258	242	229	212	200	194	183	173	148	116	101	77	74	30	10	2	1

Patients with del(17p) and/or TP53mut



No. at Risk

Zanubrutinib	75	71	68	66	64	61	55	52	51	49	45	43	39	31	25	20	19	8	5	1	0
Ibrutinib	75	70	68	59	54	48	45	41	38	36	30	29	23	13	11	6	6	4	0	0	0

Zanubrutinib demonstrated sustained PFS benefit over ibrutinib in patients with R/R CLL/SLL with a median follow-up of 42.5 months

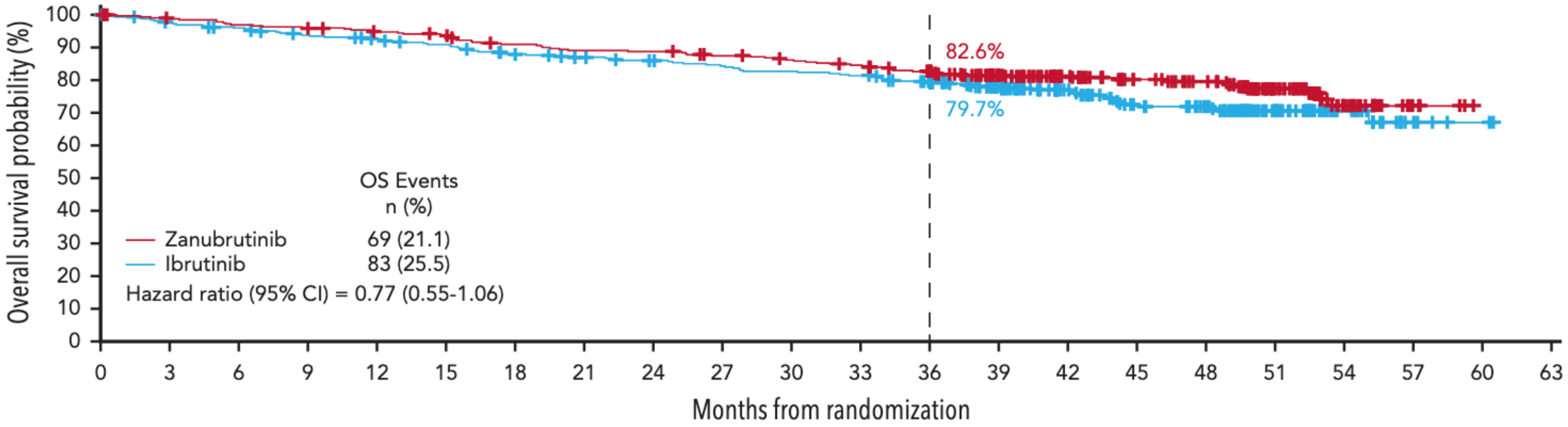
- Durable PFS benefits seen across major subgroups, including the del(17p)/TP53mut population
- PFS benefit is consistent across multiple sensitivity analyses demonstrating that PFS advantage with zanubrutinib was primarily driven by efficacy and not tolerability

Improved PFS was demonstrated with Zanubrutinib in patients with del(17p)/TP53mut

- Zanubrutinib demonstrated robust PFS benefit independent of del(17p)/TP53 Mutation Status

Brown JR, Blood. 2024 Dec 26;144(26):2706-2717.

ALPINE: OS

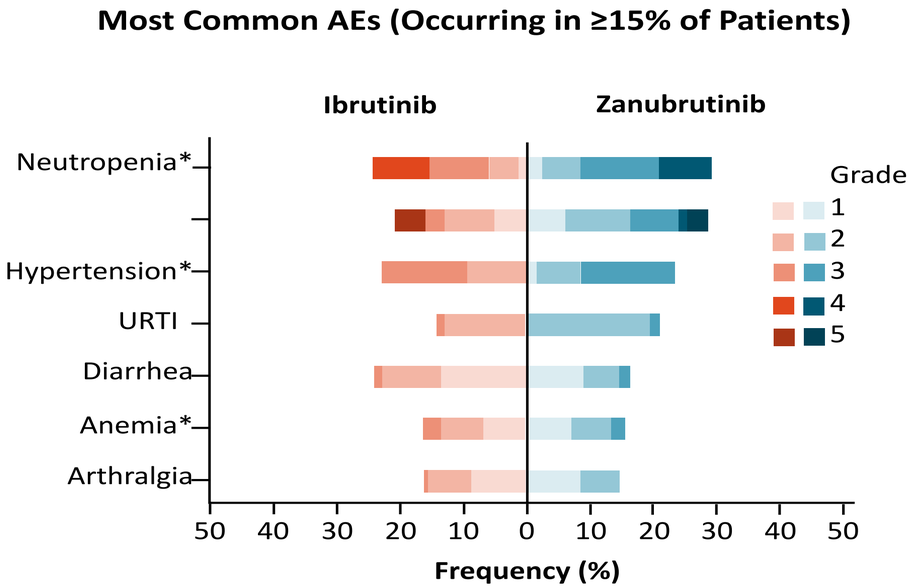


No. at Risk

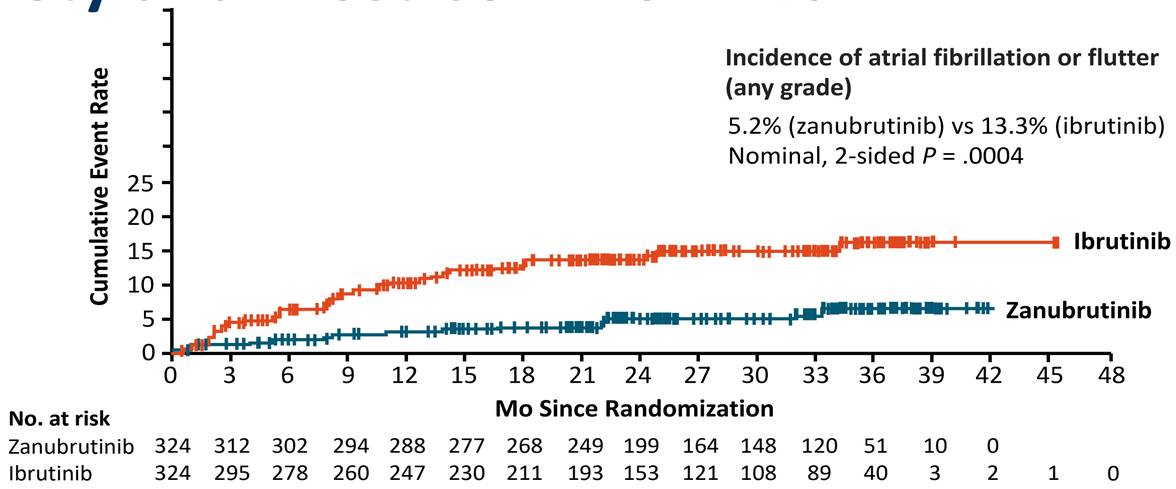
Zanubrutinib	327	319	313	310	303	298	287	281	280	273	267	261	250	209	176	152	142	81	28	5	0	0
Ibrutinib	325	314	307	297	290	283	271	264	258	252	247	243	231	190	160	134	125	75	28	6	2	0

Brown JR , Blood. 2024 Dec 26;144(26):2706-2717.

ALPINE: Overall Safety and Most Common AEs



*Pooled terms.



Zanubrutinib continues to demonstrate a more favorable safety/tolerability profile compared with ibrutinib

- 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

Event	Zanubrutinib (n = 324)	Ibrutinib (n = 324)
Median treatment duration, mo	28.4	24.3
Any-grade AE, n (%) ▪Grade ≥3 ▪Grade 5	318 (98.1) 218 (67.3) 33 (10.2)	321 (99.1) 228 (70.4) 36 (11.1)
SAE, n (%)	136 (42.0)	162 (50.0)
AE leading to the following, n (%) ▪Dose reduction ▪Dose interruption ▪Treatment discontinuation	40 (12.3) 162 (50.0) 50 (15.4)	55 (17.0) 184 (56.8) 72 (22.2)

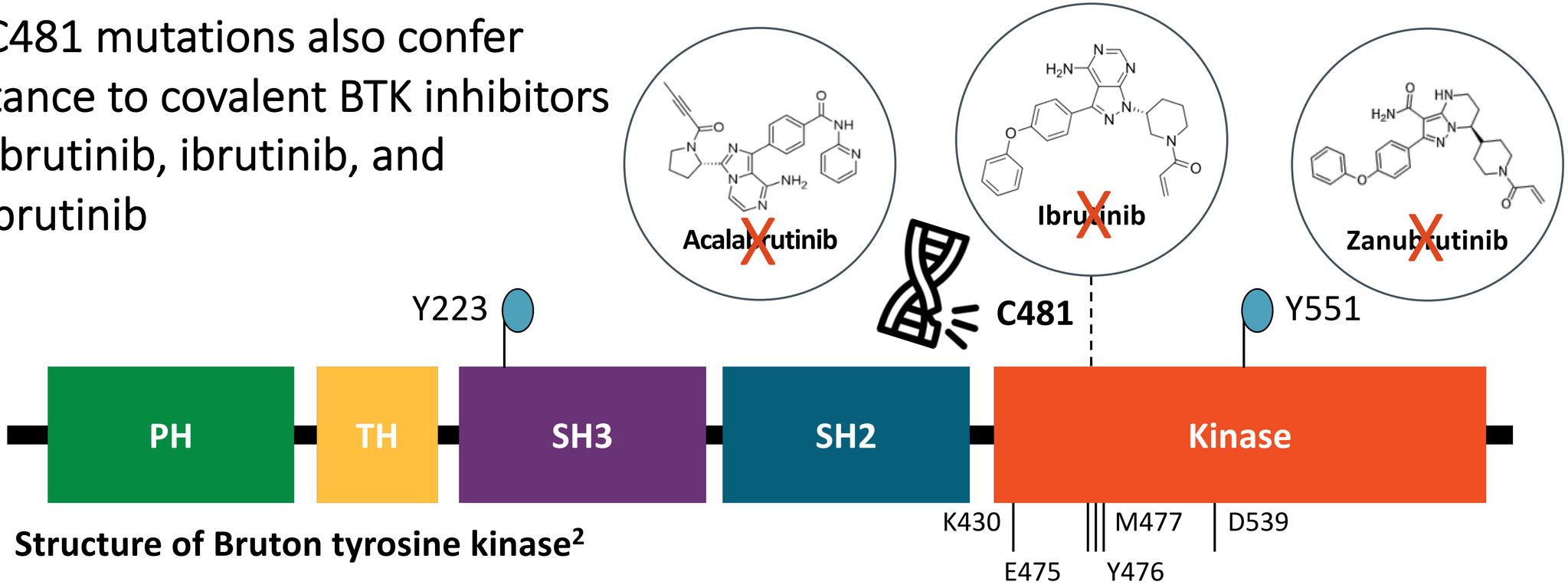
Brown JR, .N Eng J Med. 2023; 388(4):319-332.

Relapsed/Refractory CLL

TREATMENT OF THE DOUBLE REFRACTORY PATIENT

Acquired Resistance to Covalent BTK Inhibitors Is Generally Driven by Mutations in BTK at C481 Site[1]

BTK C481 mutations also confer resistance to covalent BTK inhibitors acalabrutinib, ibrutinib, and zanubrutinib

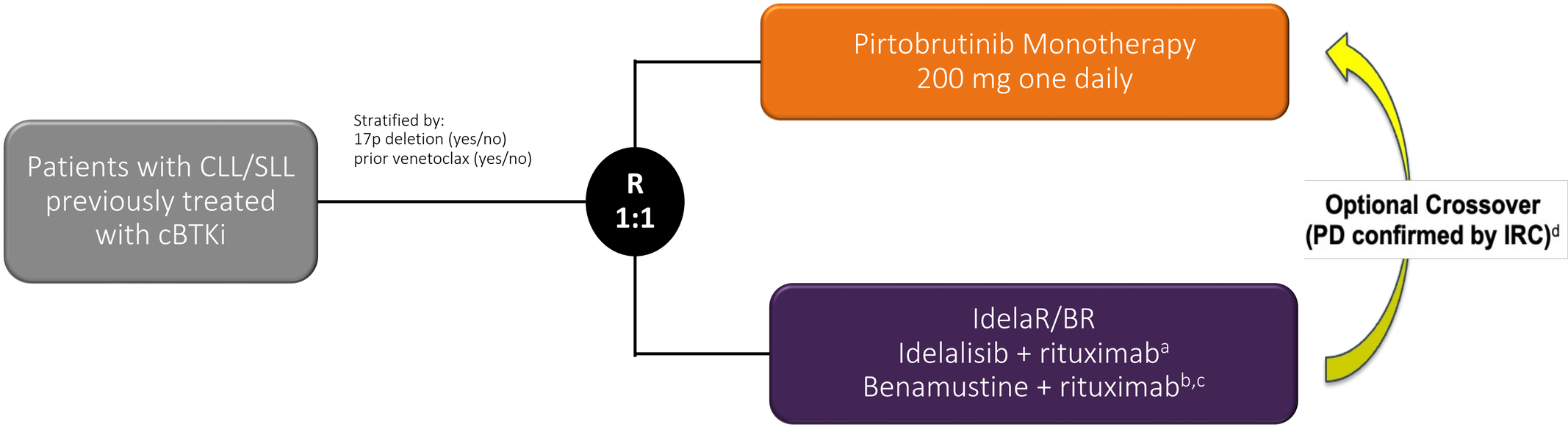


Structure of Bruton tyrosine kinase[2]

In sum, BTK resistance contributes to disease progression and diminishes the efficacy of *all covalent BTK inhibitors*

1. Woyach. NEJM 2014;370:2286. 2. Gu. J Hematol Oncol. 2021;14:40.

BRUIN: Phase I/II study with noncovalent BTK Inhibitor Pirtobrutinib (LOXO-305) for previously treated CLL



- **Primary endpoints:** MTD and recommended phase II dose (phase I), ORR (phase II)
- **Secondary endpoints:** safety, PK, ORR by investigator, DoR, PFS, OS

Sharman JP, J Clin Oncol. 2025 Aug;43(22):2538-2549.

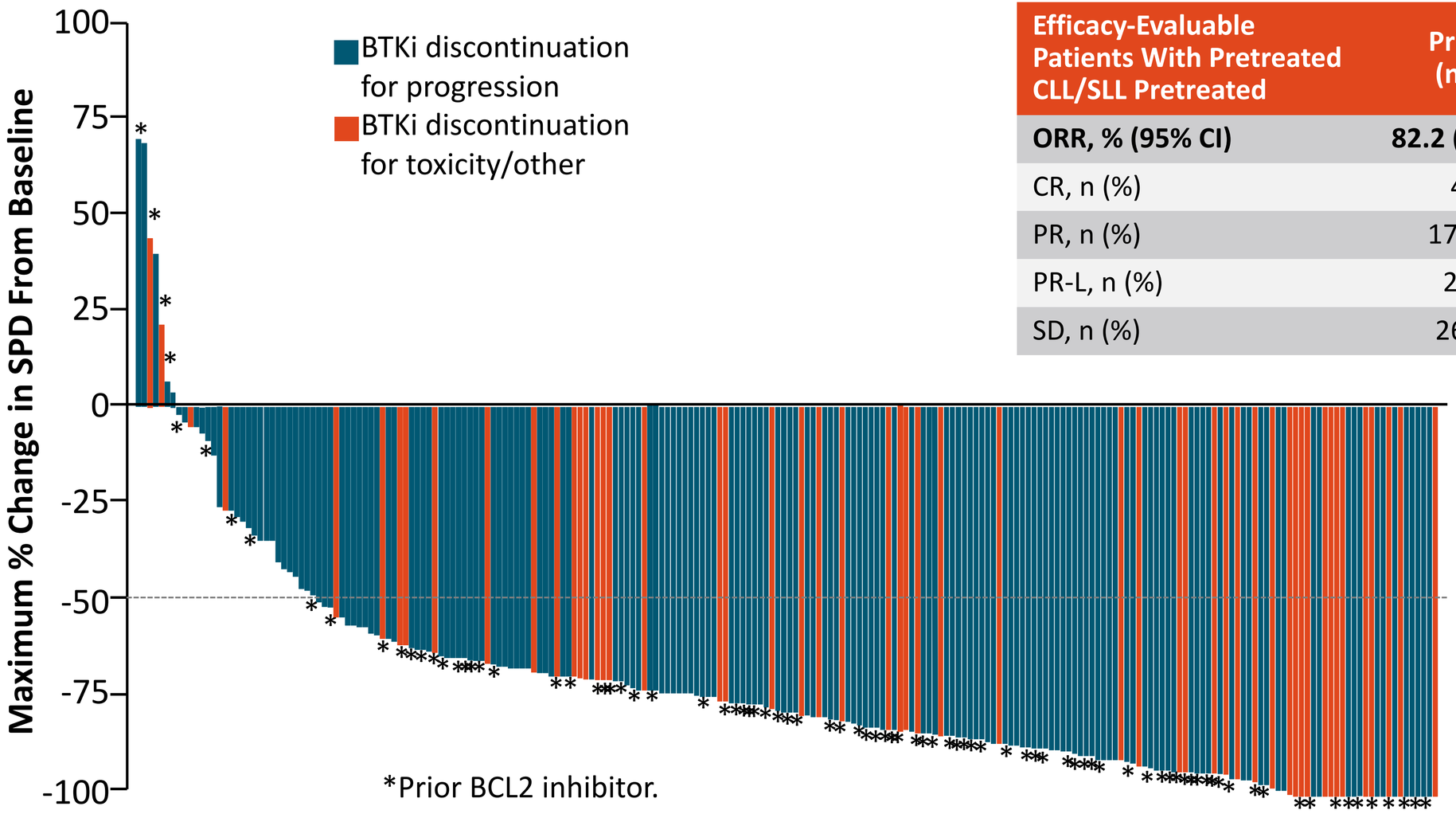
BRUIN: Baseline Characteristics

Characteristic	N = 261
Median age, yr	69 (36-88)
Male/female, n (%)	177 (68)/84 (32)
ECOG PS 0/1/2, %	53/40/7
Median prior lines systemic therapy, n (range)	3 (1-11)
Prior therapy, n (%)	261 (100)
▪ BTKi	230 (88)
▪ CD20 antibody	207 (79)
▪ Chemotherapy	108 (41)
▪ BCL2 inhibitor	51 (20)
▪ PI3K inhibitor	15 (6)
▪ SCT	6 (2)
– Allogeneic	5 (2)
– Autologous	1 (<1)

Characteristic	N = 261
Reason for discontinuing prior BTKi, %	
▪ PD	196 (75)
▪ Toxicity/other	65 (25)
Mutation status, n (%)	
▪ *BTK* C481 mutant	89 (43)
▪ *BTK* C481 wild type	118 (57)
▪ *PLCG2* mutant	33 (16)
High-risk molecular features, n (%)	
▪ del(17p)	51 (28)
▪ Mutated *TP53*	64 (37)
▪ del(17p) or *TP53* mutation	77(36)
– Both del(17p) and m*TP53*	38 (27)
▪ *IGHV* unmutated	168 (84)
▪ del(11q)	45 (25)

Sharman JP, J Clin Oncol. 2025 Aug;43(22):2538-2549.

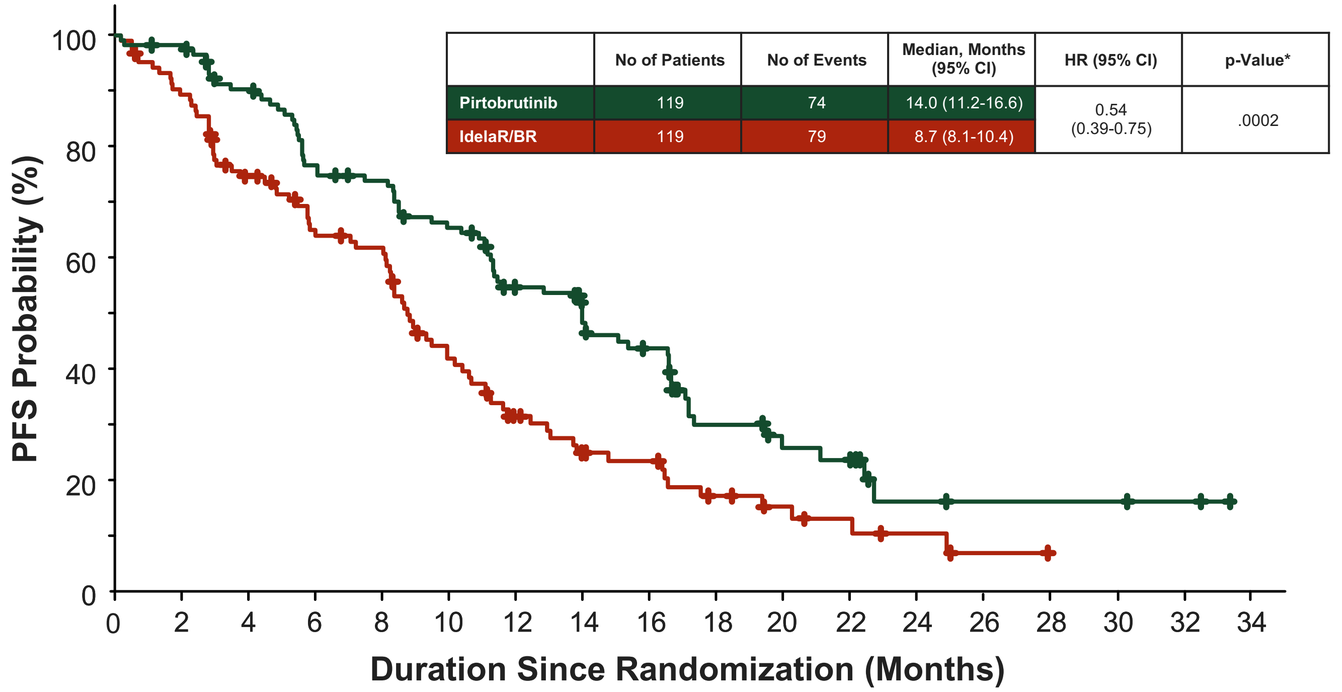
BRUIN CLL: Response



Efficacy-Evaluable Patients With Pretreated CLL/SLL Pretreated	Prior BTKi (n = 247)	Prior BTKi + BCL2i (n = 100)
ORR, % (95% CI)	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
CR, n (%)	4 (1.6)	0
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Sharman JP, J Clin Oncol. 2025 Aug;43(22):2538-2549.

Investigator-Assessed Progression-Free Survival



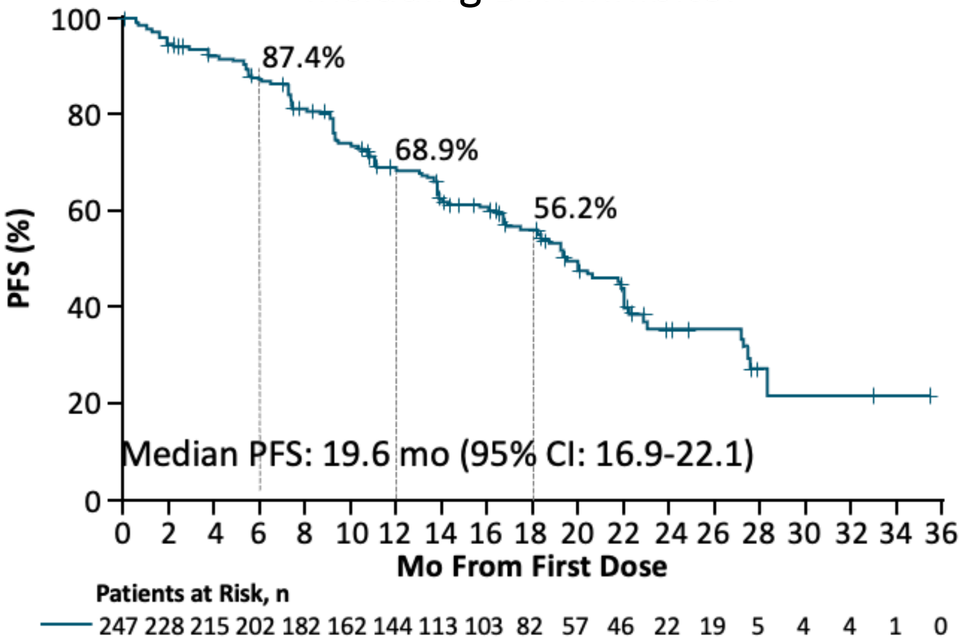
	No of Patients	No of Events	Median, Months (95% CI)	HR (95% CI)	p-Value*
Pirtobrutinib	119	74	14.0 (11.2-16.6)	0.54 (0.39-0.75)	.0002
IdelaR/BR	119	79	8.7 (8.1-10.4)		

Number at risk																		
Pirtobrutinib	119	113	100	84	79	69	54	44	36	19	12	10	4	3	3	3	2	0
IdelaR/BR	119	92	73	60	57	37	25	18	16	10	7	5	3	1	0	0	0	0

Sharman JP, J Clin Oncol. 2025 Aug;43(22):2538-2549.

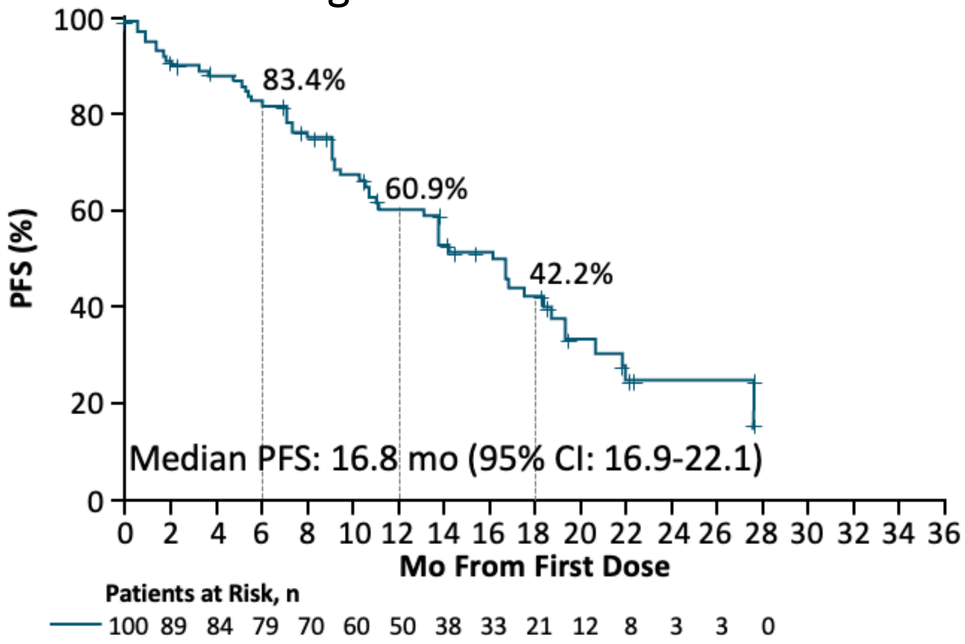
BRUIN CLL: PFS

PFS With Median of 3 Prior Lines of Therapy Including BTK Inhibitor



Median follow-up: 19.4 mo

PFS With Median of 5 Prior Lines of Therapy Including BTK Inhibitor and BCL2 Inhibitor



Median follow-up: 18.2 mo

Sharman JP, J Clin Oncol. 2025 Aug;43(22):2538-2549.

BRUIN CLL: Pirtobrutinib Safety Profile

Adverse Event, %	All Doses and Patients (N = 773)			
	TEAEs in ≥15%		TEAEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	28.7	2.1	9.3	0.8
Diarrhea	24.2	0.9	9.3	0.4
Neutropenia	24.2	20.4	14.7	11.5
Contusion	19.4	0.0	12.8	0.0
Cough	17.5	0.1	2.3	0.0
COVID-19	16.7	2.7	1.3	0.0
Dyspnea	15.5	1.0	3.0	0.1
Anemia	15.4	8.8	5.2	2.1
AEs of special interest				
Bruising	23.7	0.0	15.1	0.0
Rash	12.7	0.5	6.0	0.4
Arthralgia	14.4	0.6	3.5	0.0
Hemorrhage/hematoma	11.4	1.8	4.0	0.6
Hypertension	9.2	2.3	3.4	0.6
Atrial fibrillation/flutter[†]	2.8	1.2	0.8	0.1

Sharman JP, J Clin Oncol. 2025 Aug;43(22):2538-2549.

Conclusions: How to Sequencing Tx in CLL Pts ?

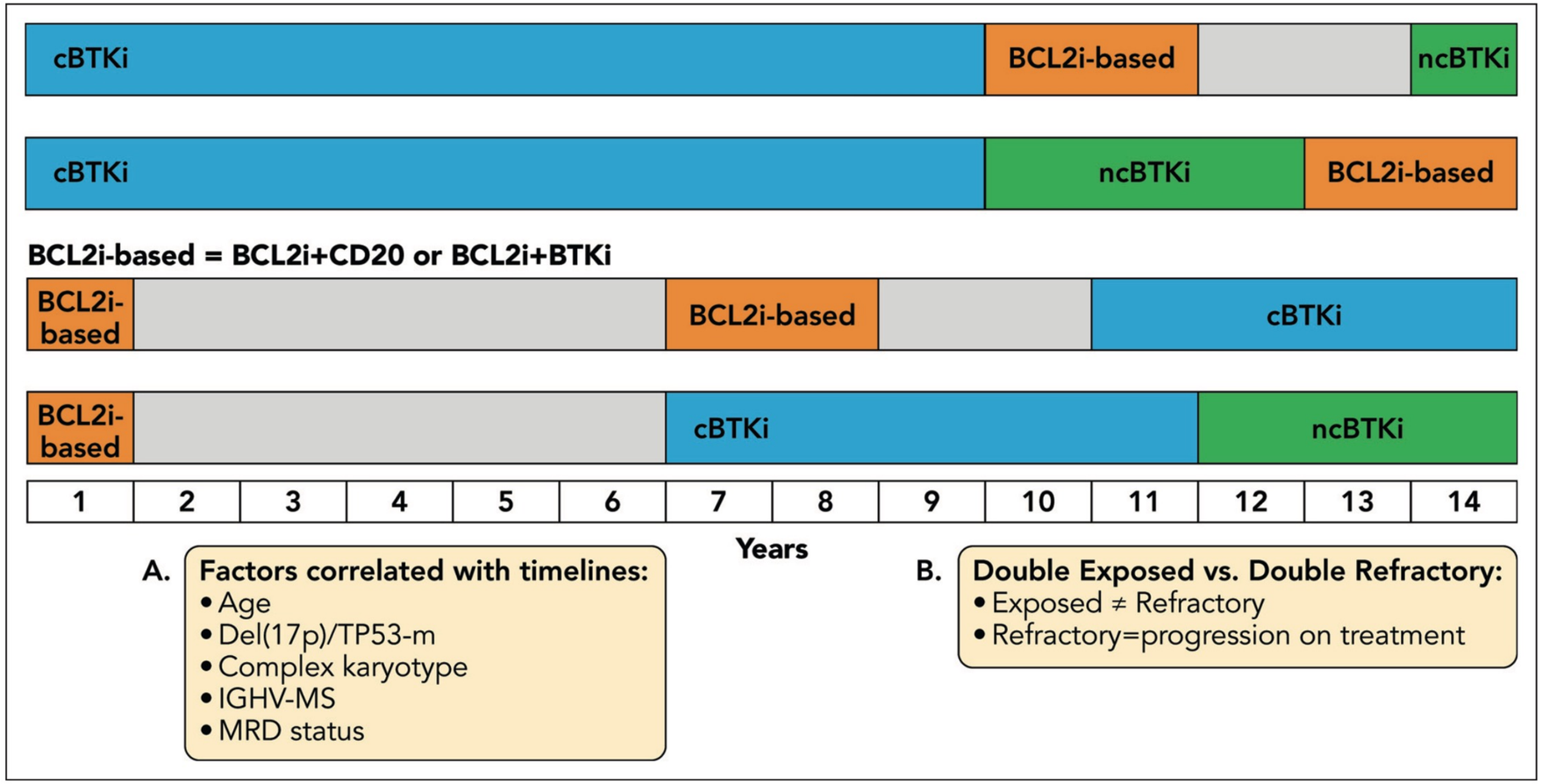


Figure 1. Targeted therapy for CLL: the "treatment big picture." Pictural of overall treatment strategies for patients with CLL who need treatment based on estimates for duration of response and PFS. First-line choice of treatment significantly contributes to time off treatment and sequence options. Time off treatment in remission is reflected as blank spaces. (A) Time-to-event timelines will vary by patient disease characteristics, choice of treatment, and depth of response. (B) Treatment exposure does not necessarily indicate treatment refractory CLL; progression on treatment does indicate refractoriness. cBTKi, covalent BTKi; IGHV-MS, IGHV gene mutation status; ncBTKi, noncovalent BTKi. Professional illustration by Patrick Lane, ScEYEnce Studios.

Wierda WG et al, Blood 2025