Advances in Chronic Lymphocytic Leukemia Targeted Therapy

2024 LOS Cancer Congress

Nakhle Saba, MD

Associate Professor of Medicine

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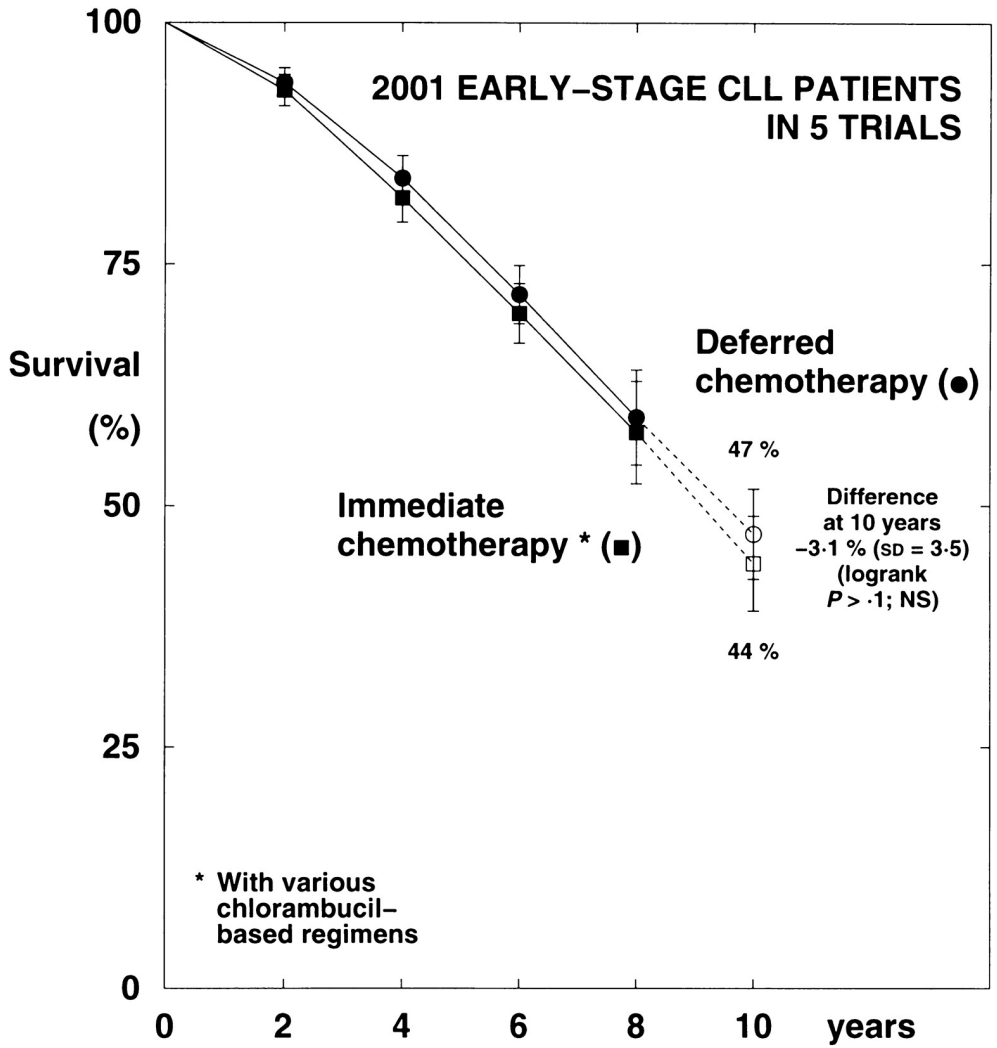
Agenda

- CLL12: Challenging the concept of "watch & wait" (EHA/ASH 2023)
- BCL2i vs. BTKi based therapies: pros & cons
- SEQUOIA: Zanubrutinib vs BR (EHA 2023 updates)
- ELEVATE-TN: Acalabrutinib ± O vs O + Clb (ASH 2023)
- ELEVATE-RR: Ibrutinib vs acalabrutinib
- ALPINE study: Ibrutinib vs zanubrutinib (ASH 2023)
- Intolerance to BTKi (EHA 2023)
- BRUIN study: Pirtobrutinib in R/R CLL
- BTK degraders
- CLL14: Ven+O vs. O Clb
- CLL13: Ven+R vs. Ven+O vs. Ven+O+I vs. CIT

“Watch & Wait” Is the SOC in Asymptomatic CLL



Deaths / person–years					
Immediate	69 / 1894	108 / 1693	102 / 1292	73 / 774	73 / 556
Deferred	62 / 1940	97 / 1737	103 / 1344	77 / 783	82 / 691

Why the “watch & wait”?

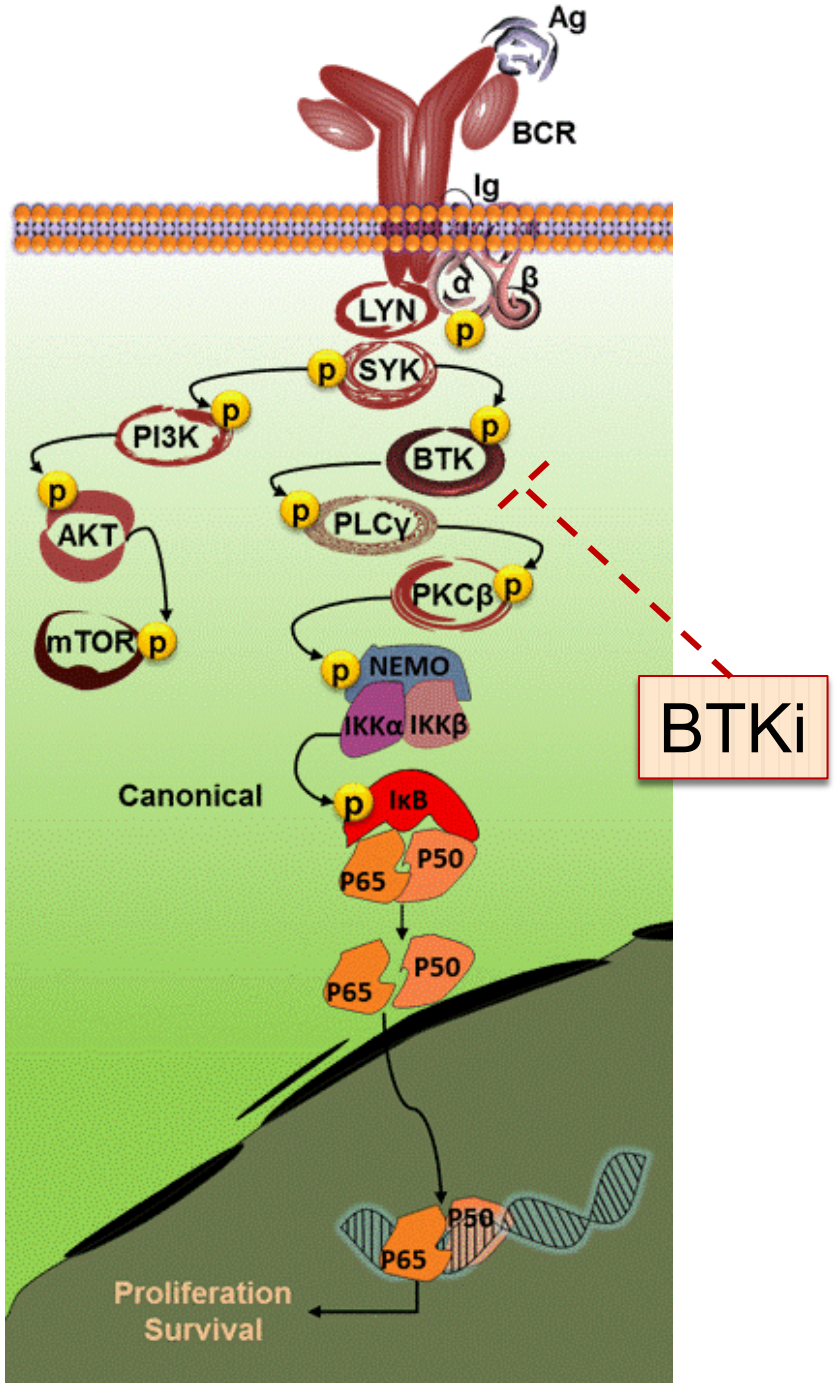
CLL remains incurable

Third of patients may not require therapy

No benefit to early intervention

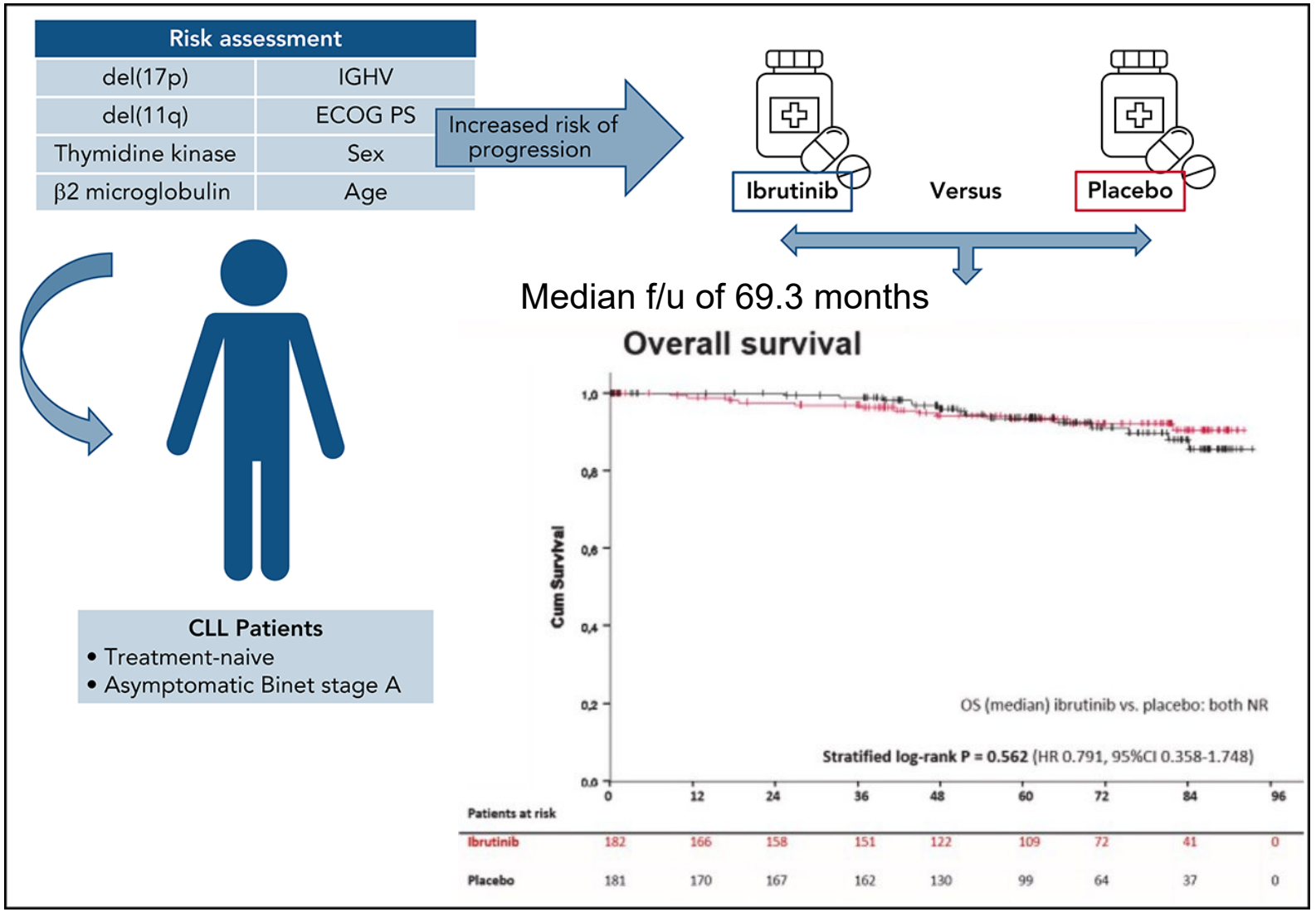
CLL Trialists' Collaborative Group. J Natl Cancer Inst. 1999

The B-Cell Receptor Pathway



Saba N, Wiestner A. *Curr Opin Hematol.* 2014

CLL12: Ibrutinib vs Placebo in Early-Stage, TN CLL



Langerbeins *et al.* Blood 2022; EHA 2023

Chemo-Free Options: BTKi vs BCL2i-Based Therapy

	BCL2i + Anti-CD20	BTKi
Pros	• Fixed duration • Low concerns for bleeding or cardiotoxicity • Performs well in low-risk CLL • Option to re-treat	• Oral, no need for infusion • Easy/convenient to start • Performs well in all risk groups • Very low TLS risk

Chemo-Free Options: BTKi vs BCL2i-Based Therapy

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Pros	• Fixed duration • Low concerns for bleeding or cardiotoxicity • Performs well in low-risk CLL • Option to re-treat	• Oral, no need for infusion • Easy/convenient to start • Performs well in all risk groups • Very low TLS risk
Cons	• Need for anti-CD20 infusion • Complicated first 2 months • TLS risk • Shortened PFS with high-risk CLL	• Lifelong commitment • Bleeding and cardiotoxicity concerns • No option to re-treat at progression

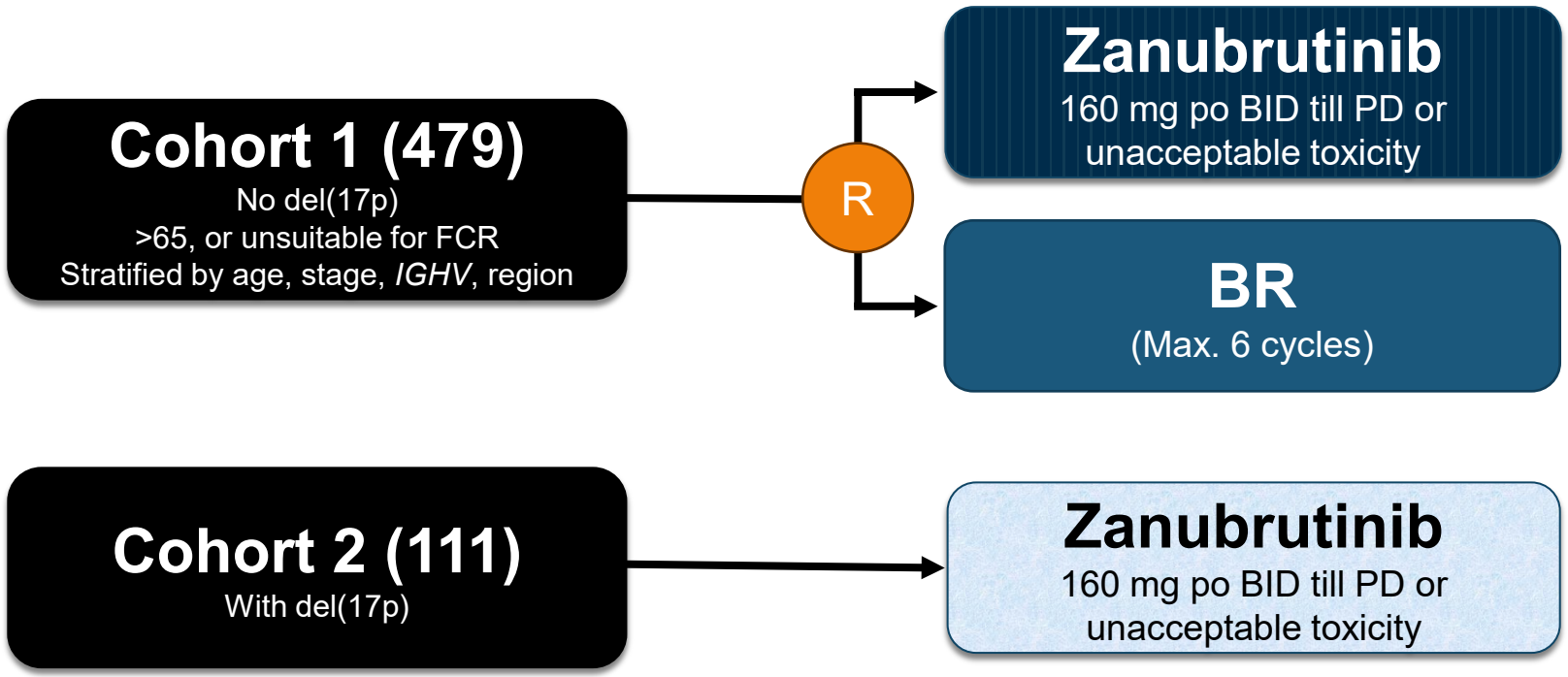
FDA-Approved BTKis

Variable	Ibrutinib[a]	Acalabrutinib[b]	Zanubrutinib[c]	Pirtobrutinib[d]
Binding to BTK	Covalent	Covalent	Covalent	Noncovalent
Dose schedule	QD	BID	QD or BID	QD
Use after progression on cBTKi	No	No	No	Yes
Use after intolerance to cBTKi	N/A	Yes	Yes	Yes
CLL/SLL	+	+	+	+
MCL	-	+	+	+
MZL	-	-	+	-
WM	+	-	+	-
FL	-	-	+	-

[a]Ibrutinib: CLL/SLL, WM.
[b]Acalabrutinib: CLL/SLL, R/R MCL.
[c]Zanubrutinib: CLL/SLL, WM, R/R MZL after least 1 anti-CD20-based regimen, FL in combination with obinutuzumab after 2 or more lines of systemic therapy.
[d]Pirtobutinib: R/R CLL/SLL and R/R MCL after at least 2 lines of systemic therapy, including a cBTKi (MCL), and cBTKi and BCL2i (CLL/SLL).

SEQUOIA: Zanubrutinib vs BR

Phase III, randomized, open label clinical trial in TN CLL



Primary endpoints

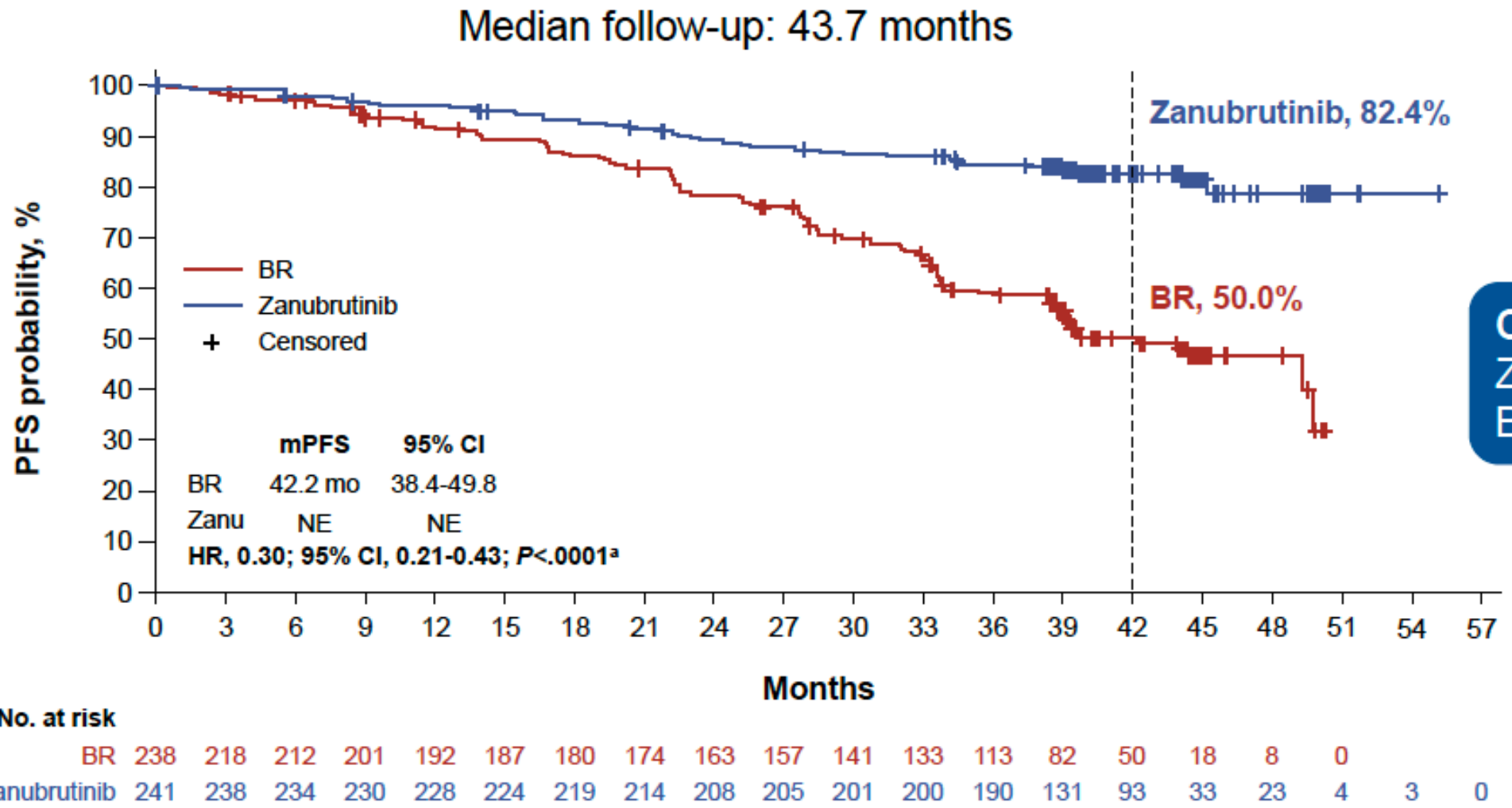
- PFS (cohort 1)

Secondary endpoints

- ORR/CR
- PFS
- DOR
- OS
- Safety

Tam *et al.* Lancet Oncol. 2022

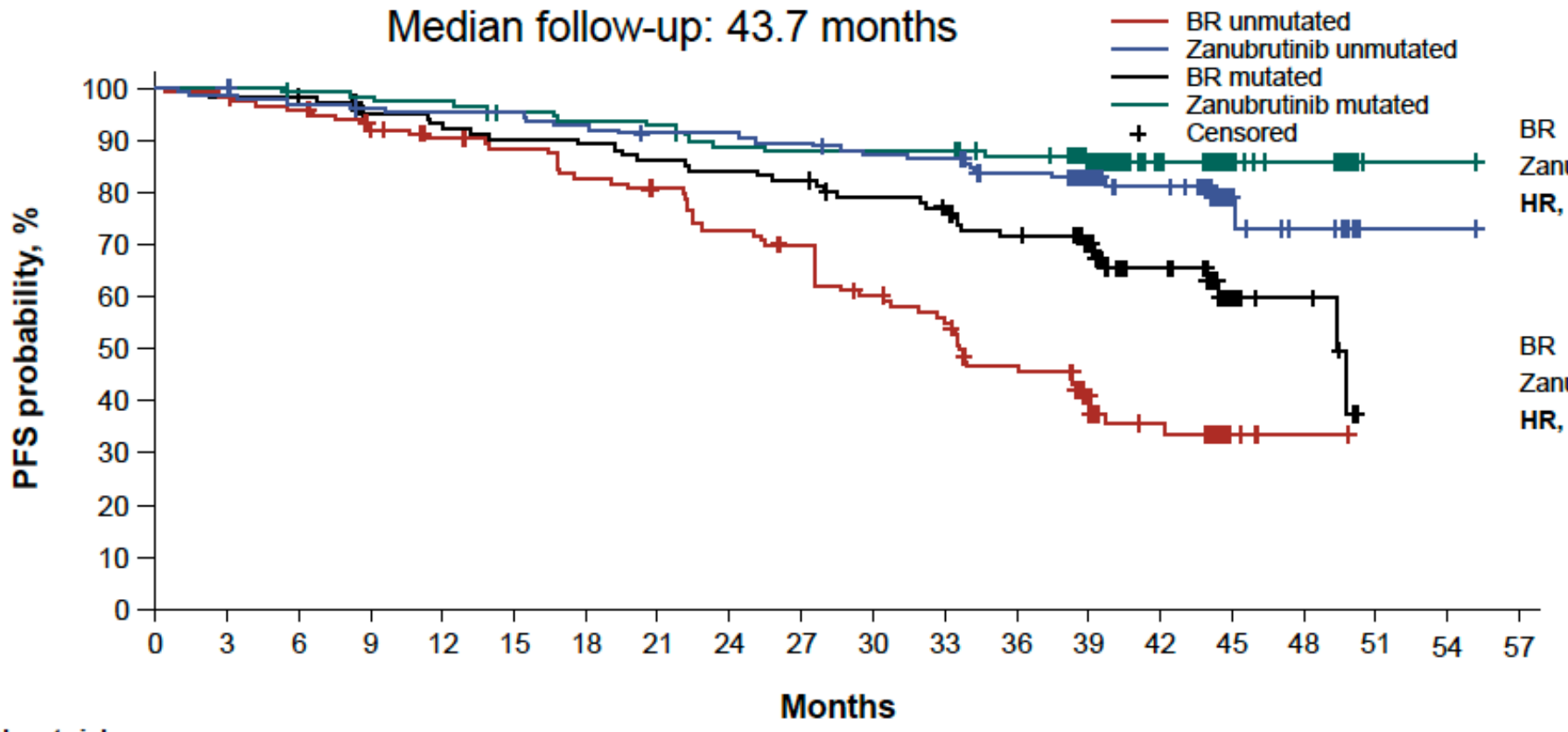
SEQUOIA: Efficacy, Cohort 1 (no del[17p])



CR/CRi rates:
Zanubrutinib, 17.4%;
BR, 21.8%

Tam *et al.* Lancet Oncol. 2022; Shadman *et al.* ICML 2023, A#154

SEQUOIA: Efficacy by *IGHV* Status



Unmutated IGHV

	mPFS	95% CI
BR	33.7 mo	29.5-39.1
Zanu	NE	NE

HR, 0.23; 95% CI, 0.14-0.37; *P*<.0001[a]

Mutated IGHV

	mPFS	95% CI
BR	49.4 mo	44.4-NE
Zanu	NE	NE

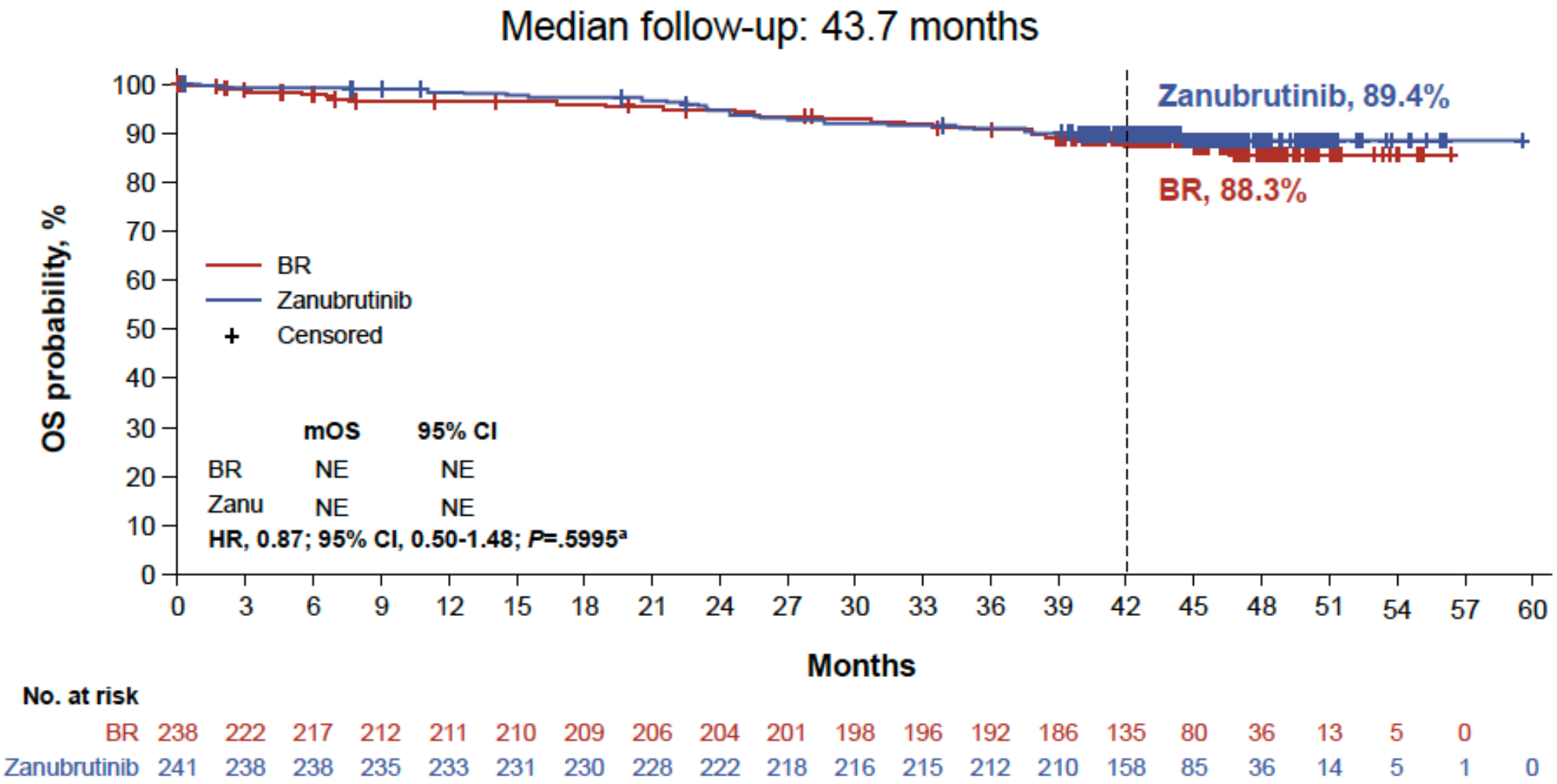
HR, 0.35; 95% CI, 0.19-0.64; *P*=.00033[a]

No. at risk

BR unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0		
Zanubrutinib unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0
BR mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	53	31	14	7	0		
Zanubrutinib mutated	109	109	107	106	105	101	99	98	93	92	92	92	89	63	43	18	13	1	1	0

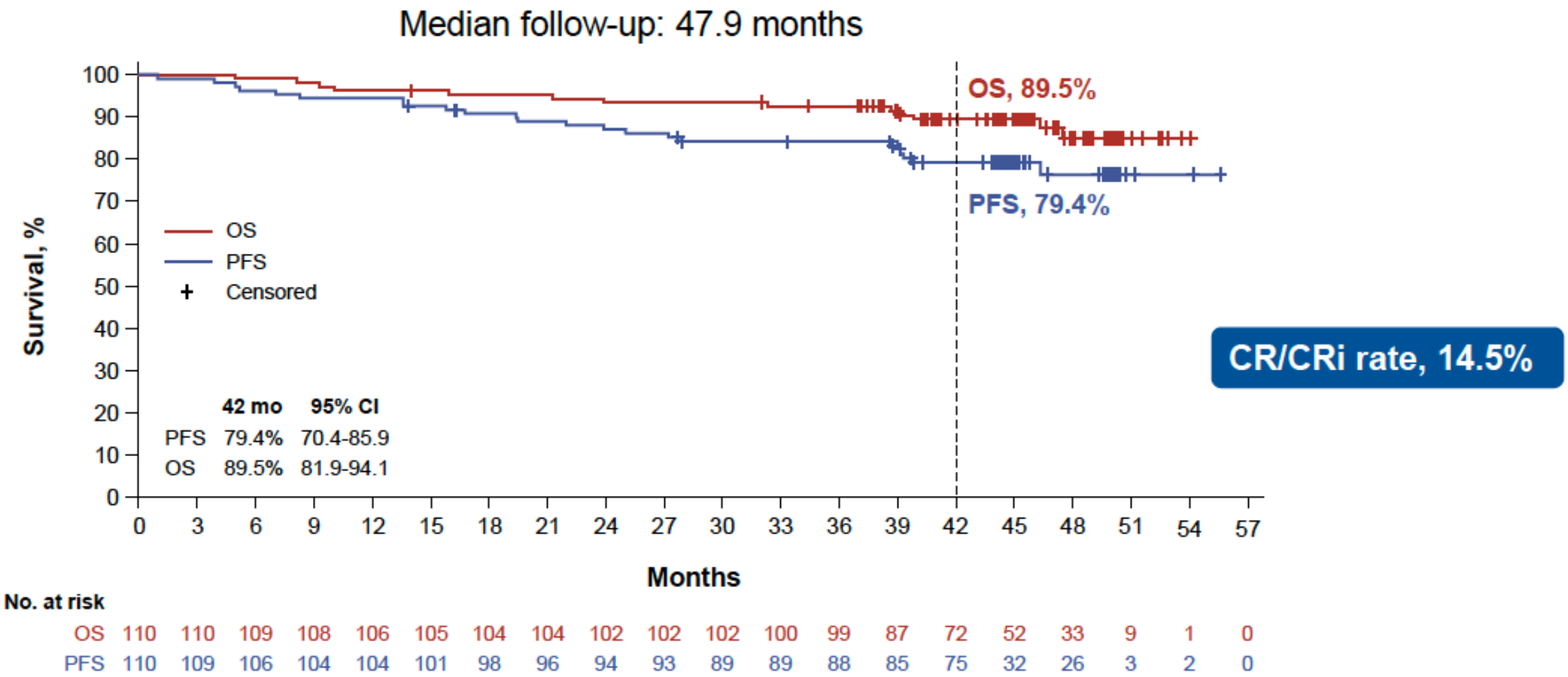
Tam *et al.* Lancet Oncol. 2022; Shadman *et al.* ICML 2023, A#154

SEQUOIA: OS



Tam *et al.* Lancet Oncol. 2022; Shadman *et al.* ICML 2023, A#154

SEQUOIA: Efficacy, Cohort 2 (del-17p)



CR/CRi rate, 14.5%

Tam *et al.* Lancet Oncol. 2022; Shadman *et al.* ICML 2023, A#154

SEQUOIA: Safety

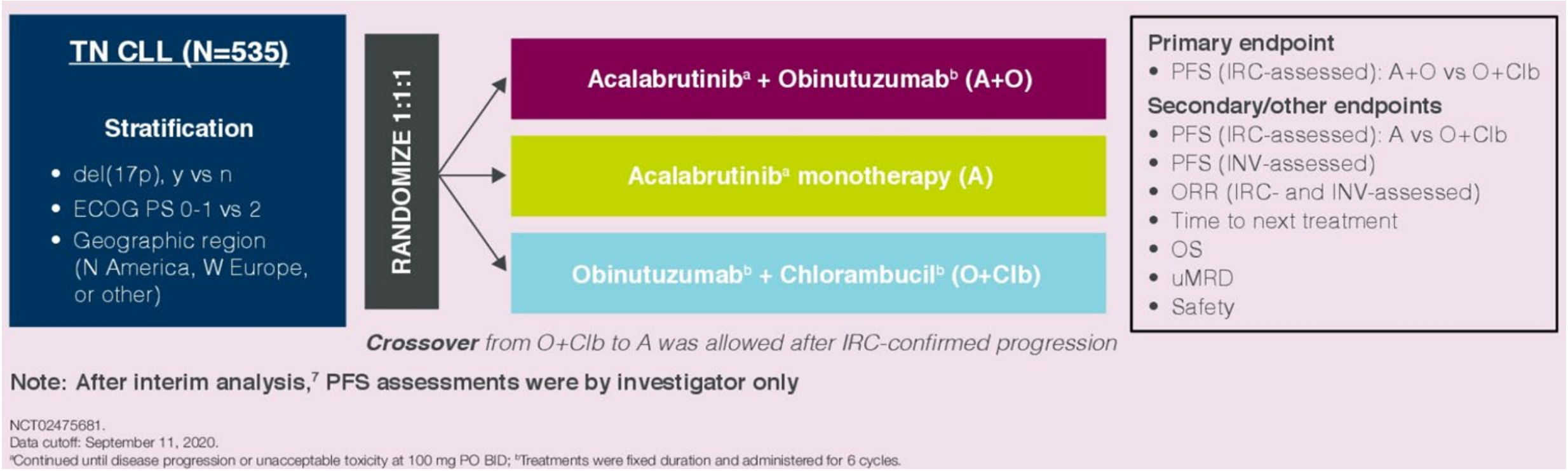
Treatment-emergent and posttreatment AEIs in Cohorts 1 and 2 (any grade and grade ≥3)

	Patients without del(17p)				Patients with del(17p)	
	Arm A: zanubrutinib (n=240)[a]		Arm B: BR (n=227)[b]		Arm C: zanubrutinib (n=111)	
AEIs, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	175 (72.9)	57 (23.8)	142 (62.6)	50 (22.0)	89 (80.2)	30 (27.0)
Bleeding	117 (48.8)	14 (5.8)	28 (12.3)	4 (1.8)	64 (57.7)	6 (5.4)
Other malignancies	45 (18.8)	22 (9.2)	28 (12.3)	11 (4.8)	27 (24.3)	8 (7.2)
Hypertension	42 (17.5)	22 (9.2)	31 (13.7)	15 (6.6)	15 (13.5)	7 (6.3)
Diarrhea	41 (17.1)	4 (1.7)	32 (14.1)	5 (2.2)	22 (19.8)	1 (0.9)
Neutropenia	40 (16.7)	30 (12.5)	129 (56.8)	116 (51.1)	21 (18.9)	18 (16.2)
Arthralgia	37 (15.4)	2 (0.8)	23 (10.1)	1 (0.4)	26 (23.4)	1 (0.9)
Anemia	17 (7.1)	1 (0.4)	47 (20.7)	5 (2.2)	7 (6.3)	0 (0)
Thrombocytopenia	15 (6.3)	5 (2.1)	41 (18.1)	18 (7.9)	9 (8.1)	2 (1.8)
Atrial fibrillation/flutter	12 (5.0)	3 (1.3)	6 (2.6)	3 (1.3)	7 (6.3)	5 (4.5)
Myalgia	9 (3.8)	0 (0)	4 (1.8)	0 (0)	8 (7.2)	1 (0.9)
Opportunistic infection	6 (2.5)	1 (0.4)	4 (1.8)	3 (1.3)	1 (0.9)	1 (0.9)

Tam *et al.* Lancet Oncol. 2022; Shadman *et al.* ICML 2023, A#154

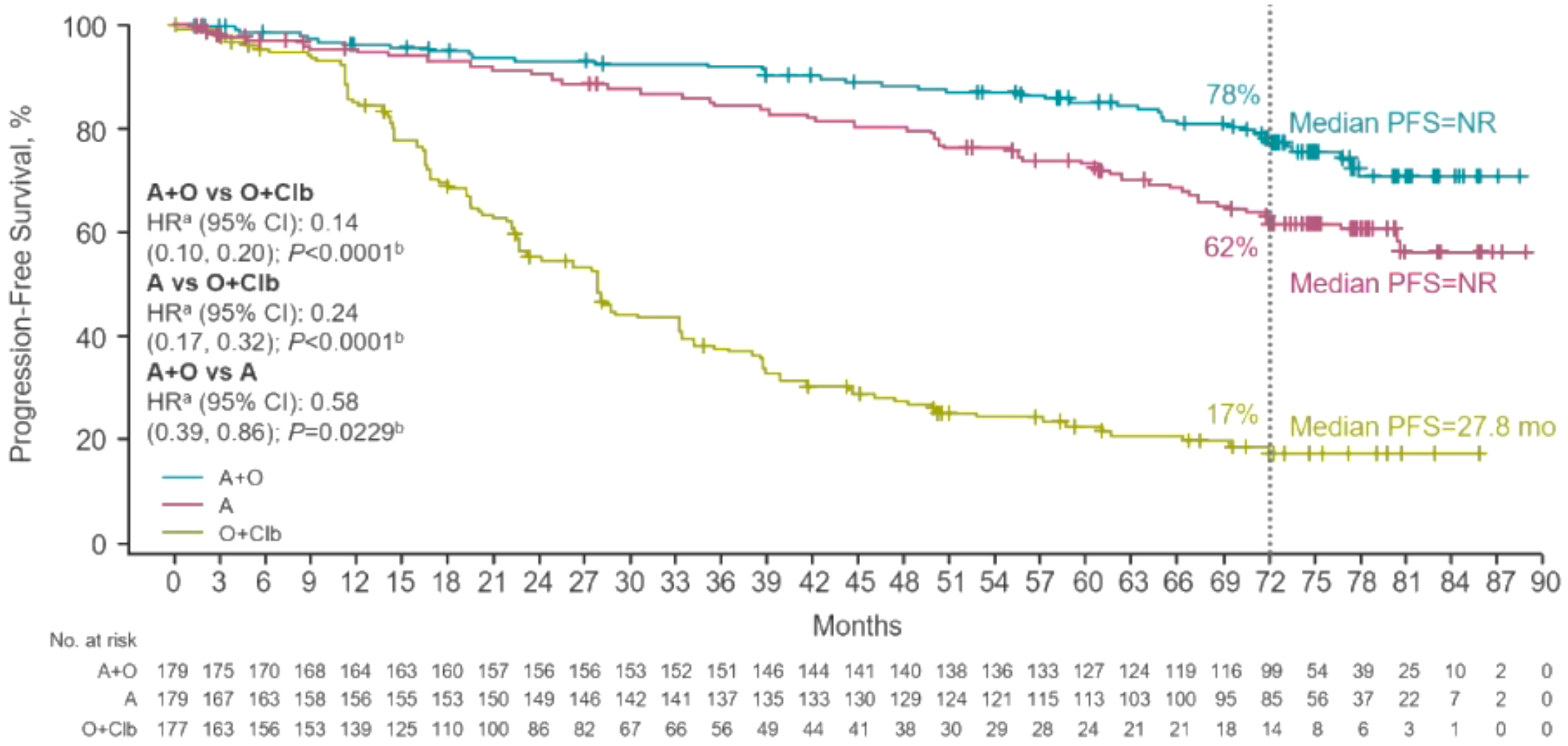
ELEVATE-TN: Acalabrutinib ± O vs O + Clb

Phase III, randomized, open-label clinical trial in TN CLL



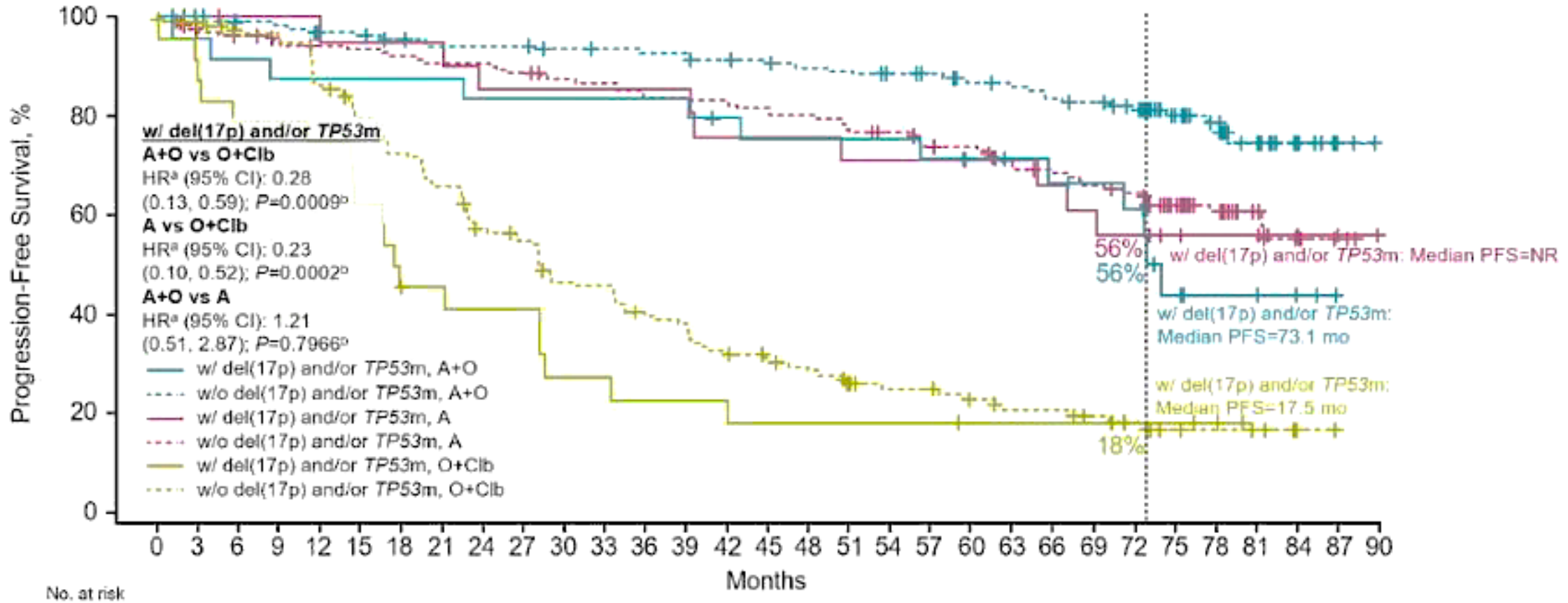
Sharman *et al.* ASCO 2022, A#7539; Sharman *et al*. ASH 2023, A#636

ELEVATE-TN: PFS



Sharman *et al*. ASH 2023, A#636

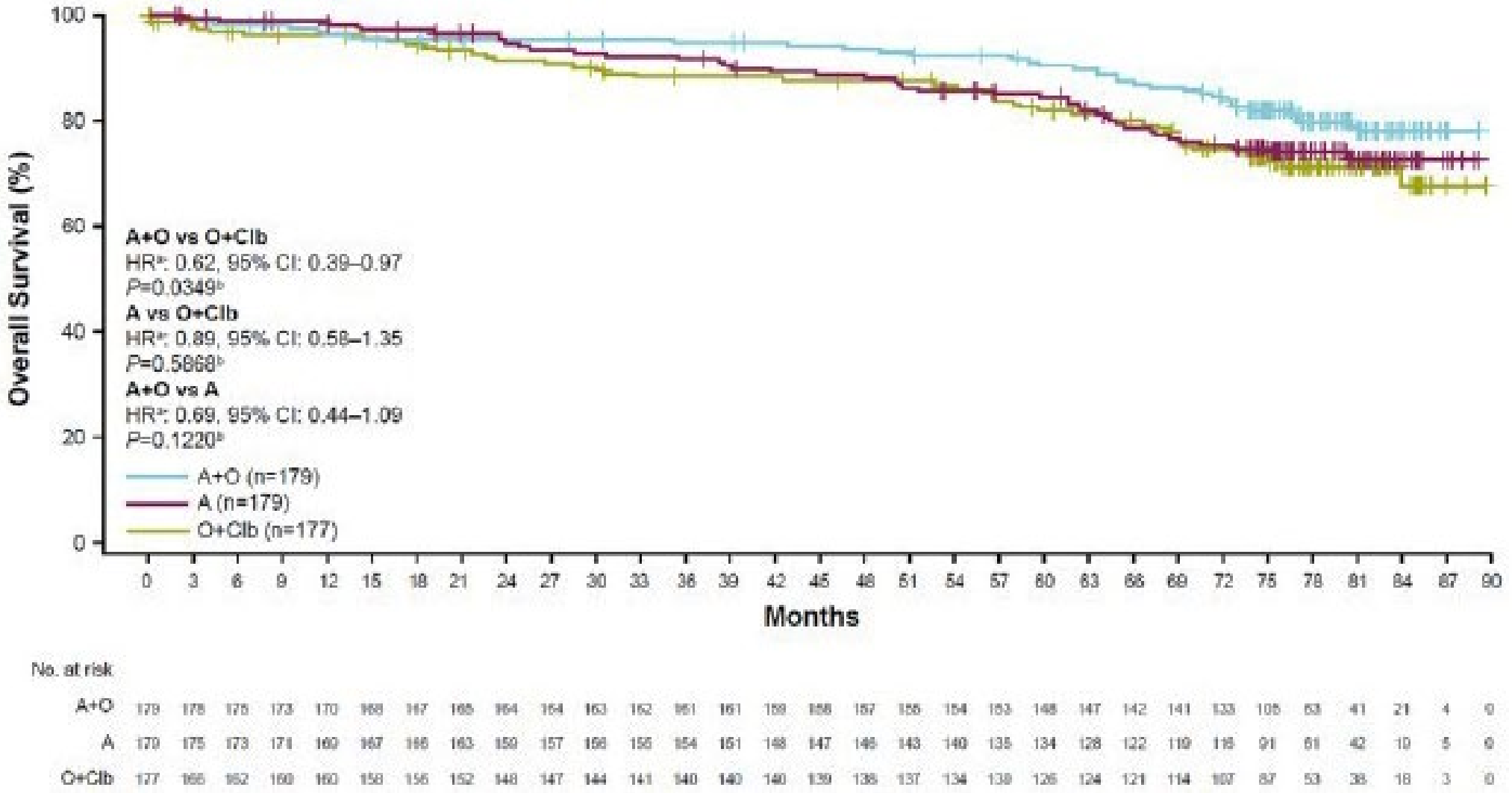
ELEVATE-TN: PFS by *TP53* Status



No. at risk																													
w/ del(17p) and/or *TP53m*, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0
w/o del(17p) and/or *TP53m*, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	2
w/ del(17p) and/or *TP53m*, A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	15	14	14	13	11	11	7	7	4	2	1
w/o del(17p) and/or *TP53m*, A	156	145	142	137	136	135	133	131	131	128	124	123	119	118	117	114	113	109	106	100	99	89	87	84	74	49	30	18	5	1
w/ del(17p) and/or *TP53m*, O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	3	3	3	3	3	1	0		
w/o del(17p) and/or *TP53m*, O+Clb	152	142	137	134	121	110	100	91	77	73	61	60	51	44	40	37	34	26	25	24	21	18	18	15	11	5	5	3	1	0

Sharman *et al*. ASH 2023, A#636

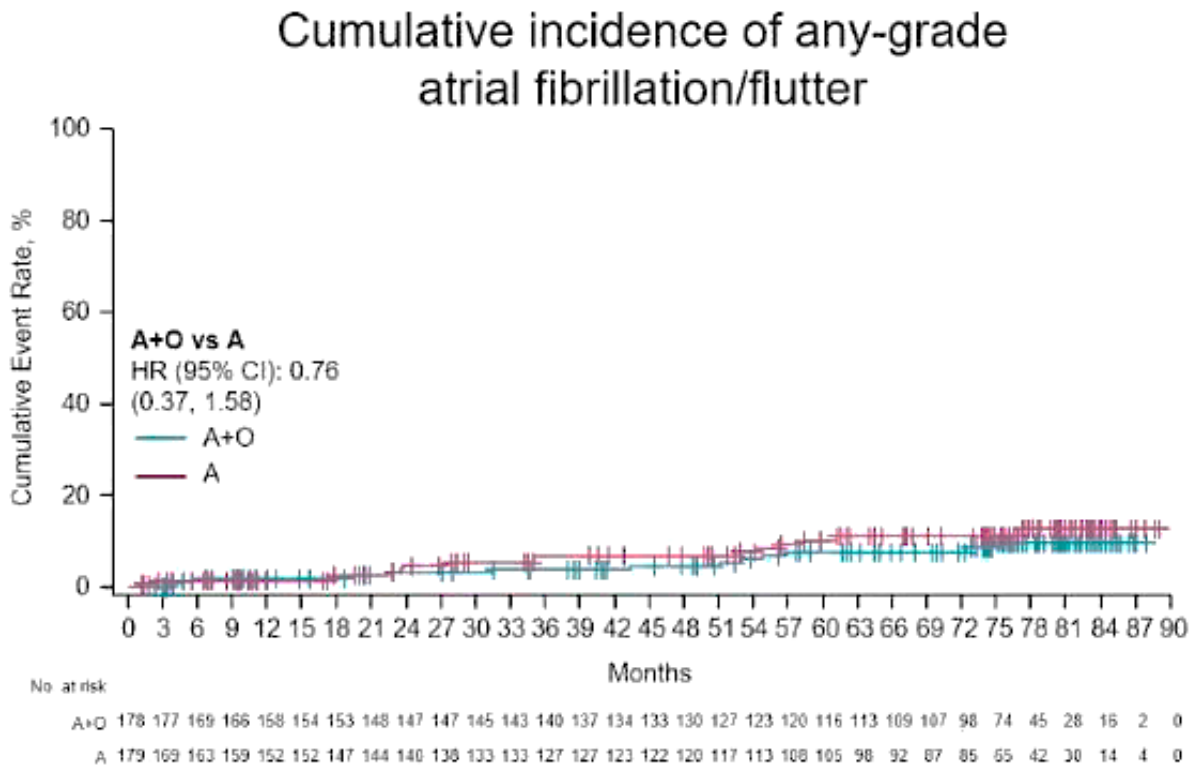
ELEVATE-TN: OS



Sharman *et al*. ASH 2023, A#636

ELEVATE-TN: Toxicity

Grade ≥3	A + O, %	A, %
Neutropenia	31	12
Thrombocytopenia	8	3
Diarrhea	6	1
COVID-19	9	7
Pneumonia	7	6
Syncope	5	2
Hypertension	4	5
Atrial fibrillation	2	2



	A + O (n = 178)		A (n = 179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Atrial fibrillation	13 (7.3%)	3 (1.7%)	16 (8.9%)	3 (1.7%)
Hypertension	20 (11.2%)	8 (4.5%)	20 (11.2%)	9 (5.0%)

Most common reasons for treatment discontinuation

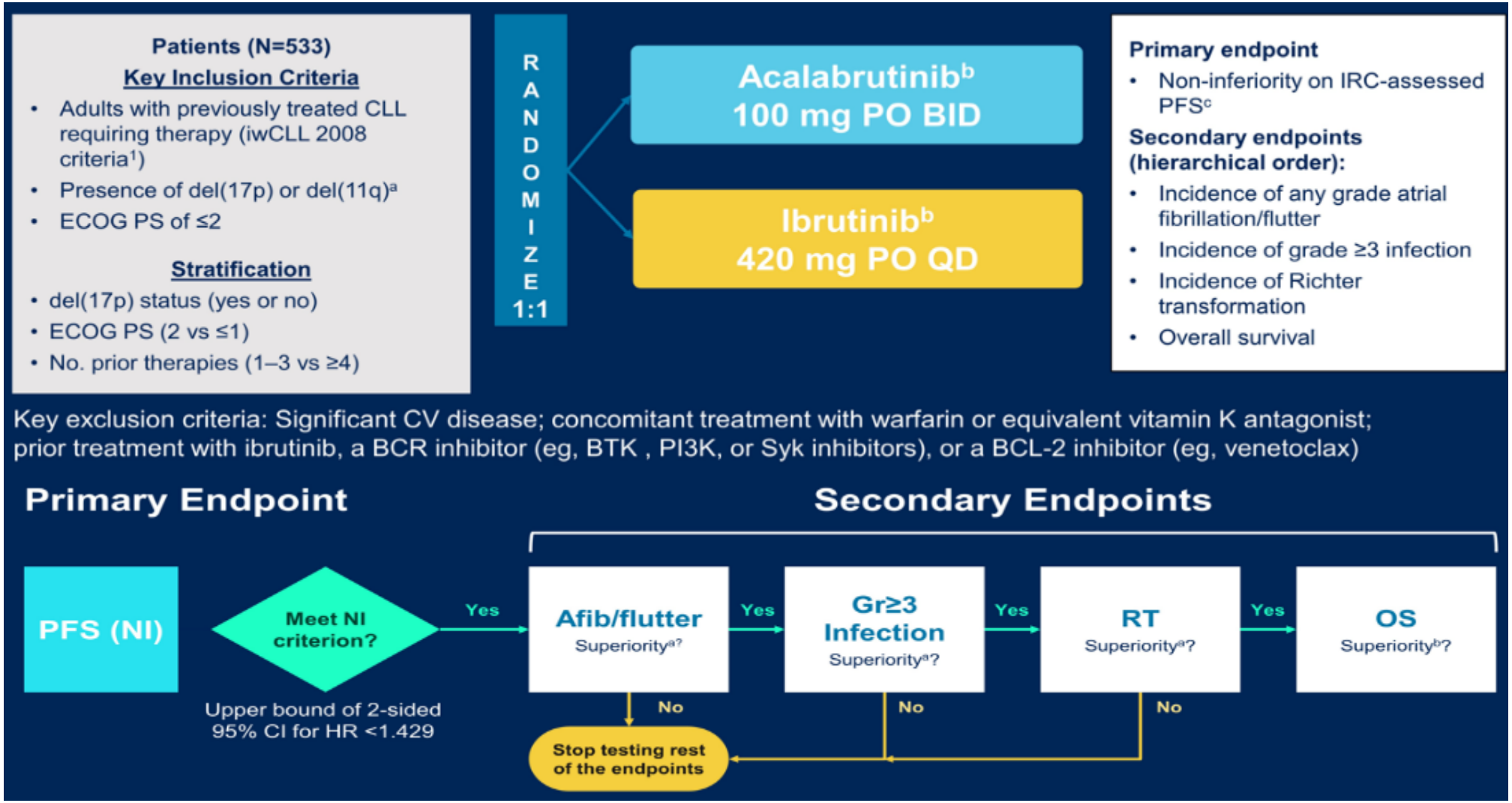
AE: 21% of A + O and 18% of A

PD: 6% of A + O and 14% of A

Sharman *et al*. ASH 2023, A#636

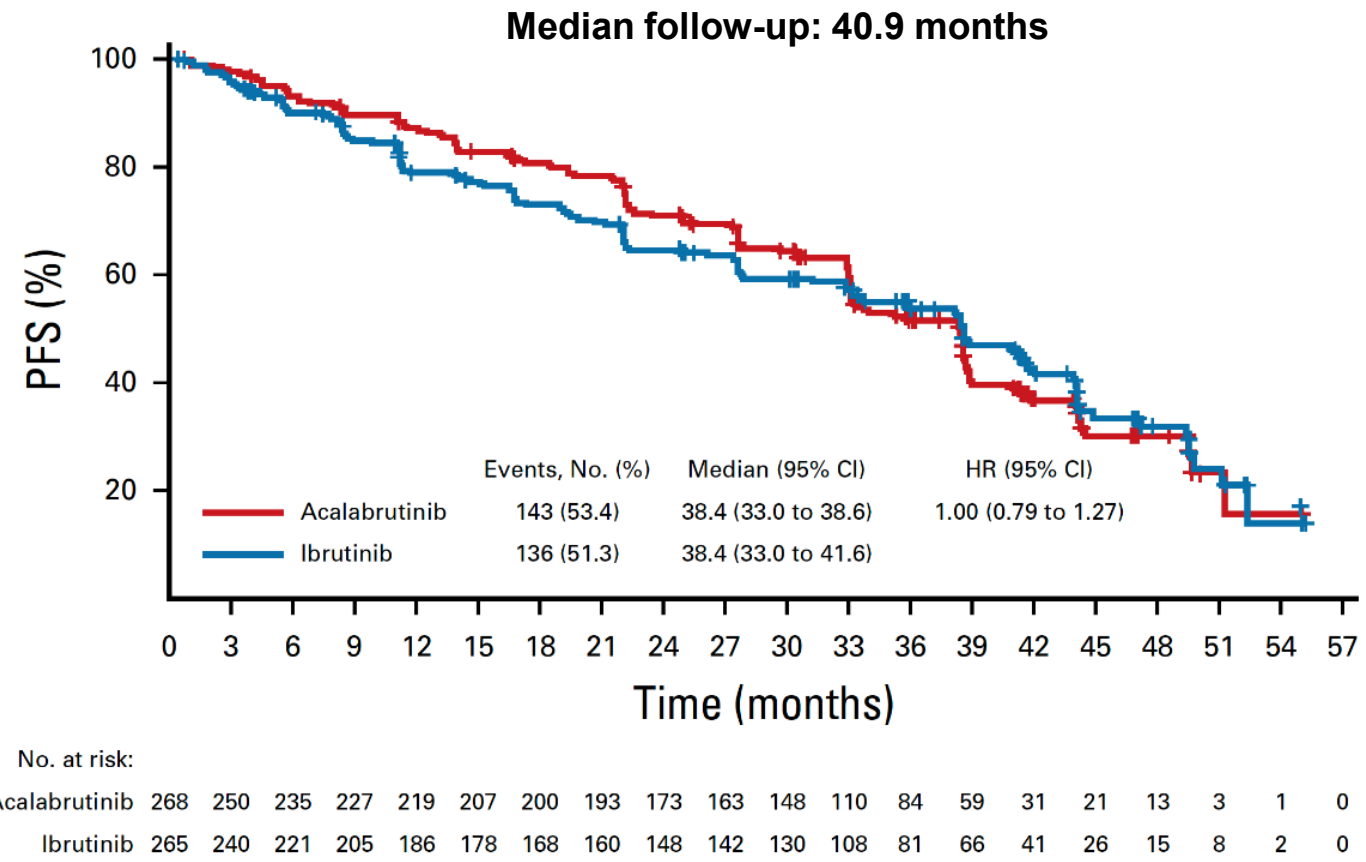
ELEVATE-RR: Acalabrutinib vs Ibrutinib

Phase III, randomized, open-label clinical trial in R/R CLL



Byrd *et al.* J Clin Oncol. 2021

ELEVATE-RR: Efficacy and Safety Results



	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Event	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Bleeding	**101 (38)**	12 (4.5)	**135 (51)**	14 (5.3)
Diarrhea[a,b]	92 (34.6)	3 (1.1)	**121 (46.0)**	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	**4 (1.5)**	53 (20.2)	0
Cough[a]	**77 (28.9)**	2 (0.8)	56 (21.3)	1 (0.4)
Fatigue[b]	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia[a]	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension[a,b]	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Vomiting	28 (10.5)	1 (0.4)	36 (13.7)	3 (1.1)
Peripheral edema	26 (9.8)	0	38 (14.4)	1 (0.4)
Rash	26 (9.8)	2 (0.8)	33 (12.5)	0
Myalgia	25 (9.4)	2 (0.8)	27 (10.3)	1 (0.4)
Atrial fibrillation[a]	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)
Urinary tract infection[a]	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain[a]	20 (7.5)	0	**34 (12.9)**	2 (0.8)
Epistaxis	19 (7.1)	1 (0.4)	28 (10.6)	1 (0.4)
Muscle spasms[a]	16 (6.0)	0	**35 (13.3)**	2 (0.8)
Dyspepsia[a]	10 (3.8)	0	**32 (12.2)**	0

Byrd *et al.* J Clin Oncol. 2021

ALPINE: Zanubrutinib vs Ibrutinib

Phase III, randomized, open-label clinical trial in R/R CLL

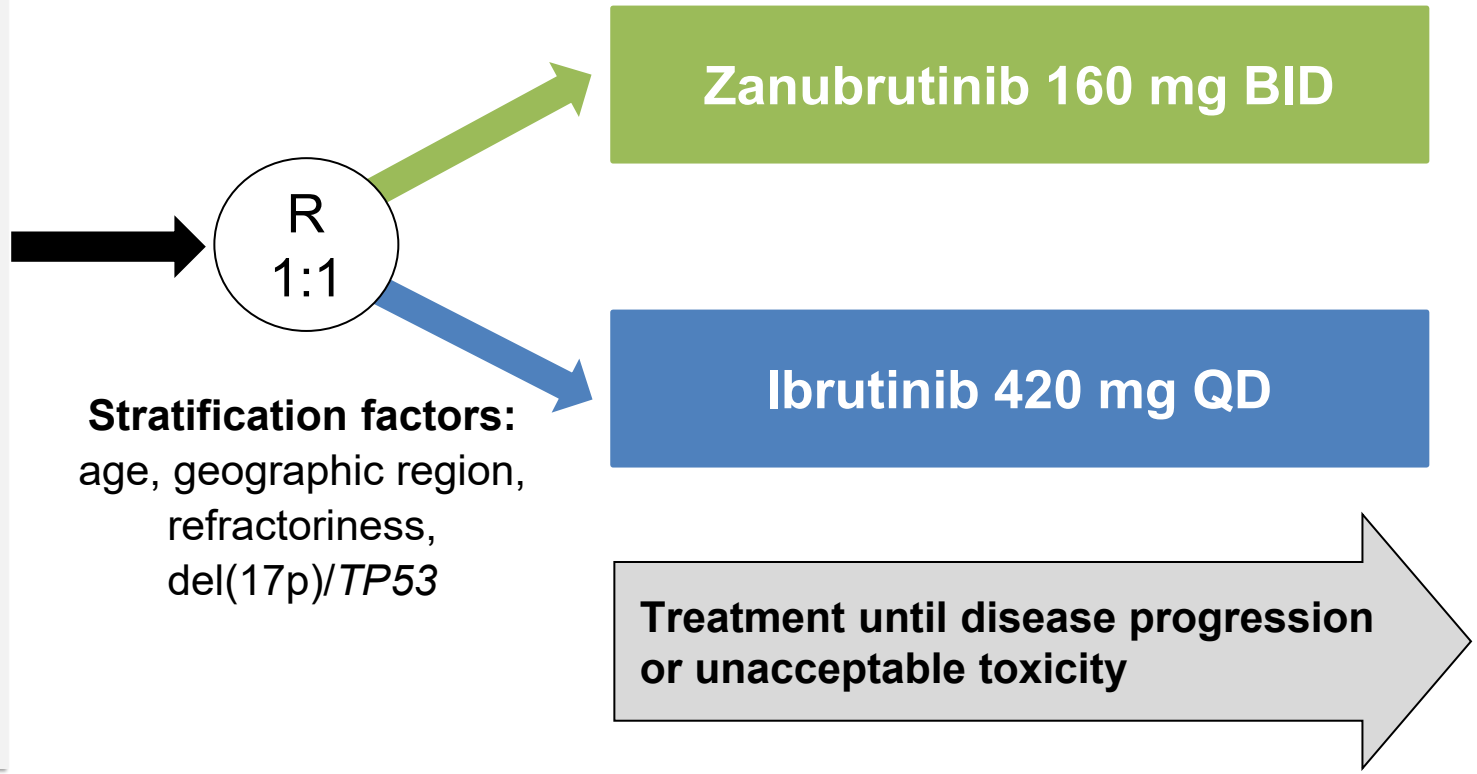
R/R CLL/SLL with ≥1 prior treatment
(Planned N = 600, Actual N = 652)

Key Inclusion Criteria

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

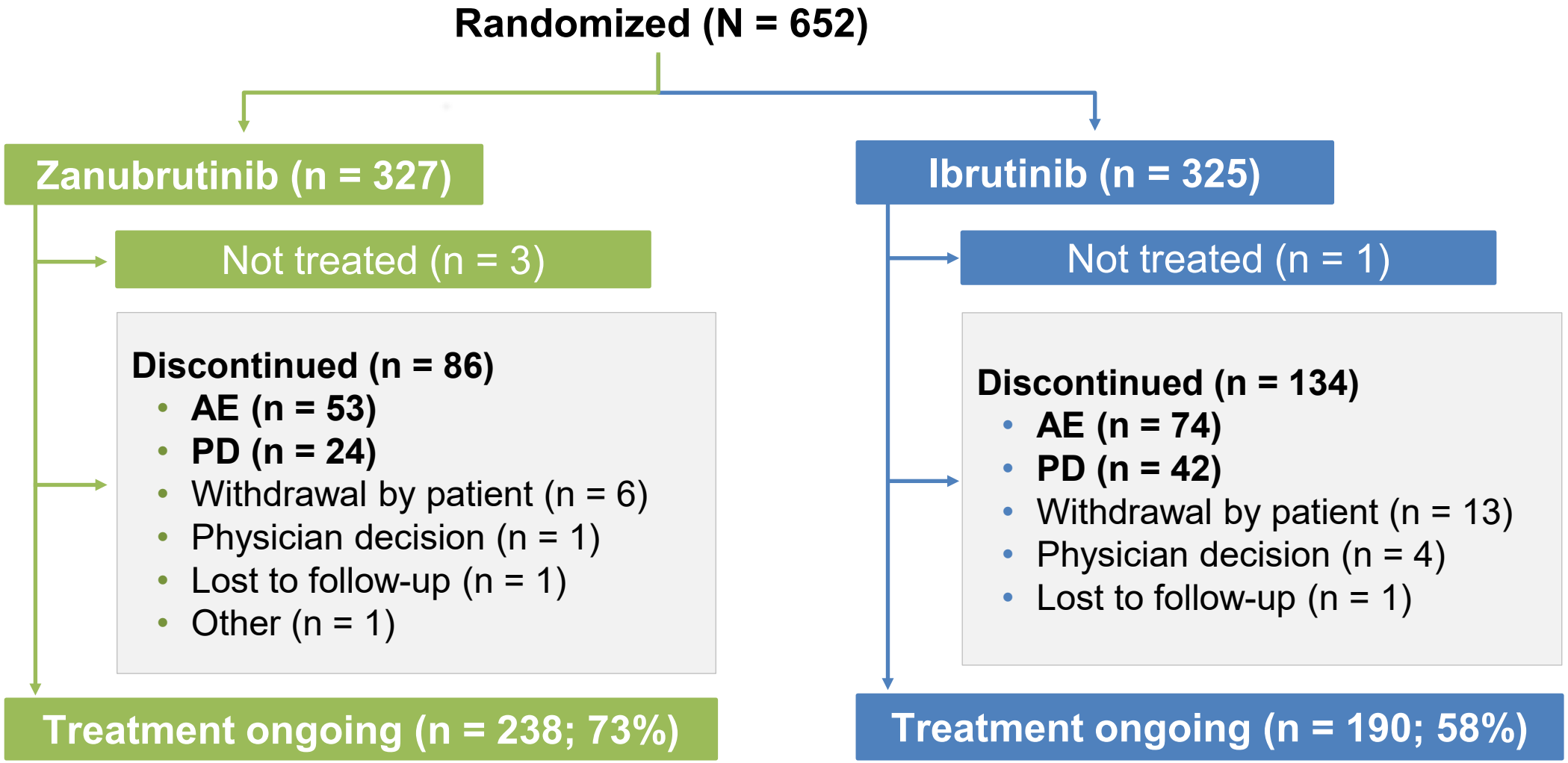
Key Exclusion Criteria

- Prior BTKi therapy
- Treatment with warfarin or other vitamin K antagonists



Brown *et al.* N Engl J Med. 2023; Brown *et al.* ASH 2023, A#202

ALPINE: Patient Disposition

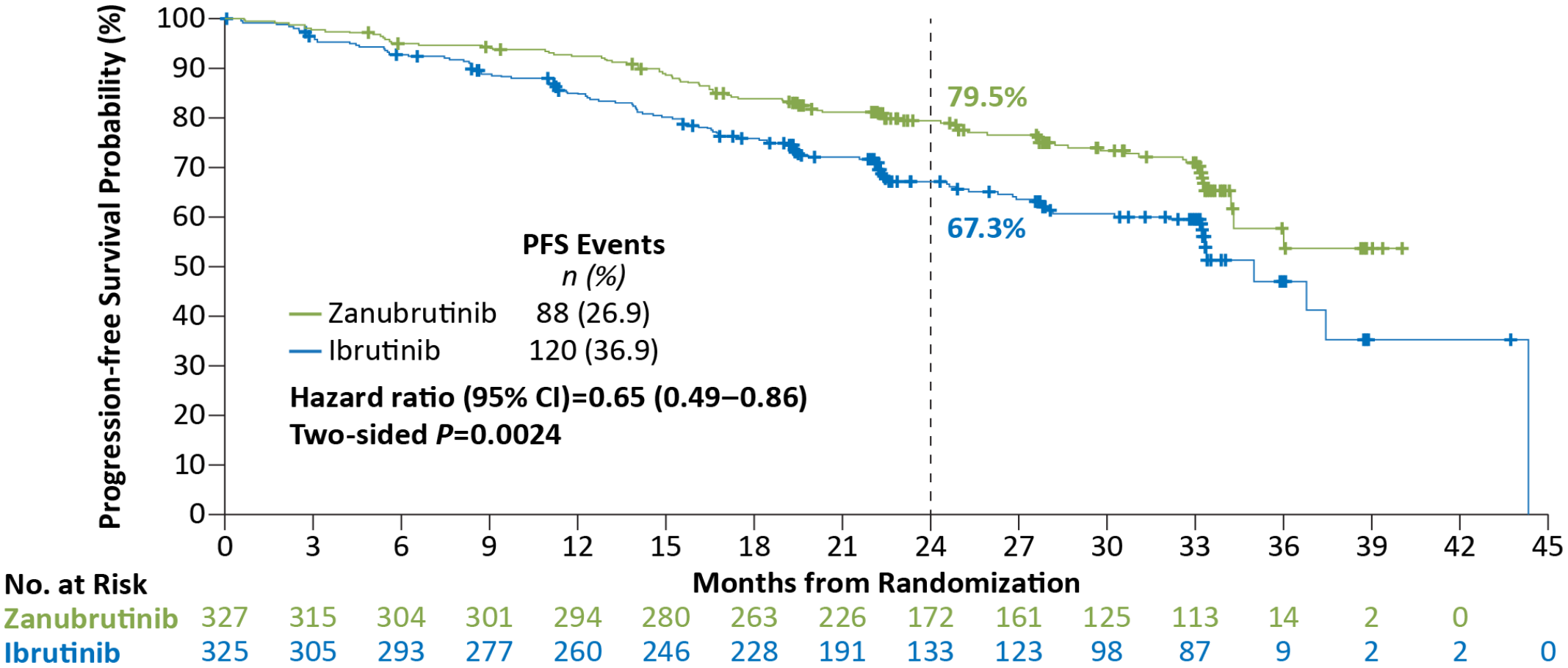


AE, adverse event; PD, progressive disease.

Brown *et al.* N Engl J Med. 2023; Brown *et al.* ASH 2023, A#202

ALPINE: Zanubrutinib PFS Is Superior to Ibrutinib

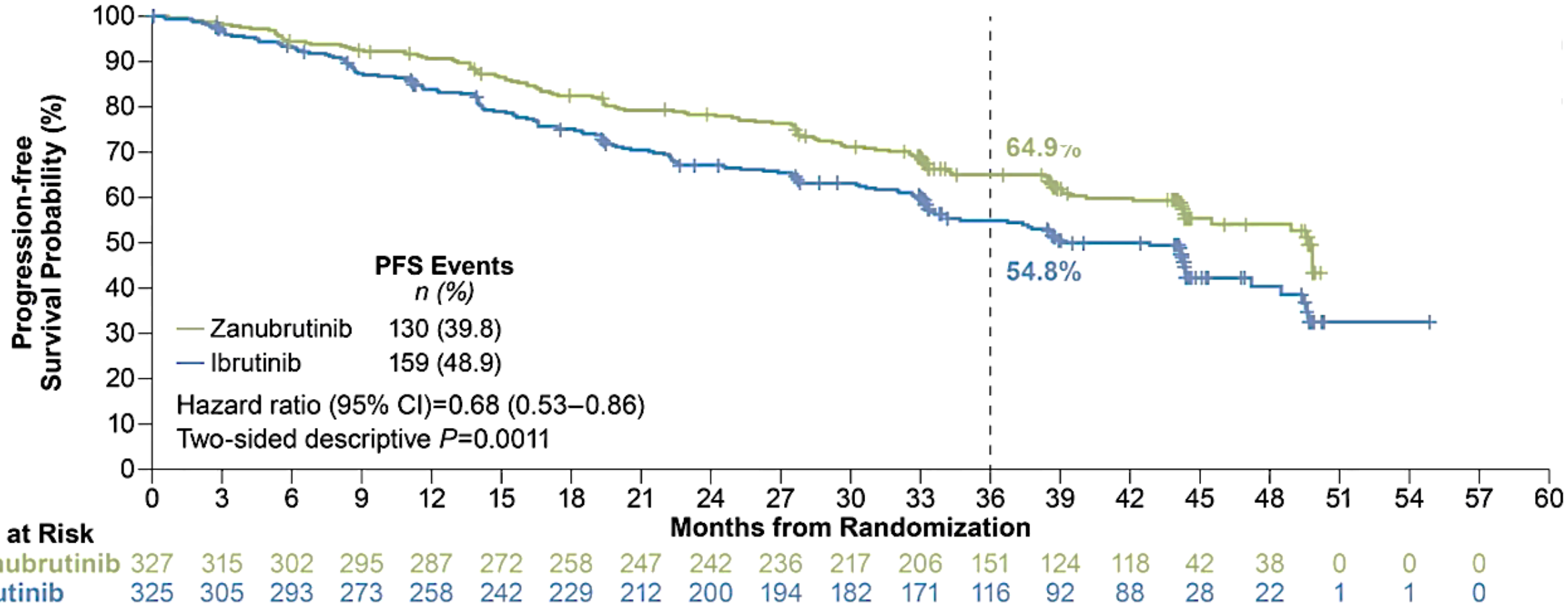
Median study follow-up: 29.6 months



Brown *et al.* N Engl J Med. 2023

ALPINE: Zanubrutinib Sustains PFS Benefit at 39 Months

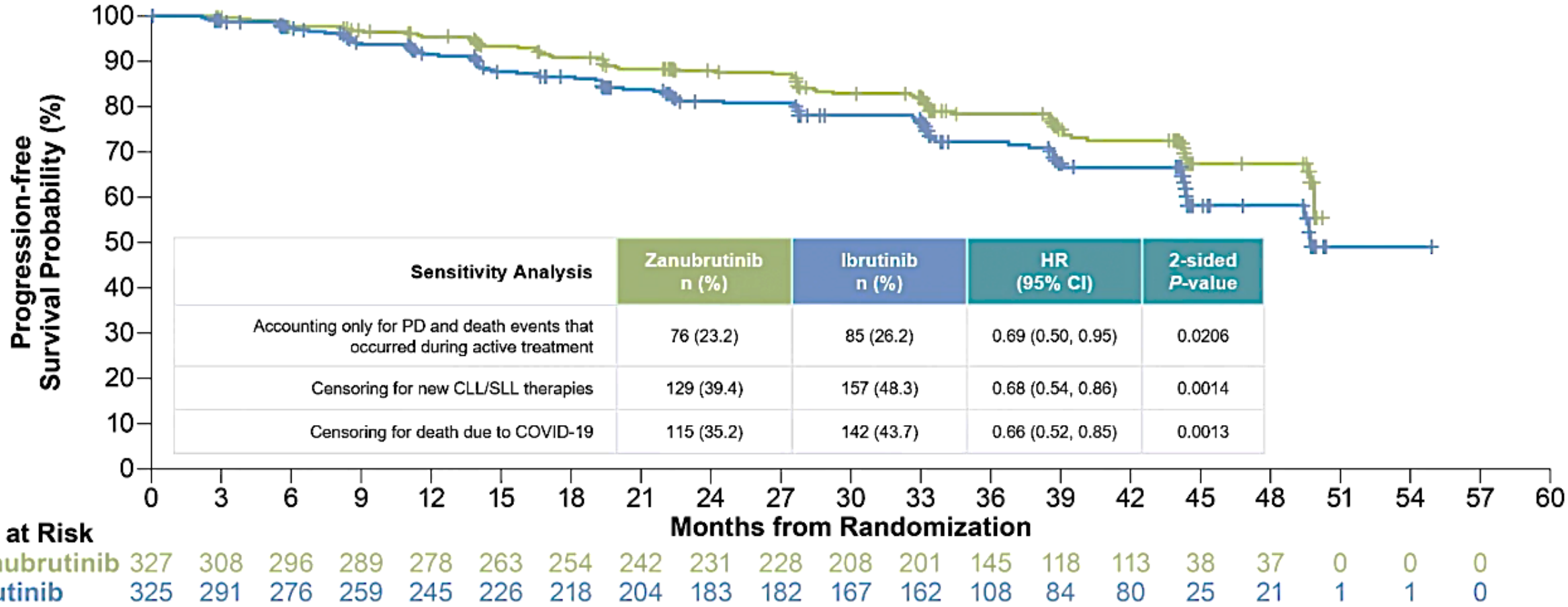
Median study follow-up: 39.0 months



Brown *et al.* ASH 2023, A#202

PFS Benefit Consistent Across Multiple Analyses

Median study follow-up: 39.0 months



Sensitivity Analysis	Zanubrutinib n (%)	Ibrutinib n (%)	HR (95% CI)	2-sided *P*-value
Accounting only for PD and death events that occurred during active treatment	76 (23.2)	85 (26.2)	0.69 (0.50, 0.95)	0.0206
Censoring for new CLL/SLL therapies	129 (39.4)	157 (48.3)	0.68 (0.54, 0.86)	0.0014
Censoring for death due to COVID-19	115 (35.2)	142 (43.7)	0.66 (0.52, 0.85)	0.0013

Brown *et al.* ASH 2023, A#202

ALPINE: Safety

	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[b]	**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[c]	**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)

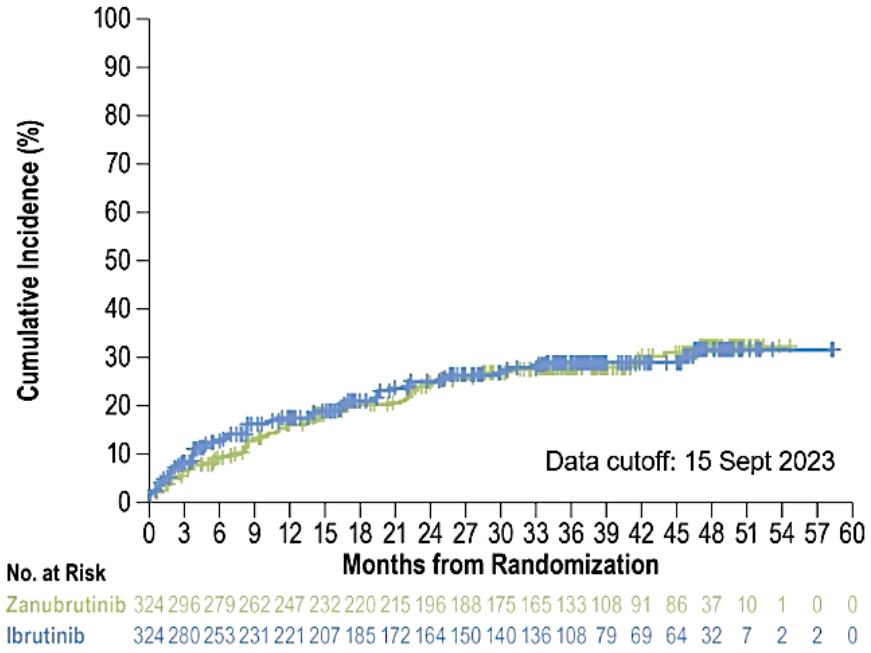
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

[c]The rate of any-grade atrial fibrillation/flutter was significantly lower with zanubrutinib vs ibrutinib (6.8% vs 16.4%, *P* <.0001).

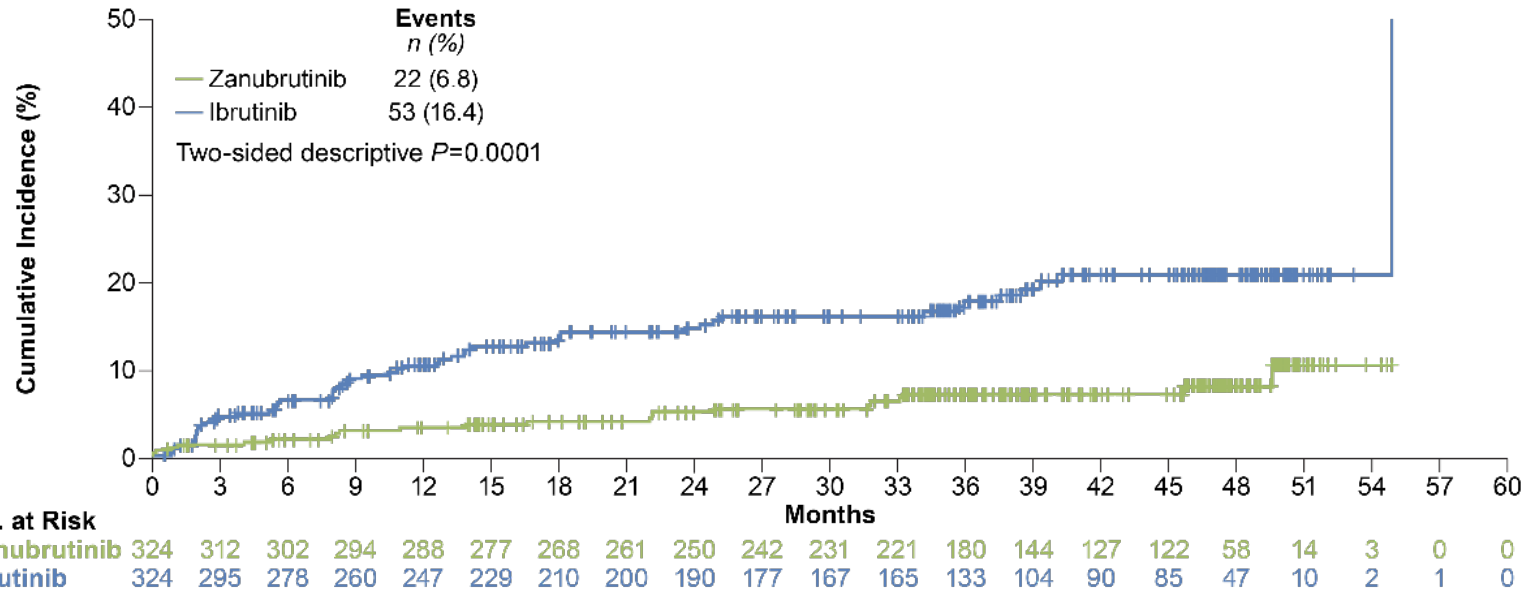
Brown *et al.* ASH 2023, A#202

A-Fib, But Not HTN, Is Lower With Zanubrutinib

HTN



A-Fib



Brown *et al.* ASH 2023, A#202

Favorable Cardiac Safety Profile With Zanubrutinib

Serious cardiac adverse events were lower with zanubrutinib vs ibrutinib

- Atrial fibrillation/flutter (3 vs 13)
- Ventricular fibrillation (0 vs 2)
- MI[a]/acute coronary syndrome (3 vs 3)

Fatal cardiac events[b]:

- **Zanubrutinib, n=0 (0%)**
- **Ibrutinib, n=6 (1.9%)**

	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)

[a]Including acute MI.

[b]Fatal cardiac event (n=6); 1 death (myocardial infarction with ibrutinib) was not listed due to discontinuation due to diarrhea 14 days prior to the fatal event.

Abbreviations: MI, myocardial infarction.

Brown *et al.* ASH 2023, A#202

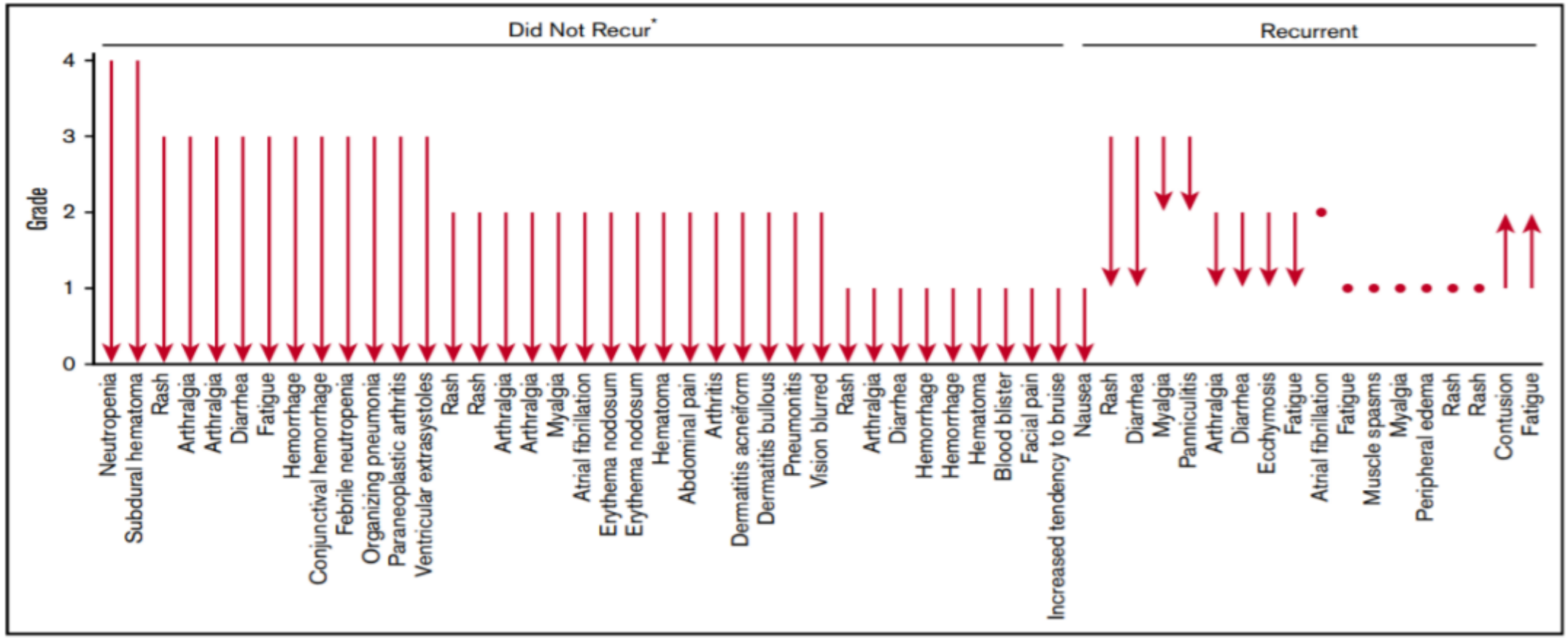
Switching between cBTKi for Intolerance

Ibrutinib
to
Acalabrutinib

Ibrutinib
to
Zanubrutinib

Acalabrutinib
to
Zanubrutinib

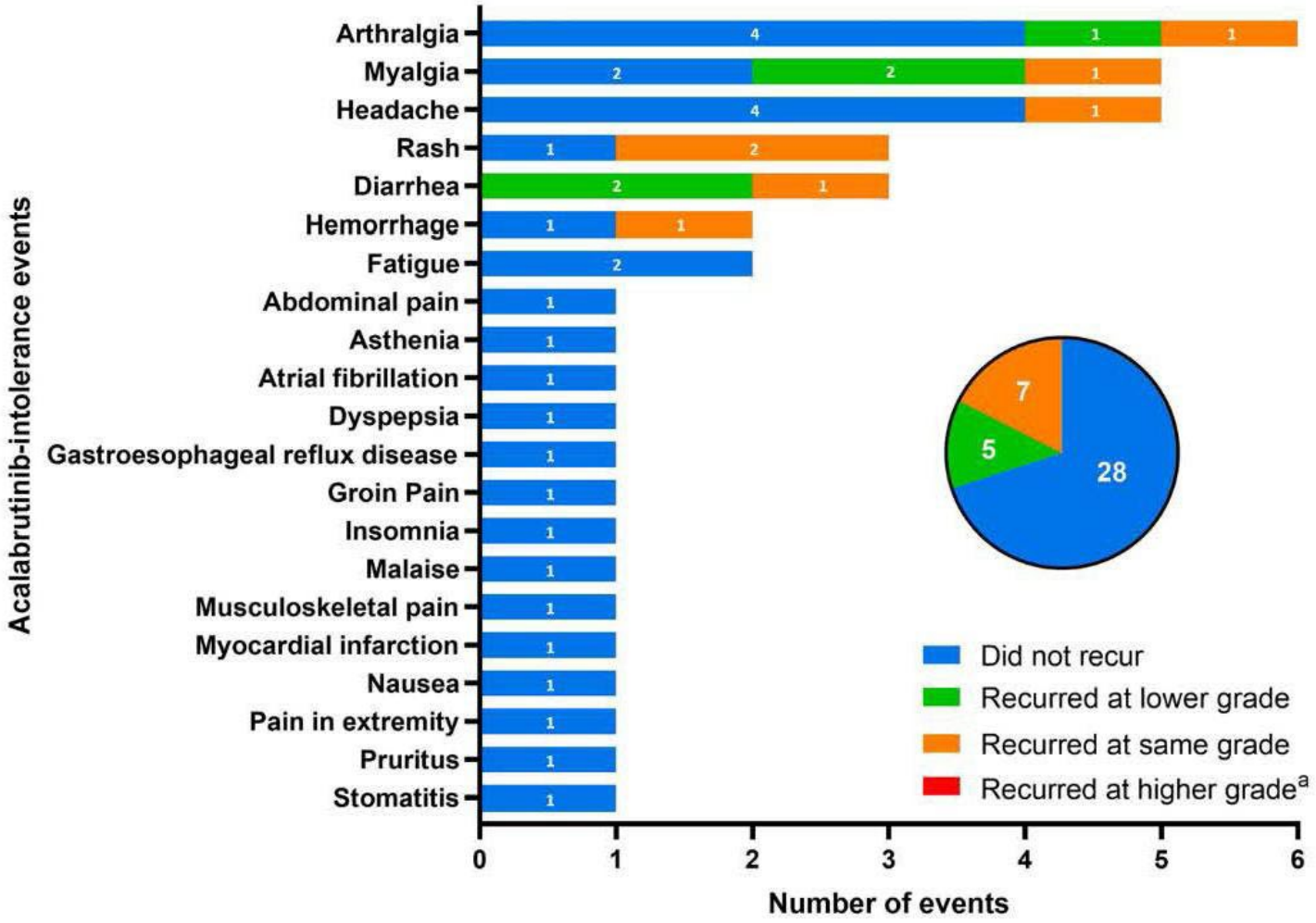
Acalabrutinib in Ibrutinib-Intolerant Patients



Of 61 ibrutinib-related AEs associated with intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib.

Awan *et al.* Blood Adv. 2019

Zanubrutinib in Acalabrutinib-Intolerant Patients



[a]No event recurred at higher grade.

40 acalabrutinib-intolerance events were reported by 27 patients

😀 70% of acalabrutinib-intolerance events did not recur at any grade with zanubrutinib

Of the 12 events that did recur, none recurred at a higher severity

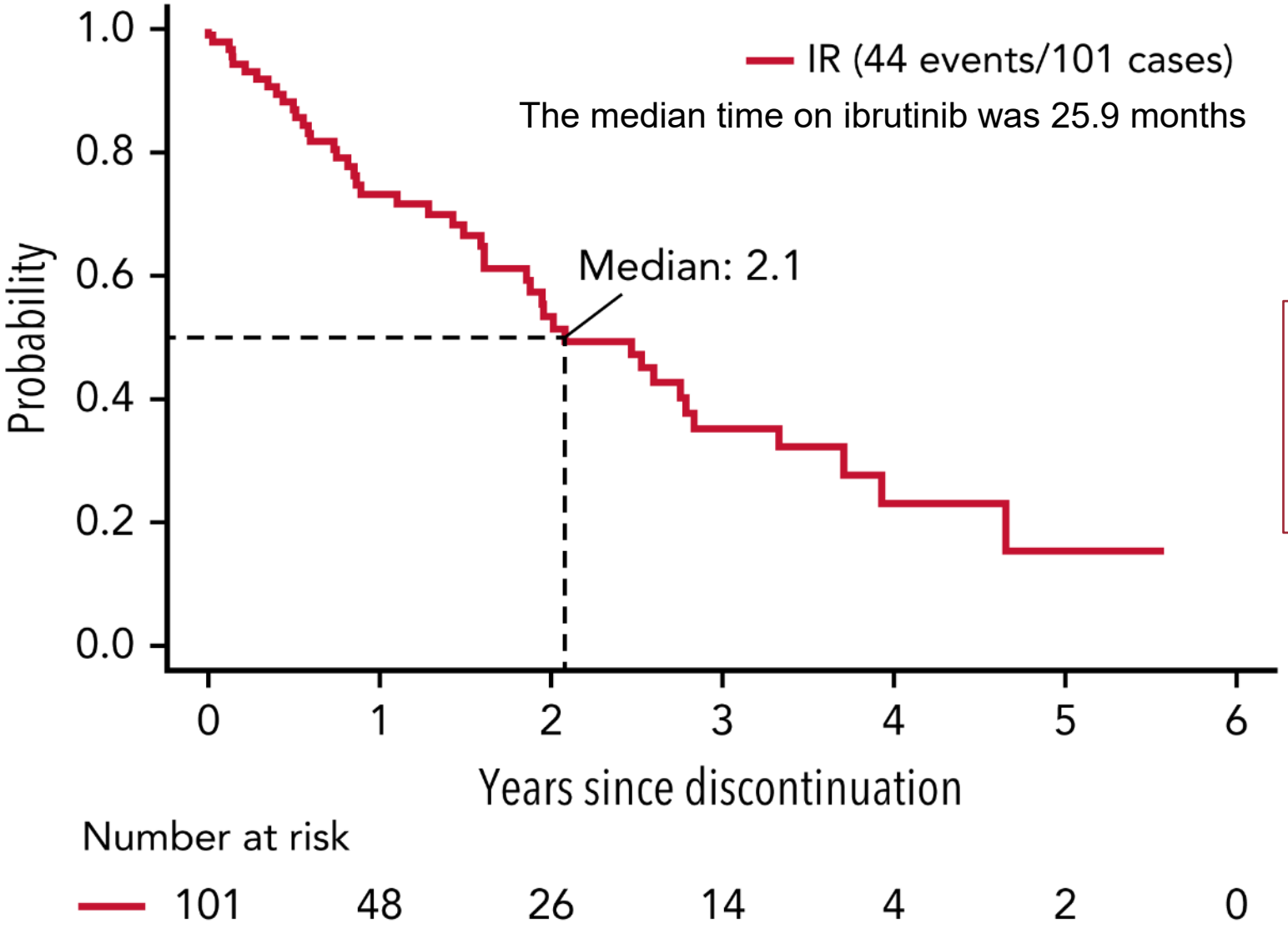
😐 7 recurred at the same grade

🙂 5 recurred at a lower grade

No event recurred at higher grade

Shadman *et al*. Lancet Haematol. 2023

PFS Following Discontinuation of Ibrutinib



Consider “watch and wait” in patients **with intolerance** despite dose reduction or switching within the same drug class.

Shanafelt *et al.* Blood 2022

BTK Inhibitors

Covalent

Ibrutinib, Acalabrutinib, Zanubrutinib, Orelabrutinib*

Non-Covalent

Pirtobrutinib, Nemtabrutinib*, Vecabrutinib*

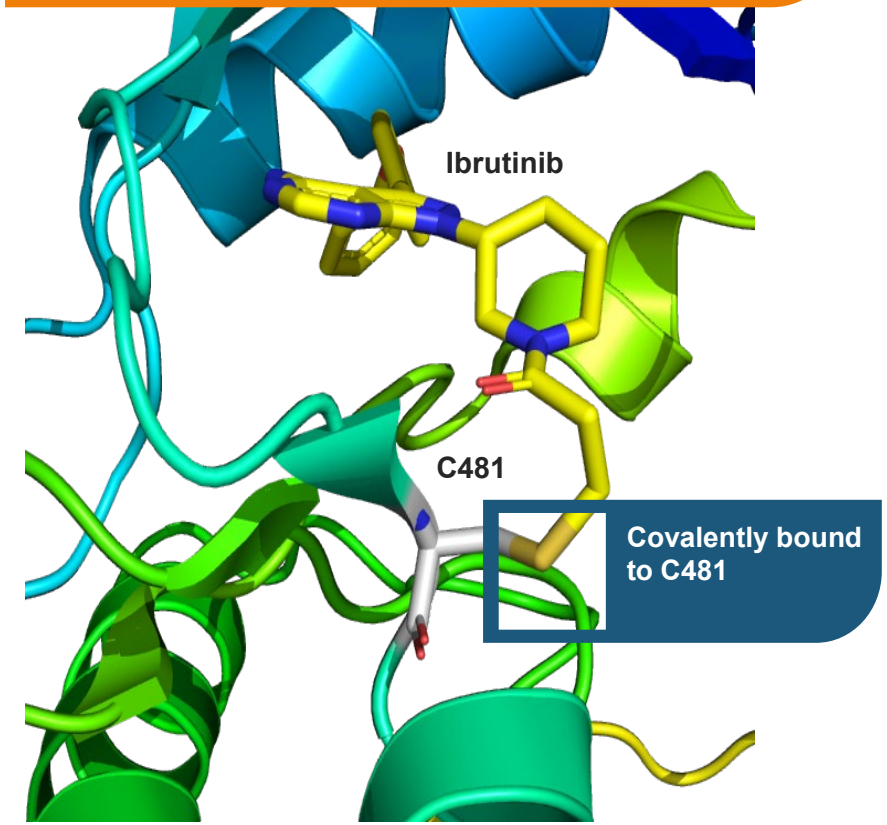
Degraders

BGB-16673*, NX-2127*

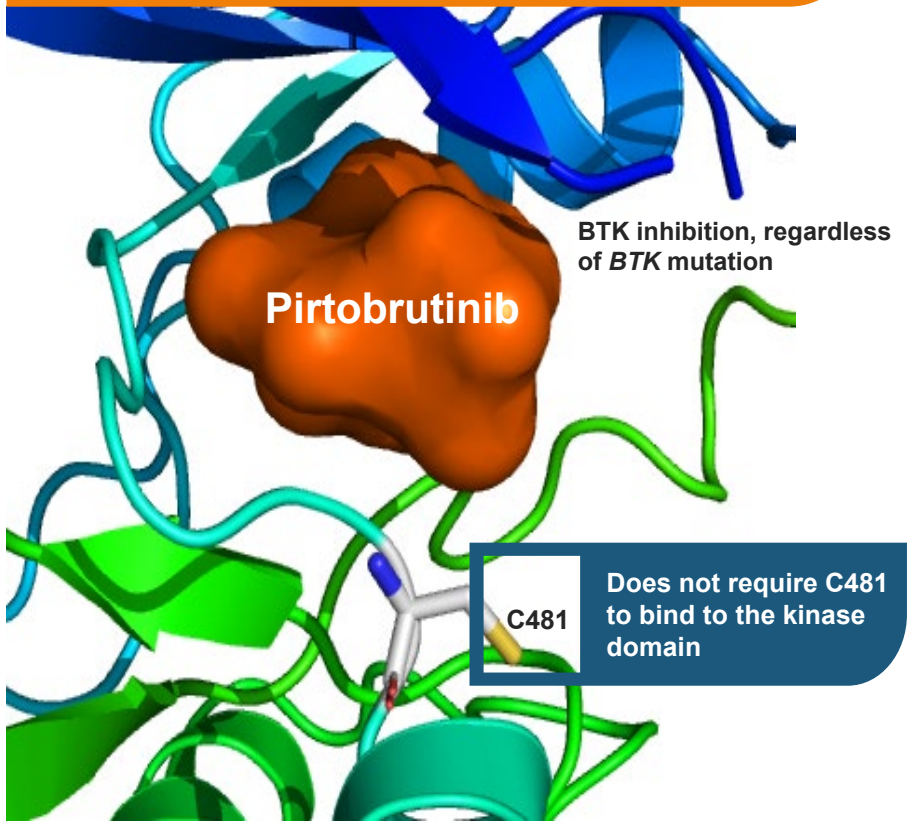
* Investigational agents, no FDA label

BTKi Resistance Mutations and Non-covalent BTKi

Covalent BTKis (ibrutinib, acalabrutinib, zanubrutinib) depend on C481 for binding

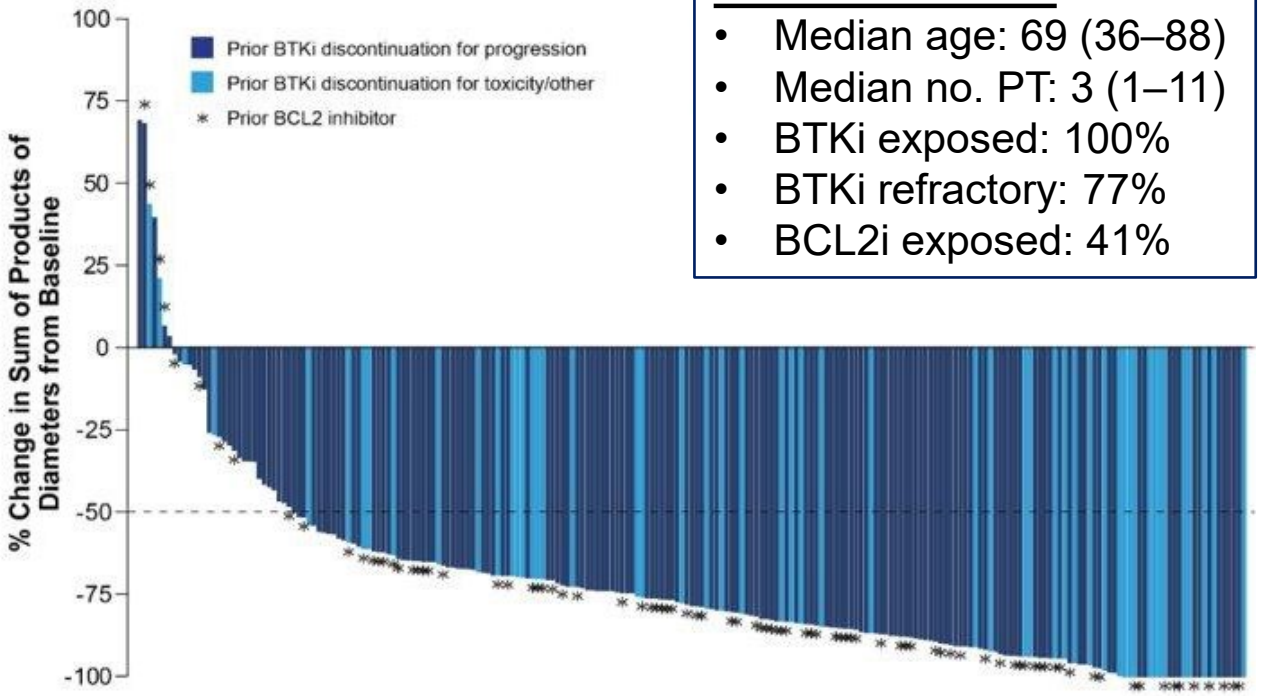


Pirtobrutinib is a noncovalent BTKi that is potent against both WT and C481-mutant *BTK*



BRUIN: A Phase I–II Trial in R/R B-Cell Cancers

RP2D: 200 mg orally once per day

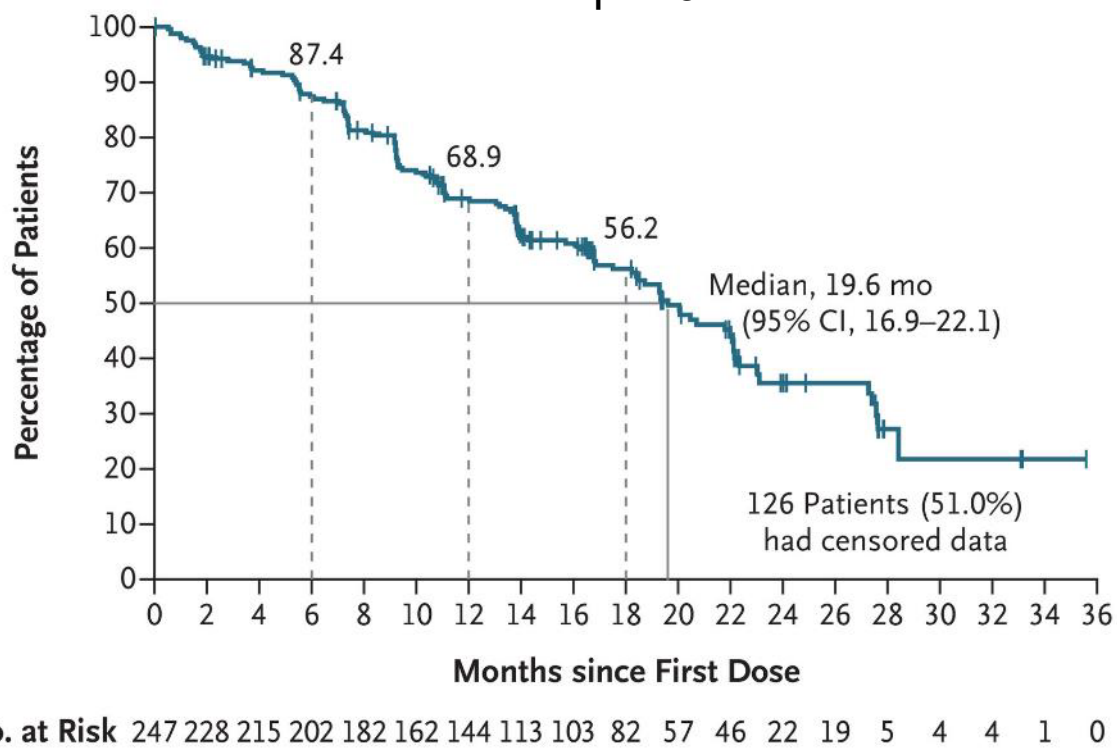


247 R/R CLL/SLL

- Median age: 69 (36–88)
- Median no. PT: 3 (1–11)
- BTKi exposed: 100%
- BTKi refractory: 77%
- BCL2i exposed: 41%

ORR: 73% (CR, 1.6%)
PR-L or better: 82%

Median follow-up: 19.4 months



Mato *et al.* N Engl J Med. 2023

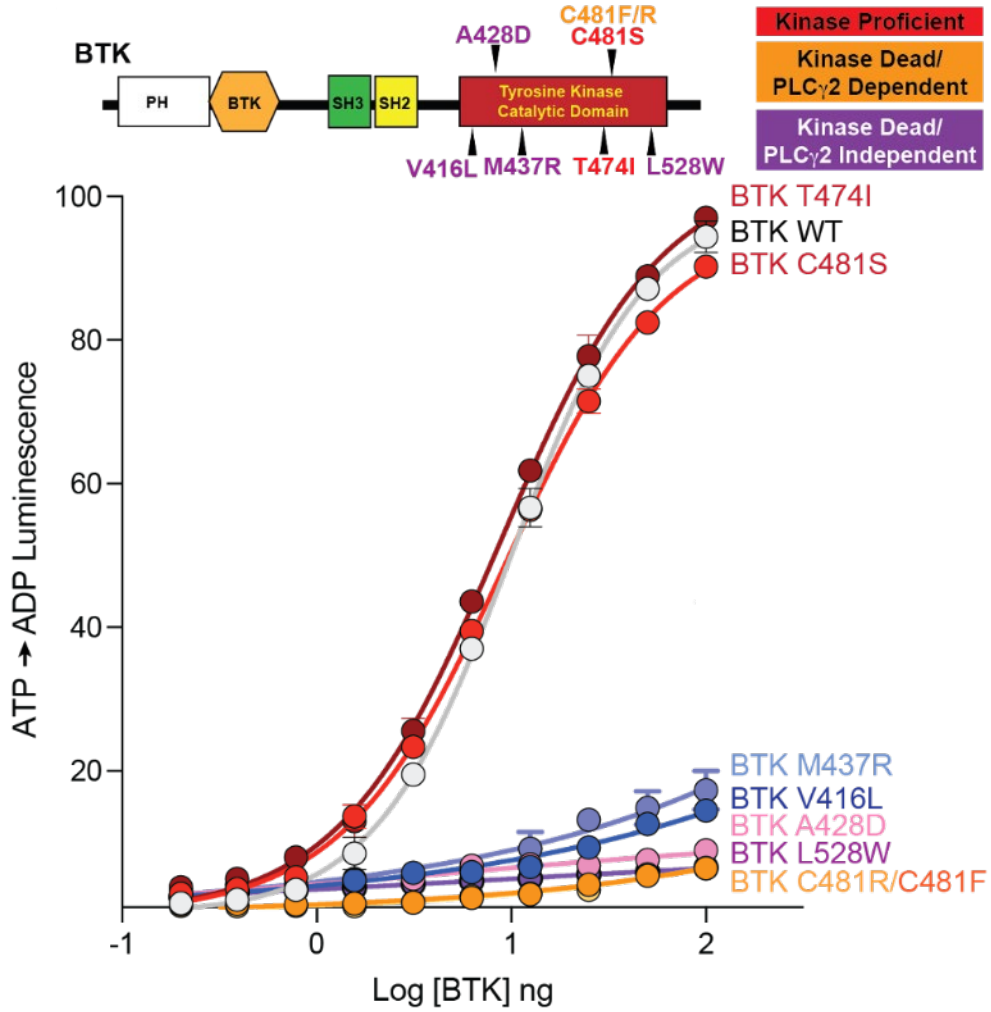
BRUIN: Safety

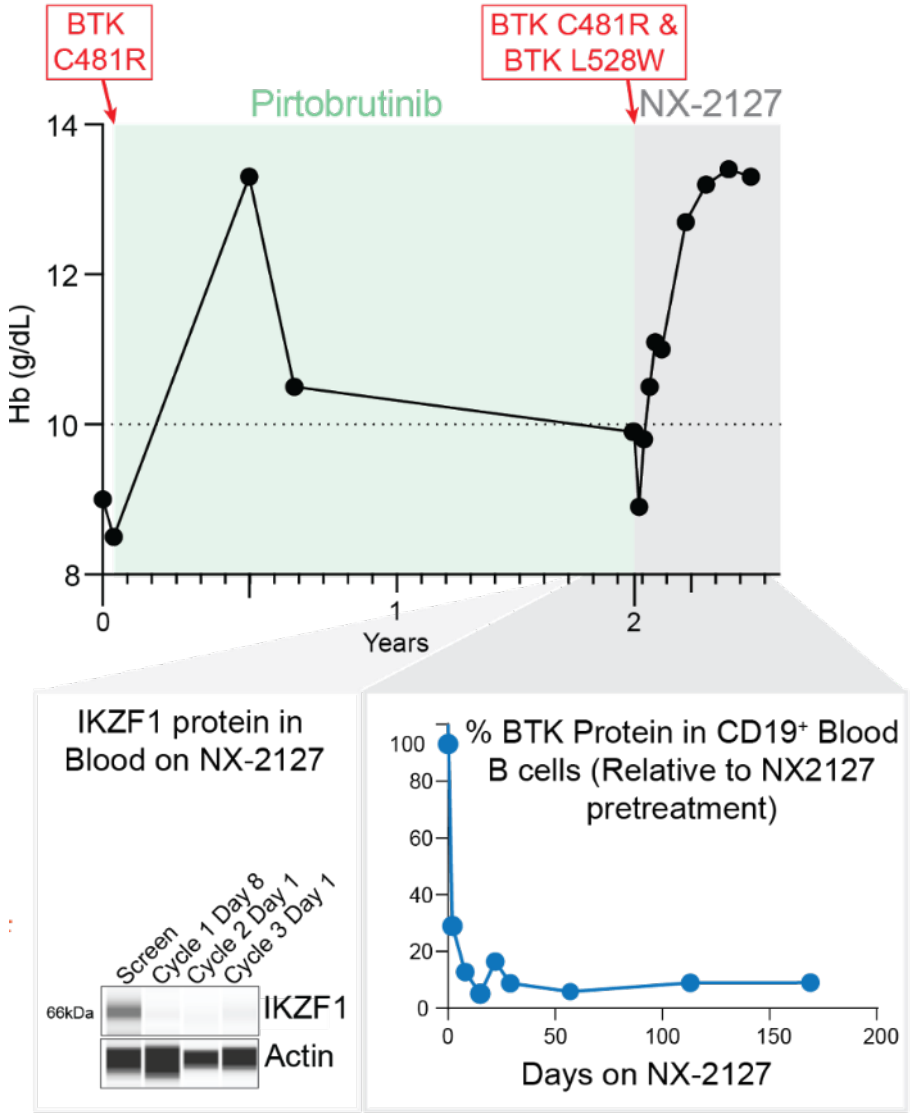
Event	Adverse Events (N=317)		Treatment-Related Adverse Events (N=317)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse events of special interest:				
Atrial fibrillation or flutter	12 (3.8)	4 (1.3)	4 (1.3)	1 (0.3)
Bleeding	135 (42.6)	7 (2.2)	75 (23.7)	3 (0.9)
Bruising	96 (30.3)	0	62 (19.6)	0
Hemorrhage	67 (21.1)	7 (2.2)	22 (6.9)	3 (0.9)
Hypertension	45 (14.2)	11 (3.5)	12 (3.8)	1 (0.3)
Infections	225 (71.0)	89 (28.1)	39 (12.3)	12 (3.8)
Neutropenia	103 (32.5)	85 (26.8)	62 (19.6)	47 (14.8)

Mato *et al.* N Engl J Med. 2023

Not All *BTK* Mutations Are Equal

Concept of **Kinase-Dead** *BTK*





Montoya *et al.* ASH 2022, A#750

A First-in-Human Trial of NX-2127, a BTK Degrader, in R/R CLL and B-Cell Malignancies

R/R CLL (N = 17)
≥2 prior line of therapy (median 6), 100% post-BTKi, 77% post-Ven

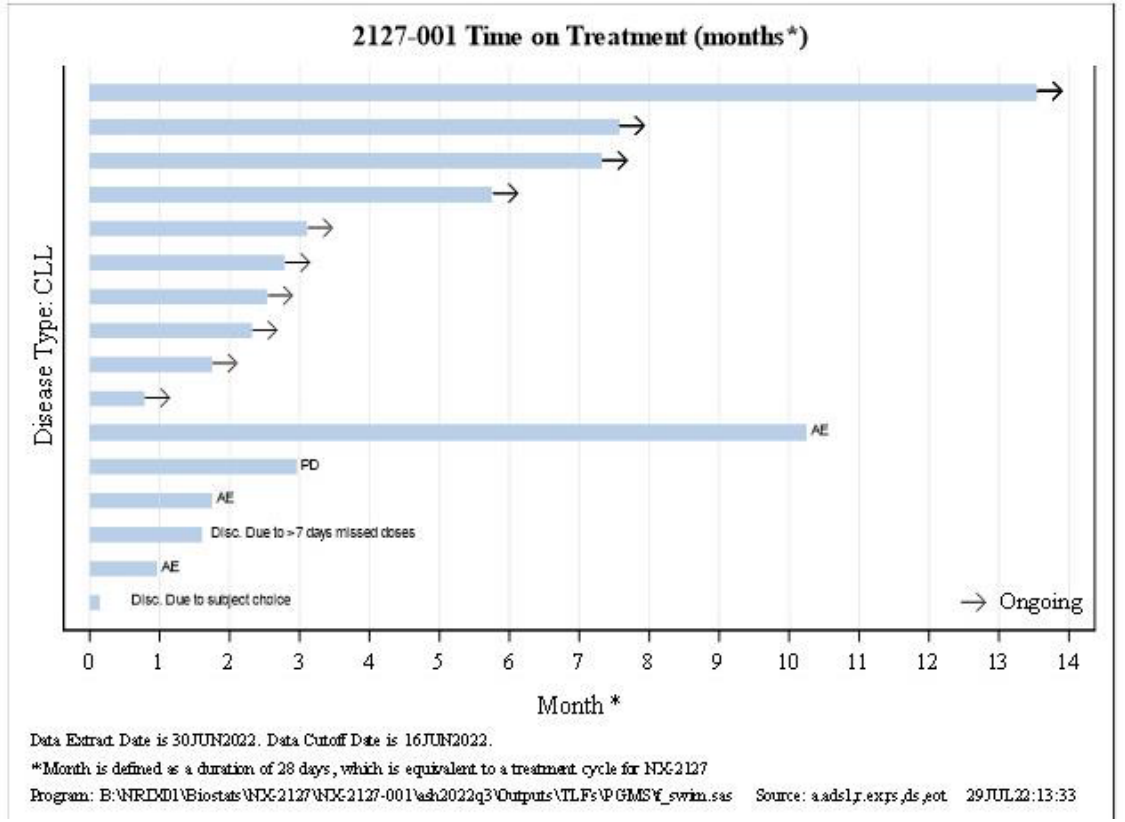
NX-2127
Dose escalation: 100, 200, 300 mg orally daily

Tolerability, Safety, Preliminary Efficacy

Table 1. Summary of treatment-emergent adverse events (TEAEs) occurring in >15% of all patients (including patients with CLL and NHL)

Preferred Term	All Grades (N=26)	Grade ≥ 3 (N=26)	Grade ≥ 3 Related (N=26)
Any AE	25 (96%)	15 (58%)	12 (46%)
Fatigue	16 (62%)	0 (0%)	0 (0%)
Neutrophil Count Decrease	10 (39%)	9 (35%)	9 (35%)
Anemia	7 (27%)	4 (15%)	2 (8%)
Contusion	7 (27%)	0 (0%)	0 (0%)
Hypertension	7 (27%)	1 (4%)	1 (4%)
Dyspnoea	5 (19%)	1 (4%)	0 (0%)
Pruritis	5 (19%)	0 (0%)	0 (0%)
Rash maculo-papular	5 (19%)	0 (0%)	0 (0%)
Blood creatinine increased	4 (15%)	0 (0%)	0 (0%)
COVID-19	4 (15%)	1 (4%)	0 (0%)
Diarrhea	4 (15%)	0 (0%)	0 (0%)
Petechiae	4 (15%)	0 (0%)	0 (0%)
Platelet count decreased	4 (15%)	1 (4%)	0 (0%)

Figure 1. CLL patient disposition



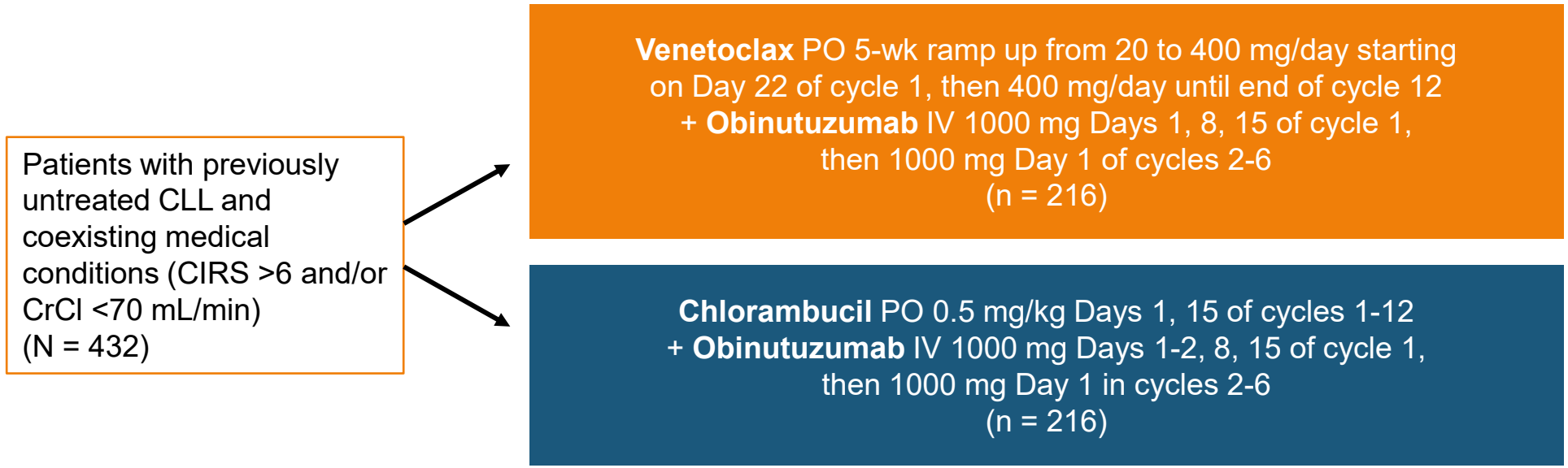
Mato *et al.* ASH 2022, A#965

Chemo-Free Options: BTKi vs BCL2i-Based Therapy

	BCL2i + Anti-CD20	BTKi
Pros	• Fixed duration • Low concerns for bleeding or cardiotoxicity • Performs well in low-risk CLL • Option to re-treat	• Oral, no need for infusion • Easy/convenient to start • Performs well in all risk groups • Very low TLS risk
Cons	• Need for anti-CD20 infusion • Complicated first 2 months • TLS risk • Shortened PFS with high-risk CLL	• Lifelong commitment • Bleeding and cardiotoxicity concerns • No option to re-treat at progression

CLL14: First-Line Obinutuzumab + Venetoclax or Chlorambucil in CLL With Coexisting Medical Conditions

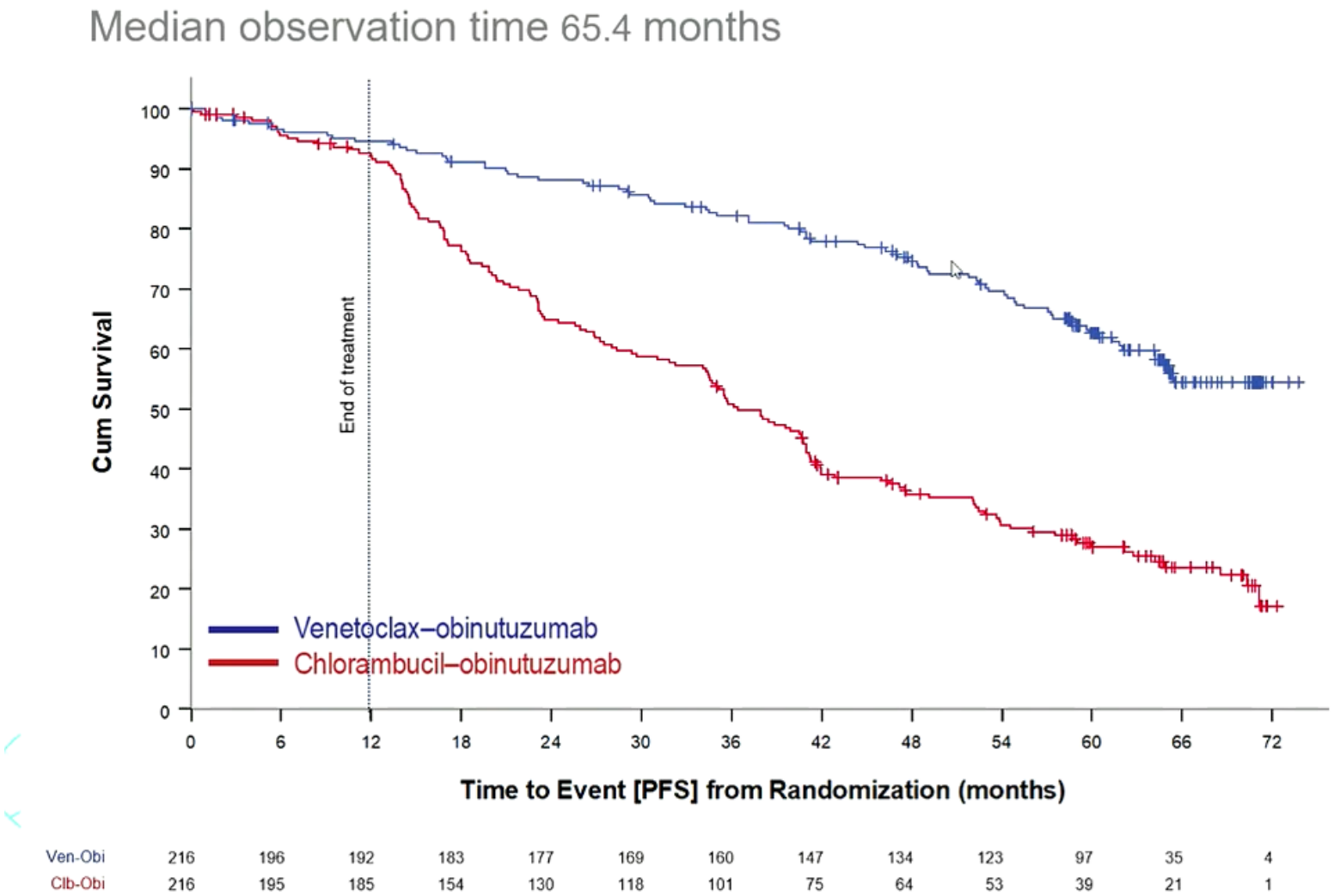
- Open-label, multicenter, randomized phase III trial



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

Fischer et al. *N Engl J Med.* 2019; Al-Sawaf et al. *Lancet Oncol.* 2020; Al-Sawaf et al. EHA 2021; Burger et al. *N Engl J Med.* 2020.

CLL14: PFS



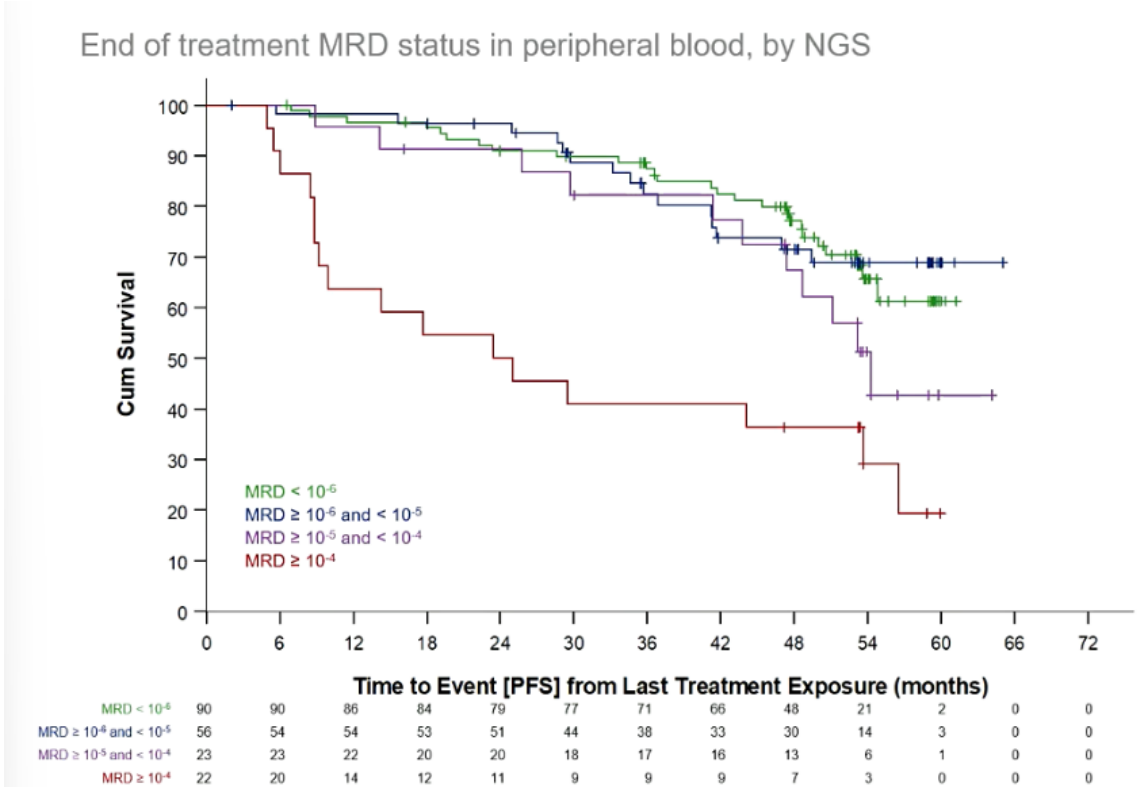
Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

5-year PFS rate
Ven-Obi: 62.6%
Clb-Obi: 27.0%

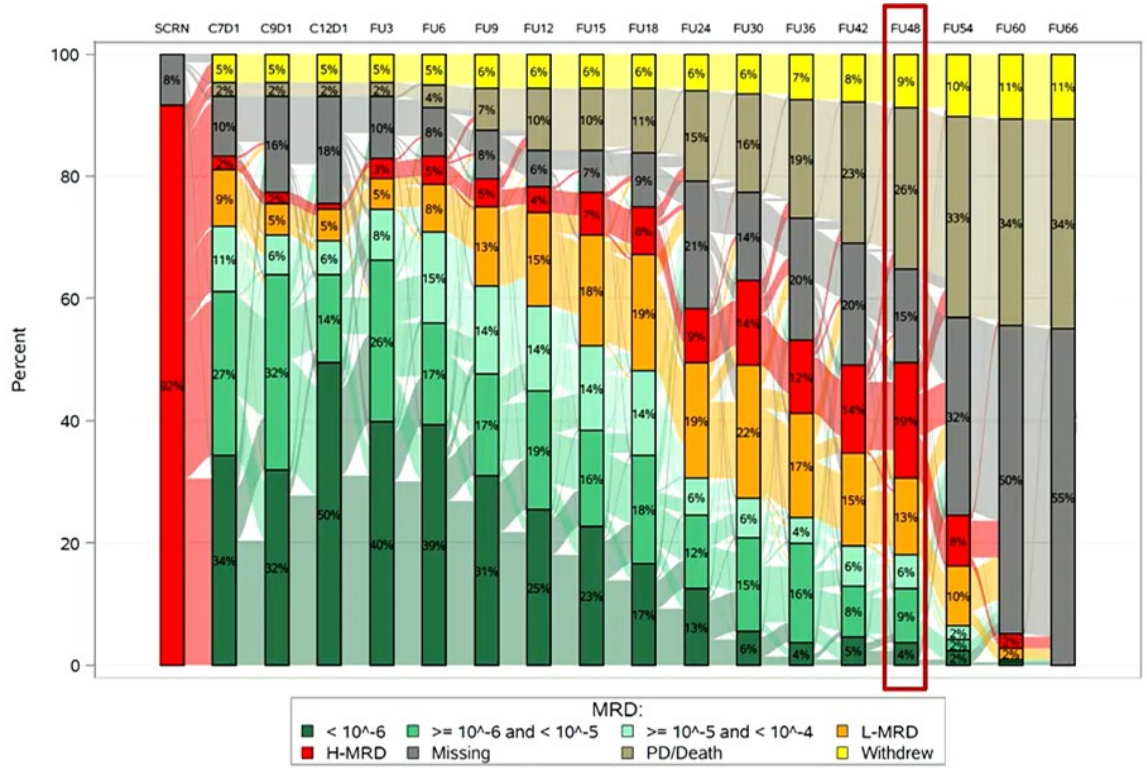
HR 0.35, 95% CI [0.26-0.46]
P<0.0001

Fischer et al. *N Engl J Med.* 2019; Al-Sawaf et al. *Lancet Oncol.* 2020; Al-Sawaf et al. EHA 2021; Burger et al. *N Engl J Med.* 2020.

CLL14: EOT MRD, and MRD Dynamics



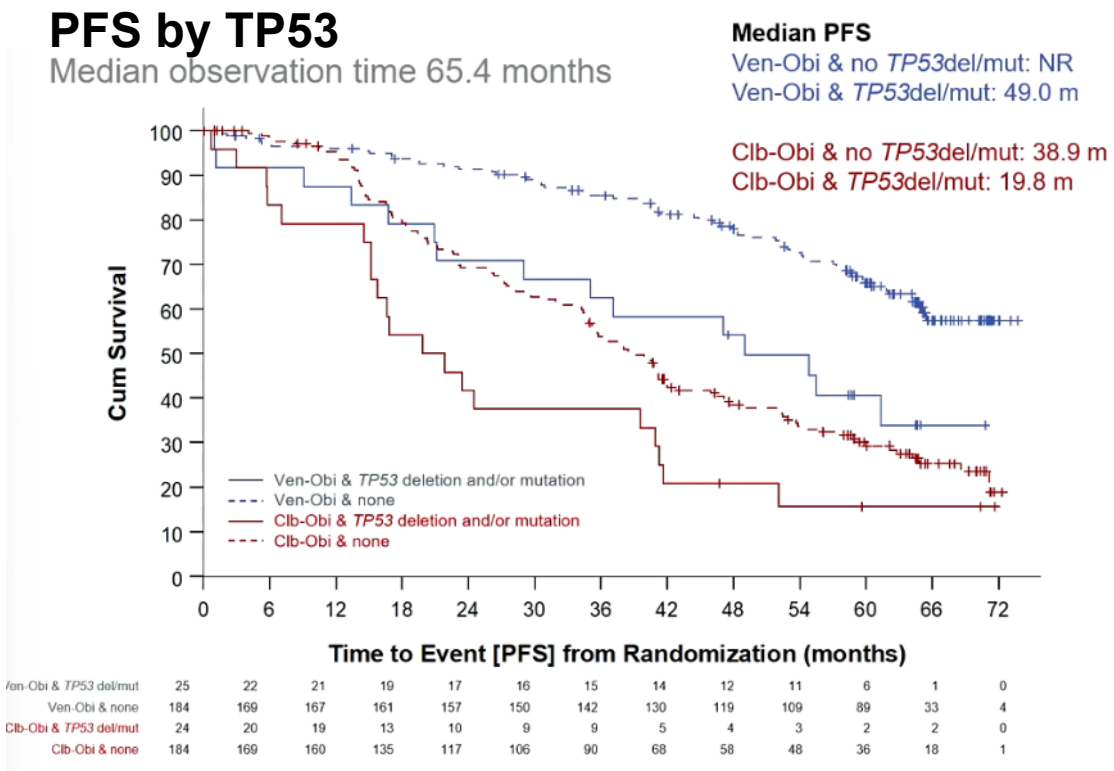
Depths of remission beyond 10^{-4} correlates with long-term PFS

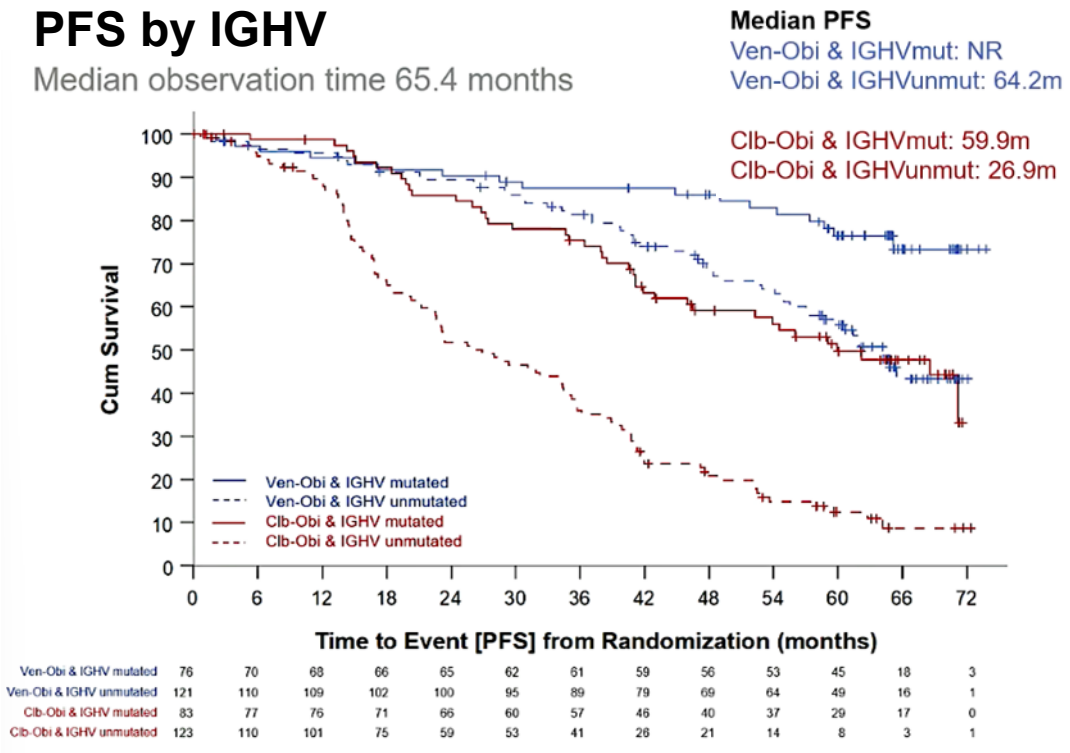


39 (18.1%) of patients had sustained MRD $<10^{-4}$ after 4 years

Fischer et al. *N Engl J Med.* 2019; Al-Sawaf et al. *Lancet Oncol.* 2020; Al-Sawaf et al. EHA 2021; Burger et al. *N Engl J Med.* 2020.

CLL14: PFS by *TP53* and *IGHV* Status

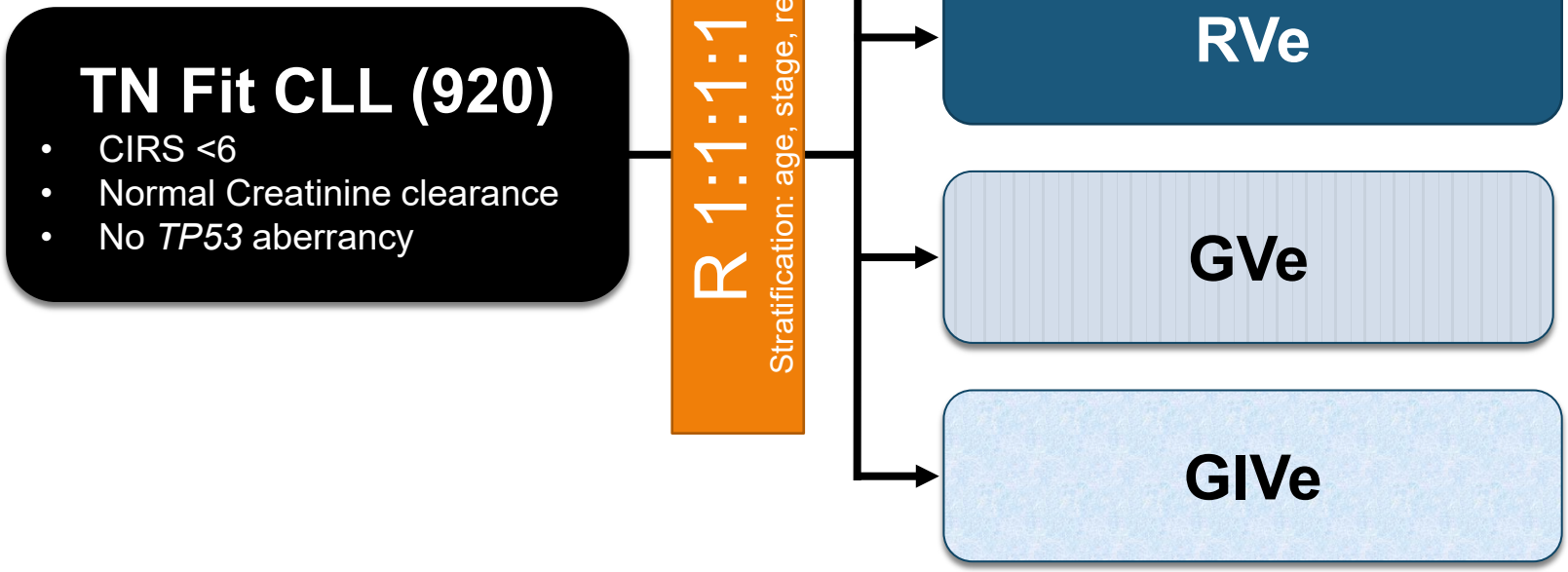




Fischer et al. *N Engl J Med.* 2019; Al-Sawaf et al. *Lancet Oncol.* 2020; Al-Sawaf et al. EHA 2021; Burger et al. *N Engl J Med.* 2020.

CLL13 Trial: A Randomized Phase III Trial

First-Line Venetoclax Combinations in TN CLL



Primary endpoints

- MRD4 at 15 months
- PFS

Secondary endpoints

- ORR/CR
- OS
- TTNT
- QoL

Rituximab 375 (500) mg/m² iv c 1-6 (before chemo)
Fludarabine 25 mg/m² iv c 1-6 d 1-3
Cyclophosphamide 250 mg/m² iv c 1-6 d 1-3
(or) Bendamustine 90 mg/m² c 1-6 d1,2

Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c2-6 d1)
Ibrutinib d 1-MRD-/PD 420 mg po daily for up to 36 month *or* until MRD negativity is achieved,
Venetoclax c1 d 22- c12 d28 400 mg po daily (ramp-up)

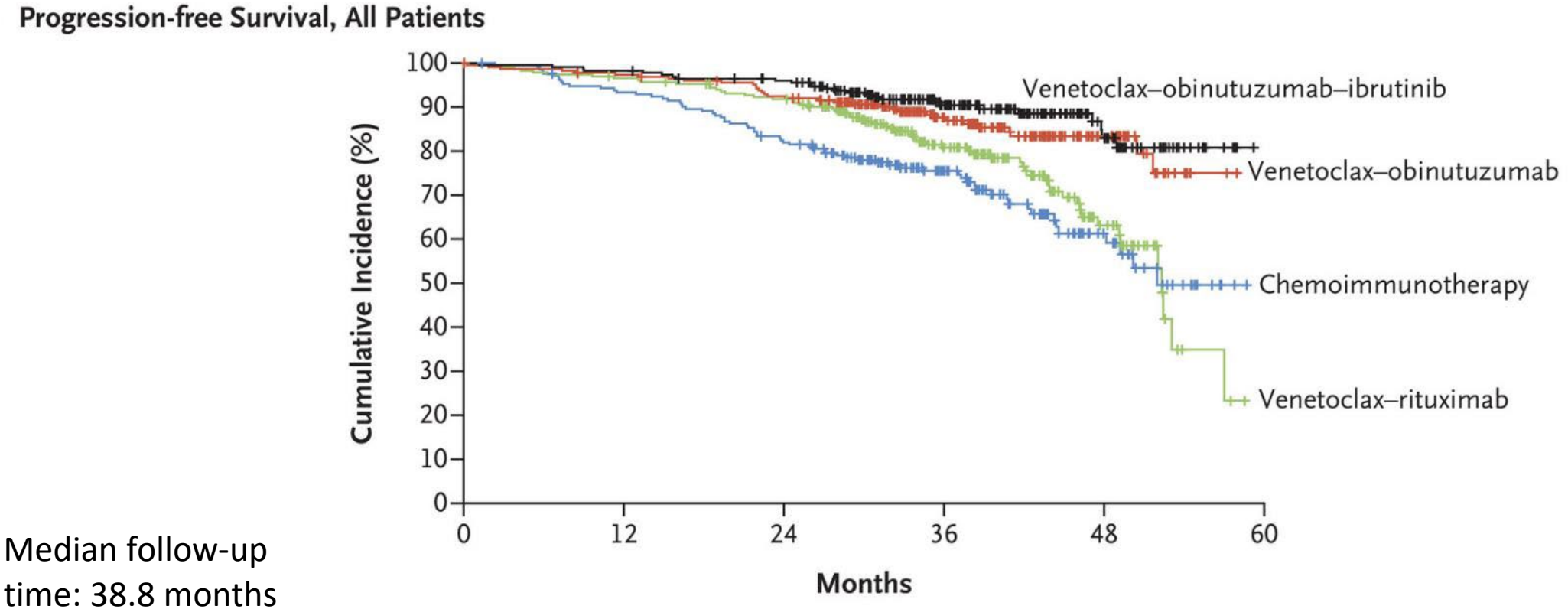
Rituximab 375 (500) mg/m² iv (c1 – 6, d1)
Venetoclax c1 d22 – c12 d28 400 mg po daily (ramp-up)

Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c2-6 d1)
Venetoclax c1 d22 – c12 d28 400 mg po daily (ramp-up)

Eichhorst et al. *N Engl J Med.* 2023.

CLL13 Trial: A Randomized Phase III Trial

First-Line Venetoclax Combinations in TN CLL



Median follow-up time: 38.8 months

No. at Risk

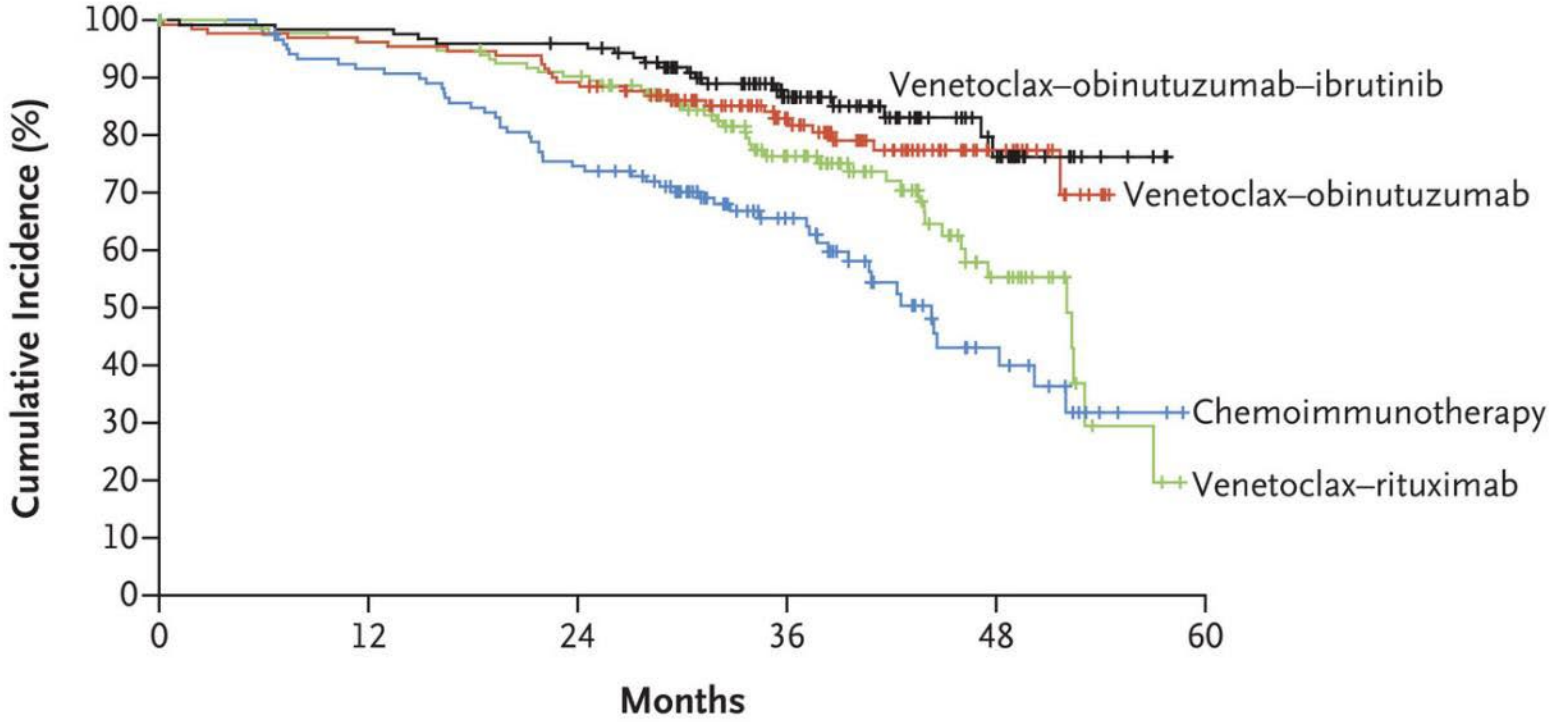
Chemoimmunotherapy	229	197	172	98	28	0
Venetoclax–rituximab	237	226	212	119	32	0
Venetoclax–obinutuzumab	229	221	208	125	42	0
Venetoclax–obinutuzumab–ibrutinib	231	227	217	132	44	0

Eichhorst et al. *N Engl J Med.* 2023.

CLL13 Trial: A Randomized Phase III Trial

First-Line Venetoclax Combinations in TN CLL

Progression-free Survival, Patients with Unmutated *IGHV*



Median follow-up time: 38.8 months

No. at Risk

Chemoimmunotherapy	131	108	88	48	14	0
Venetoclax–rituximab	134	128	119	67	20	0
Venetoclax–obinutuzumab	130	125	116	71	21	0
Venetoclax–obinutuzumab–ibrutinib	123	121	117	70	22	0

Eichhorst et al. *N Engl J Med.* 2023.

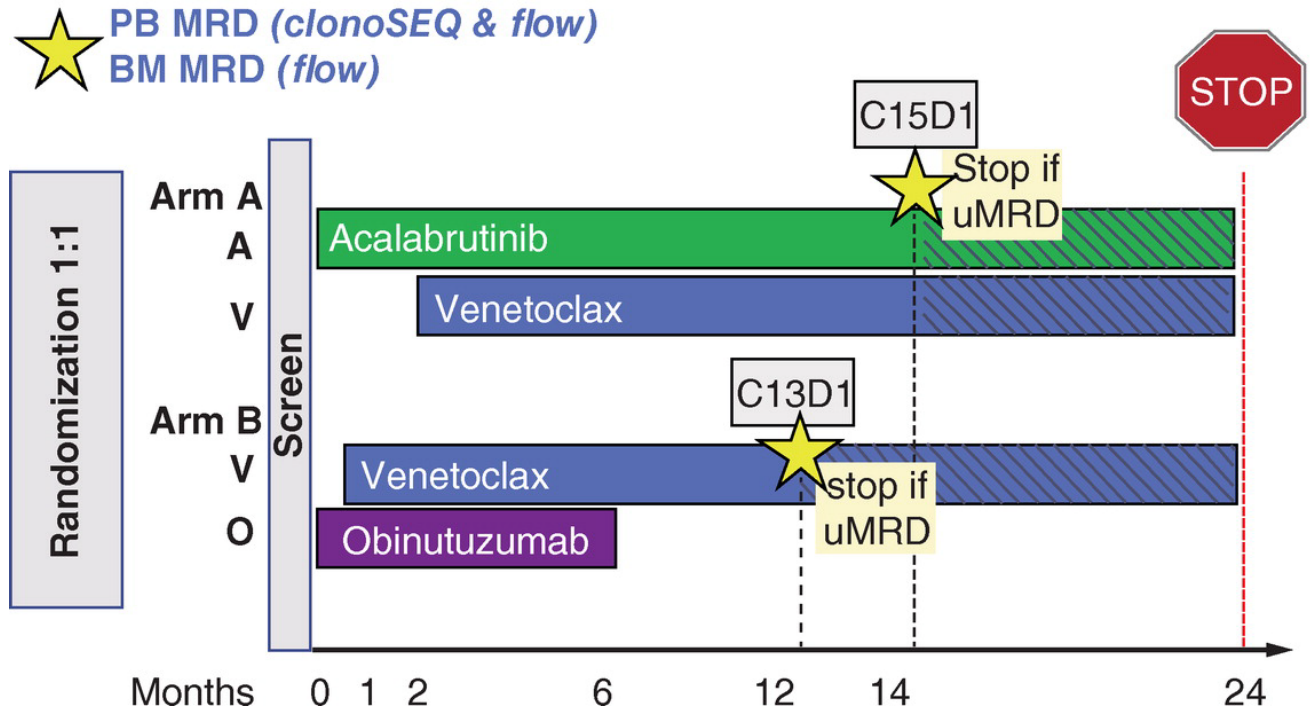
MAJIC Trial: A Randomized Phase III Trial

Acalabrutinib + Venetoclax Vs. Venetoclax + Obinutuzumab In TN CLL/SLL

MAJIC schema

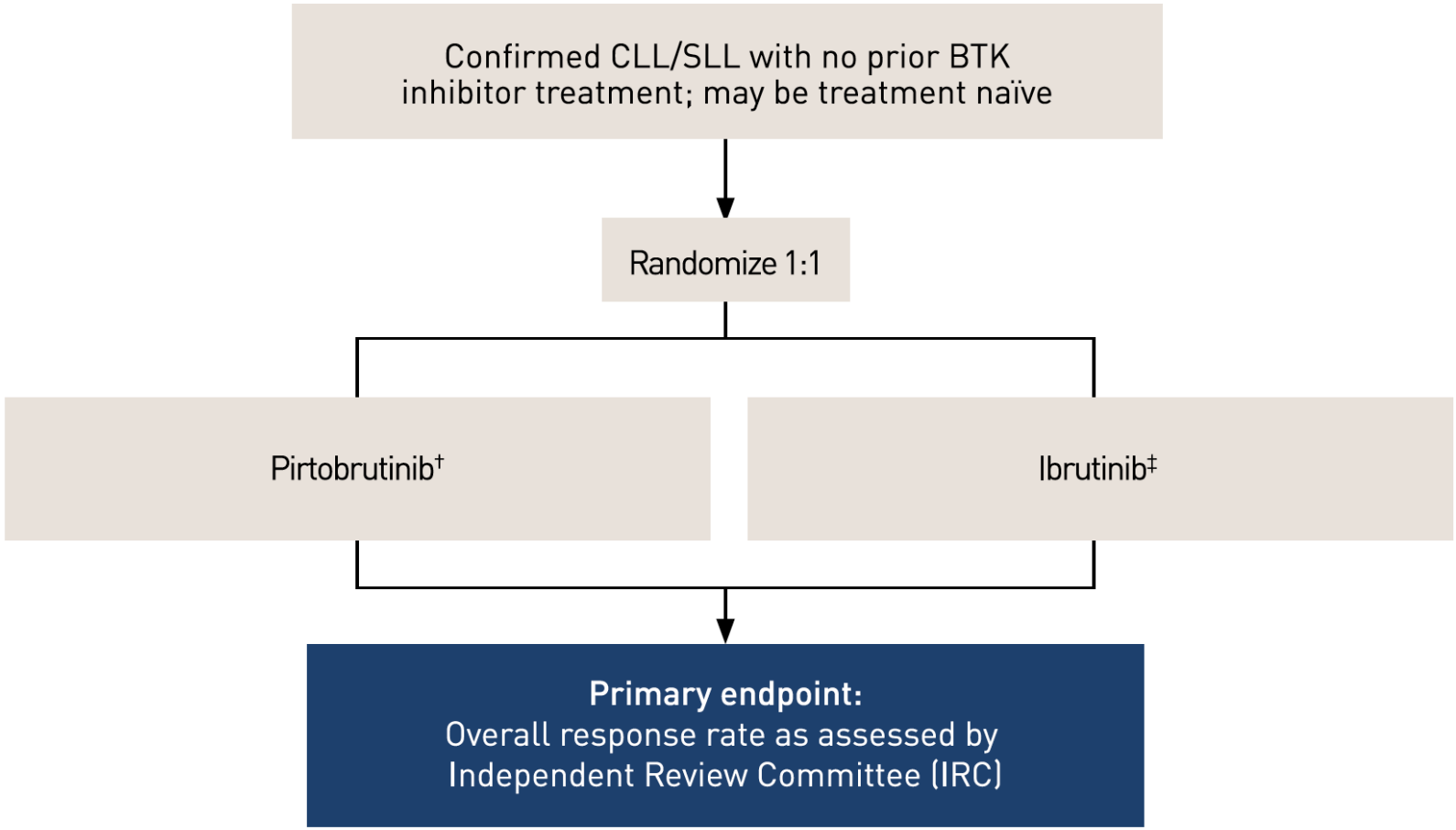
Arm A **Acalabrutinib (A)** 100 mg po BID,
Venetoclax (V) 400 mg po daily (C3D1–C14), including 5 week ramp up
STOP if uMRD and at least PR. If MRD+ continue AV to 24 months

Arm B **Venetoclax (V)** 400 mg po daily (C1D22–C12), including 5 week ramp up
Obinutuzumab (O) 1000 mg iv. (C1D1-2/8/15, C2-6 D1)
STOP if uMRD and at least PR. If MRD+ continue V to 24 months



BRUIN CLL-314: A Randomized Phase III Trial

Pirtobrutinib *Vs.* Ibrutinib in TN and R/R CLL/SLL



The primary objective is a non-inferiority ORR.
Superiority of pirtobrutinib vs. ibrutinib in EFS and PFS are key secondary objectives.

Thank You

CLL Questions?

nsaba@tulane.edu
423-946-1366