Cases from the Community: Investigators Discuss the Optimal Management of Chronic Lymphocytic Leukemia

Friday, May 29, 2026
6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

John N Allan, MD
Bita Fakhri, MD, MPH
Shuo Ma, MD, PhD
Mazyar Shadman, MD, MPH

Moderator

Jeremy S Abramson, MD, MMSc

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Dr Allen — Disclosures
Faculty

Advisory Committees	NeoGenomics
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Contracted Research	Adaptive Biotechnologies Corporation, BeOne, Bristol Myers Squibb, Genentech, a member of the Roche Group
Data and Safety Monitoring Boards/Committees	Merck
Speakers Bureaus	AbbVie Inc, BeOne

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Contracted Research	AbbVie Inc, BeOne, Genmab US Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company

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Dr Ma — Disclosures
Faculty

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Genentech, a member of the Roche Group, Lilly
Consulting Agreements	AbbVie Inc
Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeOne, Carna Biosciences, Juno Therapeutics, a Celgene Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Nurix Therapeutics Inc
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, BeOne, Lilly

Dr Shadman — Disclosures
Faculty

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Stock Options — Private Companies	Koi Biotherapeutics Inc
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Dr Abramson — Disclosures
Moderator

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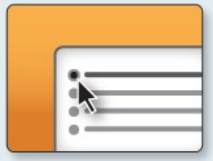
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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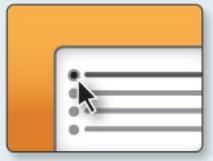
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Friday May 29	**Gastroesophageal Cancers** 11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Chronic Lymphocytic Leukemia 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Colorectal Cancer 6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)
Saturday May 30	**Ovarian Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Small Cell Lung Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday May 31	**Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Endometrial Cancer 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	CAR T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 1	**ADCs for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Novel Therapies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Relapsed/Refractory Multiple Myeloma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 2	**Myelofibrosis (Webinar)**

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Moderator

Jeremy S Abramson, MD, MMSc

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Cases from the Community

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Northside Hospital Cancer Institute
Athens, Georgia

Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
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Neil Love, MD
Research To Practice
Miami, Florida

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Agenda

Module 1: Current and Future Role of Continuous Bruton Tyrosine Kinase (BTK) Inhibitor Therapy for Previously Untreated Chronic Lymphocytic Leukemia (CLL) — Dr Fakhri

Module 2: Available and Emerging Approaches to Time-Limited Therapy for Treatment-Naïve CLL — Dr Allan

Module 3: Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Ma

Module 4: Selection and Sequencing of Therapy for R/R CLL — Dr Shadman

Module 5: Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL — Dr Abramson

Agenda

Module 1: Current and Future Role of Continuous Bruton Tyrosine Kinase (BTK) Inhibitor Therapy for Previously Untreated Chronic Lymphocytic Leukemia (CLL) — Dr Fakhri

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BTK Inhibitor Updates in Frontline CLL

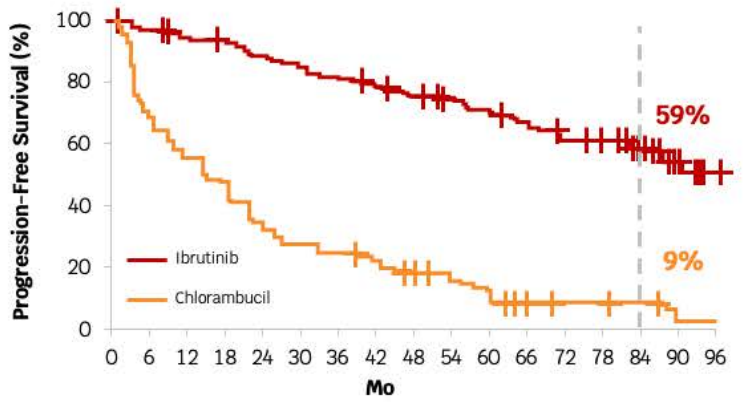
Bita Fakhri, MD, MPH
Associate Professor of Medicine
Stanford University
May 29, 2026

Learning Objectives

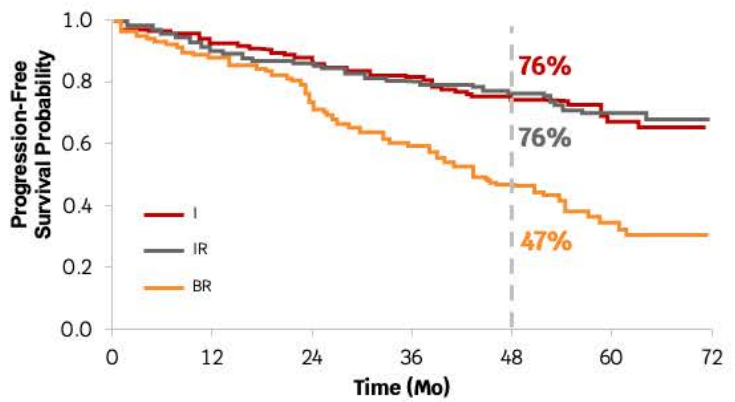
- Updates in continuous covalent BTK Inhibitor Therapy
- Updates in continuous non-covalent BTK Inhibitor Therapy

Transformation of Frontline Treatment Landscape in One Decade

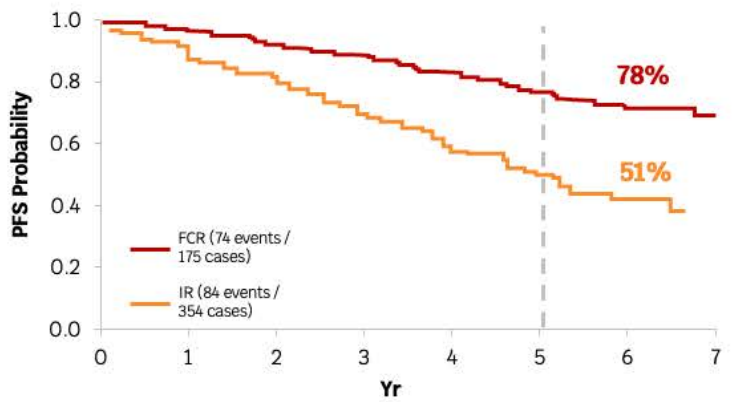
RESONATE 2 (Ibrutinib vs Chl)[1]



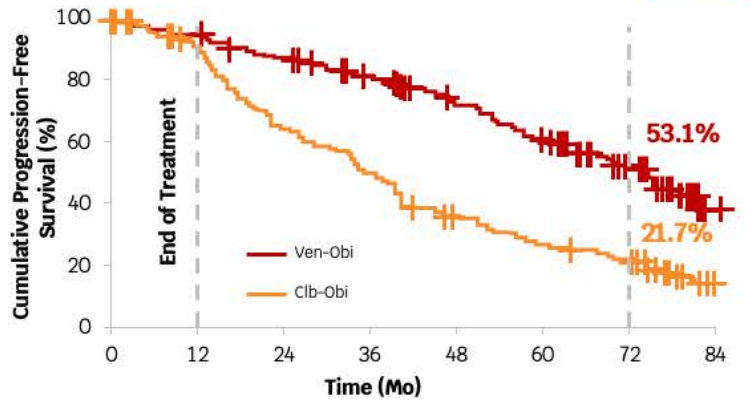
ALLIANCE (Ibrutinib vs Ibrutinib / Rituximab vs BR)[2]



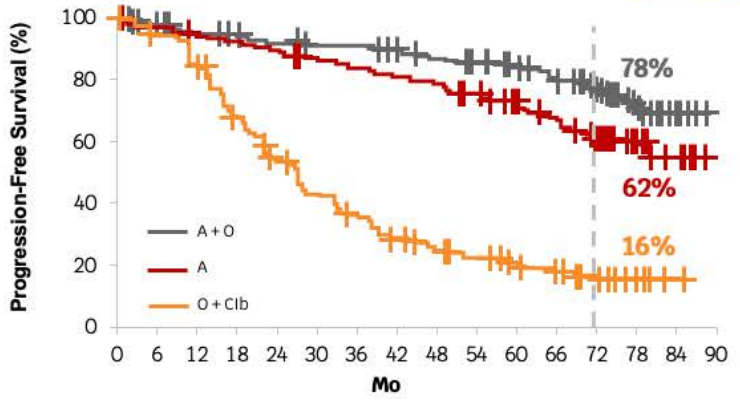
E1912 (Ibrutinib / Rituximab vs FCR)[3]



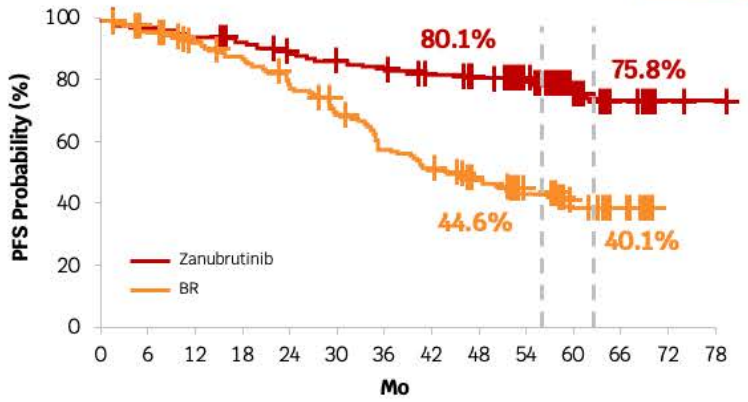
CLL14 (Ven-Obi vs Clb-Obi)[4]



ELEVATE-TN (Acala / Obi vs Acala vs Chl-Obi)[5]



SEQUOIA (Zanu vs BR)[6]



1.Barr. Blood Adv. 2022; 6:3440. 2. Woyach. Blood. 2024;143:1616. 3. Shanafelt. Blood. 2022;140:112. 4. Al-Sawaf. Blood. 2024;144:1924. 5. Sharman. Blood. 2025;146:1276. 6. Shadman. JCO. 2024;43:780.

Most Recent Updates in Continuous BTK Inhibitor Therapy

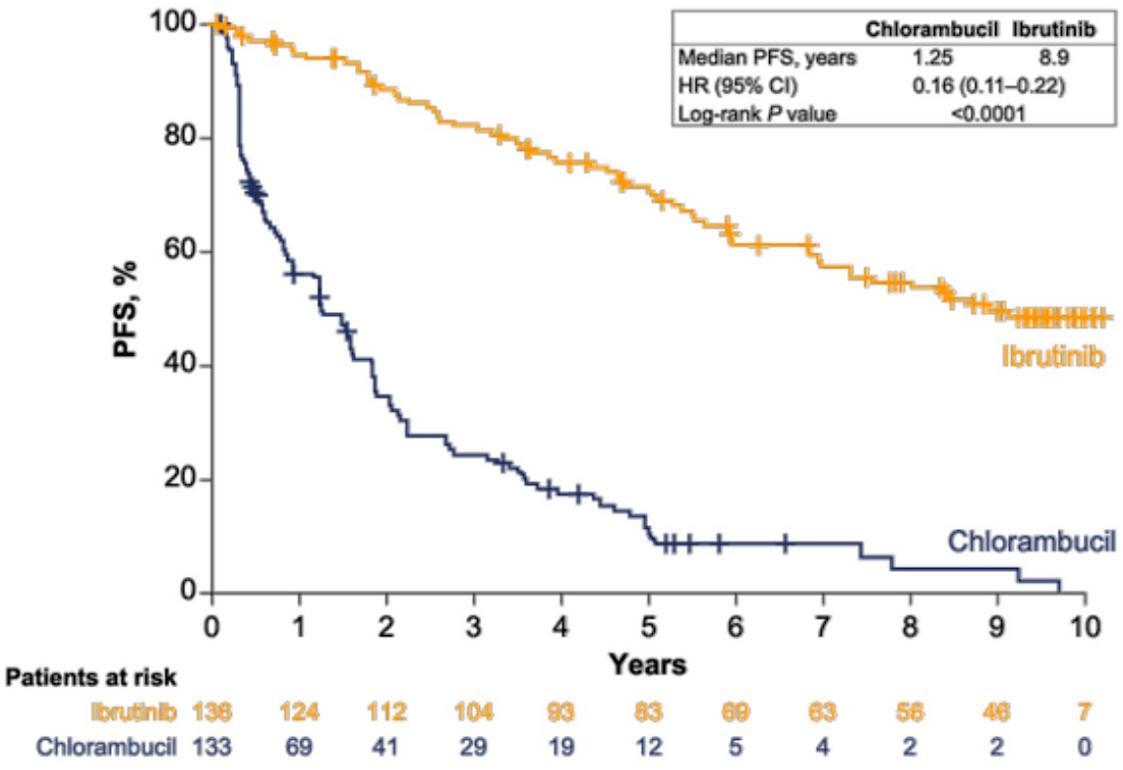
- Frontline
  - Resonate-2
  - ELEVATE-TN (acalabrutinib)
  - SEQUOIA (zanubrutinib)

- Relapsed/refractory
  - Alpine
  - ELEVATE-RR

RESONATE-2: 10-year PFS and OS

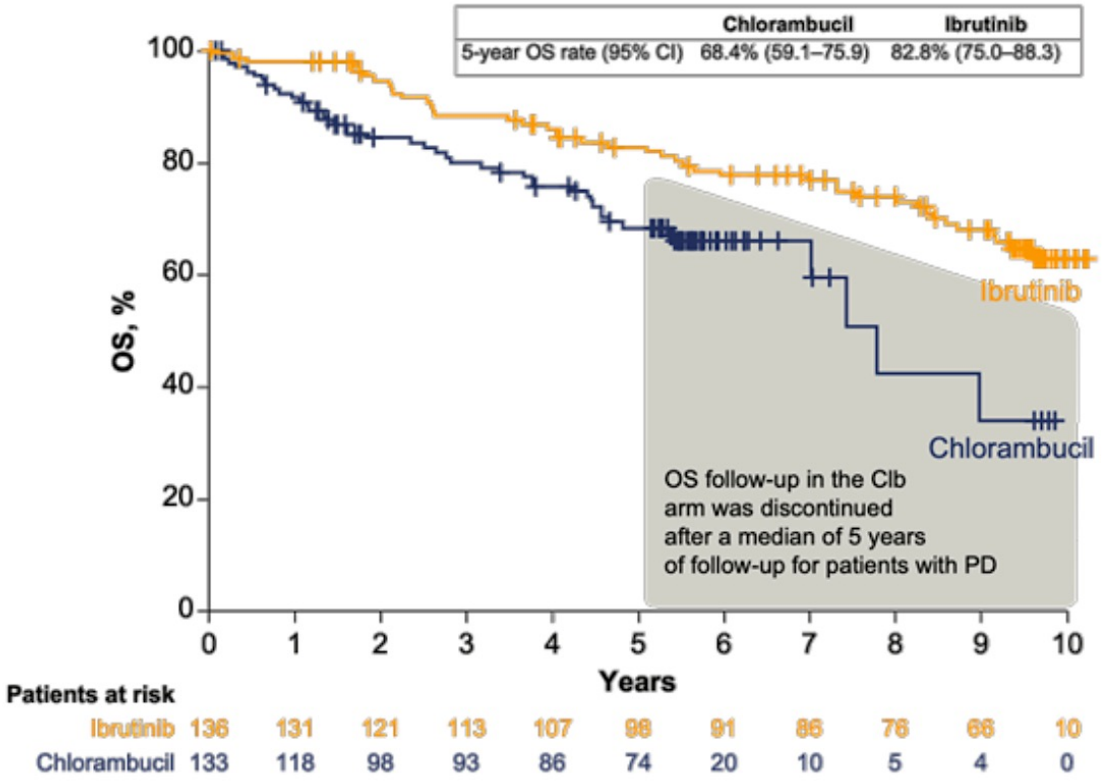
Progression-Free Survival

median F/U: 9.6 years



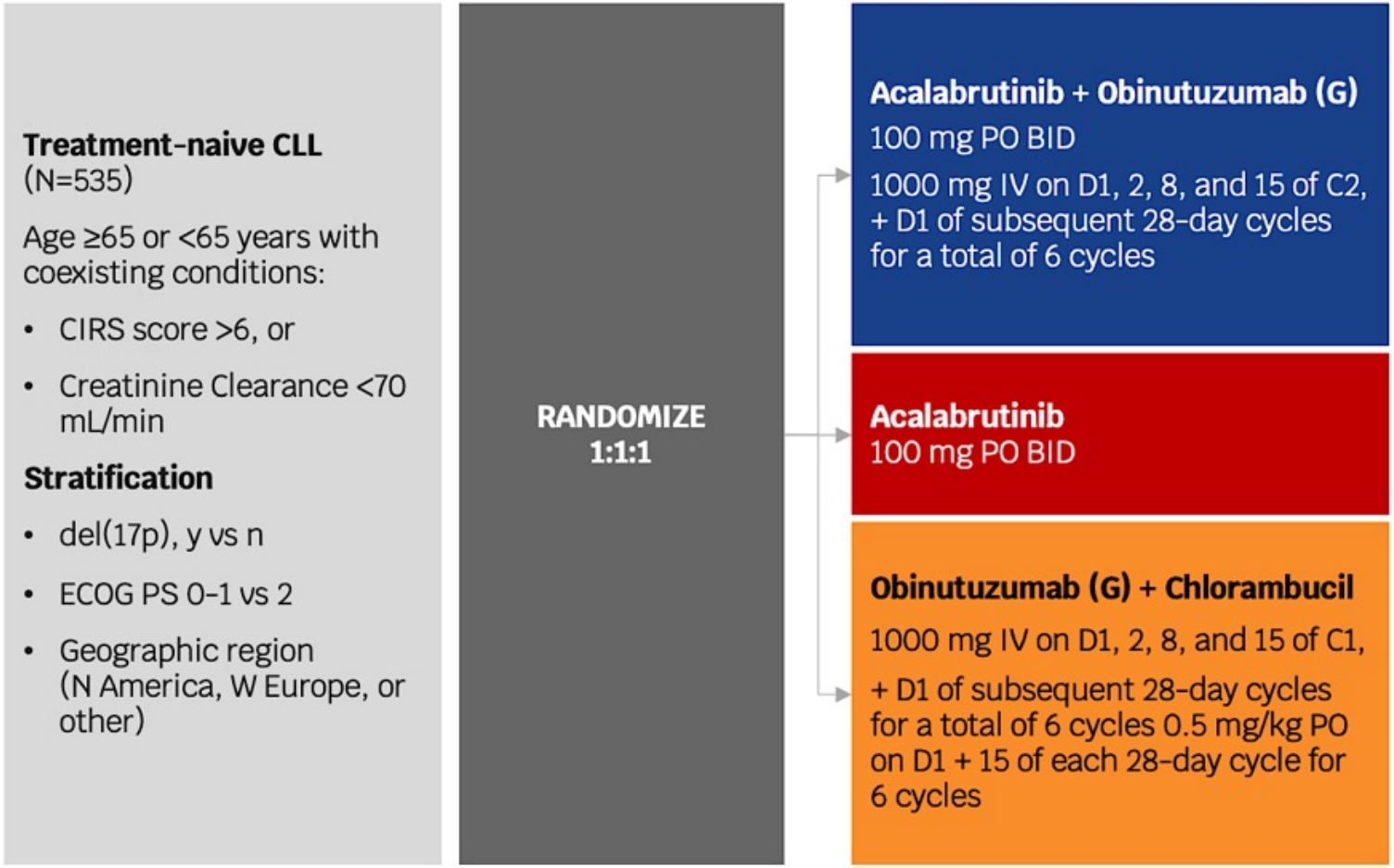
Overall Survival

median F/U: 9.6 years (5.6y for Clb)



Burger JA et al. Blood 2025;146:2168-2176

ELEVATE-TN 6 Year Follow-Up

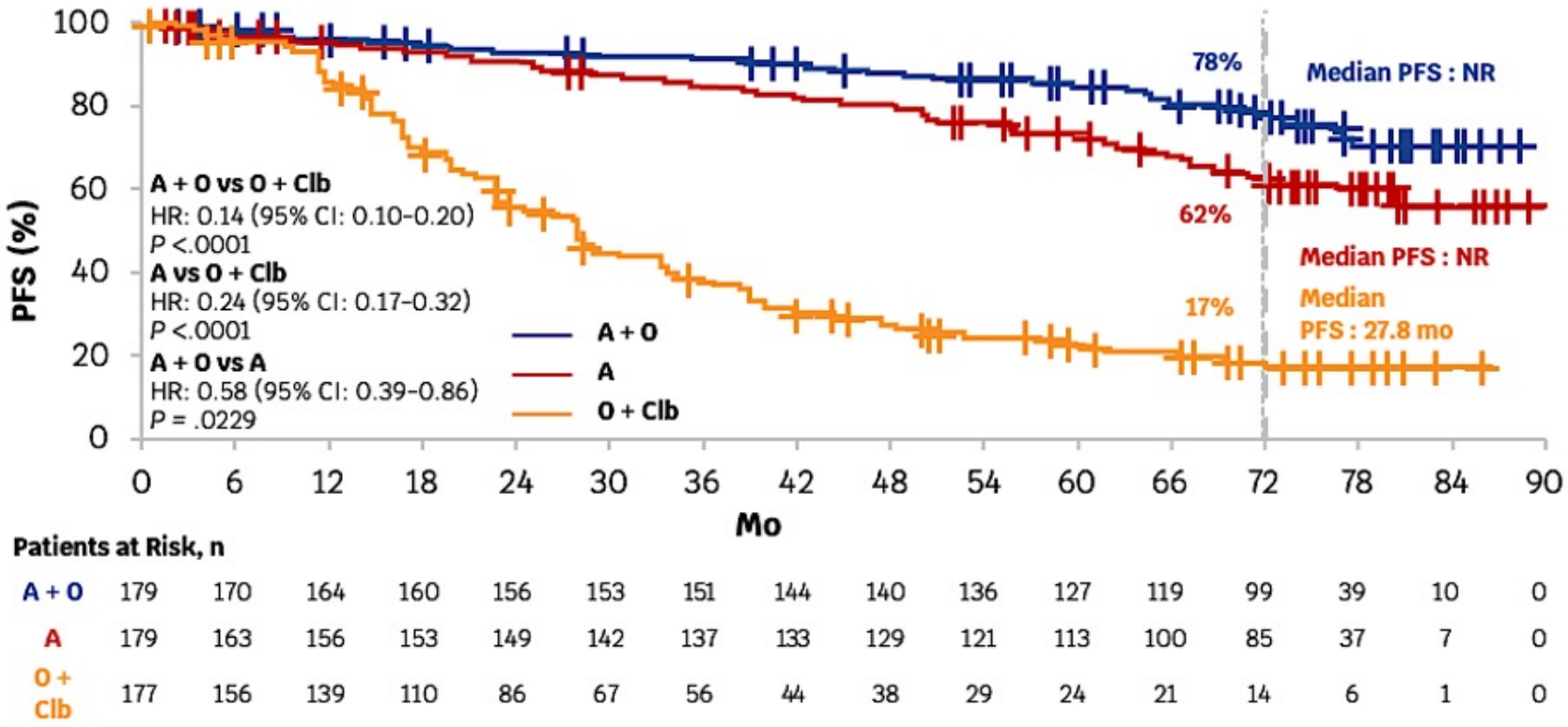


Primary endpoint: PFS (assessed by IRC), Acala-G vs G-Clb
Key secondary endpoints: PFS acalabrutinib vs G-Clb, ORR (assessed by IRC and investigator), TTNT, OS, Safety

Crossover from G-Clb to acalabrutinib was allowed after IRC confirmed progression

Sharman et al Blood 2023; Sharman et al Blood 2025

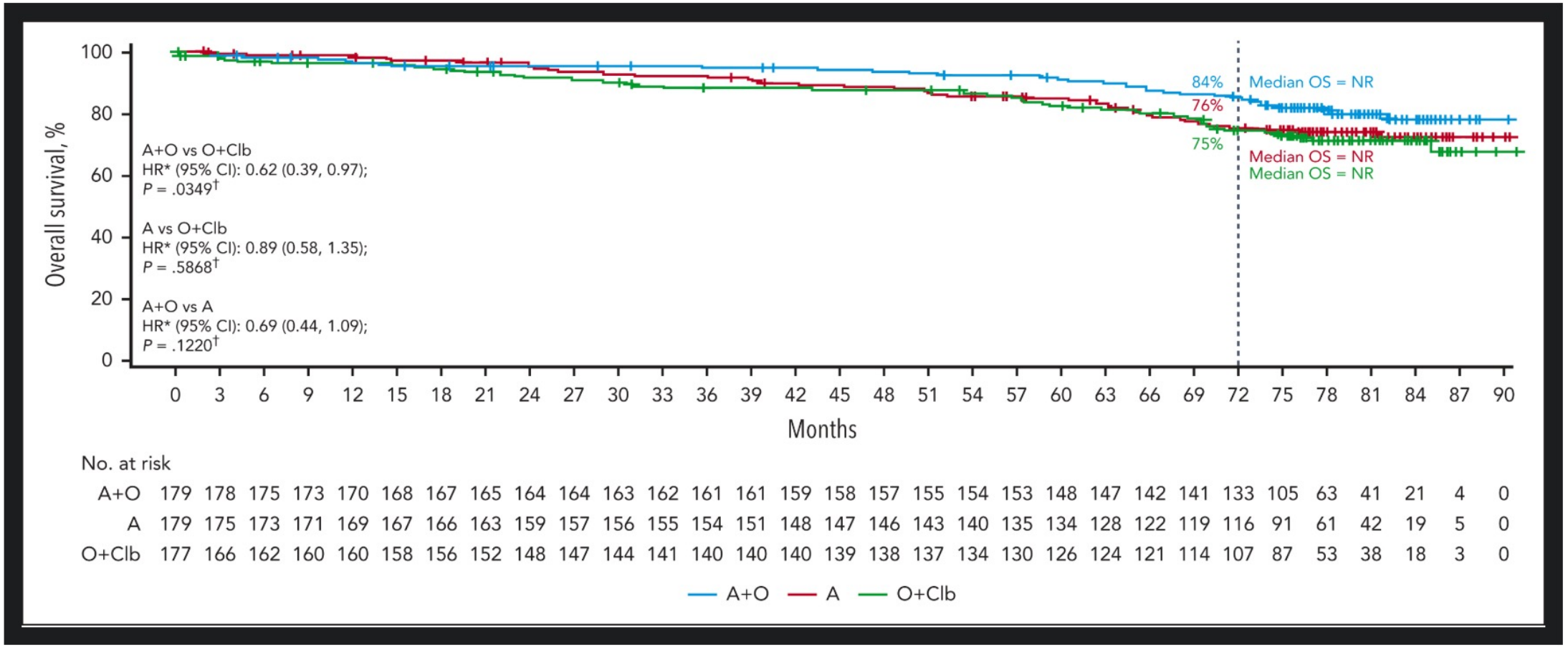
Median PFS was significantly longer for A-containing arms vs O+Clb



After median follow-up of 74.5 mo, median PFS was significantly longer in A-containing arms compared with O + Clb

Sharman et al Blood 2025

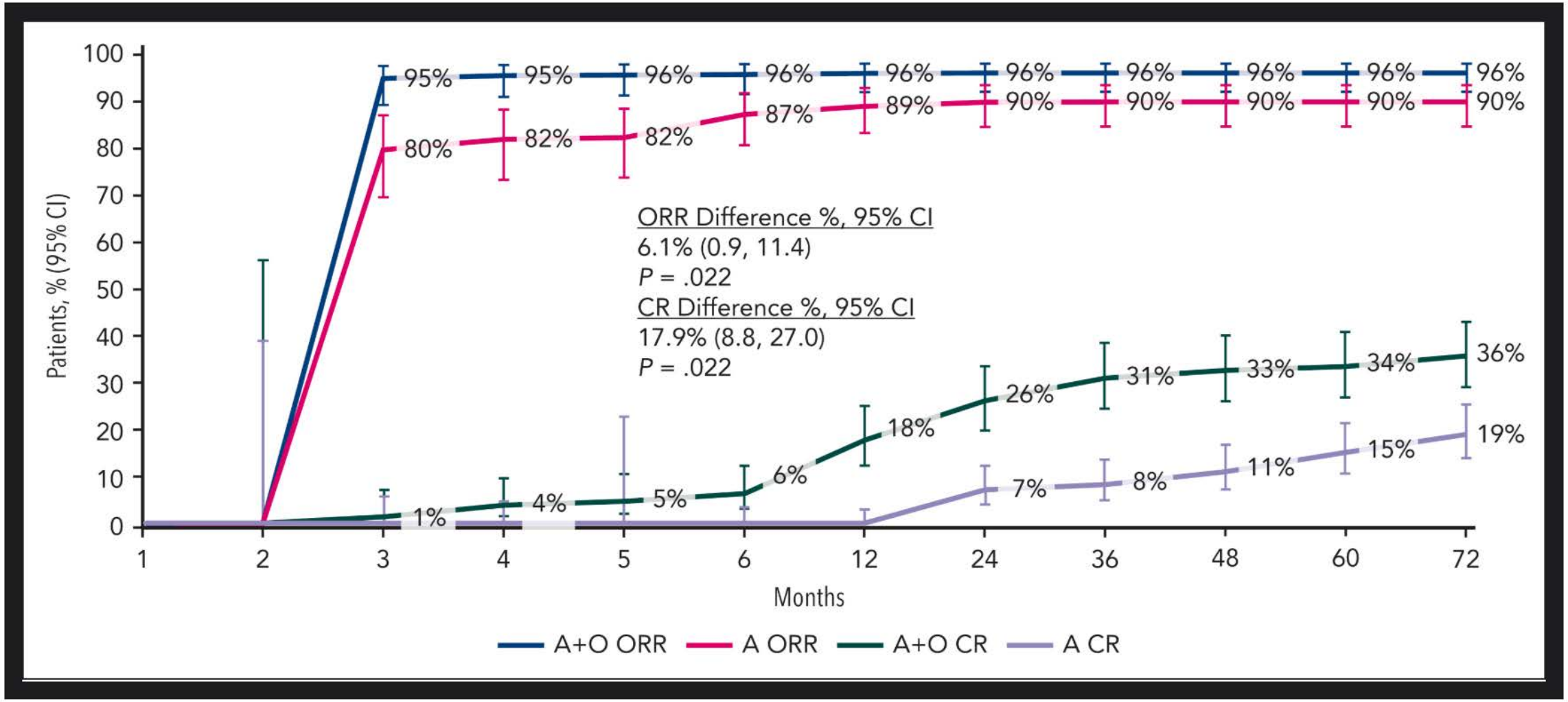
Median OS was significantly longer for A+O vs O+Clb



OS in patients overall. *HR based on stratified Cox proportional hazards model; †*P* value based on stratified log-rank test. ‡HR based on unstratified Cox proportional hazards model; §*P* value based on unstratified log-rank test. Clb, chlorambucil.

Sharman et al Blood 2025

CR rate consistently improved over time



ORRs∗ and CR/CRi rates over follow-up period in patients treated with A-O or A monotherapy. ∗Best investigator-assessed response could be determined at any scheduled, per-protocol follow-up visit. ORR is defined as achieving CR, CRi, nPR, or PR per the investigator per International Workshop on CLL 2008 criteria[21] at or before initiation of subsequent anticancer therapy. ORR does not include partial response except for lymphocytes. A, acalabrutinib; nPR, nodular partial response; O, obinutuzumab; PR, partial response.

Sharman et al Blood 2025

ELEVATE-TN: Safety Profile

Table 2. Grade 3 or higher AEs affecting 5% or more of patients

AEs (≥5% of patients), n (%)	A + O (n = 178)		A (n = 179)		O + Clb (n = 169)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	78 (43.8)	11 (6.2)	76 (42.5)	1 (0.6)	36 (21.3)	3 (1.8)
Neutropenia	61 (34.3)	55 (30.9)	23 (12.8)	21 (11.7)	77 (45.6)	71 (42.0)
COVID-19	44 (24.7)	16 (9.0)	38 (21.2)	13 (7.3)	0	0
Anemia	27 (15.2)	13 (7.3)	31 (17.3)	16 (8.9)	20 (11.8)	13 (7.7)
Thrombocytopenia	26 (14.6)	15 (8.4)	16 (8.9)	6 (3.4)	23 (13.6)	19 (11.2)
Pneumonia	25 (14.0)	13 (7.3)	27 (15.1)	11 (6.1)	5 (3.0)	3 (1.8)
Syncope	12 (6.7)	9 (5.1)	5 (2.8)	4 (2.2)	1 (0.6)	1 (0.6)

Sharman et al Blood 2025

ELEVATE-TN: AEs of Special Interest

AE, n (%)	Acalabrutinib + Obinutuzumab (n = 178)		Acalabrutinib (n = 179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	49 (27.5)	22 (12.4)	42 (23.5)	21 (11.7)
• Atrial fibrillation	13 (7.3)	3 (1.7)	16 (8.9)	3 (1.7)
Bleeding	95 (53.4)	12 (6.7)	81 (45.3)	8 (4.5)
• Major bleeding	16 (9.0)	12 (6.7)	10 (5.6)	8 (4.5)
Hypertension	20 (11.2)	8 (4.5)	20 (11.2)	9 (5.0)
Infections	147 (82.6)	63 (35.4)	144 (80.4)	50 (27.9)
SPMs	36 (20.2)	17 (9.6)	35 (19.6)	9 (5.0)
• SPMs excluding nonmelanoma skin	24 (13.5)	13 (7.3)	22 (12.3)	7 (3.9)

AEs of clinical interest were generally consistent with previous analyses

Sharman et al Blood 2025

SEQUOIA 6 Year Follow-up by 17p Deletion

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT / MRI
- Unsuitable for FCR

Arms A and B
Without del(17p)

Open label | **R 1:1**

Zanubrutinib
160 mg BID until PD, unacceptable toxicity, or end of study

Bendamustine + rituximab
Maximum 6 cycles[a]

Arms C
With del(17p)

Zanubrutinib
160 mg BID until PD, unacceptable toxicity, or end of study

Arm D

With del(17p) and/or *TP53mut*
Enrollment start dote: Nov 2019

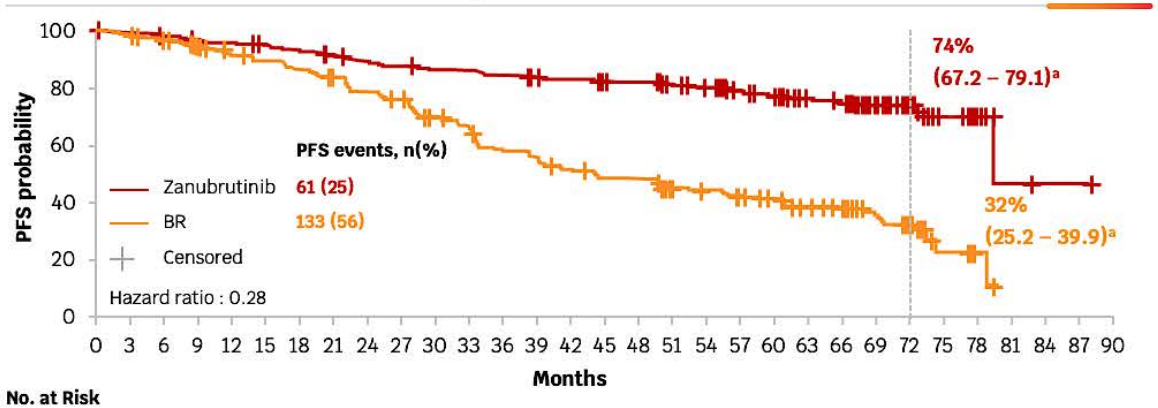
Without del(17p) and *TP53mut*
Enrollment start dote: Jon 2022

Zanubrutinib + venetoclax

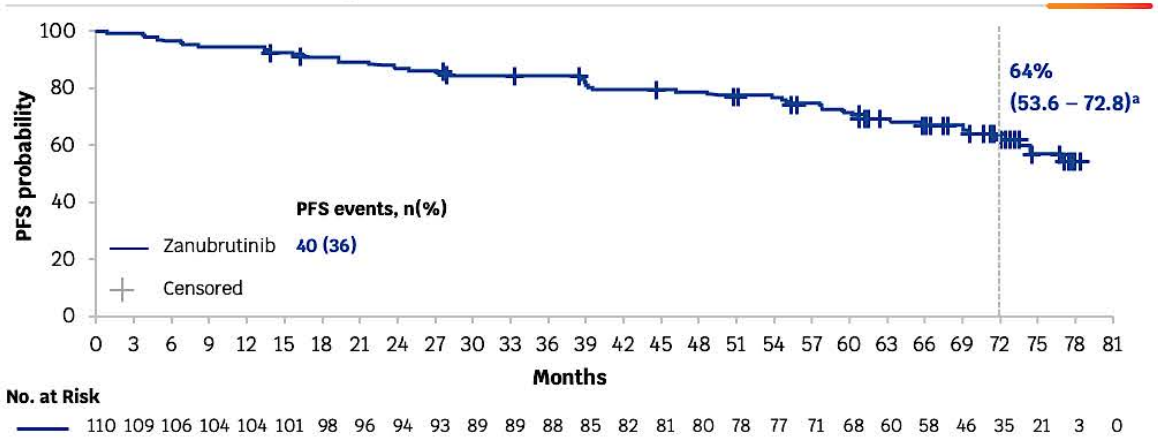
Key endpoints in Arms A, B, and C

- PFS (iny)
- ORR (inv)[b]
- OS
- Safety per CTCAE

PFS in Arms A and B (w/o del 17p)



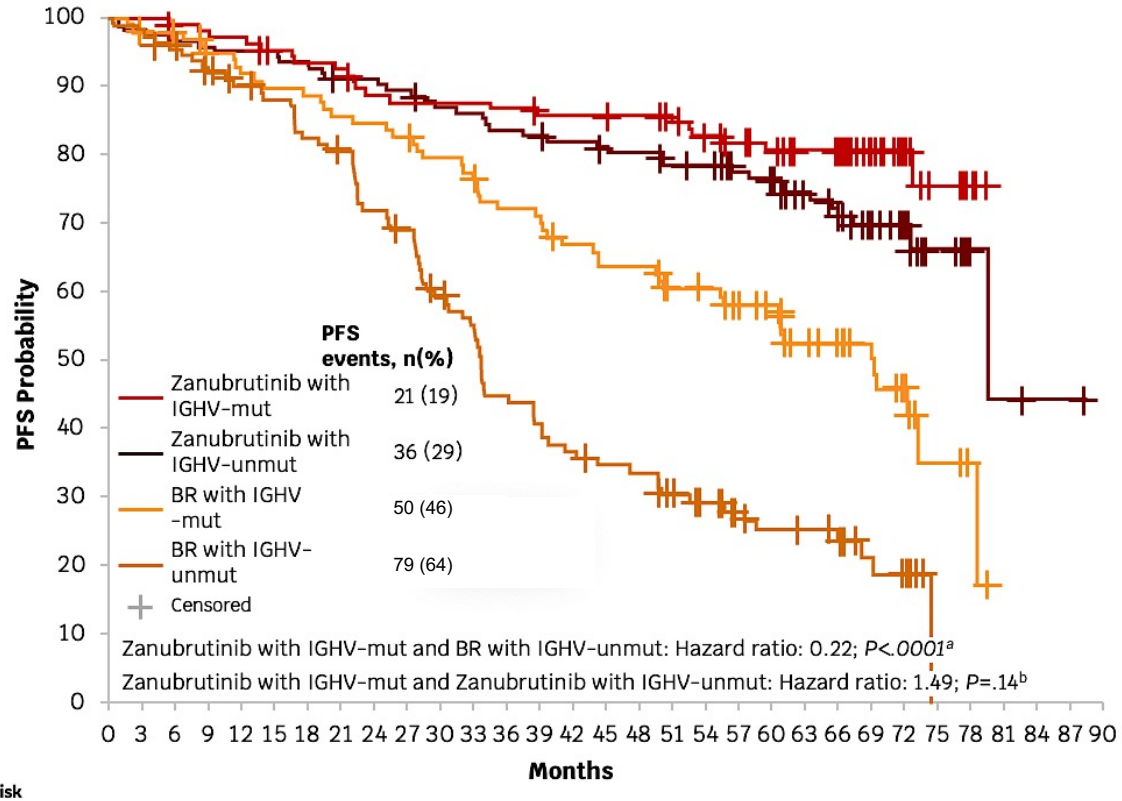
PFS in Arm C (w/del 17p)



Constantine, et al. ASH 2025

SEQUOIA: Outcomes by Del(17p) and IGHV Mutation Status

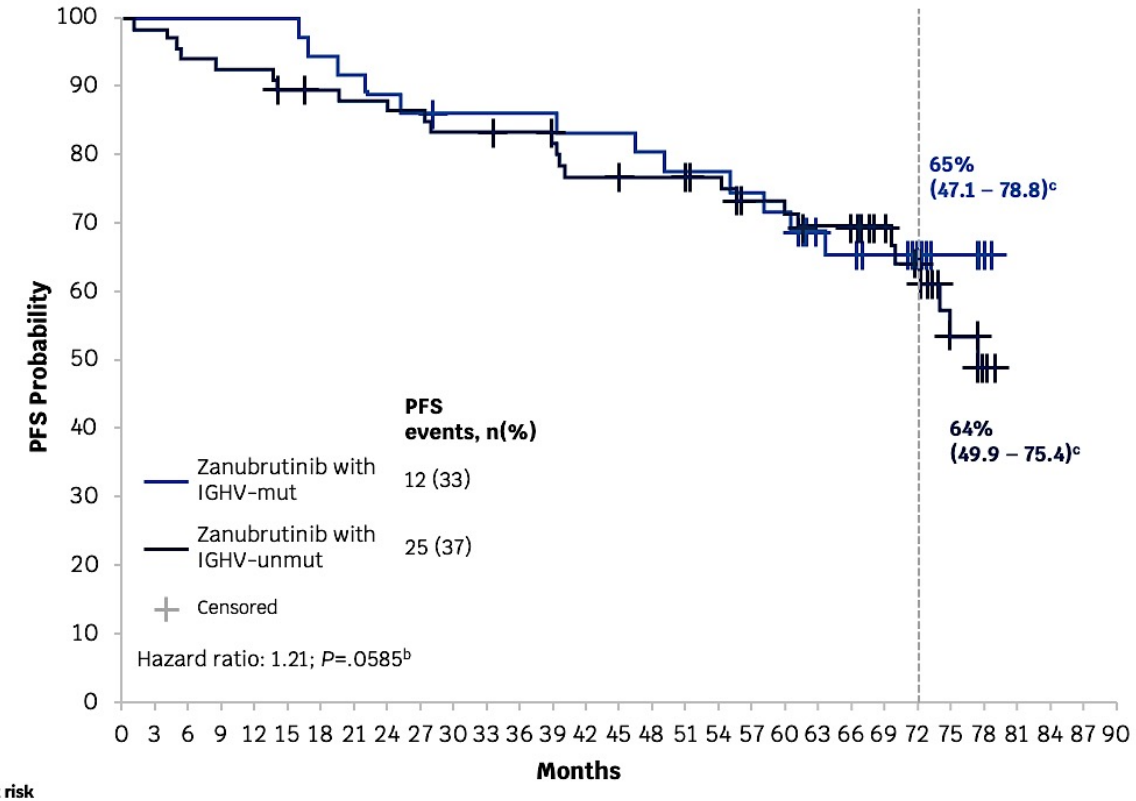
PFS in IGHV-mut and IGHV-unmut Patients in Arms A and B



No. at risk

Zanubrutinib with IGHV-mut	109	109	107	106	105	101	99	98	93	92	92	92	91	89	89	89	88	84	79	74	70	61	61	41	27	13	4	0	
Zanubrutinib with IGHV-unmut	125	122	120	118	117	117	115	111	111	109	105	104	101	100	98	95	94	88	87	77	76	66	62	53	32	14	3	2	1	1	0
BR with IGHV-mut	109	100	98	93	90	88	87	84	83	81	77	75	69	68	63	60	60	53	52	44	42	35	33	24	16	5	2	0			
BR with IGHV-unmut	123	112	108	102	96	93	87	84	75	71	60	55	44	40	36	33	32	26	25	21	18	17	15	8	8	0					

PFS in IGHV-mut and IGHV-unmut Patients in Arms C



No. at risk

Zanubrutinib with IGHV-mut	36	36	36	36	36	36	34	33	32	31	30	30	30	30	29	29	28	27	27	26	25	20	19	17	12	6	1	0	
Zanubrutinib with IGHV-unmut	67	66	63	62	62	59	58	57	56	56	53	53	52	50	47	46	46	45	44	39	38	36	36	27	21	13	2	0	

Constantine, et al. ASH 2025

SEQUOIA: Safety Profile

Treatment-Emergent and Post-Treatment AESIs (Any Grade in ≥15% of Patients)

	Arms A and B (N=467)[a]				Arms C (N=111)	
	Zanubrutinib n=240		BR n=227		Zanubrutinib n=111	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
AESI, n (%)	224 (93)	142 (59)	210 (93)	163 (72)	103 (93)	65 (59)
Anemia	24 (10)	2 (1)	48 (21)	6 (3)	11 (10)	0
Neutropenia	34 (14)	26 (11)	104 (46)	94 (41)	13 (12)	12 (11)
Contusion	57 (24)	0	9 (4)	0	24 (22)	0
Hypertension	49 (20)	31 (13)	29 (13)	15 (7)	21 (19)	11 (10)
COVID-19	100 (42)	23 (10)	21 (14)	4 (2)	43 (39)	8 (7)
Upper respiratory tract infection	51 (21)	2 (1)	34 (15)	2 (1)	32 (29)	0
Pneumonia	38 (16)	18 (8)	27 (12)	12 (5)	18 (16)	7 (6)
Urinary tract infection	38 (16)	4 (2)	23 (10)	6 (3)	18 (16)	3 (3)
Basal cell carcinoma	23 (10)	2 (1)	10 (4)	1 (0)	19 (17)	0

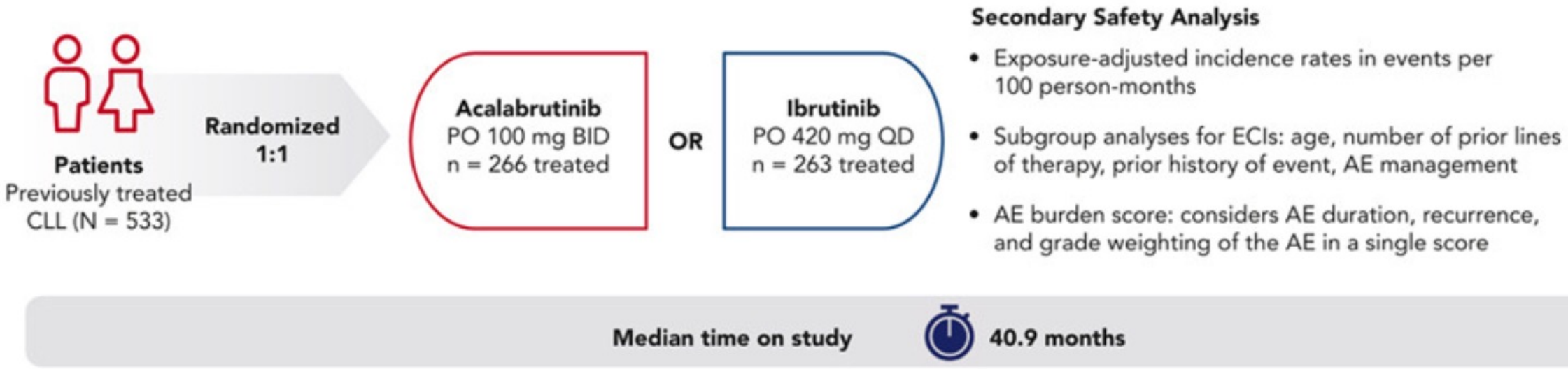
[a]The safety-evaluable population.
Abbreviations: AESI, adverse event of special interest; BR, benclamustine and rituximab.

EAIRs for Select TEAEs and Post-Treatment AESIs

EAIRs, persons per 100 person-months[a]	Arms A and B (N=467)		Arms C (N=111)
	Zanubrutinib n=240	BR n=227	Zanubrutinib n=111
Atrial fibrillation and flutter	0.16	0.10	0.15
Hemorrhage	1.57	0.32	2.03
Major hemorrhage	0.18	0.05	0.17
Hypertension	0.46	0.36	0.38
Second primary malignancies	0.47	0.40	0.64
Infections	3.40	3.37	4.16
Neutropenia	0.34	2.95	0.35

[a]EAIRs were calculated as the number of patients with an event in each TEAE category divided by the total time from the first dose date to the first event date or the exposure time if no event occurred.
Abbreviations: AESI, adverse event of special interest, BR, bendamustine and rituximab; EAIR, exposure-adjusted incidence rate; TEAE treatment-emergent adverse event.

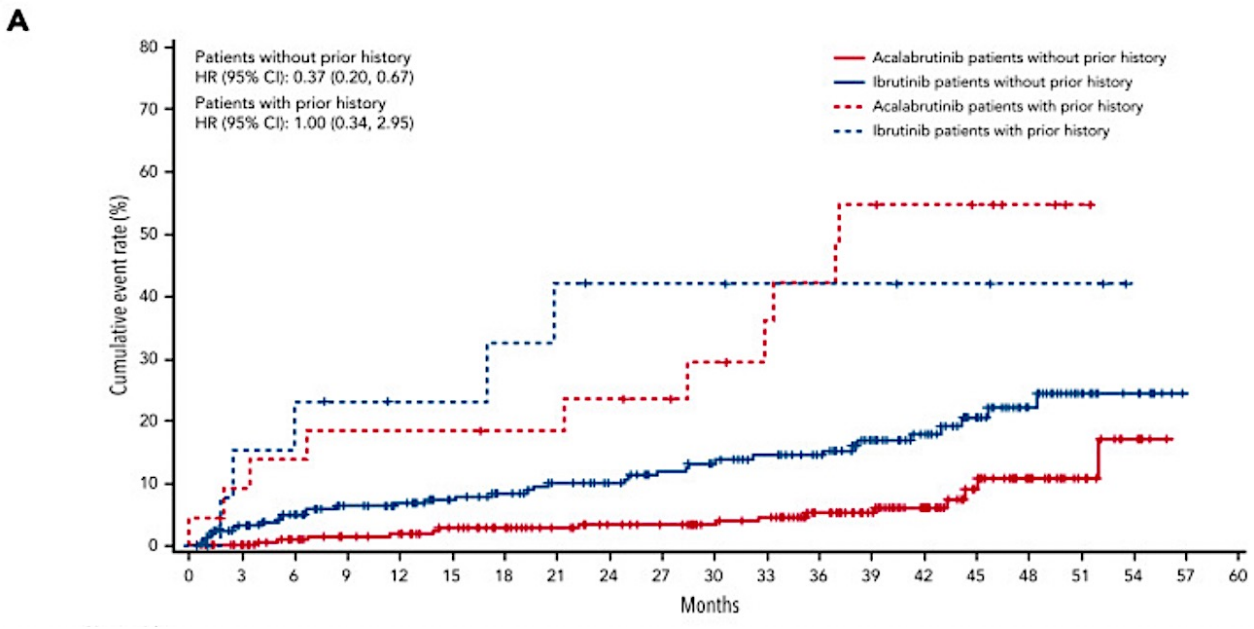
ELEVATE-RR Study Design



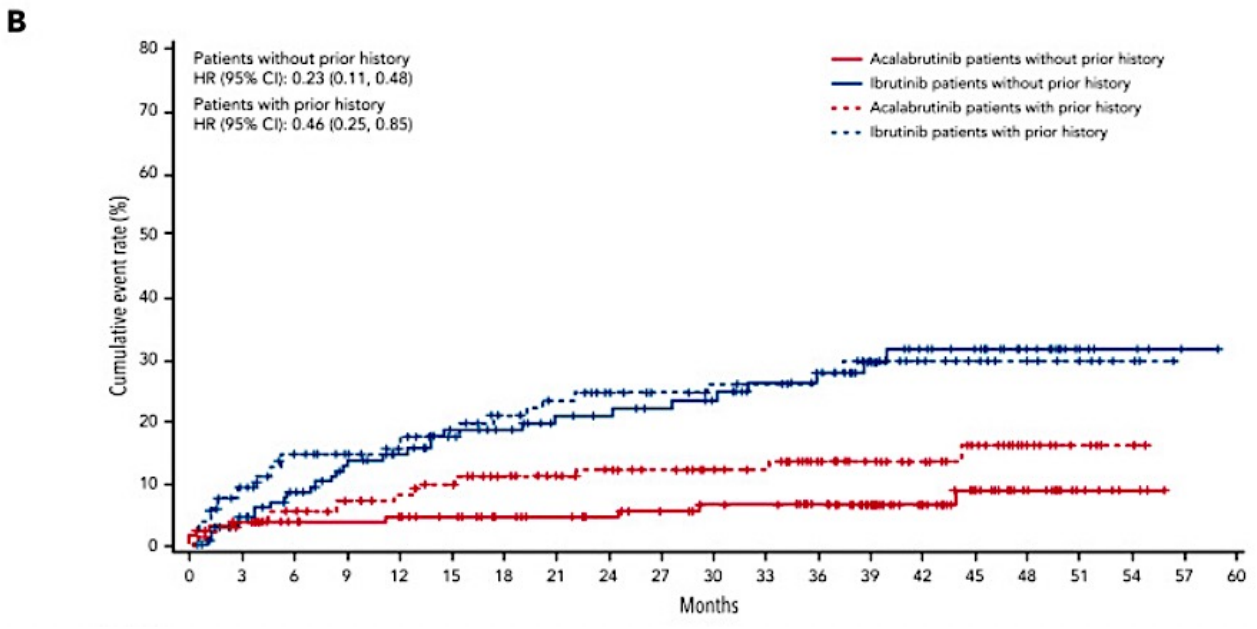
Seymour et al. Blood 2023;142:687-699

ELEVATE-RR: Adverse Events of Interest

Atrial Fibrillation/Flutter

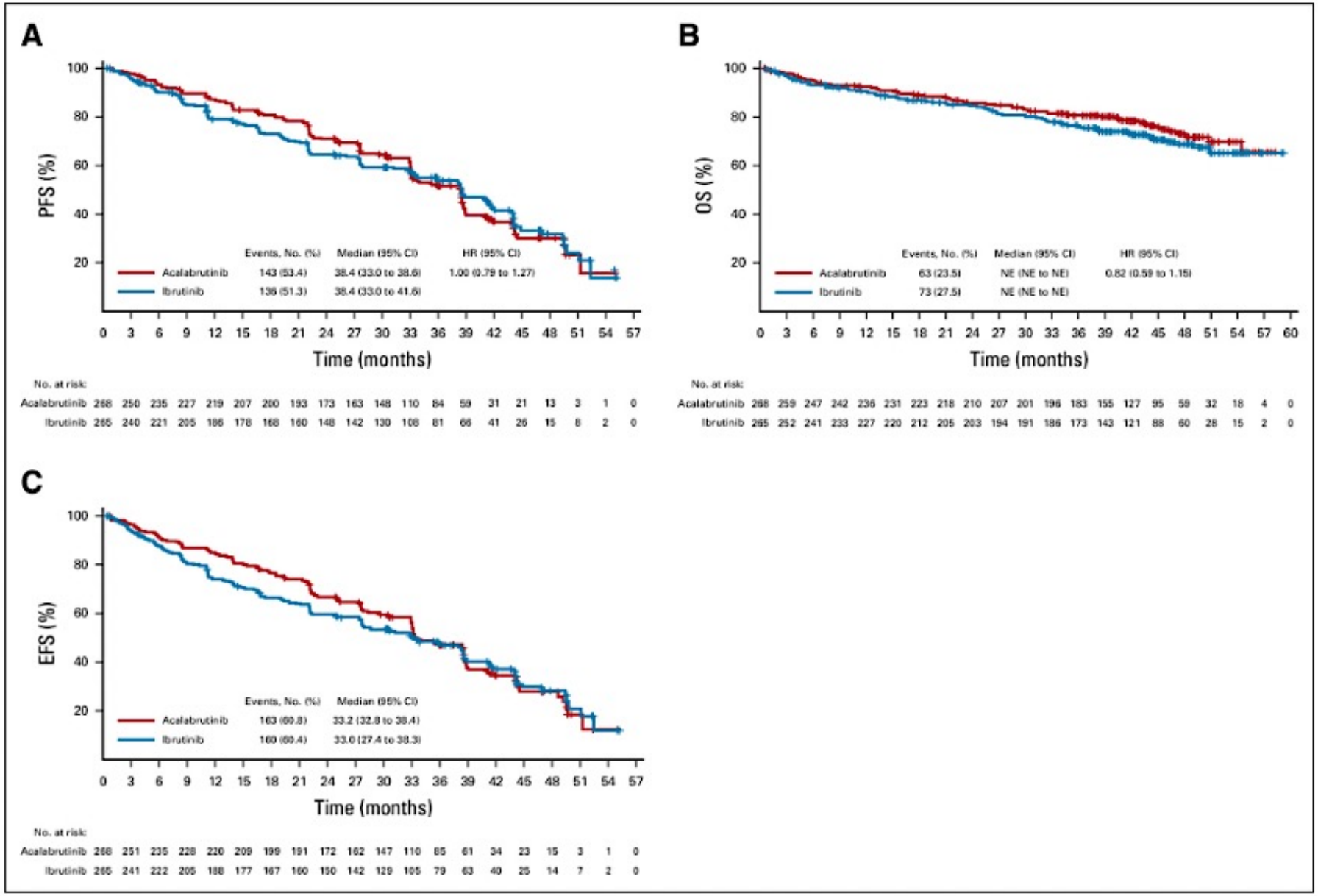


Hypertension



Seymour et al. Blood 2023;142:687-699

ELEVATE-RR: Acalabrutinib vs Ibrutinib in Rel/Ref CLL



Byrd et al. JCO 2021;39(31):3441-3452

ALPINE Study Design (NCT03734016)

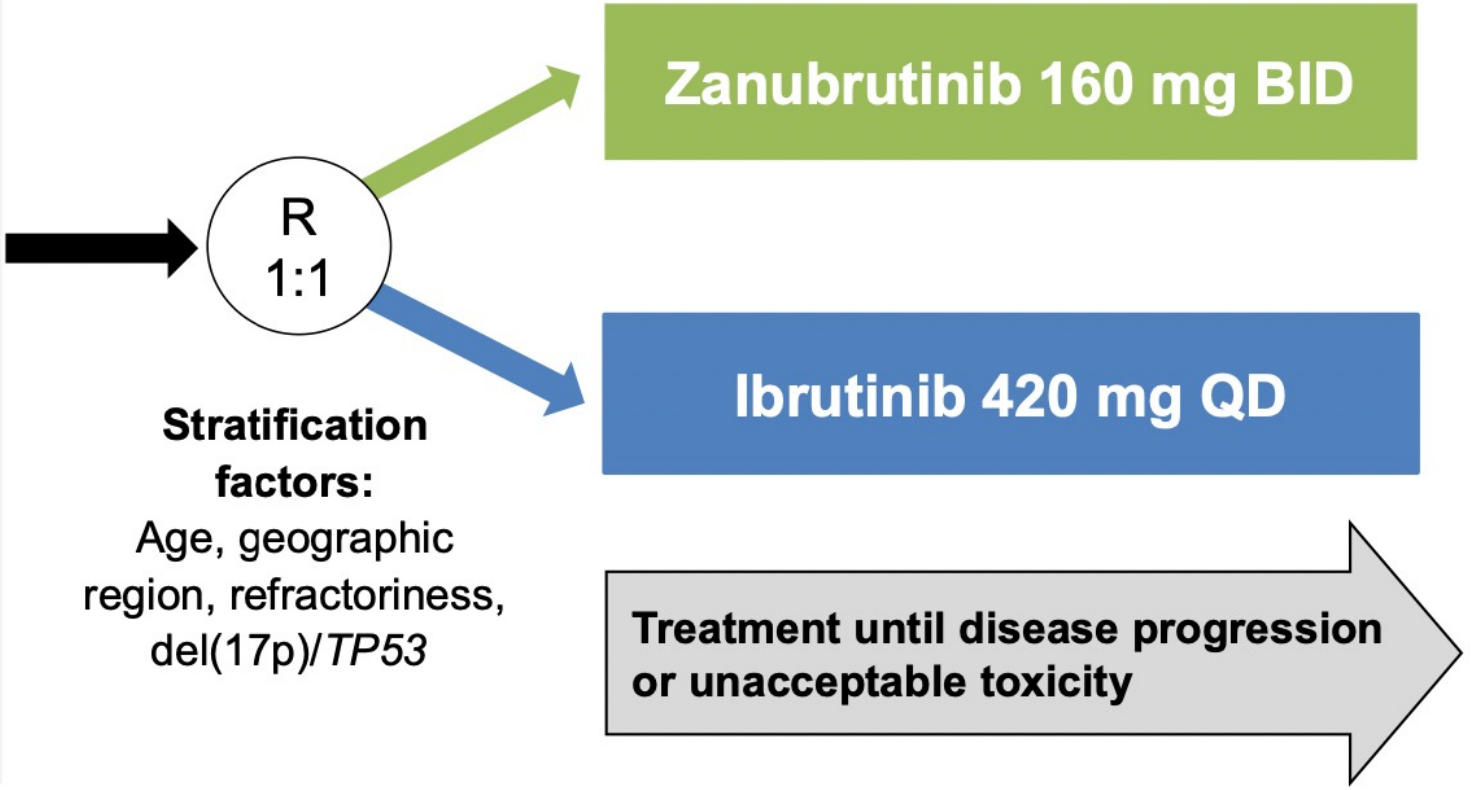
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

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

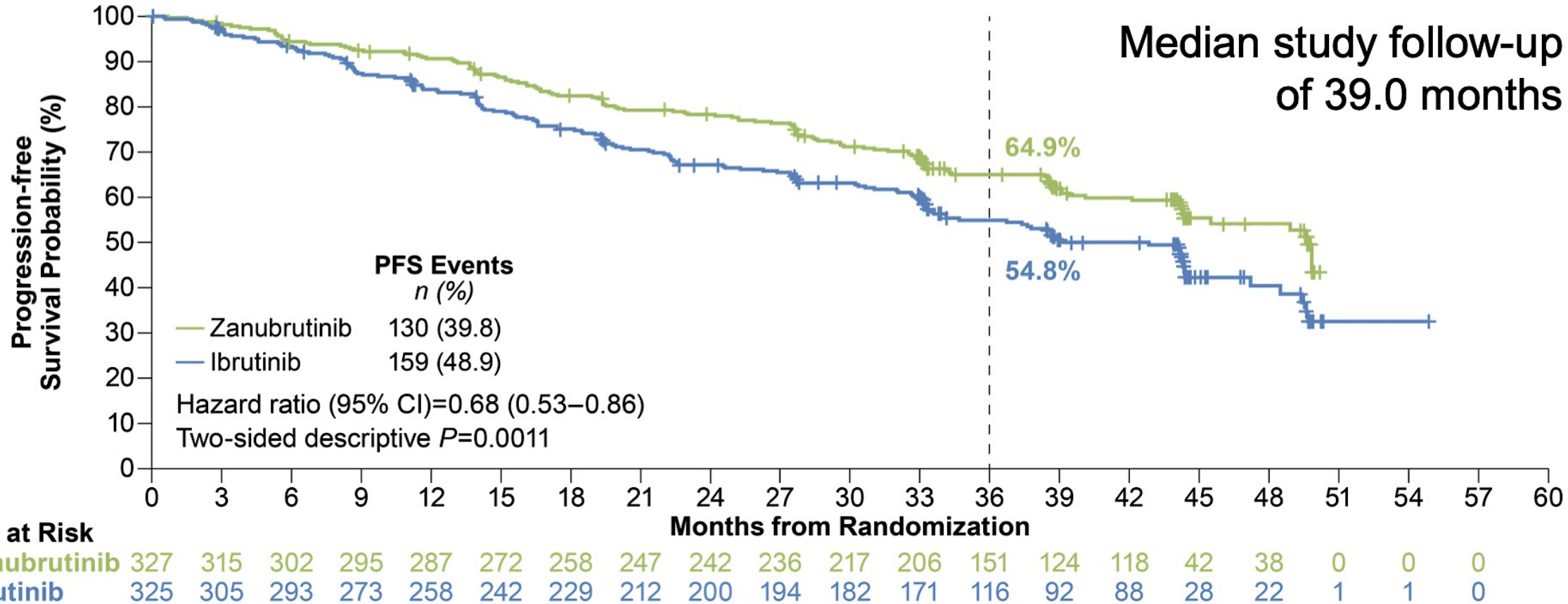
Key Exclusion Criteria

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



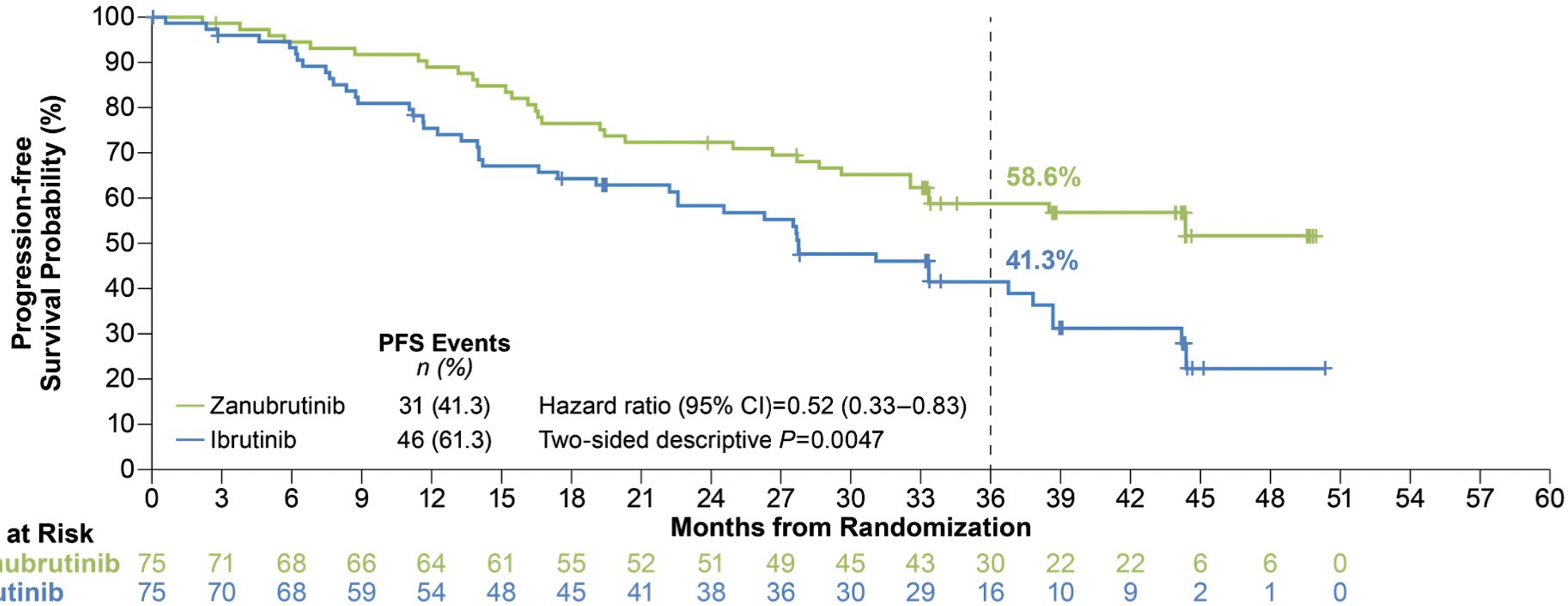
Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332. **Brown JR et al. ASH 2023**

Zanubrutinib Sustains PFS Benefit Over Ibrutinib At Extended Follow-up



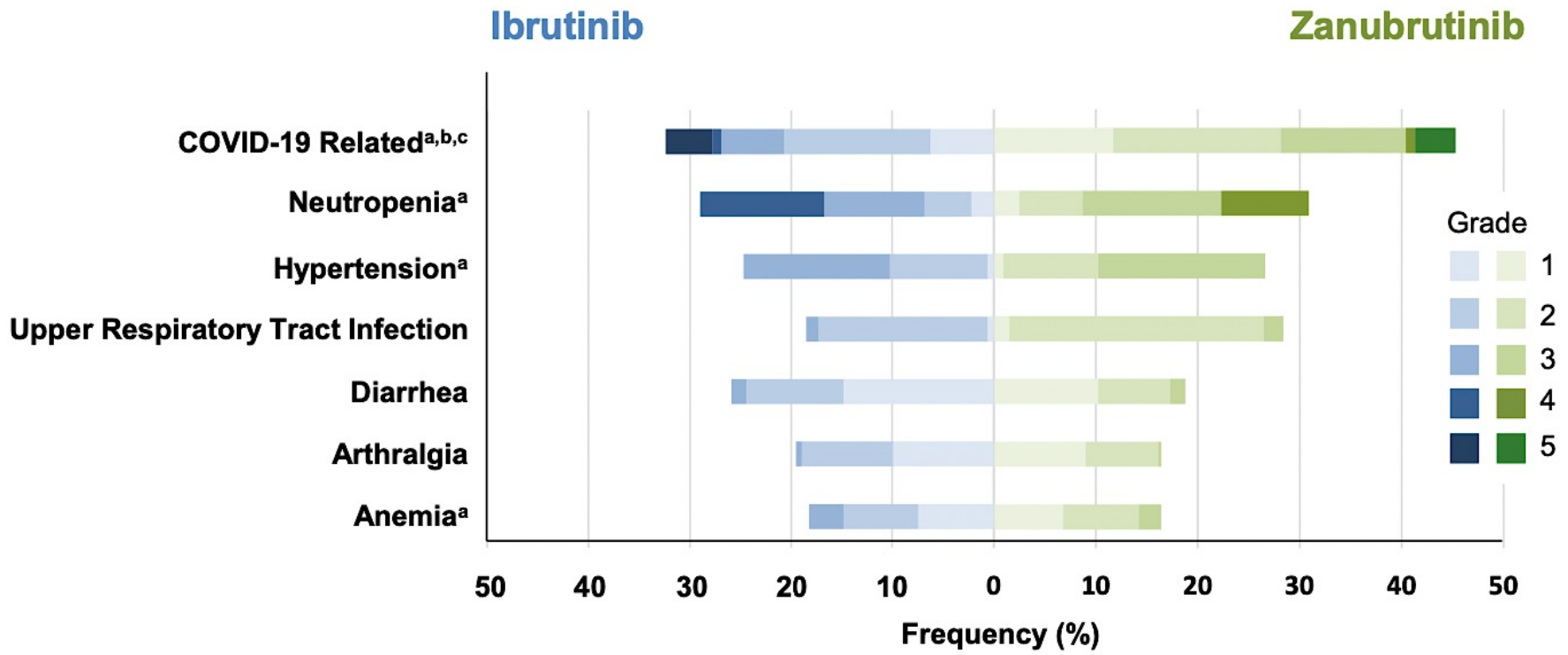
Brown JR et al. ASH 2023

Improved PFS Was Demonstrated With Zanubrutinib in Patients With del(17p)/*TP53*^{mut}



Brown JR et al. ASH 2023

Most Common Adverse Events by Grade Occurring in ≥15% of Patients in Both Arms



[a]Pooled MedDRA preferred terms
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
[c]Grade 5 COVID-related events: 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.

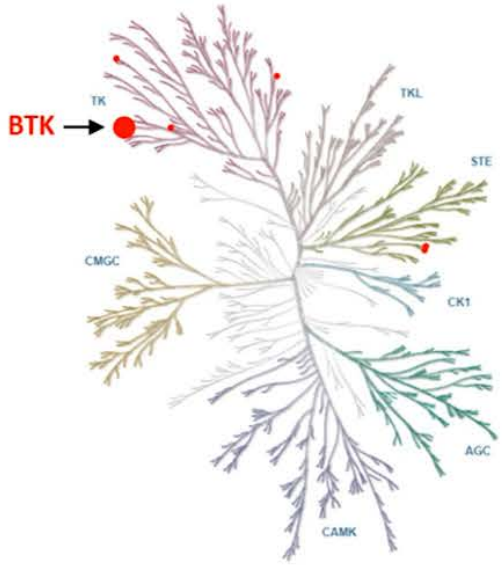
Brown JR et al. ASH 2023

Non-Covalent BTK Inhibitors in Frontline CLL

- Bruin CLL-314 trial
- Bruin CLL-313 trial

BRUIN CLL 314: Pirtobrutinib vs Ibrutinib in BTKi-Naïve Patients

Highly selective Non-Covalent for BTKi



Inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover

BRUIN CLL-314: Pirtobrutinib vs Ibrutinib in BTKi-Naïve Patients

Patients with CLL/SLL who are BTKi naïve, including TN and R/R

Stratified by:
- 17p deletion presence: Y vs N
- Prior lines of therapy: 0 vs 1 vs ≥2

R 1:1

Pirtobrutinib
200 mg PO QD

Ibrutinib
420 mg PO QD

Key Eligibility
- Confirmed diagnosis of CLL/SLL, with requirement for therapy (per iwCLL 2018 criteria)
- BTKi naïve[b]
- 17p deletion status (by FISH)
- ECOG PS 0 to 2

Primary Objectives

Non-inferiority of ORR (per iwCLL 2018 criteria):
- In ITT population, or
- In R/R population

Key Secondary Objectives

Superiority of PFS (per iwCLL 2018 criteria):
- In ITT population, or
- In R/R population

Exploratory

Analyses of endpoints in the TN population

Wang et. Al. ASH 2022. Poster 4218

Bruin CLL-314 Response Rates

	ITT Population		TN Population		R/R Population	
	Pirtobrutinib n = 331	**Ibrutinib n = 331**	**Pirtobrutinib n = 112**	**Ibrutinib n = 113**	**Pirtobrutinib n = 219**	**Ibrutinib n = 218**
ORR[a] (PR or better)						
%	**87.0**	**78.5**	**92.9**	**85.8**	**84.0**	**74.8**
95% CI[b]	82.90, 90.44	73.73, 82.85	86.41, 96.87	78.03, 91.68	78.48, 88.61	68.46, 80.39
Nominal p-value[c]	0.0035		0.0886		0.0175	
ORR[a] ratio						
ORR ratio (95% CI)	1.1080 (1.034, 1.187)		1.0797 (0.989, 1.179)		1.1233 (1.020, 1.237)	
p-value for NI[d]	<0.0001		-		<0.0001	
Best Overall Response[e], %						
CR or CRi	4.8	2.4	7.1	3.5	3.7	1.8
PR or nPR	82.2	76.1	85.7	82.3	80.4	72.9
PR-L	2.4	3.9	0.9	2.7	3.2	4.6
SD	5.4	10.9	2.7	4.4	6.8	14.2
PD	1.5	1.2	0	0	2.3	1.8
ORR including PR-L						
%	89.4	82.5	93.8	88.5	87.2	79.4
95% CI[b]	85.60, 92.52	77.95, 86.42	87.55, 97.45	81.13, 93.73	82.05, 91.33	73.37, 84.53
Nominal p-value[c]	0.0093		0.1692		0.0286	

ORR results presented are IRC-assessed

Pirtobrutinib demonstrated consistently higher ORR than ibrutinib across all patients, including TN and R/R populations

Woyach et al. ASH 2025.

Bruin CLL-314 Safety Profile

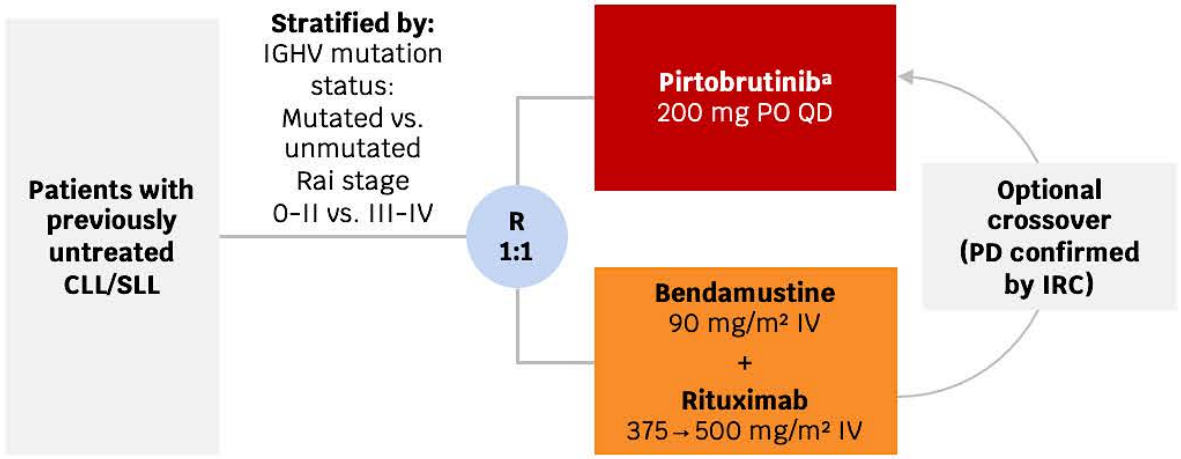
Preferred Term ≥10% of Participants in Either Arm	Pirtobrutinib n = 330		Ibrutinib n = 325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0(0)
Anemia	50 (15.2)	19 (5.8)	46 (14.2)	12 (3.7)
Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)
Diarrhea	44 (13.3)	1 (0.3)	62 (19.1)	4 (1.2)
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)
Dose modifications due to TEAEs				
Reductions	26 (7.9)		59 (18.2)	
Discontinuations	31 (9.4)		35 (10.8)	

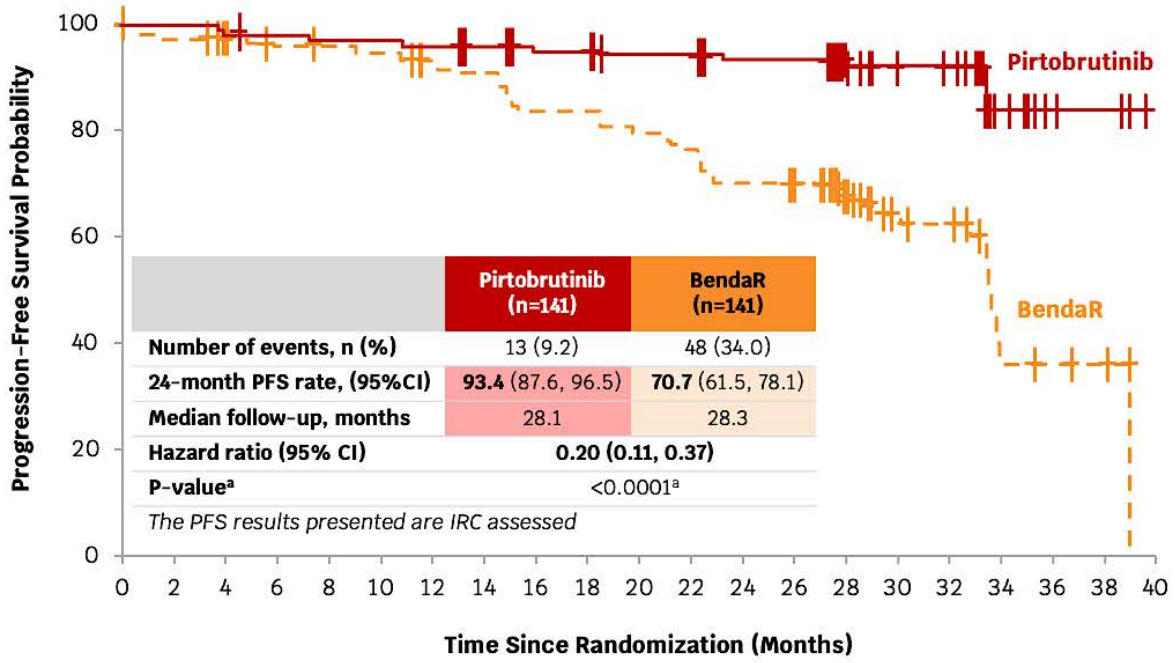
Median time on treatment was 20.5 months with pirtobrutinib and 19.3 months with ibrutinib;
1 patient developed Richter Transformation (RT) on pirtobrutinib; 4 patients developed RT on ibrutinib

Pirtobrutinib was well-tolerated with fewer dose reductions and discontinuations due to TEAEs than ibrutinib

Woyach et al. ASH 2025.

Bruin CLL-313: Pirtobrutinib vs. Chemoimmunotherapy





Number at risk

Pirtobrutinib	141	138	136	135	133	133	131	130	128	128	124	124	119	119	67	56	55	11	5	4	0
BendaR	141	122	120	116	114	111	107	105	96	96	92	87	81	77	50	38	36	6	4	3	0

Key Eligibility Criteria

- Confirmed diagnosis of CLL/SLL, with requirement for therapy (per iwCLL 2018 criteria)
- ECOG PS 0 to 2
- Naïve to systemic therapy for CLL/SLL
- No 17p deletion
- Platelets ≥75 x 10^9/L (≥50 x 10^9/L for patients with evidence of bone marrow infiltrate)
- Hemoglobin ≥8 g/dL
- Absolute neutrophil count ≥0.75 x 10^9/L

Endpoints

Primary

- PFS[e,f] (per iwCLL 2018 criteria)

Key secondary

- OS[f]

Secondary

- ORR[g] (per iWCLL 2018 criteria)
- Safety measures

Pirtobrutinib demonstrated a statistically significant and clinically meaningful PFS improvement, with an 80% reduction in risk of PD or death compared with BendaR

Jurczak, et al. ASH 2025.

Bruin CLL-313: Safety Profile

Preferred Term ≥15% of Participants in Either Arm	Pirtobrutinib (n = 140)		BendaR (n = 132)		EAIR per 100 Person-Years		
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)	Pirtobrutinib Any Grade EAIR[a]	BendaR Any Grade EAIR[a]	EAIR Ratio (95% CI)[b]
Patients with ≥1 TEAE	131 (93.6)	56 (40.0)	117 (86.6)	89 (67.4)	196.7	844.6	0.23 (0.18, 0.30)
Neutropenia	17 (12.1)	10 (7.1)	51 (38.6)	46 (34.8)	5.2	110.0	0.05 (0.03, 0.08)
COVID-19	30 (21.4)	1 (0.7)	12 (9.1)	2 (1.5)	9.9	20.9	0.47 (0.24, 0.92)
Pyrexia	12 (8.6)	0	25 (18.9)	0	3.5	49.1	0.07 (0.04, 0.14)
Upper respiratory tract infection	25 (17.9)	1 (0.7)	9 (6.8)	0	7.7	15.7	0.49 (0.23, 1.05)
Anemia	13 (9.3)	6 (4.3)	21 (15.9)	10 (7.6)	3.8	37.7	0.10 (0.05, 0.20)
Nausea	3 (2.1)	0	31 (23.5)	1 (0.8)	0.8	65.1	0.01 (0.00, 0.04)
Infusion-related reaction	0	0	20 (15.2)	4 (3.0)	0	39.0	NA

Median time on pirtobrutinib treatment was 32.3 months and on BendaR treatment was 5.6 months
Richter's transformation occurred in 1 patient treated with BendaR

Exposure adjusted TEAEs were lower with pirtobrutinib
Discontinuation due to TEAE, including deaths, occurred less frequently with pirtobrutinib (4.3%) vs. BendaR (15.4%)
Dose reduction due to TEAE also occurred less frequently with pirtobrutinib than BendaR (3.6% vs. 31.1%)

Jurczak, et al. ASH 2025.

Cases from the Community

Priya Rudolph, MD, PhD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Discussion Questions

For a patient who is otherwise asymptomatic, do you use the tempo of leukocytosis/lymphocytosis to determine whether to initiate active therapy?

Is there a specific lymph node size or time to doubling of lymph node size that would prompt you to start treatment?

If this patient had high-risk features such as del(17p) or a TP53 mutation, would that have prompted you to initiate treatment any earlier?

For patients with CLL to whom you administer a covalent BTK inhibitor as initial therapy, do you have a preference for a specific one? How do you choose between acalabrutinib and zanubrutinib in this setting?

Agenda

Module 1: Current and Future Role of Continuous Bruton Tyrosine Kinase (BTK) Inhibitor Therapy for Previously Untreated Chronic Lymphocytic Leukemia (CLL) — Dr Fakhri

Module 2: Available and Emerging Approaches to Time-Limited Therapy for Treatment-Naïve CLL — Dr Allan

Module 3: Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Ma

Module 4: Selection and Sequencing of Therapy for R/R CLL — Dr Shadman

Module 5: Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL — Dr Abramson

Weill Cornell Medicine

Available and Emerging Approaches to Time-Limited Therapy for Treatment-Naïve CLL

John N. Allan
Associate Professor of Clinical Medicine
Weill Cornell

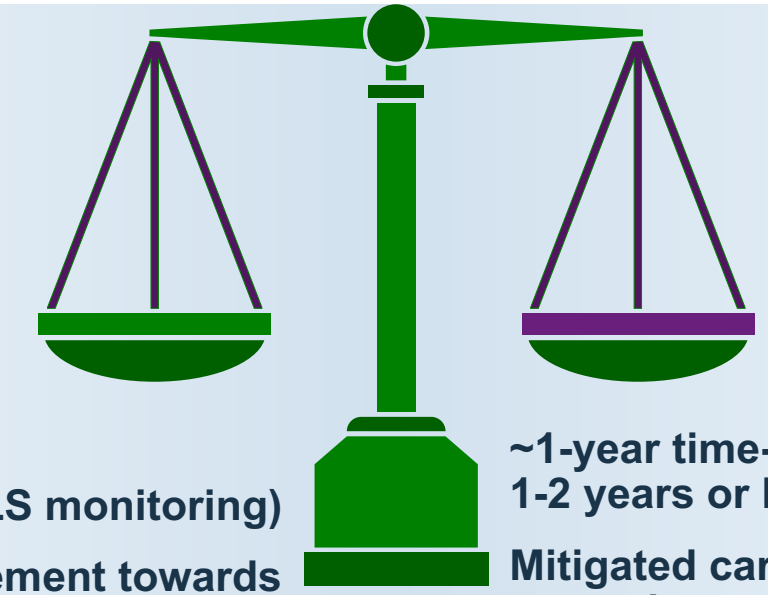
Research To Practice
ASCO 2026 Satellite Symposium
Chicago, IL, May 29, 2026

Learning Objectives

- Incorporate Long-term data with up-front venetoclax/obinutuzumab for CLL
- Review mechanistic rationale for combining BTK inhibitors and venetoclax with and without anti-CD20 antibodies for CLL
- Learn about the efficacy and safety findings from the Phase III CLL17 trial comparing continuous BTK inhibition versus time-limited venetoclax-based doublets
- Evaluate published findings from the Phase III AMPLIFY trial of fixed-duration acalabrutinib in combination with venetoclax with or without obinutuzumab for previously untreated CLL
- Identify other combinations reviewing early data with zanubrutinib in combination with Bcl-2 inhibitors (eg, venetoclax, sonrotoclax) with or without an anti-CD20 antibody in treatment-naïve CLL

Shifting Trends in Management of Frontline CLL

Treat to Progression



Fixed Duration or MRD-Guided Therapy

Convenience (no infusions or TLS monitoring)

Longer-term efficacy data (movement towards second-generation selective agents)

Survival advantage compared to chemoimmunotherapy

Improves versus diminishes immune function

Does not cause clonal hematopoiesis

Indefinite treatment

Potential for cumulative cardiac toxicity

~1-year time-limited therapy (MRD-guided may extend 1-2 years or longer)

Mitigated cardiac risks by discontinuation or use of second-generation BTKi

Less concern over long-term adherence

Potential for cost savings

Time intensive (infusions possible, venetoclax ramp-up monitoring)

Ideal Patient type for Oral Doublet vs Triplet vs. Ven-G or MRD-guided therapy is not defined (possible benefit of Triplet over Doublet in *IGHV* unmutated)

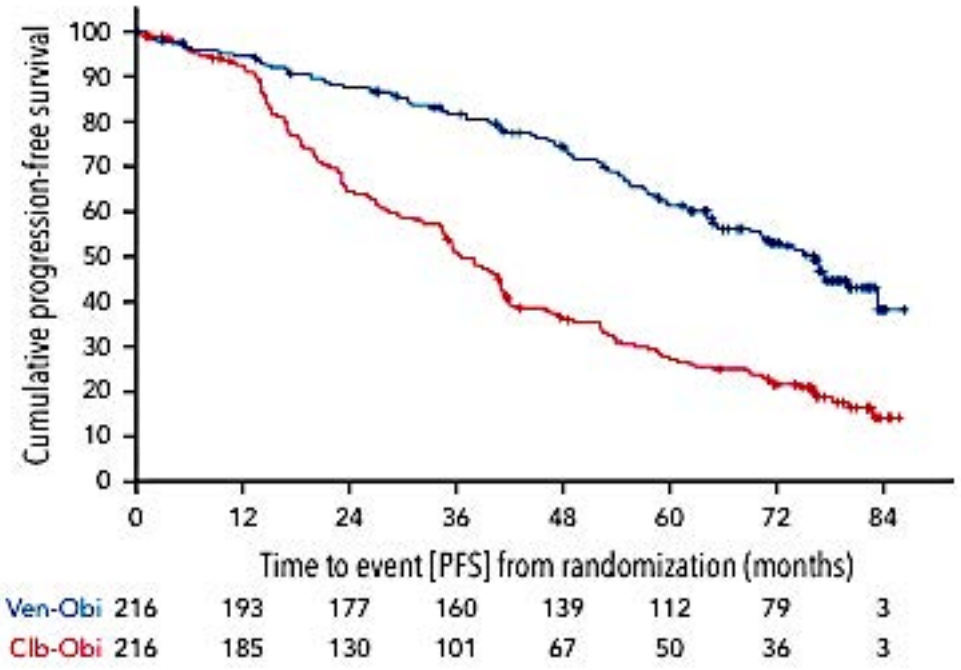
Weill Cornell Medicine

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; *IGHV*, immunoglobulin heavy-chain variable region gene; MRD, measurable residual disease; TLS, tumor lysis syndrome; Ven-G, venetoclax, obinutuzumab; vs, versus.

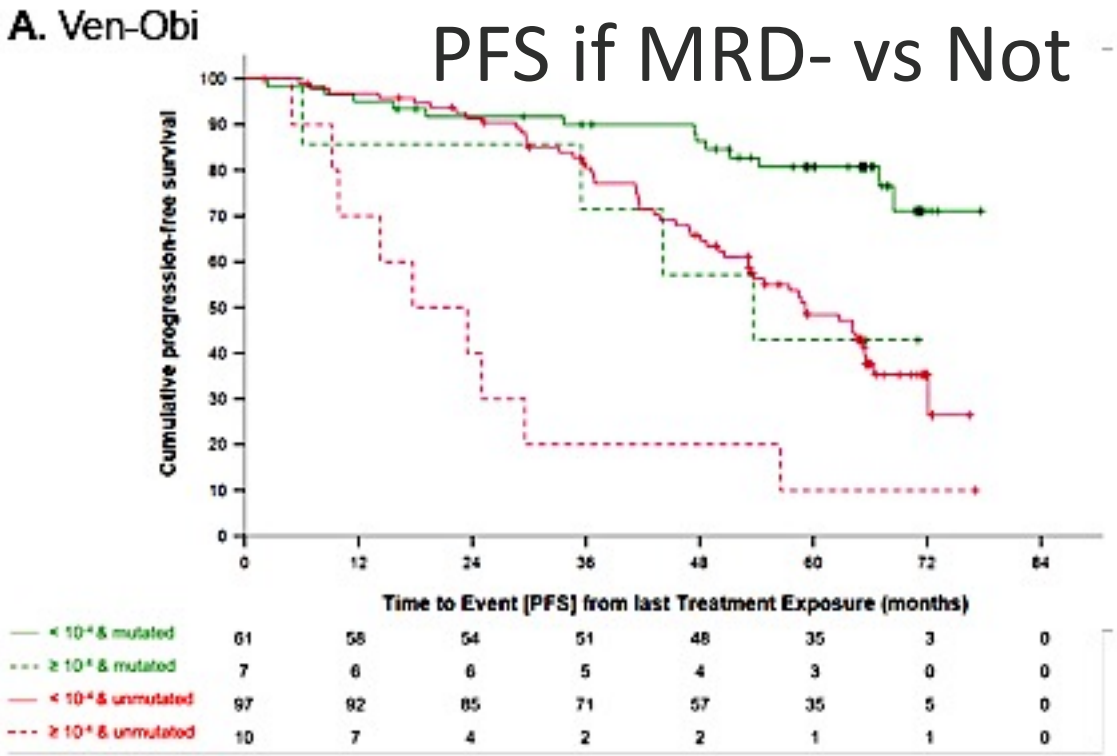
What Have We Learned from CLL14 about our Standard FD Regimen?

A

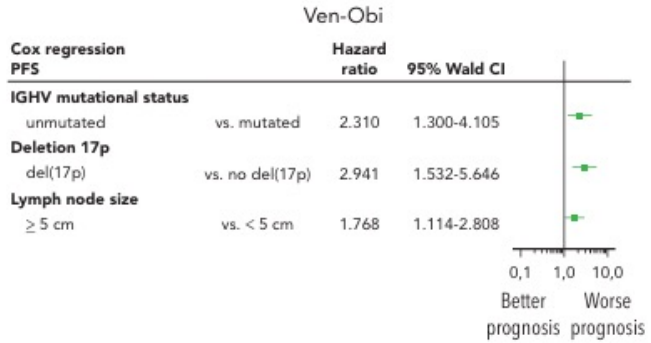
PFS



PFS if MRD- vs Not



PFS Multivariate Analysis

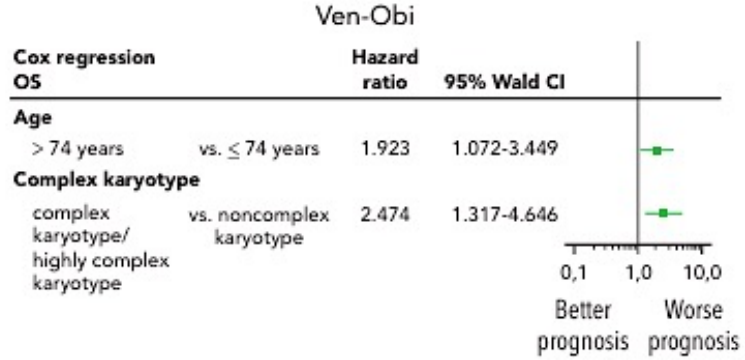


Only 8% remain uMRD at 60 months

80% had mutated IGHV

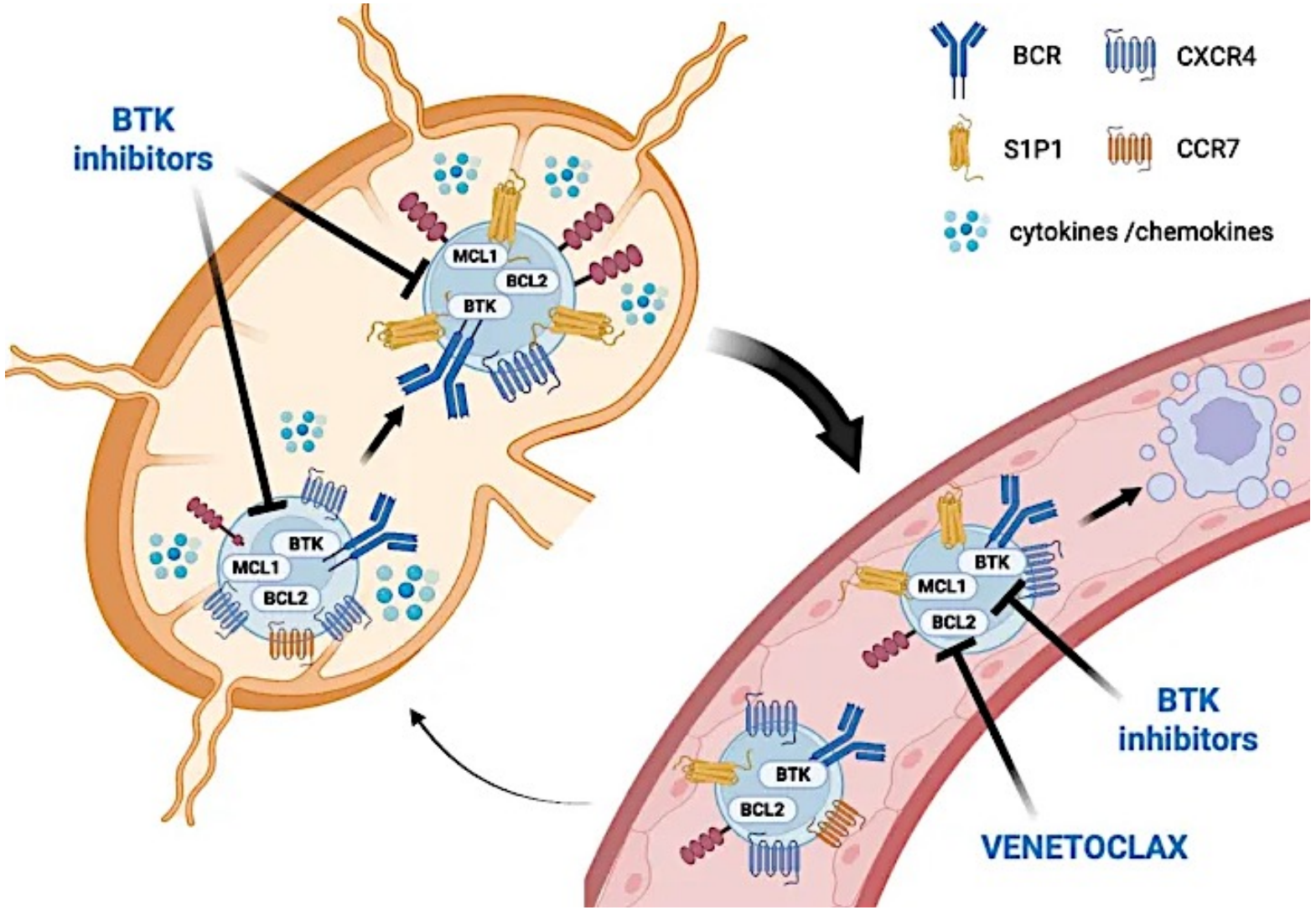
OS Multivariate Analysis

D



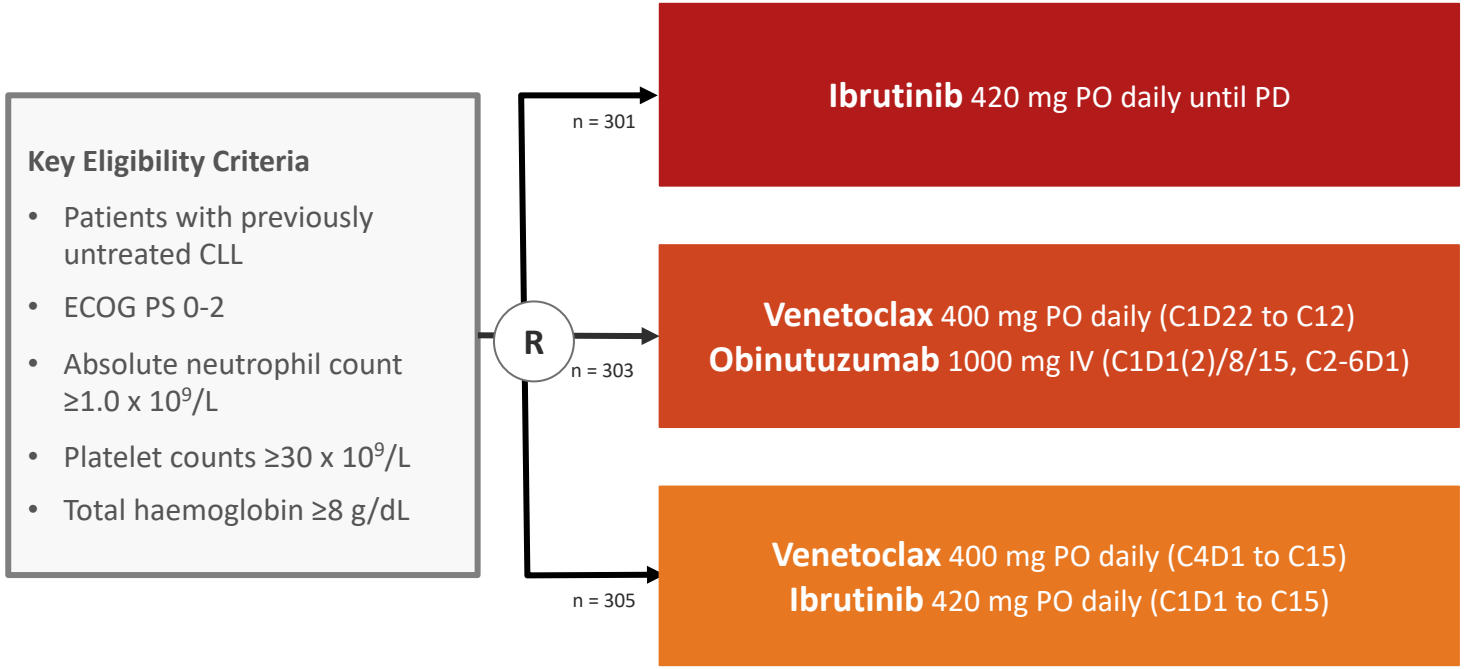
Al Sawaf et al *Blood* (2024) 144 (18): 1924–1935.

Mechanistic Rationale of Potential Synergies of BTK/BCL2 Dual Inhibition



Visetin and Mauro Oncol. Rev., 17 December 2025

CLL17: Phase 3 Trial of Continuous Ibrutinib Monotherapy vs Fixed-Duration Venetoclax-Based Regimens as First-Line Treatments for CLL



Primary Endpoints
• Investigator-assessed PFS
Key Secondary Endpoints
• Minimal residual disease • Response • OS • Safety

- 976 patients screening in 174 sites, across 13 countries
- Patient enrollment from February 2021 to November 2022
- Median observation time: 34.2 months (IQR 30.3-39.3)

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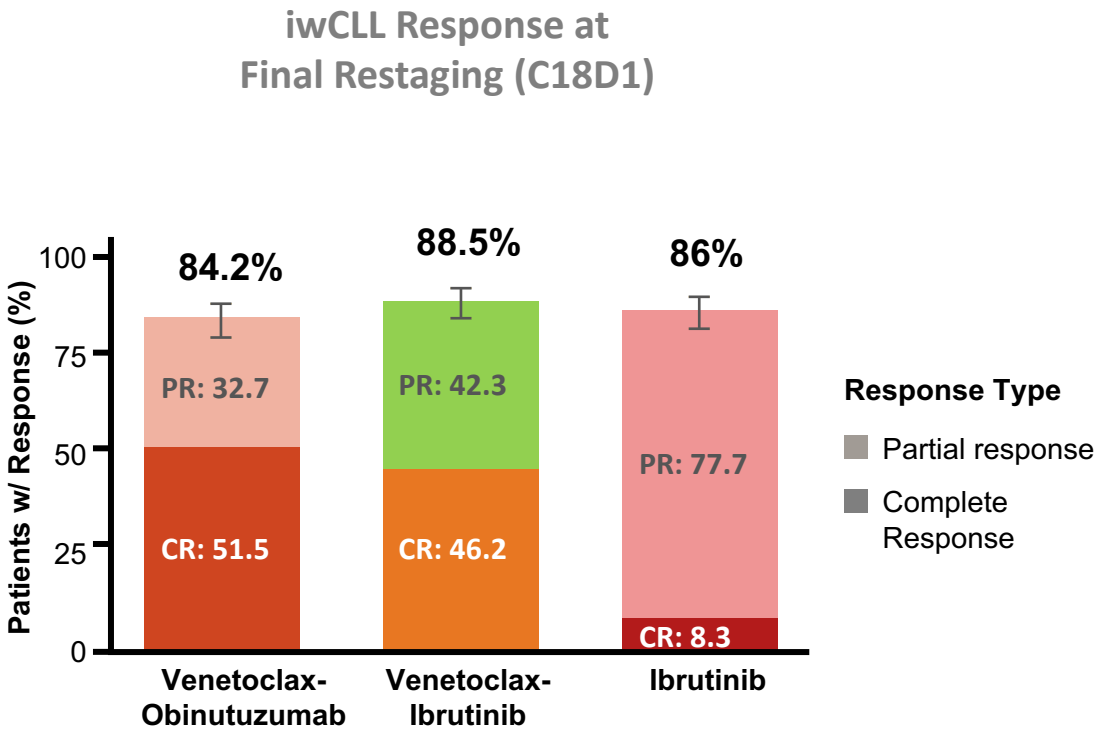
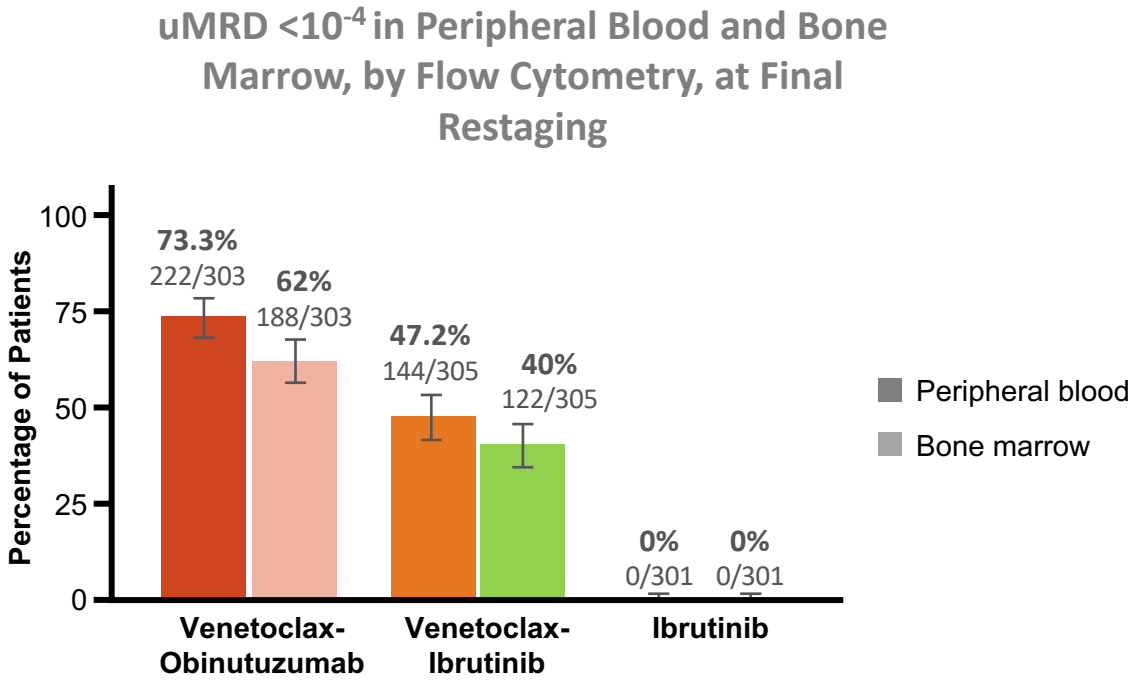
CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; IV, intravenous; PD, progressive disease; PFS, progression-free survival; PO, oral administration; OS, overall survival.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

CLL17: Response to Treatment





Weill Cornell Medicine

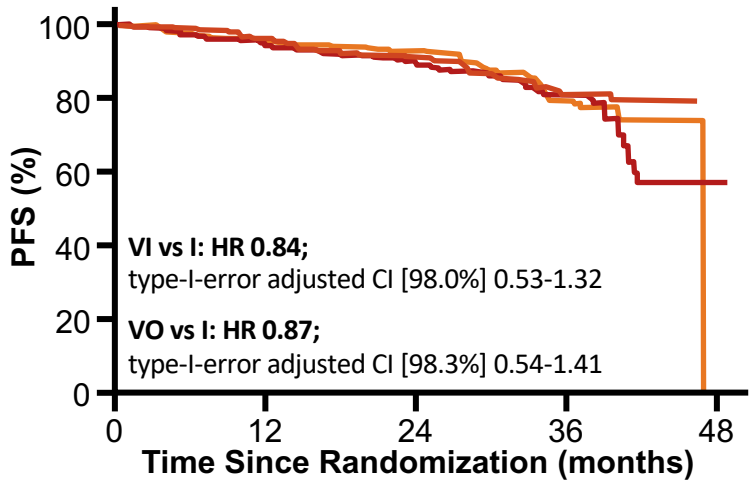
iwCLL, international workshop on CLL; uMRD, undetectable measurable residual disease.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

CLL17: Survival Across Treatment Arms

PFS by Treatment Arm



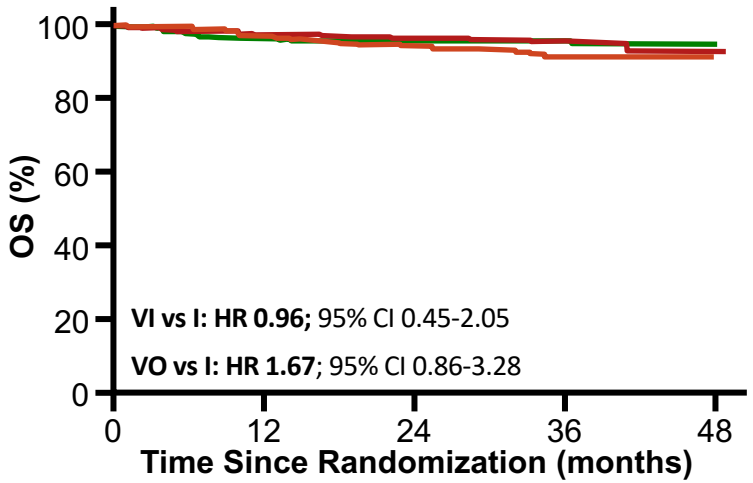
3-year PFS
VO 81.1%
I 81.0%
VI 79.4%

No. at risk

VO	303	278	256	77	0
VI	305	278	267	82	0
I	301	267	243	94	1

	VO	I	VI
PD	25	46	37
Death	21	11	13

OS by Treatment Arm



3-year OS
VO 91.5%
I 95.7%
VI 96.0%

No. at risk

VO	303	284	269	102	0
VI	305	281	279	114	1
I	301	284	276	141	2

Cause of death	VO	I	VI
Infection	12 (7 Covid)	3	7 (2 Covid)
Cardiovascular	5	5	3
PD/RT	1	0	0
SPM	4	2	2
Other	0	4	1
Total	**22**	**14**	**13**

Fixed-duration treatment with venetoclax–obinutuzumab or venetoclax–ibrutinib was noninferior to continuous ibrutinib with regards to investigator-assessed PFS.

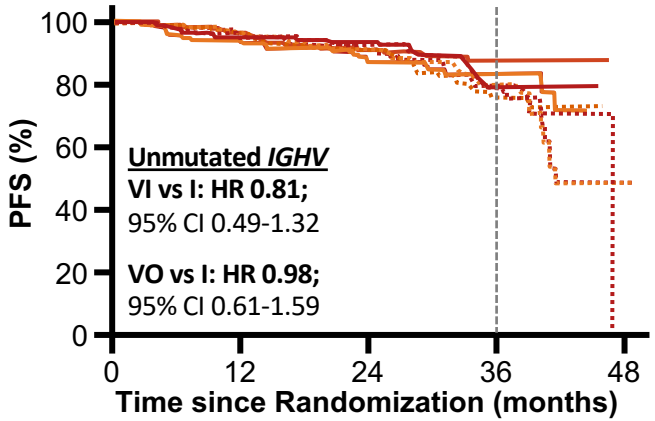
CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; I, ibrutinib; no. number; OS, overall survival; PD, progressive disease; PD/RT, progressive disease/Richter transformation; PFS, progression-free survival; SPM, second primary malignancies; VI, venetoclax–ibrutinib; VO, venetoclax–obinutuzumab.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

CLL17: PFS According to *IGHV* and *TP53*/del17p Status

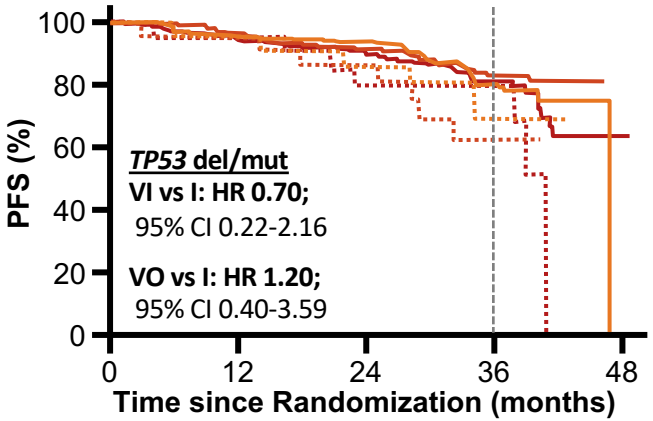
PFS According to *IGHV* status



3-year PFS	
I, u*IGHV*	79.7%
I, m*IGHV*	83.5%
VI, u*IGHV*	78.9%
VI, m*IGHV*	80.0%
VO, u*IGHV*	**75.8%**
VO, m*IGHV*	**87.6%**

No. at risk					
VO, unmutated	171	156	142	40	0
VO, mutated	129	119	111	36	0
VI, unmutated	172	157	151	50	0
VI, mutated	129	117	112	32	0
I, unmutated	171	156	145	55	1
I, mutated	126	108	95	37	0

PFS According to *TP53*/del17p status



3-year PFS	
I, *TP53*del/mut	**79.4%**
I, *TP53*-WT	**81.0%**
VI, *TP53*del/mut	69.0%
VI, *TP53*-WT	80.1%
VO, *TP53*del/mut	62.0%
VO, *TP53*-WT	82.7%

No. at risk					
VO, del/mut	23	21	16	5	0
VO, WT	280	257	240	72	0
VI, del/mut	25	20	18	4	0
VI, WT	279	257	248	78	0
I, del/mut	21	19	15	7	0
I, WT	279	247	227	87	1

CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; I, ibrutinib; *IGHV*, immunoglobulin heavy-chain variable region gene; m*IGHV*, mutated *IGHV;* PFS, progression-free survival; *TP53*del/mut, *TP53* deletion and/or mutation; u*IGHV*, unmutated *IGHV*; VI, venetoclax–ibrutinib; VO, venetoclax–obinutuzumab; WT, wild type.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

CLL17: Selected Adverse Events of Interest

	VO	VI	I
Safety population – n (%)	295	303	298
Blood and lymphatic system disorders	174 (59.0)	130 (42.9)	85 (28.5)
Febrile neutropenia	14 (4.7)	7 (2.3)	0 (0)
Neutropenia	155 (52.5)	110 (36.3)	49 (16.4)
Cardiac disorders	41 (13.9)	72 (23.8)	103 (34.6)
Atrial fibrillation	11 (3.7)	38 (12.5)	50 (16.8)
Gastrointestinal disorders	176 (59.7)	225 (74.3)	189 (63.4)
Diarrhea	80 (27.1)	143 (47.2)	104 (34.9)
Infections and infestations	225 (76.3)	243 (80.2)	238 (79.9)
COVID-19	113 (38.3)	128 (42.2)	117 (39.3)
Pneumonia	41 (13.9)	28 (9.2)	40 (13.4)

Grade 3-5 Infections	**VO**	**VI**	**I**
	295	**303**	**298**
Infections and infestations	103 (34.9)	76 (25.1)	74 (24.8)
COVID-19	47 (15.9)	26 (8.6)	20 (6.7)
Pneumonia	29 (9.8)	22 (7.3)	22 (7.4)

I, ibrutinib; VI, venetoclax–ibrutinib; VO, venetoclax–obinutuzumab.

Al-Sawaf, et al. *N Engl J Med*. Published online December 6, 2025. doi:10.1056/NEJMoa2515458

*Venetoclax + ibrutinib is not yet FDA-approved

AMPLIFY: Firstline Treatment of CLL With Acalabrutinib + Venetoclax[1,2]

Key Inclusion Criteria
- Age ≤ 18 years
- TN CLL requiring treatment per iwCLL 2018 criteria
- 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, phase 3

N = 867

R 1:1:1

- **AV (14 cycles)** n = 291
- **AVO (14 cycles)** n = 286
- **FCR/BR (6 cycles)** n = 290

Crossover not built into protocol

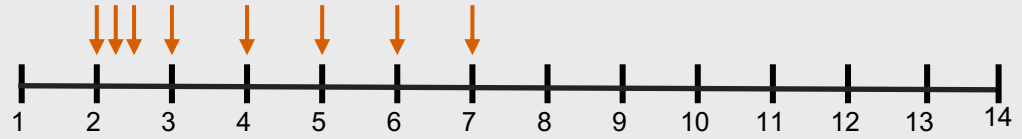
Primary endpoints
- IRC-assessed PFS (AV vs FCR/BR)
- If primary endpoint is met, secondary endpoints tested in fixed sequential hierarchy
- 1. IRC-PFS (AVO vs FCR/BR)
- 2. uMRD (AV vs FCR/BR)
- 3. uMRD (AVO vs FCR/BR)
- 4. OS (AV vs FCR/BR)
- 5. OS (AVO vs FCR/BR)

AV and AVO dosing schedule

Acalabrutinib 100 mg PO BID (cycles 1–14)

Venetoclax 400 mg PO QD (cycles 3–14)

Obinutuzumab (AVO only) 1000 mg (cycles 2–7)



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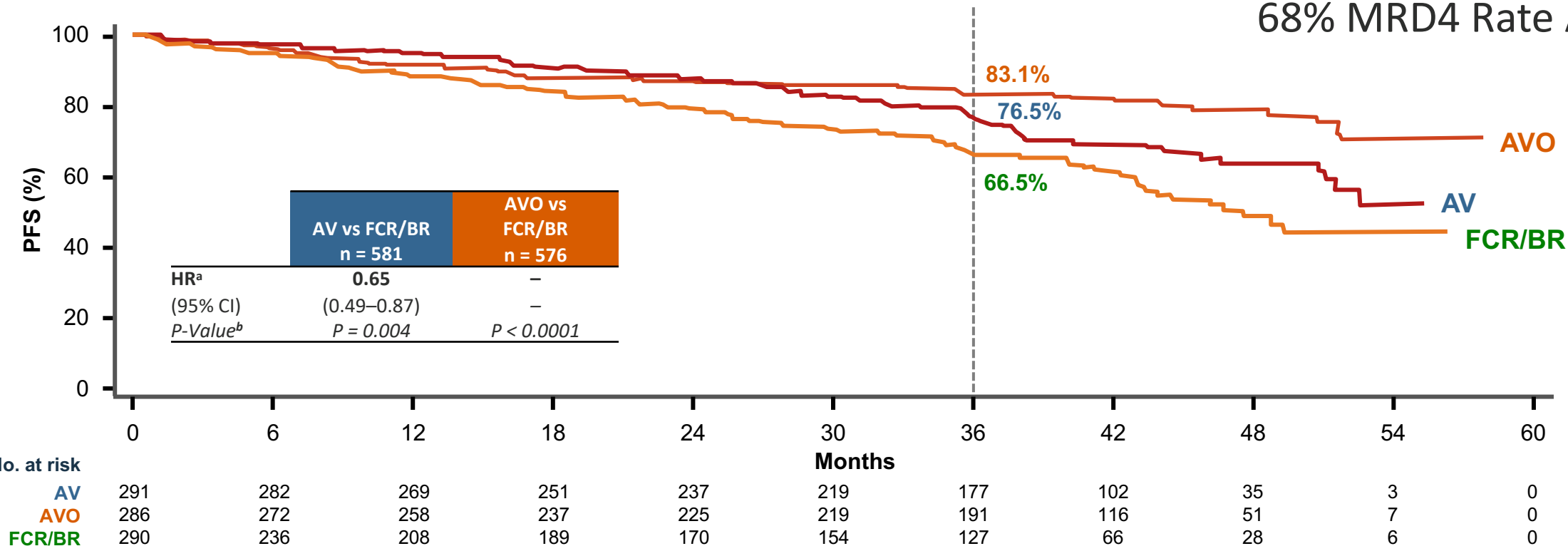
1. Brown JR, et al. *Blood.* 2024;144 (Supplement 1):1009. 2. Brown JR, et al. *N Engl J Med.* 2025 Feb 20;392(8):748-762.

AMPLIFY: IRC-Assessed PFS[1,2]

EOT
34% MRD4 Rate AV
68% MRD4 Rate AVO



No. at risk

AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR/BR	290	236	208	189	170	154	127	66	28	6	0

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

ITT population. Median follow-up from randomization: 40.8 months (range, 0-59 months).

[a]Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test. A hazard ratio and corresponding 95% confidence interval is not shown for any comparison that violated the proportional-hazards assumption.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

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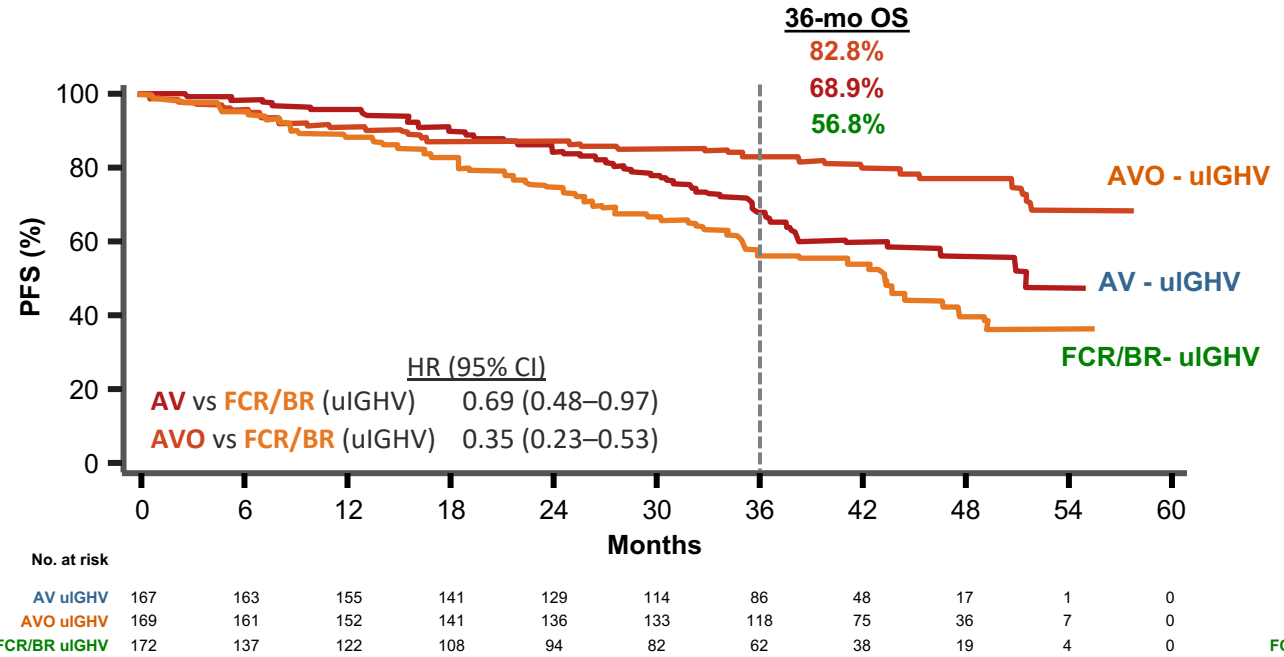
1. Brown JR. *N Engl J Med*. 2025;392(8):748-762. 2. Brown J, et al. ASH 2024. Oral session 1009.

AMPLIFY: PFS and IGHV Status[1,2]

PFS in the u*IGHV* Subgroup

	AVO - uIGHV	AV - uIGHV	FCR/BR - uIGHV
Events/N	36/169	61/167	67/172
Median (mo)	NR	51.5	43.3

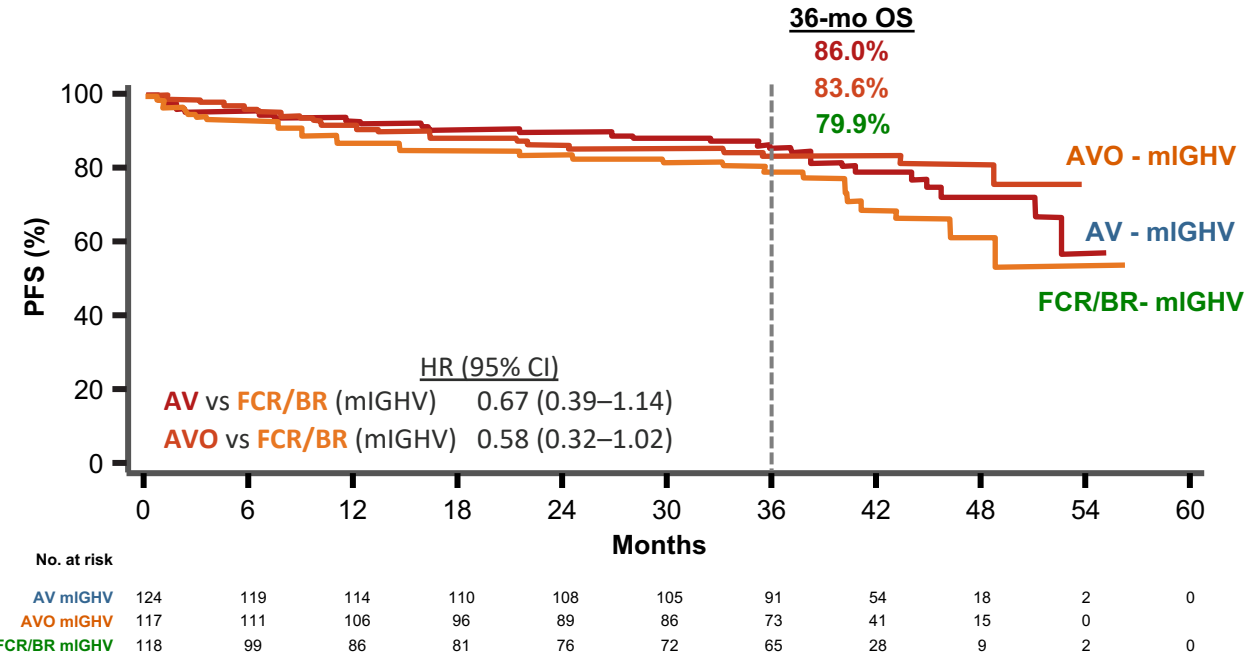


No. at risk

AV uIGHV	167	163	155	141	129	114	86	48	17	1	0
AVO uIGHV	169	161	152	141	136	133	118	75	36	7	0
FCR/BR uIGHV	172	137	122	108	94	82	62	38	19	4	0

PFS in the m*IGHV* Subgroup

	AVO - mIGHV	AV - mIGHV	FCR/BR - mIGHV
Events/N	20/117	28/124	28/118
Median (mo)	NR	NR	NR



No. at risk

AV mIGHV	124	119	114	110	108	105	91	54	18	2	0
AVO mIGHV	117	111	106	96	89	86	73	41	15	0	
FCR/BR mIGHV	118	99	86	81	76	72	65	28	9	2	0

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1. Brown JR. *N Engl J Med*. 2025;392(8):748-762. 2. Brown J, et al. ASH 2024. Oral session 1009.

AMPLIFY: AESI

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias[a]	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	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)[b]	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Data are n (%). ECIs listed by category and sub-category.
[a]Ventricular tachyarrhythmias consisted of ventricular extrasystoles (n=1 in AV arm; n=2 in AVO arm) and ventricular tachycardia (n=1 each in AV and AVO arms).
[b]Includes neutropenia, neutrophil count decreased, and febrile neutropenia.
AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECI, event of clinical interest; FCR, fludarabine-cyclophosphamide-rituximab.

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

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Brown et al NEJM 2025

FDA Approves Acalabrutinib with Venetoclax for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Press Release: February 19, 2026

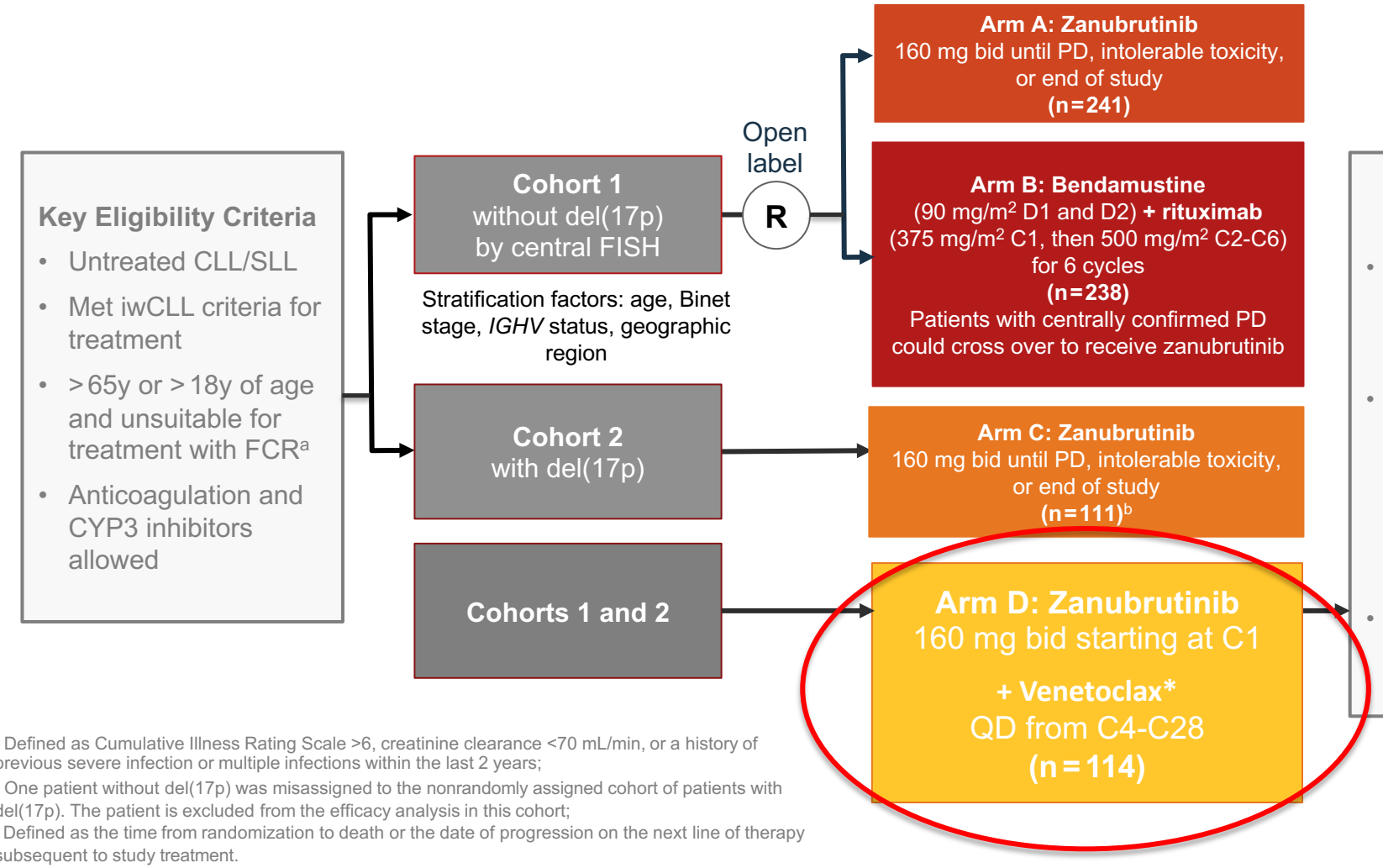
"On February 19, 2026, the Food and Drug Administration approved acalabrutinib tablets and capsules in combination with venetoclax for adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Efficacy was evaluated in AMPLIFY (NCT03836261), a randomized, multicenter trial in adult patients previously untreated for CLL without del(17p) or TP53 mutation. Patients were randomized to receive acalabrutinib and venetoclax (AV) or Investigator's choice of chemotherapy (fludarabine plus cyclophosphamide plus rituximab [FCR] or bendamustine plus rituximab [BR]).

The major efficacy outcome measure was progression-free survival (PFS) as assessed by independent review committee for the AV arm versus the investigator's choice arm (FCR/BR). The median duration of PFS follow-up was 42.6 months. Median PFS was not estimable (NE) (95% CI: 51.1, NE) in the AV arm and 47.6 months (95% CI: 43.3, NE) in the FCR/BR arm (Hazard ratio 0.65 [95% CI: 0.49, 0.87]; *p*-value 0.0038). With a median follow-up of 41.0 months, there were 18 (6%) deaths in the AV arm and 42 (14%) in the FCR/BR arm."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-acalabrutinib-venetoclax-chronic-lymphocytic-leukemia-or-small-lymphocytic-lymphoma

SEQUOIA Arm D: Phase 3 Trial of Zanu/Ven Combinations as First-line Treatment for CLL/SLL



Disease Assessments

- Response assessments conducted every 3 cycles until C28 and every 6 cycles after C28 until PD
- Bone marrow MRD repeated every 12-24 weeks in pts with CR/CRi and two consecutive PB-undetectable MRDs ~12 wks apart, optional after C27 for pts with detectable MRD in BM
- TLS at baseline and pre-venetoclax initiation

Endpoints for Arm D

- PFS
- ORR
- OS
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety

NCT03336333
Statistical analysis: Efficacy endpoints analyzed using ITT analysis and the per protocol analysis set. Safety was assessed in all patients who received >1 dose of treatment.

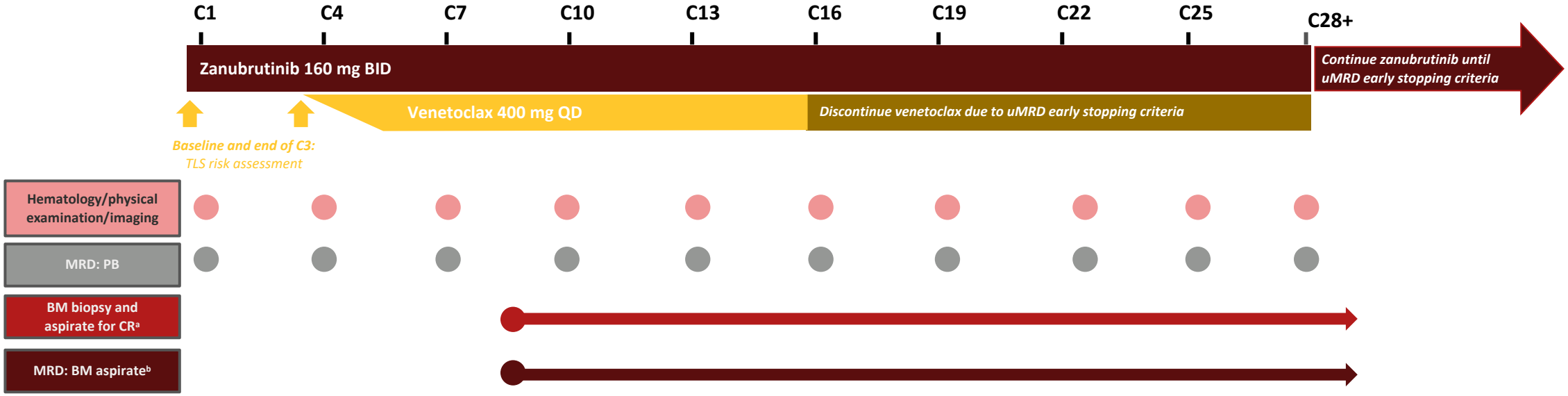
[a] Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years;
[b] One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort;
[c] Defined as the time from randomization to death or the date of progression on the next line of therapy subsequent to study treatment.

BID, twice daily; BM, bone marrow; C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; CRi, complete response; FCR, fludarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization; *IGHV*, immunoglobulin heavy chain variable region; ITT, intention-to-treat; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; QD, once daily; TLS, tumor lysis syndrome; uMRD4, undetectable minimal residual disease at 10^{-4} sensitivity.

*This regimen is not yet FDA-approved

1. Tam, et al. *Lancet Oncol*. 2022;23(8):1031-1043. 2. Shadman, et al. 17th ICML. June 13-17, 2023; Abstract 154. 3. Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

SEQUOIA Arm D: Schedule



Median follow-up: 38.5 months

uMRD-guided stopping criteria

All conditions must be met:

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD <1x10^{-4} (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received:
   - i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

aBM biopsy and aspirate are required to confirm a suspected CR/Cri (BM biopsy collection timepoint not defined per protocol), starting after cycle 9 and then annually if needed. bPatients with confirmed CR/CRi and 2 consecutive PB-uMRD results at least 12 weeks apart.

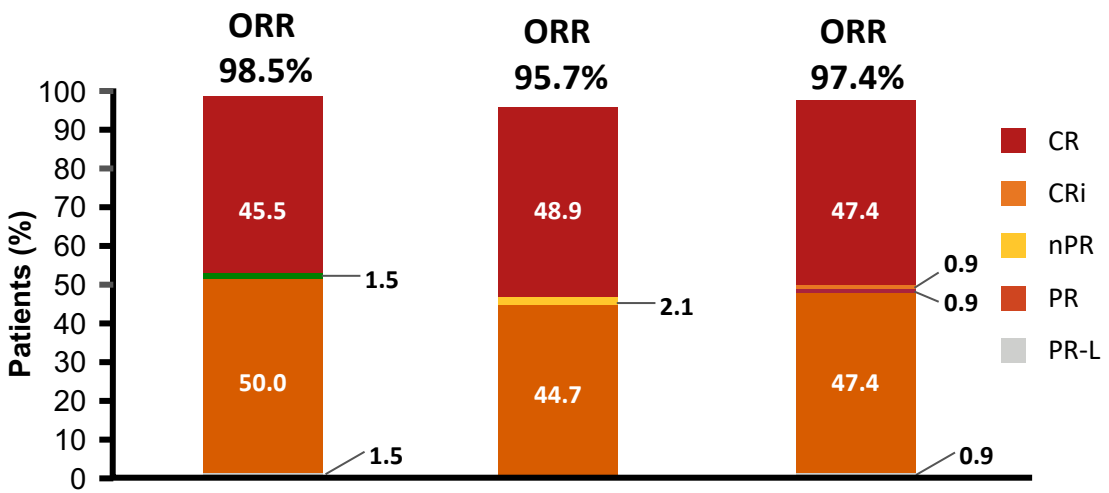
BID, twice daily; BM, bone marrow; C, cycle; CR, complete response; CRi, complete response with incomplete hematologic recovery; MRD, minimal residual disease; PB, peripheral blood; QD, once daily; TLS, tumor lysis syndrome; uMRD, undetectable minimal residual disease; uMRD4, undetectable MRD at 10^{-4} sensitivity

*This regimen is not yet FDA-approved

Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

SEQUOIA Arm D: Response and MRD Rates

Response Rates



	With del(17p) and/or *TP53*mut (n = 66)	Without del(17p) and/or *TP53*mut (n = 47)	All patients (n = 114)
Median study follow-up, Months (range)	**38.7** (0.4-58.0)	**29.6** (0.6-31.9)	**31.2** (0.4-58.0)

Peripheral Blood uMRD Rates by Genomic Risk and Treatment Duration

Outcome	Overall	del(17p) and/or *TP53*mut	No del(17p)/ *TP53*mut	Unmutated *IGHV*	Mutated *IGHV*
Best peripheral blood uMRD rate	60%	59%	62%	-	-
uMRD after 15 cycles	-	15%	40%	23%	33%
uMRD after 27 cycles	-	38%	36%	40%	29%

Treatment Discontinuation and Durability

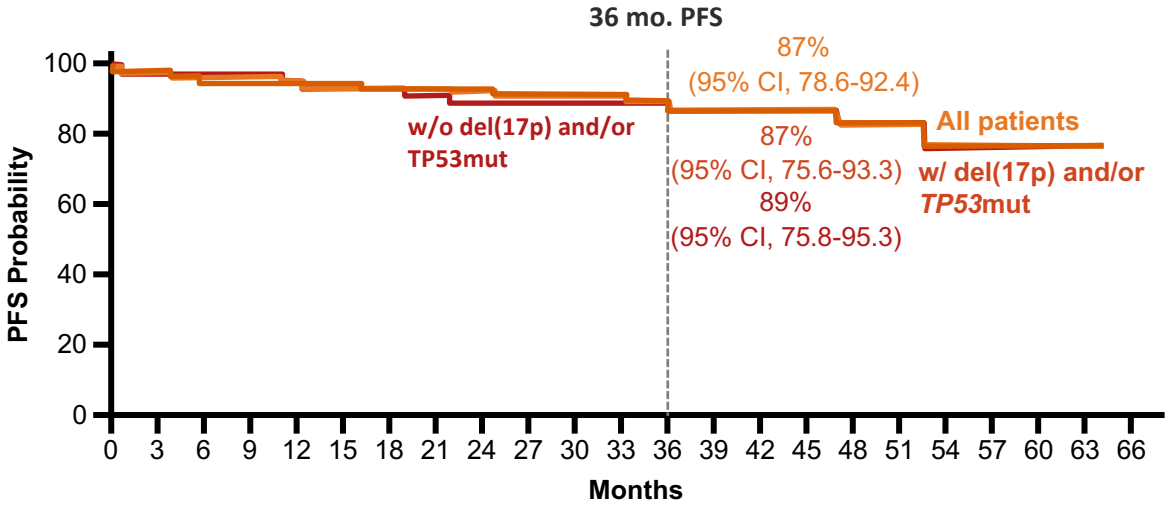
Measure	Value
Patients meeting early stopping criteria	13/114
Patients meeting criteria to stop ZV	42/114
Patients maintaining uMRD after discontinuation (18-month follow-up)	92-100%

CR, complete response; CRi, complete response with incomplete hematopoietic recovery; EOS, end of study; *IGHV*, immunoglobulin heavy-chain variable region gene; MRD, minimal residual disease; mut, mutation; nPR, nodular partial response; ORR, overall response rate; PB-uMRD, peripheral blood-undetectable minimal residual disease; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; uMRD, undetectable minimal residual disease; TP53, tumor protein p53; ZV, zanubrutinib + venetoclax.

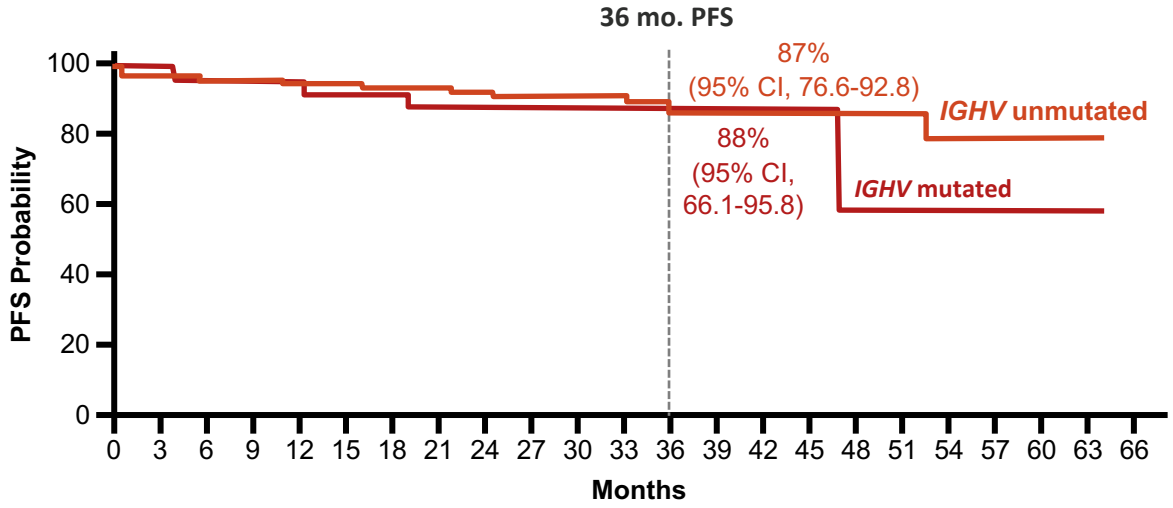
*This regimen is not yet FDA-approved

SEQUOIA Arm D: PFS

Overall Population and Patients with and without del(17p) and/or *TP53*mut



Unmutated and Mutated *IGHV*



- Median study follow-up
  - With del(17p) and/or *TP53*mut: 46.1months
  - Without del(17p) and *TP53*mut: 36.9 months

Zanu + ven demonstrated durable PFS, with comparable outcomes in patients harboring del(17p)/*TP53* mutations.

CI, confidence interval; *IGHV*, immunoglobulin heavy-chain variable region gene; ITT, intention-to-treat; mut, mutation; PFS, progression-free survival; *TP53*, tumor protein p53; ven, venetoclax; w/o, without; zanu, zanubrutinib.

Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

*This regimen is not yet FDA-approved

SEQUOIA Arm D: Safety

TEAEs in >15% of Patients

Any TEAE	All Patients (N=114)	
	Any Grade, n (%)	Grade ≥3, n (%)[a]
COVID-19	63 (55)	2 (2)
Diarrhea	49 (43)	7 (6)
Contusion	37 (33)	0
Nausea	36 (32)	0
Neutropenia/neutrophil count decreased	30 (26)	27 (24)
Fatigue	28 (25)	0
Arthralgia	24 (21)	0
Upper respiratory tract infection	22 (19)	1 (1)
Cough	21 (18)	0
Hypertension	18 (16)	10 (9)

TEAEs of Special Interest

	All Patients (N=114)	
	Any Grade, n (%)	Grade ≥3, n (%)
Any TEAE of special interest	111 (97)	50 (44)
Infections	96 (84)	14 (12)[b]
Grade 3	-	13 (11)
Hemorrhage	61 (54)	2 (3)
Neutropenia	31 (27)	27 (24)
Second primary malignancies	22 (19)	6 (5)
Skin cancers	15 (13)	0
Hypertension	18 (16)	10 (9)
Thrombocytopenia	13 (11)	5 (4)
Anemia	10 (9)	1 (1)
Major hemorrhage	4 (4)	3 (3)
Atrial fibrillation and flutter	3 (3)	2 (2)
Opportunistic infections	3 (3)	0
Tumor lysis syndrome	1 (1)	0

Zanubrutinib + venetoclax had a favorable safety profile. Five deaths occurred in this study due to AEs (none were treatment related); no new events were reported at this follow-up at 38.5 months.

[a]TEAEs in ≥5% of patients are reported. [b]Grade 5 infection occurred in one patient (pneumonia staphylococcal and septic shock).

AE, adverse event; TEAE, treatment-emergent adverse event.

Shadman, et al. ASCO 2025. May 30 – June 3, 2025. Chicago, IL. Abstract 7009.

*This regimen is not yet FDA-approved

High Level Summary of Reported Sonrotoclax Studies in 1L

Trial	Drugs	Treatment Duration	Longest Follow-up	ORR/CR	MRD4/MRD6 EOT or EOT+3	PFS (uIGHV/mIGHV)	OS	Infections Gr3 or Greater
BGB-11417-101	SO	15 cycles	12m	94%/40%	83%/75%	NR	NR	9% (COVID)
BGB-11417-101	ZS	TTP	19.3m	100%/42%	91%/NR	100%	NR	1% COVID No Gr3 or greater URTI

CELESTIAL: ZS vs VenO in 1L CLL is Enrolled and awaiting endpoint data maturity

Session Summary

- CLL17 currently at 3 years of follow-up (1.5 years after cessation) no differences between groups or approaches in PFS or OS.
    - We are starting to see some separation in curves in high risk CLL favoring continuous therapy in terms of PFS.
    - mIGHV has highest PFS rate at 3 years with VenO

- A+V is now approved in the US as a second FD option
    - uIGHV suggests a benefit from Triplet Approaches in terms of PFS over AV
    - mIGHV may still benefit from attaining MRD or using antiCD20 but may not require Triplet therapy to achieve the optimal outcome
    - Current evidence at short follow-up shows no differences in outcome based on MRD status with oral doublets thus it remains unclear how important this endpoint is for mIGHV

- Zanubrutinib/BCL2 combinations either as FD or MRD Guided Approaches are safe effective and entered into guidelines
    - Sonrotoclax is now approved in MCL on accelerated basis and demonstrates unique characteristics and MRD kinetics as compared to venetoclax
- Currently any approach is appropriate, but FD approaches are increasingly considered, still important to review preferences, comorbidities, and philosophy when choosing a therapy

Cases from the Community

Susmitha Apuri, MD

Neil Love, MD

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Discussion Questions

How would you approach tumor lysis syndrome (TLS) mitigation and monitoring for this patient?

How, if at all, does your approach to TLS mitigation and monitoring differ for patients receiving venetoclax in combination with acalabrutinib versus those receiving venetoclax in combination with obinutuzumab?

How do you approach hydration, and in which scenarios, if any, do you employ rasburicase?

How, if at all, does your algorithm for monitoring for and managing adverse events beyond TLS differ for patients receiving combination therapy with a BTK inhibitor and venetoclax versus those receiving either agent alone?

Once you've made the decision to administer up-front acalabrutinib/venetoclax, for which patients, if any, do you also incorporate an anti-CD20 antibody?

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Cases from the Community

Stephen “Fred” Divers, MD

Susmitha Apuri, MD

Neil Love, MD

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Discussion Questions

Particularly for patients who are older and/or have significant comorbidities, how do you choose between single-agent continuous BTK inhibitor therapy and a time-limited combination strategy? For patients who prefer time-limited therapy, how do you decide between venetoclax/obinutuzumab and venetoclax/acalabrutinib?

What initial treatment would you most likely recommend for Dr Apuri's patient with significant ischemic cardiomyopathy?

Which pretreatment cardiac comorbidities or cardiac incidents do you believe represent an absolute contraindication to the use of BTK inhibitor therapy? Does this differ at all for acalabrutinib versus zanubrutinib? What about for the covalent BTK inhibitors versus pirtobrutinib?

Agenda

Module 1: Current and Future Role of Continuous Bruton Tyrosine Kinase (BTK) Inhibitor Therapy for Previously Untreated Chronic Lymphocytic Leukemia (CLL) — Dr Fakhri

Module 2: Available and Emerging Approaches to Time-Limited Therapy for Treatment-Naïve CLL — Dr Allan

Module 3: Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Ma

Module 4: Selection and Sequencing of Therapy for R/R CLL — Dr Shadman

Module 5: Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL — Dr Abramson

Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Populations

Shuo Ma, MD, PhD
Professor of Medicine
Division of Hematology-Oncology
Department of Medicine
Robert H Lurie Comprehensive Cancer Center
Northwestern University
Chicago, Illinois

Considerations of BTKi vs Bcl-2i

	BTKi	BCL2i
Advantages	• Effective in all prognostic groups • Easy to initiate • Low Risk of TLS	• Limited duration therapy • Low toxicity once ramped up
Disadvantages	• Continuous therapy • **Cardiovascular side-effects** • **Bleeding side-effects**	• IgHV and *TP53* aberrant ↓PFS • **TLS risk**

Drug interactions

- CYP3A Inhibitors (eg strong azoles): dose reduce zanubrutinib, ibrutinib, venetoclax; hold acalabrutinib.
- PPI: no longer an issue with tablet formulation of acalabrutinib.
- Avoid concomitant dual anti-platelet inhibition with any BTKi.
- Apixaban is the preferred anticoagulant in patients on BTKi.

BCL2i = B-cell lymphoma 2 inhibitor; BTKi = Bruton tyrosine kinase inhibitor; TLS = tumor lysis syndrome

Adapted from Tam C. *Hematology Am Soc Hematol Educ Program.* 2021:55-58.

Content courtesy of Professor Constantine Tam, MBBS, MD

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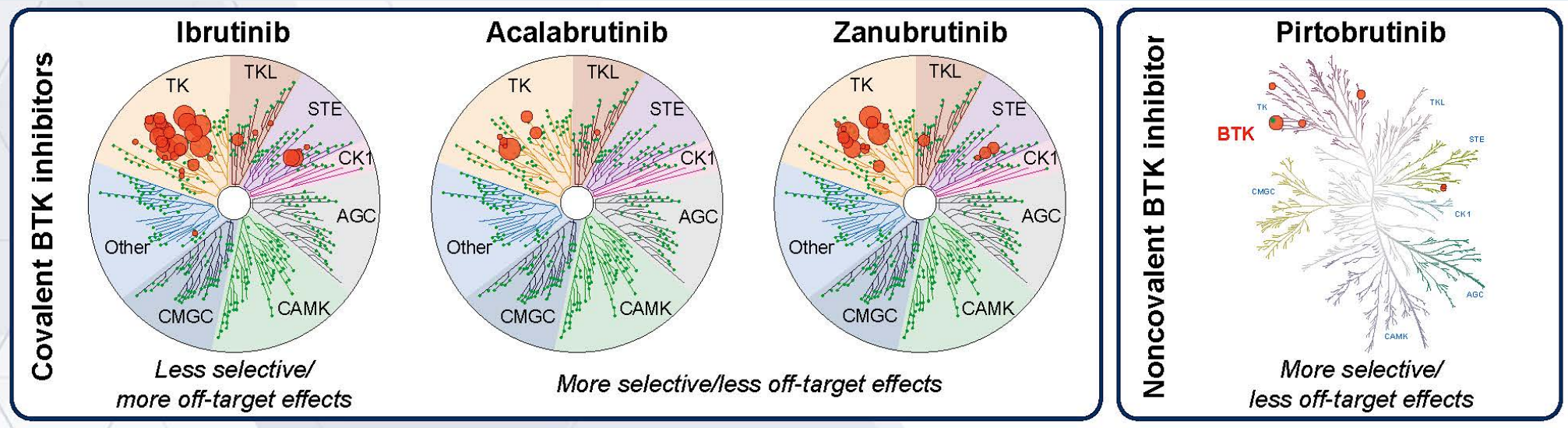
Key Differences Between BTKis

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
BTK binding	Covalent, C481	Covalent, C481	Covalent, C481	Reversible, ATP pocket, Distant from C481
Half-life	6 hours	1 hour	4 hours	20 hours >90% BTK inhibition
BTK Y223 autophosphorylation	Inhibited			Inhibited
BTK Y551 phosphorylation	No effect			Inhibited (maintenance of closed conformation)
Mechanisms of resistance	**BTK C481S:** Common	**BTK C481S:** Reported	**BTK C481S:** Reported	**Effective against C481S**

ATP, adenosine triphosphate; HCK, hematopoietic cell kinase. *With the exception of RT, in which T474I, T474S, and L528W have been reported at progression on ibrutinib.20 †For ibrutinib, acalabrutinib, and zanubrutinib, derived from review by Estupinan et al, ´ 12 >80% inhibition at clinical doses; for pirtobrutinib, listed kinases have

Thompson, PA, et al. *Blood* 2023; 141(26):3137-3142.

More selective BTKi have fewer off-target effects, leading to significantly improved safety profiles



Potential off-target effects include:

Content courtesy of Matthew S Davids, MD, MMSc

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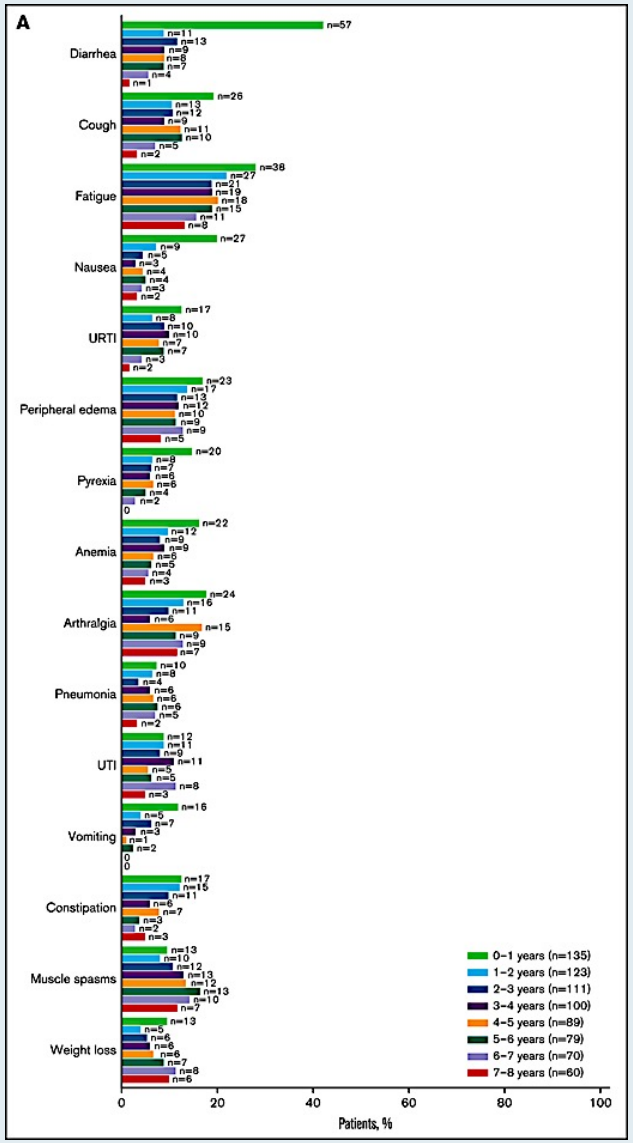
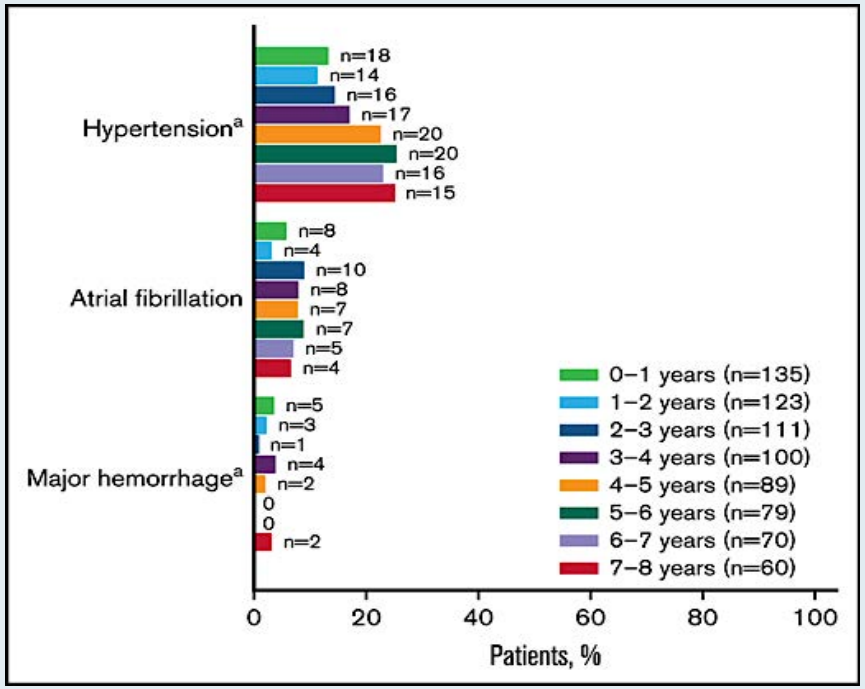
Discontinuation rates with ibrutinib are relatively high, and are due mostly to AEs





- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

- Discontinuation due to AEs may be even more common in the real-world setting (41% discontinuation at median of 17 mo.)

Mato AR et al., *Haematologica* 2018;103:874-9.

Barr PM et al. *Blood Adv* 2022;6:3440-50.

Content courtesy of Matthew S Davids, MD, MMSc

ELEVATE-RR: Acalabrutinib vs. Ibrutinib in R/R CLL

Study Design[1]

Key Eligibility Criteria
- Previously treated CLL with del(17p) or del(11q)
- ECOG ≤2

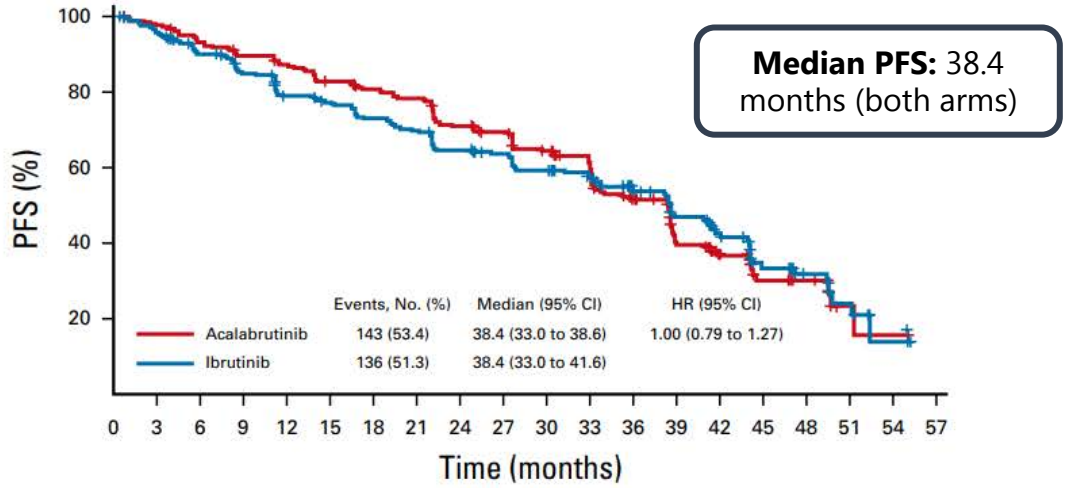
RANDOMIZE 1:1

- **Arm A**: Acalabrutinib to PD
- **Arm B**: Ibrutinib to PD

Primary endpoint
PFS by IRC
- Noninferiority[a]; tested after 250 events

Secondary endpoints[b]
- Incidence of atrial fibrillation
- Incidence of grade ≥3 infections
- Incidence of Richter's transformation
- OS

IRC-assessed PFS (median f/u: 40.9 mo)[2]

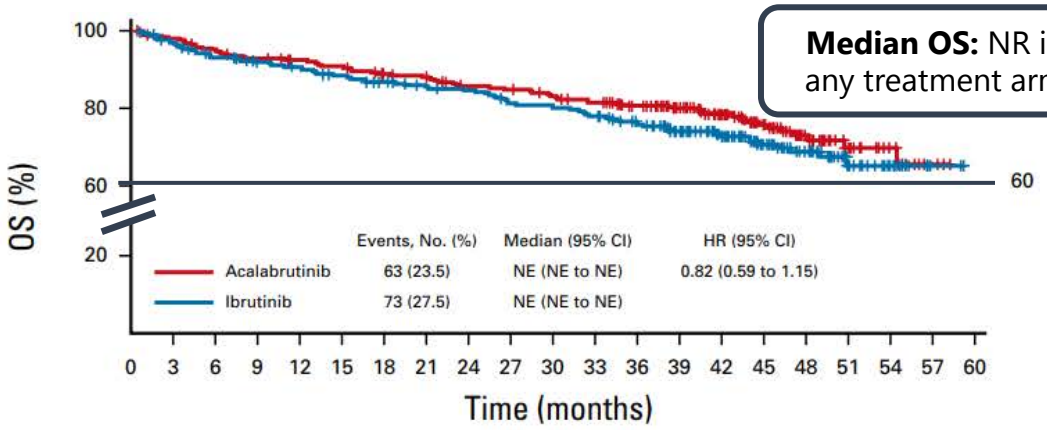


Median PFS: 38.4 months (both arms)

Prespecified subgroup analysis of IRC-assessed PFS[2]

Subgroup	Category	Acalabrutinib (Events/Patients)	Ibrutinib (Events/Patients)	HR (95% CI)
Presence of del(17)(p13.1)	Yes	76/124	72/121	**1.00 (0.73 to 1.38)**
	No	67/144	64/144	**1.00 (0.71 to 1.41)**
TP53 mutation	Yes	64/100	73/112	**0.95 (0.68 to 1.33)**
	No	79/167	63/153	**1.11 (0.80 to 1.55)**
IGHV	Mutated	13/44	13/28	**0.60 (0.28 to 1.31)**
	Unmutated	130/220	123/237	**1.09 (0.85 to 1.40)**
Complex karyotype	Yes	74/124	66/125	**1.04 (0.74 to 1.44)**
	No	52/116	56/116	**0.92 (0.63 to 1.35)**

OS (median f/u: 40.9 mo)[2]



Median OS: NR in any treatment arm

1. Hillmen P, et al. EHA 2021. Abstract S145. 2. Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

ELEVATE-RR: Acalabrutinib vs. Ibrutinib in R/R CLL - **Safety**

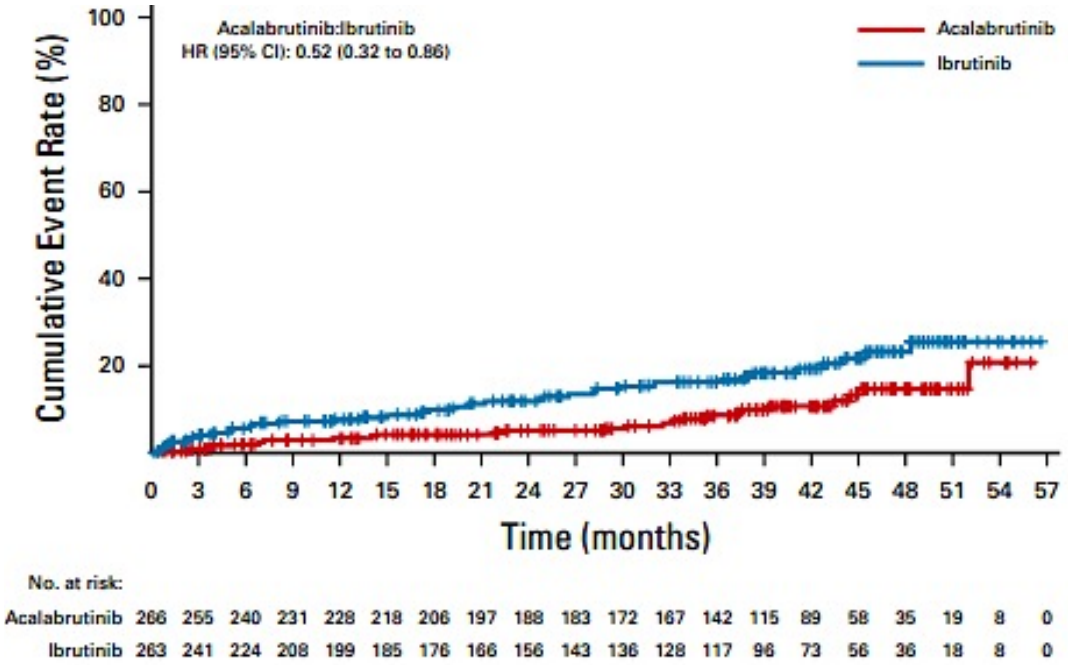
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Event	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Diarrhea	92 (34.6)	3 (1.1)	**121 (46.0)**	**13 (4.9)**
Headache	**92 (34.6)**	**4 (1.5)**	53 (20.2)	0
Cough	**77 (28.9)**	2 (0.8)	56 (21.3)	1 (0.4)
Upper respiratory tract infection	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)
Pyrexia	62 (23.3)	8 (3.0)	50 (19.0)	2 (0.8)
Anemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
Fatigue	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Nausea	47 (17.7)	0	49 (18.6)	1 (0.4)
Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)
Dyspnea	37 (13.9)	6 (2.3)	23 (8.7)	1 (0.4)
Bronchitis	34 (12.8)	3 (1.1)	23 (8.7)	2 (0.8)
Constipation	31 (11.7)	0	37 (14.1)	2 (0.8)

	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Event	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Contusion	31 (11.7)	0	**48 (18.3)**	1 (0.4)
Nasopharyngitis	29 (10.9)	0	27 (10.3)	0
Dizziness	28 (10.5)	0	26 (9.9)	0
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	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)
Urinary tract infection	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain	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	16 (6.0)	0	**35 (13.3)**	2 (0.8)
Dyspepsia	10 (3.8)	0	**32 (12.2)**	0

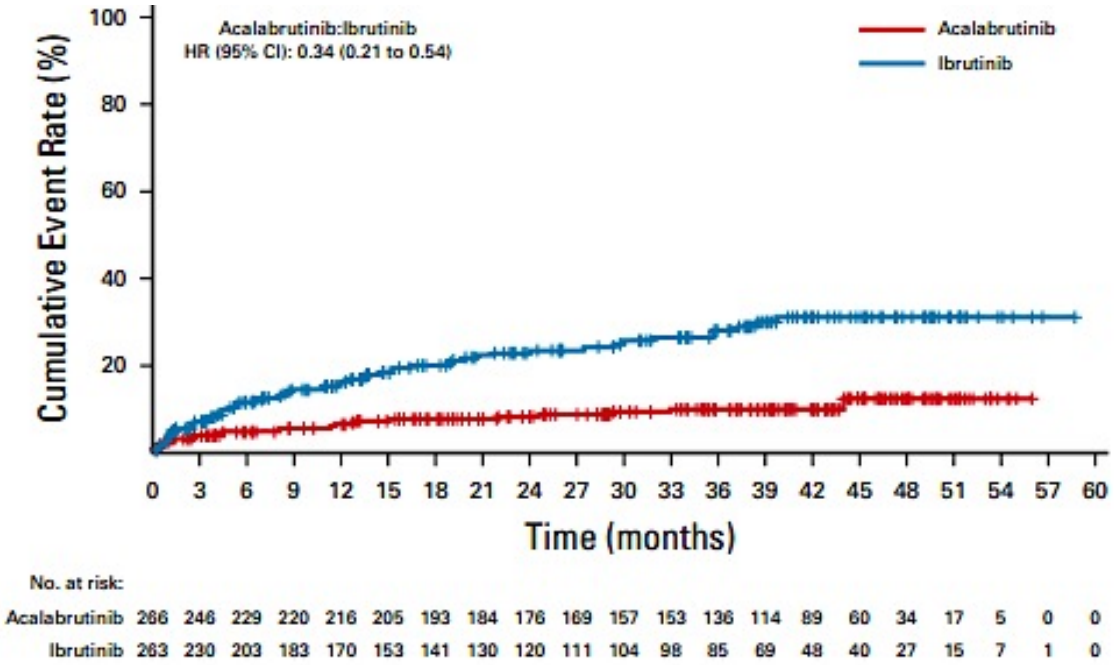
1. Hillmen P, et al. EHA 2021. Abstract S145. 2. Byrd JC, et al. J Clin Oncol. 2021;39(31):3441-3452.

ELEVATE-RR: Atrial Fibrillation and Hypertension

Cumulative Incidence of Atrial Fibrillation



Cumulative Incidence of Hypertension



1. Hillmen P, et al. EHA 2021. Abstract S145. 2. Byrd JC, et al. J Clin Oncol. 2021;39(31):3441-3452.

ALPINE: Zanubrutinib vs. Ibrutinib in R/R CLL

Study Design[1]

Key Eligibility Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- No current or past RT, prior BTKi therapy, or warfarin/other VKA

RANDOMIZE → 1:1 → Zanubrutinib 160 mg po bid / Ibrutinib 420 mg po qd

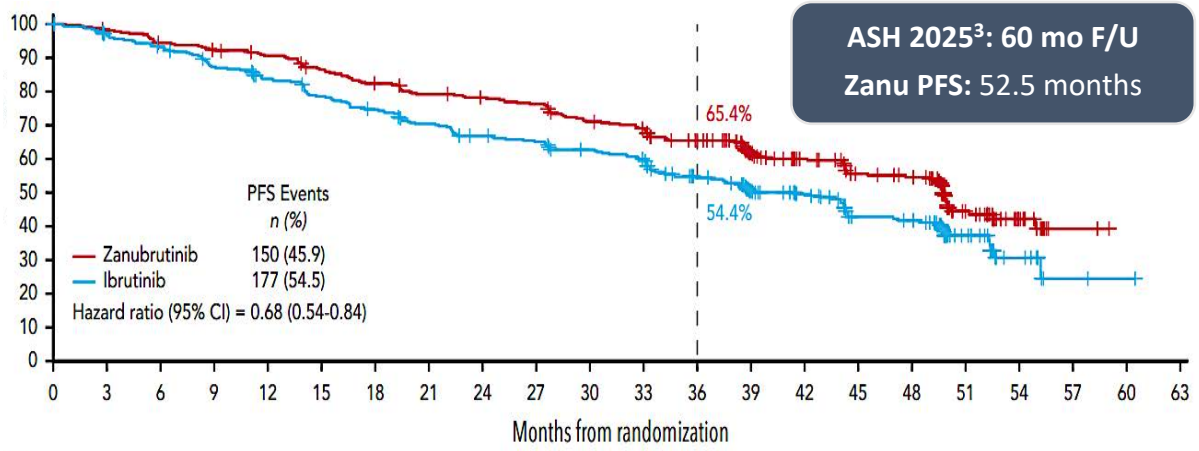
Primary endpoint

- ORR (CR+PR) noninferiority and INV-assessed superiority

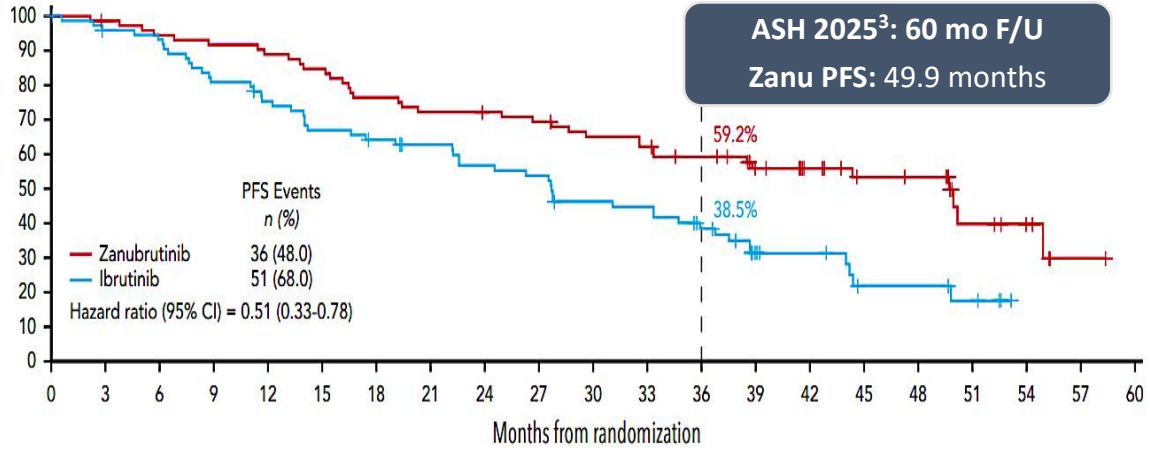
Secondary endpoints

- Any-grade Afib
- DOR
- PFS
- OS
- Time to treatment failure
- PR-L or higher
- PROs
- Safety

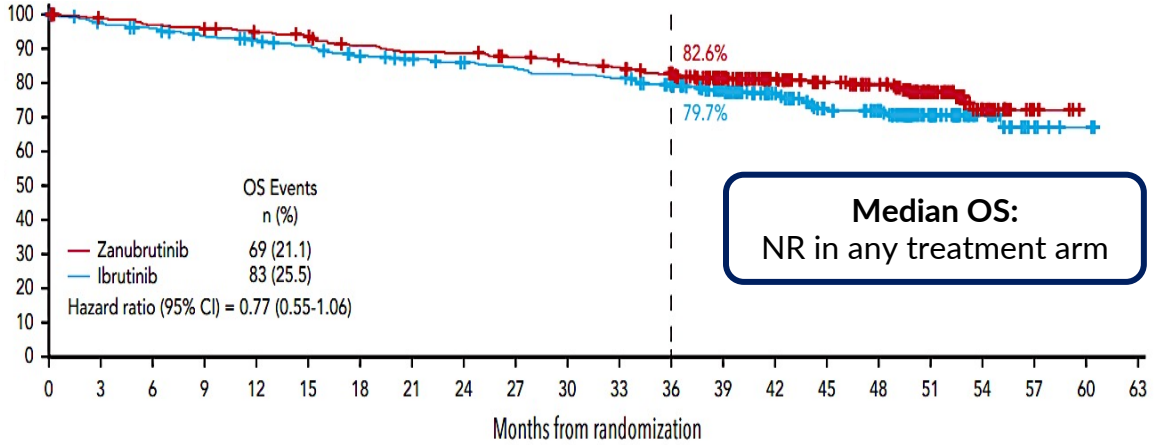
PFS – Overall (median f/u: 42.5 mo)[2]



PFS – del(17p)/*TP53* Mutated (median f/u: 42.5 mo)[2]



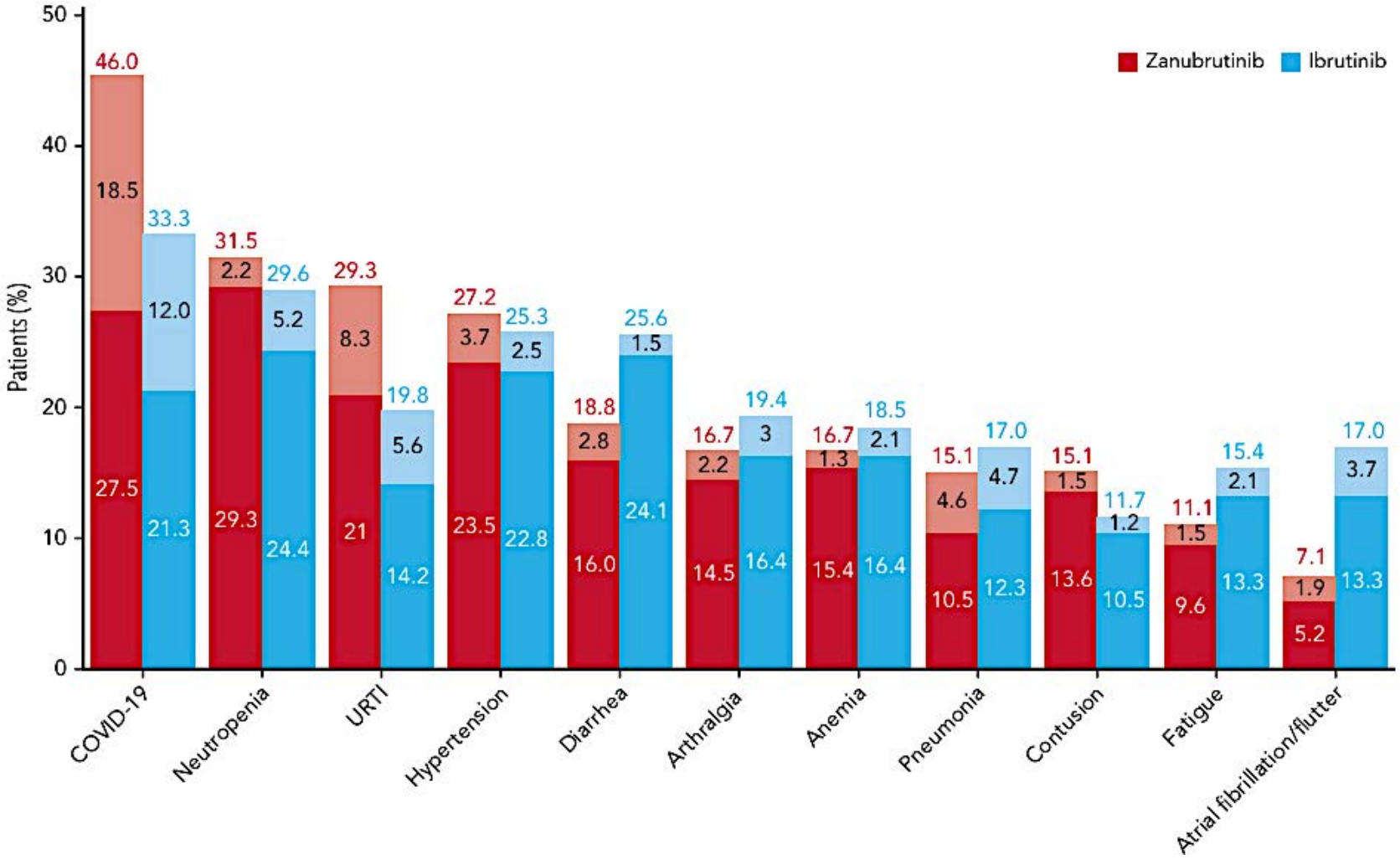
OS – Overall (median f/u: 42.5 mo)[2]



1. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332. 2. Brown JR, et al. *Blood.* 2024;144(26):2706-2717. 3. Tam C, et al. ASH 2025; abs25-10399.

ALPINE: Zanubrutinib vs. Ibrutinib in R/R CLL **- Safety**

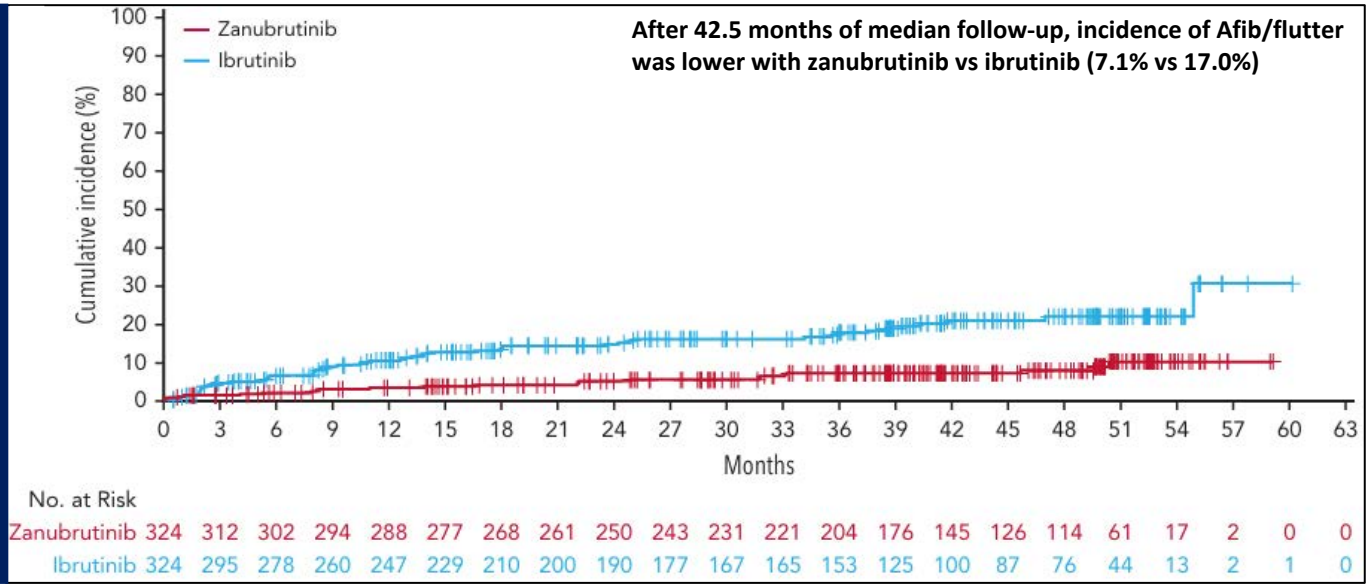
All-Grade Treatment-Emergent Adverse Events Occurring in ≥15% of Patients



References: *Brown J, et al. Blood. 2024;144(26):2706-2717.*

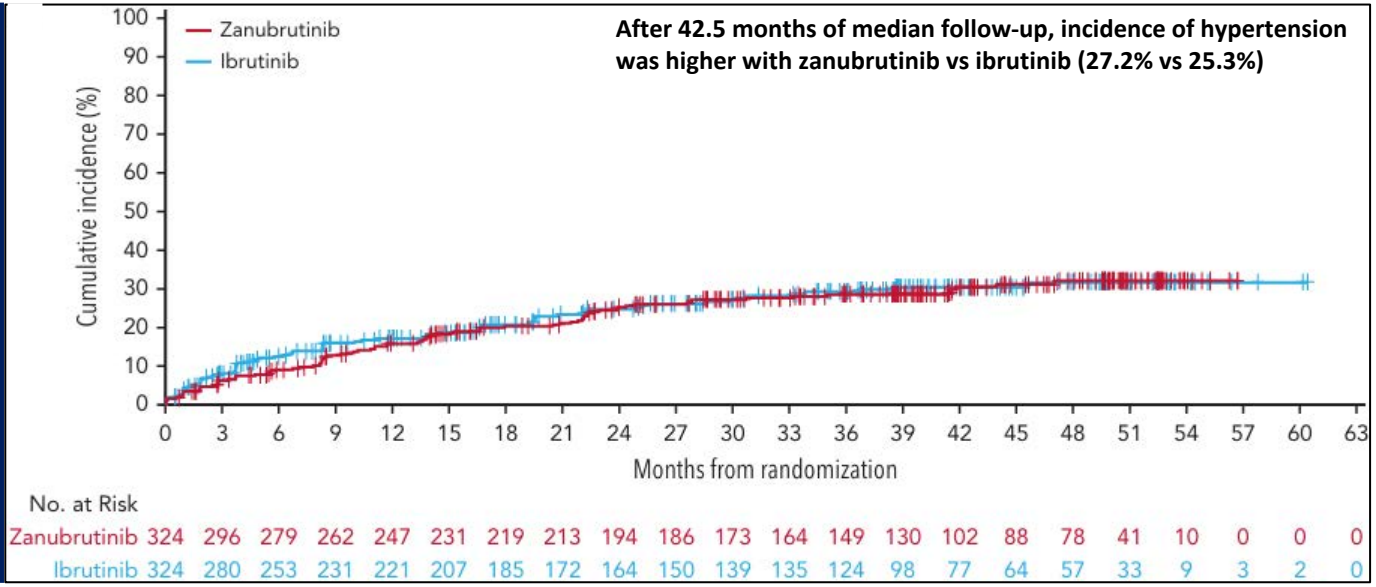
ALPINE: Atrial Fibrillation/Flutter and HTN

Time to Occurrence - Afib/Flutter



After 42.5 months of median follow-up, incidence of Afib/flutter was lower with zanubrutinib vs ibrutinib (7.1% vs 17.0%)

Time to Occurrence - Hypertension



After 42.5 months of median follow-up, incidence of hypertension was higher with zanubrutinib vs ibrutinib (27.2% vs 25.3%)

References: *Brown J, et al. Blood. 2024;144(26):2706-2717.*

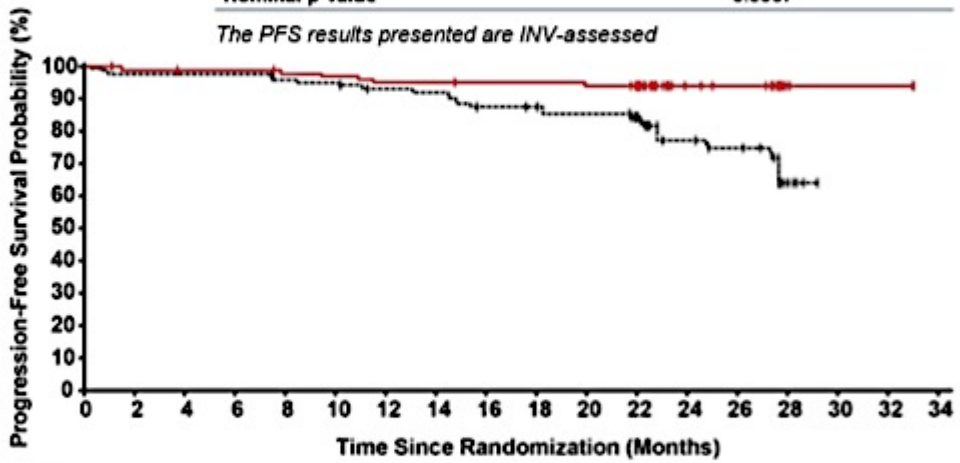
BRUIN CLL-314: Pirtobrutinib vs. Ibrutinib

Progression-Free Survival by Prior Treatment Status

TN population

	Pirtobrutinib (n=112)	Ibrutinib (n=113)
Number of events, n (%)	6 (5.4)	24 (21.2)
18-month PFS rates (95% CI)	95.3 (89.1, 98.0)	87.6 (79.7, 92.6)
Median follow-up, mo	22.5	22.4
Hazard ratio (95% CI)	0.239 (0.098, 0.586)	
Nominal p-value[a]	0.0007	

The PFS results presented are INV-assessed



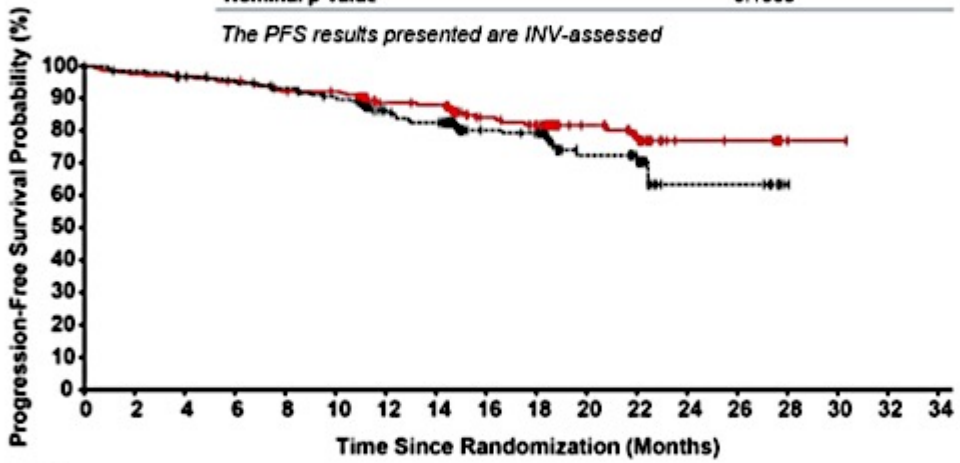
Number at risk

Pirtobrutinib	112	107	106	106	104	103	100	100	99	99	98	94	35	33	4	1	1	0
Ibrutinib	113	105	105	105	102	101	97	96	90	89	86	81	32	29	5	0	0	0

R/R population

	Pirtobrutinib (n=219)	Ibrutinib (n=218)
Number of events, n (%)	37 (16.9)	45 (20.6)
18-month PFS rate (95% CI)	81.7 (75.1, 86.7)	79.2 (72.3, 84.6)
Median follow-up, mo	18.4	15.8
Hazard ratio (95% CI)	0.729 (0.471, 1.128)	
Nominal p-value[a]	0.1563	

The PFS results presented are INV-assessed



Number at risk

Pirtobrutinib	219	212	209	205	197	195	157	155	106	99	56	46	13	12	3	2	0	0
Ibrutinib	218	205	198	192	186	179	138	131	87	84	43	37	12	12	1	0	0	0

Pirtobrutinib reduced the risk of progression or death by 76% in the TN population, the subgroup with the longest follow-up

Woyach et al. ASH 2025

BRUIN CLL-314: Pirtobrutinib vs. Ibrutinib in TN or R/R CLL

Treatment-Emergent Adverse Events

Preferred Term ≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0 (0)
Anemia	50 (15.2)	19 (5.8)	46 (14.2)	12 (3.7)
Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)
Diarrhea	44 (13.3)	1 (0.3)	62 (19.1)	4 (1.2)
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)
Dose modifications due to TEAEs				
Reductions	26 (7.9)		59 (18.2)	
Discontinuations	31 (9.4)		35 (10.8)	

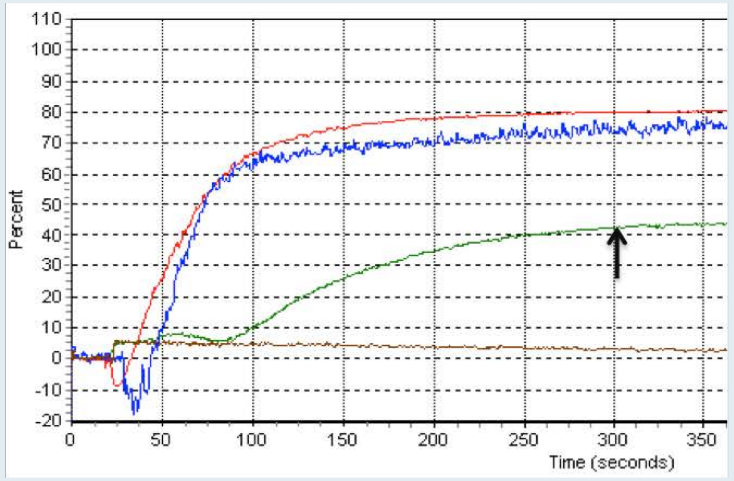
Median time on treatment was 20.5 months with pirtobrutinib and 19.3 months with ibrutinib;
1 patient developed Richter Transformation (RT) on pirtobrutinib; 4 patients developed RT on ibrutinib

Pirtobrutinib was well-tolerated with fewer dose reductions and discontinuations due to TEAEs than ibrutinib

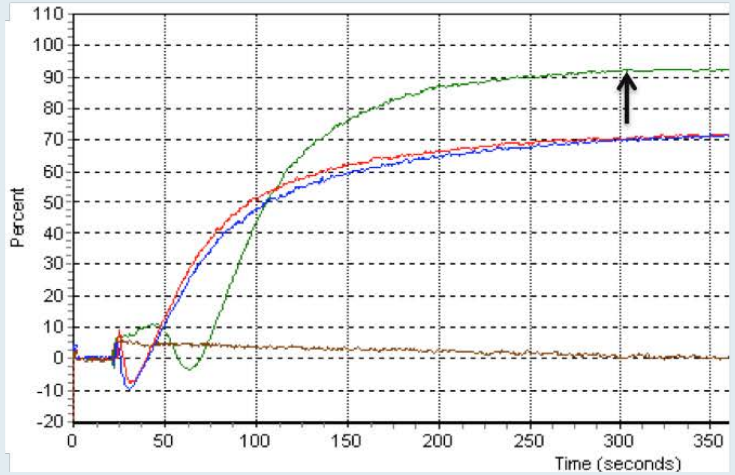
Woyach et al. ASH 2025

Platelet Inhibition by Ibrutinib

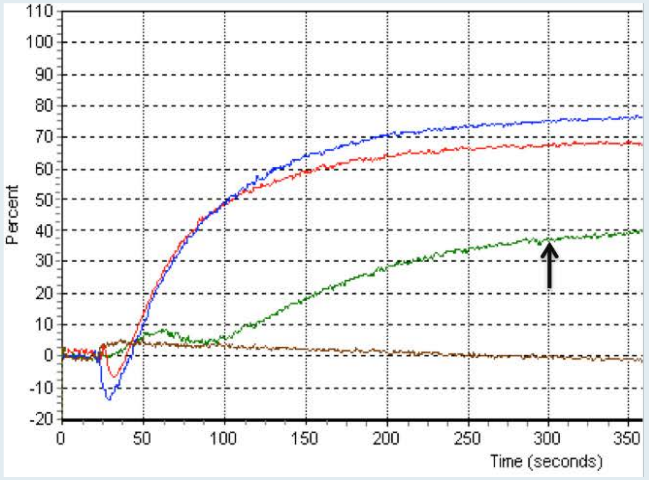
2A: STABLE IBRUTINIB THERAPY



2B: CEASED IBRUTINIB FOR 1 WEEK



2C: RESTARTED IBRUTINIB FOR 1 WEEK



collagen 10ug/ml

high dose ADP (5.0uM)

low dose ADP (2.5uM)

saline control

Kamel et al. *Leukemia* 2015;29(4): 83-7; Levade et al. *Blood* 2014;124(26):3391-5.

Content courtesy of Professor Constantine Tam, MBBS, MD

RTP RESEARCH TO PRACTICE

Bleeding Risk with BTKi Treatment

- Bleeding risk is due to inhibition of platelet function via both on-target and off-target effects of BTKi.
- Hold BTKi treatment for 3-7 days before and after an invasive procedure with bleeding risk.
- Bleeding risk is increased when BTKi is combined with other antiplatelet agents or anticoagulants. Monitor closely.
- Avoid concurrent use of BTKi with dual antiplatelet agents or warfarin because of increased bleeding risk.
- In case of intolerance to a covalent BTKi, consider switching to an alternative covalent BTKi or noncovalent BTKi.

Incidence and Management Recommendations for Select BTKi - Associated Cardiologic Adverse Events and Bleeding

Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3 %	Management
Atrial fibrillation	Ibrutinib	16, 2-5	**A**void stroke; anticoagulation **B**etter symptom control: rate vs rhythm **C**ardiovascular and other comorbidity management
	Acalabrutinib	6-9, 1-5	
	Zanubrutinib	3-6, ≤1	
	Pirtobrutinib	2.8, 1.2	
Hypertension	Ibrutinib	16-23, 8-12	Correct predisposing factors Antihypertensive therapy
	Acalabrutinib	7-9, 3-4	
	Zanubrutinib	14-17, 6-15	
	Pirtobrutinib	9.2, 2.3	
Bleeding	Ibrutinib	36-51, 3-4	Minor bleeding: no intervention Major bleeding: • Consider treatment discontinuation • Platelet transfusions regardless of platelet counts
	Acalabrutinib	36-51, 3	
	Zanubrutinib	36-45, 3	
	Pirtobrutinib	—	

Galitzia A et al. *Cancers* 2024;16:1996; Jurczak W et al. EHA 2023;Abstract P618.

RTP RESEARCH TO PRACTICE

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Volume 87, Issue 5, 10 February 2026, Pages 654-682

2025 ACC Concise Clinical Guidance

Diagnosis and Management of Cardiovascular Adverse Effects of Targeted Oncology Therapies: Bruton's Tyrosine Kinase, Immune Checkpoint, and Vascular Endothelial Growth Factor Inhibitors: 2025 ACC Concise Clinical Guidance: A Report of the American College of Cardiology Solution Set Oversight Committee

TABLE 3 Risk Factors Associated With a Higher Risk of Developing Cardiovascular Toxicity With Ibrutinib

- Older age
- Male sex
- Valvular heart disease
- Hypertension
- Presence of CVD (coronary artery disease, heart failure, ventricular arrhythmia, or pacemaker/defibrillator placement)
- Presence of left atrial abnormality on ECG
- These factors were associated with a higher risk of developing AF with ibrutinib compared with that of patients without these risk factors[46-48]

AF = atrial fibrillation; CVD = cardiovascular disease; ECG = electrocardiogram.

Ganatra S et al. *J Am Coll Cardiol* 2026;87(5):654-82.

Cardiovascular Management with BTKi

	Assessments	Action

Before BTKi	• Personal and family history
	• Clinical examination
	• Blood pressure
	• Baseline ECG
	• Echo if history of CV disease or poorly controlled HTN
		• ***Avoid BTKi*** if
		  • Personal or family history of ventricular arrhythmias
		  • Uncontrolled HTN
		  • LVEF abnormal (definitely if <30%)

Hypertension	• BP weekly x 3 months • Then monthly	• Treat >135/85 mmHg • ACE-I/ARB > others as needed
Atrial fibrillation	• Clinical examination • Consider ECG q3 monthly	• ECG if suspicion of AF • Echo and beta blockers • Apixaban if CHADS-VASC2 > 2

Adapted from Awan FT et al. *Blood Adv* 2022;6:5516-25; Munir T et al. *Acta Haematol* 2025;1-16. Content courtesy of Professor Constantine Tam, MBBS, MD

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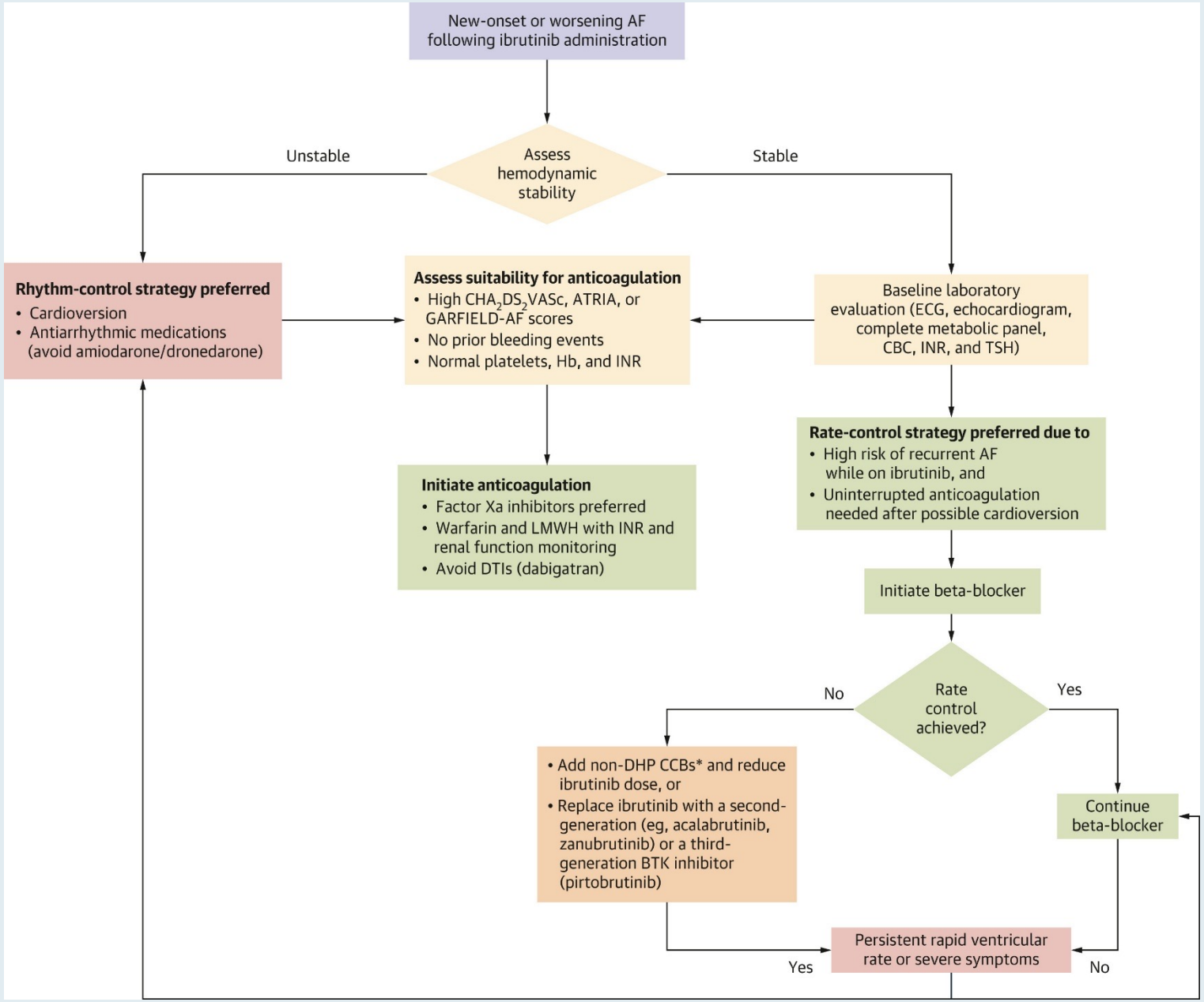
New-Onset A-fib



JACC 2026

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Incidence and Management Recommendations for Select BTK Inhibitor-Associated Noncardiovascular Adverse Events

Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3 %	Management
Neutropenia	Ibrutinib	25-39, 13-31	Growth factor support
	Acalabrutinib	21-23, 13-19	
	Zanubrutinib	37-34, 15-19	
	Pirtobrutinib	25, 20.3	
Diarrhea	Ibrutinib	22-59, <1-4	Symptomatic treatments and dose adjustments Dietary modifications, hydration, anti-diarrheal medications Probiotics
	Acalabrutinib	18-39, 1-5	
	Zanubrutinib	14-18, <1-2	
	Pirtobrutinib	24.2, 0-9	
Headache	Ibrutinib	14-18, 1-2	Moderate dose of caffeine or acetaminophen
	Acalabrutinib	22-39, <1	
	Zanubrutinib	11-12, 0-1	
	Pirtobrutinib	13.1, 0.5	

Galitzia A et al. *Cancers* 2024;16:1996; Jurczak W et al. EHA 2023;Abstract P618.

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Other BTKi/Bcl-2i Side Effects

	Comment	Solution
Nuisance side effects (myalgias, arthralgias, rash, cough, edema)	Mainly seen in ibrutinib	Dose reduce or use second-generation BTKi
Neutropenia	More common with venetoclax and zanubrutinib	Monitor or twice-weekly GCSF x 4 weeks. Usually don't need to dose reduce
Nausea/dyspepsia/diarrhea	Mainly seen in ibrutinib and venetoclax	Dose reduce (ibrutinib) or try night-time dosing (venetoclax)
Headache	Mainly seen in acalabrutinib	Caffeine and patience (usually resolves)

Brown JR et al. *N Engl J Med* 2025;392(8):748-62; Kater AP et al. *NEJM Evid* 2022;1. Shadman M et al. *J Clin Oncol.* 2025;43:2409-17; Tam C. *Hematology Am Soc Hematol Educ Program* 2021:55-8; Timofeeva N et al. *Blood Neoplasia* 2024;1:100034.

Adverse Events (AEs) with Bcl-2i-Based Therapy

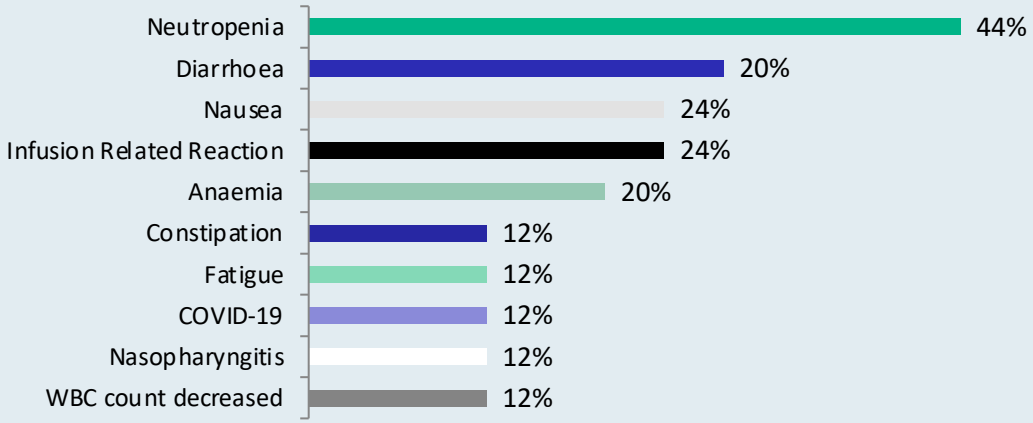
MURANO AEs[1]

	VenR (N=194)	BR (N=188)
Grade 3 or 4 adverse event — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 adverse events with at least 5% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)
Neutropenia†	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)

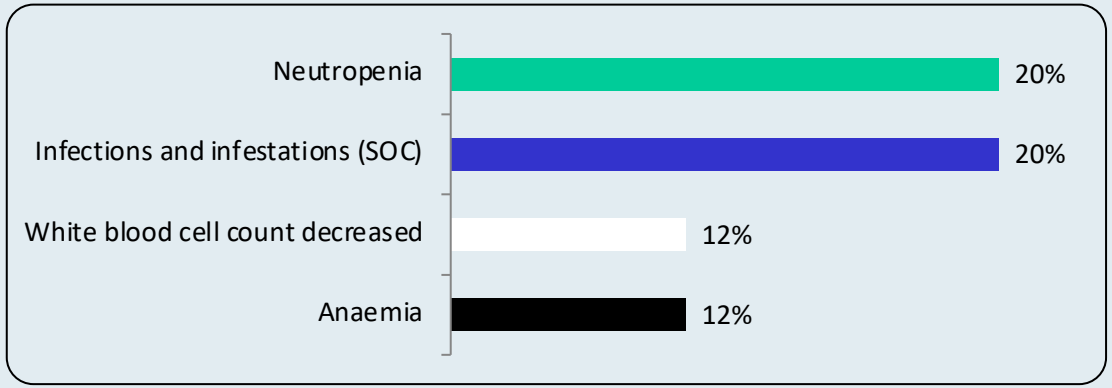
MURANO - Serious AEs[1]

	VenR (N=194)	BR (N=188)
Serious adverse events with at least 2% incidence in either group — no. of patients (%)	90 (46.4)	81 (43.1)
Pneumonia	16 (8.2)§	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
Tumor lysis syndrome	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal adverse events — no. of patients (%)	10 (5.2)§	11 (5.9)

ReVenG AEs[2] (>10% of patients, N=25)



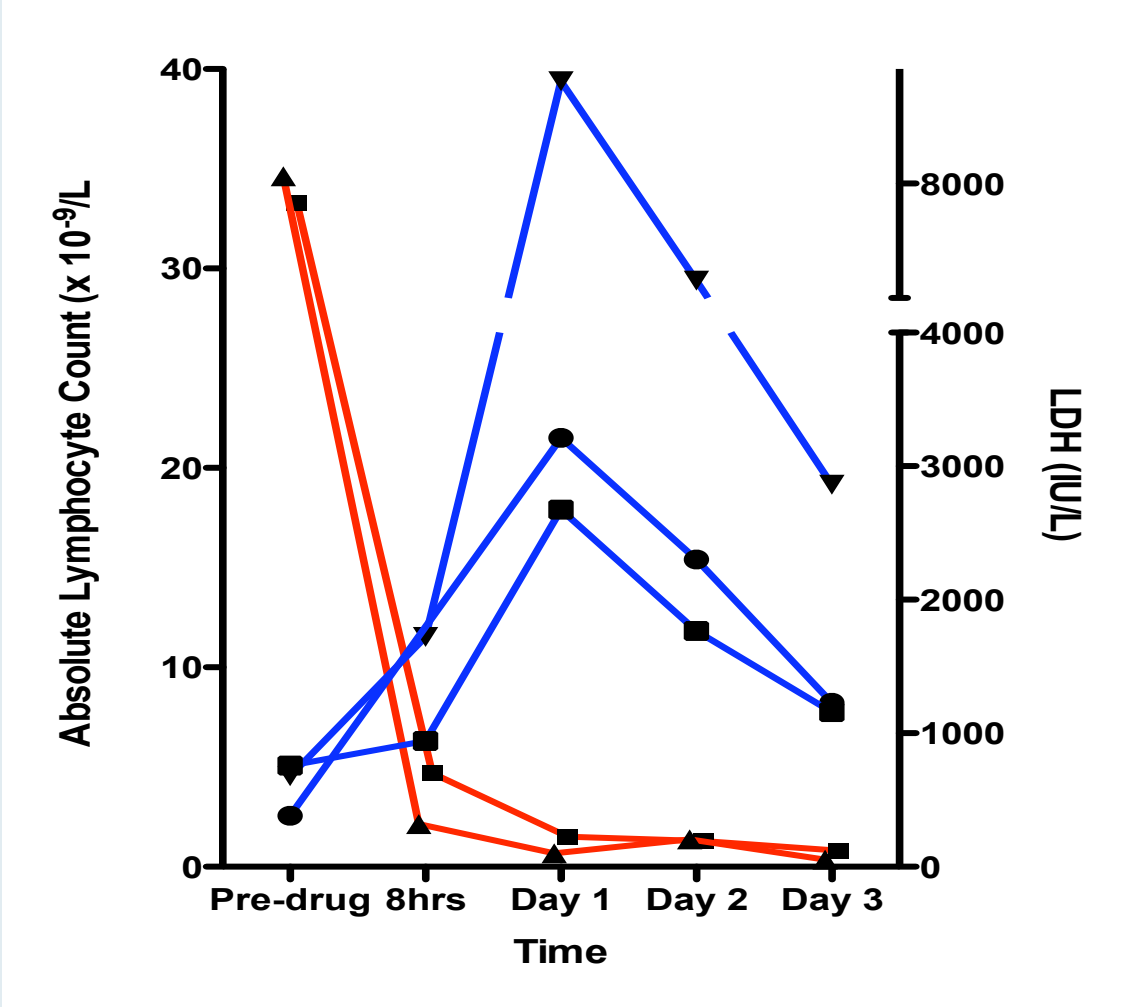
ReVenG AEs[2] (>5% Grade ≥ 3 TEAEs, N=25)



1. Seymour JF et al. *N Engl J Med* 2018;378(12):1107-20. 2. Davids M et al. EHA 2025;Abstract PF575.

Venetoclax Induces Rapid Reduction in CLL

- Single dose of 200mg (n=2) or 100mg (n=1)
- Rapid reduction in CLL within 24hrs
- Evidence of TLS in all 3 patients, one with transient disseminated intravascular coagulation



Lymphocyte Counts (Red; n = 2) and LDH (Blue; n = 3) post first dose

Souers AJ et al. *Nat Med* 2013;19:202-8; Roberts et al. 2012 EHA Congress.

Content courtesy of Professor Constantine Tam, MBBS, MD

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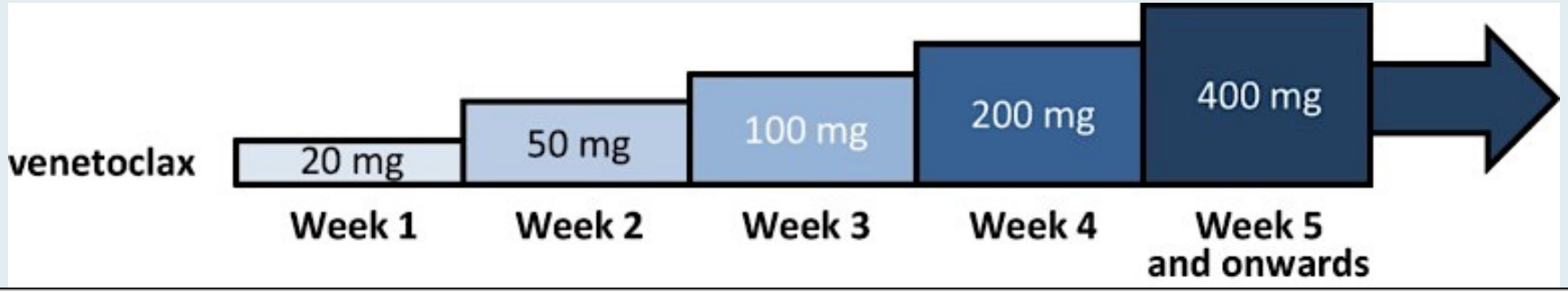
Monitoring TLS with Venetoclax



	Tumor lysis syndrome risk category		
	Low	**Medium**[a]	**High**
Definition	All measurable lymph nodes with largest diameter <5 cm AND <25 × 10^9/L ALC	Any measurable lymph node with largest diameter ≥5 and <10 cm OR ≥25 × 10^9/L ALC	Any measurable lymph node with largest diameter ≥10 cm OR ≥25 × 10^9/L ALC AND any measurable lymph node with the largest diameter ≥5 cm
Venetoclax dosing setting	Outpatient	Outpatient	Inpatient for first doses of 20 mg and 50 mg
Laboratory monitoring of clinical chemistry at 20-mg and 50-mg doses (20mg, 50mg →)	Reduced lab monitoring for low-risk patients at 0, 8, and 24 hours For hospitalized patients, lab monitoring was done at 0, 4, 8, 12, and 24 hours		
Laboratory monitoring of clinical chemistry during subsequent dose ramp-up (100mg, 200mg, 400mg →)	No need to monitor post-dose in low and medium risk.		Outpatient at 0, 8, 24 hours
Hydration and uric acid control	1–2 L/day oral fluids at 48 hours and oral uric acid-lowering agents at 72 hours prior to first dose Additional IV fluids for high-/medium-risk patients Rasburicase recommended for high-risk patients with high baseline uric acid		

[a]Patients with medium risk who had creatinine clearance <80 mg/mL were to be managed as high risk.
Abbreviations: ALC, absolute lymphocyte count; IV, intravenous.

Adapted from Cheson BD et al. *Oncologist* 2017;22:1283-91; Venetoclax PI

Content courtesy of Professor Constantine Tam, MBBS, MD

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Monitoring Venetoclax TLS: A Case Example

70-year-old male

Medical history

- LVEF of 40% due to IHD
- CKD due to T2DM
- Hypertension and hyperlipidemia

Molecular characteristics

- Unmutated *IGHV*
- *TP53* mutation and/or deletion
- Complex karyotype

Treatment history

- 6 cycles (q4w) of fludarabine + cyclophosphamide + rituximab resulting in PR with a PFS of 2 years
- Ibrutinib (420 mg daily) for 4 years with slow progression and ibrutinib as a debulking strategy until completion of venetoclax ramp-up

Assess
Tumor burden and blood

- Retroperitoneal LN: 12 cm
- Splenomegaly: 15 cm
- ALC: 30 x 10^9/L

Diagnosis:
R/R CLL at high risk for TLS

Prepare
2-3 days prior to first dose

TLS prophylaxis

- Hydration: Oral (1.5 to 2 L) (IV: 150 to 200 mL/hr as tolerated)
- Anti-hyperuricemic: Allopurinol. Consider rasburicase if baseline uric acid is elevated
- Continue ibrutinib during ramp-up

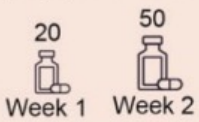
Premedications prior to infusion to reduce the risk of IRR

- 30 minutes: antihistamine and acetaminophen
- 60 minutes: IV glucocorticoid

Initiate
5-week ramp-up dosing schedule (mg/day) and blood chemistry monitoring

Weeks 1-2 (Inpatient)

- Pre-dose, 4, 8, 12 and 24 hours



Weeks 3-5 (Outpatient)

- Pre-dose, 6 to 8 hours, and 24 hours

Innovative Approaches

- Refer patient to a tertiary center for a multidisciplinary approach to patient-centered care
  - Oncology nurse coordinator to provide emotional support, guidance, coordination of care, and monitor compliance
- Educate HCPs around the clinical utility of CT scan as diagnostic and treatment decision guiding tool

Anderson MA et al. *Cancers (Basel)* 2024;16(5):980.

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BTKi + Bcl-2 Combinations

Ibrutinib + Venetoclax[1]

- Main issue is diarrhea / GI side-effects -> try splitting the drugs.
- May increase risk of CV deaths in select populations (older, WM).
- Use with extreme caution in elderly, comorbid, CV disease.

Acalabrutinib + Venetoclax / Zanubrutinib + Venetoclax[2,3]

- Much better tolerated in terms of GI toxicity.
- CV safety seems similar to 2nd gen BTKi monotherapy.

Triple BTKi/BCL2i/CD20 Combinations[4]

- Increased severe infections (esp COVID-19) > neutropenia.

1. Kater AP et al. *NEJM Evid* 2022;1. 2. Brown JR et al. *N Engl J Med* 2025;392(8):748-62. 3. Shadman M et al. *J Clin Oncol* 2025;43:2409-17.
4. Timofeeva N et al. *Blood Neoplasia* 2024;1:100034.

Content courtesy of Professor Constantine Tam, MBBS, MD

Phase III AMPLIFY Study: Combined Bcl-2i/BTKi with and without Anti-CD20 Monoclonal Antibody

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	AV		AVO			
Any adverse event	270 (92.8)	156 (53.6)	269 (94.7)	197 (69.4)	236 (91.1)	157 (60.6)
Any serious adverse event	72 (24.7)		109 (38.4)		71 (27.4)	
Serious adverse event leading to death						
Any	10 (3.4)		17 (6.0)		9 (3.5)	
Due to Covid-19	8 (2.7)		15 (5.3)		7 (2.7)	
Adverse event leading to treatment discontinuation	23 (7.9)		57 (20.1)		28 (10.8)	
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)
Neutropenia‡	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infection	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary cancer						
Any	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excluding nonmelanoma skin cancer	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Brown JR et al. *N Engl J Med* 2025;392(8):748-62.

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Cases from the Community

Susmitha Apuri, MD

Neil Love, MD

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Discussion Questions

What would you recommend for this patient with worsening fatigue/cytopenias and recurrent infections during the venetoclax ramp-up? How do you determine whether to recommend IVIG or G-CSF for these patients?

Do you recommend prophylactic antimicrobials for your patients with CLL who are going to begin treatment with venetoclax? Does this depend at all on what it will be partnered with?

For patients with CLL who are receiving fixed-duration venetoclax/obinutuzumab as initial therapy, do you generally assess for minimal residual disease (MRD) at the end of treatment? What about those receiving fixed-duration venetoclax/acalabrutinib? Are you any more likely to assess MRD status in the presence of high-risk features?

If a patient has detectable MRD after completing the recommended treatment duration with venetoclax/obinutuzumab, do you continue therapy? What about venetoclax/acalabrutinib?

How often would you check for MRD going forward in this patient's case?

Agenda

Module 1: Current and Future Role of Continuous Bruton Tyrosine Kinase (BTK) Inhibitor Therapy for Previously Untreated Chronic Lymphocytic Leukemia (CLL) — Dr Fakhri

Module 2: Available and Emerging Approaches to Time-Limited Therapy for Treatment-Naïve CLL — Dr Allan

Module 3: Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Ma

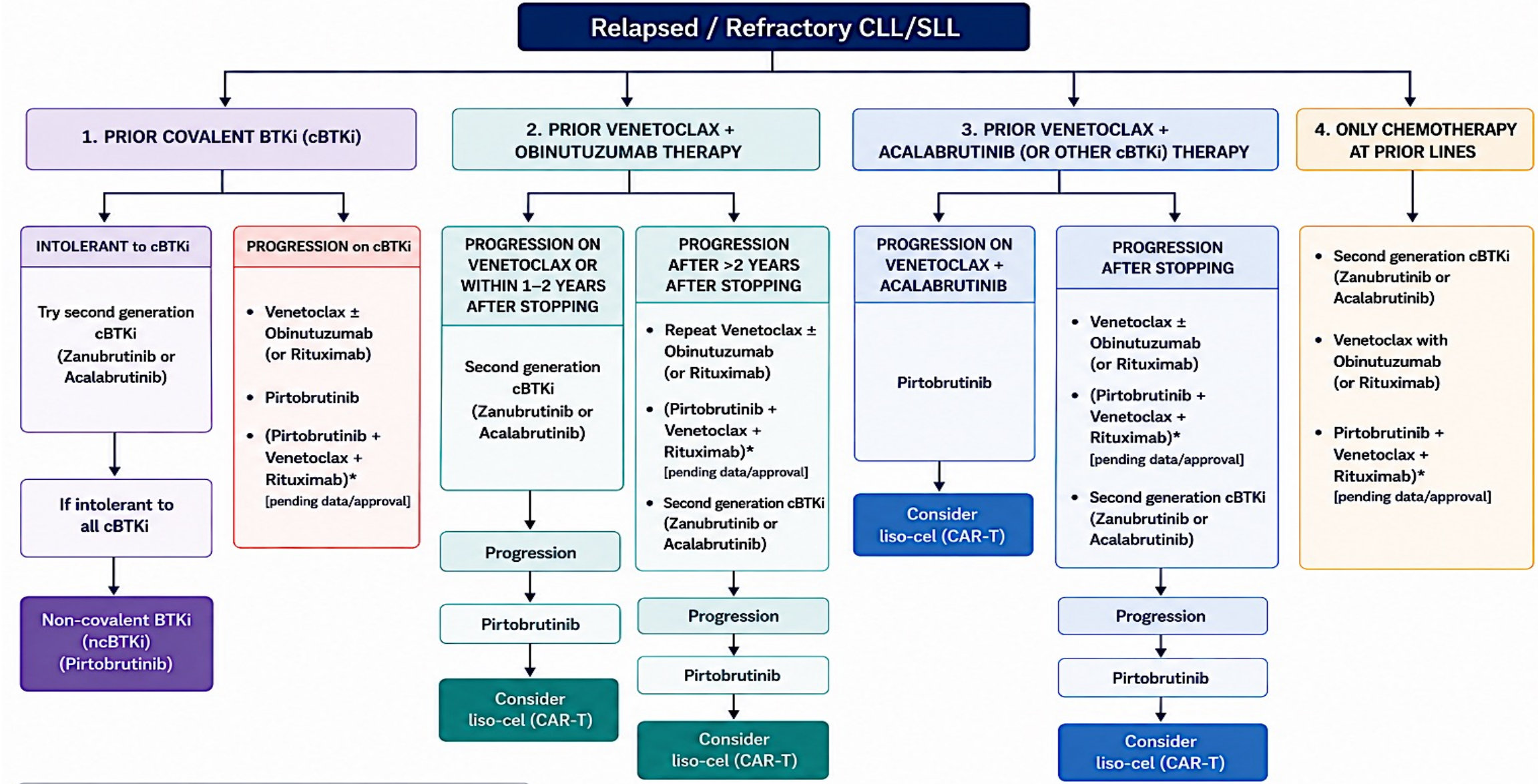
Module 4: Selection and Sequencing of Therapy for R/R CLL — Dr Shadman

Module 5: Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL — Dr Abramson

Selection and Sequencing of Therapy for R/R CLL

Mazyar Shadman, MD MPH
Professor | Innovators Network Endowed Chair
Deputy Chief Medical Officer
Medical Director, Cellular Immunotherapy
Fred Hutch Cancer Center | University of Washington
Seattle, WA

TREATMENT OF RELAPSED/REFRACTORY CLL/SLL



* Pirtobrutinib + Venetoclax + Rituximab pending data/approval

Treatment Options in R/R CLL

- BTK inhibitor monotherapy
  - Covalent BTK inhibitors
    - Acalabrutinib
    - Zanubrutinib
  - Non-covalent BTK inhibitor
    - Pirtobrutinib
- BCL2i-based therapy
  - Venetoclax-based
  - Sonrotoclax-based
- BTKi and CAR-T cell therapy
- Emerging BTK targeting agents

BTKi monotherapy

Acalabrutinib vs. Ibrutinib : ELEVATE-RR

Eligible Patients (N = 533)

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria)
- Presence of del(17p) or del(11q)[a]
- ECOG PS ≤ 2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

- Acalabrutinib[b] 100 mg PO BID
- Ibrutinib[b] 420 mg PO QD

Primary endpoint

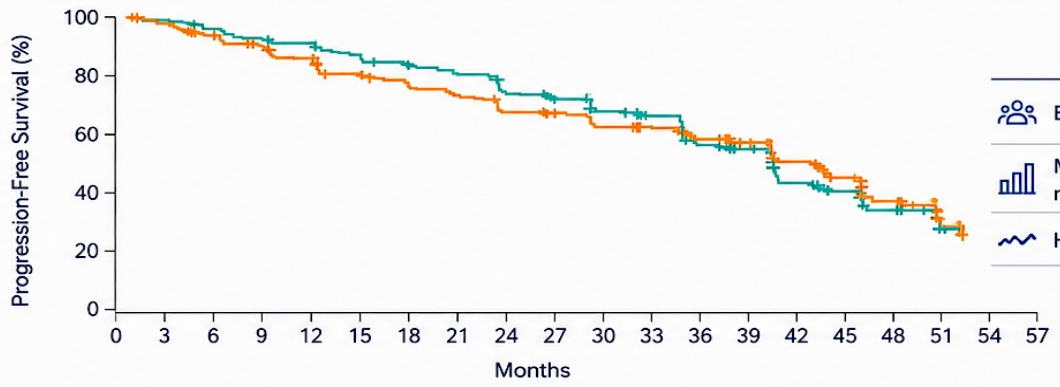
- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order)

- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonists; prior treatment with ibrutinib, a BCR inhibitor (eg, BTK, PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

[a] del(17p) or del(11q) by FISH [b] Until disease progression or unacceptable toxicity [c] Independent Review Committee



	Acalabrutinib (n = 143)	Ibrutinib (n = 136)
Events, n (%)	143 (53.4)	136 (51.3)
Median (95% CI), months	38.4 (33.0, 38.6)	38.4 (33.0, 41.6)
Hazard ratio (95% CI)	1.00 (0.79, 1.27)	

Key Findings

Median PFS

38.4 mo (both arms)

HR 1.00 (95% CI 0.79–1.27) — non-inferiority confirmed

AEs leading to discontinuation

14.9% vs 21.3%

Acala vs Ibrutinib (p=0.0016)

Afib/flutter (any grade)

9.4% vs 16.0%

Acala vs Ibrutinib (p=0.02) — 1° hierarchical secondary endpoint

High-risk population

del(17p) 45% · TP53 37–42%

Unmutated IGHV 82–89% · All pts had del(17p) or del(11q)

Byrd. J et al, JCO, 2021

Zanubrutinib vs. Ibrutinib in R/R CLL: ALPINE

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

R 1:1

- Zanubrutinib 160 mg BID
- Ibrutinib 420 mg QD

Stratification factors: age, geographic region, refractoriness, del(17p)/*TP53*

Treatment until disease progression or unacceptable toxicity

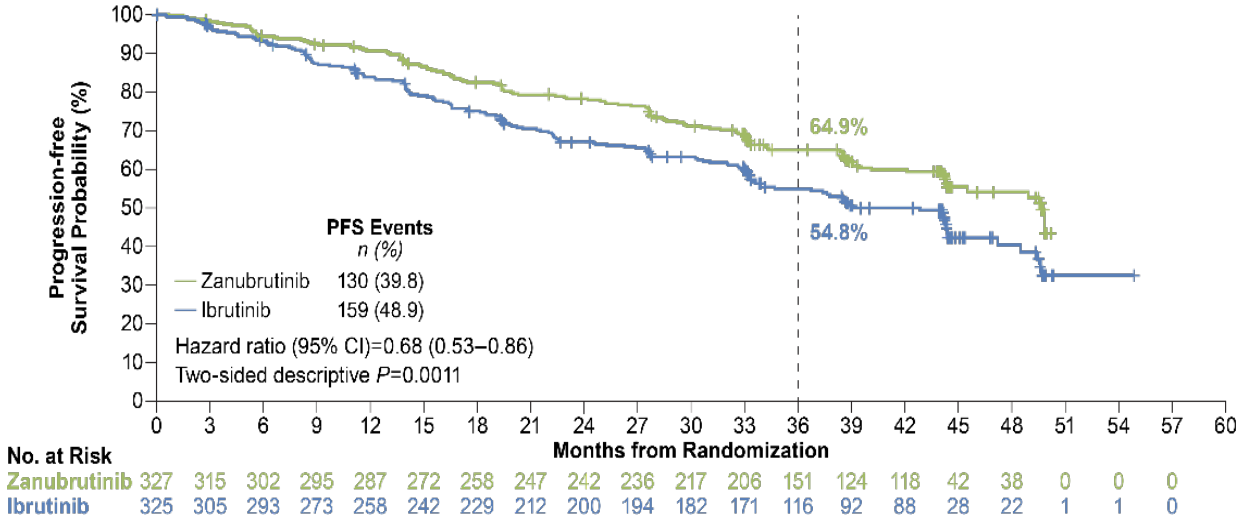
Key Results (median f/u 39 months)

PFS superiority — overall
HR 0.68
(95% CI 0.53–0.86) P=0.0011 ; Zanu 64.9% vs Ibr 54.8% at 36 mo

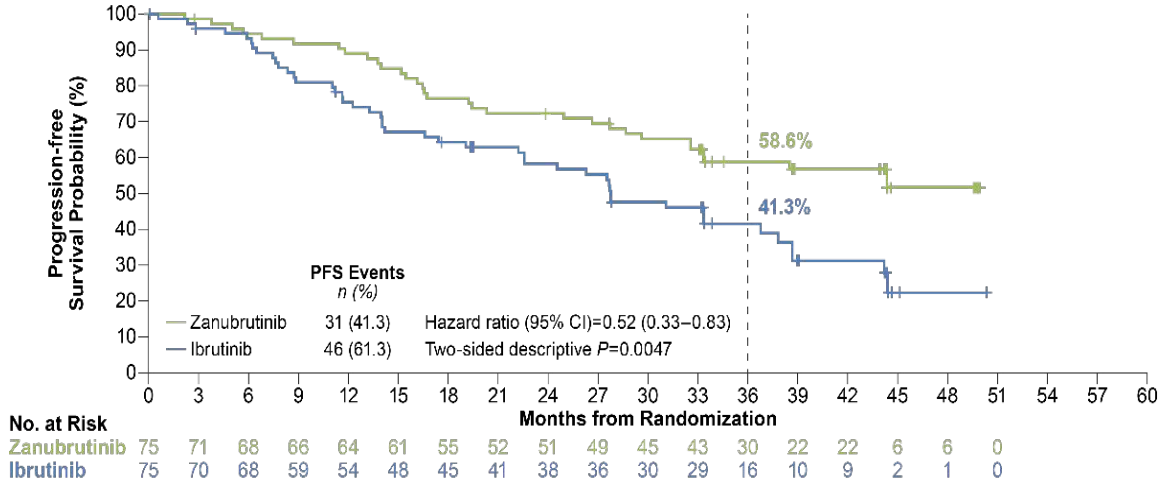
PFS — del(17p)/TP53mut subgroup
HR 0.52
(95% CI 0.33–0.83) P=0.0047; Zanu 58.6% vs Ibr 41.3% at 36 mo

AEs → discontinuation
15.4% vs 21.3%
Zanubrutinib vs Ibrutinib

PFS — Overall Population

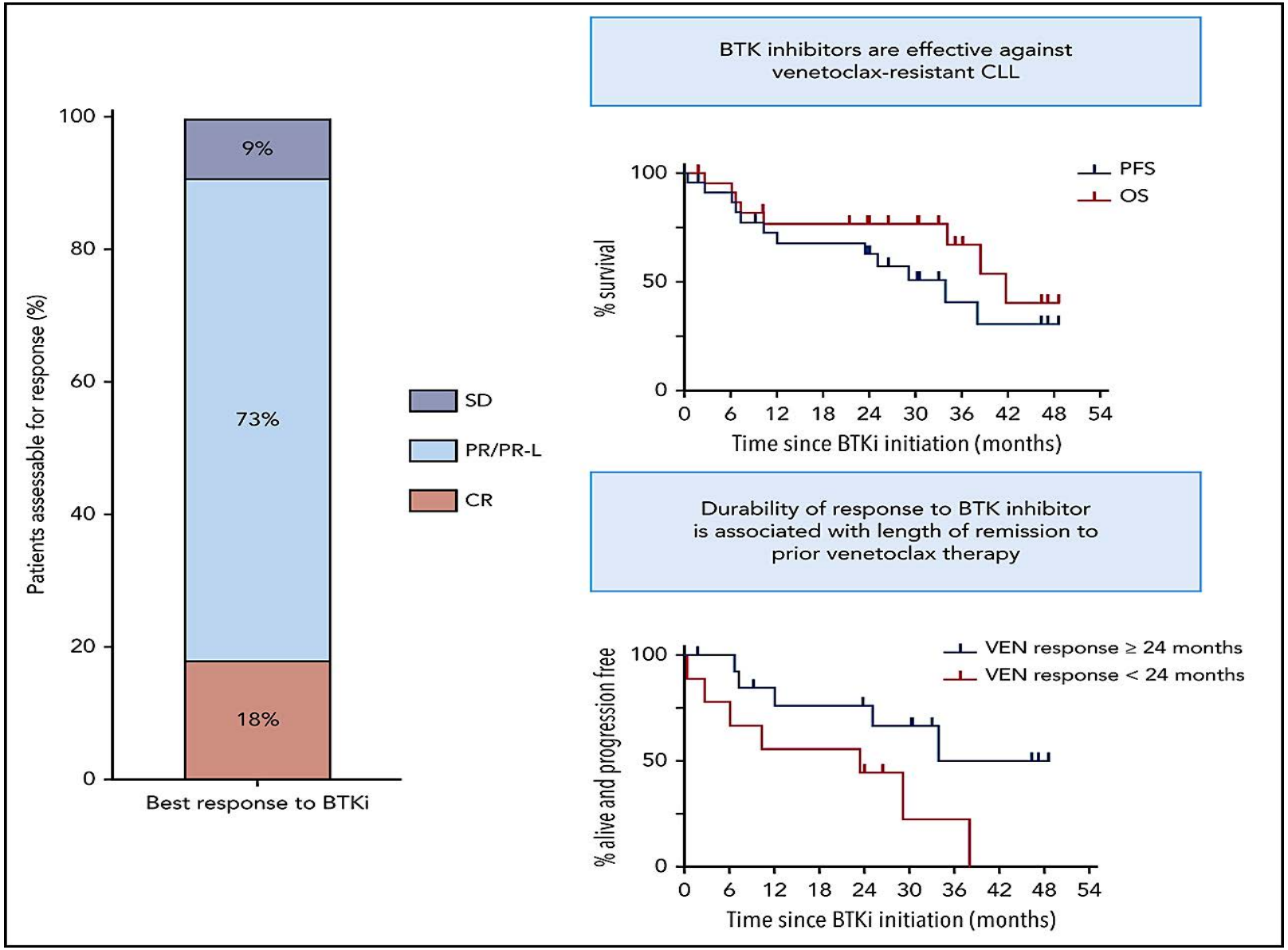


PFS — del(17p)/TP53mut Subgroup



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

BTKi therapy is effective in patients with CLL resistant to Venetoclax



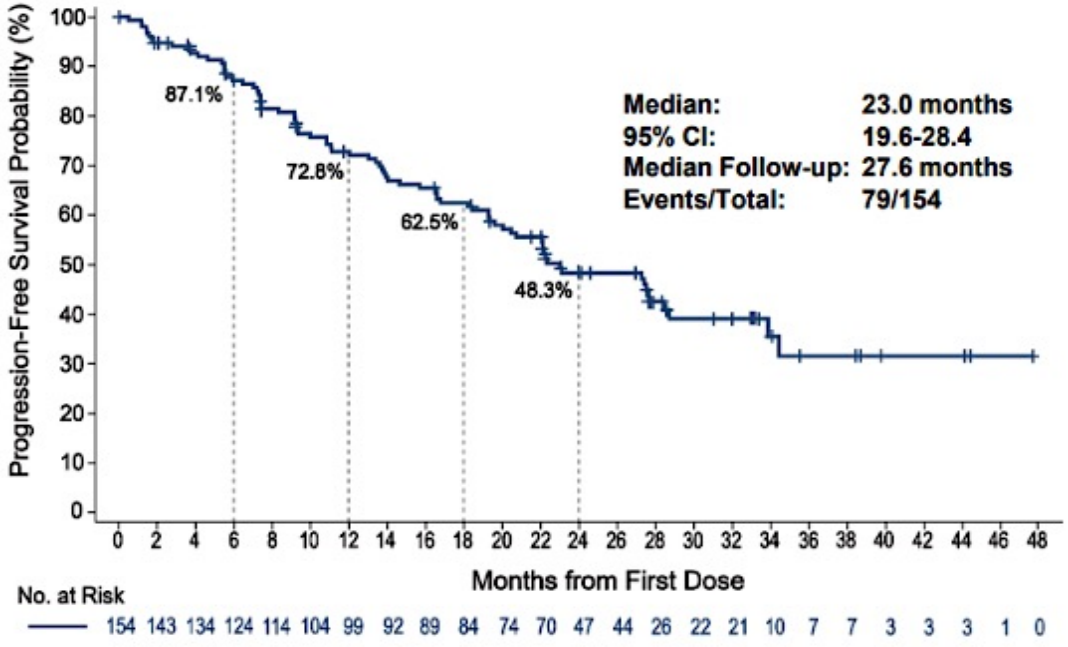
Victor S. et al. Blood, 2020,

Pirtobrutinib in BTKi exposed setting

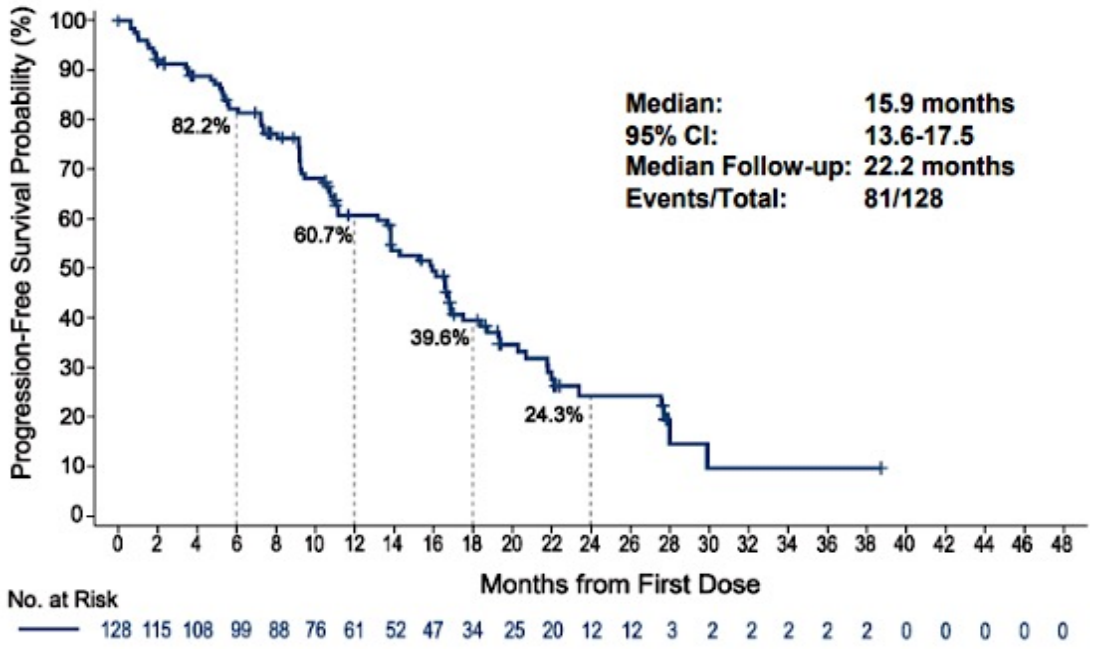
Pirtobrutinib in R/R CLL: BRUIN phase 1/2

Pirtobrutinib Progression-free Survival With Prior cBTKi, With or Without Prior BCL2i

N=154



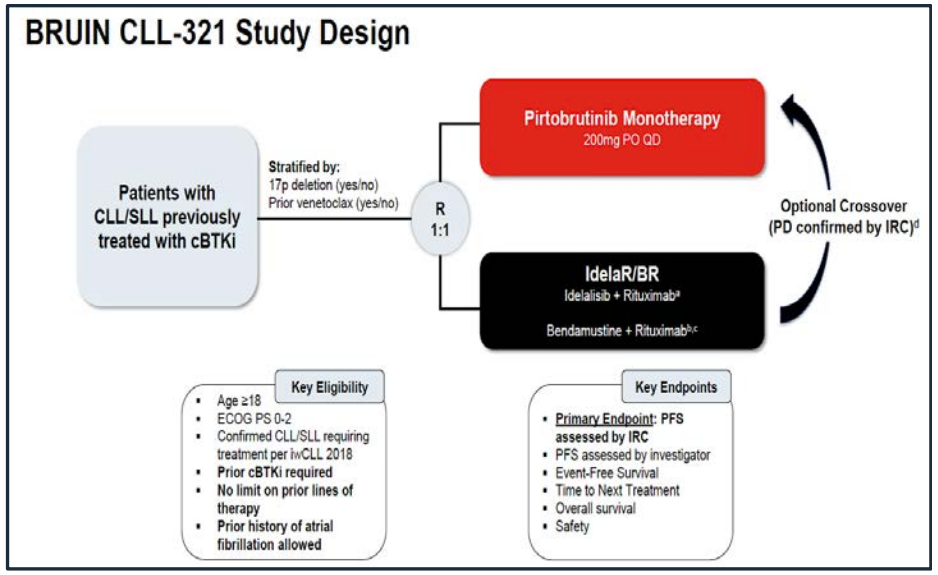
N=128

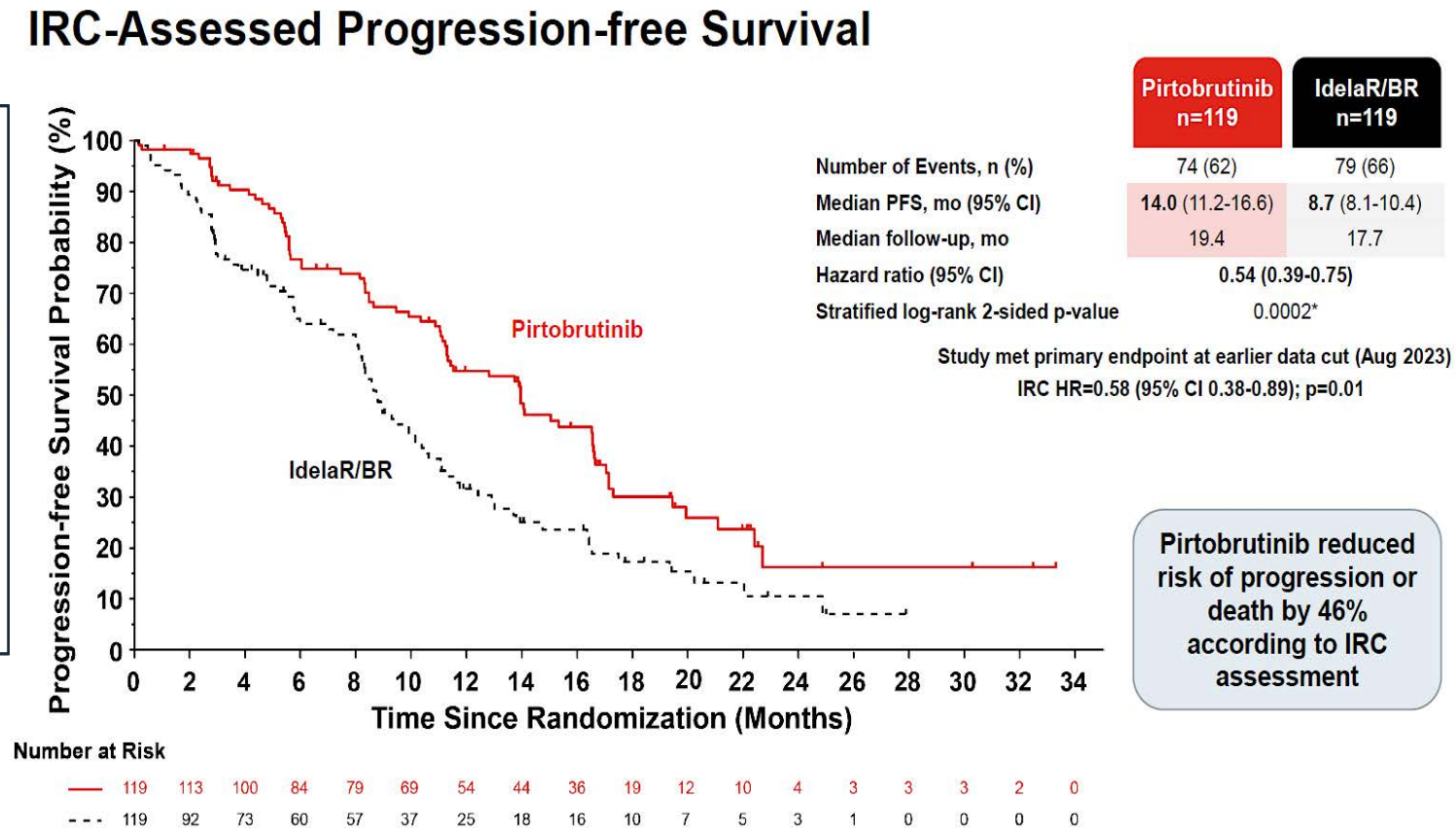


Final update: median PFS in BCL2i-N 22.3 mos; BCL2i-E 15.9 mos

Woyach JA, et al. ASH 2023. Abstract 325; Wierda WG, et al. ASH 2025. Abstract 2115.

Pirtobrutinb vs. IdelaR/BR in RR CLL: BRUIN CLL-321





	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	0.54 (0.39-0.75)	
Stratified log-rank 2-sided p-value	0.0002*	

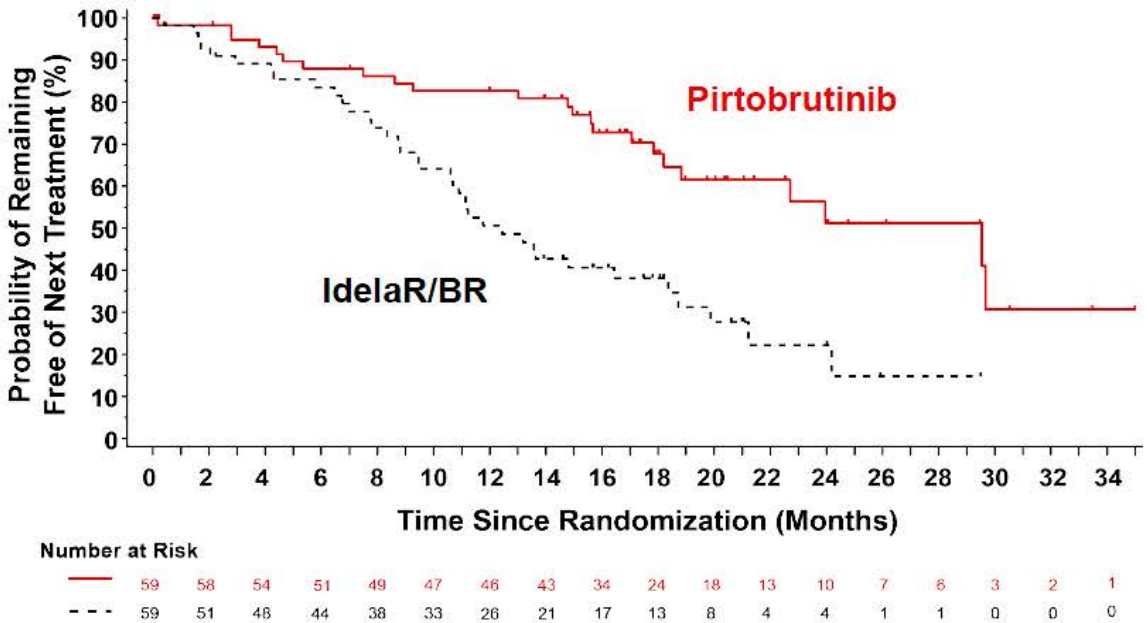
Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

Sharman J et al, JCO, 2025

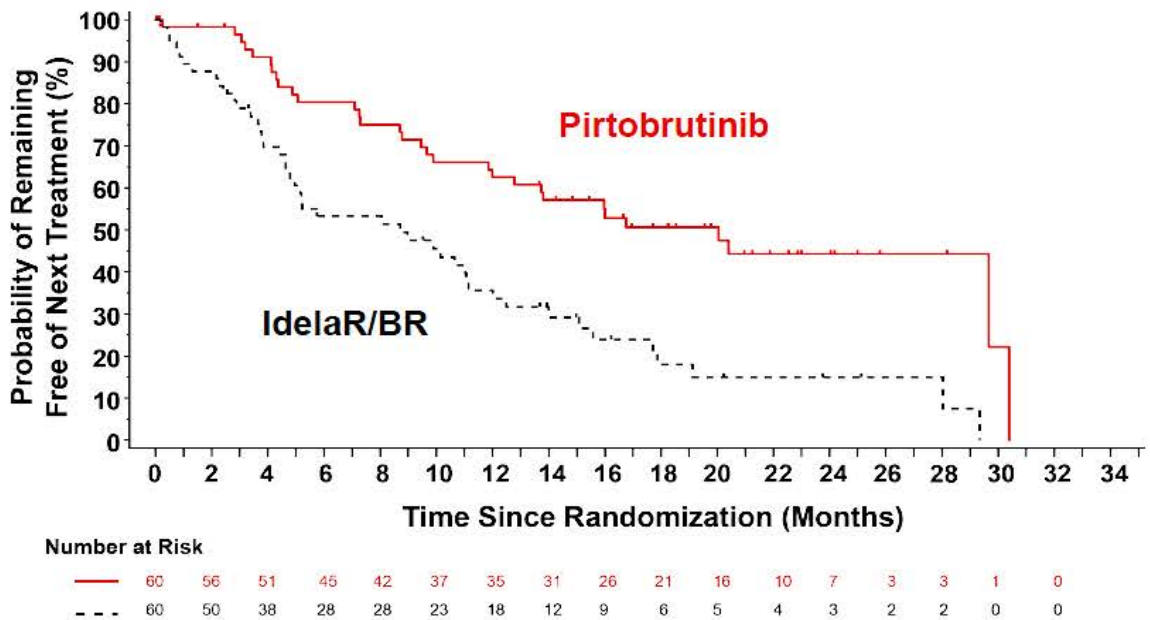
Time to Next Treatment/Death in Venetoclax Naïve and Treated pts

Venetoclax Naïve



	Pirtobrutinib n=59	IdelaR/BR n=59
Median TTNT, mo (95% CI)	29.5	12.5
Hazard ratio (95% CI)	0.36 (0.21-0.61)	
Stratified log-rank 2-sided p-value	0.0001*	

Venetoclax Treated



	Pirtobrutinib n=60	IdelaR/BR n=60
Median TTNT, mo (95% CI)	20.0	8.7
Hazard ratio (95% CI)	0.37 (0.23-0.60)	
Stratified log-rank 2-sided p-value	<0.0001*	

Sharman J et al, JCO, 2025

Pirtobrutinib after first-line cBTKi: LOXO-BTK-18001 and BRUIN CLL-321 Studies

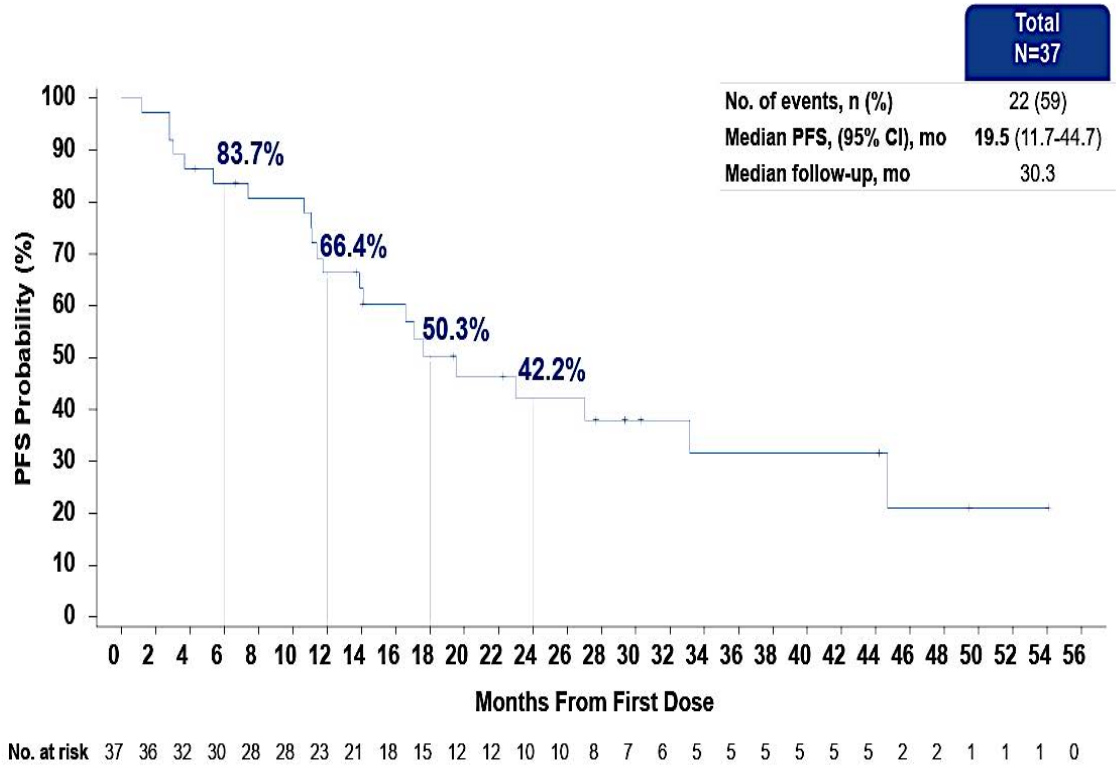
	N=37
Age, median (range)	69 (42-78)
Unmutated IGHV	85% (22/26)
Complex Karyotype (≥ 3 abnl)	65% (11/17)
Mutated TP53	43% (13/30)
Del17p	48% (15/31)
BTK C481S mutated	33% (10/30)
PLCG2 mutated	20 % (6/30)

	N=37
Prior cBTKi	100%
Ibrutinib	76%
Acalabrutinib	14%
Zanubrutinib	8%
Reason for BTKi discontinuation	
Disease progression	57%
Toxicity	35%

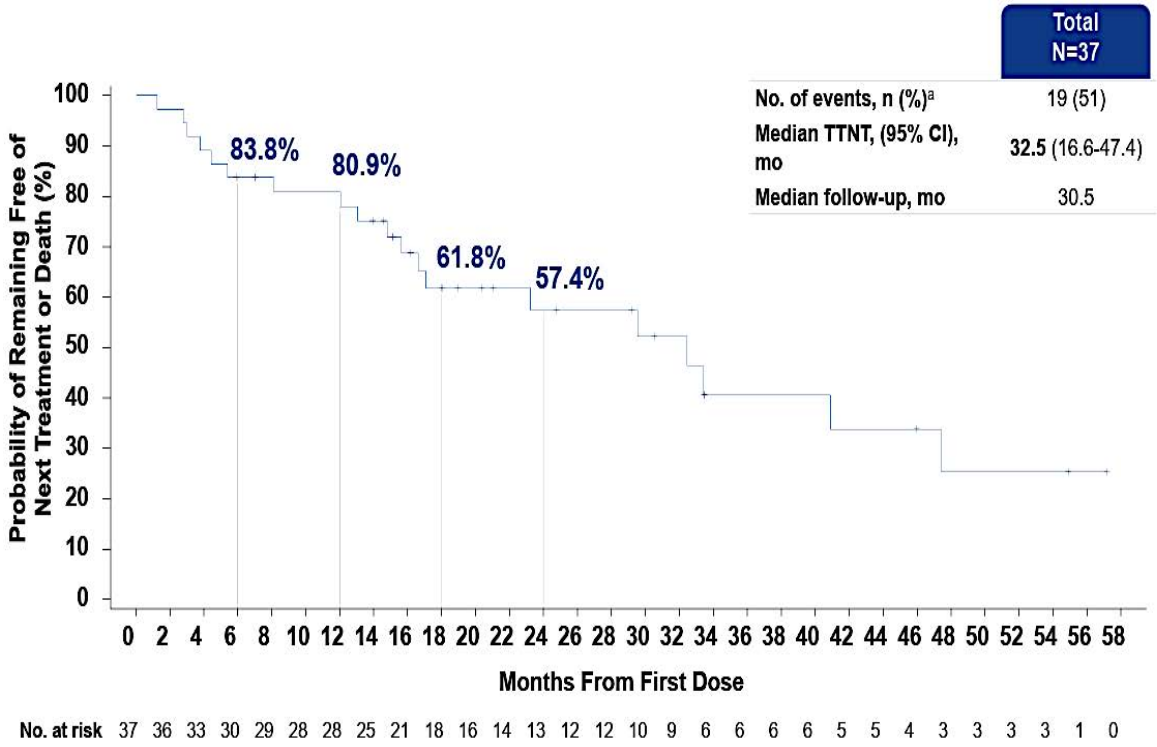
Eyre TA, ASH, 2025

Pirtobrutinib after first-line cBTKi

Investigator-Assessed PFS[a]

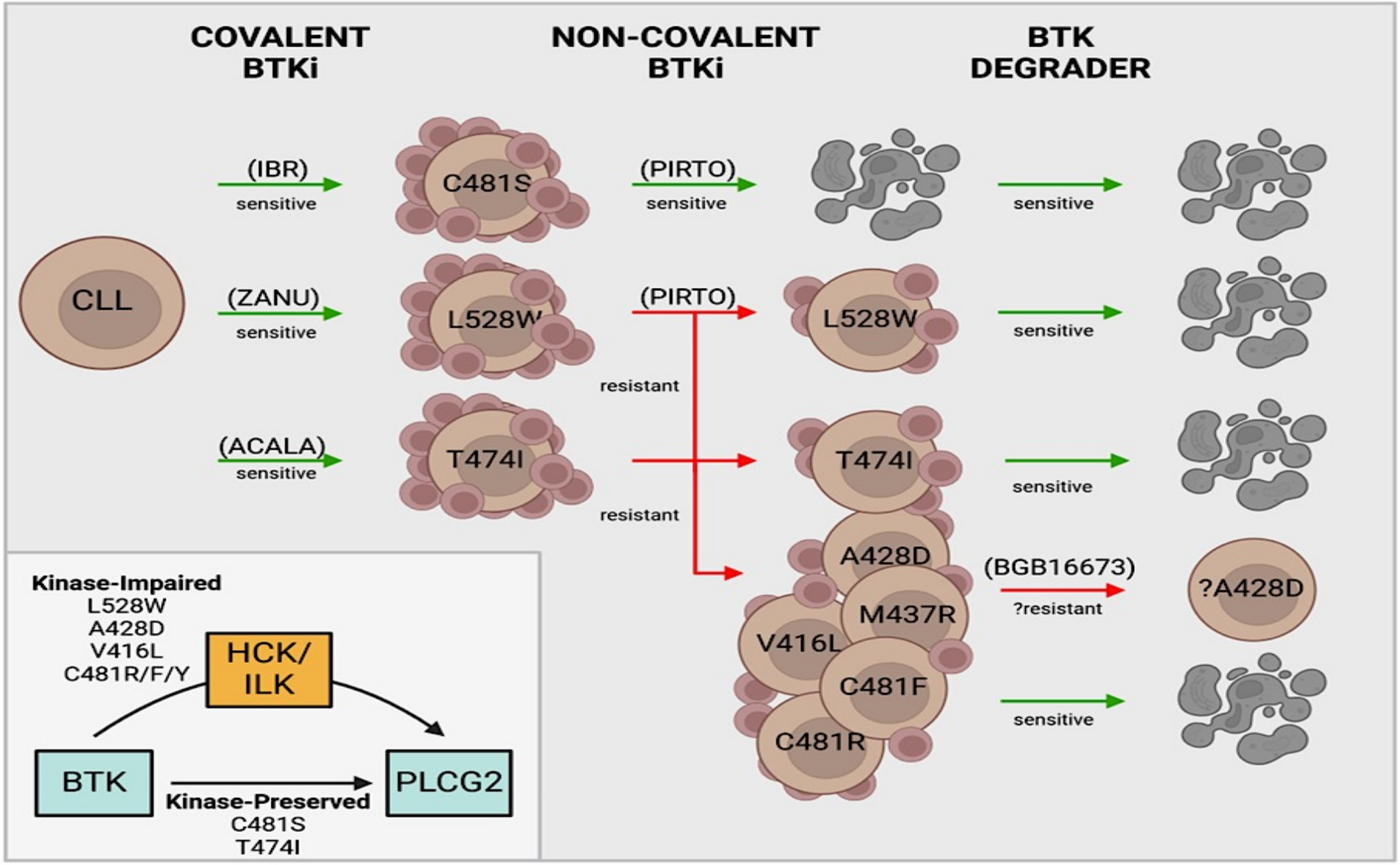


Time to Next Treatment



Eyre TA, ASH, 2025

BTK resistance mutations: Important Research Area but Not Quite Ready for Clinical Practice



Tam C et al., Blood,2025

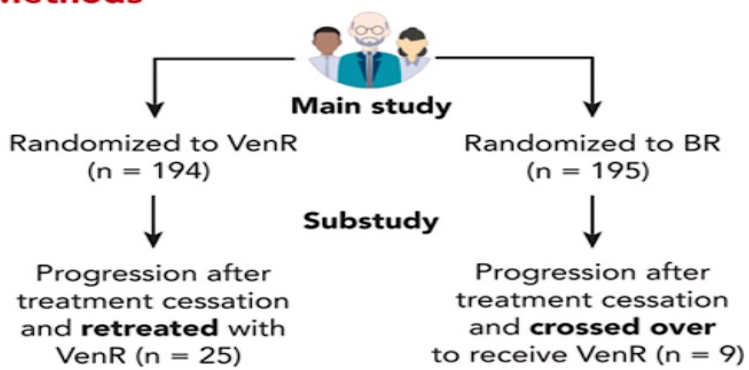
BCL2i-based therapy

Final Analysis of the MURANO Trial: Venetoclax-Rituximab (VenR) vs Bendamustine-Rituximab (BR) in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

Context of Research

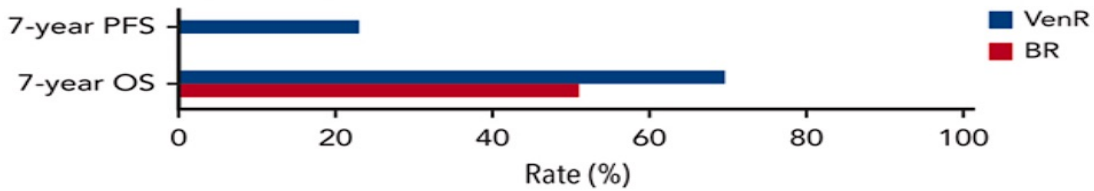
- In the **phase 3 MURANO trial** (**NCT02005471**), fixed-duration VenR resulted in superior progression-free survival (PFS) and overall survival (OS) vs BR
- We report the **final analyses** of MURANO (median follow-up: 7 years), including results of a **retreatment/crossover substudy**

Methods



Main Findings

Survival benefits with VenR vs BR were **sustained**



VenR-treated patients who achieved **undetectable minimal residual disease** (MRD) (n = 83):

Substudy Results

VenR retreatment (n = 25)
Median PFS: 23.3 months
Best overall response rate: 72.0%

VenR crossover (n = 9)
Median PFS: 26.7 months
Best overall response rate: 88.9%

Conclusions: This final long-term analysis of the MURANO trial continues to demonstrate clinically meaningful benefits for fixed-duration VenR over BR in patients with R/R CLL. Retreatment with VenR is a viable option for pretreated patients.

*Kater et al. DOI: 10.1182/**blood**.2024025525*

blood Visual Abstract

Venetoclax-Based Therapy After cBTKi in CLL: Real-World Evidence (CORE Study)

- Multicenter RWE
- CORE Registry 2018-2023
- cBTKi:
  - Ibrutinib 85% ;
  - Acalabrutinib 7%
- Ven:
  - monotherapy 60%,
  - VenR 31%;
  - VenO 9%
- Reason for cBTKi DC
  - Intolerance 43%;
  - PD 37%

Efficacy Outcomes

Population/Subgroup	ORR %	Median PFS (mo)	18-mo PFS %	Median TTNT-D (mo)
Overall (N=205)	**79.4**	**44.1**	76.2	44.2
1L cBTKi → 2L Ven	85.1	43.2	80.8	NR
2L cBTKi → 3L Ven	80.4	44.3	82.1	44.2
Intolerance (DI; N=88)	**85.0**	**NR**	84.1	NR
1L cBTKi → 2L Ven	86.4	39.5	84.1	39.5
2L cBTKi → 3L Ven	88.5	NR	89.0	NR
Progression (DP; N=76)	**76.5**	**30.1**	71.0	30.4
1L cBTKi → 2L Ven	90.0	31.9	62.2	31.9
2L cBTKi → 3L Ven	68.4	31.8	73.1	37.4
Ven+Rituximab (VR; N=64)	**71.4**	**39.5**	77.0	37.4
1L cBTKi → 2L Ven	78.9	43.2	88.4	NR
2L cBTKi → 3L Ven	73.3	36.3	85.9	37.4

ORR = physician-assessed CR or PR. PFS = venetoclax start → progression/death. TTNT-D = venetoclax start → next treatment/death. NR = not reached. 1L/2L/3L = first/second/third line.

Key Takeaways

① High real-world ORR

Overall ORR ~80% after cBTKi; consistent across 2L (85%) and 3L (80%) therapy

② Durable PFS regardless of line

Median PFS 43–44 mo in both 2L and 3L settings, even after prior CT/CIT (44 mo)

③ Intolerance > Progression

DI group: median PFS NR · DP group: median PFS ~30 mo; cBTKi progression = more aggressive disease

④ VR effective in cBTKi-exposed

Fixed-duration VR: ORR 71%, 18-mo PFS 77%; largest real-world VR dataset post-cBTKi

⑤ Compares favorably to M14-032

Median PFS 44 mo (real-world) vs 24.7 mo (M14-032 phase 2 trial) in heavily pretreated pts

Ghosh N et al. Am J Hematol. 2025;100:511–515

Venetoclax Retreatment in CLL/SLL

Cohort	n	1st Ven Regimen	Time Off Ven (mo)	2nd Ven Regimen	ORR / CR (%)	uMRD PB (%)	Median PFS
Shadman et al[49] Real-world	48	Ven mono 58% Ven-O/R 33% · Ven-BTKi 8%	21 (9–32)	Ven mono / Ven-O/R Ven-BTKi (mixed)	NR	NR	TTNTD 25.9 mo
Niemann et al[50] GAIA/CLL13	49	Ven-R · Ven-O · Ven-O-Ibr (all 1L)	~12–15	Ven-based 23 · Ven-Acala 24 Ven-O-Acala 2	NR	NR	**2-yr TFS: 81–100%**
Brander et al[51] M13-365	9	Ven-R (continuous; stop at uMRD)	**38 (17–69)**	Ven-R	**100 / 33**	**22**	**4.9 yr (PFS2: 9.5 yr)**
Kater et al[52] MURANO	25	Ven-R (≥2L 100%)	28 (14–37)	Ven-R	**72 / 24**	**32**	**23 mo (>2yr: 24; <2yr: 14)**
Davids et al[53] REVENG	25	Ven-O (≥2L 43%)	**53 (19–90)**	Ven-O (Co-1: 12 mo; Co-2: 24 mo)	**100 / 20**	**85**	NR (f/u 10 mo)
Mazot et al[54] CLL2-BAG	7	Ven-O MRD-guided (all 1L)	**68**	Ven-O MRD-guided	**100 / NR**	**43**	**33 mo**
Krestin et al[55] HOVON/REVEAL	15/44	Ven-O 47% · Ven-R 53% (all 1L)	36 (31–43)	Ven-Acala (24 mo)	**100 / 36**	**BM:21 PB:43**	1 PD at 30 mo
Ghia et al[48] CAPTIVATE	6	Ven-Ibr	NR	Ven-Ibr	**83 / 33**	NR	NR
Thompson et al[56] Real-world	46	Ven mono 37% · Ven-R 48% Ven-O/Ibr mixed	16 (3–52)	Ven mono/R/O/Ibr (mixed)	**79 / 33**	**42 (PB or BM)**	**25 mo**
Cramer et al[57] GCLLSG	13	Ven-O-Ibr 23% Ven-O 77%	29 (15–55)	Ven-O-Acala 69% Ven-O/mono mixed	**100 / NR**	**92**	**No PD at 19 mo**

ORR
72–100%
across all 10 cohorts

uMRD (PB)
32–92%
substantial heterogeneity

Median PFS
23–58 mo
when reported

Time off Ven
≥2 years
key predictor of response
(MURANO: HR 0.28)

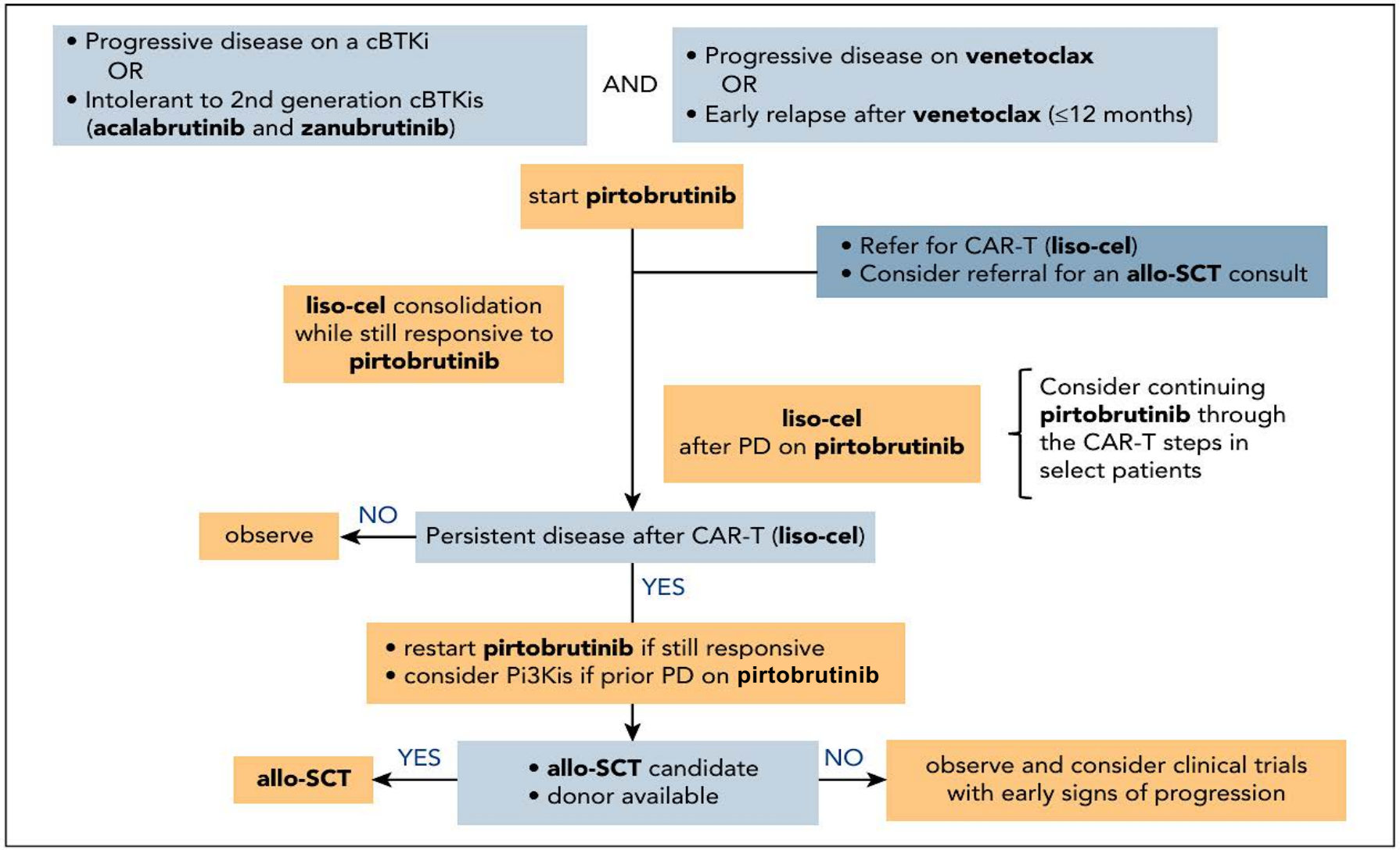
BCL2 mutations absent after FD regimens (MURANO, REVENG, CAPTIVATE) · Ven = venetoclax; O = obinutuzumab; R = rituximab; Ibr = ibrutinib; Acala = acalabrutinib; uMRD = undetectable MRD; PB = peripheral blood; BM = bone marrow; TTNTD = time to next treatment or death; TFS = treatment-free survival; FD = fixed-duration; 1L/2L = first/second-line

From Castonguay et al. Blood Advances 2026;10(10):3357

blood How I Treat

How I treat patients with CLL after prior treatment with a covalent BTK inhibitor and a BCL-2 inhibitor

Mazyar Shadman[1,2] and Matthew S. Davids[3]



Shadman M & Davids DS, Blood, 2025

Emerging BCL2i-based strategies

Pirtobrutinib + Venetoclax + Rituximab in R/R CLL

PRESS RELEASE

Pirtobrutinib significantly extended progression-free survival when added to a venetoclax time-limited regimen in patients with previously treated CLL/SLL

April 13, 2026

BRUIN CLL-322 is the first Phase 3 readout in CLL to utilize and outperform a venetoclax-containing control arm

This trial predominantly enrolled a patient population previously treated with covalent BTK inhibitors, highly relevant to current practice

These results mark the fourth positive Phase 3 study of pirtobrutinib in CLL

STUDY DESIGN

BRUIN CLL-322

Randomized, Open-label, Global Phase 3 Study
(NCT04965493)

N = 600 | 1:1 Randomization

KEY ELIGIBILITY

- CLL/SLL requiring treatment (iwCLL 2018)
- ≤1 prior line of therapy (≤20% BTKi-naïve)
- Known 17p status
- Age ≥18 years; ECOG 0–2

STRATIFICATION FACTORS

- 17p status (deleted vs wildtype)
- Prior BTKi exposure (yes vs no)

1:1 Randomization

ARM A
Pirtobrutinib + Venetoclax + Rituximab

Pirtobrutinib
- 200 mg orally once daily (C1–C28)

Venetoclax
- 20–400 mg 5-week dose ramp starting C4
- 400 mg orally once daily (C5–C28)

Rituximab
- 375 mg/m² intravenously on C1
- 500 mg/m² on D1 of C2–C6

ARM B
Venetoclax + Rituximab

Venetoclax
- 20–400 mg 5-week dose ramp starting C1
- 400 mg orally once daily (C2–C25)

Rituximab
- 375 mg/m² intravenously on C2
- 500 mg/m² on D1 of C3–C7

CYCLE LENGTH
28 days (Arm B Cycle 1 = 35 days)

STUDY ENDPOINTS

PRIMARY ENDPOINT

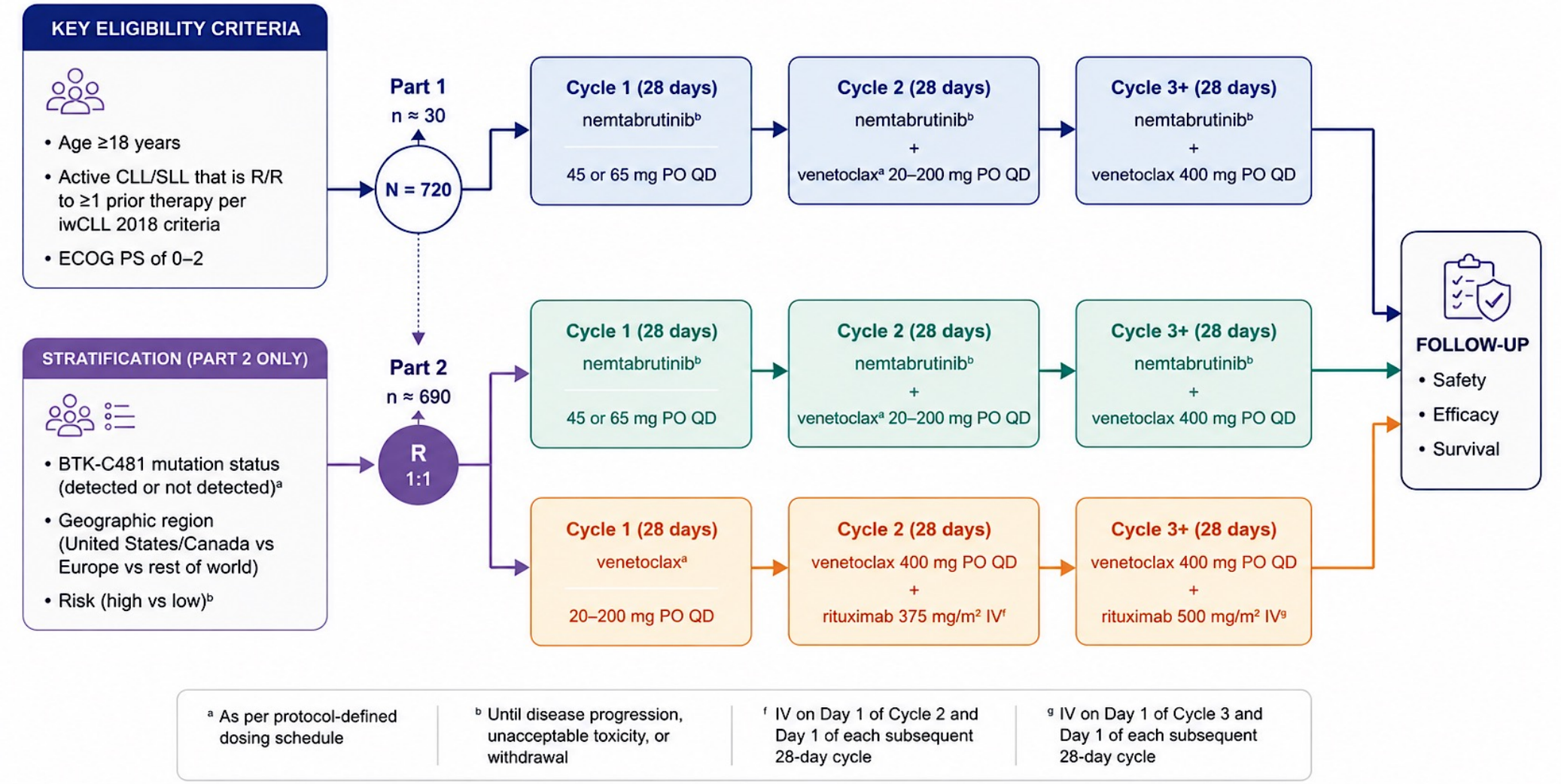
- Progression-free survival (PFS) per iwCLL 2018, as assessed by Independent Review Committee (IRC)

SECONDARY ENDPOINTS

- PFS, as assessed by investigator
- Overall response rate (ORR), as assessed by investigator and IRC
- Overall survival (OS) and time to next treatment
- Event-free survival, as assessed by investigator
- Safety and tolerability
- Patient-reported outcomes (PROs)

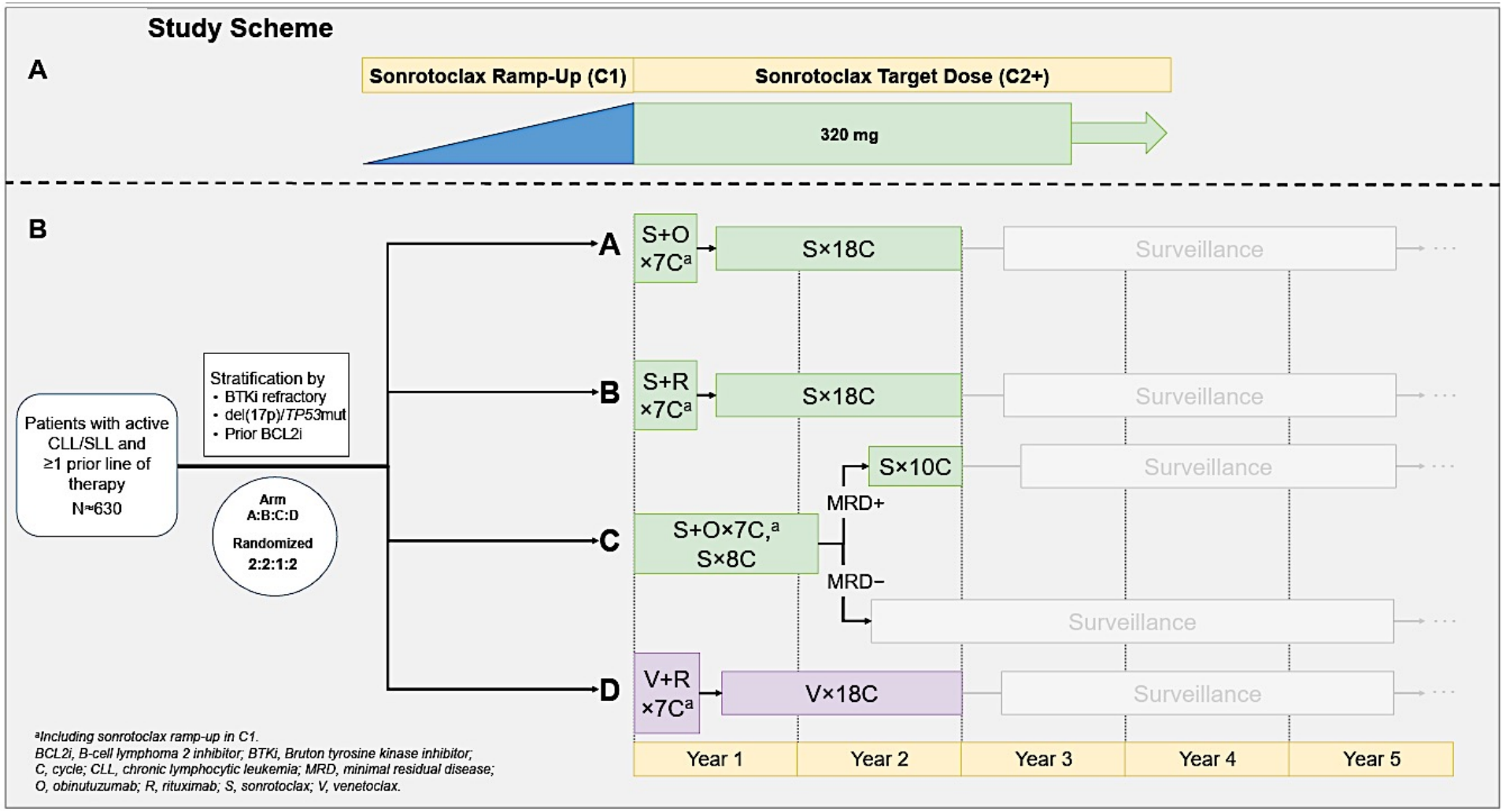
iwCLL 2018: International Workshop on CLL 2018; BTKi: Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma

Venetoclax plus Nemtabrutinib in R/R CLL: BELLWAVE-010



Lavie D. et al, iwCLL, 2025

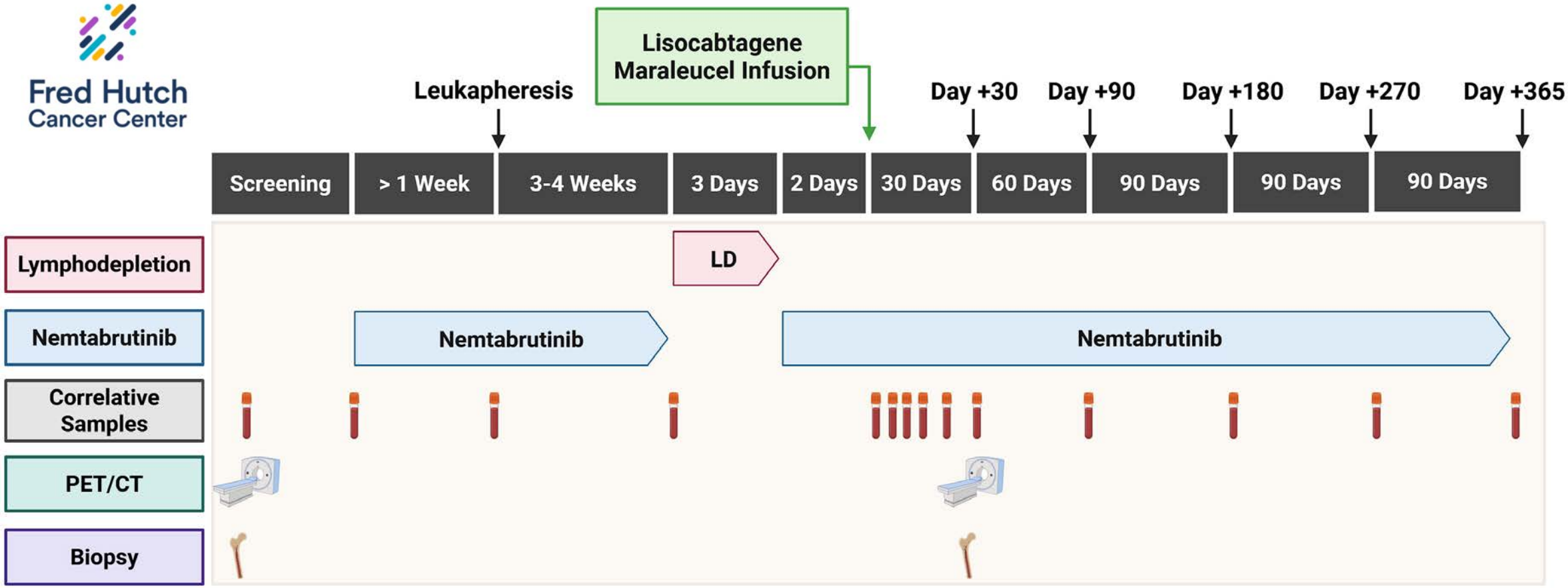
Sonrotoclax in R/R CLL: CELESTIAL-RRCLL



Al-Sawaf O, ASH, 2025 (TiP)

Emerging BTK targeting agents

Addition of Nemtabrutinib plus Liso-Cel in CLL: NemCAR CLL



NCT07194980

Novel BTK Targeting Agents in Development

	Mechanism of action	N	N of prior lines	Prior cBTKi	Prior ncBTKi	Prior BCL2i	TP53 aberrant	BTK resistance mutations	ORR	Median F/U (m)	PFS
Rocbrutinib	cBTKi and ncBTKi	42	4 (2-9)	100%	21%	45%	58%	C481S 65% T474I 31% L528W 5% PLCG2 10%	62-78%	30	Median 28 months
Bexobrutideg (NX-5948)	BTK degrader	126	3 (1-17)	84%	27%	62%	NR	BTK 40% PLCG2 8%	83%	16	Median 22 months
BGB-16673	BTK degrader	68	4 (2-10)	94%	21%	82%	67%	BTK 40% PLCG2 15%	85-94%	20	66% at 18 months

Woyach J et. Al , ASH, 2025 ; Omer Z et al, ASH, 2025; Ahn IE, et al, ASH, 2025

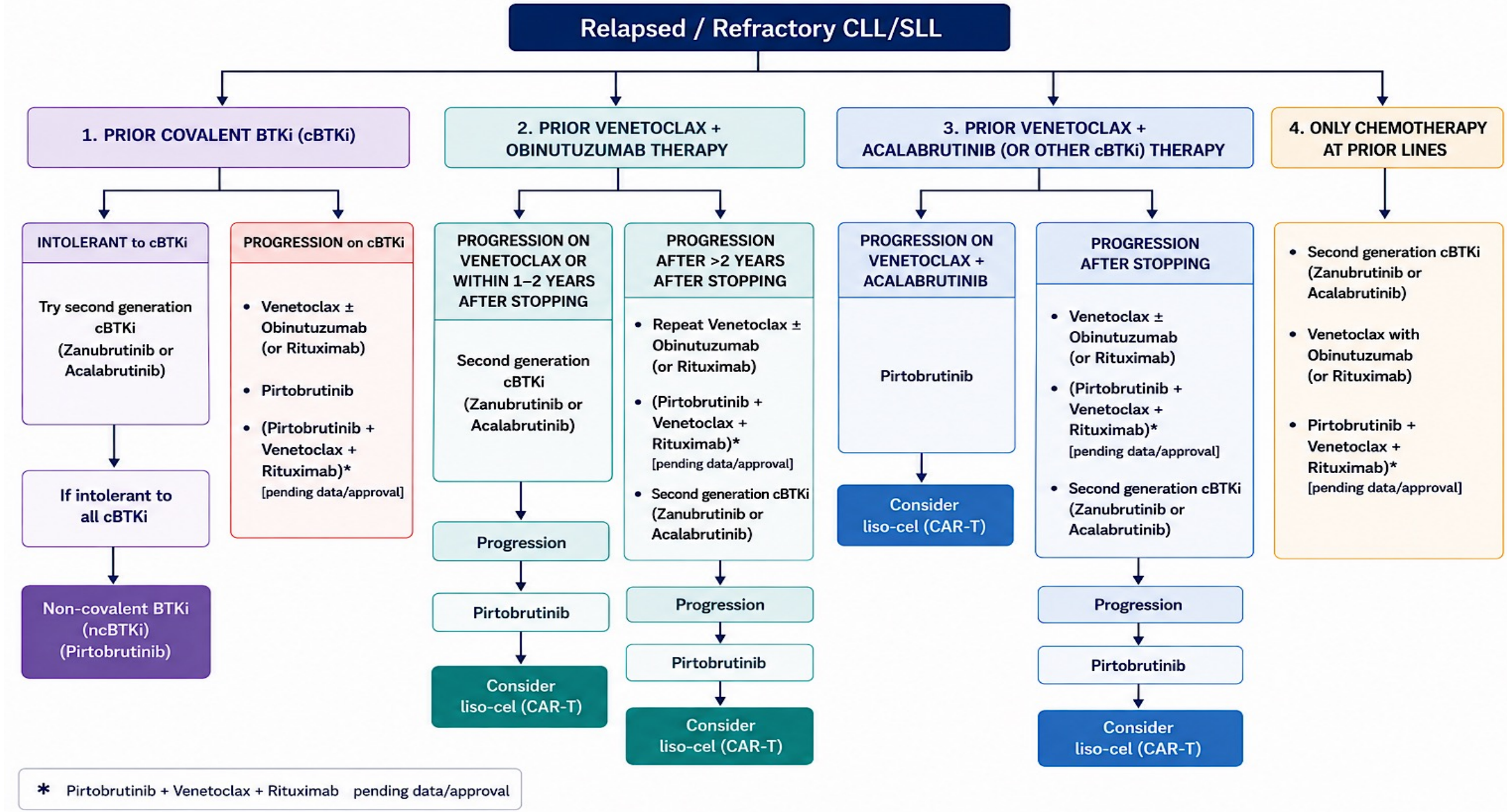
Summary

- If a covalent BTK inhibitor (cBTKi) is no longer an option (due to progression or intolerance):
  - BCL2 inhibitor–based therapy
    - Venetoclax + anti-CD20 antibody
    - PVR (Pirtobrutinib + Venetoclax + Rituximab) may become a standard-of-care option pending data and regulatory approval
    - Pirtobrutinib monotherapy

- If a BCL2 inhibitor–based regimen is no longer a feasible fixed-duration option:
  - cBTKi therapy (zanubrutinib or acalabrutinib)

- For patients with double-refractory disease, referral for CAR-T cell therapy is recommended while the disease remains under control.

TREATMENT OF RELAPSED/REFRACTORY CLL/SLL



Cases from the Community

Priya Rudolph, MD, PhD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Discussion Questions

When would you expect to see a drop and/or normalization of leukocytosis and lymphocytosis after initiation of BTK inhibitor therapy? Does this differ at all for covalent BTK inhibitors versus pirtobrutinib?

What would you recommend for this patient whose white blood cell count and absolute lymphocyte count continue to rise despite 10 months of pirtobrutinib therapy?

How might the results from the BRUIN CLL-322 trial affect the way you think through pirtobrutinib use in the R/R setting? For which specific patients would you be most inclined to favor pirtobrutinib/venetoclax/rituximab over other available options?

Would you consider substituting pirtobrutinib for a covalent BTK inhibitor for a patient with BTK inhibitor-naïve disease under any circumstances? If so, which ones?

Agenda

Module 1: Current and Future Role of Continuous Bruton Tyrosine Kinase (BTK) Inhibitor Therapy for Previously Untreated Chronic Lymphocytic Leukemia (CLL) — Dr Fakhri

Module 2: Available and Emerging Approaches to Time-Limited Therapy for Treatment-Naïve CLL — Dr Allan

Module 3: Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Ma

Module 4: Selection and Sequencing of Therapy for R/R CLL — Dr Shadman

Module 5: Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL — Dr Abramson

Mass General Brigham
Cancer Institute

CAR T-Cell Therapy and Other Novel Strategies for CLL

Jeremy S. Abramson, MD, MMSc
Professor of Medicine, Harvard Medical School
Director, Center for Lymphoma, Mass General Brigham Cancer Institute

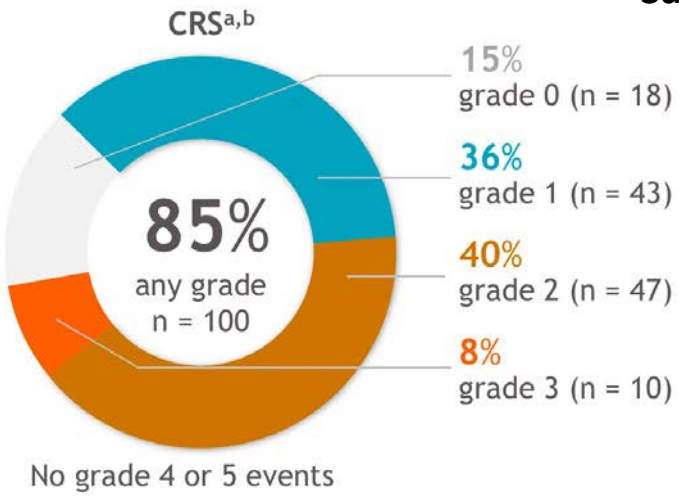
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

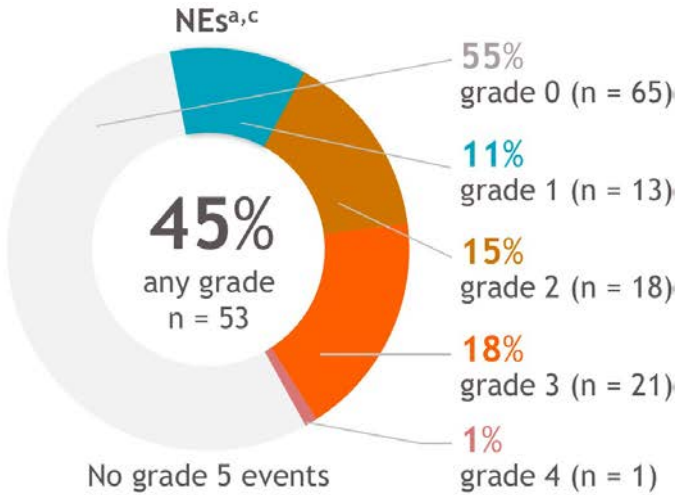
Liso-cel for relapsed/ refractory CLL and RT

TRANSCEND-CLL: lisocabtagene maraleucel in R/R CLL

Characteristic	N = 118
Median age (range), years	65 (49-82)
TP53 mutation Del(17p)	47% 42%
Median prior lines of therapy	5 (2–14)
Prior cBTKi	100%
cBTKi refractory	88%
Prior cBTKi and venetoclax	81%
cBTKi and venetoclax refractory	60%

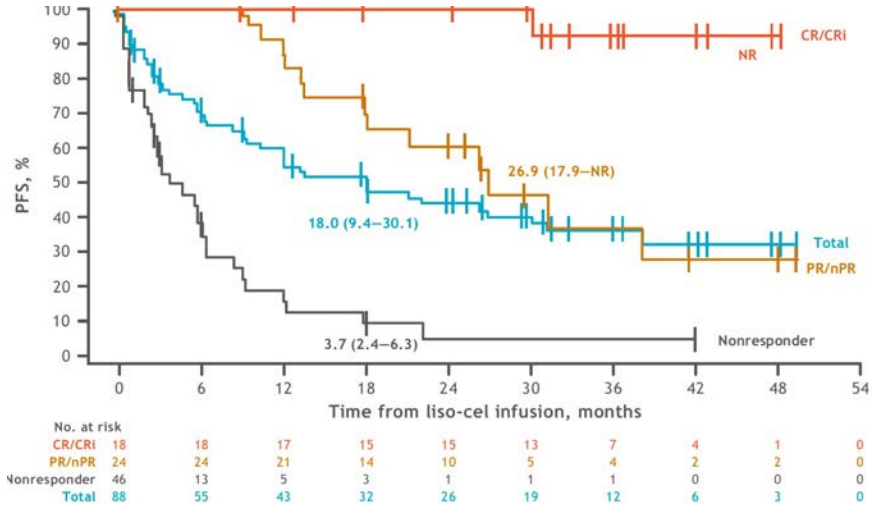
Safety



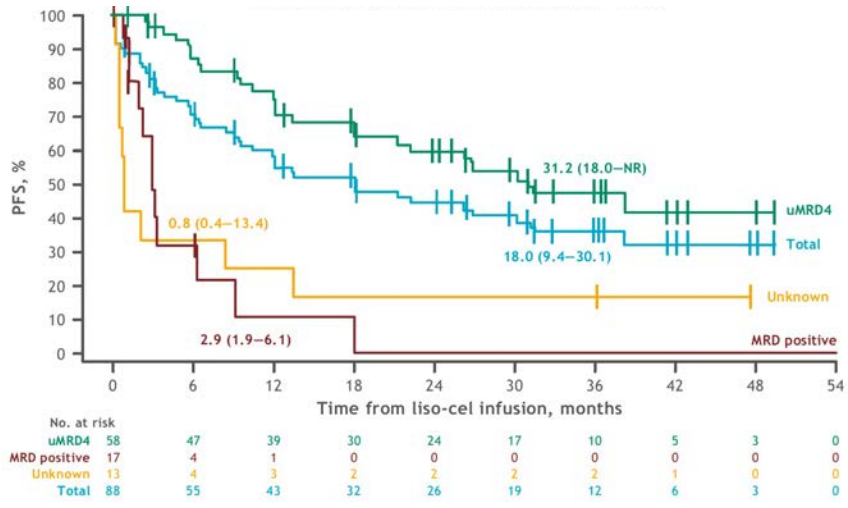


Response at DL2	N = 88
ORR CRR	48% 20%
uMRD4, blood UMRD4, marrow	66% 60%
Median PFS	18 mo

PFS by Response



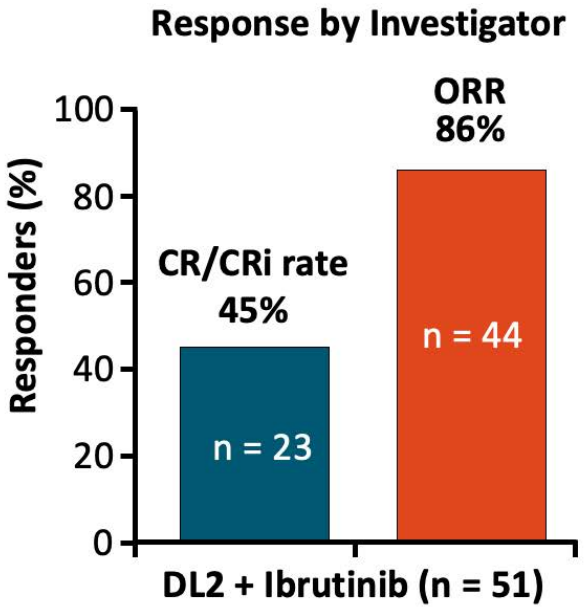
PFS by uMRD

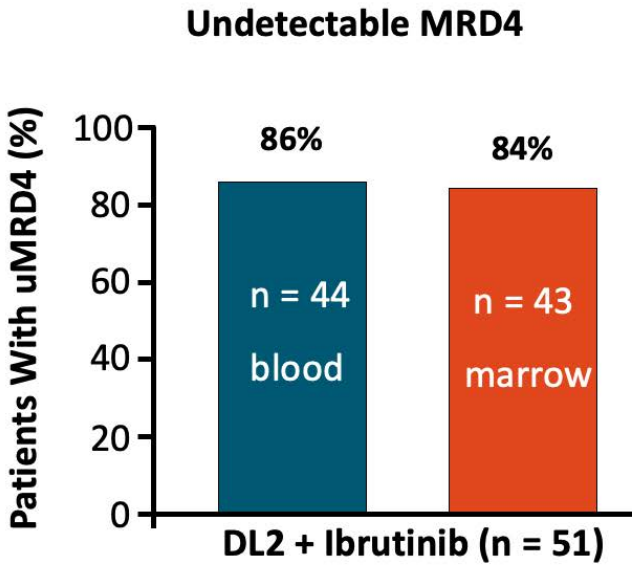


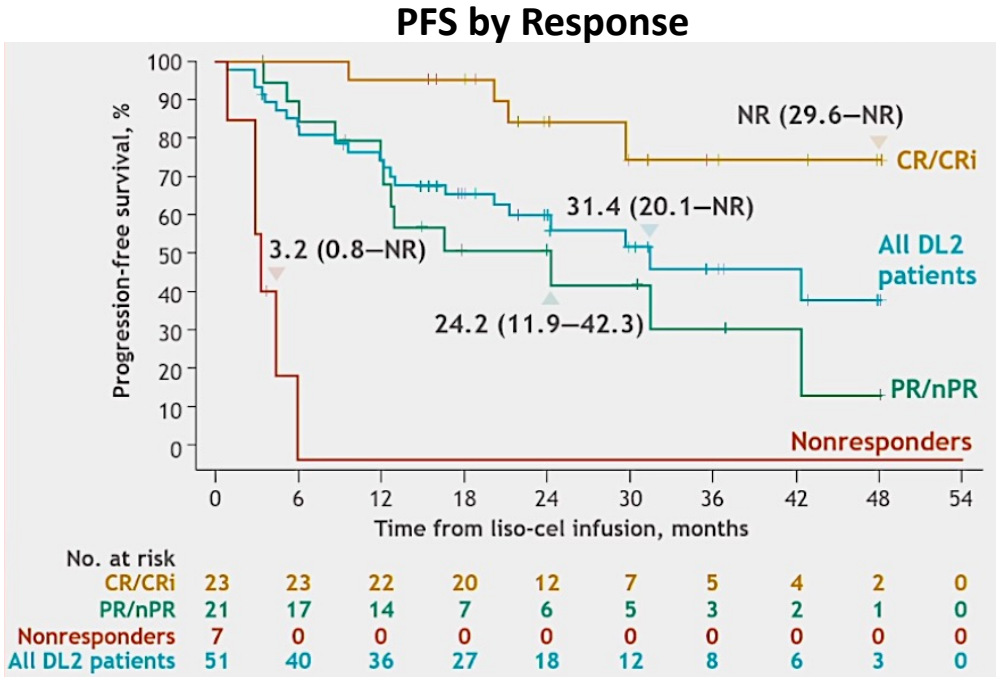
Sidiqqi, et al. Proc ASH 2024

TRANSCEND-CLL: liso-cel plus ibrutinib

Ibrutinib started/continued at enrollment and continued to at least 90 days post liso-cel







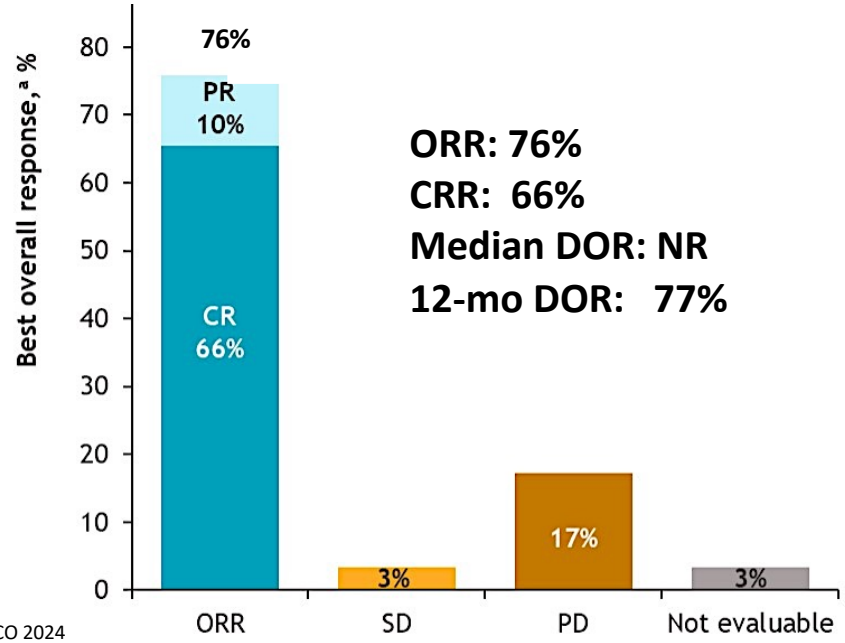
CRS	n = 56
Any grade CRS, n (%)	45 (80)
▪ Grade 1	20 (36)
▪ Grade 2	23 (41)
▪ Grade 3	2 (4)
▪ Grade 4	0
▪ Grade 5	0

Neurologic events	n = 56
Any grade neurologic event	23 (41)
▪ Grade 1	8 (14)
▪ Grade 2	9 (16)
▪ Grade 3	5 (9)
▪ Grade 4	1 (2)
▪ Grade 5	0

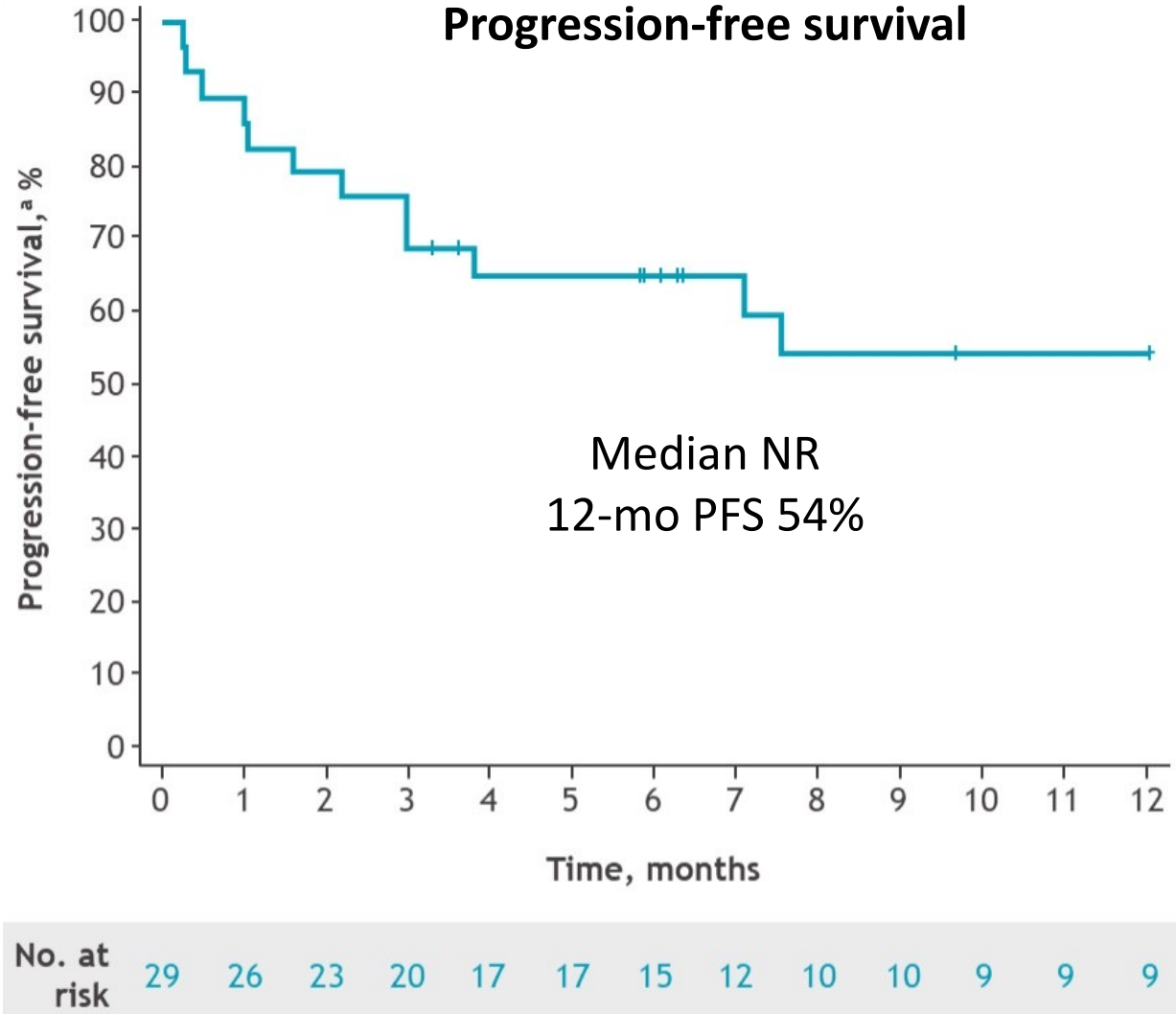
Wierda, et al. Proc ASH 2024

Liso-cel in Richter's Transformation: CIBMTR

Characteristic	N = 30
Median age (range), years	66 (44-82)
TP53 mutation Del(17p)	40% 46%
Refractory to prior line	40%
Prior chemoimmunotherapy	97%
Prior CLL therapy	77%



ORR: 76%
CRR: 66%
Median DOR: NR
12-mo DOR: 77%



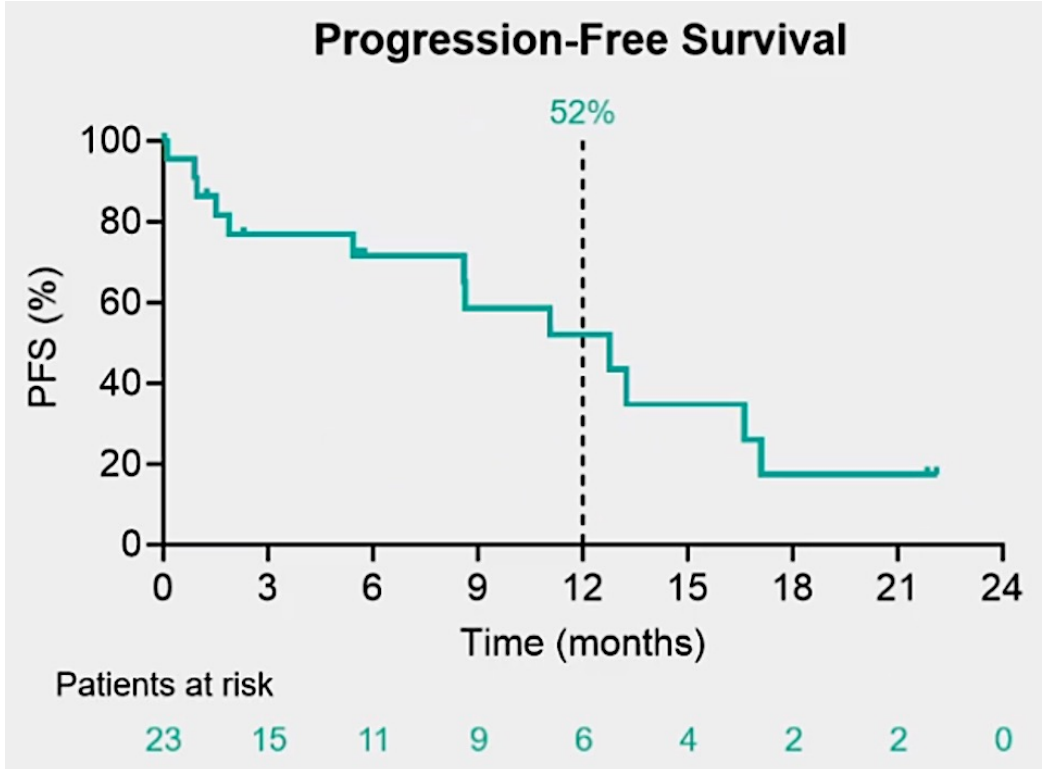
Winter, et al. Proc ASCO 2024

Bispecific Abs for relapsed/ refractory CLL and RT

Epcoritamab, an anti-CD20/CD3 bispecific antibody in relapsed/refractory CLL

Characteristic	All patients N = 23
Median age, years (range)	72 (55-83)
TP53 aberrations, n (%)	15 (65)
Median prior lines of tx, n (range)	4 (2–10)

Best response	N = 23
Best response, n (%)	
ORR	14 (61)
CR	9 (39)



Median PFS 13 months

Danilov, et al. Proc ASH 2024.

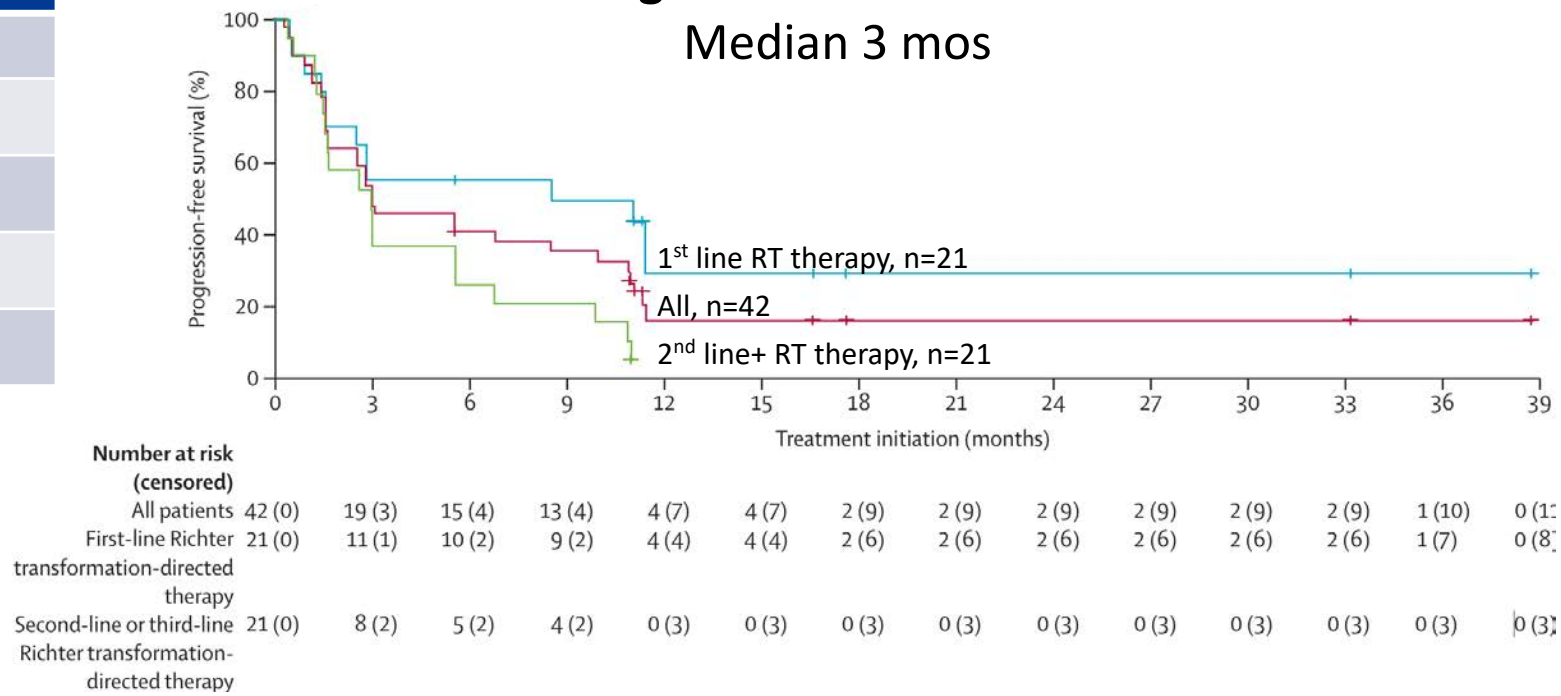
Epcoritamab in Richter's transformation

Characteristic	N = 42
Median age, years	69
Elevated LDH	76%
TP53 aberration	48%
Prior chemoimmunotherapy	95%
Prior CLL therapy	76%

Best response	N = 42
ORR	48%
CRR	40%
Median DOR	10 m

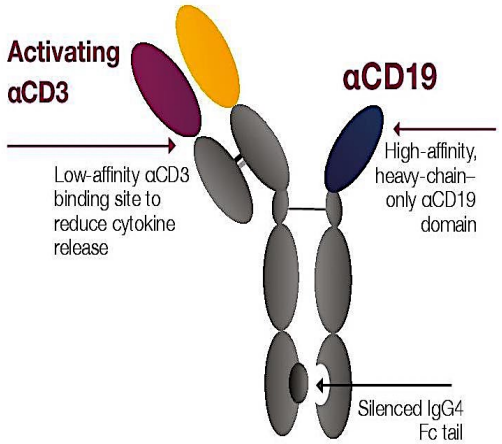
Progression-free survival

Median 3 mos



Kader, et al. Lancet Haem 2026

Surovatamig: A CD19 x CD3 bispecific antibody



SOUNDTRACK-C1 Trial Schema

Phase III Study of Surovatamig (SC) as Consolidation Therapy in CLL/SLL with unmutated IGHV

Study design
Phase III, global, randomized, open-label

Planned enrollment
~420 participants

Population
CLL/SLL with uIGHV after frontline finite therapy

Sites
~100 sites across multiple countries

1. ELIGIBILITY
Key criteria

- CLL/SLL with unmutated IGHV
- Completed frontline finite-duration therapy
- Achieved PR or better (per iwCLL criteria)
- ECOG 0–2
- Adequate organ function

2. PART 1
DOSE OPTIMIZATION / SAFETY RUN-IN

Surovatamig SC

- Step-up dosing with CRS mitigation
- Two dose levels explored
- Safety and tolerability assessment
- Determine RP3D for Part 2

Proceed to Part 2 using RP3D

3. PART 2 – RANDOMIZATION (1:1)

ARM A

Surovatamig Consolidation

Surovatamig SC (RP3D)

Step-up dosing in Cycle 1 then full dose

≈ 6 cycles (≈ 24 weeks)

1:1 R

ARM B

Observation (No active therapy)

Standard follow-up per protocol

4. ENDPOINTS

PRIMARY ENDPOINTS

- Progression-Free Survival (PFS) (Investigator assessed per iwCLL criteria)
- MRD-based Efficacy (uMRD rates in PB and BM at predefined time points)

SAFETY
Incidence of AEs, CRS, ICANS, infections

Novel agents targeting BCL2 and BTK

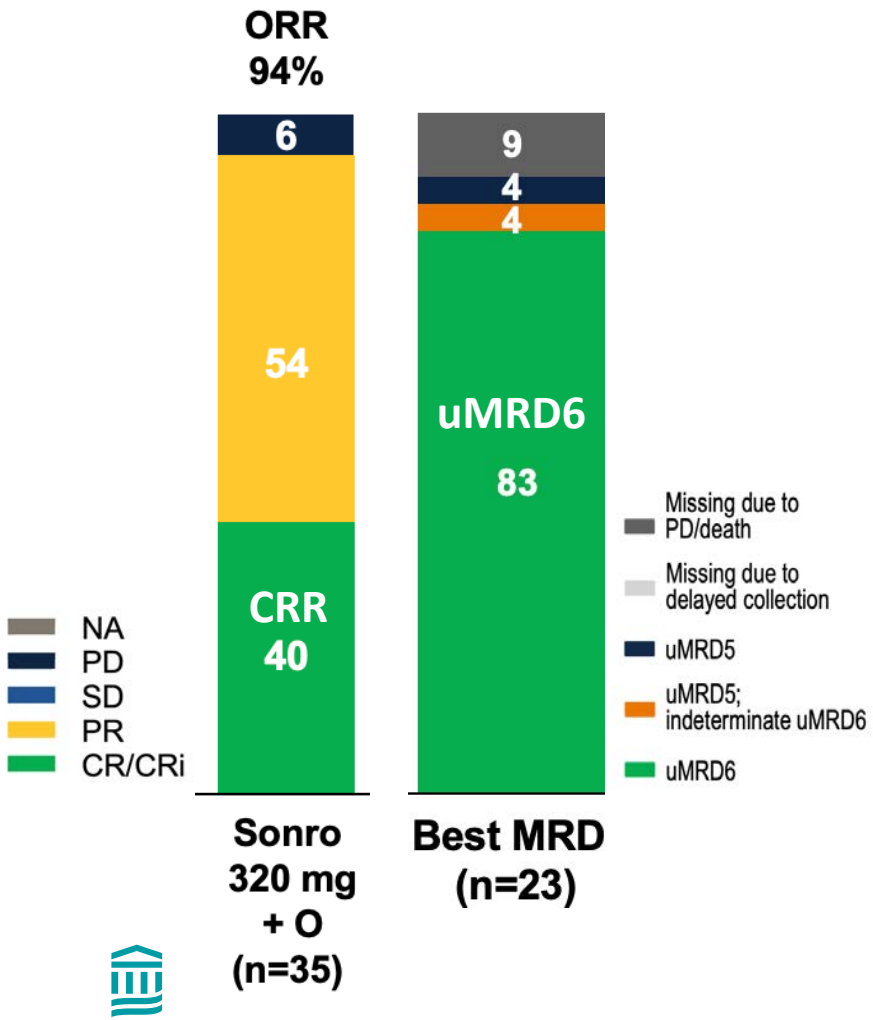
Sonrotoclax, a next-generation BCL2 inhibitor

	Sonrotoclax	Venetoclax	Clinical implication for sonrotoclax
Potency (IC_{50})	0.014 nM[1]	0.20 nM[1]	14-fold more potent, which may lead to deeper target inhibition
Selectivity (vs BCL-xL)	2000×[1]	325×[1]	Improved (6-fold) selectivity may improve tolerability
Half-life in humans	≈5 hours[2]	26 hours[3]	No accumulation may improve tolerability Short half-life results in simplified TLS monitoring

1. Liu J, et al. *Blood*. 2024;143(18):1825-1836; 2. Cheah CY, et al. ASH 2022. Abstract 962; 3. Venclexta (venetoclax). Prescribing information. AbbVie Inc; 2022.

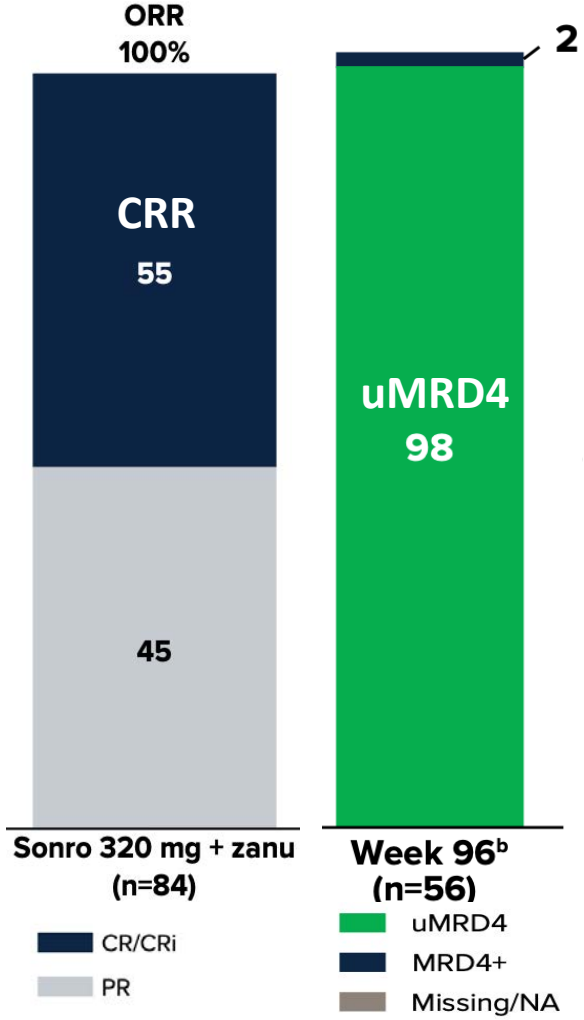
Sonrotoclax combinations in CLL: early data

Sonrotoclax + Obinutuzumab



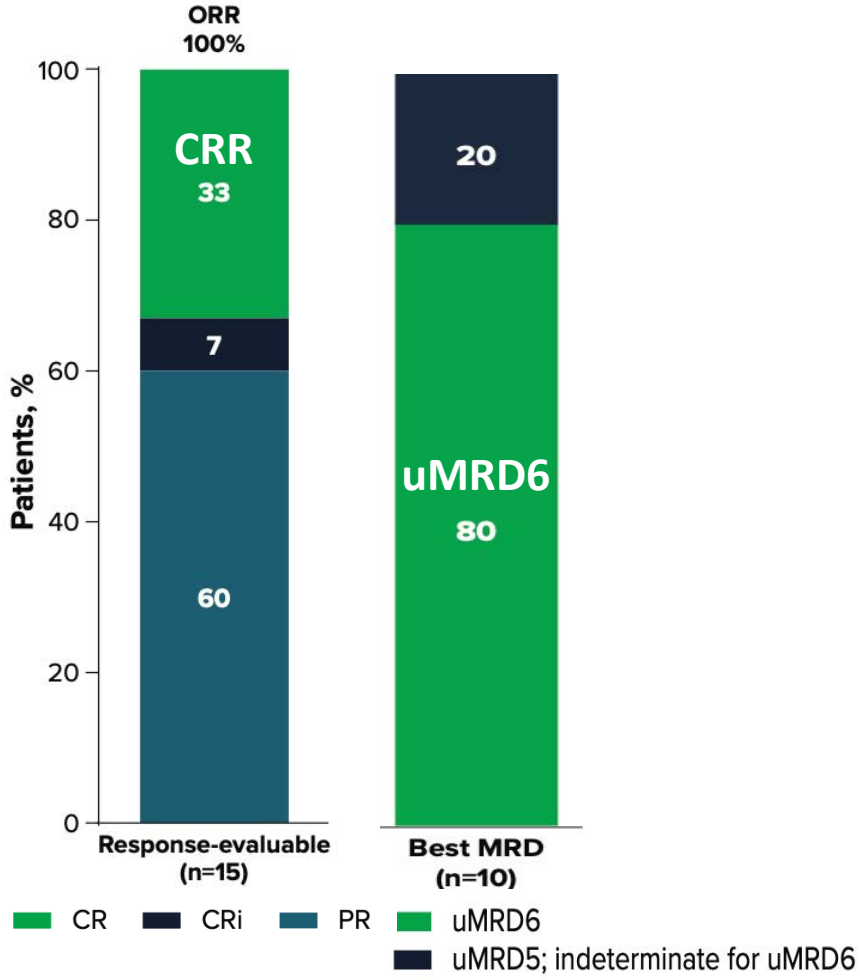
Hoffmann, et al Proc ASH 2025

Sonrotoclax + Zanubrutinib



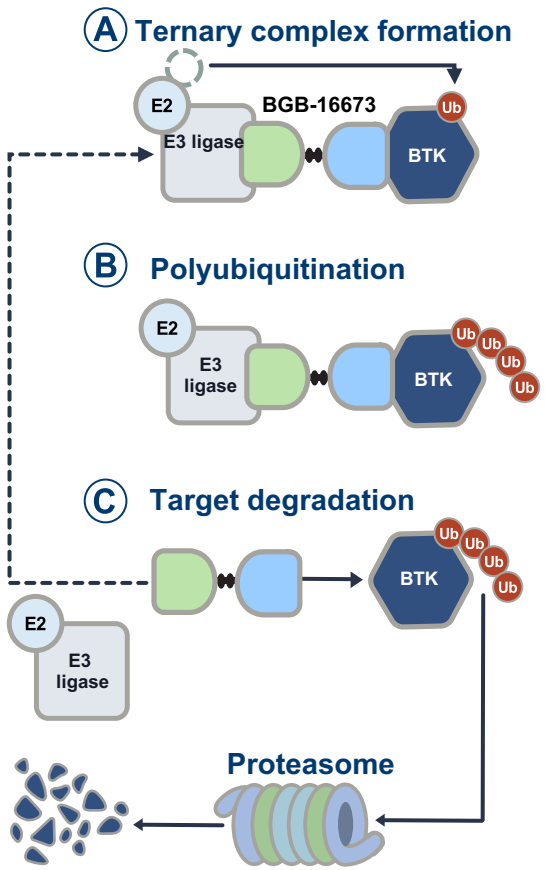
Tam, et al Proc ASH 2025

Sonrotoclax-Zanu-Obin

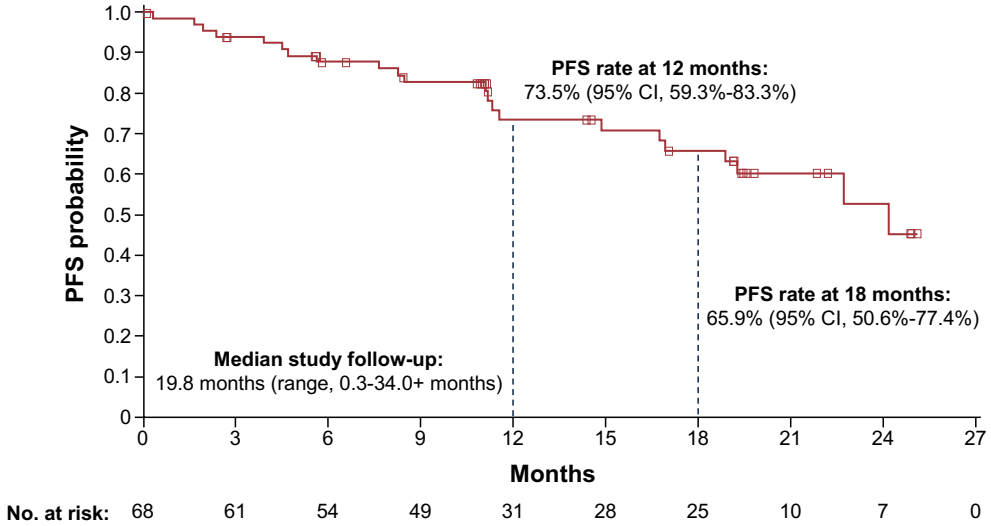


Soumerai, et al Proc ASH 2025

BGB-16673, a BTK degrader, in relapsed/refractory CLL



Characteristic	N = 68
Median age (range), years	70 (47-91)
mutTP53/del(17p)	68%
Median prior lines of therapy	4 (2–10)
Prior cBTKi	94%
Prior BCL2i	82%
Prior cBTKi and BCL2i	65%
Prior ncBTKi	21%
BTKi refractory	89%



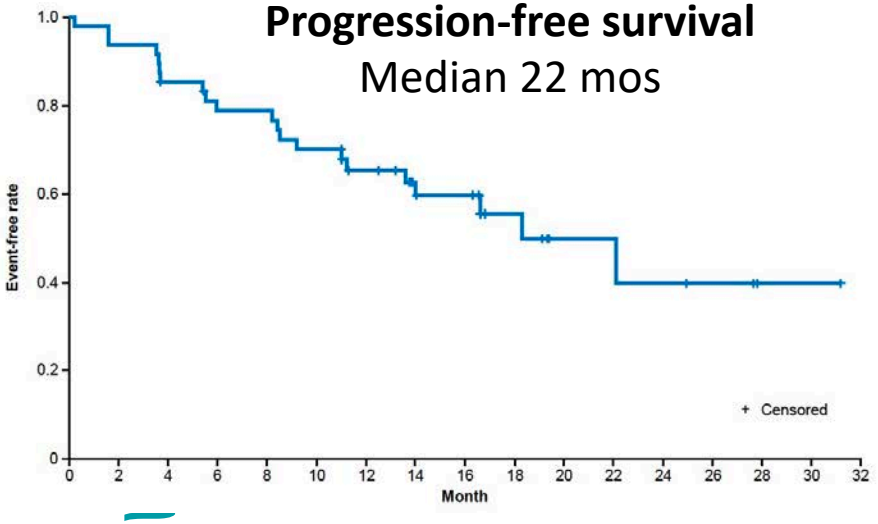
Characteristic, N (%)	ORR
All patients (n=68)	85%
Prior cBTKi + BCL2i	41/44 (93)
Prior cBTKi + BCL2i + ncBTKi	9/12 (75)
6 or more prior lines of therapy	13/16 (81)
del(17p) and/or TP53 mutation	37/46 (80)
Complex karyotype (≥3 abnormalities)	16/22 (73)
BTK mutations	20/26 (77)
PLCG2 mutations	9/10 (90)

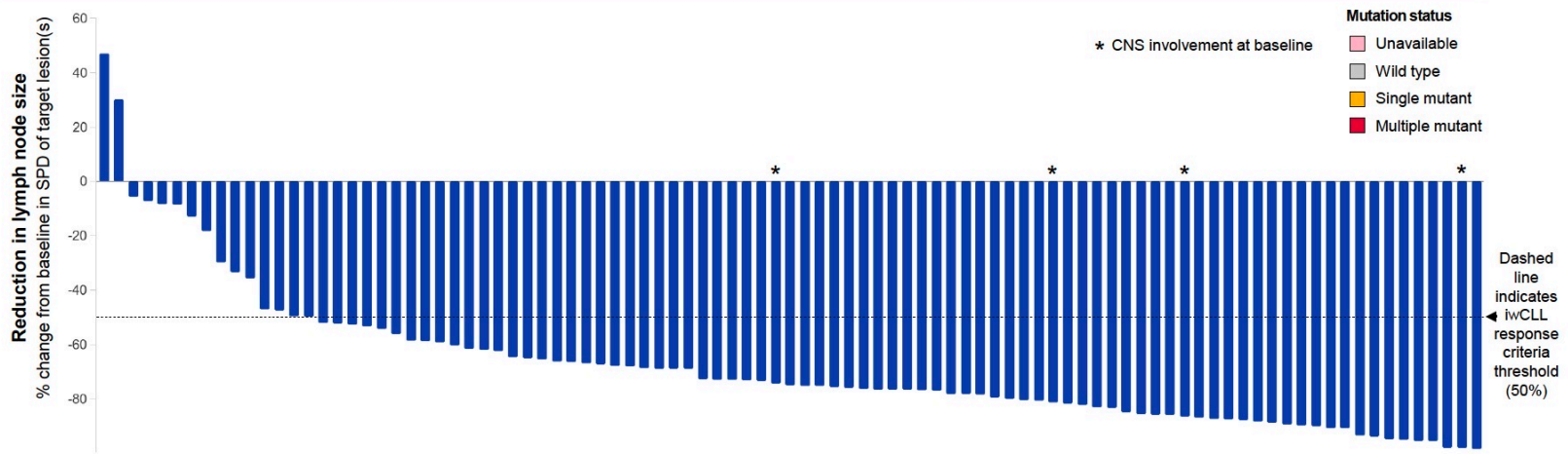
- The most common TEAEs were fatigue (36.8%) and bruising (30.9%)
- Grade ≥3 neutropenia: n=17 (25.0%); Neutropenic fever: n=1
- Atrial fibrillation: n=3 (grade 1, n=1; grade 2, n=2; all transient)
- Treatment-related major hemorrhage: n=2 (one grade 3 SDH and one grade 3 post-procedural hematuria)

Ahn, et al. Proc ASH 2025

Bexobrutideg, a BTK degrader, in relapsed/refractory CLL

Characteristic	N = 126
Median age (range), years	69 (35-88)
mutTP53	40%
BTK mutation	40%
Median prior lines of therapy	3 (1-17)
Prior c/nc BTKi	86%
Prior BCL2i	62%
Prior BTKi and BCL2i	60%





Subgroup	Number of patients with a response/total number[a]	Objective response rate, % (95% CI)
ORR in Phase 1a population	39/47	83 (69–92)
Discontinued due to PD on any prior BTKi	25/33	76 (58–89)
Prior therapy		
Prior BCL2i and BTKi	31/38	82 (66–92)
Prior non-covalent BTKi	8/13	62 (32–86)
Mutations		
TP53 mutation	15/20	75 (51–91)
Any baseline BTK mutation	14/17	82 (57–96)
C481 BTK mutation	9/9	100 (66–100)
L528/T474/V416/G541 BTK mutation	7/10	70 (35–93)
Wild-type BTK	24/29	83 (64–94)
Prior lines of systemic therapies received		
≥4 prior lines	21/26	81 (61–93)

Omer, et al. Proc ASH 2025

Cases from the Community

Stephen “Fred” Divers, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Discussion Questions

At what point in the treatment course are you referring your patients with CLL for consultation regarding CAR T-cell therapy? Does this differ based on patient age or risk status?

For patients with R/R CLL who are eligible to receive both strategies, how do you select between pirtobrutinib and CAR T-cell therapy?

How do you approach bridging therapy for patients for whom CAR T-cell therapy will be employed, and how does the pace of the disease affect this decision?

What other novel agents and strategies currently being explored in CLL are you most excited about?

Cases from the Community

Susmitha Apuri, MD
Florida Cancer Specialists
& Research Institute
Inverness and Lecanto, Florida

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Northside Hospital Cancer Institute
Athens, Georgia

Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
Hot Springs, Arkansas

Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Management of Ovarian Cancer

Saturday, May 30, 2026
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Ramez N Eskander, MD
Ursula Matulonis, MD
Alexander B Olawaiye, MD
David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

RTP
RESEARCH
TO PRACTICE

What Clinicians Want to Know: Addressing Community Oncologists' Questions About the Care of Patients with Prostate Cancer

Saturday, May 30, 2026

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Wassim Abida, MD, PhD

Rahul Aggarwal, MD

Emmanuel S Antonarakis, MD

Karim Fizazi, MD, PhD

Moderator

Rana R McKay, MD, FASCO

RTP RESEARCH TO PRACTICE

Second Opinion: Investigators Provide Perspectives on the Current and Future Management of Small Cell Lung Cancer

Saturday, May 30, 2026
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Anne Chiang, MD, PhD
Apar Kishor Ganti, MD, MS
Luis Paz-Ares, MD, PhD

Moderator

Misty Dawn Shields, MD, PhD

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RESEARCH
TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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