

Data + Perspectives: Investigators Discuss the Optimal Management of Chronic Lymphocytic Leukemia

A CME/MOC-Accredited Live Webinar

Thursday, September 17, 2026

5:00 PM – 6:00 PM ET

Faculty

Catherine C Coombs, MD

Matthew S Davids, MD, MMSc

Moderator

Neil Love, MD

Faculty



Catherine C Coombs, MD

Associate Clinical Professor
Division of Hematology/Oncology
Department of Medicine
UCI Health
Orange County, California



Matthew S Davids, MD, MMSc

Chief, Division of Lymphoma
Harold and Virginia Lash Endowed Chair
in Lymphoma Research
Dana-Farber Cancer Institute
Leader, Lymphoma Program
Harvard Cancer Consortium
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts



MODERATOR

Neil Love, MD

Research To Practice
Miami, Florida

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Dr Love — Disclosures

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Dr Coombs — Disclosures

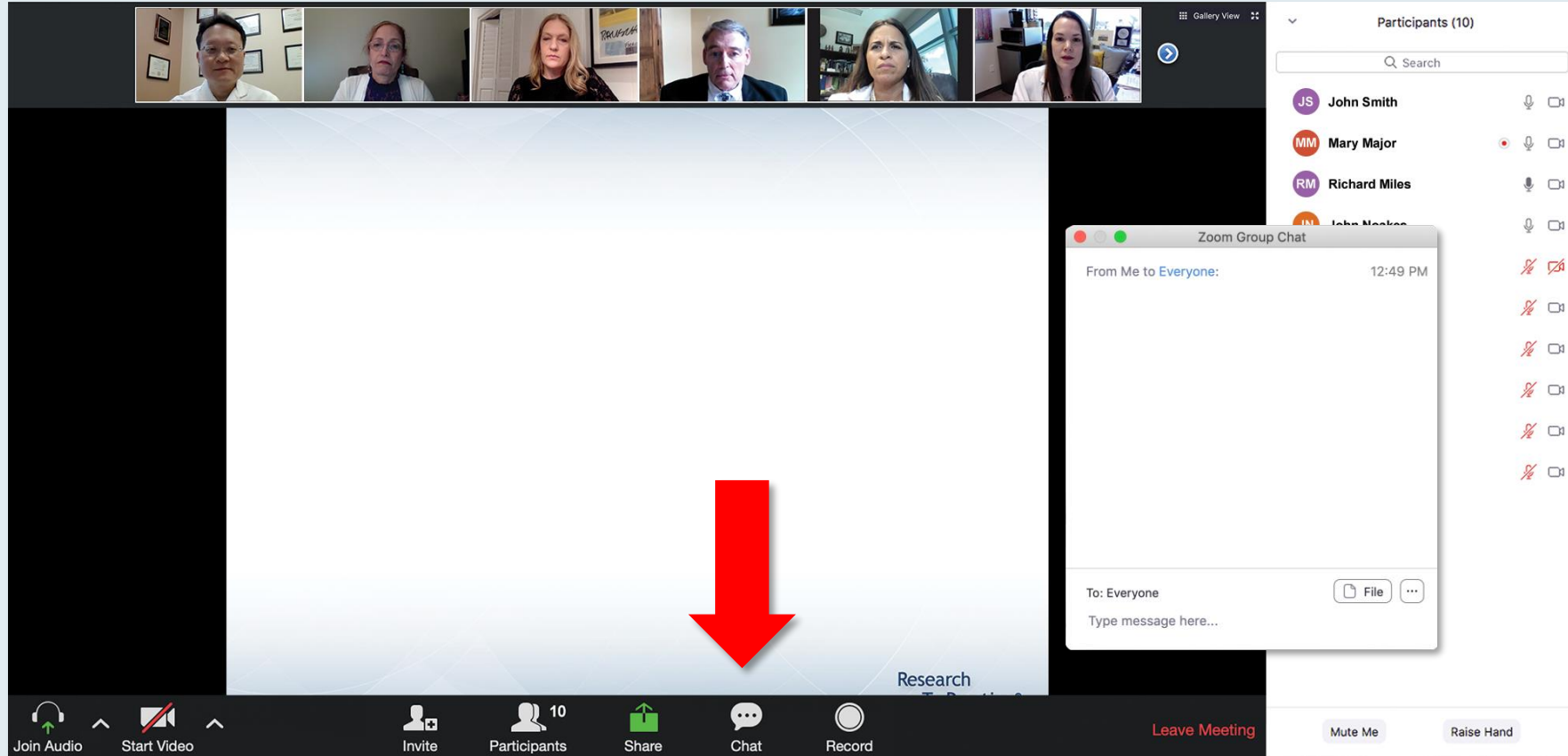
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We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

The screenshot shows a Zoom meeting interface. At the top, there are video thumbnails for participants: RTP Coordinat..., Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. Below the thumbnails is a slide titled "Meet The Professor Program Participating Faculty" featuring six faculty members with their photos and titles. On the right side, there is a chat window. The chat window has a header "Chat" and a dropdown menu set to "Panelists". It contains two messages from "Me to Panelists" dated 4:31 PM, each with a welcome message and a link to a PDF. Below the messages is a white line above the "Type message here..." submission box. A large red arrow points to this white line, indicating that it can be dragged up to expand the submission box.

Meet The Professor Program Participating Faculty

Nancy L Bartlett, MD
Professor of Medicine
Koman Chair in Medical Oncology
Washington University School of Medicine
St Louis, Missouri

Jonathan W Friedberg, MD, MMSc
Samuel E Durand Professor of Medicine
Director, James P Wilmot Cancer Institute
University of Rochester
Rochester, New York

Carla Casulo, MD
Associate Professor of Medicine
Division of Hematology/Oncology
Director, Hematology/Oncology Fellowship Program
University of Rochester
Wilmot Cancer Institute
Rochester, New York

Brian T Hill, MD, PhD
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

Christopher R Flowers, MD, MS
Chair, Professor
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

Chat

Me to **Panelists** 4:31 PM

Welcome and thank you for attending! To access the slides from today's session please use the link below.
http://images.researchtopractice.com/2021/Meetings/Slides/MTP_ToGo_CLL_2021_April1.pdf

Me to **Panelists and Attendees** 4:32 PM

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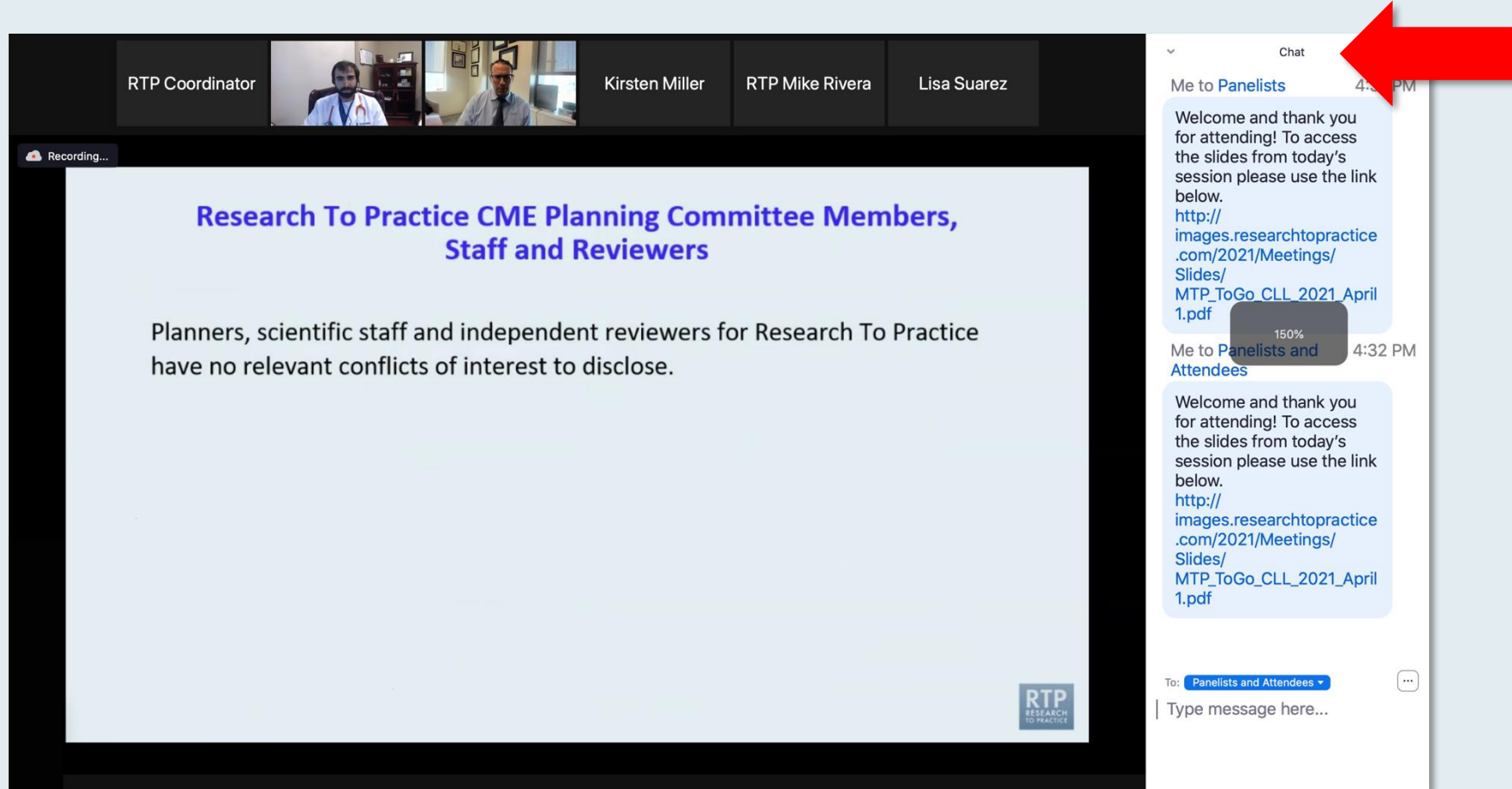
To: **Panelists and Attendees**

Type message here...

Drag the white line above the submission box up to create more space for your message.

Familiarizing Yourself with the Zoom Interface

Increase chat font size



The screenshot displays a Zoom meeting interface. At the top, a gallery view shows participants: RTP Coordinator, Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. The main area shows a presentation slide titled "Research To Practice CME Planning Committee Members, Staff and Reviewers" with the text: "Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose." The slide has an RTP logo in the bottom right corner. On the right, the chat window is open, showing a message from "Me to Panelists" with a link to a PDF. A red arrow points to the font size icon (a square with a plus sign) in the chat window's header, which is currently set to 150%.

**Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.**

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys

The screenshot shows a Zoom meeting with a presentation slide on the left and a 'Quick Survey' pop-up on the right. The slide title is 'Meet The Professor' and the topic is 'Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancer'. It mentions 'Wednesday, August 25, 5:00 PM – 6:00 PM' and lists 'Faculty: Wells A Messersmith, MD' and 'Moderator: Neil Love, MD'. The survey pop-up lists several treatment combinations with radio buttons for selection. A list of 10 participants is visible on the far right.

Meet The Professor
Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancer
Wednesday, August 25, 5:00 PM – 6:00 PM
Faculty
Wells A Messersmith, MD
Moderator
Neil Love, MD

Quick Survey

- ☐ Ceritinib +/- dexamethasone
- ☐ Pomalidomide +/- dexamethasone
- ☐ Ceritinib + pomalidomide +/- dexamethasone
- ☐ Elotuzumab + lenalidomide +/- dexamethasone
- ☐ Elotuzumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + lenalidomide +/- dexamethasone
- ☐ Daratumumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + bortezomib +/- dexamethasone
- ☐ Ixazomib + Rd
- ☐ Other

Submit

Participants (10)

- JS John Smith
- MM Mary Major
- RM Richard Miles
- JN John Noakes
- AS Alice Suarez
- JP Jane Perez
- RS Robert Stiles
- JF Juan Fernandez
- AK Ashok Kumar
- JS Jeremy Smith

The screenshot shows a Zoom meeting with a presentation slide on the left and a 'Quick Poll' pop-up on the right. The slide title is 'Regulatory and reimbursement issues aside, which would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) who has a follow-up 3 years later is found to have asymptomatic (PS 0)?'. It lists 8 treatment options. The poll pop-up lists the same 8 options with radio buttons for selection. A list of 10 participants is visible on the far right.

Regulatory and reimbursement issues aside, which would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) who has a follow-up 3 years later is found to have asymptomatic (PS 0)?

1. Nivolumab/ipilimumab
2. Avelumab/axitinib
3. Pembrolizumab/axitinib
4. Pembrolizumab/lenvatinib
5. Nivolumab/cabozantinib
6. Tyrosine kinase inhibitor (TKI) monotherapy
7. Anti-PD-1/PD-L1 monotherapy
8. Other

Quick Poll

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UNIVERSITY OF UTAH HUNTSMAN
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MB, BS
THE UNIVERSITY OF TEXAS
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Integrating New Advances into Community Oncology Practice

*A Multitumor Symposium in Partnership with
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**Saturday, October 17, 2026
7:15 AM – 12:00 PM ET**

The Ritz-Carlton Orlando Grande Lakes | Orlando, Florida

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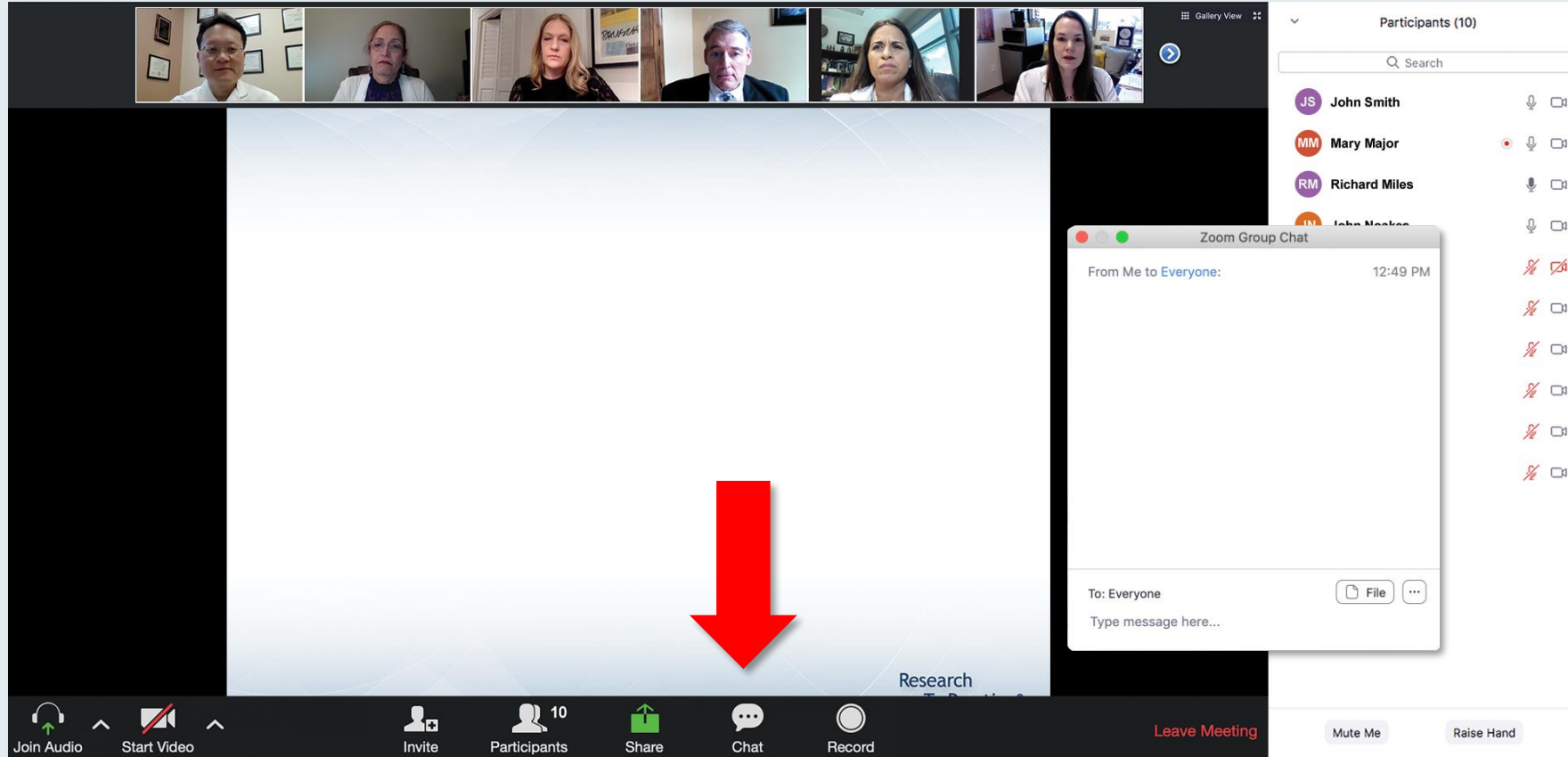


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Regulatory and reimbursement issues aside, what would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) who has a follow-up 3 years later is found to have asymptomatic disease (PS 0)?

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Agenda

Introduction: Minimal Residual Disease Assays in Community-Based Practice

Module 1: New Developments in Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Module 2: Richter Transformation

Module 3: Selection and Sequencing of Therapies for Relapsed/Refractory CLL

Agenda

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New Developments in Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Matthew S Davids, MD, MMSc

Chief, Division of Lymphoma

Harold and Virginia Lash Endowed Chair in Lymphoma Research

Dana-Farber Cancer Institute

Leader, Lymphoma Program

Harvard Cancer Consortium

Associate Professor of Medicine

Harvard Medical School

Boston, Massachusetts

Key Datasets — BTK (Bruton Tyrosine Kinase) and Bcl-2 Inhibitor Combinations

- Brown JR et al. Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia. *N Engl J Med* 2025;392(8):748-62.
- Davids MS et al. Majic: A Phase 3 Prospective, Multicenter, Randomized, Open-Label Trial of Acalabrutinib plus Venetoclax versus Venetoclax plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. ASH 2021;Abstract 1553.
- Shadman M et al. Zanubrutinib and Venetoclax for Patients with Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with and without Del(17p)/TP53 Mutation: SEQUOIA Arm D Results. *J Clin Oncol* 2025;43(21):2409-17.

Dr Davids: Case Presentation

76 y/o man was diagnosed 3 years ago with del(11q), IGHV unmutated, *TP53* wildtype CLL and observed for 3 years but now progressing with bulky lymph nodes and cytopenias and needs treatment. Co-morbidities include hypertension and well-controlled type 2 DM. He prefers time-limited therapy and is able to travel for clinic visits but this is somewhat challenging logistically for him.



How would you treat this patient?

AMPLIFY

TN CLL (N=867)

Key inclusion criteria

- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria¹
- Without del(17p) or *TP53*^a
- ECOG PS ≤2

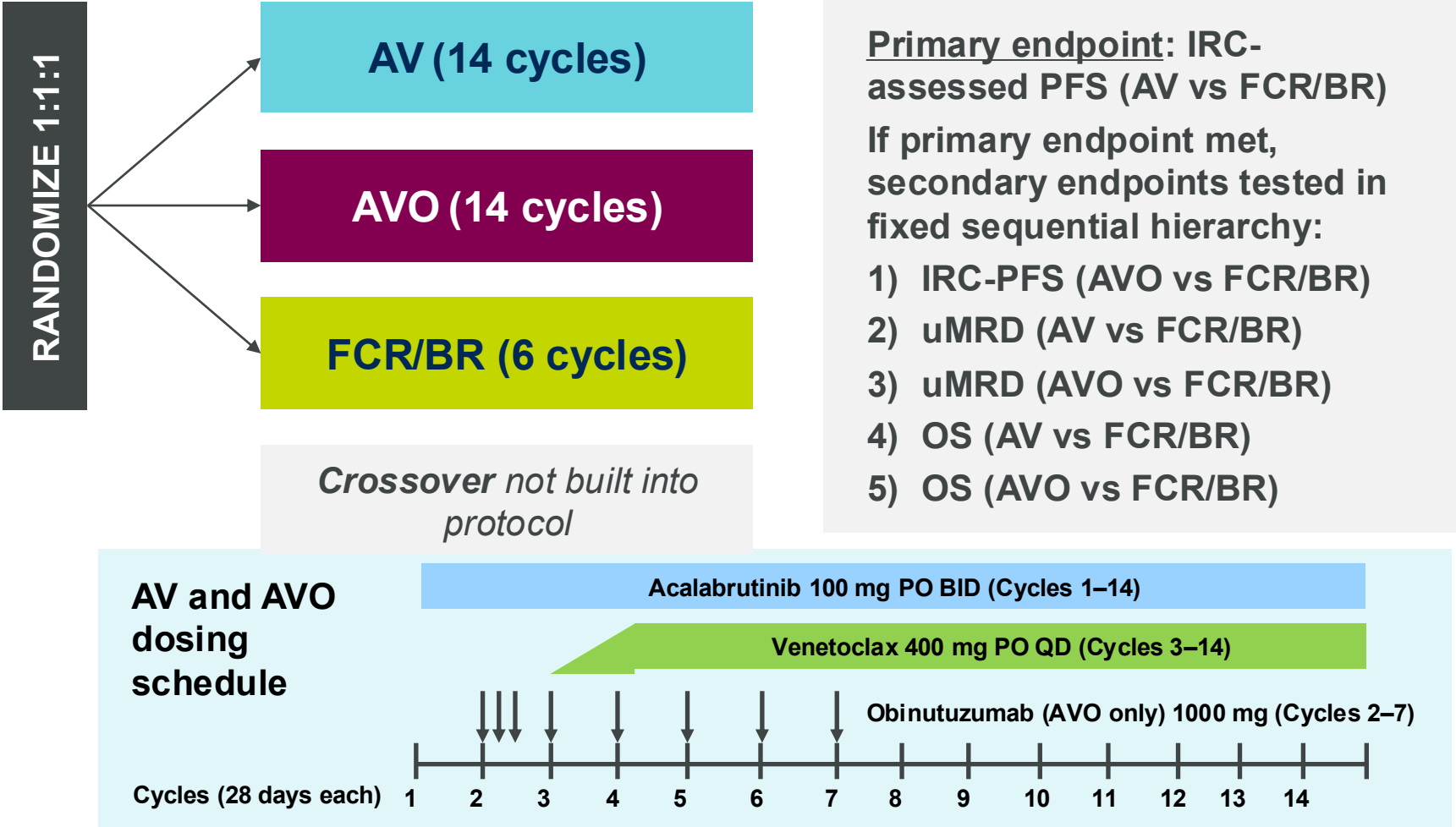
Key exclusion criteria

- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification

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

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



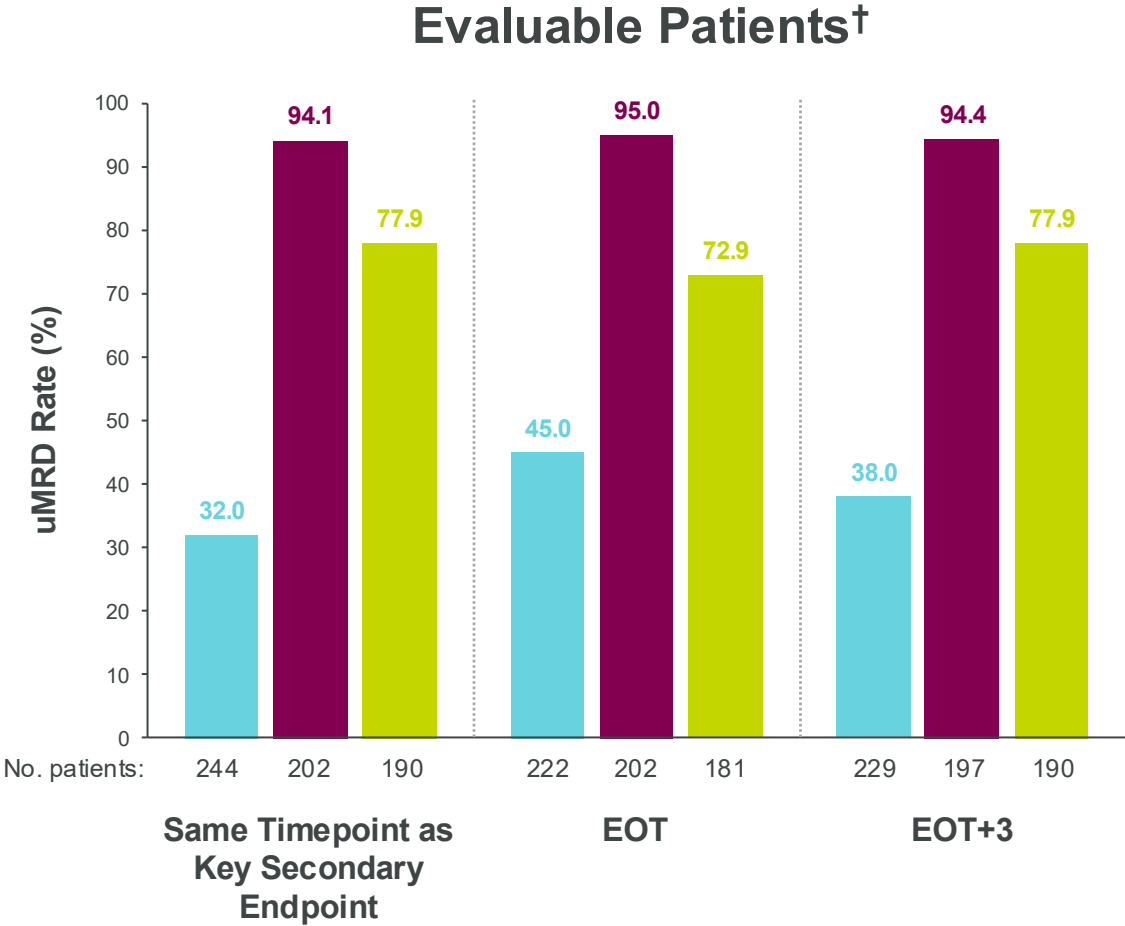
NCT03836261. Data cutoff: April 30, 2024.

^aAssayed by central lab.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CIRS-Geriatric, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene; iwCLL, International Working Group on CLL; OS, overall survival; PFS, progression-free survival; TN, treatment-naïve; uMRD, undetectable measurable residual disease.

AMPLIFY: uMRD Rates (Flow Cytometry [$<10^{-4}$] in PB)

AV AVO FCR/BR

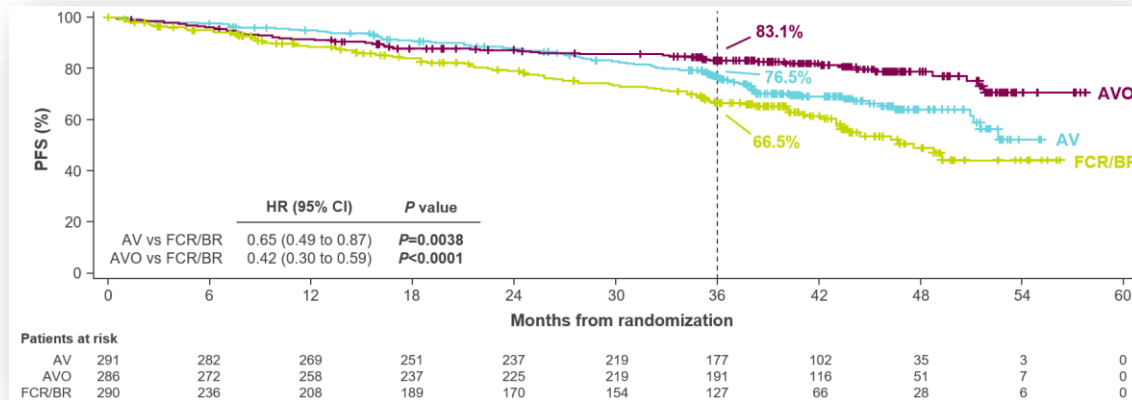


Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

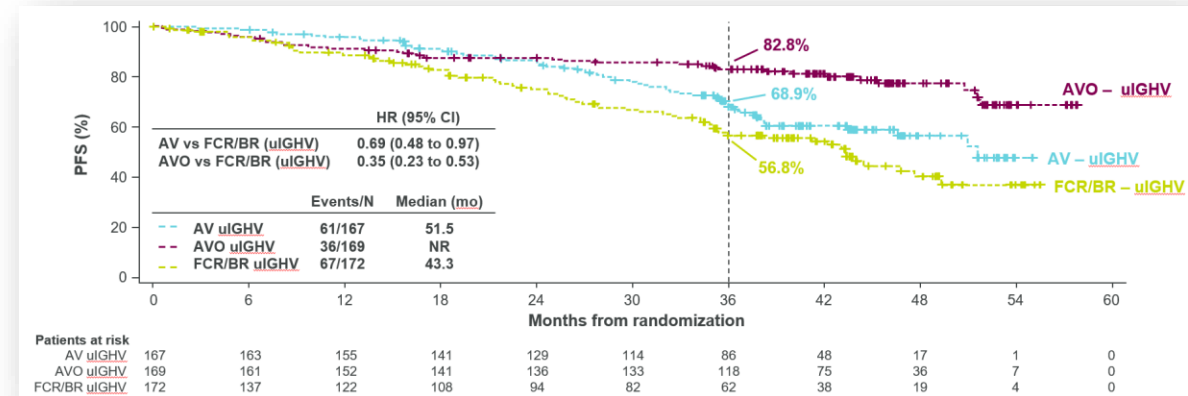
Key secondary endpoint (ITT population): AV vs FCR/BR: $P<0.0001$ (favoring FCR/BR); AVO vs FCR/BR: $P=0.0003$ (favoring AVO).
*ITT population: all randomized patients regardless of whether MRD assessment was performed at the specified time point (missing assessments considered MRD+).
[†]Evaluative patients: those with MRD assessment at the specified timepoint.
EOT: cycle 14 day 28 for AV ($\pm$ obinutuzumab); cycle 6 day 1 ($\pm$ 28-day window) (FCR/BR).

AMPLIFY: PFS

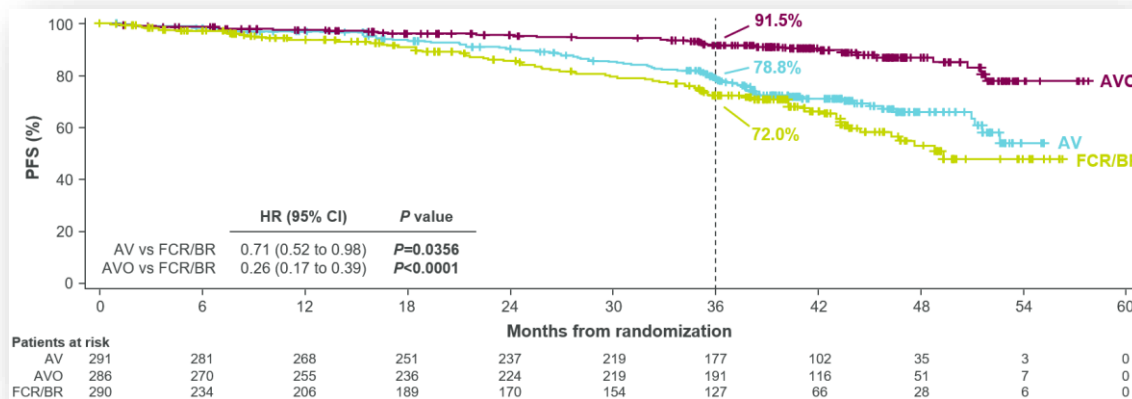
IRC-assessed (primary endpoint)



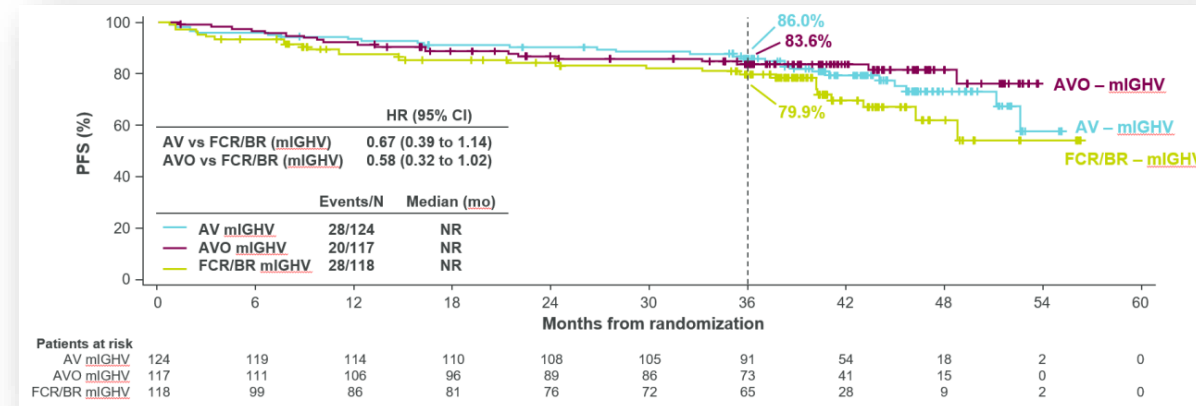
PFS - uIGHV



IRC-assessed (censoring COVID-19 deaths)



PFS - mIGHV



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

Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.

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.

AMPLIFY: Safety / Events of Clinical Interest

	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.

^aVentricular 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).

^bIncludes 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.

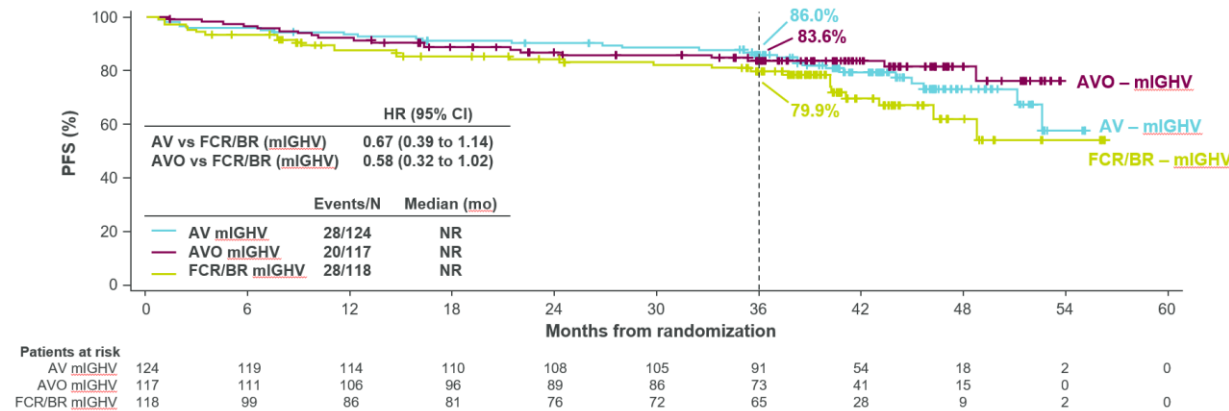
AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECI, event of clinical interest; FCR, fludarabine-cyclophosphamide-rituximab.

Dr Davids: Case Presentation

76 y/o man was diagnosed 3 years ago with del(11q), IGHV unmutated, *TP53* wildtype CLL and observed for 3 years but now progressing with bulky lymph nodes and cytopenias and needs treatment. Co-morbidities include hypertension and well-controlled type 2 DM. He prefers time-limited therapy and is able to travel for clinic visits but this is somewhat challenging logistically for him.



AMPLIFY: AV



The patient decides to start on AV, and is now about 7 months into treatment with excellent response and tolerability to date

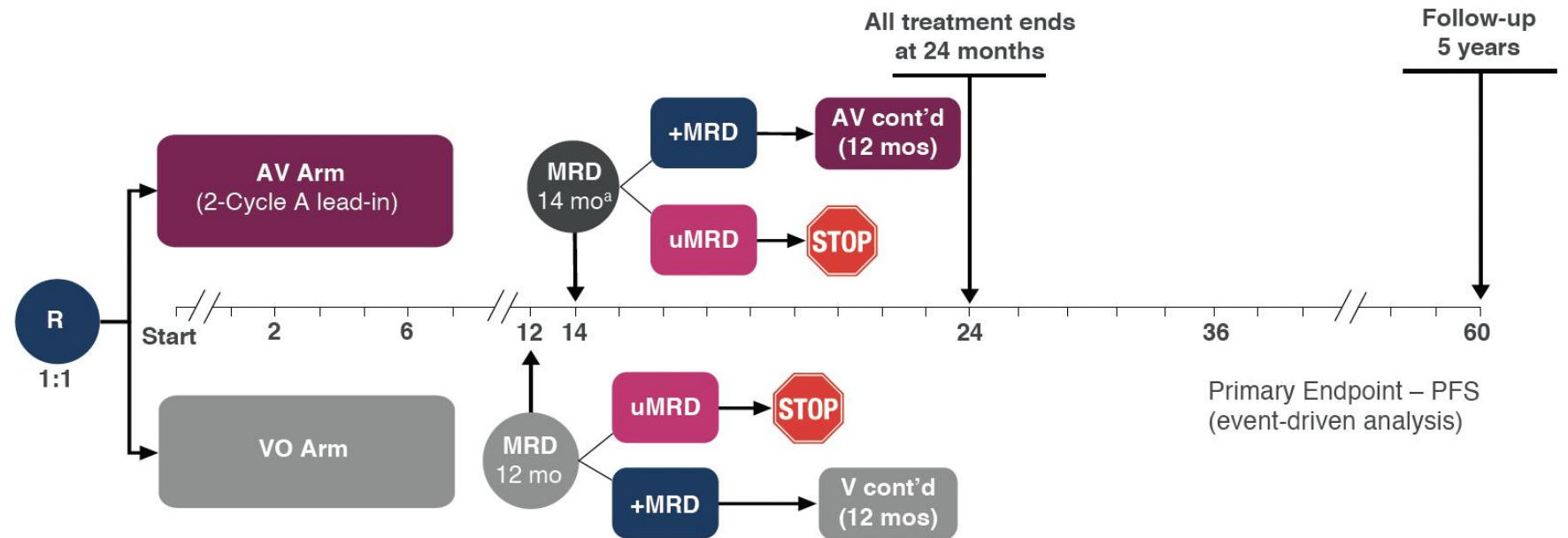
The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL treatment

- N=~600 patients recruited
- Global study with ~40 sites
- FPI: Sept 2022
- Accrual completed: March 2024

Key Eligibility Criteria

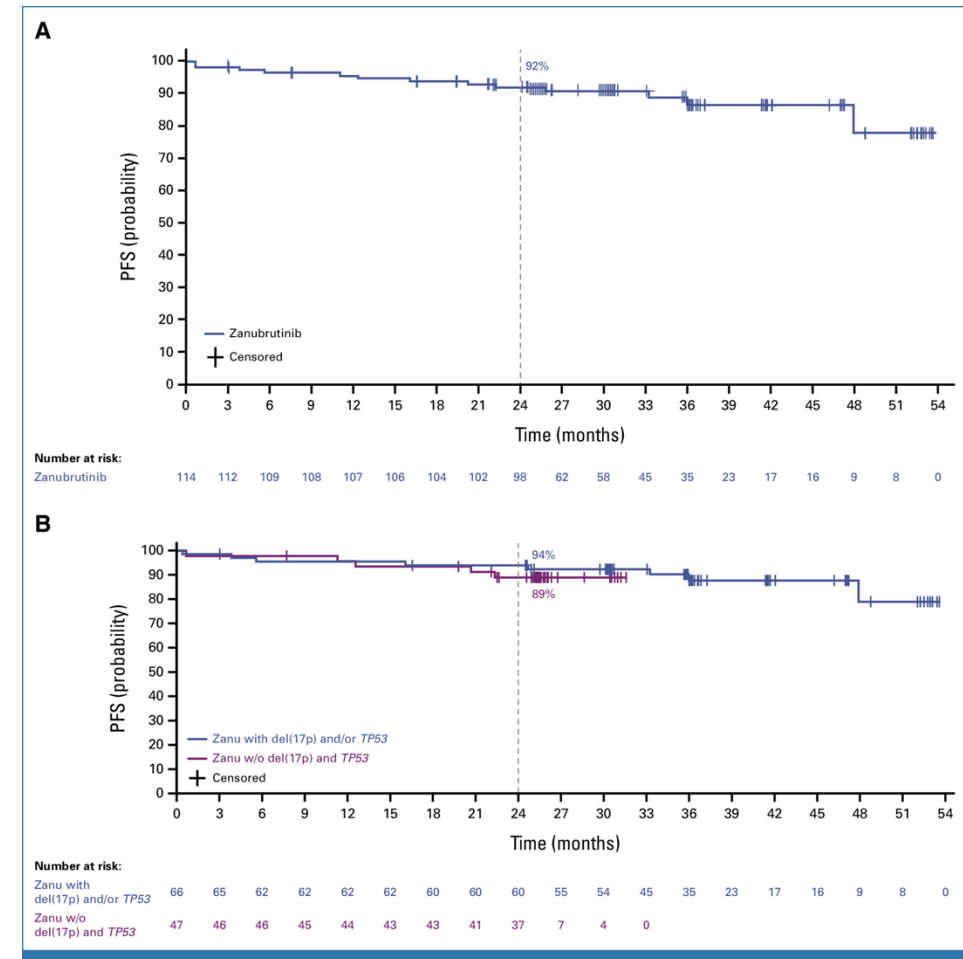
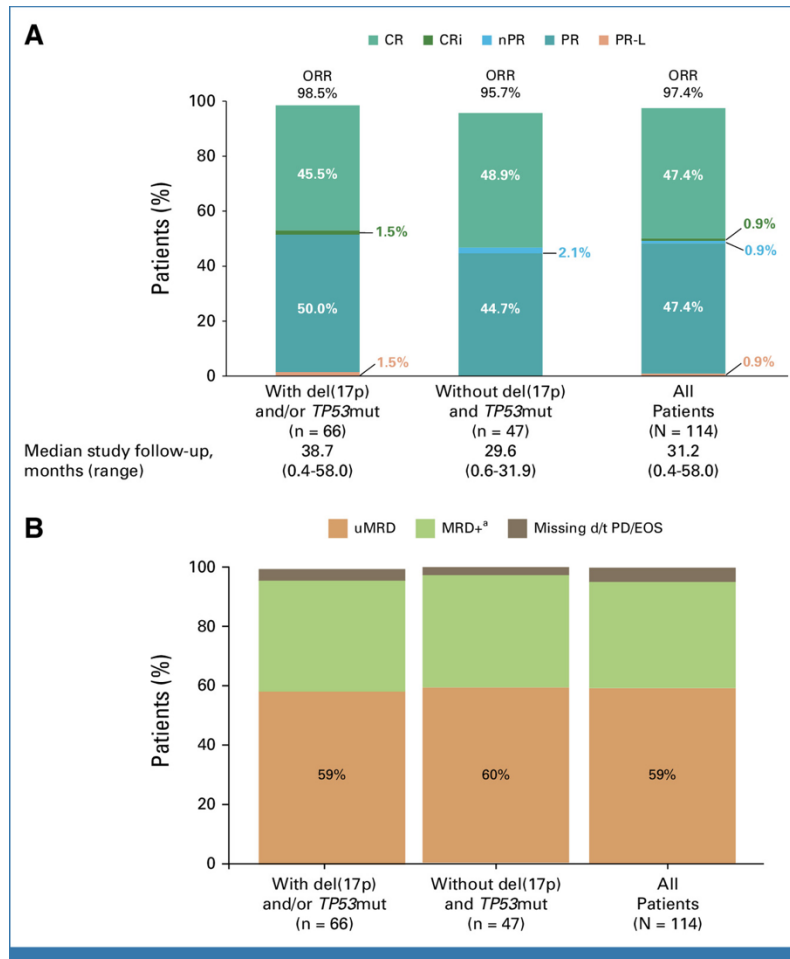
- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS



Zanubrutinib + venetoclax is an alternative BTKi/BCL-2i frontline regimen for CLL

Patients received zanu 160 mg bid starting at cycle 1 and ven qd from cycle 4-28 followed by zanu monotherapy until PD, uMRD-guided stopping criteria were met, or unacceptable toxicity



Faculty Discussion

BTK and Bcl-2 Inhibitor Combinations

- Brown JR et al. Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia. *N Engl J Med* 2025;392(8):748-62.
- Davids MS et al. Majic: A Phase 3 Prospective, Multicenter, Randomized, Open-Label Trial of Acalabrutinib plus Venetoclax versus Venetoclax plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. ASH 2021;Abstract 1553.
- Shadman M et al. Zanubrutinib and Venetoclax for Patients with Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with and without Del(17p)/TP53 Mutation: SEQUOIA Arm D Results. *J Clin Oncol* 2025;43(21):2409-17.

Key Datasets — First-Line Noncovalent BTK Inhibitors

- Jurczak W et al. BRUIN CLL-313: Randomized Phase III Trial of Pirtobrutinib versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *J Clin Oncol* 2026;44(6):466-75.
- Woyach JA et al. Pirtobrutinib versus Ibrutinib in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *J Clin Oncol* 2026;44(6):476-85.

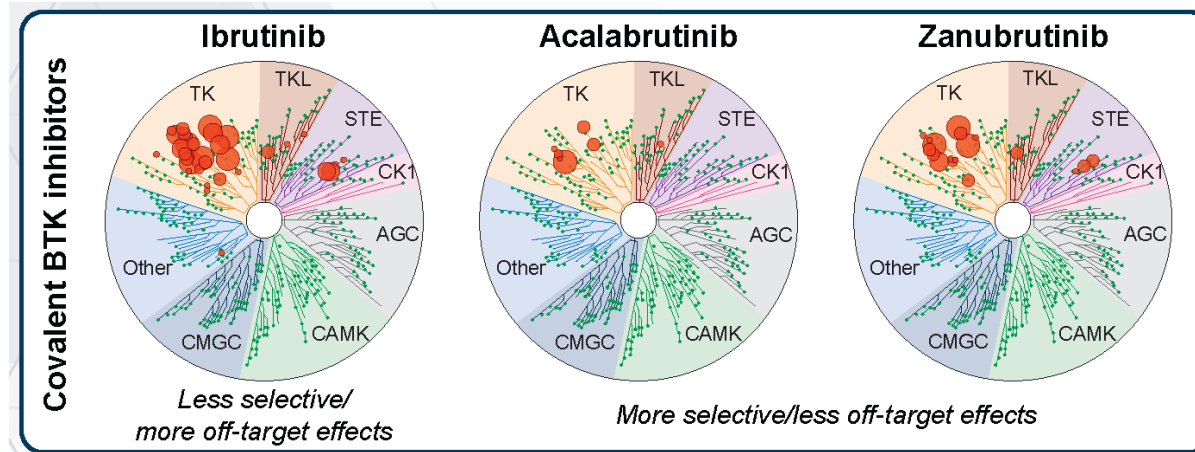
Dr Davids: Case Presentation

89 y/o man with del(11q) on FISH, IGHV unmutated, *TP53* wildtype observed for the past 3 years but now progressing with bulky lymph nodes and cytopenias and needs treatment. Co-morbidities include CAD s/p stents, mild CHF, stage 3 CKD, impaired mobility. He finds it difficult logistically to make it to clinic visits, and is becoming increasingly forgetful.



How would you treat this patient?

What are the Implications of Covalent BTKi Selectivity for Off-Target Effects?



Less selective BTK inhibitors (eg, ibrutinib) have more off-target effects, which contribute to more toxicity compared with more selective agents

Potential off-target effects include:



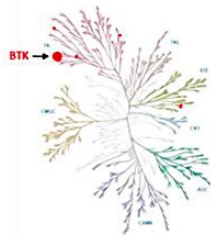
Kaptein A, et al. *Blood*. 2018;132(suppl 1):1871.

AGC, containing PKA, PKG, PKC families; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CAMK, calcium/calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; EGFR, epidermal growth factor receptor; STE, homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TK, tyrosine kinase; TKL, tyrosine kinase-like.

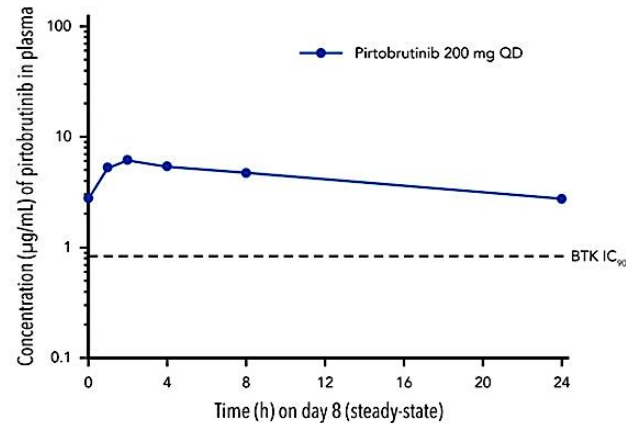
Pirtobrutinib is highly selective for BTKi with favorable PK/PD properties leading to a high level of efficacy in R/R CLL

Pirtobrutinib, A Non-Covalent Bruton Tyrosine Kinase (BTK) Inhibitor: A New Therapeutic Tool for BTK-inhibitor Refractory Lymphoproliferative Disorders

Mechanism of action: Highly selective for BTK.

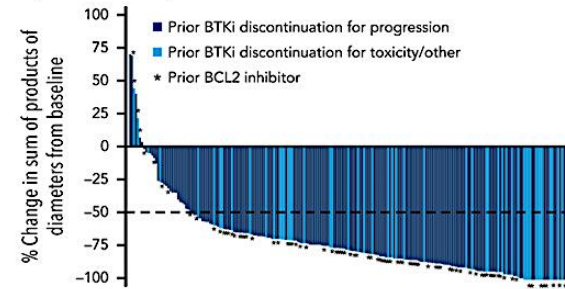


Pharmacology: Long half-life with concentration exceeding IC₉₀ throughout the dosing interval.

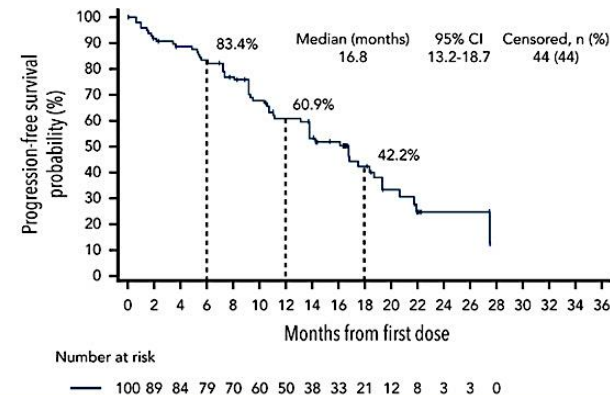


Chronic Lymphocytic Leukemia (CLL)

- ORR 82% in CLL (79% in those with prior cBTKi and venetoclax). Response rates equivalent with or without BTK C481 mutations.



- Median PFS: 16.8 months in double-refractory CLL.



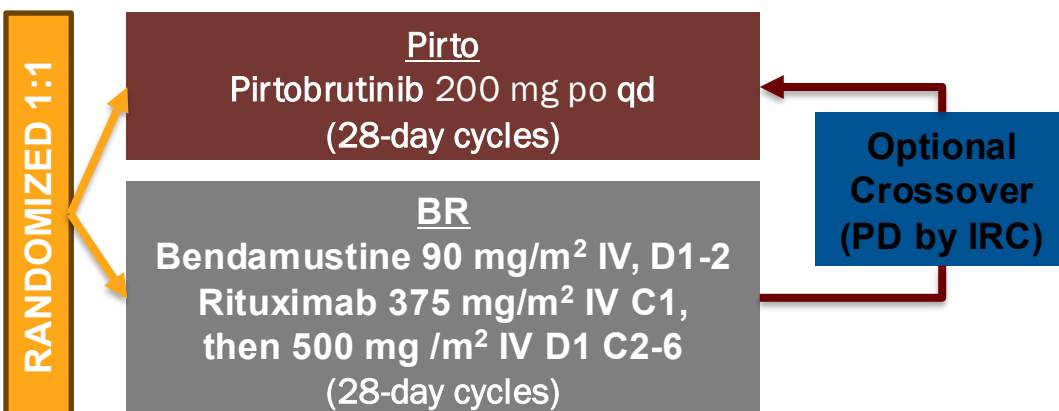
Conclusion: Pirtobrutinib achieves high response rates in heavily pre-treated patients with BTK inhibitor-refractory B-cell lymphoproliferative disorders.

Thompson & Tam, DOI 10.1182/blood.2023020240

First Results From the BRUIN CLL-313 Randomized Phase 3 Study of Pirtobrutinib vs BR in Patients With TN CLL/SLL

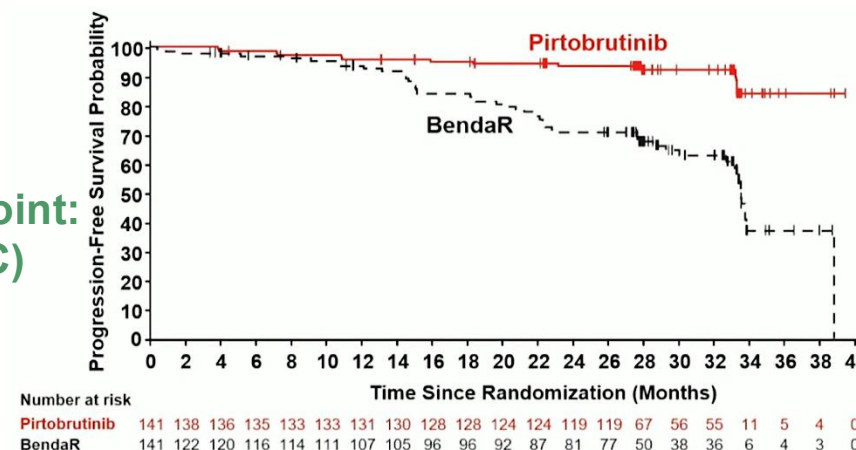
Key Eligibility Criteria

- Confirmed TN CLL/SLL, with requirement for therapy
- ECOG PS 0-2
- No del(17p)



Primary endpoint: PFS (by IRC)
Key secondary endpoint: OS
Secondary endpoints: ORR, safety

Primary Endpoint: PFS (by IRC)



PFS	Pirto (n=141)	BR (n=141)
Events, n (%)	13 (9.2)	48 (34.0)
24-month rate (95% CI), %	93.4 (87.6-96.5)	70.7 (61.5-78.1)
HR (95% CI); <i>P</i> -value	0.20 (0.11-0.37); <i>P</i> <0.0001	
Median follow-up, months	28.1	28.3

PFS Subgroup Analysis

- PFS favored Pirto across all prespecified subgroups (age at enrollment, disease type, Rai stage, β 2M, del[11q], *IGHV* mutation status, complex karyotype, *TP53* mutation)

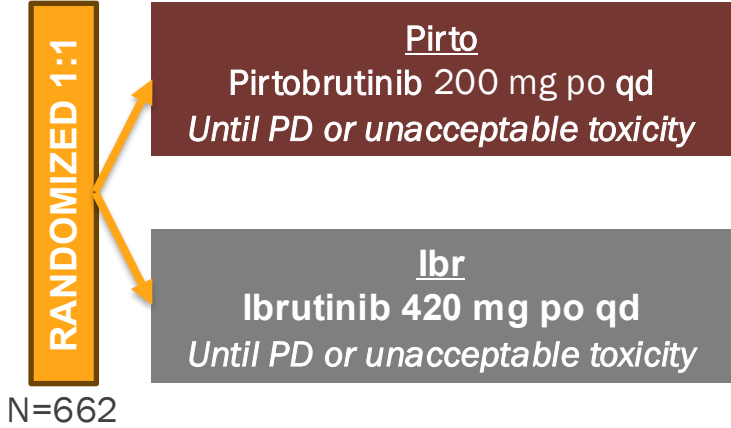
First Results From the BRUIN CLL-313 Randomized Phase 3 Study of Pirtobrutinib vs BR in Patients With TN CLL/SLL: Safety

AEs of Interest, n (%)	Pirto (n=140)		BR (n=132)		Any Grade AEs, EAIR per 100 Person-Years		
	Any grade	Grade ≥3	Any grade	Grade ≥3	Pirto	BR	EAIR ratio (95% CI)
Infection	80 (57.1)	19 (13.6)	44 (33.3)	11 (8.3)	38.3	89.7	0.43 (0.30-0.62)
Without COVID-19	72 (51.4)	19 (13.6)	38 (28.8)	9 (6.8)	30.9	74.9	0.41 (0.28-0.61)
Bleeding	36 (25.7)	1 (0.7)	2 (1.5)	0	12.5	3.3	3.73 (0.90-15.50)
Hemorrhage	17 (12.1)	1 (0.7)	2 (1.5)	0	5.2	3.3	1.55 (0.36-6.69)
Bruising	16 (11.4)	0	0	0	4.8	0	NE
Petechiae and purpura	8 (5.7)	0	0	0	2.3	0	NE
Neutropenia	21 (15.0)	13 (9.3)	68 (51.5)	60 (45.5)	6.5	169.5	0.04 (0.02-0.06)
Anemia	14 (10.0)	6 (4.3)	21 (15.9)	10 (7.6)	4.1	37.7	0.11 (0.06-0.21)
Thrombocytopenia	12 (8.6)	4 (2.9)	23 (17.4)	9 (6.8)	3.5	43.1	0.08 (0.04-0.16)
AFib and AFlutter	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.8)	0.5	3.3	0.17 (0.02-1.17)
≥75 years old	1 (5.0)	0	1 (4.3)	0	2.2	10.0	0.22 (0.01-3.46)
Hypertension	11 (7.9)	4 (2.9)	6 (4.5)	4 (3.0)	3.2	10.2	0.31 (0.11-0.84)

BRUIN CLL-314 Phase 3 Study of Pirtobrutinib vs Ibrutinib in Patients With TN and R/R CLL/SLL

Key Eligibility Criteria

- Confirmed CLL/SLL
- BTKi naïve (1L or R/R)
- del(17p)
- ECOG PS 0-2



Primary endpoint: ORR noninferiority (BICR)
Secondary endpoints: PFS superiority (BICR)

AEISs (in ≥10%), n (%)	Pirto (n=330)		lbr (n=325)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
≥1 AEIS	288 (87.3)	127 (38.5)	288 (88.6)	117 (36.0)
Infections	226 (68.5)	56 (17.0)	241 (74.2)	54 (16.6)
Bleeding	115 (34.8)	11 (3.3)	118 (36.3)	9 (2.8)
Hemorrhage	78 (23.6)	11 (3.3)	81 (24.9)	9 (2.8)
Bruising	45 (13.6)	0	39 (12.0)	0
Petechiae, purpura	17 (5.2)	0	25 (7.7)	0
Neutropenia	103 (31.2)	83 (25.2)	76 (23.4)	57 (17.5)
Anemia	51 (15.5)	20 (6.1)	51 (15.7)	12 (3.7)
Thrombocytopenia	39 (11.8)	12 (3.6)	57 (17.5)	13 (4.0)
AFib	8 (2.4)	3 (0.9)	44 (13.5)	13 (4.0)
≥75 years old	3 (4.5)	1 (1.5)	15 (21.4)	5 (7.1)

^a Most discontinued for finishing treatment (67.6% and 64.7%); "other" not listed in table (7.3% each).
Woyach J, et al., *J Clin Oncol.*, 2025

First Results From the BRUIN CLL-314 Phase 3 Study of Pirtobrutinib vs Ibrutinib in Patients With TN and R/R CLL/SLL: ORR

Response by BICR		ITT		TN		R/R	
		Pirto (n=331)	lbr (n=331)	Pirto (n=112)	lbr (n=113)	Pirto (n=219)	lbr (n=218)
ORR, % (95% CI)		87.0 (82.90-90.44)	78.5 (73.73-82.85)	92.9 (86.41-96.87)	85.8 (78.03-91.68)	84.0 (78.48-88.61)	74.8 (68.46-80.39)
Nominal <i>P</i> -value		0.0035		0.0886		0.0175	
ORR ratio (95% CI) <i>P</i> -value for noninferiority		1.1080 (1.034-1.187) <0.0001		1.0797 (0.989-1.179) -		1.1233 (1.020-1.237) <0.0001	
Best overall response, %	CR/CRi	4.8	2.4	7.1	3.5	3.7	1.8
	PR/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, % (95% CI)		89.4 (85.60-92.52)	82.5 (77.95-86.42)	93.8 (87.55-97.45)	88.5 (81.93-93.73)	87.2 (82.05-91.33)	79.4 (73.37-84.53)
Nominal <i>P</i> value		0.0093		0.1692		0.0286	

Editorials

BRUIN 313 and 314 Trials Open the Door for Noncovalent Bruton Tyrosine Kinase Inhibition as Initial Therapy for Chronic Lymphocytic Leukemia

Matthew S. Davids, MD, MMSc¹ 

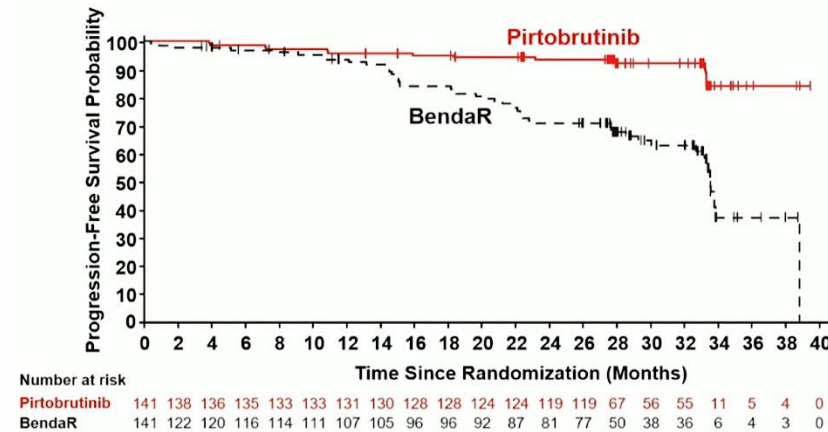
“Overall, the results of these two phase III BRUIN studies are favorable for pirtobrutinib and are supportive of regulatory approval of the drug as initial therapy for CLL.”

Dr Davids: Case Presentation

89 y/o man with del(11q) on FISH, IGHV unmutated, *TP53* wildtype observed for the past 3 years but now progressing with bulky lymph nodes and cytopenias and needs treatment. Co-morbidities include CAD s/p stents, mild CHF, stage 3 CKD, impaired mobility. He finds it difficult logistically to make it to clinic visits, and is becoming increasingly forgetful.



BRUIN-313: Pirtobrutinib



The patient elects to start on pirto, and is now about 6 weeks into treatment already with smaller lymph nodes and improving cytopenias with minimal side effects

Faculty Discussion

First-Line Noncovalent BTK Inhibitors

- Jurczak W et al. BRUIN CLL-313: Randomized Phase III Trial of Pirtobrutinib versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *J Clin Oncol* 2026;44(6):466-75.
- Woyach JA et al. Pirtobrutinib versus Ibrutinib in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *J Clin Oncol* 2026;44(6):476-85.

Agenda

Introduction: Minimal Residual Disease Assays in Community-Based Practice

Module 1: New Developments in Previously Untreated Chronic Lymphocytic Leukemia (CLL)

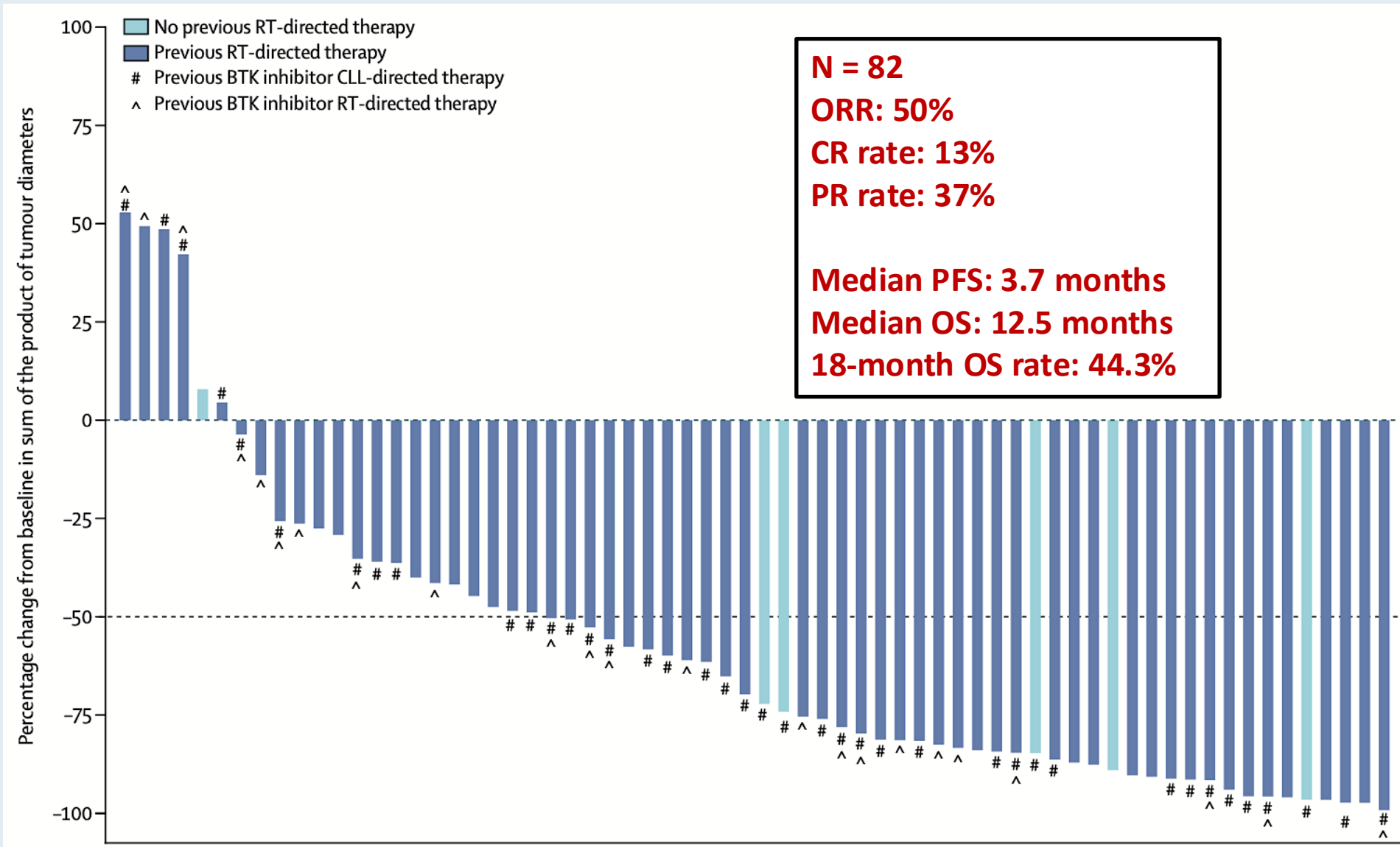
Module 2: Richter Transformation

Module 3: Selection and Sequencing of Therapies for Relapsed/Refractory CLL

Key Datasets — Richter Transformation

- Wierda WG et al. Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Patients with B-Cell Malignancies: Analysis of the Richter Transformation Subgroup from the Multicentre, Open-Label, Phase 1/2 BRUIN Study. *Lancet Haematol* 2024;11(9):e682-92.
- A Randomized Phase III Study of Pirtobrutinib plus R-CHOP vs R-CHOP for Participants with Previously Untreated Richter Transformation (PIRAMID). NCT07220187.
- CLL-RT2: A Prospective, Open-Label, Randomized, Multicenter Phase-III Trial to Evaluate the Efficacy of Pirtobrutinib and Epcoritamab Compared with R-(Mini)-CHOP for Treatment of Patients with Richter Transformation. <https://www.dcllsg.com/cll-rt2/>

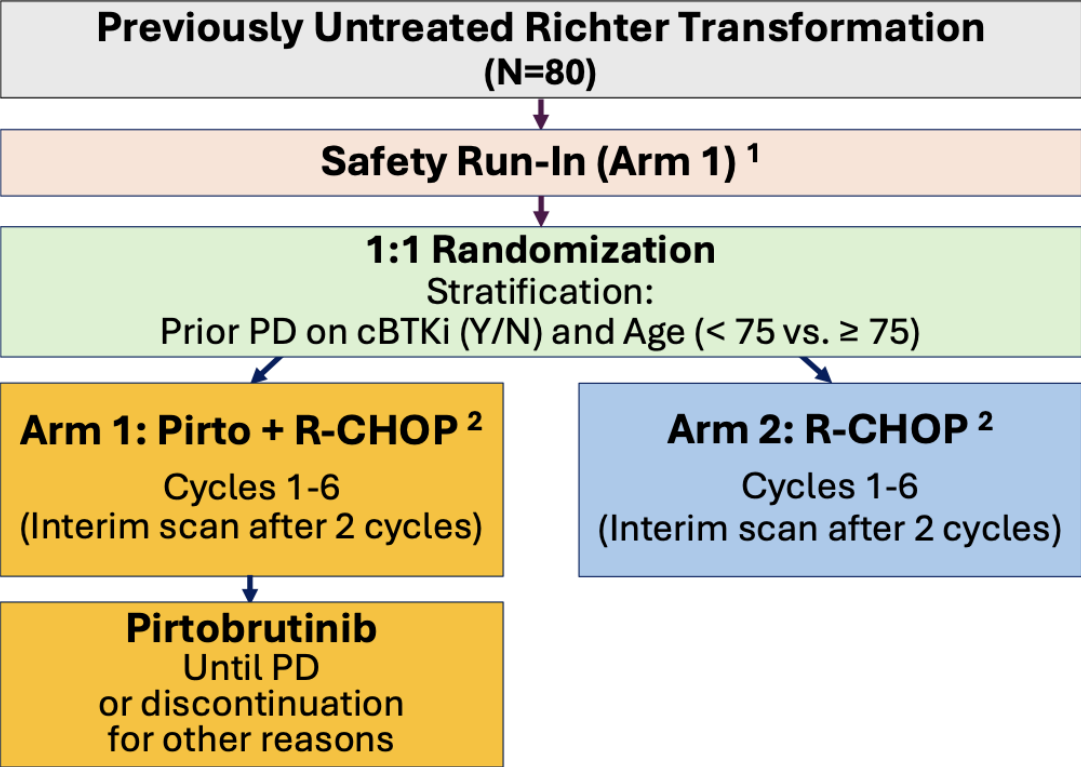
Pirtobrutinib for Richter Transformation



RT = Richter transformation; ORR = overall response rate; CR = complete response; PR = partial response

pirAMID (SWOG-S2504) Trial: Adding Pirtobrutinib to R-CHOP for Richter Transformation

S2504: A RANDOMIZED PHASE III STUDY OF **PIRTOBRUTINIB** PLUS R-CHOP VS. R-CHOP FOR PARTICIPANTS WITH PREVIOUSLY UNTREATED **RICHTER TRANSFORMATION** (*pirAMID*) The *pirAMID* trial



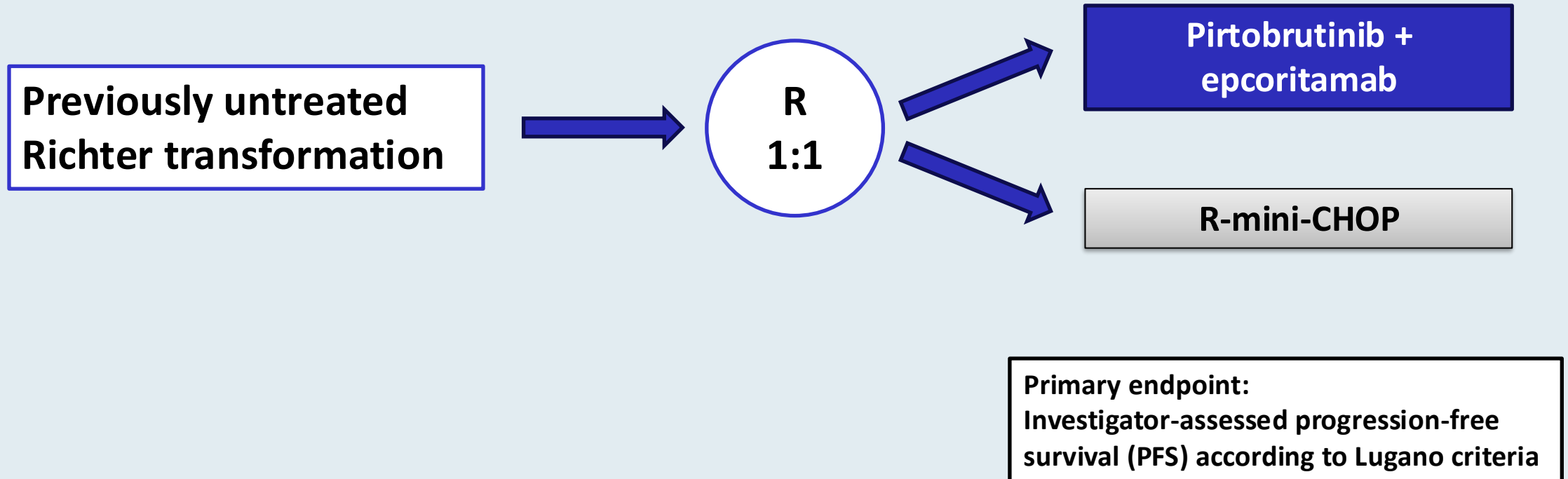
6 participants < Age 75 and 6 participants ≥ Age 75 will be non-randomly assigned to Arm 1.
• **Participants will be monitored for toxicity through Cycle 2.**

- Primary Endpoints:**
- PFS
 - OS
- Secondary Endpoints:**
- CR
 - Safety
- Translational Medicine Endpoints**
- **Primary: Evaluate association between high-risk Richter-associated mutations (*TP53*, *CDK2NA*, or *MYC*) and OS within each arm by NGS and WES analyses**

1. Refer to S2504 Sections 7.4 and 15.6 for Safety Run-In information.
2. **R-mini-CHOP for participants age 75 and older.**

■ cBTKi: covalent BTKi ■ CR: Complete remission ■ PD: Progressive disease
■ PFS: Progression-free survival ■ OS: Overall survival
■ R-CHOP: rituximab/rituximab hyaluronidase, cyclophosphamide, doxorubicin, vincristine, and prednisone

CLL-RT2: A Phase III Study of Pirtobrutinib with Epcoritamab versus R-mini-CHOP for Richter Transformation



Faculty Discussion

Richter Transformation

- Wierda WG et al. Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Patients with B-Cell Malignancies: Analysis of the Richter Transformation Subgroup from the Multicentre, Open-Label, Phase 1/2 BRUIN Study. *Lancet Haematol* 2024;11(9):e682-92.
- A Randomized Phase III Study of Pirtobrutinib plus R-CHOP vs R-CHOP for Participants with Previously Untreated Richter Transformation (PIRAMID). NCT07220187.
- CLL-RT2: A Prospective, Open-Label, Randomized, Multicenter Phase-III Trial to Evaluate the Efficacy of Pirtobrutinib and Epcoritamab Compared with R-(Mini)-CHOP for Treatment of Patients with Richter Transformation. <https://www.dcllsg.com/cll-rt2/>

Agenda

Introduction: Minimal Residual Disease Assays in Community-Based Practice

Module 1: New Developments in Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Module 2: Richter Transformation

Module 3: Selection and Sequencing of Therapies for Relapsed/Refractory CLL

Research To Practice: Relapsed Chronic Lymphocytic Leukemia

Catherine Coombs, MD
Associate Clinical Professor
University of California Irvine

Key Datasets — Treatment After a Covalent BTK Inhibitor

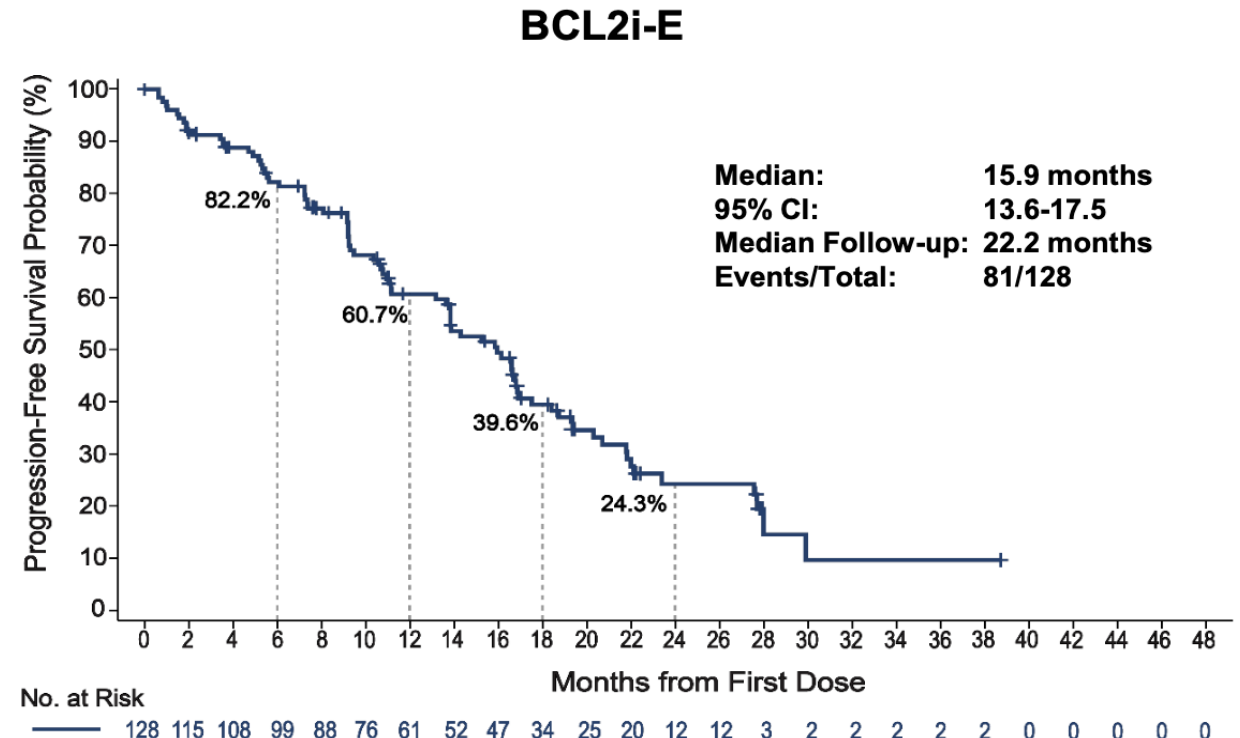
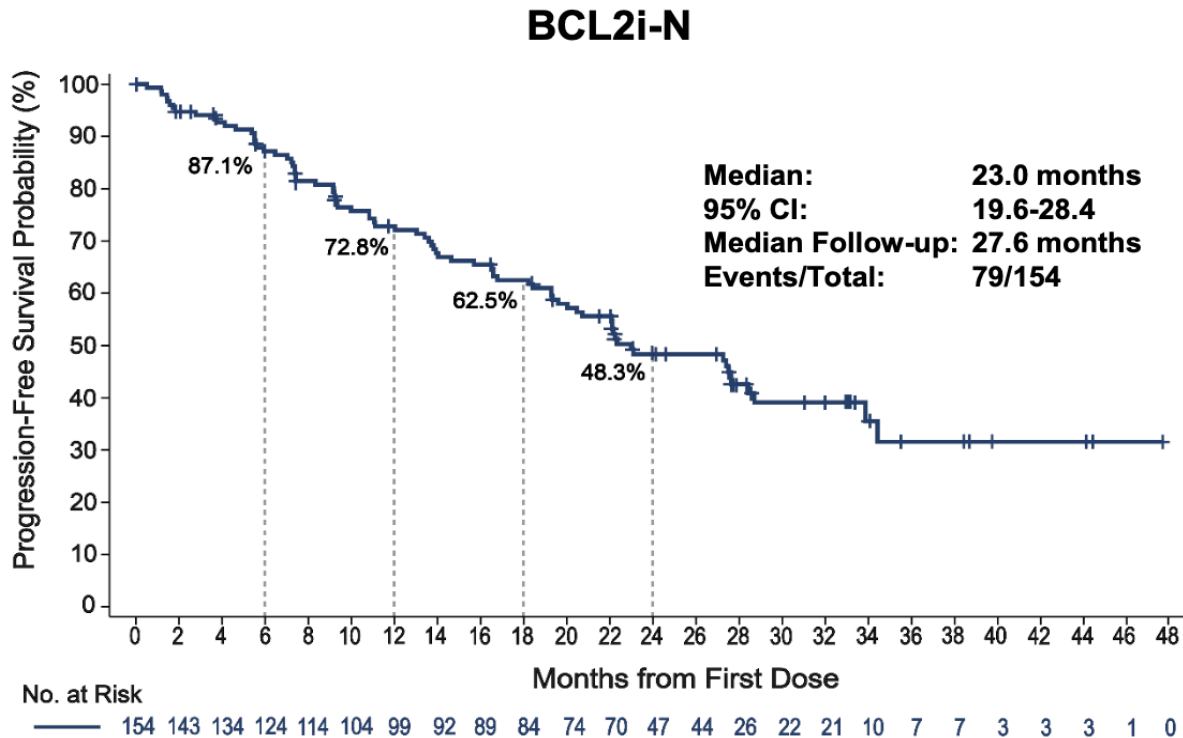
- Kater AP et al. The MURANO Study: Final Analysis and Retreatment/Crossover Substudy Results of VenR for Patients with Relapsed/Refractory CLL. *Blood* 2025;145(23):2733-45.
- Woyach JA et al. Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study. ASH 2023;Abstract 325.
- Sharman JP et al. Phase III Trial of Pirtobrutinib versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor-Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321). *J Clin Oncol* 2025;43(22):2538-49.
- Davids MS et al. Fixed Duration Pirtobrutinib plus Venetoclax-Rituximab versus Venetoclax-Rituximab for Patients with Previously Treated CLL/SLL: A Phase 3, Randomized Trial (BRUIN CLL-322). EHA 2026;Abstract LB5001.

PD on cBTKi: Evidence for Venetoclax

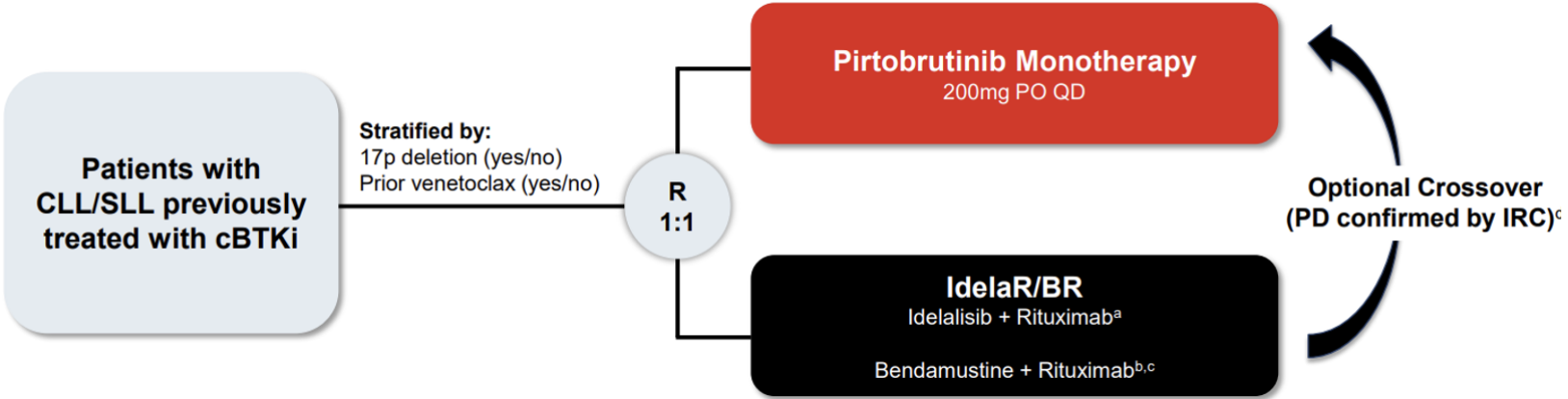
- MURANO trial leading to venR approval included only 2% post cBTKi pts
- Prospective studies including post-cBTKi cohorts used venetoclax monotherapy leading to ~24 months median PFS
- Limited prospective data for use of ven-obi post-cBTKi though this is NCCN preferred regimen

Pirtobrutinib post-BTKi

- Rationale is pirtobrutinib, a next-generation BTK inhibitor, does not interact with C481 residue so effective in both WT BTK and C481S mutated
- First studied in phase I/II BRUIN trial:

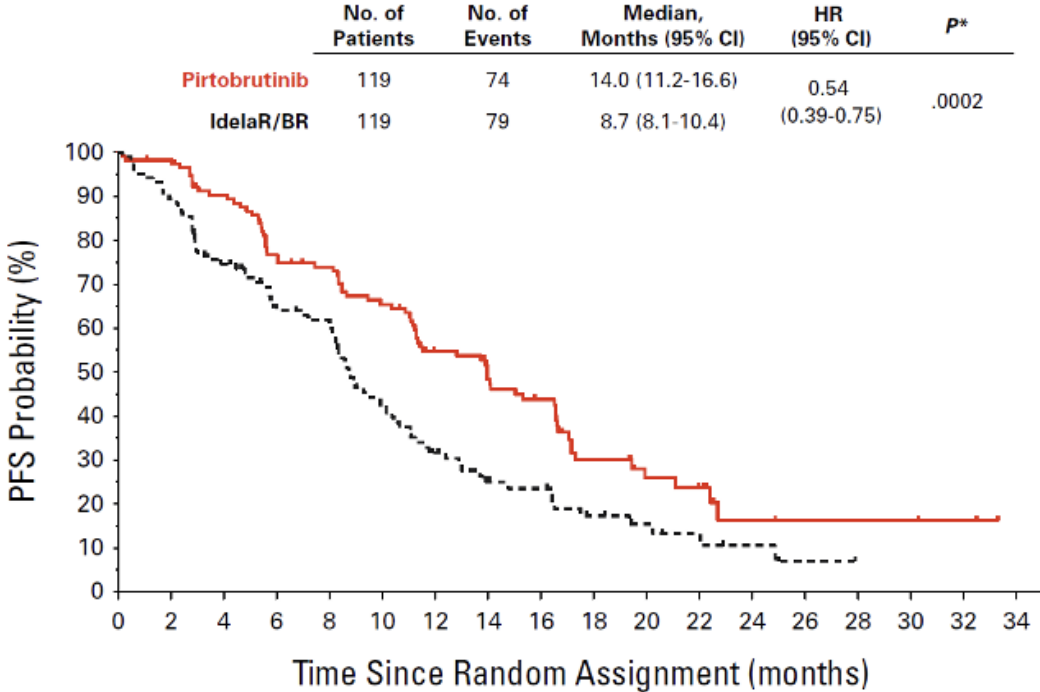


BRUIN CLL-321 trial



Progression-Free Survival as Assessed by IRC

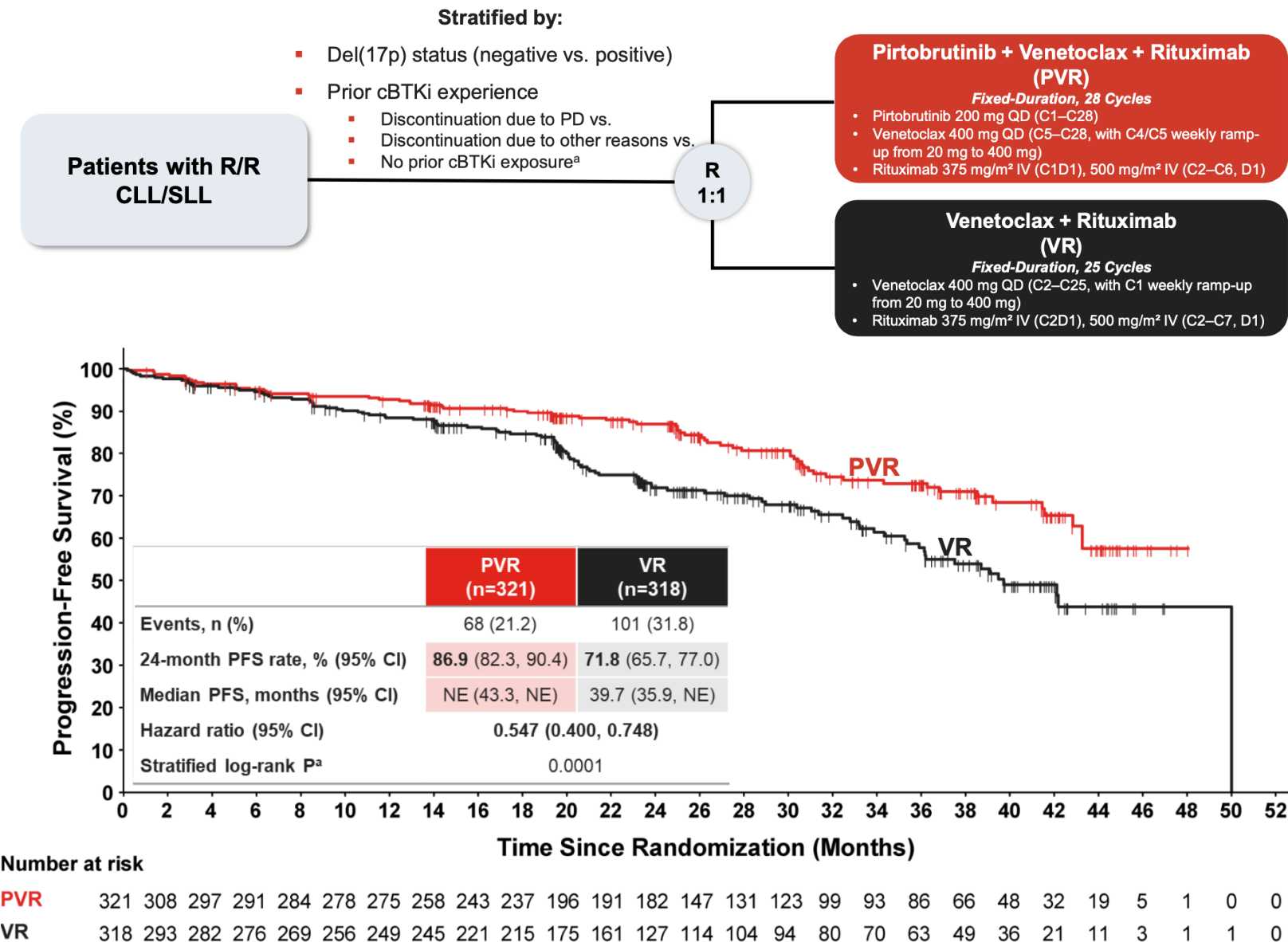
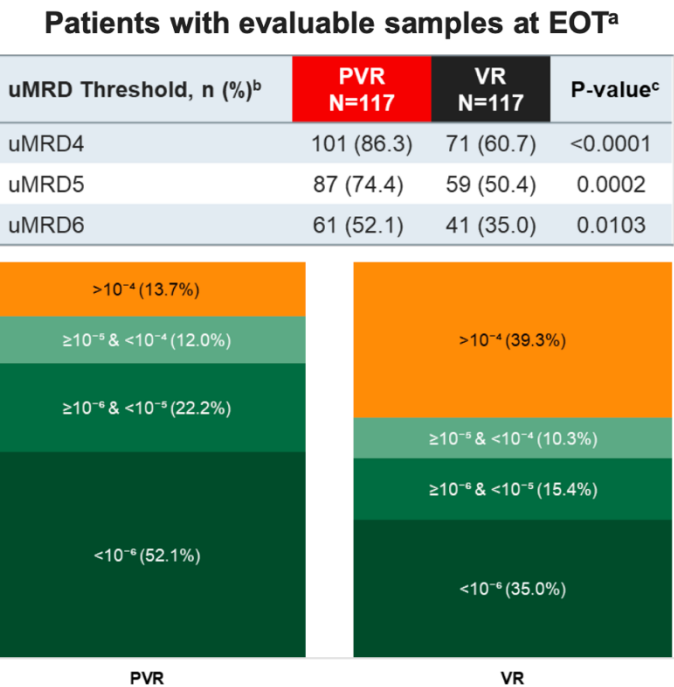
Anemia ^a	24 (20.7)	13 (11.2)	19 (17.4)	8 (7.3)
Atrial fibrillation and atrial flutter	3 (2.6)	2 (1.7)	1 (0.9)	0 (0)
Bleeding	25 (21.6)	4 (3.4)	11 (10.1)	0 (0)
Bruising ^b	9 (7.8)	1 (0.9)	3 (2.8)	0 (0)
Petechiae and purpura	6 (5.2)	1 (0.9)	1 (0.9)	0 (0)
Hemorrhage ^c	18 (15.5)	3 (2.6)	8 (7.3)	0 (0)
Hypertension	8 (6.9)	3 (2.6)	4 (3.7)	1 (0.9)
Infections ^d	74 (63.8)	25 (21.6)	54 (49.5)	21 (19.3)
Infection without COVID-19	67 (57.8)	26 (22.4)	47 (43.1)	19 (17.4)
Neutropenia ^e	31 (26.7)	24 (20.7)	37 (33.9)	30 (27.5)
Thrombocytopenia ^f	11 (9.5)	9 (7.8)	17 (15.6)	8 (7.3)



Sharman J et al JCO 2025

BRUIN CLL-322 trial, PVR regimen – not yet FDA approved

Median follow up 27.3 months



BRUIN CLL-322 safety

Preferred Term in ≥20% of Participants in Either Arm	PVR n=316		VR n=311	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE, n (%)	315 (99.7)	249 (78.8)	305 (98.1)	227 (73.0)
Neutropenia/neutrophil count decrease	191 (60.4)	157 (49.7)	168 (54.0)	136 (43.7)
Diarrhea	106 (33.5)	6 (1.9)	110 (35.4)	5 (1.6)
COVID-19	98 (31.0)	17 (5.4)	80 (25.7)	12 (3.9)
Anemia	70 (22.2)	20 (6.3)	78 (25.1)	33 (10.6)
Cough	69 (21.8)	2 (0.6)	67 (21.5)	0 (0.0)
Upper respiratory tract infection	69 (21.8)	5 (1.6)	64 (20.6)	6 (1.9)
Nausea	67 (21.2)	0 (0.0)	78 (25.1)	3 (1.0)

Median time on treatment, months

Pirtobrutinib: 24.94 (PVR)
Venetoclax: 22.37 (PVR) vs 22.93 (VR)
Rituximab: 5.52 (PVR) vs 5.52 (VR)

Discontinuations & deaths, n (%)

Discontinuations due to treatment-related TEAEs^a:
 17 (5.4) PVR vs 16 (5.1) VR
Death due to Grade 5 treatment-related TEAEs^b:
 1 (0.3) PVR vs 4 (1.3) VR

With the addition of pirtobrutinib, the overall safety profile of fixed-duration PVR was generally similar to VR alone

Faculty Discussion

Treatment After a Covalent BTK Inhibitor

- Kater AP et al. The MURANO Study: Final Analysis and Retreatment/Crossover Substudy Results of VenR for Patients with Relapsed/Refractory CLL. *Blood* 2025;145(23):2733-45.
- Woyach JA et al. Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study. ASH 2023;Abstract 325.
- Sharman JP et al. Phase III Trial of Pirtobrutinib versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor-Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321). *J Clin Oncol* 2025;43(22):2538-2549.
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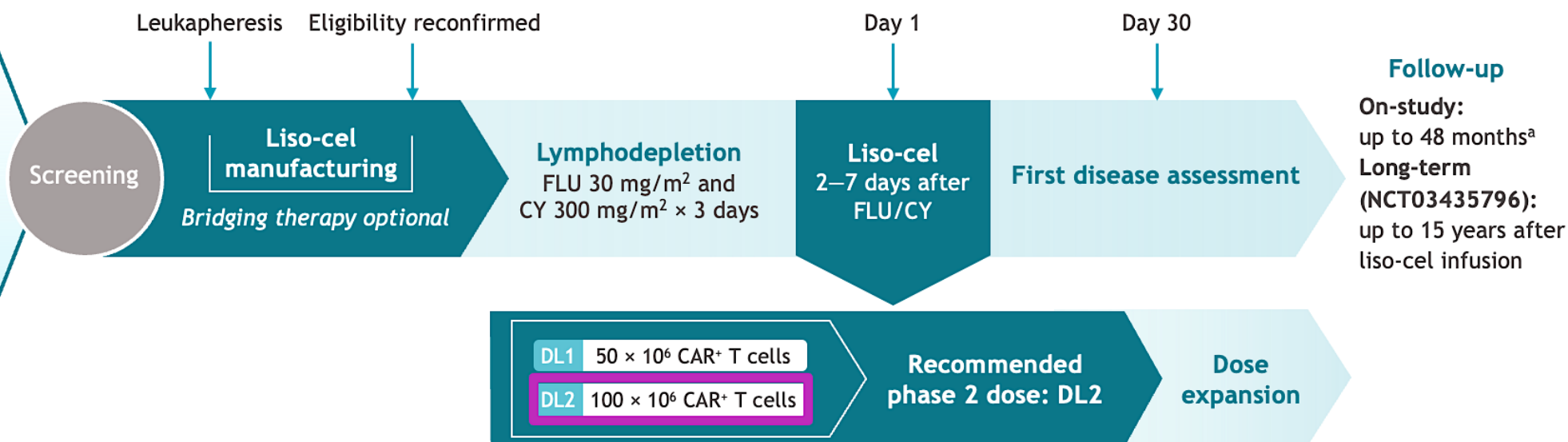
Key Datasets — CAR (Chimeric Antigen Receptor) T-Cell Therapy

- Wierda WG et al. Characteristics Associated with Response to Lisocabtagene Maraleucel (Liso-cel) in Patients (pts) with R/R CLL/SLL: Exploratory Analyses from TRANSCEND CLL 004. EHA 2024;Abstract S158.
- Siddiqi T et al. Lisocabtagene Maraleucel (Liso-cel) in Patients (pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Updated Follow-Up of Transcend CLL 004. ASH 2024;Abstract 4633.

Double exposed/refractory CLL: Lisocabtagene-maraleucel

Key eligibility criteria

- Age ≥ 18 years
- R/R CLL/SLL
- Previously failed or ineligible for BTKi
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy



Primary analysis data cut: September 29, 2022		Full efficacy-evaluable set ^b at DL2 (n = 87)
Primary endpoint	CR/CRi rate	18% (95% CI, 11–28%)
Secondary endpoints	OR rate ^c	47% (95% CI, 36–58%)
	Median DOR	35.3 months (95% CI, 19.8–not reached)
	Median PFS	18.0 months (95% CI, 9.4–30.1)
	Median OS	43.2 months (95% CI, 26.9–not reached)

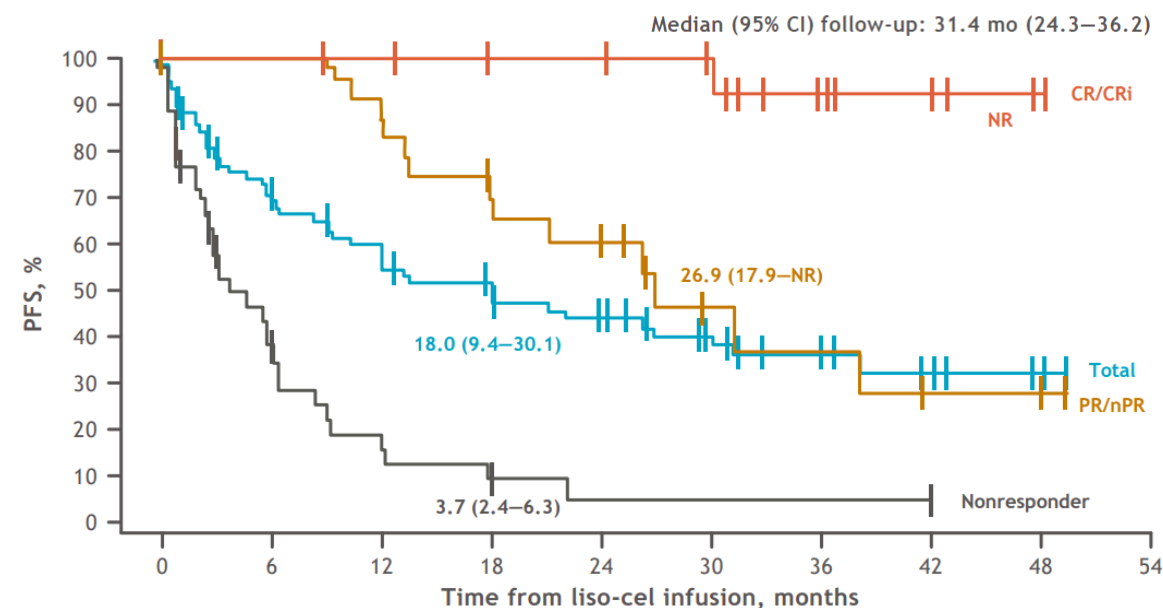
Liso-cel in CLL

CR/CRi = 20%

ORR = 44%

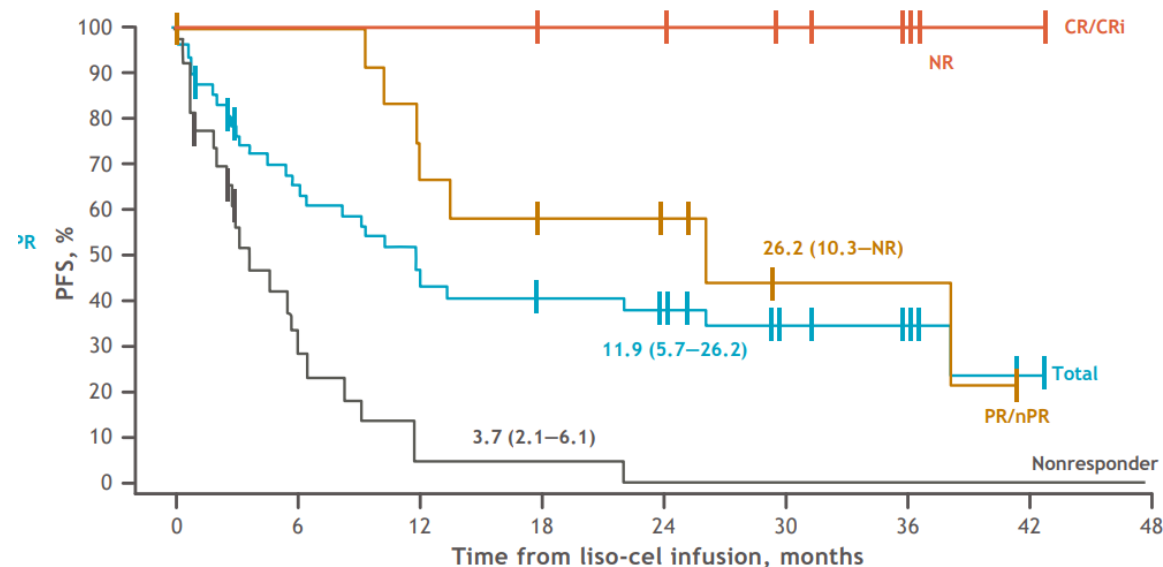


PFS in Full Population at DL2



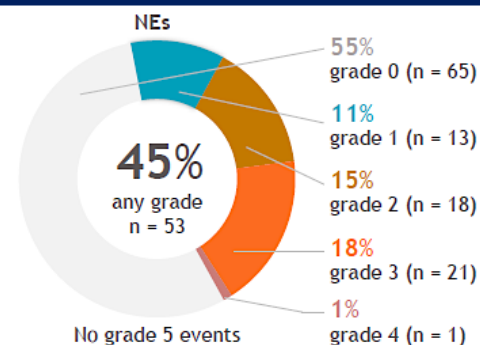
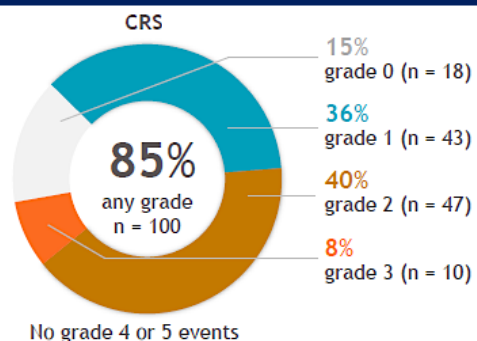
No. at risk	0	6	12	18	24	30
CR/CRi	18	18	17	15	15	13
PR/nPR	24	24	21	14	10	5
Nonresponder	46	13	5	3	1	1
Total	88	55	43	32	26	19

PFS in PEAS at DL2



No. at risk	0	6	12	18	24	30	36	42	48
CR/CRi	10	10	10	9	9	7	4	1	0
NR	5	2	2	2	2	2	2	0	0
PR/nPR	0	0	0	0	0	0	0	0	0
Total	14	9	6	6	6	6	6	1	0

Cytokine Release Syndrome and Neurological Events



Faculty Discussion

CAR T-Cell Therapy

- Wierda WG et al. Characteristics Associated with Response to Lisocabtagene Maraleucel (Liso-cel) in Patients (pts) with R/R CLL/SLL: Exploratory Analyses from TRANSCEND CLL 004. EHA 2024;Abstract S158.
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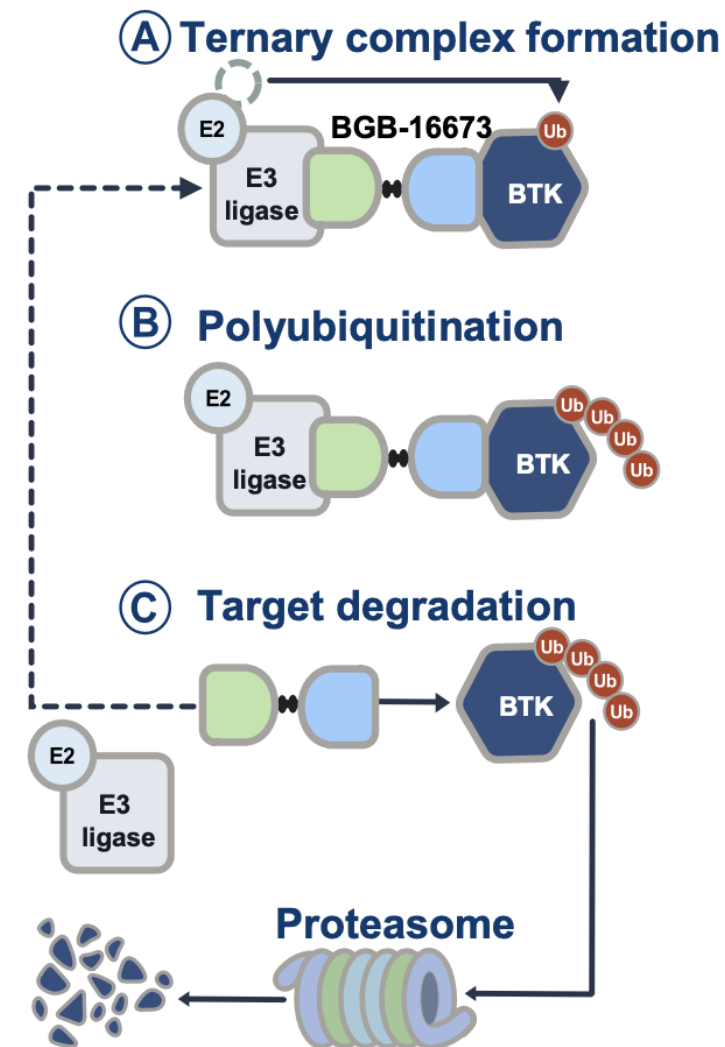
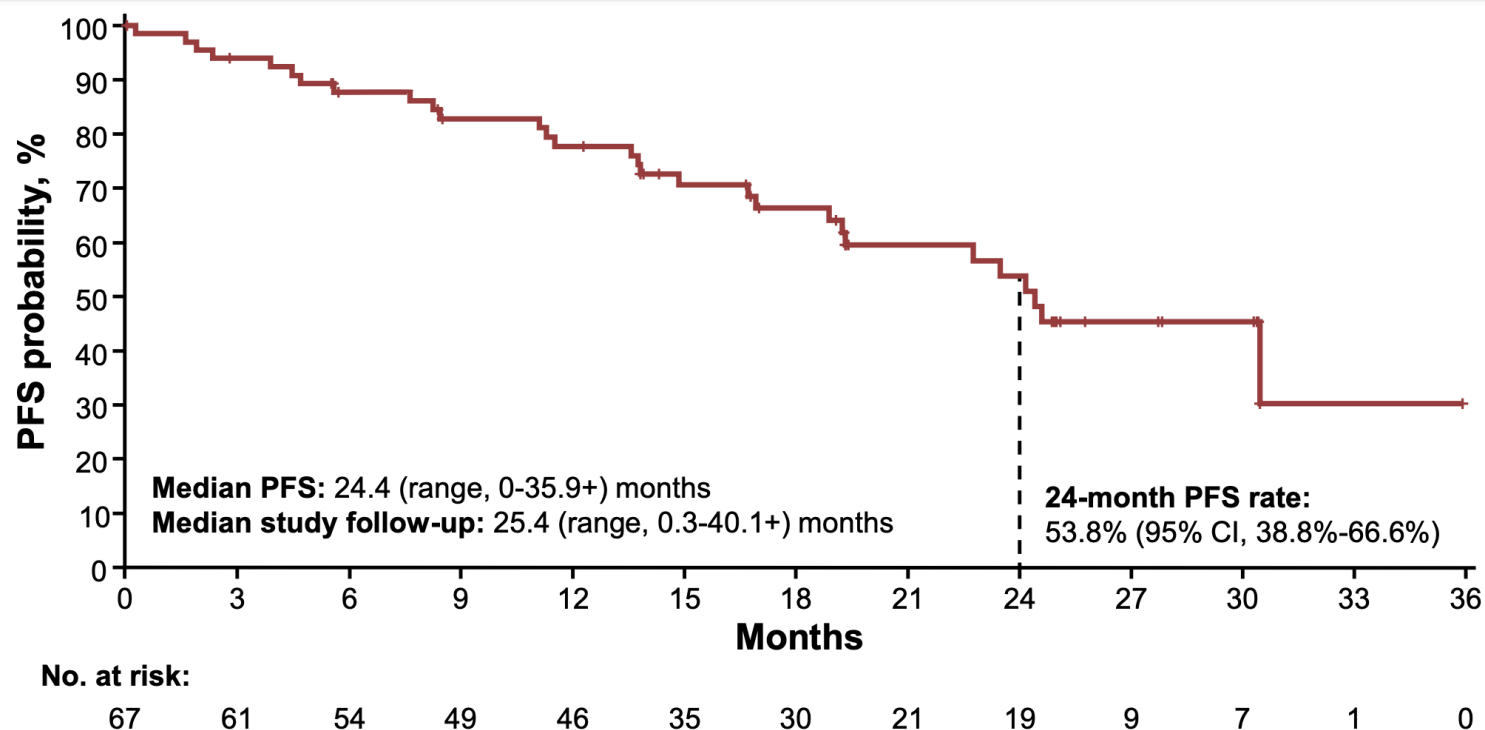
Key Datasets — BTK Degraders

- Stilgenbauer S et al. BGB-16673, a Bruton Tyrosine Kinase (BTK) Degradar, in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): A Phase 1 CADANCE-101 Study Update. EHA 2026;Abstract S152.
- Munir T et al. Updated Efficacy and Safety Data from an Ongoing Phase 1a/b Trial of the BTK Degradar Bexobrutideg (NX-5948) in Patients with CLL Across Lines of Therapy. EHA 2026;Abstract S150.
- Woyach JA et al. Updates of R/R CLL with Prior Exposure to Bruton's Tyrosine Kinase (BTK) Inhibitor and/or Bcl-2 Inhibitor in the Phase 1 Trial of LP-168 (Rocbrutinib), a Novel Covalent and Non-Covalent BTK Inhibitor. ASH 2025;Abstract 87.

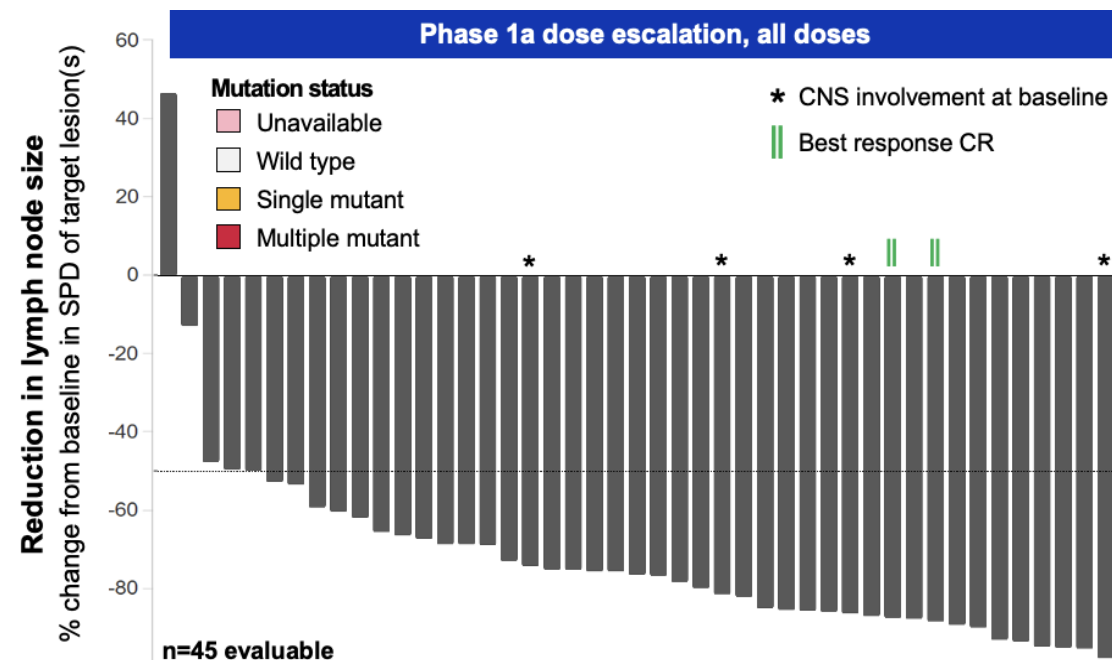
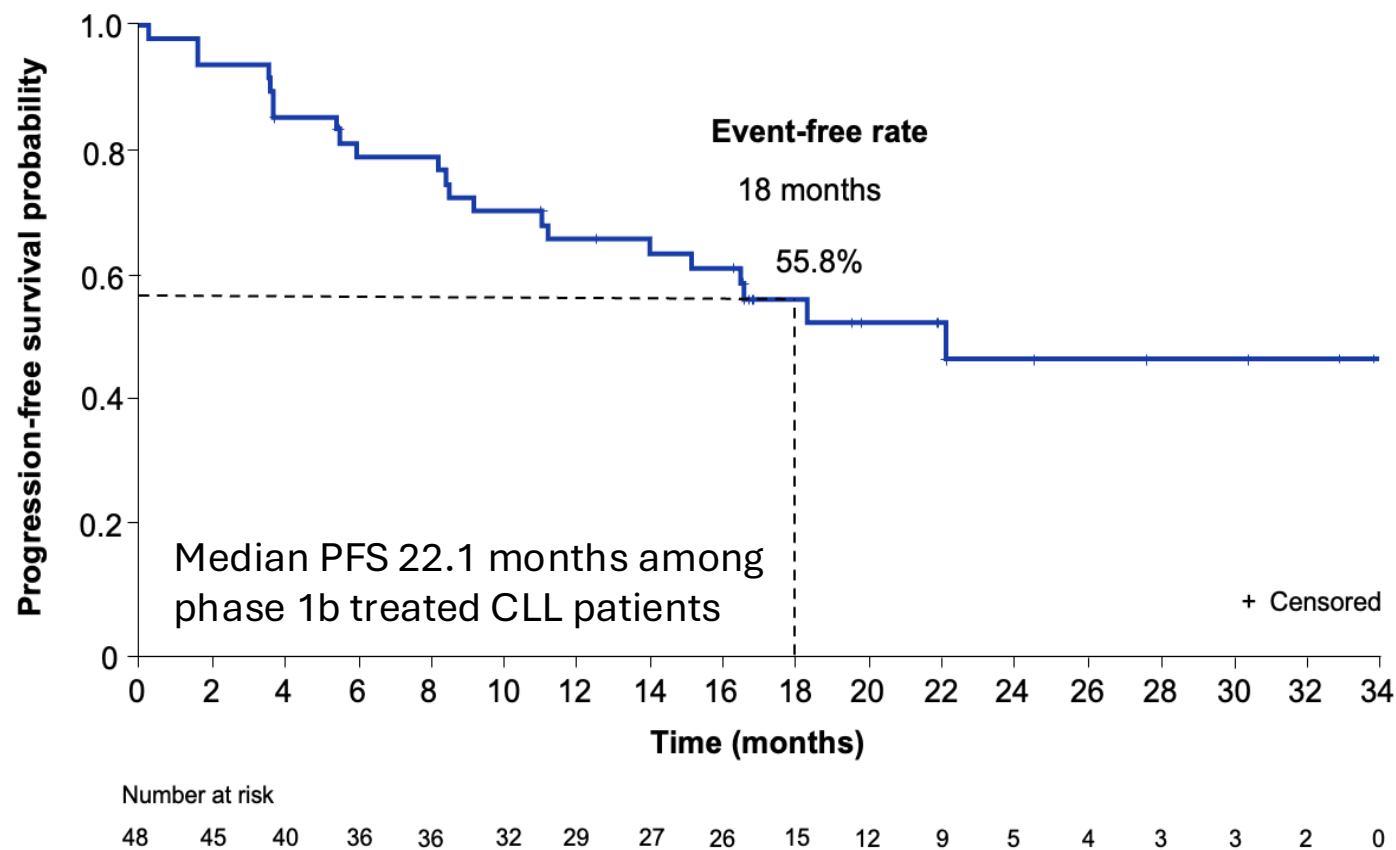
BTK degrader: Tacabrutideg (BGB-16673)

Progression-Free Survival

Durable PFS in heavily-pretreated patients across all dose levels in phase 1

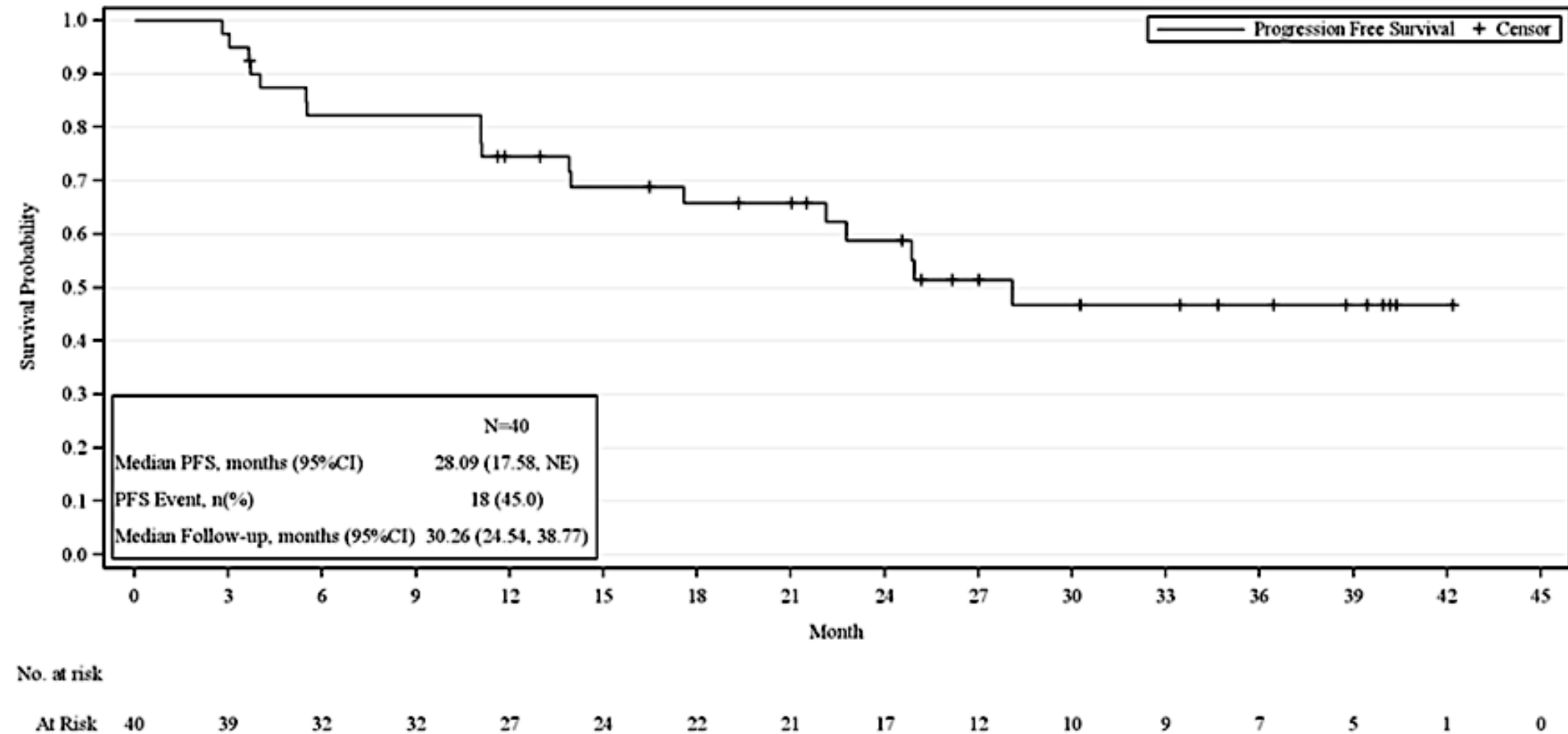


Bexobrutideg (NX-5948)



Munir T et al. EHA 2026;Abstract S150

Rocbrutinib – dual covalent and ncBTKi



Faculty Discussion

BTK Degraders

- Stilgenbauer S et al. BGB-16673, a Bruton Tyrosine Kinase (BTK) Degradar, in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): A Phase 1 CADANCE-101 Study Update. EHA 2026;Abstract S152.
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Dr Coombs - Case 1: PD on 1L cBTKi

- 84 yo M with 17p-deleted CLL who was treated with frontline ibrutinib following approximately 1 year of watch and wait
- Indication for therapy was anemia with w/u negative for other causes in setting of progressive rise in WBC/ALC, also mild thrombocytopenia
- Due to myalgias that did not improve after dose reduction to 280 mg ibrutinib, the patient was switched to acalabrutinib which he tolerated well
- After 6 cumulative years on cBTKi, pt with rising WBC ct and worsening anemia suggestive of progression

Dr Coombs - Case 1: Review of options

- Reviewed both ven-based and cBTKi-based regimens with patient
 - he expressed desire to minimize visits to clinic so that he can maintain quality of life and without disruption to hobbies/travel
- He began pirtobrutinib 200 mg daily and has tolerated well without AE

Faculty Discussion

Dr Coombs - Case 2: Teaching case

- 72 yo M with CLL, afib who presents to transfer care from his oncologist who is retiring
- Labs: WBC ct 32.7, ALC is 27.6, Hb 13.0, Platelet 103
- Exam notable for splenomegaly 8 cm below L costal margin
- B2m 4.1 (creatinine 1.4), mutated IGHV, 13q del on FISH, no TP53 mutation but DNMT3A mutation (G543A) at VAF 8.6%
- Patient expressed desire to avoid treatment unless “absolutely necessary” – is asymptomatic

Dr Coombs - Case 2

- Further w/u revealed intermittently elevated total protein, Ig levels revealed IgG 3,201 but depressed IgA, IgM with kappa 222, lambda 15.2 with K/L ratio of 14.66. SPEP with IgG kappa monoclonal protein of 2.3 g/dL
- BM bx performed to r/o concurrent myeloma, revealed 70% involvement with CLL with focal plasmacytic differentiation (immunophenotype: CD5+, CD19+, CD20 (moderate), CD22+, CD23 (dim), also surface Ig kappa (dim to moderate), negative for SOX11, LEF1, BCL6, P53, cyclin D1

Dr Coombs - Case 2

- Patient was observed for approximately 1 year. He underwent Watchman procedure for his atrial fibrillation and no longer needs anticoagulation. With increase in spleen size (up to 10 cm below L costal margin), he ultimately elected to begin therapy with BTKi + BCL2 doublet (acala + ven). He has started acalabrutinib without issue with plan to introduce ven around C3.

Faculty Discussion

Integrating New Advances into Community Oncology Practice

*A Multitumor Symposium in Partnership with
Florida Cancer Specialists & Research Institute*

**Saturday, October 17, 2026
7:15 AM – 12:00 PM ET**

The Ritz-Carlton Orlando Grande Lakes | Orlando, Florida

**Moderator
Neil Love, MD**

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us.

The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME and ABIM MOC credit is provided in the Zoom chat room.

Attendees will also receive an email in 1 to 3 business days with these instructions.