Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Bruton Tyrosine Kinase Inhibitors for Chronic Lymphocytic Leukemia

A CME/MOC-Accredited Live Webinar

Wednesday, March 11, 2026

5:00 PM – 6:00 PM ET

Faculty

Jennifer R Brown, MD, PhD

Wojciech Jurczak, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2026

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Jennifer R Brown, MD, PhD
Director, CLL Center and Institute Physician
Dana-Farber Cancer Institute
Worthington and Margaret Collette Professor
of Medicine in the Field of Hematologic Oncology
Harvard Medical School
Boston, Massachusetts

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Wojciech Jurczak, MD, PhD
Department of Clinical Oncology
Head of Lymphoma Team
Maria Skłodowska-Curie National Research Institute of Oncology
Krakow, Poland

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Dr Love — Disclosures

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Contracted Research	BeOne, iOnctura SA, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Nagoon Therapeutics Inc
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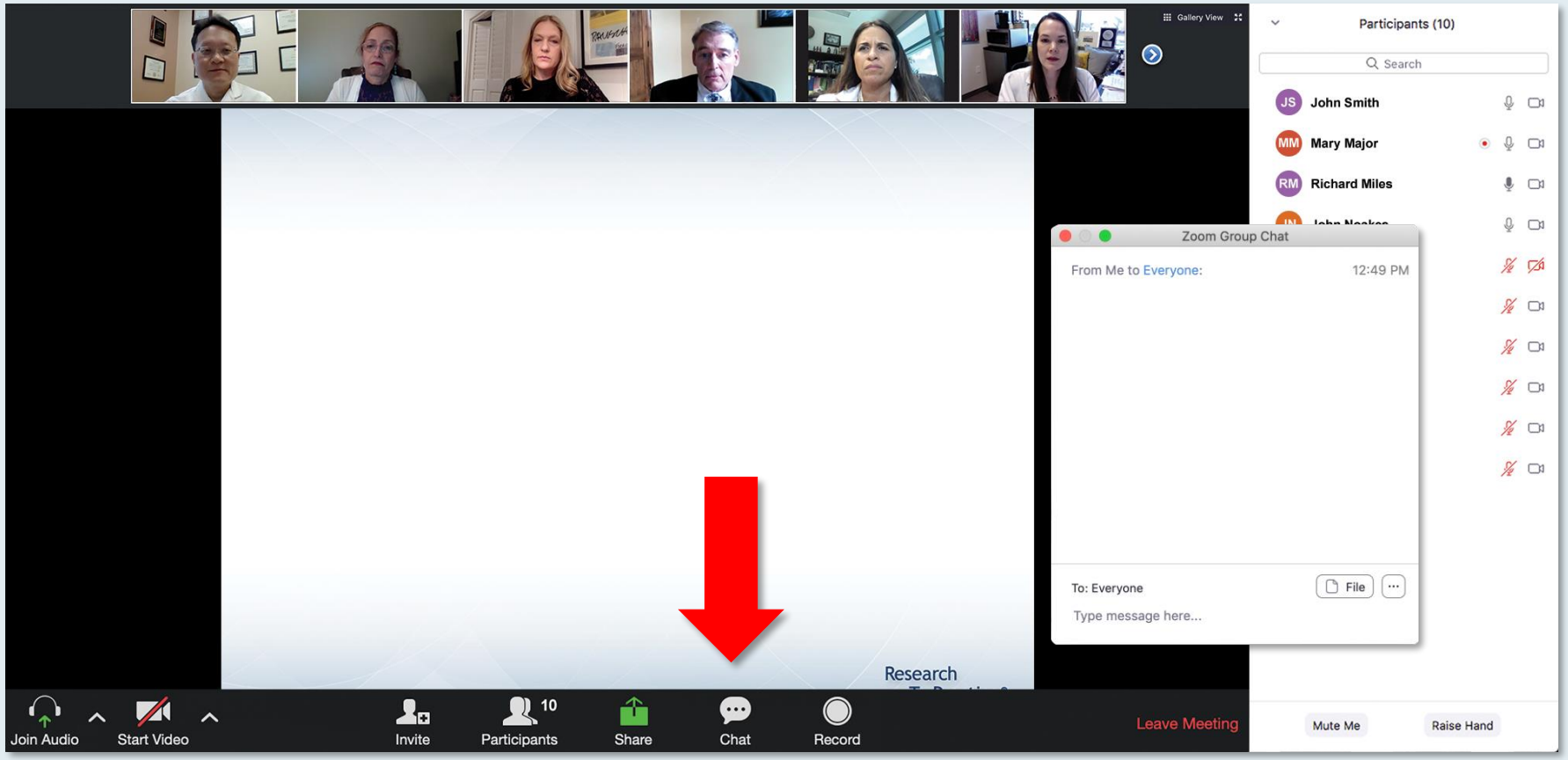

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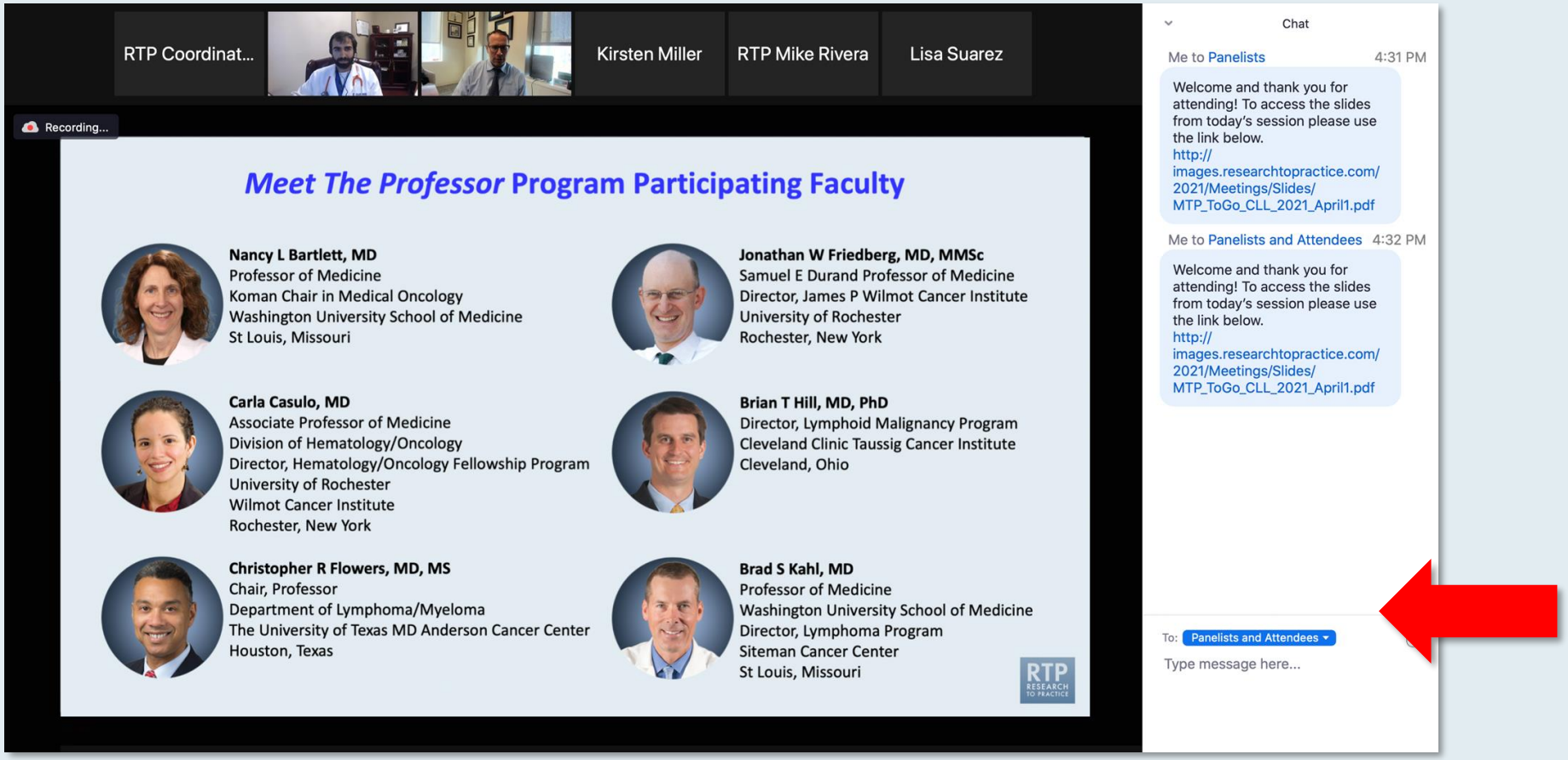

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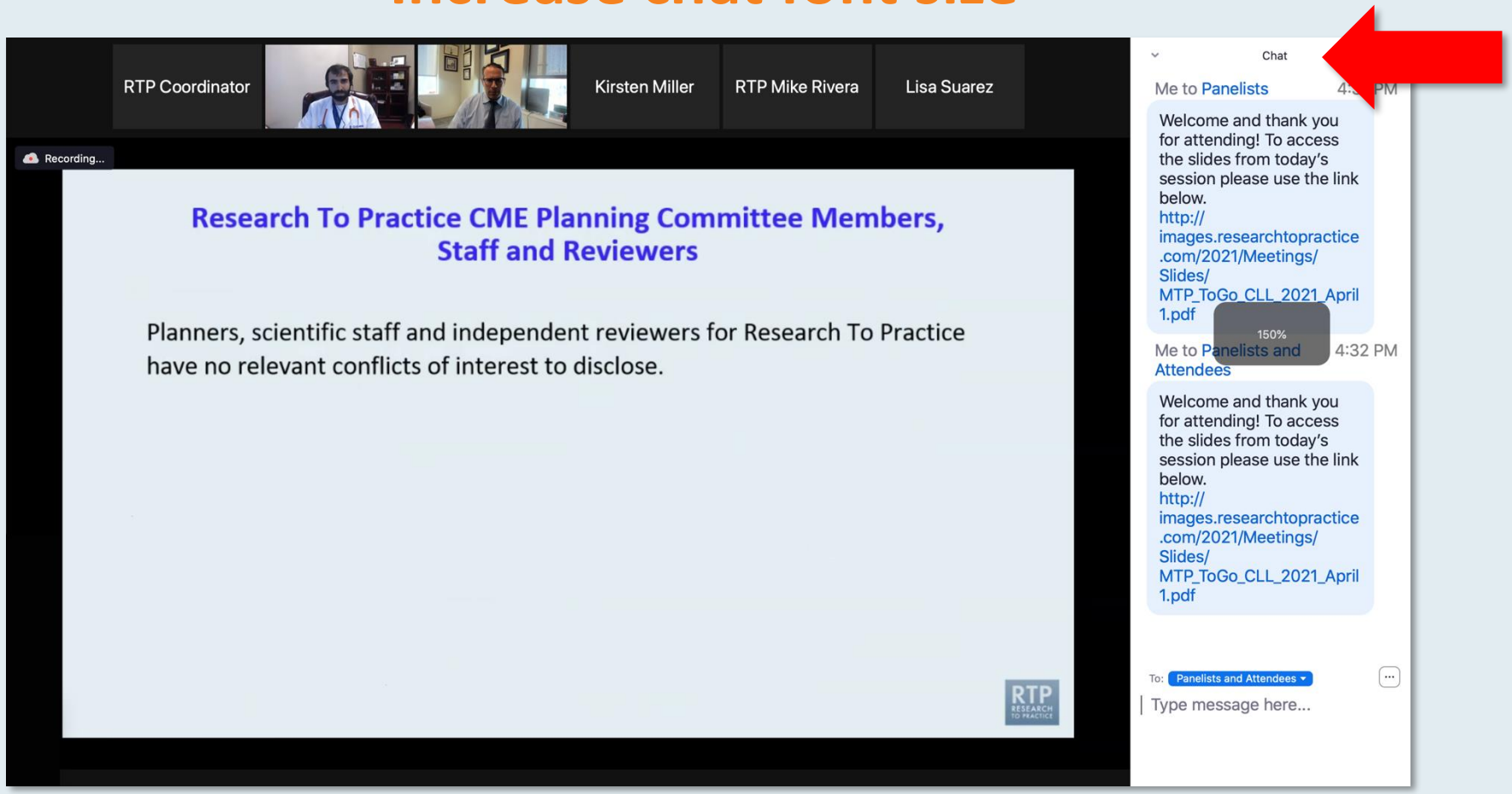

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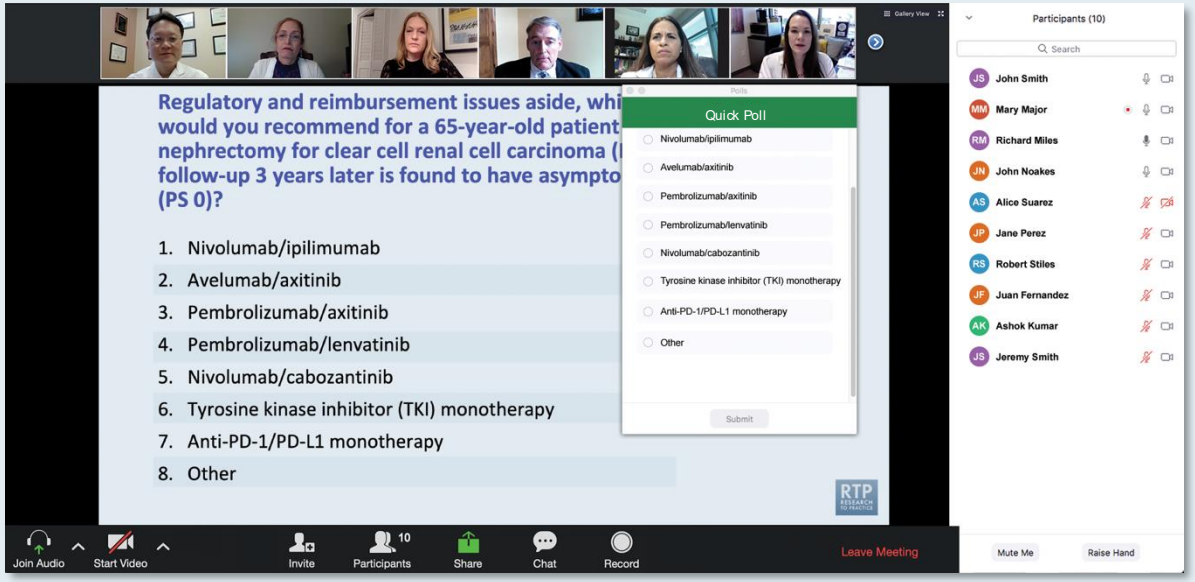

Chronic Lymphocytic Leukemia — Proceedings from a Symposium Series Preceding the 67th ASH Annual Meeting and Exposition

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What Clinicians Want to Know: First-Line and Maintenance Therapy for Patients with ER-Positive, HER2-Positive Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, March 18, 2026

5:00 PM – 6:00 PM ET

Faculty

Virginia F Borges, MD, MMSc
Ian E Krop, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Prostate Cancer

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Scott T Tagawa, MD, MS

Moderator

Neil Love, MD

RTP Year in Review 2026

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Menin Inhibitors for Acute Leukemias

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Amir Fathi, MD
Eunice S Wang, MD

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RTP Year in Review 2026

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Oral SERDs for Breast Cancer

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Tuesday, March 31, 2026
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Faculty

Aditya Bardia, MD, MPH
Erica Mayer, MD, MPH, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2026

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

EGFR-Mutant Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Tuesday, April 7, 2026
5:00 PM – 6:00 PM ET

Faculty

Suresh S Ramalingam, MD
Helena Yu, MD

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RTP Year in Review 2026

Grand Rounds

CME/MOC-Accredited Interactive Series

Regional Activities

Three Series

Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Optimizing the Use of Novel Therapies for Patients with Diffuse Large B-Cell Lymphoma

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RTP RESEARCH TO PRACTICE

Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Agenda
Bruton Tyrosine Kinase Inhibitors (BTKi) for Chronic Lymphocytic Leukemia

INTRODUCTION: I think I missed that day in med school (BTK biology)

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- Key reported trials
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  - High risk: double versus single hit, complex karyotype
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- Double exposed and refractory
- Pirtobrutinib, CAR T, bispecific antibodies, other
- BTK degraders

Thank you for joining us!

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

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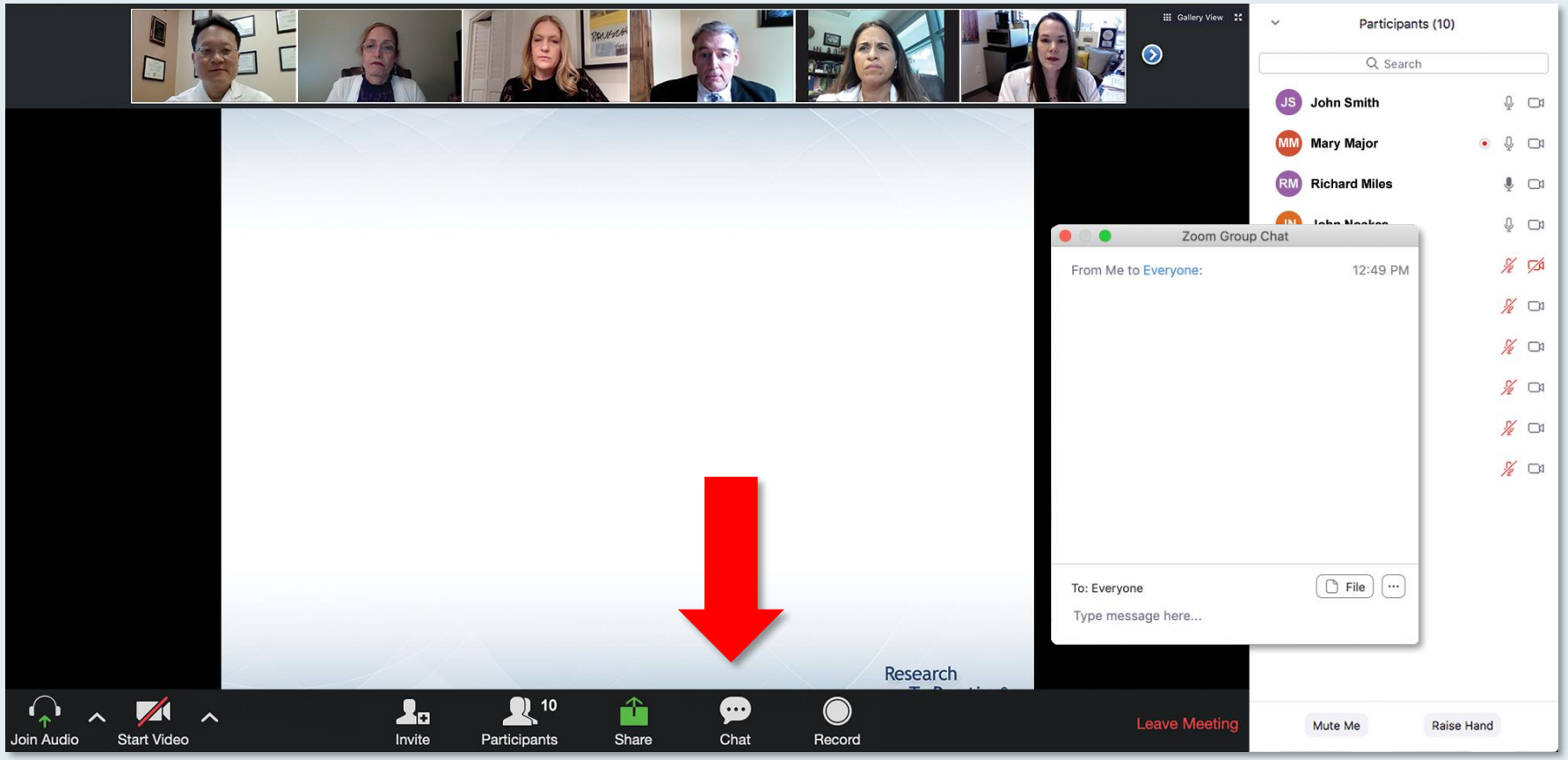

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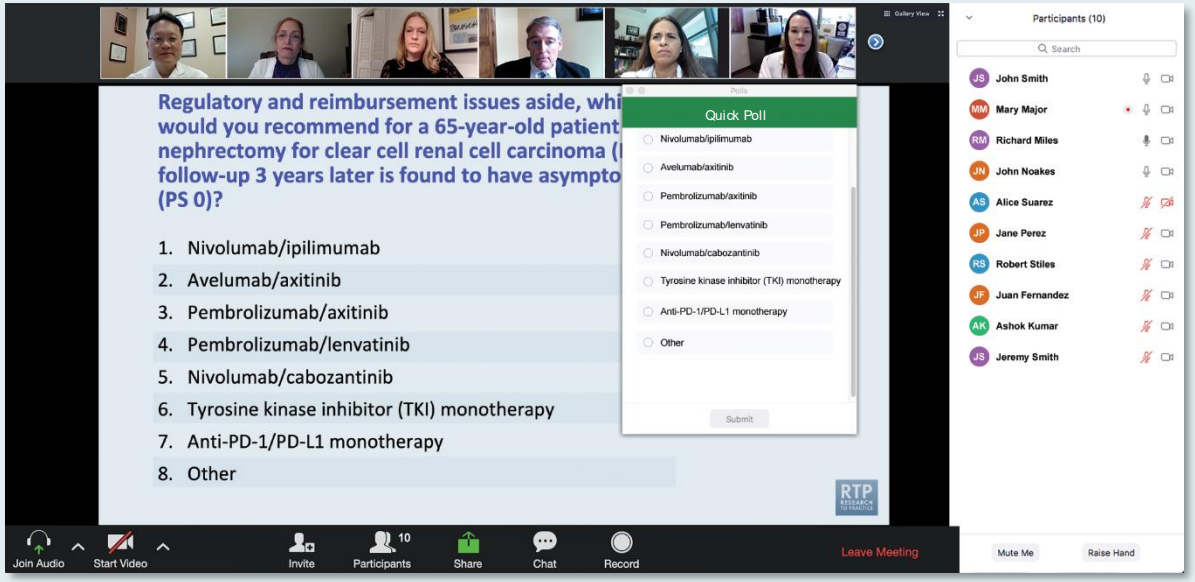

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Prof. Wojciech Jurczak MD, PhD
NIO-PIB im Marii Sklodowskiej-Curie
Garncarska 11, 31-115 Krakow, Poland
Wojciech.Jurczak@Lymphoma.edu.pl

Year in Review: BTK Inhibitors in CLL

CLL Year in Review

Jennifer R. Brown, M.D., Ph.D.
Director, CLL Center, and Institute Physician
Dana-Farber Cancer Institute
Worthington and Margaret Collette Professor of Medicine
In the Field of Hematologic Oncology
Harvard Medical School
March 11, 2026

RTP Year in Review 2026

Key Datasets

Wojciech Jurczak, MD, PhD

- Sharman JP et al. **Acalabrutinib-obinutuzumab** improves survival vs chemoimmunotherapy in **treatment-naive CLL** in the **6-year follow-up of ELEVATE-TN**. *Blood* 2025;146(11):1276-85.
- Simon F et al. **Acalabrutinib** treatment for older (aged ≥80 years) and/or frail patients with CLL: **Primary end point analysis of the CLL-Frail trial**. *Blood* 2025;146(26):3153-62.
- Tam C et al. Sustained efficacy of **zanubrutinib (zanu)** vs bendamustine + rituximab (BR) in **treatment (tx)-naive** chronic lymphocytic leukemia/small lymphocytic lymphoma (TN SLL/CLL) and continued favorable survival in non-randomized **patients (pts) with del(17p): 6-year follow-up in the phase 3 SEQUOIA study**. ASH 2025;Abstract 2129.
- Tam C et al. Long-term results of patients receiving **zanubrutinib** in **the phase 3 ALPINE study** confirm sustained benefit of zanubrutinib in patients with **relapsed/refractory** chronic lymphocytic leukemia or small lymphocytic lymphoma (R/R CLL/SLL): **Up to 6 years of follow-up** with the long-term extension (LTE1). ASH 2025;Abstract 2123.
- Tariq B et al. Relative bioavailability, food effect, and bioequivalence studies to assess a **new zanubrutinib 160-mg tablet**: Results from **2 phase 1 studies in healthy volunteers**. *Clin Pharmacol Drug Dev* 2026;15(1):e1584.

Key Datasets

Wojciech Jurczak, MD, PhD (continued)

- 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.
- Wierda W et al. **Pirtobrutinib in post-cbtki CLL/SLL: Final update from the phase 1/2 BRUIN study** with more than **5 years follow-up**. ASH 2025;Abstract 2115.
- Woyach J et al. **Pirtobrutinib** versus ibrutinib in **treatment-naïve and relapsed/refractory** chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol* 2025;[Online ahead of print].
- 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* 2025;[Online ahead of print].
- Woyach J 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.

Key Datasets

Jennifer Brown, MD, PhD

- Brown JR et al. Fixed-duration acalabrutinib combinations in **untreated** chronic lymphocytic leukemia. *N Engl J Med* 2025;392(8):748-62.
- Seymour JF et al. A **post hoc safety analysis** of fixed-duration **acalabrutinib-venetoclax combinations** vs chemoimmunotherapy: Results from the **phase 3 AMPLIFY trial**. ASH 2025;Abstract 2118.
- Davids MS et al. **Phase II study of acalabrutinib, venetoclax, and obinutuzumab** in a **treatment-naïve** chronic lymphocytic leukemia population enriched for **high-risk disease**. *J Clin Oncol* 2025;43(7):788-99.
- Swaminathan M et al. **Addition of obinutuzumab after one year of combined acalabrutinib and venetoclax** is safer and effective than early obinutuzumab in a randomized p**hase II trial** for **treatment naïve** CLL. ASH 2025;Abstract 681.
- Shadman M et al. **Zanubrutinib + venetoclax** for **treatment-naive** chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), including patients **with del(17p) and/or *TP53* mutation and unmutated immunoglobulin heavy-chain variable status**: **3-year results from SEQUOIA arm D**. ASH 2025;Abstract 5669.

Key Datasets

Jennifer Brown, MD, PhD (continued)

- Tam C et al. **Frontline treatment of sonrotoclax (BGB-11417) and zanubrutinib** for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) demonstrates high undetectable minimal residual disease (uMRD) rates with favorable tolerability: Updated data from **BGB-11417-101, an ongoing phase 1/1b study**. ASH 2025;Abstract 3891.
- Soumerai J et al. **Zanubrutinib + obinutuzumab + sonrotoclax** in patients with **treatment-naive** chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL): Initial results from an **ongoing phase 1/1b study, BGB-11417-101**. ASH 2025;Abstract 3890.
- Jain N et al. **Time-limited pirtobrutinib, venetoclax, and obinutuzumab combination** in **first-line** chronic lymphocytic leukemia. ASH 2025;Abstract 680.
- Jain N et al. **Pirtobrutinib, venetoclax, and obinutuzumab** for patients with **richter transformation: A phase 2 trial**. ASH 2025;Abstract 89.
- Ghia P et al. **Nemtabrutinib plus venetoclax** in **relapsed or refractory** chronic lymphocytic leukemia/small lymphocytic lymphoma: Results from the dose escalation and confirmation segment of the **phase 3 bellwave-010 study**. ASH 2025;Abstract 2119.
- Al-Sawaf O et al. **Fixed-duration versus continuous targeted treatment** for **previously untreated** chronic lymphocytic leukemia: Results from the randomized **CLL17** trial. ASH 2025;Abstract 1.

Agenda
Bruton Tyrosine Kinase Inhibitors (BTKi) for Chronic Lymphocytic Leukemia

INTRODUCTION: I think I missed that day in med school (BTK biology)

MODULE 1: First-line treatment

- Time-limited therapy; minimal residual disease assays
- Key reported trials
- Key planned and ongoing trials
- Key clinical questions
  - High risk: double versus single hit, complex karyotype
  - Standard risk: IGVH mutated vs unmutated
  - Older/frail/comorbidities

MODULE 2: Relapsed/refractory disease

- Progression on BTKi, venetoclax/anti-CD20
- Double exposed and refractory
- Pirtobrutinib, CAR T, bispecific antibodies, other
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BTKi for CLL

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Statistics for the dummies

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

Biology and Pharmacology of Select Agents to Treat CLL

- Chemotherapy
- Anti-CD20 antibodies
- BTK inhibitors (covalent and noncovalent)
- Bcl-2 inhibitors
- BTK degraders

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Select Key Papers

Trial	Comparison	Citation
CLL17	Ibr/Veneto vs Ibr and Veneto/obin vs Ibr	Al-Sawaf et al. ASH 2025
ALPINE	Zanubrutinib vs ibrutinib	Tam et al. ASH 2025
SEQUOIA	Zanubrutinib vs BR	Tam et al. ASH 2025
PVO fixed duration	Pirto/veneto/obinutuzumab	Jain et al. ASH 2025
BGB-11417-101	Sonrotoclax/zanubrutinib	Soumerai et al. ASH 2025
Delayed obinutuzumab	Acala/Veneto + obinutuzumab	Swaminathan et al. ASH 2025
AMPLIFY	Acala/Veneto vs FCR or BR	Brown et al. ASH 2025, NEJM 2025
BRUIN-314	Pirtobrutinib vs ibrutinib	Woyach et al. ASH 2025, JCO 2025
BRUIN-313	Pirtobrutinib vs BR	Jurczak et al. ASH 2025, JCO 2025
AV;AVO fixed duration	Acala/Veneto/Obinutuzumab	Davids et al. JCO 2025
FLAIR	Venetoclax/ibrutinib vs FCR	Munir et al. NEJM 2024, 2025
BRUIN-321	Pirtobrutinib vs BR or IR	Sharman et al. JCO 2025

Select Ongoing Trials

Trial	Comparison
MAJIC (NCT05057494)	Acala/Veneto vs Veneto/Obinu
NCT06073821	Sonrotoclax/zanu vs Veneto/obinu
NCT07277231	Sonrotoclax/zanu vs Veneto/acala
NCT07321652	Zanubrutinib vs zanu/sonrotoclax
NCT05197192	Acala/Veneto/obinu vs Veneto/obinu

Questions About First-Line Treatment

- How should minimal residual disease (MRD) assays be utilized in community practice?
- Which MRD assay?
- What specific value is the goal?
- For time-limited treatment, when should MRD assays be performed?

AMPLIFY Trial

“AV is a very well tolerated time-limited option with easier administration compared to ven/obin and without the toxicities of ibrutinib/venetoclax, and so we do expect this to become pretty widely used. I myself am actually using it for some patients who might have gotten continuous BTK inhibitor before. This way we can get them off therapy pretty easily, and they can have time off therapy, less toxicity, less potential for resistance, but without the work involved in doing, for example, venetoclax/obinutuzumab.

The FLAIR data demonstrated patients didn’t get any BTK mutations in the I + V arm, but they did in the I arm. In addition, AVO is highly effective, especially in the unmutated patients. In evaluable patients it had a 95% rate of undetectable MRD. But cautions required regarding infection, so this is really best for younger, fitter patients with higher-risk disease.”

Dr Jennifer R Brown

Questions About First-Line Treatment

- **Should the time it takes to achieve MRD negativity be considered in determining duration of treatment?**
- **How should patients who retain MRD positivity after the planned treatment duration be approached?**
- **In what situations, if any, would you deploy the strategy reported by MD Anderson of delayed obinutuzumab after up-front BTK/Bcl-2 inhibitors?**

Questions About First-Line Treatment

- **How do you clinically compare the global efficacy and tolerability of acalabrutinib and zanubrutinib? What about pharmacokinetics?**
- **In what situations, if any, do you believe there is a role for pirtobrutinib for treatment-naïve CLL?**

Comparison of BTKIs

“Numerically, zanubrutinib has greater efficacy than ibrutinib. In clinical practice, I think that both second-generation inhibitors are great drugs, and the problem starts when someone starts claiming that one is superior to the other. Perhaps if we took the 4 approved BTK inhibitors, pirto is the best both in terms of efficacy, as it overcomes the resistance, and in terms of tolerance, because it's magnificently selective. But we do not have pirto long-time observations, as even in the BRUIN Phase I and II study, we just have a 5-year follow-up. So none of those things could be proven in an affirmed way.

The dose of zanu and the pharmacokinetics of zanu gives us a possible basis for a better efficacy. Because if you look at IC50, the inhibitory concentration at which half of the Bruton tyrosine kinase activity is inhibited. Now, for ibrutinib it's 6 hours a day. For acala, it's 5 hours a day. For zanu, it's round the clock. But if you compare IC50 between zanu and pirto, pirto is round the clock as well, but not IC50, but IC90. So it may be that certain drugs have a potentially better clinical capacity of killing the cells, but whether this will be relevant clinically, we are not able to prove.

Perhaps a more important issue is time-indefinite therapy versus time-limited therapy.”

Prof Wojciech Jurczak

Questions About First-Line Treatment

- For patients without high-risk biomarkers, how does IGVH status affect treatment choice?
- In what situations do you recommend continuous BTKi therapy?
- How much of an issue is toxicity with pirtobrutinib/venetoclax/obinutuzumab?
- Why do you think this was observed?

Questions About First-Line Treatment

- How do you approach much older patients or those with important comorbidities?
- How do you evaluate the patient for potential use of a Bcl-2 inhibitor?
- How do you clinically compare the global efficacy and tolerability of venetoclax and sonrotoclax? What about pharmacokinetics?
- How would you compare the logistical demands of venetoclax ramp-up to those of sonrotoclax?

Sonrotoclax

“Sonrotoclax is more selective than venetoxlax, therefore less off-target inhibition, therefore slightly less adverse events. Then we have the possibility of a more pronounced inhibition, maybe even 14 times more pronounced, which may mean more efficacy. Thirdly, it's also efficient in certain mutations where venetoclax is not working. We gave used sonrotoclax monotherapy in a study, and most of the patients, who were a difficult to treat group, responded. We really were truly astonished. I think that a combination of sonrotoclax with zanubrutinib, which is now in Phase III, is going to change our perspective, but not sooner than 2 or 3 years.”

Prof Wojciech Jurczak

Questions About First-Line Treatment

- How should disease be managed for patients with del(17p), P53 or both?
- What about patients with complex cytogenetics?
- How do IGVH status and other biomarkers factor in?
- For high-risk situations, if continuous BTKi treatment is used, which BTKi?
- In what situations is time-limited treatment a consideration?

High-Risk Disease

“There are increasing data that 2-hit p53 aberration, deletion 17p is probably higher risk than 1-hit, and then similarly if there’s an unmutated IGHV associated with p53 that’s likely higher risk. And so time-limited therapy is probably better in 17p patients who have 1-hit PFS, or mutated IGHV, who have mitigation of their risk in terms of their disease.

But you could still use this time-limited combo in any 17p patient if they particularly strongly wanted it, but if I were doing that I would consider monitoring MRD in remission, like we did in the study, and then consider early reinitiation of therapy so that you don’t lose control of the disease. This regimen’s also now actually in the NCCN Guidelines for 17p-deleted patients.”

Dr Jennifer R Brown

Questions About First-Line Treatment: Future Directions

- **Do you foresee a time in which biomarkers will be used to specifically select patients for therapy who are currently observed off treatment?**
- **What are the key design elements, endpoints and questions being addressed in ongoing Phase III trials for treatment-naïve disease?**
- **Is there a significant efficacy advantage of one BTKi over another, and if so, how much is from the inherent antitumor activity versus better tolerability and more time on treatment?**

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])."

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

RTP RESEARCH TO PRACTICE

AMPLIFY Conclusions

- **AV very well tolerated time-limited option with easier administration**

- **AVO highly effective especially in IGHV unmutated patients (95% uMRD in evaluable patients)**
  - **Caution required regarding infection, best for younger, fit patients with higher risk disease**

Courtesy of Jennifer R Brown, MD, PhD

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

AMPLIFY Safety

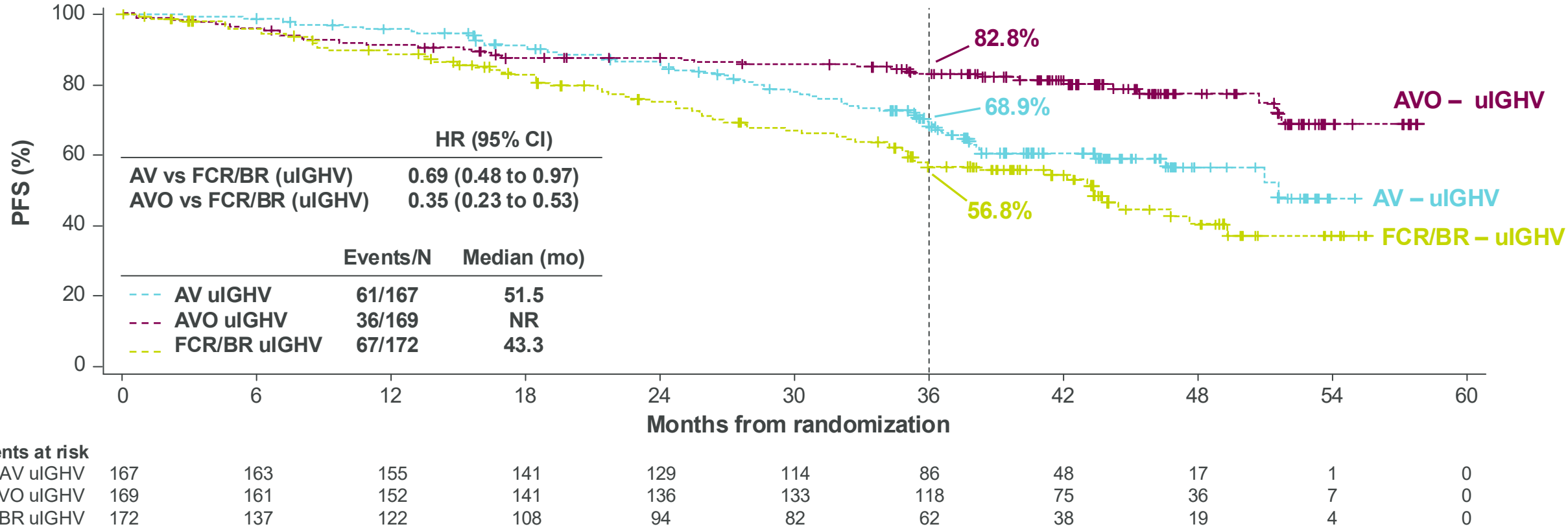
- **Cardiac and infectious risks were higher in anti-CD20 antibody containing arms, compared to AV**

- **AV for 14 months was very well-tolerated, low rate of infection and very few cardiac events**

Courtesy of Jennifer R Brown, MD, PhD

Seymour JF et al. ASH 2025;Abstract 2118

Fixed-Duration Acalabrutinib Combinations: PFS in the uIGHV Subgroup



Patients at risk

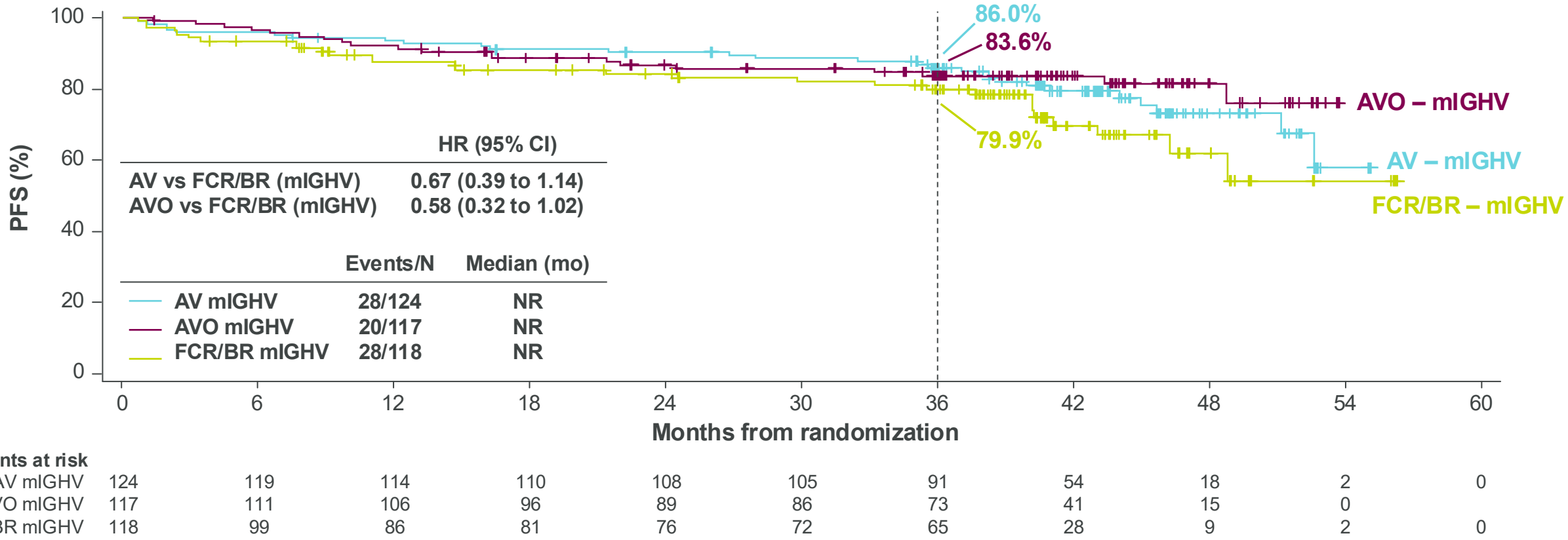
AV uIGHV	167	163	155	141	129	114	86	48	17	1	0
AVO uIGHV	169	161	152	141	136	133	118	75	36	7	0
FCR/BR uIGHV	172	137	122	108	94	82	62	38	19	4	0

PFS assessed by IRC; PFS by IGHV status was a prespecified analysis (ITT population).
Hazard ratio (95% CI) computed using an unstratified Cox proportional-hazards model.
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; uIGHV, unmutated immunoglobulin heavy-chain variable region gene.

Courtesy of Jennifer R Brown, MD, PhD

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

Fixed-Duration Acalabrutinib Combinations: PFS in the mIGHV Subgroup



Patients 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

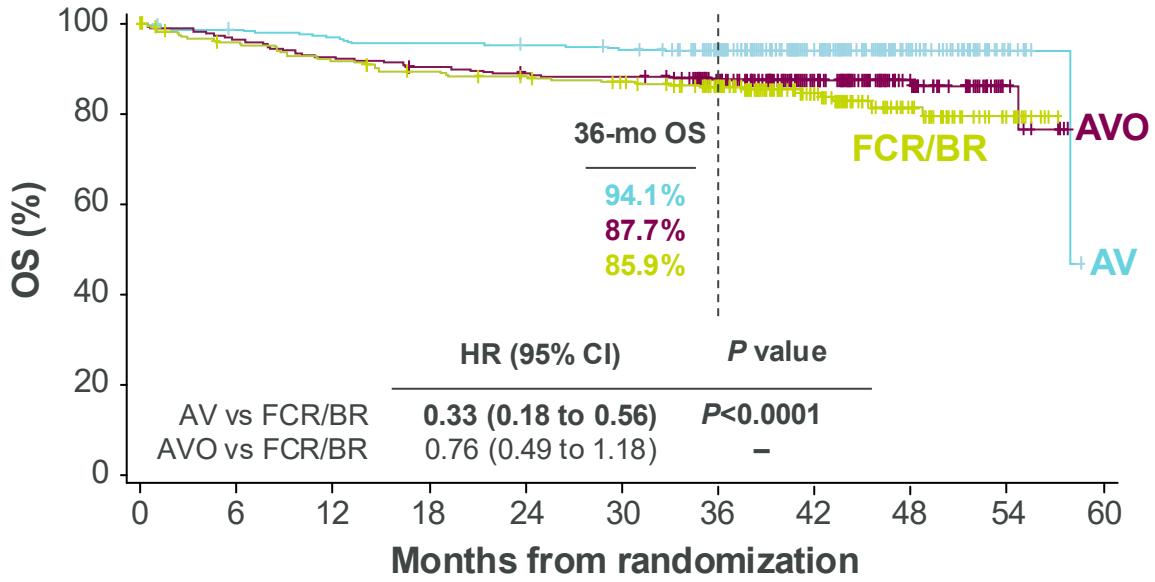
PFS assessed by IRC; PFS by IGHV status was a prespecified analysis (ITT population).
Hazard ratio (95% CI) computed using an unstratified Cox proportional-hazards model.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; mIGHV, mutated immunoglobulin heavy-chain variable region gene; NR, not reached; PFS, progression-free survival.

Courtesy of Jennifer R Brown, MD, PhD

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

Fixed-Duration Acalabrutinib Combinations: Overall Survival

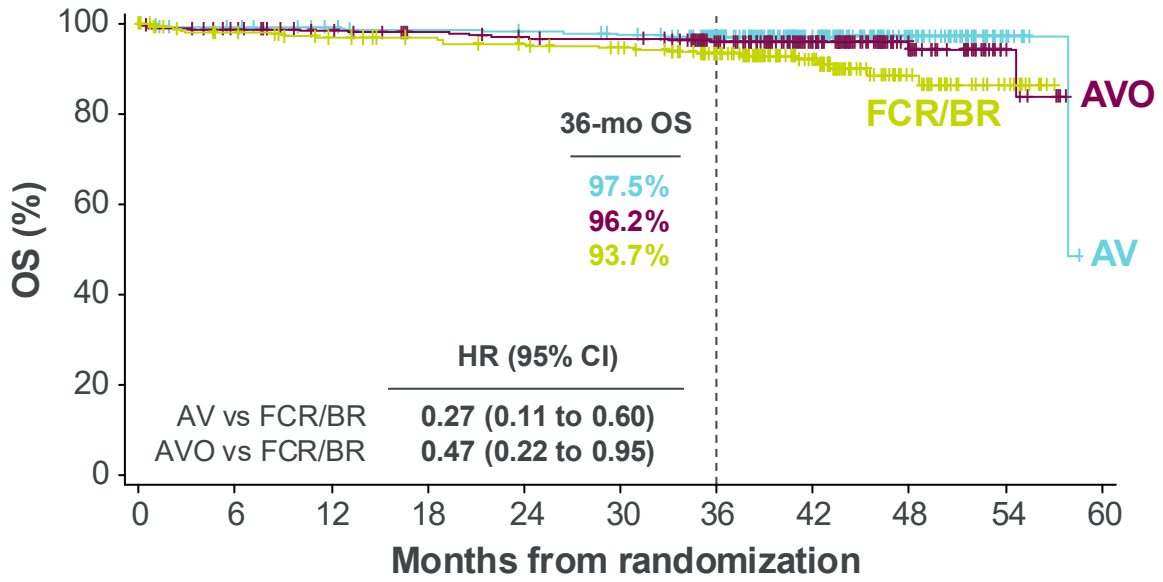
OS Prolonged With AV vs FCR/BR



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

OS Prolonged With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

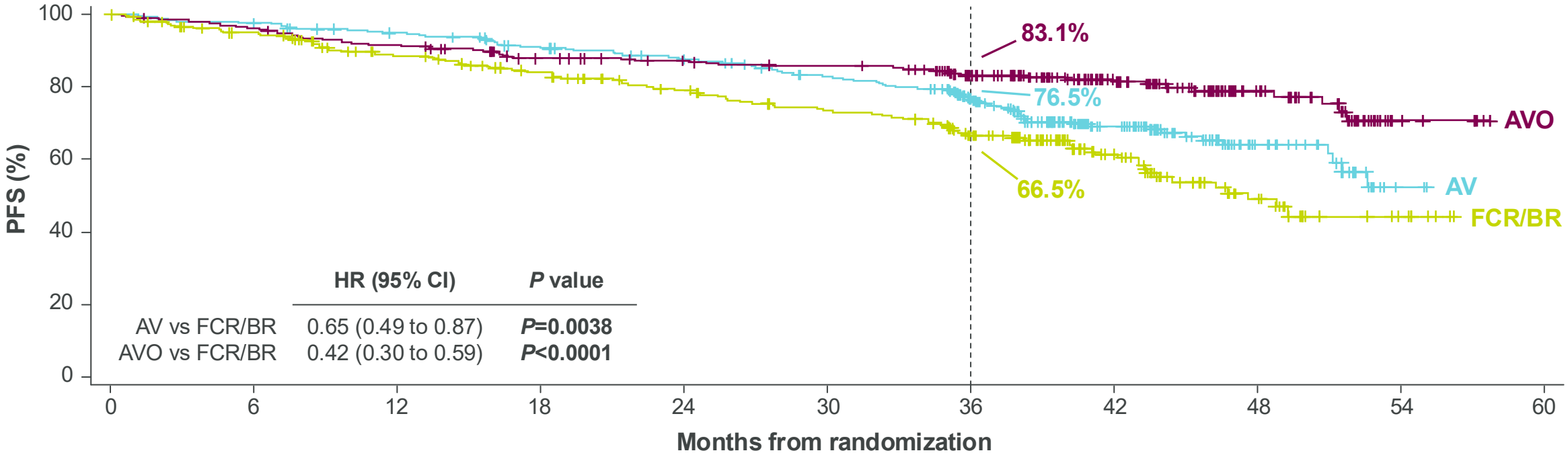
COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

ITT population.
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; ITT, intent-to-treat; OS, overall survival.

Courtesy of Jennifer R Brown, MD, PhD

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

Fixed-Duration Acalabrutinib Combinations: IRC-assessed PFS



Patients 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

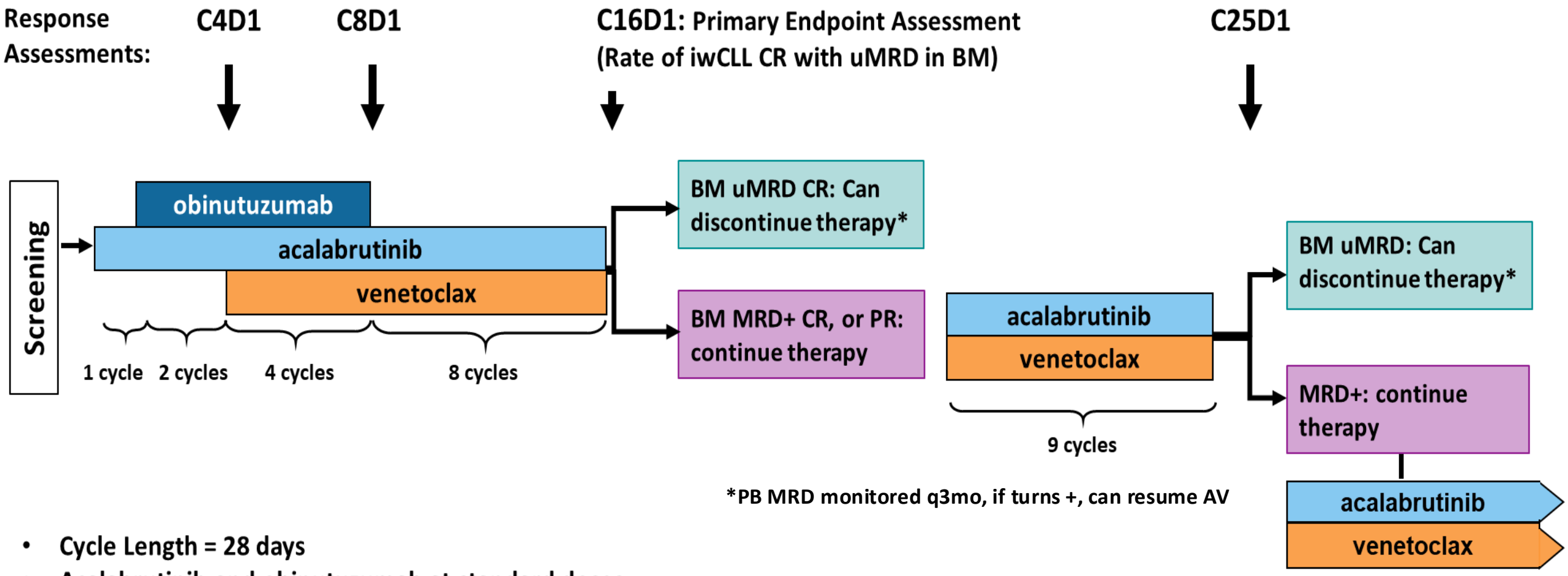
Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

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

Courtesy of Jennifer R Brown, MD, PhD

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

DFCI AVO: Study Schema

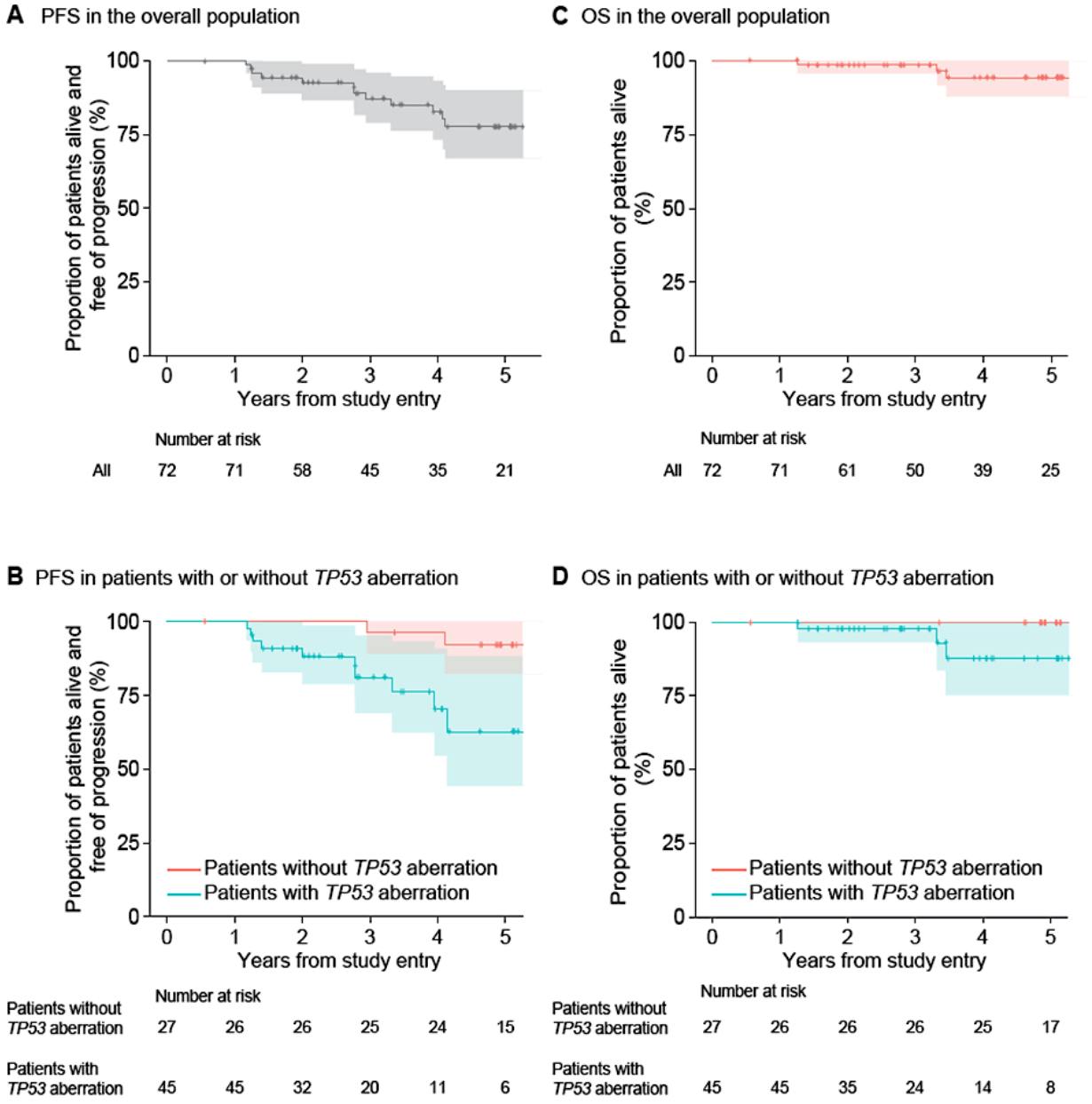


- Cycle Length = 28 days
- Acalabrutinib and obinutuzumab at standard doses
- Venetoclax 20mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose
- MRD at C16 & C25 assessed by multicolor flow cytometry (10^{-4})

Courtesy of Jennifer R Brown, MD, PhD

Davids MS et al. J Clin Oncol 2025;43(7):788-99.

DFCI AVO: Survival & Recurrence



- **Rate of BM-uMRD by flow at 10^{-4} at start of C16 was:**
  - **78% in the overall population**
  - **71% in *TP53*-aberrant pts**
- **PB-uMRD at 10^{-5} by ClonoSEQ was 54.4% at start of C16 and C25**
- **35 pts (51%) had MRD recurrence**
  - **Median time to MRD recurrence was 32.2 months**
- **70% 4-year PFS in pts with *TP53* aberration; 96% in pts without *TP53* aberration**
- **10 pts have had clinical progression, 4 with transformation events, including Richter's DLBCL (n=2) and Hodgkin lymphoma (n=2)**
- **3 pts have died, one each due to gr 5 COVID-19 infection during treatment, complications from polysubstance abuse, and progression of Richter's**

Courtesy of Jennifer R Brown, MD, PhD

Davids MS et al. J Clin Oncol 2025;43(7):788-99.

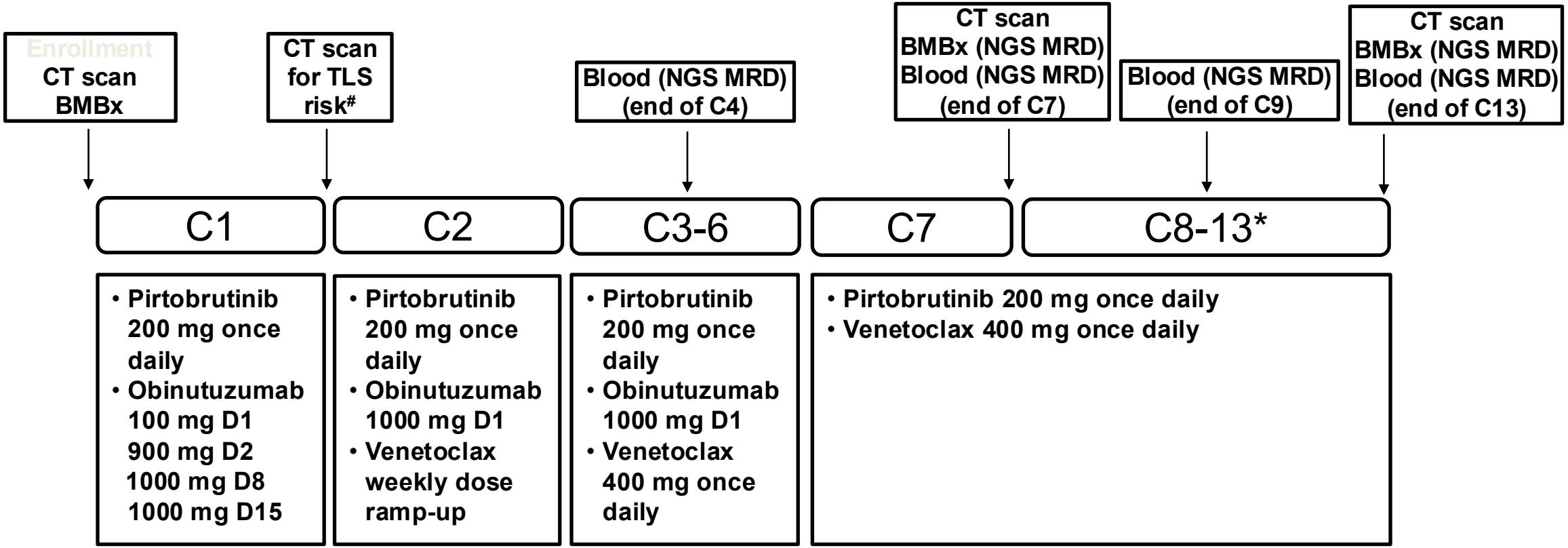
MRD-Guided AVO

- **Well tolerated, high rates of uMRD, but PFS still shorter in del 17p patients (70% 4 yr)**
  - **Likely best in one-hit TP53 aberration or with mutated IGHV**

- **If using time-limited combo in del 17p patients, would use this and consider monitoring MRD in remission, for consideration of early re-initiation**

Courtesy of Jennifer R Brown, MD, PhD

PVO Trial: Treatment Schema



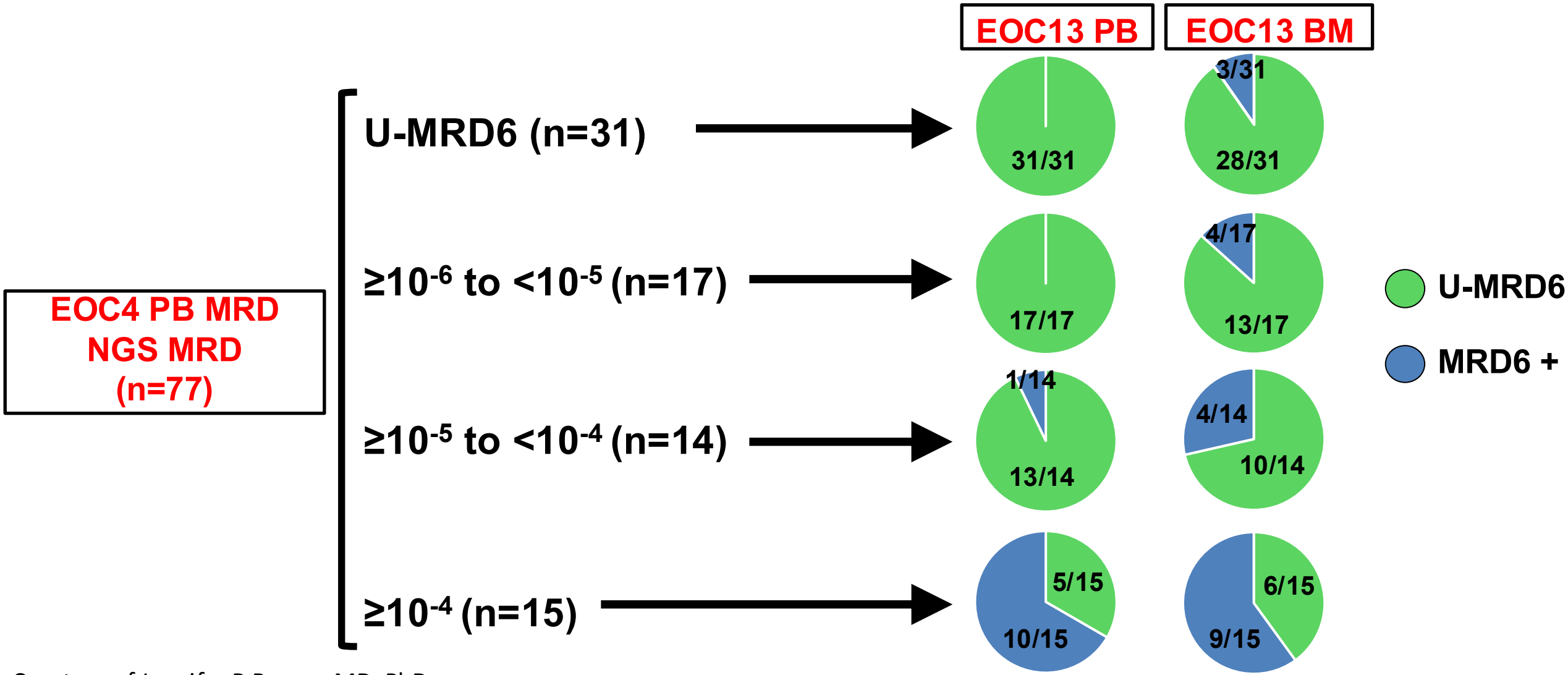
#CT imaging is repeated for TLS risk assessment only if baseline CT had nodes ≥5 cms

- Each cycle is 28 days
- NGS MRD assessed by clonoSEQ assay (Adaptive Biotechnologies)
- *For pts who are MRD+ at ≥10^{-5} in either PB or BM at end of C13 can continue pirtobrutinib + venetoclax for an additional 12 cycles
- All pts monitored by PB NGS MRD q3 mos for first 12 mos off therapy, and then q6 mos

Courtesy of Jennifer R Brown, MD, PhD

Jain N et al. ASH 2025;Abstract 680

PVO Trial: Early PB U-MRD predicts for U-MRD6 in PB/BM at 12 cycles of combination



Courtesy of Jennifer R Brown, MD, PhD

Jain N et al. ASH 2025;Abstract 680

PVO Trial: Adverse Events

- Grade 3-4 neutropenia and thrombocytopenia occurred in 54 (67%) and 14 (17%) pts, respectively. 50 (63%) pts required G-CSF.
- 4 (5%) pts had neutropenic fever (diverticulitis, n=1; pneumonia, n=1; sinusitis, n=1; parainfluenza infection, n=1)
- Venetoclax and pirtobrutinib were dose-reduced respectively; most common reason for dose reduction was neutropenia
- 2 (2%) pts developed atrial fibrillation (including 1 in the setting of COVID-19 infection)

Courtesy of Jennifer R Brown, MD, PhD

Jain N et al. ASH 2025;Abstract 680

PVO in Frontline CLL

- **MDACC single center study, short follow-up (21.6 mos)**
- **Very high rates of uMRD but also high rates of neutropenia and thrombocytopenia**
- **Caution warranted -- ? Explore alternative schedules like delayed obinutuzumab; consider in relapsed patients**

Courtesy of Jennifer R Brown, MD, PhD

Marrow uMRD4 Rates in Unmutated IGHV

Time points	ACA+VEN (n=34)	ACA+VEN+OBIN (n=32)	Odds ratio [95% CI]	p-value
	BM uMRD4, n (%)			
End of C9	6 (18)	20 (62)	7.78 [2.38-24.23]	0.0003
End of C14	9 (26)	24 (75)	8.33 [2.66-23.89]	0.0002
Late obin	27/34 (79)	7/32 (22)	-	-
End of C20	30 (88)	27 (84)	0.72 [0.20-2.82]	0.730
End of C26	30 (88)	26 (81)	0.58 [0.17-2.07]	0.505

Courtesy of Jennifer R Brown, MD, PhD

Conclusions

- Addition of obin to ACA+VEN led to higher uMRD4 rates
  - Both with early (EOT – 71%) and late (EOT – 83%) addition of obin
- Obin added after 1 year of combined ACA+VEN was safer
  - Grade ≥3 neutropenia with early obin – 52% in C1-14 vs. 12% with late obin in C15-26
  - Grade ≥3 infection rates were lower as well (26% vs. 2%, respectively)

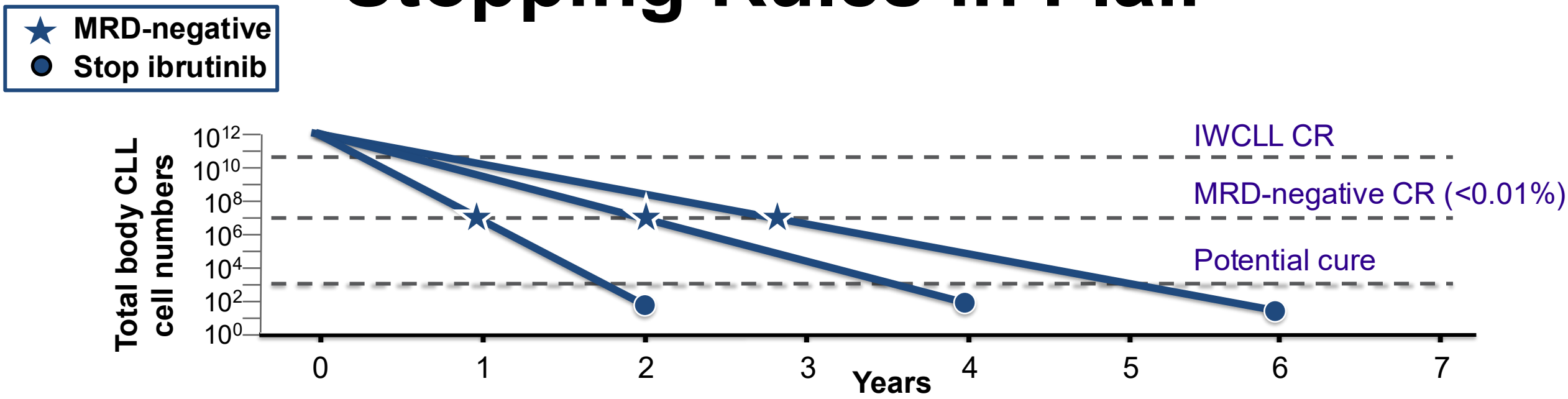
Courtesy of Jennifer R Brown, MD, PhD

Delayed Addition of Obinutuzumab

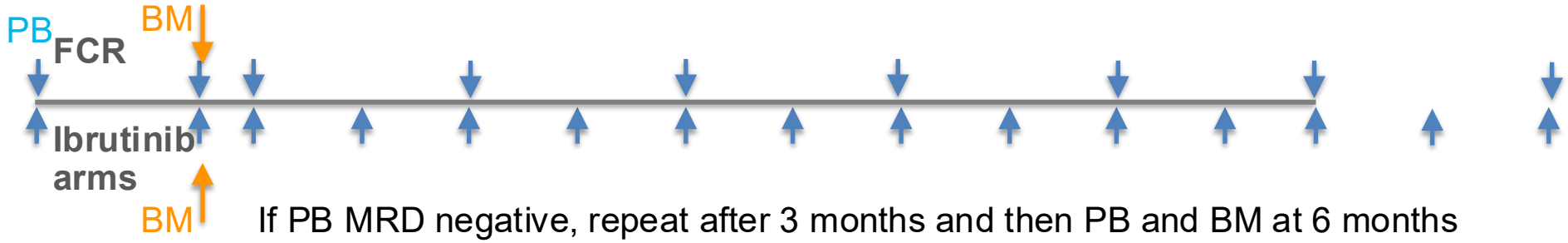
- **MDACC single institution study**
- **uMRD similar with early vs late addition of obinutuzumab in this study, with less neutropenia and less grade 3+ infection**
- **Duration of therapy longer compared to AMPLIFY regimen but may extend applicability to less fit patients**

Courtesy of Jennifer R Brown, MD, PhD

Stopping Rules in Flair

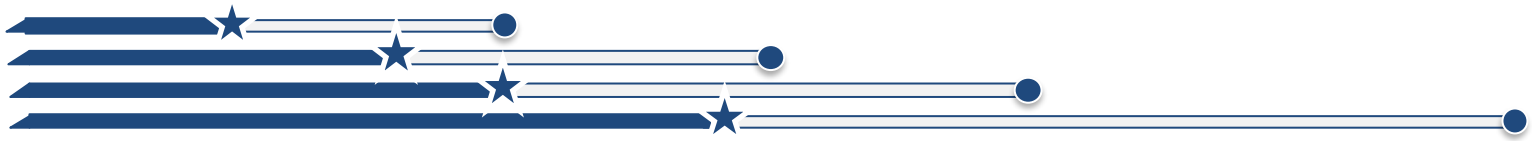


Testing schedule
(Central lab, MRD flow, MRD negative <1 CLL cell in 10^4)



If PB MRD negative, repeat after 3 months and then PB and BM at 6 months
– if all MRD negative, then first PB MRD negative result is time to MRD negativity

Stopping rules
2 to 6 years Ibrutinib
Or ibr+venetoclax
Double time after MRD negative



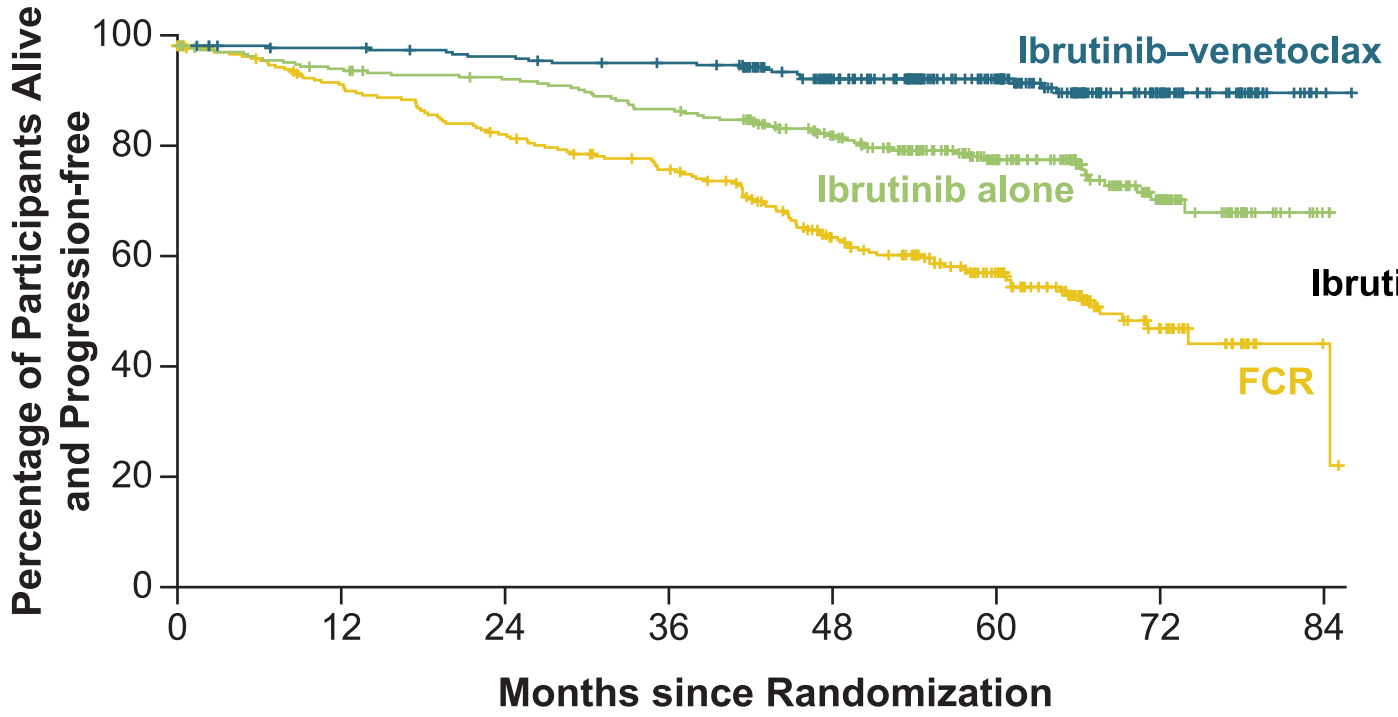
Restart ibrutinib if becomes MRD positive prior to Year 6

Courtesy of Jennifer R Brown, MD, PhD

Munir et al. *N Engl J Med* 2024;390:326-337DOI: 10.1056/NEJMoa231006

FLAIR: Updated PFS

All Participants



	Total No. of Events	Median Progression-free Survival (95% CI) *mo*
Ibrutinib–Venetoclax	18	NR
Ibrutinib Alone	59	NR
FCR	112	69.22 (61.04–NR)

Hazard Ratio for Disease Progression or Death (95% CI)

Ibrutinib–venetoclax vs. ibrutinib alone: 0.29 (0.17–0.49); P<0.001
Ibrutinib–venetoclax vs. FCR: 0.13 (0.08–0.21); P<0.001
Ibrutinib alone vs. FCR: 0.44 (0.32–0.60)

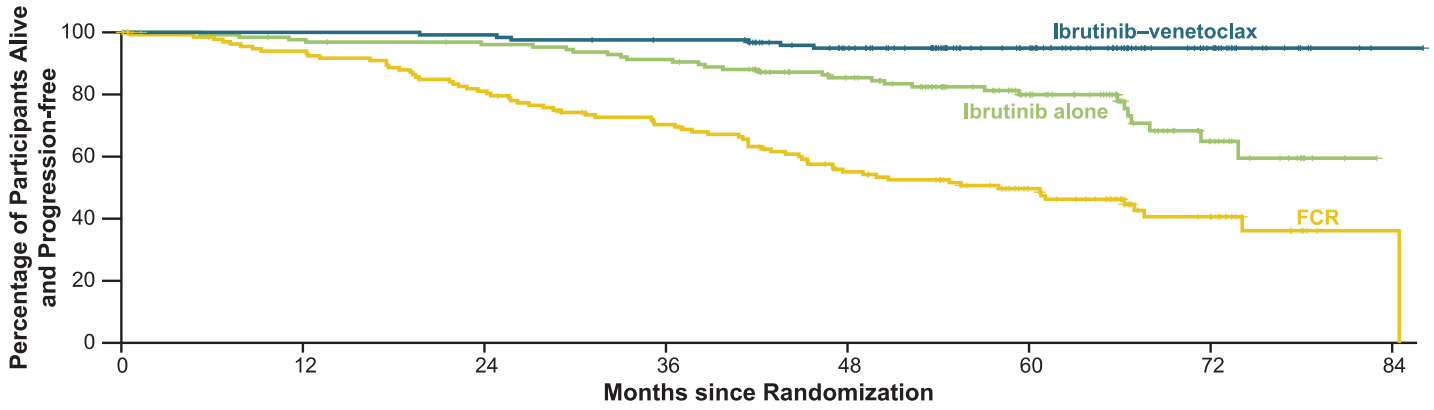
No. at Risk (no. with data censored)								
Ibrutinib–venetoclax	260 (0)	254 (5)	248 (7)	242 (10)	206 (39)	139 (106)	49 (193)	2 (240)
Ibrutinib alone	263 (0)	248 (4)	239 (8)	225 (8)	190 (31)	121 (91)	46 (159)	2 (202)
FCR	263 (2)	232 (13)	208 (14)	187 (19)	140 (37)	94 (70)	29 (124)	2 (150)

Courtesy of Jennifer R Brown, MD, PhD

Munir T, et. al. *N Engl J Med*. 2025 Sep 25;393(12):1177-1190.

FLAIR: PFS by IGHV Mutation Status

Participants with Unmutated *IGHV*



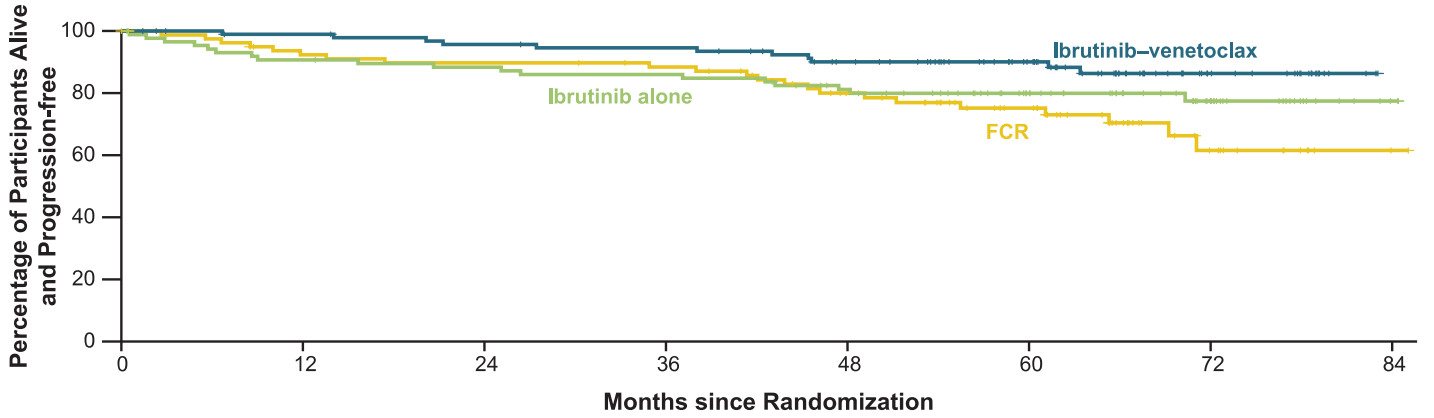
No. at Risk (no. with data censored)								
Ibrutinib–venetoclax	123 (0)	123 (0)	122 (0)	118 (2)	100 (17)	62 (55)	24 (93)	1 (116)
Ibrutinib alone	129 (0)	124 (2)	120 (4)	114 (4)	92 (19)	57 (49)	17 (83)	0 (99)
FCR	139 (1)	124 (7)	107 (7)	90 (10)	66 (15)	44 (31)	17 (52)	1 (67)

	Total No. of Events	Median Progression-free Survival (95% CI) *mo*
Ibrutinib–Venetoclax	6	NR
Ibrutinib Alone	30	NR
FCR	71	57.95 (45.31–74.05)

Hazard Ratio for Disease Progression or Death (95% CI)

Ibrutinib–venetoclax vs. ibrutinib alone:
0.20 (0.08–0.48)
Ibrutinib–venetoclax vs. FCR:
0.07 (0.03–0.15)
Ibrutinib alone vs. FCR:
0.35 (0.23–0.53)

Participants with Mutated *IGHV*



No. at Risk (no. with data censored)								
Ibrutinib–venetoclax	97 (0)	92 (4)	88 (5)	86 (6)	76 (12)	57 (31)	20 (66)	0 (86)
Ibrutinib alone	87 (0)	78 (1)	75 (2)	73 (2)	65 (6)	47 (23)	22 (47)	2 (67)
FCR	82 (1)	71 (5)	69 (5)	66 (7)	53 (14)	38 (26)	12 (48)	1 (59)

	Total No. of Events	Median Progression-free Survival (95% CI) *mo*
Ibrutinib–Venetoclax	11	NR
Ibrutinib Alone	18	NR
FCR	22	NR

Hazard Ratio for Disease Progression or Death (95% CI)

Ibrutinib–venetoclax vs. ibrutinib alone:
0.51 (0.24–1.08)
Ibrutinib–venetoclax vs. FCR:
0.36 (0.18–0.76)
Ibrutinib alone vs. FCR:
0.73 (0.39–1.37)

Courtesy of Jennifer R Brown, MD, PhD

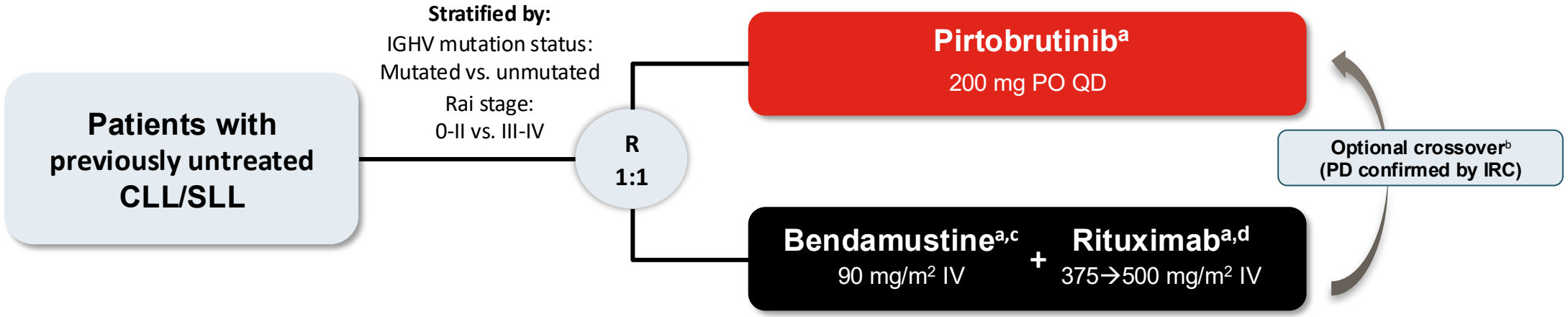
Munir T, et. al. *N Engl J Med*. 2025 Sep 25;393(12):1177-1190.

FLAIR Conclusions

- **First study to show a PFS benefit (and an OS benefit!) for a time-limited approach – required MRD guidance and/or longer duration of therapy (median 27 mos)**
- **As usual this is driven by outcomes in IGHV UM patients – likely over-treatment for IGHV M patients**

Courtesy of Jennifer R Brown, MD, PhD

BRUIN CLL-313: Study Design



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 × 10^9/L (≥50 × 10^9/L for patients with evidence of bone marrow infiltrate)
- Hemoglobin ≥8 g/dL
- Absolute neutrophil count ≥0.75 × 10^9/L

Endpoints

Primary

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

Key secondary

- OS[f]

Secondary

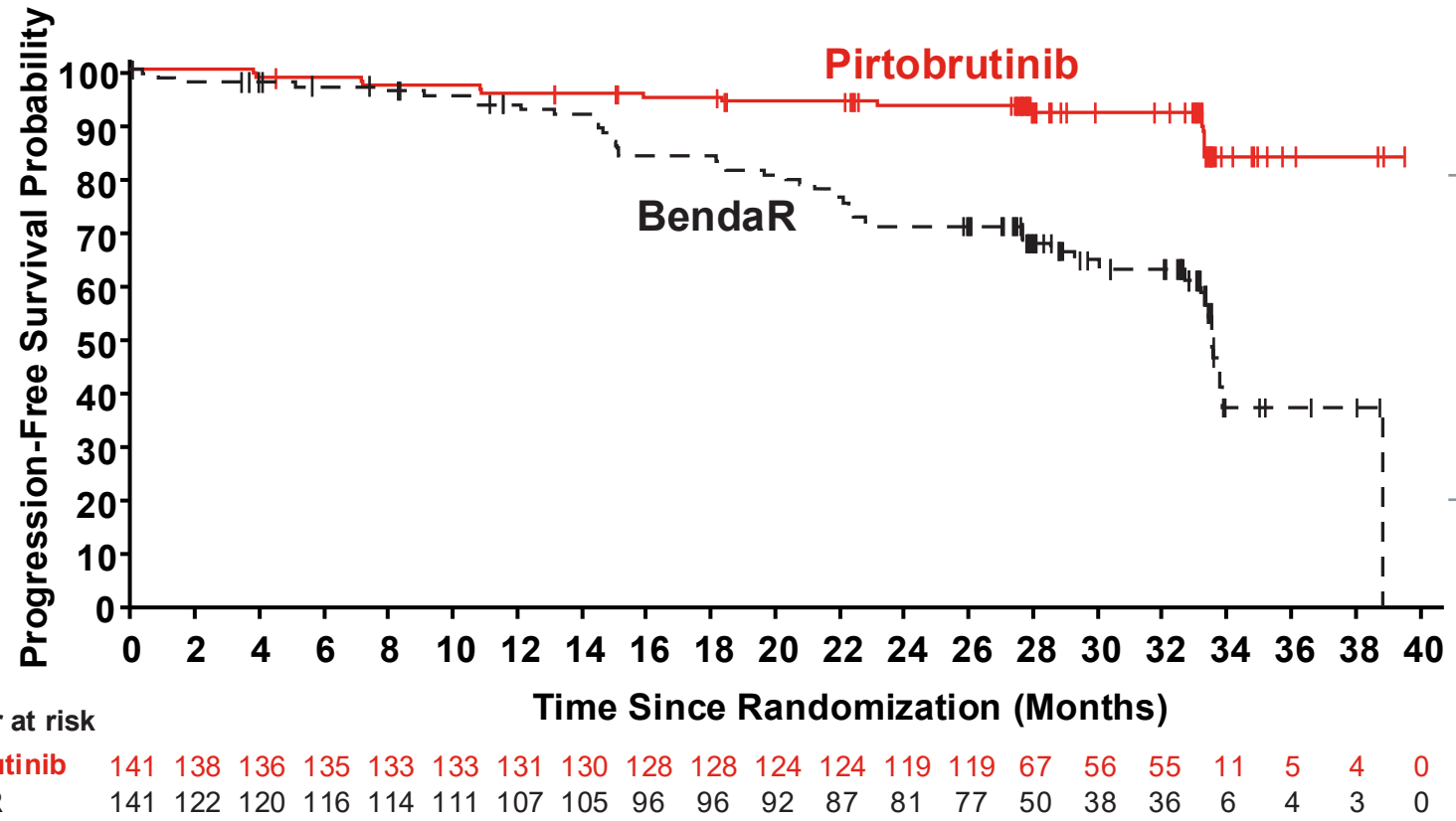
- ORR[g] (per iwCLL 2018 criteria)
- Safety measures

Jurczak et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN CLL-313: Primary Endpoint, PFS



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

	Pirtobrutinib (n=141)	BendaR (n=141)
Number of events, n (%)	13 (9.2)	48 (34.0)
24-month PFS rate, (95% CI)	**93.4** (87.6, 96.5)	**70.7** (61.5, 78.1)
Median follow-up, months	28.1	28.3
Hazard ratio (95% CI)	**0.20 (0.11, 0.37)**	
p-value[a]	<0.0001[a]	

The PFS results presented are IRC assessed

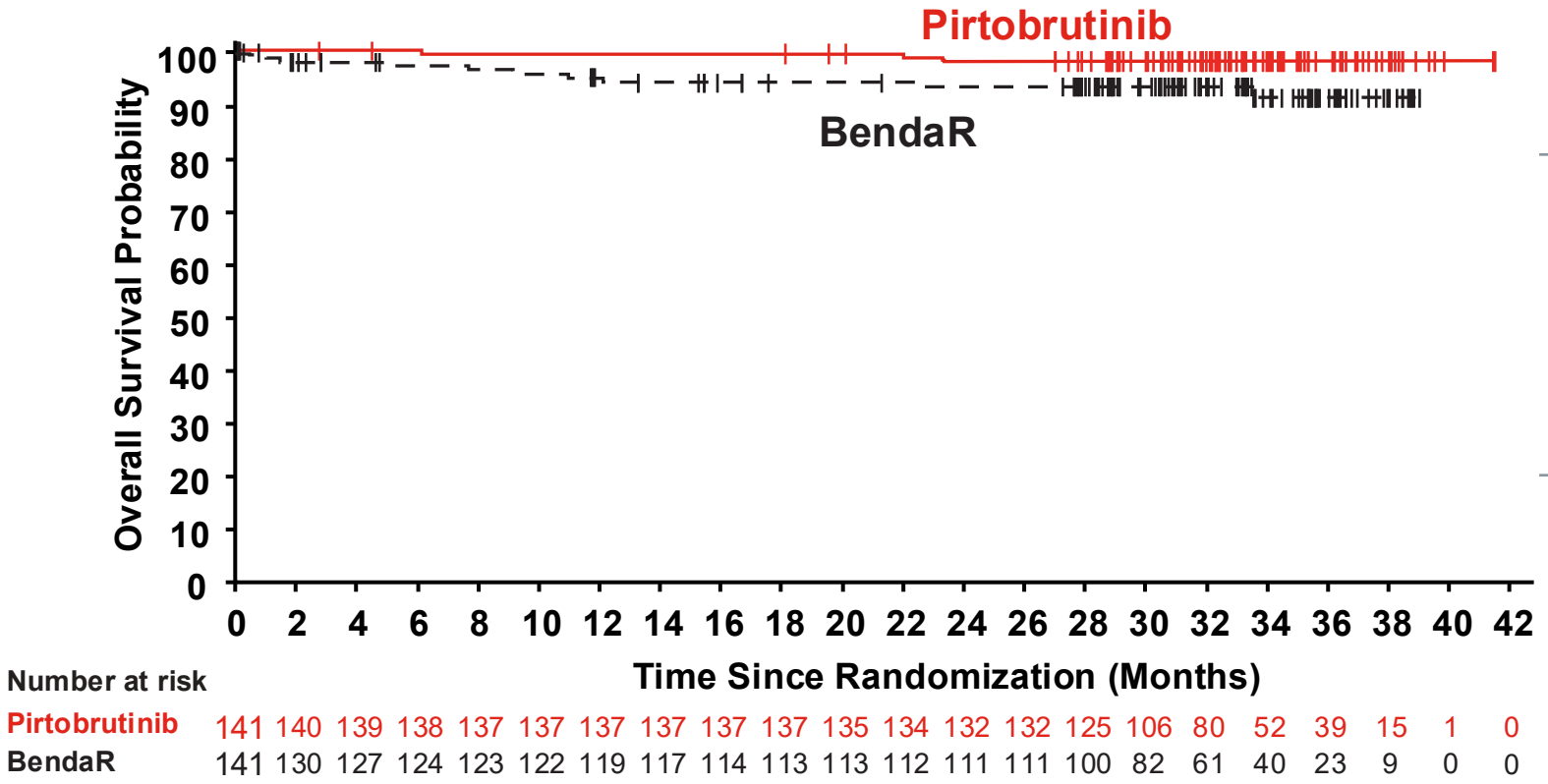
Pirtobrutinib demonstrated a statistically significant and clinically meaningful PFS improvement, with an 80% reduction in risk of PD or death compared with BendaR

Jurczak et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN CLL-313: Primary Endpoint, OS



	Pirtobrutinib n=141	BendaR n=141
Number of events, n (%)	3 (2.1)	10 (7.1)
24-month OS rate, (95% CI)	**97.8** (93.3, 99.3)	**93.0** (87.0, 96.3)
Median follow-up, months	32.7	31.7
Hazard ratio (95% CI)	**0.26 (0.07, 0.93)**	
p-value	0.0261[a]	

Effective crossover rate[b]:

52.9% (18/34)

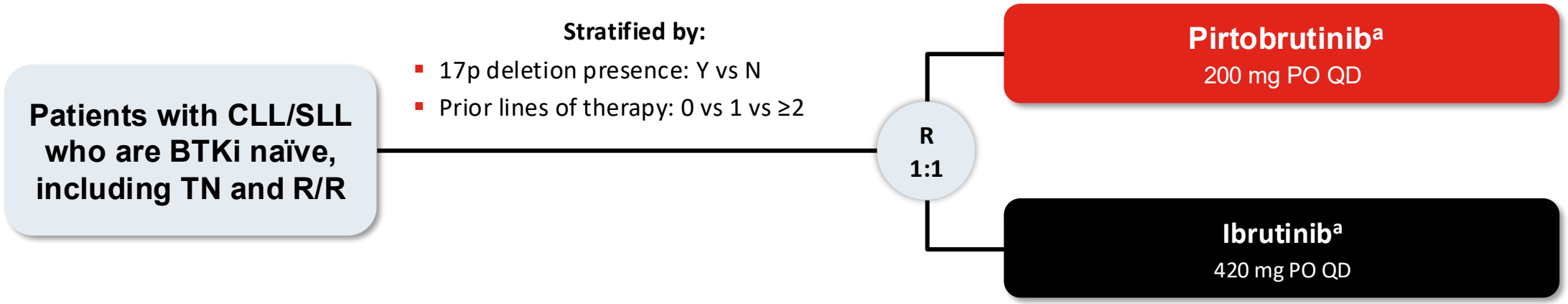
OS data were immature, but trended in favor of pirtobrutinib, despite a high effective crossover rate

Jurczak et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN CLL-314: Study Design



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[c,d,e] (per iwCLL 2018 criteria):

- In ITT population, or
- In R/R population

Key Secondary Objectives

Superiority of PFS[d,e] (per iwCLL 2018 criteria):

- In ITT population, or
- In R/R population

Exploratory

Analyses of endpoints in the TN population

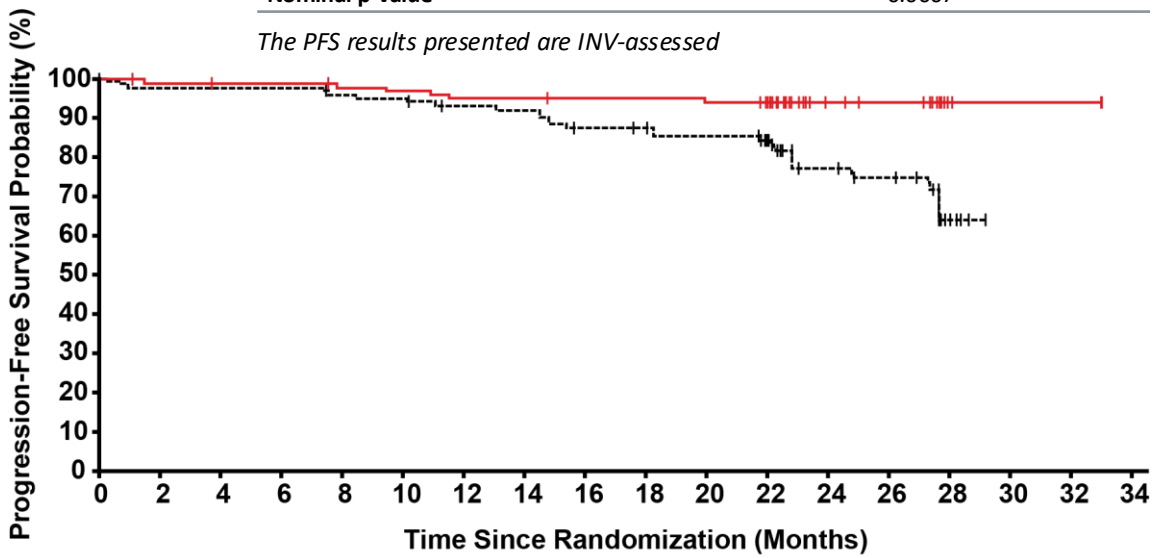
Woyach et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

BRUIN CLL-314: PFS – key secondary endpoint

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

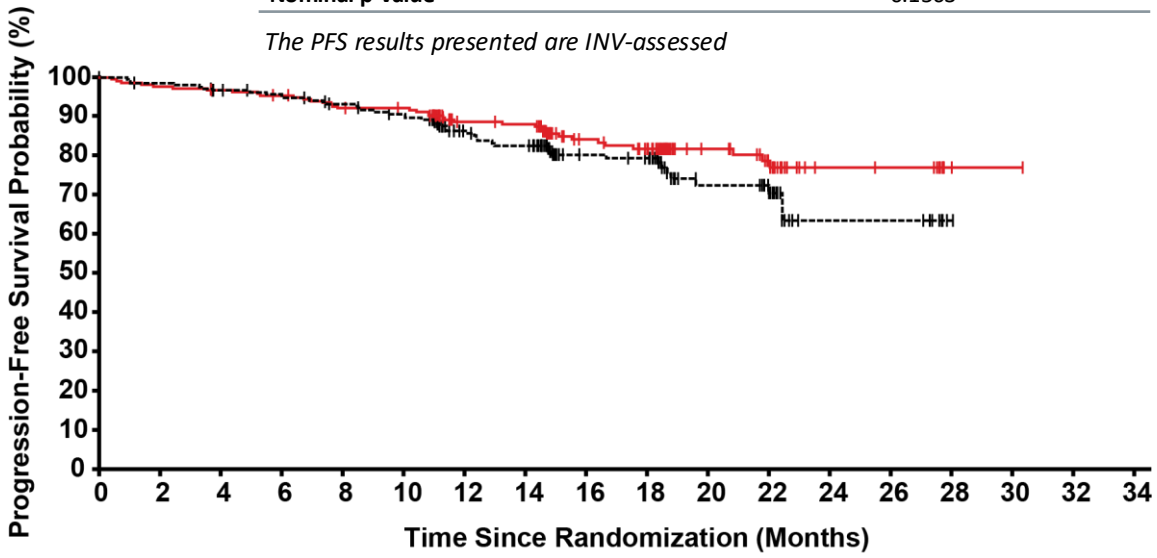


Number at risk

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

Woyach et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN CLL-314: Treatment Emergent AE

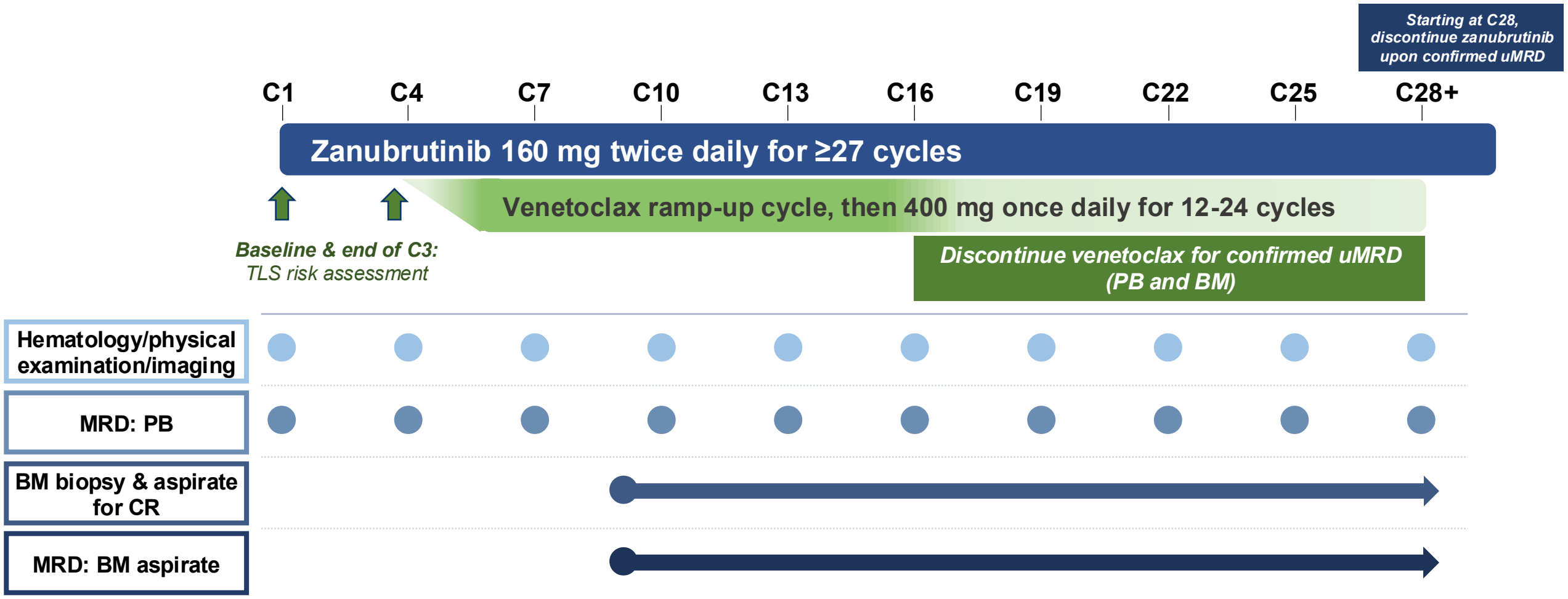
Preferred Term ≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	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)	

Woyach et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

SEQUOIA (BGB-3111-304)

Arm D Treatment Regimen and Response Assessment Schedule



Courtesy of Jennifer R Brown, MD, PhD

Shadman M et al. ASH 2025;Abstract 5669

PFS in 3 yr SEQUOIA Arm D

N=66 patients with del17p +/- *TP53* mutation

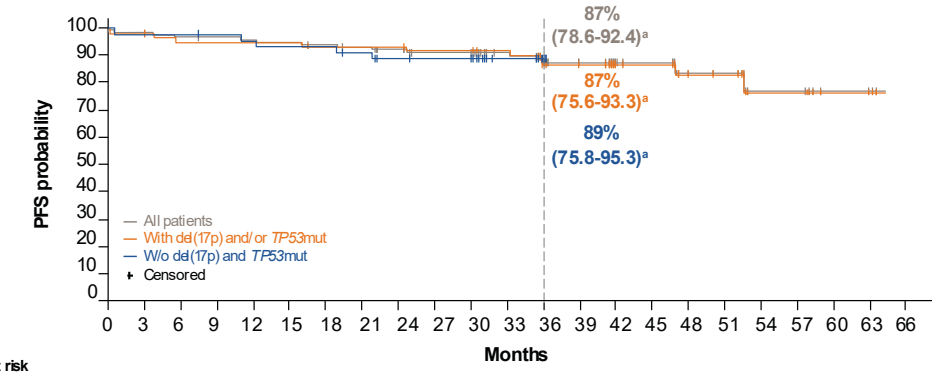
N=47 patients without *TP53* Aberration

After 15 cycles, uMRD rates: 15% in del(17p) and/or TP53mut 40% in patients without

After 27 cycles, uMRD rates: were 38% and 36%, respectively

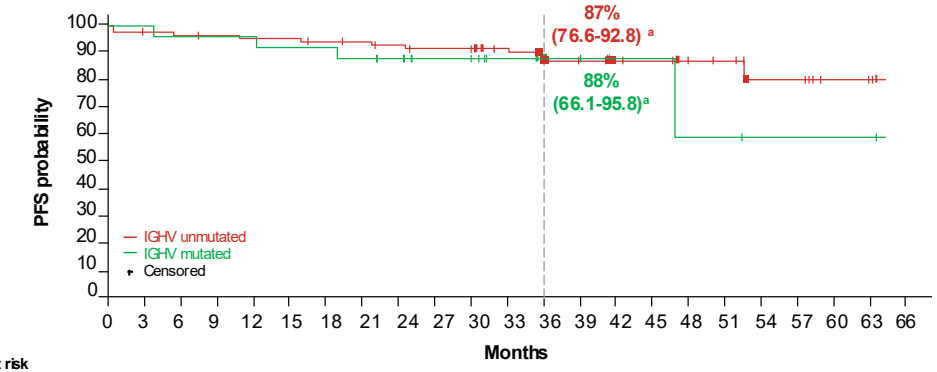
Figure 4. PFS

A. Overall population and patients with del(17p) and/or *TP53*mut and without



No. at risk																							
All patients	114	112	109	108	107	106	104	102	99	95	95	81	58	42	27	25	18	16	10	10	6	5	0
With del(17p) and/or *TP53*mut	66	65	62	62	62	62	60	60	60	58	58	56	45	42	27	25	18	16	10	10	6	5	0
W/o del(17p) and *TP53*mut	47	46	46	45	44	43	43	41	38	37	37	25	13	0									

B. Unmutated and mutated IGHV



No. at risk																							
IGHV unmutated	86	84	82	81	80	80	78	77	75	73	73	64	47	35	23	21	16	14	9	9	5	4	0
IGHV mutated	24	24	23	23	23	22	22	21	20	18	18	14	10	6	3	3	2	2	1	1	1	1	0

aCI values.
Abbreviations: IGHV, immunoglobulin heavy-chain variable region; mut, mutation; PFS, progression-free survival.

Courtesy of Jennifer R Brown, MD, PhD

Shadman M et al. ASH 2025;Abstract 5669

SEQUOIA Arm D

- **Technically MRD guided but effectively continuous zanubrutinib with additional venetoclax cytoreduction for 12-24 months**

- **Highly effective so far especially in *TP53* aberrant patients; likely overtreatment for others**

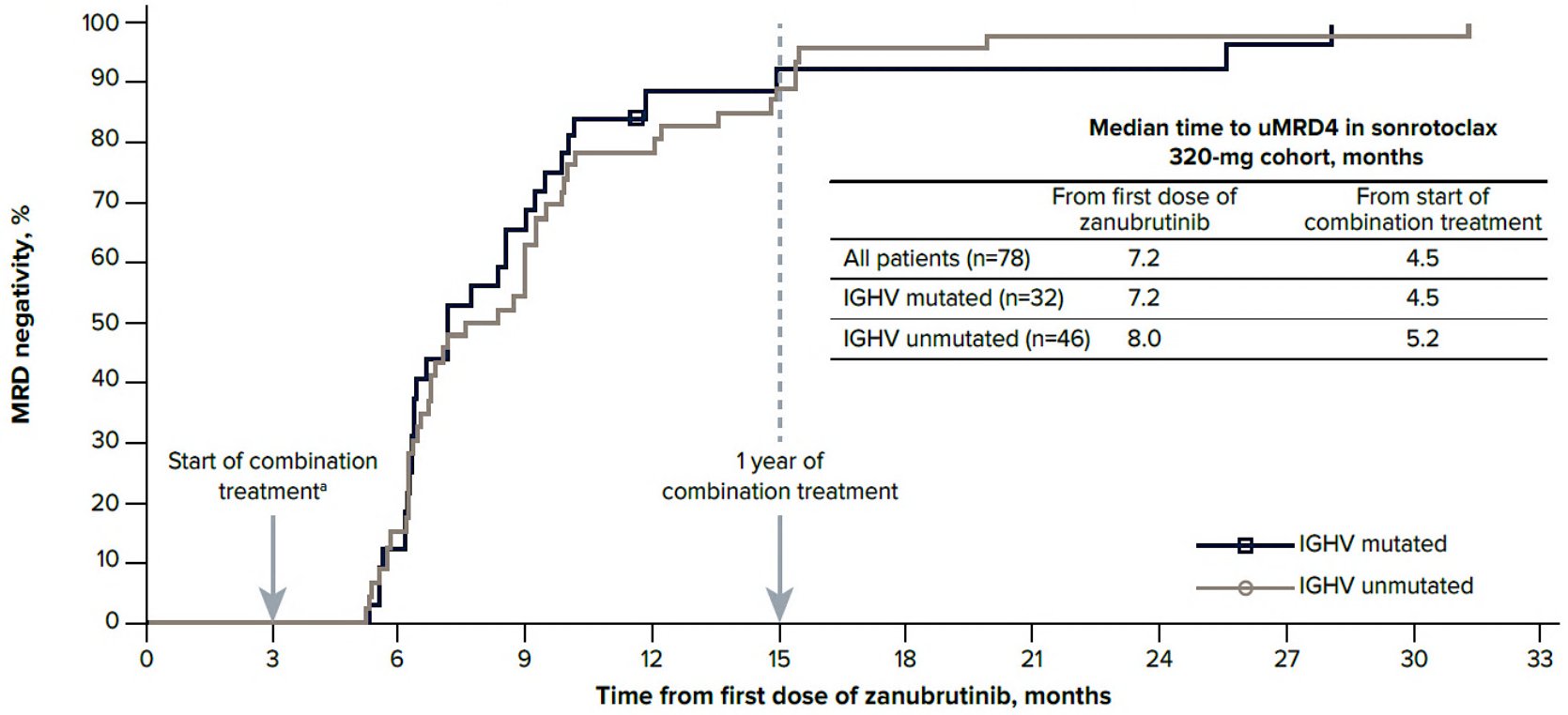
Courtesy of Jennifer R Brown, MD, PhD

Zanubrutinib Sonrotoclax Frontline Phase 1/1b Study

8-12 weeks of zanubrutinib lead-in (320 mg once daily or 160 mg twice daily),
then zanubrutinib + sonrotoclax until disease progression, intolerance, or elective discontinuation allowed for both drugs at 96 wks

With median follow-up of 30.7 months, no PFS events have been observed at the sonrotoclax RP2D of 320 mg

Figure 6. Time to uMRD4 by IGHV Status, Sonrotoclax 320-mg Cohort



Median time to uMRD4 in sonrotoclax 320-mg cohort, months

	From first dose of zanubrutinib	From start of combination treatment
All patients (n=78)	7.2	4.5
IGHV mutated (n=32)	7.2	4.5
IGHV unmutated (n=46)	8.0	5.2

Courtesy of Jennifer R Brown, MD, PhD

Tam C et al. ASH 2025;Abstract 3891

Zanubrutinib Sonrotoclax Frontline Phase 1/1b Study

- **Sonrotoclax is 10X more potent than venetoclax and has activity against G101V resistance mutation**
- **Data are promising but await larger studies – registration trial is fully accrued**

Courtesy of Jennifer R Brown, MD, PhD

Zanu-Obin-Sonro

Figure 1. BGB-11417-101 Study Design

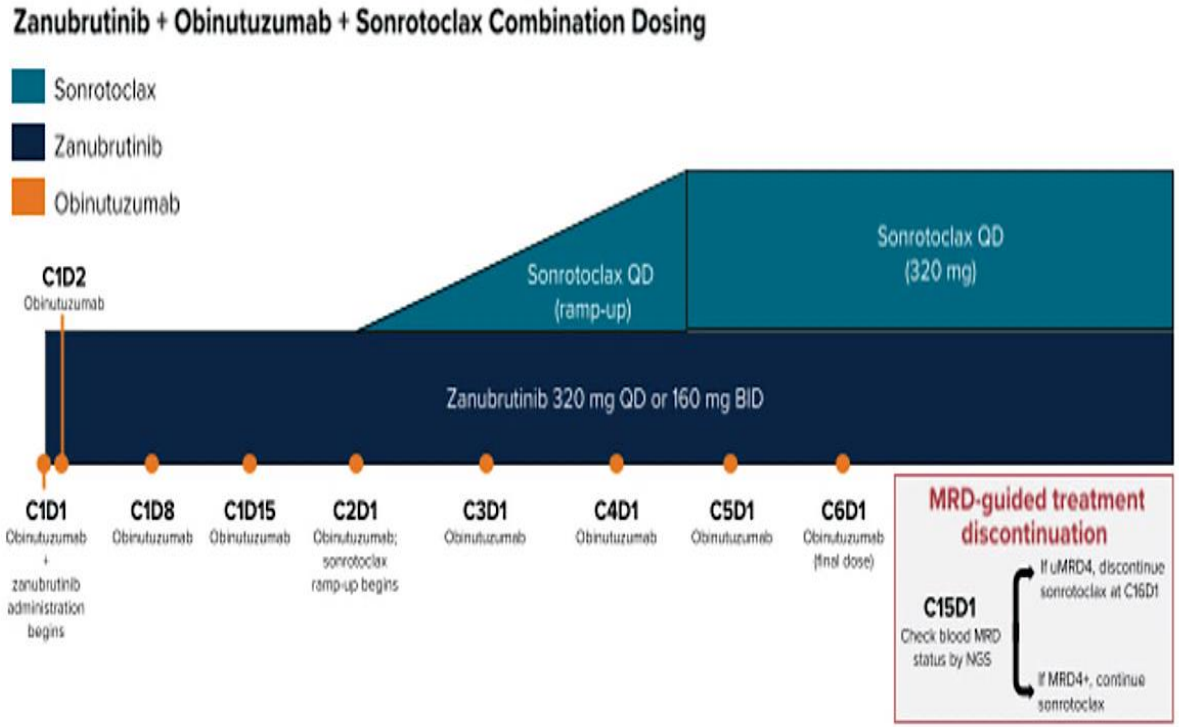
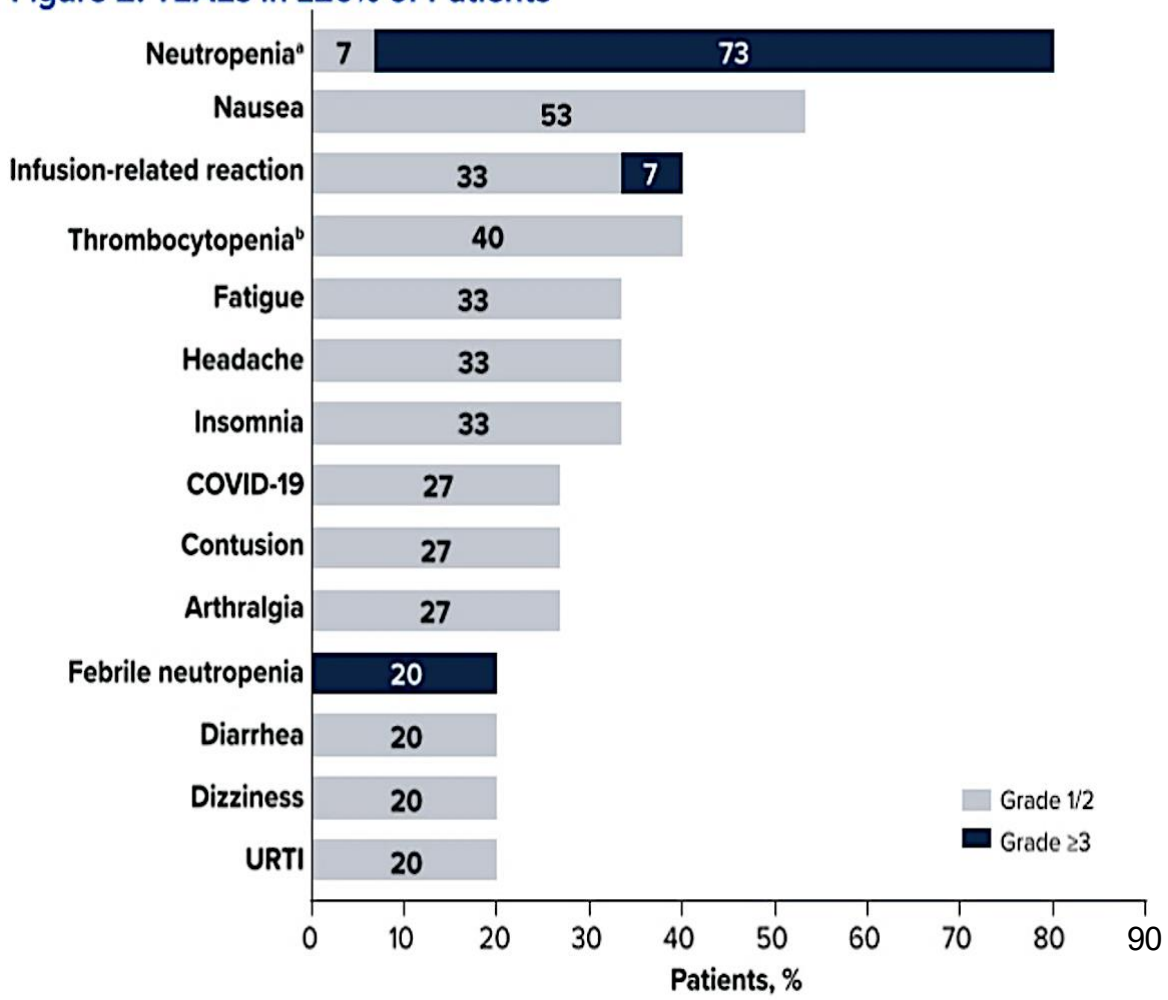


Figure 2. TEAEs in ≥20% of Patients

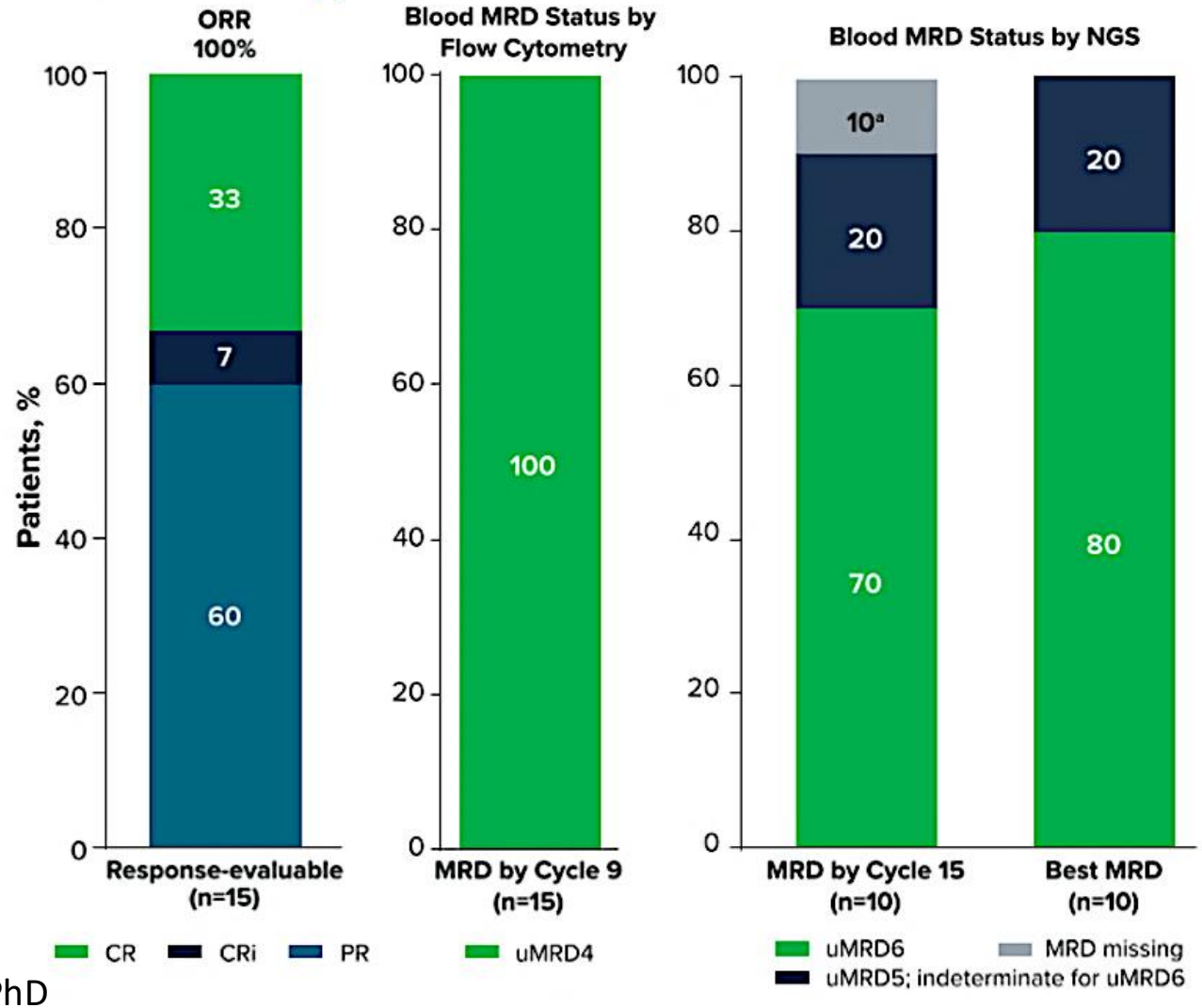


Courtesy of Jennifer R Brown, MD, PhD

Soumerai J et al. ASH 2025;Abstract 3890

Zanu-Obin-Sonro

Figure 3. Response Rates and Blood MRD Status With Sonrotoclax 320 mg Combination Therapy



Courtesy of Jennifer R Brown, MD, PhD

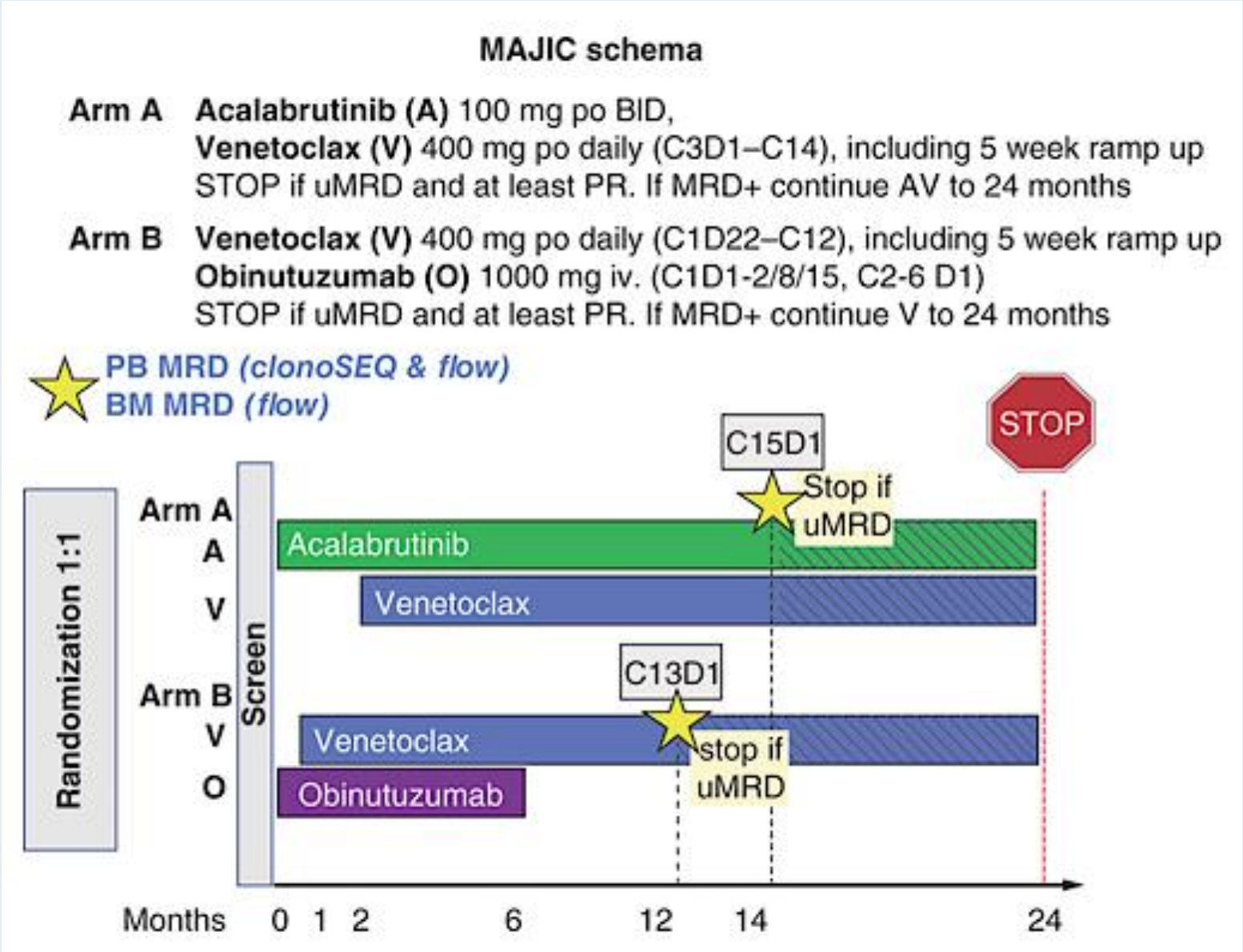
Soumerai J et al. ASH 2025;Abstract 3890

Zanu-Obin-Sonro

- Three drug regimen
- Very high rate of grade 3 neutropenia but febrile neutropenia low-average for these regimens
- Very promising MRD rates, will they be sustained longer than in BOVEN?
  - Possibly yes as all patients go to cycle 15

Courtesy of Jennifer R Brown, MD, PhD

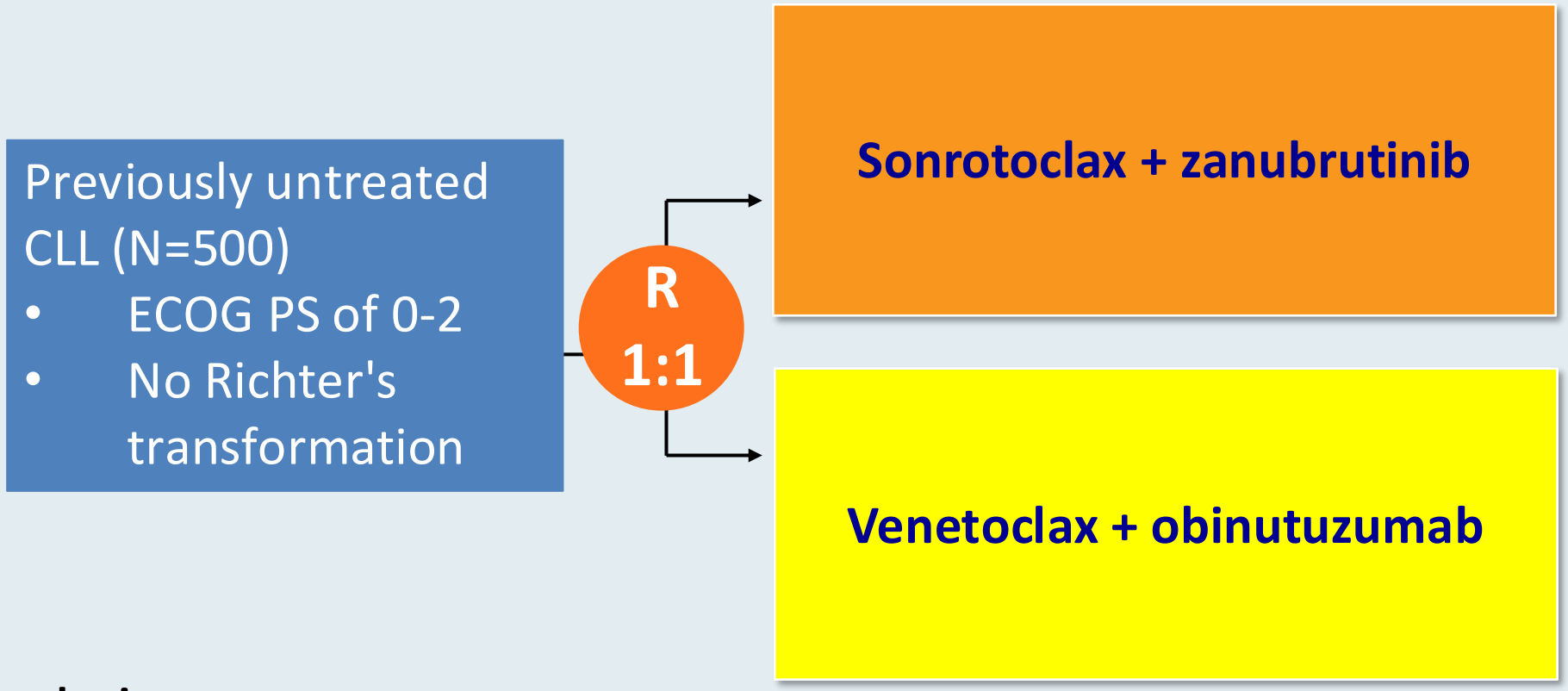
MAJIC: A Phase III Open-Label Study



uMRD = undetectable minimal residual disease; PR = partial remission; PB = peripheral blood; BM = bone marrow

Ryan CE et al. *Future Oncol* 2022;18(33):3689-99; www.clinicaltrials.gov. NCT05057494. Accessed March 2026.

Phase III Study of Sonrotoclax and Zanubrutinib

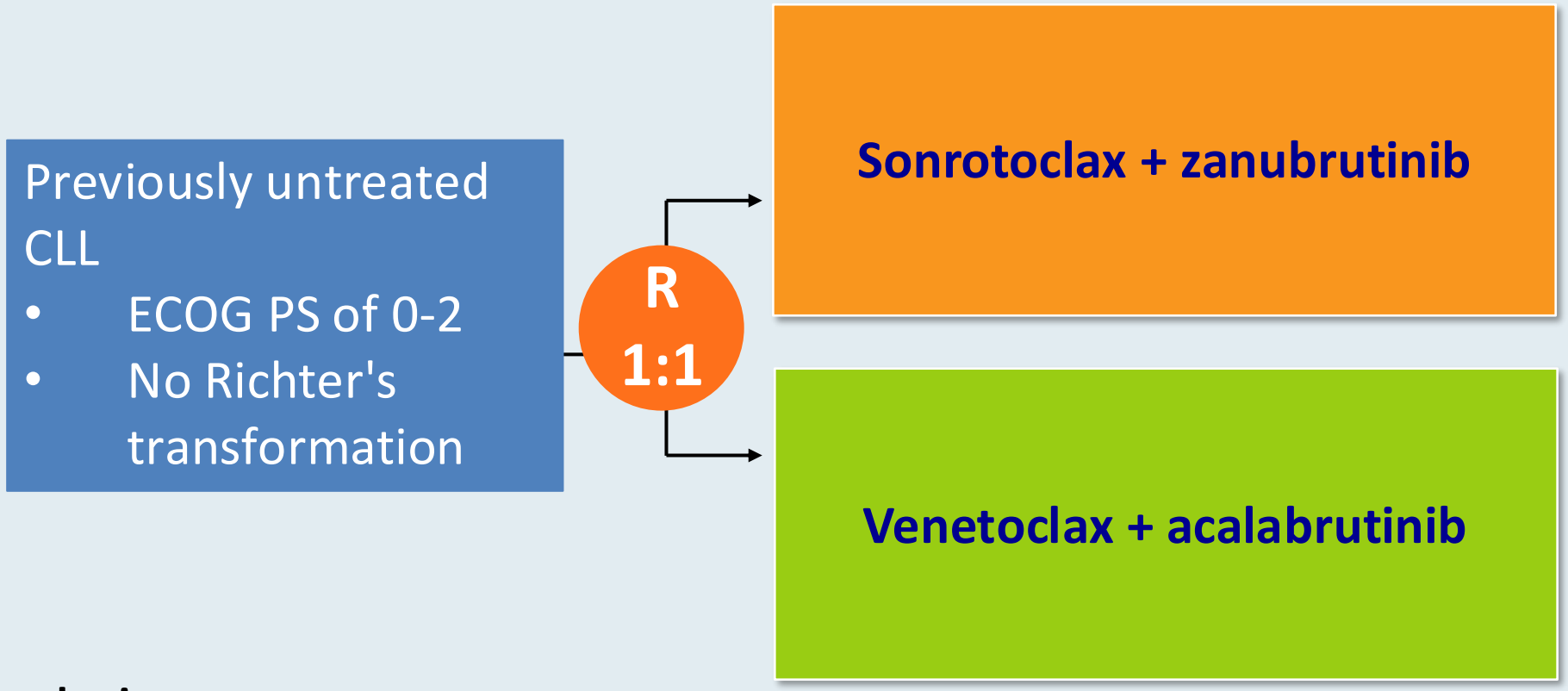


Primary endpoints

- Progression-free survival by independent review committee
- Rate of uMRD4

www.clinicaltrials.gov. NCT07277231. Accessed March 2026.

Phase III Study of Sonrotoclax and Zanubrutinib



Primary endpoints

- Progression-free survival by independent review committee
- Rate of uMRD4

www.clinicaltrials.gov. NCT07277231. Accessed March 2026.

Phase III Study of Sonrotoclax and Zanubrutinib

Previously untreated CLL/SLL

Arm 1:

Zanubrutinib PO BID on days 1-28 of each cycle

Restaging at C15 D1

Continue therapy if at least partial remission vs proceed to follow-up

Arm 2:

Zanubrutinib PO BID on days 1-28 of each cycle; sonrotoclax PO QD on days 1-28 of each cycle beginning at cycle 4

Restaging at C15 D1: Detectable MRD, objective response to therapy

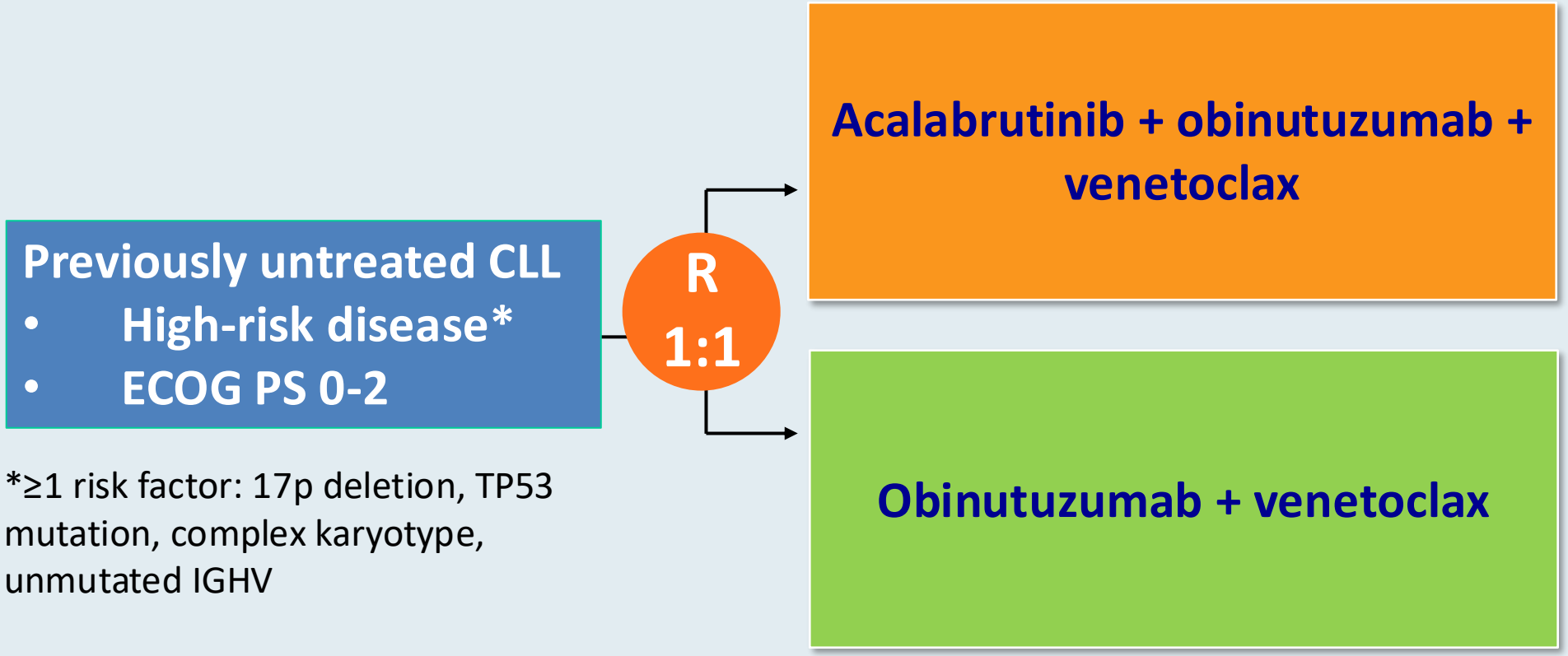
Arm 2B: Continue zanubrutinib PO BID sonrotoclax PO QD + sonrotoclax

Arm 2C: Discontinue therapy on C15, D28; Proceed to follow-up

Primary endpoint:

Progression-free survival

Phase III Study of Acalabrutinib/Venetoclax/Obinutuzumab



*≥1 risk factor: 17p deletion, TP53 mutation, complex karyotype, unmutated IGHV

Primary endpoint: Progression-free survival

www.clinicaltrials.gov. NCT05197192. Accessed March 2026.

Agenda
BTKi for CLL

INTRODUCTION: I think I missed that day in med school (BTK biology)

MODULE 1: First-line treatment

- Time-limited therapy; minimal residual disease assays
- Key reported trials
- Key planned and ongoing trials
- Key clinical questions
  - High risk: double versus single hit, complex karyotype
  - Standard risk: IGVH mutated vs unmutated
  - Older/frail/comorbidities

MODULE 2: Relapsed/refractory disease

- Progression on BTKi, venetoclax/anti-CD20
- Double exposed and refractory
- Pirtobrutinib, CAR T, bispecific antibodies, other
- BTK degraders

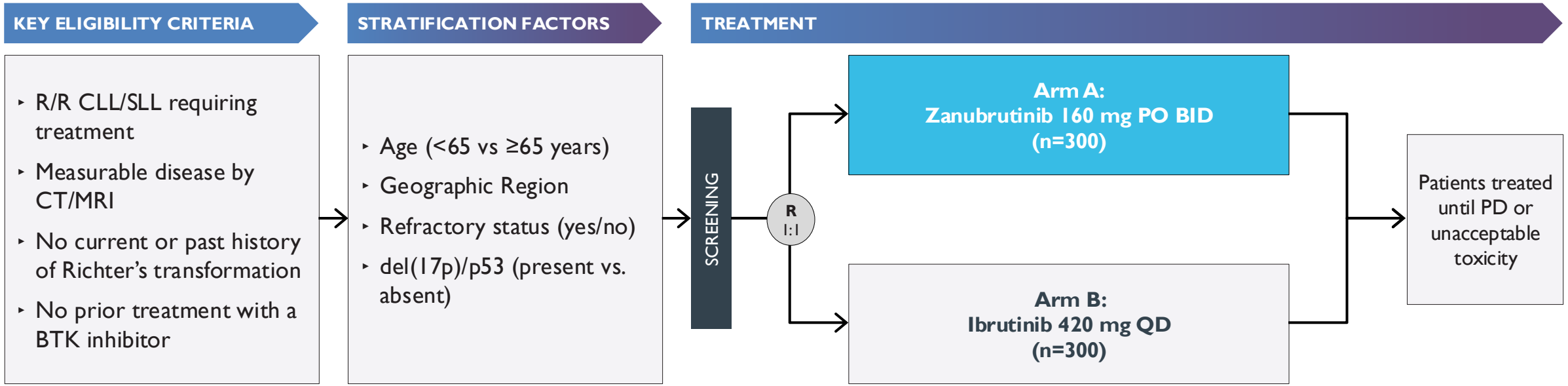
Questions About Relapsed/Refractory Disease

- What is your current approach to patients with double-exposed or double-refractory disease?
- How would you currently compare indirectly the benefits of pirtobrutinib to BTK degraders for patients whose disease is refractory to covalent BTKis?
- Do you see BTK degraders (versus pirtobrutinib) being incorporated for patients who experience disease progression on a covalent BTKi?
- What is your current approach to patients with Richter's transformation?

ALPINE: Study design

Study Identifier: BGB-3111-305, NCT03734016

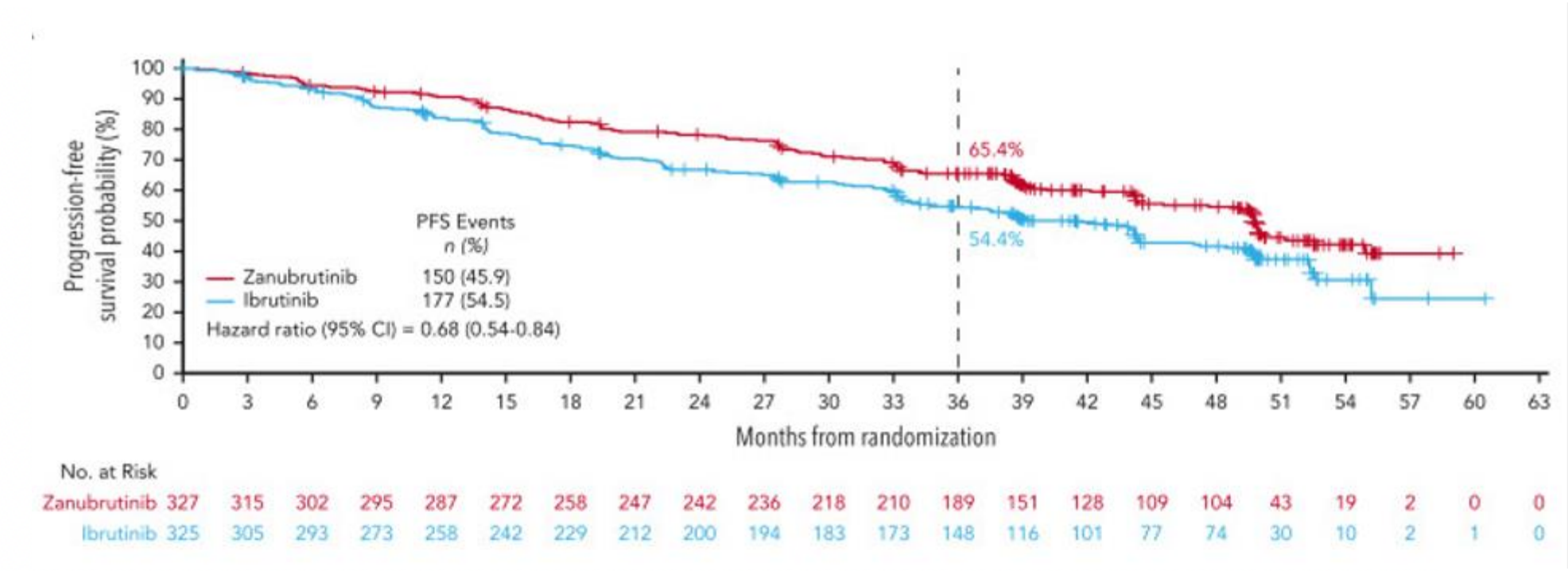
Primary Endpoint: ORR (PR+CR) noninferiority and superiority as assessed by investigator
Key Secondary Endpoint: PFS, incidence of atrial fibrillation
Other Secondary Endpoints: OS, DoR, time to treatment failure, PR-L or higher, PRO, safety



Brown et al., NEJM 2023, Tam et al., ASH 2025

National Research Institute of Oncology

ALPINE: Efficacy (initial & subsequent analysis)



No. at Risk

Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

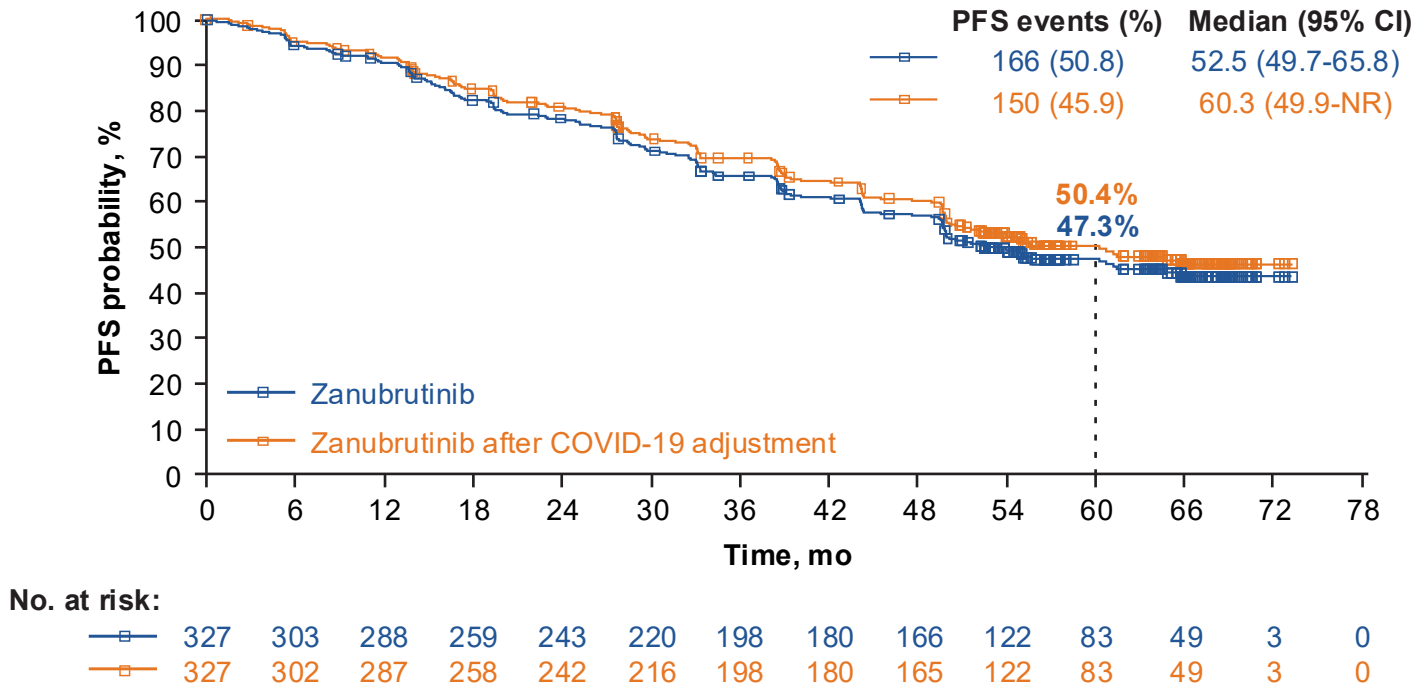
Brown et al., NEJM 2023, Tam et al., ASH 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

ALPINE: Efficacy (5 year follow-up)

Median follow-up (ALPINE + LTE1): 63.4 months (95% CI: 57.3-64.5)

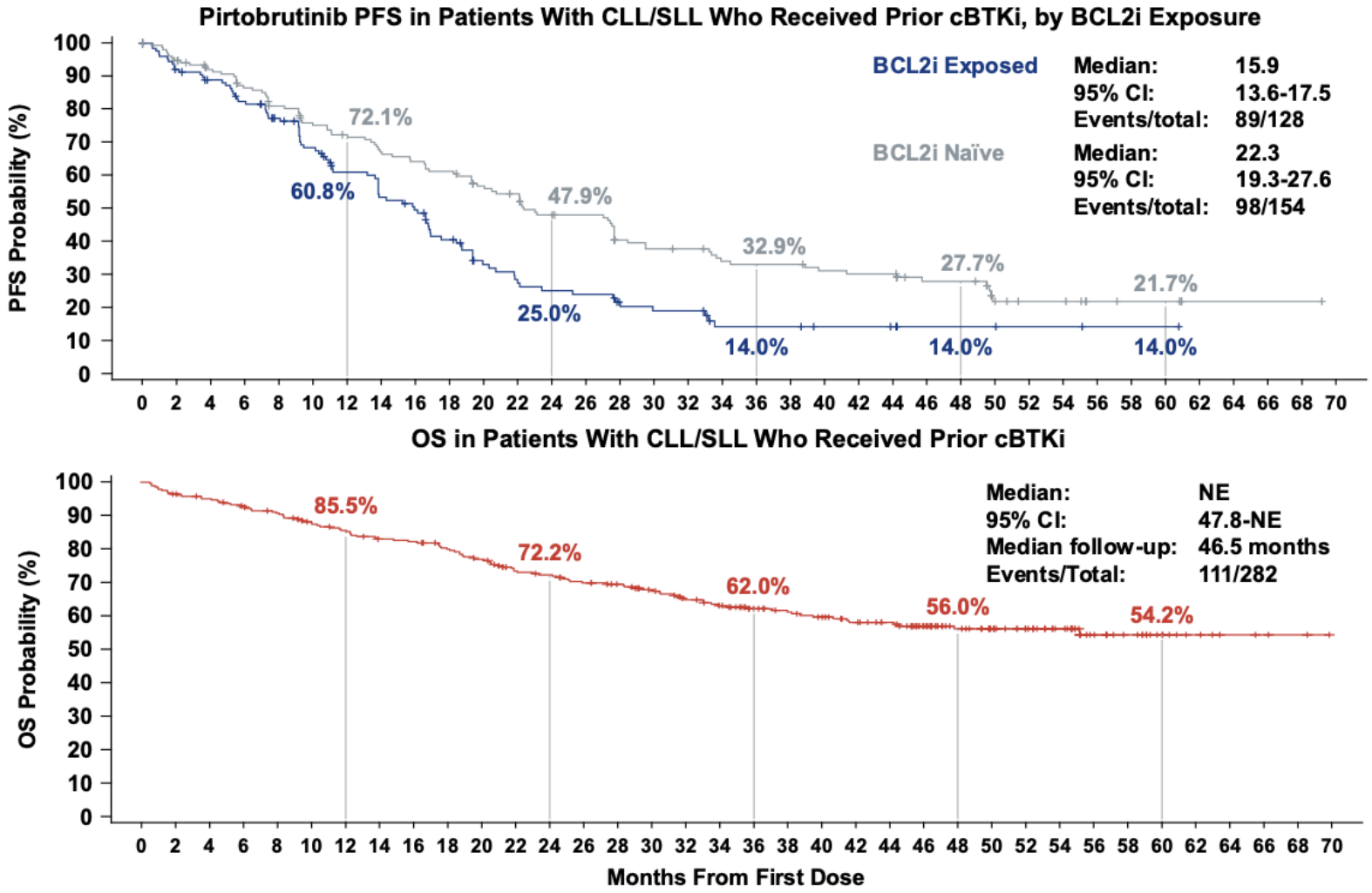


Brown et al., NEJM 2023, Tam et al., ASH 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN Phase 1/2: 5 year follow-up

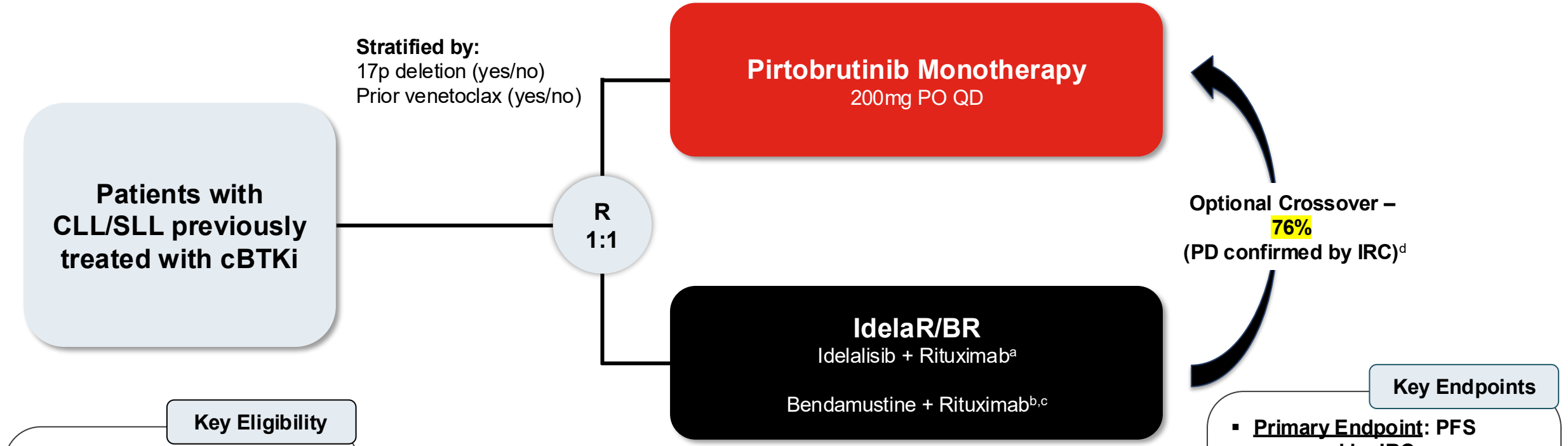


Wierda et al., ASH 2025;Abstract 2115

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN 321: Study design



Key Eligibility

- Age ≥18
- ECOG PS 0-2
- Confirmed CLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**

Key Endpoints

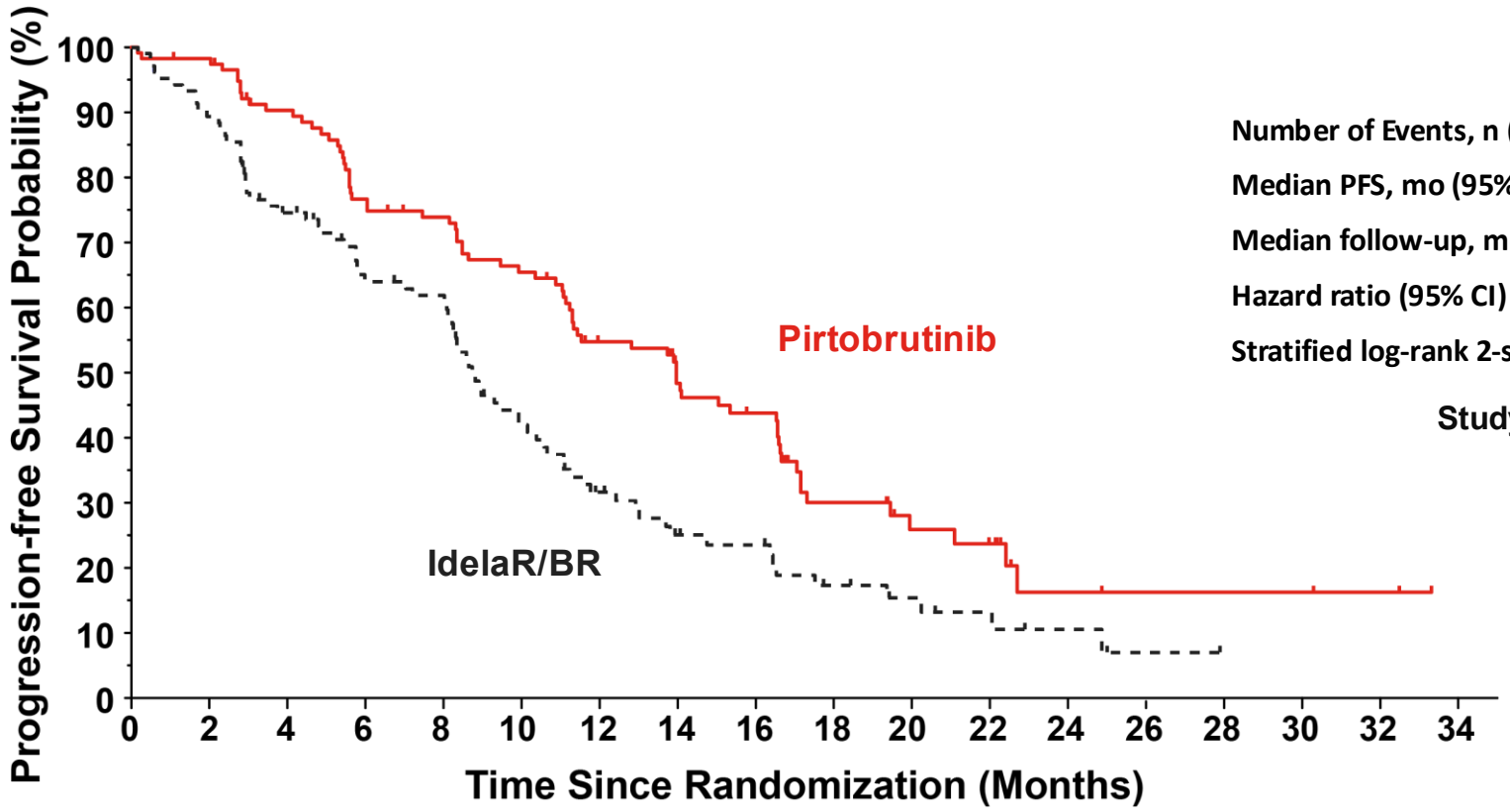
- **Primary Endpoint: PFS assessed by IRC**
- PFS assessed by investigator
- Event-Free Survival
- Time to Next Treatment
- Overall survival
- Safety

Sharman et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

BRUIN 321: Efficacy (5 year follow-up)



Number at Risk

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

	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 et al., JCO 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

APPENDIX

ELEVATE-TN: Study Design

Previously Untreated CLL

Key inclusion criteria include: Age ≥65 y **or** 18-65 y **and** ≥1 of the following criteria:

- CrCl = 30-69 mL/min
- CIRS-G score >6

Primary end point

PFS by IRC: Arm A vs B

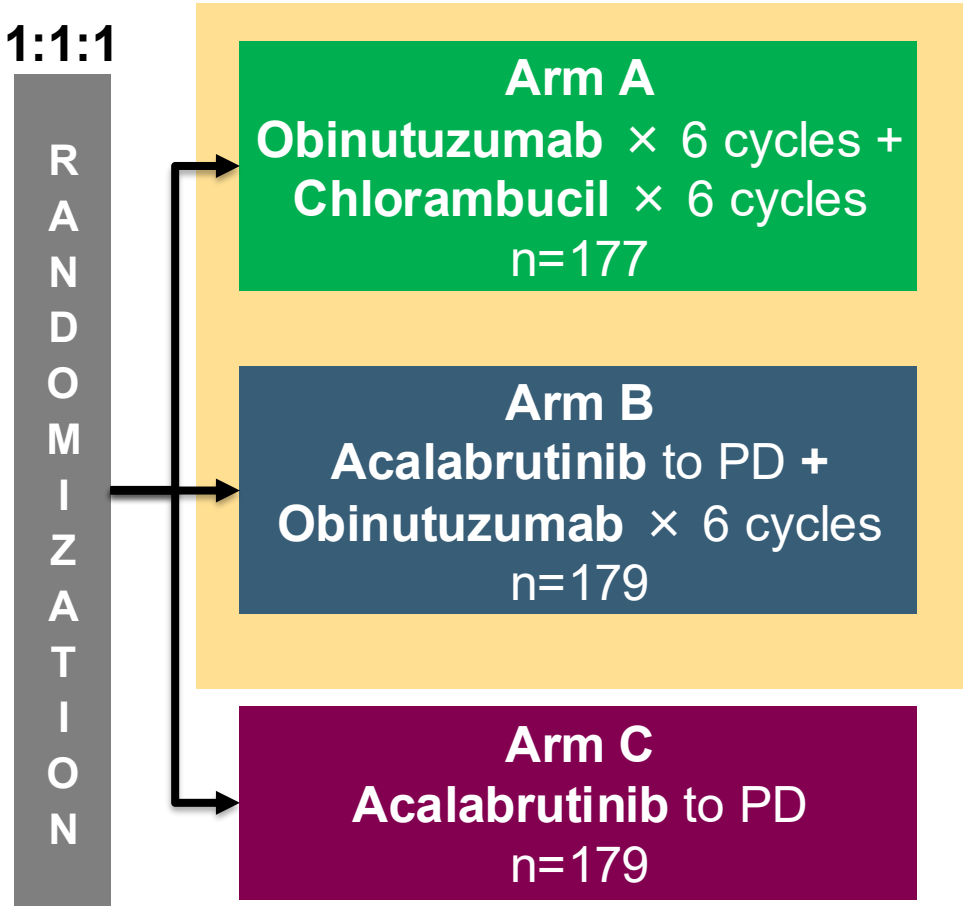
Secondary end points

- PFS by IRC: Arm A vs C
- ORR by IRC, OS, TTNT (Arm A vs B and A vs C)
- Safety

N=535

Stratification

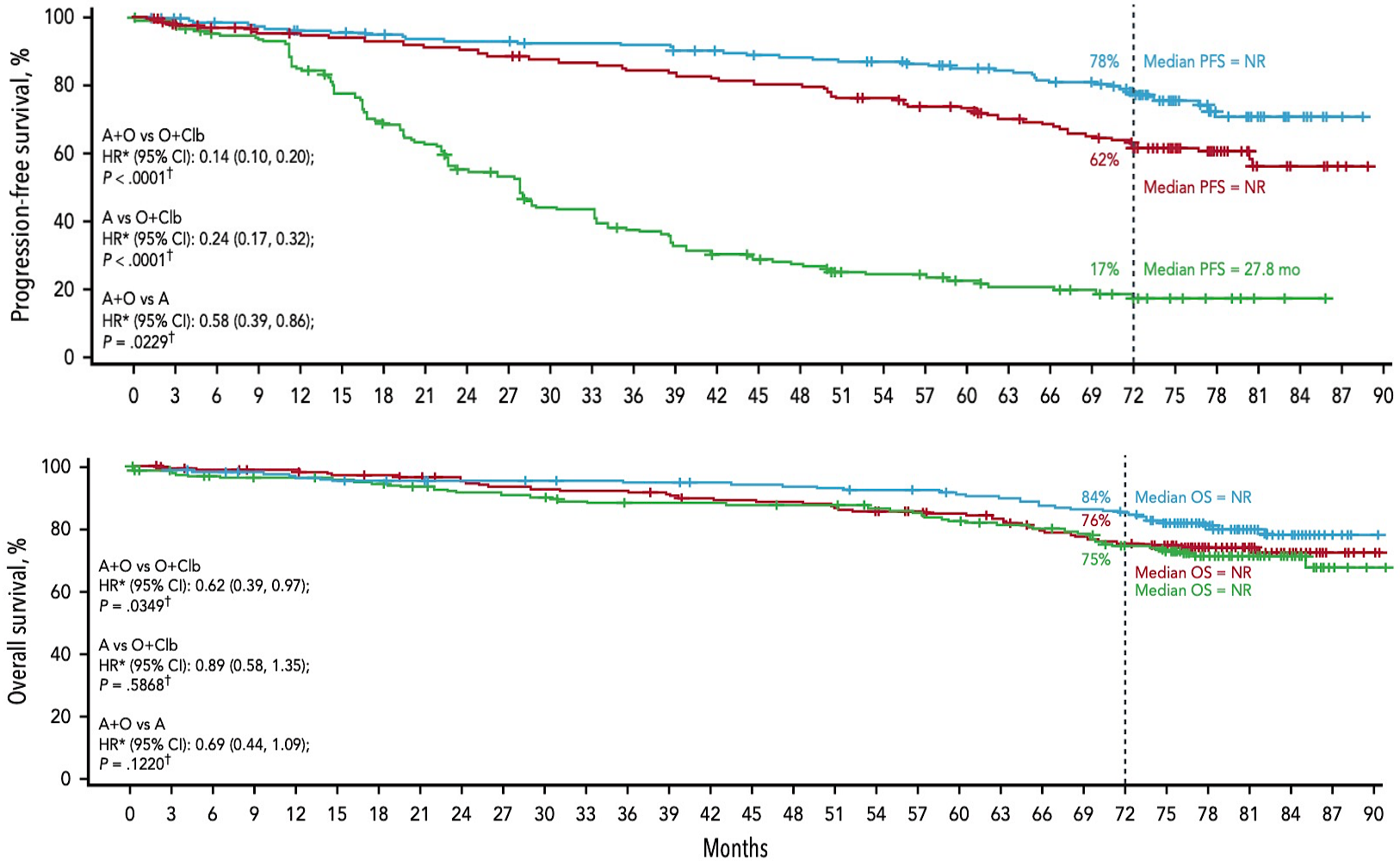
- Del(17p) status (~9%)
- Geographic region
- ECOG PS (0-1 vs 2)



Crossover was allowed upon IRC-confirmed PD from Arm A to Arm C

Sharman et al., Blood 2025; Lancet 2020

ELEVATE-TN: Efficacy (6 year follow-up)



Acalabrutinib + obinutuzumab
Acalabrutinib monotherapy
Obinutuzumab + chlorambucil

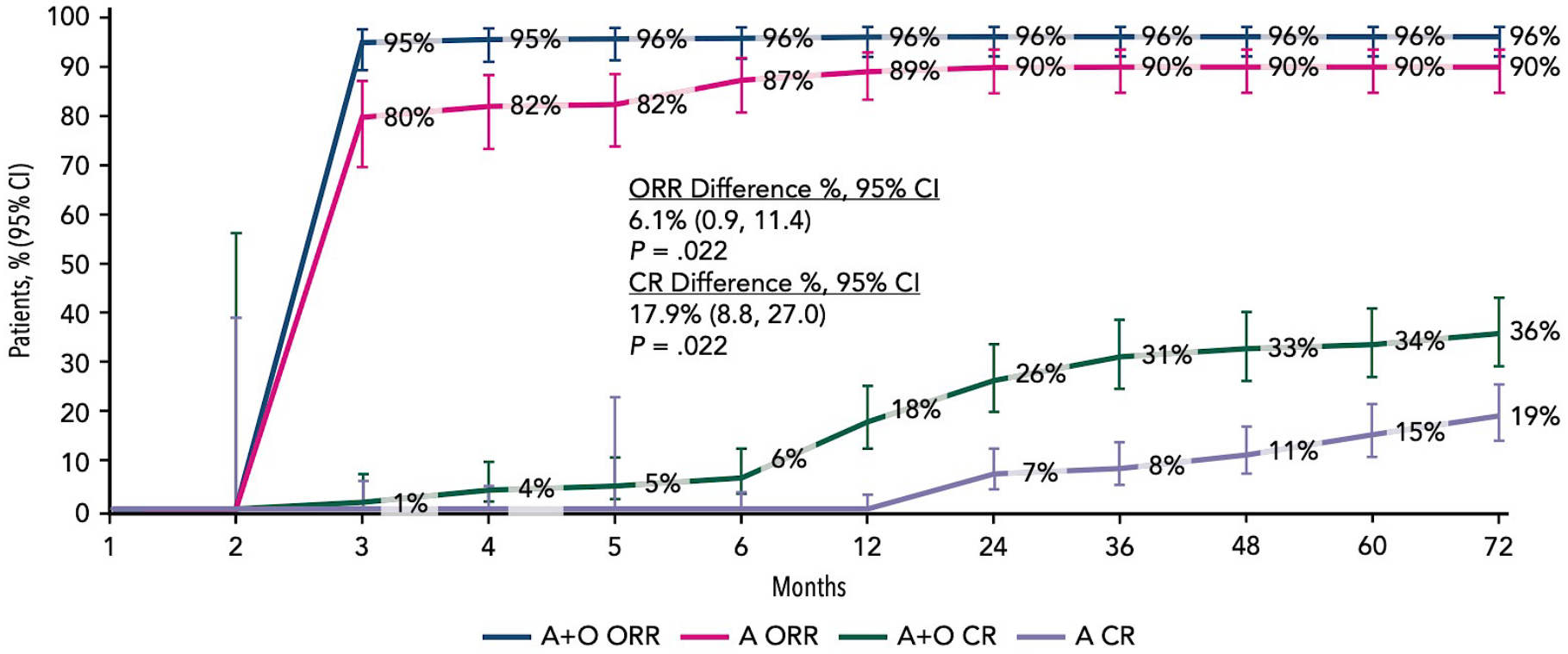
	A + O (n = 178)	
	Any grade	Grade ≥3
Diarrhea	78 (43.8)	11 (6.2)
Neutropenia	61 (34.3)	55 (30.9)
COVID-19	44 (24.7)	16 (9.0)
Anemia	27 (15.2)	13 (7.3)
Thrombocytopenia	26 (14.6)	15 (8.4)
Pneumonia	25 (14.0)	13 (7.3)
Syncope	12 (6.7)	9 (5.1)

Sharman et al., Blood 2025; Lancet 2020

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

ELEVATE-TN: Efficacy (ORR & CR, 6 year follow-up)

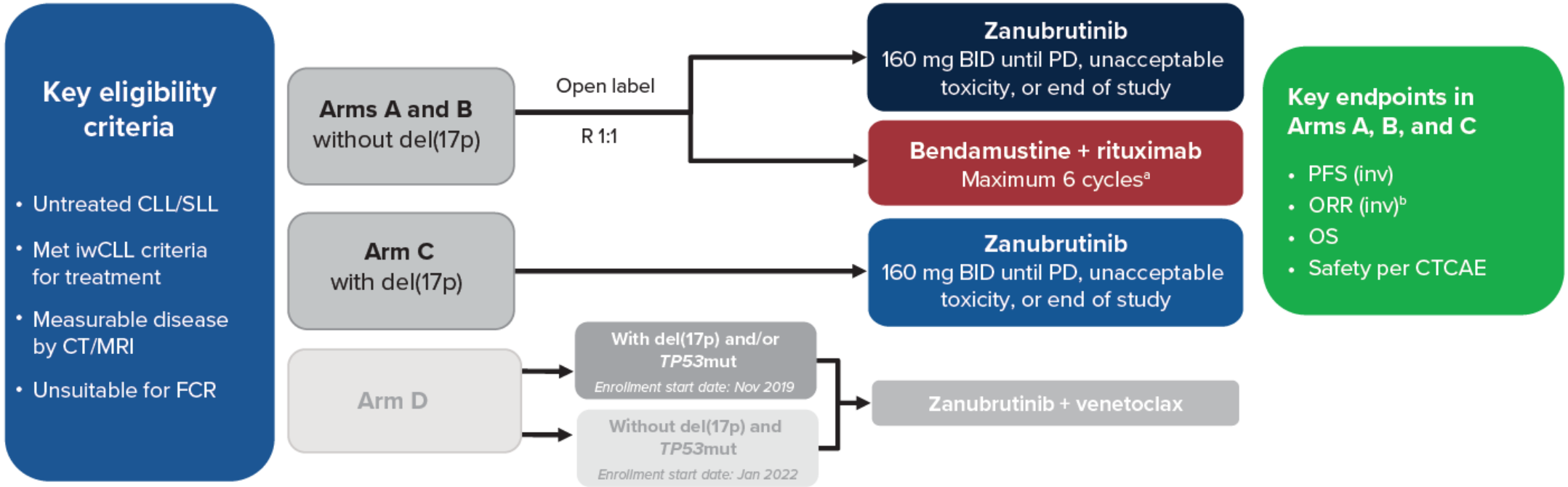


Sharman et al., Blood 2025; Lancet 2020

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

SEQUOIA: Study design



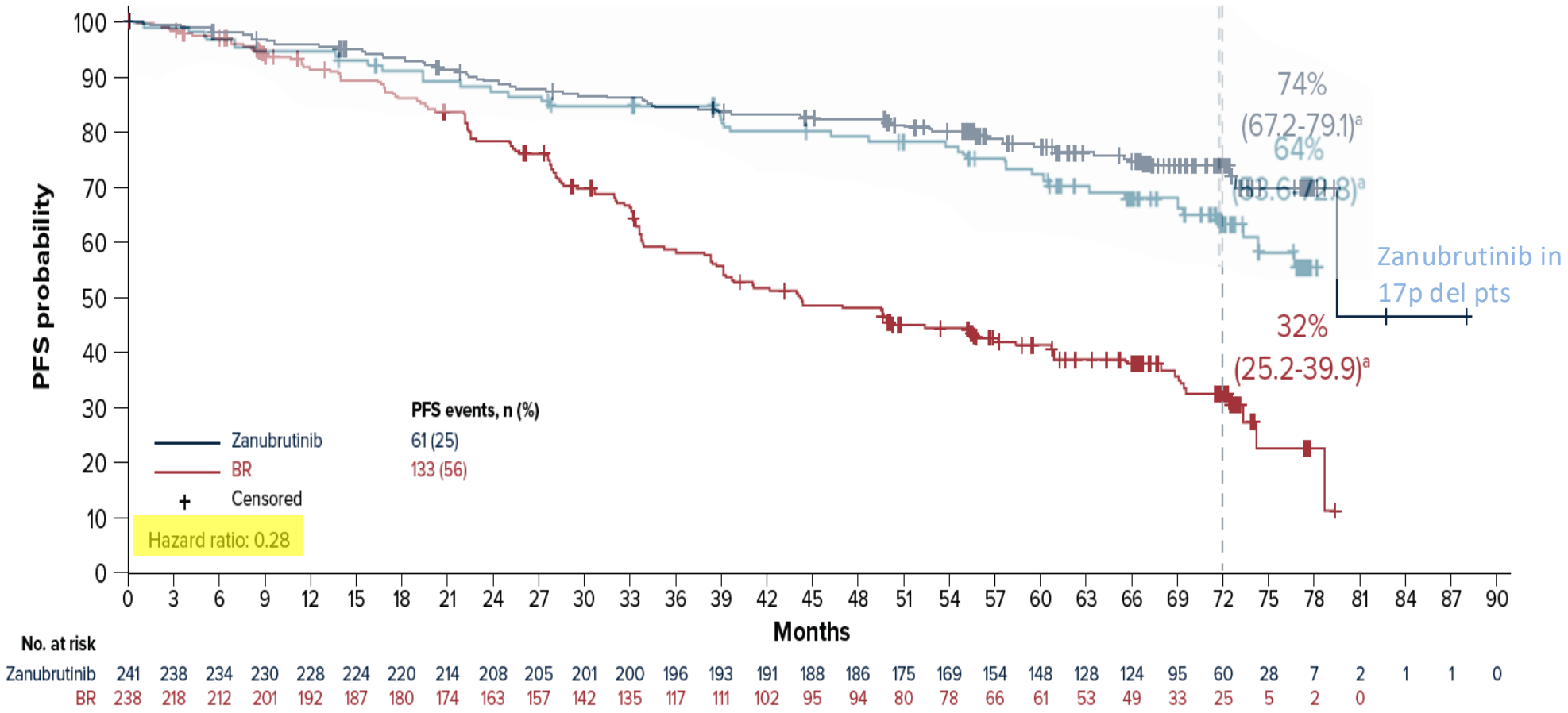
- Here, the updated efficacy and safety results in Arms A vs B and Arm C with a median follow-up of approximately 6 years are presented

Tam et al., ASH 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

SEQUOIA: Efficacy (6 year follow-up)



Tam et al., ASH 2025

Courtesy of Wojciech Jurczak, MD, PhD

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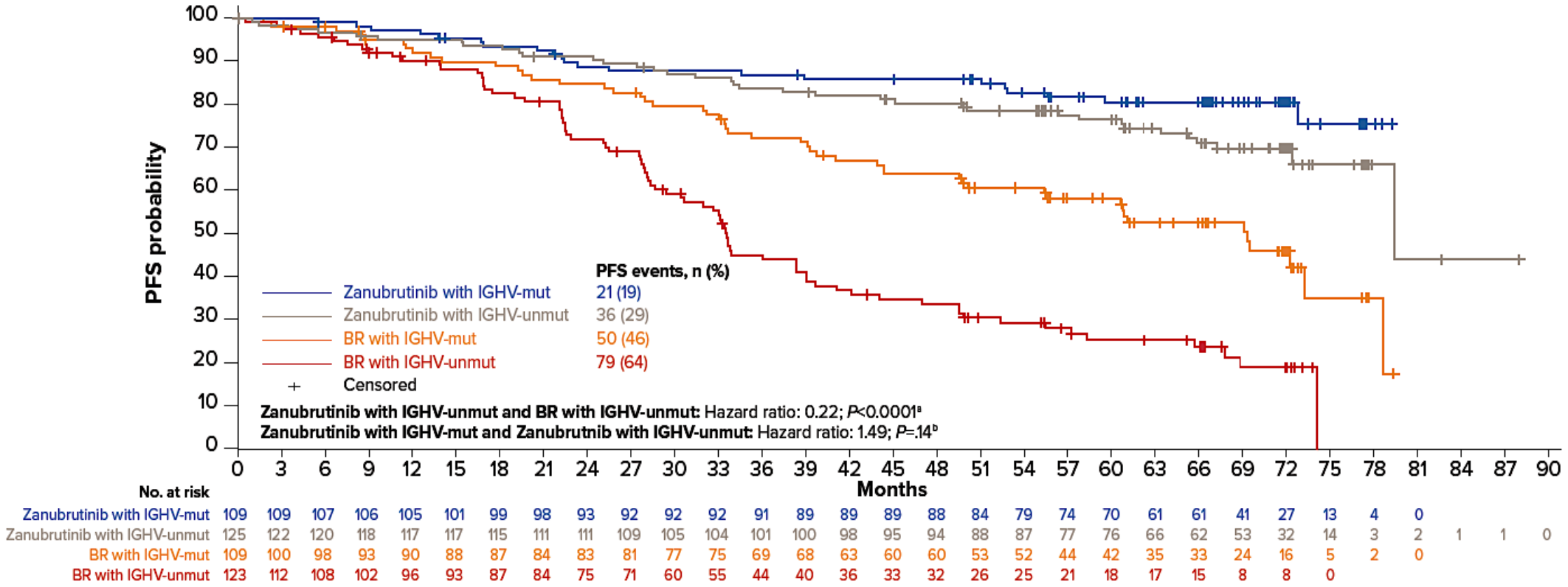
SEQUOIA: Efficacy (6 year follow-up)



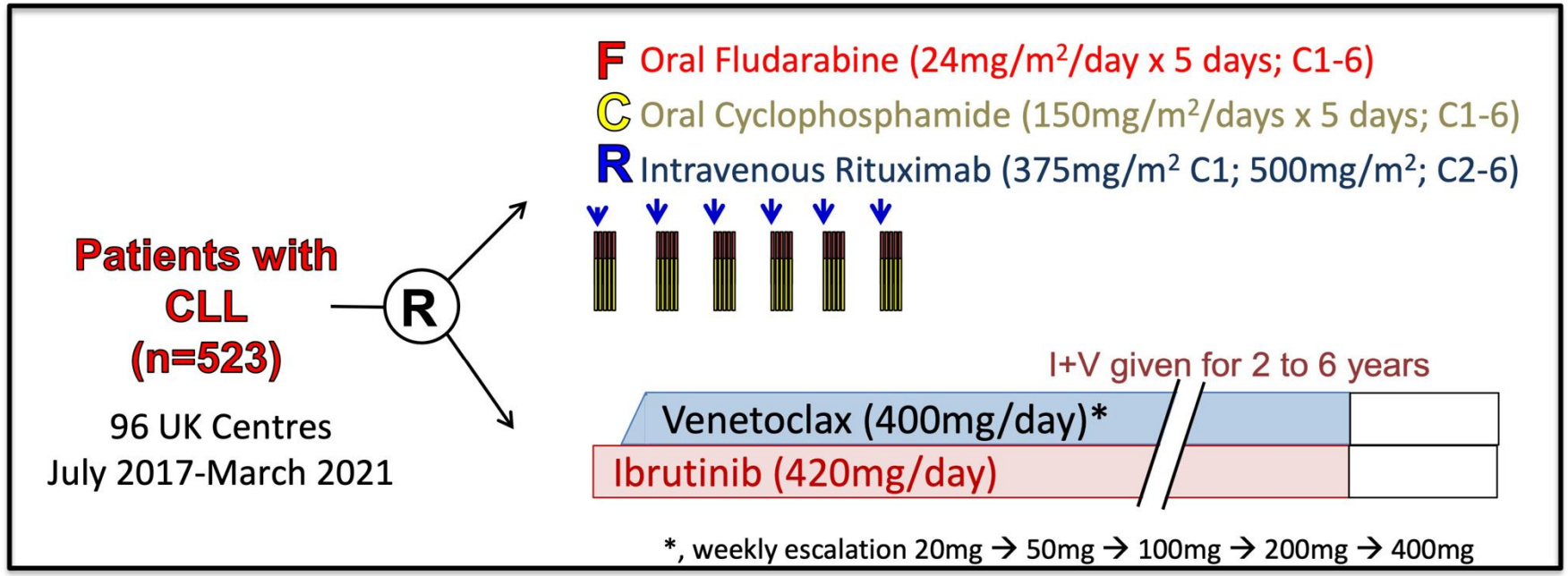
- Zanubrutinib demonstrated consistent PFS benefit, regardless of IGHV status

Tam et al., ASH 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

FLAIR: Study design



Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

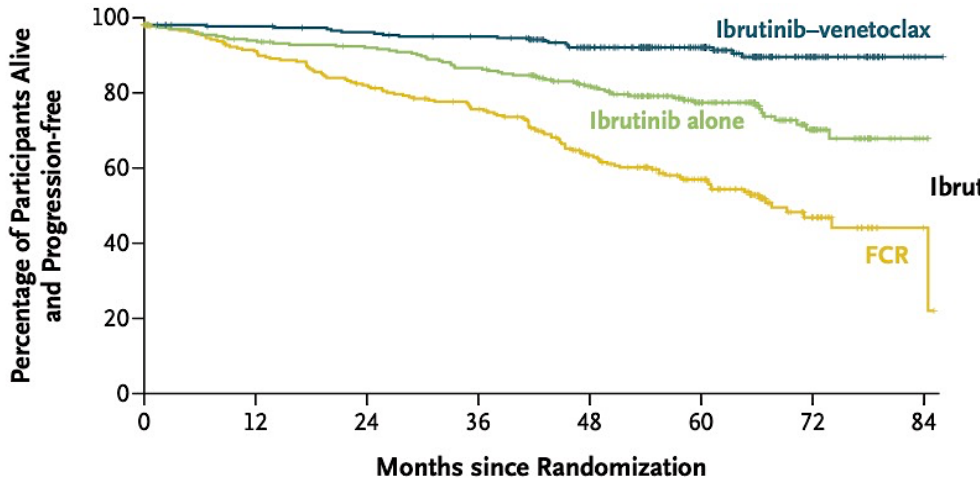
Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Munir et al., NEJM 2024, 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

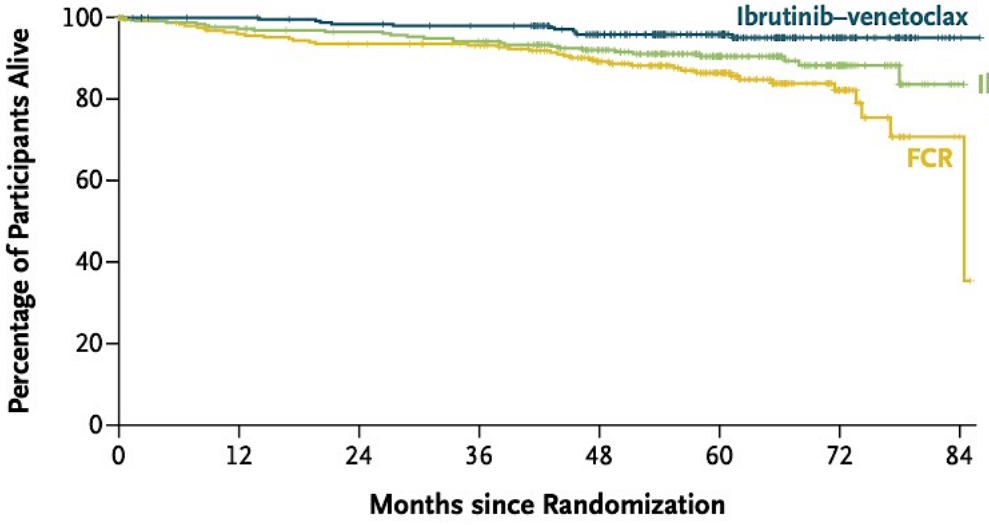
FLAIR: Efficacy (PFS & OS)



	Total No. of Events	Median Progression-free Survival (95% CI)
		mo
Ibrutinib–Venetoclax	18	NR
Ibrutinib Alone	59	NR
FCR	112	69.22 (61.04–NR)

Hazard Ratio for Disease Progression or Death (95% CI)

Ibrutinib–venetoclax vs. ibrutinib alone: 0.29 (0.17–0.49); P<0.001
Ibrutinib–venetoclax vs. FCR: 0.13 (0.08–0.21); P<0.001
Ibrutinib alone vs. FCR: 0.44 (0.32–0.60)



	Total No. of Events	Median Overall Survival (95% CI)
		mo
Ibrutinib–Venetoclax	11	NR
Ibrutinib Alone	26	NR
FCR	39	NR

Hazard Ratio for Death (95% CI)

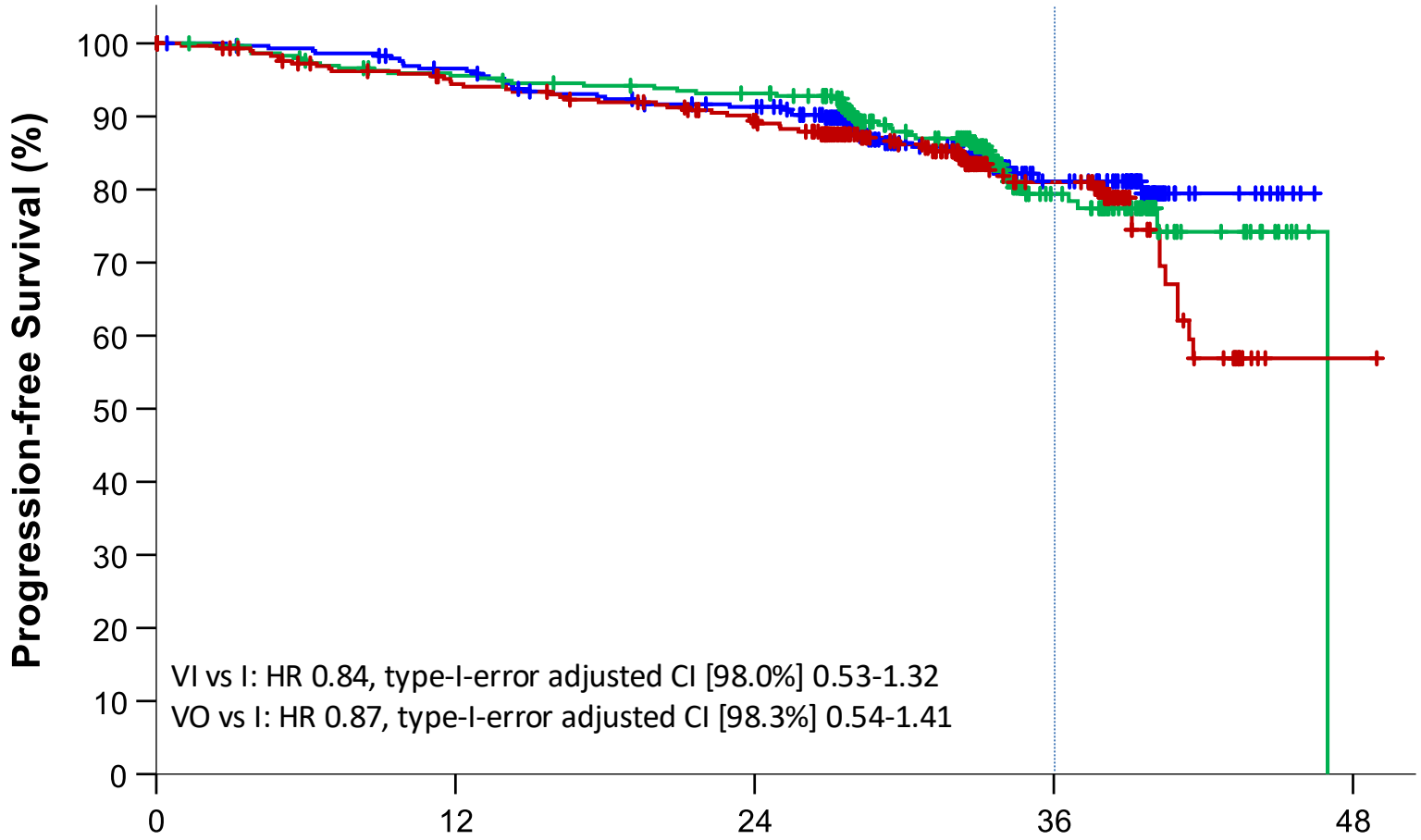
Ibrutinib–venetoclax vs. ibrutinib alone: 0.41 (0.20–0.83)
Ibrutinib–venetoclax vs. FCR: 0.26 (0.13–0.50)
Ibrutinib alone vs. FCR: 0.64 (0.39–1.05)

Munir et al., NEJM 2024, 2025

Courtesy of Wojciech Jurczak, MD, PhD

National Research Institute of Oncology

CLL17: Progression-free survival



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

3-year-PFS

I	81.0%
VI	79.4 %
VO	81.1%

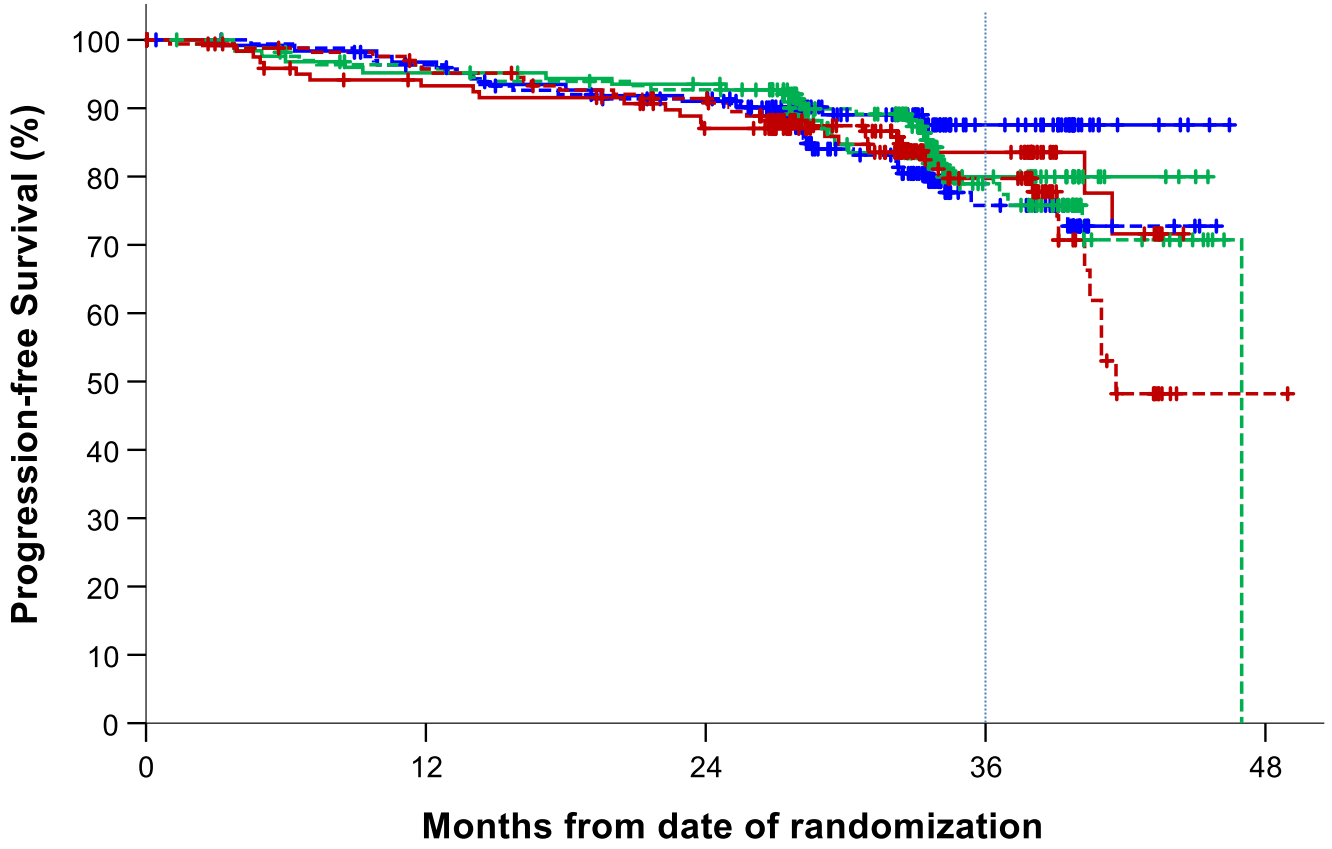
	PD	Death
I	46	11
VI	37	13
VO	25	21

Courtesy of Jennifer R Brown, MD, PhD

Al-Sawaf O et al. ASH 2025;Abstract 1

CLL17: Progression-free survival

According to IGHV status



Patients 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

Courtesy of Jennifer R Brown, MD, PhD

3-year-PFS

----- I, uIGHV	79.7%
— I, mIGHV	83.5%
----- VI, uIGHV	78.9%
— VI, mIGHV	80.0%
----- VO, uIGHV	75.8%
— VO, mIGHV	87.6%

Unmutated IGHV:

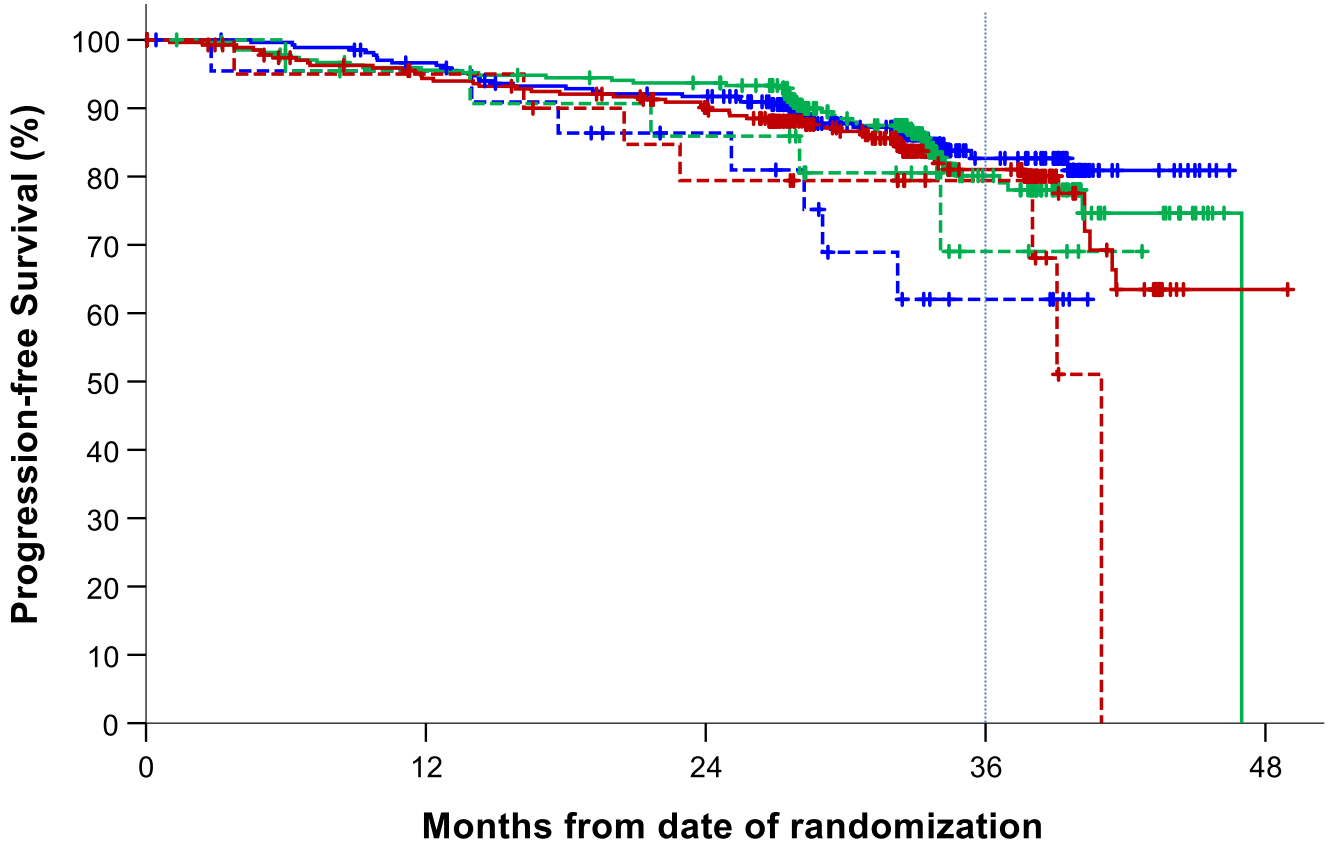
VI vs I: HR 0.81, 95% CI 0.49-1.32

VO vs I: HR 0.98, 95% CI 0.61-1.59

Al-Sawaf O et al. ASH 2025;Abstract 1

CLL17: Progression-free survival

According to *TP53*/del17p status



Patients 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

Courtesy of Jennifer R Brown, MD, PhD

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%

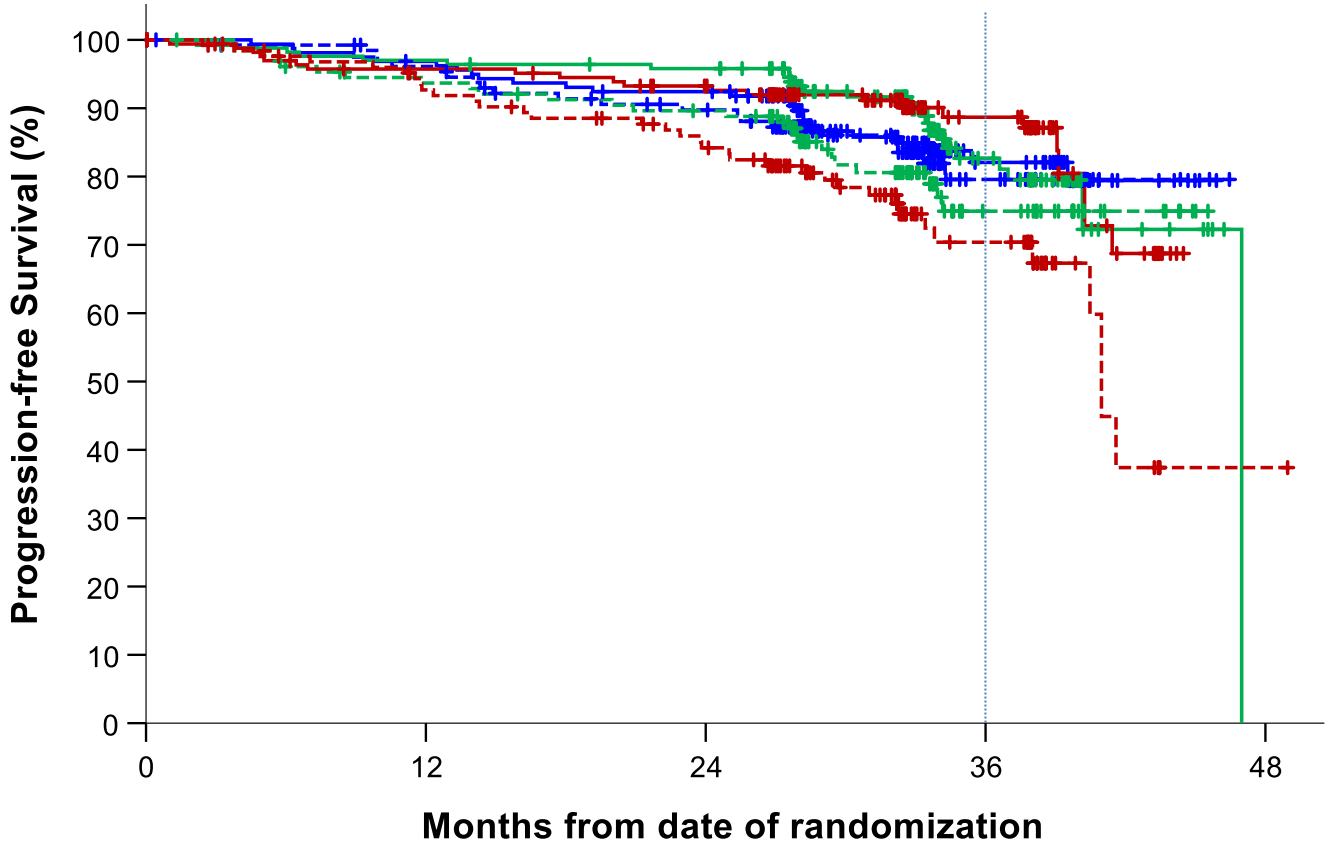
***TP53* del/mut:**

VI vs I: HR 0.70, 95% CI 0.22-2.16

VO vs I: HR 1.20, 95% CI 0.40-3.59

Progression-free survival

According to fitness (cumulative illness rating scale >6 and/or GFR <70 ml/min)



Patients at risk					
VO, unfit	134	123	109	30	0
VO, fit	167	153	145	47	0
VI, unfit	136	116	109	29	0
VI, fit	169	162	158	53	0
I, unfit	130	112	97	33	1
I, fit	171	155	146	61	0

3-year-PFS

----- I, unfit	70.4%
—— I, fit	88.7%
----- VI, unfit	74.9%
—— VI, fit	82.7%
----- VO, unfit	79.6%
—— VO, fit	82.1%

Unfit:

VI vs I: HR 0.66, 95% CI 0.40-1.11

VO vs I: HR 0.58, 95% CI 0.34-0.99

Courtesy of Jennifer R Brown, MD, PhD

CLL17 Conclusions

- 12-15 month fixed duration regimens have similar PFS to continuous ibrutinib, with 3 yr follow-up
- For del17p, already trending worse with the VO > VI regimen
- Unfit patients did most poorly with continuous ibrutinib

Courtesy of Jennifer R Brown, MD, PhD

Al-Sawaf O et al. ASH 2025;Abstract 1

PVO in RT

- ORR rate of 80% (12/15) with combined pirtobrutinib, venetoclax, and obinutuzumab for 2 yrs in pts with Richter transformation (median 1 prior CLL tx, 1 prior RT tx)
- 12-mo PFS and OS rates were 80% and 85.6%, respectively
  - Among 10 pts with R/R RT, 12-mo PFS and OS rates of 80% and 90%, respectively
- Among the responders (n=12), 12-mo duration of response is 100%
- Toxicity profile was similar to triplet combination regimens in CLL

Courtesy of Jennifer R Brown, MD, PhD

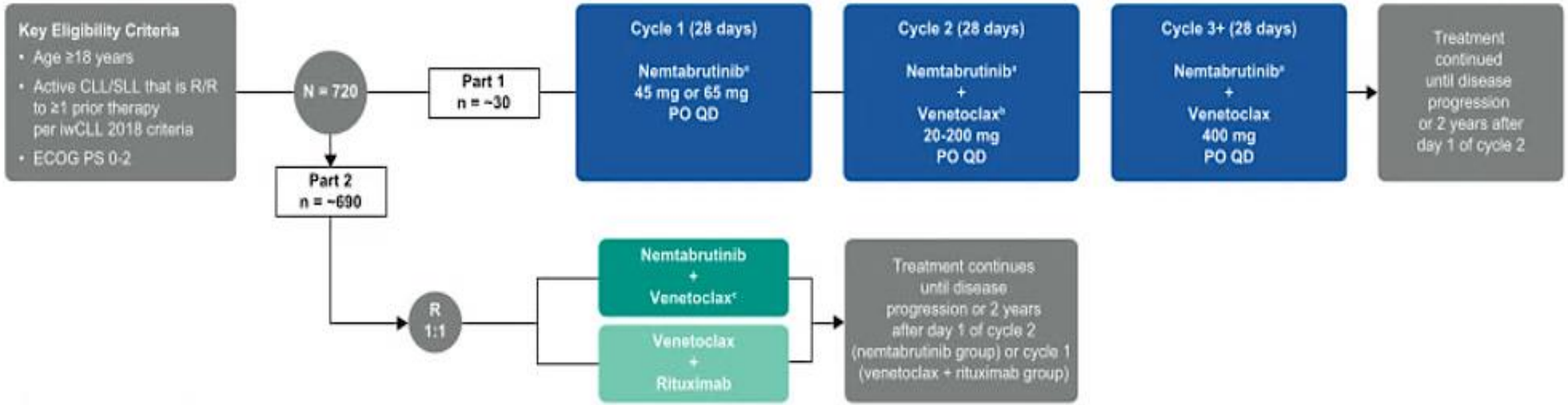
Jain N et al. ASH 2025;Abstract 89

PVO in RT

- **Very preliminary, very few patients**
- **Shows promise**
- **Similar toxicity to the CLL regimen, i.e. significant cytopenias**

Courtesy of Jennifer R Brown, MD, PhD

Nemtabrutinib + Ven in R/R CLL

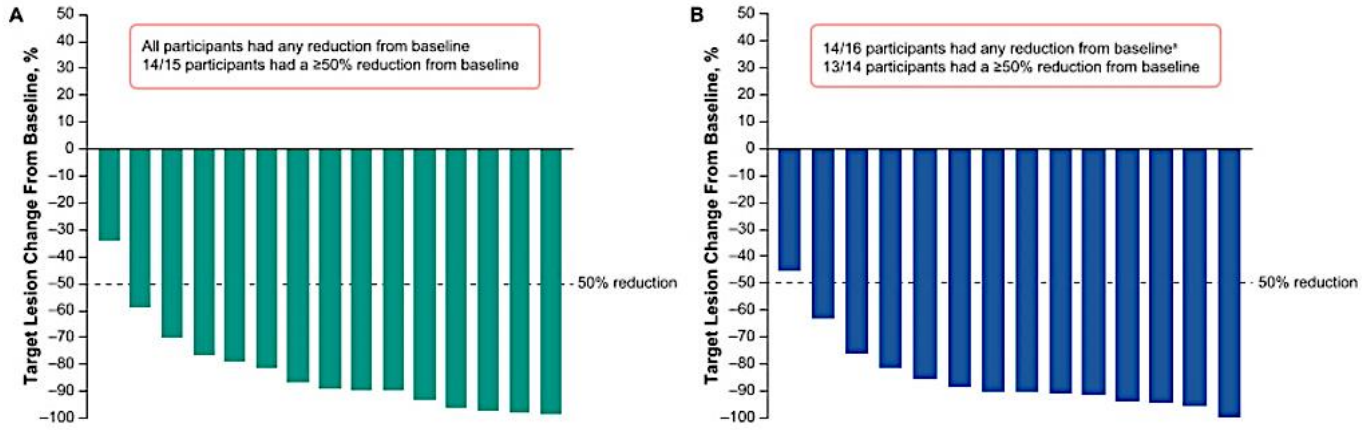


Courtesy of Jennifer R Brown, MD, PhD

Ghia P et al. ASH 2025;Abstract 2119

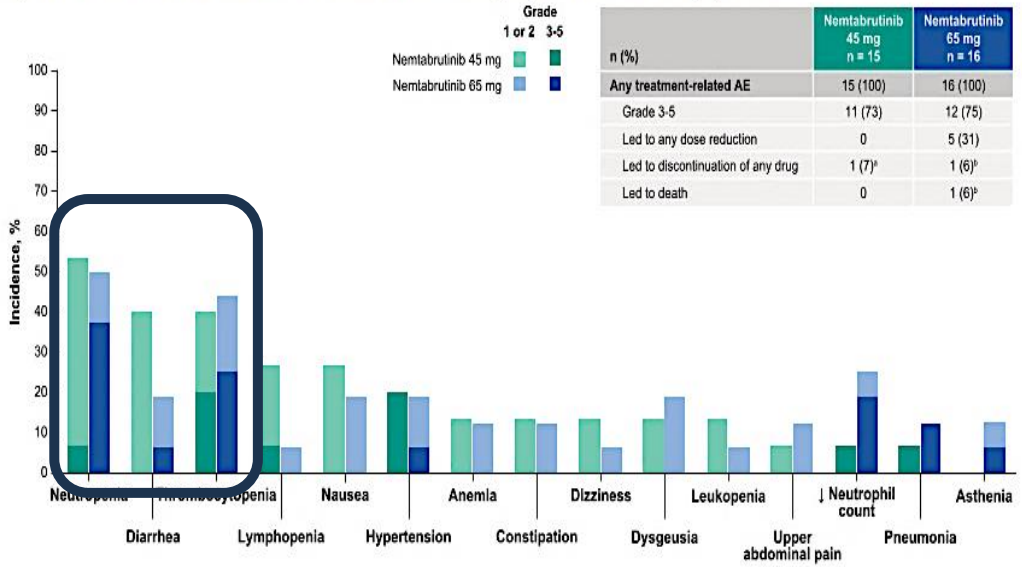
Nemta + Ven in R/R CLL

Figure 4. Best percentage change from baseline in target lesion size per iwCLL 2018 criteria by investigator review in the DLT-evaluable population for the (A) 45-mg dose group and (B) 65-mg dose group



Includes participants with ≥1 postbaseline target lesion.
[a]2 participants had no postbaseline assessment available for response evaluation.

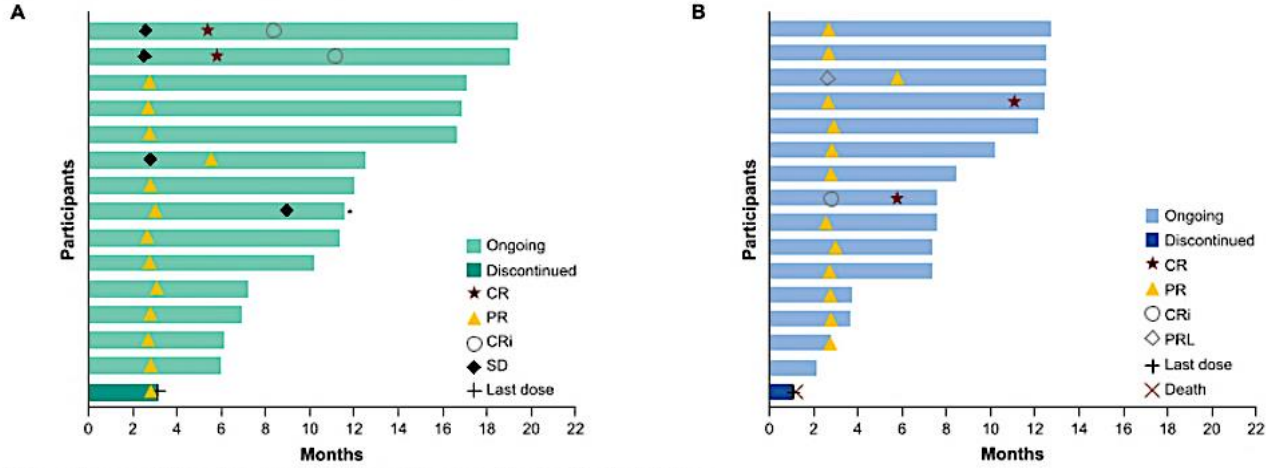
Figure 3. Treatment-related AEs with incidence of ≥5% in either dose group in the DLT-evaluable population



n (%)	Nemtabrutinib 45 mg n = 15	Nemtabrutinib 65 mg n = 16
Any treatment-related AE	15 (100)	16 (100)
Grade 3-5	11 (73)	12 (75)
Led to any dose reduction	0	5 (31)
Led to discontinuation of any drug	1 (7)[a]	1 (6)[b]
Led to death	0	1 (6)[b]

[a]Endocarditis (grade 4).
[b]Pneumonia (grade 5).

Figure 5. Time on study treatment and response per iwCLL 2018 criteria by investigator review in the DLT-evaluable population for the (A) 45-mg dose group and (B) 65-mg dose group



CRi, complete response with incomplete marrow recovery; PRL, partial response with lymphocytosis; SD, stable disease.
*Subsequent to the data cutoff date, response was changed from SD to not evaluable due to infection and was later updated to PR.

Courtesy of Jennifer R Brown, MD, PhD

Ghia P et al. ASH 2025;Abstract 2119

Nemta + Ven in R/R CLL

- **Phase 1b component prior to randomized trial vs ven R in 2nd line CLL**
- **Tested 45 and 65 mg nemta – similar efficacy but improved tolerability with 45 mg, which was selected to move forward**
- **Comparative efficacy vs covalents or pirto would be most interesting, based on the patient population**

Courtesy of Jennifer R Brown, MD, PhD

What Clinicians Want to Know: First-Line and Maintenance Therapy for Patients with ER-Positive, HER2-Positive Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, March 18, 2026

5:00 PM – 6:00 PM ET

Faculty

Virginia F Borges, MD, MMSc
Ian E Krop, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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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.

RTP Year in Review 2026