Cases from the Community
Investigators Discuss Available Research Guiding the Selection of Therapy for Patients with Chronic Lymphocytic Leukemia

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025
11:30 AM – 1:30 PM

Faculty

Matthew S Davids, MD, MMSc
Bita Fakhri, MD, MPH
Professor Constantine Tam, MBBS, MD
Jennifer Woyach, MD

Moderator

Neil Love, MD

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Faculty

Matthew S Davids, MD, MMSc
Associate Professor of Medicine
Harvard Medical School
Leader, Lymphoma Program
Dana-Farber/Harvard Cancer Center
Director of Clinical Research
Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

Bita Fakhri, MD, MPH
Assistant Professor of Medicine (Hematology)
Stanford University School of Medicine
Stanford, California

Professor Constantine Tam, MBBS, MD
Head of Lymphoma Service
Alfred Health
Professor of Haematology
Monash University
Melbourne, Australia

Jennifer Woyach, MD
Professor
Division of Hematology
Department of Internal Medicine
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Dr Davids — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Galapagos NV, Genentech, a member of the Roche Group, Genmab US Inc, Janssen Biotech Inc, Lilly, MEI Pharma Inc, Merck, Nuvalent, Schrödinger, Takeda Pharmaceuticals USA Inc
Contracted Research	Ascentage Pharma, AstraZeneca Pharmaceuticals LP, MEI Pharma Inc, Novartis
Nonrelevant Financial Relationships	UpToDate

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Dr Fakhri — Disclosures
Faculty

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Pharmacyclics LLC, an AbbVie Company
Contracted Research	AbbVie Inc, BeOne, Genmab US Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company

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Prof Tam — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Woyach — Disclosures
Faculty

Advisory Committees and Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeOne, Genentech, a member of the Roche Group, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Newave, Pharmacyclics LLC, an AbbVie Company
Contracted Research	AbbVie Inc, Karyopharm Therapeutics, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MingSight Pharmaceuticals, MorphoSys, Schrödinger, Verastem Inc

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Dr Love — Disclosures

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Expert Second Opinion
Investigators Discuss the Optimal Management of Myelofibrosis and Systemic Mastocytosis

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

3:15 PM – 5:15 PM ET

Faculty

Professor Claire Harrison
Andrew T Kuykendall, MD
Stephen T Oh, MD, PhD
Jeanne Palmer, MD
Raajit K Rampal, MD, PhD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Expert Second Opinion
Investigators Discuss the Role of Novel Treatment Approaches in the Care of Patients with Follicular Lymphoma and Diffuse Large B-Cell Lymphoma

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

7:00 PM – 9:00 PM ET

Faculty

Nancy L Bartlett, MD
John P Leonard, MD
Matthew Matasar, MD
Loretta J Nastoupil, MD
Professor Pier Luigi Zinzani

Moderator

Neil Love, MD

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CASES FROM THE COMMUNITY
Investigators Discuss the Role of Antibody-Drug Conjugates in the Management of Triple-Negative and HR-Positive Metastatic Breast Cancer

Part 1 of a 3-Part CME Satellite Symposium Series

Tuesday, December 9, 2025

7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)

Faculty

Javier Cortés, MD, PhD

Professor Peter Schmid, FRCP, MD, PhD

Rita Nanda, MD

Priyanka Sharma, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Management of HER2-Positive Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series

Wednesday, December 10, 2025

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

Faculty

Professor Giuseppe Curigliano, MD, PhD
Nadia Harbeck, MD, PhD
Ian E Krop, MD, PhD
Nancy U Lin, MD
Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

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

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

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Cases from the Community: Investigators Discuss Available Research Guiding the Management of Relapsed/Refractory Multiple Myeloma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Monday, December 15, 2025

5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD, FACP, FASCO

María-Victoria Mateos, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Practical Perspectives on the Current and Future Management of Immune Thrombocytopenia — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Tuesday, December 16, 2025

5:00 PM – 6:30 PM ET

Faculty

Hanny Al-Samkari, MD

Francesco Zaja, MD

Additional faculty to be announced

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Practical Perspectives on the Current Role of Bispecific Antibodies in the Management of Lymphoma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Wednesday, December 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Michael Dickinson, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

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Grand Rounds

CME/MOC-Accredited Interactive Series

Through April 2026

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

Optimizing Therapy for Patients with Hormone Receptor-Positive Localized Breast Cancer

Host a 1-hour session at your institution:
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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

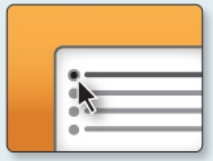
The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

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



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

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

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

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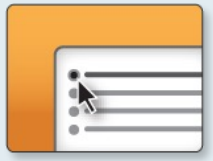
Clinicians Attending via Zoom

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



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

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

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
  An email will be sent to all attendees when the activity is available.
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RTP Playlist with Neil Love, MD

BREAST CANCER

Dr Hope Rugo: Interview (28 min)

SMALL CELL LUNG CANCER

Drs Stephen Liu and Charles Rudin: Cases (58 min)

GASTROESOPHAGEAL CANCER

Drs Geoffrey Ku and Zev Wainberg: Cases (61 min)

PROSTATE CANCER

Drs Emmanuel Antonarakis and Karim Fizazi: Year in Review (60 min)

ENDOMETRIAL AND OVARIAN CANCER

Dr Shannon Westin: Interview (52 min)

NEUROENDOCRINE TUMORS

Drs Simron Singh and Jonathan Strosberg: Meeting (50 min)

NON-HODGKIN LYMPHOMA

Drs Jeremy Abramson, Joshua Brody, Christopher Flowers, Ann LaCasce and Tycel Phillips: Meeting, cases (59 min)

CHRONIC LYMPHOCYTIC LEUKEMIA

Drs Jennifer Brown and Paolo Ghia: Year in Review (59 min)

ACUTE MYELOID LEUKEMIA

Dr Jorge Cortes: Interview (43 min)

MULTIPLE MYELOMA

Drs Natalie Callander and Sagar Lonial: Patient videos (59 min)

IMMUNE THROMBOCYTOPENIA

Drs Hanny Al-Samkari, James Bussel and Nichola Cooper: Think Tank (117 min)

OCULAR TOXICITES IN ONCOLOGY

Dr Neel Pasricha: Interview (54 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

RTP Playlist with Neil Love, MD

Webinar for patients and families on relapsed multiple myeloma with Drs Natalie Callander and Sagar Lonial.

Relapsed Multiple Myeloma: Where We Were, Where We Are (4 min)

Common Questions from the Beginning (5 min)

Choosing Treatment Options (4 min)

Clinical Research Trials (6 min)

Neuropathy (5 min)

Chimeric Antigen Receptor (CAR) T-Cell Therapy (6 min)

Bispecific Antibodies (8 min)

Antibody-Drug Conjugates: Belantamab Mafadotin (8 min)

Interacting with the Oncology Team (5 min)

Other Questions (4 min)

Recording of Entire Webinar (62 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

ASH and SABCS RTP Video Participants

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ASH and SABCS RTP Participating Faculty

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Cases from the Community
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Professor Constantine Tam, MBBS, MD
Jennifer Woyach, MD

Moderator

Neil Love, MD

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Contributing General Medical Oncologists

Bhavana (Tina) Bhatnagar, DO
WVU Cancer Institute
Wheeling, West Virginia

Zanetta S Lamar, MD
Florida Oncology and Hematology
Naples, Florida

Brian P Mulherin, MD
Hematology Oncology of Indiana
Indianapolis, Indiana

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Erik Rupard, MD
Penn State Cancer Institute
Reading, Pennsylvania

Sean Warsch, MD
Messino Cancer Centers
Asheville, North Carolina

Jennifer Yannucci, MD
Low Country Cancer Care
Savannah, Georgia

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Agenda

Module 1: Current and Emerging Approaches to First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Davids

Module 2: Optimal Management of Adverse Events with Bruton Tyrosine Kinase and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Prof Tam

Module 3: Selection and Sequencing of Therapy for Relapsed/Refractory CLL — Dr Woyach

Module 4: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Fakhri

Agenda

Module 1: Current and Emerging Approaches to First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Davids

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Module 3: Selection and Sequencing of Therapy for Relapsed/Refractory CLL — Dr Woyach

Module 4: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Fakhri

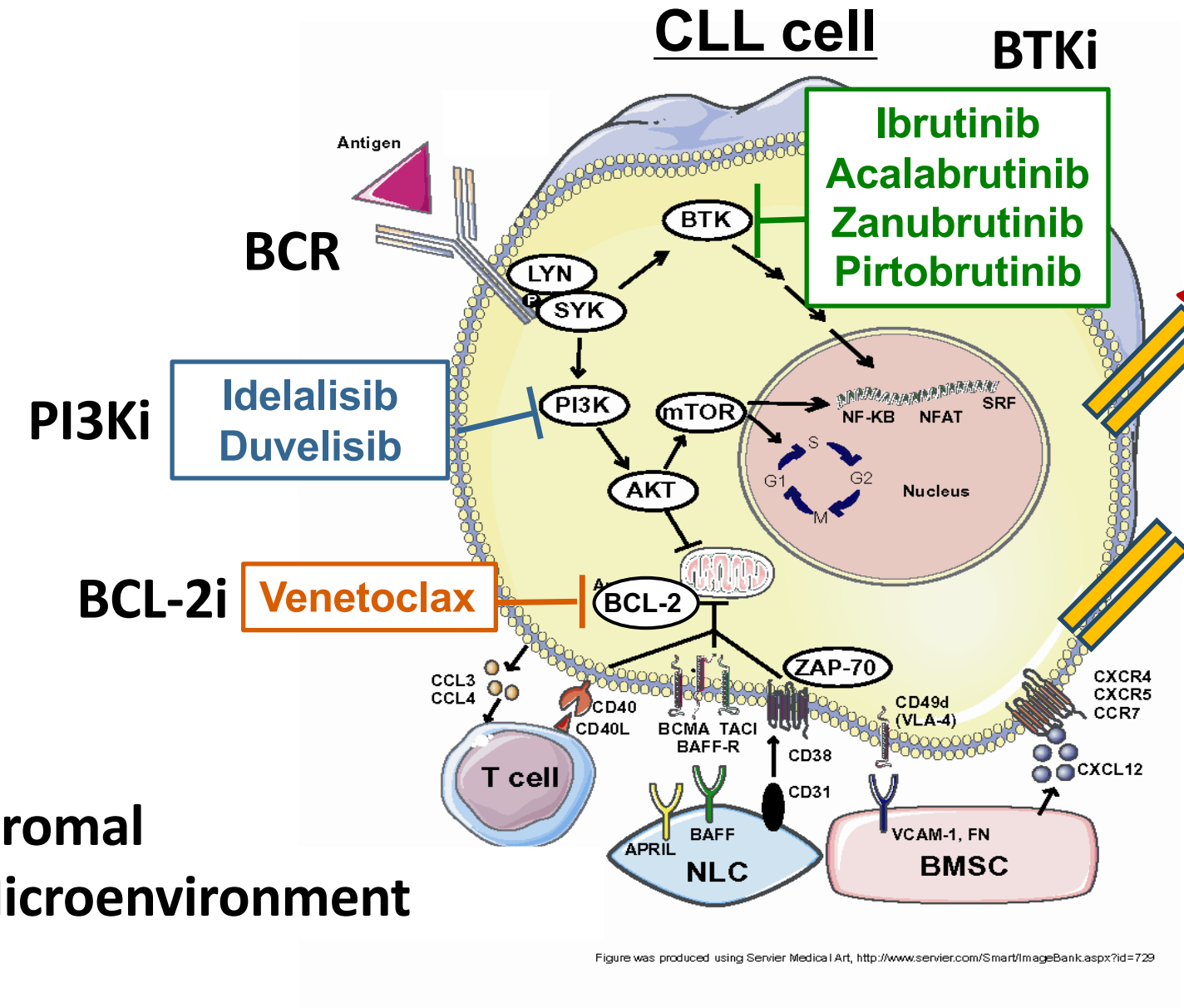
Dana-Farber Cancer Institute

Current and Emerging Approaches to First-Line Therapy for CLL

Matthew S. Davids, MD, MMSc
Clinical Research Director | Division of Lymphoma | Dana-Farber Cancer Institute
Associate Professor of Medicine | Harvard Medical School

December 5, 2025 | RTP ASH Friday Satellite Symposium | Orlando, Florida, USA

A diverse array of targeted therapies are approved in CLL

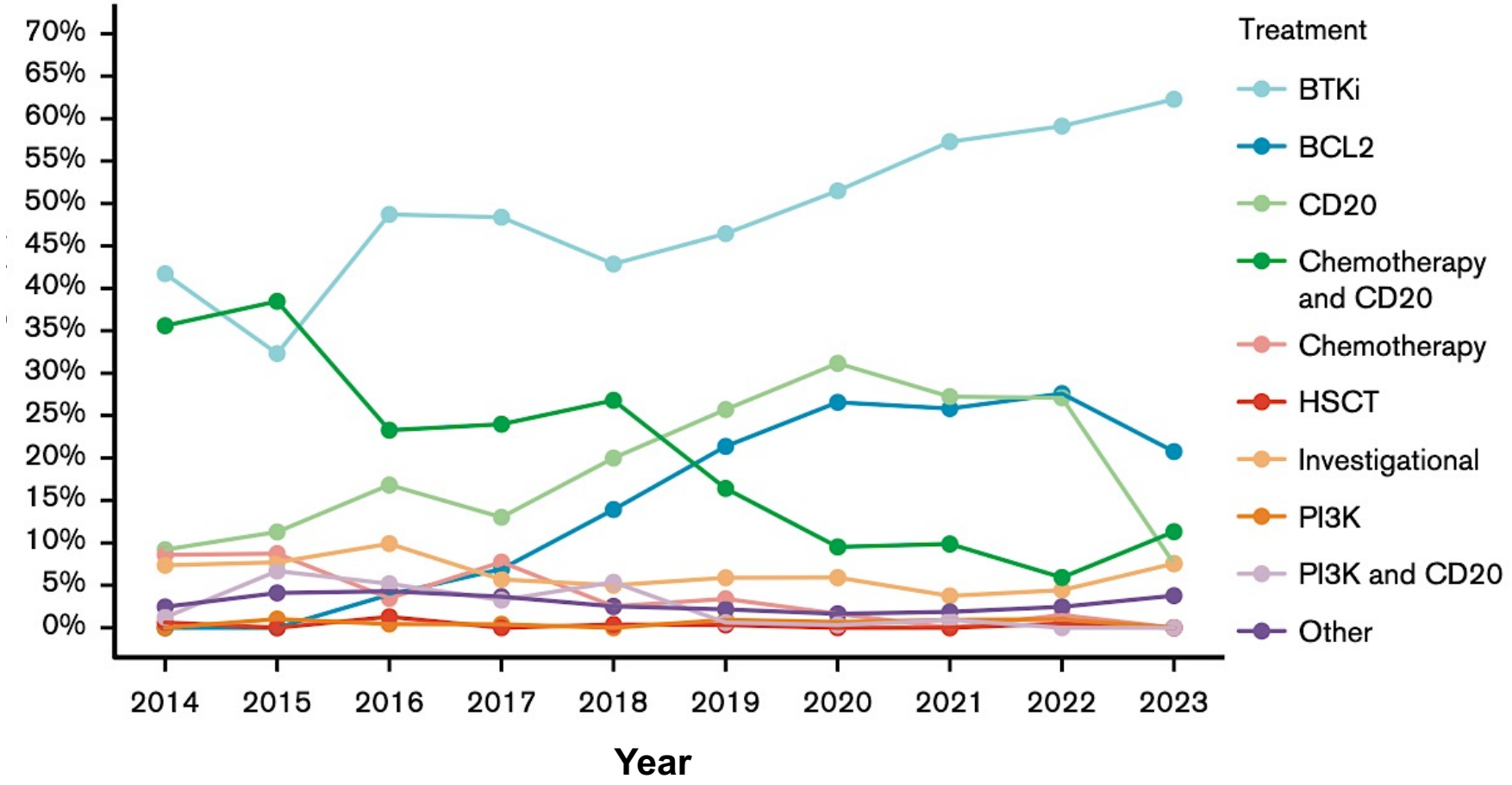


Adapted from Davids MS and Brown JR. *Leuk Lymph*, 2012;53:2362-2370.

Treatment Patterns in the US Show Increasing Use of Targeted Agents With Less CIT Use Over Time

- From electronic health records of 1,283 patients with CLL within a real-world database

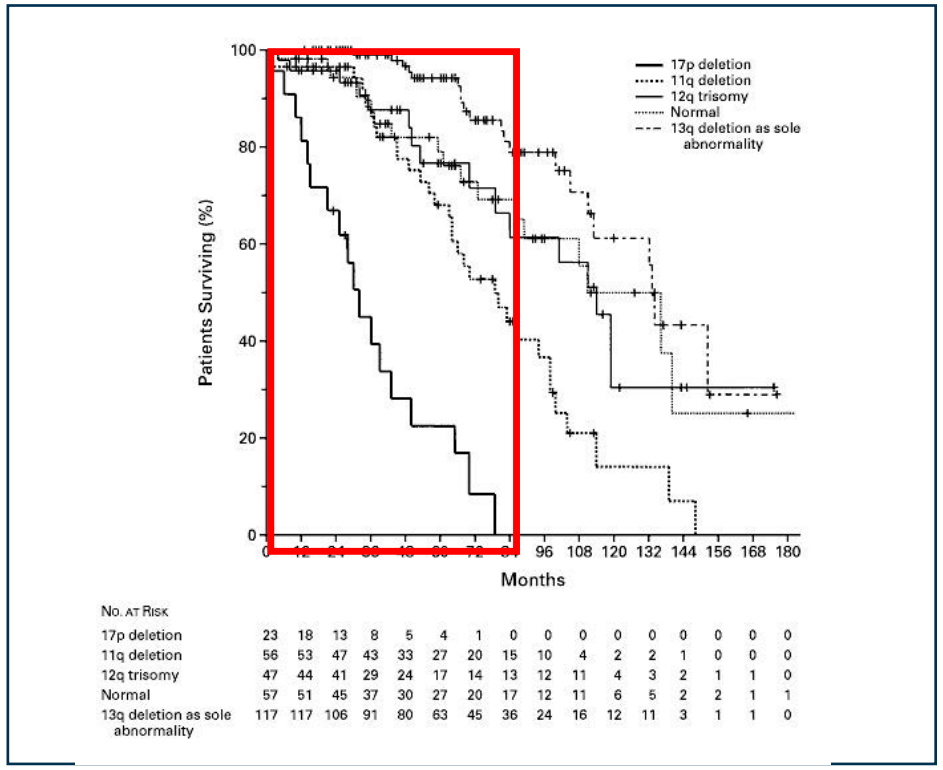
CLL Treatments Received From 2014-2022, in patients receiving ≥2 lines of therapy



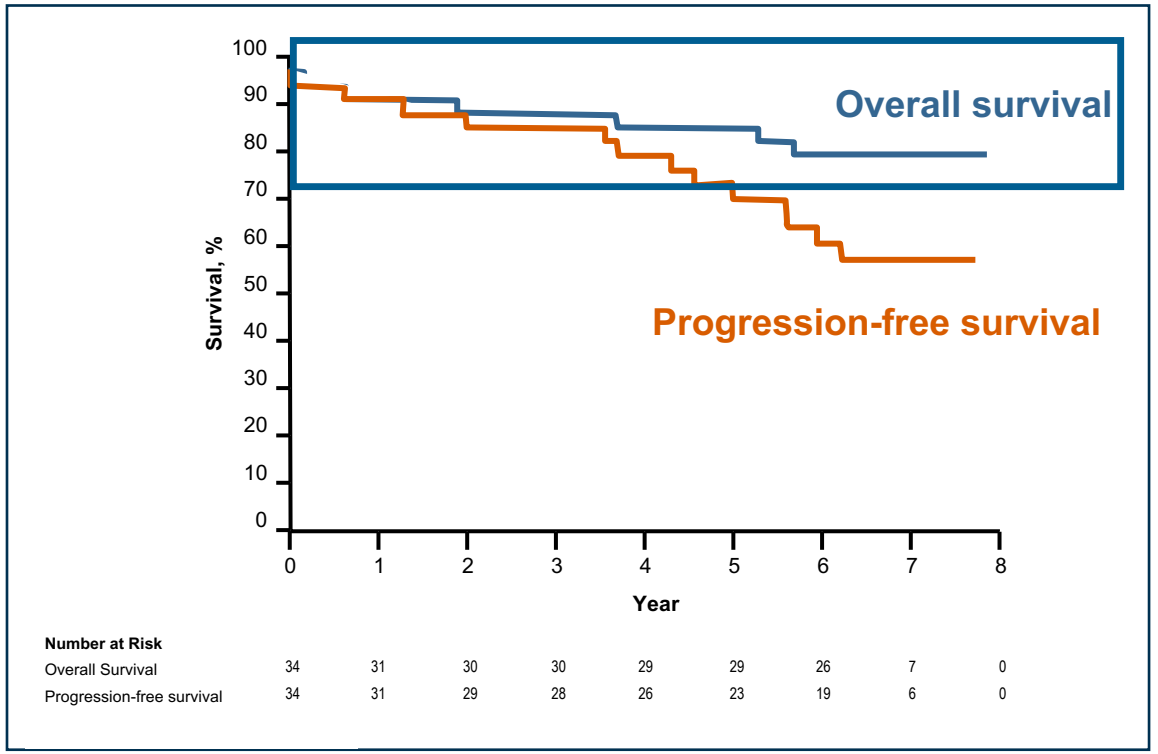
Davids MS et al. *Blood Neoplasia*. 2024;2:100047.

Covalent BTK Inhibitors Have Revolutionized the Treatment of CLL

Chemotherapy



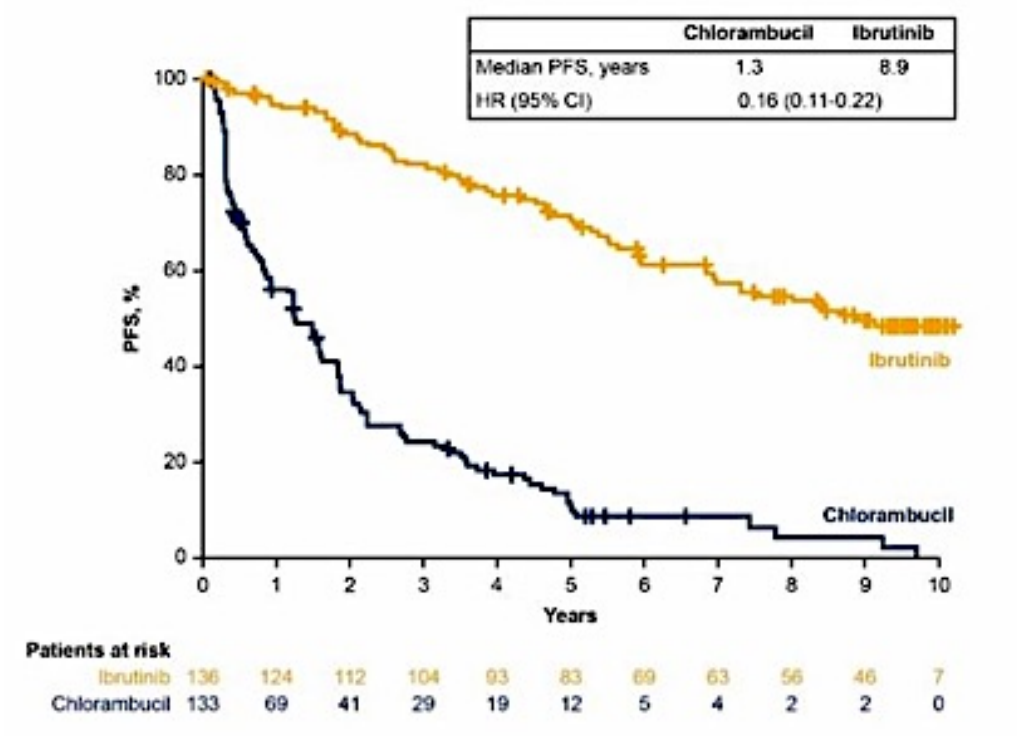
Ibrutinib



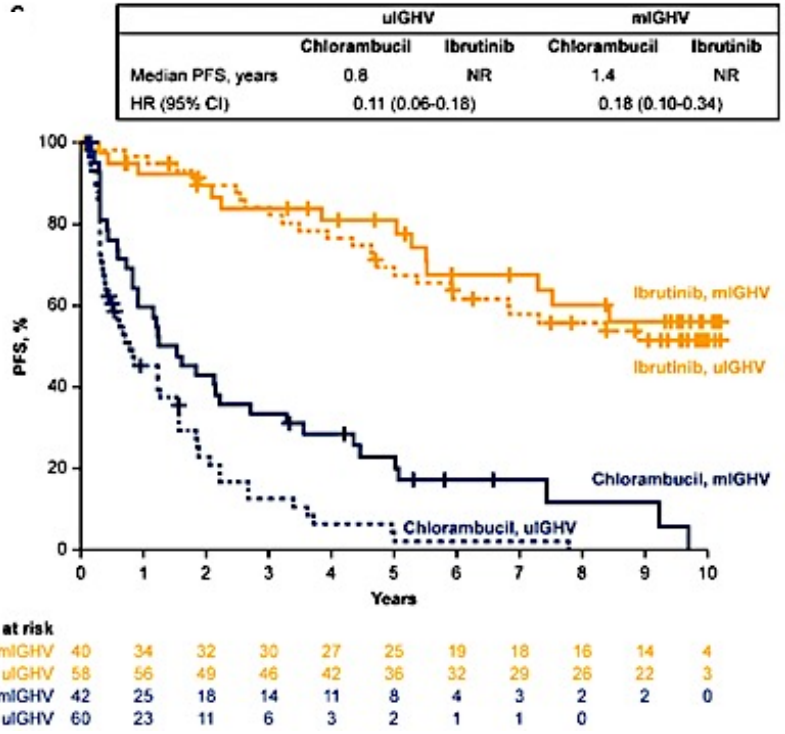
Döhner H, et al. *N Engl J Med*. 2000;343:1910-1916. Ahn IE, et al. *N Engl J Med*. 2020;383(5):498-500. Itsara A, et al. *Blood.* 2023;142(1_Suppl):201.
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; OS, overall survival.

RESONATE-2: 10 Year Final Analysis Ibrutinib vs Chlorambucil

PFS



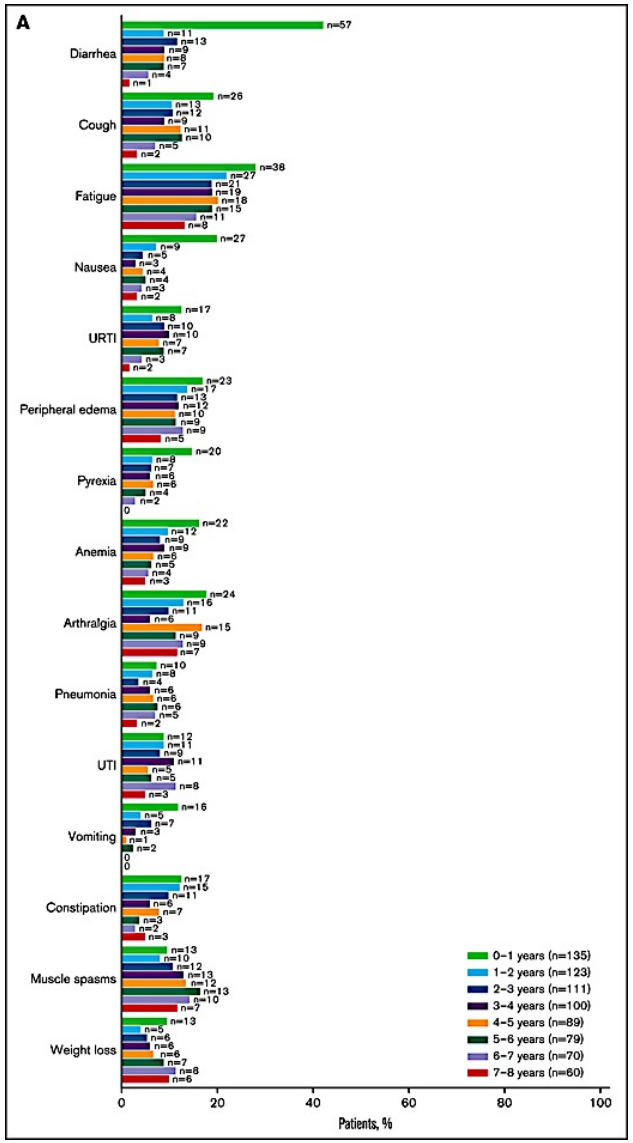
PFS by IGHV

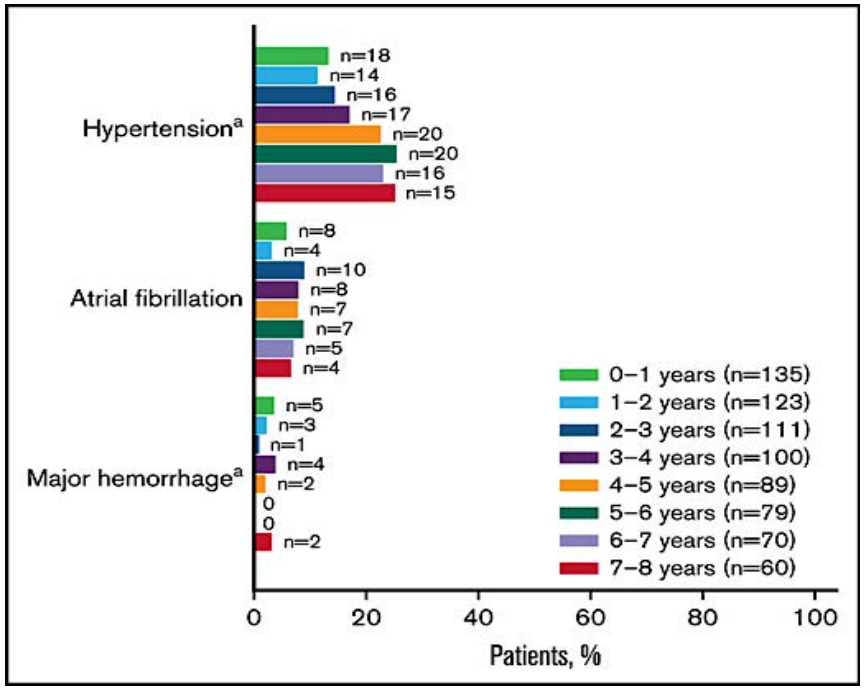


DISCONTINUATIONS	Ibrutinib N = 135
Median (range) duration of ibrutinib treatment, years	6.2 (0.06–10.2)
Continuing ibrutinib at study closure, n (%)	37 (27)
Discontinued ibrutinib, n (%)	
Due to AE	44 (33)
Due to PD	18 (13)

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

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





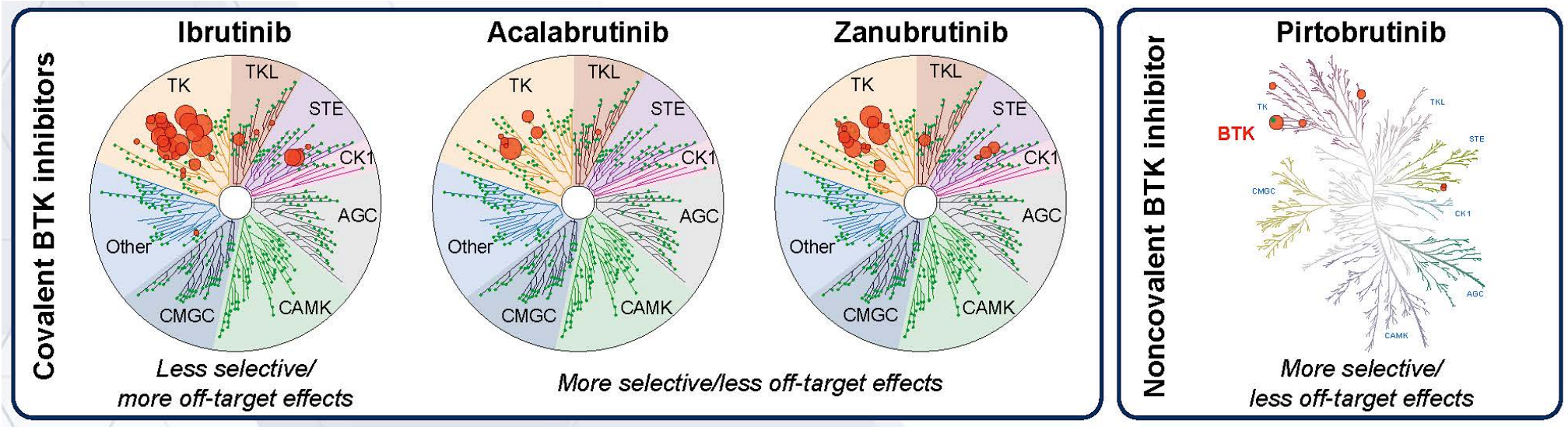
- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

Barr PM et al. *Blood Adv.* 2022;6:3440-3450.

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

Mato AR et al., *Haematologica.* 2018;103:874-879.

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



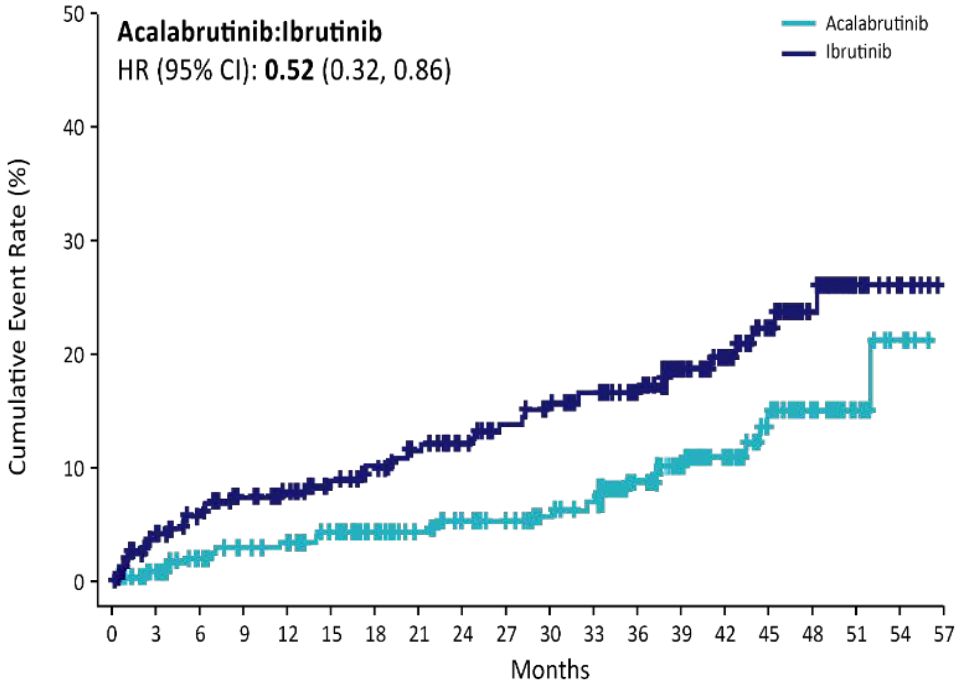
Potential off-target effects include:

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

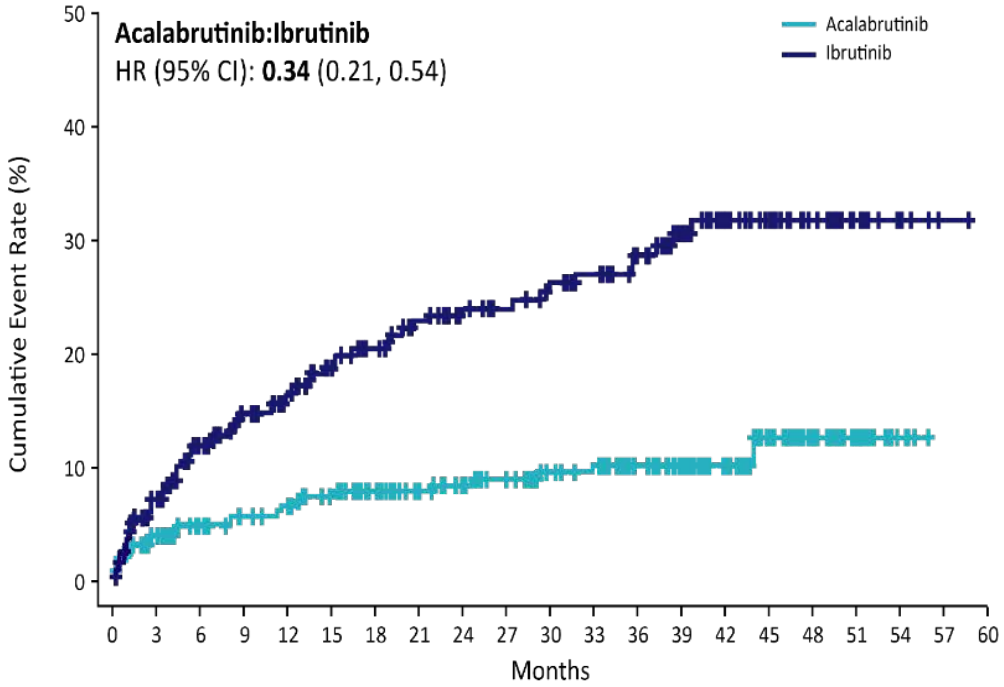
AGC, containing PKA, PKG, PKC families; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CAMK, calcium/calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; EGFR, epidermal growth factor receptor; STE, homologs of yeast Sterile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

ELEVATE RR Trial: Lower Cumulative Incidence of Atrial Fibrillation and Hypertension With Acalabrutinib

Afib/Flutter, Any Grade



Hypertension, Any Grade

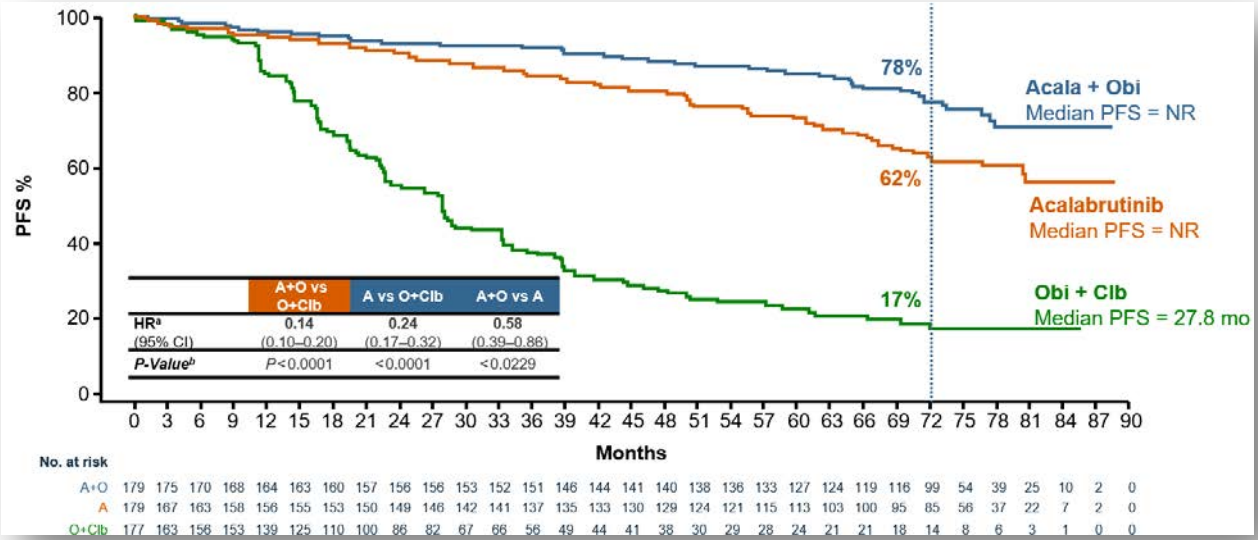


Overall, AEs led to treatment discontinuation in 14.7% of acalabrutinib-treated pts vs 21.3% of ibrutinib-treated pts

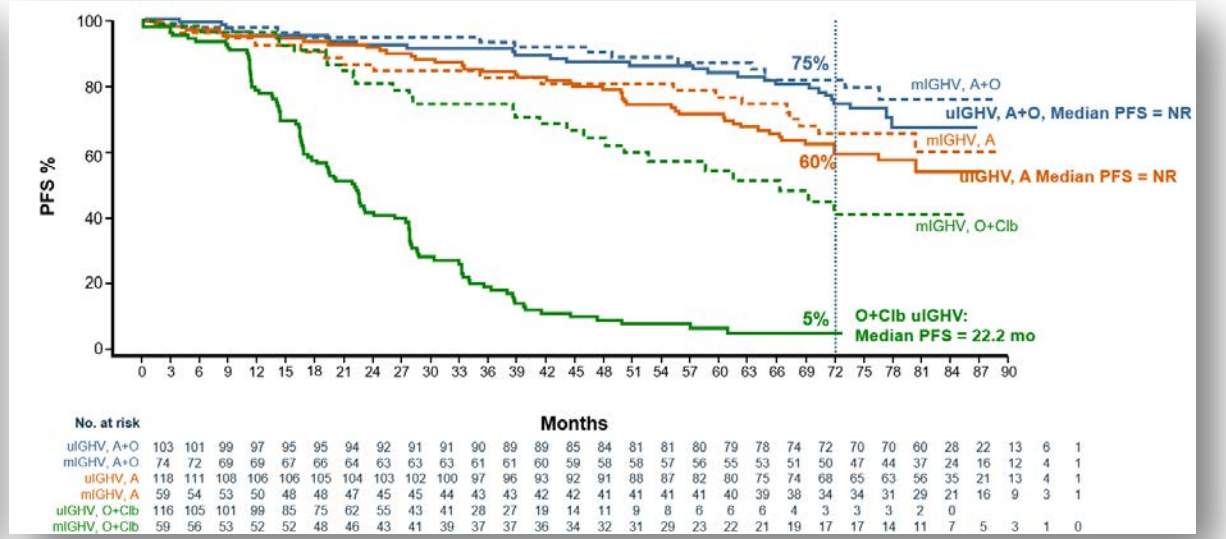
Byrd JC, et al. *J Clin Oncol*. 2021;39:3441-3452.
AE, adverse event.

ELEVATE-TN (6 Year Update): Median PFS Was Significantly Longer for Acalabrutinib-Containing Arms vs O+Clb with no Difference based on IGHV

Full study population



Study population by IGHV

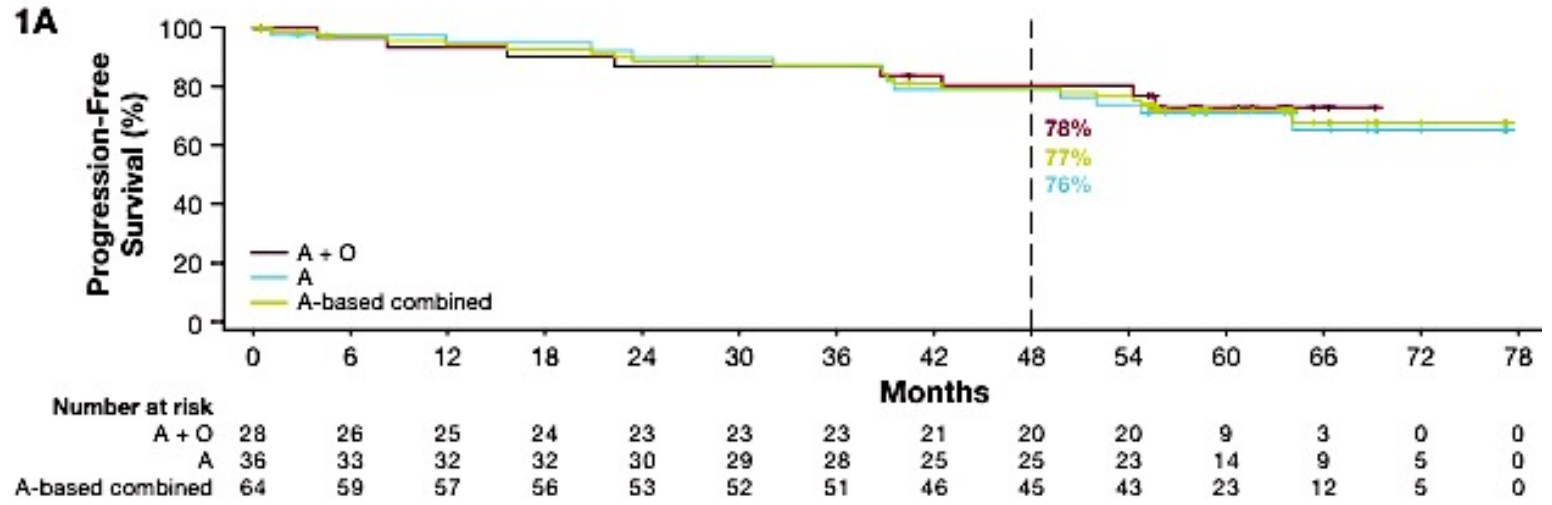


[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

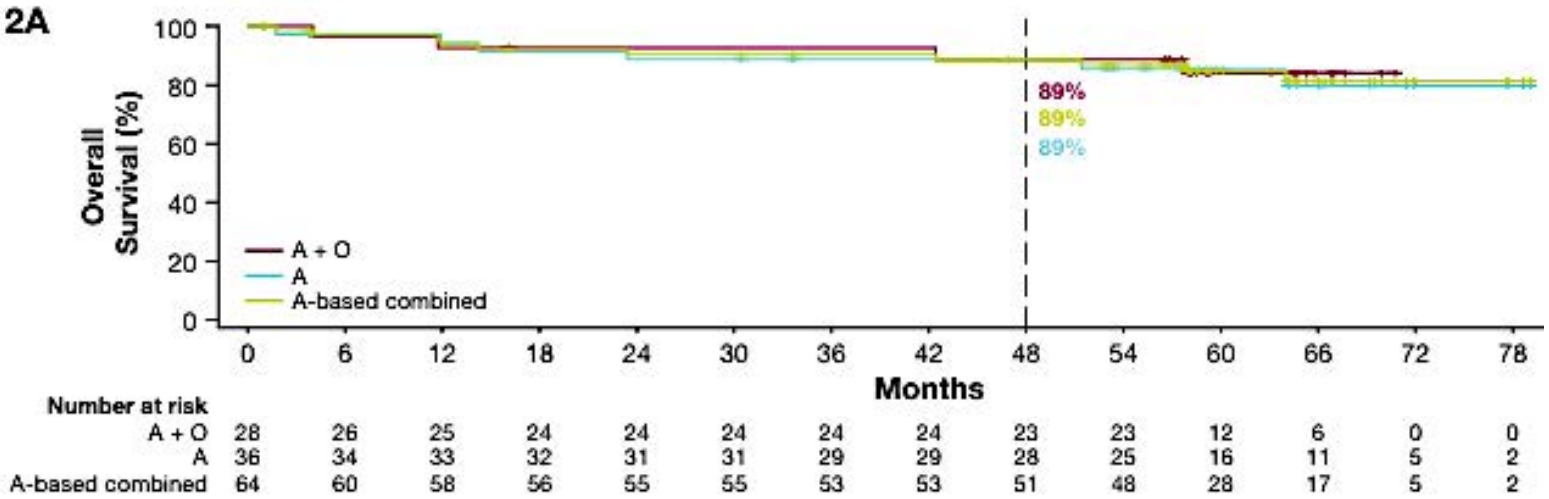
Sharman JP, et al. *Blood.* 2025;146:1276-1285.

Survival Data with Acalabrutinib in Frontline *TP53* Aberrant CLL

PFS

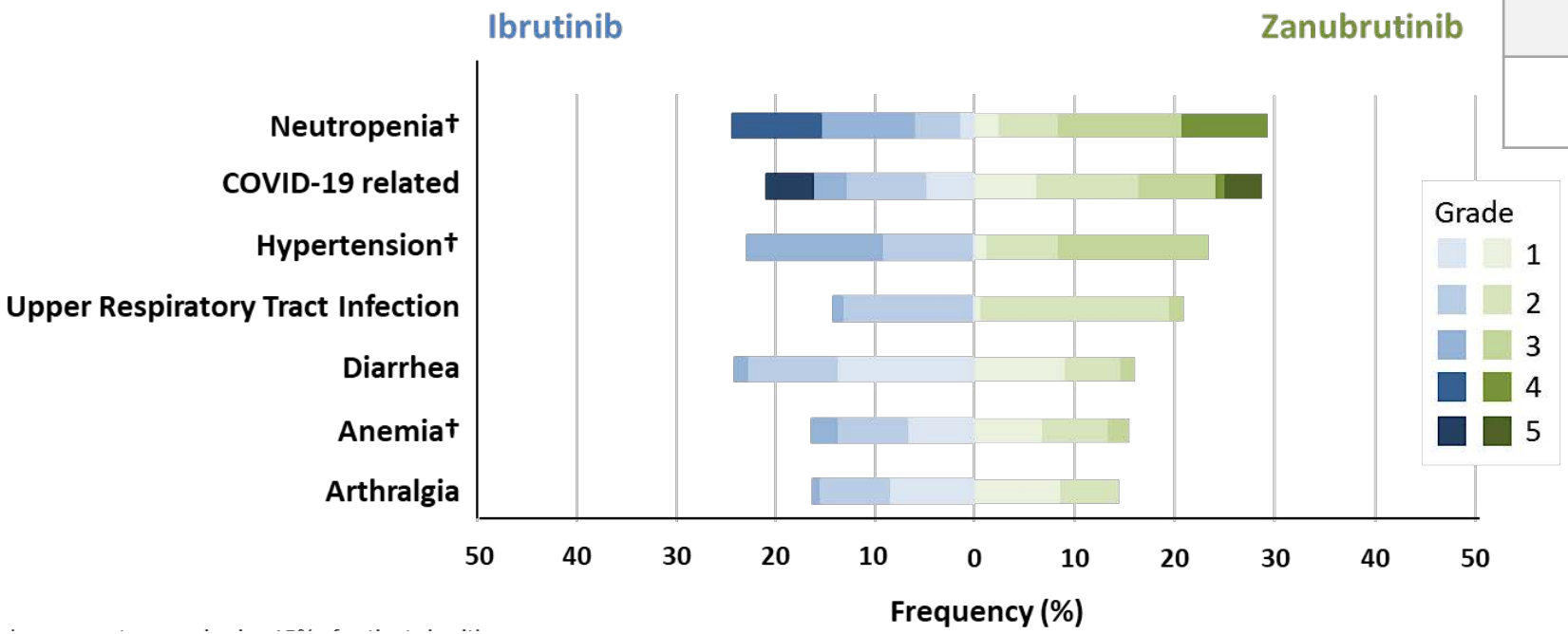


OS



Davids MS et al., *Blood Adv.* 2024;8:3345-3359.

ALPINE Trial: Ibrutinib vs. Zanubrutinib in R/R CLL
Most Common Adverse Events*

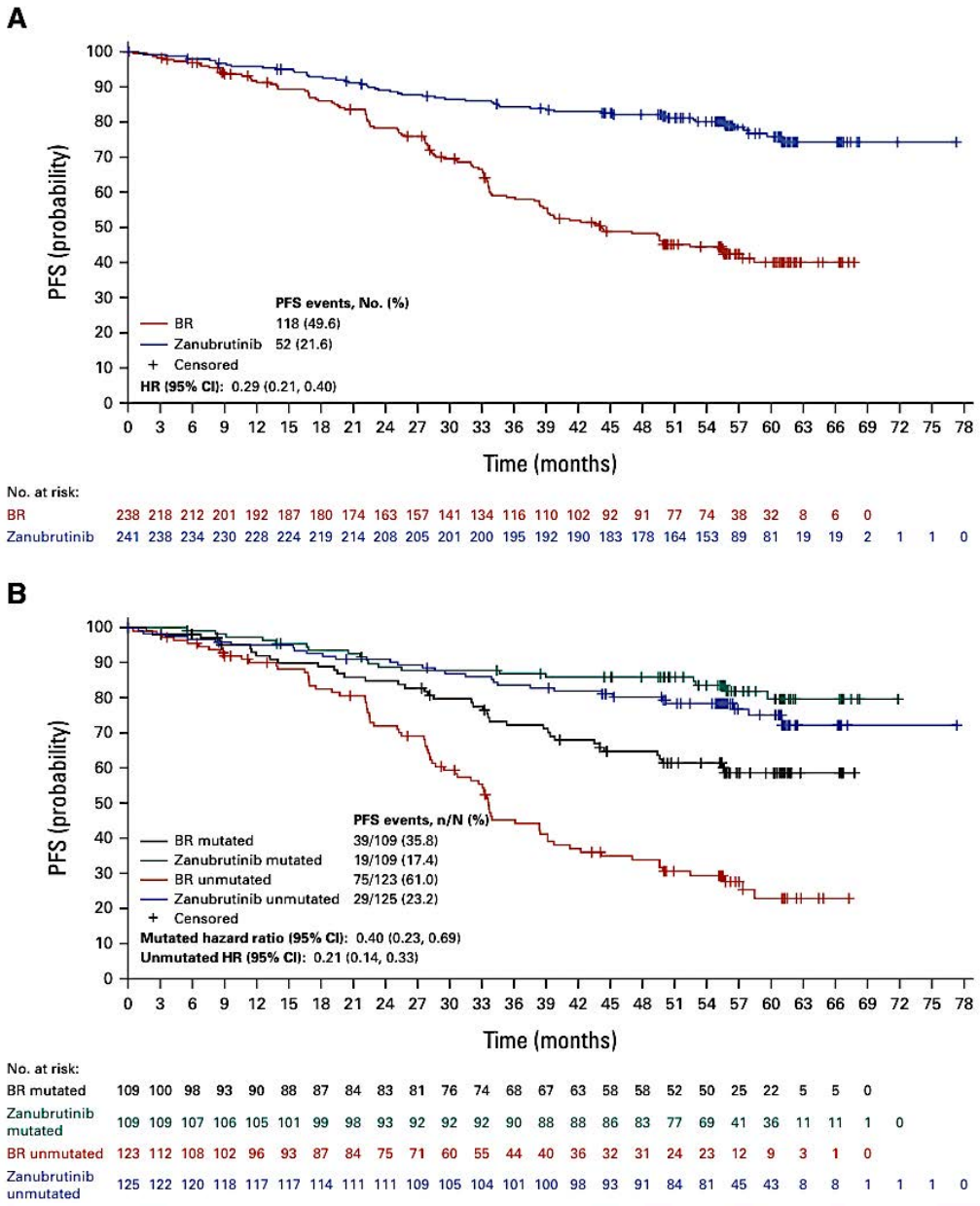


Adverse Events Leading to	Zanubrutinib (N=324)	Ibrutinib (N=324)
Dose reduction	40 (12.3)	55 (17.0)
Dose interruption	162 (50.0)	184 (56.8)
Treatment discontinuation	50 (15.4)	72 (22.2)

*Adverse events occurring in ≥15% of patients in either arm.
†Pooled terms.

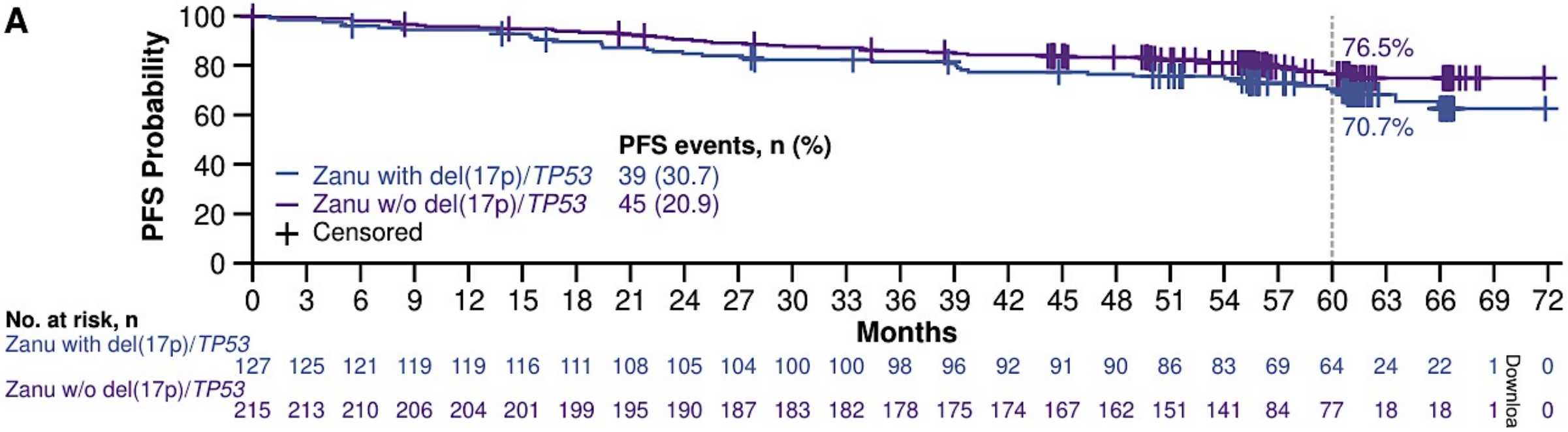
Brown JR, et al. *N Engl J Med*. 2023;388:319-332

SEQUOIA Cohort 1: PFS in Patients Without del(17p) Was Superior with Zanubrutinib vs. BR



Shadman M, et al. *J Clin Oncol*. 2025;43:780-787.

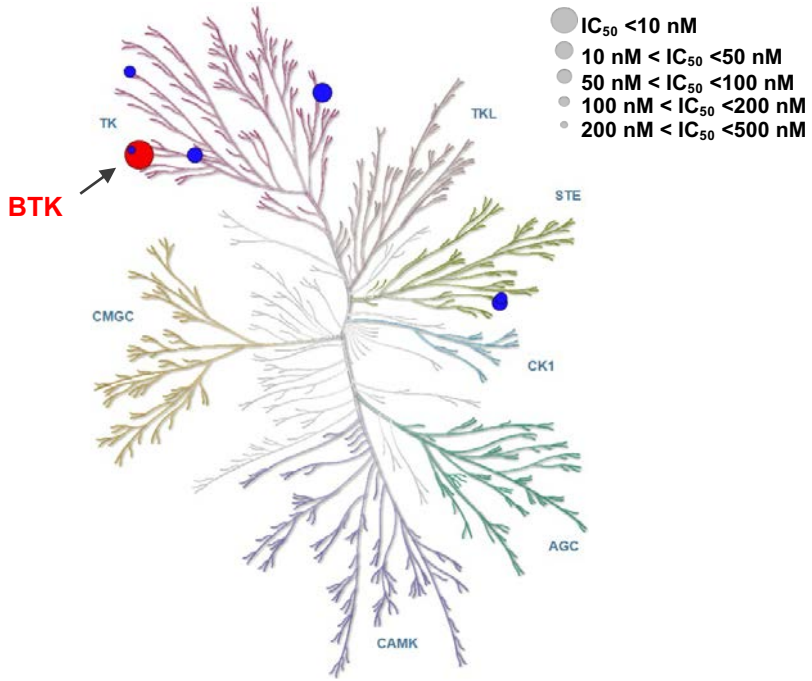
SEQUOIA Arm C: PFS in Patients With del(17p) Had Sustained PFS with Zanubrutinib monotherapy



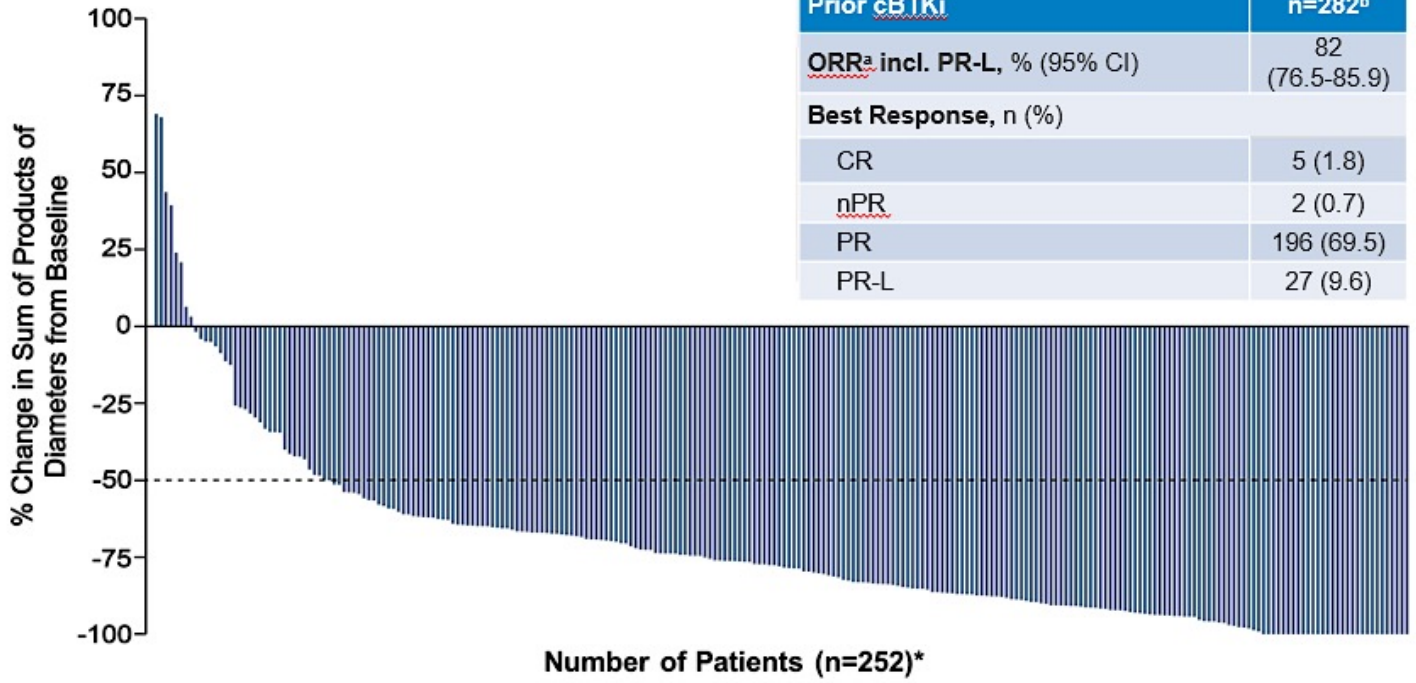
Tam CS et al. *Blood Adv*, 2025;bloodadvances.2025015986

Pirtobrutinib is a highly selective, noncovalent BTK Inhibitor that is highly active in R/R CLL

Highly selective for BTK[1,2]



Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	82 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



- Median PFS for entire study population: 19.4 months

- Inhibits both WT and C481-mutant BTK with equal low nM potency[3]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[3]

1. Mato AR, et al. *Lancet.* 2021;397:892-901. 2. Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(suppl 1):S216. 3. Gomez EB, et al. *Blood*. 2023;142:62-72.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; IC, inhibitory concentration; nM, nanomolar; WT, wild type.

BRUIN 313 and 314 Phase 3 Trials: frontline pirtobrutinib in CLL has arrived

Publication Number: 683

Abstract Title : Pirtobrutinib vs ibrutinib in treatment-naïve and relapsed/refractory CLL/SLL: Results from the first randomized phase III study comparing a non-covalent and covalent BTK inhibitor

Category: 600s - Hematologic Malignancy

Review Category: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological

Authors

Jennifer Woyach[1], Lugui Qiu[2], Sebastian Grosicki[3], Tomasz Wrobel[4], Marcelo Capra[5], Jaroslaw Czyz[6], Shuhua Yi[2], Ki-Seong Eom[7], Anna Panovská[8], Wojciech Jurczak[9], Kamel Laribi[10], Lutz Jacobasch[11], Ross Baker[12], Richy Agajanian[13], Alejandro Berkovits[14], Muhit Özcan[15], Stephane Lepretre[16], Catherine Coombs[17], Paula Cramer[18], Katharine Lewis[19, 20], Marisa Hill[21], Katherine Bao[21], Yuanyuan Bian[21], Amy Ruppert Stark[21], Ching Ching Leow[21], William Wierda[22]

Conclusion: In this first head-to-head study, in cBTKi-naïve CLL/SLL, including pts with treatment naïve CLL, pirtobrutinib demonstrated NI of ORR vs ibrutinib in both ITT and R/R populations. PFS, while not yet mature, trended in favor of pirtobrutinib, with the most pronounced effect in the TN population, which had the longest follow-up at this data cut.

Abstract 87, Sunday, 12/7/25, 5:30-5:45PM, W224ABEF

Publication Number: LBA-3

Abstract Title : Pirtobrutinib vs bendamustine plus rituximab (BR) in patients with CLL/SLL: First results from a randomized phase III study Examining a non-covalent BTK inhibitor in untreated patients

Category: 600s - Hematologic Malignancy

Review Category: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological

Authors

Wojciech Jurczak[1], Michal Kwiatek[2], Jaroslaw Czyz[3], Ederson de Mattos[4], Ki-Seong Eom[5], Alexander Egle[6], Anna Panovská[7], Zhanet Grudeva-Popova[8], Hsuan-Jen Shih[9], Luis Felipe Casado Montero[10], Paolo Sportoletti[11], Vu Minh Hua[12], James D'Olimpio[13], Shinsuke Iida[14], Rodrigo Ito[15], Katherine Bao[15], Anne Fink[15], Weiji Su[15], Amy Ruppert Stark[15], Alejandro Levy[15], Tomasz Wrobel[16]

Conclusions: In BRUIN CLL-313, pirtobrutinib significantly improved IRC-assessed PFS versus BR for pts with treatment-naïve CLL/SLL with one of the largest treatment effects ever observed for a single-agent BTKi against this comparator. Pirtobrutinib was well tolerated, consistent with its known safety profile, with low rates of discontinuation and atrial fibrillation/flutter. While OS data remained immature, a notable trend favoring pirtobrutinib was observed, despite 52.9% of BR pts crossing over to receive pirtobrutinib after PD. Taken together, these data suggest that pirtobrutinib may be considered a potential new standard-of-care treatment for pts with untreated CLL/SLL, including older pts who may receive only one line of therapy.

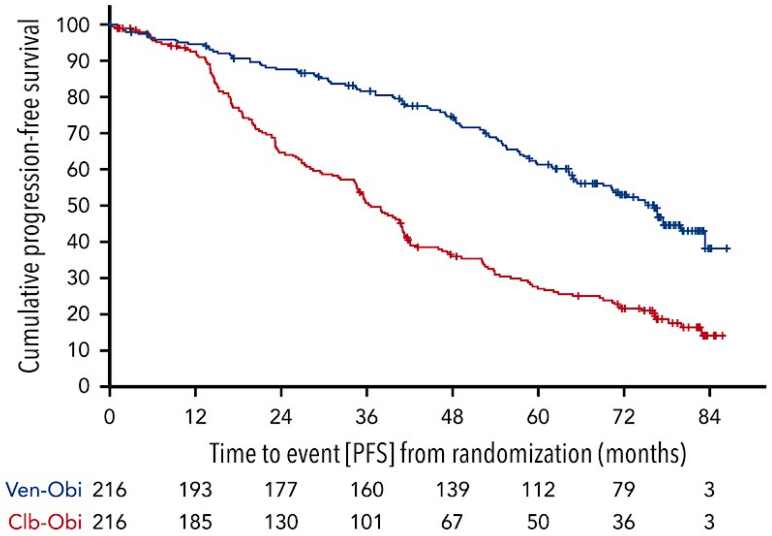
Abstract LBA-3, Tuesday, 12/9/25, 8-8:15AM, West Hall D2

Fixed Duration Ven-Obi vs Chl-Obi

6-Year PFS Follow-Up of CLL14

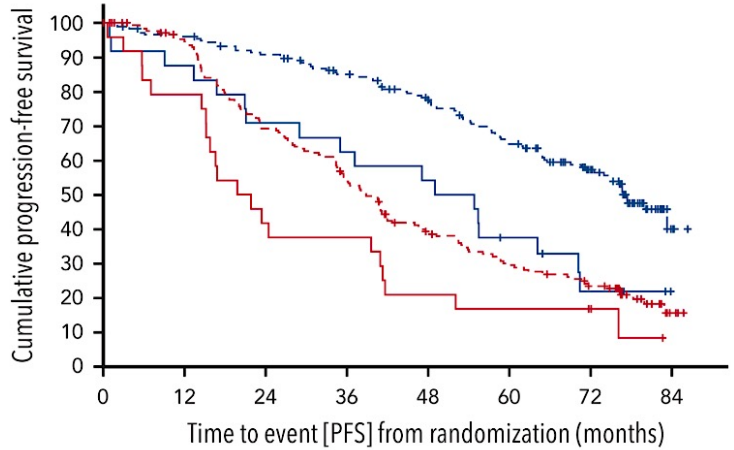
Overall population

A



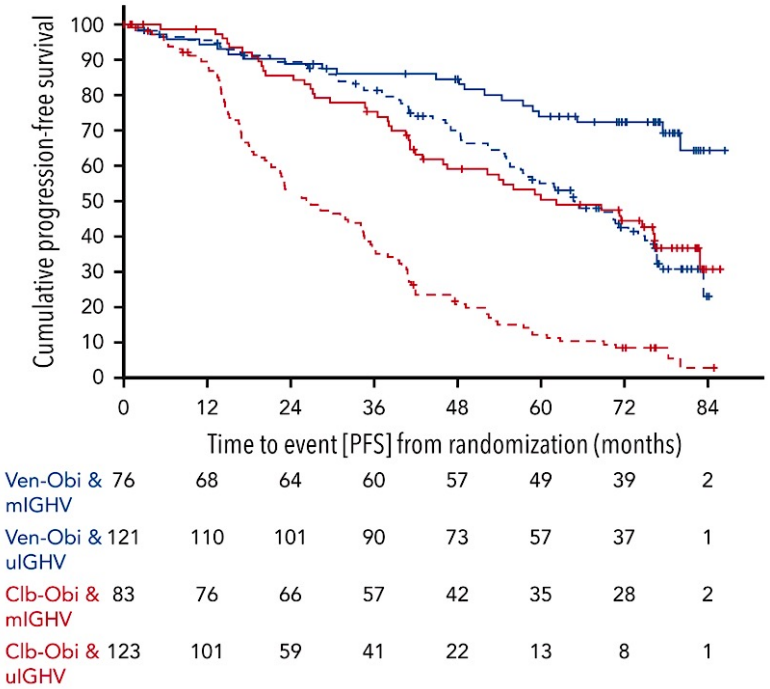
By *TP53* status

B



By IGHV status

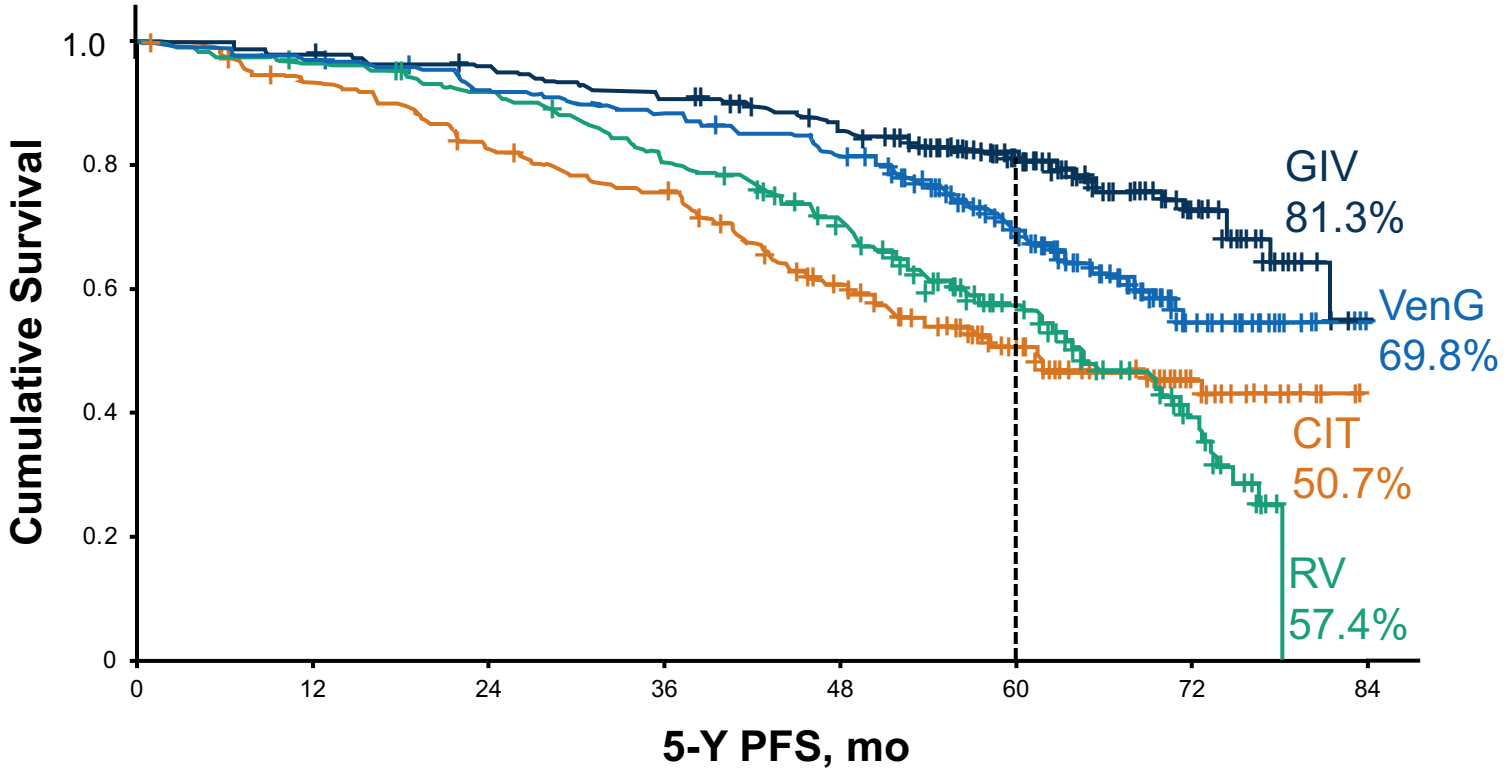
C



Al-Sawaf O et al. *Blood*, 2024;144:1924-1935.

GAIA/CLL13 Showed Long-Term Benefits Ven-based therapy in fit patients

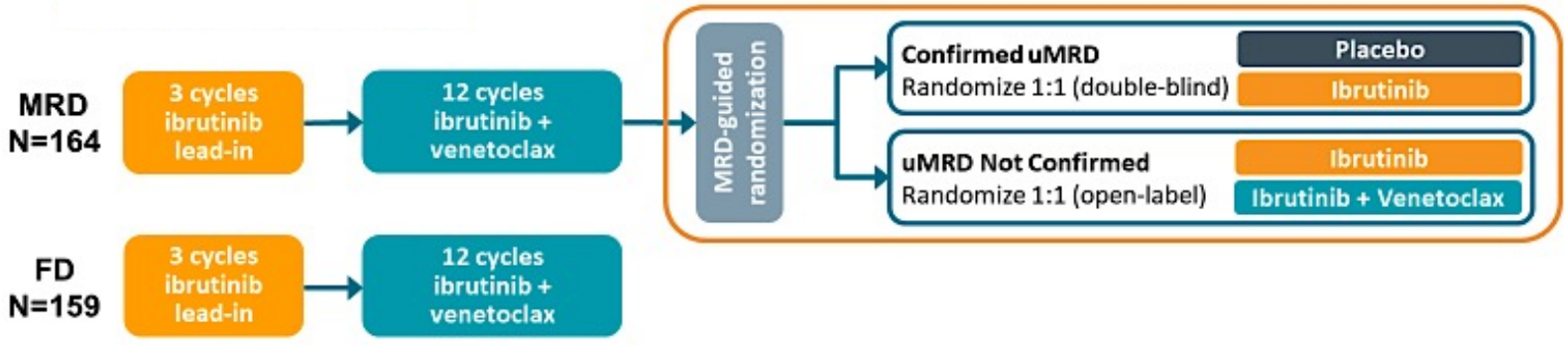
- With >5 years of follow-up, triplet therapy with GIV prolongs PFS vs VenG (likely driven by the difference in patients with uIGHV)[1]
- PFS continues to be superior for VenG and GIV compared with CIT and RV, but no OS differences were observed between treatment groups

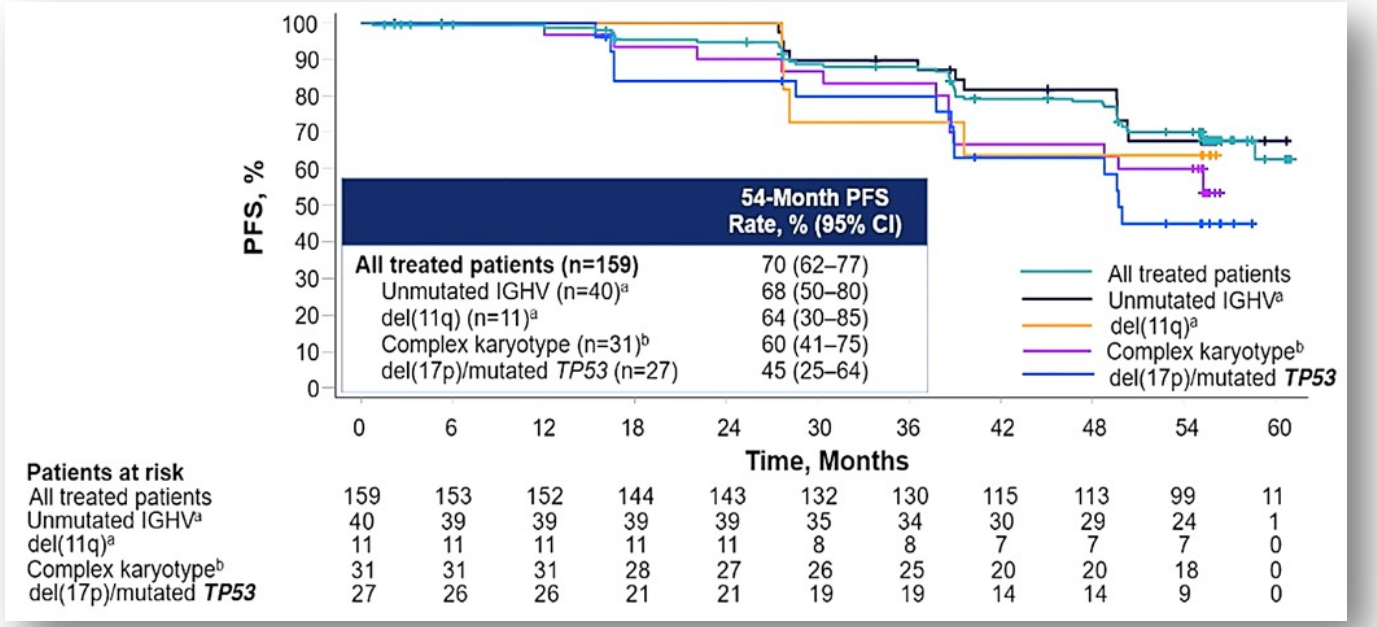


	HR (97.5% CI)	*P*
GIV vs CIT	0.34 (0.24-0.50)	< .001
GIV vs RV	0.35 (0.24-0.51)	< .001
GIV vs VenG	0.61 (0.41-0.91)	.0046
VenG vs RV	0.59 (0.42-0.81)	< .001
VenG vs CIT	Not satisfied	< .001
RV vs CIT	Not satisfied	.53

1. Furstenau M et al. EHA 2025. Abstract S191.

CAPTIVATE MRD Cohort: 5-year follow-up and retreatment data





- Median PFS not yet reached for all genetic subgroups except *TP53* aberrant

Ghia P, et al. *Blood*. 2023;142(1_Suppl):633.

Phase 3 GLOW Study of Fixed-Duration Ibr+Ven vs. Clb+O for TN CLL in Elderly or Unfit Patients

Key Eligibility Criteria

- Previously untreated CLL
- ≥65 years of age or <65 years with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known *TP53* mutation
- ECOG PS ≤2

R 1:1

Ibrutinib 420 mg po qd lead-in (3 cycles) followed by **ibrutinib + venetoclax (Ibr+Ven)** (12 cycles; venetoclax ramp-up 20-400 mg over 5 weeks beginning C4)
n=106

Chlorambucil (Clb) 0.5 mg/kg on D1 & D15 x 6 cycles
+
Obinutuzumab (O) 1000 mg D1-2, D8, D15 of C1, and D1 of C2-6
n=105

Primary endpoint
- IRC-assessed PFS

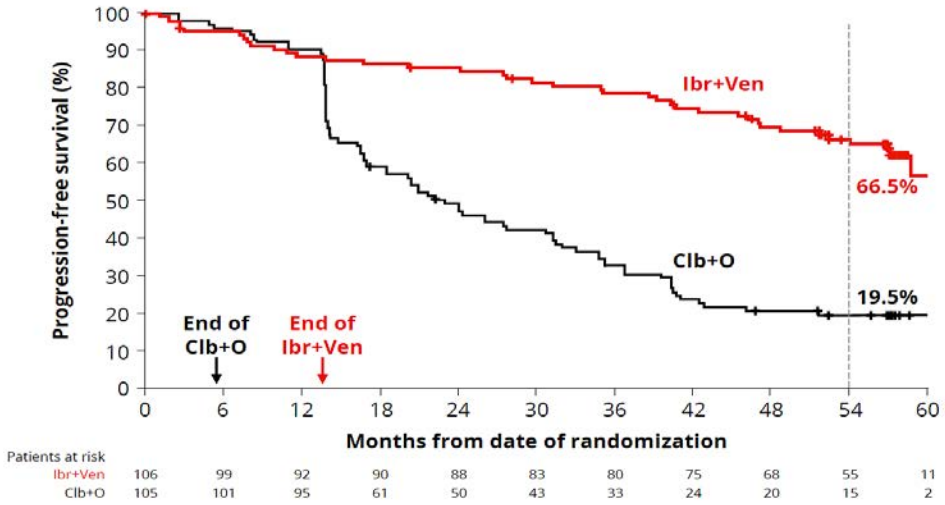
Key secondary endpoints
- uMRD rates, CRR, ORR OS, TTNT, safety

Safety	Ibr+Ven (n=106)		Clb+O (n=105)	
Total number of deaths	19		39	
Reasons for deaths, n	On treatment	Post randomized treatment[a]	On treatment	Post randomized treatment[a]
Infection related	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2[b]	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	**7**	**12**	**2**	**37**

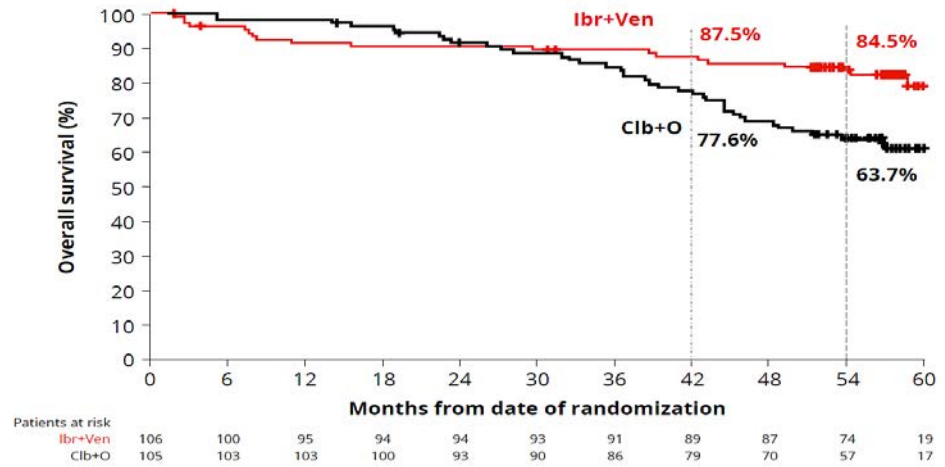
[a] Either before or after initiation of subsequent antileukemic therapy. [b] 1 patient had 3 causes of death: tachy-brady syndrome, cardiac failure, and pneumonia.

Moreno C, et al. *Blood.* 2023;142(1_Suppl):634.

INV-Assessed PFS (Median Follow-Up: 57 Months)



OS (Median Follow-Up: 57 Months)[2]



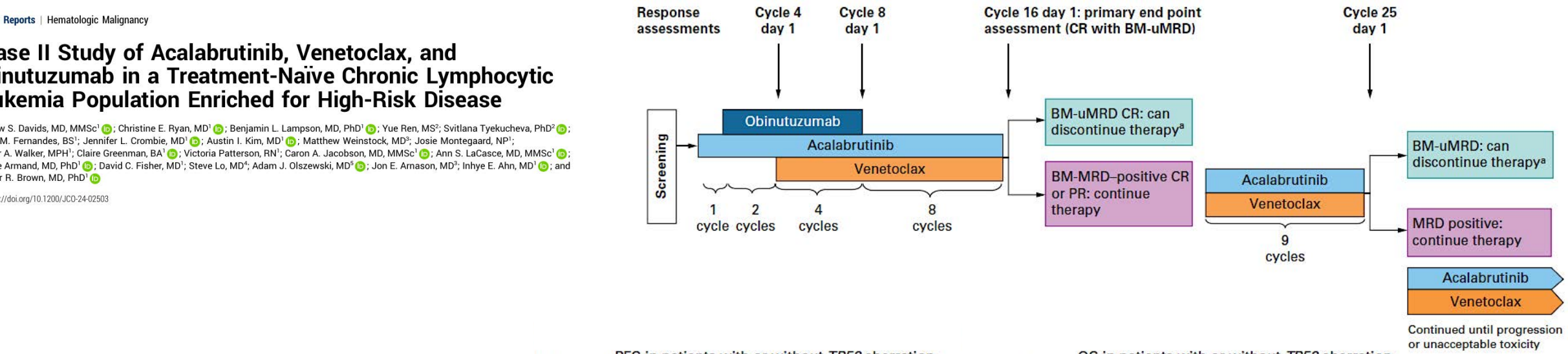
Phase 2 AVO Study in Population Enriched for High Risk CLL

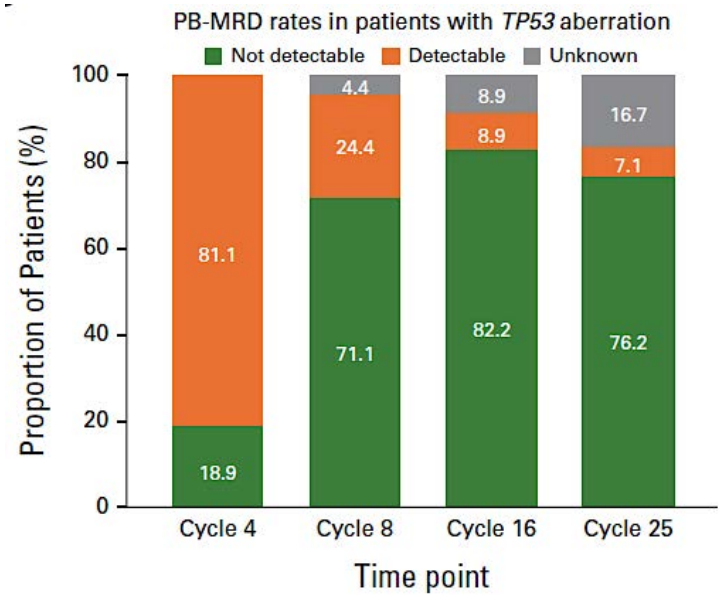
Original Reports | Hematologic Malignancy

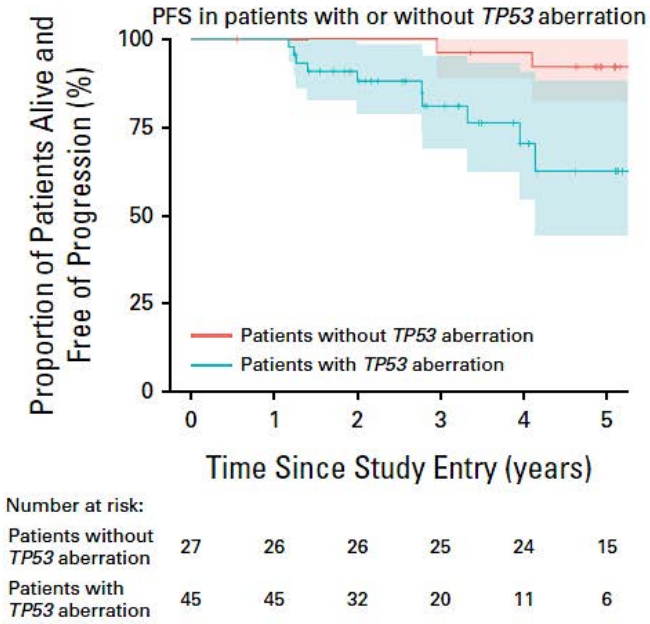
Phase II Study of Acalabrutinib, Venetoclax, and Obinutuzumab in a Treatment-Naïve Chronic Lymphocytic Leukemia Population Enriched for High-Risk Disease

Matthew S. Davids, MD, MMSc[1]; Christine E. Ryan, MD[1]; Benjamin L. Lampson, MD, PhD[1]; Yue Ren, MS[2]; Svitlana Tyekucheva, PhD[2]; Stacey M. Fernandes, BS[1]; Jennifer L. Crombie, MD[1]; Austin I. Kim, MD[1]; Matthew Weinstock, MD[3]; Josie Montegaard, NP[1]; Heather A. Walker, MPH[1]; Claire Greenman, BA[1]; Victoria Patterson, RN[1]; Caron A. Jacobson, MD, MMSc[1]; Ann S. LaCasce, MD, MMSc[1]; Philippe Armand, MD, PhD[1]; David C. Fisher, MD[1]; Steve Lo, MD[4]; Adam J. Olszewski, MD[5]; Jon E. Arnason, MD[3]; Inhye E. Ahn, MD[1]; and Jennifer R. Brown, MD, PhD[1]

DOI https://doi.org/10.1200/JCO-24-02503

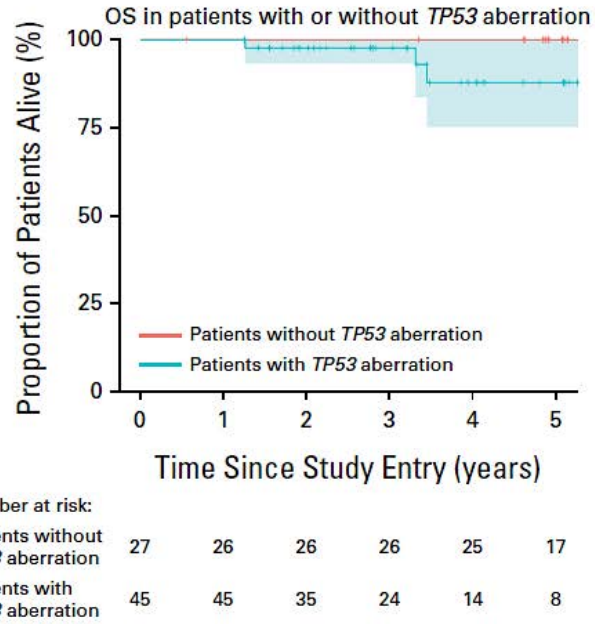






Number at risk:

Patients without *TP53* aberration	27	26	26	25	24	15
Patients with *TP53* aberration	45	45	32	20	11	6

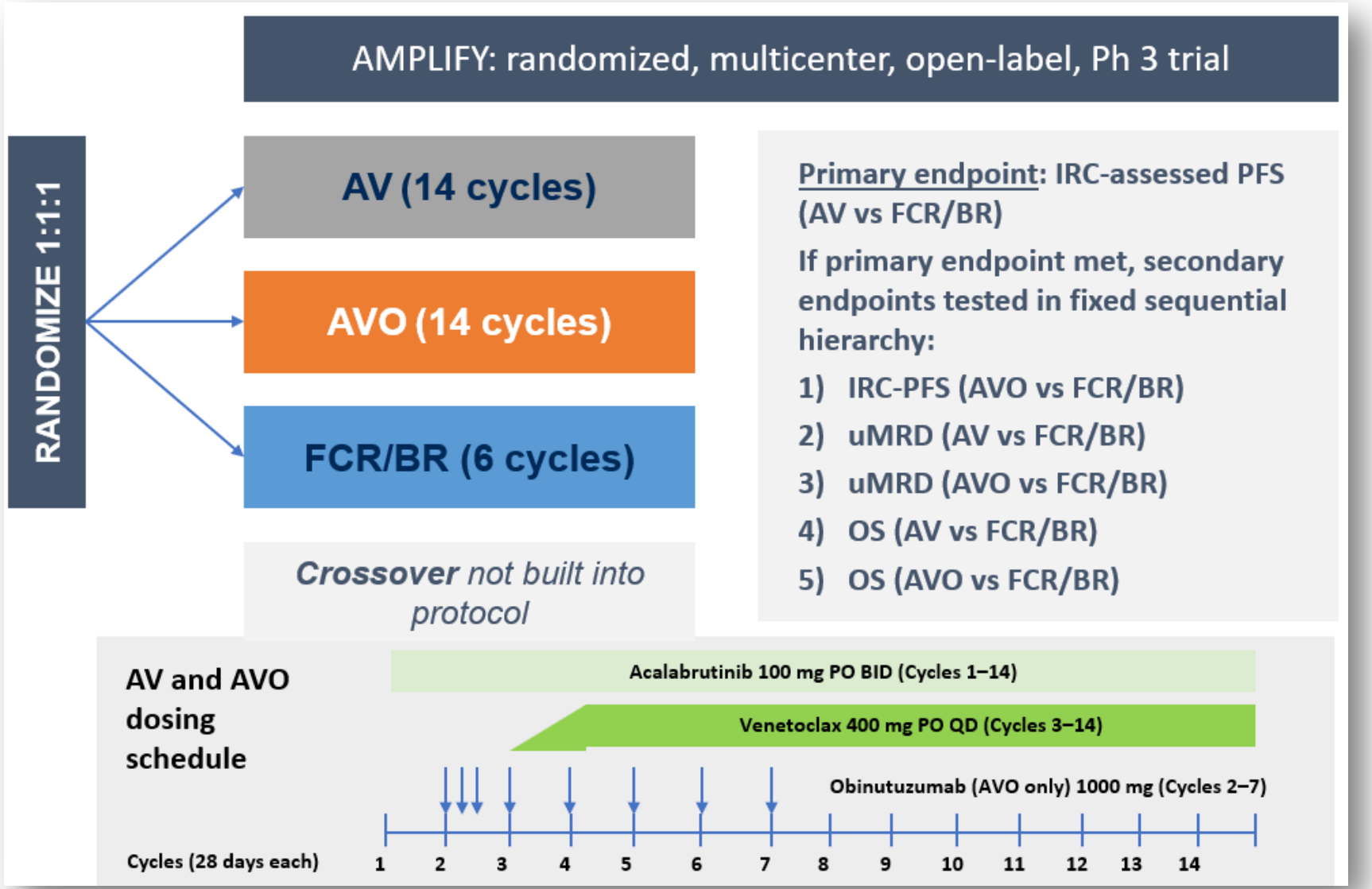


Number at risk:

Patients without *TP53* aberration	27	26	26	26	25	17
Patients with *TP53* aberration	45	45	35	24	14	8

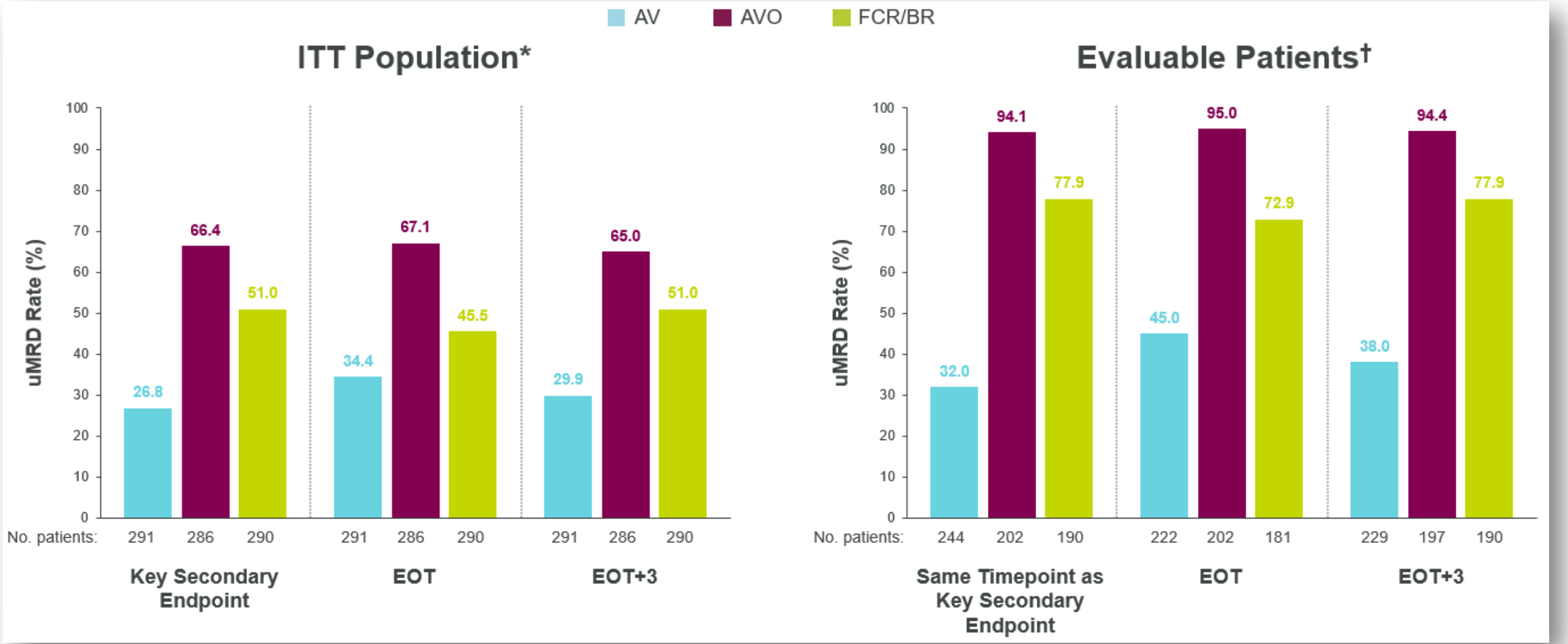
Davids MS et al. *J Clin Oncol*, 2025;43:788-799.

Phase 3 AMPLIFY Study



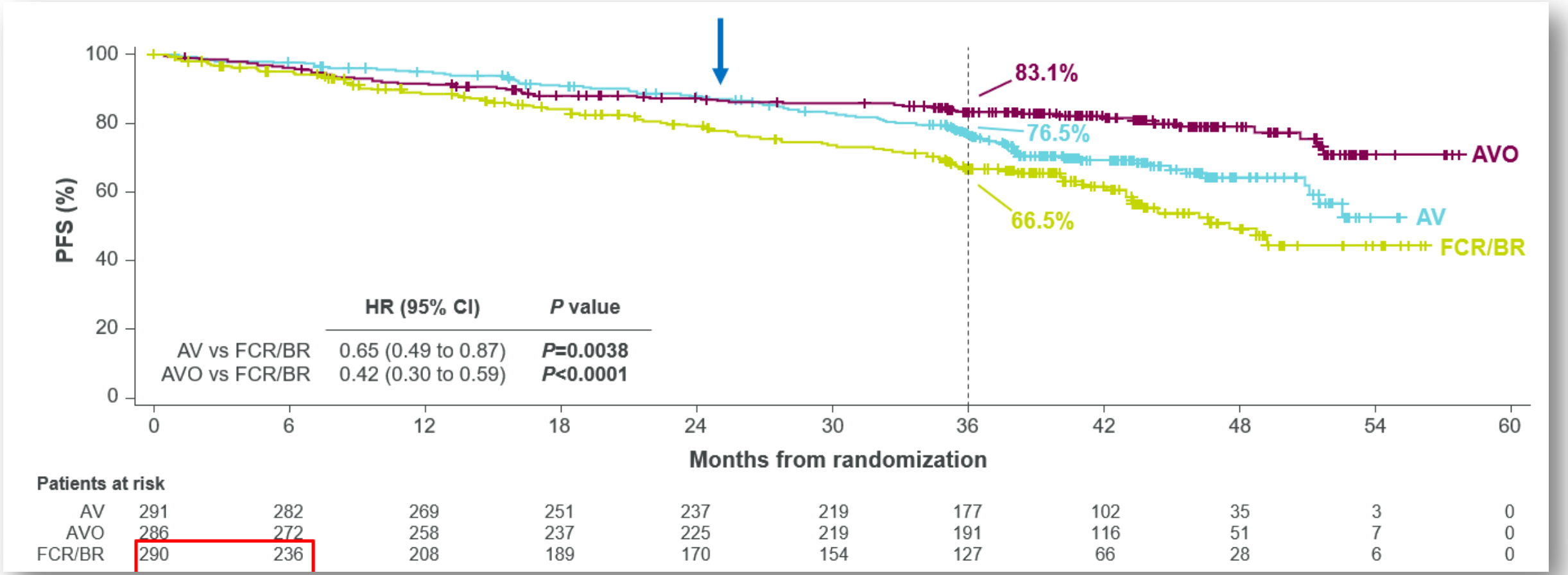
Brown JR et al. *NEJM*. 2025;392:748-762.

Phase 3 AMPLIFY Study



Brown JR et al. *NEJM*. 2025;392:748-762.

Phase 3 AMPLIFY Study

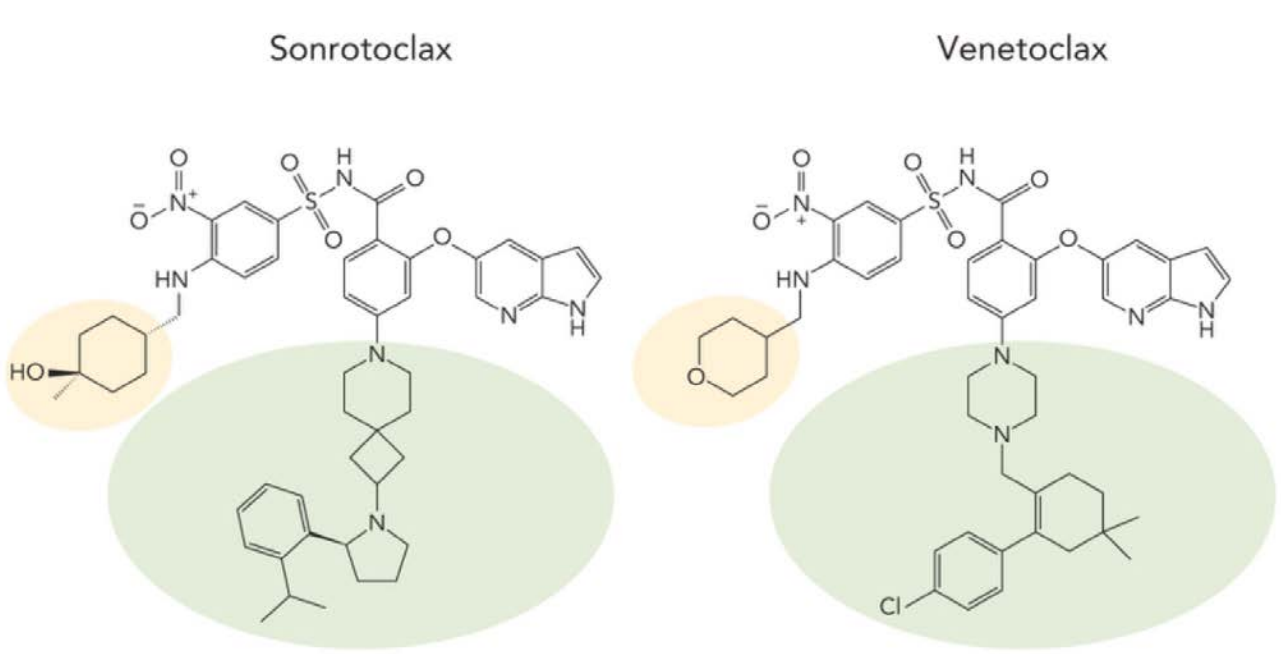


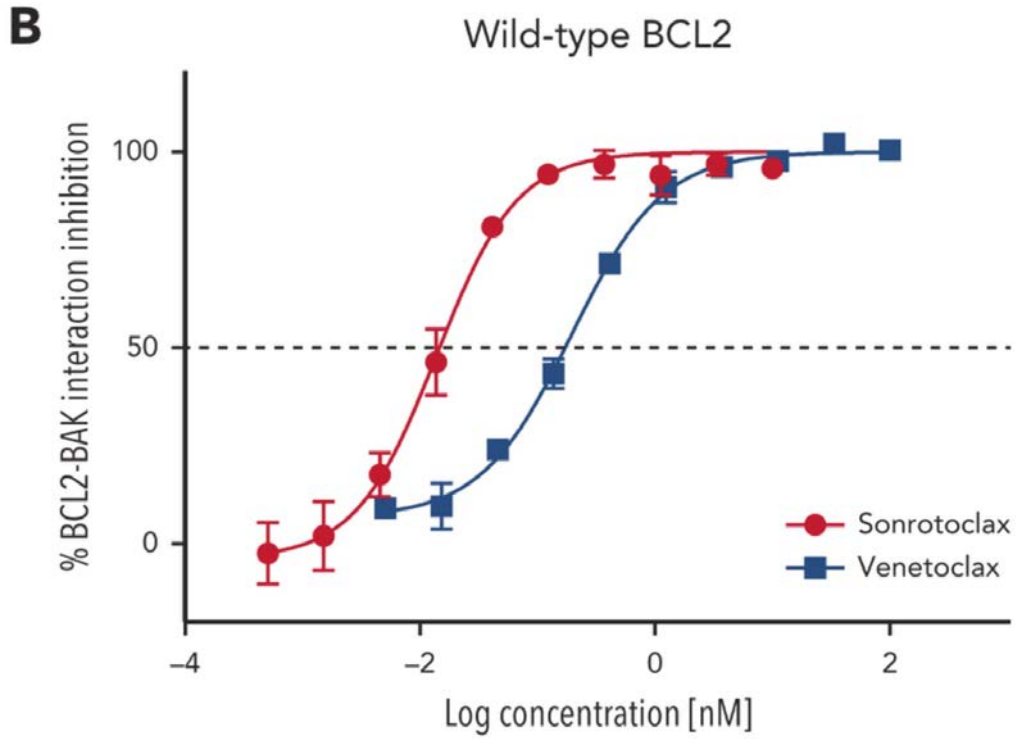
Benefit of AVO seen primarily in uIGHV:

	HR (95% CI)		HR (95% CI)
AV vs **FCR/BR** (mIGHV)	0.67 (0.39–1.14)	**AV** vs **FCR/BR** (uIGHV)	0.69 (0.48–0.97)
AVO vs **FCR/BR** (mIGHV)	0.58 (0.32–1.02)	**AVO** vs **FCR/BR** (uIGHV)	0.35 (0.23–0.53)

Brown JR et al. *NEJM*. 2025;392:748-762.

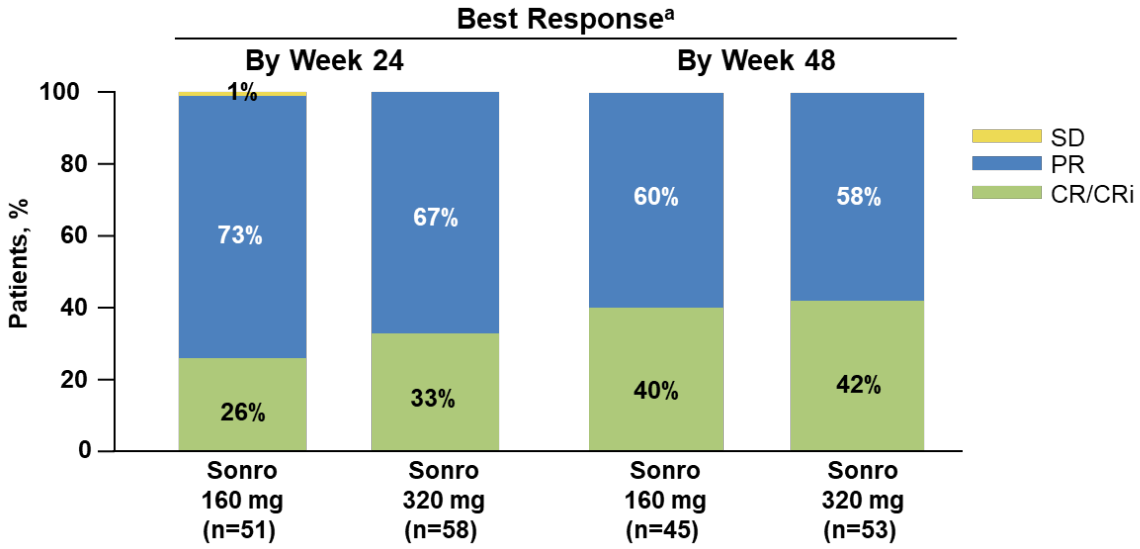
Sonrotoclax is a Next-Generation, Potent and Selective BCL2 inhibitor

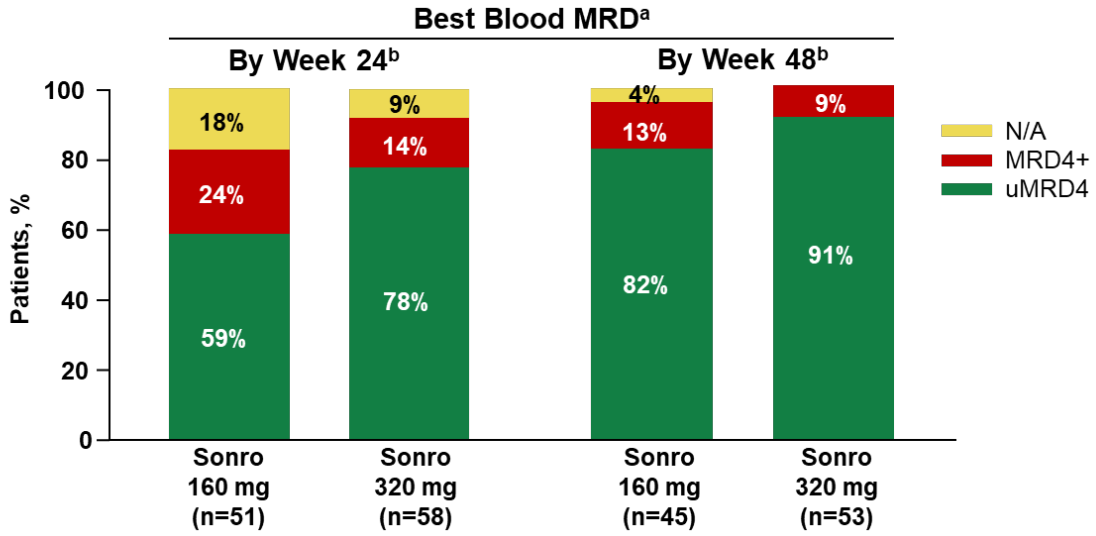


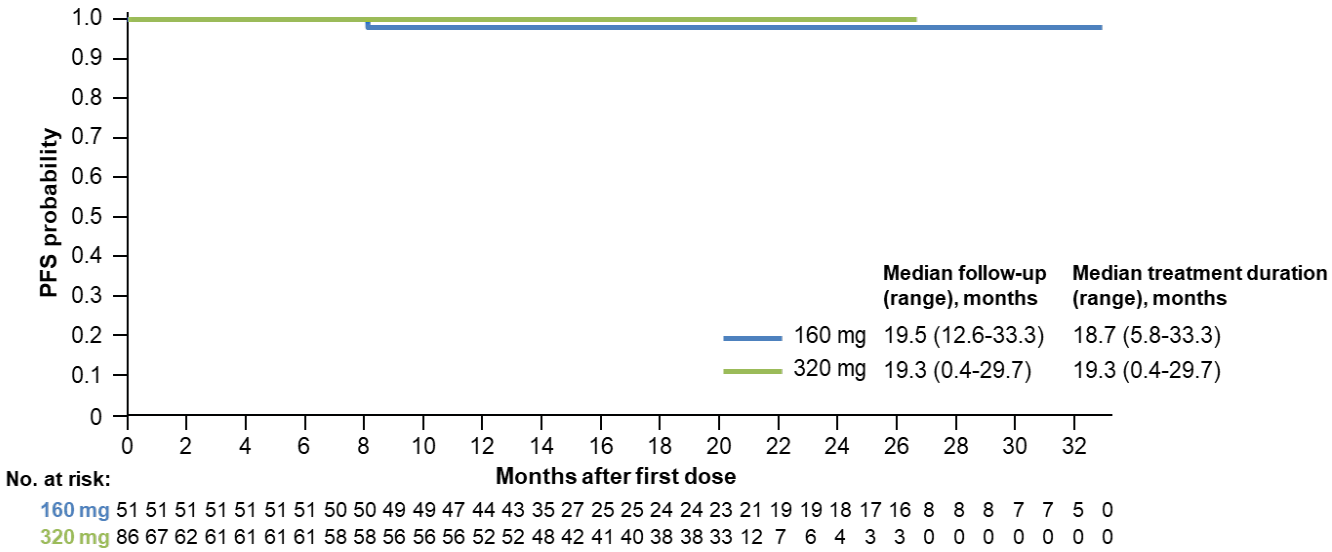


Liu J et al. Blood. 2024;143(18):1825-1836.

Next Generation BCL-2i Sonrotoclax Plus Zanubrutinib is Active and Well-Tolerated in 1L CLL

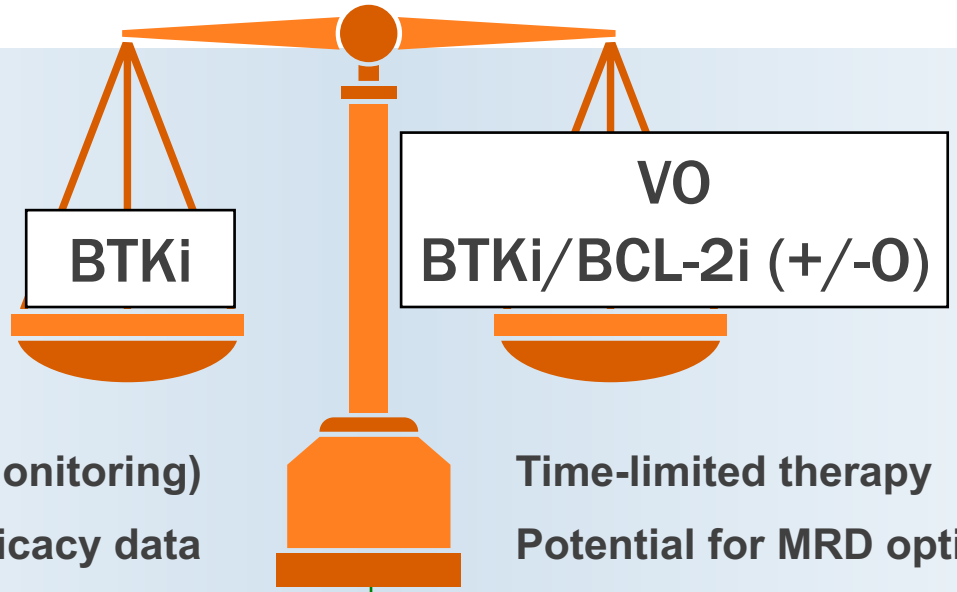






Soumerai JD et al. *Blood*. 2024;144(1_Suppl):1012.

Continuous BTKi vs. Time-Limited Ven Combos in TN CLL: Clinical Considerations



Convenience (no infusions or TLS monitoring)

Longer-term efficacy data

Prospective data for efficacy of venetoclax at time of BTKi progression

Indefinite treatment

Potential for cumulative cardiac toxicity

Time-limited therapy

Potential for MRD optimization

Lower cardiac or bleeding risks

Less concern with long-term adherence

Potential for cost-savings

Possibility of retreatment

Time-intensive (infusions, venetoclax ramp-up)

The CLL17 trial is comparing continuous BTKi to time-limited venetoclax-based doublets

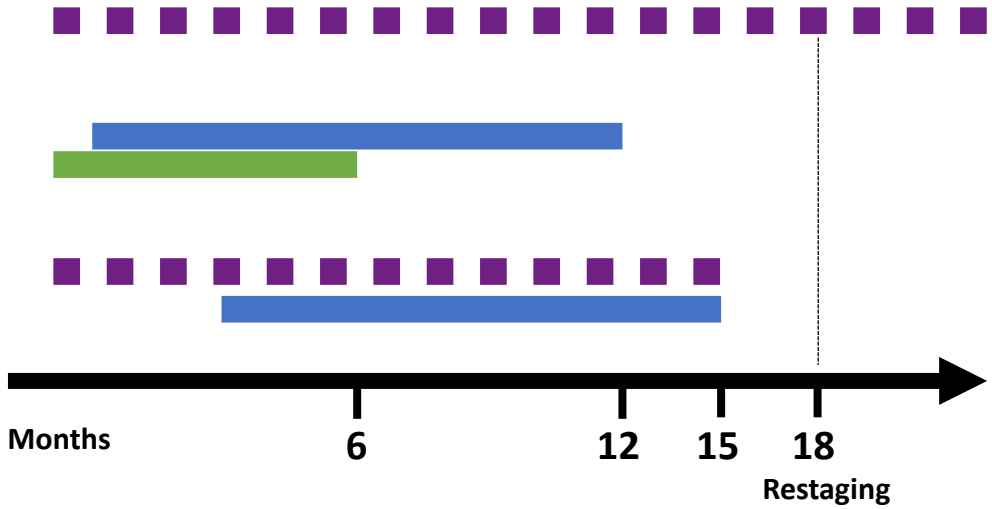
CLL17[1,2]

Phase 3 trial in 1L CLL, including those with adverse prognostic factors

Abstract **1**, Sunday, 12/7/25, 2:05-2:20PM, West Hall D2

Ibr mono | Ven + Obin | Ven + I

Stratification by fitness, del(17p)/*TP53*^{mut}, IGHV
RANDOMIZATION[2]



Ibrutinib D1 420 mg PO daily until PD or intolerance

Venetoclax 400 mg PO daily (C1 D22 – C12 D28)
Obinutuzumab 1000 mg IV (C1 D1(2)/8/15, C2–6 D1)

Ibrutinib 420 mg PO daily (C1 D1 – C15 D28)
Venetoclax 400 mg PO daily (C4 D1 – C15 D28)

1. ClinicalTrials.gov. NCT04608318. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04608318 (accessed August 2021);
2. DCLLSG. CLL17 Trial. Available at: https://www.dcllsg.de/en/trial/cll17/CLL17_Synopsis_v1.2_20200923.pdf (accessed August 2021)

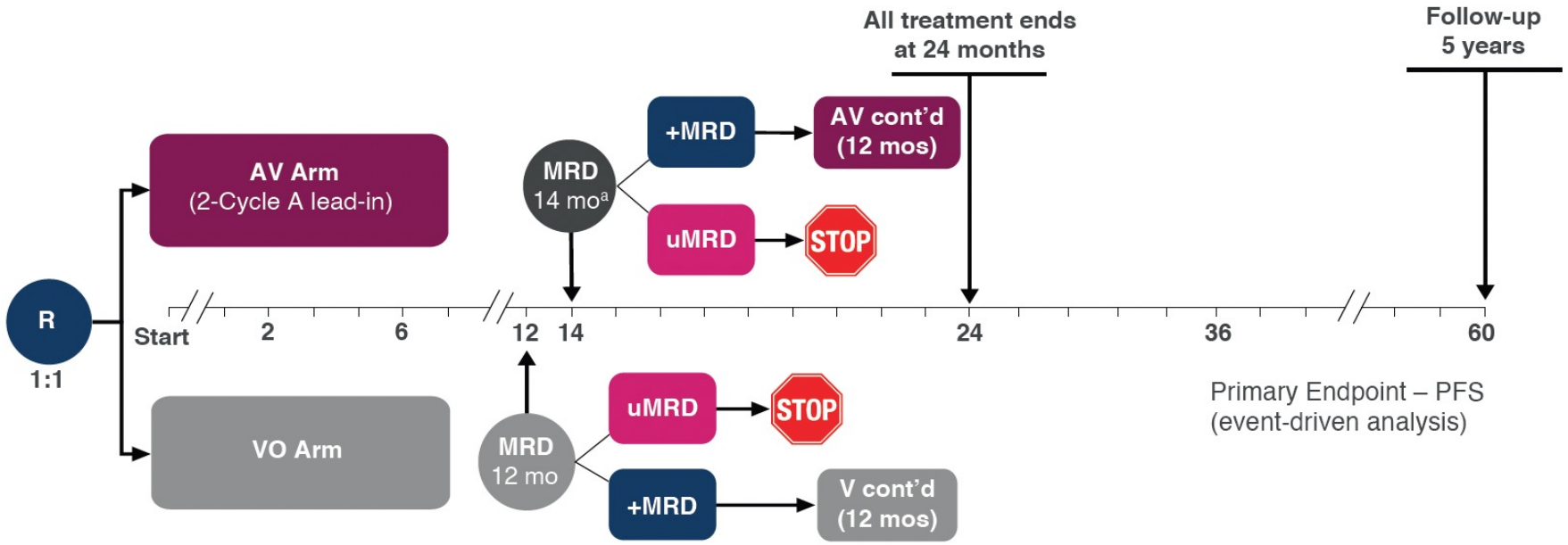
The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL treatment

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

Key Eligibility Criteria

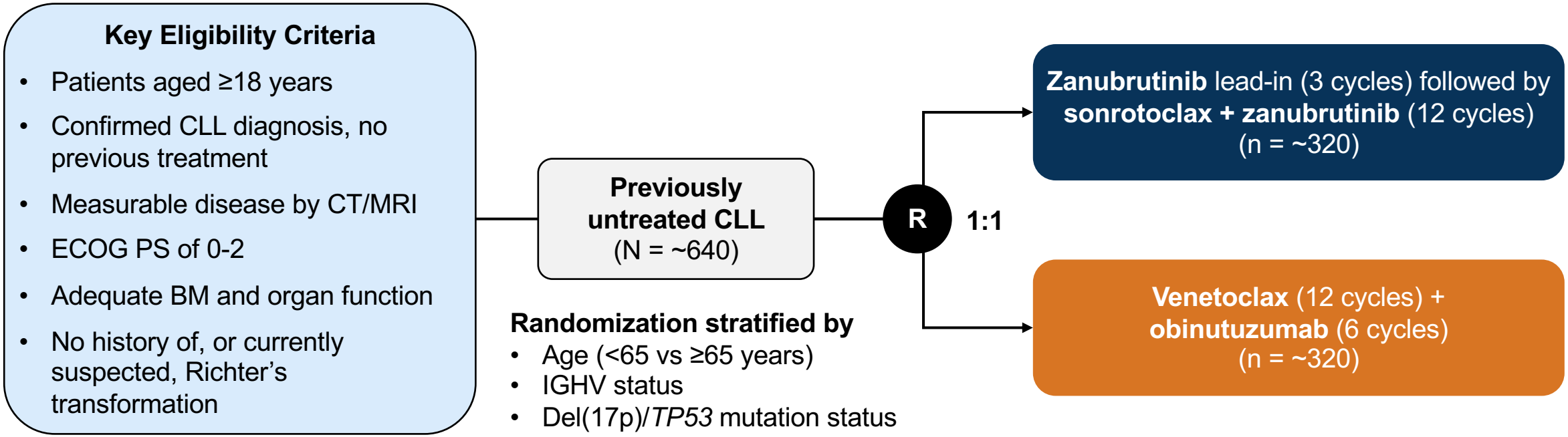
- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS



Davids MS et al. *Blood*. 2021;138(1_Suppl):1553.

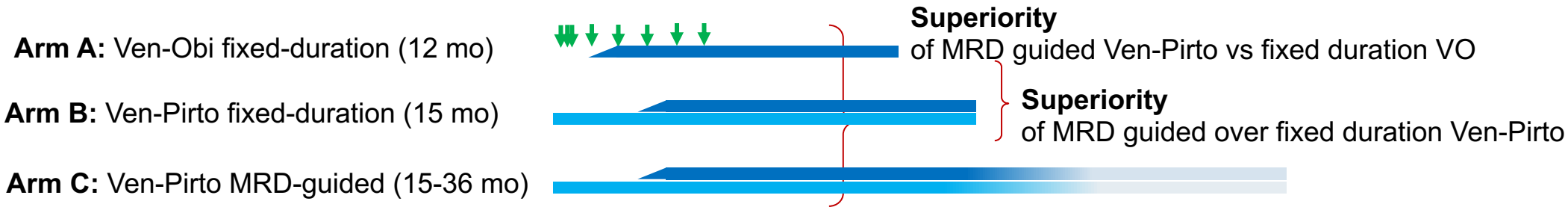
CELESTIAL-TN: Zanubrutinib-Sonrotoclax is Being Assessed in TN-CLL



- **Primary endpoints:** PFS (IRC; iwCLL 2018)
- **Secondary endpoints:** CRR (IRC and INV), rates of uMRD4 (BM and PB), OS, PFS (INV), ORR (IRC and INV), DOR (IRC and INV), patient-reported outcomes, safety, and tolerability

Shadman M et al. ASCO 2024;Abstract TPS7087.

CLL18 TRIAL (GCLLSG)



Primary endpoint: PFS

Assumptions: PFS @36 months: 80% for arms A & B, 90% for arm C.

Test design: Two-sided 2.5% significance level per each superiority testing with targeted hazard ratio = 0.472

1:1:1 randomization

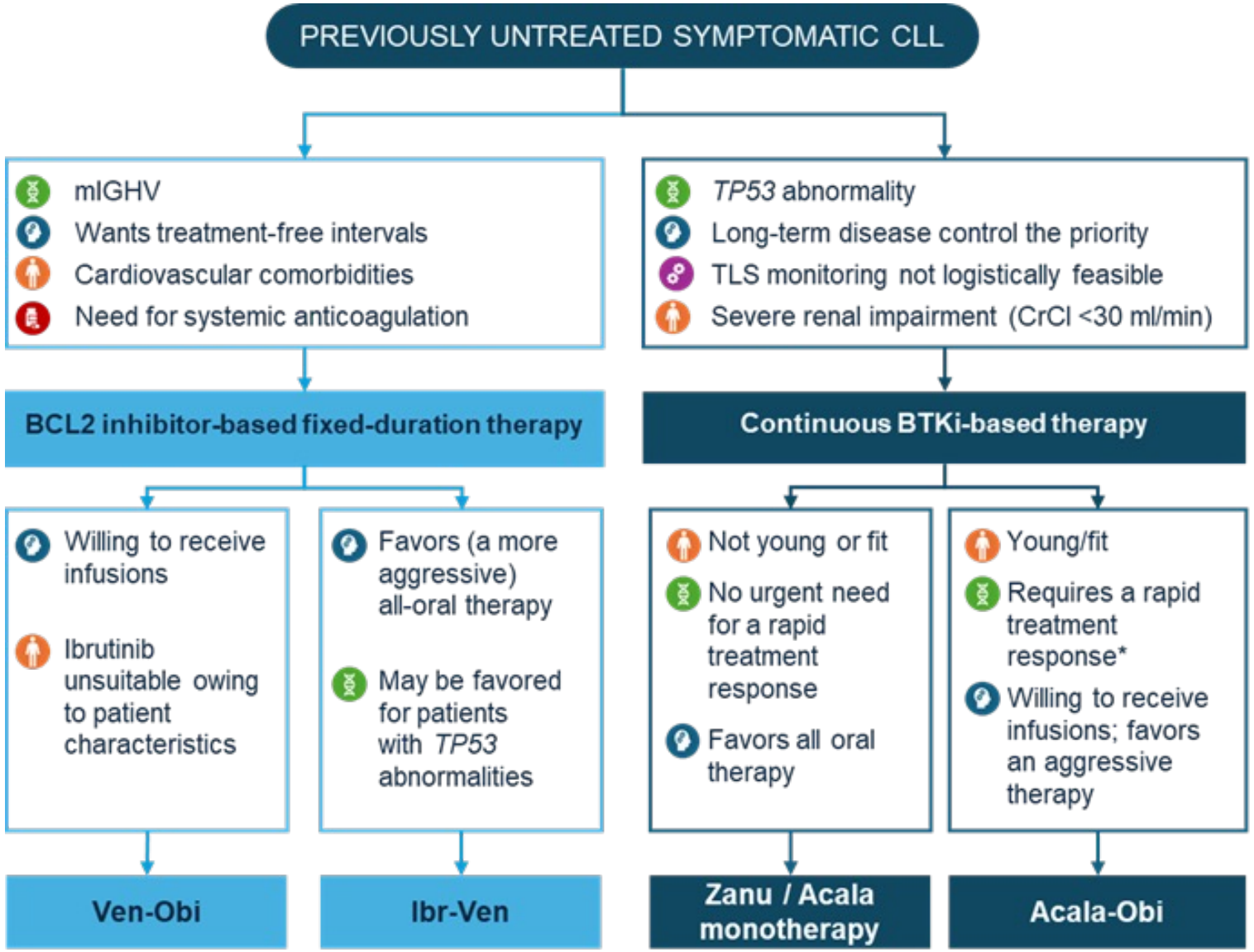
Total required sample size: 813 pts (271 per arm)

Recruitment rate: 50 pts per month, 20 pts per month during months 1-6
Analysis time points:

- Accrual period: 20 months
- PFS final analysis as soon as 68 events are reached for each superiority testing (approximately month 41)

(slide courtesy of PI, Dr Paula Cramer)

Toward a more practical guide to optimal frontline CLL therapy



Speaker's Personal Opinion

Dana-Farber Cancer Institute

Harvard Medical School

Frontline CLL Treatment: Key Take-Aways

- Role of CIT in CLL is now very limited
- Continuous covalent (c) BTKi is a highly effective approach
- 2nd-gen cBTKi (acala and zanu) now preferred over ibrutinib
- VO, IV (ex-US), AV, and AVO: time-limited regimens with durable benefit
- Continuous vs time-limited therapy discussions should be individualized, data are coming
- 1L MRD-guided therapy duration, non-covalent BTKi, new BCL-2i are on the horizon
- CLL remains a dynamic, fast-changing field with continually improving patient outcomes

Case Presentation: 75-year-old man with a plethora of comorbidities but good performance status requires treatment for CLL

Dr Tina Bhatnagar (Wheeling, West Virginia)

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Discussion Questions

How do you typically manage CLL-related autoimmune hemolytic anemia?

In addition to the AMPLIFY regimen, what other treatment options would you have discussed with the patient?

How does a history of CAD affect your initial treatment recommendation for a patient with CLL?

Dr Jennifer Yannucci
(Savannah, Georgia)

Case Presentation: 50-year-old man, a Jehovah's Witness under observation for IGHV-mutated CLL, develops pulmonary emboli and worsening lymphadenopathy and is anticoagulated and started on zanubrutinib

Dr Zanetta Lamar
(Naples, Florida)

Case Presentation: 75-year-old man with history of atrial fibrillation on apixaban receives zanubrutinib

Discussion Questions

Do you believe older patients are less interested in time-limited therapy?

How would you have managed this case? How do you choose between acalabrutinib and zanubrutinib?

Discussion Questions

How, if at all, does the specific type of anticoagulation a patient is receiving affect your use of BTKis?

Does your approach to CLL treatment vary for patients who are not able to receive blood products? If so, in what manner?

What, if any, is the nonresearch role of MRD assays in CLL?

Agenda

Module 1: Current and Emerging Approaches to First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Davids

Module 2: Optimal Management of Adverse Events with Bruton Tyrosine Kinase and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Prof Tam

Module 3: Selection and Sequencing of Therapy for Relapsed/Refractory CLL — Dr Woyach

Module 4: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Fakhri

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

Constantine Tam
Alfred Hospital and Monash University
Victoria, Australia

Considerations of BTKi vs BCL2i

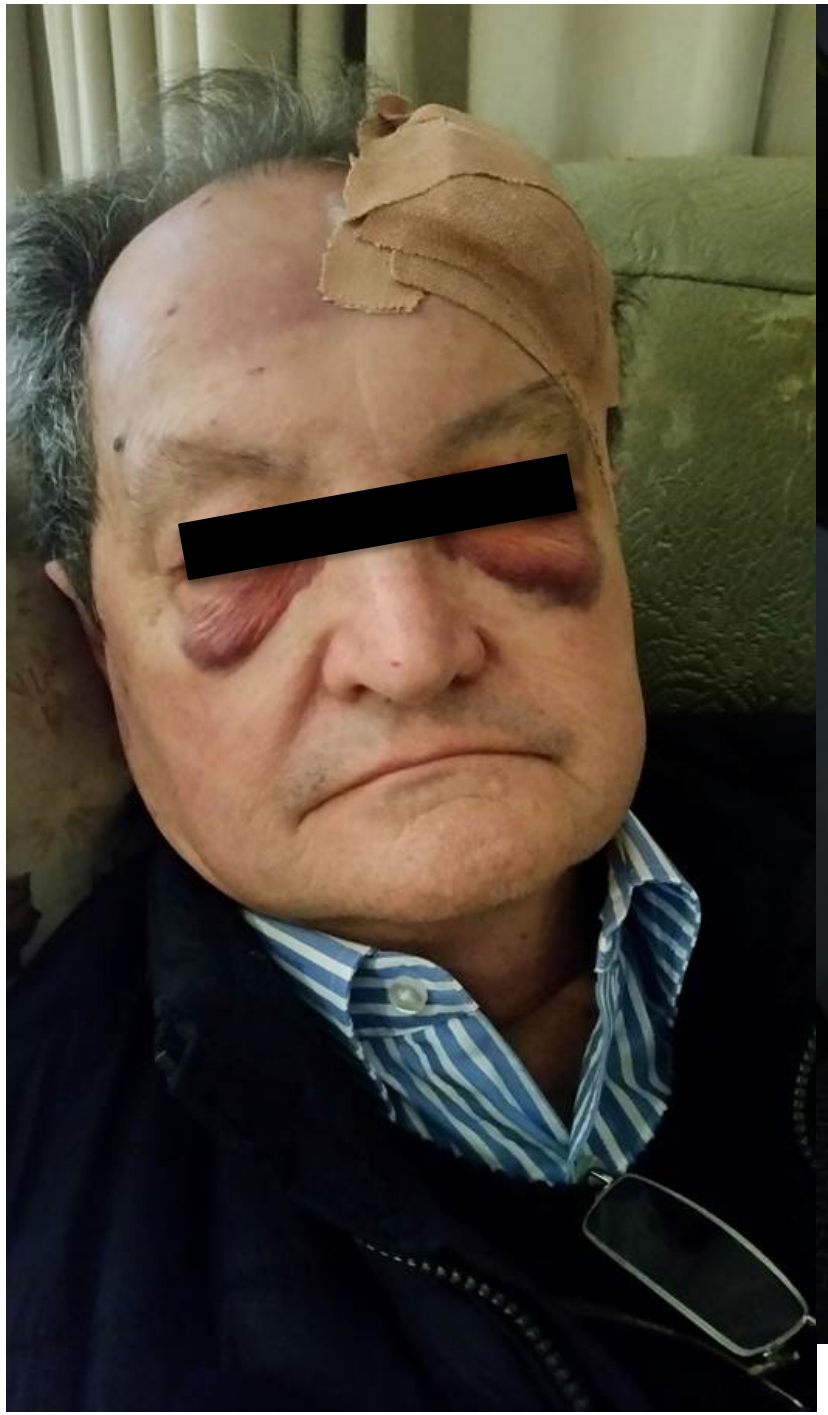
	BTKi	BCL2i
Advantages	• Effective in all prognostic groups • Easy to initiate • Low Risk of TLS	• Limited duration therapy • Low toxicity once ramped up
Disadvantages	• Continuous therapy • **Cardiovascular side-effects** • **Bleeding side-effects**	• IgHV and *TP53* aberrant ↓PFS • **TLS risk**

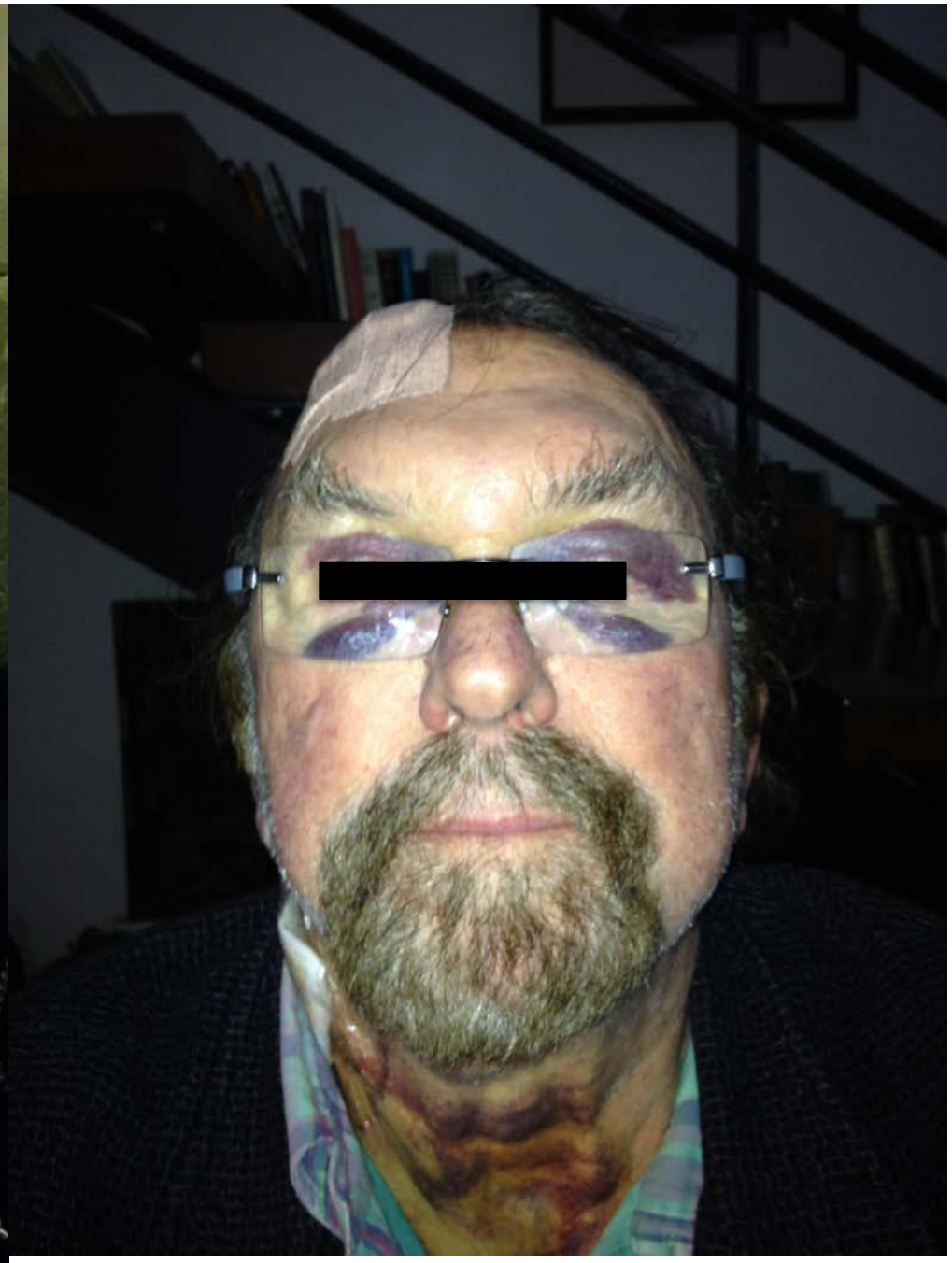
Drug interactions

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

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

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

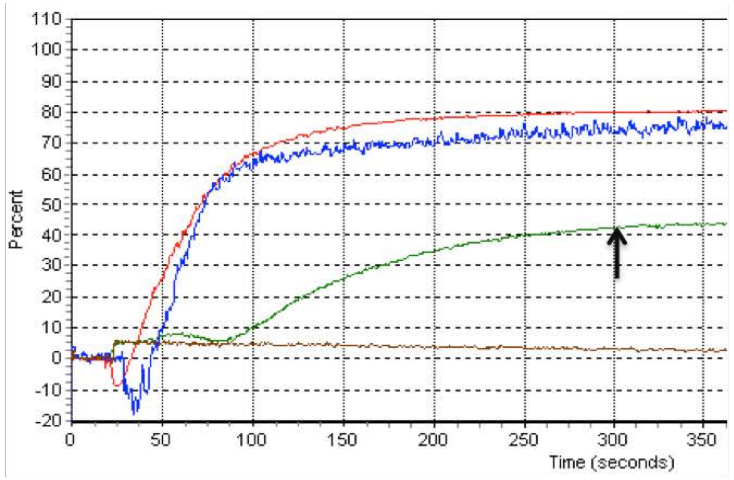




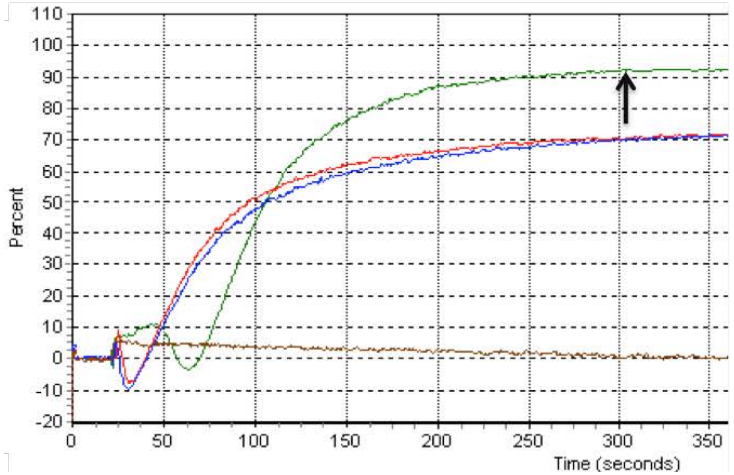
Cases supplied by Dr C S Tam

Discovery of Platelet Inhibition by Ibrutinib

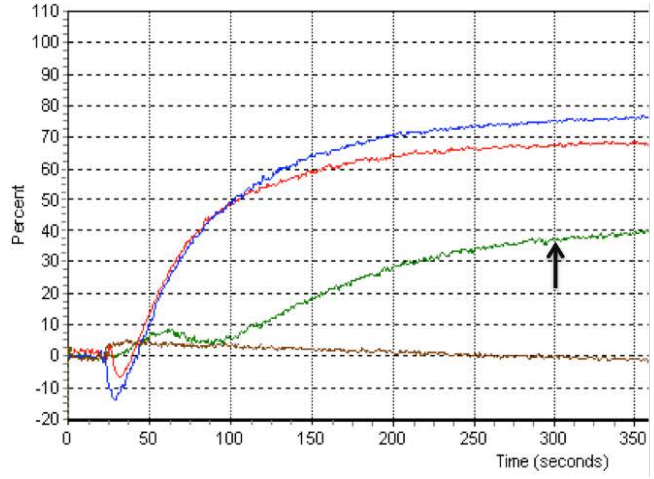
2A: STABLE IBRUTINIB THERAPY



2B: CEASED IBRUTINIB FOR 1 WEEK



2C: RESTARTED IBRUTINIB FOR 1 WEEK



collagen 10ug/ml

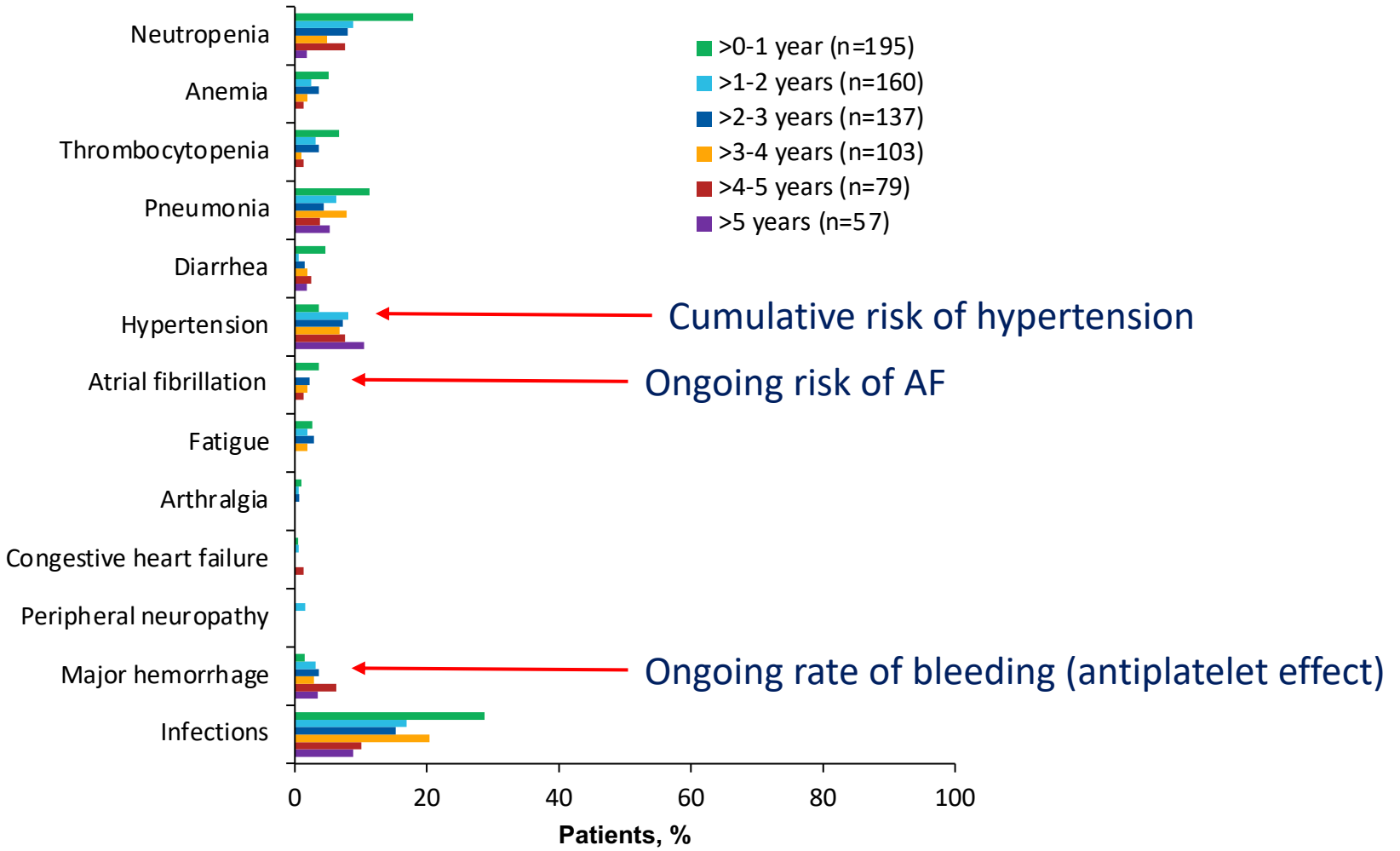
high dose ADP (5.0uM)

low dose ADP (2.5uM)

saline control

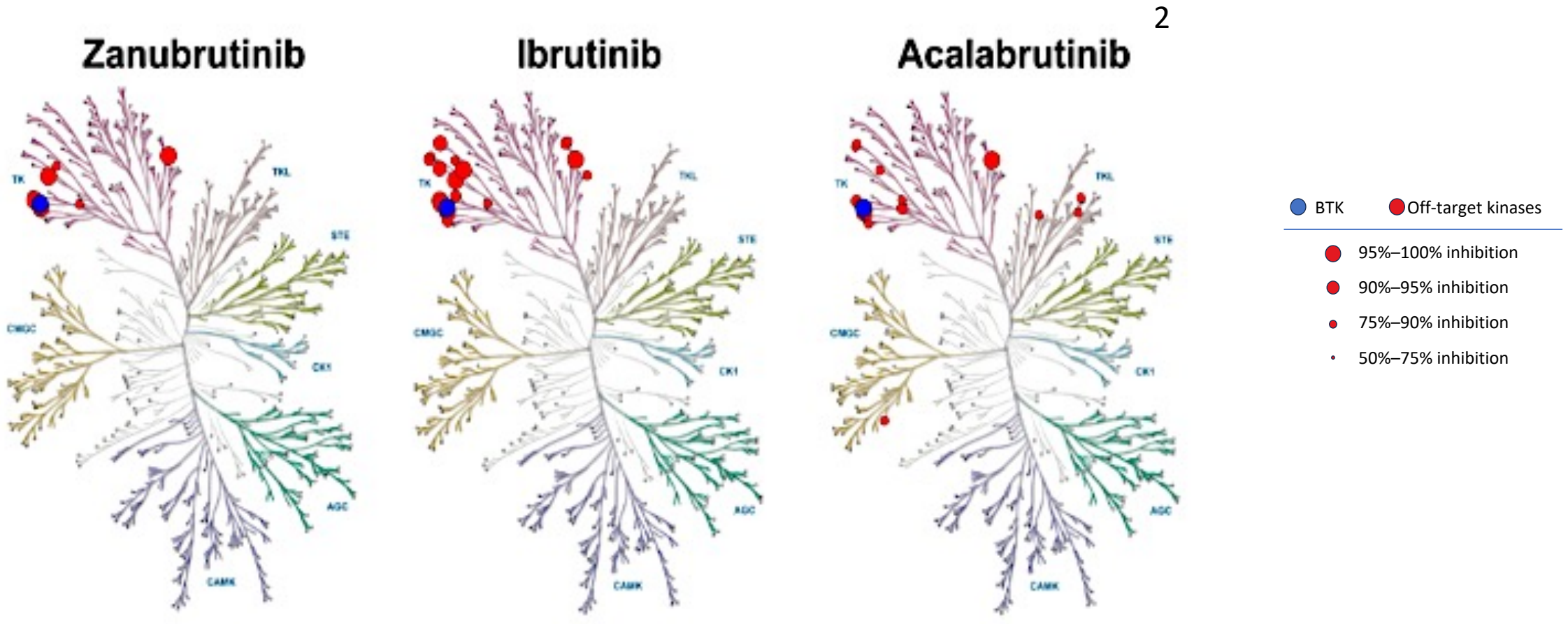
Kamel et al., Leukemia. 2015; 29(4): 783-7; Levade et al., Blood. 2014; 124(26): 3391-5

RESONATE: Grade ≥3 AEs of Clinical Interest with Ibrutinib



Munir T *et al. Am J Hematol* 2019;94(12):1353–63

Second-generation BTKis are more specific[1–3]



The clinical significance of zanubrutinib pharmacokinetic data has not been established and does not necessarily predict clinical effects

1. Herman SEM et al. *Clin Cancer Res* 2017;23:2831–41; 2. Shadman M et al. *Blood* 2021;138(Suppl_1):1410; 3. Brown JR et al. Oral presentation/Abstract 202 presented at the ASH Annual Meeting, 09–12 December 2023.

Phase 3 Ibrutinib vs Second-Generation BTK Studies

	Atrial Fibrillation	Hypertension	Major Bleeding
ELEVATE-RR (acala CLL)[1]	↓	↓	**No difference**
ALPINE (zanu CLL)[2]	↓	**No difference**	**No difference**
ASPEN (zanu WM)[3]	↓	↓	**No difference**

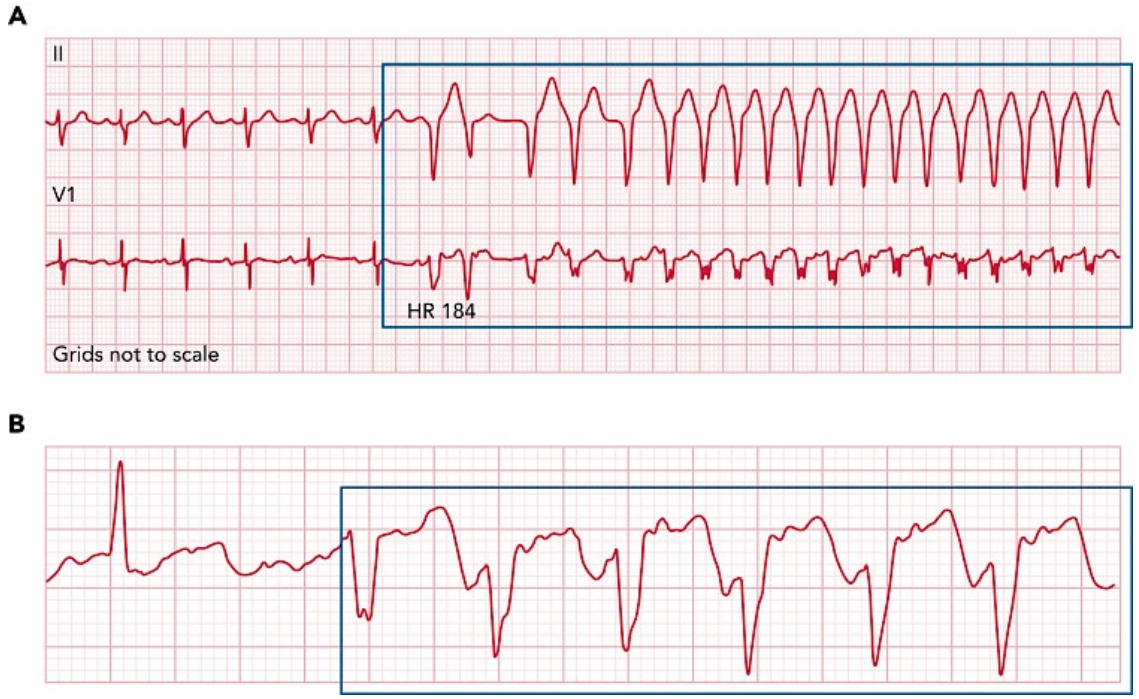
1. Byrd JC et al. *J Clin Oncol.* 2021;39:3441-3452; 2. Brown JR et al. *N Engl J Med.* 2023;388:319-332; 3. Dimopoulos M et al. *J Clin Oncol.* 2023;41:5099-5106.

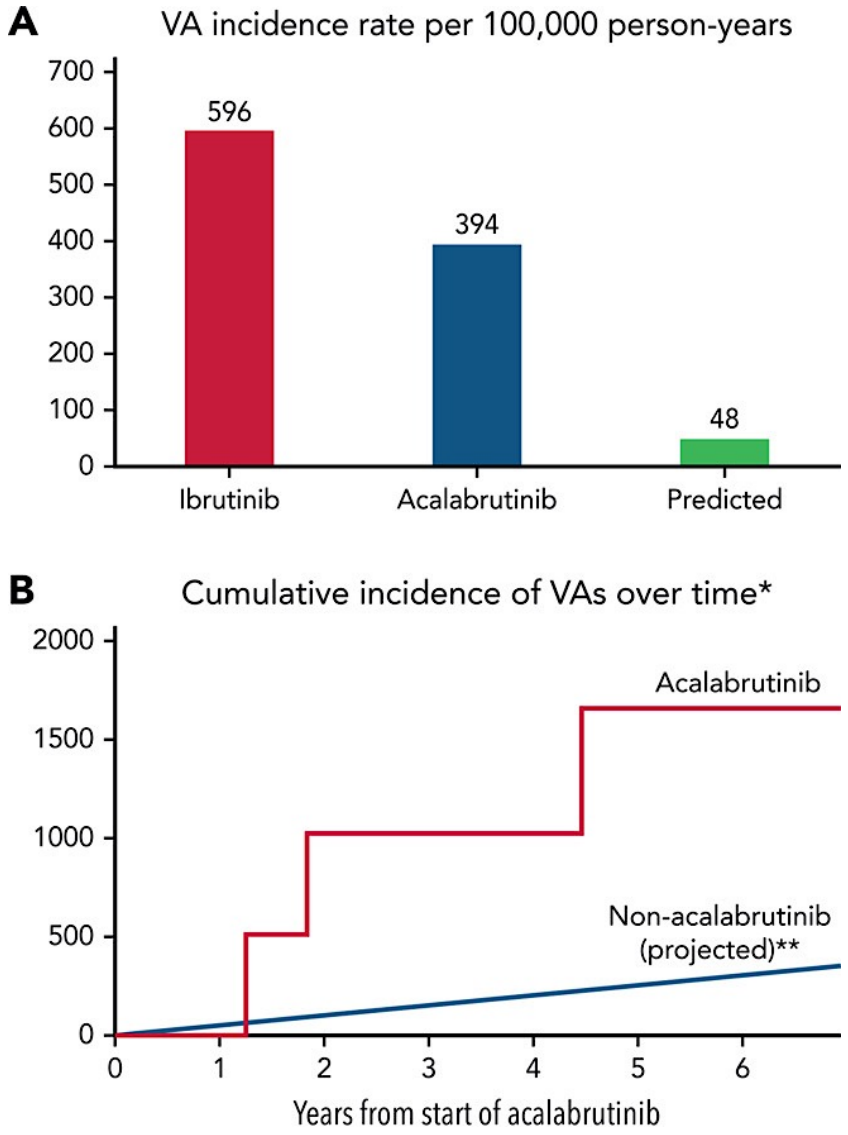
Ventricular Arrhythmias Likely Class Effect

LYMPHOID NEOPLASIA

Ventricular arrhythmias and sudden death events following acalabrutinib initiation

Seema A. Bhat,[1,*] John Gambril,[2,*] Leylah Azali,[3,*] Sunnia T. Chen,[2,*] Lindsay Rosen,[3] Marilly Palettas,[4] Tracy E. Wiczer,[3] Sujay Kalathoor,[2] Qiuhong Zhao,[1] Kerry A. Rogers,[1] Adam Kittai,[1] Michael Grever,[1] Farrukh Awan,[5] Patrick Ruz,[2] John C. Byrd,[6] Jennifer Woyach,[1] and Daniel Addison[2,7,*]





Bhat SA et al. *Blood.* 2022;140:2142-2145.

Cardiovascular Management in BTKi

	Assessments	Action

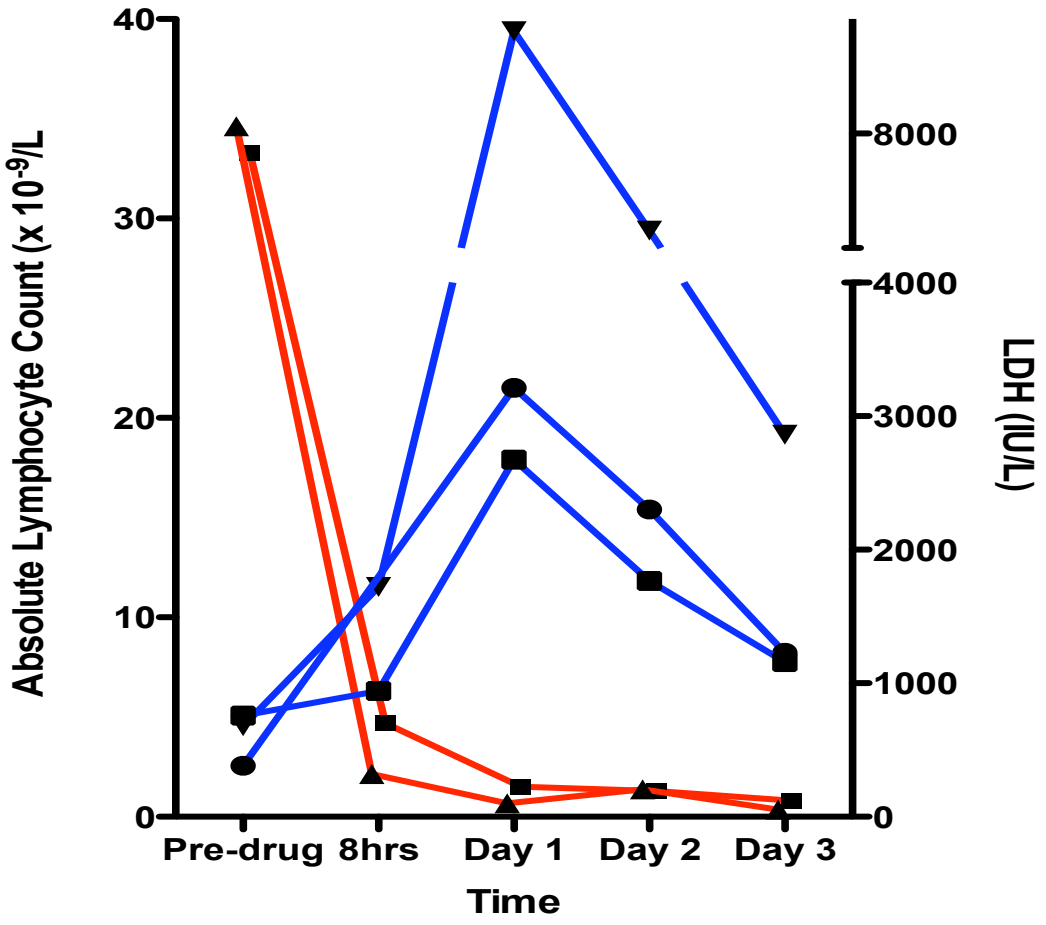
Before BTKi	• Personal and family history.
	• Clinical examination.
	• Blood pressure.
	• Baseline ECG.
	• Echo if history of CV disease or poorly controlled HTN.
		• ***Avoid BTKi*** if
		  • Personal or family history of ventricular arrhythmias;
		  • Uncontrolled HTN;
		  • LVEF abnormal (definitely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

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

Adapted from Awan FT et al. *Blood Adv.* 2022;6:5516-5525; Munir T et al. *Acta Haematol* 2025;1-16.

ABT-199 Induces Rapid Reduction in CLL

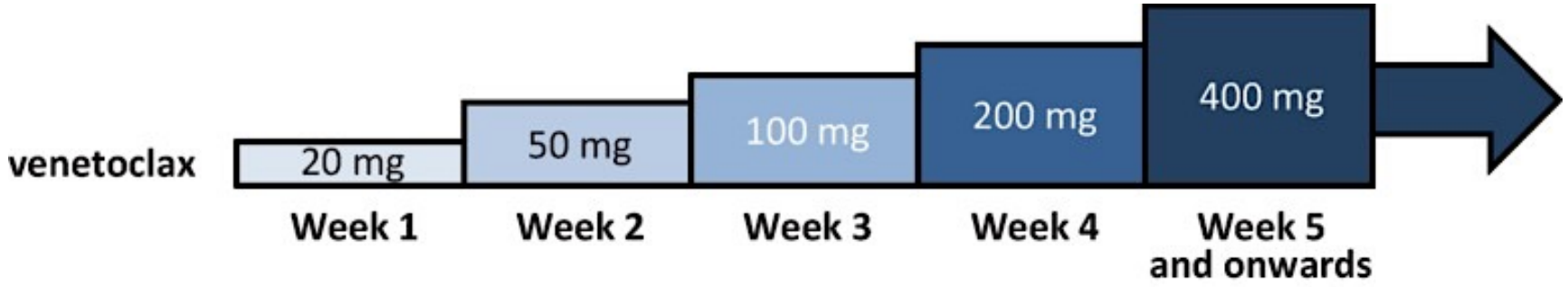
- Single dose of 200mg (n=2) or 100mg (n=1)
- Rapid reduction in CLL within 24hrs
- Evidence of TLS in all 3 patients, one with transient disseminated intravascular coagulation



Souers AJ et al. *Nat Med.* 2013;19:202-208; Roberts et al, 2012 EHA Congress

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

Monitoring Venetoclax TLS



	Tumor lysis syndrome risk category		
	Low	**Medium**[a]	**High**
Definition	All measurable lymph nodes with largest diameter <5 cm AND <25 × 10^9/L ALC	Any measurable lymph node with largest diameter ≥5 and <10 cm OR ≥25 × 10^9/L ALC	Any measurable lymph node with largest diameter ≥10 cm OR ≥25 × 10^9/L ALC AND any measurable lymph node with the largest diameter ≥5 cm
Venetoclax dosing setting	Outpatient	Outpatient	Inpatient for first doses of 20 mg and 50 mg
Laboratory monitoring of clinical chemistry at 20-mg and 50-mg doses	Reduced lab monitoring for low-risk patients at 0, 8, and 24 hours For hospitalized patients, lab monitoring was done at 0, 4, 8, 12, and 24 hours		
Laboratory monitoring of clinical chemistry during subsequent dose ramp-up	Outpatient at 0, 8, 24 hours		
Hydration and uric acid control	1–2 L/day oral fluids at 48 hours and oral uric acid-lowering agents at 72 hours prior to first dose Additional IV fluids for high-/medium-risk patients Rasburicase recommended for high-risk patients with high baseline uric acid		

20mg, 50mg →

100mg, 200mg, 400mg →

PI Update: No need to monitor post-dose in low and medium risk.

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

Adapted from Cheson BD et al. *Oncologist.* 2017;22:1283-1291; Venetoclax PI

Other BTKi/BCL2i Side-Effects

	Comment	**Solution**
Nuisance Side-Effects (Myalgias, Arthralgias, Rash, Cough, Edema)	Mainly seen in ibrutinib.	Dose reduce or use 2nd Gen BTKi.
Neutropenia	More common with venetoclax and zanubrutinib.	Monitor or twice-weekly GCSF x 4 weeks. Usually don't need to dose reduce.
Nausea / Dyspepsia / Diarrhea	Mainly seen in ibrutinib and venetoclax.	Dose reduce (ibrutinib) or try night-time dosing (venetoclax).
Headache	Mainly seen in acalabrutinib.	Caffeine and patience (usually resolves).

Brown JR et al. *N Engl J Med.* 2025;392(8):748-762; Kater AP et al. *NEJM Evid.* 2022;1. Shadman M et al. *J Clin Oncol.* 2025;43:2409-2417; Tam C. *Hematology Am Soc Hematol Educ Program.* 2021:55-58; Timofeeva N et al. *Blood Neoplasia*. 2024;1:100034.

BTKi + BCL2 Combinations

Ibrutinib + Venetoclax[1]

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

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

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

Triple BTKi/BCL2i/CD20 Combinations[4]

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

1. Kater AP et al. *NEJM Evid.* 2022;1. 2. Brown JR et al. *N Engl J Med.* 2025;392(8):748-762. 3. Shadman M et al. *J Clin Oncol.* 2025;43:2409-2417. 4. Timofeeva N et al. *Blood Neoplasia*. 2024;1:100034.

Case Presentation: 94-year-old man has CLL and concurrent locally advanced Merkel cell carcinoma of the scalp

Dr Erik Rupard (Reading, Pennsylvania)

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Discussion Questions

What is the pathophysiology and spectrum of CLL-related second cancers?

What is your clinical experience with dermatologic cancers in patients with CLL?

Case Presentation: 53-year-old woman under observation for IGHV-unmutated CLL develops progressive splenomegaly (20 cm) and receives obinutuzumab/venetoclax

Dr Sean Warsch (Asheville, North Carolina)

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Discussion Questions

How does splenomegaly affect your approach to TLS prevention with venetoclax-based regimens?

In what situations, if any, do you use an accelerated ramp-up approach with venetoclax? Is this generally done in an inpatient setting?

Discussion Questions

Is TLS still a meaningful issue with venetoclax ramp-up dosing? What other AEs do you routinely encounter in your patients receiving venetoclax?

How do you assess the practical potential for a patient to receive a venetoclax regimen in terms of transportation, adherence, etc?

In what situations, if any, do you still use chemotherapy (FCR, BR) as initial treatment for patients with CLL?

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Agenda

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Selection and Sequencing of Therapy for R/R CLL

Jennifer Woyach, MD
Bertha Bouroncle MD and Andrew Pereny Chair of Medicine
Division of Hematology

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Initial Considerations When Approaching Relapsed CLL

Relapse can take different forms

- Increase in WBC after time-limited therapy is complete
- Detection of lymph nodes by CT scan

Don’t treat

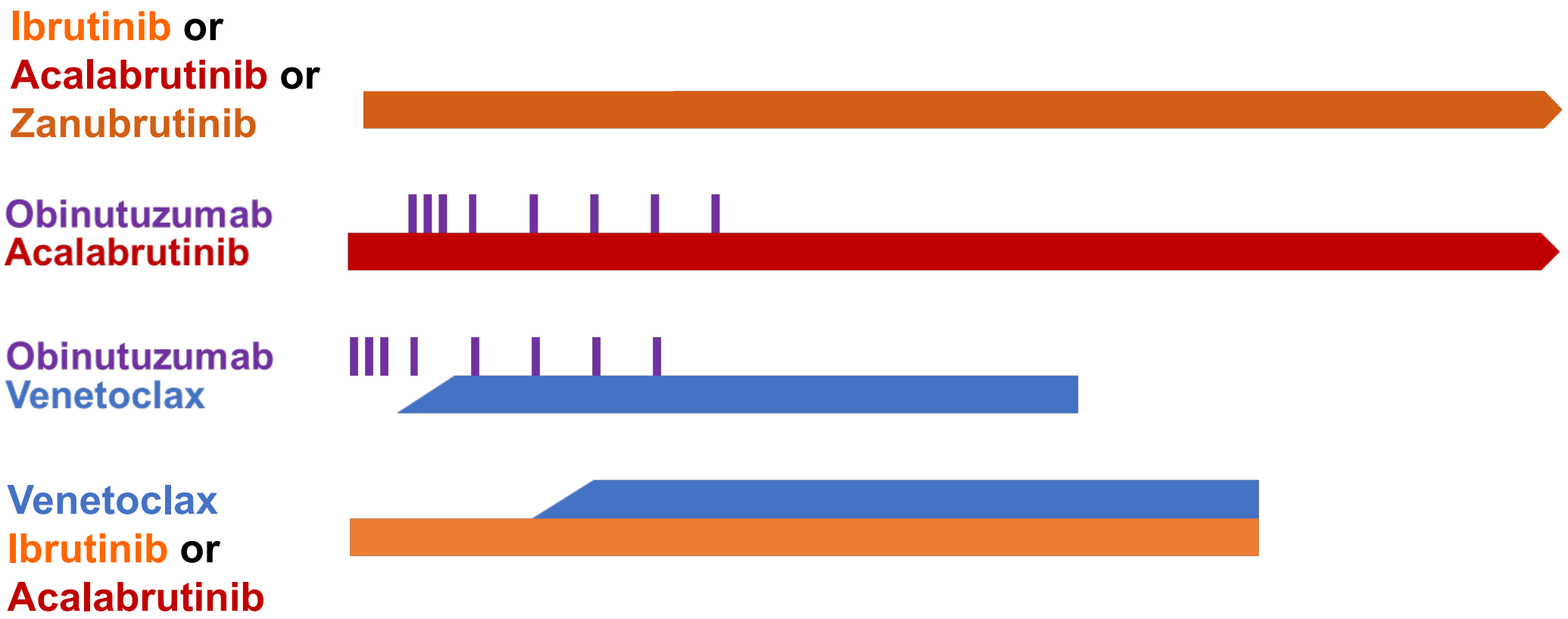
- Detection of lymph nodes by exam
- Increase in WBC during continuous treatment

Don’t treat (yet)

- Return of autoimmune conditions
- Symptomatic increase of nodes or spleen
- Return of fatigue or other constitutional symptoms

Start treatment

Current Frontline Treatment Regimens



Modified from Rogers/Woyach ASH Education Book 2024.

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How Does Initial Treatment Impact Subsequent Choices?

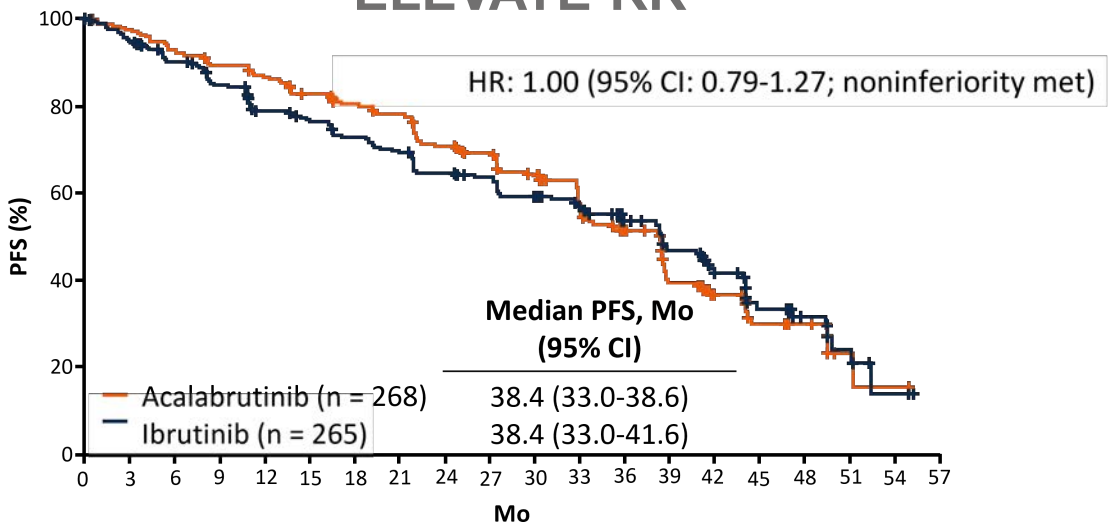
- Fixed duration therapy?
  - Chemoimmunotherapy
  - Venetoclax + obinutuzumab
  - BTKi + venetoclax
- BTK inhibitor given continuously?

If Initial Treatment Was Fixed Duration

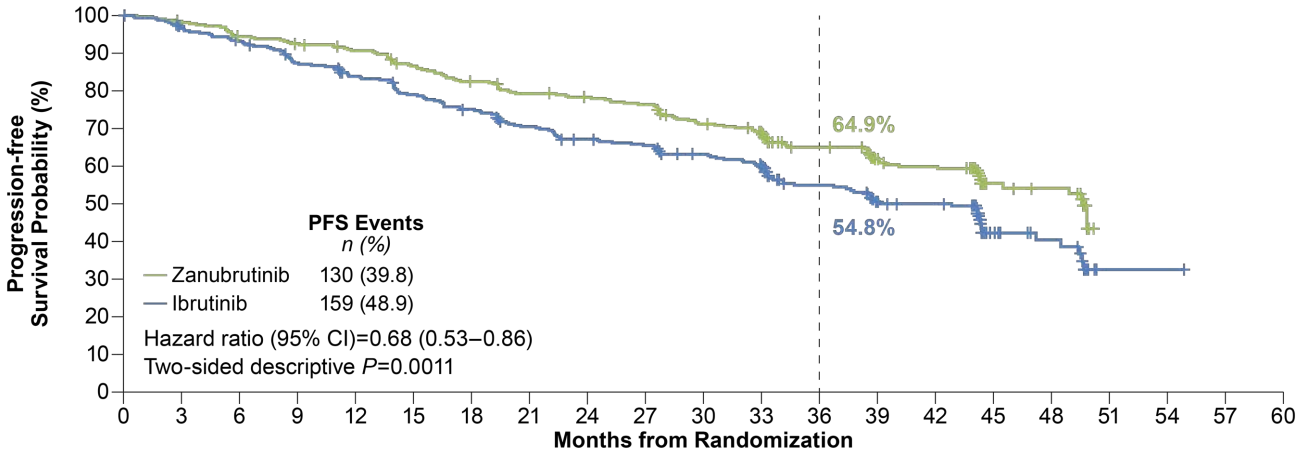
What do the data show?

BTK Inhibitors Produce Extended PFS after CIT

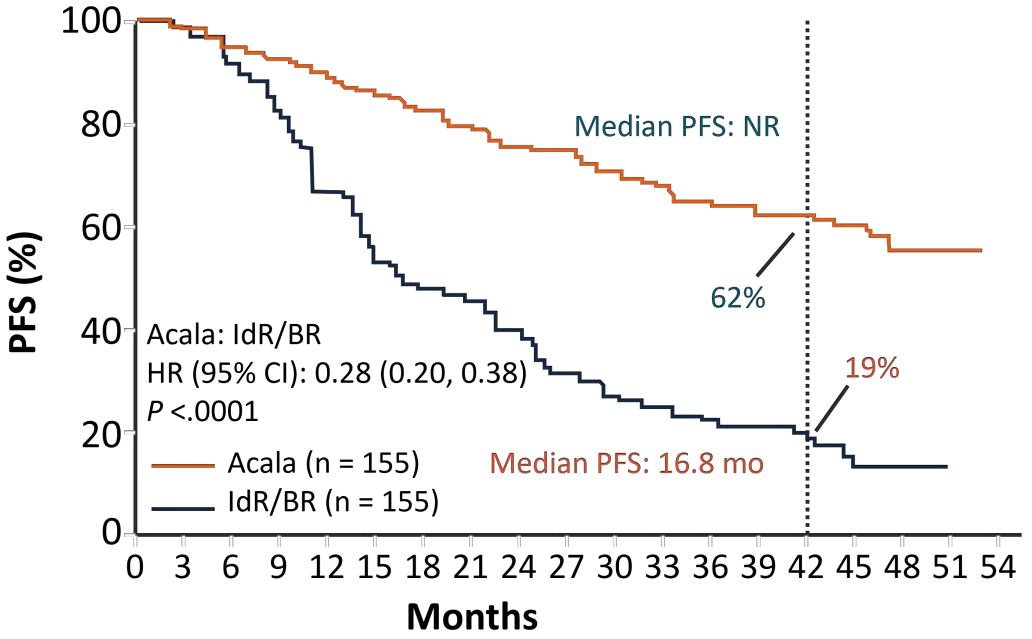
ELEVATE-RR



ALPINE



ASCEND



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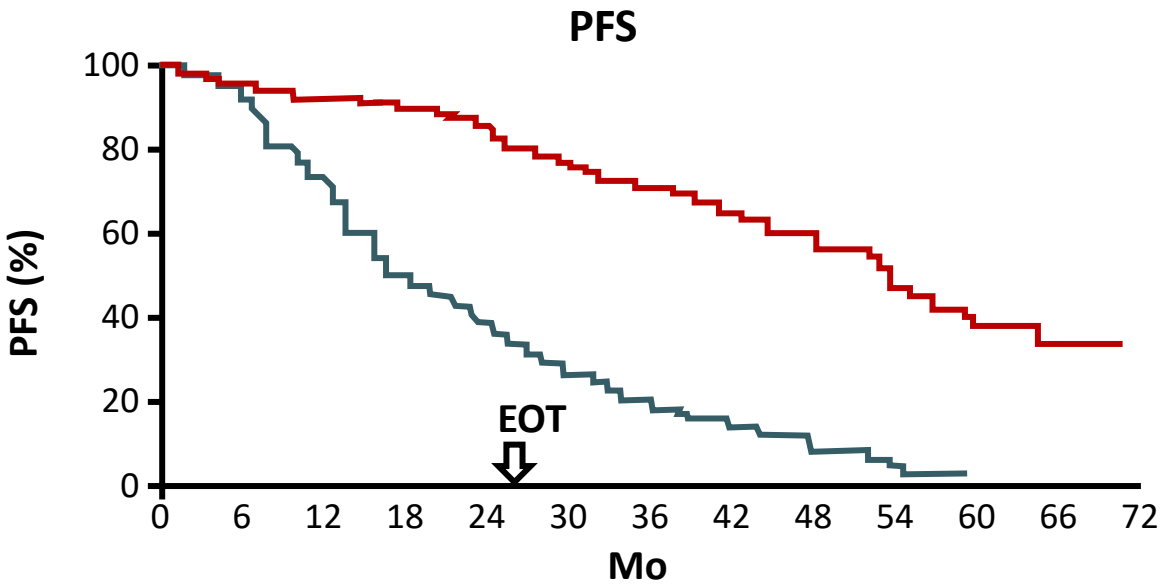
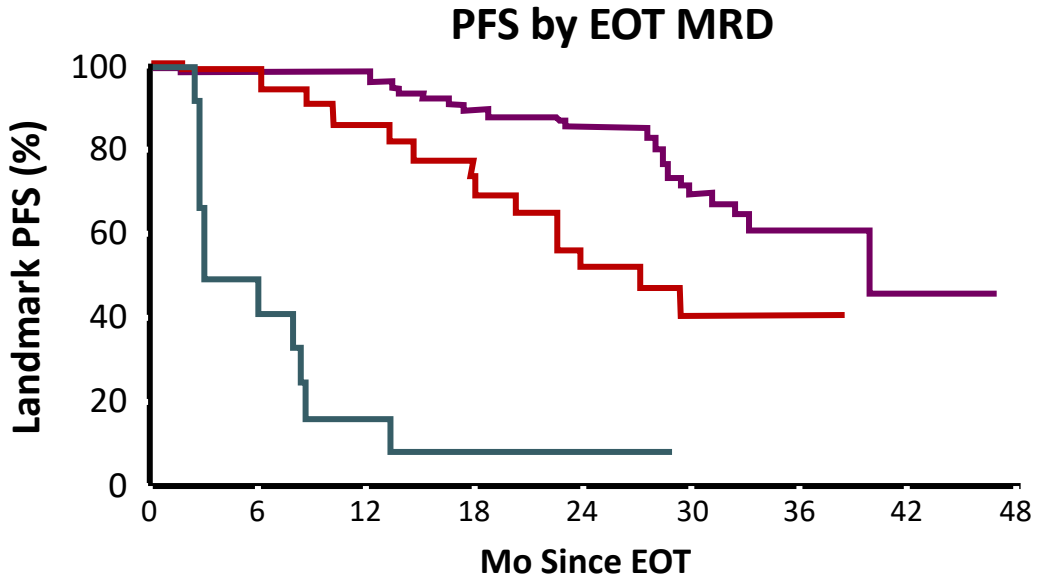
Ghia et al, Hemasphere 2022; Byrd et al JCO. 2021; Brown et al, NEJM 2023

Venetoclax + Rituximab Produces Extended PFS after CIT





	Median PFS, Mo (95% CI)
VenR (n = 194)	53.6 (48.4-57.0)
BR (n = 195)	17.0 (15.5-21.7)

	PFS Since EOT, %	
Category	24-Mo	36-Mo
uMRD ($<10^{-4}$), n = 83	85.4	61.3
Low-MRD+ ($\geq10^{-4}$-10^{-2}), n = 23	52.2	40.7
High-MRD+ ($\geq10^{-2}$) n = 12	8.3	

Seymour. Blood. 2022;140:839.

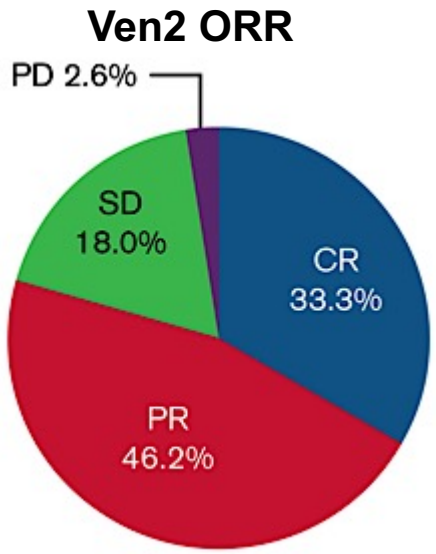
If initial therapy was venetoclax/obinutuzumab

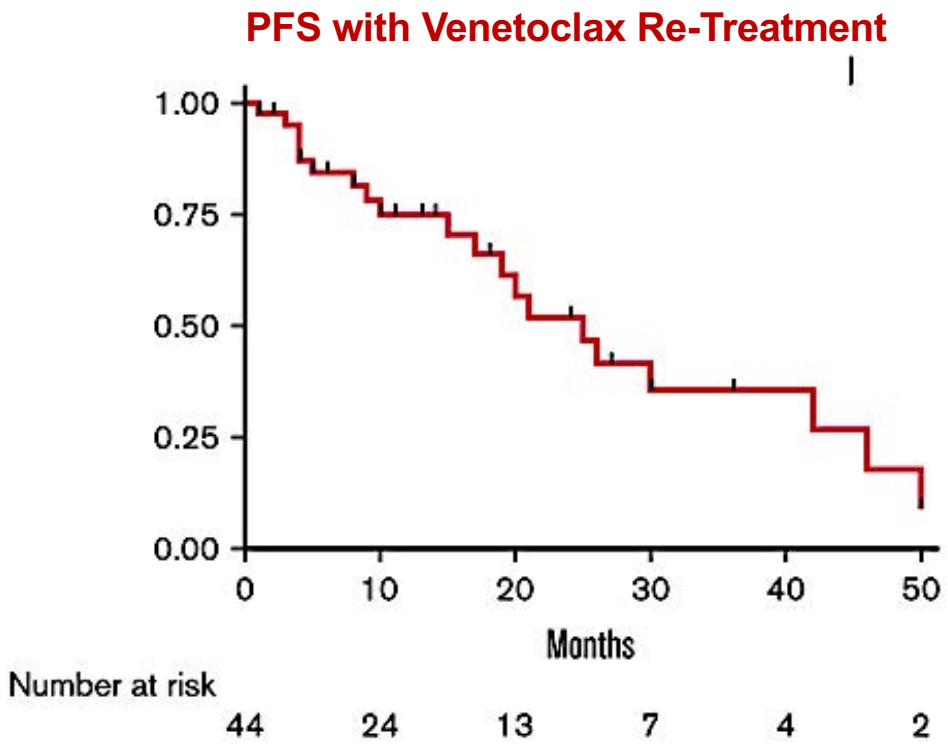
- BTK inhibitors remain an option
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
- Could also consider repeating initial therapy depending on remission duration

What do the data show?

Venetoclax Retreatment Appears Promising

- MURANO retreatment data
  - 18 evaluable patients received subsequent venetoclax post-relapse
    - ORR 72.2%, 5.6% CR/Cri
- Retrospective multicenter data
  - 46 patients, 91% R/R
    - ORR 79.5%, med PFS 25 mo





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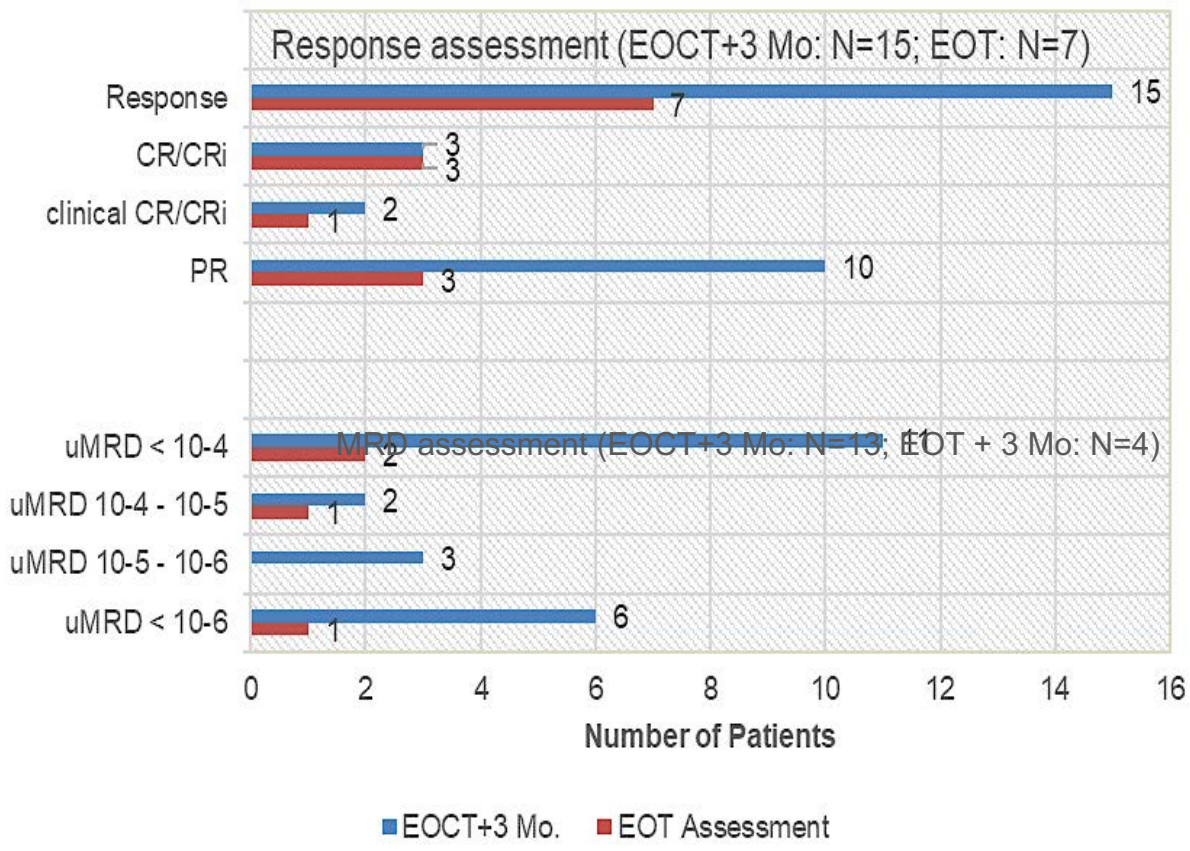
Seymour. Blood. 2022; Thompson. Blood. 2022

Venetoclax retreatment: Preliminary ReVenG data

AT BASELINE	TOTAL (N=25) n (%)
Age – Median (range)	67 (41-84)
≥ 65 years	15 (60)
Gender	
Female	7 (28)
Male	18 (72)
Tumor Lysis Syndrome Risk Category	
Low	11 (44)
Medium	9 (36)
High	5 (20)
Total CIRS Score	
≤ 6	19 (83)
> 6	4 (17)
Genetic characteristics (n=21 with available data)	
17p deletion status	
Deleted	3 (14)
Not deleted	18 (85)
***TP53* mutational status**	
Mutated	8 (38)
Wildtype	13 (62)
Either del(17p) or *TP53* mutated	8 (38)
IGHV mutational status	
Mutated	3 (14)
Unmutated	18 (86)
Acquired mutation in *BCL-2*	0 (0)

Davids et al, EHA/ICML 2025

Response and MRD assessment



Davids et al., EHA/ICML, 2025

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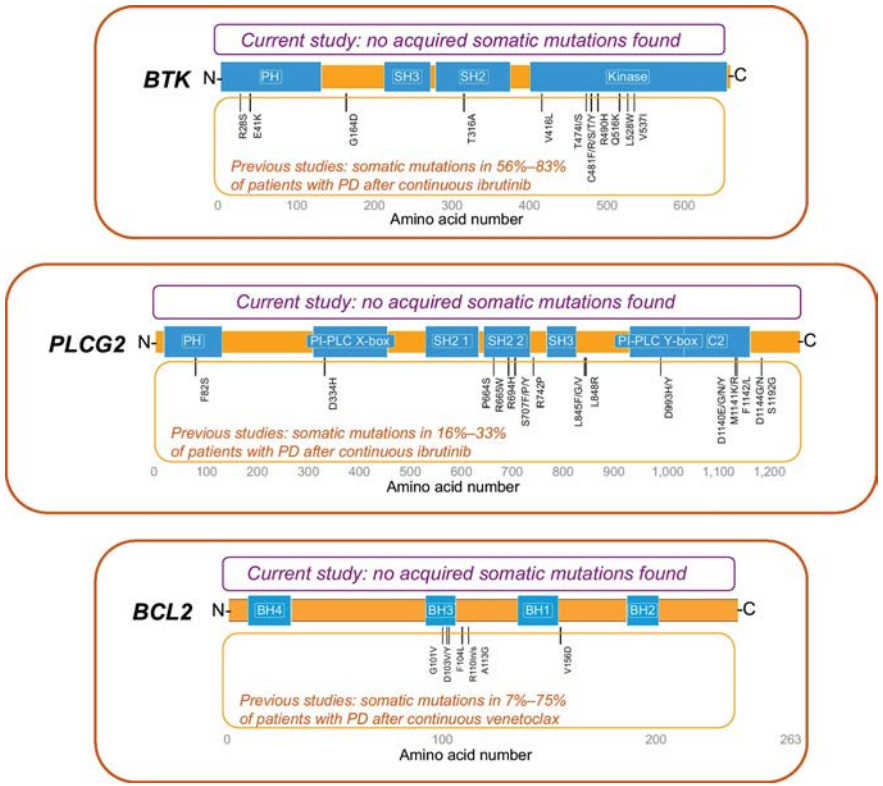
What if prior treatment was BTKi + Venetoclax?

- No prospective data exist (yet)
- Retrospective and anecdotal data suggest retreatment with either agent, or potentially both, is effective
- For what limited data exist, resistance mutations are not seen



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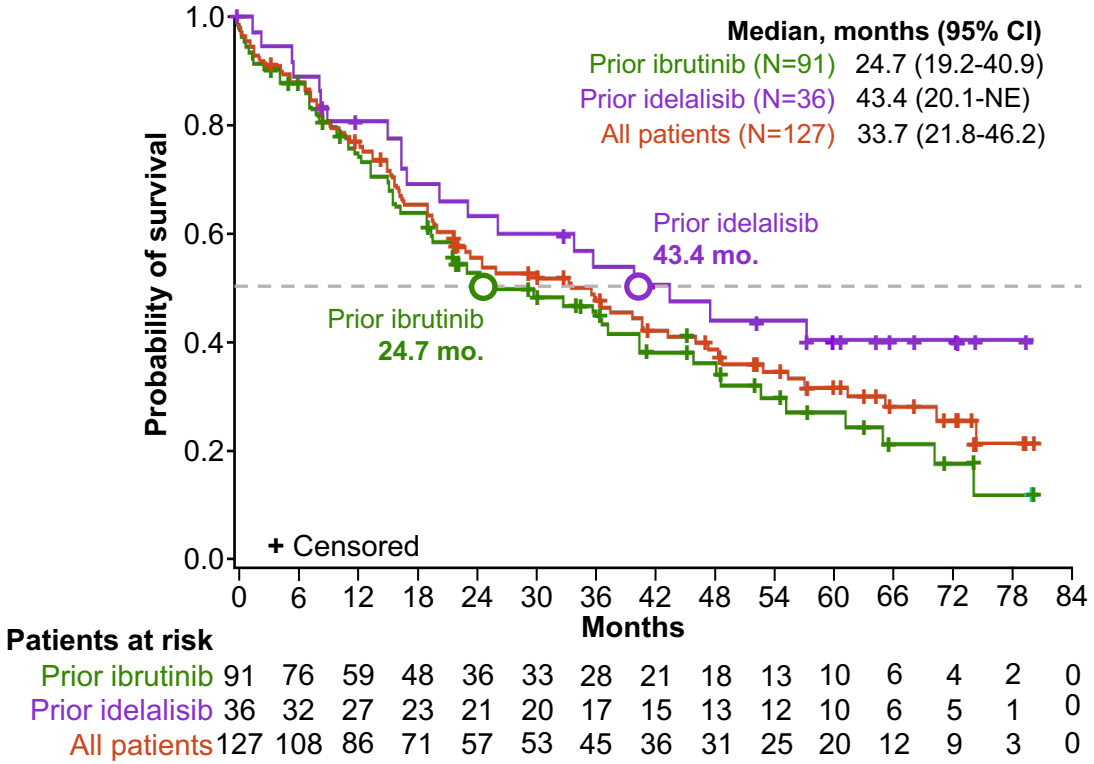
Jain et al, Clin Cancer Res 2024; Tam et al, Blood 2022

If Prior Treatment Was Covalent BTK Inhibitor . . .

- If progression occurs after a cBTKi is discontinued for toxicity, treatment with an alternate cBTKi is effective
- Resistance to ibrutinib, acalabrutinib, and zanubrutinib is driven primarily by mutations in *BTK* (C481S)
- In the presence of this mutation, covalent inhibitors bind noncovalently, and binding kinetics and short half-life make these agents less effective
- However, the C481S mutation does not appear to alter CLL dependence on the BCR pathway
- Zanubrutinib also can induce L528W mutation in BTK and acalabrutinib the T474I mutation

Venetoclax is Effective in the Post-BTKi Setting

Multicenter study of venetoclax monotherapy in patients previously treated with ibrutinib or idelalisib



Woyach et al. iwCLL 2023

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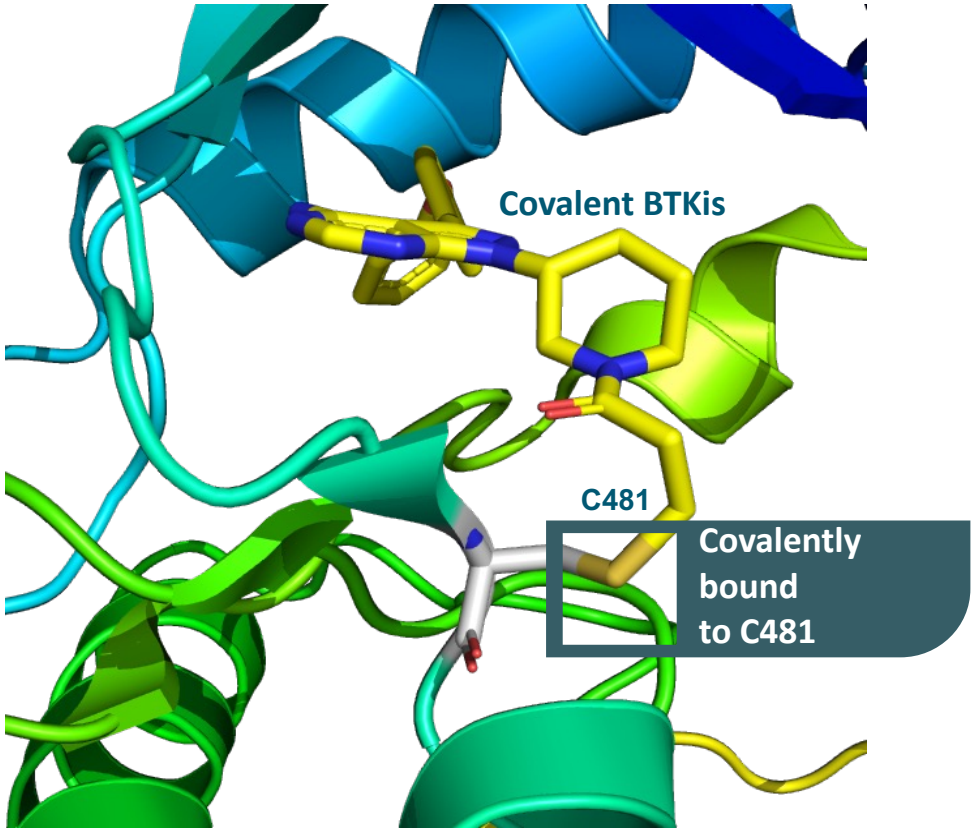
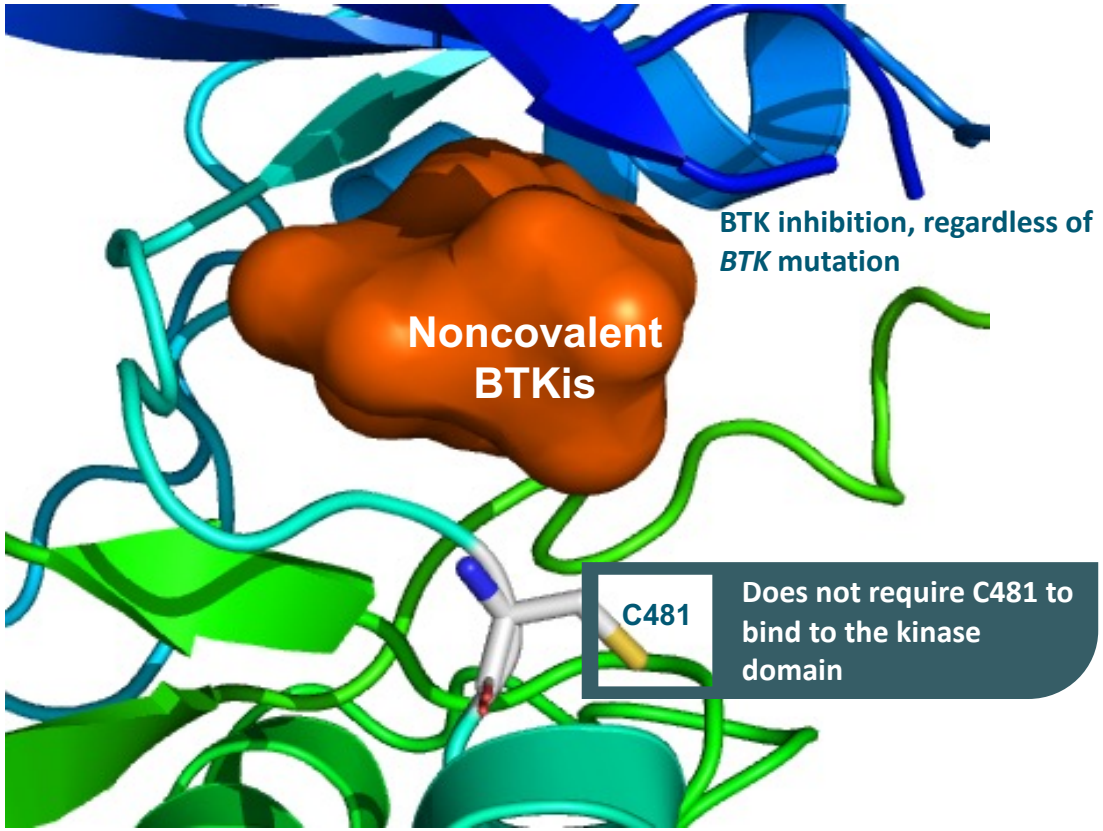
Noncovalent BTK Inhibition

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib) Require WT *BTK* for Activity

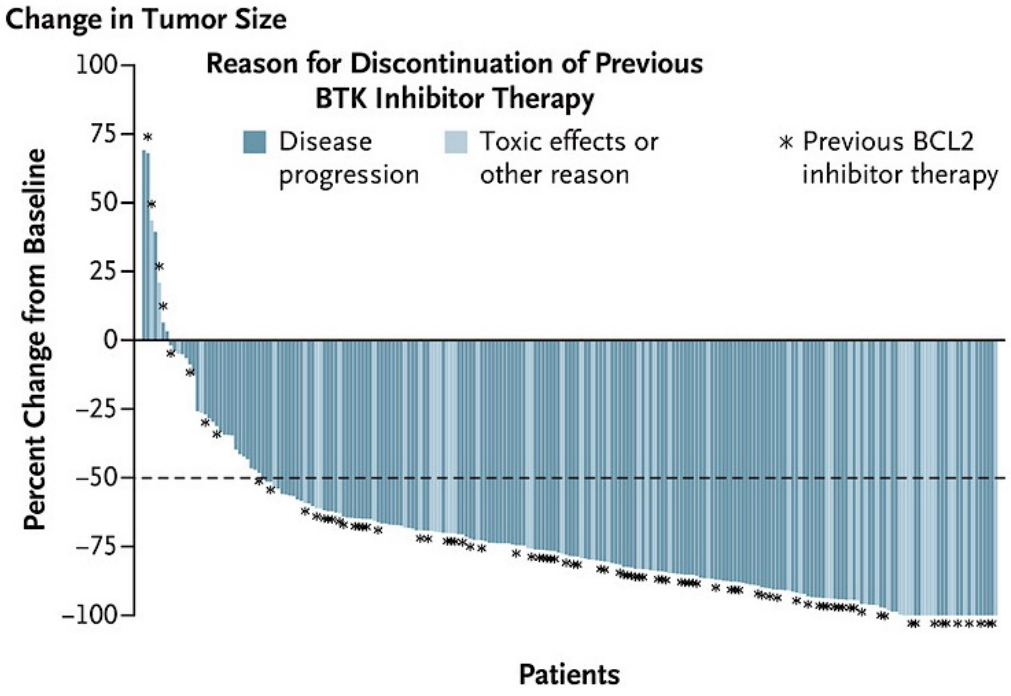


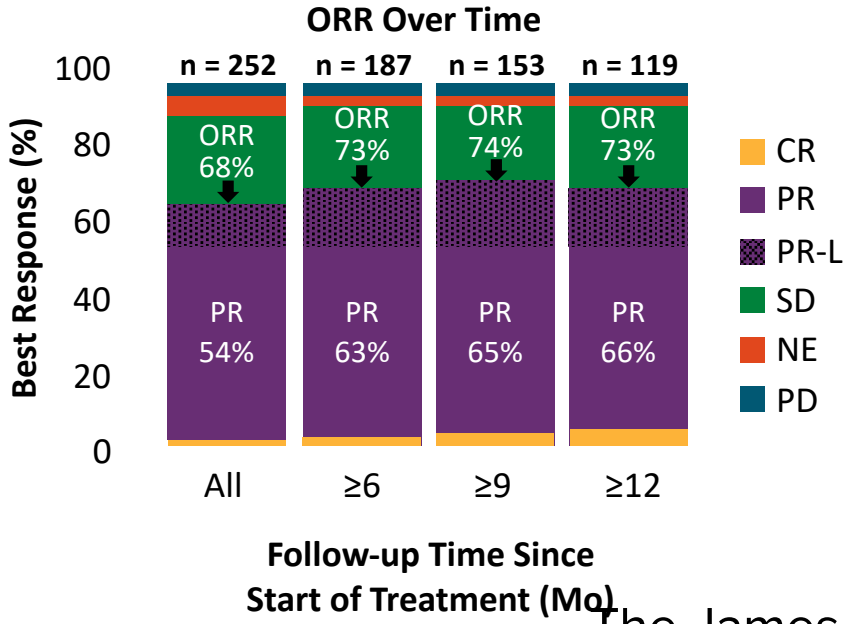
Noncovalent BTK Inhibitors (Pirtobrutinib, Nemtabrutinib) Are Active Against Both WT and C481-Mutated *BTK*



BRUIN: Pirtobrutinib for Previously Treated CLL/SLL

- Phase I/II study (with dose escalation and expansion in phase I) of pirtobrutinib for patients with CLL/SLL* or B-cell non-Hodgkin lymphoma and ≥2 prior therapies including BTK inhibitor
  - Pirtobrutinib: next-generation, highly selective, **noncovalent** BTK inhibitor that promotes apoptosis and inhibits BCR signaling in xenograft models with wild-type *BTK* and those harboring *BTK* C481S mutation

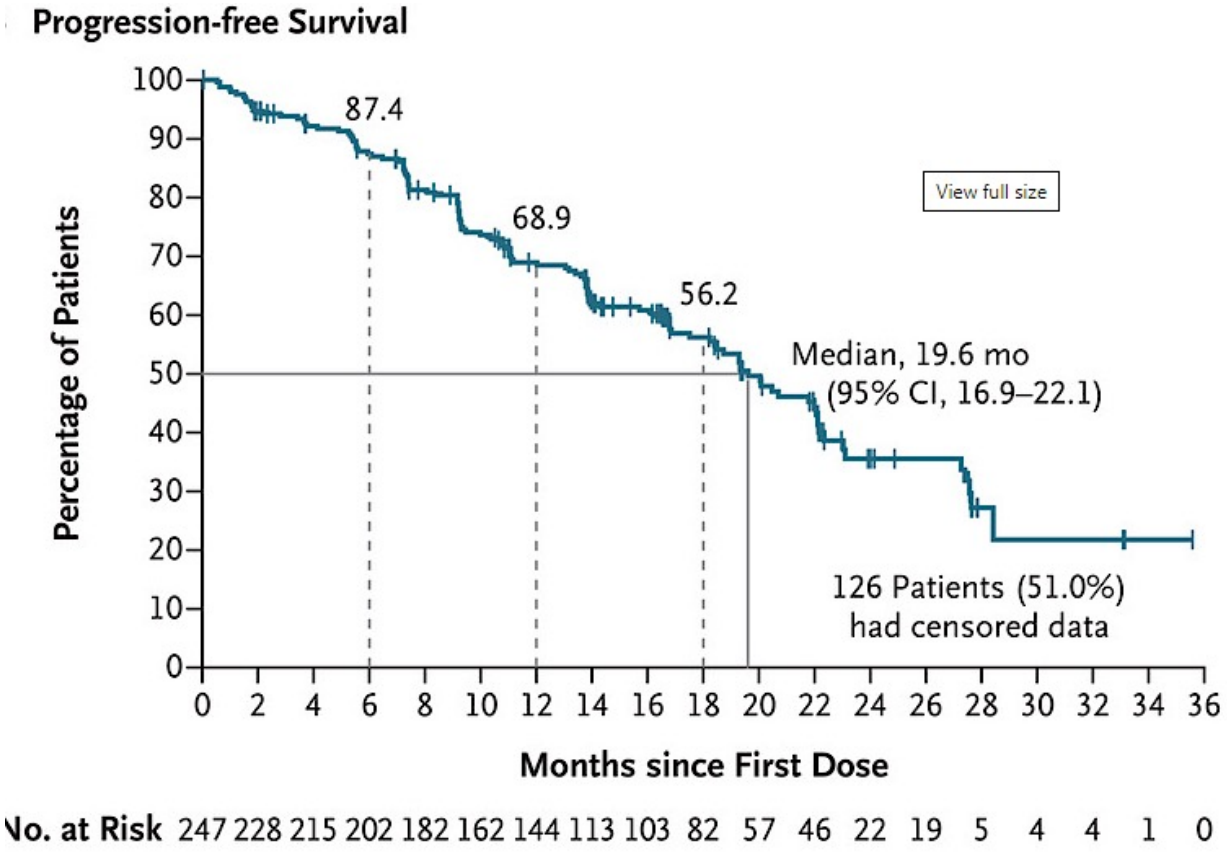


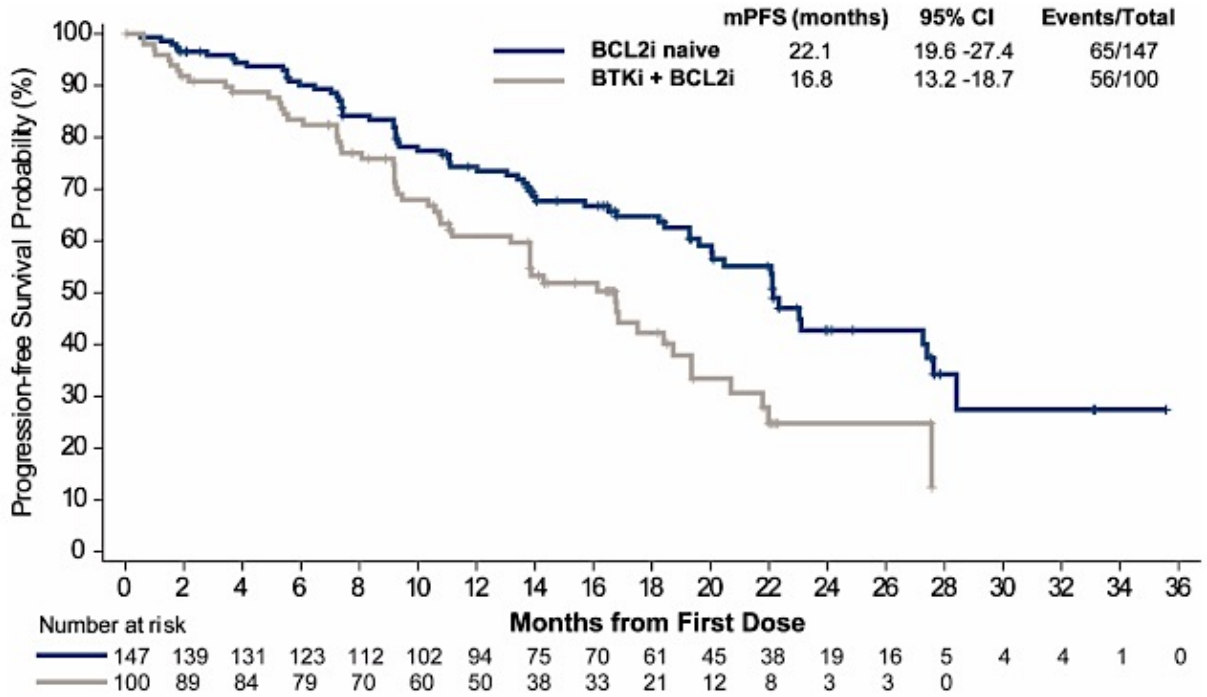


*Safety population: n = 296; efficacy population: n = 252 (all previously treated with BTK inhibitor).

Mato. N Engl J Med. 2023; 289:33-44.

BRUIN CLL/SLL: PFS





Mato. NEJM 2023

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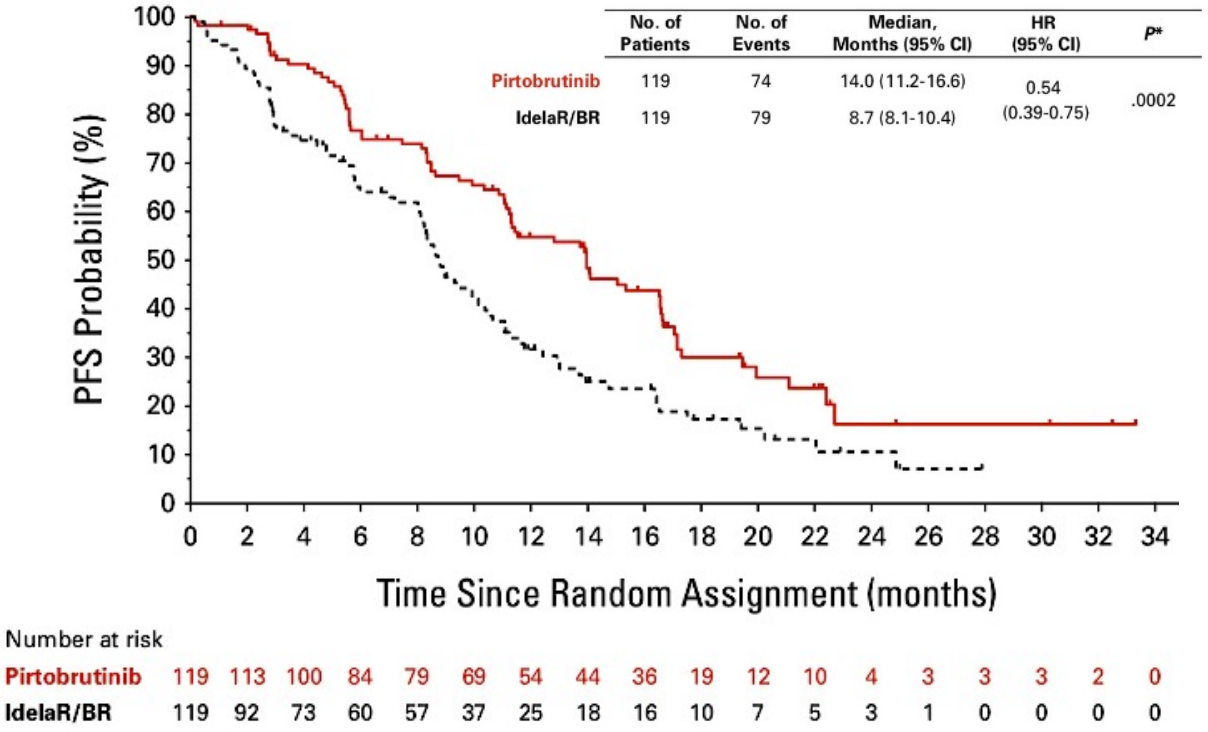
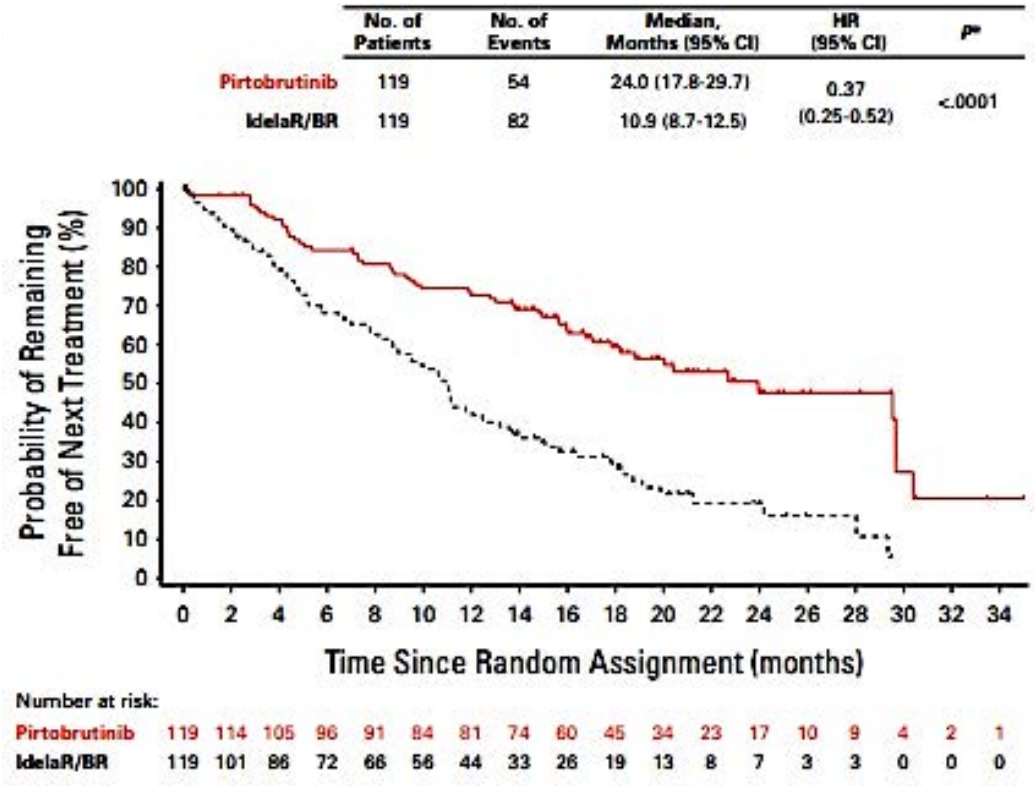
BRUIN CLL 321

- Phase III study comparing pirtobrutinib with dealer's choice idelalisib/rituximab or bendamustine/rituximab in CLL previously treated with a cBTKi





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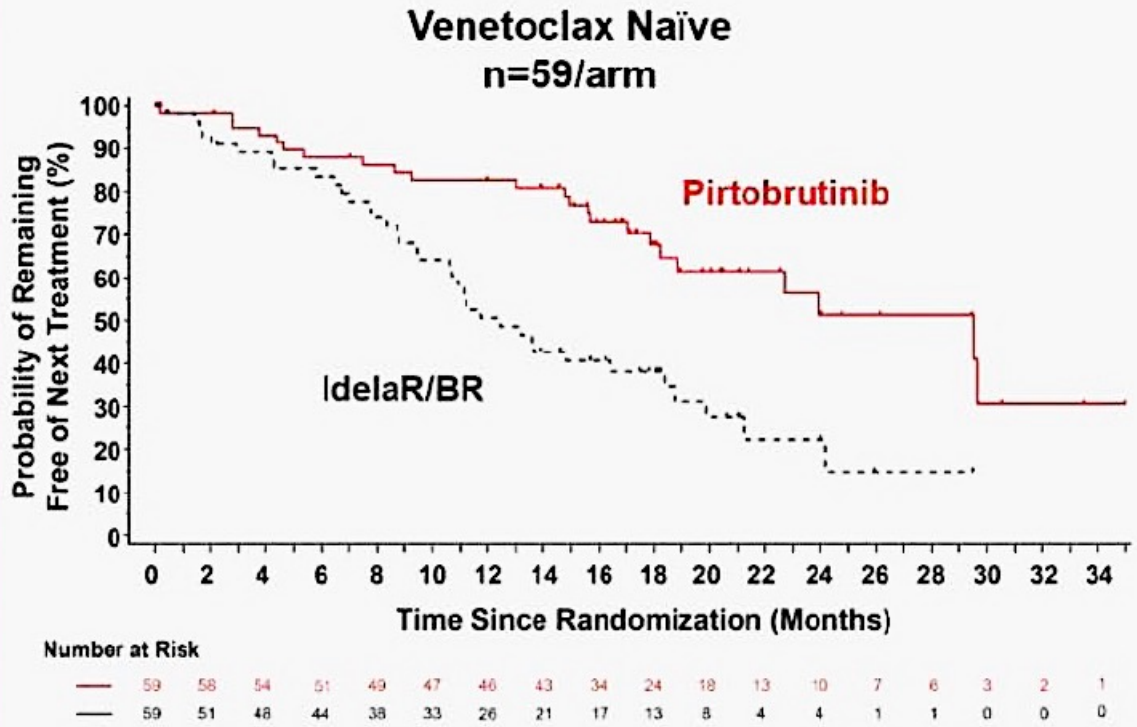
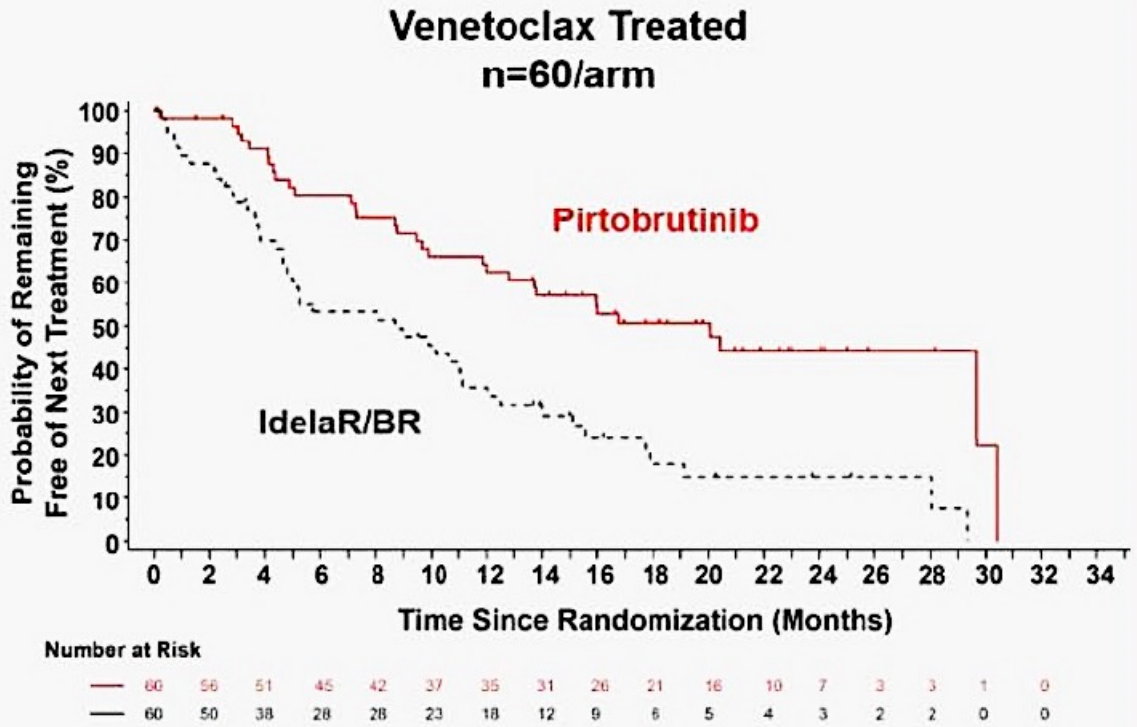
Sharman et al, J Clin Oncol 2025

BRUIN CLL 321: Time to Next Treatment or Death in Venetoclax Naïve and Treated Patients



	Pirtobrutinib n=119	IdelaR/BR n=119
Median TTNT, mo (95% CI)	29.5	12.5
Hazard ratio (95% CI)	0.36 (0.21- 0.61)	
Stratified log-rank 2-sided p-value	0.0001*	



	Pirtobrutinib n=119	IdelaR/BR n=119
Median TTNT, mo (95% CI)	20.0	8.7
Hazard ratio (95% CI)	0.37 (0.23- 0.60)	
Stratified log-rank 2-sided p-value	<0.0001*	

Sharman et al. ASH 2024;Abstract 886.

FDA Grants Traditional Approval to Pirtobrutinib for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Press Release: December 3, 2025

"The Food and Drug Administration granted traditional approval to pirtobrutinib for adults with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have previously been treated with a covalent BTK inhibitor. In 2023, FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

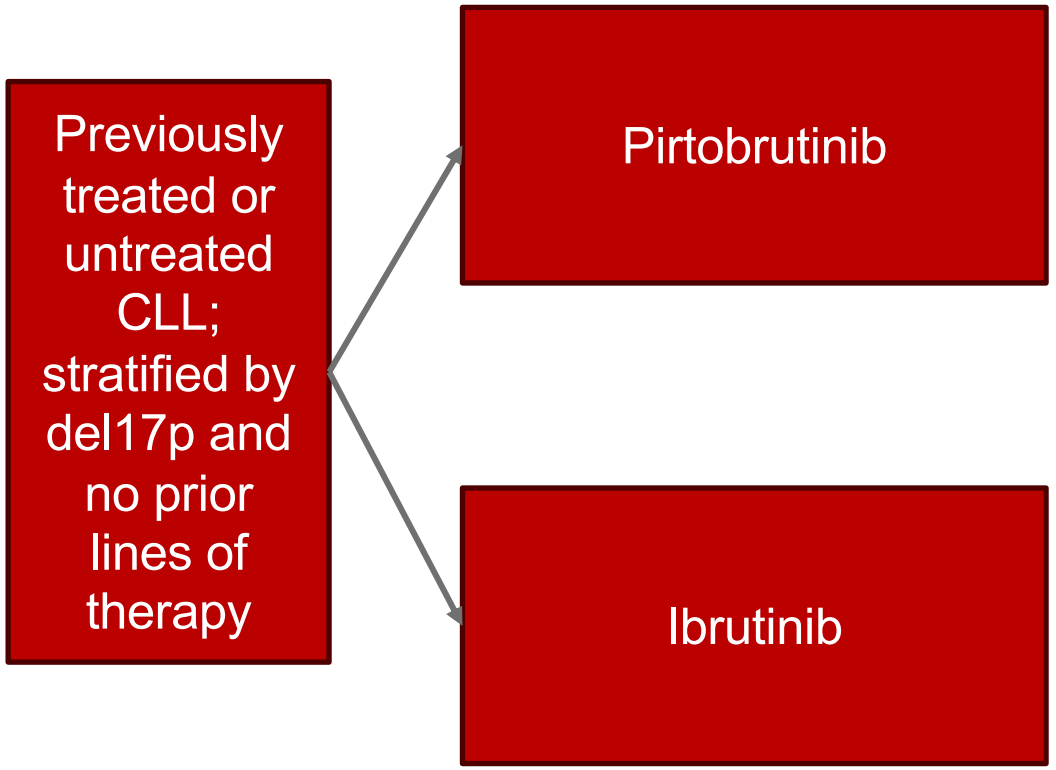
Efficacy was evaluated in BRUIN-CLL-321 (NCT 04666038), a randomized, open-label, active-controlled trial. The trial randomized 238 patients who were previously treated for CLL/SLL, including a covalent BTK inhibitor. Patients previously treated with a non-covalent BTK inhibitor were not permitted. Patients were randomized (1:1) to receive either pirtobrutinib or investigator's choice of idelalisib plus a rituximab product (IR) or bendamustine plus a rituximab product (BR).

The primary efficacy outcome measure was progression-free survival (PFS), as assessed by an independent review committee using 2018 iwCLL criteria. Median PFS was 11.2 months (95% CI: 9.5, 11.4) in the pirtobrutinib arm and 8.7 months (95% CI: 7.2, 10.2) in the investigator's choice of IR/BR arm (Hazard ratio 0.58 [95% CI: 0.38, 0.89]; *p*-value 0.0105). Of the 119 patients in the investigator's choice arm, 50 crossed over to receive pirtobrutinib therapy. At an updated analysis with a median follow-up time of 19.8 months, the HR for overall survival (OS) was 1.09 (95% CI: 0.68, 1.75)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

RTP RESEARCH TO PRACTICE

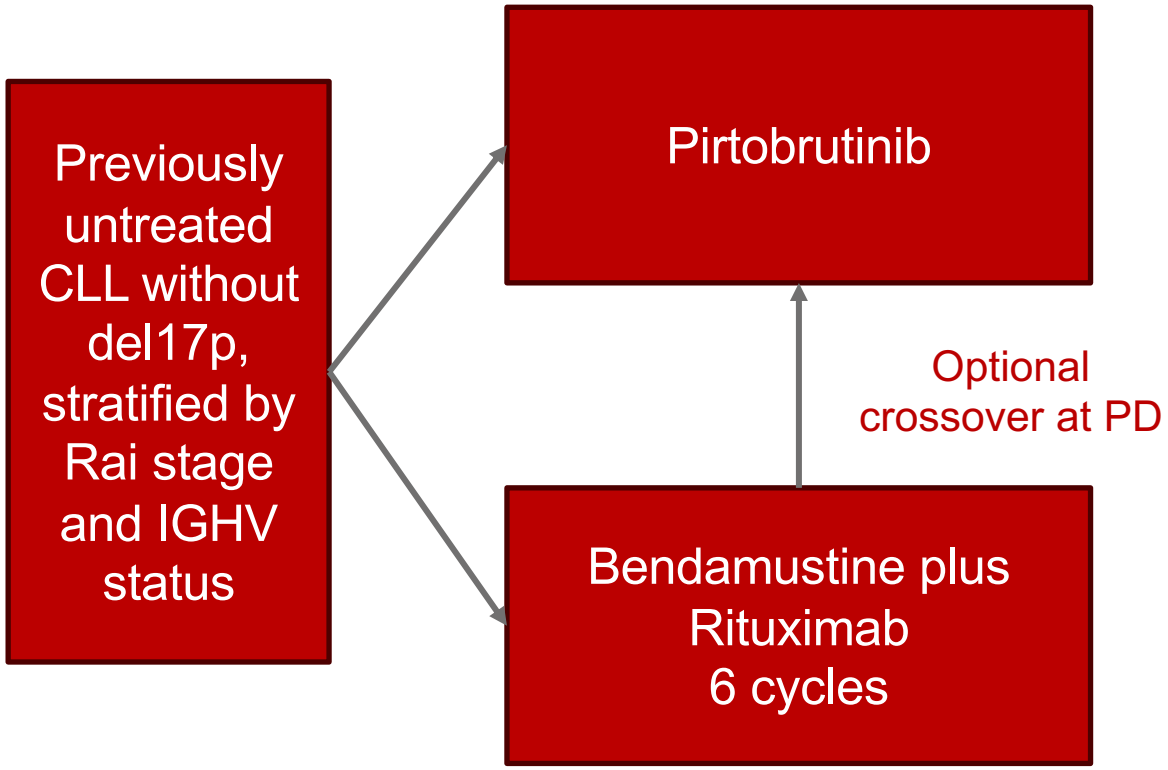
ASH 2025: BRUIN CLL-314



	Pirtobrutinib	Ibrutinib
ORR (ITT) %	87.0	78.6
ORR (TN) %	92.9	85.8
18 mo PFS (RR) %	81.7	79.2
18 mo PFS (TN) %	95.3	87.6
Atrial fibrillation %	2.4	13.5
Dose reductions for toxicity %	7.9	18.2
Discontinuation for toxicity %	7.9	7.3

Woyach et al, ASH 2025 Abstract 683

ASH 2025: BRUIN CLL-313



	Pirtobrutinib	BR
24 month PFS%	93.4	70.7
Discontinuation for toxicity%	4.3	15.2
Atrial fibrillation%	1.4	NR

OS improved for pirtobrutinib vs BR

HR 0.257 (95% CI: 0.070, 0.934; p=0.0261)

52.9% effective crossover rate

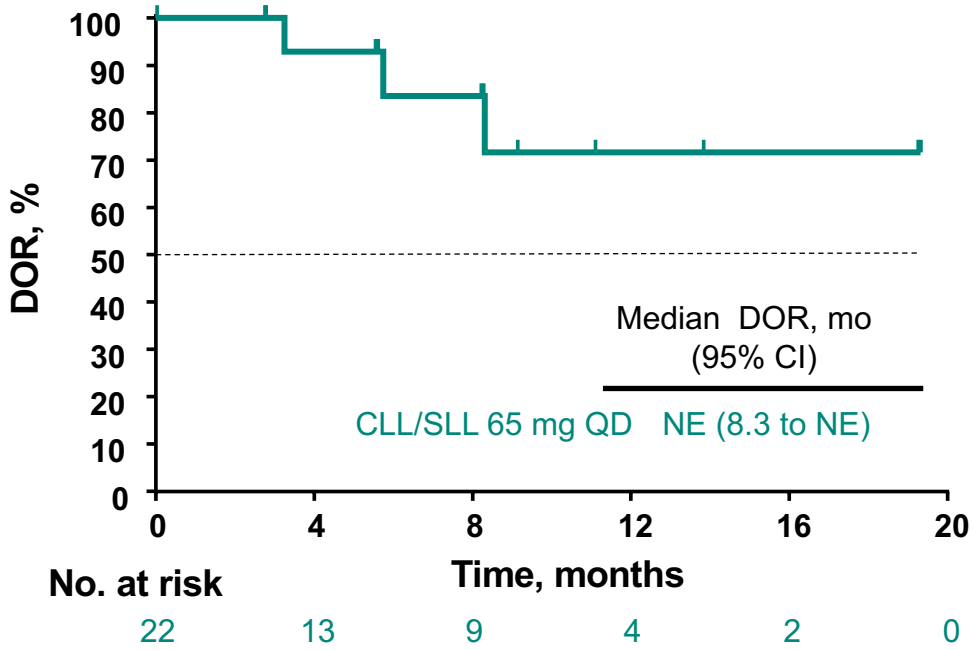
The James

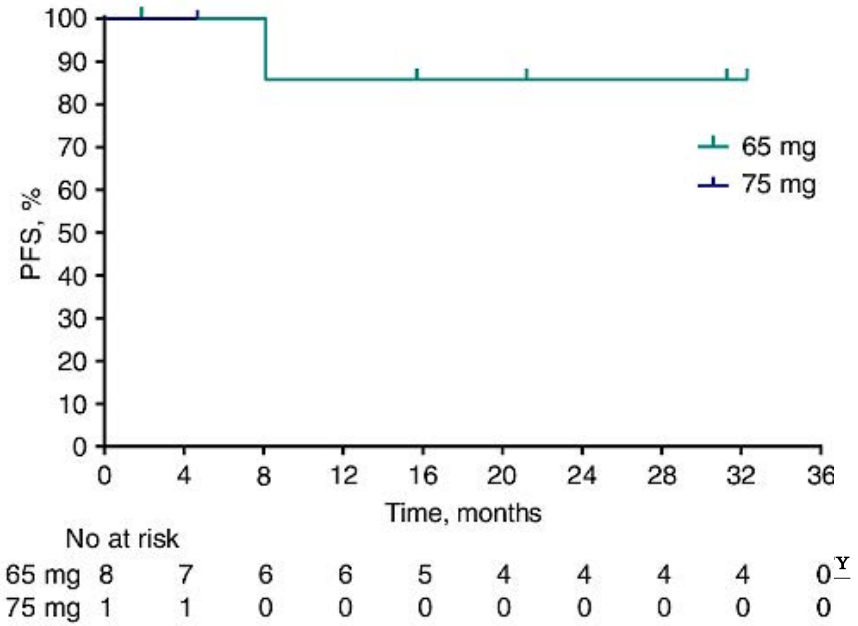
The Ohio State University Comprehensive Cancer Center

Jurczak et al, ASH 2025 Abstract LBA-3

Nemtabrutinib Phase 1 Trial

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%) [40.8-73.6]**
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]





Woyach et al, Cancer Discov 2024

Take home points

- Sequencing of therapy in CLL begins in the frontline setting
- Fixed duration regimens offer the potential for retreatment
- Non-covalent BTKi are effective after covalent BTKi
- CLL-313 and CLL-314 demonstrate potential for pirtobrutinib prior to covalent BTKi, even in the frontline setting
- This will be an exciting year at ASH!

Case Presentation: 77-year-old man with high-risk (del[TP53]) CLL experiences disease progression on ibrutinib and then venetoclax/obinutuzumab

Dr Tina Bhatnagar (Wheeling, West Virginia)

RTP
RESEARCH
TO PRACTICE

Discussion Questions

How do you define “high-risk” CLL? What is your usual approach to up-front treatment for these patients?

How do you decide whether (and when) to re-treat with a venetoclax-based regimen for a patient who responds to venetoclax-based time-limited treatment and then experiences disease progression?

Discussion Questions

What is known about outcomes with pirtobrutinib treatment in patients with CLL and del(17p) or TP53 mutations?

Based on available data and your personal clinical experience, how would you compare the side effects and toxicities of pirtobrutinib versus the covalent BTKis (arthralgias/rash, atrial fibrillation, bleeding)?

Discussion Questions

Would you have any hesitation about employing pirtobrutinib in a patient who experienced significant tolerability issues with a covalent BTK inhibitor in the past?

Case Presentation: 82-year-old man with IGHV-unmutated CLL who previously received FCR now experiences disease relapse after 5 years of acalabrutinib. A BTK C481S resistance mutation is detected

Dr Priya Rudolph (Athens, Georgia)

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TO PRACTICE

Discussion Questions

Considering the recent FDA approval of pirtobrutinib for patients with CLL who have experienced relapse on a covalent BTKi, for which patients will you use it in the second line ahead of Bcl-2 inhibitor-based treatment?

Do you generally assess BTK resistance mutations in all patients who experience disease progression on a covalent BTKi? How, if at all, does the presence of specific BTK resistance mutations impact your approach to CLL management?

Discussion Questions

Based on the emerging results from BRUIN CLL-313 and BRUIN CLL-314, are there situations in which you will consider employing pirtobrutinib as first-line treatment?

Agenda

Module 1: Current and Emerging Approaches to First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Davids

Module 2: Optimal Management of Adverse Events with Bruton Tyrosine Kinase and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Prof Tam

Module 3: Selection and Sequencing of Therapy for Relapsed/Refractory CLL — Dr Woyach

Module 4: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Fakhri

Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL

Bita Fakhri, MD, MPH
Assistant Professor of Medicine
Stanford University School of Medicine

Outline

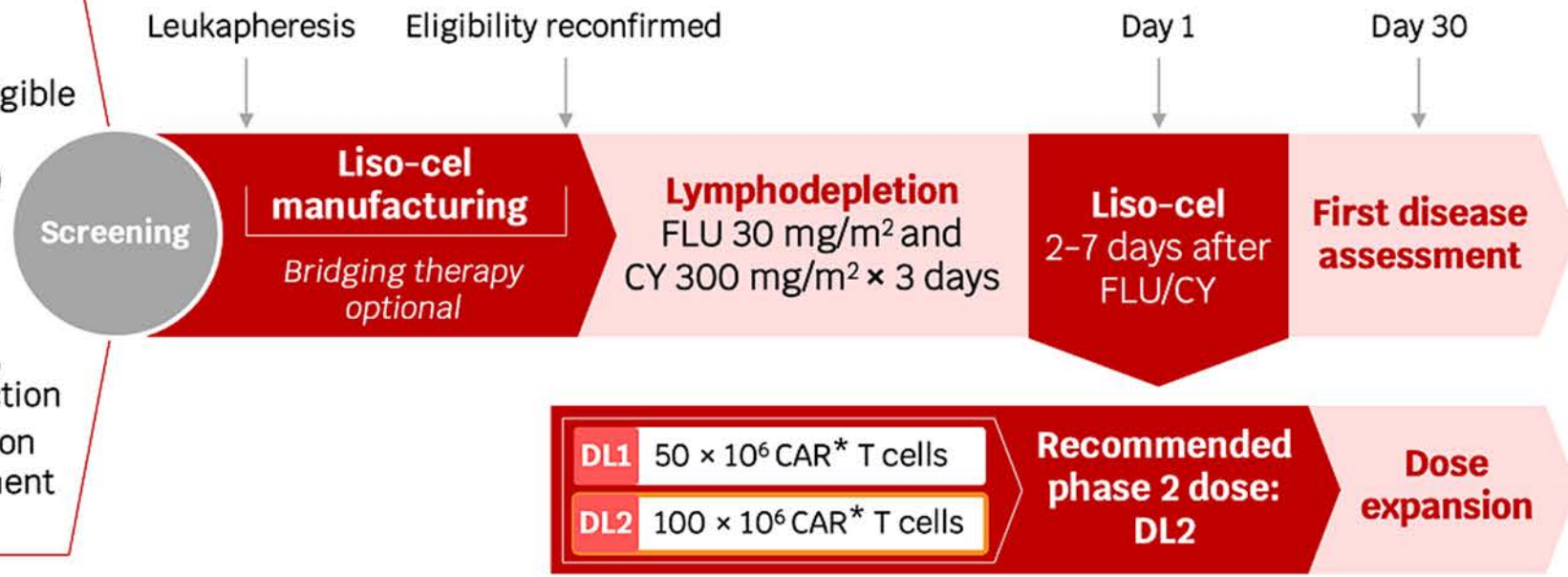
- CAR T therapy
- CAR T plus ibrutinib
- Epcoritamab in CLL
- Epcoritamab in Richter transformation
- RWO of liso-cel in Richter transformation
- BTK degraders

CAR T Therapy

TRANSCEND CLL 004: phase 1/2, open-label, multicenter study

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



Follow-up

On-study:
up to 48 months[a]

Long-term (NCT03435796):
up to 15 years after liso-cel infusion

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)

Wierda et. al. EHA 2024 Oral Presentation.

Phase 1/2 TRANSCEND CLL-004: Baseline Characteristics

	Full study population (n = 118)	BTKi progression/venetoclax failure subset (n = 71)	Prior BTKi exposure and venetoclax-naïve subset (n = 23)
Median (range) age, y	65 (49–82)	66 (49–78)	59 (49–75)
Median (range) prior lines of systemic therapy	5 (2–14)	5 (2–14)	3 (2–11)
Bulky lymph nodes,[a] n (%)			
Yes	54 (46)	33 (46)	7 (30)
Unknown	9 (8)	8 (11)	0
High-risk cytogenetics,[b] n (%)	98 (83)	61 (86)	17 (74)
Del(17p)	49 (42)	33 (46)	7 (30)
TP53 mutation	55 (47)	36 (51)	8 (35)
Unmutated IGHV	55 (47)	32 (45)	12 (52)
Prior BTKi, n (%)	118 (100)	71 (100)	23 (100)
BTKi refractory[c]	104 (88)	71 (100)	19 (83)
BTKi relapsed[d]	2 (2)	0	1 (4)
BTKi intolerant only	12 (10)	0	3 (13)
Prior venetoclax, n (%)	95 (81)	71 (100)	0
Venetoclax refractory[c]	90 (76)	68 (96)	0
Venetoclax relapsed[d]	0	0	0
Venetoclax intolerant only	4 (3)	3 (4)	0
Prior BTKi and venetoclax, n (%)	95 (81)	71 (100)	0
BTKi progression/venetoclax failure[e]	71 (60)	71 (100)	0
Prior chemoimmunotherapy, n (%)	102 (86)	63 (89)	23 (100)
Received bridging therapy, n (%)	90 (76)	56 (79)	15 (65)

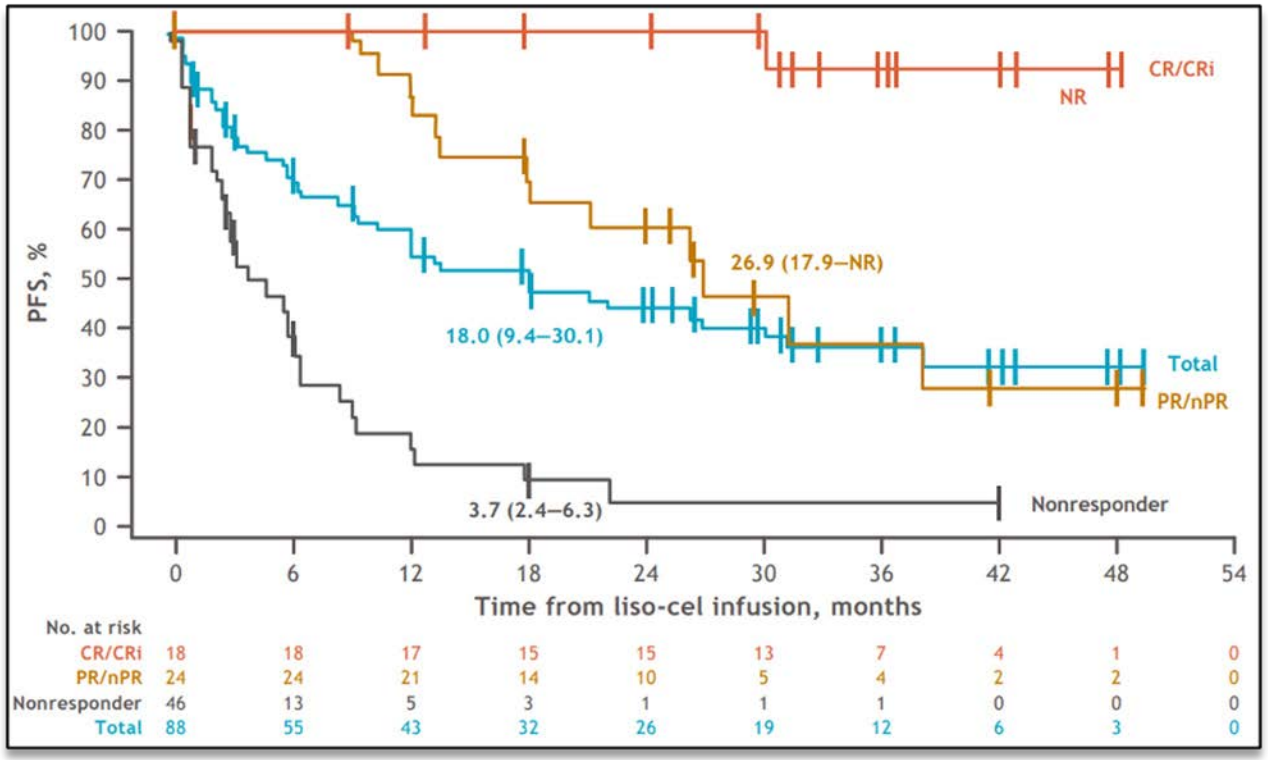
Siddiqi et al; ASH 2024

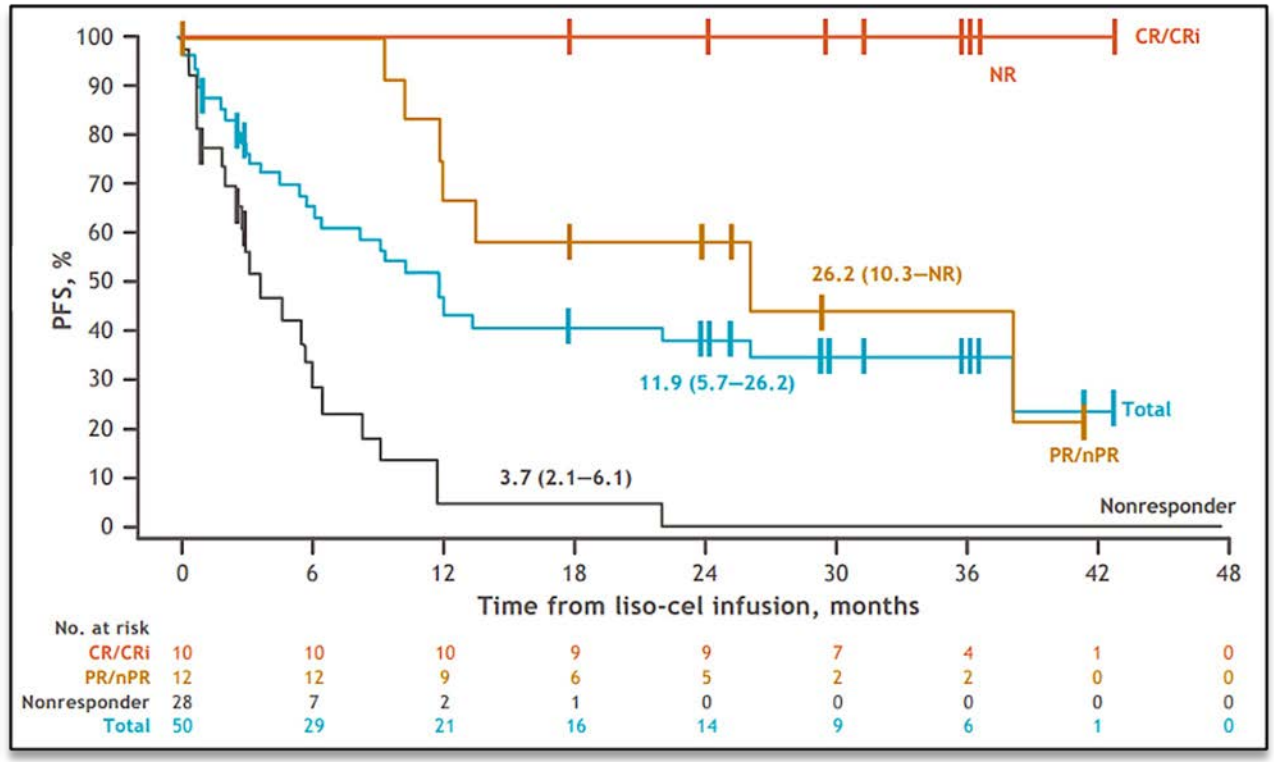
Phase 1/2 TRANSCEND CLL-004: Response at DL2

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)	Prior BTKi exposure and venetoclax-naïve subset at DL2 (n = 18)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	18 (20) [13–30]	10 (20) [10–34]	4 (22) [6–48]
Key secondary endpoints			
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37–59]	22 (44) [30–59]	11 (61) [36–83]
uMRD4 rate in blood, n (%) [95% CI]	58 (66) [55–76]	32 (64) [49–77]	12 (67) [41–87]
Exploratory endpoint: uMRD4 rate in marrow, n (%) [95% CI]	53 (60) [49–70.5]	30 (60) [45–74]	12 (67) [41–87]
Other secondary endpoints			
Best overall response, n (%)			
CR/CRi	18 (20)	10 (20)	4 (22)
PR/nPR	24 (27)	12 (24)	7 (39)
SD	34 (39)	21 (42)	6 (33)
PD	6 (7)	4 (8)	0
Not evaluable	6 (7)	3 (6)	1 (6)
Median (range) time to first response, months	1.3 (0.8–17.4)	1.2 (0.8–17.4)	2.6 (0.9–6.3)
Median (range) time to first CR/CRi, months	4.4 (0.8–18.0)	2.1 (0.8–18.0)	9.0 (3.2–15.2)

Siddiqi et al; ASH 2024

Phase 1/2 TRANSCEND CLL-004: PFS (median follow up 31.4 months)





Siddiqi et al; ASH 2024

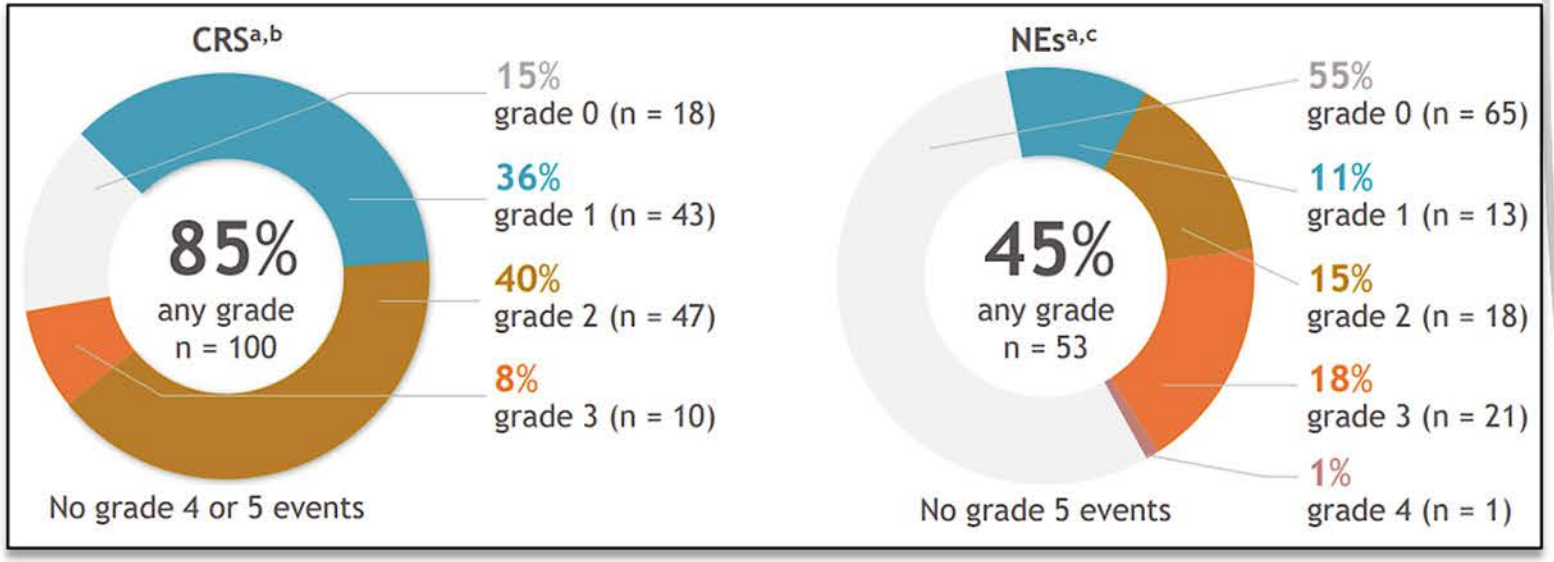
Phase 1/2 TRANSCEND CLL-004: Safety

Adverse Events of Special Interest (AESI)

	Full Study Population (n = 118)
Prolonged cytopenias,[a] n (%)	64 (54)
Grade ≥3 Infections,[b] n (%)	21 (18)
Second Primary Malignancy, [c] n (%)	11 (9)

[a]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at Day 30 after liso-cel infusion; [b] Includes grade ≥ 3 TEAEs from infections and infestations (System Organ Class) by AE high-level group term; [c]AEs from the 90-day TE period, post-TE period, and LTFU were included.

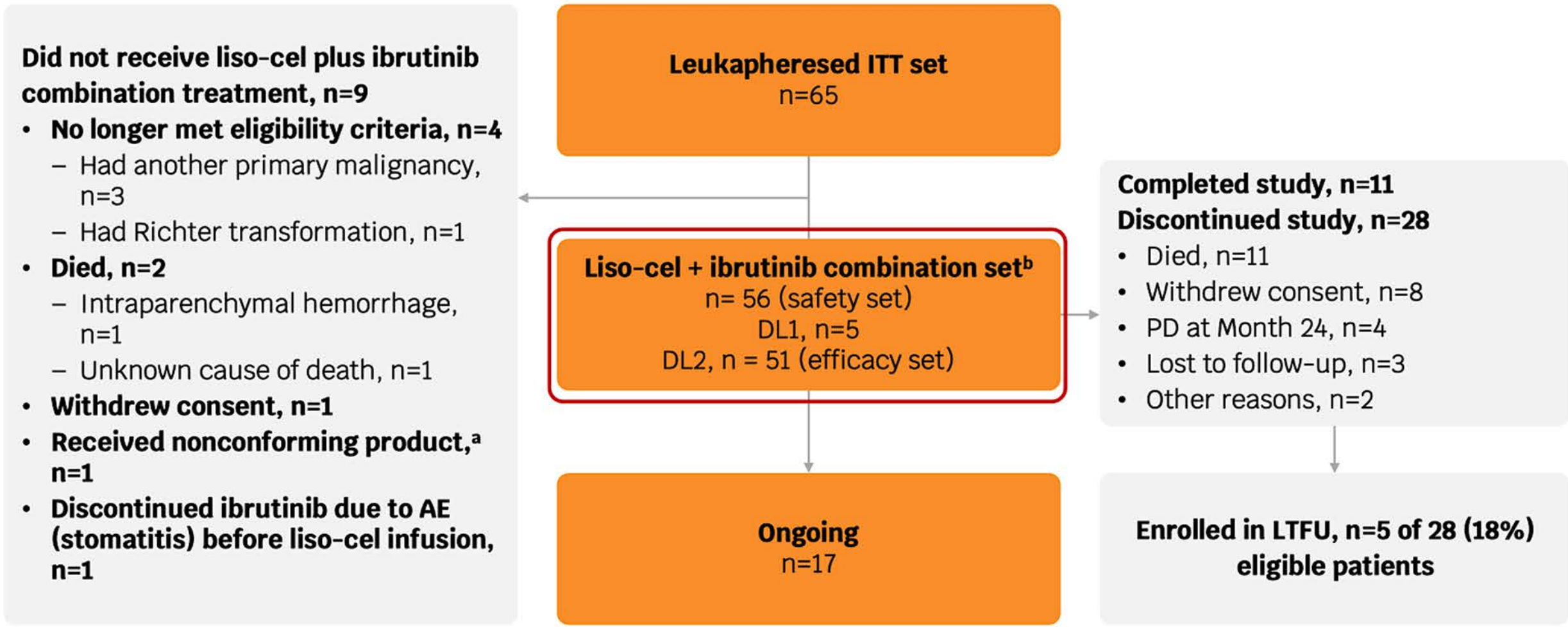
CRS and Neurological Events (NE)



[a]Summed percentages for grouped grades within each graph may not equal the any-grade percentage due to rounding; [b]CRS was graded based on the Lee 2014 criteria 3 ; [c]NEs were defined as investigator-identified neurological AEs related to liso-cel.

Siddiqi et al; ASH 2024

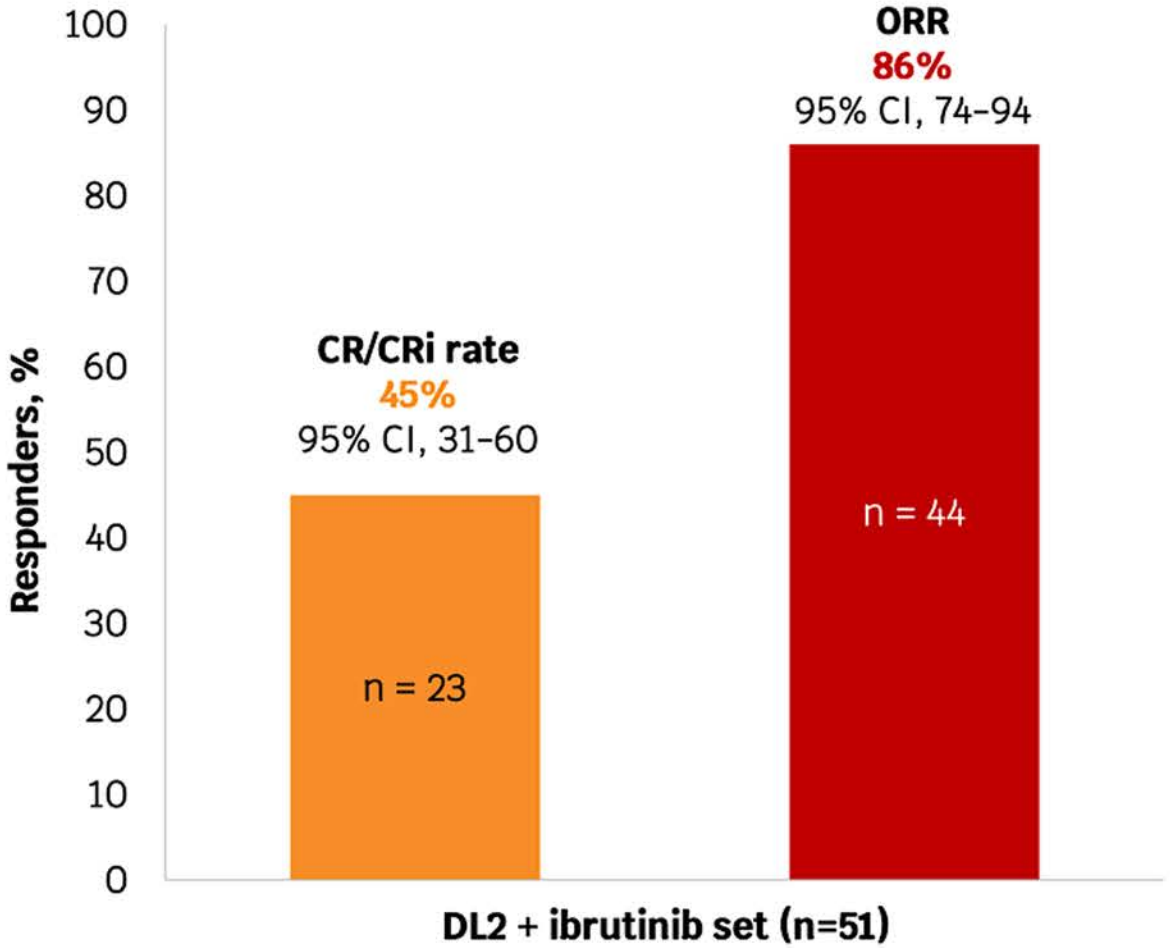
TRANSCEND CLL 004: Liso-cel +Ibrutinib cohort



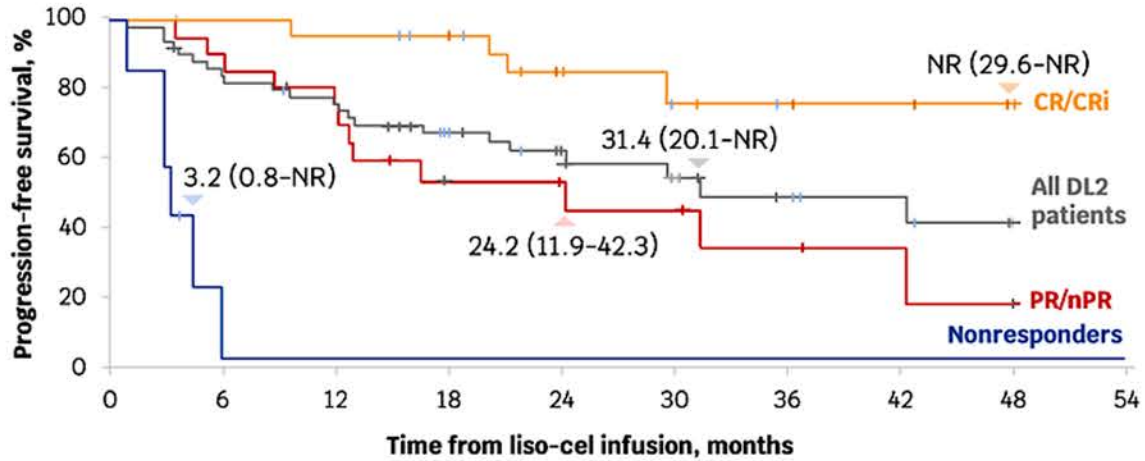
Wierda W. et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

TRANSCEND CLL 004: Liso-cel +Ibrutinib cohort: Key Efficacy Outcomes @ 24.3 mos

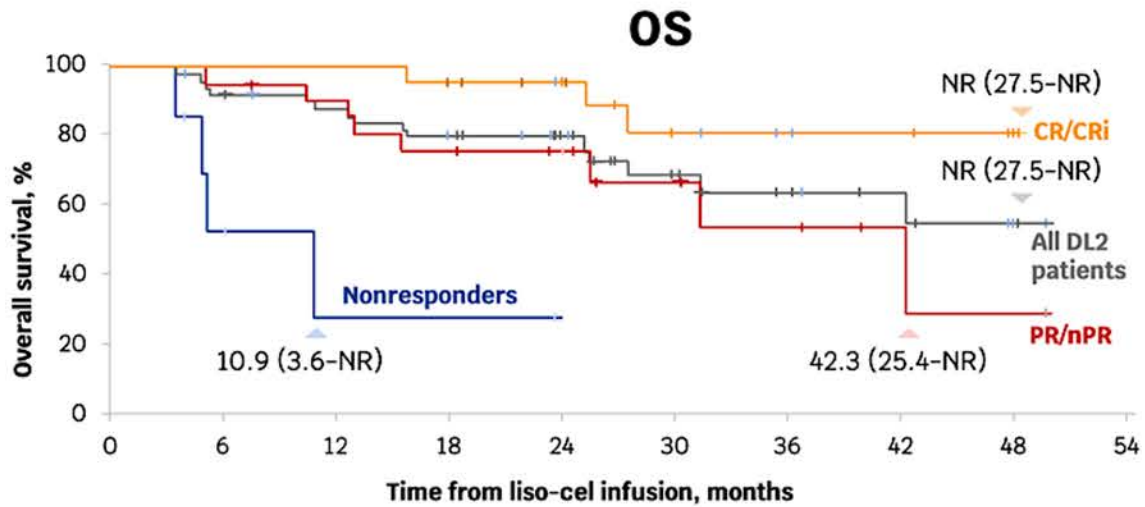
Response by INV



PFS



OS



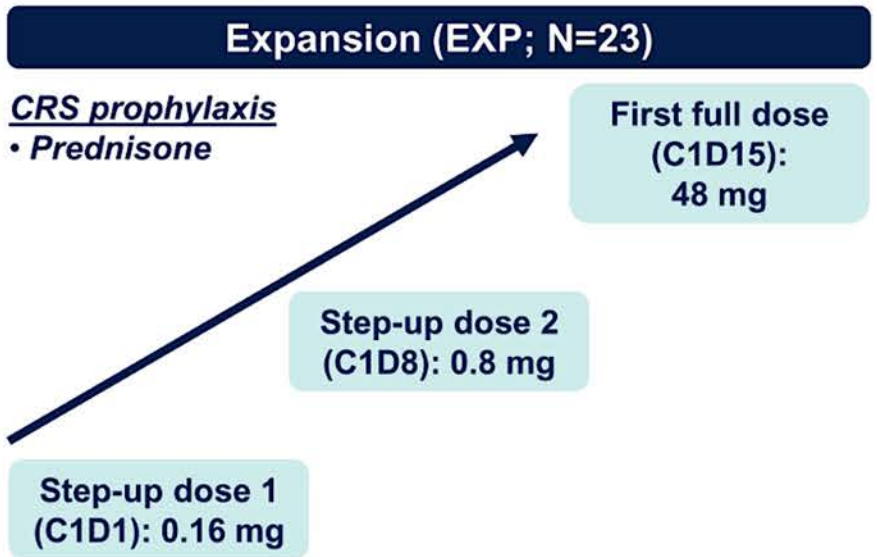
Wierda W. et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

CD3 x CD20 Bispecific T Cell Engagers

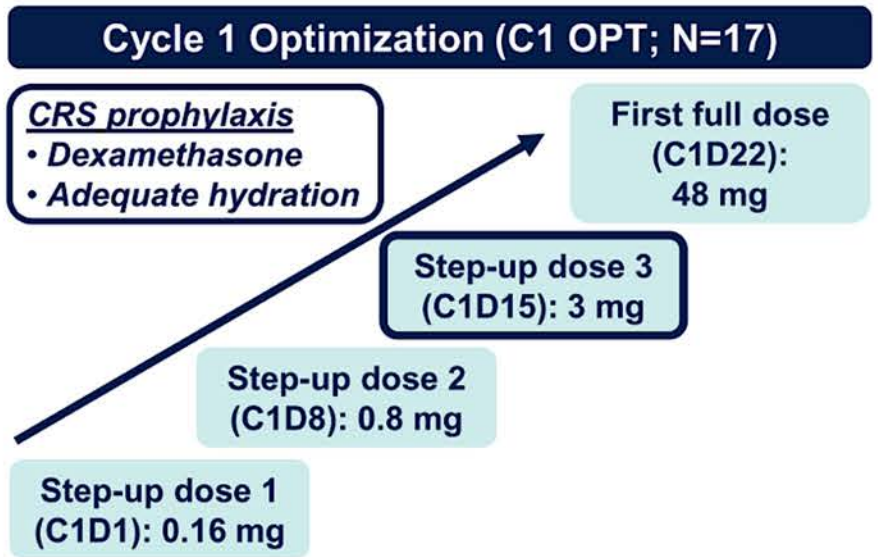
Study Design: EPCORE® CLL-1 Expansion and C1 Optimization

Key inclusion criteria

- $CD20^+$ R/R CLL
- ≥2 prior lines of systemic therapy
- ECOG PS 0–2
- Measurable disease with ≥5×10^9/L B lymphocytes (expansion only)
- No prior allogeneic HSCT



Data cutoff: May 28, 2024
Median follow-up: 22.8 months



Data cutoff: May 28, 2024
Median follow-up: 2.9 months

- **Primary endpoint (EXP):** Overall response rate
- **Primary endpoint (C1 OPT):** Incidence and severity of CRS, ICANS, and clinical TLS
- **Key secondary endpoints (EXP):** CR rate, time to response, MRD (PBMCs using the clonoSEQ® assay), and safety/tolerability

- To ensure patient safety and better characterize CRS, inpatient monitoring was required for at least 24 hours after each epcoritamab dose in C1

Danilov et al; ASH 2024

Comparable High-Risk R/R CLL Populations Between EXP and C1 OPT

Characteristic	EXP N=23	C1 OPT N=17
Median age, years (range)	72 (55–83)	68 (56–81)
Male sex at birth, n (%)	17 (74)	14 (82)
Race, n (%)[a]		
White	19 (83)	14 (82)
Black or African American	0	1 (6)
Not reported	3 (13)	2 (12)
CLL characteristics (local lab), n (%)		
High risk		
Rai stage III–IV[b]	13 (57)	10 (59)
Binet stage C[c]	2 (9)	6 (35)
Beta-2 microglobulin >3.5 mg/L	19 (83)	10 (59)
IGHV unmutated	16 (70)	12 (71)
Unknown	3 (13)	3 (18)
TP53 aberration	15 (65)	10 (59)
Unknown	2 (9)	2 (12)

Treatment History	EXP N=23	C1 OPT N=17
Median time from initial diagnosis to first dose, **years** (range)	13 (6–19)	11 (6–18)
Median time from last treatment to first dose, **months** (range)	0.7 (0.1–49.4)	1.6 (−0.7–39.6)
Median number of prior lines of therapy (range)	**4 (2–10)**	**4 (2–10)**
≥4 prior lines of therapy, n (%)	14 (61)	9 (53)
Prior therapy, n (%)[d]	23 (100)	17 (100)
Chemoimmunotherapy	23 (100)	12 (71)
Small molecules		
BTK inhibitor[e]	23 (100)	17 (100)
Pirtobrutinib	1 (4)	5 (29)
Refractory to BTK inhibitor	20 (87)	16 (94)
BCL-2 inhibitor	19 (83)	15 (88)
Discontinuation due to progression	10 (43)	10 (59)
Relapsed <12 months from last dose	3 (13)	4 (24)

Danilov et al; ASH 2024

Deep Responses Across Subgroups

Response, n (%)	EXP mFU: 22.8 months					C1 OPT mFU: 2.9 months
	Full Analysis Set N=23	Response Evaluable n=21	*TP53* Aberration n=15	*IGHV* Unmutated n=16	Double Exposed[a] n=19	Response Evaluable n=10
Overall response[b]	**14 (61)**	**14 (67)**	**10 (67)**	**10 (63)**	**10 (53)**	**6 (60)**
Complete response	9 (39)	9 (43)	5 (33)	7 (44)	7 (37)	1 (10)
Partial response	5 (22)	5 (24)	5 (33)	3 (19)	3 (16)	5 (50)
Stable disease	4 (17)	4 (19)	2 (13)	3 (19)	4 (21)	2 (20)
Progressive disease	1 (4)	1 (5)	1 (7)	0	1 (5)	1 (10)

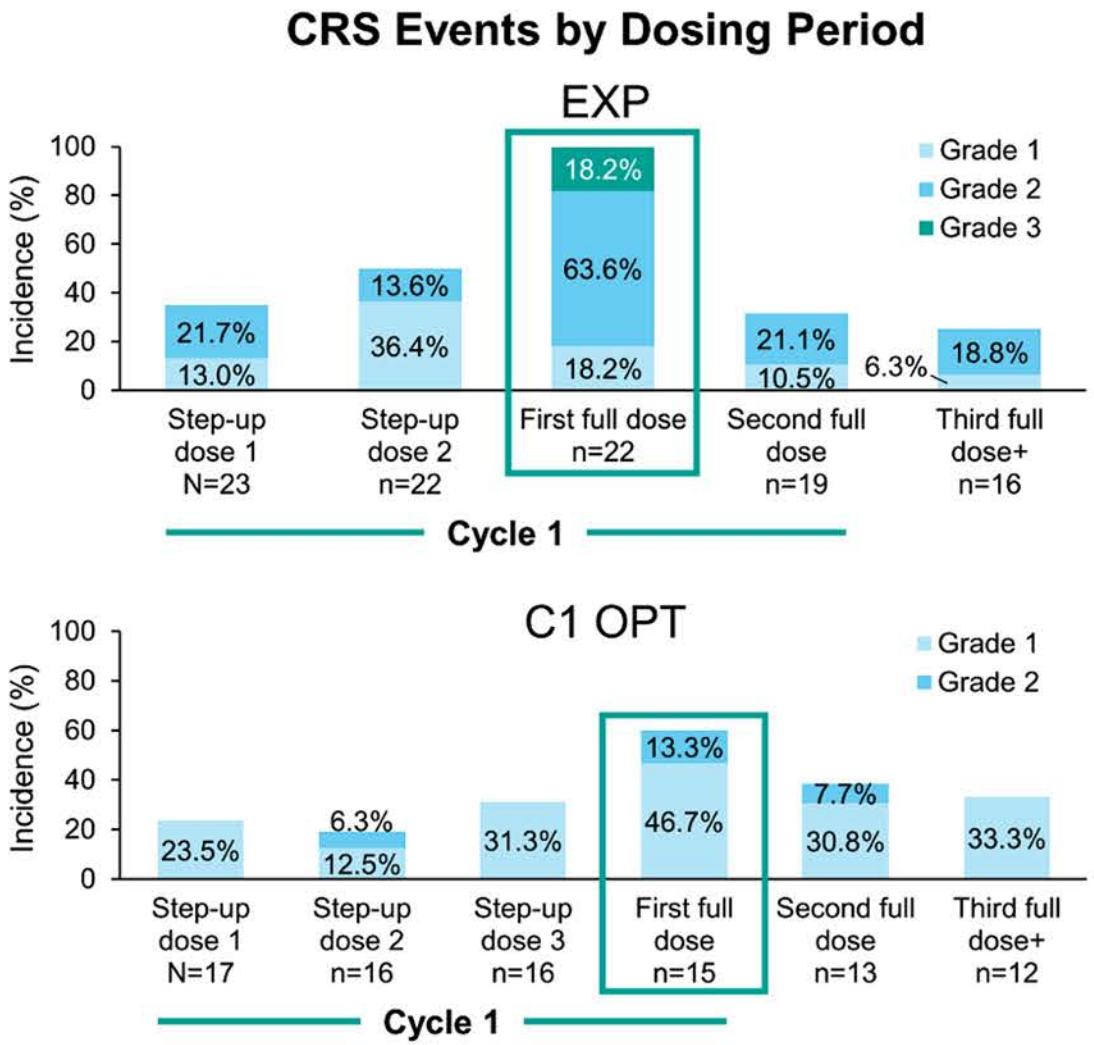
- With limited follow-up, the C1 OPT regimen does not appear to affect epcoritamab efficacy
- uMRD4 in PBMCs was observed in most responders, including all patients with CR who were tested for MRD

EXP MRD Negativity, n/n (%)[c]	uMRD4	uMRD6[d]
Overall response[b]	9/12 (75)	8/12 (67)
Complete response	7/7 (100)	6/7 (86)
Partial response	2/5 (40)	2/5 (40)
Full analysis set	9/23 (39)	8/23 (35)

Danilov et al; ASH 2024

C1 OPT Mitigated Adverse Events of Interest Including ICANS and Clinical TLS

	EXP N=23	C1 OPT N=17
CRS, n (%)	**22 (96)**	**14 (82)**
Grade 1	2 (9)	12 (71)
Grade 2	16 (70)	2 (12)
Grade 3	4 (17)	0
Treated with tocilizumab, n (%)	20 (87)	6 (35)
Leading to treatment discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	22/22 (100)	14/14 (100)
Median time to resolution, days (range)	3 (1–16)	3.5 (1–7)
ICANS, n (%)	**3 (13)**	**0**
Grade 1	1 (4)	0
Grade 2	2 (9)	0
Clinical TLS, n (%)	**1 (4)**	**0**
Grade 2	1 (4)	0



Danilov et al; ASH 2024

Richter’s Syndrome

Background and Study Design

- Epcoritamab is a subcutaneous CD3×CD20 bispecific antibody approved for R/R DLBCL and FL[1], and has shown promising efficacy and manageable safety in patients with RT[2]
- Here, we report updated efficacy and safety results of epcoritamab monotherapy from the expansion cohort (Arm 2A) of the EPCORE CLL-1 trial, with a focus on patients receiving epcoritamab as 1L RT-directed treatment for efficacy outcomes and in all RT patients for pharmacodynamic and safety outcomes

EPCORE® CLL-1 (NCT04623541) RT Monotherapy Expansion Cohort

Key RT inclusion criteria

- Prior clinical history of CLL or SLL
- Biopsy-proven transformation to CD20+ DLBCL
- Ineligible for or declined chemotherapy
- Measurable disease by PET and/or CT/MRI
- ≤2 prior LOTs for RT
- ECOG PS 0–2

Hospitalization was required for 24 hours after the first full dose of epcoritamab (C1D15)

Median follow-up: overall RT 22.9 months (range, 0.5+ to 39.9)
1L RT 23.9 months (range, 0.5+ to 39.9)

Overall RT (N=42)
1L RT (n=21)

2 step-up dosing[a]

Epcoritamab 48 mg
28-day cycles
QW C1–3
Q2W C4–9
Q4W C10+

→ Efficacy assessment by PET-CT obtained Q6W until C6, and then Q24W thereafter

→ Treatment until disease progression or unacceptable toxicity

Primary endpoint: ORR by IRC
Key secondary endpoints: CR rate, DoR, DoCR, time to response and to CR, PFS, OS, and safety/tolerability

Kater, et al; iwCLL 2025

Baseline Characteristics

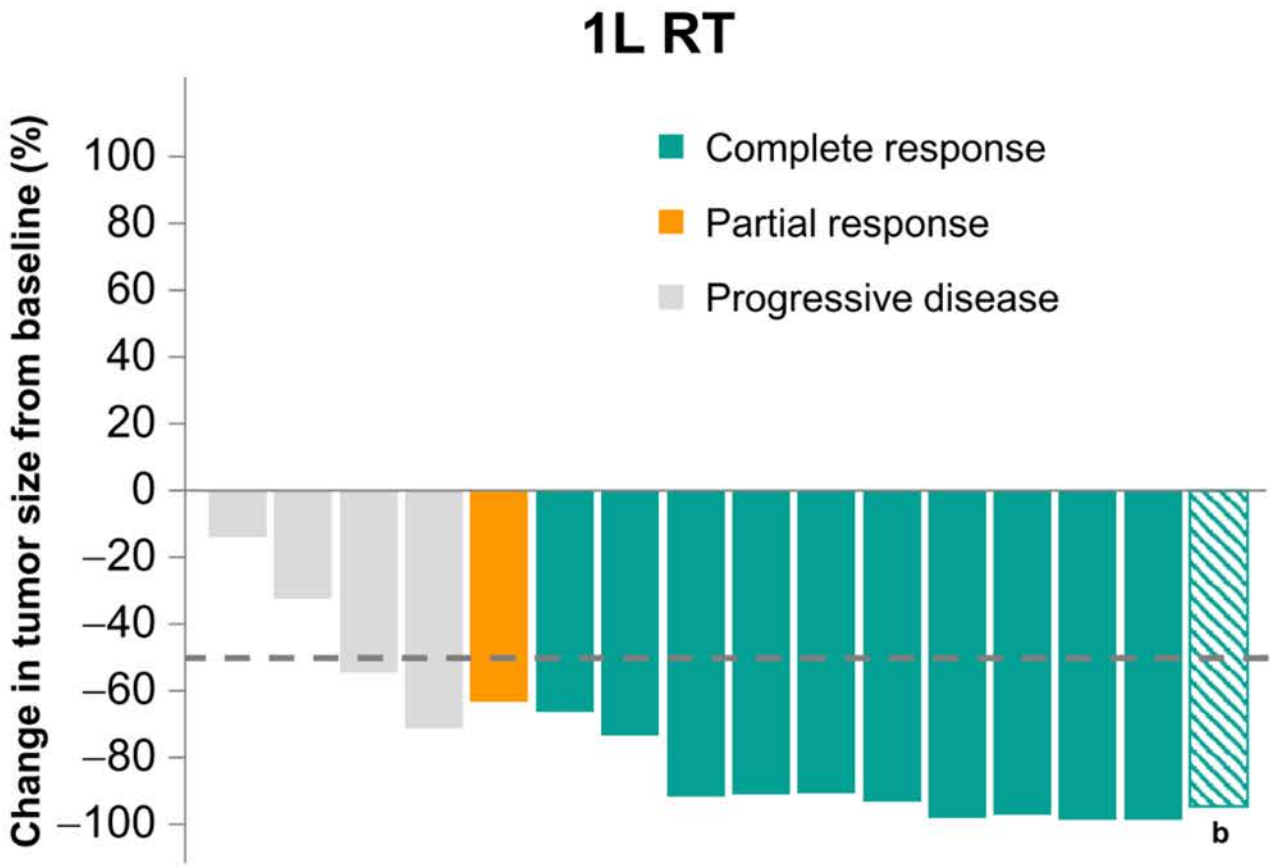
Treatment History	Overall RT (N=42)	1L RT (n=21)
Prior CLL/SLL therapy, n (%)[a]	32 (76)	20 (95)
Chemoimmunotherapy	24 (57)	16 (76)
BCL-2 inhibitor	17 (40)	13 (62)
BTK inhibitor	22 (52)	14 (67)
CAR T cell therapy	1 (2)	1 (5)
Prior lines of CLL/SLL therapy, median (range)[b]	2.0 (1–7)	2.5 (1–7)
Prior RT therapy, n (%)	21 (50)	NA
R-CHOP regimens	16 (38)	NA
R-EPOCH regimens	2 (5)	NA
BCL-2 inhibitor	5 (12)	NA
BTK inhibitor	6 (14)	NA

Baseline Characteristics	Overall RT (N=42)	1L RT (n=21)
Median age, years (range)	69 (50–80)	67 (50–79)
Male sex at birth, n (%)	32 (76)	17 (81)
Ann Arbor stage, n (%)		
III	15 (36)	7 (33)
IV	23 (55)	12 (57)
TP53 aberration		
With *TP53* aberration[c]	20 (48)	11 (52)
Without *TP53* aberration	14 (33)	7 (33)
Missing	8 (19)	3 (14)
CLL/SLL diagnosis to RT, median, years (range)	7.6 (0–23.9)	11.8 (0.3–23.9)
RT to first study dose, median, months (range)	2.4 (0.4–86.5)	1.1 (0.4–2.6)

Kater, et al; iwCLL 2025

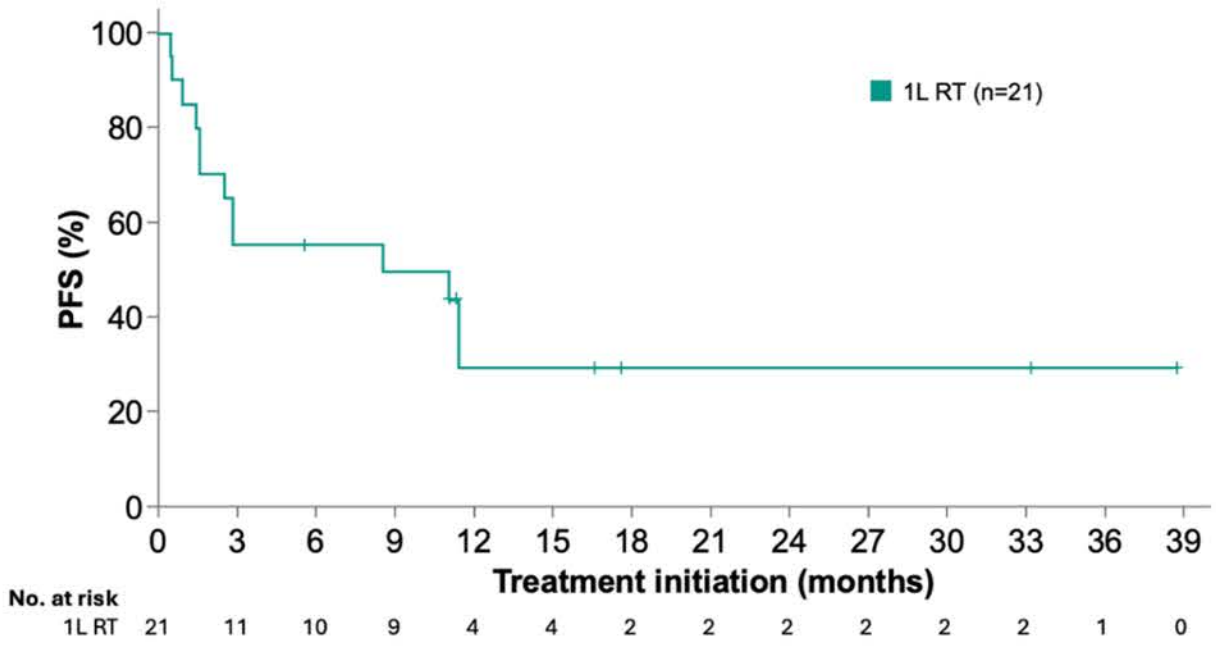
High Response Rates and Reduction in Tumor Size

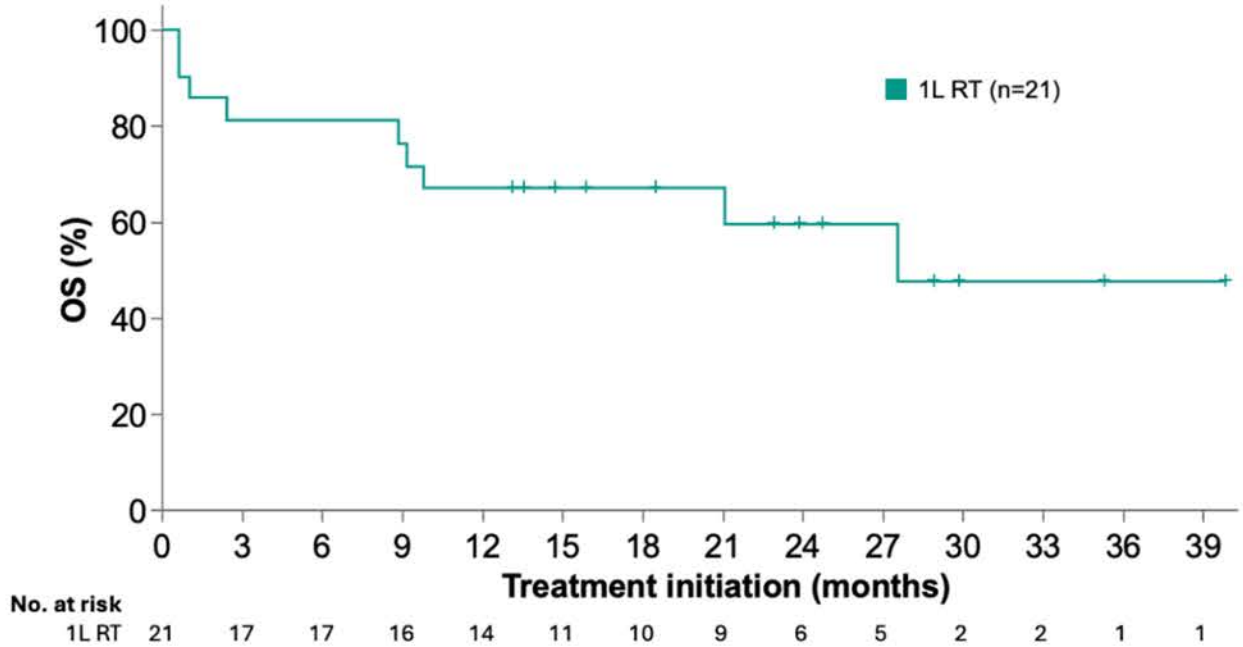
Response, n (%)	1L RT (n=21)
Overall response rate [95% CI]	12 (57) [34.0–78.2]
Complete response	11 (52)
Partial response	1 (5)
Stable disease	0
Progressive disease	5 (24)
No assessment[a]	4 (19)



Kater, et al; iwCLL 2025

PFS and OS





	1L RT (n=21)
PFS events, n	13
Median PFS, (95% CI)	8.5 (1.5–NR)
Estimated patients remaining progression-free at 6 months, %	55

mDOR not reached

	1L RT (n=21)
OS events, n	9
Median OS, (95% CI)	27.5 (9.1–NR)
Estimated patients remaining alive at 24 months, %	59

Kater, et al; iwCLL 2025

Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients with Richter's transformation from the CIBMTR

Key eligibility criteria

- Patients with Richter's transformation (RT) and evidence of single infusion with commercially available liso-cel in the US
- >1 visit after infusion and
- ≥ 6 months followup before data cutoff date Aug, 4 2023

Baseline Characteristics

- 30 patients with RT
- Received treatment for CLL before RT – 24 (77%)
- Received treatment for RT before liso-cel infusion – 30 (100%)
- Prior agents used for RT – BTKi, BCL2i, anti-CD20, chemoimmunotherapy
- Bridging therapy prior to liso-cel infusion – 13/27 (48%)

Winter et al; ASCO 2024

Response to liso-cel in Richter's Transformation

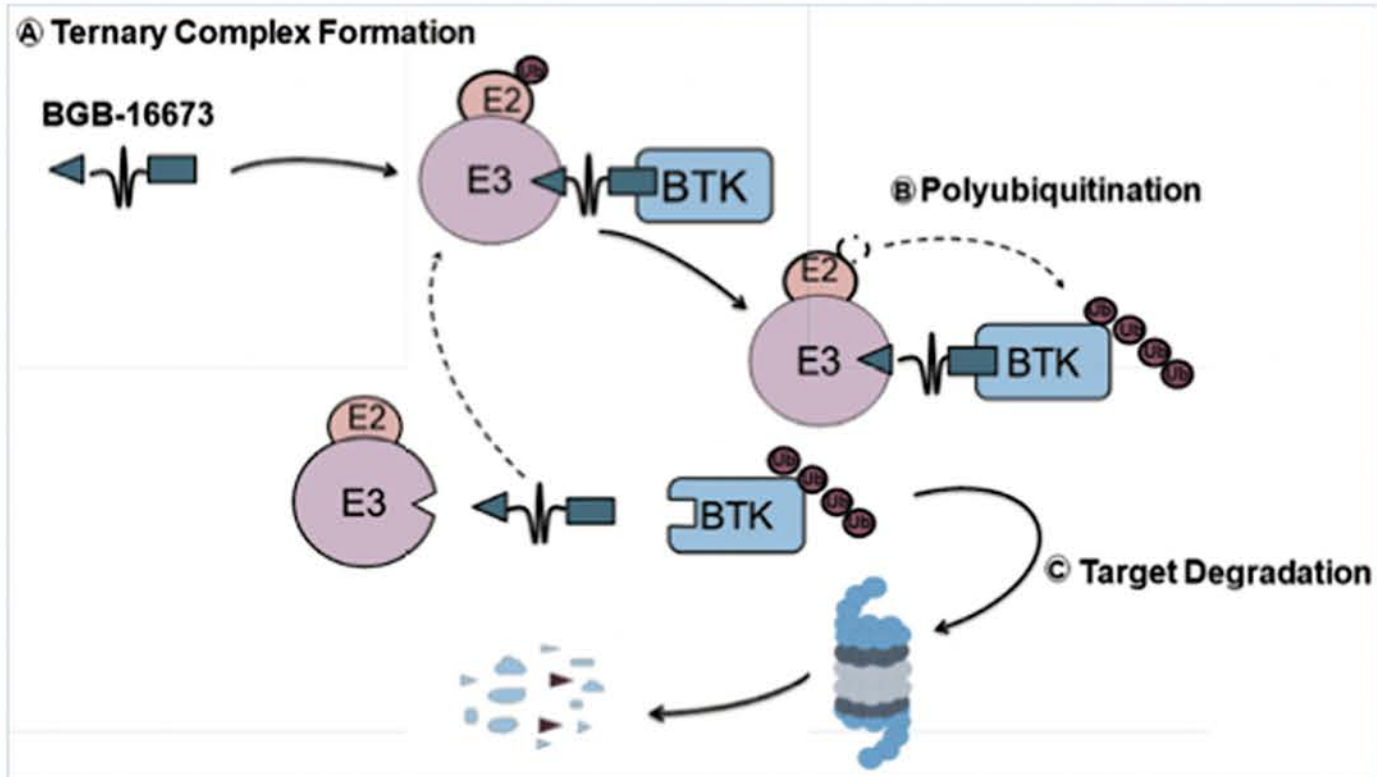
Median follow up	12.3 months
ORR	76% (CR 66%, PR10%)
PFS	• Median NR • 6 month 65% • 12 month 54%
OS	• Median NR • 6 month 79% • 12 month 67%

Winter et al; ASCO 2024

BTK Degraders

BTK Degraders

Figure 1. CDAC mechanism of action



Abbreviations: BTK, bruton tyrosine kinase; CDAC, chimeric degradation activating compound; E2, ubiquitin-conjugating enzymes; E3, ubiquitin ligases; Ub, ubiquitin.

Thompson, et al; ASH 2024

CaDAnCE-101 (BGB-16673-101)

- CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing open-label, phase 1/2 study evaluating BGB-16673 monotherapy in patients with B-cell malignancies.
- Eligible patients must have confirmed R/R CLL/SLL (≥2 prior therapies), an ECOG performance status of 0-2 (0-1 in the EU), and adequate organ function.
- In the US, EU, and Australia, patients must have previously received a covalent BTK inhibitor (cBTKi). Patients received BGB-16673 once daily orally.
- The primary phase 1 objectives were to assess safety/tolerability and to establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to assess overall response rate (ORR).

Study population per abstract with a median follow up 18 m

Characteristics		N = 67 (as of 23MAY2025)
Dose levels	50 mg	N = 1
	100 mg	N = 22
	200 mg	N = 17
	350 mg	N = 15
	500 mg	N = 12
Median age (range)		70 (47-91)
Median prior lines of therapy (range)		4 (2-10)

Characteristics		N = 67 (as of 23MAY2025)
Prior lines of therapy	cBTKi	N = 63 (94%)
	ncBTKi	N = 14 (21%)
	BCL2i	N = 55 (82%)
Del(17p) and/or TP53 mutation		N = 44 (66%)
Unmutated IGHV		N = 38/49 (78%)
BTK mutation		N = 24/63 (38%)
PLCG2 mutation		N = 10/63 (16%)

Inhye Ahn, oral abstract; Saturday, December 6, 09:30 AM - 09:45 AM EST; ASH 2025

Safety profile of CaDAnCE-101 (BGB-16673-101)

- Any-grade TEAEs in ≥25% of patients:
  - fatigue (37.3%)
  - contusion/bruising (31.3%)
  - diarrhea (28.4%)
  - neutropenia (28.4%)

TEAEs led to treatment discontinuation in 12 patients (18%):

three (4.5%) had subdural hemorrhage, maculopapular rash, and disseminated aspergillosis.

four patients (6%) had TEAEs that led to death (all due to infections, including 1 fungal infection); no deaths were deemed related to treatment.

Inhye Ahn, oral abstract; Saturday, December 6, 09:30 AM - 09:45 AM EST; ASH 2025

Efficacy profile of CaDAnCE-101 (BGB-16673-101)

- In 66 response-evaluable patients **ORR (PR-L or better) was 86.4%** (n=57), with a 4.5% (n=3) complete response (CR)/CR with incomplete marrow recovery rate.
- At **200 mg**, **ORR was 94%** (15/16), including 1 CR.
- The median time to first response was 2.8 months (range, 2.0-19.4 months).
- Thirty-three patients (49.3%) remained on treatment for ≥12 months.
- **Responses deepened over time**: of 22 patients with initial PR-L, 15 transitioned to partial response (PR); of 16 patients with initial stable disease, 1 transitioned to PR-L and 10 to PR.
- Responses were seen in patients previously treated with a cBTKi or ncBTKi, double (cBTKi and BCL2i) and triple exposure (cBTKi, BCL2i, and ncBTKi), with and without BTK mutations, with del(17p) and/or TP53 mutation, and with PLCG2 mutation.
- The **12-month progression-free survival rate was 79%**
- 15 patients (22%) had progressive disease (2 associated with Richter transformation to diffuse large B-cell lymphoma), and 4 (6%) died. Further exploratory analyses will be presented at the meeting.
- The 200 mg dose is currently being investigated in phase 2 and 3 studies.

Inhye Ahn, oral abstract; Saturday, December 6, 09:30 AM - 09:45 AM EST; ASH 2025

Other Novel Agents at ASH

PRESENTATION ID 86
OCCC - W224ABEF
Bexobrutideg (NX-5948), a novel Bruton's tyrosine kinase (BTK) degrader, demonstrates rapid and durable clinical responses in Relapsed/Refractory chronic lymphocytic leukemia (CLL): New and updated findings from an ongoing Phase 1a/b trial
Zulfa Omer, MD

Saturday, December 6
09:30 AM - 11:00 AM EST

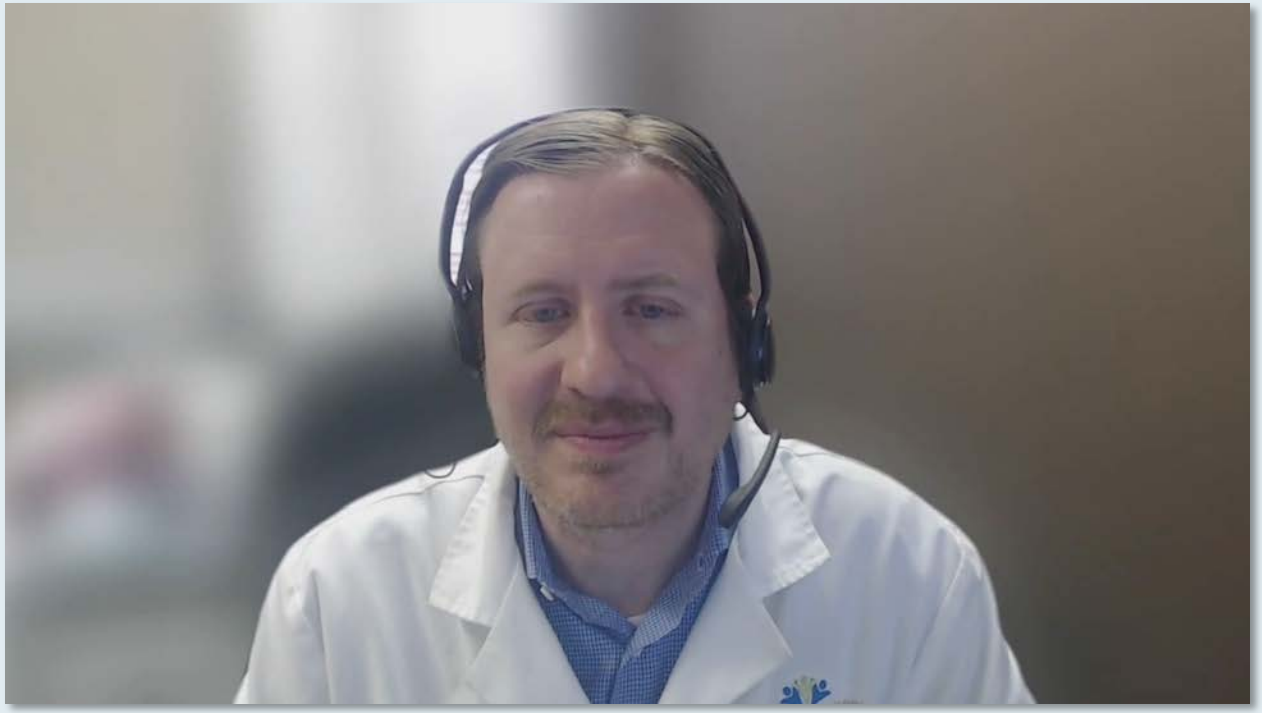
PRESENTATION ID 87
OCCC - W224ABEF
Updates of R/R CLL with prior exposure to Bruton's tyrosine kinase (BTK) inhibitor and/or bcl-2 inhibitor in the Phase 1 trial of LP-168 (Rocbrutinib), a novel COVALENT and non-COVALENT BTK inhibitor
Jennifer Woyach, MD

Saturday, December 6
09:30 AM - 11:00 AM EST

PRESENTATION ID 88
OCCC - W224ABEF
Results of a registrational Phase 2 study of lisaftoclax monotherapy for treatment of patients (pts) with Relapsed/Refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who had failed Bruton's tyrosine kinase inhibitors (BTKis)
Keshu Zhou

Saturday, December 6
09:30 AM - 11:00 AM EST

Case Presentation: 72-year-old man with multiregimen-relapsed CLL experiences 18-month response to pirtobrutinib



Dr Brian Mulherin (Indianapolis, Indiana)

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TO PRACTICE

Discussion Questions

At what point do you consider CAR T-cell therapy with lisocabtagene maraleucel (liso-cel) for patients with R/R CLL?

How do age, performance status and comorbidities factor into the decision of whether and when to recommend CAR T-cell therapy to a patient with R/R CLL?

When is bridging therapy utilized, and which agents are generally used (eg, pirtobrutinib)?

Discussion Questions

Given that bispecific antibodies are clinically available in follicular lymphoma and diffuse large B-cell lymphoma, are there any circumstances in which you would try to access one outside of a clinical trial for a patient with CLL who had exhausted other therapies?

Discussion Questions

How do BTK degraders differ from BTK inhibitors in terms of their mechanism of action?

Given that BGB-16673 has been granted a fast-track designation by the FDA, do you anticipate that it will eventually reach the clinic? Where do you see BTK degraders fitting into the existing treatment paradigm? If you were able to access this agent, are there patients currently in your practice to whom you'd like to administer it?

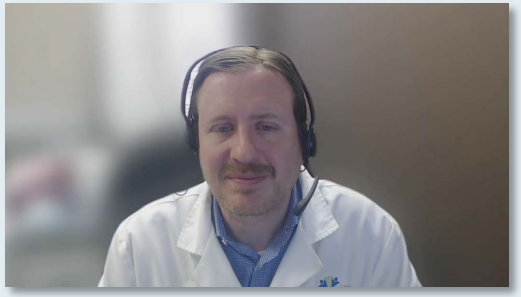
Discussion Questions

How do BTK degraders differ from BTK inhibitors in terms of their mechanism of action? Where do you see BTK degraders fitting into the existing treatment paradigm?

Contributing General Medical Oncologists

Bhavana (Tina) Bhatnagar, DO
WVU Cancer Institute
Wheeling, West Virginia

Zanetta S Lamar, MD
Florida Oncology and Hematology
Naples, Florida



Brian P Mulherin, MD
Hematology Oncology of Indiana
Indianapolis, Indiana

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Erik Rupard, MD
Penn State Cancer Institute
Reading, Pennsylvania

Sean Warsch, MD
Messino Cancer Centers
Asheville, North Carolina

Jennifer Yannucci, MD
Low Country Cancer Care
Savannah, Georgia

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Expert Second Opinion
Investigators Discuss the Optimal Management of Myelofibrosis and Systemic Mastocytosis

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

3:15 PM – 5:15 PM ET

Faculty

Professor Claire Harrison
Andrew T Kuykendall, MD
Stephen T Oh, MD, PhD
Jeanne Palmer, MD
Raajit K Rampal, MD, PhD

Moderator

Neil Love, MD

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

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

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. Online/Zoom attendees: The CME credit link is posted in the chat room.

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