Integrating New Advances into the Care of Patients with Cancer

A Multitumor Symposium in Partnership with the American Oncology Network

CME/MOC, NCPD and ACPE Accredited

Saturday, November 8, 2025
10:00 AM – 3:00 PM CT

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Gainor, Langer and Shields*

Module 2 — Chronic Lymphocytic Leukemia: *Dr Rogers*

Module 3 — Ovarian Cancer: *Dr Konecny*

Module 4 — Gastroesophageal Cancers: *Dr Shah*

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Chronic Lymphocytic Leukemia Faculty

Kerry A Rogers, MD
Associate Professor
Division of Hematology
The Ohio State University
Columbus, Ohio

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

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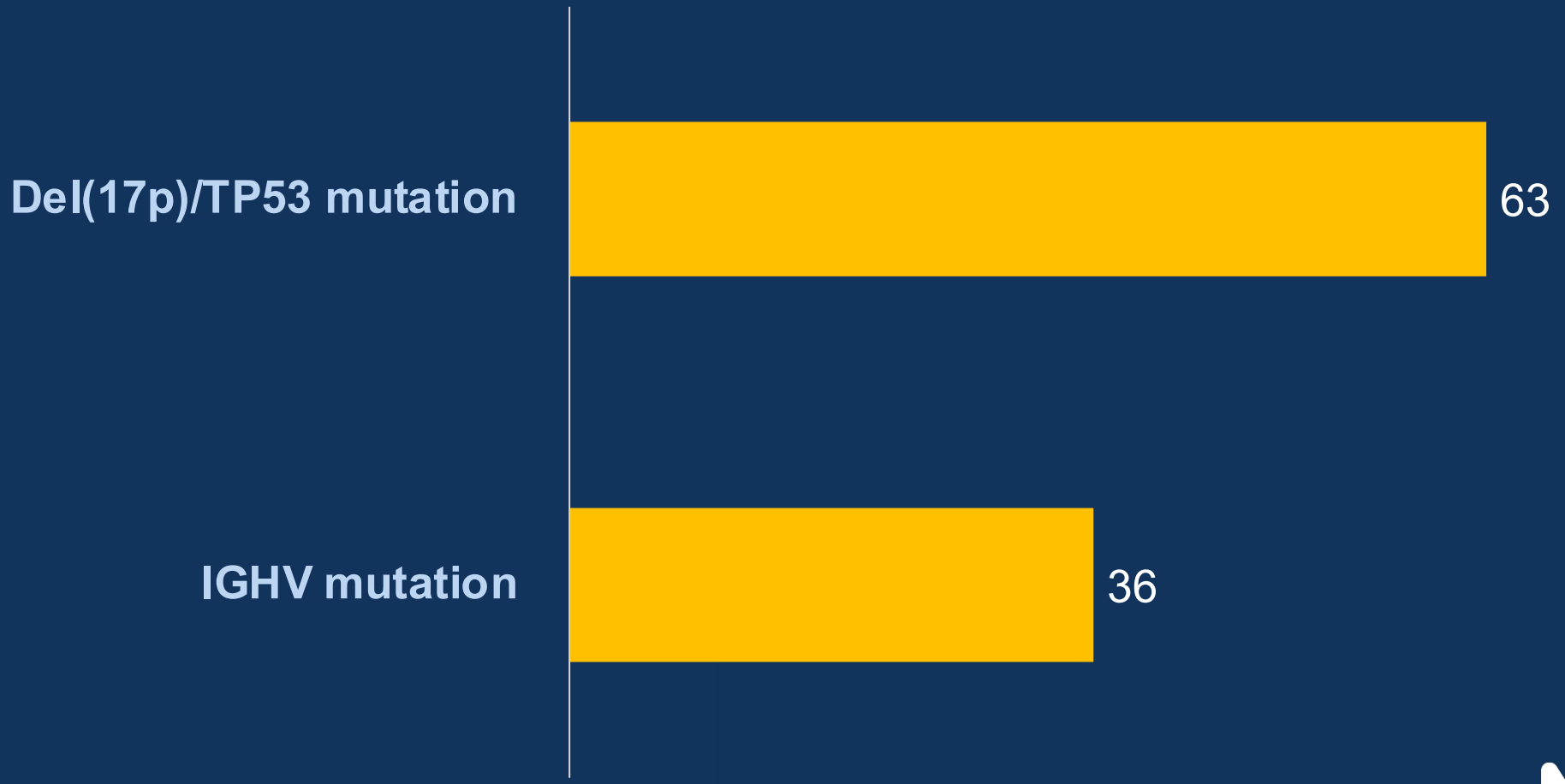
Dr Rogers — Disclosures

Advisory Committees	Genentech, a member of the Roche Group, Janssen Biotech Inc
Consulting Agreements	AbbVie Inc, Alpine Immune Sciences, AstraZeneca Pharmaceuticals LP, BeOne, Genentech, a member of the Roche Group, Lilly
Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Lilly
Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP

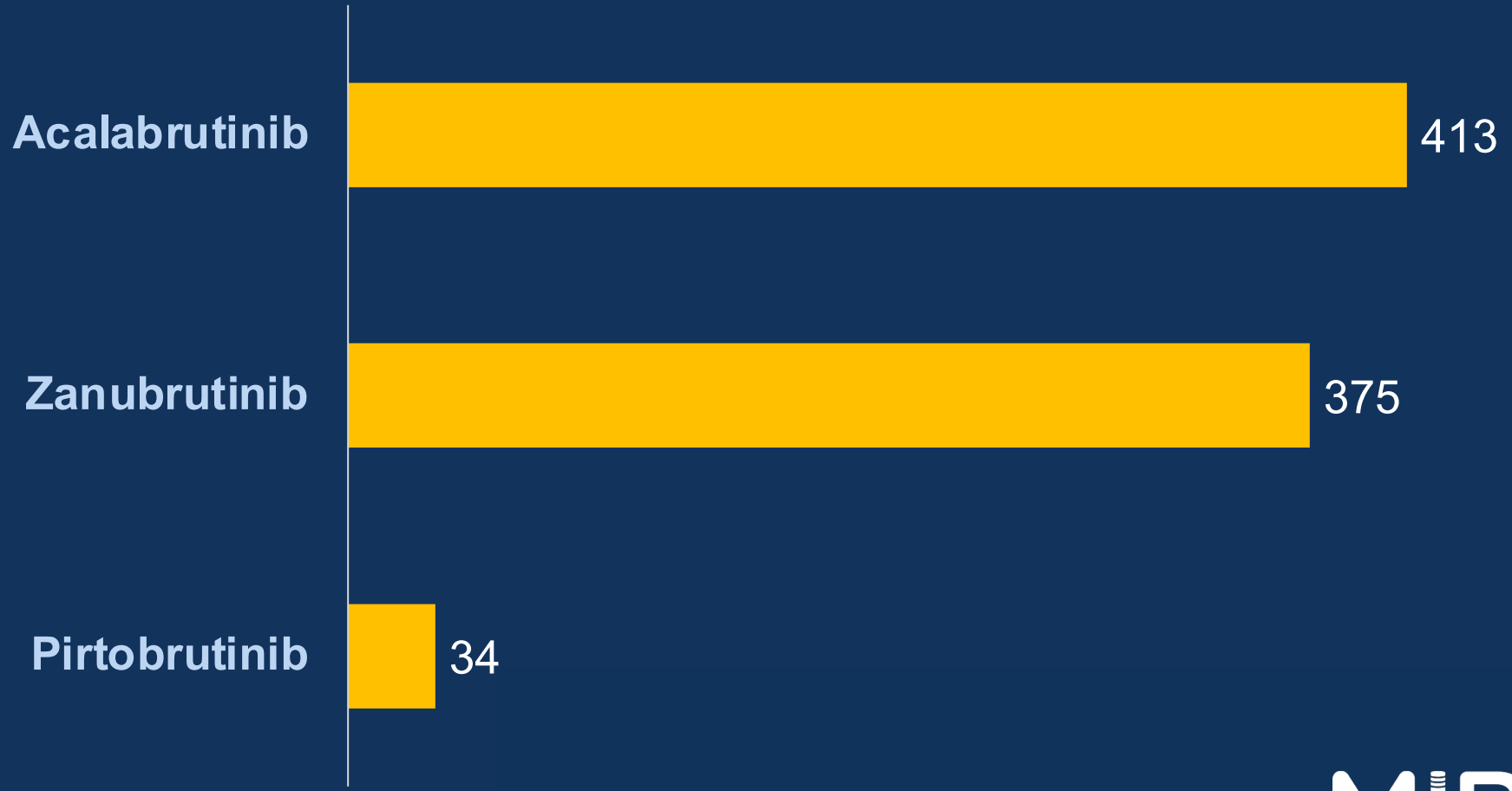
Dr Divers — Disclosures

Advisory Committees	Daiichi Sankyo Inc

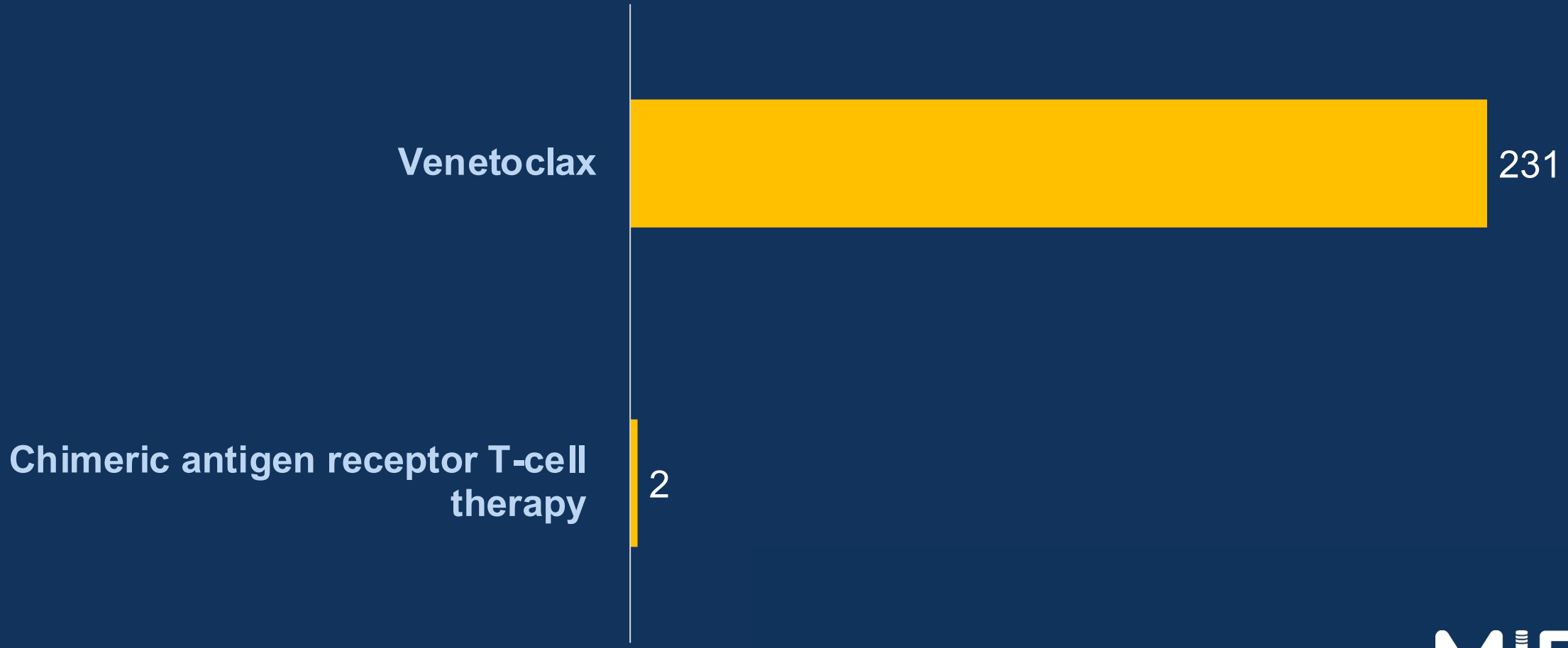
Snapshot of AON Practice
Chronic Lymphocytic Leukemia



Snapshot of AON Practice
Chronic Lymphocytic Leukemia — Bruton Tyrosine Kinase Inhibitors



Snapshot of AON Practice
Chronic Lymphocytic Leukemia — Other Treatments



Chronic Lymphocytic Leukemia

Kerry A Rogers, MD
Associate Professor
Division of Hematology, The Ohio State University
November 8th, 2025

The James
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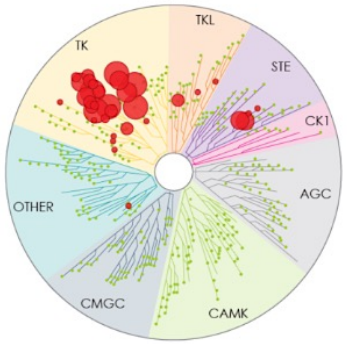
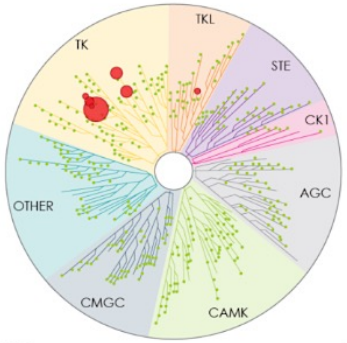
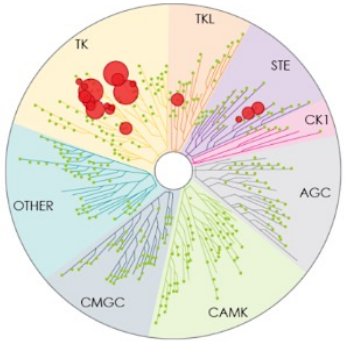
COMPREHENSIVE CANCER CENTER

Initial CLL Treatment Regimens

- Both continuous and fixed-duration options
- Choice depends on CLL features and patient factors

	Continuous BTKi	Venetoclax + Obinutuzumab	BTKi + Venetoclax +/- Obinutuzumab
Agents/ Regiments	• Acalabrutinib +/- O • Zanubrutinib • Ibrutinib	• Venetoclax + Obinutuzumab (VO)	• Acalabrutinib + Venetoclax +/- O (AV, AVO)
Schedule	 • Continuously dosed	 • Venetoclax C2-12 • Obinutuzumab C1-6)	 • Acalabrutinib C1-14 • Venetoclax C3-14 • (Obinutuzumab C2-7)
Key Points	• Indefinite • Best PFS in del(17p) and/or TP53 mutated CLL • Easiest to start and take	• Fixed-duration • Initiation is visit-intensive • Infusions are not preferred	• Fixed-duration • All oral and fewer visits than VO with AV
Major Toxicities	• BTKi cardiotoxicities • Bleeding risk • Ongoing drug costs	• TLS risk • Cytopenias can be more • Infusion reactions	• Still has BTKi cardiac toxicities, just less • Fewer visits at initiation

The FDA Approved Covalent BTK Inhibitors

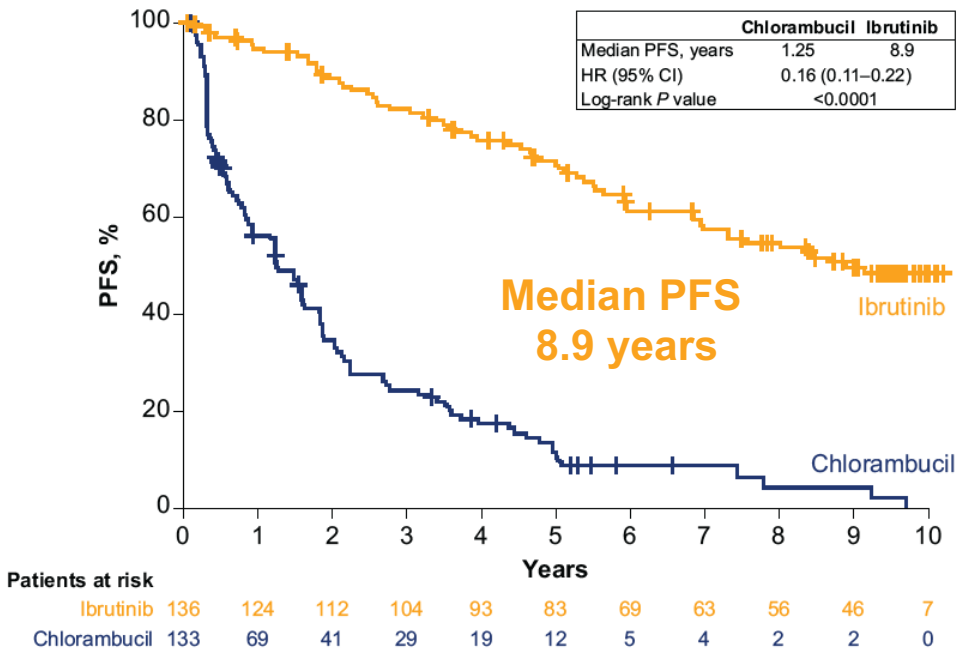
	Ibrutinib	Acalabrutinib	Zanubrutinib
FDA Approvals	CLL/SLL, WM	CLL/SLL, MCL	CLL/SLL, MCL, WM, MZL, FL
Dosing	420mg PO daily	100mg PO BID	160mg PO BID or 320mg PO daily
FDA approved combinations	Rituximab, Obinutuzumab	Obinutuzumab, + *Venetoclax - pending*	-
Selectivity			
Key Facts	• First-in-class • Inhibits ITK • Highest rates of afib	• More selective • Less atrial fibrillation • Less hypertension	• More selective • Less atrial fibrillation • Most approvals

CLL = Chronic Lymphocytic Leukemia, SLL = Small Lymphocytic Lymphoma, MCL = Mantle Cell Lymphoma, WM = Waldenstrom's Macroglobulinemia, MZL = Marginal Zone Lymphoma, FL = Follicular Lymphoma

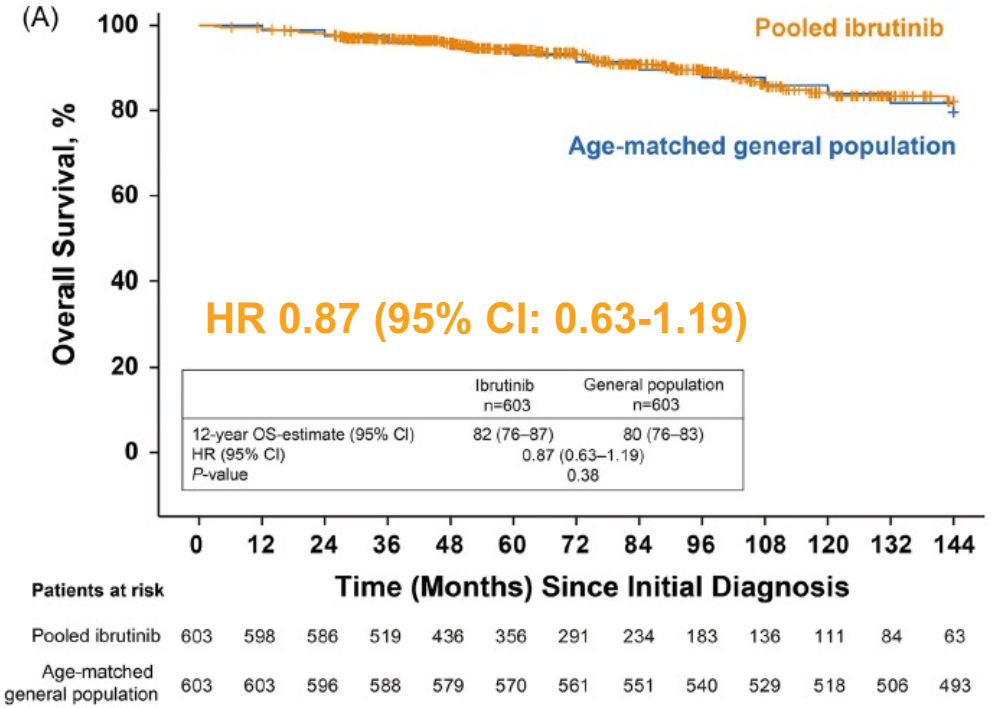
Efficacy of BTK Inhibitors – Ibrutinib (1st in Class)

- Progression-free and overall survival advantage over chemotherapy
- Most patients can expect normal survival

PFS with Ibrutinib (RESONATE-2)



OS from CLL Diagnosis in Patients in Firstline Ibrutinib Studies

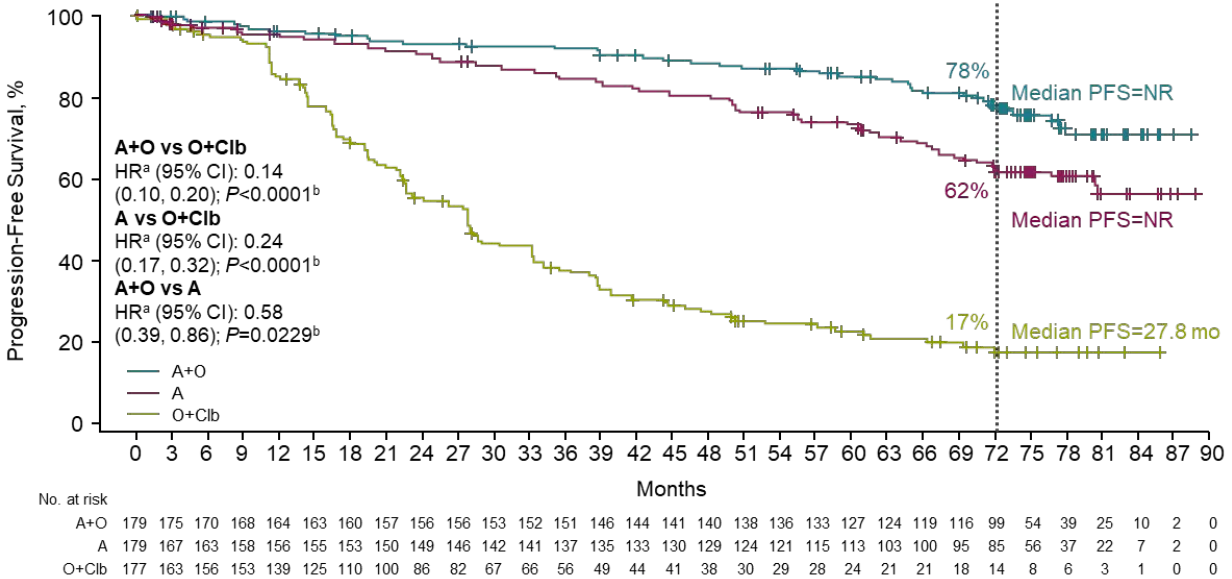


Burger et al., EHA 2024; Ghia et al., Hematologica 2024

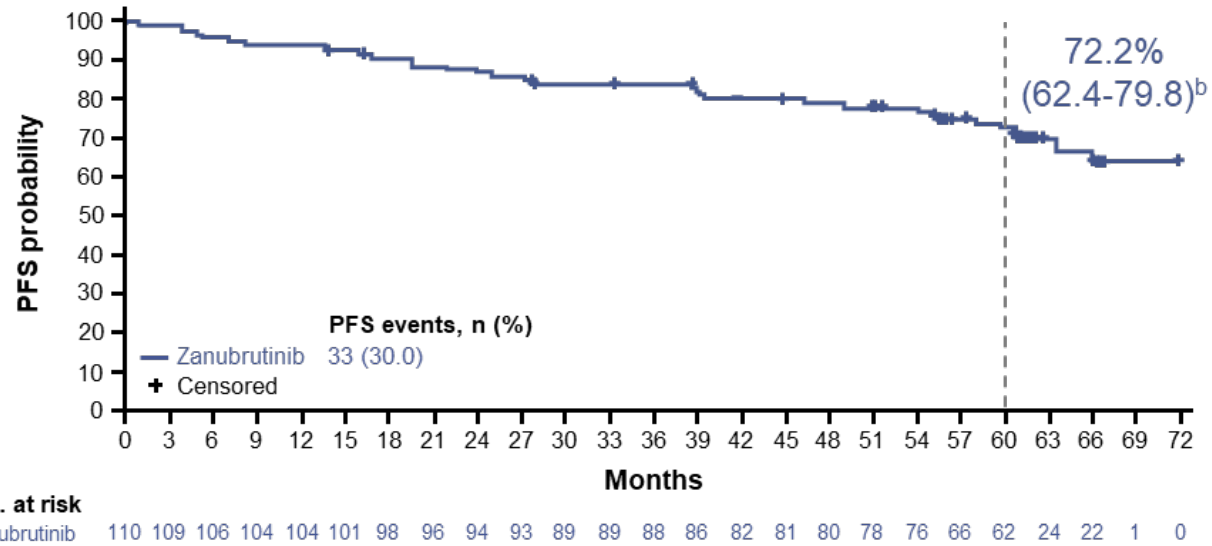
Acalabrutinib and Zanubrutinib Are Highly Effective

- Outstanding PFS with other covalent BTKi
  - PFS similar in patients with or without del(17p) CLL
  - Obinutuzumab can improve the PFS when added to acalabrutinib in patients without del(17p) CLL

Acalabrutinib 6-year Follow Up (PFS) ELEVATE-TN



Zanubrutinib 5-year Follow Up (PFS) Sequoia Arm C – del(17p) CLL

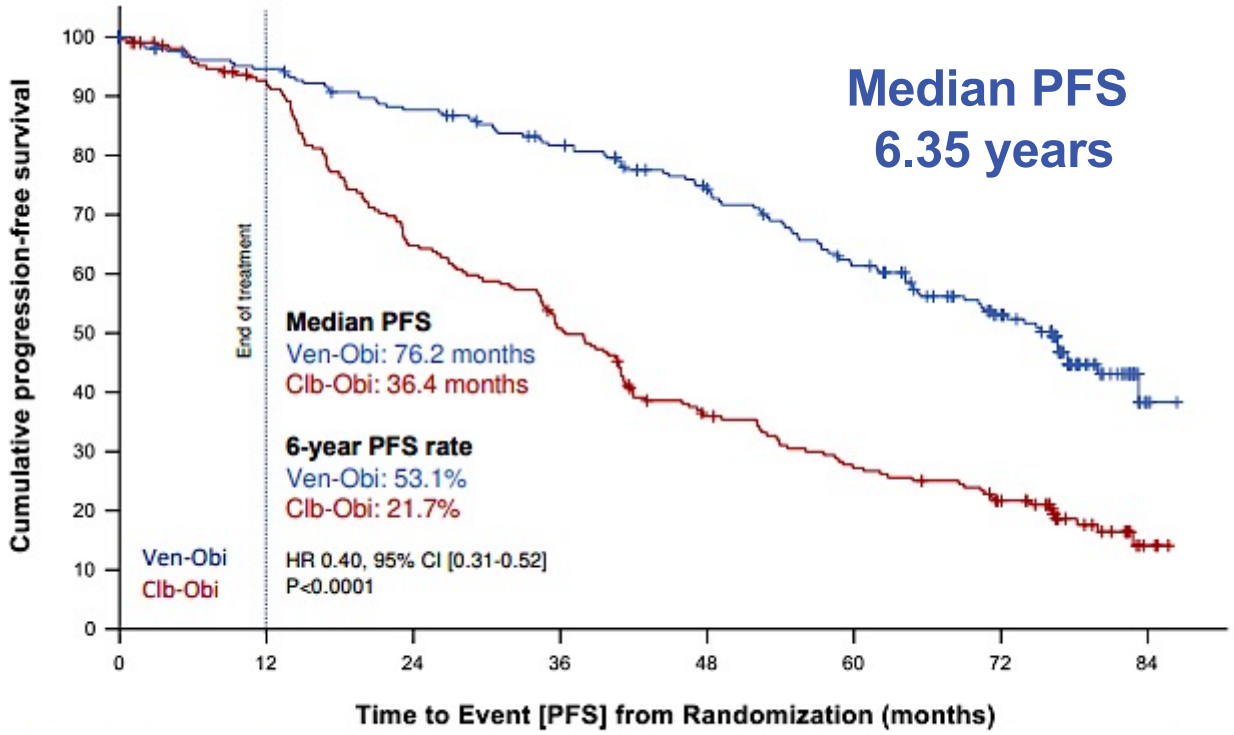


Sharman et al., ASH 2023; Tam et al., ASCO 2025 abstract 7011

CLL14: Venetoclax + Obinutuzumab for 1 year

- Phase 3 study in older patients or those with comorbidities
- Clear benefit to venetoclax and obinutuzumab (HR 0.35, p<0.0001)

PFS with Venetoclax/Obinutuzumab



Al-Sawaf O et al. Blood 2024

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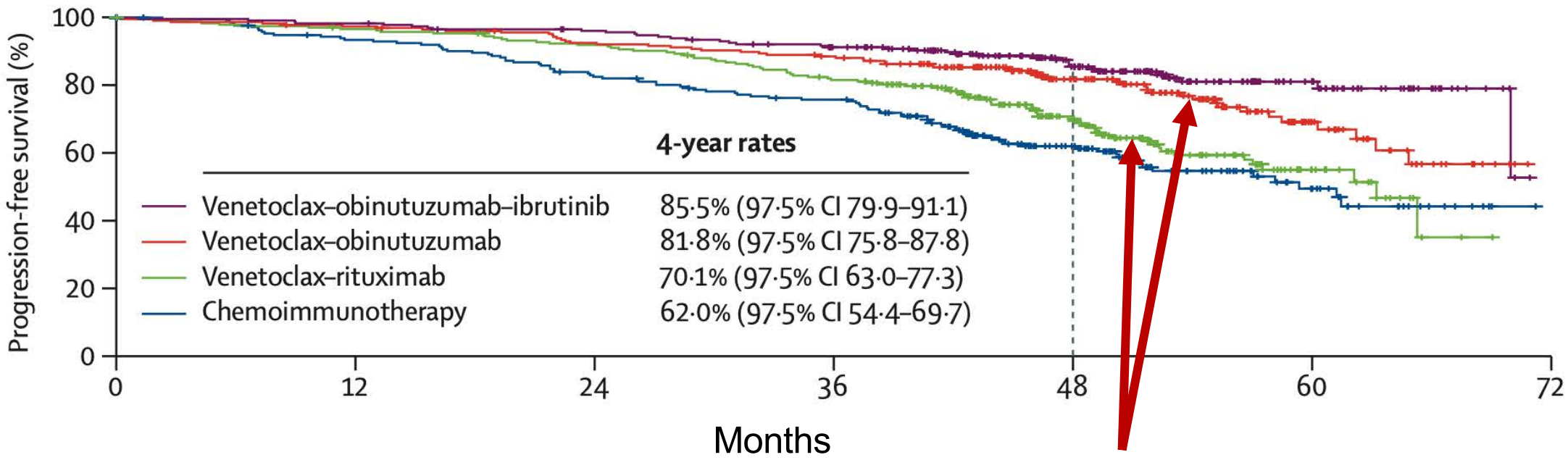
CLL13: Venetoclax Regimens in Fit Patients

- Established venetoclax and obinutuzumab in young, fit patients
- Obinutuzumab makes a difference over rituximab!

PFS with Venetoclax Combinations vs CIT (FCR vs BR)



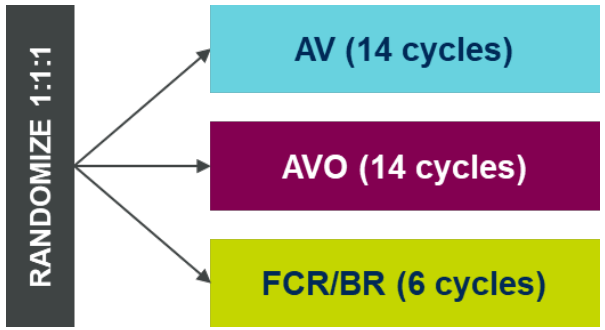
Ven/Obin vs Ven/R
HR 0.57, p=0.011

Furstenau et al., Lancet Onc 2024

AMPLIFY: AV or AVO vs FCR/BR

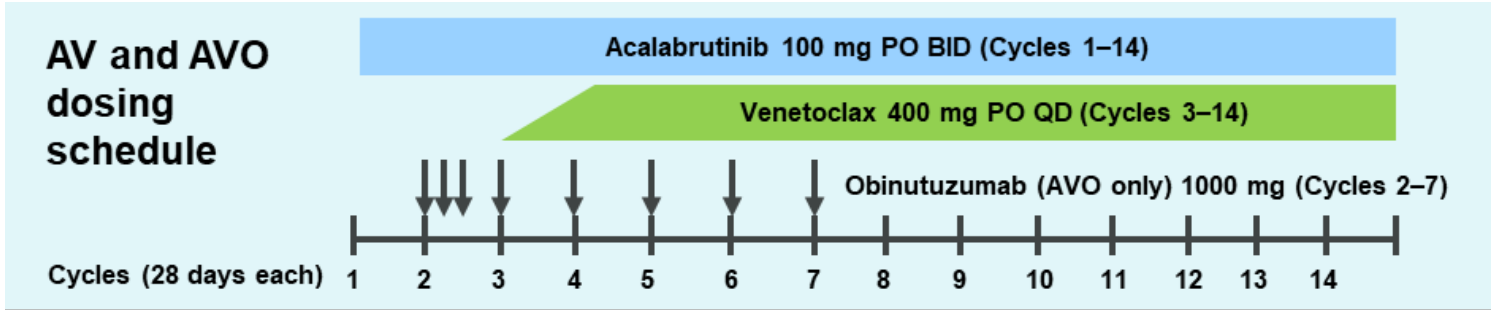
- Randomized phase 3 study of initial treatment
  - Fit patients (CIRS-Geriatric >6 excluded)
  - Excludes del(17p) and/or TP53 mutated CLL
- Compares PFS with AV to FCR/BR then AVO to FCR/BR

Randomization



Stratified by: age (>65 vs ≤65 years), IGHV mutational status, Rai stage (≥3 vs <3), and geographic region

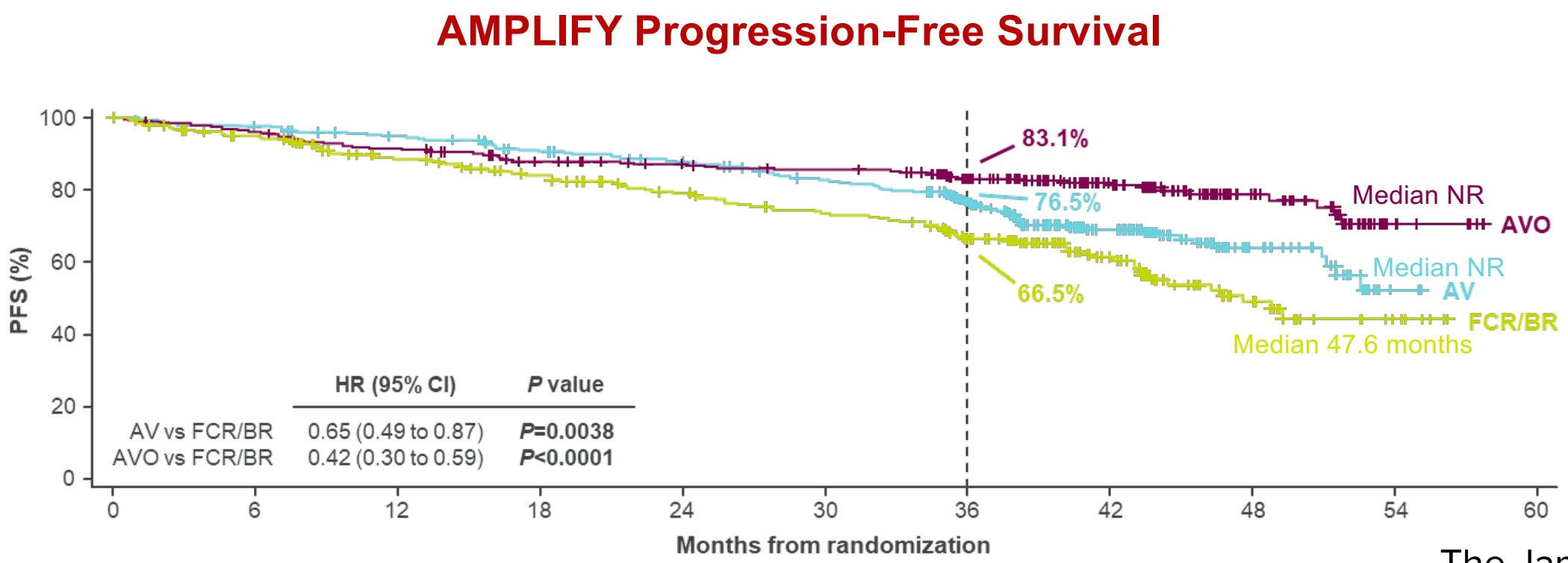
Study Treatment for AV +/-O



Brown et al., ASH 2024

AMPLIFY: Progression-Free Survival

- Both AV and AVO had improved PFS compared to FCR/BR
- The study was not designed to compare AV to AVO



Brown et al., ASH 2024

AV+/- O Toxicities

- Limited treatment duration decreased frequency of hypertension and atrial arrhythmias
- Infection remained common, particularly with AVO

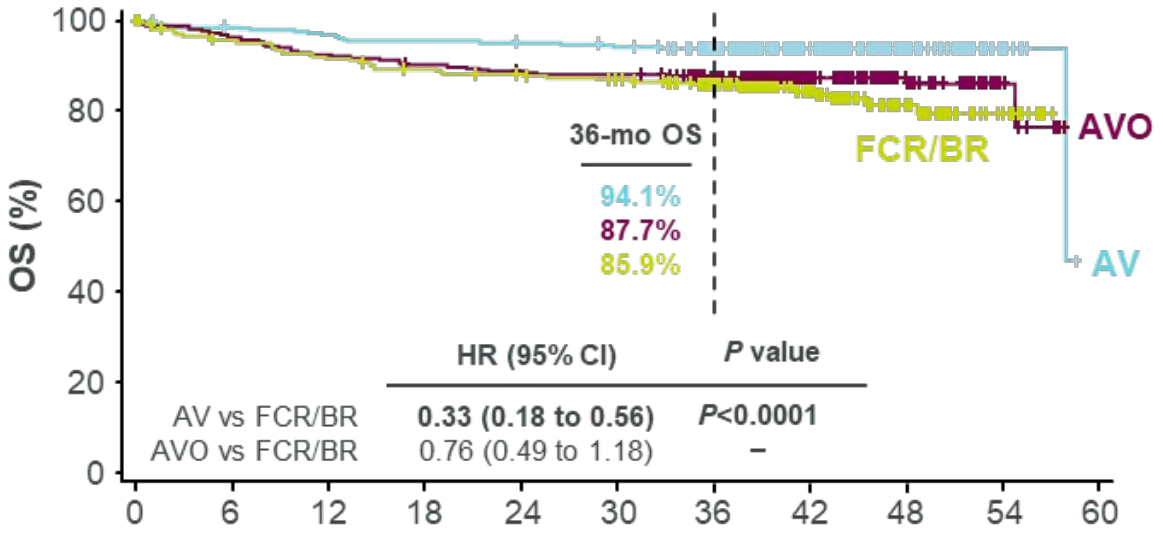
	AV (n=291)		AVO (n=284)		CIT (n=259)	
n (%)	*Any Grade*	*Grade 3+*	*Any Grade*	*Grade 3+*	*Any Grade*	*Grade 3+*
Afib/flutter	2 (0.7)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	2 (1.2)
Hypertension	12 (4.1)	8 (2.7)	11 (3.9%)	6 (2.1%)	7 (2.7%)	2 (0.8%)
Major Hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Infection	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
TLS	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Brown et al., NEJM 2025

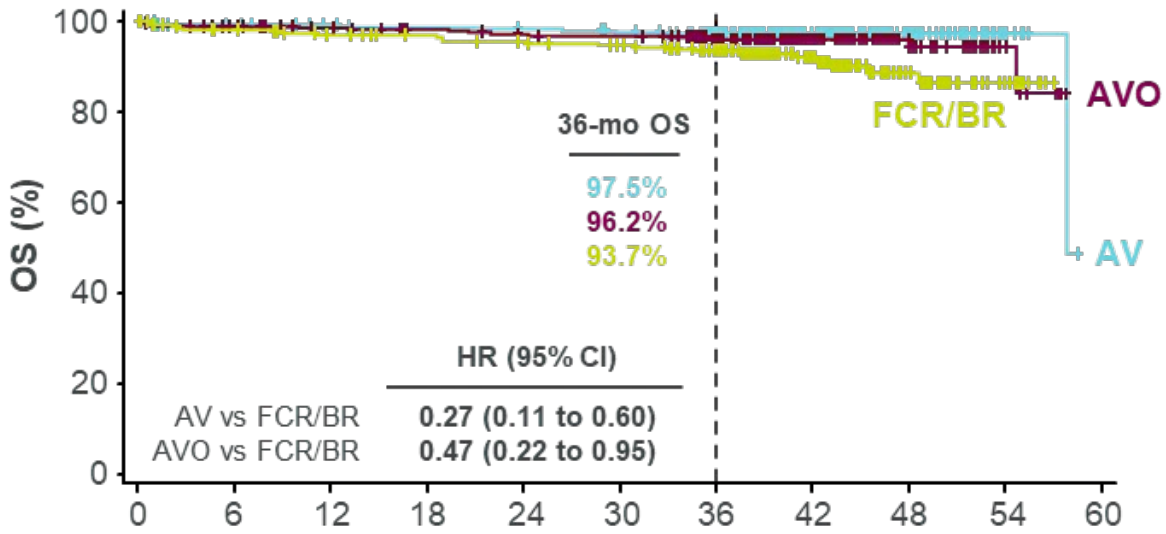
AMPLIFY: Overall Survival and COVID-19 Deaths

- There were more deaths from COVID-19 in anti-CD20 antibody containing arms (AVO n=25, FCR/BR n=21, and AV n=10)
- This highlights infection risk with obinutuzumab

Overall Survival



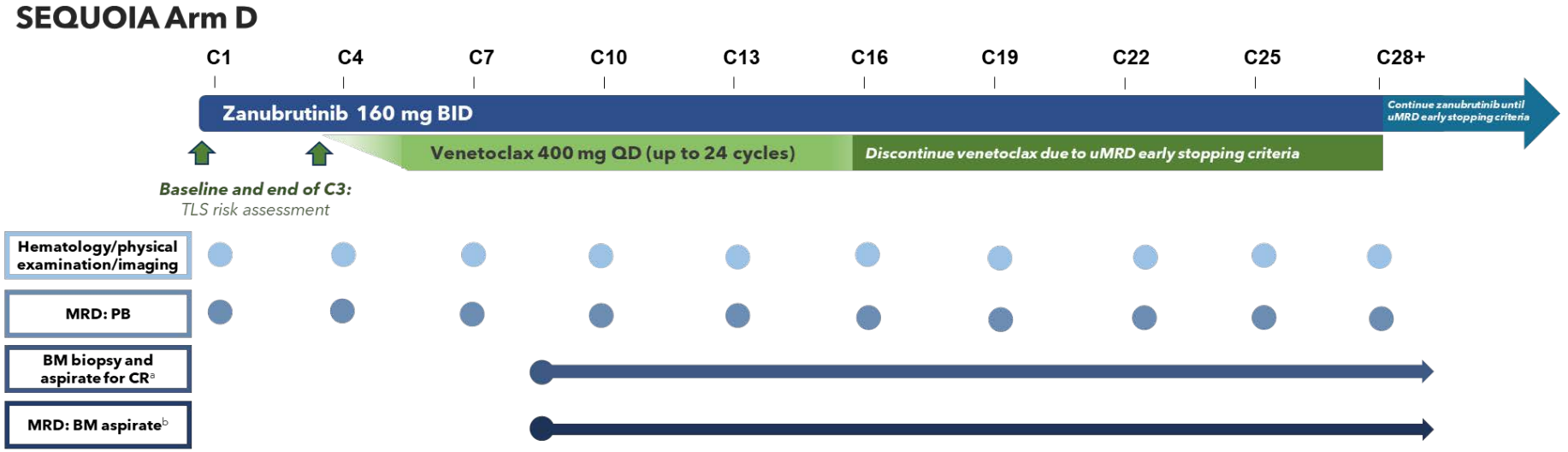
Overall Survival with COVID-19 Deaths Censored



Brown et al., ASH 2024

SEQUOIA Arm D: ZV with MRD Guided Duration

- Non-randomized arm of a phase 3 study for treatment-naïve CLL
  - Originally for patients with del(17p) and/or TP53 mutations (n=66)
  - Amended to include patients without TP53 alteration (n=47)
- Complex MRD and response guided stopping rules



uMRD-guided stopping criteria

All conditions must be met:

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD $<1 \times 10^{-4}$ (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM tests conducted ≥12 weeks apart
4. Received:
   - Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

Shadman et al., ASCO 2025 abstract 7009

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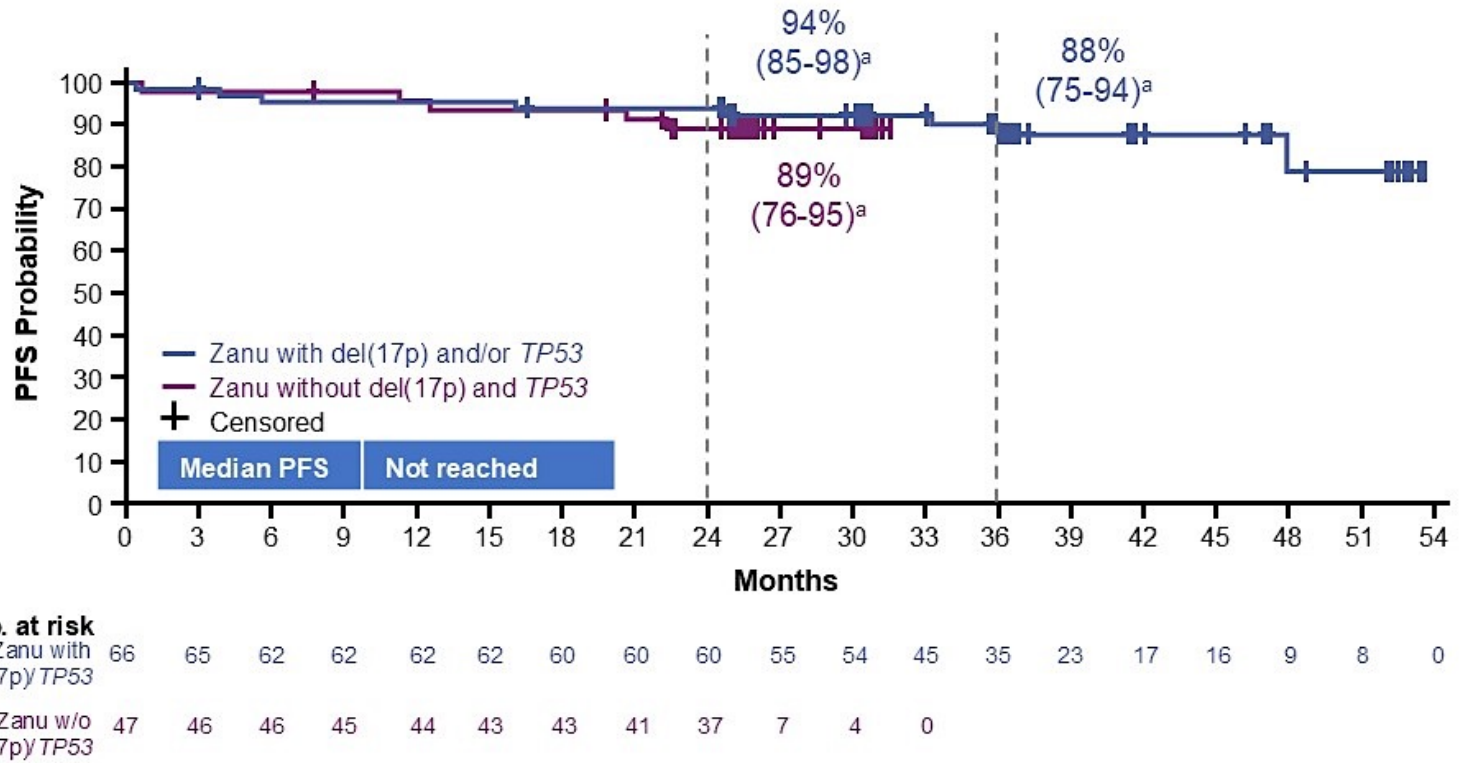
SEQUOIA Arm D: Progression-Free Survival

- Median follow-up was 38.7 months for patients with del(17p)/TP53 mutation and 29.6 months for patients without del(17p)/TP53 mutation
- 11 of 114 (9.6%) met MRD-stopping criteria and discontinued treatment



Shadman et al., ASCO 2025 abstract 7009

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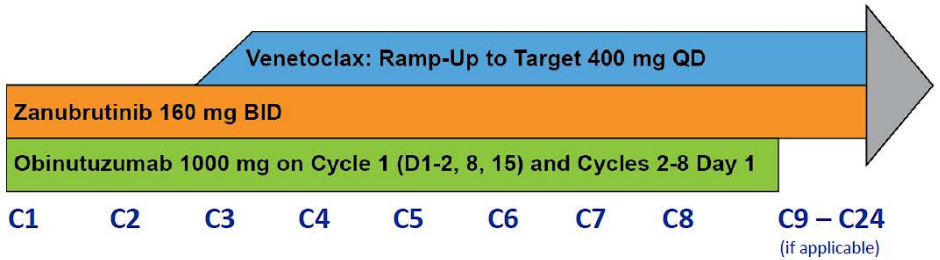
BOVen: Phase 2 Study of ZVO

- Treatment-naïve CLL patients with any genetic disease features
- Treatment duration is based on achieving uMRD

Study Treatment Schedule

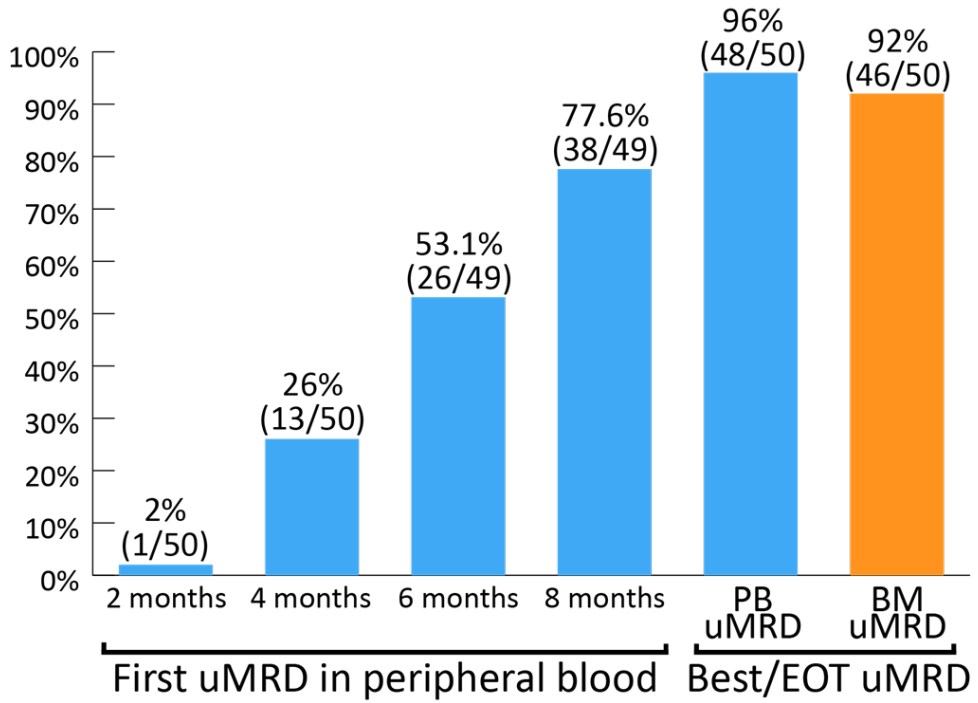
Key eligibility criteria
Previously untreated CLL/SLL
Requires treatment (iwCLL guidelines)
ECOG 0-2
ANC ≥1,000, PLT count ≥75 (unless due to CLL)
Coumadin and dual antiplatelet excluded



Treatment duration / MRD-directed treatment discontinuation criteria

- Treatment duration: Min 8 months to Max 24 months (including 2-month doublet lead-in prior to venetoclax)
- Peripheral blood MRD (flow cytometry) assessed every 2 cycles
  - If PB uMRD <10^{-4} (flow), then BM MRD assessment within 14 days
  - If PB and BM uMRD <10^{-4} (flow), then repeat PB MRD assessment after 2 additional cycles
  - If PB x 2 (consecutively) and BM uMRD <10^{-4} (primary endpoint), treatment is discontinued

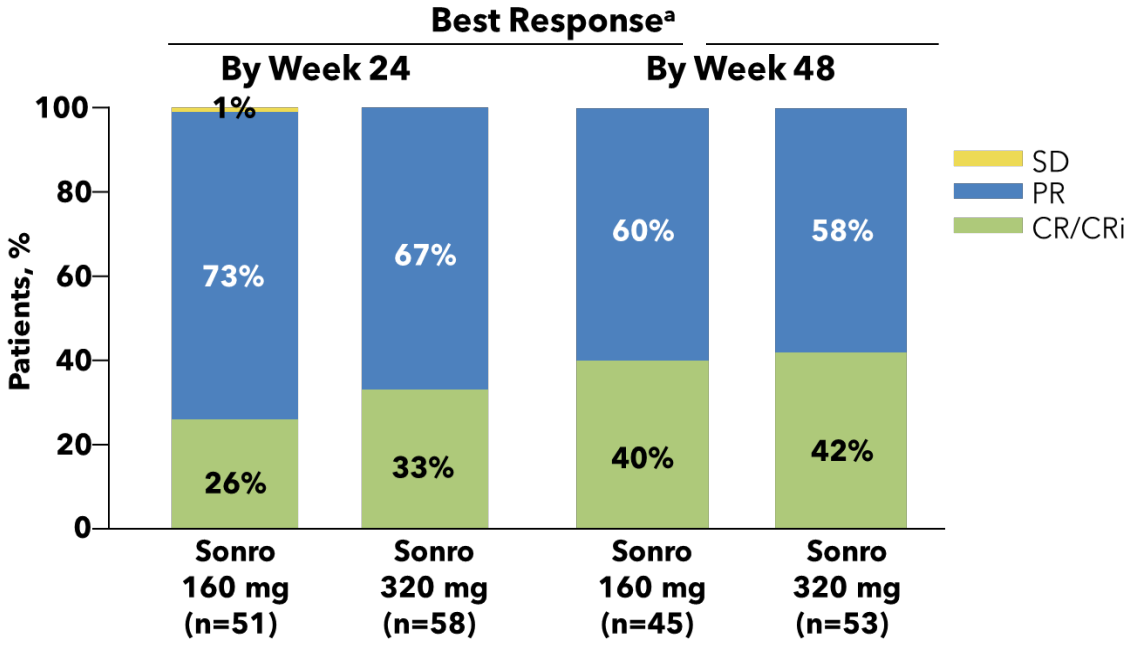
uMRD by Flow Cytometry (1x10^{-4})

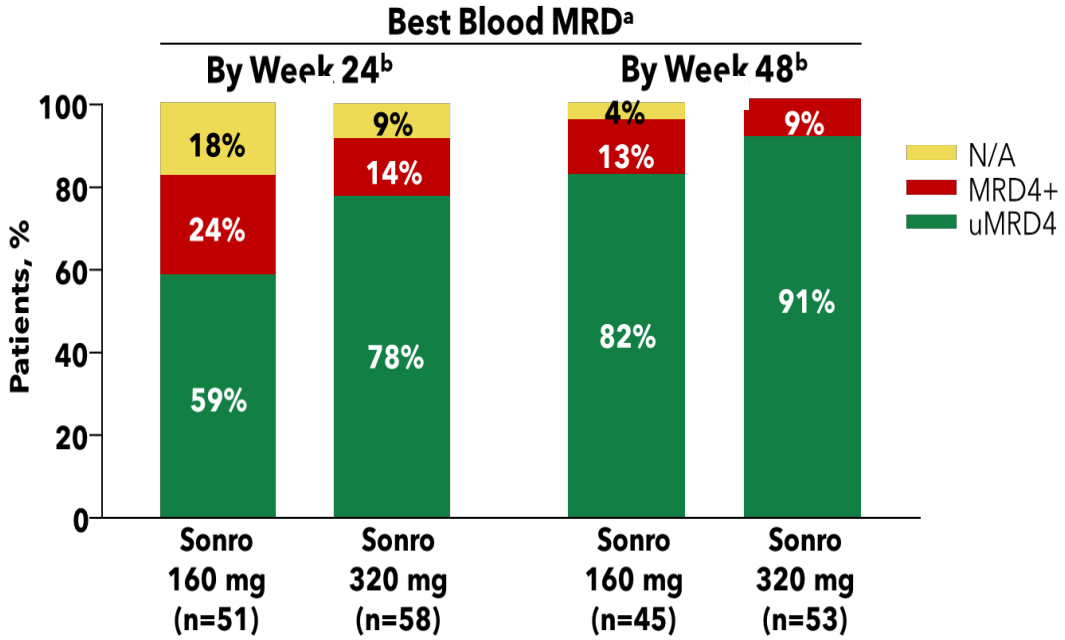


Soumerai et al., ASH 2024 Abstract 1867

Phase I/Ib Study: Zanubrutinib and Sonrotoclax

- Sonrotoclax is a potent and selective BCL2 inhibitor with activity against BCL-xL
- It was combined with zanubrutinib 320mg at 2 doses (160mg and 320mg) with favorable safety and high response rates

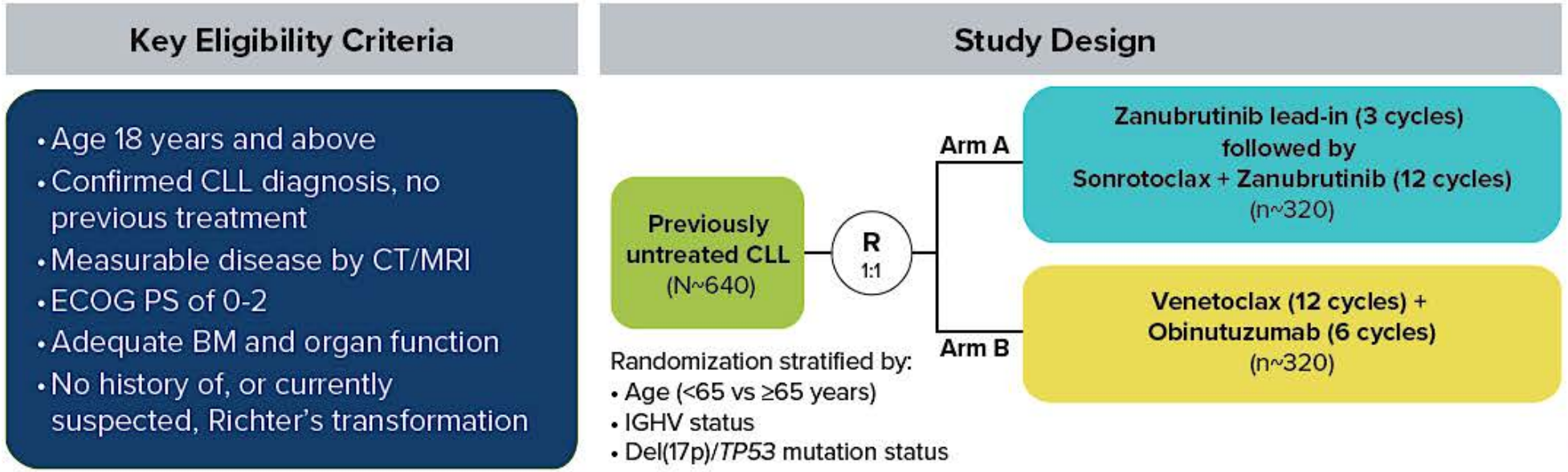




Soumerai et al., ASH 2024 Abstract 1012

CELESTIAL-TNCLL: VO vs ZS

- Phase 3 study of venetoclax/obinutuzumab (VO) vs zanubrutinib/sonrotoclax (ZS) in untreated CLL
- Primary endpoint is PFS by ICR



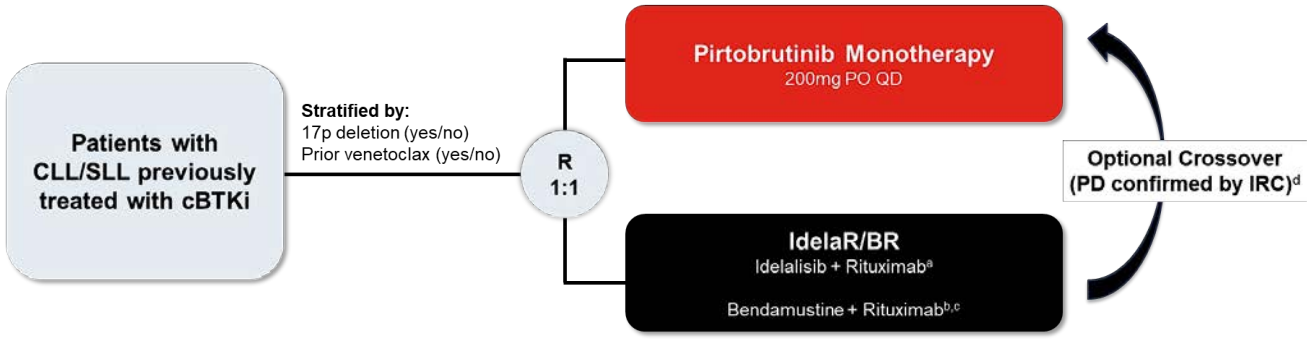
Patten et al., ASH 2024 Abstract 3275.1

BRUIN CLL-321: Pirtobrutinib vs IdelaR/BR

- Study of the non-covalent BTKi, pirtobrutinib, in R/R CLL
- Enrolled similar population to prior phase 1/2 study of pirtobrutinib

Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median lines of prior systemic therapy, n (range)	3 (1-13)	3 (1-11)
Prior therapy, n (%)		
cBTKi	119 (100)	119 (100)
Ibrutinib	100 (84)	106 (89)
Acalabrutinib	17 (14)	20 (17)
Zanubrutinib	10 (8)	7 (6)
Other[c]	5 (4)	3 (3)
>1 Prior cBTKi	17 (14)	18 (15)
BCL2 inhibitor[d]	60 (50)	62 (52)
Chemotherapy	81 (68)	83 (70)
Anti-CD20 Antibody	86 (72)	83 (70)
PI3K inhibitor	11 (9)	11 (9)
Immunomodulator	2 (2)	3 (3)
Autologous Stem Cell Transplant	1 (1)	0 (0)
Allogeneic Stem Cell Transplant	2 (2)	1 (1)
Reason for any prior cBTKi discontinuation[e], n (%)		
Disease progression	85 (71)	87 (73)
Toxicity	20 (17)	22 (18)
Other	14 (12)	8 (7)

Study Diagram



Sharman et al., ASH 2024 Abstract 886

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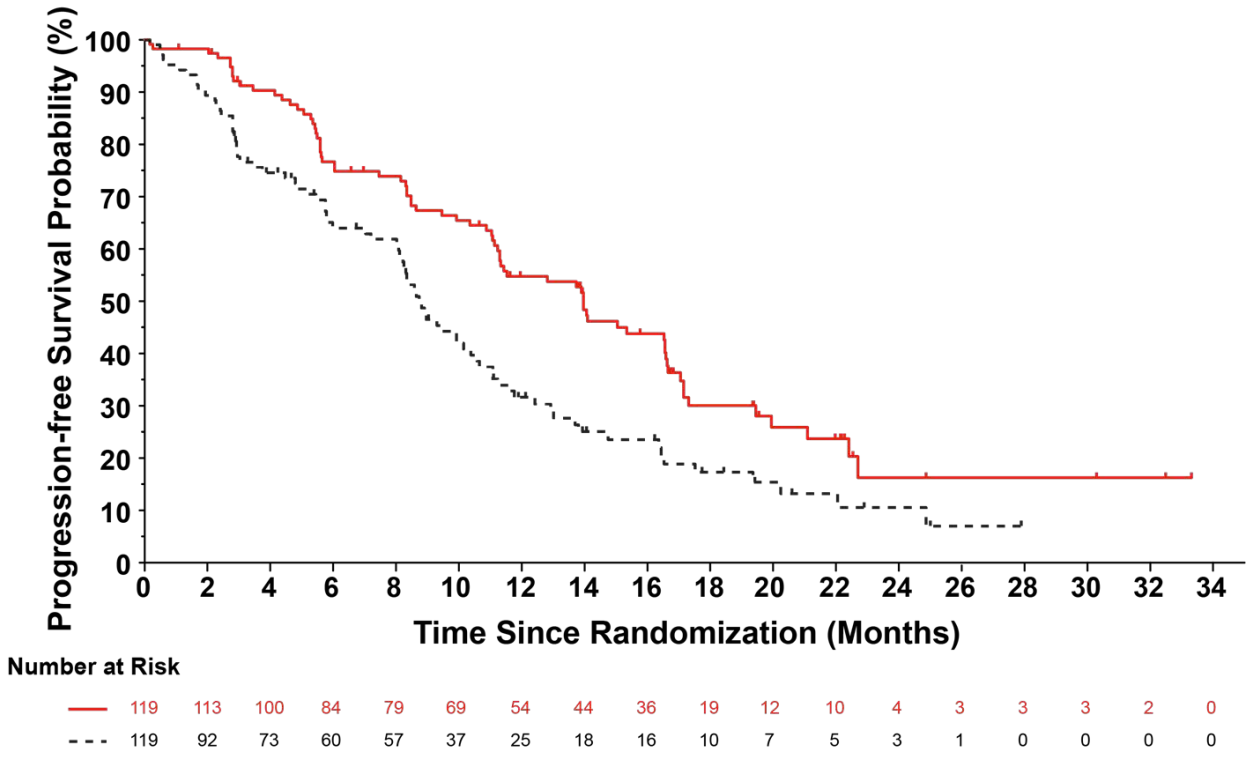
BRUIN CLL-321: PFS

- PFS was improved with pirtobrutinib, but was short for CLL
- Overall survival was similar between arms

Progression-Free Survival



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

Sharman et al., ASH 2024 Abstract 886

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BRUIN CLL-321: Safety Data

- Atrial fibrillation: 3 (2.6%) pirtobrutinib, 1 (0.9%) idelaR/BR
- Hypertension: 8 (6.9%) pirtobrutinib, 4 (3.7%) idelaR/BR

TEAE	Pirtobrutinib (n = 116), IR[a]	IdelaR or BR (n = 109), IR[a]	IRR (95% CI)[b]	P[c]
Infections[d]	94.5	125.5	0.75 (0.53 to 1.07)	.11
Pneumonia[e]	20.4	19.5	1.04 (0.54 to 2.03)	.90
COVID-19	11.1	33.4	0.33 (0.17 to 0.65)	.001
Anemia	18.5	30.3	0.61 (0.33 to 1.12)	.11
Neutropenia[f]	26.4	66.5	0.40 (0.25 to 0.64)	<.001
Cough	14.3	30.8	0.47 (0.25 to 0.88)	.02
Diarrhea	15.3	63.7	0.24 (0.14 to 0.42)	<.001
Pyrexia	11.1	52.4	0.21 (0.11 to 0.40)	<.001
Fatigue	9.5	34.2	0.28 (0.14 to 0.55)	<.001
Nausea	9.8	38.3	0.26 (0.13 to 0.51)	<.001
Vomiting	5.8	29.6	0.19 (0.08 to 0.44)	<.001
ALT increased	2.8	33.6	0.08 (0.03 to 0.25)	<.001
Weight decreased	2.8	28.5	0.10 (0.03 to 0.29)	<.001

Sharman JP et al. J Clin Oncol 2025;43:2538-49.

Phase 3 Studies with Pirtobrutinib as Initial Treatment

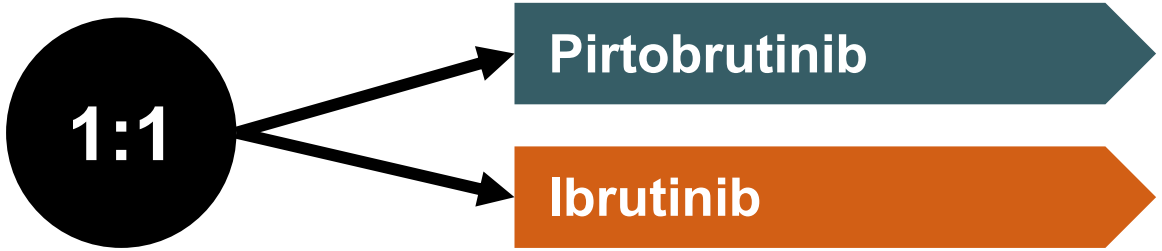
- Pirtobrutinib is being tested as an initial therapy
  - Compared to bendamustine and rituximab
  - Compared to ibrutinib (subgroup of treatment-naïve patients)

	BRUIN CLL-314	BRUIN CLL-313
Treatment Arms	▪ Pirtobrutinib ▪ Ibrutinib	▪ Pirtobrutinib ▪ Bendamustine/rituximab (BR)
Prior Treatment(s)	Both untreated and previously treated	Untreated
Primary Endpoint	ORR	PFS

clinicaltrials.gov

BRUIN CLL-314: Pirtobrutinib vs Ibrutinib

- 662 patients were randomized: 225 TN and 437 R/R
- Primary endpoint was ORR and powered for non-inferiority
- Pirtobrutinib was non-inferior for ORR in ITT and R/R cohorts



	ORR ITT	18-month PFS ITT	Atrial Fibrillation Hypertension
Pirtobrutinib	87.0%	86.9%	2.4% 10.6%
Ibrutinib	78.6%	82.3%	13.5% 15.1%

p<0.0001

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Woyach et al., ASH 2025 (abstract)

BRUIN CLL-313: Pirtobrutinib vs BR

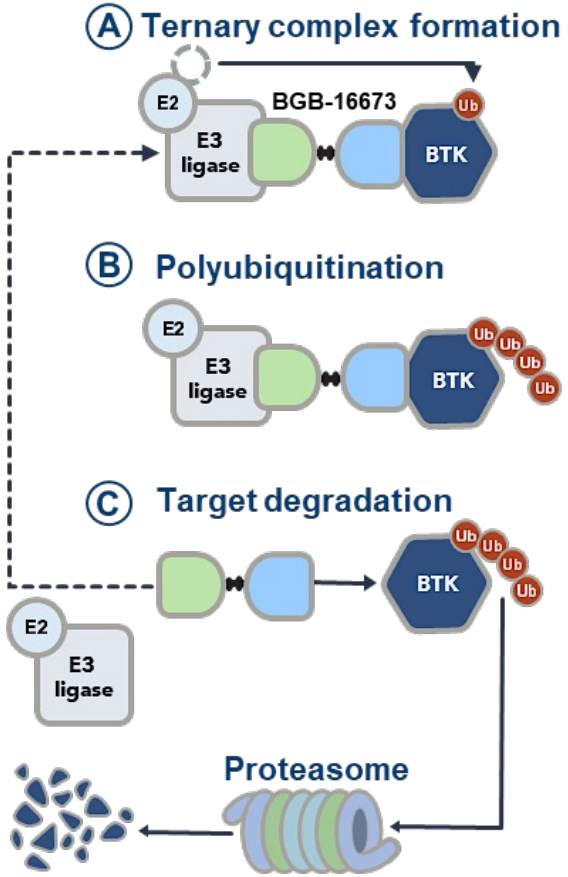
- Randomized phase 3 in treatment-naïve patients with CLL/SLL without 17p deletions
- Positive results announced for the study:
  - Statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to chemoimmunotherapy
  - The overall safety profile of pirtobrutinib was generally consistent with previously reported trials
- Data not yet available but expected soon

https://www.prnewswire.com/news-releases/lillys-jaypirca-pirtobrutinib-the-first-and-only-approved-non-covalent-reversible-btk-inhibitor-significantly-improved-progression-free-survival-in-patients-with-treatment-naive-cllsll-302548399.html

BTK Degraders – Mechanism of Action

- Targets BTK for Degradation by the proteosome
- In CLL this is effective even with BTK mutations

Mechanism of BTK Degraders

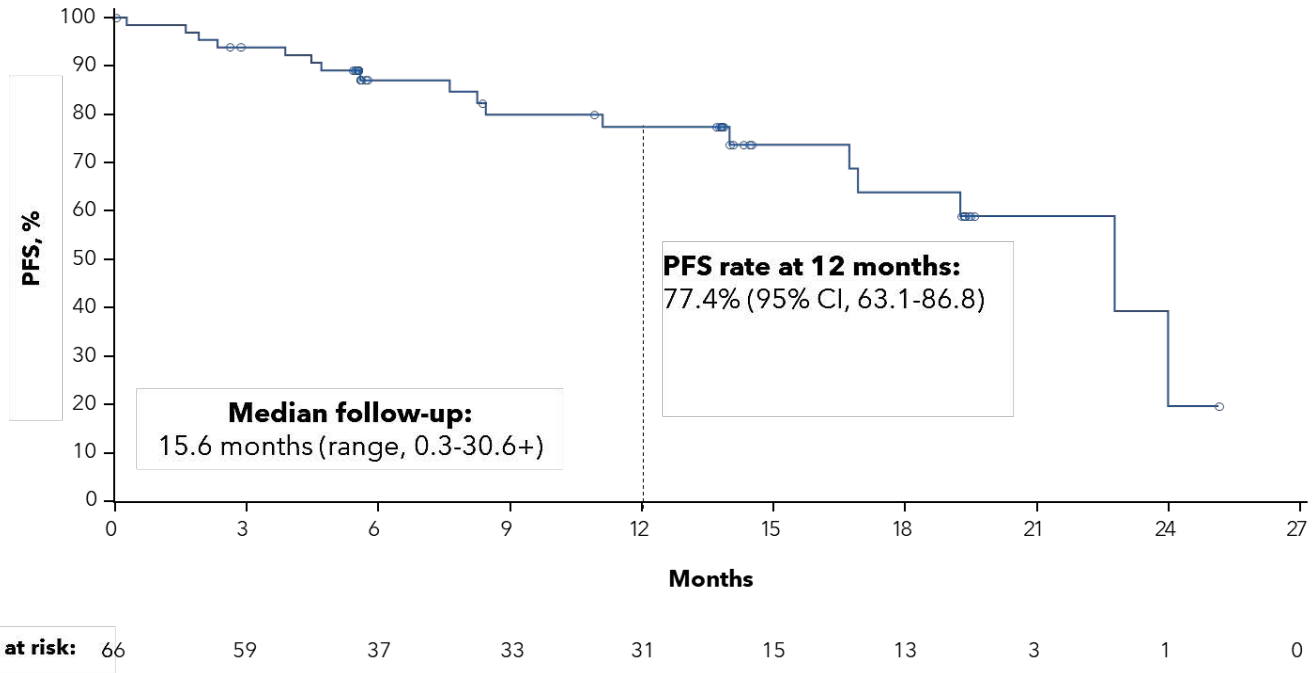


Scarfo et al., EHA 2025 abstract S158

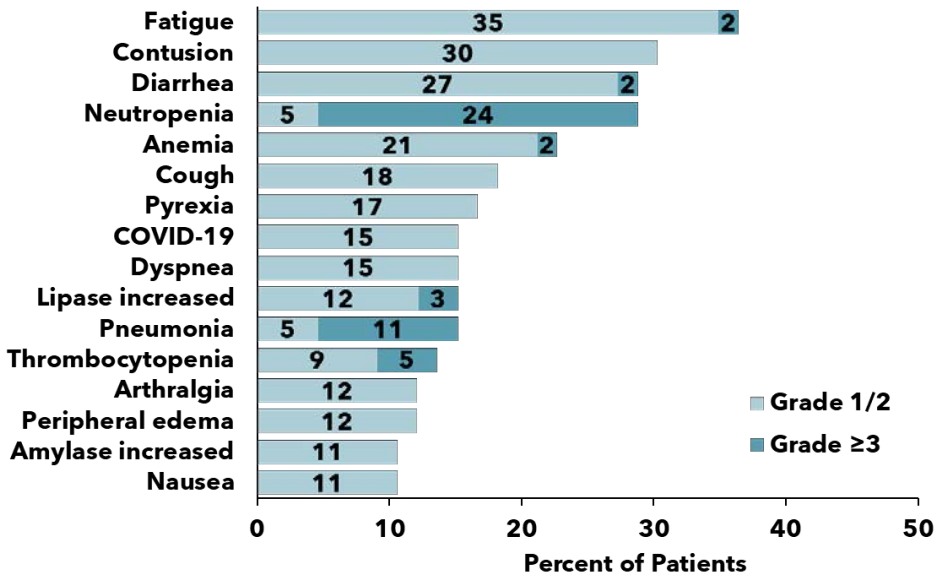
CaDAnCe-101: Phase 1 Study of the BTKI Degrader BGB-16673

- 66 CLL patients with a median of 4 (range 2-10) prior treatments
- BTK mutations were present in 38.1% (24 of 63 tested)

PFS with BGB-16673



Adverse Events ≥10% of Patients



Scarfo et al., EHA 2025 abstract S158

Case Presentation: 75-year-old man with CLL and PMH of atrial fibrillation

Dr Zanetta Lamar (Naples, Florida)

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QUESTIONS FOR THE FACULTY

In general, what is your preferred initial treatment for an otherwise healthy patient with IGHV-mutated CLL with no del(17p) or TP53 mutation? How, if at all, does age influence the decision?

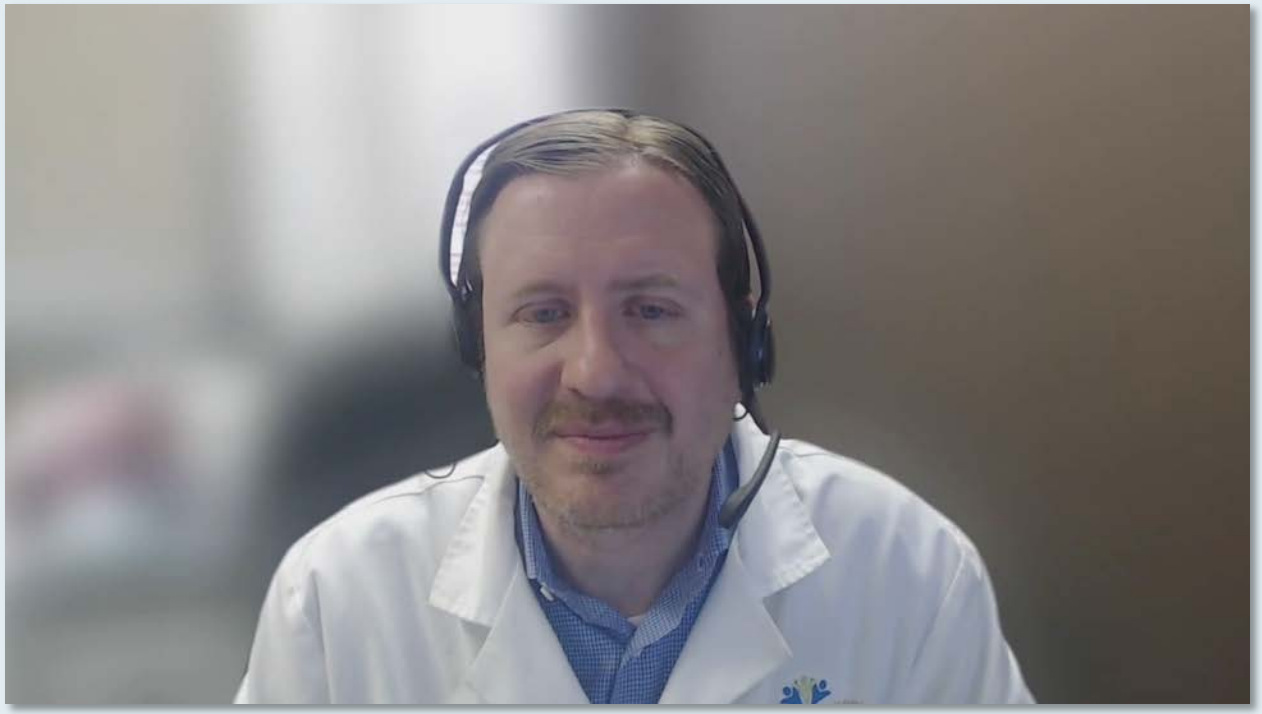
For a patient with CLL for whom you are going to initiate treatment with a BTK inhibitor, which do you prefer? How do various comorbidities influence your selection?

QUESTIONS FOR THE FACULTY

If a patient with CLL who is receiving first-line zanubrutinib develops issues with bruising or bleeding, would switching to pirtobrutinib be a reasonable option assuming it was accessible?

Would you consider using MRD, in addition to routine scans, to determine whether discontinuation of a BTK inhibitor might be feasible?

Case Presentation: 82-year-old fit man with IGHV-unmutated, TP53-mutant symptomatic CLL



Dr Brian Mulherin (Indianapolis, Indiana)

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QUESTIONS FOR THE FACULTY

In general, what is your preferred initial treatment for an otherwise healthy patient with IGHV-unmutated CLL with no del(17p) or TP53 mutation? How, if at all, does age influence the decision?

In general, what is your preferred initial treatment for an otherwise healthy patient with CLL and a del(17p) or TP53 mutation? How, if at all, does age influence the decision? What about IGHV status?

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QUESTIONS FOR THE FACULTY

For a patient with CLL who is interested in time-limited treatment, how will you decide between venetoclax/obinutuzumab and acalabrutinib/venetoclax +/- obinutuzumab assuming the latter becomes available?

Would you be comfortable using zanubrutinib instead of acalabrutinib in combination with venetoclax?

QUESTIONS FOR THE FACULTY

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?

Case Presentation: 84-year-old woman with IGHV-mutated recurrent CLL who receives pirtobrutinib

Dr Sean Warsch (Asheville, North Carolina)

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QUESTIONS FOR THE FACULTY

In general, for a patient with CLL with disease progression after 6 years on a covalent BTK inhibitor who then receives venetoclax/obinutuzumab with further progression after 2 years, what would be your preferred next treatment? What if the covalent BTK inhibitor was discontinued after 1 year due to intolerance?

QUESTIONS FOR THE FACULTY

For a patient who receives pirtobrutinib for double-refractory CLL, in general what treatment would you recommend on disease progression?

What do we know about response to covalent BTK inhibitors after progression on pirtobrutinib? Is there reason to believe this strategy would or would not be effective?

Case Presentation: 78-year-old woman with recurrent del(17p) CLL who receives venetoclax/obinutuzumab

Dr Jennifer Yannucci (Savannah, Georgia)

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QUESTIONS FOR THE FACULTY

In general, what is the minimum duration of remission after discontinuation of venetoclax/obinutuzumab before you will consider re-treatment? Does this differ in the front-line versus the relapsed setting?

Based on available data and your personal clinical experience, how would you compare the novel Bcl-2 inhibitor sonrotoclax to venetoclax in terms of efficacy and tolerability?

QUESTIONS FOR THE FACULTY

How do BTK degraders differ from BTK inhibitors?
Have you observed definitive clinical benefit from these agents?
Where do you think they may fit into current treatment algorithms?
What role, if any, do you see for this agent in R/R CLL?

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