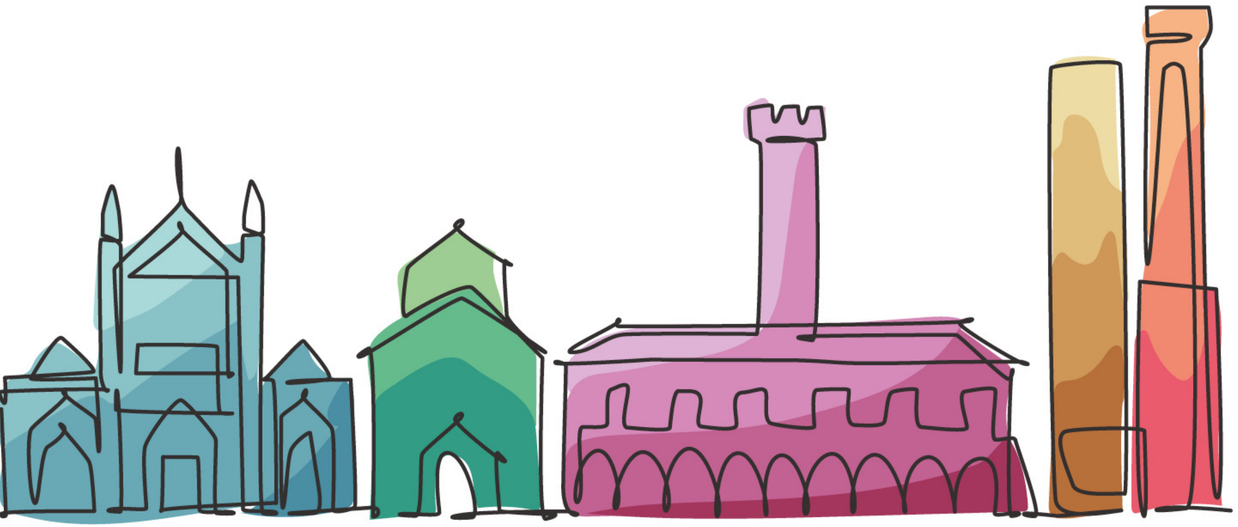
PRECEPTORSHIP



Un confronto sulla gestione delle malattie linfoproliferative al Sant'Orsola di Bologna

Bologna, NH DE LA GARE, 6 ottobre 2025

LEUCEMIA LINFATICA CRONICA… DIETRO L'ANGOLO

Alessandro Broccoli

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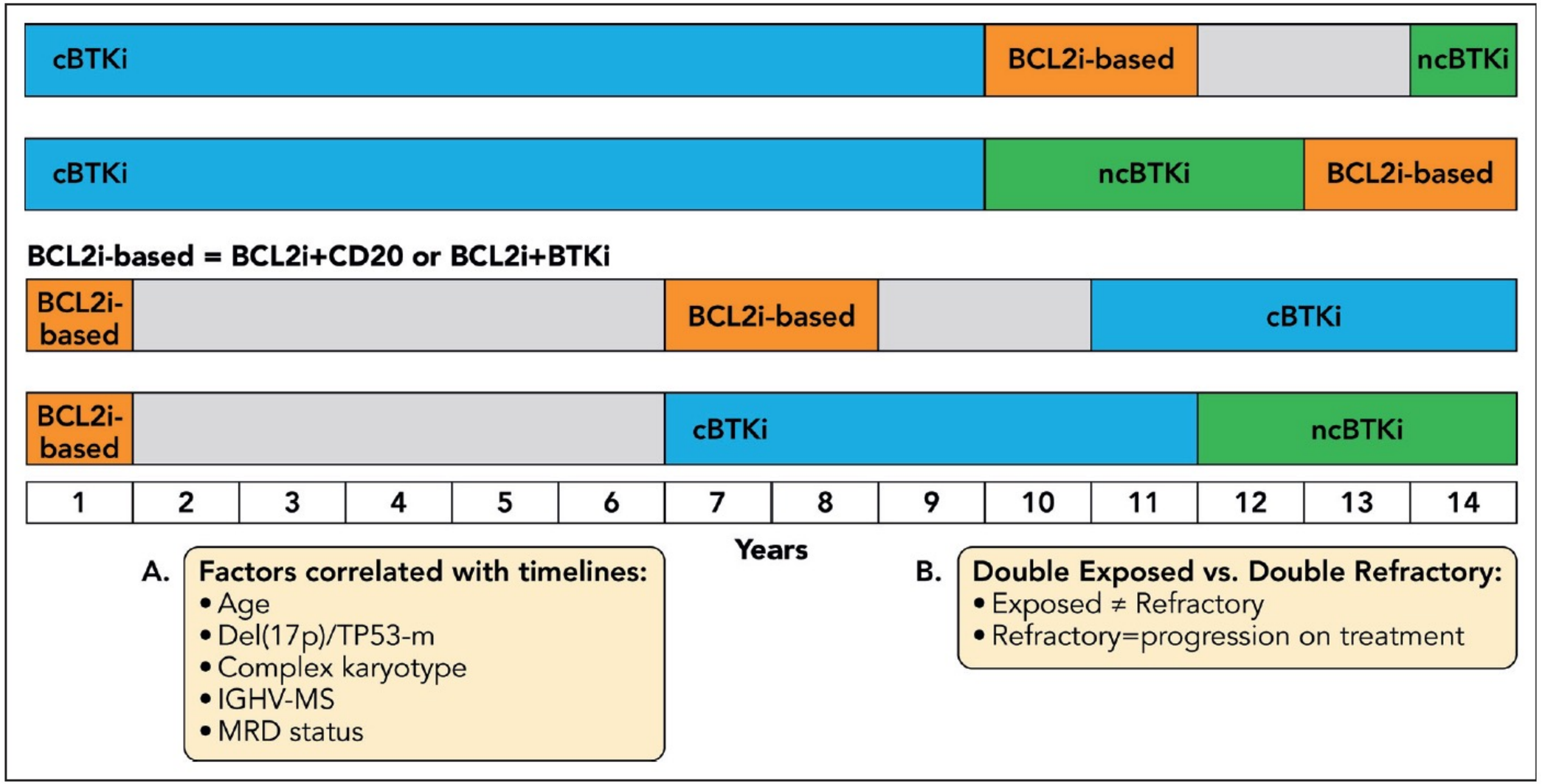
Disclosures: ALESSANDRO BROCCOLI

Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sandoz	X				X	X
Gilead				X	X	X
Merck	X					X
Janssen	X			X		X
Takeda		X		X	X	X
Kyowa Kirin	X			X	X	X
Incyte						X
Recordati						X
Astra Zeneca				X	X	
Roche				X		X
GlaxoSmithKline		X		X	X	
BeOne	X			X	X	X
Eli Lilli						X

Treatment sequencing rationale



Wierda WG. *Blood*, 2025; 146: 779-788

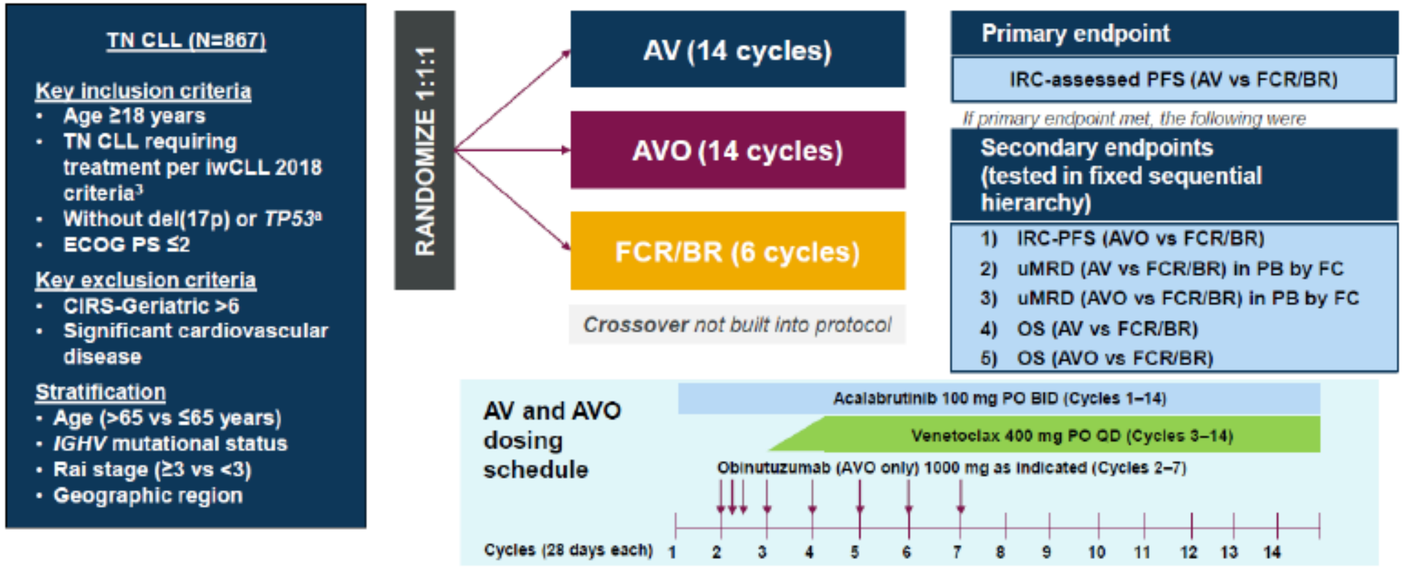
CLL just around the corner: what are we now working on?

Targeted therapy	Opportunity/goal	Potential strategies
All	Minimize toxicities	More selective targeted agents
	Improve PFS and OS	More effective targeted treatments
	Improve outcomes for high risk	More effective targeted treatments
	Avoid resistance	Clarify mechanisms of resistance
	Avoid RT	Clarify mechanisms of RT
	Active immune restoration	Understand immune dysfunction and develop interventions
	Increase access and improve affordability	Work with government authorities, insurance providers, and pharmaceutical industry toward common patient-centric goals
Continuous	Convert to time-limited treatment	Develop consolidation strategies Generate data with time-limited BTKi Define stopping rules
Time-limited	Shorten time-limited treatment	Optimize targeted combination and treatment duration
	Increase uMRD4-6 rate	Optimize targeted combination and treatment duration Treatment modification for persistent MRD at early time point
	Simplify BCL2i ramp-up	Safely lessen monitoring requirements
	Develop curative treatment	Optimize targeted combination and treatment duration

uMRD4-6, uMRD at 10^{-4} to 10^{-6} sensitivity. RT, Richter transformation

Wierda WG. *Blood*, 2025; 146: 779-788

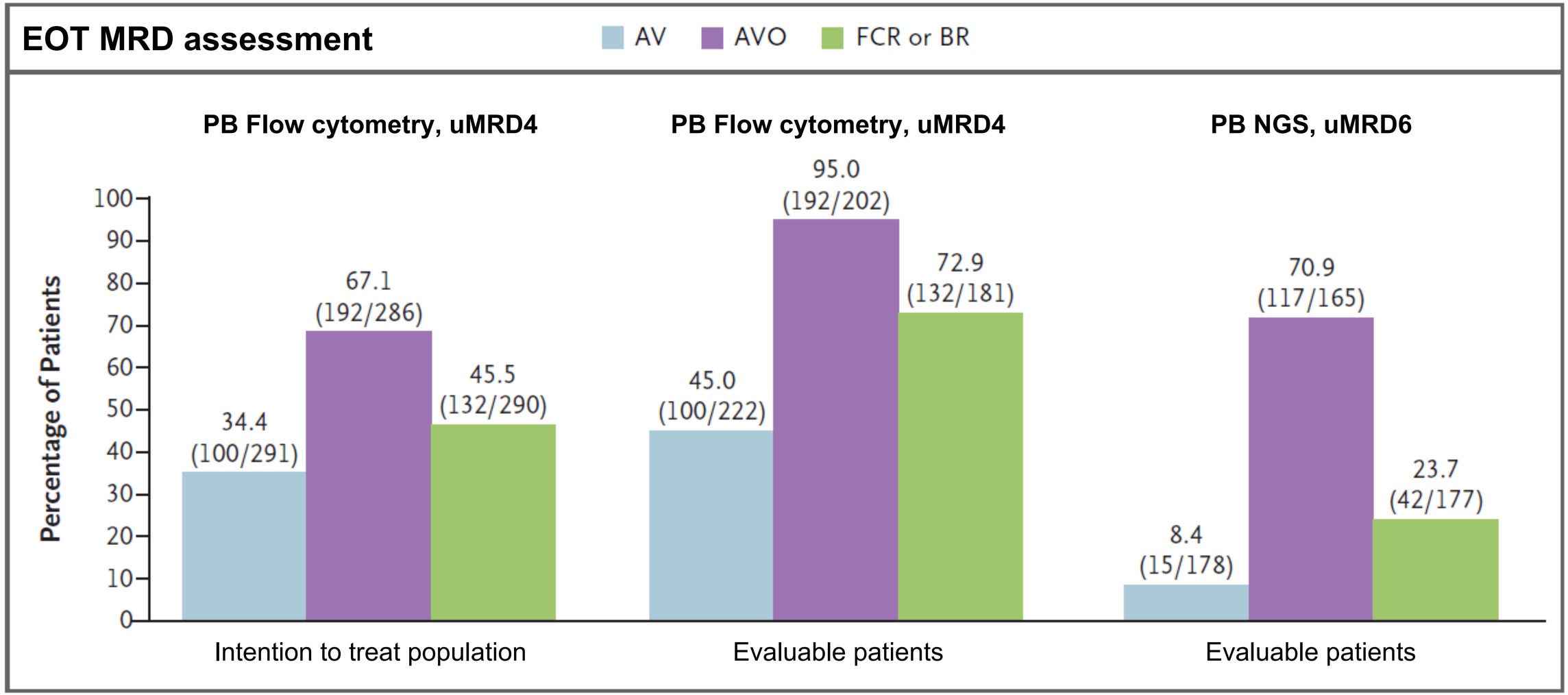
Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia



Characteristic	AV (n = 291)	AVO (n = 286)	FCR/BR (n = 290)
Median age, yr (range)	61 (31-84)	61 (29-81)	61 (26-86)
ECOG PS 2, n (%)	28 (9.6)	14 (4.9)	26 (9.0)
Rai stage			
▪ 0-II	154 (52.9)	170 (59.4)	163 (56.2)
▪ III-IV	137 (47.1)	116 (40.6)	127 (43.8)
del(11q) present	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated *IGHV*	167 (57.4)	169 (59.1)	172 (59.3)

Brown JR. *N Engl J Med*, 2025; 392: 748-762

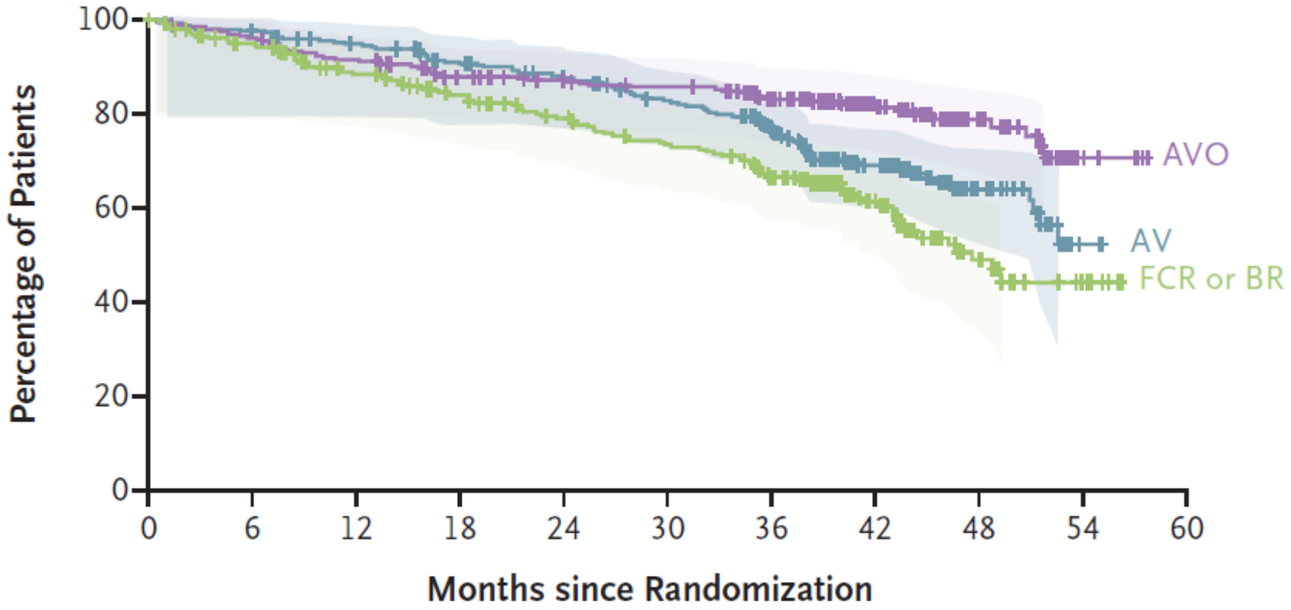
Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia



Brown JR. *N Engl J Med*, 2025; 392: 748-762

Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia

Progression-free Survival, Assessed by Blinded Independent Central Review



No. at Risk											
AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR or BR	290	236	208	189	170	154	127	66	28	6	0

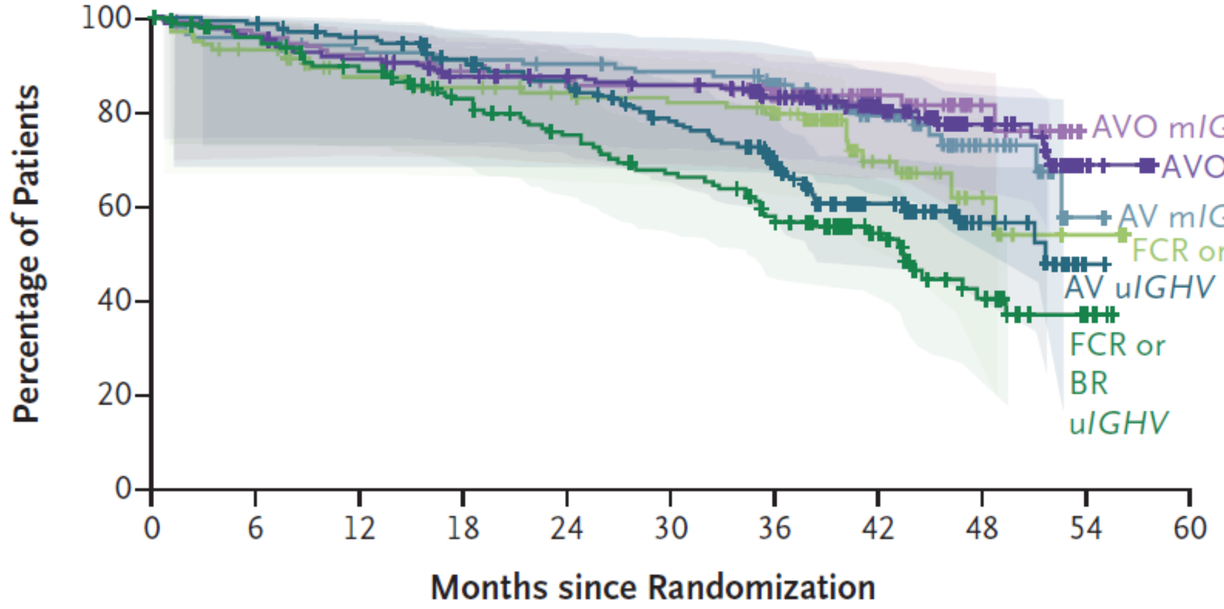
	No. of Events/ Total No. of Patients	Median Progression-free Suvival	Progression-free Survival at 36 Months
		mo	%
AV	89/291	NC	76.5
AVO	56/286	NC	83.1
FCR or BR	95/290	47.6	66.5

	Hazard Ratio for Disease Progression or Death (95% CI)	P Value
AV vs. FCR or BR	0.65 (0.49–0.87)	0.004
AVO vs. FCR or BR	–	<0.001

Brown JR. *N Engl J Med*, 2025; 392: 748-762

Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia

Progression-free Survival According to *IGHV* Mutation Status, Assessed by Blinded Independent Central Review



	No. of Events/ Total No. of Patients	Median Progression-free Suvival	Progression-free Survival at 36 Months
		mo	%
AV m*IGHV*	28/124	NC	86.0
AV u*IGHV*	61/167	51.5	68.9
AVO m*IGHV*	20/117	NC	83.6
AVO u*IGHV*	36/169	NC	82.8
FCR or BR m*IGHV*	28/118	NC	79.9
FCR or BR u*IGHV*	67/172	43.3	56.8

No. at Risk

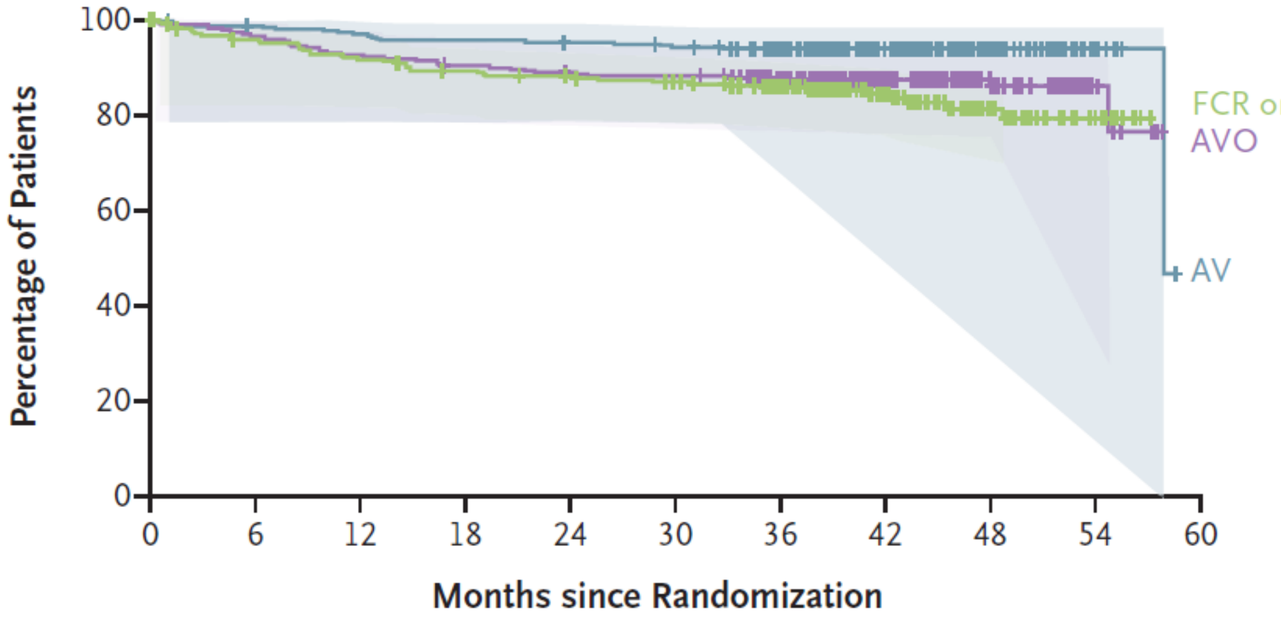
AV m*IGHV*	124	119	114	110	108	105	91	54	18	2	0
AV u*IGHV*	167	163	155	141	129	114	86	48	17	1	0
AVO m*IGHV*	117	111	106	96	89	86	73	41	15	0	
AVO u*IGHV*	169	161	152	141	136	133	118	75	36	7	0
FCR or BR m*IGHV*	118	99	86	81	76	72	65	28	9	2	0
FCR or BR u*IGHV*	172	137	122	108	94	82	62	38	19	4	0

	Hazard Ratio for Disease Progression or Death (95% CI)
AV vs. FCR or BR (m*IGHV*)	0.67 (0.39–1.14)
AV vs. FCR or BR (u*IGHV*)	0.69 (0.48–0.97)
AVO vs. FCR or BR (m*IGHV*)	0.58 (0.32–1.02)
AVO vs. FCR or BR (u*IGHV*)	–

Brown JR. *N Engl J Med*, 2025; 392: 748-762

Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia

Overall Survival



No. at Risk											
AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR or BR	290	247	236	228	223	217	182	98	45	13	0

	No. of Events/ Total No. of Patients	Median Overall Suvival	Overall Survival at 36 Months
		mo	%
AV	18/291	57.8	94.1
AVO	37/286	NC	87.7
FCR or BR	42/290	NC	85.9

	Hazard Ratio for Death (95% CI)	P Value
AV vs. FCR or BR	0.33 (0.18–0.56)	<0.001
AVO vs. FCR or BR	0.76 (0.49–1.18)	–

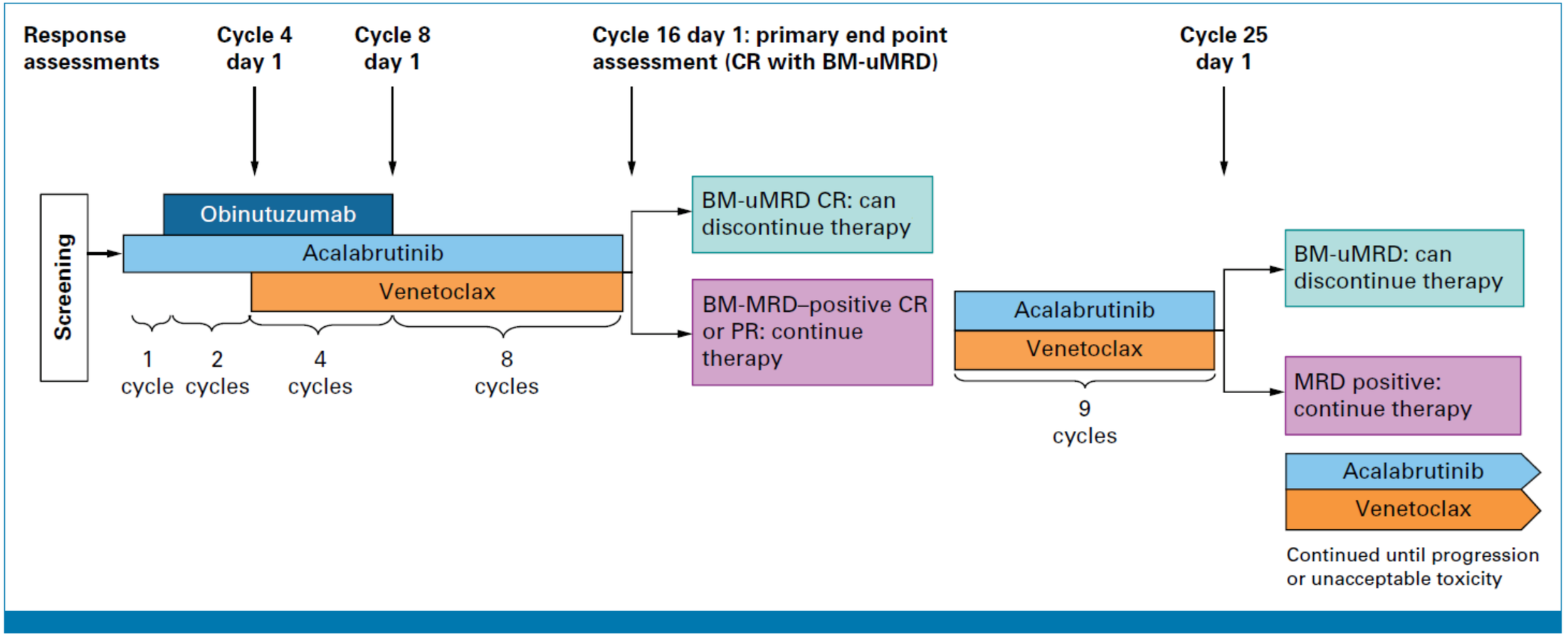
Brown JR. *N Engl J Med*, 2025; 392: 748-762

Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia

AEs of Clinical Interest, n (%)	AV (n = 291)		AVO (n = 284)		FCR/BR (n = 259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
▪ Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
▪ Ventricular tachyarrhythmias	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
▪ Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Secondary primary malignancy	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
▪ Excluding nonmelanoma skin cancer	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
TLS	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Brown JR. *N Engl J Med*, 2025; 392: 748-762

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



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

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

Characteristic	All Participants (N = 72)	*TP53* Aberration (n = 45)
Age, years, median (range)	63 (36-80)	65 (36-80)
Cytogenetics		
TP53 aberration	45 (62.5)	45 (100.0)
Del(17p) with *TP53* mutation	31 (43.1)	31 (68.9)
Del(17p) without *TP53* mutation or *TP53* unknown	3 (4.2)	3 (6.7)
TP53 mutation without del(17p) or del(17p) unknown	11 (15.3)	11 (24.4)
Del(13q)	33 (45.8)	19 (42.2)
Del(11q)	17 (23.6)	7 (15.6)
Trisomy 12	14 (19.4)	11 (24.4)
Del(6q)	4 (5.6)	2 (4.4)
IGHV status, unmutated	54 (75.0)	37 (82.2)
NOTCH1 mutation	12 (16.7)	8 (17.8)
SF3B1 mutation	13 (18.0)	11 (24.4)
Complex karyotype	20 (27.8)	17 (37.8)

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

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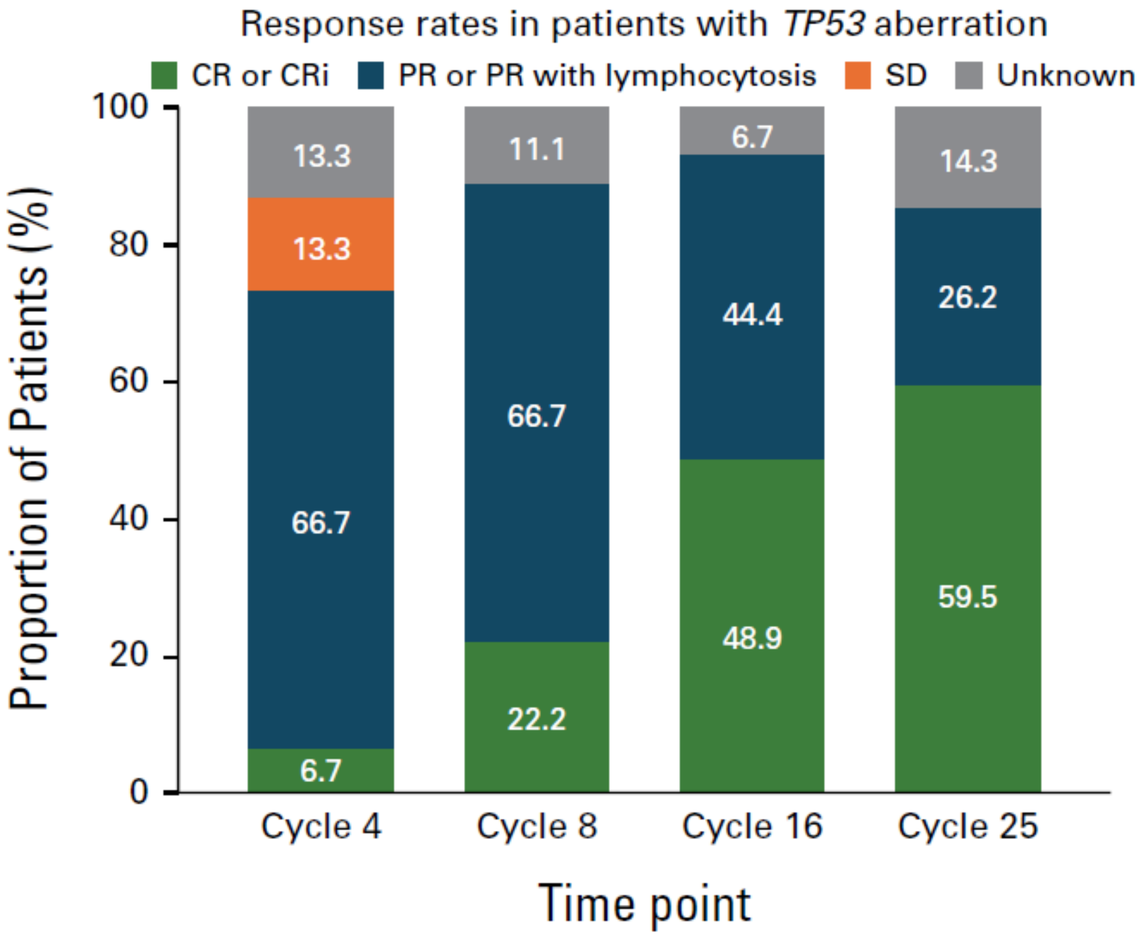

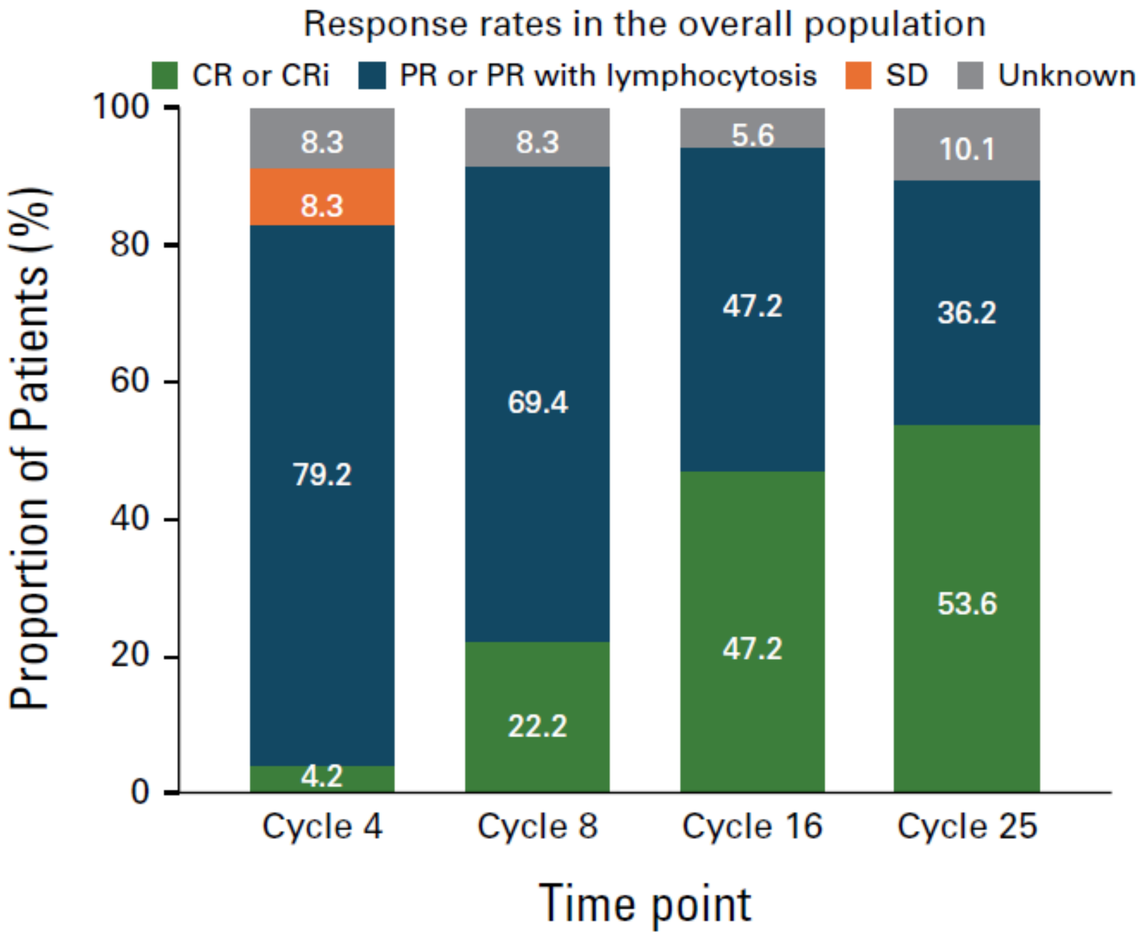

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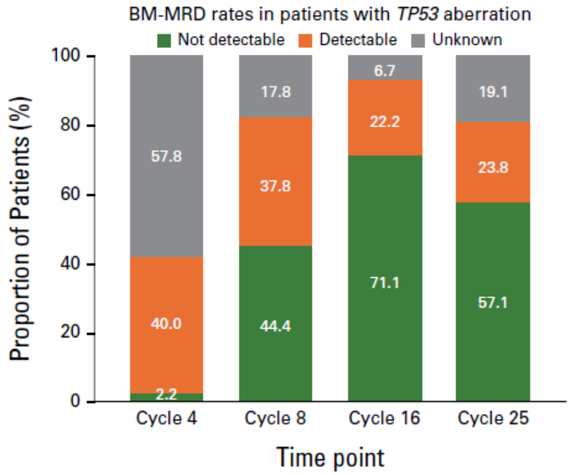

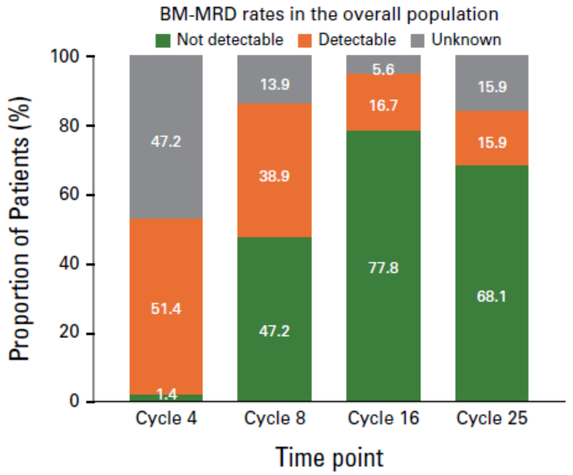

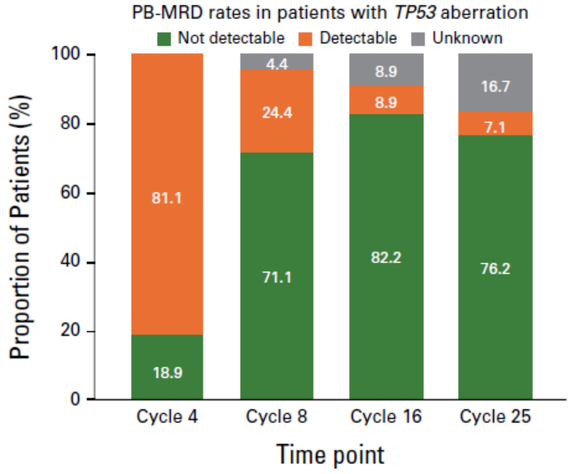

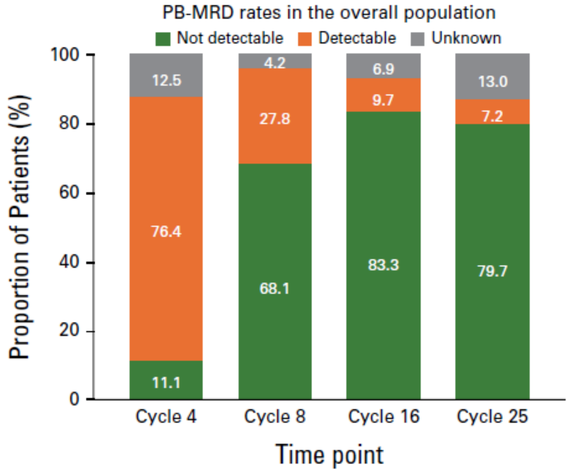

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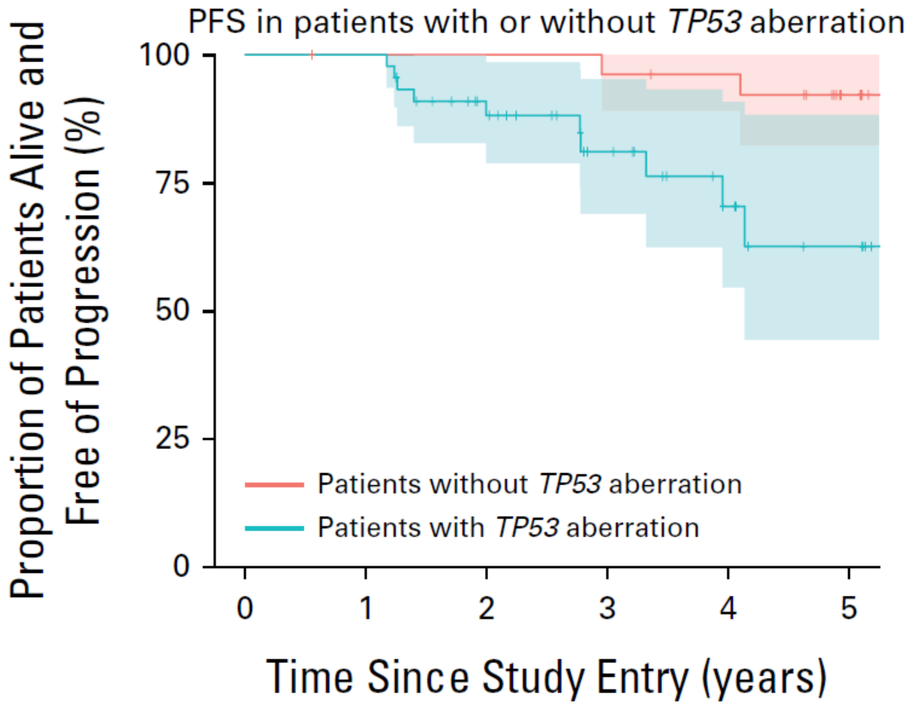
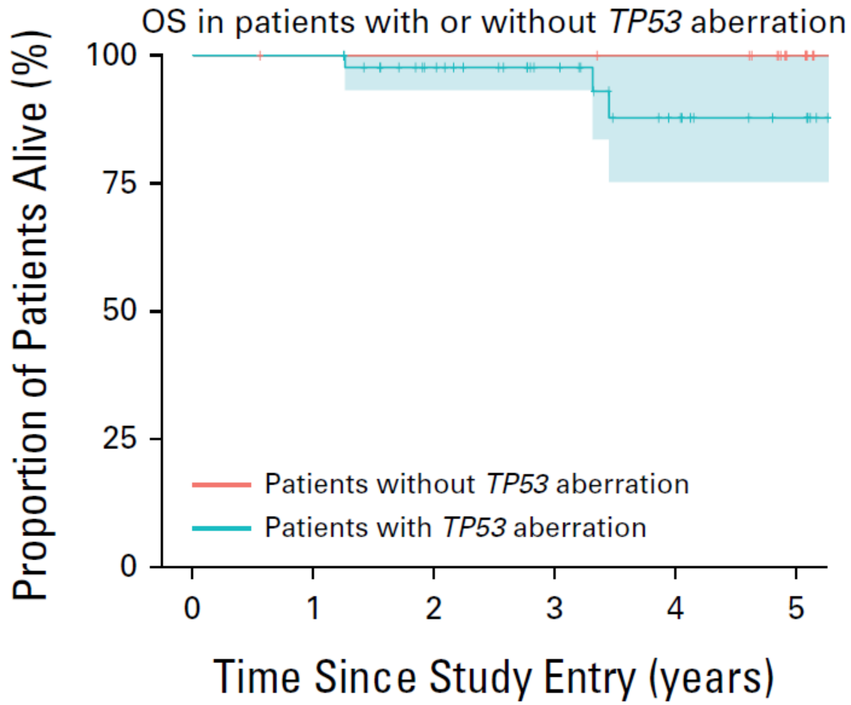


Number at risk:						
Patients without *TP53* aberration	27	26	26	25	24	15
Patients with *TP53* aberration	45	45	32	20	11	6



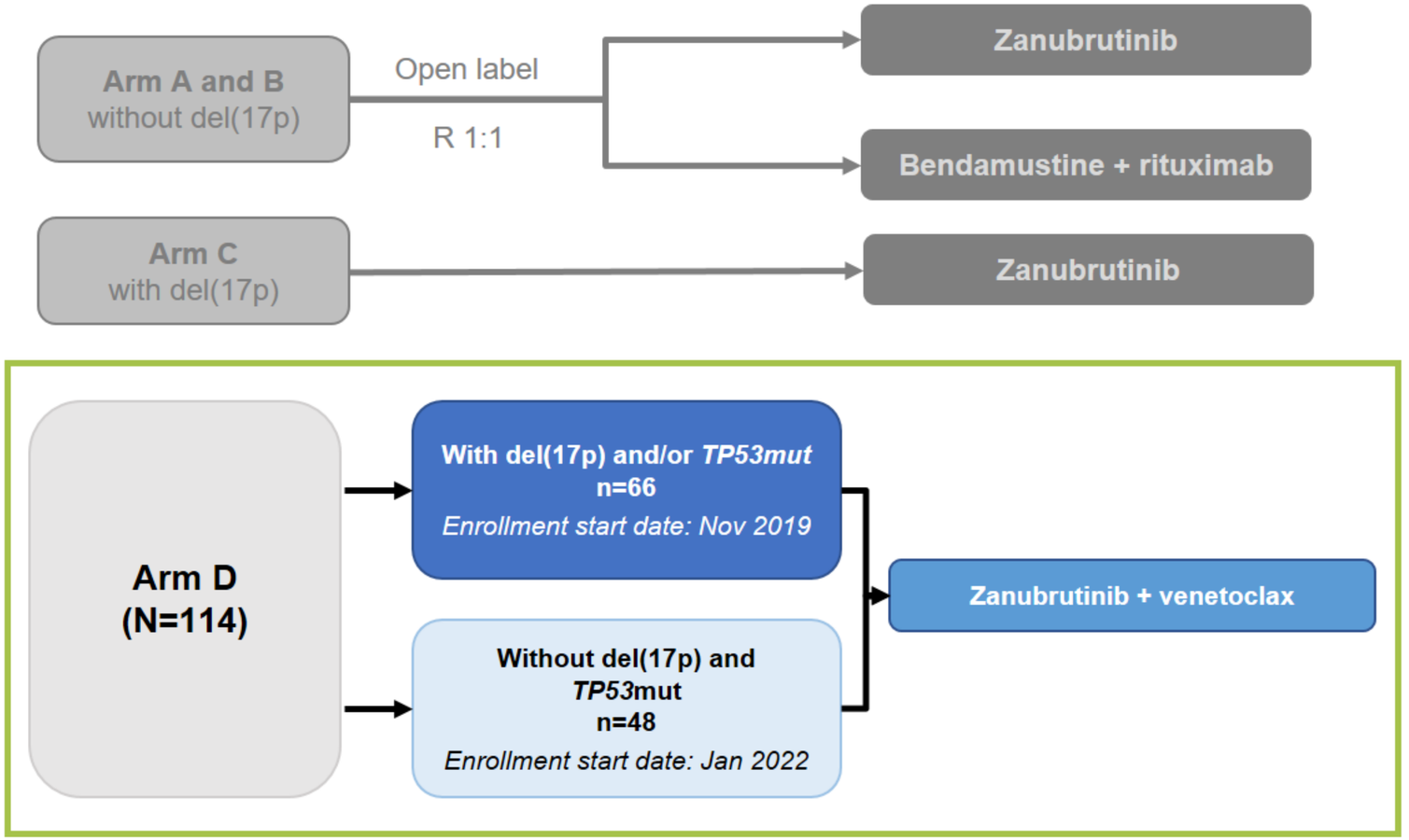
Number at risk:						
Patients without *TP53* aberration	27	26	26	26	25	17
Patients with *TP53* aberration	45	45	35	24	14	8

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

Zanubrutinib and Venetoclax for Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del(17p)/*TP53* Mutation: SEQUOIA Arm D Results

Key eligibility criteria

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

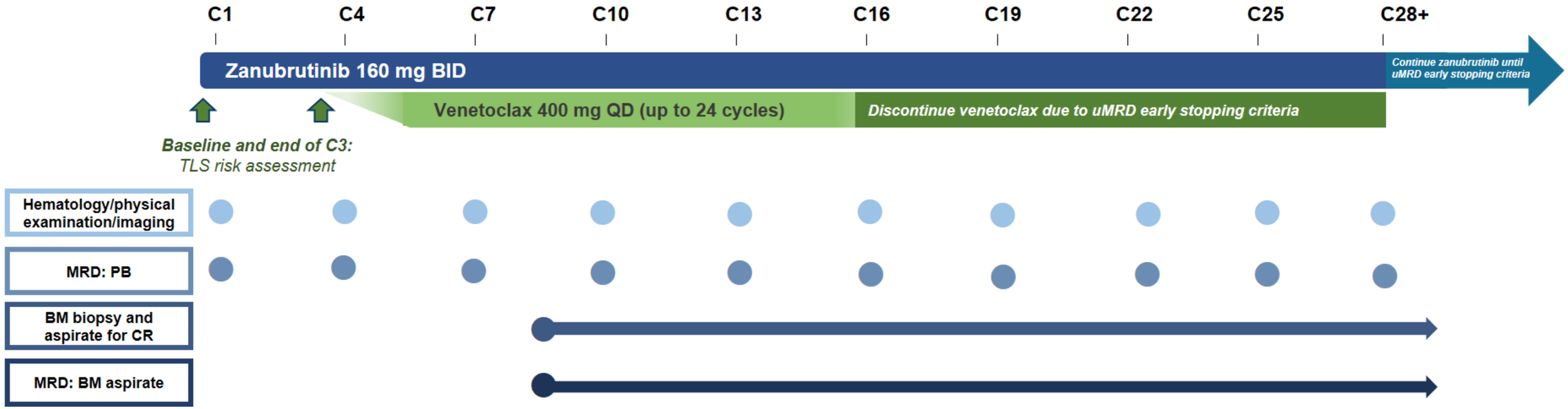


Endpoints for Arm D

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

Shadman M. *J Clin Oncol*, 2025; 43: 2409-2417

Zanubrutinib and Venetoclax for Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del(17p)/*TP53* Mutation: SEQUOIA Arm D Results



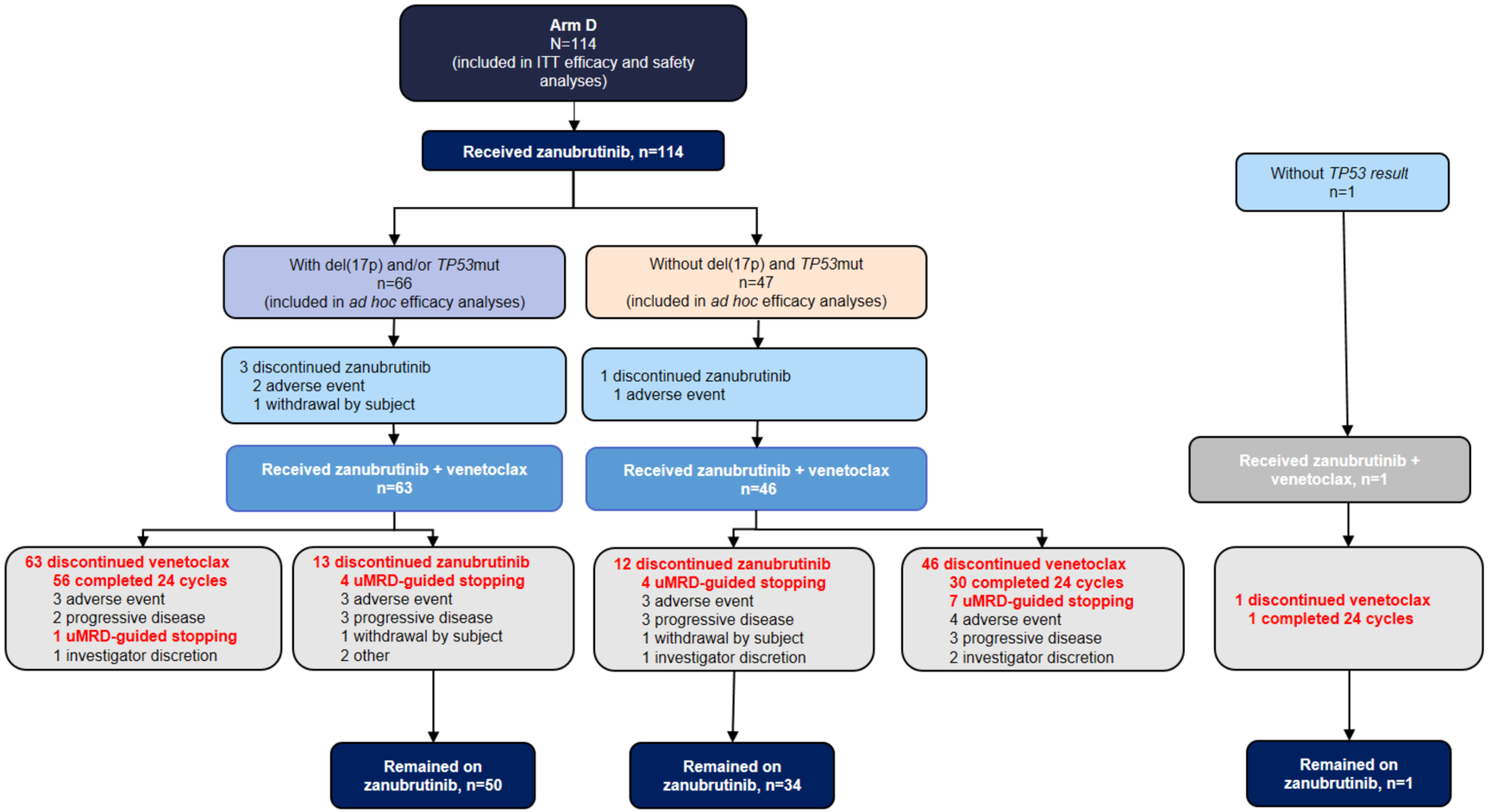
uMRD-guided stopping criteria

All conditions must be met:

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD $<1\times10^{-4}$ (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received
   - i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

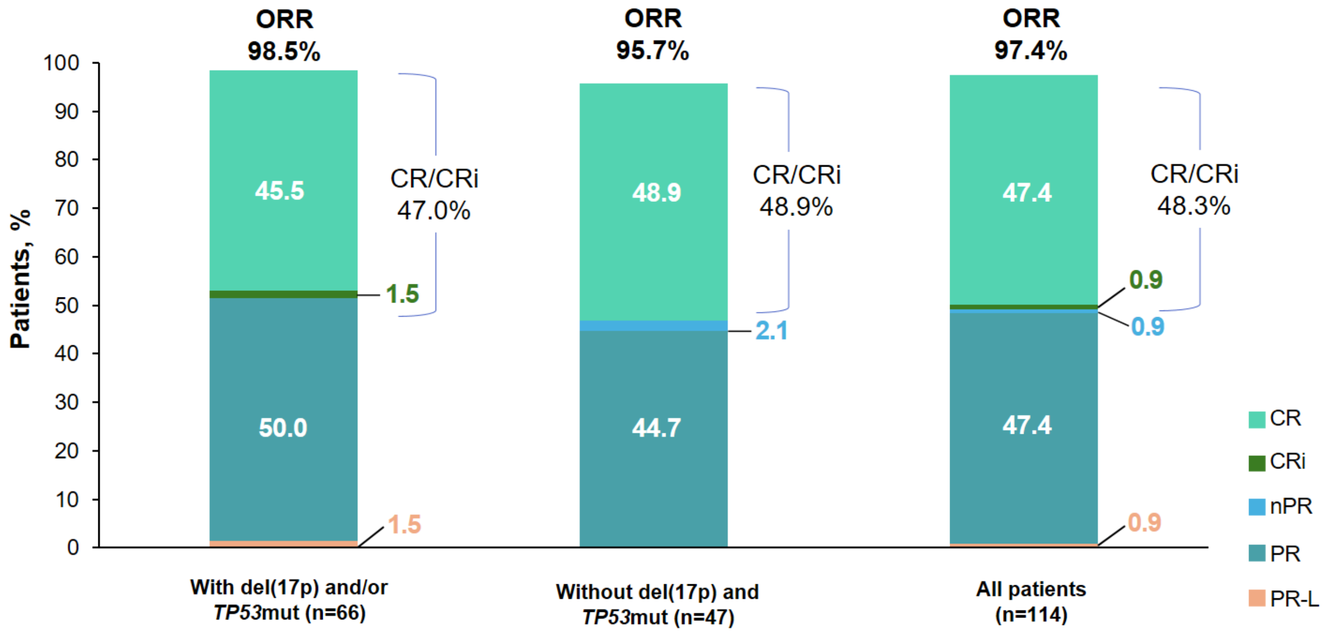
Shadman M. *J Clin Oncol*, 2025; 43: 2409-2417

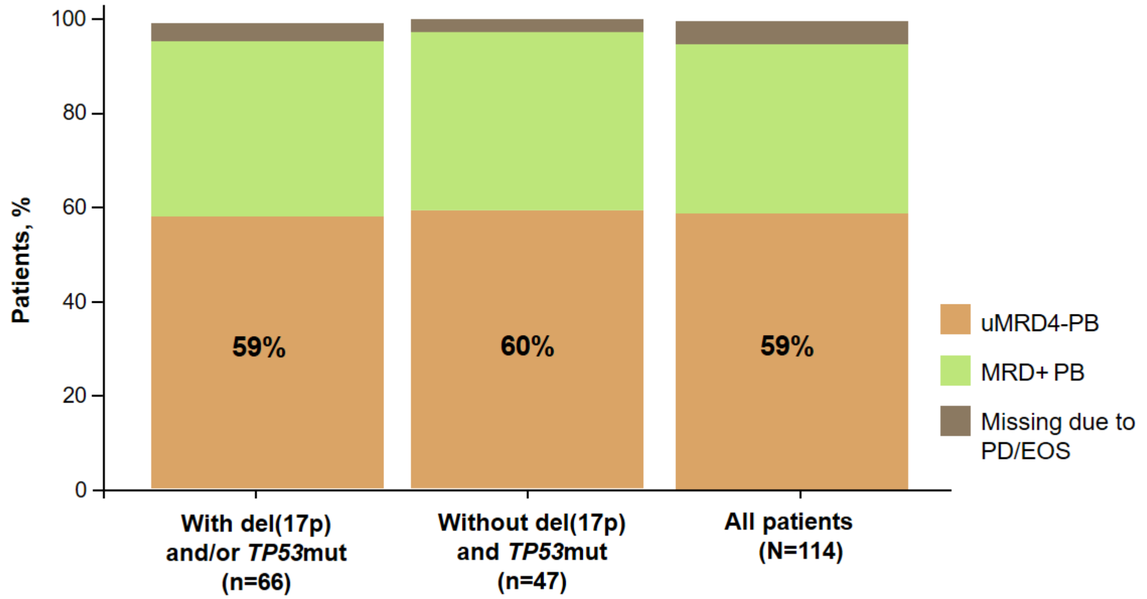
Zanubrutinib and Venetoclax for Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del(17p)/*TP53* Mutation: SEQUOIA Arm D Results



Shadman M. *J Clin Oncol*, 2025; 43: 2409-2417

Zanubrutinib and Venetoclax for Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del(17p)/*TP53* Mutation: SEQUOIA Arm D Results





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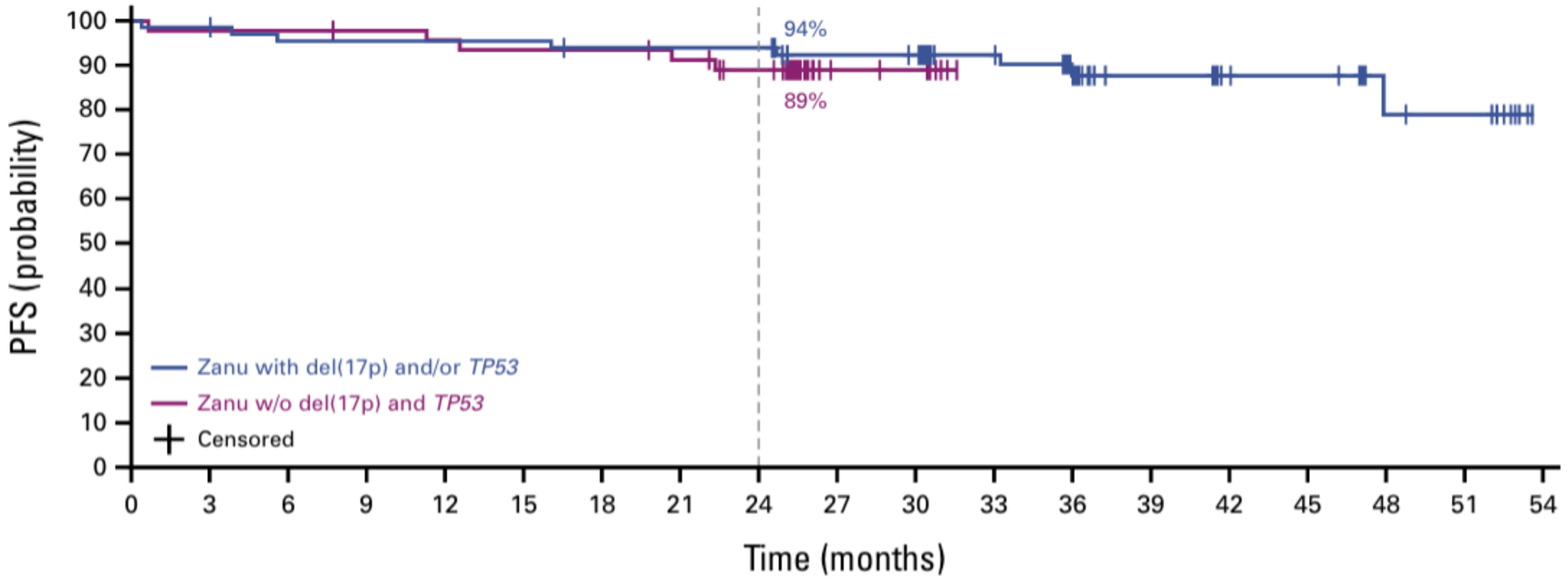
Zanubrutinib and Venetoclax for Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del(17p)/*TP53* Mutation: SEQUOIA Arm D Results



Number at risk:

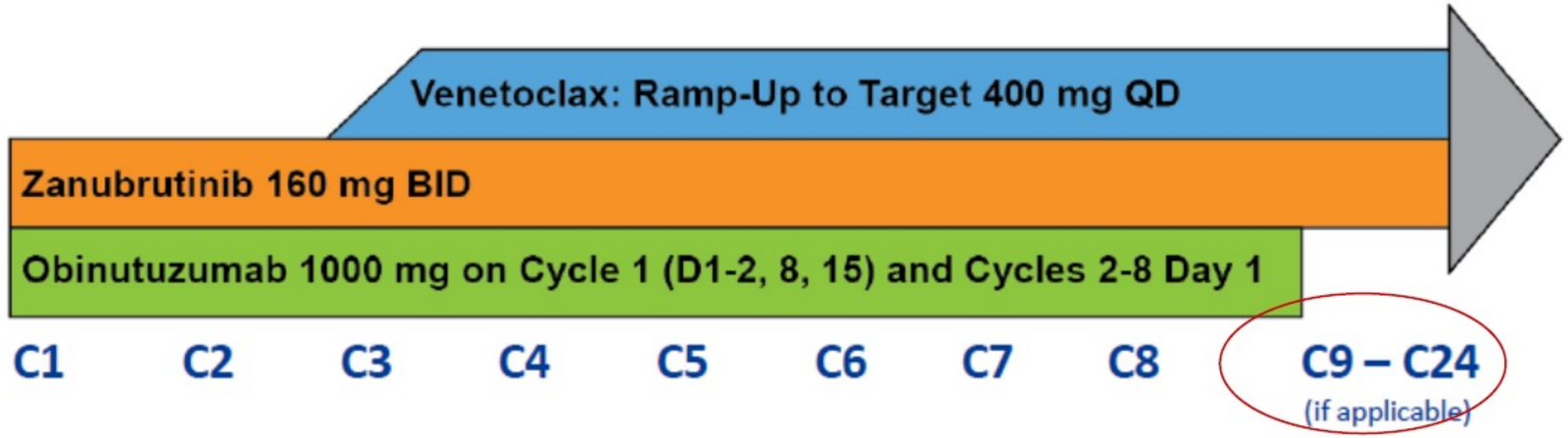
Zanu with del(17p) and/or *TP53*	66	65	62	62	62	62	60	60	60	55	54	45	35	23	17	16	9	8	0
Zanu w/o del(17p) and *TP53*	47	46	46	45	44	43	43	41	37	7	4	0							

Shadman M. *J Clin Oncol*, 2025; 43: 2409-2417

Multicenter Phase II Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Treatment-Naïve Chronic Lymphocytic Leukemia: 5-Year Follow up, Retreatment Outcomes, and Impact of MRD Kinetics (△MRD400)

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



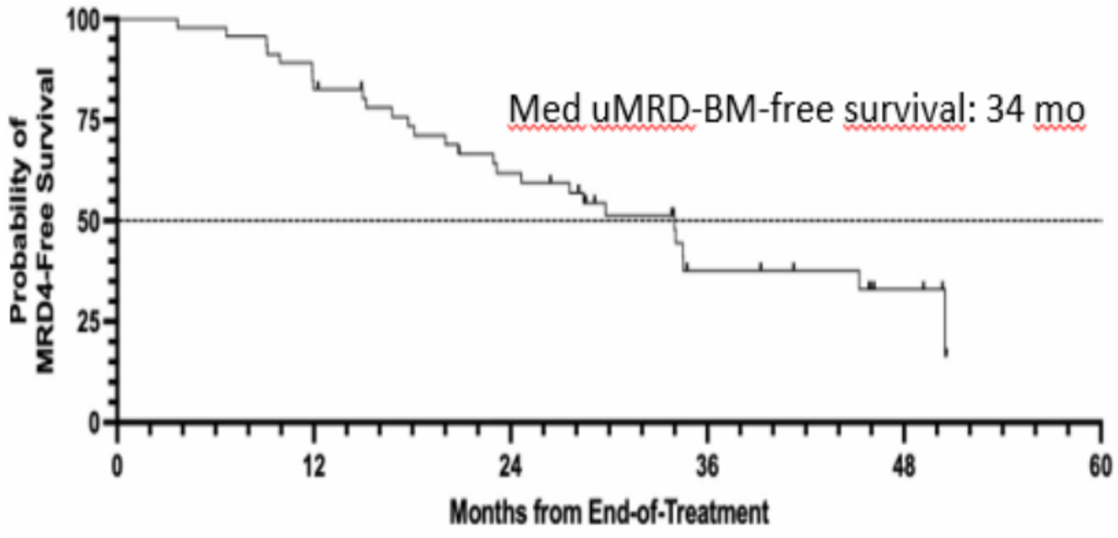
Treatment duration / MRD-directed treatment discontinuation criteria

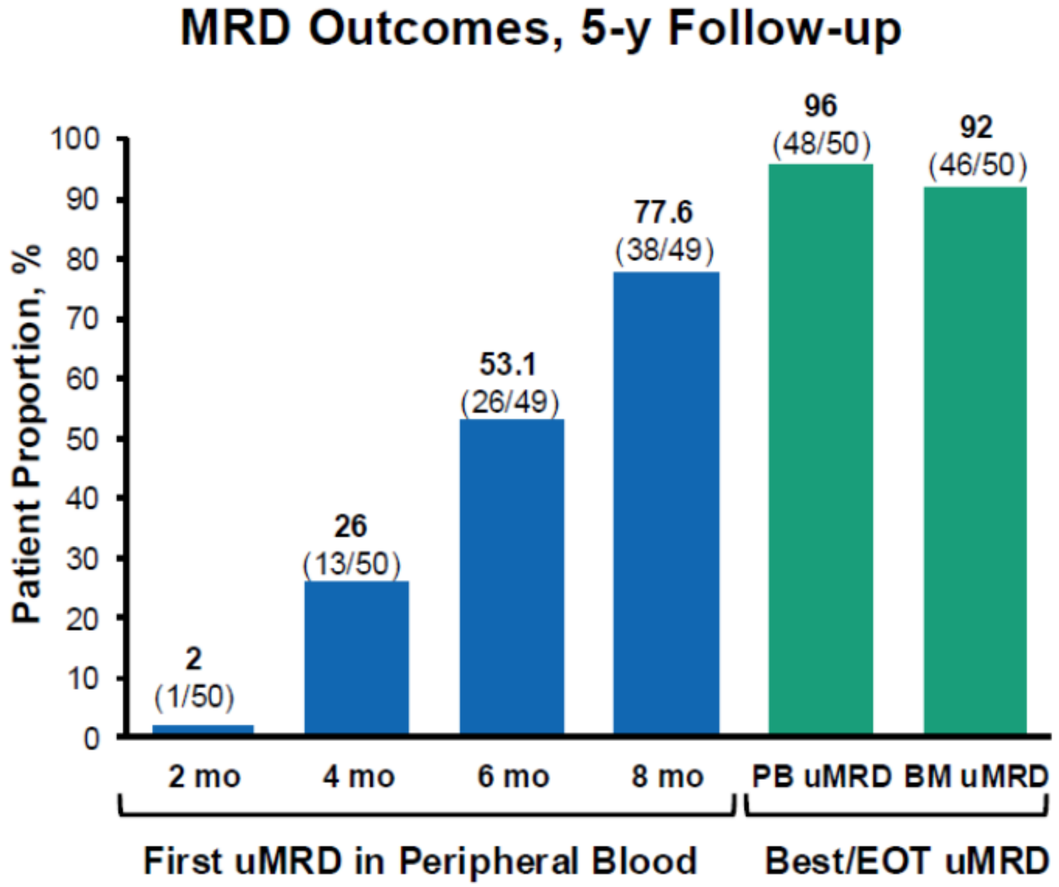
- Treatment duration: Min 8 months to Max 24 months (including 2-month doublet lead-in prior to venetoclax)
- Peripheral blood MRD (flow cytometry) assessed every 2 cycles
  - If PB uMRD $<10^{-4}$ (flow), then BM MRD assessment within 14 days
  - If PB and BM uMRD $<10^{-4}$ (flow), then repeat PB MRD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

Soumerai JD. *Blood (ASH annual meeting abstracts)*, 2024; 144 (S1): 1867

Multicenter Phase II Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Treatment-Naïve Chronic Lymphocytic Leukemia: 5-Year Follow up, Retreatment Outcomes, and Impact of MRD Kinetics (△MRD400)

	52 patients
Median FU	*57 mo*
Med. age	*62 yrs*
Unmutated IGHV	*71%*
TP53 del/mut	*17%*
Response evaluable	*50/52*





Soumerai JD. *Blood (ASH annual meeting abstracts)*, 2024; 144 (S1): 1867

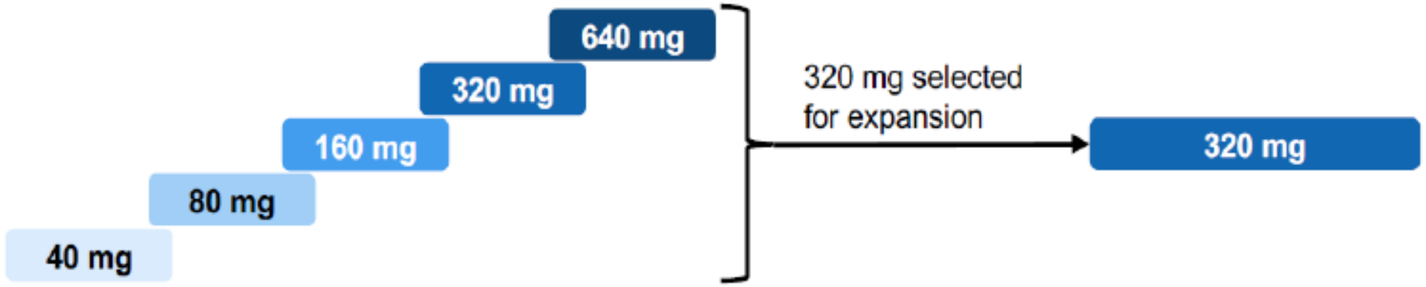
Sonrotoclax and Zanubrutinib as Frontline Treatment for CLL Demonstrates High MRD Clearance Rates with Good Tolerability: Data from an Ongoing Phase 1/1b Study BGB-11417-101

Sonrotoclax: potent and selective BCL2 inhibitor with short half life (4 hours)

BCL2 Member Kinase	IC_{50} (nM)	
	Venetoclax	Sonrotoclax
BCL2	0.20 ± 0.015	0.014 ± 0.0021
BCL-xL	65 ± 9.1	28 ± 3.6
BCL-W	2730 ± 250	1803 ± 83
MCL1	>10000	>10000
BCL2A1	>10000	>10000

Sonrotoclax + zanubrutinib dose finding (weekly ramp-up) → **Sonrotoclax + zanubrutinib expansion (daily or weekly ramp-up)**

- **R/R CLL/SLL**, R/R MCL, TN CLL/SLL
- **R/R CLL/SLL**, R/R MCL, TN CLL/SLL



Median follow-up (range): 19.3 mo (0.4-35.7)

Soumerai JD. *Blood (ASH annual meeting abstracts)*, 2024; 144 (S1): 1012

Sonrotoclax and Zanubrutinib as Frontline Treatment for CLL Demonstrates High MRD Clearance Rates with Good Tolerability: Data from an Ongoing Phase 1/1b Study BGB-11417-101

TN patients
zanubrutinib treatment
x 8-12 weeks

→

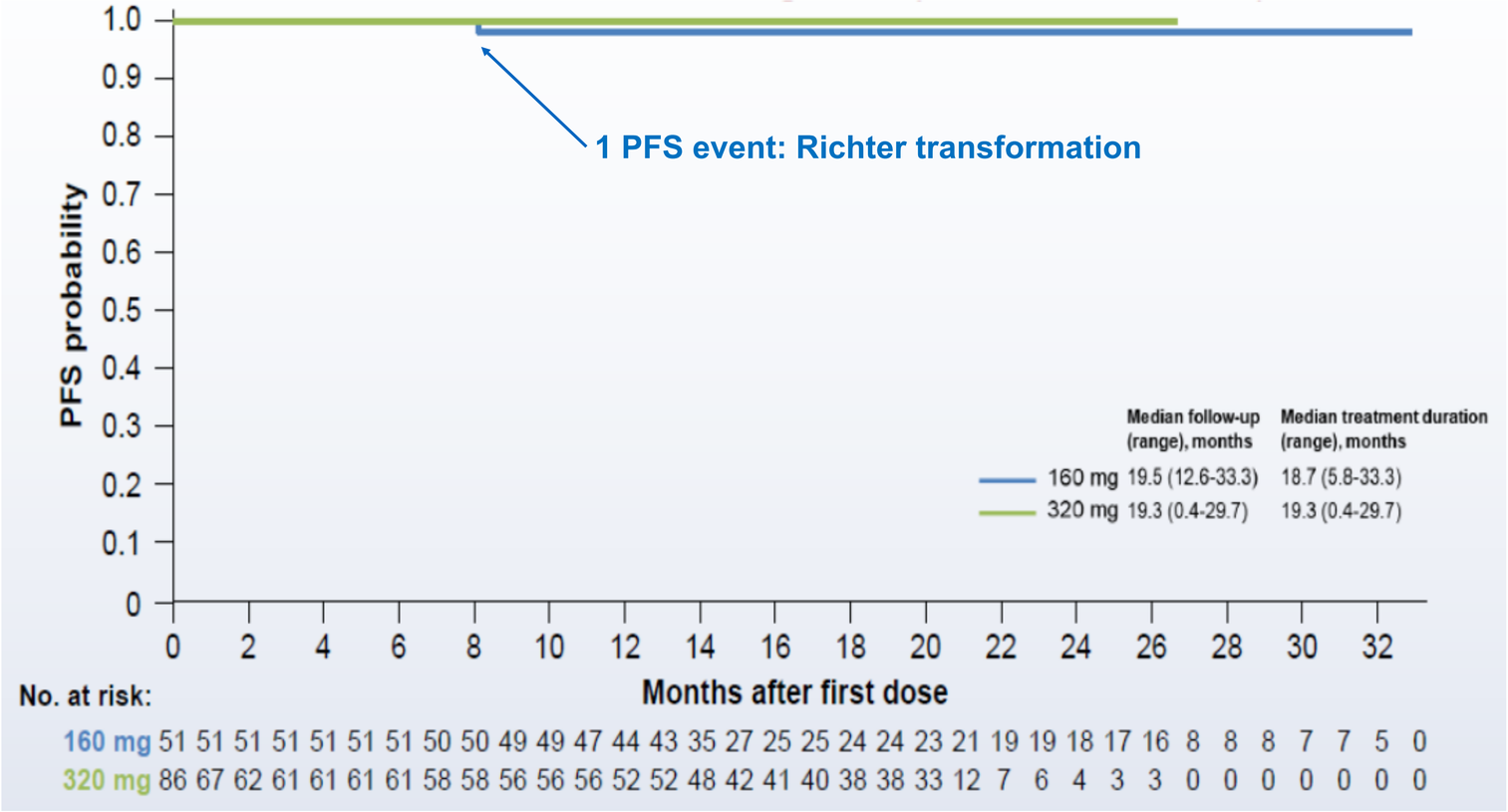
zanubrutinib combined with
sonrotoclax daily ramp-up to
160 mg or 320 mg

Characteristics	Sonro 160 mg + zanu (n=51)	Sonro 320 mg + zanu (n=86)	All Patients (N=137)
Study follow-up, median (range), months	19.5 (12.6-33.3)	19.3 (0.4-29.7)	19.4 (0.4-33.3)
Age, median (range), years	63 (38-82)	61 (32-84)	62 (32-84)
Risk status, n/tested (%)			
del(17p)	5/45 (11.1)	6/77 (7.8)	11/122 (9.0)
TP53 muta	11/47 (23.4)	13/62 (21.0)	24/109 (22.0)
del(11q)	10/45 (22.2)	11/77 (14.3)	21/122 (17.2)
IGHV status, n/tested (%)			
Unmutated IGHV	32/47 (68.1)	32/60 (53.3)	64/107 (59.8)
High tumor bulk[b] at baseline, n/tested (%)	22/51 (43.1)	17/82 (20.7)	39/133 (29.3)

Soumerai JD. *Blood (ASH annual meeting abstracts)*, 2024; 144 (S1): 1012

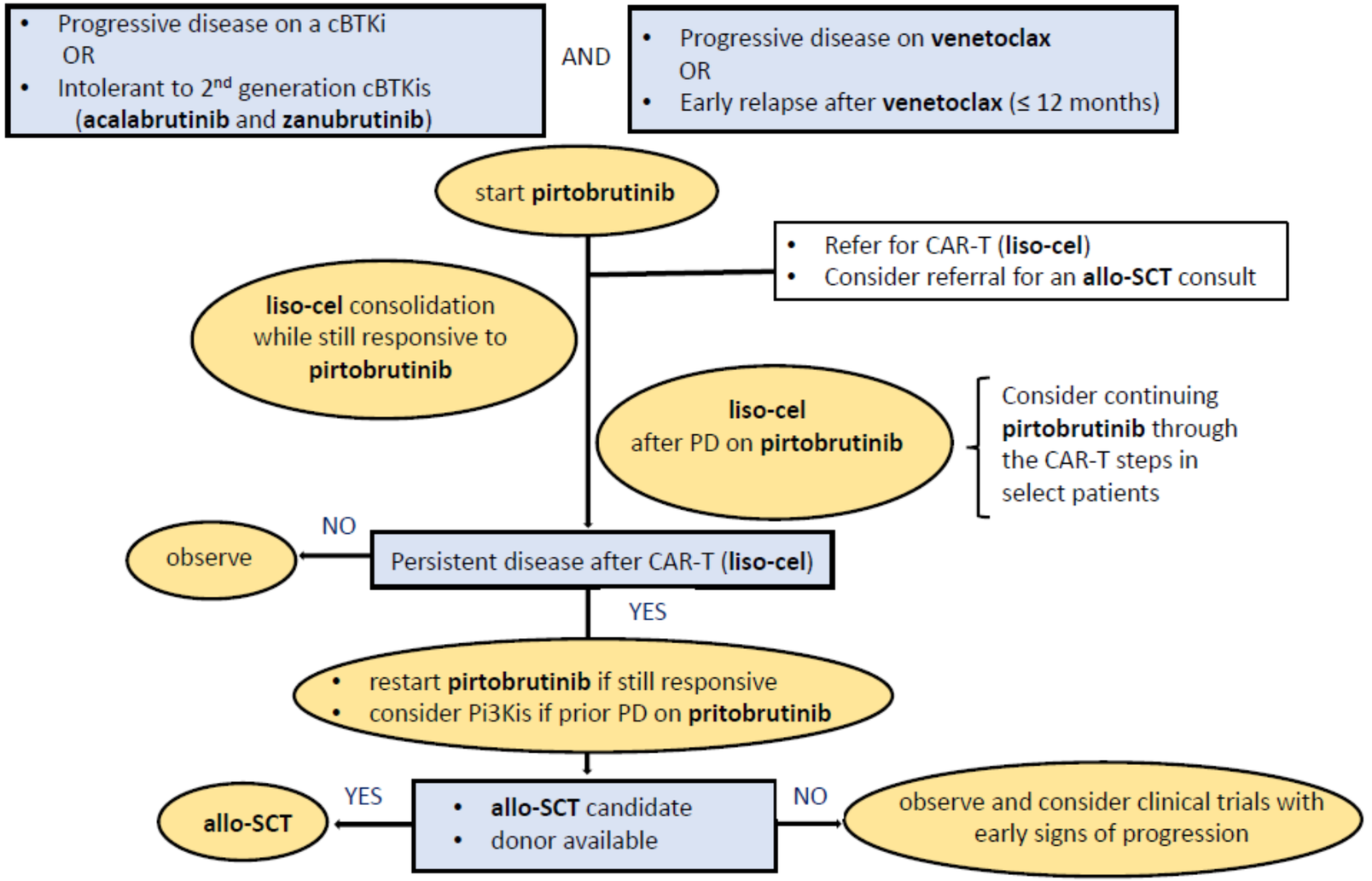
Sonrotoclax and Zanubrutinib as Frontline Treatment for CLL Demonstrates High MRD Clearance Rates with Good Tolerability: Data from an Ongoing Phase 1/1b Study BGB-11417-101

	SONRO 160 mg	SONRO 320 mg
OR rate	100%	100%
CR rate	41%	42%
uMRD4-PB @ wk 24	59%	78%
uMRD4-PB @ wk 48	82%	91%



Soumerai JD. *Blood (ASH annual meeting abstracts)*, 2024; 144 (S1): 1012

When is the right time for cellular therapy?



Shadman M. *Blood*, 2025; in press

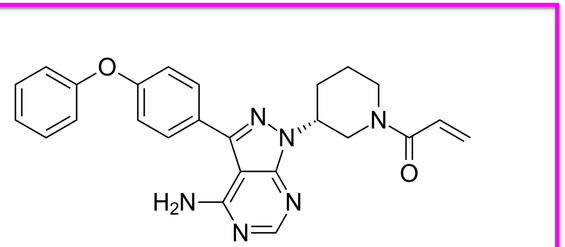
The post double-refractoriness treatment scenario

	N	Median follow-up (months)	Response rate	Duration of response (months)
Approved agents				
pirtobrutinib				
BRUIN	128	22.2	ORR:80%; PR/PR-L: 80%	PFS (in double exposed): 15.9
BRUIN-321	60	19.4	Not reported	TTNT†: 20
lisocabtagene maraleucel				
monotherapy	50*	27	ORR: 44%; CR/CRi: 20%	PFS (in double progressed): 11.9
with ibrutinib	51*	24.3	ORR: 86%; CR/CRi:45%	PFS in 70% venetoclax exposed :31.4; In pts who achieved CR/CRi: not reached
Investigational drugs				
BGB-16673	60 (16 at 200mg)	10.2	ORR:77.6% (93.8%); CR/CRi: 4.1% (6.3%); PR/PR-L: 73.4 (82.3%)	PFS (in double exposed) : not reached
NX-5948	60	not reported	ORR: 75.5-84.2%;CR:0; PR:73.5%-84.2%; PR-L:0-2%	DOR (in double exposed) : not reached
epcoritamab	23	not reported	ORR:61%; CR/CRi:39%	PFS (in double exposed): 12.8 months

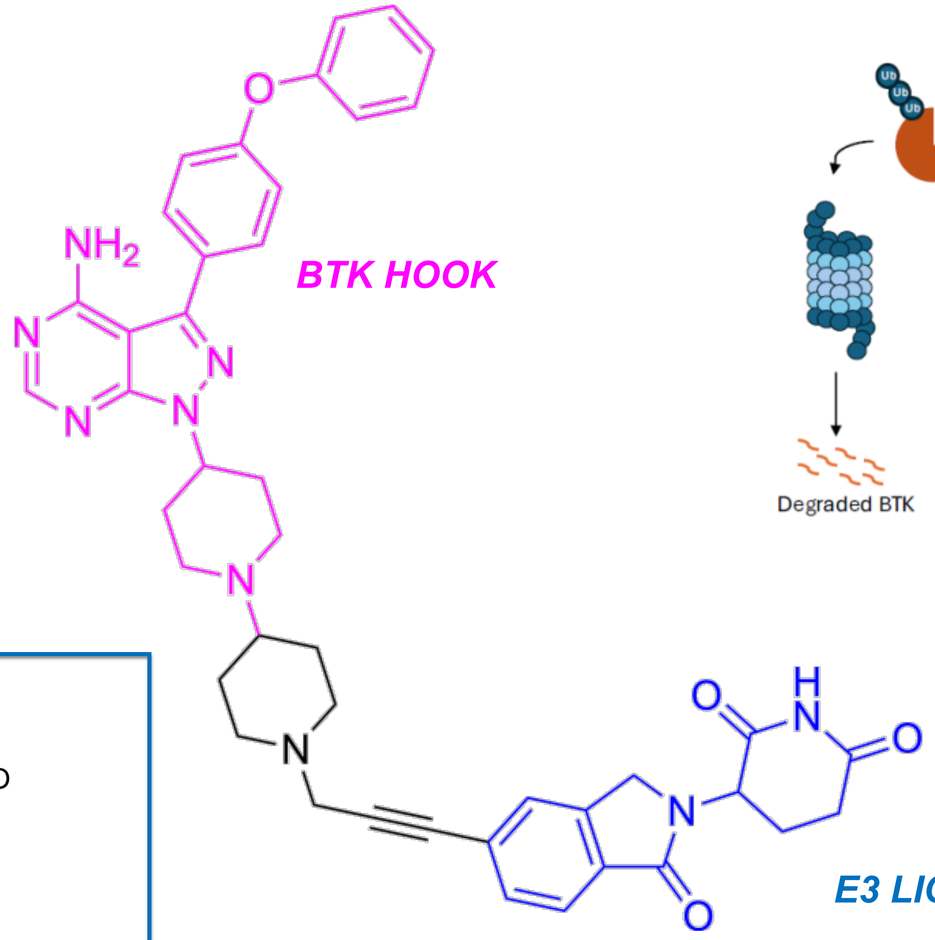
*dose level 2; † PFS not reported for the double exposed population
BCL2: B-cell Lymphoma 2; cBTK: covalent Bruton Tyrosine Kinase PFS: progression-free survival; TTNT: time to next treatment

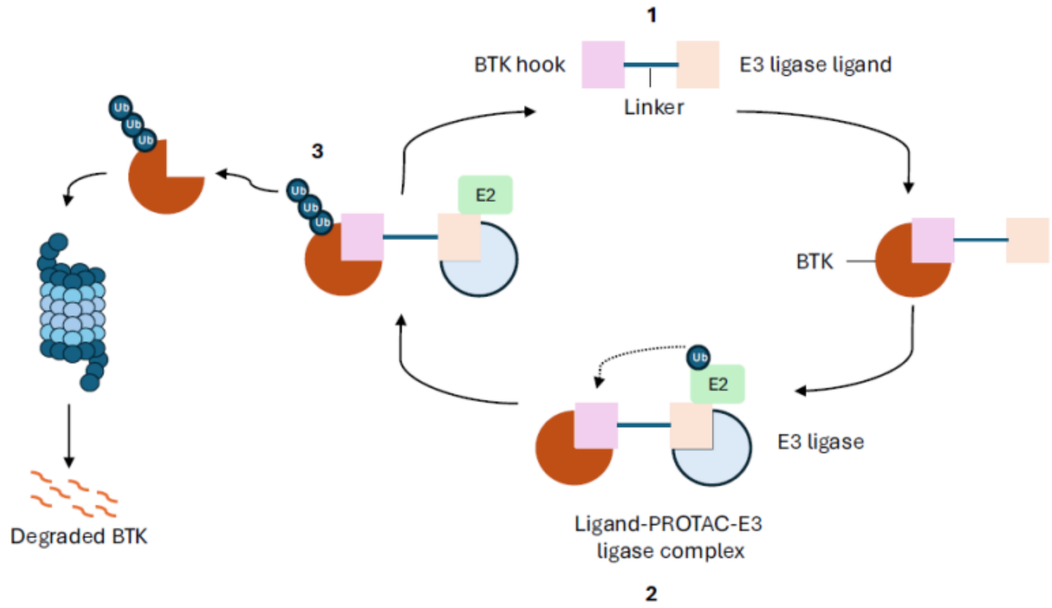
Shadman M. *Blood*, 2025; in press

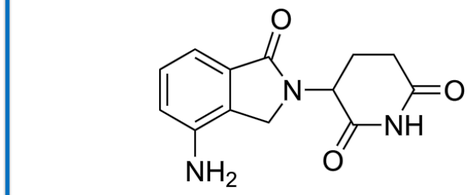
Mechanism of action of BTK degraders



ibrutinib







lenalidomide

Salvaris RT. *Cancers*, 2025; 17: 557

UPDATED EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL: RESULTS FROM THE ONGOING PHASE (PH) 1 CADANCE-101 STUDY

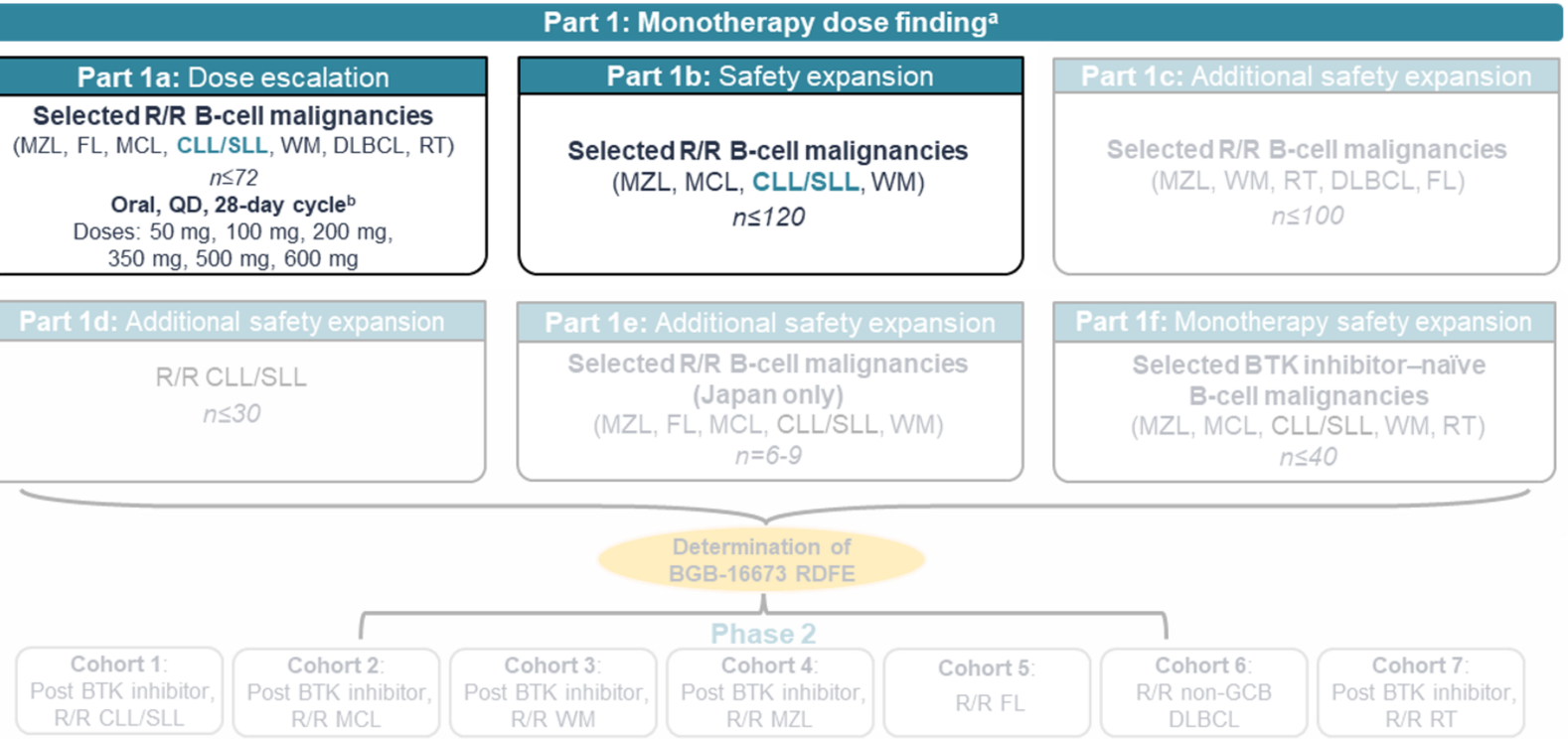
CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for CLL/SLL

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, includ. cBTKi if approved for disease
- ECOG PS 0-2 & adequate end-organ function

Key study objectives for part 1

- **Primary:** safety[c] & tolerability, MTD, & RDFE
- **Secondary:** PK, PD, & preliminary antitumor activity[d]



[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to Common Terminology Criteria for Adverse Events v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [d]Response was assessed per iwCLL 2018 criteria after 12 weeks in patients with CLL.
cBTKi=covalent Bruton tyrosine kinase inhibitor, CLL=chronic lymphocytic leukemia, DLBCL=diffuse large B-cell lymphoma, ECOG PS=Eastern Cooperative Oncology Group performance status, FL=follicular lymphoma, GCB=germinal center B cell, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, MCL=mantle cell lymphoma, MTD=maximum tolerated dose, MZL=marginal zone lymphoma, PD=pharmacodynamics, PK=pharmacokinetics, R/R=relapsed/refractory, RDFE=recommended dose for expansion, RT=Richter transformation, SLL=small lymphocytic lymphoma, WM=Waldenström macroglobulinemia.

Scarfò L. *EHA meeting abstracts*, 2025; S158a

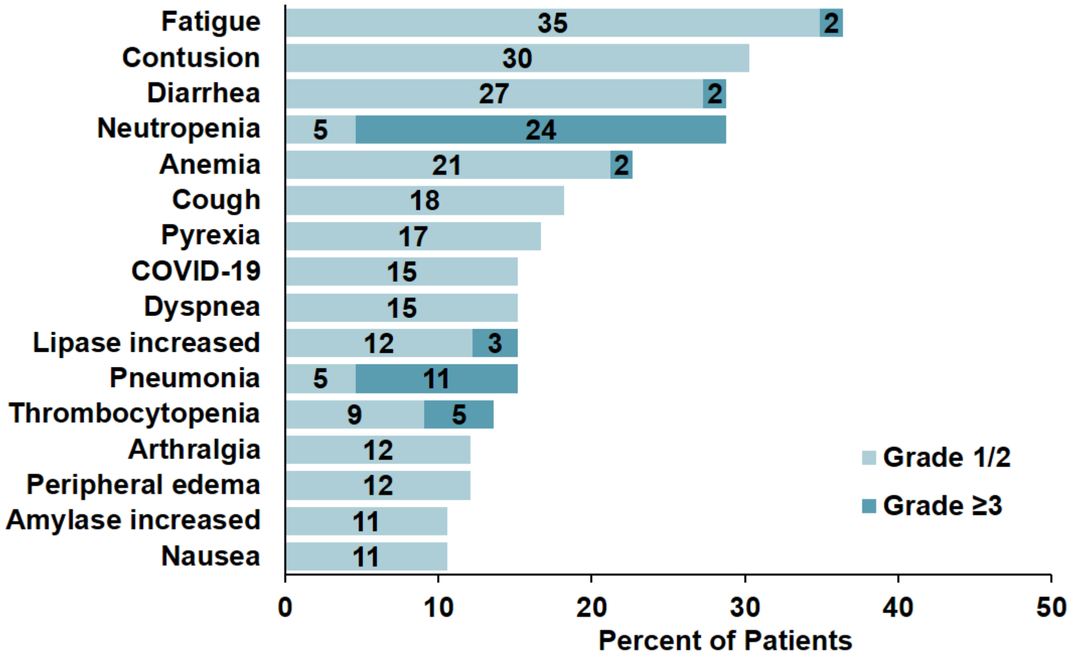
UPDATED EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL: RESULTS FROM THE ONGOING PHASE (PH) 1 CADANCE-101 STUDY

	Total (N=66)
Age, median (range), years	70 (47-91)
Male, n (%)	45 (68.2)
ECOG PS, n (%)	
0	38 (57.6)
1	27 (40.9)
2	1 (1.5)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	29/62 (46.8)
Unmutated IGHV	38/49 (77.6)
del(17p) and/or *TP53* mutation	43/66 (65.2)
Complex karyotype (≥3 abnormalities)	22/44 (50.0)

	Total (N=66)
Mutation status, n/N (%)	
BTK mutation present	24/63 (38.1)
PLCG2 mutation present	10/63 (15.9)
BTK and *PLCG2* mutation present	5/63 (7.9)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	47 (71.2)
cBTK inhibitor	62 (93.9)
ncBTK inhibitor	14 (21.2)
BCL2 inhibitor	54 (81.8)
cBTK + BCL2 inhibitors	42 (63.6)
cBTK + ncBTK + BCL2 inhibitors	12 (18.2)
Discontinued prior BTK inhibitor due to PD, n/N (%)	55/62 (88.7)

Scarfò L. *EHA meeting abstracts*, 2025; S158a

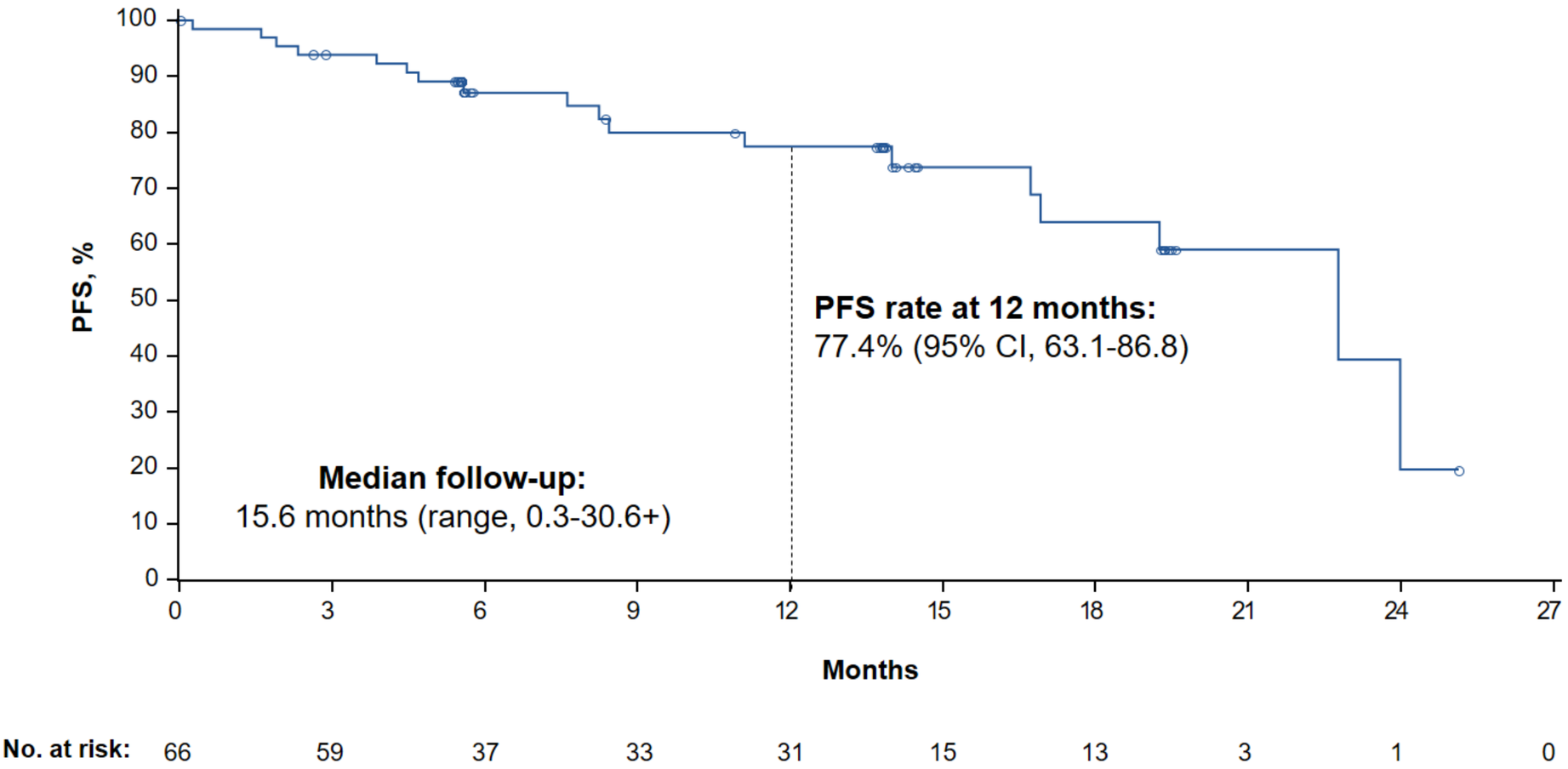
UPDATED EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL: RESULTS FROM THE ONGOING PHASE (PH) 1 CADANCE-101 STUDY



Subgroup	ORR, n/N with known status (%)
Double exposure (previously received cBTKi + BCL2i)	38/42 (90.5)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	9/12 (75.0)
del(17p) and/or *TP53* mutation	35/43 (81.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
BTK mutations	18/24 (75.0)
PLCG2 mutations	9/10 (90.0)

Scarfò L. *EHA meeting abstracts*, 2025; S158a

UPDATED EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL: RESULTS FROM THE ONGOING PHASE (PH) 1 CADANCE-101 STUDY



Scarfò L. *EHA meeting abstracts*, 2025; S158a

BEXOBRUTIDEG (NX-5948), A NOVEL BRUTON'S TYROSINE KINASE (BTK) DEGRADER, DEMONSTRATES RAPID AND DURABLE CLINICAL RESPONSES IN RELAPSED/REFRACTORY CLL: UPDATED FINDINGS FROM AN ONGOING PHASE 1A STUDY

Characteristics	Patients with CLL/SLL (n=48)
Median age, years (range)	68.5 (35–88)
Sex, n (%)	
Male	32 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	3 (6.3)
Race, n (%)	
Black or African American	3 (6.3)
White	42 (87.5)
Other	1 (2.1)
ECOG PS, n (%)	
0	19 (39.6)
1	29 (60.4)
CNS involvement, n (%)	5 (10.4)
Median prior lines of therapy (range)	4.0 (2–12)
Previous treatments[a], n (%)	
BTKi	47 (97.9)
cBTKi	47 (97.9)
ncBTKi[b]	13 (27.1)
BCL2i	40 (83.3)
BTKi and BCL2i	39 (81.3)
CAR-T therapy	3 (6.3)
Bispecific antibody	3 (6.3)
PI3Ki	14 (29.2)
Chemo/chemo-immunotherapies (CIT)	35 (72.9)
Mutation status[c] (n=47), n (%)	
BTK	18 (38.3)
TP53	21 (44.7)
PLCγ2	7 (14.9)
BCL2	6 (12.8)

[a]Patients could have received multiple prior treatments; [b]All patients who received ncBTKi also previously received cBTKi; [c]Mutations presented here were centrally sequenced

Data cutoff: 12 Mar 2025

Omer Z. *EHA meeting abstracts*, 2025; PF571a

BEXOBRUTIDEG (NX-5948), A NOVEL BRUTON'S TYROSINE KINASE (BTK) DEGRADER, DEMONSTRATES RAPID AND DURABLE CLINICAL RESPONSES IN RELAPSED/REFRACTORY CLL: UPDATED FINDINGS FROM AN ONGOING PHASE 1A STUDY

CLL response-evaluable patients[a]	Response analysis (n=47)
Objective response rate (ORR),[b] % (95% CI)	80.9 (66.7–90.9)
Best response, n (%)	
CR	1 (2.1)
PR	37 (78.7)
PR-L	0 (0.0)
SD	7 (14.9)
PD	2 (4.3)
Median follow-up, months[c] (range)[d]	9.0 (1.6–26.1)

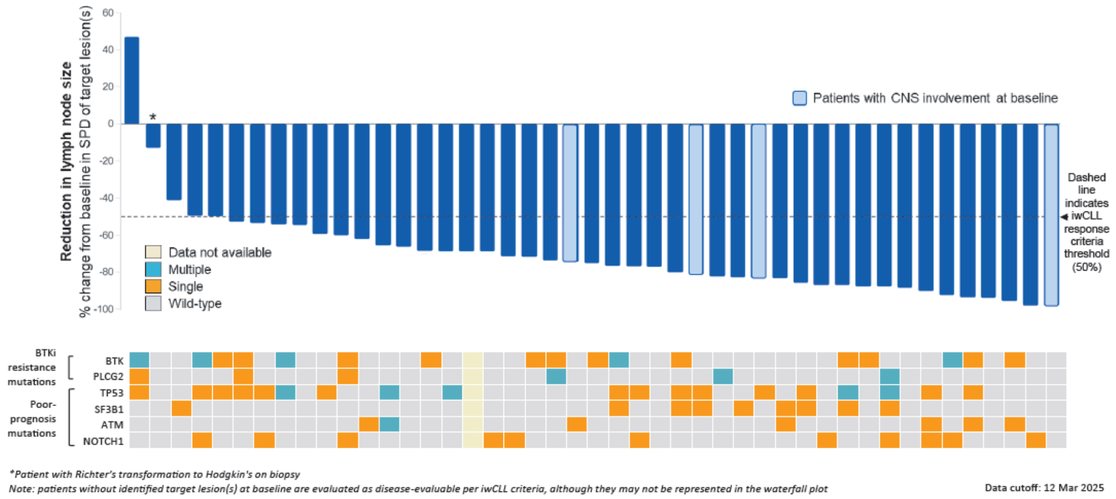
[a]*Patients who were treated with bexobrutideg having ≥1 post-baseline disease assessment or documented clinical PD*
[b]*Objective response rate was evaluated using iwCLL criteria and included CR + PR + PR-L*
[c]*Kaplan-Meier estimate;* [d]*Observed values*

Data cutoff: 12 Mar 2025

TEAEs, n (%)	Patients with CLL/SLL (n=48)		
	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	22 (45.8)	–	–
Diarrhea	15 (31.3)	2 (4.2)	–
Fatigue[b]	15 (31.3)	–	–
Neutropenia[c]	14 (29.2)	11 (22.9)	–
Rash[d]	13 (27.1)	1 (2.1)	1 (2.1)
Petechiae	12 (25.0)	–	–
Headache	12 (25.0)	–	–
Thrombocytopenia[e]	11 (22.9)	1 (2.1)	–
Anemia	9 (18.8)	2 (4.2)	–
COVID-19[f]	9 (18.8)	–	–
Peripheral edema	9 (18.8)	–	–
Cough	8 (16.7)	–	–
Lower respiratory tract infection	7 (14.6)	1 (2.1)	1 (2.1)
Nausea	7 (14.6)	–	–
Pneumonia[g]	6 (12.5)	2 (4.2)	2 (4.2)
Arthralgia	6 (12.5)	–	–
Upper respiratory tract infection	5 (10.4)	–	–
Vomiting	5 (10.4)	1 (2.1)	–
Respiratory syncytial virus infection	2 (4.2)	1 (2.1)	2 (4.2)

[a]*Purpura/contusion includes episodes of contusion or purpura;* [b]*Fatigue was transient;* [c]*Aggregate of 'thrombocytopenia' and 'platelet count decreased';* [d]*Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular';* [e]*Aggregate of 'neutrophil count decreased' or 'neutropenia';* [f]*Aggregate of 'COVID-19' and 'COVID-19 pneumonia';* [g]*Aggregate of 'pneumonia' and 'pneumonia klebsiella'*

Data cutoff: 12 Mar 2025



*Patient with Richter's transformation to Hodgkin's on biopsy
Note: patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL criteria, although they may not be represented in the waterfall plot

Data cutoff: 12 Mar 2025

Omer Z. *EHA meeting abstracts*, 2025; PF571a

Conclusions

- Appropriate treatment sequencing is the key concept for long-term disease control in patients with chronic lymphocytic leukemia: this includes planning allogeneic transplantation in selected cases, whenever required.
- Newer combinations including new drugs within time-limited strategies are aimed at minimizing toxicities (including lessening monitoring requirements) and improving survival.
- Also high-risk patients may take advantage from a frontline time-limited approach.
- Minimal residual disease: not necessarily a treatment endpoint (albeit a prerequisite if treatment conceived as curative) but a guide to define the best treatment duration (shorten in some cases, prolong in others).
- New drugs in development in highly treated/multi-relapsed patiens: try to overcome BTK resistance.