Lymphoma Leukemia & Myeloma Congress

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Sequencing BTKi vs BCL2- Frontline and relapsed

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Disclosures

- **Javier Pinilla-Ibarz, MD, PhD:** Consultant – Janssen/Pharmacyclics, Abbvie, AstraZeneca, Beigene, Lilly, Novartis, BMS, Merck; speaker's bureau – Janssen/Pharmacyclics, Abbvie, AstraZeneca, Beigene, Lilly

Learning Objectives

- Evaluate recent clinical trial data and real-world evidence for targeted therapies in CLL/SLL, such as BTK and BCL-2 inhibitors
- Identify effective risk stratification techniques to personalize and select targeted therapies based on unique patient characteristics

CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; BTK = Bruton tyrosine kinase; BCL-2 = B-cell lymphoma 2.

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How Do We Define High-Risk at Dx in 2024 in the Era of Targeted Therapy?

Before targeted therapy	On targeted therapy in RR after CIT	On targeted therapy front line
Del 17p	Del 17p	~~Del 17p~~
Del 11q	Del 11q	~~Del 11q~~
IgHV unmutated	~~IgHV unmutated~~	~~IgHV unmutated~~
IgHV subset 2	IgHV Subset 2	~~IgHV Subset 2~~
Complex karyotype	(IGLV3-21R110)	(IGLV3-21R110)
	Complex karyotype	~~Complex karyotype~~

RR = relapsed/refractory; CIT = chemoimmunotherapy; IgHV = immunoglobulin heavy chain variable.

NCCN Guidelines Version 3.2024
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Acalabrutinib[f,g,*] ± obinutuzumab (category 1) • Venetoclax[f,h] + obinutuzumab (category 1) • Zanubrutinib[f,g,*] (category 1)	• Ibrutinib [f,g,i,*] (category 1) • Ibrutinib[f,g,*] + obinutuzumab (category 2B) • Ibrutinib[f,g,*] + rituximab[j] (category 2B) • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[k,l] • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[m] + anti-CD20 mAb[n,o] ▸ Obinutuzumab ± chlorambucil[p] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[n] (category 2B; category 3 for patients <65 y without significant comorbidities)

National Comprehensive Cancer Network (NCCN). *CLL/SLL Guidelines*. Accessed Sep 13, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

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SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation

SECOND-LINE OR THIRD-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Acalabrutinib[f,g,q,*] (category 1) • Venetoclax[f,h] + rituximab (category 1) • Zanubrutinib[f,g,q,*] (category 1)	• Ibrutinib[f,g,i,*] (category 1) • Venetoclax[f,h] • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• For relapse after a period of remission (if previously used) ▸ Venetoclax[f,h] ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) • Resistance or intolerance to prior covalent BTKi therapy ▸ Pirtobrutinib[f,**]

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi- AND VENETOCLAX-BASED REGIMENS[e]
Other Recommended Regimens (alphabetical order by category)
• Chimeric antigen receptor (CAR) T-cell therapy
▸ Lisocabtagene maraleucel (CD19-directed)[r]
• Small-molecule inhibitors[f]
▸ Duvelisib
▸ Idelalisib[s] ± rituximab
▸ Pirtobrutinib[**] (if not previously given)
▸ Ibrutinib[g,*] + venetoclax[h] (category 2B)
• FCR[j,l]
• Lenalidomide[t] ± rituximab
• Obinutuzumab
• Bendamustine[m] + rituximab[o] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities)
• HDMP + anti-CD20 mAb[n] (category 2B)

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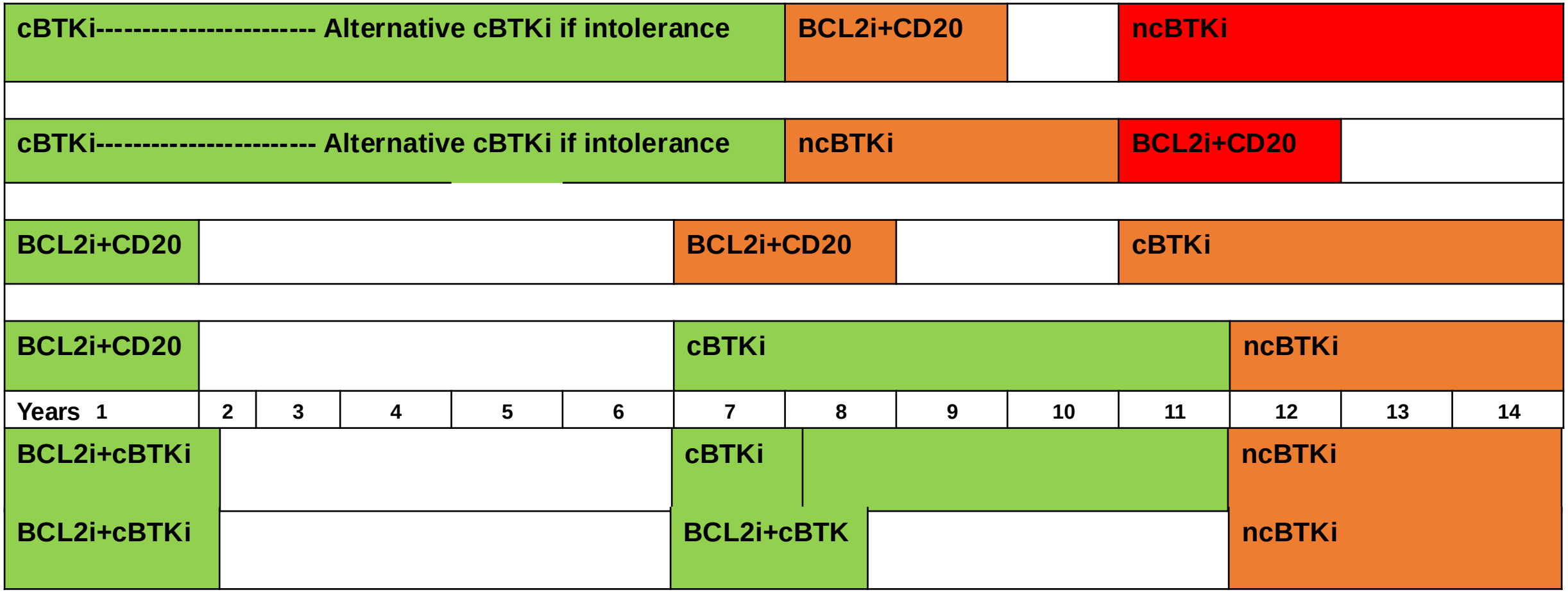
Sequencing Targeted CLL Therapies



cBTKi = covalent BTKi
ncBTKi = non-covalent

Double exposed *vs* double refractory

- Exposed ≠ refractory
- Refractory= progression on treatment

Faculty's opinion.

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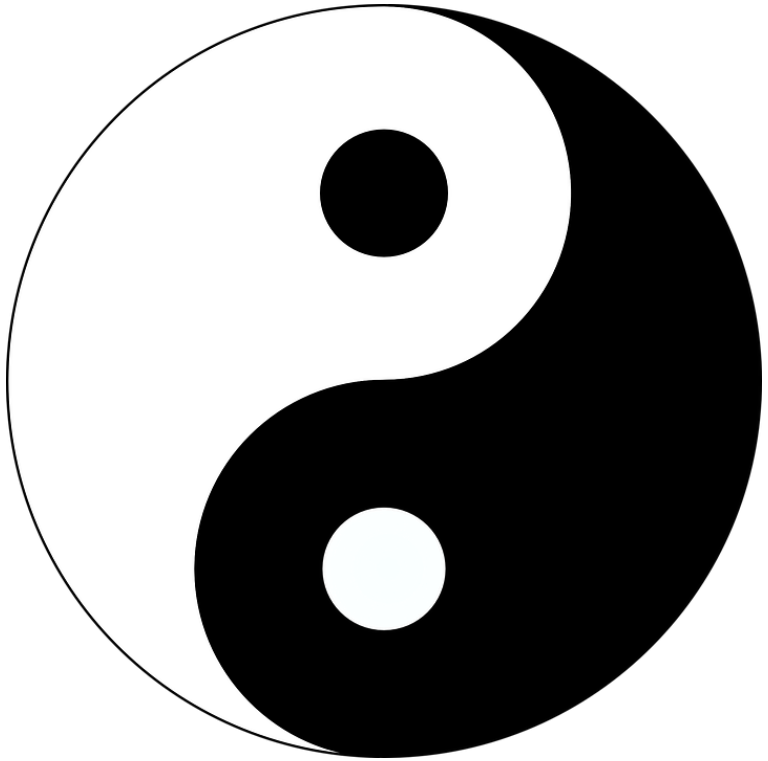
The Dilemma Continues between Long-Term Therapy vs Fixed Duration



Key Learning Points

- Testing for genetic factors only predicts time to treatment but no response to therapy in first line
- At this time, no significant differences between treatment until progression vs limited therapy approaches
- Patient preference should be accounted for in final treatment decisions

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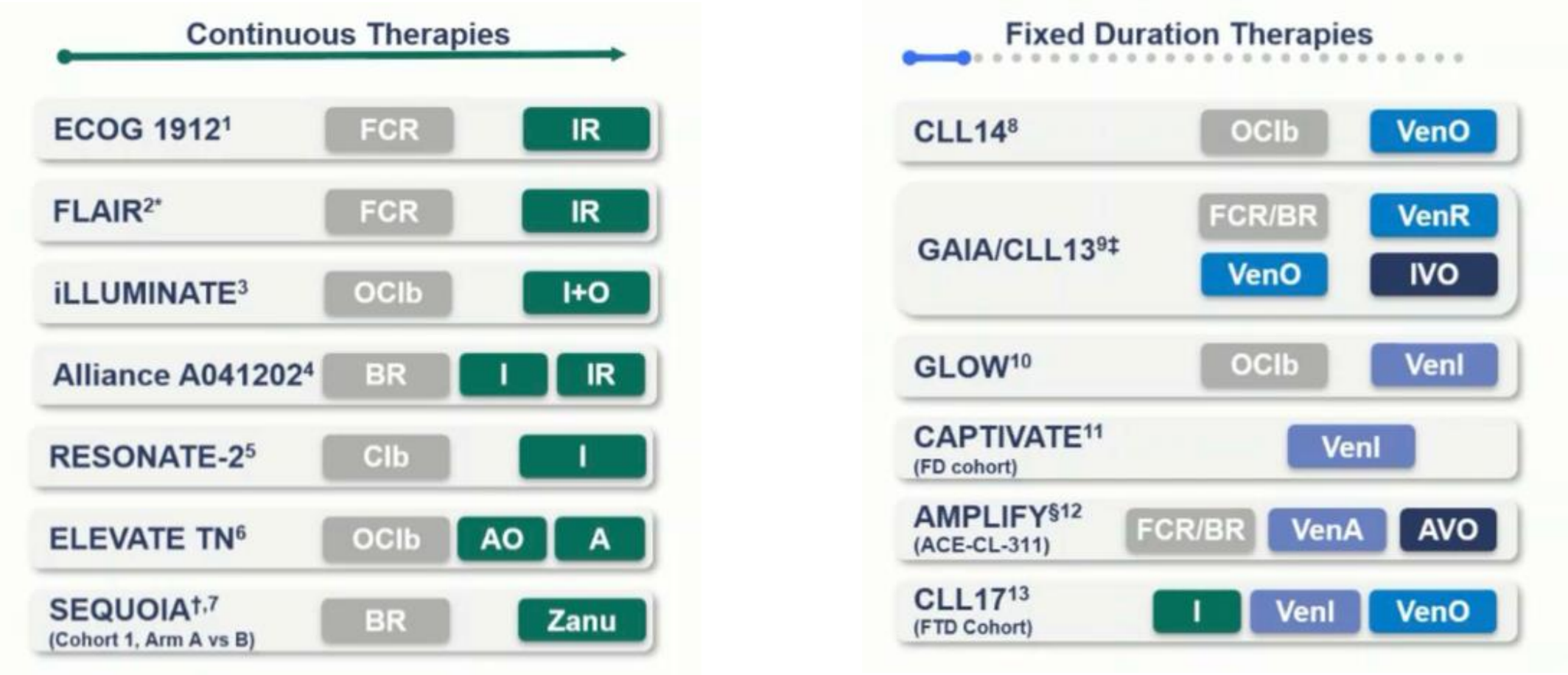
Continuous Therapy vs Fixed Duration

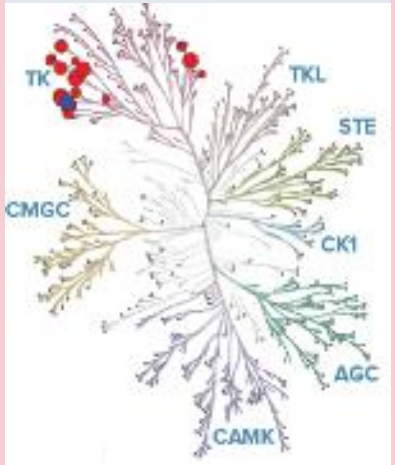


Shanafelt TD, et al. *New Engl J Med.* 2019; 381:435-443. Hillman P, et al. *Lancet Oncol,* 2023,24:535-552. Moreno C, et al. *Lancet Oncol.* 2019,20:43-56. Woyach JA, et al. *Blood,* 2021;138:639. Barr PM, et al. *Blood Adv.* 2022;6:3400-3450. Sharman JP, et al. *Leukemia.* 2022;36:1171-1175. Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043. AlSawaf O, et al. *Nat Commun.* 2023;14:2147. Eichhorst B, et al. *N Eng J Med.* 2023;338:1739-1754. Kater AP, et al. *NEJM Evid.* 2022;1:711. Tam CS, et al. *Blood.* 2022;139:3278-3289. National Institute of Health (NIH). Accessed Sept 25, 2024. https://clinicaltrials.gov/study/NCT04608318; NCT03836261

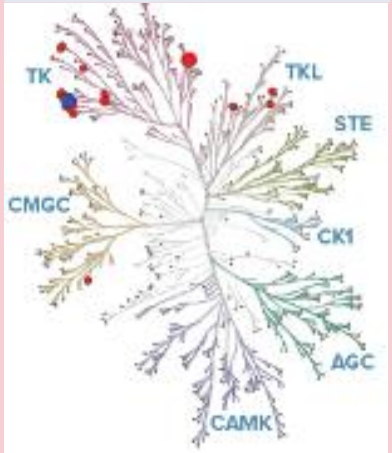
Several Covalent BTKi to Consider with Differences in BTKi Specificity, MOA, and Potential for Off-Target Effects

Covalent

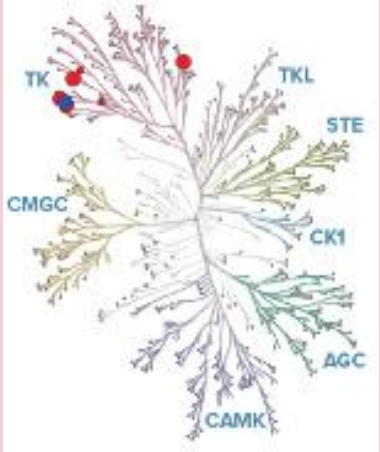
Ibrutinib



Acalabrutinib



Zanubrutinib

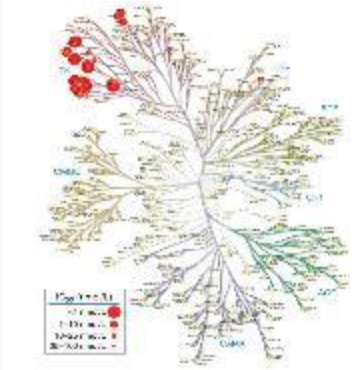


- BTK
- Off target kinases

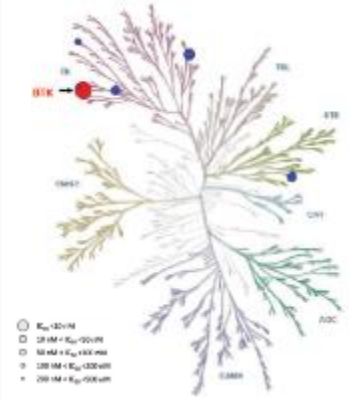
- 95-100% inhibition
- 90-95% inhibition
- 75-90% inhibition
- 50-75% inhibition

Noncovalent

Nemtabrutinib



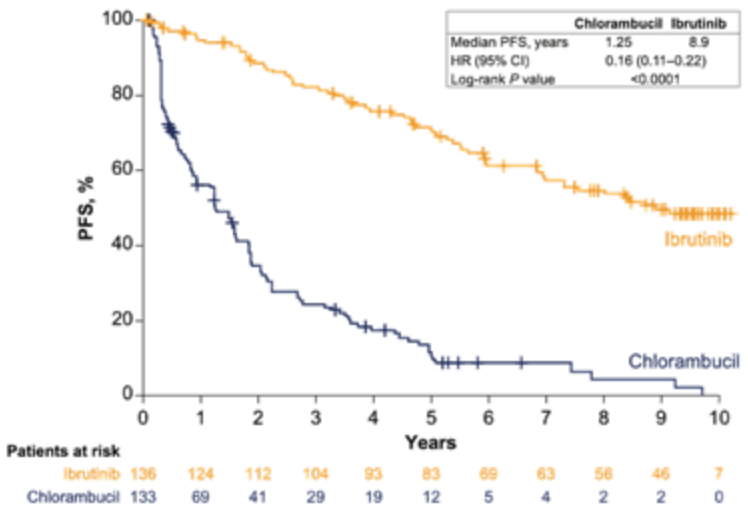
Pirtobrutinib

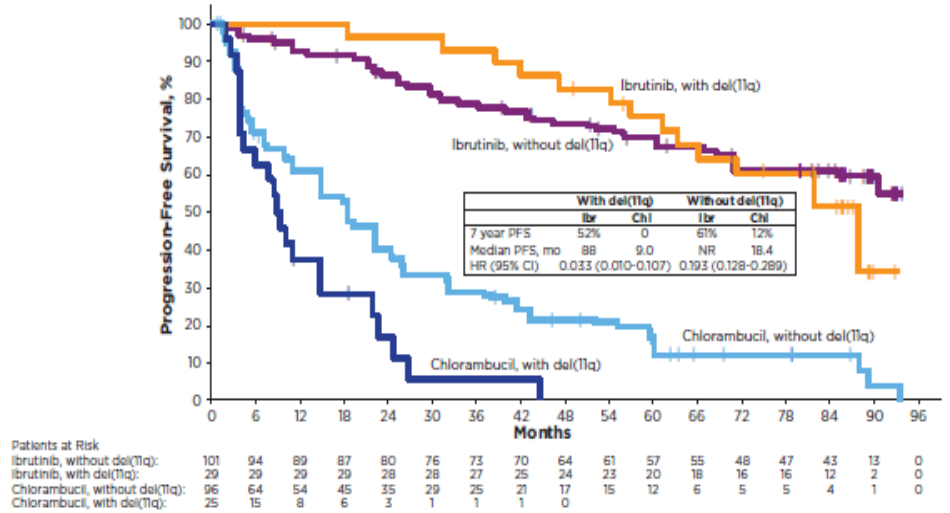


MOA = mechanism of action.

Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45. Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300-1315. Brandhuber B, et al. Presented at: Society of Hematologic Oncology (SOHO) Sixth Annual Meeting; Sep 12-25, 2018; Houston, TX. CLL-200.

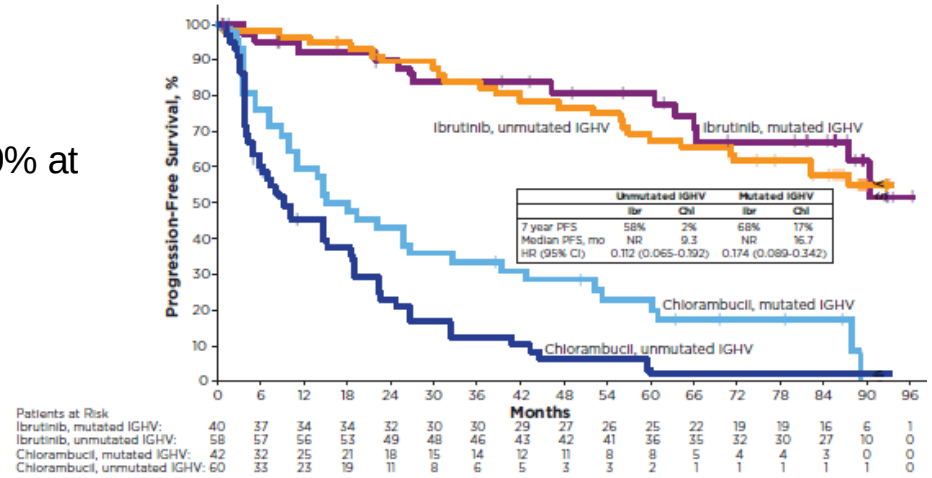
RESONATE-2: Median PFS Reached at 8.9 Years





	Ibrutinib n=136
Median duration of ibrutinib treatment, years	6.2
Continuing ibrutinib on study, n (%)	57 (42)
Discontinued ibrutinib, n (%)	
AE	**32 (24)**
PD	**18 (13)**
Death	12 (9)
Withdrawal by patient	9 (7)
Investigator decision	7 (5)

PFS with ibrutinib: 59% at 84 mo



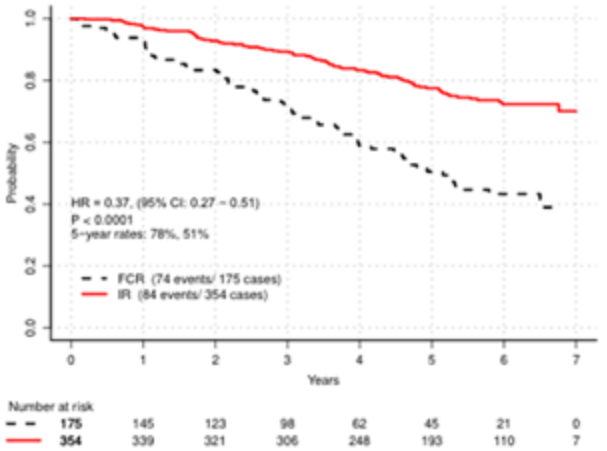
PFS = progression free survival; AE = adverse event; PD = progressive disease.

Barr PM, et al. *Blood Adv*. 2022;6(11):3440-3450. Burger J, et al. Presented at: European Hematology Association (EHA); June 13, 2024; Madrid, Spain. P1841.

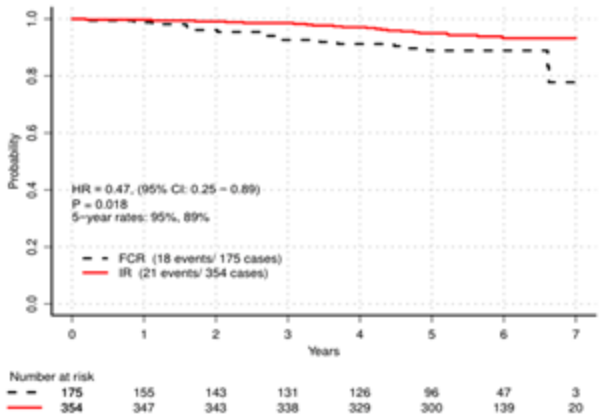
E1912: 5 Years Updated PFS, OS by IGHV Status

Reason for Discontinuation	All Patients Who Started IR N=352
Progression or death	37 (10.5%)
Adverse event or complication	77 (21.9%)
Other reason*	24 (6.8%)

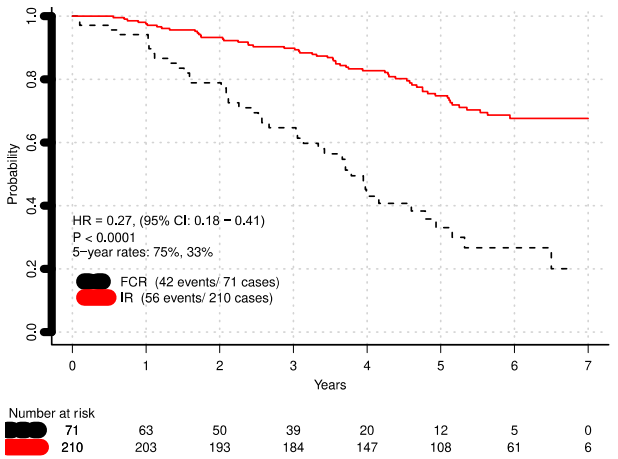
PFS



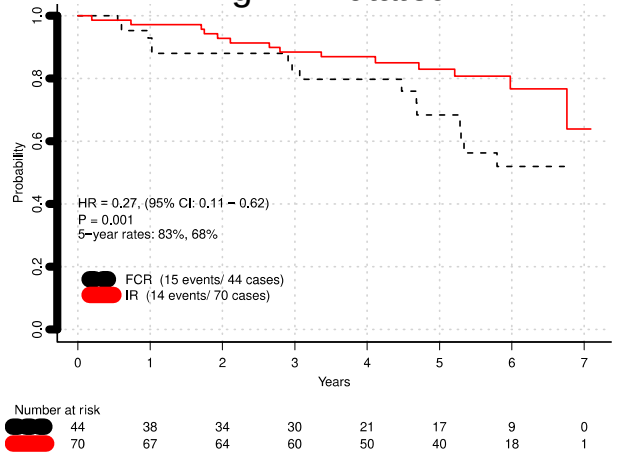
OS



IgHV unmutated



IgHV mutated

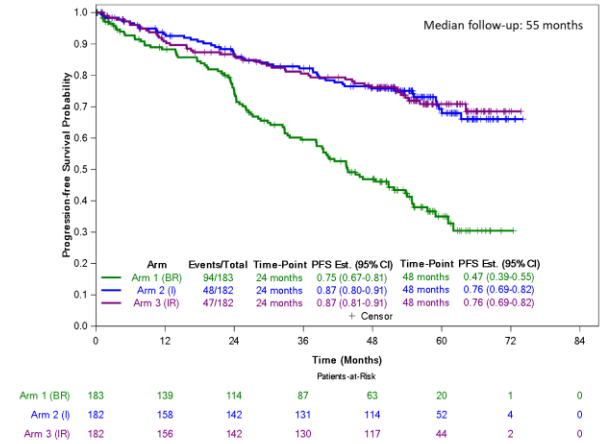


OS = overall survival; FCR = fludarabine, cyclophosphamide, rituximab; IR = ibrutinib, rituximab.

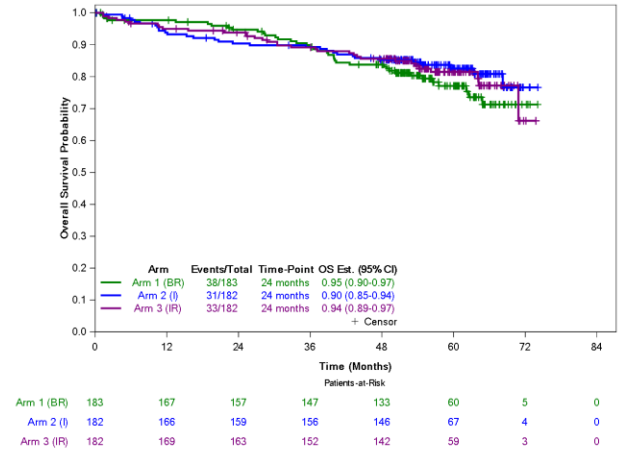
Shanafelt TD, et al. *Blood*. 2022;140(2):112-120.

A041202: First-Line Ibrutinib ± Rituximab vs Bendamustine + Rituximab in Older Patients with CLL/SLL

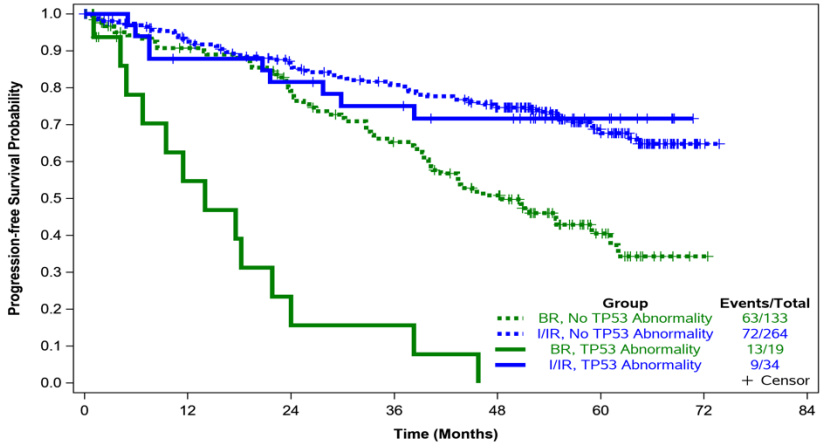
PFS



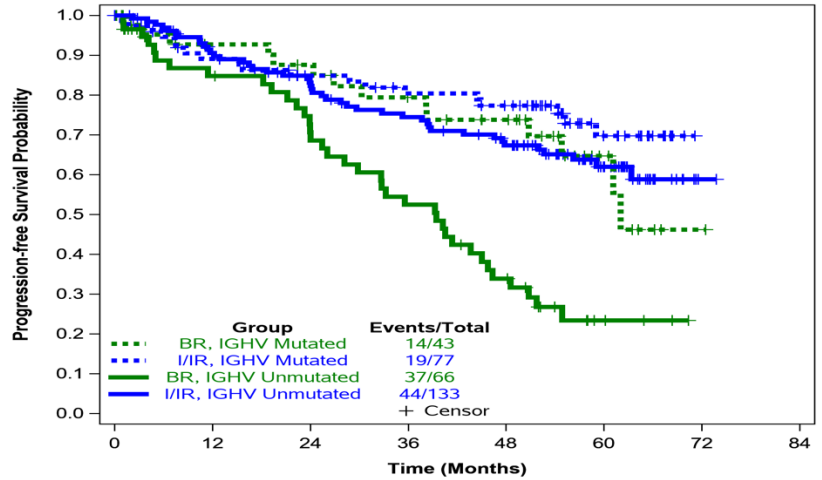
OS



TP53



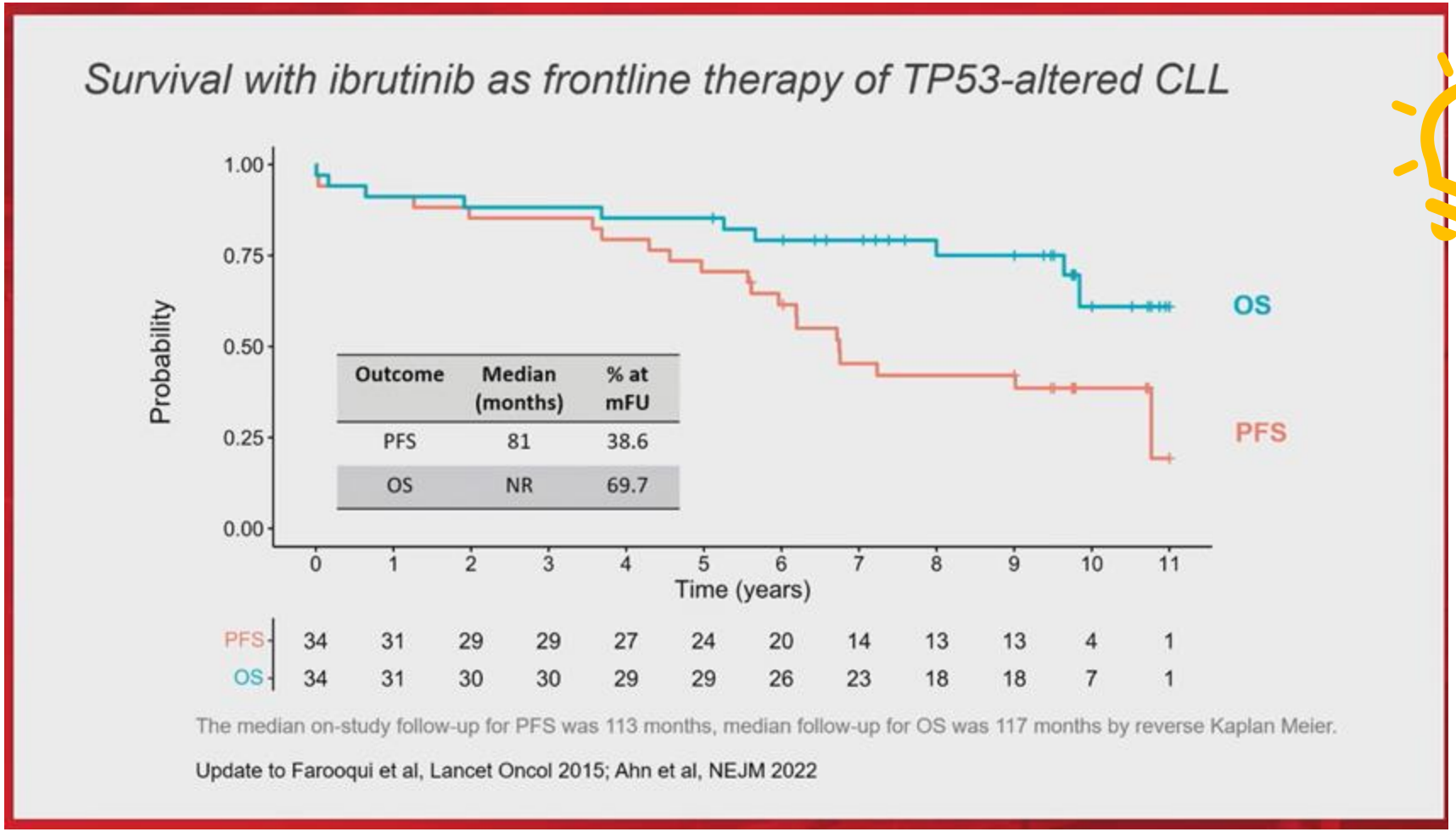
IGHV



Woyach JA, et al. *Blood.* 2021;138(Suppl 1):639.

PFS and OS in TP53 Altered, Treatment-Naïve CLL

- OS at 117 months (~10 years) was 69.7%
- mPFS was 81 months (~7 years)



Itsara A, et al. Presented at: American Society of Hematology (ASH) 2023; December 9, 2023; San Diego, CA. 201.

ELEVATE-TN: 6-Year Follow-Up Results

Study Design

TN CLL (N=535)

Key inclusion criteria

- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region

RANDOMIZE 1:1:1

- A[a] + O[b]
- A[a]
- O[b] + Clb[b]

Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

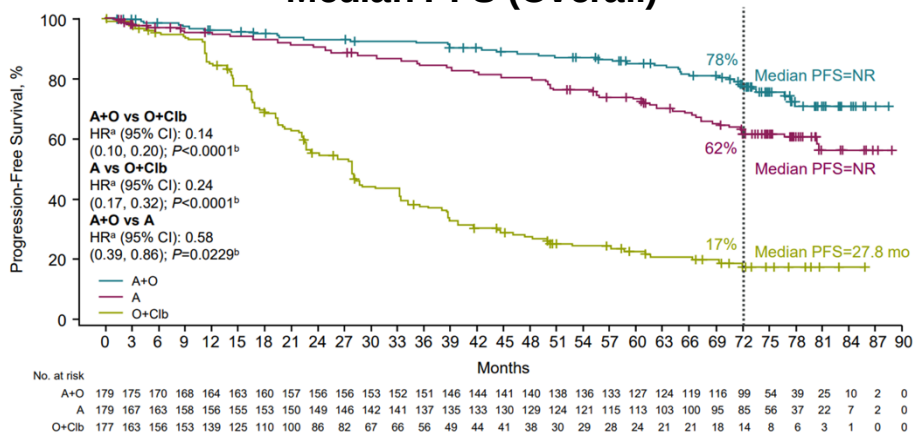
Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

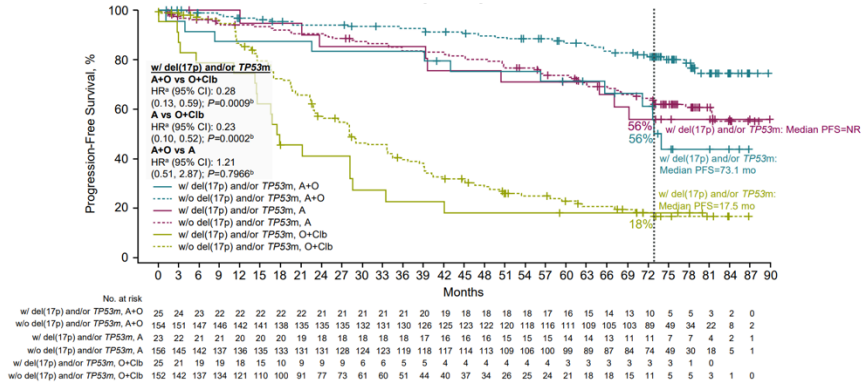
***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

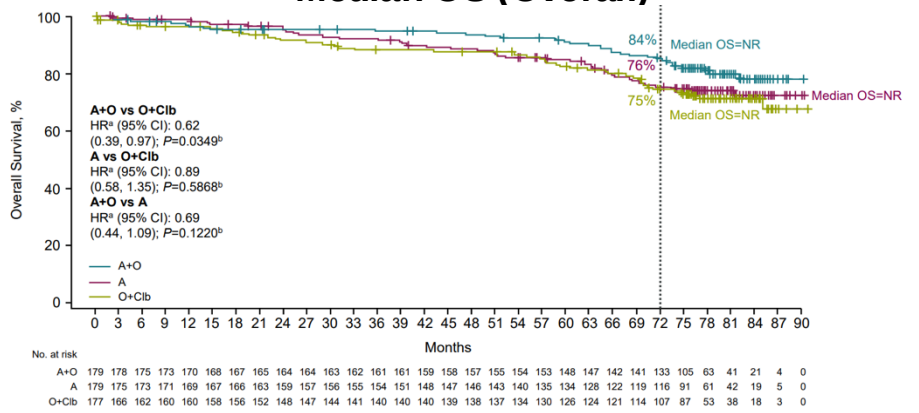
Median PFS (Overall)



Median PFS (del[17p]) and/or TP53 Mutation)



Median OS (Overall)

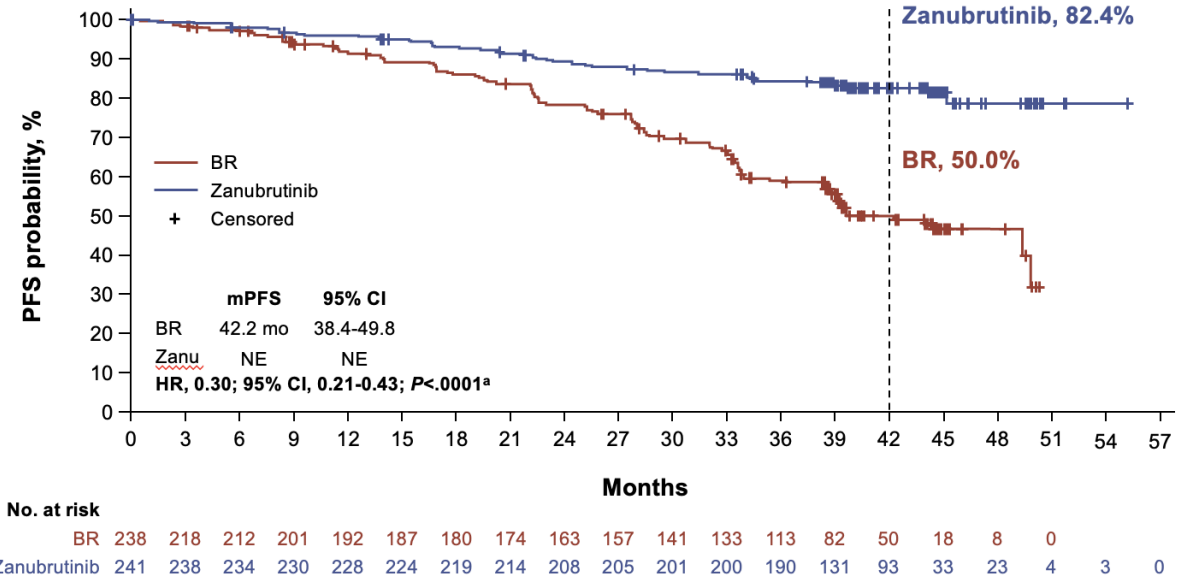


ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; INV = investigator; ORR = objective response rate; TTNT = time to next treatment; uMRD = undetectable minimal residual disease.

Sharman JP, et al. Presented at: ASH; December 10, 2023; San Diego, CA. 636. Itsara A, et al. Presented at ASH; December 9, 2023; San Diego, CA. 201.

SEQUOIA Cohort 1: PFS and OS in Patients without del(17p)

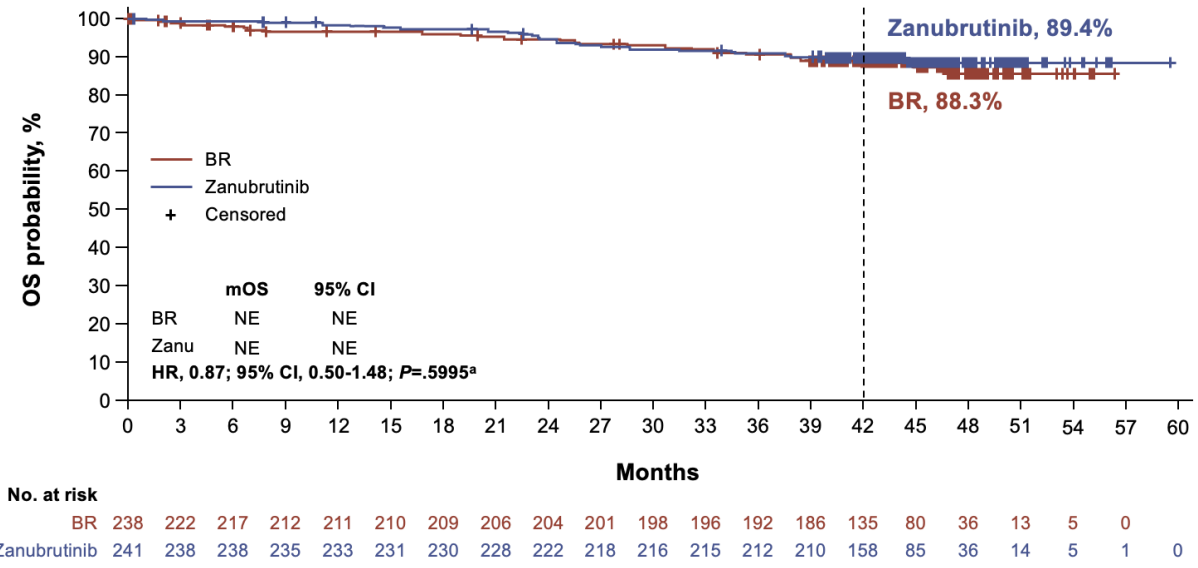
Progression Free Survival



No. at risk

BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0

Overall Survival



No. at risk

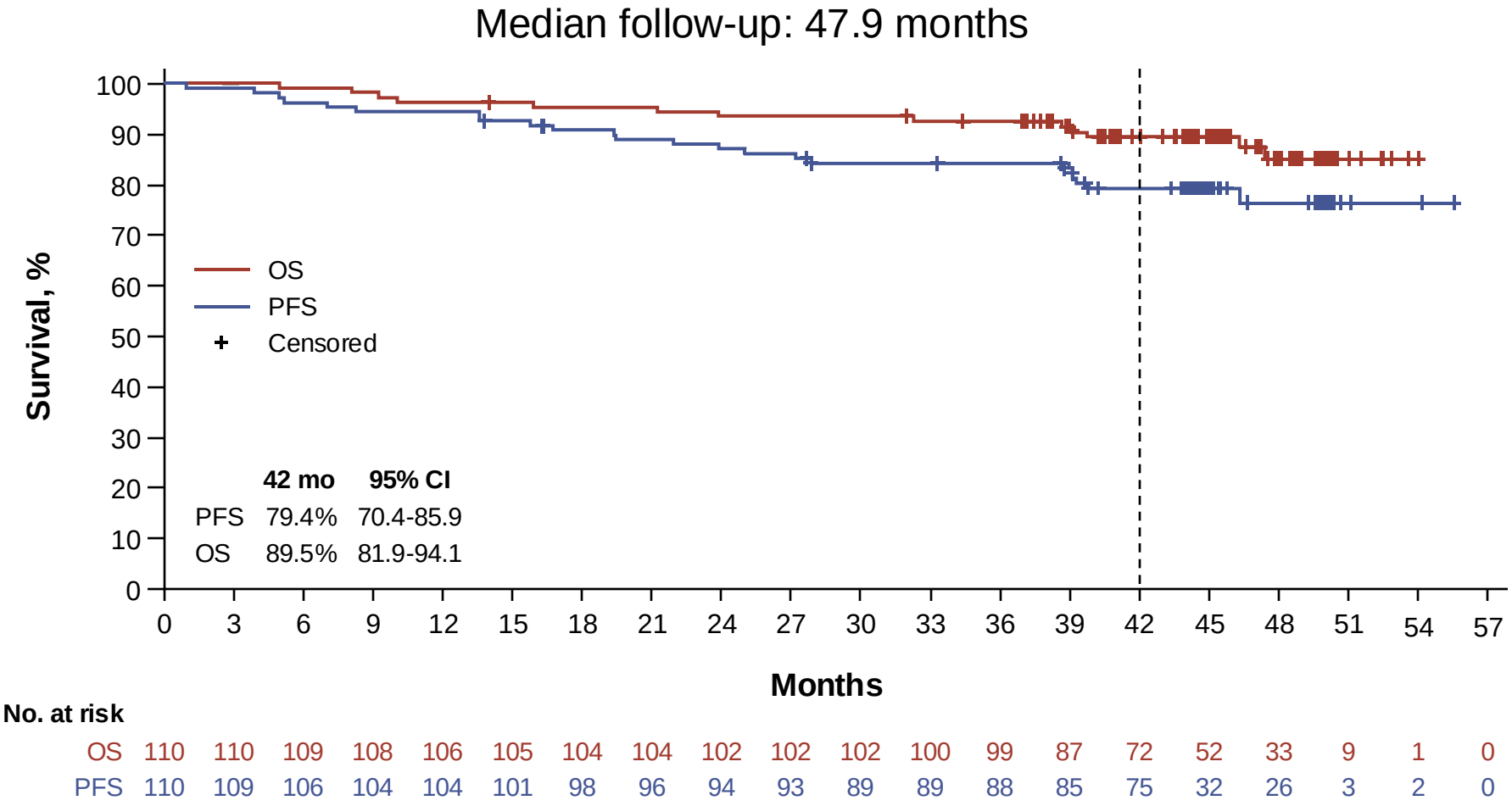
BR	238	222	217	212	211	210	209	206	204	201	198	196	192	186	135	80	36	13	5	0	
Zanubrutinib	241	238	238	235	233	231	230	228	222	218	216	215	212	210	158	85	36	14	5	1	0

Median follow-up: 43.7 months

BR = bendamustine, rituximab; NE = not evaluated.

Shadman JP, et al. Presented at: 17th International Conference on Malignant Lymphoma (ICML); June 13-17, 2023; Lugano, Switzerland. 154.

SEQUOIA Cohort 1: PFS and OS in Patients with del(17p)



Shadman JP, et al. Presented at: ICML 2023; June 13-17, 2023; Lugano, Switzerland. 154.

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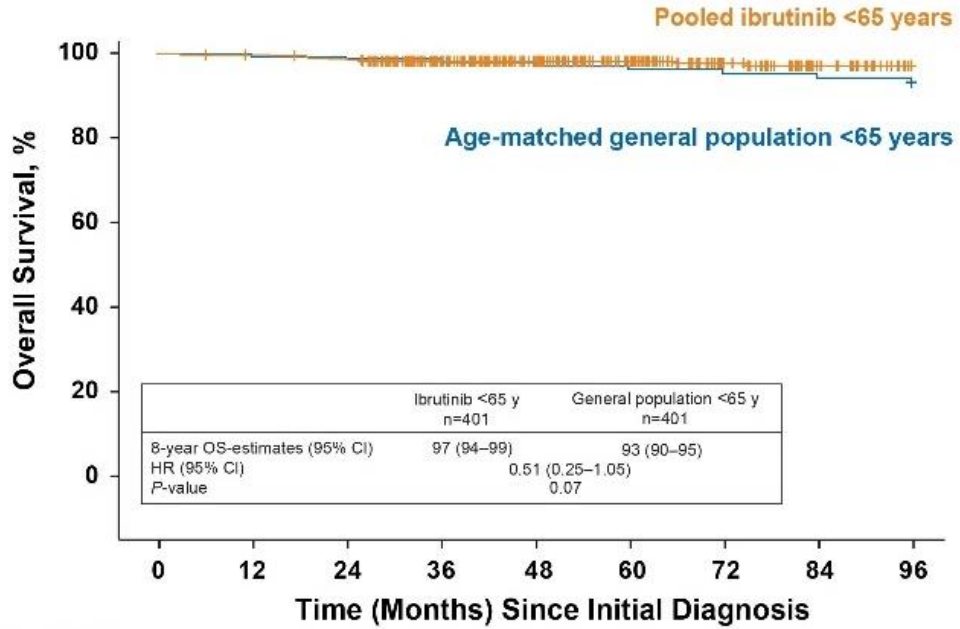
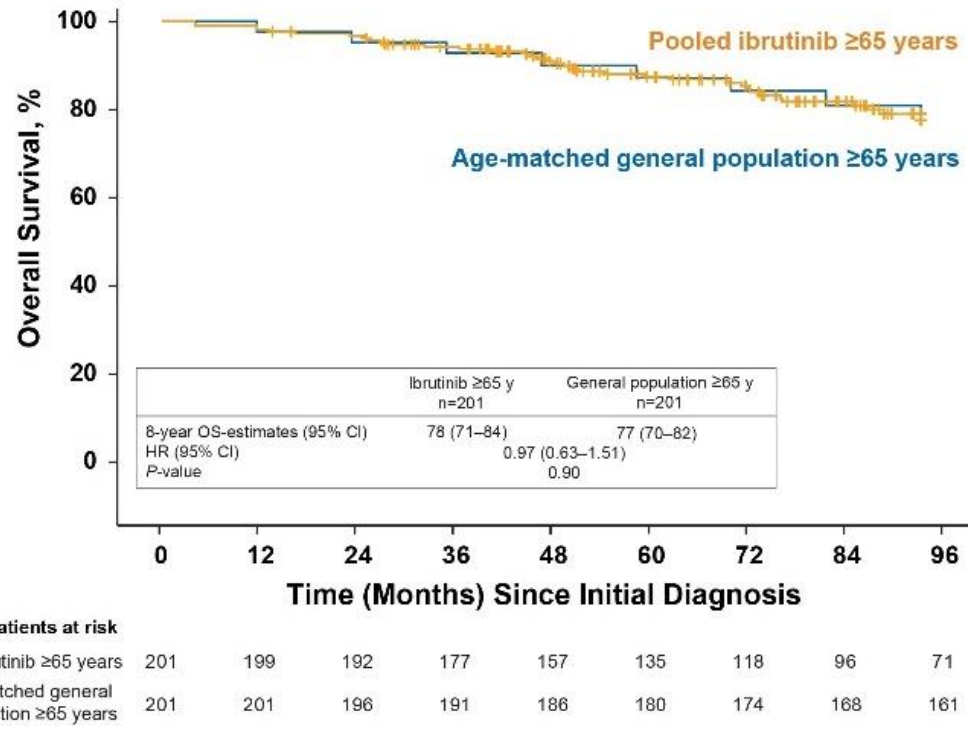
Patients with CLL Treated with Continuous BTKi Are Living Longer, therefore QoL Becomes Paramount when Selecting Treatment

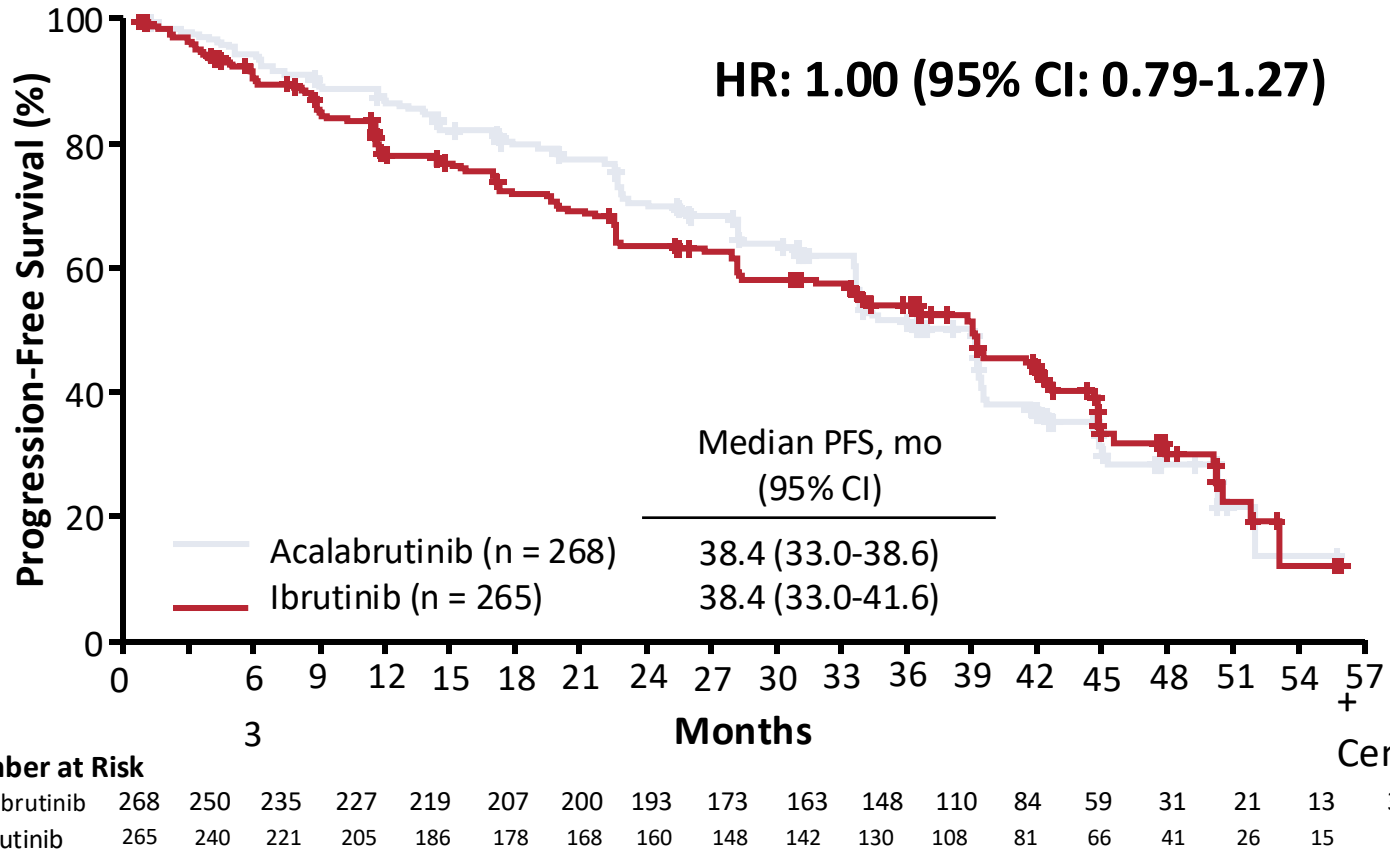




Ghia P, et al. *Hemasphere*. 2024;8(5):e74.

ELEVATE-RR: Noninferiority Met on IRC-Assessed PFS

- Noninferiority met on IRC-assessed PFS



Median follow-up: 41 months

	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS (95% CI), %		
12 months	86.7 (81.8-90.3)	78.8 (73.1-83.4)
24 months	70.9 (64.8-76.1)	64.5 (58.1-70.2)
36 months	51.4 (44.7-57.8)	53.8 (47.0-60.1)

Noninferiority achieved if upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

NI = noninferiority.

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

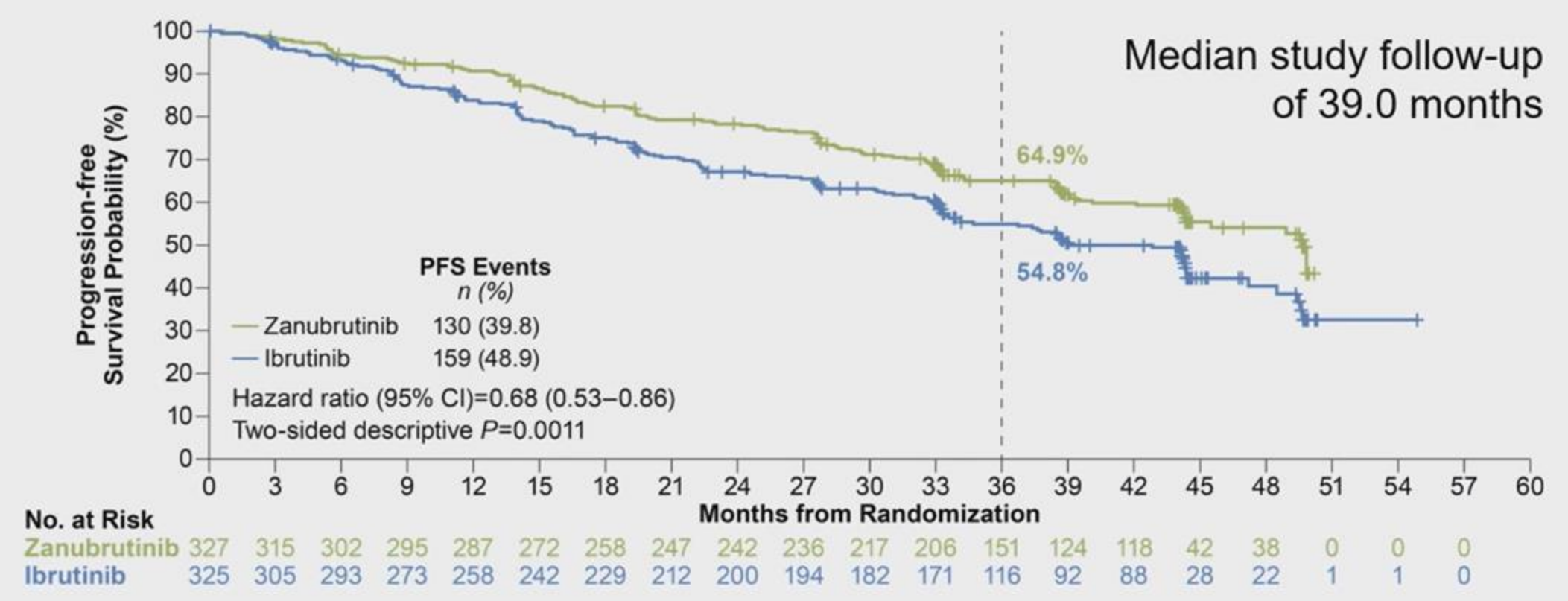
ELEVATE-RR: AEs of Clinical Interest

AE, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
▪ Atrial fibrillation/flutter	**25 (9.4)**	13 (4.9)	**42 (16.0)**	10 (3.8)
▪ Ventricular arrhythmias	0	0	3 (1.1)	1 (0.4)
Bleeding events	**101 (38.0)**	10 (3.8)	**135 (51.3)**	12 (4.6)
▪ Major bleeding events	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Hypertension	**25 (9.4)**	**11 (4.1)**	**61 (23.2)**	**24 (9.1)**
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
ILD/pneumonitis	**7 (2.6)**	1 (0.4)	**17 (6.5)**	2 (0.8)
SPMs, excluding NMSC	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

SPM = second primary malignancy; NMSC = non-melanoma skin cancer; ILD = interstitial lung disease.

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

ALPINE: Zanubrutinib Sustains PFS Benefit at 36 Mo



Brown JR, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 202.

AEs of Special Interest Occurring in ≥ 2 Patients

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic Infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 Related[b]	**145 (44.8)**	**56 (17.3)**	**105 (32.4)**	**38 (11.7)**
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major Hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

[a]Pooled MedDRA preferred terms.
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

The rate of any grade atrial fibrillation/flutter was significantly lower with zanubrutinib vs ibrutinib (6.8% vs 16.4%, $p<0.0001$).
Brown JR, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 202.

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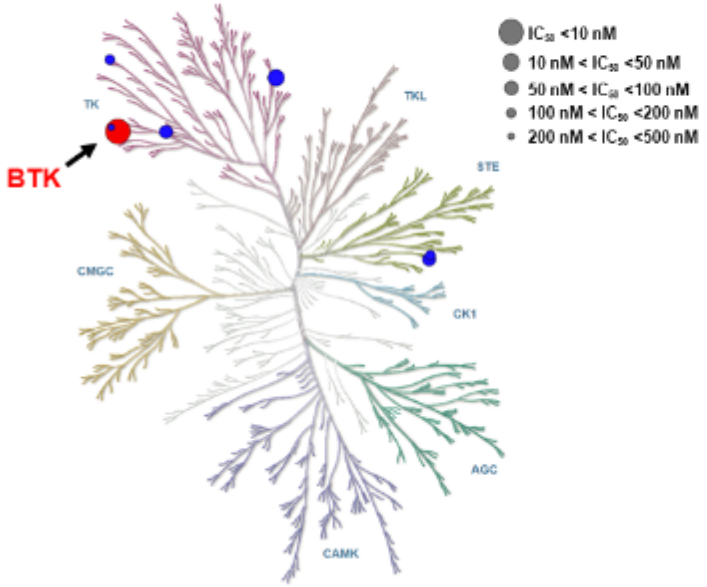
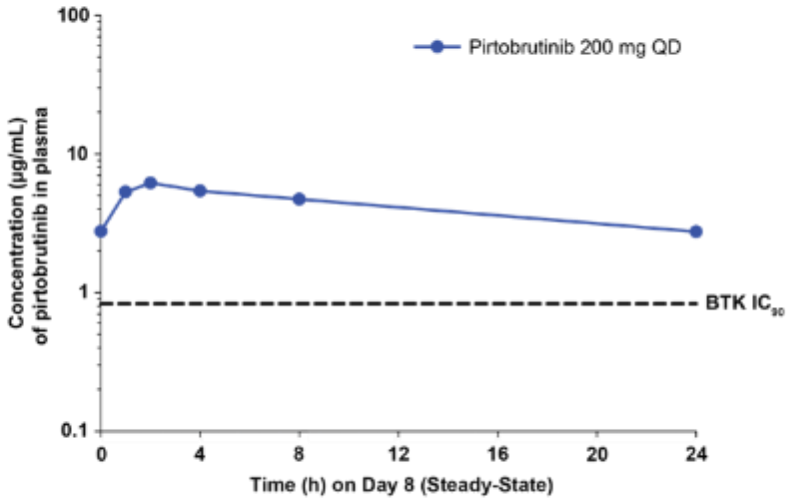
Pirtobrutinib Is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

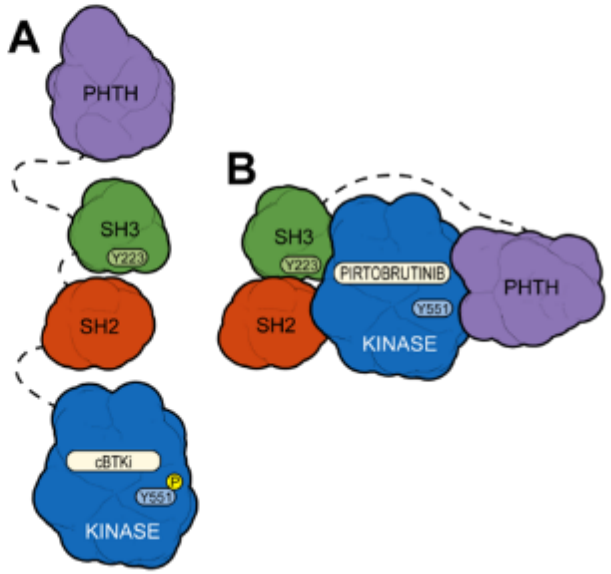
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]

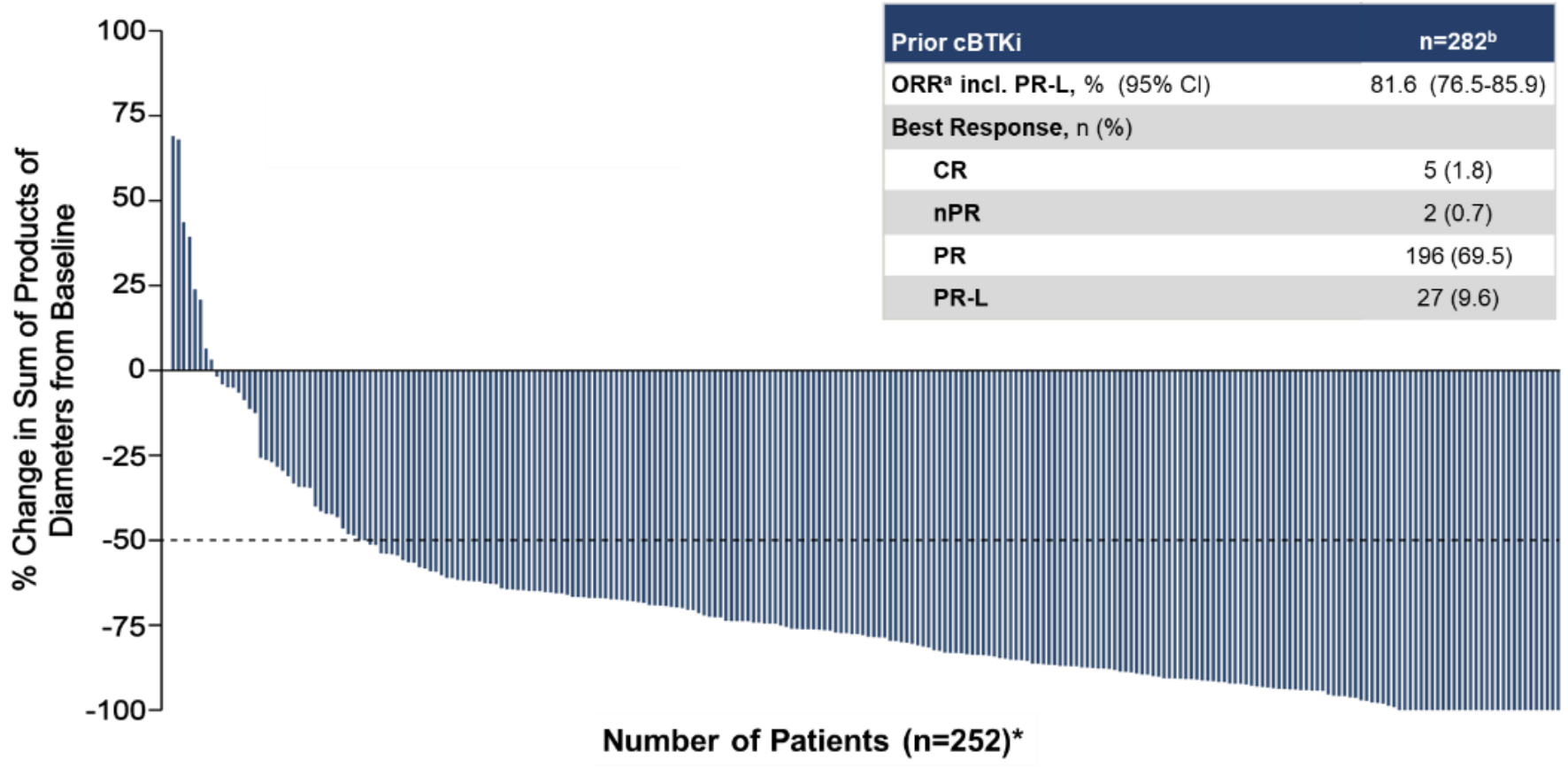


- Inhibits both WT and C481-mutant BTK with equal low nM potency
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling

Mato AR, et al. *Lancet*. 2021;397(10277):892-901. Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk.* 2018;18(Suppl.1):S216. Gomez EB, et al. *Blood*. 2023;142(1):62-72. Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

Pirtobrutinib Efficacy in All Patients with CLL/SLL Who Received Prior cBTKi

Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. [b]Post-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment.

Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

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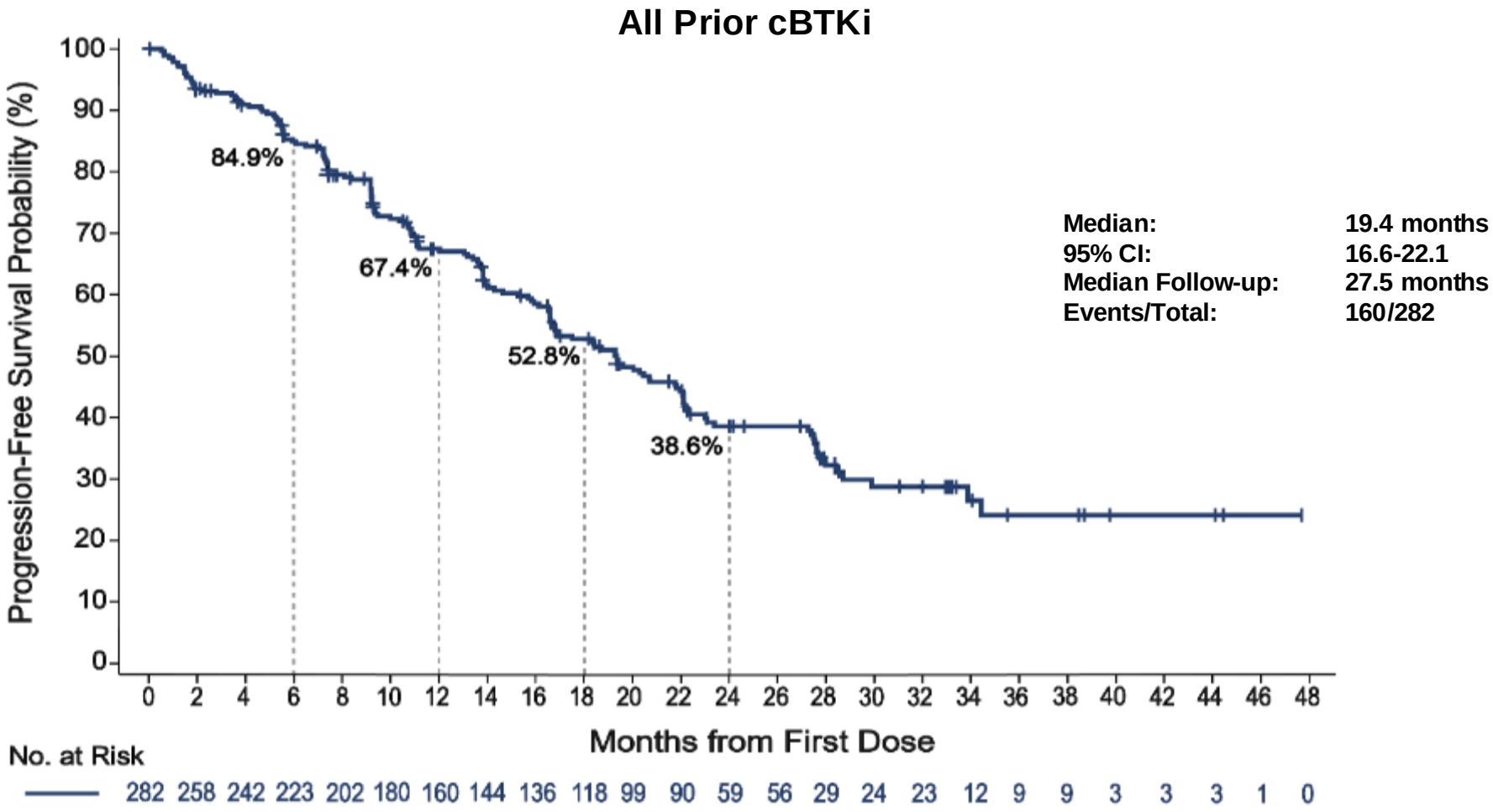
Pirtobrutinib PFS in Patients with Prior cBTKi



Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

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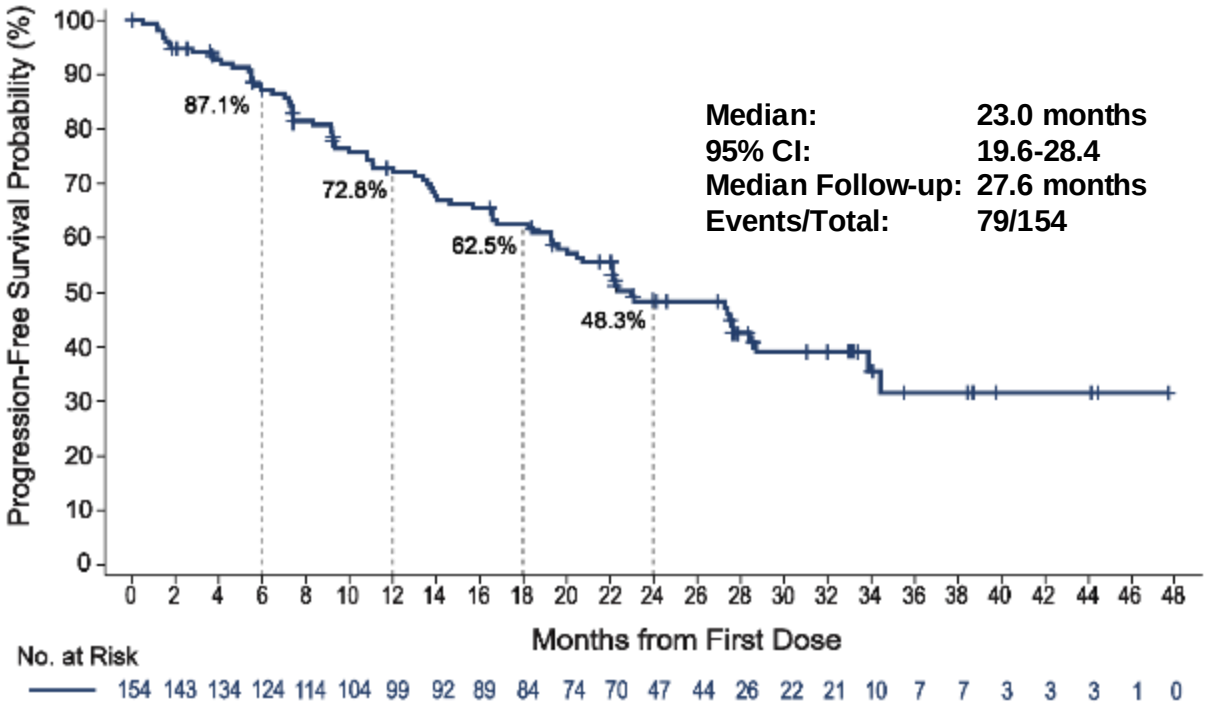
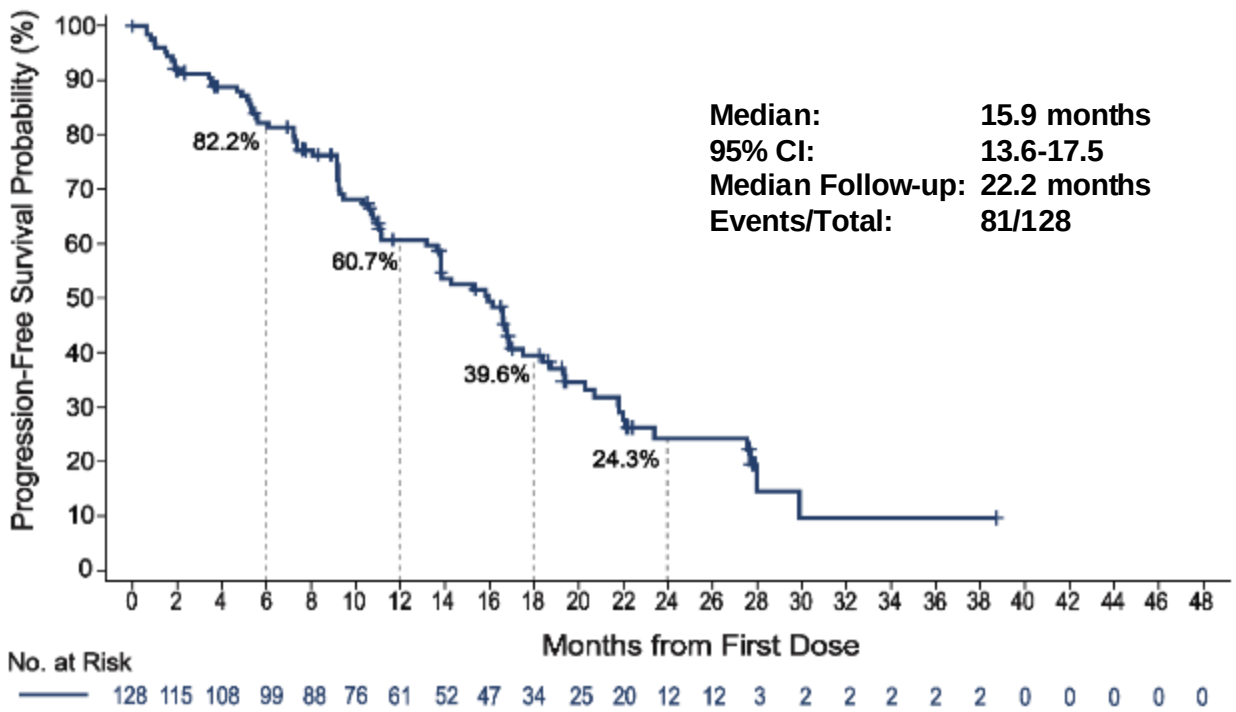
Pirtobrutinib PFS with Prior cBTKi, with or without Prior BCL2i

BCL2i-N



Median:	23.0 months
95% CI:	19.6-28.4
Median Follow-up:	27.6 months
Events/Total:	79/154

BCL2i-E



Median:	15.9 months
95% CI:	13.6-17.5
Median Follow-up:	22.2 months
Events/Total:	81/128

Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

Pirtobrutinib Safety Profile of Patients Who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
Dyspnea	22.3	2.1	0.7	0.4
Nausea	22.0	0.0	3.5	0.0
Abdominal pain	21.3	1.8	2.1	0.4
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)

11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had treatment-related AEs leading to pirtobrutinib dose reduction

7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had treatment-related AEs leading to pirtobrutinib discontinuation

Safety profiles of BCL2i-N and BCL2i-E subgroups were similar

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors; [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3; [c]Aggregate of neutropenia and neutrophil count decreased; [d]Aggregate of all preferred terms including infection and COVID-19; [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion; [f]Aggregate of all preferred terms including rash; [g]Aggregate of all preferred terms including hemorrhage or hematoma; [h]Aggregate of atrial fibrillation and atrial flutter; [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

Woyach JA, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 325.

Key Learning Points

- BTKi treatment is superior to any form of CIT
- Very long-term efficacy data up to 10 years even in high risk
  - For patients treated with ibrutinib, mPFS at 7 years with OS of 70% at 10 years
- Most discontinuations are secondary to intolerance
- Low rates of progression even in high-risk disease in front line
- BTKi has a class effect AEs but second generation are better tolerated
- Cardiovascular toxicities should be taken into consideration in high-risk patients
- Non-covalent inhibitors can keep patients on BTKi after covalent failures

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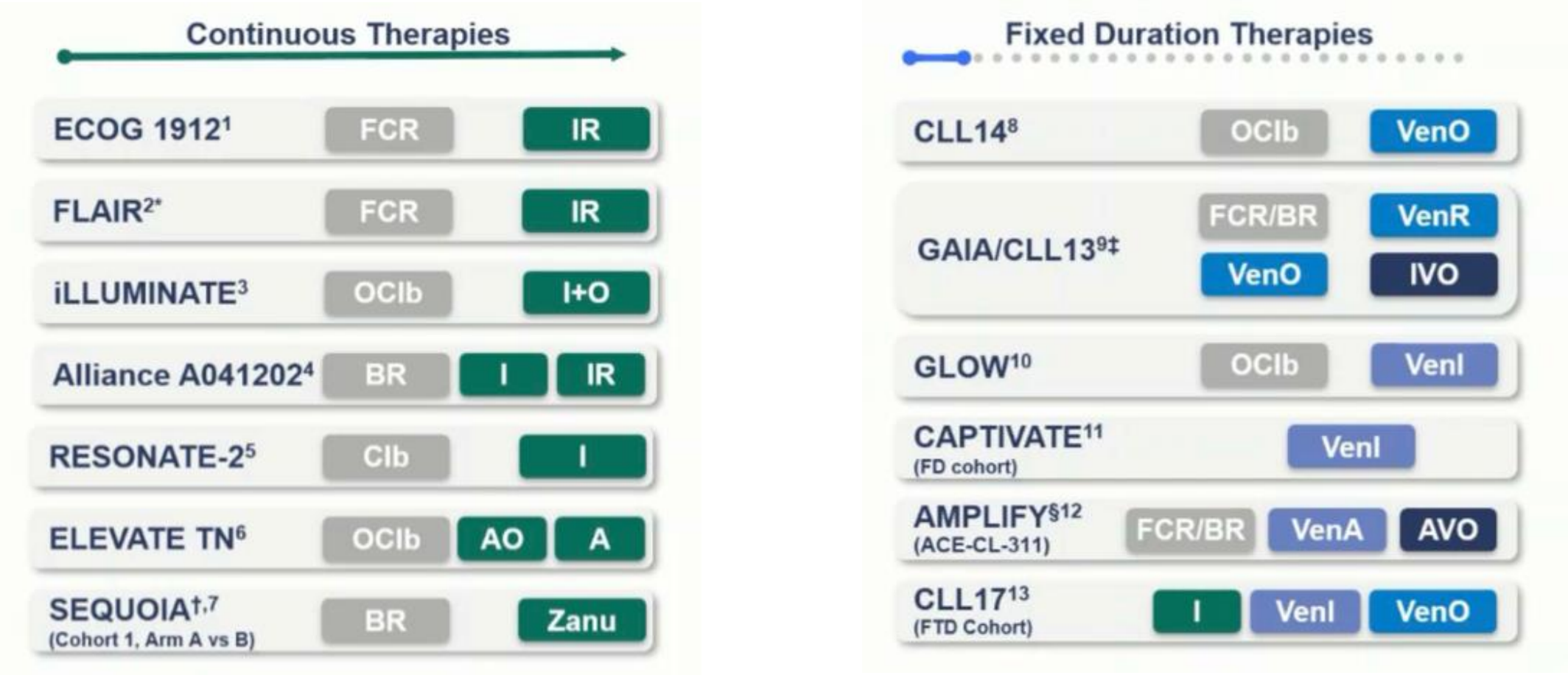
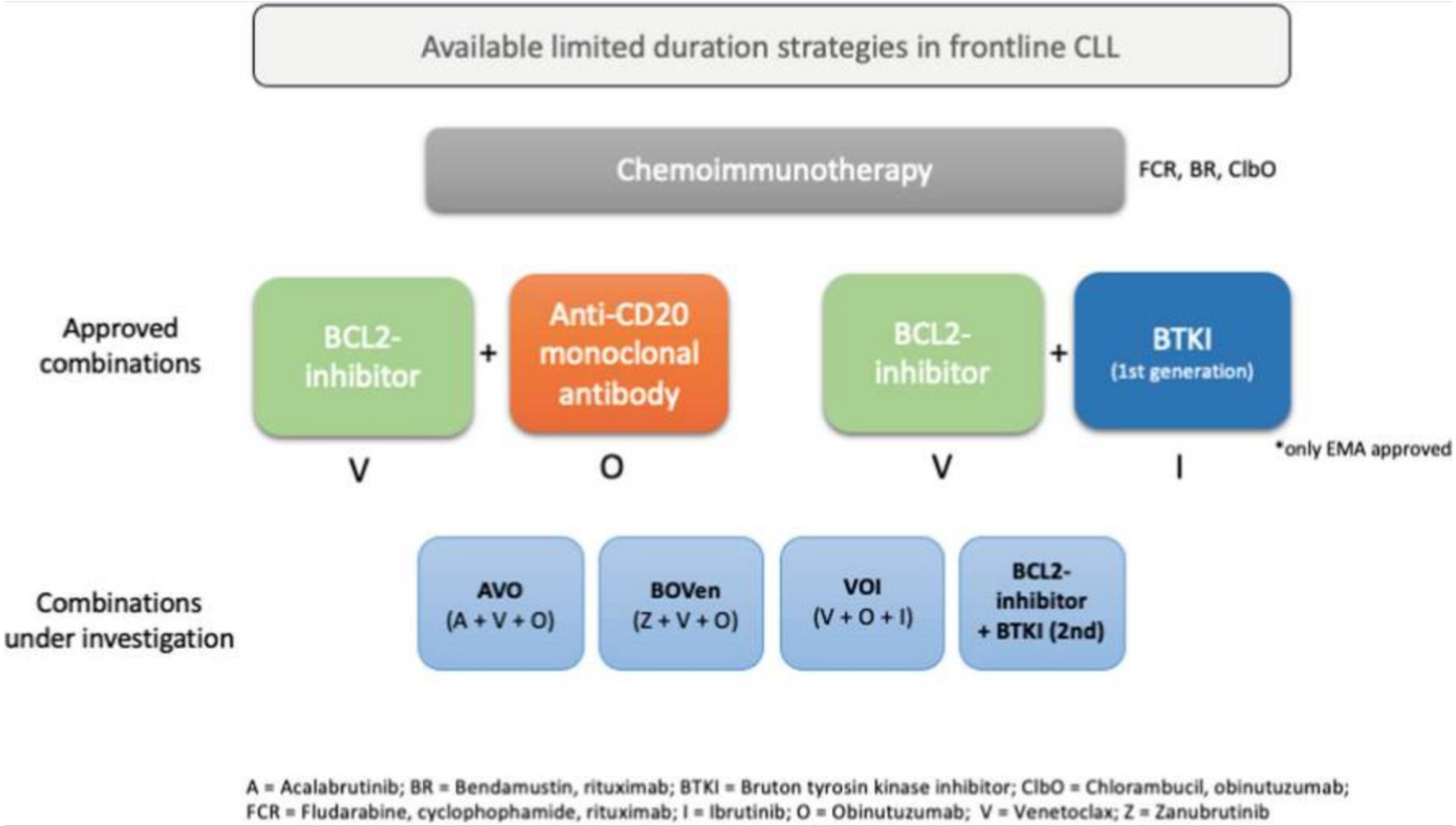
Continuous Therapy vs Fixed Duration



Shanafelt TD, et al. *New Engl J Med.* 2019; 381:435-443. Hillman P, et al. *Lancet Oncol,* 2023,24:535-552. Moreno C, et al. *Lancet Oncol.* 2019,20:43-56. Woyach JA, et al. *Blood,* 2021;138:639. Barr PM, et al. *Blood Adv.* 2022;6:3400-3450. Sharman JP, et al. *Leukemia.* 2022;36:1171-1175. Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043. AlSawaf O, et al. *Nat Commun.* 2023;14:2147. Eichhorst B, et al. *N Eng J Med.* 2023;338:1739-1754. Kater AP, et al. *NEJM Evid.* 2022;1:711. Tam CS, et al. *Blood.* 2022;139:3278-3289. National Institute of Health (NIH). Accessed Sept 25, 2024. https://clinicaltrials.gov/study/NCT04608318; NCT03836261.



Stumpf J, et al. *Curr Oncol Rep*. 2024;26(2):136-146.

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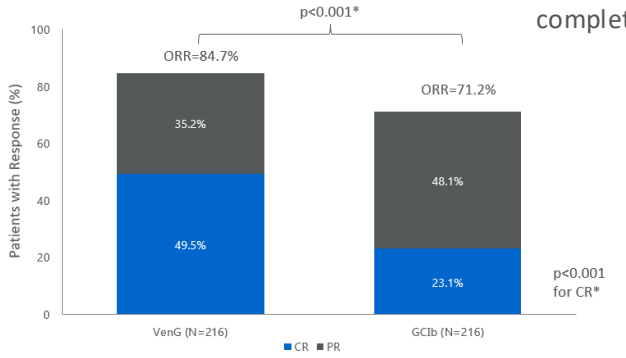
CLL14: Venetoclax + Obinutuzumab in TN CLL

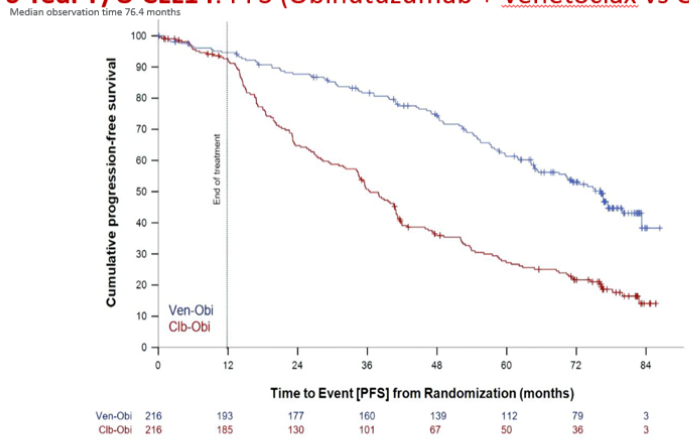
OVERALL AND COMPLETE RESPONSE RATES AT EOT+3



*EOT+3, 3 months after treatment completion.

p<0.001 for CR*

6 Year F/U CLL14: PFS (Obinutuzumab + Venetoclax vs Obinutuzumab + Chlorambucil)



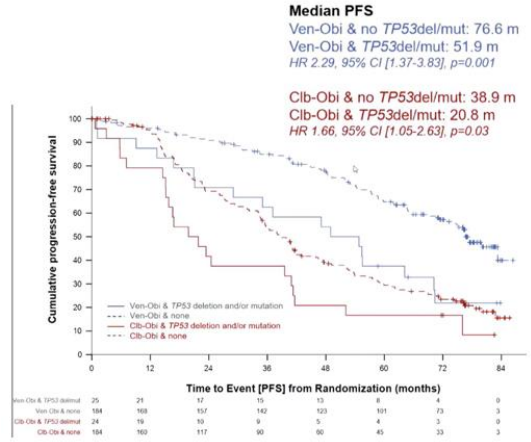
Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

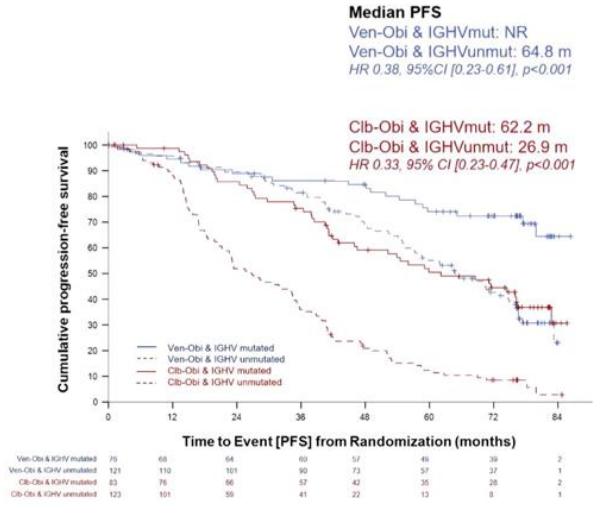
HR 0.40, 95% CI [0.31-0.52]
P<0.0001

Key Takeaway: Obinutuzumab + Venetoclax improved PFS over Obinutuzumab + Chlorambucil
[53% of patients are still in remission 5 years after completing fixed-duration therapy]

PFS by TP53



PFS by IGHV



Fischer K, et al. *N Engl J Med.* 2019;380:2225-2236. al-Sawaf O, et al. Presented at: EHA 2023; June 8, 2023; Madrid, Spain. S145.

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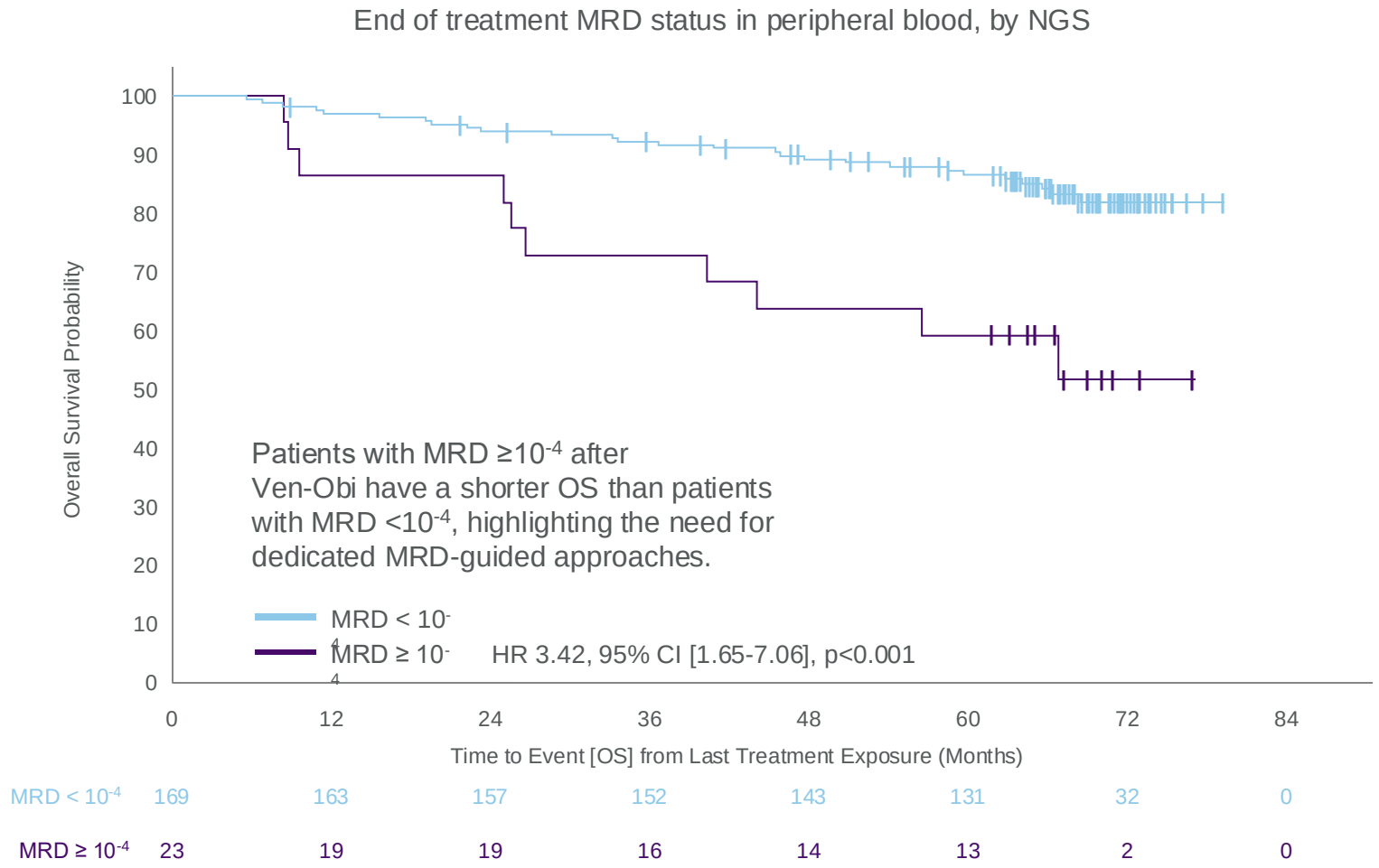
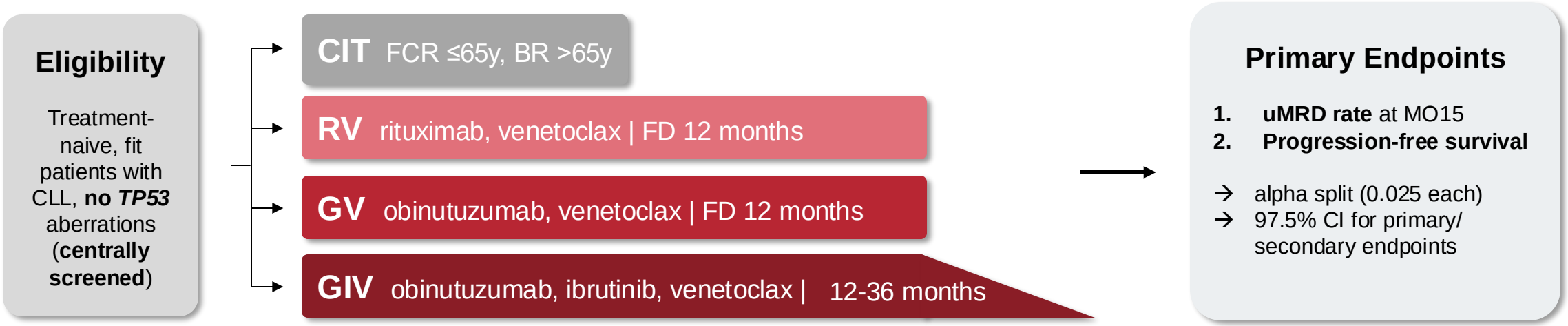
Landmark OS after Ven-Obi According to MRD Status



- 53.1% treated with ven+obi remain without PFS event five years after tx
- Over 60% have not required a second-line treatment
- EOT MRD status significantly correlates with PFS and OS
- Benefit observed across all subgroups, including TP53del/mut and uIGHV
- No new safety signals or 2ry malignancies

Median observation time 76.4 months.
al-Sawaf O, et al. Presented at: EHA 2023; June 8, 2023; Madrid, Spain. S145.

4-Year Follow-Up from the Phase 3 GAIA/CLL13 Trial



Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

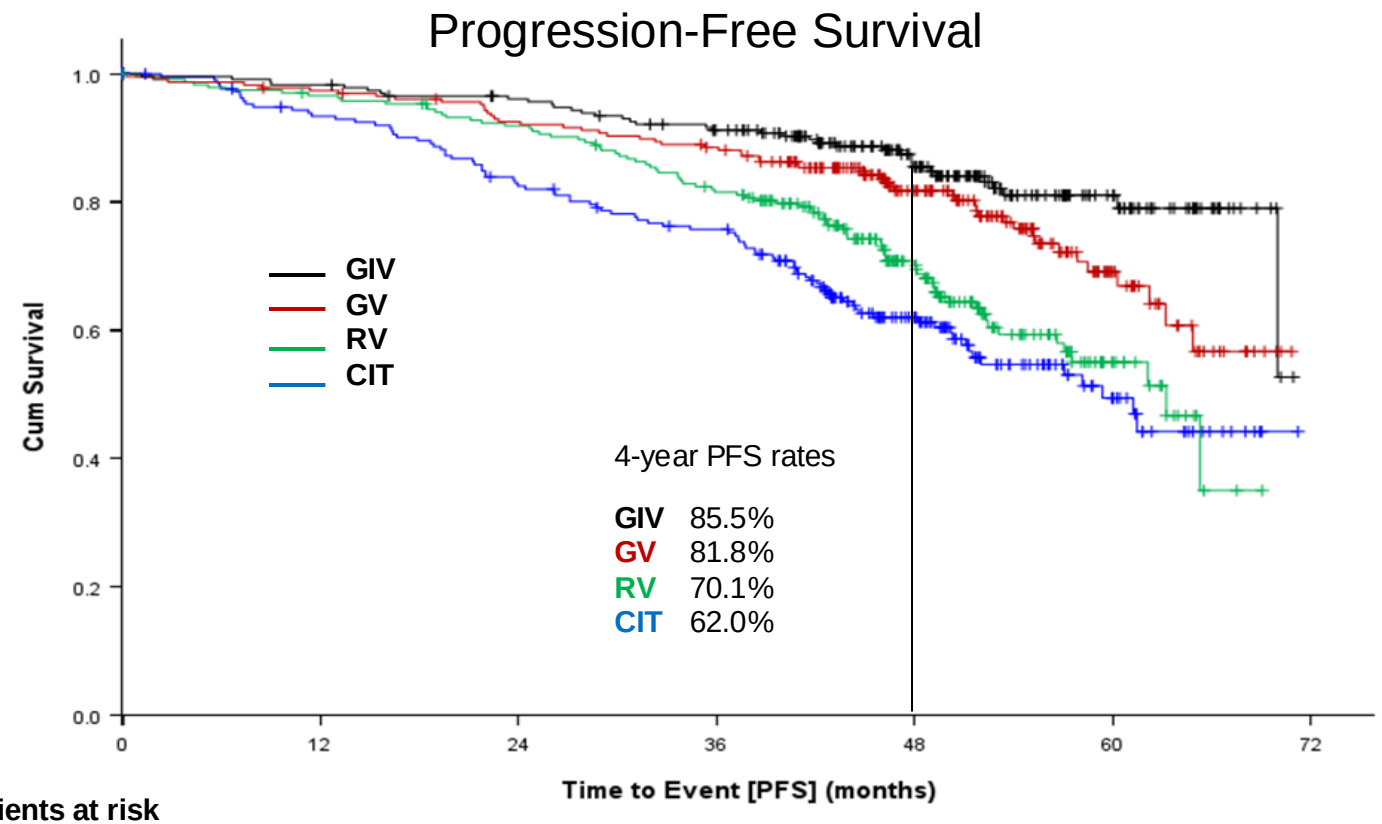
Follow-up analysis (data cut-off: 01/2023)

Median observation time
50.7 months (IQR: 44.6-57.9)

Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.

Efficacy: PFS



Patients at risk						
CIT	229	197	173	156	84	24
RV	237	227	214	188	106	21
GV	229	222	209	198	121	32
GIV	231	227	218	201	130	44

PFS comparisons

GIV *vs* **CIT**: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* **RV**: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* **GV**: HR 0.63, 97.5%CI: 0.39-1.02, *p*=0.03

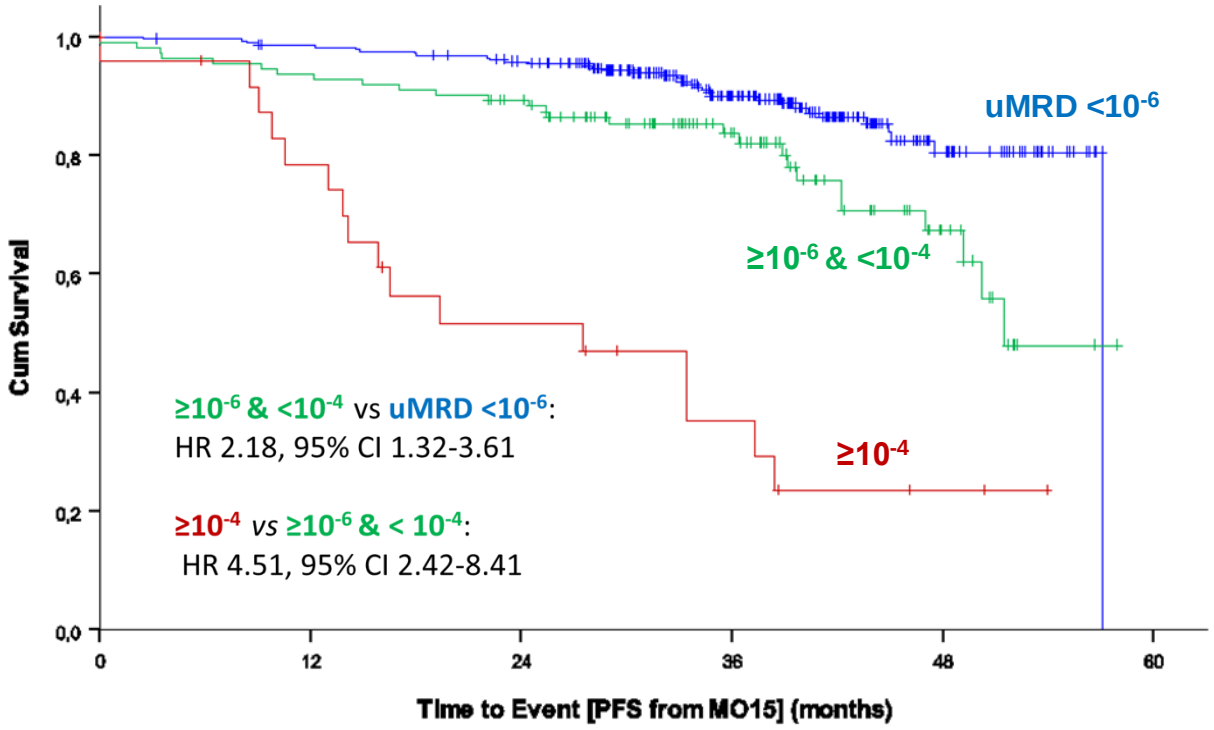
GV *vs* **CIT**: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* **RV**: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

RV *vs* **CIT**: HR 0.78, 97.5%CI: 0.55-1.10, *p*=0.1

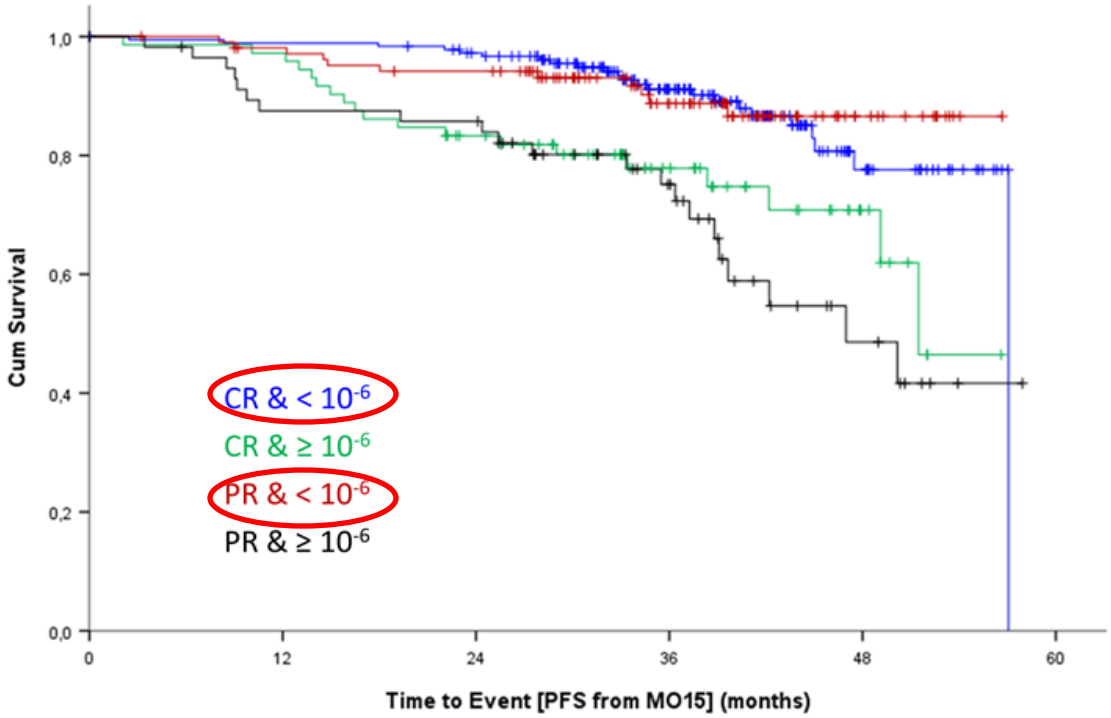
Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.

Correlation PB MRD/PFS

PFS by MRD level at MO15, GV/GIV



PFS by MRD level & response at MO15, GV/GIV

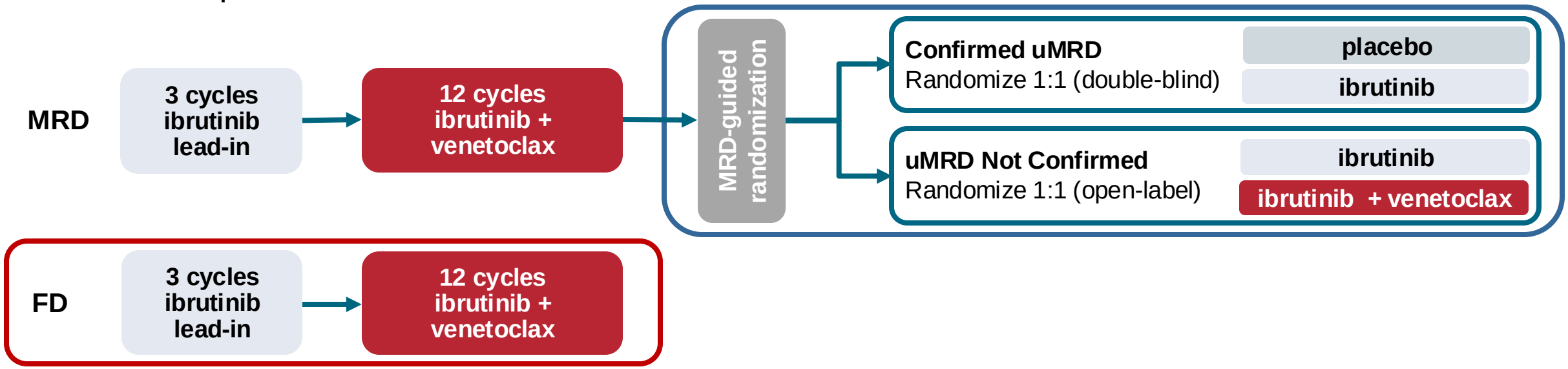


Pts at risk					
CR & <10-6	183	180	172	105	25
CR & ≥10-6	72	70	56	29	9
PR & <10-6	105	100	95	56	13
PR & ≥10-6	58	49	48	28	8

Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



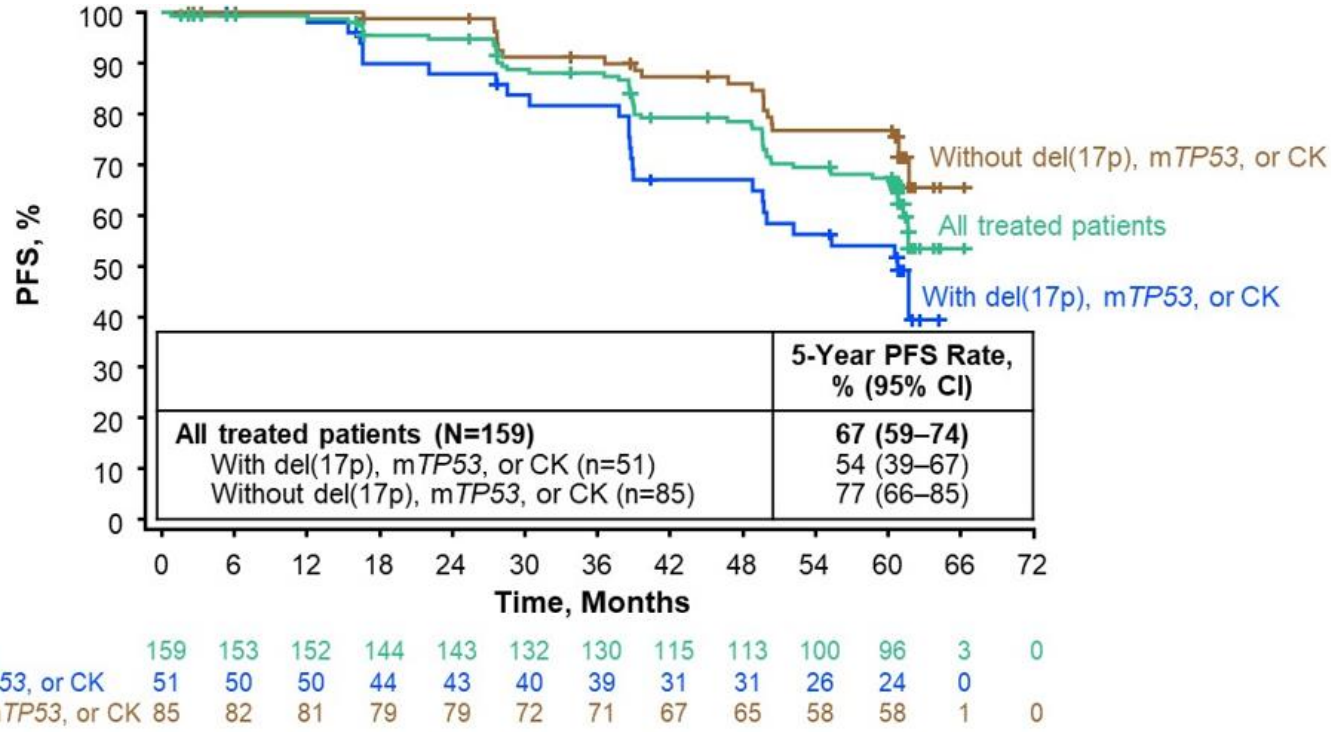
- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment

BM = bone marrow; FD = fixed-duration; PB = peripheral blood.
Ghia P, et al. *JCO.* 2021;39:7501-7501.

PFS in the FD Cohort

PFS in All Treated Patients and by del(17p), m*TP53,* or CK

Median time on study: 61.2 months (range, 0.8-66.3)



High-risk feature	n	5-year PFS rate, % (95% CI)
With del(17p)/m*TP53*	27	41 (21-59)
Without del(17p)/m*TP53*	129	73 (64-80)
With CK[a]	31	57 (37-72)
Without CK[a]	102	72 (61-80)
With del(11q)[b]	11	64 (30-85)
Without del(11q)[b]	74	79 (67-87)

- Overall median PFS was not reached with up to 5.5 years of follow-up

[a]Defined as ≥3 chromosomal abnormalities by conventional CpG-stimulated cytogenetic; [b]Excluding patients with del(17p)/mTP53 or CK.
CK = complex karyotype.
Wierda WG, et al. *JCO*. 42:7009-7009.

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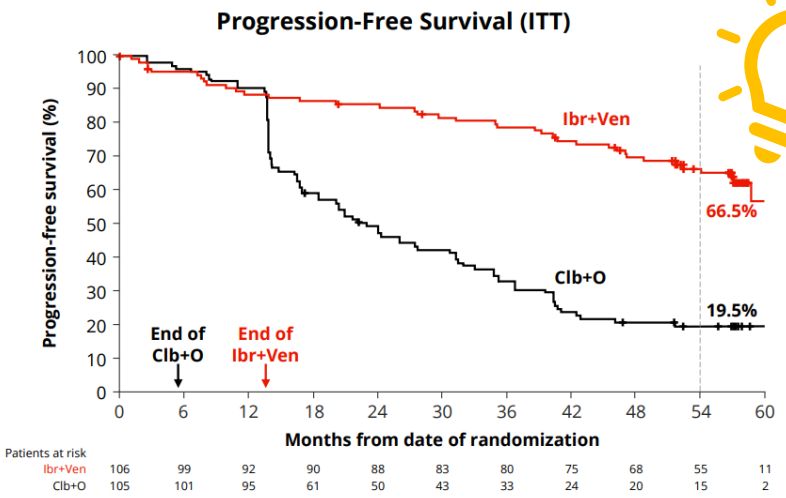
Phase III GLOW Ibrutinib+Venetoclax: Median PFS Was Not Reached with up to 57mo of Follow-Up



Eligibility criteria
- Previously untreated CLL
- ≥ 65 years of age or < 65 years with CIRS > 6 or CrCl < 70 mL/min
- No del17p or known *TP53* mutation
- ECOG PS 0-2

N = 211

Randomized 1:1

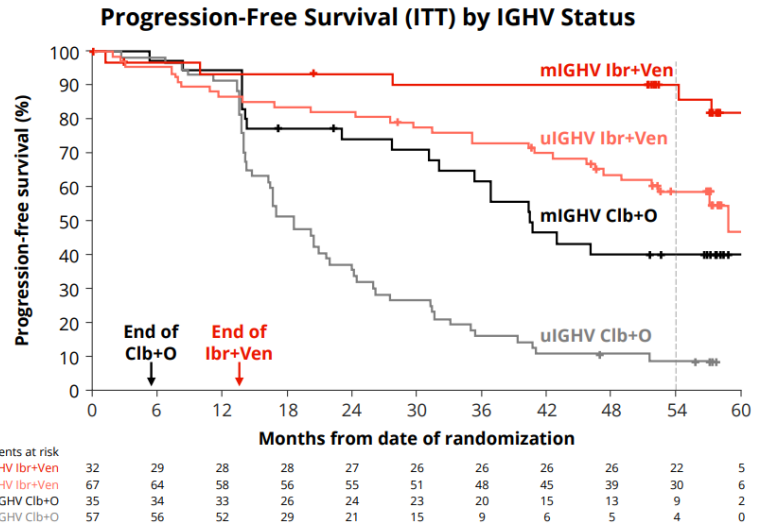
Stratified by IGHV mutational status and presence of del11q

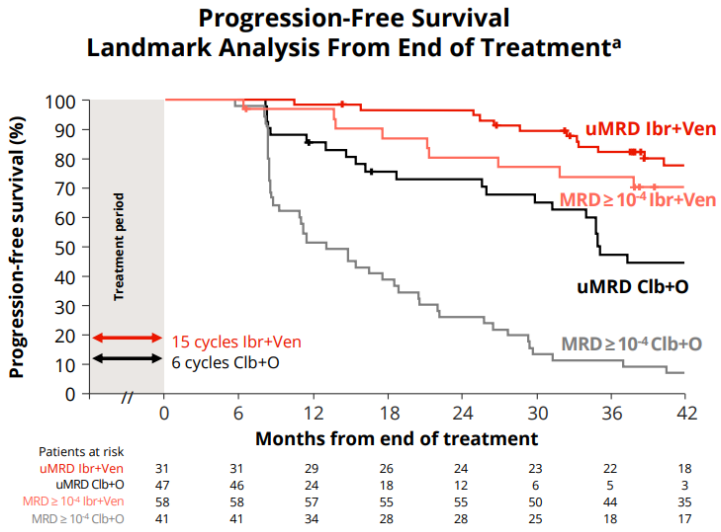
Ibrutinib 420 mg daily for a 3-cycle lead-in followed by **ibrutinib + venetoclax** for 12 cycles (venetoclax ramp-up 20-400 mg over 5 weeks beginning C4) **N = 106**

Chlorambucil 0.5 mg/kg on D1 and D15 for 6 cycles + **Obinutuzumab** 1000 mg on D1-2, D8, and D15 of C1, and D1 of C2-6 **N = 105**

- Primary end point: IRC-assessed PFS
- Key secondary end points: uMRD rates, CRR, ORR, OS, TTNT
- **Current analysis[a,b]: investigator-assessed PFS, uMRD, OS, TTNT, and safety (second primary malignancies)**

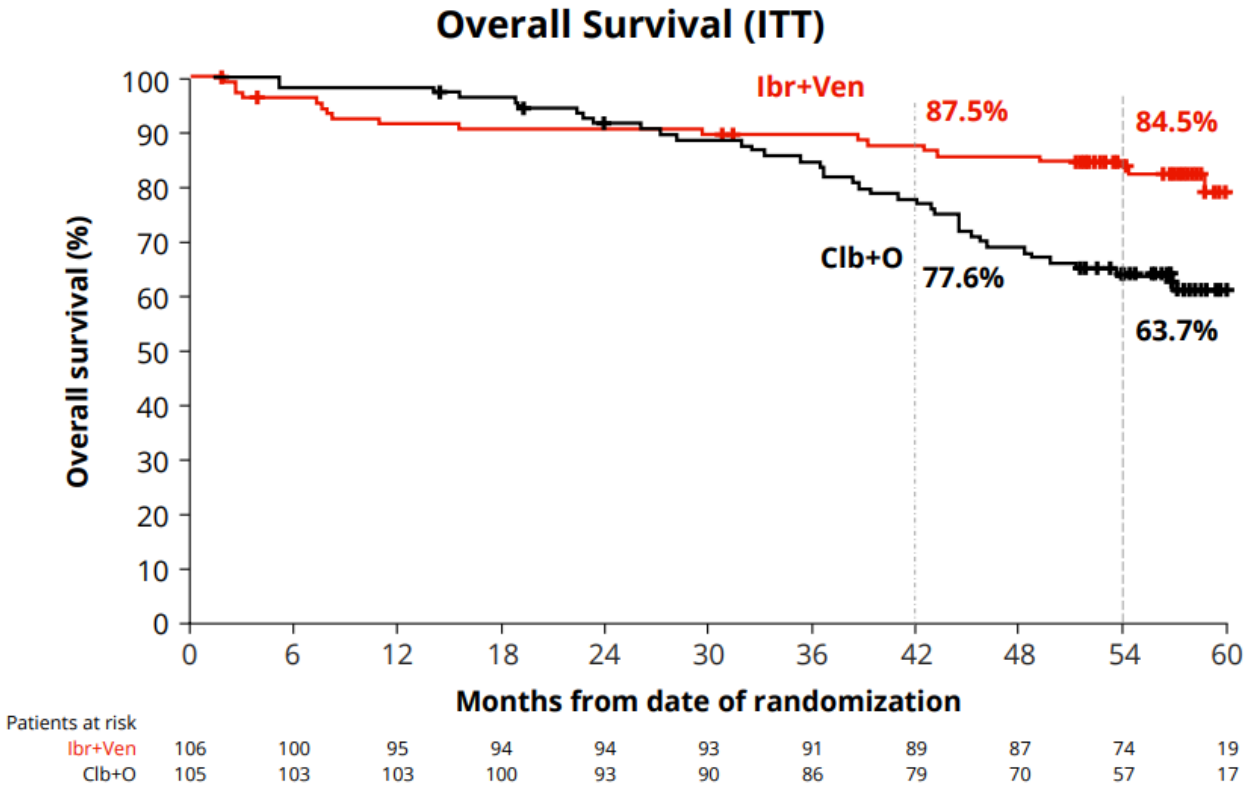
- Estimated PFS rates at 42 months post tx
  - mIGHV CLL: 91% for uMRD at EOT+3, 92% for patients with MRD ≥ 10 -4 at EOT+3
  - uIGHV CLL: 78% for patients with uMRD at EOT+3, 50% for patients with MRD ≥ 10-4 at EOT+3





Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634.

Phase III GLOW Ibr +Ven Remained Associated with Improved OS at 57 Months of Study Follow-Up



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); $p = 0.0038$
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634.

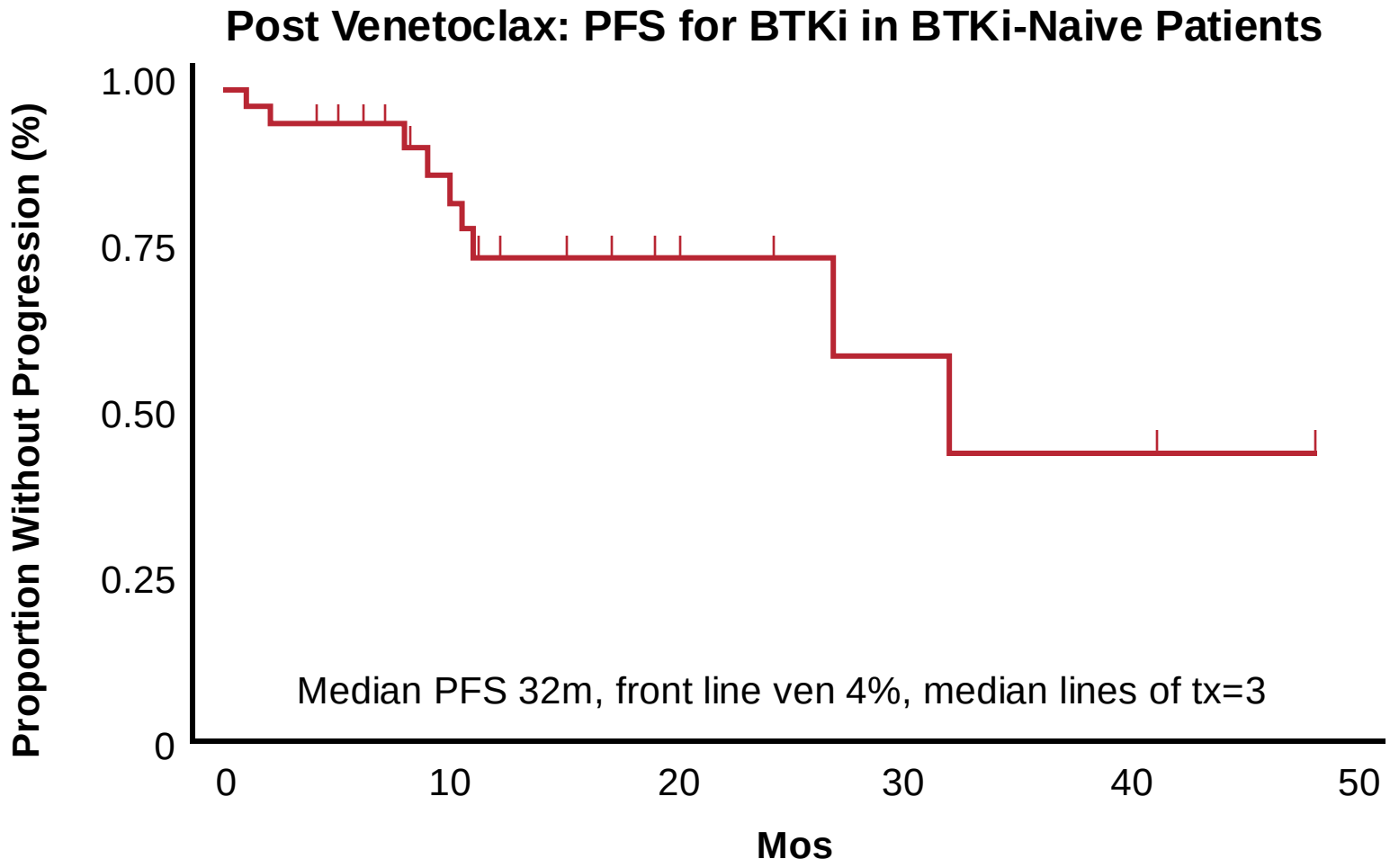
Key Learning Points

- Fixed duration with venetoclax and obinutuzumab results in high levels of MRD- that translate in better PFS and OS compare with MRD+
  - CLL14 trial shows long-term PFS benefits for patients with high-risk CLL
- Double oral combination will offer another convenience fix duration strategy
  - In Phase 3 GLOW trial, ibrutinib + venetoclax showed a 57-month PFS of 66.5% in first-line treatment in older or unfit patients
- Fixed duration combinations may lead to lower rates of cumulative toxicity/ongoing risks as well as less financial toxicity

Lymphoma · Leukemia & Myeloma Congress

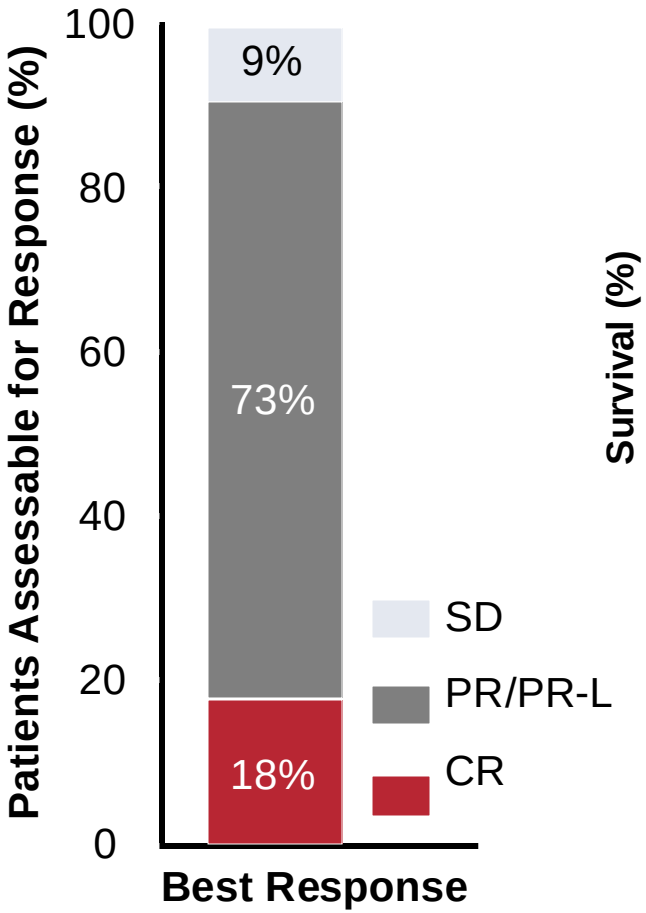
Outcomes Data after Targeted Therapy Failure

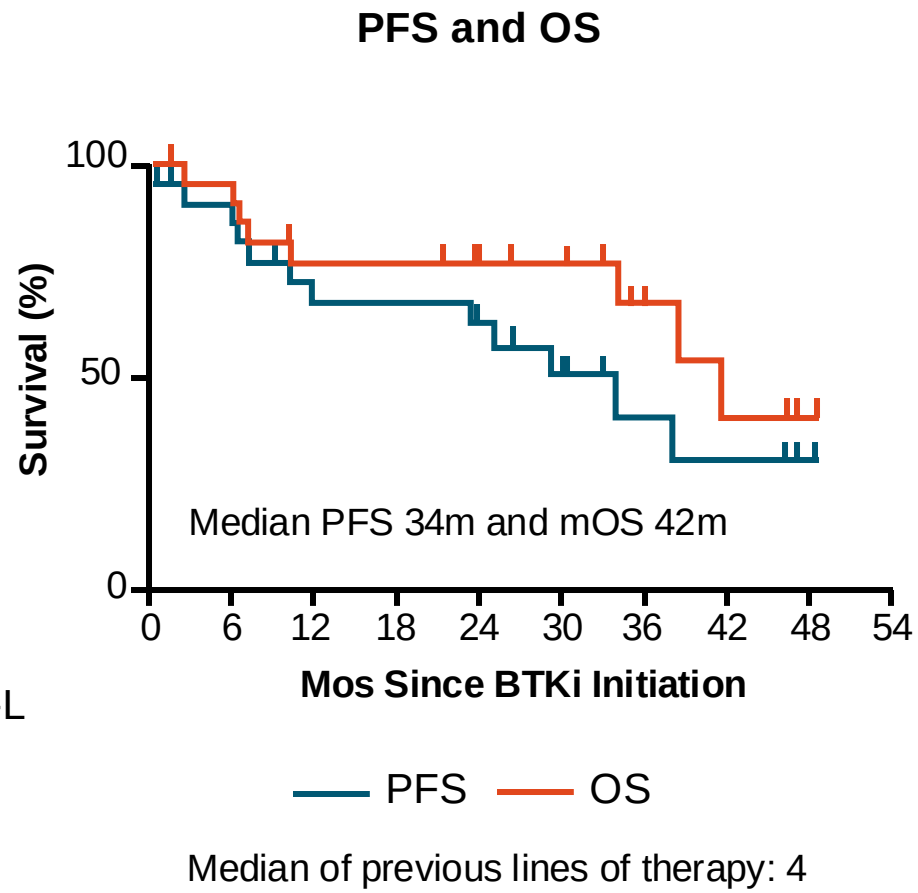
BTKi after Venetoclax in BTKi-Naïve Patients

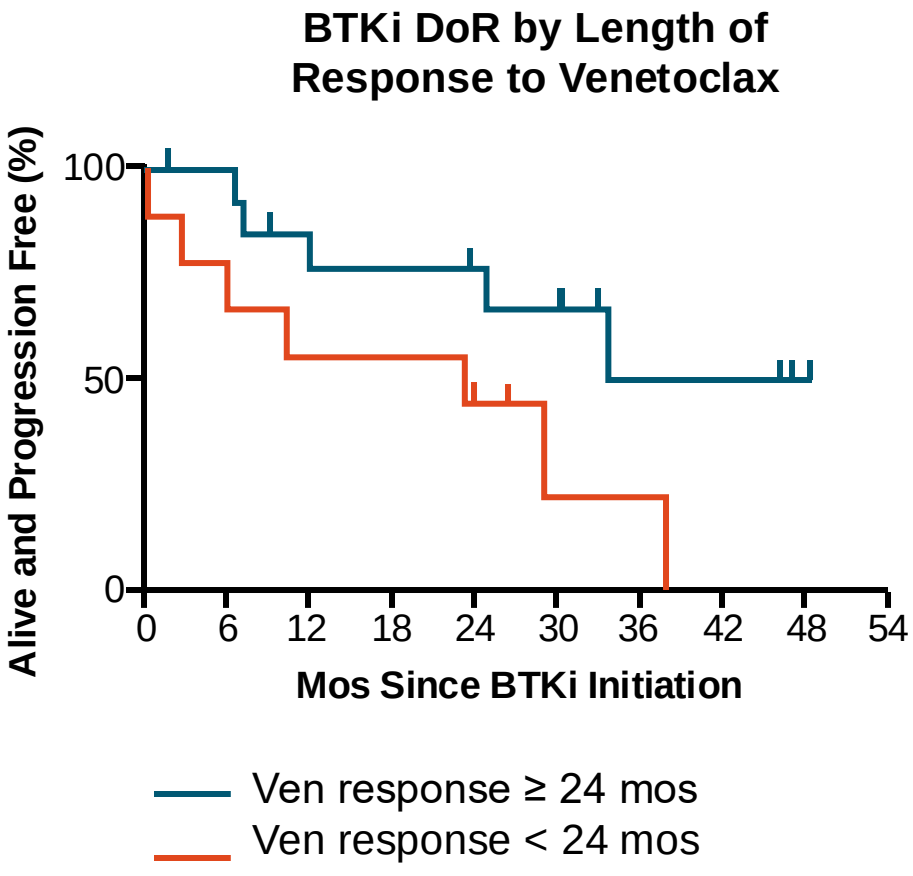


Mato AR, et al. *Clin Cancer Res*. 2020;26(14):3589-3596.

BTKi Therapy in Patients with CLL Resistant to Ven







DOR = duration of response; SD = stable disease.

Lin VS, et al. *Blood*. 2020;135(25):2266-2270.

Phase IIIb VENICE I Trial of Ven in R/R CLL: Efficacy

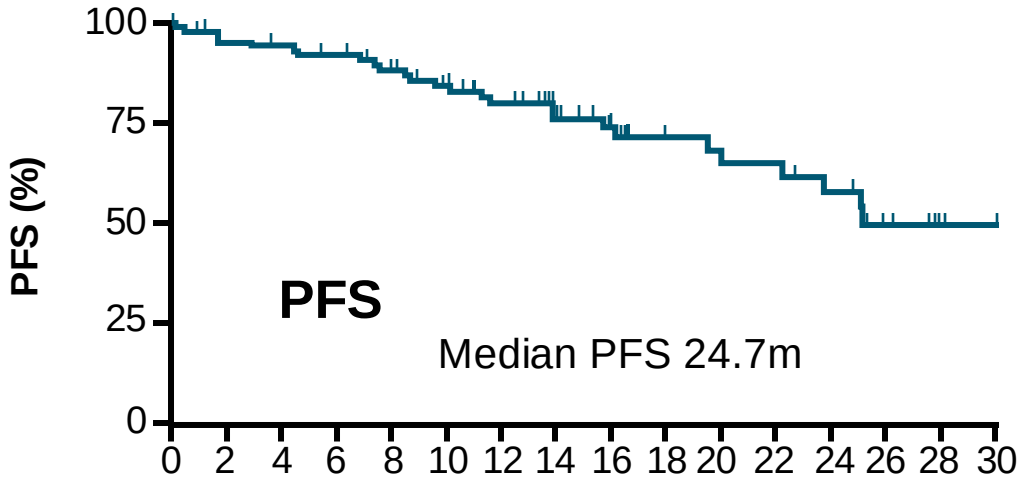
			BCRi Treated (n = 67)
Response at week 48, n (%) [95% CI] ▪ CR/CRi ▪ PR/nPR	84 (32.6) [26.9-38.6] 121 (46.9) [40.7-53.2]	67 (35.1) [28.3-42.3] 96 (50.3) [43.0-57.6]	17 (25.4) [15.5-37.5] 25 (37.3) [25.8-50.0]
ORR, n (%) [95% CI]	206 (79.8) [74.4-84.6]	163 (85.3) [79.5-90.0]	43 (64.2) [51.5-75.5]
OS, n (%)	216 (83.7)	168 (88.0)	48 (71.6)
Median PFS, mos (95% CI) ▪ 17p/*TP53* mutated ▪ Best PB uMRD ▪ CR/CRi ▪ PR/nPR	30.5 (28.6-30.5) 28.6 (28.6-30.5) Not reached Not reached 30.5 (-, -)	30.5 (29.6-30.5) -- -- -- --	28.6 (28.6,-) -- -- -- --
PFS at 24 mos, % (95% CI]	77.0 (70.7-82.2)	79.4 (71.9-85.2)	69.9 (56.8-79.7)
Best PB uMRD at (10^{-4}, using NGS; ITT), n (%) ▪ CR/CRi ▪ PR/nPR	98 (38.0) - -	77 (40.3) 30/67 (44.8) 43/96 (44.8)	21 (31.3) 12/17 (70.6) 8/26 (30.8)

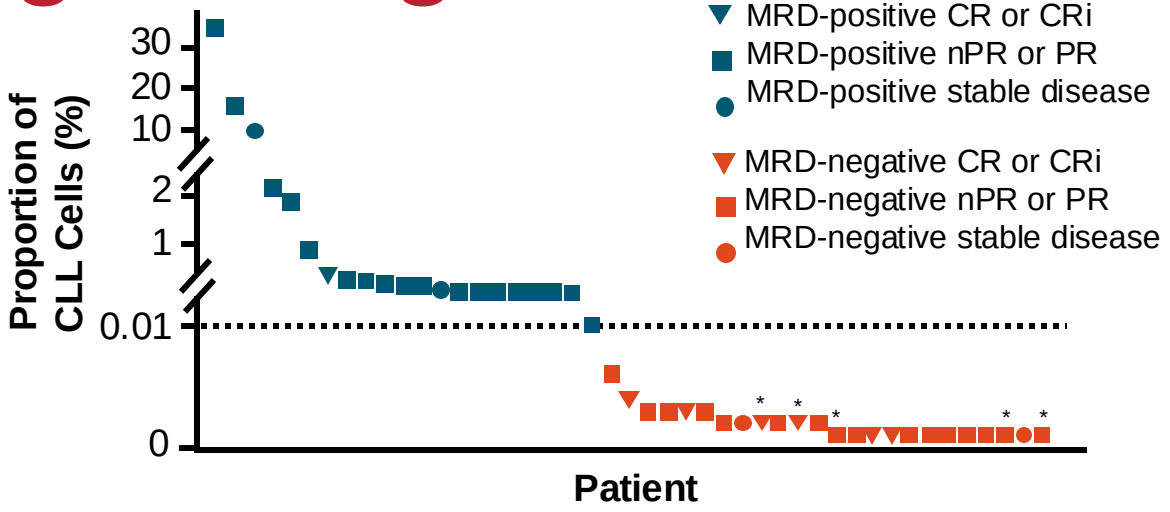
Median lines of tx 2; front line ibrutinib 1%.

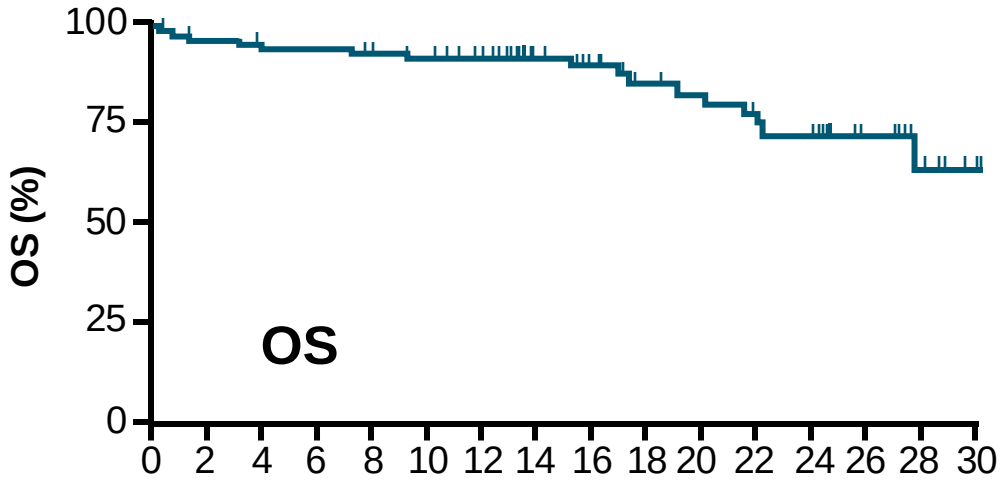
nPR = nodular PR.

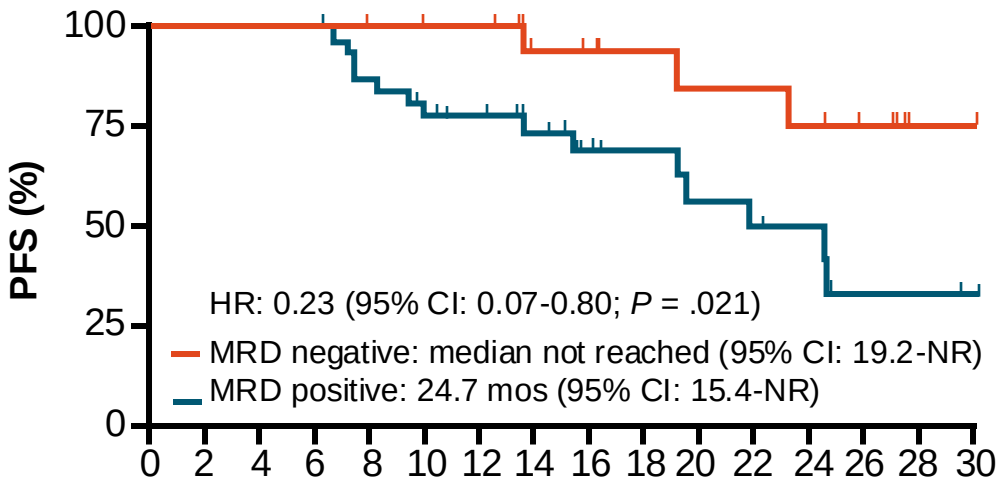
Kater AP, et al. Presented at: ASH 2020; December 5, 2020; virtual. 125.

Venetoclax for CLL Progressing after Ibrutinib









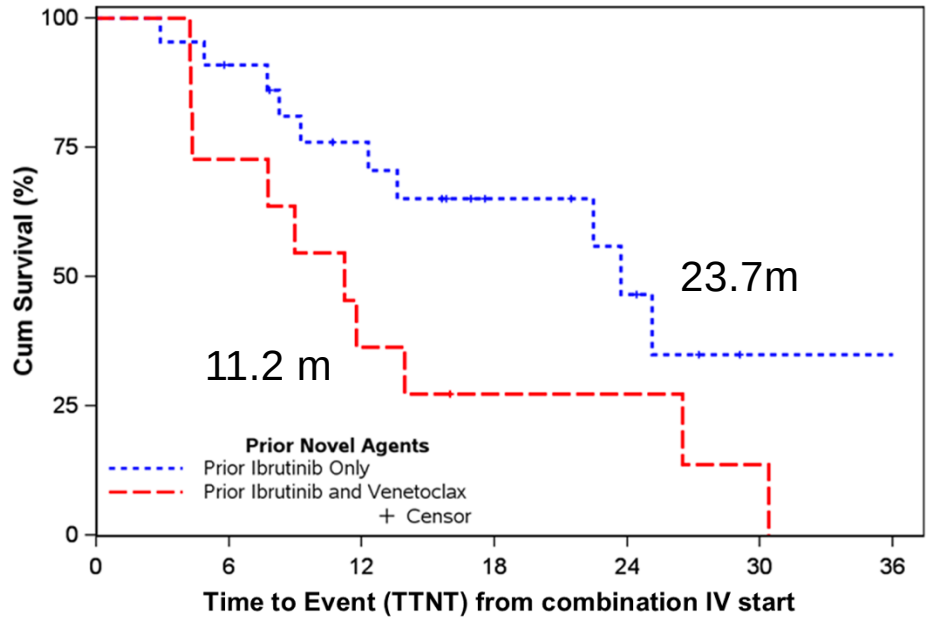
Median previous lines of tx 5.

Jones JA, et al. *Lancet Oncol*. 2018;19(1):65-75.

Patients with CLL Treated with I+V after Progression of I Alone of Sequential I and V

TTNT from I+V Start

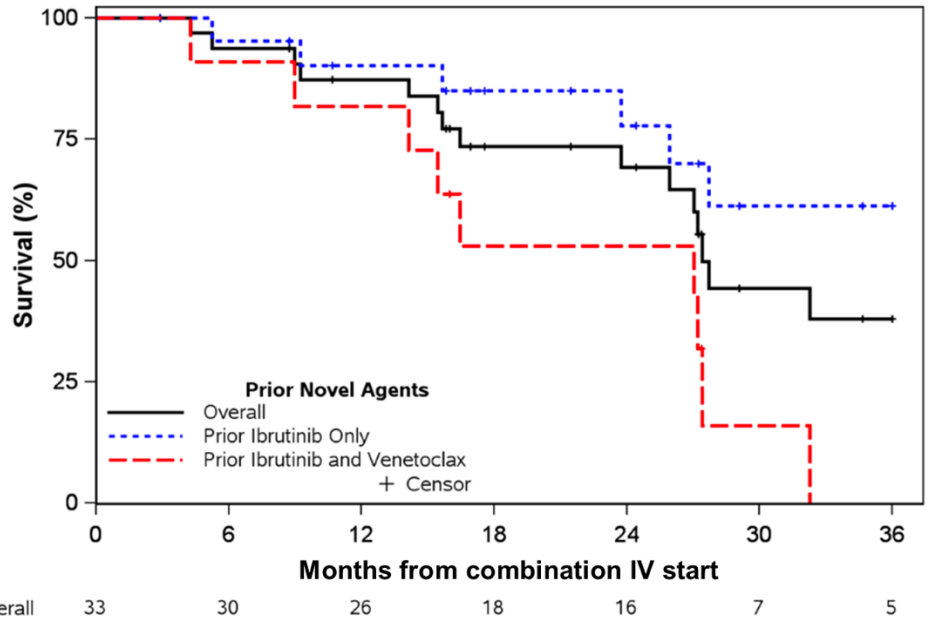
(B)



Prior Ibrutinib Only	22	19	14	8	5	1	1
Prior Ibrutinib and Venetoclax	11	8	4	2	2	1	0

OS from I+V Start

(C)



Overall	33	30	26	18	16	7	5
Prior Ibrutinib Only	22	20	17	13	11	6	5
Prior Ibrutinib and Venetoclax	11	10	9	5	5	1	0

Median lines of previous therapy: 4.

Hampel PJ, et al. *Br J Haematol*. 2022;199(2):239-244.

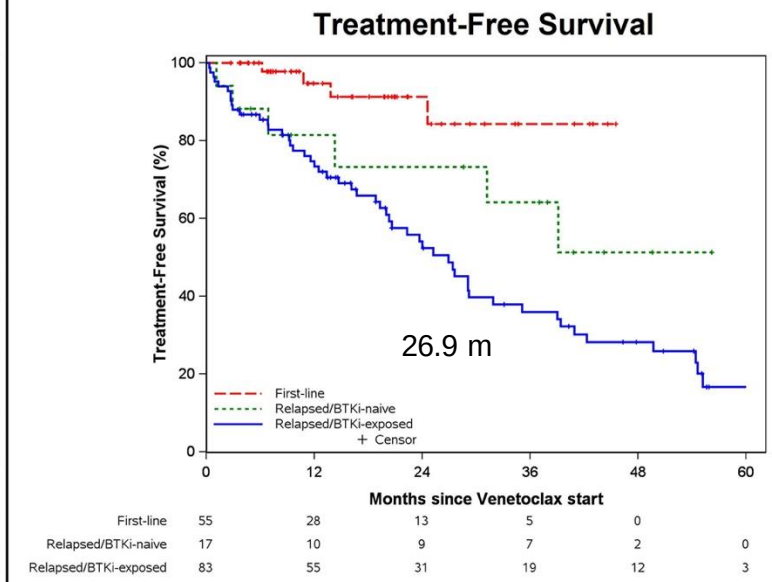
Patients with CLL Treated with Ven after BTKi Exposure

Table 1: Baseline characteristics at the time of venetoclax start

Parameter		Number (%) or Median [range]			
		All patients	Firstline	Relapsed/ BTKi-naïve	Relapsed/BTKi-exposed
N		**155**	**55**	**17**	**83**
Age, years		66 [41-93]	65 [41-84]	67 [51-83]	68 [43-93]
Males		108 (70)	36 (66)	12 (71)	60 (72)
Prior lines of therapy		1 [0-11]	0	1 [1-6]	3 [1-11]
Combination with anti-CD20mAb	Rituximab	45 (29)	0 (0)	8 (47)	37 (45)
	Obinutuzumab	80 (52)	55 (100)	9 (53)	16 (19)
	Monotherapy	30 (19)	0 (0)	0 (0)	30 (36)
Rai stage, n=148	0	20 (14)	2 (4)	2 (13)	16 (20)
	I-II	62 (42)	30 (58)	5 (31)	27 (34)
	III-IV	66 (45)	20 (39)	9 (56)	37 (46)
Absolute Lymphocyte Count (x 10^9/L)*, n=150		22.4 [0-539]	80.7 [0-539]	16.2 [4-108]	13.0 [0.3-533]
IGHV mutation status*, n=129	Unmutated	93 (72)	20 (39)	8 (57)	8 (13)
FISH*, n=134	None detected	20 (15)	11 (21)	4 (27)	5 (8)
	Other	5 (4)	0 (0)	0 (0)	5 (8)
	13q-	34 (25)	16 (30)	4 (27)	14 (21)
	Trisomy 12	23 (17)	11 (21)	2 (13)	10 (15)
	11q-	28 (21)	13 (25)	4 (27)	11 (17)
	17p-	24 (18)	2 (4)	1 (7)	21 (32)
Complex karyotype*, n=69	Complex (≥3 abnormalities)	27 (39)	3 (12)	3 (38)	21 (58)
TP53 Disruption (either del17p or *TP53* mutation)*, n=136	Present (Abnormal)	32 (24)	2 (4)	2 (13)	28 (41)

*not available for all patients

Figure 1: Treatment-free survival from the start of venetoclax for patients grouped by disease scenario



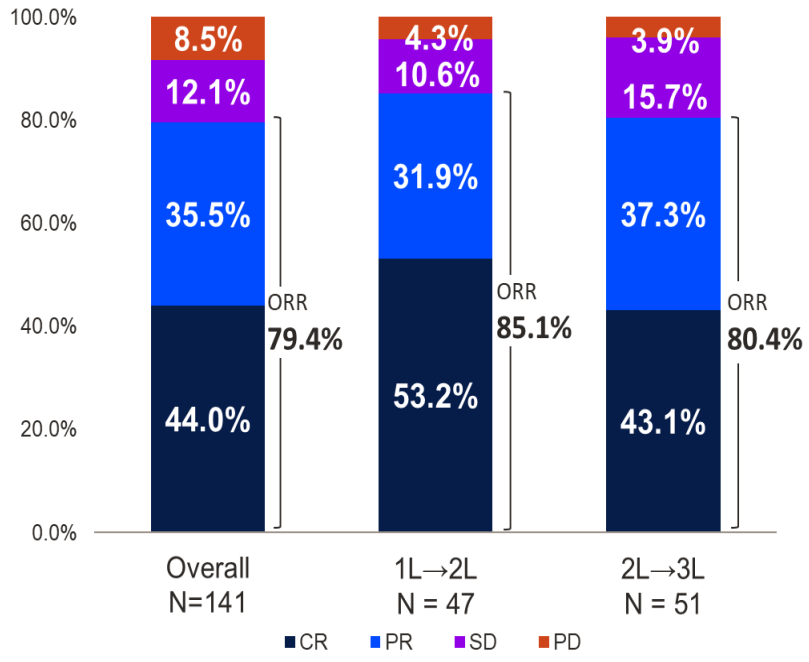
Median lines of previous therapy 3.

FISH = fluorescence in situ hybridization.

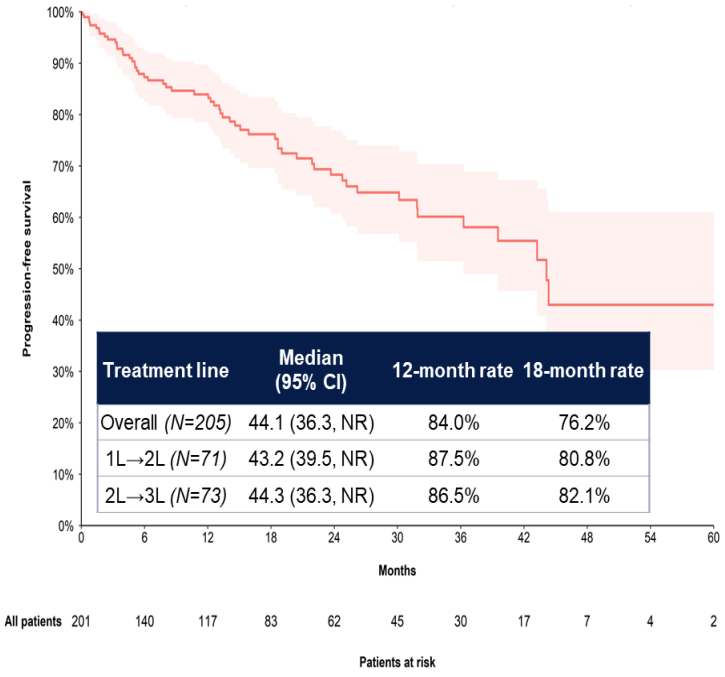
Hampel PJ, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 3276.

Venetoclax-Based Therapy after BTKi Failure in 1st or 2nd Line

ORR

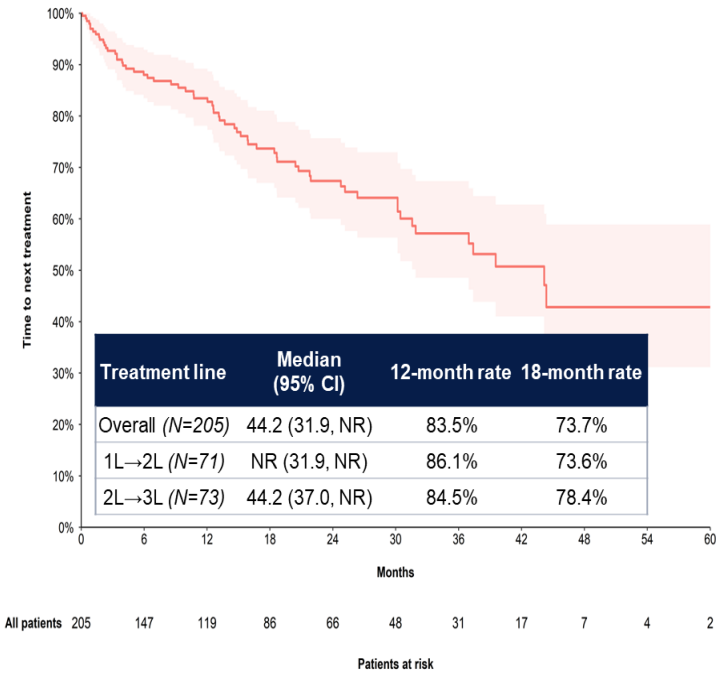


PFS



Treatment line	Median (95% CI)	12-month rate	18-month rate
Overall *(N=205)*	44.1 (36.3, NR)	84.0%	76.2%
1L→2L *(N=71)*	43.2 (39.5, NR)	87.5%	80.8%
2L→3L *(N=73)*	44.3 (36.3, NR)	86.5%	82.1%

TTNT-D



Treatment line	Median (95% CI)	12-month rate	18-month rate
Overall *(N=205)*	44.2 (31.9, NR)	83.5%	73.7%
1L→2L *(N=71)*	NR (31.9, NR)	86.1%	73.6%
2L→3L *(N=73)*	44.2 (37.0, NR)	84.5%	78.4%

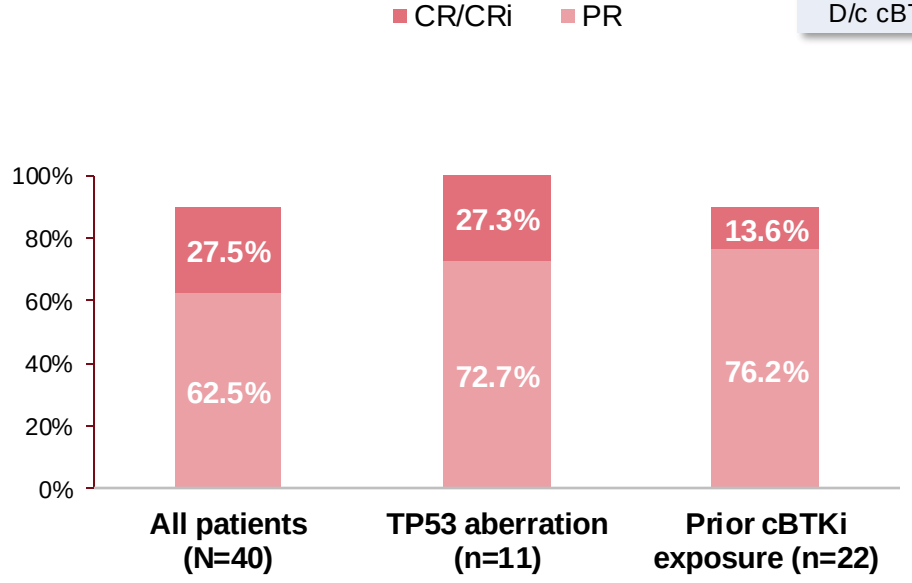
Abbreviations: 1L: first-line; 2L: second line; 3L: third-line; CI: confidence interval; CR: complete response; NR: not reached; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease; TTNT-D: time to next treatment or death

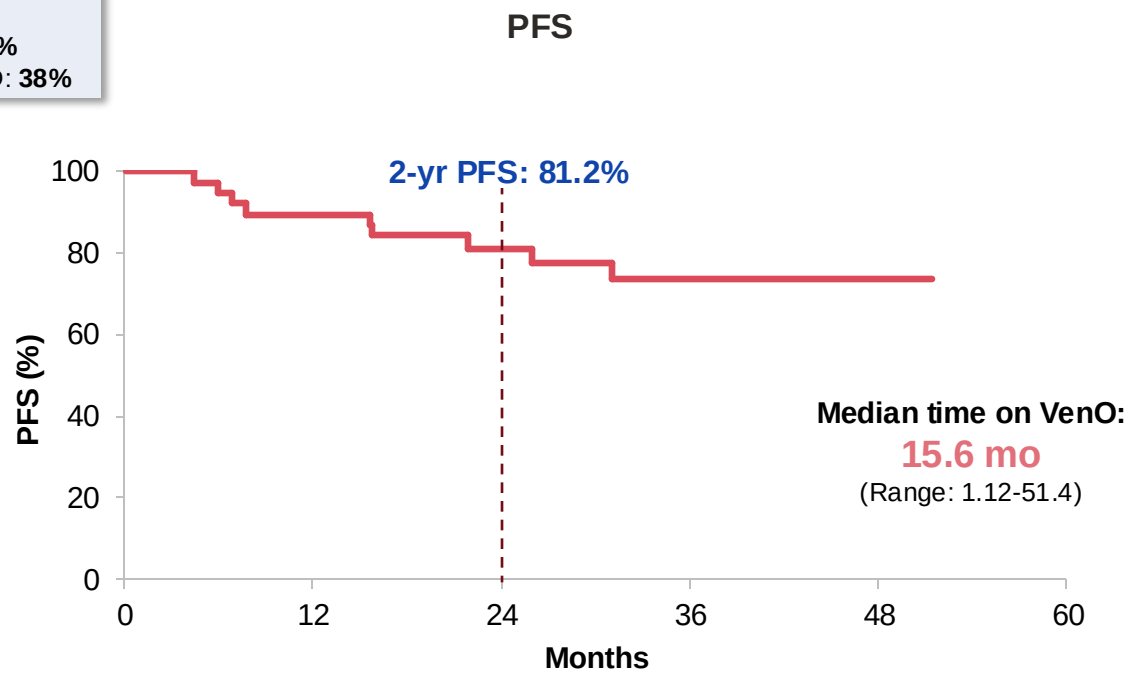
Ghosh N, et al. Presented at: ASH 2023; December 9, 2023; San Diego, CA. 1908.

VenObinu after cBTKi Failure in 2nd Line

CIT or cBTKi → VenO
median follow-up: 32.0+ months

Median prior LOT:
1 (1-6)
Prior cBTKi: **55%**
D/c cBTKi due to PD: **38%**



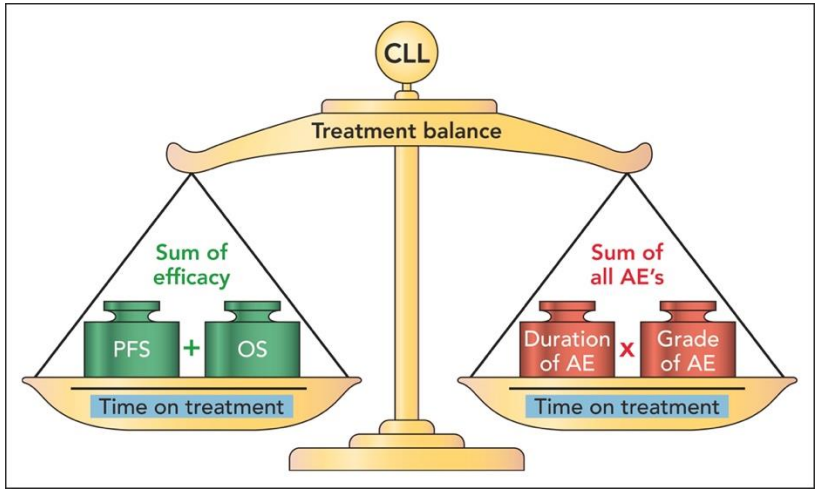


Lei MM, et al. *Leuk Lymphoma*. 2024. [Epub ahead of print.]

Key Learning Points

- After BTKi or venetoclax failures, treatment with alternative targeted agents may produce good responses
- However, the durability of the response depends on previous lines of therapy, including CIT
- Not much data reported after first line BTKi or venetoclax primary failure but is likely better

Summary



Modern therapy is very effective but can achieve different goals

Continuous Therapy	Goals of Therapy
• BTK inhibitors	• Disease control • Prolonged PFS • Independent from response, MRD

Be prepared to review goals of care with patients and empower their decision-making

Fixed Duration	Goals of Therapy
• Venetoclax + obinutuzumab	• Disease eradication • Prolonged PFS • Undetectable MRD

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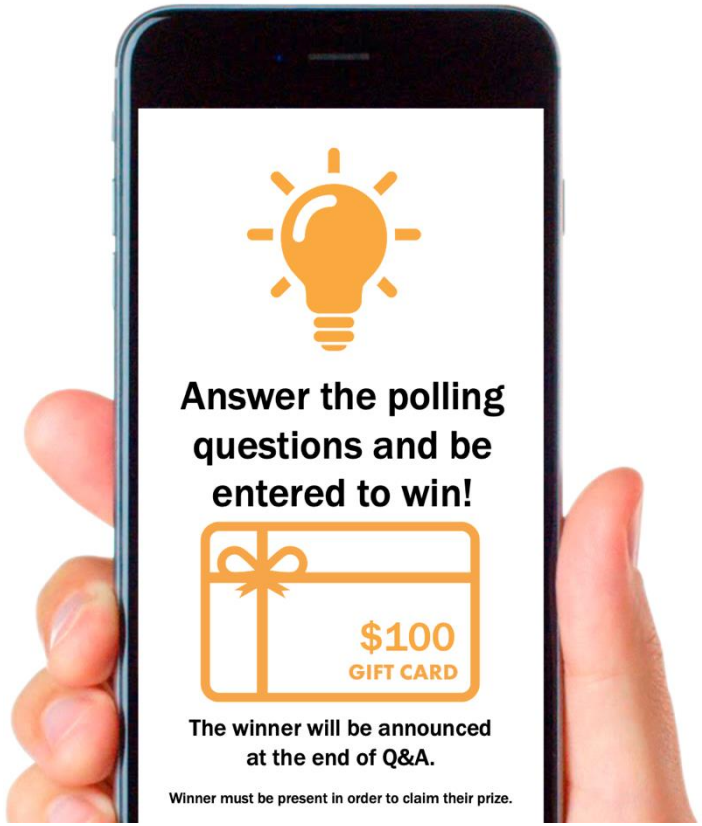
Please participate in our **polling** questions.

To participate: Scan QR code or Go to https://app.meet.ps/attendee/llm24



Lymphoma Leukemia & Myeloma Congress

October 16–19, 2024

New York, NY

lymphomaandmyeloma.com

Combination Studies of BTKi and BCL2 Inhibitors

John N. Allan

Weill Cornell Medicine

Disclosures

- **John N. Allan:** Consultant – Abbvie, Adaptive Biotechnologies, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, NeoGenomics, Merck, Pharmacyclics; advisory board – Abbvie, Adaptive Biotechnologies, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, NeoGenomics, Merck, Pharmacyclics; research/grant support – BeiGene, Celgene/BMS, Genentech

Learning Objectives

- Identify strengths and limitations of current treatment regimens for CLL/SLL in the context of patient risk stratification in 1st and later lines
- Evaluate the most recent real-world and clinical data, including long-term patient outcomes data, for BTK inhibitors as monotherapy and in combination with other targeted agents for CLL/SLL
- Describe common AEs associated with BTK inhibitors and strategies to manage/mitigate them in clinical practice

CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; BTK = Bruton's tyrosine kinase; AE = adverse event.

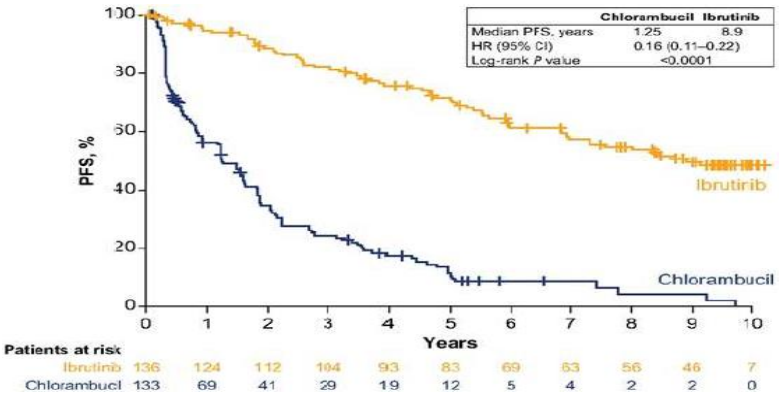
Topic Overview

- Overview of time limited approaches with BTK/BCL2 combinations
  - CAPTIVATE
  - GLOW
  - CLL 13
  - SEQUOIA Arm D
- Toxicity comparisons of time limited approaches
- Resistance and retreatment after time limited therapy

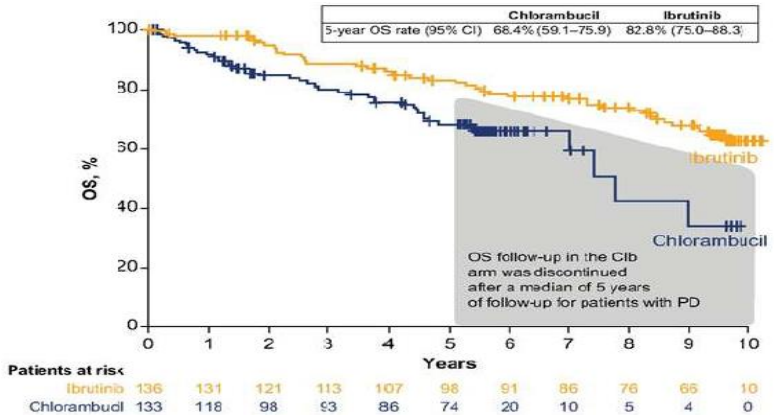
BCL2 = B-cell leukemia/lymphoma 2.

RESONATE-2 10 Year Final Analysis

PFS



OS



Discontinuations

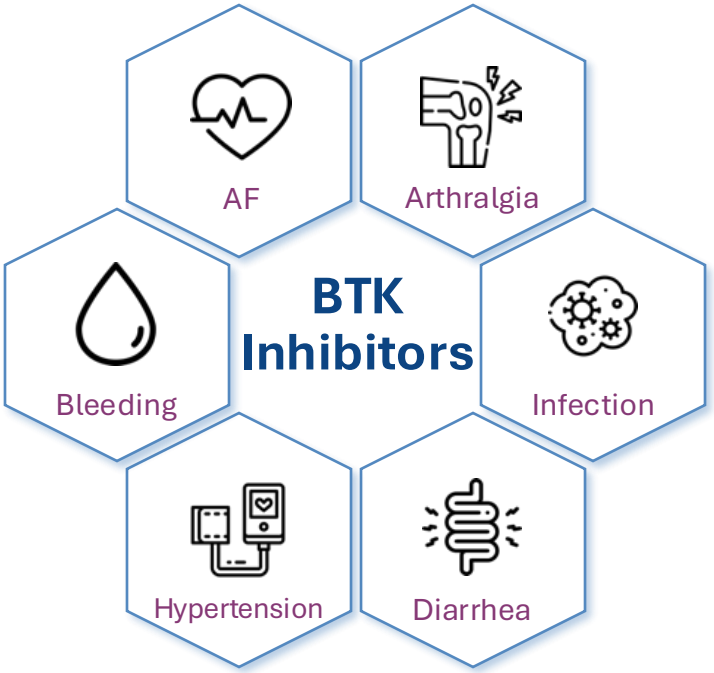
	Ibrutinib N=135
Median (range) duration of ibrutinib treatment, years	6.2 (0.06–10.2)
Continuing ibrutinib at study closure, n (%)	37 (27)
Discontinued ibrutinib, n (%)	
Due to AE	44 (33)
Due to PD	18 (13)

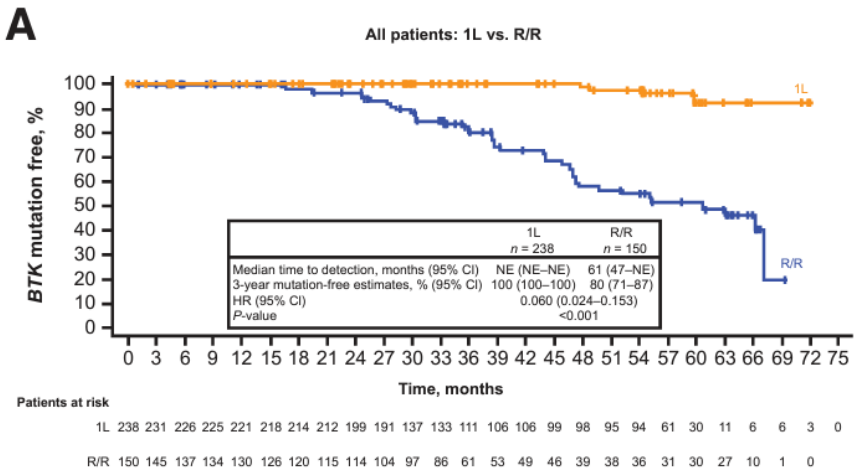
AE, adverse event.

PFS = progression-free survival; OS = overall survival; PD = progressive disease.

Burger J, et al. Presented at: European Hemotology Association (EHA) 2024; June 13, 2024; Madrid, Spain. P670.

Time Limited Combination Approaches May Address Toxicity and Resistance

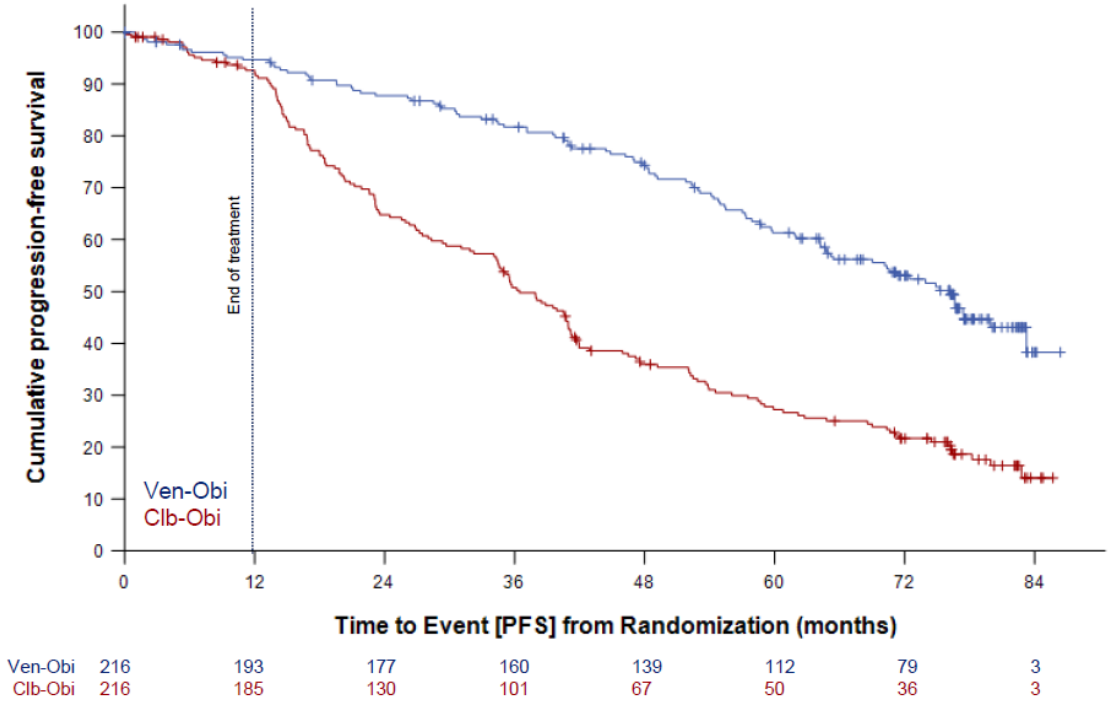




RR = relapsed/refractory; NE = not estimable; 1L = first line; AF = atrial fibrillation.

Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):336-345. Woyach JA, et al. *Clin Cancer Res*. 2023;29(16):3065-3073.

CLL14 6 Year PFS



Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

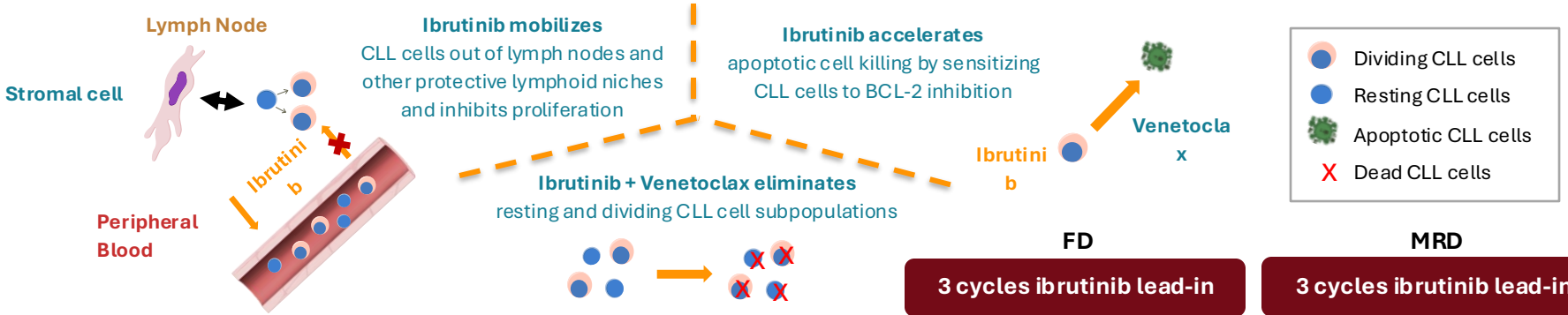
HR 0.40, 95% CI [0.31-0.52]
P<0.0001

6 Year TTNT 65%
uMRD mIGHV 5yr PFS ~80+%
uMRD uIGHV 5yr PFS ~50%

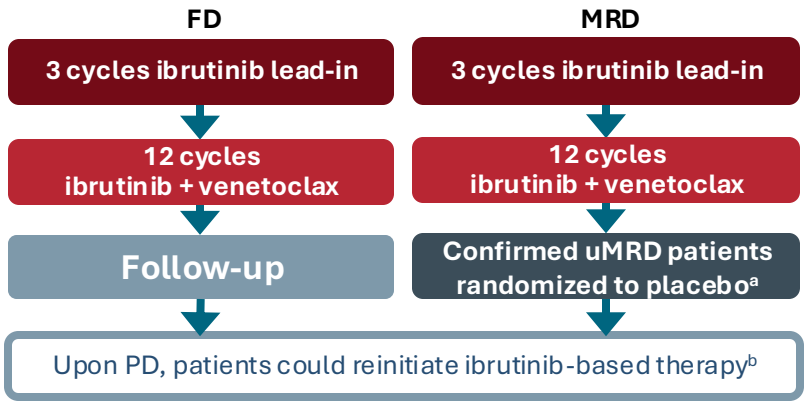
IGHV = immunoglobulin heavy chain variable; m/u = mutated/unmutated.
Al-Sawaf O, et al. *Hemasphere*. 2023;7(Suppl):e064430a.

Lymphoma · Leukemia & Myeloma Congress

CAPTIVATE: Ibrutinib and Venetoclax Work Synergistically Through Distinct and Complementary Modes of Action



- This presentation reports outcomes after fixed-duration treatment with ibrutinib + venetoclax in the phase 2 CAPTIVATE study demonstrating
  - Patients with high-risk genomic features (fixed duration [FD] cohort [N=159]) derive meaningful survival benefits from fixed-duration ibrutinib + venetoclax
  - Ibrutinib-based retreatment (FD cohort [N=159] and MRD cohort placebo arm [n=43]) appears to have a positive benefit-risk profile



[a]Patients with confirmed uMRD (defined as uMRD [<10^{-4} by 8-color flow cytometry] serially over ≥3 cycles in both peripheral blood and bone marrow) after 12 cycles of ibrutinib + venetoclax were randomly assigned 1:1 to receive placebo or ibrutinib; only the placebo arm was included in the current analysis. [b]Patients with PD after completion of fixed-duration ibrutinib + venetoclax could reinitiate single-agent ibrutinib (FD cohort or MRD cohort placebo arm); patients with PD >2 years after treatment completion could reinitiate fixed-duration ibrutinib + venetoclax (FD cohort). Ibrutinib + venetoclax is approved for first-line treatment of CLL/SLL in 78 countries across the world.

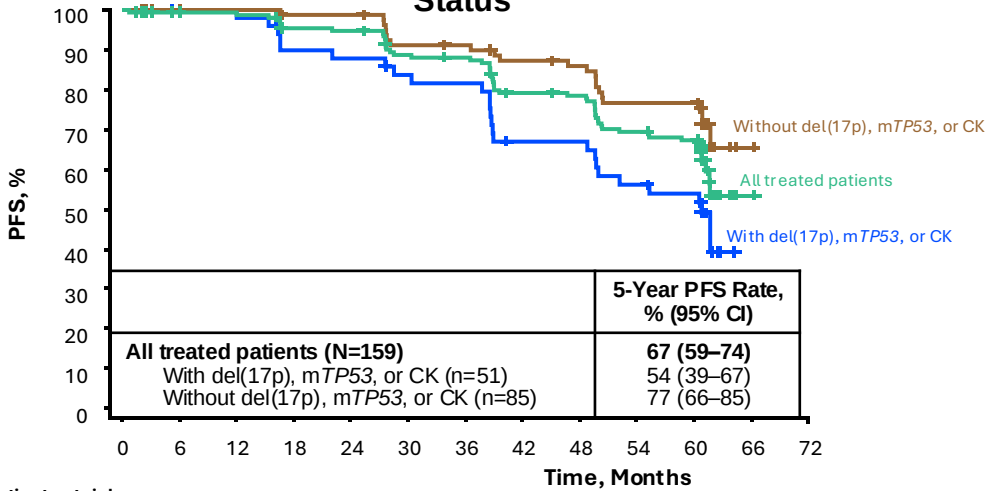
Lu P, et al. *Blood Cancer J.* 2021;11(2):39. Deng J, et al. *Leukemia.* 2017;31:2075-2084. Herman SEM, et al. *Clin Cancer Res.* 2015;21:4642-4651.

Overall Median PFS Was Not Reached with Up to 5.5 Years of Follow-Up

Median time on study: 61.2 months (range, 0.8–66.3)

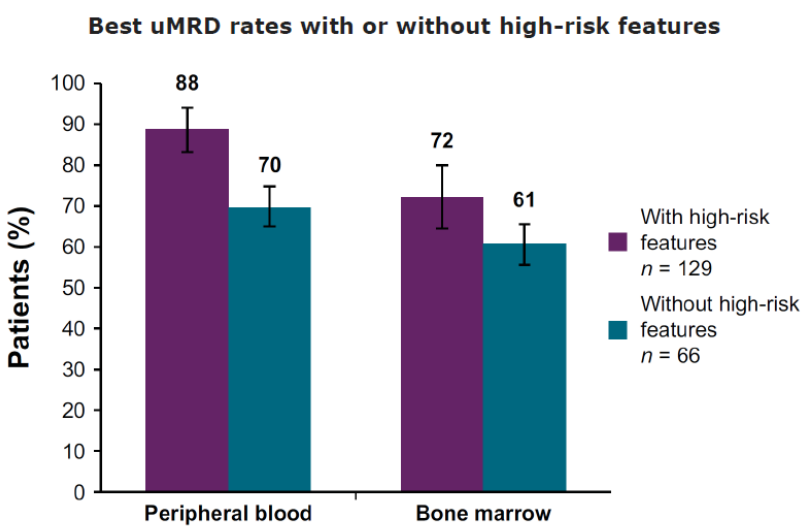
	With feature		Without feature	
High-risk feature	**n**	**5-Year PFS rate, % (95% CI)**	**n**	**5-Year PFS rate, % (95% CI)**
del(17p)/m*TP53*	27	41 (21–59)	129	73 (64–80)
CK[a]	31	57 (37–72)	102	72 (61–80)
del(11q)[b]	11	64 (30–85)	74	79 (67–87)

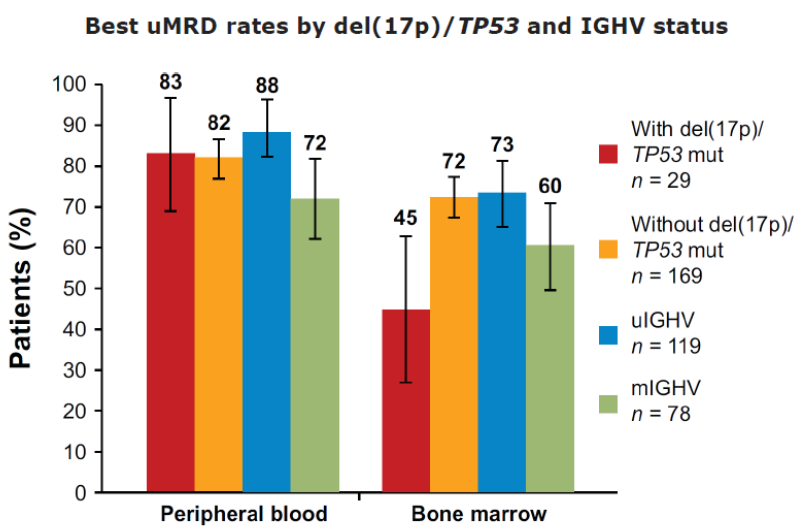
PFS in All Treated Patients and by del(17p), m*TP53*, or CK Status



CK = complex karyotype.
[a]Defined as ≥3 chromosomal abnormalities by conventional CpG-stimulated cytogenetics; [b]Excluding patients with del(17p)/mutated TP53 or CK.
Wierda WG, et al. *JCO.* 2024;42:7009-7009.

CAPTIVATE: Best MRD Rates and Risk Factors of FD

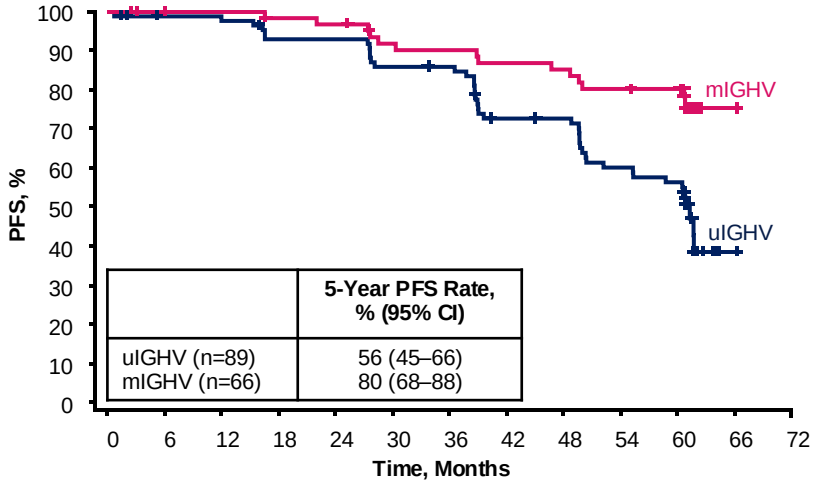




Allan JN, et al. *Clin Cancer Res.* 2023;29(14):2593-2601.

FD Cohort: 5-Year PFS Rates by IGHV Mutation Status (N=159)

PFS by IGHV Mutation Status (All patients)

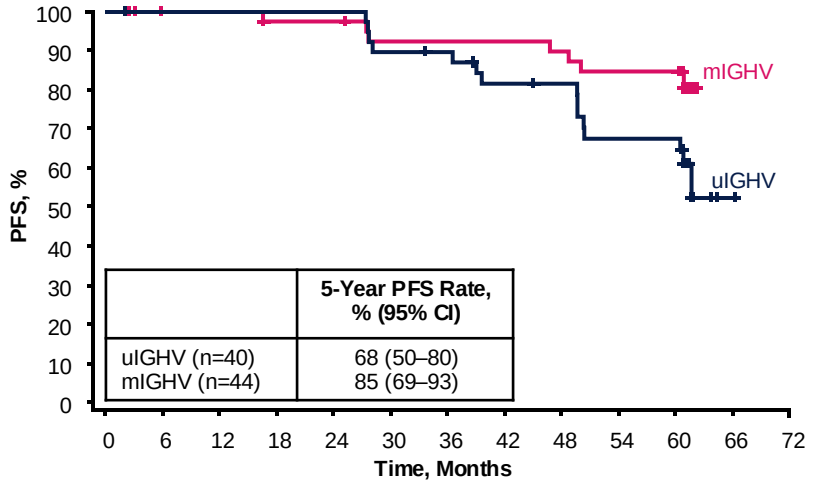


	5-Year PFS Rate, % (95% CI)
uIGHV (n=89)	56 (45–66)
mIGHV (n=66)	80 (68–88)

Patients at risk

uIGHV	89	85	85	79	79	73	72	59	58	48	45	1	0
mIGHV	66	64	63	61	60	55	54	52	51	48	47	1	0

PFS by IGHV Mutation Status (Excluding Patients with del(17p), m*TP53*, or CK)



	5-Year PFS Rate, % (95% CI)
uIGHV (n=40)	68 (50–80)
mIGHV (n=44)	85 (69–93)

Patients at risk

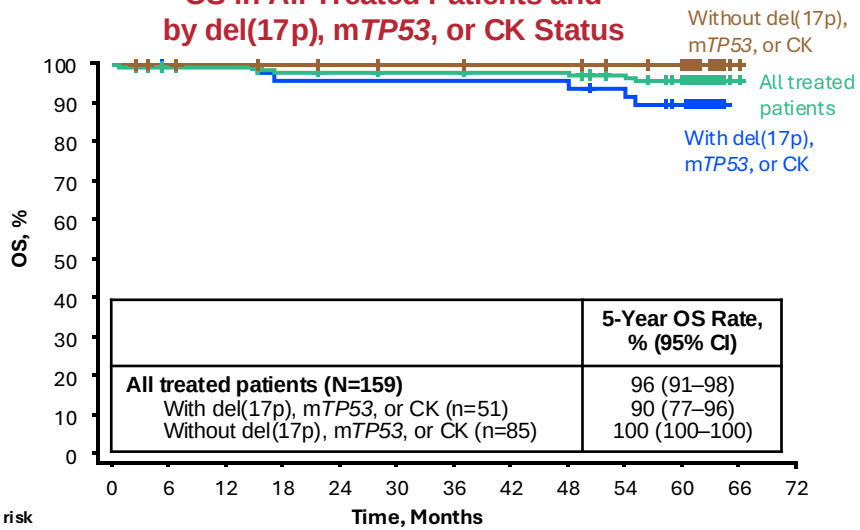
uIGHV	40	39	39	39	39	35	34	30	29	24	24	1	0
mIGHV	44	42	41	39	39	36	36	36	35	33	33	0	

- Presence of del(17p), m*TP53*, and/or CK had a substantial impact on PFS in patients with uIGHV and mIGHV

Wierda WG, et al. *JCO.* 2024;42:7009-7009.

FD Cohort: 5-Year OS Rates Were ≥90% Regardless of Genomic Risk Features

OS in All Treated Patients and by del(17p), m*TP53*, or CK Status

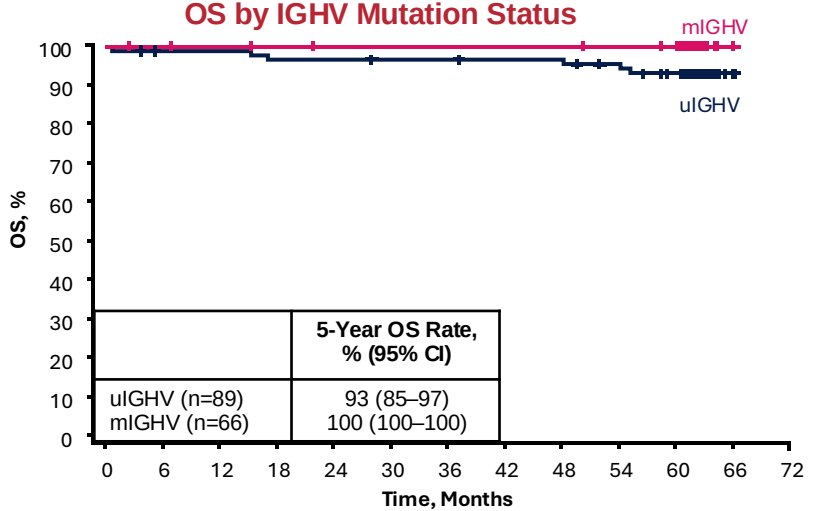


	5-Year OS Rate, % (95% CI)
All treated patients (N=159)	96 (91–98)
With del(17p), m*TP53*, or CK (n=51)	90 (77–96)
Without del(17p), m*TP53*, or CK (n=85)	100 (100–100)

Patients at risk

All treated patients	159	155	154	151	150	149	149	148	148	144	138	4	0
With del(17p), m*TP53*, or CK	51	50	50	48	48	48	48	48	48	46	42	0	
Without del(17p), m*TP53*, or CK	85	83	82	81	80	79	79	78	78	76	75	1	0

OS by IGHV Mutation Status



	5-Year OS Rate, % (95% CI)
uIGHV (n=89)	93 (85–97)
mIGHV (n=66)	100 (100–100)

Patients at risk

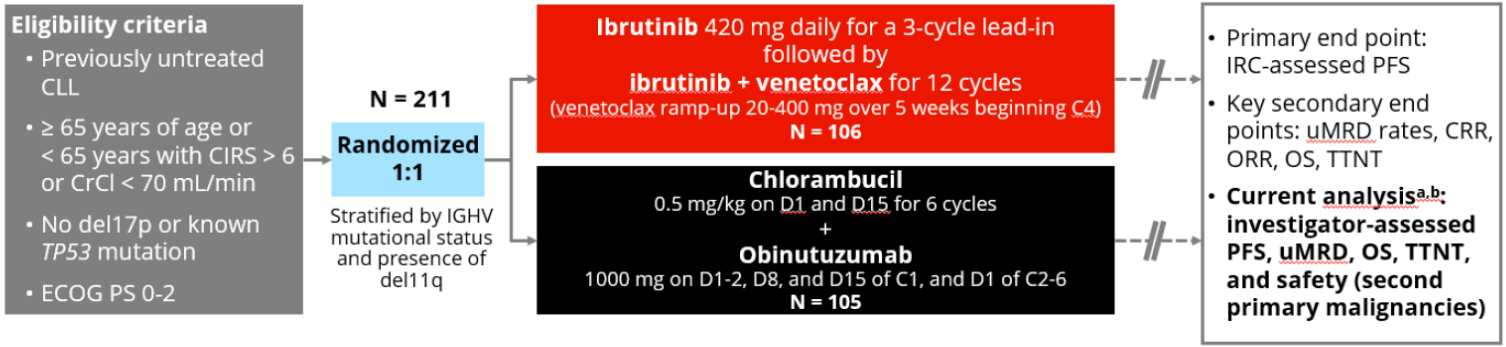
uIGHV	89	86	86	84	84	83	83	82	82	79	74	2	0
mIGHV	66	65	64	63	62	62	62	62	62	61	60	1	0

- 5-year OS rates were ≥95% regardless of MRD status in PB or BM at 3 months after EOT or in PB at 12 months after EOT

OS = overall survival; BM = bone marrow; PB = peripheral blood; EOT = end of treatment.

Wierda WG, et al. *JCO.* 2024;42:7009-7009.

GLOW Study Schema 57m Update



- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

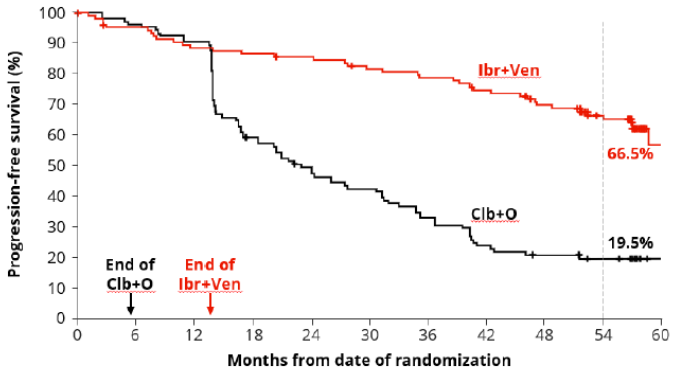
[a]All p values are nominal. [b]uMRO in PB by NGS via assay.

NGS = next generation sequencing; TTNT = time to next treatment; CR = complete response rate; CIRS = cumulative illness rating scale; ECOG = Eastern Cooperative Oncology Group.

Moreno C, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 10, 2023; San Diego, CA. 634.

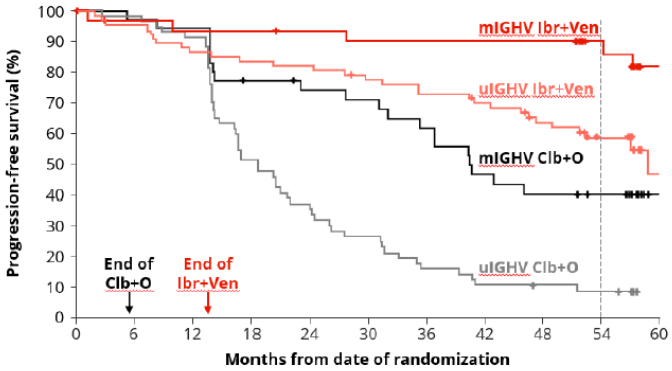
GLOW 5 Year Follow-Up: PFS

Progression-free survival (ITT)



- **Ibr+Ven reduced the risk of progression or death by 74%** vs Clb+O
  - HR 0.256 (95% CI 0.172–0.382); p<0.0001
- Estimated 54-month PFS rates at 57 months of follow-up:
  - **66.5%** for Ibr+Ven
  - **19.5%** for Clb+O

Progression-free survival (ITT) by IGHV status



Estimated 54-month PFS rates:
- **Ibr+Ven:**
  - 90% for patients with mIGHV
  - 59%, for patients with uIGHV
- **Clb+O:**
  - 40% for patients with mIGHV
  - 8% for patients with uIGHV

Clb = chlorambucil; O = obinutuzumab; ITT = intention to treat.

Moreno C, et al. Presented at: ASH Annual Meeting; December 10, 2023; San Diego, CA. 634.

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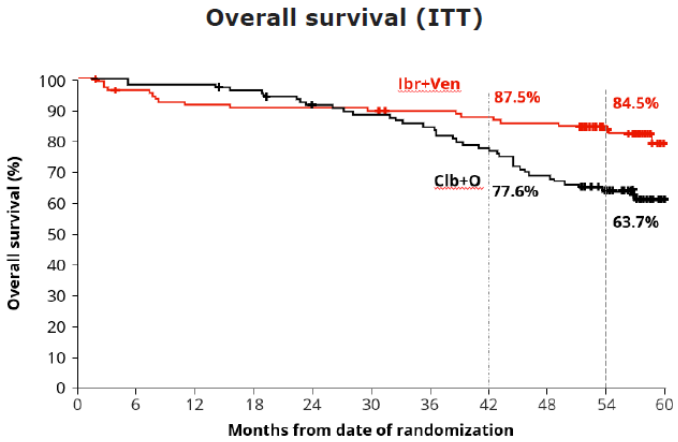
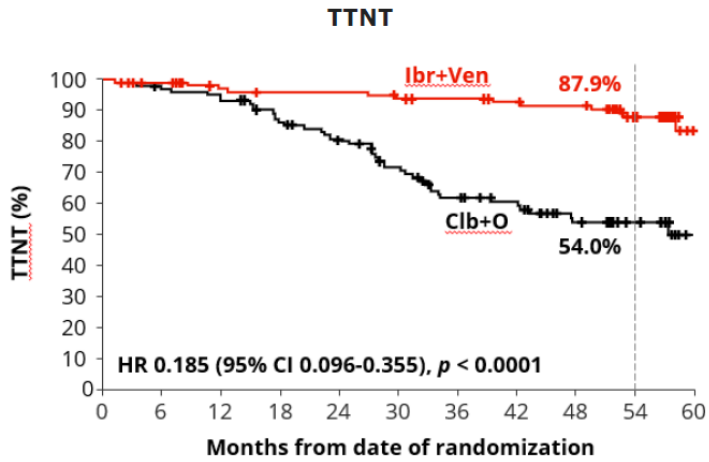
GLOW 5 Yr OS and TTNT

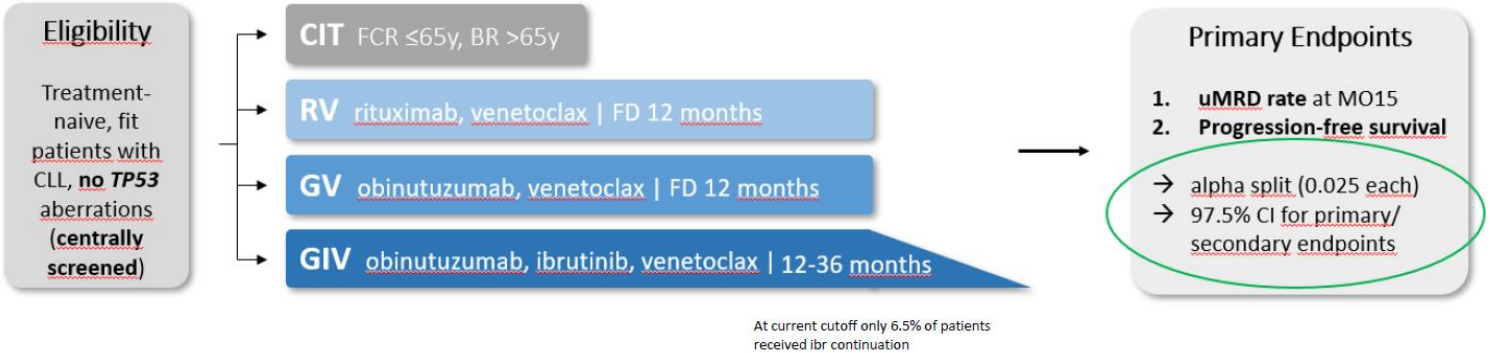


- **Ibr+Ven reduced the risk of death by 55%** vs Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); p=0.0038
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O



Moreno C, et al. Presented at: ASH Annual Meeting; December 10, 2023; San Diego, CA. 634.

CLL13/GAIA: Study Schema and Patient Population



Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

Follow-up analysis (data cut-off: 01/2023)

Median observation time
50.7 months (IQR: 44.6-57.9)

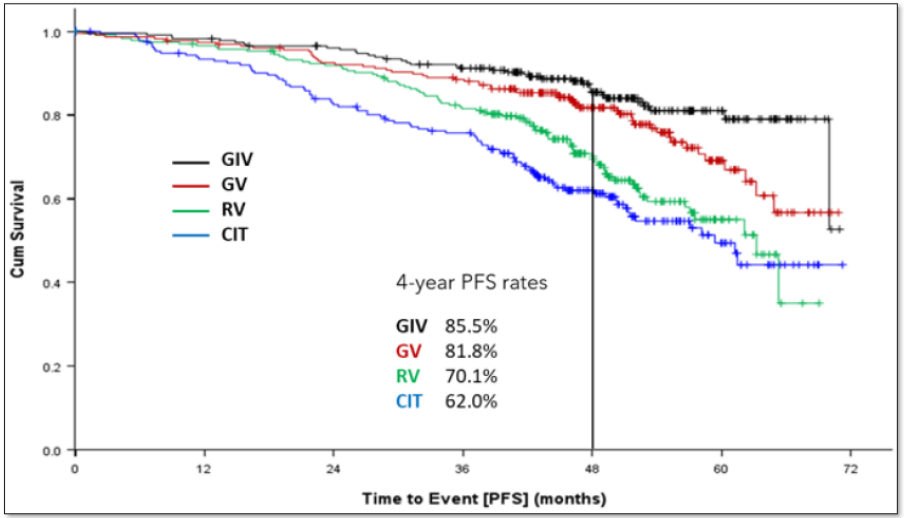
Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

GV = venetoclax-obinutuzumab; CIT = chemoimmunotherapy; GIV = GV + ibrutinib; RV = ven-rituximab; FCR = fludarabine-cyclophosphamide-rituximab.

Fürstenau M, et al. Presented at: ASH Annual Meeting; Dec 10, 2023; San Diego, CA. 635.

CLL13/GAIA 4 Yr PFS

- Median observation time: 50.7 months



PFS comparisons

GIV vs **CIT**: HR 0.30, 97.5% CI 0.19-0.47, **p<0.001**

GIV vs **RV**: HR 0.38, 97.5% CI 0.24-0.59, **p<0.001**

GIV vs **GV**: HR 0.63, 97.5% CI 0.39-1.02, p=0.03

GV vs **CIT**: HR 0.47, 97.5% CI 0.32-0.69, **p<0.001**

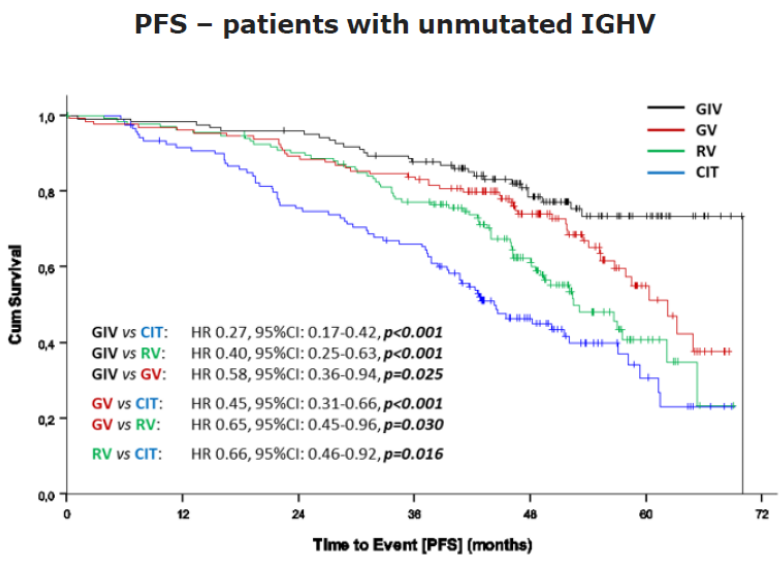
GV vs **RV**: HR 0.57, 97.5% CI 0.38-0.84, **p=0.001**

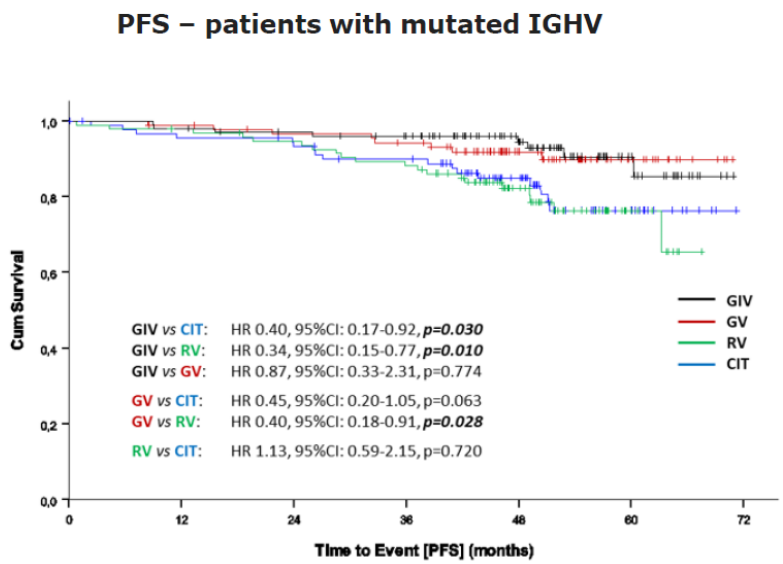
RV vs **CIT**: HR 0.78, 97.5% CI 0.55-1.10, **p=0.1**

Obinutuzumab regimens statistically significantly improve PFS

Fürstenau M, et al. Presented at: ASH Annual Meeting; Dec 10, 2023; San Diego, CA. 635.

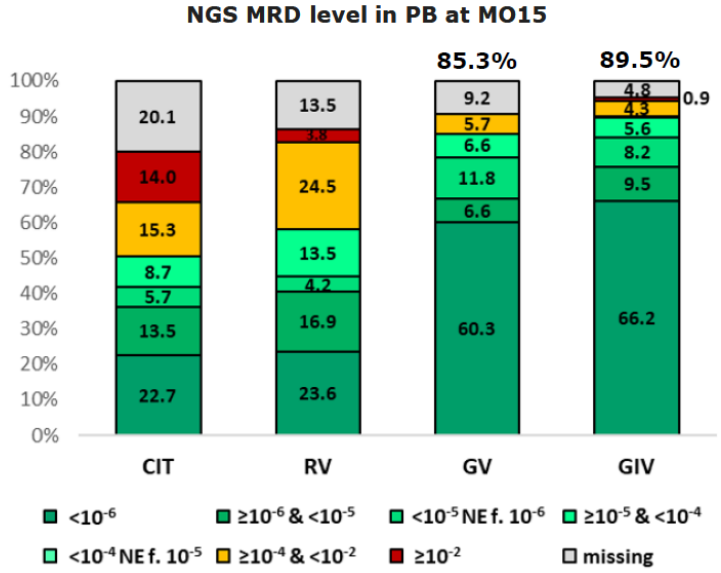
PFS Benefit of GIV Currently Restricted to uIGHV Subtype

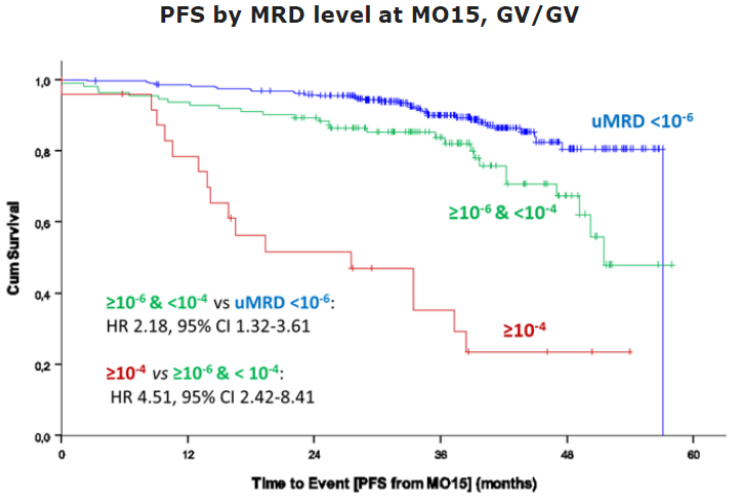




Fürstenau M, et al. Presented at: ASH Annual Meeting; Dec 10, 2023; San Diego, CA. 635.

CLL13/GAIA and MRD Outcomes

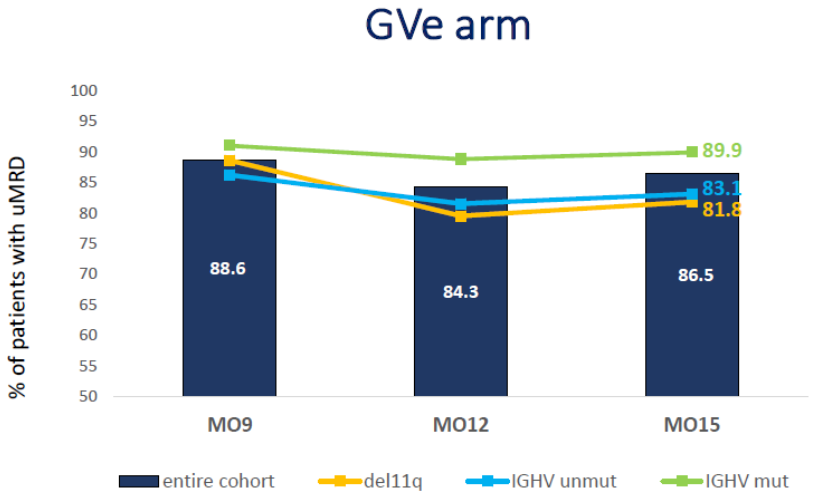


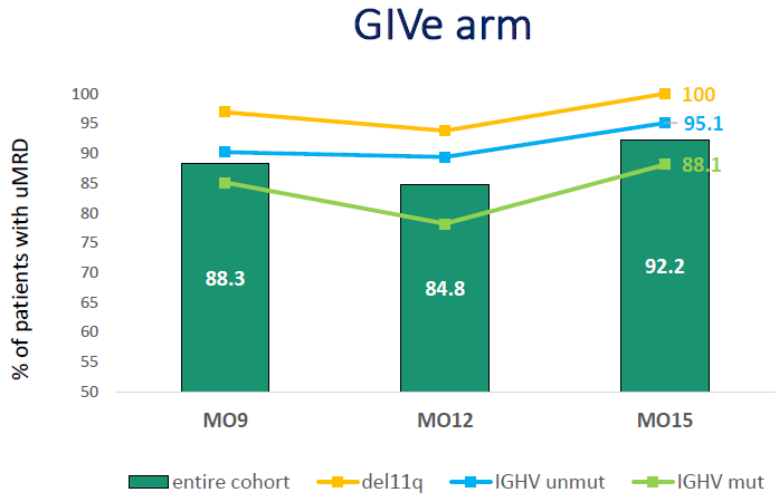


	CLL14 VenG	GLOW I+V	CAPTIVATE I+V
EoT+3	40% 1x10^{-6} 74% 1x10^{-4}	43.5% 1x10^{-5} 54.7% 1x10^{-4}	57% 1x10^{-4}

Fürstenau M, et al. Presented at: ASH Annual Meeting; Dec 10, 2023; San Diego, CA. 635.

Differential uMRD Rates for uIGHV and Del 11q with Addition of BTKi





Fürstenau M, et al. Presented at: ASH Annual Meeting, December 11, 2021; Atlanta, GA.

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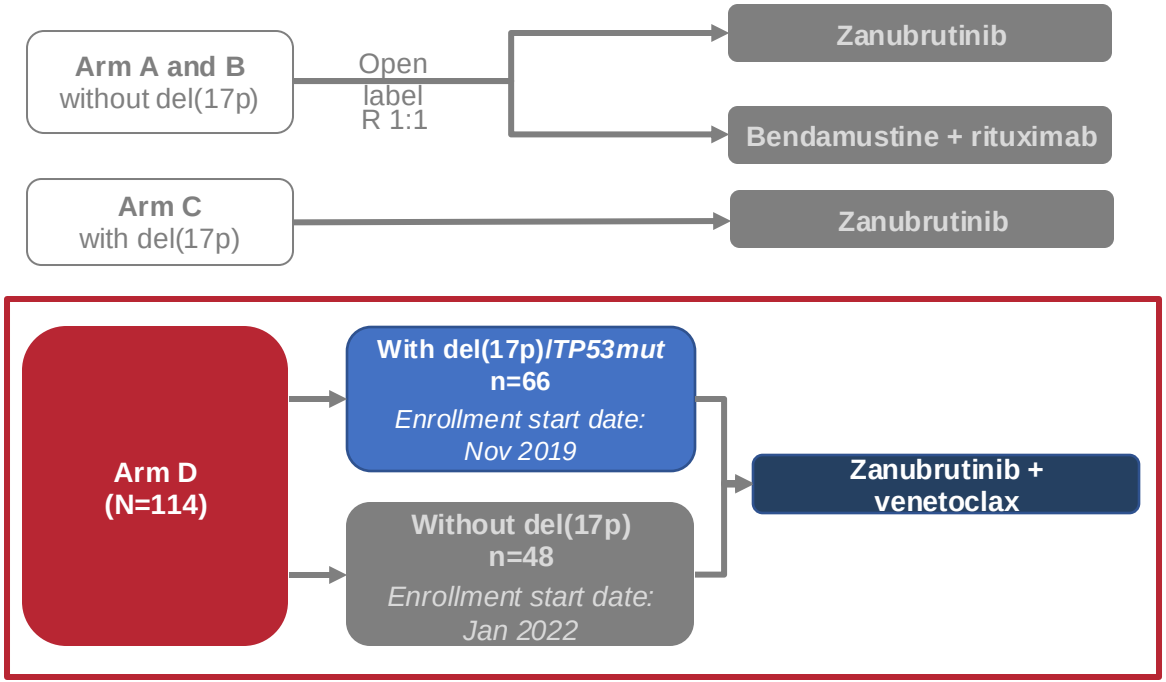
SEQUOIA Study Design: Arm D Cohort with del(17p) and/or *TP53mut*

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT/MRI
- For Arm D: central confirmation of del(17p) by FISH and/or local *TP53* mutation



Endpoints for Arm D

- ORR (INV)[a]
- PFS (INV)
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety per CTCAE
- Pharmacokinetics

[a] Reponses assessed per modified iwCLL criteria for CLL and Lugano criteria for SLL.
CTCAE = Common Terminology Criteria for Adverse Events; FISH = fluorescence in situ hybridization.
Ghia P, et al. Presented at: EHA 2024; June 13, 2024; Madrid, Spain. S160.

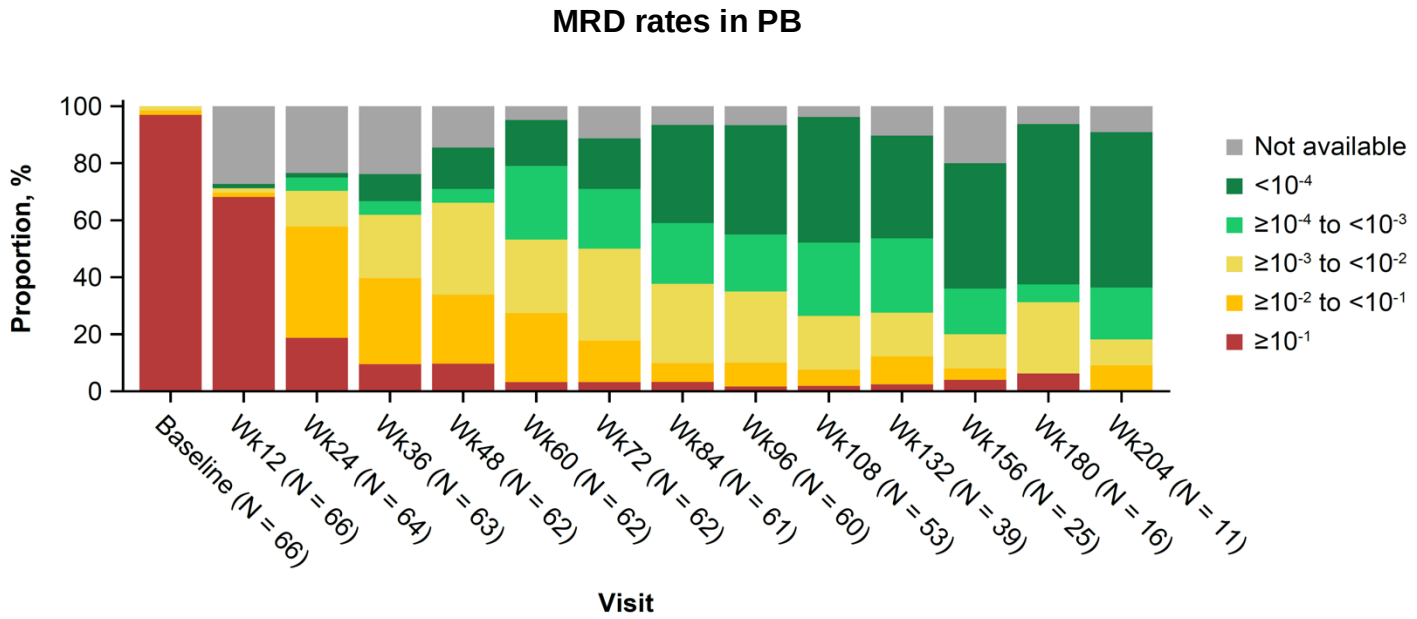
SEQUOIA Arm D Included Only a High-risk Population

Characteristic	Zanubrutinib + venetoclax (n=66)
Age, median (range), years	66 (26-87)
≥65 years, n (%)	36 (55)
Male sex, n (%)	34 (52)
White race, n (%)	58 (88)
ECOG performance status, n (%)	
1	32 (48)
2	2 (3)
SLL, n (%)	3 (5)
Bulky disease, n (%)	
Any target lesion LDi ≥5 cm	29 (44)
Any target lesion LDi ≥10 cm	5 (8)
Genotype status, n (%)	
del(17p) positive and/or *TP53* mutated	66 (100)
del(17p) positive and *TP53* mutated	42 (64)
del(17p) positive and *TP53* unmutated	17 (26)
del(17p) negative and *TP53* mutated	7 (11)
Unmutated IGHV	56 (85)
Complex karyotype, n (%)	
≥3 abnormalities	33 (50)
≥5 abnormalities	24 (36)
del(17p) % of abnormal nuclei, median (range)	60.5 (1-98)

LDi = longest diameter.

Ghia P, et al. Presented at: EHA 2024; June 13, 2024; Madrid, Spain. S160.

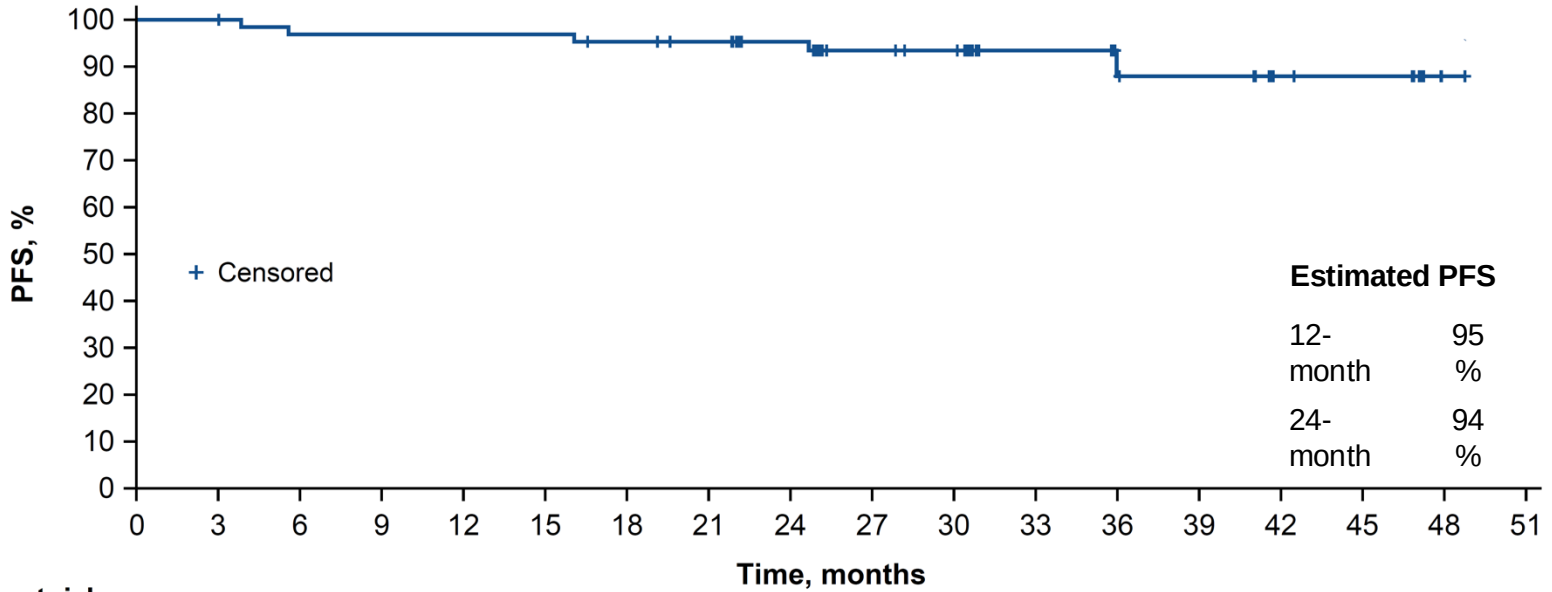
Rates of uMRD in PB Increased with Longer Treatment Duration



Best uMRD rate: 59% (39/66) in ≥1 PB sample; 37% (13/35) in ≥1 BM sample; [a] CAPTIVATE EOT W60 and EOT +3 W72 best uMRD in PB 55%

Ghia P, et al. Presented at: EHA 2024; June 13, 2024; Madrid, Spain. S160.

With Median Study Follow-up of 31.6 Months, Median PFS Was Not Reached



No. of patients at risk

Zanubrutinib	65	65	62	62	62	62	60	58	51	37	35	22	16	15	10	9	1	0

Ghia P, et al. Presented at: EHA 2024; June 13, 2024; Madrid, Spain. S160.

AMPLIFY Press Release July 2024

- "Fixed-duration [acalabrutinib] plus venetoclax, with or without obinutuzumab, significantly improved progression-free survival in 1st-line chronic lymphocytic leukaemia in AMPLIFY Phase III trial"

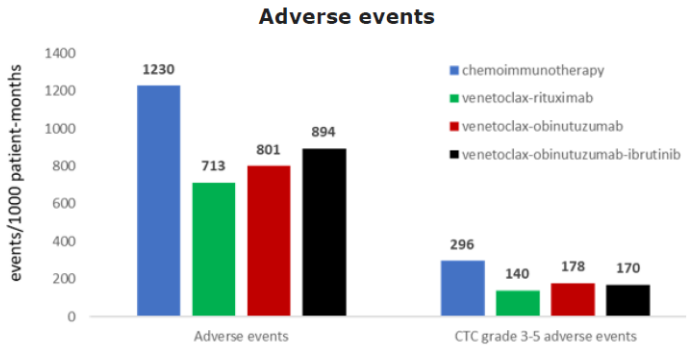
***BusinessWire*. July 29, 2024. Accessed Sept 27, 2024. https://tinyurl.com/4zm28vjt.**

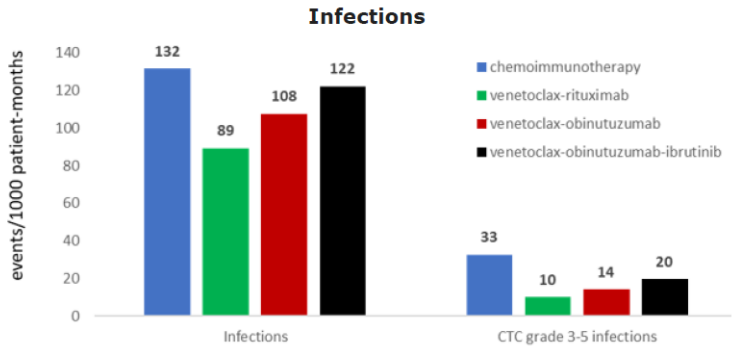
Ongoing Combination Studies in Frontline CLL

NCT#	Phase	Trial Arms	N	Primary Endpoint
NCT04608318	3	Ibr vs I+V vs VenG	897	PFS
NCT03737981	3	IbrG vs IVG	454	PFS
NCT03701282	3	IbrG vs IVG	720	PFS
NCT03836261	3	AcalaVen vs AVG vs FCR/BR	984	PFS
NCT05057494	3	AcalaVen vs VenG	750	PFS
NCT05197192	3	AVG vs VenG	650	PFS
NCT03336333	2	ZanuVen in del17p	86	MRD
NCT04639362	2	I+V + Obin consolidation if MRD+	85	MRD
NCT05650723	2	Once-daily ZanuVen ZanuVenG consolidation if MRD+	50	MRD
NCT05677919	2	PirtoVen with extension of therapy if MRD+	45	MRD
NCT05536349	2	PirtoVenG triplet FD	60	MRD

Safety and Retreatment

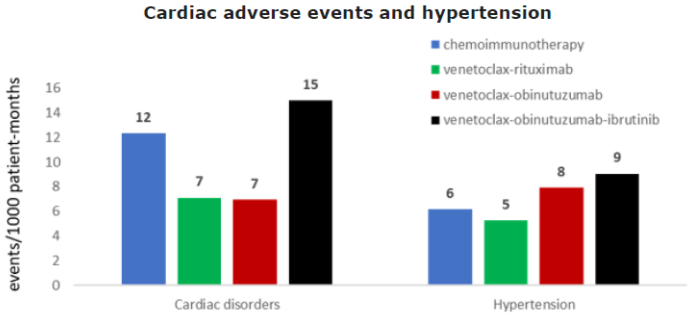
CLL13/GAIA: Safety





Exposure-adjusted incidence rates:

- Events per 1000 patient-months **based on the treatment period.**
- Treatment period = **start of treatment until the end of treatment + 84 days** or until start of first subsequent treatment whichever occurred first.



Fürstenau M, et al. Presented at: ASH Annual Meeting; Dec 10, 2023; San Diego, CA. 635.

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Safety Profile: CLL13

Adverse Events ≥ CTC Grade 3 Overview

Severe AEs occurring in ≥5% of pts and AEs of interest independent from incidence

	CIT	RVe	GVe	GIVe
All patients [SP]	**216**	**237**	**228**	**231**
Anemia	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)
Neutropenia	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)
Thrombocytopenia	22 (10.2)	10 (4.2)	42 (18.4)	37 (16.0)
Febrile neutropenia	**24 (11.1)**	**10 (4.2)**	**7 (3.1)**	**18 (7.8)**
Infections	**43 (19.9)**	**27 (11.4)**	**32 (14.0)**	**51 (22.1)**
Tumor lysis syndrome*	**9 (4.2)**	**24 (10.1)**	**20 (8.8)**	**15 (6.5)**
Bleeding events	1 (0.5)	1 (0.4)	1 (0.4)	4 (1.7)
Atrial fibrillation	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)
Pts completed treatment (%)	**176 (81.5%)**	**219 (92.4 %)**	**214 (93.9%)**	**197 (85.3%)***
Reduced dose intensity (%)	**32 (14.8%)**	**44 (19.3%)**	**47 (21.5%)**	**81# (36.5%)**

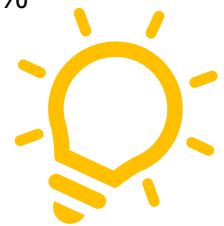
CAPTIVATE Grade 3 AEs

Neutropenia: ~34%

Febrile neutropenia ~1%

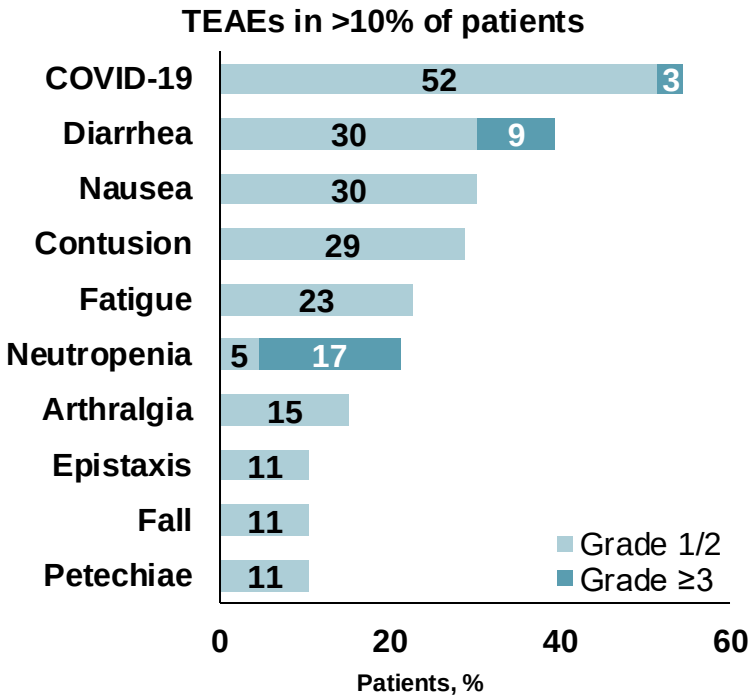
Infections ~6%

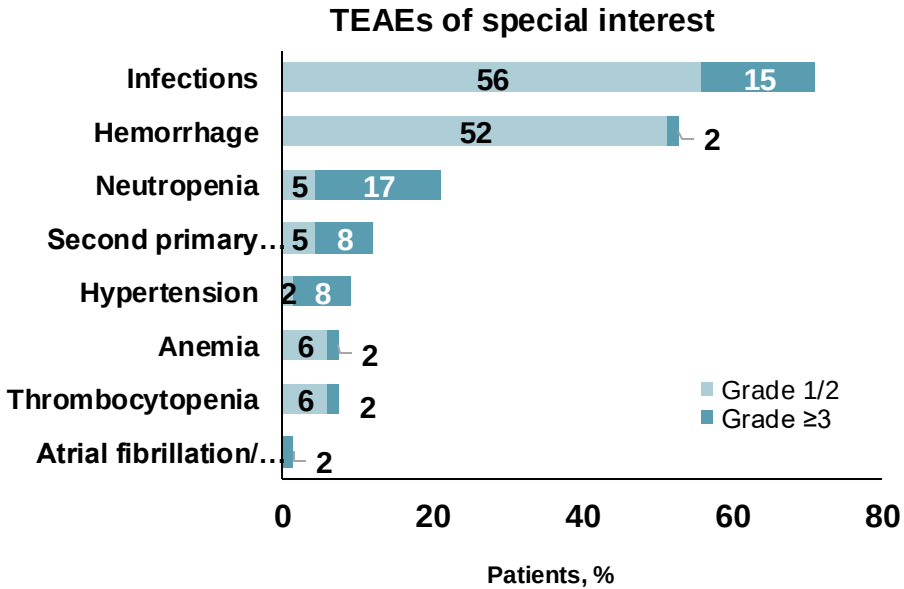
TLS ~<1%



Eichhorst B, et al. *Blood.* 2021;138(Suppl 1):71.

Safety Summary SEQUOIA Arm D

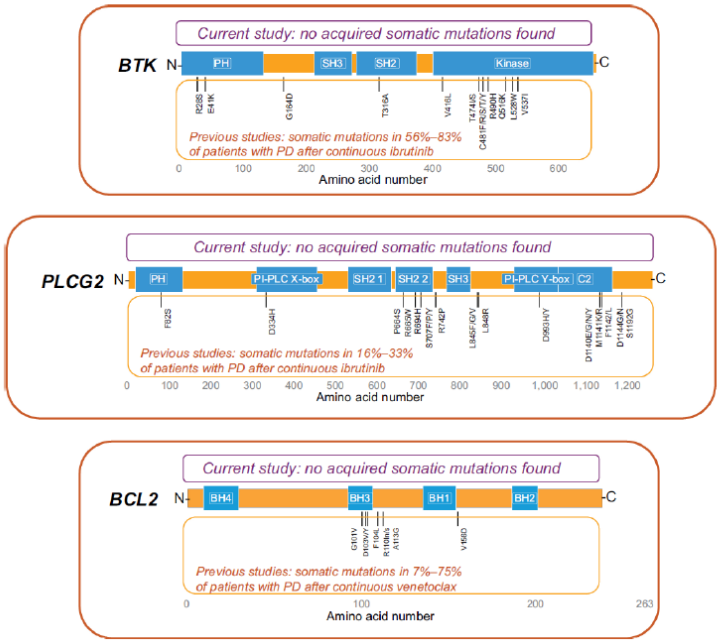




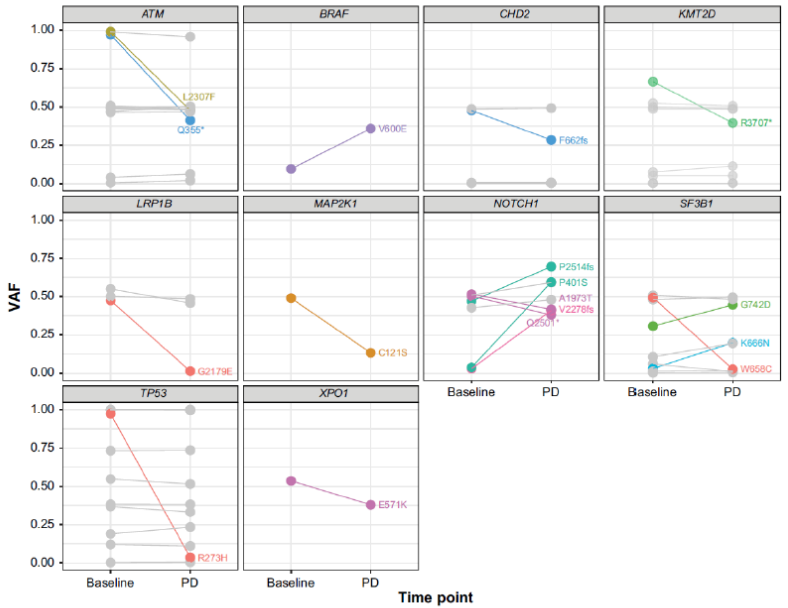
[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
TEAE = treatment-emergent adverse event.
Ghia P, et al. Presented at: EHA 2023; June 8, 2023; Frankfurt, DE. P617.

CAPTIVATE: No Acquisition of BTK/PLCG2/BCL2 Mutations

Mutational sites analyzed in 29 PD patients with matched samples



Among 20 of 29 evaluable subjects, 55% had VAF changes of 10% or greater, only 7 of 17 changing variants increased at PD



VAF = variant allele frequency.

Jain N, et al. *Clin Cancer Res.* 2024;30(3):498-505.

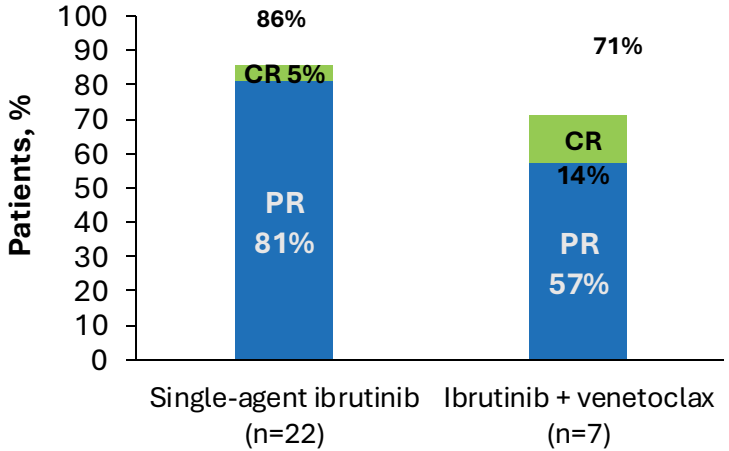
Responses Observed with Ibrutinib-Based Retreatment

- Of 61 patients with CLL PD after completion of fixed-duration ibrutinib + venetoclax, 32 (52%) initiated retreatment with single-agent ibrutinib (n=25) or ibrutinib + venetoclax (n=7)
- Median time on retreatment on study
  - 21.9 months (range, 0.0–50.4) for single-agent continuous ibrutinib
  - 13.8 months (range, 3.7–15.1) for 15-month fixed-duration ibrutinib + venetoclax

Study Entry Baseline Characteristics: Retreated Patients

Characteristic	Single-agent ibrutinib (n=25)	Ibrutinib + venetoclax (n=7)	All Retreated Patients (n=32)
Median age (range), years	56 (39–71)	63 (49–69)	59 (39–71)
Male, n (%)	15 (60)	6 (86)	21 (66)
Rai stage III/IV, n (%)	4 (16)	2 (29)	6 (19)
High-risk genomic features, n (%) Unmutated IGHV del(17p)/mutated TP53 del(11q)[d] Complex karyotype[e]	20 (80) 5 (20) 6 (24) 9 (36)	5 (71) 5 (71) 1 (14) 2 (29)	25 (78) 10 (31) 7 (22) 11 (34)
Bulky LN disease ≥5 cm, n (%)	10 (40)	1 (14)	11 (34)

Best Response in Evaluable Patients to Date[c]



[a]Per protocol, only patients with PD >2 years after completion of treatment were eligible to reinitiate ibrutinib + venetoclax. [b]Four patients exited the study during ibrutinib + venetoclax retreatment and completed retreatment off study. [c]Three patients who initiated single-agent ibrutinib retreatment had not yet undergone response assessment. [d]Without del(17p) per Döhner hierarchy. [e]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

Wierda WG, et al. *JCO.* 2024;42:7009-7009.

Key Learning Points

- Time limited approaches can provide high rates of response, uMRD, and durable treatment free remissions
- Triplet therapy may improve depth of remissions and subsequent pfs particularly for higher risk patients (Del11q, uIGHV)
- Toxicity appears increased with triplet therapy as compared to oral doublets or Veng when evaluating infections, neutropenia, and completion of therapy
- PFS and OS appear comparable to current VenG time limited therapy and has advantage of debulking and ease of initiation
- Currently progressors after I+V have not shown acquisition of resistance mutations and retreatment with single agent BTKi or doublet therapy is feasible.
- We await H2H trials evaluating current standards and doublets vs triplets

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How Should We Be Using Measurable Residual Disease (MRD) Data?

Andy Rawstron

Haematological Malignancy Diagnostic Service
Leeds Cancer Centre

Disclosures

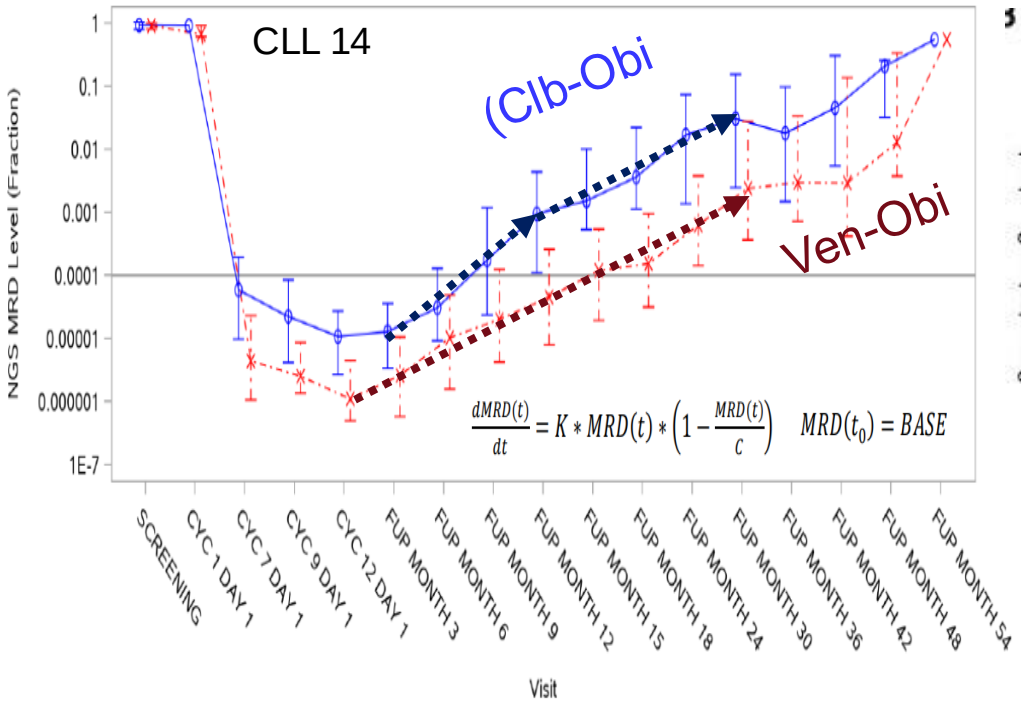
- **Andy Rawstron:** Advisory board – AbbVie, Beigene, Janssen, Roche; research/grant support – AbbVie, BD Biosciences, Beckman Coulter, Beigene, Celgene, Janssen, Pharmacyclics, Roche; honoraria – AbbVie, BD Biosciences, Beckman Coulter; Janssen; consultant – Beigene, Celgene, Pharmacyclics

Learning Objective

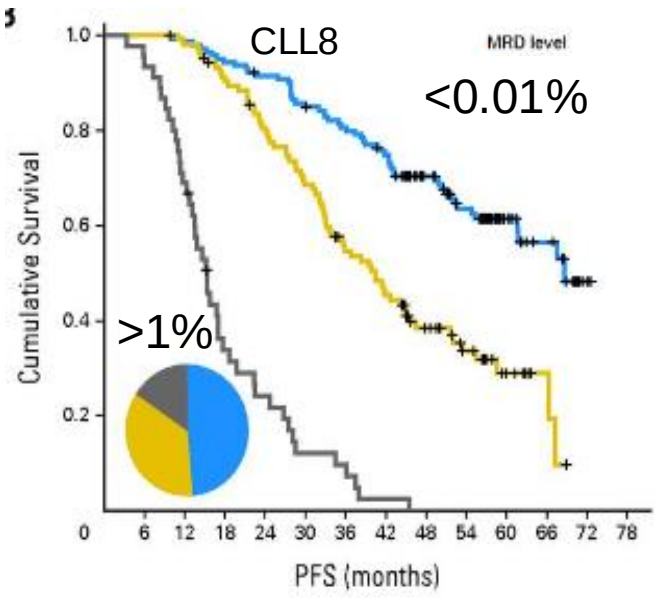
- Discuss the importance of MRD evaluation and molecular profiling for treatment selection and sequencing in CLL/SLL

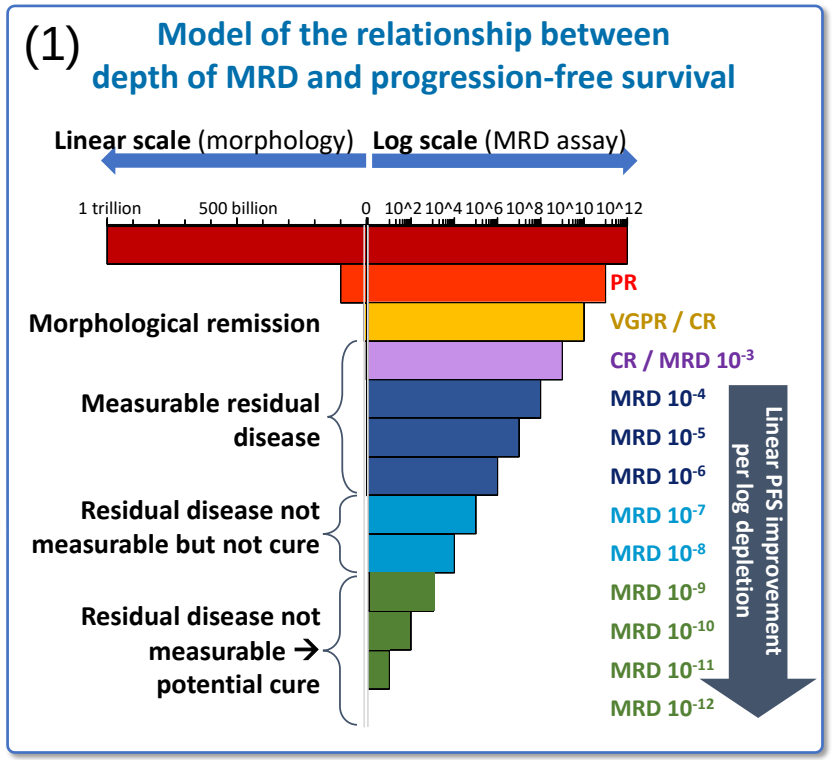
CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma.

MRD and Time to Progression: Linear Improvement in PFS per Log Depletion for Fixed Duration Treatment



Time to progression depends on disease level at end of treatment (BASE) and growth rate (K)

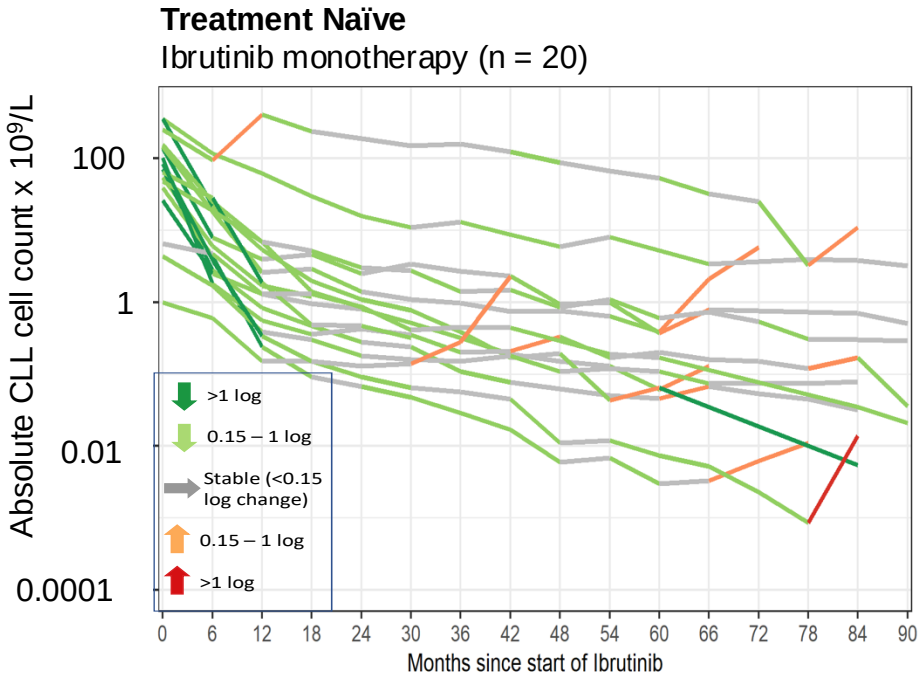




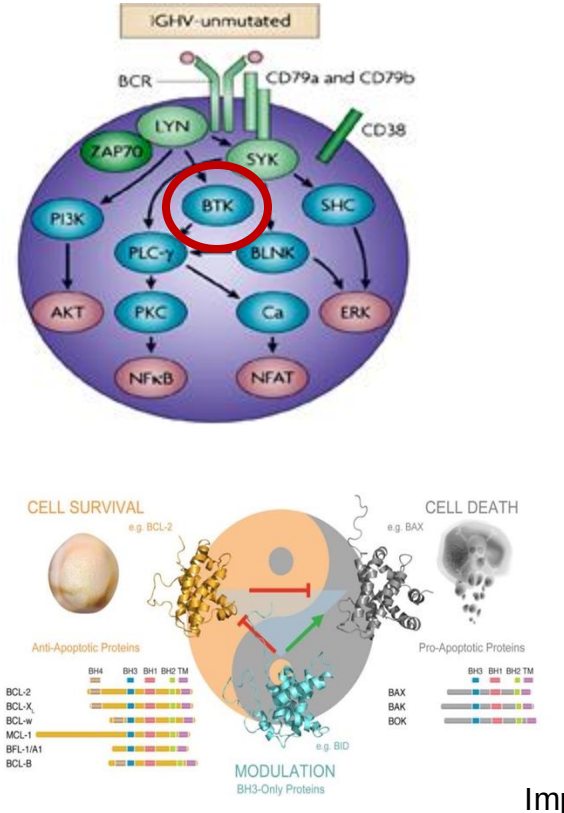
(1)Content represents the speaker's own opinion and not published data.
PFS = progression free survival; Clb = chlorambucil; Obi = Obinutuzumab; Ven = venetoclax. FCR = fludarabine, cyclophosphamide, rituximab; CIT = chemoimmunotherapy; VGPR = very good partial response; CR = complete response.
al-Sawaf O, et al. *J Clin Oncol*. 2021;39(36):4049-4060. Bottcher, et al. *J Clin Oncol*. 2012;30(9):980-8.

MRD Kinetics with Targeted Agents

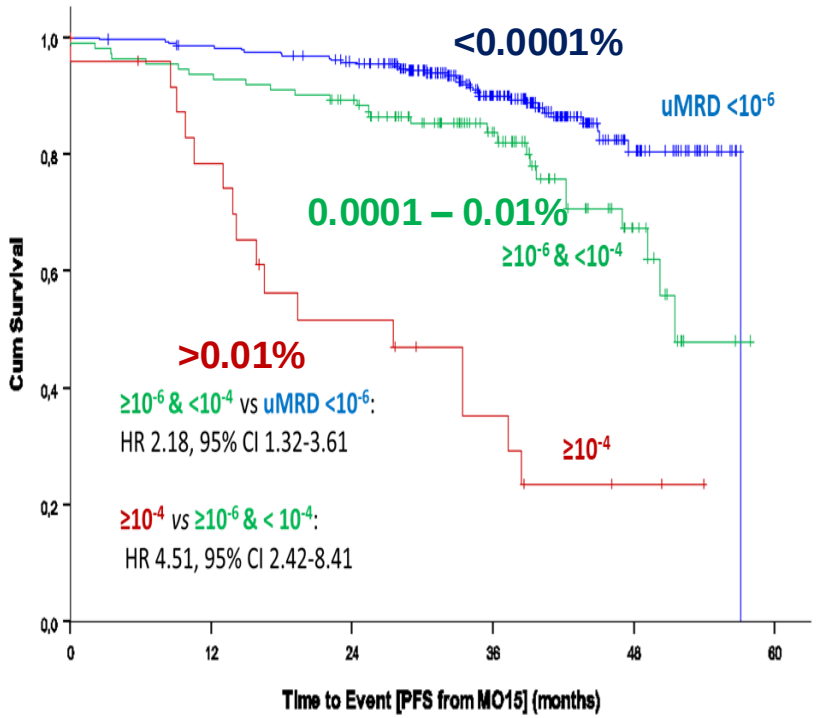
B-cell receptor inhibitors (BTKi): prolonged remission with persistent detectable disease – **MRD is irrelevant**



TN CLL BTKi monotherapy IcICLLe trial: 1-2 log reduction in first year with gradual depletion (~0.2log/year) after



BCL2-pathway inhibitors (BCL2i): **deep** (<1 CLL cell per million) & **rapid** depletion in a high proportion of patients



Impact of MRD in first-line venetoclax combinations in CLL: 4-year follow-up from the phase 3 GAIA/CLL13 trial.

Rawstron AC, et al. *Blood*. 2016;128(22):2049. Fürstenau M, et al. *Lancet Oncol*. 2024;25(6):744-759.

BM uMRD4* (<0.01%) Is the IWCLL Threshold but MRD Is a Continuous Variable with Multiple Informative Thresholds, Not a Pos/Neg Test

- **Flow, qPCR, or ddPCR: MRD5**
  - Reference centers – several per country
  - Flow: Rapid turnaround, commercial kits available, but fresh samples only and operator dependent
  - dd/qPCR: Can use stored/batched DNA but it is a patient-specific assay that needs pre-treatment DNA
- **Next-gen sequencing (NGS): MRD6**
  - Highly sensitive, FDA-cleared, and IVDR commercial assays available
  - Needs pre-treatment DNA, some assays not quantitative and can be expensive

uMRD = undetectable MRD,
4 / 5 / 6 denotes $\log_{10}$ normal cells (denominator)

MRD status*	CLL cells per million total cells	Comments
>1% or “high MRD”	>10 thousand	High risk of progression within the following year
0.01-1% or “intermediate MRD”	100 – 10K	Intermediate risk of progression
<0.01% or uMRD4	<100	iwCLL guideline threshold (confirmed in BM)
uMRD5	<10	Technical target for confirmation of uMRD4
uMRD6	<1	Detection limit for FDA-approved HTS assay

*** Individual reports should include: Point estimate (CLL % of total cells); # total cells assessed or DNA equivalent, and assay limit of detection / quantitation (specific to assay and sample).**

Rawstron AC, et al. *Leukemia.* 2016;30(4):929-36. Van der Velden, et al. *Leukemia* 2007;21(4):604-11. Drandi, et al. *Methods Mol Biol.* 2018:1768:229-256. Ching, et al. *BMC Cancer.* 2020;20(1):612. Bottcher, et al. *J Clin Oncol.* 2012;30(9):980-988; Seymour, et al. *Blood.* 2022;140(8):839-850. Hallek, et al. *Blood.* 2018;131(25):2745-2760. FDA. Accessed Oct 11, 2024. https://www.fda.gov/media/134605/. FDA. Accessed Oct 11, 2024. https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-next-generation-sequencing-based-test-detect-very-low-levels-remaining-cancer.

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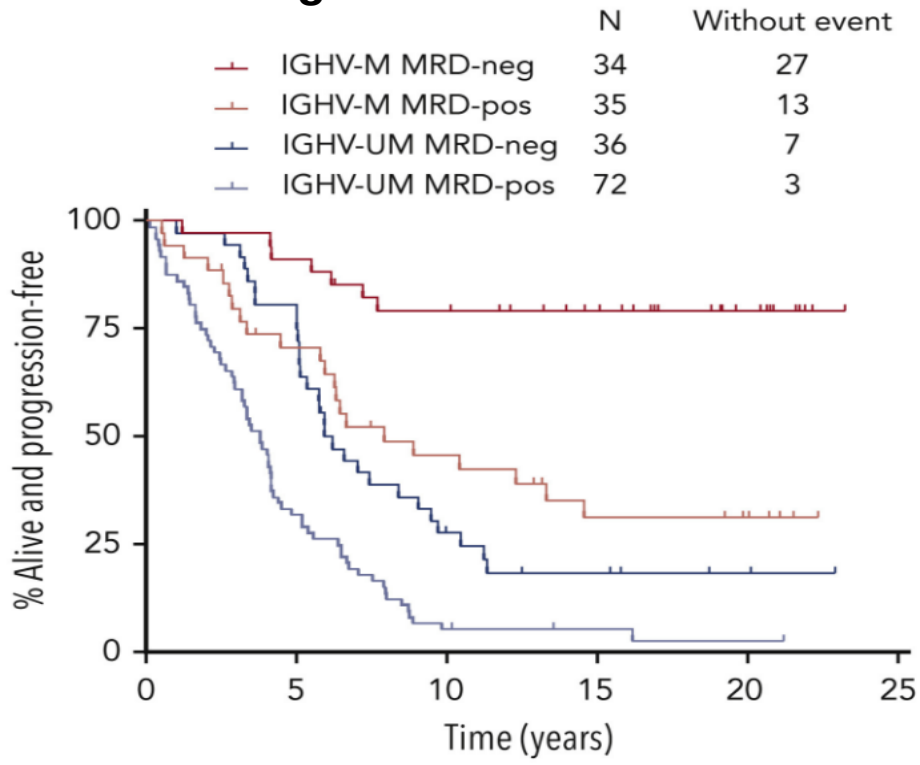
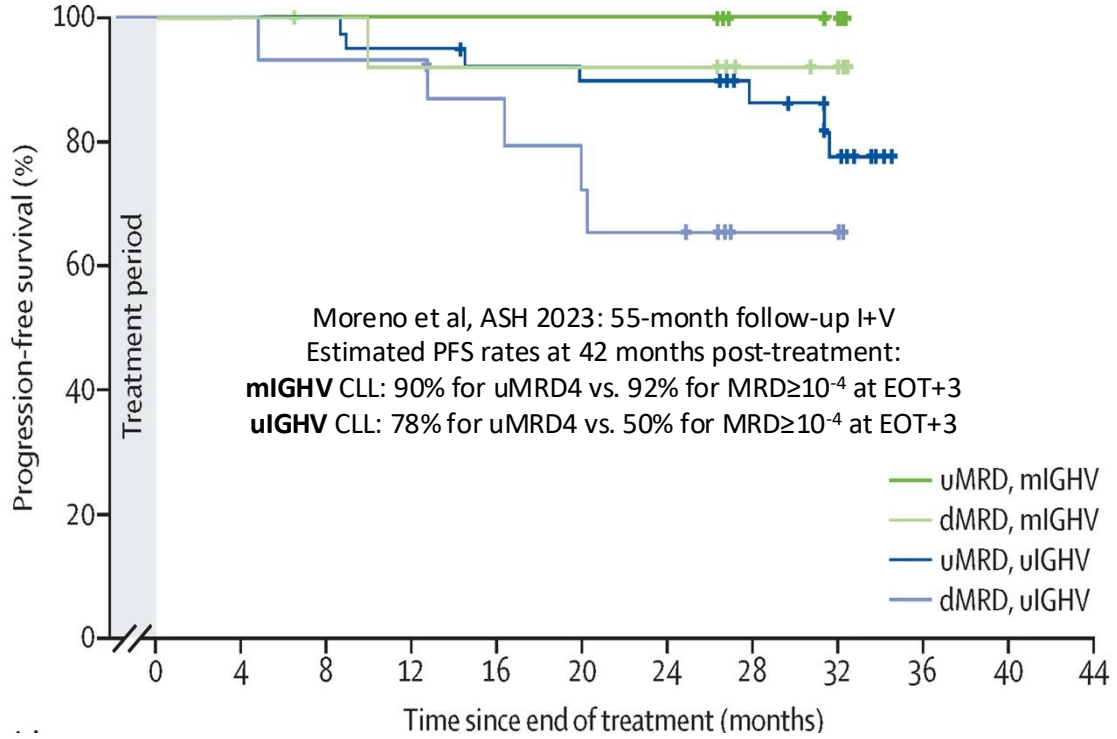
IGHV-Mutation Status: Different Implications for MRD in IGHV-Mutated (M-CLL) vs IGHV-Unmutated (U-CLL)

Sustained (>10yr) remission in some M-CLL achieving uMRD4 after CIT



Similar PFS for uMRD4 vs detectable MRD in M-CLL after fixed-duration IBR+VEN



IGHV = immunoglobulin heavy-chain variable region gene.

Thomson P, et al. *Blood.* 2023;142(21):1784-1788. Niemann CU, et al. *Lancet Oncol*. 2023;24(12):1423-1433. Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634.

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MRD in Combination with Molecular Profiling

MRD is an independent prognostic factor in CIT (1)

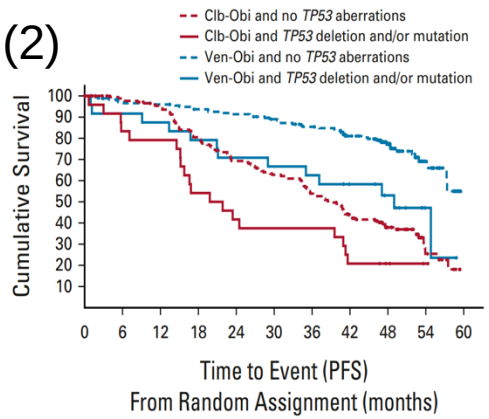
Table 2. Multivariable Analyses of the Effects of Prognostic Factors on PFS and OS as Assessed by End of Treatment Landmark

Variable	PFS HR	PFS 95% CI	PFS *P*	OS HR	OS 95% CI	OS *P*
Total CIRS score				1.21	1.05 to 1.39	.010
Age > 65 years				1.65	1.03 to 2.64	.038
Del(17p)	9.67	4.61 to 20.25	< .001	5.02	2.24 to 11.26	< .001
Del(11q)	1.32	1.00 to 1.75	.049			
IGHV unmutated	2.40	1.76 to 3.27	< .001	3.35	1.84 to 6.12	< .001
Treatment arm			.001			
FC *v* FCR	0.87	0.64 to 1.19	.387			
BR *v* FCR	1.63	1.18 to 2.24	.003			
Partial response	1.48	1.11 to 1.96	.007			
MRD positivity in PB	3.55	2.69 to 4.69	< .001	2.34	1.50 to 3.66	< .001

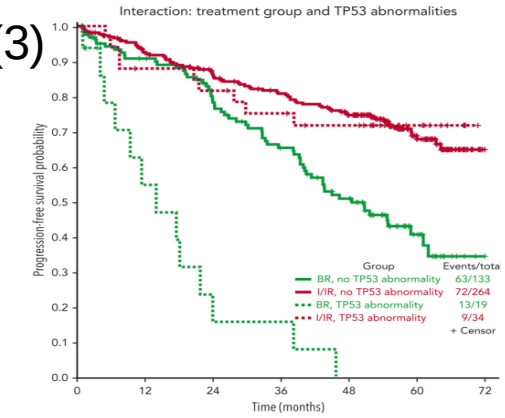
NOTE. Blank cells denote the lack of a significant association in multivariable analysis. Multivariable analyses for PFS and OS were performed on 515 and 516 patients, respectively, with all data available.
Abbreviations: BR, bendamustine plus rituximab; CIRS, cumulative illness rating scale; FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PFS, progression-free survival.

Continuous BTKi treatment may be preferable for CLL patients with TP53 abnormalities

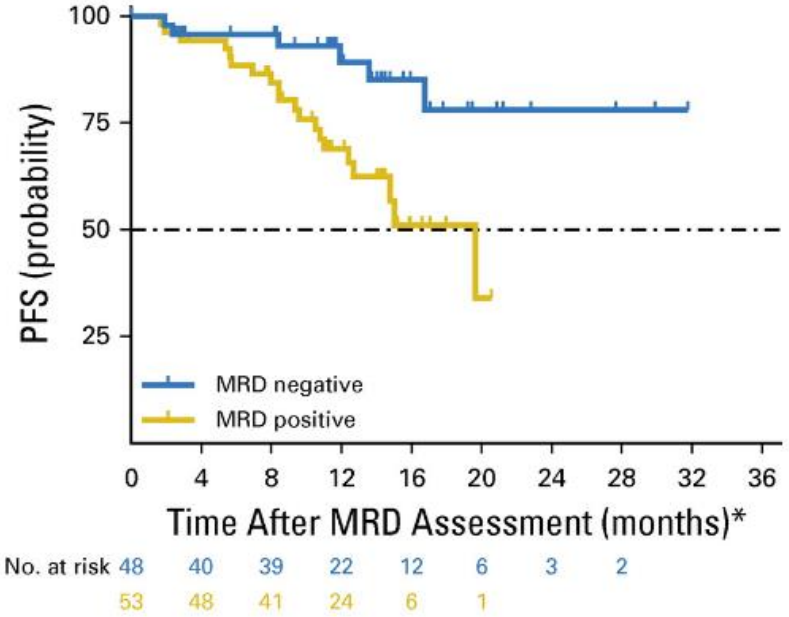
(2)



(3)



(3) VEN for TN/RR CLL with del(17p)



- BTK / PLCG2 mutations: Primarily in BTKi monotherapy trials – MRD not informative
- BCL2 mutations: Infrequent cause of resistance – insufficient events

R/R = relapsed/refractory; TN = treatment-naïve. B = bendamustine. I = ibrutinib. R = rituximab.

(1) Kovacs G, et al. *J Clin Oncol*. 2016;34(31):3758-3765 (2) al-Sawaf O, et al. J Clin Oncol. 2021;39(36):4049-4060; (3) Woyach J et al., Blood. 2024 Apr 18;143(16):1616-1627. (4) Stilgenbauer S, et al. *J Clin Oncol*. 2018;36(19):1973-1980.

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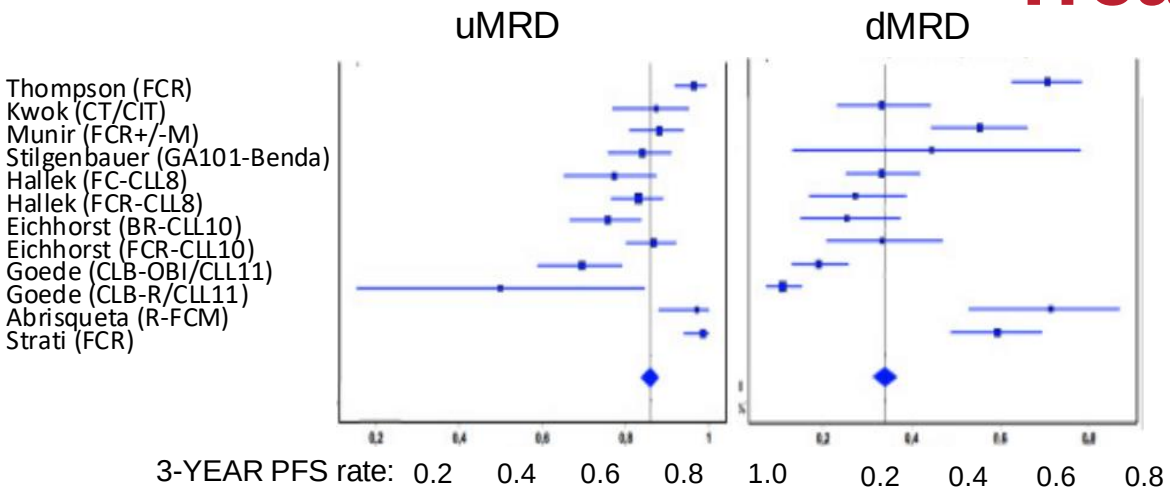
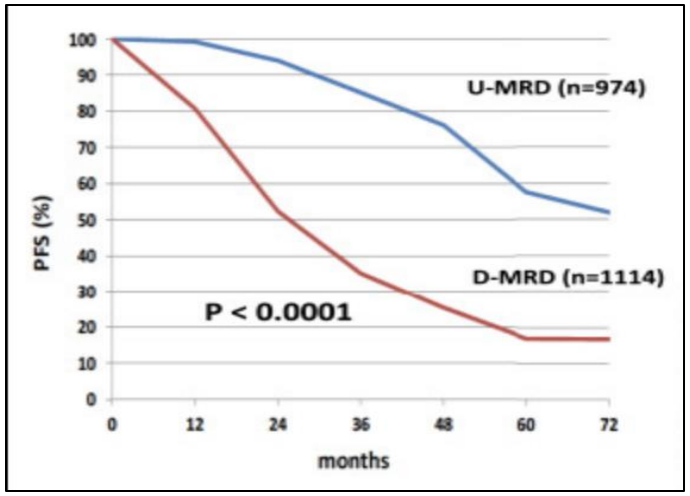
Meta-Analysis of MRD in CLL: Updated to Included Targeted Treatments





Study and Treatment	uMRD	dMRD	Hazard Ratio [95% CI]
MURANO, Ven + Ritux	93	56	0.28 [0.13, 0.60]
E1912, FCR	37	85	0.26 [0.09, 0.72]
iLLUMINATE, Chlb + Obinu	29	87	0.29 [0.14, 0.62]
iLLUMINATE, Ibr + Obinu	43	70	0.46 [0.20, 1.07]
HELIOS, Benda + Ritux	18	271	0.91 [0.47, 1.76]
HELIOS, Ibr + Benda + Ritux	76	213	0.55 [0.27, 1.15]
CLL-11, Chlb + Obinu	87	144	0.16 [0.08, 0.32]
GENUINE, Ibr + Ubli	27	37	0.11 [0.02, 0.49]
GAIA CLL-13, All treated patients	648	184	0.20 [0.14, 0.30]
GREEN, Benda + Obinu	94	64	0.19 [0.06, 0.58]
GLOW, Chlb + Obinu	18	87	0.52 [0.19, 1.38]
GLOW, Ibr + Ven	55	51	0.40 [0.09, 1.77]
RE Model (Q = 25.51, df = 11, p = 0.01; I^2 = 55.6%)			0.32 [0.22, 0.45]

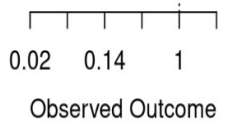
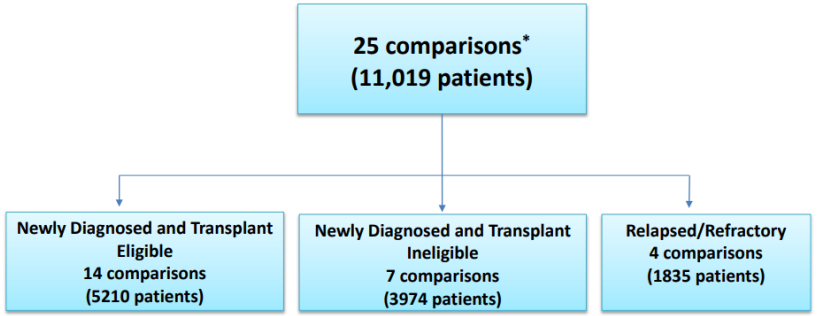


Figure 1. Forest plot of hazard ratios in individual studies for PFS

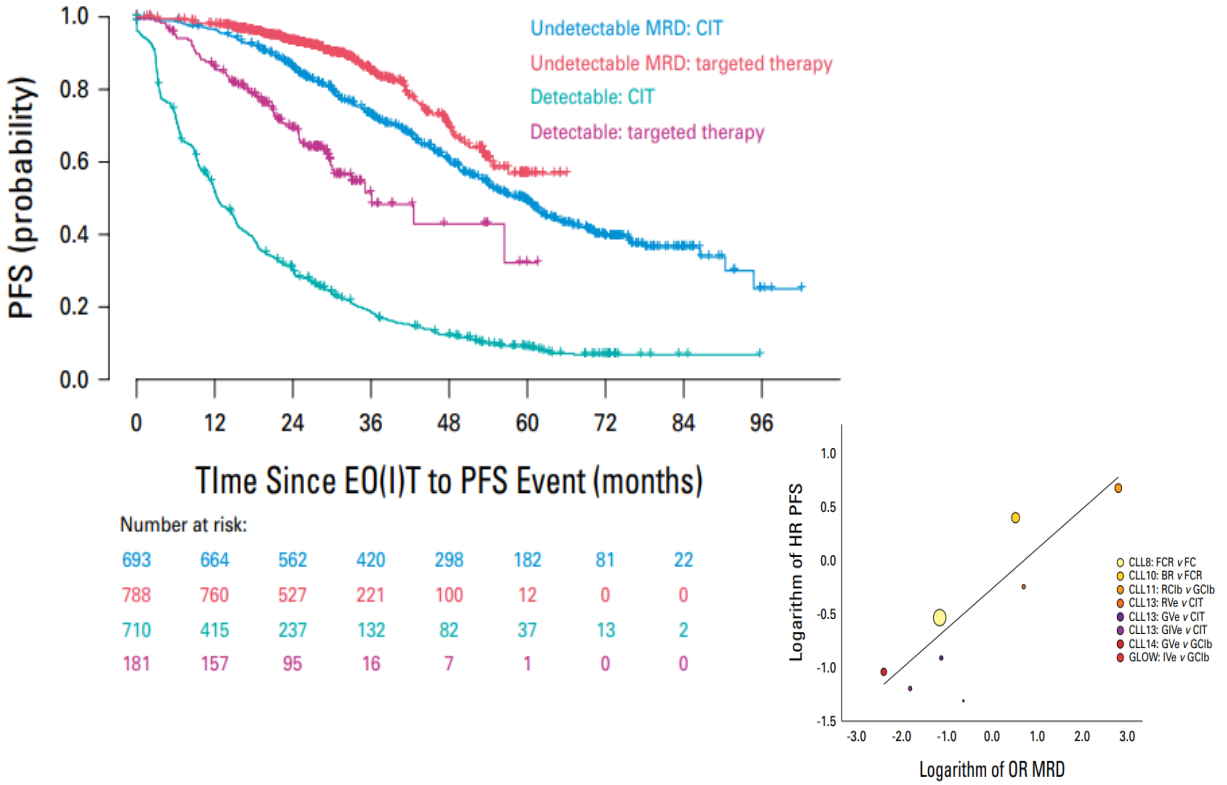
Molica S, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(7):423-430. Rios Olais FAA, et al. *Blood.* 2023:142(Suppl 1):1916. Rios-Olais FA, et al. *JAMA Oncol*. 2024;10(9):1221-1227.

MRD as a Regulatory Endpoint: Lessons from MM



- **"MRD-negative CR at 9 or 12 months"**
  - Lack of strong trial-level association for MRD and PFS/OS → *MRD is not a validated surrogate endpoint*
  - Strong individual-level association for MRD and PFS/OS → *MRD is prognostic*
- Does the evidence support the use of MRD as an accelerated approval endpoint in MM clinical trials? → **Vote 12:0 in favor**
  - April 12, 2024 Meeting of the Oncologic Drugs Advisory Committee Meeting

PB uMRD4 in CLL trials: patient-level correlation confirmed but while treatment-effect correlation remains uncertain.



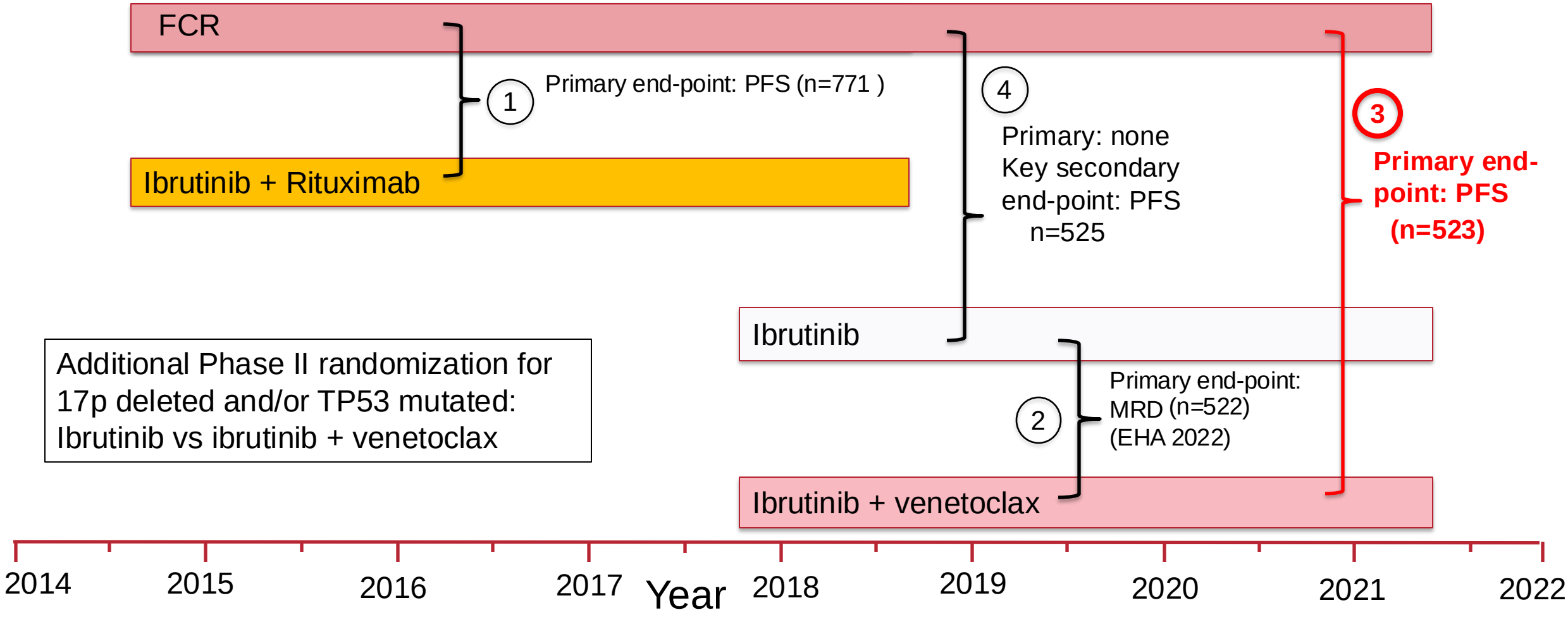
MM = multiple myeloma.

Simon F, et al. *J Clin Oncol*. 2024:JCO2401192. FDA. Accessed Oct 4, 2024. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024. al-Sawaf O, et al. *J Clin Oncol*. 2024:JCO2401192.

How Should We Be Using MRD Data?

- MRD for response assessment
  - Different thresholds have different implications: Curative time-limited treatment will require eradication below MRD6 / 1 CLL cell per million
  - Biological factors (IGHV) and treatment type affect depth/duration of MRD responses
  - Most trials have MRD as a primary or secondary endpoint. Individual patient-level data is prognostic and potentially applicable to accelerated drug approval

Adaptive Design of FLAIR



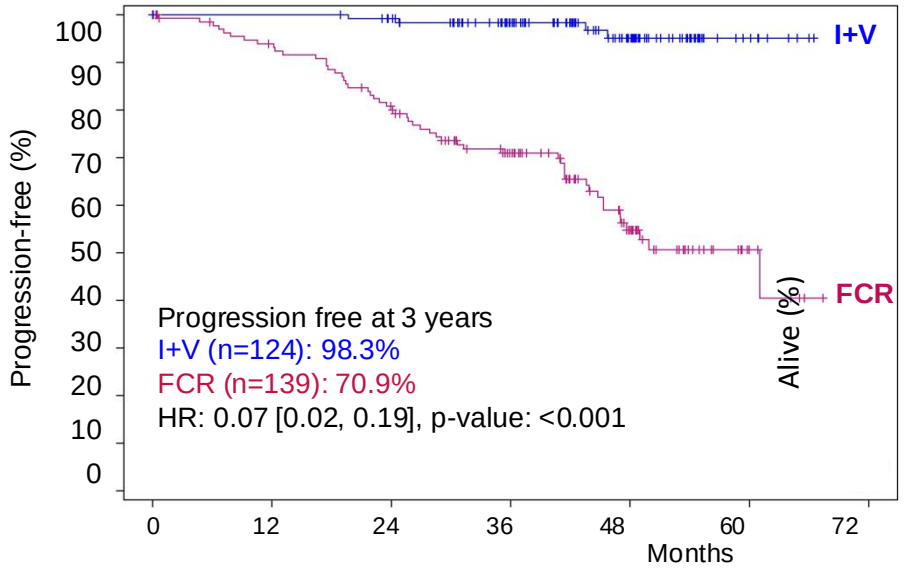
Hillmen P, et al. *Lancet Oncol*. 2023;24(5):535-552. Munir T, et al. *N Engl J Med*. 2024;390(4):326-337.

FLAIR: Outcome by IGHV Mutation Status

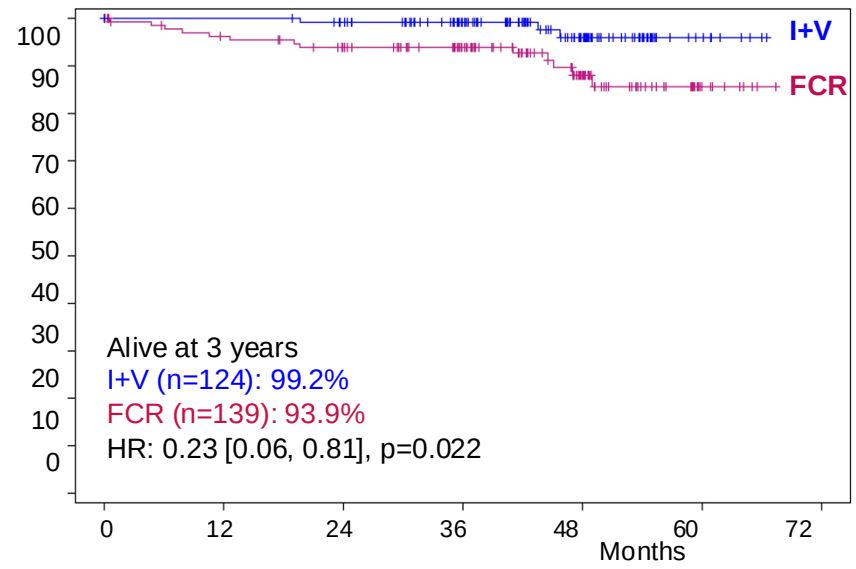
IGHV unmutated (excl. subset 2)

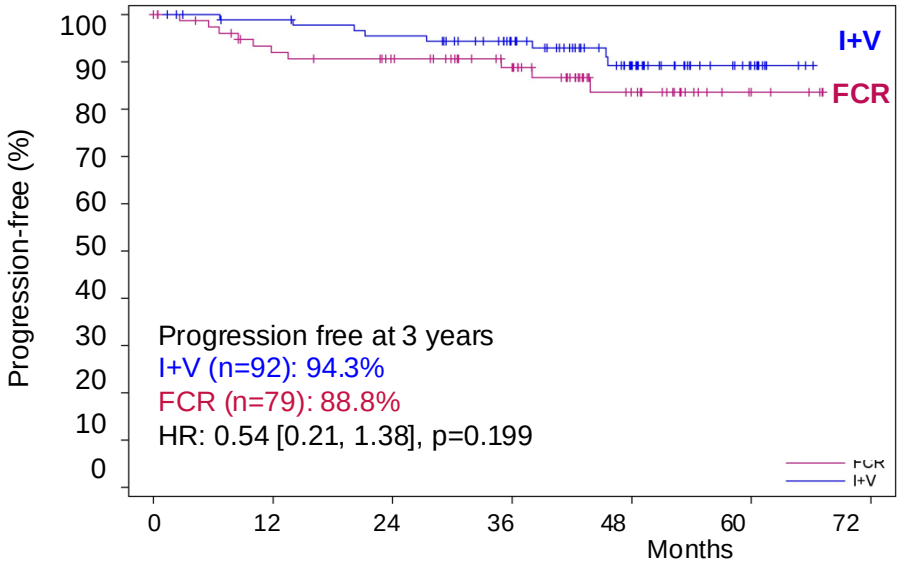
IGHV mutated (excl. subset 2)

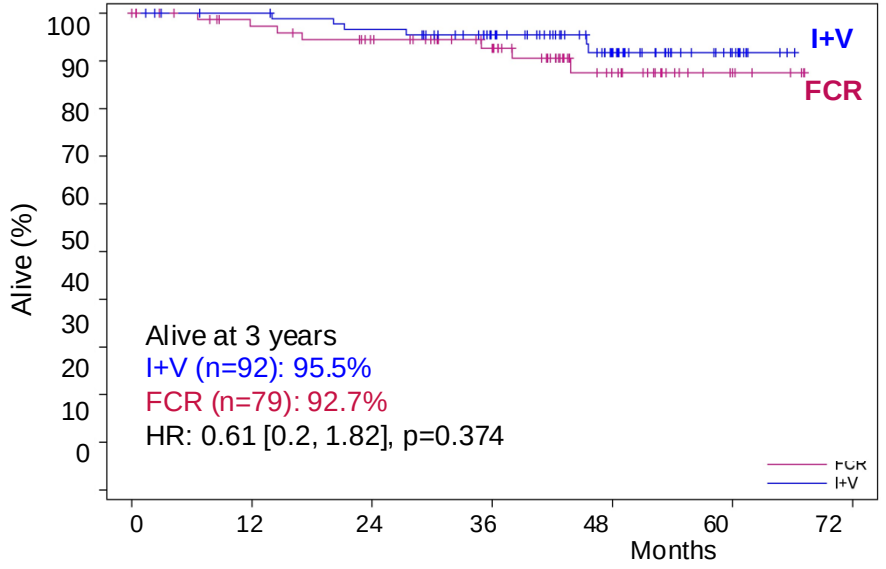
Progression Free Survival



Overall Survival

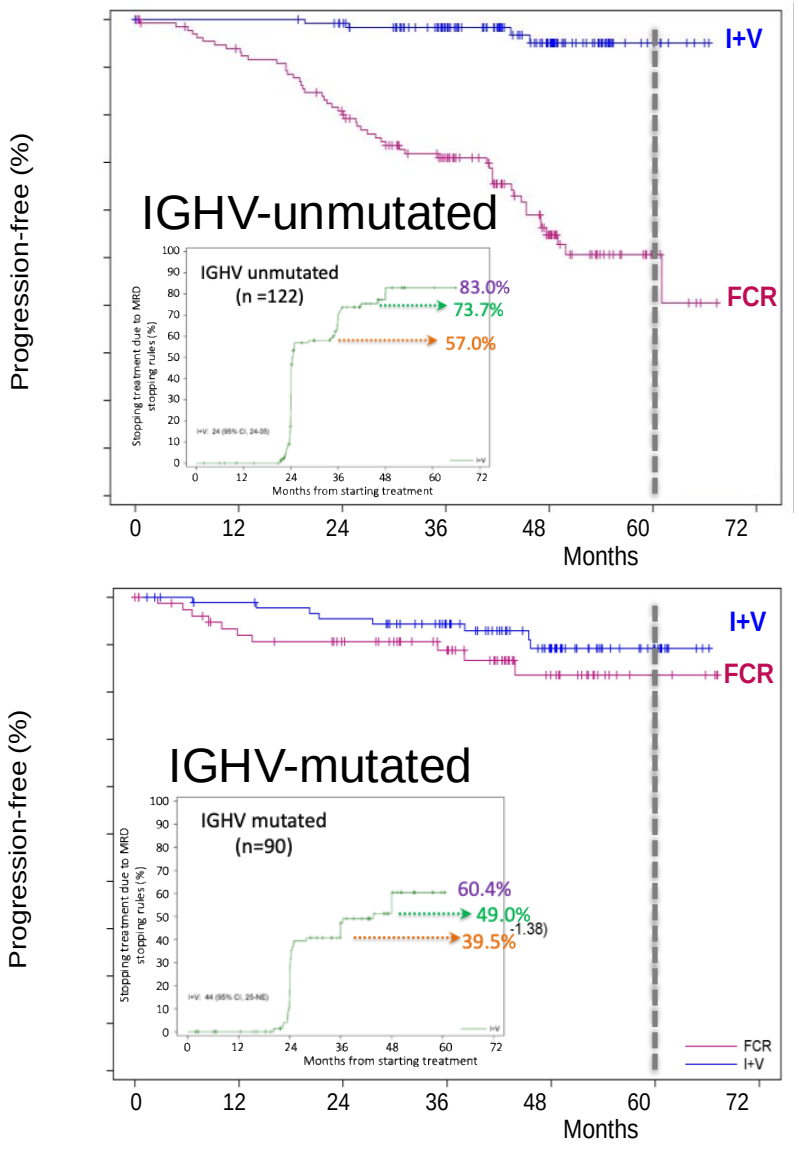






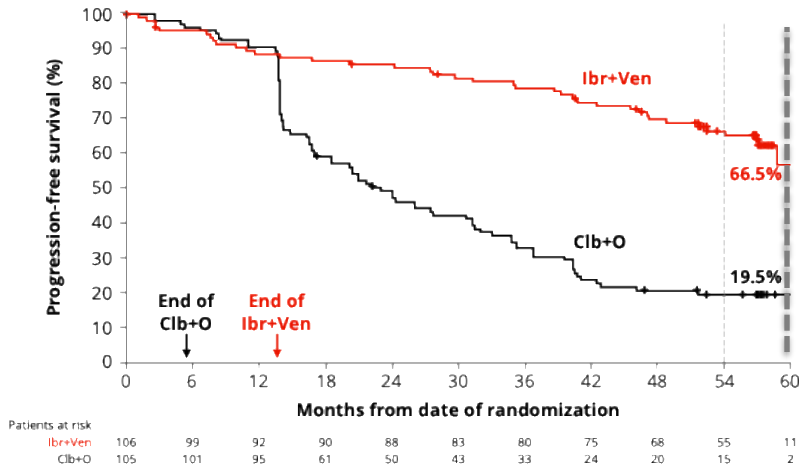
Munir T, et al. *N Engl J Med*. 2024;390(4):326-337.

MRD-driven I + V (FLAIR)

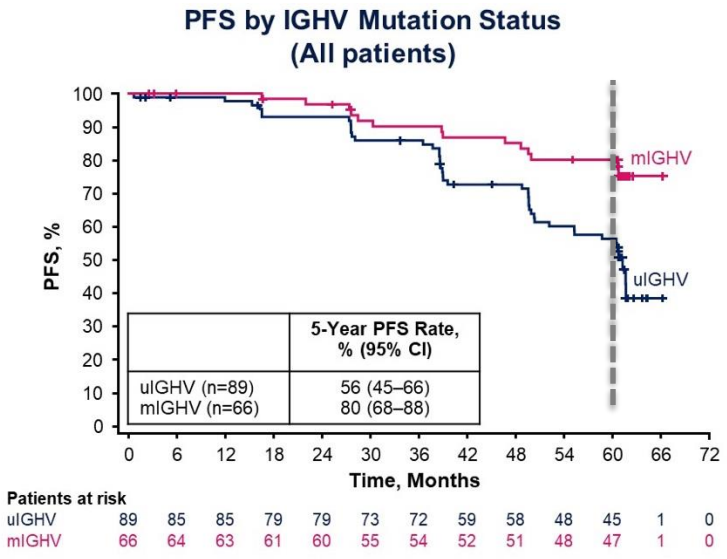


Fixed duration I + V

GLOW- Median FU 57 months

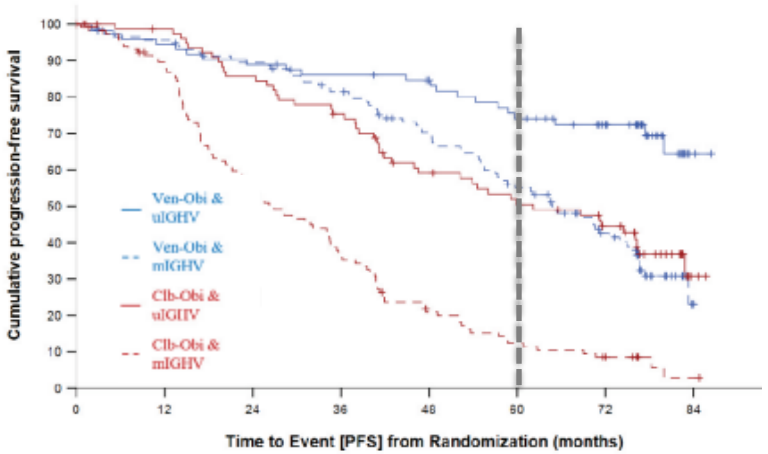


CAPTIVATE- Median FU 61.2 months

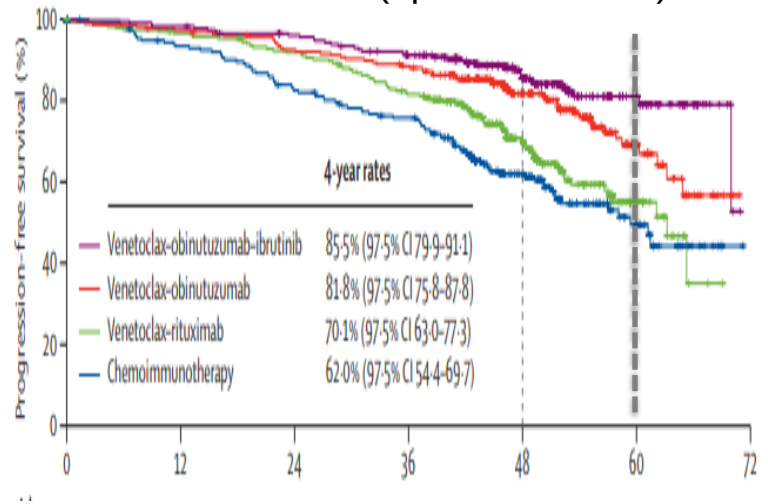


Fixed duration V+O

CLL14– PFS by IGHV status



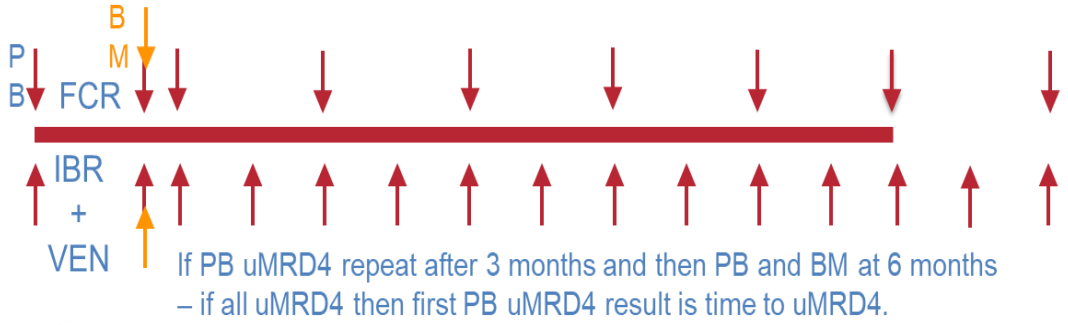
CLL13– OS for CIT, fixed duration Ven-Obi or Ven-R, and MRD-guided Ven-Ibr-Obi (up to 36 months)

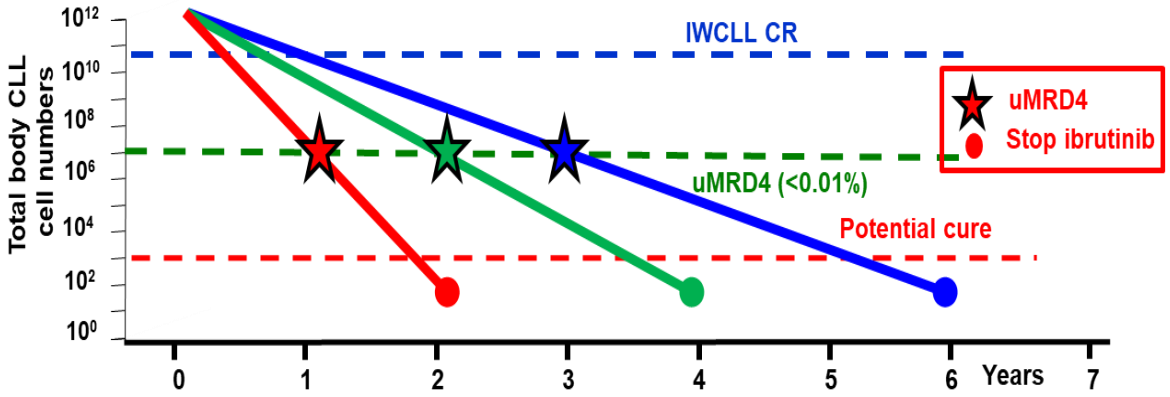


Munir T, et al. *N Engl J Med*. 2024;390(4):326-337. Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634. al-Sawaf O, et al. *Blood*. 2024:blood.2024024631. Wierda WG, et al. *JCO*. 2024;42:7009-7009. Fürstenau M, et al. *Lancet Oncol*. 2024;25(6):744-759.

Stopping Rules for Ibrutinib + Venetoclax in FLAIR

Testing schedule (Central lab, MRD flow to uMRD5 (<1 CLL cell in 10^5))

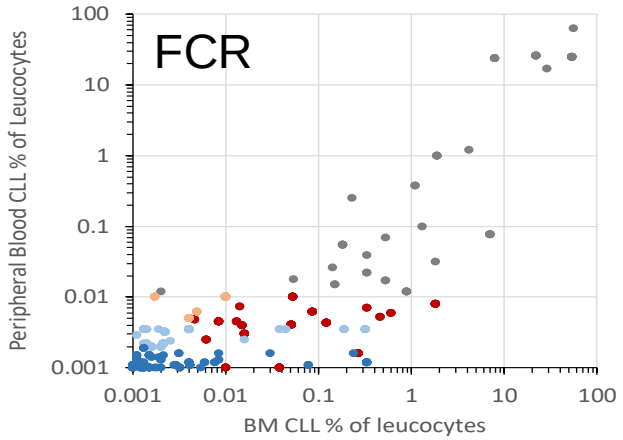




Defining treatment duration
2 to 6 years ibrutinib or both ibr+venetoclax
Double time after MRD negative

Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

PB uMRD5 (<0.001%) equates to BM uMRD4 (<0.01%) or better across different arms of the FLAIR trial

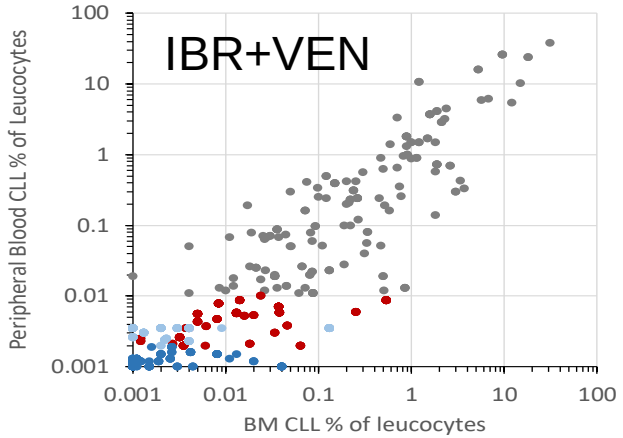


Log difference in BM vs. PB MRD : 0.54 (-0.78 – 2.1)

Proportion with BM uMRD4 (<0.01%):

92% with PB uMRD5 (<0.001%)

24% with PB dMRD5 (0.001 – 0.01%)



Log difference in BM vs. PB MRD : 0.01 (-1.05 – 1.82)

Proportion with BM uMRD4 (<0.01%):

91% with PB uMRD5 (<0.001%)

48% with PB dMRD5 (0.001 – 0.01%)

Munir T, et al. *N Engl J Med*. 2024;390(4):326-337. Rawstron A, et al. Presented at: ASH 2023; De 10, 2023; San Diego, CA. 632

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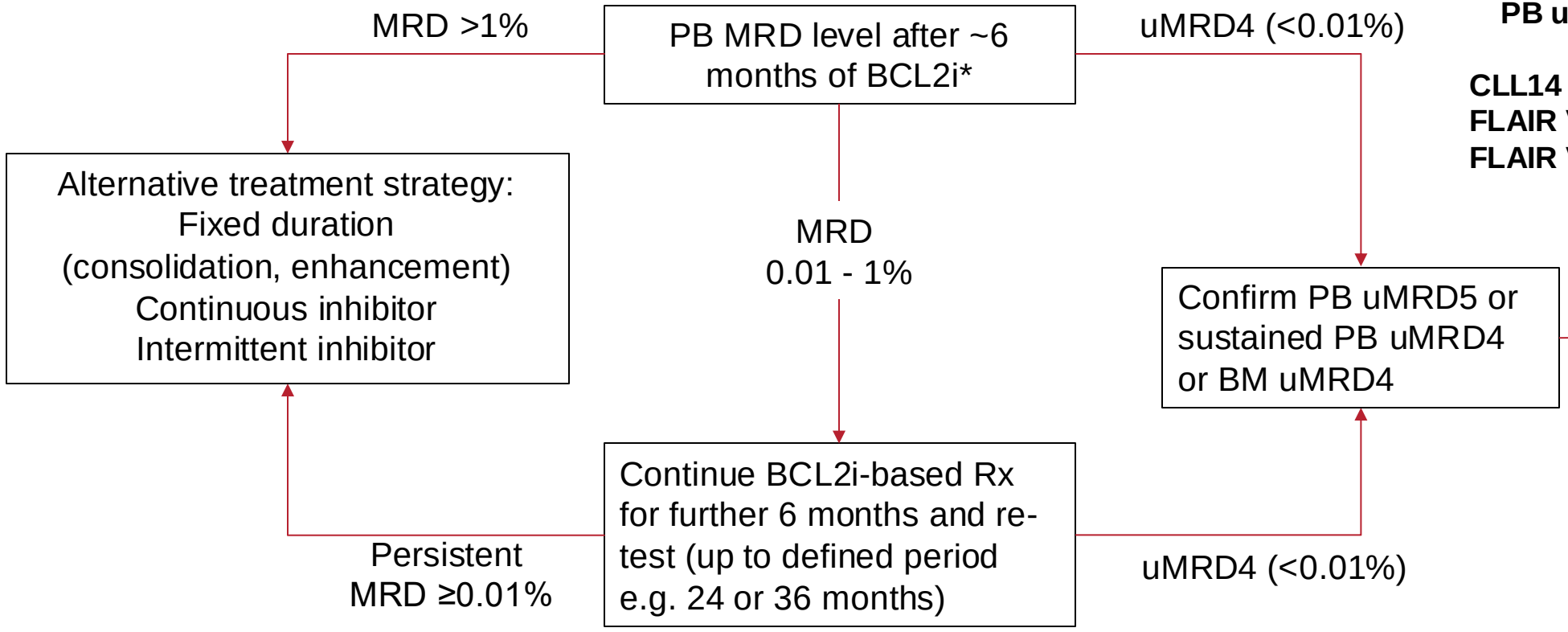
Possible Pathway for MRD-Guided Treatment with BCL2i-Based Treatment



PB uMRD4 rate after 6 months of venetoclax exposure:

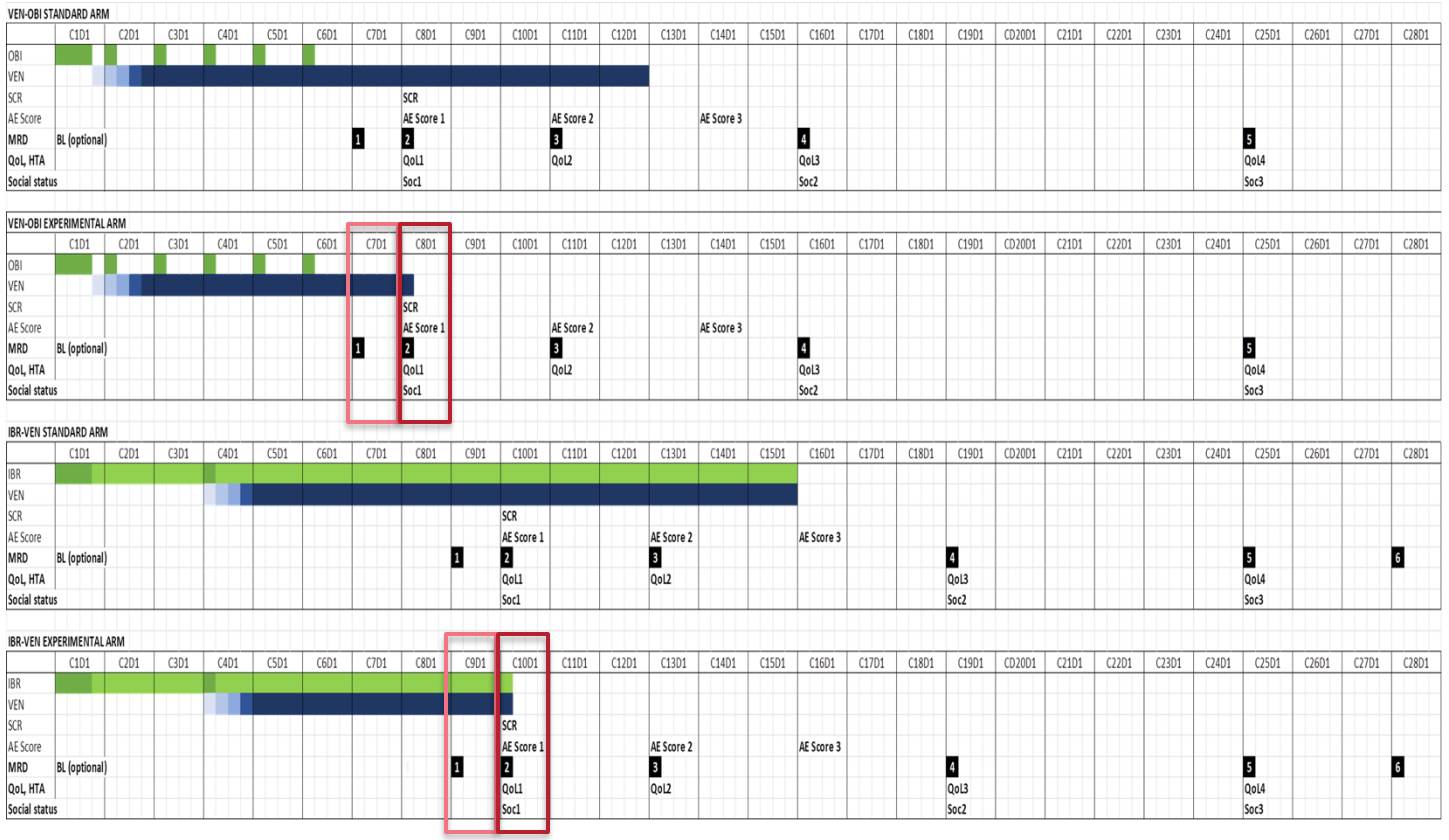
CLL14 VEN+OBI	**72% (1)**
FLAIR VEN+IBR uIGHV	**55% (2)**
FLAIR VEN+IBR mIGHV	**35% (2)**

**** BM uMRD4 is not cure. BM uMRD6 may equate to cure for some.**

al-Sawaf O, et al. *Blood*. 2024:blood.2024024631. Munir T, et al. *N Engl J Med*. 2024;390(4):326-337. Some content represents the speaker's own opinion and not published data.

Residual Disease Assessment in Hematologic Malignancies to Improve Patient-Relevant Outcomes across Europe (RESOLVE)

- MRD-driven treatment in CLL and AML
- RESOLVE consortium aimed at establishment of standardized, decentralized MRD analysis across Europe
- CLL Ven-Obi or IBR+Ven: PB uMRD5 randomized to early cessation vs standard duration treatment
- Certification process for RESOLVE centers starting in April 2024
  - Use dry pre-formulated commercially available kits
  - Target decision at MRD5 in the PB



CORDIS EU. Accessed Oct 11, 2024. https://cordis.europa.eu/project/id/101136502. EU CT 2024-512503-39-00 (protocol not yet available on clinicaltrialsregister.eu). https://ericll.org/project-categories/active #9 Resolve trial: an international, multi-center, randomized, controlled pragmatic clinical trial.

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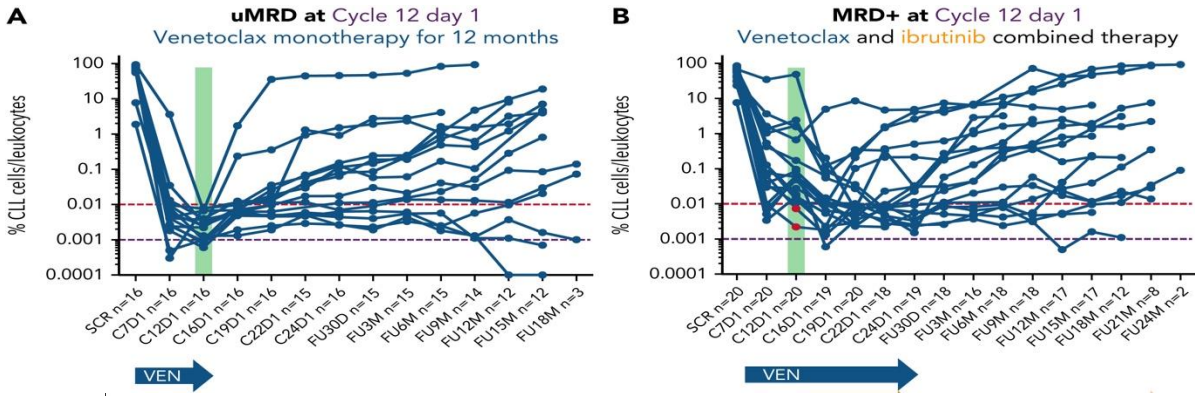
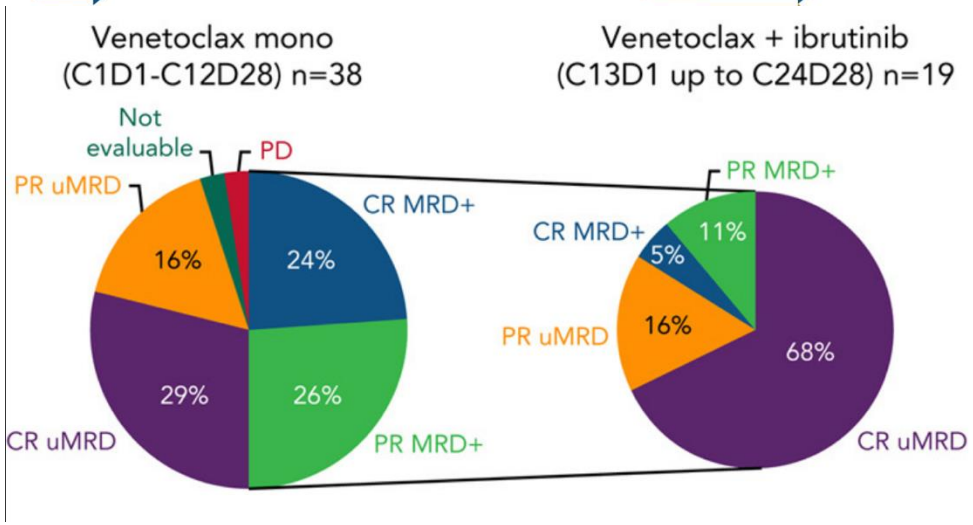
Approaches to Achieve uMRD: Guided Duration, MRD-Driven Enhancement / Consolidation with BCL2i +/- BTK Inhibitors/Degrader +/- anti-CD20/CD19/BiTE





- **NCT04758975**: Venetoclax, Rituximab and Ibrutinib in TN Patients With CLL Undetectable Minimal Residual Disease (uMRD) (VALUABLE)
- **NCT04560322**: Venetoclax-Obinutuzumab +/- Acalabrutinib in R/R CLL
- **NCT05650723**: Zanubrutinib and Venetoclax as Initial Therapy for Chronic Lymphocytic Leukemia (CLL) With Response-based Obinutuzumab
- **NCT06367374**: MRD Guided Sonrotoclax and Zanubrutinib in Newly Diagnosed CLL/SLL
- **NCT05317936**: Pirtobrutinib (LOXO-305) Consolidation for MRD Eradication in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL) Treated With Venetoclax
- **NCT05478512**: Front-line VenObi Combination Followed by Ven or VenZan Combination in Patients With Residual Disease: a MRD Tailored Treatment for Young Patients With High-risk CLL (VIS)
- **NCT06544785**: Zanubrutinib With Obinutuzumab in Untreated Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Consolidation/enhanced treatment strategy must balance log depletion, time on treatment, toxicity & duration of treatment break

Scarfò L, et al. *Blood*. 2022;140(22):2348-2357.

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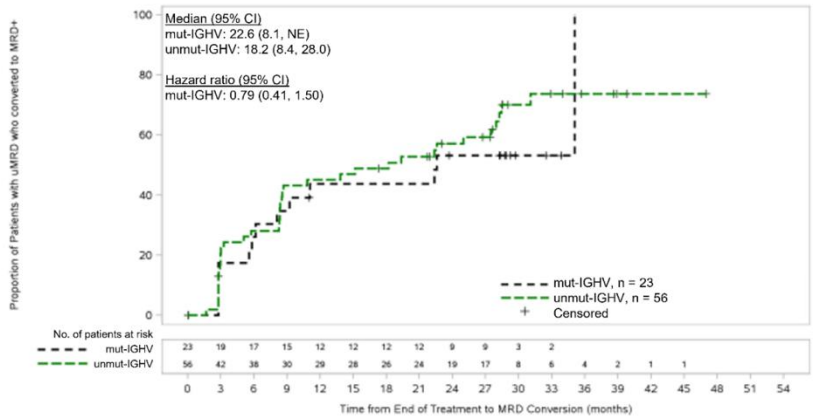
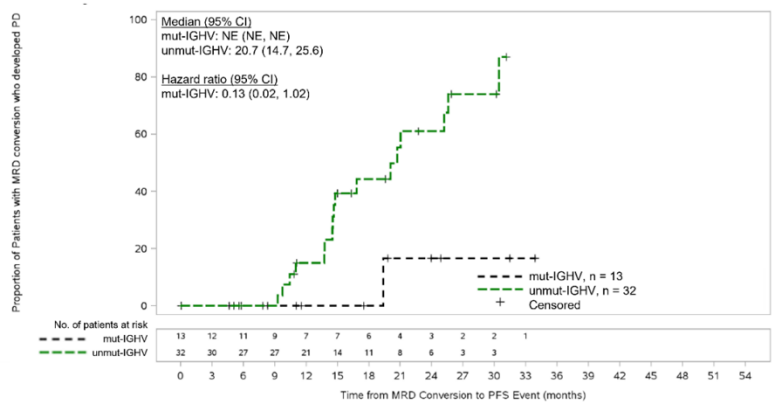
Post-Treatment Monitoring: Typically Several Years from First Detection of MRD until Clinical Progression

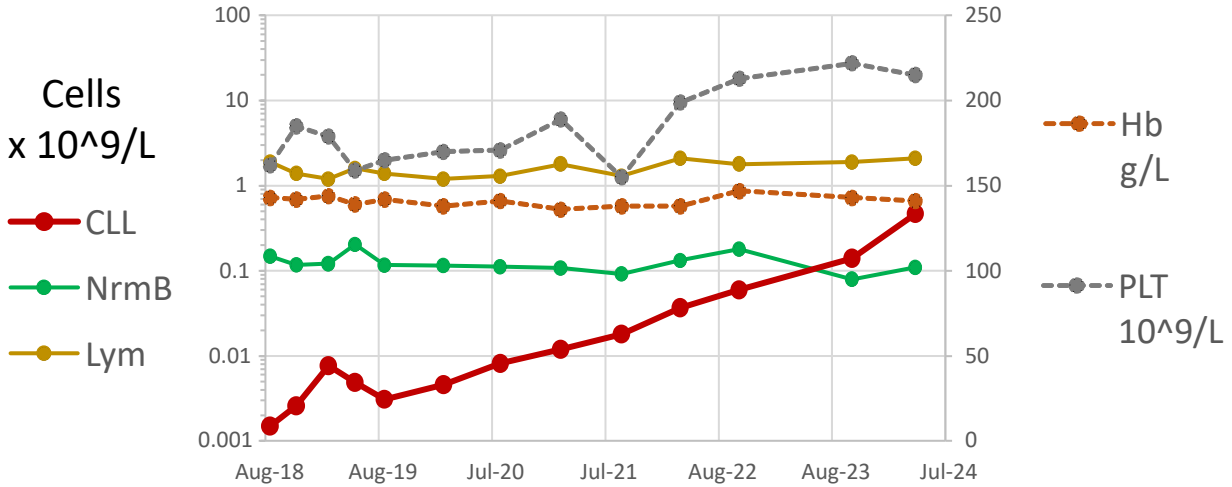
(B) Time from EOT to MRD conversion in patients with uMRD status at EOT



(C) Time from MRD conversion to PFS event



[1] Normal B cells can recover and persist for several years after first detection of residual disease.



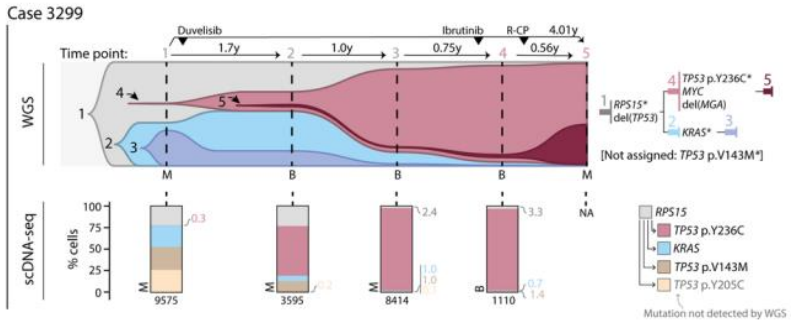
[1]Sequential post-treatment (FCR) MRD monitoring in a single patient from Leeds Teaching Hospitals – unpublished data.
Seymour JF, et al. *Blood*. 2022;140(8):839-850.

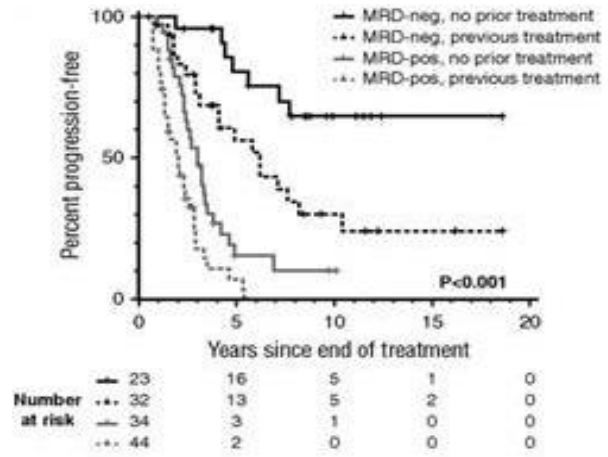
How Should We Be Using MRD Data?

- MRD-guided duration of treatment
  - MRD-guided I+V significantly improved PFS and OS in IGHV-unmutated U-CLL and was well tolerated with no unexpected toxicities
  - Sustained PB uMRD4 or single PB uMRD5/uMRD6 can be used as a surrogate for BM uMRD4
  - Multiple approaches to guiding treatment duration / intensity are under investigation
  - Early re-introduction of treatment based on detection of MRD has **not** been demonstrated to be safe or effective to date

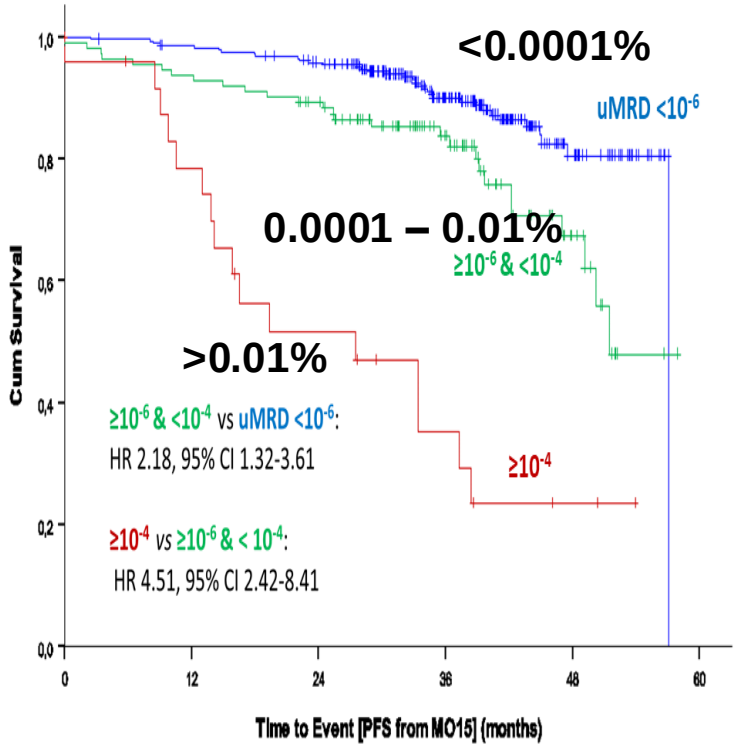
Treatment Strategies Under Evaluation

Frontline MRD-driven disease eradication





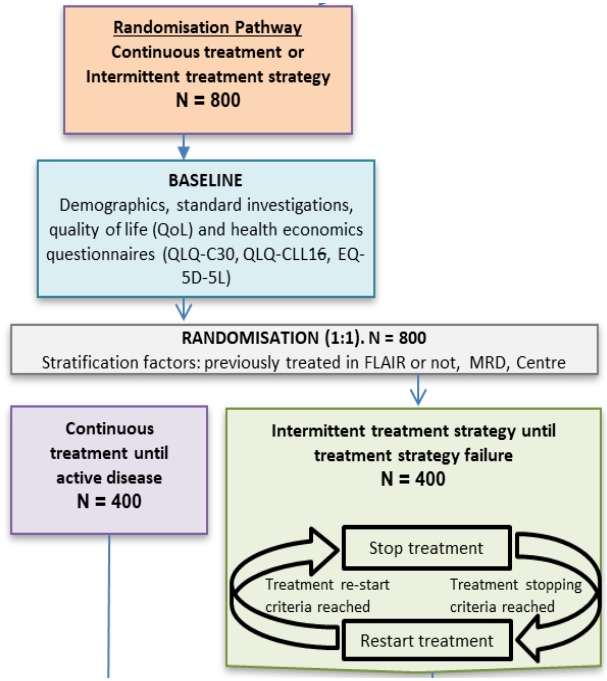
MRD-optimized fixed duration targeted treatment: PFS1 + PFS2 may be better than MRD-driven eradication



Disease control with treatment breaks

STATIC

Intermittent vs. continuous treatment strategies in CLL



Nadeu F, et al. *Nat Med*. 2022;28(8):1662-1671. Kwok M, et al. *Blood*. 2016;128(24):2770-2773. Fürstenau M, et al. *Lancet Oncol*. 2024;25(6):744-759. ISRCTN. Accessed Oct 11, 2024. https://www.isrctn.com/ISRCTN51675454.

Key Learning Points

- uMRD is a key response assessment in clinical trials and is being used more often in routine practice for supportive information
- In the near future we may be able to accelerate the approval of new treatments based on blood MRD responses (pending confirmation of long-term benefit)
- Strategies to optimize the depth of response while minimizing toxicity using MRD to guide treatment are under evaluation

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