Il suono DELL' INNOVAZIONE
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IL FUTURO DELLA CLL

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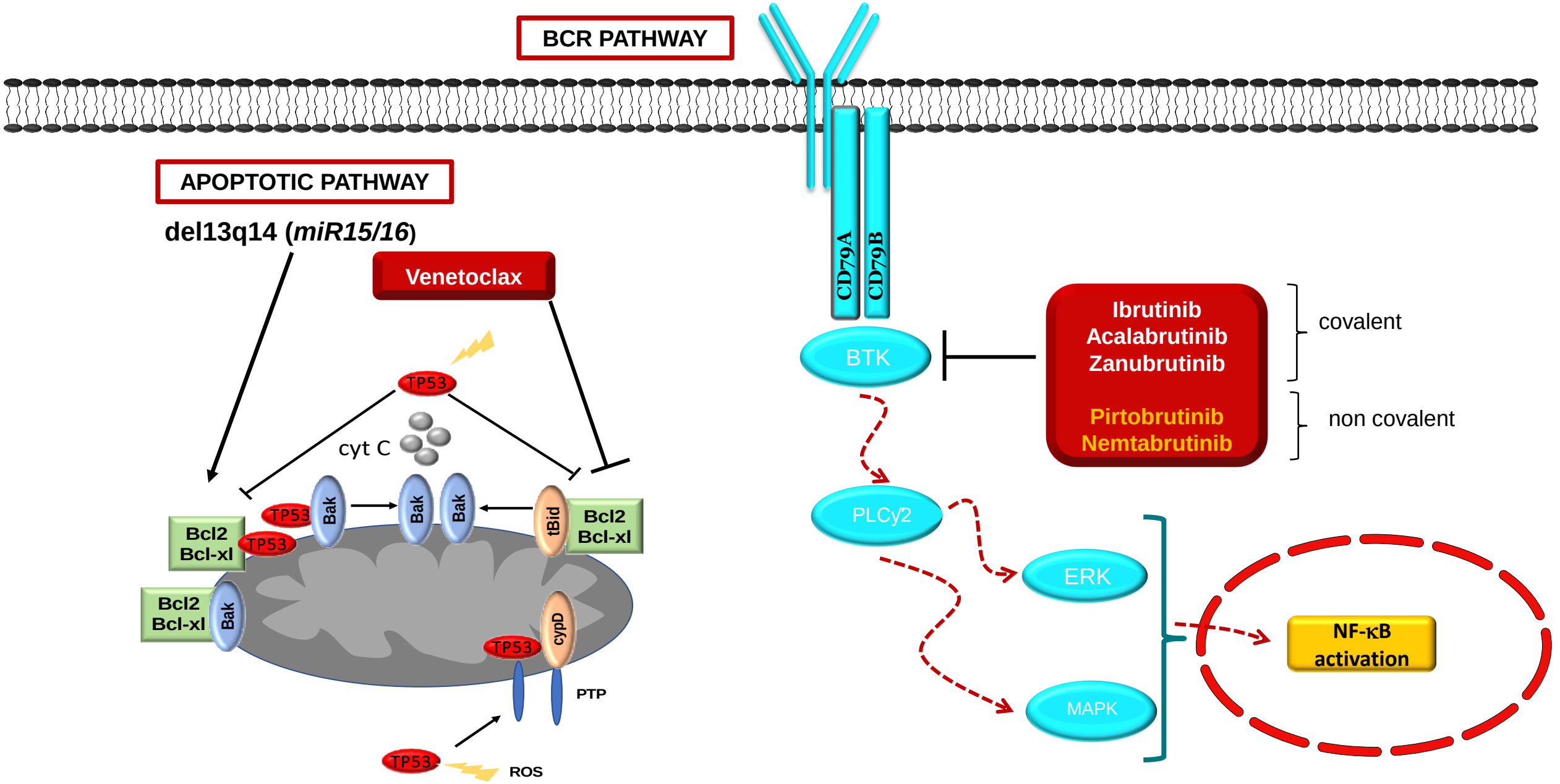
DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					√	√	
AstraZeneca					√	√	
BeiGene					√	√	
Gilead	√						
Incyte					√	√	
Johnson & Johnson					√	√	
Lilly					√	√	

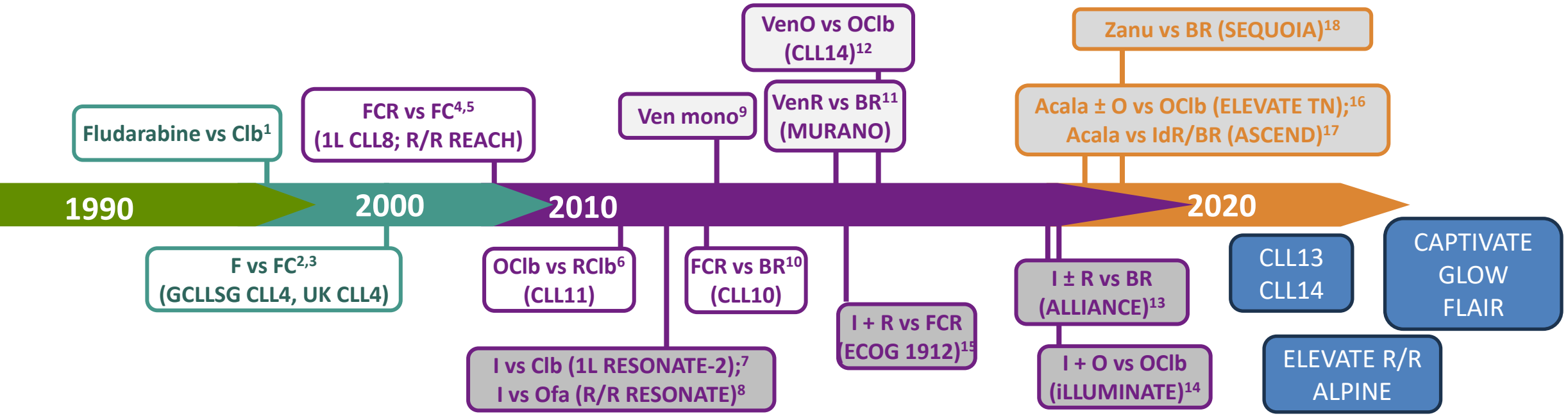
Agenda

- Actionable molecular pathways
- The future in 1L CLL
- The future in R/R CLL

Actionable molecular targets for CLL therapy



Evolution of CLL Treatment – Key Treatment Milestones



Goals of therapy

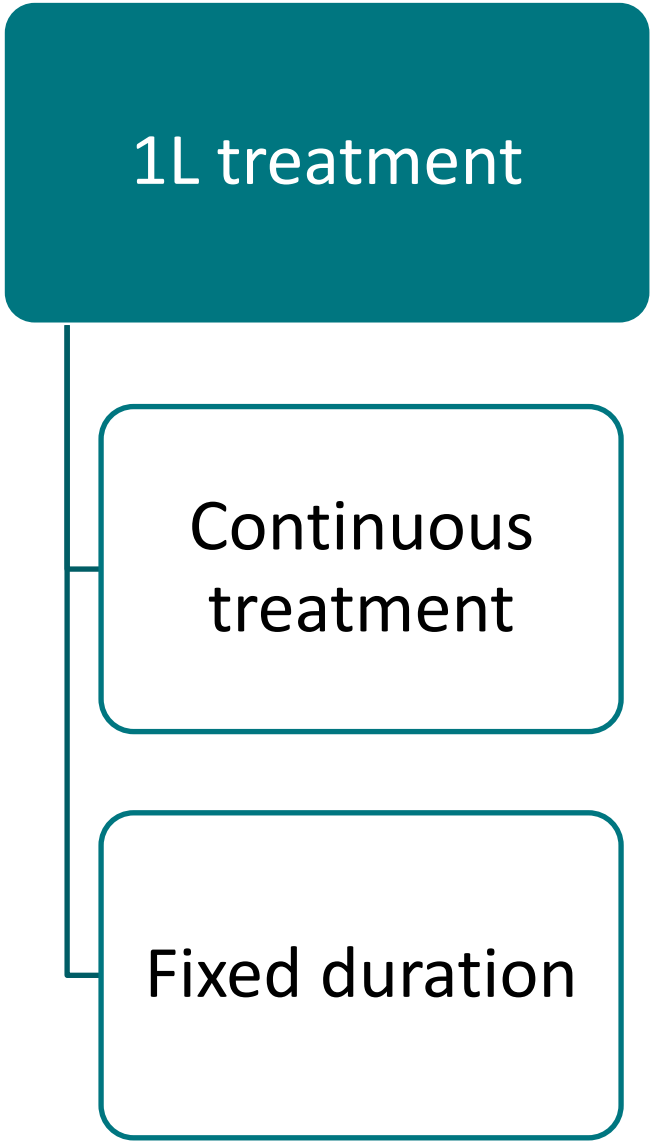
Alleviating symptoms → **Improving survival** → **Reducing toxicity, while improving outcomes in more patients**

*1. Rai KR, et al. N Engl J Med 2000; **343:**1750–1757; 2. Eichhorst BF, et al. Blood 2006; **114:**3382–3391;*
*3. Catovsky D, et al. Lancet 2007; **370:**230–239; 4. Hallek M, et al. Lancet 2010; **376:**1164–1174; 5. Robak T, et al. J Clin Oncol 2010; **8:**1756–1765;*
*6. Goede V, et al. N Engl J Med 2014; **370:**1101–1110; 7. Burger JA, et al. N Engl J Med 2015; **373:**2425–2437; 8. Byrd JC, et al. N Engl J Med 2014; **372:**213–223;*
*9. Roberts AW, et al. N Engl J Med 2016; **374:**311–322; 10. Eichhorst B, et al. Lancet Oncol 2016; **17:**928–942; 11. Seymour JF, et al. N Engl J Med 2018; **378:**1107–1120;*
*12. Fischer K, et al. N Engl J Med 2019; **380:**2225–2236; 13. Woyach JA, et al. N Engl J Med 2018; **379:**2517–2528 (incl. suppl.); 14. Moreno C, et al. Lancet Oncol 2019; **20:**43–56;*
*15. Shanafelt TD, et al. N Engl J Med 2019; **381:**432–443; 16. Sharman JP, et al. Lancet 2020; **379:**1278–1291; 17. Ghia P, et al. J Clin Oncol 2020; **38:**2849–2861; 18. Tam CS, et al. Lancet Oncol 2022; **23**:1031-1043. .*

Agenda

- Actionable molecular pathways
- The future in 1L CLL
- The future in R/R CLL

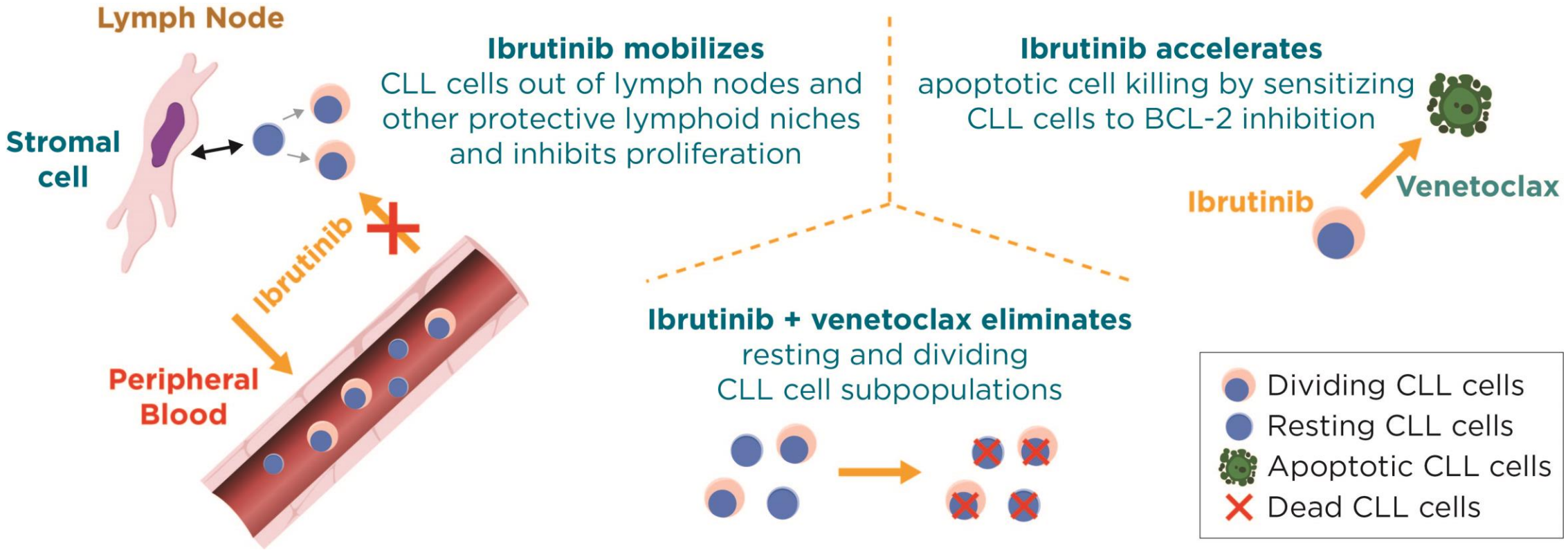
Therapeutic options in treatment-naïve CLL



	Continuous treatment until progression	Fixed duration (12-15 mo)
BTKi single agent		
Ibrutinib	√	
Acalabrutinib	√	
Zanubrutinib	√	
Venetoclax + Obinutuzumab		√
Ibrutinib + Venetoclax		√
Acalabrutinib + Venetoclax +/- Obinutuzumab		√

Presenter's view

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



BCL-2, B cell lymphoma 2; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EU, European Union; OS, overall survival; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease. [1]Lu P et al. *Blood Cancer J.* 2021;11:39. [2]Deng J et al. *Leukemia.* 2017;31:2075-2084. [3]Herman ES et al. *Clin Cancer Res.* 2015;21:4642-4651. [4]Burger JA et al. *Leukemia.* 2020;34:787-798. [5]Shanafelt T et al. *N Engl J Med.* 2019;381:432-443. [6]Venclexta [package insert]. South San Francisco, CA: Genentech USA Inc; 2021.

Kinome selectivity of BTKi

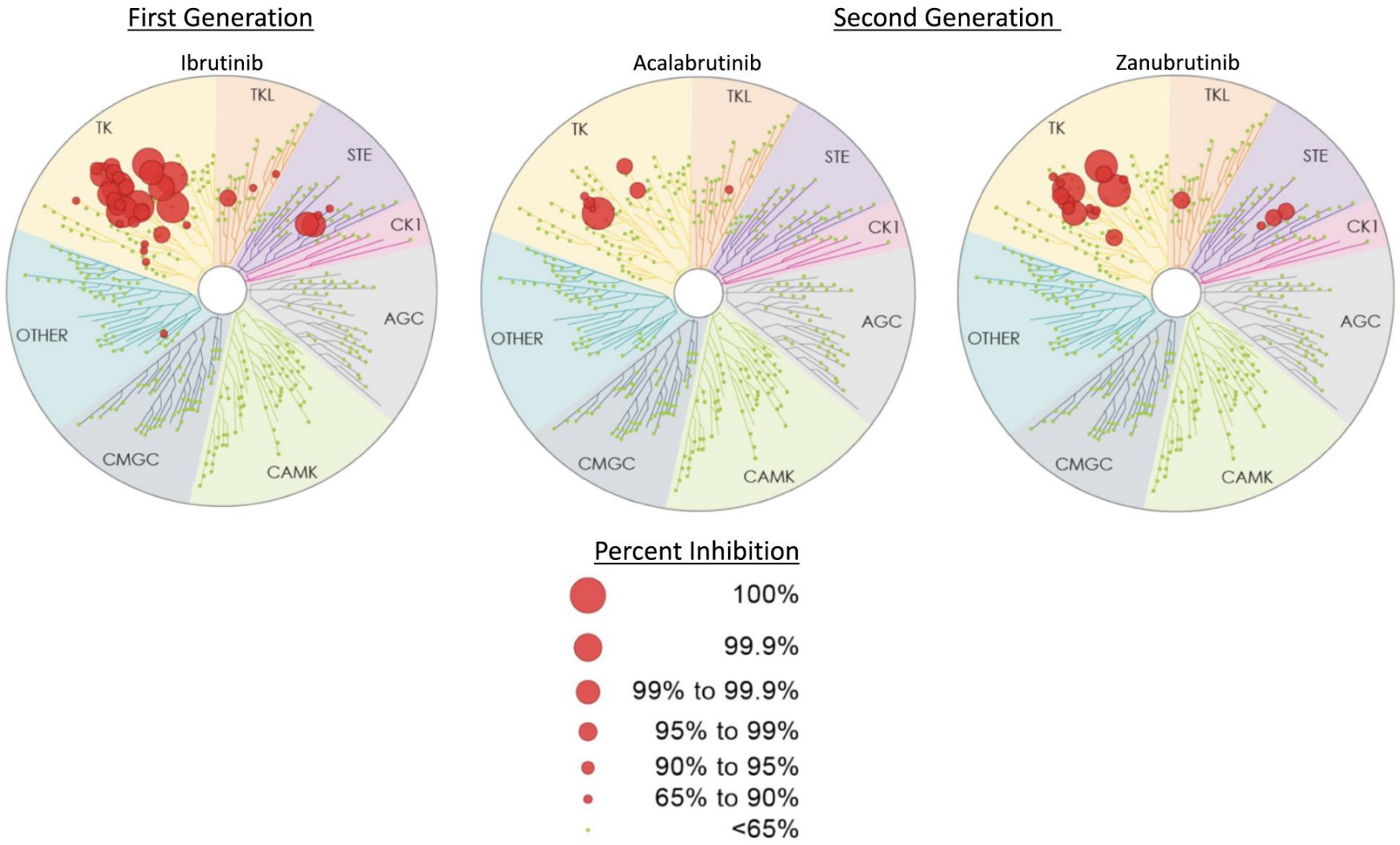
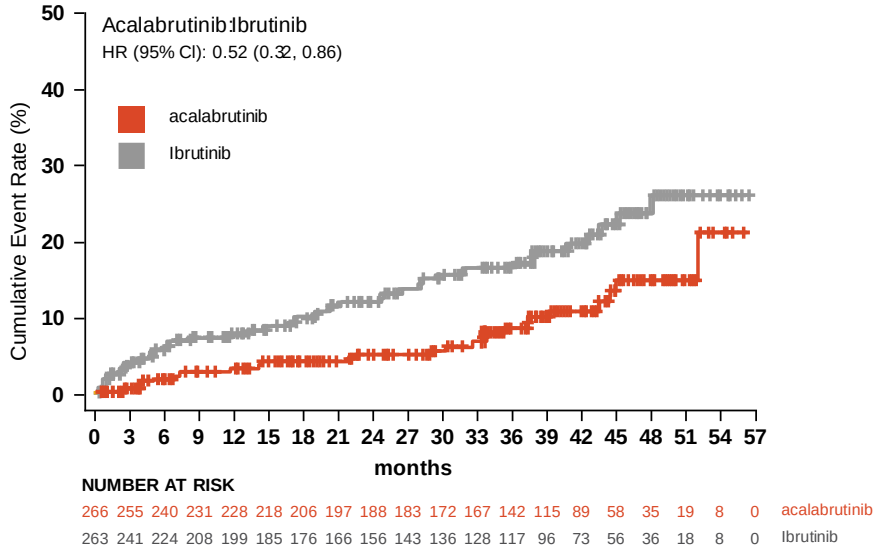


Figure 3 BTK Inhibitor Kinome Map. Figure modified from Kaptein A, de Bruin G, Emmelot-van Hoek M, van de Kar B, de Jong A, Gulrajani M, et al. Potency and Selectivity of BTK Inhibitors in Clinical Development for B-Cell Malignancies. Blood. 2018;132(Supplement 1):1871. Copyright 2018, with permission from Elsevier.[13]

ELEVATE-RR: Secondary Endpoint - Atrial Fibrillation Events

Lower incidence of any grade atrial fibrillation or flutter for acalabrutinib (9.4%) vs ibrutinib (16%)[1]

	Acalabrutinib (n=266)	Ibrutinib (n=263)	*P*-value
Median duration of treatment exposure (months)	38.3	35.5	-
Atrial fibrillation events, no. (%)			
Any grade (secondary endpoint)*	25 (9.4)†	42 (16.0)	0.02
	HR (95% CI): 0.52 (0.32 to 0.86)		
Grade ≥3*	13 (4.9)	10 (3.8)	-
Incidence among patients without prior history of atrial fibrillation/ flutter	15/243 (6.2)	37/249 (14.9)	-
Atrial fibrillation events leading to treatment discontinuation (any grade)	0	7 (2.7)	-



Adapted from Byrd JC, et al. J Clin Oncol. 2021

*Includes events with the preferred terms of atrial fibrillation and atrial flutter (a patient was only counted once if he or she experienced both types of events); atrial flutter was reported in one patient in the acalabrutinib arm and two patients in the ibrutinib arm (one of the two ibrutinib patients also had an atrial fibrillation event and was counted only once for the combined atrial fibrillation or flutter term).[1]
†Part of the multiple testing procedure; difference in any-grade incidence rates was -6.6%(95% CI; -12.2 to -0.9), *P*=0.02.[1]
CI = Confidence interval; HR = Hazard ratio.
1. Byrd JC, et al. J Clin Oncol. 2021;39(31):3441-3452.

Sinergy of BTKi-BCL2i as a class effect

How to ACALABRUTINIB synergize with VENETOCLAX[1]

- **Lymphocytosis***
- **CLL cells priming for apoptosis**
- **pro-apoptotic protein BIM expression**
- **survival in CLL mouse models alone and at higher level with venetoclax**

- **CLL cells migration towards SDF-1 (CXCL12)**
- **anti-apoptotic protein Mcl-1 expression**

When acalabrutinib and ibrutinib were tested in the same e*x vivo* experiment at same conditions they similarly Increased[1,2]:

- **BCL-2 dependence in CLL cells**
- **CLL cell sensitivity to BCL-2 inhibition**
- **expression of the BH3-only protein BIM**
- **CLL cell death when combined with venetoclax**

*LYMPHOCYTOSIS [1,3,4,5] was consistently associated to acalabrutinib treatment, with early onset (peak at 3/7/14 days) and ALC increase of 40-67%, followed by a decline

In one study[6] Acalabrutinib exhibited lower ALC from Month 6 to Month 12 compared to ibrutinib especially in IGHV mutated pts. Kinetics of BTKi-induced lymphocytosis vary according to +12 presence and CD49d expression[6,7].

1. Patel et al. Leukemia. 2018 April ; 32(4): 920–930. doi:10.1038/leu.2017.321; 2. Deng Leukemia. 2017 October ; 31(10): 2075–2084. doi:10.1038/leu.2017.32; 3. Byrd 2016 N Engl J Med 2016;374:323-32; 4. Furman Leukemia 2021 Nov, 35(11):3201-3211.; 5 Alsadhan Clin Cancer Res. 2023 September 15; 29(18): 3612–3621; 6. Innocenti 2024 HemaSphere. 2024;8:e144; 7. Laurenti Poster iwCLL 2025

AMPLIFY Study Design

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

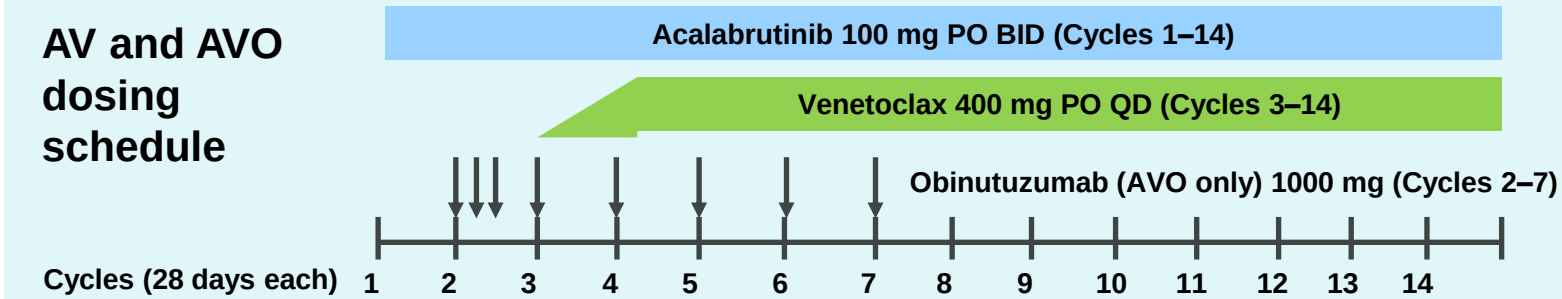
***Crossover** not built into protocol*

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:

1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

AV and AVO dosing schedule



NCT03836261. Data cutoff: April 30, 2024.
[a]Assayed by central lab.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CIRS-Geriatric, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene; iwCLL, International Working Group on CLL; OS, overall survival; PFS, progression-free survival; TN, treatment-naive; uMRD, undetectable measurable residual disease.

1. Hallek M, et al. *Blood*. 2018;131:2745-60.

Brown et al, NEJM 2025

Demographics and Baseline Characteristics

Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Age, median (range), yr	61 (31–84)	61 (29–81)	61 (26–86)
≤65 yr	212 (72.9)	210 (73.4)	213 (73.4)
>65 yr	79 (27.1)	76 (26.6)	77 (26.6)
Male sex	178 (61.2)	198 (69.2)	183 (63.1)
ECOG PS score			
0–1	262 (90.0)	272 (95.1)	262 (90.3)
2	28 (9.6)	14 (4.9)	26 (9.0)
Geographic region*			
Europe	184 (63.2)	179 (62.6)	183 (63.1)
North America	50 (17.2)	51 (17.8)	50 (17.2)
Other	57 (19.6)	56 (19.6)	57 (19.7)
Rai stage			
0–II	154 (52.9)	170 (59.4)	163 (56.2)
III–IV	137 (47.1)	116 (40.6)	127 (43.8)
del(11q) present	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated IGHV	167 (57.4)	169 (59.1)	172 (59.3)
Complex karyotype (≥3 aberrations)	45 (15.5)	46 (16.1)	42 (14.5)

Data are n (%) unless otherwise specified.

*Europe includes Eastern and Western Europe; Other includes Argentina, Australia, Brazil, China, Korea, Saudi Arabia, South Africa, and Taiwan.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene.

Brown et al, NEJM 2025

Demographics and Baseline Characteristics (2 of 2)

Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
11q deletion	51 (17.5)	56 (19.6)	46 (15.9)
Unmutated *IGHV*	167 (57.4)	169 (59.1)	172 (59.3)
Complex karyotype (≥3 aberrations)	45 (15.5)	46 (16.1)	42 (14.5)
β2-microglobulin, >3.5 mg per liter	169 (58.1)	151 (52.8)	143 (49.3)
Any cytopenia at baseline			
Hemoglobin <11 g/dl	103 (35.4)	85 (29.7)	94 (32.4)
Platelet count <100 × 10^9 per L	66 (22.7)	68 (23.8)	58 (20.0)
Absolute neutrophil count ≤1.5 ×10^9 per L	20 (6.9)	25 (8.7)	20 (6.9)

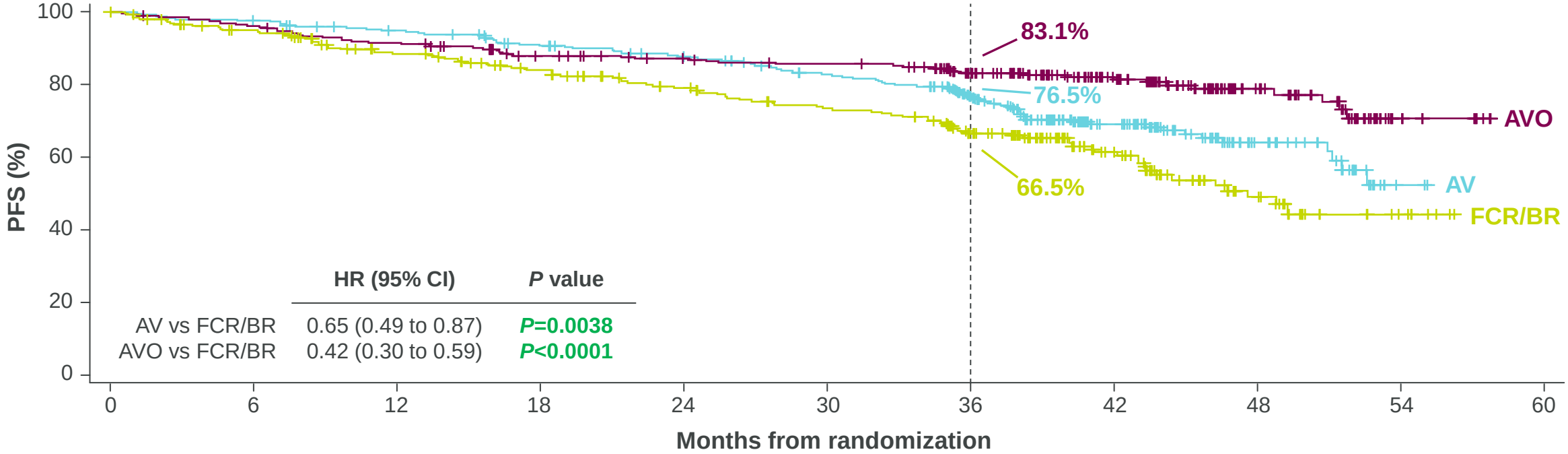
Data are n (%) unless otherwise specified.

1. Brown JR, et al. *N Engl J Med*. 2025. 2. Brown JR, et al. Presented at: ASH Annual Meeting; Dec 7-10, 2024. San Diego, California.

Brown et al, NEJM 2025

IRC-assessed PFS of AV and AVO is superior vs FCR/BR

Median follow-up = 40.8 months



Patients at risk

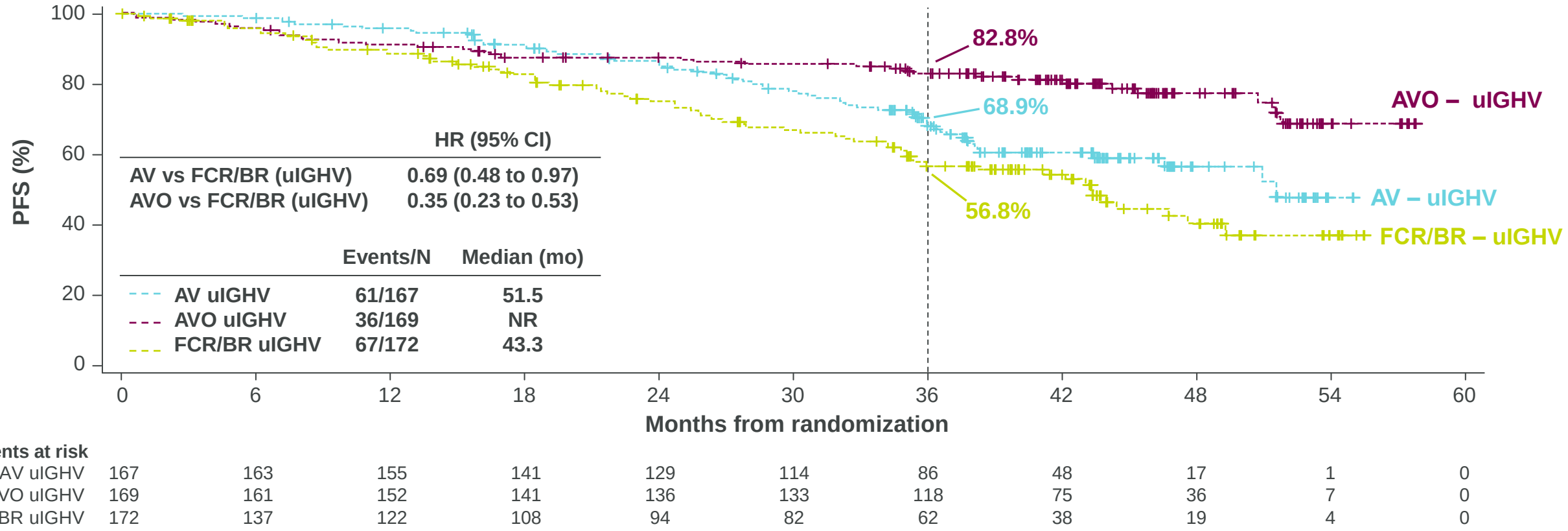
AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR/BR	290	236	208	189	170	154	127	66	28	6	0

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

ITT population. Median follow-up from randomization: 40.8 months (range, 0–59 months).
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

Brown et al, NEJM 2025

PFS in the uIGHV Subgroup



Patients at risk

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

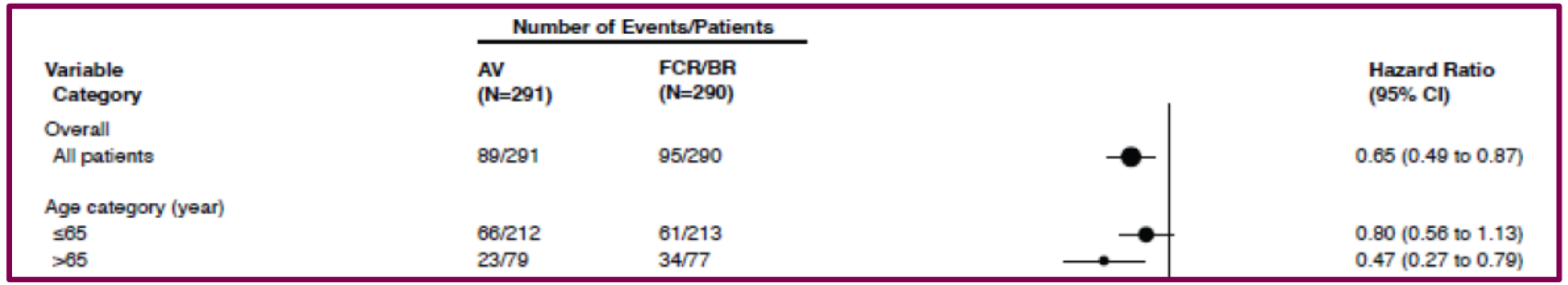
PFS assessed by IRC; PFS by IGHV status was a prespecified analysis (ITT population).
Hazard ratio (95% CI) computed using an unstratified Cox proportional-hazards model.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR,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

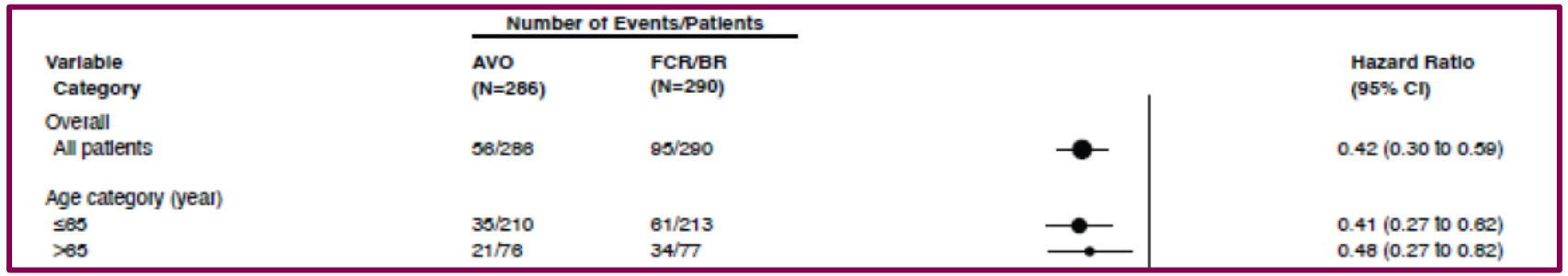
Brown et al, NEJM 2025

AMPLIFY efficacy analysis in elderly

	AV N=291	AVO N=286	FCR/BR N=290
Median age	61 years	61 years	61 years
Age range	31–84	29–81	26-86
N° pts > 65 years	**79 (27.1%)**	**76 (26.6%)**	**77 (26.6%)**

290 Were assigned to investigator's choice of chemoimmunotherapy (intention-to-treat population)
143 Were assigned to fludarabine–cyclophosphamide–rituximab
147 Were assigned to bendamustine–rituximab



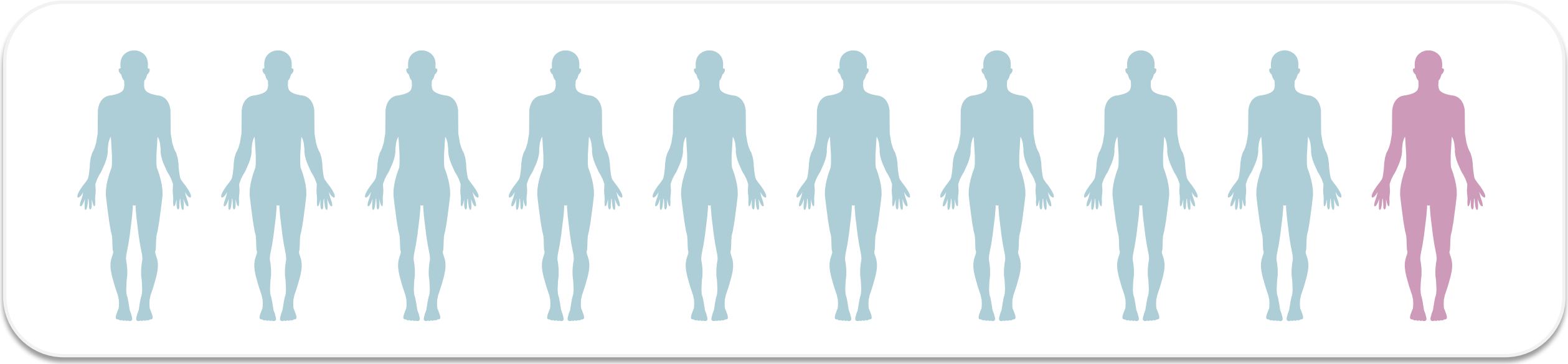


Significant PFS benefit, especially in > 65y pts

Brown et al. *NEJM* vol. 392,8 (2025): 748-762. doi:10.1056/NEJMoa2409804
Brown et al. *NEJM* vol. 392,8 (2025): 748-762. doi:10.1056/NEJMoa2409804; Supplementary

AMPLIFY: TTNT

9 out of **10** patients do not require subsequent treatment at 36 months with AV



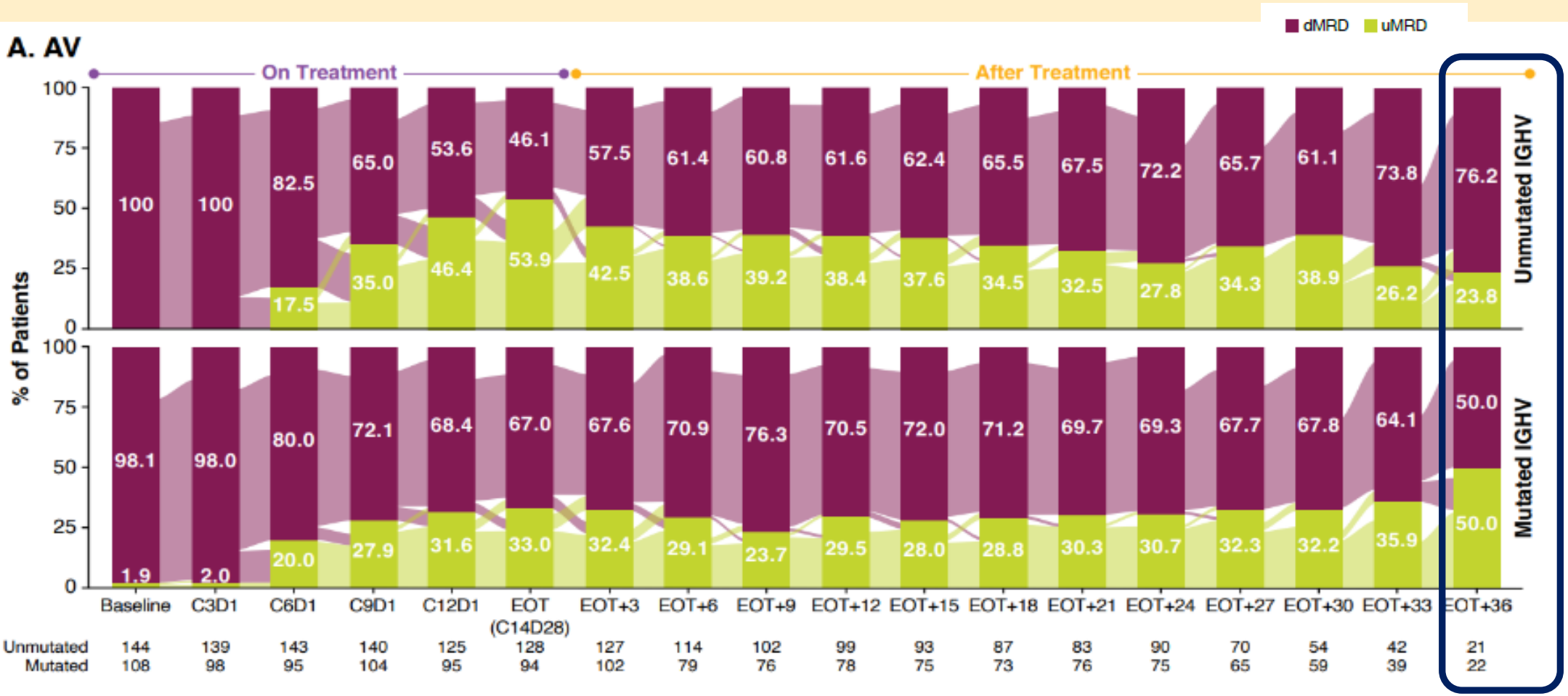
Ghia et al. ASH 2025 abstract 3898

Efficacy outcomes comparison for FD regimens

	3 years PFS	*3 years TTNT*	*uMRD rate EOT+3*
AMPLIFY	76.5%[1]	**88.5%**[2]	38%[1]
CAPTIVATE	88%[3]	**89%**[4]	57%[5]
GLOW	77%[6]	**92%**[6]	55%[7]

1 Brown et al. *N Engl J Med*. 2025;392(8):748-762.; **2** Ghia et al ASH 2025 abstract 3898; **3** Barr et al. *J Clin Oncol 41*, 7535-7535(2023); **4** Barr et al. *J Clin Oncol 41*, 7535-7535(2023) extrapolated from KM curves; **5** Tam et al. *Blood* vol. 139,22 (2022): 3278-3289 supplementary material; **6** Niemann et al *The Lancet. Oncology* vol. 24,12 (2023): 1423-1433 extrapolated from KM curves; **7** Kater et al. *NEJM evidence* vol. 1,7 (2022): EVIDoa2200006.

Stable persistence of undetectable MRD (uMRD) over time (AV) regardless of IGHV mutational status in AMPLIFY



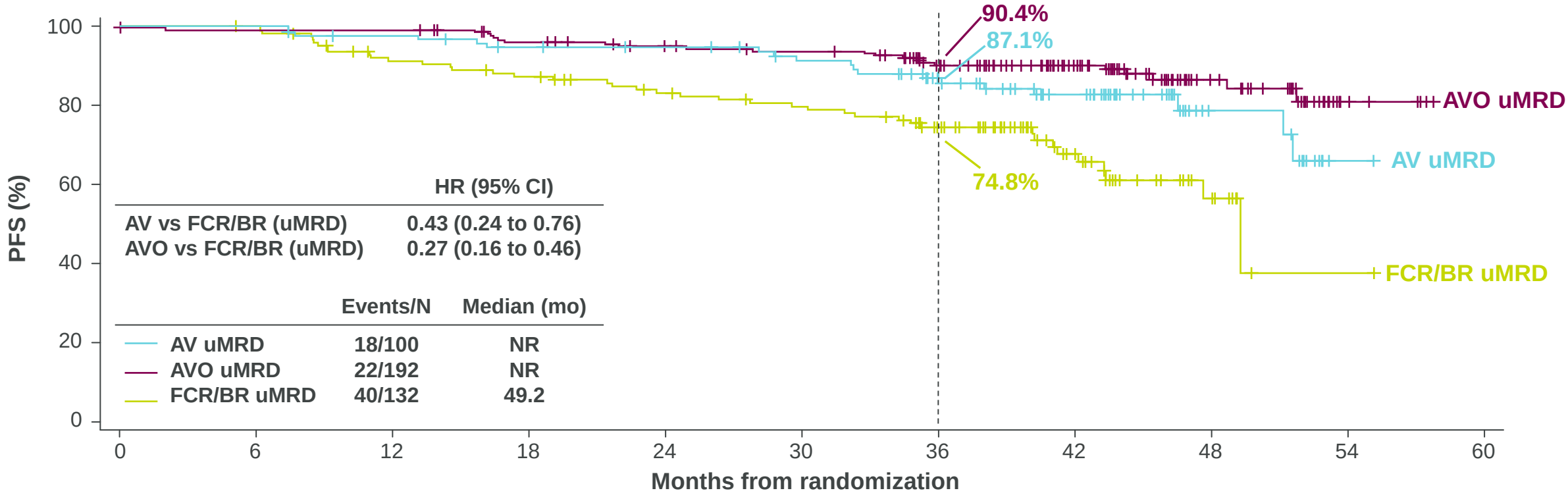
23.8% uMRD

50% uMRD

uMRD > 10^{-5}

Ghia et al., Poster Presentation EHA 2025

PFS in the uMRD Subgroup at EOT (Flow Cytometry [<10^{-4}] in PB)



Patients at risk

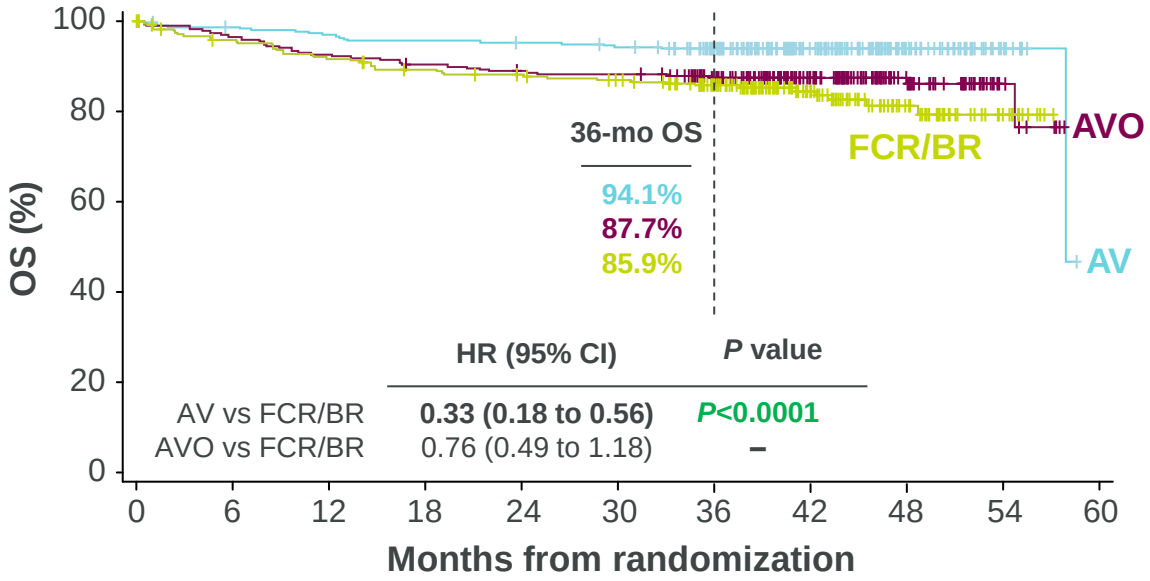
AV uMRD	100	100	96	91	89	83	67	47	13	1	0
AVO uMRD	192	190	190	179	169	165	143	95	39	7	0
FCR/BR uMRD	132	131	116	110	100	94	78	34	12	1	0

PFS assessed by IRC among MRD-evaluable patients; uMRD assessed by flow cytometry (10^{-4}) in peripheral blood.
Hazard ratio (95% CI) computed using an unstratified Cox proportional-hazards model.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; EOT, end of therapy; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; MRD, measurable residual disease; NR, not reached; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable measurable residual disease.

Brown et al., N Engl J Med 2025

Overall Survival

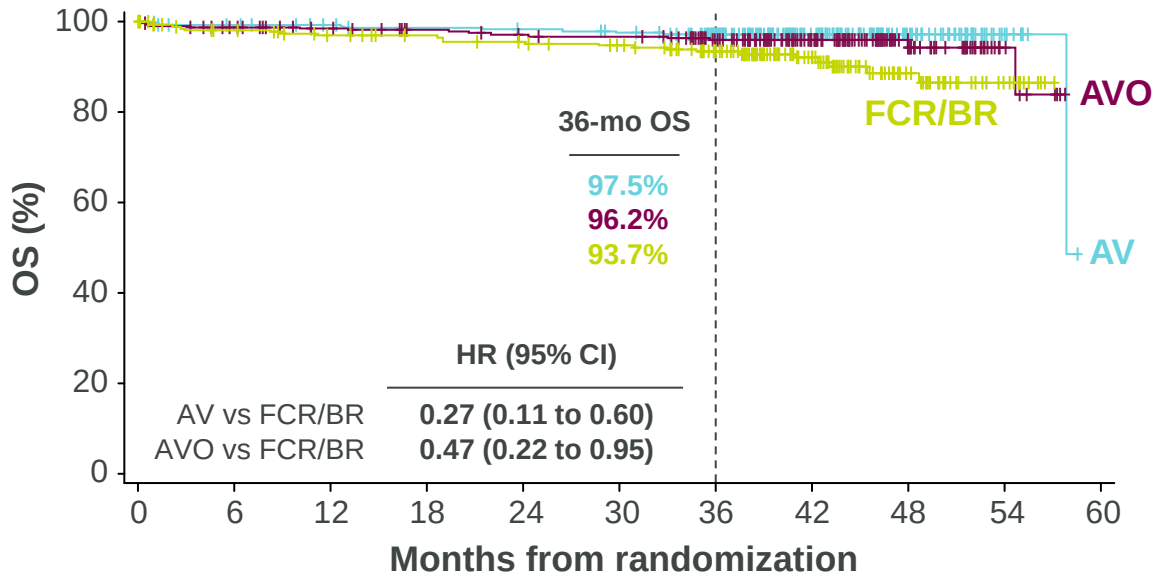
OS Prolonged With AV vs FCR/BR



Patients at risk

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

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



Patients at risk

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

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

ITT population.
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Brown et al, NEJM 2025

Events of Clinical Interest

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias[a]	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)[b]	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Data are n (%). ECIs listed by category and sub-category.

[a]Ventricular tachyarrhythmias consisted of ventricular extrasystoles (n=1 in AV arm; n=2 in AVO arm) and ventricular tachycardia (n=1 each in AV and AVO arms).

[b]Includes neutropenia, neutrophil count decreased, and febrile neutropenia.

AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.

AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; ECI, event of clinical interest; FCR, fludarabine-cyclophosphamide-rituximab.

AMPLIFY: Conclusions

- **AMPLIFY provides the first phase 3 evidence of fixed-duration therapy combining a 2G BTKi with venetoclax (with or without anti-CD20) in TN CLL**

- **This interim analysis of AMPLIFY (median follow-up: 40.8 months) in fit patients with TN CLL demonstrated:**
  - **Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR**
    - **Including in the uIGHV subgroup**
  - **Longer OS with AV versus FCR/BR (primary analysis) and longer OS with both AV and AVO vs FCR/BR (censoring COVID-19 deaths)**
  - **Highest uMRD rates in the AVO arm (ITT and evaluable populations)**
    - **Longer PFS in those with uMRD at EOT (all 3 treatment arms)**

- **Incidence of cardiac AEs remained low in both the AV and AVO regimens**

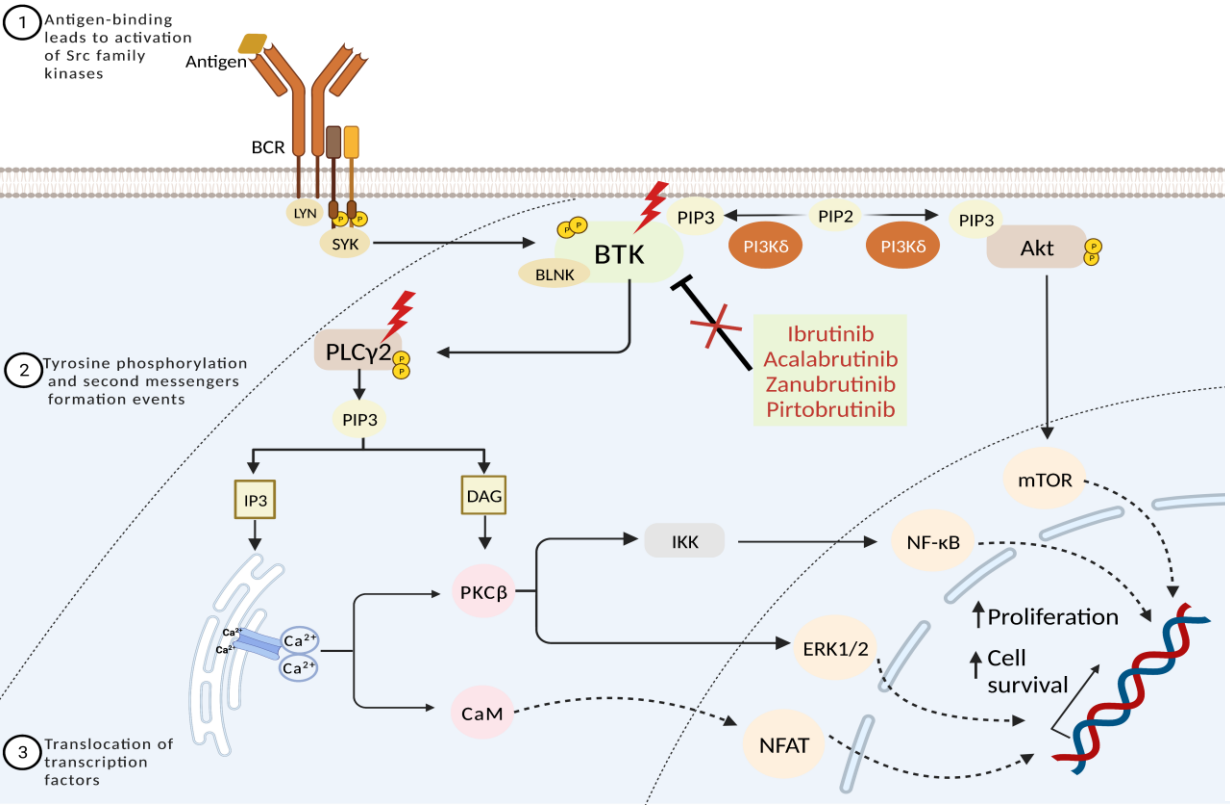
2G, second generation; AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BCL2i, B cell lymphoma 2 inhibitor; BR, bendamustine-rituximab; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EOT, end of therapy; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; TN, treatment-naive; uIGHV, unmutated immunoglobulin heavy-chain variable region gene; uMRD, undetectable measurable residual disease.

Agenda

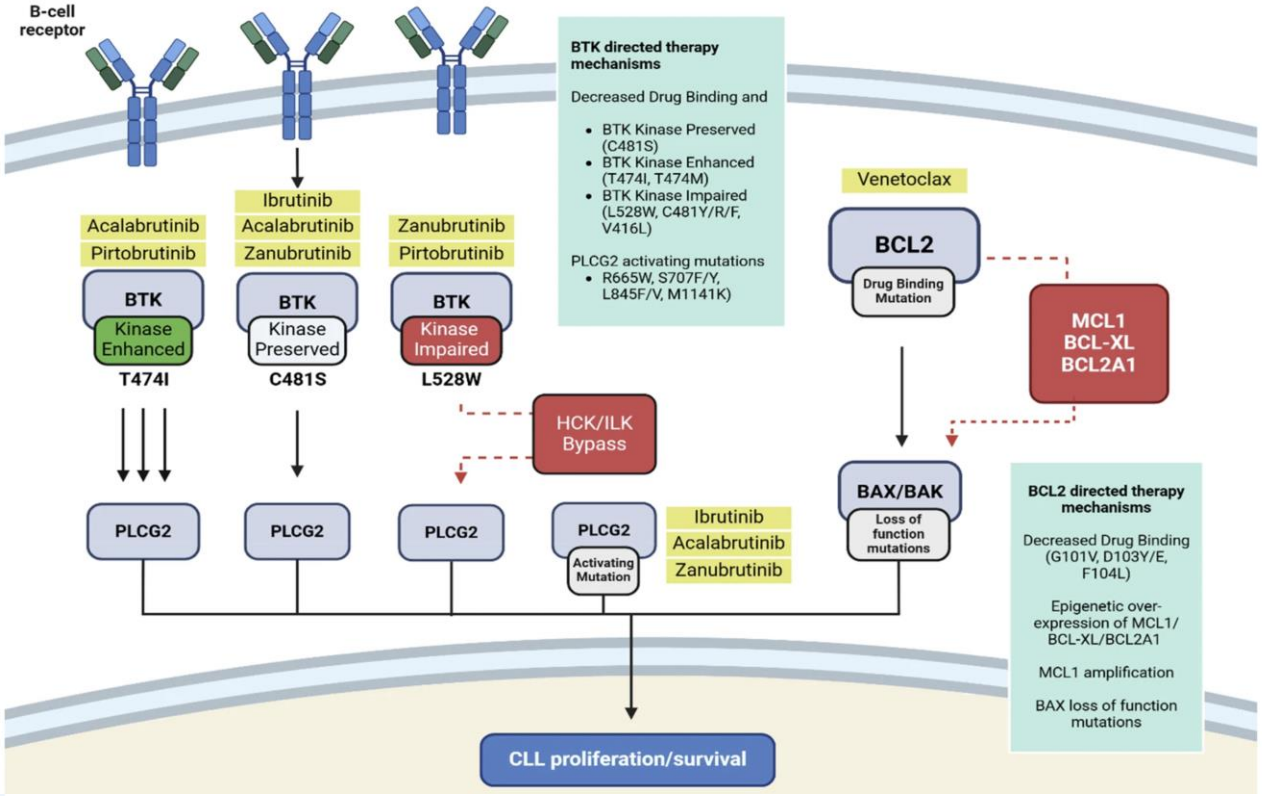
- Actionable molecular pathways
- The future in 1L CLL
- The future in R/R CLL

Molecular mechanisms of resistance to cBTKi may impact on therapeutic sequencing

Mutations of *BTK* and *PLCγ2* induce resistance to cBTKi



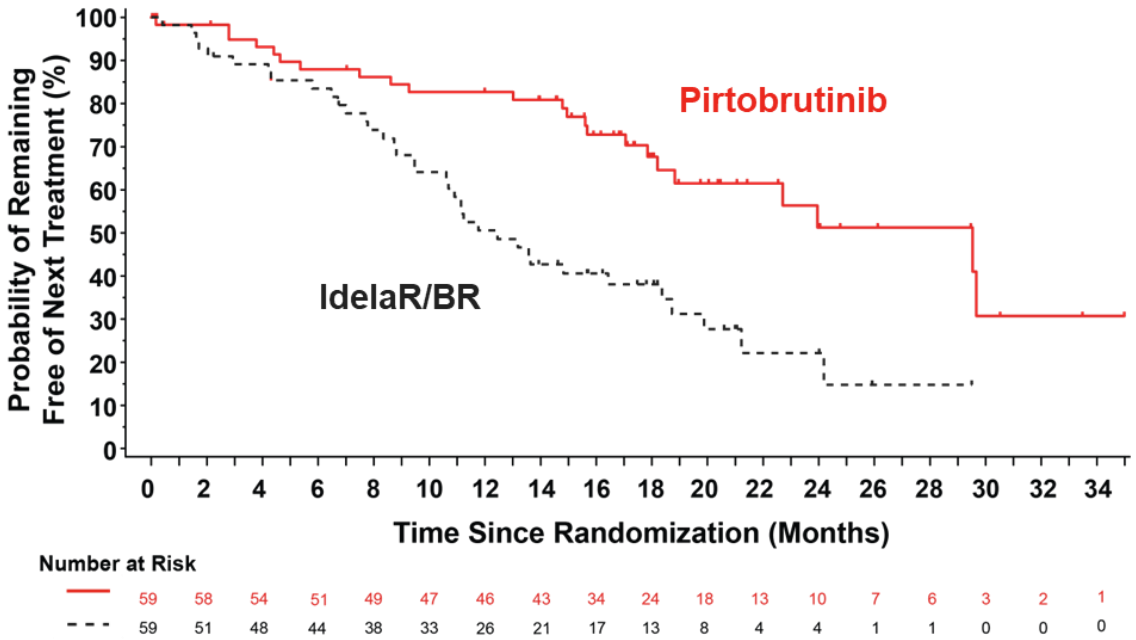
Not all *BTK* resistance mutations are equal and some confer resistance to both cBTKi and ncBTKi



Maher et al, Int J Mol Sci 2023, 24:10374; Tam et al., Blood 2025, 145:1005; Blombery et al, Leukemia 2025, 39:2049-2060

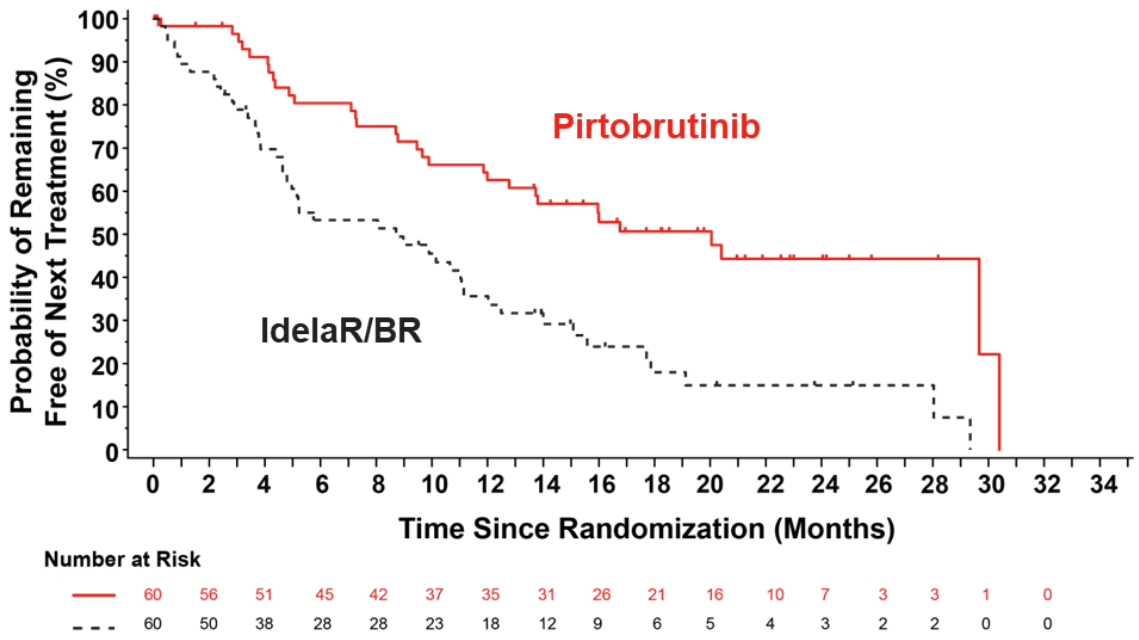
Pirtobrutinb: Time to Next Treatment or Death in Venetoclax Naïve and Treated Patients

Venetoclax Naïve



	Pirtobrutinib n=59	IdelaR/BR n=59
Median TTNT, mo (95% CI)	29.5	12.5
Hazard ratio (95% CI)	0.36 (0.21-0.61)	
Stratified log-rank 2-sided p-value	0.0001*	

Venetoclax Treated



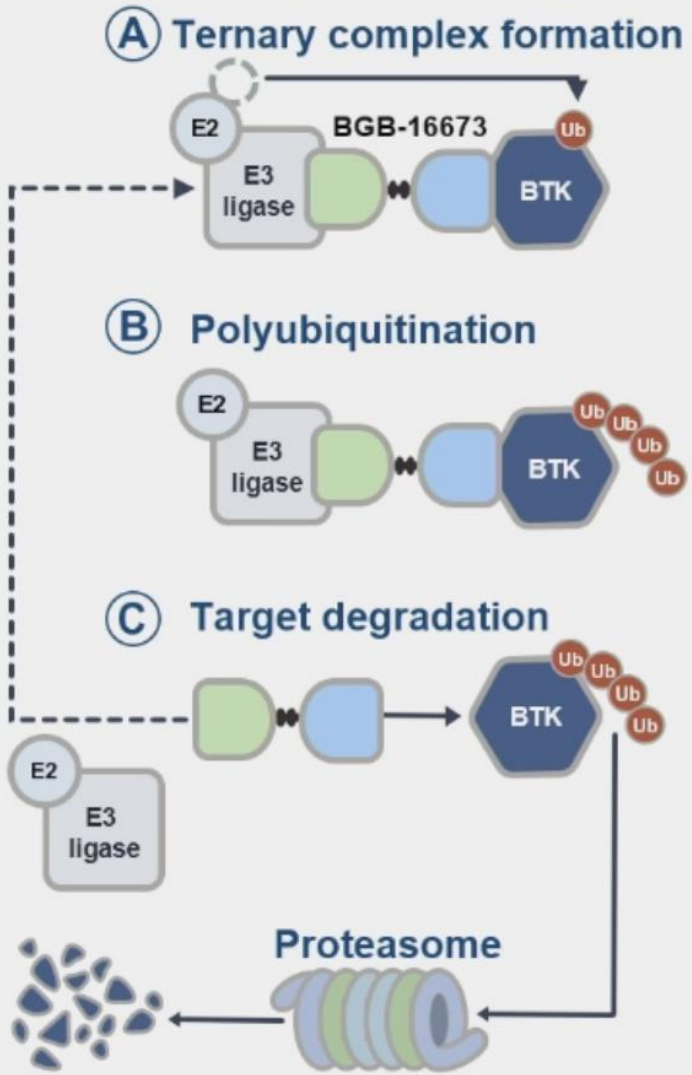
	Pirtobrutinib n=60	IdelaR/BR n=60
Median TTNT, mo (95% CI)	20.0	8.7
Hazard ratio (95% CI)	0.37 (0.23-0.60)	
Stratified log-rank 2-sided p-value	<0.0001*	

*nominal p-value. Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; IdelaR, idelalisib + rituximab; IRC, independent review committee; mo, months; TTNT, time to next treatment.

Sharman J et al, J Clin Oncol 2025

BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

- Many patients with CLL/SLL experience disease progression with BTK inhibitors, which can be caused by resistance mutations in BTK[1-3]
- BGB-16673 is a bivalent CNS-penetrating small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W), leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[6]
- We present updated safety and efficacy results in patients with R/R CLL/SLL and preliminary efficacy results in patients with R/R RT from phase 1 of CaDAnCe-101



cBTK, covalent BTK; CNS, central nervous system; ncBTK, noncovalent BTK; RT, Richter transformation; ub, ubiquitin.

1. Moreno C. *Hematol Am Soc Hematol Educ Program*. 2020;2020:33-40; 2. Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; 3. Wang E, et al. *N Engl J Med*. 2022;386:735-743; 4. Feng X, et al. EHA 2023. Abstract P1239; 5. Wang H, et al. EHA 2023. Abstract P1219; 6. Seymour JF, et al. ASH 2023; Abstract 4401.

Thompson et al, ASH 2024

High Overall Response Rates in All Biologic Subsets

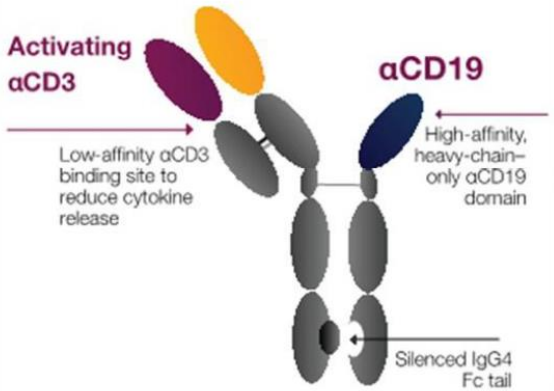
Characteristic, n/N with known status (%)	Total (N=49)[a]
Double exposure (previously received cBTKi + BCL2i)	26/30 (86.7)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	7/12 (58.3)
del(17p) and/or *TP53* mutation	23/31 (74.2)
Complex karyotype	11/15 (73.3)
***BTK* mutations**	10/16 (62.5)
***PLCG2* mutations**	4/6 (66.7)

[a] Efficacy-evaluable population.
BCL2i, BCL2 inhibitor; cBTKi, covalent BTK inhibitor; ncBTKi, non-covalent BTK inhibitor.

Thompson et al, ASH 2024

Bispecific mAbs for CLL: the Ph 1/2 SOUNDTRACK-E study

Figure 1. Surovatamig Structure and SOUNDTRACK-E Study Design



SOUNDTRACK-E (NCT06564038) is a Phase 1/2 Dose-Escalation, Global, Multicenter Trial Evaluating Surovatamig With 3 Substudies[a]

Substudy 1 (R/R CLL/SLL)

Cohort 1A	Cohort 1B	Cohort 1C
R/R CLL/SLL (3L+)	R/R CLL/SLL (2L+)	R/R CLL/SLL (3L+)
SC surovatamig monotherapy	SC surovatamig in combination with acalabrutinib	IV surovatamig monotherapy
Target N=~46	Target N=~46	Target N=~46
Finite treatment	Finite treatment	Finite treatment

Treatment Schedule

- Cohorts 1A and 1B: SC surovatamig administered with double step-up dosing in cycle 1; target dose every 2 weeks (**Fig. 2**)
- Cohort 1B: Surovatamig in combination with acalabrutinib 100 mg PO BID beginning in cycle 2 (**Fig. 3**)
- Cohort 1C: IV surovatamig administered with triple step-up dosing in cycle 1; target dose given every 2 weeks (**Fig. 2**)

Study Endpoints

- **Primary:** safety, tolerability
- **Secondary:** efficacy, PK, immunogenicity

[a]Substudy 2: R/R MCL; substudy 3: TN LBCL or R/R B-NHL. LBCL substudy will not be conducted in the US.

Key inclusion criteria

All patients

- Age ≥18 y
- ECOG PS 0–2
- Adequate organ function
- Confirmation of CD19 expression if patient received previous anti-CD19 therapy

Substudy 1

- Histologically documented CLL/SLL by WHO criteria
- Disease requiring treatment per iwCLL 2018 criteria[8]
- Cohorts 1A or 1C: ≥2 prior lines of therapy (including a BTKi or BCL2i)
- Cohort 1B: ≥1 prior line of therapy and BTKi sensitive

Figure 3. Dose-escalation Scheme (Combination Therapy)

At least 2 dose levels of DL2 and DL3 of surovatamig within the combination therapy dose escalation will be backfilled.

Davids et al, iwCLL 2025

Multiple sequencing options for CLL treatment in the clinical practice: need to define the optimal sequencing

A	cBTKi	Ven + antiCD20	ncBTKi
B	cBTKi	ncBTKi	Ven + antiCD20
C	Ven + antiCD20	cBTKi	ncBTKi
D	cBTKi + Ven	cBTKi	ncBTKi
E	cBTKi + Ven	Ven + antiCD20	ncBTKi
F	cBTKi + Ven	cBTKi + Ven	ncBTKi

Intersectionality in CLL management

Prior to treatment

Understanding the patient preference of treatment

On treatment

Continuing the patient conversation

Do we need to introduce Intersectionality?

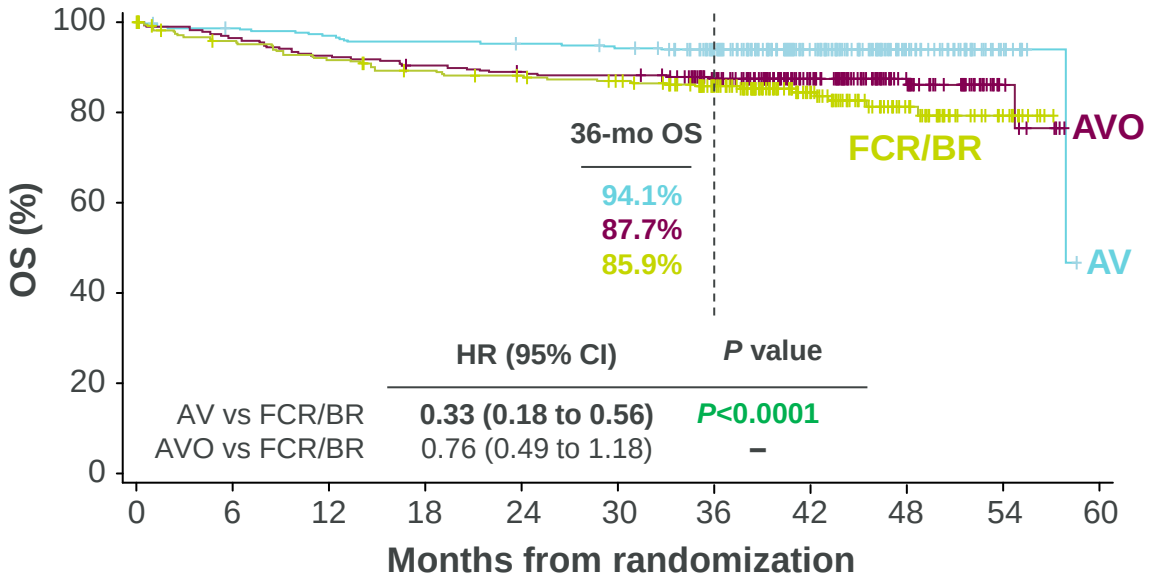
Intersectionality, a concept introduced by Kimberlé Crenshaw in 1989, describes the way in which different aspects of an individual's identity "intersect" to create unique experiences and effects. Its application in patient care is crucial, as it encompasses how different identities impact health care delivery and outcomes.

Non-clinical factors which influence treatment choice in CLL

1. Health system-related factors
2. Social domains-related factors

Overall Survival

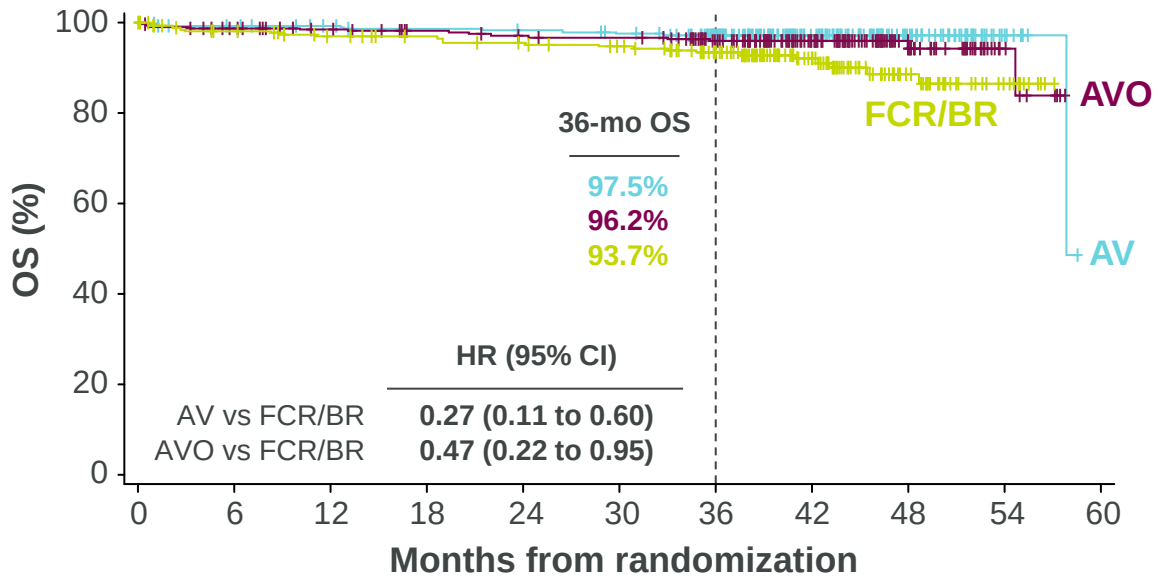
OS Prolonged With AV vs FCR/BR



Patients at risk

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

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



Patients at risk

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

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

ITT population.
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Brown et al, NEJM 2025

ELDERLY in FD studies

	Age < 65 years	Age > 65 years	Del(17p)/TP53m
I+V	**CAPTIVATE** [1] **(Phase II)** *n=114*	**GLOW**[2] **(Phase III)** ***n= 90***	**CAPTIVATE** [1] **(Phase II)**
A+V	**AMPLIFY**[3] **(Phase III)** *n= 212*	***n=79***	**MAJIC**[7] **(Phase III – ongoing)**
A+V+O	**AMPLIFY**[3] **(Phase III)** *n= 210*	***n=76***	**DAVIDS et al., 2025**[4] **(Phase II)**
V+O	**CLL13**[5] **(Phase III)** *n=147*	**CLL14**[6] **(Phase III)** *n=72** (> 75 yrs)	**CLL14**[6] **(Phase III)**

1 Tam et al. *Blood* vol. 139,22 (2022): 3278-3289. doi:10.1182/blood.2021014488**; 2** Kater et al. *NEJM evidence* vol. 1,7 (2022): EVIDoa2200006. doi:10.1056/EVIDoa2200006**; 3** Brown et al. *NEJM* vol. 392,8 (2025): 748-762. doi:10.1056/NEJMoa2409804**; 4** Davids et al. *Journal of clinical oncology* vol. 43,7 (2025): 788-799. doi:10.1200/JCO-24-02503**; 5** Fürstenau et al. *The Lancet. Oncology* vol. 25,6 (2024): 744-759. doi:10.1016/S1470-2045(24)00196-7**; 6** Al-Sawaf et al. *Blood* vol. 144,18 (2024): 1924-1935. doi:10.1182/blood.2024024631 **7.** Ryan et al., Future Oncol. 2022 Oct;18(33):3689-3699. doi: 10.2217/fon-2022-0456. Epub 2022 Sep 14

Study Design - GAIA/CLL13

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

Final analysis (data cut-off: 02/2024)

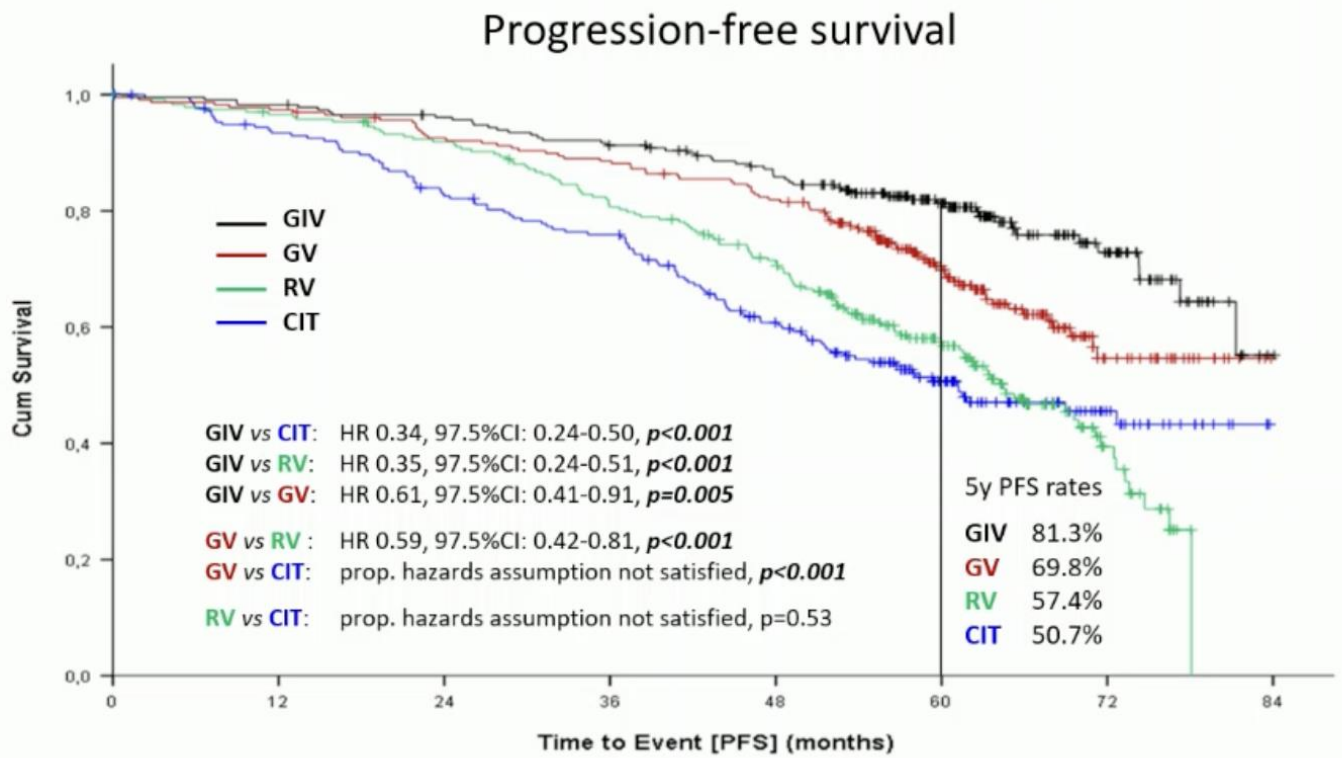
Median observation time
63.8 months (IQR: 57.4-71.3)

Median observation time after end of treatment
54.0 months (IQR: 47.3-61.1)

Furstenau et al, EHA 2025

Efficacy – PFS

Median observation time: 63.8 months



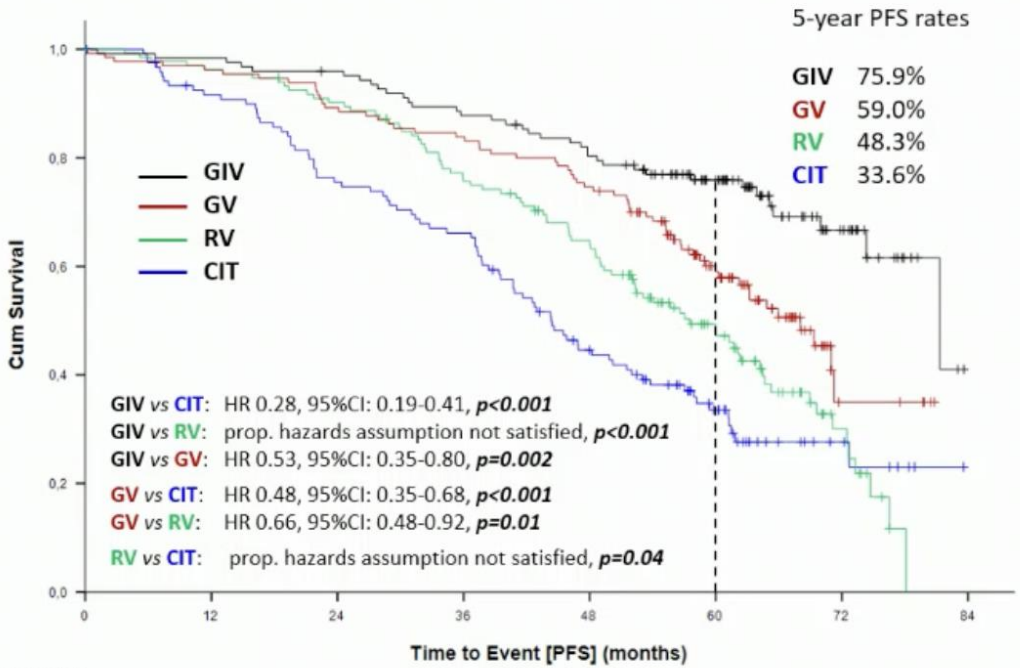
Patients at risk

CIT	229	198	174	159	119	67	21
RV	237	227	214	187	160	89	20
GV	229	223	210	201	185	109	25
GIV	231	227	219	207	189	126	44

Furstenau et al, EHA 2025

Efficacy – PFS

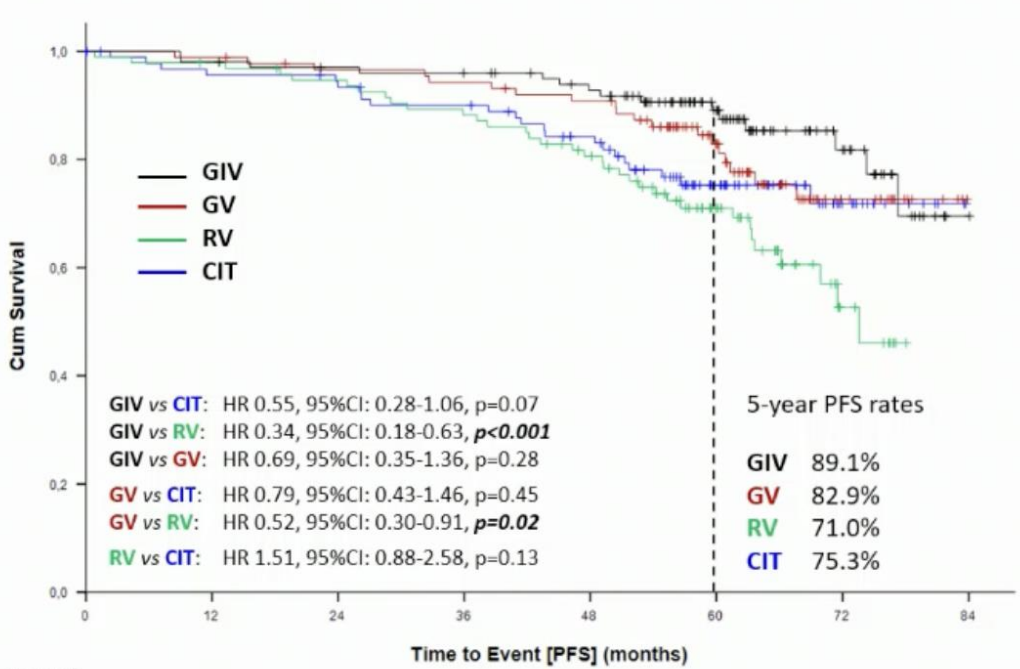
PFS – unmutated IGHV



Patients at risk

CIT	131	108	89	78	49	27	7
RV	134	128	119	99	82	44	11
GV	130	125	116	109	97	54	5
GIV	123	121	117	107	97	67	21

PFS – mutated IGHV

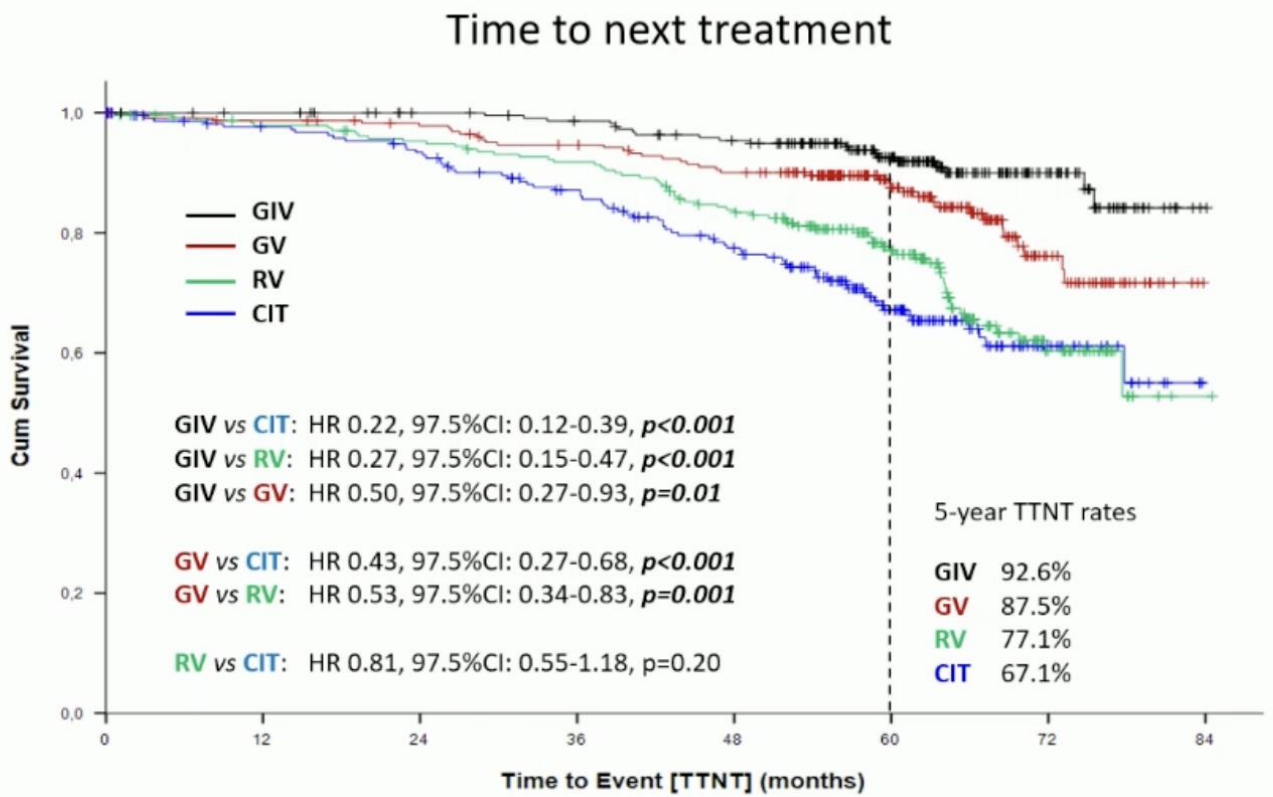


Patients at risk

CIT	95	87	84	80	70	40	14
RV	95	92	88	82	72	42	9
GV	89	88	84	82	78	49	15
GIV	101	99	96	94	87	57	23

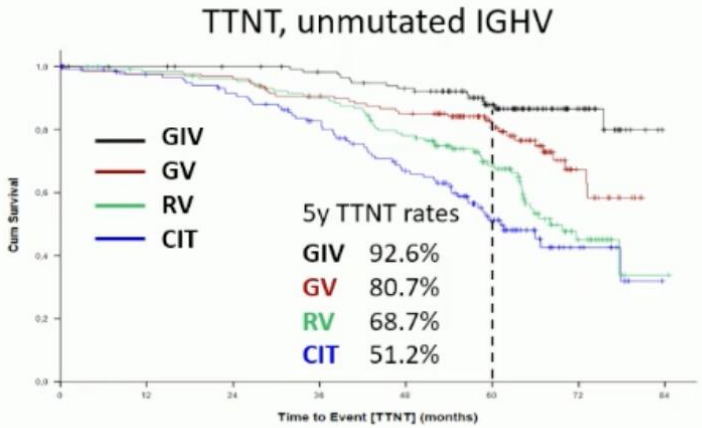
Furstenau et al, EHA 2025

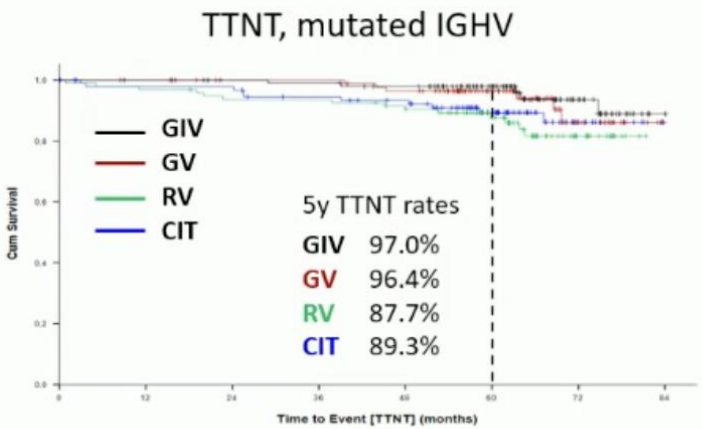
Efficacy – TTNT



Patients at risk

CIT	229	206	196	175	148	88	23
RV	237	227	219	210	188	119	33
GV	229	224	218	208	196	124	36
GIV	231	228	220	214	202	141	48





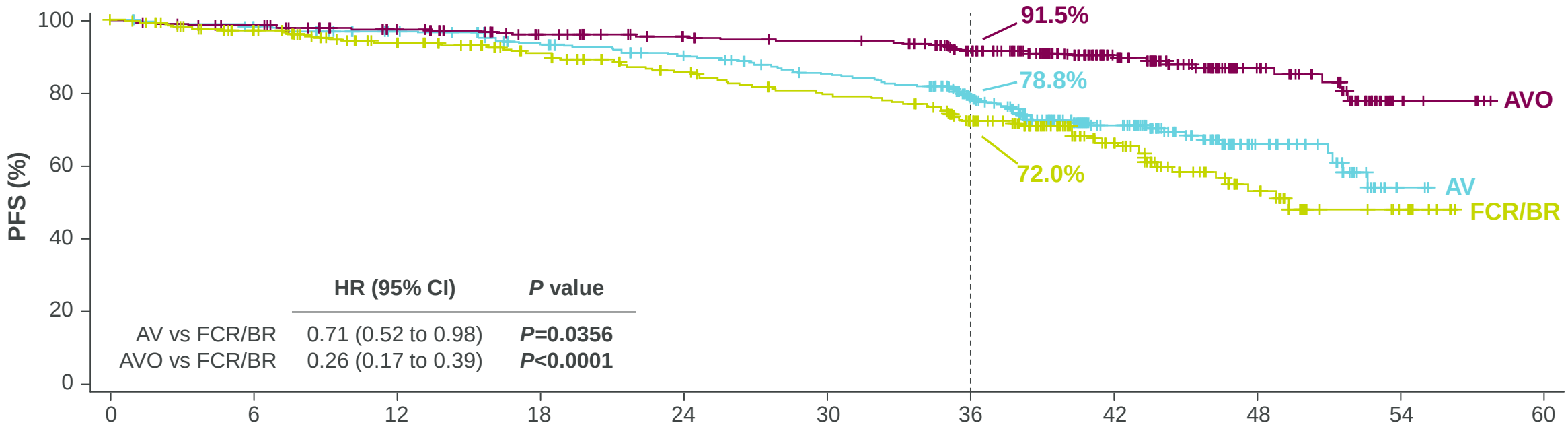
Furstenau et al, EHA 2025

Summary

- After a median observation time of 63.8 months **GV and GIV show superior PFS** compared to chemoimmunotherapy and RV
- Patients treated with **GIV have longer PFS** compared to GV
- Unmutated IGHV was independently associated with shorter PFS in all treatment arms
- **No overall survival difference** was observed between treatment arms
- In addition to PFS, other factors **like OS, treatment-associated toxicities and differences in QoL** have to be considered when **comparing GV and GIV**

Furstenau et al, EHA 2025

PFS Censoring COVID-19 Deaths (Prespecified Analysis)



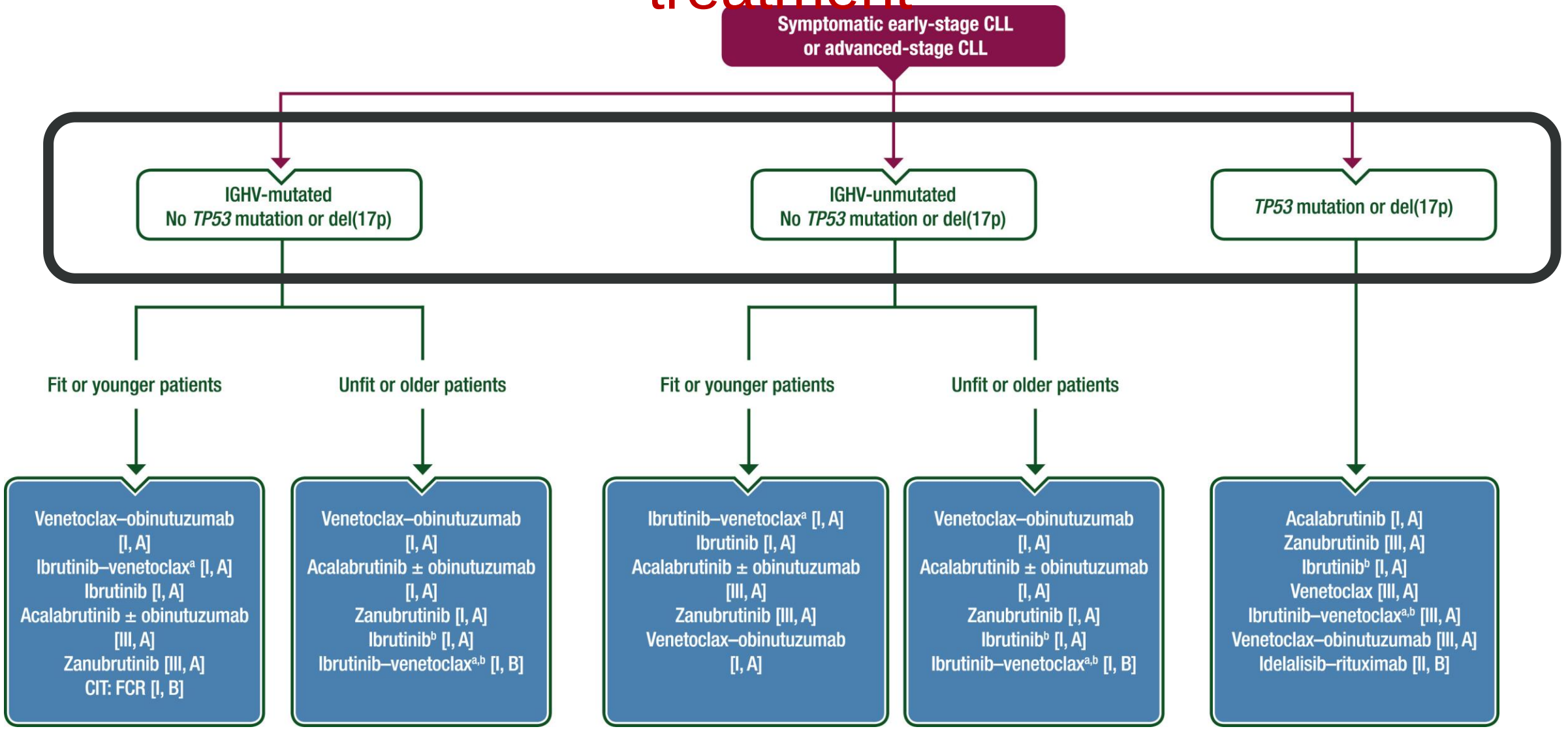
Patients at risk

AV	291	281	268	251	237	219	177	102	35	3	0
AVO	286	270	255	236	224	219	191	116	51	7	0
FCR/BR	290	234	206	189	170	154	127	66	28	6	0

Median PFS: NR (AV and AVO) and 49.2 mo (FCR/BR)

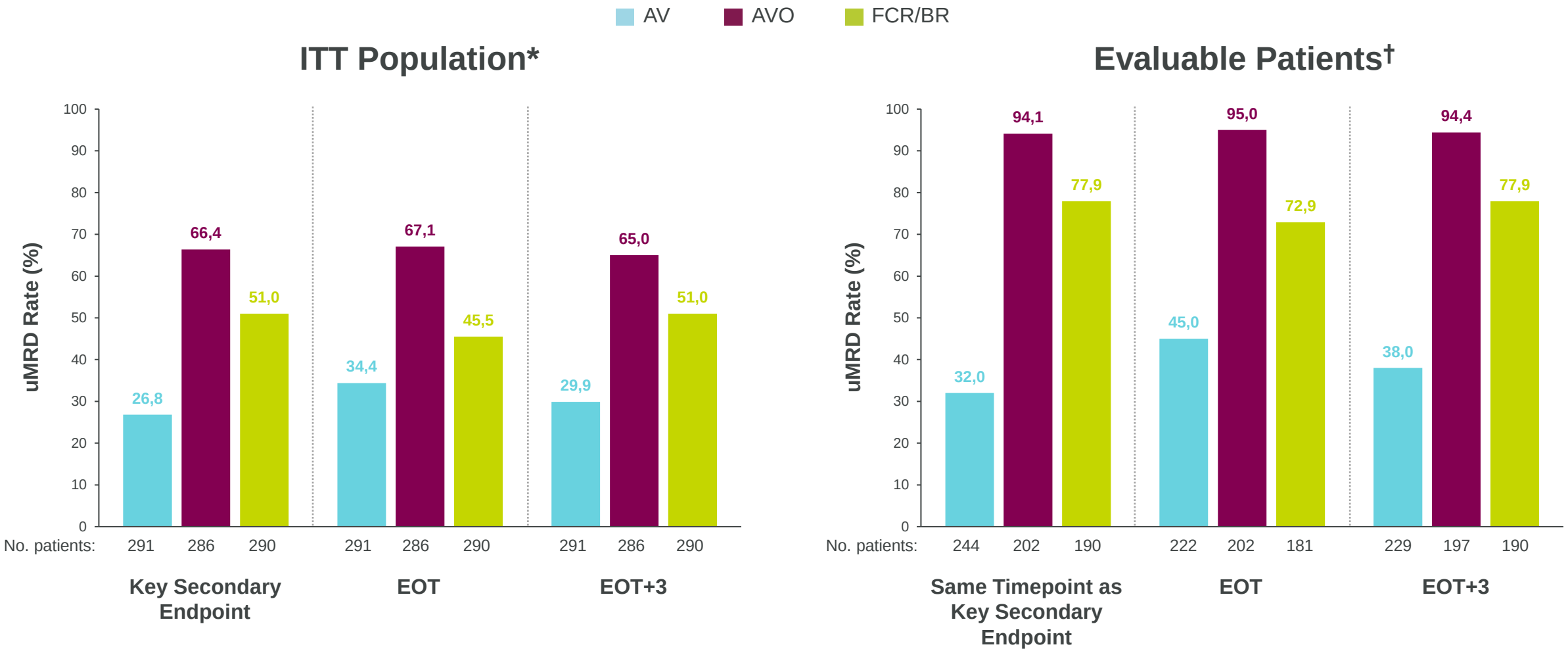
Total COVID-19 deaths (censored for PFS sensitivity): AV, 10 (**8**), AVO, 25 (**25**), FCR/BR, 21 (**18**); patients with PD event prior to COVID-19 death were not censored for PFS.
PFS was assessed by IRC; median follow-up from randomization: 40.8 months (range, 0–59 months).
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; NR, not reached; PD, progressive disease; PFS, progression-free survival.

CLL biomarkers in the ESMO guidelines for 1L treatment



Eichhorst *et al., Ann Oncol*. 2024.

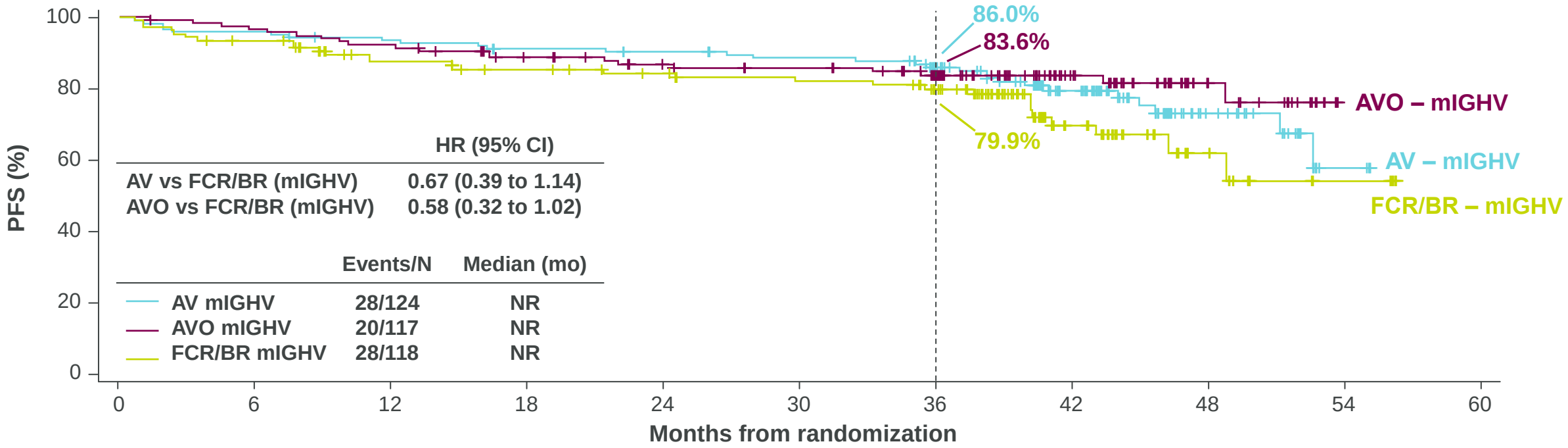
uMRD Rates (Flow Cytometry [<10^{-4}] in PB)



Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

Key secondary endpoint (ITT population): AV vs FCR/BR: *P*<0.0001 (favoring FCR/BR); AVO vs FCR/BR: *P*=0.0003 (favoring AVO).
*ITT population: all randomized patients regardless of whether MRD assessment was performed at the specified time point (missing assessments considered MRD+).
†Evaluable patients: those with MRD assessment at the specified timepoint.
EOT: cycle 14 day 28 for AV (± obinutuzumab); cycle 6 day 1 (±28-day window) (FCR/BR).
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; EOT, end of therapy; EOT+3, end of therapy plus 12 weeks; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat; MRD+, detectable measurable residual disease; PB, peripheral blood; uMRD, undetectable measurable residual disease.

PFS in the mIGHV Subgroup



Patients at risk

AV mIGHV	124	119	114	110	108	105	91	54	18	2	0
AVO mIGHV	117	111	106	96	89	86	73	41	15	0	
FCR/BR mIGHV	118	99	86	81	76	72	65	28	9	2	0

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

Brown et al, NEJM 2025