Il suono DELL' INNOVAZIONE
Bologna Palazzo De' Toschi 27-28 novembre 2025

La ridefinizione dell' alto rischio nella CLL

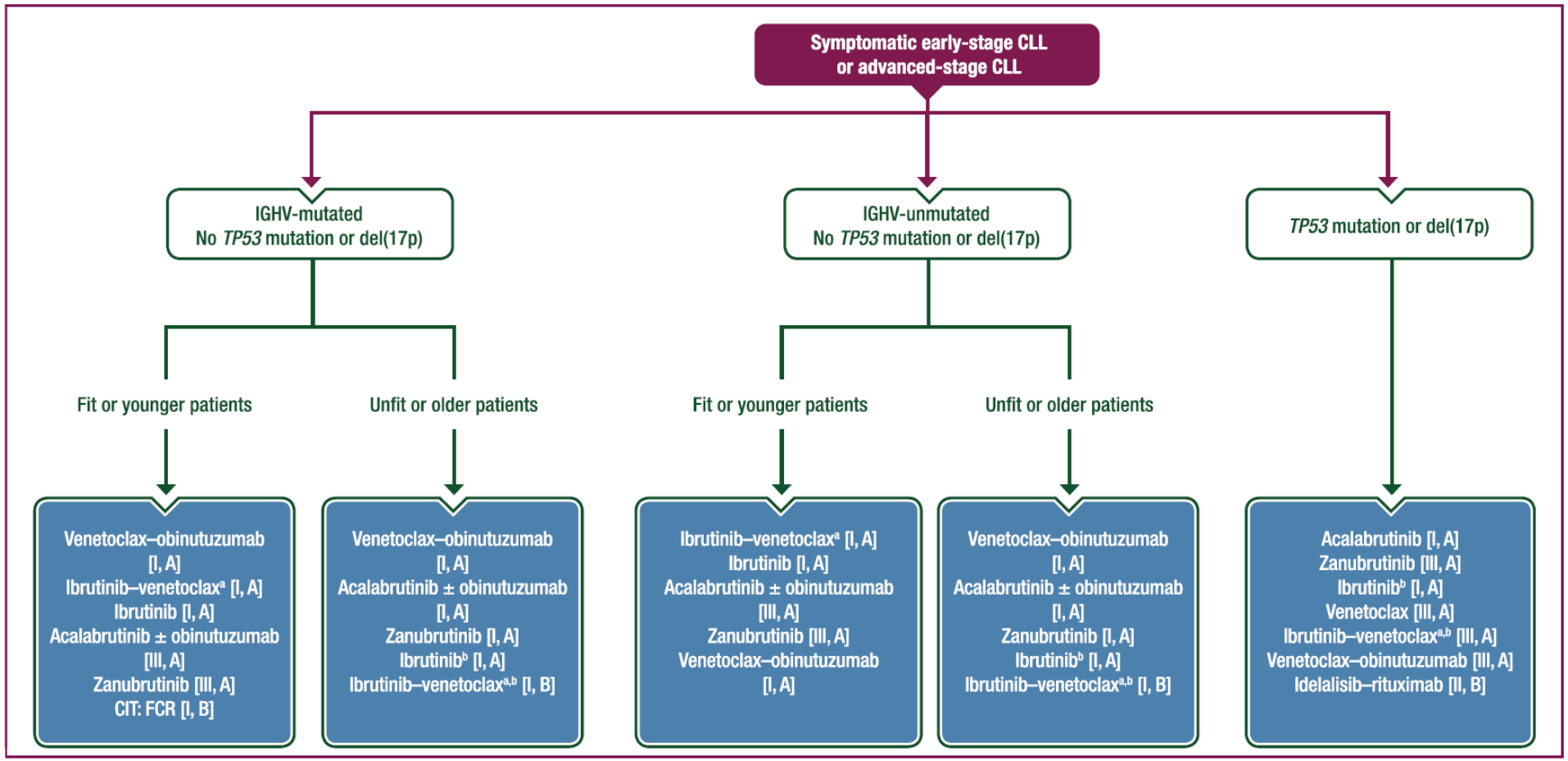
Luca Laurenti
Fondazione Policlinico Universitario A Gemelli-IRCCS-Roma

DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X				X	X	
AstraZeneca	X				X	X	
Beigene					X	X	
Johnson & Johnson					X	X	
Lilly					X	X	

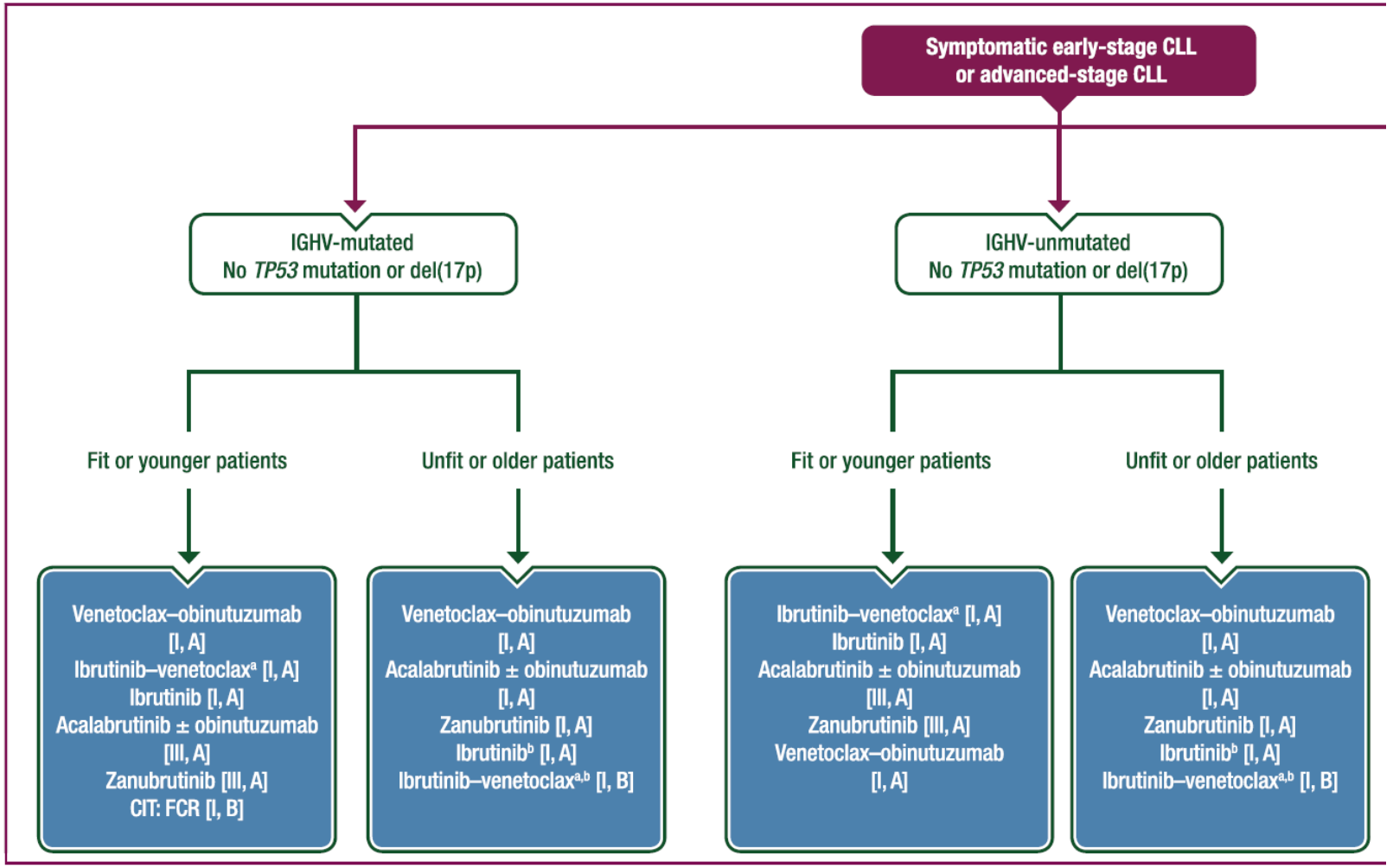
ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆

B. Eichhorst[1†], P. Ghia[2,3†], C. U. Niemann[4], A. P. Kater[5], M. Gregor[6], M. Hallek[1,7], M. Jerkeman[8] & C. Buske[9], on behalf of the ESMO Guidelines Committee*



Eichhorst, P. Ghia, C.U. Niemann, A.P. Kater, M. Gregor, M. Hallek, M. Jerkeman, C. Buske, ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆, Annals of Oncology, 2024.

The role of IGHV Mutational Status



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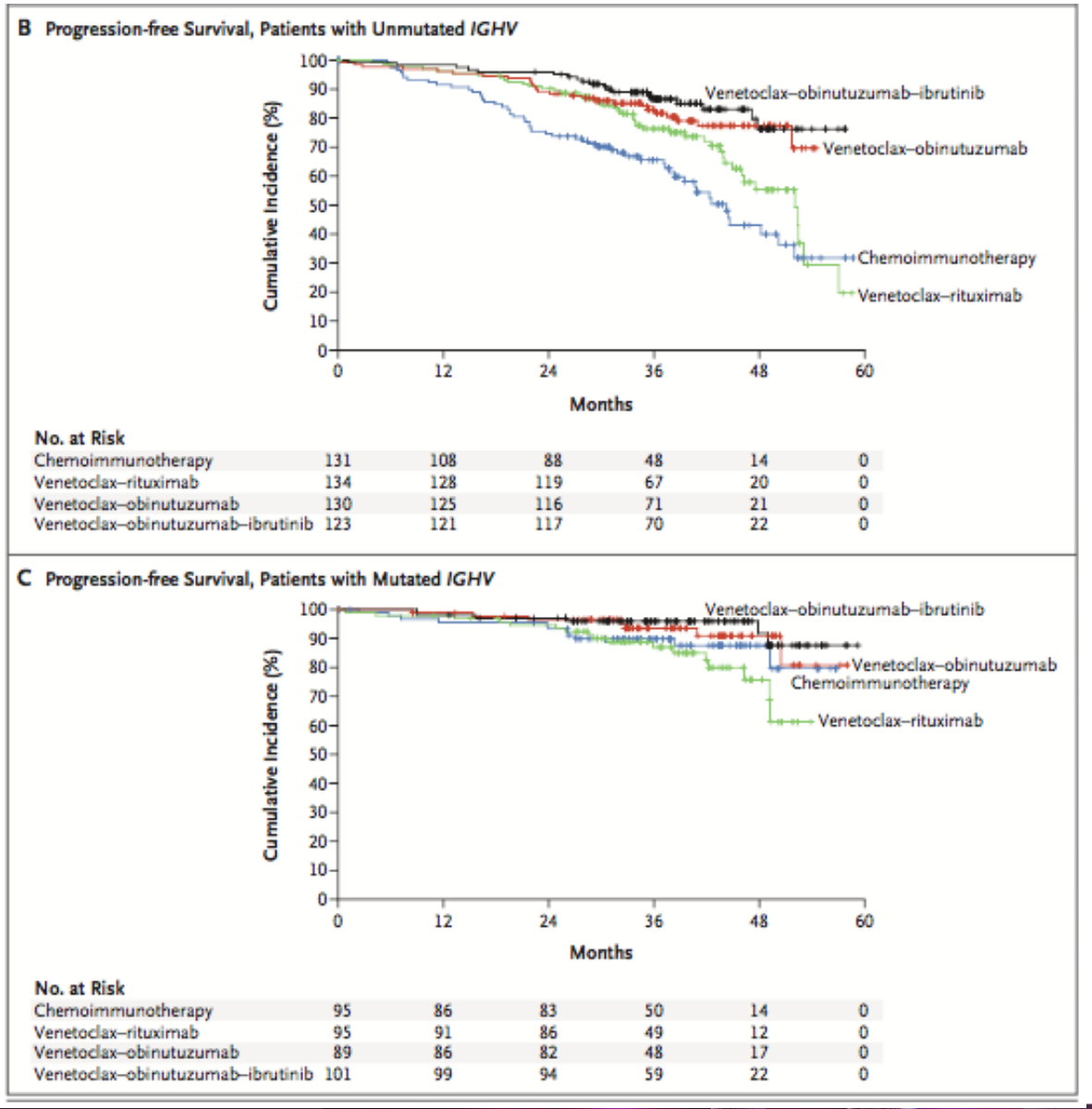
CLL13
Fit/YOUNG
Median age 62



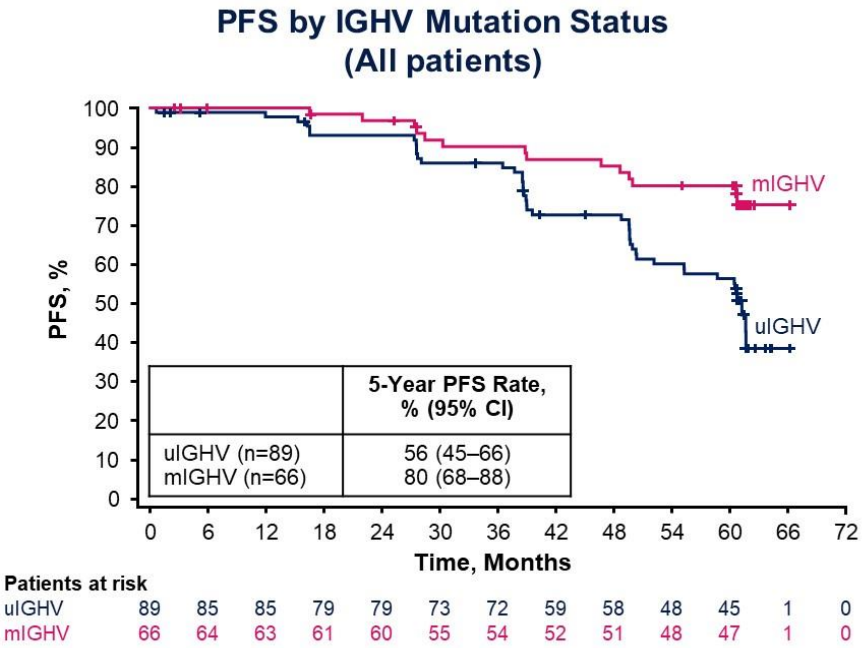
PFS 82,9%
36 months

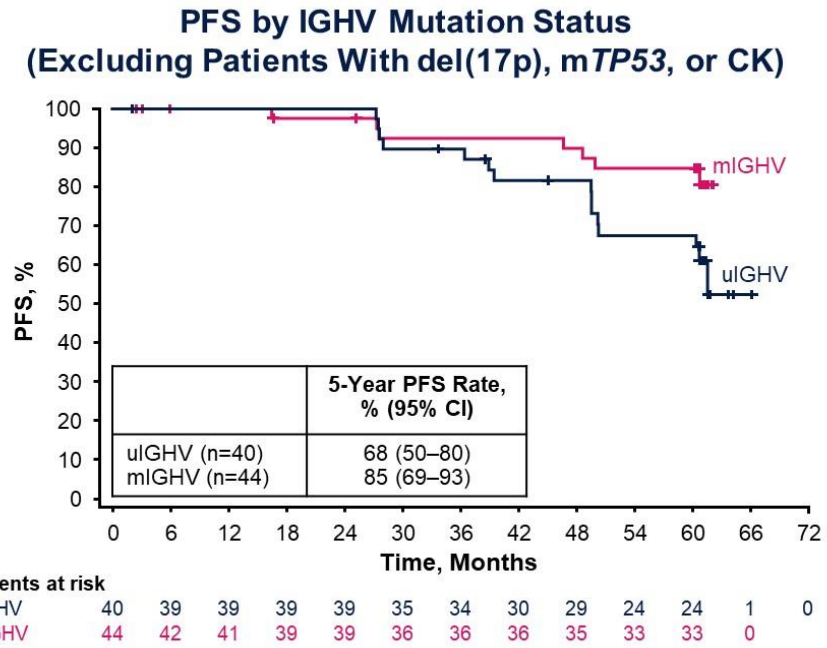
PFS 93,6%
36 months

Captivate 5,5 yy F-UP
Young/FIT

Median Age 60

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



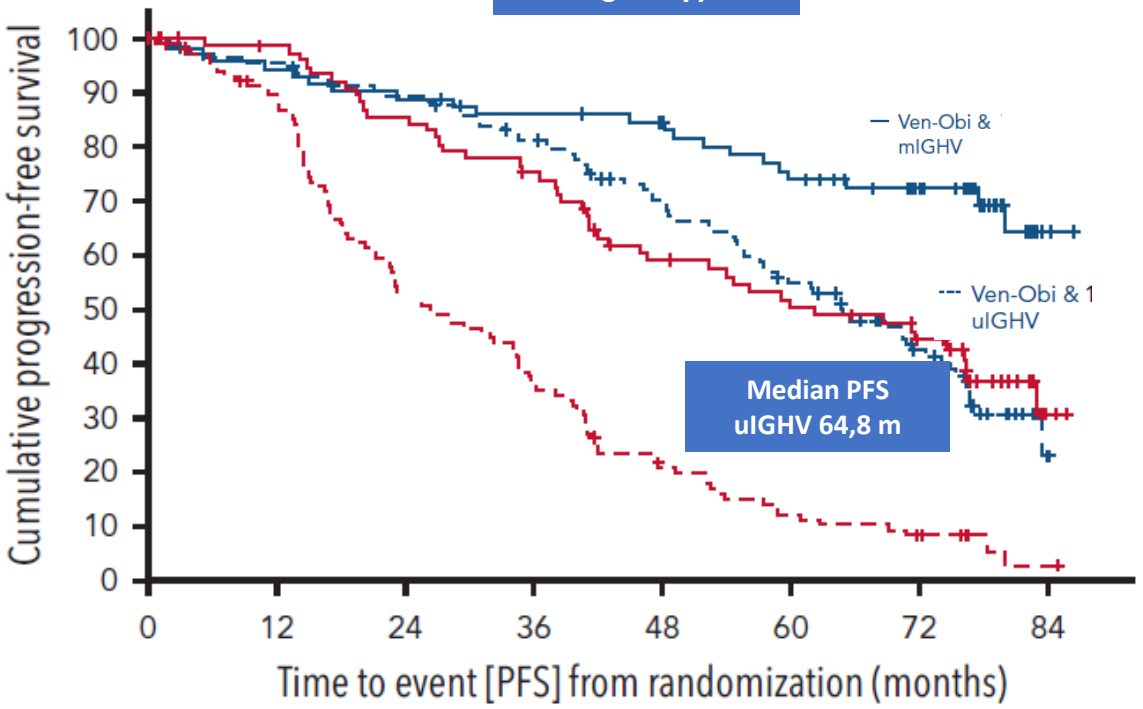


- Presence of del(17p), m*TP53*, and/or CK had a substantial impact on PFS in patients with uIGHV and mIGHV

mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

FIX DURATION THERAPY: Impact of IGHV Status On PFS

CLL14
Age 72 yy

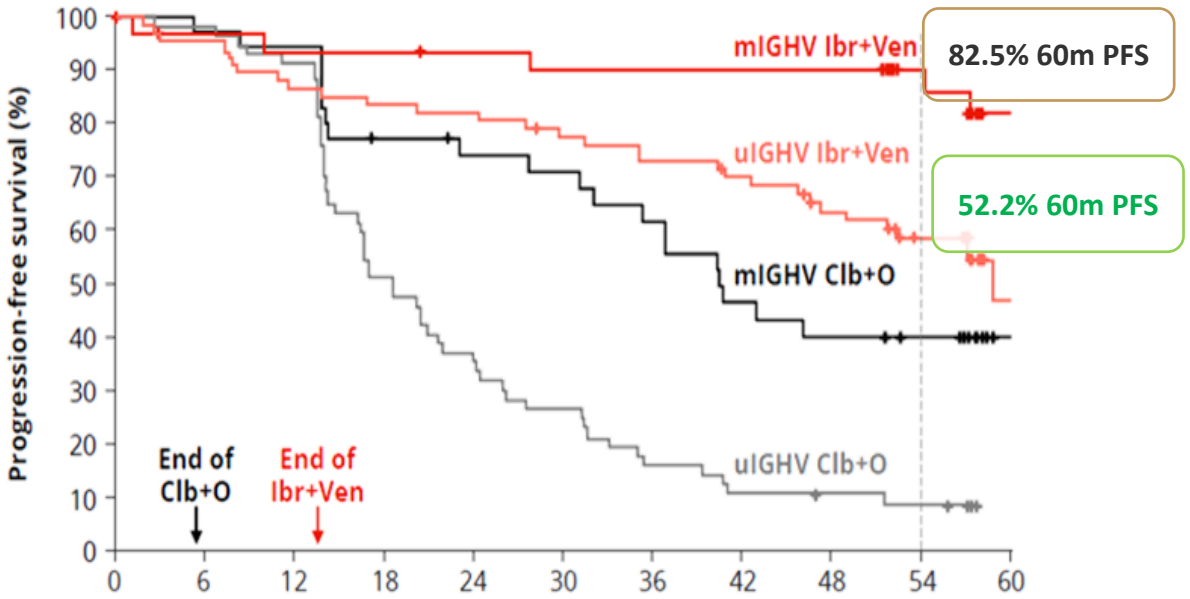


Median PFS with VO

mIGHV	**NR**
uIGHV	**64.8 months**

Al-Sawaf O,Blood. 2024 Oct 31;144(18):1924-1935. doi: 10.1182/blood.2024024631. PMID: 39082668; PMCID: PMC11551846.

GLOW
Age 71yy



60m PFS rate with IV

mIGHV	**82.5%**
uIGHV	**52.2%**

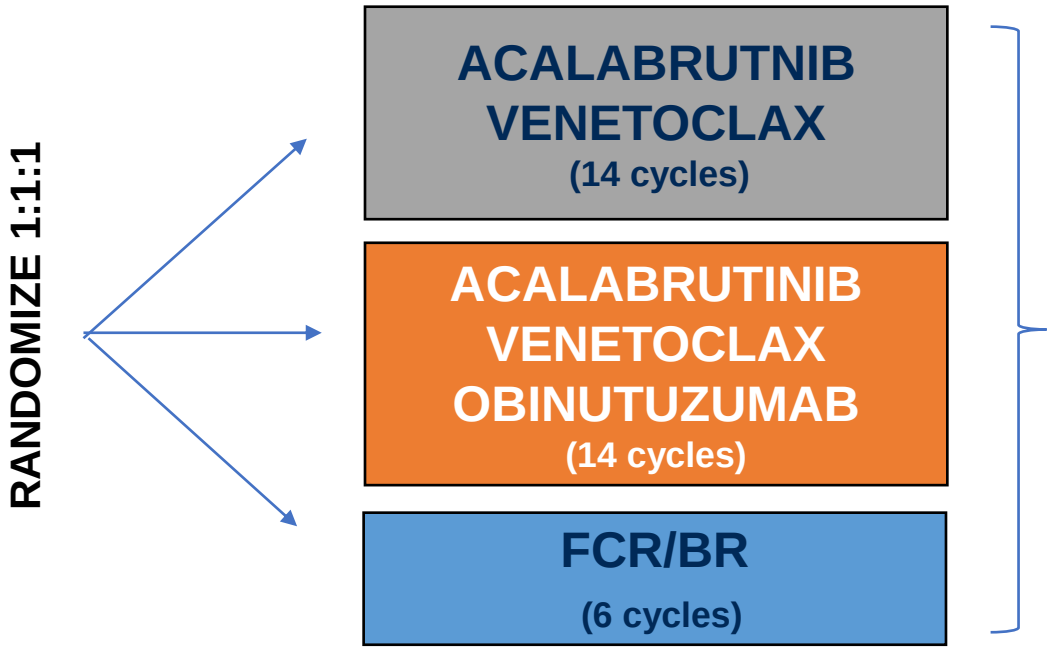
Carsten Utoft Niemann, . *Blood* 2024; 144 (Supplement 1): 1871. doi: https://doi.org/10.1182/blood-2024-203269.

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

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- Without del(17p) or *TP53*
- ECOG PS ≤2

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



Primary endpoint:

IRC-assessed PFS (AV vs FCR/BR)

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

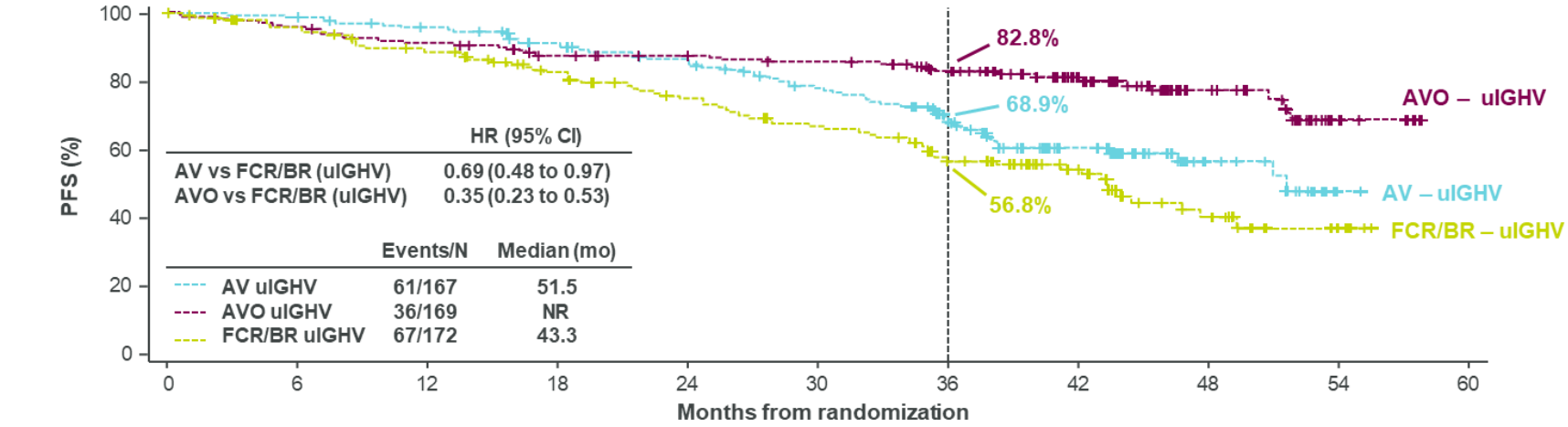
1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV or AVO vs FCR/BR)
3) OS (AV or AVO vs FCR/BR)

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)

Brown JR ASH 2024

FIX DURATION THERAPY: Impact of IGHV Status On PFS

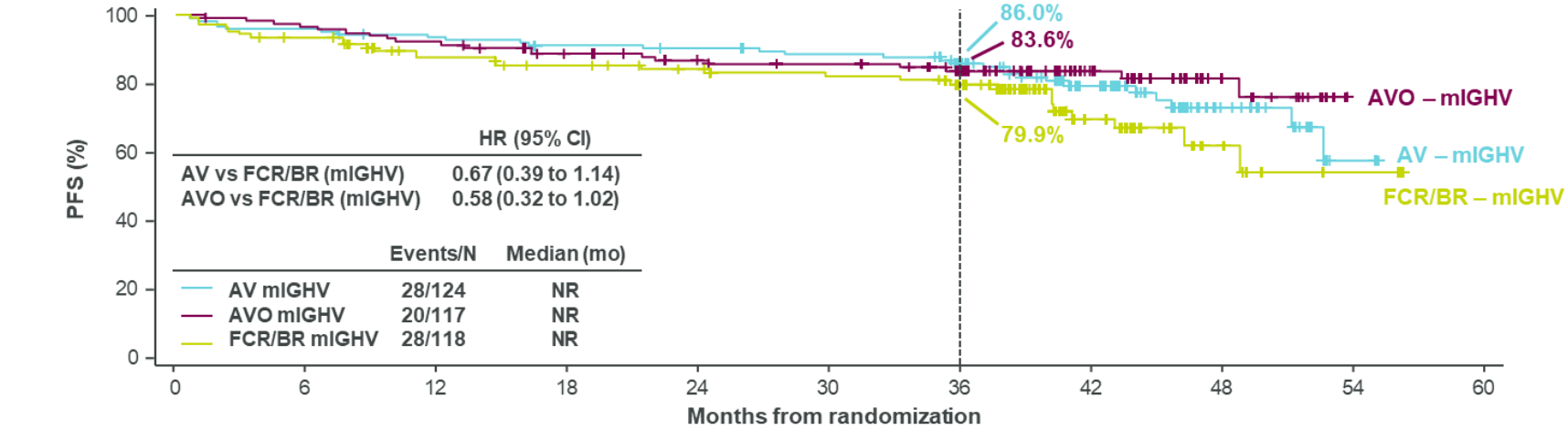


Patients at risk

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

AMPLIFY uIGHV

Age 61 yy FIT



Patients at risk

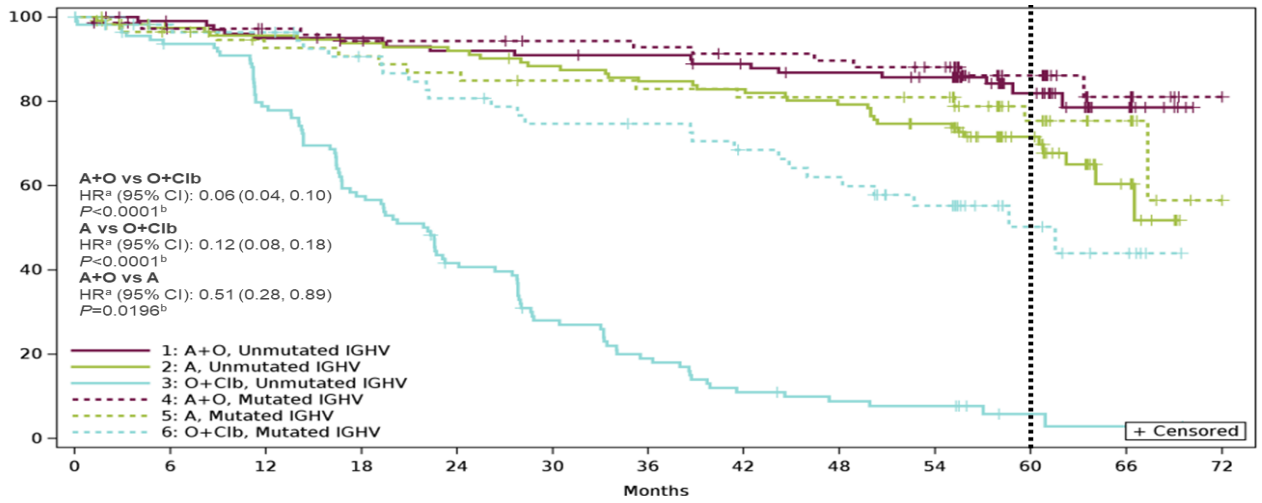
AV mIGHV	124	119	114	110	108	105	91	54	18	2	0
AVO mIGHV	117	111	106	96	89	86	73	41	15	0	
FCR/BR mIGHV	118	99	86	81	76	72	65	28	9	2	0

AMPLIFY mIGHV

Brown JR, et al. *N Engl J Med.* 2025;392(8):748-762.

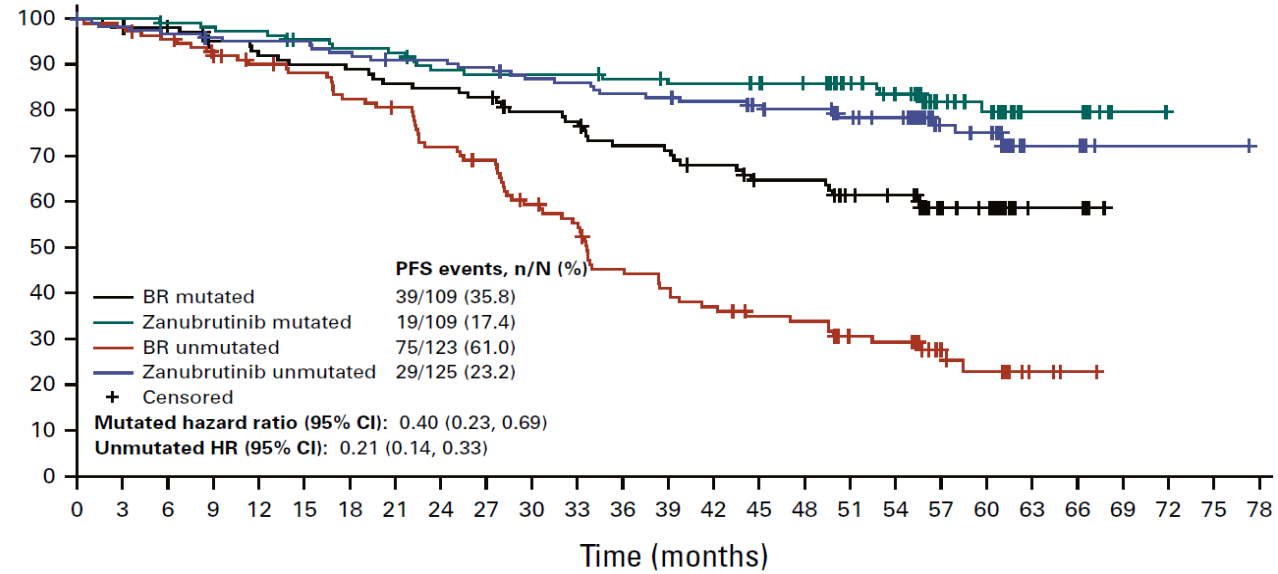
BTKi until progression: Impact of IGHV Status On PFS

Acalabrutinib
Unmut IGHV
ELEVATE-TN



5-Year
PFS 72%
Age 70

Zanubrutinib
Unmut IGHV
SEQUOIA (Arm A+B)



5-Year
PFS 76%
Age 71

Shadman M. et al.,. J Clin Oncol. 2025 Mar;43(7):780-787. doi: 10.1200/JCO-24-02265. Epub 2024 Dec 8. PMID: 39647999; PMCID: PMC11855994.

EHA Library. P. Sharman J. 06/10/22; 357528; P666

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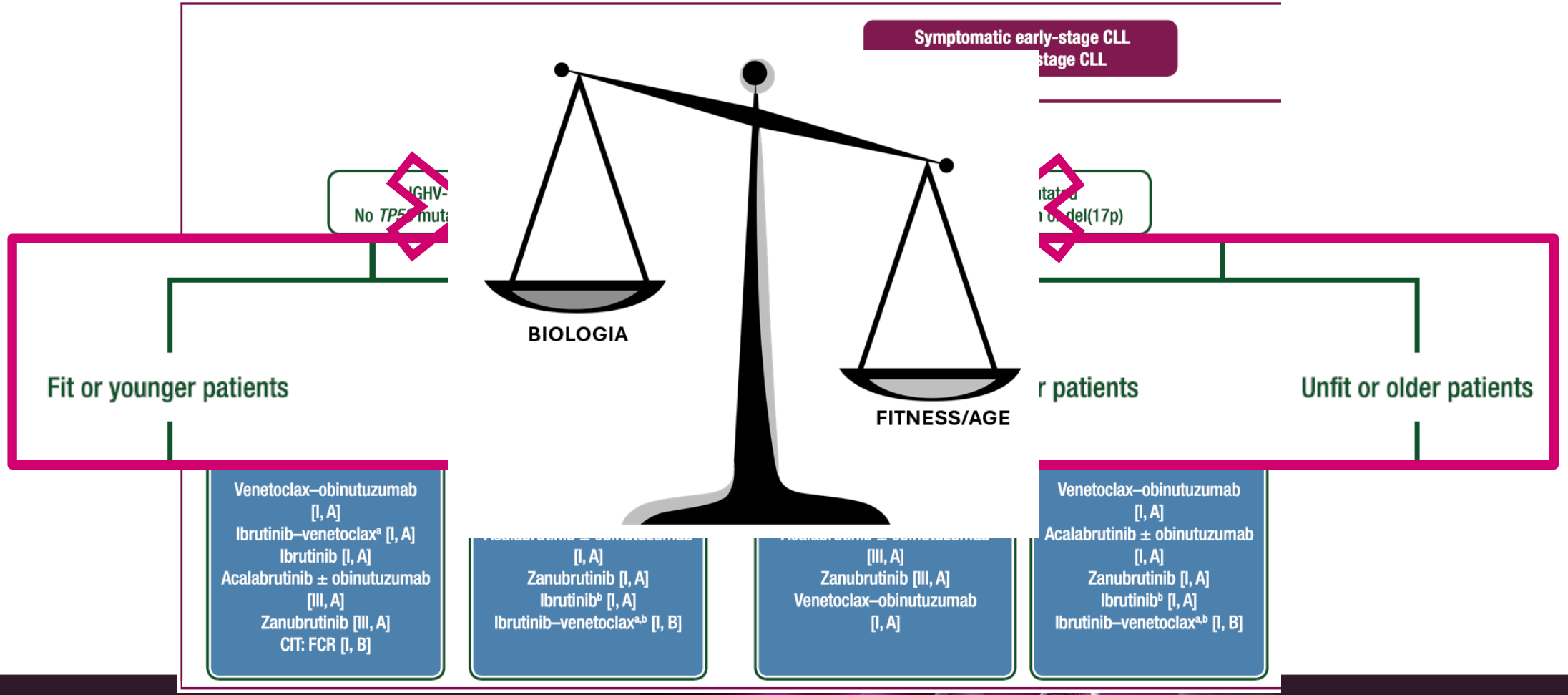

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CLL17

Abstract Title : Fixed-duration versus continuous targeted treatment for previously untreated chronic lymphocytic leukemia: Results from the randomized CLL17 trial

Three-yr PFS was 81.1% in the VO arm compared to 81.0% in the I arm (HR 0.87, type-I-error adjusted CI [98.3%] 0.54-1.41) and 79.4% in the VI arm (compared to I arm: HR 0.84, type-I-error adjusted CI [98.0%] 0.53-1.32), respectively, with the upper limit of each adjusted CI below the pre-defined non-inferiority margin, providing early evidence of non-inferiority.

At final staging (C18D1), the ORR was 84.2% in the VO arm, 88.5% in the VI arm, and 86.0% in the I arm, with a CR rate of 51.5%, 46.2%, and 8.3%, respectively; the uMRD ($<10^{-4}$) rate in ITT population in peripheral blood was 73.3% (62.0% in bone marrow) in the VO arm, 47.2% (40.0% in bone marrow) in the VI arm and 0% (0% in bone marrow) in the I arm.

At 3 yrs, the OS rate was 91.5% in the VO arm, compared to 95.7% in the I arm (HR 1.67, 95% CI 0.86-3.28) and 96.0% in the VI arm (compared to I: HR 0.96, 95%CI 0.45-2.05), respectively.

For pts with unmutated IGHV, 3-yr PFS in the VO arm was 75.8% (87.6% for mutated IGHV) compared to 79.7% (83.5%) in the I arm (HR 0.98, 95% CI 0.61-1.59), and 78.9% (80.0%) in the VI arm (compared to I: HR 0.81, 95% CI 0.49-1.32). For pts with del(17p)/*TP53*mut, 3-yr PFS in the VO arm was 62.0% (82.7% for pts without del(17p)/*TP53*mut) compared to 79.4% (81.0%) in the I arm (HR 1.20, 95% CI 0.40-3.59), and 69.0% (80.1%) in the VI arm (compared to I: HR 0.70, 95% CI 0.22-2.16).

Al-Sawaf et al., abs25-2071 ASH 2025

Median age 66 aa (34-90), CIRS 0-18

CLL17	ORR C18 D1	CR	uMRD BM	PFS 3y F-UP	PFS uIGHV 3y F-UP	PFS mIGHV 3y F-UP	PFS del17p/TP53 3y F-UP
VO	84,2%	51,5%	62%	81,1%	75,8%	87,6%	62%
VI	88,5%	46,2%	40%	79,4%	78,9%	80%	69%
I	86%	8,3%	0%	81%	79.7%	83,5%	79,4%

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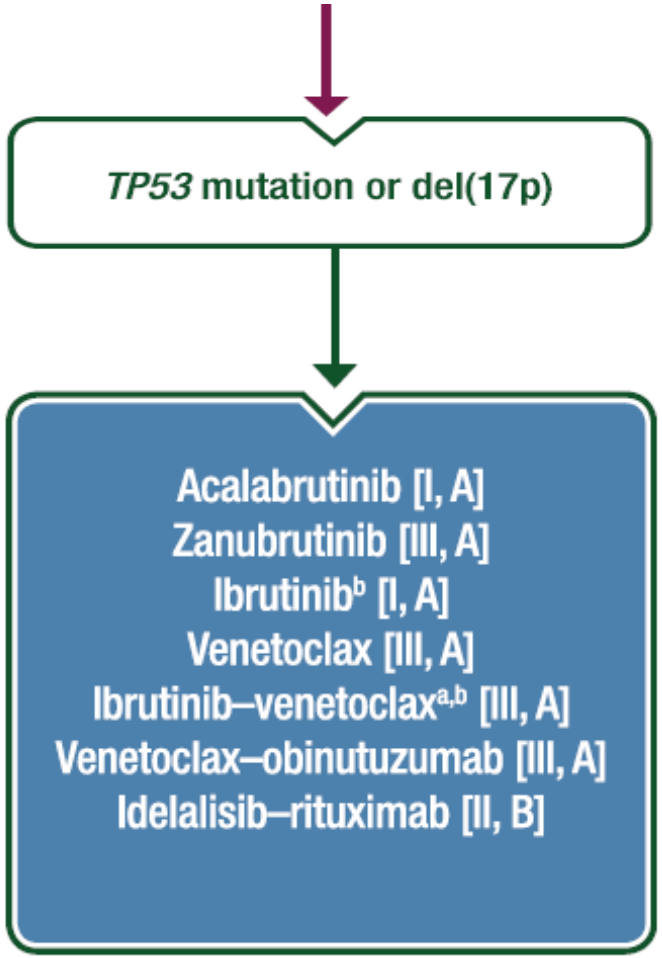
The role of TP53 or Del(17p)



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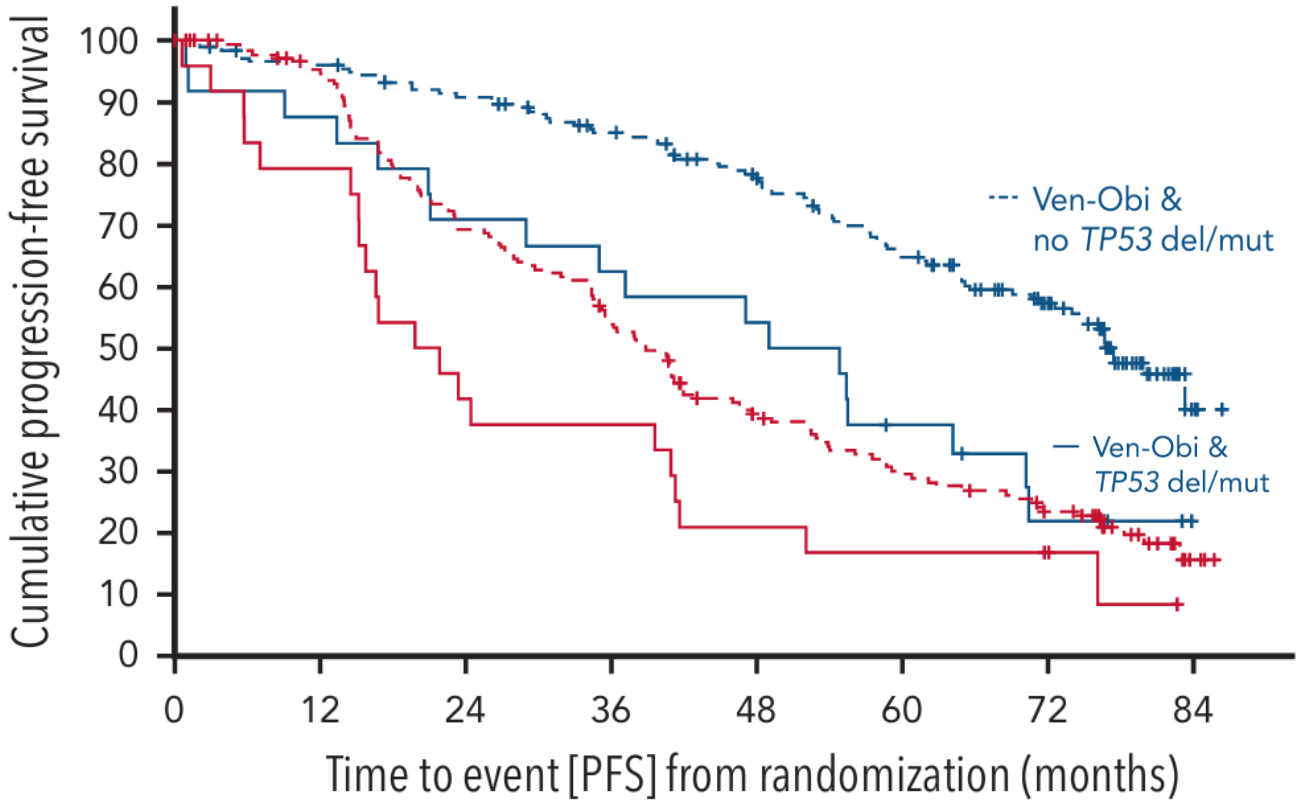
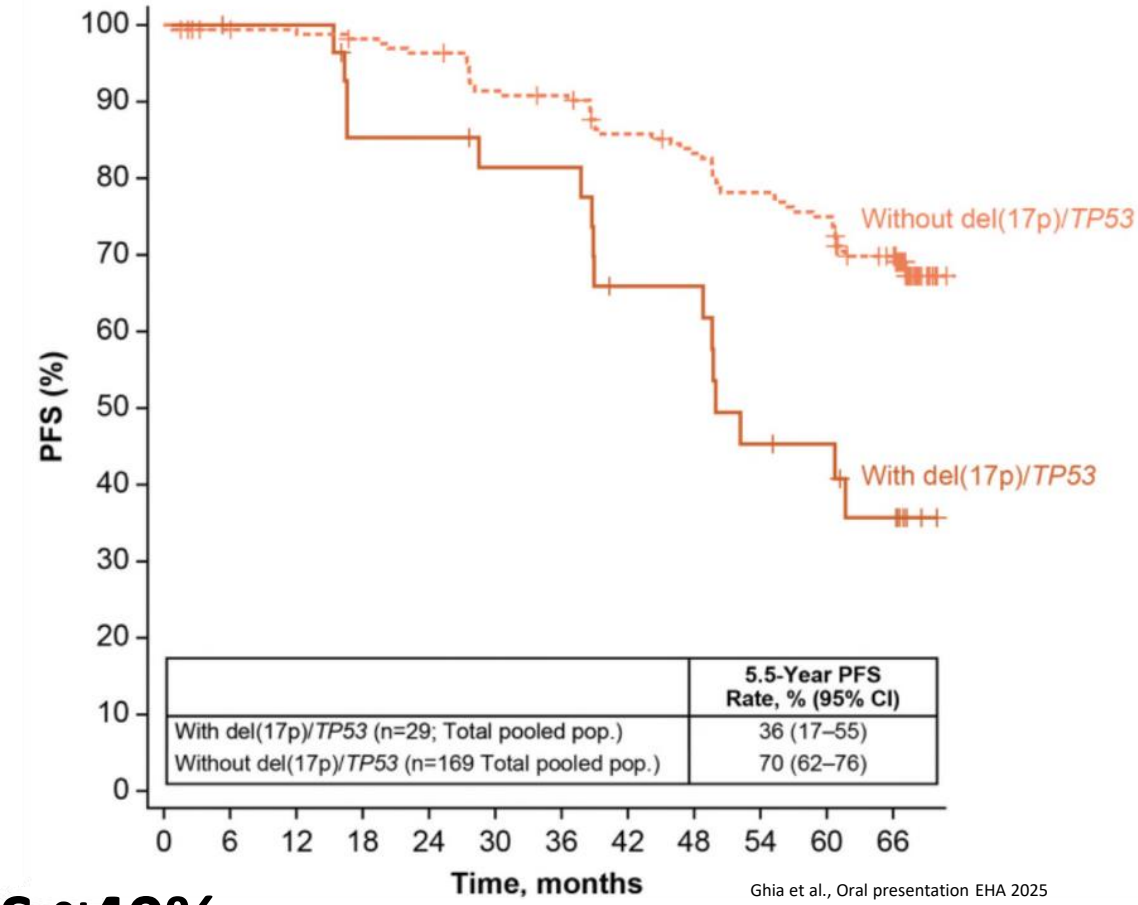
Fixed-Duration Therapy: efficacy outcomes in TP53 del/mut

Venetoclax + Obinutuzumab
CLL14



Al-Sawaf O, . Blood. 2024 Oct 31;144(18):1924-1935. doi: 10.1182/blood.2024024631.

Ibrutinib + Venetoclax
CAPTIVATE



Ghia et al., Oral presentation EHA 2025

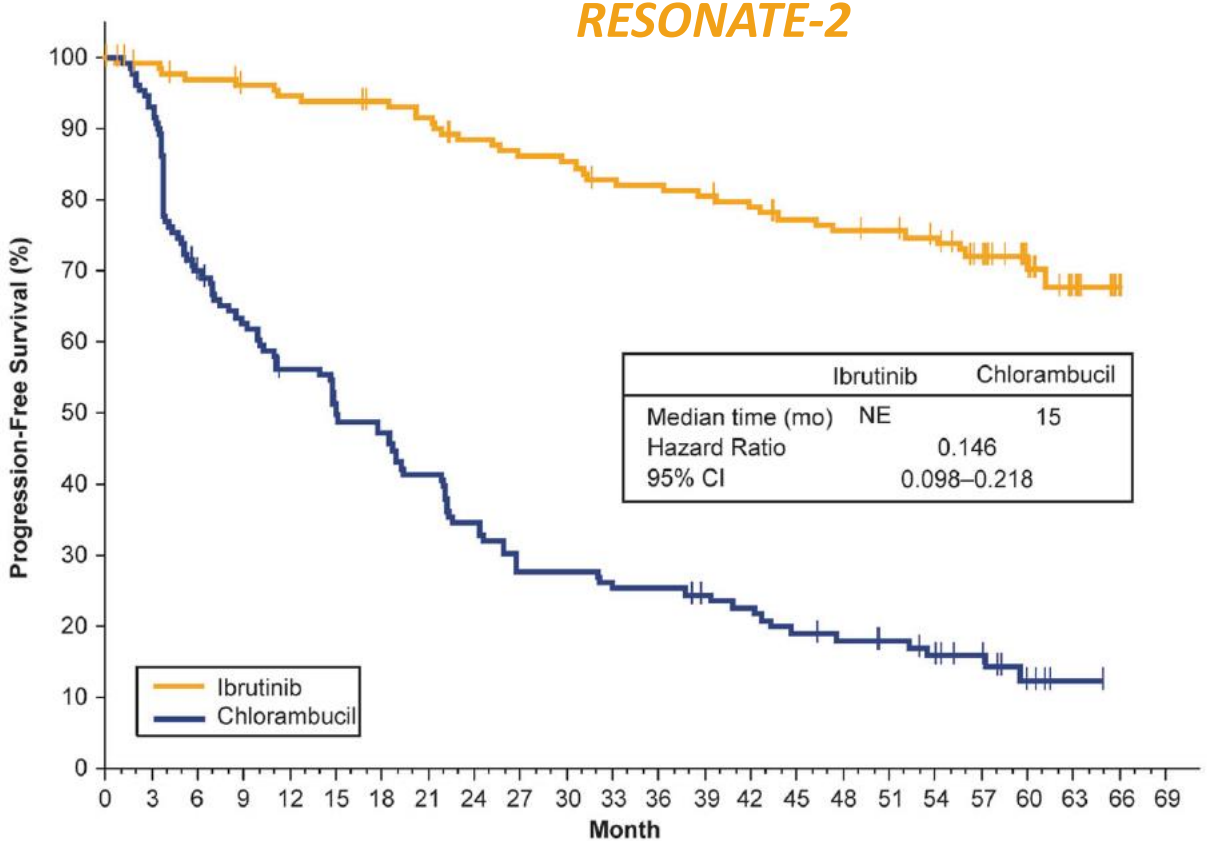
5-Year PFS ~40%

BTK Inhibitors until progression:

efficacy outcomes in TP53 del/mut

Ibrutinib without TP53/Del17p

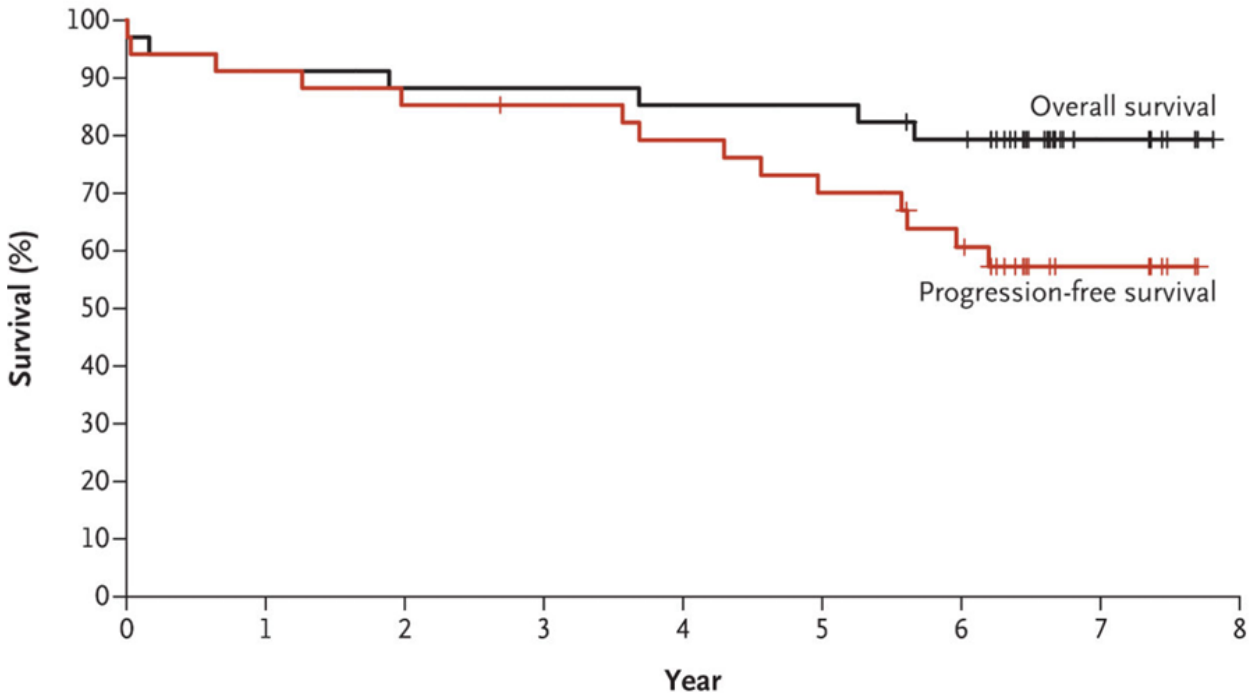
RESONATE-2



5-Year PFS 70%

Ibrutinib with TP53 del/mut

I. E. Ahn et al - N Engl J Med (2020)

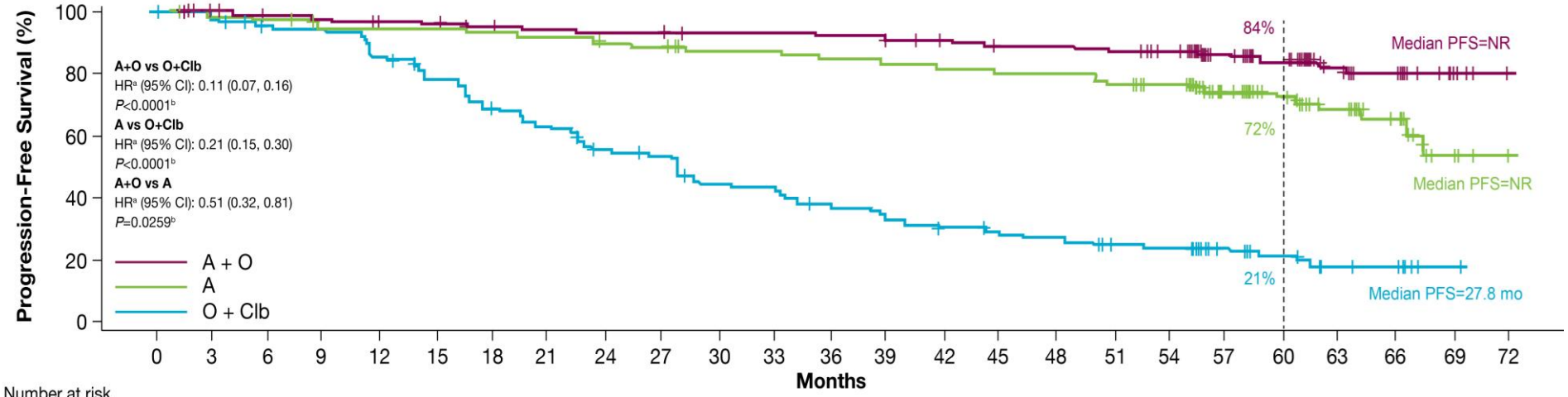


5-Year PFS 70%

Burger JA. Leukemia. 2020 Mar;34(3):787-798. doi: 10.1038/s41375-019-0602-x. Epub 2019 Oct 18. PMID: 31628428; PMCID: PMC7214263. Ahn IE, Tian X, Wiestner A. N Engl J Med. 2020 Jul 30;383(5):498-500. doi: 10.1056/NEJMc2005943. PMID: 32726539; P

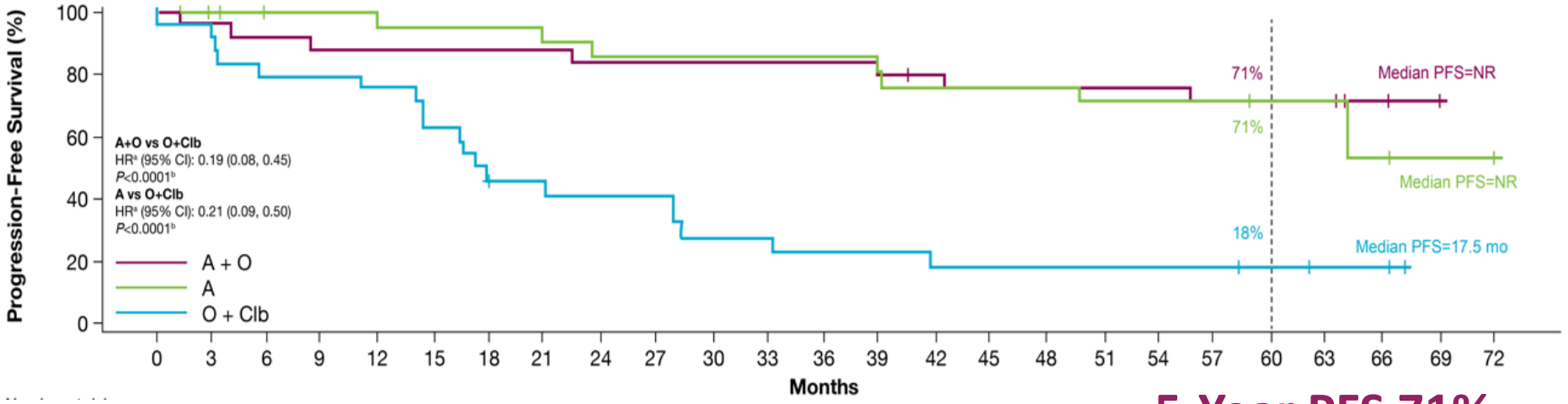
BTK Inhibitors until progression: efficacy outcomes in TP53 del/mut

Acalabrutinib ITT ELEVATE-TN



5-Year PFS 72%

Acalabrutinib TP53 del/mut ELEVATE-TN

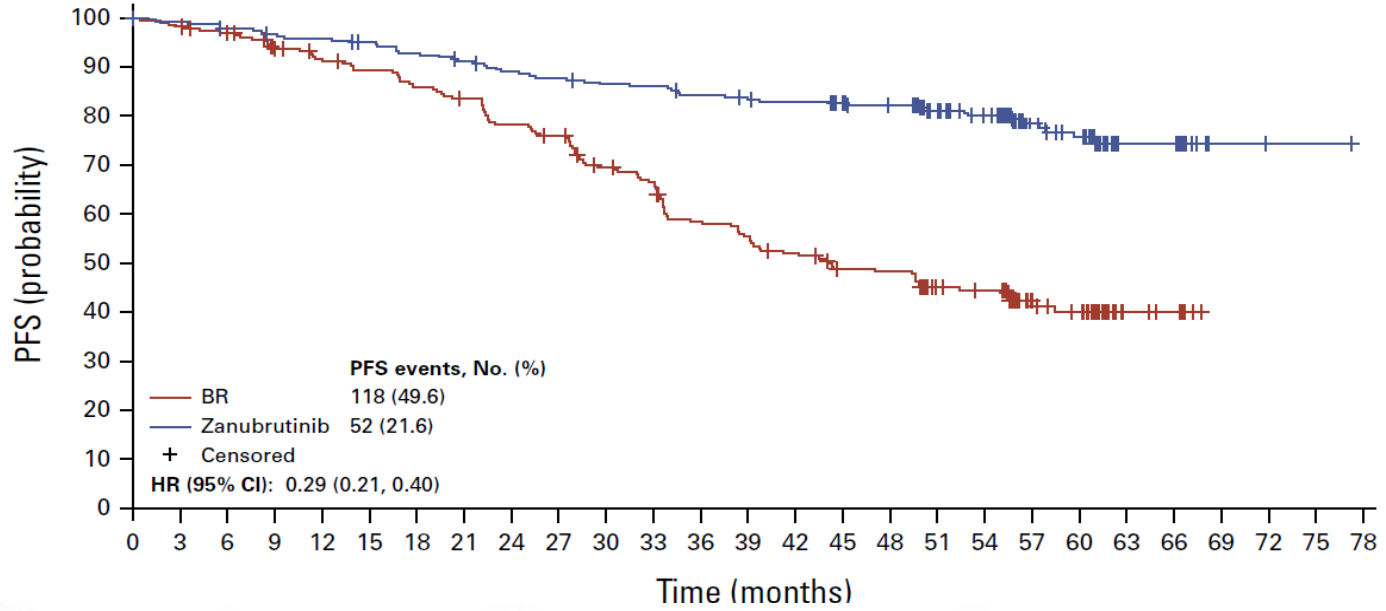


5-Year PFS 71%

EHA Library. P. Sharman J. 06/10/22; 357528; P666

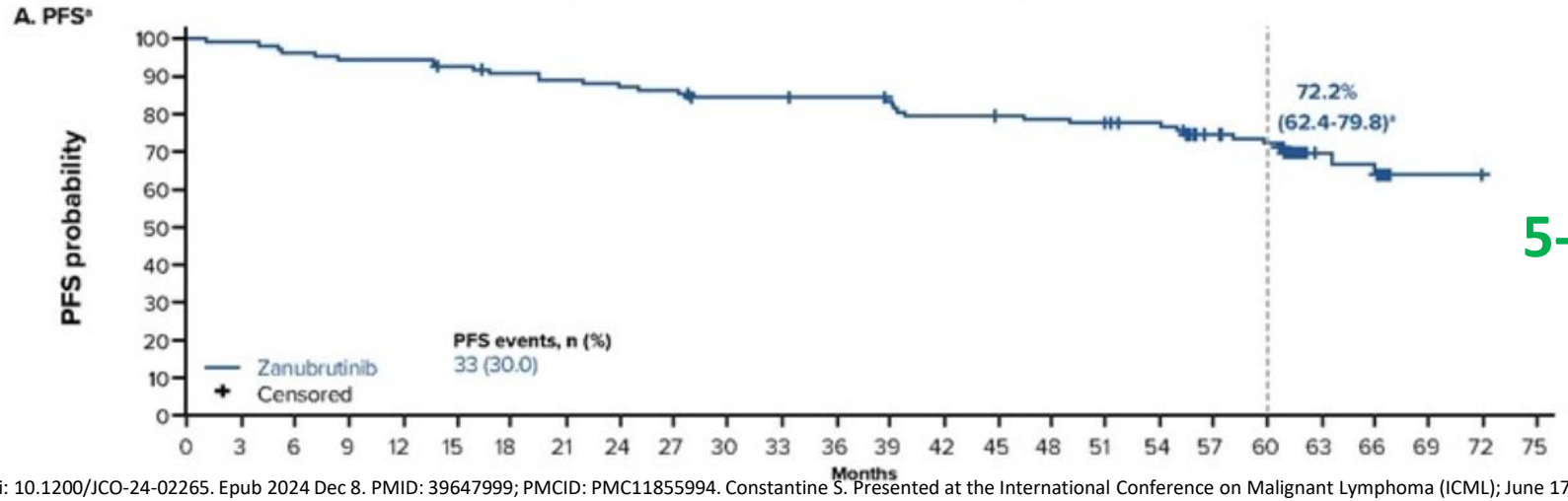
BTK Inhibitors until progression:efficacy outcomes in TP53 del/mut

Zanubrutinib ITT SEQUOIA (Arm A+B)



5-Year PFS 76%

Zanubrutinib del17/TP53mut SEQUOIA (Arm C)



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Shadman M. et al.,. J Clin Oncol. 2025 Mar;43(7):780-787. doi: 10.1200/JCO-24-02265. Epub 2024 Dec 8. PMID: 39647999; PMCID: PMC11855994. Constantine S. Presented at the International Conference on Malignant Lymphoma (ICML); June 17-21, 2025; Lugano, Switzerland Data originally presented at the 2025 ASCO Annual Meeting; May 30-June 3, 2025; Chicago, IL, USA, Abstract #7011

BTKi phase III trials: Events of Clinical Interest
@5Y Follow Up

	IBRUTINIB RESONATE-2[1]		ACALABRUTINIB ELEVATE-TN[2]		ZANUBRUTINIB SEQUOIA[3]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Atrial fibrillation	16%	5%	7.3%	1.1%	7.1%	1.4%
Bleeding	NA	11%	43.6%	3.4%	52.1%	7.5%
Hypertension	26%	9%	8.9%	3.9%	22.9%	12.1%

1.Burger JA et al. Leukemia, 2020
2. Sharman JP et al. Poster Presented at: ASCO 2022.
3. Shadman M et al. Journal of Clinical Oncology, 2024
NA: not available

Median age 66 aa (34-90), CIRS 0-18

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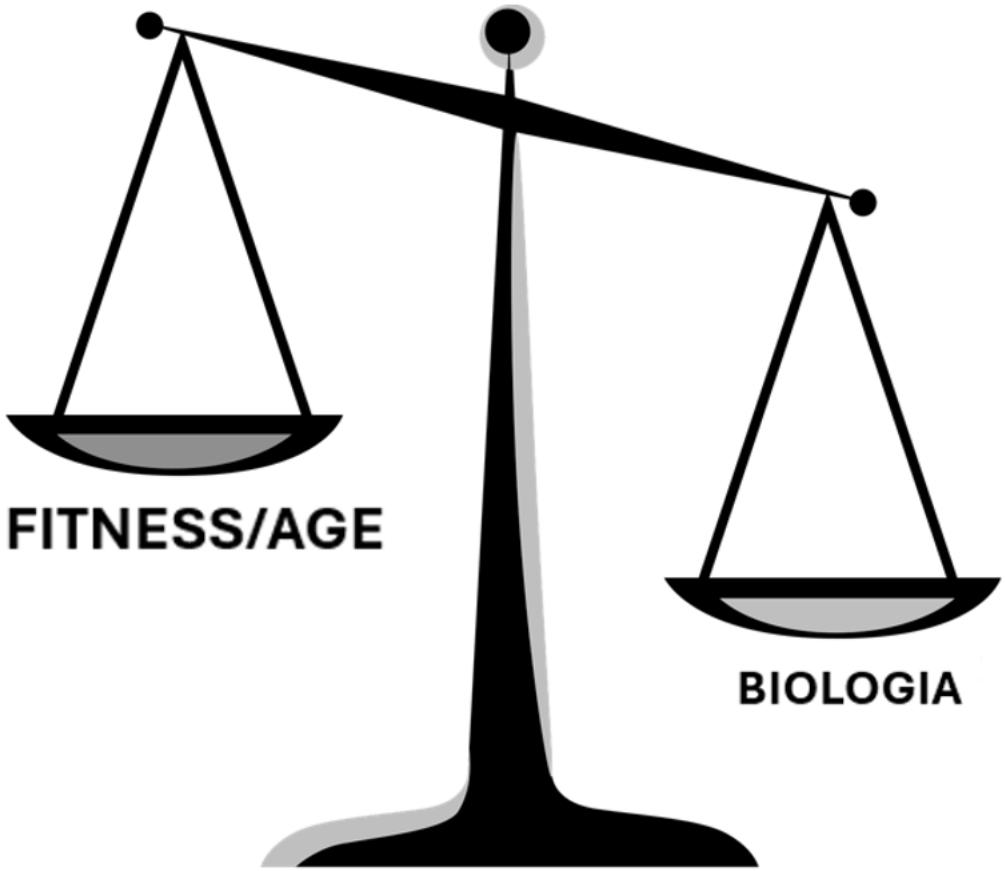

TP53 mutation or del(17p)

Acalabrutinib [I, A]
Zanubrutinib [III, A]
Ibrutinib[b] [I, A]
Venetoclax [III, A]
Ibrutinib–venetoclax[a,b] [III, A]
Venetoclax–obinutuzumab [III, A]
Idelalisib–rituximab [II, B]

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