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Milano, Milan Hilton Hotel

4-5 maggio 2026

Oltre la biologia *TP53* e IGHV nella CLL

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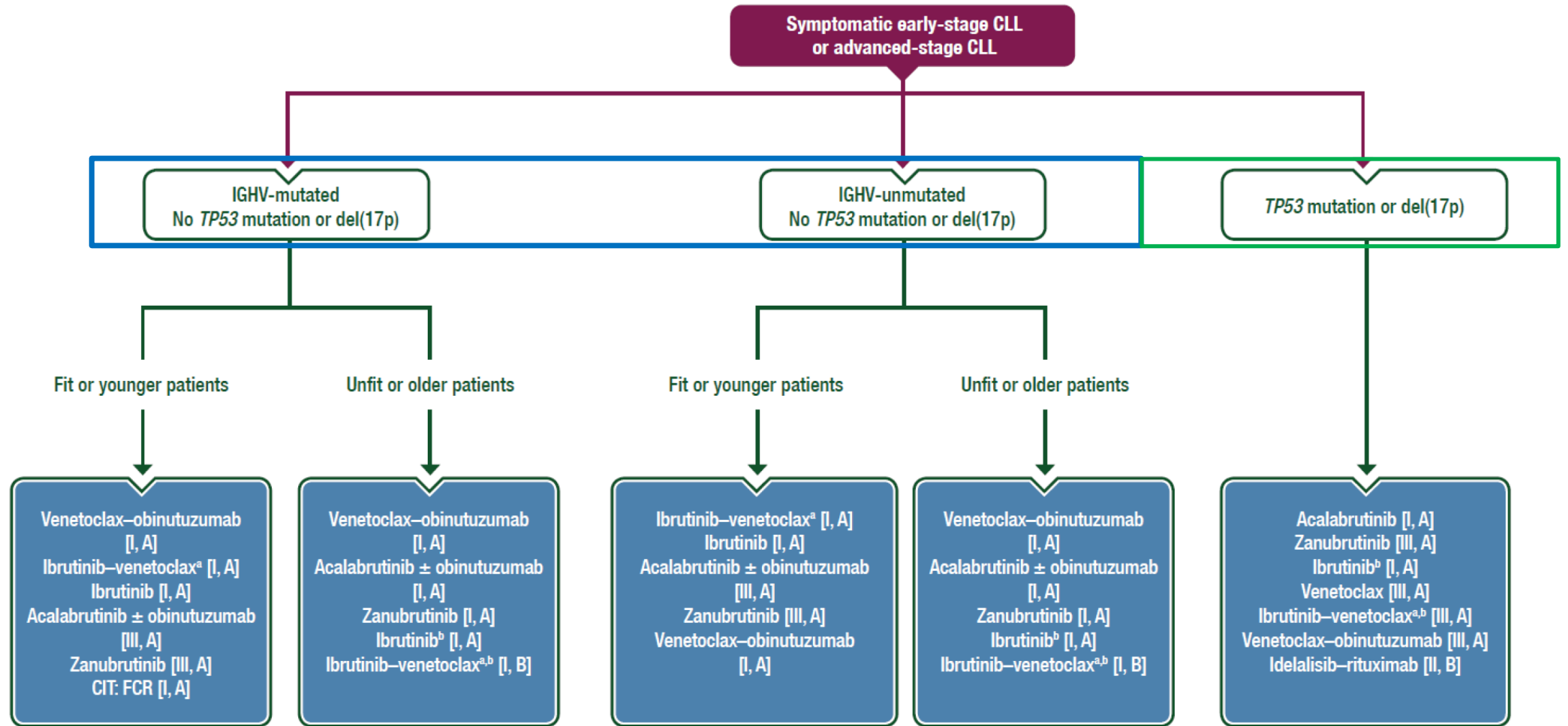
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Disclosures: Paolo Ghia

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BeOne	x		x			x	
BMS	x		x			x	
J&J	x		x			x	
Lilly/Loxo	x		x			x	
MSD	x		x			x	
Nurix			x			x	
Roche			x			x	

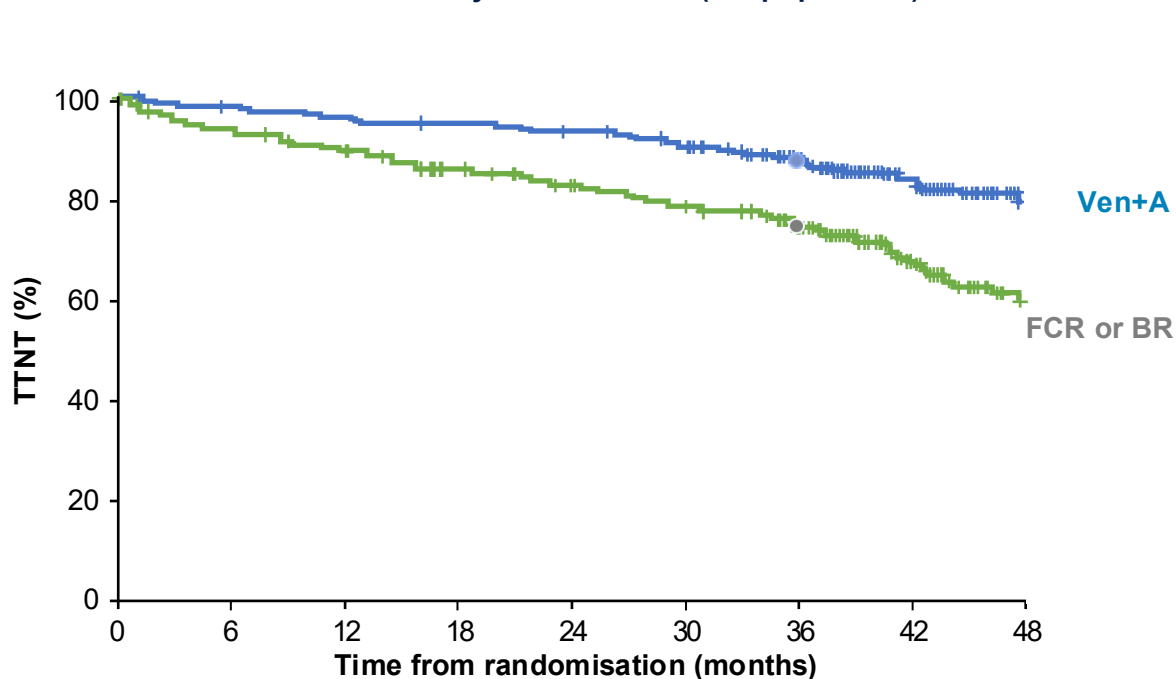
“Old” ESMO Clinical Practice: frontline therapy



AMPLIFY Study

Ven+A demonstrated a delay in TTNT vs FCR/BR, regardless of IGHV status

TTNT by treatment arm (ITT population)



No. at risk

	0	6	12	18	24	30	36	42	48
Ven+A	291	284	278	273	268	258	215	130	50
FCR or BR	291	243	230	214	203	191	158	82	42

	Ven+A (n=291)	FCR/BR (n=290)
Events, n	52/290	84/289
36-mo TTNT	88.5%	75.2%
HR (95% CI) Ven+A vs FCR/BR	0.45 (0.32, 0.64)	—

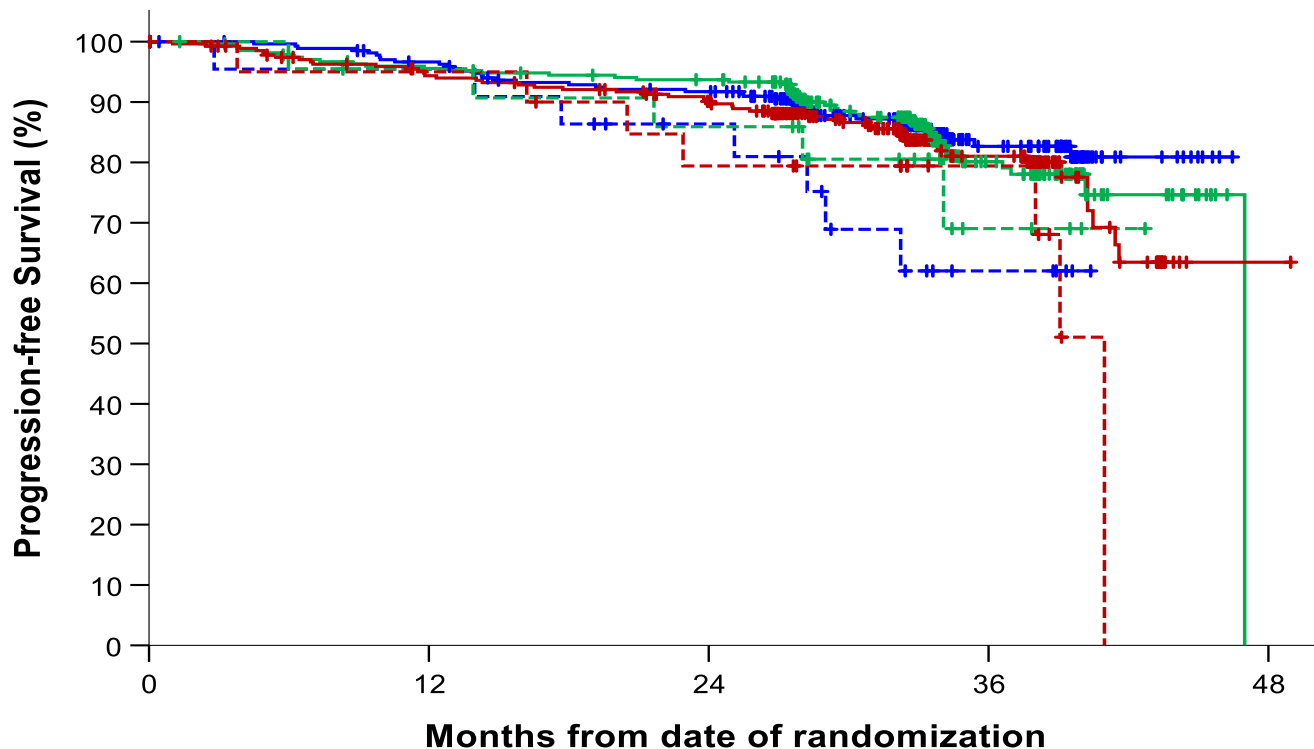
A

Mutation Status	Events/Patients, n		Hazard Ratio (95% CI)
	AV (N=291)	FCR/BR (N=290)	
Overall			
All subjects	52/290	84/289	0.46 (0.32, 0.64)
IGHV mutational status			
Mutated	13/124	23/118	0.43 (0.21, 0.83)
Unmutated	39/167	61/172	0.50 (0.33, 0.74)

Ghia P, et al. ASH, Orlando, 6–10 December 2025. Poster 3898.

CLL17 Study: Progression-free survival

According to *TP53*/del(17p) status



3-year-PFS

--- I, <i>TP53</i> del/mut	79.4%
— I, <i>TP53</i> -WT	81.0%
--- VI, <i>TP53</i> del/mut	69.0%
— VI, <i>TP53</i> -WT	80.1%
--- VO, <i>TP53</i> del/mut	62.0%
— VO, <i>TP53</i> -WT	82.7%

Patients at risk

VO, del/mut	23	21	16	5	0
VO, WT	280	257	240	72	0
VI, del/mut	25	20	18	4	0
VI, WT	279	257	248	78	0
I, del/mut	21	19	15	7	0
I, WT	279	247	227	87	1

TP53 del/mut:

VI vs I: HR 0.70, 95% CI 0.22-2.16

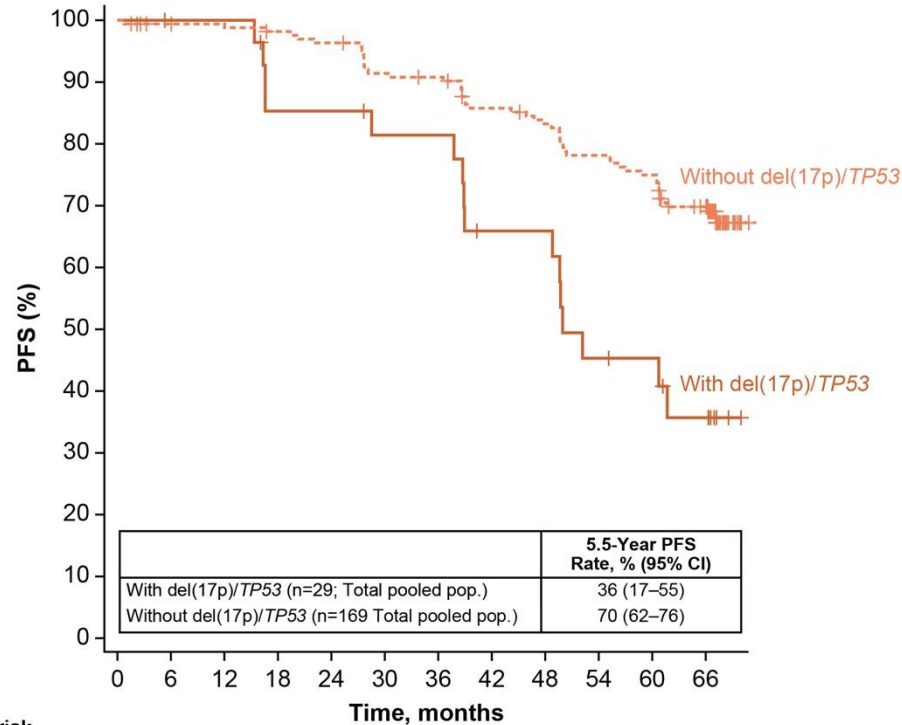
VO vs I: HR 1.20, 95% CI 0.40-3.59

Al Sawaf O, et al. ASH, Orlando, 6–10 December 2025. Oral presentation.

CAPTIVATE Study: Ibrutinib+Venetoclax

Overall Median PFS and OS (Total Pooled Population)

PFS by del(17p)/TP53 Mutation Status

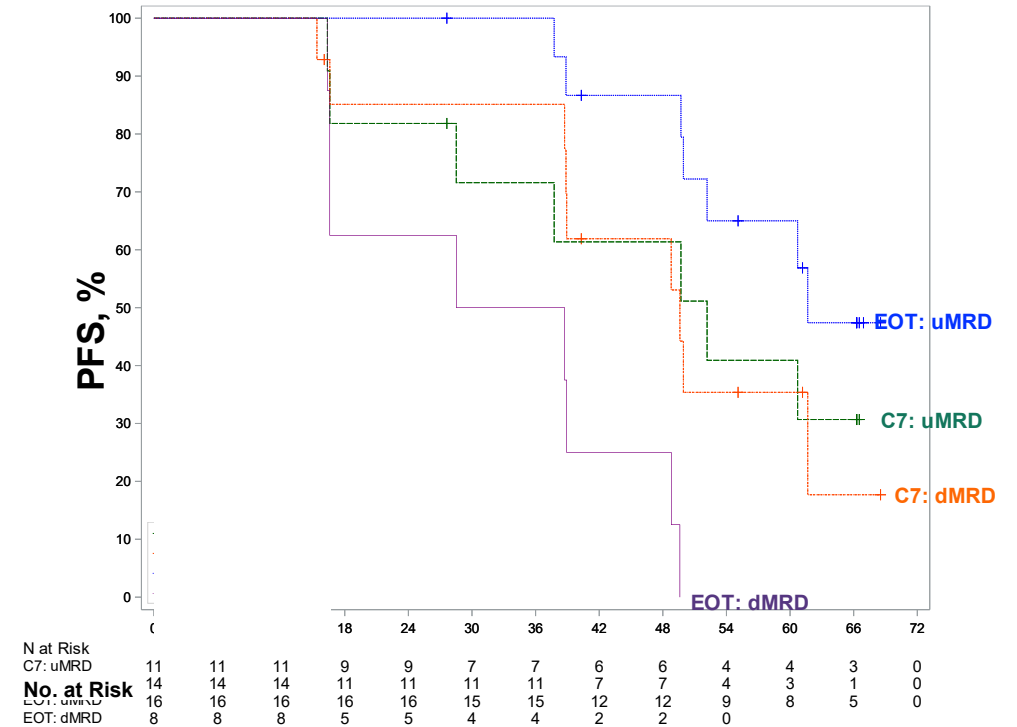


Patients at risk

With del(17p)/TP53	29	28	28	23	23	21	21	16	16	11	10	7
Without del(17p)/TP53	169	164	163	160	157	148	146	136	131	123	118	103

FD Cohort ^a	% (95% CI)
With del(17p)/TP53 (n=27; FD cohort only)	30 (12-49)
Without del(17p)/TP53 (n=129; FD cohort only)	66 (57-74)

PFS by MRD Status in Patients With del(17p)/TP53 (FD Cohort)



5.5-Year PFS, % (95% CI)

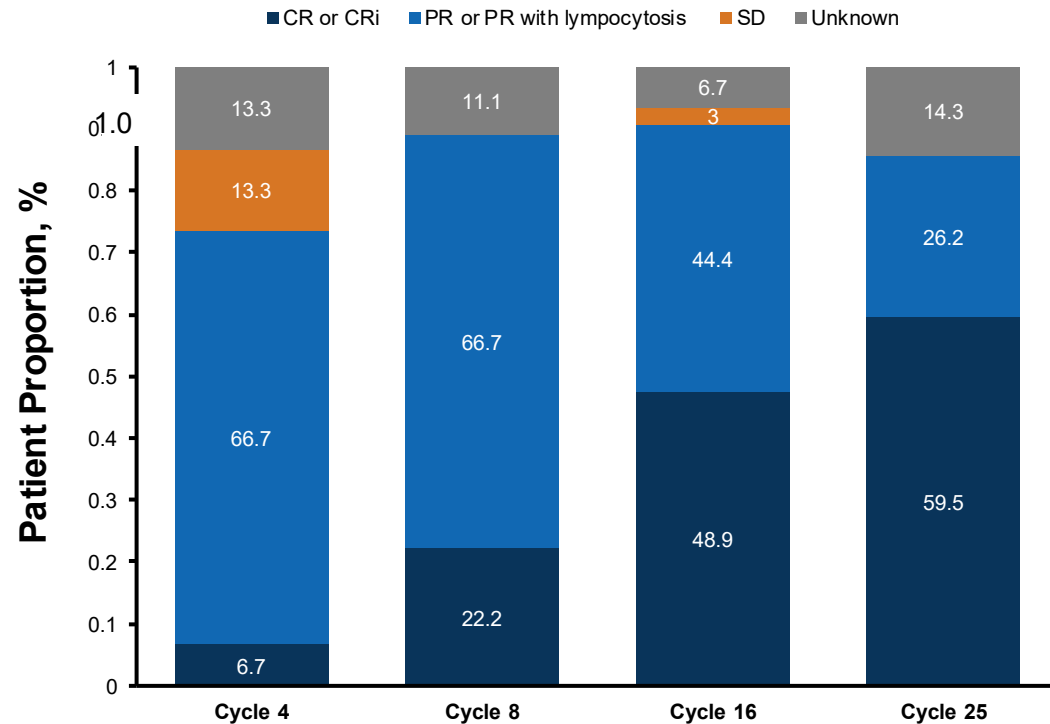
MRD status at C7	
uMRD4 (n = 11)	31 (7-59)
dMRD (n = 14)	18 (1-50)
MRD status at EOT	
uMRD4 (n = 16)	47 (20-71)
dMRD (n = 8)	0 (NE-NE)

MRD-Guided AVO in patients enriched for High-Risk Features

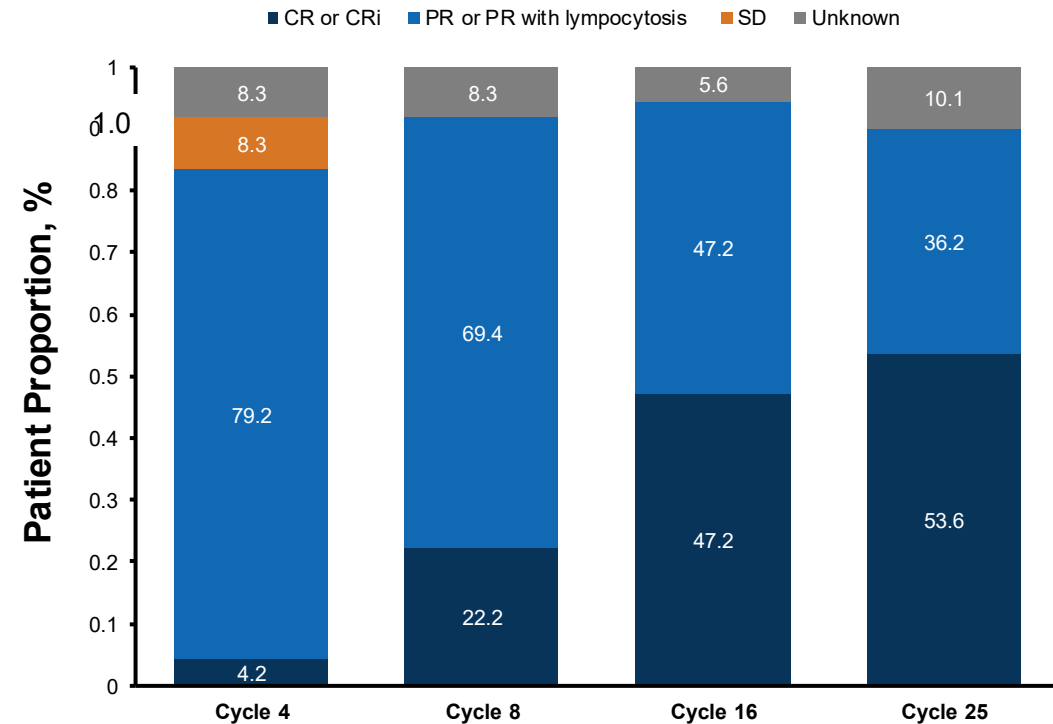
Clinical responses and MRD rates

- The CR with BM-uMRD rates at the start of cycle 16 were 42% in patients with *TP53* aberration and 42% in all-comers, and the **BM-uMRD rates were 71% and 78%**, respectively

Response Rates in Patients With *TP53* Aberration



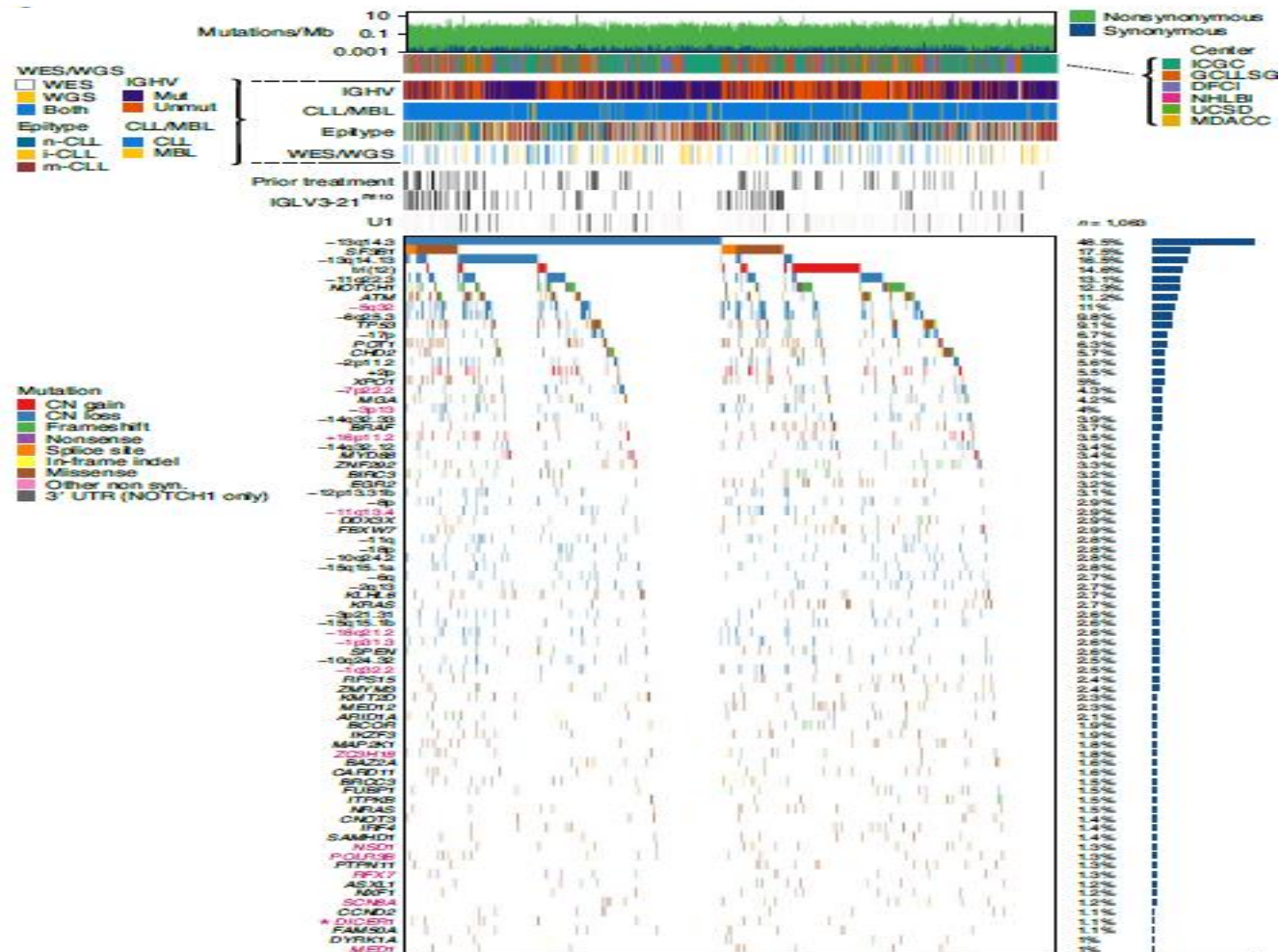
Response Rates in the Overall Population



- Four-year PFS and OS for patients with or without *TP53* aberrations were 70%/96% and 88%/100%, respectively.

Genomic drivers in CLL

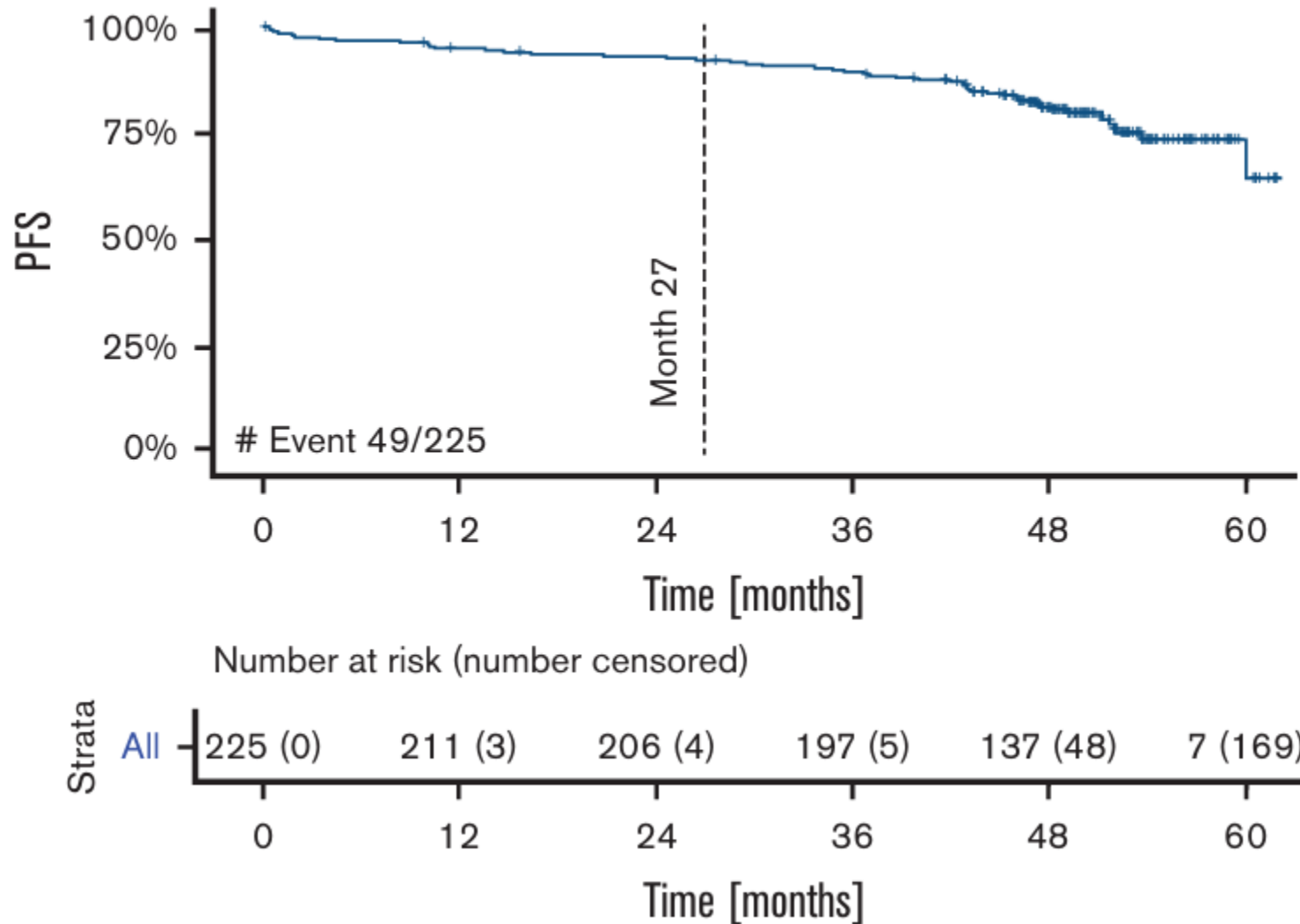
202 distinct candidate genetics drivers in 1148 pts with CLL from 6 institutions



Knisbacher BA, et al. Nat Genetics 2022

HOVON-VISION MRD-guided Ven-Ibr in R/R CLL

225 pts, median 1 prior Rx, median F/U 52 months



PFS 81% @ 4 years
No difference in study arms

NO impact of *NOTCH1mut*

BCOR HR 2.8 } OS
CCND2 HR 5.9 } OS
XPO1 HR 5.7 } OS
NRAS HR 7.7 PFS

“BCNX” cluster P < 0.001
Median PFS 52 Mo

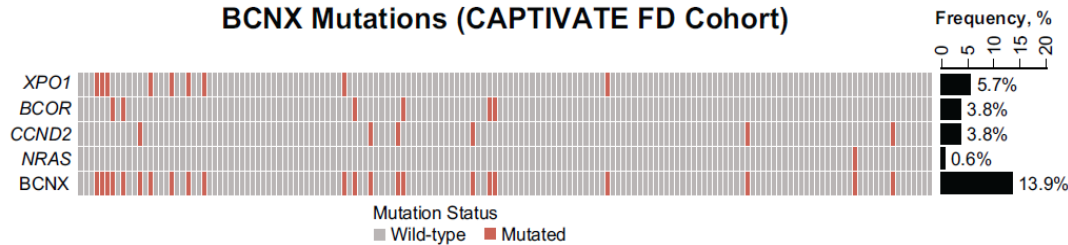
Brieghel C, et al. ASH Abstr 2024

Niemann C, et al. Blood Adv 2025

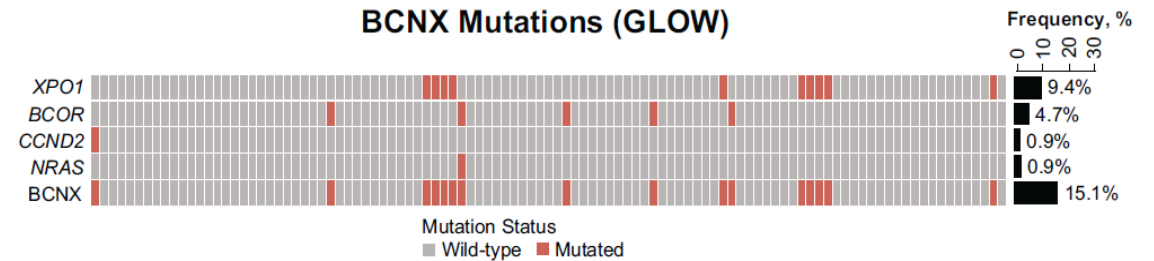
BCNX cluster NOT confirmed in CAPTIVATE & GLOW

- At baseline, mutations in any of the 4 genes in the proposed BCNX signature (*BCOR*, *CCND2*, *NRAS*, or *XPO1*)⁴ were found in 13.9% of patients in the CAPTIVATE FD cohort, 15.1% of patients in GLOW, and 13.4% of patients in the CAPTIVATE MRD cohort

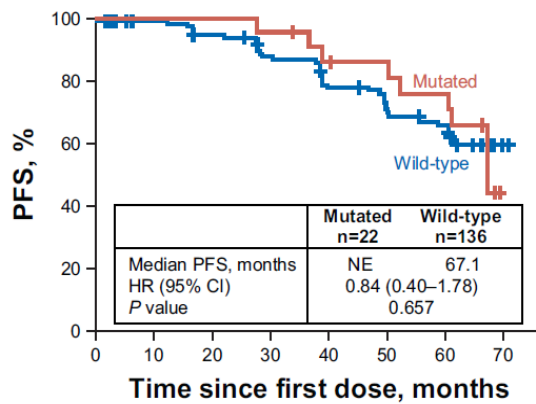
BCNX Mutations (CAPTIVATE FD Cohort)



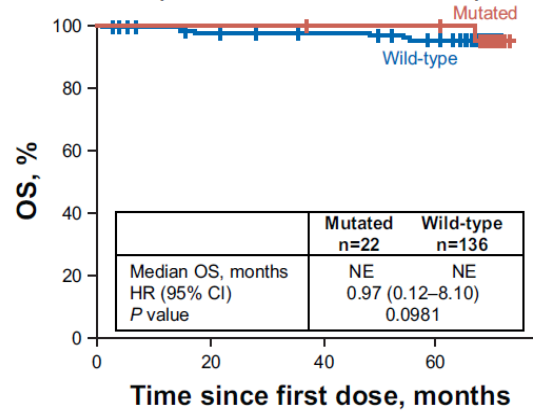
BCNX Mutations (GLOW)



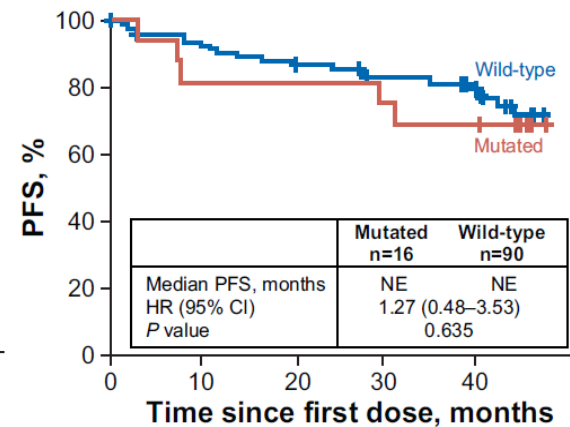
PFS by BCNX Status (CAPTIVATE FD Cohort)



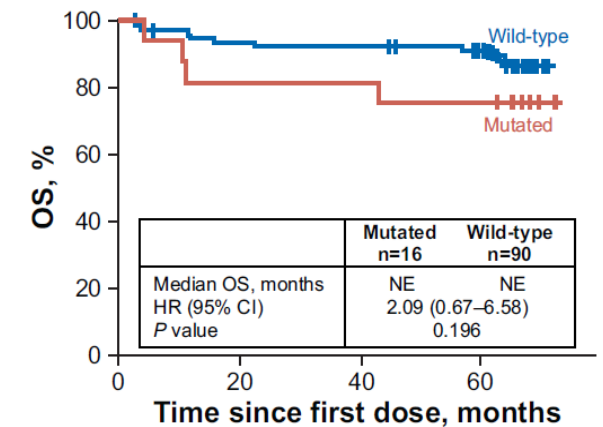
OS by BCNX Status (CAPTIVATE FD Cohort)



PFS by BCNX Status (GLOW)



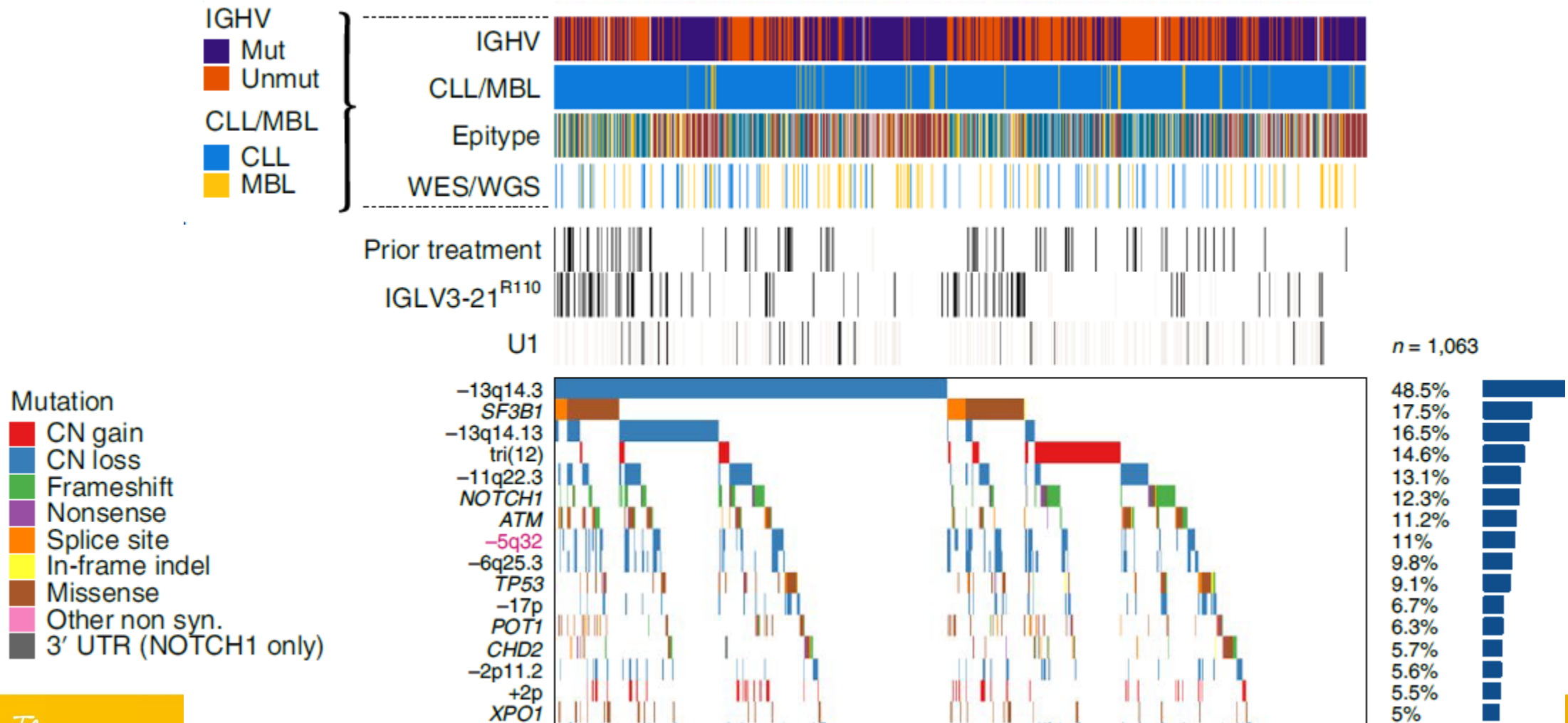
OS by BCNX Status (GLOW)



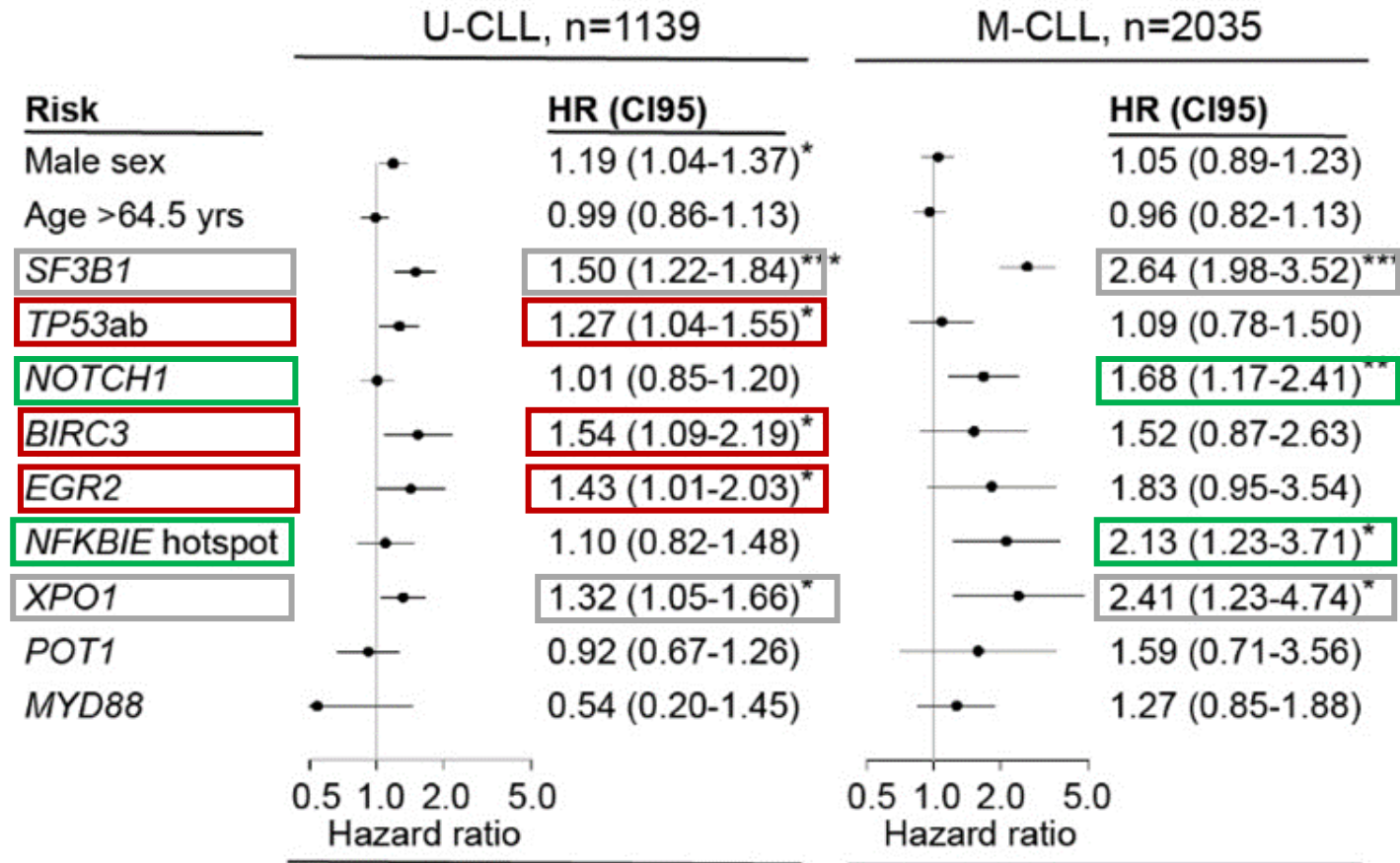
Cheung LW, et al. ASH Abstract 2025

Genomic drivers in CLL

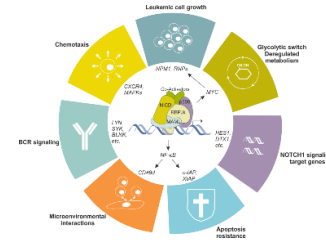
202 distinct candidate genetics drivers in 1148 pts with CLL from 6 institutions



Gene mutations associates with TTFT depending on IGHV status



NOTCH1mut predicts resistance to anti-CD20 mAbs



*...NOTCH1^{mut} was identified as a predictive marker for decreased benefit from the addition of **rituximab** to fludarabine-cyclophosphamide...*

Stilgenbauer et al. Blood 2014; 123(21):3247-54

*...a benefit of **ofatumumab** addition to FC treatment was observed among NOTCH1^{wt} but not among NOTCH1^{mut} patients...*

Tausch et al. EHA 2017; P248

Continuous single agent **venetoclax** in R/R CLL

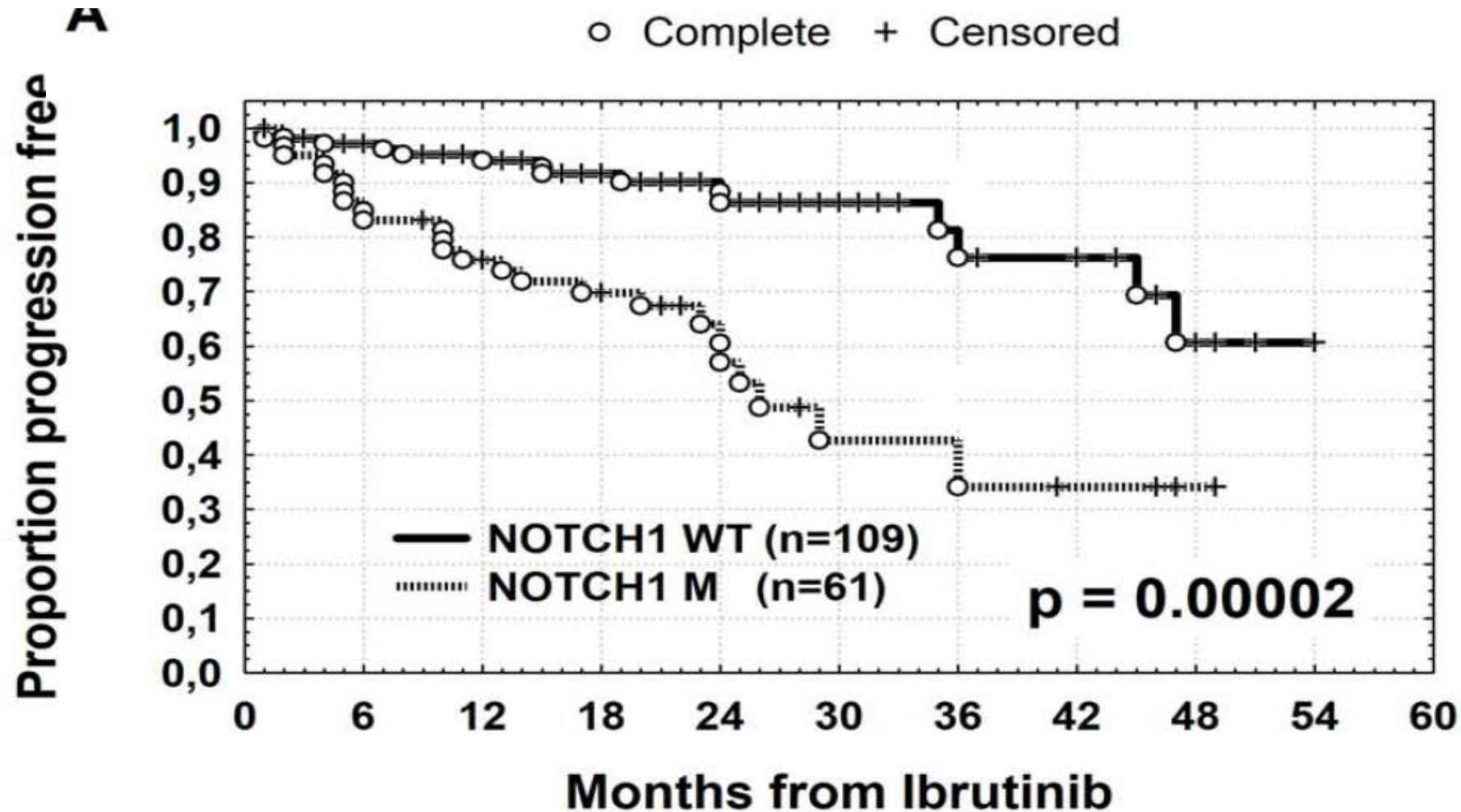
Multivariate predictors of DoR

Pre-treatment factor (n)	Hazard Ratio [95% CI]
Max node size in cm	
≥ 5 - < 10 (124)	2.5 [1.7 – 3.7]
≥ 10 (48)	2.8 [1.7 – 4.6]
Number of prior therapies	NS
F-refractory (107)	1.5 [1.1 – 2.2]
BCRi refractory (112)	2.5 [1.5 – 4.1]
<i>TP53</i> mut and/or del(17p) (224)	1.8 [1.2 – 2.5]
<i>NOTCH1</i> mut (26)	1.8 [1.1 – 3.0]

Roberts AW, et al. *Blood* 134:111-22, 2019

Impact of NOTCH1mut with Ibrutinib therapy in R/R CLL

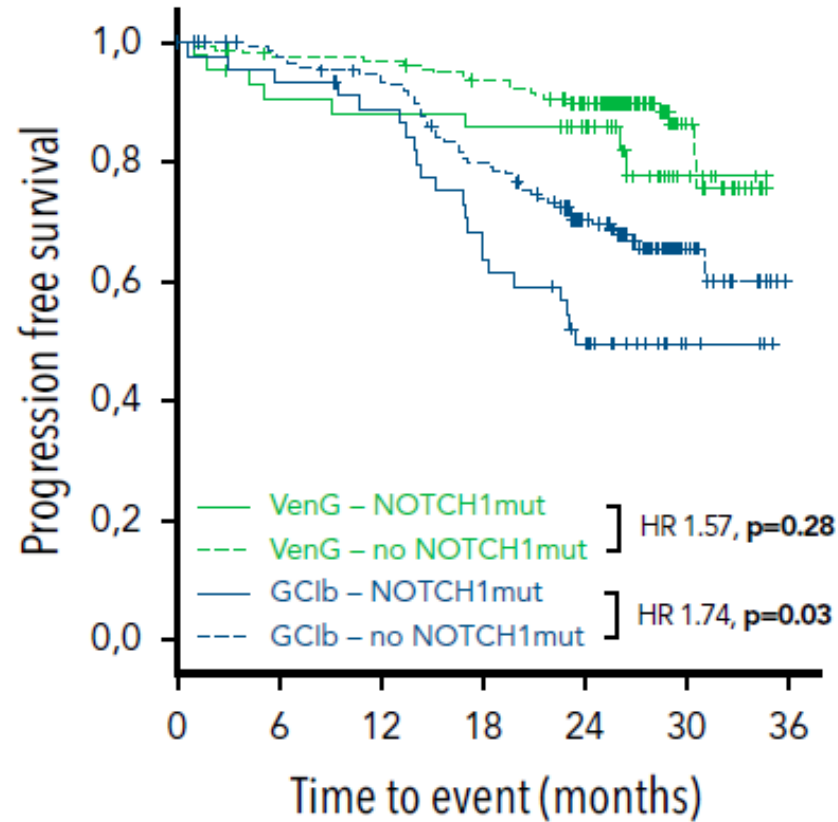
180 pts with R/R disease; impact confirmed in MVA



Del Poeta G, et al. Haematologica 2020

Impact of NOTCH1mut in CLL14 frontline study

NOTCH1mut 22% in Ven-Obi arm; 28 Mo median F/U

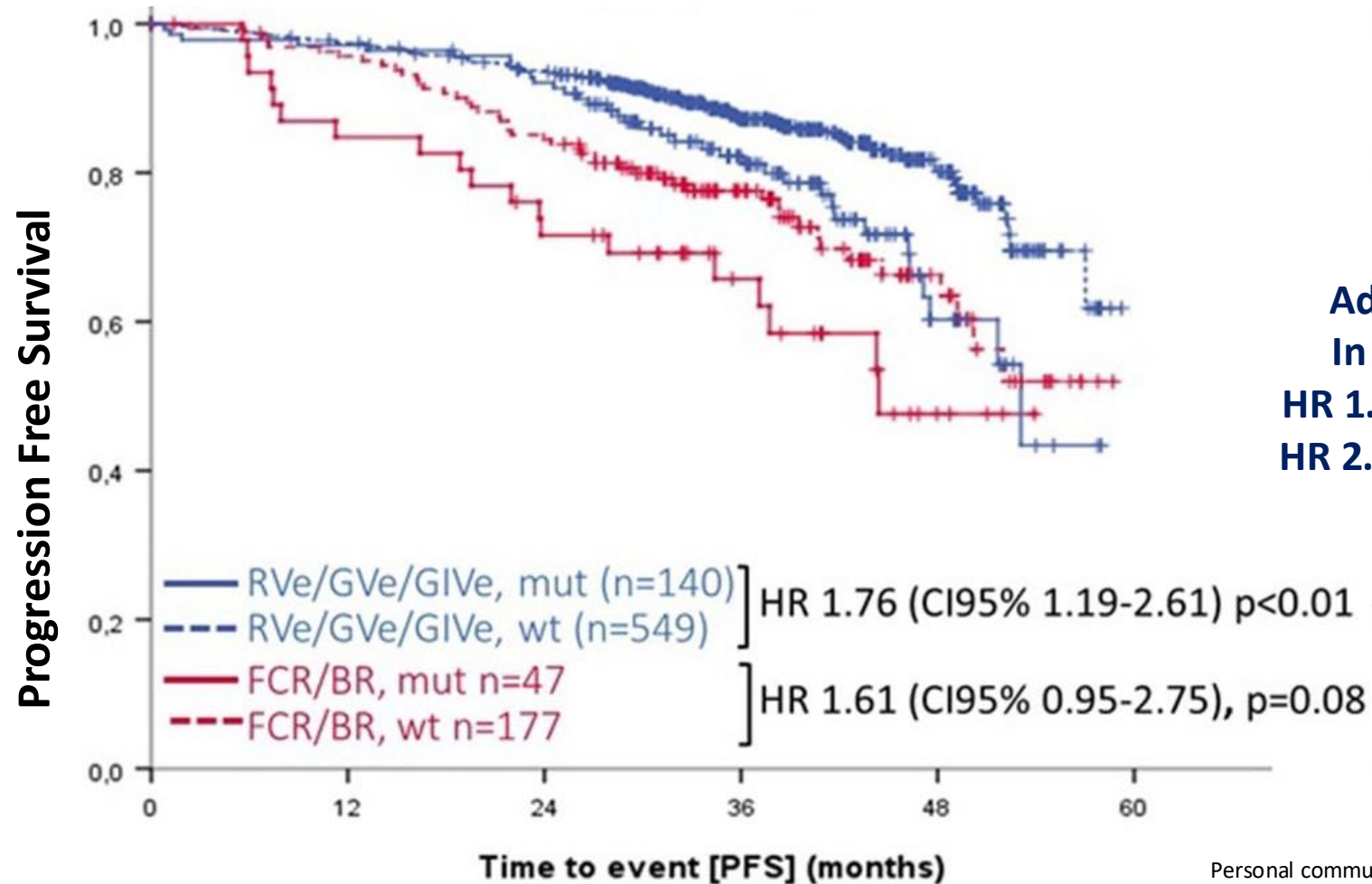


164	154	153	146	122	18	0
47	38	37	36	30	7	0
162	148	141	119	89	17	0
48	42	39	29	20	4	0

Tauch E, et al. Blood 2020

Impact of NOTCH1mut in GAIA-CLL13 frontline study

NOTCH1mut 21% overall and similar in all arms; 39 Mo median F/U

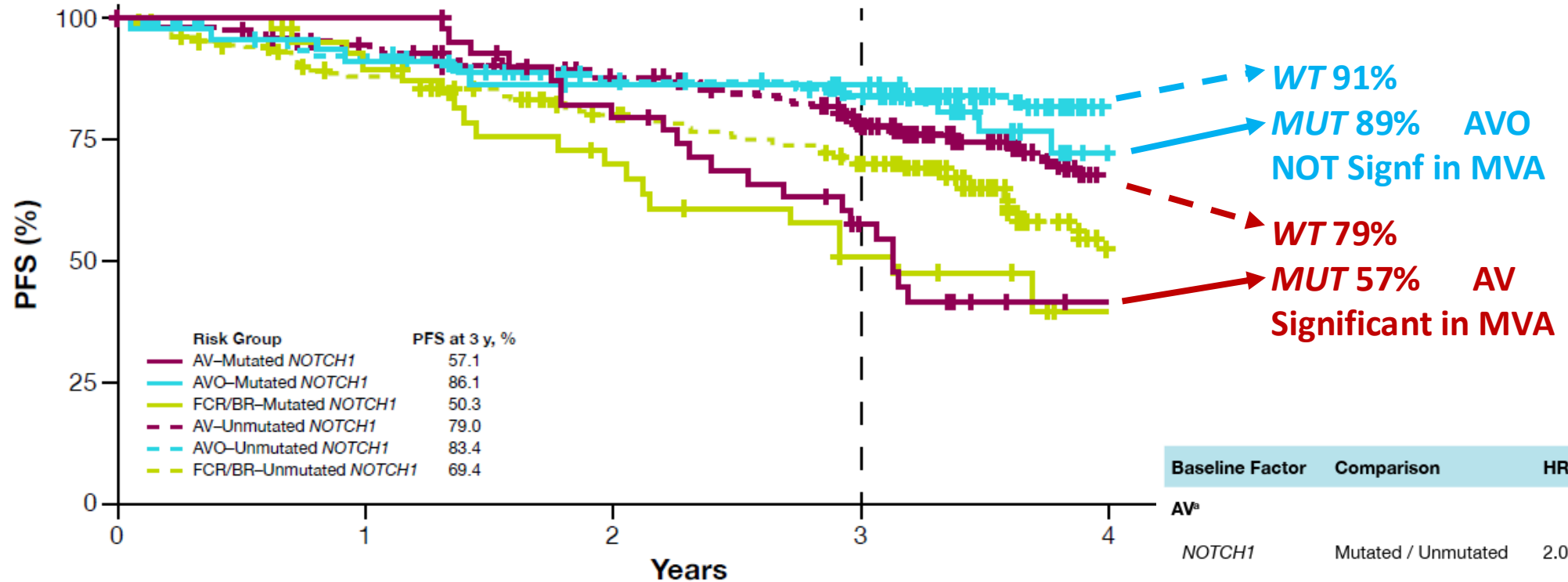


**Adverse impact of NOTCH1mut
In Ven-combos persists in MVA
HR 1.81 (1.36-2.36) for PFS; P < 0.05
HR 2.09 (1.12 – 3.90) for OS; P < 0.05**

Personal communication Stephan Stilgenbauer - *Tauch E, et al. ASH abstract 2022*

Impact of *NOTCH1mut* in AMPLIFY frontline study

***NOTCH1mut* 16% overall and similar in all arms**



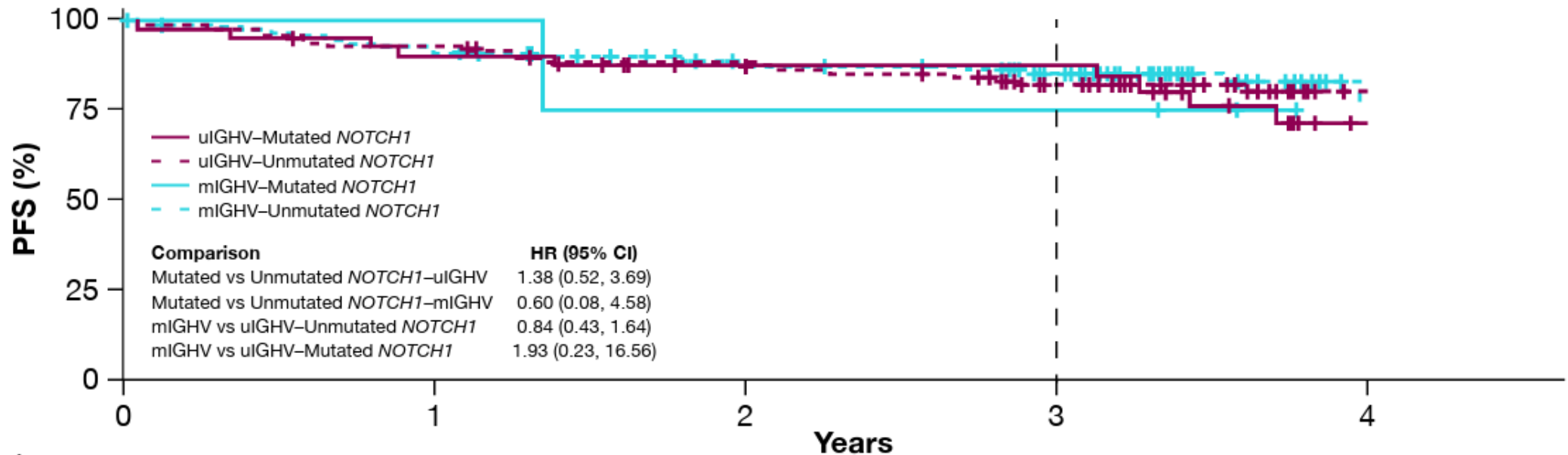
Baseline Factor	Comparison	HR (95% CI)	P value
AV^a			
<i>NOTCH1</i>	Mutated / Unmutated	2.03 (1.14, 3.60)	0.016
Bulky disease	≥5 cm / <5 cm	1.98 (1.19, 3.28)	0.008

No. at risk (no. of events)	0	1	2	3	4
AV-m <i>NOTCH1</i>	41 (0)	40 (0)	30 (8)	18 (16)	5 (21)
AVO-m <i>NOTCH1</i>	45 (0)	39 (4)	36 (6)	34 (6)	8 (10)
FCR/BR-m <i>NOTCH1</i>	50 (0)	34 (4)	23 (11)	14 (17)	3 (19)
AV-um <i>NOTCH1</i>	228 (0)	208 (14)	186 (26)	142 (45)	29 (58)
AVO-um <i>NOTCH1</i>	222 (0)	203 (17)	176 (26)	148 (35)	42 (37)
FCR/BR-um <i>NOTCH1</i>	216 (0)	160 (23)	134 (37)	105 (54)	25 (67)

Ghia P, et al. ASH Abstract 2025

Impact of *NOTCH1mut* in AMPLIFY frontline study

Within AVO treatment arm, no impact of IGHV or *NOTCH1mut* status



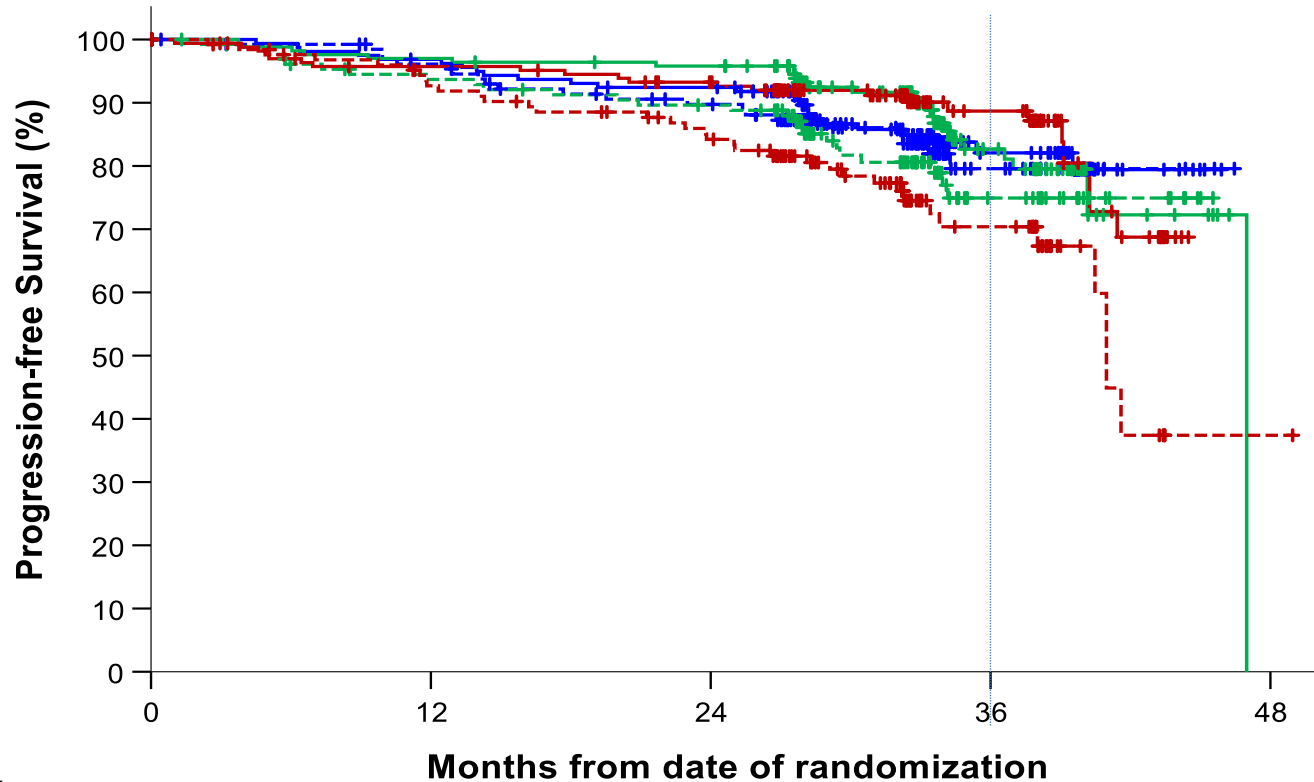
No. at risk (no. of events)

	0	1	2	3	4
uIGHV-m <i>NOTCH1</i>	41 (0)	35 (4)	33 (5)	30 (5)	7 (9)
uIGHV-um <i>NOTCH1</i>	116 (0)	107 (9)	94 (14)	79 (20)	25 (21)
mIGHV-m <i>NOTCH1</i>	4 (0)	4 (0)	3 (1)	3 (1)	0 (1)
mIGHV-um <i>NOTCH1</i>	107 (0)	97 (8)	82 (13)	64 (15)	14 (17)

Ghia P, et al. ASH Abstract 2025

CLL17 study: Progression-free survival based on **fitness**

According to fitness (cumulative illness rating scale >6 and/or GFR <70 ml/min)



3-year-PFS

---	I, unfit	70.4%
—	I, fit	88.7%
---	VI, unfit	74.9%
—	VI, fit	82.7%
---	VO, unfit	79.6%
—	VO, fit	82.1%

	0	12	24	36	48
Patients at risk					
VO, unfit	134	123	109	30	0
VO, fit	167	153	145	47	0
VI, unfit	136	116	109	29	0
VI, fit	169	162	158	53	0
I, unfit	130	112	97	33	1
I, fit	171	155	146	61	0

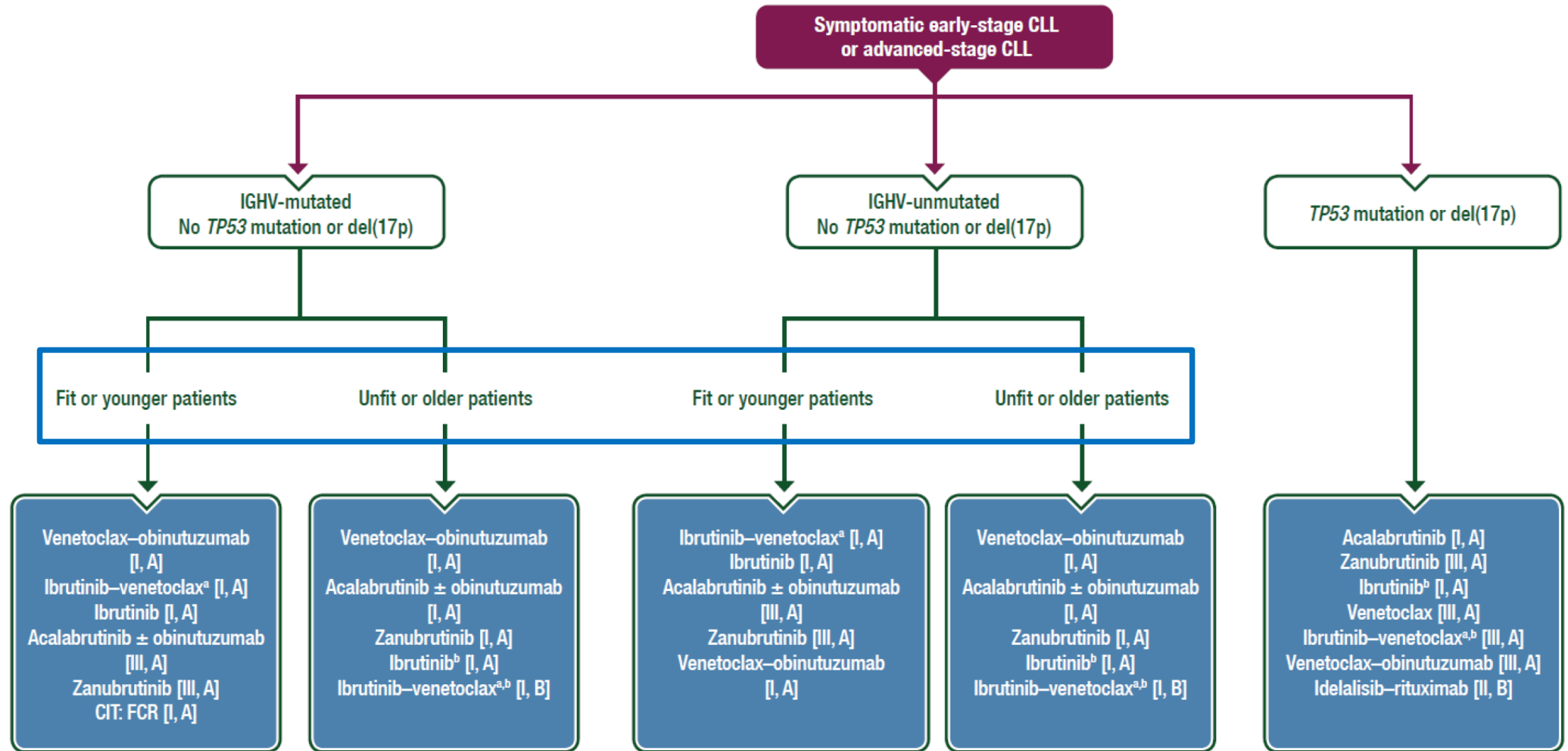
Unfit:

VI vs I: HR 0.66, 95% CI 0.40-1.11

VO vs I: HR 0.58, 95% CI 0.34-0.99

Al Sawaf O, et al. ASH, Orlando, 6–10 December 2025. Oral presentation.

“Old” ESMO Clinical Practice: frontline therapy



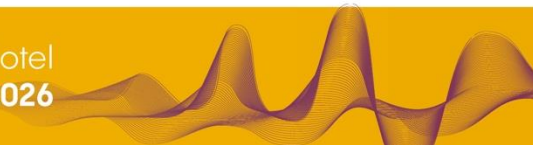
Beyond biology (*TP53* and *IGHV*): a glimpse into the future

	Treatment Preferences for Genetic Subgroups Based on Efficacy and Tolerability			Treatment-Related Logistics		AEs, Comorbidities, and Comedication					
	mIGHV	uIGHV	del(17p)/ <i>TP53</i> mut	Finite duration and treatment-free interval	Convenient initiation of therapy	Accumulation of AEs	Bleeding risk	TLS risk	CV events	Reduced renal function	Infection risk during treatment
Ibrutinib	Orange	Light Green	Light Green	Red	Dark Green	Orange	Orange	Dark Green	Orange	Light Green	Light Green
Acalabrutinib	Light Green	Dark Green	Dark Green	Red	Dark Green	Orange	Orange	Dark Green	Orange	Light Green	Light Green
Zanubrutinib	Light Green	Dark Green	Dark Green	Red	Dark Green	Orange	Orange	Dark Green	Orange	Light Green	Light Green
Acalabrutinib + obinutuzumab	Light Green	Dark Green	Light Green	Red	Light Green	Orange	Orange	Light Green	Orange	Orange	Orange
Venetoclax + obinutuzumab	Dark Green	Dark Green	Light Green	Dark Green	Orange	Dark Green	Dark Green	Orange	Dark Green	Orange	Orange
Ibrutinib + venetoclax	Dark Green	Dark Green	Light Green	Dark Green	Orange	Dark Green	Light Green	Light Green	Orange	Orange	Light Green

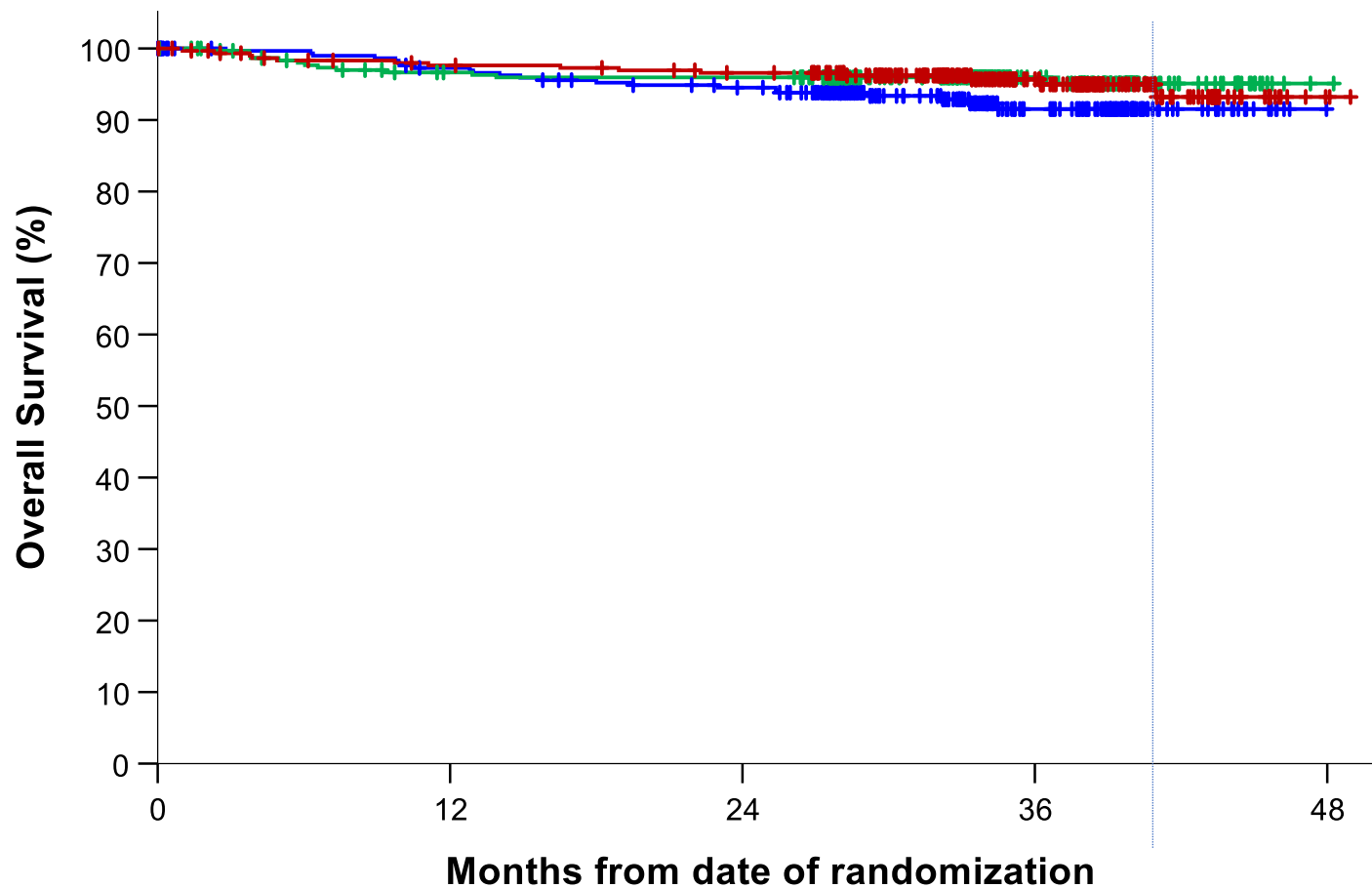
Color code rating for treatment options



Tausch E et al. Hematology ASH Educ Program. 2024



CLL17 Study: overall survival



Patients at risk

	0	12	24	36	48
VO	303	284	269	102	
VI	305	281	279	114	
I	301	284	276	141	

3-year-OS

I 95.7%

VI 96.0%

VO 91.5%

Causes of death

	Infection	Cardio-vascular	PD/RT	SPM	Other	Total
I	3	5	0	2	4	14
VI	7 (2 Covid)	3	0	2	1	13
VO	12 (7 Covid)	5	1	4	0	22

VI vs I: HR 0.96, 95% CI 0.45-2.05

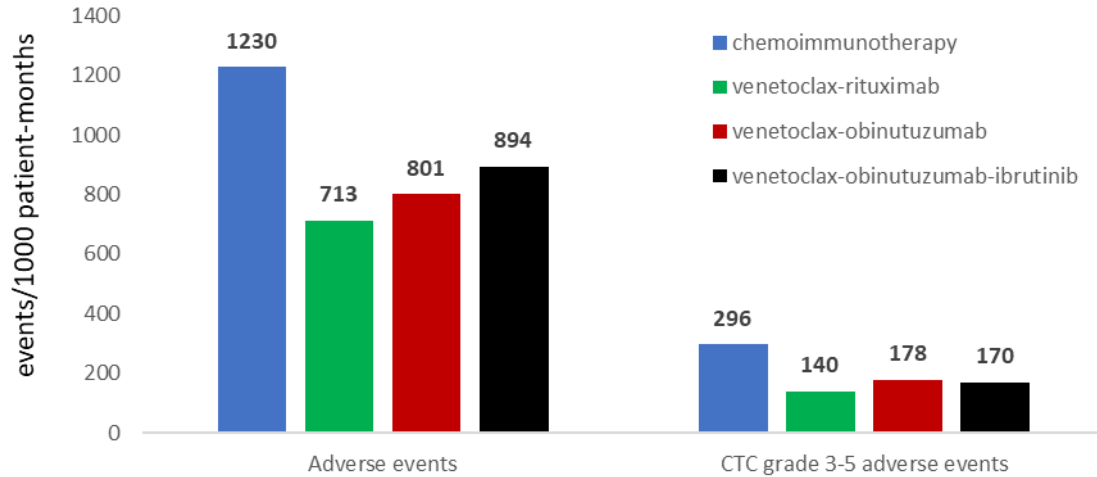
VO vs I: HR 1.67, 95% CI 0.86-3.28

2 AI Sawaf O, et al. ASH, Orlando, 6–10 December 2025. Oral presentation.

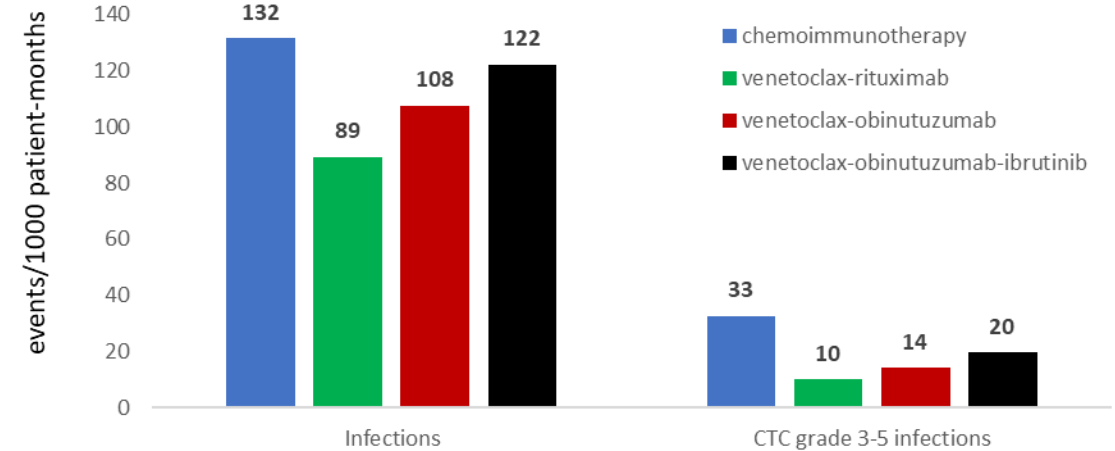
GAIA/CLL13: Venetoclax-based therapy versus CIT in 1L CLL

Safety

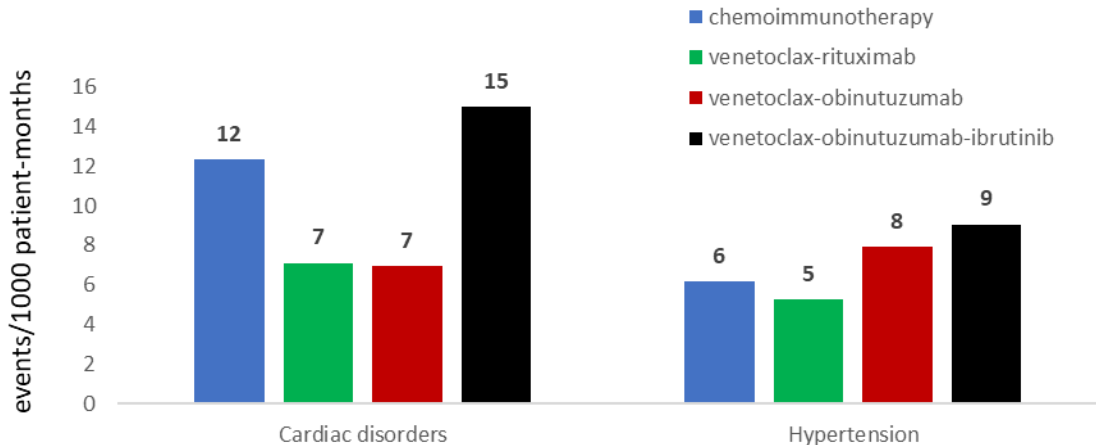
Adverse events



Infections



Cardiac adverse events and hypertension



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. ASH 2023

AMPLIFY: 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.

^aVentricular 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).

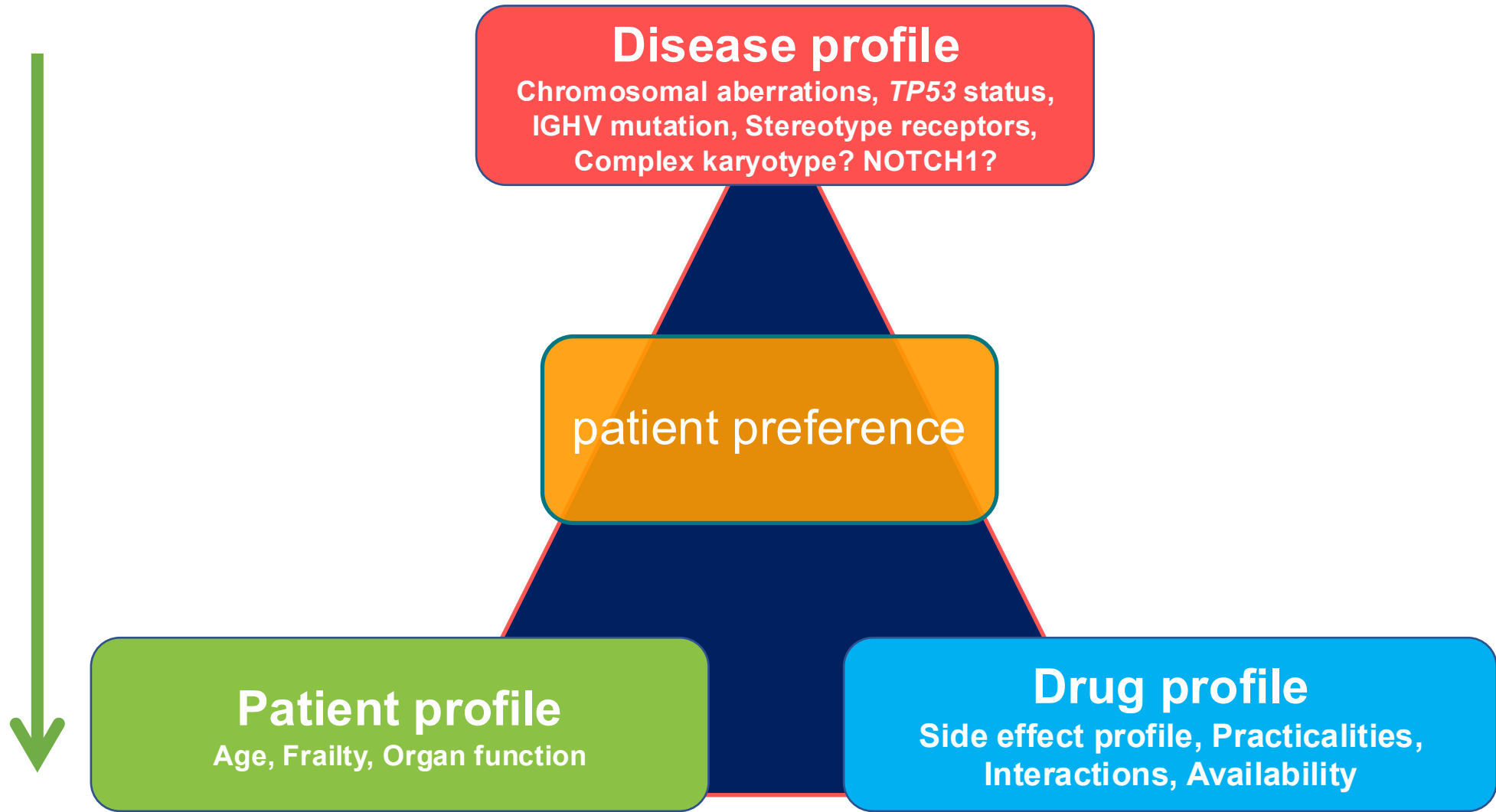
^bIncludes neutropenia, neutrophil count decreased, and febrile neutropenia.

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.

Personalized approach for patients with CLL

- Improvement in symptoms/QoL
- Disease control
- Protracted treatment free interval
- Prolonged survival
- Cure





Università Vita-Salute San Raffaele - IRCCS Ospedale San Raffaele

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