4th edition Unmet challenges in high risk hematological malignancies:
from benchside to clinical practice - Turin – March 26th, 2026

Role of combination treatment in first line

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Disclosures

Honoraria: Roche, Janssen, Gilead, AbbVie, Lilly, AstraZeneca, Adaptive, BeiGene

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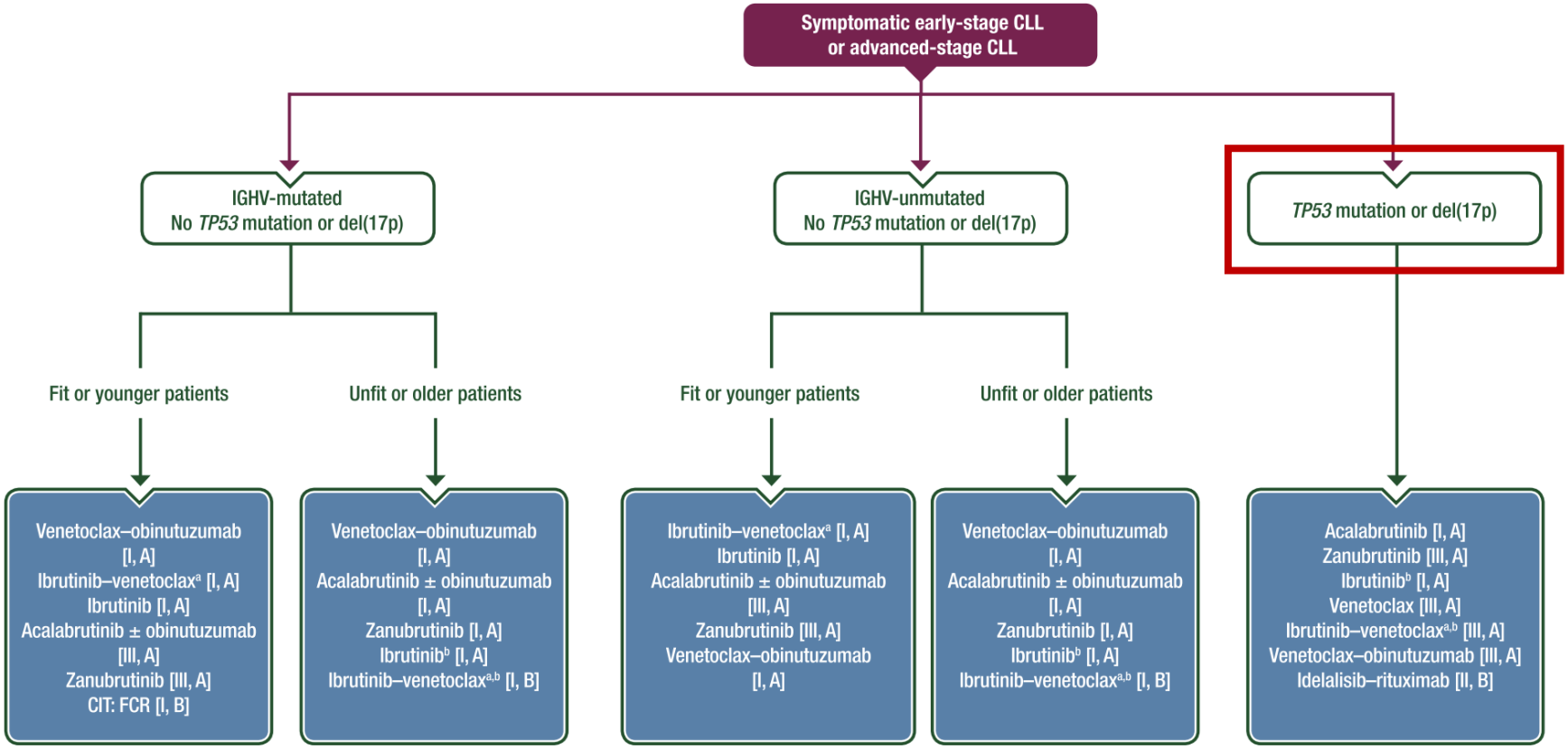
„*Unmet* challenges“ in CLL

- Poor response to treatment
- Short duration of response
- Acquired resistance
- Frequent treatment-related toxicities

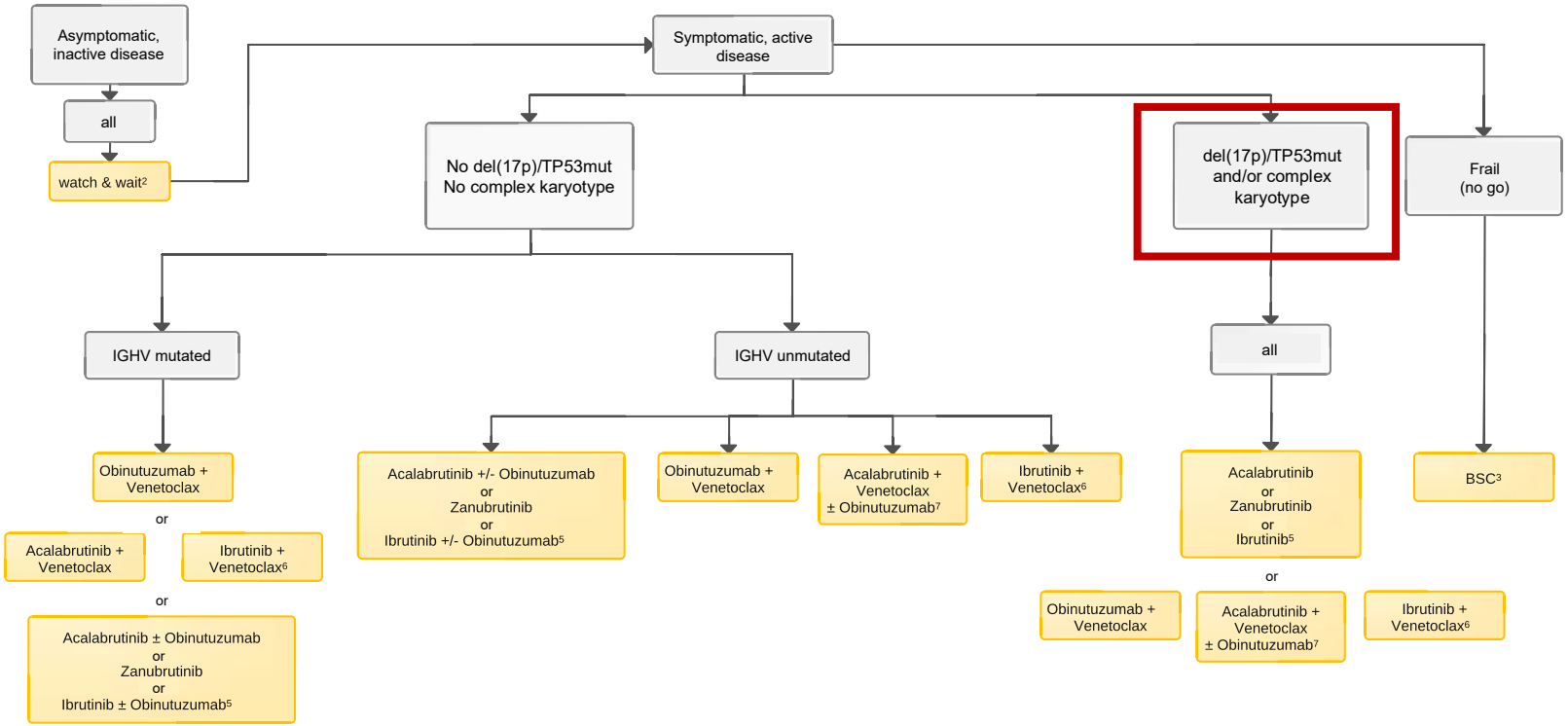
„*Unmet* challenges“ in CLL

- Poor response to treatment → *low ORR, low rates of uMRD*
- Short duration of response → *short PFS, TTNT, OS*
- Acquired resistance → *BTK mutations, BCL2 mutations*
- Frequent treatment-related toxicities → *cardiovascular events, cytopenia, infections*

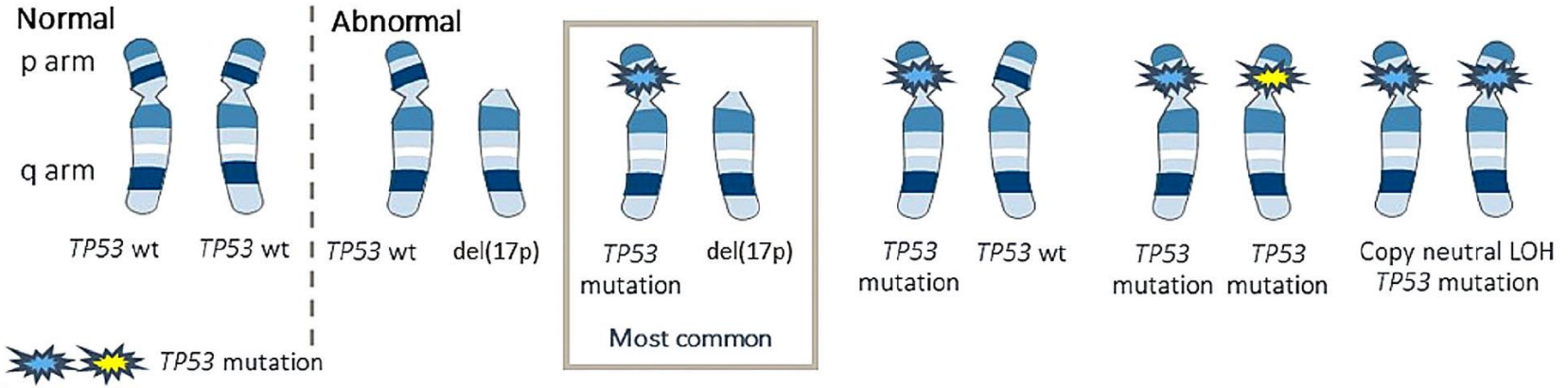
„High-risk“ in treatment guidelines: ESMO/EHA



„High-risk“ in treatment guidelines: ESMO/EHA



TP53 aberrations in CLL

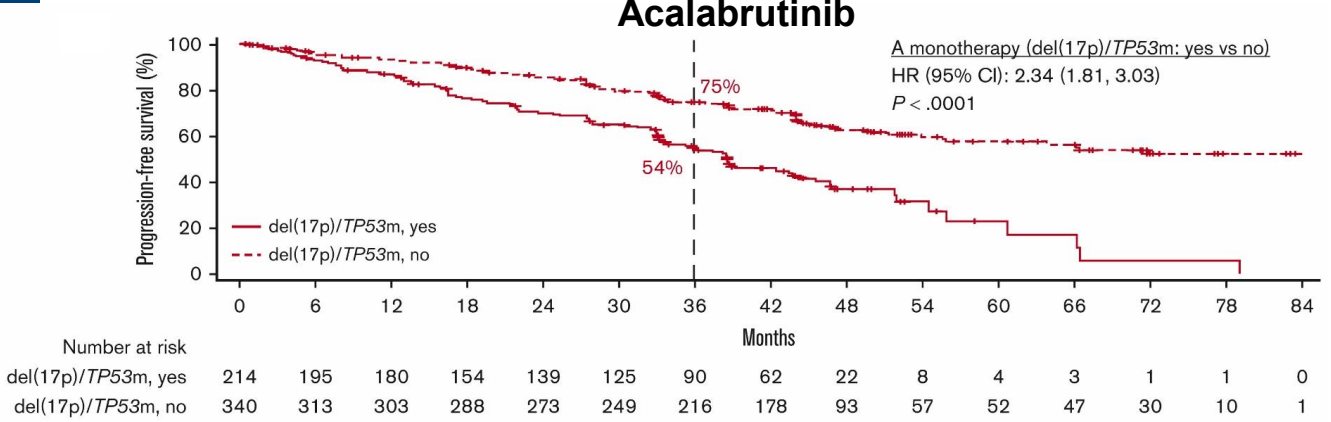


Proportion of all TP53 aberations (%)	~10%	~60%	~30%

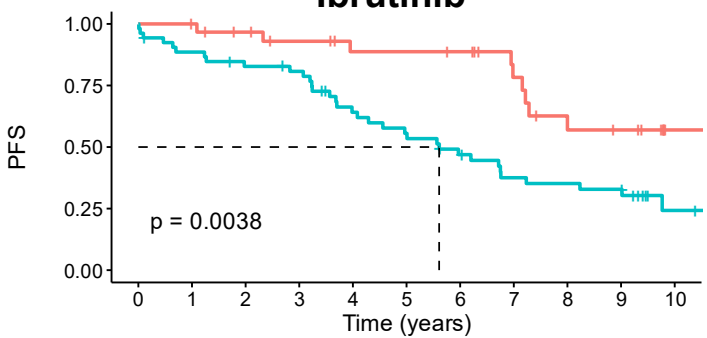
Campo et al,, Haematologica, 2018

TP53 with continuous targeted treatment

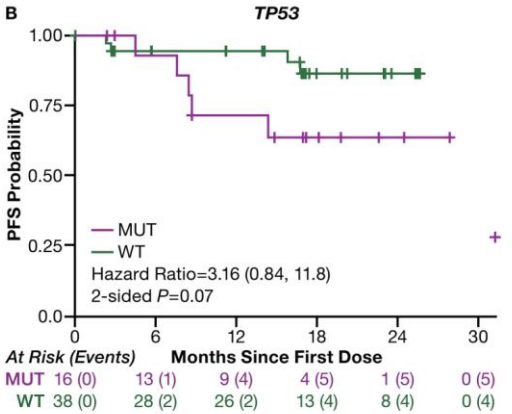
Acalabrutinib



Ibrutinib



Zanubrutinib



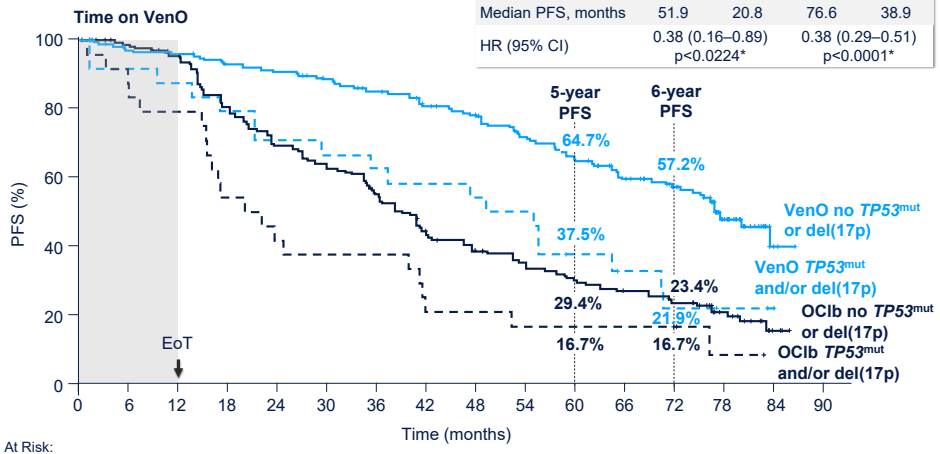
Significantly shorter PFS with continuous BTKi when *TP53* altered.

Davids et al, Blood Adv, 2024; Xu et al, Haematologica, 2024; Itsara et al, ASH 2023

TP53 with combination treatment

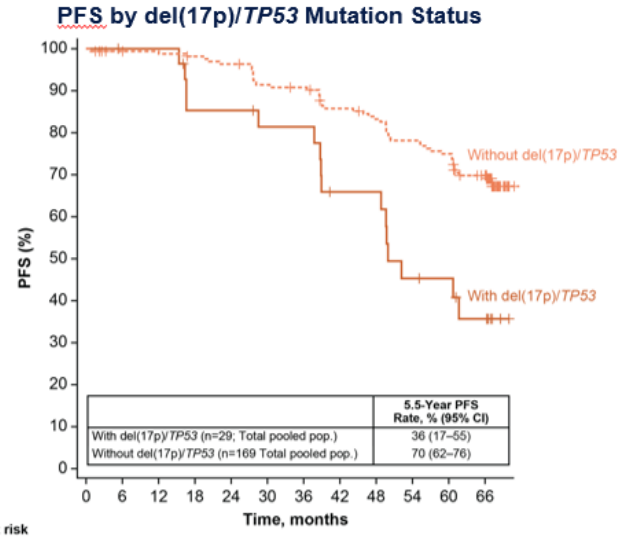
Ven-Obi

	TP53^{mut} and/or del(17p)		No *TP53*^{mut} or del(17p)	
	VenO	OClb	VenO	OClb
Median PFS, months	51.9	20.8	76.6	38.9
HR (95% CI)	0.38 (0.16–0.89) p<0.0224*		0.38 (0.29–0.51) p<0.0001*	



At Risk:														
OClb *TP53*^{mut} and/or del(17p)	24	20	19	13	10	9	9	5	5	4	4	4	3	1
VenO *TP53*^{mut} and/or del(17p)	25	22	21	19	17	16	15	14	13	12	8	6	4	2
OClb no *TP53*^{mut} or del(17p)	184	169	160	135	117	106	90	68	60	51	45	40	33	17	3
VenO no *TP53*^{mut} or del(17p)	184	170	168	161	157	150	142	131	123	112	101	87	73	34	3

Ven-Ibru



	5.5-Year PFS Rate, % (95% CI)
With del(17p)/*TP53* (n=29; Total pooled pop.)	36 (17–55)
Without del(17p)/*TP53* (n=169 Total pooled pop.)	70 (62–76)

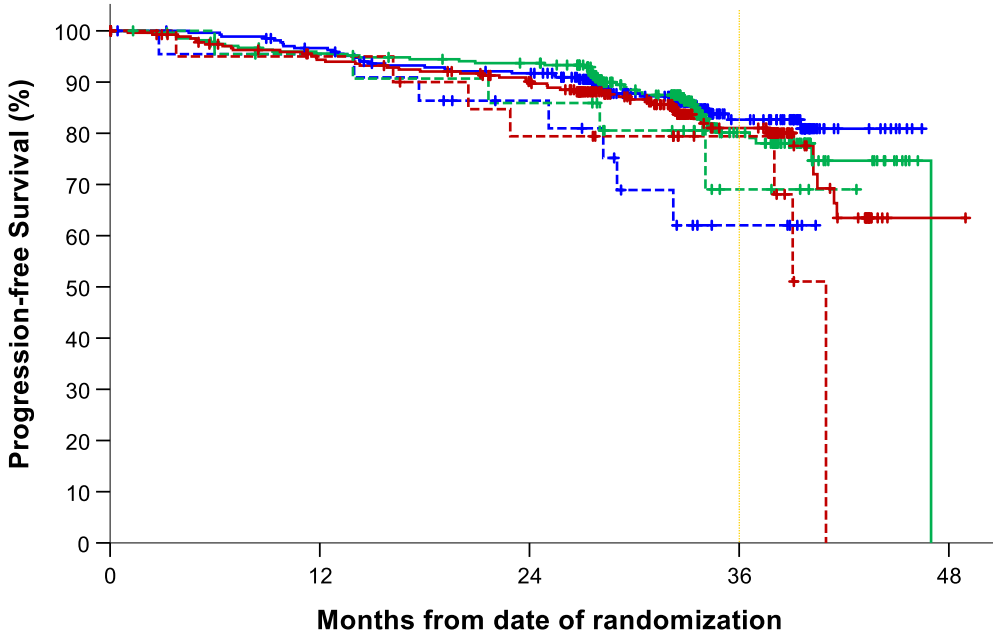
Patients at risk												
With del(17p)/*TP53*	29	28	28	23	23	21	21	16	16	11	10	7
Without del(17p)/*TP53*	169	164	163	160	157	148	146	136	131	123	118	103

FD Cohort*	5.5-Year PFS Rate, % (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)

Al-Sawaf et al, Blood, 2024

Ghia et al, ICML, 2025

CLL17 PFS according to *TP53* with I, VI and VO



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

3-year-PFS

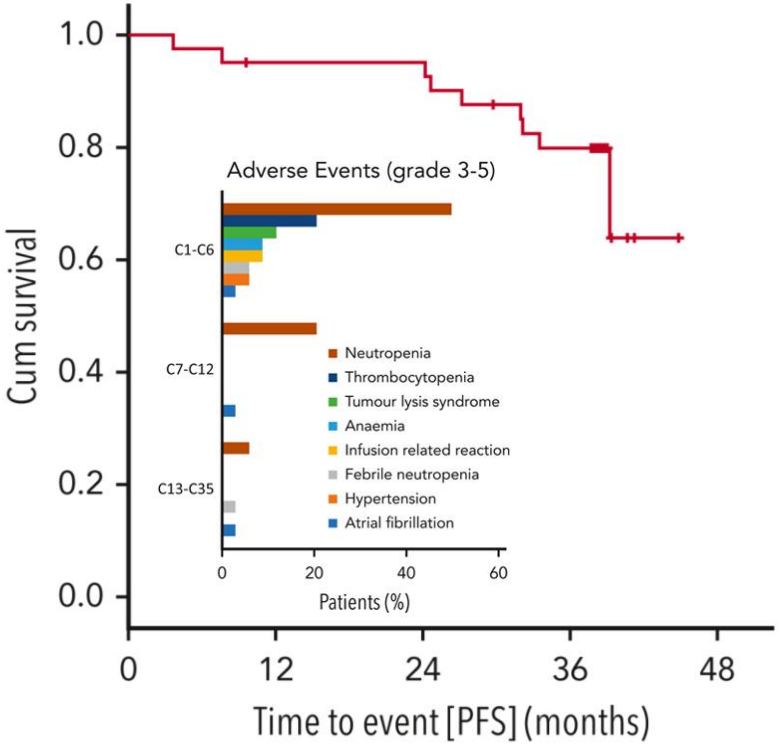
---- I, *TP53*del/mut	79.4%
— I, *TP53*-WT	81.0%
---- VI, *TP53*del/mut	69.0%
— VI, *TP53*-WT	80.1%
---- VO, *TP53*del/mut	62.0%
— VO, *TP53*-WT	82.7%

***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

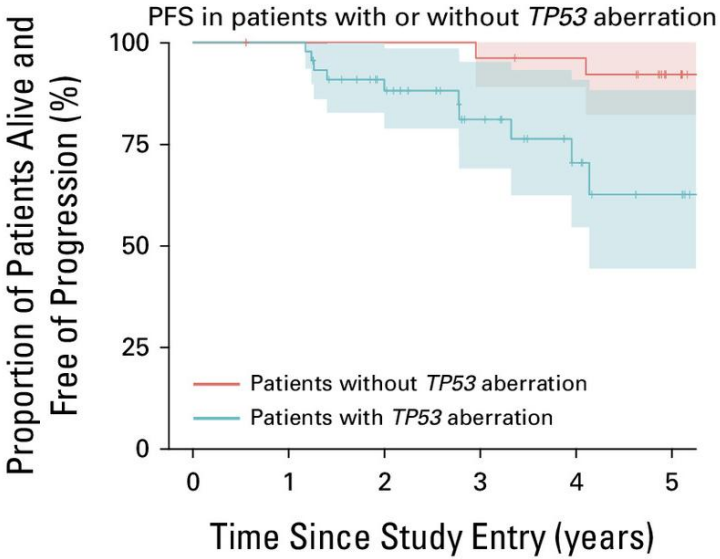
Al-Sawaf et al, ASH 2025

Triple treatment to improve efficacy in *TP53* altered CLL

GIVe Study: Obinutuzumab-Ibrutinib-Venetoclax



AVO Study: Acalabrutinib-Venetoclax-Obinutuzumab



Number at risk:

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

Huber et al, Blood, 2023

Davids et al, J Clin Oncol, 2024

Caution: Toxicity with triple combinations

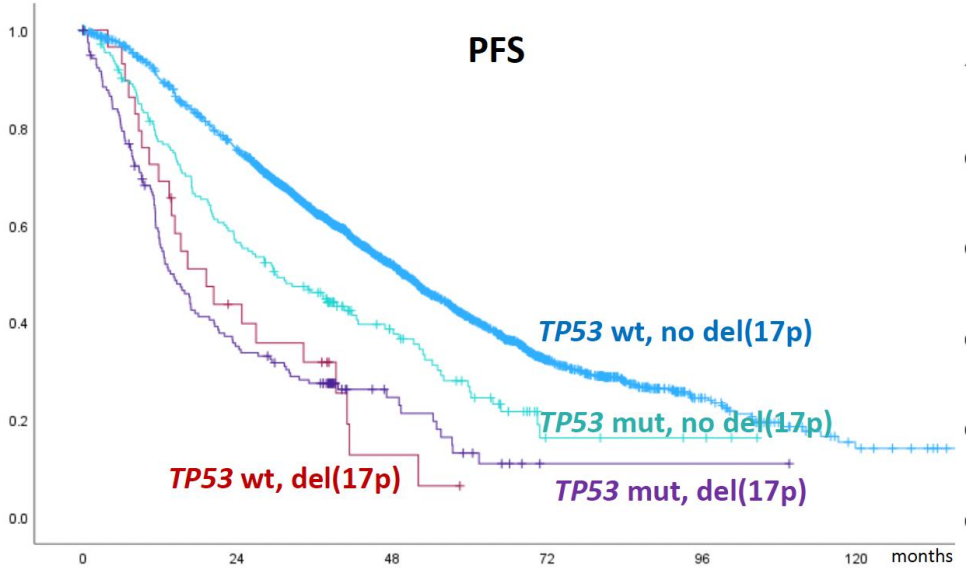
	CIT	RVe	GVe	GIVe
All patients [SP]	**216**	**237**	**228**	**231**
Anemia	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)
Neutropenia	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)
Thrombocytopenia	22 (10.2)	10 (4.2)	42 (18.4)	37 (16.0)
Febrile neutropenia	24 (11.1)	10 (4.2)	7 (3.1)	**18 (7.8)**
Infections	43 (19.9)	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)

Eichhorst et al, EHA 2024

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

Brown et al, ASH 2024

Mutation versus deletion – does it matter?



No del(17p) – *TP53* mut (n=177)
No del(17p) – *TP53* wt (n=3276)
HR 1.609, p<0.001

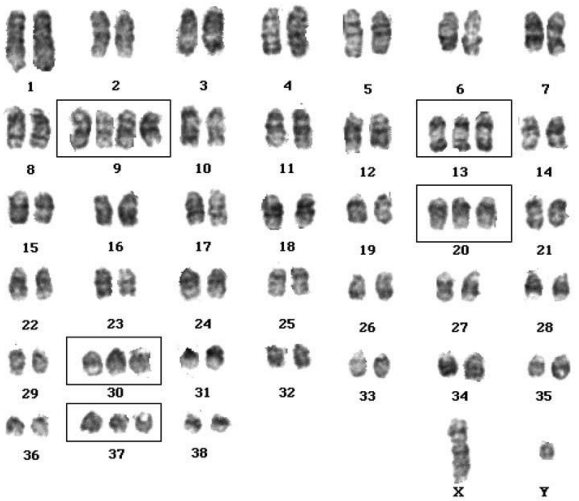
Del(17p) – *TP53* mut (n=157)
Del17p – *TP53* wt (n=31)
HR 1.010 , p=0.96

Patients with *TP53* mutation PLUS deletion 17p have a worse prognosis than patients with just a mutation.

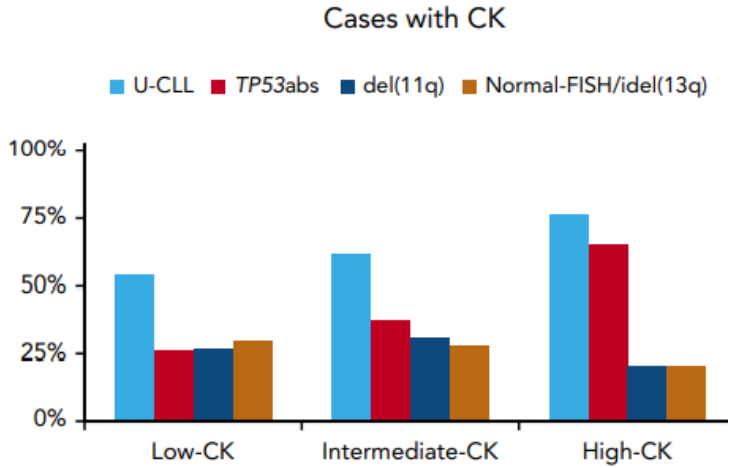
(Cave: small subgroups, heterogenous fixed-duration treatments)

Bertossi et al, EHA, 2024

Complex karyotype

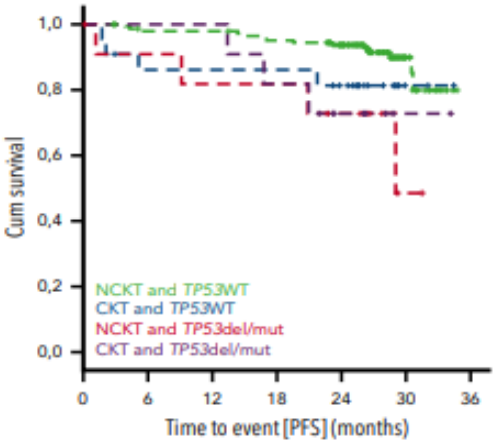


Definition of low CKT: 3 chromosomal aberrations
Definition of intermediate CKT: 4 chromosomal aberrations
Definition of high CKT: ≥ 5 chromosomal aberrations

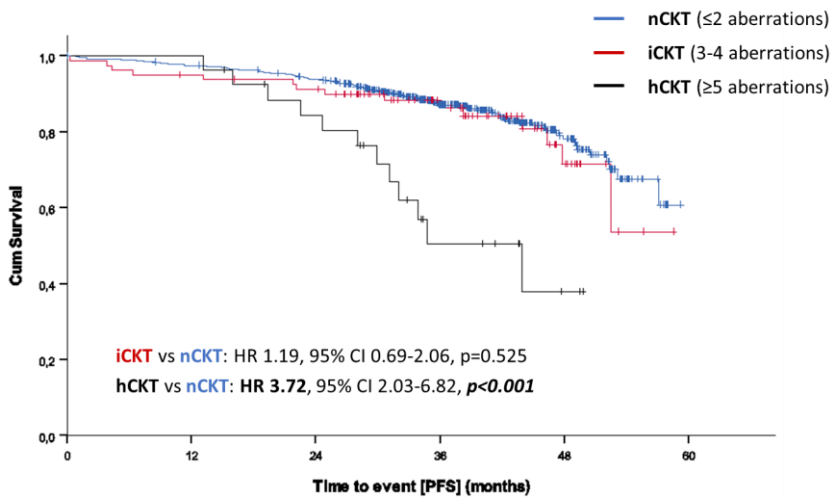


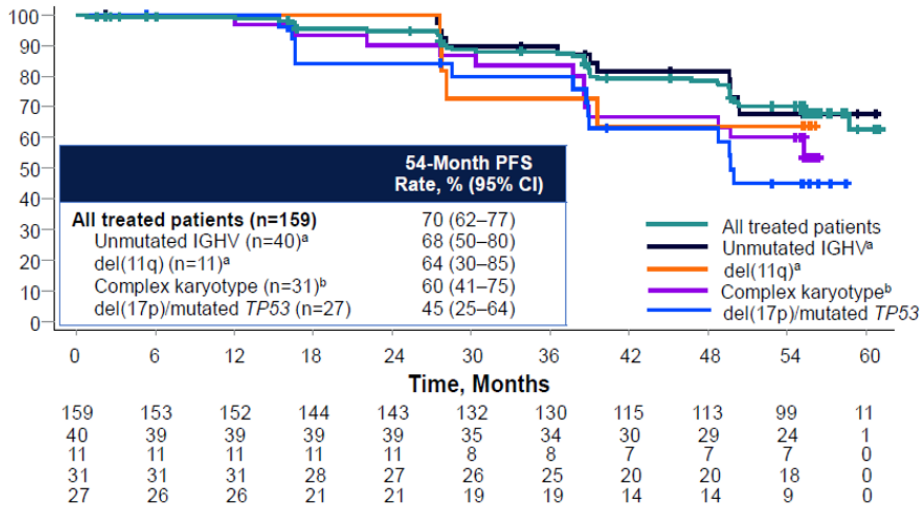
Baliakas et al., Blood 2019

Complex karyotype



No at risk							
NCKT and *TP53*WT	150	140	140	135	120	21	0
CKT and *TP53*WT	22	18	18	18	15	2	0
NCKT and *TP53*del/mut	12	10	9	9	6	1	0
CKT and *TP53*del/mut	11	11	11	9	5	1	0

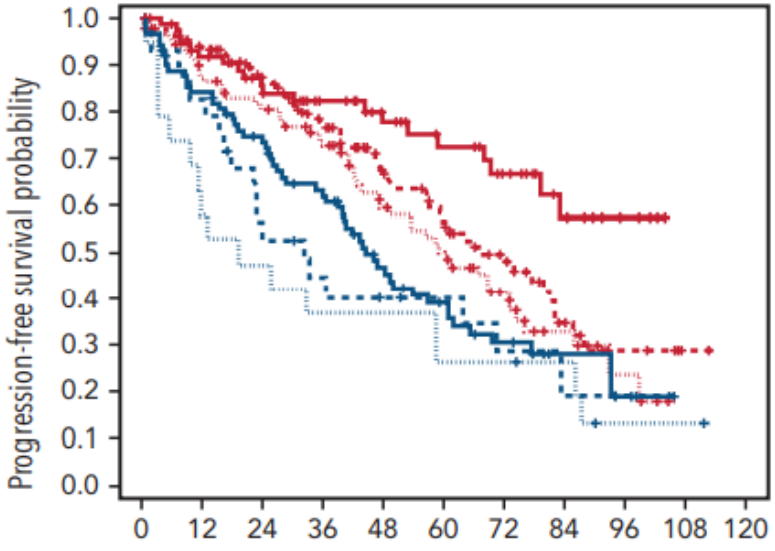




159	153	152	144	143	132	130	115	113	99	11
40	39	39	39	39	35	34	30	29	24	1
11	11	11	11	11	8	8	7	7	7	0
31	31	31	28	27	26	25	20	20	18	0
27	26	26	21	21	19	19	14	14	9	0

Al-Sawaf et al, Blood, 2020; Fürstenau et al, Blood, 2023; Ghia et al, ICML 2023

Complex karyotype



Cytogenetic abnormalities	Events/ Total	Median (95% CI)
0	20/74	NR (79-NR)
1–2	60/155	67 (57–82)
3–4	50/90	60 (47–73)
5–9	56/89	45 (36–61)
10–14	19/29	32 (18–70)
> = 15	16/19	19 (6–58)

Logrank *P*-value; <.0001 + censor

Patients-at-risk

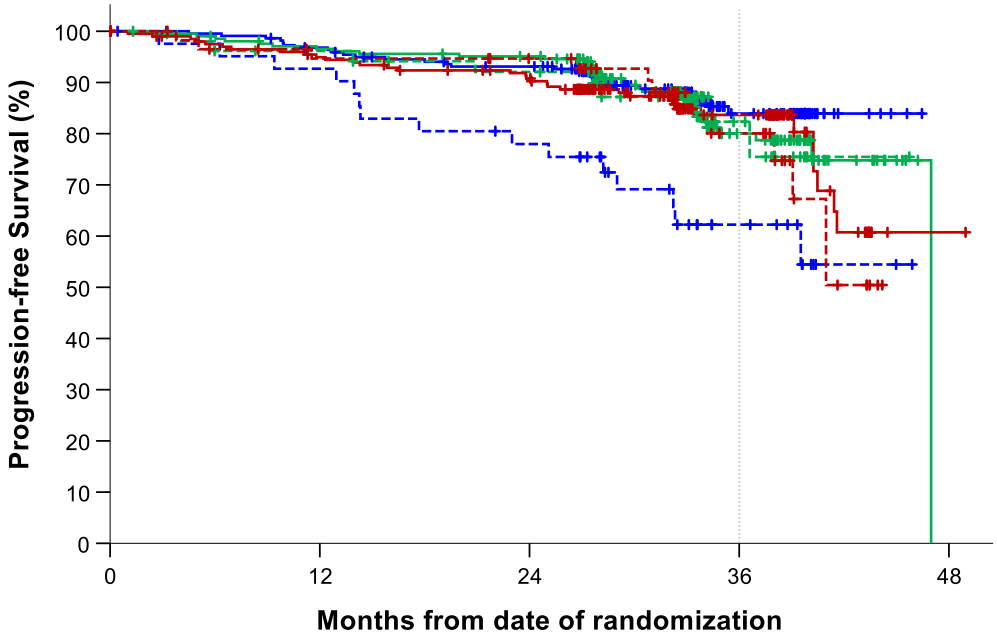
0-	74	64	50	43	33	27	21	12	4	0	
1-2-	155	132	107	77	55	42	29	12	6	1	0
3-4-	90	75	65	55	39	32	21	11	4	0	
5-9-	89	73	60	48	31	23	16	6	3	0	
10-14-	29	23	14	10	8	7	5	2	1	0	
> = 15-	19	11	9	7	7	5	5	4	1	1	0

Prognostic impact of CKT with fixed-duration and continuous targeted treatment.

Kittai et al, Blood, 2020

PROGRESSION-FREE SURVIVAL

According to complex karyotype status



Patients at risk					
VO, CKT	42	38	31	12	0
VO, NCKT	223	211	198	60	0
VI, CKT	53	48	44	13	0
VI, NCKT	212	196	191	62	0
I, CKT	58	52	49	18	0
I, NCKT	207	185	172	69	1

3-year-PFS

I, CKT	80.1%
I, NCKT	83.7%
VI, CKT	82.3%
VI, NCKT	80.0%
VO, CKT	62.2%
VO, NCKT	83.9%

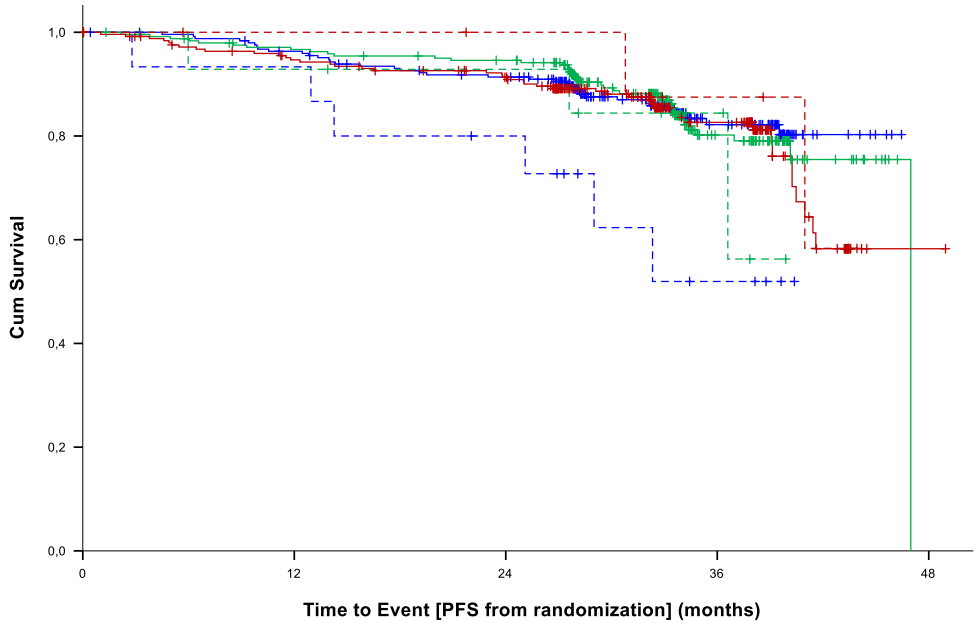
CKT:

VI vs I: HR 0.90, 95% CI 0.36-2.25

VO vs I: HR 1.98, 95% CI 0.92-4.26

PROGRESSION-FREE SURVIVAL

According to **highly** complex karyotype status (≥5)



Patients at risk					
VG, HCKT	15	14	11	4	0
VG, CKT/NCKT	250	235	218	68	0
VI, HCKT	14	13	12	4	0
VI, CKT/NCKT	251	231	223	71	0
I, HCKT	10	9	8	4	0
I, CKT/NCKT	255	228	213	83	1

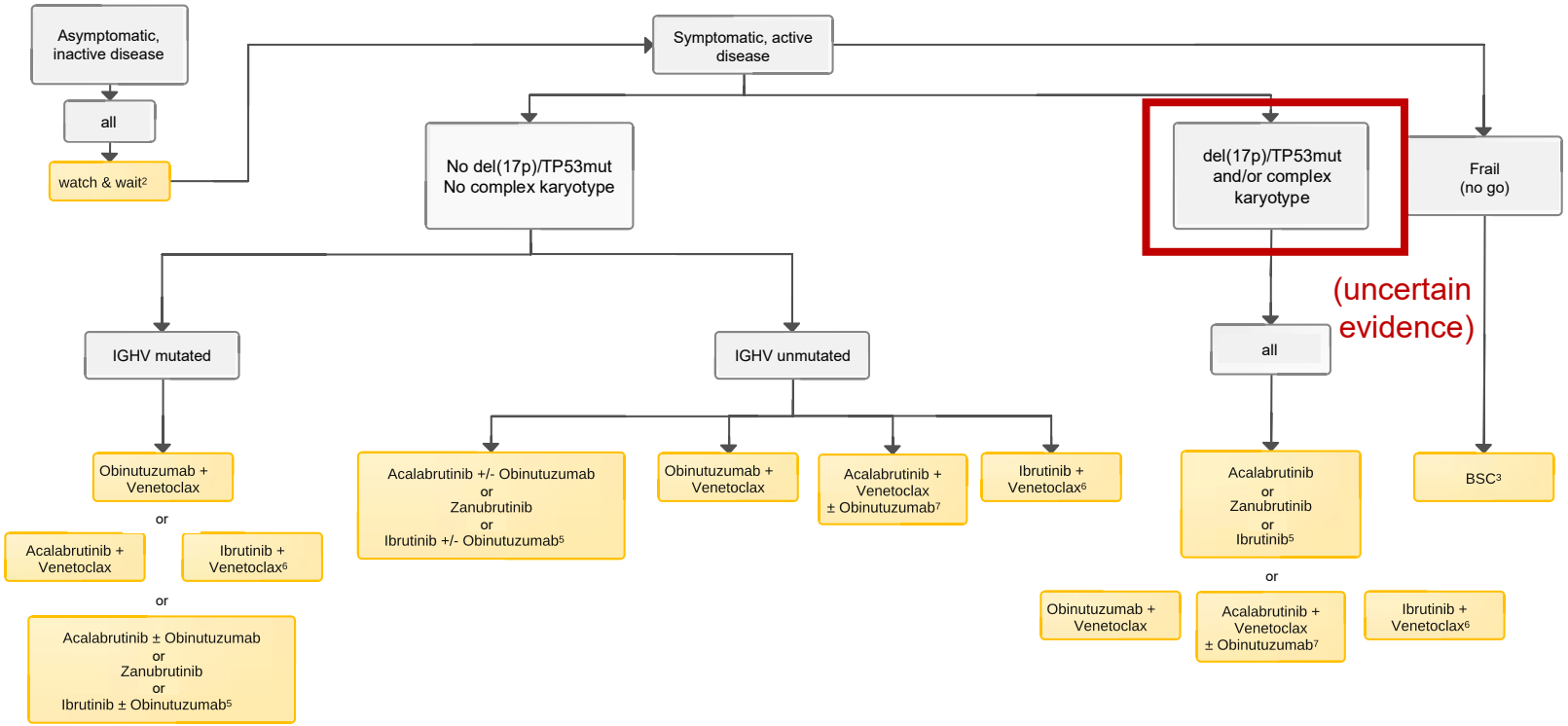
3-year-PFS

----	I, HCKT	87.5%
—	I, CKT/NCKT	82.6%
----	VI, HCKT	
—	84.4%	
	VI, CKT/NCKT	
----	VO, HCKT	51.9%
—	VO, CKT/NCKT	82.2%

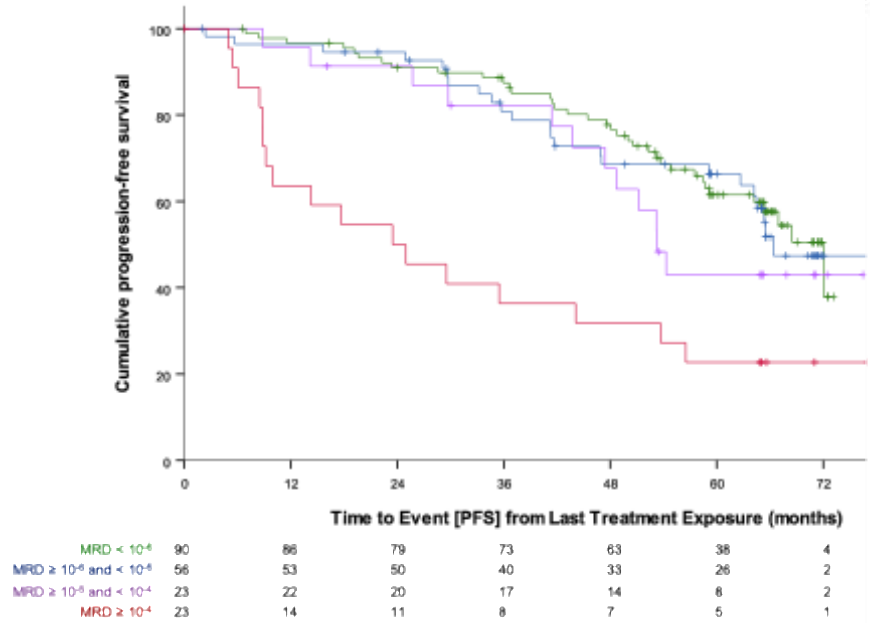
Cave: Very small subgroups and limited observation time.

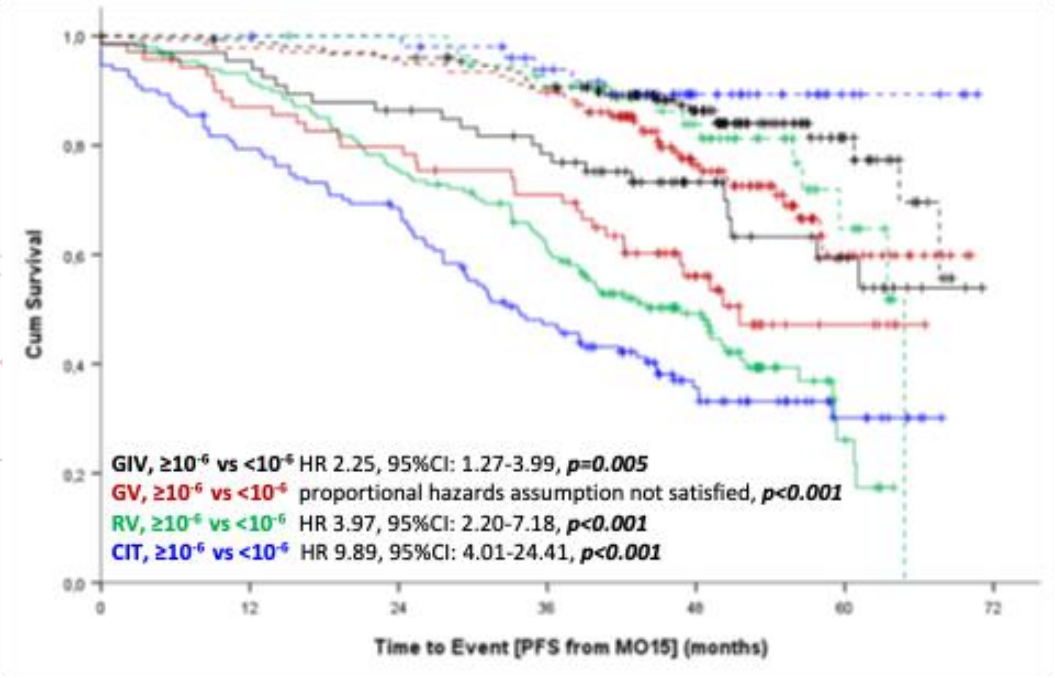
Unpublished data

„High-risk“ in treatment guidelines: ESMO/EHA



“Unmet challenge“ beyond genomics: dMRD

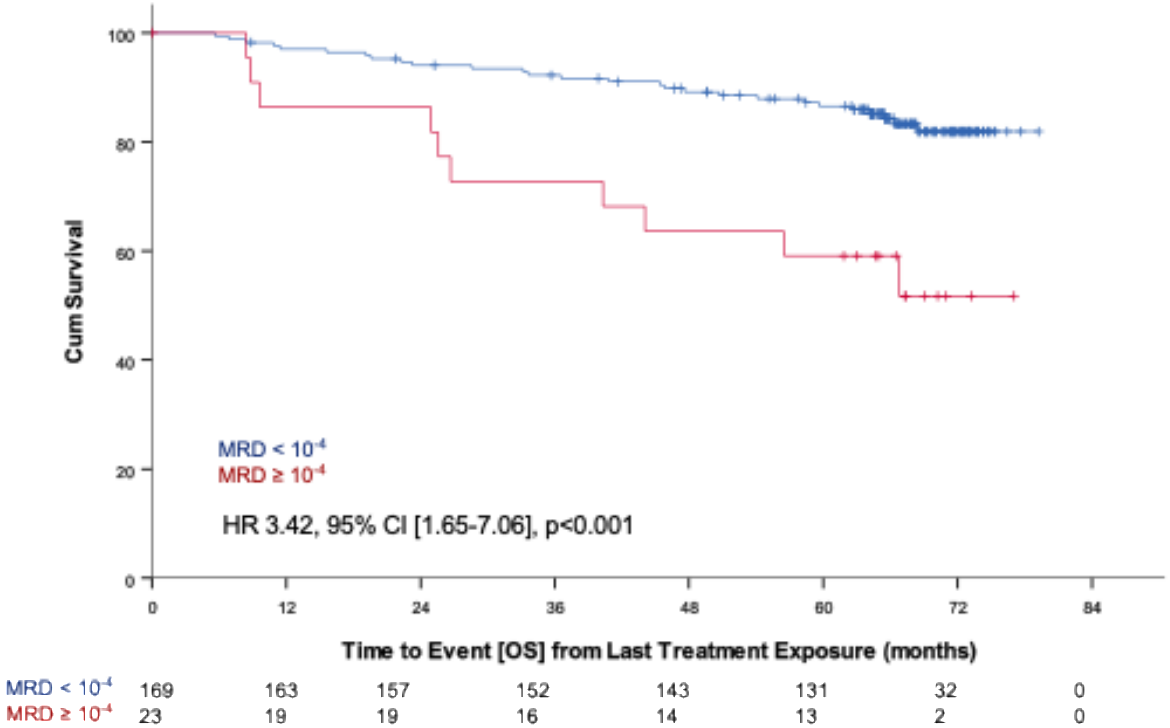




Patients with detectable MRD >10^{-4} have a poor prognosis, regardless of treatment

Al-Sawaf et al, Blood 2024; Fürstenau et al, EHA 2025

“Unmet challenge“ beyond genomics: dMRD



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Al-Sawaf et al, Blood 2024

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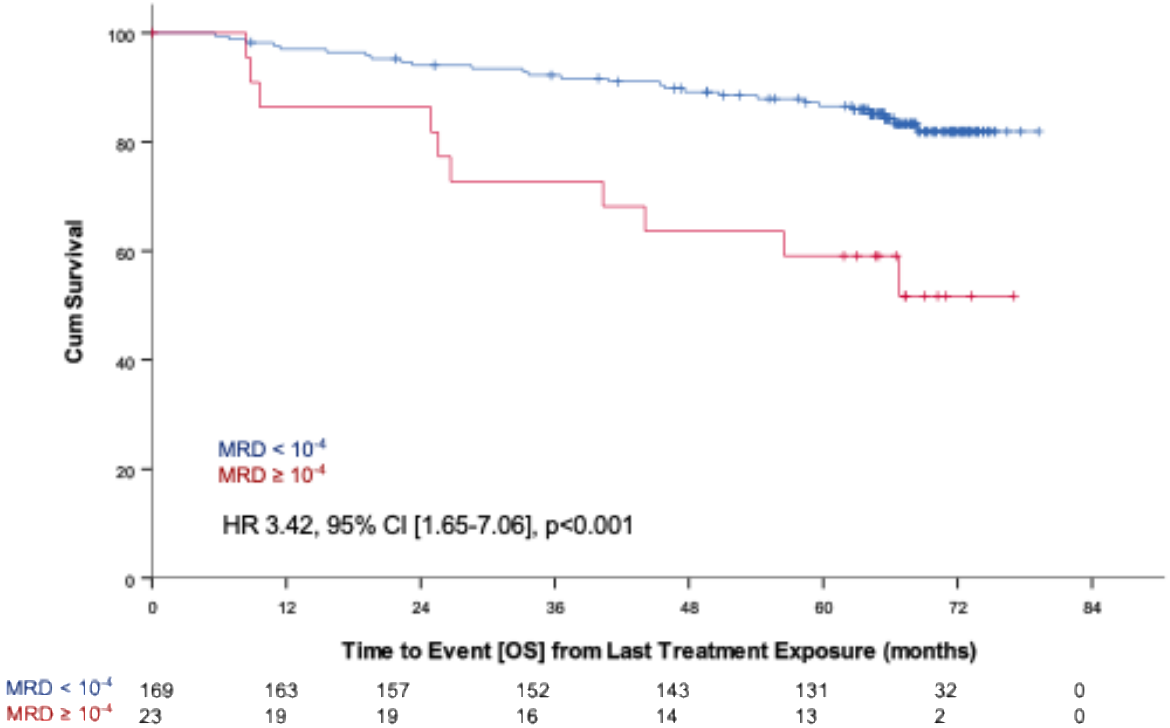
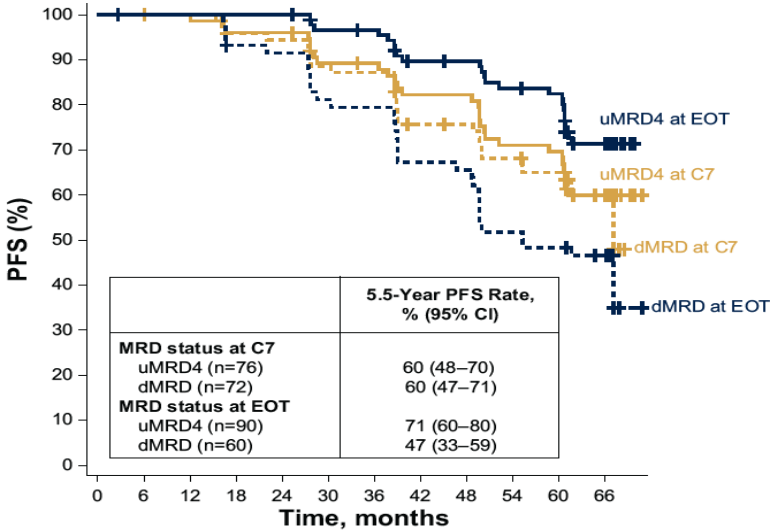


Patients with detectable MRD >10^{-4} have a poor prognosis, regardless of treatment

Al-Sawaf et al, Blood 2024

“Unmet challenge“ beyond genomics: dMRD

Ibru-Ven

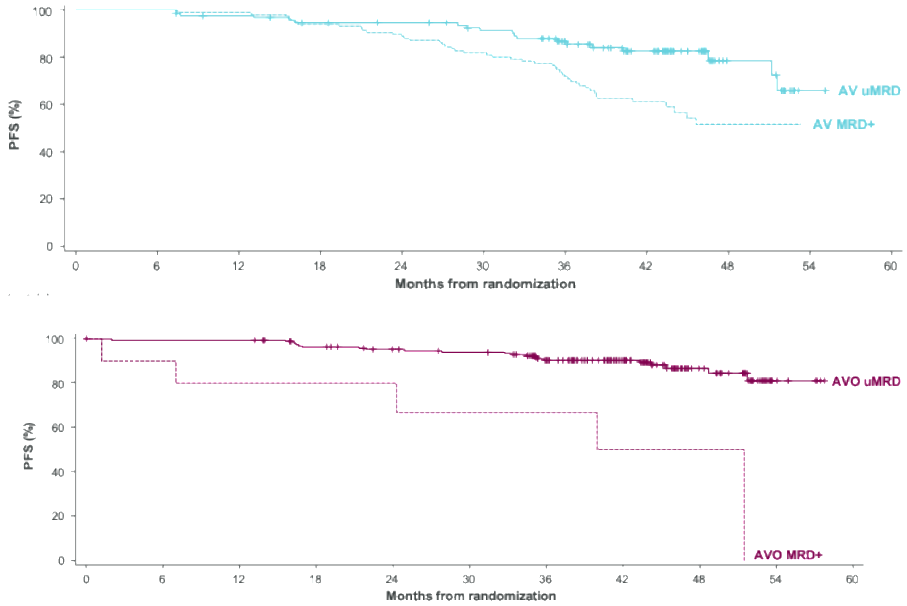


	5.5-Year PFS Rate, % (95% CI)
MRD status at C7	
uMRD4 (n=76)	60 (48–70)
dMRD (n=72)	60 (47–71)
MRD status at EOT	
uMRD4 (n=90)	71 (60–80)
dMRD (n=60)	47 (33–59)

Patients at risk

uMRD4 at C7	76	76	75	72	72	65	64	59	59	51	50	40
dMRD at C7	72	72	72	67	66	62	61	51	50	45	42	35
uMRD4 at EOT	90	90	90	90	90	85	84	76	75	70	68	54
dMRD at EOT	60	59	59	54	53	47	46	39	38	30	28	25

Acala-Ven



Patients with detectable MRD >10^{-4} have a poor prognosis, regardless of treatment

Ghia et al, EHA 2025

Brown et al, ASH 2024

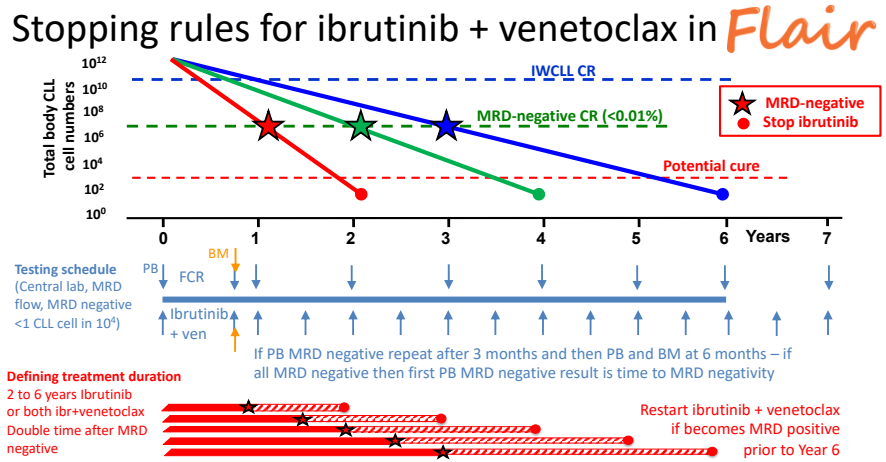
MRD-guided therapy

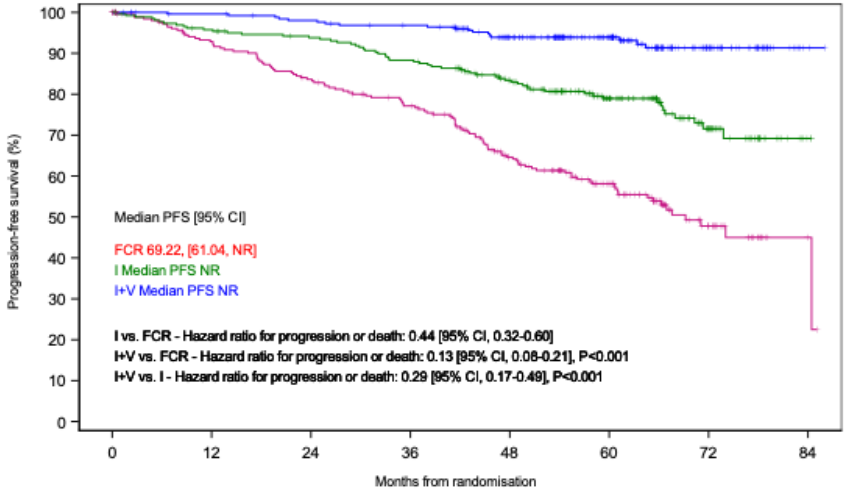
To establish MRD-guided therapy in routine care, we need to identify

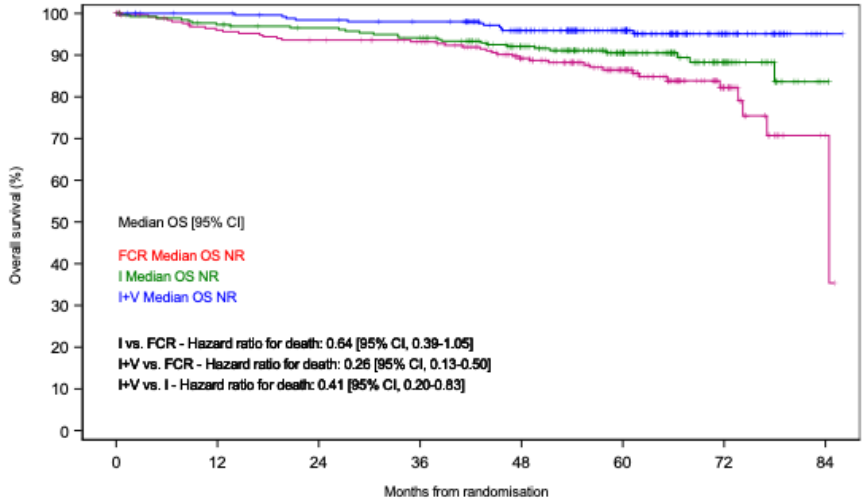
- In which **compartment**, by which **method**, and **how often** to measure MRD
- identify whether MRD in any way correlates or impacts **QoL**
- confirm that MRD-guided therapy has **benefits** over fixed-duration/continuous therapy (=> **randomization**)

FLAIR

So far the only randomized trial with MRD-guidance versus no MRD-guidance (but not fixed-duration I+V).





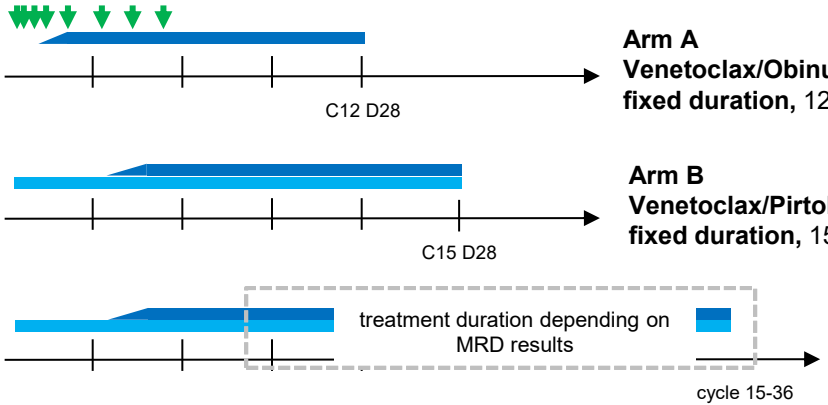


Munir et al, *NEJM* 2025

CLL18

Treatment naive, all comer CLL/SLL (irrespective of fitness, comorbidity and risk factors)

R



Arm A
Venetoclax/Obinutuzumab fixed duration, 12 cycles

Arm B
Venetoclax/Pirtobrutinib fixed duration, 15 cycles

Arm C
Venetoclax/Pirtobrutinib MRD-guided 15-36 cycles

venetoclax
obinutuzumab
pirtobrutinib

Superiority of MRD guided Ven-Pirto vs fixed-duration Ven-Obi

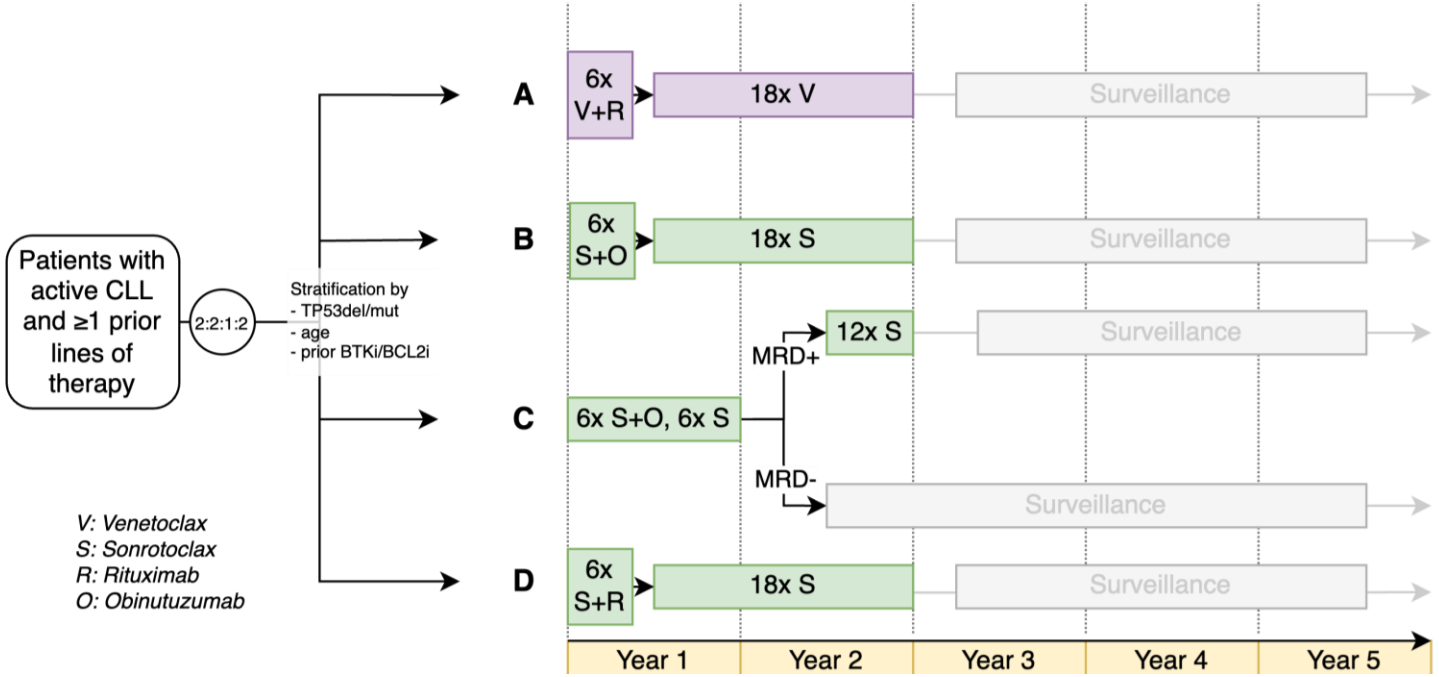
Superiority of MRD guided Ven-Pirto vs fixed-duration Ven-Pirto

Total required sample size: 813 pts (271 per arm, 1:1:1 randomization)

Recruitment rate: 50 pts per month, 20 pts per month during months 1-6, accrual period: 20 months
Primary endpoint PFS analysis once 68 events for each superiority testing (approximately month 41)

CLL-RR1

The CLL-RR1 study



Unmet challenges and combination therapies

- ***TP53* del/mut or CKT**: Current preference for continuous BTKi, but combinations with Ven+BTKi also effective

  Pending follow-up from CLL17 data

- **dMRD**: Highly prognostic for combination therapies, but not much else in routine care

  Include in CLL18 and CLL-RR1 to study benefits of MRD-guidance