IOR
Un istituto
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Predictive biomarkers

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DISCLOSURES OF COMMERCIAL SUPPORT

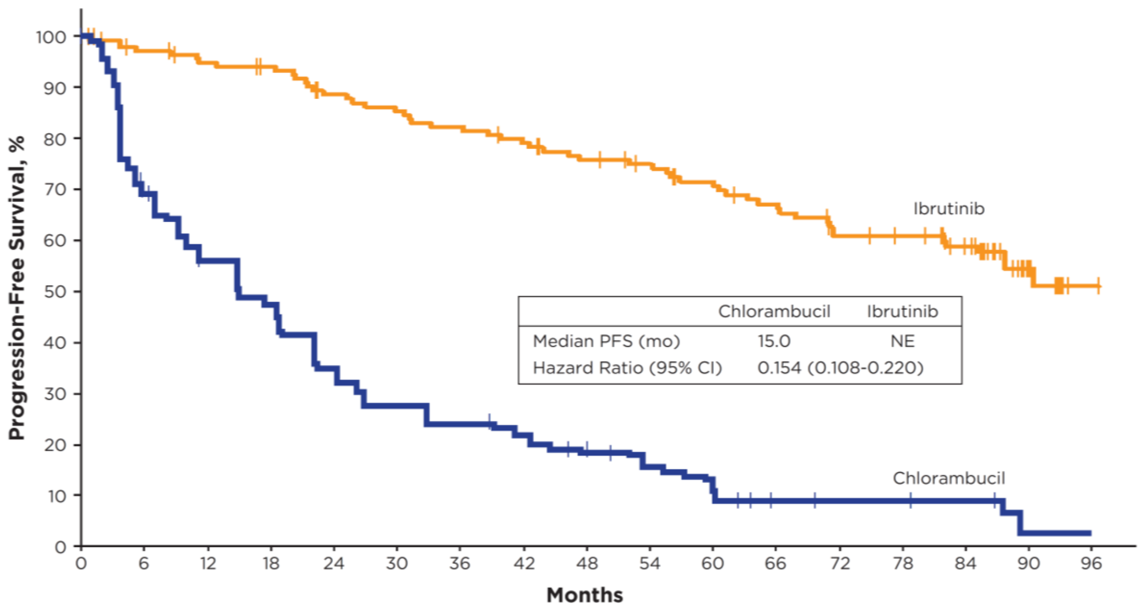
Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
AbbVie	X					X	
AstraZeneca	X					X	
BeiGene	X					X	
BMS						X	
Janssen	X					X	

Why not CIT?

		PFS	OS
iLLUMINATE	Clb-G vs IG	↑	=
ELEVATE TN	Clb-G vs A +/-G	↑	↑
CLL14	Clb-G vs VG	↑	↑
A041202	BR vs I +/-R	↑	=
SEQUOIA	BR vs Z	↑	=
E1912	FCR vs IR	↑	↑
CLL13	FCR vs VG	↑	=
FLAIR	FCR vs I	↑	=

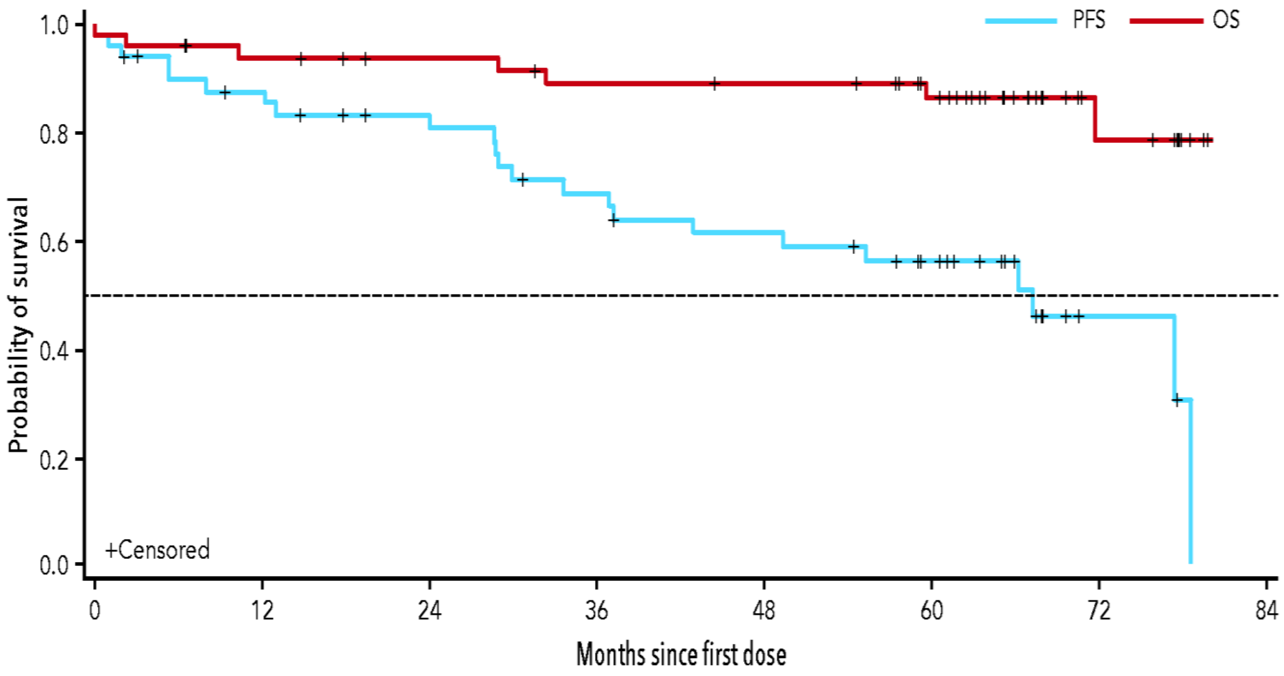
Sequencing: option 1 – BTKi → BCL2i

Median FU: 82.7 mo



	Chlorambucil	Ibrutinib
Median PFS (mo)	15.0	NE
Hazard Ratio (95% CI)	0.154 (0.108-0.220)	

Median FU: 5.3 y

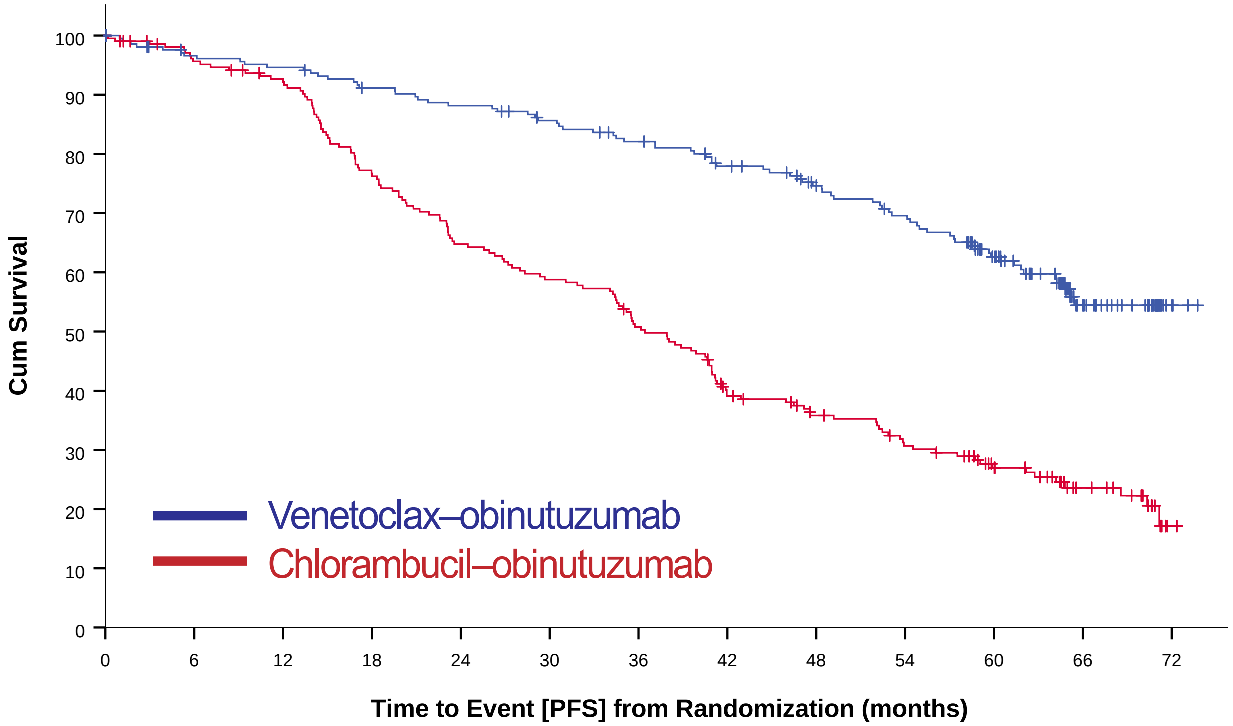


Barr PM, Blood Adv. 2022

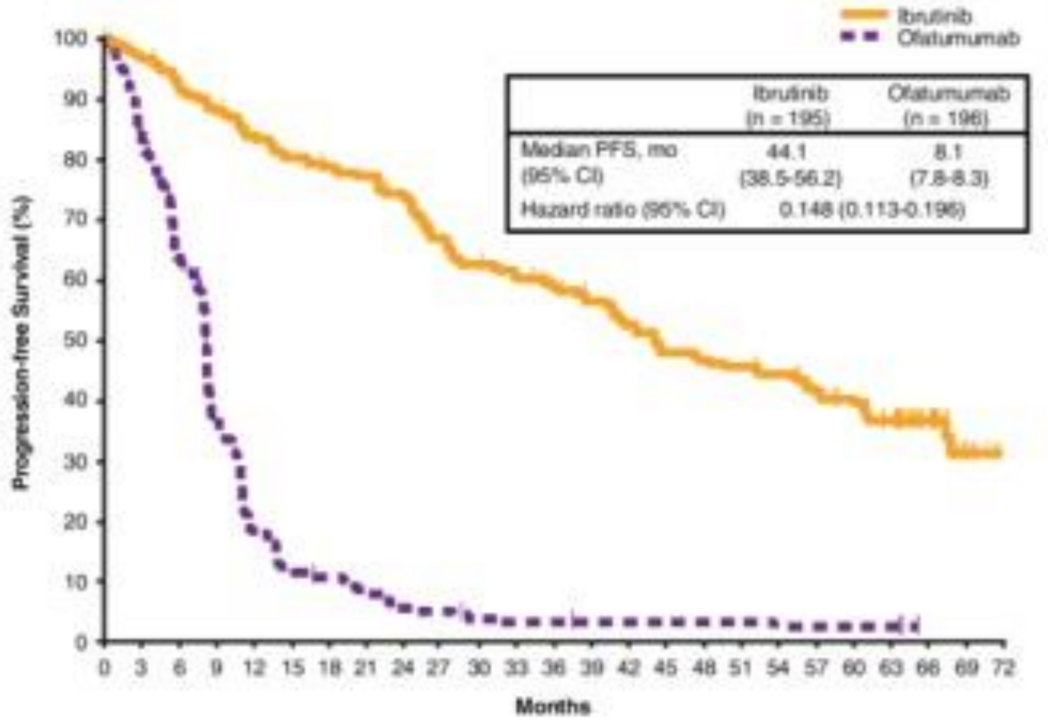
Ma S, Blood. 2021

Sequencing: option 2 – BCL2i → BTKi

Median FU: 65.4 mo



Median FU: 65.3 mo



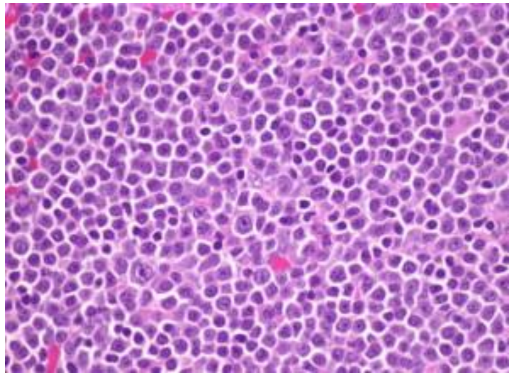
EHA 2022 Abstract S148

Munir T, Am J Hematol. 2019

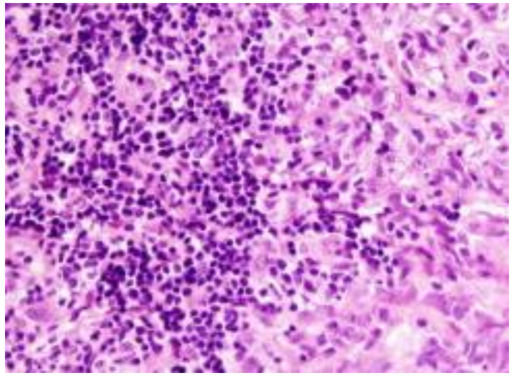
Histology

Clinical implications of differentiating histologically aggressive CLL vs Richter syndrome

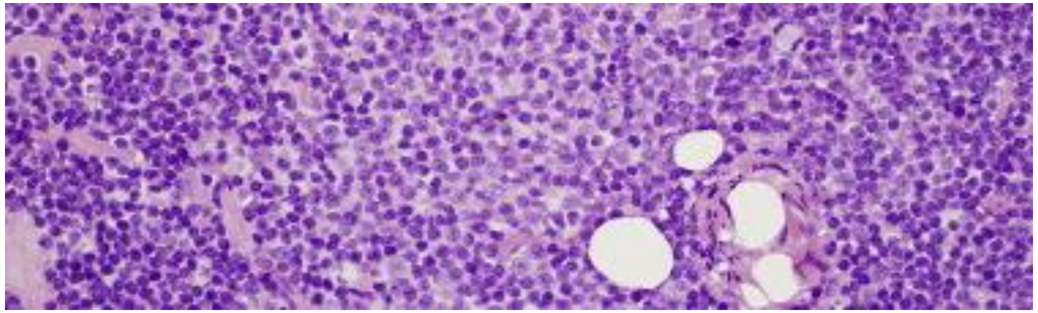
CLL



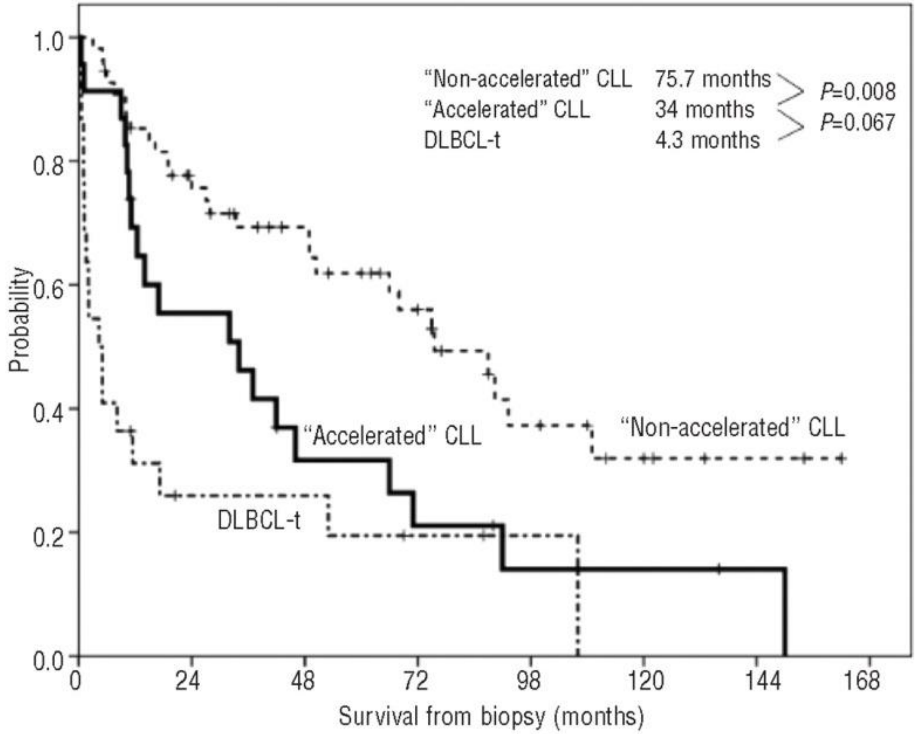
RS



Histologically aggressive CLL



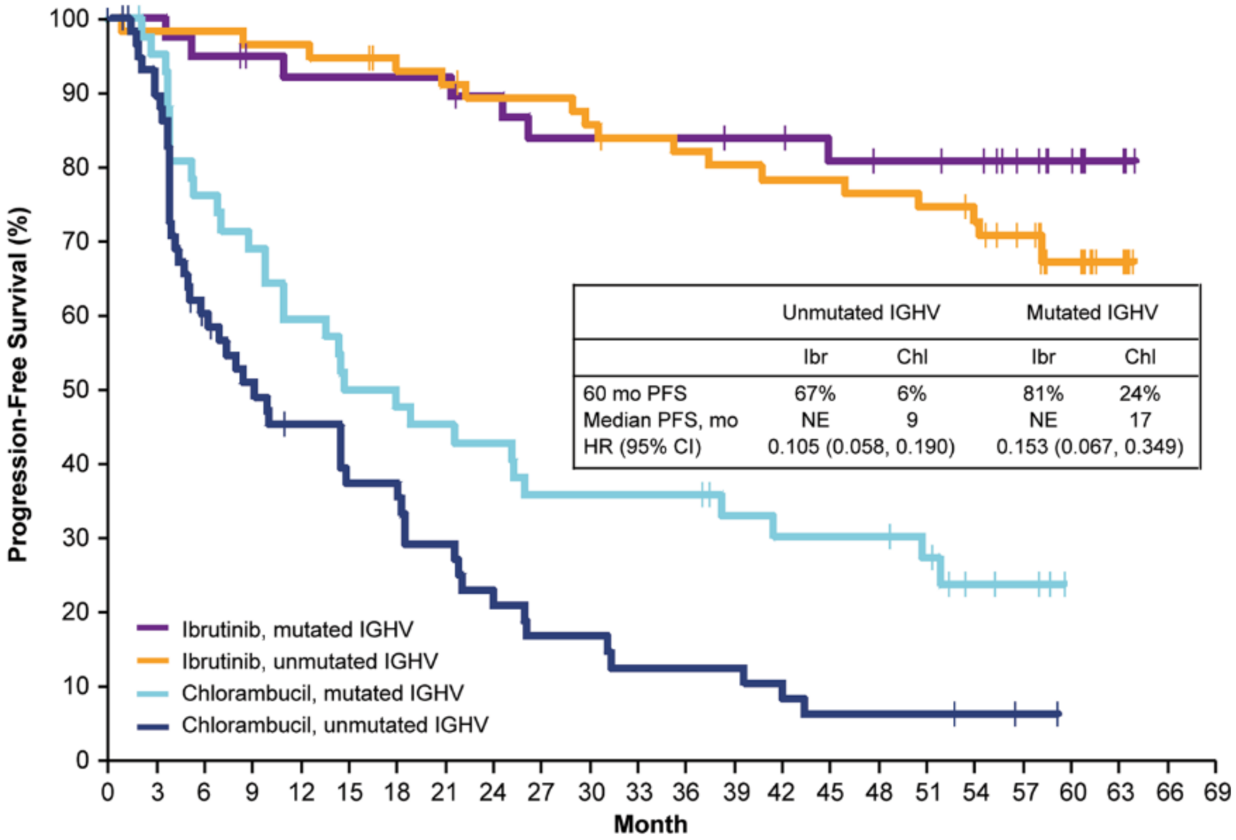
Survival from biopsy according to the histology



Giné E *et al. Haematologica* 2010; 95 (9): 1526–1533.

IGHV status

RESONATE2 - PROGRESSION FREE SURVIVAL IN U-CLL AND M-CLL

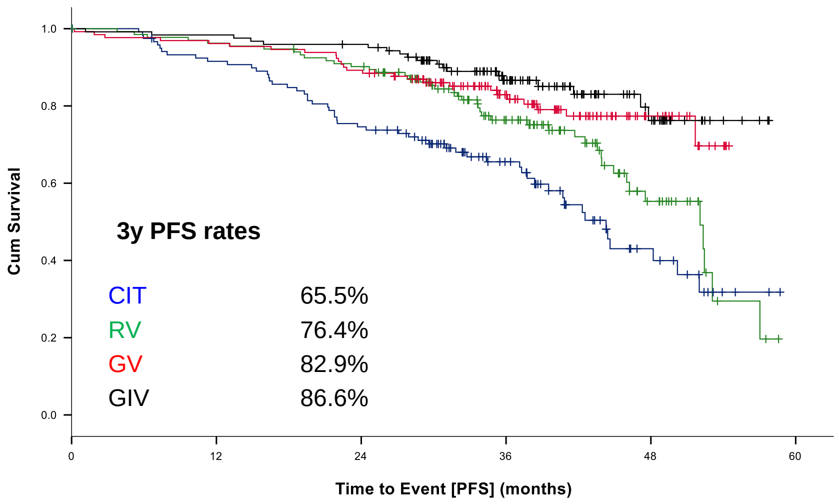


	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
60 mo PFS	67%	6%	81%	24%
Median PFS, mo	NE	9	NE	17
HR (95% CI)	0.105 (0.058, 0.190)		0.153 (0.067, 0.349)	

Burger JA, *et al.* Leukemia. 2020

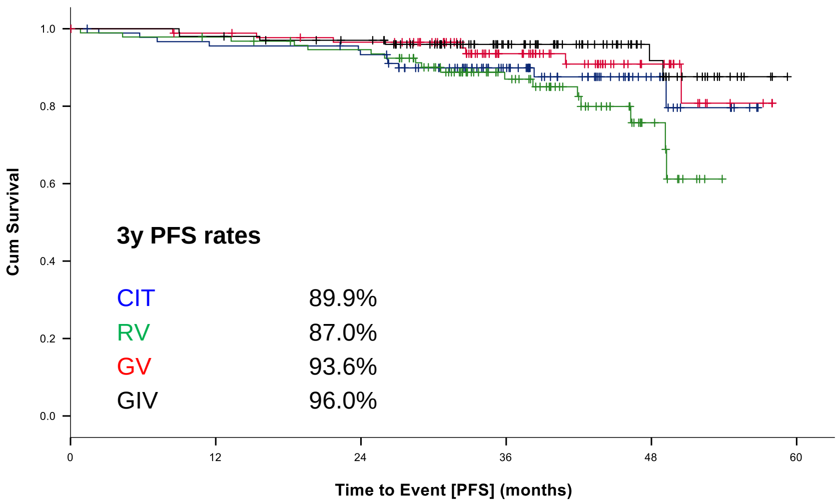
CLL13 - PFS ACCORDING TO IGHV STATUS

Unmutated IGHV



CIT	131	108	88	48	14
RV	134	128	119	67	20
GV	130	125	116	71	21
GIV	123	121	117	70	22

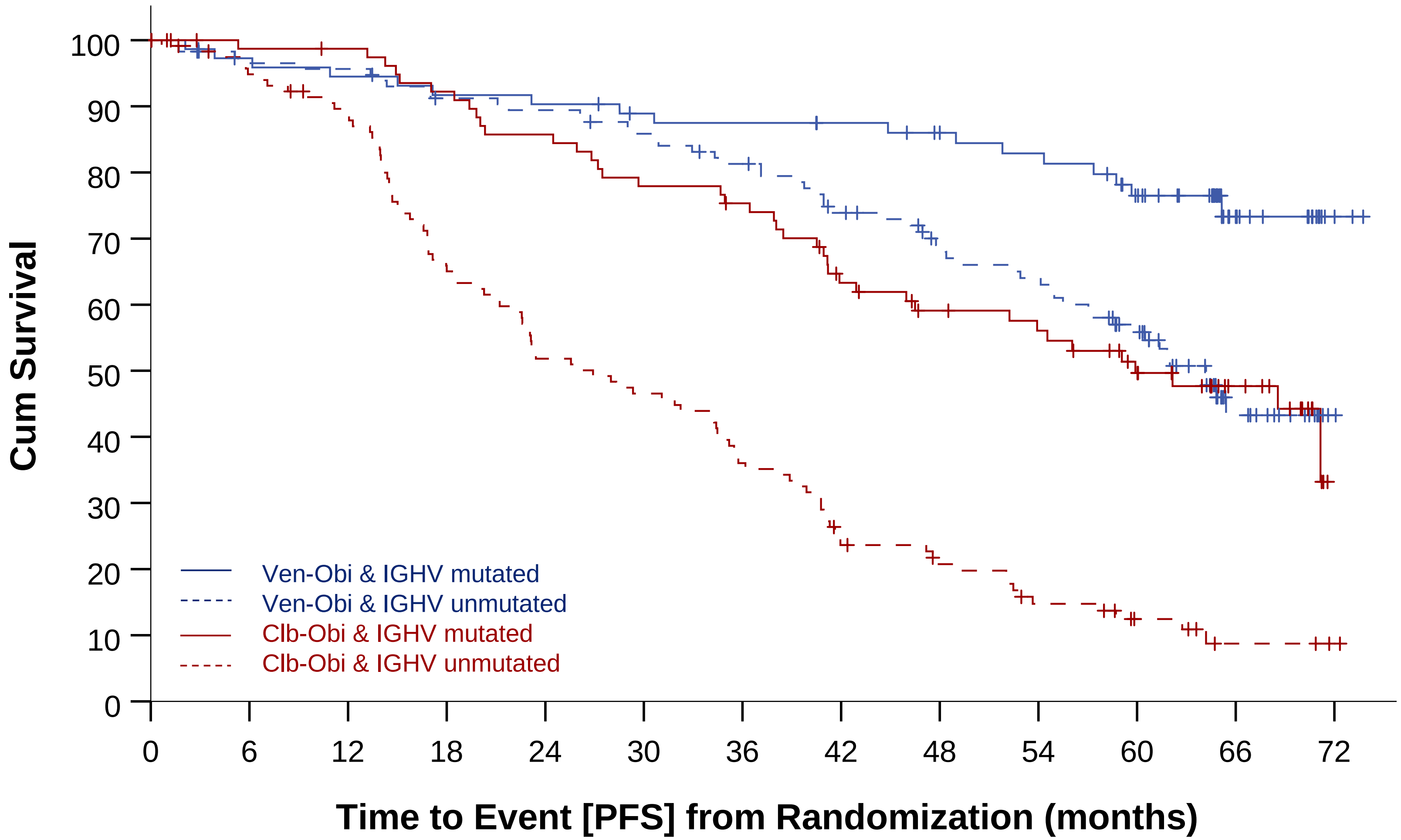
Mutated IGHV



CIT	95	86	83	50	14
RV	95	91	86	49	12
GV	89	86	82	48	17
GIV	101	99	94	59	22

Eichhorst. EHA 2022. Abstr LB2365

PROGRESSION-FREE SURVIVAL – IGHV status



Ven-Obi & IGHV mutated	76	70	68	66	65	62	61	59	56	53	45	18	3
Ven-Obi & IGHV unmutated	121	110	109	102	100	95	89	79	69	64	49	16	1
Clb-Obi & IGHV mutated	83	77	76	71	66	60	57	46	40	37	29	17	0
Clb-Obi & IGHV unmutated	123	110	101	75	59	53	41	26	21	14	8	3	1

Median PFS

Ven-Obi & IGHVmut: NR

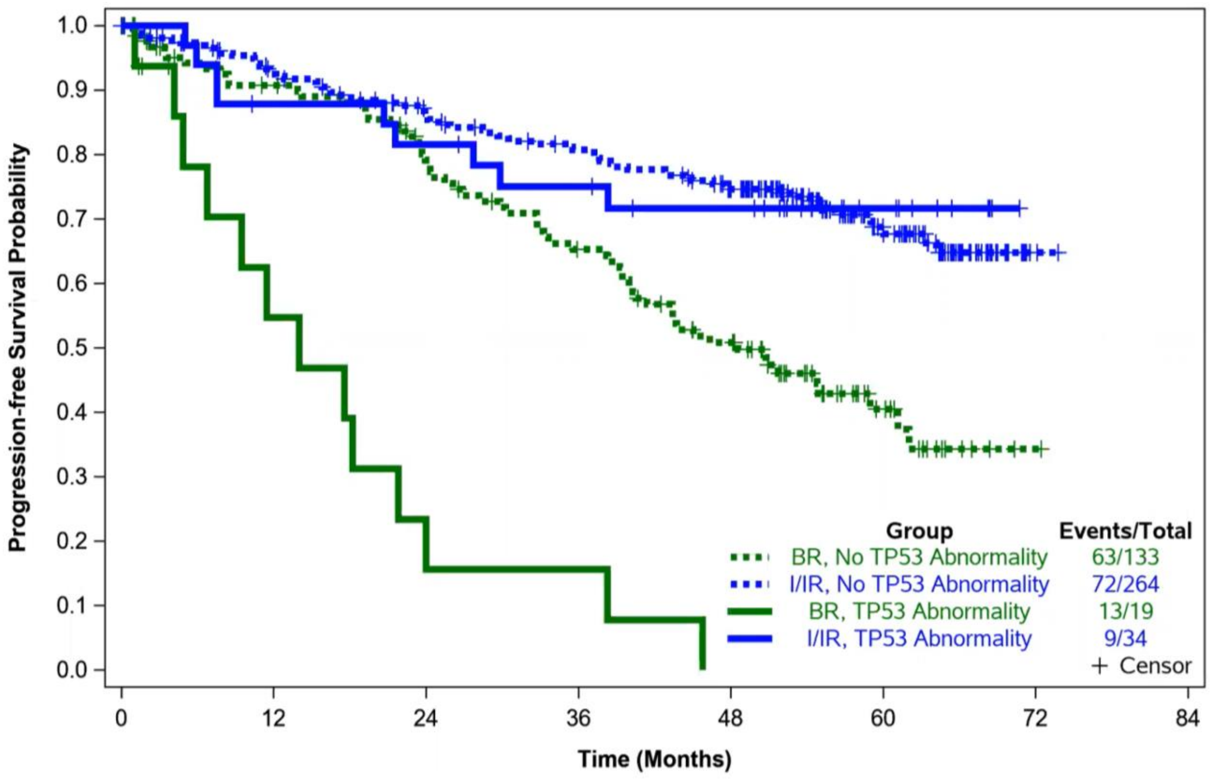
Ven-Obi & IGHVunmut: 64.2m

Clb-Obi & IGHVmut: 59.9m

Clb-Obi & IGHVunmut: 26.9m

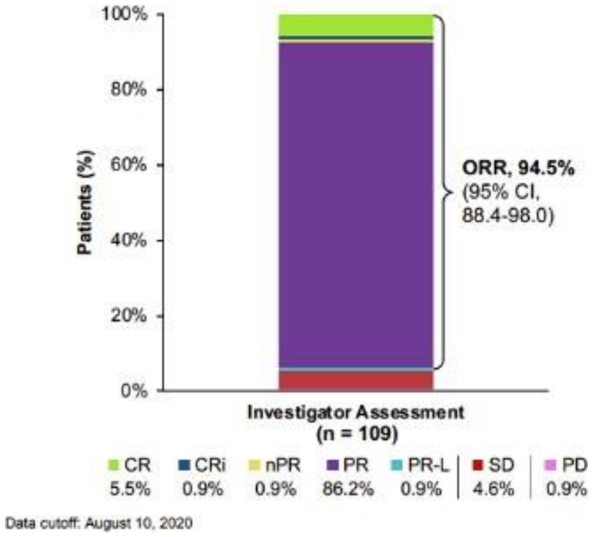
TP53 status

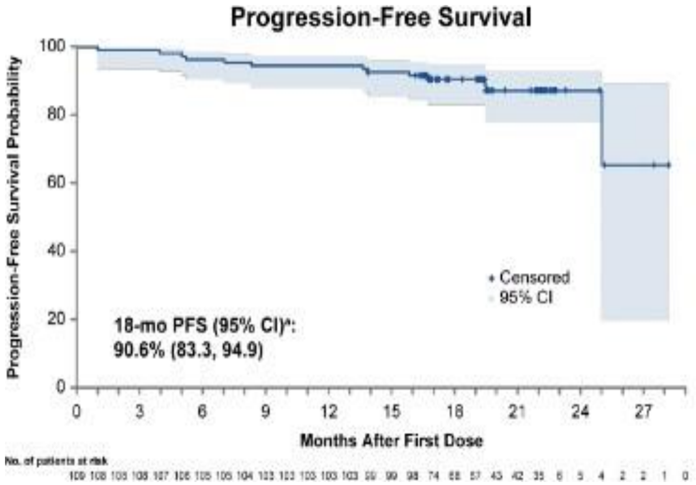
ALLIANCE A041202: PROGRESSION FREE SURVIVAL IN TP53ABN AND TP53WT

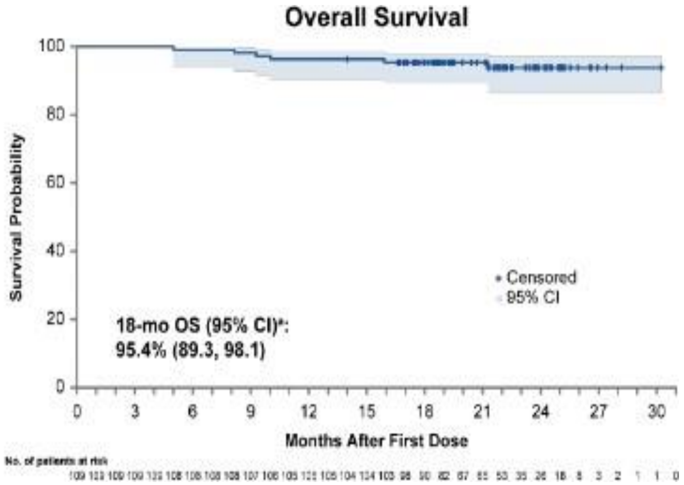


Woyach J, et al. Blood (2021) 138 (Supplement 1): 639.

SEQUOIA – ARM C, del(17p): zanubrutinib





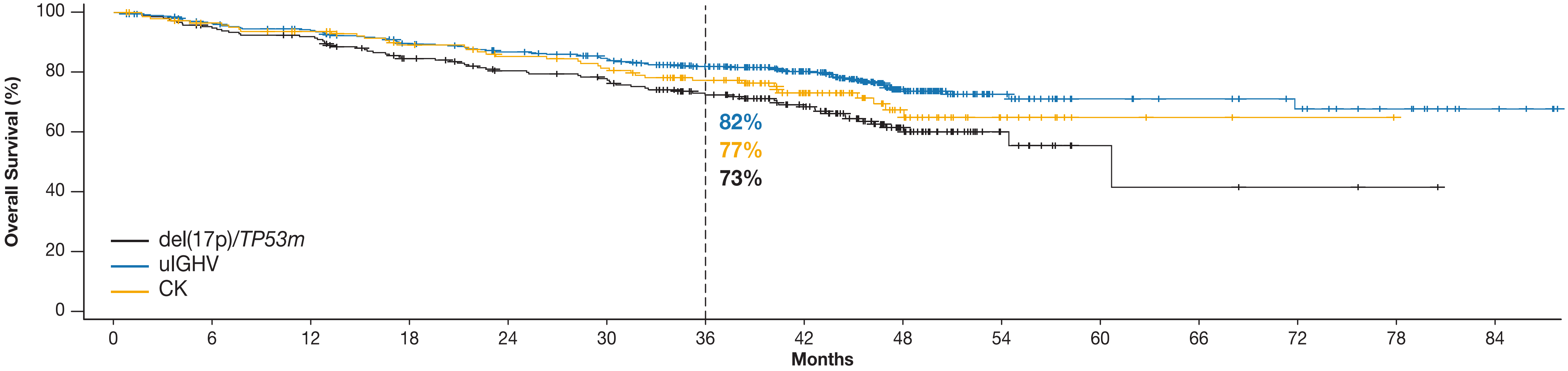


- **DoR** ≥18 mo: **87.7%** (95% CI, 78.0–9 3.0)
- **OS** at 18 mo: **95.4%** (95% CI, 89.3–98.1)

Brown *et al*., ASH 2020

Davids MS, Sharman JP, Ghia P, et al. Long-Term efficacy of acalabrutinib-based regimens in patients with chronic lymphocytic leukemia and higher-risk genomic features: pooled analysis of clinical trial data [Poster]. Presented at: European Hematology Association (EHA) Congress; June 9-12, 2022; Vienna, Austria. Poster. P667

OS in R/R CLL with Acalabrutinib-based Regimens for Del(17p)/*TP53*m, uIGHV, or CK



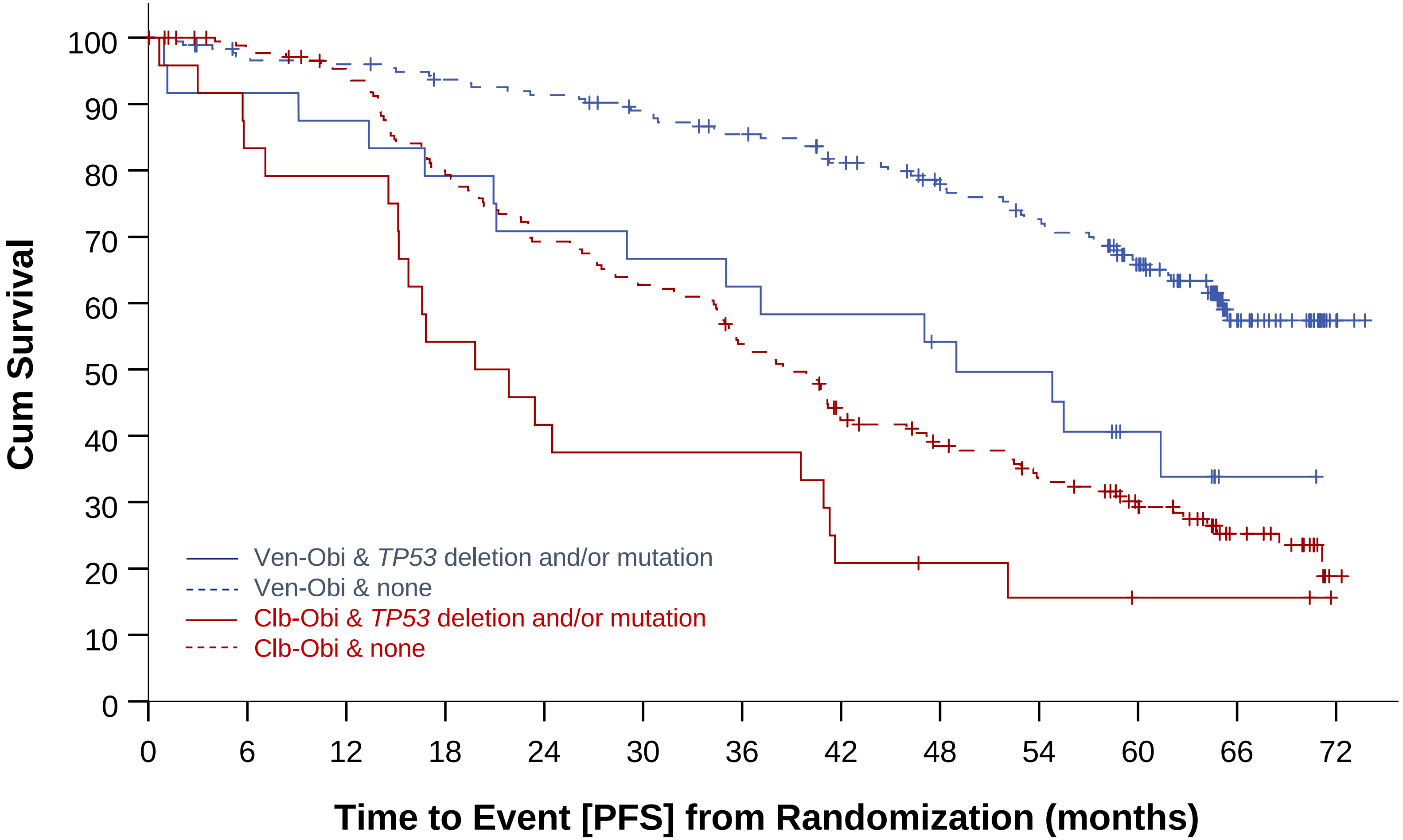
Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
del(17p)/*TP53m*	214	199	191	169	155	147	124	96	45	13	4	3	2	1	0
uIGHV	408	386	372	348	331	314	282	229	121	48	28	25	20	14	5
CK	146	135	128	118	110	104	88	60	27	11	3	2	1	0	0

CI = confidence interval; CK = complex karyotype; CLL = chronic lymphocytic leukemia; OS = overall survival; R/R = relapsed/refractory; *TP53*m = mutated tumor protein 53; uIGHV = unmutated immunoglobulin heavy chain variable region genes.

Davids MS, et al. Poster Presented at: EHA; June 9-12, 2022; Vienna, Austria

PROGRESSION-FREE SURVIVAL – *TP53* status



Median PFS

Ven-Obi & no *TP53*del/mut: NR

Ven-Obi & *TP53*del/mut: 49.0 m

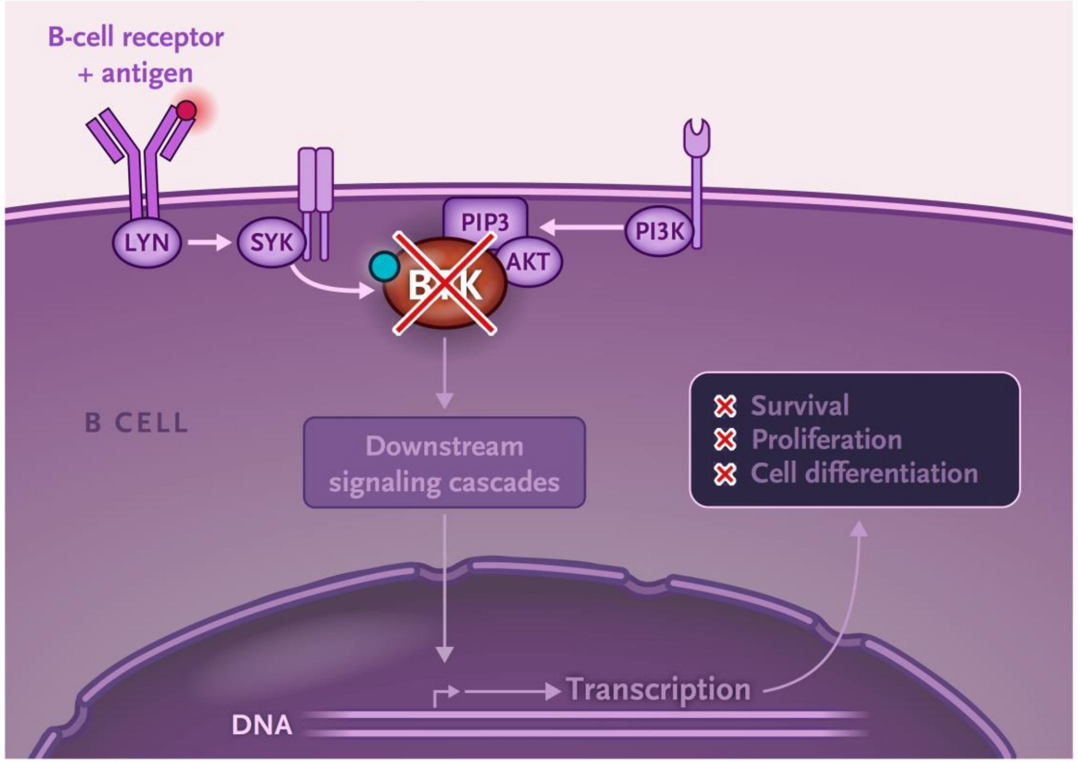
Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 19.8 m

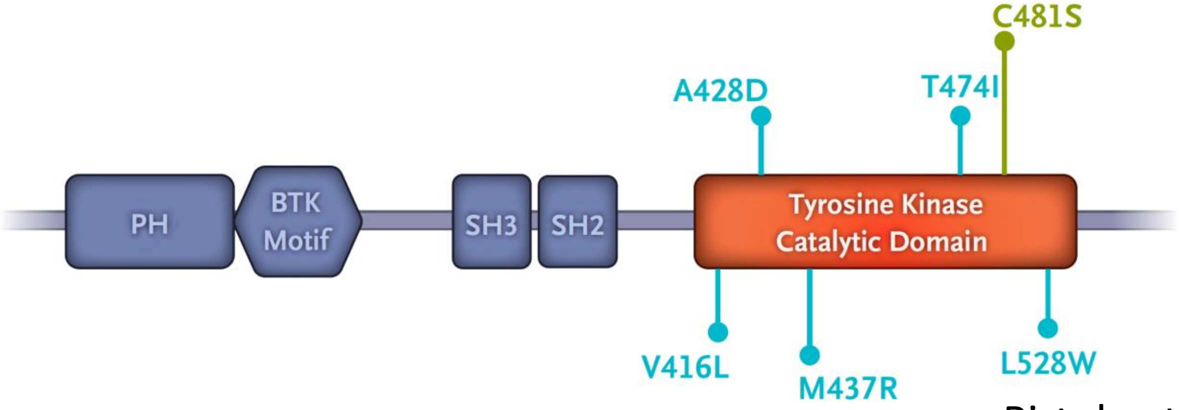
Ven-Obi & *TP53* del/mut	25	22	21	19	17	16	15	14	12	11	6	1	0
Ven-Obi & none	184	169	167	161	157	150	142	130	119	109	89	33	4
Clb-Obi & *TP53* del/mut	24	20	19	13	10	9	9	5	4	3	2	2	0
Clb-Obi & none	184	169	160	135	117	106	90	68	58	48	36	18	1

Mutations of resistance

Mutations conferring resistance to BTKi



Ibrutinib
Acalabrutinib



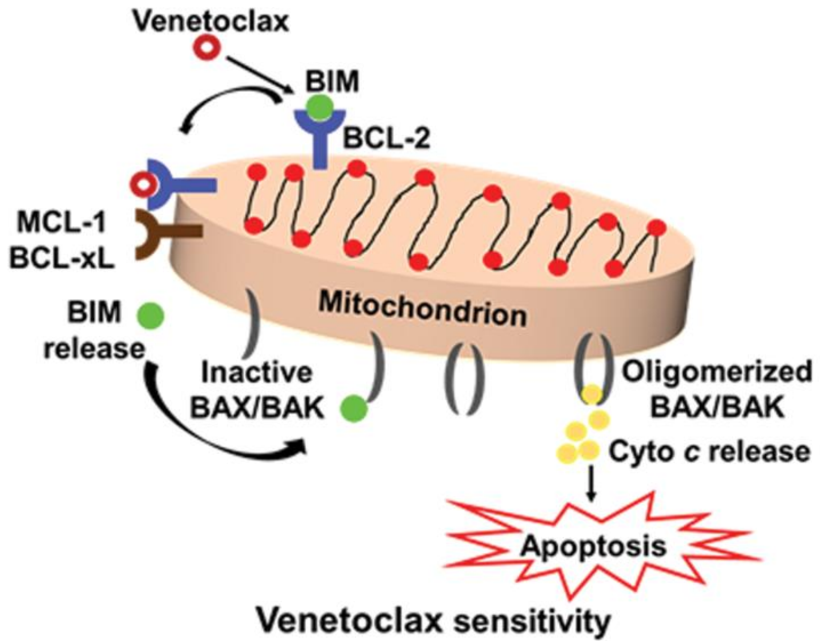
Pirtobrutinib
Zanubrutinib

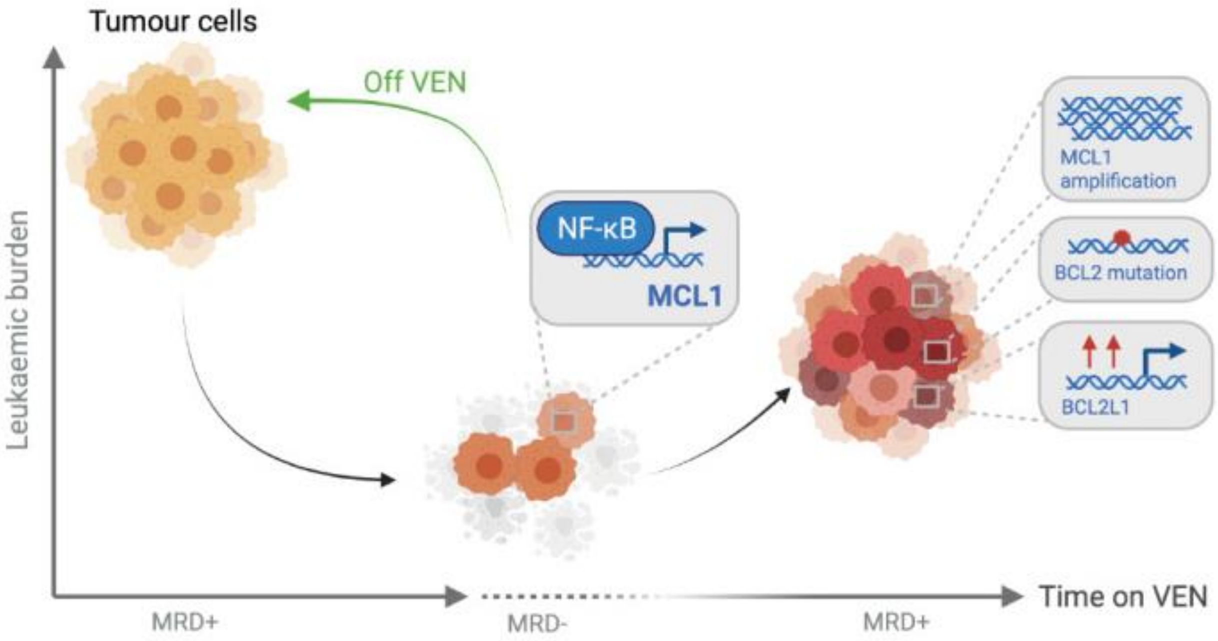
Binding Affinities of BTK Inhibitors

	Noncovalent				Covalent
	Pirtobrutinib	ARQ-531	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

Wang E, N Engl J Med. 2022
Blombery P,. Blood Adv. 2022

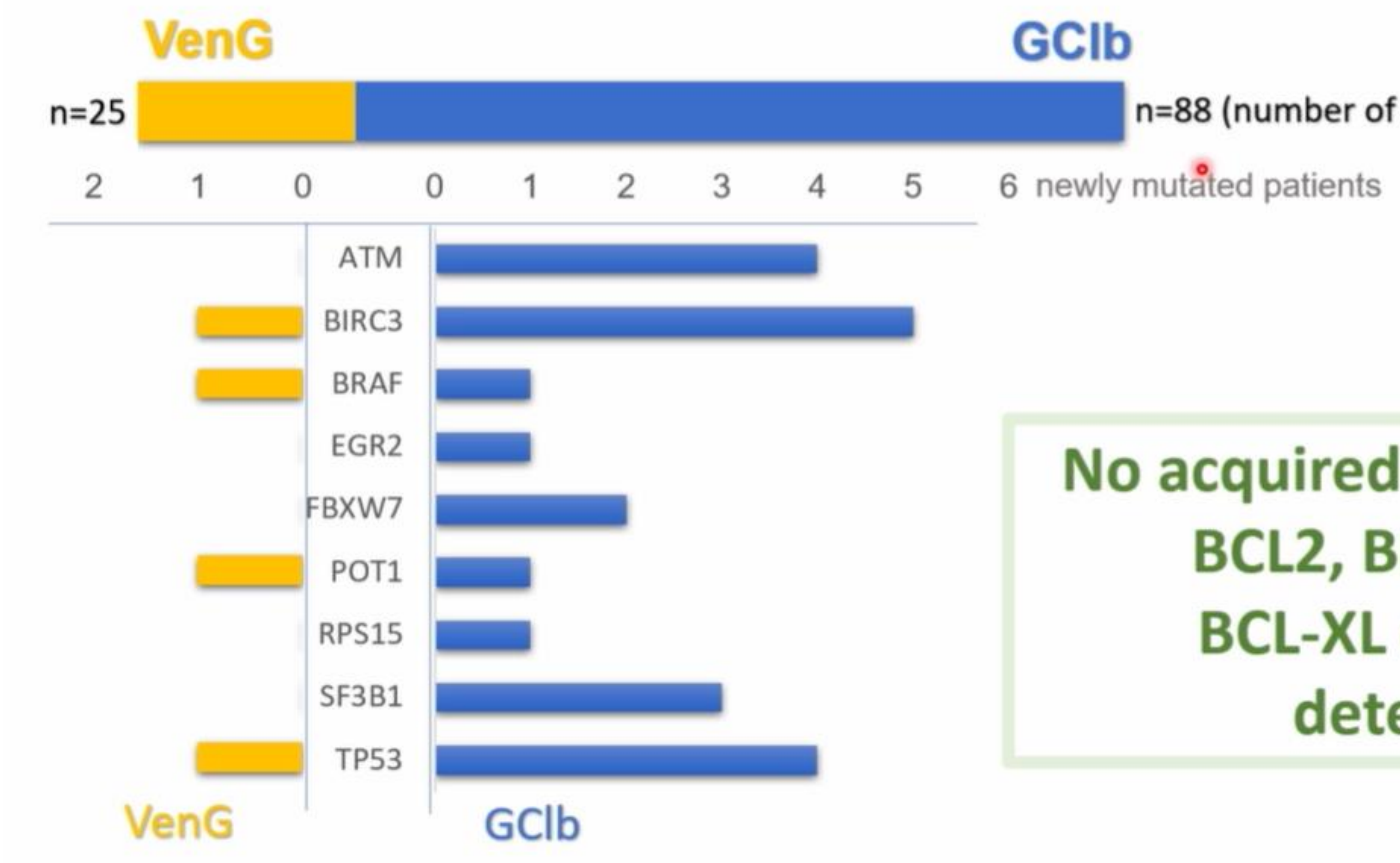
Mechanisms of resistance to Venetoclax





Thijssen R, Blood. 2022
Kapoor I, Cell Death Dis. 2020

Acquired mutations after VenG



No acquired mutations in BCL2, BIM, BAX, BCL-XL or MCL1 detected

Tausch E, EHA 2021

Summary

- What are the predictive biomarkers?
  - Disease histology
  - Mutations of resistance
  - *TP53* status and IGHV status are prognostic but not predictive