Predictive biomarkers and prognostic scores

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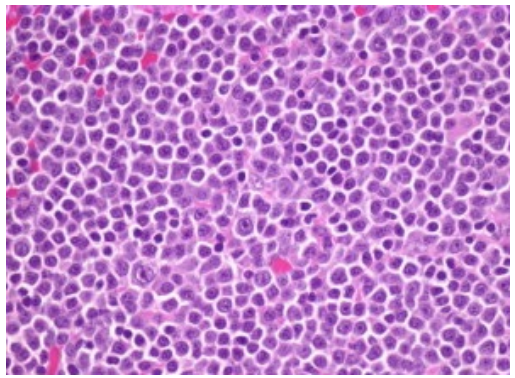
Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
AbbVie	X					X	
AstraZeneca	X					X	
BeiGene	X					X	
BMS						X	
Janssen	X					X	

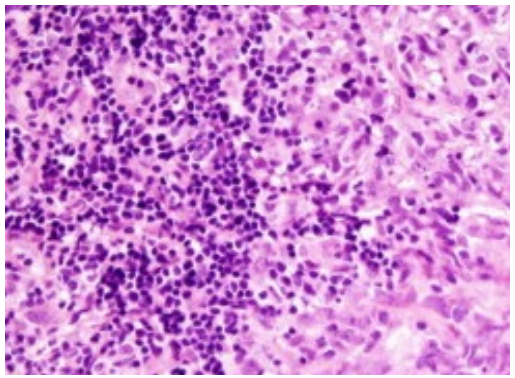
Histology

Clinical implications of differentiating histologically aggressive CLL vs Richter syndrome

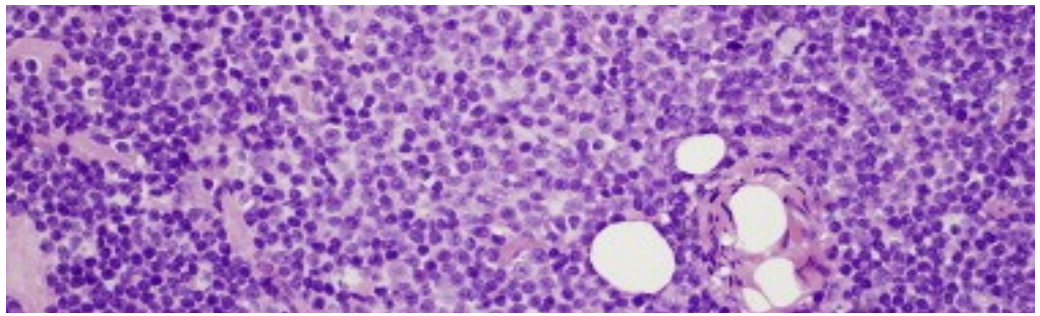
CLL



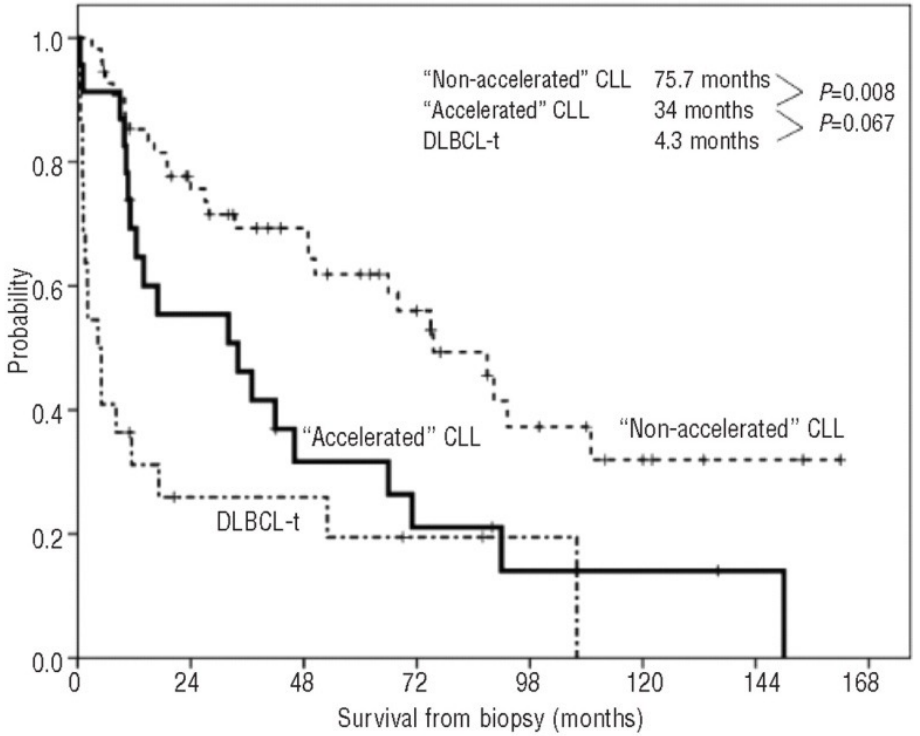
RS



Histologically aggressive CLL

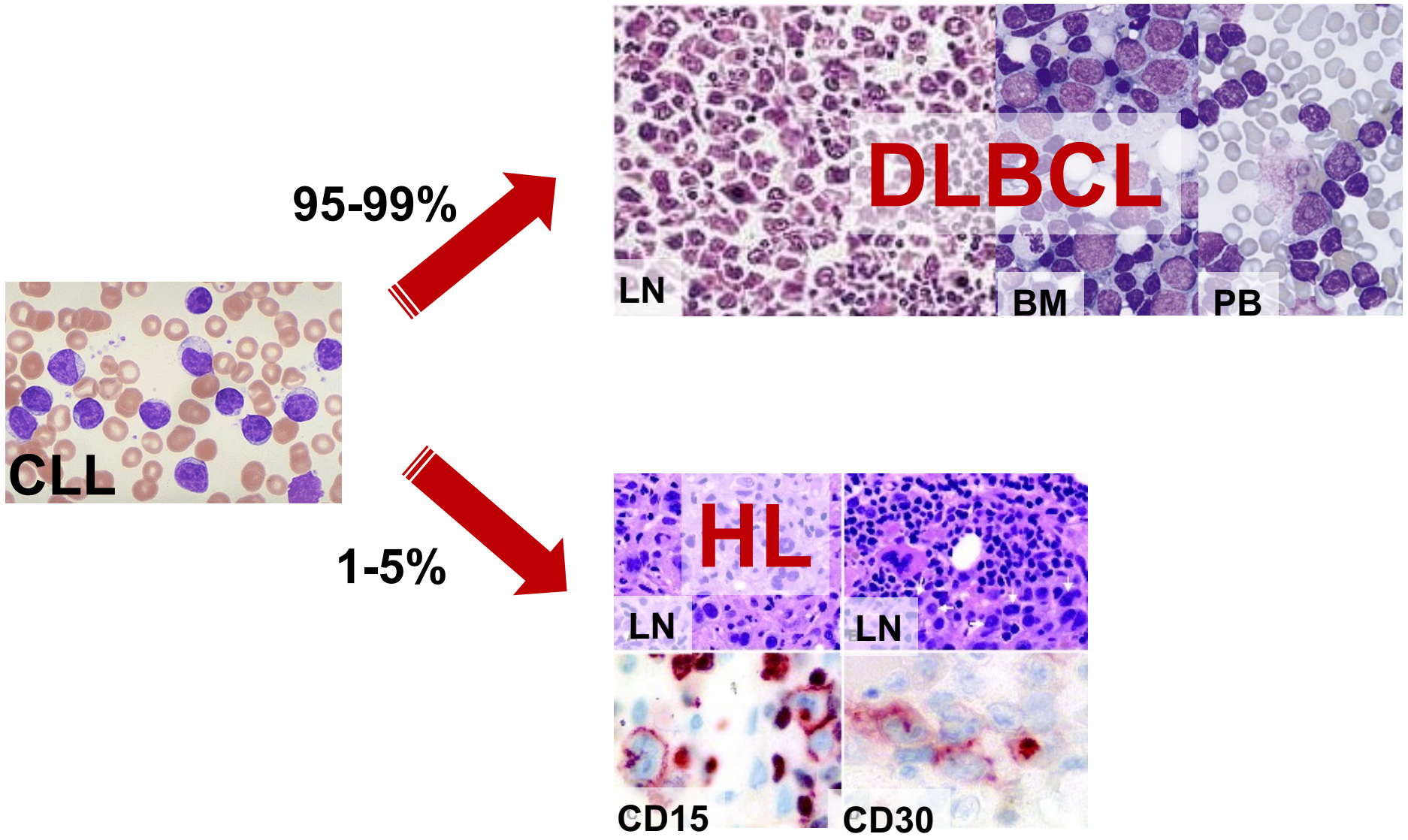


Survival from biopsy according to the histology



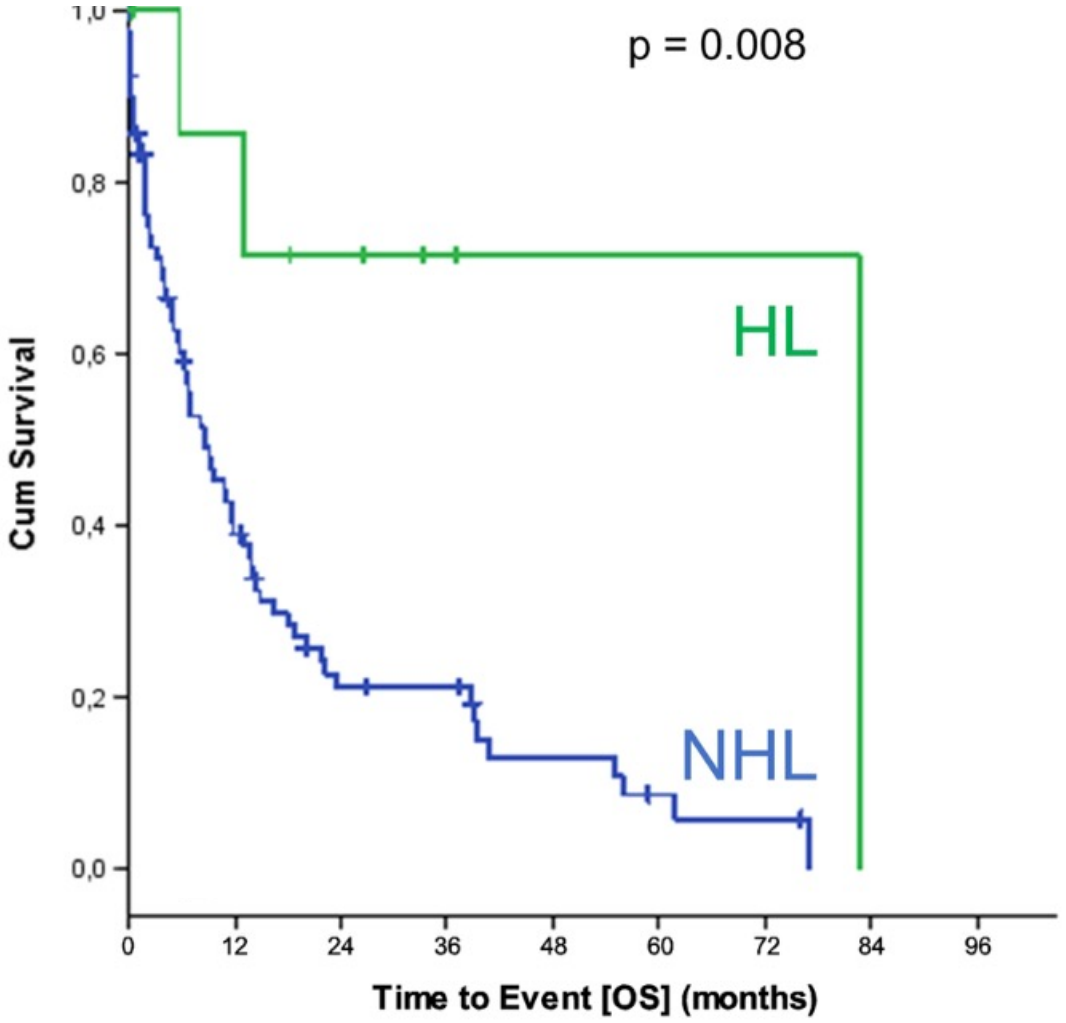
Giné E *et al. Haematologica* 2010; 95 (9): 1526–1533.

Richter syndrome subtypes



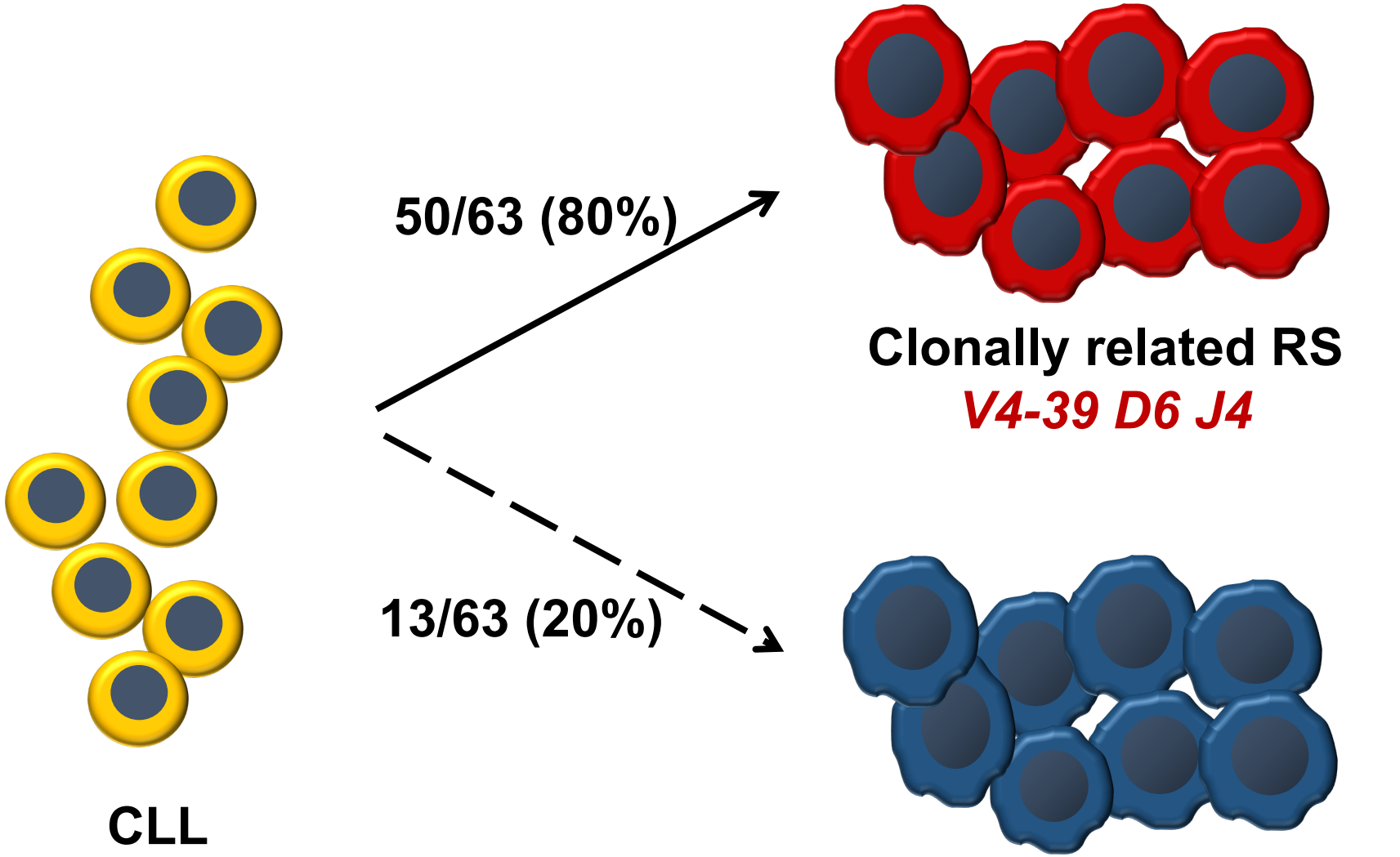
ICC and WHO-HAEM5

cHL arising in patients with CLL must be treated as per LBCL guidelines



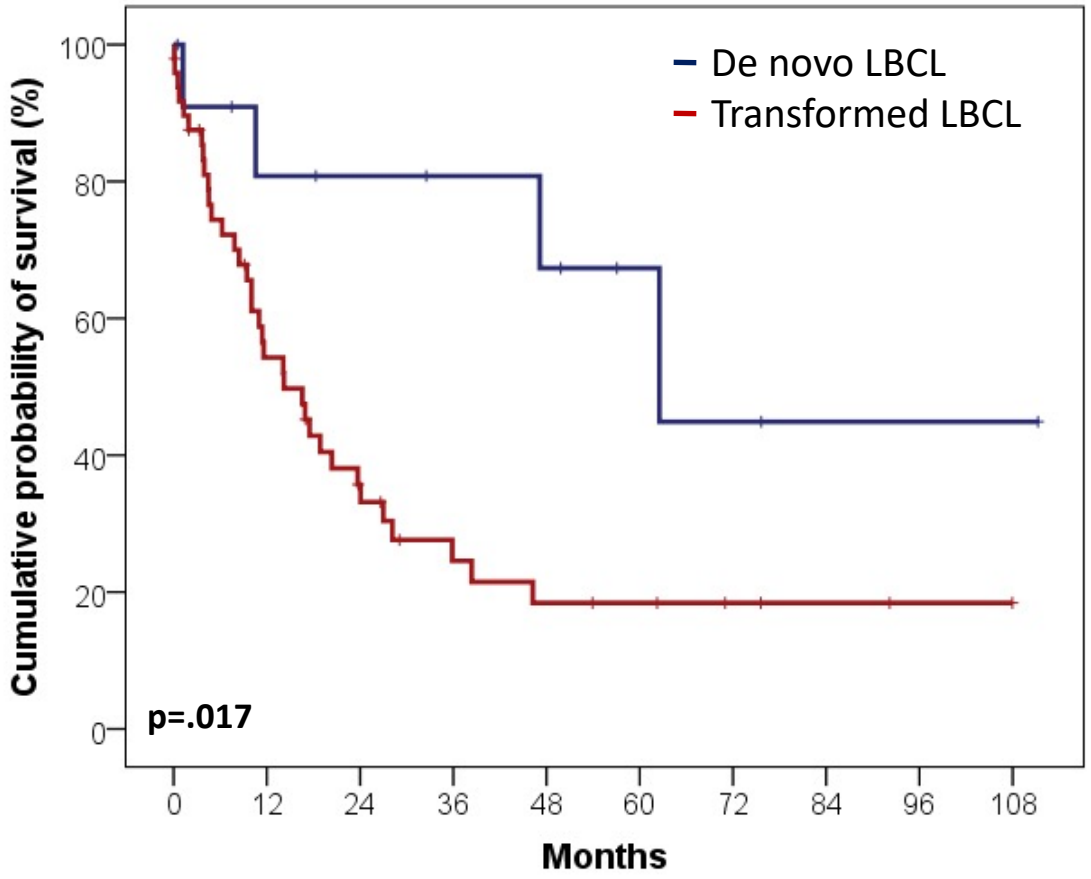
Al-Sawaf O et al. Leukemia 2021

Clonally related vs unrelated variant of Richter syndrome



Rossi et al, Blood 2011

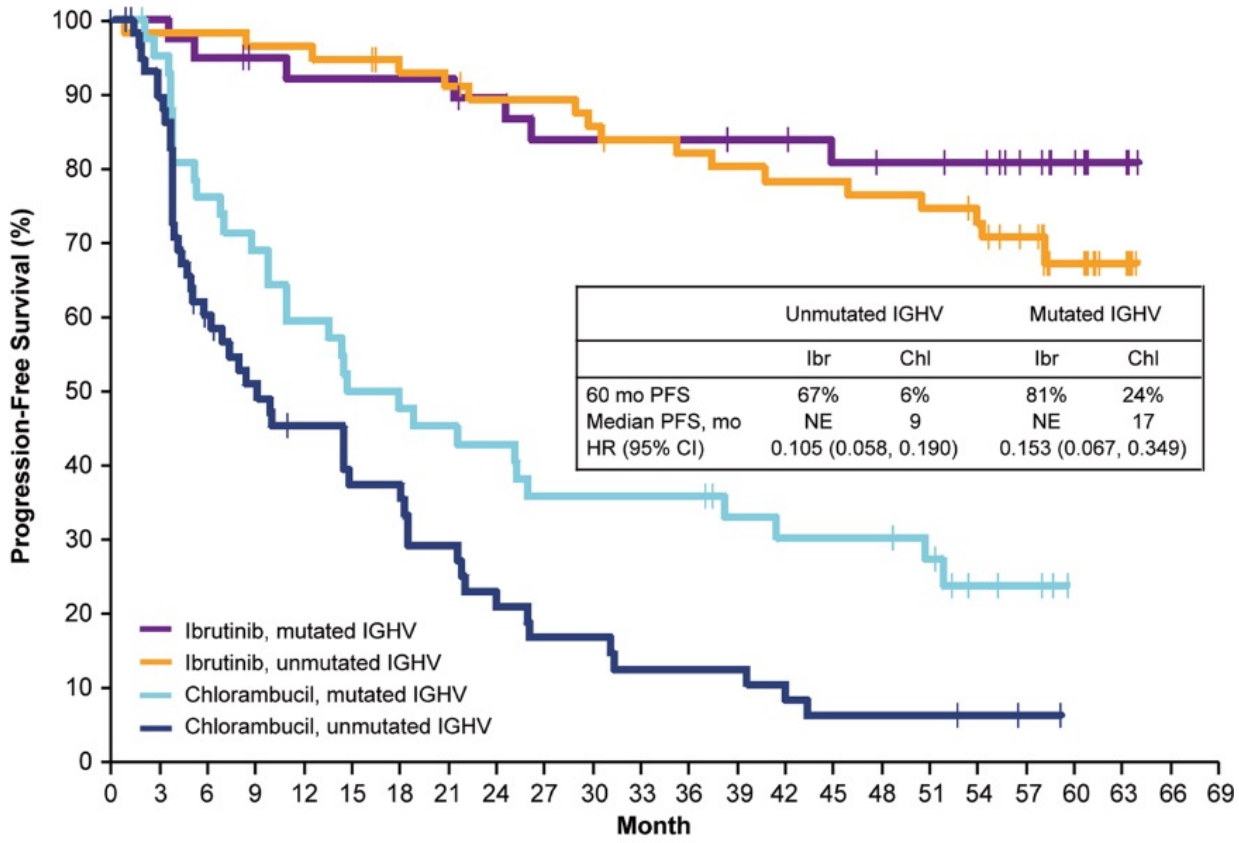
De novo LBCL arising in patients with CLL must be treated as per LBCL guidelines



Rossi et al, Blood 2011

IGHV status

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

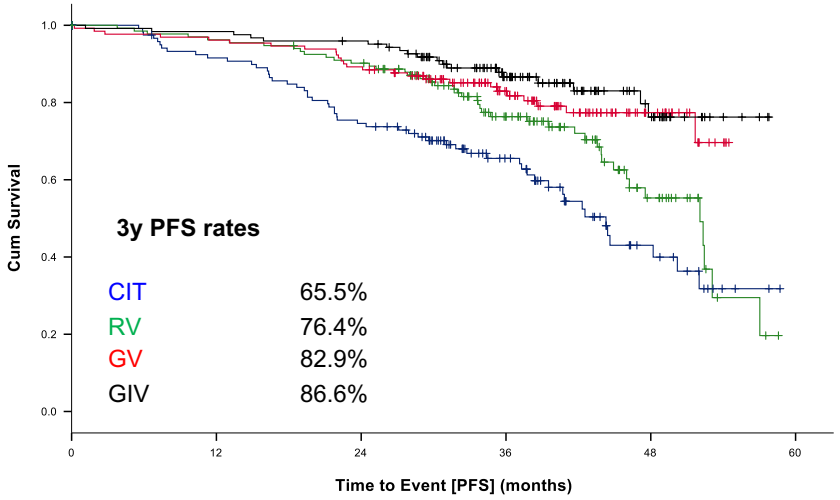


	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
60 mo PFS	67%	6%	81%	24%
Median PFS, mo	NE	9	NE	17
HR (95% CI)	0.105 (0.058, 0.190)		0.153 (0.067, 0.349)	

Burger JA, *et al.* Leukemia. 2020

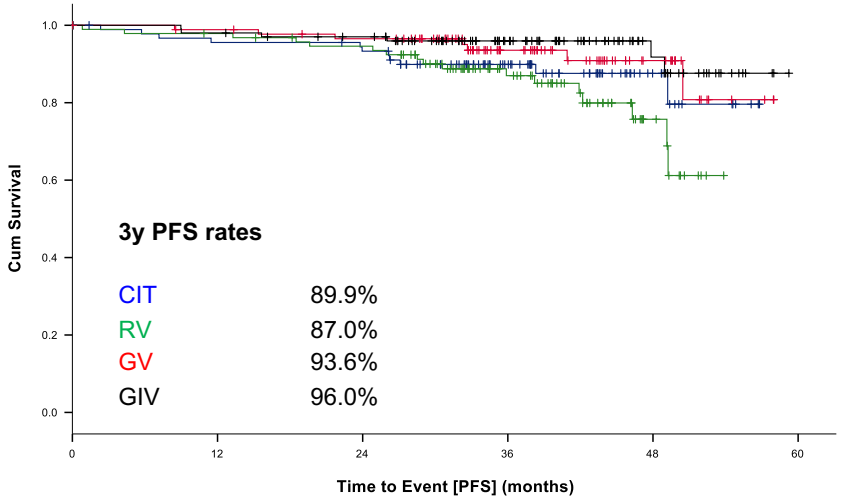
CLL13 - PFS ACCORDING TO IGHV STATUS

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

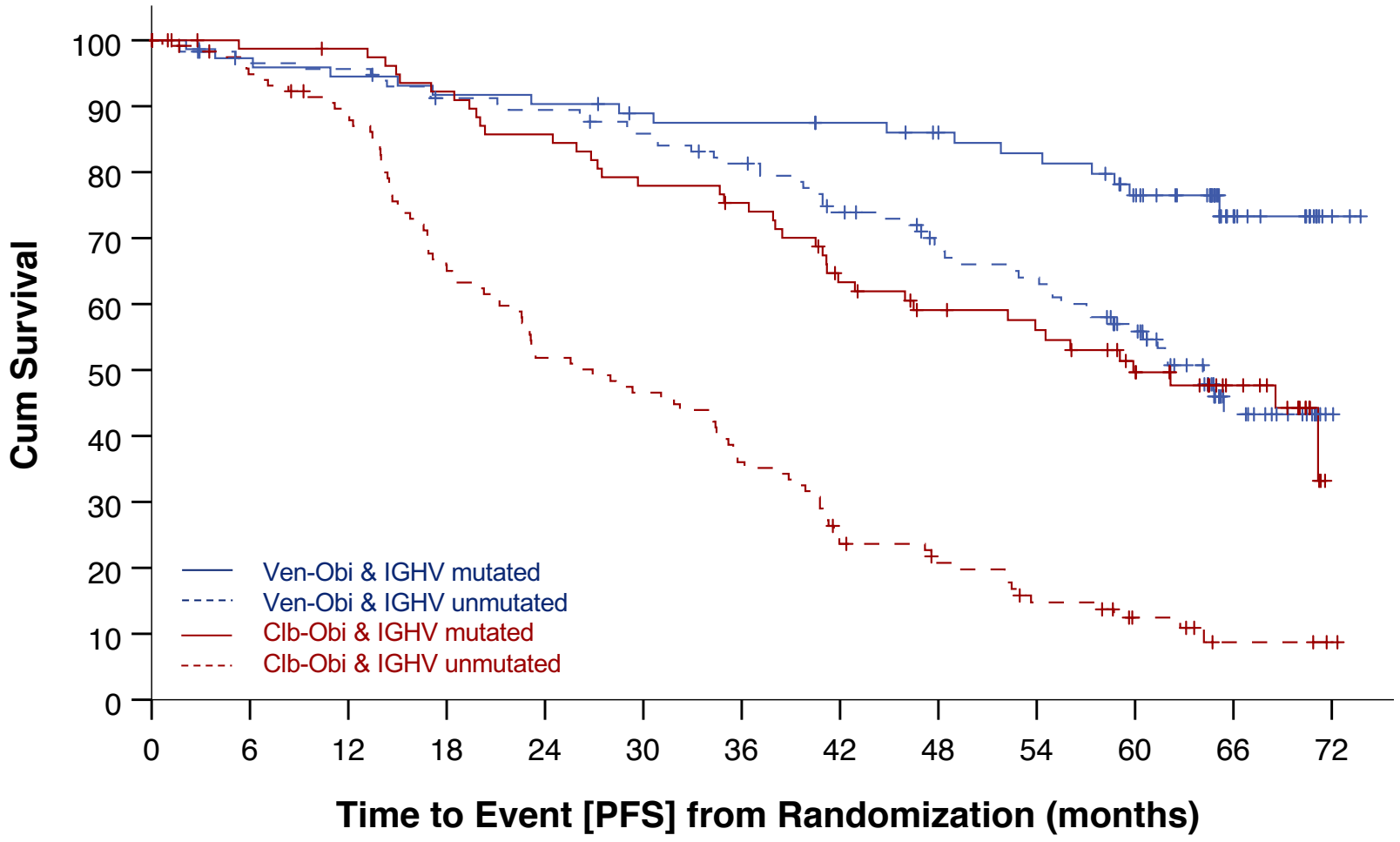
Mutated IGHV



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

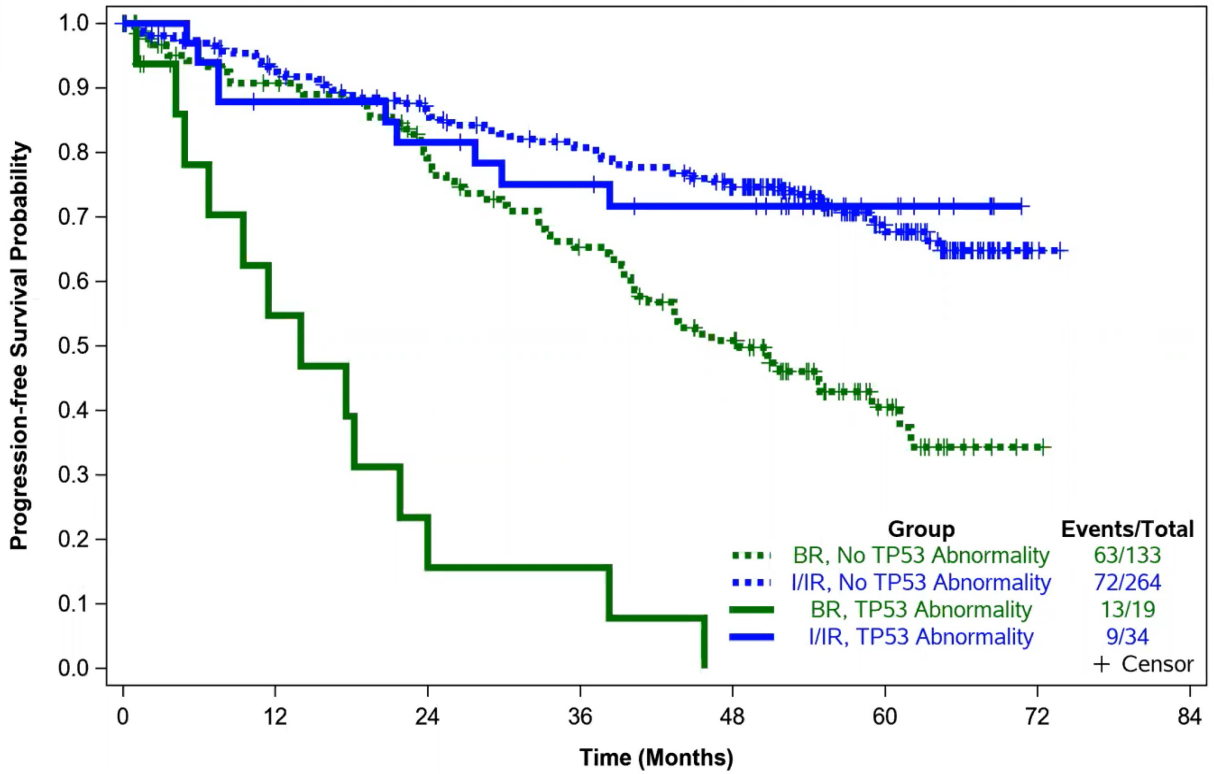
Ven-Obi & IGHVunmut: 64.2m

Clb-Obi & IGHVmut: 59.9m

Clb-Obi & IGHVunmut: 26.9m

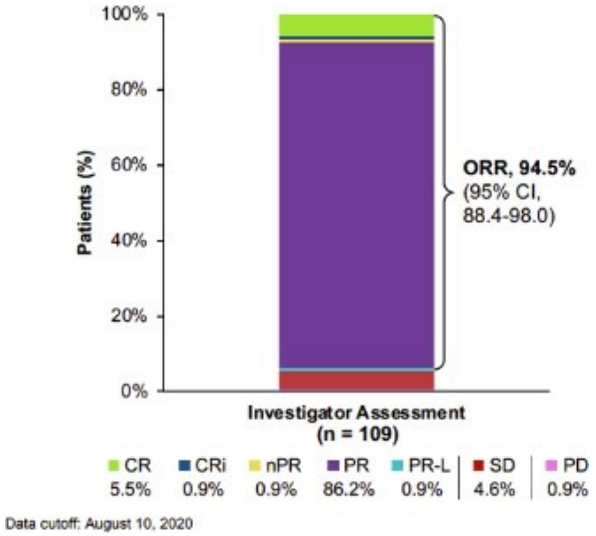
TP53 status

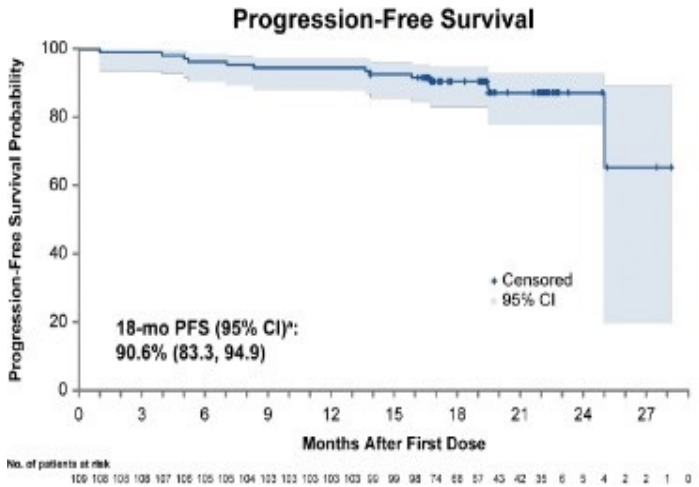
ALLIANCE A041202: PROGRESSION FREE SURVIVAL IN TP53ABN AND TP53WT

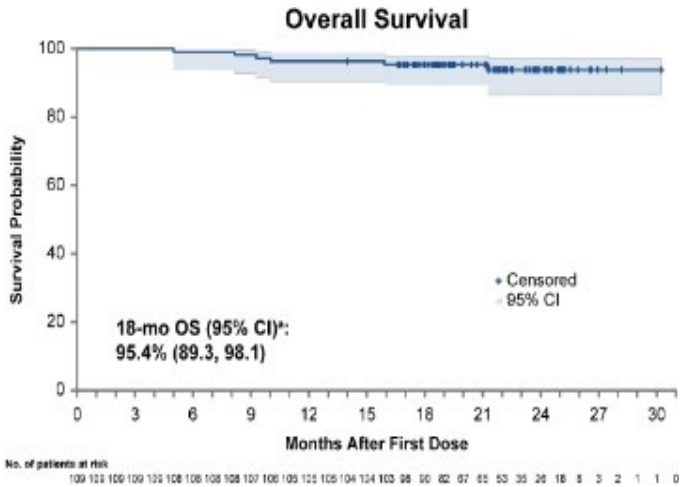


Woyach J, et al. Blood (2021) 138 (Supplement 1): 639.

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



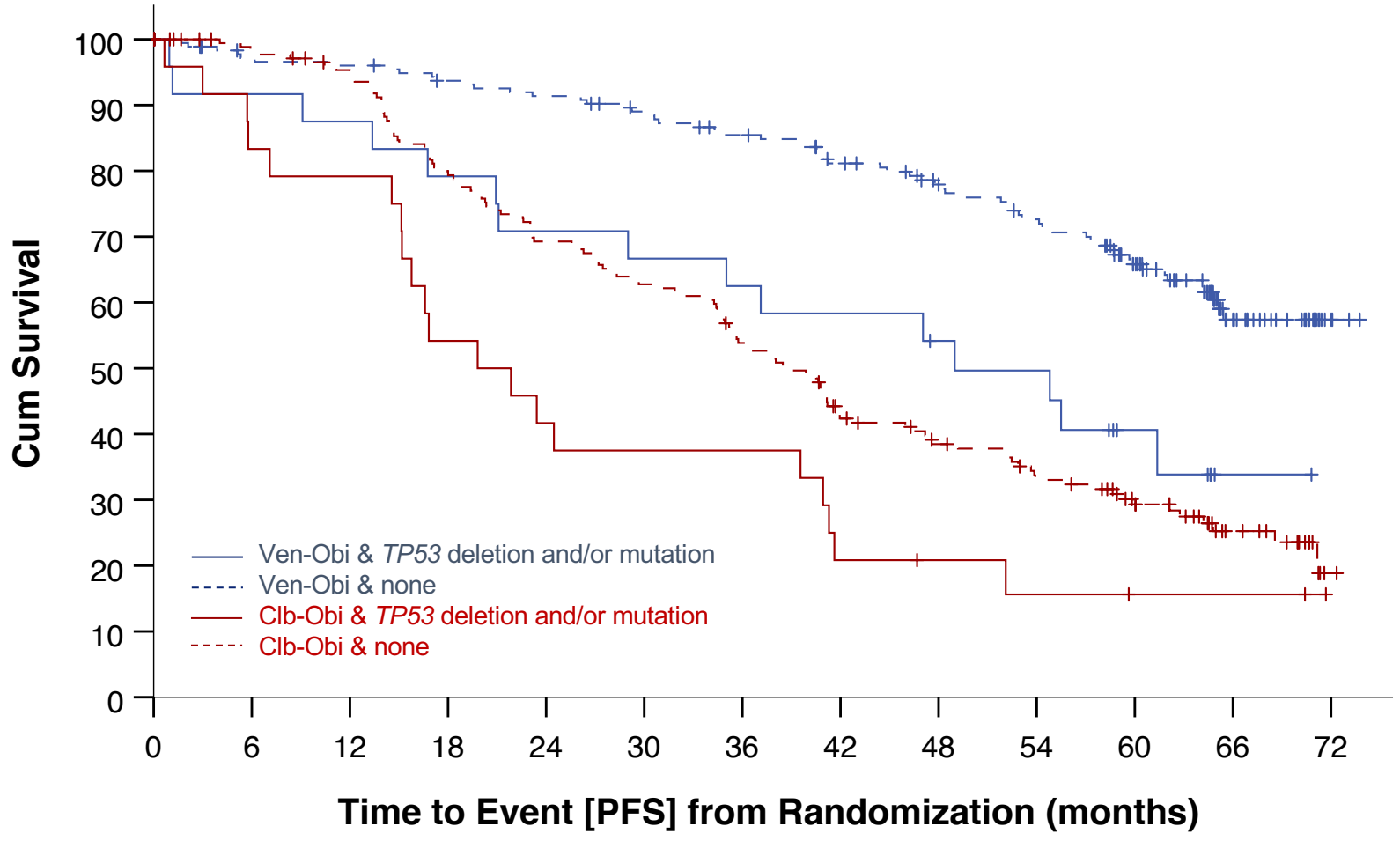




- **DoR** ≥18 mo: **87.7%** (95% CI, 78.0–9 3.0)
- **OS** at 18 mo: **95.4%** (95% CI, 89.3–98.1)

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

PROGRESSION-FREE SURVIVAL – *TP53* status



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

Median PFS

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

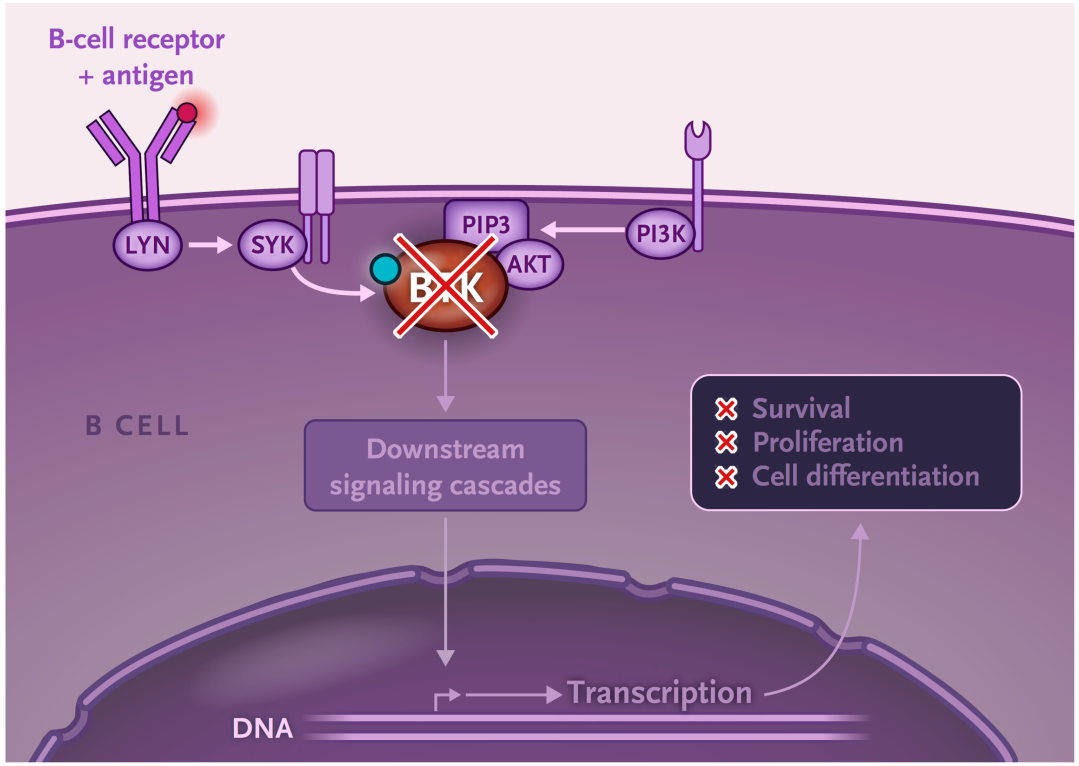
Ven-Obi & *TP53*del/mut: 49.0 m

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

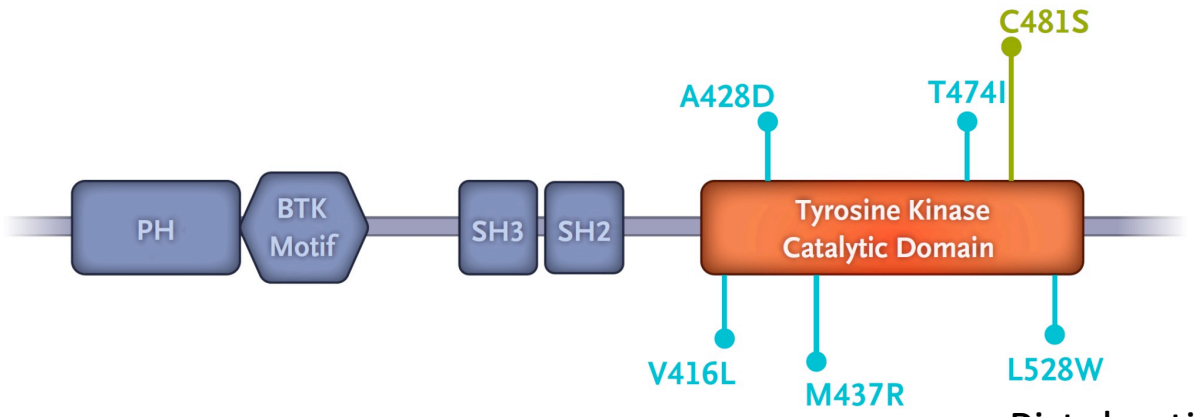
Clb-Obi & *TP53*del/mut: 19.8 m

Mutations of resistance

Mutations conferring resistance to BTKi



Ibrutinib
Acalabrutinib



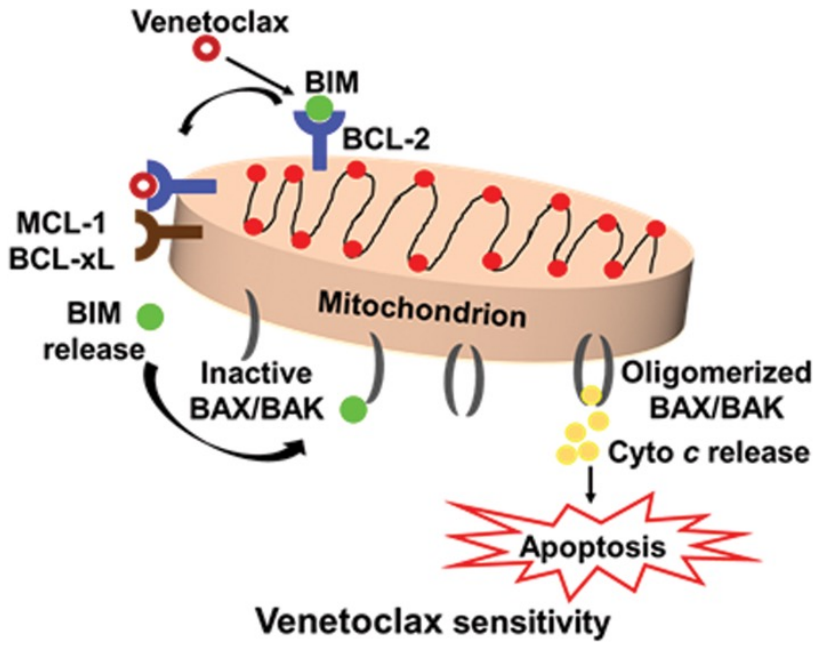
Pirtobrutinib
Zanubrutinib

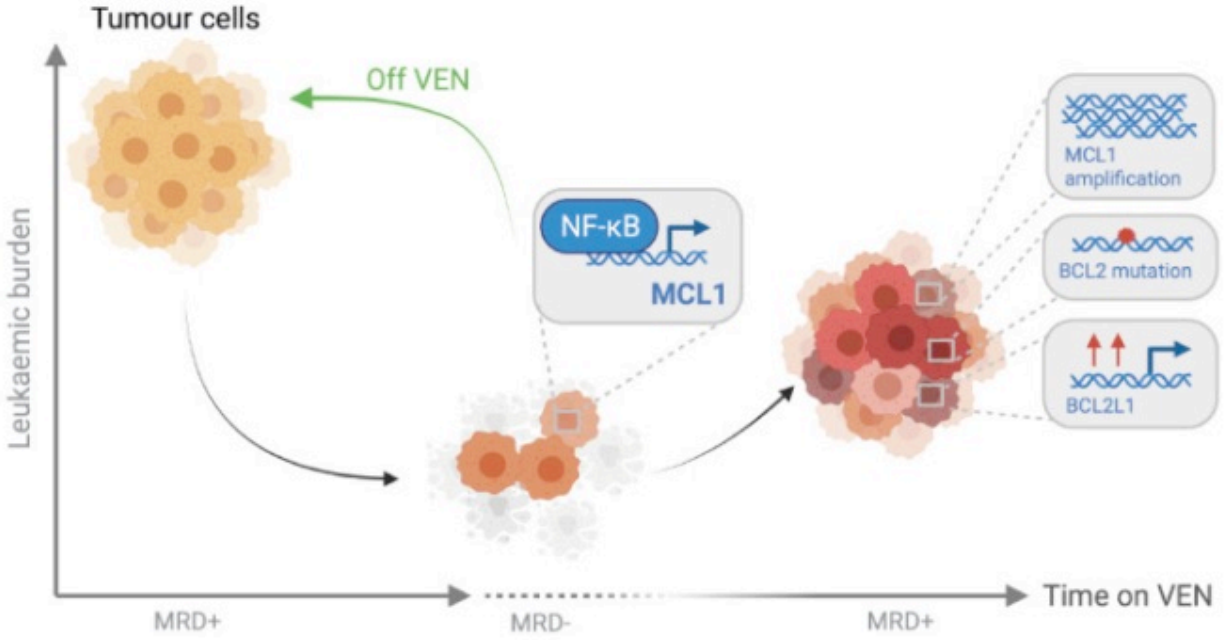
Binding Affinities of BTK Inhibitors

	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

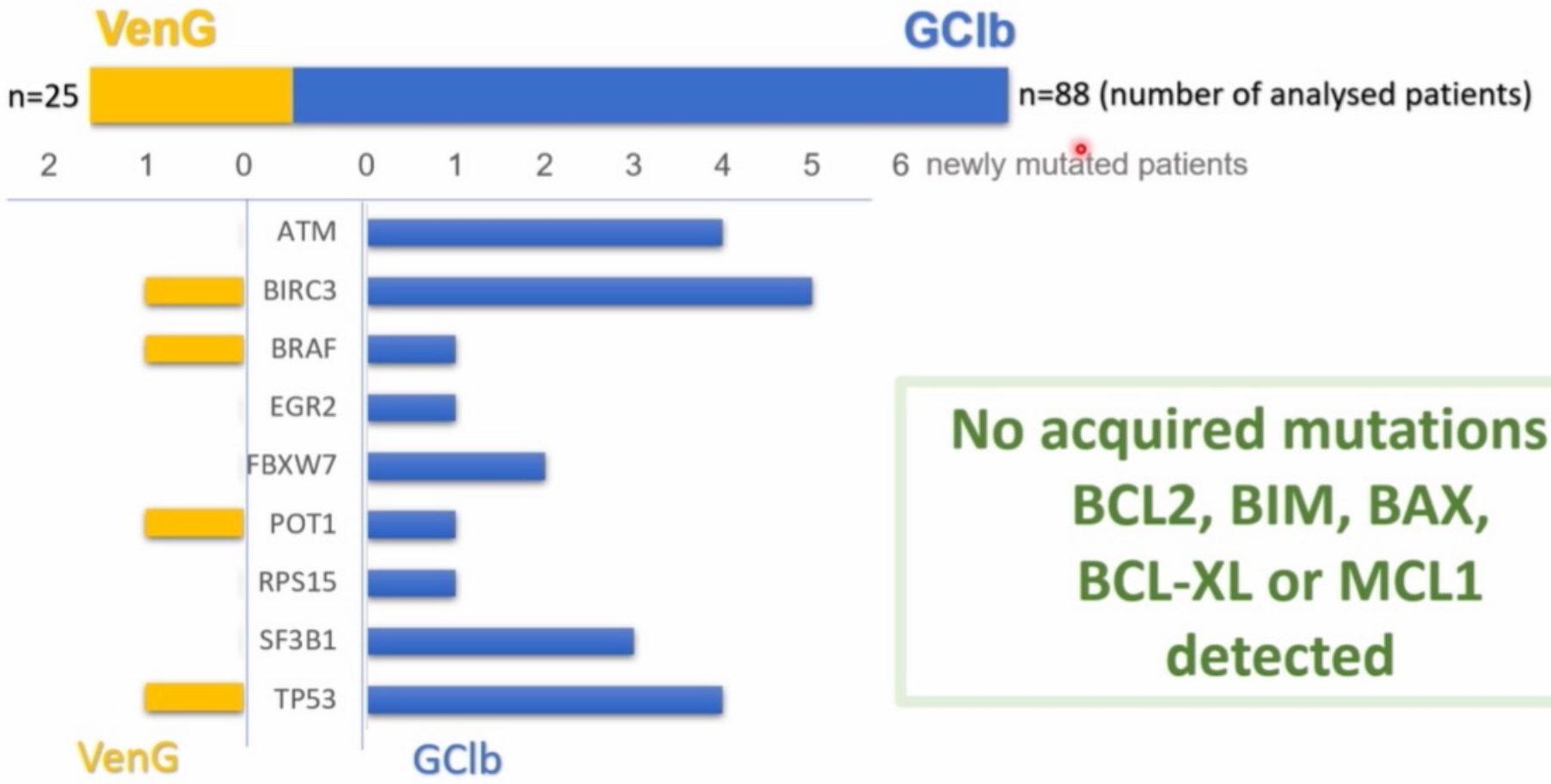
Mechanisms of resistance to Venetoclax





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

Time to first treatment

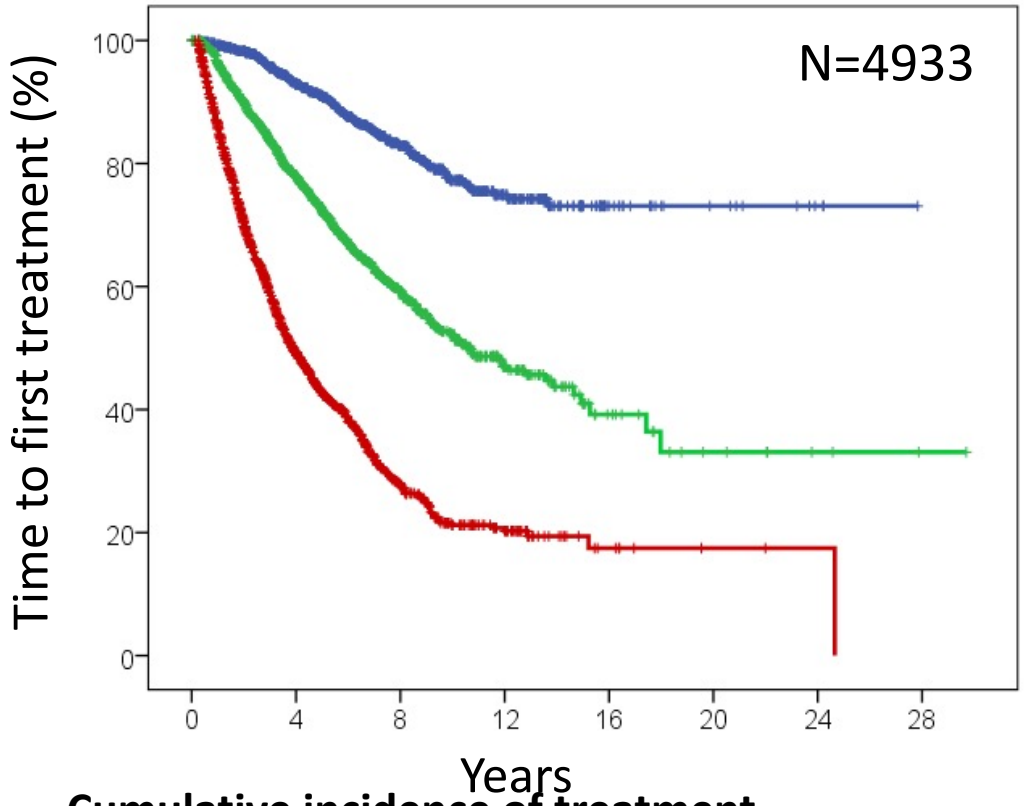
IPS-E captures the three main patterns of time to first therapy

Condoluci A, Blood. 2020

Variable	Points
IGHV unmutated	1
Lymphocytes >15x10^9/L	1
Nodal involvement	1

Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2-3

Validation
Smolej L, Br J Haematol. 2020
Morabito F, et al. Eur J Haematol. 2021
González-Gascón, EHA24; EP707

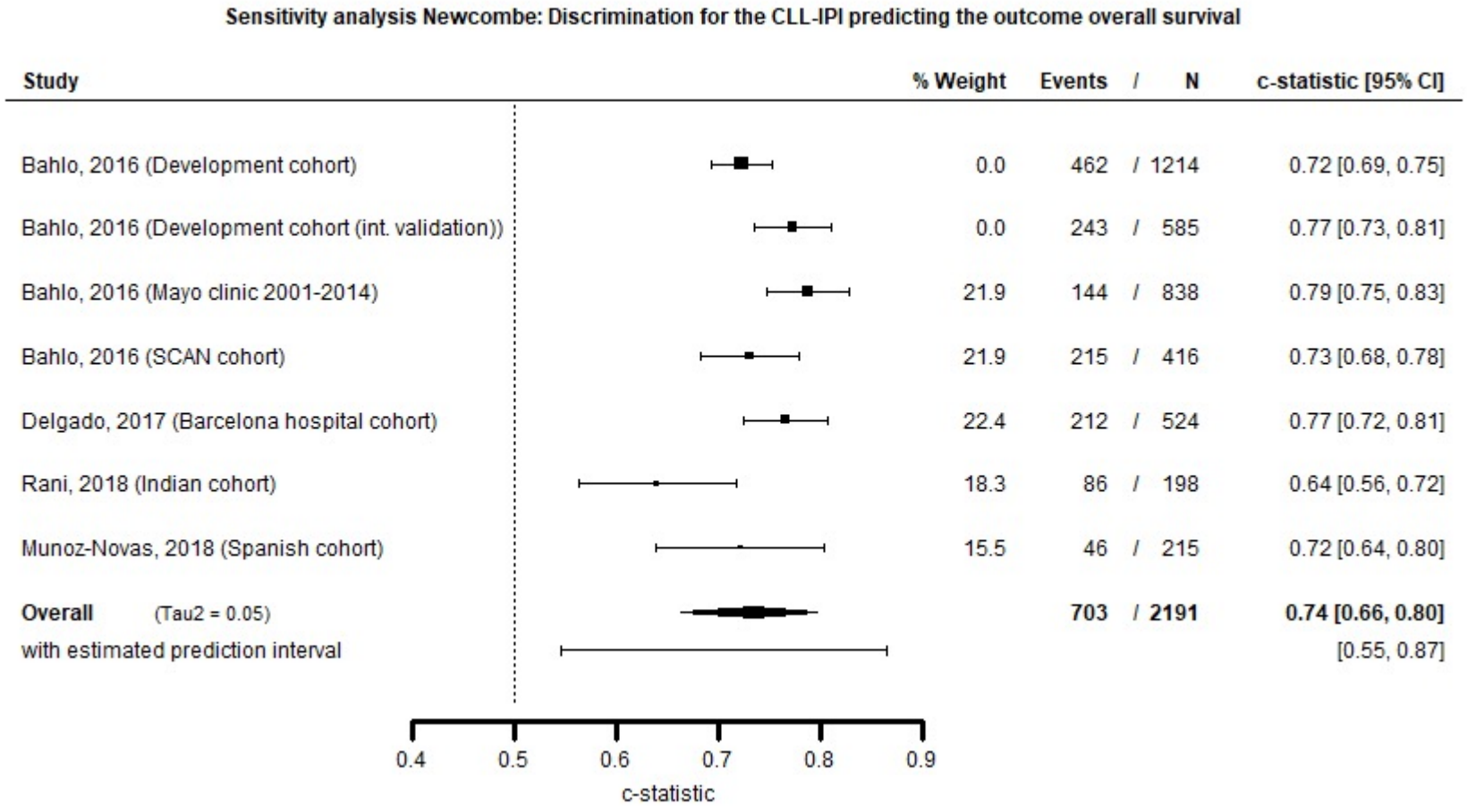


Cumulative incidence of treatment

	1 year	5 years
Low risk	<1%	8%
Intermediate risk	3%	28%
High risk	14%	61%

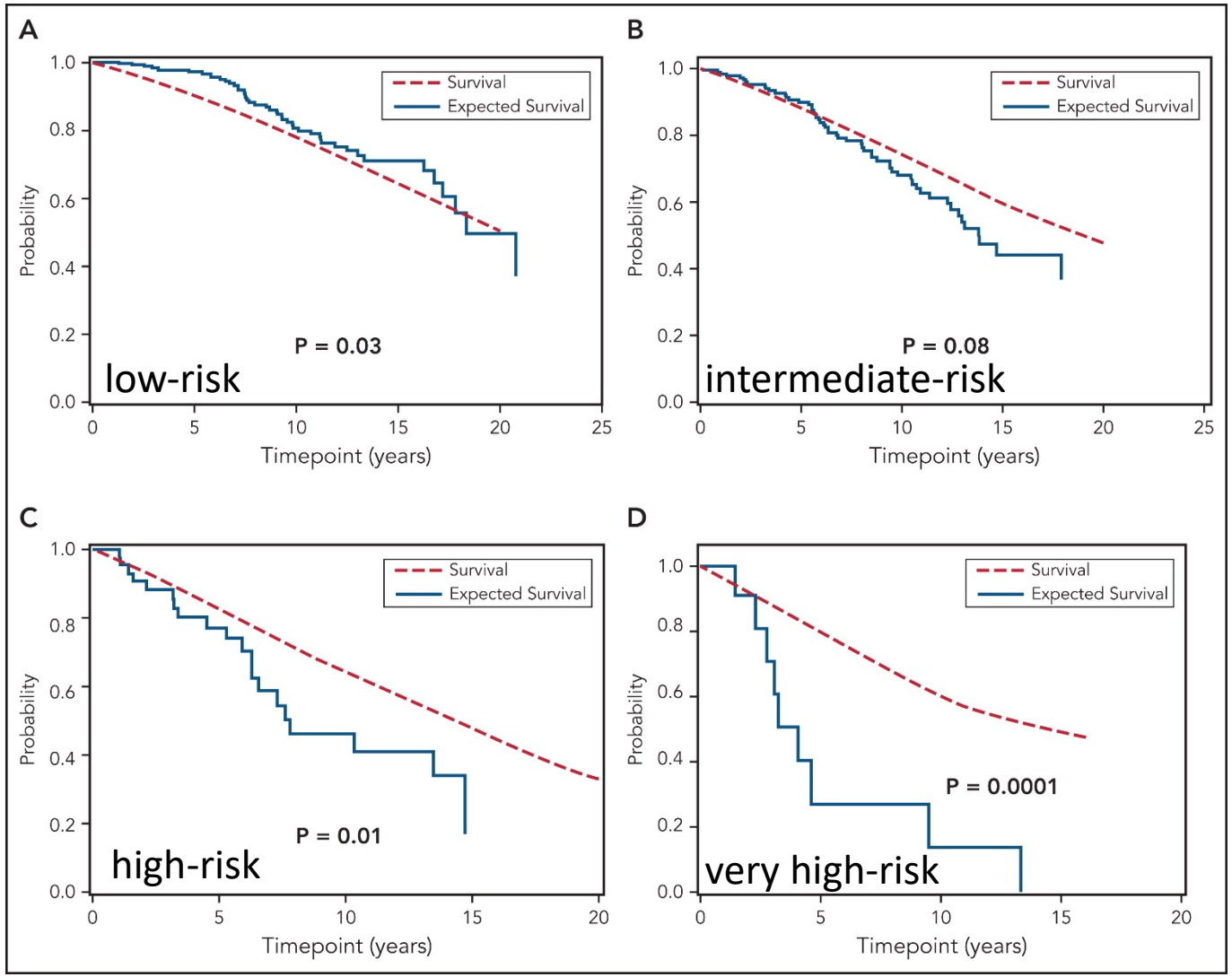
Overall survival

CLL-IPI is strongly validated at a ca. 70% accuracy



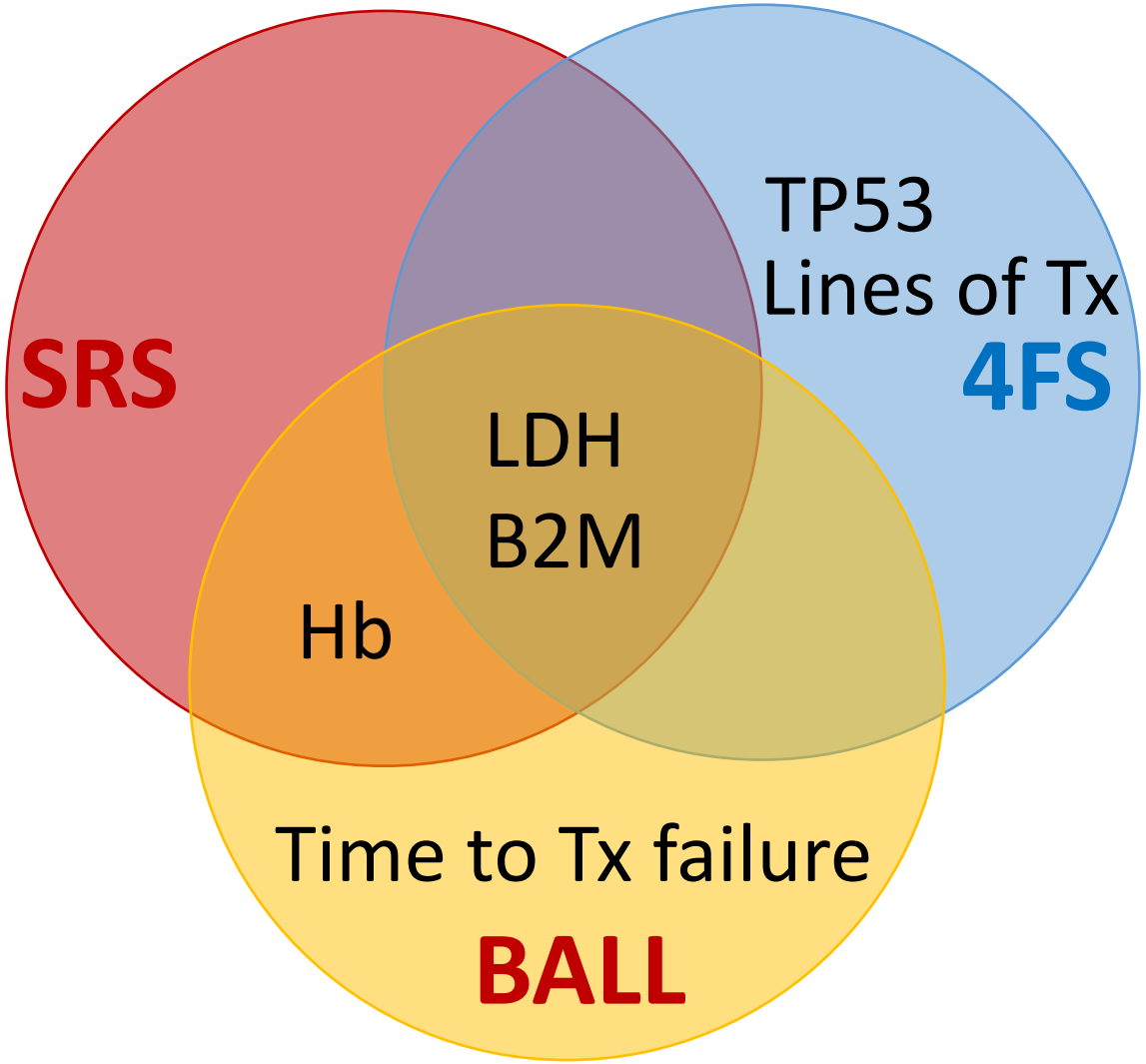
Kreuzberger N, Cochrane Database Syst Rev. 20200%

Survival of Rai 0 CLL patients, according to the CLL-IPI risk score, relative to the general population



Parikh SA, Blood. 2021

What is the most robust biomarker?



IGHV mutation status: not selected as independent variable

Summary

- IPS-E for TTFT prognostication in early stage CLL
- CLL-IPI for OS prognostication in early stage CLL
- IGHV and *TP53* are no longer strong biomarkers in patients treated with BTKi
- Biomarkers in patients treated with time limited venetoclax tx are unknown