SESSIONE 6 - LA LEUCEMIA LINFATICA CRONICA

What's new in prognostic factors?

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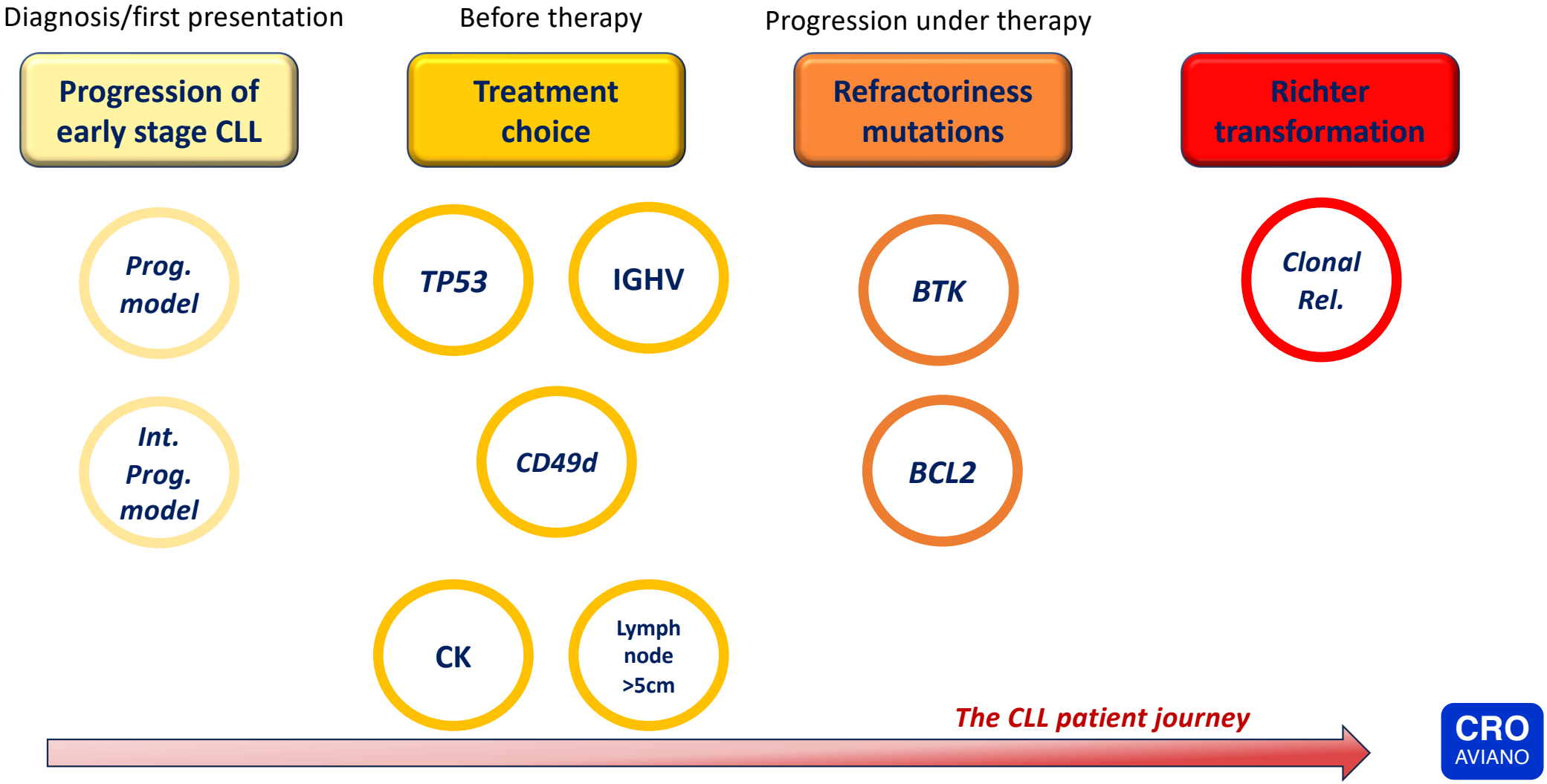
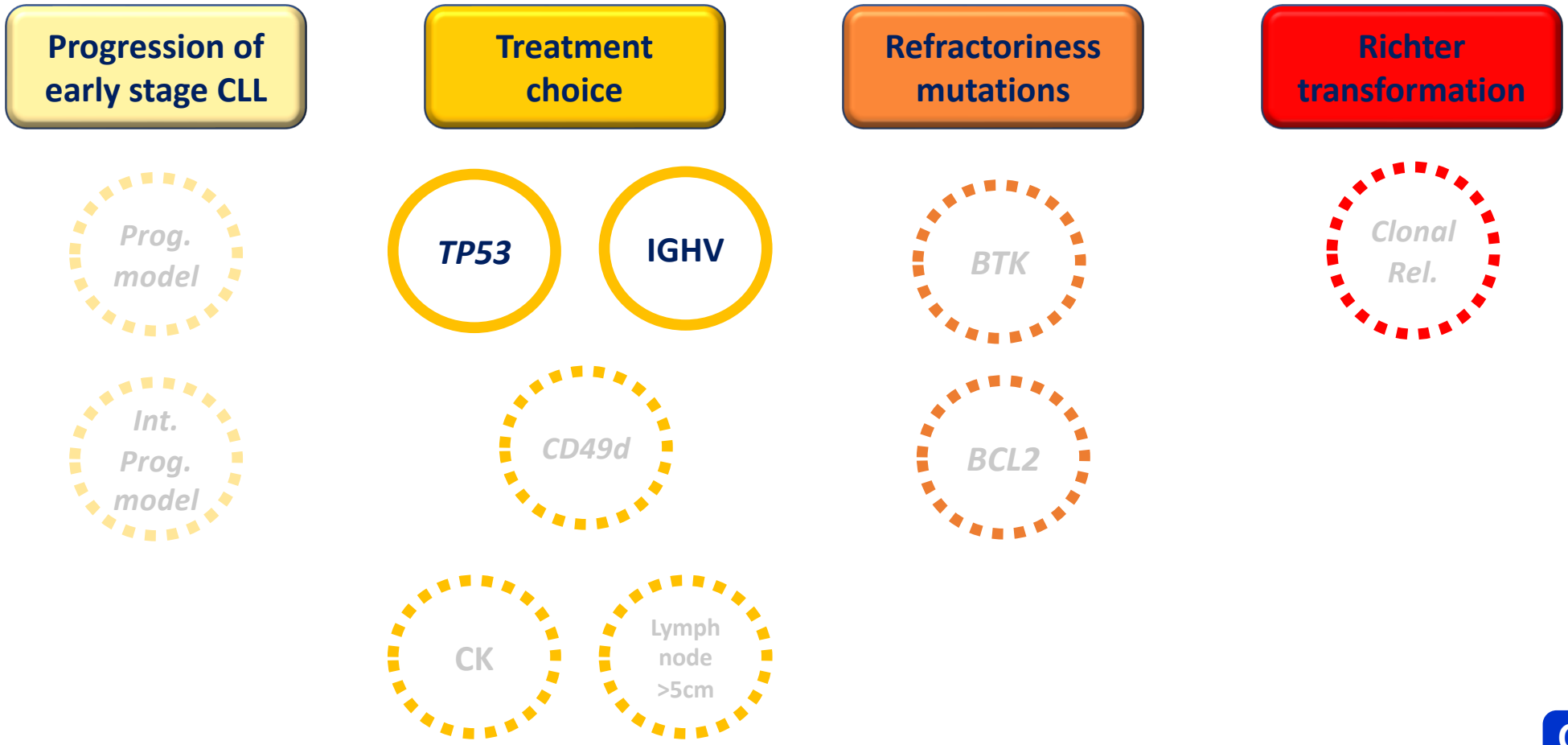
RENDE (CS) 23-24 MAGGIO 2025

Highlights in EMATOLOGIA

Biomarkers in CLL in the era of pathway inhibitors



Biomarkers in CLL in the era of pathway inhibitors *according to guidelines*



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Biomarkers in CLL in the era of pathway inhibitors *according to guidelines*

Predictive biomarkers

Less informative today than in the past when the choice was between CIT and target therapies

Prognostic biomarkers

Richter syndrome

Death

Progression

Treatment tailoring

TP53

IGHV

Patient counseling

Frequency of follow-up

Identify those appropriate for early intervention trials

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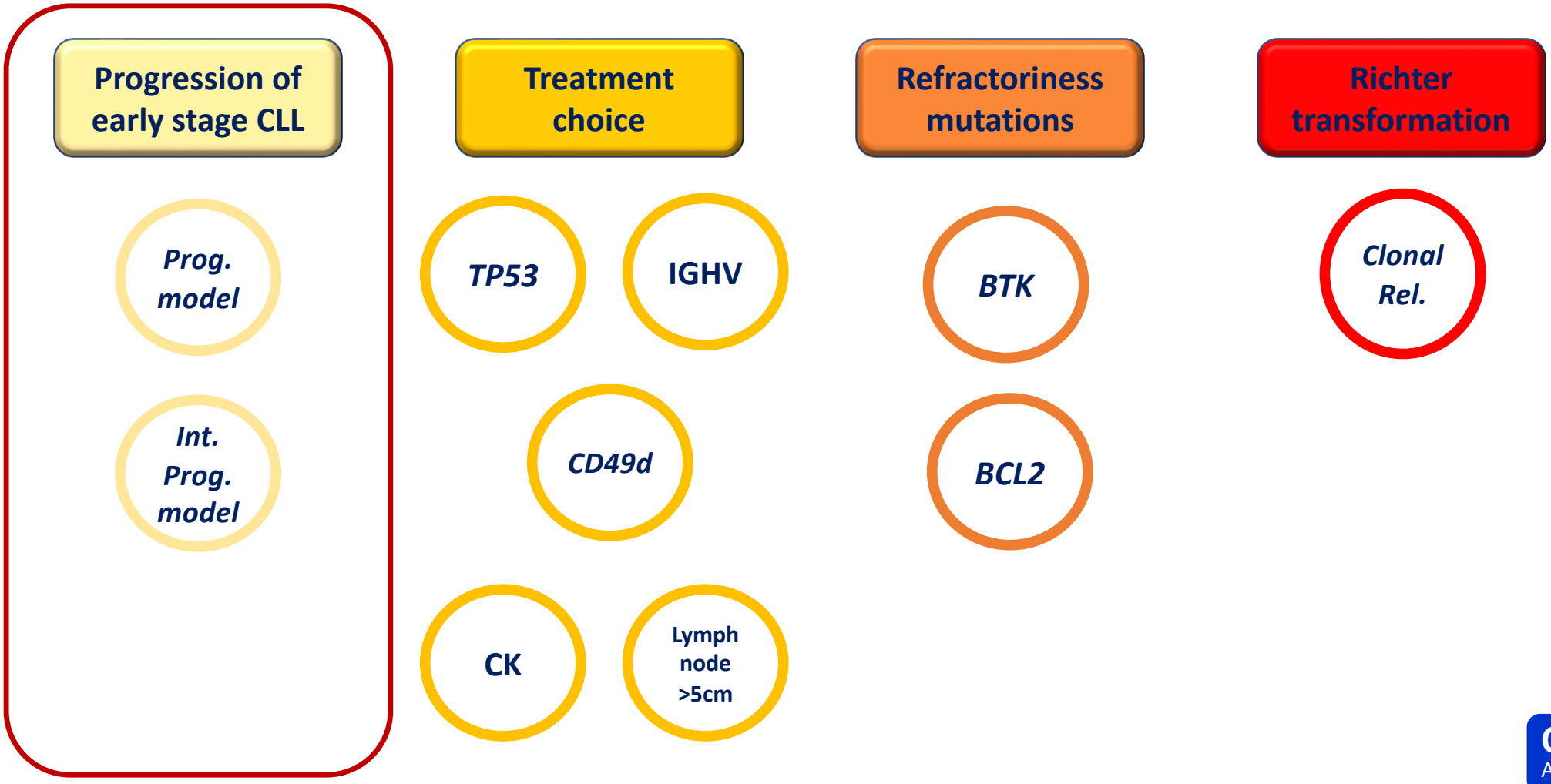
Biomarkers in CLL in the era of pathway inhibitors



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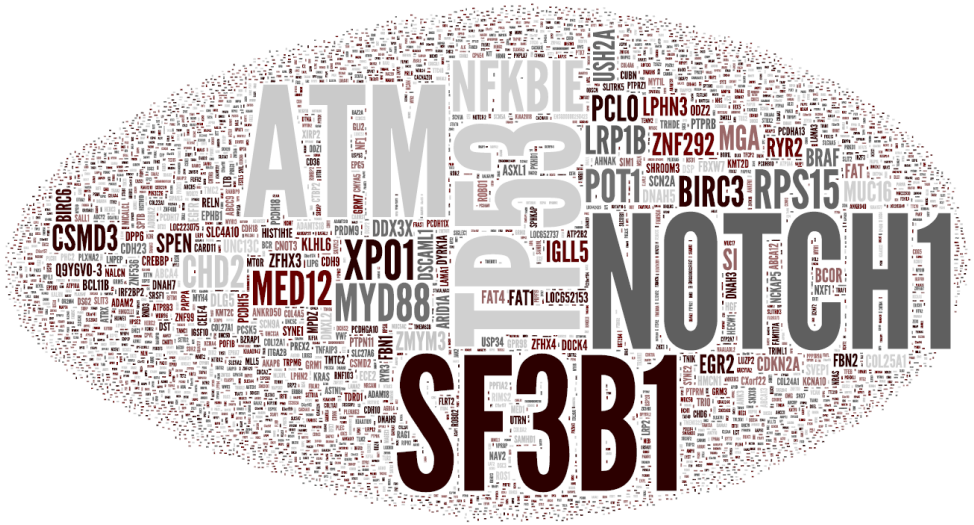
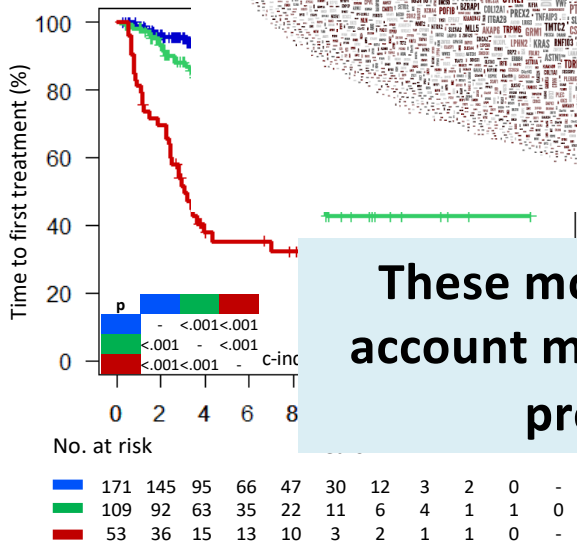
Prognostic score for early stage CLL patients

Binet A CLL patients

Variable	
ALC >15 10^9/l	1
Palpable LN	1
UM-IGHV	1

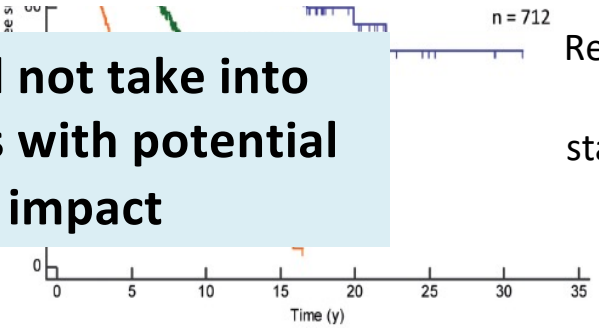




These models did not take into account mutations with potential prognostic impact

Rai 0 CLL patients

Variable	Point(s)
	0
diate-risk	1-2
k	3-5



1) Information on W&W phase

2) Risk-adapted BTKi therapies overcoming the W&W phase

Results of CLL12 do not justify any change to the current standard of “watch and wait.”

Condoluci *et al., Blood.* 2020

Cohen *et al., Haematologica*. 2019

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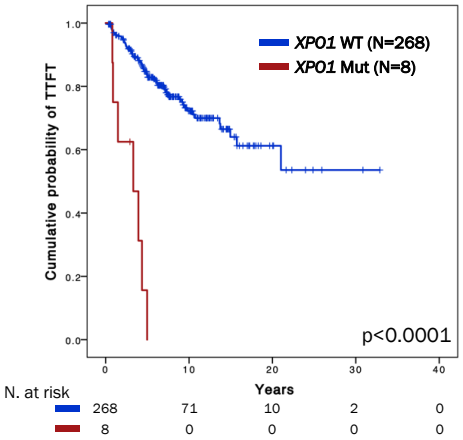
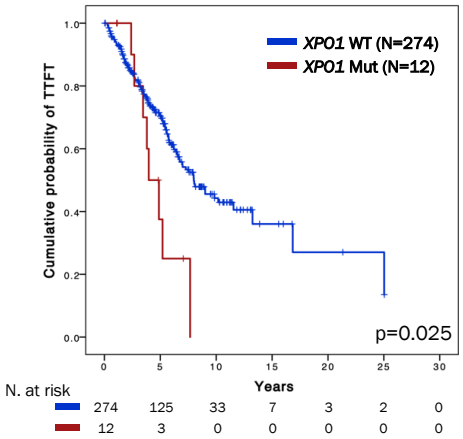
Clinical impact of *XPO1* mutations in early stage CLL

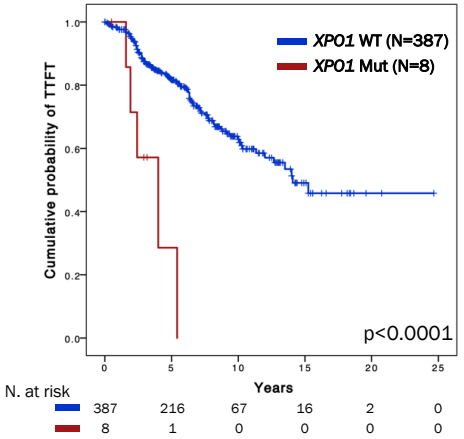
Training cohort



1st validation cohort

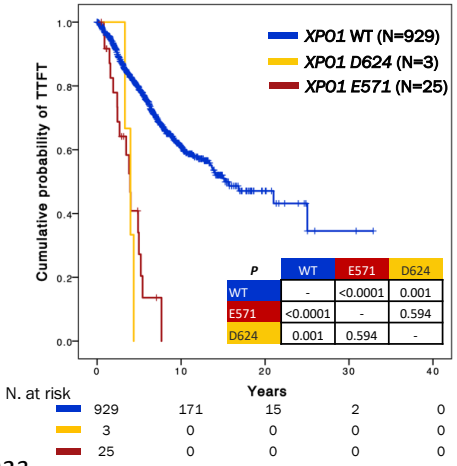


2nd validation cohort

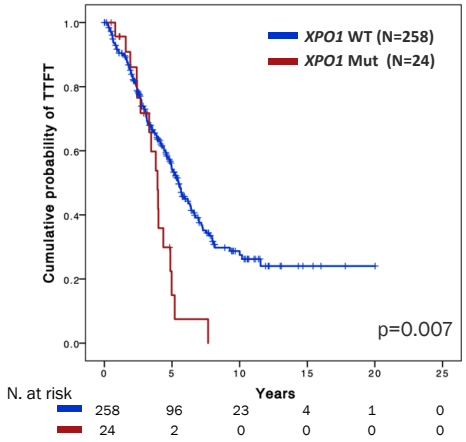


28/297
2.9%

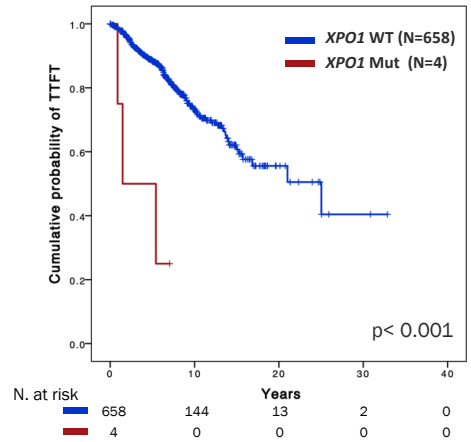
All patients



IGHV unmutated



IGHV mutated

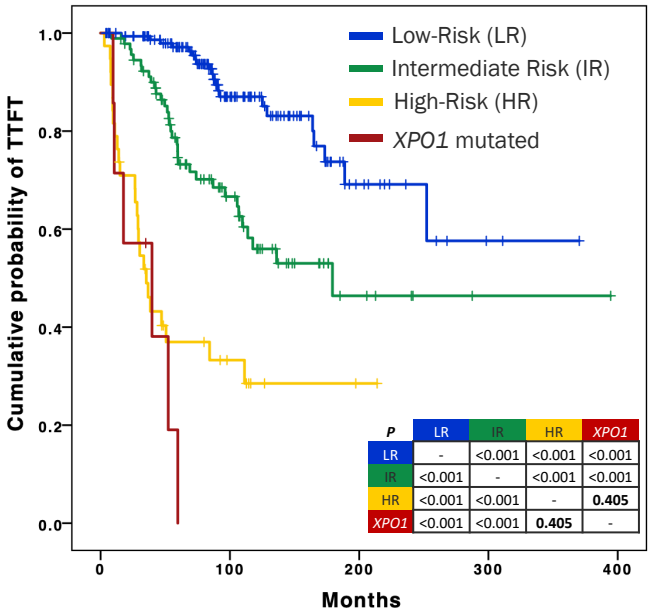


Moia et al., BJH 2023

XPO1 mutations integrate early stage CLL prognostic scores

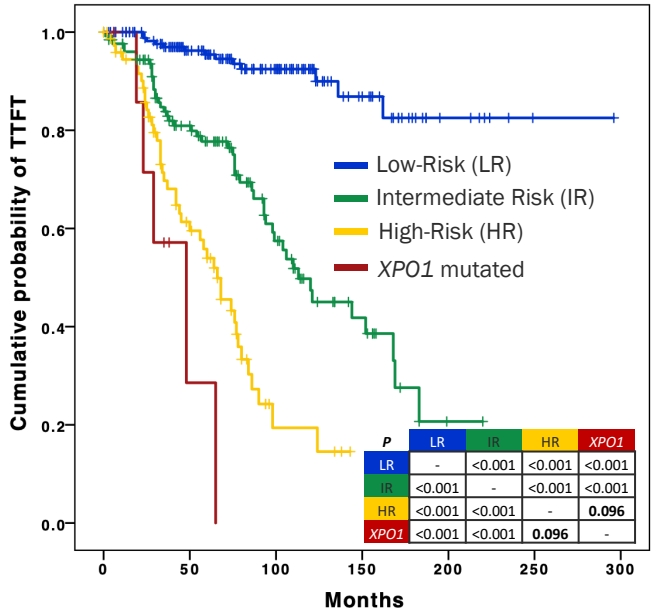
Binet A prognostic model[1]
N=295 patients

Variable	HR	95% C.I.	p value
Unmutated IGHV	3.85	2.44-6.06	<0.0001
Palpable lymph nodes	2.49	1.57-3.97	<0.001
Lymphocyte >15,000/µL	1.98	1.23-3.20	0.005
***XPO1* mutations**	**2.74**	**1.11-6.74**	**0.028**



Rai 0 prognostic model[2]
N=395 patients

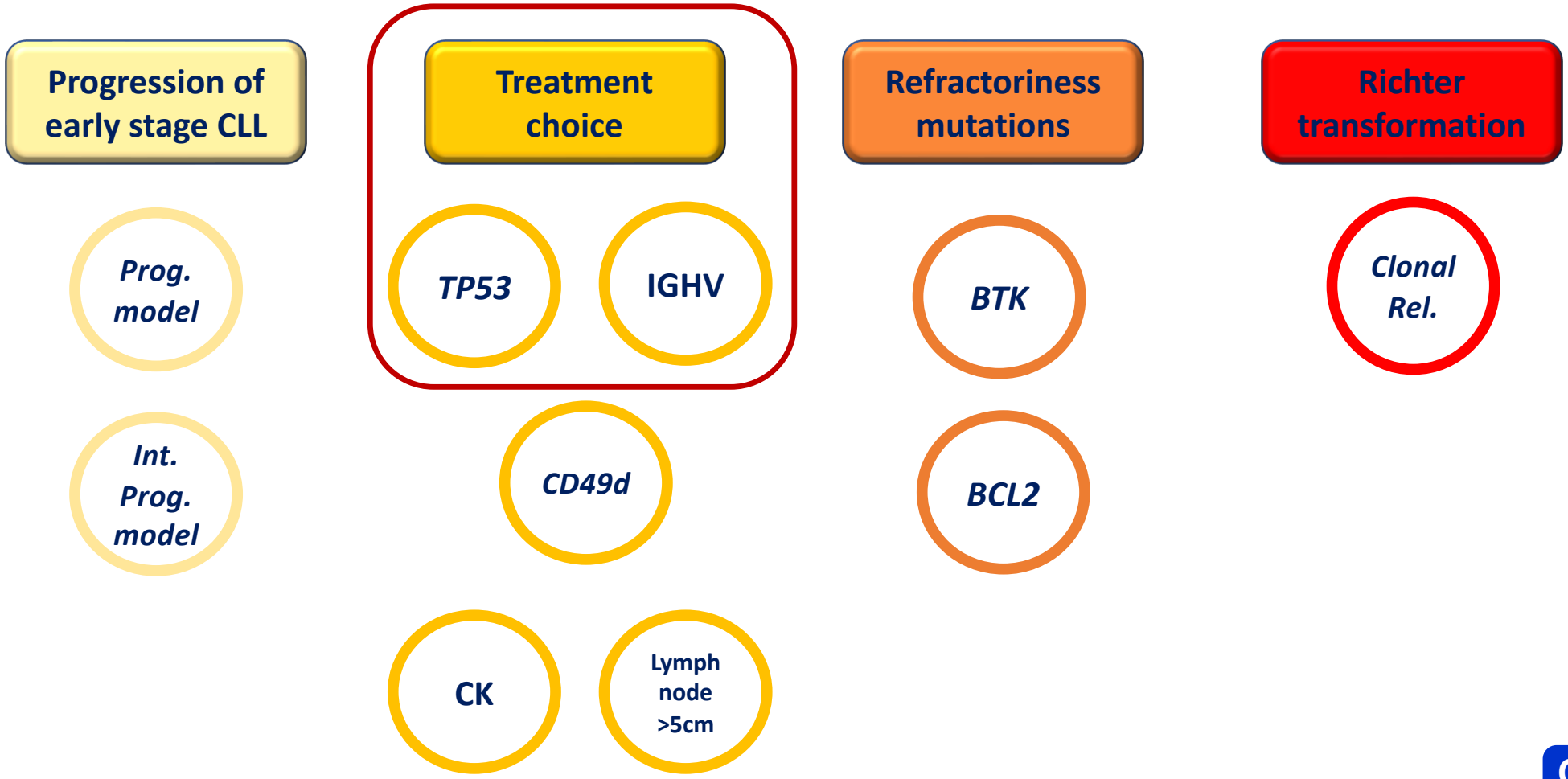
Variable	HR	95% C.I.	p value
WBC > 32,000/µL	2.96	1.98-4.30	<0.001
Unmutated IGHV	2.67	1.75-4.07	<0.001
Del 17p	1.97	1.06-3.67	0.032
Tris 12	1.76	1.11-2.78	0.016
Del 11q	2.31	1.36-3.39	0.002
***XPO1* mutations**	**4.08**	**1.55-10.71**	**0.004**



[1]Condoluci *et al., Blood.* 2020; [2]Cohen *et al., Haematologica*. 2020

Moia et al., BJH 2023

Biomarkers in CLL in the era of pathway inhibitors



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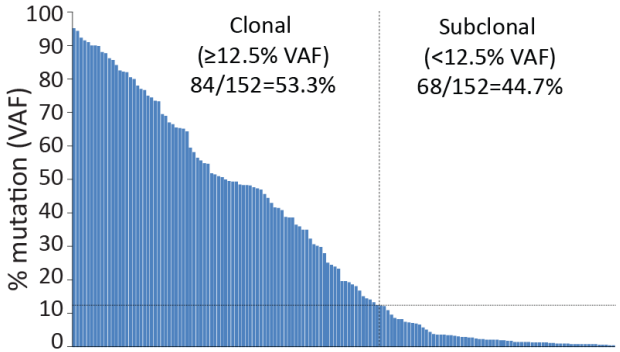
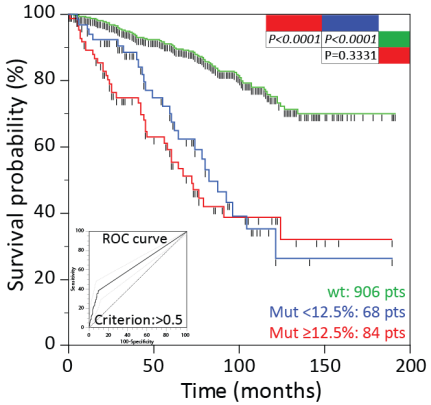
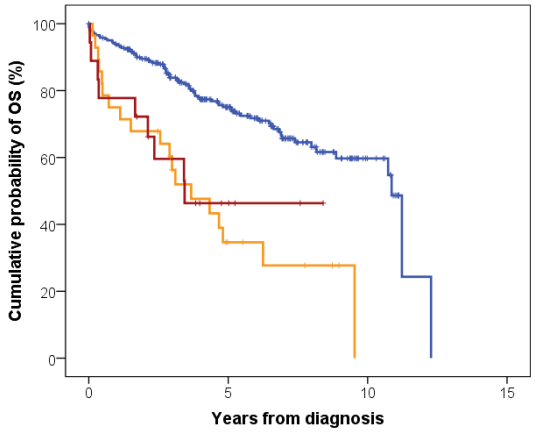
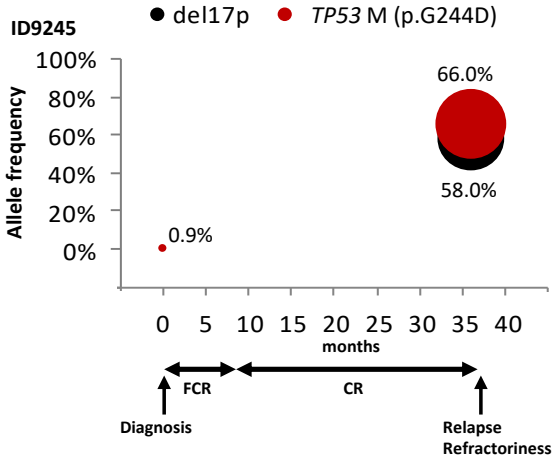
TP53 mutational status and OS – CIT

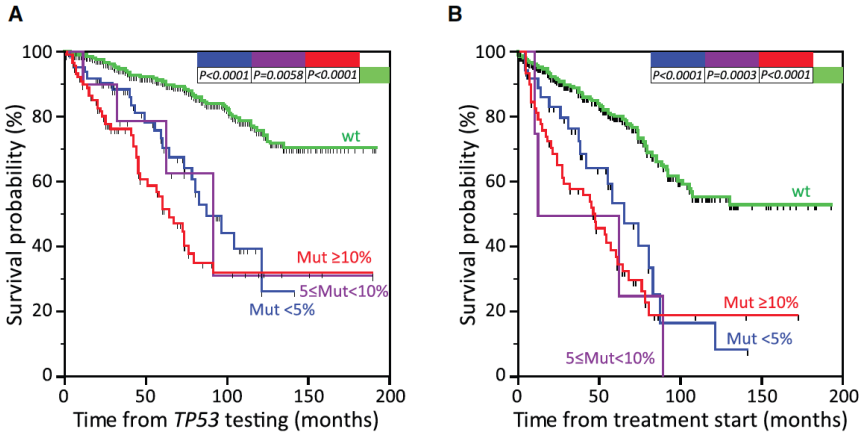




wt	534	464	153	27	0
Mut clonal	56	35	12	2	0
Mut subclonal	40	32	10	1	0







Rossi et al, Blood, 2014
Bomben et al.,et al, Clin Cancer Res 2021

Front-line therapeutic algorithm – ESMO guidelines (2021)

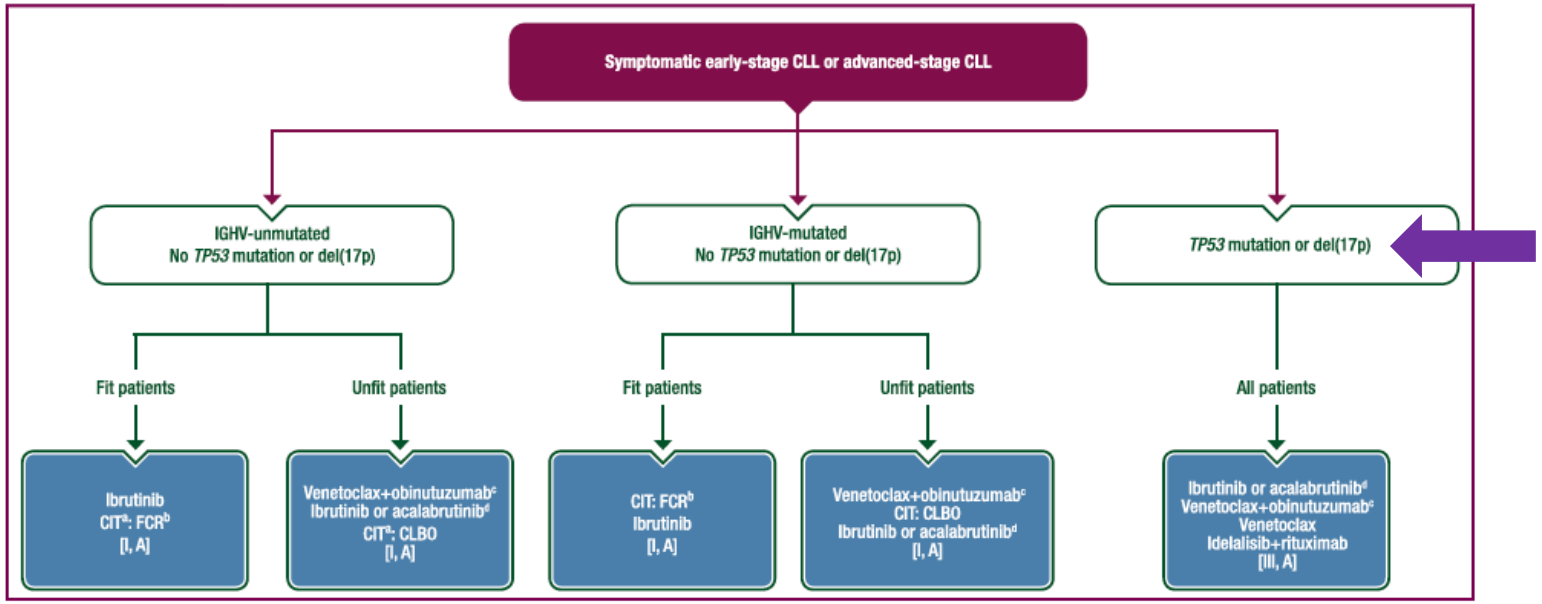


Figure 1. Front-line therapy.
The order of the recommended treatments for each subgroup is based on expert opinion considering time-limited as more valuable therapy, if there is equal evidence for two different treatment options.
BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.
[a] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability.
[b] BR might be considered alternatively in patients above the age of 65 years.
[c] If available.
[d] If approved and available.

Eichhorst et al.,et al, Ann Oncol 2021

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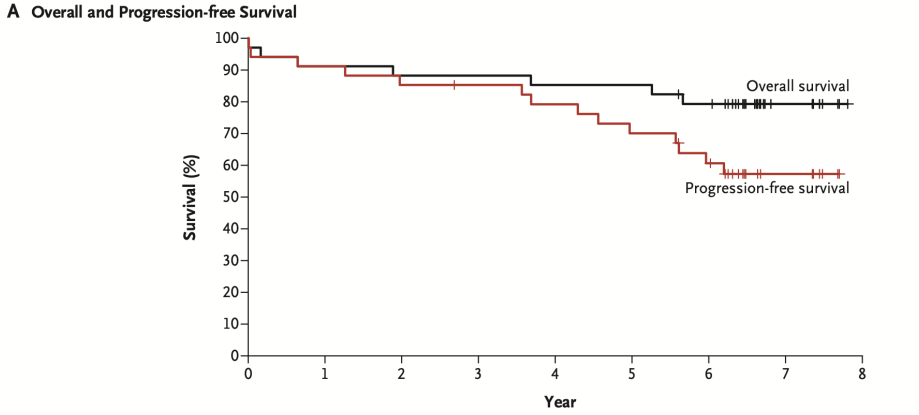
Ibrutinib allows to obtain prolong survival rates also in high risk *TP53* disrupted CLL

i) TP53

TP53 mut and/or 17p del

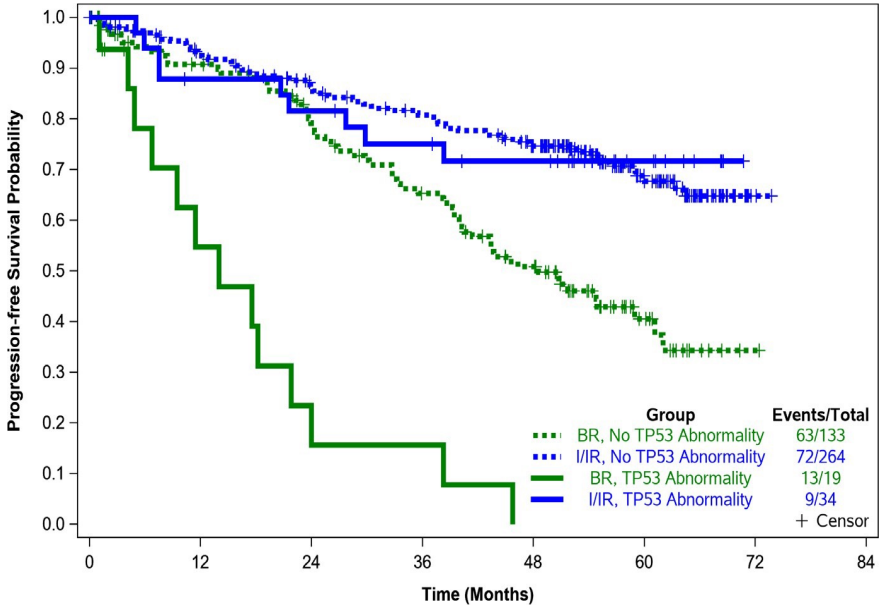
Phase 2 trial dedicated to *TP53* disrupted cases



B Summary of Survival

	2 Yr	3 Yr	4 Yr	5 Yr	6 Yr
			% (95% CI)		
Overall Survival	88 (78–100)	88 (78–100)	85 (74–98)	85 (74–98)	79 (67–94)
Progression-free Survival	85 (74–98)	85 (74–98)	79 (67–94)	70 (56–88)	61 (46–80)

Phase 3 Alliance trial



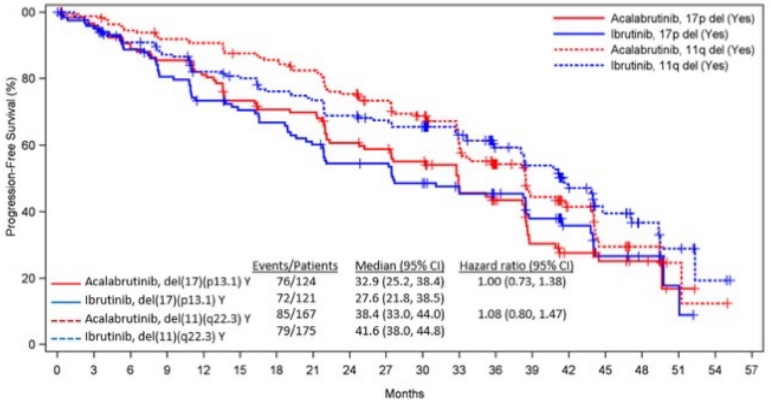
Ahn *et al., NEJM*. 2020; Woyach *et al., ASH* 2021

Acalabrutinib and zanubrutinib are active in *TP53* disrupted patients

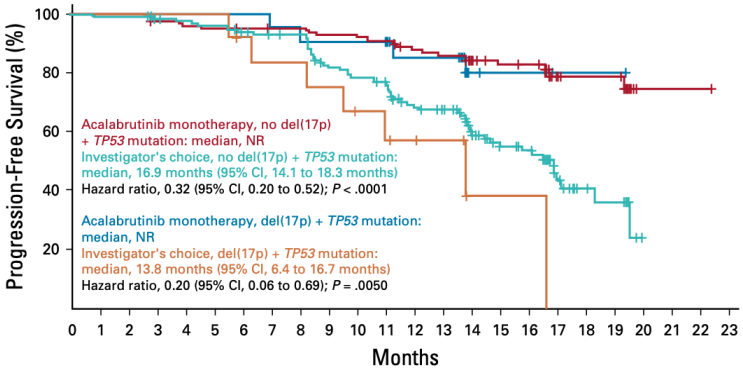
TP53 mut and/or 17p del

i) TP53

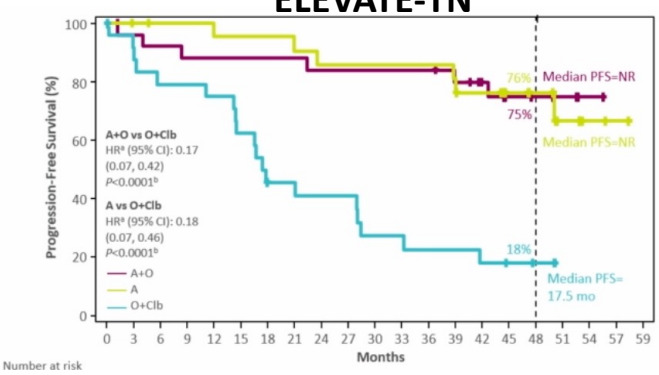
ACALABRUTINIB
ELEVATE-RR



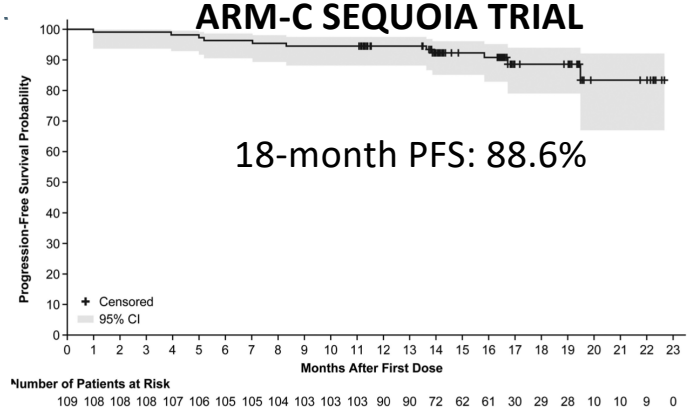
ACALABRUTINIB
ASCEND



ACALABRUTINIB
ELEVATE-TN



ZANUBRUTINIB
ARM-C SEQUOIA TRIAL

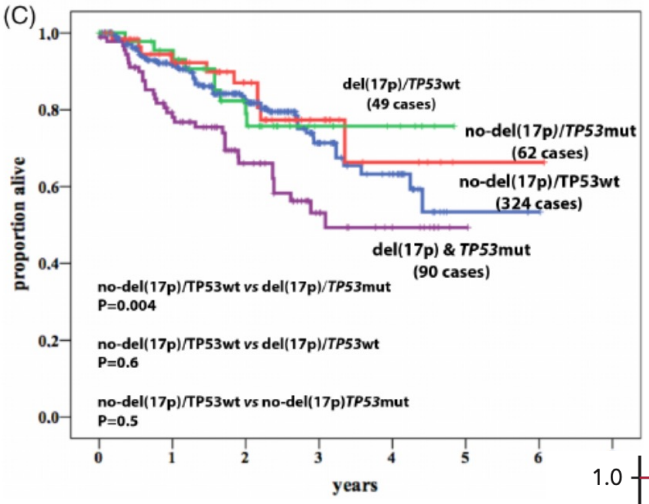


Byrd *et al.*, *JCO*. 2021; *Ghia et al., JCO.* 2020; Sharman *et al., Lancet*. 2020; Tam *et al., Haematologica*. 2021.

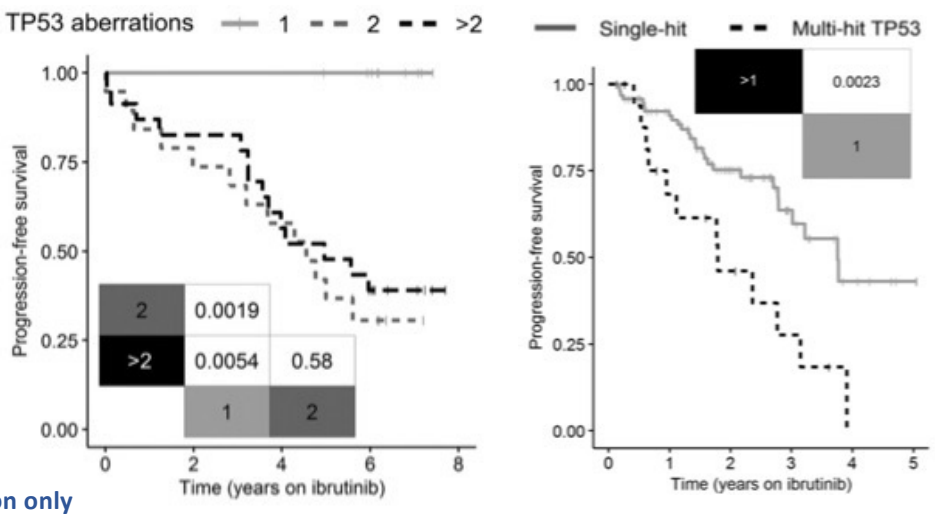
Clinical impact of different types of *TP53* abnormalities

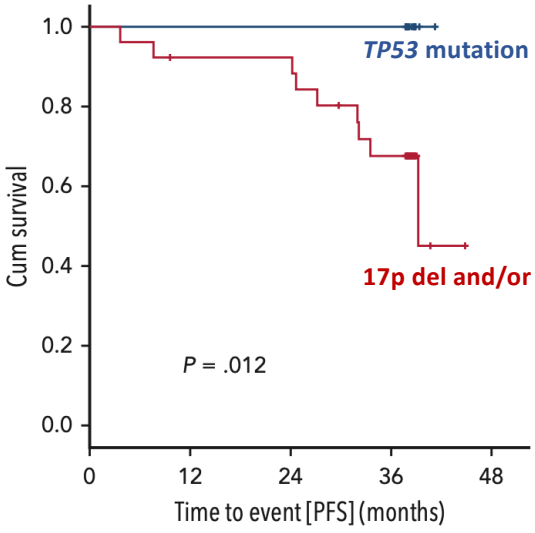
i) TP53

Italian multicentre cohort



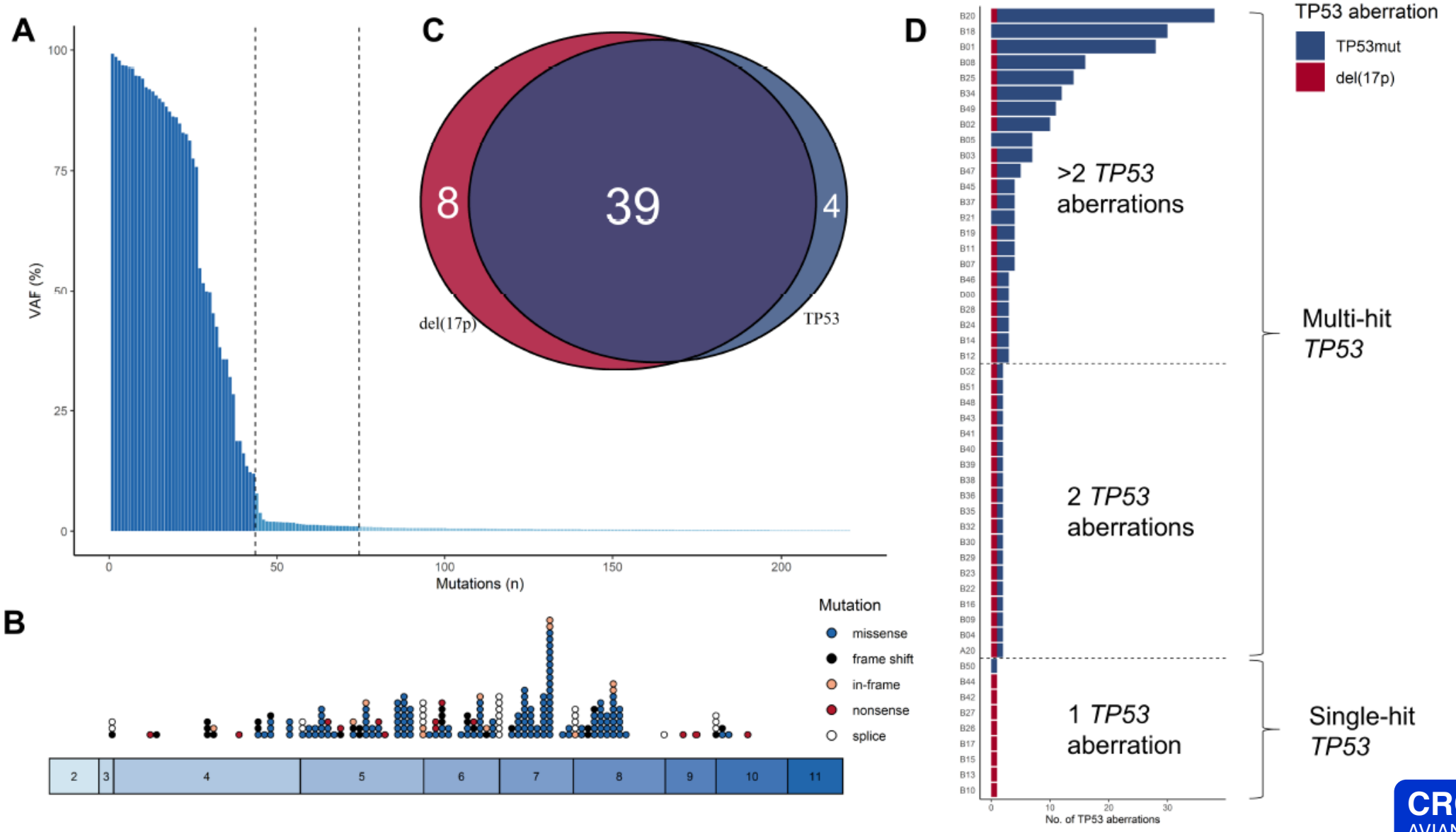
Phase 2 trial and Danish cohort





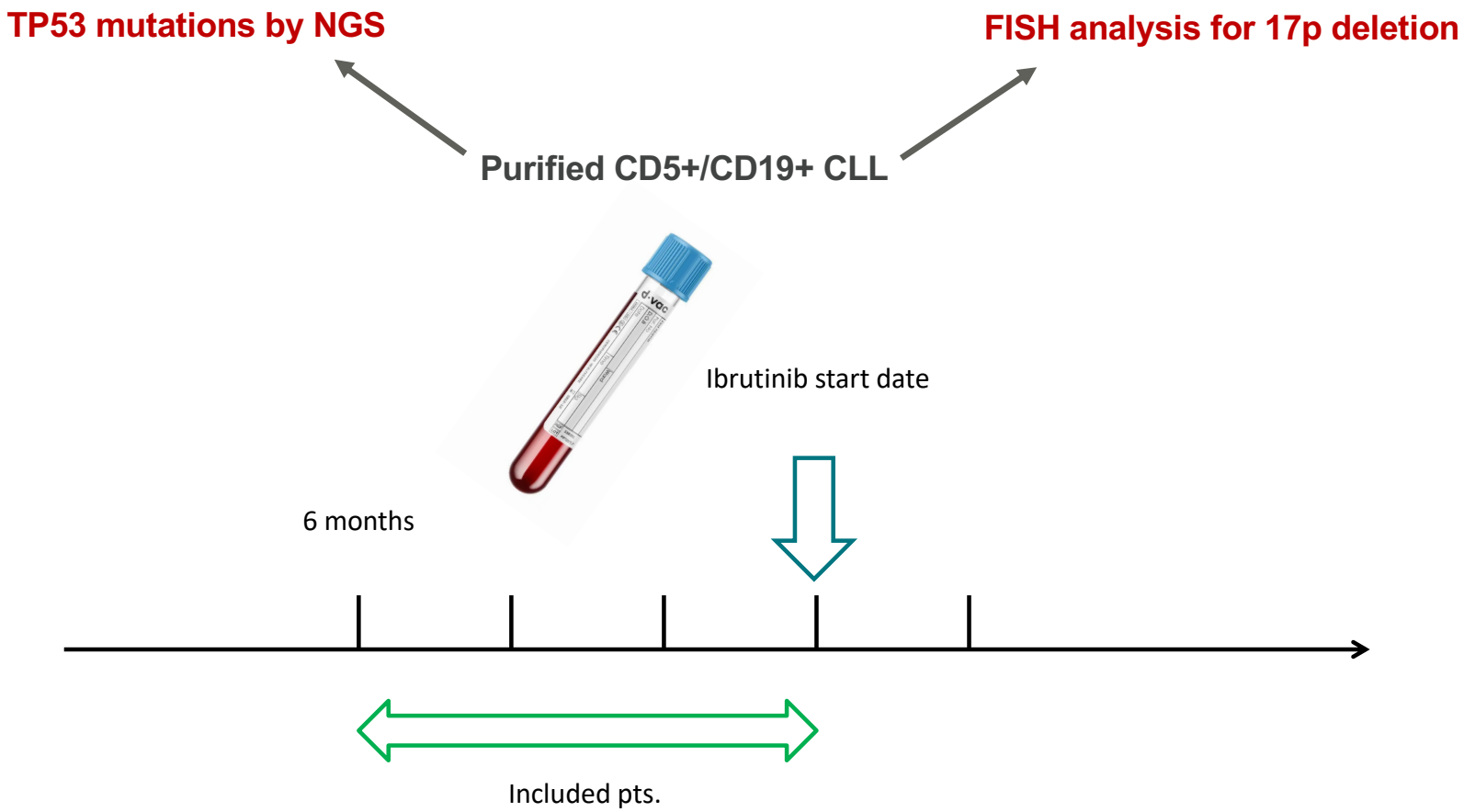
Phase 2 CLL2-GIVe trial

Morabito *et al., Am J Hematol*. 2021; Brieghel *et al., Clin Cancer Res*. 2021; Huber *at al., Blood*. 2023



Brieghel et al, Clin Cancer Res, 2021

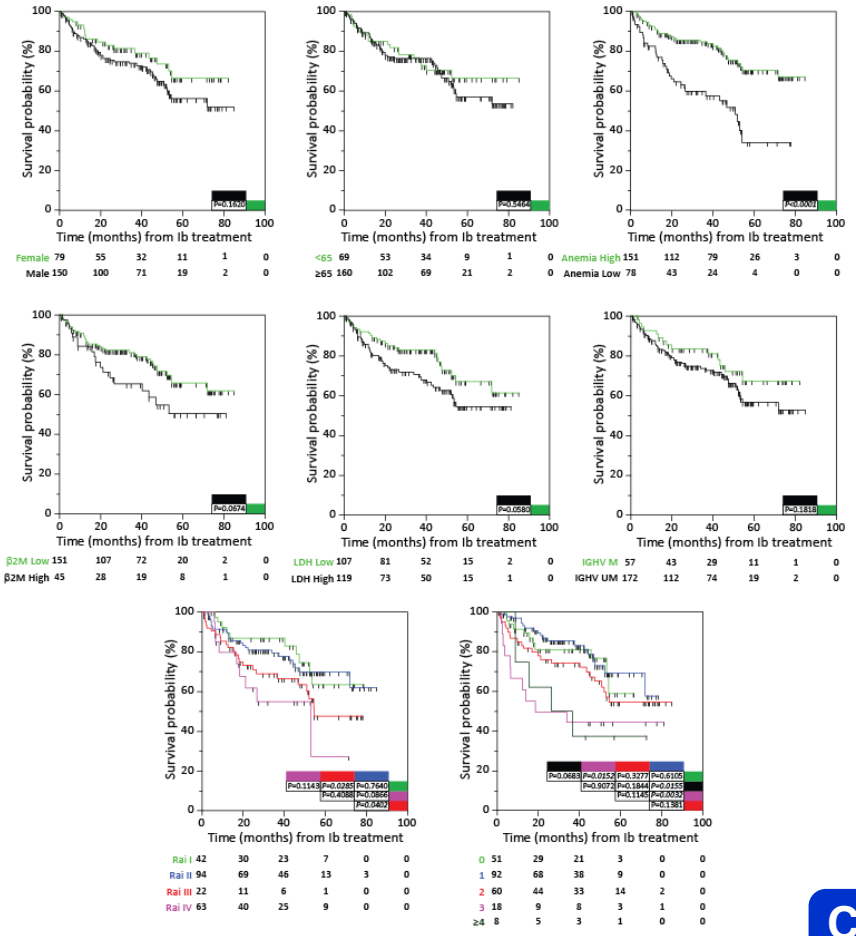
CLL retrospective multicenter cohort (n=229)



Bomben et al.,et al, Leukemia 2023

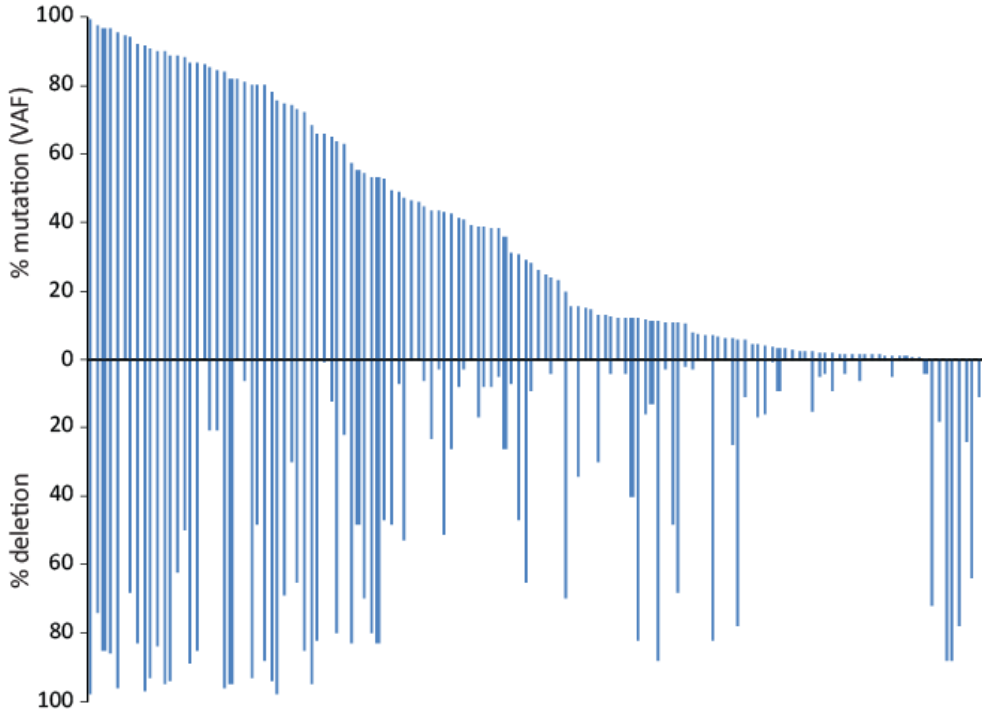
CLL retrospective multicenter cohort (n=229)

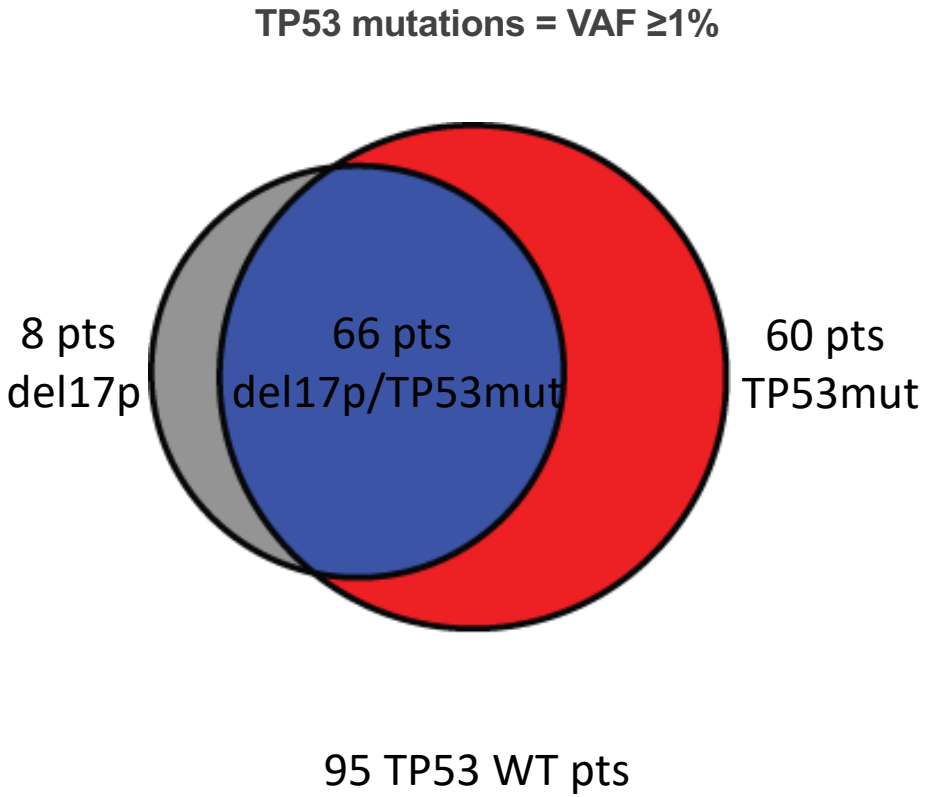
Parameter	Category	N	%
Age	<65	69	30.1
	≥65	160	69.9
Gender	Female	79	34.5
	Male	150	65.5
Previous Line of therapy[a]	0	51	22.3
	1	92	40.2
	2	60	26.2
	3	18	7.9
	>3	8	3.5
Rai stage	0	0	0.0
	I	42	18.3
	II	94	41.0
	III	22	9.6
	IV	63	27.5
	Missing	8	3.5
del11q	Present	56	24.5
	Absent	171	74.7
	Missing	2	0.9
Hemoglobin g/L	>120 for men / >110 for women	151	65.9
	≤120 for men / ≤110 for women	78	34.1
β2 microglobulin mg/L	<5	151	65.9
	≥5	45	19.7
	Missing	33	14.4
Lactate dehydrogenase U/ml	Normal	108	47.2
	Elevated	119	52.0
	Missing	2	0.9
IGHV	Mutated	76	33.2
	Unmutated	153	66.8



Bomben et al.,et al, Leukemia 2023

TP53 aberrations





Bomben et al.,et al, Leukemia 2023

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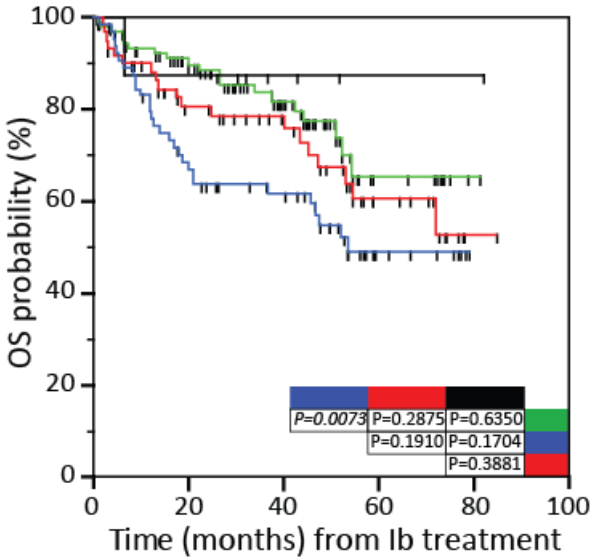
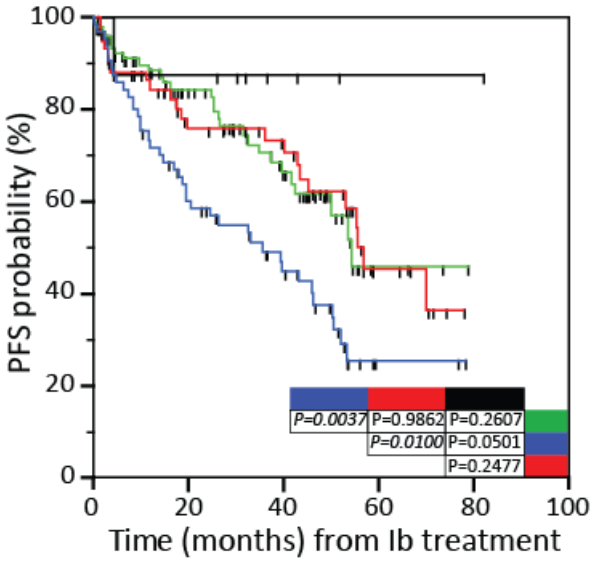
TP53 aberrations and OS/PFS



non-del17/non-TP53mut	95	68	40	9	1	0
del17p/non-TP53mut	8	7	3	1	1	0
non-del17/TP53mut	60	39	39	12	1	0
del17/TP53mut	66	41	31	8	0	0



non-del17/non-TP53mut	95	54	30	3	0	0
del17p/non-TP53mut	8	7	3	1	1	0
non-del17/TP53mut	60	35	27	7	0	0
del17/TP53mut	66	36	21	2	0	0

Bomben et al.,et al, Leukemia 2023

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Multivariable analysis

	OS							
	UVA				MVA[a]			
	HR	LCI	UCI	P	HR	LCI	UCI	P
Gender (Male)	1.47	0.86	2.51	0.1644	-			
Age (≥65 y)	1.18	0.69	2.00	0.5489	-			
Rai stage (I-II versus III-IV)[c]	1.82	1.12	2.94	***0.0147***	ni			
Previous Line of therapy (0-1 versus >1)	1.93	1.19	3.12	***0.0077***	1.91	1.17	3.13	***0.0093***
Anemia	2.86	1.77	4.62	***<0.0001***	2.47	1.51	4.05	***0.0003***
β2 microglobulin (high)[d]	1.68	0.96	2.95	0.0689	-			
LDH (high)[e]	1.61	0.98	2.65	0.0607	ni			
IGHV (UM)	1.49	0.83	2.68	0.1849	-			
del11q (present)[d]	1.31	0.77	2.22	0.3233	-			
del17p/non-*TP53* mut[f]	0.60	0.08	4.50	0.6208	0.71	0.09	5.35	0.7391
non-del17p/TP53mut[f]	1.46	0.77	2.76	0.2467	1.43	0.74	2.79	0.2917
del17p/TP53mut[f]	2.16	1.21	3.85	***0.009***	2.27	1.24	4.14	***0.0077***

	PFS							
	UVA				MVA[b]			
	HR	LCI	UCI	P	HR	LCI	UCI	P
	1.73	1.08	2.78	***0.0233***	ni			
	1.03	0.66	1.61	0.8928	-			
	1.65	1.08	2.51	***0.0201***	ni			
	2.34	1.54	3.55	***<0.0001***	2.44	1.59	3.74	***<0.0001***
	2.25	1.49	3.41	***0.0001***	2.04	1.33	3.13	***0.0011***
	1.61	0.99	2.61	0.0526	-			
	1.74	1.14	2.67	***0.0108***	ni			
	1.81	1.07	3.08	***0.0272***	ni			
	1.21	0.76	1.93	0.4199	-			
	0.33	0.05	2.42	0.2756	0.34	0.05	2.53	0.2942
	1.02	0.58	1.77	0.9556	0.90	0.51	1.61	0.7340
	2.01	1.24	3.25	***0.0047***	2.05	1.24	3.37	***0.0049***

OS and PFS were computed from date of ibrutinib treatment to date of death or progression/suspension or last follow-up

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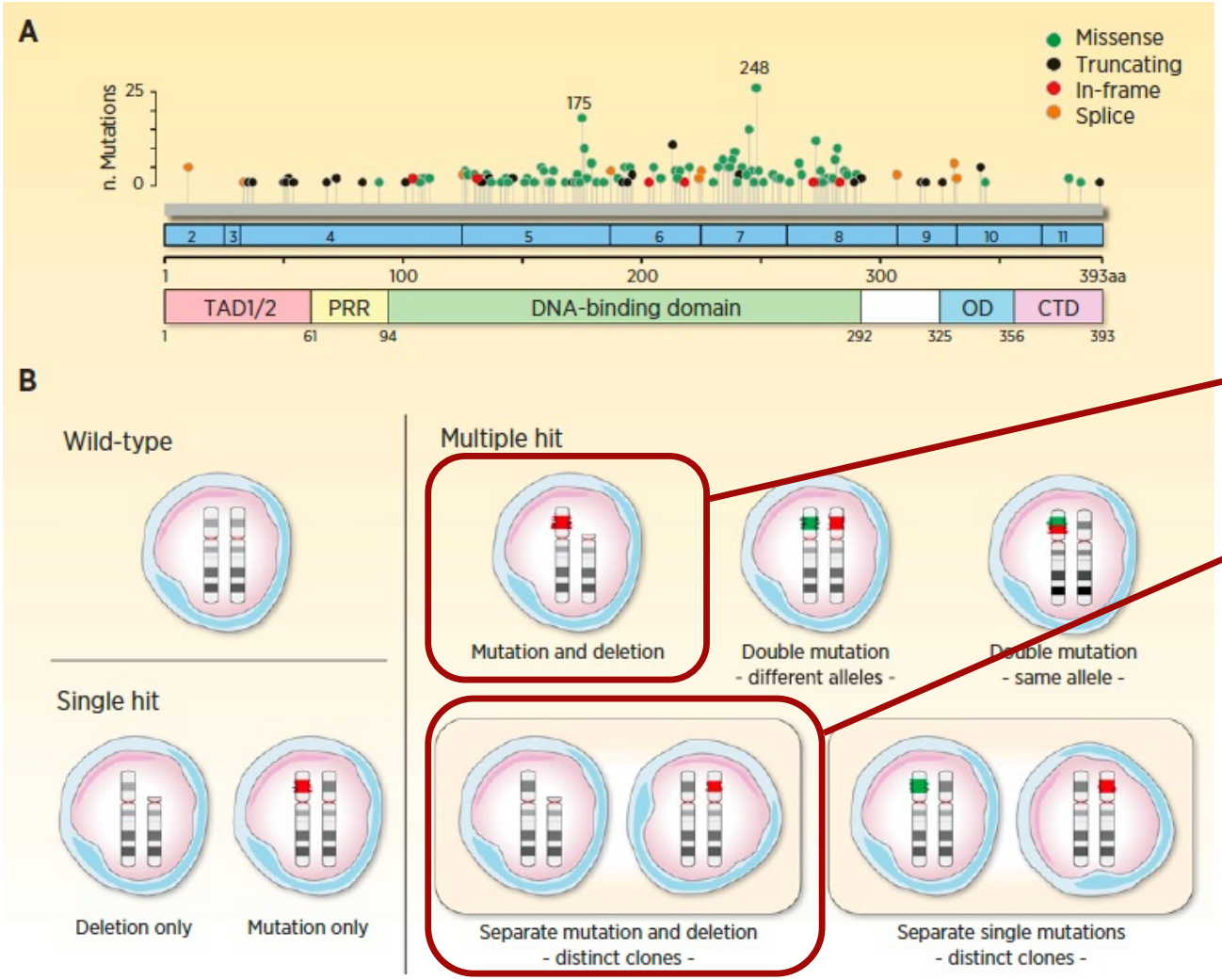
Bomben et al.,et al, Leukemia 2023

Clinical impact of different types of *TP53* abnormalities

i) TP53

Bomben et al.,et al, Clin Cancer Res 2021



CK proxy?

BTKi are active in most of TP53 disrupted patients

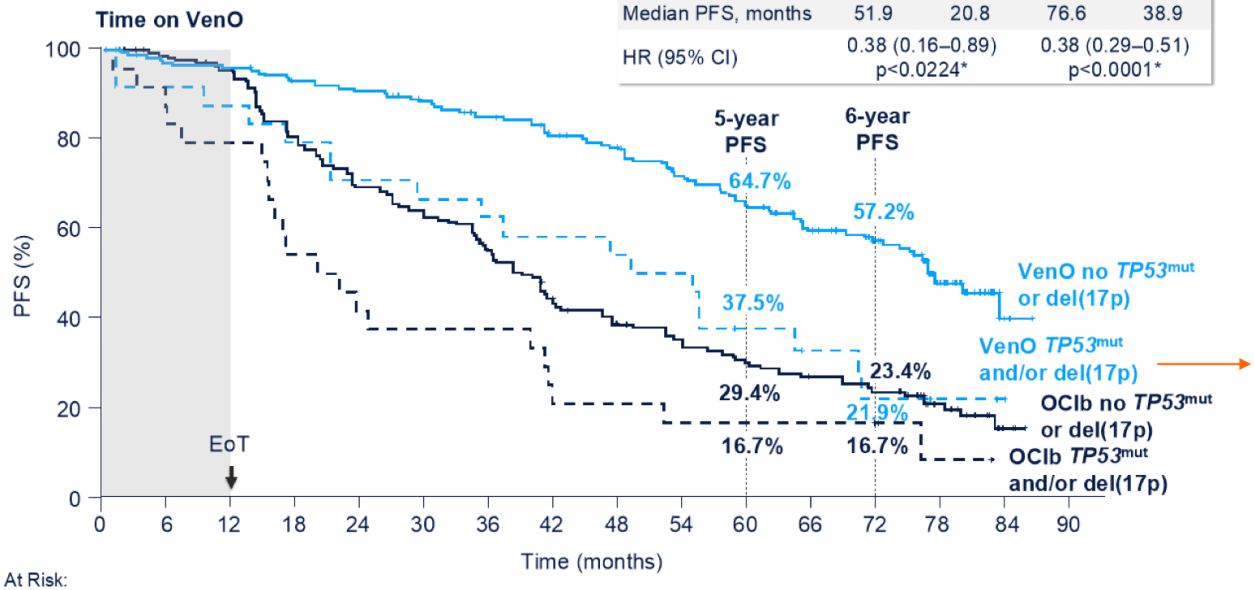
CRO AVIANO

Clinical impact of *TP53* in the CLL14 trial

TP53 mut and/or 17p del

i) TP53

	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*	



Median PFS 52 months

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-Obi mitigates, but does not abolish, the negative prognostic impact of *TP53* disruption

Al-Sawaf *et al.*, iwCLL 2023

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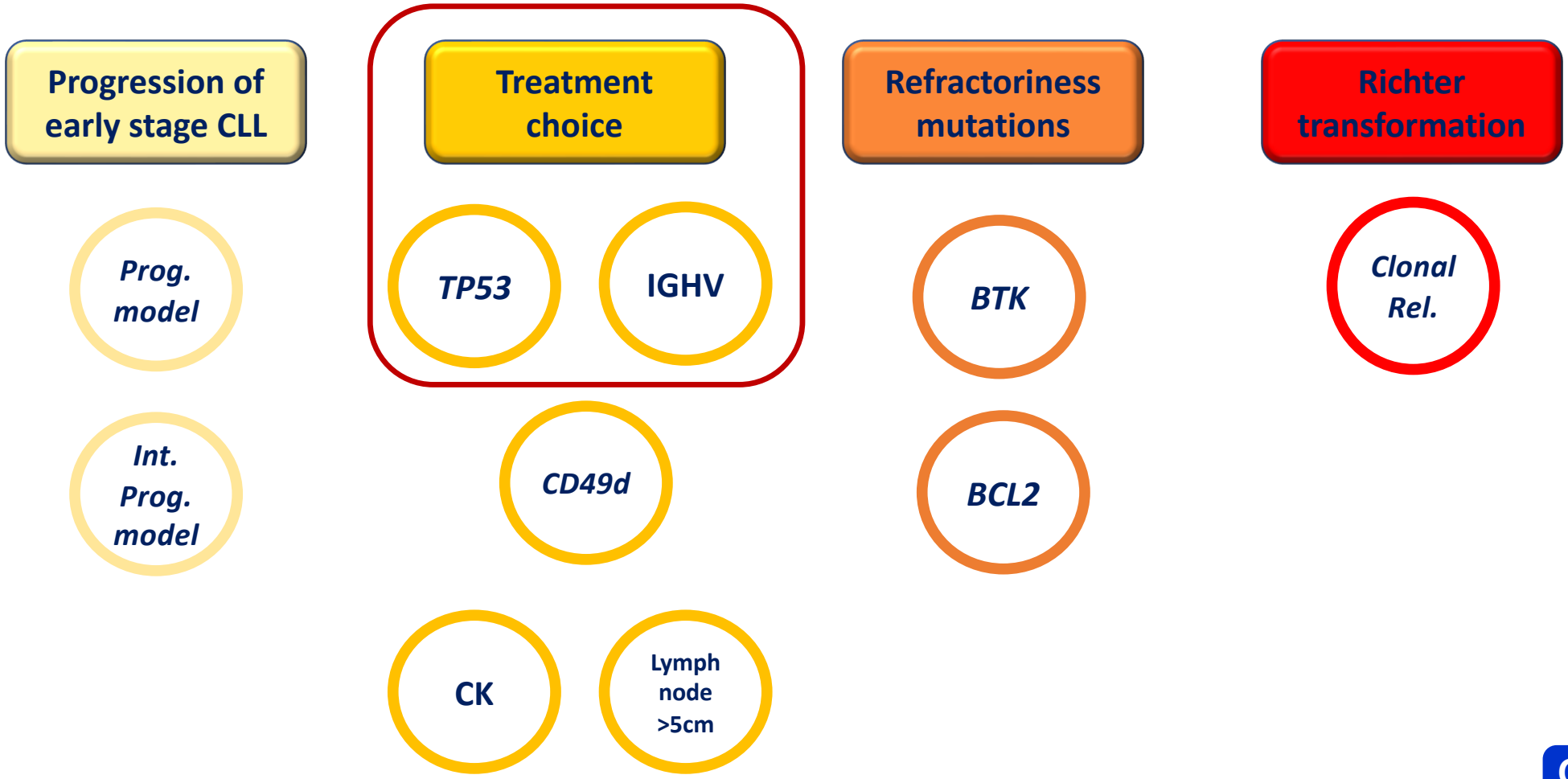
Biomarkers in CLL in the era of pathway inhibitors



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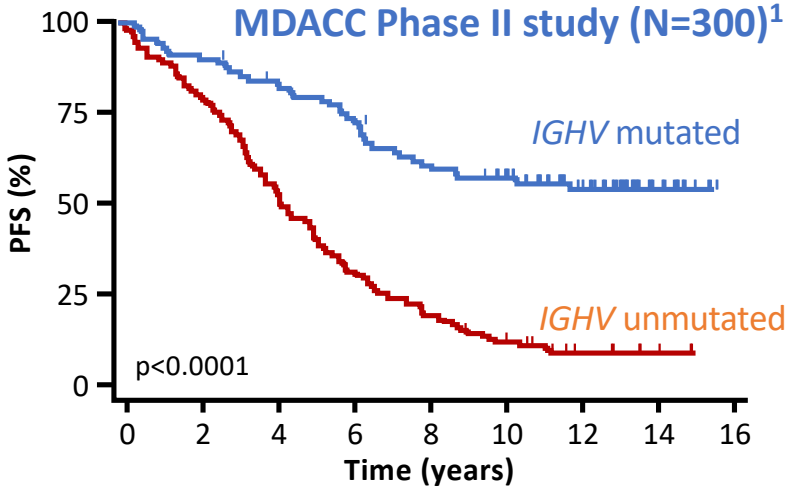
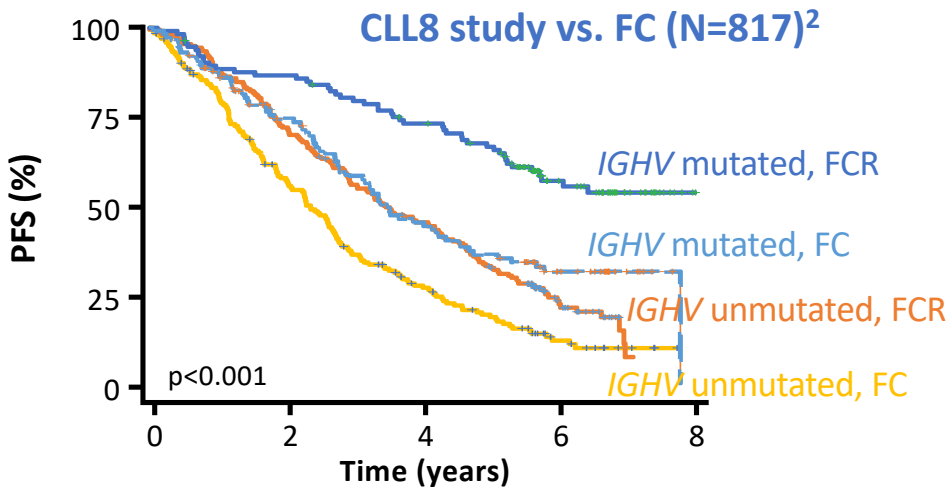
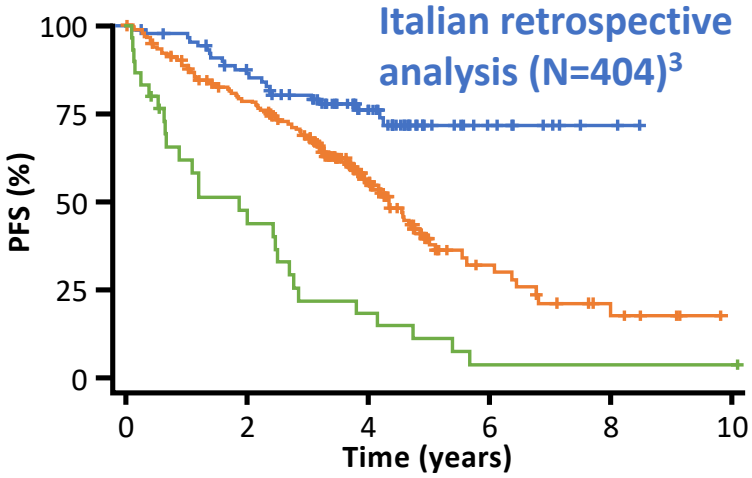
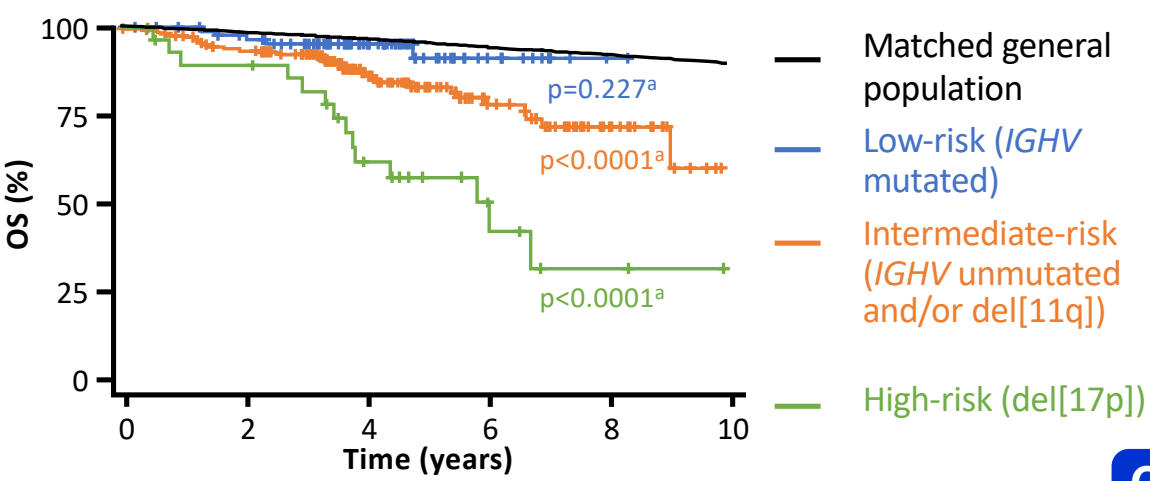
Impact of *IGHV* mutation status on outcome after FCR









1. Thompson PA, *et al. Blood* 2016; 127:303–309. 2. Fischer K, *et al. Blood* 2016; 127:208–215. 3. Rossi D *et al. Blood* 2015; 126 1921–1924.

CRO AVIANO

Front-line therapeutic algorithm – ESMO guidelines (2021)

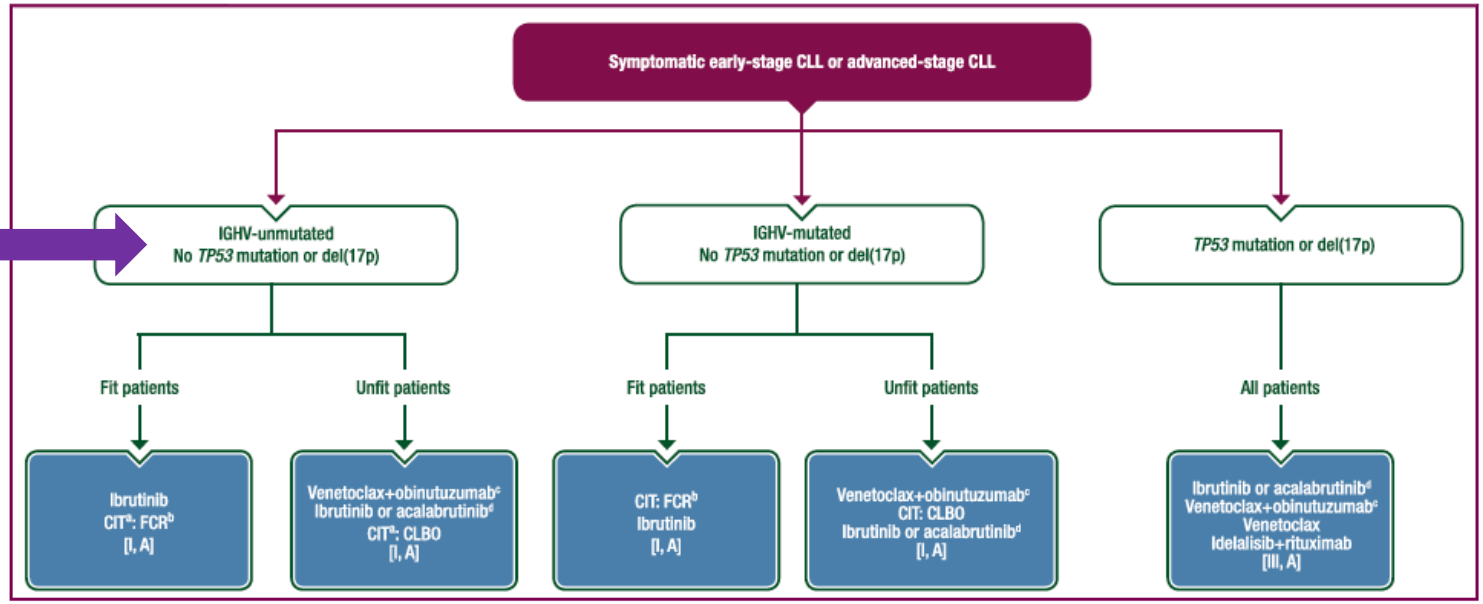


Figure 1. Front-line therapy.
The order of the recommended treatments for each subgroup is based on expert opinion considering time-limited as more valuable therapy, if there is equal evidence for two different treatment options.
BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.
[a] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability.
[b] BR might be considered alternatively in patients above the age of 65 years.
[c] If available.
[d] If approved and available.

Eichhorst et al.,et al, Ann Oncol 2021

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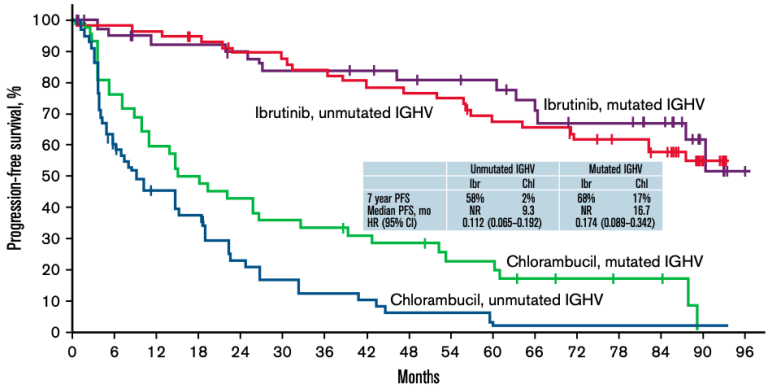
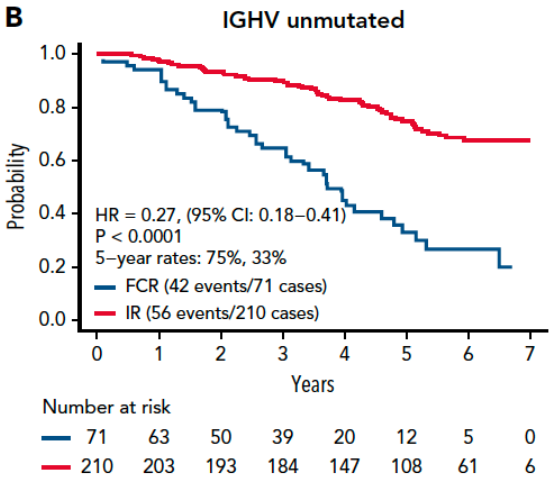
BTKi overcome the prognostic value of IGHV mutational status

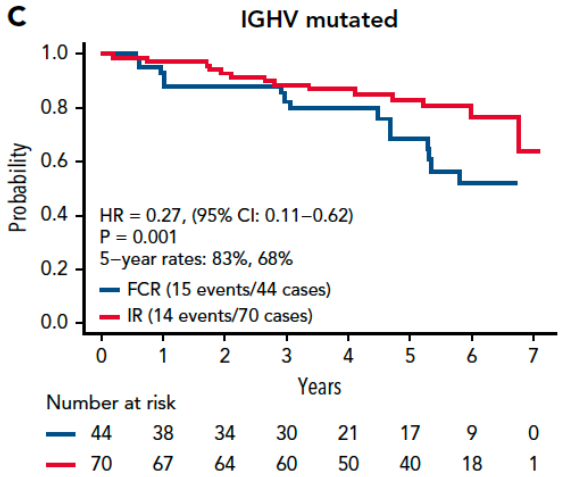
ii) IGHV

RESONATE 2 trial

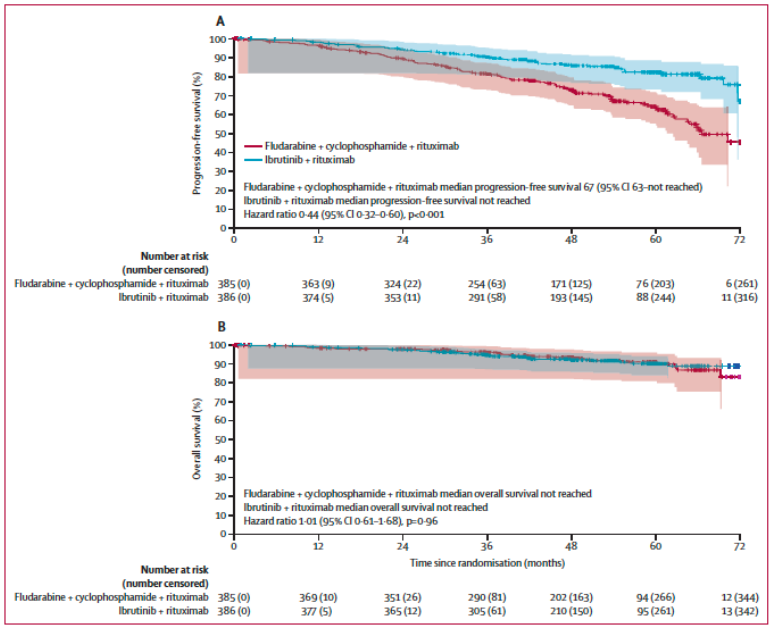


E1912 trial





FLAIR trial



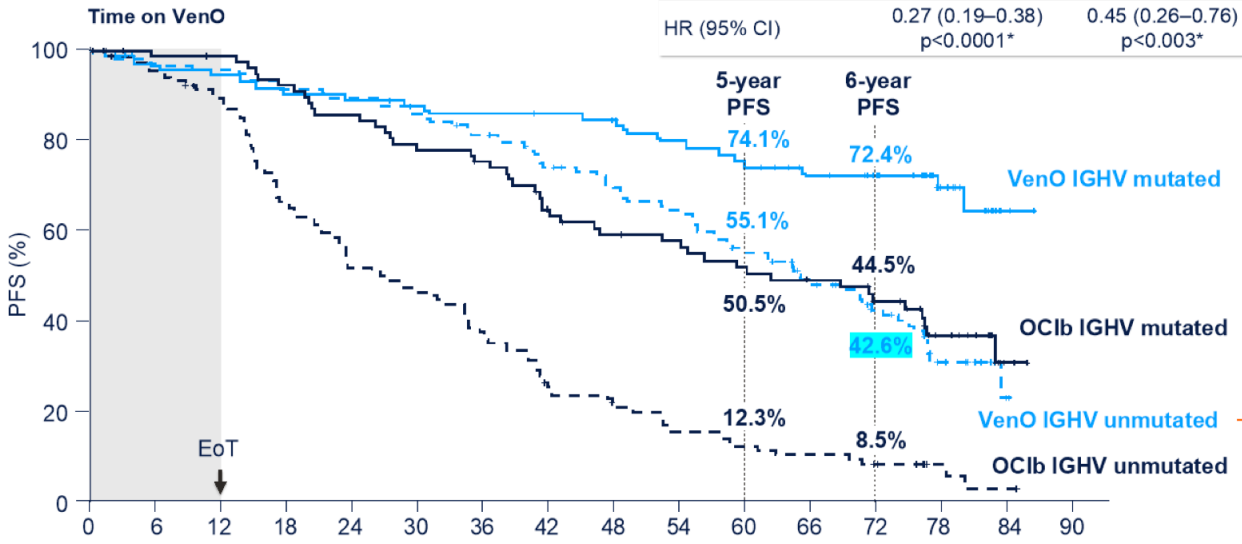
	IR, % (n = 352)	FCR, % (n = 158)	*P* value
Cardiac	7.7	0	<.001
Atrial fibrillation	4.5	0	.004
Other Cardiac*	4.3	0	.008

Barr *et al.*, *Blood Adv*. 2022; Shanafelt *et al., Blood*. 2022; Hillmen *et al., Lancet Oncol*. 2023

Venetoclax + antiCD20 mitigates but not completely overcome the negative prognostic impact of unmutated IGHV genes

ii) IGHV

	IGHV unmutated		IGHV mutated	
	VenO	OCIb	VenO	OCIb
Median PFS, months	64.8	26.9	NE	62.2
HR (95% CI)	0.27 (0.19–0.38) p<0.0001*		0.45 (0.26–0.76) p<0.003*	



Median PFS 65 months

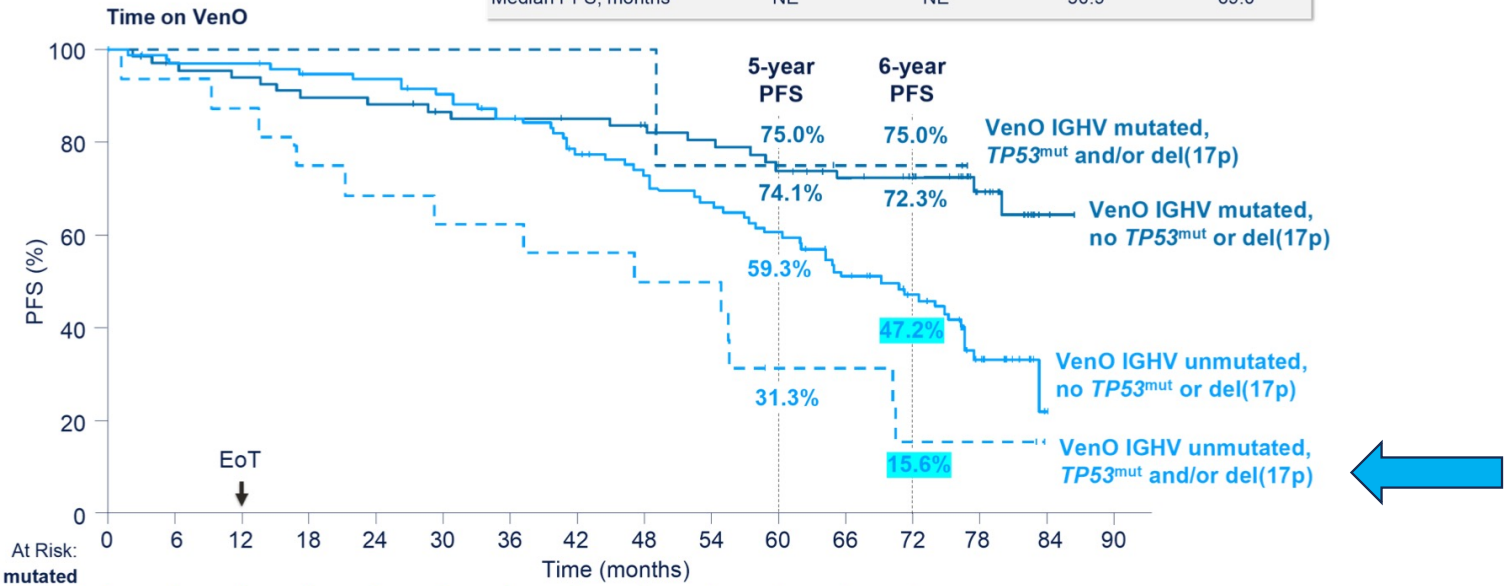
At Risk:															
OCIb IGHV mutated	83	77	76	71	66	60	57	46	42	39	35	33	28	15	2
VenO IGHV mutated	76	70	68	65	64	61	60	59	57	53	49	44	39	19	2
OCIb IGHV unmutated	123	110	101	75	59	53	41	26	22	16	13	11	8	3	1
VenO IGHV unmutated	121	111	110	103	101	96	90	80	73	68	57	47	37	17	1

Al-Sawaf *et al.*, iwCLL 2023

The poor outcome of unmutated IGHV in Venetoclax + antiCD20 treated patients is reinforced by *TP53* disruption

ii) IGHV

	VenO			
	IGHV mutated		IGHV unmutated	
	With *TP53*^{mut} and/or del(17p)	No *TP53*^{mut} or del(17p)	With *TP53*^{mut} and/or del(17p)	No *TP53*^{mut} or del(17p)
Median PFS, months	NE	NE	50.9	69.0



At Risk:															
VenO IGHV mutated															
TP53^{mut} and/or del(17p)	5	4	4	4	4	4	4	4	4	3	3	2	2		
No *TP53*^{mut} or del(17p)	71	66	64	61	60	57	56	55	53	50	46	42	37	19	2
VenO IGHV unmutated															
TP53^{mut} and/or del(17p)	16	15	14	12	11	10	10	9	8	8	4	4	2	2	
No *TP53*^{mut} or del(17p)	103	94	94	90	89	85	79	70	64	59	52	43	35	15	1

Al-Sawaf *et al.*, iwCLL 2023

Front-line therapeutic algorithm – from 2021 ESMO guidelines to….

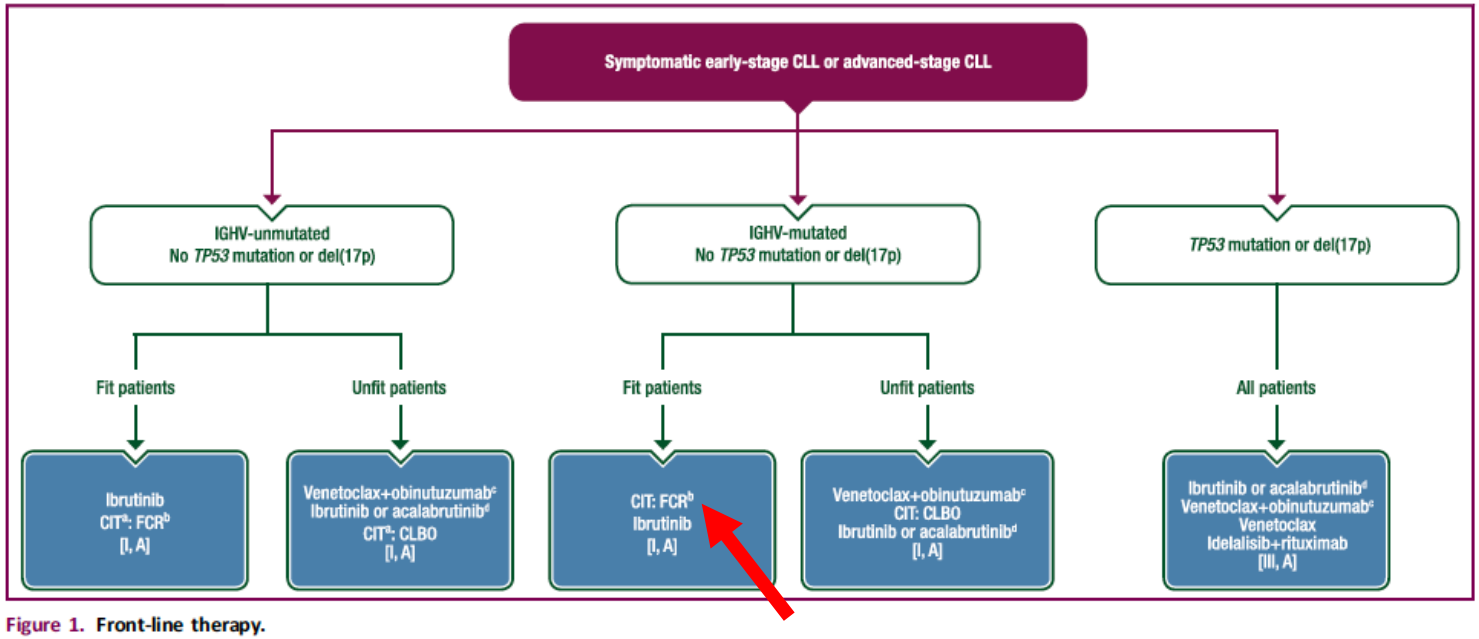


Figure 1. Front-line therapy.

The order of the recommended treatments for each subgroup is based on expert opinion considering time-limited as more valuable therapy, if there is equal evidence for two different treatment options.

BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.

[a] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability.

[b] BR might be considered alternatively in patients above the age of 65 years.

[c] If available.

[d] If approved and available.

Eichhorst et al.,et al, Ann Oncol 2021

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Front-line therapeutic algorithm – ESMO guidelines (2024)

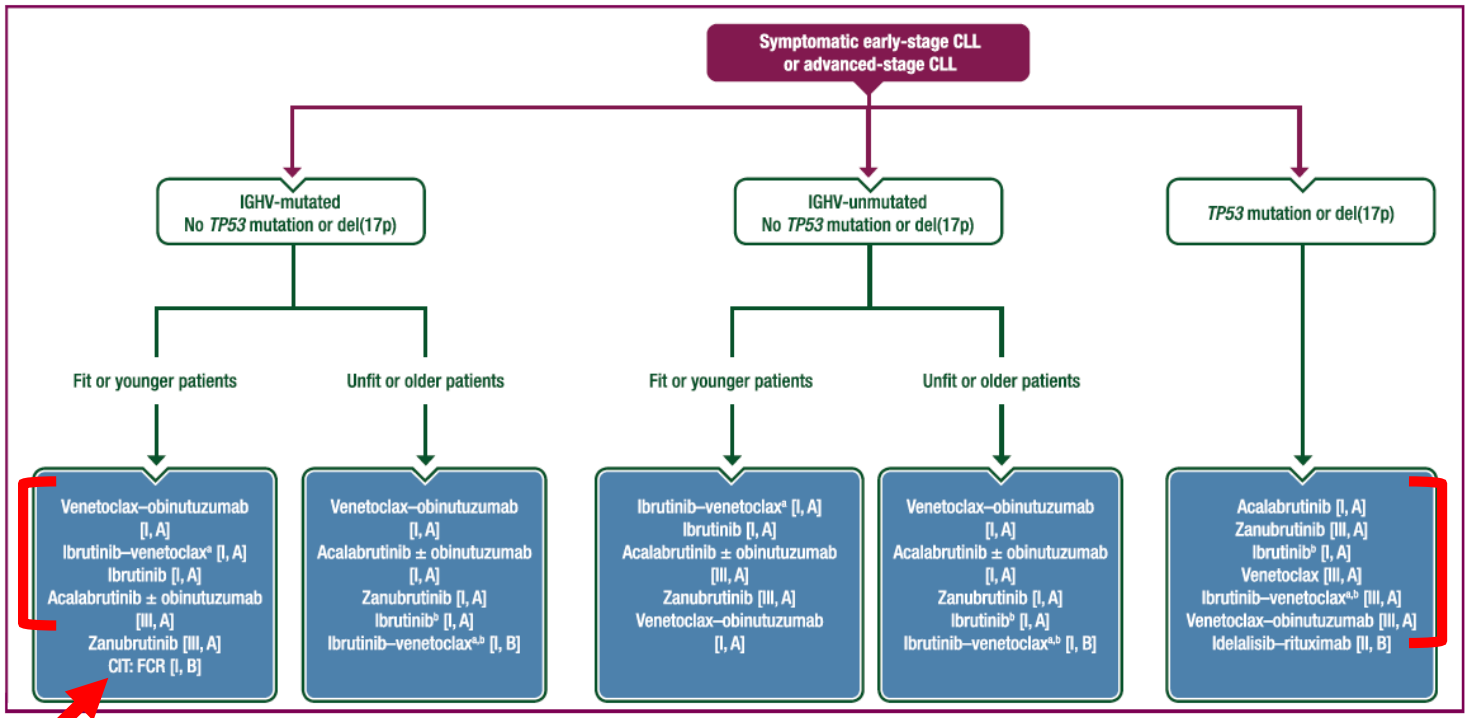

Figure 1. First-line therapy.
The order of the recommended treatments for each subgroup is based on the authors' expert opinion, which considers time-limited therapy as more valuable, if there is equal evidence for different treatment options.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; del, deletion; FCR, fludarabine—cyclophosphamide—rituximab; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease.
[a]Ibrutinib—venetoclax with a 15-month fixed duration or with an MRD-guided duration.
[b]Ibrutinib or ibrutinib—venetoclax should be considered carefully in older patients with cardiac comorbidities.

1) FCR no longer present

2) Same drugs but swopped

Eichhorst et al, Ann Oncol 2024

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Biomarkers in CLL in the era of pathway inhibitors *according to guidelines*

Predictive biomarkers

Less informative today than in the past when the choice was between CIT and target therapies

Prognostic biomarkers

Richter syndrome

Death

Progression

Treatment tailoring

TP53

IGHV

Patient counseling

Frequency of follow-up

Identify those appropriate for early intervention trials

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Biomarkers vs. Patient-characteristics and Risk Stratification in CLL Therapy

IGHV status

TP53 status

Biomarkers:

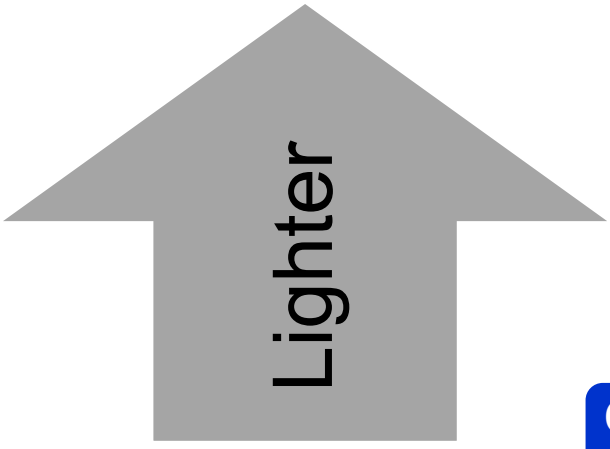
Relative Importance

Patient characteristics:

- Co-morbidities
- Co-therapies
- Logistics
- Preference

Bulky disease

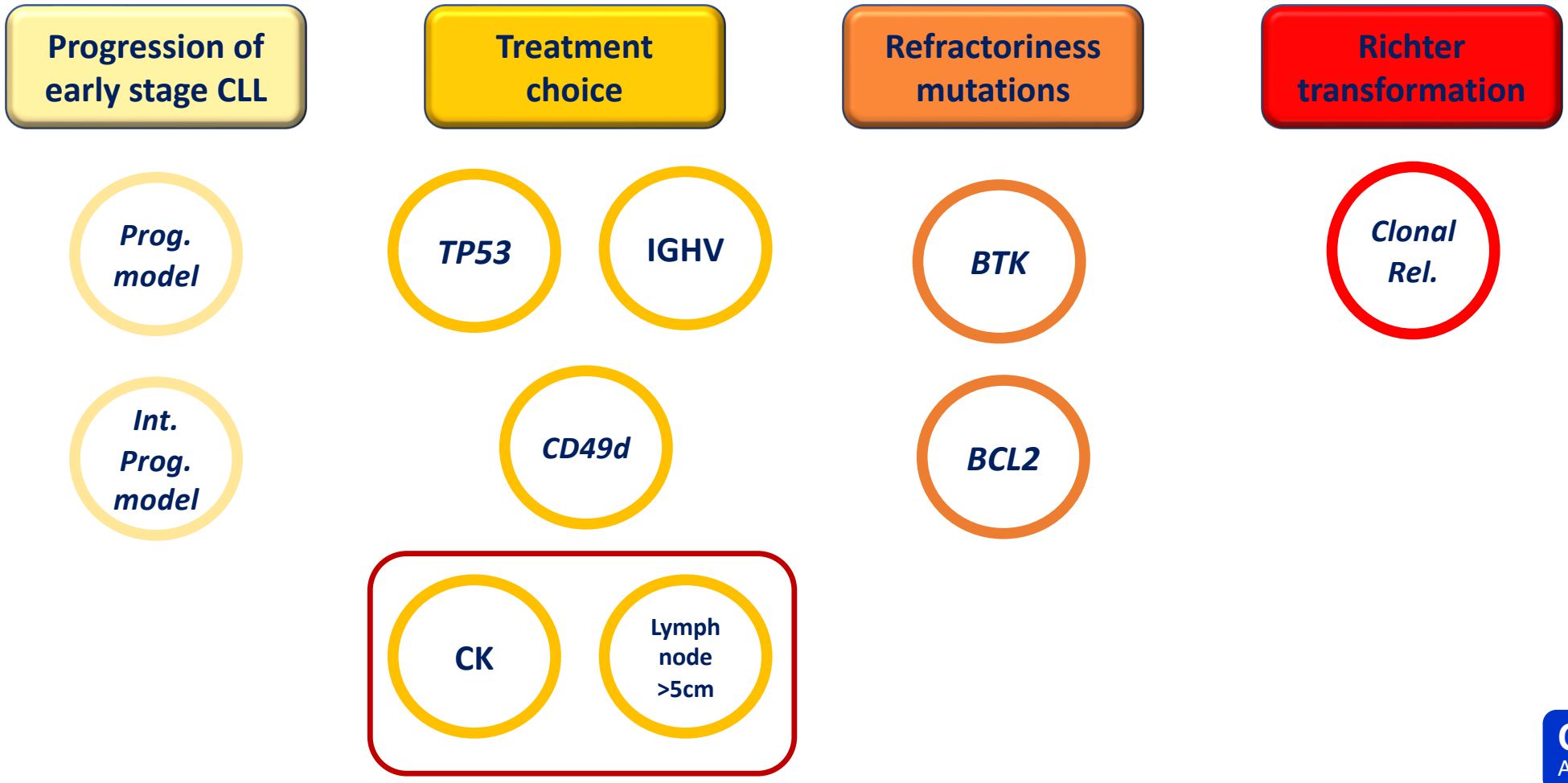
Intolerance/Resistance



Courtesy of Davide Rossi, Bellinzona, CH

CRO AVIANO

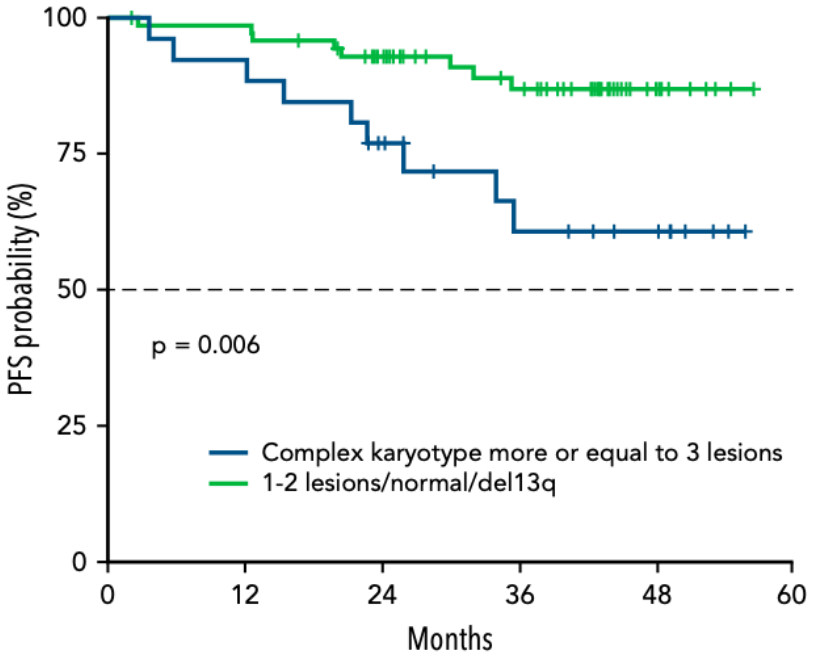
Biomarkers in CLL in the era of pathway inhibitors

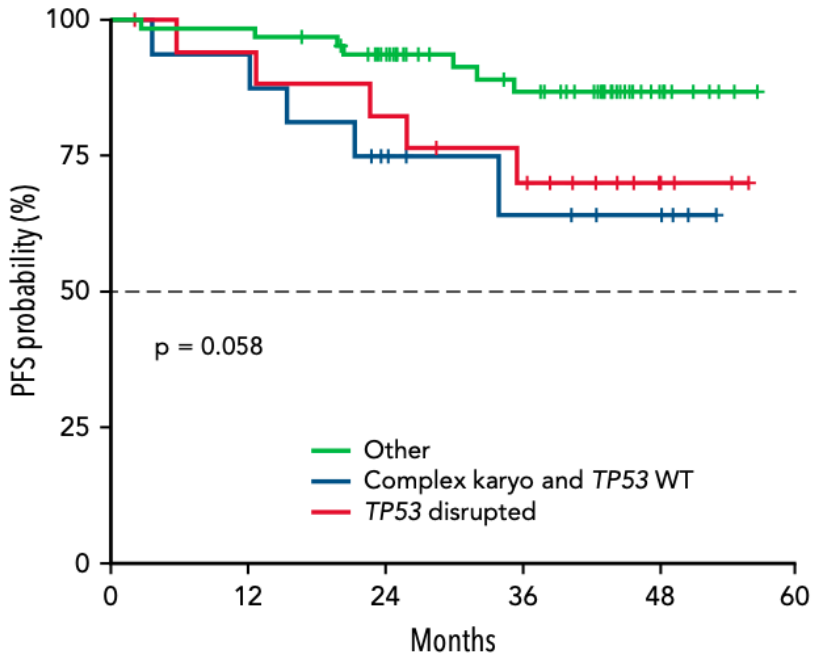


CRO AVIANO

Complex karyotype predicts PFS in ibrutinib-treated patients: Results from the GIMEMA1114 trial

iii) CK





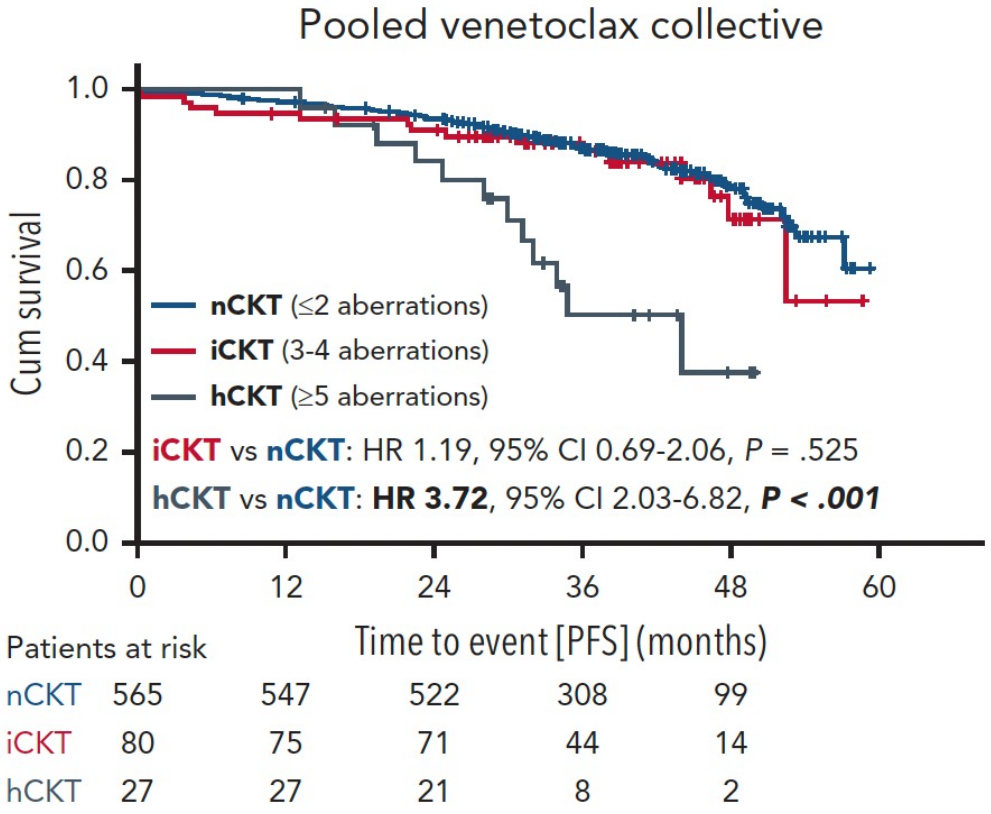
CK>3 lesions = Borderline significance when devoid of TP53 disruption

Rigolin et al., Blood 2021

Molecular predictors of PFS in CLL with venetoclax-based combinations in the CLL13/GAIA trial

iii) CK

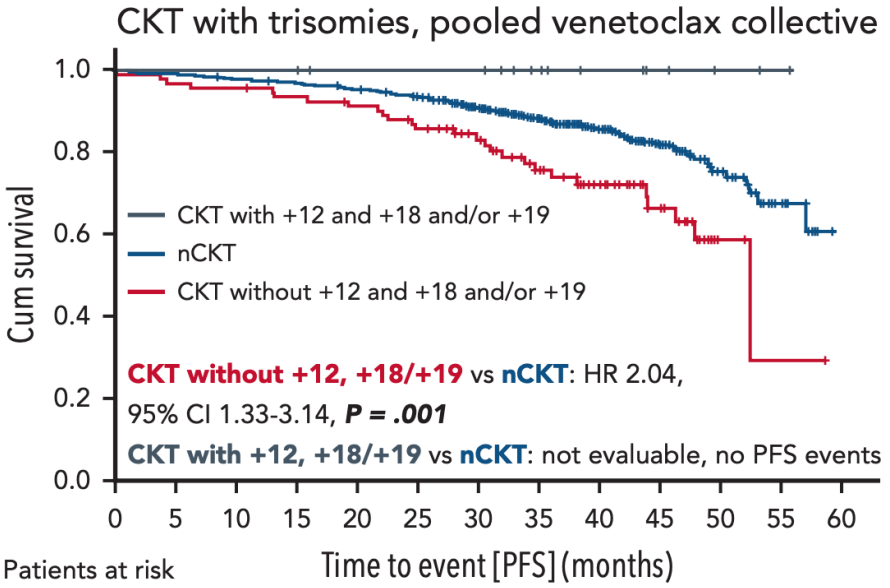
hCKT ➡ poor PFS



Patients at risk					
nCKT	565	547	522	308	99
iCKT	80	75	71	44	14
hCKT	27	27	21	8	2

+12, +18, +19 ➡ excellent PFS

D



Patients at risk					
nCKT	565	547	522	308	99
CKT without +12, +18/19	92	87	79	45	13
CKT with +12, +18/19	15	15	13	7	3

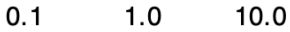
Furstenau et al., Blood 2023

Large lymph nodes predict outcomes in venetoclax-treated patients

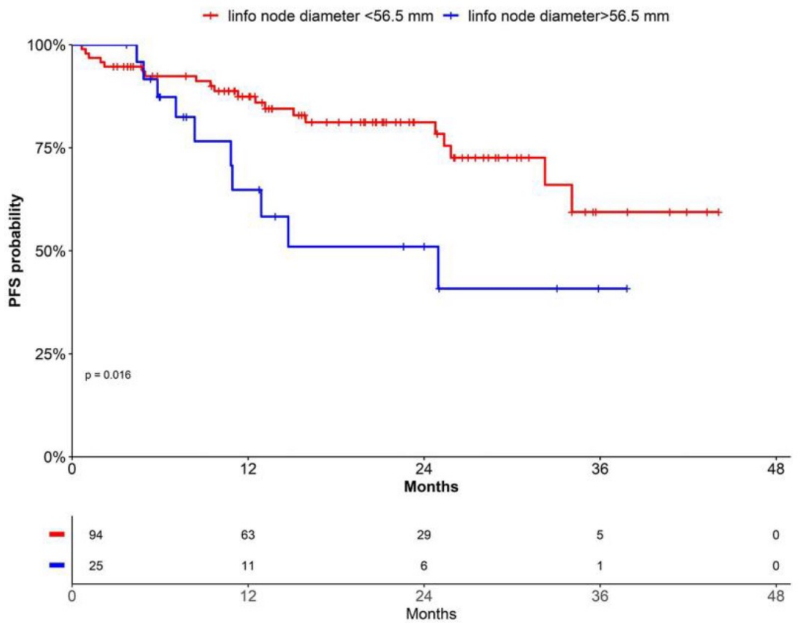
iv) Lymph Node

Multivariate analysis from the CLL14 trial

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Lymph node size			
≥ 5 cm	vs. < 5 cm	2.922	1.849-4.617
Deletion 17p			
del(17p)	vs. no del(17p)	3.578	1.952-6.557

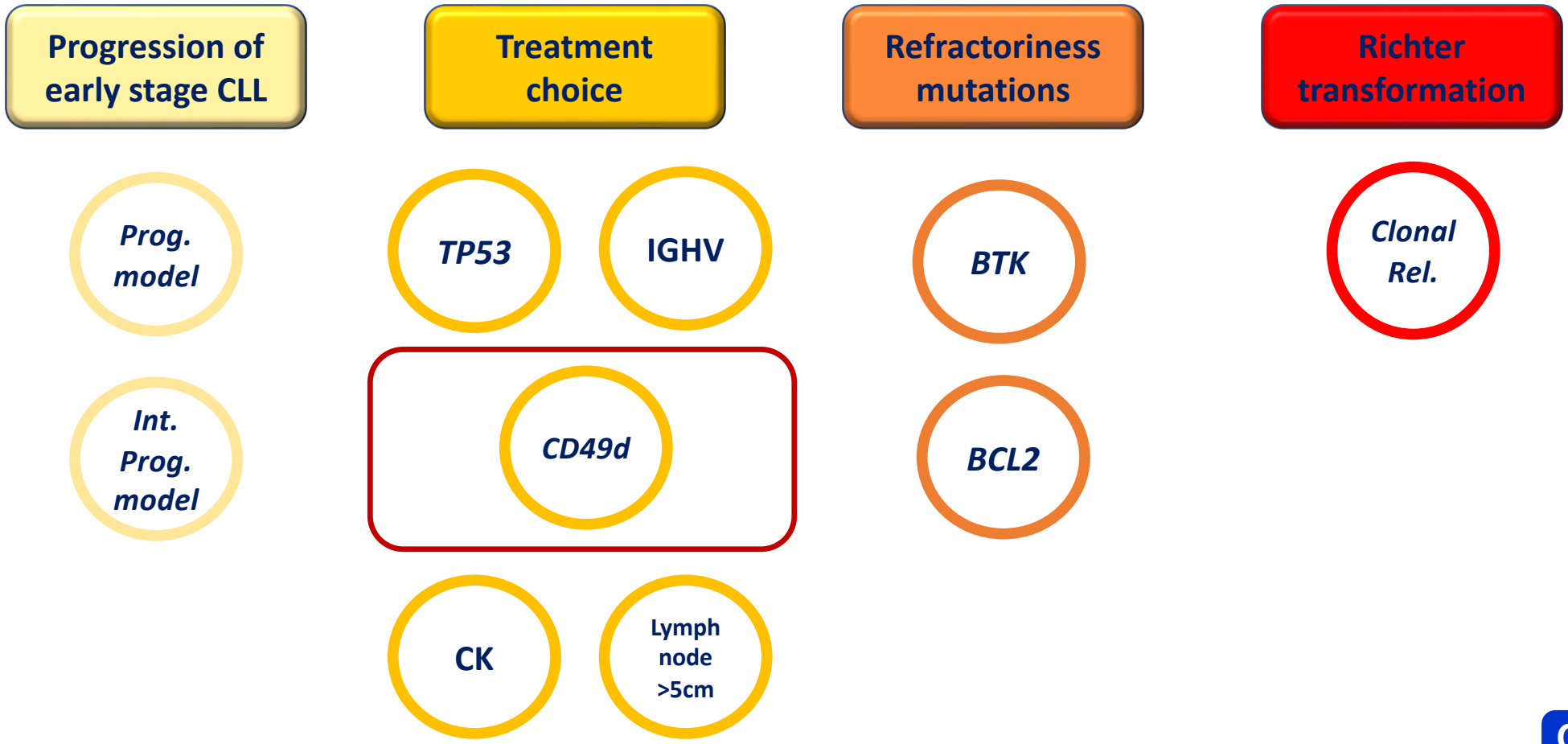


Real-life italian cohort



Al-Sawaf *et al.*, Nat Comm 2023; Autore *et al., Hematol Oncol*. 2023

Biomarkers in CLL in the era of pathway inhibitors



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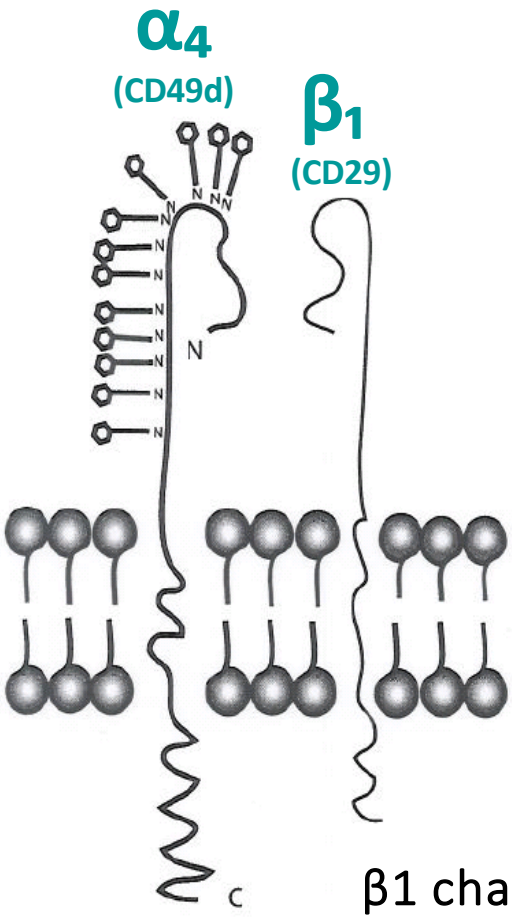
VLA-4 (CD49d/CD29)



- heterodimeric integrin formed by non-covalent association of α_4 (CD49d; 155kDa) and β_1 (CD29; 150kDa) subunits
- It functions as a matrix and cell receptor
- It is expressed on:
  - eosinophils
  - basophils
  - NK cells
  - monocytes
  - T cells
  - B cells
  - thymocytes
  - myeloma cells

β1 chain (CD29) = common chain

α4 chain (CD49d) = binding specificity

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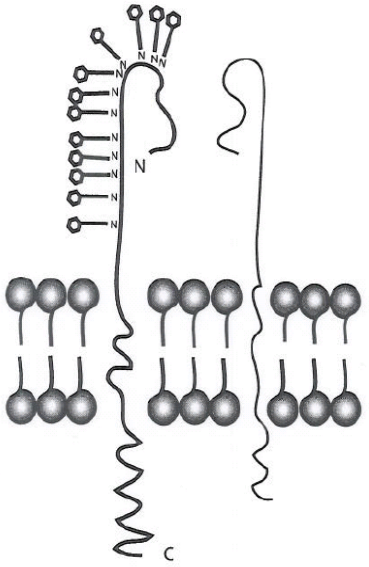
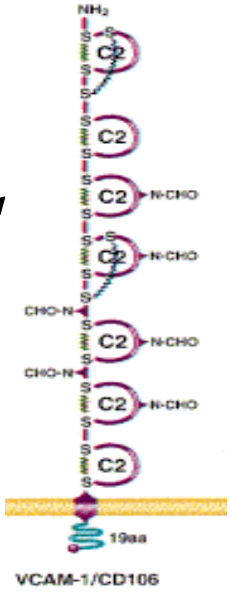
LIGANDS OF CD49d

CD49d

Other Names

Integrin α4-chain, VLA-4-α-chain.

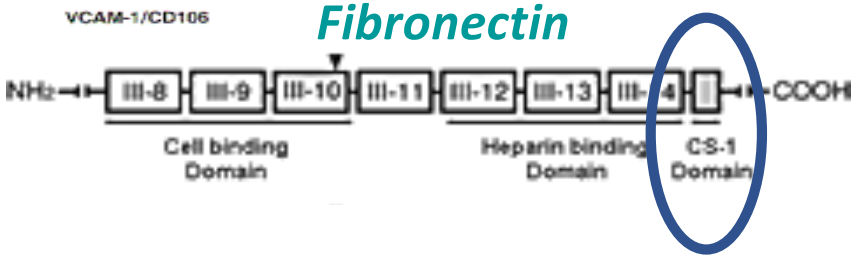




VCAM-1

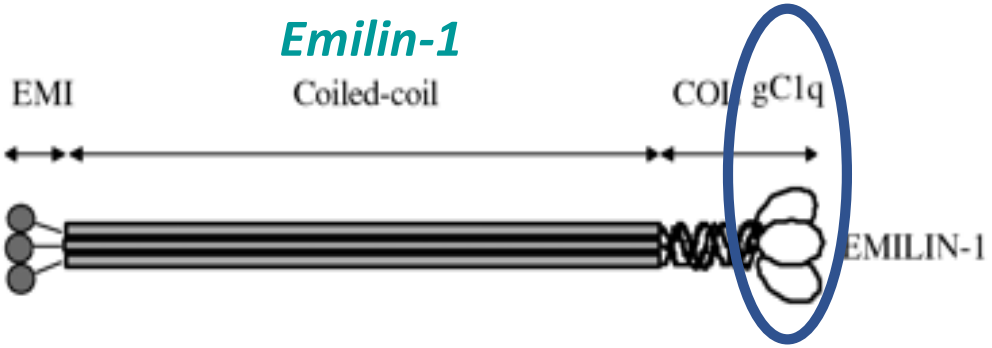
(Elices et al., 1990)

Fibronectin



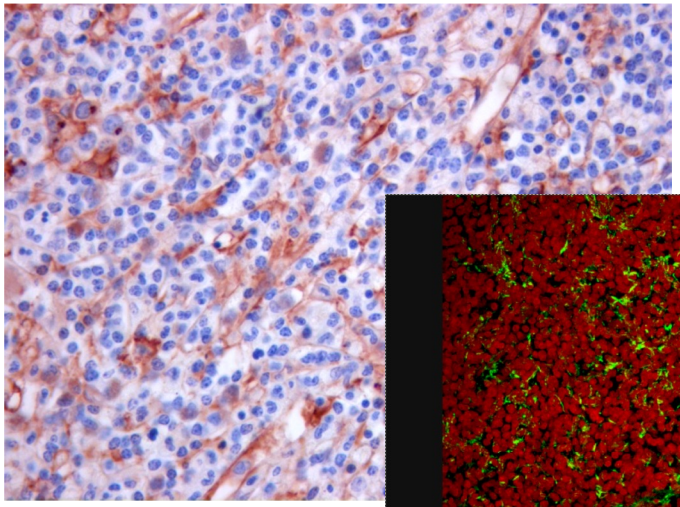
(Wayner et al., 1989)

Emilin-1

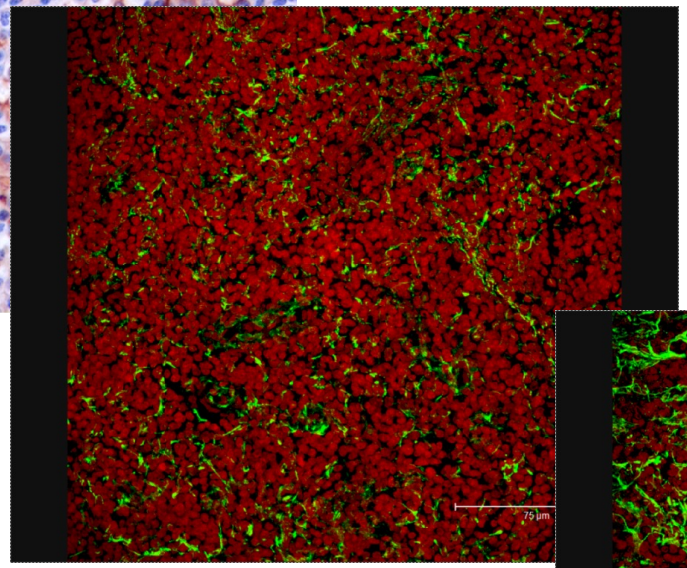


CRO AVIANO

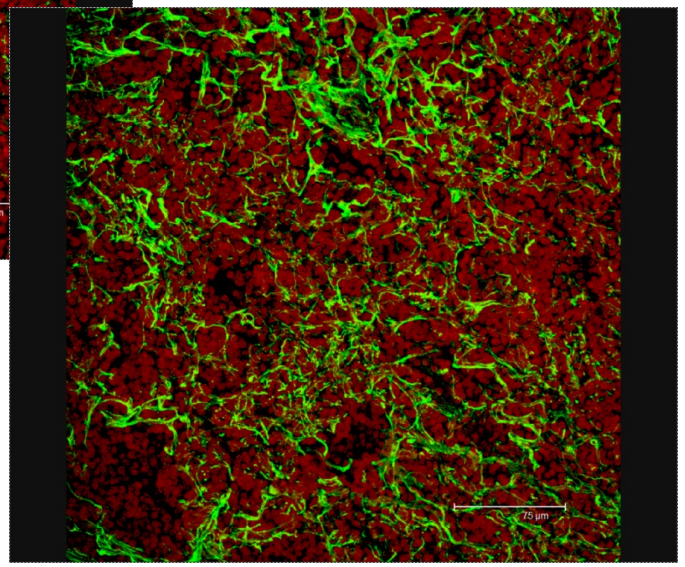
In vivo: CD49d ligands expression in CLL-involved area



VCAM-1



Fibronectin



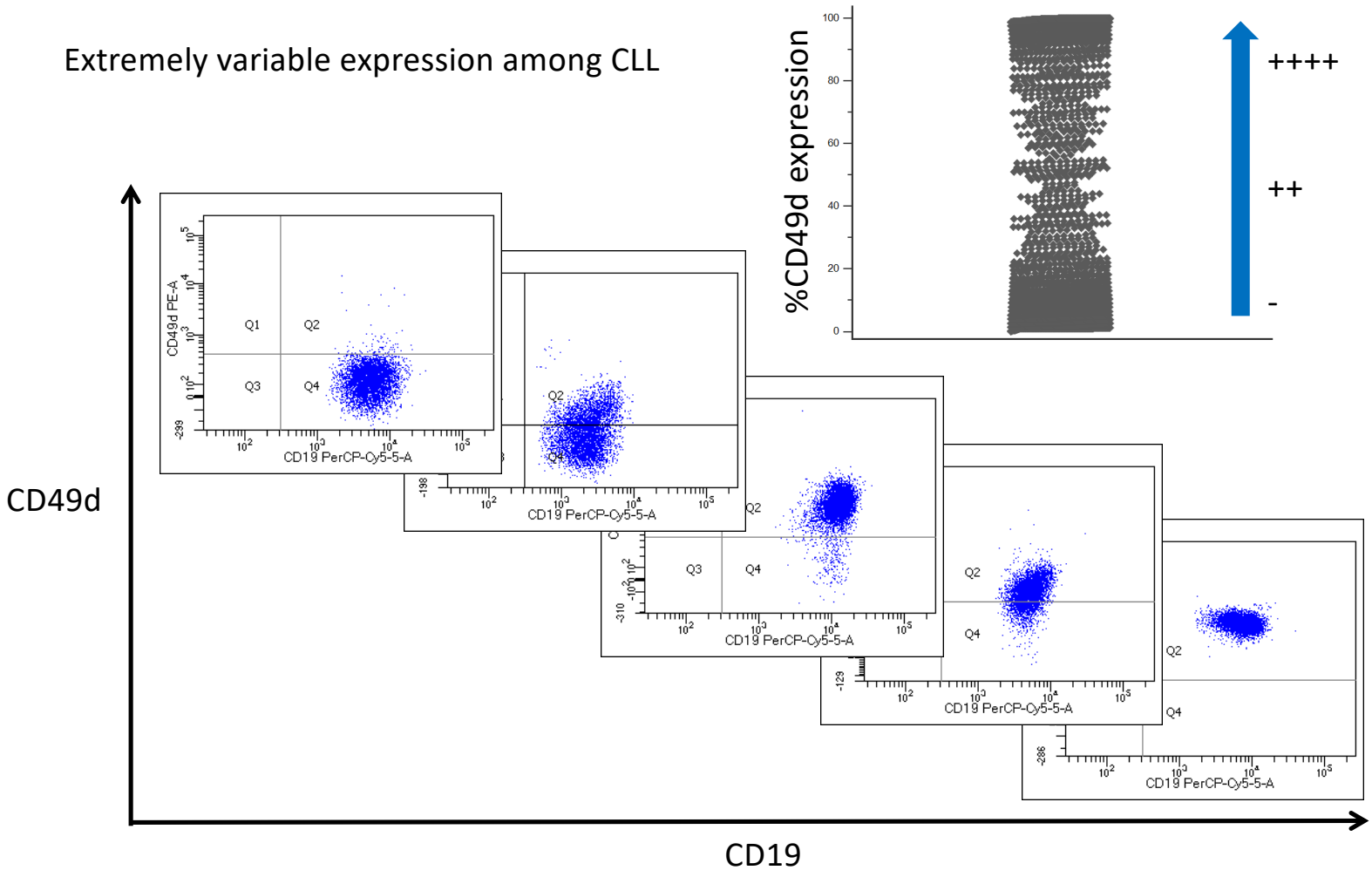
Emilin-1

Zucchetto et al. Cancer Res, 2009
Tissino et al., Hematol Oncol, 2022

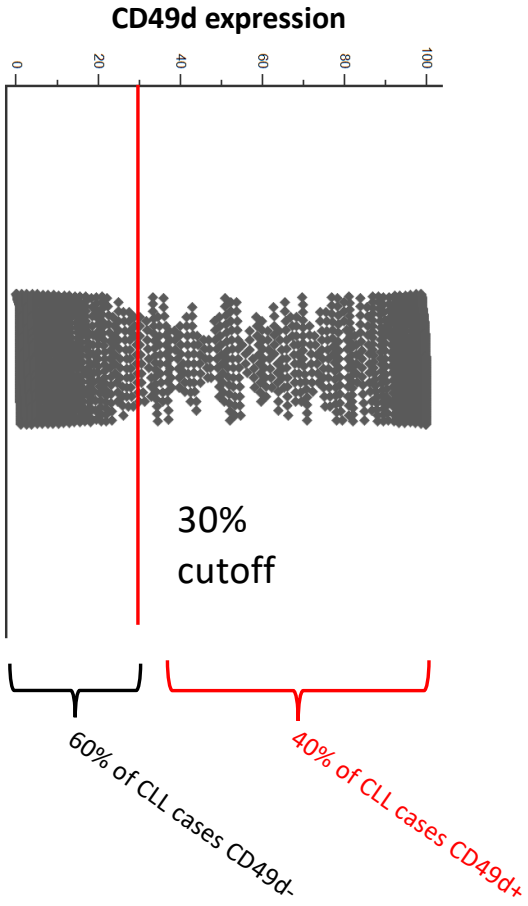
CRO AVIANO

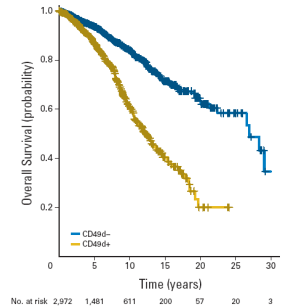
CD49d expression in CLL

Extremely variable expression among CLL



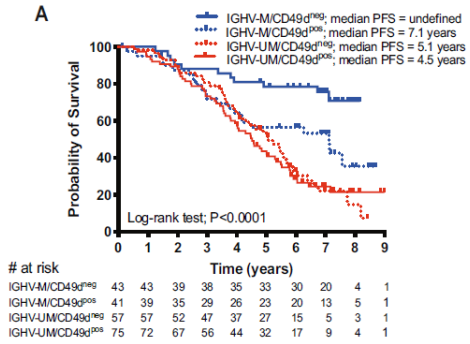
CD49d expression and prognosis





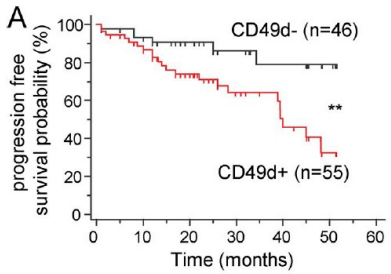
Prognosticator of shorter overall survival and treatment-free survival in the context of chemoimmunotherapy

Gattei V. et al. 2008 Blood; 111:865-73
Shanafelt TD. *et al. 2008 Br J Haematol; 140:537-46*
Bulian P. et al. 2014 JCO; 32:897-904
Tissino E. et al. 2020, Blood; 135:1244-54



Predictor of shorter progression-free survival in the context of FCR/FCR-like regimens (ARCTIC/ADMIRE clinical trials)

Pepper AGS. et al. 2022, Leukemia; 36:271-74



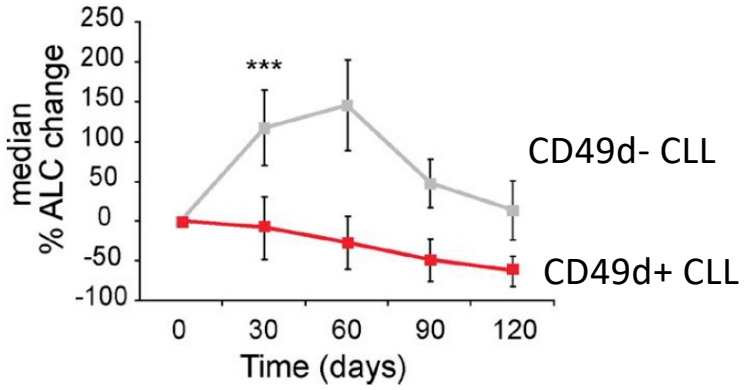
Prognosticator of shorter progression-free survival in the context of BTKi therapy

Tissino E. et al. 2018, J Exp Med; 215:681-97
Tissino E. et al. 2020, Blood; 135:1244-54
Alsadhan A. et al. 2023, Clin Cancer Res

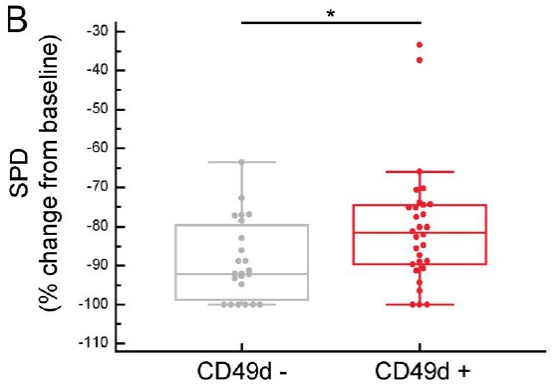
CRO AVIANO

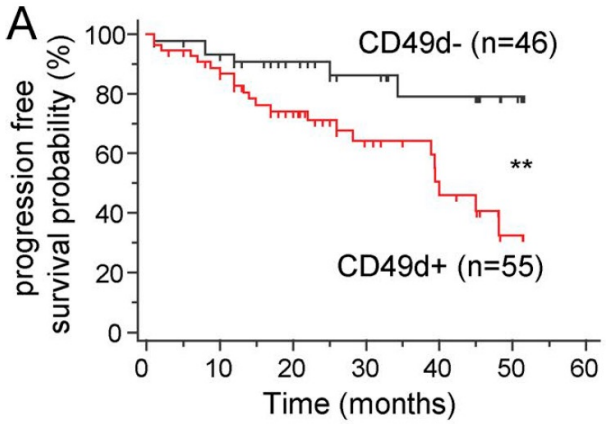
CD49d expression: clinical consequences in ibrutinib-treated CLL

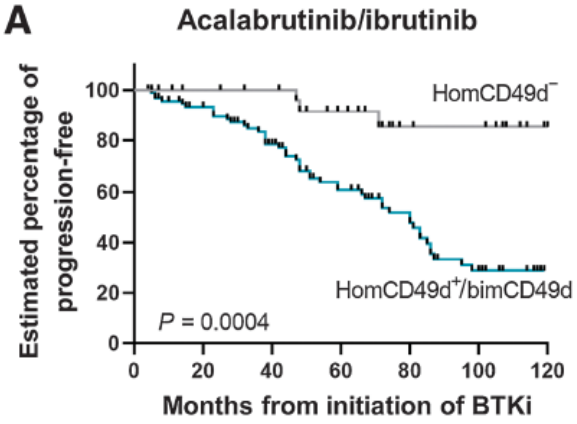
Reduced redistribution lymphocytosis



Reduced lymph node shrinkage





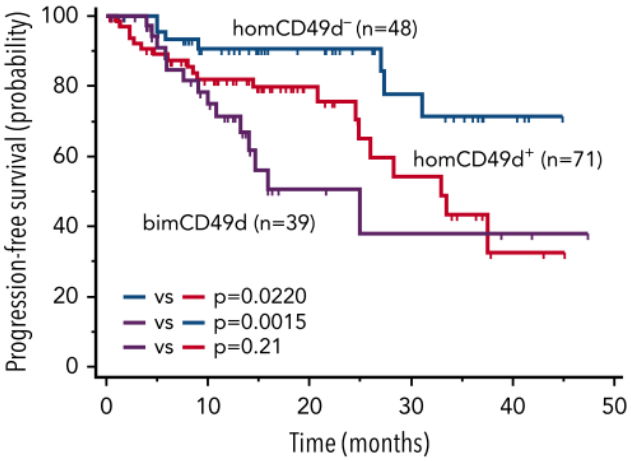


Tissino E. et al. J Exp Med, 2018
Alsadhan A. et al. Clin Cancer Res, 2023

CRO AVIANO

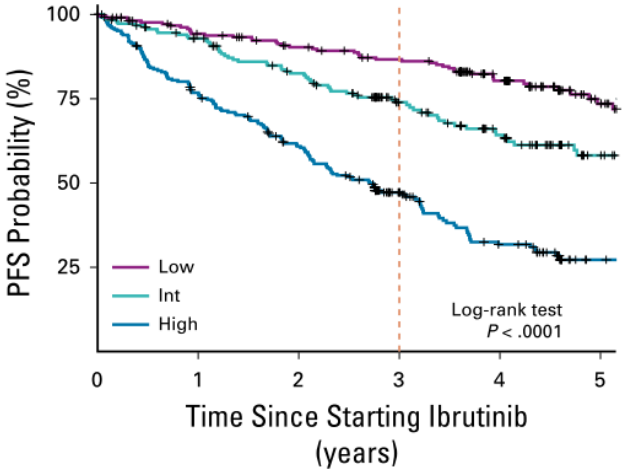
CD49d expression and the 4-factor prediction model for ibrutinib-treated CLL

CD49d expression



Tissino E. et al. 2018, J Exp Med; 215:681-97
Tissino E. et al. 2020, Blood; 135:1244-54
Alsadhan A. et al. 2023, Clin Cancer Res

4-Factor model



0+1 pts (low risk)

2 pts (int. risk)

3+4 pts (high risk)

- *TP53 mut and/or 17p del*
- *B2M >5.0 mg/dl*
- *LDH>250 U/L*
- *Previous lines >0*

Ahn et al, JCO 2021
Morabito *et al., Am J Hematol*. 2021

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CD49d expression and the 4-factor prediction model for ibrutinib-treated CLL

Received: 26 April 2024 | Accepted: 9 June 2024

DOI: 10.1002/hem3.128

HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

LETTER

CD49d expression is included in a revised 4-factor model predicting outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: A multicenter real-world experience

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«real-world» multicenter italian cohort n=410 cases

Bomben et al, HemaSphere 2024

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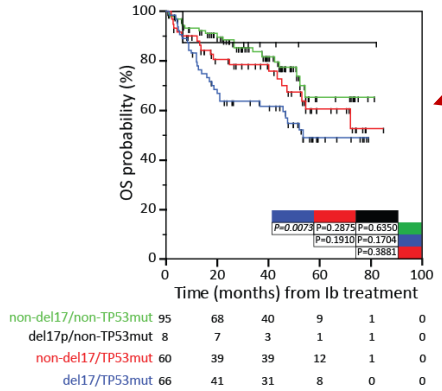
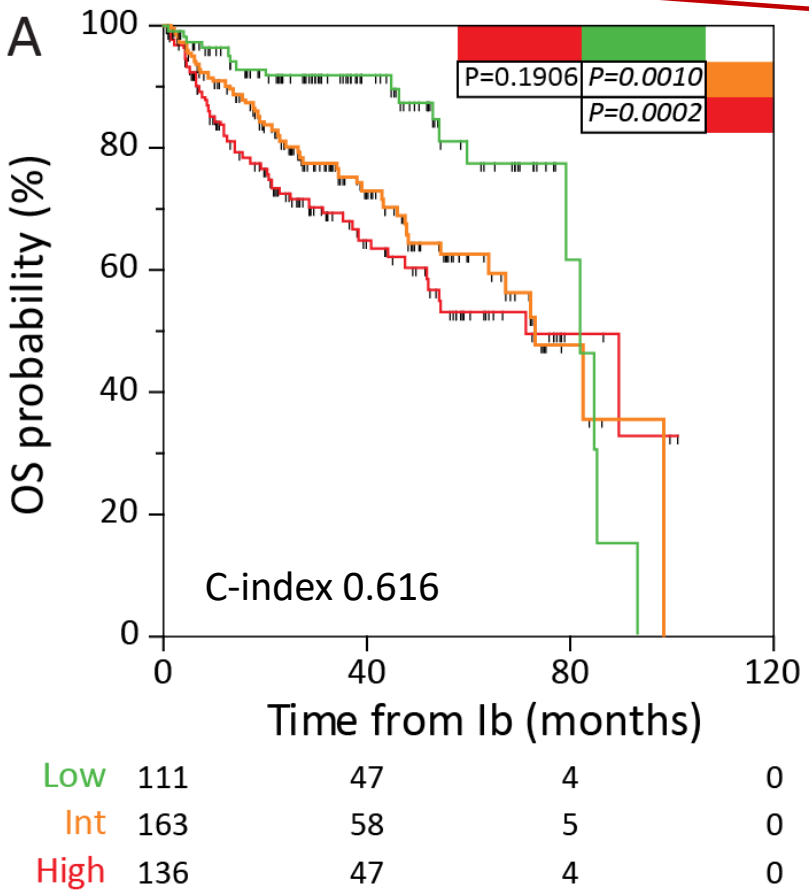
Revision of the canonical 4-factor

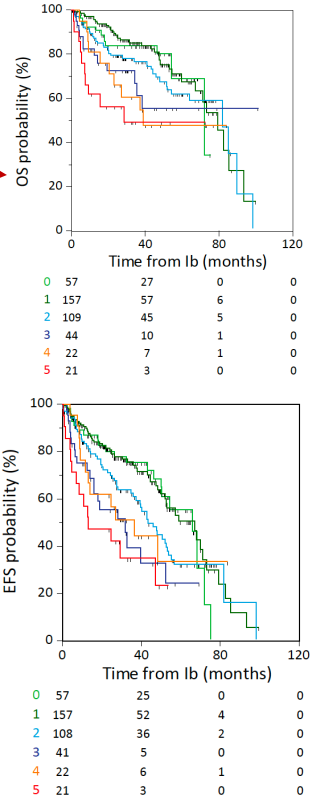


TP53 disrupted = TP53 mut and 17p del

Morabito *et al., Am J Hematol*. 2021
Bomben et al, Leukemia 2023

TP53 mut and/or 17p del
B2M >5.0 mg/dl
LDH>250 U/L
Previous lines>0





Previous lines >1

Bomben et al, HemaSphere 2024

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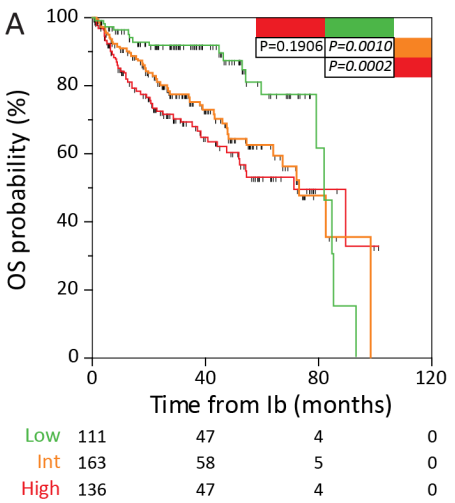
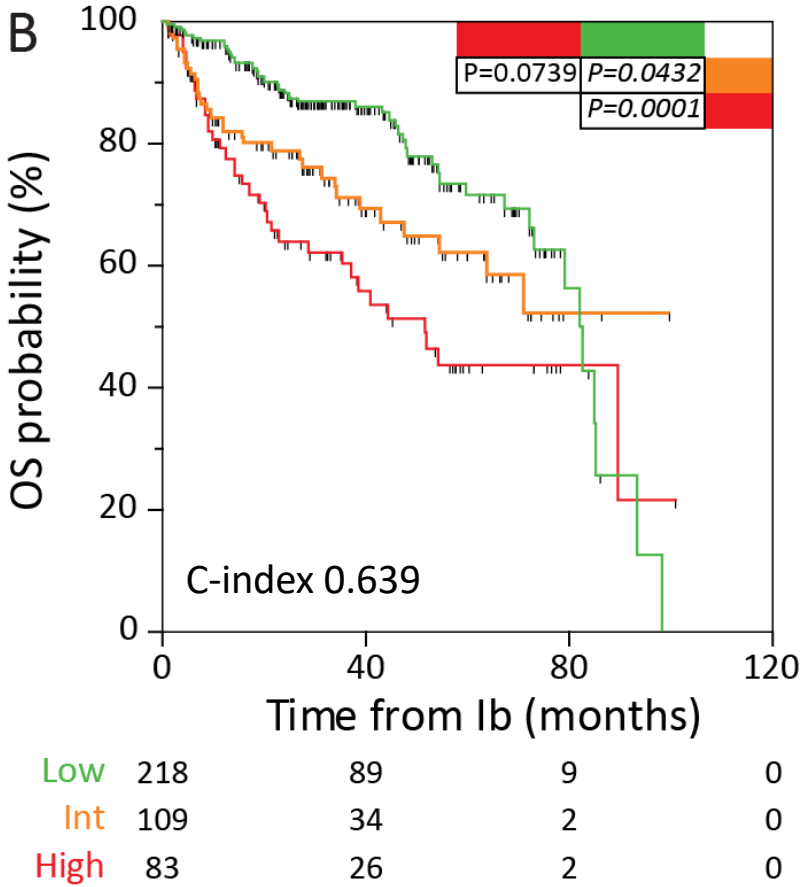
Modified 4-factor

Bomben et al, HemaSphere 2024





*TP53 mut **and** 17p del*
B2M >5.0 mg/dl
LDH>250 U/L
*Previous lines**>1***

The modified 4-factor outperformed the canonical 4-factor score (C-indices 0.616 vs 0.639; P<0.0001).

Modified 4-factor and CD49d

Bomben et al, HemaSphere 2024

MVA 1

	UVA				MVA			
	HR	LCI	UCI	P	HR	LCI	UCI	P
CD49d (low vs high+bimodal)	2.20	1.40	3.45	***0.0006***	1.96	1.24	3.10	***0.0040***
Modified 4-factor intermediate[a]	1.59	1.01	2.49	***0.0455***	1.55	0.98	2.43	0.0585
Modified 4-factor high[a]	2.40	1.55	3.72	***0.0001***	2.10	1.34	3.24	***0.0011***

MVA 2

	UVA				MVA			
	HR	LCI	UCI	P	HR	LCI	UCI	P
Previous Line of therapy (0-1 versus >1)	1.70	1.17	2.49	***0.0053***	1.75	1.19	2.57	***0.0043***
β2M (low vs high)	1.62	1.10	2.39	***0.0141***	1.49	1.01	2.20	***0.0451***
TP53 disruption (wt, del17p only, TP53 mut only versus del17p and TP53 mut)	1.50	1.01	2.21	***0.0445***	1.54	1.03	2.31	***0.0374***
CD49d (low vs high+bimodal)	2.20	1.40	3.45	***0.0006***	2.16	1.36	3.43	***0.0011***
LDH (low vs high)	1.68	1.16	2.43	***0.0061***	ni			

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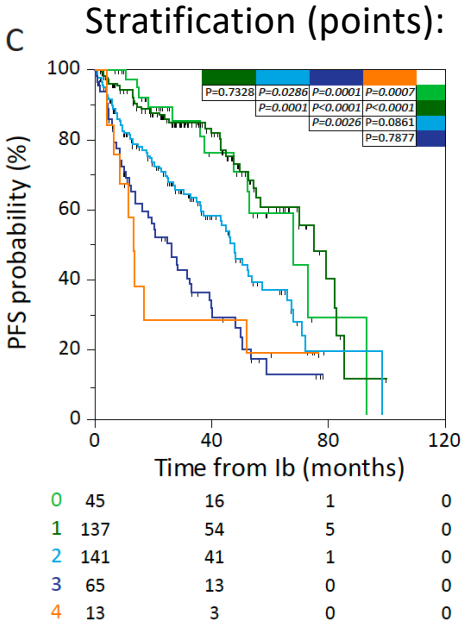
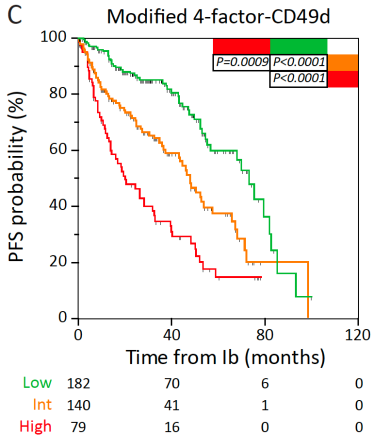
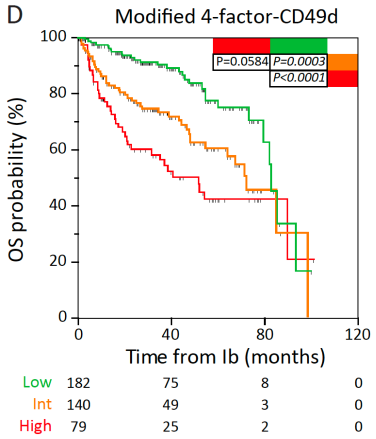
Novel 4-factor-CD49d

Bomben et al, HemaSphere 2024



- 0+1 (low risk)
- 2 (int. risk)
- 3+4 (high risk)





The 4-factor-CD49d outperformed the modified 4-factor score
(C-indices 0.663 vs 0.639; P<0.0001)

1 - TP53 disruption (mutation & deletion)

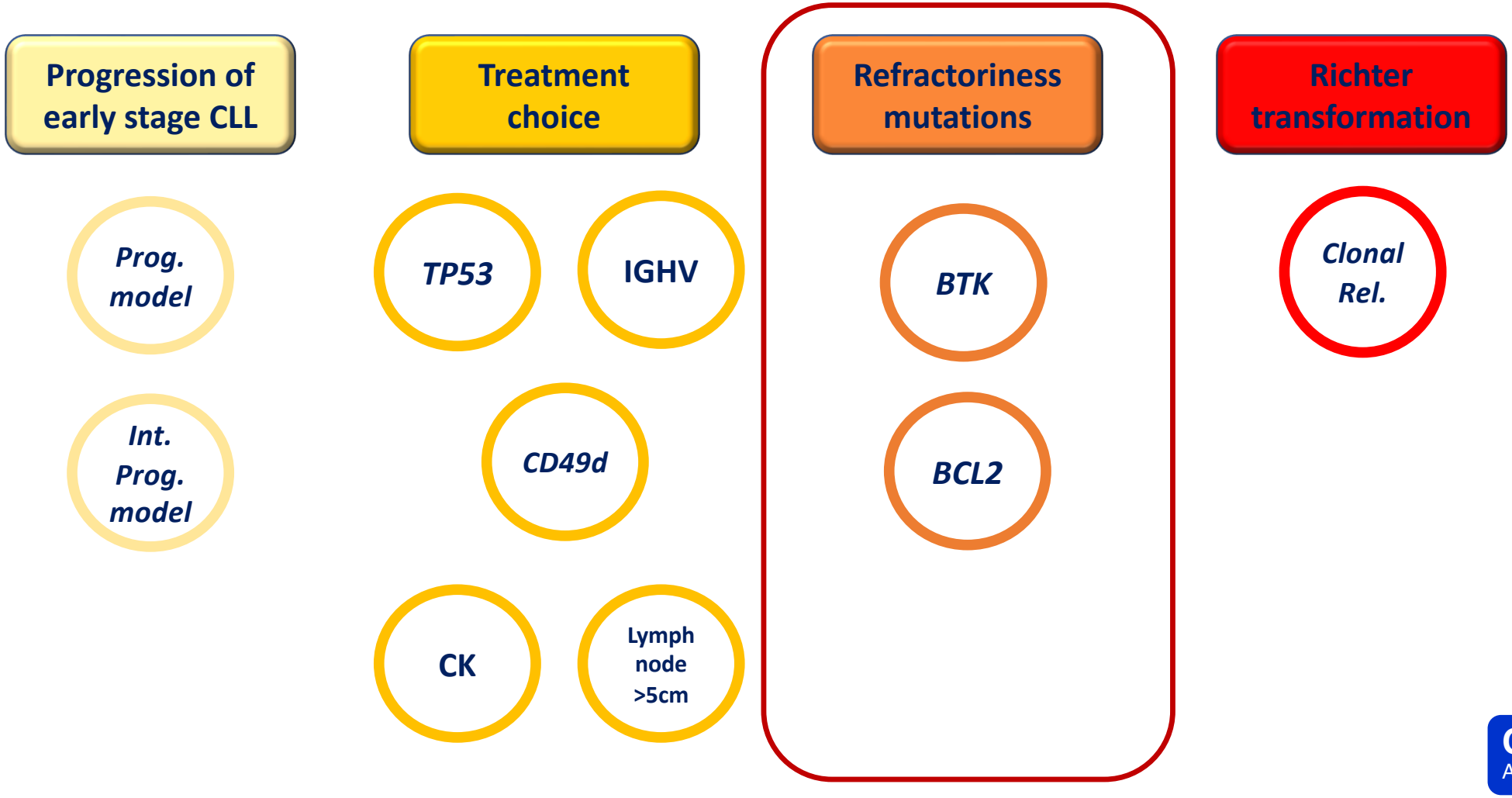
2 – High B2M serum levels (>5.0 mg/dl)

3 – >1 previous line of therapy

4 – High CD49d expression

CRO AVIANO

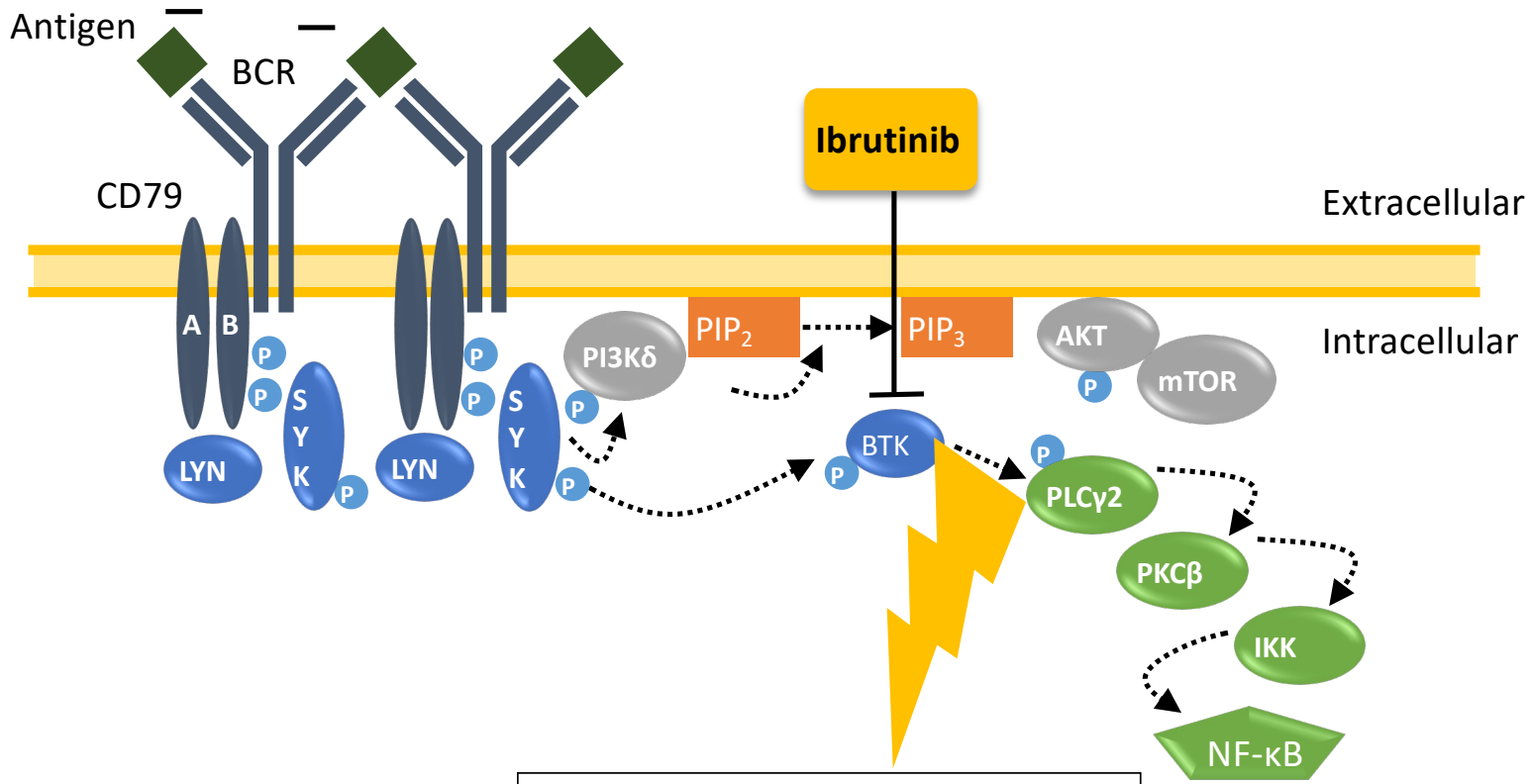
Biomarkers in CLL in the era of pathway inhibitors



CRO AVIANO

BTK mutations can be responsible for BTKi resistance

2/3 of refractory/relapsing patients

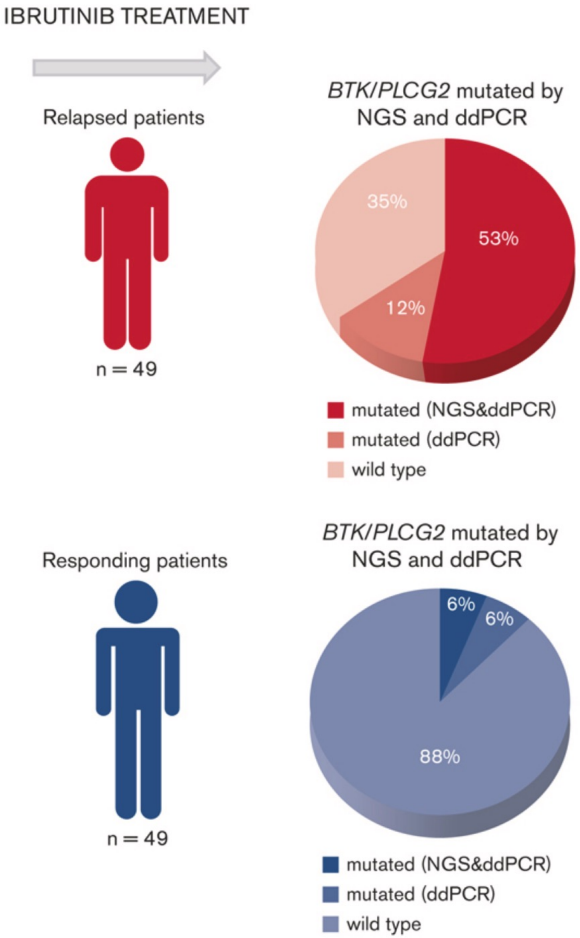


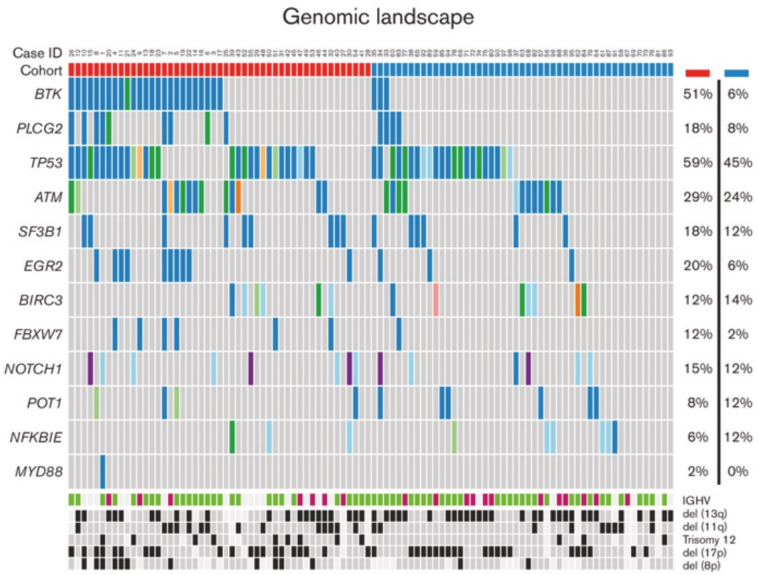
***BTK* C481S mutation**
***PLCG2* mutation**
Absent in ibrutinib naïve patients

Wiestner, JCO 2013
Woyach, NEJM 2014
Famà, Blood 2014

CRO AVIANO

BTK mutations are not the sole responsible for BTKi resistance





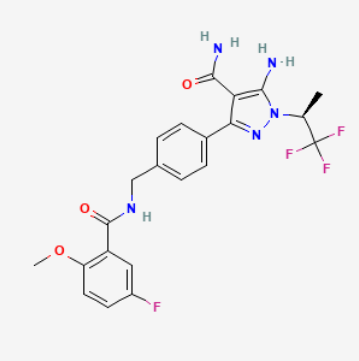
- **One-third of patients** with CLL relapsing on ibrutinib do not carry BTK/PLCG2 mutations, even with a 0.1% sensitivity
- **Additional mechanisms**, such as del(8p), EGR2 and NF-κB pathway mutations, may be cooperating in determining progression on ibrutinib

Bonfiglio *et al., Blood Adv* 2023

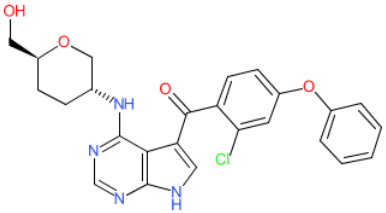
CRO AVIANO

Non-covalent BTK-Inhibitors in CLL inhibit both wildtype and C481-mutant BTK

Pirtobrutinib

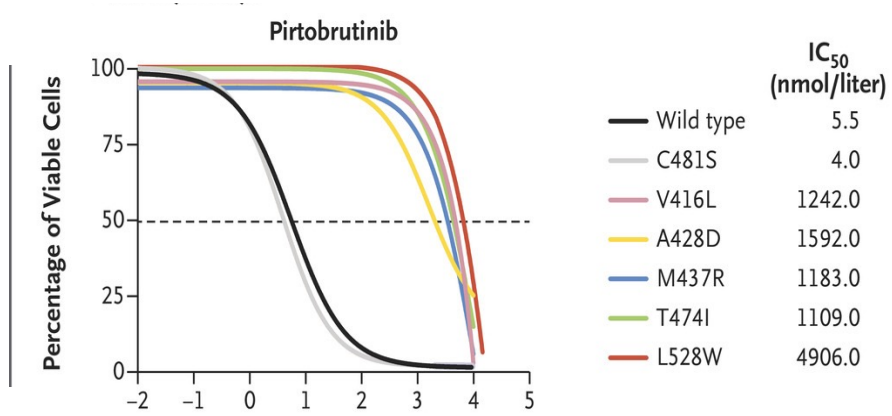


Nemtabrutinib



Non-covalent Covalent

	Pirtobrutinib	Nemtabrutinib	Vecabrutinib	Fenebrutinib	Ibrutinib	Acalabrutinib	Zanubrutinib
Wild type	Normal	Normal	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal	Decreased	Decreased
L528W	None	None	Decreased	Normal	None	Decreased	None
C481S	Normal	Normal	Normal	Normal	Decreased	Decreased	Decreased

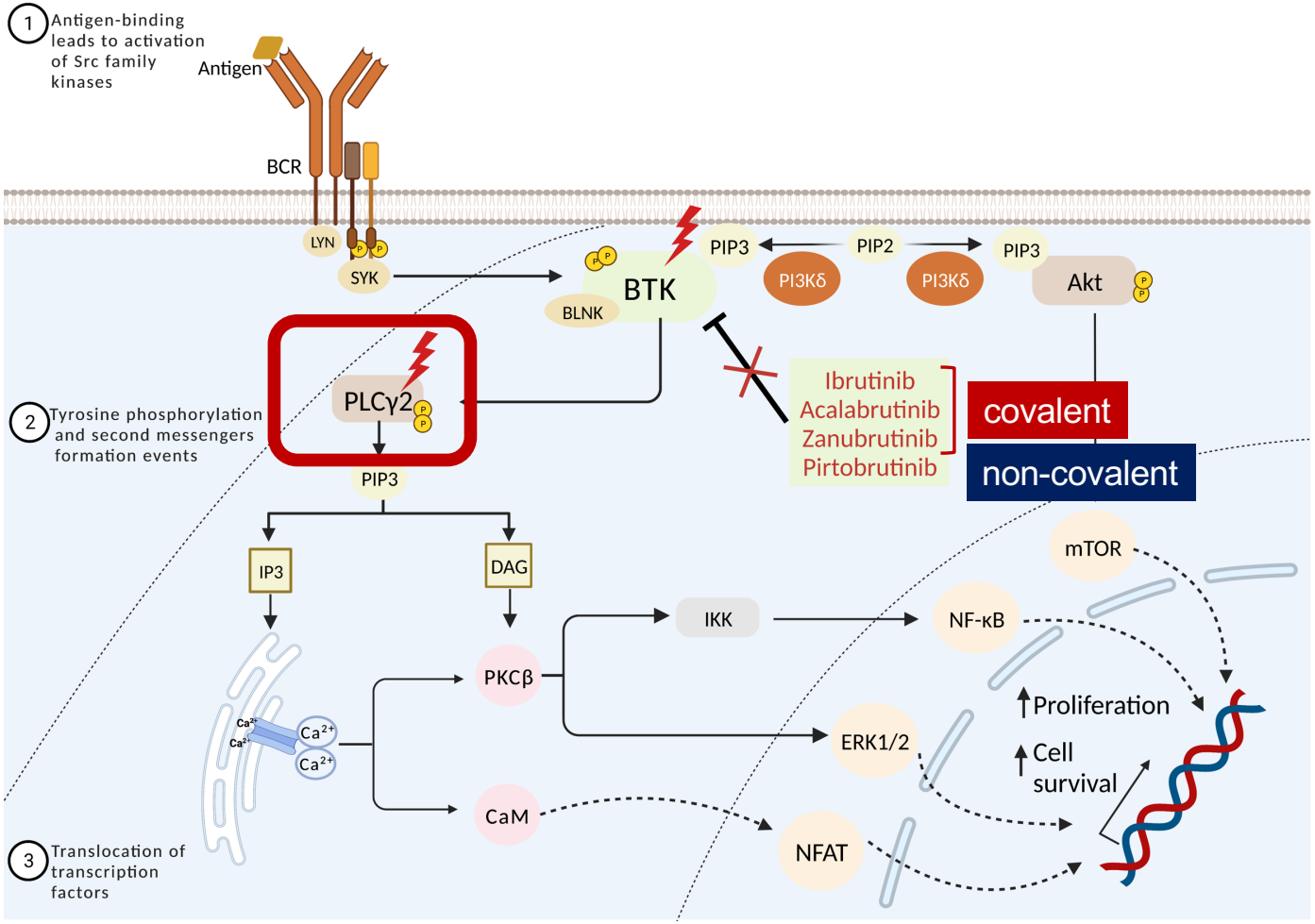


Zain R, et al. Front. Immunol. 2021; 12:694853.

Blombery *et al., Blood Adv*. 2022

CRO AVIANO

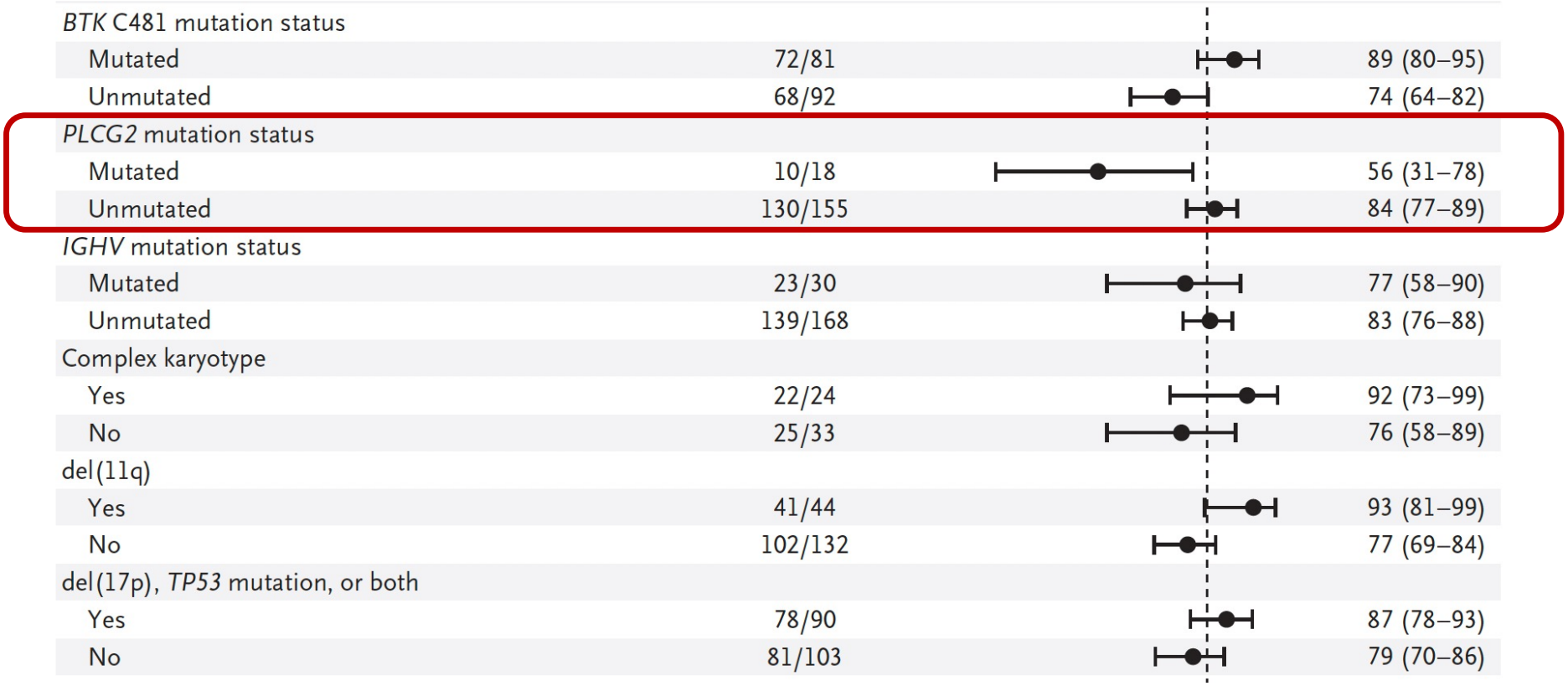
Gain-of-function PLCγ2 mutations bypass BTK targeting and constitutively activate BCR signalling



Maher et al, Int J Mol Sci 2023

CRO AVIANO

Response to the non-covalent BTK inhibitor pirtobrutinib according to biomarkers in the Bruin phase 1-2 trial for CLL previously treated with covalent BTKi



BTK C481 mutation status		
Mutated	72/81	89 (80–95)
Unmutated	68/92	74 (64–82)
PLCG2 mutation status		
Mutated	10/18	56 (31–78)
Unmutated	130/155	84 (77–89)
IGHV mutation status		
Mutated	23/30	77 (58–90)
Unmutated	139/168	83 (76–88)
Complex karyotype		
Yes	22/24	92 (73–99)
No	25/33	76 (58–89)
del(11q)		
Yes	41/44	93 (81–99)
No	102/132	77 (69–84)
del(17p), *TP53* mutation, or both		
Yes	78/90	87 (78–93)
No	81/103	79 (70–86)

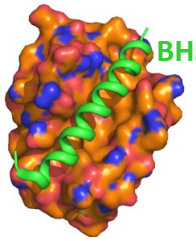
Response was 70-80% across clinical and molecular subgroups, with the **exception of patients expressing PLCG2 mutations**, for which additional data are needed

Mato et al, NEJM 2023

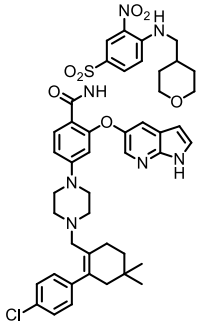
CRO AVIANO

Venetoclax Is a Highly Selective, Potent, Oral BCL-2 Inhibitor Designed to Induce Apoptosis in Malignant Cells

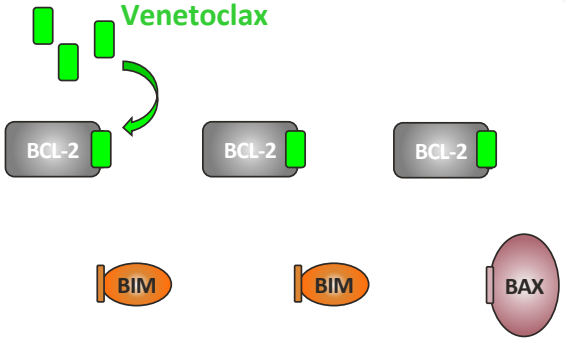
Pro-survival proteins (e.g. BCL-2) sequester pro-death proteins by binding to their BH3 motifs[1,2]

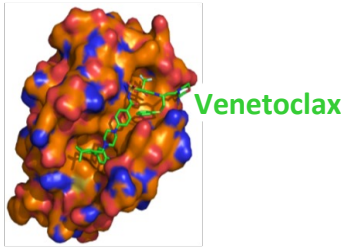


Venetoclax[3]



Venetoclax competes for binding to pro-survival proteins, freeing pro-death proteins[3–5]



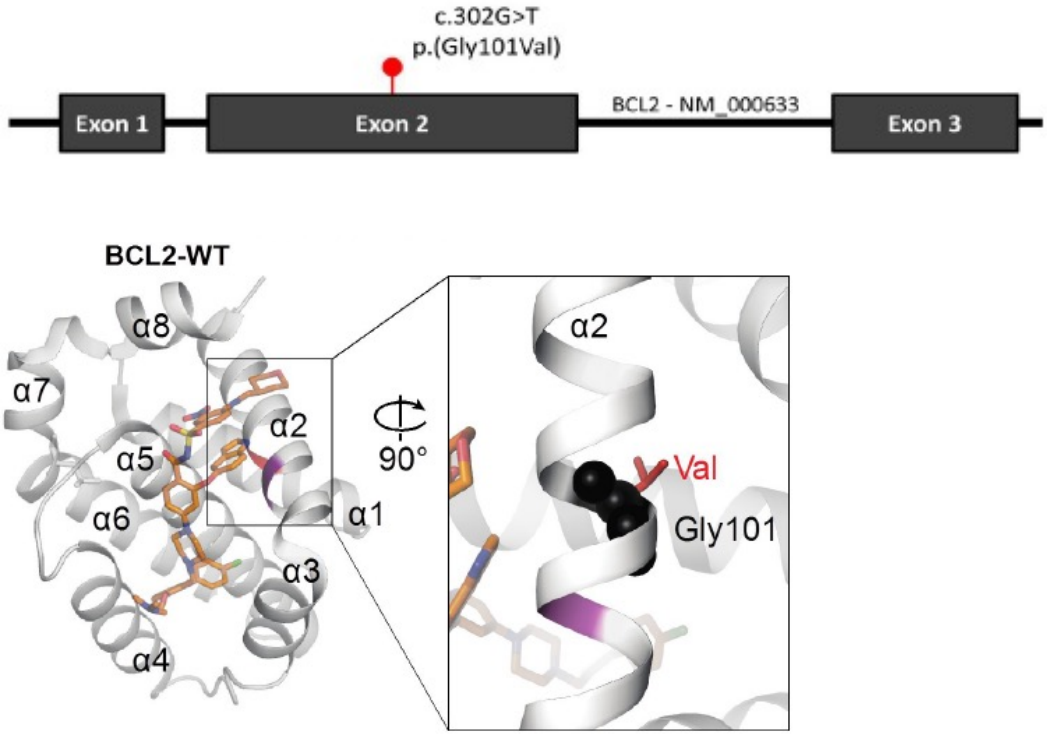


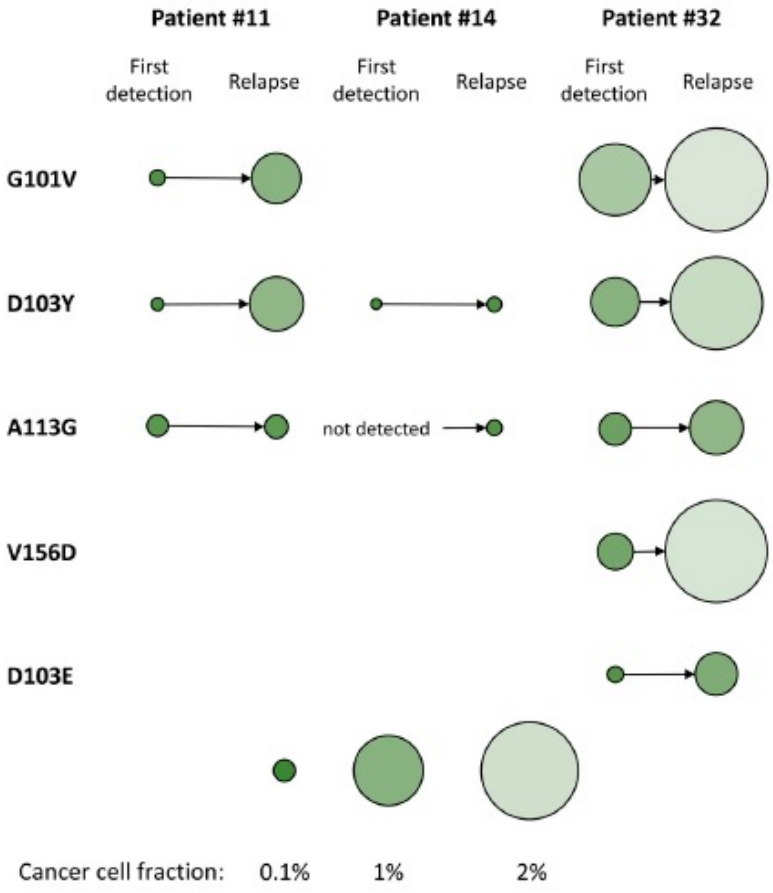
1. Plati J, *et al. Integr Biol (Camb)* 2011; **3:**279–296; 2. Czabotar PE, *et al. Nat Rev Mol Cell Biol* 2014; **15:**49–63;
3. Souers AJ, *et al. Nat Med* 2013; **19:**202–208 (incl. suppl.); 4. Oltersdorf T, *et al. Nature* 2005; **435:**677–681; 5. Tse C, *et al. Cancer Res* 2008; **68:**3421–3428.

CRO AVIANO

Prognosticators/Predictors in the context of BCL2 inhibitors

Gly101Val was the first identified = reduced the ability of VEN to displace **BIM**



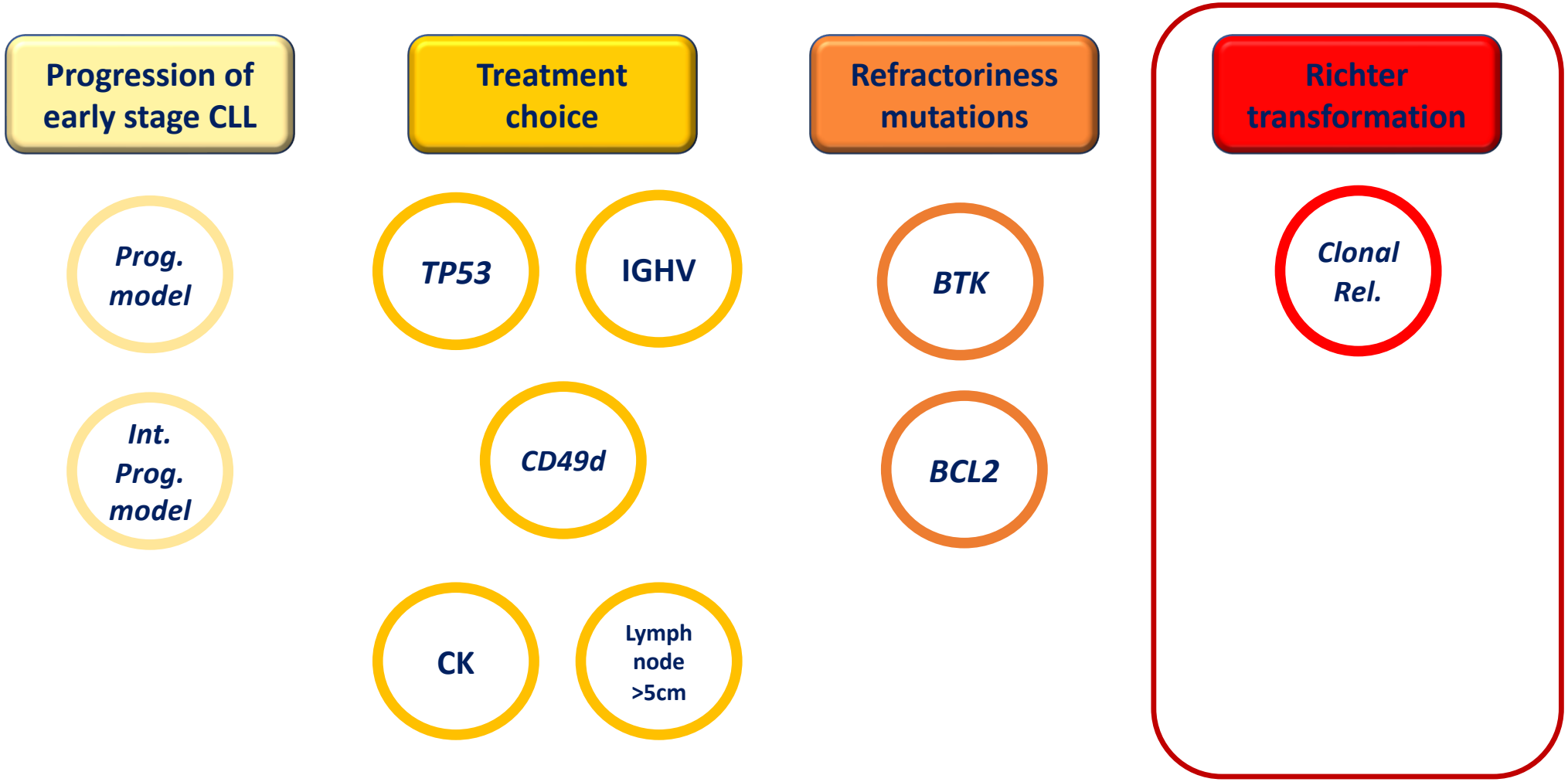


Blombery, P., et al., Cancer discovery, 2018. Blombery P., et al., ASH 2018, oral abstract LBA-7

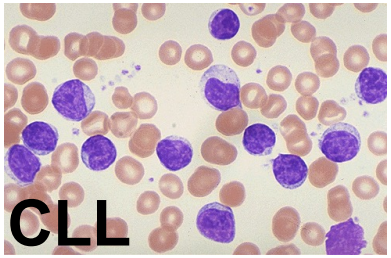
CRO AVIANO

Biomarkers in CLL in the era of pathway inhibitors

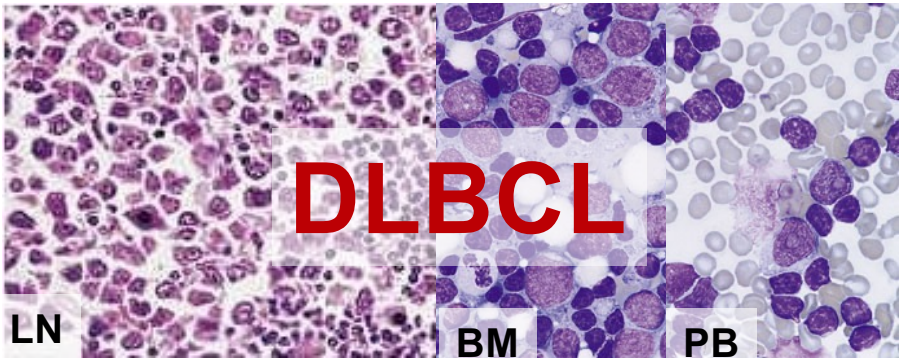
CRO AVIANO



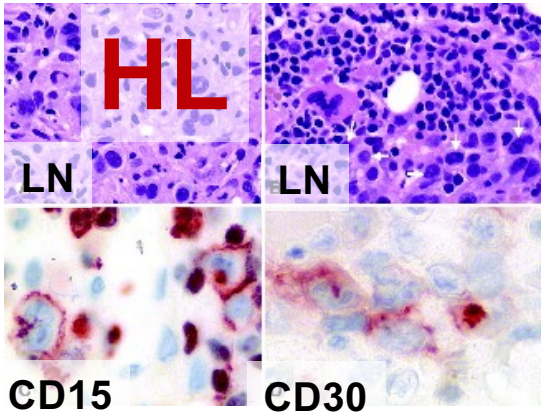
Definition of Richter syndrome



95-99%

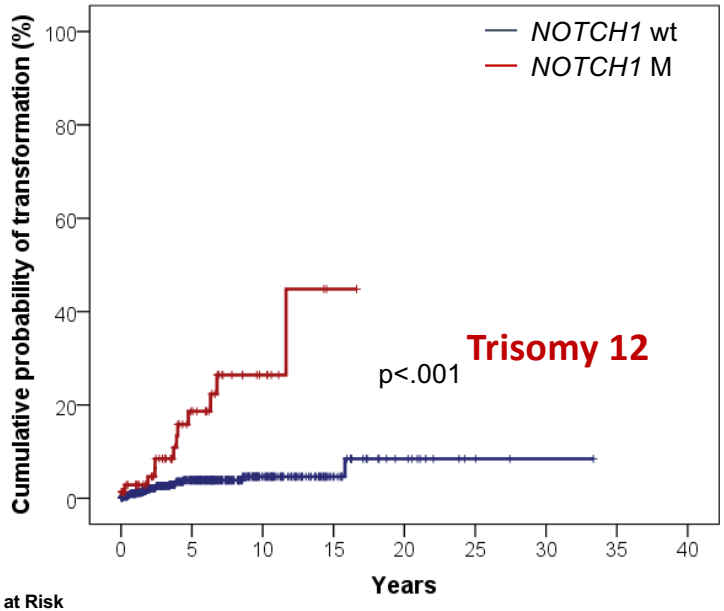


1-5%



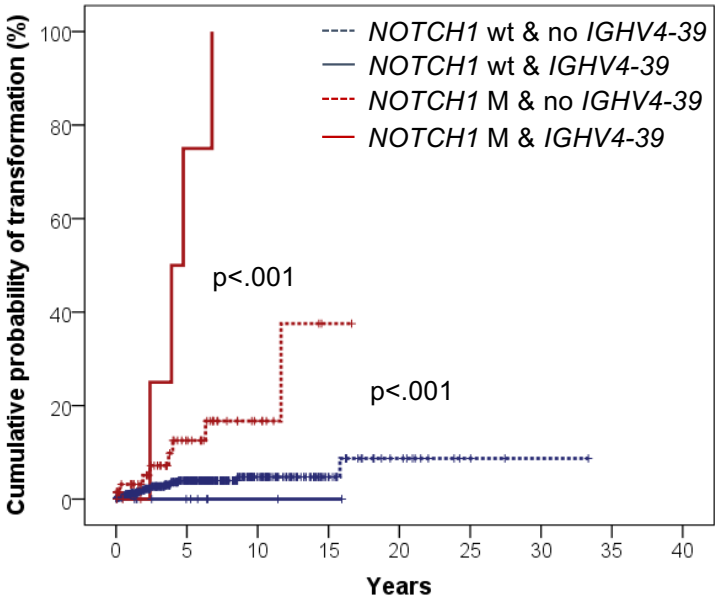
Müller-Hermelink HK, et al, WHO Classification 2008

Risk of Richter transformation according to *NOTCH1* mutation status and IGHV usage at CLL diagnosis



No. at Risk									
NOTCH1 wt	531	279	92	31	11	3	1	0	0
NOTCH1 M	74	28	8	1	0	0	0	0	0

	Events	Total	5-year risk	95% CI
NOTCH1 wt	18	531	3.9%	2.0-5.8
NOTCH1 M	12	74	18.6%	7.3-29.9



No. at Risk									
NOTCH1 wt & no *IGHV4-39*	519	273	90	30	11	3	1	0	0
NOTCH1 wt & *IGHV4-39*	12	12	12	12	0	0	0	0	0
NOTCH1 M & no *IGHV4-39*	67	27	8	1	0	0	0	0	0
NOTCH1 M & *IGHV4-39*	7	1	0	0	0	0	0	0	0

	Events	Total	5-year risk	95% CI
NOTCH1 wt & no *IGHV4-39*	18	519	4.0%	2.1-5.9
NOTCH1 wt & *IGHV4-39*	0	12	0	
NOTCH1 M & no *IGHV4-39*	8	67	12.5%	2.9-22.1
NOTCH1 M & *IGHV4-39*	4	7	75.0%	32.5-100

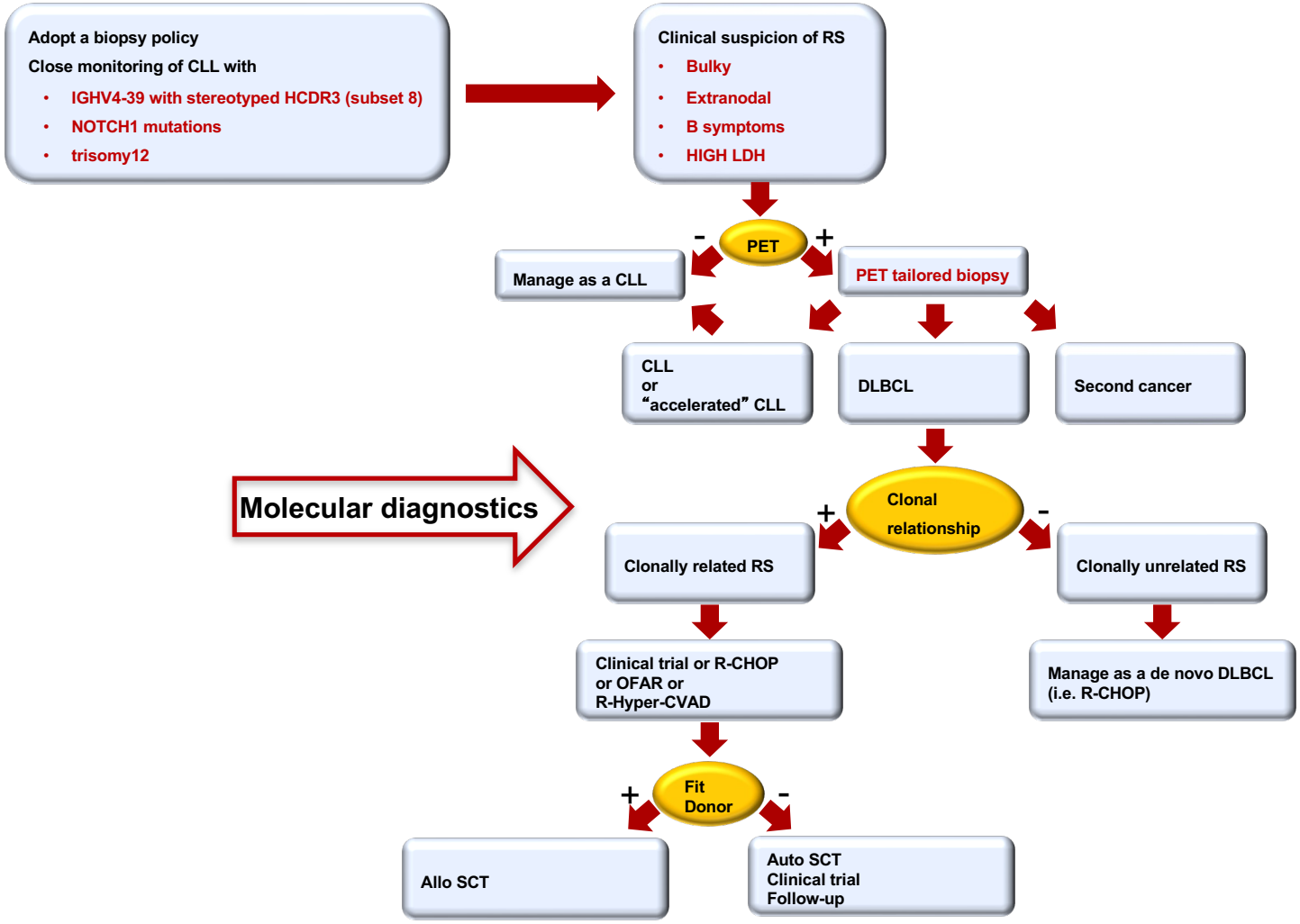
Trisomy 12

NOTCH1 mutations

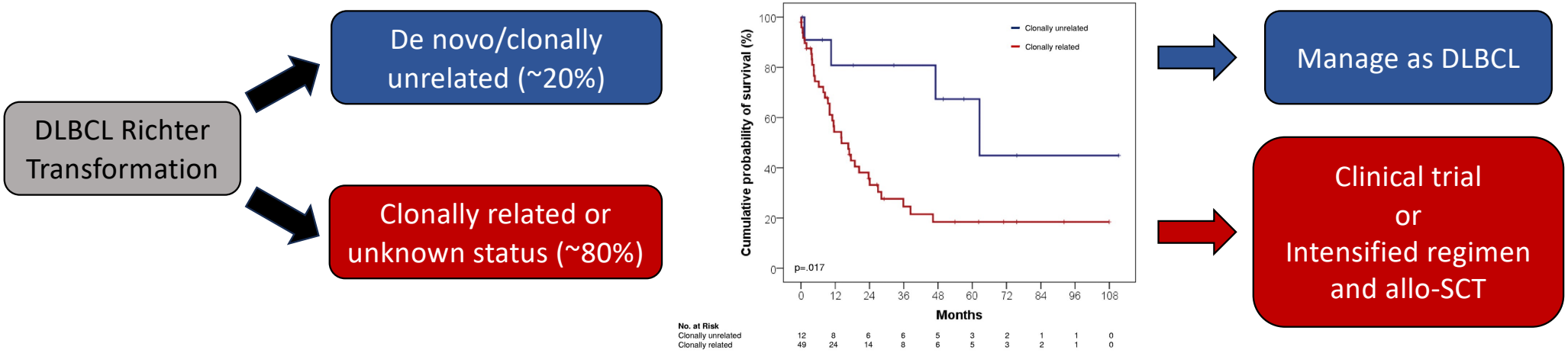
BCR Subset #8

Rossi *et al., Blood*. 2013

Clinical management of RS



Clonal relationship represents the most important prognostic/predictive factor in Richter transformation



Open issues on clonal relashionship in Richter syndrome

- Hurdles to collect tissue biopsy
- IGHV analysis not performed in all centers
- Hurdles in the evaluation of IGHV sequences especially in cases with concomitant presence of CLL and RS cells
- Need to confirm the prognostic role of clonal relashionship in large datasets
- Need to define the best treatment regimen for each molecular group

NCCN Guidelines Version 2.2023, Histologic Transformation (Richter's) and Progression;
Rossi *et al., Blood*. 2011; Parikh *et al., Blood*. 2014; Abrisqueta *et al., Blood*. 2017

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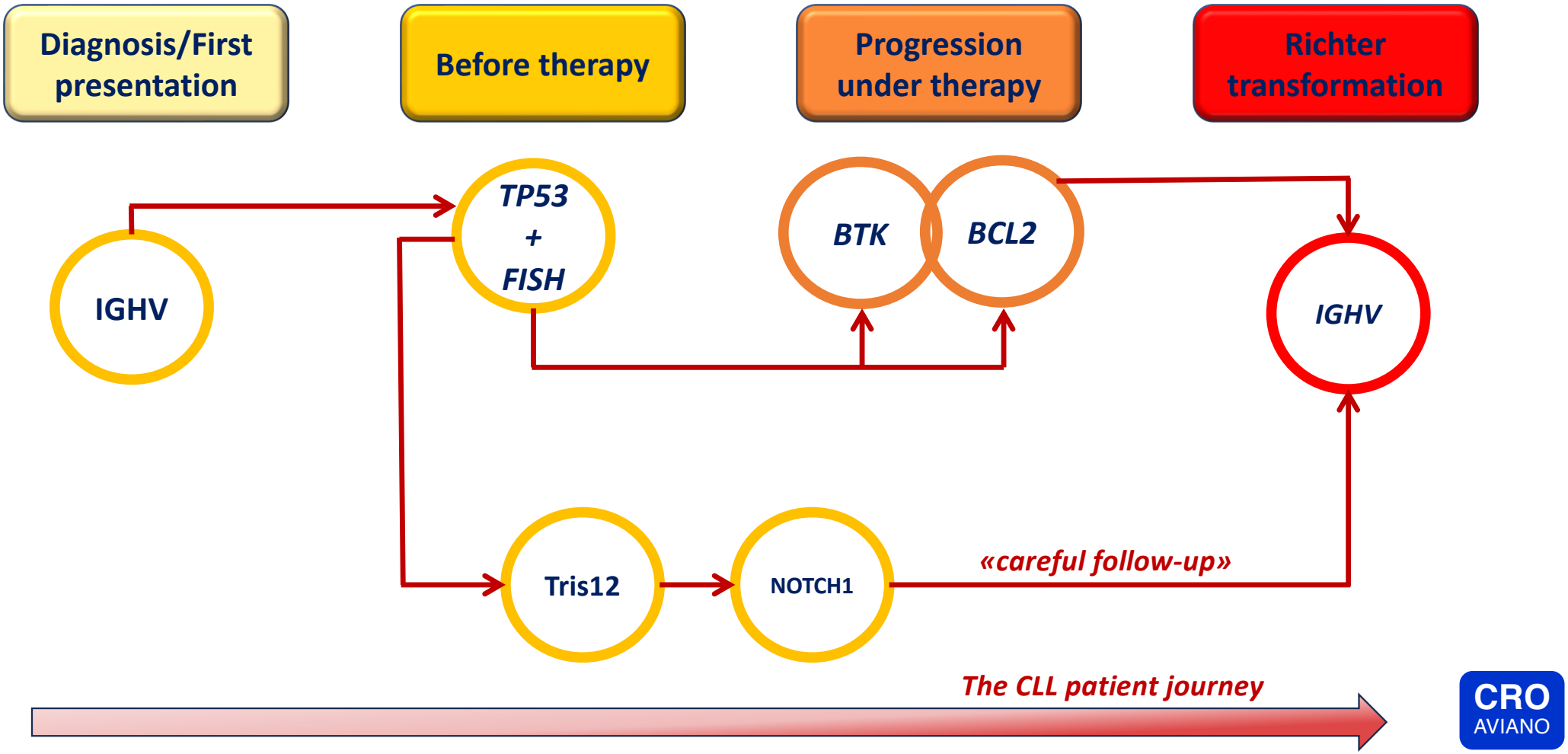
Biomarkers in CLL in the era of pathway inhibitors



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