Terapia a durata fissa: fitness e stato mutazionale

Gianluca Gaidano, M.D., Ph.D.

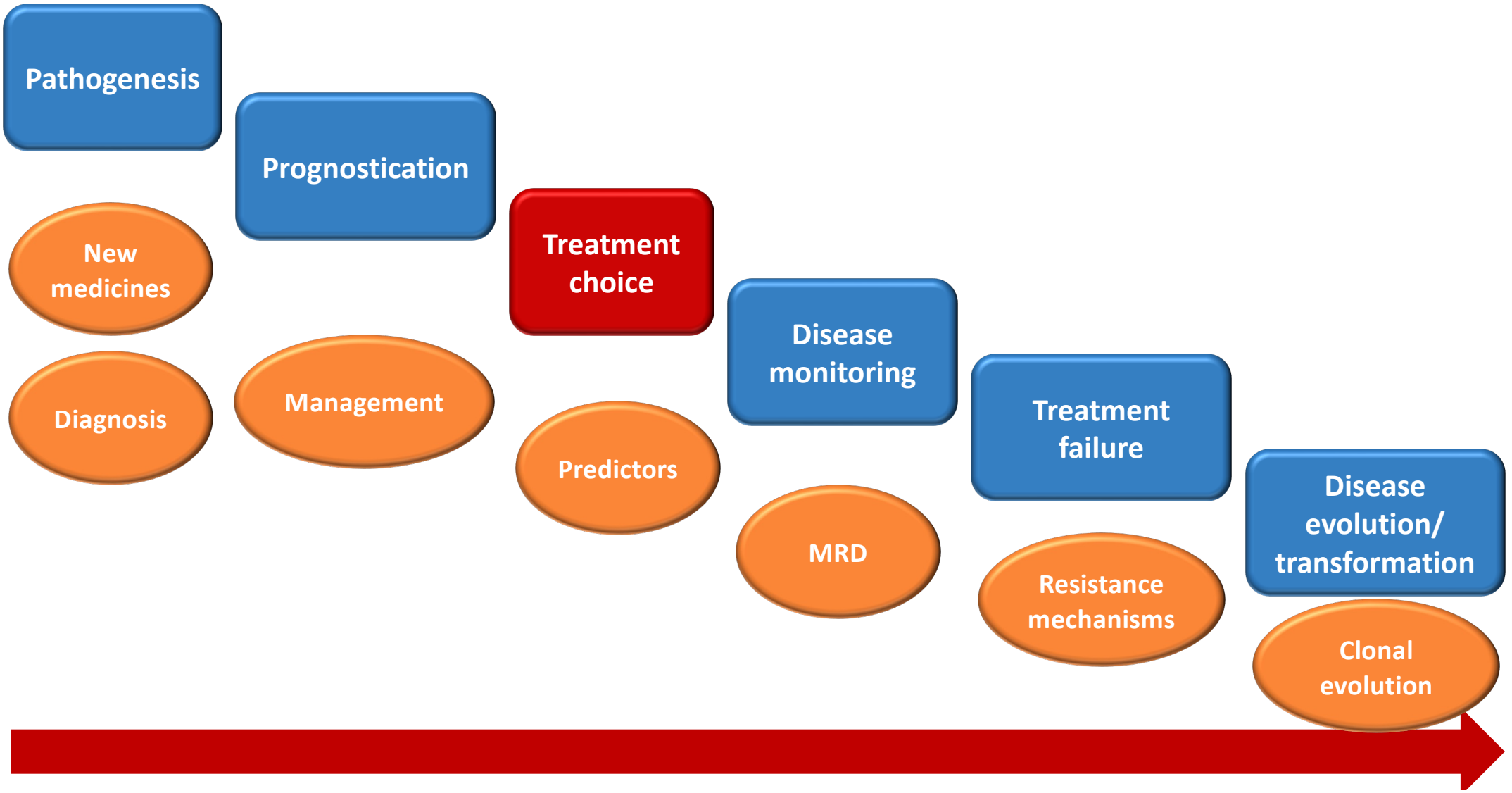
UNIVERSITÀ DEL PIEMONTE ORIENTALE

Division of Hematology
Department of Translational Medicine
Università del Piemonte Orientale
Novara, Italy

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					√	√	
AstraZeneca					√	√	
BeiGene					√	√	
Hikma					√		
Incyte					√	√	
Johnson & Johnson					√	√	
Lilly					√	√	

Applications of molecular biology in CLL



Baseline evaluation of CLL: “Always” only tests in the clinical practice

	Diagnosis	Monitoring	Treatment	Richter
History + Physical	√	√	√	√
CBC + Differential	√	√	√	√
PB phenotyping*	√			
Serum chem, Ig, DAT			√	√
Ches X-ray			√	
FISH			√	
TP53 mutation			√	
IGHV mutation			√	

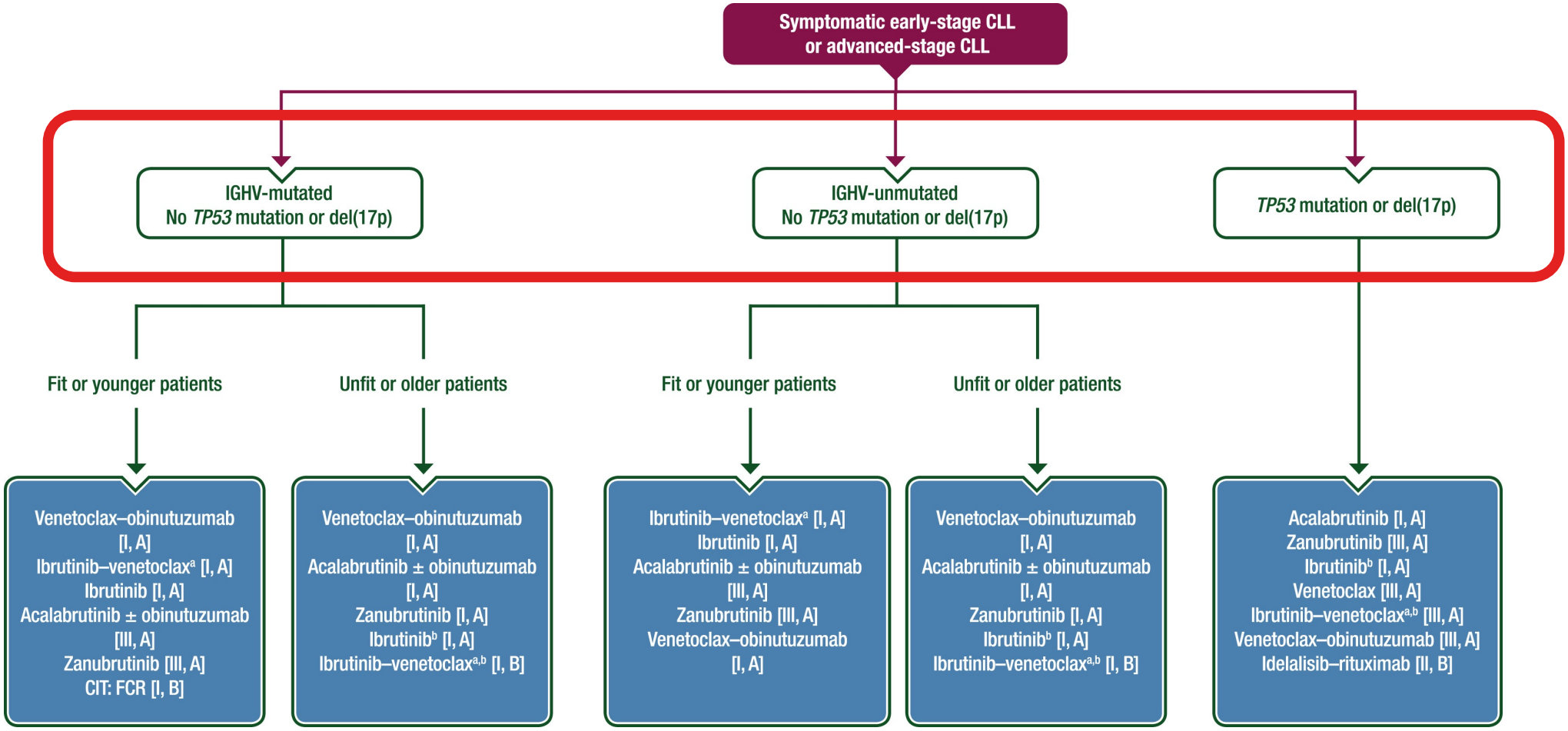
+ additional tests
Kittai et al., Blood 2025

*kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD200

Molecular tests at treatment requirement according to iwCLL guidelines

FISH	del(13q)	no predictive value / not useful for choosing treatment
	del(11q)	no predictive value / not useful for choosing treatment
	del(17p)	
	add(12)	no predictive value / not useful for choosing treatment
DNA seq	*TP53* mut	*TP53* mutation only is rare; in general coupled with del(17p)
	IGHV mut	Predictive value in ESMO but not in NCCN guidelines

CLL biomarkers in the ESMO guidelines for 1L treatment



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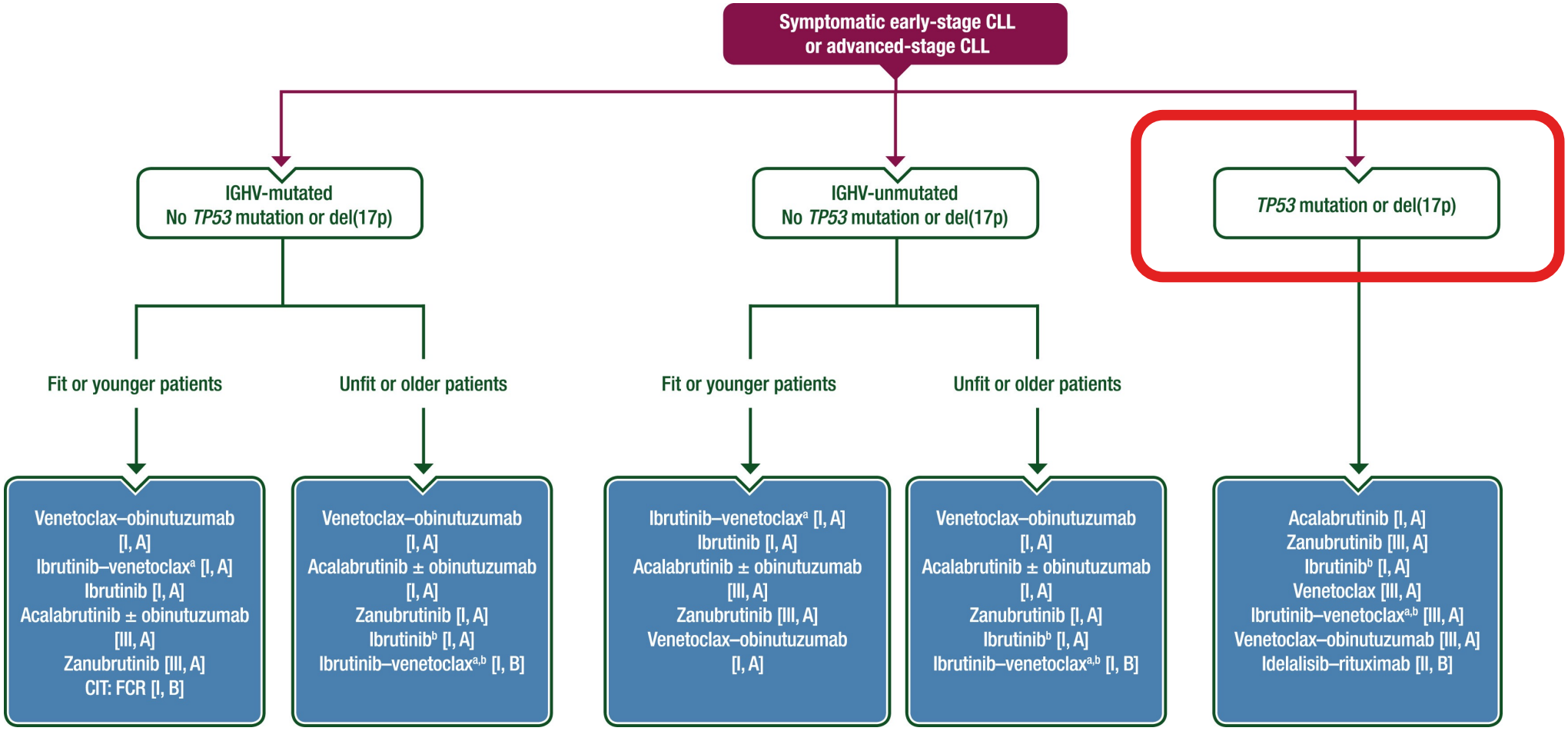
Eichhorst *et al., Ann Oncol*. 2024.

CLL biomarkers in the ESMO guidelines for 1L treatment



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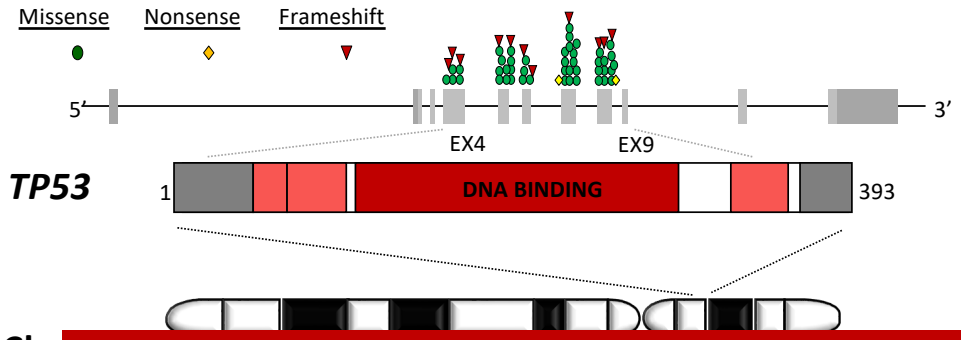
Eichhorst *et al., Ann Oncol*. 2024.

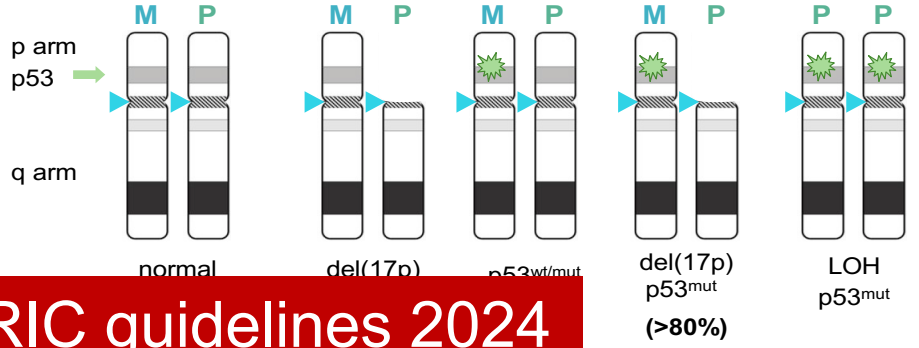
Clinical applications of predictive and prognostic biomarkers in CLL: Guideline recommendations

	General practice	Clinical trial
FISH for del(13q), del(11q), del(17p), add(12)	Always	Always
TP53 mutations	Always	Always
IG genes	Always	Always

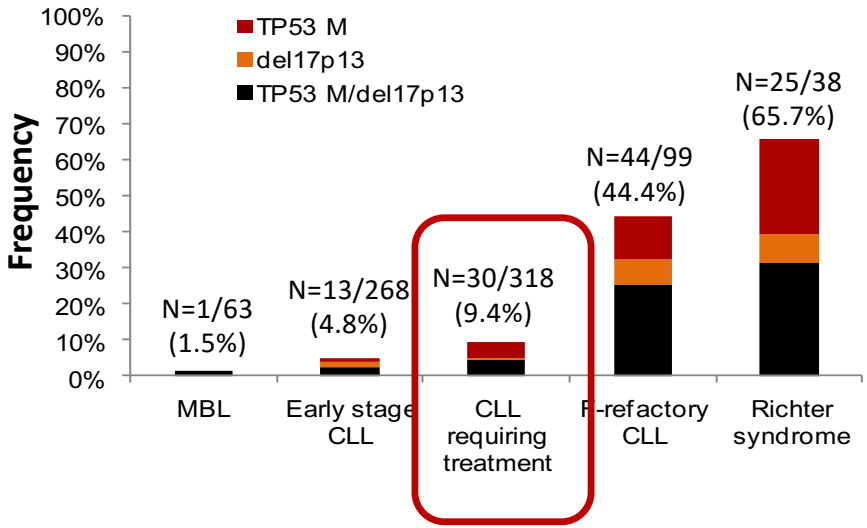
Hallek et al. *Blood* 2018; 131 (25): 2745–2760

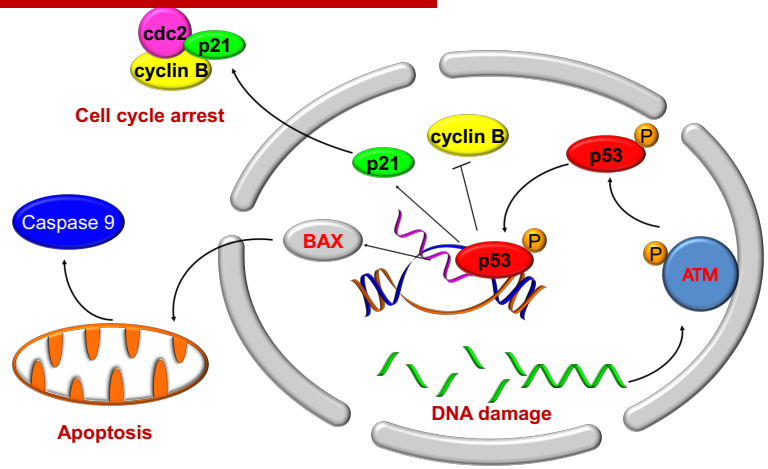
TP53 abnormalities in CLL





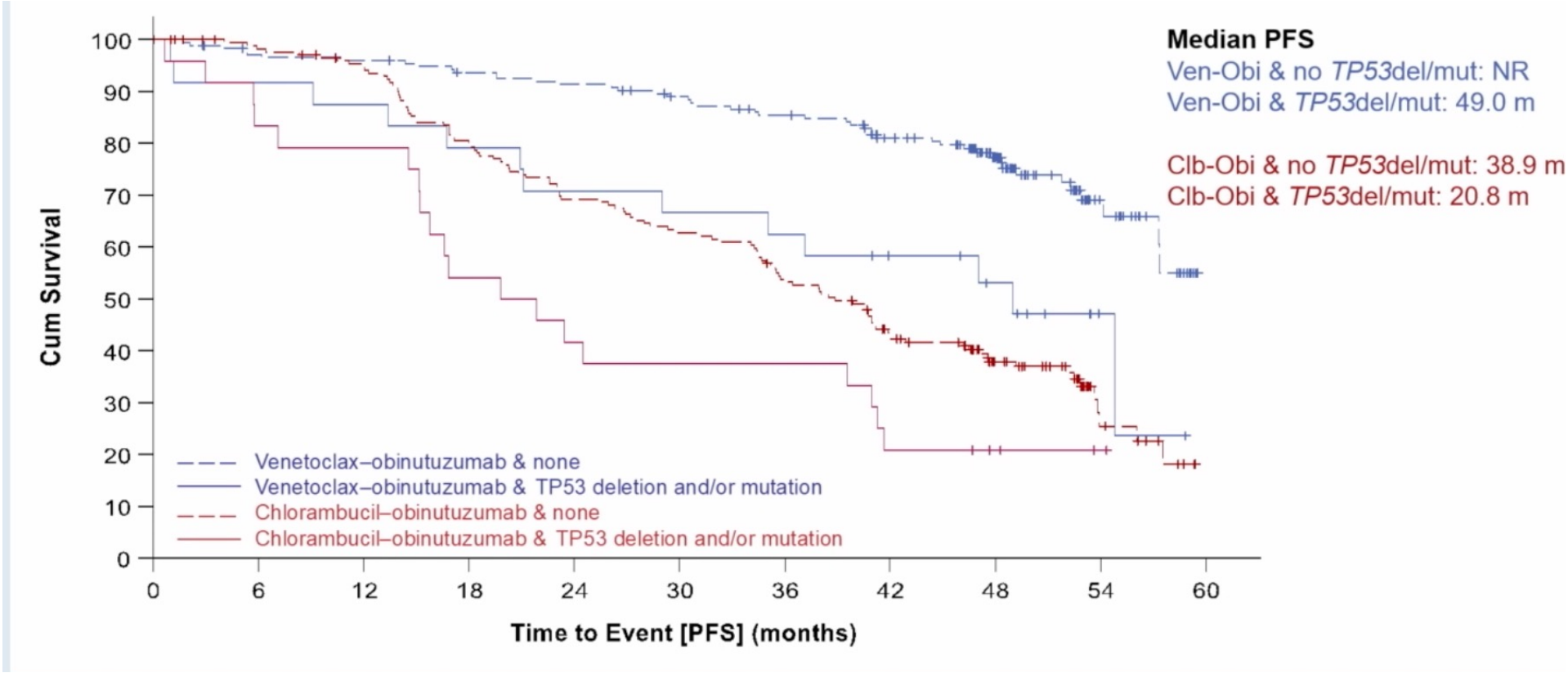
Which TP53 mutation cut off? ERIC guidelines 2024





Dohner et al, New Engl J Med 2000 ; Zenz et al J Clin Oncol 2010; Rossi et al Blood 2011; Zainuddin et al, Leuk Res 2011; Rossi et al Blood 2014

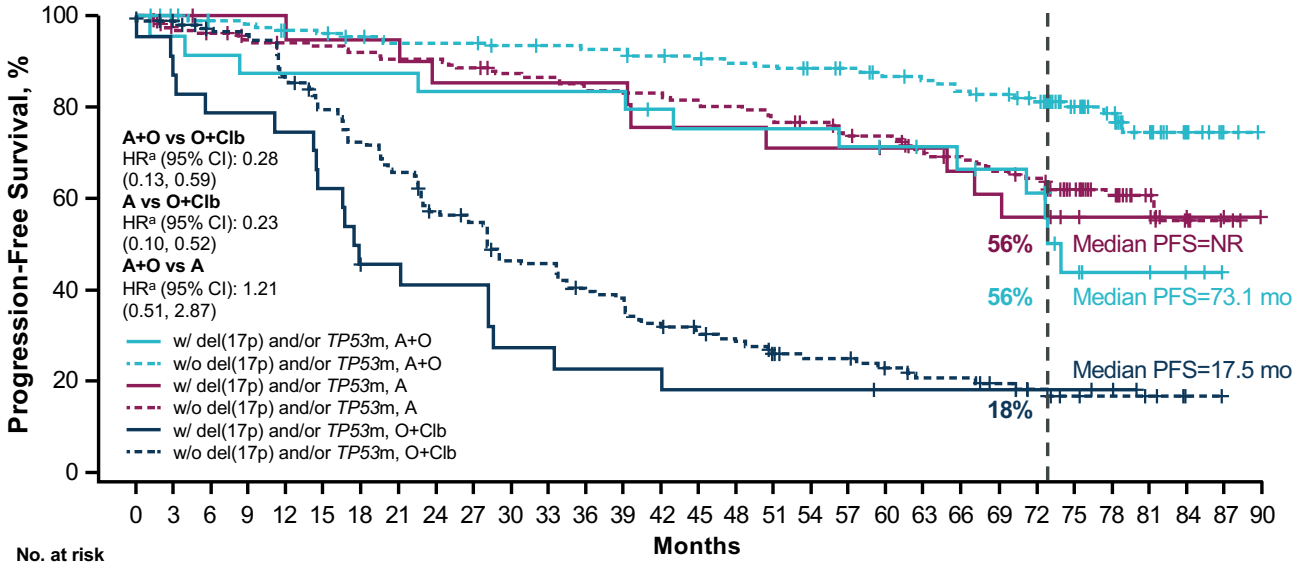
Clinical impact of *TP53* in the CLL14 trial



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

Al-Sawaf *et al.*, EHA 2021 S146

ACALABRUTINIB: combination of longest follow up + best safety profile
Investigator-Assessed PFS in Patients With Del(17p) and/or Mutated *TP53*



No. at risk

w/ del(17p) and/or *TP53m*, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0
w/o del(17p) and/or *TP53m*, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	2
w/ del(17p) and/or *TP53m*, A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	15	14	14	13	11	11	7	7	4	2	1
w/o del(17p) and/or *TP53m*, A	156	145	142	137	136	135	133	131	131	128	124	123	119	118	117	114	113	109	106	100	99	89	87	84	74	49	30	18	5	1
w/ del(17p) and/or *TP53m*, O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	3	3	3	3	3	1	0		
w/o del(17p) and/or *TP53m*, O+Clb	152	142	137	134	121	110	100	91	77	73	61	60	51	44	40	37	34	26	25	24	21	18	18	15	11	5	5	3	1	0

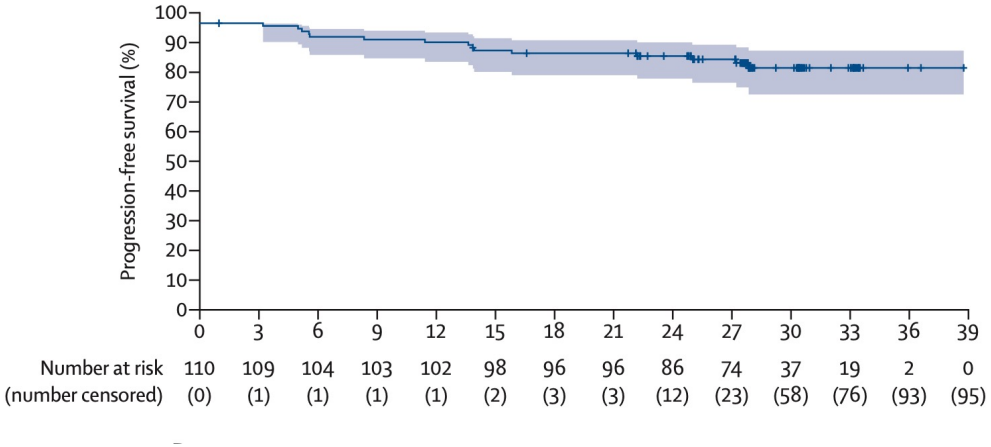
[a]Hazard ratio based on unstratified Cox proportional-hazards model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = Obinutuzumab; PFS = progression free survival; *TP53* = tumour protein p53; vs = versus.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

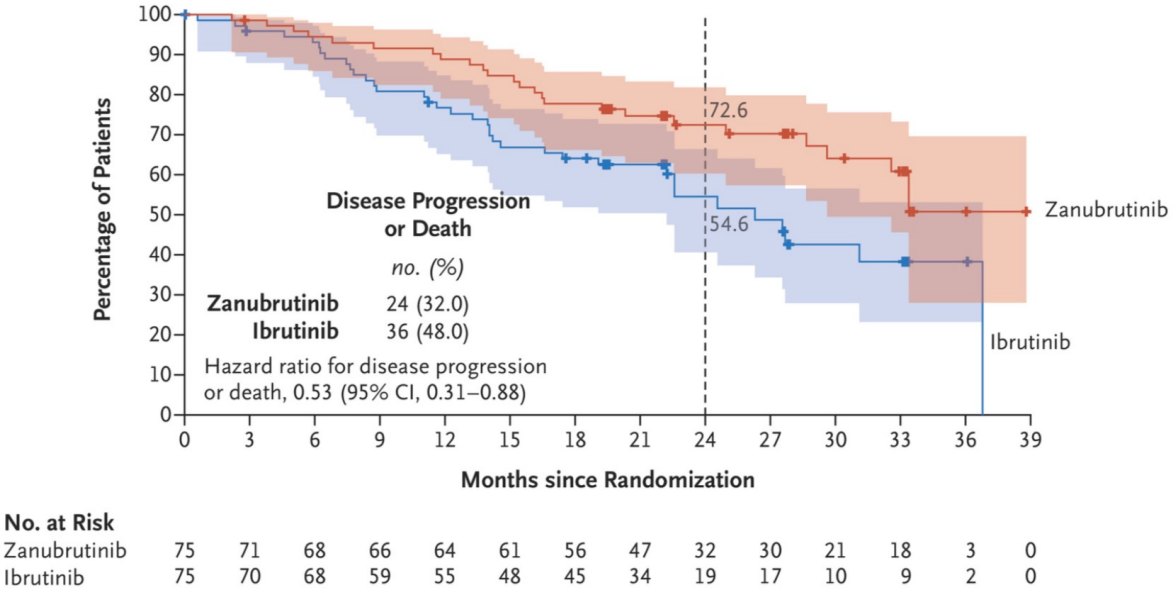
Zanubrutinib activity in *TP53* disrupted patients

ARM C SEQUOIA TRIAL



In the ARM C of the SEQUOIA trial the 24 months of *TP53* disrupted patients was 88.9%

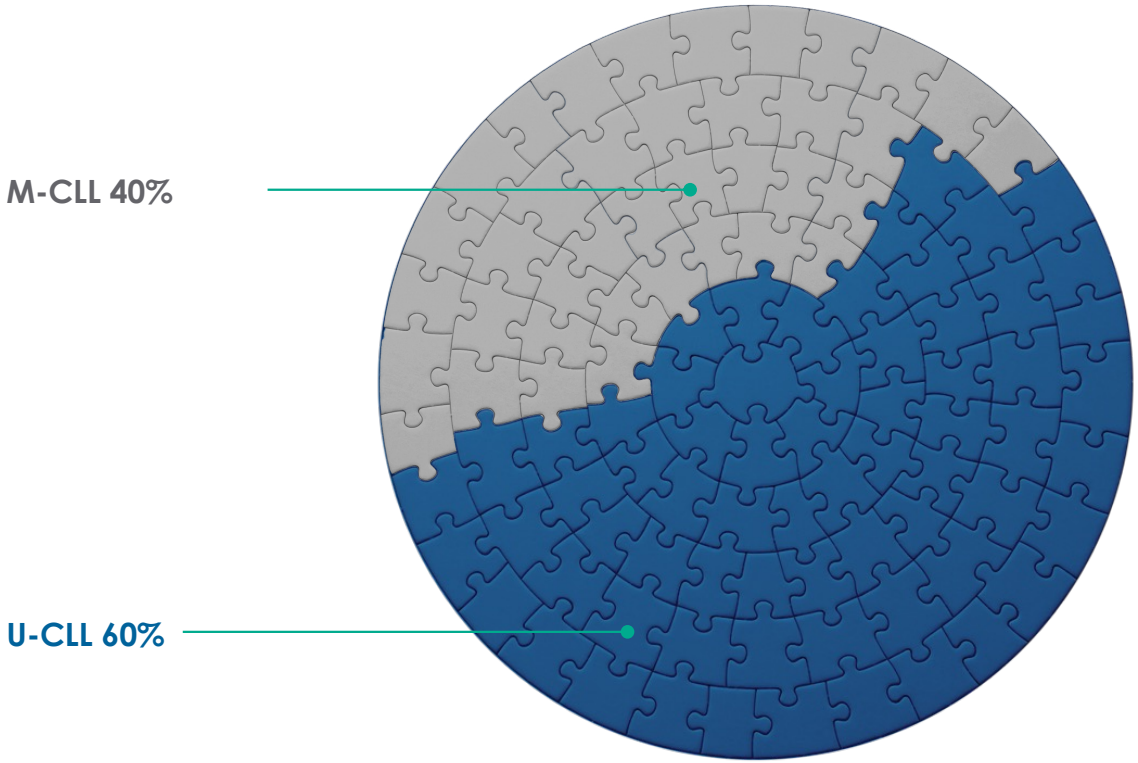
ALPINE TRIAL



In the ALPINE trial zanubrutinib was more effective compared to ibrutinib in *TP53* disrupted patients

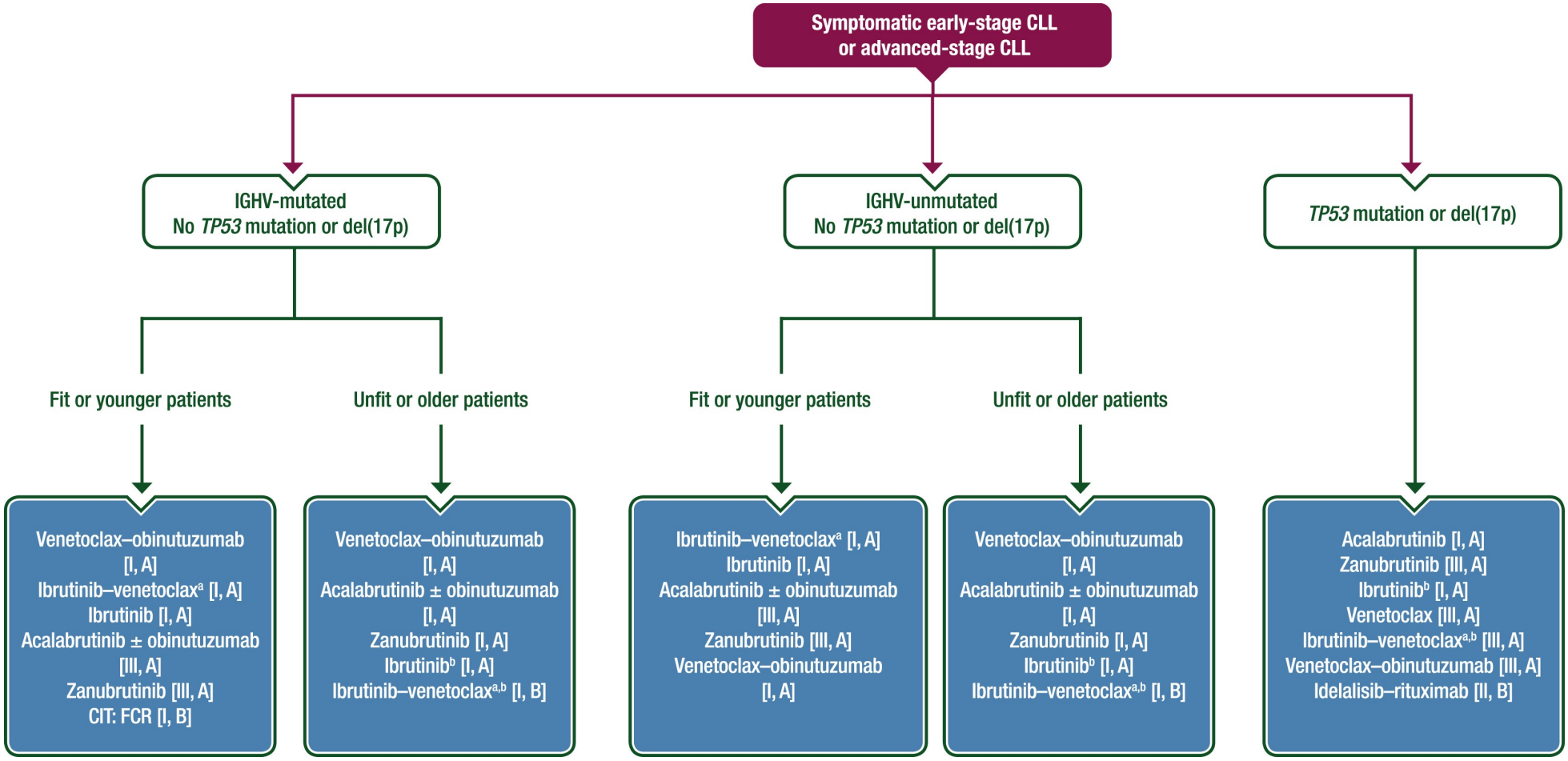
Tam *et al., Lancet Oncol*. 2022; Brown *et al., NEJM* 2023

Around 60% of CLL patients requiring treatment have an unmutated IGHV mutational status (U-CLL)



Performing IGHV testing and treating appropriately will have a significant impact on patients' outcomes[1]

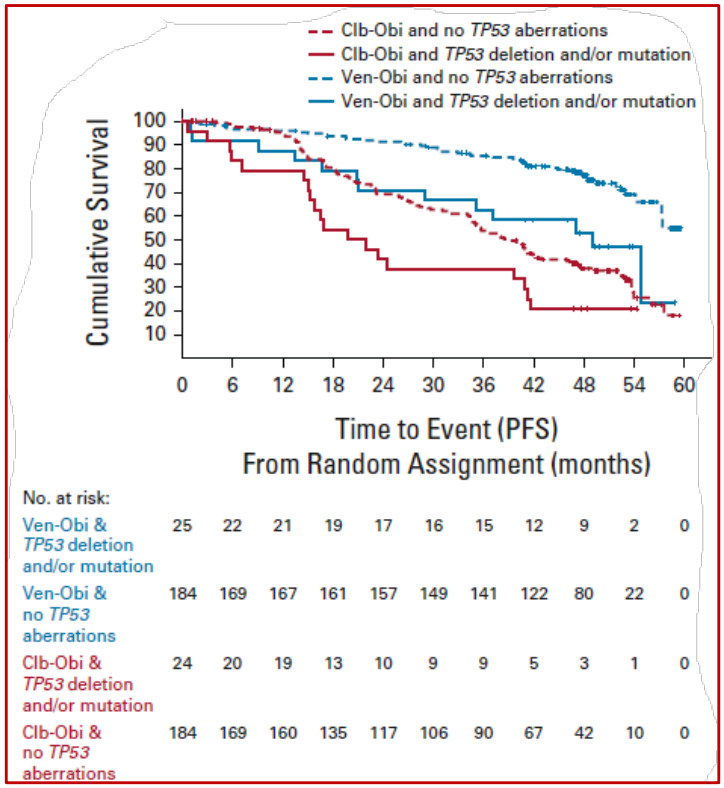
CLL biomarkers in the ESMO guidelines for 1L treatment

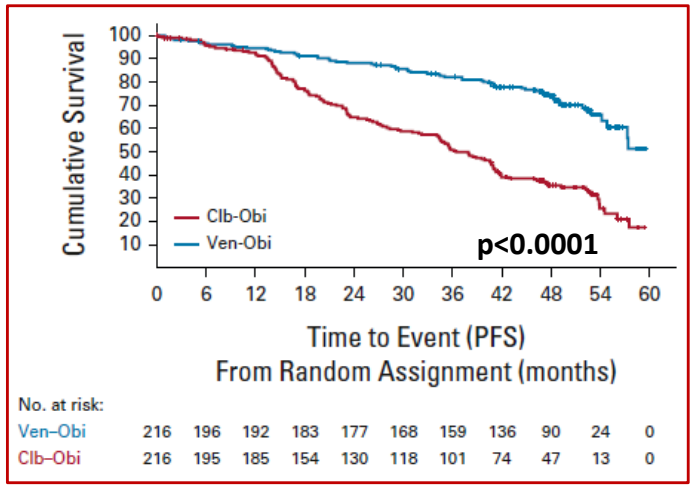


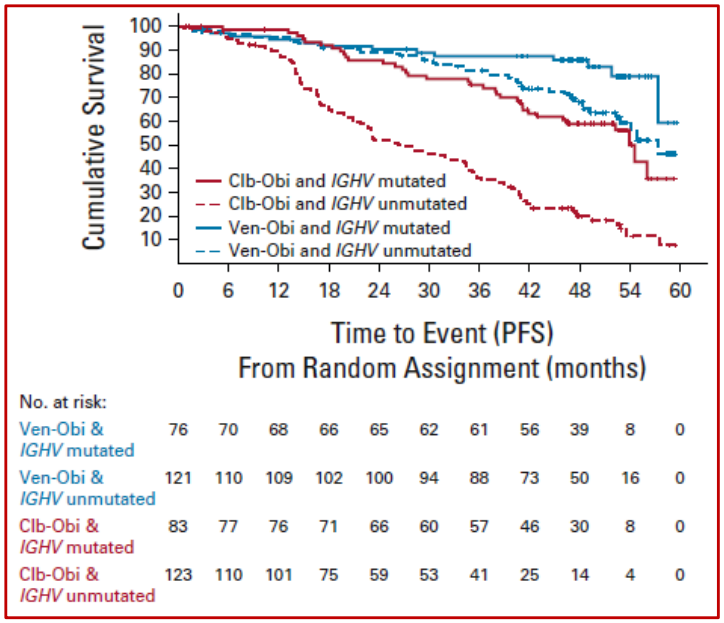
eha

Eichhorst *et al., Ann Oncol*. 2024.

Venetoclax-obinutuzumab vs Clb-Obi in previously untreated CLL (CLL14)







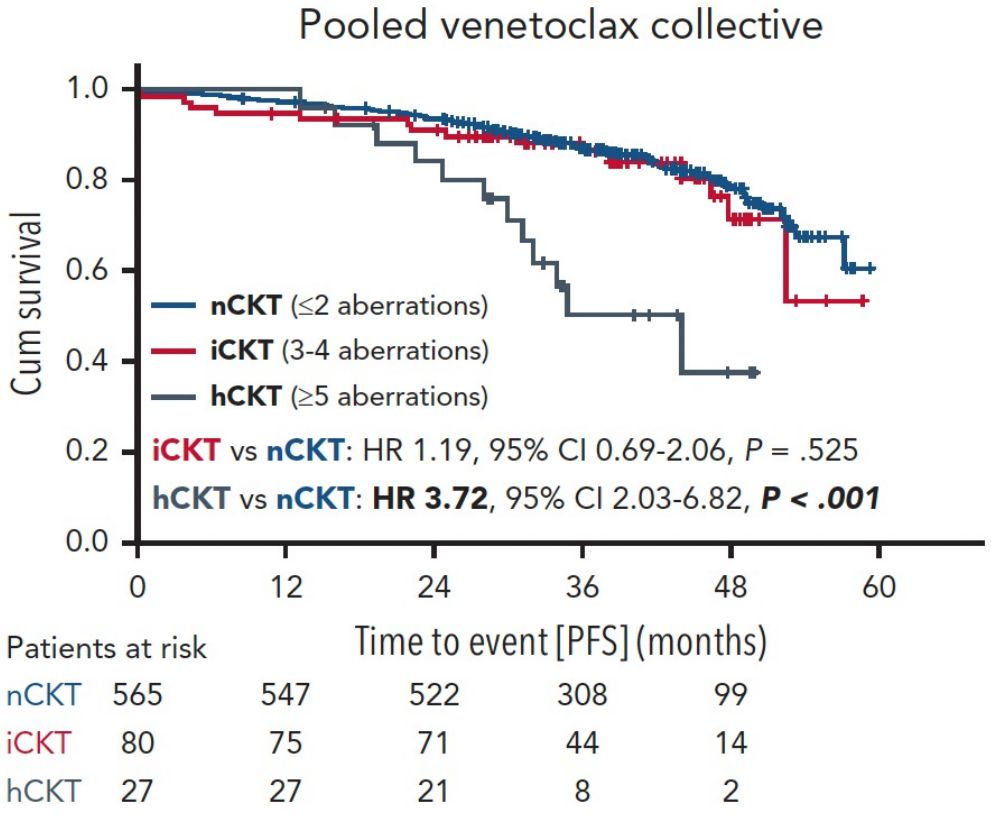
Ven-Obi mitigates, but does not completely overcome, the negative prognostic impact of *TP53* abnormalities and of unmutated IGHV genes

Al-Sawaf *et al.*, *J Clin Oncol*. 2021

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

iii) CK

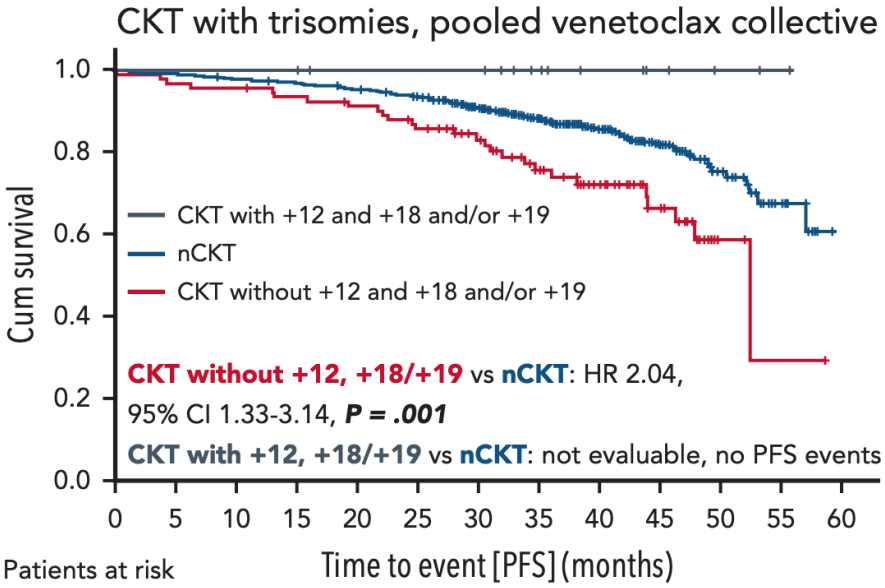
hCKT ➡ poor PFS



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

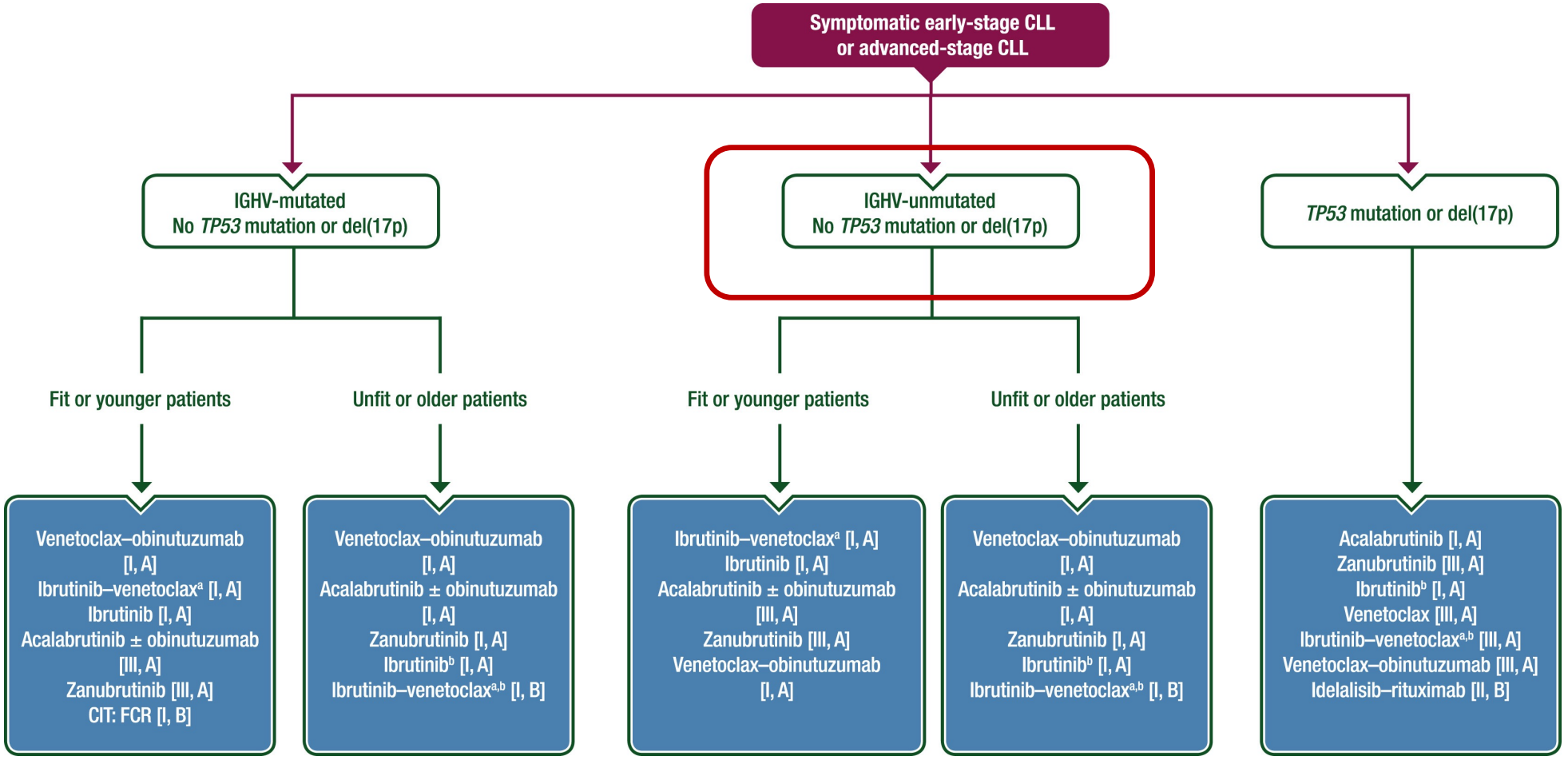
D



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

CLL biomarkers in the ESMO guidelines for 1L treatment



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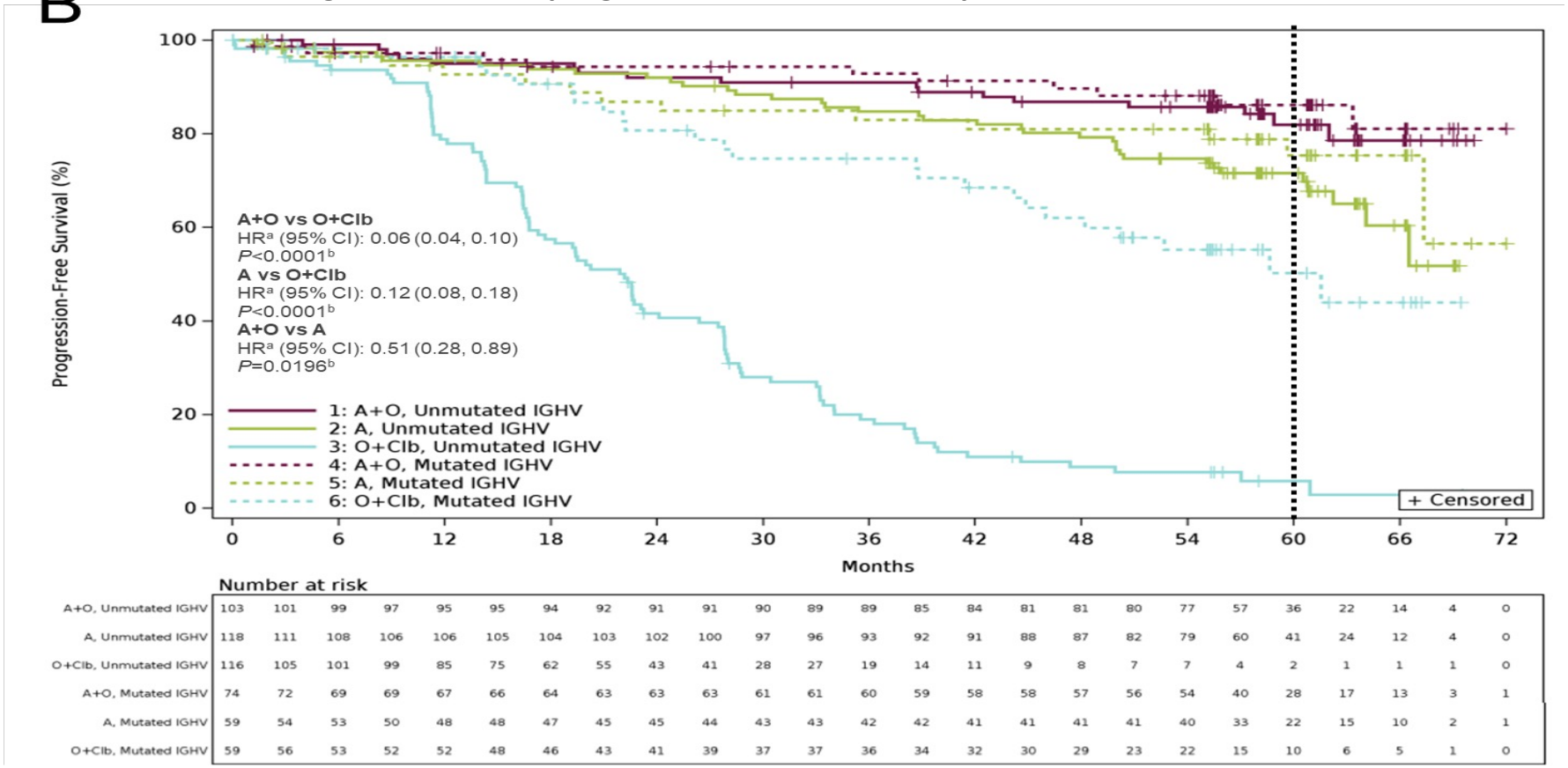
Eichhorst *et al., Ann Oncol*. 2024.

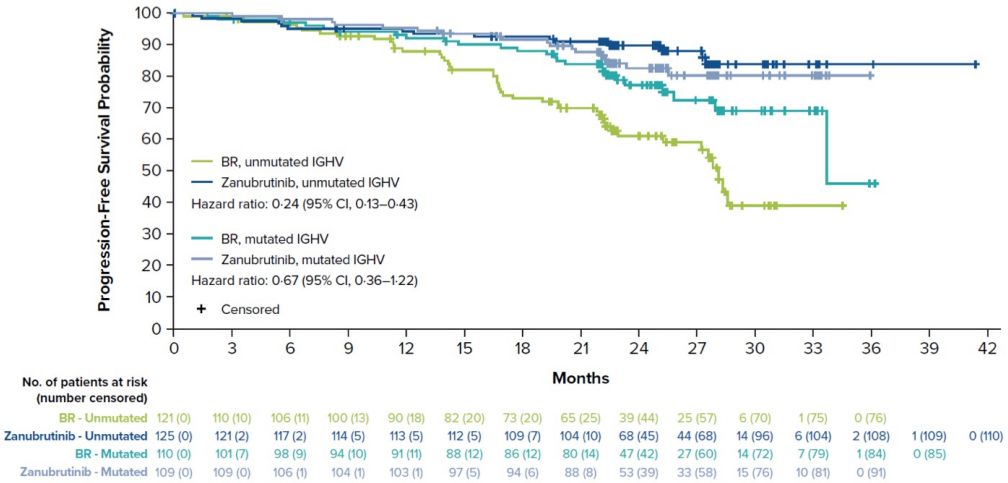
ELEVATE-TN 5-year follow-up: Inv PFS in patients with uIGHV & IGHVm

Investigator-assessed progression-free survival in patients with uIGHV & IGHVm (B):

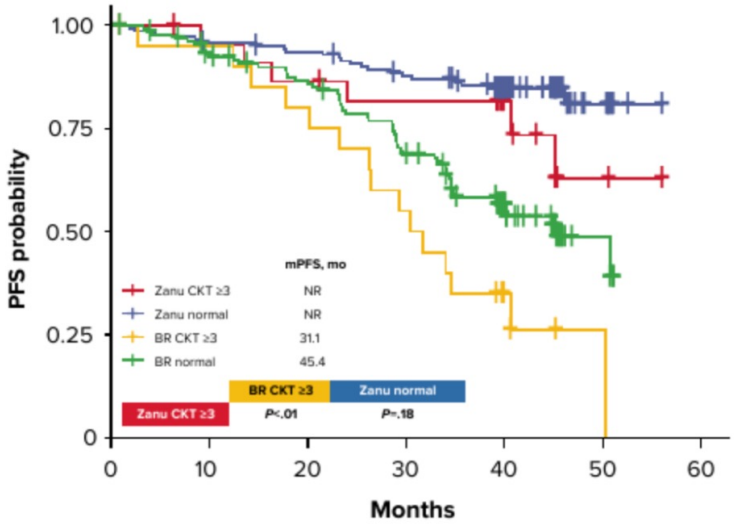


Sharman et al, Lancet 2020; Sharman et al, ASCO 2022

Zanubrutinib activity according to IGHV mutational status and complex karyotype



Zanubrutinb overcomes the prognostic impact of IGHV mutational status



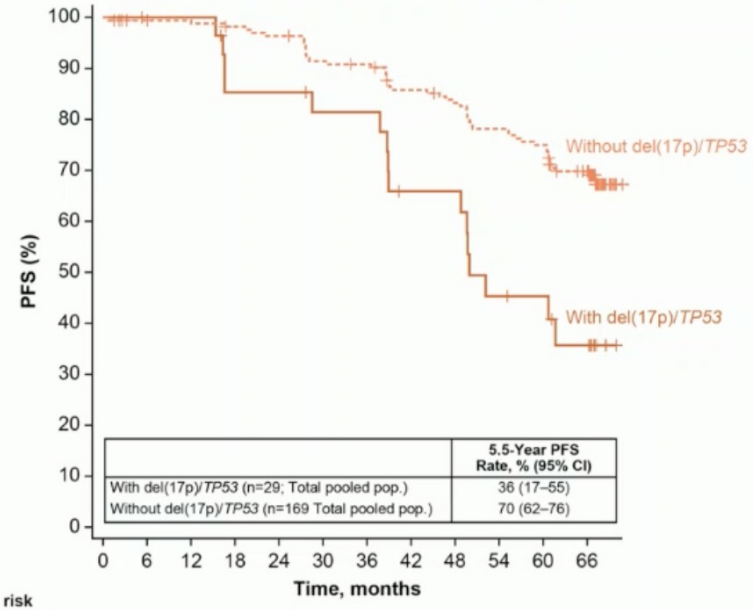
Zanubrutinb overcomes the prognostic impact complex karyotype

Tam *et al., Lancet Oncol*. 2022; Xu *et al*., ASH2023 #1092.

Captivate: Impact of biomarkers

Impact of del(17p)/mutated *TP53* and IGHV Status On Long-Term PFS (Total Pooled Population)

PFS by del(17p)/*TP53* Mutation Status



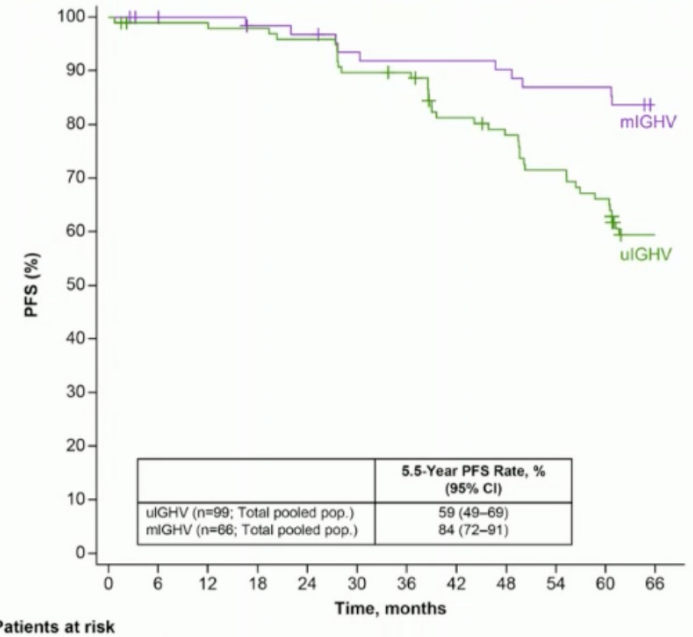
	5.5-Year PFS Rate, % (95% CI)
With del(17p)/*TP53* (n=29; Total pooled pop.)	36 (17–55)
Without del(17p)/*TP53* (n=169 Total pooled pop.)	70 (62–76)

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[a]	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)

PFS by IGHV Status in Patients Without del(17p)/mutated *TP53*



	5.5-Year PFS Rate, % (95% CI)
uIGHV (n=99; Total pooled pop.)	59 (49–69)
mIGHV (n=66; Total pooled pop.)	84 (72–91)

Patients at risk

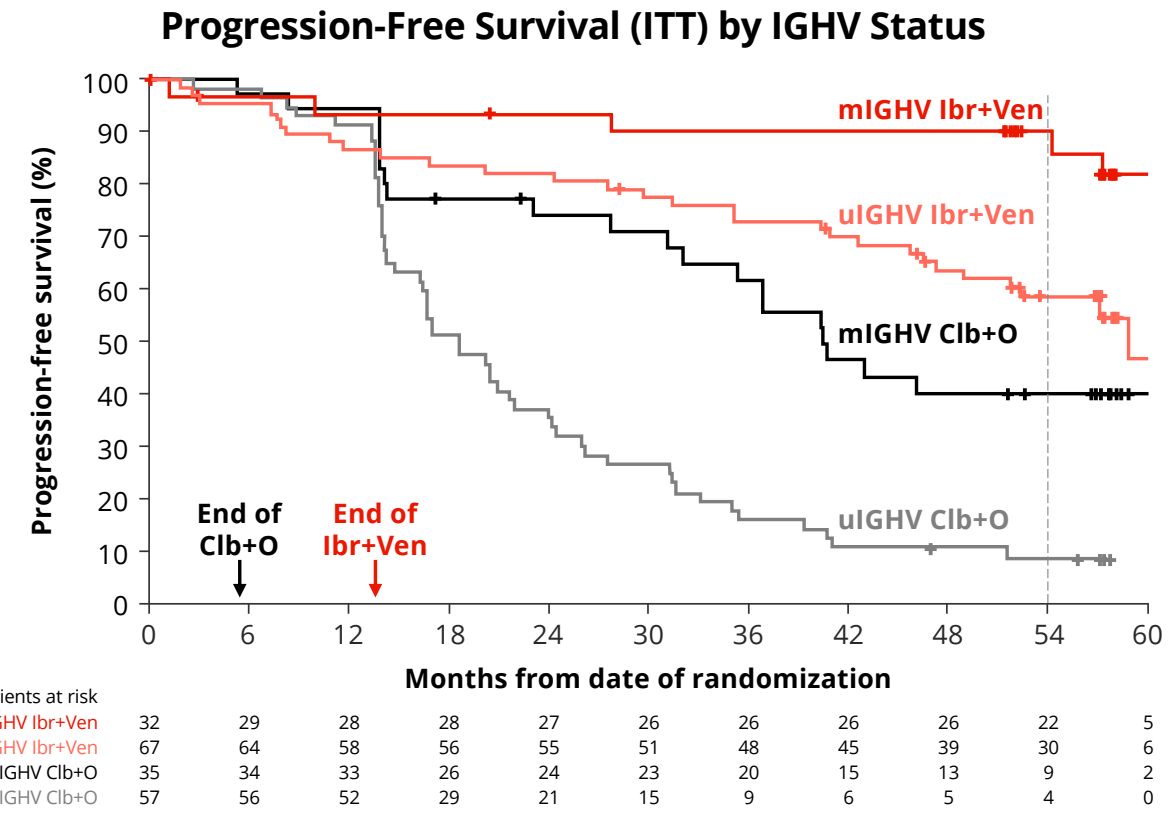
mIGHV	66	64	63	61	60	57	56	56	55	53	53	49
uIGHV	99	96	96	95	93	87	86	76	72	66	61	50

FD Cohort[a]	5.5-Year PFS Rate, % (95% CI)
uIGHV (n=71; FD cohort only)	53 (40–64)
mIGHV (n=55; FD cohort only)	80 (66–89)

[a]See Supplementary Information for details. mIGHV, mutated IGHV.

Ghia *et al., EHA 2025*

GLOW: At 57 Months of Follow-up, Ibr+Ven Improved PFS Versus Clb+O Regardless of IGHV Status



Patients at risk											
mIGHV Ibr+Ven	32	29	28	28	27	26	26	26	26	22	5
uIGHV Ibr+Ven	67	64	58	56	55	51	48	45	39	30	6
mIGHV Clb+O	35	34	33	26	24	23	20	15	13	9	2
uIGHV Clb+O	57	56	52	29	21	15	9	6	5	4	0

- Estimated 54-month PFS rates:
  - **Ibr+Ven:**
    - 90% for patients with mIGHV
    - 59% for patients with uIGHV
  - **Clb+O:**
    - 40% for patients with mIGHV
    - 8% for patients with uIGHV

Results based on updated IGHV reclassifications
Investigator-assessed progression-free survival was analyzed
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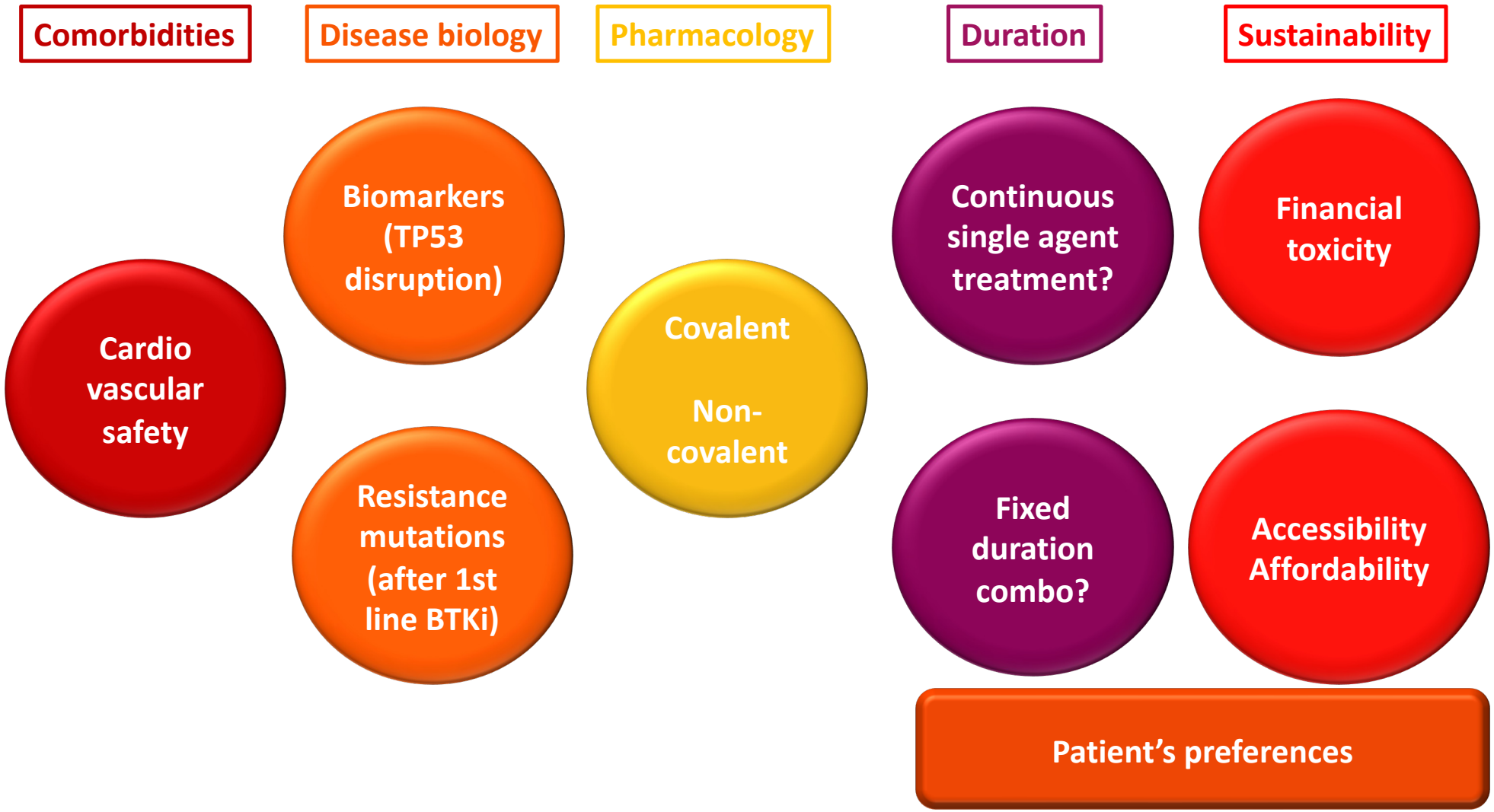
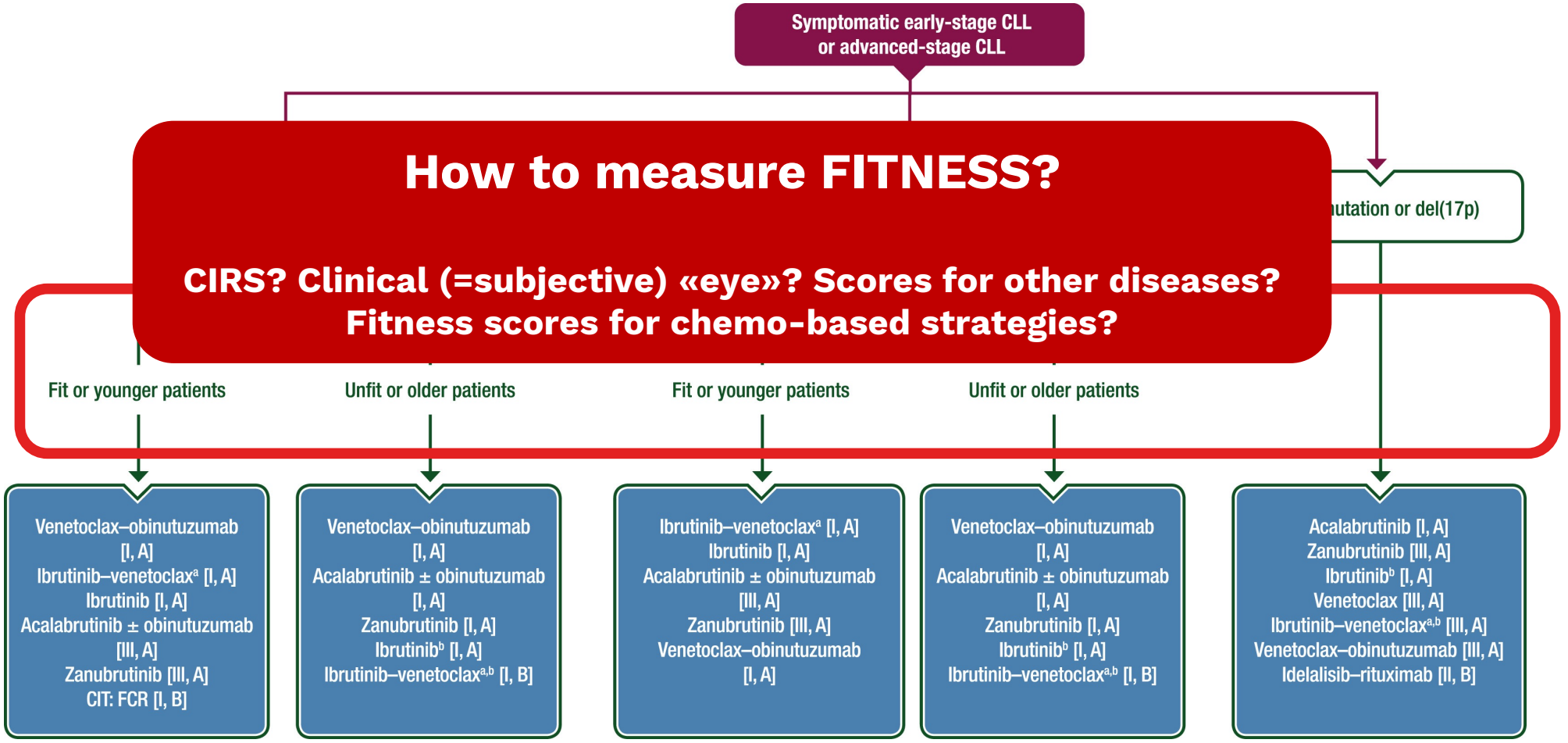
Presented by George Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

Considerations for 1L treatment choice



CLL biomarkers in the ESMO guidelines for 1L treatment



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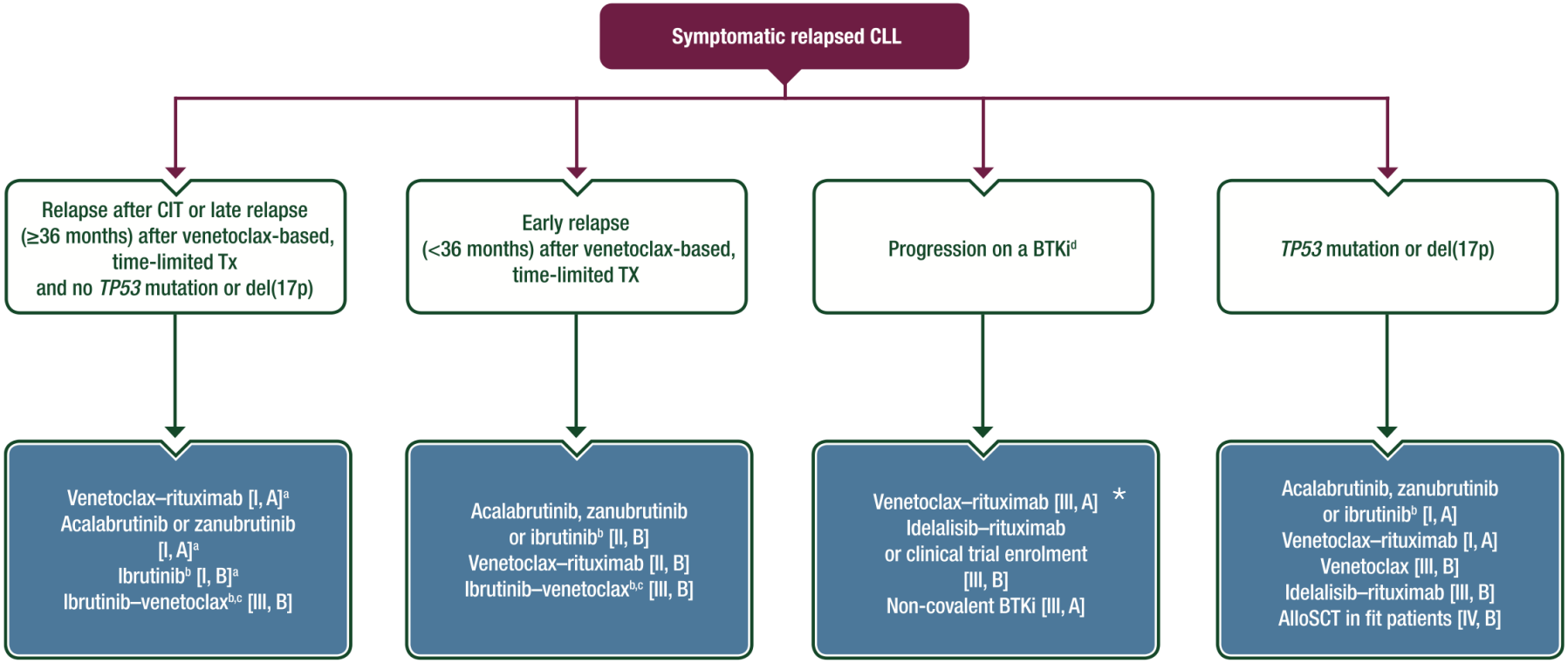
Eichhorst *et al., Ann Oncol*. 2024.

ESMO guidelines for R/R CLL (2024)

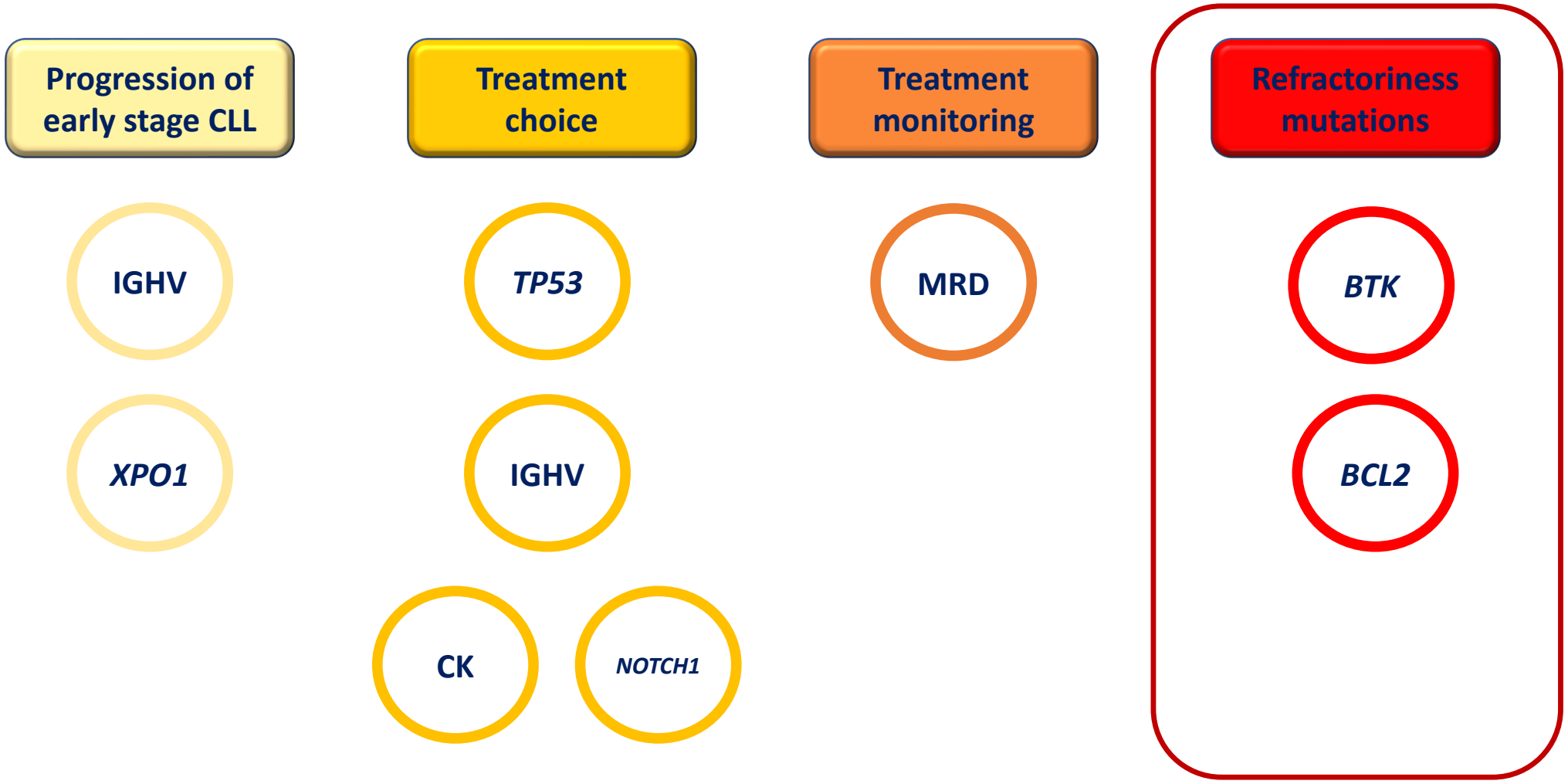


[a]For relapse after CIT, BTKis or venetoclax—rituximab should be considered equally, depending on comorbidities, comedication, access and preference.
[b]Ibrutinib should be considered carefully particularly in older patients with cardiac comorbidities.
[c]Not EMA approved, not FDA approved in relapse.
[d]If a patient relapses after prior treatment with a BTKi, which was stopped due to side-effects, changing to a different BTKi or rechallenge could be considered [III, B].

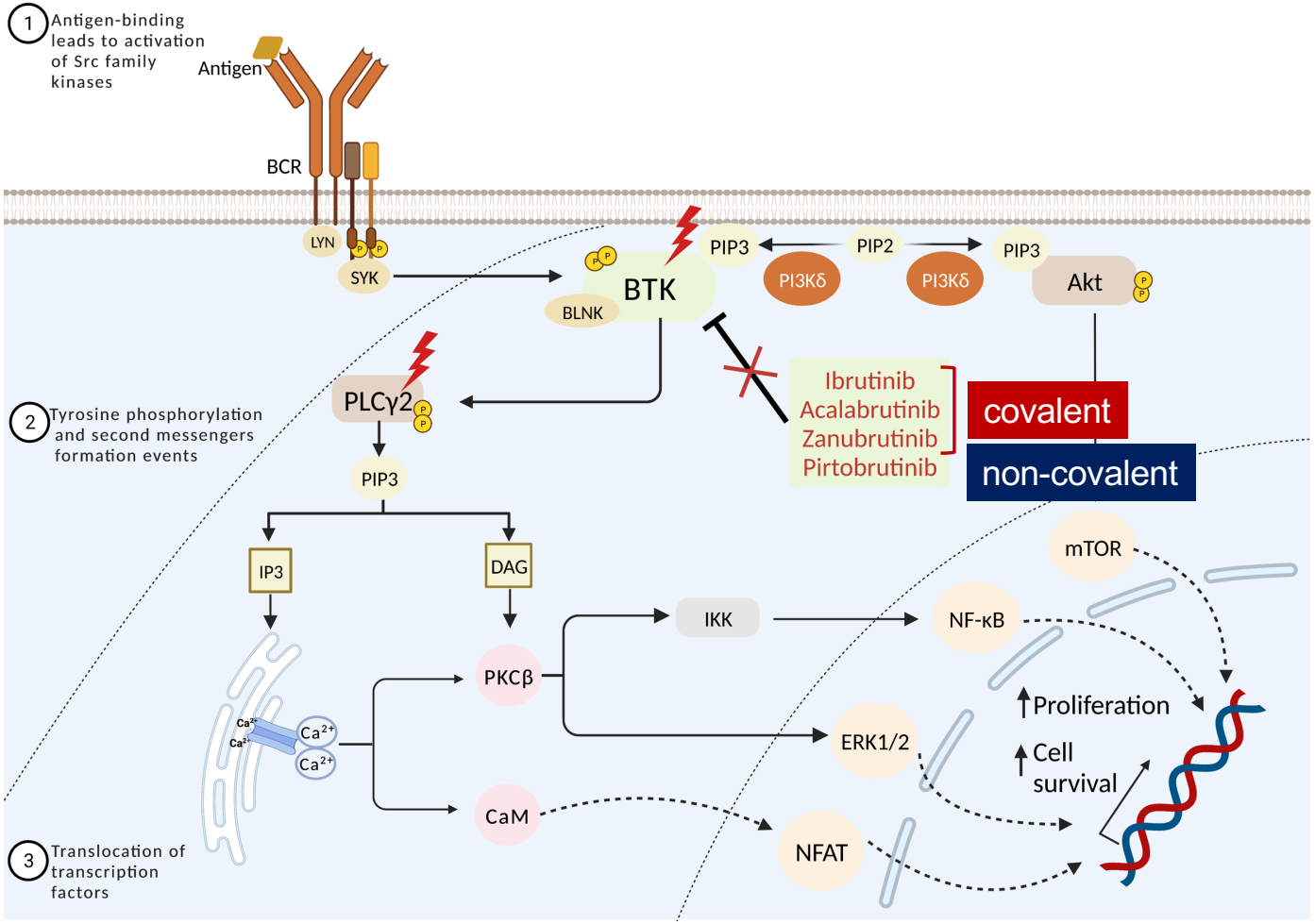
* *not an option in double refractory patients (refractory to both BTKi and BCL2i)*

Eichorst *et al., Ann Oncol.* 2024

Biomarkers in CLL in the era of pathway inhibitors

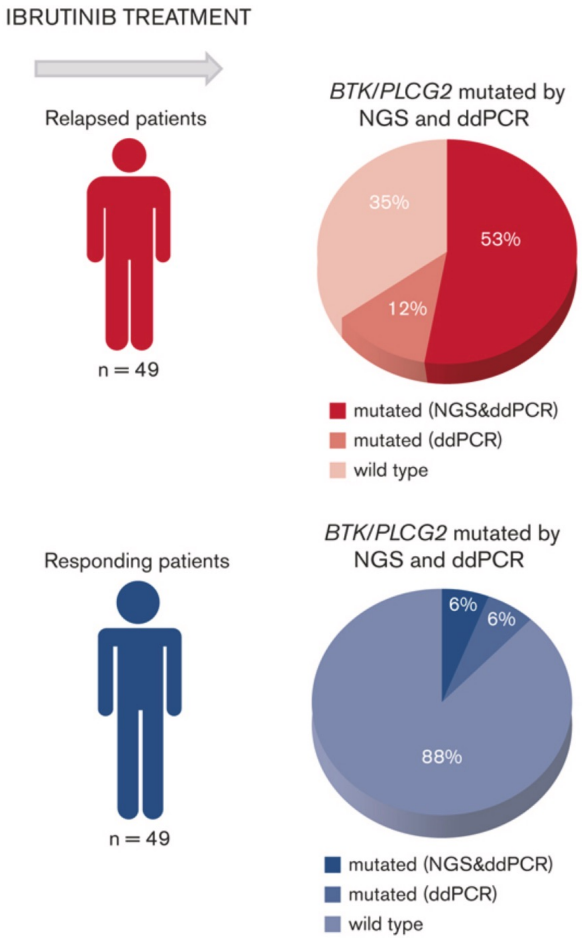


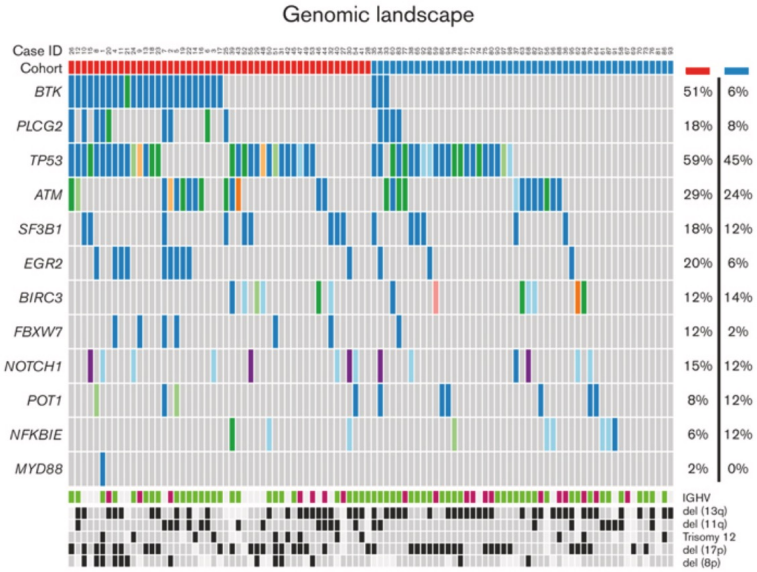
BTK targeting by covalent and non-covalent BTK inhibitors



Maher et al, Int J Mol Sci 2023

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

BTK targeting by covalent and non-covalent BTK inhibitors

Biomarker	Prevalence before treatment	Prevalence at progression	Mechanism of resistance	Predictive value
BTK point mutations of C481: C481S/R/Y/G	N/A	~50%	Reduced affinity for covalent BTKi	Poor response to covalent BTKi
BTK point mutations of the tyrosine kinase domain: L528W, V416L, T474I, M437R, A428D	N/A	~16%	Binding impairment of non-covalent BTKi	Poor response to covalent and non-covalent BTKi
PLCG2 mutations: R665W, L845G, C849R, D993H	N/A	13%	Constitutively active PLCγ2	Poor response to BTKi
BCL2 mutations: G101V, D103Y, F104I	N/A	~15%	Binding impairment of BCL2is	Poor response to BCL2i
Upregulation of MCL-1 and/or BCL-xL	N/A	N/A	Enhanced apoptosis evasion	Poor response to BCL2i
High serum [IL-10]	N/A	N/A	Reduced T cell response through IL-10R stimulation	Poor response to PD-1/PD-L1 immune checkpoint inhibitors
Low serum [IL-6]	N/A	N/A	CAR-T cell exhaustion due to defective IL-6R stimulation	Poor response to CAR-T cells
Low levels of $CD27^{+}CD45RO^{-}$ $CD8^{+}$ T cells	N/A	N/A	Reduced population of active CAR-T cells	Poor response to CAR-T cells

Maher et al, Int J Mol Sci 2023

Mutations of resistance to BTKi

BTK C481 mutations

- preclude irreversible binding of covalent BTKi to BTK
- result in a greatly reduced drug potency

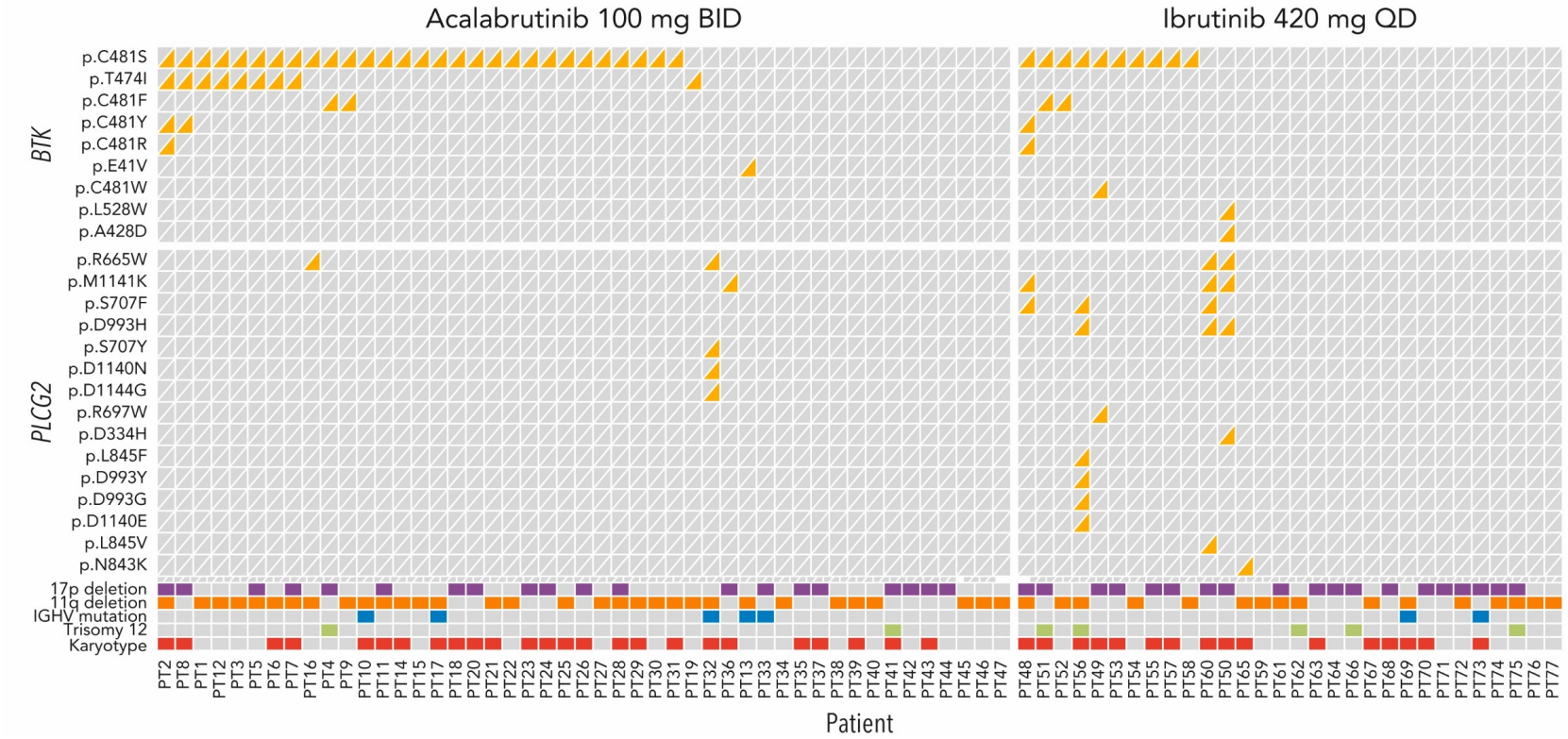
BTK T474 gatekeeper

- interfere with BTKi (both covalent and noncovalent) binding to BTK
- allow for normal B-cell signaling

BTK L528W kinase-dead

- hinder BTK catalytic activity
- B-cell signaling is thought to continue via a BTK scaffolding

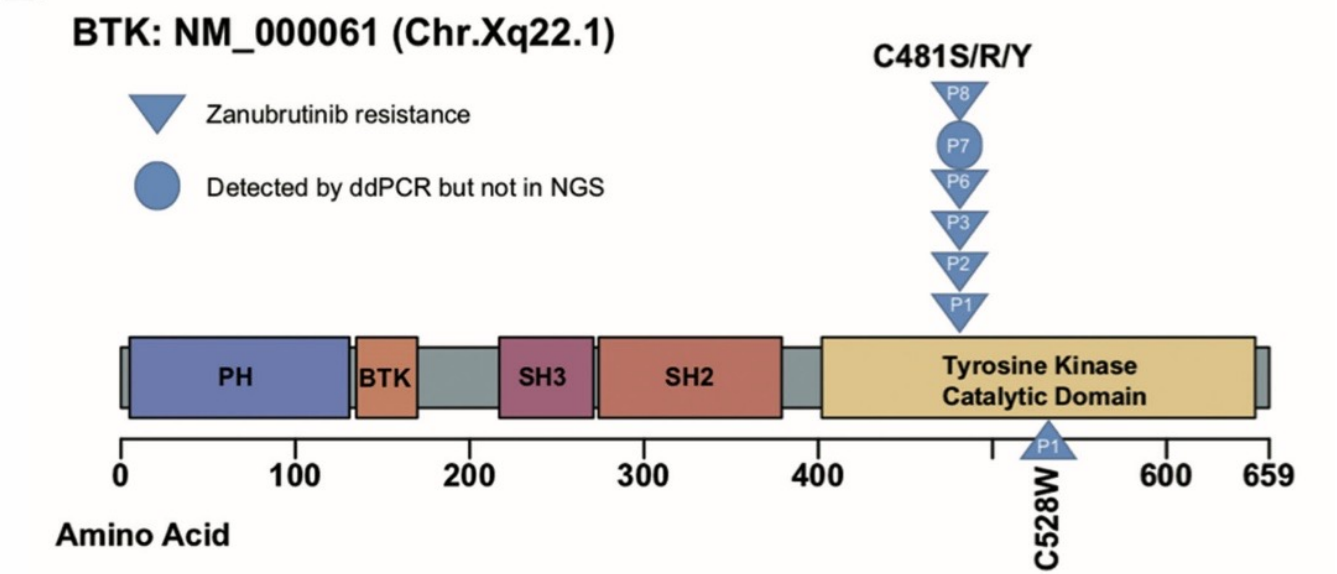
Genetic resistance to Ibrutinib and Acalabrutinib



- *BTK* C481 is the most common
- *BTK* Gatekeeper T474I is observed with A but not I
- *BTK* Kinase-dead mutation L528W rare
- *PLCG2* M co-occur with *BTK* M in I but not A

Woyach JA, Blood. 2024

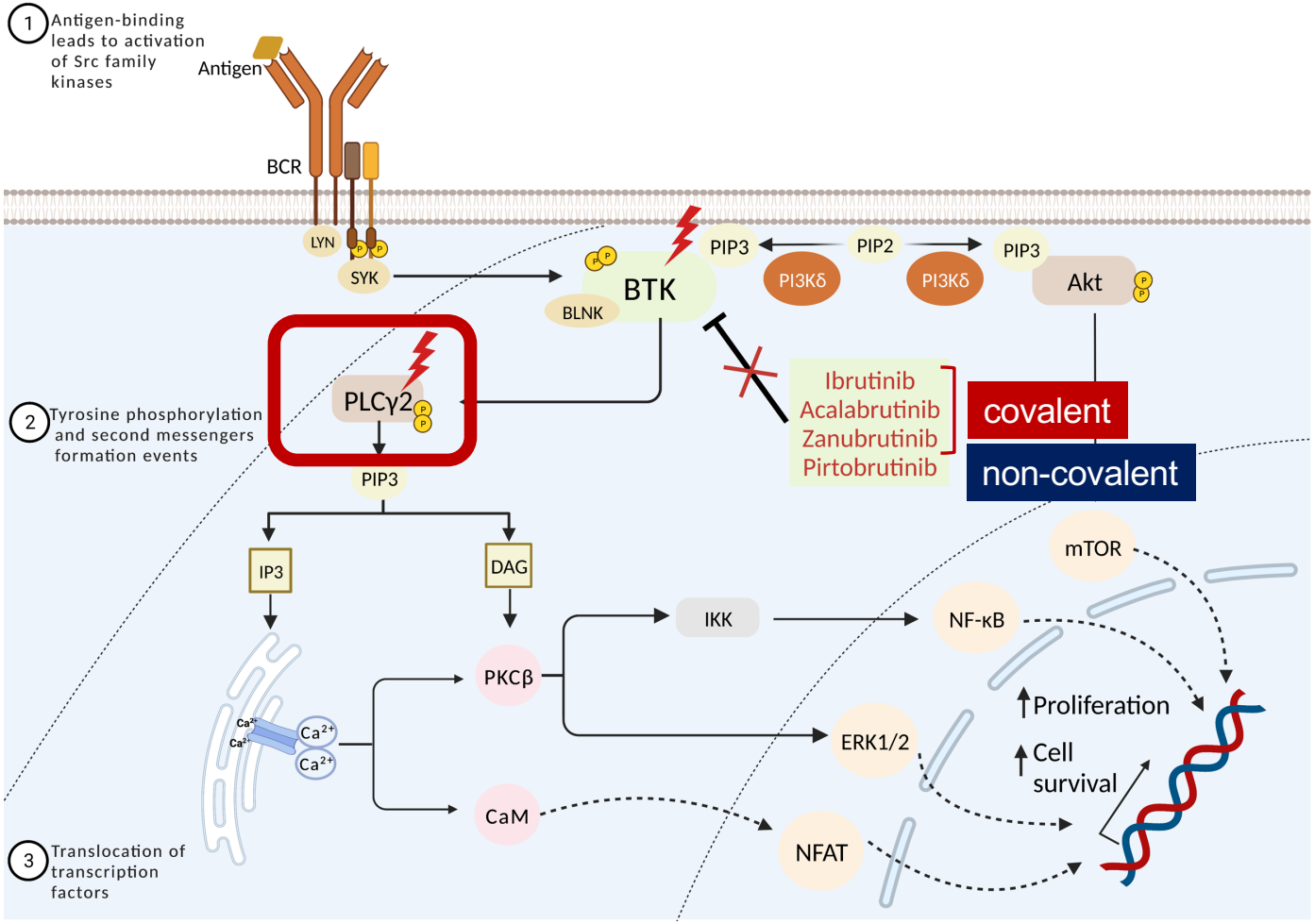
Genetic resistance to Zanubrutinib



- *BTK* C481 is the most common
- *BTK* Kinase-dead mutation L528W in 50%
- *BTK* Gatekeeper T474I not observed
- *PLCG2* M exclusive with BTK M
- Small numbers (23 cases from 3 cohorts)

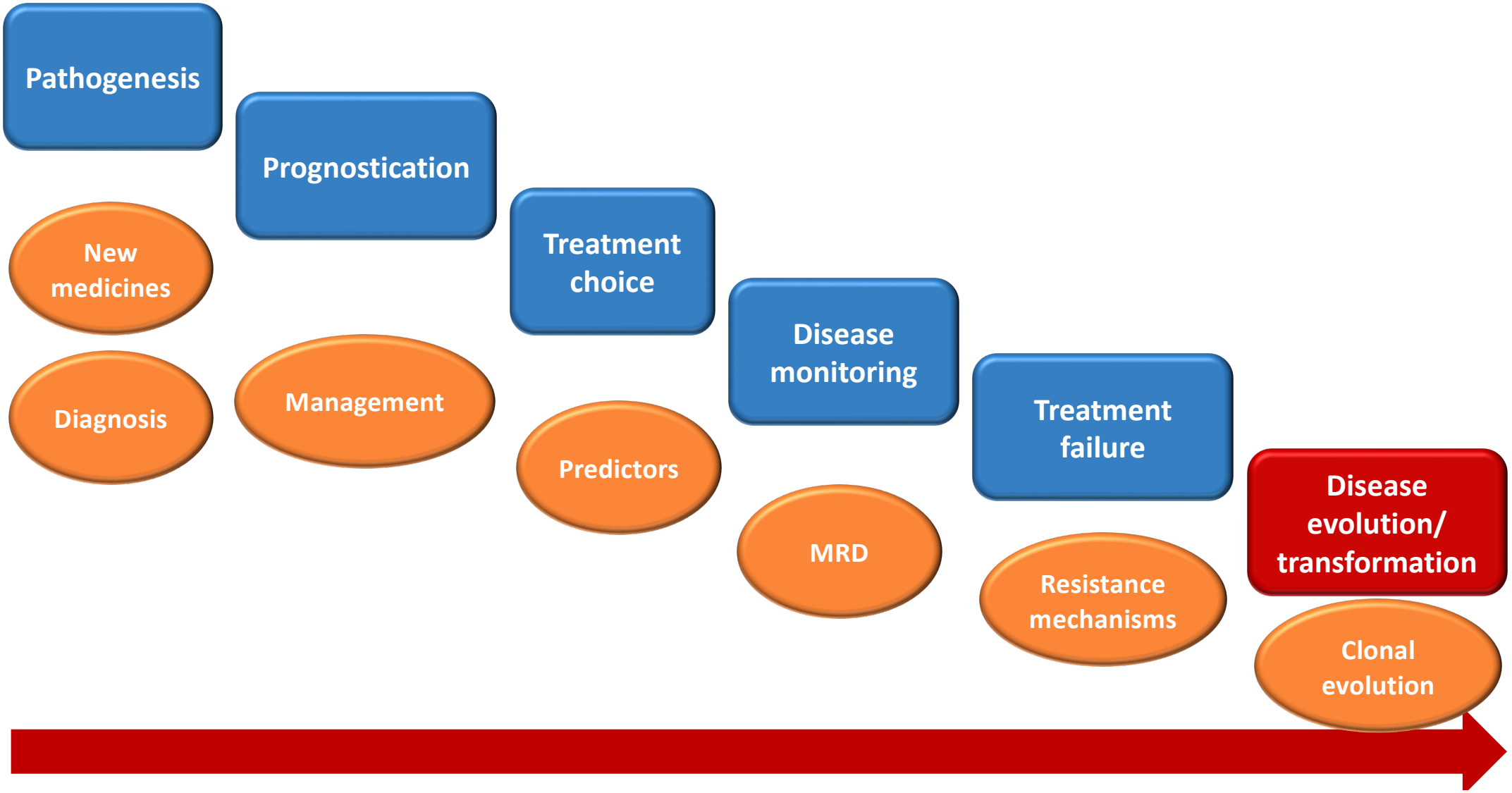
Blombery P, Blood Adv. 2022
Zhu H, Blood. 2022
Brown JR, Blood. 2023

Gain of Function PLCγ2 mutations bypass BTK targeting and constitutively activate BCR signaling



Maher et al, Int J Mol Sci 2023

Applications of molecular biology in CLL

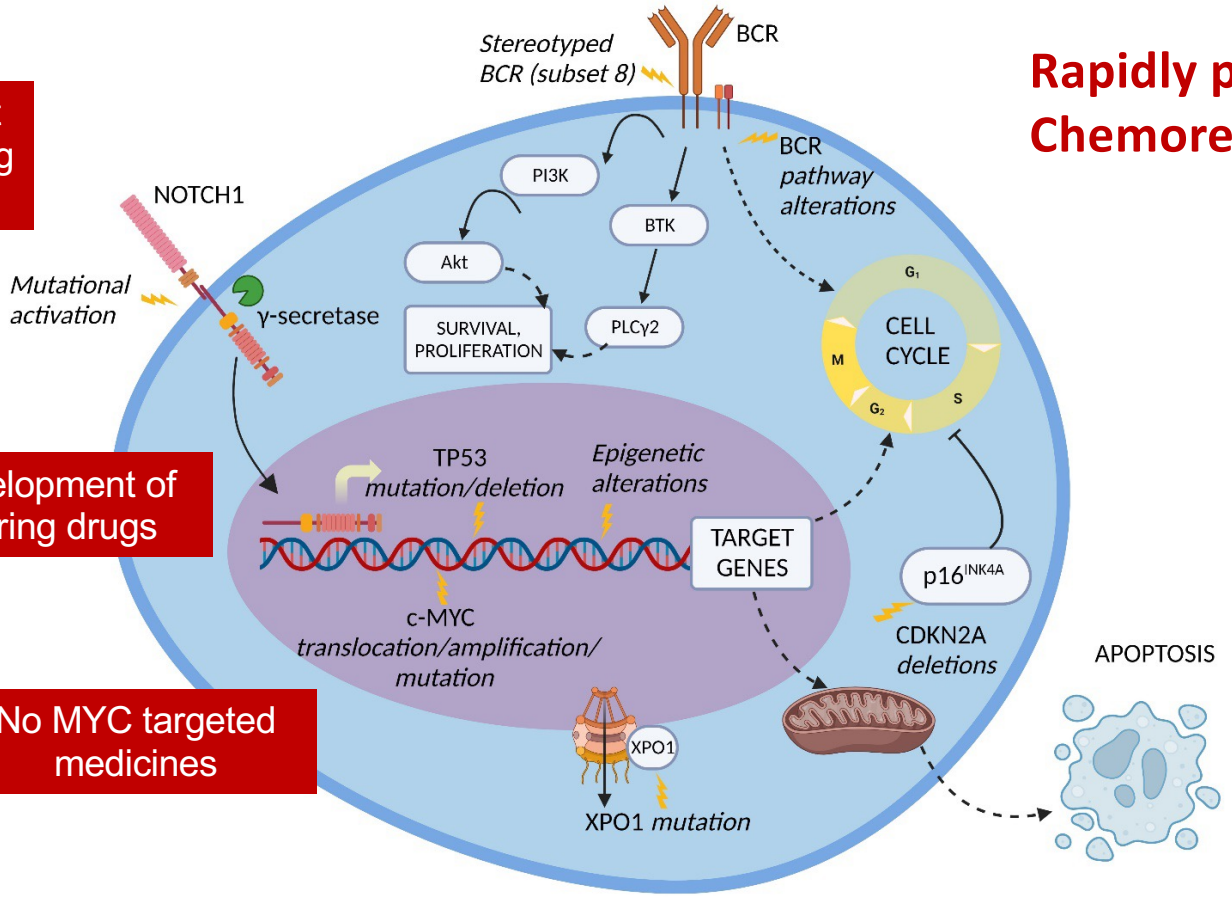


Reasons for treatment failure in Richter syndrome

Slow development of NOTCH targeting medicines

Difficult development of TP53 restoring drugs

No MYC targeted medicines



Rapidly progressive kinetics
Chemorefractoriness

Mouhssine and Gaidano, Cancers, 2022

blood

Title: International Consensus Statement on Diagnosis, Evaluation, and Research of Richter Transformation: ERIC Recommendations

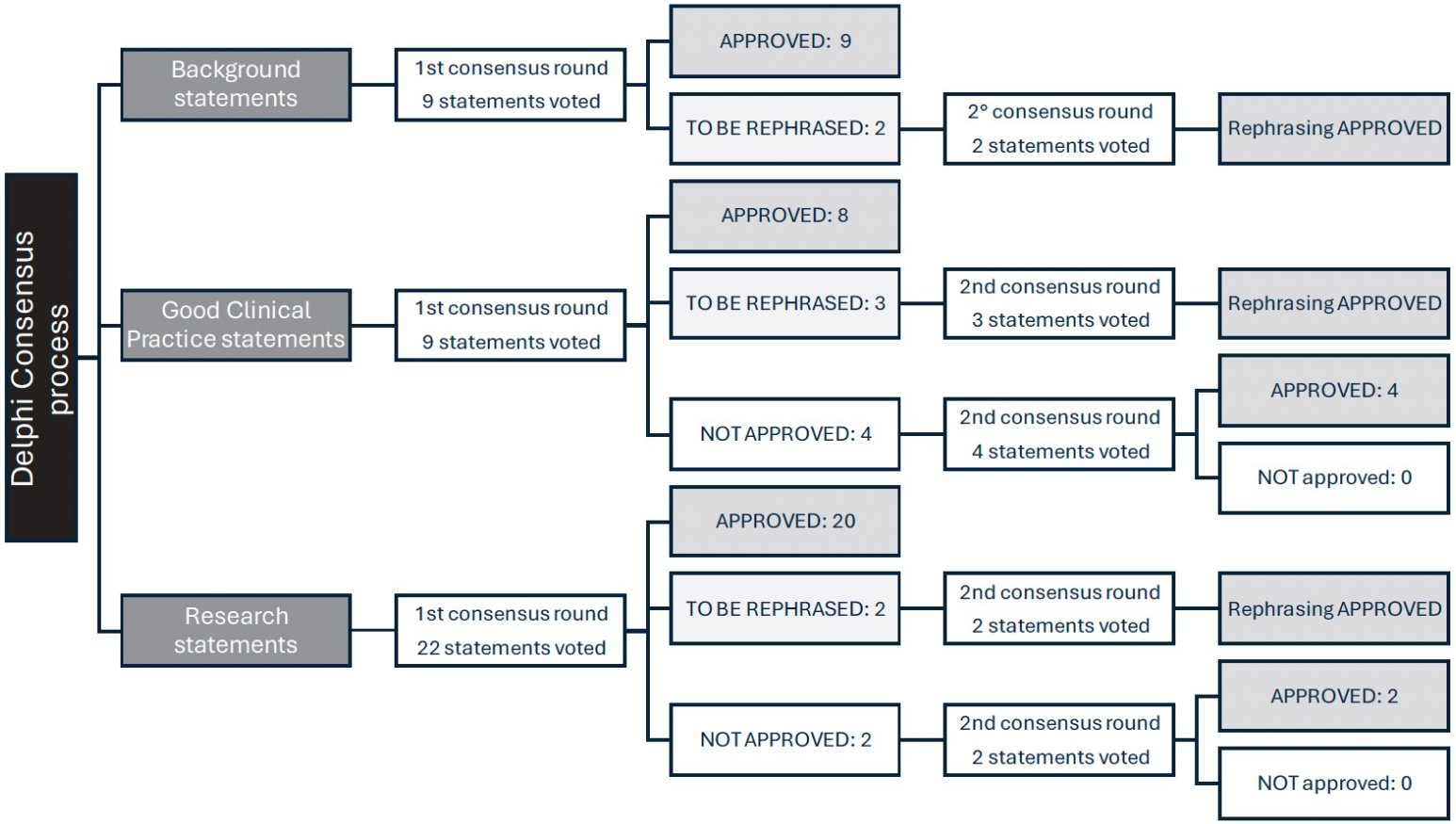
Short Title: Consensus Statements for Richter Transformation

Authors: Adam S Kittai*[1], Monia Marchetti*[2], Othman Al-Sawaf[3], Ohad Benjamini[4], Alexey V Danilov[5], Matthew S Davids[6], Barbara Eichhorst[3], Toby A Eyre[7], Anna Maria Frustaci[8], Michael Hallek[3], Paul J. Hampel[9], Yair Herishanu[10], Rodney J Hicks[11], Arnon P Kater[12], Rebecca L King[13], Jose Martin-Subero[14,15], Carolyn Owen[16], Erin Parry[6], Maurilio Ponzoni[17,18], Davide Rossi[19], Tanya Siddiqi[5], Stephan Stilgenbauer[20], Constantine S Tam[21], Elisa ten Hacken[22], Philip A Thompson[23,24], William Wierda[25], Gianluca Gaidano[#26], Jennifer A Woyach[#27], and Paolo Ghia[#18,28]

*ASK, MM – Contributed equally to this study
[#]GG, JAW, and PG – Contributed equally to this study

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

The Delphi process



Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Statements pertinent to RT diagnosis

1.2.1. RT should be suspected in patients with clinical decline, B-symptoms, elevated LDH, rapidly enlarging lymphadenopathy, and/or discordant response to CLL treatment
There should be strong consideration for RT in patients with discordant enlarging lymphadenopathy (e.g. one nodal group growing rapidly compared to others)

1.2.2. In patients with a clinical suspicion of RT, a PET-CT should be attained

1.2.3. The most accessible lesion with the highest avidity should be targeted for biopsy
SUV avidity of <5 suggests a low likelihood of RT

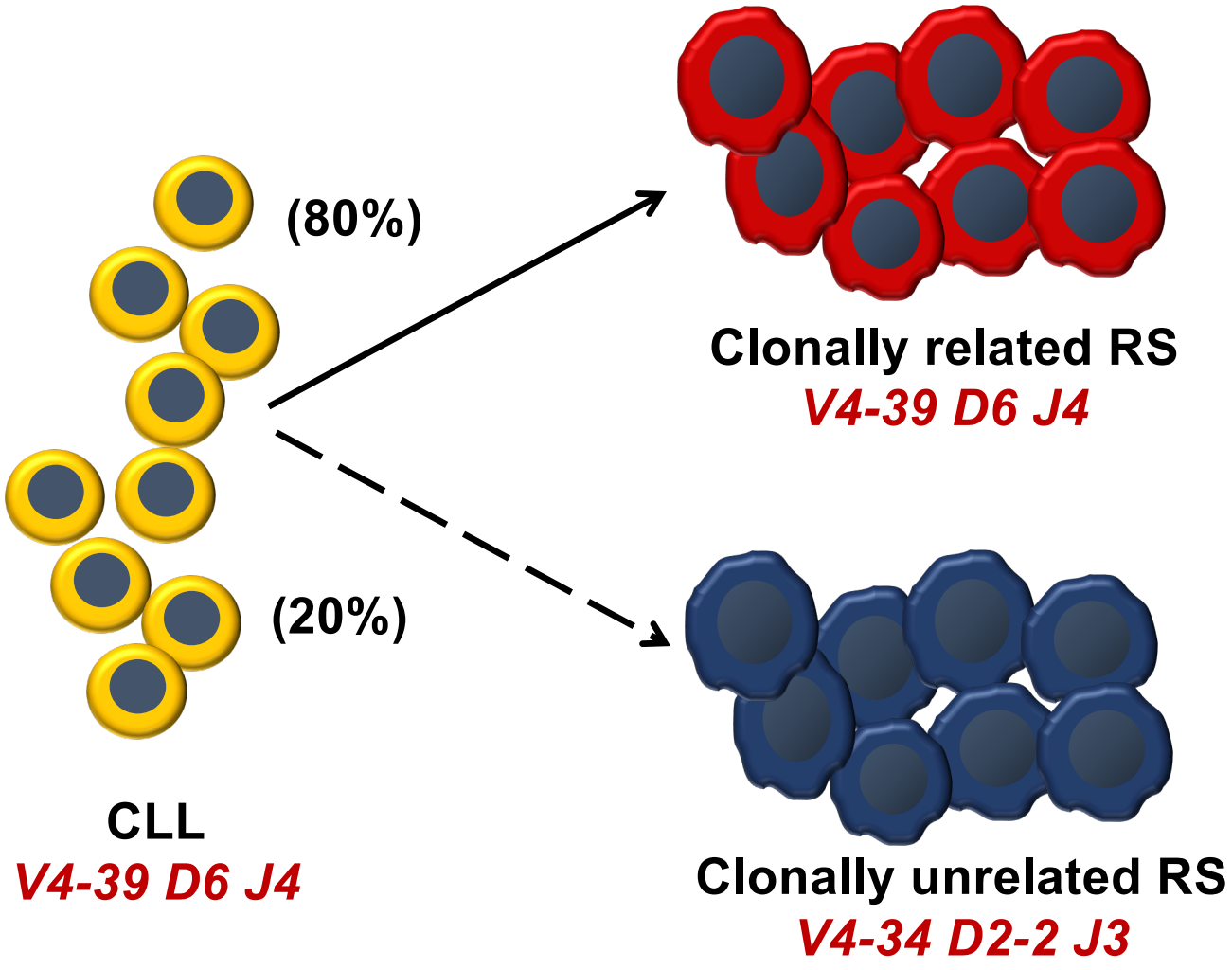
1.2.4. Biopsy of the affected tissue for histology assessment is needed to diagnose RT

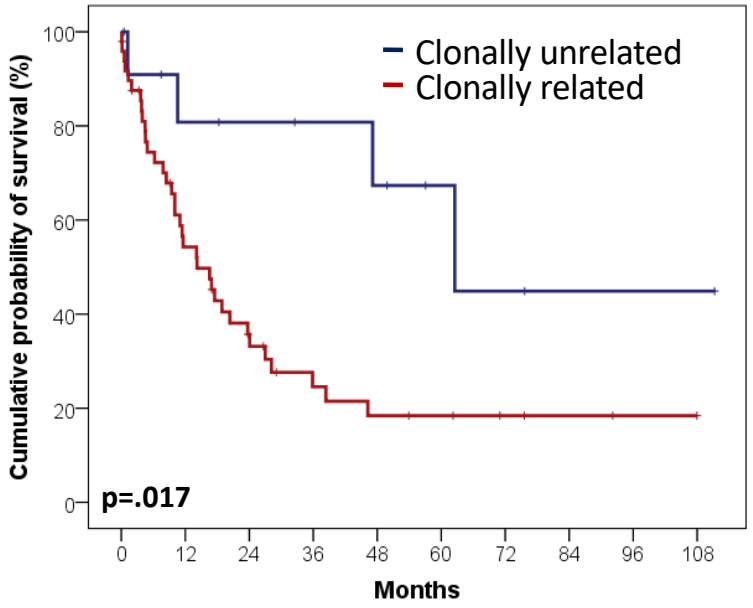
1.2.5. We strongly recommend attaining an excisional biopsy for diagnosis

1.2.6. All efforts should be made to have pathology reviewed by an expert hemopathologist

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Clonal relationship in Richter transformation

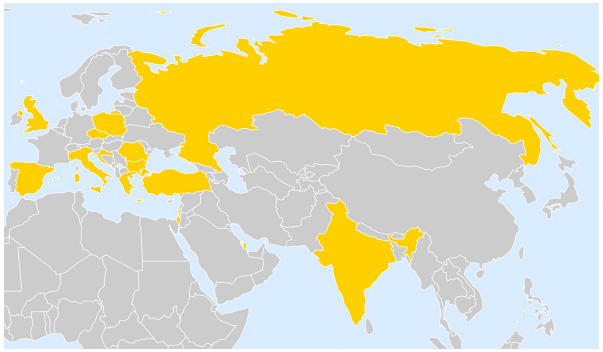




Rossi *et al., Blood.* 2011

ERIC Richter study: Patient characteristics

A total of 316 Richter transformation cases were collected from 24 hematological centers in 14 countries



ERIC countries involved till now in the project

Patients characteristic at the time of CLL

Variables	N (%)
Median age at CLL diagnosis	61 years (IQR 52-67)
Gender	
Female	121 (34.4%)
Male	231 (65.6%)
Binet stage	
A	161 (51.3%)
B	110 (35.0%)
C	43 (13.7%)
IGHV mutational status	
Mutated	52 (25.5%)
Unmutated	152 (74.5%)
***TP53* mutated**	
Yes	32 (23.2%)
No	106 (76.8%)
Median number of CLL lines of therapy	3 (IQR 2-4)
Treated with BTKi at any line of treatment	
Yes	124 (40.7%)
No	181 (59.3%)
Treated with BCL2i at any line of treatment	
Yes	62 (22.1%)
No	218 (77.9%)

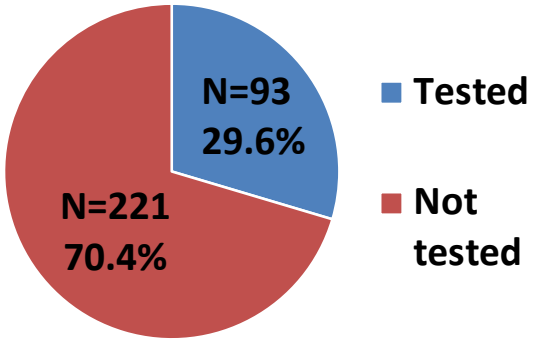
Patients characteristic at the time of RT

Variables	N (%)
Median age at Richter	68 years (IQR 60-74)
Median time from CLL diagnosis to Richter transformation	5.6 years (IQR 2.3-9.1)
***TP53* mutated**	
Yes	28 (41.8%)
No	39 (58.2%)
Histology of Richter	
DLBCL	268 (84.8%)
Hodgkin lymphoma	28 (8.9%)
Other	20 (6.3%)

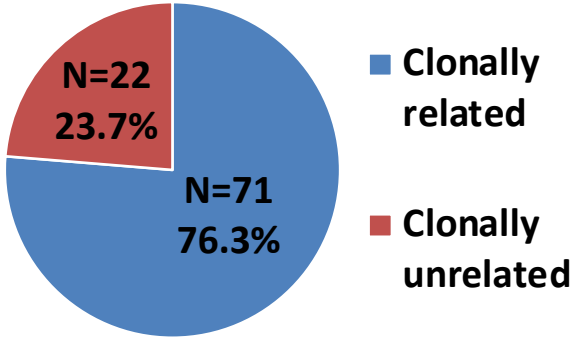
Moia et al, ERIC 2024

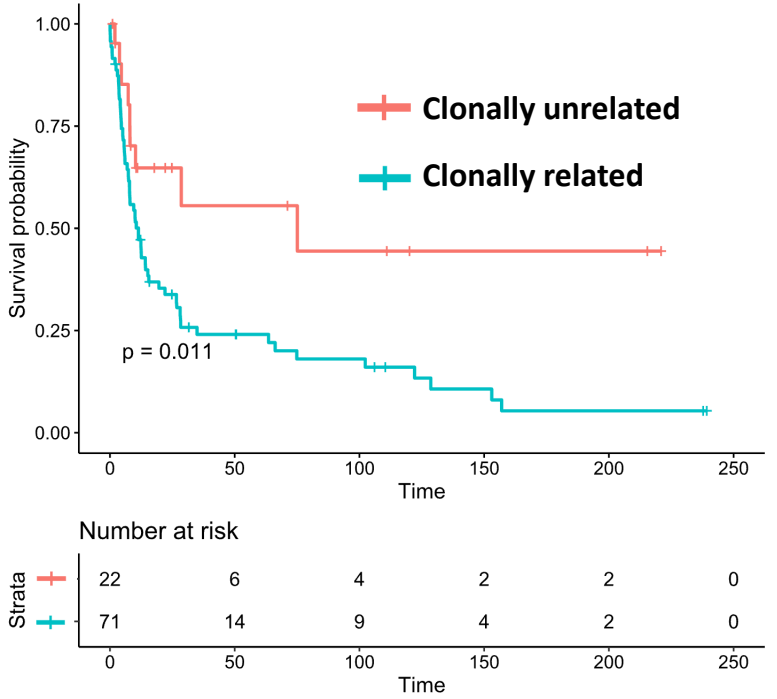
ERIC Richter study: Clonal relationship represents the most important prognostic/predictive factor in Richter transformation

Clonal relationship assessment



Clonal relationship results





Clonally related Richter significantly associated with shorter survival

Moia et al, ERIC 2024

Statements pertinent to RT diagnosis

1.2.7. Clonal relationship of the RT tissue and antecedent CLL cells should be tested, as it is one of the strongest prognostic factors for RT survival: patients with clonally unrelated RT have a markedly better prognosis

2.2.1. Clonality should be determined by comparing IG gene rearrangement from the RT tissue to the IG gene rearrangement in the CLL cells

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

International Consensus Statement on Diagnosis, Evaluation, and Research of Richter Transformation

Context of Research

Richter transformation (RT) remains a rare entity and is associated with dismal outcomes. There is no consensus on the study or management of RT currently published.

Aim of This Study

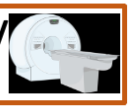
We convened a group of 29 international experts on RT to establish consensus recommendations on the diagnosis, evaluation, and research of RT.

Findings

Diagnosis/ Prognosis

-We strongly recommend attaining an excisional biopsy on the most metabolically active, accessible lymph node for diagnosis.
-Current standard of care treatment with RCHOP-like regimens has poor efficacy.

Prognostication/ Staging



-Clonality should be determined by comparing IG gene rearrangements from the RT tissue and the CLL cells.
-We recommend using a pre-treatment PET-CT to establish the extent of the disease.

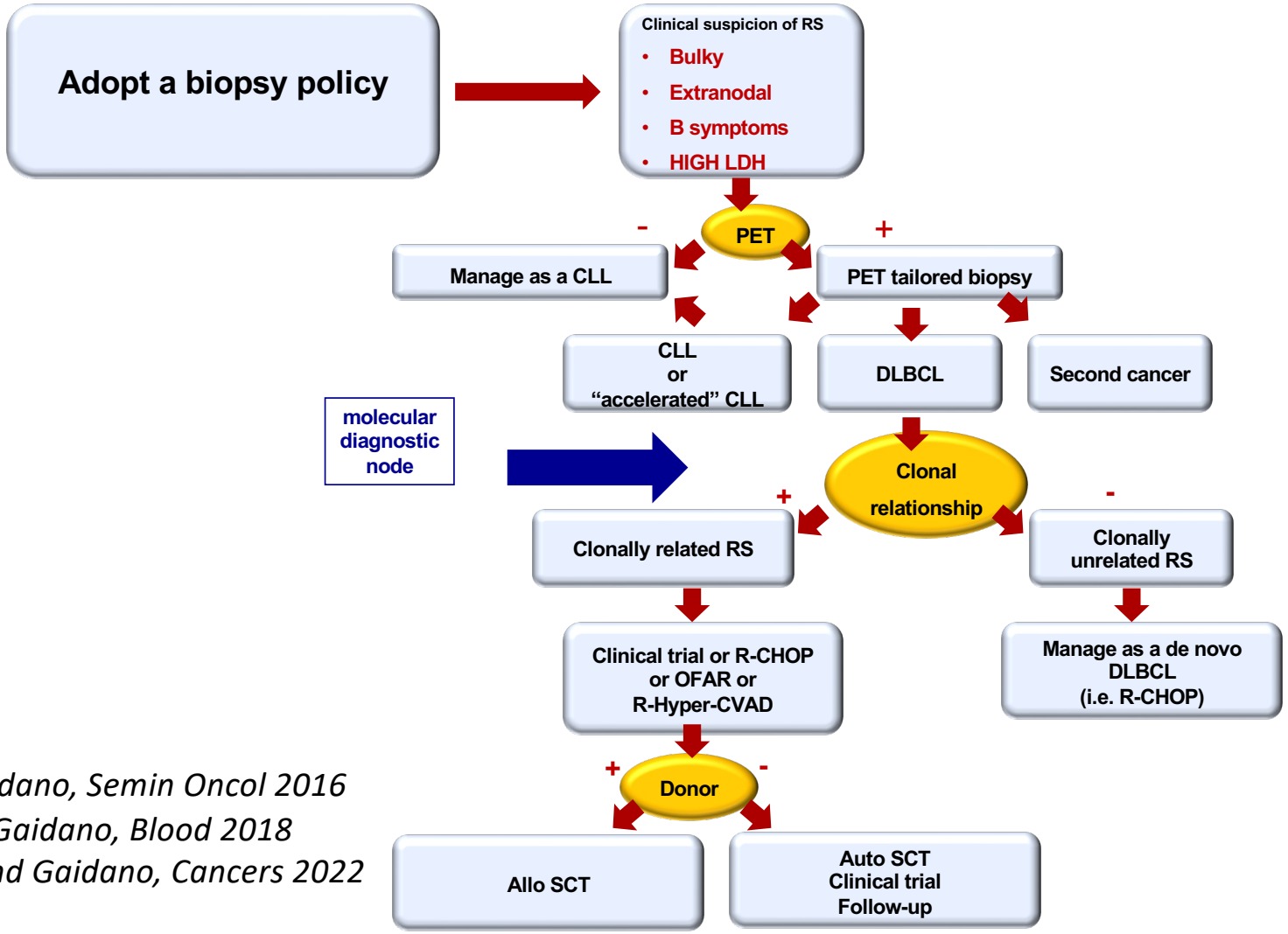
Clinical Trial Recommendations

-If at all possible, patients with RT should be treated on clinical trials.
-Response of RT and CLL should be objectively assessed and reported based on both Lugano criteria as well as iwCLL guidelines.

Conclusions: Given the poor outcomes associated with RT, participation in clinical trials should be encouraged. Prospective clinical studies along with collection of primary longitudinal samples are needed to develop rational therapeutic strategies for this disease.

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Clinical algorithm for managing Richter transformation



Rossi and Gaidano, Semin Oncol 2016
Rossi, Spina, Gaidano, Blood 2018
Mouhssine and Gaidano, Cancers 2022

Conclusions

- BCR signaling pathway and BCL2-mediated inhibition of apoptosis represent the mainstay of CLL pathogenesis and provide actionable therapeutic targets
- Biomarkers are relevant in 1L treatment choice also in the era of pathway inhibitors
- Chemoimmunotherapy has no longer a role in CLL treatment if pathway inhibitors are accessible
- Continuous therapy with BTKi overcomes the adverse prognostic impact of disrupted *TP53*
- Multiple chemo-free options are available for 1L treatment according to molecular predictors, fitness, age and patient preferences
- Treatment sequencing of R/R patients highly depends on 1L therapy
- Richter transformation should be appropriately suspected and diagnosed, also considering the new therapeutic developments