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EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

Session 6: CLL

Clinical management of CLL from biomarkers to treatment choice

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Disclosures

Scientific Advisory Board: AbbVie, Astra Zeneca, BeiGene, Incyte, Janssen, Lilly

Speakers Bureau: Abbvie, Astra Zeneca, Janssen

Learning Objectives

1. Understand the relevance of biology and biomarkers in the management of CLL
2. Manage asymptomatic CLL
3. Navigate among the treatment options currently available for treatment-naïve CLL
4. Manage treatment of relapsed/refractory CLL
5. Define a diagnostic and therapeutic approach for Richter transformation

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CLL *vs.* Monoclonal B cell lymphocytosis (MBL)

	NCI 1996 guidelines	IWCLL 2008 & 2018 guidelines
CLL	Lymphocytes $\geq$ $5.0x10^9/L$	Monoclonal B lymphocytes: $\geq$ $5.0x10^9/L$ *
MBL	*Not included*	Monoclonal B lymphocytes: < $5.0x10^9/L$

*Clonal B lymphocytes must have the typical CLL phenotype (CD19+ CD20+ CD23+ CD5+ sIg low)

Definition and classification

Conceptual frame

	CLL L = leukemia	SLL L = lymphoma
Clinical presentation	liquid	solid
Molecular features	del13q, +12, del11q, *TP53*, *NOTCH1*, *SF3B1*, *BIRC3*, *XPO1*, IGHV M/UM	
Nosology	**CLL / SLL**	

Classification

WHO 4th ed, 2017

- Although CLL and SLL are the ***same*** disease, the term SLL is used for cases with a circulating CLL cell count < $5x10^9$/L and ***documented*** nodal, splenic or other extramedullary involvement
- SLL is diagnosed in 10-20% of cases, and as many as 20% evolve into frank CLL
- Of 22 SLL citations, 19 are as CLL/SLL

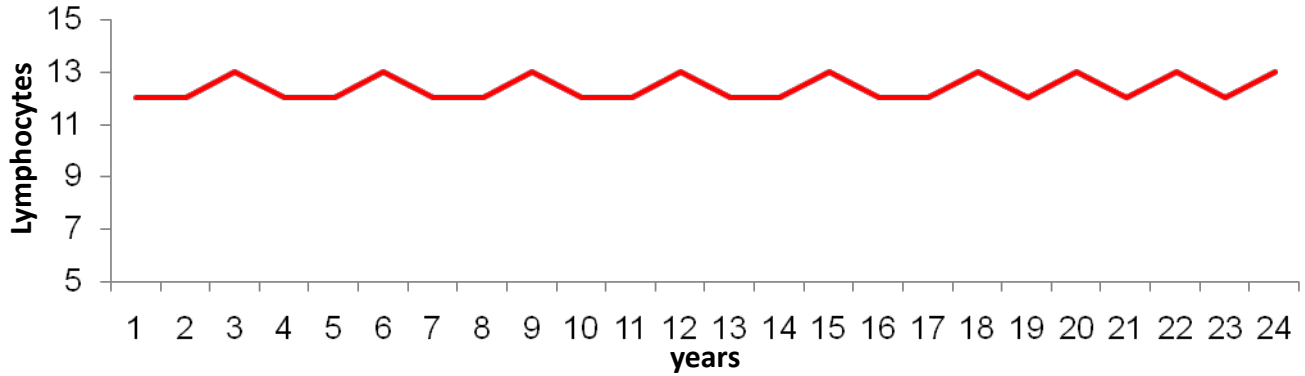
ICD-O code: 9823/3

WHO-HAEM5: same as WHO 4th edition

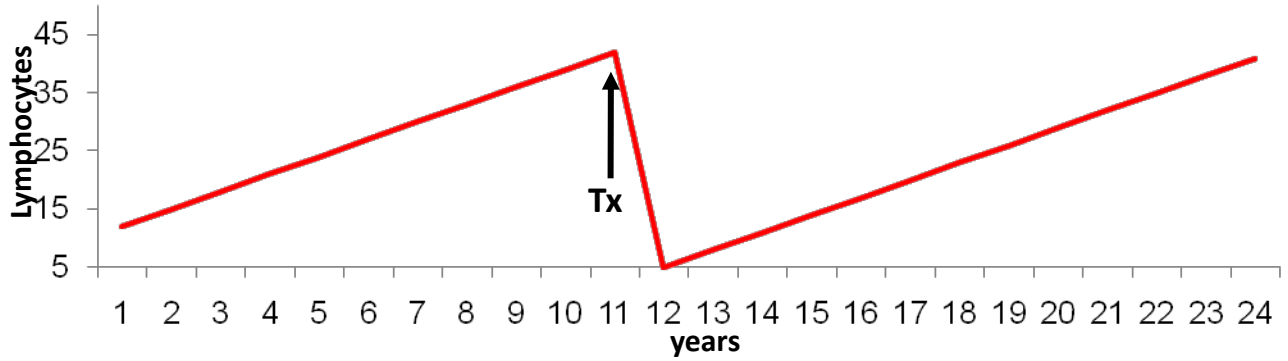
ICC: same as WHO 4th edition

CLL: Homogeneous phenotype but heterogeneous clinical course

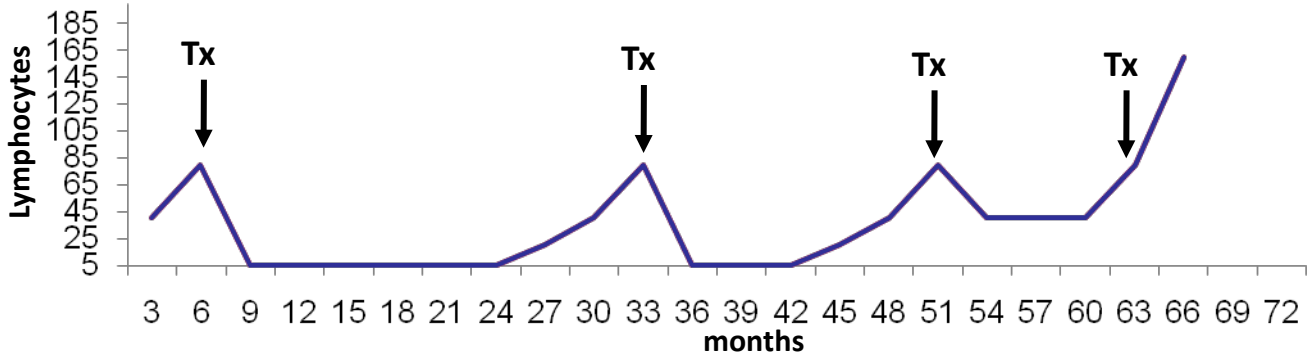
Highly stable



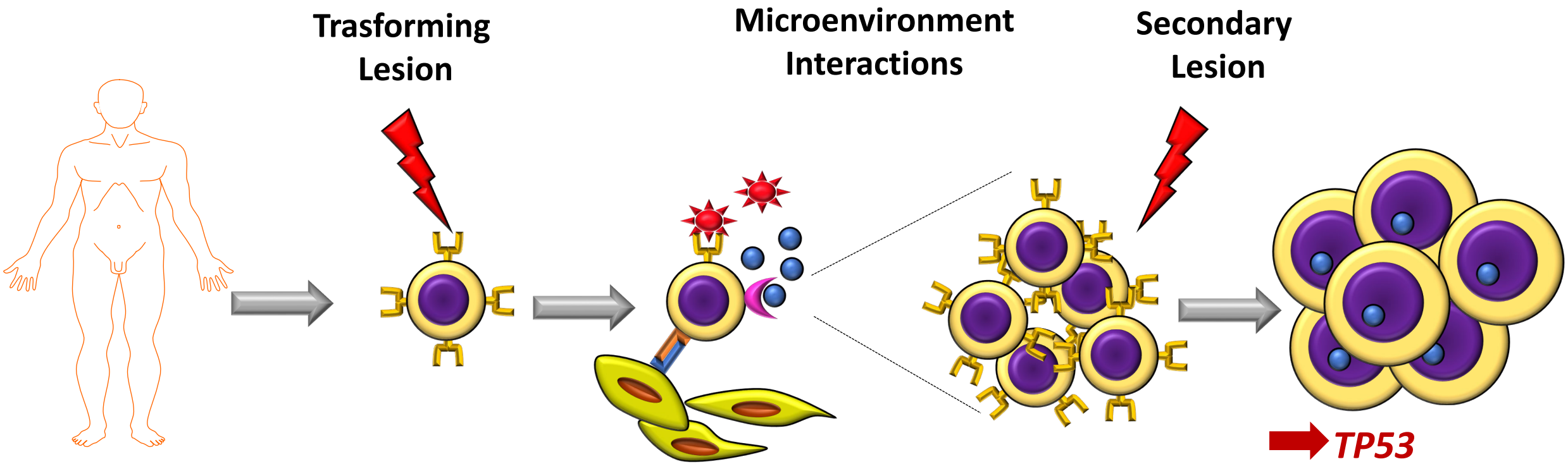
Slowly progressive



Rapidly progressive



Pathogenesis of CLL reveals therapeutic predictors and targets



Predisposition

Polygenic
IRF4, IRF8
Other

Initiation

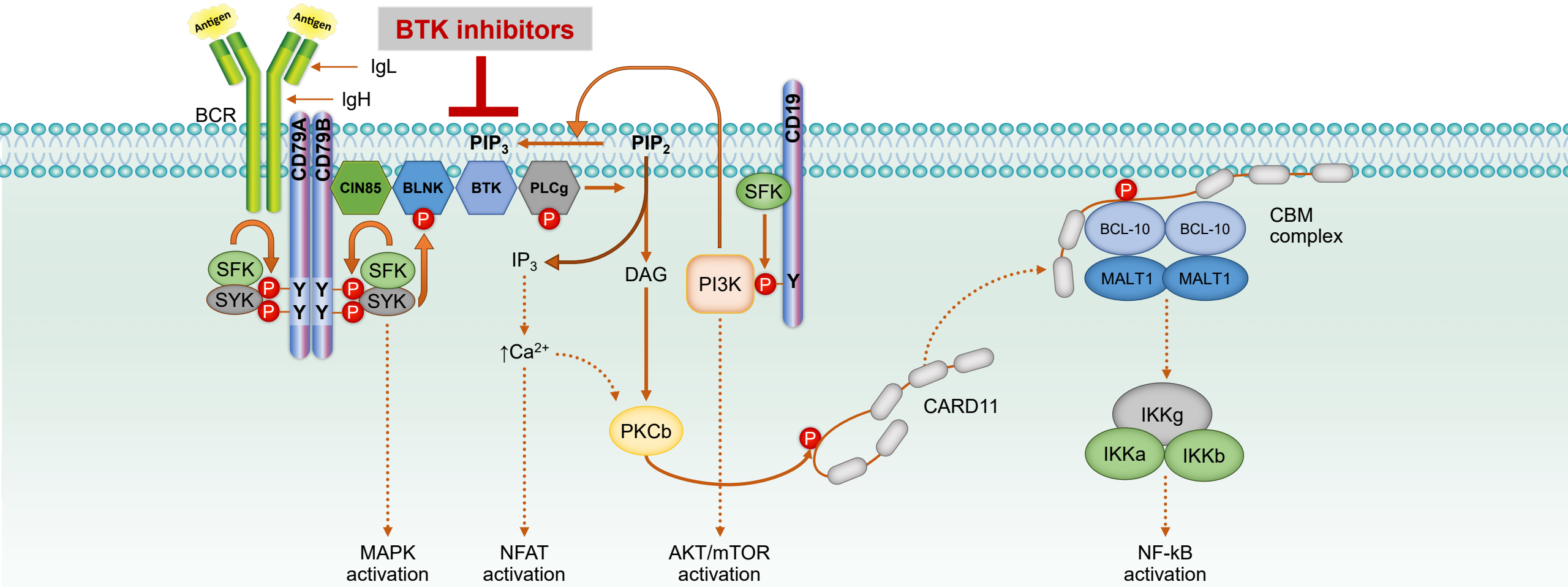
Del13q (BCL2)
+12
MYD88

Promotion/Accumulation

BCR TLR
CD38 VLA-4
NOTCH CXCR4

Gaidano et al, Hematology 2017; Mouhssine and Gaidano, Cancers 2023; Moia and Gaidano, Semin Hematol 2024

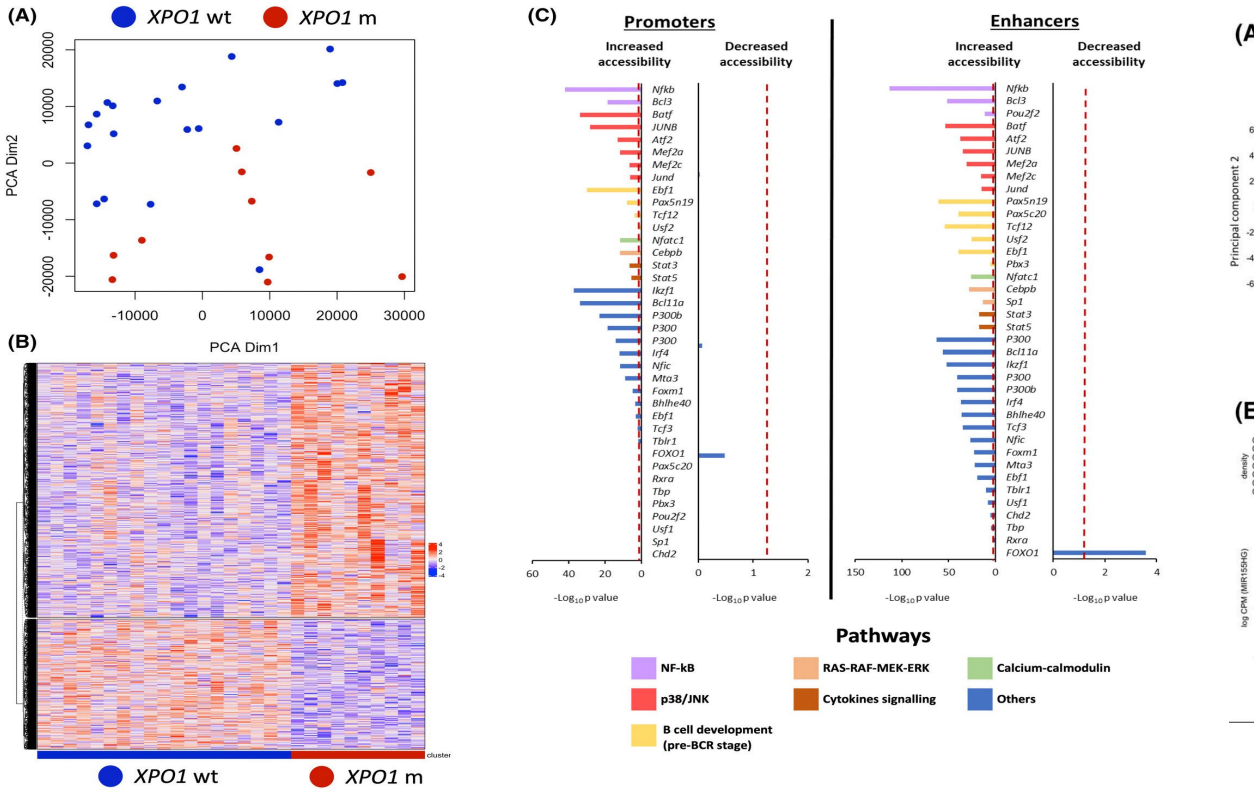
Role of BTK in the BCR signaling pathway

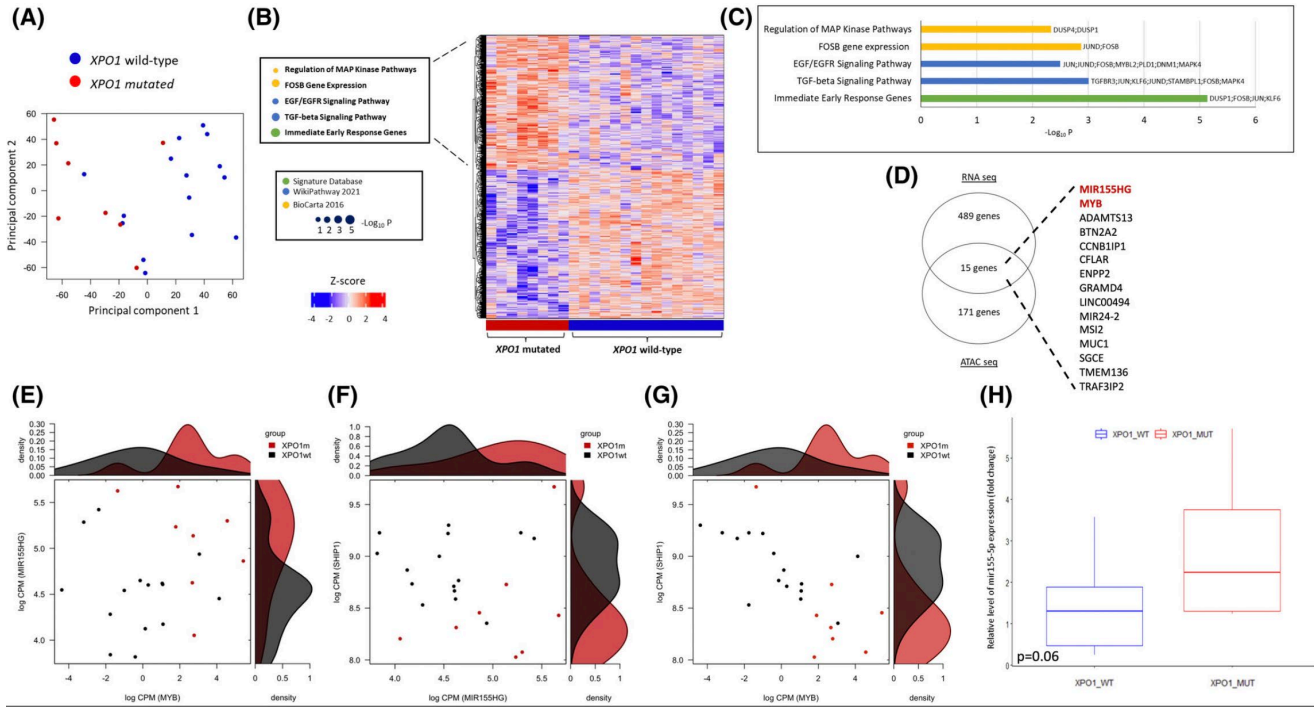


AKT = protein kinase B; BCL-10 = B-cell lymphoma/leukemia 10; BCR = B-cell receptor; BLNK = B-cell linker protein; BTK = Bruton tyrosine kinase; CARD11 = caspase recruitment domain-containing protein 11; CIN85 = Cbl-interacting protein of 85 kDa; CBM = CARD11–BCL-10–MALT1; CD = cluster of differentiation; DAG = diacylglycerol; IgH = immunoglobulin heavy chain; IgL = immunoglobulin light chain; IKK = inhibitor of NF-κB kinase; MALT1 = mucosa-associated lymphoid tissue lymphoma translocation protein 1; MAPK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; NF-kB = nuclear factor kappa-light chain enhancer of activated B cells; NFAT = nuclear factor of activated T cells; PI3K = phosphoinositide 3-kinase; PIP = phosphatidylinositol; PKC = protein kinase C; PLC = phospholipase C; SFK = SRC-family kinase; SYK = spleen tyrosine kinase.

- Adapted from Young RM et al. *Nat Rev Drug Discov*. 2013;12(3)229-43

Mutations of the *XPO-1* nuclear exporter confer different chromatin accessibility and a trascriptome profile featuring cytokine and BCR signaling





- By ATAC-seq, chromatin regions that were more accessible in *XPO1* mutant CLL were enriched of binding sites for transcription factors regulated by **pathways emanating from the B-cell receptor (BCR), including NF-κB signalling, p38-JNK and RAS-RAF-MEK-ERK**
- *XPO1* mutant CLL, consistent with the chromatin accessibility changes, were enriched with transcriptomic features associated with **BCR and cytokine signalling**

Moia et al., Br J Haematol 2023

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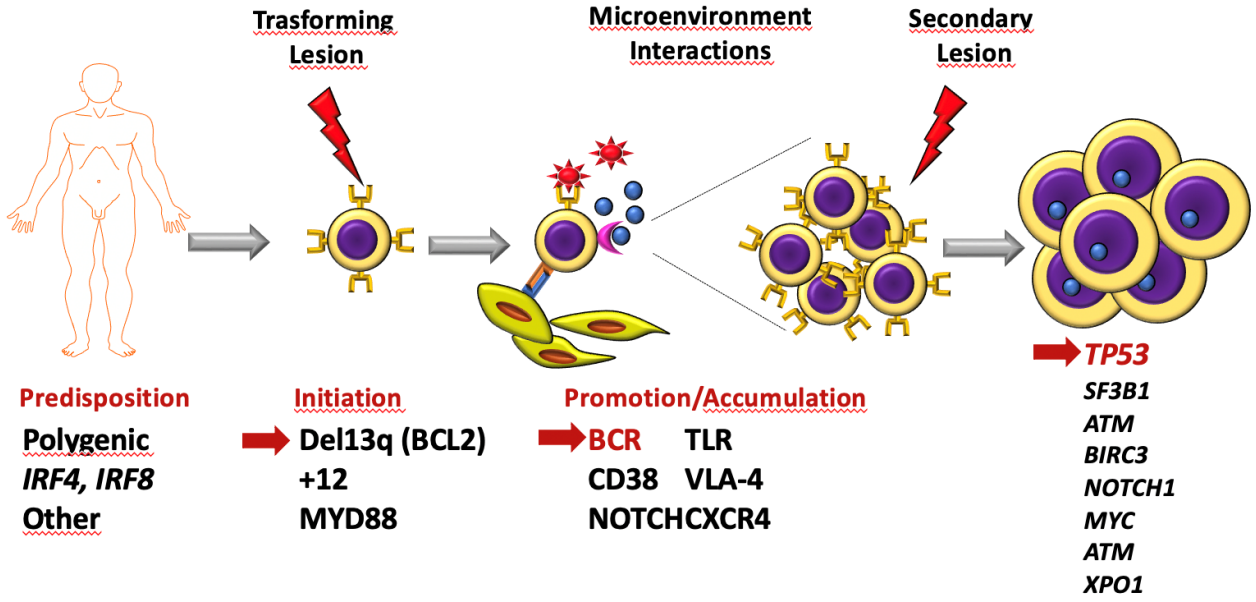
Clinical relevance of CLL translational molecular biology



Predictive biomarkers

- **Treatment tailoring**

Pathway inhibitors

- **Chemo-free treatment**

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Asymptomatic CLL

Watch and wait

- Explain in detail to the patient
- Clarify with the General Practioner

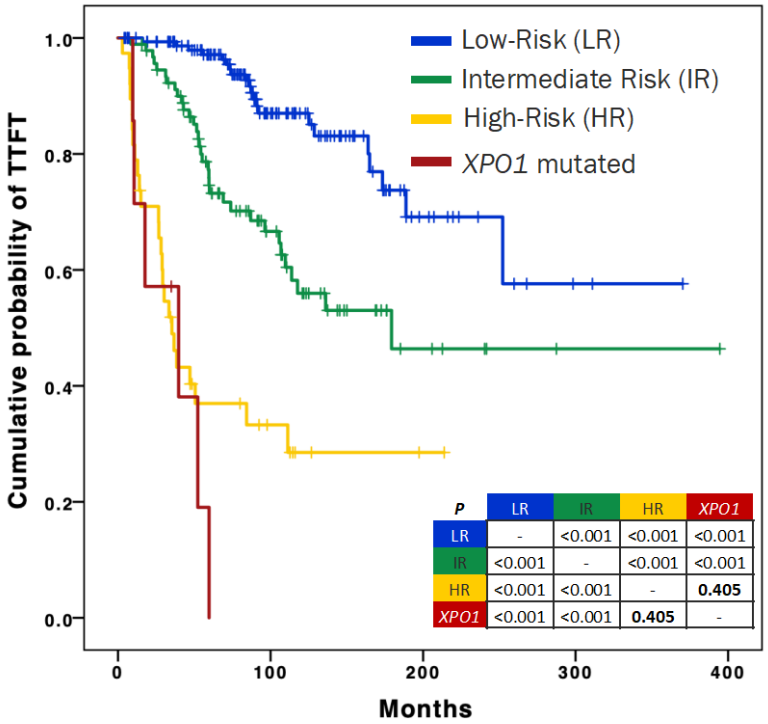
Hallek *et al. Blood*. 2018

Early stage CLL prognostic scores

IPS-E[1]

N=295 patients

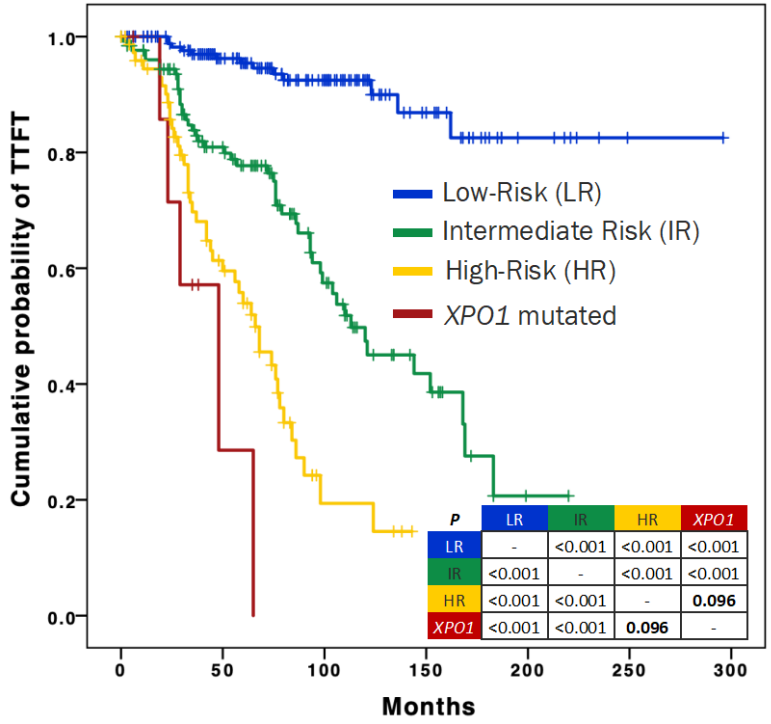
Variable	HR	95% C.I.	p value
Unmutated IGHV	3.85	2.44-6.06	<0.0001
Palpable lymph nodes	2.49	1.57-3.97	<0.001
Lymphocyte >15,000/µL	1.98	1.23-3.20	0.005
***XPO1* mutations**	**2.74**	**1.11-6.74**	**0.028**



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.* 2023

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When to treat?
Revised iwCLL guidelines: The concept of active disease

Active disease should be clearly documented to initiate therapy.

At least one of the following criteria should be met:

- Evidence of progressive marrow failure
- Massive (i.e., ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period, or lymphocyte doubling time (LDT) of less than 6 months
- Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids
- Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine)
- Disease-related symptoms

Hallek et al., Blood. 2018; 131(25):2745-2760

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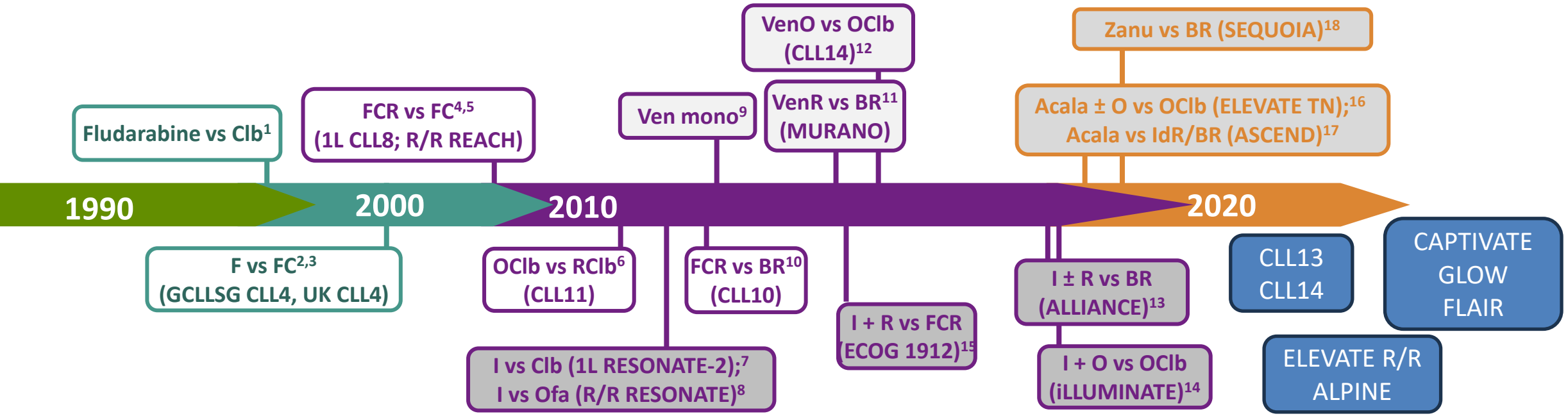
Evolution of CLL Treatment – Key Treatment Milestones



Goals of therapy

Alleviating symptoms → **Improving survival** → **Reducing toxicity, while improving outcomes in more patients**

*1. Rai KR, et al. N Engl J Med 2000; **343:**1750–1757; 2. Eichhorst BF, et al. Blood 2006; **114:**3382–3391;*
*3. Catovsky D, et al. Lancet 2007; **370:**230–239; 4. Hallek M, et al. Lancet 2010; **376:**1164–1174; 5. Robak T, et al. J Clin Oncol 2010; **8:**1756–1765;*
*6. Goede V, et al. N Engl J Med 2014; **370:**1101–1110; 7. Burger JA, et al. N Engl J Med 2015; **373:**2425–2437; 8. Byrd JC, et al. N Engl J Med 2014; **372:**213–223;*
*9. Roberts AW, et al. N Engl J Med 2016; **374:**311–322; 10. Eichhorst B, et al. Lancet Oncol 2016; **17:**928–942; 11. Seymour JF, et al. N Engl J Med 2018; **378:**1107–1120;*
*12. Fischer K, et al. N Engl J Med 2019; **380:**2225–2236; 13. Woyach JA, et al. N Engl J Med 2018; **379:**2517–2528 (incl. suppl.); 14. Moreno C, et al. Lancet Oncol 2019; **20:**43–56;*
*15. Shanafelt TD, et al. N Engl J Med 2019; **381:**432–443; 16. Sharman JP, et al. Lancet 2020; **379:**1278–1291; 17. Ghia P, et al. J Clin Oncol 2020; **38:**2849–2861; 18. Tam CS, et al. Lancet Oncol 2022; **23**:1031-1043. .*

Test for predictive biomarkers before staring CLL treatment

Prognostic biomarkers

Richter syndrome

Death

Toxicity

Progression

Patient counseling

Frequency of follow-up

Predictive biomarkers

continuous BTKi

FD: Ibrutinib-Venetoclax

FD: Venetoclax-obinutuzumab

(chemoimmunotherapy)*

Treatment tailoring

- **TP53 status**
- **IGHV mutation status**

*to be considered only in case of no access to pathway inhibitors

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

Progression of early stage CLL

- IGHV
- *XPO1*

Treatment choice

- *TP53*
- IGHV
- CK
- *NOTCH1*

Treatment monitoring

- MRD

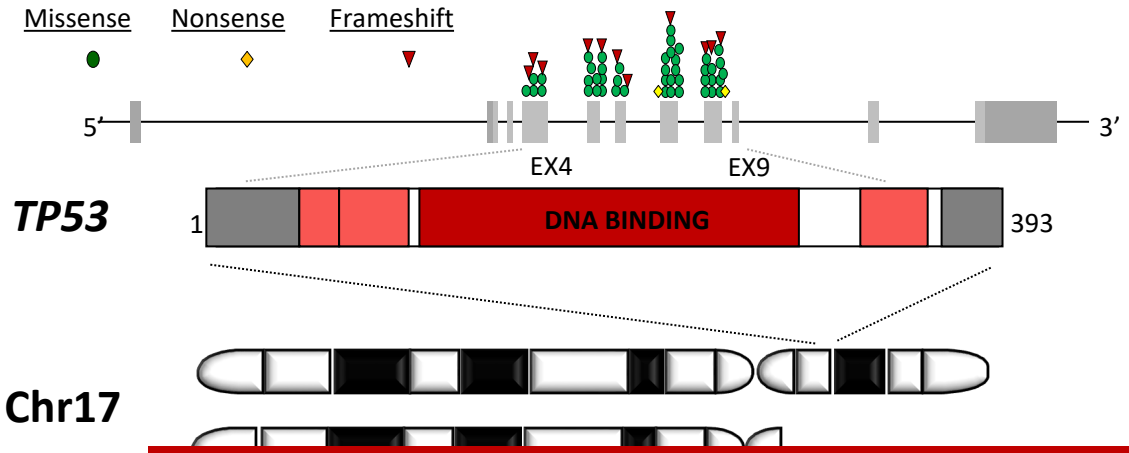
Refractoriness mutations

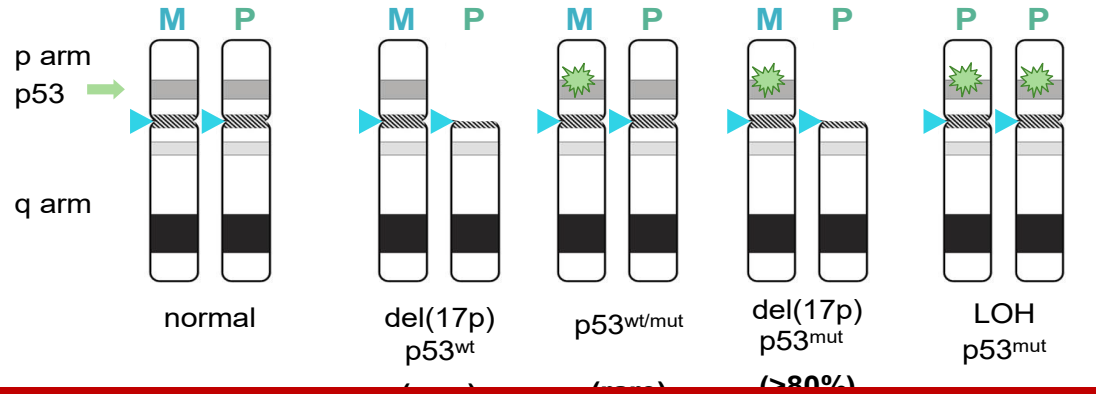
- *BTK*
- *BCL2*

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

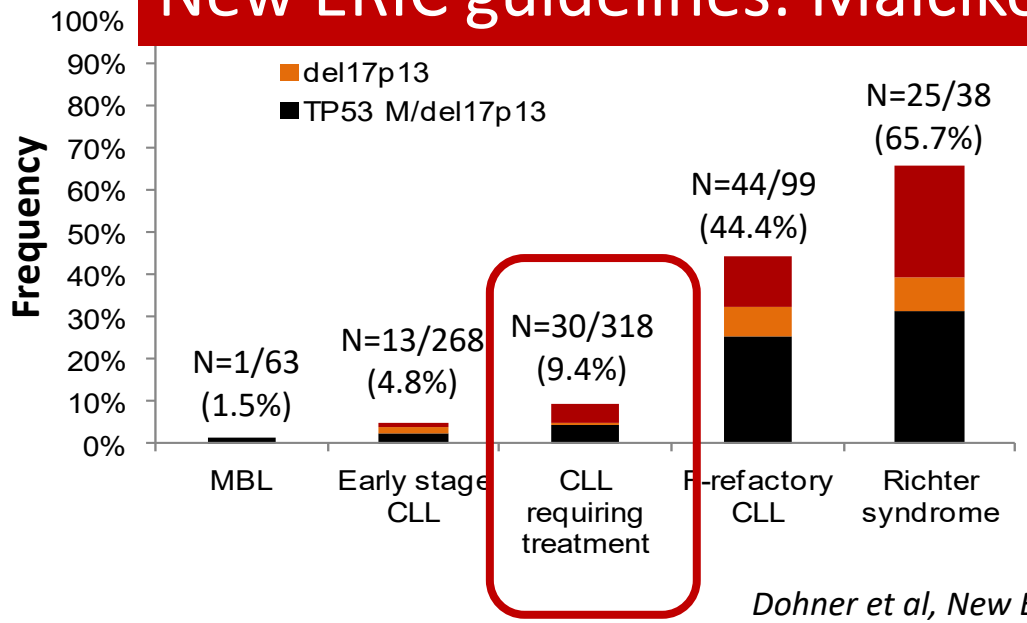
Hallek et al. *Blood* 2018; 131 (25): 2745–2760

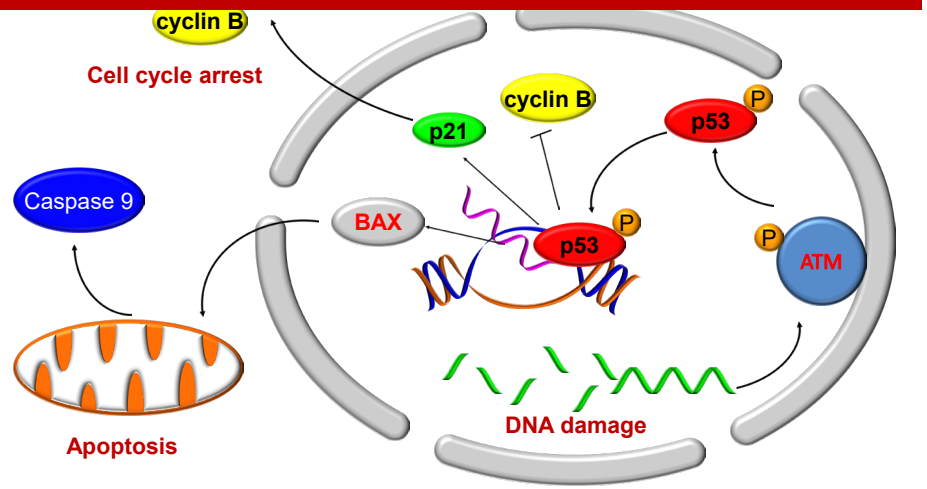
TP53 abnormalities in CLL





New ERIC guidelines: Malcikova et al, *Leukemia* 2024; 38:1455-1468





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; Maher et al, Int J Mol Sci 2023

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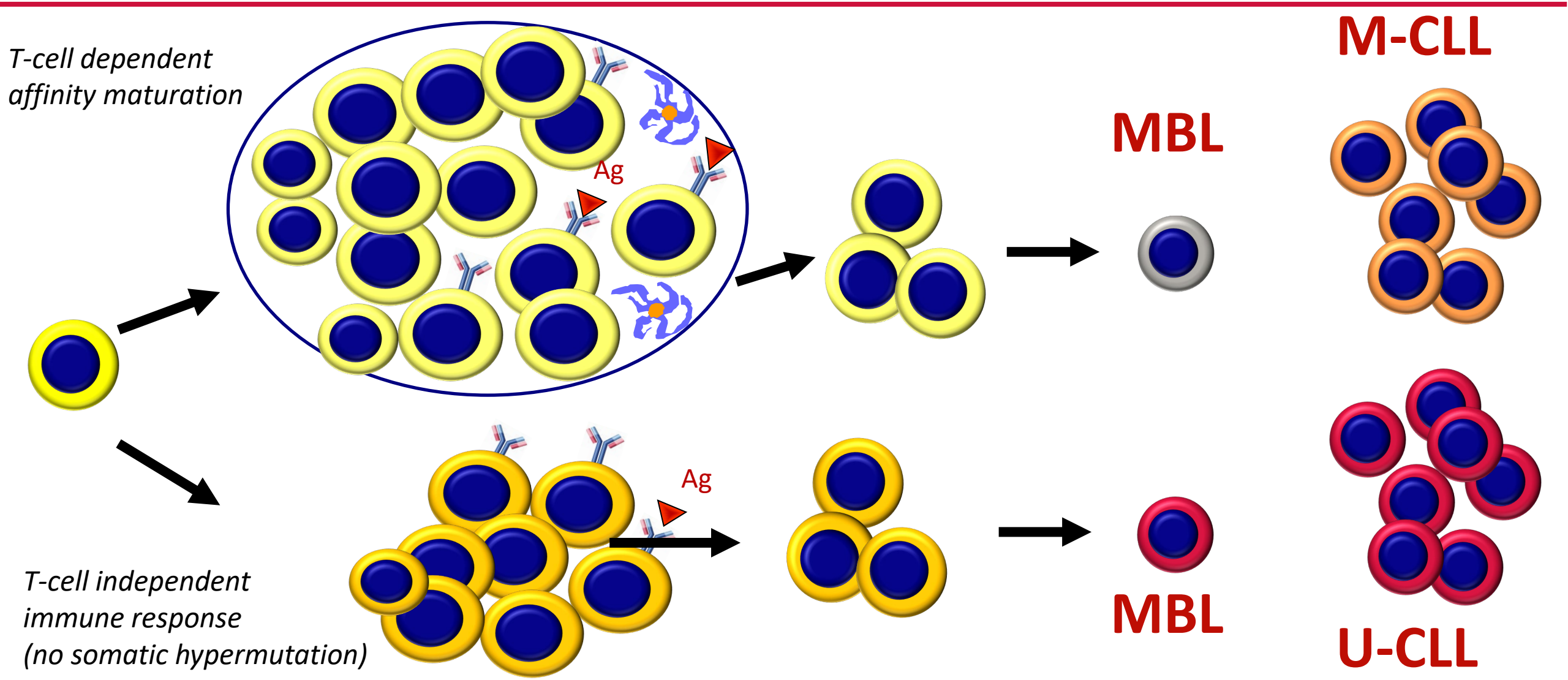
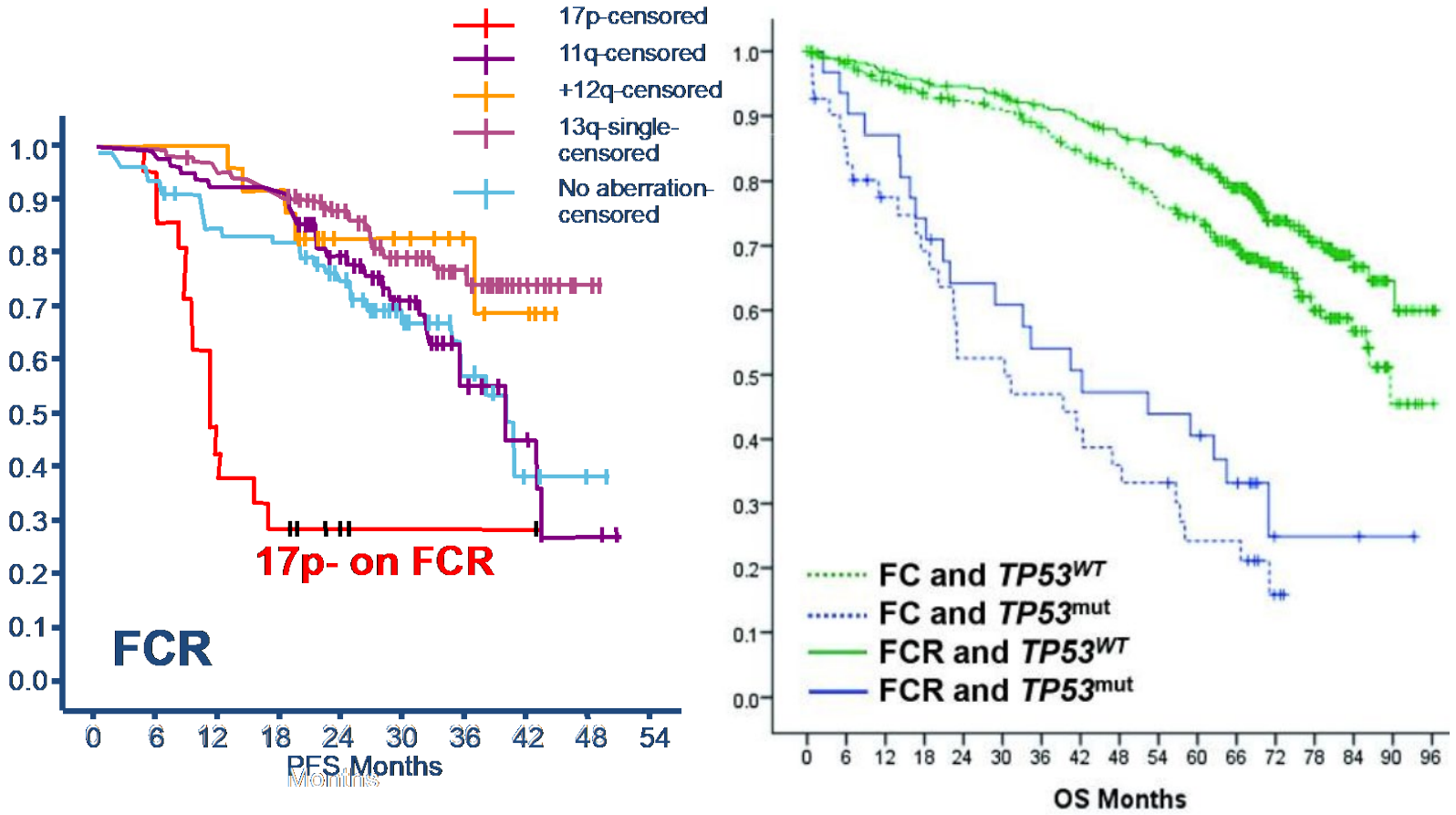
IGHV mutated (M) vs unmutated (U) CLL



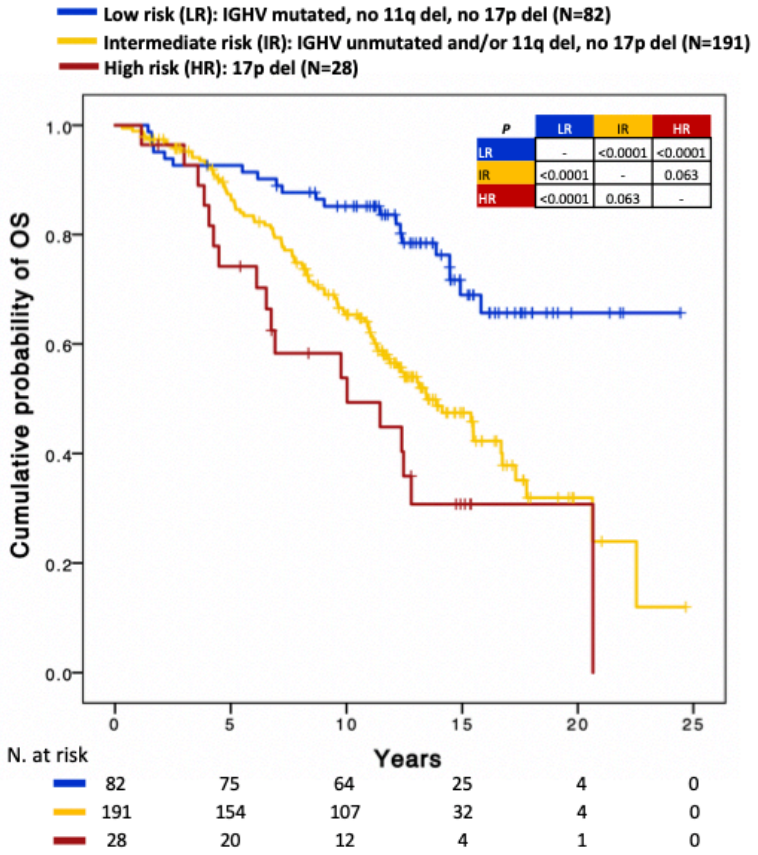
Gaidano et al, J Clin Invest 2012; Moia and Gaidano, Semin Hematol 2024

TP53 disrupted patients and IGHV unmutated cases do not benefit from chemoimmunotherapy

CLL8 clinical trial

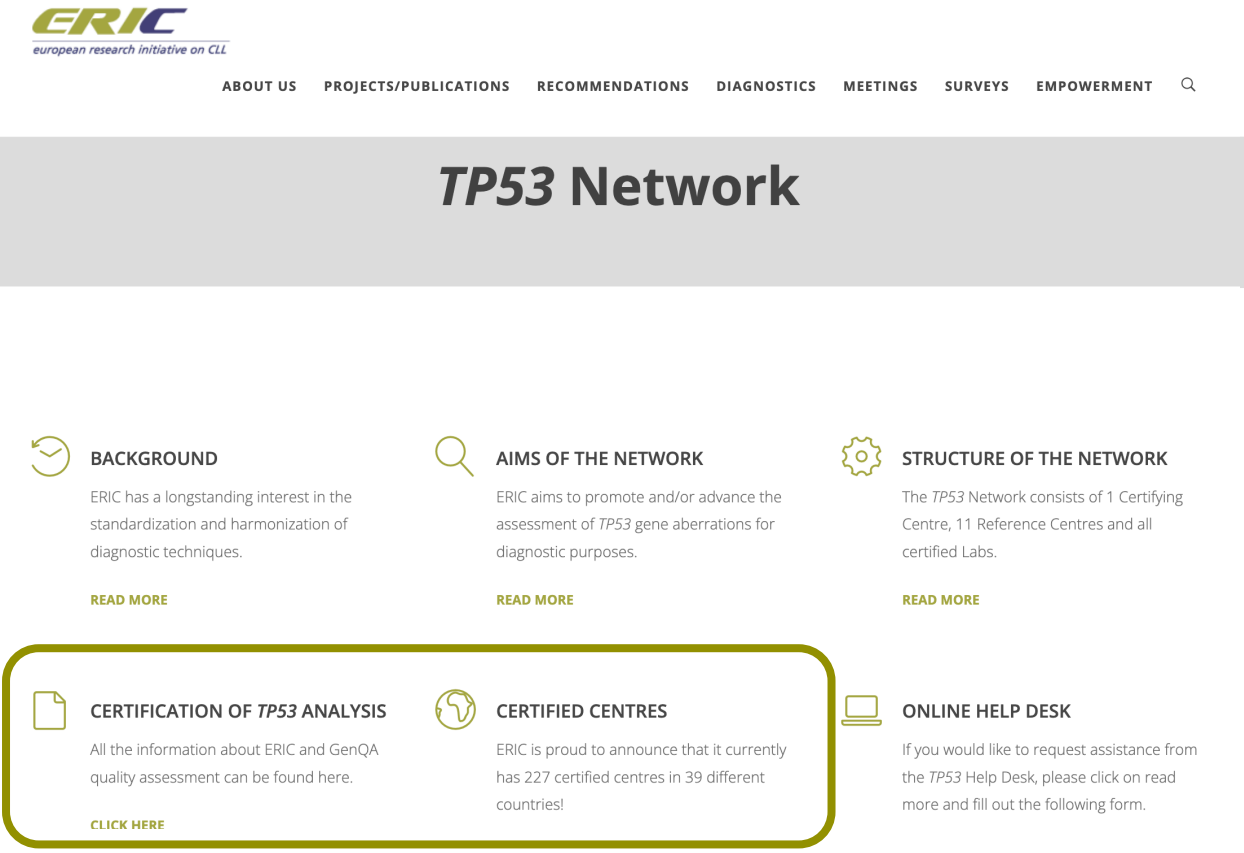


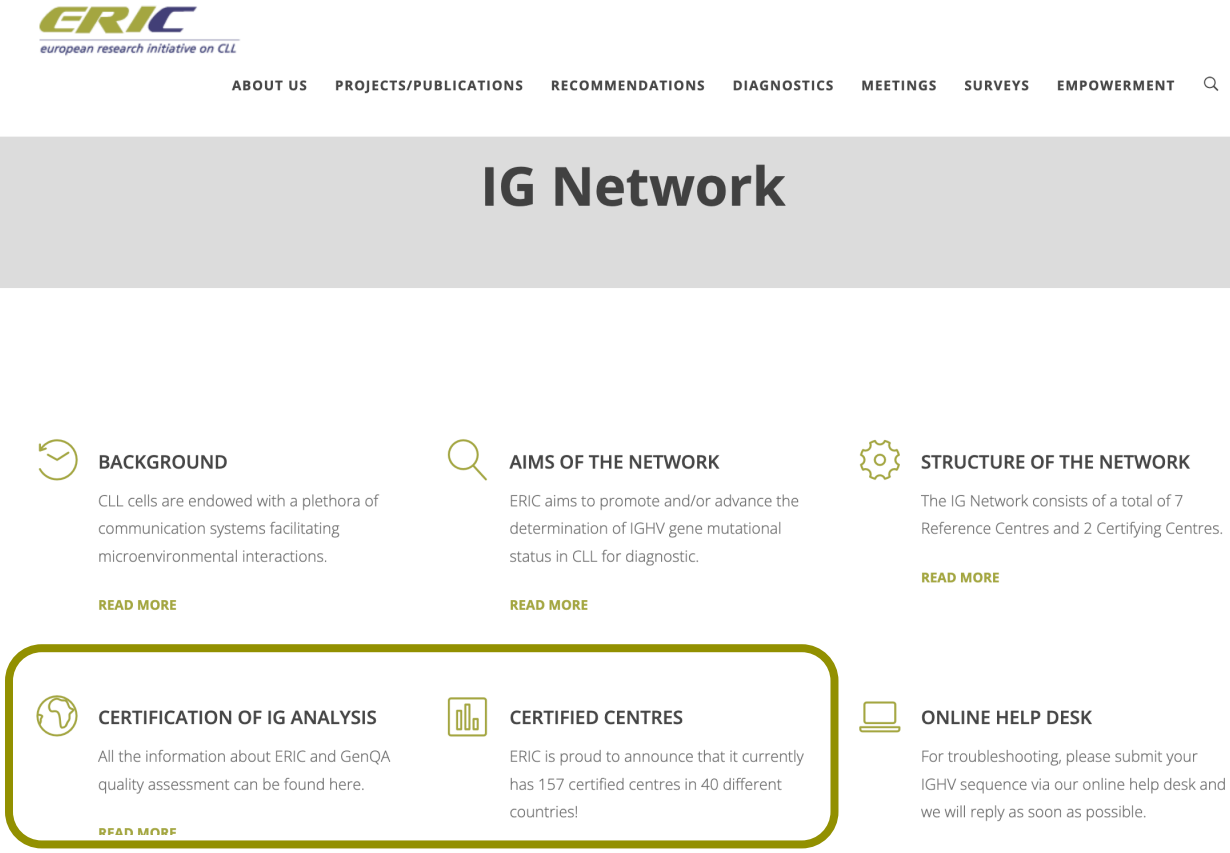
RWE cohort
Median follow up 15.8 y



Stilgenbauer et al. Blood 2014; Hallek et al., ASH. 2009; Rossi et al., Blood. 2015; Moia et al. Hematol Oncol 2023

http://www.ericll.org/





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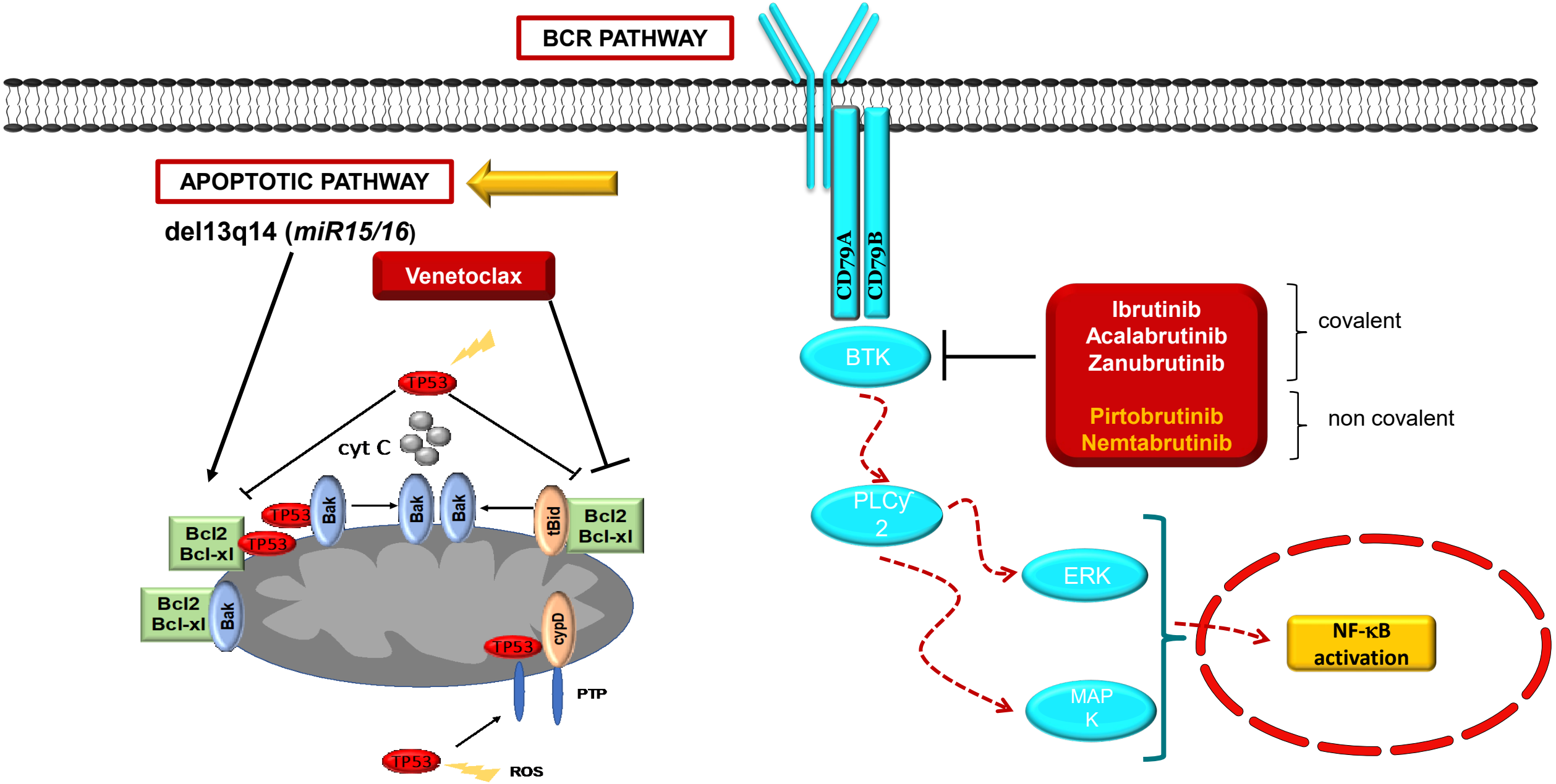
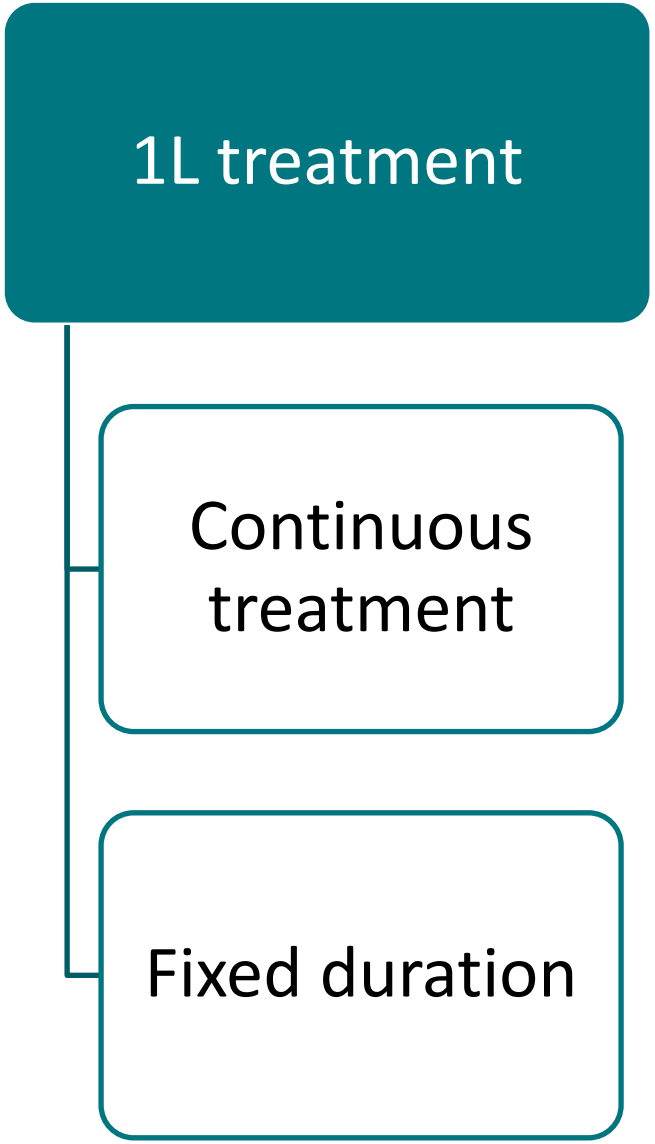
Molecular targets for CLL therapy

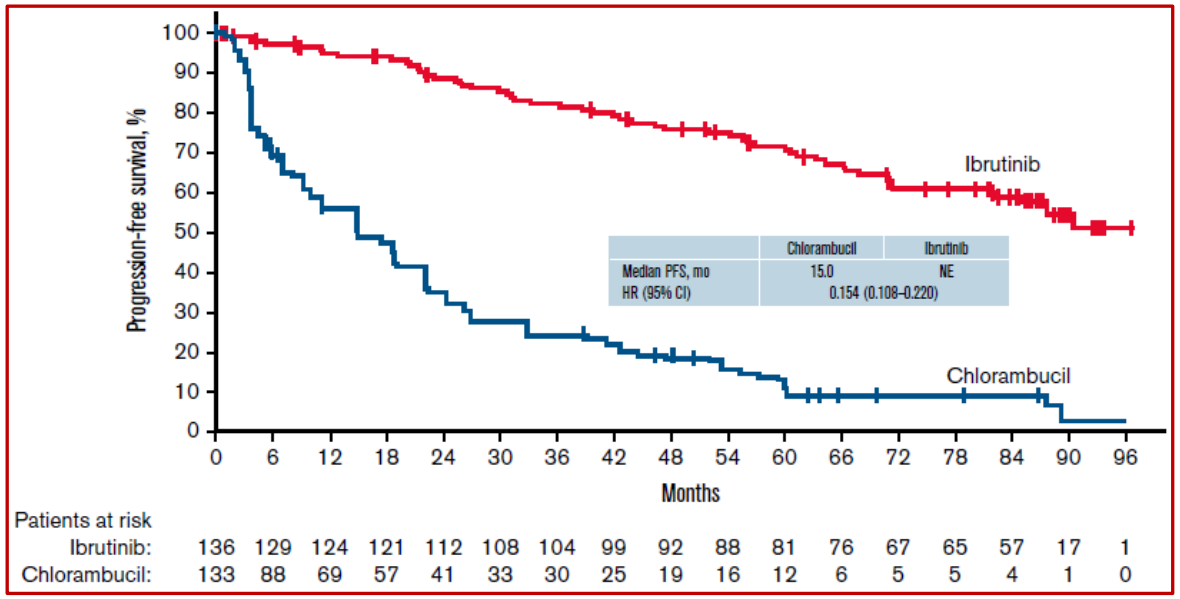


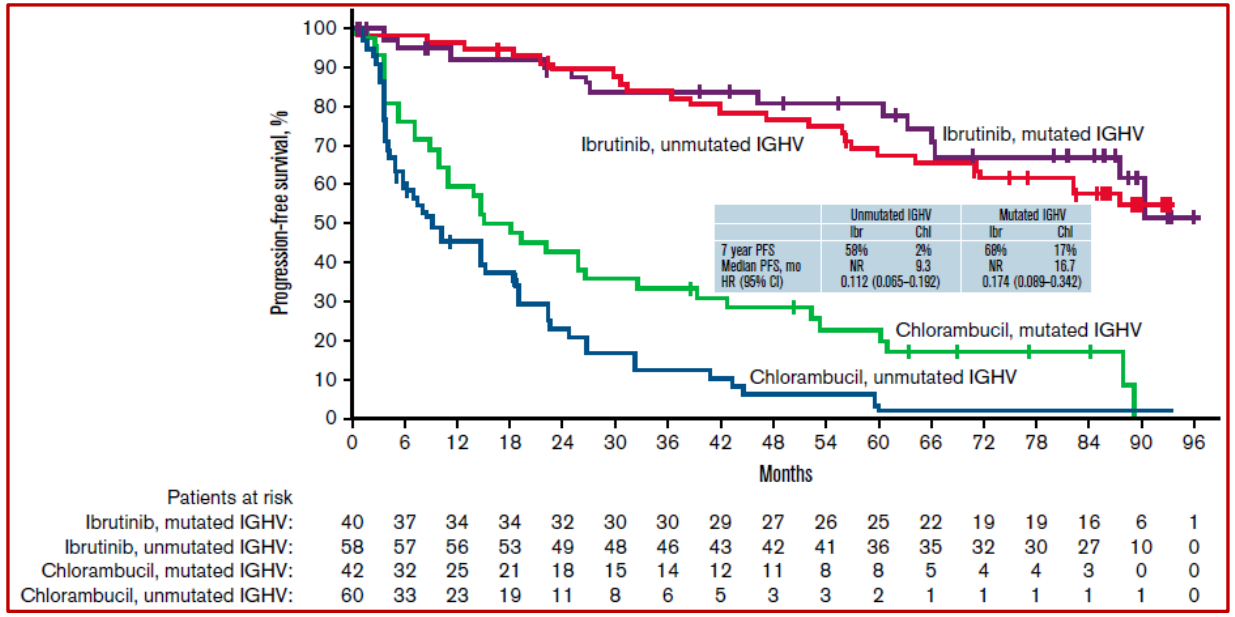
Therapeutic options in treatment-naïve CLL

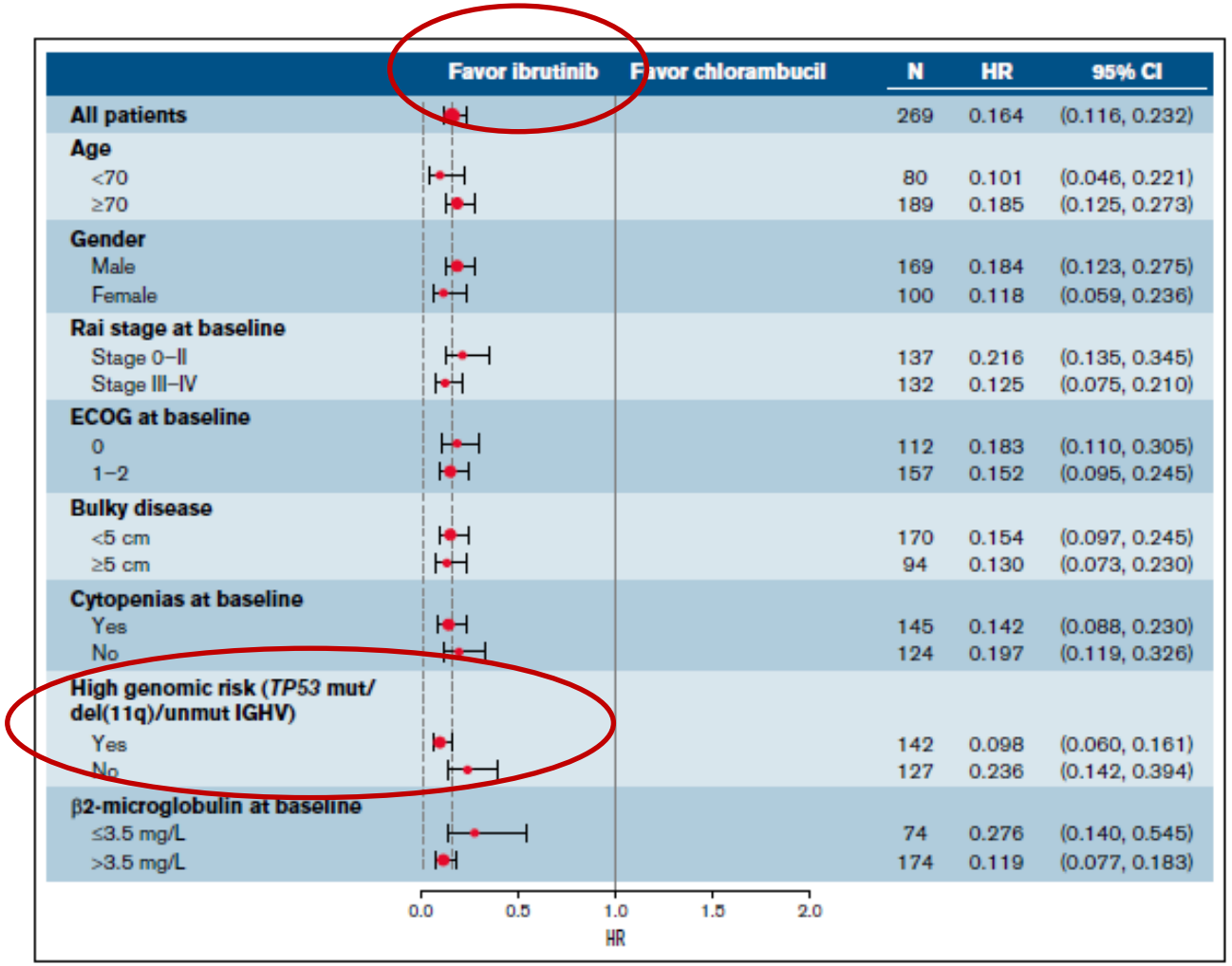


	Continuous treatment until progression	Fixed duration (12-15 mo)
BTKi single agent		
Ibrutinib	√	
Acalabrutinib	√	
Zanubrutinib	√	
Venetoclax + Obinutuzumab		√
Ibrutinib + Venetoclax		√

Ibrutinib single agent in previously untreated CLL (RESONATE-2): 8 y update



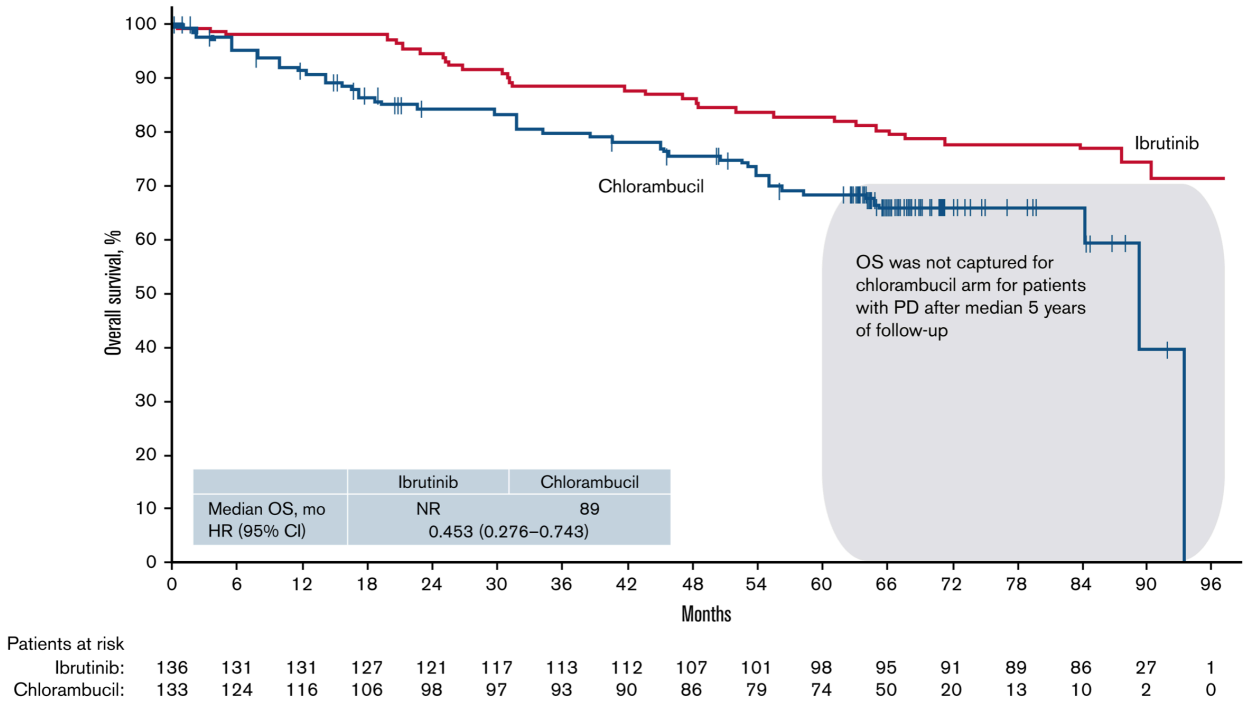




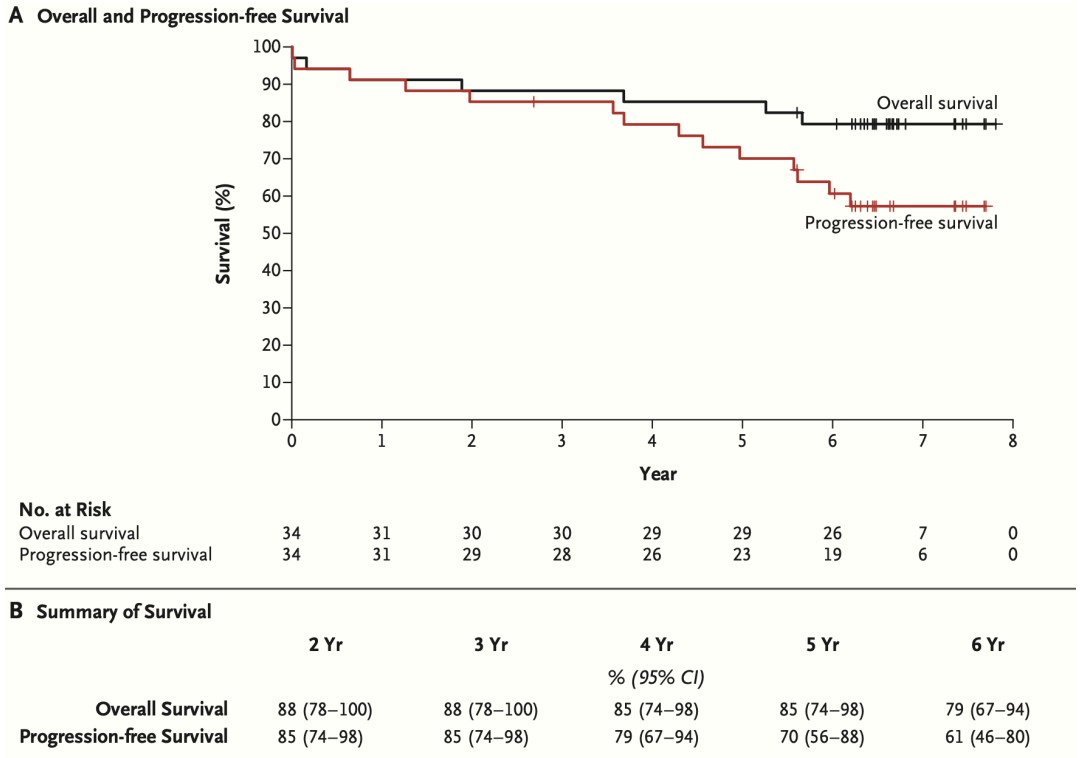
Barr *et al*, *Blood Adv*. 2022

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

Resonate-2



Phase 2 trial dedicated to *TP53* disrupted cases



Barr *et al*, *Blood Adv*. 2022; Ahn *et al.*, *NEJM*. 2020

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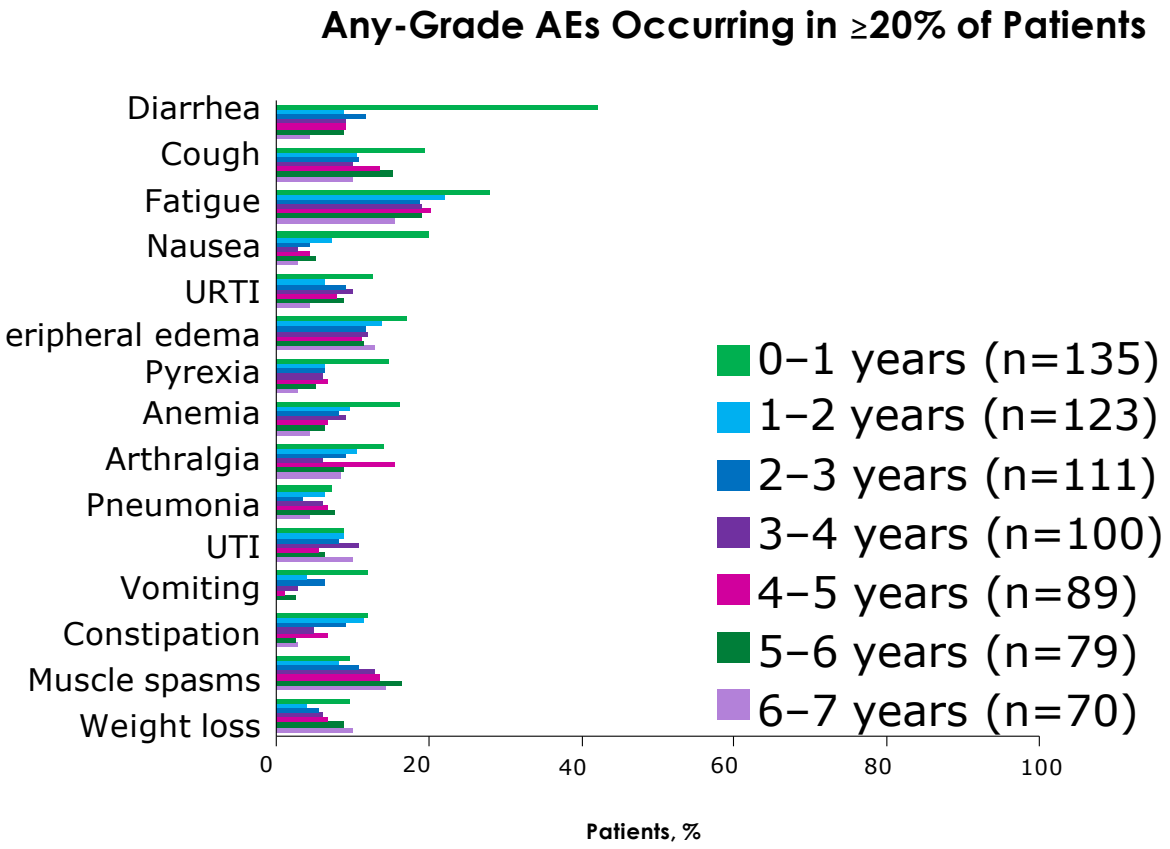
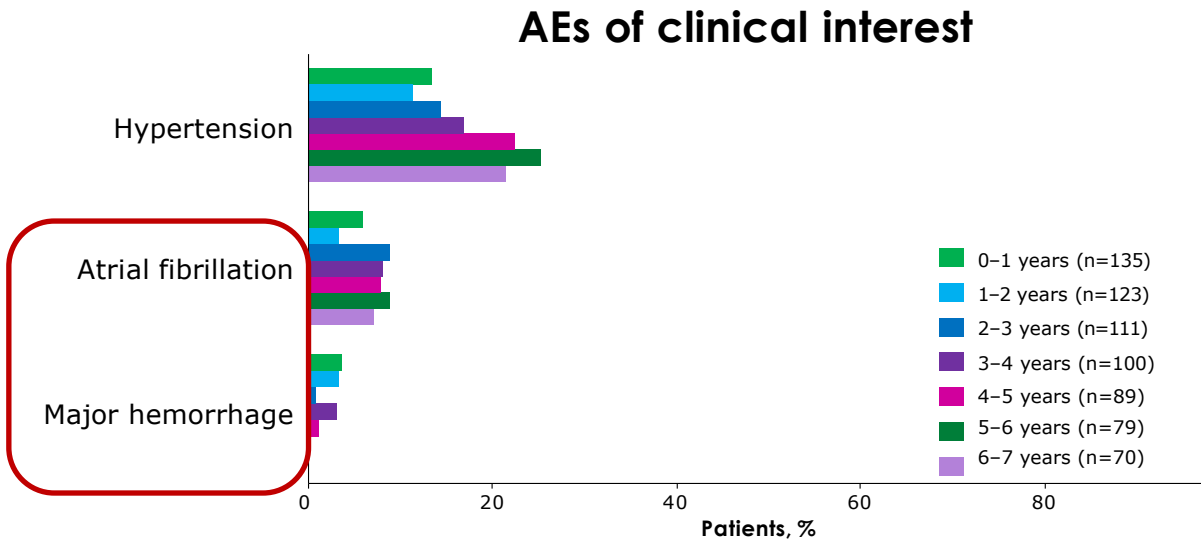
Long term safety





Safety remained acceptable with no new adverse events

Ghia P, et al. EHA2021, Abstract: EP636

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Kinome selectivity of BTKi

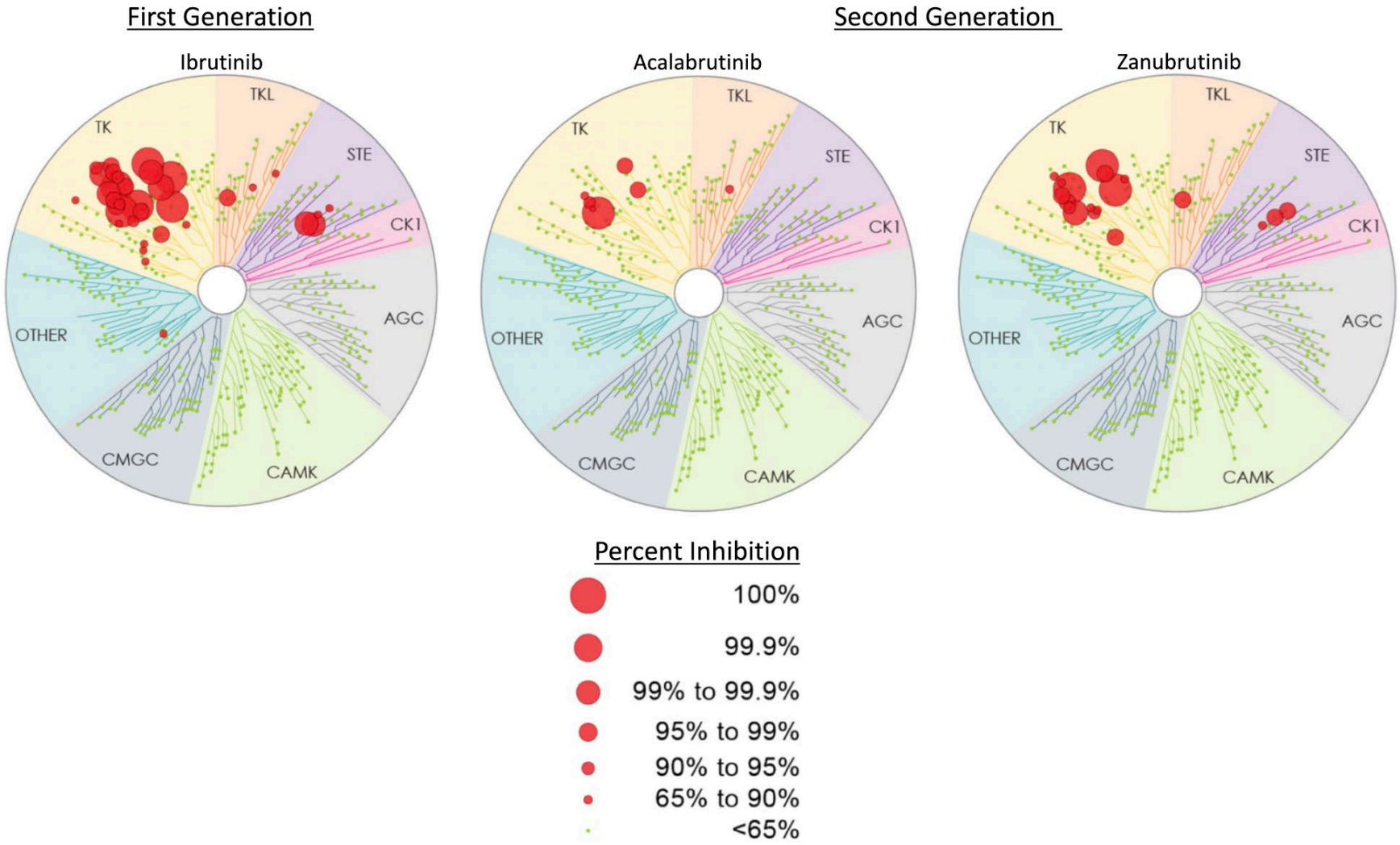
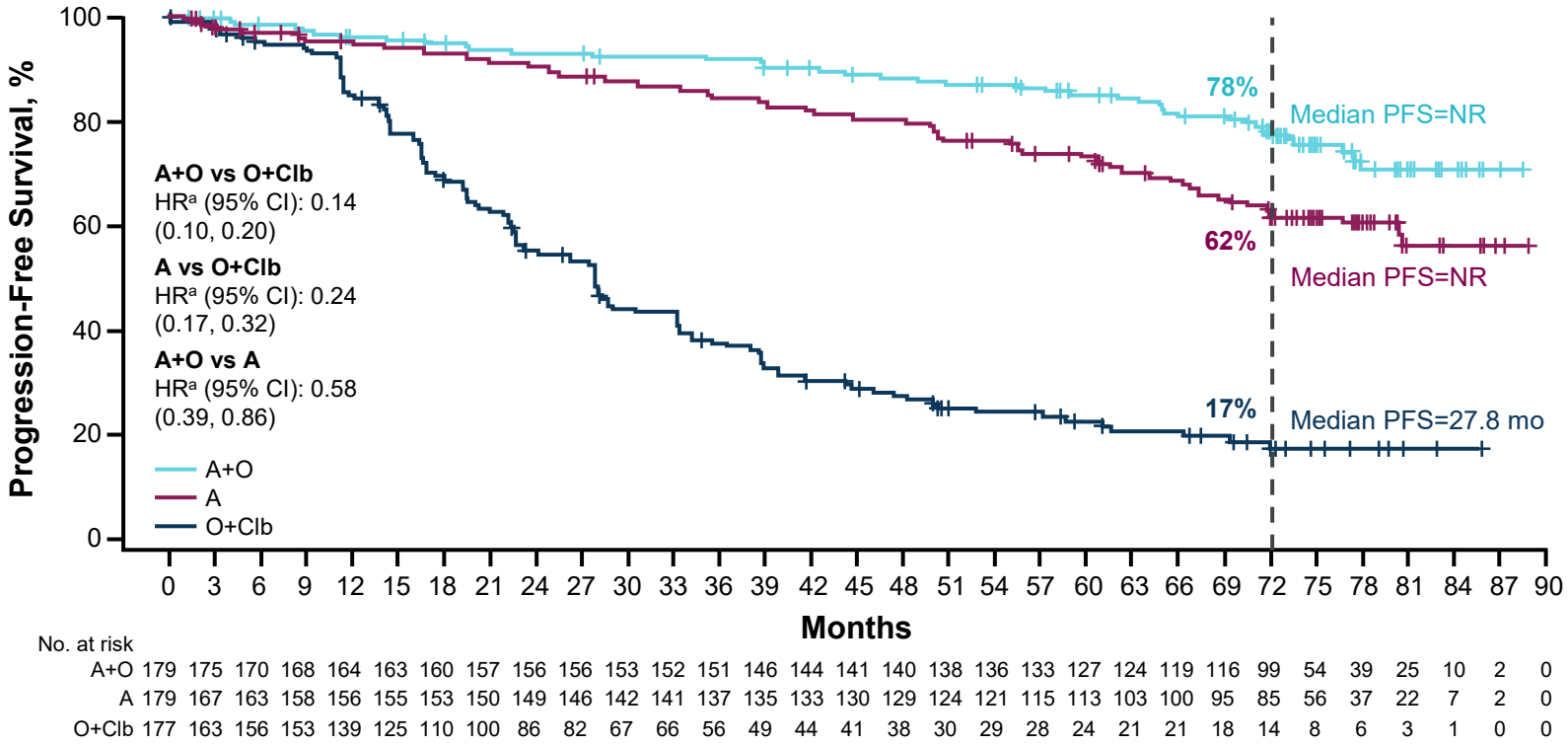


Figure 3 BTK Inhibitor Kinome Map. Figure modified from Kaptein A, de Bruin G, Emmelot-van Hoek M, van de Kar B, de Jong A, Gulrajani M, et al. Potency and Selectivity of BTK Inhibitors in Clinical Development for B-Cell Malignancies. Blood. 2018;132(Supplement 1):1871. Copyright 2018, with permission from Elsevier.[13]

ELEVATE-TN 6 y update: Investigator-Assessed PFS

- Median PFS was NR for A+O and A vs. 27.8 months for O+Clb.
- Estimated 72 months PFS rates were 78% for A+O, 62% for A monotherapy, and 17% for O+Clb.

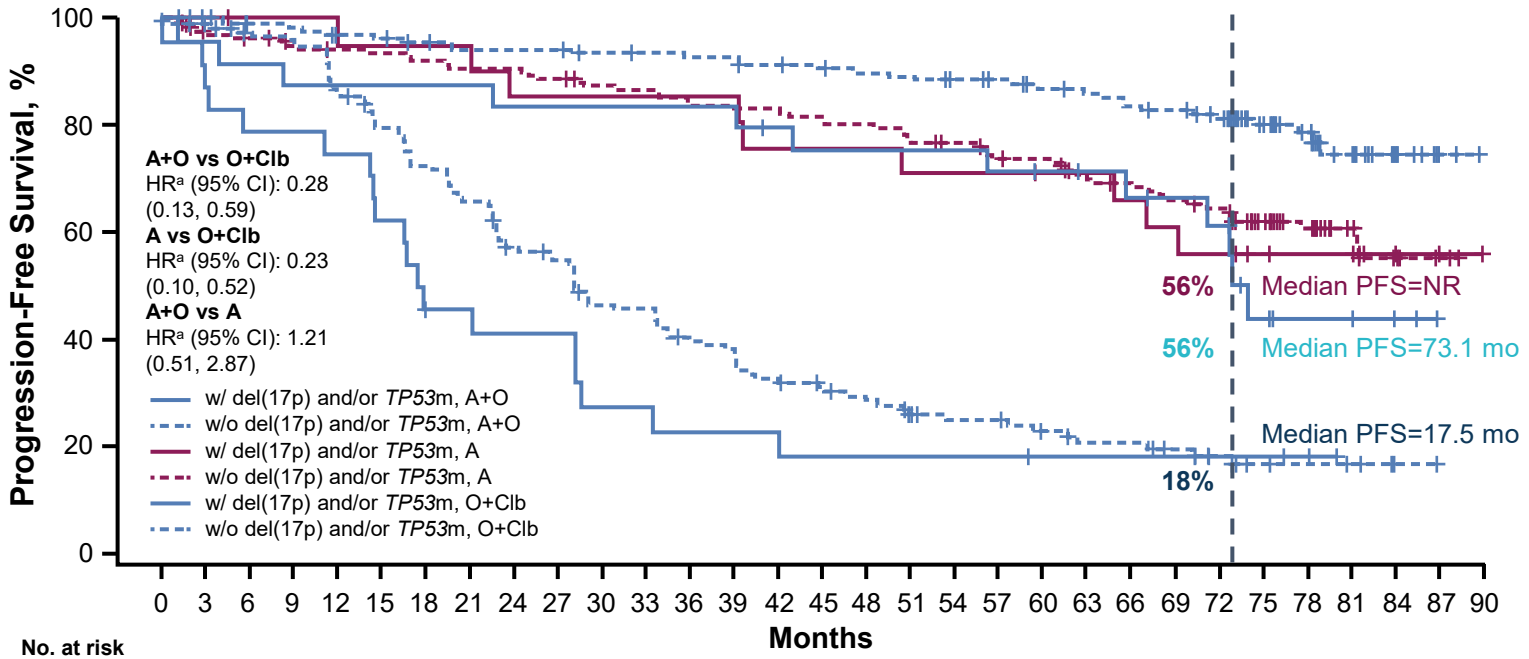


[a]Hazard ratio based on stratified Cox proportional-hazard model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = Obinutuzumab; PFS = progression free survival; PFS 2 = time to second disease progression or death; vs = versus.

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

ELEVATE-TN 6y follow-up: efficacy of Acalabrutinib in in *TP53* disrupted patients



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.

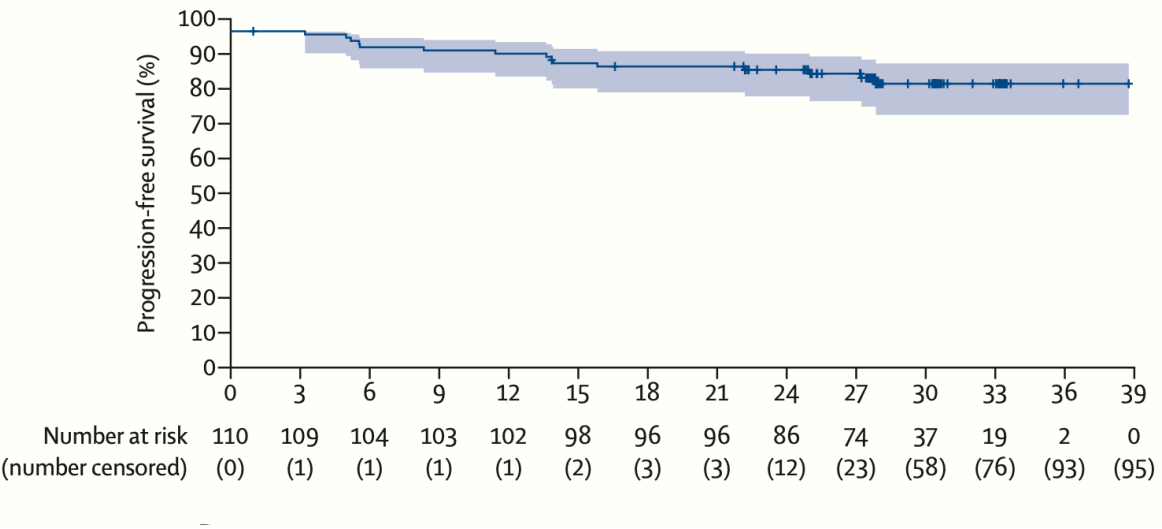
A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = Obinutuzumab; PFS = progression free survival; *TP53* = tumour protein p53; vs = versus.

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

eha

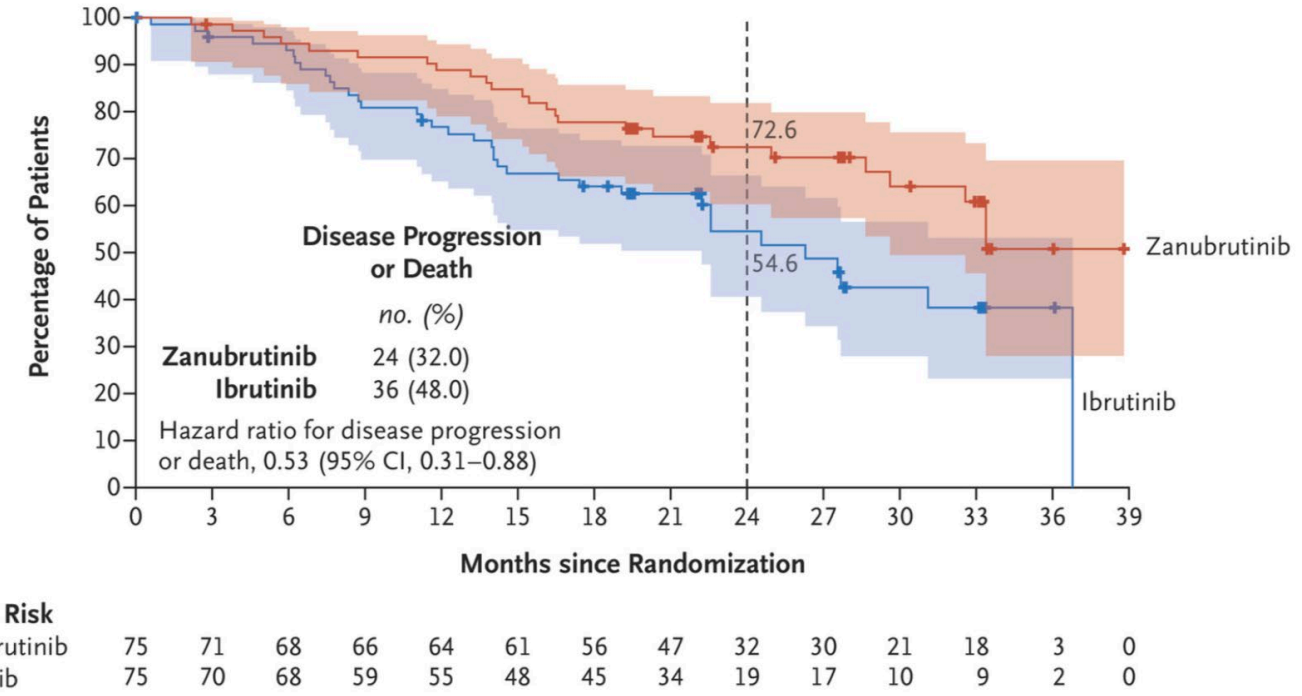
Zanubrutinib activity in *TP53* disrupted patients

ARM C SEQUOIA TRIAL



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

ALPINE TRIAL

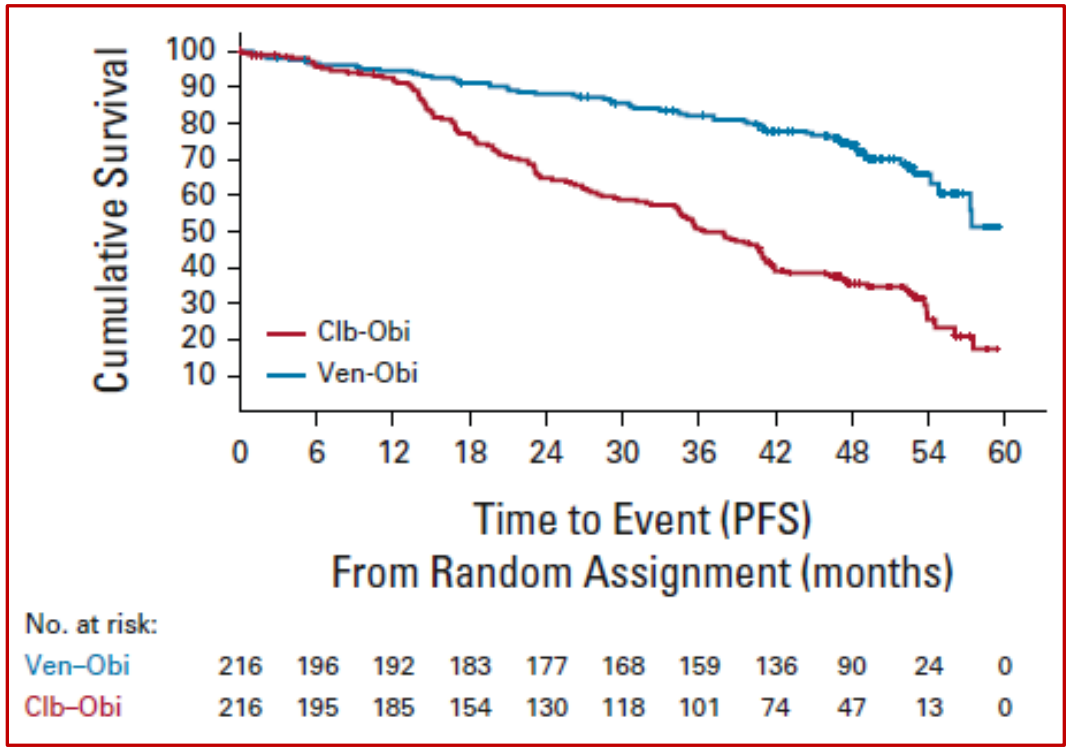


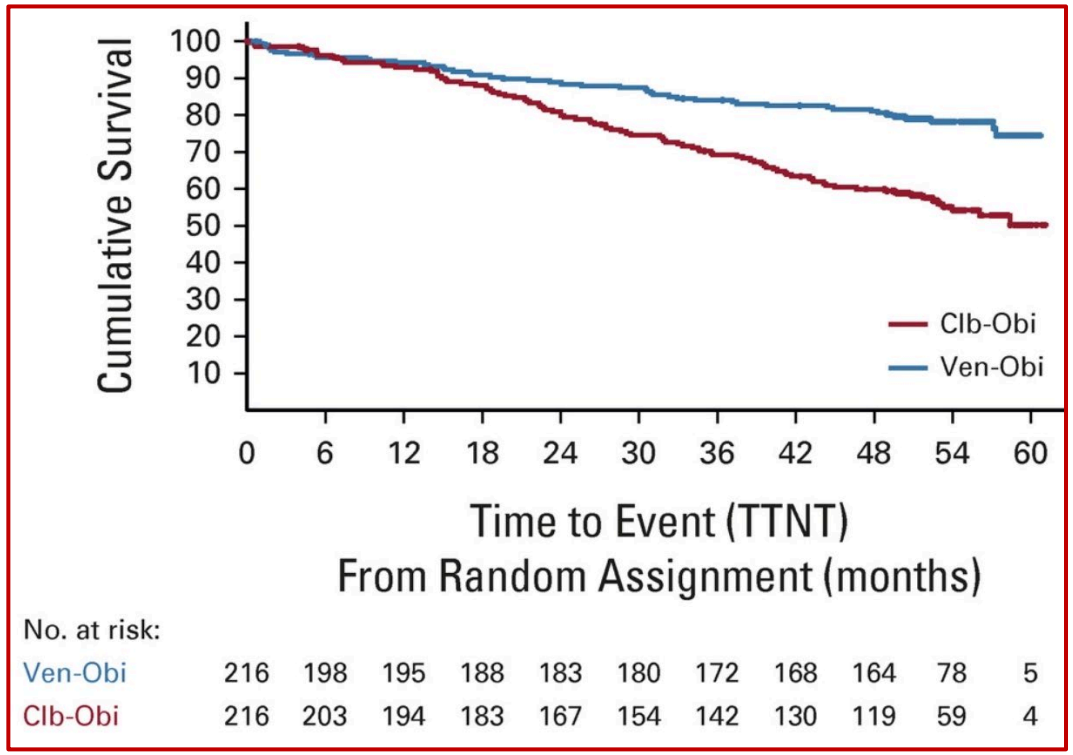
In the ALPINE trial zanubrutinib was more effective compared to ibrutinib in *TP53* disrupted patients

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

eha

Venetoclax-Obinutuzumab (fixed duration) is superior to Clb-Obinutuzumab in previously untreated CLL (CLL14 trial)

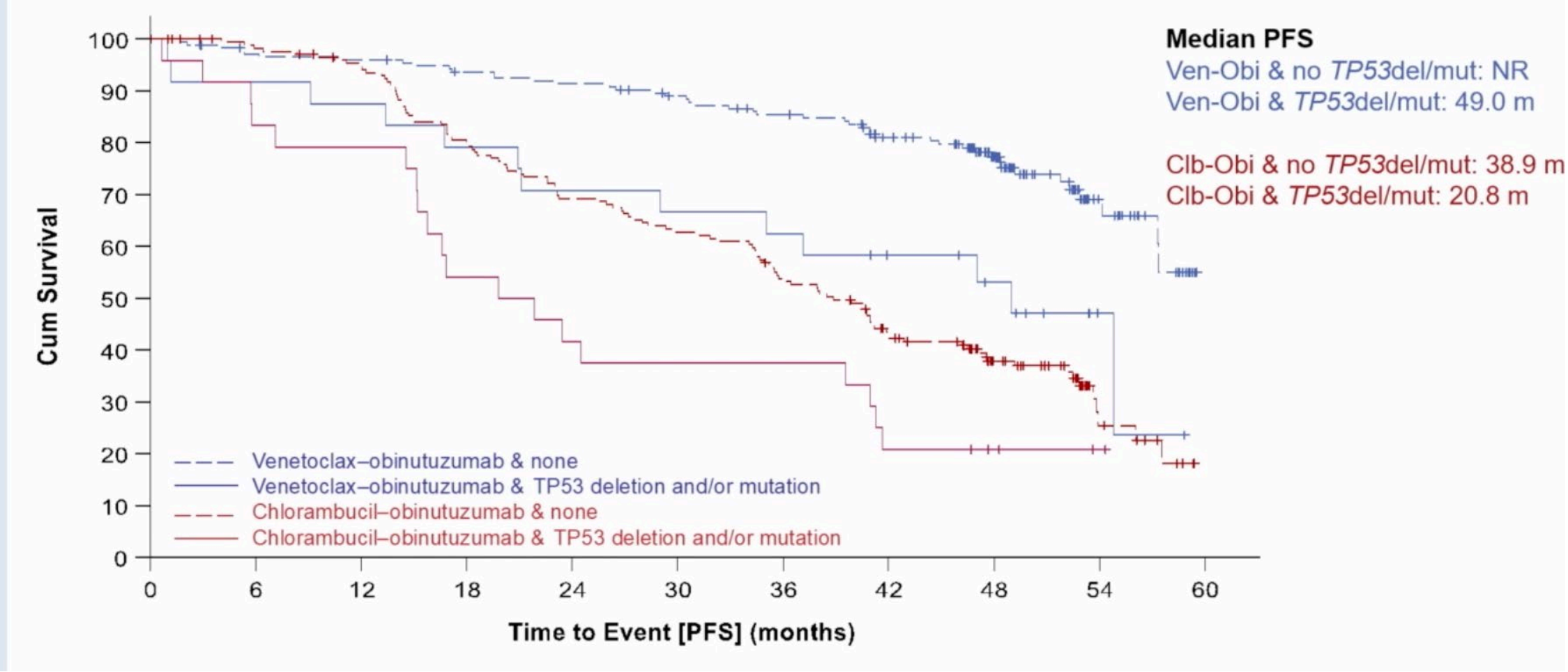




Al-Sawaf *et al.*, *J Clin Oncol*. 2021

eha

Clinical impact of *TP53* in the CLL14 trial

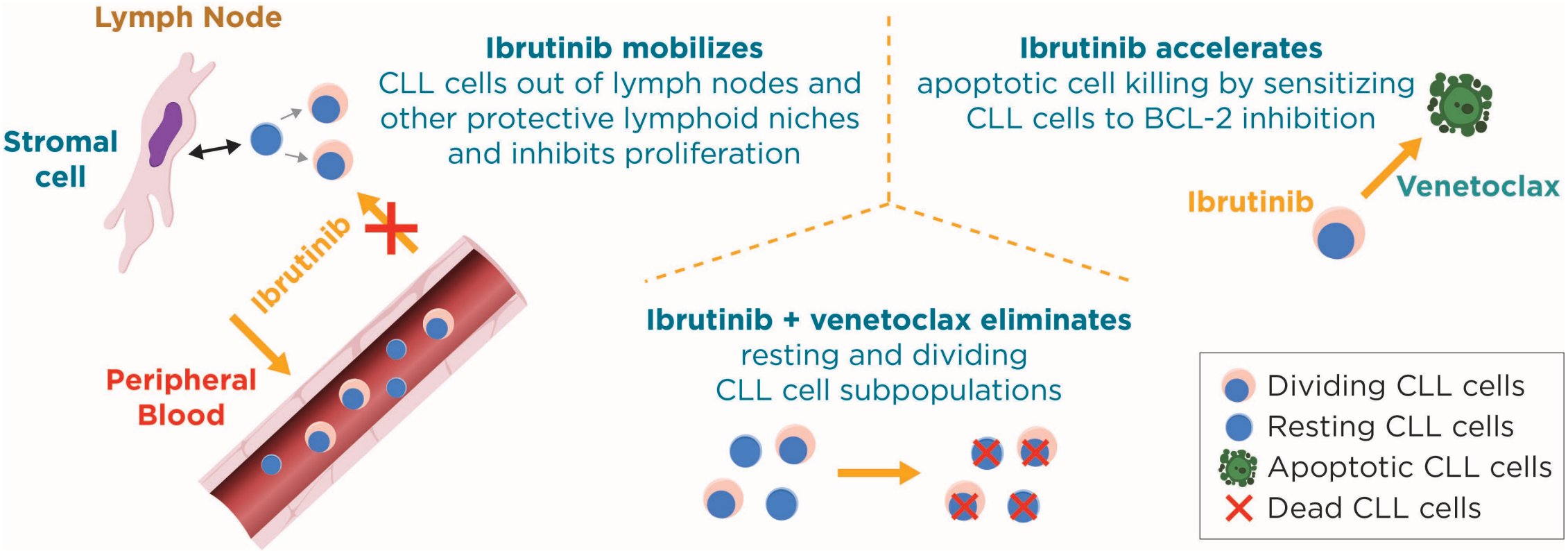


Ven-Obi mitigates, but does not abolish, the negative prognostic impact of *TP53* disruption

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

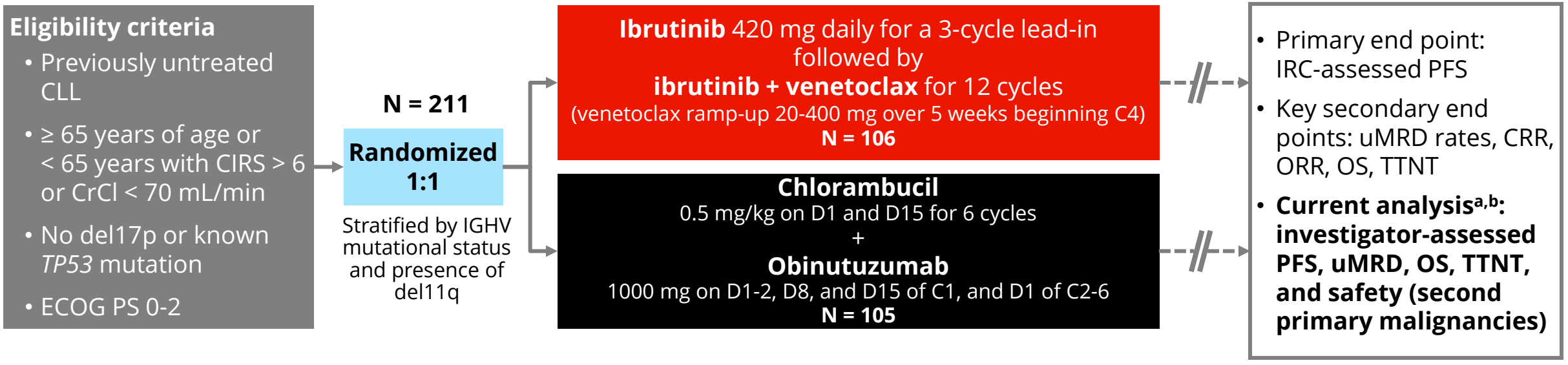
eha

Ibrutinib and Venetoclax Work Synergistically Through Distinct and Complementary Modes of Action



BCL-2, B cell lymphoma 2; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EU, European Union; OS, overall survival; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease. [1]Lu P et al. *Blood Cancer J.* 2021;11:39. [2]Deng J et al. *Leukemia.* 2017;31:2075-2084. [3]Herman ES et al. *Clin Cancer Res.* 2015;21:4642-4651. [4]Burger JA et al. *Leukemia.* 2020;34:787-798. [5]Shanafelt T et al. *N Engl J Med.* 2019;381:432-443. [6]Venclexta [package insert]. South San Francisco, CA: Genentech USA Inc; 2021.

GLOW: Phase 3 GLOW Study (NCT03462719) Evaluating Fixed-Duration Ibr+Ven in Previously Untreated CLL

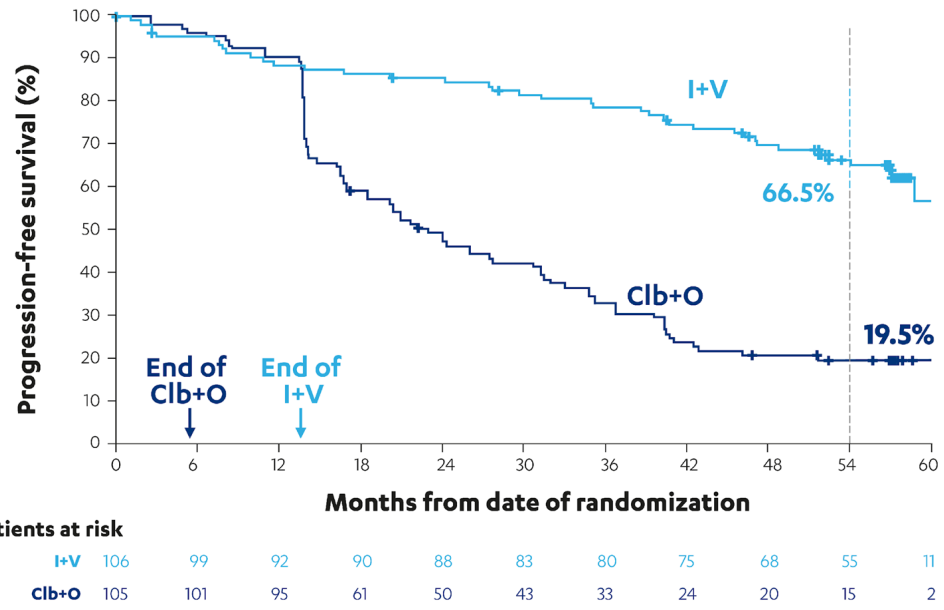


- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

[a]All *p* values are nominal. [b]uMRD in PB by NGS via Clonoseq assay.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; CRR, complete response rate; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; mIGHV, mutated IGHV; NGS, next-generation sequencing; ORR, overall response rate; PB, peripheral blood; uIGHV, unmutated IGHV.
1. Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-1433.

Phase 3 GLOW trial

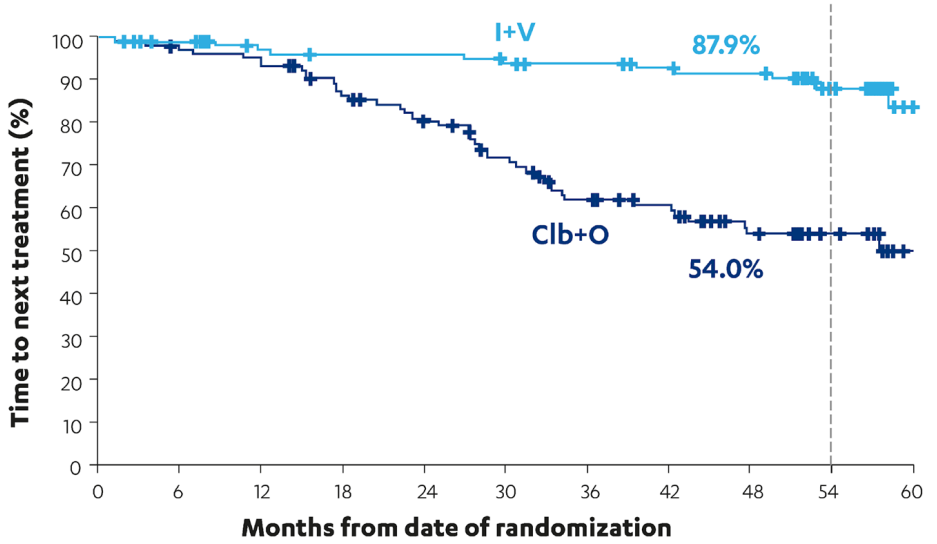
GLOW: PFS in patients treated with I+V vs. Clb+O (median follow-up: 57 months)[1]



Patients at risk

I+V	106	99	92	90	88	83	80	75	68	55	11
Clb+O	105	101	95	61	50	43	33	24	20	15	2

GLOW: TTNT for patients treated with I+V vs. Clb+O (median follow-up: 57 months)[1]



Patients at risk

I+V	106	99	93	91	91	88	86	83	81	67	17
Clb+O	105	101	97	87	79	67	55	49	37	28	7

- **PFS was superior** with I+V vs. Clb+O in previously untreated patients with CLL who are ≥ 65 years or have comorbidities
- **54-month PFS rates** were 66.5% for I+V and 19.5% for Clb+O

- **I+V prolonged TTNT** and reduced the risk of requiring second-line therapy by **82%** versus Clb+O (HR 0.185 [95% CI, 0.096–0.355]; p < 0.0001)

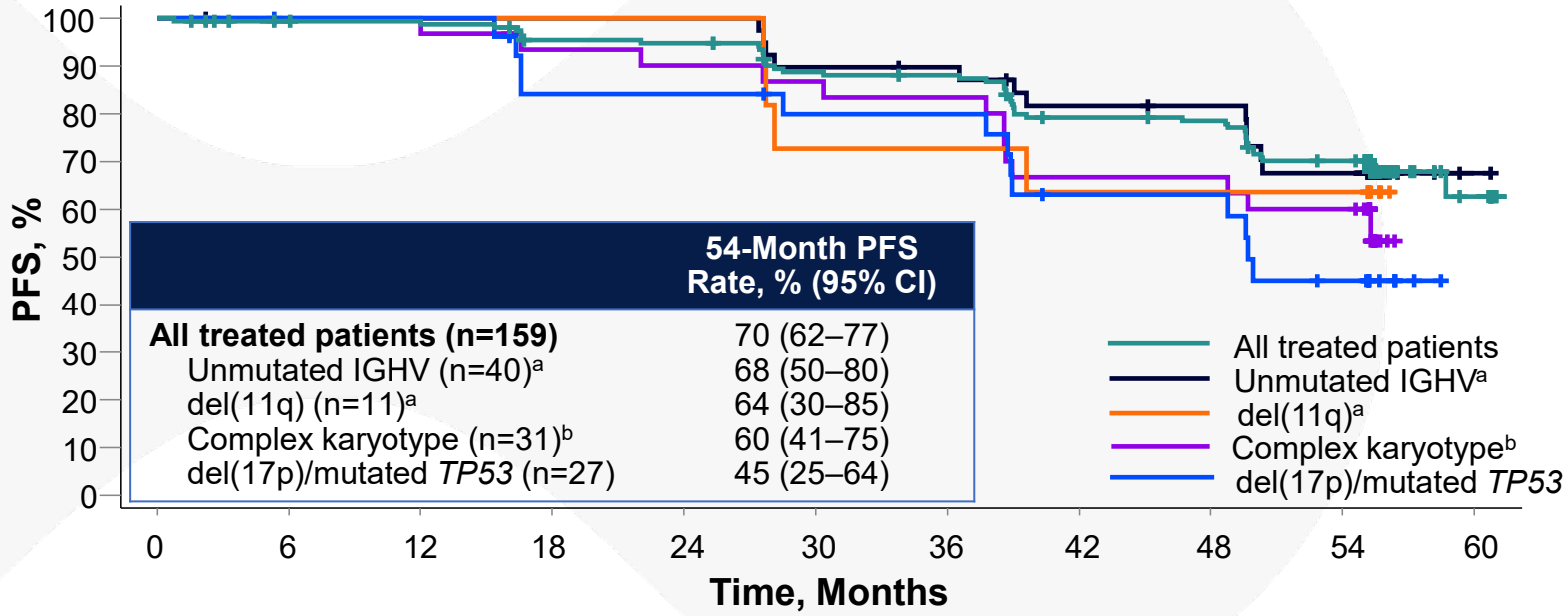
CI, confidence interval; Clb+O, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; HR, hazard ratio; I+V, ibrutinib plus venetoclax; PFS, progression-free survival; TTNT, time to next treatment.

1. Moreno C, et al. ASH 2023 oral presentation #634.

eha

CAPTIVATE FD Cohort:
Overall Median PFS Was Not Reached With Up To 5 Years Of Follow-Up

- With median time on study of 56 months (range, 1–61), 54-month PFS and OS rates were 70% (95% CI, 62–77) and 97% (95% CI, 93–99), respectively
  - PFS promising across most high-risk features; numerically lower in those with del(17p)/mutated *TP53*



Patients at risk

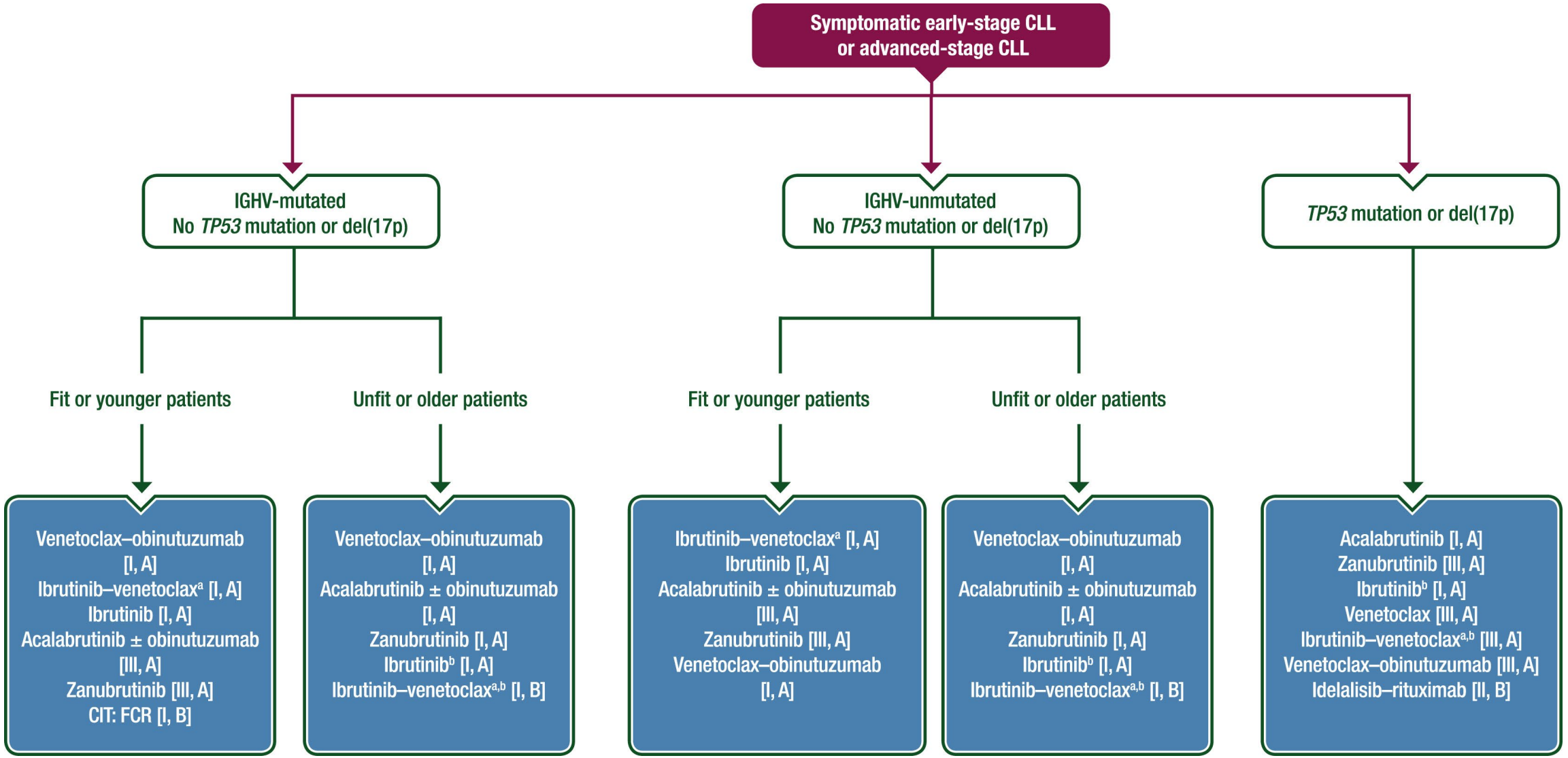
All treated patients	159	153	152	144	143	132	130	115	113	99	11
Unmutated IGHV[a]	40	39	39	39	39	35	34	30	29	24	1
del(11q)[a]	11	11	11	11	11	8	8	7	7	7	0
Complex karyotype[b]	31	31	31	28	27	26	25	20	20	18	0
del(17p)/mutated *TP53*	27	26	26	21	21	19	19	14	14	9	0

- Best response rates remain: CR/CRi, 58%; ORR, 96%[1]
  - In patients who achieved CR/CRi (n=92), median duration of CR/CRi was not reached

CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PFS, progression-free survival.
[a]Excluding patients with del(17p)/mutated *TP53* or complex karyotype. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.
[1]Barr PM et al. *J Clin Oncol.* 2023;41(suppl 16). Abstract 7535.

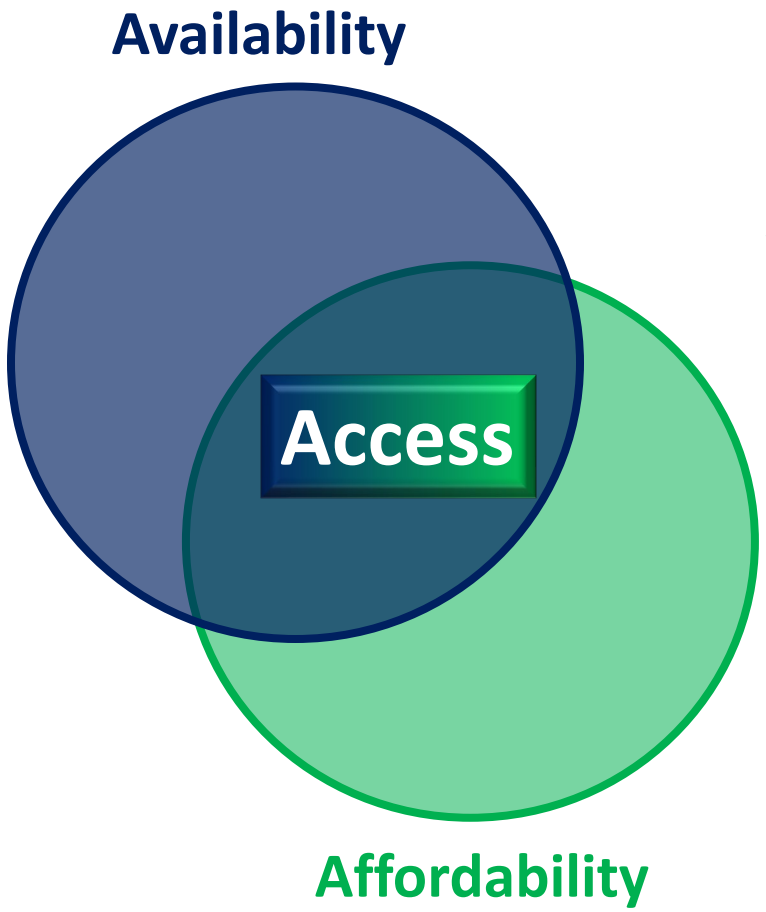
Ghia et al., ASH 2023, #633

ESMO guidelines for first-line treatment



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

Any role left for chemo-immunotherapy in CLL?



YES

No role left for chemo-immunotherapy

NO

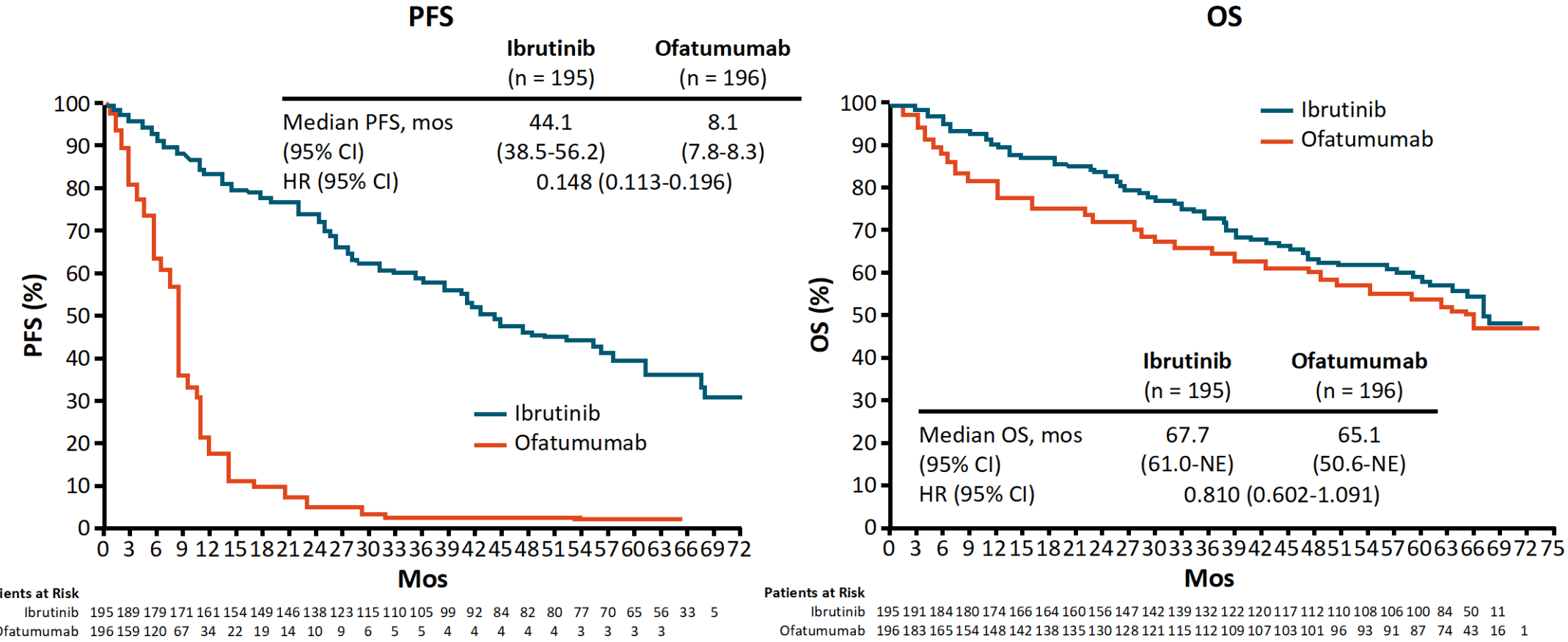
Forced role left for chemo-immunotherapy
(possibly limited to TP53 wt cases)

Learning Objectives

1. Understand the relevance of biology and biomarkers in the management of CLL
2. Manage asymptomatic CLL
3. Navigate among the treatment options currently available for treatment-naïve CLL
4. **Manage treatment of relapsed/refractory CLL**
5. Define a diagnostic and therapeutic approach for Richter transformation

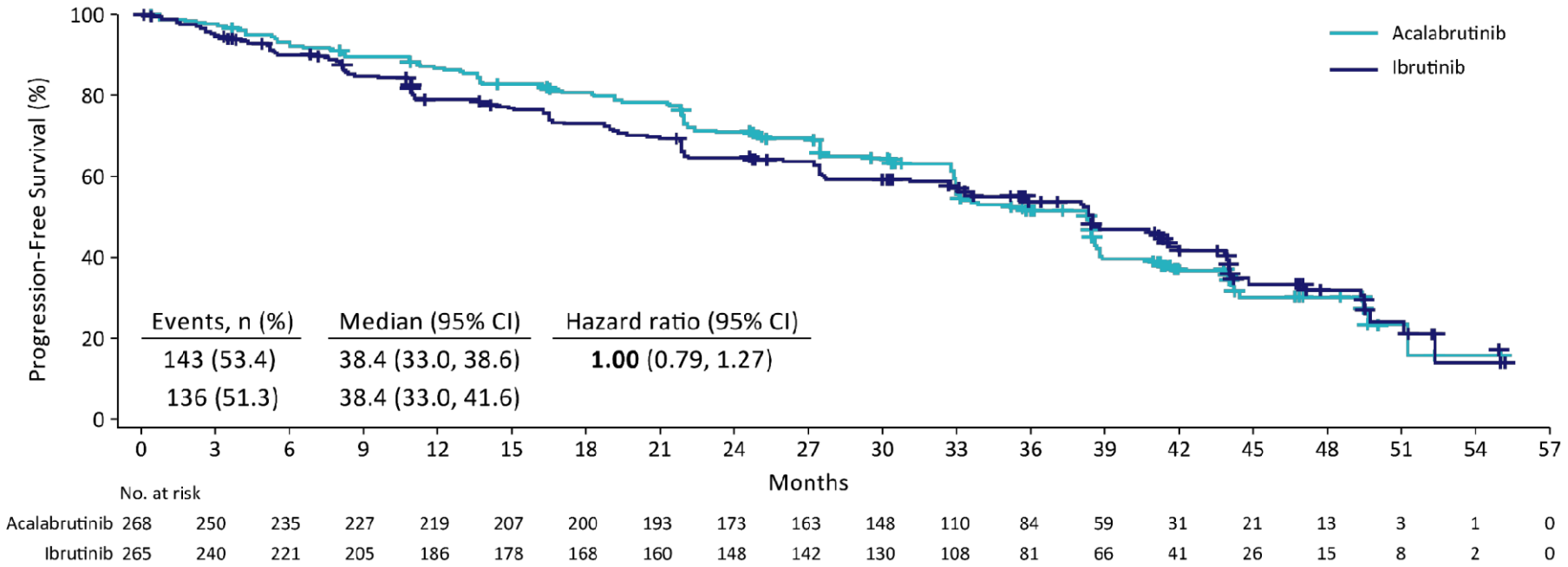
Phase 3 RESONATE trial: final analysis

- Final analysis with up to 6 yrs of ibrutinib follow-up



Munir. Am J Hematol. 2019;94:1353.

ELEVATE-RR: acalabrutinib is non inferior to ibrutinib in terms of PFS



Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Byrd *et al.*, *JCO* 2021

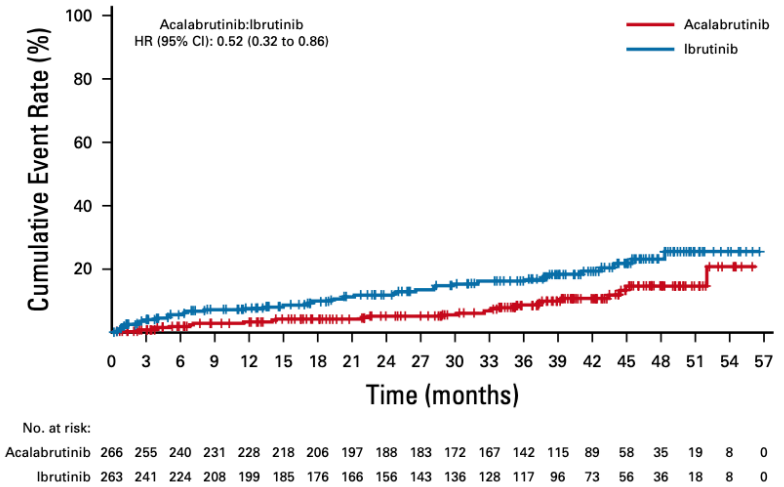
eha

ELEVATE-RR: lower rates of cardiac event with acalabrutinib vs ibrutinib

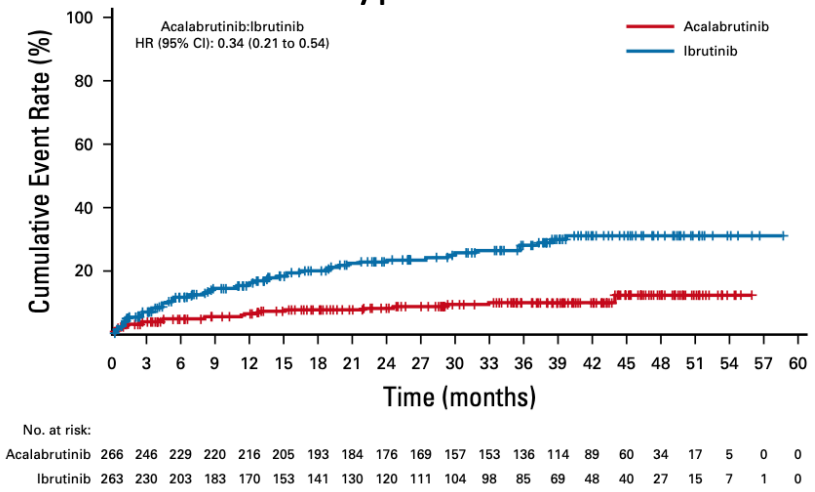
Events, n (%)	Any grade		[illegible]	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold red** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined [illegible]
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most [illegible] UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

Atrial fibrillation



Hypertension



Acalabrutinib showed a better safety profile compared to ibrutinib especially in terms of cardiovascular toxicities

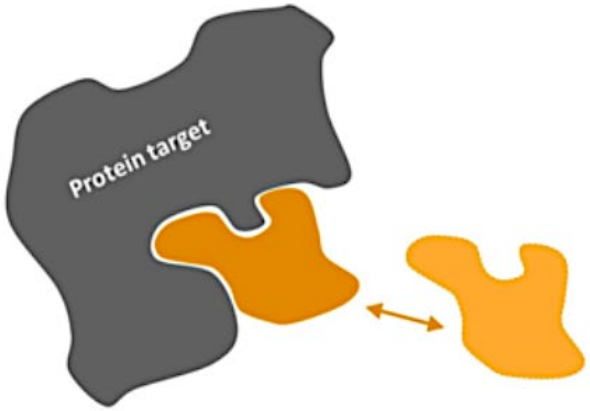
Byrd *et al., JCO* 2021

eha

Dynamics of target interaction of reversible vs. covalent inhibitors

Reversible inhibitors

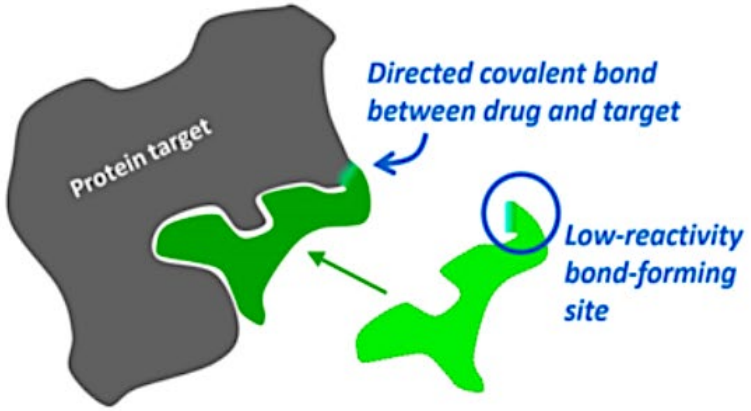
Traditional reversible drugs are in equilibrium with their target – continually binding, unbinding, & rebinding



$$[D] + [T] \rightleftharpoons [DT]$$

Covalent inhibitors

Covalent irreversible drugs bind specifically to a drug target and form a precisely directed, permanent bond with their target



$$[D] + [T] \rightarrow [DT]$$

Pirtobrutinib is highly active in heavily pre-treated CLL patients

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients (N=247)
Median age (range) — yr	69 (36–88)
Sex — no. (%)	
Male	168 (68.0)
Female	79 (32.0)
World Health Organization classification — no. (%)	
CLL	246 (99.6)
SLL	1 (0.4)
Rai stage — no. (%)	
0–II	131 (53.0)
III or IV	102 (41.3)
Missing data	14 (5.7)
Bulky disease ≥5 cm — no. (%)	78 (31.6)
ECOG performance-status score — no. (%)†	
0	133 (53.8)
1	97 (39.3)
2	17 (6.9)
No. of previous lines of systemic therapy	
Median (range)	3 (1–11)
Distribution — no. (%)	
1	19 (7.7)
2	55 (22.3)
3	57 (23.1)
≥4	116 (47.0)
Previous therapy — no. (%)	
BTK inhibitor‡	247 (100)
Anti-CD20 antibody	217 (87.9)
Chemotherapy	195 (78.9)
BCL2 inhibitor	100 (40.5)
PI3K inhibitor	45 (18.2)
CAR T-cell therapy	14 (5.7)
Allogeneic stem-cell transplantation	6 (2.4)
Median time from diagnosis to first dose of pirtobrutinib (IQR) — yr	11 (8–15)
Reason for discontinuation of any previous BTK inhibitor — no. (%)§	
Disease progression	190 (76.9)
Toxic effects or other reason	57 (23.1)
Mutation status — no./total no. (%)	
BTK C481	
Mutated	84/222 (37.8)
Not mutated	138/222 (62.2)
PLCG2	
Mutated	18/222 (8.1)
Not mutated	204/222 (91.9)
High-risk molecular features — no./total no. (%)¶	
17p deletion	51/176 (29.0)
TP53 mutation	87/222 (39.2)
17p deletion, *TP53* mutation, or both	90/193 (46.6)
Both 17p deletion and *TP53* mutation	48/170 (28.2)
Unmutated *IGHV*	168/198 (84.8)
Complex karyotype‖	24/57 (42)
11q deletion	44/176 (25.0)

* Data are for the BRUIN trial patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who had previously received a Bruton's tyrosine kinase (BTK) inhibitor. Percentages may not total 100 because of rounding. BCL2 denotes B-cell lymphoma 2, CAR chimeric antigen receptor, IQR interquartile range, and PI3K phosphatidylinositol 3-kinase.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
‡ Ten patients who had received previous covalent BTK inhibitor therapy had also received previous noncovalent BTK inhibitor therapy.
§ In the event that more than one reason for discontinuation was noted, disease progression took priority.
¶ Molecular characteristics were determined centrally and are presented on the basis of data availability, in those patients with a sufficient sample to pass assay quality control.
‖ Complex karyotype was defined as the presence of three or more chromosomal abnormalities.

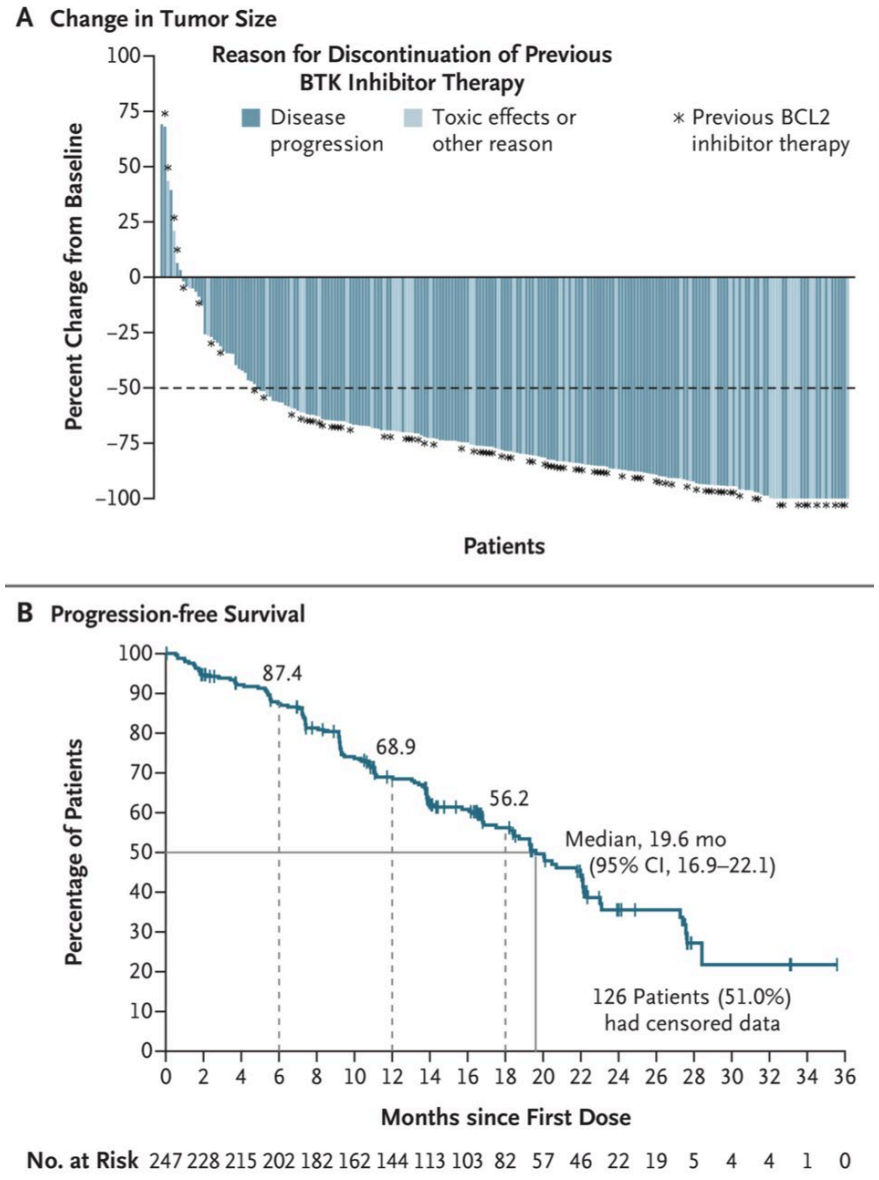


Table 3. Safety Profile of Pirtobrutinib in Patients with CLL or SLL.

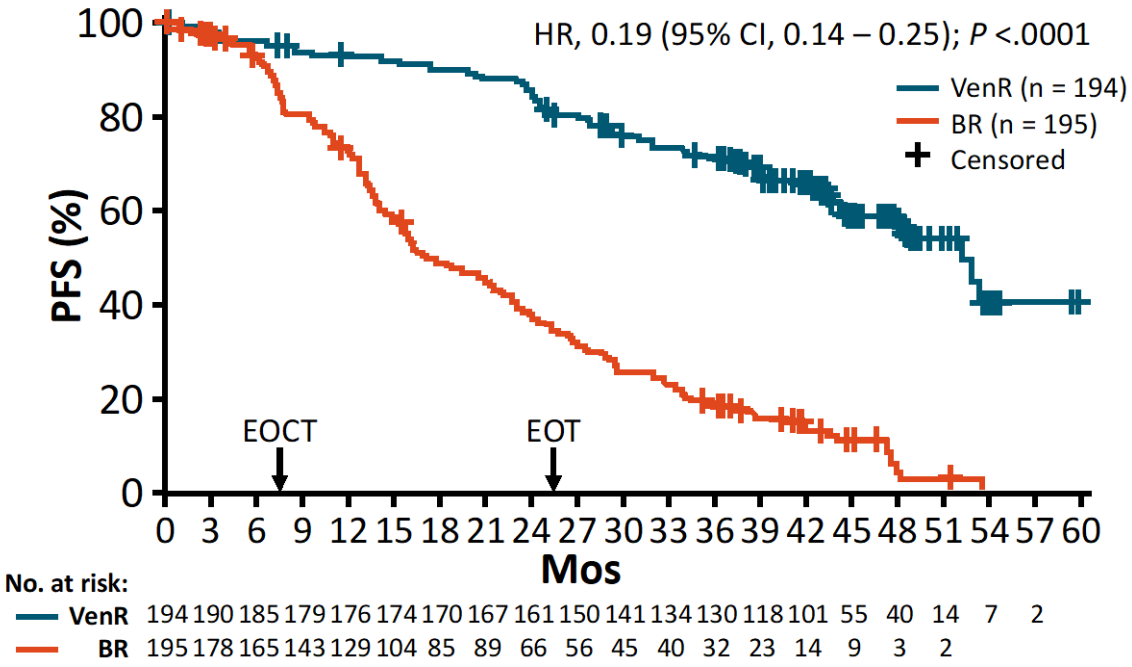
Event	Adverse Events (N=317)		Treatment-Related Adverse Events (N=317)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse events†				
Fatigue	100 (31.5)	6 (1.9)	11 (3.5)	1 (0.3)
Diarrhea	84 (26.5)	2 (0.6)	28 (8.8)	1 (0.3)
Contusion	77 (24.3)	0	52 (16.4)	0
Cough	77 (24.3)	0	5 (1.6)	0
Coronavirus disease 2019	76 (24.0)	16 (5.0)	5 (1.6)	0
Nausea	60 (18.9)	0	10 (3.2)	0
Abdominal pain	57 (18.0)	5 (1.6)	7 (2.2)	1 (0.3)
Dyspnea	55 (17.4)	3 (0.9)	2 (0.6)	0
Headache	55 (17.4)	2 (0.6)	17 (5.4)	1 (0.3)
Upper respiratory tract infection	52 (16.4)	1 (0.3)	11 (3.5)	0
Back pain	51 (16.1)	3 (0.9)	3 (0.9)	0
Anemia	48 (15.1)	28 (8.8)	15 (4.7)	7 (2.2)
Adverse events of special interest‡				
Atrial fibrillation or flutter§	12 (3.8)	4 (1.3)	4 (1.3)	1 (0.3)
Bleeding	135 (42.6)	7 (2.2)	75 (23.7)	3 (0.9)
Bruising¶	96 (30.3)	0	62 (19.6)	0
Hemorrhage	67 (21.1)	7 (2.2)	22 (6.9)	3 (0.9)
Hypertension	45 (14.2)	11 (3.5)	12 (3.8)	1 (0.3)
Infections	225 (71.0)	89 (28.1)	39 (12.3)	12 (3.8)
Neutropenia‖	103 (32.5)	85 (26.8)	62 (19.6)	47 (14.8)

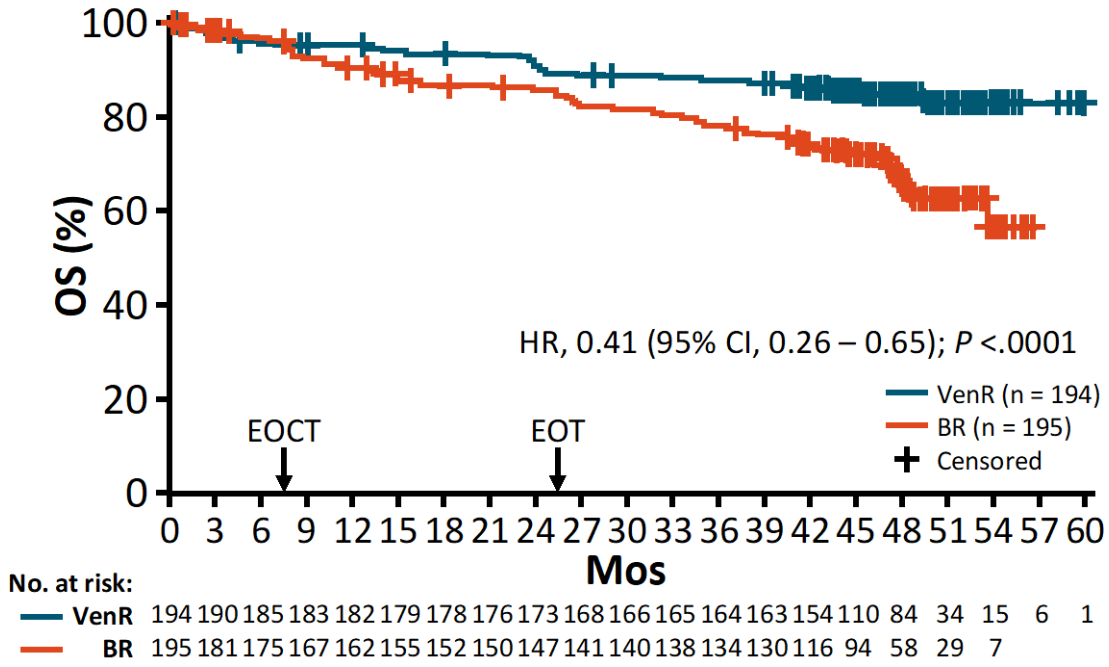
* Relatedness of adverse events to treatment was determined by the investigator.
† Shown are events that were reported in at least 15% of the patients.
‡ Adverse events of special interest are those that were previously associated with covalent BTK inhibitors. All terms are composite terms, except hypertension.
§ Of the 12 cases of atrial fibrillation or flutter in the overall safety population, 3 occurred in patients with a medical history of atrial fibrillation.
¶ Bruising included contusion, petechiae, ecchymosis, and increased tendency to bruise.
‖ This term is an aggregate of neutropenia and decreased neutrophil count.

Mato *et al., NEJM* 2023

eha

MURANO: 4 years FU with updated PFS and OS

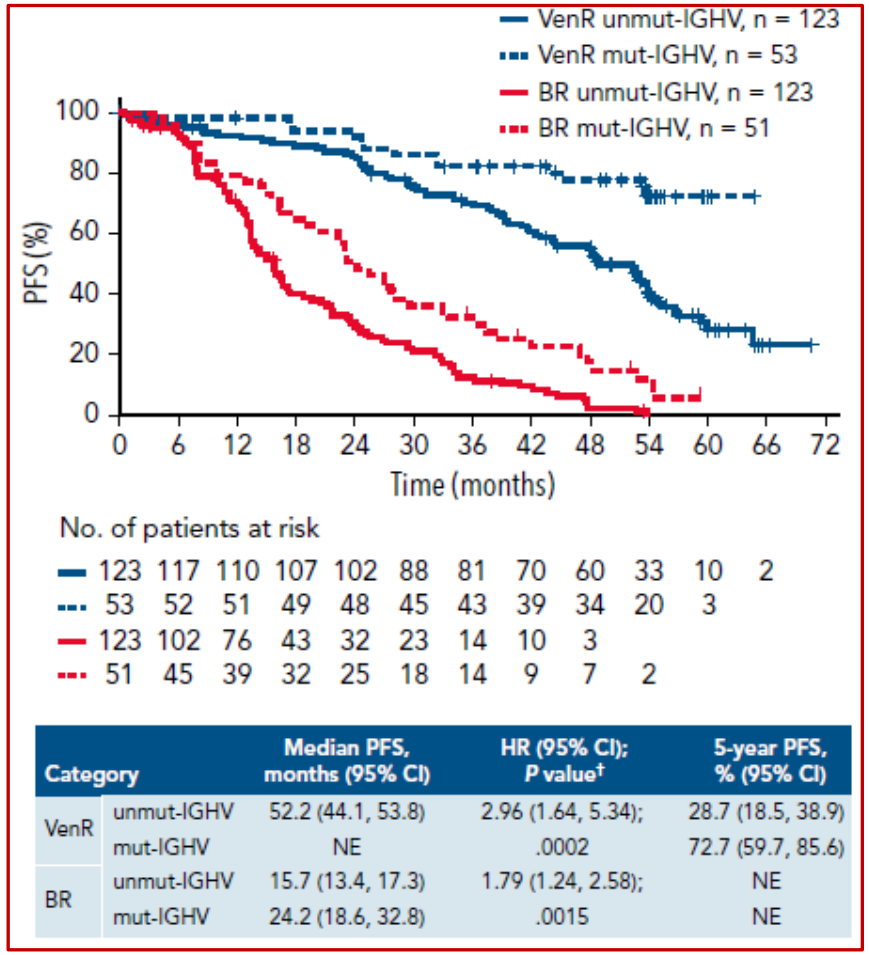




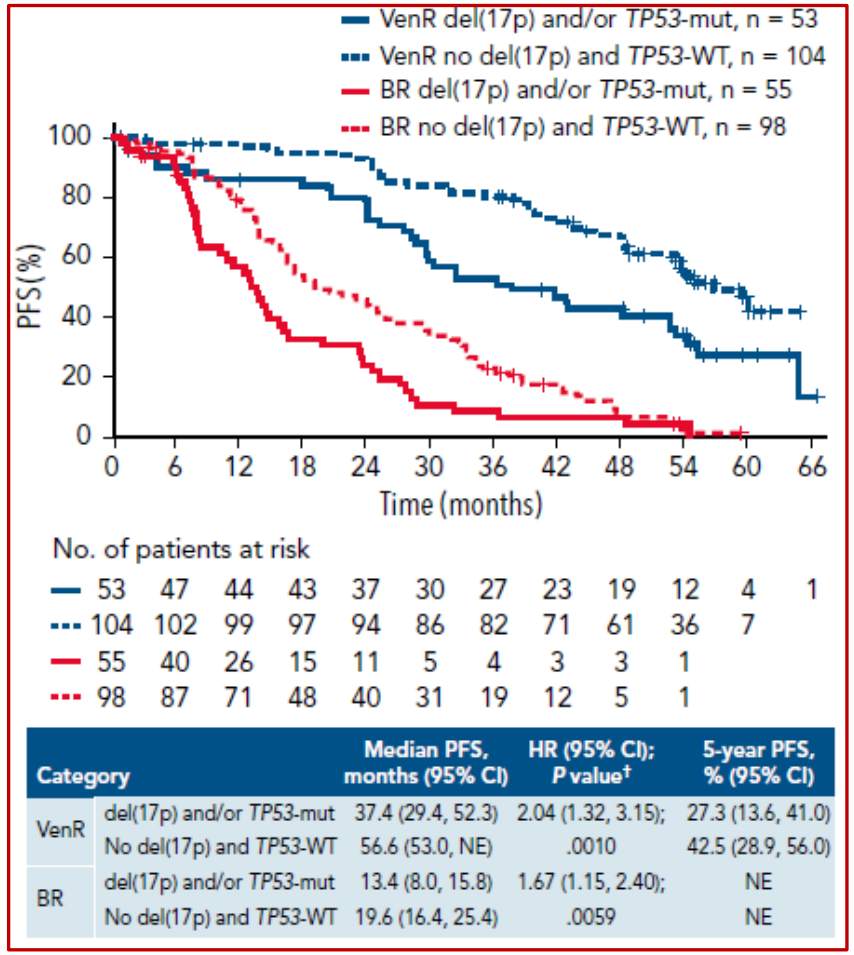
- Median follow-up: 48.0 mos

Parker. J Clin Oncol. 2020;38:4042.

MURANO trial: prognostic biomarkers



Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	unmut-IGHV	52.2 (44.1, 53.8)	2.96 (1.64, 5.34);	28.7 (18.5, 38.9)
	mut-IGHV	NE	.0002	72.7 (59.7, 85.6)
BR	unmut-IGHV	15.7 (13.4, 17.3)	1.79 (1.24, 2.58);	NE
	mut-IGHV	24.2 (18.6, 32.8)	.0015	NE



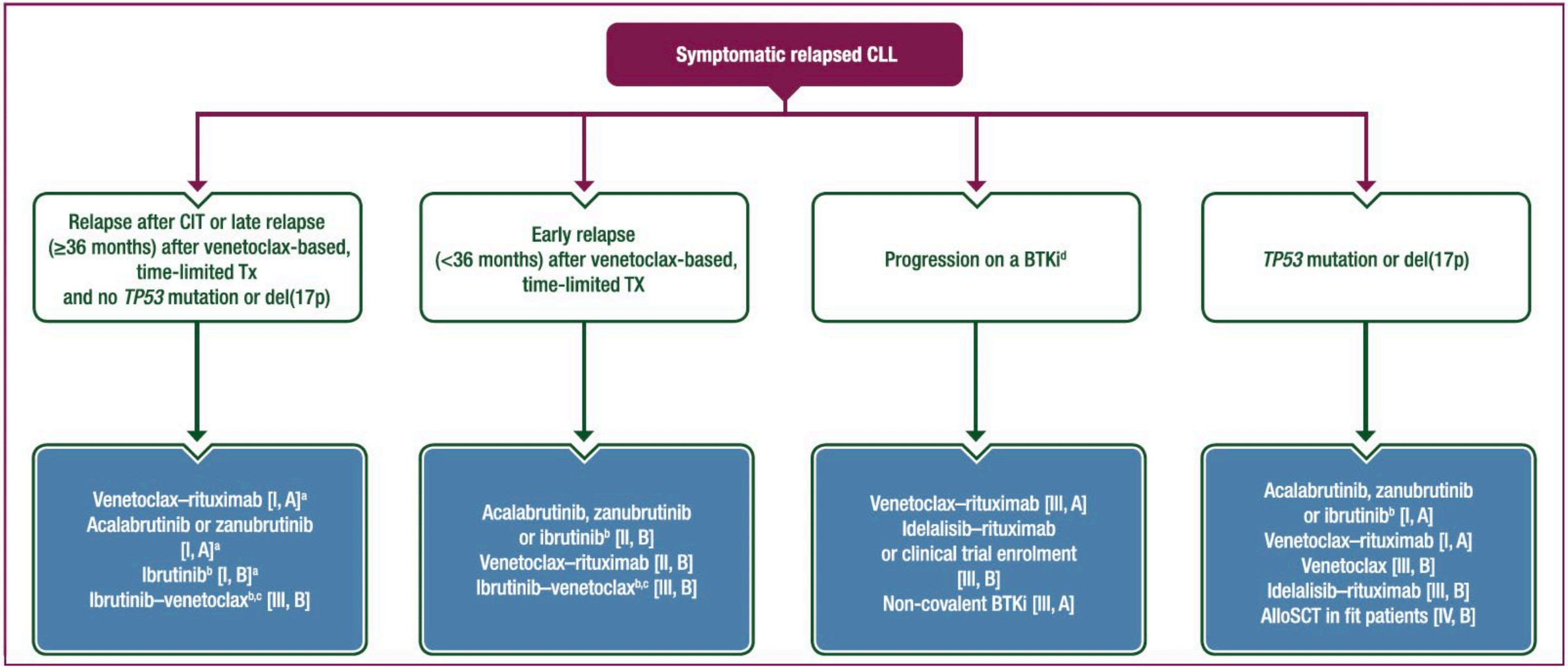
Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	del(17p) and/or *TP53*-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and *TP53*-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or *TP53*-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);	NE
	No del(17p) and *TP53*-WT	19.6 (16.4, 25.4)	.0059	NE

Venetoclax-rituximab smoothed but not completely overcome the prognostic impact of IGHV mutational status and of *TP53* disruptions

Seymour *et al.*, *Blood*. 2022

eha

ESMO guidelines for R/R treatment



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

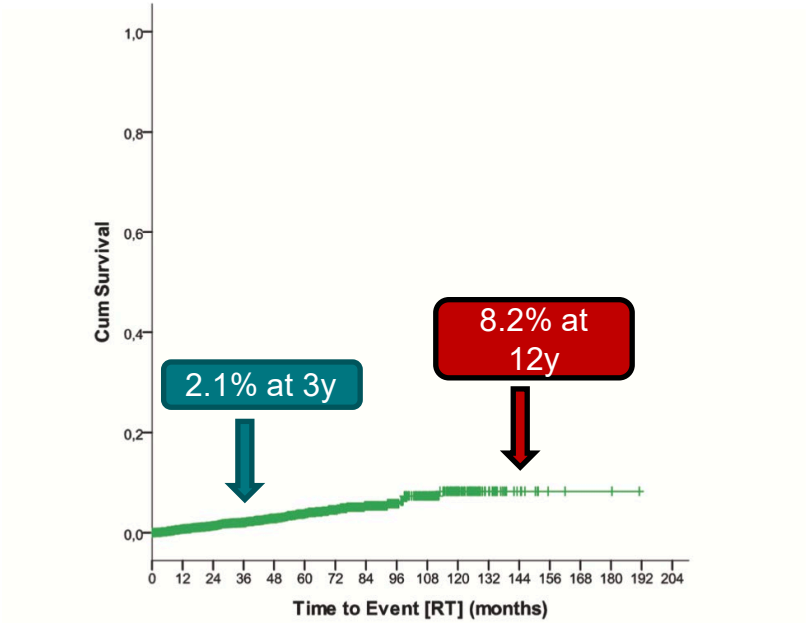
Learning Objectives

1. Understand the relevance of biology and biomarkers in the management of CLL
2. Manage asymptomatic CLL
3. Navigate among the treatment options currently available for treatment-naïve CLL
4. Manage treatment of relapsed/refractory CLL
5. **Define a diagnostic and therapeutic approach for Richter transformation**

Richter transformation in the GCLLSG trials

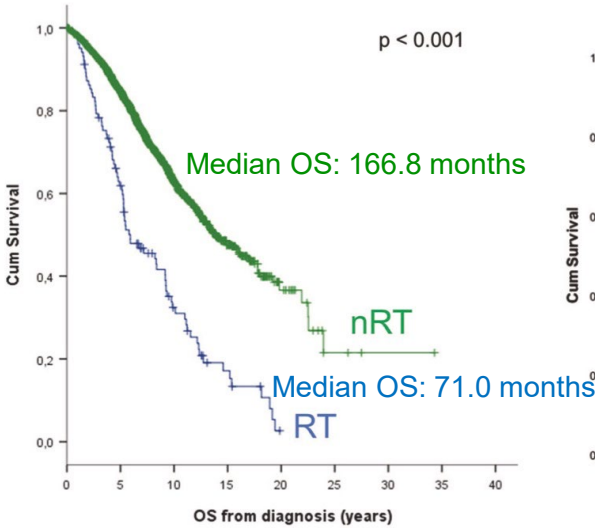
2975 patients with CLL enrolled in phase 2 and phase 3 trials of the GCLLSG
Median observation time was 53 months

Time to Richter transformation from first-line CLL treatment

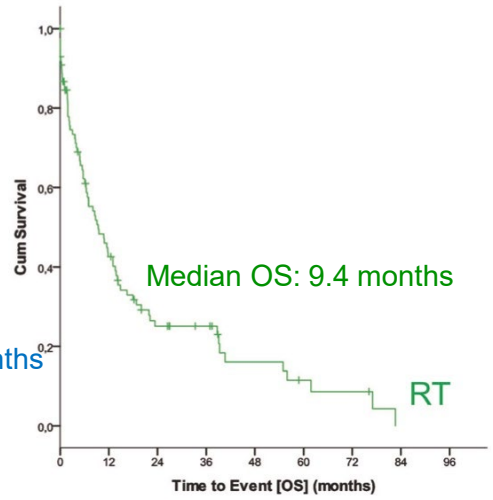


RT-free	Pts, N	Events, N	Median months	3-year Survival, %	6-year Survival, %	9-year Survival, %	12-year Survival, %
All patients	**2971**	99 (3.3)	NR	97.9	95.4	92.6	91.7

Survival from diagnosis in patients with and without Richter



Survival after Richter diagnosis



Al-Sawaf et al Leukemia 2020

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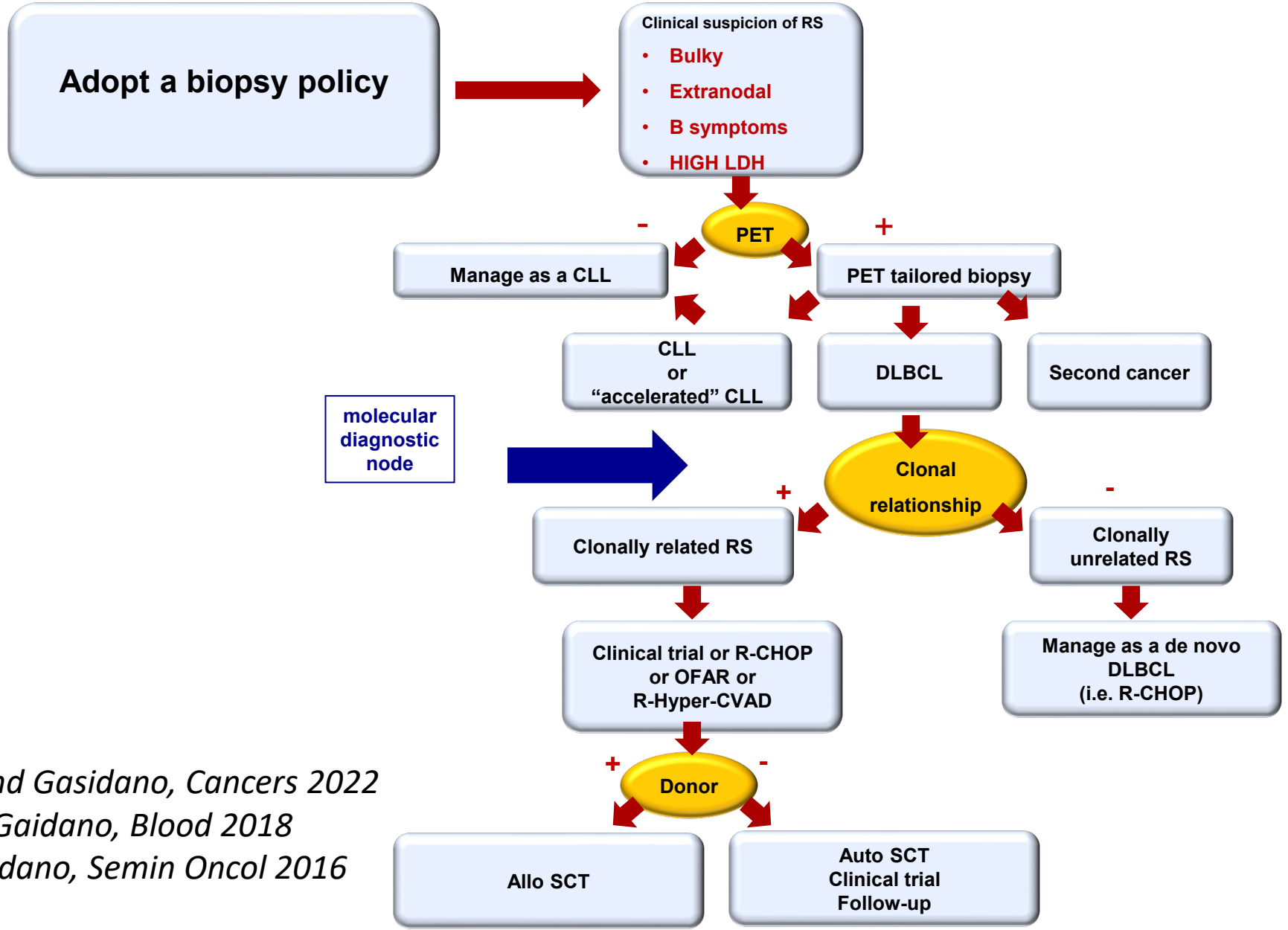
Clinical algorithm for managing Richter transformation



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

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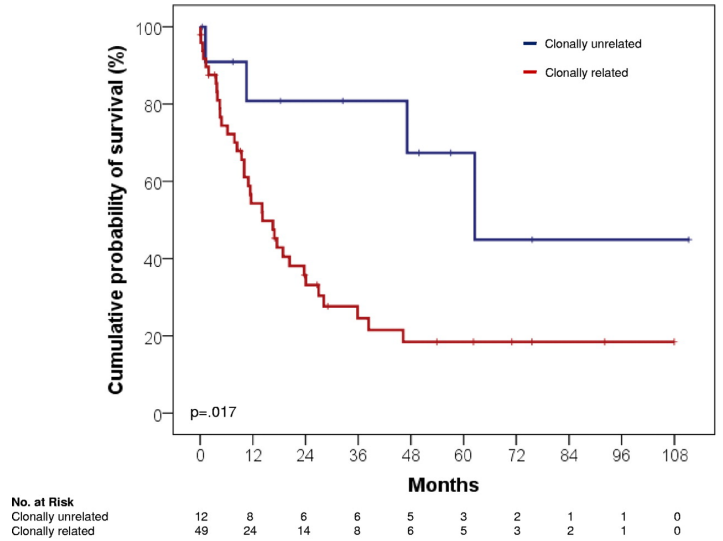
Clonal relationship represents the most important prognostic/predictive factor in Richter transformation

DLBCL Richter Transformation

De novo/clonally unrelated (~20%)

Clonally related or unknown status (~80%)



Manage as DLBCL

Clinical trial or Intensified regimen and allo-SCT

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

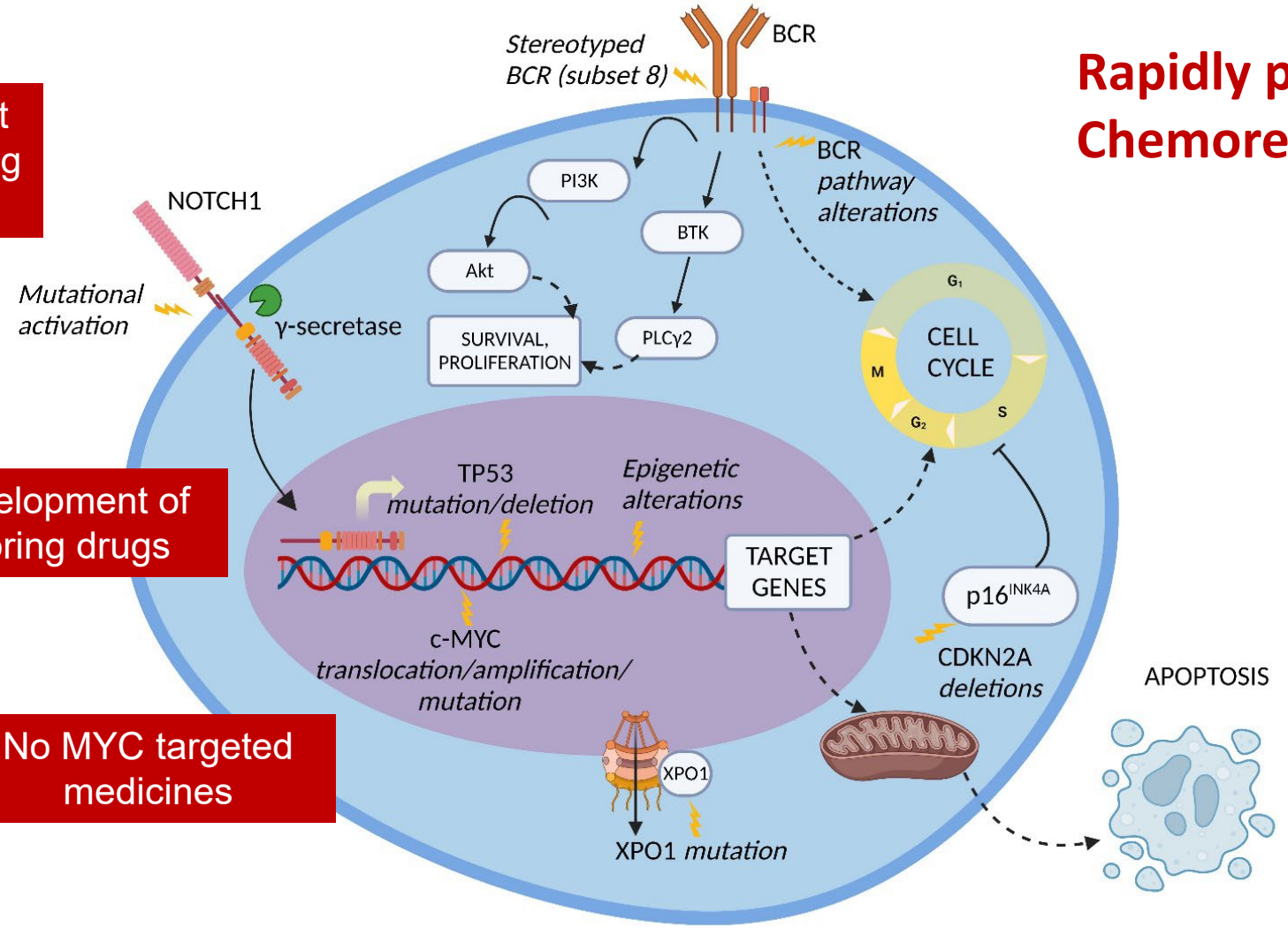
eha

Reasons for treatment failure in clonally related Richter transformation

Slow development of NOTCH targeting medicines

Difficult development of TP53 restoring drugs

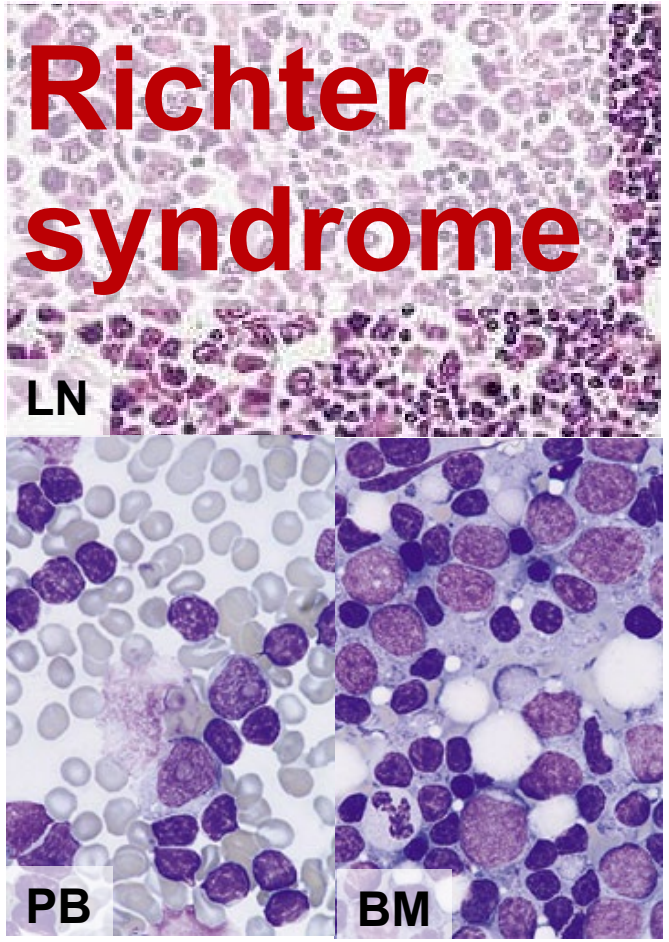
No MYC targeted medicines



Rapidly progressive kinetics
Chemorefractoriness

Mouhssine and Gaidano, Cancers, 2022

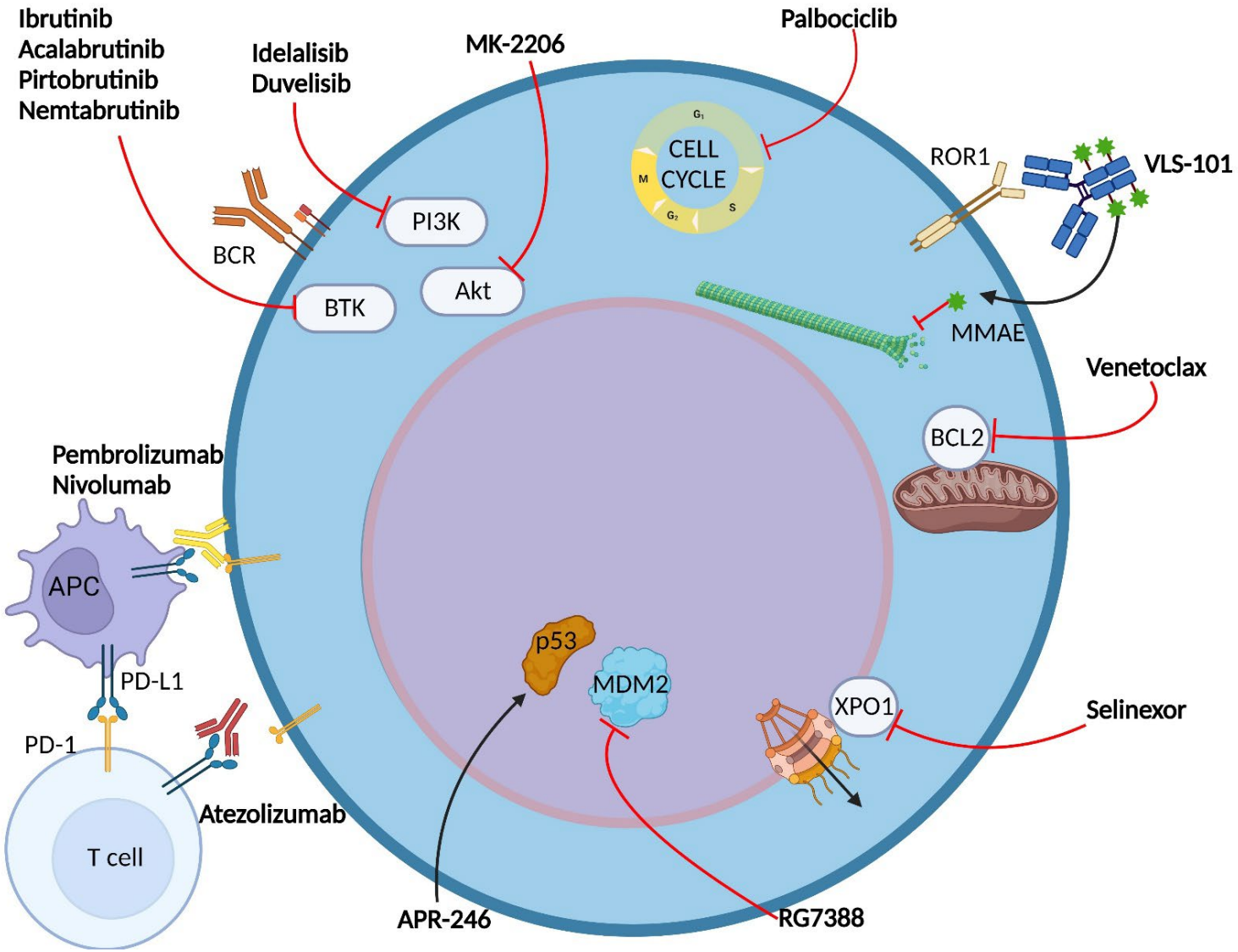
Reasons for treatment failure in Richter transformation



- Biology of the tumor
- Lack of dedicated treatments
- Patient frailty
- Late recognition

- No standard of care
- R-CHOP frequently used, followed by allo/auto HSCT in eligible patients
- Need for developing chemo-free strategies for Richter transformation

Molecular vulnerabilities of Richter transformation



Mouhssine and Gaidano, Cancers, 2022

Anti PD-1 in combination with target agents

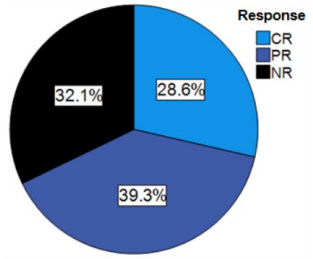
THE LANCET Oncology *Tedeschi et al., 2024*

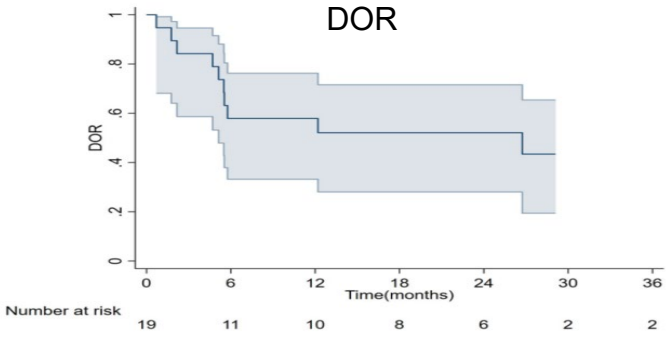
Venetoclax, atezolizumab and obinutuzumab combination in DLBCL-RT: the phase 2 MOLTO trial

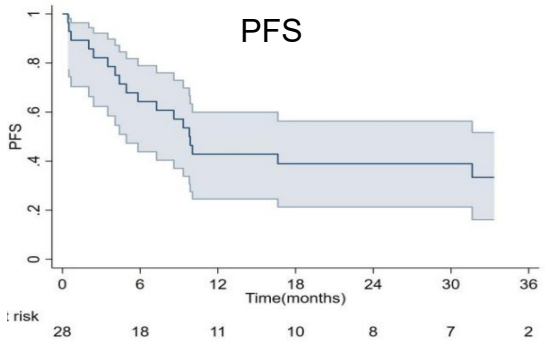
28 pts

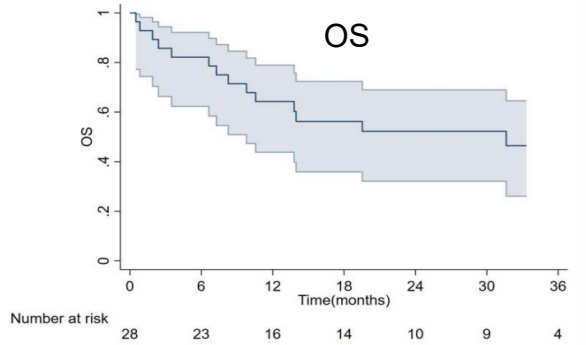
Median previous CLL Tx: 1
Previuos untreated RT: 100%
Clonally related: 83.3%
Unknown: 16%

ORR ITT: 68.3%









nature medicine *Al Sawaf O et al., 2023*

Tislelizumab plus zanubrutinib for Richter transformation: the phase 2 RT1 trial

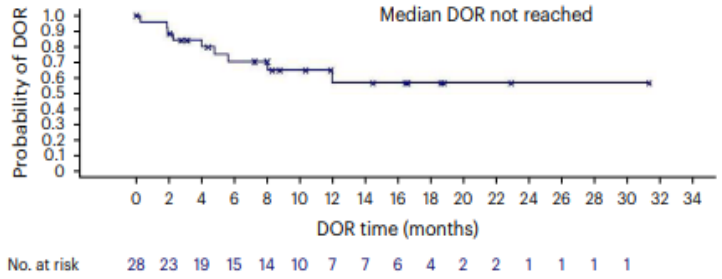
57 pts
ORR ITT: 47.5%

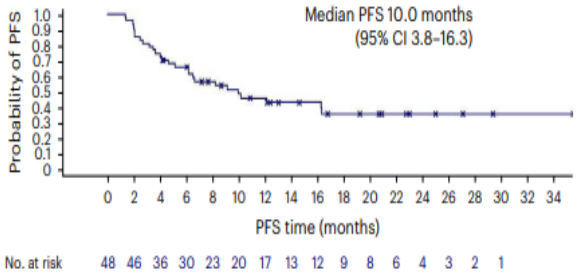
→ **9 discontinued before C2 (induction)**

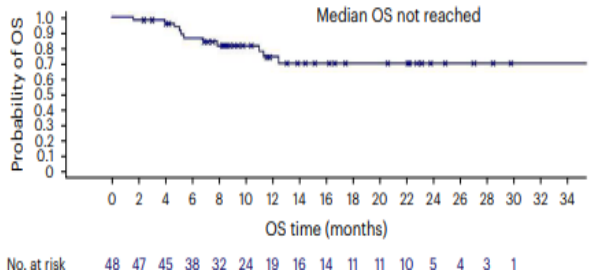
48 pts

Median previous CLL Tx: 3
Previuos untreated RT: 79%
Clonally related: 54%
Unknown: 46%

ORR. 58.3%







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

Discussion points

- How to manage CLL if pathway inhibitors are not fully accessible
- How to balance patient preferences with guideline recommendations for choosing treatment
- How to manage cardiac effects of BTKi
- What is the most appropriate treatment sequencing in TP53 wild type patients
- How to raise a clinical suspicion and provide appropriate management of Richter transformation

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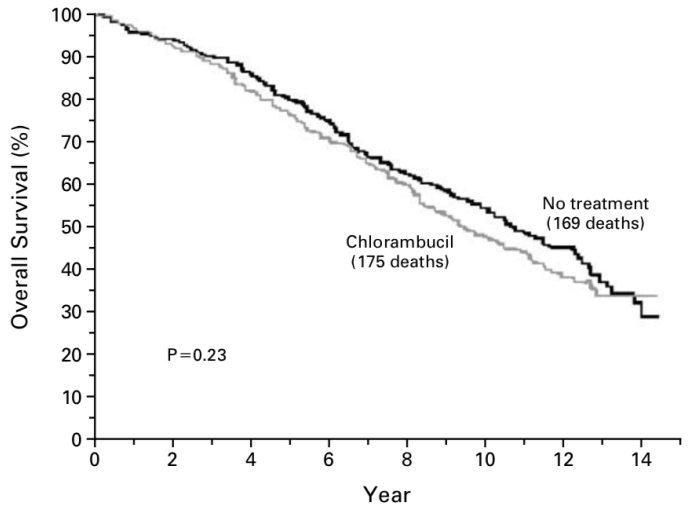
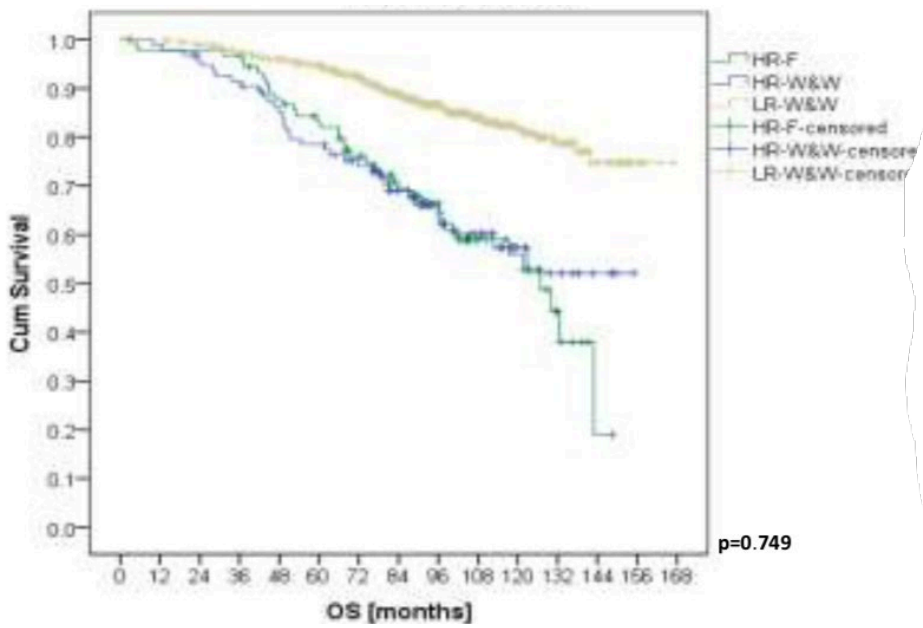
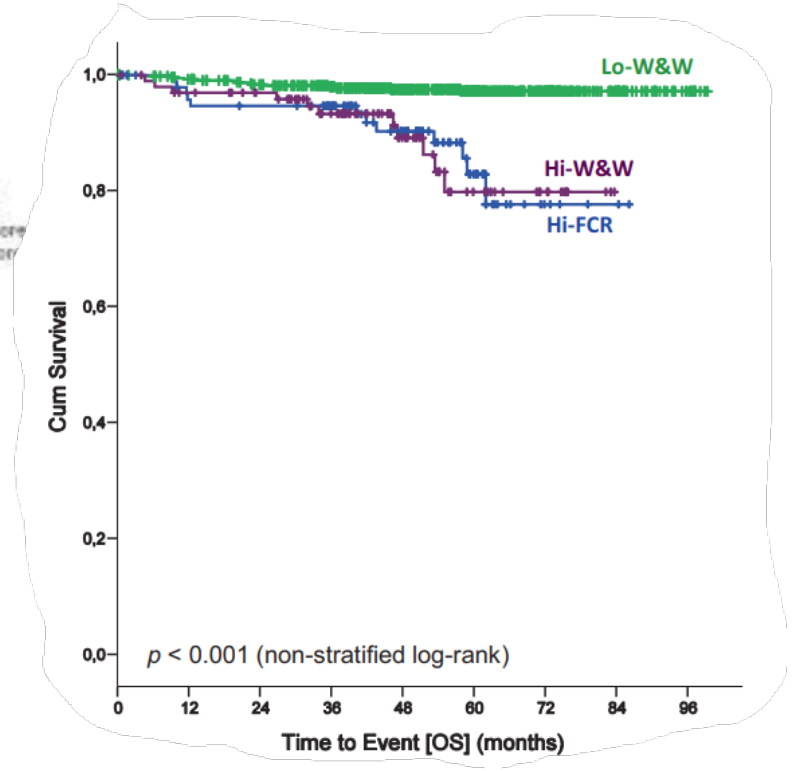
Back up slides

Early intervention in Binet A CLL does not improve patients outcome



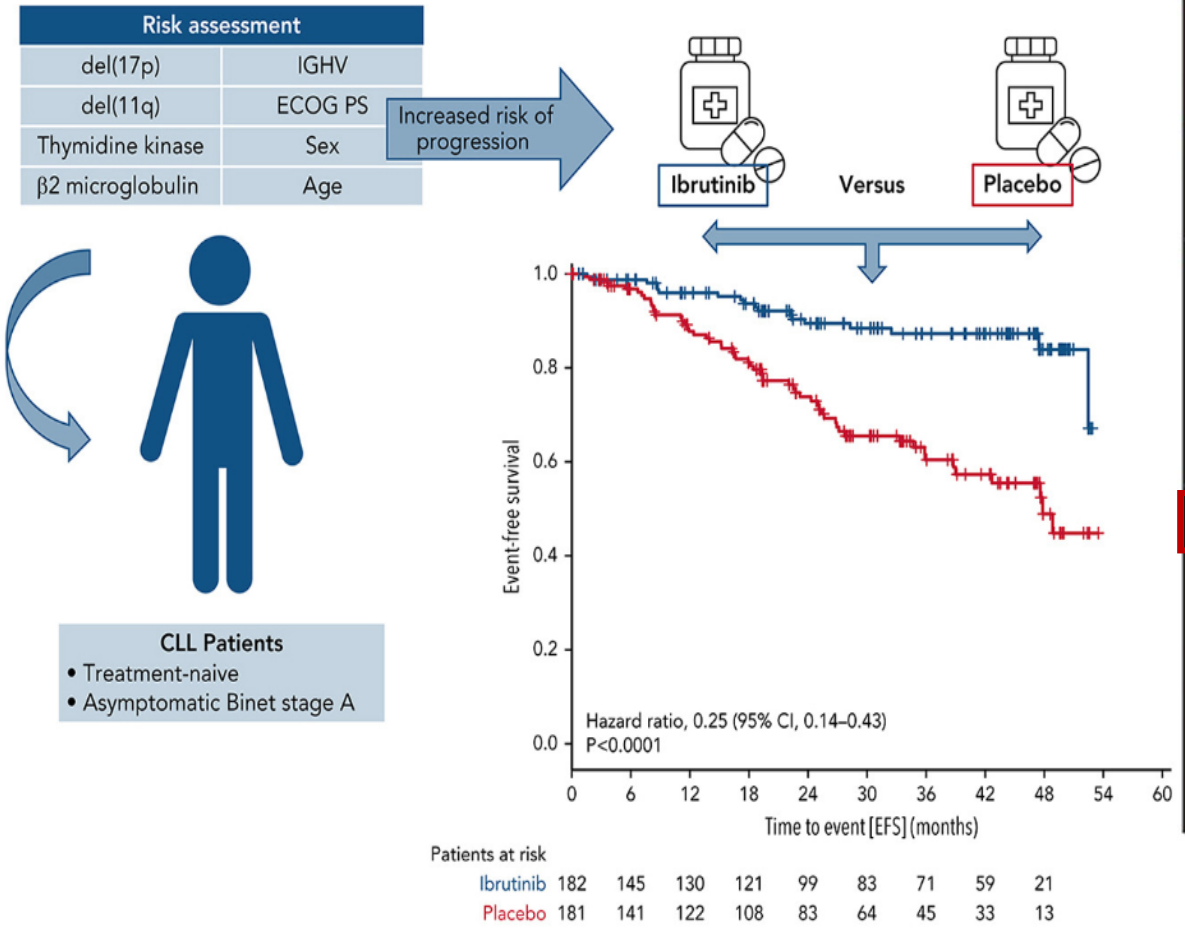




Early intervention can postpone events of disease progression and the need of therapy, especially in high-risk Binet A CLL patients, but, despite this effect, **there is no OS benefit**

Dighiero *et al., NEJM*. 1998; Hoechstetter *et al., Leukemia.* 2017; Herling *et al., Leukemia.* 2020.

CLL12 trial: ibrutinib vs placebo in treatment-naïve, high-risk, early-stage CLL



	Ibrutinib (n = 158)			Placebo (n = 155)		
	Any grade	Grade 1-2	Grade ≥3	Any grade	Grade 1-2	Grade ≥3
Any serious AEs, n (%)	62 (39.2)	11 (6.9)	51 (32.3)	58* (37.4)	4 (2.6)	53 (34.2)
Total n of serious adverse events	112	18	94	108*	8	99
Serious AEs with ≥2% incidence in either group, n (%)†						
Atrial fibrillation	9 (5.7)	1 (0.6)	8 (5.1)	1 (0.6)		1 (0.6)
Acute myocardial infarction	1 (0.6)	1 (0.6)		4 (2.6)		4 (2.6)
Pneumonia	7 (4.4)		7 (4.4)	6 (3.9)		6 (3.9)
Basal cell carcinoma	3 (1.9)	1 (0.6)	2 (1.3)	6* (3.9)		5 (3.2)
Any AE of clinical interest, n (%)	113 (71.5)	86 (54.4)	27 (17.1)	77 (49.7)	53 (34.2)	24 (15.5)
Total no. of AEs of clinical interest	280	245	35	164	135	29
Cardiac arrhythmias	34 (21.5)	21 (13.3)	13 (8.2)	12 (7.7)	10 (6.5)	2 (1.3)
Bleeding	53 (33.5)	47 (29.7)	6 (3.8)	23 (14.8)	20 (12.9)	3 (1.9)
Hypertensive disorders	18 (11.4)	15 (9.5)	3 (1.9)	7 (4.5)	4 (2.6)	3 (1.9)
Cardiac event other than arrhythmia	12 (7.6)	7 (4.4)	5 (3.2)	16 (10.3)	7 (4.5)	9 (5.8)
Diarrhea	63 (39.9)	60 (38.0)	3 (1.9)	46 (29.7)	39 (25.2)	7 (4.5)

Ibrutinib is effective in patients with high-risk, early-stage CLL, but **the results do not justify changing the current standard of "watch and wait"**, keeping in mind the relevant cardiovascular toxicity associated with ibrutinib

Langerbeins *et al., Blood*. 2022

Evaluation of patients with CLL before treatment

Assessment before treatment	Clincal practice	Trial
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound†	Possible	NGI

Hallek *et al., Blood*. 2018