Leucemia linfatica cronica e leucemia a cellule capellute: Stato dell'arte

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Disclosures

Scientific Advisory Board: AbbVie, Astra-Zeneca, BeiGene, Incyte, Johnson & Johnson, Lilly

Speakers Bureau: Abbvie, Astra-Zeneca, Hikma, Johnson & Johnson

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

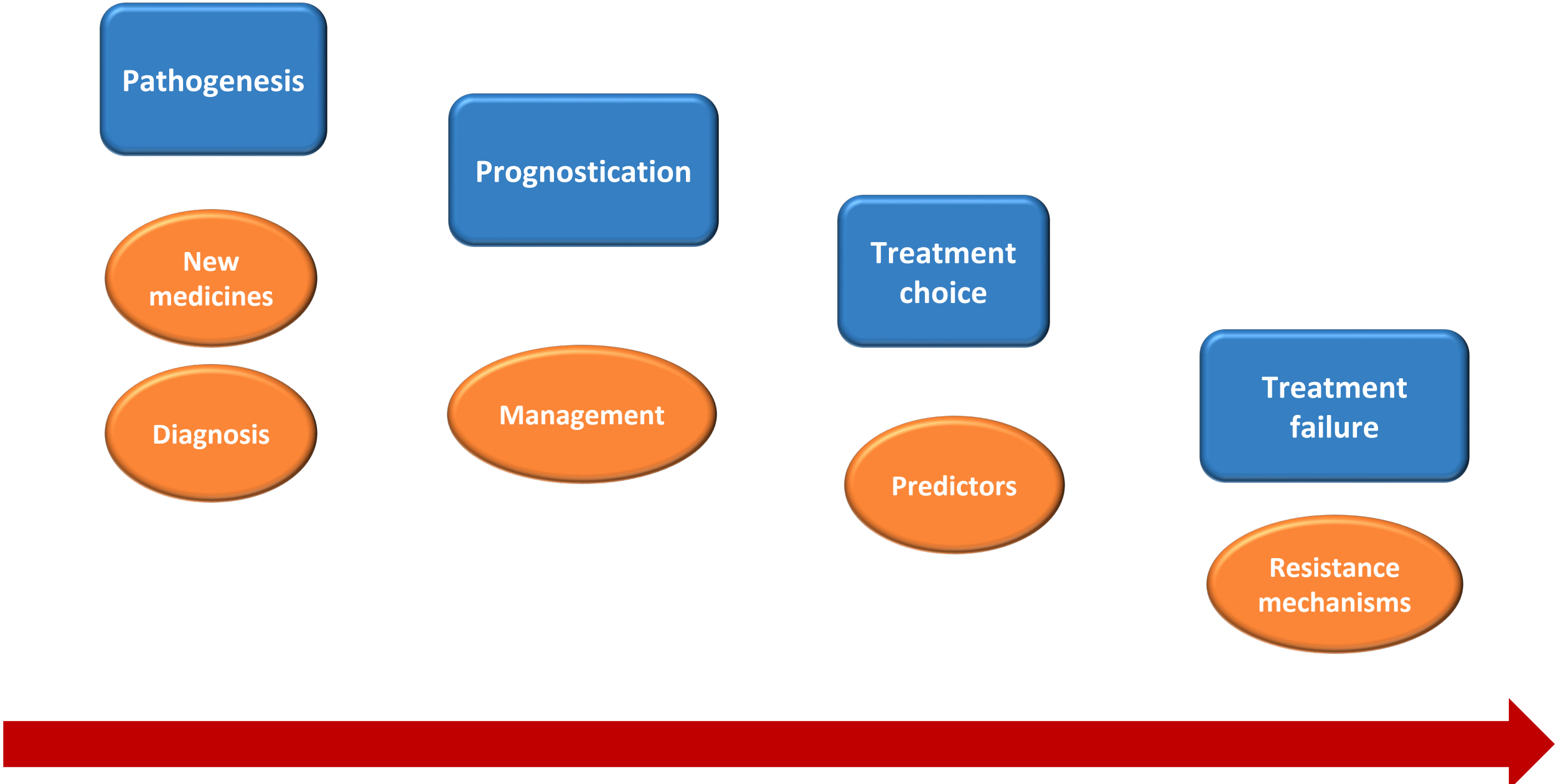
	NCI 1996 guidelines	IWCLL 2008 & 2018 guidelines
CLL	Lymphocytes ≥ $5.0x10^9$/L	Monoclonal B lymphocytes: ≥ $5.0x10^9$/L *
MBL	*Not included*	Monoclonal B lymphocytes: < $5.0x10^9$/L

«De-leukemization» of a substatial fraction of individuals

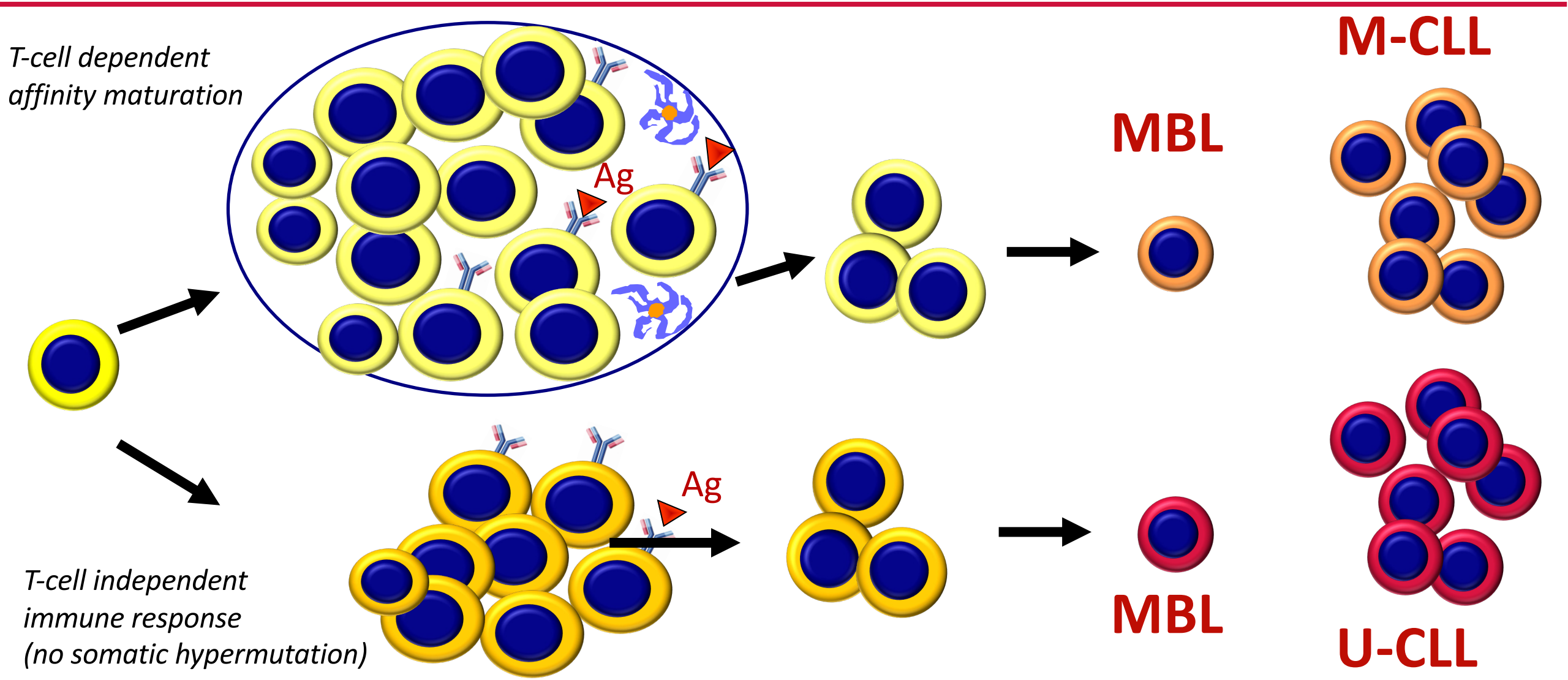
*Clonal B lymphocytes must have the typical CLL phenotype (CD19+ CD20+ CD23+ CD5+ sIg low)

Rawstron et al, NEJM 359:575-583, 2008

Outline of conceptual and translational evolution in CLL

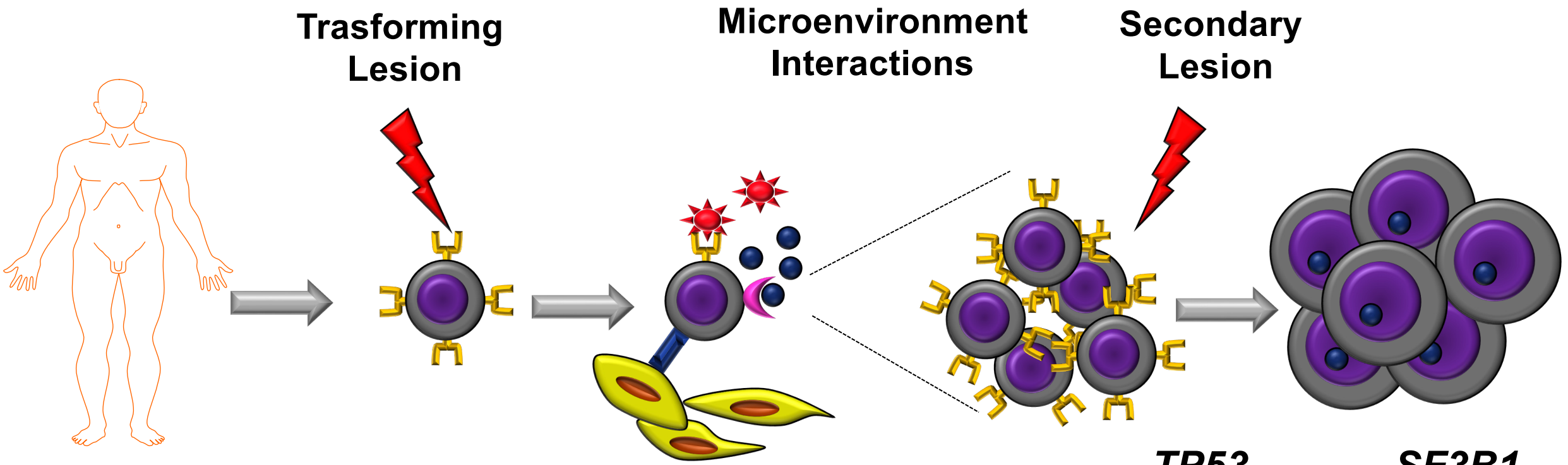


IGHV mutated (M) vs unmutated (U) CLL



Damle et al., Blood 94:1840-1847, 1999; Hamblin et al., Blood 94:1848-1850, 1999; Gaidano G, Foà R, Dalla-Favera R, J Clin Invest 122:3432-3438, 2012

Pathogenesis of CLL



Predisposition

Polygenic
IRF4, IRF8
Other

Initiation

del13q
+12
MYD88

Promotion/Accumulation

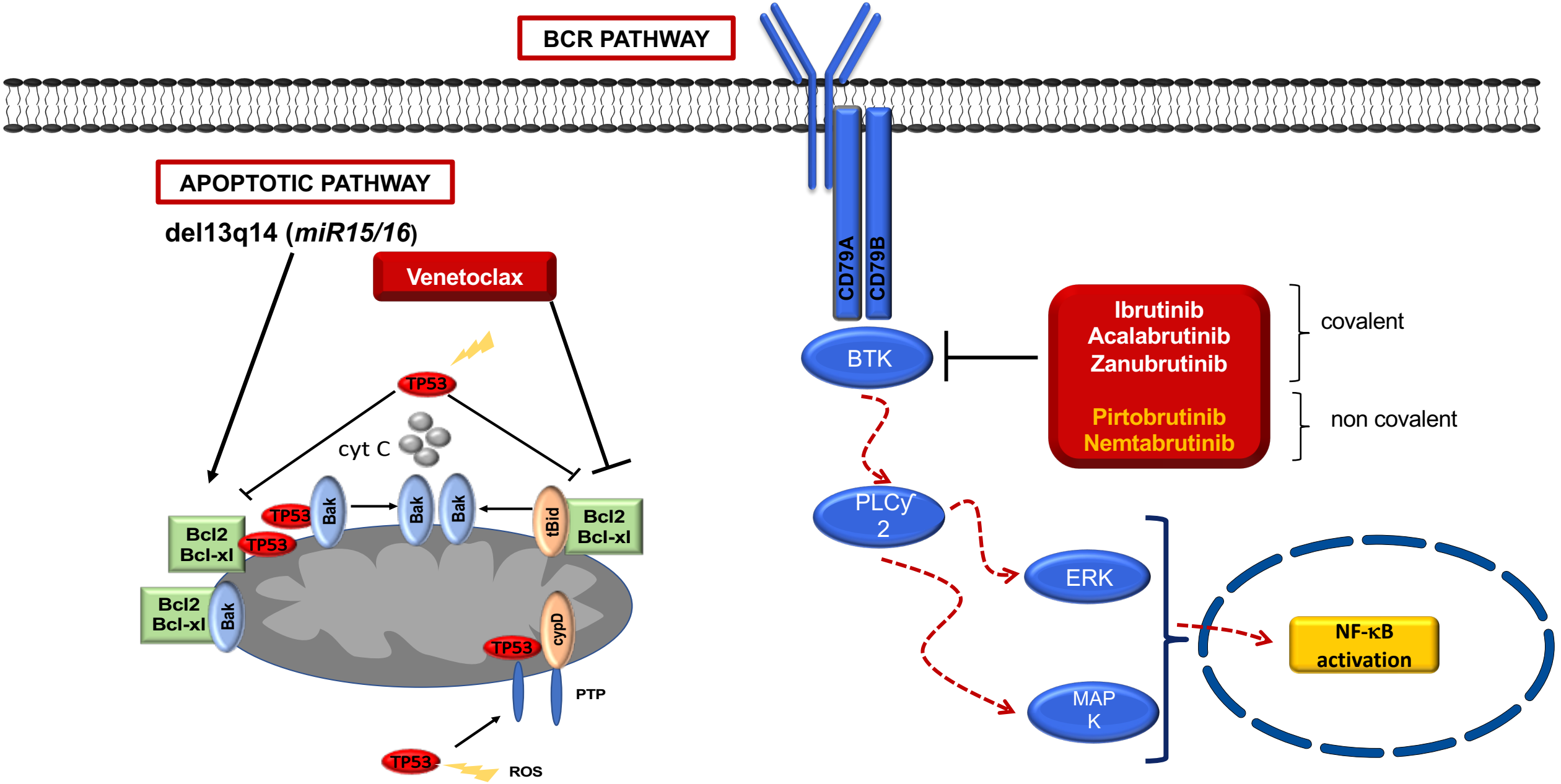
BCR
CD38
NOTCH
TLR
VLA-4
CXCR4

TP53
ATM
NOTCH1
ATM
Other

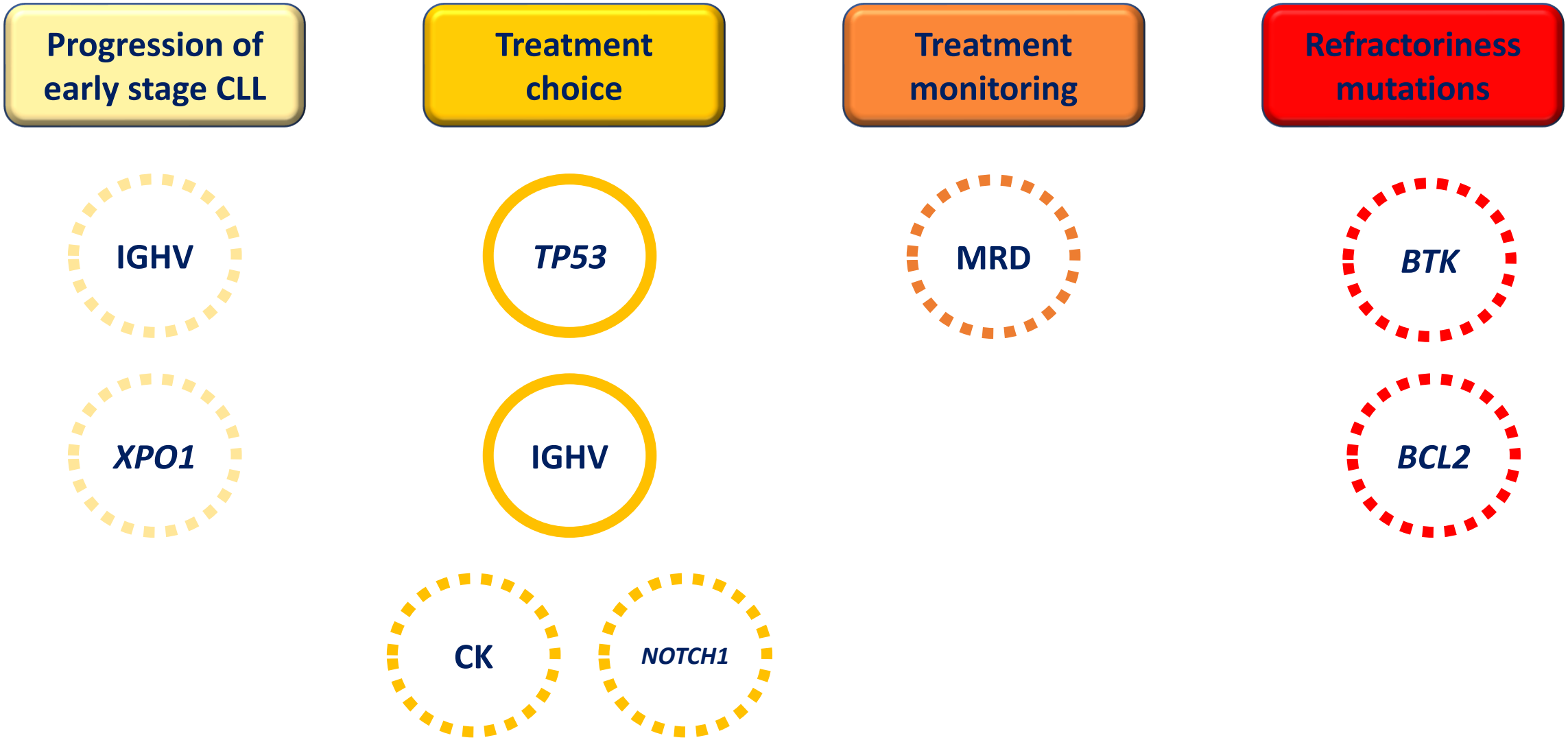
SF3B1
BIRC3
MYC
CDKN2A

Deaglio et al., Blood 108:1135-1144, 2006; Ghia et al., J Intern Med 264:549-562, 2008; Scupoli and Pizzolo, Exp Rev Hematol, 5:341-348, 2012; Dal Bo et al., Semin Hematol 51:168-176, 2014; Gaidano and Rossi, Hematology ASH 2017:329-337, 2017; Moia and Gaidano, Semin Hematol 61:83-90, 2024

Therapeutic targets in CLL



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

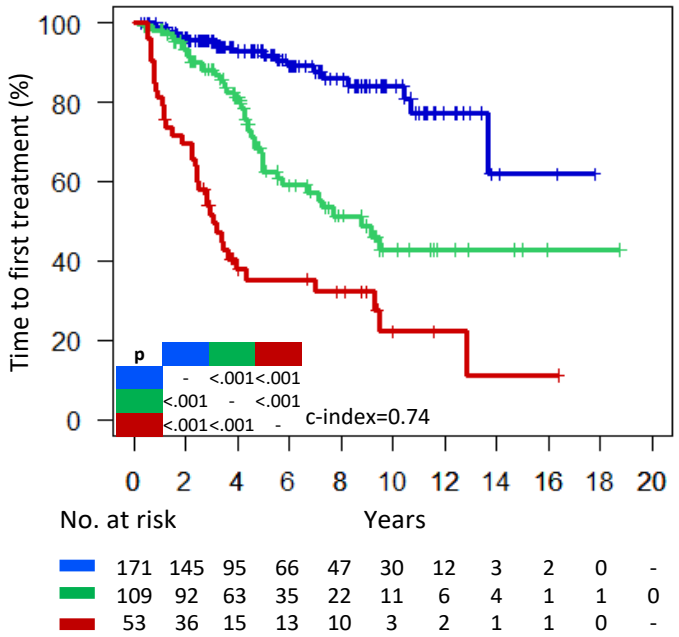


Prognostic score for early stage CLL patients

Binet A CLL patients

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

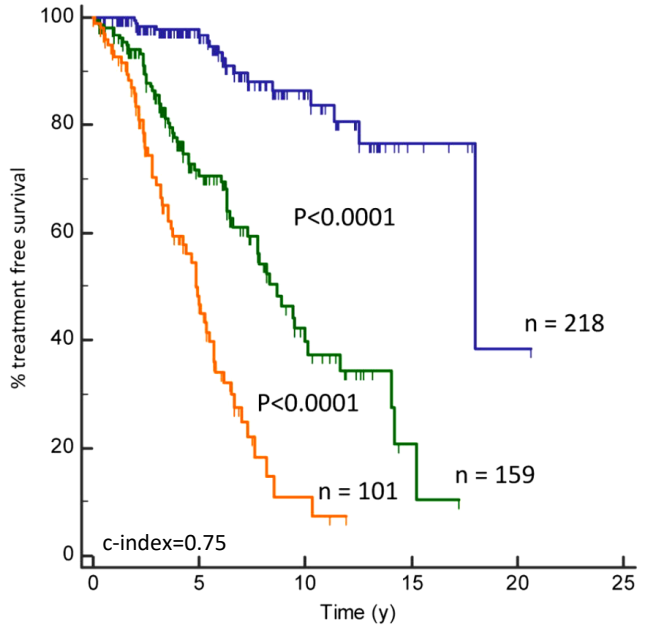
Risk group	Score
Low-risk	0
Intermediate-risk	1
High-risk	2-3



Rai 0 CLL patients

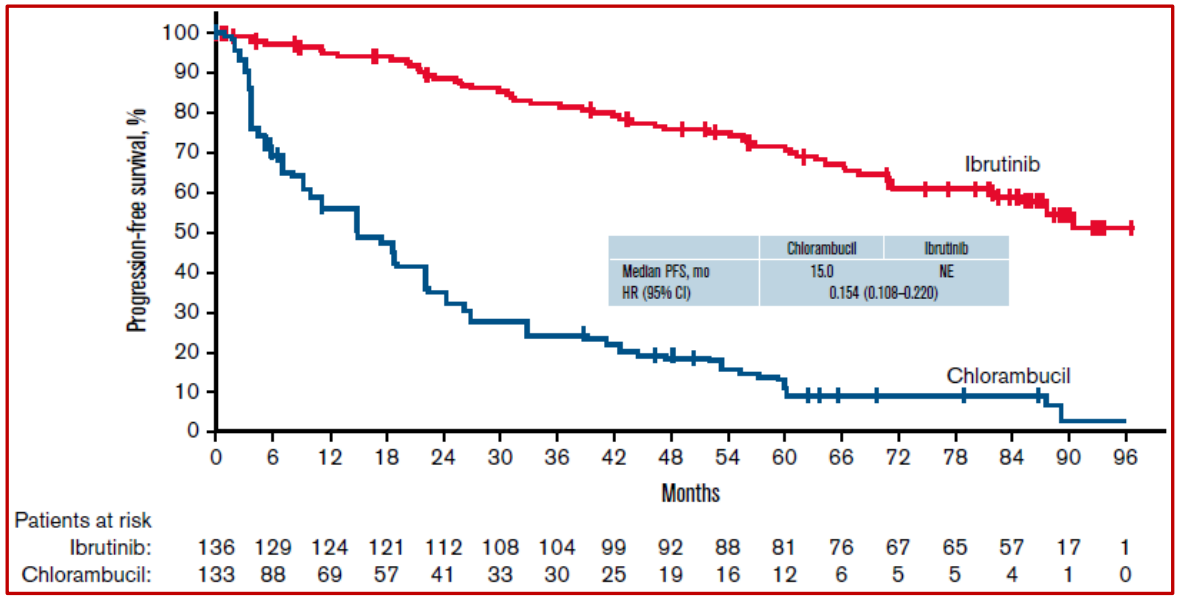
Variable	Point(s)
UM-IGHV	2
Del 17p	2
Del 11q	1
Tris 12	1
WBC >32 10^9/l	1

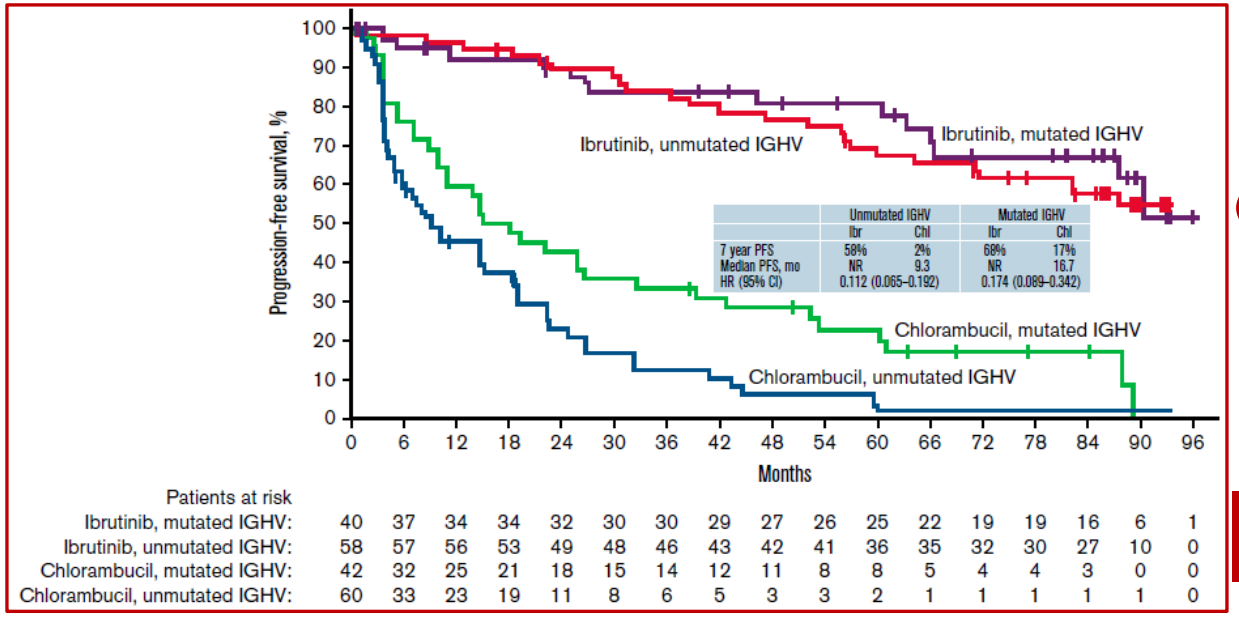
Risk group	Score
Low-risk	0
Intermediate-risk	1-2
High-risk	3-5

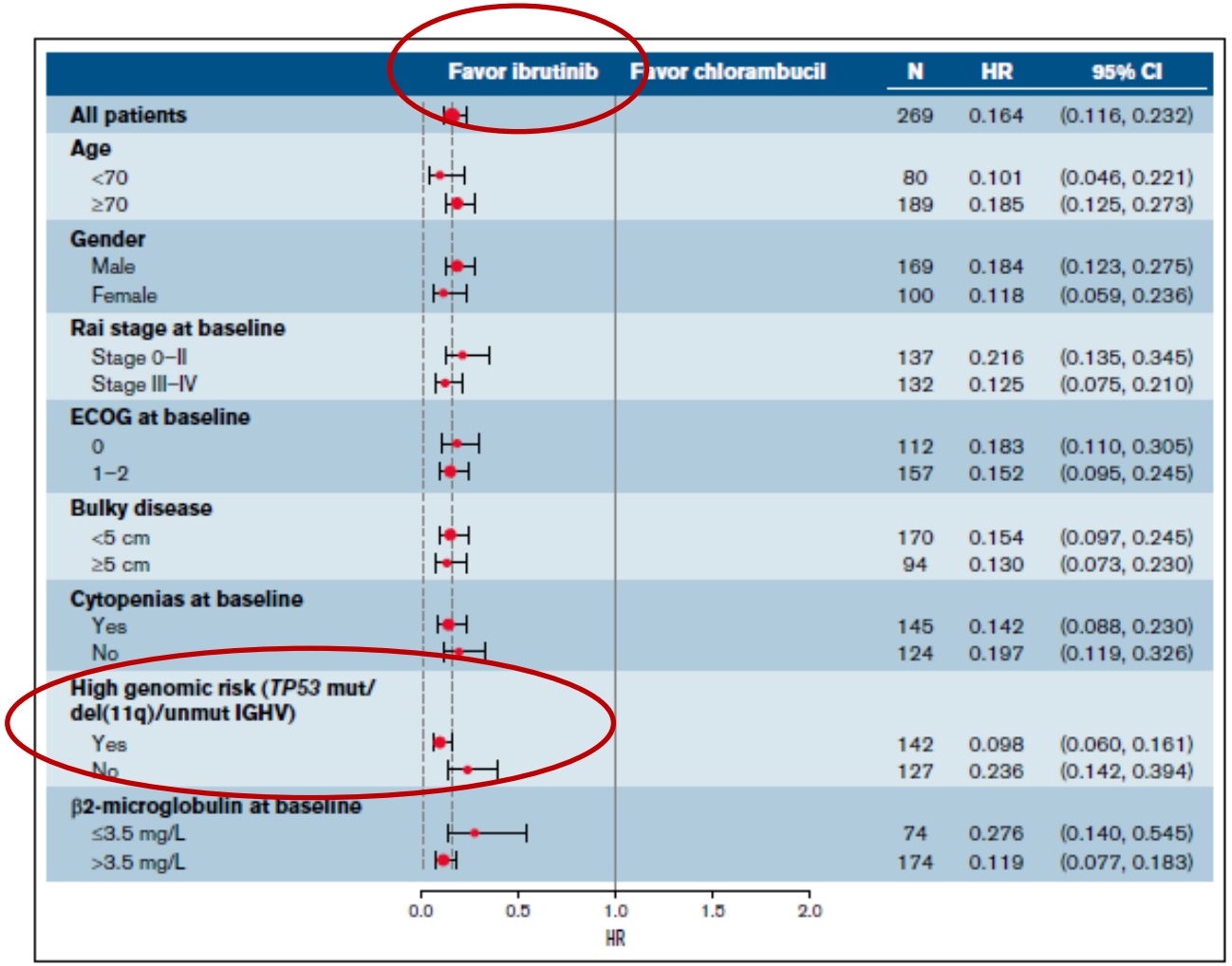


Condoluci *et al., Blood.* 2020; Cohen *et al., Haematologica*. 2019

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



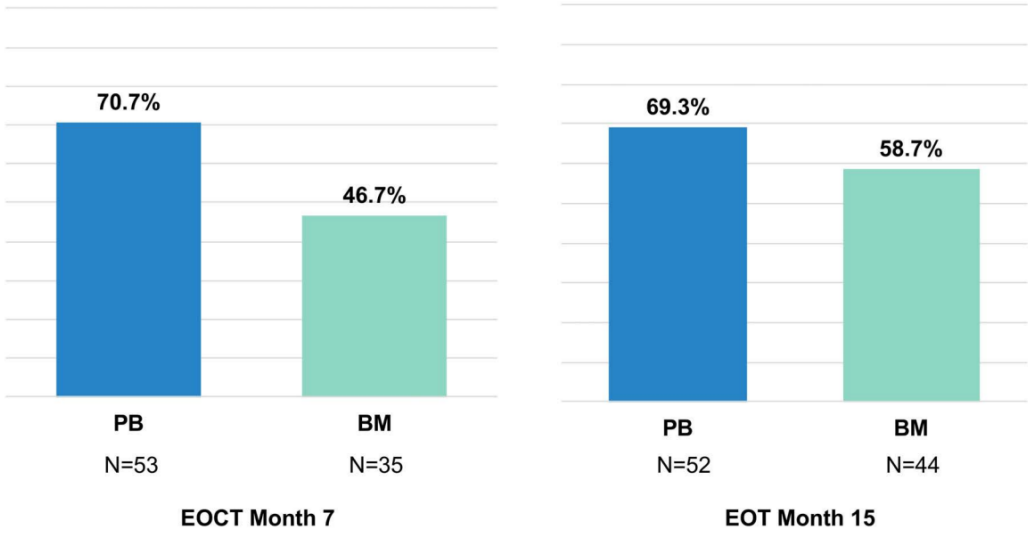




Ibrutinib overcomes the poor prognosis of unmutated IGHV

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

GIMEMA phase II LLC1518 - VERITAS study



uMRD (10^{-4}) at end of combination treatment (EOCT) and at end of treatment (EOT)

Front-line VenR associates with a high rate of complete remissions and durable response with undetectable MRD in young patients with chronic lymphocytic leukemia and unfavorable genetic characteristics

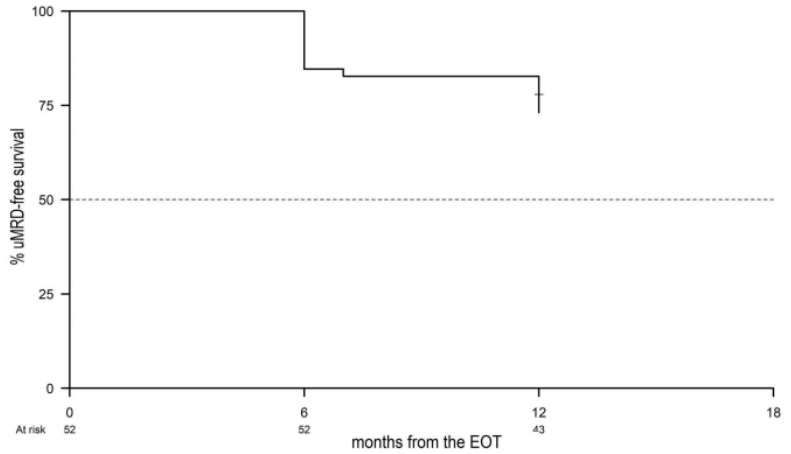


Figure 4. Undetectable minimal residual disease-free survival. uMRD: undetectable minimal residual disease; EOT: end of treatment.

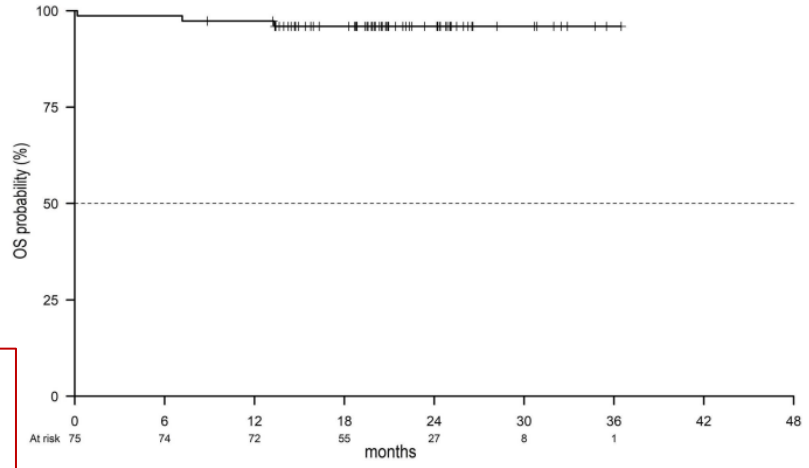


Figure 5. Overall survival of the whole cohort of 75 patients enrolled in the study. OS: overall survival.

Mauro et al., Haematologica 108:2091-2100, 2023

Increasing relevance of RWE studies: the case of *TP53* and BTKi

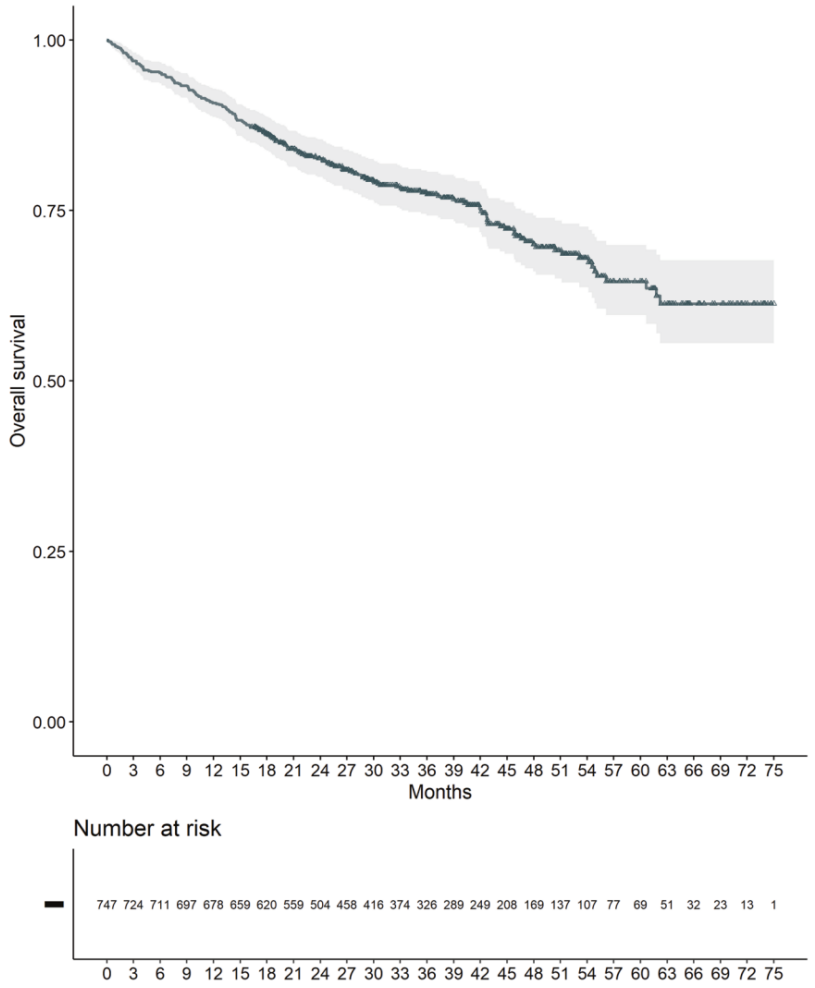


Fig. 2 Overall survival (OS). Median OS was not reached with a 24-month survival probability of 82.6%.

- Ibrutinib is an effective first line treatment for *TP53* disrupted CLL patients treated in the real world practice, in both academic centers and in community hospitals

- The experience of prescribing centers had no impact on outcome in this high risk population

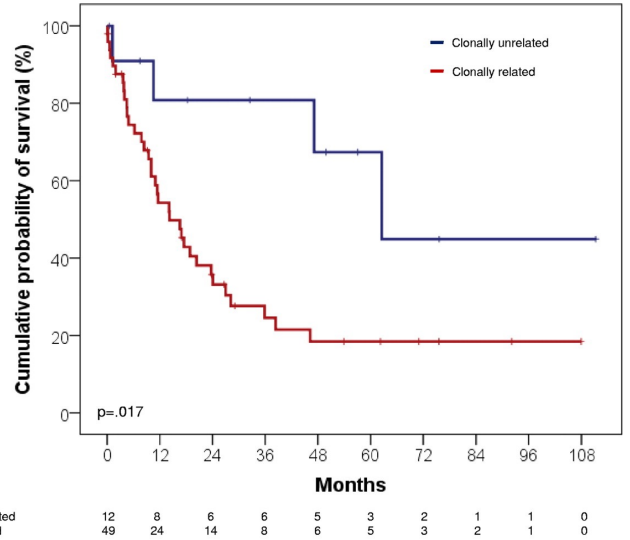
Value of the GIMEMA network and its dissemination activities

Rigolin et al., Blood Cancer J 13:99, 2023

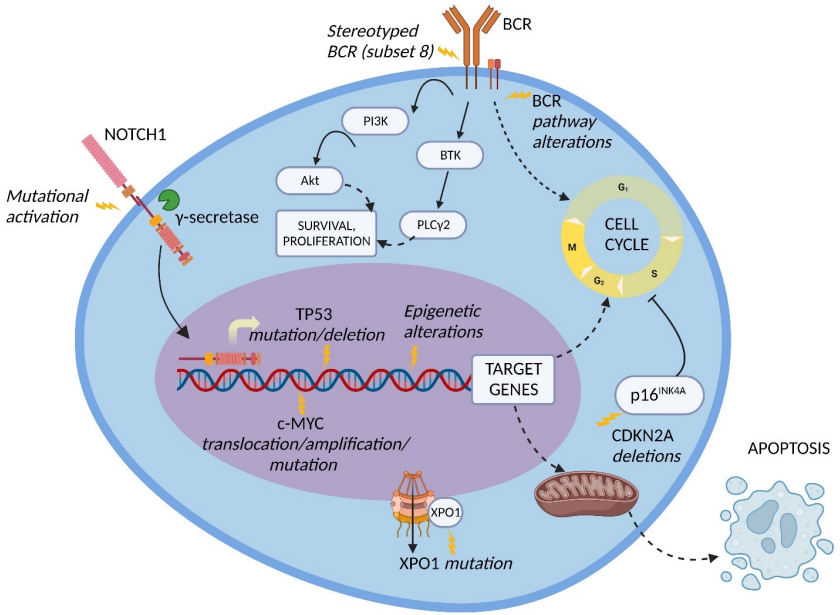
Clonal relationship represents the most important prognostic/predictive factor in Richter transformation

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

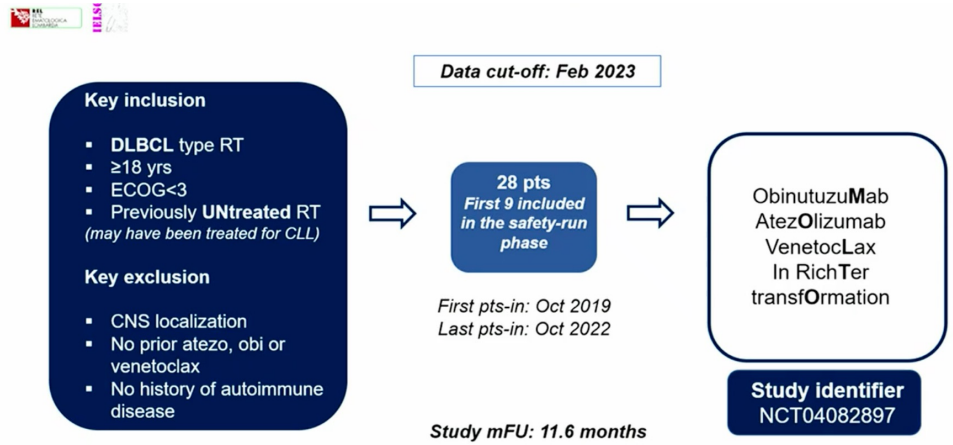


Rapidly progressive kinetics
Chemorefractoriness

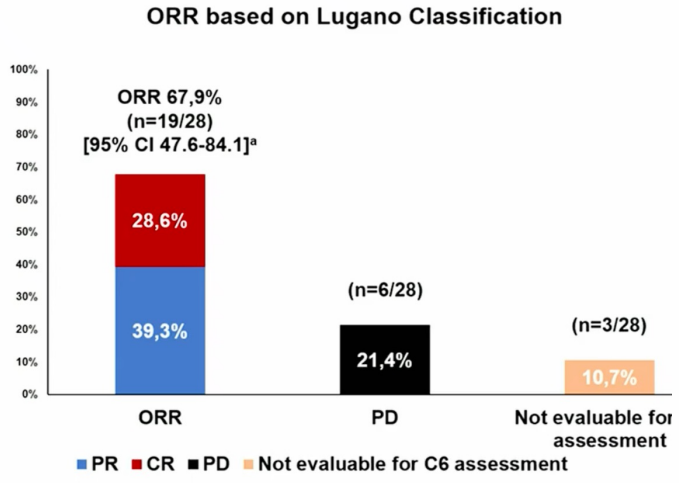
- Slow development of NOTCH targeting medicines
- Difficult development of TP53 restoring drugs
- No MYC targeted medicines

Rossi et al., Blood. 2011; Mauro et al, Am J Hematol 2017; Favini et al., Br J Haematol 2022; Parikh et al., Blood. 2014; Abrisqueta et al., Blood. 2017

Novel paradigms in Richter transformation treatment: MOLTO trial



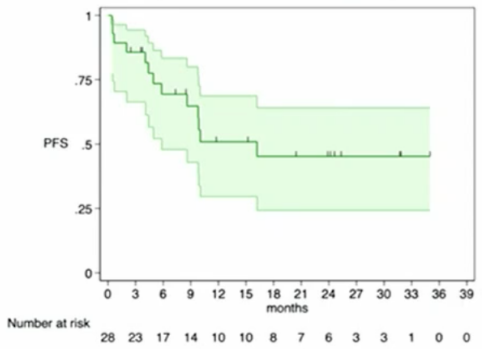
Treatment response at Cycle 6 (ITT)



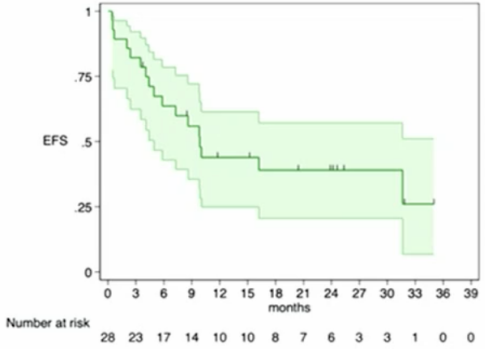
Survival outcomes

Median follow-up: 11.6 months (range 0.5-37.3 months)

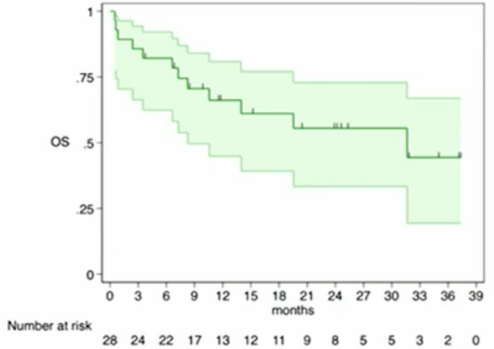
Time to Progression
12-mo TTP 50.9% [95%CI (29.6-68.8)]
(median 16.2 months)



EFS
12-mo EFS 43.9% [95%CI (24.8-61.5)]
(median 9.9 months)

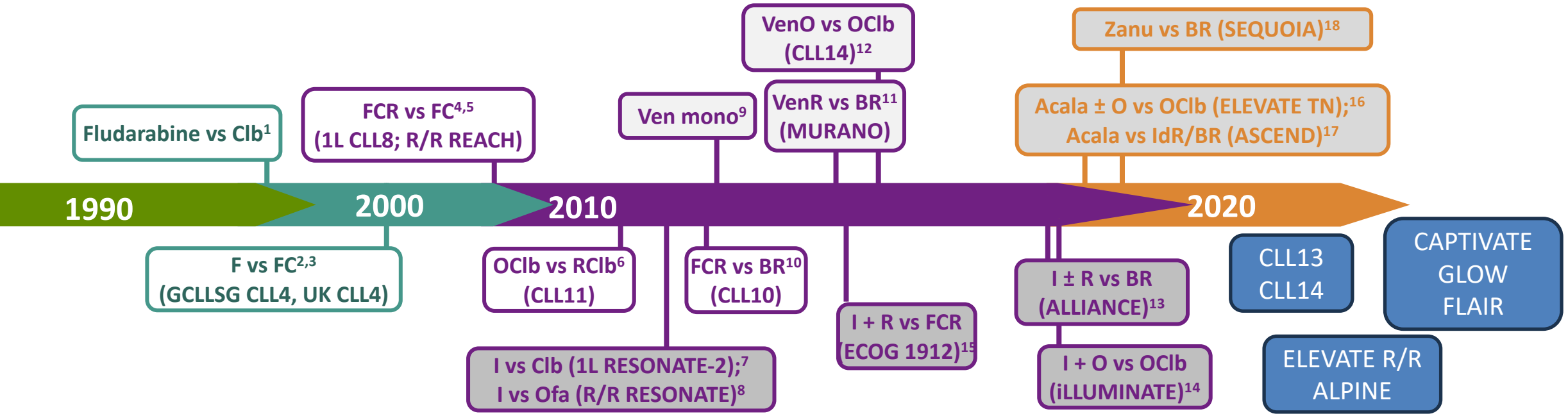


OS
12-mo OS 66.2% [95% CI (44.8-80.9)]
(median 31.6 months)



Frustaci *et al.*, *ICML*. 2023

Evolution of CLL Treatment – Key Treatment Milestones



Goals of therapy

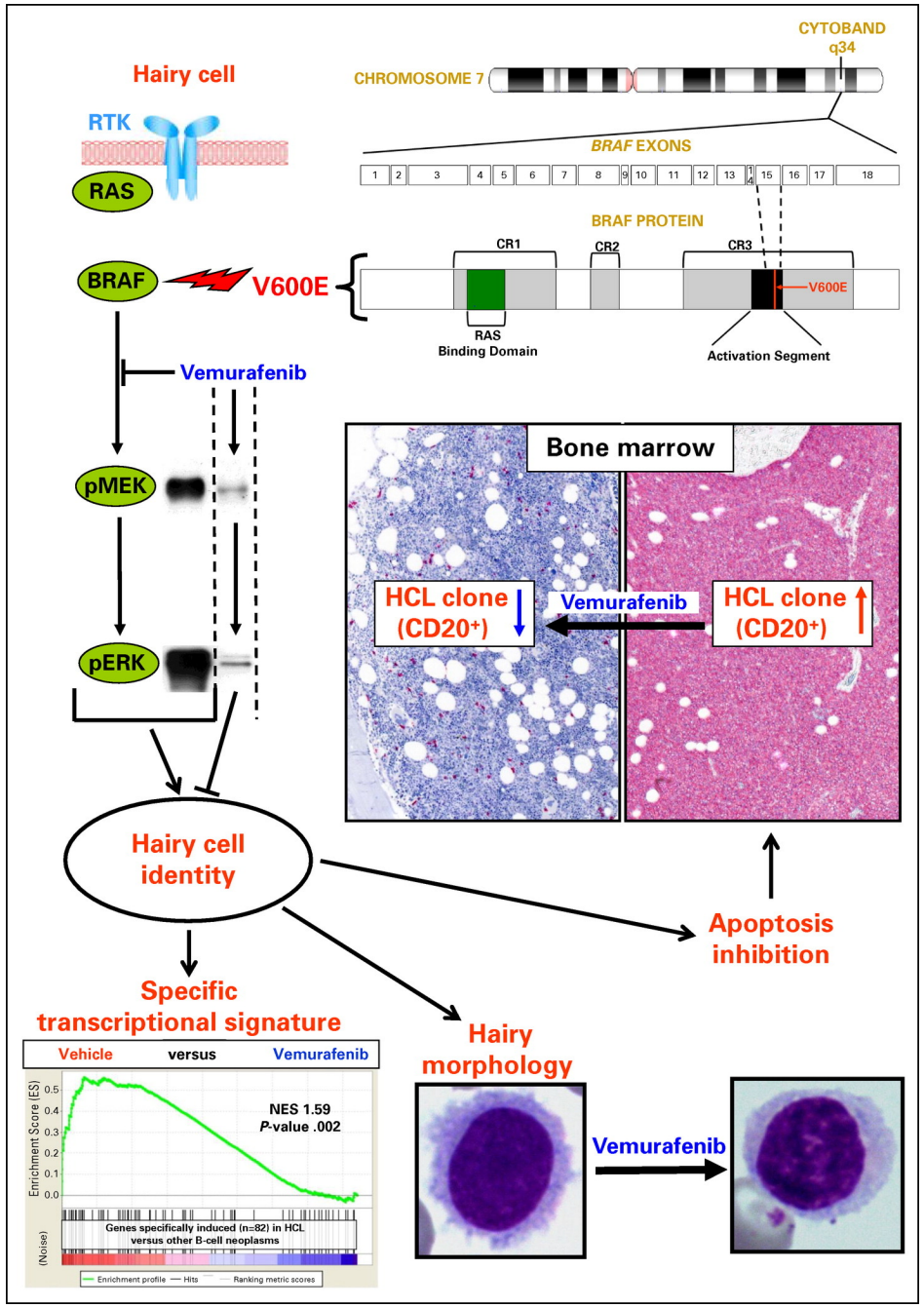
Alleviating symptoms → **Improving survival** → **Reducing toxicity, while improving outcomes in more patients**

*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. .*

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)



PRECISION MEDICINE in HAIRY CELL LEUKEMIA

2011: Identification of BRAF V600E in 100% HCL
(Tiacci et al., N Engl J Med 364:2305-2315, 2011)

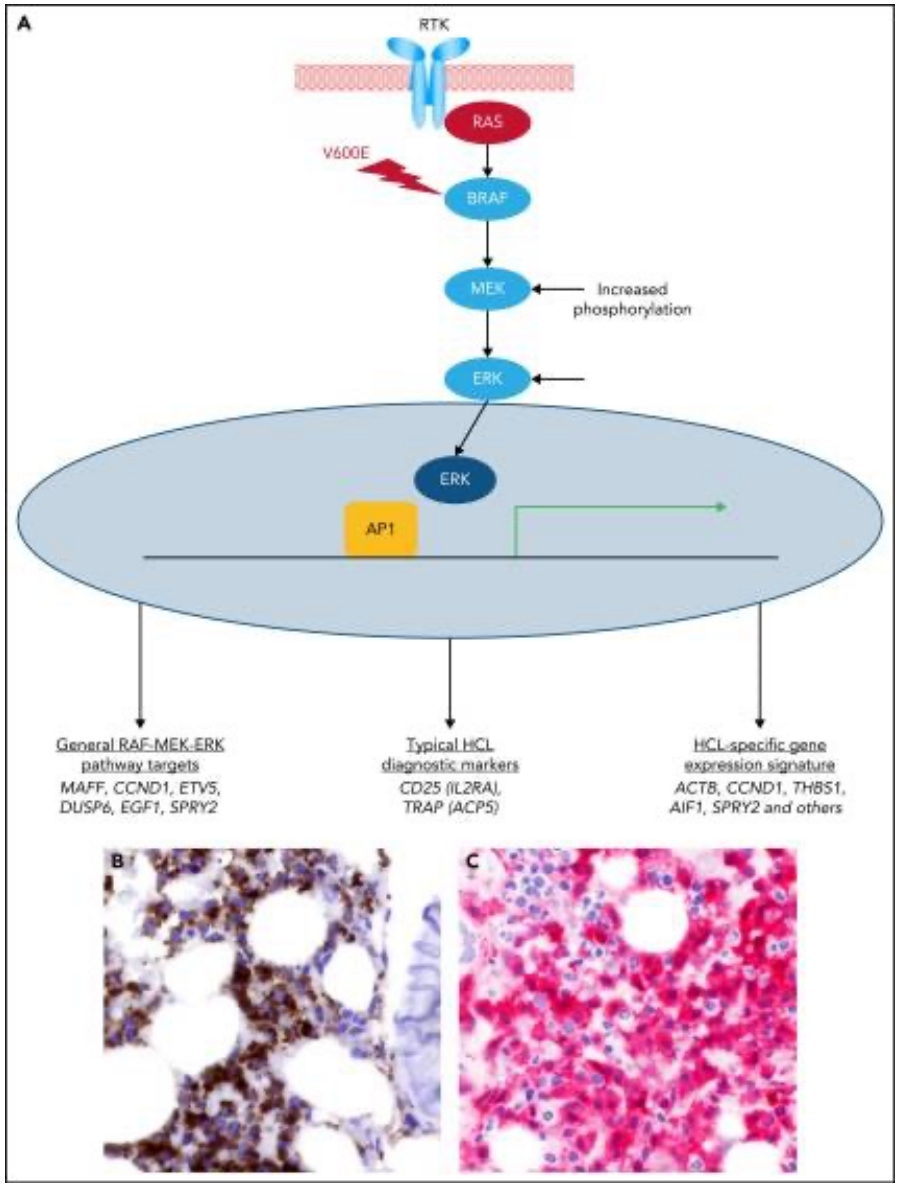
2015: Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia
(Tiacci et al., N Engl J Med 373:1733-1747, 2015)

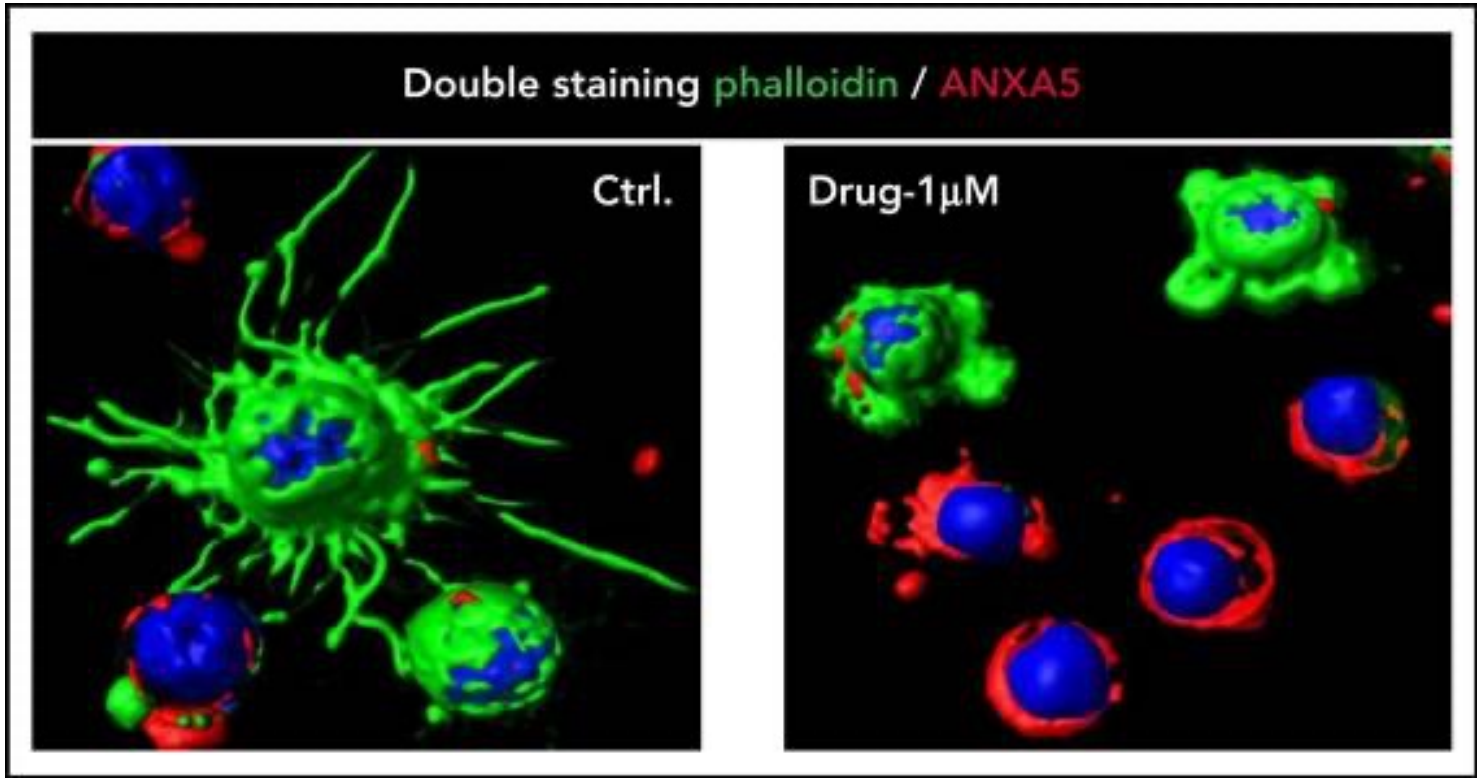
2021: Vemurafenib plus Rituximab in Refractory or Relapsed Hairy-Cell Leukemia
(Tiacci et al., N Engl J Med 384:1810-1823, 2001)

Resistance associated with MEK-ERK activation

Oct 24, 2021: Co-inhibition of BRAF and MEK-ERK in HCL

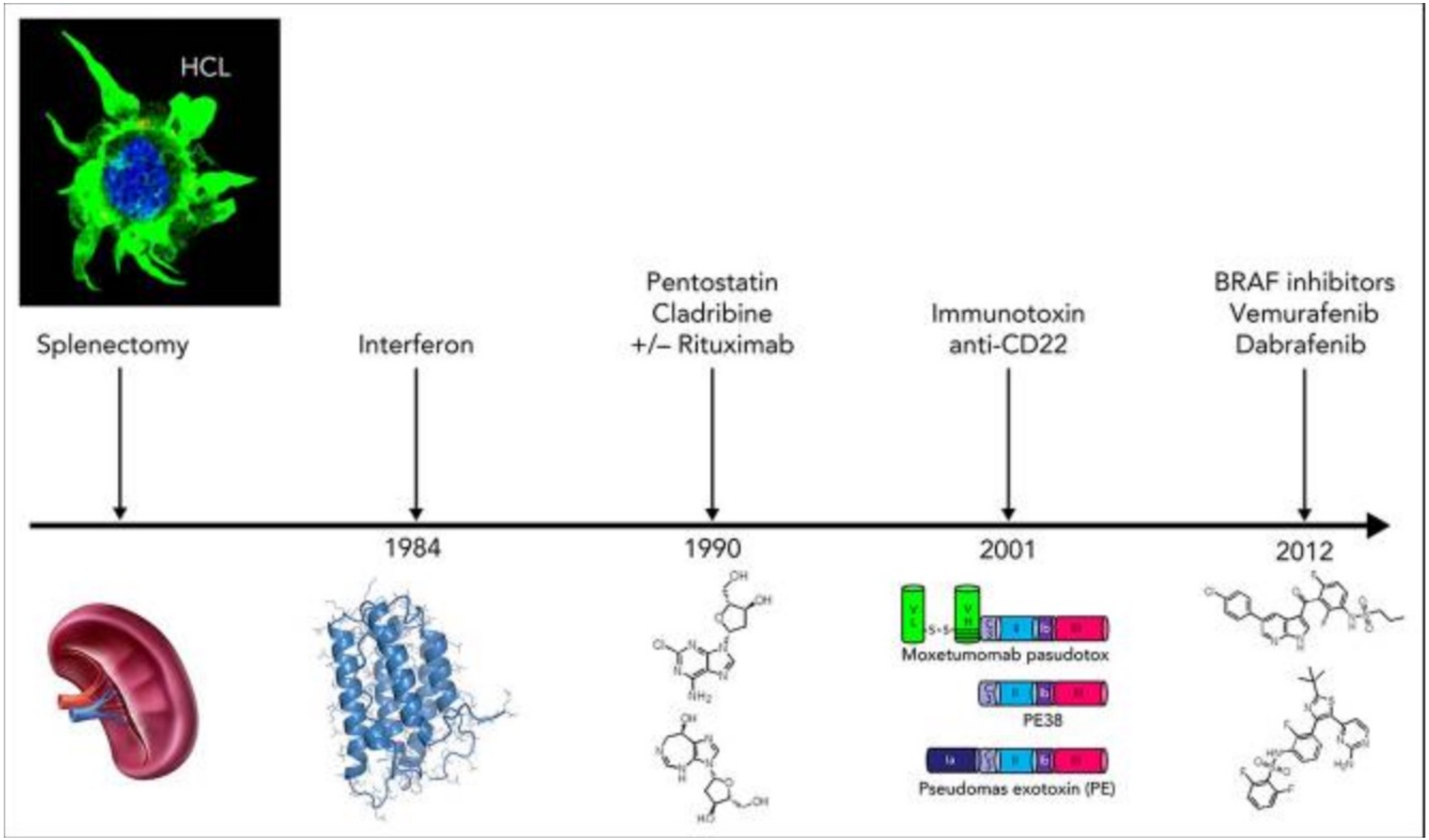
BRAF V600E in HCL pathogenesis





Falini B, De Carolis L, Tiacci E. Blood 139:2294-2305, 2022

Evolution of hairy cell leukemia treatment



Falini B, De Carolis L, Tiacci E. Blood 139:2294-2305, 2022