XIX CONGRESSO NAZIONALE SIES 2026

TP53 nelle neoplasie linfoproliferative

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Firenze | 4-6 marzo 2026
Palazzo degli Affari

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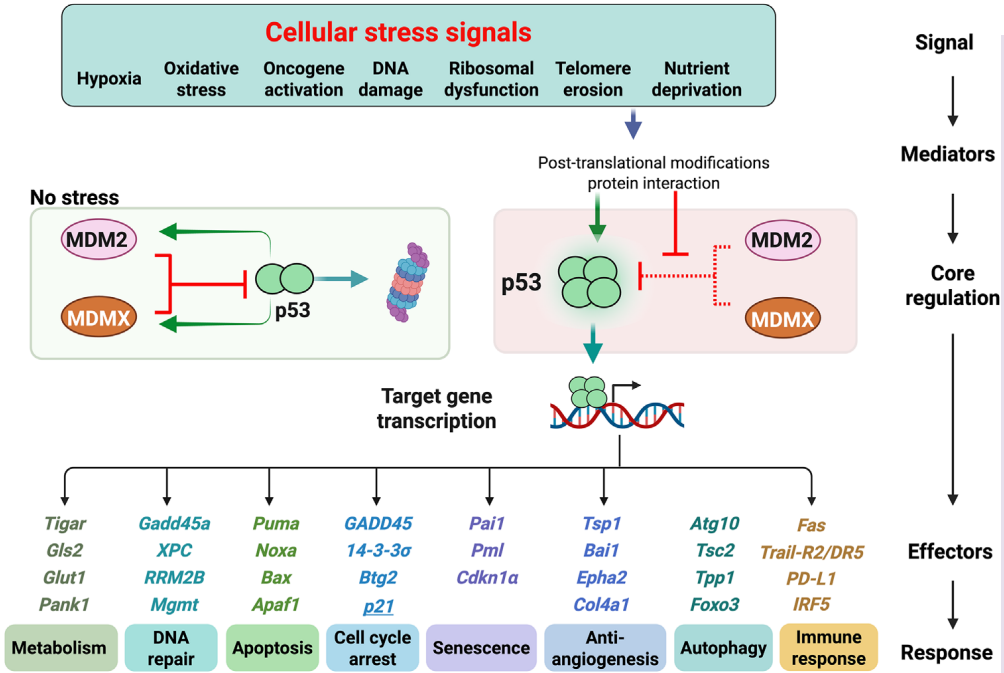
Disclosures of Gian Matteo Rigolin

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZenca							x
Janssen-Cilag							x
BeOne							x
Pfizer							x
Roche							
Eli Lilly							
BMS							
AbbVie							
Sanofi							

p53 signaling pathways



Tumor-suppressor TP53 is crucial to

- maintaining biological homeostasis
- mediating in damaged cells
  - cell-cycle arrest
  - senescence
  - apoptosis

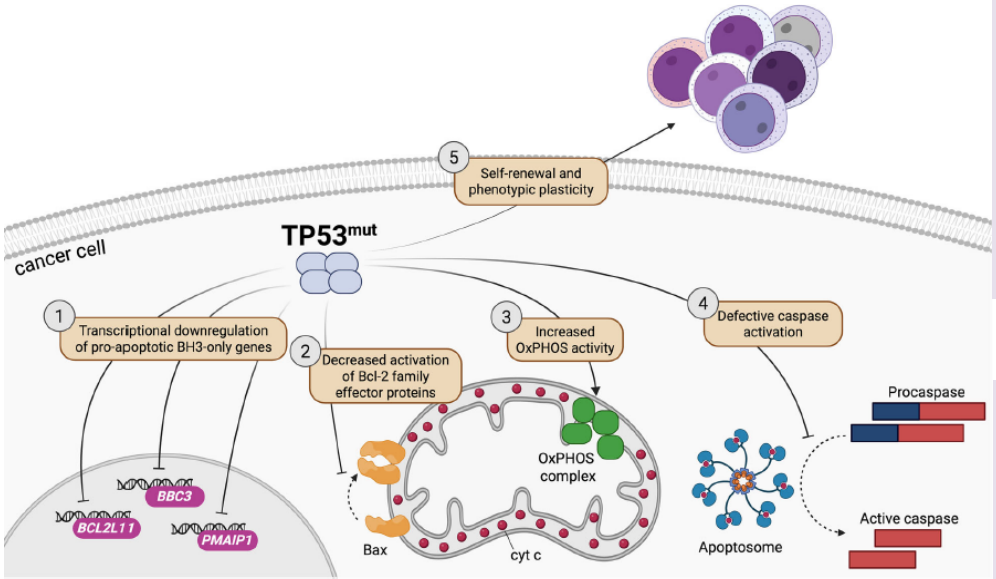
TP53 disruptions impact on cancer trough:

1. - mutant p53 **loss of function**
2. - mutant p53 **dominant-negative**
3. - mutant p53 **gain of function**

Baliakas P, Soussi T. J Intern Med. 2025 Aug;298(2):78-96.

TP53 in lymphoproliferative disorders

Effects of TP53 in cancer



Tamellini E, et al. Cell Death Dis. 2025 Nov 10;16(1):819.

TP53 is working through a 2-hit mechanism.

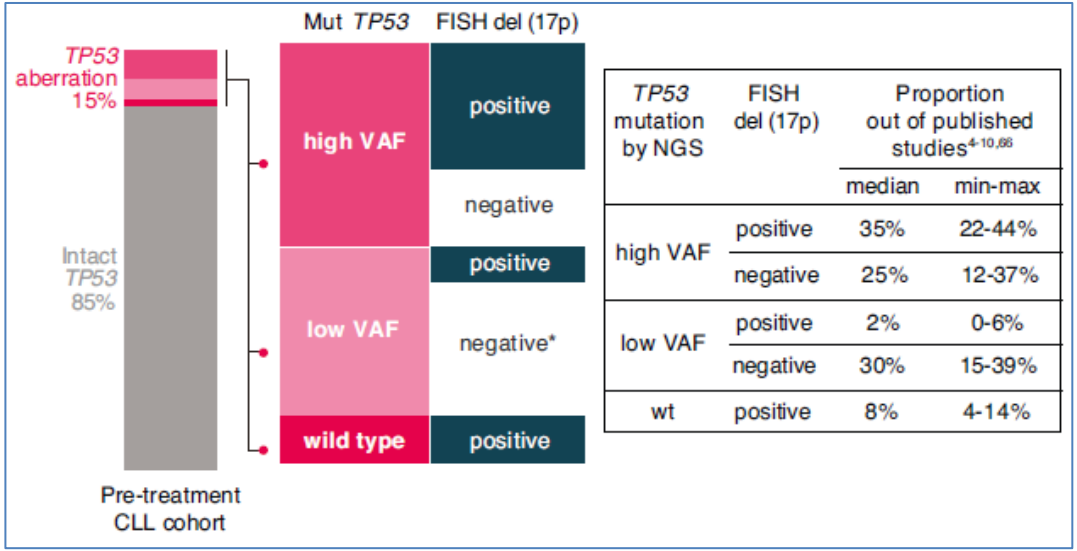
The 1st hit is usually Single Nucleotide Variants

The 2nd hit could be:

- **Del 17p,**
- **Additional muts in the 2nd TP53 allele**
- **Copy neutral loss of heterozygosity (cnLOH)**

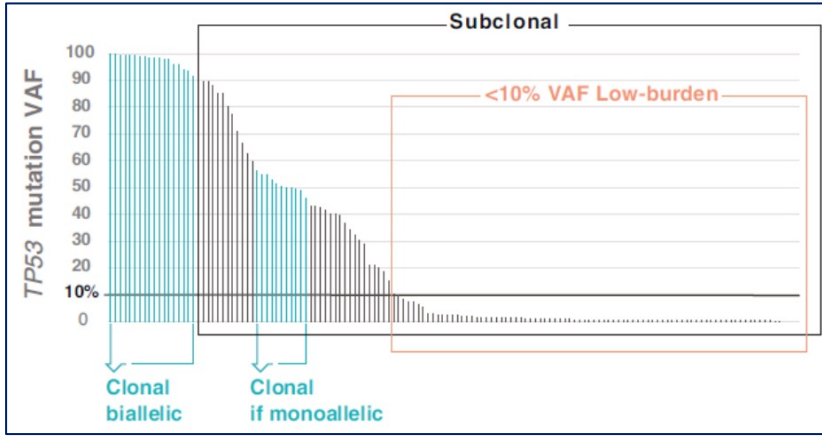
TP53 alterations in

- **Chronic Lymphocytic Leukemia**
- **Mantle Cell Lymphoma**
- **Diffuse Large B Cell Lymphoma**
- **Waldenstrom Macroglobulinemia**



TP53 mutation by NGS	FISH del (17p)	Proportion out of published studies[4-10,66]	
		median	min-max
high VAF	positive	35%	22-44%
	negative	25%	12-37%
low VAF	positive	2%	0-6%
	negative	30%	15-39%
wt	positive	8%	4-14%

TP53 ALTERATIONS IN CLL



The frequency of TP53 abns is

- higher in those with UM-IGHV genes.

- low at diagnosis (5-10%), higher at frontline treatment (10–20%), and in later disease stages, predominantly in CIT-treated pts and Richter transformation (up to 50%).

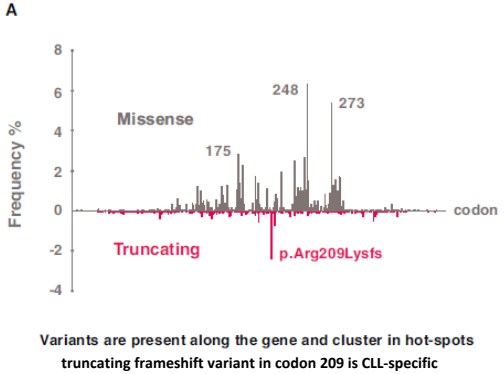
Spectrum of TP53 defects in CLL

A. Variants distribution

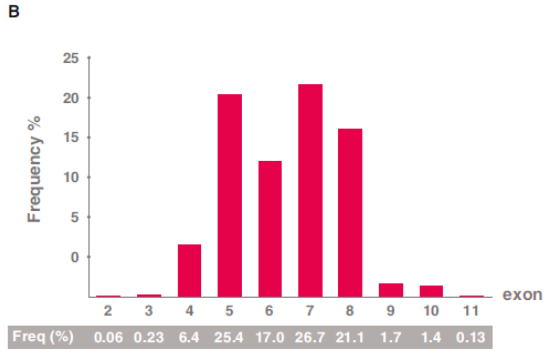
B. Exon distribution of variants.

C. Proportion of variant types

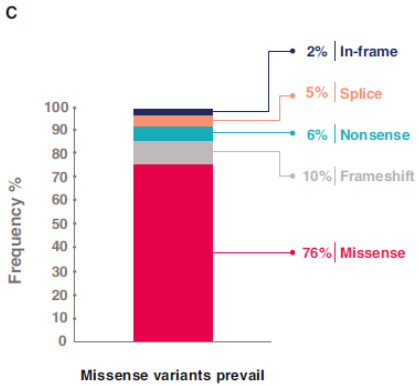
D. Proportion of variant types



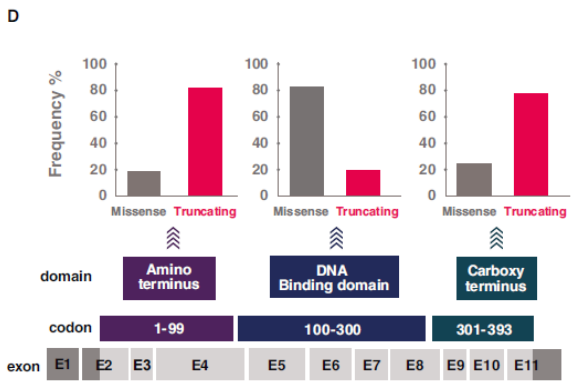
Variants are present along the gene and cluster in hot-spots
truncating frameshift variant in codon 209 is CLL-specific



Majority of variants in exons 5-8



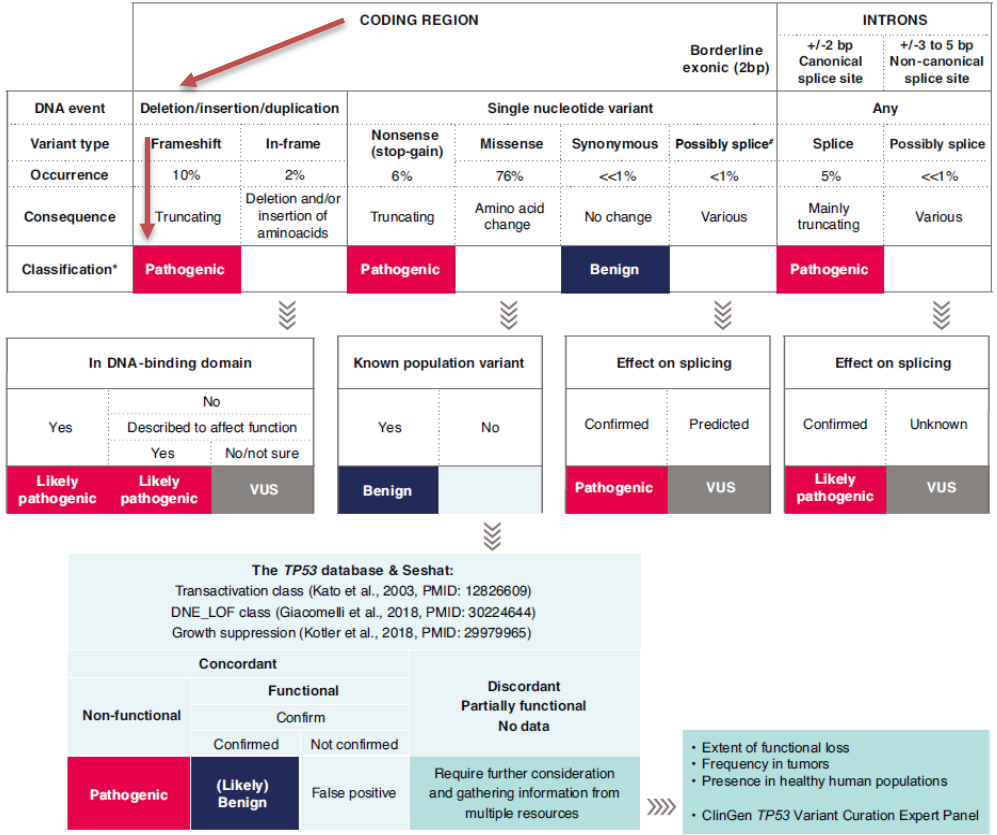
Missense variants prevail



Truncating variants prevail in N- and C- terminus

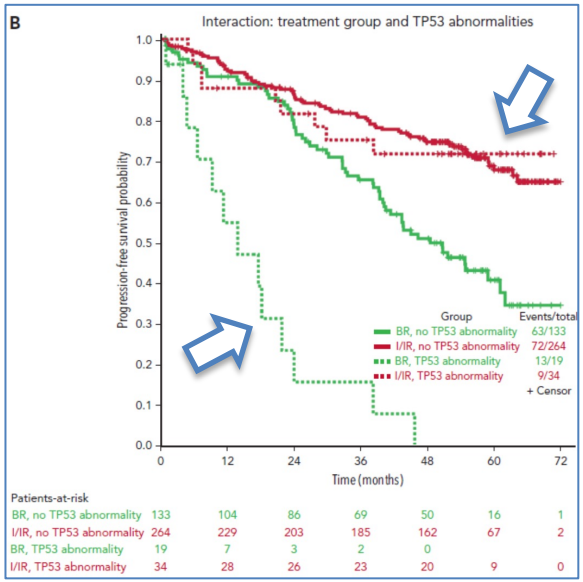
Classification of TP53 variants detected in CLL

A **classification algorithm** showing the basic principles of assigning variants into pathogenicity/oncogenicity classes.



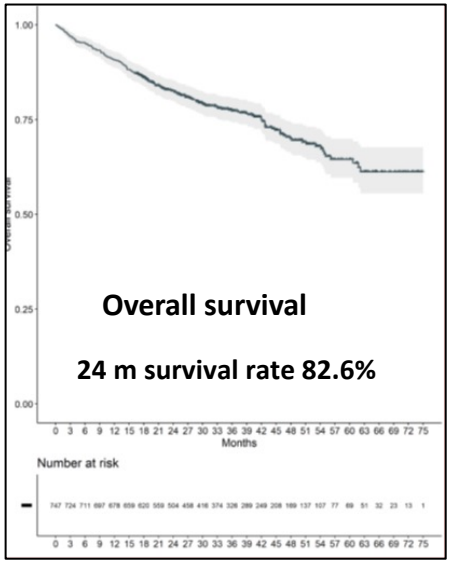
Prognostic and Predictive value of TP53 alterations in CLL

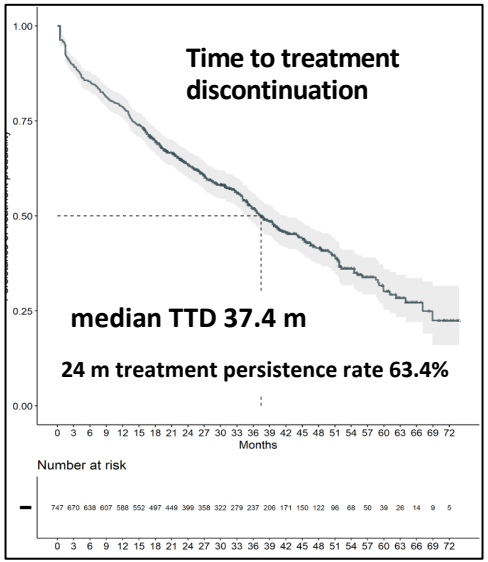
- TP53abs **predictive value** is clear for CIT regimens
- **Targeted agents outperformed CIT in the frontline and R/R settings.**



The A041202 study of ibr regimens for older untreated CLL

Woyach JA et al. *Blood*. 2024;143(16):1616-1627.





CLL with TP53 abns and 1st line ibrutinib

Rigolin GM, et al. *Blood Cancer J*. 2023;13(1):99.

Prognostic and Predictive value of TP53 alterations in CLL

The role of TP53 abns in choosing between targeted agent regimens is less well studied (decision on risk of toxicities)

The prognostic impact of TP53 appears to be stronger with time-limited regimens than with continuous therapy (no definitive conclusions)

Stage	del(17p) or *TP53*mut	*IGHV*	Therapy
Inactive disease, Binet A-B, Rai 0–II	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III–IV	Yes	Irrelevant	Acalabrutinib[1], zanubrutinib, ibrutinib, or venetoclax + ibrutinib, or venetoclax + obinutuzumab idelalisib-rituximab (only if contraindications for other options)
	No	mutated	Venetoclax + obinutuzumab,[2] or venetoclax + ibrutinib,[2] or acalabrutinib[1], zanubrutinib, ibrutinib Chemoimmunotherapy[3] with FCR (BR above 65 years) or chlorambucil-obinutuzumab (unfit)
		unmutated	Acalabrutinib[1] , zanubrutinib, ibrutinib, or venetoclax + ibrutinib,[2] or venetoclax + obinutuzumab[2]

(1) The addition of obinutuzumab to acalabrutinib may be considered.
(2) Consider and discuss with the patient: Continuous vs. fixed-duration therapy, specific side effects of drug classes (myelosuppression, infections, secondary malignancies for CIT; cardiovascular toxicity and bleeding for BTKi (Acalabrutinib < Ibrutinib); TLS and infections for Ven-Obi; autoimmune disease and opportunistic infections for Idelalisib.
(3) Chemoimmunotherapy in regions where other options are not available or approved.

Hallek M. Am J Hematol. 2025 Mar;100(3):450-480.

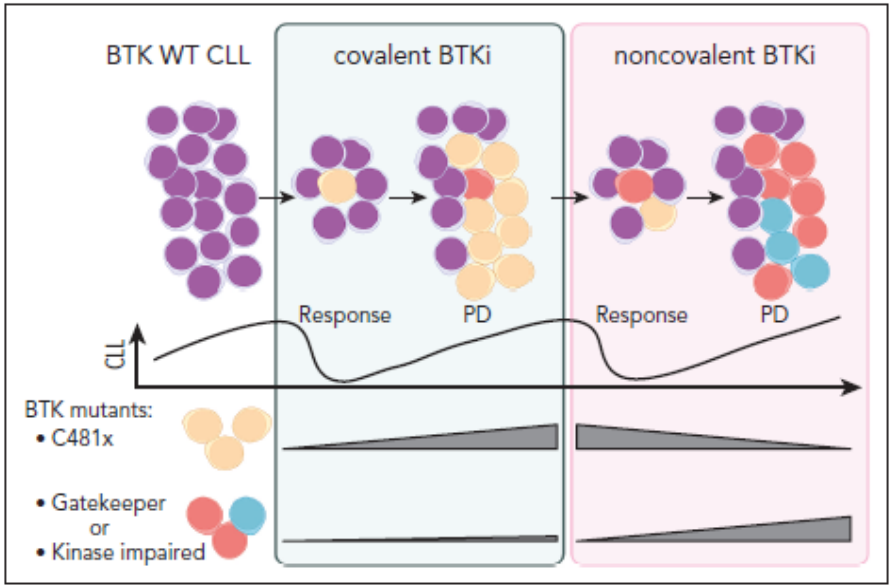
Relevance of TP53 abns with novel agents

Targeted agents

- act independently of the p53 pathway
- no preferential pattern of evolution of TP53-aberrant clones

To be clarified

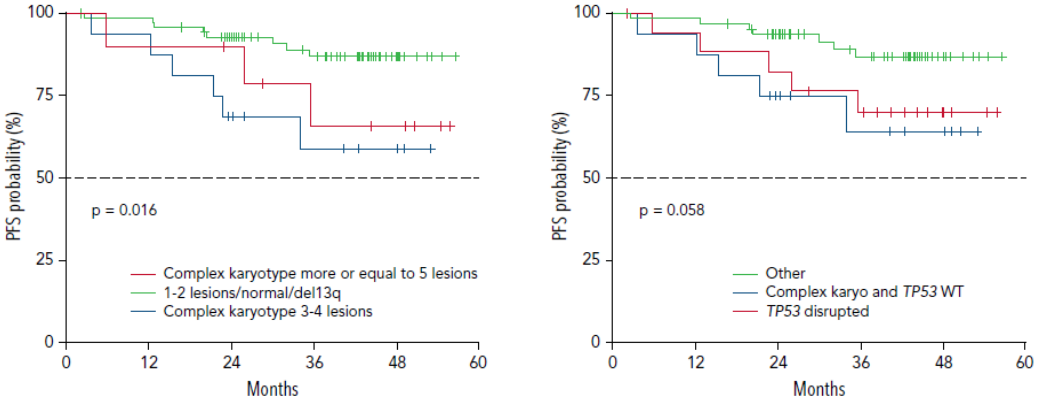
- how the TP53-aberrant clone evolve
- Mechanisms of resistance (1/3 of pts have no mutations at PD).
- the role of genomic instability/complexity



Brown JR, et al. *Blood*. 2026;147(1):24-34.
Jebaraj BMC, Stilgenbauer S. Blood. 2026 Jan 1;147(1):3-4.
Bonfiglio S, et al. Blood Adv. 2023;7(12):2794-2806

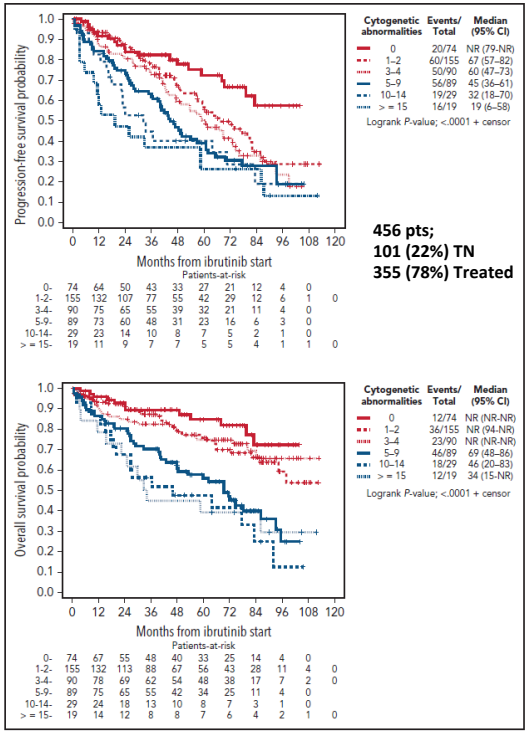
Karyotype complexity and outcome in CLL treated with ibrutinib

1st line ibr-R: the GIMEMA LLC1114 phase 2 study



In MVA, the CK was significantly associated with a shorter PFS (P = .009) along with a worse ECOG PS (P = .048).

Rigolin GM, et al. Blood. 2021;138(25):2727-2730.



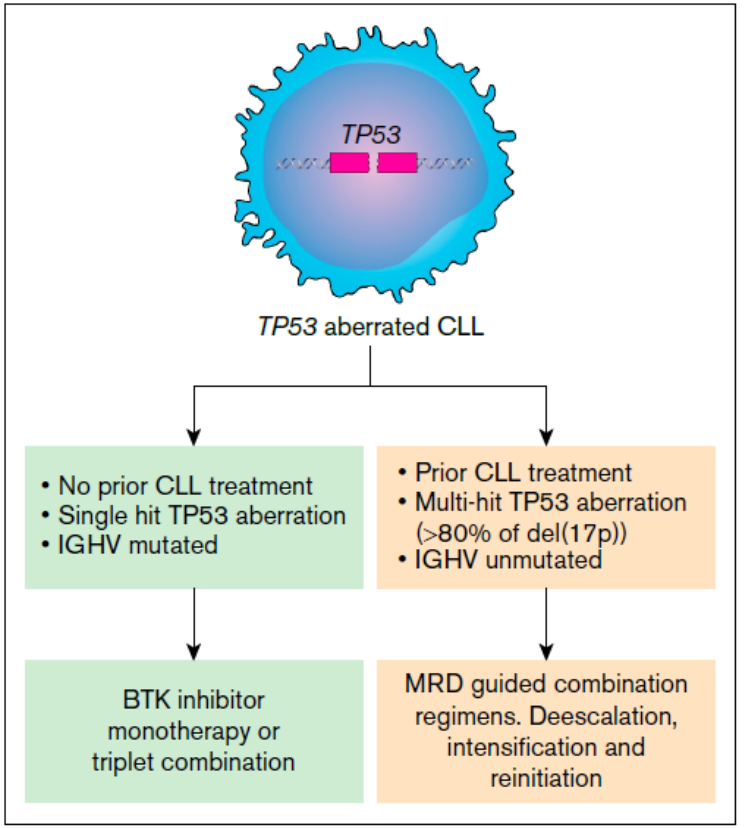
In MVA, karyotypic complexity independently associated with a worse PFS and OS

Kittai AS, etal. Blood 2021;138:2372-2382.

Open questions in CLL

Given that pts with TP53 disuptions still perform worse

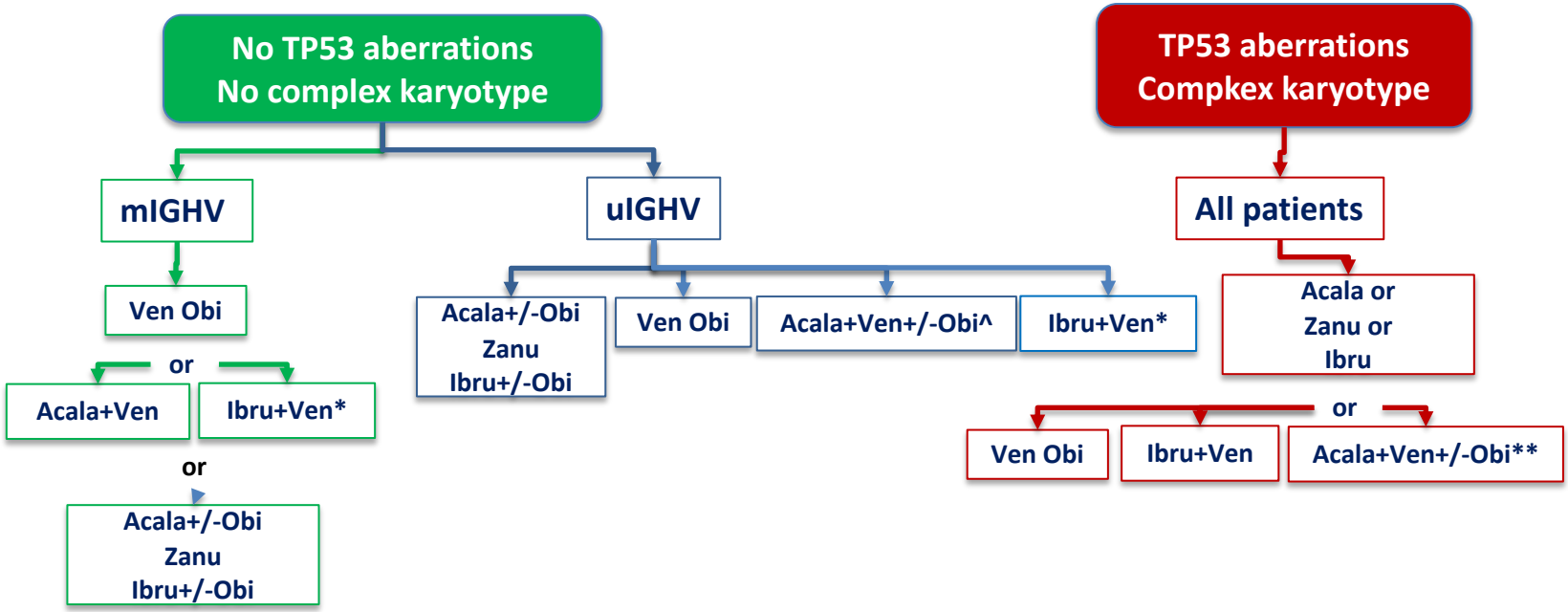
1. **Which types and combinations of TP53 abns are predictive for tailoring treatment.**
   - **Mono, bi-allelic, multiple clones, micro clones, M/UM IGHV**
2. **The role of genomic complexity**
   - **karyotype, CGH arrays, chromothripsis, others**
3. **Is BTK inhibitor monotherapy sufficient?**
4. **What treatment alternative?**



Niemann CU. *Blood Adv*. 2026;10(3):707-709.

First line therapy of CLL in 2025

Symptomatic early stage or advanced-stage CLL



*When using I+V, cardiac toxicity must be considered, especially in elderly patients. ^When using AV+Obinutuzumab, infectious complications should be considered, especially in older patients

Clemens-Martin Wendtner, Othman Al-Sawaf, Mascha Binder, Peter Dreger, Michael Gregor, Michael Hallek, Ulrike Holtkamp, Henriette Huber, Thomas Nösslinger, Ron Pritzkuleit, Katharina Prochazka, Johannes Schetelig, Simon Schliffke, Ingo Schwaner, Philipp Bernhard Staber, Eugen Tausch, Minna Voigtländer, Thorsten Zenz, Barbara Eichhorst, Stephan Stilgenbauerhttps://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html

TP53 in Mantle Cell Lymphoma

10- 40% of ND MCL, higher frequency at relapse.

- **Associated with a del17p, high Ki-67%, CK, blastoid histology, and MYC rearrangement.**

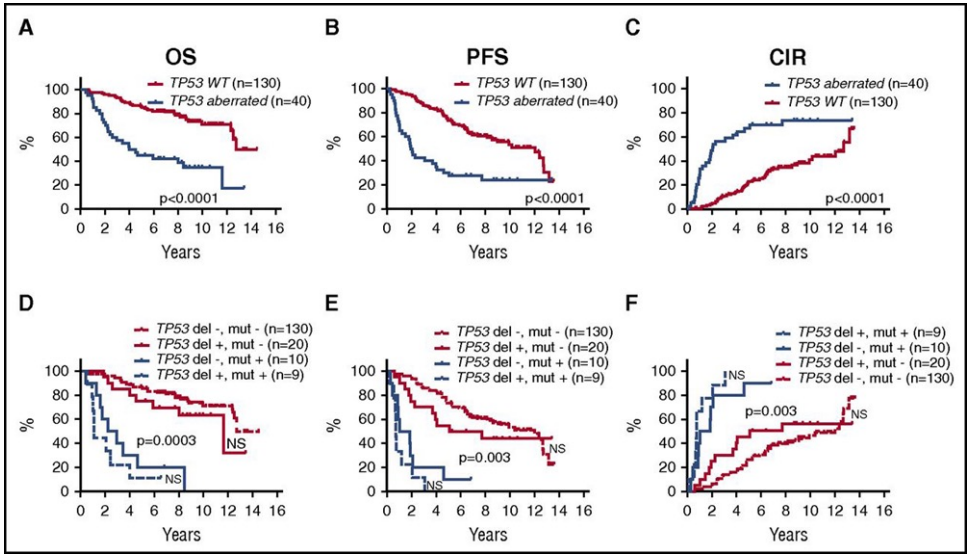
TP53 muts (w/wo del17p) had the worst OS.

- **Independent of genomic complexity**
- **Concomitant mutations in NOTCH1, CDKN2A, NSD2, and SMARCA4 associated with ibr-ven resistance**

High-risk MCL (unstable genome)

Nadeu F, et al. Blood. 2020;136(12):1419-1432.
Jain P & Wang M. Blood. 2025;145(7):683-695.

Prognostic impact of TP53 deletions and mutations in MCL

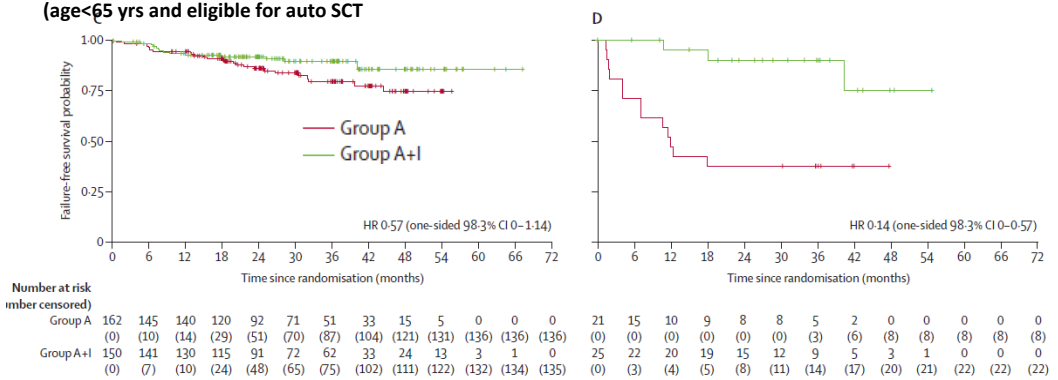


Eskelund CW, et al. Blood. 2017;130(17):1903-1910.

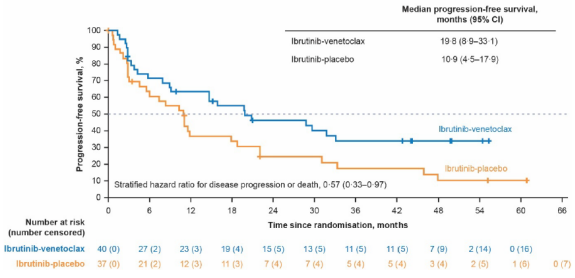
TP53 and targeted agents

In ND MCL, the TRIANGLE trial demonstrated a failure-free survival benefit with the addition of ibrutinib to induction and maintenance therapy in pts with p53 overexpression

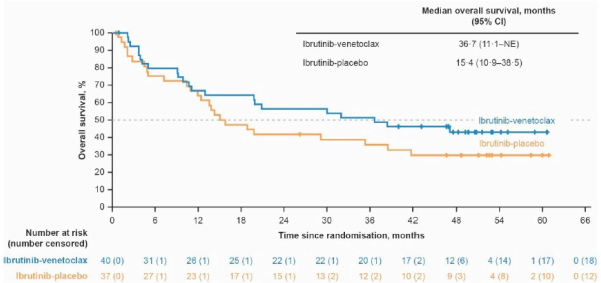
Failure-free survival for group A+I *vs* group A in low (≤50%) p53 (C), and high (>50%) p53 (D) (age<65 yrs and eligible for auto SCT



In r/r classical MCL, the SYMPATICO trial ibr + ven resulted in higher response rates and survival benefit in TP53-mut



C



Dreyling M, et al. Lancet. 2024;403(10441):2293-2306.
Wang M, J et al. Lancet Oncol 2025;26:200–213

Zanubrutinib, obinutuzumab, venetoclax for 1st-line treatment of MCL with *TP53* mutation

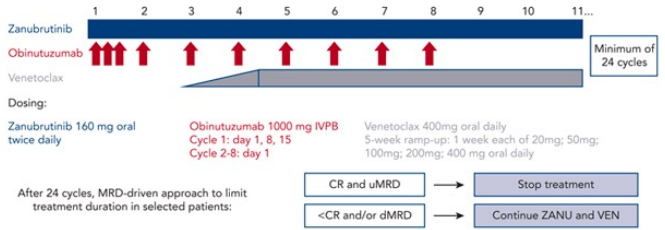
- **BOVen was safe and effective for untreated TP53-mutant MCL.**
- **Longer follow-up would determine the sustainability of such responses.**

Context of Research

- *TP53*-mutant MCL is associated with poor survival outcomes with standard chemoimmunotherapy.
- We tested dual BTK and BCL2-inhibition with anti-CD20 monoclonal antibody therapy in *TP53*-mutant MCL

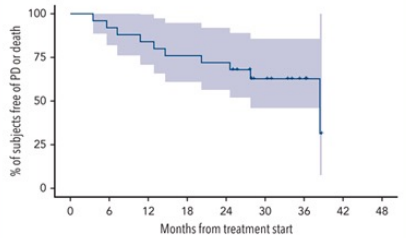
Patients and Methods

- Phase 2 clinical trial of zanubrutinib, obinutuzumab, and venetoclax (NCT03824483). Primary outcome measure: 2-year progression-free survival
- Enrolled 25 MCL patients with *TP53* mutation. Treatment schema (BOVen):

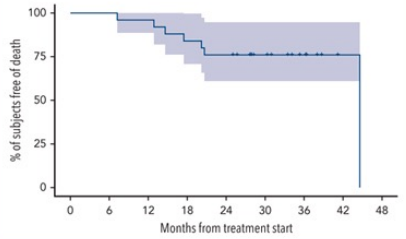


Main Outcomes

- Best Overall Response Rate 96% (24/25) and Complete Response Rate 88% (22/25).
- Toxicity was manageable. 32% (8/25) w/neutropenia, no febrile neutropenia, 20% (5/25) received growth factor support.
- 2-year PFS: 72% (56, 92)

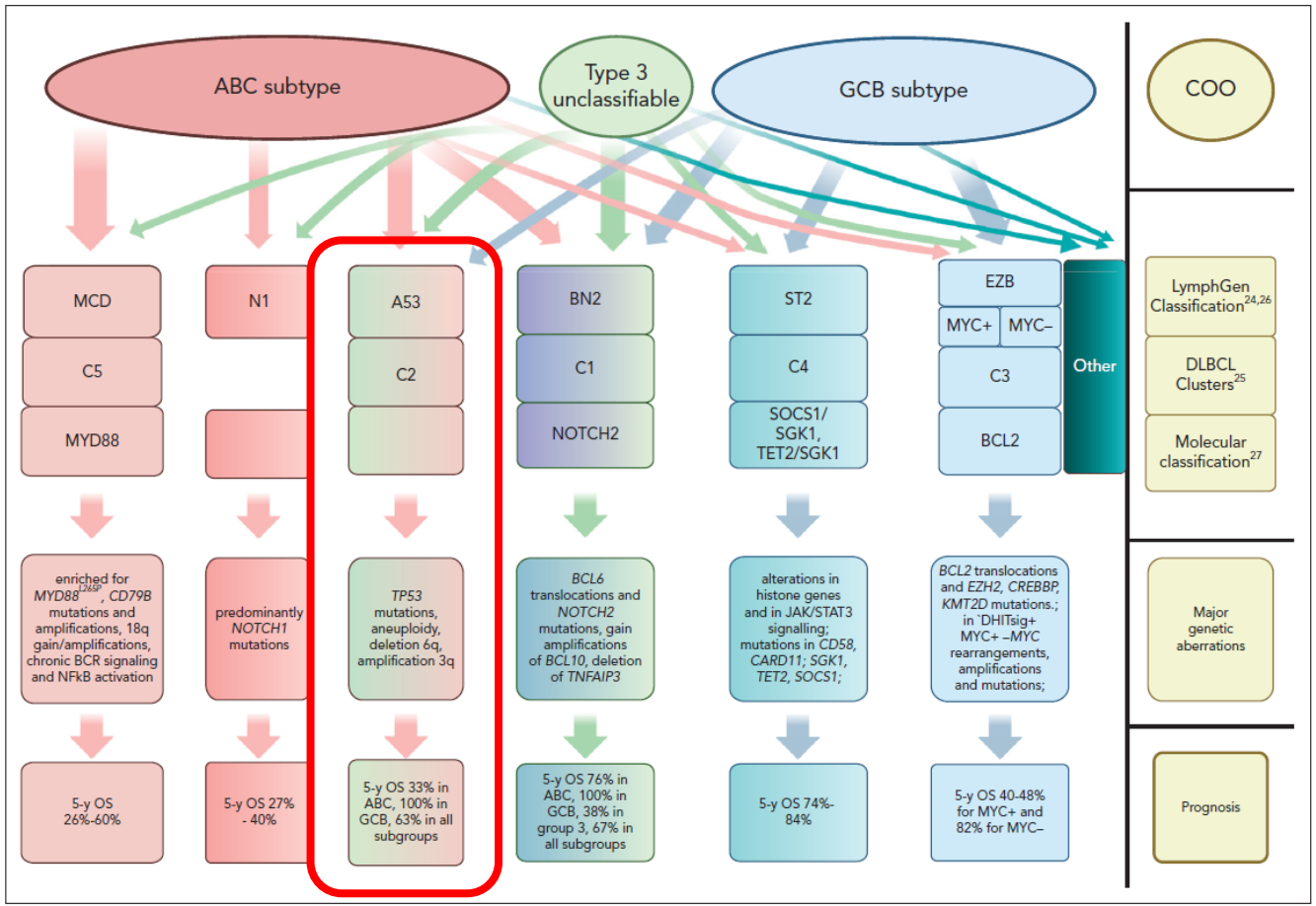


- 2-year OS: 76% (61, 95)



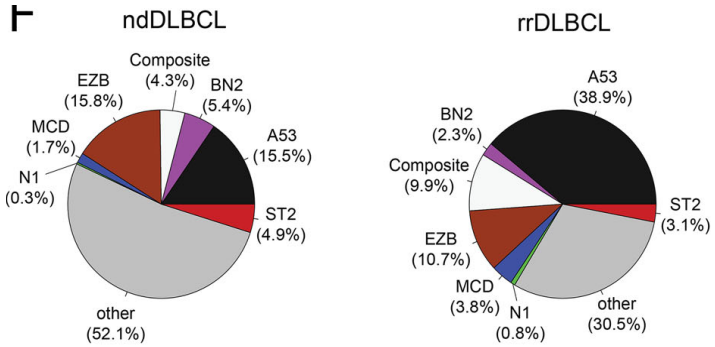
Kumar A, al. Blood 2025;145:497–507.

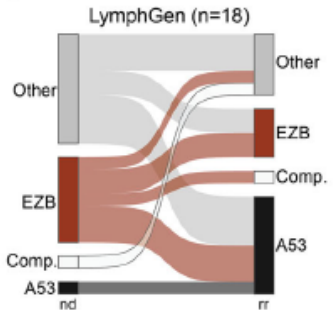
DLBCL: Relationship between COO and probabilistic genetic subtypes

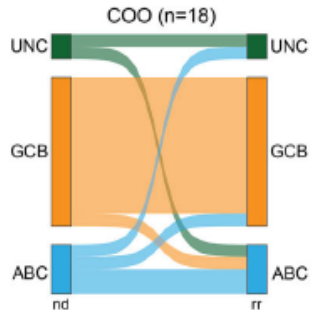


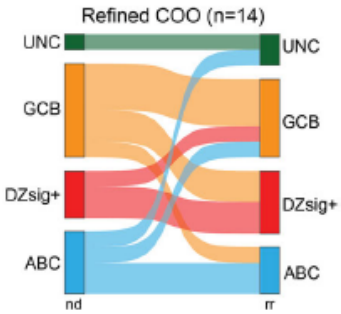
Dabrowska-Iwanicka A, Nowakowski GS. *Blood*. 2024;144(25):2573-2582.

Mechanisms of treatment resistance and relapse in DLBCL







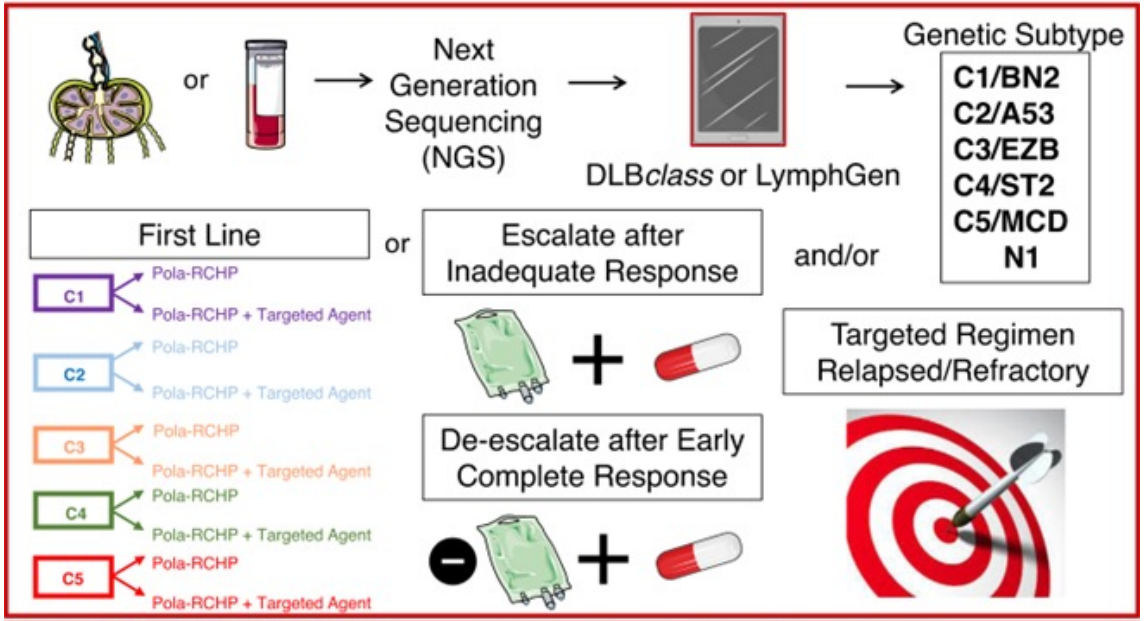


rrDLBCL pts have

- **More DNA gains, losses, and rearrangements including TP53 depletion**
- **More TP53 somatic mutations, 17p13 copy number variations and higher TP53 VAF**
- **Clonal expansion of tumor populations harboring TP53 mutations**

Alterations in TP53 represent one the different subtypes of specific mechanisms of resistance

DLBCL Molecular Subtypes to Tailor Treatment

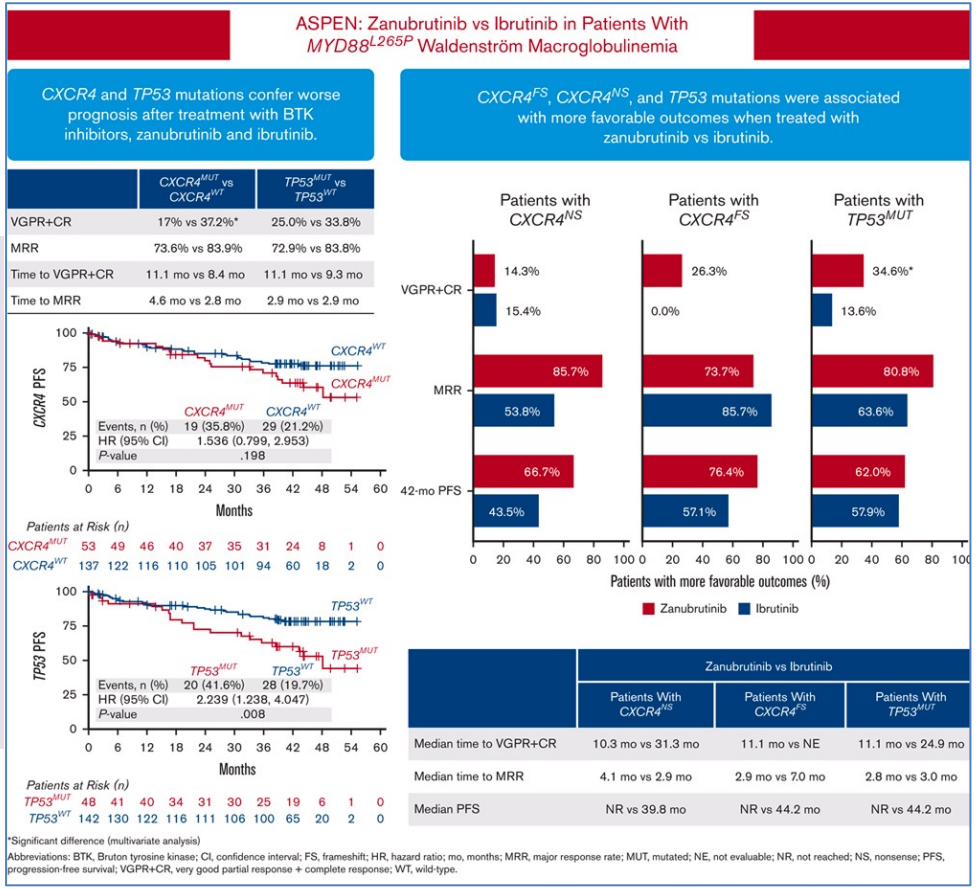


Conclusions: Genetic subtypes can be determined using NGS and DLB*class* or LymphGen classifiers. Treatment could be tailored in first line with the proposed LymphoMatch clinical trial algorithm, or in patients with inadequate or early complete responses, and/or in relapsed/refractory DLBCL. Rutherford SC. DOI

TP53 and Waldenström macroglobulinemia

TP53 abns

- In 5-10% treatment-naïve pts
- In 25%-30% of previously treated pts
- shorter OS and PFS with BTKi
- May guide treatment considerations
  - Pts with CXCR4 or TP53 muts had more favorable outcomes with zanu vs ibr



Tam CS, et al. Blood Adv. 2024 Apr 9;8(7):1639-1650.
Treon SP, et al. Blood. 2024 Apr 25;143(17):1702-1712.

Conclusions

- Treatment with targeted agents might prevent the expansion of TP53-mut clones.
- Data on TP53 mutations is still evolving in the targeted agent setting.
- The importance of precise classification of TP53 abns in the design of clinical trials in order to obtain robust evidence for improving the treatment tailoring.

TP53 status	Strategies	Drugs
No p53	p53 gene delivery	Gendicine
wt p53	Disruption of wtp53-MDM2/MDM4 interaction	Nutlin; RG7112; SAR405838; KT253
p53 missense variants	Restoration of p53 functions	APR-46; ATO; PC14586; CP-31398; COTI-2; RETRA
	Eradication of p53 variants	
	Synthetic lethality	Adavosertib
	boost anti-tumor immunity	SGT-53
p53 nonsense variants	Restoration of p53 functions	Aminoglycosides 5-Fluorouridine

Baliakas P, Soussi T. J Intern Med. 2025 Aug;298(2):78-96.