Low burden TP53 mutations in Chronic Lymphocytic Leukemia: What impact do they have in the era of new target therapies?

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Padova, 22 maggio 2024
Hotel NH Padova

I have no conflicts of interest to declare

CASO CLINICO

Donna, 52 anni

APR: sostanzialmente muta.

Diagnosi: Marzo 2020
Riscontro occasionale di linfocitosi B con restrizione clonale Kappa e fenotipo CD20 +/- a bassa intensità di espressione, CD5+, CD23+, CD11C +/-, CD10-, CD38+, CD200+, sIg K a bassa intensità

- Emocromo: linfocitosi (Ly 17.32x10^9/L), Hb 124 g/L, plts 354x10^9/L, restanti parametri nei limiti salvo lieve ipogammaglobulinemia
- Fattori prognostici: trisomia 12, NOTCH1 mutato, IGHV um, non mutazioni puntiformi di TP53

Si concludeva per leucemia linfatica cronica, RAI I, Binet B, CLL-IPI intermedio
Si proseguiva con solo follow-up

CASO CLINICO

Fine 2022: Comparsa di saltuarie sudorazioni notturne, aumento delle adenopatie e della linfocitosi.

Emocromo: Ly 78.9 x10^9/L, Hb 70 g/L, plts 360 x10^9/L, LAD 225 U/L

Eseguiva pertanto una nuova TC total body: «*innumerevoli nodularità linfonodali a distribuzione pressochè ubiquitaria, dall'aspetto confluente e a margini polilobulati in particolare nelle stazioni del collo (le più grandi con asse maggiore di circa 3 cm), ascellare (con asse maggiore di 3 cm), del retroperitoneo e nel ventaglio mesenteriale con assi maggiori di circa 3 cm. Aumentate le dimensioni dei linfonodi inguinali, le più grandi con asse maggiore di 4 cm. In ambito addominale fegato di dimensioni aumentate. Splenomegalia con asse bipolare di circa 16 cm*».

La paziente veniva candidata all'arruolamento nel trial FIGHT attivo nel nostro centro (*Fixed-duration therapy with ibrutinib and obinutuzumab (GA-101) in treatment-naïve patients with CLL)*

Ma….
Veniva esclusa per il riscontro agli esami centralizzati di una mutazione di TP53 con una VAF dello 0.5% !!

CASO CLINICO – What therapeutic choice?

- Young and fit woman
- No comorbidities
- Unmutated IGHV
- TP53 low VAF → should it be considered?

??

Fixed duration

- Venetoclax + obinutuzumab
- (Ibrutinib + Venetoclax)

Continuous therapy

- BTKi

REVIEW ARTICLE OPEN

CHRONIC LYMPHOCYTIC LEUKEMIA

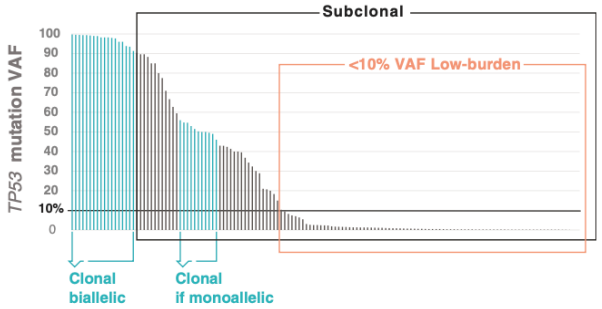
ERIC recommendations for *TP53* mutation analysis in chronic lymphocytic leukemia—2024 update

Jitka Malcikova[1,2,18], Sarka Pavlova[1,2,18], Panagiotis Baliakas[3], Thomas Chatzikonstantinou[4], Eugen Tausch[5], Mark Catherwood[6], Davide Rossi[7], Thierry Soussi[3,8], Boris Tichy[2], Arnon P. Kater[9], Carsten U. Niemann[10], Frederic Davi[11,12], Gianluca Gaidano[13], Stephan Stilgenbauer[5], Richard Rosenquist[14,15], Kostas Stamatopoulos[4], Paolo Ghia[16,17,19]✉ and Sarka Pospisilova[1,2,19]✉

2024 ERIC RECOMMENDENDATION

Table 1. Overview of ERIC recommendations for *TP53* analysis.

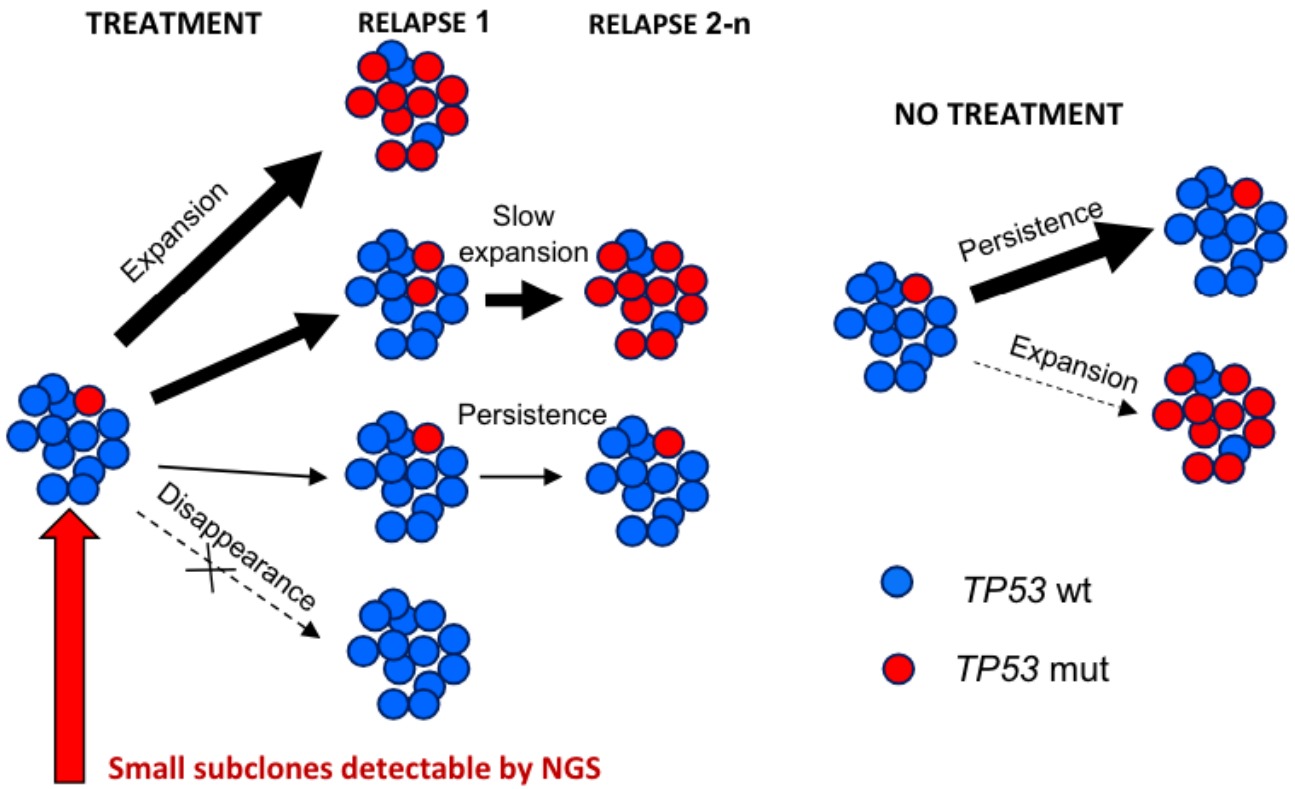
ERIC recommendation			
Patients		Sampling	Always when deciding about treatment in both the frontline and the relapsed/refractory setting.
Material		Type of material	Peripheral blood (PB)
		Tumor cell enrichment	Optimally separate CD19^{+} cells. Alternatively, choose the method of separation based on content of CLL cells, if the information about the blood count is available.
		Nucleic acid	DNA
		Covered region	Optimum: exons 2-11 (coding region), Minimum: exons 4–10, Always include splice sites (at least ±2 intronic bp)
Procedure	Sanger sequencing	PCR protocol	Check primer sequences for presence of population variants.
		Sequencing	Both strands (forward + reverse)
		Data analysis	Use software designed for somatic variant detection
	NGS – preferred methodology	Library preparation	Amplicon or capture-based approaches are applicable. DNA input should be sufficient to achieve the aimed limit of detection.
		Limit of detection (LoD)	Should be set to detect low-VAF variants (≤ 5% VAF).
		Sequencing depth	Covering all bases in the coding region with a sufficient number of reads should be a standard.
		Data analysis	Pipeline set to reliably distinguish variants from background noise
		Validation	Validate/verify the method before introducing it into diagnostics



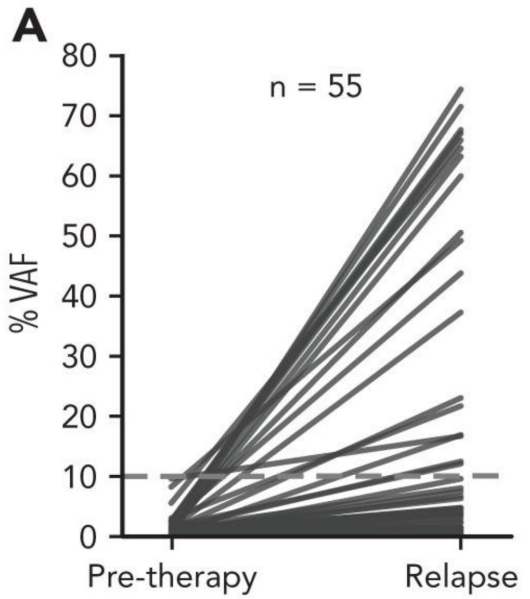
- At a minimum the sequence region of the TP53 gene **must include exons 4-10;**
- Optionally exons 2-11 should be analyzed;
- **NGS is capable of detecting variants below the sensitivity threshold of Sanger sequencing**, even VAFs as low as <1%;
- Due to the low detection limit of NGS, multiple subclonal mutations within the TP53 gene may be detected in some patients;
- The poor outcome of TP53-mutated patients treated with chemoimmunotherapy in clinical trials is based on data obtained using Sanger sequencing only;
- Several publications have suggested that TP53 mutations within minor clones are clinically relevant.

Malcikova et al., Leukemia 2024

CLONAL EVOLUTION



- Presence of minor subclonal TP53 mutation represents a warning – could expand during the disease course
- Therapy provides a selection advantage for more aggressive clones



Malcikova et al., Blood 2021

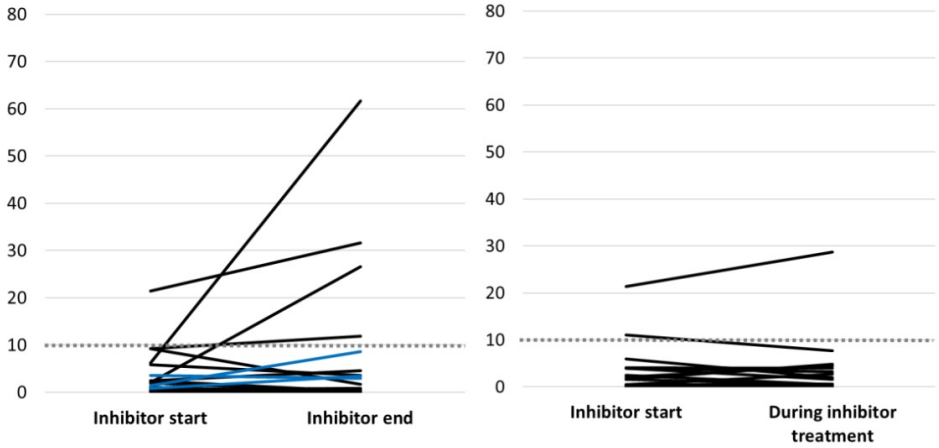
CLONAL EVOLUTION

LETTERS TO THE EDITOR

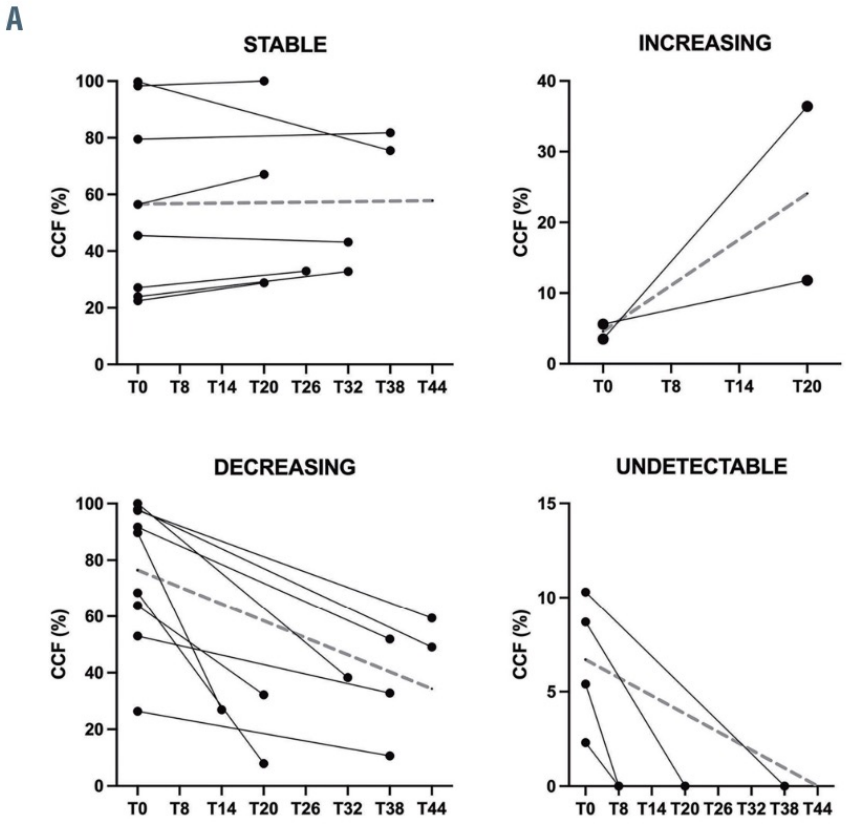
Treatment with ibrutinib does not induce a *TP53* clonal evolution in chronic lymphocytic leukemia

Luciana Cafforio, Sara Raponi, Luca Vincenzo Cappelli, Caterina Ilari, Roberta Soscia, Maria Stefania De Propris, Paola Mariglia, Gian Matteo Rigolin, Antonella Bardi, Nadia Peragine, Alfonso Piciocchi, Valentina Arena, Francesca Romana Mauro, Antonio Cuneo, Anna Guarini, Robin Foa, Ilaria Del Giudice

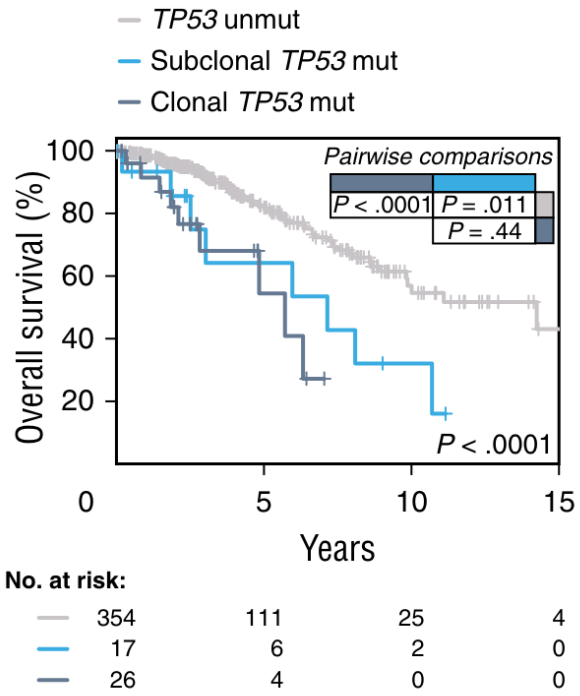
Vol. 107 No. 1 (2022): January, 2022 https://doi.org/10.3324/haematol.2020.263715



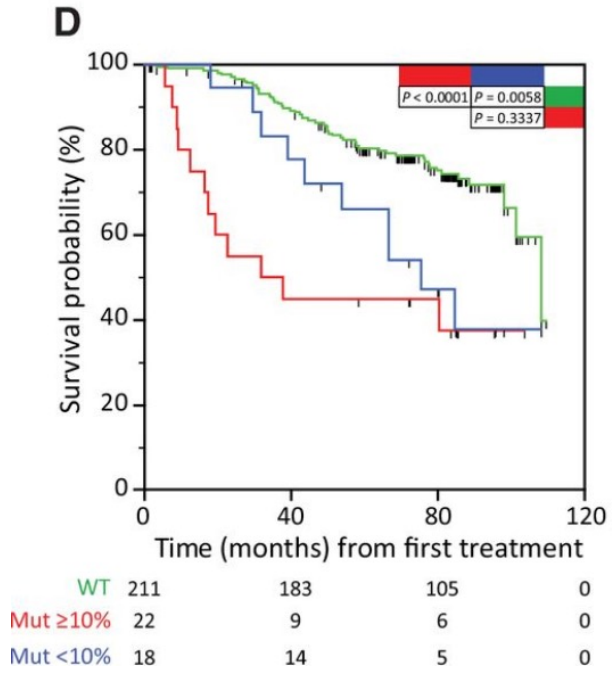
Malcikova et al., Blood 2021



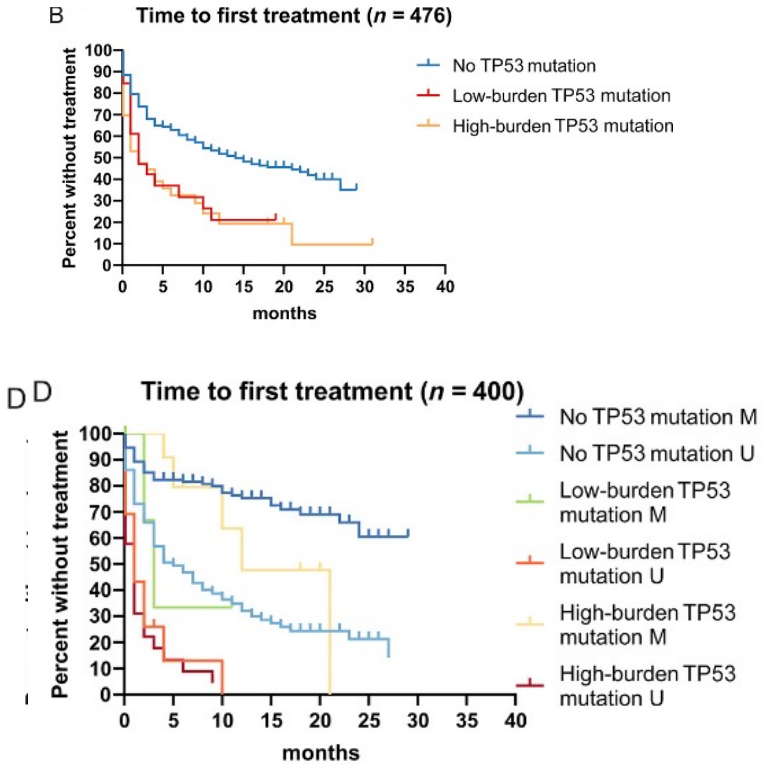
PROGNOSTIC IMPACT – CIT



Nadeu et al., Blood 2016

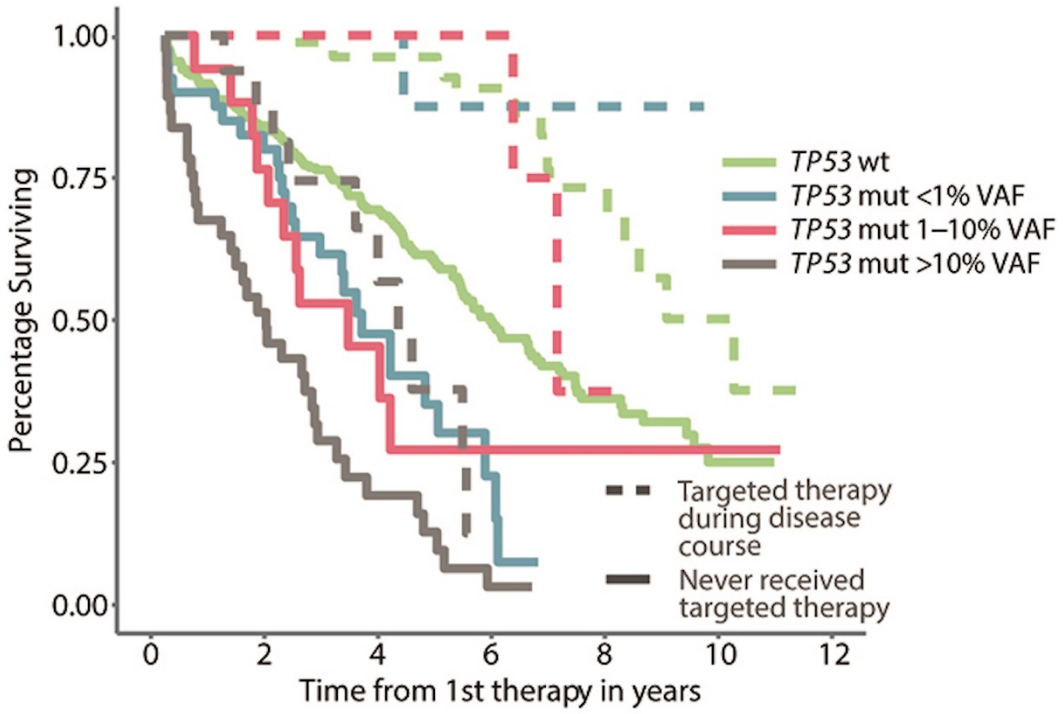


Bomben et al, Clinical Cancer Research 2021

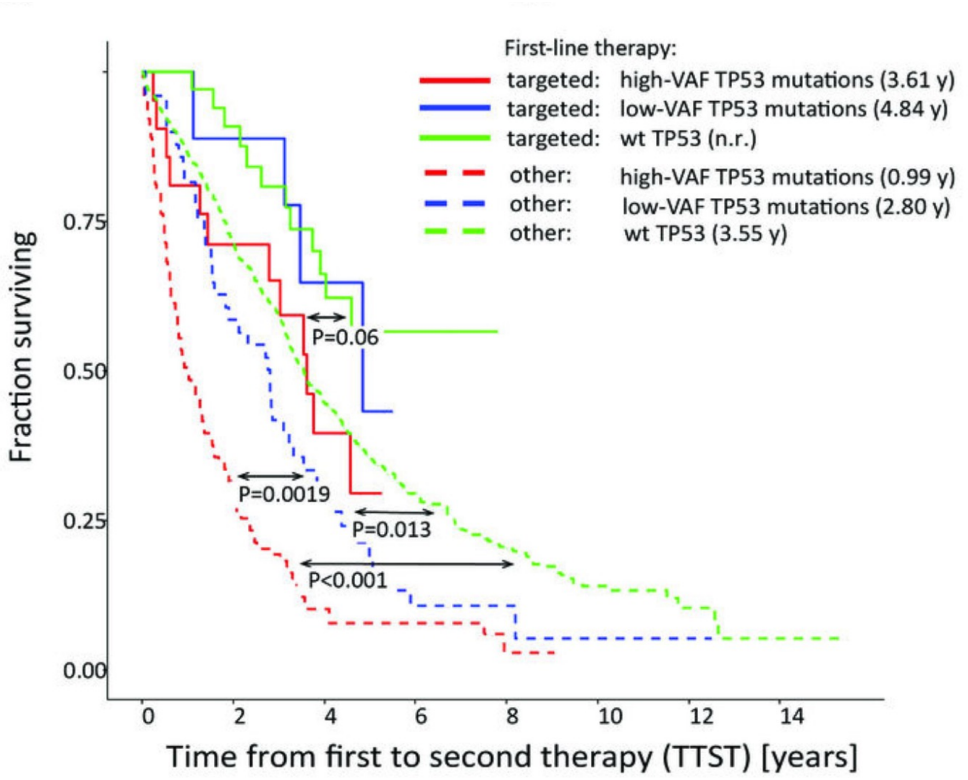


Laszlo et al., The Journal of Pathology 2023

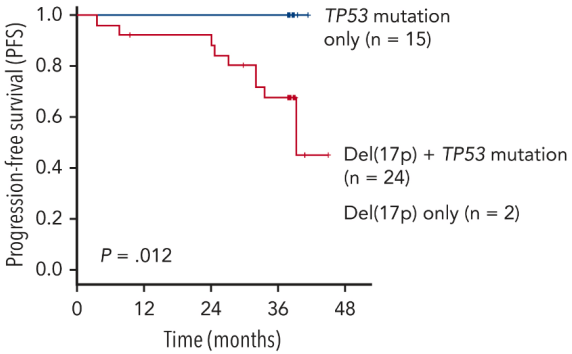
PROGNOSTIC IMPACT – CIT vs Target therapies

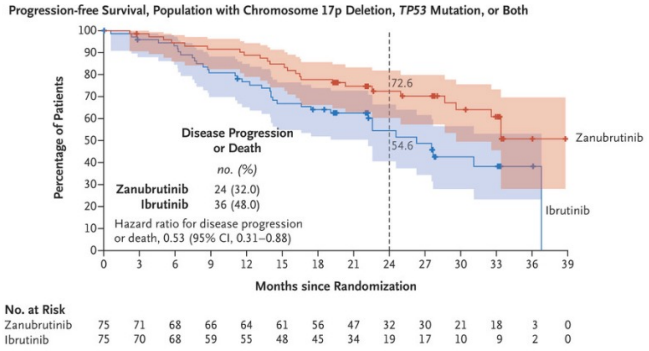


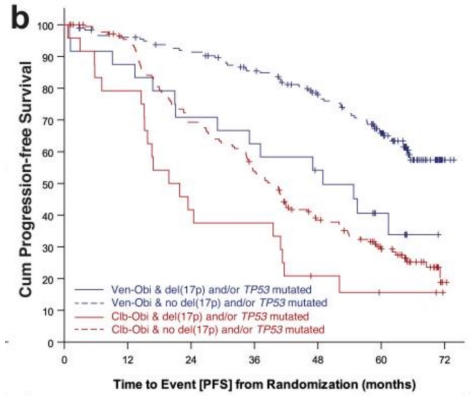
Malcikova et al., Blood 2021

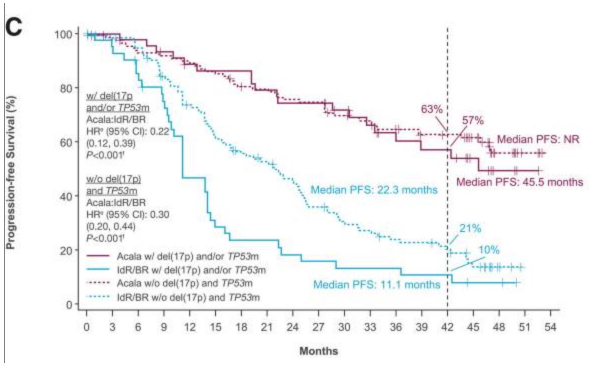


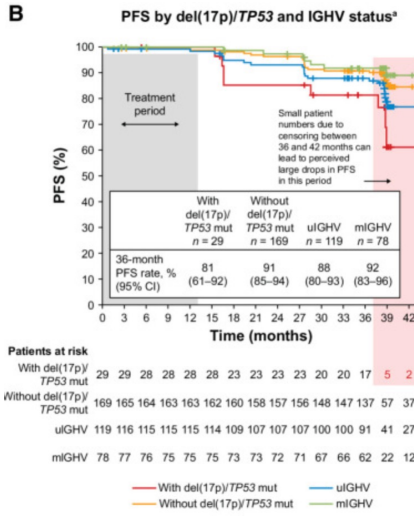
Pavlova et al., ASH 2023

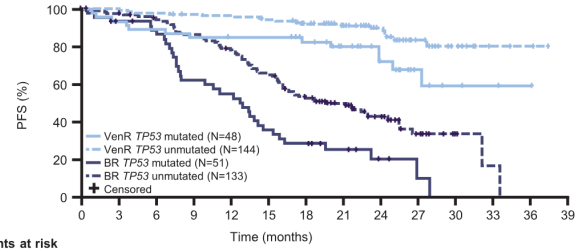












No. of patients at risk

VenR *TP53* mutated	48	44	42	40	39	39	34	25	17	8	4	2	1
VenR *TP53* unmutated	144	144	141	138	136	133	122	90	59	25	10	3	2
BR *TP53* mutated	51	40	37	26	23	15	12	7	3	1			
BR *TP53* unmutated	133	126	117	107	96	80	62	47	32	11	3	1	

CASO CLINICO - therapeutic choice

Mar 2023 – Feb 2024: avviata terapia secondo schema **Obinutuzumab-Venetoclax**
Terapia ben tollerata salvo lievi artralgie e neutropenia G1.

Rivalutazione di fine terapia

- Emocromo: WBC 3.12,Lly 0.83, Hb 122, Plts 255
- Biopsia osteo-midollare: negativa per localizzazione di CLL
- TC total body: alcuni linfonodi superiori a 1.5 cm

→ PARTIAL RESPONSE

- MRD citofluorimetrica: 0,0052% di cellule linfoidi B CD5+, CD38+, CD43+, CD81low su sangue periferico, 0.0097% di cellule linfoidi B CD5+, CD38+, CD43+, CD81low su sangue midollare

→ MRD NEGATIVITA'

IN CONCLUSION

- Patients with high burden TP53 defects greatly benefit from targeted treatments
- While low-VAF variants impact clinical outcomes for patients receiving CIT in the frontline setting, their clinical impact for patients treated with novel therapies remains to be evaluated in larger cohorts.
- Should be patients with low VAF treated similarly to patients with dominant TP53 mutated sublcones?
- What detection sensitivity do we really need?

Grazie per l’attenzione!