1157 - SIGNIFICANCE OF *TP53* ABERRATIONS IN CONTEXT OF OTHER PATHOGENIC SEQUENCE VARIANTS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA IN THE ERA OF TARGETED THERAPY

Zuzana Kubová*[1)], Veronika Kašková*[2)], Anna Petráčková[2)], Peter Turcsányi[1)], Jiřina Maňáková[2)], Jakub Savara[3)], Vít Doleží[3)], Petr Gajdoš[3)], Tomáš Papajík[1)], Eva Kriegová[2)]

[1)]Hemato – oncology Dept., University Hospital Olomouc, Czech Republic
[2)]Immunology Dept., Faculty of Medicine, Palacký University and University Hospital Olomouc, Czech Republic
[3)]Faculty of Electrical Engineering and Computer Science, Technical University of Ostrava, Czech Republic
*Kubová, Kašková contributed equally

XIV IWCLL International Workshop on CLL OCTOBER 6-9, 2023 BOSTON

BACKROUND:

Significant progress has been made in the treatment of chronic lymphocytic leukemia (CLL) over the past few decades. Targeted therapy replaced chemoimunotherapy in most patients. Improvement of progression-free survival (PFS) Bruton tyrosine kinase inhibitors (BTKi)-based therapy in patients with TP53 disrupted CLL has been proven.

AIM:

Analysis of the prognostic value of both isolated *TP53* aberrations and in combination with other CLL associated pathogenic sequence variants (PSV) in the cohort of BTKi-treated CLL patients.

METHODS:

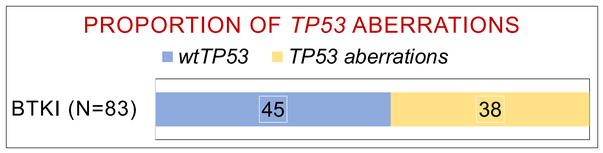
- ANALYSIS OF A SET OF 83 BTKi TREATED CLL PATIENTS, BETWEEN YEARS 2014 - 2022 AT HEMATO-ONCOLOGY DEPARTMENT UNIVERSITY HOSPITAL IN OLOMOUC

BTKi PATIENTS	N = 83 (49 %)	
SEX	Men	N = 49 (59 %)
	Female	N = 34 (41 %)
MEDIAN AGE	67 years (46 – 85)	
PRIOR TREATMENT	Naive	N = 6 (7 %)
	Pretreated	N = 77 (93%)
	4 and more lines	N = 11 (13%)
TYPE OF BTKi	Ibrutinib	N = 73 (88 %)
	2nd generation BTKi	N = 10 (12%)

METHODS:

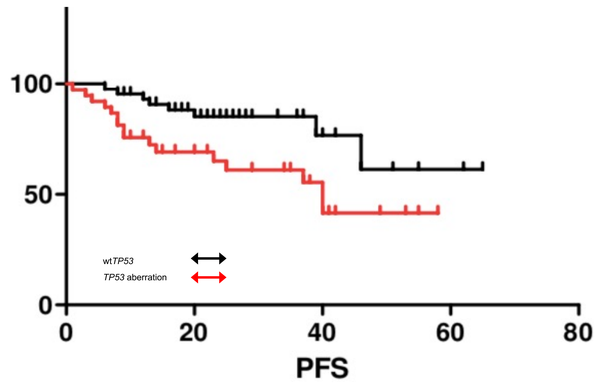
- **EVALUATION OF:**
  - *TP53* MUTATIONS BY NEXT- GENERATION SEQUENCING (NGS)
  - 17p DELETIONS BY FLUORESCENCE IN SITU HYBRIDIZATION (FISH)
  - OTHER PSV BY BOTH NGS AND FISH ACCORDING TO TYPE
- **ANALYSIS OF:**
  - COMPARISON *TP53wt* (without mutation and/or 17p deletion) VERSUS *TP53* ABERRATED (with mutation and/or deletion of 17p) PATIENTS
  - SIGNIFICANCE OF INDIVIDUAL TYPE OF *TP53* ABERRATIONS
  - PFS EFFECT OF OTHER CLL ASSOCIATED PSV ALONE AND IN COMBINATION WITH *TP53* DISRUPTION

PROPORTION OF *TP53* ABERRATIONS



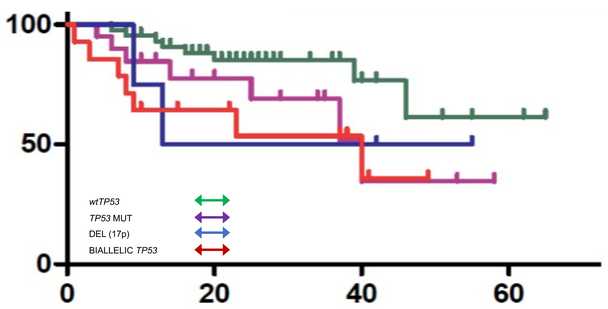
RESULTS:

- PFS was significantly longer in *TP53wt* patients versus *TP53* disrupted groups (p = 0.017).
- Median PFS was not reached in these patients compared to 40 months in patients with *TP53* disruption.



SURVIVAL ACCORDING TO THE TYPE OF ABERRATION:

- Significant effect of biallelic aberration compared to *TP53wt* patients was demonstrated (p = 0.012), while in *TP53* mutated patients this trend was only indicated (p = 0.086).



	wt*TP53*	*TP53* MUT	DEL (17p)	BIALLELIC *TP53*
NO PTS.	45	20	4	14
MEDIAN PFS	NOT REACHED (NR)	40	39	40

Supported by grant IGA_LF_2023_005, IGA_LF_2023_010, MH_CZ-DRO (FNOL, 00098892)

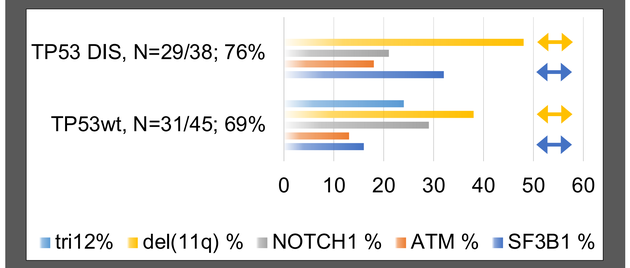
CLL ASSOCIATED PATHOGENIC SEQUENCE VARIANTS

***TP53* DISRUPTED**

- *SF3B1* (12/38; 32 %)
- *ATM* (7/38; 18 %)
- *NOTCH1* (8/38; 21 %)
- Del(11q) (14/38; 48 %)
- Other CLL - associated aberrations *BIRC3 KRAS NRAS BRAF FBXW7 EGR2 NFKBIE XPO1 POT1 RPS15* tri(12)

***TP53* WT**

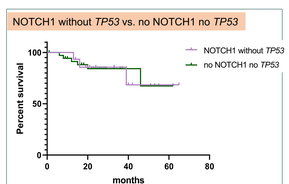
- *SF3B1* (7/45; 16 %),
- *ATM* (6/45; 13%), *NOTCH1* (13/45; 29 %), +12 (11/45; 24 %)
- del(11q) (17/45; 38 %)



HIGH PROPORTION OF OTHER CLL PSV IN BOTH SUBGROUPS WERE OBSERVED (76% VS. 69%)

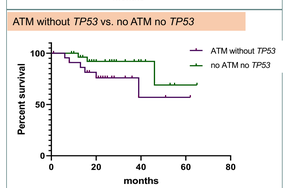
MOST COMMON IN *TP53* DISRUPTED SUBGROUP WERE SF3B1 AND DEL(11Q)

ISOLATED ABERRATION WITHOUT *TP53* DISRUPTION DOES NOT SHORTEN SURVIVAL



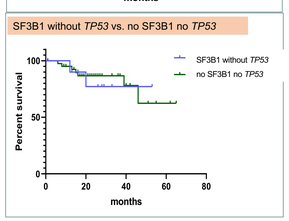
Log-rank (Mantel-Cox) test
Chi squqre 0.02687
P value **0.8698**

Median survival	
NOTCH1 without *TP53*	NR
no NOTCH1 no *TP53*	NR
No. patients	
NOTCH1 without *TP53*	14
no NOTCH1 no *TP53*	37



Log-rank (Mantel-Cox) test
Chi square 2.324
P value **0.1274**

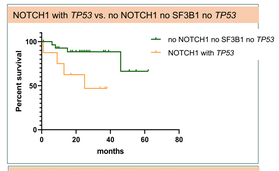
Median survival	
ATM without *TP53*	NR
no ATM no *TP53*	NR
No. patients	
ATM without *TP53*	23
no ATM no *TP53*	21



Log-rank (Mantel-Cox) test
Chi square 0.06481
P value **0.7990**

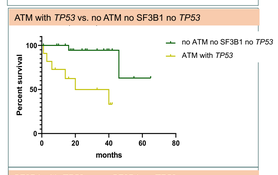
Median survival	
SF3B1 without *TP53*	NR
no SF3B1 no *TP53*	NR
No. patients	
SF3B1 without *TP53*	10
no SF3B1 no *TP53*	41

TP53 DISRUPTION IN COMBINATION WITH OTHER CHANGES SIGNIFICANTLY SHORTENS SURVIVAL



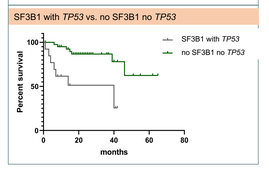
Log-rank (Mantel-Cox) test
Chi squqre 5.345
P value **0.0208**

Median survival	
NOTCH1 with *TP53*	25
no NOTCH1 no SF3B1 no *TP53*	NR
No. patients	
NOTCH1 with *TP53*	8
no NOTCH1 no SF3B1 no *TP53*	28



Log-rank (Mantel-Cox) test
Chi squqre 10.07
P value **0.0015**

Median survival	
ATM with *TP53*	20
no ATM no SF3B1 no *TP53*	NR
No. patients	
ATM with *TP53*	11
no ATM no SF3B1 no *TP53*	21

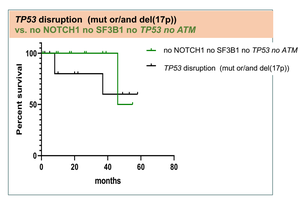


Log-rank (Mantel-Cox) test
Chi square 11.29
P value **0.0009**

Median survival	
SF3B1 with *TP53*	40
no SF3B1 no *TP53*	NR
No. patients	
SF3B1 with *TP53*	13
no SF3B1 no *TP53*	41

TP53 DISRUPTION ONLY VERSUS NO CHANGES – NO SIGNIFICANT DIFFERENCE IN PFS

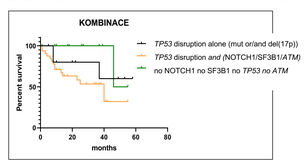
- PFS impact of combination of other variants (*NOTCH1* p=0.021, *ATM* p=0.002, *SF3B1* p=0.009) in presence of *TP53* was confirmed compared to no PSV together with *wtTP53*.
- To support results that *TP53* disruption has impact only in combination of other PSV, we analyzed subgroup of patients with isolated *TP53* disruption without any other common change in comparison to patients with no changes at all and we found that the difference of PFS between these two groups did not reach significance (p = 0.312).



Log-rank (Mantel-Cox) test
Chi squqre 1.020
P value **0.3124**

Median survival	
TP53 disruption (mut or/and del(17p))	NR
no NOTCH1 no SF3B1 no *TP53 no ATM*	50.5
No. patients	
TP53 disruption (mut or/and del(17p))	12
no *NOTCH1* no *SF3B1* no *TP53 no ATM*	12

TP53 DISRUPTED ALONE VS. *TP53* DISRUPTED IN COMBINATION WITH OTHER PSV VS. NO CHANGES



MEDIAN SURVIVAL	MONTHS	P VALUE
TP53 disruption alone (mut or/and del(17p))	NR	0.312
no NOTCH1 no SF3B1 no *TP53 no ATM*	50.5	
MEDIAN SURVIVAL	MONTHS	P VALUE
TP53 disruption *and (NOTCH1/SF3B1/ATM)*	40	0.015
no *NOTCH1* no *SF3B1* no *TP53 no ATM*	50.5	

CONCLUSION:

DESPITE IMPROVEMENT OF SURVIVAL IN OUR BTKI TREATED COHORT, NEGATIVE PROGNOSTIC VALUE OF *TP53* ABERRATION, STILL REMAINED PRESERVED. HOWEVER, THERE IS A NEED TO EVALUATED THE SIGNIFICANCE IN THE CONTEXT OF OTHER CLL ASSOCIATED PATHOGENIC SEQUENCE VARIANTS.