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POSTER ABSTRACTS

631.CHRONIC MYELOID LEUKEMIA: BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY

TP53 mutations and Their Impact on Survival in Patients with Myeloproliferative Neoplasms

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Introduction: *TP53* mutations in patients with myeloproliferative neoplasms (MPN) are associated with poor prognosis, including progression to blast phase MPN. However, low variant allele fraction (VAF) *TP53* mutations have been reported to remain stable over years in chronic phase MPN. A major unmet clinical need in MPN is the ability to discriminate patients with *TP53*-mutant MPN who are at high-risk of secondary AML (sAML) and warrant immediate intervention from those who are at lower risk of sAML in whom active surveillance can be employed. Therefore, we sought to identify parameters associated with leukemic transformation and overall survival in the context of MPN with genetic aberrations in *TP53*.
Materials and Methods: We retrospectively analyzed a cohort of 947 MPN patients from the Dana-Farber Cancer Institute Hematologic Malignancies Data Repository (HMDR) with at least one clinical next-generation sequencing (NGS) panel performed. Patient characteristics such as age at MPN diagnosis, gender, MPN subtype and driver mutations were recorded. Furthermore, information about the course of disease was extracted including occurrence of sAML and overall survival (Figure 1). We also analyzed type and number of additional mutations as well as cytogenetics. With respect to *TP53*-specific parameters, we evaluated the number of *TP53* mutations, *TP53* VAF, loss of heterozygosity (LOH) at the *TP53* locus, phenotypic annotations of *TP53* (i.e. PHANTM score) and 17p deletion. We defined "multi-hit" *TP53* as the presence of two or more *TP53* mutations, *TP53* VAF higher than 50%, *TP53* mutation plus 17p deletionor *TP53* mutation and documented LOH.
Results: A total of 947 patients were analyzed, of which 40 harbored at least one detectable *TP53* mutation. A total of 13 patients were found to have a multi-hit *TP53* mutations defined by > 50% VAF in 6 patients, two or more *TP53* mutations in 5 patients and *TP53* mutation + 17p deletion in 5 patients. The MPN diagnosis at time of *TP53* mutation detection was post ET/PV myelofibrosis (secondary MF) (n=23, 58%), primary myelofibrosis (MF) (n=7, 18%), pre-fibrotic MF (n=2, 5%), essential thrombocythemia (ET) (n=6, 15%) and polycythemia vera (PV) (n=2, 5%). Two patients with ET and one patient with PV did not have a concurrent in-house bone marrow biopsy performed at the time the *TP53* mutation was detected. Two patients with ET developed sAML within 12 months of *TP53* mutation detection, without prior mention of fibrosis. Age at first MPN diagnosis was not significantly different between patients with or without *TP53* mutation. The average time from initial MPN diagnosis to

detection of the first *TP53* mutation was 9 years (range: 0-33 years). The most common MPN driver mutation among patients with *TP53* mutations was *JAK2* (75%), followed by *CALR* (13%)and *MPL* (5%). Out of all *TP53*-mutated patients, 8% showed a triple negative status. The most frequent additional mutations among patients with *TP53* mutations were *TET2* (25%), *U2AF1* (15%), *ASXL1* (13%), and *DNMT3A* (10%). There was no significant difference between single-hit and multi-hit *TP53* status regarding MPN subtype, driver mutations and co-mutations (Table 1). Seven patients (single-hit: 15%, multi-hit: 23%) with a *TP53* mutation developed sAML during the course of their disease, compared with only 3% of all patients without a *TP53* mutation and 50% (single-hit: 41%, multi-hit: 69%) were deceased at the time of the last follow-up compared to 18% of all patients without a *TP53* mutation.

We focused on overall survival from the initial MPN diagnosis and considered whether patients developed bone marrow fibrosis during their disease course (Figure 1). Survival did not differ significantly between single-hit *TP53* and patients with multi-hit *TP53* ($p=0.2$), but survival did differ significantly between multi-hit *TP53* patients and *TP53* wildtype patients with MF/prefibrotic MF/Secondary MF ($p=0.02$) as well as compared to all MPN patients without a *TP53* mutation ($p<0.001$). Survival was not significantly different between single-hit *TP53* and *TP53* wildtype MF/prefibrotic MF/Secondary MF patients ($p=0.4$).

Conclusions: In a large cohort of 947 molecularly characterized MPN patients, 4% of the cohort developed a *TP53* mutation during their course of disease. 18% of all *TP53*-mutant patients developed sAML with an adverse effect on overall survival for patients with multi-hit but not single-hit *TP53* mutations.

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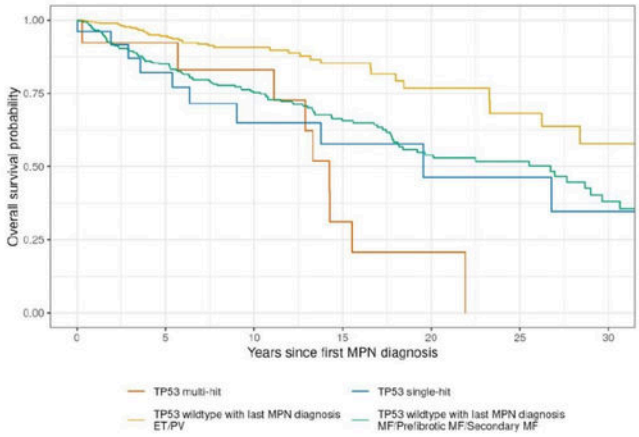
Figure 1: Overall Survival from first MPN diagnosis by *TP53* type with *TP53* wildtype patients split by last MPN diagnosis



At Risk

TP53 multi-hit	13	10	9	3	1	0	0
TP53 single-hit	27	16	10	7	4	4	3
TP53 wildtype with last MPN diagnosis ET/PV	478	232	107	57	26	16	7
TP53 wildtype with last MPN diagnosis MF/Prefibrotic MF/Secondary MF	403	247	157	100	54	35	16

Median OS (95% CI): 14.2 (11.1, 15.5) years for *TP53* multi-hit, 19.5 (9.0, 33.7) years for *TP53* single-hit, 26.7 (18.2, 29.6) years for *TP53* wildtype with last MPN diagnosis MF/Prefibrotic MF/Secondary MF, and 32.4 (26.2, NA) years for *TP53* wildtype with last MPN diagnosis ET/PV.

p-value via log-rank test: <0.001 (2.7e-8)

Table 1. Patient characteristics

	TP53 type, n (%)				p-value[2]
	Wildtype with subtype ET or PV (n=478)	Wildtype with subtype MF, Prefibrotic MF or Secondary MF (n=403)	Single-hit (n=27)	Multi-hit[1] (n=13)	
Age at first MPN diagnosis (median, range)	59 (9, 97)	60 (19, 87)	62 (19, 82)	62 (32, 83)	0.3
< 60 years	259 (54)	204 (51)	13 (48)	6 (46)	0.7
≥ 60 years	219 (46)	199 (49)	14 (52)	7 (54)	
Sex					
Female	272 (57)	184 (46)	11 (41)	6 (46)	0.005
Male	206 (43)	219 (54)	16 (59)	7 (54)	
Last MPN diagnosis					
PV	217 (45)	-	2 (7)	-	0.5[5]
ET	261 (55)	-	4 (15)	2 (15)	
MF	-	193 (48)	6 (22)	1 (8)	
Prefibrotic MF	-	23 (6)	2 (7)	-	
Secondary MF	-	187 (46)	13 (48)	10 (77)	
Molecular genetics					
Number of co-mutations (in addition to *TP53*) found on rapid heme panel (median, range)			1 (0, 5)	1 (0, 4)	>0.9
JAK2			21 (78)	9 (69)	0.7
CALR			2 (7)	3 (23)	0.3
MPL			1 (4)	1 (8)	>0.9
TET2			8 (30)	2 (15)	0.5
U2AF1			3 (11)	3 (23)	0.4
ASXL1			3 (11)	2 (15)	>0.9
DNMT3A			2 (7)	2 (15)	0.6
PHANTM score (median, range)[3]			1.01 (-0.39, 1.49)	1.24 (-0.54, 1.52)	0.049
≤ 1			12 (48)	3 (23)	0.2
> 1			13 (52)	10 (77)	
Cytogenetics[4]					
Abnormal karyotype			8 (50)	10 (100)	0.009
Complex karyotype			3 (19)	8 (80)	0.004

[1] *TP53* "multi-hit" is defined as having two or more *TP53* mutations, *TP53* VAF > 50%, *TP53* mutation plus 17p deletion, or *TP53* mutation plus LOH

[2] Kruskal-Wallis rank sum test used for age at earliest RHP; Wilcoxon rank sum test used for all other continuous variables; Fisher's exact test used for all categorical variables

[3] PHANTM score missing for 2 *TP53* single-hit patients

[4] Cytogenetics missing for 11 *TP53* single-hit patients and 3 *TP53* multi-hit patients

[5] Only considering differences between *TP53* single-hit and *TP53* multi-hit

Figure 1

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