Concurrent *DDX41* and *TP53* Alterations in Myeloid Neoplasms: Single-Institution Real-World Clonal Dynamics and Outcomes

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INTRODUCTION

- Germline *DDX41* mutations define a distinct clinicogenomic subtype of MDS/AML — older age, male predominance, normal karyotype and generally favorable outcomes[1].
- *DDX41*-mutated disease has been reported to attenuate the adverse prognostic impact of *TP53* alterations[2].
- Whether that holds in real-world patients with concurrent *DDX41* and *TP53* alterations — and how the two clones behave over time — remains unknown.

AIM

- To characterize baseline features, clonal dynamics, AML transformation and survival in patients with concurrent *DDX41* and *TP53* alterations.
- Specifically: (1) *TP53* and *DDX41* VAF trajectories from diagnosis to progression/transformation; (2) emergence of multi-hit *TP53*, del(17p) and complex karyotype; (3) overall survival from initial diagnosis and from AML transformation.

METHODS

- Single-center retrospective review of 13 patients with concurrent *DDX41* and *TP53* alterations; diagnoses assigned by WHO 2022 classification[3].
- NGS and cytogenetics/FISH reviewed at initial diagnosis and at progression or AML transformation.
- Multi-hit *TP53* defined as ≥2 *TP53* mutations, a *TP53* mutation with del(17p)/17p loss, or *TP53* VAF >50%. Complex karyotype defined as ≥3 abnormalities[4].
- Overall survival estimated by Kaplan–Meier from initial diagnosis and from AML transformation; remaining endpoints summarized descriptively.

CONCLUSIONS

- AML transformation was frequent (8/10, 80%) and outcome after transformation was dismal: median OS 5.1 months from AML transformation.
- TP53 detectable at MDS diagnosis marked aggressive disease: median time to AML 9.4 vs 45.2 months when TP53 was undetectable at baseline.
- The germline-range DDX41 VAF stayed fixed near 50% while TP53 clones expanded or newly emerged, with accrual of multi-hit TP53, complex karyotype and del(17p); a second DDX41 variant was documented in 5/8 at transformation, newly in 3/8.
- These real-world data do not support near-complete mitigation of TP53-associated risk by DDX41 mutation — TP53 clonal evolution remains clinically relevant and supports serial molecular monitoring.

RESULTS

80%
MDS → AML transformation (8/10)

62.5%
multi-hit *TP53* at transformation (5/8)

9.4 vs 45.2 mo
months to AML by baseline *TP53* status

5.1 mo
median OS from AML transformation

Table 1. Cohort characteristics

Characteristic	n = 13
Age at diagnosis, median (range), y	68.5 (55.9–85.8)
Male	11 (84.6%)
Initial diagnosis: MDS	10 (76.9%)
Initial diagnosis: de novo AML	3 (23.1%)
***DDX41* variant 1 VAF, median (range)**	**49.0% (21.0–51.8)**
Second *DDX41* variant at baseline	4 (30.8%)
***TP53* mutation at baseline**	**8 (61.5%)**
TP53 VAF at baseline, range	2.0–57.4%
Multi-hit *TP53* at baseline	3 (23.1%)
del(17p) at baseline	1 (7.7%)
Complex karyotype at baseline	6 (46.2%)
MDS → AML transformation	**8/10 (80.0%)**
Time to AML, median (range), mo	17.7 (1.6–92.2)
Allogeneic HCT	**6 (46.2%)**
CR/CRi to AML-directed therapy	4/9 (44.4%)
Alive at last follow-up	**3 (23.1%)**
Alive: allo-HCT vs no allo-HCT	3/6 vs 0/7

Figure 1. Overall survival (Kaplan–Meier)

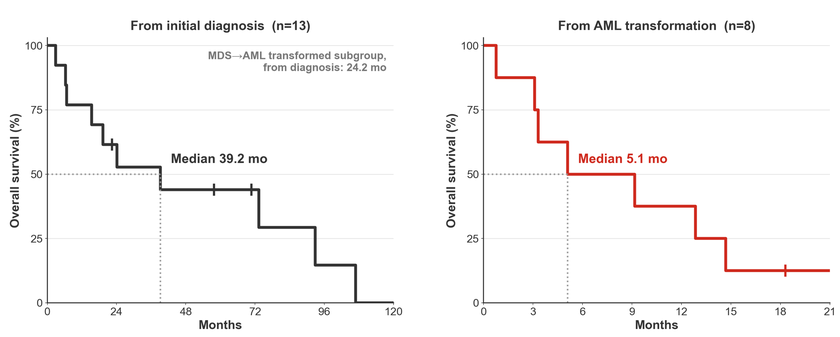
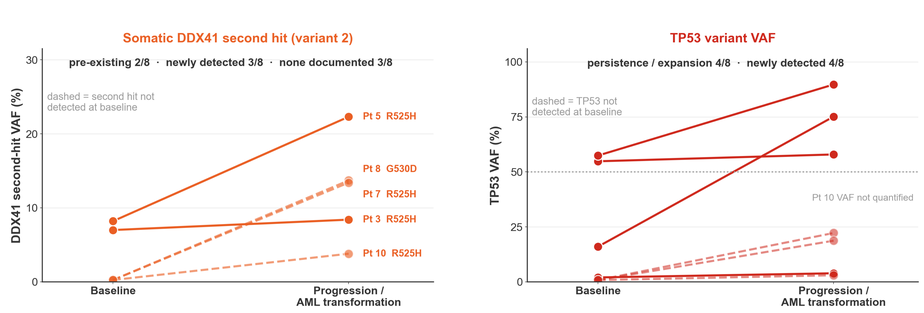
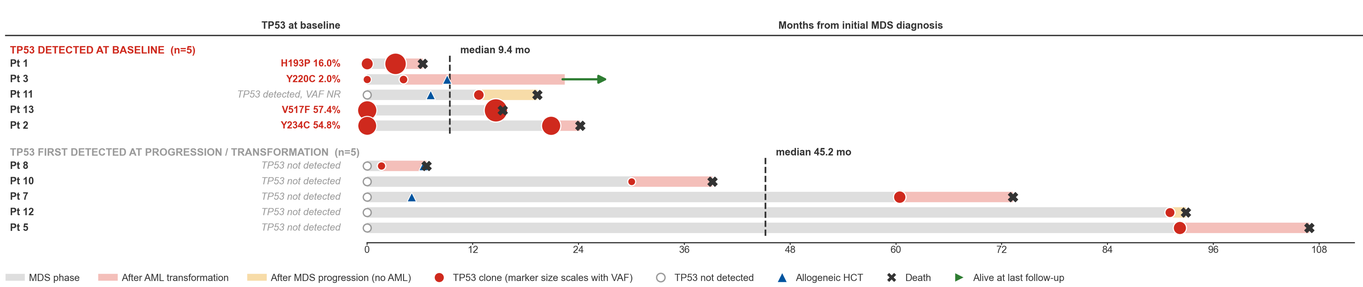


Figure 2. DDX41 second-hit and TP53 clonal dynamics



Both panels show the 8 patients who transformed from MDS to AML. R525H — the canonical DDX41 somatic second hit — accounted for 4 of the 5 second-hit variants. All second hits remained subclonal (3.8–22.3%), whereas the germline-range DDX41 variant 1 stayed near 50% throughout (median |Δ| 0.9 percentage points).

Figure 3. Clonal evolution, disease course and high-risk *TP53* features in the 10 patients with an initial MDS diagnosis



	TP53 at progression / AML transformation	Multi-hit TP53	del(17p)	Complex KT	2nd DDX41 variant at progression / transformation
TP53 DETECTED AT BASELINE (n=5)					
Pt 1	H193P 75.1%	Yes	No	Yes	—
Pt 3	Y220C 3.9%	No	No	No	R525H 8.4% (baseline 7.0%)
Pt 11	R282W 11.1%; C238Y 10.4%	Yes	No	Yes	Q208R 17.3% (baseline)
Pt 13	V517F 89.7%	Yes	No	Yes	—
Pt 2	Y234C 57.9%; I195T 3.5%	Yes	No	Yes	—*
TP53 FIRST DETECTED AT PROGRESSION / TRANSFORMATION (n=5)					
Pt 8	R213Q 3.0%	No	No	No	G530D 13.7% (new)
Pt 10	P278A (VAF NQ)	NA	NA	NA	R525H 3.8% (new)
Pt 7	R175H 18.7%	Yes	Yes	Yes	R525H 13.4% (new)
Pt 12	R248Q 8.6%	No	No	No	—
Pt 5	D281V 22.2%	Yes	Yes	Yes	R525H 22.3% (baseline 8.2%)

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