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ELEVENTH ANNUAL MEETING

Characteristics and outcomes of patients with myelodysplastic syndrome and *DDX41* mutation

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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INTRODUCTION

DDX41 , located on chromosome 5q35.3, is the most frequently mutated gene in myeloid malignancies with germline predisposition. The resulting DDX41 protein is widely expressed and is involved in multiple and diverse cellular functions. The prognostic impact of *DDX41* mutation in MDS remains poorly defined. Responses and outcomes with specific treatments, have not been assessed.

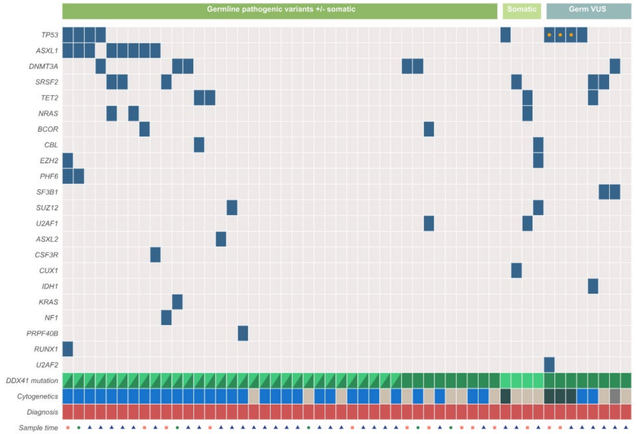
AIM

To analyze a large cohort of patients with MDS with *DDX41* mutations, focusing on response to therapies including venetoclax, survival and HSCT outcomes

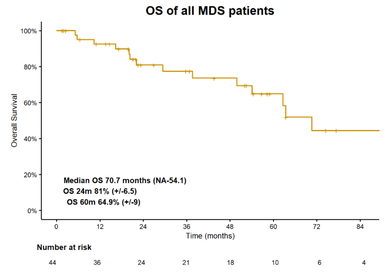
METHODS

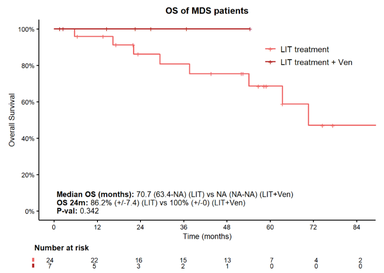
- Single-center retrospective study spanning 2010-2022 that included patients with MDS with available NGS testing. Among them, patients with *DDX41* mutations were identified and analyzed.
- *DDX41* mutation was performed using targeted NGS testing using an 81-gene panel.
- *DDX41* germline mutation testing was performed using DNA isolated from cultured skin fibroblasts from a skin punch biopsy.
- *DDX41* variants with a VAF <40% were presumed to be somatic variants
- *DDX41* variants with a VAF ≥40% or with confirmation in skin biopsy.
- Germline variants were further classified as pathogenic/likely pathogenic according to the ACMG/AMP guidelines.

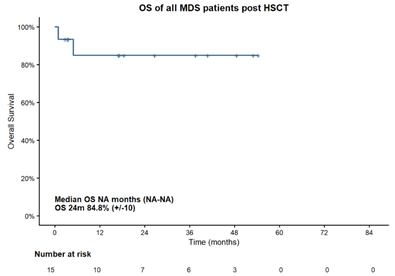
RESULTS & CONCLUSIONS



Disease status	Treatment	Response
Previously untreated	Low intensity treatment (n=24, 75%)	**CR:** 15 (62.5%) **mCR:** 5 (20.9%)
	Low intensity treatment + venetoclax (n=7, 21.9%)	**CR:** 6 (85.7%)
	Other (n=1, 3.1%)	**CR:** 1 (100%)
Relapse/ Refractory	Intensive treatment (n=1, 16.7%)	**mCR:** 1 (100%)
	Low intensity treatment (n=1, 16.7%)	**CR:** 1 (100%)
	Low intensity treatment + venetoclax (n=2, 33.3%)	**CR:** 1 (50%) **mCR:** 1 (50%)
	Other (n=2, 33.3%)	**CR:** 2 (100%)







	MDS patients (n=52)
Age, years	68 (49-88)
Sex male, n (%)	40 (76.9)
WBC, median (range)	2.1 (0.7-7.3)
ANC, median (range)	0.9 (0-4.7)
Hgb, median (range)	11.2 (6.8-14.4)
Platelets, median (range)	92 (12-282)
BM blasts, median (range)	10 (1-18)
Cytogenetics	**Diploid:** 32 (61.5%) **Abn 5/5q:** 4 (7.7%) **Abn 7:** 3 (5.8%) **+8:** 3 (5.8%) **Complex:** 4 (7.7%)
IPSS-R	**Very low:** 1 (1.9%) **Low:** 10 (19.2%) **Intermediate:** 19 (36.5%) **High:** 12 (23.1%) **Very high:** 7 (13.5%) **No classifiable:** 3 (5.8%)
IPSS-M	**Very low:** 2 (3.8%) **Low:** 14 (26.9%) **Moderate low:** 7 (13.5%) **Moderate high:** 6 (11.5%) **High:** 8 (15.4%) **Very high:** 4 (7.7%) **No classifiable:** 11 (21.2%)
MDS status	**MDS:** 44 (84.6%) **R/R MDS:** 8 (15.4%)
DDX41 mutations	**Somatic:** 4 (7.7%) **Germline:** 9 (17.3%) **Somatic + Germline:** 31 (59.6%) **VUS:** 8 (15.4%)

Conclusions

- Most patients with MDS with *DDX41* mutations have a combination of germline and somatic mutation, usually with a normal karyotype.
- Response rate are high, and it seems venetoclax could increase OS although not statistically significative.
- Outcomes after HSCT are encouraging in patients with MDS with *DDX41* mutation.

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