STAG2-Mutated MDS: Not Only Loss-of-Function?

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INTRODUCTION

STAG2, a core component of the cohesin complex, is recurrently mutated in myelodysplastic neoplasms (MDS) and associated with **high-risk disease** and **adverse prognosis in MDS**.
Although incorporated into the Molecular International Prognostic Scoring System (IPSS-M) model, the clinical impact of distinct *STAG2* mutation subtypes remains unclear.

METHODS

We analyzed 4 independent datasets (Cleveland Clinic, Genome4all, MDS Unit Florence, IPSS-M database), comprising 3008 MDS patients.

STAG2-mutated cases were stratified by:

- Mutation typology assigned based on published functional evidence from *in vitro* and *in vivo* experimental models (Cancer Knowledgebase – Genomenon);
- Variant Allele Frequency, dichotomized at the cohort median (41.2%).

Table 1 : Cohort characteristics

Characteristic	STAG2-mutated patients
Total patients	**258**
Sex, n (%)	
Male	188 (72.9%)
Female	69 (26.7%)
Not available	1 (0.4%)
Age, years	
Median	71.8
Range	23-95
WHO 2022 classification, n (%)	
MDS-LB	58 (22.5%)
MDS-SF3B1mut	8 (3.1%)
MDS-IB1	63 (24.4%)
MDS-IB2	123 (47.7%)
MDS-U	6 (2.3%)
IPSS-M risk category, n (%)	
Very Low	5 (1.9%)
Low	12 (4.7%)
Moderate Low	9 (3.5%)
Moderate High	23 (8.9%)
High	82 (31.8%)
Very High	119 (46.1%)
Not available	8 (3.1%)

AIM

This study aimed to characterize the prognostic relevance of *STAG2* mutational features in MDS:

- Mutation type (loss-of-function [LOF] vs. undetermined function alteration [UND])
- Variant allele frequency (VAF)

in order to improve risk stratification beyond current scoring systems.

RESULTS

Cohort (Table 1)

- 258/3008 patients carried *STAG2* mutations.
- MDS with increased blasts was the most frequent diagnosis.
- IPSS-M risk distribution was largely represented by high-risk categories.

Mutation burden

- 96% of *STAG2*mut patients had at least 1 co-mutation.
- Median: 5 mutations per case (range 0-13).
- 46 patients (17.8%) had more than one *STAG2* mutation.
- 74 patients (28.7%) carried *STAG2* LOF mutations and 182 patients (70.5%) UND [N.B. cases with ≥1 LOF alteration were classified as LOF despite additional UND variants].

Prognostic impact into IPSS-M category (Fig. 1a)

- **HR MDS** (Very High, High and Moderate High categories): LOF patients exhibited significantly worse OS compared to UND (median OS: 15 vs.28 months; p <0.001).
- The survival disadvantage was consistent across **High** (OS: p = 0.010; LFS: p = 0.024) and **Very High** (OS: p = 0.001; LFS: p = 0.021) subgroups.

Co-mutational profile (Fig. 1b)

- *ASXL1* was the most frequent *STAG2* co-mutated gene (64.3%).
- *ASXL1* was the only gene significantly enriched in LOF patients compared to UND within the Higher group (86.6% vs. 62.7%; FDR = 0.004). The co-mutation landscape did not differ significantly between *STAG2*_und and *STAG2*_LOF patients in the IPSS-M High and Very High categories.

VAF did not correlate with mutation typology, nor did it independently predict survival outcomes across any endpoint.

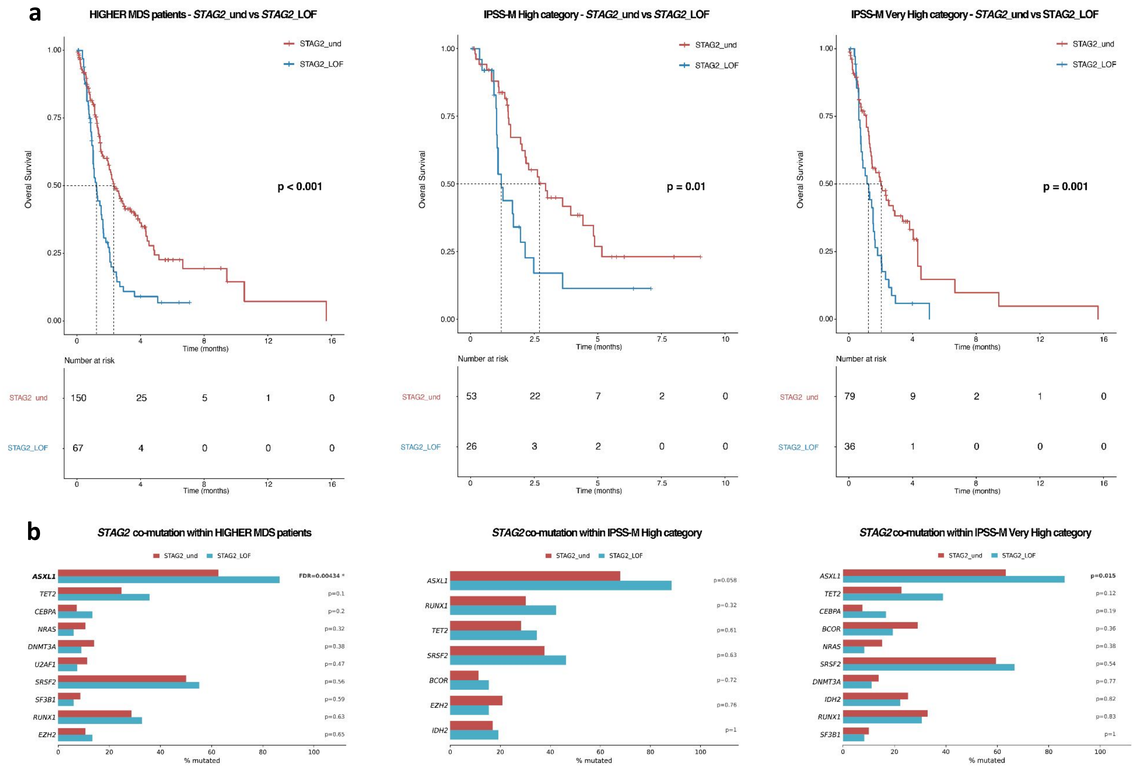

Fig. 1: LOF vs UND *STAG2* mutation overall survival and co-mutational profile. a Kaplan-Meier overall survival curves comparing *STAG2*_und (red) and *STAG2*_LOF patients (blue) in the HIGHER MDS cohort and in the IPSS-M High and Very High categories. *STAG2*_LOF patients exhibited significantly shorter OS than *STAG2*_und patients across all cohorts (HIGHER: p < 0.001; IPSS-M High: p = 0.01; IPSS-M Very High: p = 0.001). Numbers at risk are reported below each survival curve. **b** Distribution of recurrent co-mutations in *STAG2*_und (red) and *STAG2*_LOF patients (blue) across the HIGHER MDS cohort and the IPSS-M High and Very High categories. *ASXL1* mutations were significantly enriched in STAG2_LOF patients within the overall HIGHER MDS cohort (FDR = 0.00434).

CONCLUSIONS

These findings suggest that ***STAG2* mutational subtype characterization** may provide **higher prognostic stratification** within high-risk PSS-M categories, supporting its integration into refined clinical risk algorithms for MDS.

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SOHO ANNUAL MEETING 2026