Synergistic Epigenetic-Cohesin Disruption in Myelodysplastic Syndromes (MDS): ASXL1/STAG2 Defines an Ultra High-Risk Phenotype Amenable to BCL-2 Inhibition.

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INTRODUCTION

-Myelodysplastic syndromes (MDS) are characterized by recurrent somatic mutations that drive clonal progression and leukemic transformation.

-ASXL1 (an epigenetic regulator) and **STAG2** (a cohesin complex component) mutations are established drivers of poor prognosis in myeloid malignancies.

-The clinical and biologic synergy resulting from simultaneous disruption of this epigenetic-cohesin axis remains insufficiently characterized.

AIM

-To characterize the co-occurrence prevalence and prognostic impact of dual **ASXL1/STAG2** mutations in patients with MDS.

-To evaluate if this co-mutational profile defines an ultra-high-risk clinical phenotype with therapeutic vulnerability to BCL-2 inhibition (Venetoclax).

METHOD

-Study Population: Retrospective cohort analysis of 3,323patients within the International Working Group for MDS (IWG-MDS) IPSS-M cohort

-Data Access: Genomic and clinical data were analyzed utilizing cBioPortal for Cancer Genomics..

-Statistical Analysis:

.Co-occurrence tendencies were evaluated using **Fisher's exact test**

.Overall survival (OS) was analyzed using the **Kaplan-Meier method** with significance determined by the **log-rank test**.

CONCLUSIONS

-The **ASXL1/STAG2 double-mutant axis is the dominant driver** of an ultra-high-risk clinical phenotype in MDS, independent of *RUNX1* status.

-Conventional, institutional standard-of-care regimens are highly inadequate for this cohort, resulting in a low median OS of **16.64 months**.

-The epigenetic-cohesin disruption points to a high BCL-2 dependency state. We propose targeting this population with **BCL-2 inhibitors (Venetoclax)** to overcome treatment resistance.

RESULTS

-**High Co-occurrence Rate:** A highly significant co-occurrence was identified between *ASXL1* and *STAG2* mutations ($n = 209$, 6.28%; $p < 0.001$).

-Extreme Risk Stratification: 69.37% ($n = 145$) of double-mutant patients fell into IPSS-M High or Very High-risk tiers, compared to only **19.99%** ($n = 455$) in the unaltered cohort.

-Significantly Inferior Survival: Double-mutants experienced a drastically reduced median OS of **16.64 months** compared to **48.99 months** in the unaltered group (HR: 2.484, 95% CI: 1.936–3.188, $p < 0.001$).

-RUNX1 Co-mutations:*RUNX1* mutated in **48.8%** ($n = 102$) of the double-mutant cohort, but its presence did not further worsen median OS (15.55 vs. 17.46months; $p = 0.296$), identifying the *ASXL1/STAG2* axis as the primary disease driver.

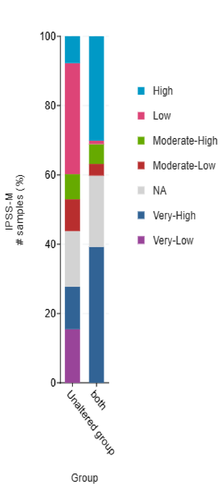
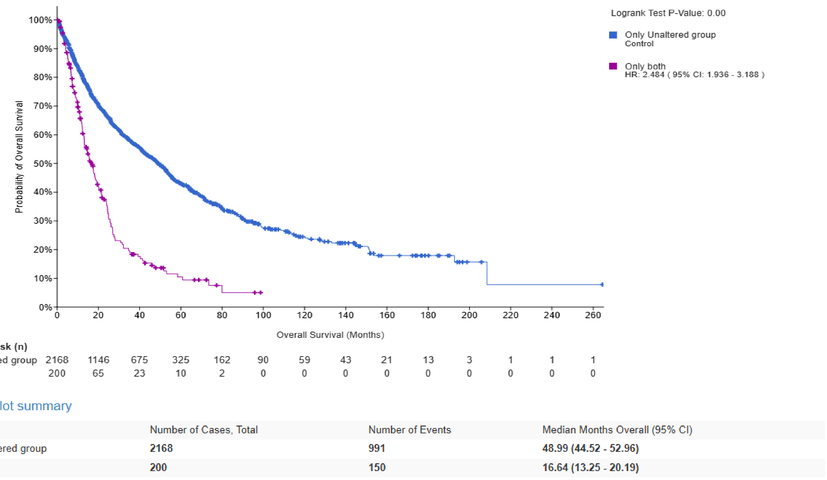


Figure 1. IPSS-M Risk Distribution. Dual *ASXL1/STAG2* mutants ("both") show a severe shift to High/Very-High risk tiers (69.37%) compared to the unaltered cohort (19.99%).



Survival plot summary

	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
Only Unaltered group	**2168**	**991**	**48.99 (44.52 - 52.96)**
Only both	**200**	**150**	**16.64 (13.25 - 20.19)**

Figure 2. Overall Survival by Mutational Status. (A) Kaplan-Meier curves and **(B)** survival summary table showing a highly significant overall survival disadvantage in the dual *ASXL1/STAG2* mutant cohort ("Only both") compared to the unaltered control ($p < 0.001$).

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