



XIX CONGRESSO
NAZIONALE
SIES 2026

MDS AND IPSS-M:
THE PROGNOSTIC VALUE OF FUNCTIONAL
CLASS AND MUTATION POSITION

Giorgio Mattiuz, PhD

Firenze | 4-6 marzo 2026
Palazzo degli Affari



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MDS AND IPSS-M:
THE PROGNOSTIC VALUE OF **MUTATIONAL
FEATURES**

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NONE							



State of the Art

- Approximately **95% of patients** with MDS have somatic mutations.
- The **IPSS-M**, which takes into account the presence (yes/no) of mutations on specific genes, is currently the **most sensitive prognostic method** for stratifying patient risk.
- However, **different mutations within the same gene can have distinct biological effects** and could influence prognosis differently.

Hypothesis (I)

“**Mutation Features** in terms of:

- Functional Class (gof/lof/und),
- Protein Domain (in/out),
- Hotspot,
- Variant Allele Frequency,

can correlate with prognostic outcomes”



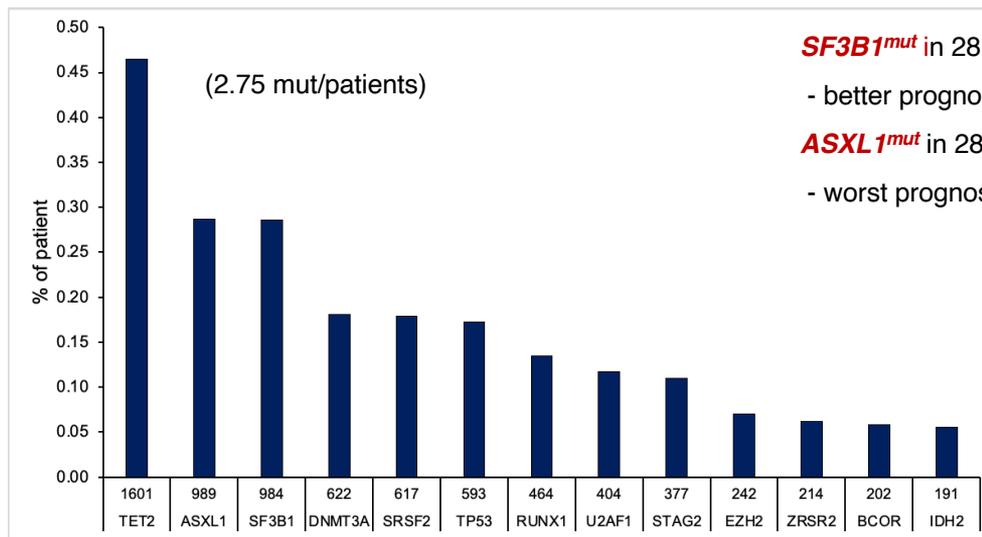
Clinical and Mutational Characteristics

	Median (Min - Max)		
	Min	Max	
N_patients	3443		
Sex_ratio	M:F = 1.86		
Age	71 (17.1 - 97)		
BM blasts %	4 (0 - 76)		
WBC(k/uI)	3.5 (0.1 - 12.8)		
ANC	1.64 (0 - 10.24)		
HB(g/dl)	9.6 (2.1 - 19.6)		
PLT(k/uI)	114 (0 - 1103)		
N_mut	2 (1 - 13)		
Clinical Data	Total (n)		
	Total (%)		
	MDS-EB1	697	20.24
	MDS-MLD-RS	397	11.53
	MDS-MLD	856	24.86
	MDS-SLD	280	8.13
	MDS-EB2	779	22.63
	MDS-SLD-RS	358	10.40
MDS-U	76	2.21	
WHO 2016	Very Low	347	10.08
	Low	891	25.88
	Moderate Low	383	11.12
	Moderate High	372	10.8
	High	588	17.08
	Very High	742	21.55
	Missing	120	3.49
	TOTALE	3443	100
IPSSM Category	Very Low	347	10.08
	Low	891	25.88
	Moderate Low	383	11.12
	Moderate High	372	10.8
	High	588	17.08
	Very High	742	21.55
	Missing	120	3.49
	TOTALE	3443	100

AA change effect	Count (n)
Total_Mut	9480
Gain-Of-Function	1473 (15.54%)
Loss-Of-Function	2425 (25.58%)
und	5566 (58.71%)
noeffect	16 (0.17)
Protein Domain	
out	4059
in	5421

Four different data sets:

- 1) MDS-Unit - AOUC
- 2) IPSS-M public data
- 3) GenoMed4All - IRCCS-HUMANITAS Research Hospital
- 4) Cleveland Clinic Department of Haematology Oncology and Blood Diseases



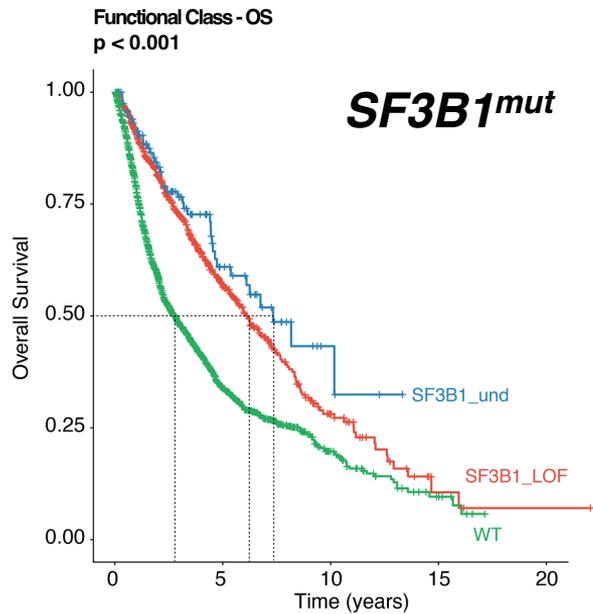
SF3B1^{mut} in 28.5% of patients (n = 984)

- better prognosis

ASXL1^{mut} in 28.7% of patients (n = 989)

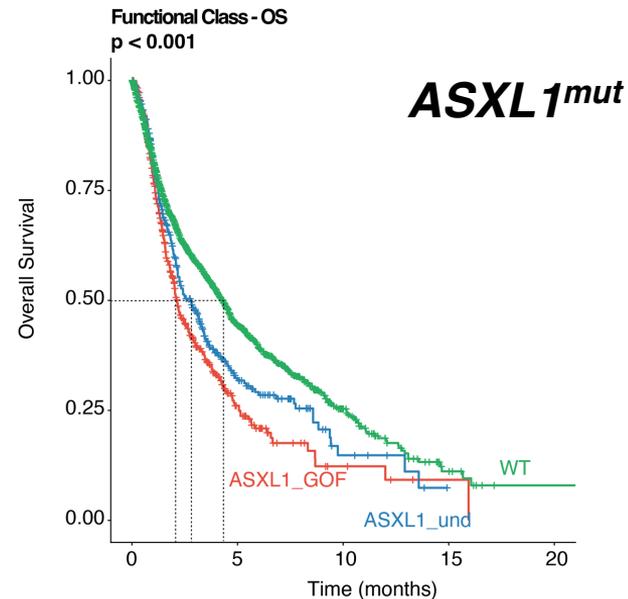
- worst prognosis

FUNCTIONAL CLASS features on Overall Survival



Number at risk

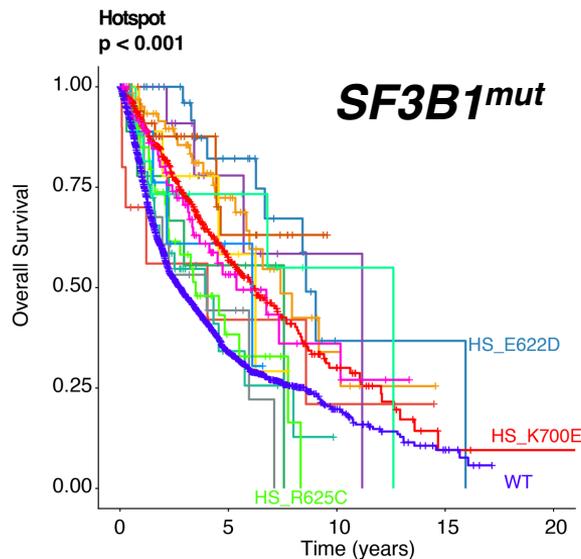
SF3B1_LOF	795	198	33	3	1
SF3B1_und	126	33	4	0	0
WT	2446	334	53	8	0



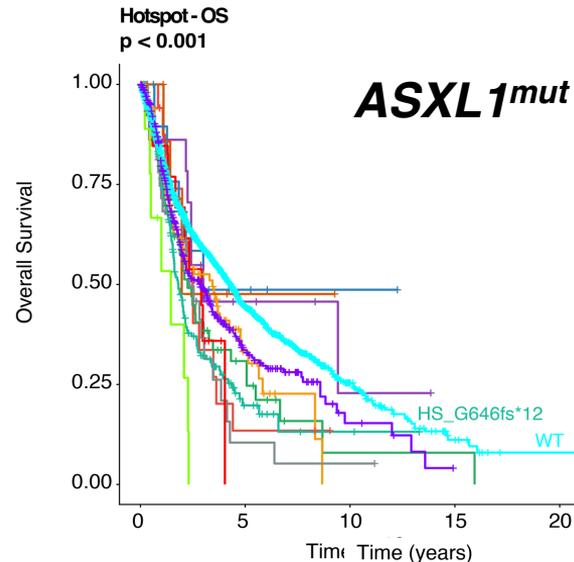
Number at risk

ASXL1_GOF	489	44	5	1	0
ASXL1_und	411	54	7	0	0
WT	2467	467	78	10	1

HOTSPOT features on Overall Survival

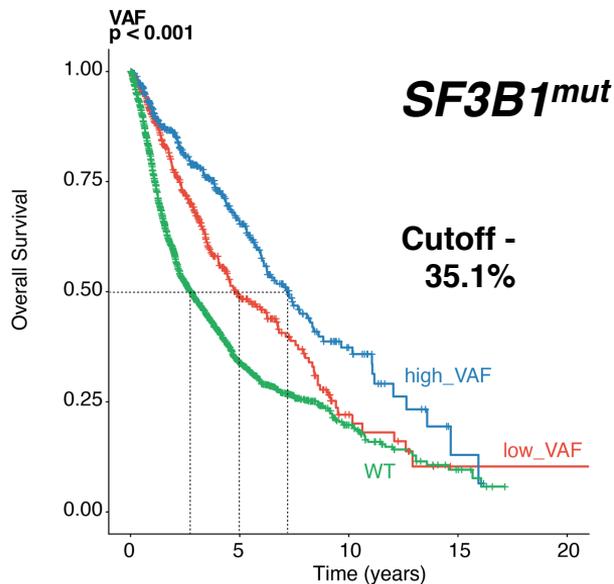


	0	5	10	15	20
HS_D781G	10	2	1	0	0
HS_E622D	34	15	1	1	0
HS_G742D	9	3	0	0	0
HS_H662D	13	4	1	0	0
HS_H662Q	66	22	4	0	0
HS_K666N	45	4	0	0	0
HS_K666R	38	9	0	0	0
HS_K666T	17	4	0	0	0
HS_K700E	518	133	25	2	1
HS_N626D	10	9	0	0	0
HS_R625C	43	7	0	0	0
HS_R625L	20	5	1	0	0
HS_T663I	9	2	0	0	0
WT	2446	334	53	8	0
other_MUT	89	18	4	0	0



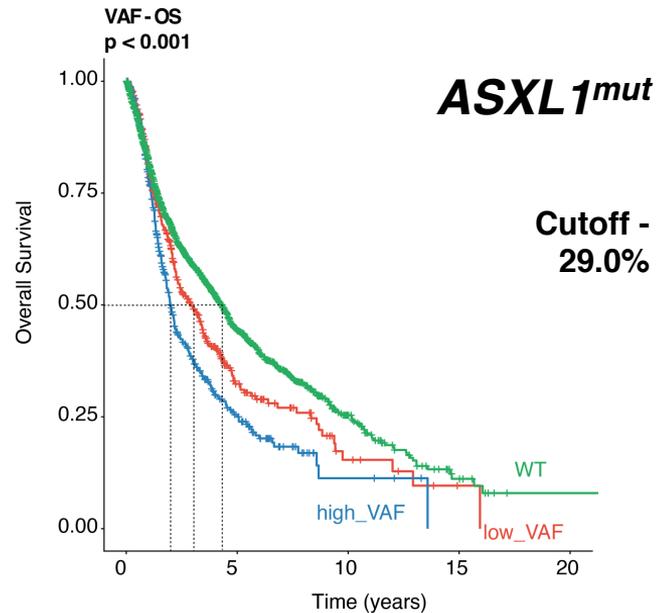
	0	5	10	15	20
HS_630_637del	17	2	0	0	0
HS_E635Rfs*15	22	3	1	0	0
HS_E635fs*15	65	10	1	1	0
HS_G642fs	15	4	1	0	0
HS_G646Wfs*12	101	11	0	0	0
HS_G646fs*12	197	11	2	0	0
HS_R1068*	10	1	0	0	0
HS_R693*	34	2	1	0	0
HS_Y591*	13	0	0	0	0
HS_Y591fs*1	10	0	0	0	0
WT	2467	467	78	10	1
other_MUT	416	54	6	0	0

VAF features on Overall Survival



Number at risk

low_VAF	461	92	12	1	1
high_VAF	460	139	25	2	0
WT	2446	334	53	8	0



Number at risk

low_VAF	455	50	8	1	0
high_VAF	445	48	4	0	0
WT	2467	467	78	10	1



Hypothesis (II)

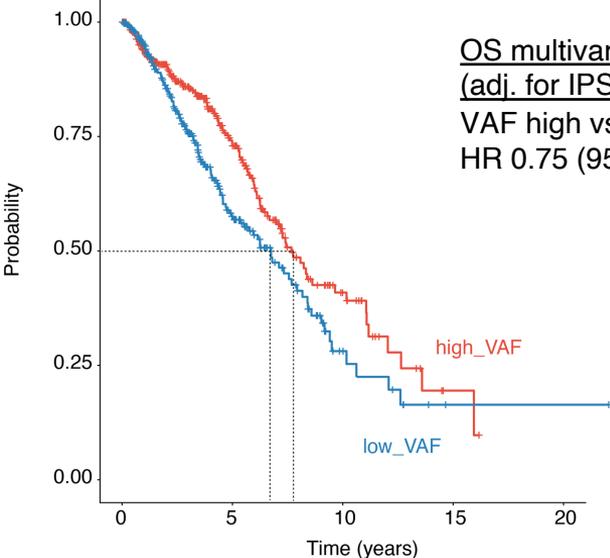
“Within identical IPSS-M risk categories,

Mutation Features

can reveal hidden prognostic layers”

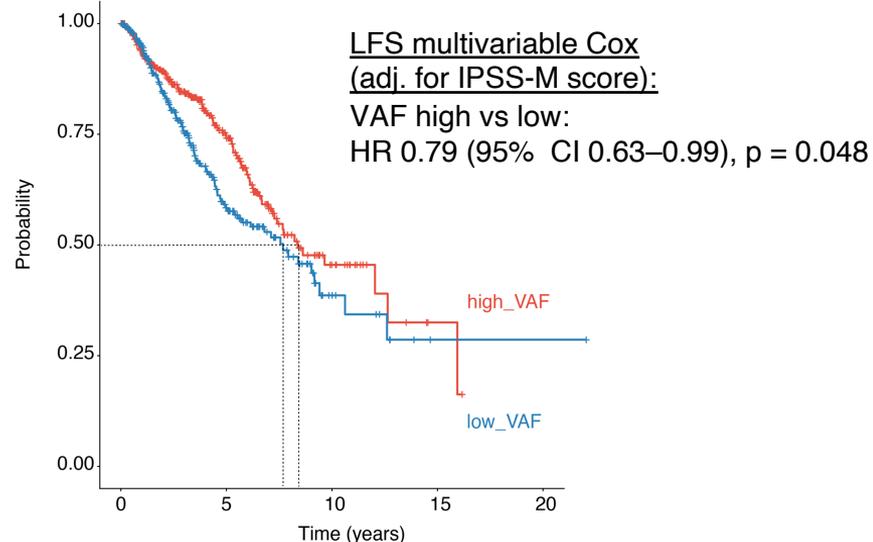
VAF of *SF3B1*^{mut} predicts OS and LFS in Lower Risk MDS

SF3B1 VAF - OS in IPSS-M Low category (binary)
p = 0.0072



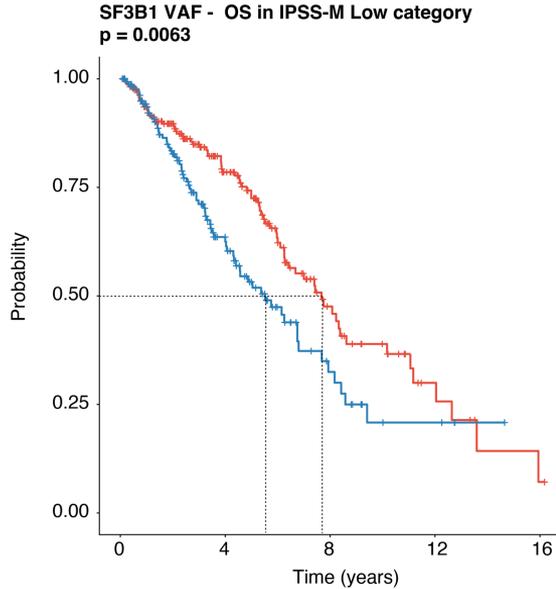
	0	5	10	15	20
high_VAF	376	128	23	2	0
low_VAF	335	80	11	1	1

SF3B1 VAF - LFS in IPSS-M Low category (binary)
p = 0.0283



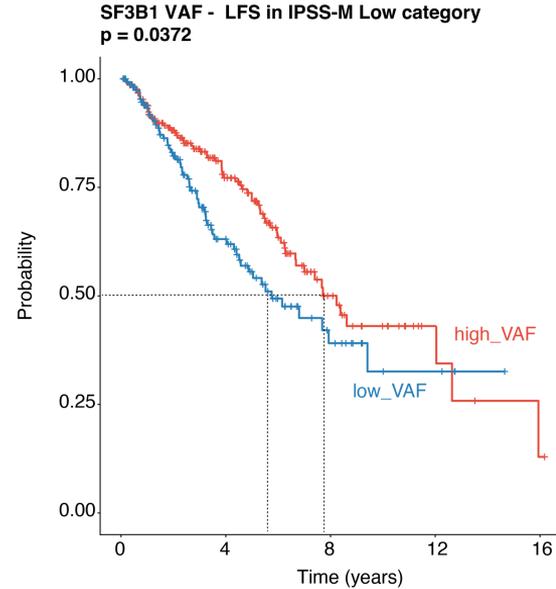
	0	5	10	15	20
high_VAF	362	123	19	2	0
low_VAF	326	78	11	1	1

Within IPSS-M Low category, *SF3B1*^{mut} VAF stratifies OS and LFS



Number at risk

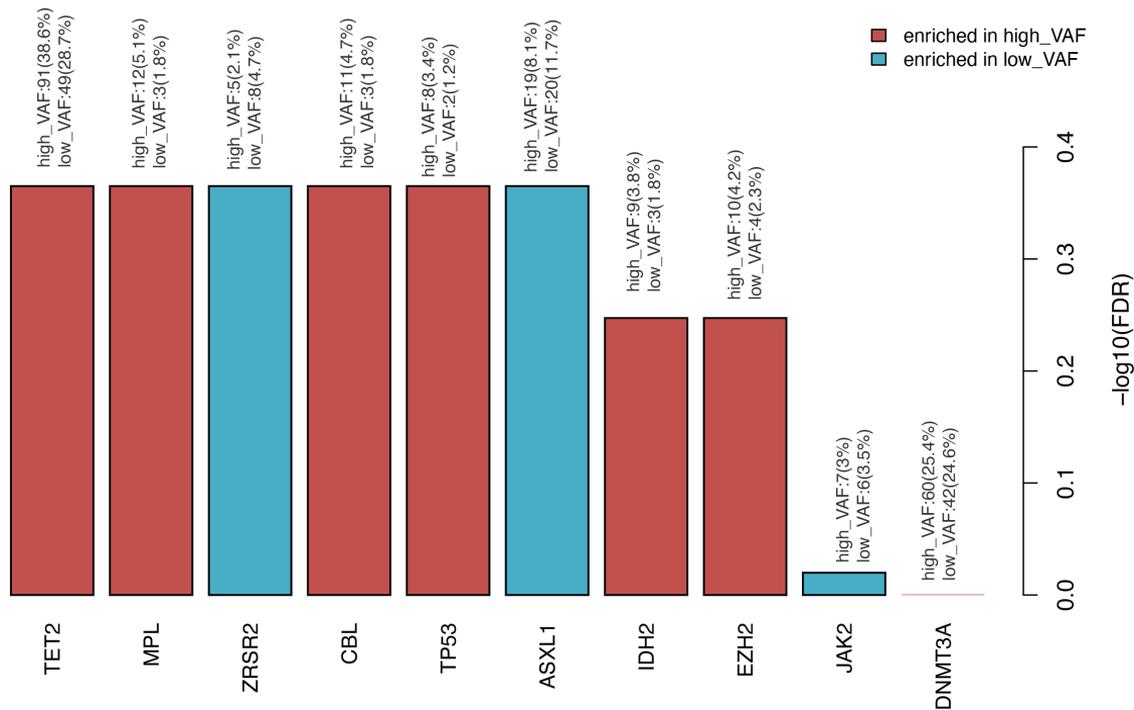
high_VAF	236	101	28	7	1
low_VAF	171	59	13	4	0



Number at risk

high_VAF	227	95	24	5	1
low_VAF	165	56	13	4	0

SF3B1 High vs Low VAF: co-mutations profile



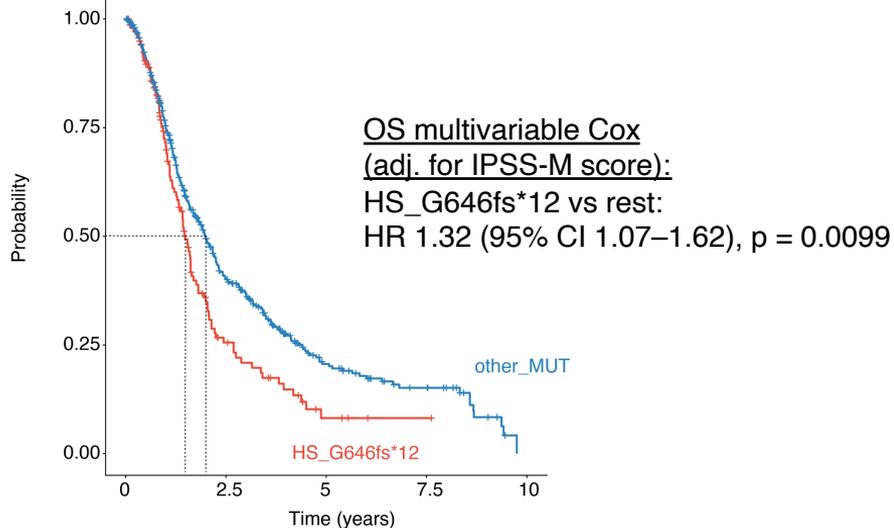
N(high_VAF)=236; N(low_VAF)=171; genes_tested=11
 FDR<0.05: 0 genes

TP53^{mut} features:
 5 mut LOF – 3 mut UND
 8 mutations IN-Domain
 14.1 VAF median
 No recurrent hotspot

ASXL1^{mut} features:
 9 mut GOF – 14 mut UND
 23 mutations OUT-Domain
 9.69 VAF median
 No recurrent hotspot

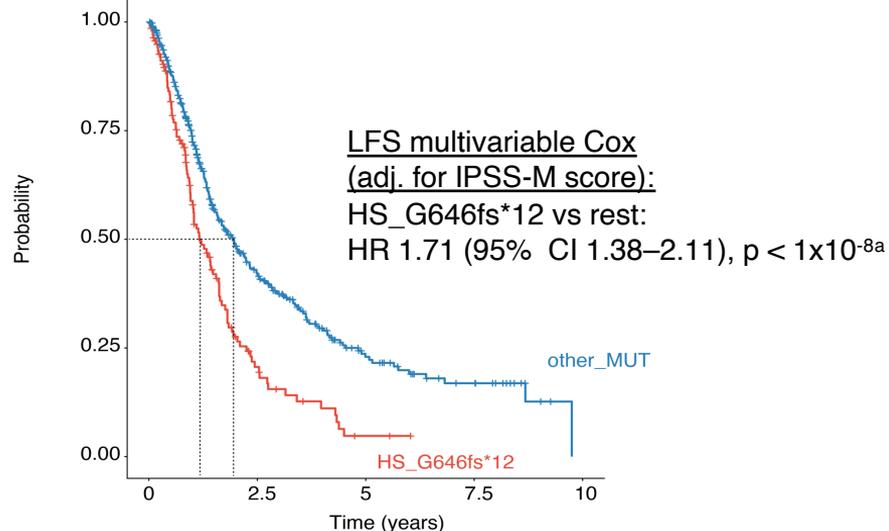
ASXL1 G646fs*12 predicts worse OS and LFS in Higher Risk MDS

ASXL1 G646FS*12 - OS in IPSS-M High category (binary)
 $p = 0.0022$



	0	2.5	5	7.5	10
Number at risk					
HS_G646fs*12	144	23	4	1	0
other_MUT	457	139	40	19	0

ASXL1 G646FS*12 - LFS in IPSS-M High category (binary)
 $p < 0.001$

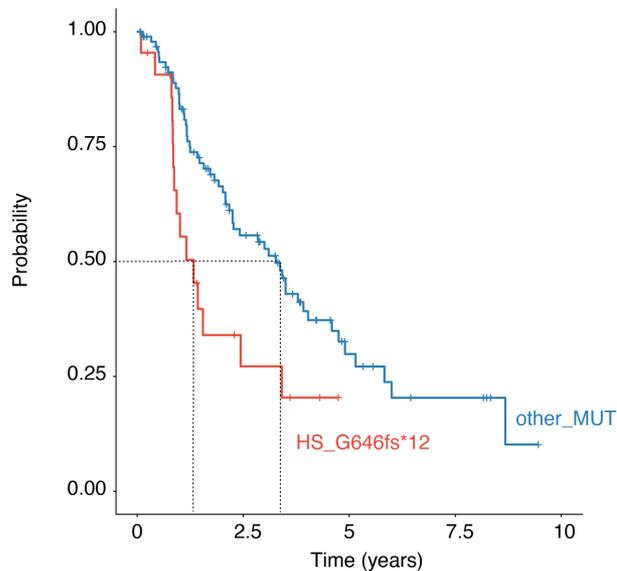


	0	2.5	5	7.5	10
Number at risk					
HS_G646fs*12	139	17	2	0	0
other_MUT	439	118	33	14	0



Within IPSS-M Mod. High category **ASXL1 G646fs*12 stratifies OS and LFS**

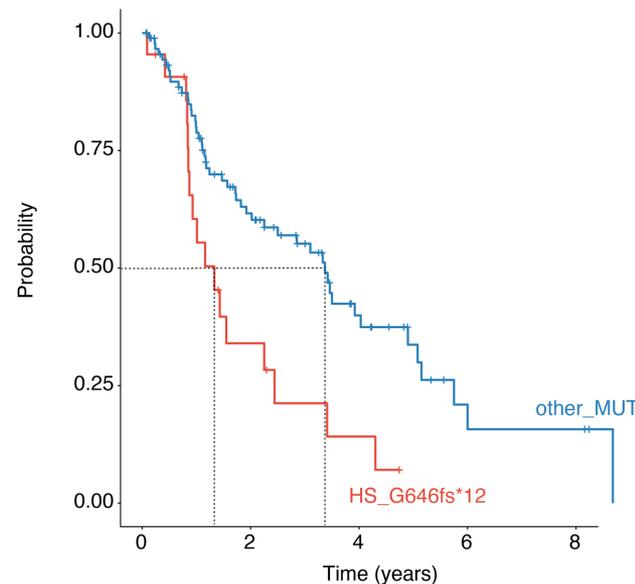
ASXL1 G646fs*12- OS in IPSS-M Moderate High category
p = 0.0139



Number at risk

HS_G646fs*12	22	4	0	0	0
other_MUT	98	41	11	5	0

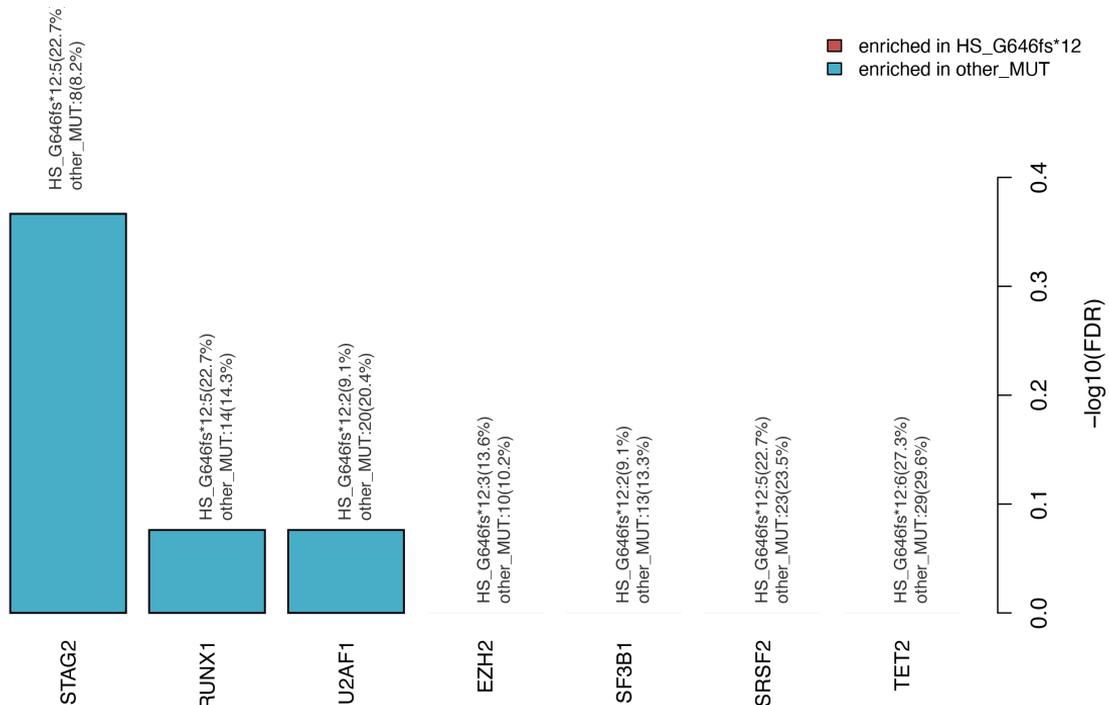
ASXL1 G646fs*12- LFS in IPSS-M Moderate High category
p = 0.003



Number at risk

HS_G646fs*12	22	6	2	0	0
other_MUT	94	44	16	4	3

ASXL1^{mut} G646fs*12: co-mutations profile



N(HS_G646fs*12)=22; N(other_MUT)=98; genes_tested=7;
FDR<0.05: 0 genes

Conclusion

- **IPSS-M score system can be improved implementing the Mutation Features**
 - > supporting a more precise, clinically actionable genomic refinement strategy intra-IPSS-M
- ***SF3B1* – Variant Allele Frequency Adds Risk Layering Within IPSS-M:**
 - > *SF3B1* VAF independently stratifies OS and LFS after IPSS-M adjustment and, critically, provides additional prognostic discrimination within the IPSS-M Low category.
- ***ASXL1* – G646fs*12 as an Independent Hotspot-Driven Risk Determinant**
 - >G646fs*12 hotspot confers independently worse OS and LFS and refines risk stratification within the IPSS-M Moderate High group.
- No relevant clinical differences have been observed.



MDS UNIT:

V. Santini, MD

G. Andreossi

C. Amato

B. Caciagli, PhD

E. Celoni

M.G. Raddi, MD

A. Consagra, MD

L. Rigodanza, MD

S. De Pourcq, PhD



UNIVERSITÀ
DEGLI STUDI
FIRENZE

Dipartimento di
Medicina Sperimentale
e Clinica



Azienda
Ospedaliero
Universitaria
Careggi

IRCCS-HUMANITAS Research Hospital:

M. Della Porta, MD

Giulia Maggioni, MD



Department of Hematologic

Oncology and Blood Disorders

J. Maciejewski, MD, PhD

