POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
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MDS: Biologia e prognosi

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DICHIARAZIONE

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Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **: NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **Diaceutics, Jazz, Astellas, Syros**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **Celgene, Novartis**
- Partecipazione ad Advisory Board: **Celgene/BMS, Syros**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**

Outline

- Application of
  - ✓ ICC and WHO classification
  - ✓ IPSS-M
- «Unfavourable» SF3B1 mutations
- TP53 mutations
- Germ-line predisposition

#463, A Product of "Clash of Titans" or True Reflection of Disease Biology? Validation of 2022 WHO and ICC Classifications in a Large Dataset of Patients with Myelodysplastic Syndrome

Morphology

MORPHOLOGY		WHO 2016	WHO 2022	ICC 2022
Ring Sideroblasts	RS ≥15%	MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD) and multi-lineage dysplasia (MDS-RS-MLD)	MDS with ring sideroblasts (**MDS-RS**): Low blast, *SF3B1* wild-type	No RS specific category
Number of Dysplastic Lineages	1 vs. >1	MDS with single lineage dysplasia (MDS-SLD) and multi-lineage dysplasia (MDS-MLD)	Dysplastic lineages are removed MDS with low blasts (**MDS-LB**): <5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (**MDS, NOS-SLD**) and multi-lineage dysplasia (**MDS, NOS-MLD**)
Blasts	5-9%	MDS with excess blasts-1 (MDS-EB1): 5-9% BM blasts	MDS with increased blasts-1 (**MDS-IB1**): 5-9% BM and/or 2-4% PB blasts	MDS with excess blasts (**MDS-EB**; 5-9% BM and/or 2-9% PB blasts or Auer rods)
	10-19%	MDS excess blasts-2 (MDS-EB2): 10-19% BM or PB blasts or Auer rods	MDS with increased blasts-2 (**MDS-IB2**): 10-19% BM or 5-19% PB blasts or Auer rods	**MDS/AML** (10-19% BM or PB blasts)
Added Subgroup	WHO	Not included	MDS, hypoplastic (**MDS-h**): Hypocellular marrow (age-adjusted)	Not included
		Not included	MDS with fibrosis (**MDS-f**): BM blasts 5-19%, PB blasts 2-19%; BM Fibrosis- grade ≥ 2	Not included
Removed		MDS unclassifiable	Not included	Not included

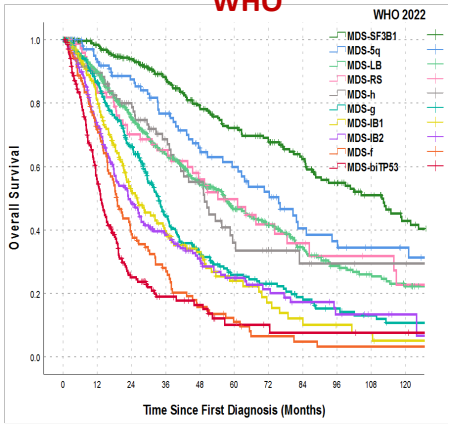
Genetics

GENETICS		WHO 2016	WHO 2022	ICC 2022
Common Genetically Defined Subgroups	*SF3B1*	No specific category	**MDS-*SF3B1***: MDS with low blasts (BM <5%, PB <2%) and *SF3B1* mutation - No del 5q, -7, complex karyotype - No *TP53, RUNX1, EZH2,* or *NPM1* mutations	**MDS-*SF3B1***: MDS with low blasts (BM <5%, PB <2%) and *SF3B1* mutation - *SF3B1* VAF ≥10% - No del 5q, -7, complex karyotype - No multi-hit *TP53* or *RUNX1* mutations
	5q	MDS with isolated del(5q)	**MDS-5q**: MDS with low blasts and isolated del 5q	**MDS del(5q)**: MDS with isolated Del 5q or with 1 other cytogenetic abnormality except -7/del(7)
	TP53 mutation (supersedes all other MDS categories)	Not included	**MDS-bi*TP53***: MDS with biallelic *TP53* inactivation - ≥2 *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH	**MDS with mutated *TP53*** **MDS/AML with mutated *TP53*** - MDS (blast <10%): Criteria same as WHO or, 1 *TP53* mutation plus complex karyotype - MDS/AML (blast 10-19%): Any *TP53* mutation (VAF ≥10%)
Other genetic Subgroups	MDS-related gene mutations and cytogenetic abnormalities	Not included	**MDS with low or excess blasts with other defined gene alterations**	**MDS/AML with myelodysplasia related gene mutations** **MDS/AML with myelodysplasia related cytogenetic abnormalities**

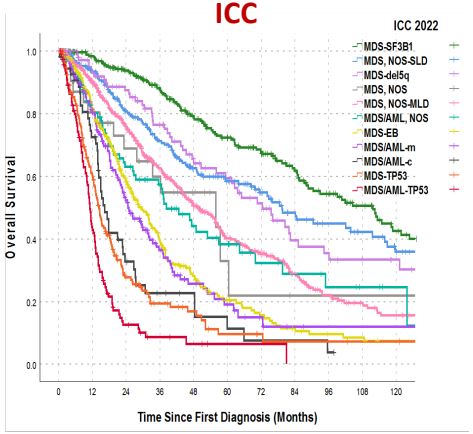
Courtesy of Ball et al, Abs 463

❖ 2231 molecularly annotated pts with MDS. Median duration of follow up: 60.2 months (Moffitt Cancer Ctr)

WHO

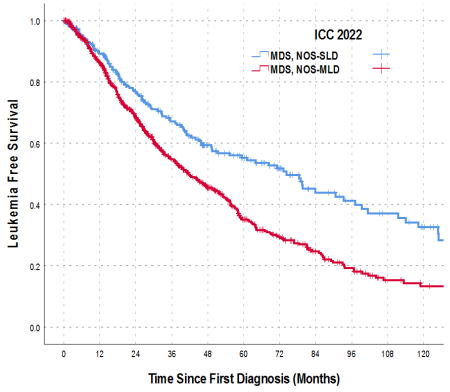


ICC



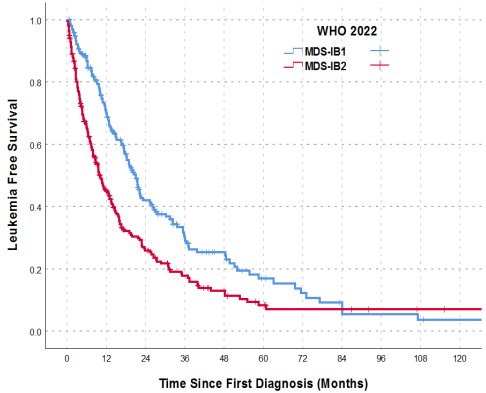
ICC

Single vs multilineage dysplasia



WHO: Increased blasts

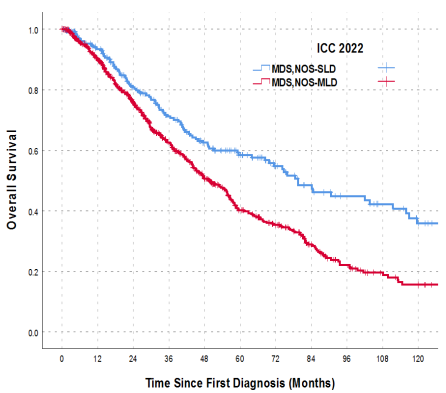
5-9% vs 10-19%

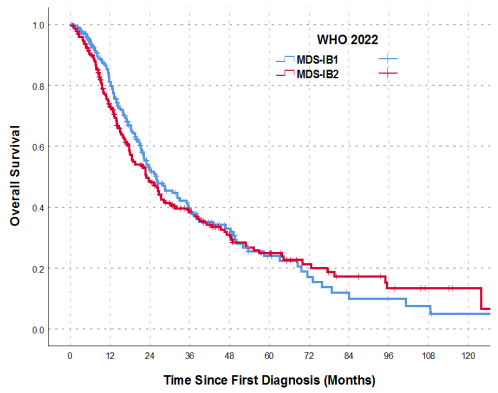


Subgroups	No. (%)	mLFS	mOS
Overall	2231 (100%)	30.9 mo	40.9 mo
MDS-*SF3B1*	276 (12%)	109.4 mo	111.6 mo
MDS-5q	110 (5%)	62.9 mo	75.6 mo
MDS-LB	595 (27%)	47.8 mo	56.8 mo
MDS-RS	82 (4%)	50.5 mo	54.3 mo
MDS-h	98 (4%)	42.3 mo	49.6 mo
MDS-g *	325 (15%)	22.1 mo	33.3 mo
MDS-IB1	193 (9%)	21.0 mo	25.9 mo
MDS-IB2	224 (10%)	10.0 mo	22.9 mo
MDS-f	118 (5%)	13.7 mo	18.9 mo
MDS-bi*TP53*	210 (9%)	10.0 mo	13.2 mo

* Low or increased blasts with *RUNX1*, *IDH1/2*, Cohesin complex mutations, *SF3B1* with blast ≥5%; [LFS- Leukemia free survival, OS- Overall survival]

Subgroups	No. (%)	mLFS	mOS
Overall	2202 (100%)	31.6 mo	41.2 mo
MDS-*SF3B1*	275 (13%)	105.7 mo	111.6 mo
MDS, NOS-SLD	248 (11%)	74.2 mo	79.4 mo
MDS-del5q	110 (5%)	62.9 mo	75.6 mo
MDS, NOS	32 (1%)	55.8 mo	55.8 mo
MDS, NOS-MLD	606 (27%)	41.5 mo	49.6 mo
MDS/AML, NOS	83 (4%)	14.0 mo	38.4 mo
MDS-EB	324 (15%)	21.0 mo	29.4 mo
MDS/AML with MDS-Related Mutations	163 (7%)	11.5 mo	24.7 mo
MDS/AML with MDS-Related Cytogenetic Abnormalities	55 (3%)	11.2 mo	16.3 mo
MDS-m*TP53*	191 (9%)	11.5 mo	14.5 mo
MDS/AML-m*TP53*	115 (5%)	6.4 mo	11 mo





Courtesy of Ball et al, Abs 463

CONCLUSIONS

Variables	LFS		OS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Number of Dysplastic Lineages	**1.73** (1.35-2.21)	**<0.001**	**1.68** (1.31-2.16)	**<0.001**
Blast Count Category*	1.46 (0.53-3.99)	0.453	1.39 (0.51-3.80)	0.514
BM Fibrosis Grade	1.11 (0.98-1.26)	0.086	**1.14** (1.00-1.30)	**0.038**
SF3B1 Mutation	**0.57** (0.44-0.74)	**<0.001**	**0.59** (0.46-0.77)	**<0.001**
Multi-hit *TP53***	**3.09** (2.06-4.61)	**<0.001**	**3.39** (2.25-5.12)	**<0.001**

* Blast <5% vs. 5-9% vs. ≥ 10%
** *TP53*-VAF ≥ 50% or, ≥ 2 *TP53* mutations (VAF > 10% each) or, 1 *TP53* mutation plus loss of 17p (by Karyotyping or FISH)

- Both WHO and ICC classification systems for MDS has room for improvement
- Molecularly defined entities (*SF3B1*, deletion 5q, and "multi-hit" *TP53*) are clearly unique
- *TP53* mutation predicted most dismal LFS and OS in both WHO and ICC systems, and "multi-hit *TP53* state" remained independent predictor of survival

Favours

⇨ **WHO**

- Survival of MDS-RS (*SF3B1*-WT) was similar to MDS-LB, and MDS-MLD had worse outcomes than MDS-SLD

⇨ **ICC**

- Blast ≥5% correlated better with OS than ≥10%; however, precise blast cut-off needs to be further examined
- Grade 2/3 fibrosis was associated with worse OS in MDS-IB group, and was independent predictor of OS

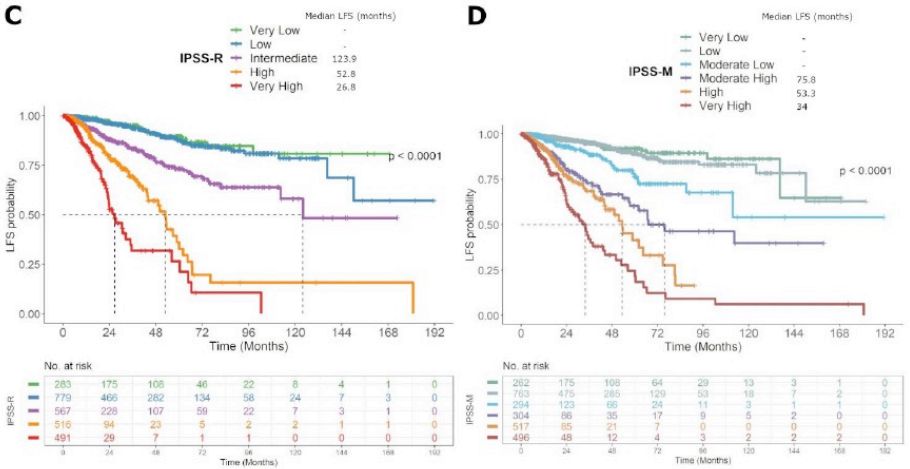
⇨ **WHO**

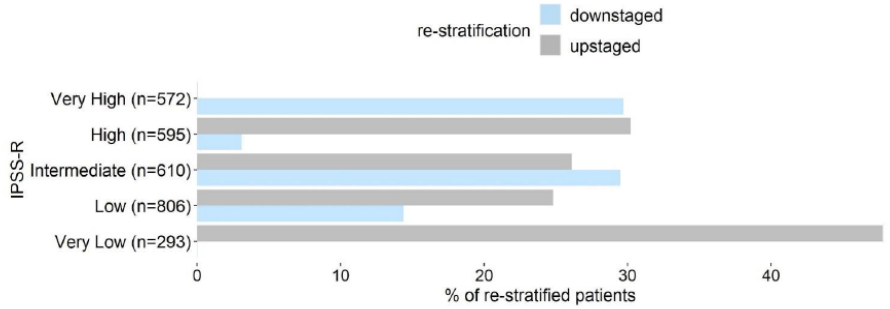
- Future validation in multicenter dataset (VALIDATE) is planned to support our findings

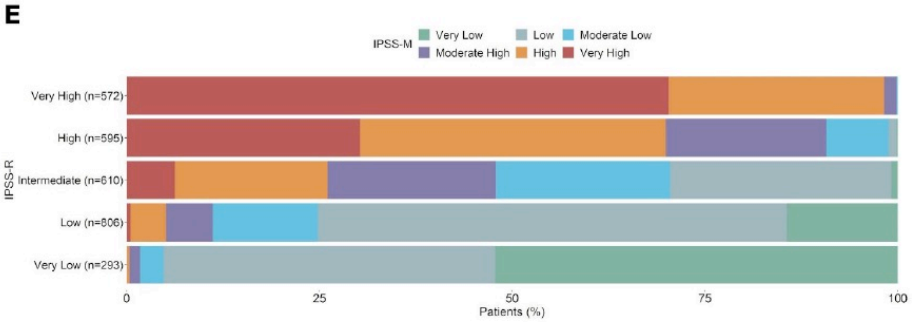
Courtesy of Ball et al, Abs 463

#464, Real-World Validation of Molecular International Prognostic Scoring System (IPSS-M) for Myelodysplastic Syndromes

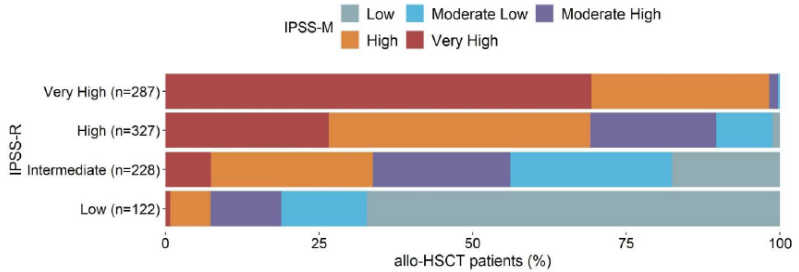
n=2876 pts







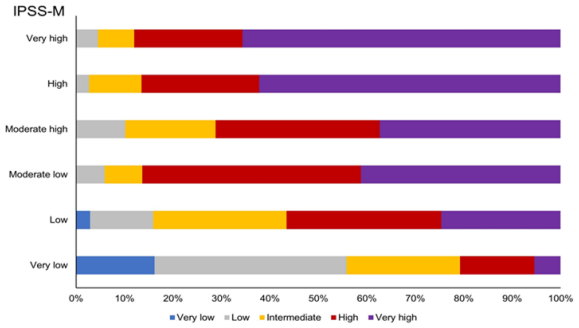
HSCT, n=964 pts

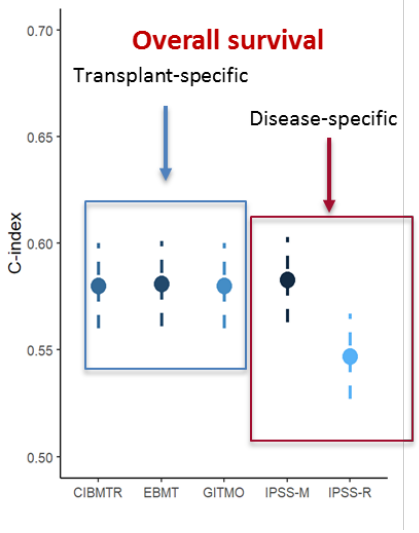


Sauta E, Abs 464
and J Clin Oncol, in press

#4762, Allogeneic stem cell transplant for myelodysplastic syndrome in the new molecular era of IPSS-M

- 416 patients with MDS, HSCT between 1998 and 2021
- Compared to IPSS-R, the incorporation of molecular information led to a significant re-stratification of patients (*P*<0.001)
- About 30% of patients previously assigned to IPSS-R intermediate risk group were upstaged to higher risk categories
- At least 57% of cases carried IPSS-M molecular markers

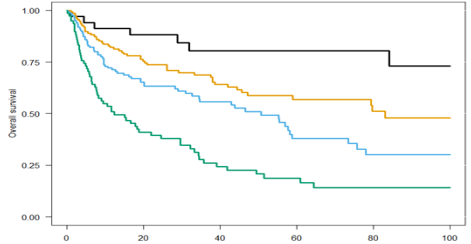




Combined clinical-molecular MDS transplant model

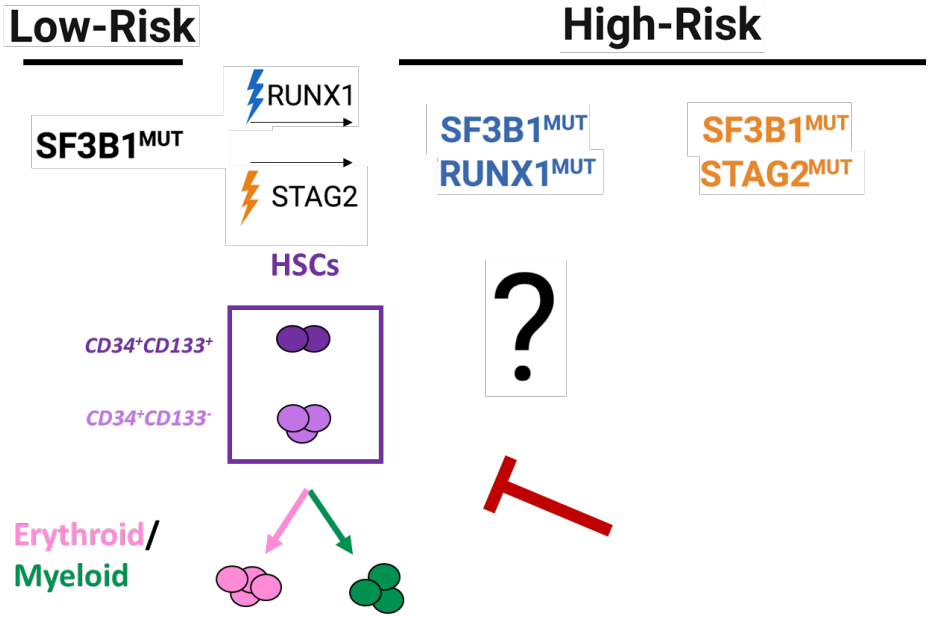
Factor	Hazard ratio	95% confidence interval	*P*	Score
Age				
≤50	Reference			
>50	1.342	1.06-1.65	0.01	1
Performance status				
90-100	Reference			
<90	1.55	1.15-2.10	0.004	1
Monosomal karyotype				
Absent	Reference			
Present	2.34	1.61-3.40	<0.001	2
***TP53* mutations**				
Absent	Reference			
Present	2.41	1.66-3.51	<0.001	2

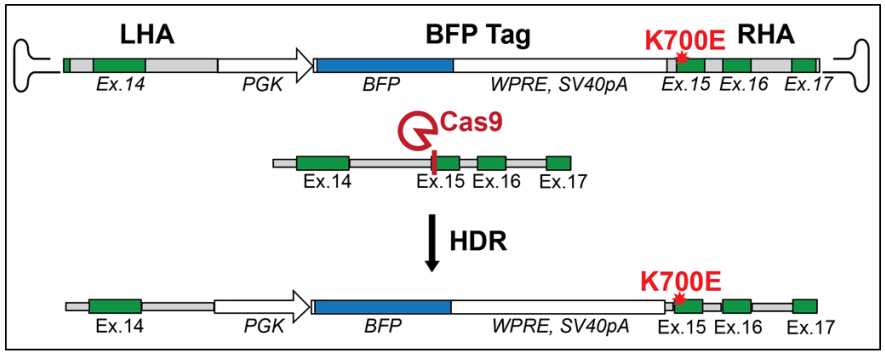
4 risk-groups



Gurnari C, Abs 4762, & Leukemia, in press.

#86, Clonal Trajectories and Therapeutic Targeting of High-Risk SF3B1-Mutant Myelodysplastic Syndrome





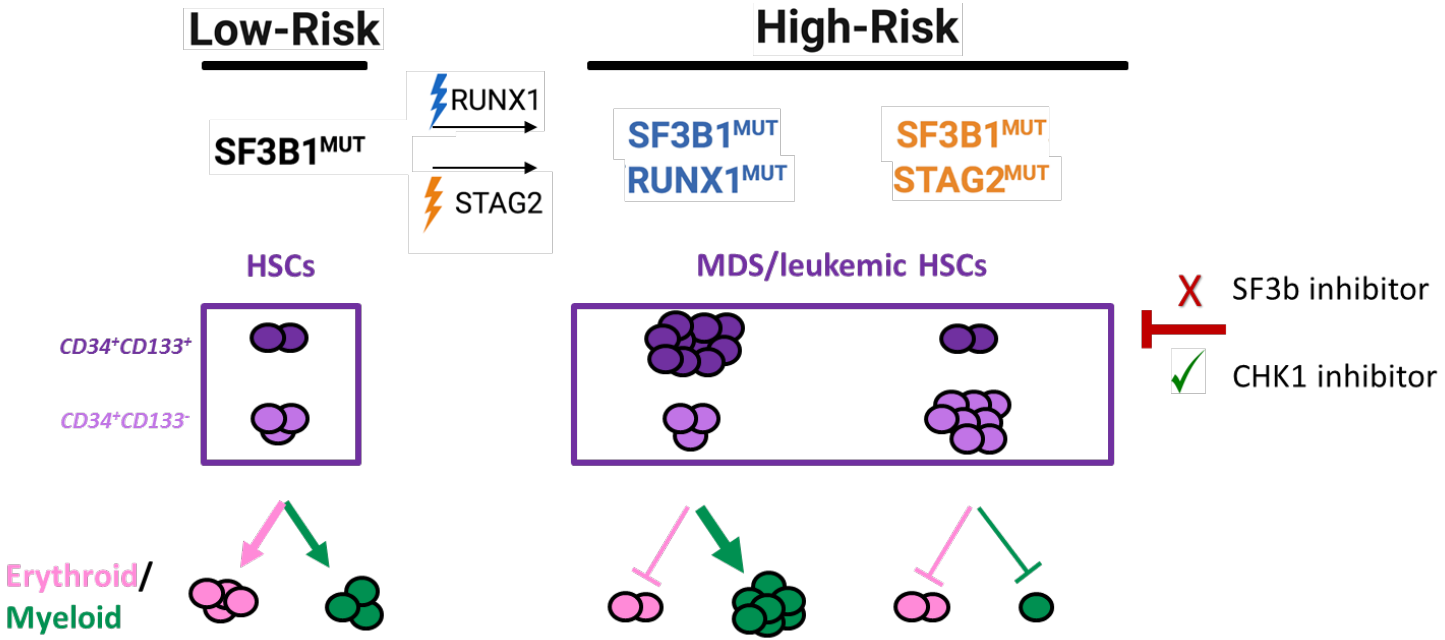
SF3B1^{K700E} knock-in

+

AAVS1 (S-A) or RUNX1 (S-R) or STAG2 (S-S)

Courtesy of Sarchi M et al, Abs 86

Conclusions



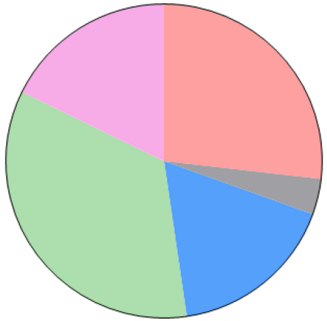
- Secondary RUNX1 expression promoted myeloid skewing at the expense of the erythroid lineage
- Secondary STAG2 expression induced a block in differentiation, impairing both myeloid and erythroid differentiation
- Response to SF3b inhibitors decreased

Created with BioRender.com

Courtesy of Sarchi M et al, Abs 86

#857, A Clinically Practicable Approach to Predict TP53 Allelic Configurations in Myeloid Neoplasia

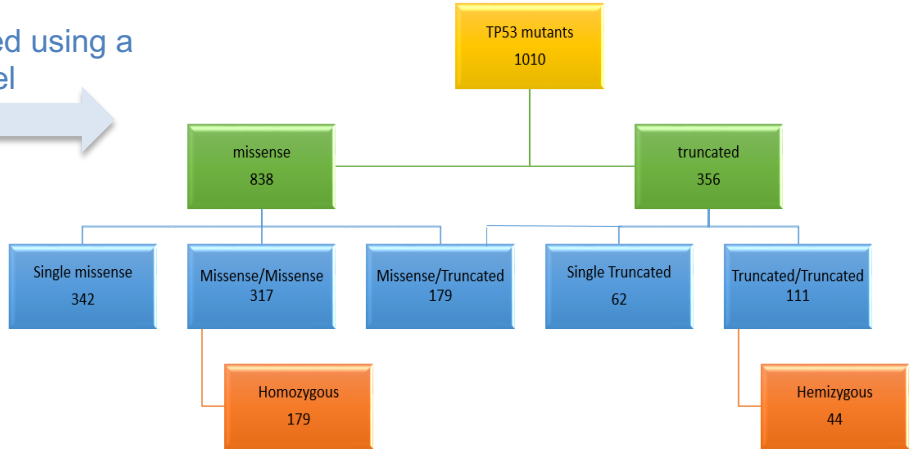
Study population



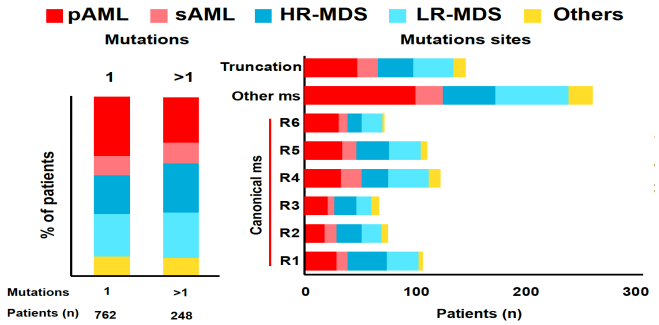
1985 pAML
272 sAML
1273 HR-MDS
2558 LR-MDS
1312 MDS/MPN

7400 patients

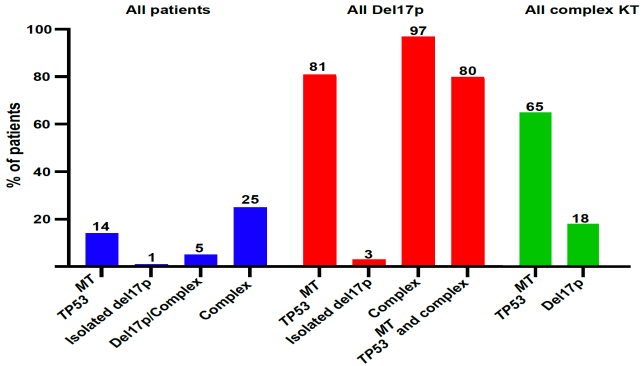
NGS performed using a 56 genes panel



Frequencies of single and and multiple *TP53* mutations and canonical missense locations



Cytogenetics abnormalities in relation to the TP53 mutational status.



Bahaj et al, Abs 857

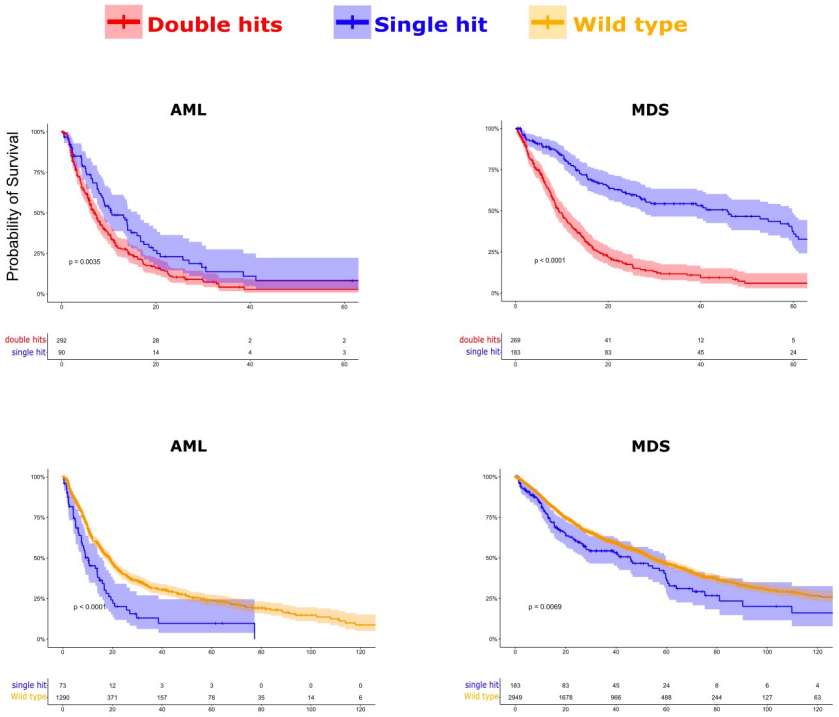
Clinical outcome of patients with *TP53* mutations

Irrespective of **configuration** (missense vs truncated or canonical vs non-canonical), *TP53*^{MT} carriers had worse overall survival (OS) compared to *TP53*^{WT} 95%CI 2.53-3.02]).

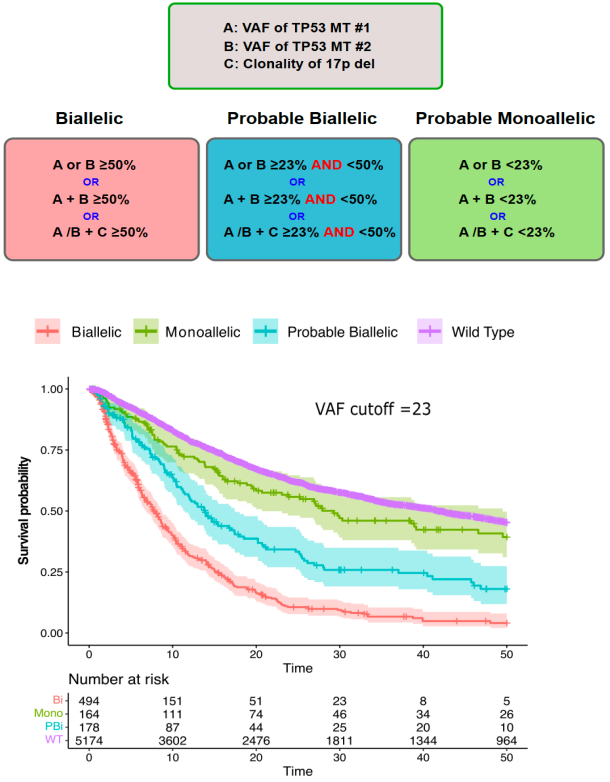
♦ Single *TP53* hit
- one *TP53* mutation
- Isolated 17p deletion

♦ Double *TP53* hits *TP53*^{MT} and:
- Another *TP53*^{MT} or
- 17p deletion or
- *TP53* locus UPD

Classical definition

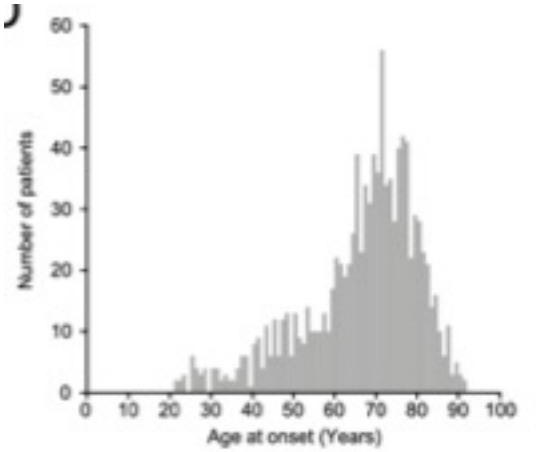


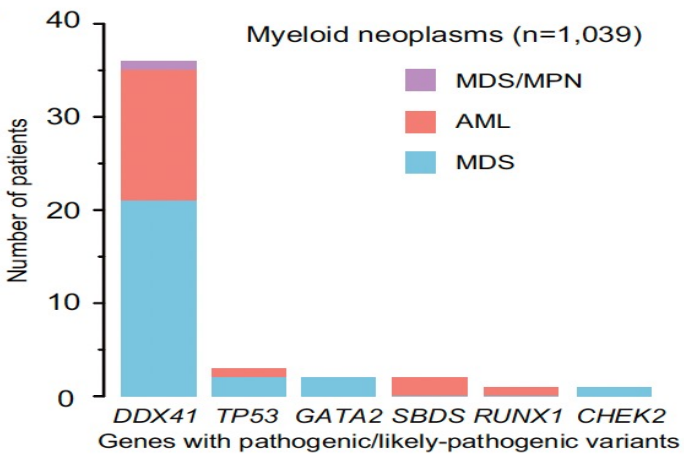
Novel algorythm

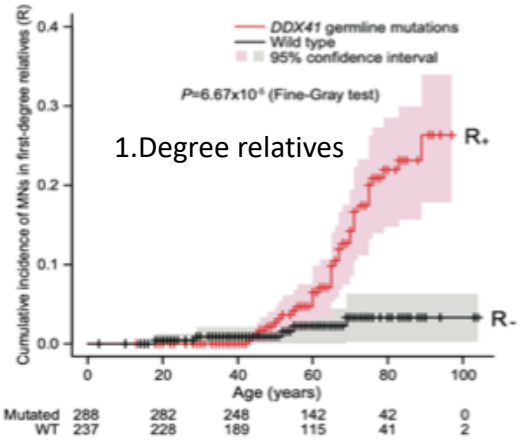


#85, Germline Risks and Clinical Impacts of DDX41 Mutations in Myeloid Malignancies

- 346 DDX41 mutations in 9082 pts
- **DDX41** germline mutations explain **~80% of known germline predisposition** to MNs in adults, and the life-long risk was approximately 50%.
- 10-fold more enriched in Japanese MN cases compared to a Japanese general population, particularly males (20.7 vs 5)
- DDX41-mutated MDS patients rapidly progressed to AML, but only those with **truncating variants**.
- **Co-mutation patterns** at diagnosis and at progression to AML were different between DDX41-mutated and -WT cases, where none of the co- mutations affected clinical outcomes.
- **Negative effect of TP53 mutations**, including multi-hit allelic status on survival, was almost completely mitigated by the presence of DDX41 mutations







Makishima H, Abs 85 and Blood 2022

Conclusions

- 2022 WHO and ICC classifications of MDS need extensive validation, and hopefully harmonization
- The IPSS-M risk score efficiently stratify patients with MDS also in the context of HSCT
- Double-hit TP53 and/or a VAF cut-off of 23% may identify pts with unfavourable MDS/AML subtypes
- DDX41 mutations are frequent in MDS (~5% of cases) and 1. degree relatives of germ-line carriers have a significantly increased risk of developing a MN at older ages