A Classification of Myelodysplastic Syndromes That Aids Clinical Decision-Making

Mario Cazzola, MD

Fondazione IRCCS Policlinico San Matteo

& University of Pavia, Pavia, Italy

Disclosures

- No potential conflict of interest to disclose
- No discussion of off-label uses

Classification is the Language of Medicine

- Classification is the language of medicine: diseases must be described, defined, and named before they can be diagnosed, treated, and studied

Cazzola. Blood. 2016 May 19;127(20):2361-4

The Classification Schism in Hematopathology

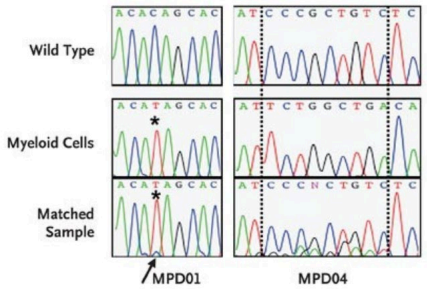
2022:

- International Consensus Classification
- WHO-5

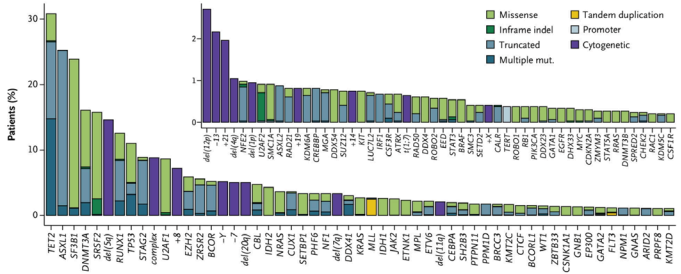
Aster. J Clin Oncol. 2023 Mar 10;41(8):1523-1526

The Molecular Revolution in MDS

2009: Somatic mutation of TET2 in myeloid malignancies (NEJM. 2009;360:2289-3019)

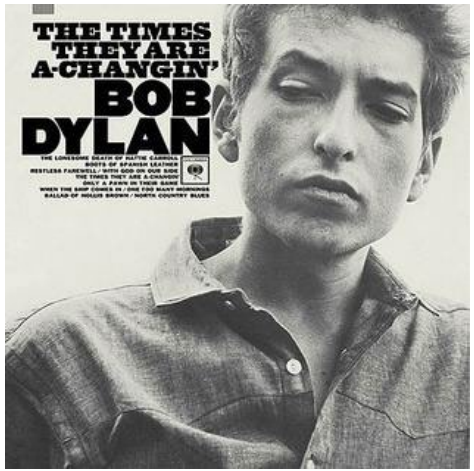


2022: Genomic landscape of MDS (NEJM Evid 2022;1:7)



9254 oncogenic mutations across 121 genes

The Impact of Next-Generation Sequencing on Diagnosis, Classification, and Prognostication of Myeloid Malignancies



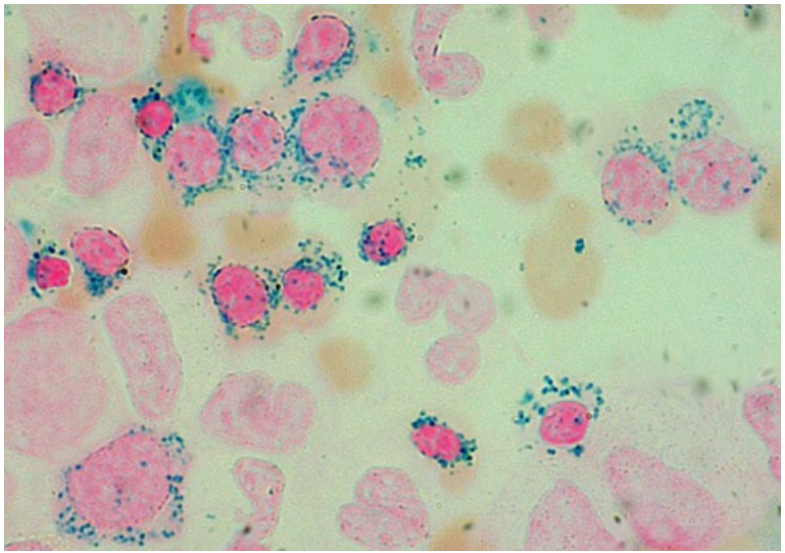
Conservatives (*morphology*)

vs

Progressives (*genomics*)

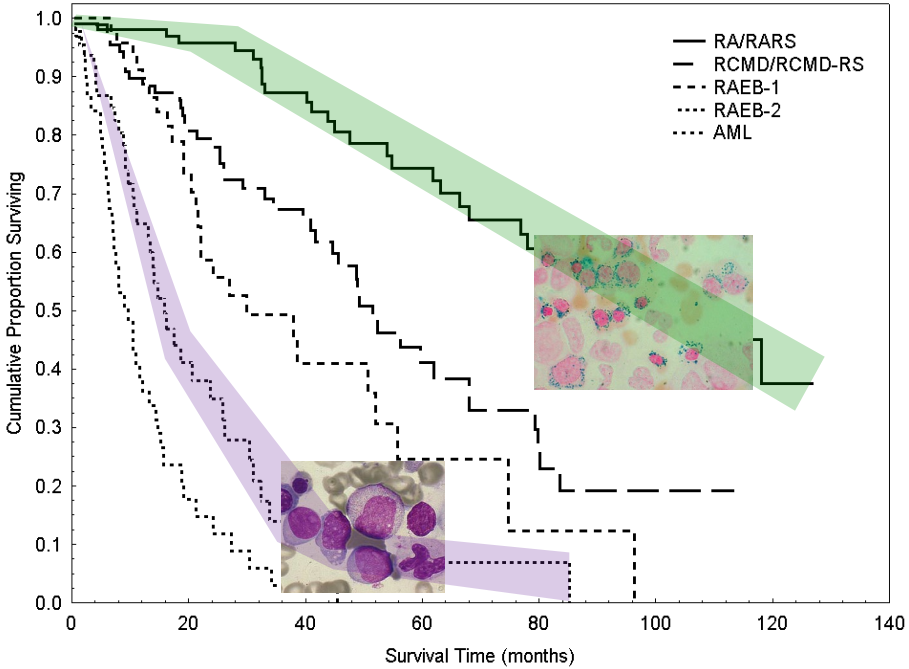
Gurbuxani et al. Am Soc Clin Oncol Educ Book. 2023 Jun;43:e390026

MDS with Ring Sideroblasts



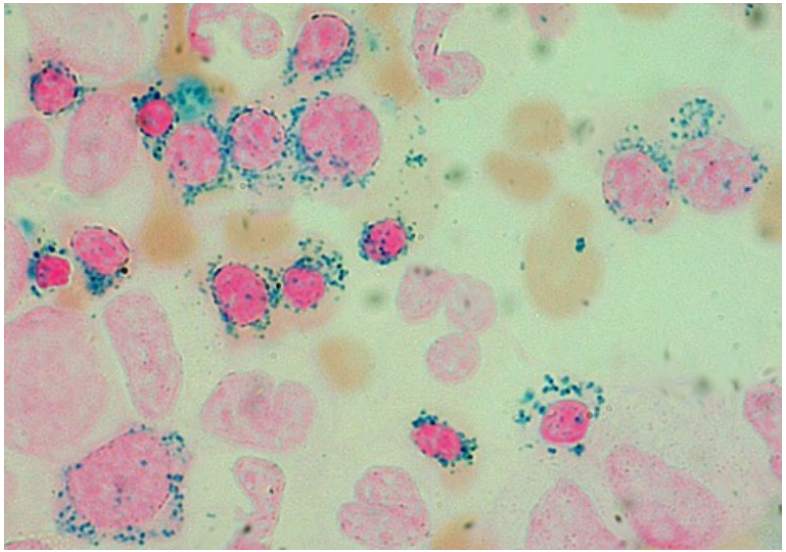
Bennett et al. Br J Haematol. 1982 Jun;51(2):189-99

MDS with Ring Sideroblasts: Prognostic Relevance of Morphology



Malcovati et al. J Clin Oncol. 2005 Oct 20;23(30):7594-603

Myelodysplastic Syndrome with Ring Sideroblasts

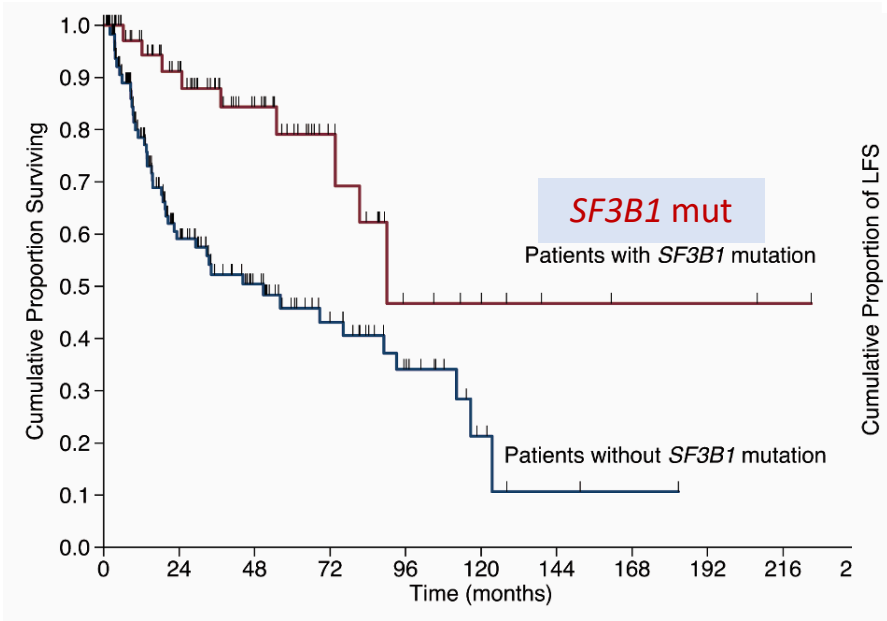


→ *SF3B1* mut

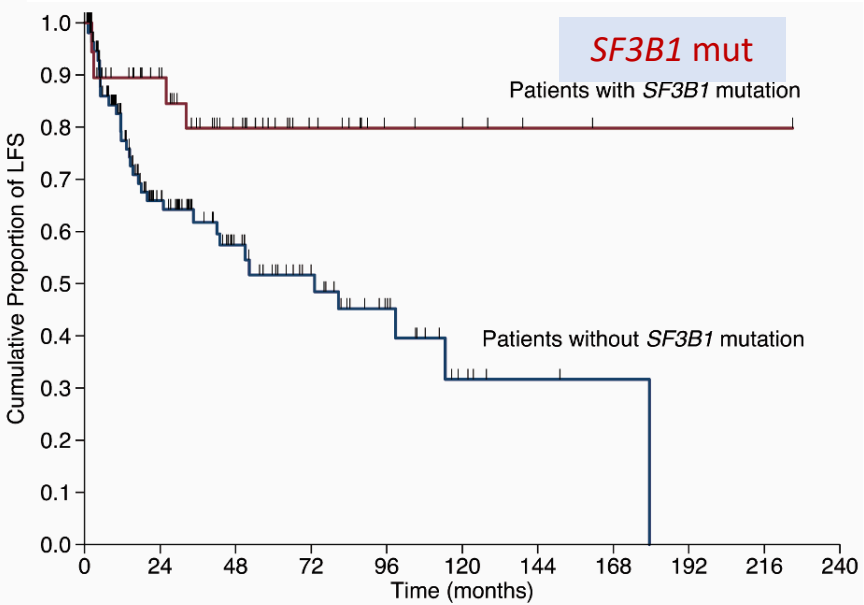
Papaemmanuil et al. N Engl J Med. 2011 Oct 13;365(15):1384-95

Clinical Significance of *SF3B1* Mutation in MDS

Overall survival

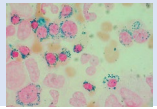


Leukemia-free survival

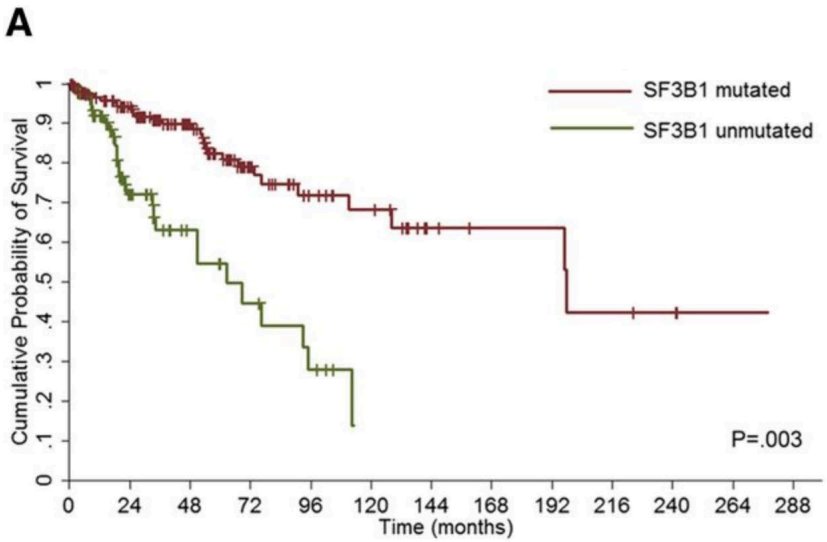


Malcovati et al. Blood. 2011 Dec 8;118(24):6239-46

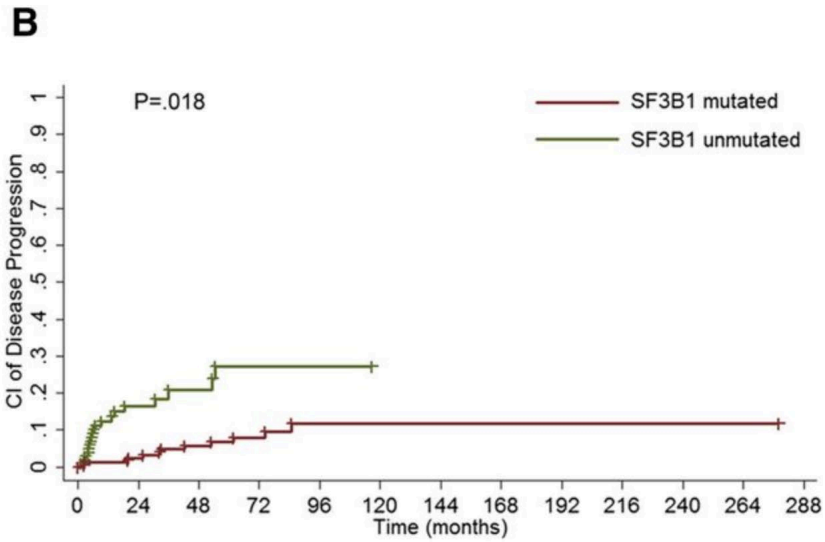
Clinical Significance of *SF3B1* Mutation in MDS with Ring Sideroblasts



Overall survival

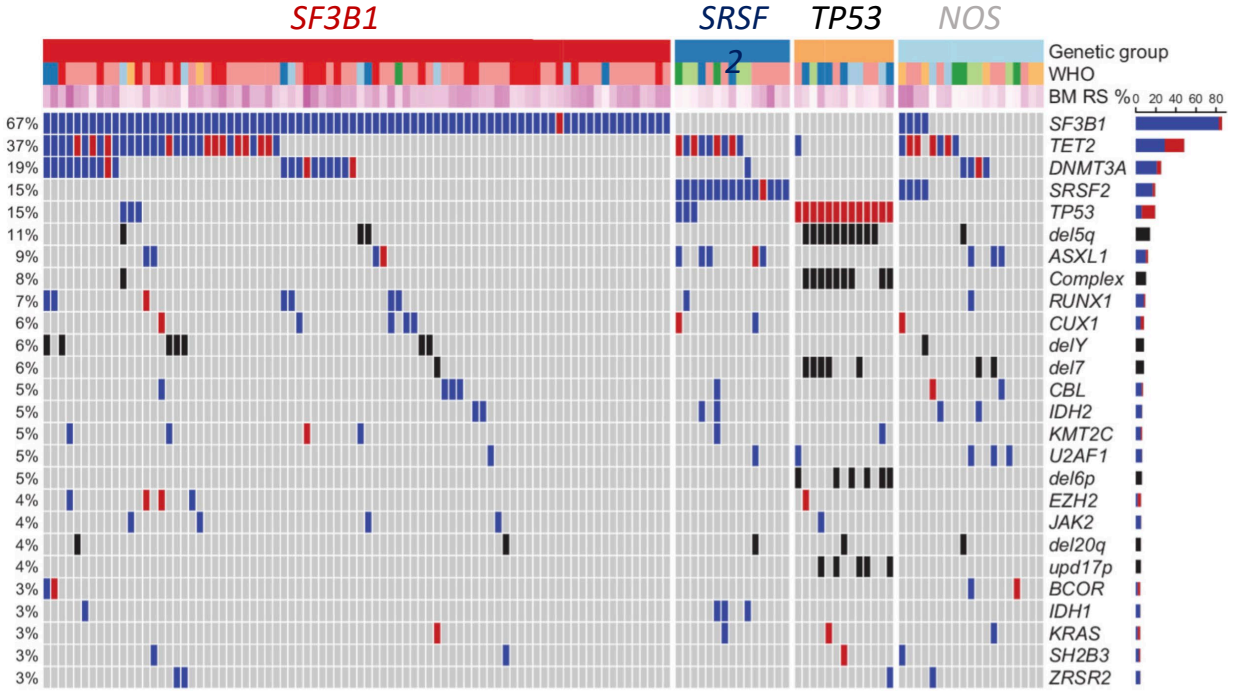


Leukemia-free survival



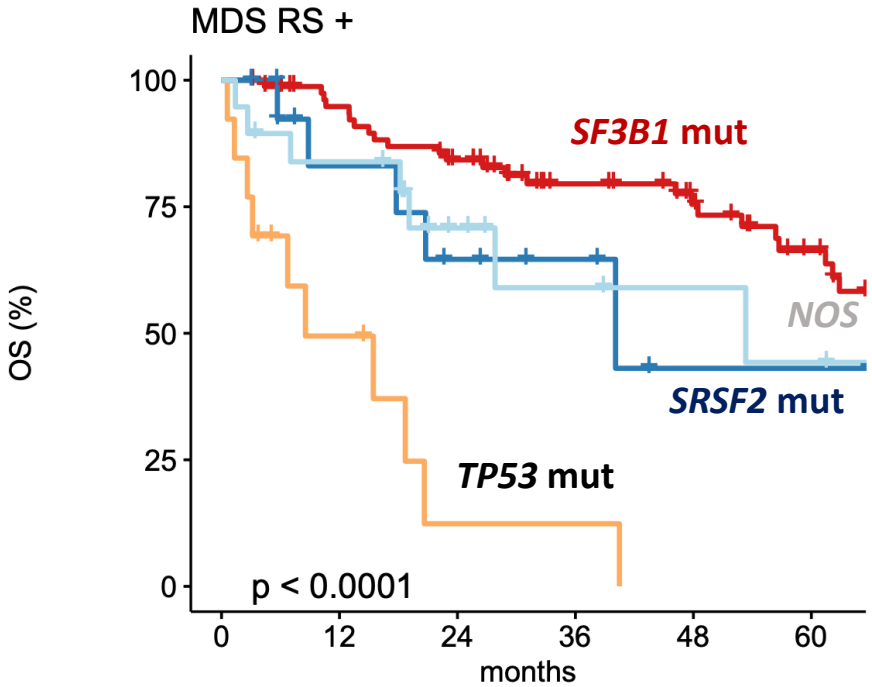
Malcovati et al Blood. 2015 Jul 9;126(2):233-41

Mutational Landscape of MDS with Ring Sideroblasts



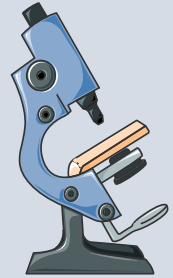
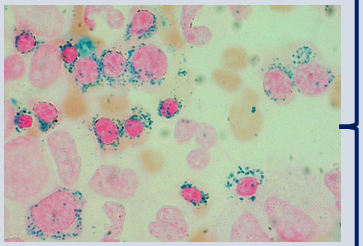
Todisco et al. Clin Cancer Res. 2023 Oct 13;29(20):4256-4267

Mutational Landscape of MDS with Ring Sideroblasts: Clinical Correlates



Todisco et al. Clin Cancer Res. 2023 Oct 13;29(20):4256-4267

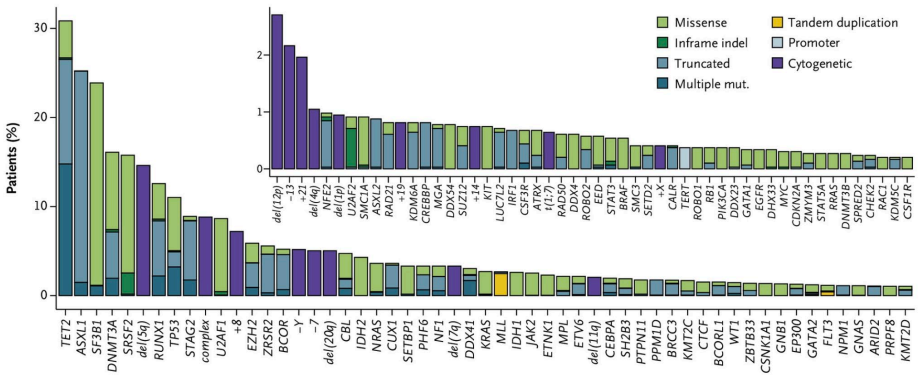
Genomic Subtypes of MDS with Ring Sideroblasts

Morphology	Genomic profiling	
  Myelodysplastic syndrome with ring sideroblasts (MDS subtype with a relatively indolent clinical course)	**Somatic mutation in *SF3B1* (~80% of MDS patients with ring sideroblasts)**	**A benign disorder mainly characterized by ineffective erythropoiesis and isolated anemia, with a low risk of leukemic transformation**
	Somatic mutation in *SRSF2*	**A subtype of MDS with ring sideroblasts with poor prognosis**
	Somatic mutation in *TP53* (multi-hit state)	**A subgroup of MDS with ring sideroblasts with very poor outcomes**
	No otherwise specified	**A heterogeneous subgroup of MDS patients with ring sideroblasts**

Molecular Taxonomy of MDS and Its Clinical Implications

- 3,233 treatment-naive patients with MDS or related neoplasms

- Gene mutations, CNAs, and cnLOH events were derived from targeted capture DNA sequencing of a 152-gene panel enriched with genome-wide CNA probes



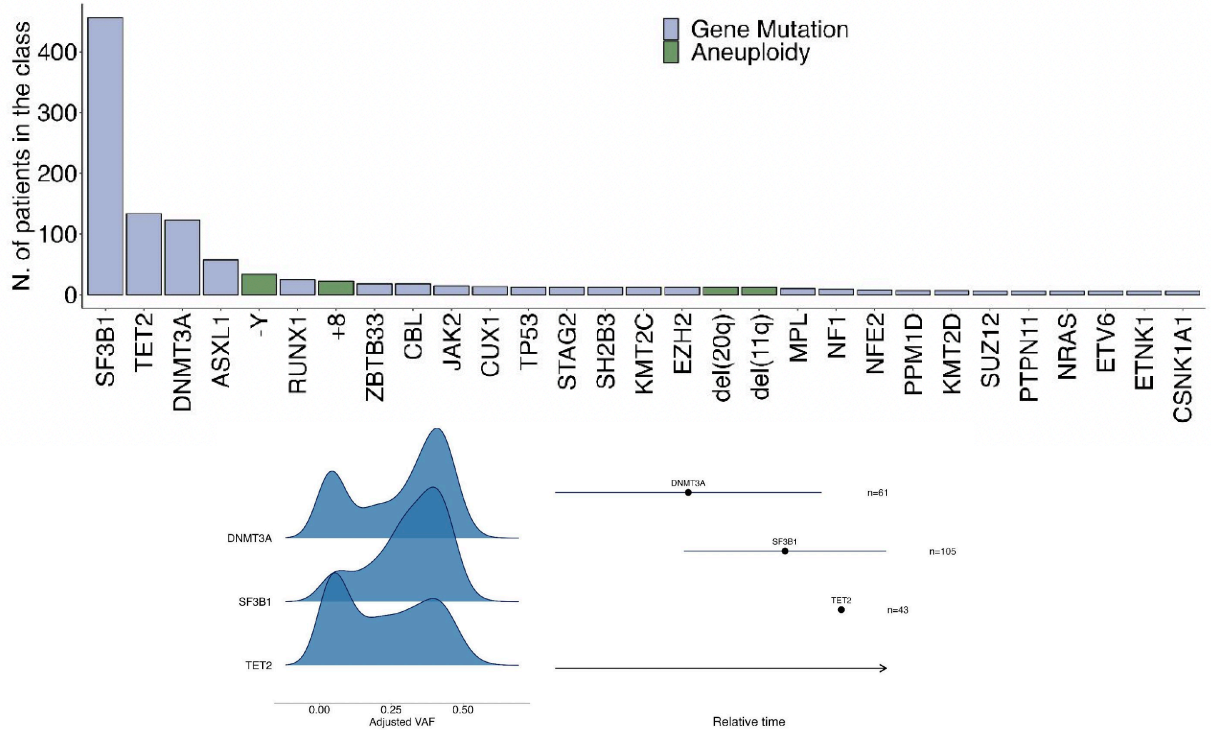
Bernard et al. 2023

Molecular Taxonomy of MDS and Its Clinical Implications

Molecular subgroup	Median overall survival (years)	Risk of leukemic transformation	Clinical implications
MDS with no recurrent genetic event	>8	Very low	Non clonal disorder
SF3B1-mutant MDS	>5	Low	Ring sideroblasts, anemia responsive to luspatercept
ZRSR2-mutant MDS	>5	Low	Male patients
Molecularly NOS MDS	>4	Low	
CCUS-like MDS	>4	Low	Cytopenia related to clonal hematopoiesis
MDS with del(5q)	>4	Low	Responsive to lenalidomide
MDS with biallelic *TET2* mutation	>4	Low	
DDX41-mutant MDS	2-4	High	Potential germline predisposition
U2AF1-mutant MDS (37)	2-4	High	
U2AF1-mutant MDS (154)	2-4	High	
SRSF2-mutant MDS	2-4	High	
BCOR/L1-mutant MDS	2-4	High	
IDH-STAG2-mutant MDS	0-2	High	
MDS with t(1;7)	0-2	High	
-7/*SETBP1*-mutant MDS	0-2	High	
EZH2-ASXL1-mutant MDS	0-2	High	
AML-like MDS	0-2	Very high	
TP53-complex MDS	0-2	Very high	Poorly responsive to any currently available treatment

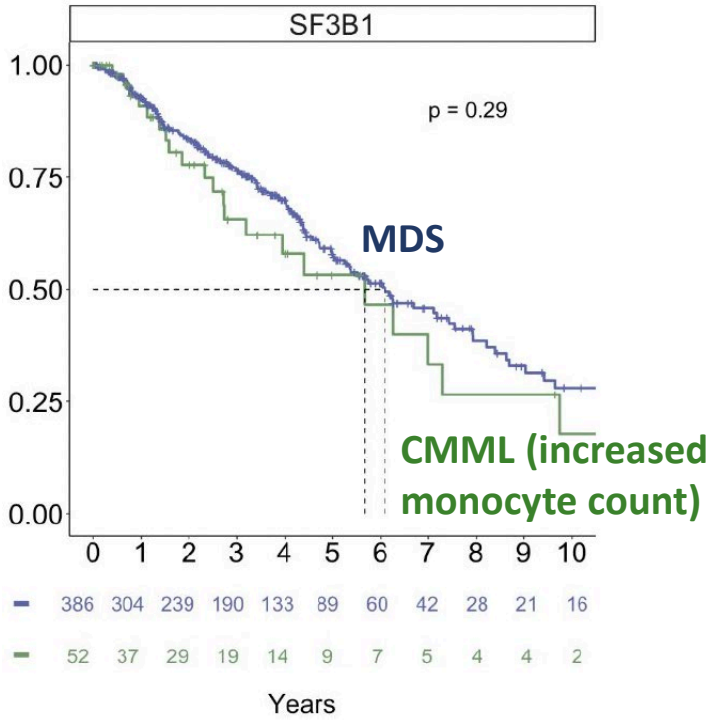
Bernard et al. 2023

SF3B1-Mutant MDS



Bernard et al. 2023

SF3B1-Mutant Myeloid Neoplasms



Bernard et al. 2023

Conclusions

- Genomic profiling allows the identification of MDS molecular subgroups associated with distinct clinical phenotypes and outcomes.

- Developing a classification of MDS based on genomic classes may significantly benefit clinical decision-making.