Myelodysplastic syndromes:
chaos and order

Prognostic factors in MDS

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Prognosis linked to treatment

- Age, comorbidites, cytogenetics (genetics) and blasts, as well as the patient's voice, guide treatment; **prognostic scores may be useful**[1,2]
- **Cytopenias** impact quality of life and may contribute to a worse prognosis[3]
- **Progression** is associated with mortality[4]
  - An ideal treatment must improve survival
- Most drug agencies have approved drugs according to IPSS prognostic scoring
    - *Some IPSS Intermediate-1 risk patients are high risk according to revised IPSS*

1. Greenberg P, et al. NCCN Guidelines on Myelodysplastic Syndromes V.2.2015;
2. Greenberg P, et al. Blood 2012;120:2454–65;
3. Steensma, DP, et al. Leuk. Res 2008;32:691–8;
4. Malcovati L, et al. Haematologica 2011;96:1433–40

International Prognostic Scoring System - IPSS

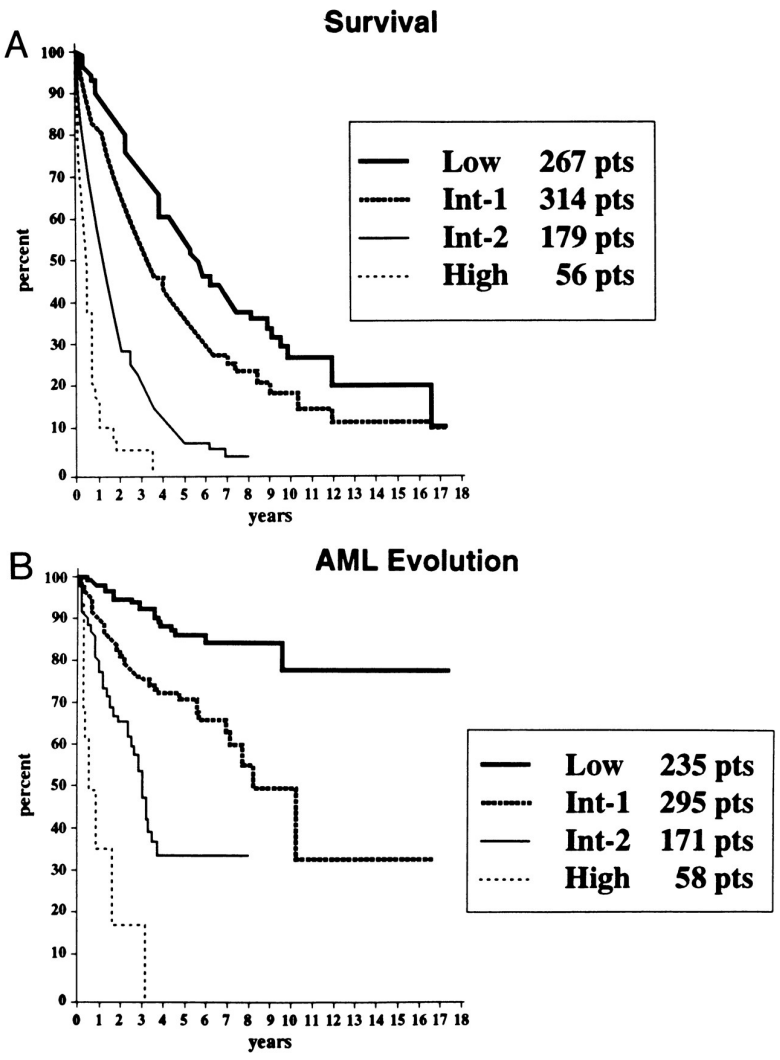
Variable	0	0.5	1	1.5	2
BM blasts %	<5	5-10	-	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias°	0/1	2/3			

**Good*: normal, -Y, del(5q), del(20q); *Poor*: complex, chromosome 7 anomalies; *Intermediate*: other abnormalities.

°Hemoglobin < 10 g/dL, absolute neutrophil count < 1,500/μL, platelet count < 100,000/μL.

Scores for risk groups are as follows:

Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, 2.



Greenberg P, et al *Blood 1997;89:2079-2088*

Revised International Prognostic Scoring System (IPSS-R)

IPSS-R Risk category	Risk score	Median Survival (yrs)	AML/25%
Very low	≤ 1.5	8.8 (7.8-9.9)	NR (14.5-NR)
Low	> 1.5–3	5.3 (5.1-5.7)	10.8 (9.2-NR)
Intermediate	> 3–4.5	3.0 (2.7-3.3)	3.2 (2.8-4-4)
High	> 4.5–6	1.6 (1.5-1.7)	1.4 (1.1-1.7)
Very High	> 6	0.8 (0.7-0.8)	0.73 (0.7-0.9)

Greenberg PL, et al. Blood. 2012;120:2454-65

Revised International Prognostic Scoring System (IPSS-R)

Cytogenetic Risk Group	IPSS-R Karyotype Abnormalities
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities
Very Poor	Complex with > 3 abnormalities

IPSS-R Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Bone Marrow Blast %	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet Count (x 109/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Absolute Neutrophil Count (x 109/L)	≥ 0.8	< 0.8			
	0	0.5			

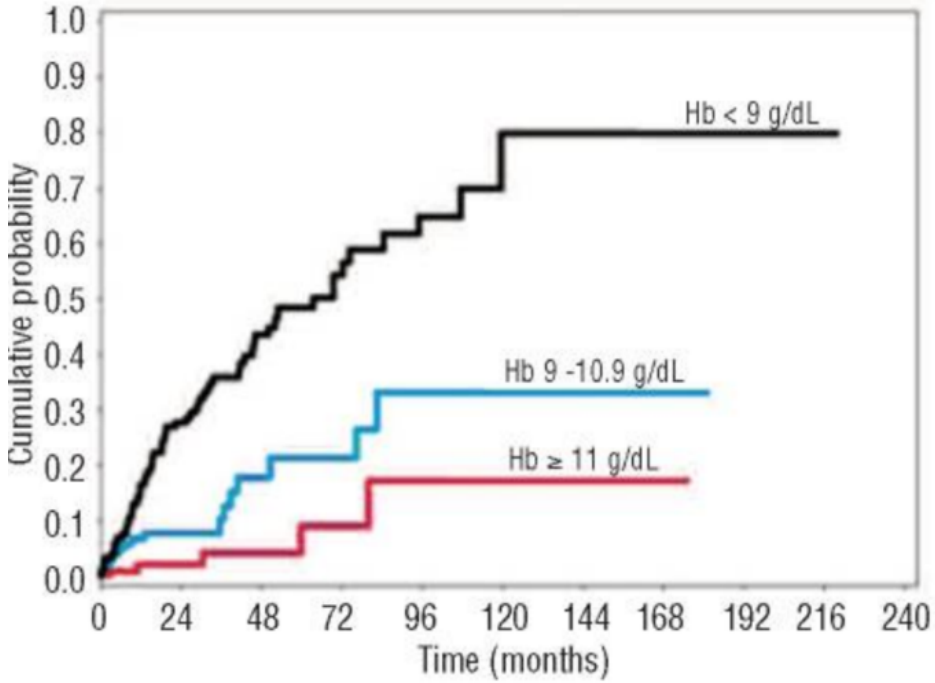
Greenberg PL, et al. Blood. 2012;120:2454-65

IMPACT OF ANEMIA
Hb levels
Transfusions

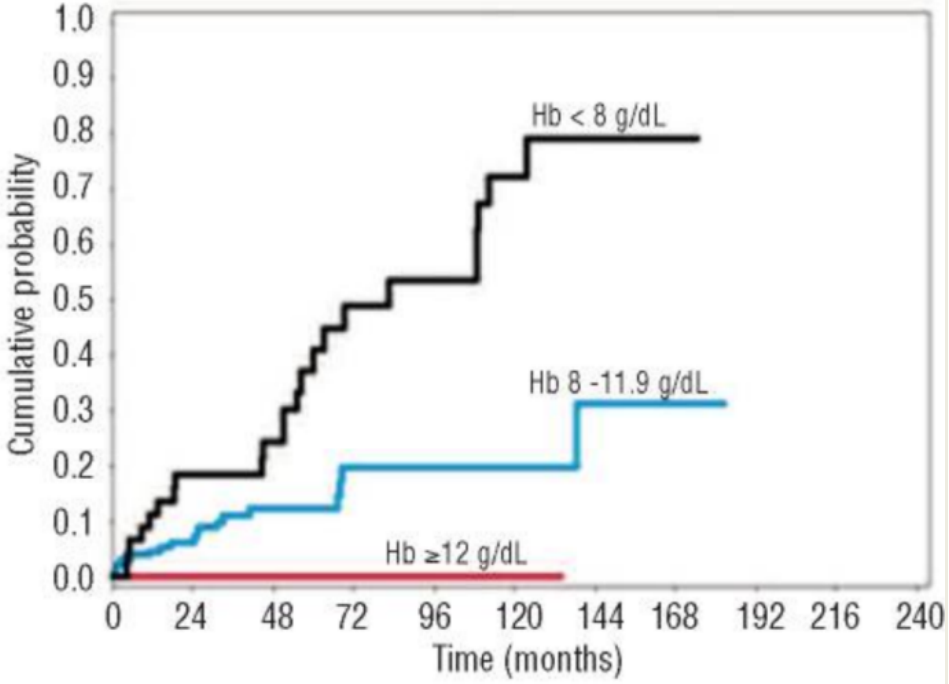
Hb levels and risk of non-leukaemic death (NLD)

A retrospective analysis of 840 MDS patients from a single centre (median age = 66 years, range 18–92)

Rates of NLD in males (n=504)



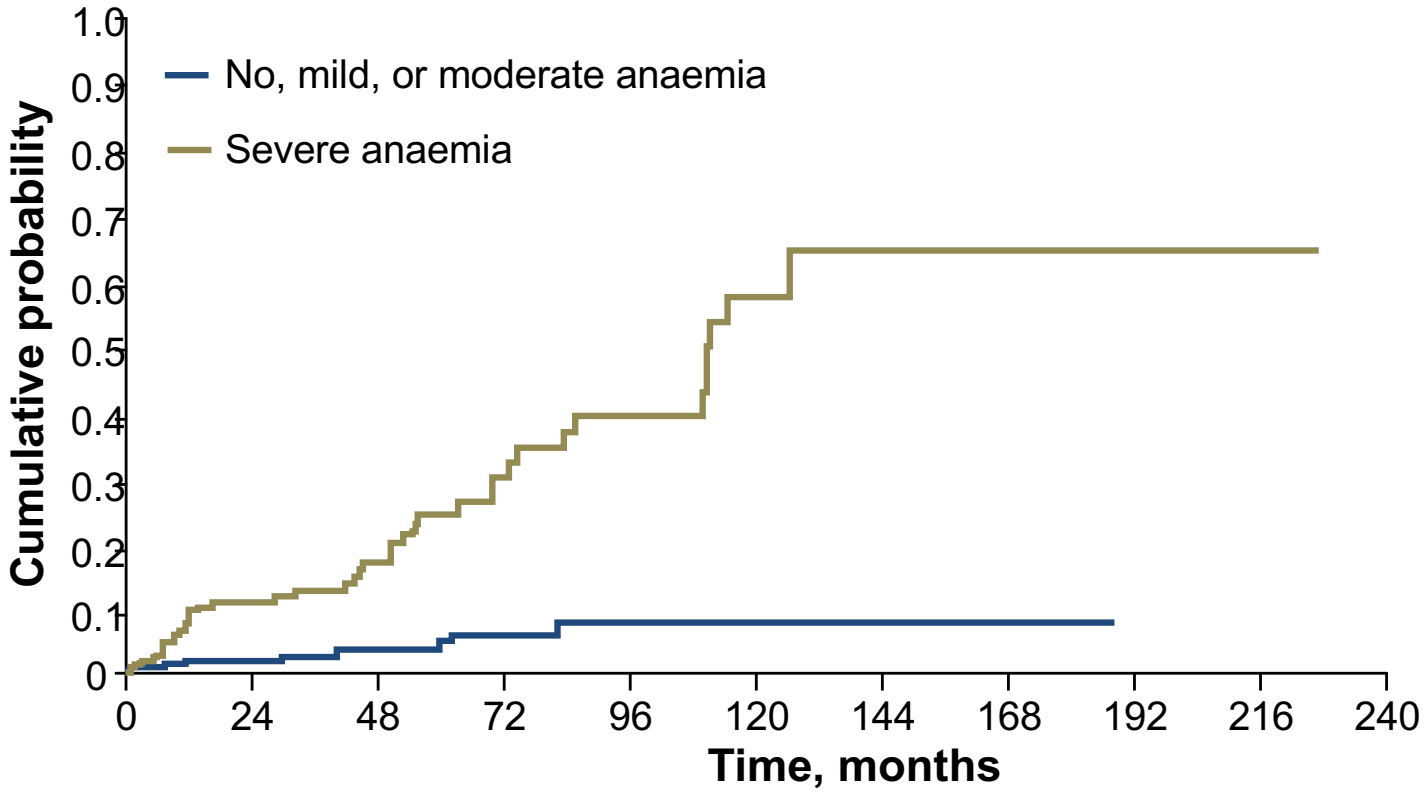
Rates of NLD in females (n=336)



Malcovati L, et al. Haematologica 2011;96:1433–40

Severe anaemia is associated with an increased risk of cardiac death

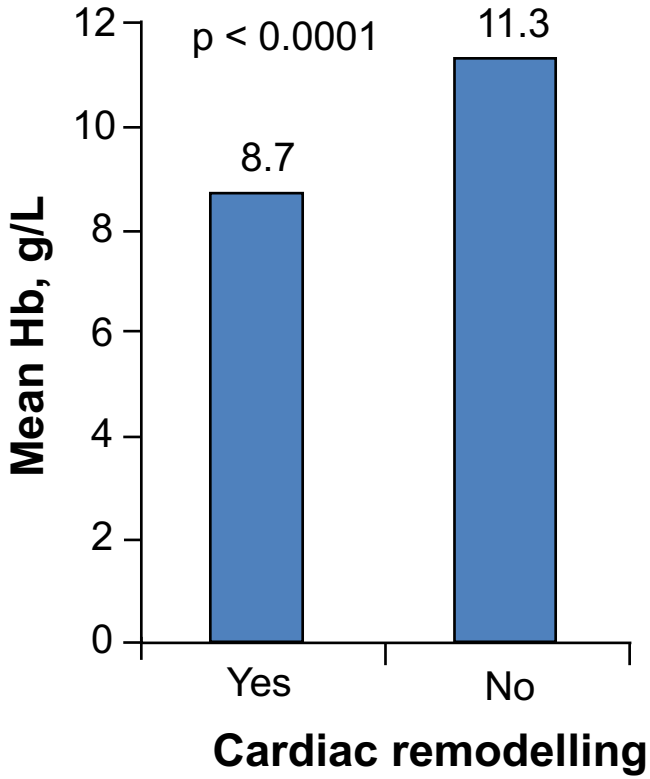
A retrospective analysis of 840 MDS cases from a single centre



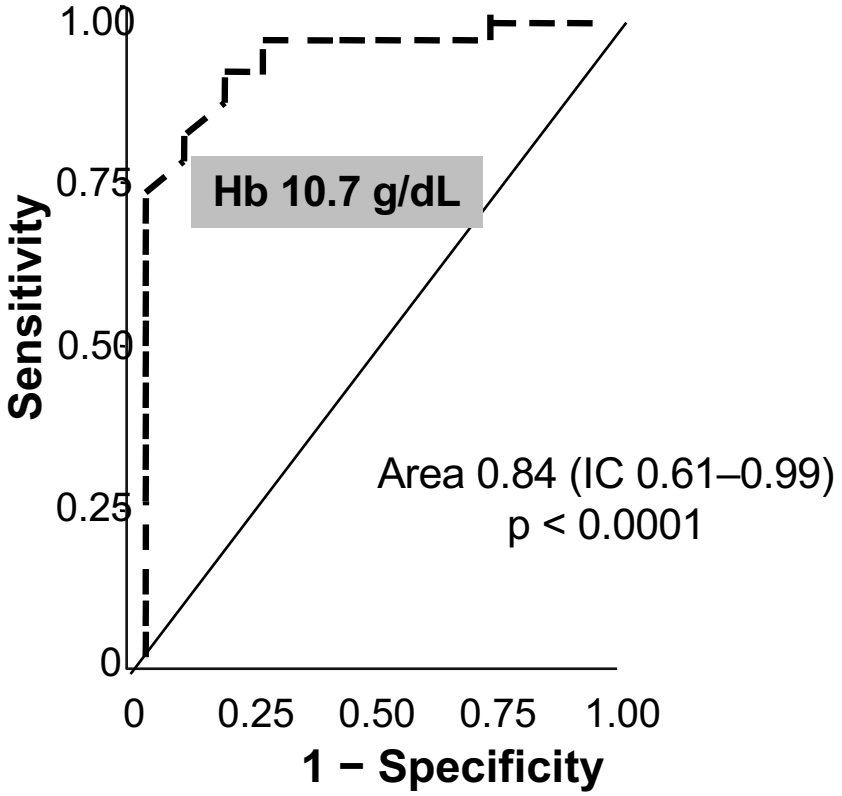
Malcovati L, et al. Haematologica 2011;96:1433–40

Hb levels and risk of cardiac organ damage

Hb levels in patients with evidence of cardiac remodelling



Hb levels predictive for LVH (multivariate analysis p = 0.017)



Oliva EN, et al. Leuk Res 2005;29:1217–9

* Evidence of LVH according to the Devereux formula.
LVH, left ventricular hypertrophy;;

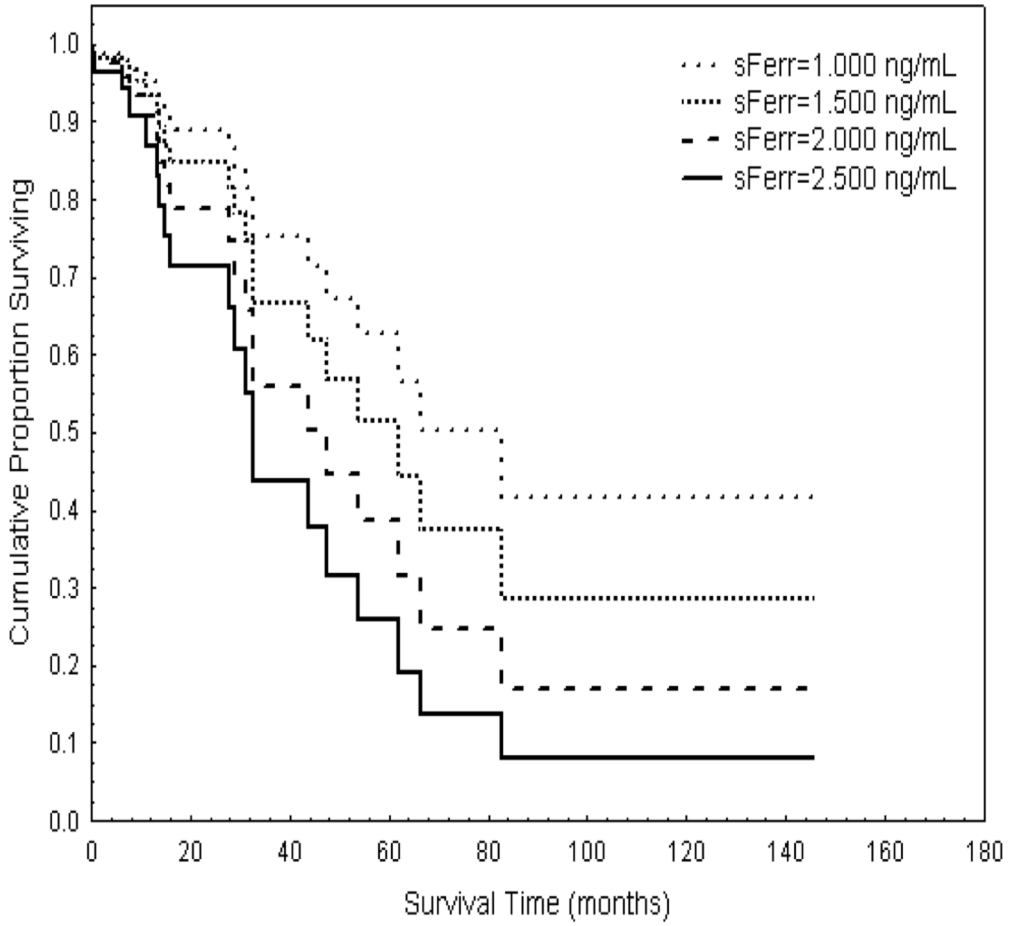
Two key findings

- Incidence of cardiac remodelling in transfusion-dependent vs transfusion-independent patients was 92% vs 48%
- For every 1 g/dL increase in Hb, there is a predicted 49% (CI: 69–20%) decrease in the risk of remodelling (p = 0.004)

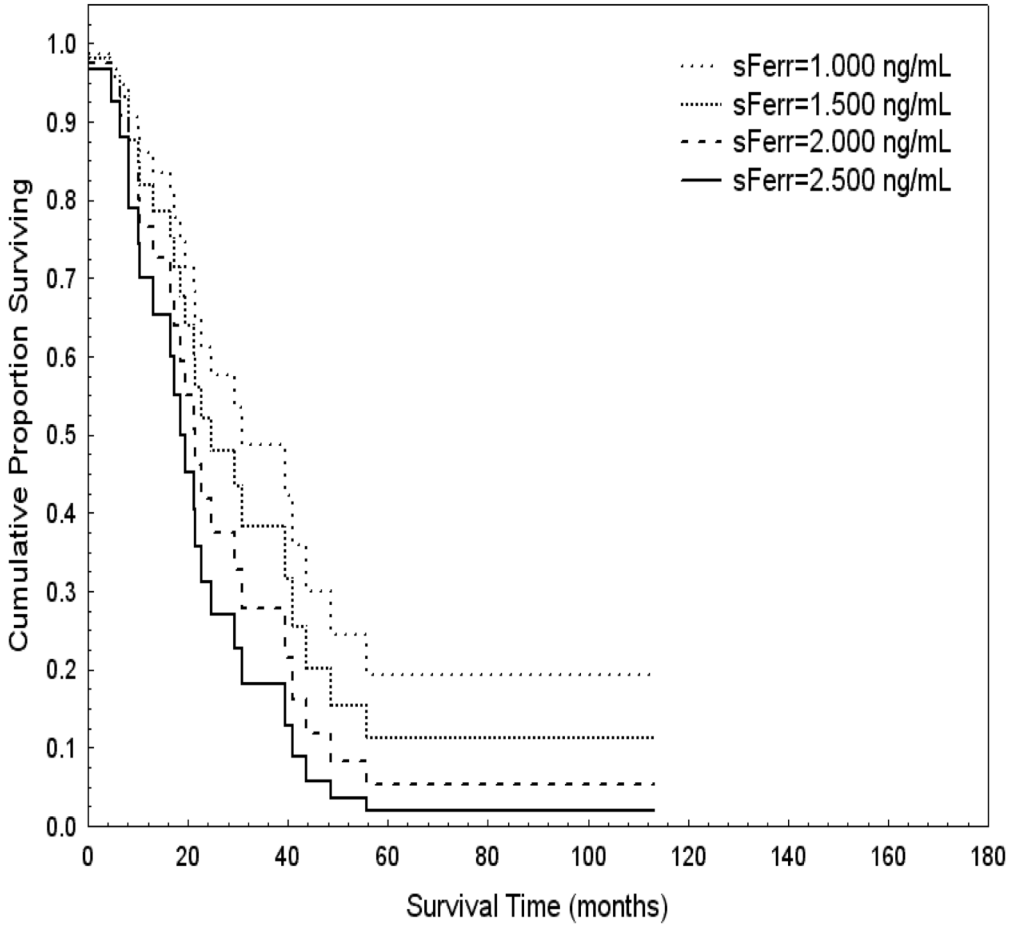
Oliva EN, et al. Leuk Res 2005;29:1217–9

Survival of transfusion-dependent patients according to iron overload

RA/RARS/5q-
(HR=1.42, P<.001)

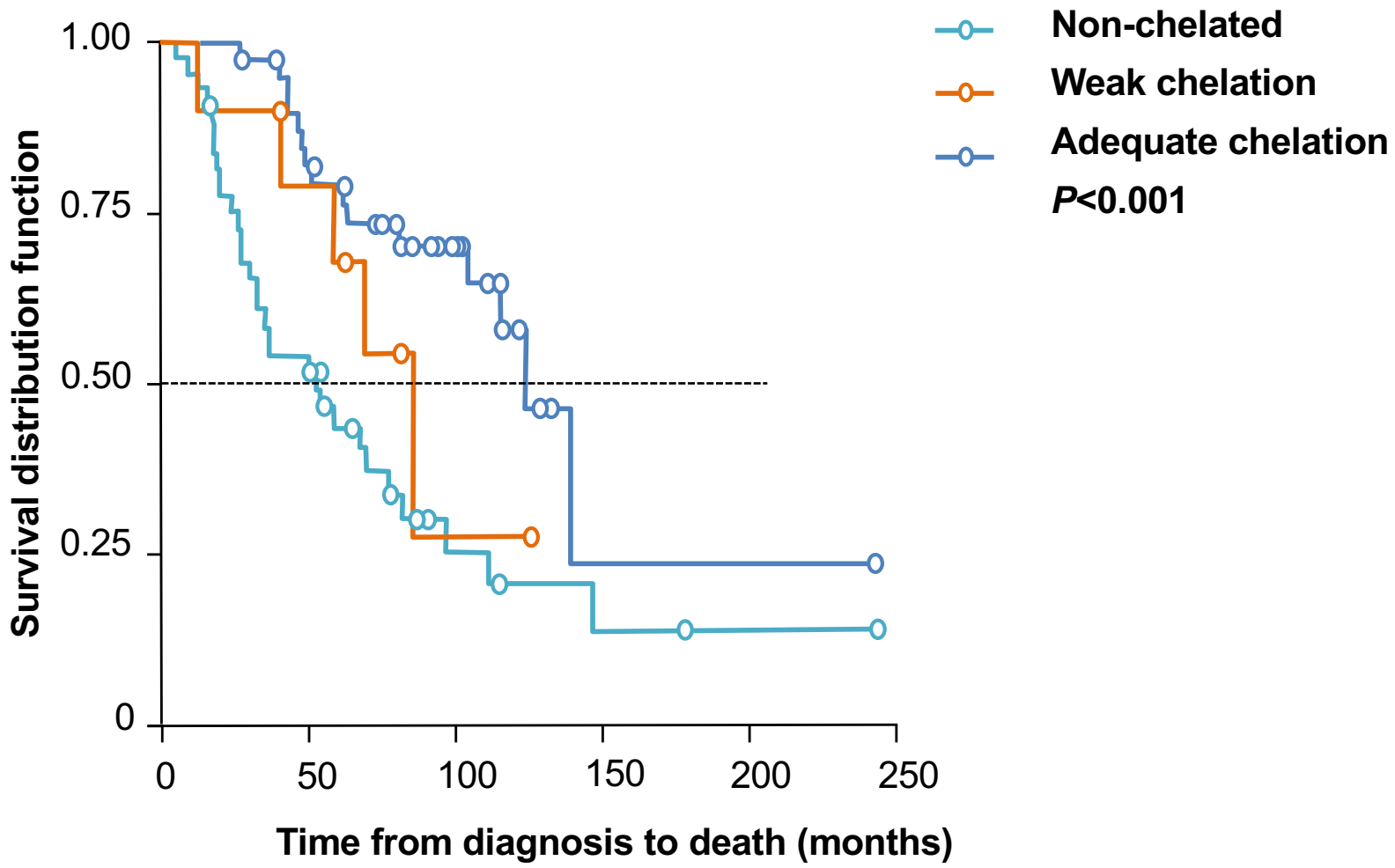


RCMD/RCMD-RS
(HR=1.33, P=.07)



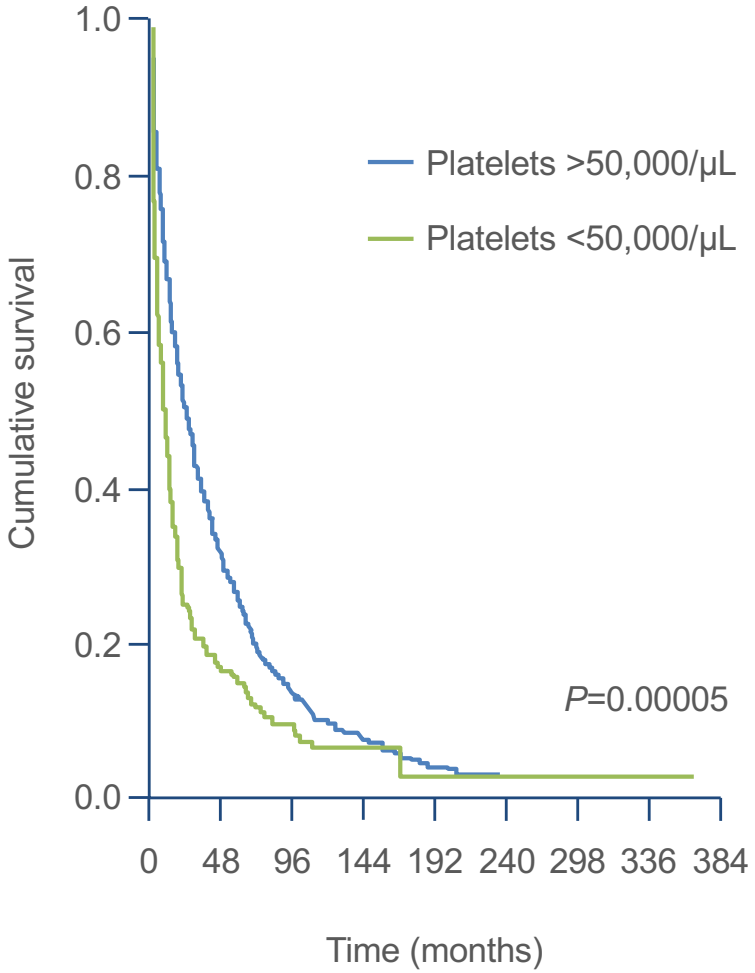
Malcovati L, et al. Haematologica 2006;91:1588-1590

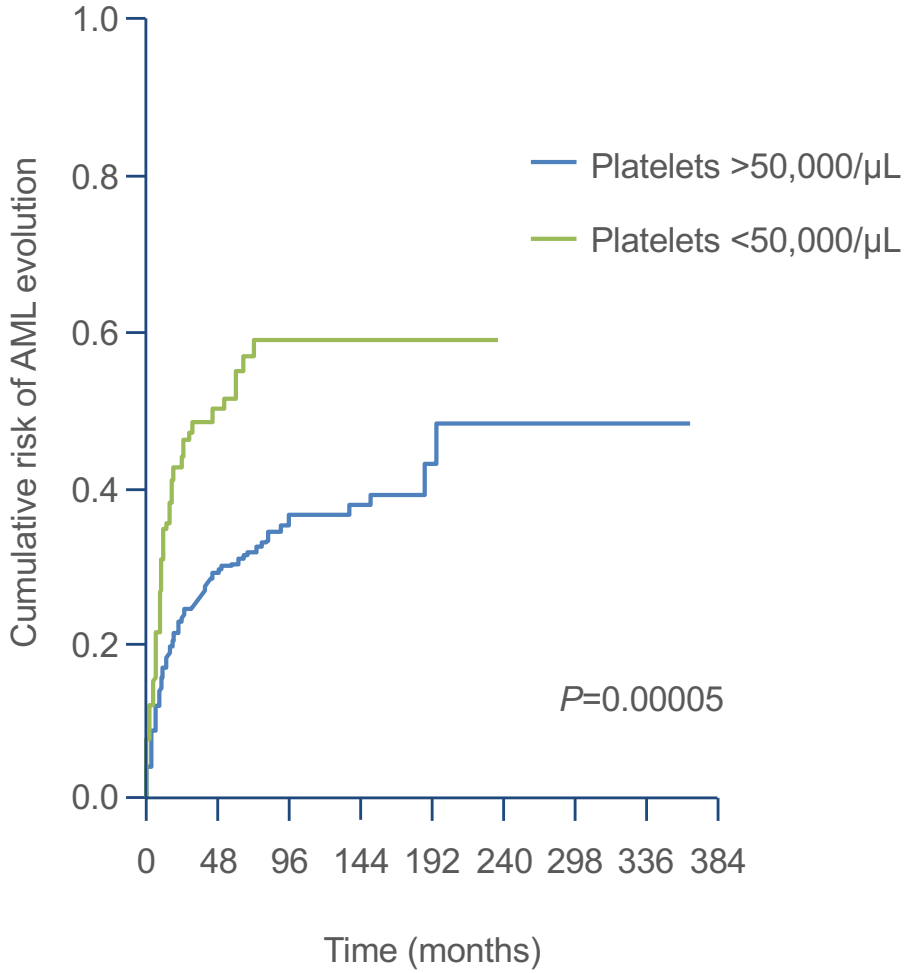
Effects of chelation on survival in patients with MDS with transfusional iron overload



Rose C et al. Leuk Res 2010;34:864–70

Thrombocytopenia is associated with poor outcomes in MDS: Impact on survival and risk of transformation into AML



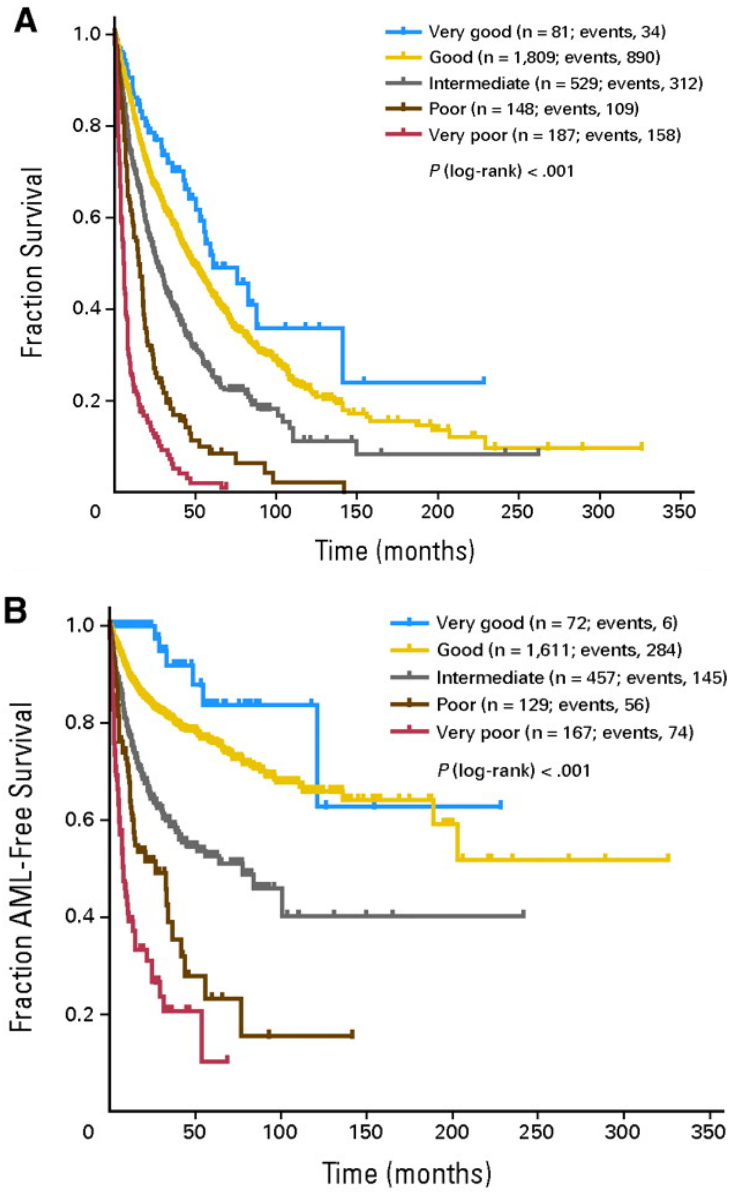


- Neukirchen J *et al. Eur J Haematol* 2009;83:477–482

IMPACT OF GENETICS

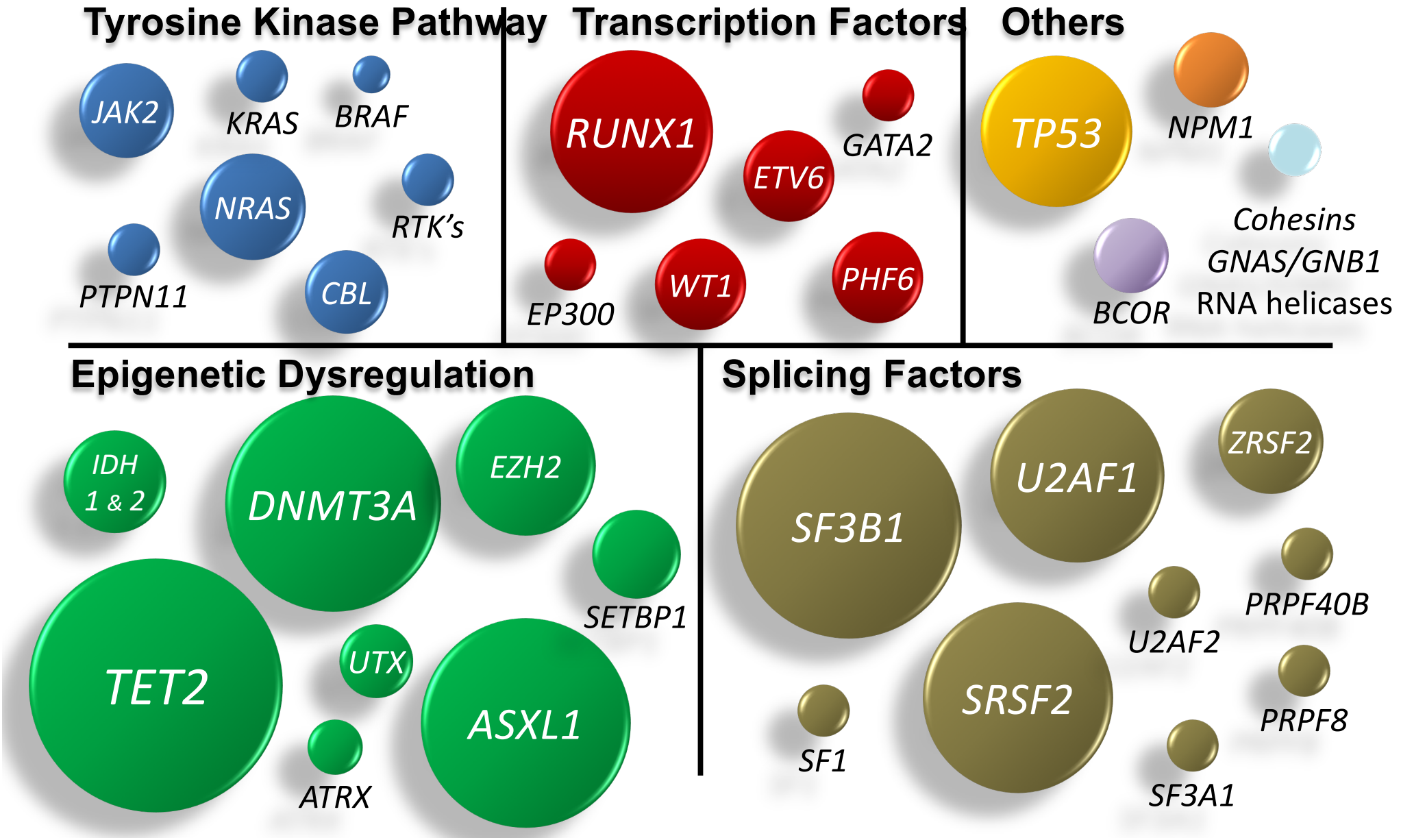
Comprehensive Cytogenetic Scoring System for MDS

Prognostic Subgroup	No. of Patients	%	Abnormality		
			Single	Double	Complex
Very good	81	2.9	del(11q) −Y	—	—
Good (reference)	1,809	65.7	Normal del(5q) del(12p) del(20q)	Including del(5q)	—
Intermediate	529	19.2	del(7q) +8 i(17q) +19 Any other Independent clones	Any other	—
Poor	148	5.4	inv(3)/t(3q)/ del(3q) −7	Including −7/del(7q)	3
Very poor	187	6.8	—	—	> 3



J Clin Oncol. 2012;30:820-9.

MDS, a disease of epigenetics and splicing and…



17 mutations with prognostic significance

1996 MDS patients from combined Datasets from the International Working Group for Prognosis in MDS-Molecular Committee with survival data

Gene	Function	Chromosome	Incidence (%)	Clinical Significance
NRAS	Activated signaling	1p13.2	5–10	Associated with poor prognosis
CBL	Activated signaling	11q23.3	< 5	More frequent in CMML and JMML
JAK2	Activated signaling	9p24.1	< 5	More frequent in RARS-T
ASXL1	Chromatin modifier	20q11	15–25	Independent poor prognostic risk
EZH2	Chromatin modifier	7q35	5–10	Independent poor prognostic risk
TET2	DNA methylation	4q24	20–25	Associated with normal karotype, more frequent in CMML
DNMT3A	DNA methylation	2p23	12–18	Poor prognosis
IDH1	DNA methylation	2q33.2	< 5	More frequent in AML
IDH2	DNA methylation	15q26.1	< 5	More frequent in AML
RUNX1	Myeloid transcription factor	21q22.3	10–15	Independent poor prognostic risk
ETV6	Myeloid transcription factor	12p13.2	< 5	Independent poor prognostic risk
SF3B1	Splicesome	2q33.1	18–30	Favorable prognosis, associated with ring sideroblasts
SRSF2	Splicesome	17q25.1	10–15	Poor prognosis, more frequent in CMML
U2AF1	Splicesome	21q22.3	8–12	Poor prognosis
ZRSR2	Splicesome	Xp22.1	5–10	Poor prognosis
TP53	Tumor supressor	17p13.1	8–12	Independent poor prognostic risk, associated with complex karyotype

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; JMML, juvenile myelomonocytic leukemia; RARS-T, ring sideroblasts and thrombocytosis.

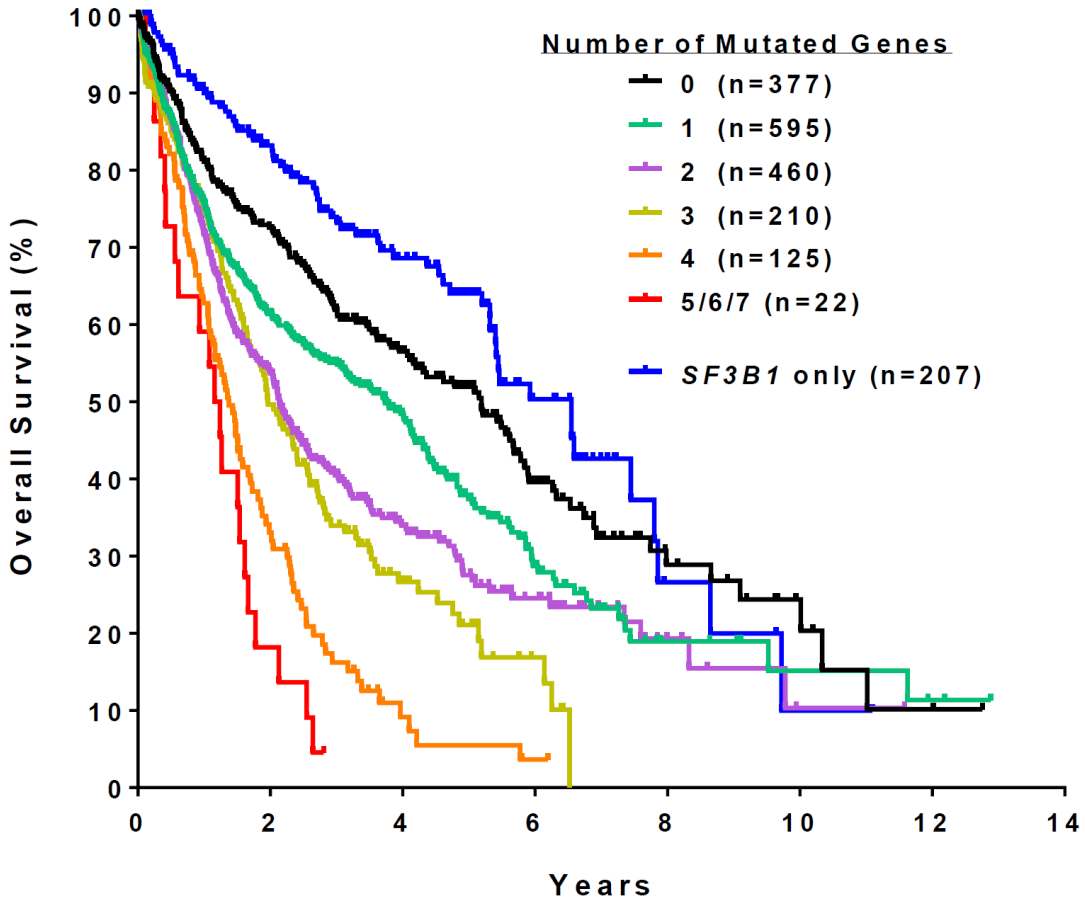
Adopted from Nybakken and Bagg.[6]

Overall survival in MDS patients according to number of mutations and SF3B1

1996 MDS patients from combined Datasets from the International Working Group for Prognosis in MDS-Molecular Committee with survival data

ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1

SF3B1



Somatic Mutations in MDS – independent prognostic value

Mutated genes with prognostic significance independent of IPSS-R:

TP53 (HR 2.37, CI 1.94-2.90),
CBL (HR 1.57, CI 1.22-2.03),
EZH2 (HR 1.55, CI 1.22-2.03),
RUNX1 (HR 1.50, CI 1.24-1.83)

U2AF1 (HR 1.29, CI 1.06-1.58)
ASXL1 (HR 1.21, CI 1.04-1.41)

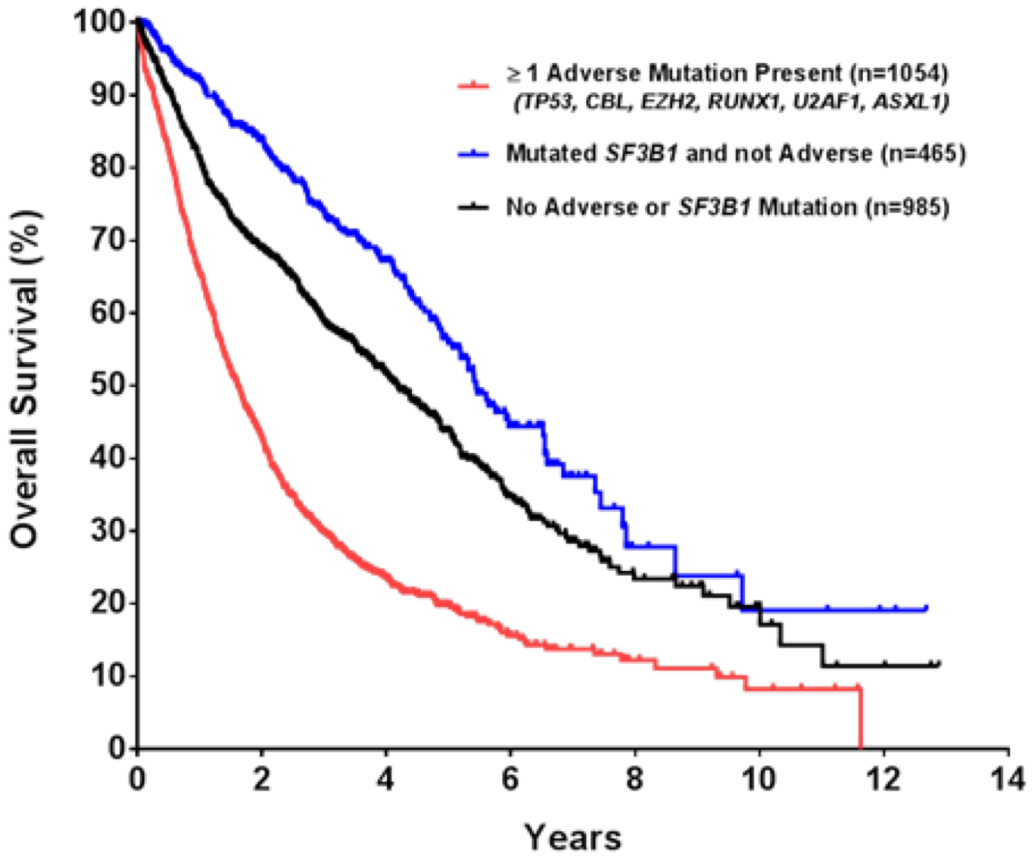
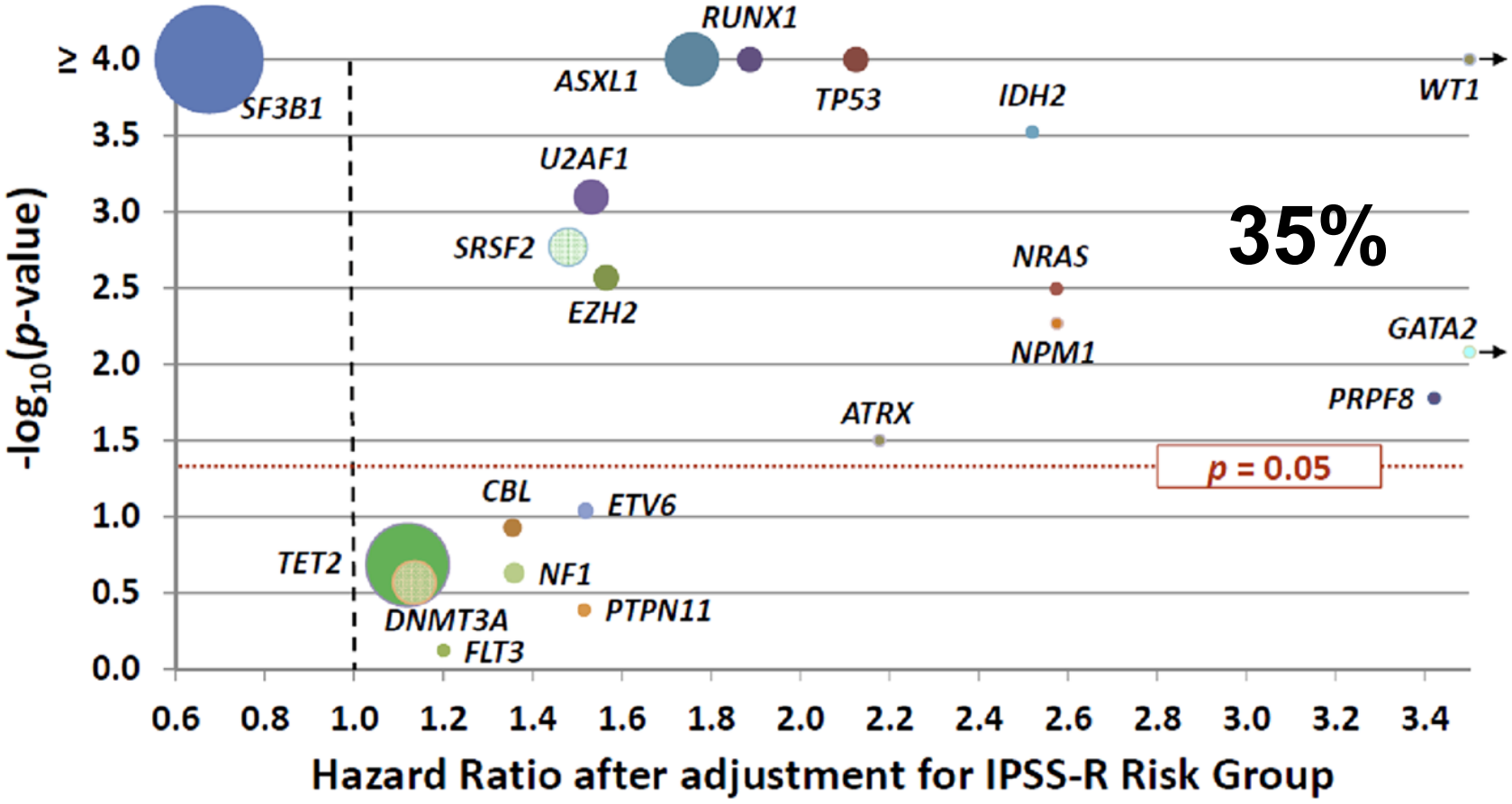


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

Bejar R, et al. Blood 2015

Hazard ratio of death adjusted for IPSS-R risk group for mutations in patients with <5% bone marrow blasts.

MDS patients from combined Datasets from the International Working Group for Prognosis in MDS-Molecular Committee with survival data

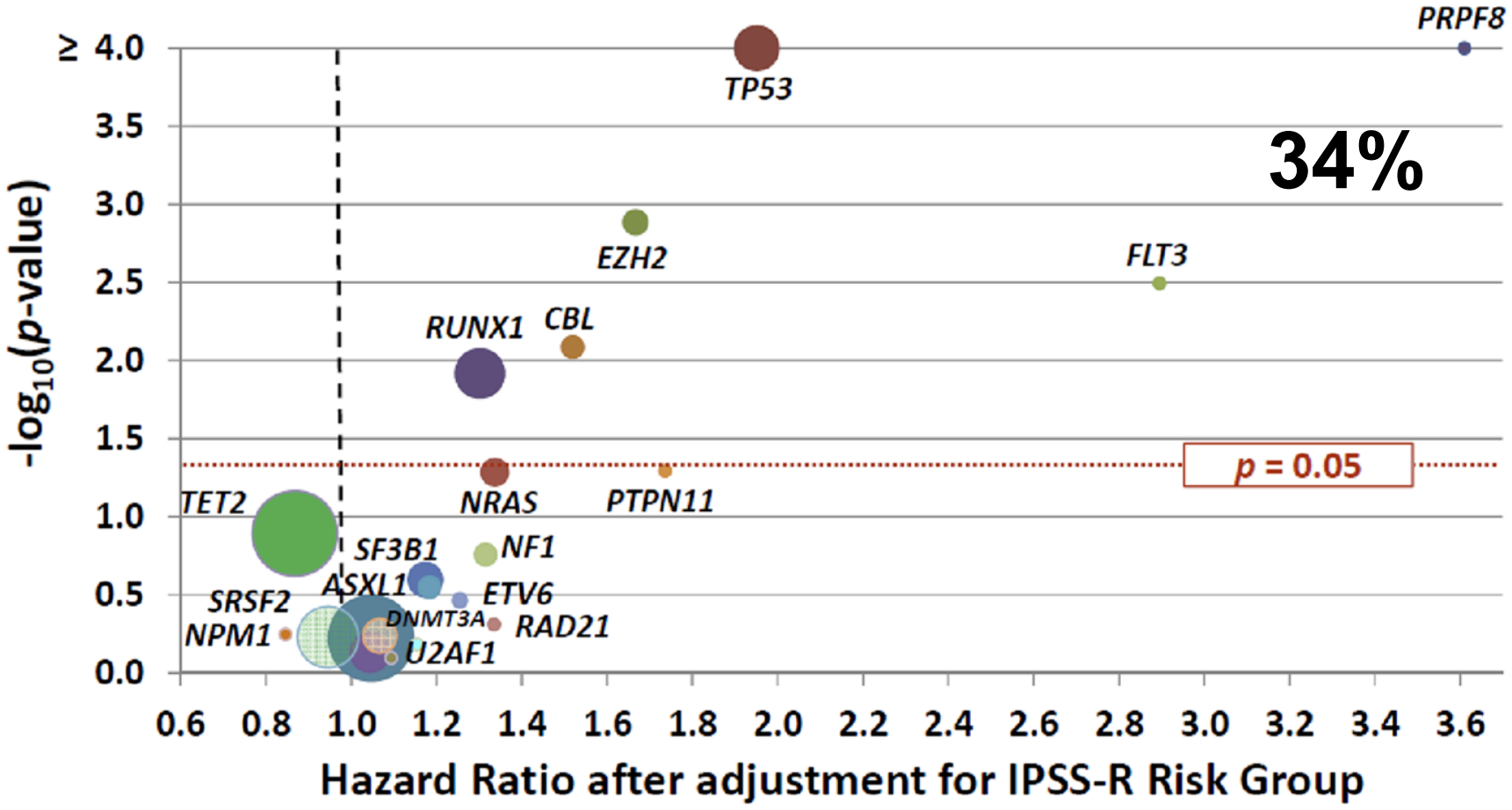


The hazard ratio for each gene compares patients with a mutation in that gene to those without one in that gene.

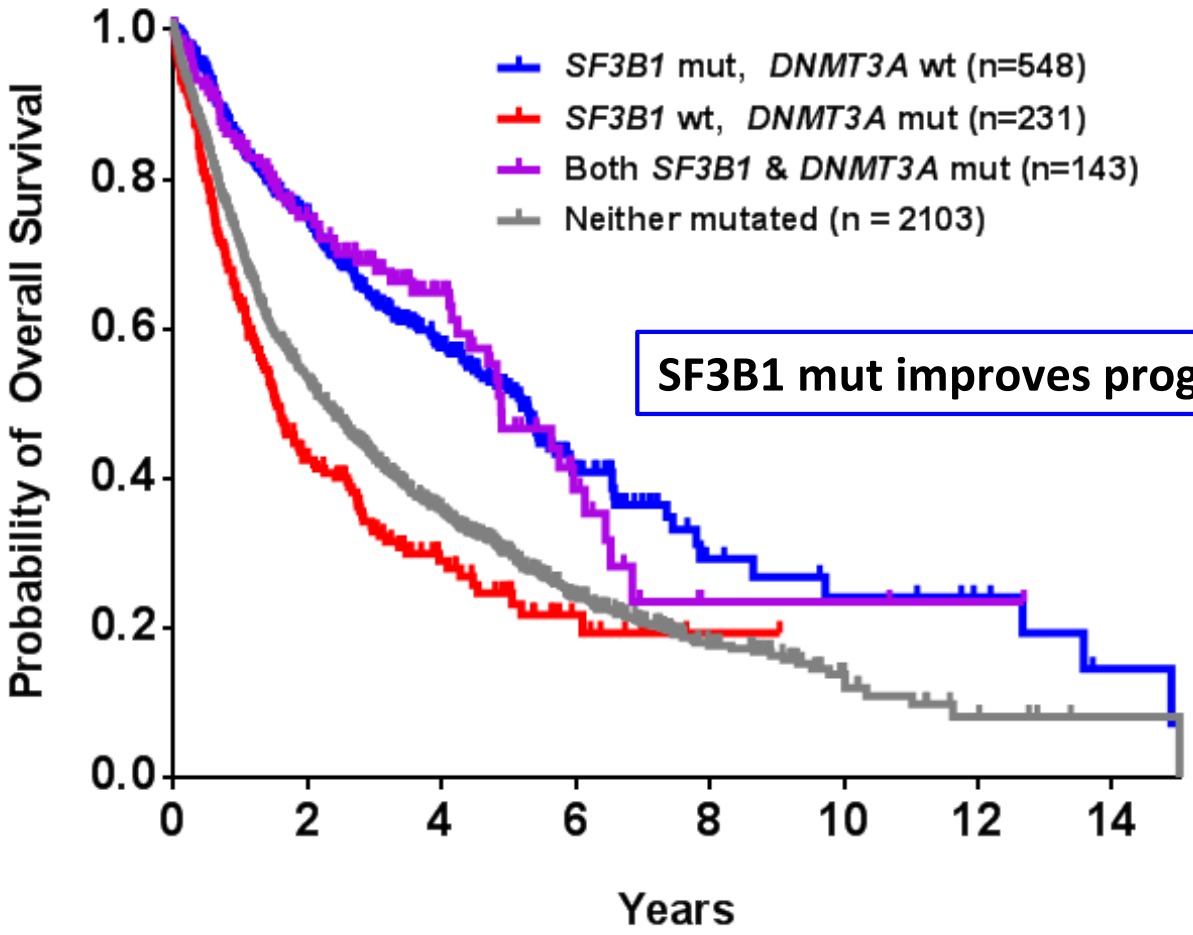
The size of the marker indicates the frequency with which the gene is mutated in this population

Hazard ratio of death adjusted for IPSS-R risk group for mutations in patients with 5-30% bone marrow blasts.

MDS patients from combined Datasets from the International Working Group for Prognosis in MDS-Molecular Committee with survival data



Prognostic value of SF3B1

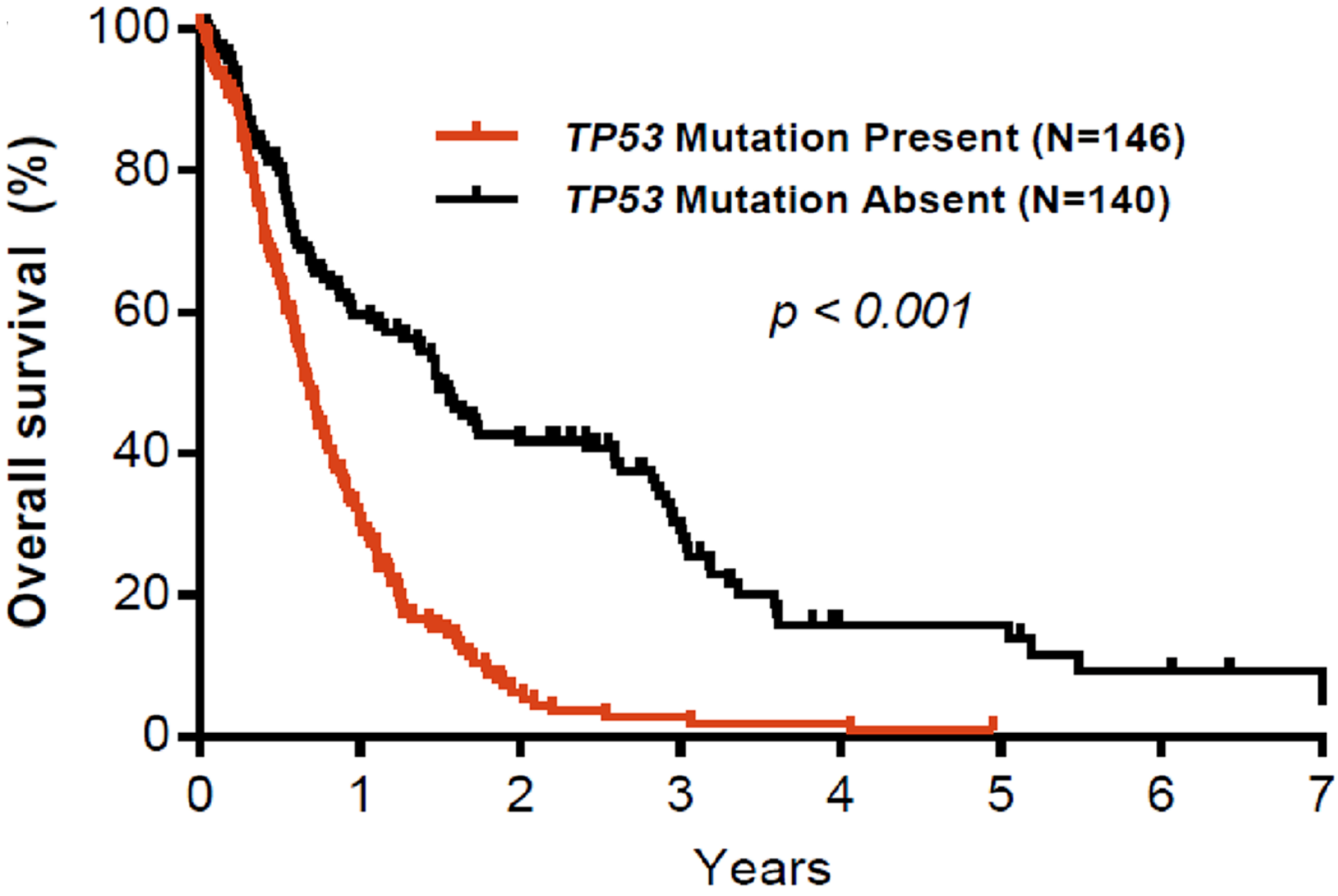


SF3B1 mut improves prognosis of DNMT3A mut

Courtesy to R. Bejar, 2016

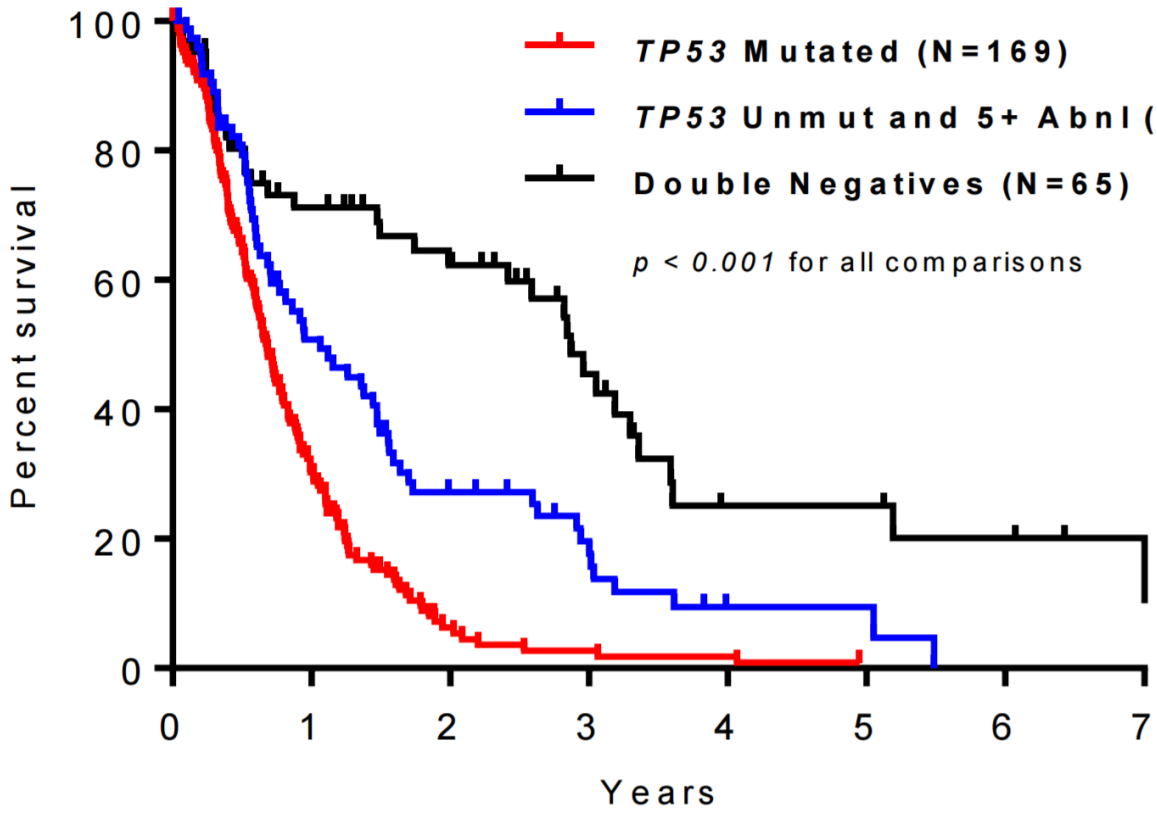
Overall survival in 286 complex karyotype patients with MDS stratified by *TP53* mutation status.

MDS patients from combined Datasets from the International Working Group for Prognosis in MDS-Molecular Committee with survival data



Karyotype and p53

	Univariate		Multivariable	
Three element model	HR [95% CI]	p-value	HR [95% CI]	p-value
Monosomal Yes vs. No	2.01 [1.48-2.74]	<0.001	1.34 [0.95-1.89]	0.092
Number of Abnormalities 5+ vs. 3 or 4	2.33 [1.71-3.17]	<0.001	1.58 [1.11-2.25]	0.011
TP53 Mutation vs. No mutation	2.55 [1.93-3.35]	<0.001	2.08 [1.56-2.77]	<0.001



Median Overall Survival:

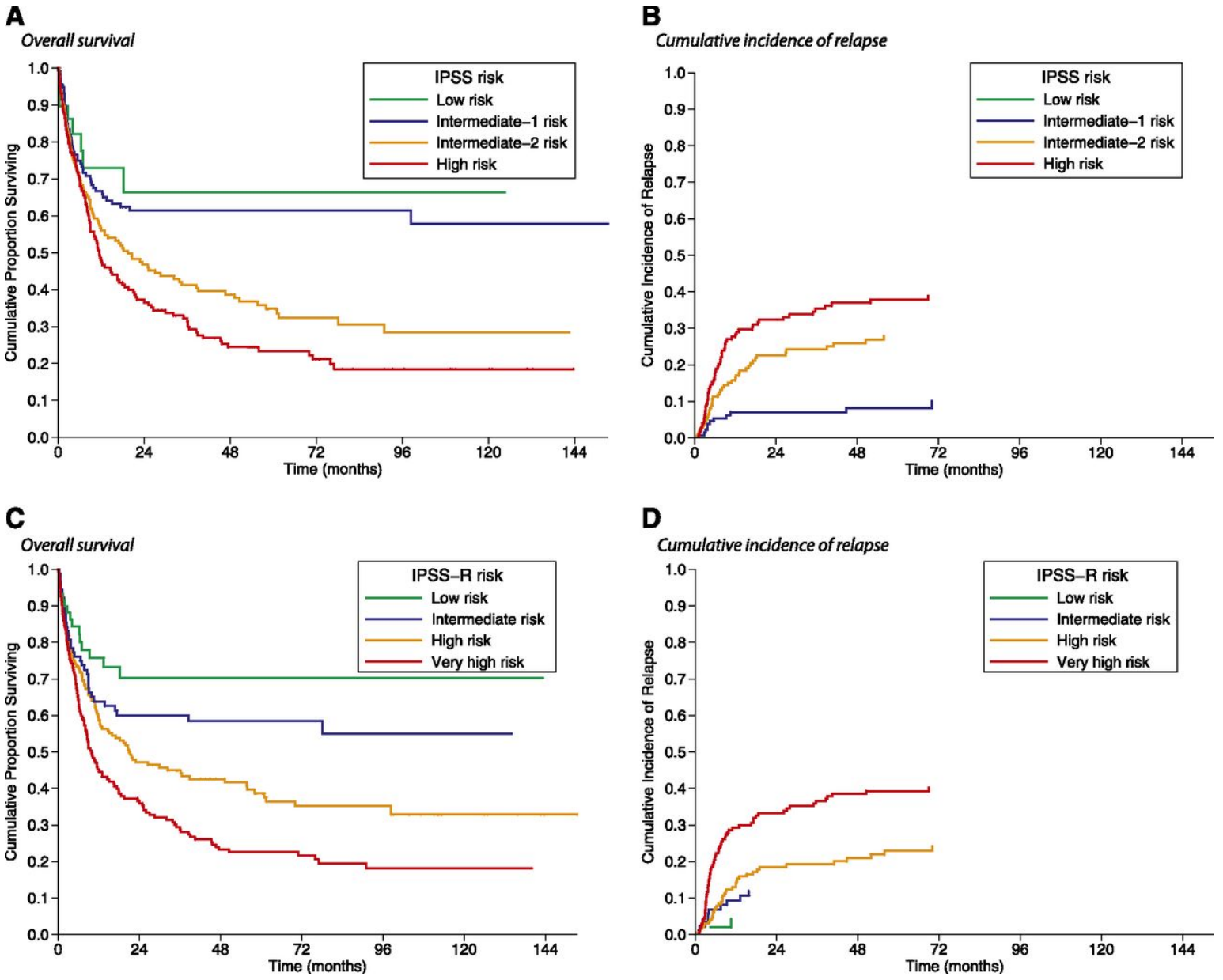
8.1 months

12.8 months

34.3 months

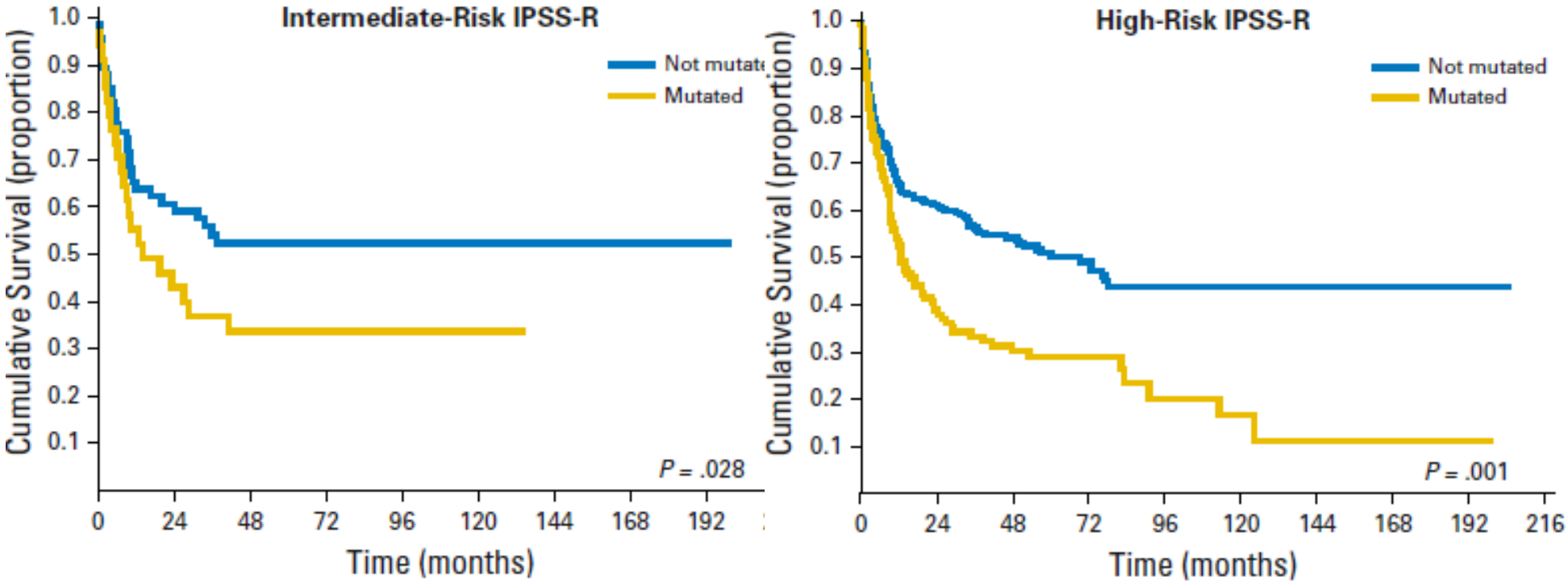
PROGNOSTIC FACTORS IN PATIENTS UNDERGOING ALLOSCT

Survival and relapse following allogeneic HSCT stratified according to IPSS or IPSS-R risk.



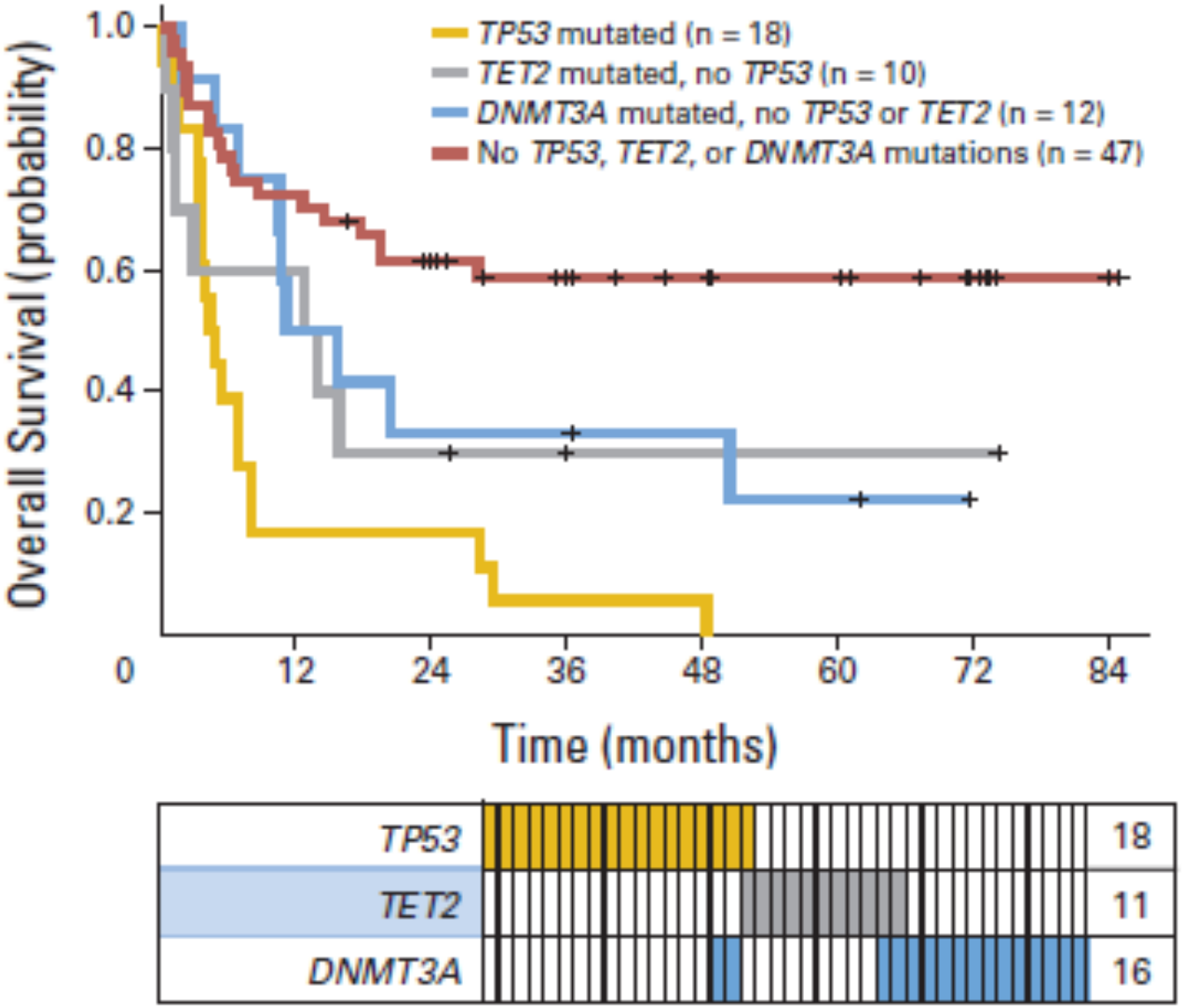
Della Porta MG et al. Blood 2014; Della Porta MG et al. Leukemia. 2015

Clinical Impact of Somatic Mutations in Patients With MDS Receiving HSCT, Stratified According to IPSS-R



Della Porta et al. JCO.2016

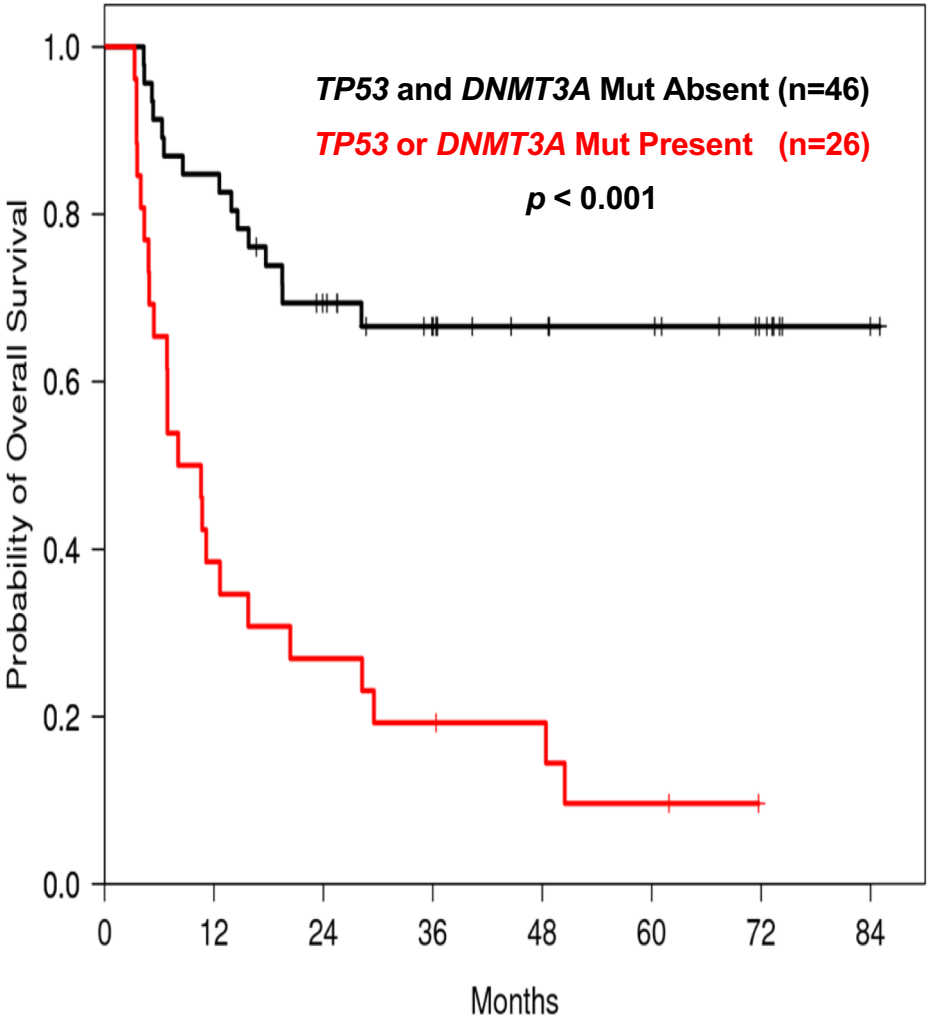
Somatic Mutations Predict Poor Outcome After HSCT



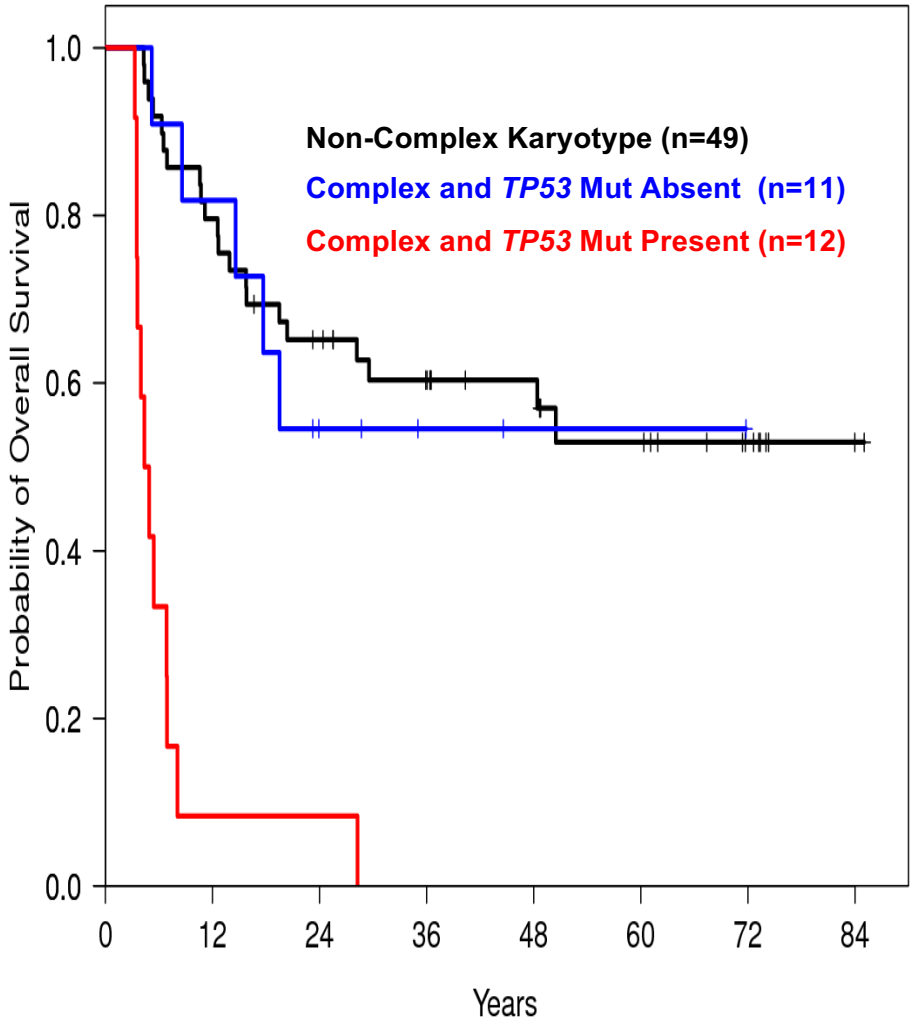
Bejar R et al. J Clin Oncol 2014;32:2691-2698

Mutations and their impact on HSCT outcome

OS After HSCT



OS in CK +/- *TP53* Mutation



Bejar, JCO 2014

Variables affecting HSCT outcome

1514 MDS patients enrolled in the Center for International Blood and Marrow Transplant Research Repository

Variable	Patients (N = 1514)	Hazard Ratio for Death (95% CI)	P Value
	no. (%)		
Patient-related variable			
Age at transplantation			<0.001
0–39 yr	241 (16)	1.00	
≥40 yr	1273 (84)	2.05 (1.66–2.53)	
Karnofsky performance-status score†			<0.001
90–100	817 (54)	1.00	
<90	419 (28)	1.51 (1.29–1.77)	
Missing data	278 (18)	—	
Disease-related variable			
IPSS-R cytogenetic risk group before transplantation			<0.001
Good or very good	579 (38)	1.00	
Intermediate	269 (18)	0.73 (0.60–0.89)	0.002
Poor	287 (19)	0.89 (0.74–1.08)	0.24
Very poor	125 (8)	1.76 (1.41–2.20)	<0.001
Missing data	254 (17)	—	
Bone marrow blasts before transplantation‡			0.03
0–2%	377 (25)	1.00	
3–5%	269 (18)	1.21 (0.98–1.48)	0.07
6–9%	238 (16)	1.23 (1.00–1.52)	0.06
10–19%	289 (19)	1.34 (1.10–1.63)	0.003
Missing data	341 (23)	—	

Lindsley, et al. NEJM, 2017

Variables affecting HSCT outcome

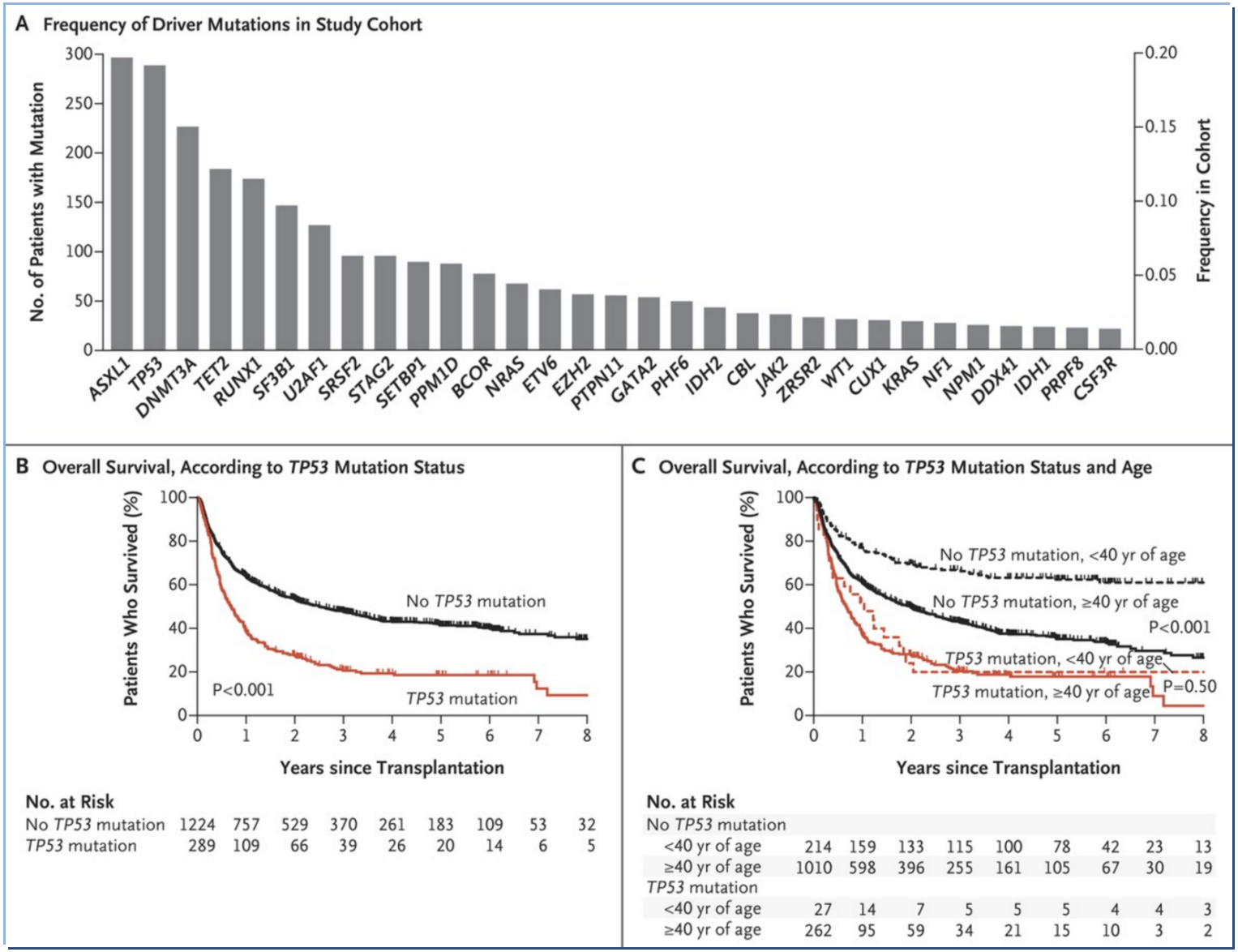
1514 MDS patients enrolled in the Center for International Blood and Marrow Transplant Research Repository

Variable	Patients (N = 1514)	Hazard Ratio for Death (95% CI)	P Value
	no. (%)		
Platelet count before transplantation			0.01
≥100×10⁹/liter	547 (36)	1.00	
50–99×10⁹/liter	344 (23)	1.01 (0.84–1.21)	>0.99
<50×10⁹/liter	538 (36)	1.24 (1.06–1.45)	0.00
Missing data	85 (6)	—	
Type of MDS			<0.00
Primary MDS	1203 (79)	1.00	
Therapy-related MDS	311 (21)	1.34 (1.15–1.57)	
Transplantation-related variable			
Conditioning regimen			0.00
Myeloablative	789 (52)	1.00	
Reduced intensity	582 (38)	1.13 (0.98–1.30)	0.10
Nonmyeloablative	130 (9)	1.45 (1.16–1.82)	0.00
Missing data	13 (1)	—	
Graft type			0.60
Bone marrow	221 (15)	1.00	
Peripheral-blood stem cell	1114 (74)	1.05 (0.87–1.27)	0.60
Cord blood	168 (11)	1.13 (0.87–1.47)	0.35

Lindsley, et al. NEJM, 2017

Mutations and their impact on HSCT outcome

1514 MDS patients enrolled in the Center for International Blood and Marrow Transplant Research Repository



Lindsley, et al. NEJM, 2017

Therapy and outcome in the context of genomic alterations

Lenalidomide

- *TP53*^{mut} and possibly *CSNK1A1*^{mut} are associated with the lack of achievement of complete cytogenetic response in del5q MDS

  (Jadersten JCO 2012, Kulasekararaj BJH 2014, Smith et al Lancet Haem)

- DDX41 (inherited)- response to Lenalidomide

Hypomethylating agents

- *TET2*^{mut} respond better, but no impact on OS *(Itzykson, Leukemia 2011)*
- *TET2*^{mut} and *DNMT3A*^{mut} respond better, impact PFS
- *ASXL1*^{wt} and/or *SF3B1*^{mut} impact on OS *(Traina,Leukemia, 2014)*
- *TET2*^{mut} plus *ASXL1*^{wt} impact on response *(Bejar, MDSF, 2013 and Blood 2014)*
- *TP53*^{mut}and complex karyotye impacting positively on response (Welch, Nejm, 2016)

Therapy and outcome in the context of genomic alterations

LUSPATERCEPT

Subgroup n (%)	IWG HI-E Response Rate	RBC-TI Response Rate
All	**24 of 49 (49)**	
RS+	22 of 40 (55)	
RS-	2 of 7 (29)	
SF3B1 mutation	18 of 30 (60)	
Any SF mutation	20 of 36 (58)	
EPO < 200 U/L	16 of 25 (64)	
EPO 200–500 U/L	4 of 11 (36)	
EPO > 500 U/L	4 of 13 (31)	
Prior ESA	16 of 35 (46)	
ESA naïve	8 of 14 (57)	

EPO, erythropoietin; ESA, erythropoietin stimulating agent ; RS, ring sideroblasts; SF, splicing factor; SF3B1, Splicing Factor 3b, Subunit 1.

Platzbecker U, et al. Biomarkers of Ineffective Erythropoiesis Predict Response to Luspatercept in Patients with Low or Intermediate-1 Risk MDS: Final Results from the Phase 2 PACE-MDS Study. *Poster presented at: Annual Meeting and Exposition of the American Society of Hematology* 2015; December 5–8; Orlando, FL. Abstract 2862.

Summary

- Prognostic assessment remains a critical component of the personalization of care for patients with MDS as treatment is highly risk adapted.
- Anemia, is one of the most important prognostic factors in MDS patients.
- IPSS-R currently considered the gold standard; however, the risk may be both under- and overestimated
- Mutations, particularly TP53mut, remain prognostically adverse across risk groups.
- A fraction of lower-risk patients will carry a favorable SF3B1 mutation.
- Complex karyotype patients without a TP53 mutation may have substantially longer overall survival than predicted by the IPSS-R.
- TP53 is independently associated with a dismal prognosis even after treatment or stem cell transplantation.
- Few mutations, such as SF3B1, are favorable and modify the unfavorable impact of other specific mutations such as DNMT3A on overall survival.
- Not only are somatic gene mutations advantageous in understanding the biology of MDS and prognosis, they also offer potential as biomarkers and targets for the treatment of patients with MDS.