FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

L'attuale approccio clinico al paziente con **Sindrome Mielodisplastica**

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MDS - Stratificazione prognostica e scelta terapeutica individualizzata

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Agenda

- Perchè uno score prognostico
- Sistemi di score prognostici attualmente in uso
- Impatto della citogenetica sulla prognosi

- Biologia molecolare: nuovi score prognostici…
- … ma anche Terapia Personalizzata

Utilità di uno score prognostico

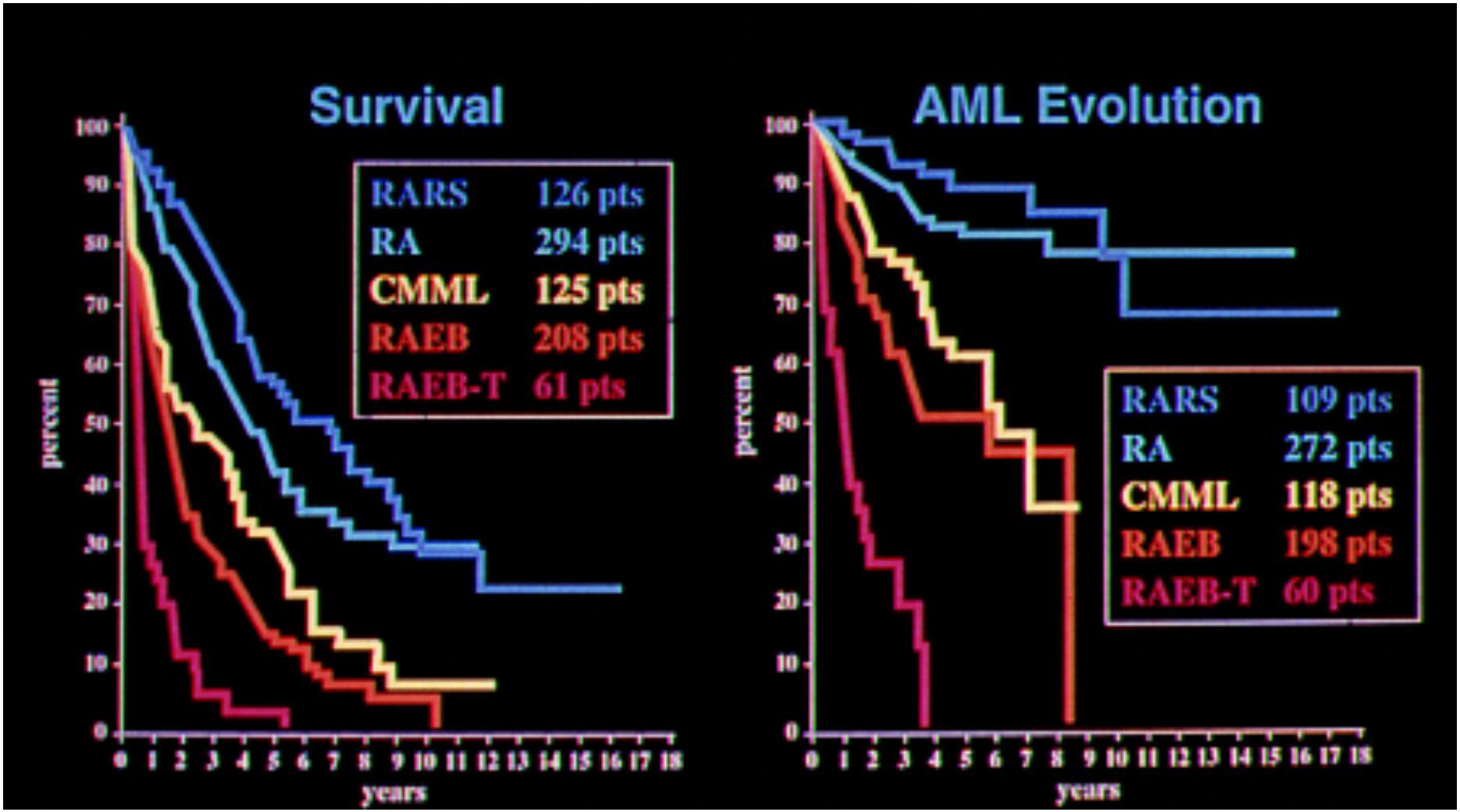
- Fornire al singolo paziente informazioni sulla sua prognosi
- Aiuto a prendere decisioni cliniche
- Permettere una stratificazione per rischio nei protocolli clinici
- Definire indicazioni per i nuovi farmaci (EMEA, FDA)

Sindrome mielodisplastica: Introduzione

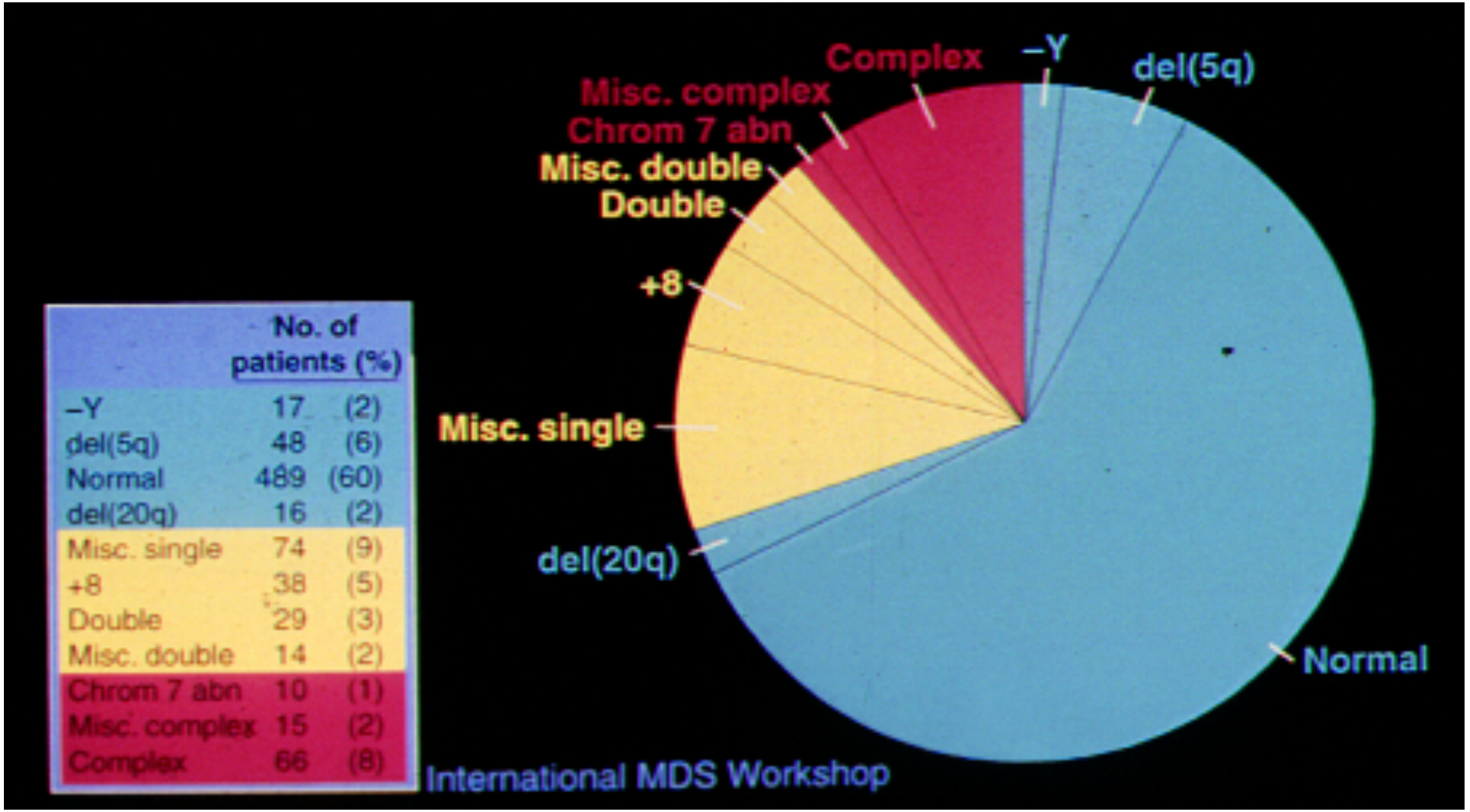
- Un gruppo eterogeneo di neoplasie maligne delle cellule staminali che danno luogo a un'ematopoiesi inefficace a carico di una o più linee mieloidi
  - Citopenia progressiva
  - Alterazioni funzionali
  - Midollo osseo ipercellulare
  - Propensione alla trasformazione leucemica
- Classificate nel 1982 dal Gruppo Cooperativo Franco-Americano-Britannico (FAB) come sindromi mielodisplastiche (MDS)
- La MDS è comune almeno quanto la leucemia linfocitica cronica, che è la forma di leucemia più comune nel mondo occidentale

List A et al. Myelodysplastic Syndromes: diagnosis and emerging therapies. Postgraduate Institute for Medicine. Carden Jennings, Virginia, 2004
Kurzrock R. Semin Hematol 2002. 39(3 Suppl 2):18–25
Hamblin TJ. Epidemiology of MDS. In: Bennett JM (ed). MDS: Pathobiology and Clinical Management. New York: Marcel Dekker Inc.; 2002
http:// www.hmds.org.uk/mds.html

FAB Classification



Cytogenetic Abnormalities in MDS



	No. of patients	(%)
–Y	17	(2)
del(5q)	48	(6)
Normal	489	(60)
del(20q)	16	(2)
Misc. single	74	(9)
+8	38	(5)
Double	29	(3)
Misc. double	14	(2)
Chrom 7 abn	10	(1)
Misc. complex	15	(2)
Complex	66	(8)

International Prognostic Scoring System (IPSS)

- L'intento è di creare una definizione per i pazienti con *outcome* simili in base ai fattori di rischio, nonostante la morfologia disparata
- Si basa sugli *outcome* di 816 pazienti con SMD *de novo* non trattati, arruolati in ampi studi istituzionali o nazionali
- I pazienti con leucemia mielomonocitica cronica proliferativa (CMML)(GB >12,000/µl) sono stati esclusi
- Fattori di rischio considerati: citogenetica, classificazione FAB, % blasti, citopenie, età, sesso e due pregressi sistemi di punteggio

From Greenberg P et al. Blood 1997;89:2079–2088. Copyright American Society of Hematology,

IPSS Risk Score – De novo MDS

International MDS Risk Analysis Workshop - 1997

Score	0	0.5	1	1.5	2
Marrow blasts, %	< 5	5–10		11–20	21–30
Karyotype	Favorable	Int.	Poor		
Number of cytopenias	0–1	2–3			

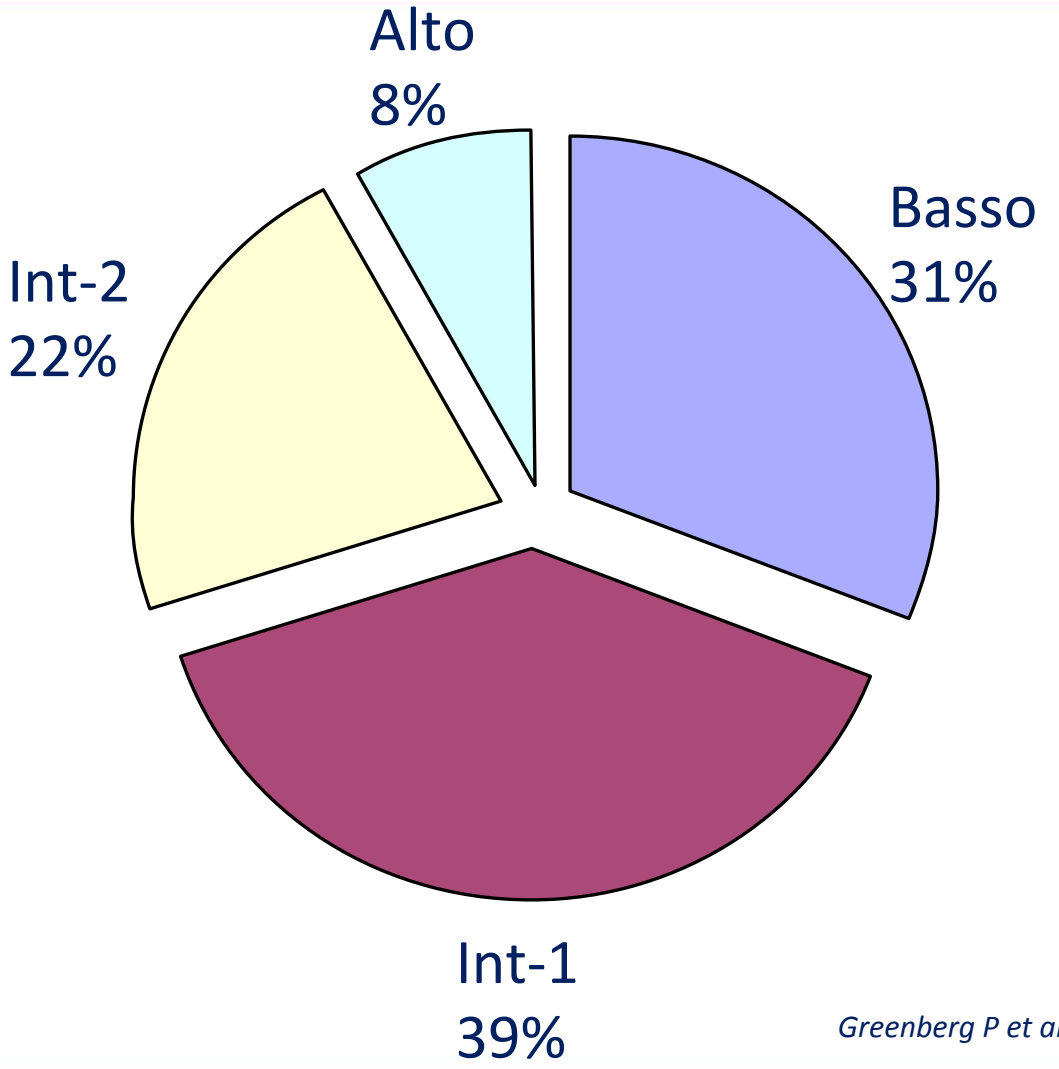
Low	0
Intermediate-1	0.5–1
Intermediate-2	1.5–2
High	> 2.5

Cytogenetic Subgroups: Low Risk, normal, del 5q, del 20q, -Y; Intermediate: others; High: complex, chromosome 7 abnormalities

Cytopenias: Hb <10g/dL, platelets <100,000/μL, neutrophils <1,800/μL

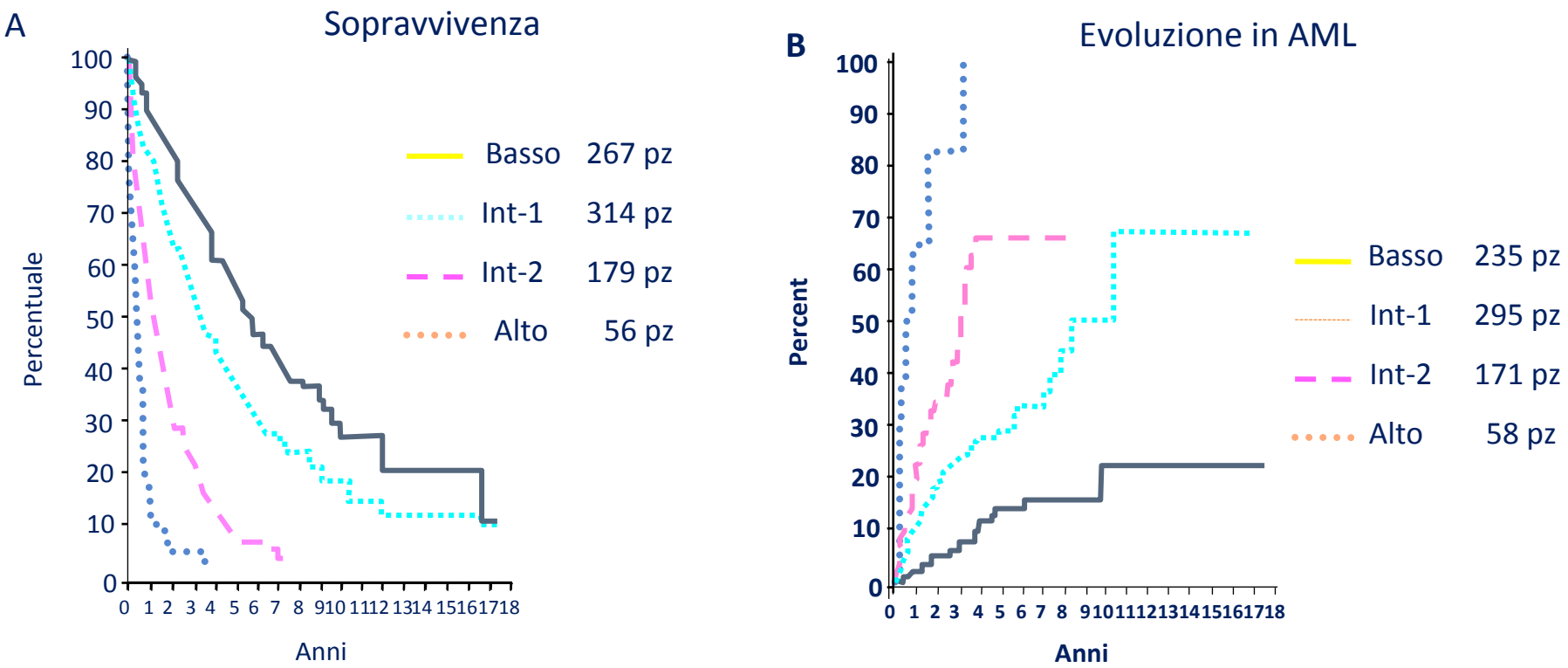
Greenberg P, et al. Blood. 1997;89:2079-88

Categorie di rischio IPSS: distribuzione dei pazienti



Greenberg P et al. Blood. 1997;89:2079

Sopravvivenza e progressione verso AML Classificazione del rischio IPSS



From Greenberg P et al. Blood 1997;89:2079–2088. Copyright American Society of Hematology,

International Prognostic Scoring System (IPSS) vs. Età

Gruppo di rischio	Età < 60 anni	Età > 60 anni	Età > 70 anni
Low (0)	11.8	4.8	3.9
Int-1 (0.5-1.0)	5.2	2.7	2.4
Int-2 (1.5-2.0)	1.8	1.1	1.2
High (2.5-3.5)	0.3	0.5	0.4

Greenberg, et al. Blood:1997

WHO- based Prognostic Scoring System (WPSS)

- La prima proposta di questo sistema è stata fatta da un Gruppo Cooperativo Italo-Tedesco

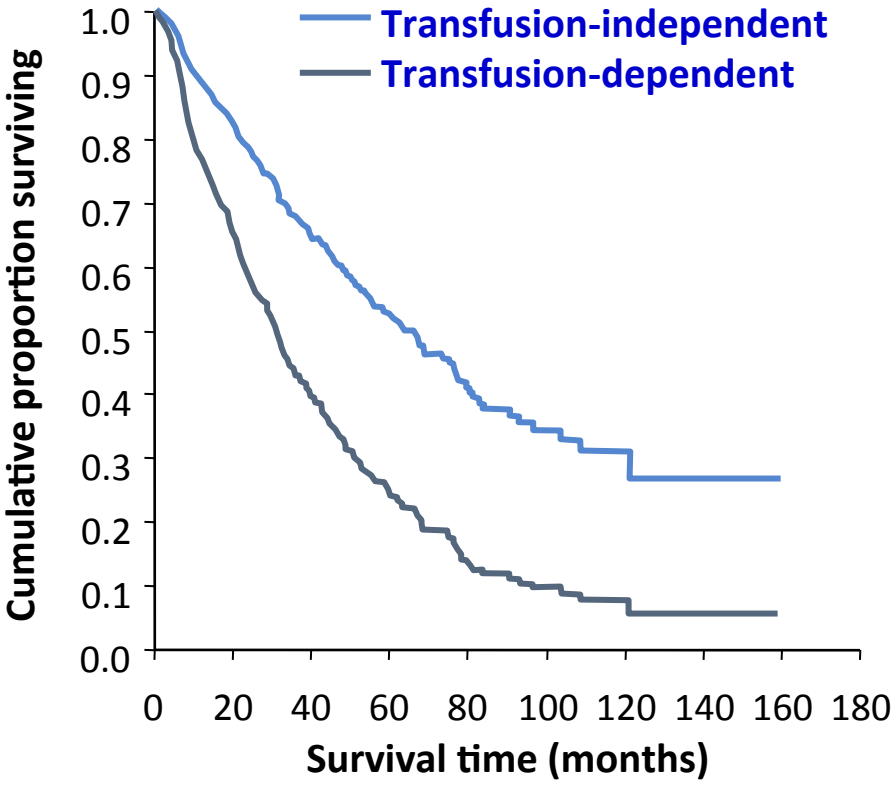
- Basato su:
  1. classificazione morfologica WHO
  2. gruppi di rischio del cariotipo secondo IPSS
  3. fabbisogno trasfusionale dei singoli pazienti

L'inclusione della richiesta trasfusionale come fattore di rischio è basata sui dati presentati dai ricercatori italiani, che mostrano una prognosi peggiore per i pts. che dipendono da regolari trasfusioni

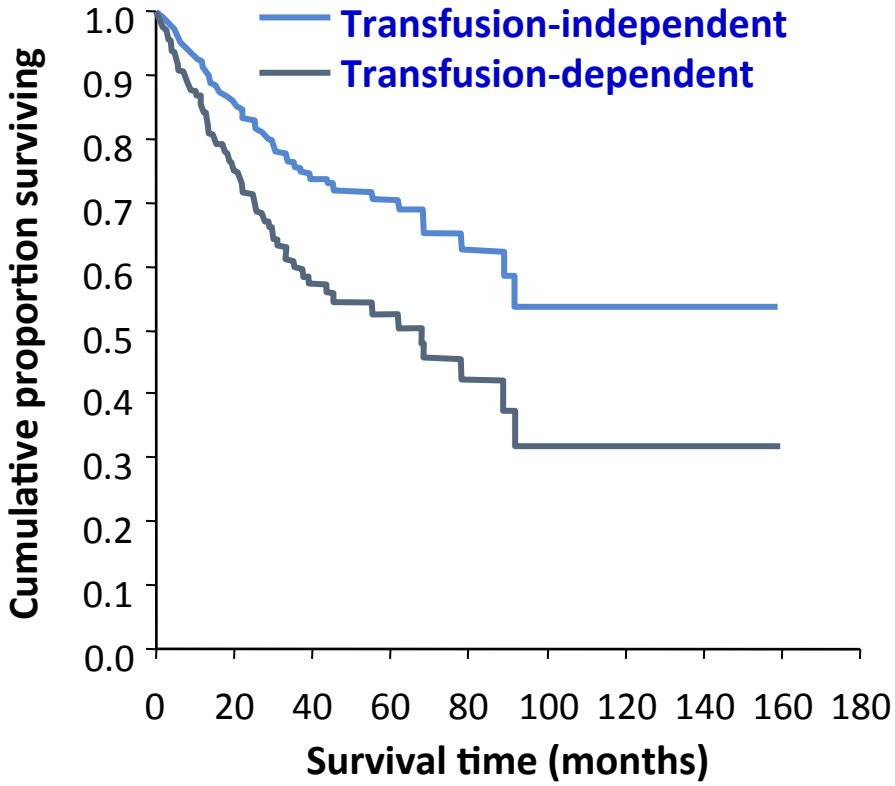
- Validata in maniera dinamica

Survival of MDS patients according to transfusion dependency

Overall survival
(HR = 1.91, p < 0.001)

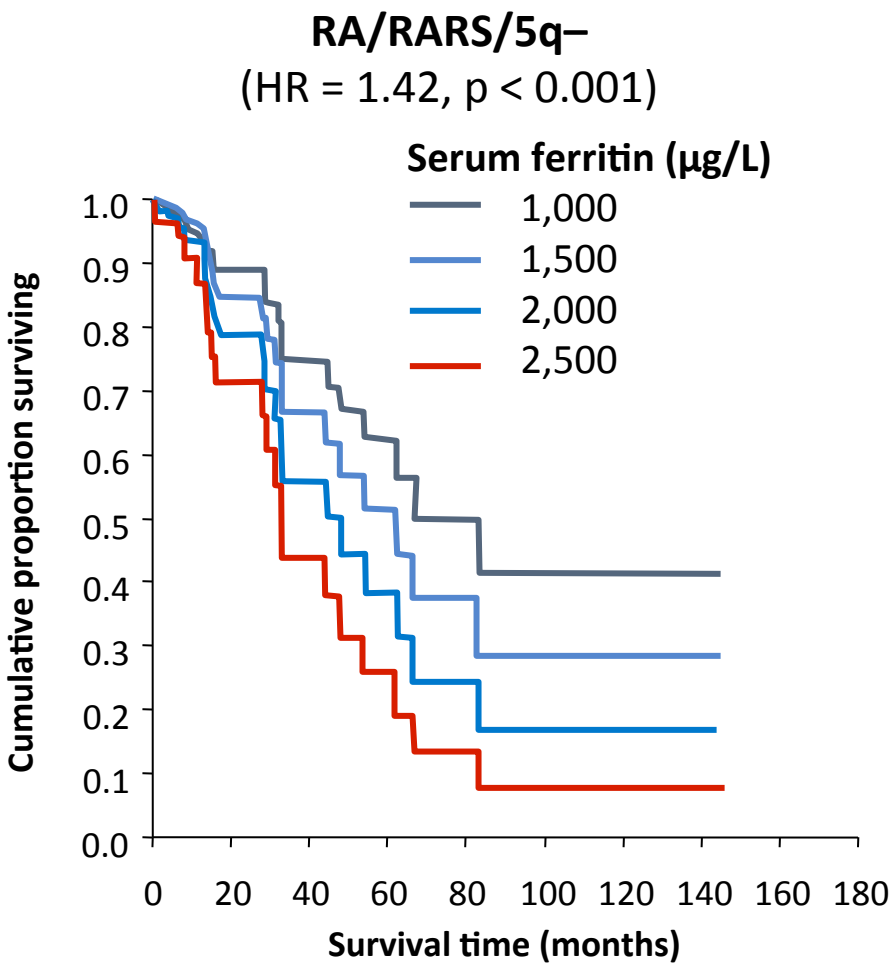


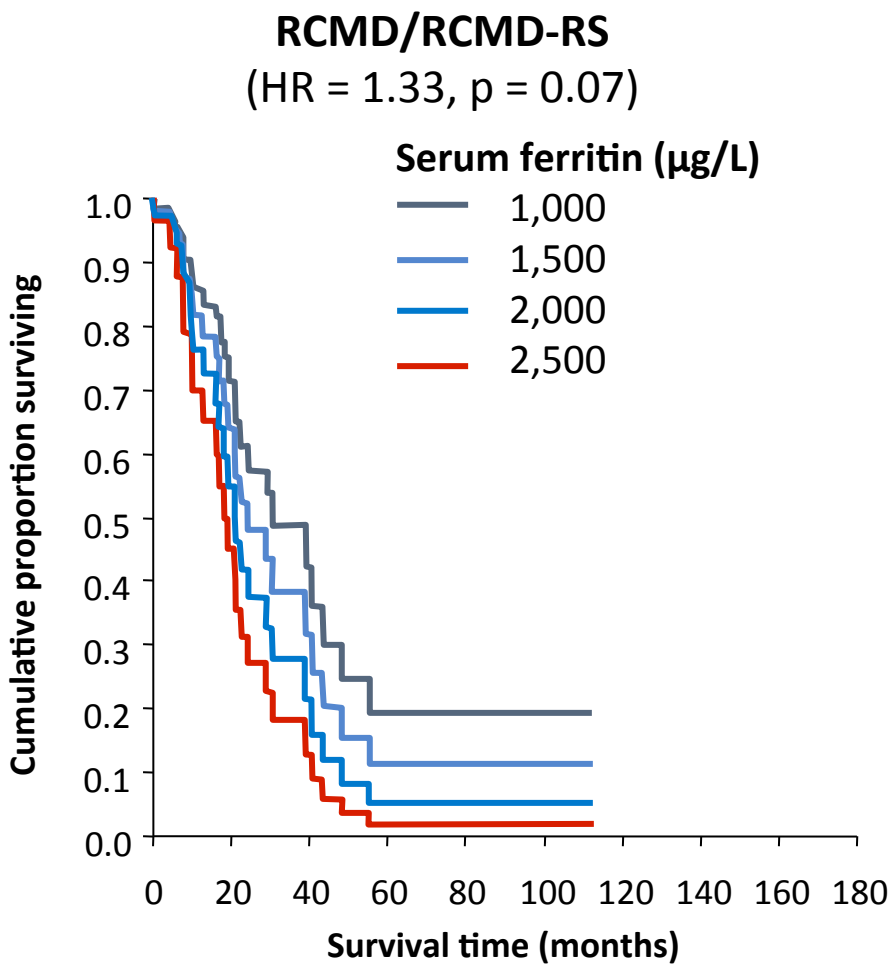
Leukaemia-free survival
(HR = 1.84, p = 0.001)



Malcovati L, et al. J Clin Oncol. 2005;23:7594-603.

Survival of MDS patients according to ferritin level



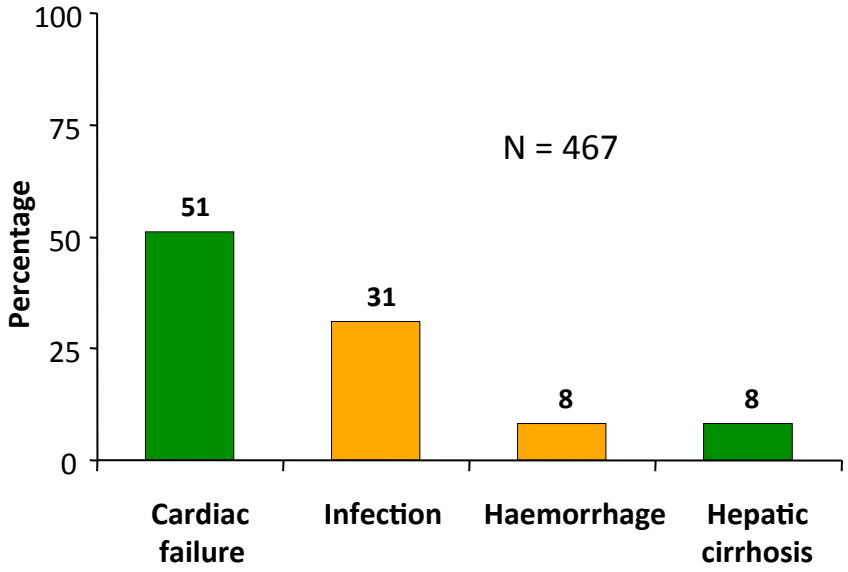


RA = refractory anaemia; RARS = RA with ringed sideroblasts;
RCMD = refractory cytopenia with multilineage dysplasia.

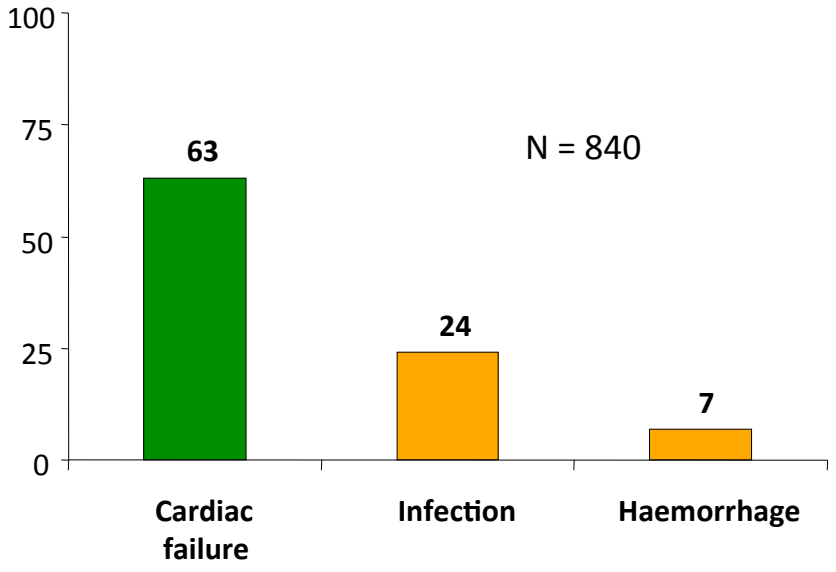
Malcovati L, et al. Haematologica. 2006;91:1588-90

Non-leukaemic death in patients with MDS

Probability of non-leukaemic death in low-risk MDS patients according to transfusion dependency[1]



Non-leukaemic cause of death in patients with MDS[2]



1. Malcovati L, et al. J Clin Oncol. 2005;23:7594-603.
2. Della Porta et al. Blood. 2007;110:[abstract 2453].

Trasfusioni e prognosi: classificazione WPSS

	Punteggi			
Calcolo punteggi WPSS	**0**	**1**	**2**	**3**
Sottotipo WHO	**RA, RARS, 5q-**	**RCMD, RCMD-RS**	**RAEB-1**	**RAEB-2**
Richiesta trasfusionale	**Nessuna**	**Regolare**	**–**	**–**
Rischio citogenet. IPSS	Buono	Intermedio	Elevato	–

Modificata da Malcovati L, et al. *J Clin Oncol* 2007;25:3503-3510

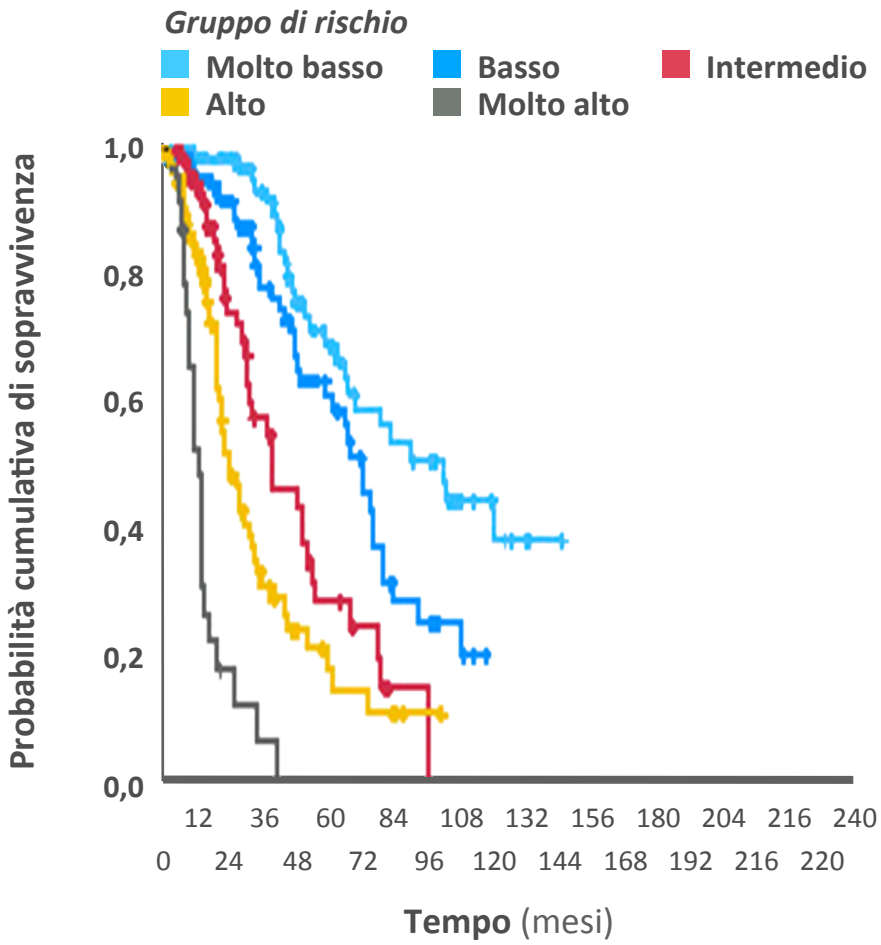
Trasfusioni e prognosi: classificazione WPSS

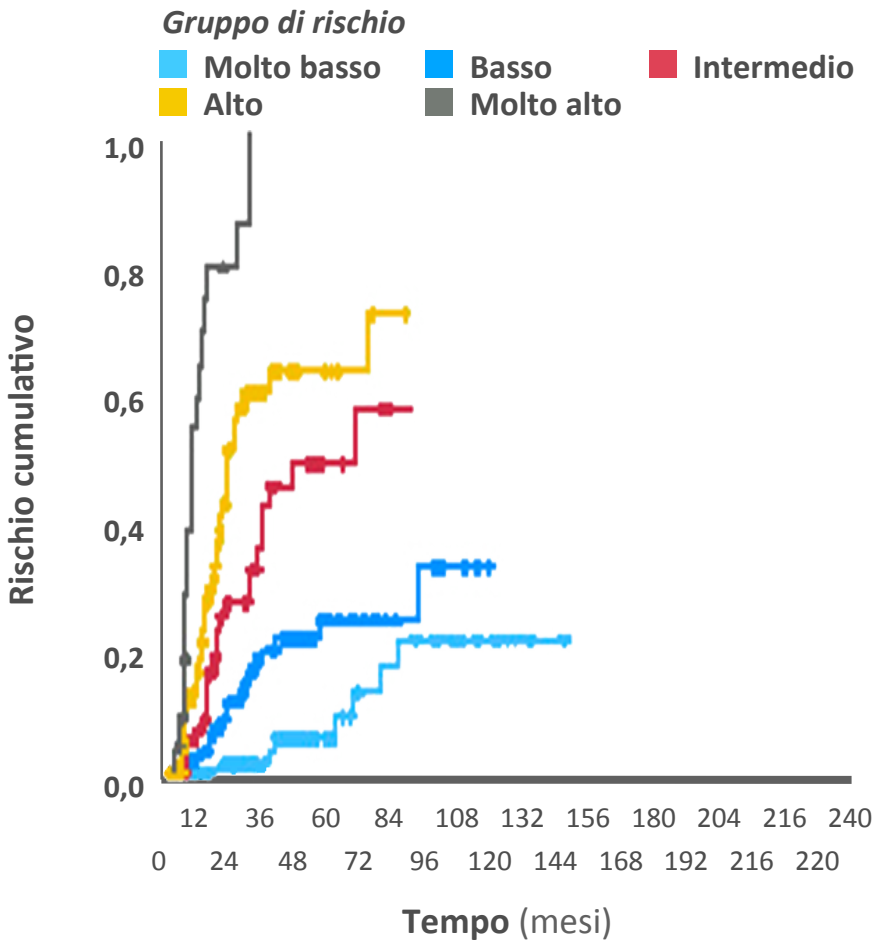
	Punteggi			
Calcolo punteggi WPSS	**0**	**1**	**2**	**3**
Sottotipo WHO	**RA, RARS, 5q-**	**RCMD, RCMD-RS**	**RAEB-1**	**RAEB-2**
Richiesta trasfusionale	**Nessuna**	**Regolare**	**–**	**–**
Rischio citogenet. IPSS	Buono	Intermedio	Elevato	–

Calcolo di rischio WPSS	**Punteggio**	**Sopravvivenza mediana** (mesi)
Molto basso	0	138
Basso	1	63
Intermedio	2	44
Alto	3-4	19
Molto alto	5-6	8

Malcovati L, et al. *J Clin Oncol* 2007;25:3503-3510

WHO-based Prognostic Scoring System (WPSS): Sopravvivenza e rischio di evoluzione leucemica





Malcovati L, et al. *J Clin Oncol* 2007;25:3503-3510.

WHO- based Prognostic Scoring System (WPSS)

Questo sistema di scoring mostra cinque gruppi di rischio, che si distinguono per una significativa differente mediana dei tempi di sopravvivenza (OS)

Il gruppo di rischio "very low" comprende:

- **pts con MDS unilineage (Displasia eritroide con o senza sideroblasti ad anello)**
- **con basso rischio citogenetico secondo IPSS**
- **senza necessità di trasfusioni**
- **pts non trasfusione-dipendenti con Sindrome del 5q-**

Questo sottogruppo ha una OS mediana che non differisce dalla mortalità standard rapportata all'età e, pertanto, rappresenta la reale MDS-LR

D'altra parte, sebbene le popolazioni ad alto rischio, (come la RAEB-t e la CMML) sono escluse dalla classificazione WHO MDS, la vera popolazione ad alto rischio nell'WPSS ha presentato tempi di OS mediana che sono comparabili a quelli di pts con AML non trattata

Classificazione rWPSS

	Punteggi			
Calcolo punteggi WPSS	**0**	**1**	**2**	**3**
Sottotipo WHO	**RA, RARS, 5q-**	**RCMD, RCMD-RS**	**RAEB-1**	**RAEB-2**
Anemia severa	**No**	**Sì**	**–**	**–**
Rischio citogenet. IPSS	Buono	Intermedio	Elevato	–

Anemia severa: Hb < 9 g/dl (M) o < 8 g/dl (F)

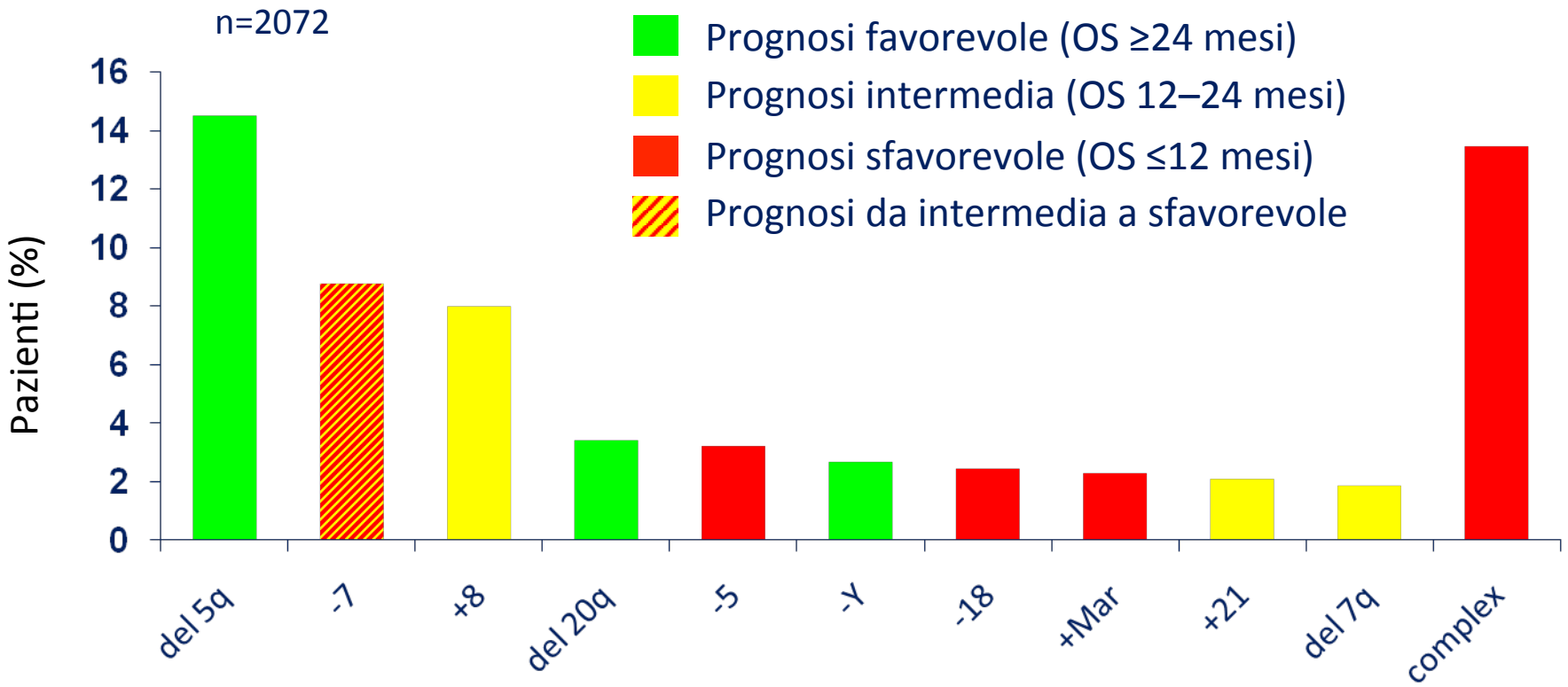
MDS classifications and scoring systems

- 1997 IPSS/IMRAW (FAB): 816 pts/7 DSs
  - Marrow blasts, cytogenetics, cytopenias
- 2001 WHO classification
  - Dysplastic subgroups, RAEB-1,2, del(5q)
- 2007 WPSS: 1165 pts/3 DBs
  - WHO subgroups, IPSS cytogenetics, RBC Txns
- 2001-2011 New features described as possible additional prognostic factors: needed refined consensus system

IWG-PG: Aims for Refining IPSS

- Determine impact of newer features for prognostic power
- Incorporate larger cytogenetic subgroups
  & Re-assess their prognostic impact
- Analyze depth of cytopenias
- Provide classification w/ improved prognostic ability
- Maintain continuity, feasibility, flexibility
- 17 DBs/6388 pts

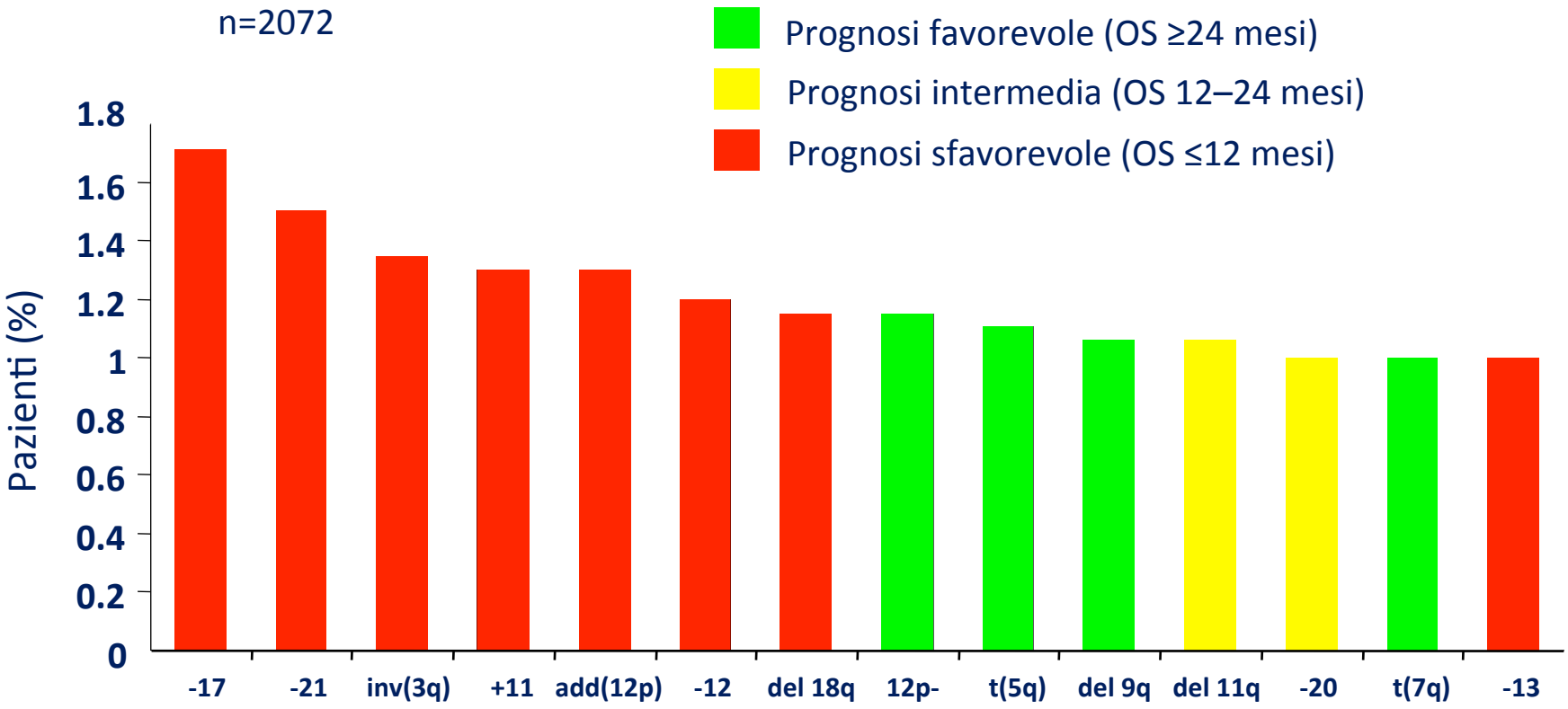
Alterazioni cromosomiche più frequenti nei pazienti con SMD



OS = sopravvivenza globale

Haase D et al. Blood 2005;106:232a

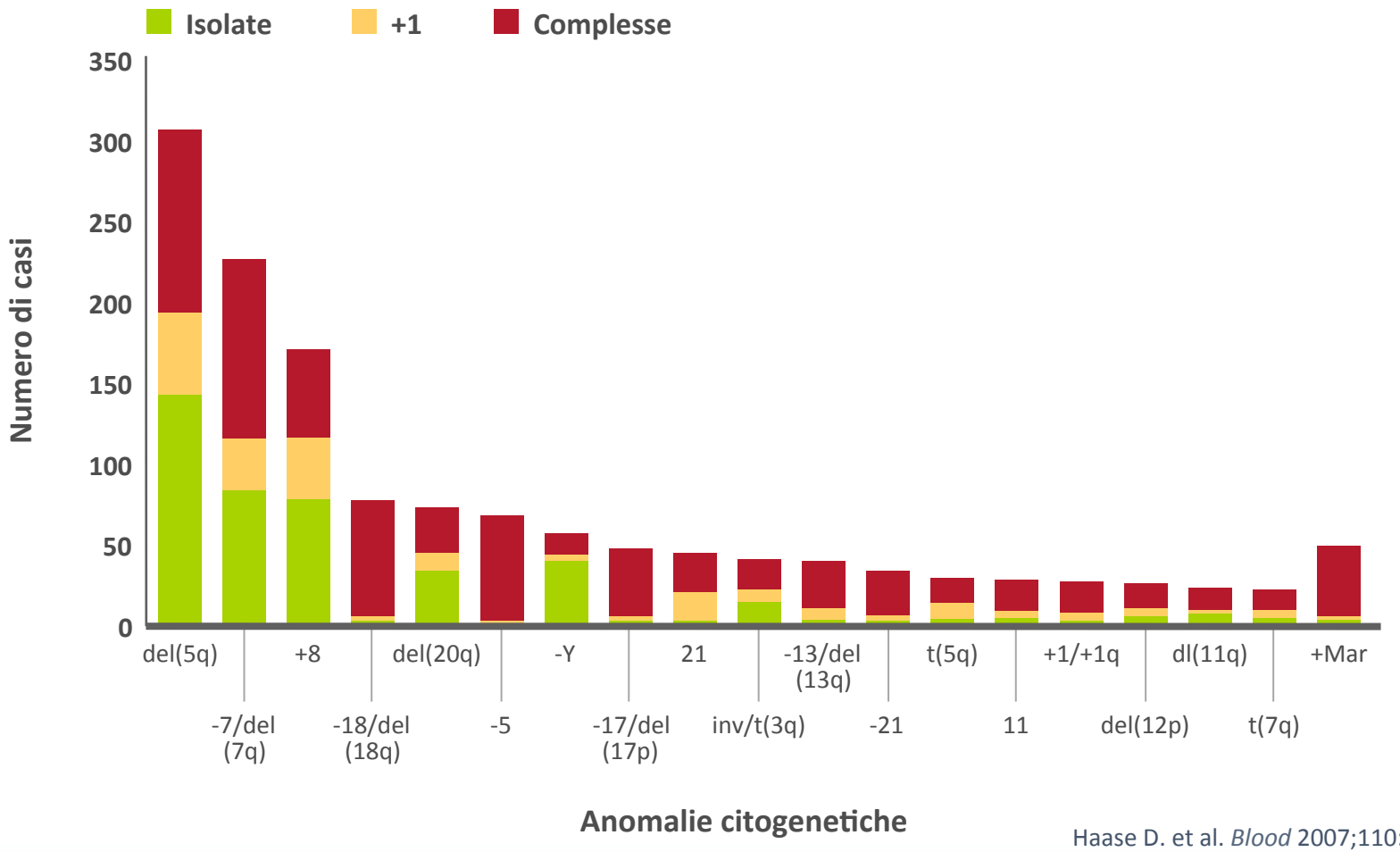
Alterazioni cromosomiche meno frequenti in pazienti con SMD



Haase D *et al*. *Blood* 2005;106:232a

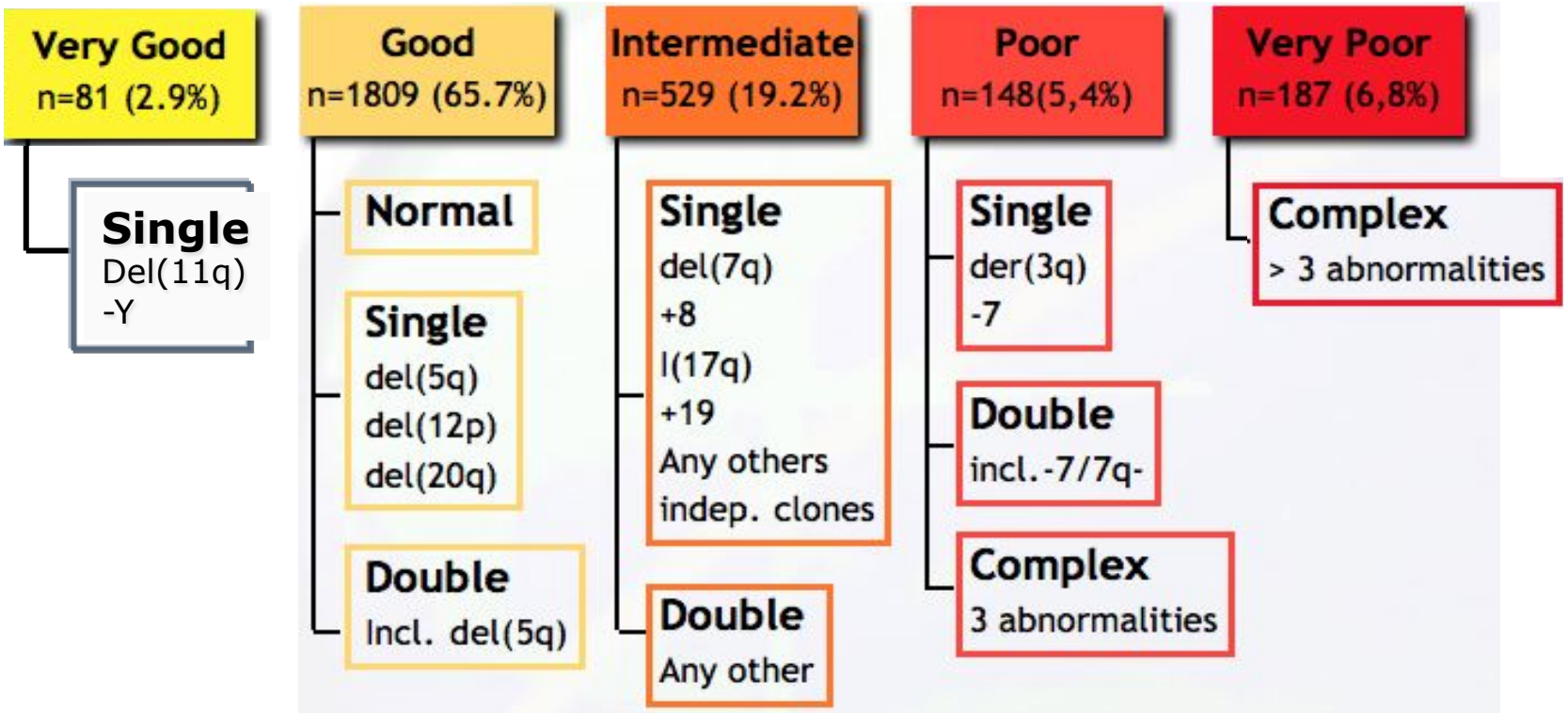
Frequenza delle più comuni anomalie citogenetiche suddivise in isolate, con 1 anomalia addizionale e complesse

Database che include 2124 pazienti con SMD



Haase D. et al. *Blood* 2007;110:4385-4395

IPSS-R: Cytogenetic Prognostic Groups



Schanz et al.: JCO:2011

IPSS-R Variables & Weighted Scores*

*Regression analysis for survival and AML evolution

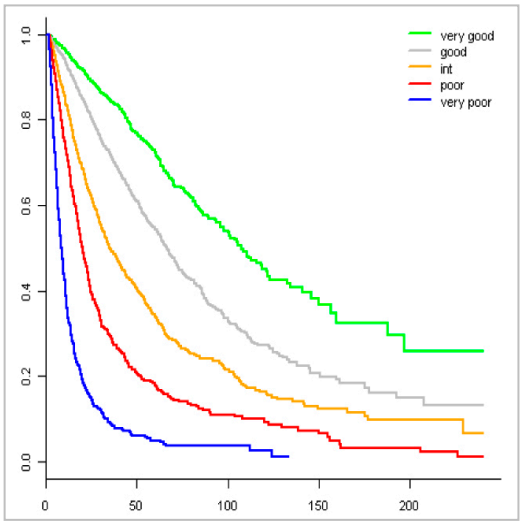
Cytogenetics	V. Good 0	Good 2	Interm. 4	Poor 6	V. Poor 8
BM Blast %	<5% 0	5-10% 2	11-20% 4	21-30% 6	
Hgb	≥10 0	<10 2			
ANC	>0.8 0	≤0.8 1			
Platelets	≥100 0	<100 1			

IPSS-R: Prognostic Risk Groups/Scores

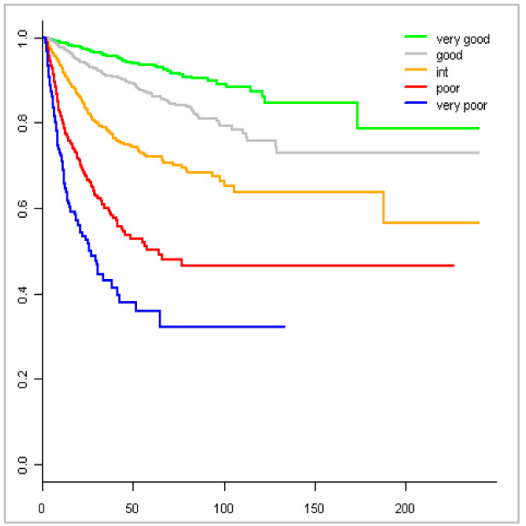
Risk Category	Score
1. **Very Low:**	0 - 2
2. **Good:**	>2 - 3.5
3. **Intermediate**:	>3.5 - 5
4. **High:**	>5 - 6
5. **Very High:**	>6

IPSS-R Survival

n=7012



Freedom from AML



	Very Low	Good	Inter-mediate	Poor	Very High
Med. OS	8.7	5.3	3.0	1.6	0.8
AML 25%	NR	10.7	4.0	1.4	0.8

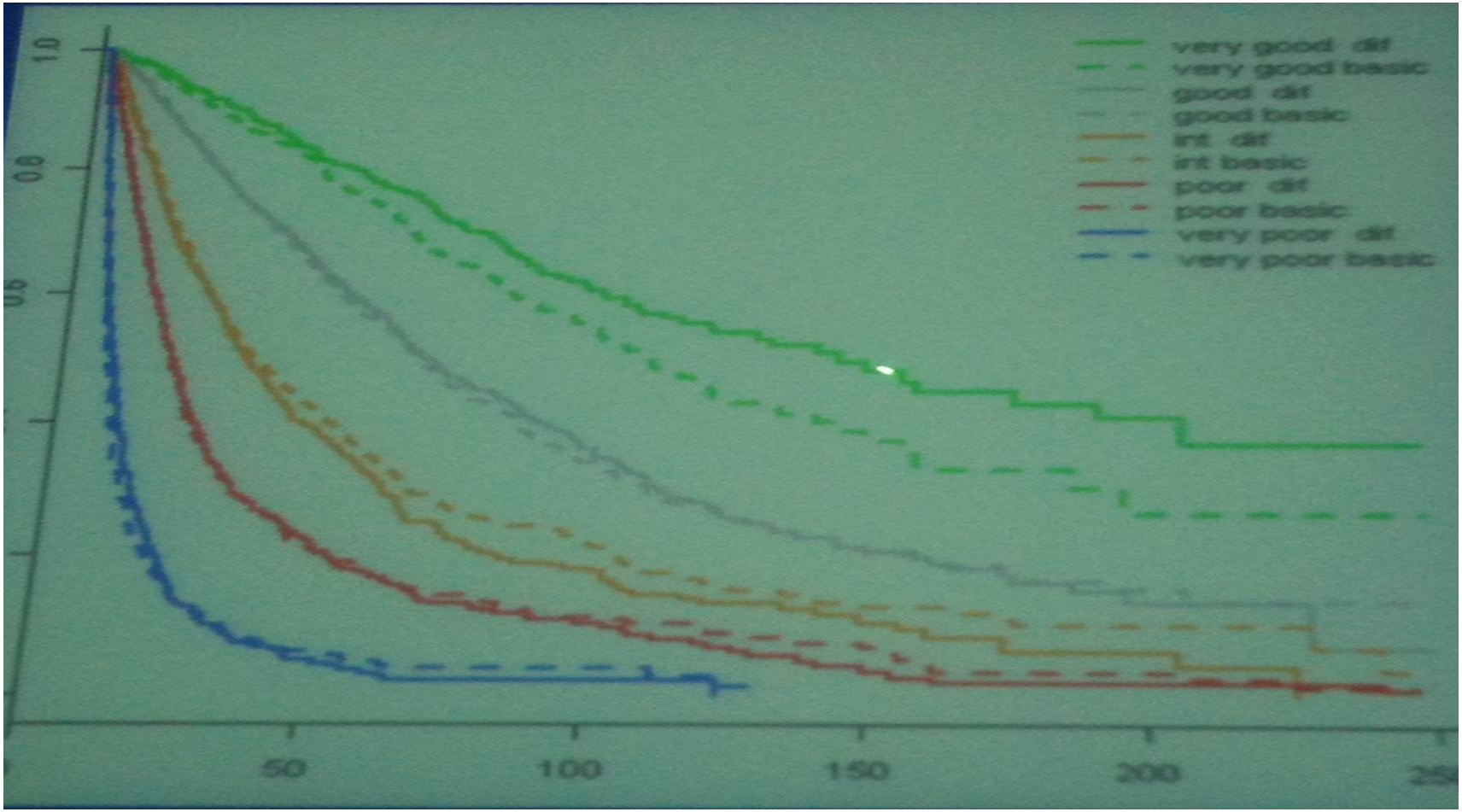
IPSS-Revised

- Refined cytogenetic subgroups (*16 vs 7*) & prognostic categories (*5 vs 3*)
- Analyzed depth of cytopenias
- Improved predictive power w/ more precise prognostic subgroups (*5 vs 4*)

IPSS- R: Additive Prognostic Variables

	Total cases	Survival	AML
Age	100%	++	-
PS/ECOG	36%	++	-
Ferritin	43%	++	-
Fibrosis	19%	-	+/-
LDH	59%	+	-
Beta2-M	15%	(++)	-

IPSS-R Survival: Impact of Age



IPSS- R: Additive Prognostic Variables

	Total cases	Survival	AML
Age	100%	++	-
PS/ECOG	36%	++	-
Ferritin	43%	++	-
Fibrosis	19%	-	+/-
LDH	59%	+	-
Beta2-M	15%	(++)	-

IPSS Modifying Factors

Age & Co-morbidity	Low/Int-1
Secondary MDS	Shorter natural history
Thrombocytopenia severity	Greater bleeding risk
RBC-TD or Ferritin	Increased AML, decreased OS
BM pathology	$CD34^+$ clusters (ALIP), marrow fibrosis
Other Chromosome abnormalities*	▪ Favorable: -12/12p, 15q- ▪ Unfavorable: 3q21/26, double with -7, Monosomal, complex >3
Unfavorable molecular profile	▪ $_{mu}$*RUNX1,ETV6,DNMT3a,TP53* ▪ *microRNA-181*

Hasse D, et al. Blood 2007; 110: 4385

Genetic Pathways & Somatic Mutations

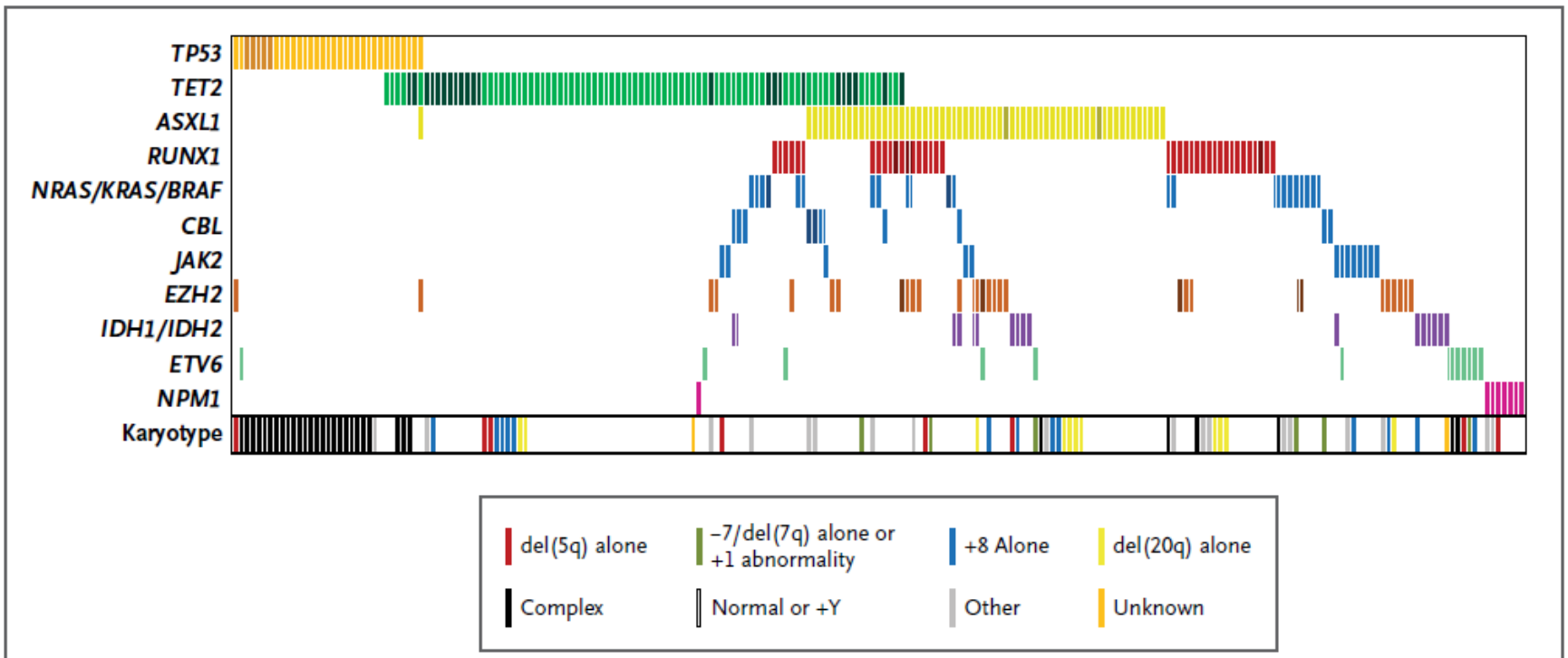


Figure 1. Mutations and Cytogenetic Abnormalities in 223 Samples with at Least One Mutation.

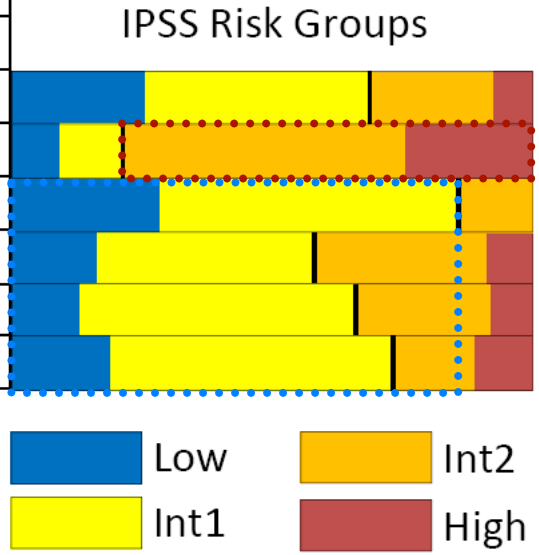
Mutations in the 11 most frequently mutated gene groups are shown by colored bars. Each column represents 1 of the 223 samples with a mutation in one or more of the genes listed. Darker bars indicate samples with two or more distinct mutations in that gene group. The karyotype of each of the 223 samples is also shown.

Bejar et al. N Engl J Med. 2011;364:2496-506

Five Mutations Identify Unfavorable Prognosis Independent of IPSS

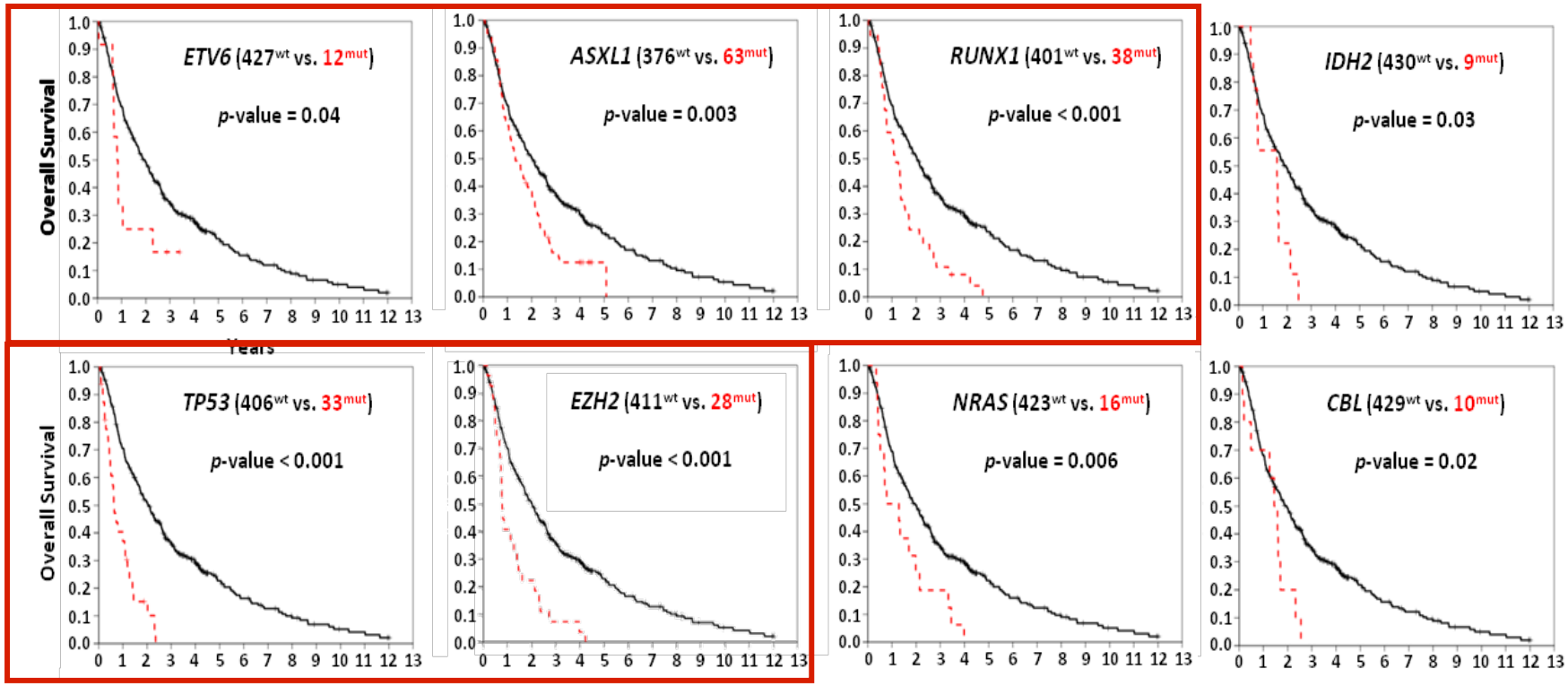
MDS n=439, 18 genes

	HR (95% CI)	p-value
Age		
≥55 yrs vs. <55 yrs	1.81 (1.20-2.73)	0.004
IPSS Risk Group		
Int1 vs. Low	2.29 (1.69-3.11)	<0.001
Int2 vs. Low	3.45 (2.42-4.91)	<0.001
High vs. Low	5.85 (3.63-9.40)	<0.001
Mutational Status - Present vs. Absent		
TP53 Mutation	2.48 (1.60-3.84)	<0.001
EZH2 Mutation	2.13 (1.36-3.33)	<0.001
ETV6 Mutation	2.04 (1.08-3.86)	0.029
RUNX1 Mutation	1.47 (1.01-2.15)	0.047
ASXL1 Mutation	1.38 (1.00-1.89)	0.049



Bejar et al. N Engl J Med. 2011;364:2496-506

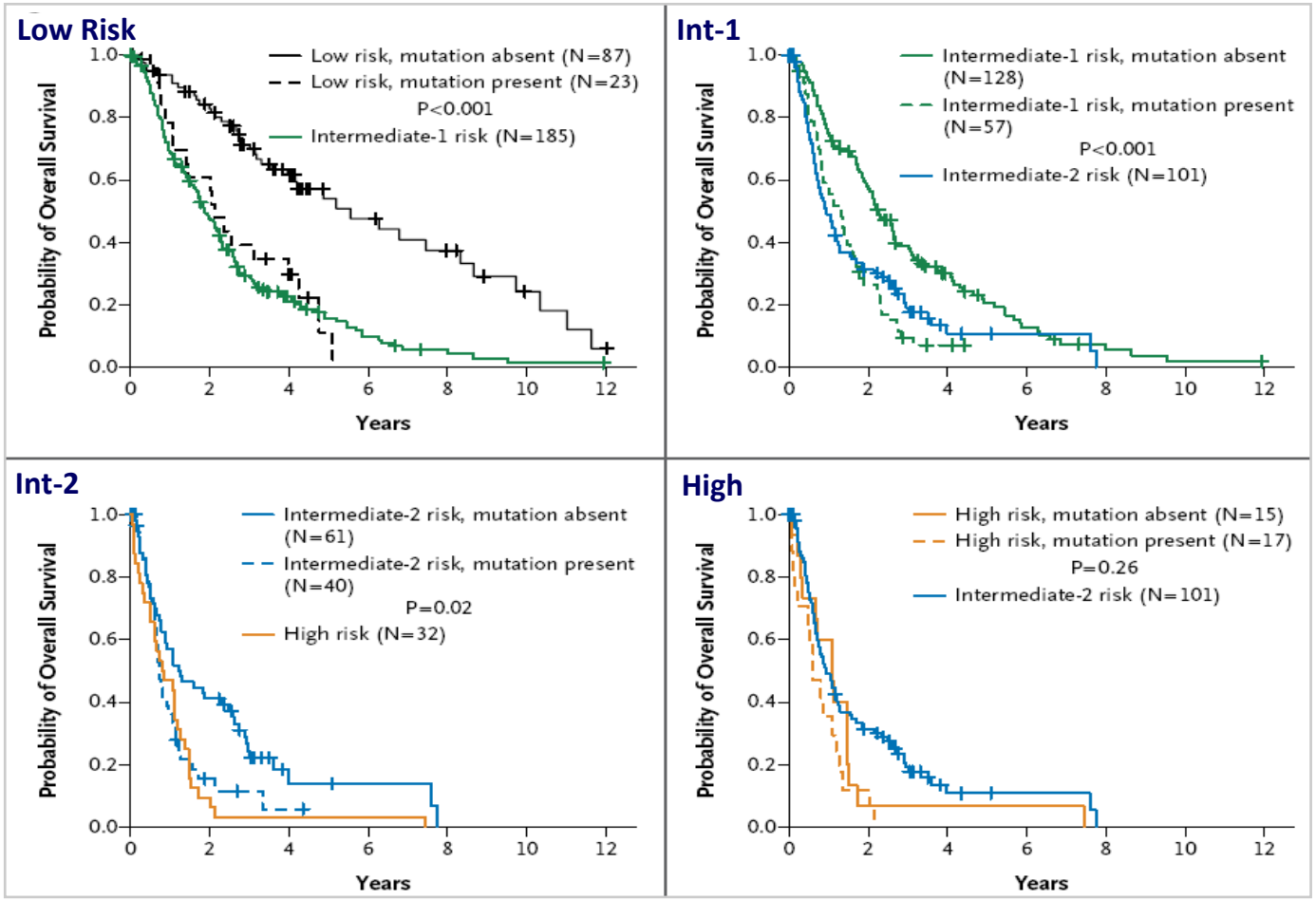
Gene Point Mutations - Independent Predictors of Overall Survival



- Multivariable analysis, mutations of *TP53* (HR, 2.48), EZH2 (HR, 2.13), ETV6 (HR, 2.04), RUNX1 (HR, 1.47), and ASXL1 (HR, 1.38) were ***independent predictors of ↓OS vs. age, sex, IPSS***

Bejar et al. N Engl J Med. 2011;364:2496-506

Overall Survival According to IPSS Risk Category & Mutation Status

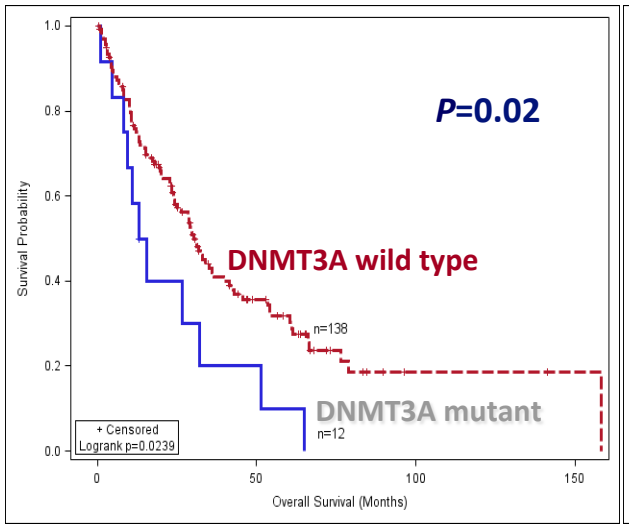


Bejar et al. N Engl J Med. 2011;364:2496-506

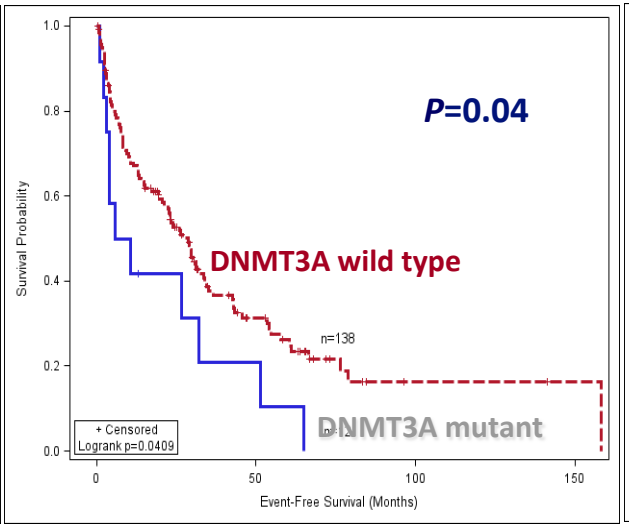
Impact of *DNMT3A* Mutations on Outcome

- 13 somatic mutations in 12/150 MDS patients (8%)
- 2 truncating, 11 missense in MTase domain, all heterozygous

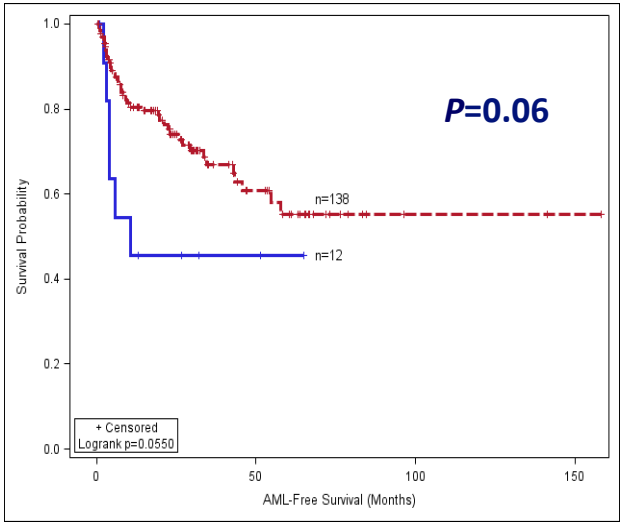
Overall Survival



Event-free Survival



LFS

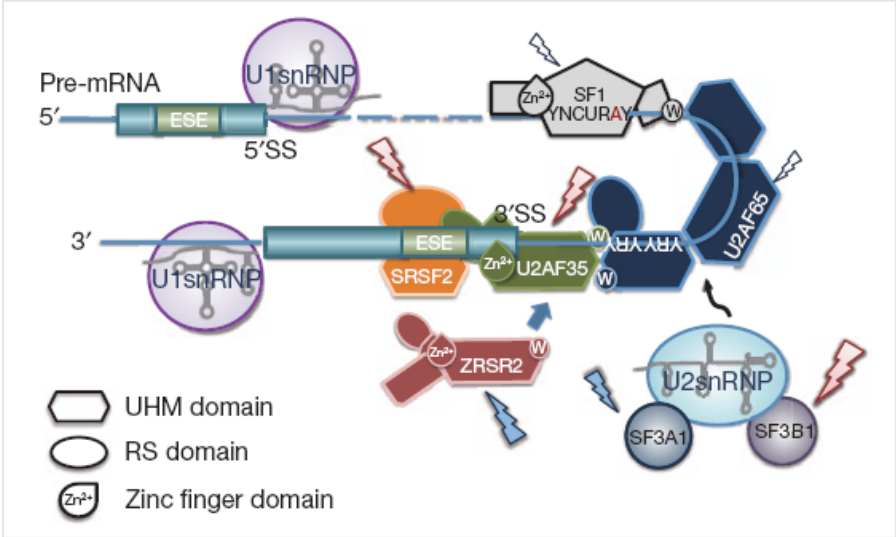


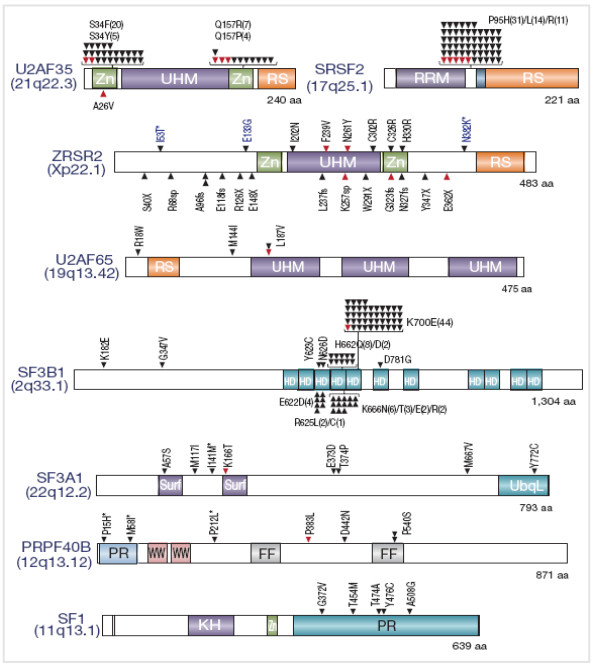
DNMT3A mutations occur in all morphologic and IPSS categories, and associated with inferior OS, EFS and LFS

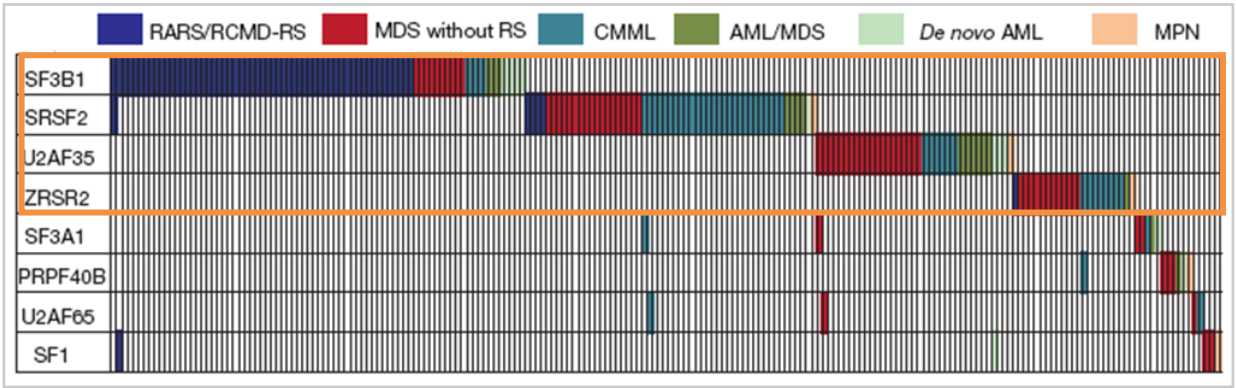
Walter M, et. al. Leukemia. 2011;25(7):1153

Frequent Mutations in Components of Splicing Machinery in MDS

- Exome sequencing (n=29)
- Targeted sequencing of 8 genes (5 snRNPs, 3 accessory proteins) in the spliceosome complex (n=582)







Affected genes involved in 3'-splice site recognition

Yoshida K, et al. Nature. 2011; 478: 64

*small nuclear ribonuclear proteins

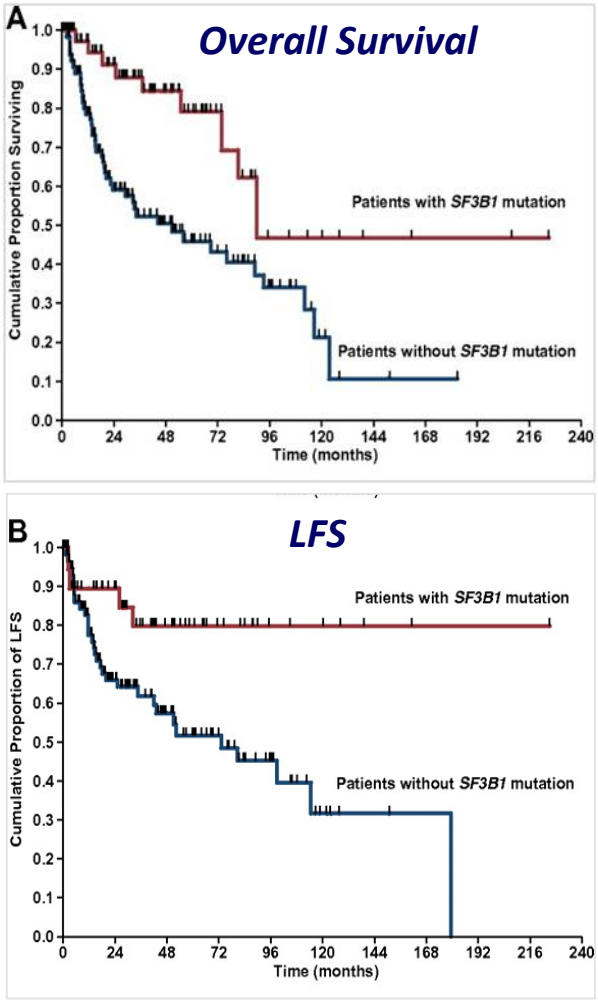
SF3B1 Mutations In MDS and Other Malignancies

Subtype	Total	Variants	%
RA	91	9	9.9%
RARS	59	40	67.8%
RCMD	53	3	5.7%
RCMD-RS	23	13	56.5%
RAEB-1, RAEB 2	110	6	5.5%
Other	18	1	5.6%
Total	72	354	20.3%

Histology	Total	Variants	%
AML	57	3	5.3%
Breast cancer	172	2	1.2%
Renal cancer	30	1	3.3%
CLL	40	2	5.0%
Multiple myeloma	32	1	3.1%
Salivary	27	1	3.7%
Cancer cell lines	746	8	1.1%

Papaemmanuil E, et al. NEJM 2011; 365: 1384

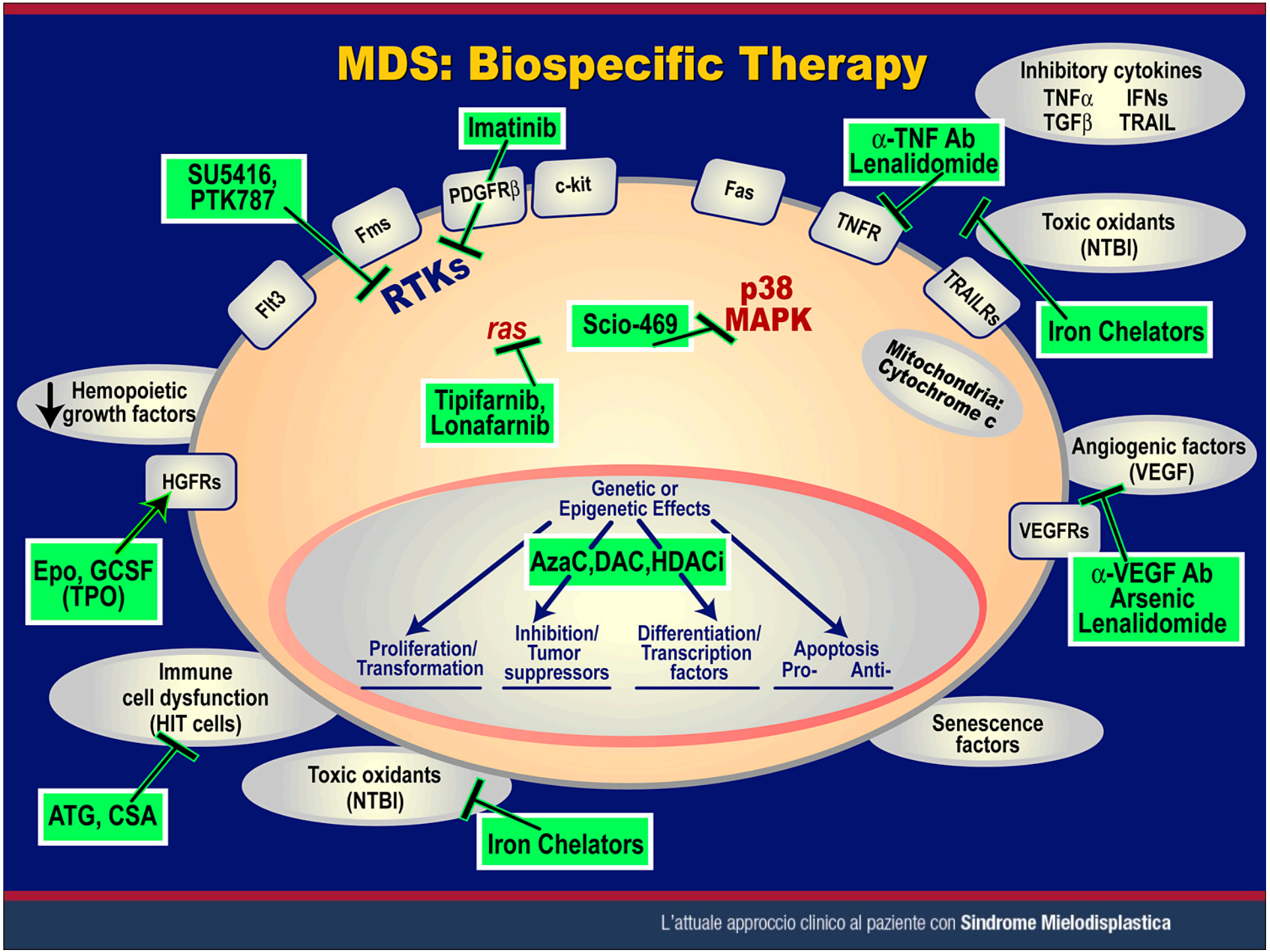
SF3B1 Mutation is an Independent Prognostic Variable for OS and LFS



Multivariate Analysis

Risk Factor	HR	*P* value
Age <70 vs. ≥70	1.53	0.224
Gender (M vs. F)	0.69	0.292
IPSS risk group	2.16	<0.001
***SF3B1* mutant**	0.21	0.038

Malcovati L et al. Blood 2011;118:6239-6246


MDS: Biospecific Therapy
Inhibitory cytokines
TNFα IFNs
TGFβ TRAIL
α-TNF Ab
Lenalidomide
Imatinib
SU5416,
PTK787
PDGFRβ
c-kit
Fas
TNFR
Fms
Flt3
RTKs
TRAILRs
Toxic oxidants
(NTBI)
Iron Chelators
p38
MAPK
Scio-469
ras
Tipifarnib,
Lonafarnib
Mitochondria:
Cytochrome c
Hemopoietic
growth factors
HGFRs
Epo, GCSF
(TPO)
Angiogenic factors
(VEGF)
VEGFRs
α-VEGF Ab
Arsenic
Lenalidomide
Genetic or
Epigenetic Effects
AzaC,DAC,HDACi
Proliferation/
Transformation
Inhibition/
Tumor
suppressors
Differentiation/
Transcription
factors
Apoptosis
Pro- Anti-
Immune
cell dysfunction
(HIT cells)
ATG, CSA
Toxic oxidants
(NTBI)
Iron Chelators
Senescence
factors

Target therapy

Chronic myelomonocytic leukemia

with t (5;12)

or other

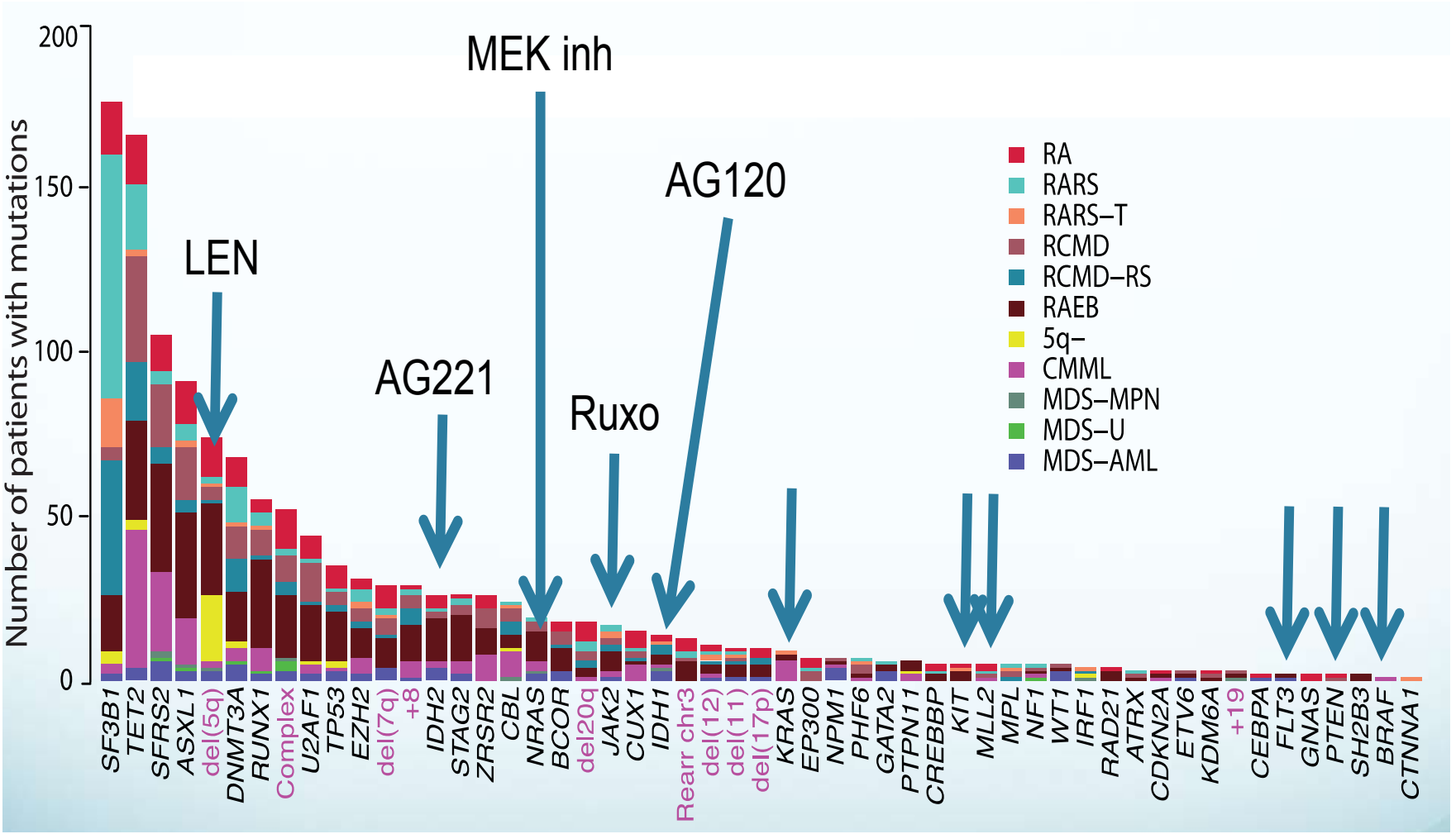
translocations involving

PDGFbetaR (5q31-33)

IMATINIB MESYLATE

Apperley et al , NEJM 2002

Actionable (or "Druggable") mutations



Papaemmanueil et al Blood 2013

AG-221, an Oral, Selective, First-in-class potent inhibitor of the IDH2 Mutant Enzyme

Phase 1 study on IDH2+ advanced Hematol Malignancies

Best overall response by disease in response-evaluable patients[a]
(includes patients from dose-escalation and expansion)

	R/R AML[b] n=111	Untreated AML n=22	MDS n=14	Other[c] n=10	Total[d] N=157
CR, n (%) (95% CI)	20 (18.0) (11.4, 26.4)	3 (13.6) (2.9, 34.9)	2 (14.3) (1.8, 42.8)	1 (10.0) (0.3, 44.5)	26 (16.6) (11.1, 23.3)
CRp	1	—	1	1	3
PR	16	2	—	—	18
mCR[e]	8	1	4	1	14
CRi	1	1	—	—	2
SD	49	7	4	7	67
PD	7	5	2	—	14
NE	9	3	1	—	13
ORR, n (%) (95% CI)	46 (41.4) (32.2, 51.2)	7 (31.8) (13.9, 54.9)	7 (50.0) (23.0, 77.0)	3 (30.0) (6.7, 65.2)	63 (40.1) (32.4, 48.2)

[a] Includes patients with a Day 28 or later response assessment or discontinued earlier than Day 28 for any reason as of 1 May 2015
[b] Includes 36 patients from Arms 1 and 2 of expansion, with 3 CRs and 12 objective responses
[c] Includes CMML n=3; CMML-2 n=4; blastic plasmacytoid dendritic cell neoplasm n=1; MDS transformed to AML n=1; refractory AML n=1
[d] Disease type missing for 1 patient
[e] Includes morphologic leukemia-free state

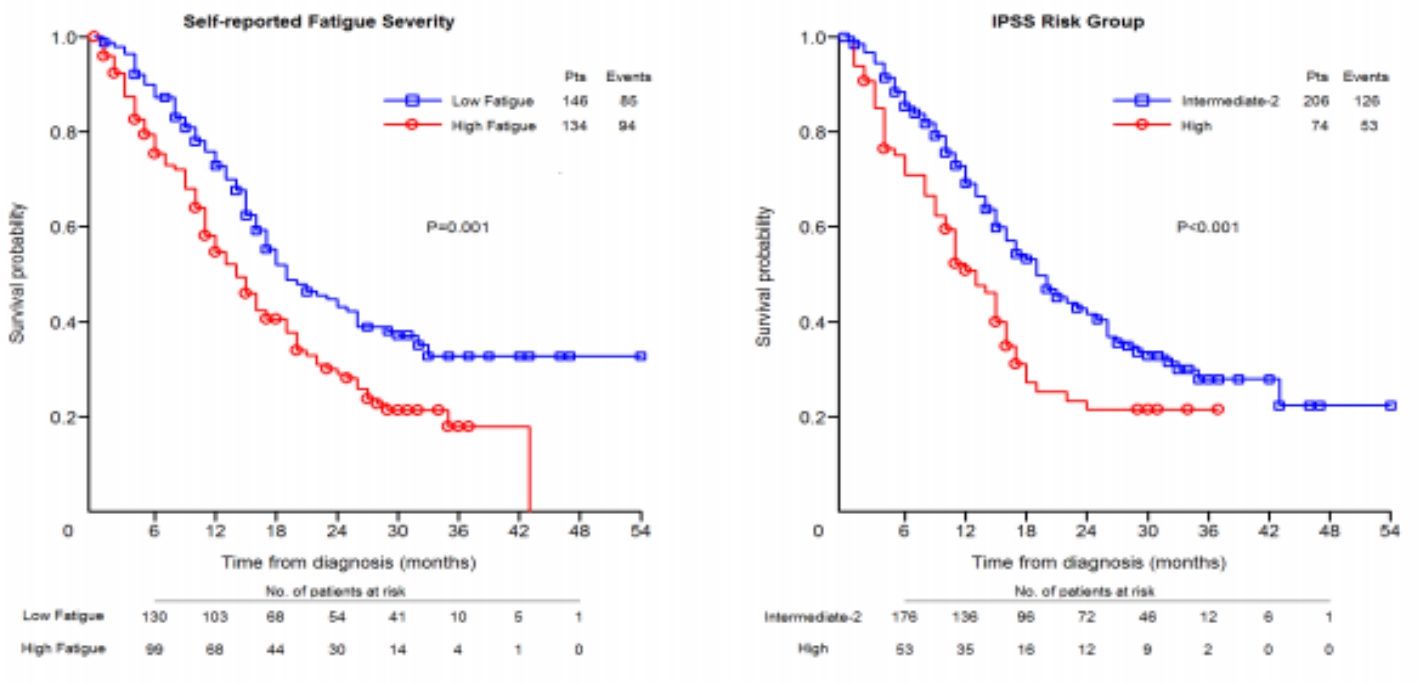
DiNardo C, et al. Poster Presentation (P569) at the 20th Congress of the European Hematology Association (EHA); June 11-14, 2015; Vienna, Austria

Rationale for development of PD1-PDL1 inhibitors in MDS & AML

- PD-L1 expression may suppress the immune function in AML (Dolen S. et al., 2013),
- PD-1/PD-L1 signaling is likely involved in MDS pathogenesis and transformation to AML (Yang et al., 2014, Ogata et al., 2012, Tamura et al., 2005, Zhang et al., 2009, Zhou et al., 2010),
- PD-1/PD-L1 pathway is likely involved in the resistance of MDS and AML cells to HMAs and other therapy (Yang et al., 2014, Kronig et al., 2013),
- Myeloid cell lines and patients treated by HMAs demonstrated **up-regulation of PD-L1 expression** (Yang et al., 2014),
- There are potential mechanisms of therapeutic synergy between epigenetic modulators and PD-1/PDL1 pathway blockade (Yang et al., 2014, Bramer et al., 2013),

Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study

Overall Survival by baseline patient's self-reported fatigue severity and IPSS risk group



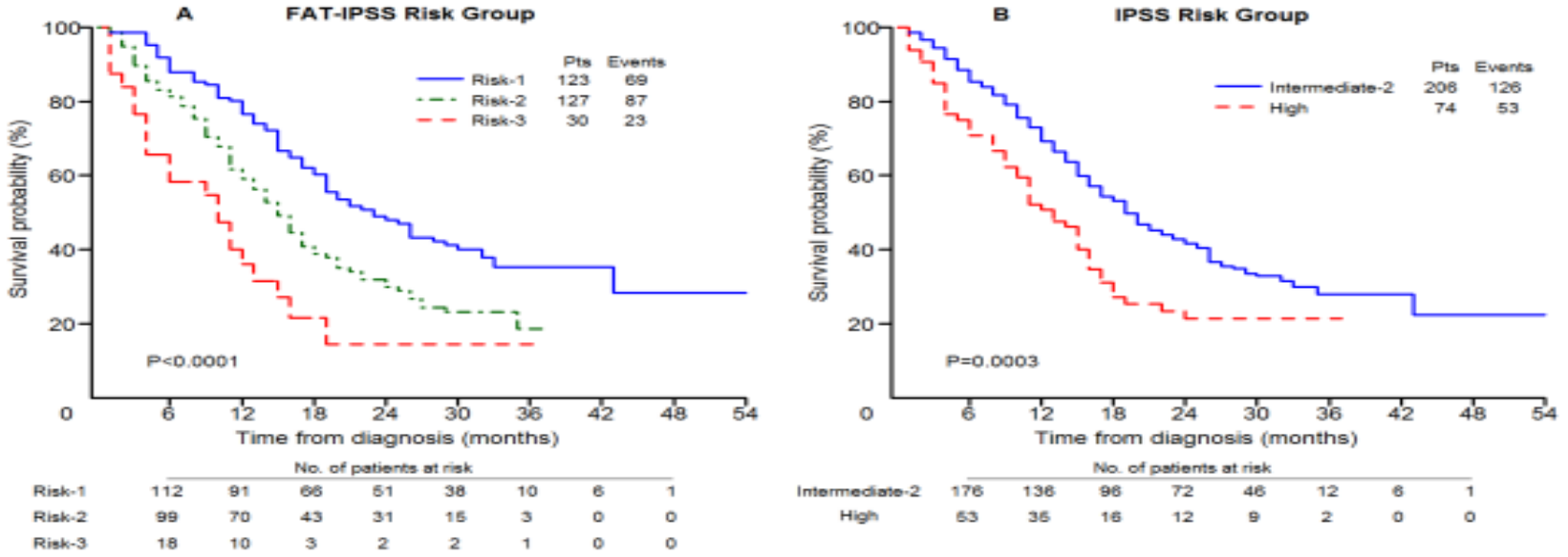
Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30; IPSS: International Prognostic Scoring System; CI: confidence interval.

Legend: Low fatigue: patients reporting a baseline EORTC QLQ-C30 fatigue score below median value (34 points). High fatigue: patients reporting a baseline EORTC QLQ-C30 fatigue score equal or above the median value. Median overall survival time: low fatigue, 19 months (95% CI 17 - 26 months), high fatigue, 14 months (95% CI 11 - 17). Intermediate-2 IPSS score, 20 months (95% CI 17 - 24 months), high IPSS risk score, 13 months (95% CI 9 - 16 months).

Efficace F. et al. Lancet Oncol 2015 Nov;16(15):1506-14

Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study

Figure 1. Overall Survival by the new FAT-IPSS and the standard IPSS risk group classification



Abbreviations: FAT-IPSS, Fatigue-based International Prognostic Scoring System; IPSS: International Prognostic Scoring System.

Legend: fatigue is the patient's self-reported Fatigue scale from the EORTC QLQC30 questionnaire. The fatigue scale ranges from 0 to 100 points, a higher score indicating a higher fatigue burden.

Efficace F. et al. Lancet Oncol 2015 Nov;16(15):1506-14

Conclusioni

- **Corretta stratificazione prognostica del paziente alla diagnosi ed in corso di malattia**

- **Indispensabile lo studio citogenetico su tutti i pazienti con MDS, indipendentemente dall'età**

- **Biologia molecolare, non soltanto per comprendere meglio la patologia ma anche per rifinire ulteriormente la valutazione prognostica (mIPSS) ed identificare potenziali bersagli terapeutici (target therapy)**

- **... senza dimenticare la valutazione clinica del paziente, il performance status, le comorbidità ed i Patient Reported Outcomes (PRO)**