MDS ad alto rischio

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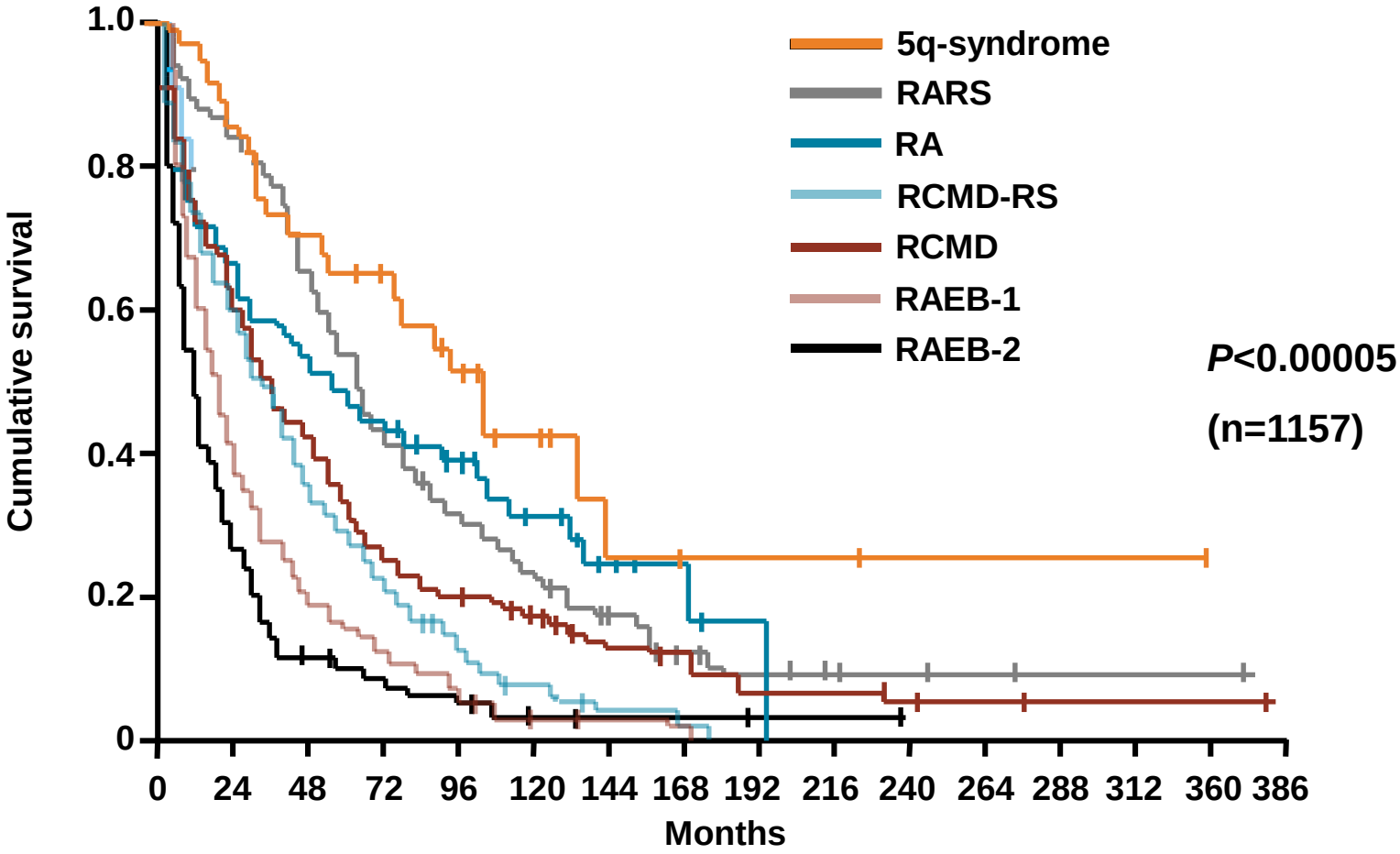
PROGNOSTIC ASSESSMENT IN MDS

- **DISEASE-RELATED FACTORS**
- **PATIENT-RELATED FACTORS**

Classificazioni delle sindromi mielodisplastiche: WHO 2008

Categoria WHO 2008	Sangue periferico	Midollo osseo
Citopenia refrattaria con displasia unilineare (RCUD): anemia refrattaria, neutropenia refrattaria, piastrinopenia refrattaria	▪ Uni-o bi-citopenia ▪ Blasti assenti o rari (<1%)	▪ Displasia unilineare ≥10% cellule di 1 linea mieloide ▪ Blasti <5% ▪ Sideroblasti ad anello <15%
Anemia refrattaria con sideroblasti ad anello (RARS)	▪ Anemia ▪ Assenza di blasti	▪ Displasia eritroide isolata ▪ Blasti <5% ▪ Sideroblasti ad anello ≥15%
Citopenia refrattaria con displasia multilineare (RCMD)	▪ Citopenia(e) ▪ Blasti assenti o rari (<1%) ▪ Non corpi di Auer ▪ Monociti <1 x 10^9/l	▪ Displasia in ≥10% delle cellule in 2 o più linee mieloidi ▪ Blasti <5% ▪ Assenza di corpi di Auer ▪ Sideroblasti ad anello ±15%
Anemia refrattaria con eccesso di blasti–1 (RAEB-1)	▪ Citopenia(e) ▪ Blasti <5% ▪ Non corpi di Auer ▪ Monociti <1 x 10^9/l	▪ Displasia uni- o multilineare ▪ Blasti 5-9% ▪ Assenza di corpi di Auer
Anemia refrattaria con eccesso di blasti–2 (RAEB-2)	▪ Citopenia(e) ▪ Blasti 5-19% ▪ Corpi di Auer ± ▪ Monociti <1 x 10^9/l	▪ Displasia uni- o multilineare ▪ Blasti 10-19% ▪ Corpi di Auer ±
Sindrome mielodisplastica inclassificabile (MDS-U)	▪ Citopenie ▪ <1% blasti	▪ Displasia in ≤10% delle cellule in 1 o più linee mieloidi + anomalia citogenetica considerata evidenza di SMD ▪ Blasti <5%
Sindrome mielodisplastica associata a del(5q) isolata	▪ Anemia ▪ Blasti assenti o rari (<1%) ▪ Conta piastrine normale o aumentata	▪ Megacariociti normali o aumentati con nuclei ipolobati ▪ Blasti <5% ▪ Assenza di corpi di Auer ▪ Anomalia citogenetica del(5q) isolata

Survival of patients with MDS based on WHO criteria



Germing U *et al*. *Haematologica* 2006;91:1596–1604

International Prognostic Scoring System (IPSS)

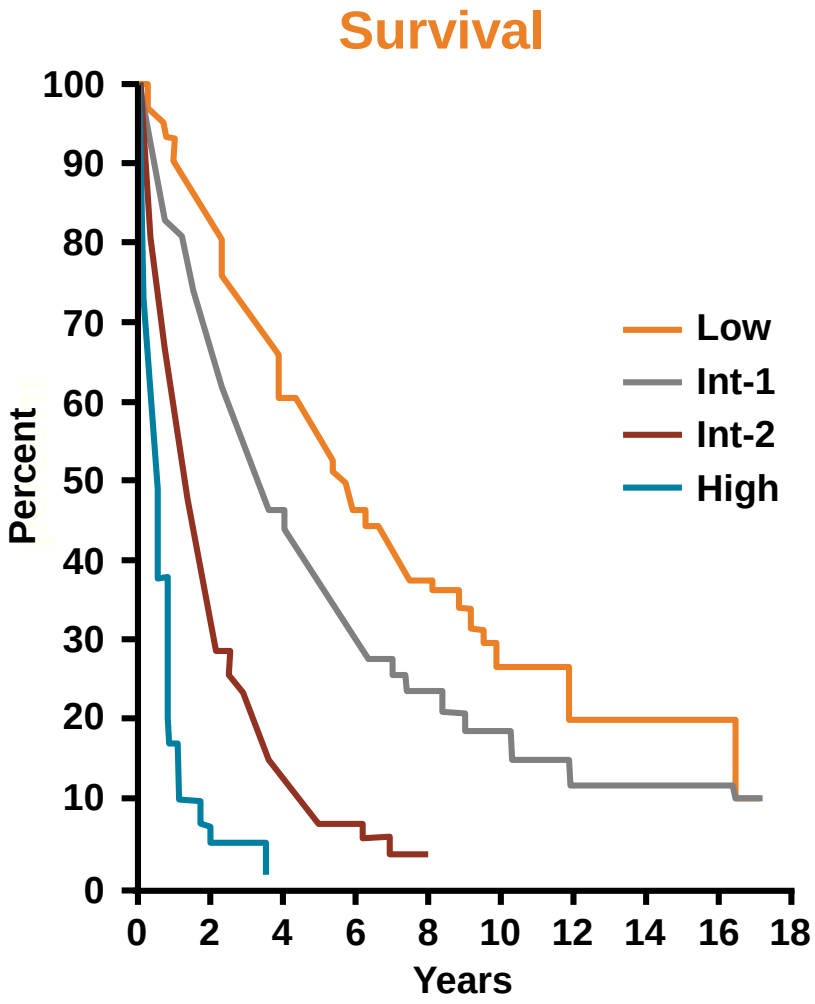
Prognostic variable	Points				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5–10	–	11–20	21–29
Number of cytopenias[1]	0–1	2–3	–	–	–
Cytogenetic category[2]	Good	Intermediate	Poor		

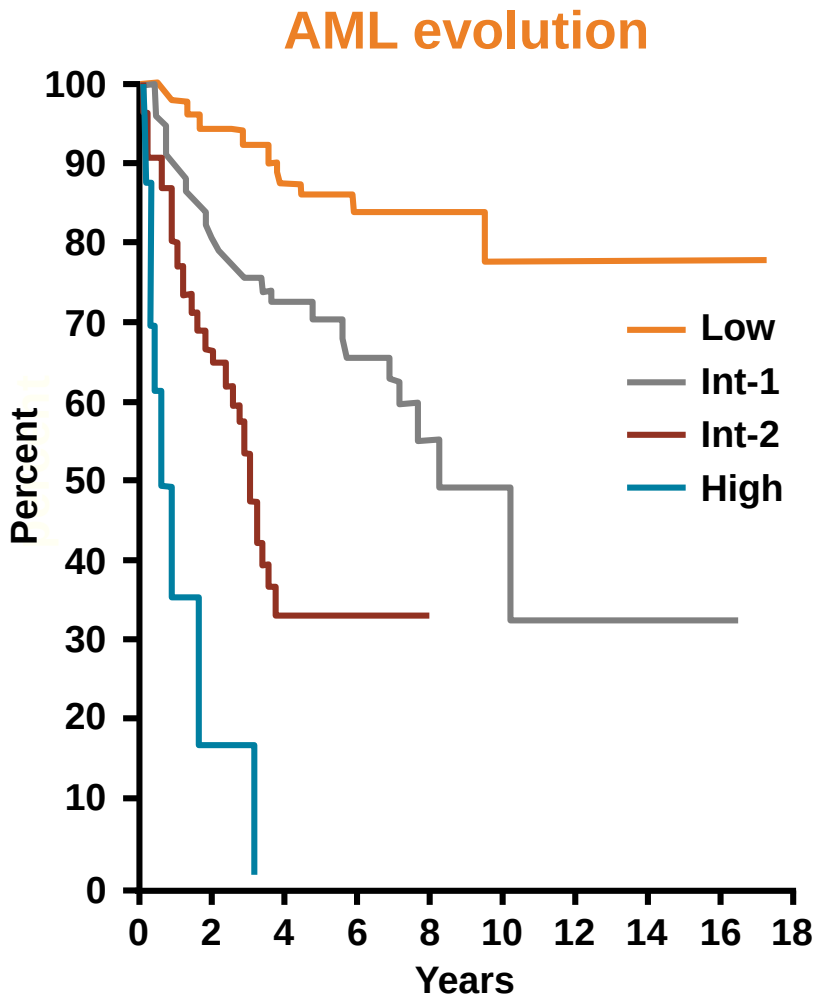
Risk groups	Score	Median survival (years)		
		≤60	>60	All patients
Low	0	11.8	4.8	5.7
Intermediate I	0.5–1.0	5.2	2.7	3.5
Intermediate II	1.5–2.0	1.8	1.1	1.2
High	≥2.5	0.3	0.5	0.4

[1]Platelets <100,000/µL, Hemoglobin <10 g/dL, Neutrophils <1800/µL; [2]Good = normal, 5q-, 20q-, -Y; intermediate = other anomalies; poor = complex (≥3 abnormalities), chromosome 7 anomalies

Greenberg P *et al. Blood* 1997;89:2079–2088

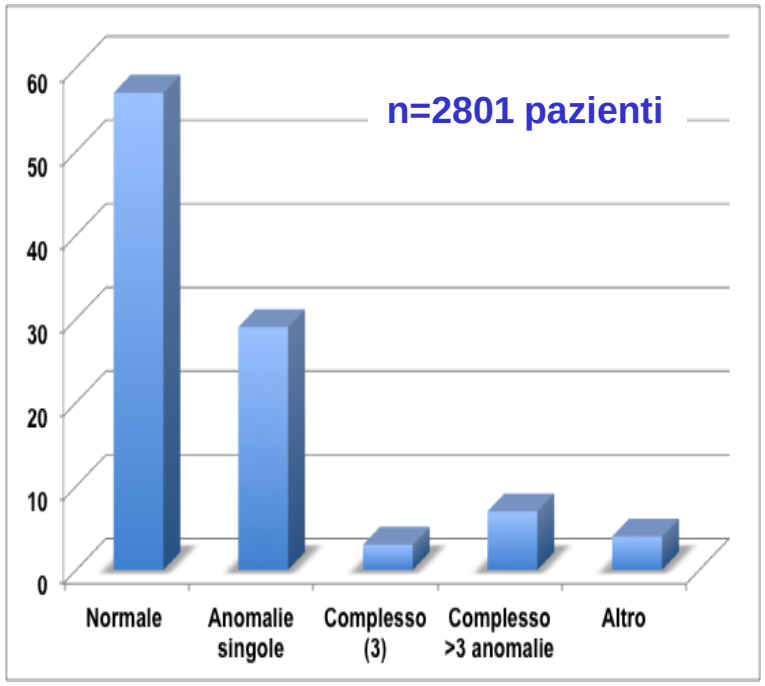
Cumulative survival of patients with MDS by IPSS



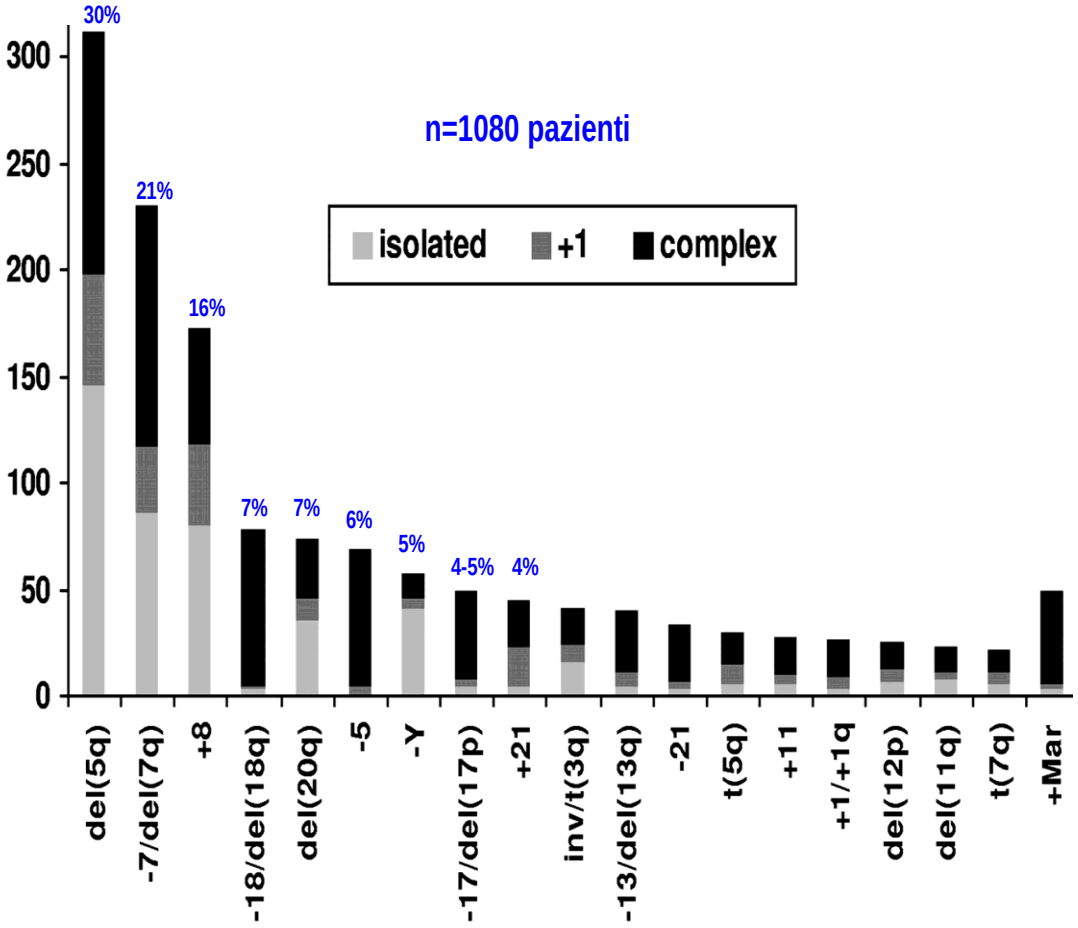


Greenberg P *et al. Blood* 1997;89:2079–2088

Alterazioni del Cariotipo nelle MDS



Schanz et al, JCO 2012

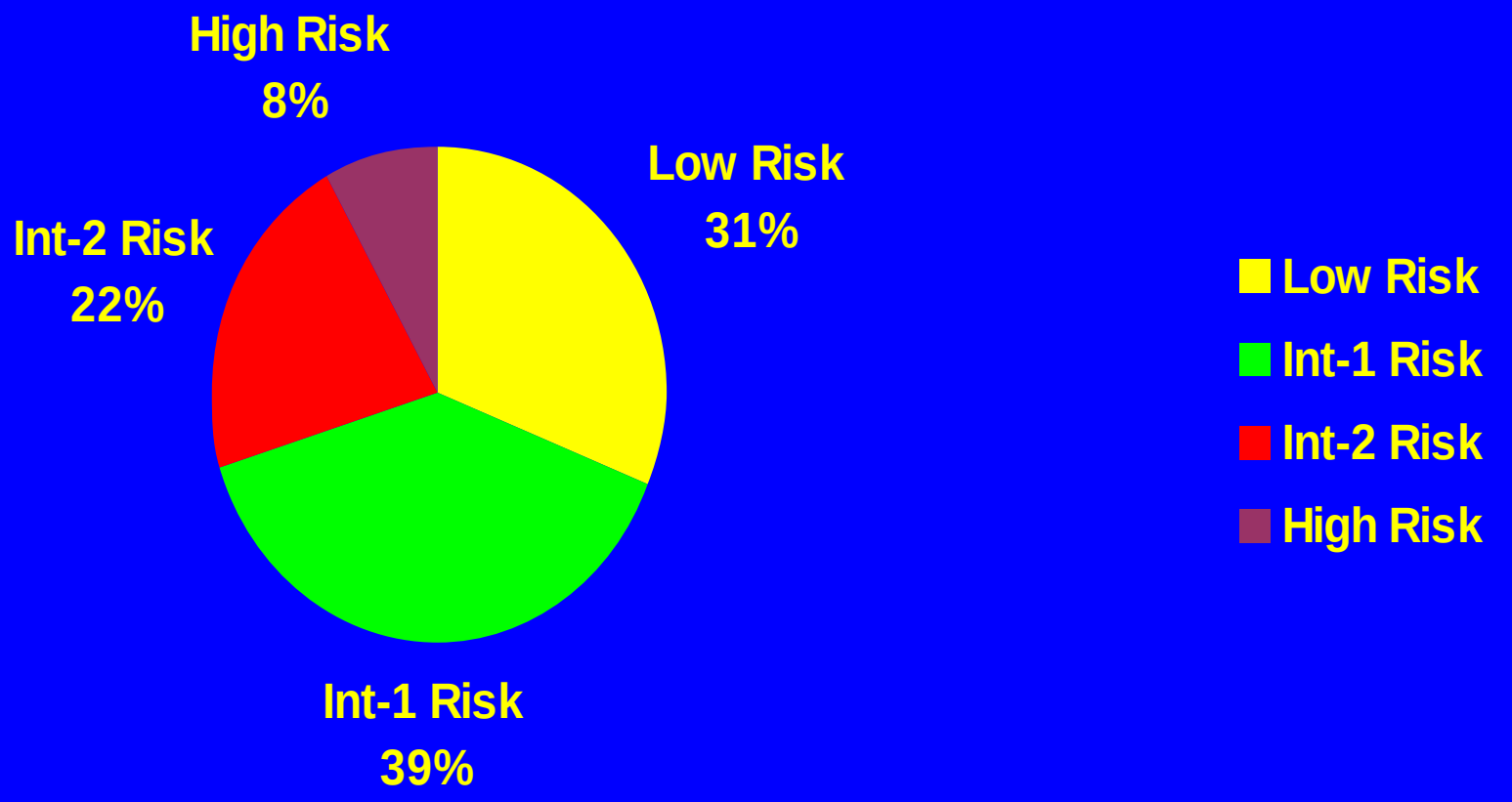


Haase et al, Blood 2007

Table 2. Diagnostic approach to MDS

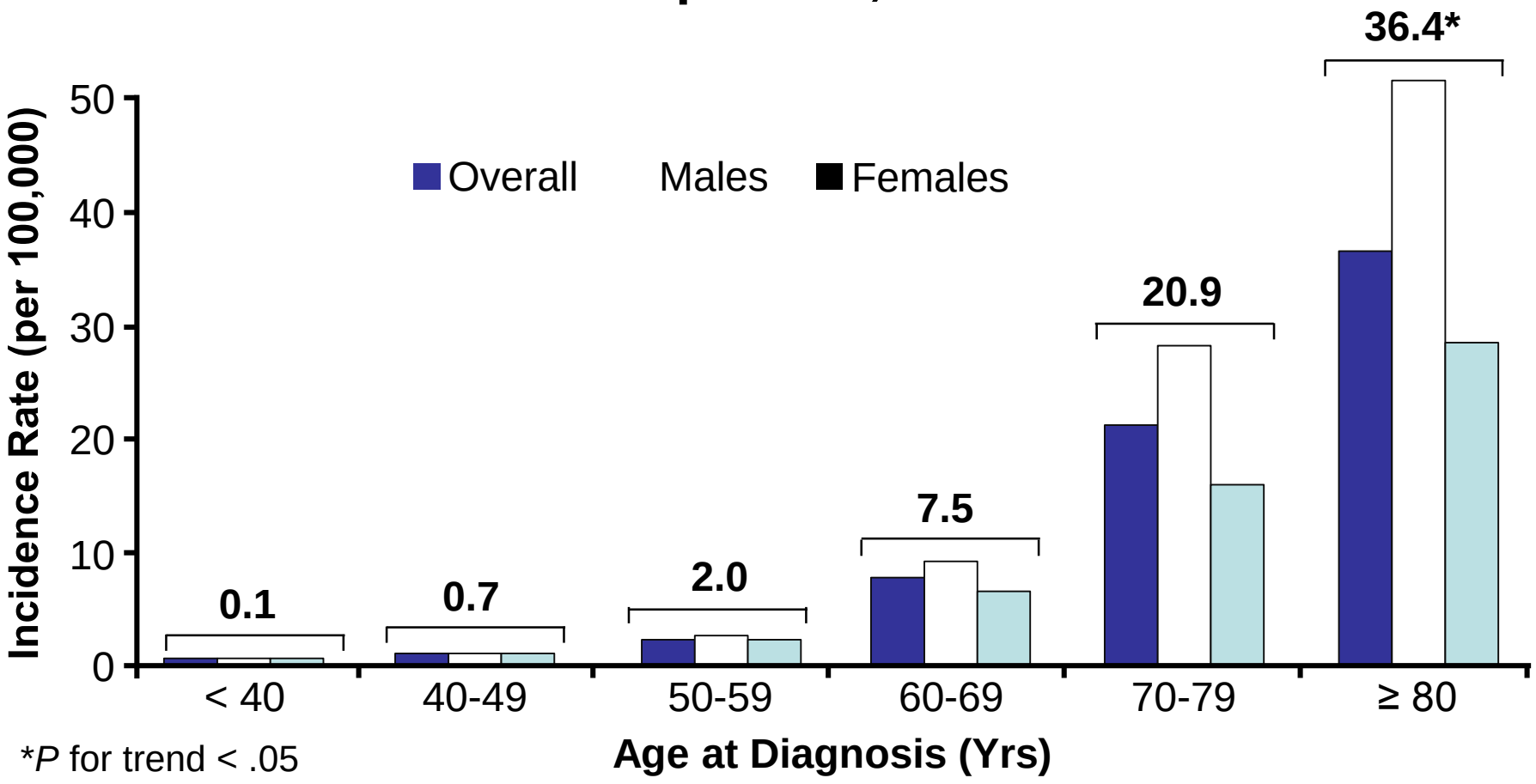
Diagnostic tool	Diagnostic value	Priority
Peripheral blood smear	• Evaluation of dysplasia in one or more cell lines • Enumeration of blasts	Mandatory
Bone marrow aspirate	• Evaluation of dysplasia in one or more hematopoietic cell lines • Enumeration of blasts • Enumeration of ring sideroblasts	Mandatory
Bone marrow biopsy	• Assessment of cellularity, $CD34^+$ cells, and fibrosis	Mandatory
Cytogenetic analysis	• Detection of acquired clonal chromosomal abnormalities that can allow a conclusive diagnosis and also prognostic assessment	Mandatory

IPSS Risk Categories: Patient Distribution



Epidemiology

- **Overall incidence: 3.4 per 100,000**



**P* for trend < .05

Rollison DE, et al. Blood. 2008;112:45-52.

IPSS: Median Survival (yrs)

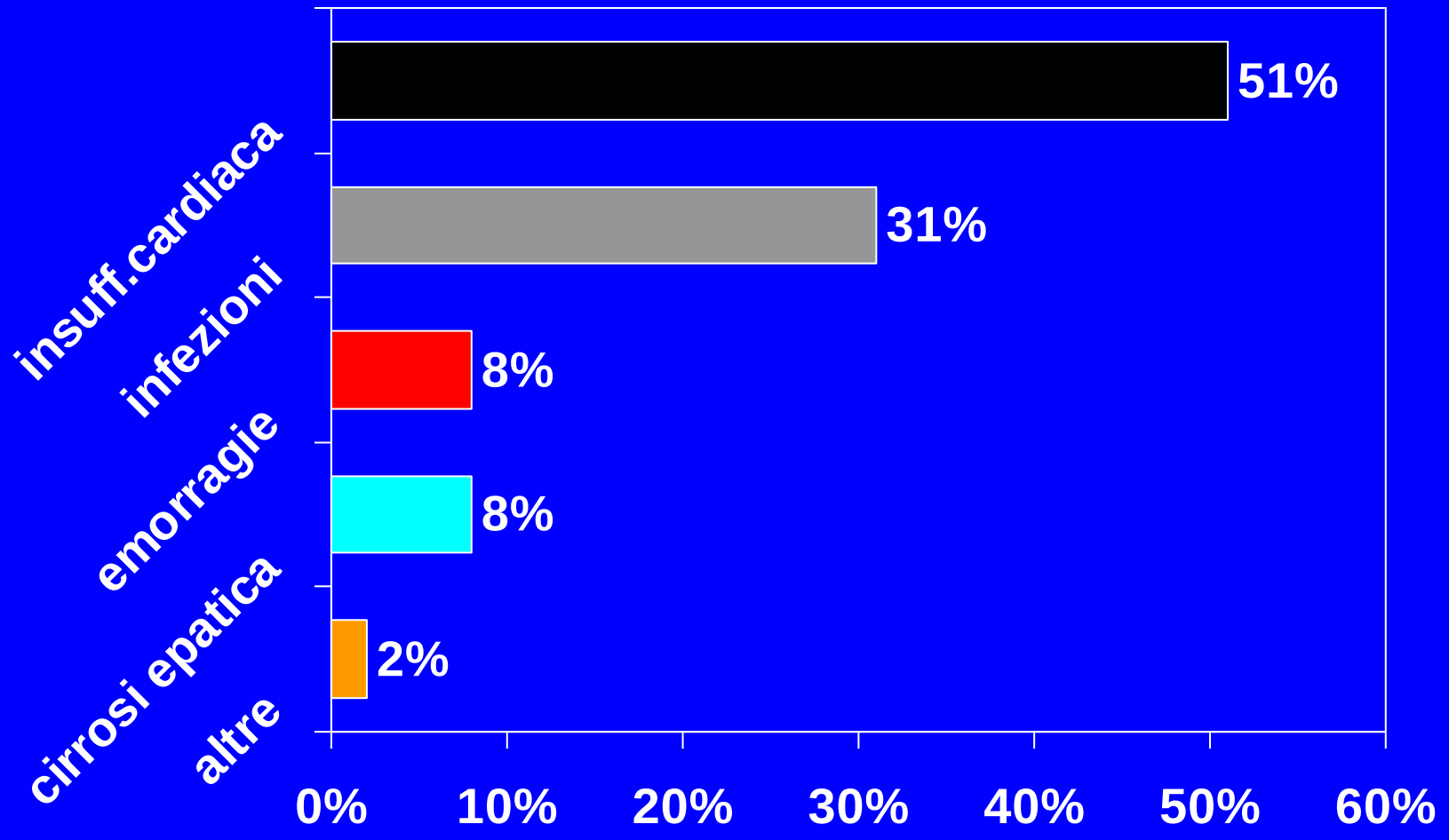
Greenberg, et al. Blood 1997;89:2079-88

IPSS risk group (pts)	Age < 60	Age > 60	Age > 70
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

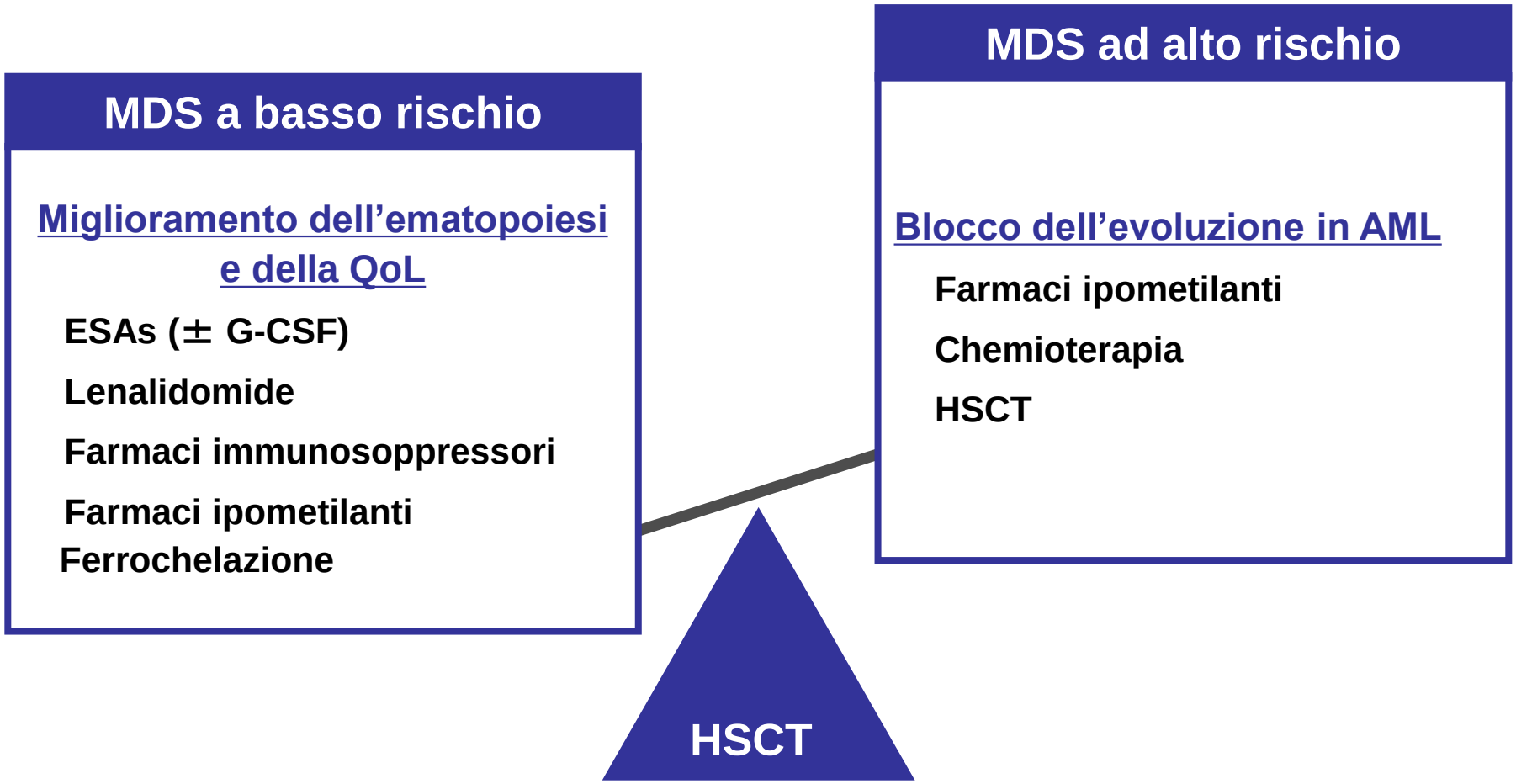
MDS: CAUSE DI MORTE IN FUNZIONE DEL RISCHIO IPSS *(Greenberg et al., 1997)*

RISCHIO IPSS	MORTI (TOTALE)	MORTI PER AML	MORTI PER ALTRE CAUSE
LOW	48%	19%	81%
INT-1	61%	30%	70%
INT-2	86%	33%	67%
HIGH	88%	45%	55%

MDS: CAUSE DI MORTE NON LEUCEMICHE
(Malcovati et al., 2005)



Terapia delle MDS



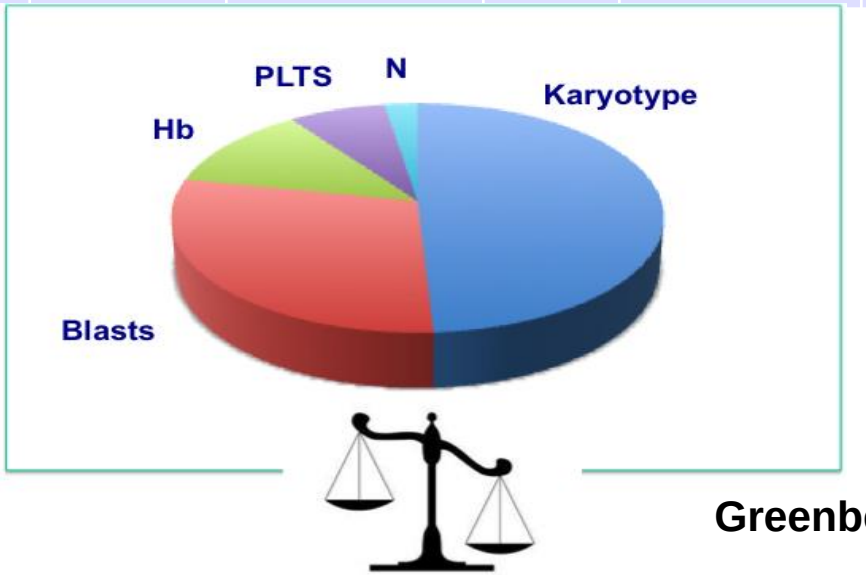
Significato Prognostico del Cariotipo

	Molto Favorevole	Favorevole	Intermedio	Sfavorevole	Molto Sfavorevole
	del(11q) -Y (singole)	Normale der(1;7) del(5q) del(12p) del(20q) (singole)	7q- +8 i(17p) +21 +19 altre (singole)	der(3)(q21q26) -7 (singole)	<u>Complesso</u> >3 anomalie
		Doppie con 5q-	Altre doppie	Complesso 3 anomalie	
				Doppie con –7/7q-	
Sopravv. globale	61 mesi	49	26	16	6

Schanz J et al. JCO 2012

Revised International Prognostic Scoring System (IPSS-R)

Score	0	0.5	1	1.5	2	3	4
Cariotipo	Molto favorevole		Favorevole		Intermedio	Sfavorevole	Molto sfavorevole
Blasti (%)	< 2		>2–< 5%		5–10 %	> 10	
Emoglobina	≥ 10		8–<10	< 8			
Piastrine	≥ 100	50–<100	< 50				
Neutrofili	≥ 0.8	< 0.8					



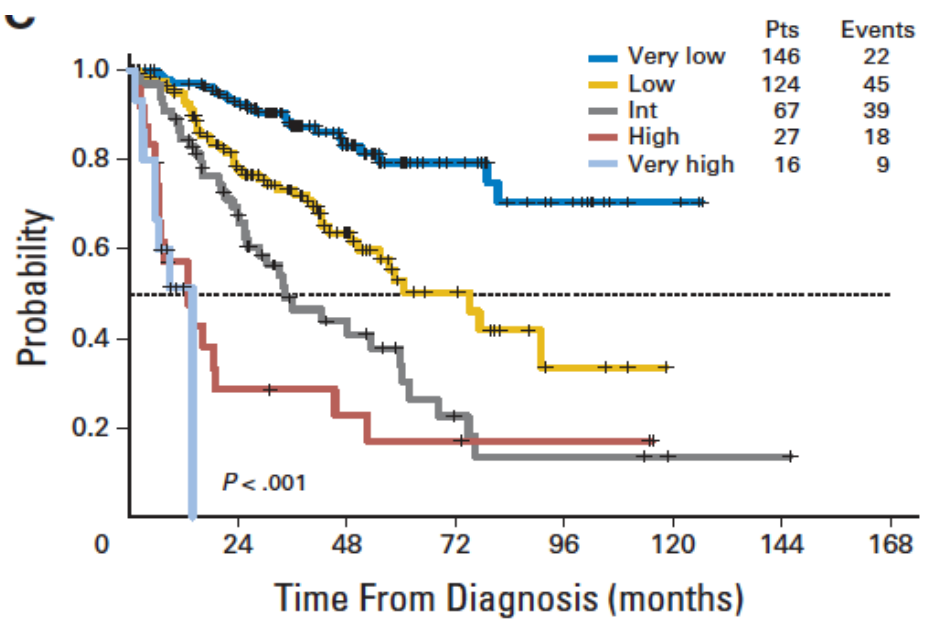
Greenberg et al. Blood 2012

Revised IPSS

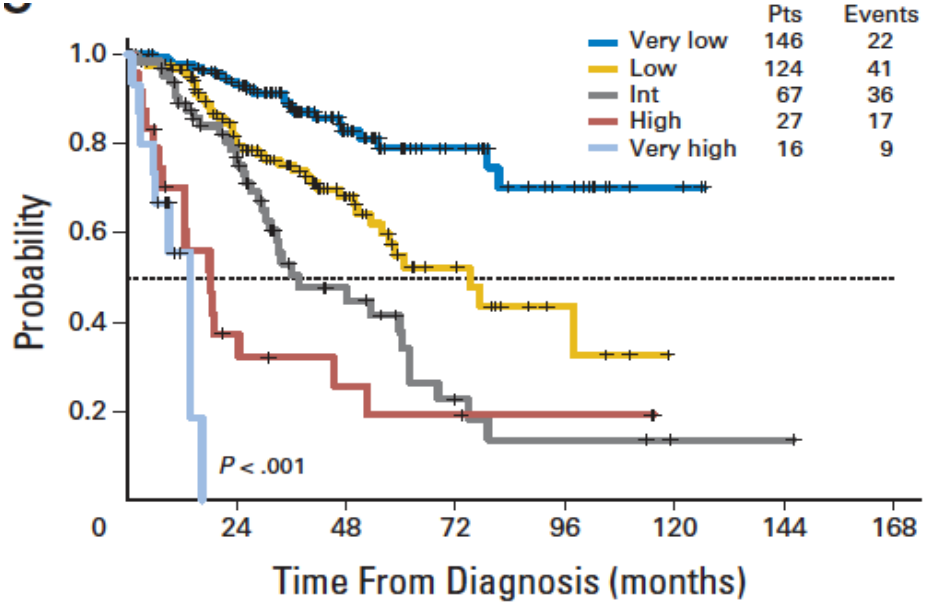
Categoria di rischio	Rischio	Sopravvivenza (mesi)	Evoluzione leucemica (25%, anni)
Molto basso	≤ 1.5	8.8	NR
Basso	> 1.5–3	5.3	10.8
Intermedio	> 3–4.5	3.0	3.2
Alto	> 4.5–6	1.6	1.4
Molto alto	> 6	0.8	0.7

Greenberg et al. Blood 2012

Leukemia-free Survival



Overall Survival



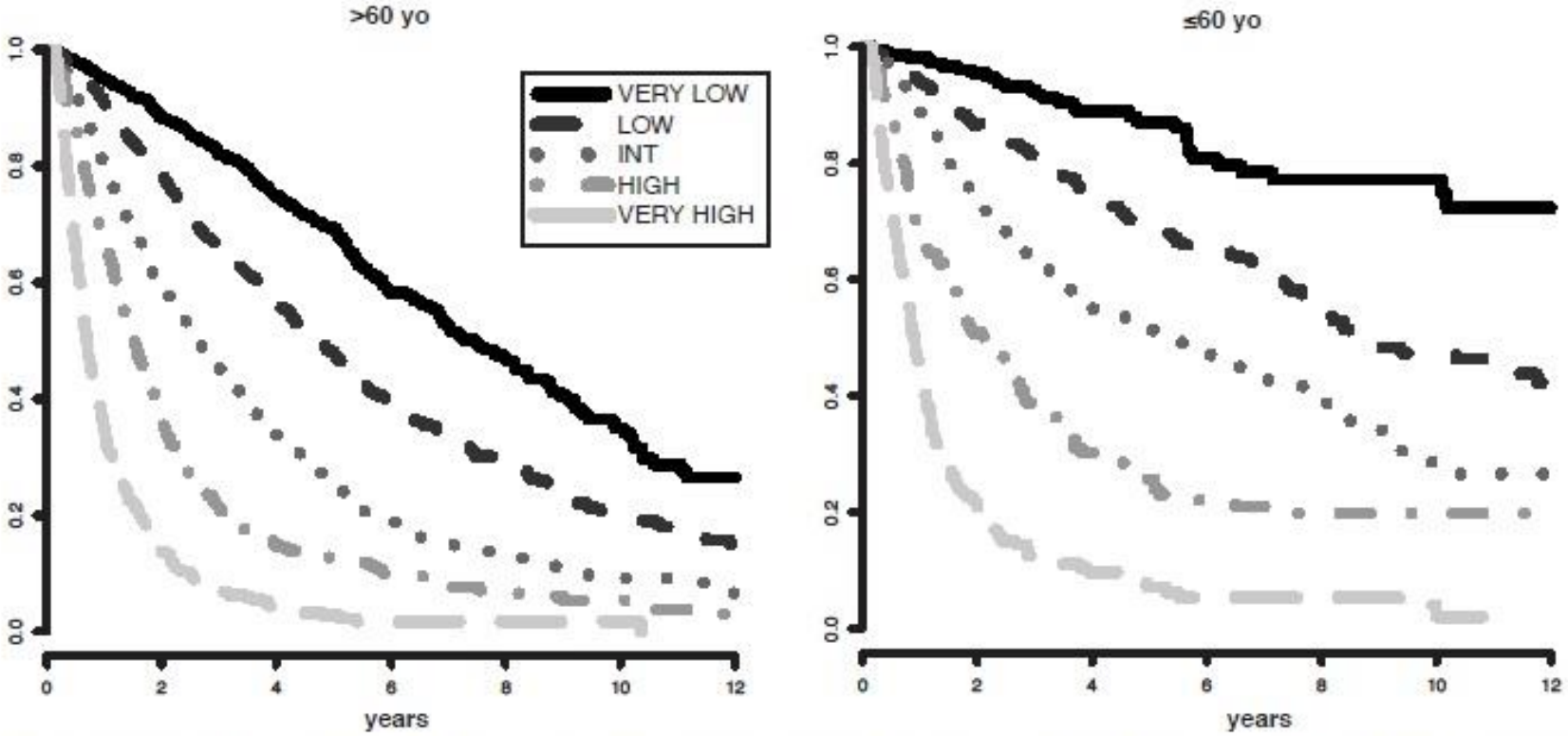


Figure 5. Survival based on patient ages > 60 years vs ≤ 60 years related to their IPSS-R prognostic risk-based categories (Kaplan-Meier curves). Age-related differential survivals are shown for patients in all groups, particularly for those in lower risk categories.

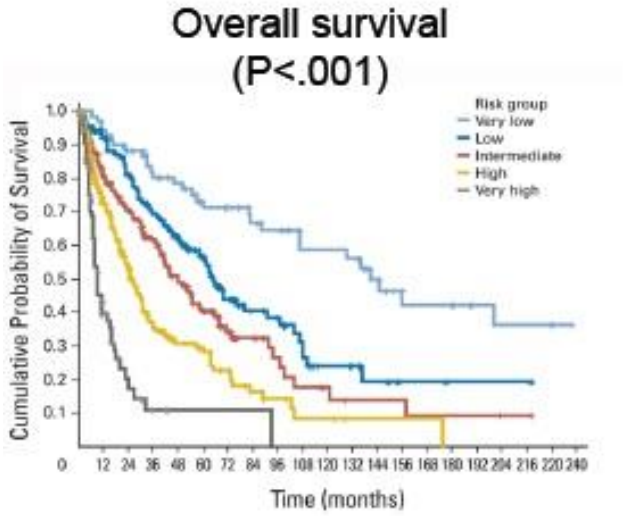
WHO classification-based Prognostic Scoring System (WPSS)

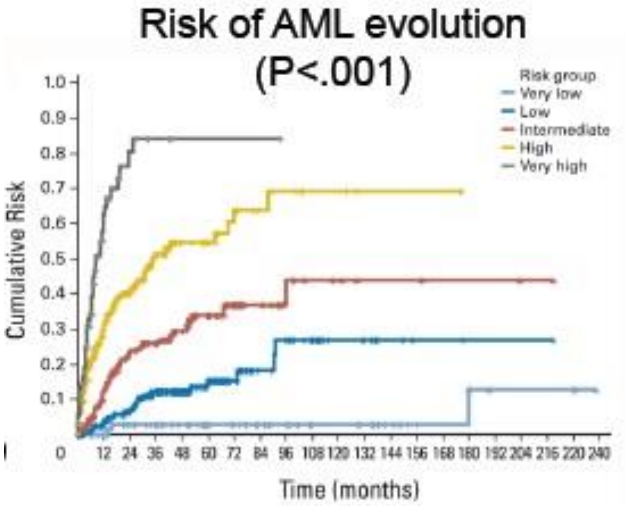
Variable	Points			
	0	1	2	3
WHO category	RA, RARS, MDS with isolated deletion (5q)	RCMD	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	-
Severe anemia**	Absent	Present	-	-
Bone marrow fibrosis	The presence of grade 2-3 bone marrow fibrosis involves a shift to a one-step more advanced risk group after accounting for WHO category, karyotype, and transfusion requirement			

* Good: normal, del(5q) only, del(20q) only, -Y only; Poor: very complex (>2) abnormalities, chromosome 7 anomalies; Intermediate: other abnormalities.

** Severe anemia: Hemoglobin <9 g/dL in males or <8 g/dL in females.

Risk groups: very low (0), low (1), intermediate (2), high (3-4), very high (5-6)



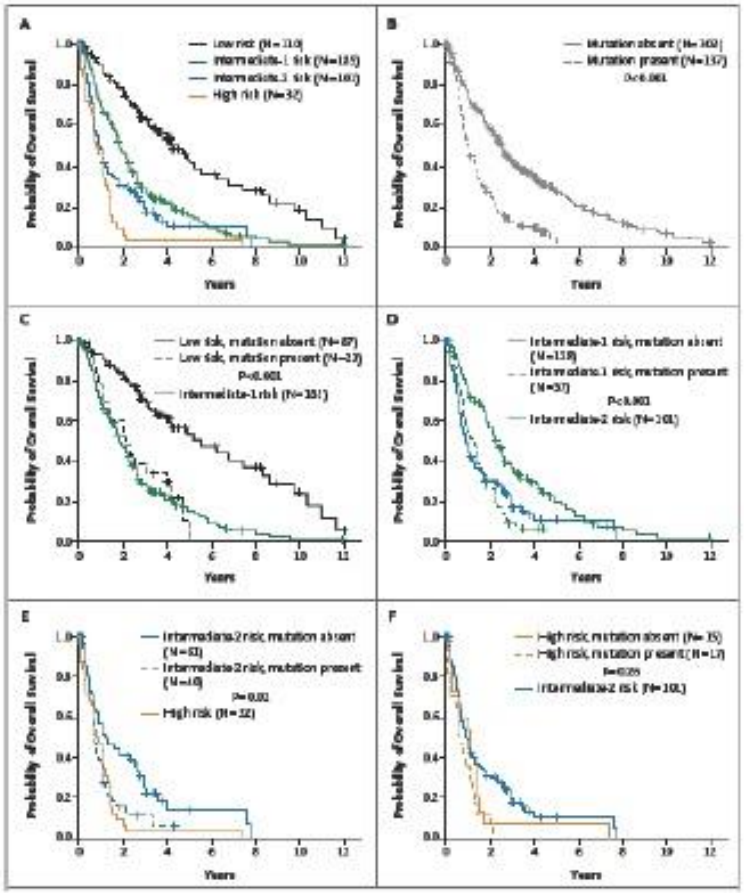


Malcovati, J Clin Oncol 2007; 25: 3503-10;
Malcovati, Haematologica 2011; 96: 1433-40

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Table 2. Hazard Ratios for Death in a Multivariable Model.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00–1.89)	0.049

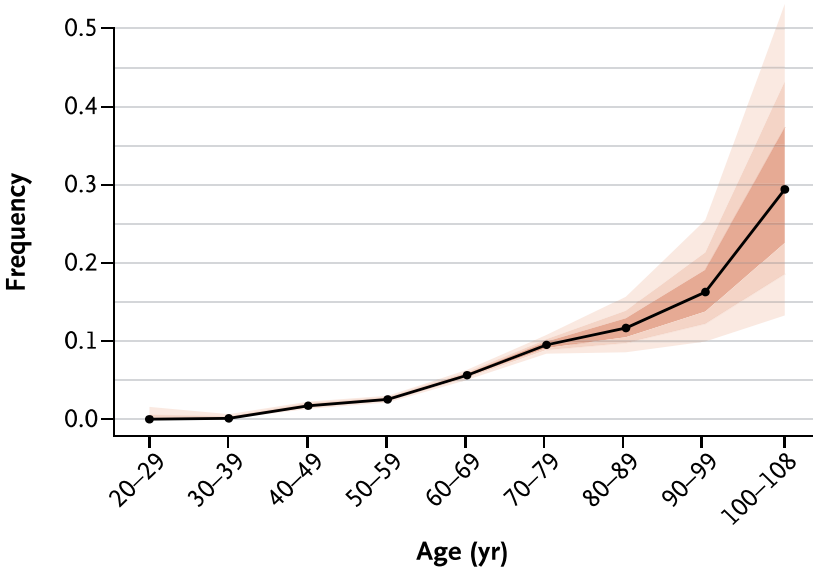


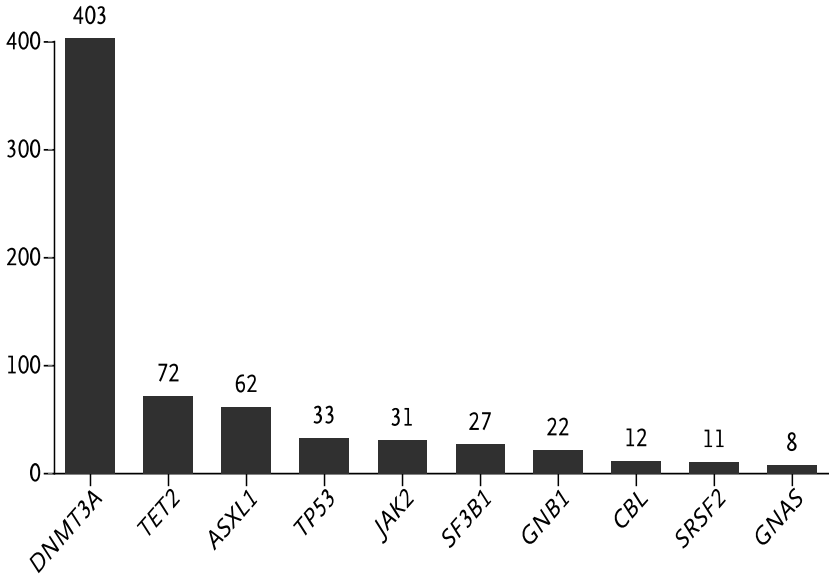
N Engl J Med 2011; 364:2496-2506

Bejar, N Engl J Med 2011; 364: 2496-2506

Mutazioni somatiche negli Anziani Sani

- Su 17182 individui, le mutazioni somatiche risultavano rare nelle persone di eta' inferiore a 40 anni.
- 70 - 79 anni: 9.5% (219 su 2300 persone),
- 80 - 89 anni: 11.7% (37 su 317)
- 90 - 108 anni: 18.4% (19 su 103).





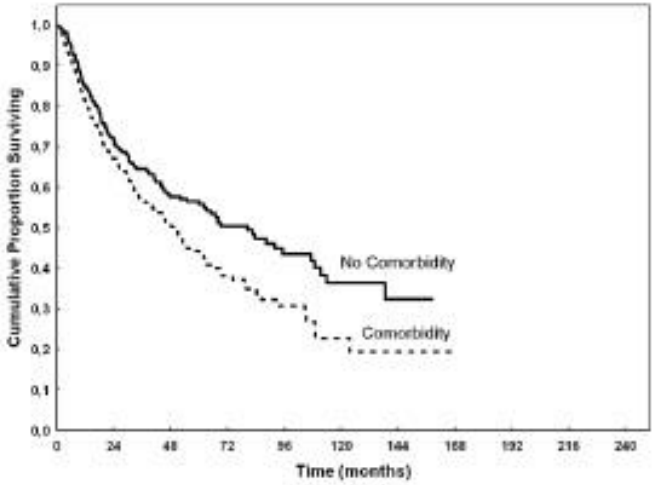
Jaiswal et al,
Genovese et al, NEJM 2014

PROGNOSTIC ASSESSMENT IN MDS

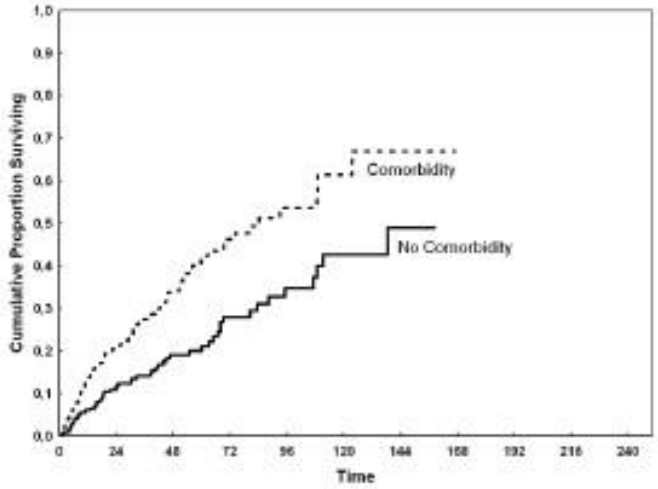
- **DISEASE-RELATED FACTORS**
- **PATIENT-RELATED FACTORS**

Clinical impact of comorbidity in patients with MDS

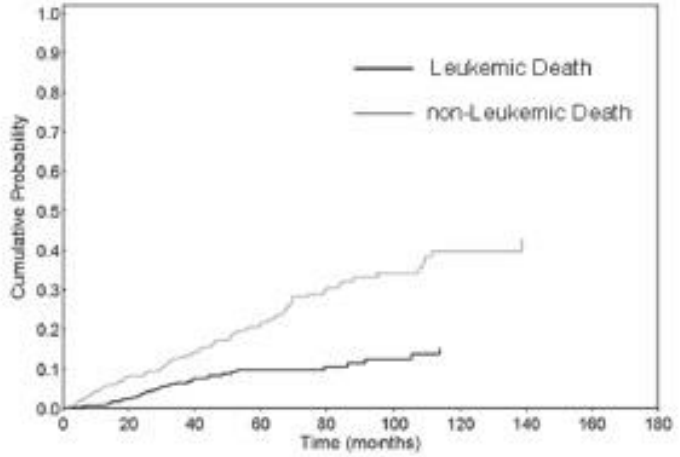
Overall Survival



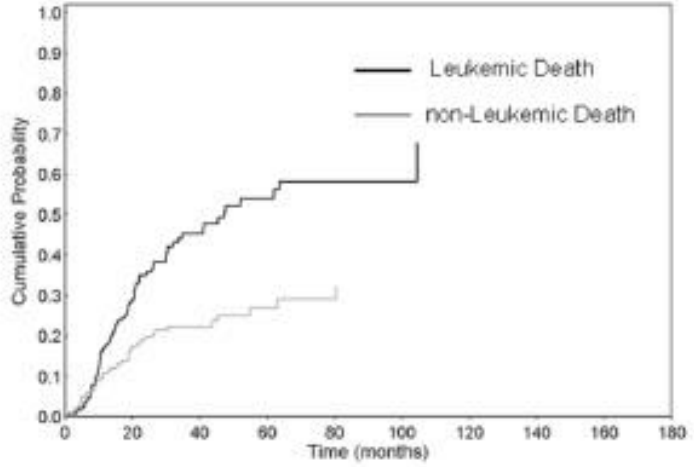
Non-Leukemic Death



RA/RARS/RCMD



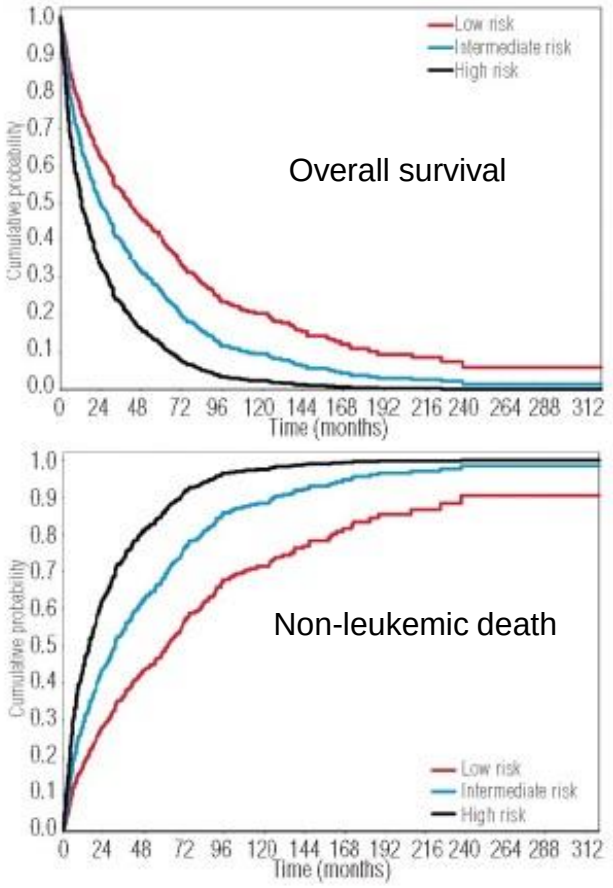
RAEB-1/RAEB-2



Della Porta, Haematologica 2009; 94: 602-6

MDS-specific Comorbidity Index (MDS-CI)

Comorbidity	*HR obtained through a multivariable Cox survival analysis with NLD as a dependent covariate*	*Variable weighted score (to be taken into account if the specific comorbidity is present)*
Cardiac disease	3.57 (p<.001)	2
Moderate-to-severe hepatic disease	2.55 (p=.01)	1
Severe pulmonary disease	2.44 (p=.005)	1
Renal disease	1.97 (p=.04)	1
Solid tumor	2.61 (p<.001)	1
MDS-CI risk	*Sum of individual variable scores*	*Proportion of patients in the learning cohort belonging to the risk group (%)*
Low risk	0	546/840 (65%)
Intermediate risk	1-2	244/840 (29%)
High risk	<2	50/840 (6%)



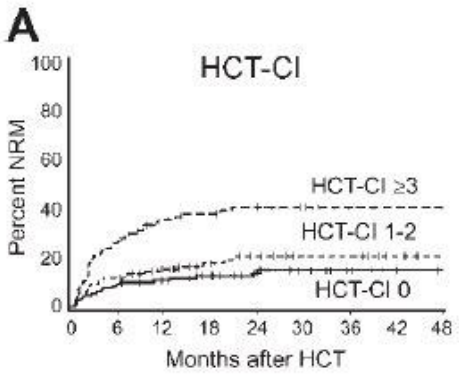
Della Porta, Haematologica 2011; 96: 441-9

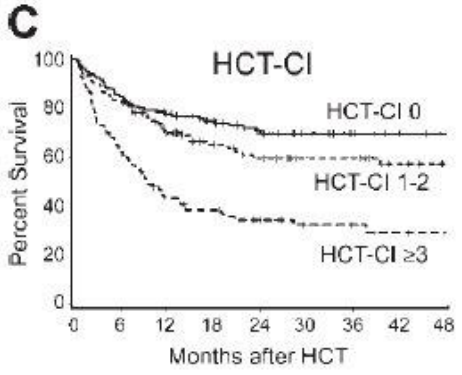
Hematopoietic cell transplantation (HCT)-specific comorbidity index

Comorbidity	HCT-CI weighted scores
Arrhythmia	1
Cardiac‡	1
Inflammatory bowel disease	1
Diabetes	1
Cerebrovascular disease	1
Psychiatric disturbance†	1
Hepatic, mild‡	1
Obesity†	1
Infection†	1
Rheumatologic	2
Peptic ulcer	2
Moderate/severe renal‡	2
Moderate pulmonary‡	2
Prior solid tumor‡	3
Heart valve disease	3
Severe pulmonary‡	3
Moderate/severe hepatic‡	3

		HCT-CI			
		NRM		Survival	
Score	No.	HR* (95% CI)	2-year, %	HR* (95% CI)	2-year, %
0	38	1.0	14	1.0	71
1 to 2	34	1.42 (0.8-2.7)	21	1.31 (0.8-2.0)	60
3 or more	28	3.54 (2.0-6.3)	41	2.69 (1.8-4.1)	34

*Adjusted for age, disease risk, and conditioning.





Sorror, Blood 2005; 106: 2912-9

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes

Version 1.2016

NCCN.org

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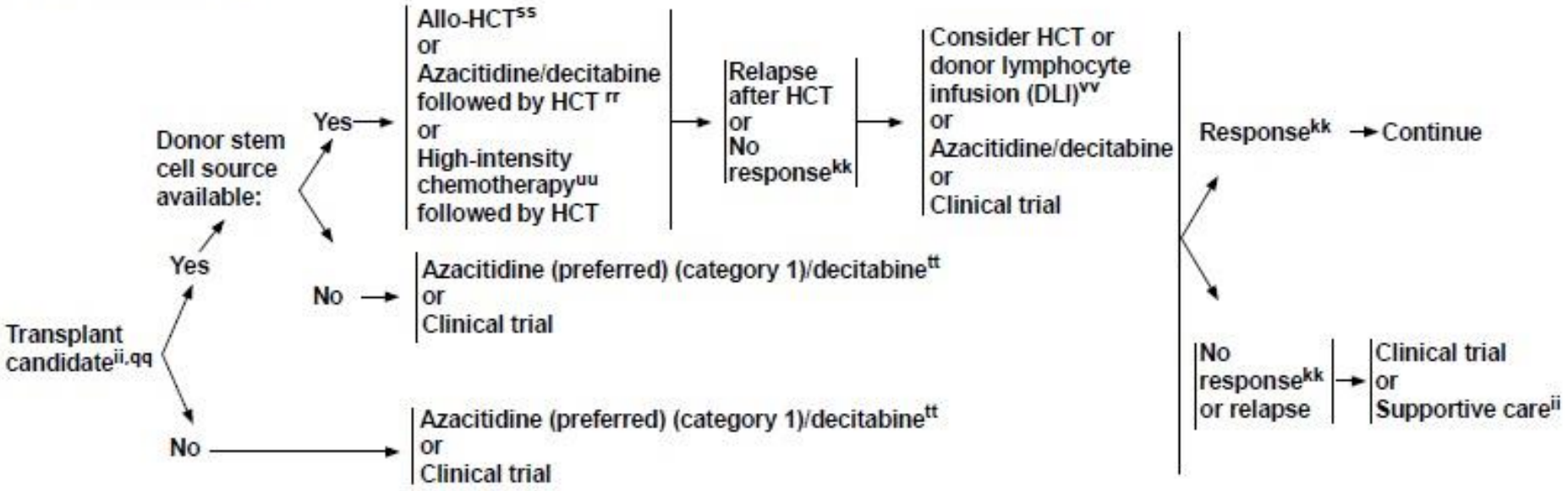
PROGNOSTIC CATEGORY[ff] TREATMENT

IPSS: Intermediate-2, High
IPSS-R: Intermediate,[gg] High, Very High
WPSS: High, Very High



[ff]Presence of comorbidities should also be considered for evaluation of prognosis. See Comorbidity Indices in the Discussion.

[gg]Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending on additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels.

[ii]See Supportive Care (MDS-B).

[kk]Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

[qq]Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

[rr]Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability. However, these agents should not be used to delay available HCT.

[ss]HCT: Allogeneic-matched sibling including standard and reduced-intensity preparative approaches or MUD.

[tt]While the response rates are similar for both drugs, survival benefit from a phase III randomized trial is reported for azacitidine and not for decitabine. Azacitidine or decitabine therapy should be continued for at least 4 to 6 cycles to assess response to these agents. In patients who have clinical benefit, continue treatment with hypomethylating agent as maintenance therapy.

[uu]High-intensity chemotherapy:

- Clinical trials with investigational therapy (preferred), or
- Standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HCT.

[vv]Consider second transplant or DLI immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

blood
2013 122: 2943-2964
doi:10.1182/blood-2013-03-492884 originally published online August 26, 2013

Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet

Luca Malcovati, Eva Hellström-Lindberg, David Bowen, Lionel Adès, Jaroslav Cermak, Consuelo del Cañizo, Matteo G. Della Porta, Pierre Fenaux, Norbert Gattermann, Ulrich Germing, Joop H. Jansen, Moshe Mittelman, Ghulam Mufti, Uwe Platzbecker, Guillermo F. Sanz, Dominik Selleslag, Mette Skov-Holm, Reinhard Stauder, Argiris Symeonidis, Arjan A. van de Loosdrecht, Theo de Witte and Mario Cazzola

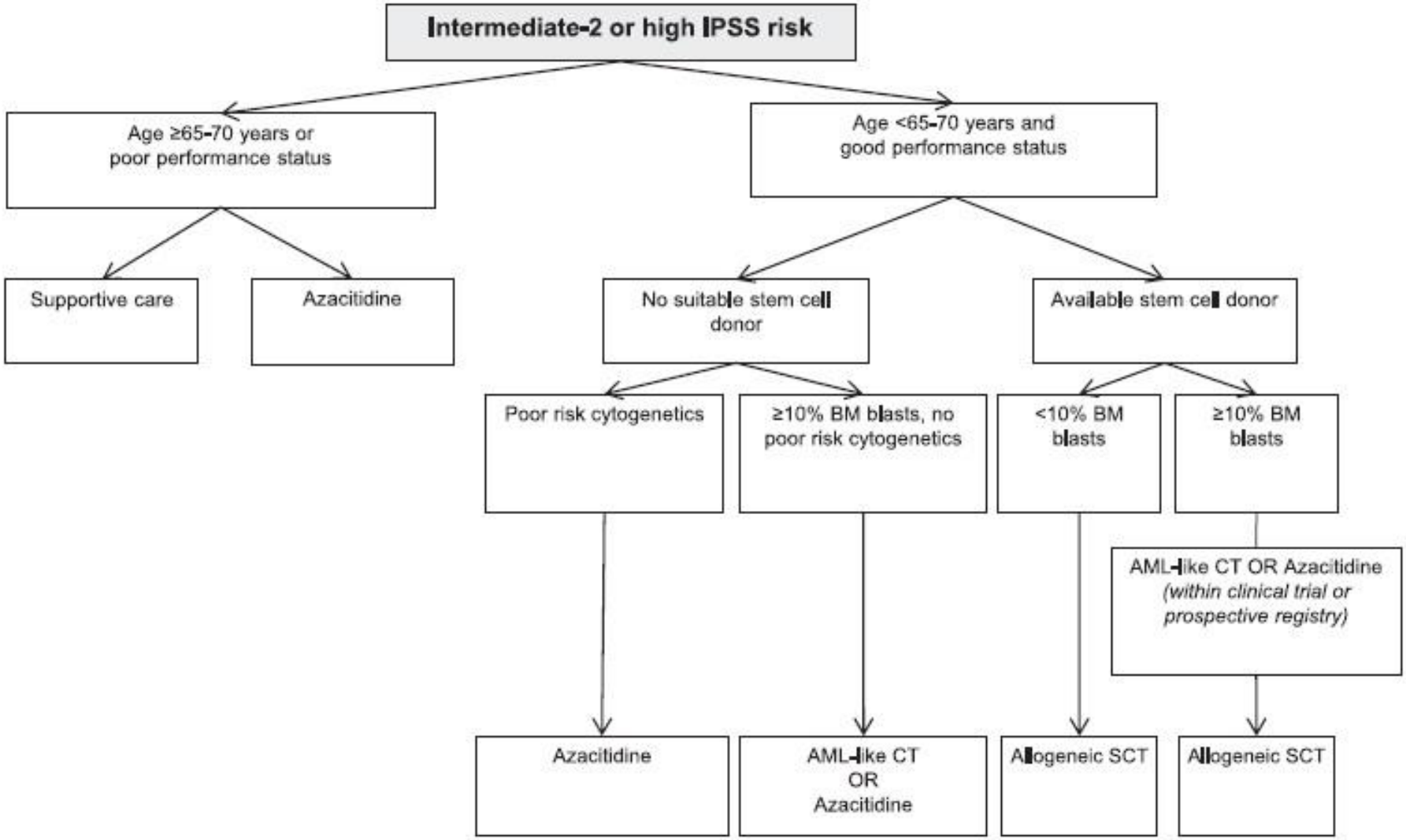


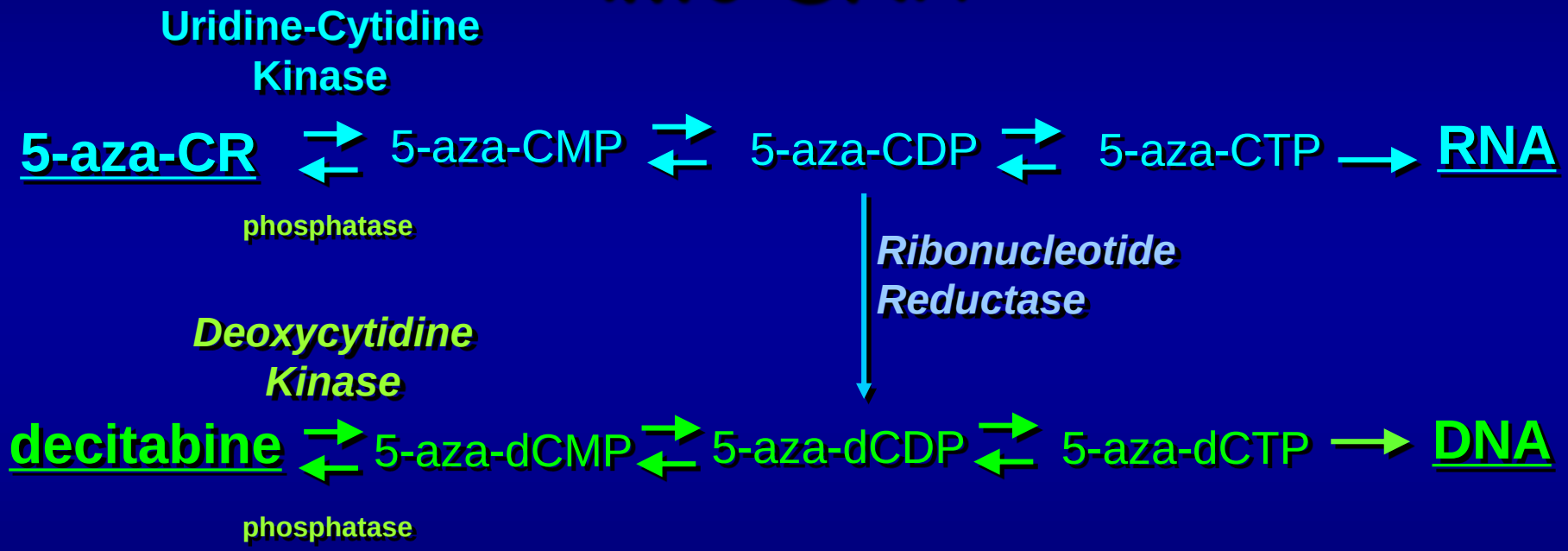
Figure 3. Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score. CT, chemotherapy.

AZACITIDINE AND DECITABINE IN MDS: PHASE III RANDOMIZED TRIALS

Author	N° of Patients	Therapy	Response (ORR)	Survival (OS) (months)
Silverman et al., 2002: CALGB 9221	**191**	**AZA vs BSC**	**AZA: 60%** **BSC: 5%**	**AZA: 20** **BSC: 14** **Accounting for crossover:** **AZA: 18** **BSC: 11**
Fenaux et al., 2009: AZA-001	**358**	**AZA vs CCR**	**AZA: 49%** **CCR: 41%**	**AZA: 24** **CCR: 15**
Kantarjian et al., 2006: D-0007	**170**	**DAC vs BSC**	**DAC: 30%** **BSC: 7%**	**DAC: 14** **BSC: 14.9**
Lubbert et al., 2011: EORTC-06011	**233**	**DAC vs BSC**	**DAC: 34%** **BSC: 2%**	**DAC: 10.1** **BSC: 8.5**

AZA: azacitidine; DAC: decitabine; BSC: Best supportive care; CCR: Conventional care regimens; ORR: Overall response rate; OS: Overall survival.

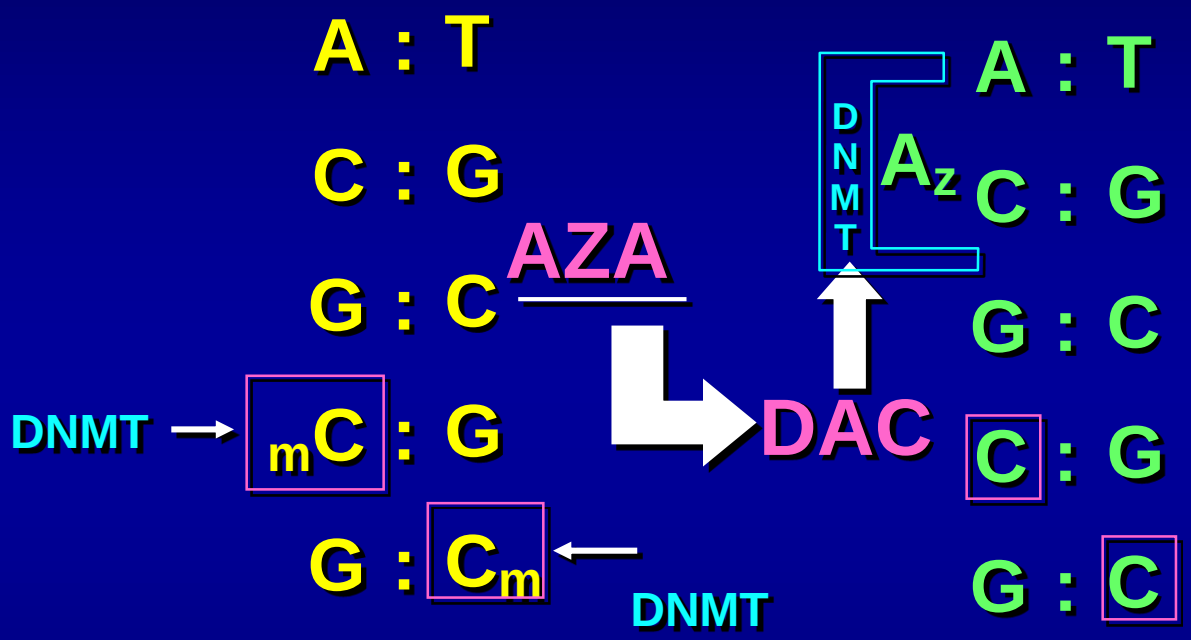
Mechanism of 5-azacytidine and 5-aza-2' deoxycytidine incorporation into DNA



Attadia, 1993

Jones, 2004

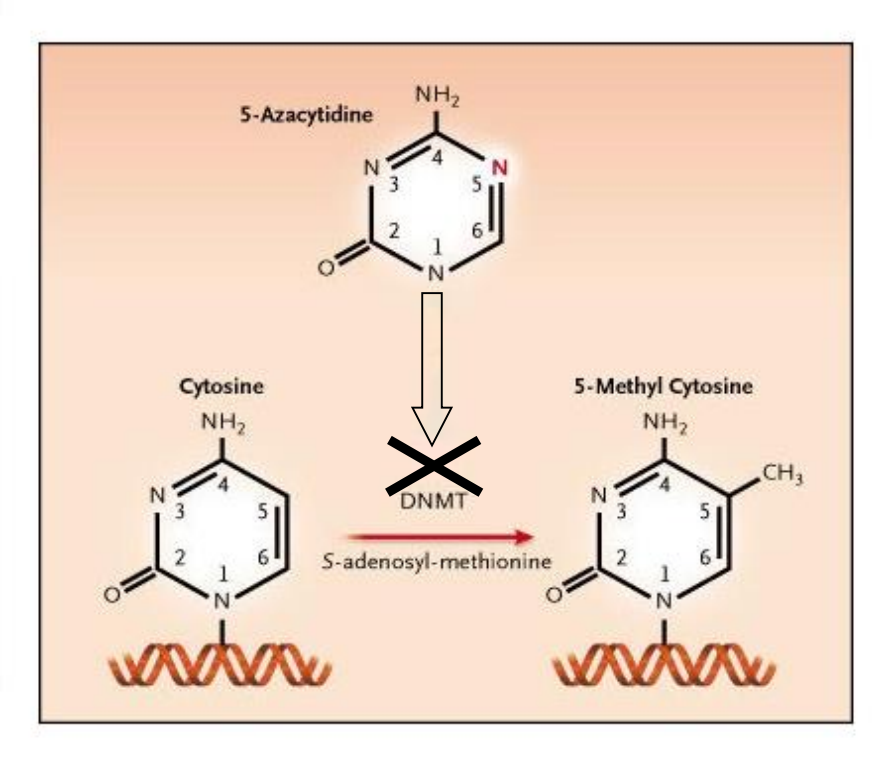
DNA Methyltransferase Inhibitor Induced DNA Hypomethylation



- DNMTi are incorporated into DNA *in lieu* of cytosine residue
- Inactivates DNMT
- Leads to formation of newly synthesized DNA with unmethylated cytosine residues
- Results in hypomethylation and transcription of previously quiescent genes

Silverman L. *The Oncologist* 2001. 6 (S5): 8-14.
Permission from *The Oncologist*, AlphaMed Press.

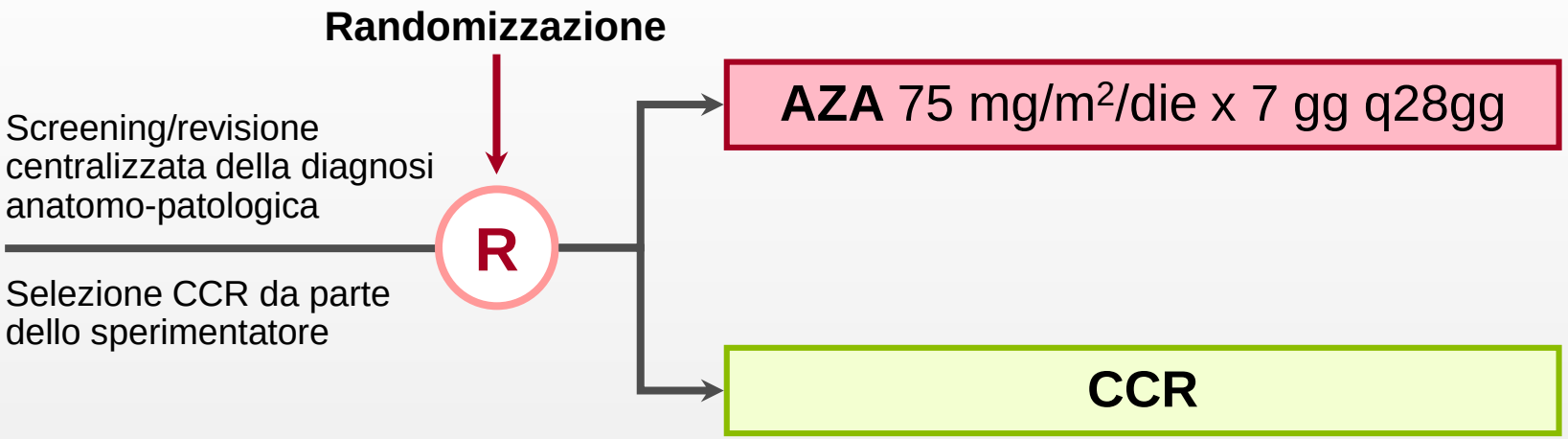
Terapie Demetilanti: Azacitidina



L'azacitidina causa ipometilazione del DNA e diretta citotossicità nelle cellule ematopoietiche anormali

L'incorporazione dell'azacitidina nel DNA inibisce le metiltransferasi, causando la demetilazione di regioni che regolano, attraverso l'interazione con determinati fattori, la trascrizione genica di geni critici per la proliferazione ed il differenziamento

Studio sulla sopravvivenza con azacitidina



- Migliore terapia di supporto (BSC) da sola
- Ara-C a basse dosi (LDAC, 20 mg/m^2/die x 14 gg q28-42gg)
- Chemioterapia standard (7 + 3)

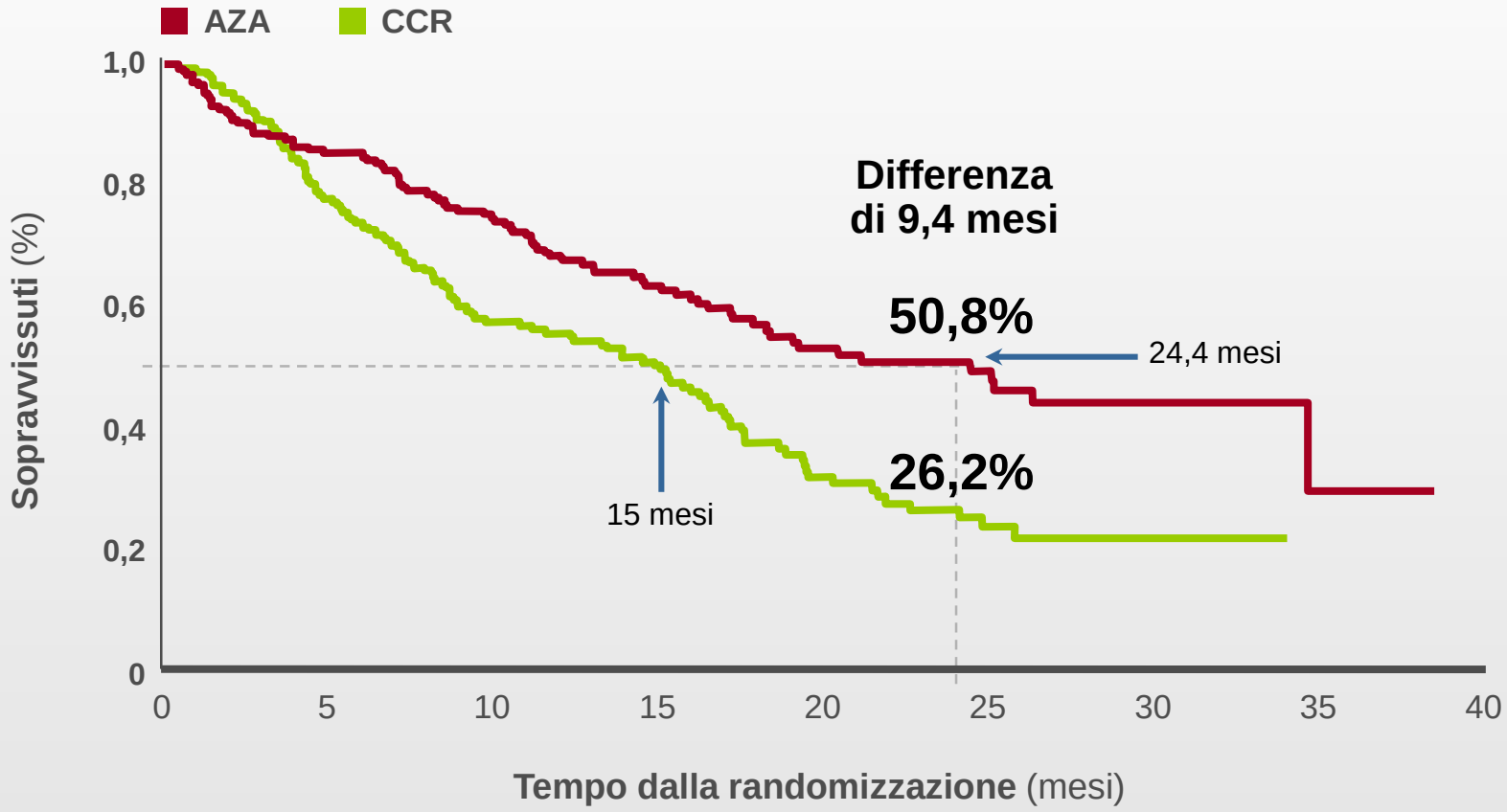
BSC inclusa in ogni braccio
La terapia è stata continuata fino a comparsa di tossicità inaccettabile, evoluzione in AML o progressione della malattia

AML, leucemia mieloide acuta; Ara-C, citosina arabinoside; AZA, azacitidina; CCR, regimi terapeutici convenzionali; LDAC, Ara-C a basse dosi.

Modificata da Fenaux P, et al. *Lancet Oncol* 2009;10:223-232.

Sopravvivenza globale: azacitidina 75 mg/m^2/die x 7 giorni vs CCR

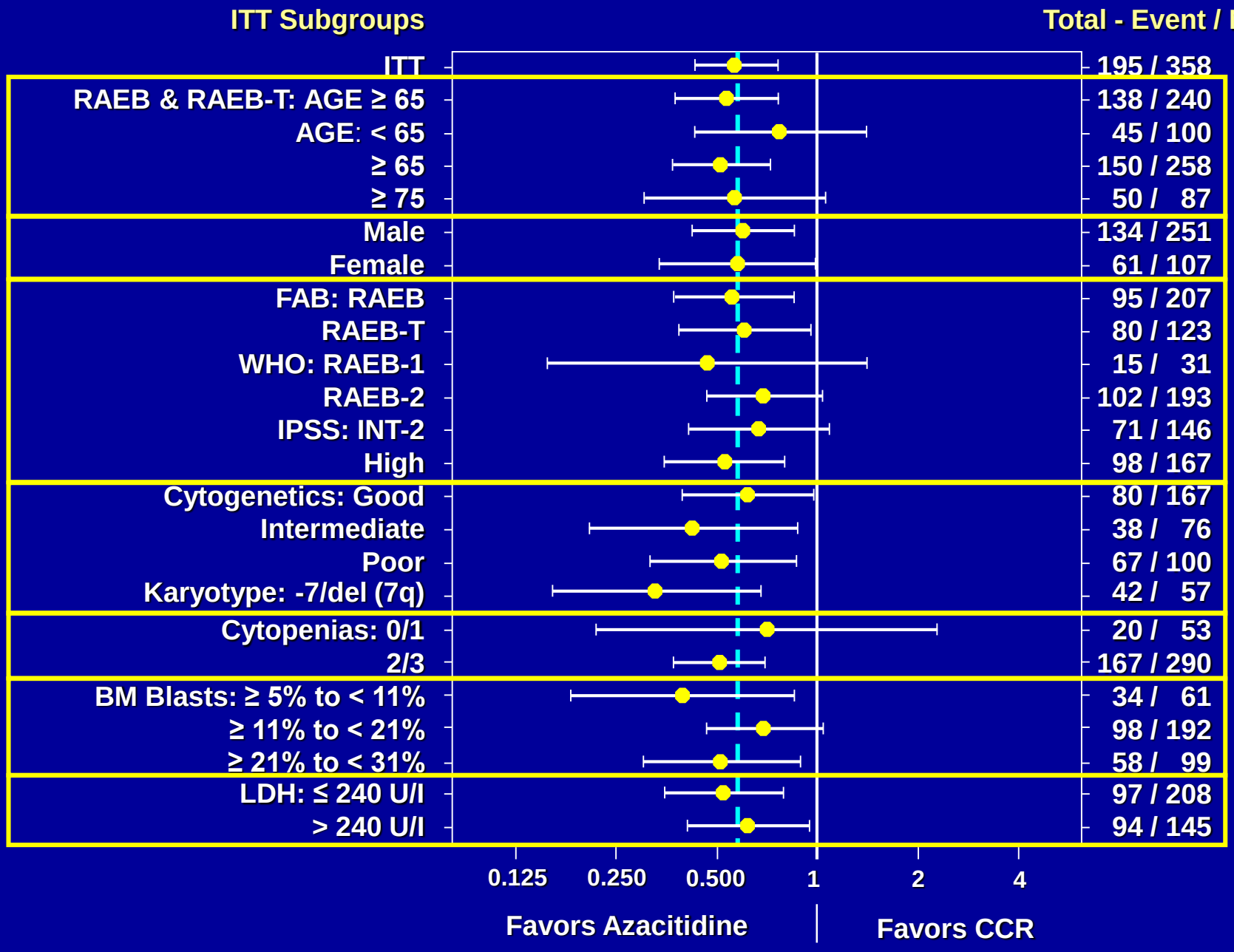
Popolazione ITT



AZA, azacitidina; CCR, regimi terapeutici convenzionali; ITT, Intent-to-Treat.

Modificata da Fenaux P, et al. *Lancet Oncol* 2009;10:223-232.

Hazard Ratio and 95% CI for Overall Survival



AZACITIDINA: INDICAZIONI AIFA
(G.U. n°86 14 aprile 2009), determin. 1 aprile 2009

- **sindromi mielodisplastiche (SMD) a rischio intermedio-2 e alto** secondo l'International Prognostic Scoring System (IPSS);
- **leucemia mielomonocitica cronica (LMMC) con il 10-29% di blasti midollari** senza disordine mieloproliferativo;
- **leucemia mieloide acuta (LMA) con 20-30% di blasti** e displasia multilineare, secondo la classificazione dell'Organizzazione Mondiale della Sanità (OMS)

Secondary Endpoints

- Time to AML or death
  - 13 mos with AZA vs 7.6 mos with CCR, p=0.003
- Time to AML
  - 26.1 mos with AZA vs 12.4 with CCR, p=0.004
- RBC Transfusion Independence
  - 45% with AZA vs 11% with CCR, p<0.0001
- Infections Requiring IV Antimicrobials
  - Reduced by 33% with AZA vs CCR

2006 Modified IWG MDS Response Criteria

Category	Response Criteria (≥ 4 Wks)
CR	▪ Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines ▪ Persistent dysplasia will be noted ▪ Hb: ≥ 11 g/dL, platelets: ≥ 100 x 10^9/L, neutrophils: ≥ 1.0 x 10^9/L, blasts: 0%
PR	All CR criteria if abnormal before treatment except: ▪Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% ▪Cellularity and morphology not relevant
Marrow CR	▪ Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment ▪ Peripheral blood: if HI responses, they will be noted in addition to marrow CR
SD	▪ Failure to achieve at least PR, but no evidence of progression for > 8 wks

Cheson BD, et al. Blood. 2006;108:419-425.

2006 Modified IWG Criteria for Hematologic Improvement

Hematologic Improvement	Pretreatment Level*	Response Criteria (≥ 8 Wks)
Erythroid	< 11 g/dL	Hemoglobin increase by ≥ 1.5 g/dL
Platelet	< 100 x 10^9/L	▪ If baseline > 20 x 10^9/L: Absolute increase ≥ 30 x 10^9/L ▪ If baseline < 20 x 10^9/L: Increase to > 20 x 10^9/L and by at least 100%
Neutrophil	< 1.0 x 10^9/L	Absolute increase > 0.5 x 10^9/L and by at least 100%
Progression or relapse after HI	--	≥ 1 of the following: ▪Reduction in hemoglobin by ≥ 1.5 g/dL ▪≥ 50% decrease in granulocytes or platelets from maximum response ▪Transfusion dependence

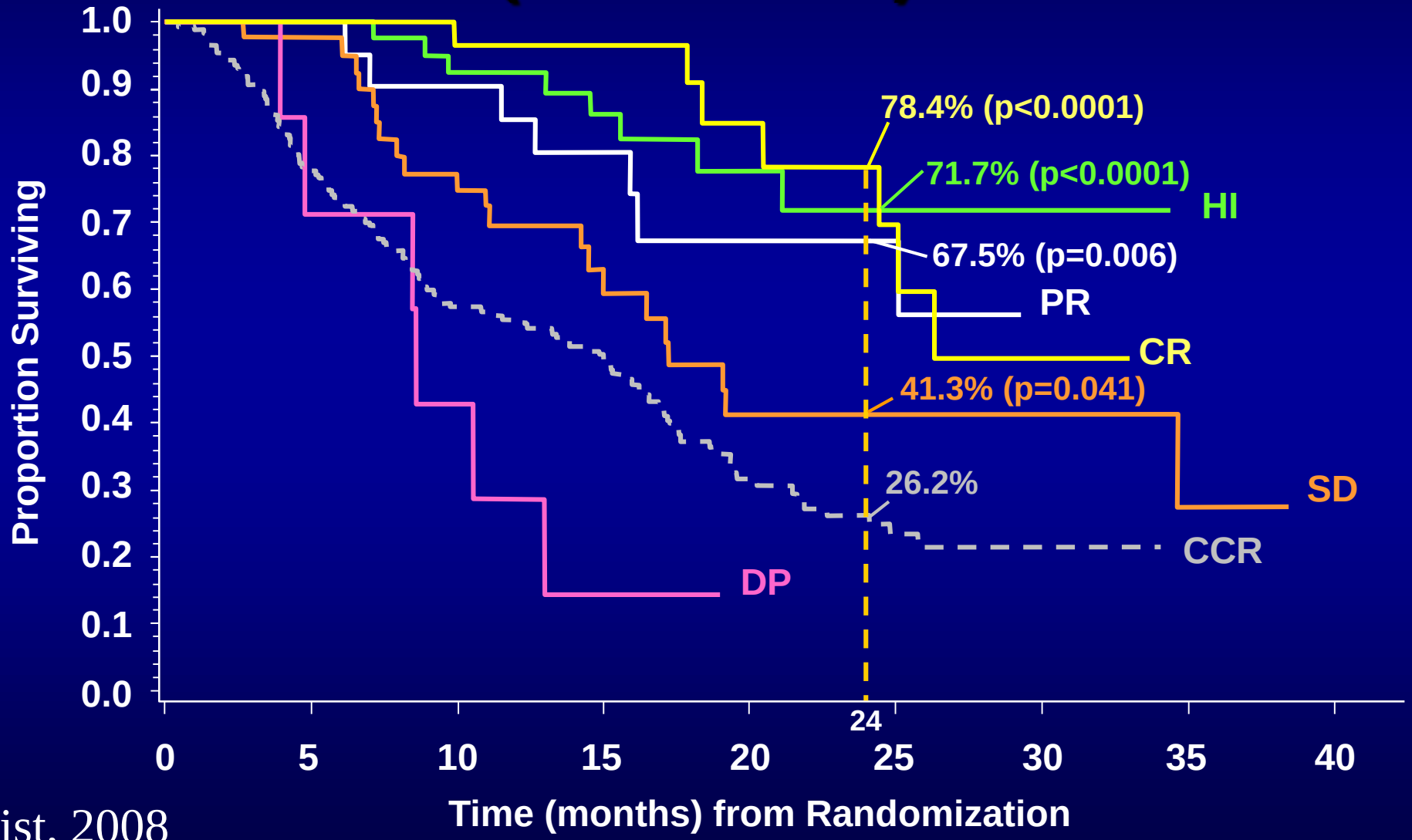
*Average of ≥ 2 measurements (not influenced by transfusions) ≥ 1 week apart.

Cheson BD, et al. Blood. 2006;108:419-425.

Secondary Endpoints: IWG (2000) RR and HI

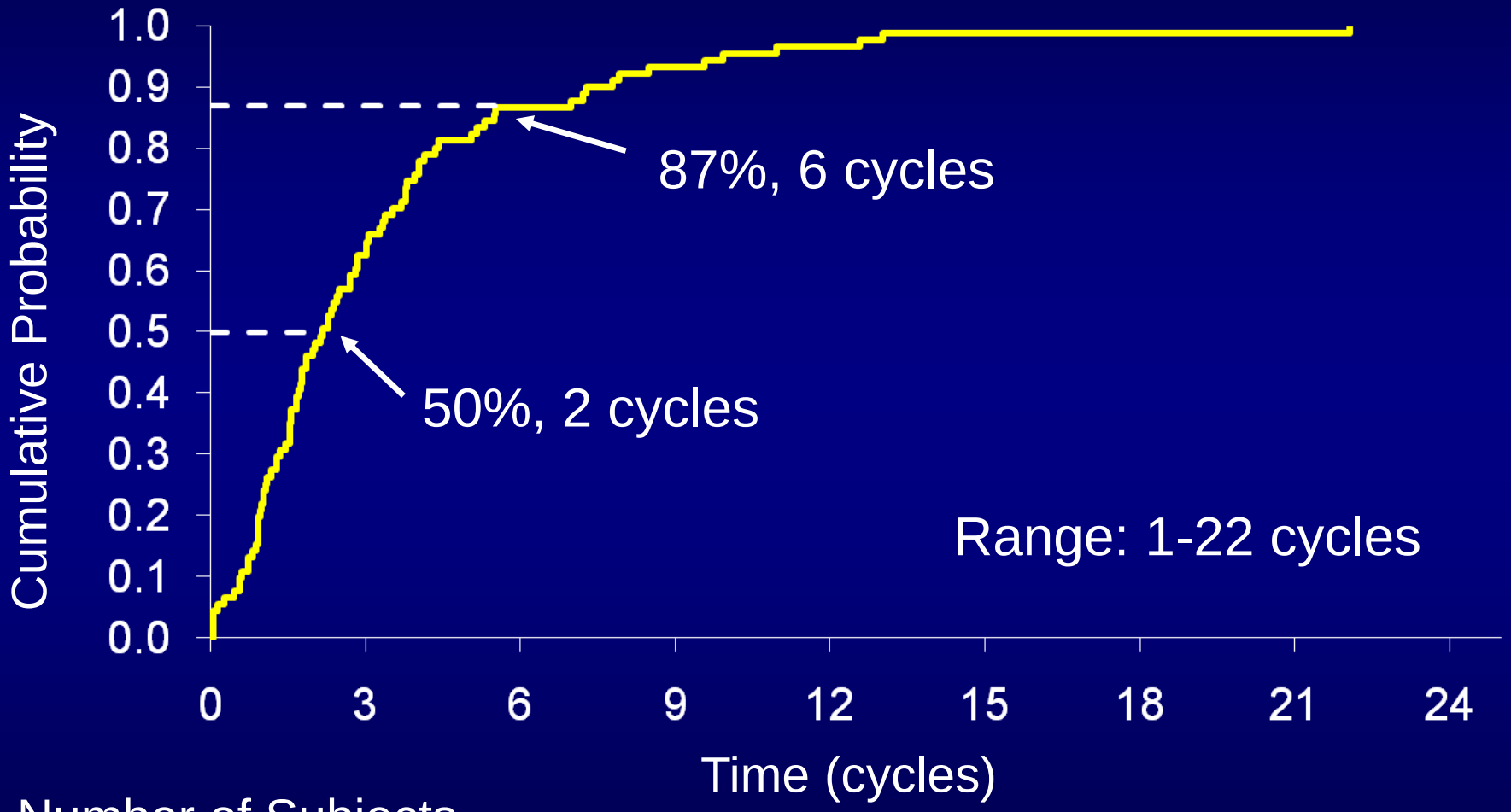
Response	AZA N=179 (%)	CCR N=179 (%)	CCR Regimens: BSC Only N=105 (%)	CCR Regimens: LDAC N=49 (%)	CCR Regimens: Std Chemo N=25 (%)	P-Value AZA vs CCR
Overall (CR+PR)	29	12	5	12	40	0.0001
CR	17	8	1	8	36	0.02
PR	12	4	4	4	4	0.009
IWG HI						
Major+Minor	49	29	31	25	28	<0.0001
HI-E Major	40	11	8	10	22	<0.0001
HI-P Major	33	14	10	19	20	0.0003
HI-N Major	19	18	20	11	24	0.87

OS with AZA by Best Response (IWG 2000)



List, 2008

Time to First Response (CR, PR, or HI)



Number of Subjects

91	34	12	6	3	1	1	1

Silverman, 2008

Original Article

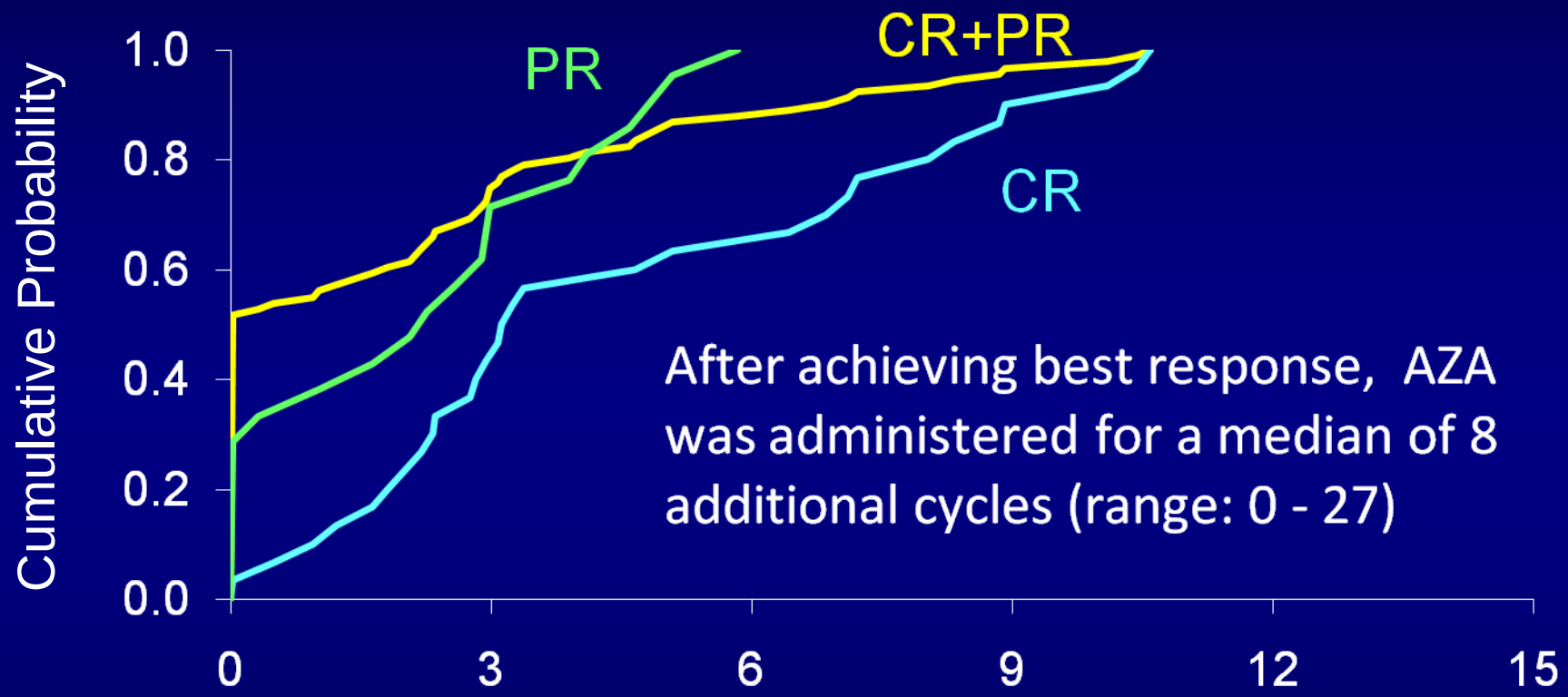
Continued Azacitidine Therapy Beyond Time of First Response Improves Quality of Response in Patients With Higher-Risk Myelodysplastic Syndromes

Lewis R. Silverman, MD[1]; Pierre Fenaux, MD[2]; Ghulam J. Mufti, MD[3]; Valeria Santini, MD[4]; Eva Hellström-Lindberg, MD[5]; Norbert Gattermann, MD[6]; Guillermo Sanz, MD[7]; Alan F. List, MD[8]; Steven D. Gore, MD[9]; and John F. Seymour, MBBS[10]

BACKGROUND: In the AZA-001 trial, azacitidine (75 mg/m^2/d subcutaneously for Days 1-7 of every 28-day cycle) demonstrated improved survival compared with conventional care regimens in patients with International Prognostic Scoring System-defined intermediate-2- or high-risk myelodysplastic syndrome and World Health Organization-defined acute myeloid leukemia with 20% to 30% bone marrow blasts. **METHODS:** This secondary analysis of the AZA-001 phase 3 study evaluated the time to first response and the potential benefit of continued azacitidine treatment beyond first response in responders. **RESULTS:** Overall, 91 of 179 patients achieved a response to azacitidine; responding patients received a median of 14 treatment cycles (range, 2-30). Median time to first response was 2 cycles (range, 1-16). Although 91% of first responses occurred by 6 cycles, continued azacitidine improved response category in 48% of patients. Best response was achieved by 92% of responders by 12 cycles. Median time from first response to best response was 3.5 cycles (95% confidence interval [CI], 3.0-6.0) in 30 patients who ultimately achieved a complete response, and 3.0 cycles (95% CI, 1.0-3.0) in 21 patients who achieved a partial response. **CONCLUSIONS:** Continued azacitidine therapy in responders was associated with a quantitative increase in response to a higher response category in 48% of patients, and therefore may enhance clinical benefit in patients with higher-risk MDS. *Cancer* **2011;117:2697–702.** © *2011 American Cancer Society.*

KEYWORDS: azacitidine, myelodysplastic syndrome, quality of response, higher-risk disease, treatment duration.

Time to Best Response After a First Response



Number of Subjects					
CPH	91	29	12	6	0
PR	21	9	1	0	0
CR	30	20	11	6	0

Silverman, 2008

Azacitidine in the elderly

Sub-Analysis of AZA 001 study

87 elderly (≥75 years) patients with higher-risk MDS

AZA (n=38) vs CCR (n=49)

AZA significantly improved OS : 2-year OS 55% vs 15% ($p<0.001$)

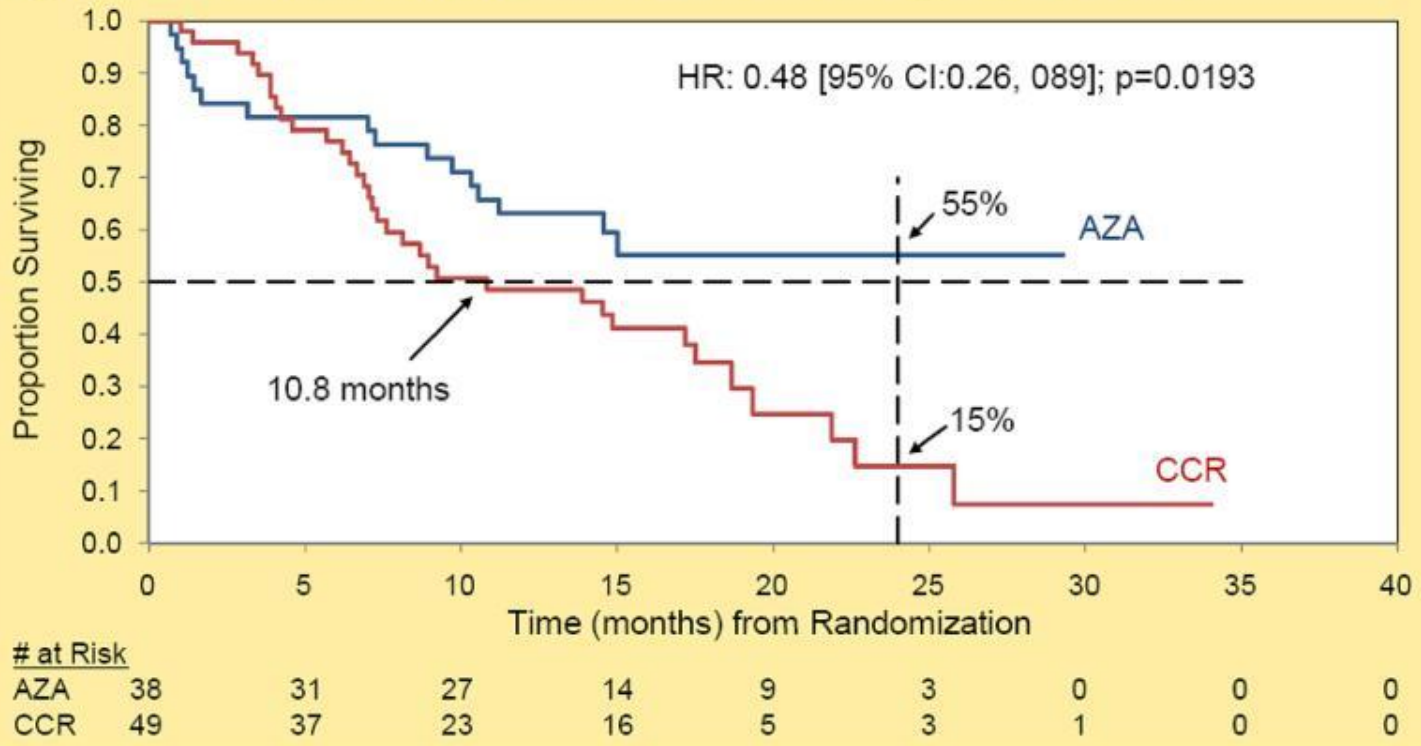
Grade 3–4 anemia, neutropenia, and thrombocytopenia with AZA vs CCR were 13% vs 4%, 61% vs 17%, and 50% vs 30%, respectively.

HMA is the treatement of choice even for elderly patients with high risk MDS

Seymour , Crit Rev Oncol Hematol. 2010

Azacitidine in MDS (≥75 years)

Figure 2. Overall Survival in Patients ≥75 Years of Age: AZA vs CCR



# at Risk									
AZA	38	31	27	14	9	3	0	0	0
CCR	49	37	23	16	5	3	1	0	0

Median follow-up: 17.7 months

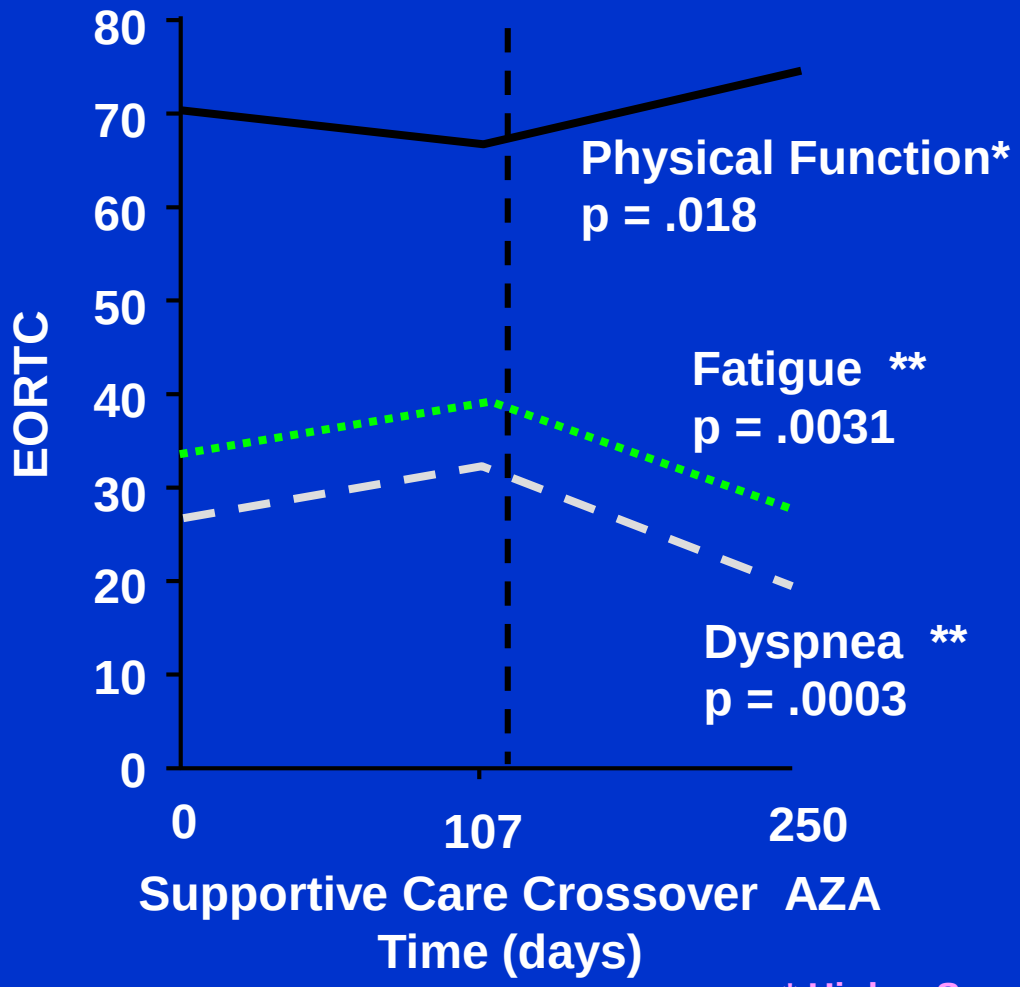
Median OS **AZA vs CCR: not reached vs 10.8 months, p=0.0193**

2-year survival AZA vs CCR: **55 vs 15%, p<0.001**

Seymour JF, et al. Crit Rev Oncol Hematol 2010:epub ahead of print

Quality of Life Impact:

EORTC Fatigue, Dyspnea & Physical Functioning of Crossover Patients on Supportive Care for 4 months Prior to Crossover (N=30)

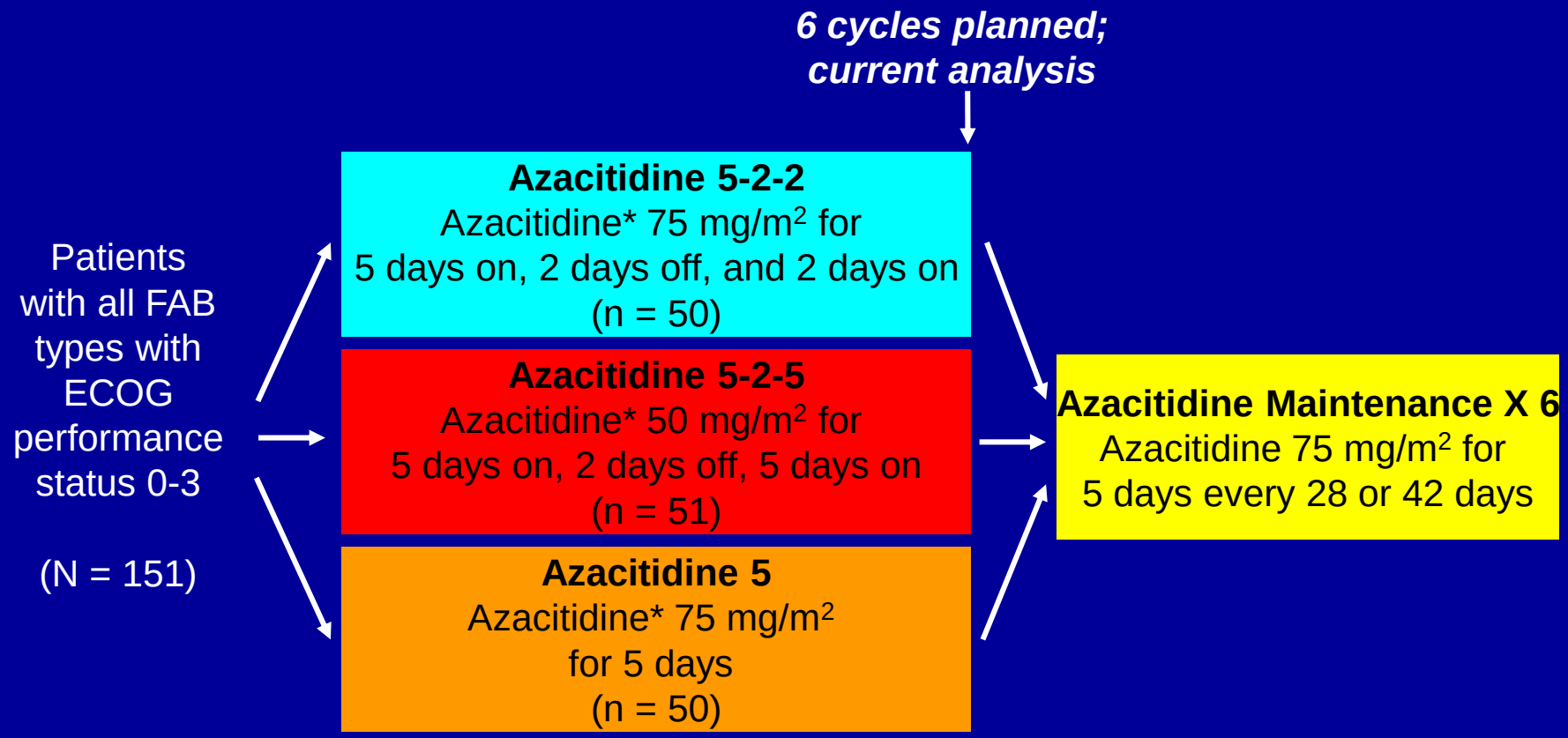


Kornblith et al., *J Clin Oncol* 2002; 20: 2441-52

* Higher Scores = Better Functioning

** Lower Scores = Symptom Improvement

Phase II Evaluation of Alternate Azacitidine Schedules (Lyons, JCO 2009)

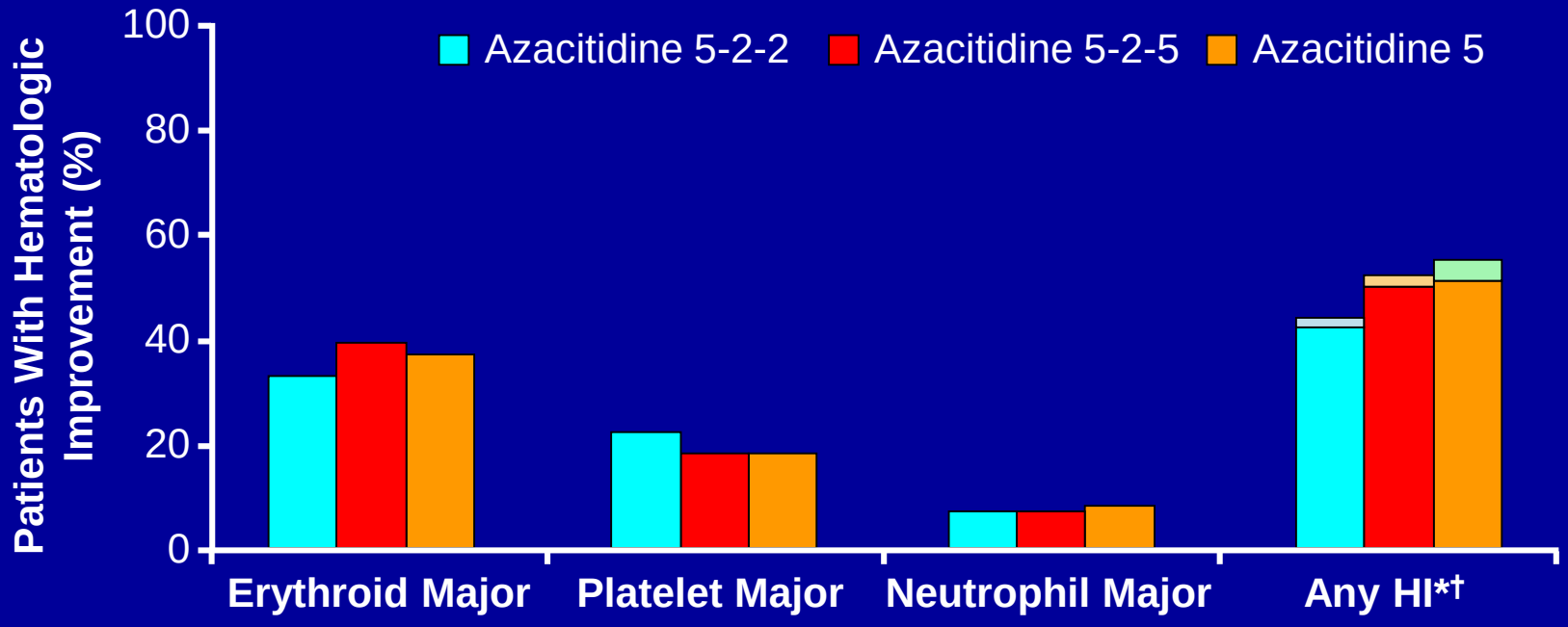


*Azacitidine given subcutaneously. Each treatment cycle lasted 28 days.

Lyons RM, et al. J Clin Oncol 2009; 27:1850-6

Phase II Evaluation of Alternative Azacitidine Schedule (Lyons JCO 2009)

- Efficacy of 3 alternative dosing regimens comparable to established 7-day schedule



*Patients counted only once for best response in an improvement category.
†Minor improvement shown as light-colored segments at top of bars.

Lyons RM, et al. J Clin Oncol 2009; 27:1850-6

Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*

Valeria Santini[1], Pierre Fenaux[2], Ghulam J. Mufti[3], Eva Hellström-Lindberg[4], Lewis R. Silverman[5], Alan List[6], Steven D. Gore[7], John F. Seymour[8], Jay Backstrom[9], Charles L. Beach[9]

[1]Azienda Ospedaliera Universitaria Careggi, Florence, Italy; [2]Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris (AP-HP) and Paris University, Paris, France; [3]King's College Hospital, London, UK; [4]Karolinska University Hospital, Stockholm, Sweden; [5]Mount Sinai School of Medicine, New York, NY, USA; [6]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [7]Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [8]Peter MacCallum Cancer Centre, and University of Melbourne, Melbourne, Australia; [9]Celgene Corporation, Summit, NJ, USA

Abstract

Objective: Myelodysplastic syndrome (MDS) treatment can initially worsen patients' clinical condition and they may discontinue therapy before achieving benefit. We present previously unpublished data from two large phase III trials describing common adverse events (AEs) associated with azacitidine and methods to manage them. *Methods:* In the Cancer and Leukemia Group B (CALGB) 9221 study, patients with any French-American-British (FAB) subtype of MDS were randomized to azacitidine or best supportive care (BSC). After 56 d, patients randomized to BSC with disease progression could cross over to receive azacitidine. In the AZA-001 study, patients with higher-risk MDS (FAB-defined refractory anemia with excess blasts (RAEB), RAEB in transformation, or chronic myelomonocitic leukaemia and IPSS int-2 or high) were randomized to azacitidine or to conventional care regimens (CCR), which included low-dose ara-C, BSC, or intensive chemotherapy. In both studies, azacitidine dose was 75 mg/m^2/d SC for 7 d every 28 d. AEs were graded per National Cancer Institute's Common Toxicity Criteria version 2.0 (AZA-001) or CALGB Expanded CTC (CALGB 9221). *Results:* In safety-evaluable patients in AZA-001 (N = 175) or CALGB 9221 (N = 150), the most common AEs with azacitidine included hematologic (eg, cytopenias) and non-hematologic administration-related events (eg, injection-site reactions and gastrointestinal disorders). Most AEs were transient and resolved during ongoing therapy (> 83%). Hematologic AEs, most frequently observed during early treatment cycles, decreased during subsequent cycles and were usually managed with dosing delays (23–29%). Gastrointestinal symptoms were primarily managed with anti-emetics and laxatives. *Conclusion:* Hematologic and non-hematologic AEs with azacitidine decreased in frequency as treatment continued. Awareness of the onset, duration and management of AEs can facilitate treatment, permitting patients to continue therapy for maximum benefit.

Table 2 Most common[1] adverse events (AEs) with azacitidine

Adverse event[2]	Percent of patients			
	AZA-001 (*N* = 175)		CALGB 9221 (*N* = 150)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with at least 1 individual AE occurring in ≥ 20% of patients in the azacitidine group in AZA-001	97.7	80.0	100.0	92.7
Anemia	51.4	13.7	74.0	60.7
Neutropenia	65.7	61.1	34.0	24.0
Thrombocytopenia	69.7	58.3	68.7	56.0
Constipation	50.3	1.1	39.3	3.3
Diarrhea	21.7	0.6	40.0	3.3
Nausea	48.0	1.7	67.3	5.3
Vomiting	26.9	0	48.0	2.7
Fatigue	24.0	3.4	47.3	5.3
Injection-site erythema	42.9	0	33.3	0.7
Injection-site reaction	29.1	0.6	3.3	0
Pyrexia	30.3	4.6	51.3	2.0

[1]Greater than or equal to 20% of azacitidine-treated patients in AZA-001.

[2]Multiple reports of the same preferred term for a patient are counted only once.

Table 3 Median durations of common adverse events[1] with azacitidine

Adverse event	AZA-001 (*N* = 175)			CALGB 9221 (*N* = 150)		
	Percent (%) of patients	Percent (%) of events resolved[2]	Median duration (d)	Percent (%) of patients	Percent (%) of events resolved[2]	Median duration (d)
Anemia	51.4	88.2	14	71.3	97.8	8
Neutropenia	65.7	88.3	16	34.0	98.4	9
Thrombocytopenia	69.7	86.5	15	68.0	96.0	8
Constipation	50.3	91.9	8	38.7	83.3	17
Diarrhea	21.7	95.8	3	36.0	93.5	8
Nausea	48.0	95.0	4	66.7	93.8	10
Vomiting	26.9	97.9	1	48.0	98.2	5
Fatigue	24.0	85.9	8	38.7	83.1	33
Injection-site erythema	42.9	97.0	12	32.7	84.9	30
Injection-site reaction	29.1	97.9	12	13.3	83.3	18
Pyrexia	30.3	91.9	5	51.3	93.0	7

[1]Greater than or equal to 20% of azacitidine-treated patients in AZA-001.

[2]Multiple reports of the same preferred term for a patient are counted, and percentages are based on the total number of events.

Table 4. Common AEs* with Azacitidine by Cycle

System Organ Class Preferred Term†	Percent of Patients by Cycles								
	AZA-001					9221			
	Cycles 1-2 (N=175)	Cycles 3-4 (N=147)	Cycles 5-6 (N=130)	Cycles 7-8 (N=107)	Cycles 9-10 (N=89)	Cycles 1-2 (N=150)	Cycles 3-4 (N=122)	Cycles 5-6 (N=83)	Cycles 7-12‡ (N=66)
Anemia	32.6	18.4	13.8	11.2	13.5	66.7	52.5	34.9	28.8
Neutropenia	50.3	31.3	27.7	18.7	20.2	26.7	24.6	21.7	22.7
Thrombocytopenia	54.3	29.9	25.4	19.6	21.3	58.0	44.3	30.1	40.9
Constipation	35.4	19.7	13.1	9.3	16.9	22.0	9.0	3.6	16.7
Diarrhea	12.0	7.5	3.8	4.7	4.5	21.3	13.9	10.8	10.6
Nausea	36.0	19.0	11.5	14.0	11.2	44.7	21.3	21.7	24.2
Vomiting	17.7	10.9	5.4	7.5	5.6	32.7	8.2	9.6	9.1
Fatigue	12.6	9.5	3.1	5.6	3.4	27.3	15.6	15.7	22.7
Injection site erythema	34.9	21.1	17.7	15.9	11.2	23.3	11.5	6.0	9.1
Injection site reaction	20.6	12.9	9.2	9.3	9.0	2.7	0	1.2	0
Pyrexia	16.0	6.1	3.8	5.6	6.7	24.7	21.3	14.5	25.8

* ≥20% of azacitidine-treated patients in AZA-001.
† Multiple reports of the same preferred term during a cycle counted once.
‡ CALGB 9221 data not reported in same cycle groupings as AZA-001 after cycles 5-6.

In both studies, most AEs occurred during the first 2 cycles, and tended to decrease in frequency with subsequent cycles

Santini V et al. Eur J Haematol 2010;Epub ahead of print

Table 5 Cytopenias at baseline

Adverse event grade at baseline	Number of Azacitidine-treated patients (%)	
	AZA-001 ($N = 175$)	CALGB 9221 ($N = 150$)
Hemoglobin (g/dL)		
Grade 0–2	156 (89.1)	107 (71.3)
Grade 3	16 (9.1)	30 (20.0)
Grade 4	0	10 (7.3)
Platelets (10^9/L)		
Grade 0–2	97 (55.4)	80 (53.3)
Grade 3	62 (35.4)	57 (38.0)
Grade 4	5 (2.9)	6 (4.0)
ANC (10^9/L)		
Grade 0–2	80 (45.7)	40 (26.7)
Grade 3	48 (27.4)	22 (14.7)
Grade 4	38 (21.7)	23 (15.3)

ANC, absolute neutrophil count.

Table 6 Selected infection rates (Grade 3 or 4)

	Number of events (Rate per patient-year of exposure)			
	AZA-001[1]		CALGB 9221	
	Azacitidine $N = 114$	BSC $N = 102$	Azacitidine $N = 150$	BSC $N = 92$
Infections – total[2]	55 (0.51)	24 (0.41)	29 (0.21)	16 (0.37)
Bacteremia	1 (0.01)	0	0	0
Bronchitis	0	0	1 (0.01)	0
Cellulitis	2 (0.02)	3 (0.05)	1 (0.01)	1 (0.02)
Clostridium Difficile colitis	3 (0.03)	0	0	0
Lower respiratory tract infection	2 (0.02)	0	0	0
Neutropenic sepsis	3 (0.03)	0	0	0
Pneumonia	14 (0.13)	8 (0.14)	7 (0.05)	4 (0.09)
Sepsis	6 (0.06)	3 (0.05)	2 (0.01)	4 (0.09)
Urinary tract infection	3 (0.03)	0	0	1 (0.02)

BSC, best supportive care.

[1]Includes patients preselected to BSC in AZA-001 who were then randomized to and received azacitidine ($n = 114$) or BSC ($n = 102$).

[2]Includes events not listed here.

Table 7 Selected bleeding event rates (Grade 3 or 4)

	Number of events (Rate per patient-year of exposure)			
	AZA-001[1]		CALGB 9221	
	Azacitidine $N = 114$	BSC $N = 102$	Azacitidine $N = 150$	BSC $N = 92$
Bleeding events – total[2]	37 (0.34)	27 (0.46)	20 (0.14)	7 (0.16)
Gastrointestinal hemorrhage	1 (0.01)	1 (0.02)	0	0
Gingival bleeding	3 (0.03)	0	3 (0.02)	0
Hemorrhoidal bleeding	1 (0.01)	0	0	0
Melena	0	3 (0.05)	1 (0.01)	0
Mouth hemorrhage	2 (0.02)	1 (0.02)	1 (0.01)	0
Rectal hemorrhage	2 (0.02)	1 (0.02)	2 (0.01)	0
Cerebral hemorrhage	3 (0.03)	4 (0.07)	0	0
Hematuria	2 (0.02)	1 (0.02)	0	3 (0.07)
Epistaxis	10 (0.09)	10 (0.17)	7 (0.05)	0

BSC, best supportive care.

[1]Includes patients preselected to BSC in AZA-001 who were then randomized to and received azacitidine ($n = 114$) or BSC ($n = 102$).

[2]Includes events not listed here.

Table 2 Common side effects of azacitidine and recommendations for management

Adverse event	Monitoring	Prophylaxis	Therapy
Hematologic	CBC at regular intervals	Consider G-CSF if expected neutropenia exceeds 10 days	Delay next cycle until recovery of CBC
			Reduce dose in next cycle if blood values do not recover within 2 weeks of designated day 1 of next cycle
			Transfusion of RBC and platelets as required
Infection	Regular clinical examination Educate patient to seek medical care promptly if temp >38.5°C occurs	Consider G-CSF in following cycles Consider antibiotics (e.g., quinolones)	Antibiotics following guidelines for neutropenic fever
Nausea and emesis		Premedicate with antiemetics (metoclopramide, alizapride or 5-HT3 antagonist)	Escalate antiemetic regimen (5-HT3 antagonist, dexamethasone)
Diarrhea			I.V. fluids
			Loperamide
Constipation		Consider laxatives when using high dose 5-HT3 antagonists	Laxatives, stool softener
Injection site reaction	Clinical examination	Correct injection technique	Symptomatic (evening primrose oil, cooling compresses, soothing lotion)
		Rotation of injection sites	Topical steroids

CBC complete blood count, *RBC* red blood cell, *G-CSF* granulocyte-colony stimulating factor

HMA & renal insufficiency

- 41 patients at MDACC
- azacitidine or decitabine
- The median number of administered cycles was 3.
- Most patients (95%) received a standard dose of the drugs
- Nine patients (22%) required treatment interruptions or discontinuation
- and 10 patients (24%) required dose reductions.

Clin Lymphoma Myeloma Leuk. 2010 Jun;10(3):205-10.

HMA & renal insufficiency

Overall response rate : 63%

51% grade 3 or 4 myelosuppression

Hospitalization was required in 68%

median OS was 8.6 months.

→The use of HA in patients with RI is feasible, but is associated with a higher incidence of toxicity. Dose adjustments and the use of growth factor may be necessary for some patients.

Clin Lymphoma Myeloma Leuk. 2010 Jun;10(3):205-10.

AZA Prognostic scoring system for OS

Performance Status ≥ 2	1
IPSS cytogenetic group Intermediate High	 1 2
Transfusion ≥ 4 CGR/8 w	1
Peripheral circulating blasts	1

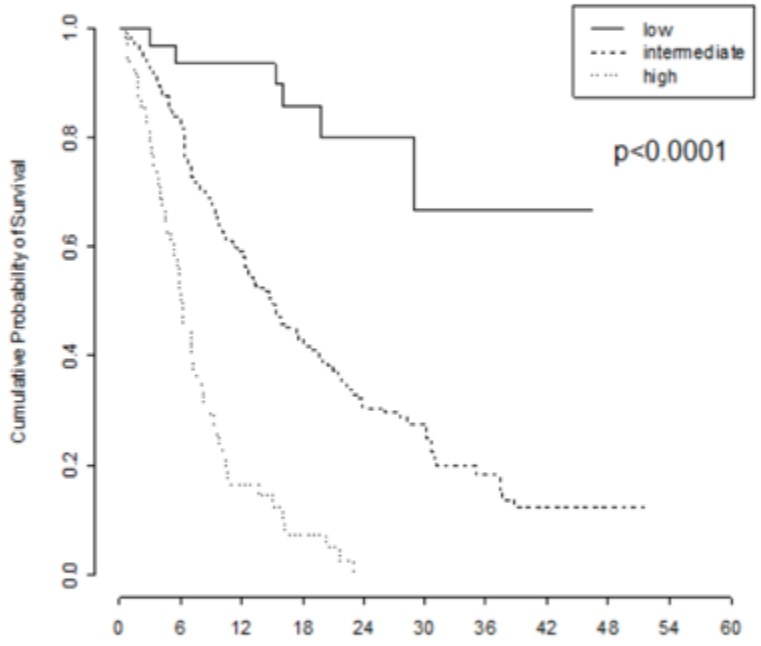
RISK GROUP	
LOW RISK GROUP	0
INTERMEDIATE RISK GROUP	1-3
HIGH RISK GROUP	4-5

Groupe Francophone des Myélodysplasies

Itzykson & Thépot, *Blood*, 2011

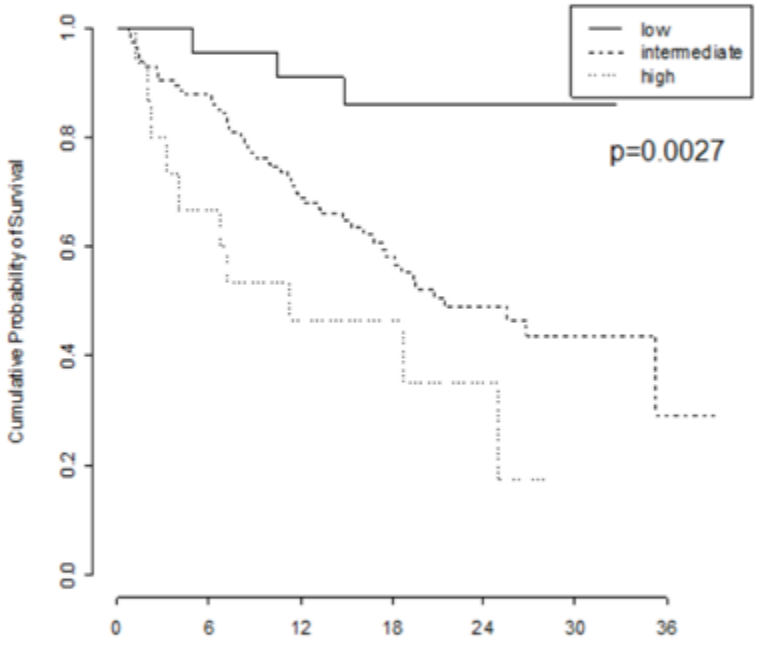
AZA Prognostic scoring system for OS

a. ATU cohort (development)



	N at RISK	Median OS
LOW	30 (11%)	NA
INT	191 (71%)	15,0 mo
HIGH	48 (18%)	6,1 mo

b. AZA-001 cohort (validation)



	N at RISK	Median OS
LOW	23 (15%)	NA
INT	114 (75%)	21,4 mo
HIGH	15 (10%)	9,3 mo

Itzykson & Thépot, *Blood*, 2011

Survival according to IPSS and IPSS-R

IPSS

	Intermediate-2	High
	56%	44%
Median OS	16.1 months	9.4 months

P=0.04

***p*IPSS-R**

	Intermediate	Poor	Very Poor
	9%	23%	67%
Median OS	30.7 months	23.1 months	10 Months

P=0.7

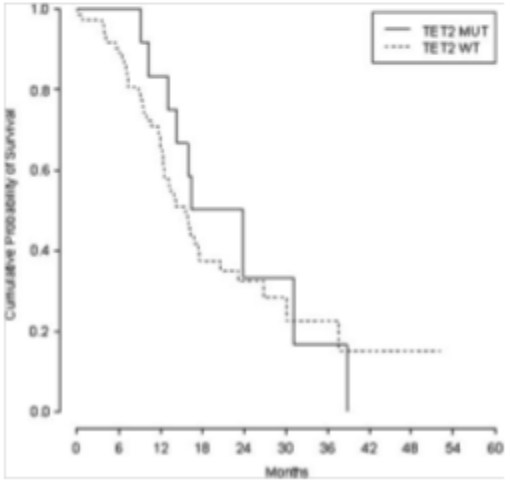
$P<10^{-3}$

Groupe Francophone des Myélodysplasies

M. Lamarque, ASH 2012

Impact of TET2 mutation in patients treated with AZA

	all	TET2 mutated	TET2 WT	p*
Patients	103	17 (17%)	86 (83%)	
Cycles of AZA	7 [1-39]	11 [4-34]	6 [1-39]	0,016
High risk cytogenetics	30 (34%)	1 (7%)	29 (39%)	0,01
Complete Response	24 (23%)	7 (41%)	17 (20%)	0,07
ORR (including HI)	53 (52%)	14 (82%)	39 (45%)	0,007



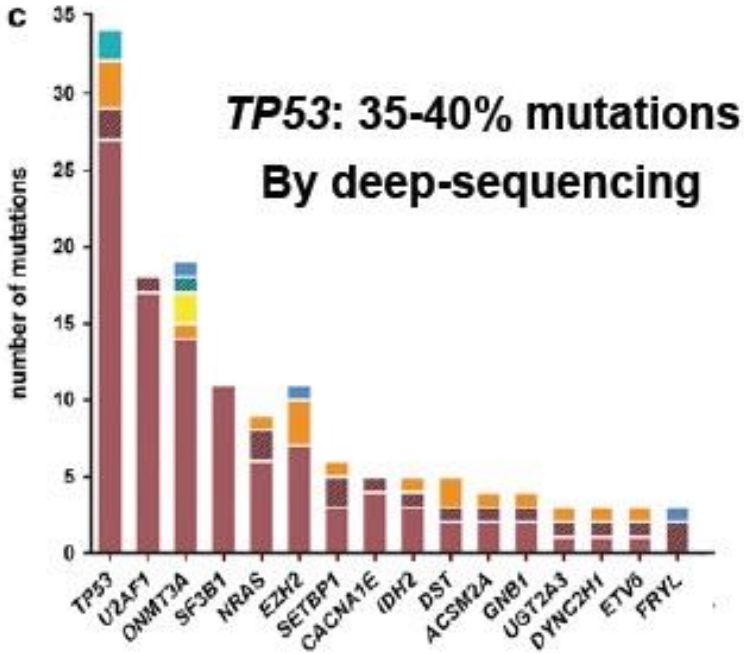
Higher Response Rate in TET 2 mutated patients

Response duration and overall survival were, however, comparable in the MUT and WT groups.

Groupe Francophone des Myélodysplasies

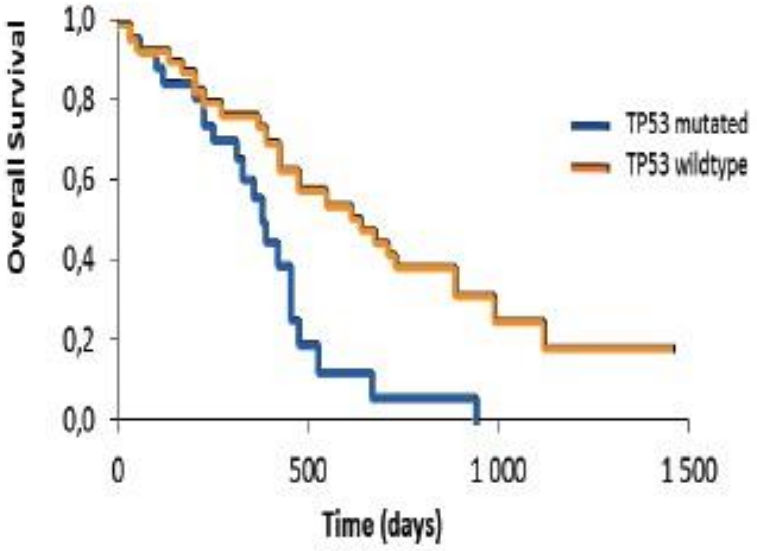
R. Itzykson *et al.*

Impact of TP53 in AZA treated pts



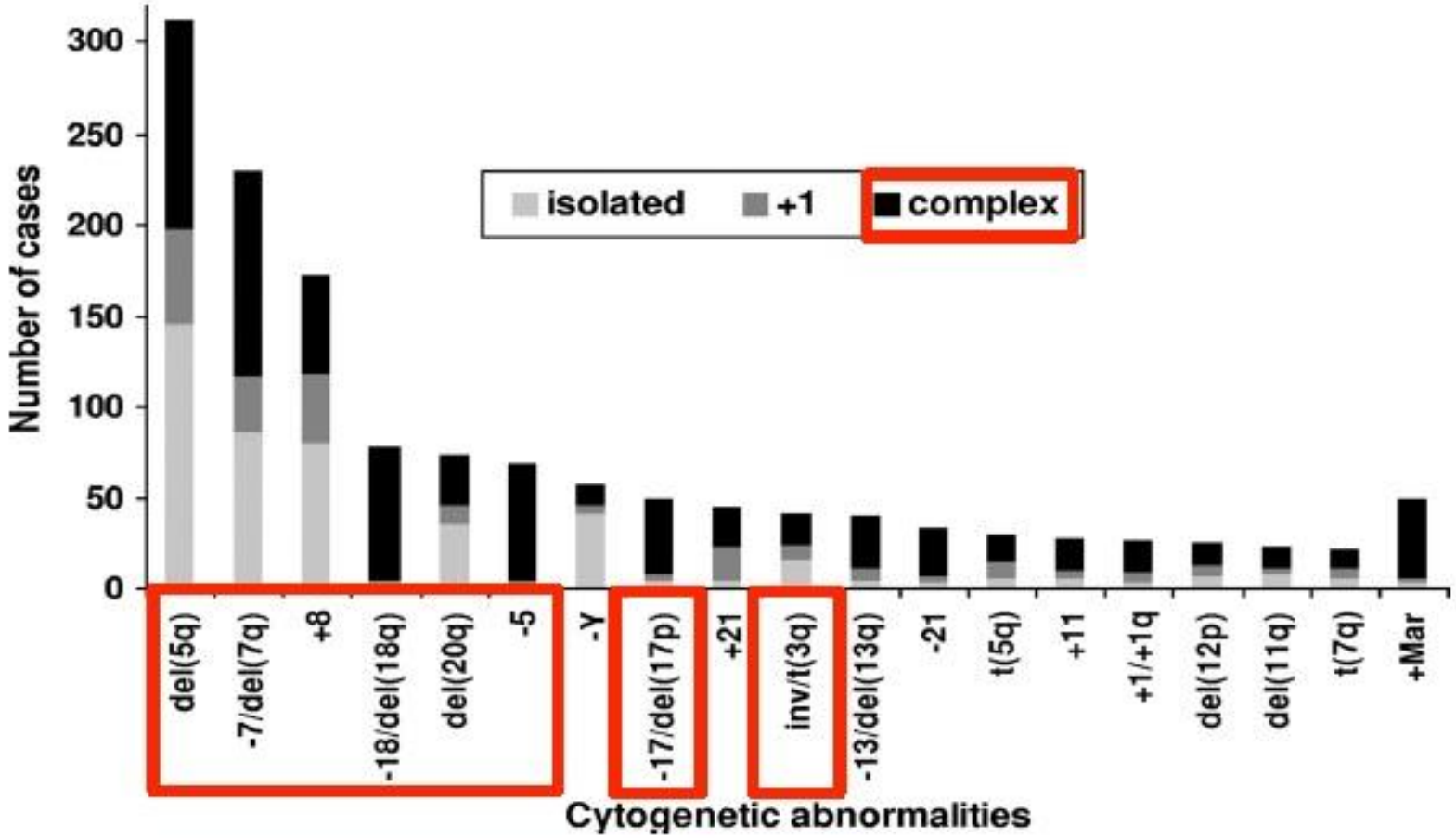
***TP53*: 35-40% mutations**

By deep-sequencing



Bally *Leuk Res 2014*; Walter *Leukemia* 2013

In MDS, cytogenetics if often unfavorable



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

Elderly AML/MDS treated with Chemotherapy

- 1065 elderly AML
- MRC AML 11 trial

Abnormality	Total no.	CR and reason for failure			Relapse risk at 5 years, % (SE)	Overall survival at 5 years, % (SE)
		CR rate, %	Induction deaths, %	Resistant disease, %		
Overall	1065	55	18	26	79 (1.8)	13 (1.1)
Favorable						
t(15;17)	43	63	33	5	26 (9.1)§	38 (8.2)‖
t(8;21)	23	87	0‖	13	84 (12.4)	35 (9.9)
inv(16)	12	75	17	8	89 (10.5)	17 (10.8)
Intermediate						
No abnormality	507	63	20	17	78 (2.5)	15 (1.7)
Sole +8	41	51	17	32	95 (4.9)	5 (3.4)
11q23*	7	86	0	14	100 (0.0)	0 (0.0)
Other intermediate†	221	54	16	30§	84 (3.6)	11 (2.2)
Adverse						
Noncomplex adverse‡	66	45‖	14	41§	81 (8.1)	7 (3.9)
Complex (with no favorable)	145	26§	19	56§	91 (5.1)§	2 (1.2)§

Grimwade et al. Blood. 2001

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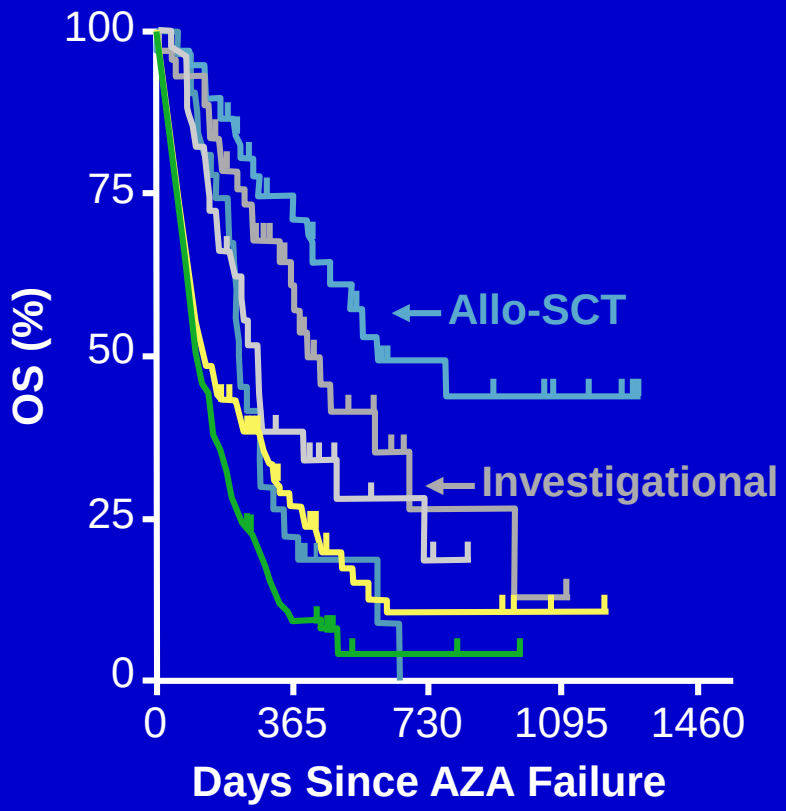
Grimwade et al. Blood. 2001

Salvage Therapy After Azacitidine Failure: GFM and AZA001 Studies

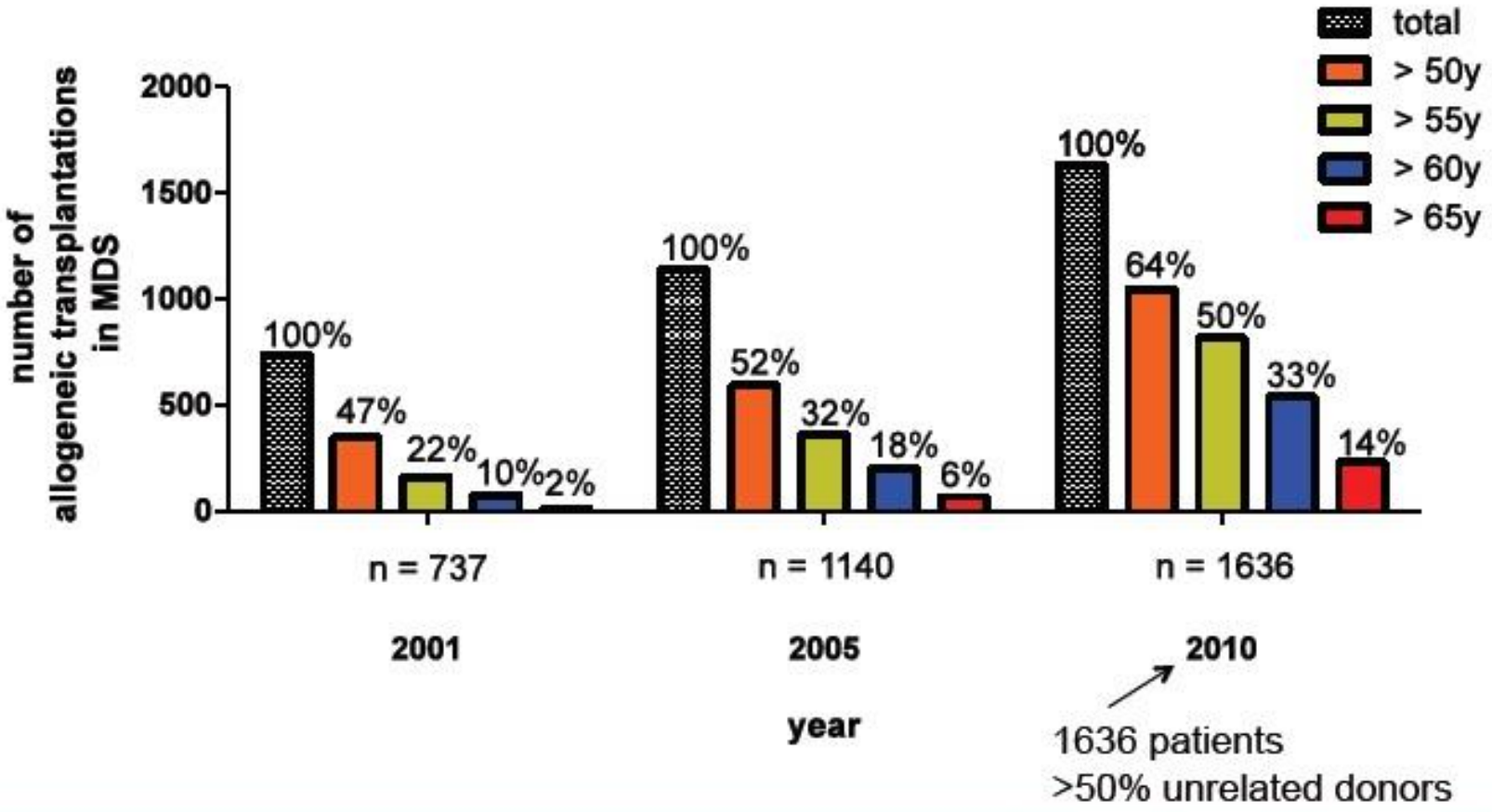


Type of Salvage	N	ORR	Median OS, Mos
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

*Log-rank comparison of BSC vs intensive CT (*P* = .04), investigational therapy (*P* < .001), or alloSCT (*P* < .001).
†Comparison of intensive CT vs investigational therapy (*P* = .05), intensive CT vs ASCT (*P* = .008), or IT vs ASCT (*P* = .09).

Prébet T, et al. J Clin Oncol. 2011;29:3332-3327.

INCREASE OF NUMBER OF TRANSPLANTS IN ELDERLY MDS/sAL PATIENTS



Kröger N. Blood 2012;119: 5632-5639

HLA-identical siblings is available for only 30%

Alternative donors are matched unrelated donors, which can be found for 80-90% for white but less than 20% for ethnic minorities in donor registries

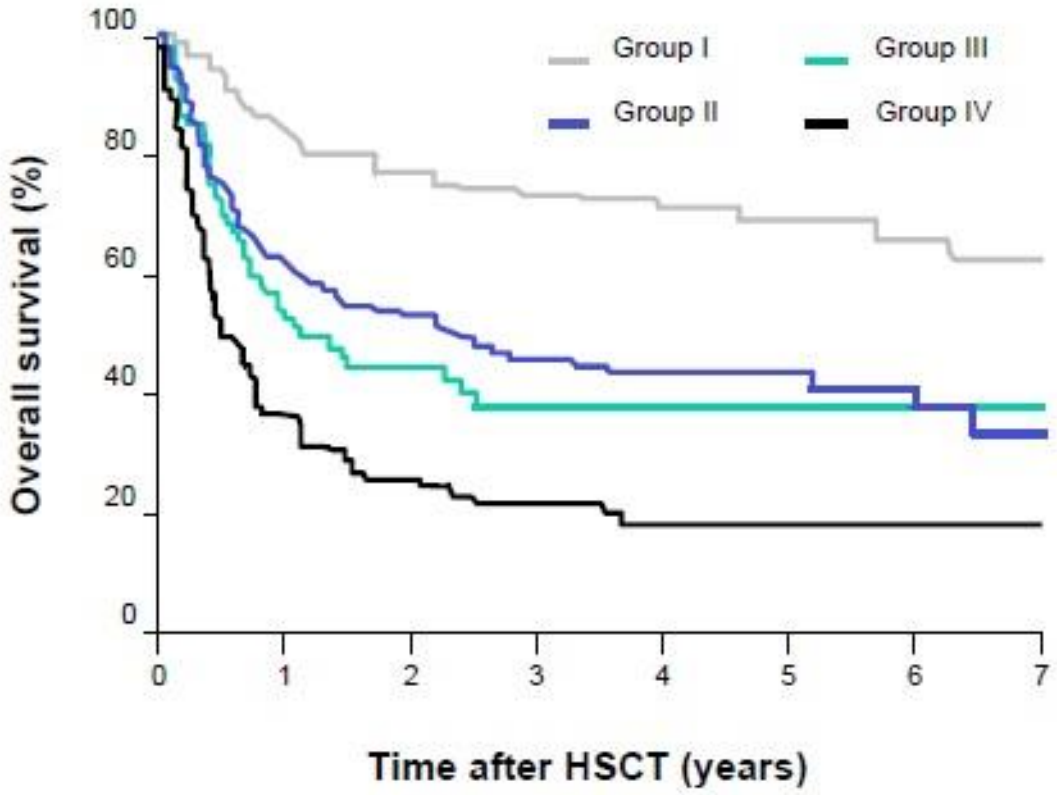
For those patients with no HLA-matched donor there are three possibilities:

- cord blood transplantation

- mismatched unrelated donor

- haplo-identical transplantation

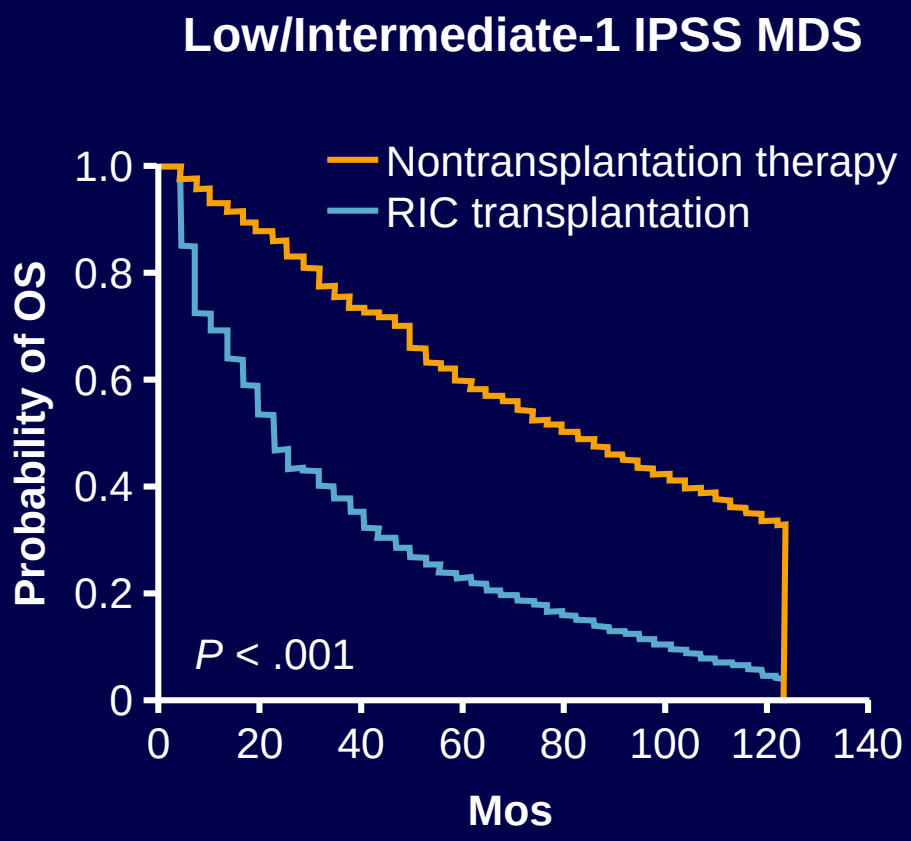
- **Disease-related**
  - disease stage
  - cytogenetics
  - response to (chemo-)therapy
- **Related to transplantation procedure**
  - conditioning intensity
  - **donor age, type**
- **Patient-related**
  - age
  - comorbidity index
  - transfusion burden
  - iron overload

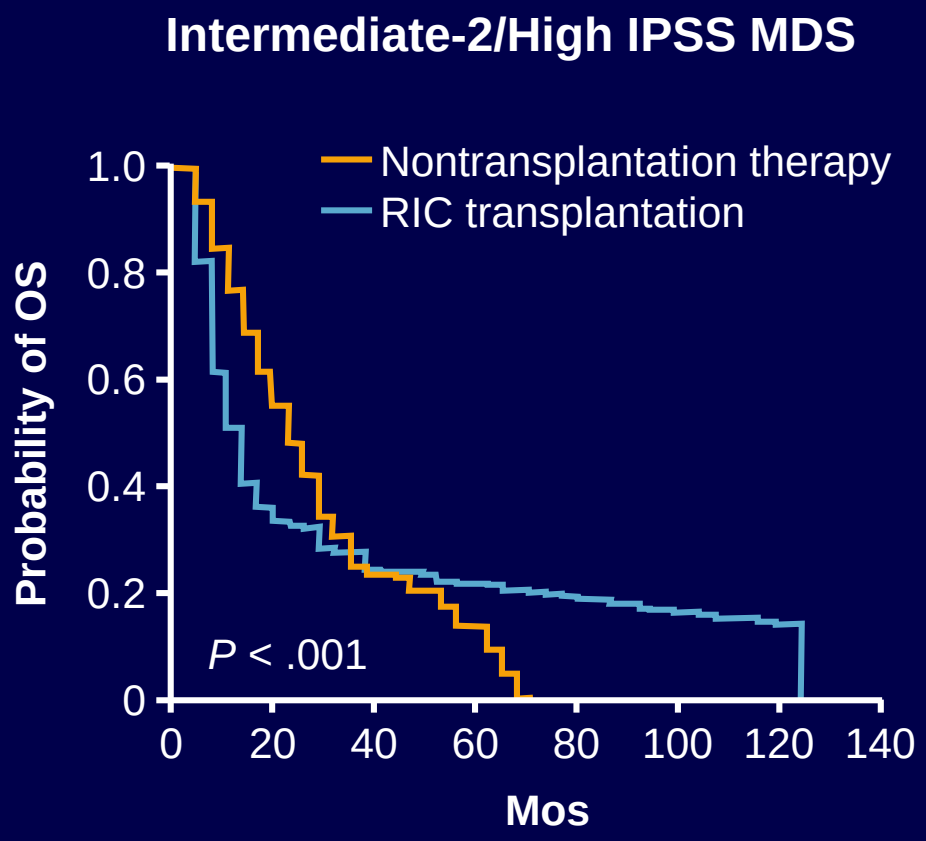


Overall survival decreases with increasing HCT-CI score and disease risk of AML/MDS patients

Sorror ML, et al. J Clin Oncol. 2007;25:4246-54.

Role of RIC Allogeneic HCT in Older Patients With De Novo MDS





Koreth J, et al. J Clin Oncol. 2013;31:2662-2670.

BMT for MDS: EBMT Analysis

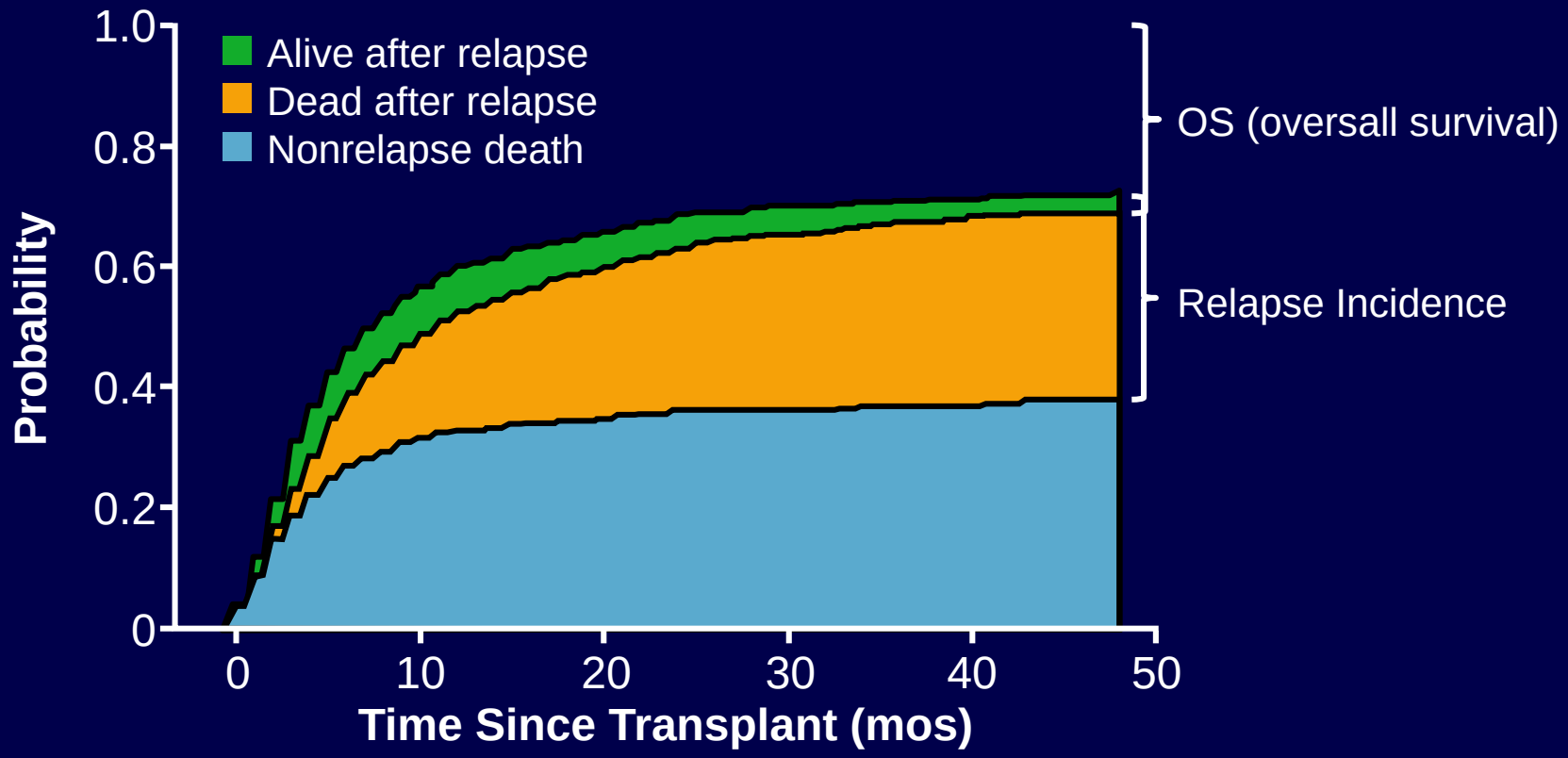
- A retrospective multi-center analysis of MDS patients ≥ 50 years who received transplantation within the EBMT since 1998

Parameter	N = 1333
Median age, yrs	56
▪ Pts 50 to 60 yrs, n (%)	884 (66)
▪ Pts > 60 yrs, n (%)	449 (34)
Transplant donor	
▪ HLA-matched sibling, n (%)	811 (61)
▪ Unrelated donor, n (%)	522 (39)
Conditioning type, n (%)	
▪ SMC	500 (38)
▪ RIC	833 (62)

Lim Z, et al. J Clin Oncol. 2010;28:405-411.

BMT for MDS: EBMT Survival Results

- Overall 4-yr OS: 31%
  - 4-yr OS: 50 to 60 yrs of age, 34%; > 60 yrs, 27%



Lim Z, et al. J Clin Oncol. 2010;28:405-411.

Allogeneic SCT in MDS: Outcomes

- Analysis of post-SCT outcomes for 701 MDS pts who underwent transplant from 2002 to 2006
  - Median age (range), yrs: 53 (22-78)
  - 65% had advanced disease at the time of transplant
  - Data reported to CIBMTR

3-Yr Outcomes, %	MRD	8/8 URD	7/8 URD	*P* Value 8/8 URD vs MRD*	*P* Value 7/8 URD vs MRD*
TRM	30	41	42	.01	.03
Relapse	32	24	27	.058	.30
Survival	47	38	31	.04	.003
DFS	40	35	29	.22	.04

*Pointwise pairwise comparison.

Saber W, et al. ASH 2012. Abstract 355.

Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet

Disease risk scored according to the IPSS, age, and presence of comorbidity graded according to the Hematopoietic Cell Transplantation Comorbidity Index were recognized as the most relevant clinical variables to be considered in order to judge a patient eligible for allogeneic SCT.

The decision to perform an allogeneic SCT should be shared as much as possible with the patient, whose attitude to risk should be taken into account.

Fit patients up to age 65 to 70 years with IPSS intermediate-2 or high risk and those with IPSS intermediate-1 risk with excess blasts or poor-risk cytogenetics are candidates for allogeneic SCT (recommendation level B).

Malcovati L et al. Blood 2013, 122: 2943-2964

Costs of potentially anemia-altering drugs in MDS

• An evaluation of the costs of specific drugs (r-HuEPO, azacytidine, decitabine, lenalidomide) and their sequential use in the lower-risk IPSS (low and intermediate-1) subgroups based on the NCCN guidelines

• Results estimate an average annual cost for potentially anemia-altering drugs of $ 63,577 per patient, ranging from $ 26,000 to $ 95,000, depending on the specific therapies.

• In patients for whom the therapies fail, annual costs for iron chelation plus red blood cell transfusions are estimated to average $ 41,412

• The economic impact of drug therapy should be weighed against the patient's potential for improvement in clinical outcomes, quality of life, and transfusion requirements.

Greenberg PL et al, J Natl Compr Canc Netw. 2008 Oct;6(9):942-53.

Appropriatezza

1. Health Interventions

("intervento giusto al paziente giusto")

2. Timing

("al momento giusto e per la durata giusta")

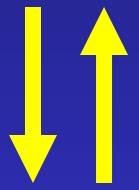
3. Setting

("nel posto giusto")

4. Professional

("dal professionista giusto")

Appropriatezza professionale



Appropriatezza organizzativa


GUARDI QUI: LE CURE PIÙ TECNOLOGICHE, I FARMACI PIÙ RECENTI, GLI INTERVENTI PIÙ MODERNI.
UNA CURA SOBRIA E RISPETTOSA È CHIEDERE TROPPO?
Sergio Staino