FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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

Attualità nel trattamento dell'anemia

Enrico Balleari

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Genova

Incidenza e rilevanza clinica dell'anemia in corso di SMD

Anemia is present in 2/3 of MDS patients at diagnosis

almost all MDS patients develop anemia during the course

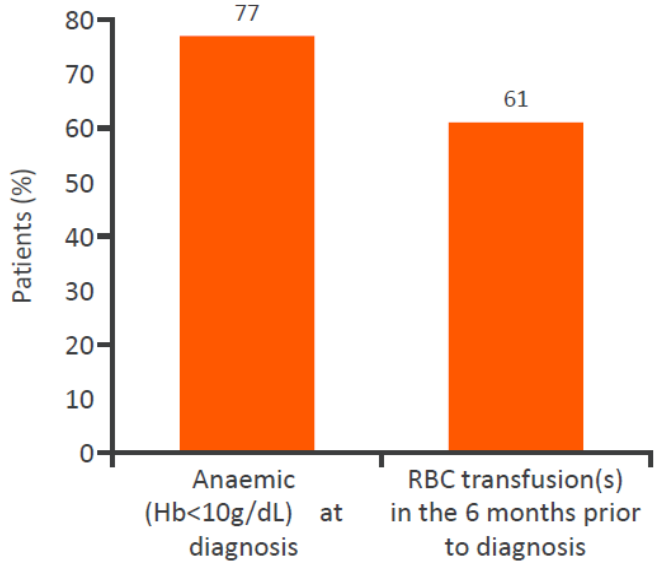
it is responsable for main morbidity and mortality

Santini V, Semin Hematol, 2015

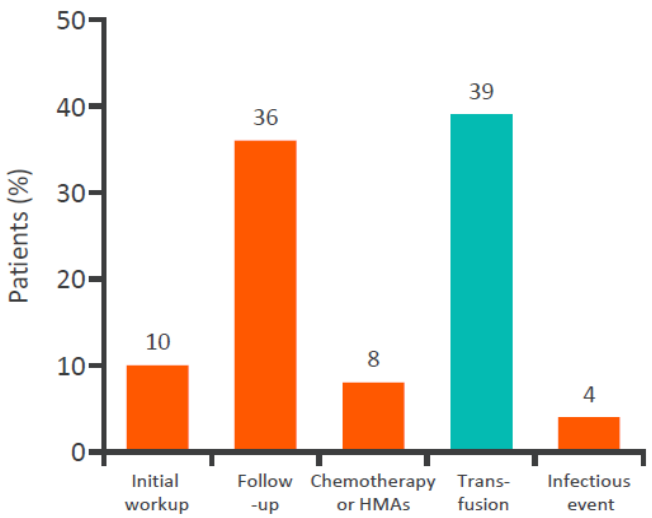
Incidenza e rilevanza clinica dell'anemia in corso di SMD

Anaemia is a major clinical burden in patients with MDS

Most patients with MDS are anaemic at diagnosis and have received RBC transfusions*



The most common reason for patients with MDS to attend a clinic is transfusion requirement*

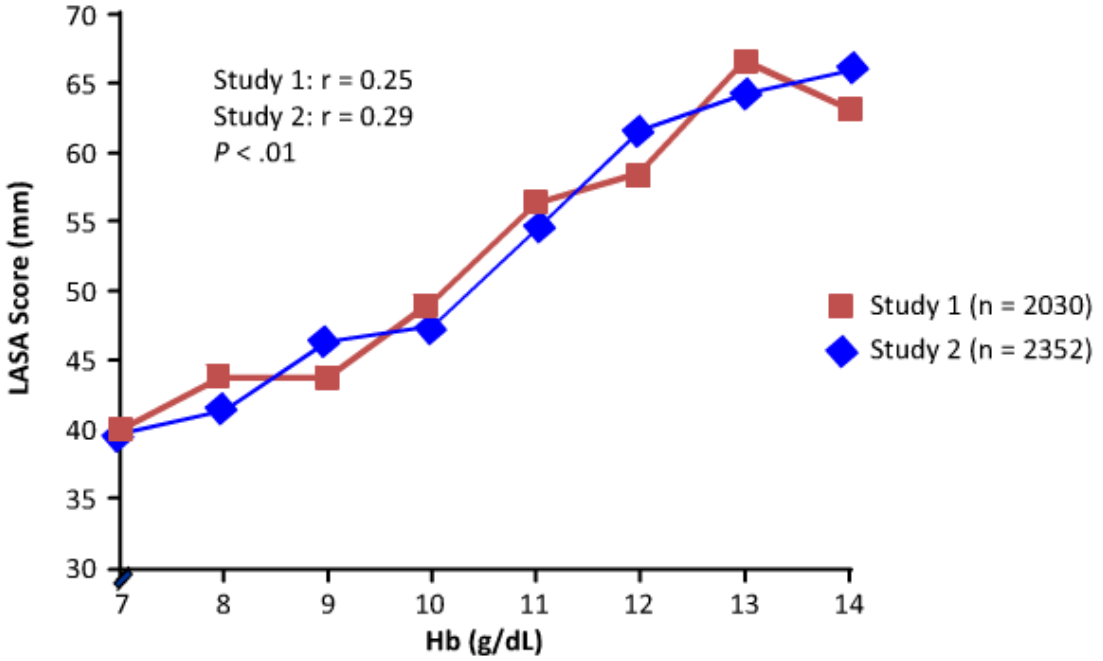


*based on a cross-sectional study of 907 patients with MDS who attended one of 74 French centres over a 1-week period
Hb = haemoglobin; HMA = hypomethylating agent
MDS = myelodysplastic syndromes; RBC = red blood cell

Kalaeidi et al Hematologica , 2010

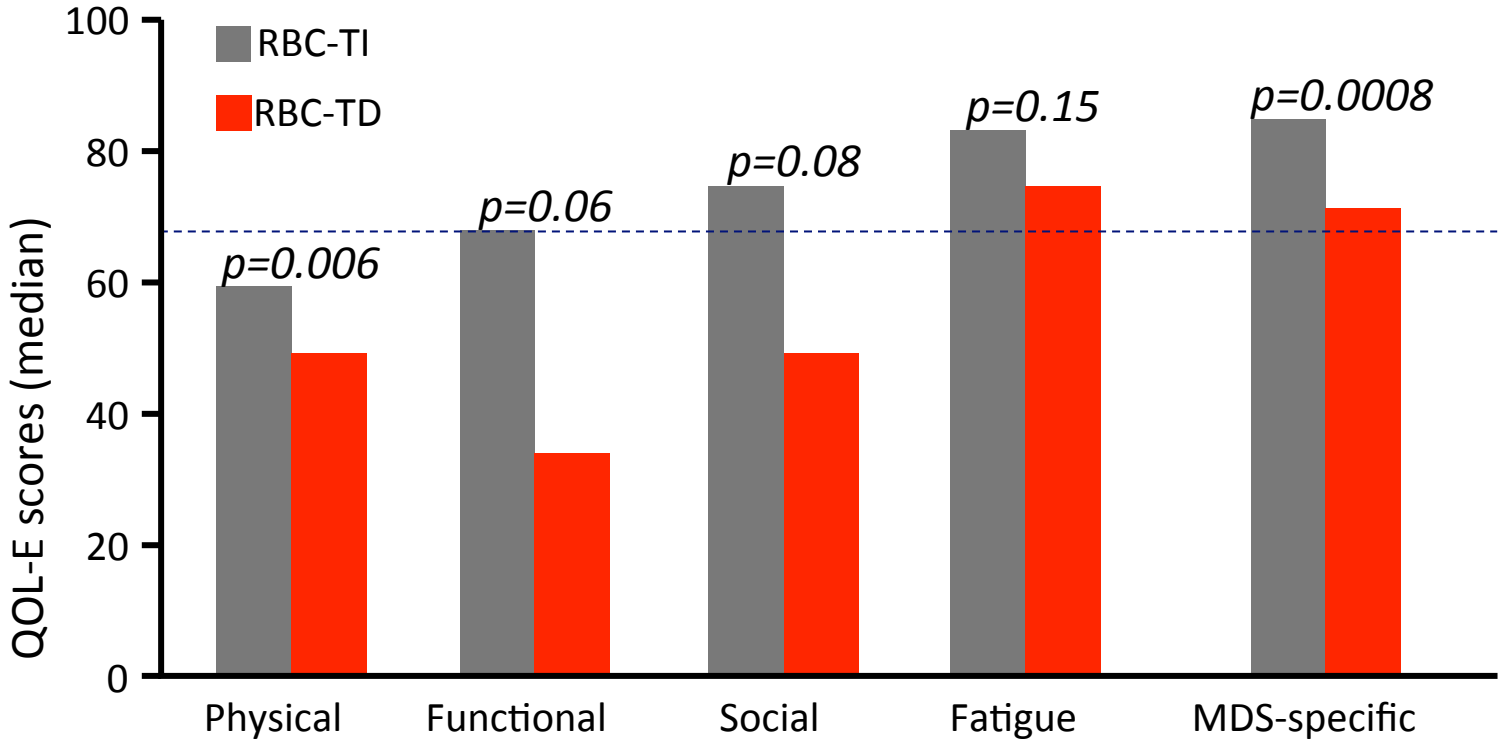
Incidenza e rilevanza clinica dell'anemia in corso di SMD

Relation between Hb level and QoL



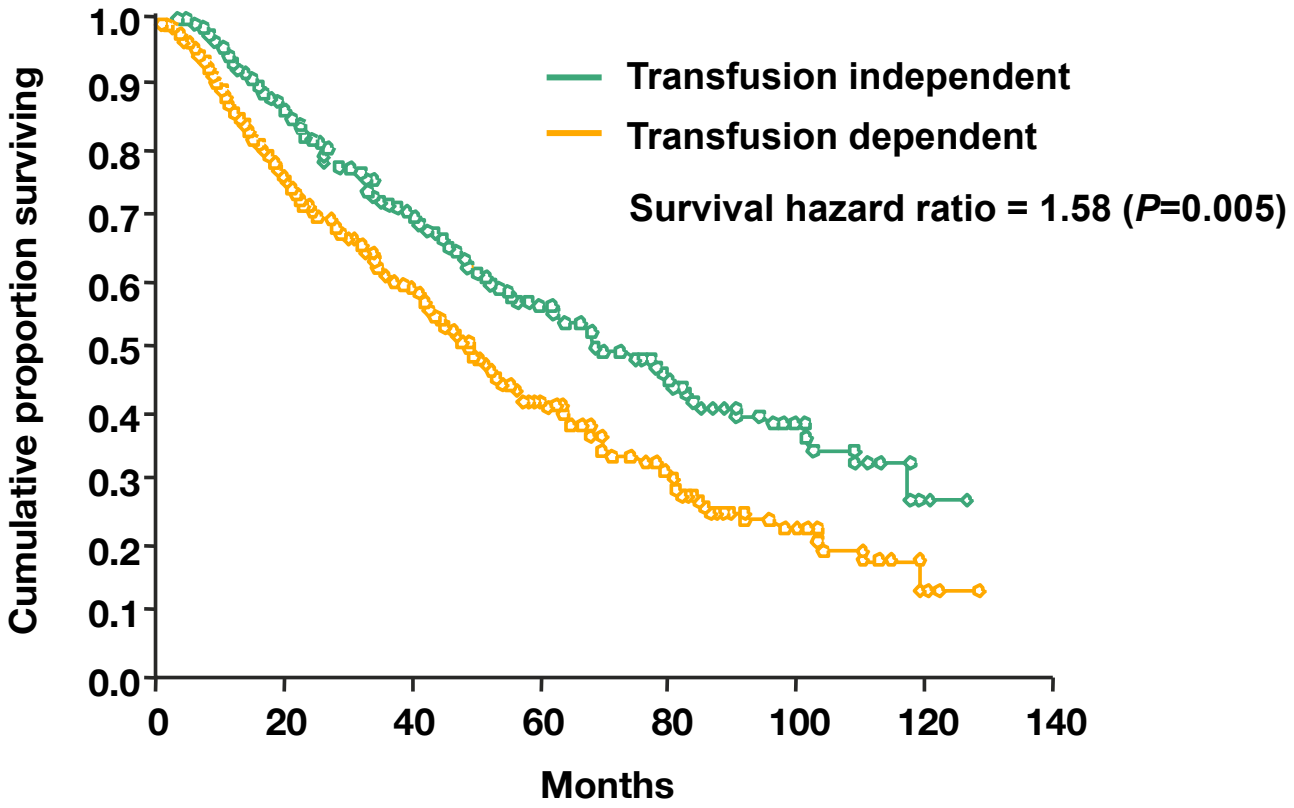
Crawford J, et al. Cancer. 2002;15:888-895.

Quality of Life (QoL) at diagnosis in low-intermediate IPSS risk MDS



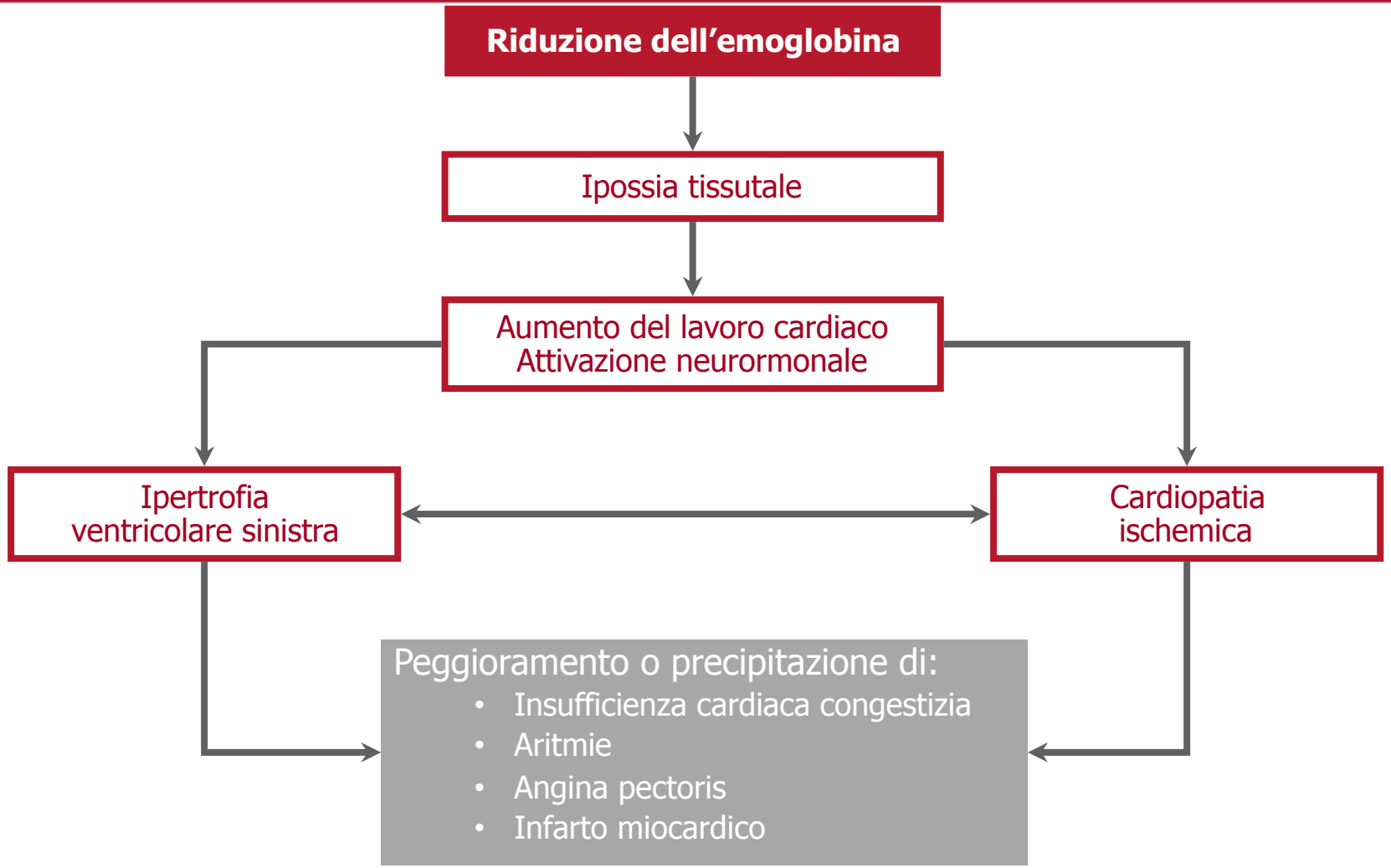
Oliva EN, et al. Am J Blood Res, 2012

La trasfusione-dipendenza aumenta significativamente la mortalità nelle SMD



Cazzola M & Malcovati L. N Engl J Med 2005

Anemia e malattie cardiovascolari



Cardiac consequences of low Hb levels

Anemia in MDS pts is associated with cardiac remodeling:

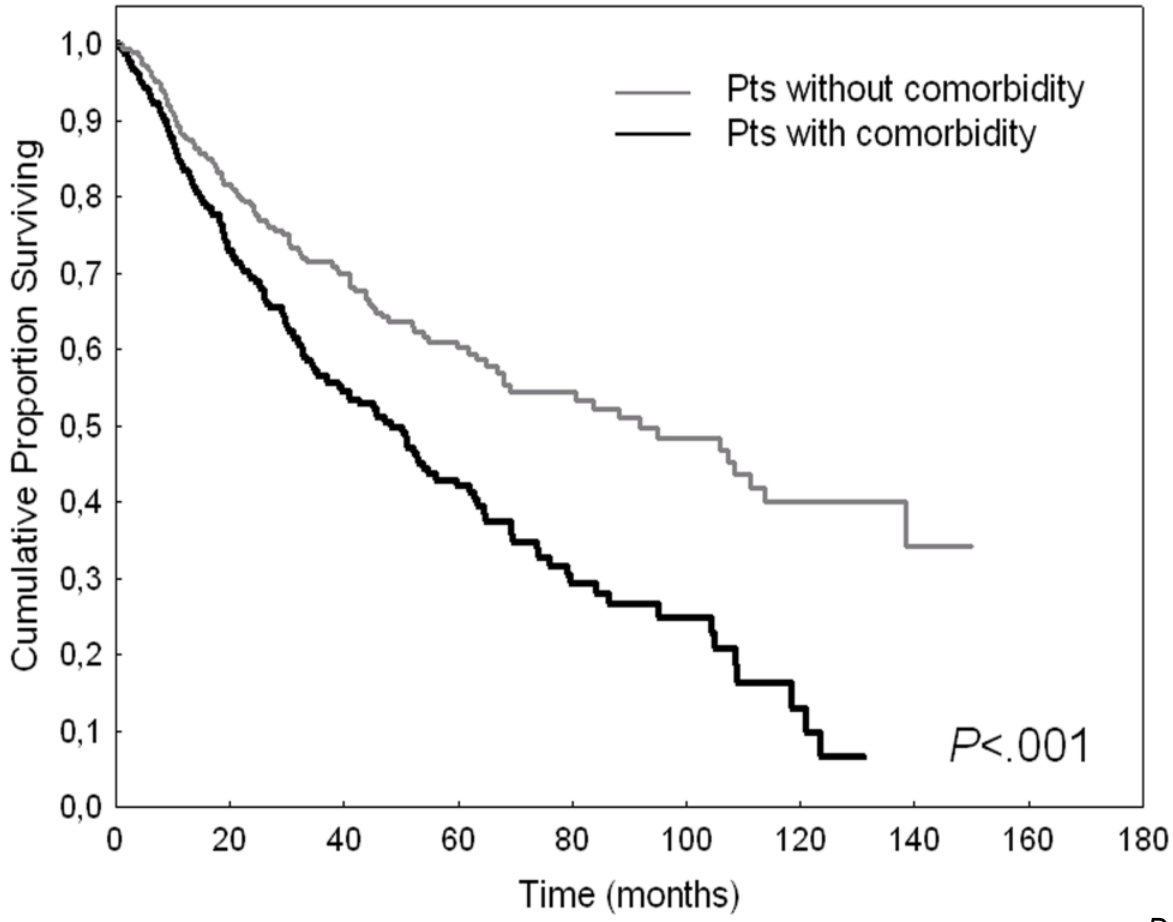
– 11 of 12 of transfusion-dependent vs 13 of 27 transfusion independent patients (92% vs 48%; *P* = 0.017)

Hb levels independently indicated cardiac hypertrophy (*P* = 0.004)
– Each 1 g/dL Hb increase predicted a 49% reduction in risk of cardiac remodeling (*P* < 0.0001)

Oliva EN, et al. Leuk Res 2005

Comorbidità in corso di SMD e sopravvivenza in relazione alla loro presenza alla diagnosi

Overall survival



Dalla Porta et al Haematologica 2011

Age and comorbidities deeply impact on clinical outcome of patients with myelodysplastic syndromes

E. Balleari[a,*], C. Salvetti[a], L. Del Corso[a], R. Filiberti[b], A. Bacigalupo[a], A. Bellodi[a], G. Beltrami[a], M. Bergamaschi[a], G. Berisso[c], T. Calzamiglia[d], A.M. Carella[a], M. Cavalleri[e], A. Da Col[a], S. Favorini[a], G.L. Forni[f], R. Goretti[g], M. Miglino[a], L. Mitscheuning[a], E. Molinari[a], O. Racchi[h], M. Scudeletti[e], R. Tassara[i], M. Gobbi[a], R. Lemoli[a], M. Clavio[a]

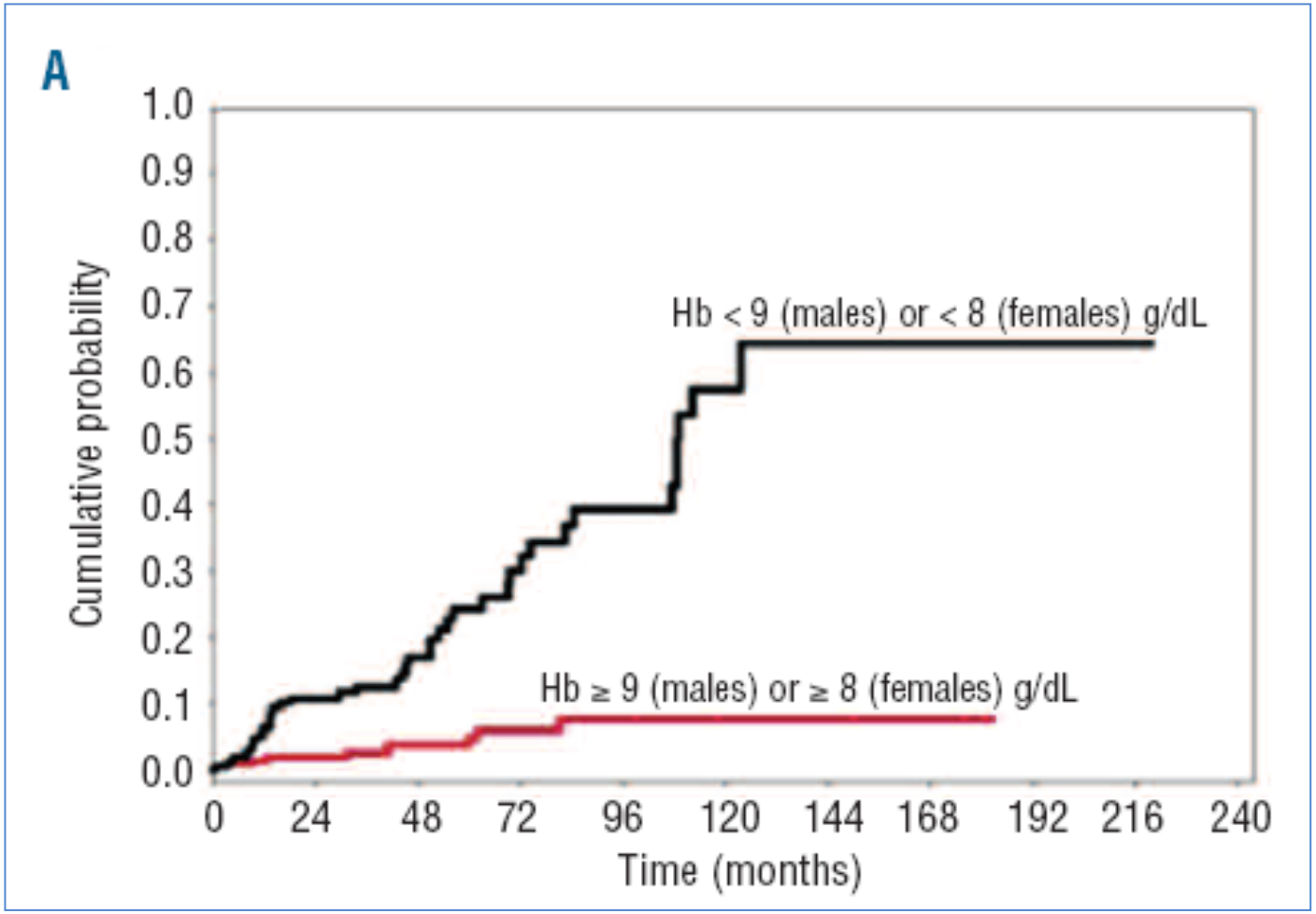
Table 3
Survival of MDS patients according to relevant clinical factors.

	N	All patients (n = 318)		
		Mean (95%CI)	Median (95%CI)	p
Overall survival (months)	318	118.0 (102.3–133.8)	92.7 (54.5–130.9)	
Gender				0.001
Male	178	78.0 (64.3–91.7)	56.2 (29.5–82.9)	
Female	140	149.3 (128.4–170.2)	NR[a]	
Age				0.008
≤75	166	133.5 (113.2–153.7)	122.8 (103.1–143.8)	
>75	152	82.5 (63.5–101.4)	44.3 (28.9–59.8)	
Hb (g/dL)				<0.001
<8	15	25.8 (9.8–41.8)	16.6 (3.5–29.7)	
8–9	112	66.3 (53.4–79.2)	49.8 (31.8–67.7)	
>=10	167	142.0 (122.5–161.5)	NR	
Cardiac disease				<0.001
0	243	133.7 (115.9–151.5)	NR	
2	75	48.3 (37.2–59.4)	38.7 (26.9–50.5)	
IPSS				<0.001
Low	151	140.7 (118.9–162.4)	NR	
Intermediate-1	86	88.8 (70.7–106.9)	NR	
Intermediate-2	32	35.6 (24.4–46.8)	28.9 (13.2–44.6)	
High	7	7.2 (2.3–12.0)	2.9 (0.1–10.9)	
IPSS-R				<0.001
Very low	62	136.1 (117.9–154.3)	NR	
Low	123	125.3 (100.3–150.4)	92.7 (90.9–94.2)	
Intermediate	39	58.1 (36.6–79.5)	39.6 (22.8–56.4)	
High	28	42.2 (26.8–57.5)	28.9 (23.2–34.7)	
Very high	16	13.4 (6.4–20.5)	10.2 (7.2–13.2)	
HCT-CI				0.13
Low	141	113.4 (95.7–131.0)	122.8 (102.9–144.1)	
Intermediate	94	102.3 (72.8–131.8)	53.0 (29.6–76.4)	
High	83	94.4 (70.8–118.0)	71.2 (41.7–100.6)	
MDS-CI				0.001
Low	197	136.6 (116.5–156.6)	NR	
Intermediate	99	81.3 (60.8–101.8)	53.0 (33.8–72.2)	
High	22	48.1 (30.3–65.8)	38.7 (0.1–95.9)	

[a] Not reached.

Balleari E, et al, Leuk Res 2015

Relazione tra grado di anemia e mortalità cardiaca



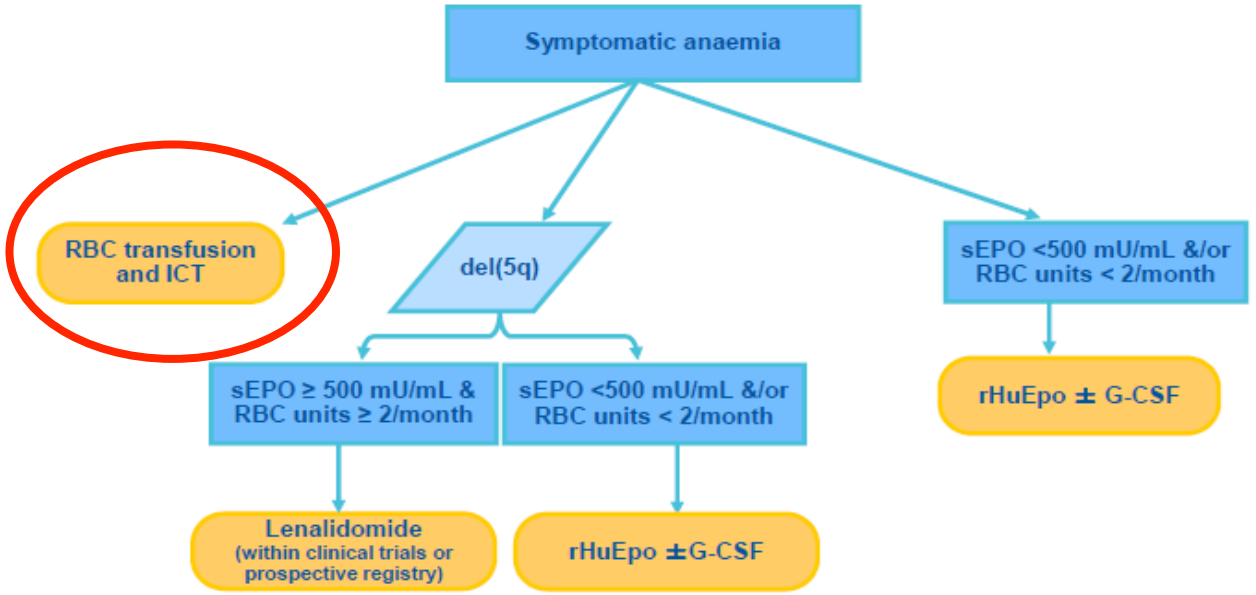
Malcovati et al, Hematologica 2011

Quali sono le caratteristiche di un trattamento efficace per l'anemia?

- **Normalizzazione dell'Hb (o suo adeguato incremento)**
- **Abolizione/Riduzione delle emotrasfusioni**

Gordon MS. Oncologist 2002, Cheson. Blood 2006

Therapeutic options for lower-risk MDS (ELN)



Malcovati L. *Blood*. Epub August 26th 2013.

Therapeutic options for lower-risk MDS (ELN)

RBC transfusions

- Recommended for
  - Severe/synptomatic anemia
- associated with
  - Higher morbidity
  - Increased hospitalitation
  - Shorter OS
- Problems
  - Hemoglobin levels usually maintained <10 g/dL
  - Fluctuating Hb levels
  - Intolerance reactions, Alloimmunization, Infections
  - Shortage of blood
  - Non negligible costs
- Iron overload

RBC transfusions

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  - Hemoglobin levels usually maintained <10 g/dL
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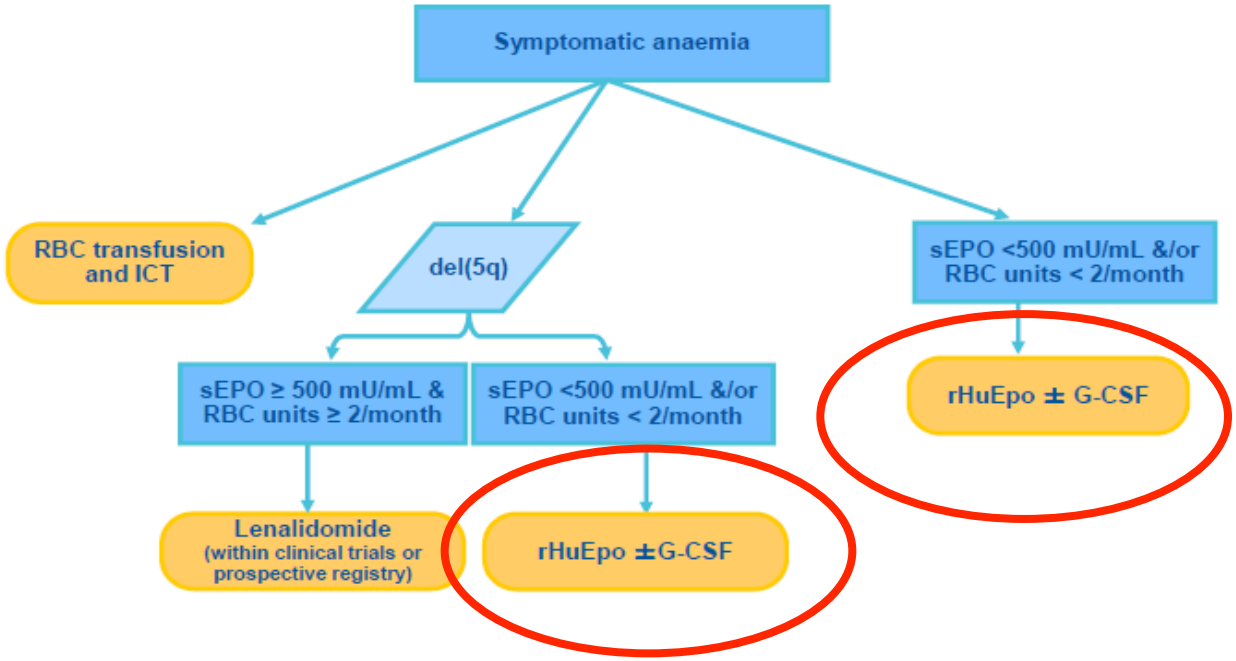
  - Non negligible costs
- **Iron overload**

1. Lawrence LW. *Clin Lab Sci* 2004;17:178–86
2. Balducci, *Cancer* 2006;106(10):2087–94
3. Gardin & Fenaux *Rev Clin Exp Hematol* 2004;8:E3
4. NCCN Guidelines for MDS. Source: www.nccn.org

Therapeutic options for lower-risk MDS (ELN)



Malcovati L. *Blood*. Epub August 26th 2013.

The new era of ESAs in clinical practice

THE LANCET

Volume 328, Issue 8517, 22 November 1986, Pages 1175-1178

Originally published as Volume 2, Issue 8517

EFFECT OF HUMAN ERYTHROPOIETIN DERIVED FROM RECOMBINANT DNA ON THE ANAEMIA OF PATIENTS MAINTAINED BY CHRONIC HAEMODIALYSIS

ChristopherG Winearls [a], MartinJ Pippard [c], MichaelR Downing [d], DesmondO Oliver [b], Cecil Reid [c]

ORIGINAL ARTICLE ARCHIVE

Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin

Joseph W. Eschbach, M.D., Joan C. Egrie, Ph.D., Michael R. Downing, Ph.D., Jeffrey K. Browne, Ph.D., and John W. Adamson, M.D.

N Engl J Med 1987; 316:73-78 | January 8, 1987 | DOI: 10.1056/NEJM198701083160203

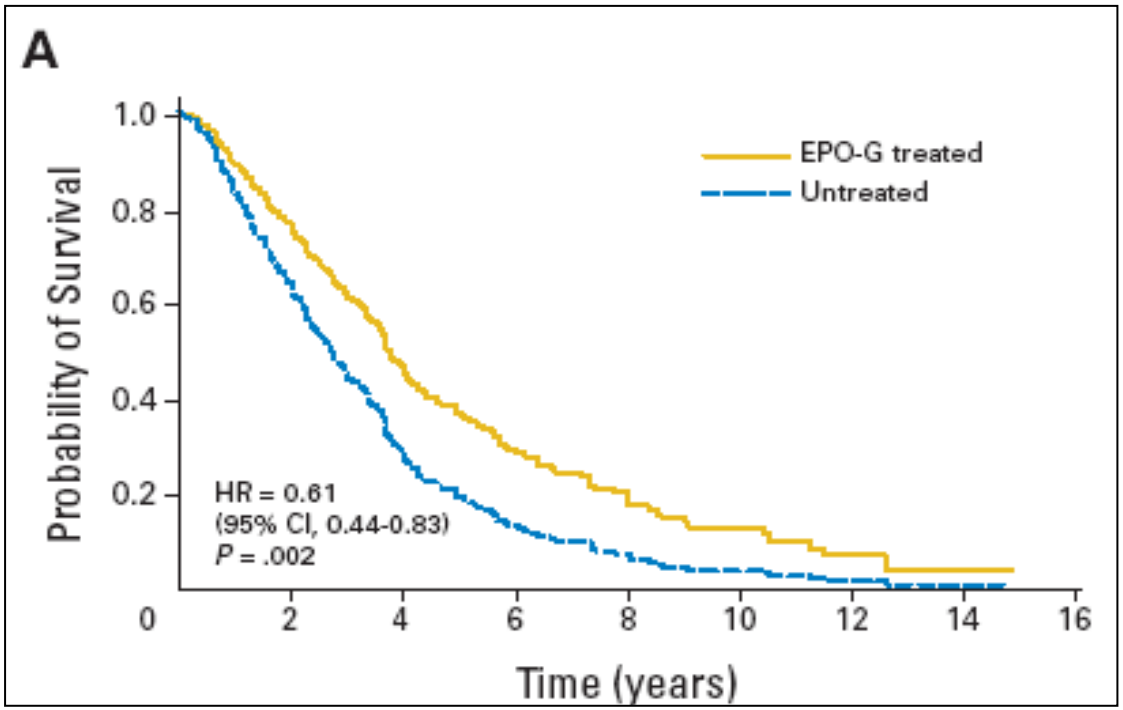
Pro- e contro del supporto trasfusionale vs ESAs

TRASFUSIONE		VS	ESAs	
PRO	**CONTRO**		**PRO**	**CONTRO**
Azione rapida	Effetto transitorio Reazioni trasfusionali TRALI*		Sicurezza	Azione lenta
100% efficacia	Sovraccarico di ferro Infezioni		Incremento duraturo dell'Hb	60% efficacia
Familiare	Non conveniente		Utile	Costosa

*** Malattia polmonare acuta da trasfusione**

1. Glaspy J et al. J Clin Oncol 1997; 15: 1218-34
2. Österborg et al. J Clin Oncol 2002; 20: 2486-2494

terapia con ESAs: impatto sulla sopravvivenza



Jadersten et al, JCO 2008

Pt treated with EPO+G-CSF

for 12-18 months

(n=121)

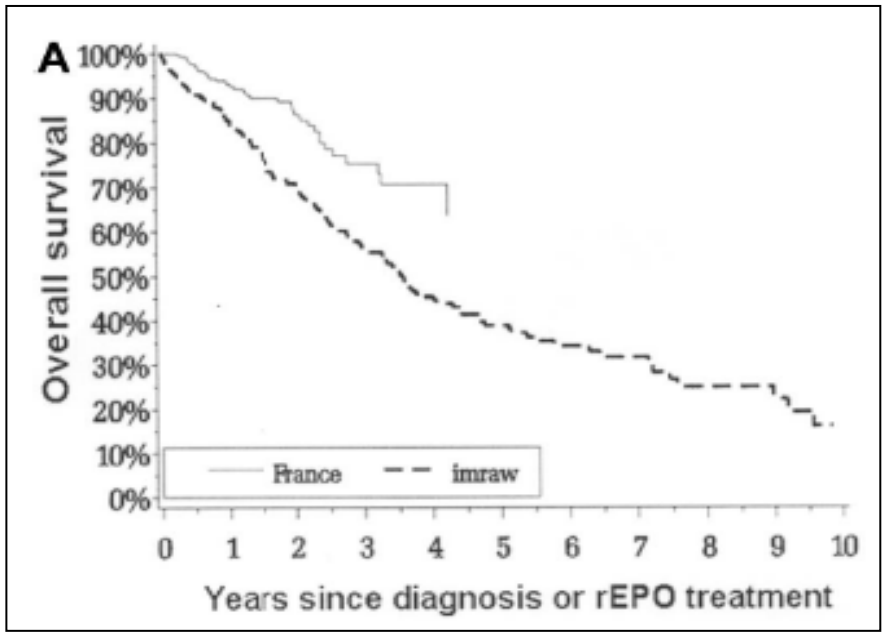
Pt Not treated

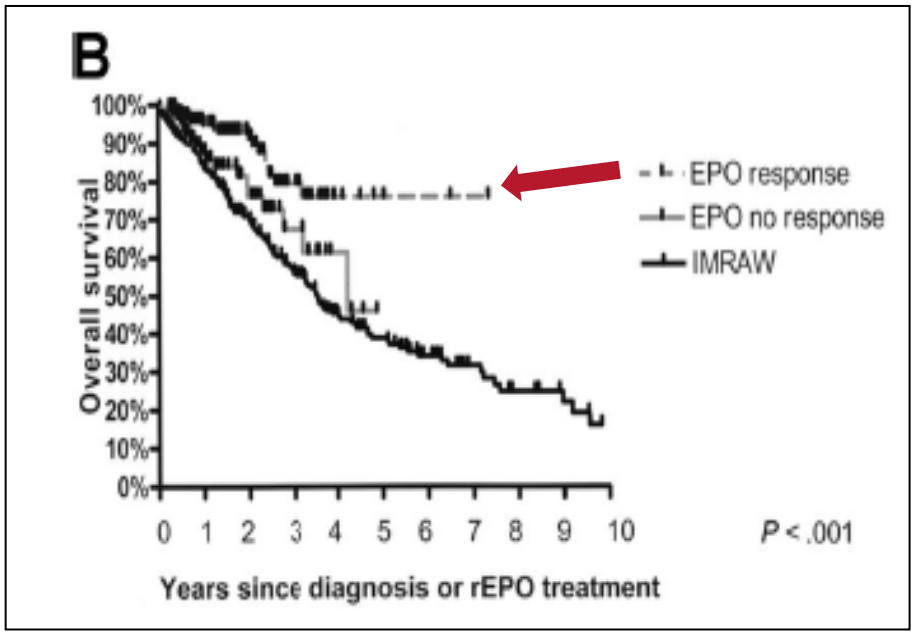
(n=237)

At multivariate analysis treatment with EPO+ G-CSF was associated with:

- better overall survival **HR: 0.61 [0.44-0.83] *p=0.002***
- lower risk of NLD **HR: 0.66 [0.44-0.99] *p=0.042***

terapia con ESAs: impatto sulla sopravvivenza





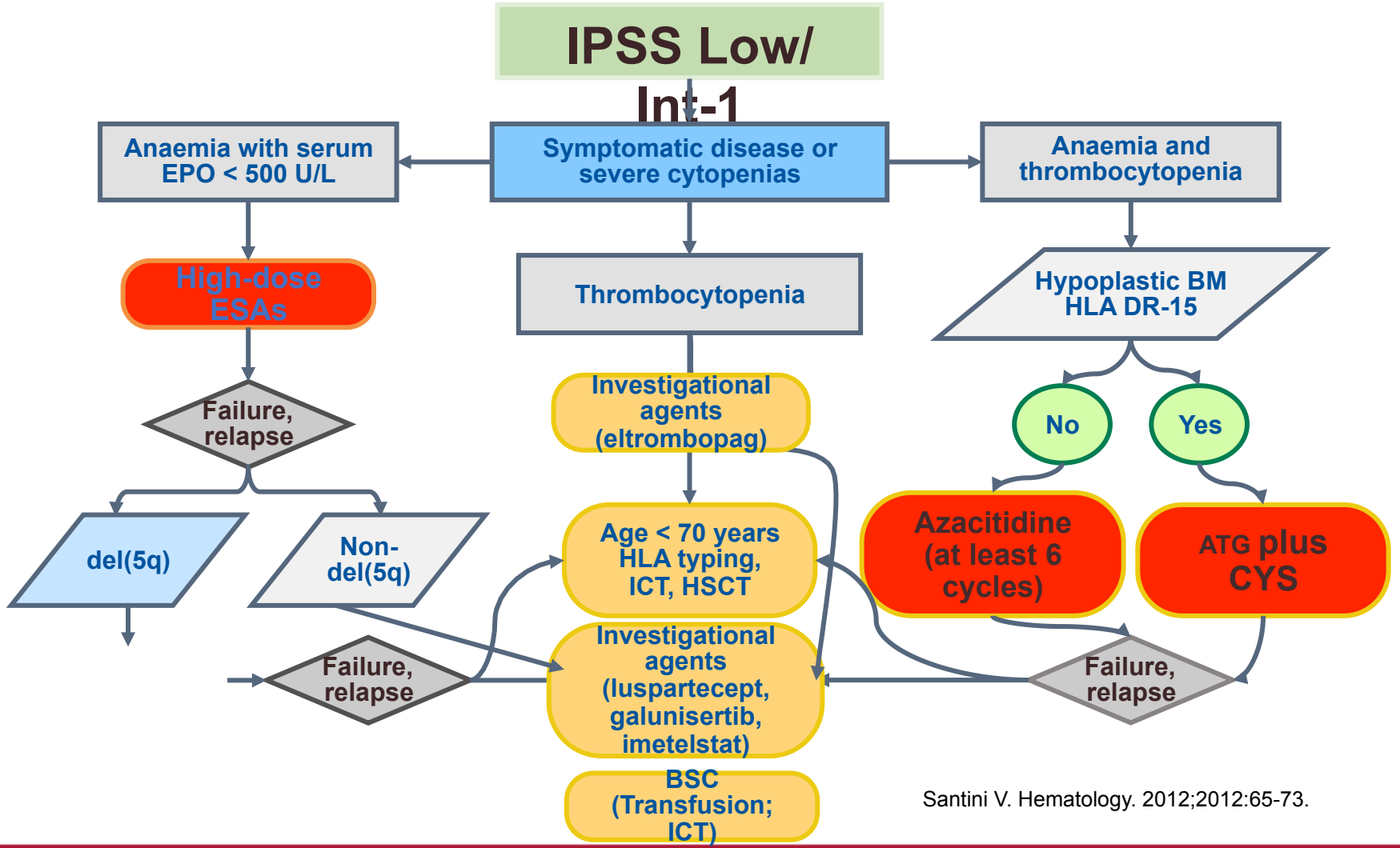
At multivariate analysis the use of rEPO is independently associated with a longer OS

HR: 0.43 [CI 95% 0.25-0.72]

The advantage in survival is limited to patients responding to rEPO

Park S. et al, Blood 2008

Therapeutic options for lower-risk MDS: SIE guidelines (modified per age limits)



Santini V. Hematology. 2012;2012:65-73.

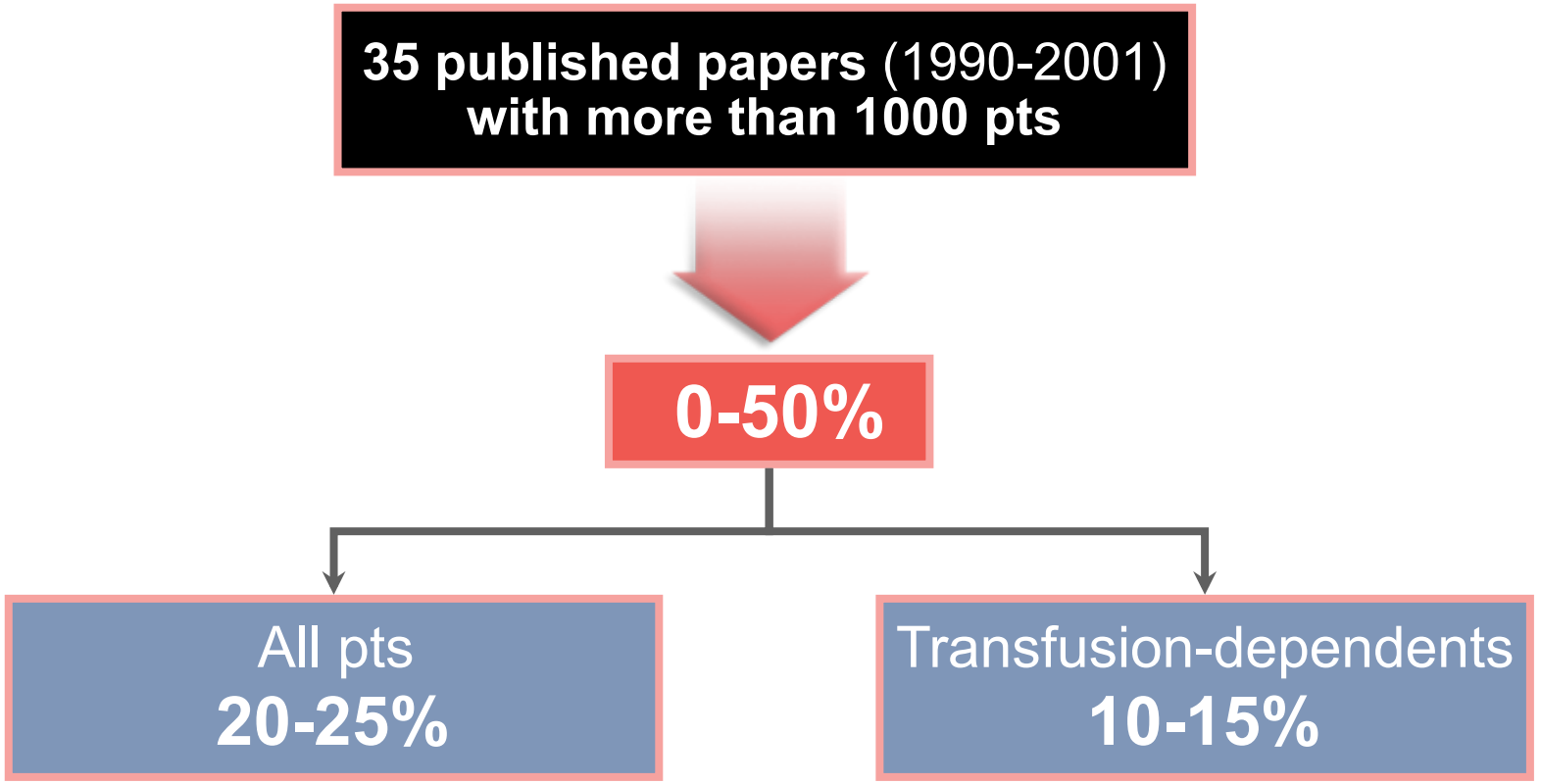
Problemi aperti nell'uso degli ESAs per il paziente anemico con SMD

Ottimizzazione nella selezione dei pazienti

Ottimizzazione della schedula di trattamento

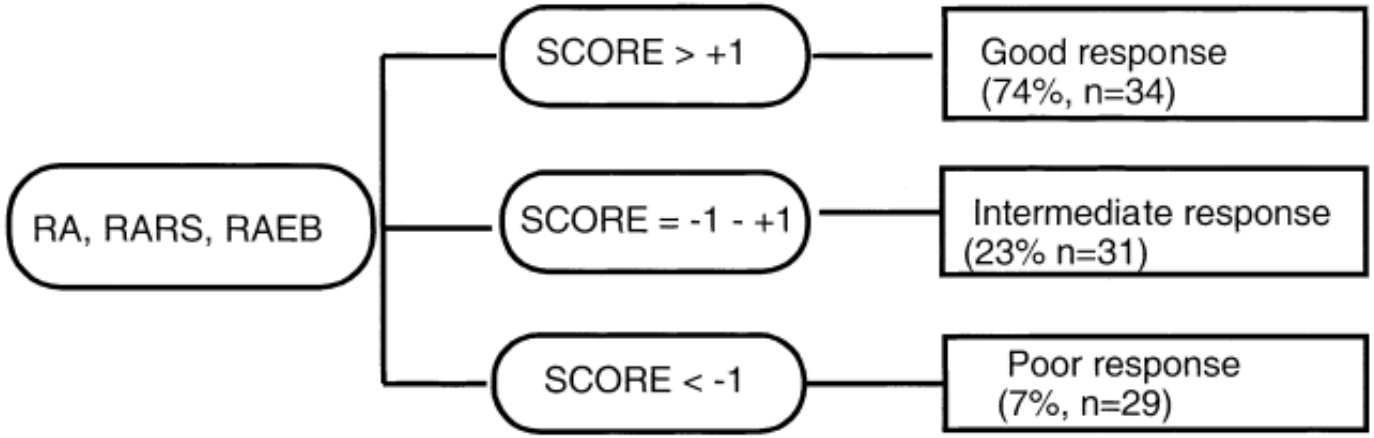
Approccio clinico per i casi non rispondenti

Risposta all'EPO nei primi studi ('90)



Hellstrom-Lindberg et al. Semin Hematol 2002

NORDIC group scoring system for predicting response to EPO *



Treatment response criteria

CR	Stable Hemoglobin >11.5 g/dl
PR	Increase in Hb with >1.5 g/dl or total stop in RBC transf.

Treatment response score

S-EPO U/l	<100	+ 2
	100-500	+ 1
	>500	- 3
Transf. U RBC / m	<2 units / m	+ 2
	= or >2 units / m	- 2

*(EPO +G)

Hellstrom-Lindberg et al. Br J Haematol 1997

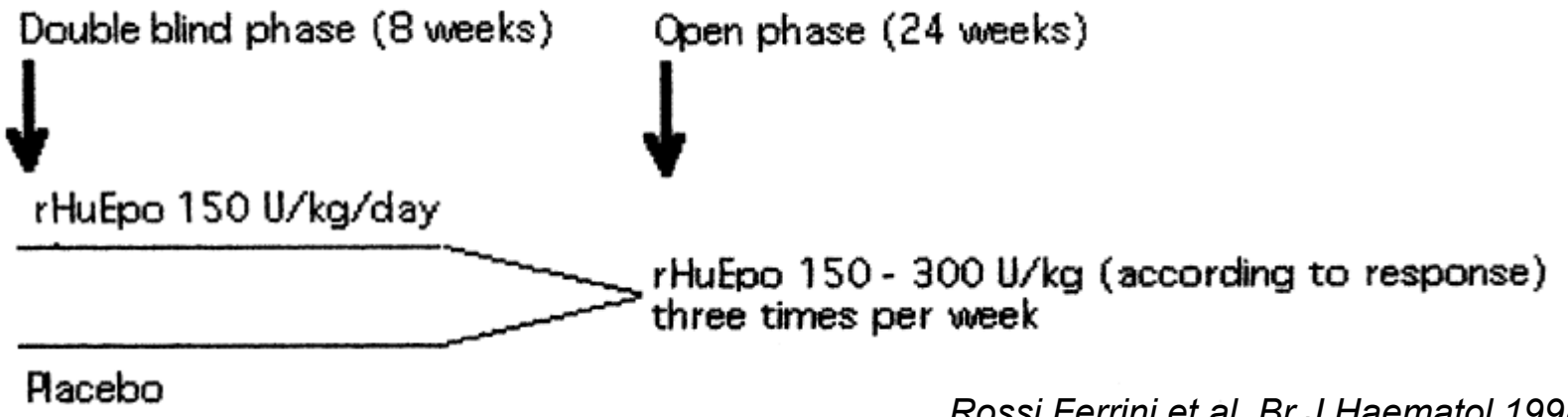
EPO induces erythroid response in “lower-risk” MDS a Multicenter Italian Study

A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes

ITALIAN COOPERATIVE STUDY GROUP FOR rHuEpo IN MYELODYSPLASTIC SYNDROMES*

Received 2 April 1998; accepted for publication 10 September 1998

1998



Rossi Ferrini et al, Br J Haematol 1998

EPO induces erythroid response in “lower-risk” MDS a Multicenter Italian Study

Epoetin alfa 150 IU/kg daily (n=44) or placebo (n=43)

- Untransfused: from Hb 8.35±0.73 to 10.07±1.87 g/dL
- Placebo: from Hb 8.4±0.66 to 8.19±0.92 g/dL

Erythroid response	Epoetin	Placebo	*P* value
Overall	37%	11%	0.007
RA	50%	5.9%	0.007
RARS	38%	18%	0.6
RAEB	17%	11%	0.1
Untransfused	60%	0%	0.004
Pre-transfused	22%	14%	0.7

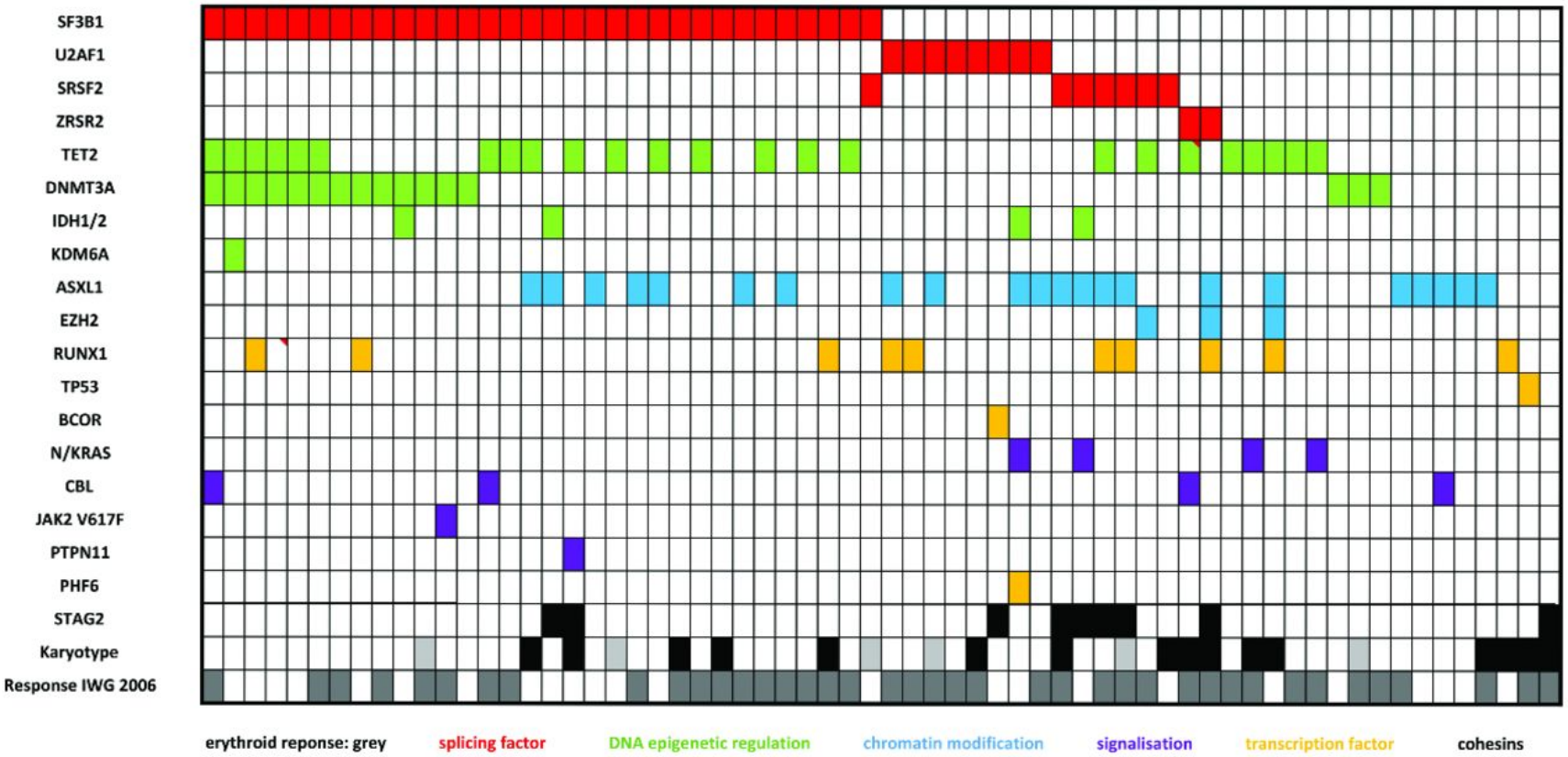
Rossi Ferrini et al, Br J Haematol 1998

Factors predictive for response to ESAs

- **Biologics**
  - Blasts < 10%
  - Normal Caryotype
  - Endogenous EPO < 500 U/L
  - Number of mutations
- **Clinics**
  - Diagnosis of refractory anemia
  - IPSS low or intermediate-1
  - Short disease duration
  - Trasfusion-independence

Adapted from Santini V. The Oncologist 2011

somatic mutations are predictive of response to ESAs in lower-risk MDS



>2 somatic mutations predict for no response to ESAs in LR-MDS

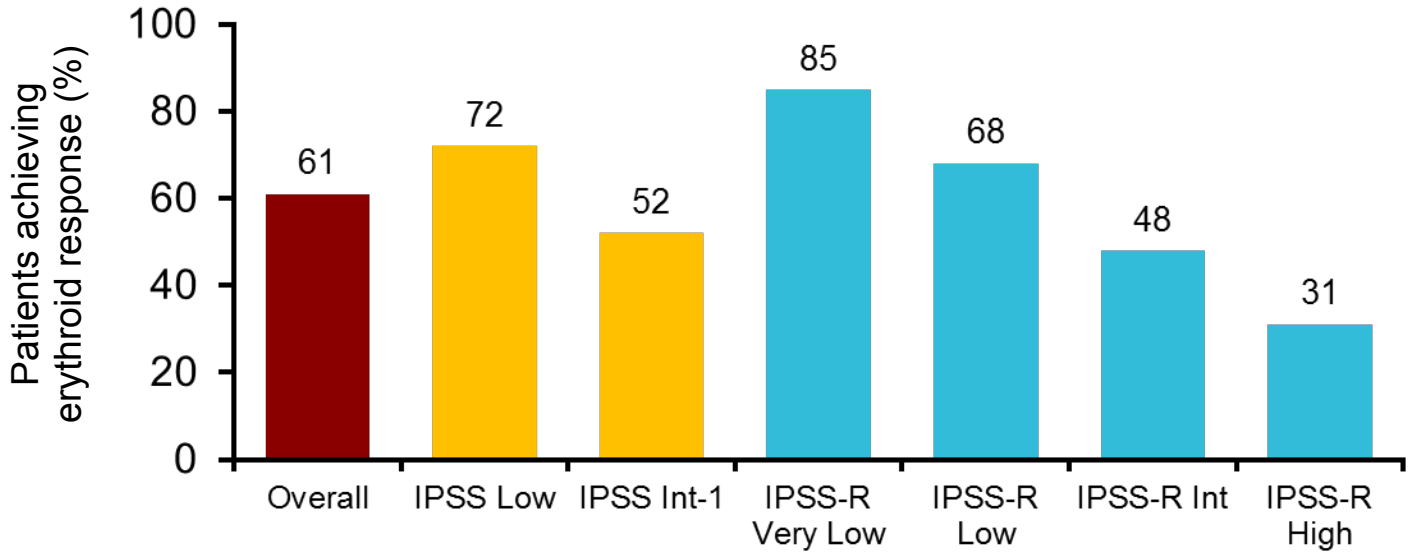
HI-E 74% in the 51 patients with ≤ 2 mutations *versus*

46% in the 28 patients with >2 mutations (P=0.01)

Kosmider O et al, Haematologica 2016

IPSS-R is useful in predicting response to ESA

Patients with IPSS Low/Int-1 MDS and overall favorable prognostic factors of response to ESA according to the Nordic score (n = 456)



Santini V, et al. Blood. 2013;122:2286-8.

“European” ESA score for predicting response to ESAs

In multivariate analysis, **IPSS-R, serum EPO, and serum ferritin** were significantly associated with erythroid response ($p < 0.0001$, $p < 0.0001$, $p = 0.002$, respectively)

- EPO > 200 = 1
- Ferritin > 350 = 1
- IPSSR:
  - Very low = 0
  - Low = 1
  - Intermediate = 2
  - High = 3

Score	Response Rate
0	85%
1	80%
2	64%
3	40%
≥4	20%

Santini V, et al. Blood. 2013;122:2286-8.

Canadian Predictive Model of Response to ESAs in MDS

	Co-efficient (SE)	OR
IPSS score Low vs. Int-1/Int-2	1.10 (0.44)	2.9
EPO mU/mL (<100 vs. ≥ 100)	2.02 (0.46)	7.5

- IPSS:
  - Low: 0
  - Int-1/Int-2: 1
- EPO:
  - <100: 0
  - ≥100: 2

$p < 0.0001$

Score	Response	n = 112
0	35 (81%)	43
1	16 (57%)	28
2	6 (33%)	18
3	4 (17%)	23

Houston BL et al. 13th Annual MDS Symposium, 2015

“EPO transatlantic venture ”
To validate Canadian ESA Score using FISM and GROM Cases

Total number of Italian patients	**N = 788**
EPO pre-ESA initiation values	
N	667
Mean ± SD	137.33 ± 275.80
Inter-quartiles	28.0, 127.0
Median (range)	58.0 (0 – 3420.0)
EPO pre-ESA initiation <100	
≥ 100	217 (32.53%)
< 100	450 (67.47%)
ESA Overall Response *(723 available patients)*	
No	269 (37.21%)
Yes	454 (62.79%)
IPSS group *(742 available patients)*	
Low	392 (52.83%)
Int-1	298 (40.16%)
Int-2	52 (7.01%)
IPSS Low category	
Low	392 (52.83%)
Int-1 / Int-2	350 (47.17%)
IPSSR group *(621 available patients)*	
Very Low	146 (23.51%)
Low	327 (52.66%)
INT	89 (14.33%)
High	49 (7.89%)
Very High	10 (1.61%)

from FISM (#555) and GROM (#233)

Buckstein R et al. MDS 2017

EPO transatlantic venture : the "ITACA score"

Independent variable	Parameter Estimation: Coefficient	SE of Coefficient	p-value	OR	95% CI of OR		Model Fitting Information R^2 (%)
Intercept	-1.6766	0.4513	0.0002				23.9%
IPSS group (Low vs. Int-1/Int-2)	1.0762	0.4411	**0.0147**	2.933	1.250	7.121	
EPO category at pre-initiation (<100 vs. ≥100)	2.0194	0.4631	**<.0001**	7.534	3.135	19.488	

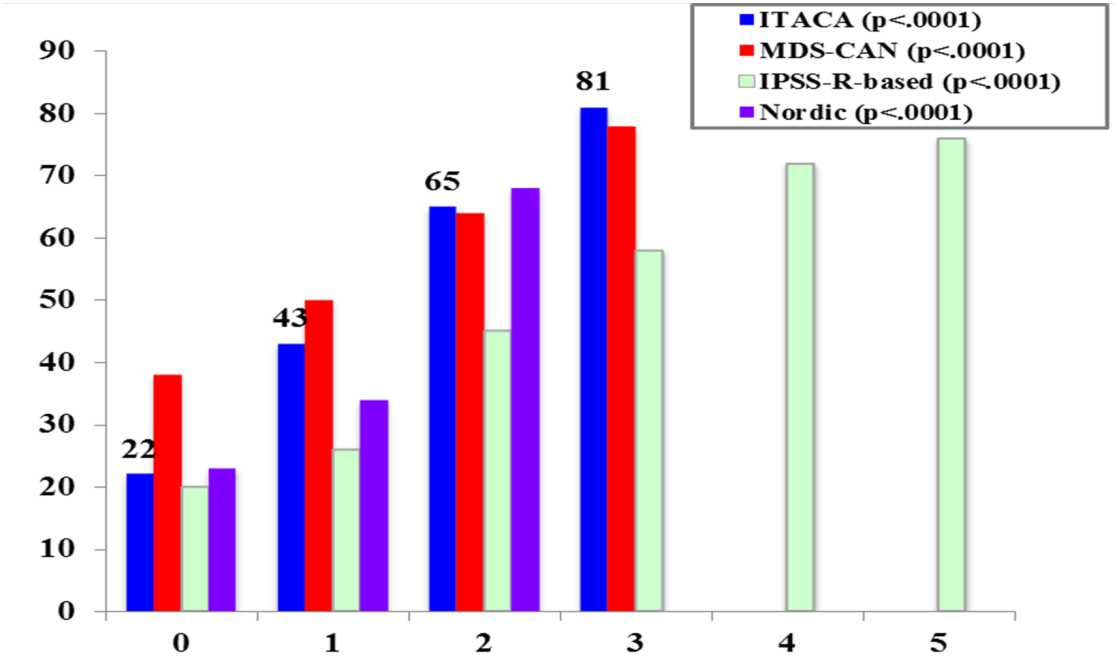
	ESA Overall Response: No	Yes	Total	Fisher exact p-value
In All available Patients (N = 586)				
Score 0	47 (22.07%)	166 (77.93%)	213	**<.0001**
Score 1	65 (34.95%)	121 (65.05%)	186	
Score 2	42 (45.65%)	50 (54.35%)	92	
Score 3	54 (56.84%)	41 (43.16%)	95	
Total	208	378	586	

Score	Response	n = 112
0	35 (81%)	43
1	16 (57%)	28
2	6 (33%)	18
3	4 (17%)	23

Note: Score = 0: Low IPSS with EPO<100
Score = 3: INT-1/INT-2 with EPO≥100

Buckstein R et al. MDS International Symposium 2017

ITACA: A New Validated International ESA-Response Score



- **ITACA has the highest discriminating power for predicting ESA response based on the highest Somers D, greatest decline in Aikaike information criterion (AIC) and highest G^2 compared with the other models.**

Note: Score = 0: Low IPSS with EPO<100
Score = 3: INT-1/INT-2 with EPO≥100

Buckstein R et al. MDS International Symposium 2017

La appropriata selezione dei pazienti migliora l'outcome della terapia con ESAs

15% di risposte

Pazienti SMD non selezionati

- Tutti i sottotipi WHO/FAB

>60% di risposte

Pazienti SMD selezionati per

- Diagnosi recente
- Trasfusione-indipendenza
- EPO sierica <200 U/l (<500 U/l)
- Citogenetica normale
- IPSS Low-risk, Int-1

Problemi aperti nell'uso degli ESAs per il paziente anemico con SMD

Ottimizzazione nella selezione dei pazienti

Ottimizzazione della schedula di trattamento

Approccio clinico per i casi non rispondenti

Effetti del prolungamento della dose

Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: a phase II trial in 281 patients.

Dose r-hEPO 150 U/Kg x3/w (30-40.000 U/w)

Risposta a 12 settimane	Risposta a 26 settimane
28%	48%

Terpos et al Br J Haematol 2002

EPO dose and schedule

"Standard" therapy

epoetin 150 IU/kg tiw or 40,000 IU qw

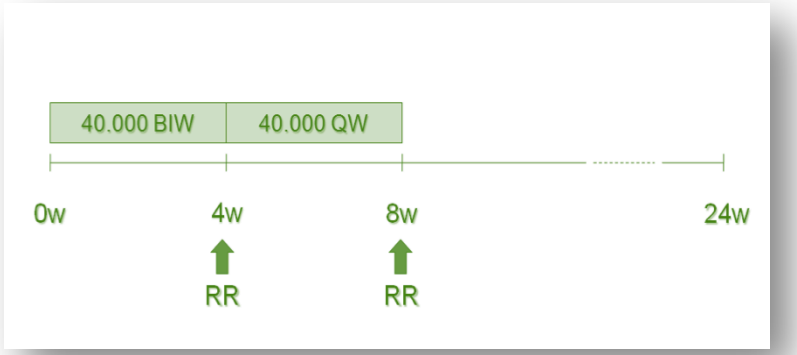
vs

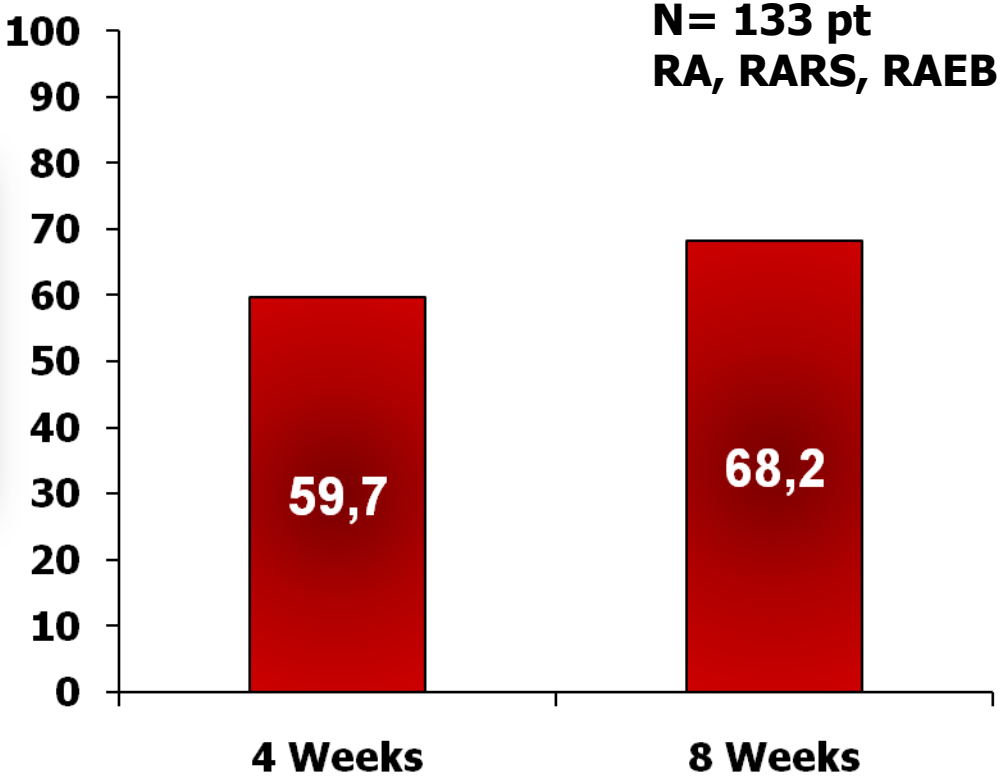
"High-dose" therapy

epoetin 300 IU/kg tiw or 80,000 IU qw

IS MORE BETTER IN MDS?

Risposta ematologica Epo 80.000 UI: Somministrazione 40.000 UI BIW





Epo alfa 80.000 UI
Somministrazione 40.000 UI BIW: 68% di risposta

Aloe-Spiriti, Annals of Hematology 2005

Meta-analysis of erythroid response to EPO alpha

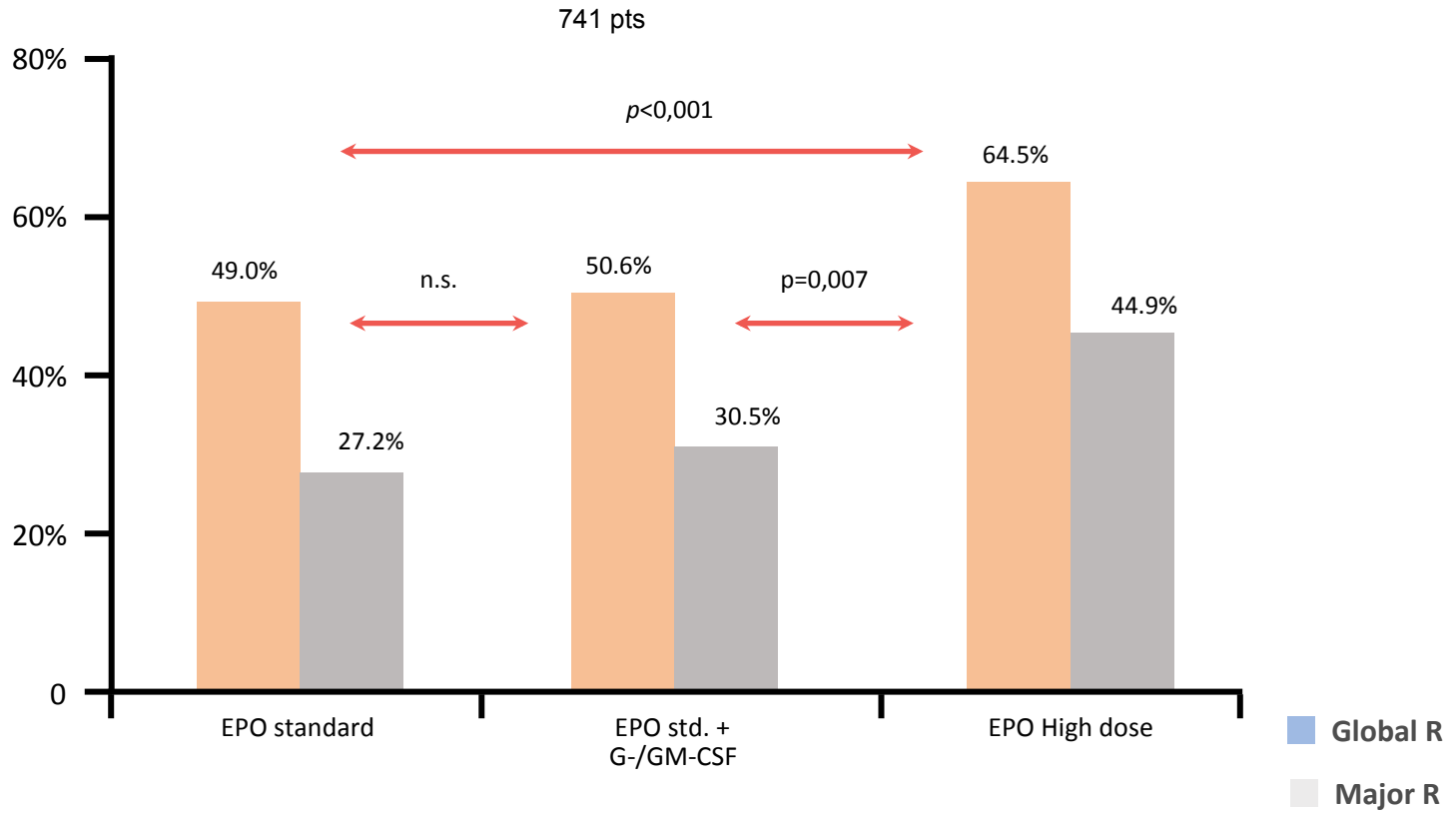
Acccording to EPO alpha dosage

•15 studies
• Pts # 741

Dosage EPO	N° studies	N° pts
EPO alpha Std dose 30-40K/week	5 studies	393 pts
EPO alpha + G-/GM-CSF 30-40K/week	6 studies	152 pts
EPO alpha Higher dose 60-80K/week	4 studies	196 pts

Mundle et al, Cancer 2009

Meta-analysis of erythroid response to EPO alpha



Higher dosing regimens of epoetin alfa (weekly dose 60–80 K U) correlate with higher response rate

Modified from Moyo V et al Ann Hematol 2008 87:527–536 and Mundle S, et al. ancer 2009;115:706-715.

Meta-analysis of erythroid response to EPO alpha

Table 1. Baseline Characteristics of Patients Treated With Different Therapeutic Strategies Using Epoetin α

Characteristic	Std-Dose EPO	Std-Dose EPO+G-/GM-CSF	High-Dose EPO
Starting EPO dose, U/wk	30,000-40,000	30,000-40,000	60,000-80,000
No. of studies	5	6	4
No. of enrolled patients	406	181	213
No. of evaluable patients	393	152	196
RA/RARS (range), %	69 (53-100)	75 (47-81)	84 (68-100)*,†
Women, % (range)	46 (38-75)	43 (25-58)	51 (27-64)
Transfusion-dependent patients (range), %	35 (25-83)	76 (37-100)*	39 (18-61)†
Mean age (range), y	71.2 (62-74)	69.2 (62-73)	70.5 (65-74)
Mean baseline Hb (range), g/dL	8.7 (7.6-10.7)	8.5 (8.2-8.8)	8.6 (8.2-8.8)
Mean sEPO (range), mU/mL	403.8 (300-418)	167.7 (49-354)*	70.1 (44-129)*
Initial EPO wkly dose (range), U	32,445 (30,000-40,000)	34,213 (13,000-40,000)	78,740 (74,000-80,000)*,†

Std indicates standard; EPO, epoetin α; G-/GM-CSF, granulocyte–/granulocyte macrophage–colony-stimulating factor; RA, refractory anemia; RARS. refractory anemia with ringed sideroblasts; Hb, hemoglobin; sEPO, serum endogenous erythropoietin.

*The distribution in the high-dose EPO group was significantly different compared with standard-dose group ($p < 0.05$);

† the distribution in the high-dose EPO group was significantly different compared with standard-dose group ($p < 0.05$).

Mundle et al, Cancer 2009

Higher Versus Standard EPO Doses in MDS

a retrospective survey from Italian Registry of Myelodisplastic Syndromes (FISM)

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

103 pts treated with EPO 40.000 IU twice a week (H cohort) vs
206 pts treated with EPO 40.000 UI weekly (S cohort)

	Standard dose	Higher dose
	N (%)	N(%)
Gender		
Male	105 (51)	74 (72)
Female	101 (49)	29 (28)
Age, median (range)	77 (46-98)	75 (30-96)
Adjusted IPSS-R score		
Low-very low	127 (62)	62 (60)
Intermediate-/ very high	79 (38)	41 (40)
IPSS score		
Low-/ Intermediate 1	180 (92)	91 (95)
Intermediate 2 - High	15 (8)	5 (5)
Transfusion-dependency		
No	152 (74)	77 (75)
Yes	54 (26)	26 (25)
EPO at diagnosis		
<200	167 (81)	82 (80)
200-500	25 (12)	12 (12)
>500	14 (7)	9 (9)
Hemoglobin (g/dL)		
<=10	158 (77)	78 (76)
>10	48 (23)	25 (24)

Balleari et al, ASH 2016 abstr 1387

Higher Versus Standard EPO Doses in MDS

a retrospective survey from Italian Registry of Myelodisplastic Syndromes (FISM)

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

individual and clinical variables in the two cohorts

	Standard dose	Higher dose	p
Hb pre-treatment (median)	9.1 mg/dL	8.9 mg/dL	P=0.9
IPSS score			
low/intermediate 1 (%)	92	95	
Intermediate 2/ high (%)	8	5	P= 0.6
Transfusion-dependency			
No dependency (%)	74	75	
Dependency (%)	26	25	P=0.9
EPO at diagnosis (median)	69 IU	79 UI	P=0.3

Balleari et al, ASH 2016 abstr 1387

Higher Versus Standard EPO Doses in MDS

a retrospective survey from Italian Registry of Myelodisplastic Syndromes (FISM)

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

clinical variables predicting response to therapy *(multivariate analysis)*

	No response	Response	p
	N (%)	N(%)	
IPSS score			0.002
Low/intermediate 1	118 (43)	153 (56)	
Intermediate 2 / high	16 (80)	4 (20)	
Transfusion-dependency			P<0.001
No dependency	94 (41)	135 (59)	
Dependency	52 (65)	28 (35)	
EPO at diagnosis			<0.001
<=200	105 (42)	147 (58)	
>200	41 (72)	16 (28)	

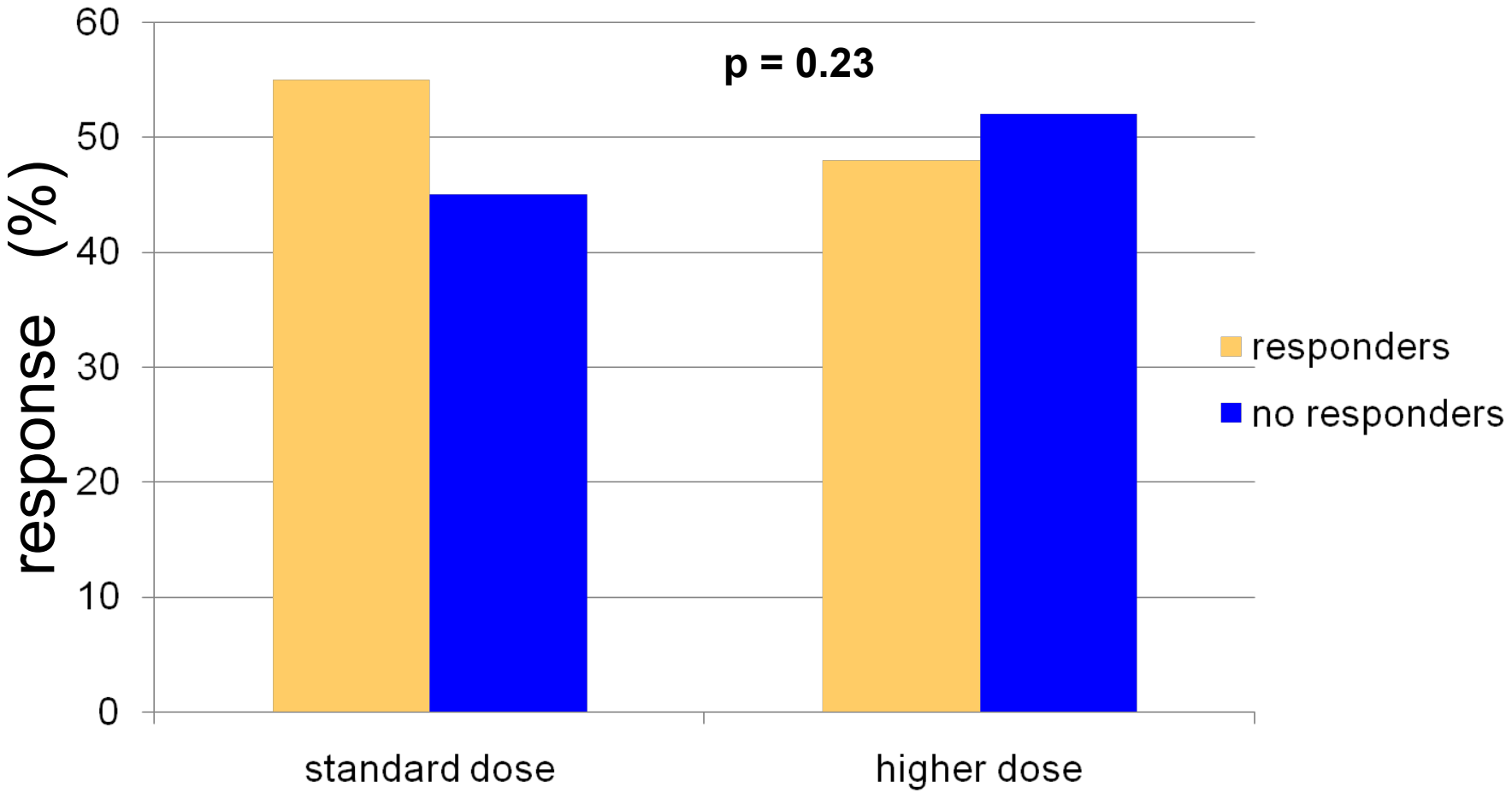
Balleari et al, ASH 2016 abstr 1387

Higher Versus Standard EPO Doses in MDS

a retrospective survey from Italian Registry of Myelodisplastic Syndromes (FISM)

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Erythroid response to EPO



Balleari et al, ASH 2016 abstr 1387

La appropriata selezione dei pazienti migliora l'outcome della terapia con ESAs

15% di risposte

Pazienti SMD non selezionati

- Tutti i sottotipi WHO/FAB

>60% di risposte

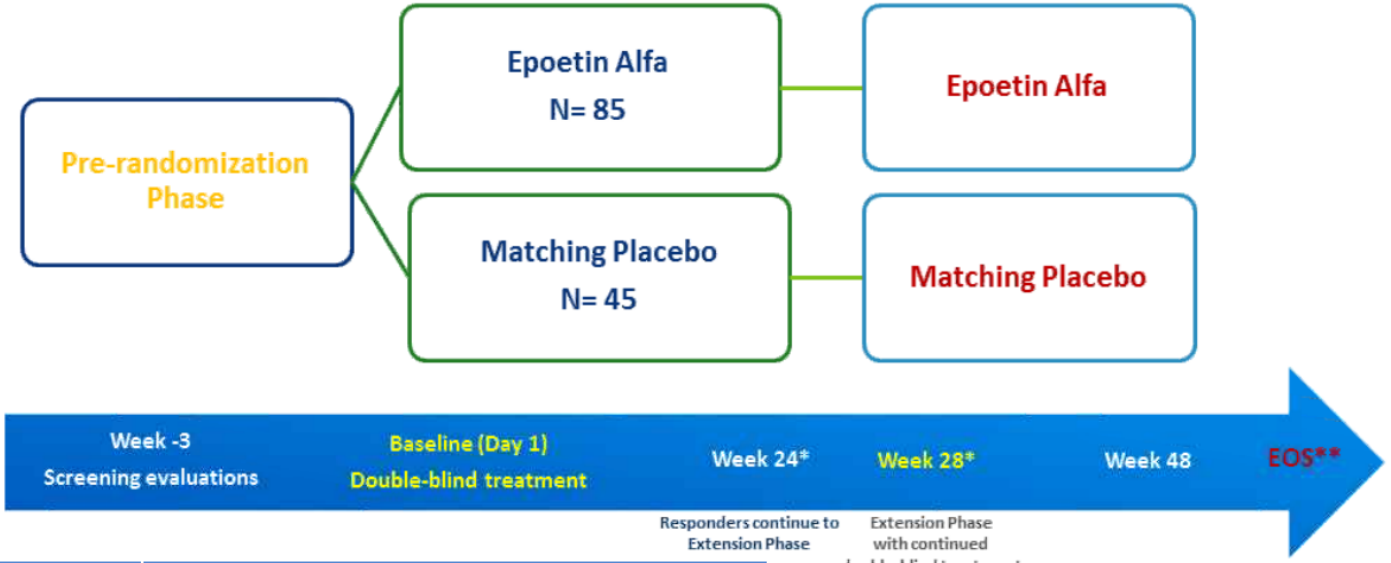
Pazienti SMD selezionati per

- Diagnosi recente
- Trasfusione-indipendenza
- EPO sierica <200 U/l (<500 U/l)
- Citogenetica normale
- IPSS Low-risk, Int-1

Indipendentemente dalla dose

Randomized, double-blind, placebo-controlled, multicenter study evaluating epoetin alfa versus placebo in anemic patients with IPSS low-INT1 risk MDS

Authors: Pierre Fenaux, MD[1]; Valeria Santini, MD[2]; Maria Antonietta Aloe Spiriti, MD[3]; Aristoteles Giagounidis, MD[4]; Rudolf Schlag, MD[5]; Atanas Radinoff, MD[6]; Liana Gercheva-Kyuchukova, MD[7]; Achilles Anagnostopoulos, MD[8]; Esther Oliva, MD[9]; Argiris Symeonidis, MD[10]; Anna Potamianou, MD[11]; Hari Haralampiev, MD[11]; Robert Wapenaar, MSc[11]; Iordanis Milionis, MSc[11]; Uwe Platzbecker, MD[12]



Inclusion criteria	Exclusion criteria
Low or Int-1 IPSS	Secondary MDS
Hb ≤ 10 g/dL	History of malignancies
Serum EPO < 500 mU/ml	Prior use of ESAs or disease changing agents
Transf. Need ≤ 4 units/8 weeks	Treatment with G-CSF or GM-CSF
Adequate B12, folate and iron	History of DVT or ischemic events
	Uncontrolled hypertension
	PRCA or positive antiEPO Ab

Fenaux et al., Haematologica. 2016

Demographic & Baseline Characterististics

Epoetin alfa MDS
(EPOANE3021 Study)

	Placebo	Epoetin Alfa	Total
	45	85	130
Age (years)			
Mean (SD)	74.1 (9.2)	74.3 (8.6)	74.2 (8.8)
Median	75.0	75.0	75.0
Range	(36, 87)	(40, 94)	(36, 94)
(Lower 95% CI, Upper 95% CI for the mean)	(71.3,76.8)	(72.4,76.1)	(72.7,75.7)
Sex			
Male	25 (55.6%)	46 (54.1%)	71 (54.6%)
Female	20 (44.4%)	39 (45.9%)	59 (45.4%)
IPSS Risk Category			
Low = 0	23 (51.1%)	35 (41.2%)	58 (44.6%)
Intermediate 1 = 0.5 to 1.0	22 (48.9%)	49 (57.6%)	71 (54.6%)
Intermediate 2 = 1.5 to 2.0	0	0	0
High = ≥2.5	0	0	0
Missing	0	1 (1.2%)	1 (0.8%)
p-value			0.355

Hemoglobin (g/L) Baseline (Day 1)		
	Placebo	Epoetin Alfa
N	45	85
Mean (SD)	91.8 (8.5)	91.2 (9.4)
Median	94.0	93.0
Range	(69.0, 105.0)	(67.6, 110.0)
(Lower 95% CI, Upper 95% CI for the Mean)	(89.3, 94.4)	(89.2, 93.2)
ITT subjects per stratification group		
Strata 1: Transfusion='No' and serum erythropoietin level less than 200 mU/mL	20 (44.4%)	38 (44.7%)
Strata 2: Transfusion='Yes' and serum erythropoietin level less than 200 mU/mL	19 (42.2%)	33 (38.8%)
Strata 3: Transfusion='No' and serum erythropoietin level at least 200 mU/mL	0	1 (1.2%)
Strata 4: Transfusion='Yes' and serum erythropoietin level at least 200 mU/mL	6 (13.3%)	12 (14.1%)

Fenaux et al., Haematologica. Jun 2016

Definizione di risposta eritroide (IWG 2006)

Table 4. Proposed modified International Working Group response criteria for hematologic improvement[7]

Hematologic improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, $< 100 \times 10^9$/L)	Absolute increase of $\geq 30 \times 10^9$/L for patients starting with $> 20 \times 10^9$/L platelets Increase from $< 20 \times 10^9$/L to $> 20 \times 10^9$/L and by at least 100%†
Neutrophil response (pretreatment, $< 1.0 \times 10^9$/L)	At least 100% increase and an absolute increase $> 0.5 \times 10^9$/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Primary Endpoint IWG 2006 ER by Response Review Committee

Epoetin alfa MDS
(EPOANE3021 Study)

	Placebo	Epoetin Alfa
	45	85
Subjects with Erythroid Response[a] at any time during the first 24 Weeks of study	2 (4.4%)	27 (31.8%)
p-value [b]		<.001
Subjects with Erythroid Response by stratification group		
Stratum 1: Transfusion='No' and serum erythropoietin level <200 mU/mL	1 (5.0%)	18 (47.4%)
Stratum 2: Transfusion='Yes' and serum erythropoietin level <200 mU/mL	1 (5.3%)	9 (27.3%)
Stratum 3: Transfusion='No' and serum erythropoietin level ≥200 mU/mL	0	0
Stratum 4: Transfusion='Yes' and serum erythropoietin level ≥200 mU/mL	0	0
p-value [c]		<.001
Subjects with Erythroid Response by IPSS Risk Category		
N		
Low = 0	2 (8.7%)	16 (45.7%)
Intermediate 1 = 0.5 to 1.0	0	10 (20.4%)
Intermediate 2 = 1.5 to 2.0	0	0
High = >=2.5	0	0
p-value [c]		<.001

[a] Erythroid Response determined by the Response Review Committee (RRC) according to the IWG 2006 criteria: Hb increase by ≥1.5 g/dL or relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks and lasting at least 8 weeks.
[b] p-value for treatment group differences are based on the Fisher exact test, 2-sided.
[c] p-value for treatment group differences are based on the Cochran-Mantel-Haenszel test, 2-sided.

ad hoc analysis

conducted in subjects who responded at any time of the study, regardless the IWG 2006 criteria

Epoetin alfa MDS
(EPOANE3021 Study)

	Placebo	Epoetin Alfa
	45	85
Subjects achieved Primary endpoint[a]	2 (4.4%)	27 (31.8%)
p-value [b]		**<.001**
Subjects with Erythroid Response at any time during the first 24 Weeks of study (ad hoc analysis)	2 (4.4%)	39 (45.9%)
p-value [b]		**<.001**

[a] *Erythroid Response determined by the Response Review Committee (RRC) according to the IWG 2006 criteria: Hb increase by ≥1.5 g/dL or relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks and lasting at least 8 weeks.*

[b] *p-value for treatment group differences are based on the Fisher exact test, 2-sided.*

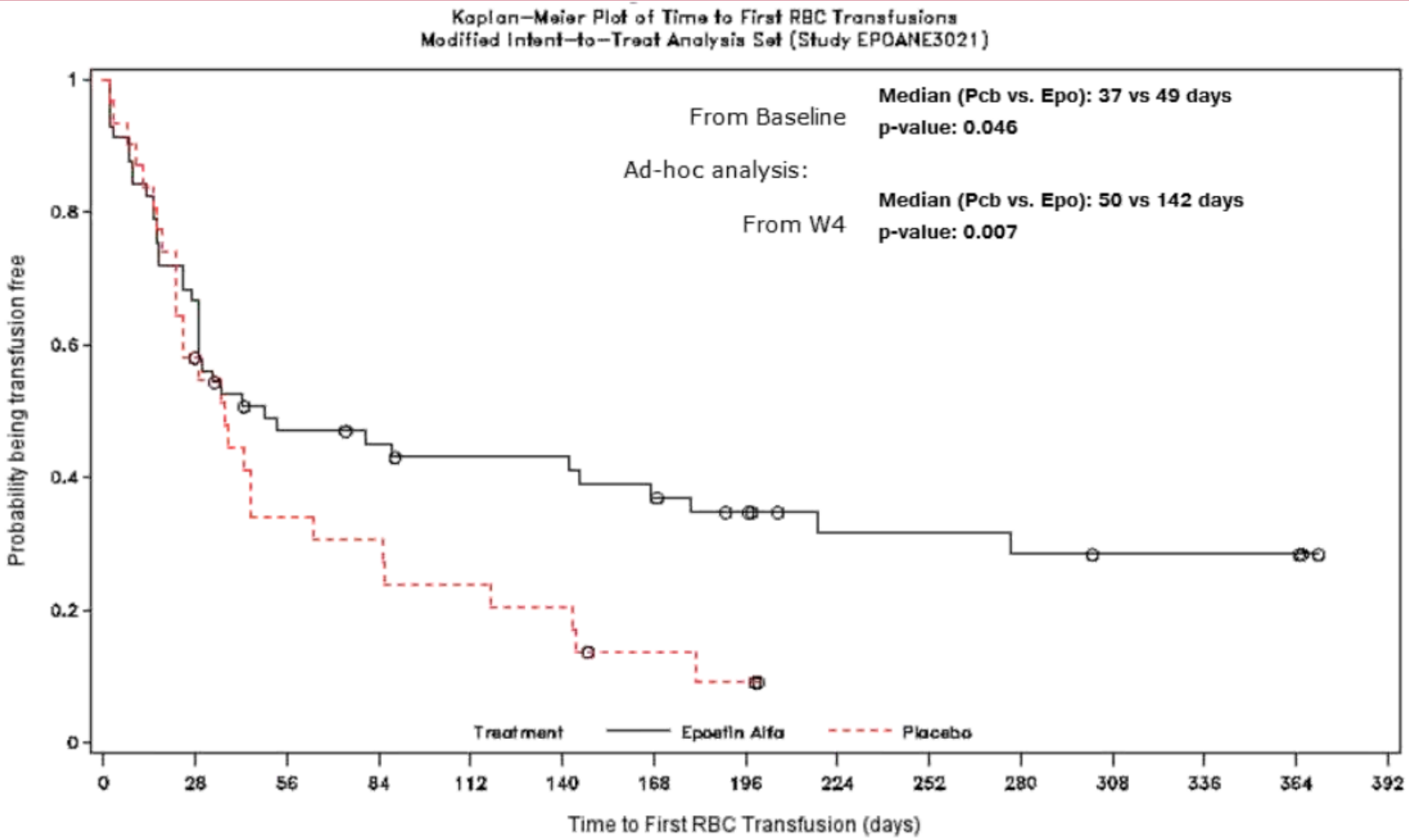
	Placebo	Epoetin Alfa
	45	85
Strata 1: Transfusion='No' and serum erythropoietin level <200 mU/mL	1 (5.0%)	18 (47.4%)
Strata 2: Transfusion='Yes' and serum erythropoietin level <200 mU/mL	1 (5.3%)	9 (27.3%)
Strata 3: Transfusion='No' and serum erythropoietin level ≥200 mU/mL	0	0
Strata 4: Transfusion='Yes' and serum erythropoietin level ≥200 mU/mL	0	0
p-value [c]		<.001

[c] p-value for treatment group differences are based on the Cochran-Mantel-Haenszel test, 2-sided.

Fenaux et al., Haematologica. Jun 2016; 101(s1):71

Secondary Endpoint – Time to First RBC Transfusion

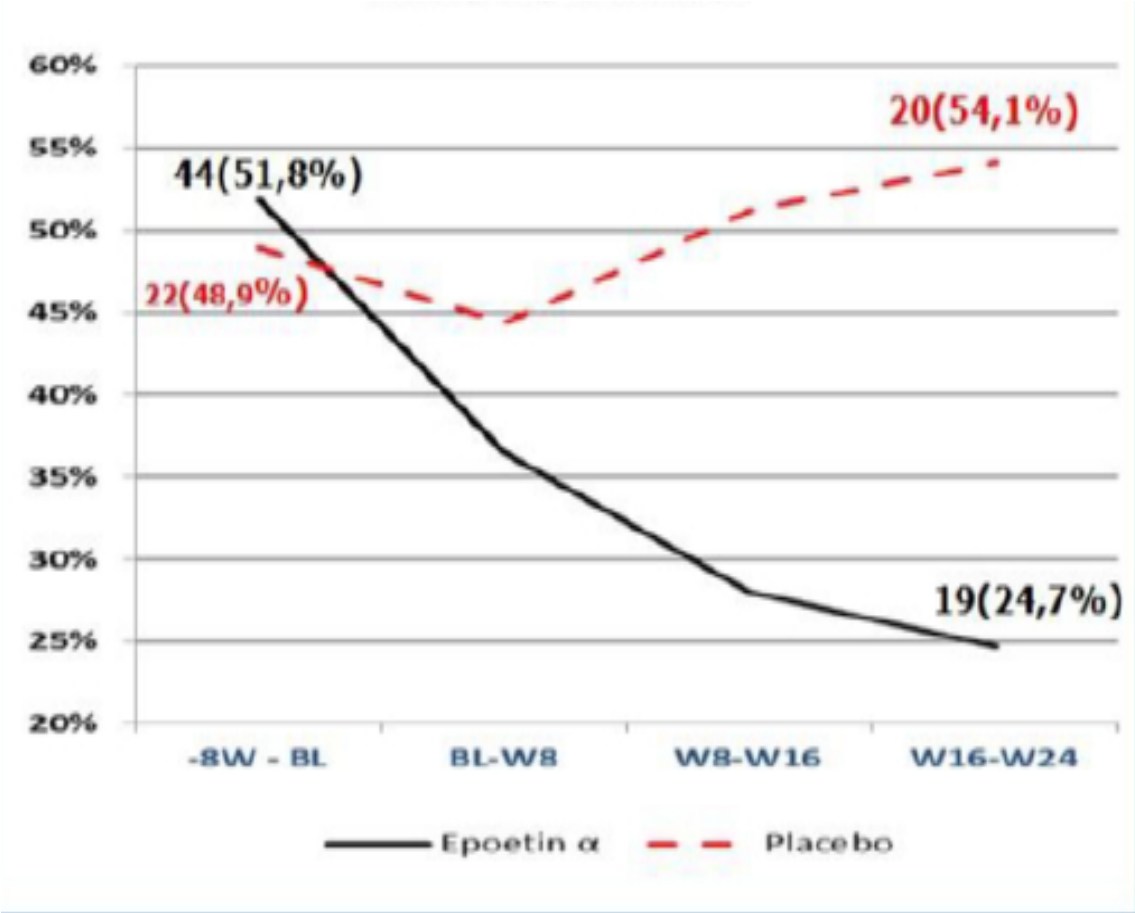
Epoetin alfa MDS
(EPOANE3021 Study)



Fenaux et al., Haematologica. Jun 2016; 101(s1):71

Secondary Endpoint
% of patients receiving transfusions

Epoetin alfa MDS
(EPOANE3021 Study)



Fenaux et al., Haematologica. Jun 2016; 101(s1):71

EPOANE3021
Safety Summary (up to 24 wks)

	Placebo	Epoetin Alfa
N	45	85
Subjects reporting at least one treatment-emergent adverse event	40 (88.9%)	66 (77.6%)
Subjects reporting at least one treatment-emergent serious adverse event	8 (17.8%)	22 (25.9%)
Subjects discontinued from study due to adverse event	6 (13.3%)	9 (10.6%)
Subjects reporting at least one thrombovascular events (TVE) at any time	0	4 (4.7%)
Subjects had disease progression	4 (8.9%)	11 (12.9%)
Subjects progressed to Acute Myeloid Leukemia (AML)	2 (4.4%)	3 (3.5%)
Subjects reporting a treatment-emergent adverse event with a fatal outcome*	1 (2.2%)	4 (4.7%)

** None of the death/fatal events were reported as related to product*

Fenaux et al., Haematologica. Jun 2016; 101(s1):71

Autorizzazione all'uso di EPO-alfa (Eprex®) nelle SMD *(aprile 2017)*

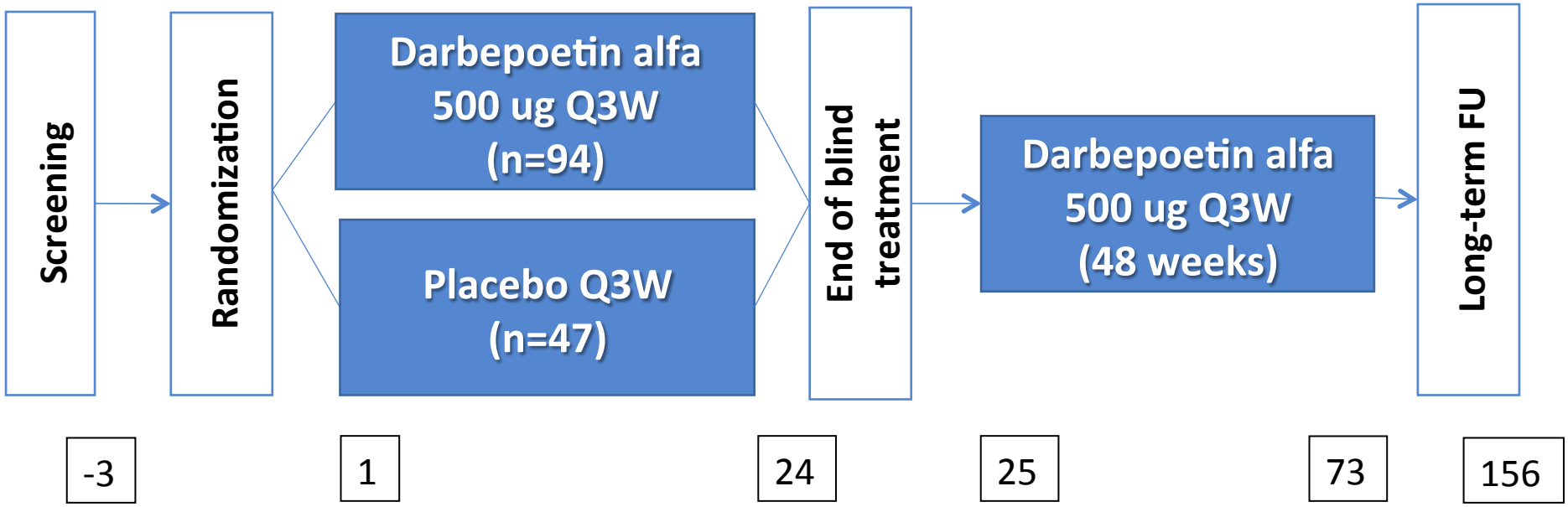
- Attraverso il c.d. **Processo di Mutuo Riconoscimento**, guidato dall'Agenzia Nazionale del Farmaco Francese, sulla scorta dei risultati dello Studio **EPOANE 3021** e dei dati di safety tratti da **3 Registri Europei (GFM, Dusseldorf e FISM*)** l'EPO-alfa (EPREX®) ha ottenuto dall'AIFA la seguente indicazione:

  «EPREX è indicato per il trattamento dell'anemia sintomatica (concentrazione di emoglobina ≤10 g/dL) in adulti con sindromi mielodisplastiche (MDS) primarie a rischio basso o intermedio-1 e bassa eritropoietina sierica (<200 mU/mL)»

- Ciò comporta tra l'altro il riconoscimento ad EPREX un periodo di 1 anno di esclusività del dato, che non permette quindi, per questo periodo di tempo, l'estrapolazione automatica ai biosimilari per questa specifica indicazione

** più di 500 pazienti trattati con EPO–alfa e monitorati a partire dal 1999*

ARCADE STUDY: A Phase 3 Randomized Placebo-Controlled Double-Blind Trial of Darbepoetin Alfa in the Treatment of Anemia in Patients With Low or Intermediate-1 Risk MDS



Key efficacy endpoints

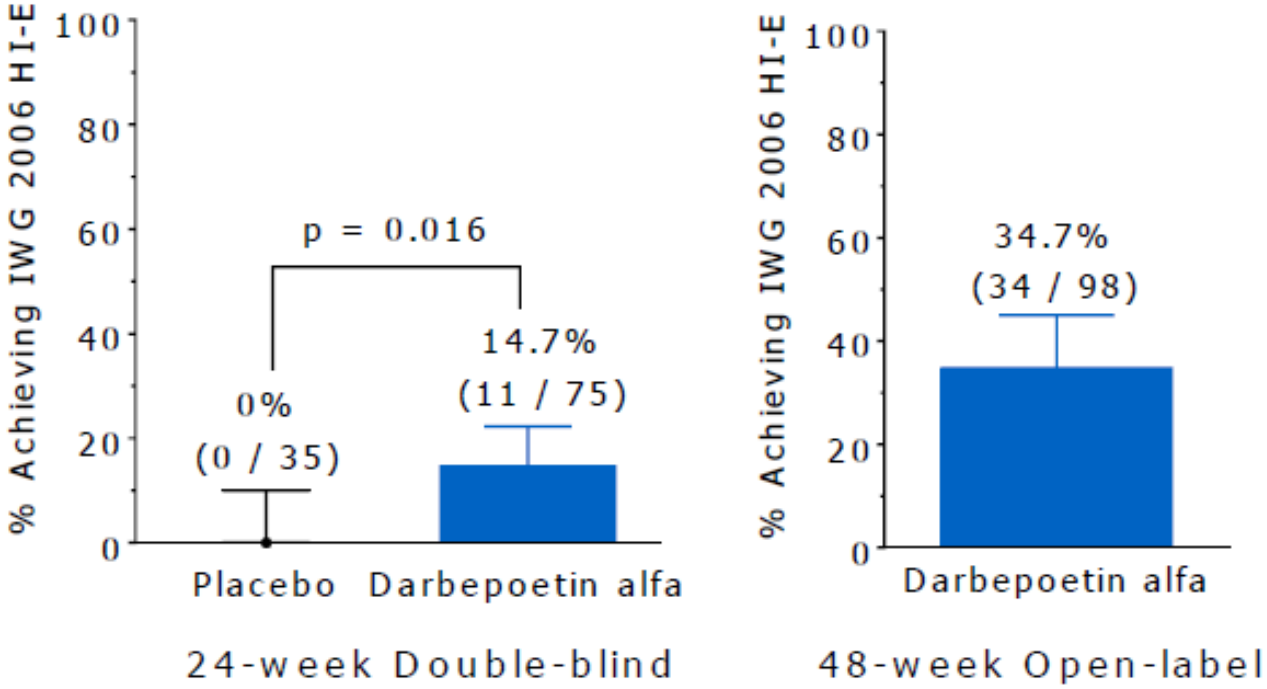
(1°) transfusion incidence from weeks 5 to 24

(2°) erythroid response (HI-E) per IWG 2006 criteria (≥1.5 g/dL increase from baseline in Hb with a mean rise of ≥1.5 g/dL for 8 weeks without transfusions)

→ The dose was reduced if Hb was >12.0 g/dL or if Hb increased by >1.5 g/dL in 3 weeks without transfusion

Platzbecker et al., EHA 2016

ARCADE STUDY : HI-E Rates



- 24-week Double-blind Period:

– All patients with HI-E (n = 11) had a baseline serum EPO level <100 mU/mL.

- 48-week Open-label Period: HI-E rate of 34.7%

– 81% (102/126) of patients increased dose frequency (from Q3W to Q2W) over the 48 weeks (twice as long as the blinded period)

Platzbecker et al., EHA 2016

Real-life use of EPO in lower-risk MDS

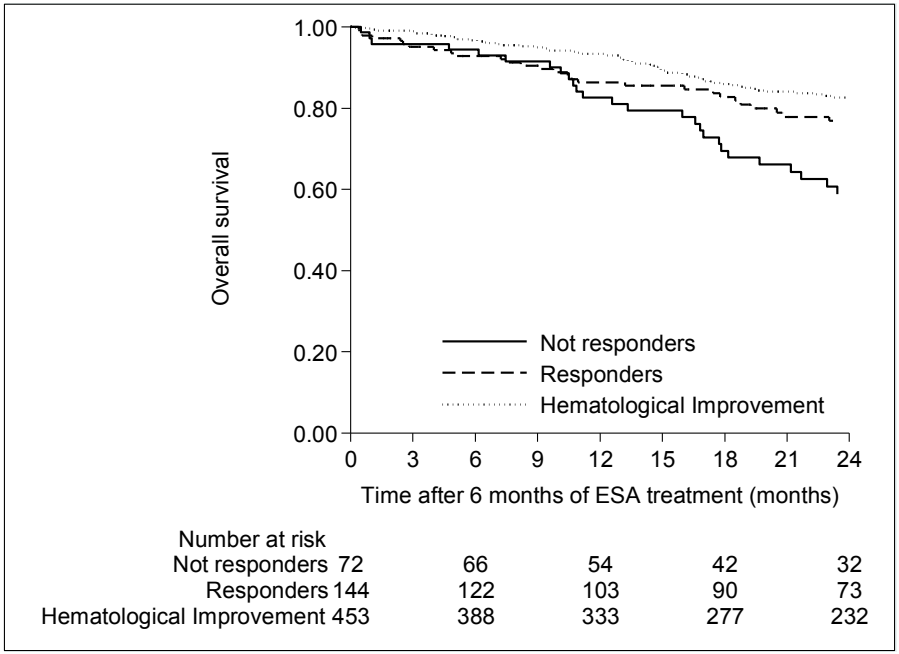
FISM retrospective study

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

✓758 pts

- ✓ Selection criteria:
  - ✓ Lower-risk IPSS (low or intermediate-1);
  - ✓ Transfusion –independence (Nordic Group criteria);
  - ✓ Endogenous EPO levels (< 500 mU/mL);

- ✓ Any eryhtroid response : **79%**



Messa E. et al, manuscript in preparation

Problemi aperti nell'uso degli ESAs per il paziente anemico con SMD

Ottimizzazione nella selezione dei pazienti

Ottimizzazione della schedula di trattamento

Approccio clinico ai casi non rispondenti

ESA refractory/relapsing MDS patients

- Response to EPO (and other ESAs) has a positive impact on both Qol and overall survival in MDS anemic pts;

However:

- It is observed in no more than ≈ 50-70% even in pts with a good probability to be responding
- The median duration of response is ≈ 1,5 - 2 y

Outcome of ESA refractory/relapsing MDS patients

ORIGINAL ARTICLE

Long-term outcome of anemic lower-risk myelodysplastic syndromes without 5q deletion refractory to or relapsing after erythropoiesis-stimulating agents

C Kelaidi, S Park, R Sapena, O Beyne-Rauzy, V Coiteux, N Vey, A Stamatoullas, B Choufi, J Delaunay, M-P Gourin, S Cheze, C Ravoet, A Ferrant, M Escoffre-Barbe, L Aljassem, E Raffoux, R Itzykson, L Adès, F Dreyfus and P Fenaux, on behalf of the Groupe Francophone des Myélodysplasies (GFM)

186Pts (120 refractory/ 66 relapsing)
OS 36 m for early failures

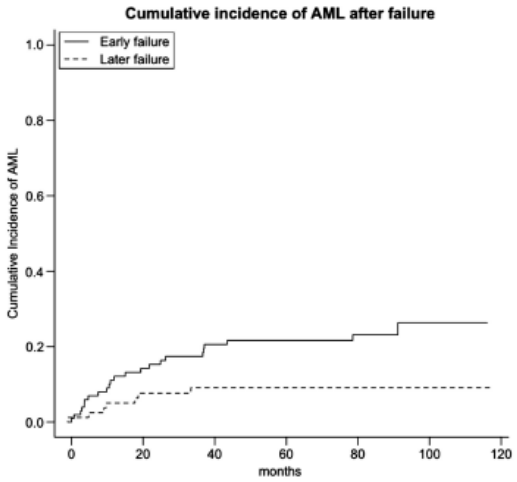


Figure 1. Cumulative incidence of AML after failure in patients with early and later failure.

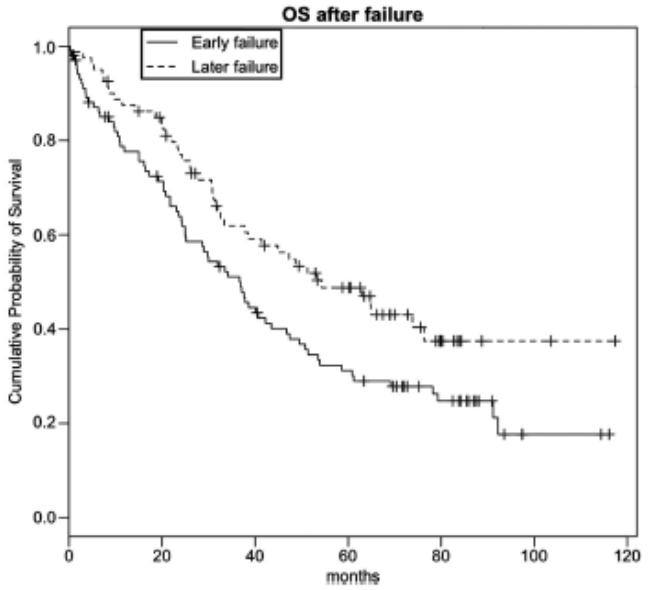


Figure 2. OS after failure in patients with early and later failure.

Kelaidi et al Leukemia 2013

Outcome of ESA refractory/relapsing MDS patients

VOLUME 35 · NUMBER 14 · MAY 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome of Lower-Risk Patients With Myelodysplastic Syndromes Without 5q Deletion After Failure of Erythropoiesis-Stimulating Agents

1698 pts
ESA response rate 61,5%

Median duration of response 17 months

1147 pts with failure
-654 refractory
-494 relapsing

2nd line treatment

BSC	627	(61%)
HMA	194	(16.9%)
Len	148	(12.9%)
Others	108	(9.4%)

Park S et al, JCO 2017

Outcome of ESA refractory/relapsing MDS patients

VOLUME 35 · NUMBER 14 · MAY 10, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Median OS
Refractory 52.2 months
Relapsing 60.4 months

Outcome of Lower-Risk Patients With Myelodysplastic Syndromes Without 5q Deletion After Failure of Erythropoiesis-Stimulating Agents

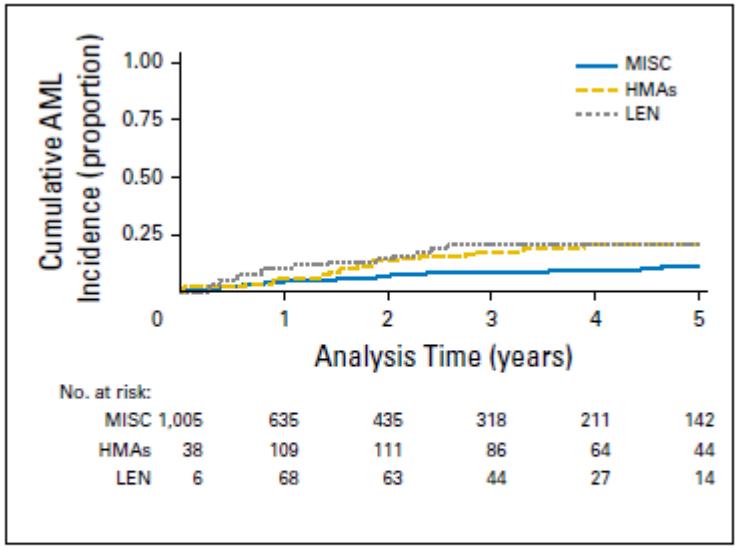


Fig 2. Simon-Makuch model (with treatment as a time-dependent variable) of cumulative acute myeloid leukemia (AML) incidence in patients receiving lenalidomide (LEN) or hypomethylating agents (HMAs) versus other treatments or RBC transfusion only (MISC) as second-line treatment (from erythropoiesis-stimulating agent failure; $P = .05$).

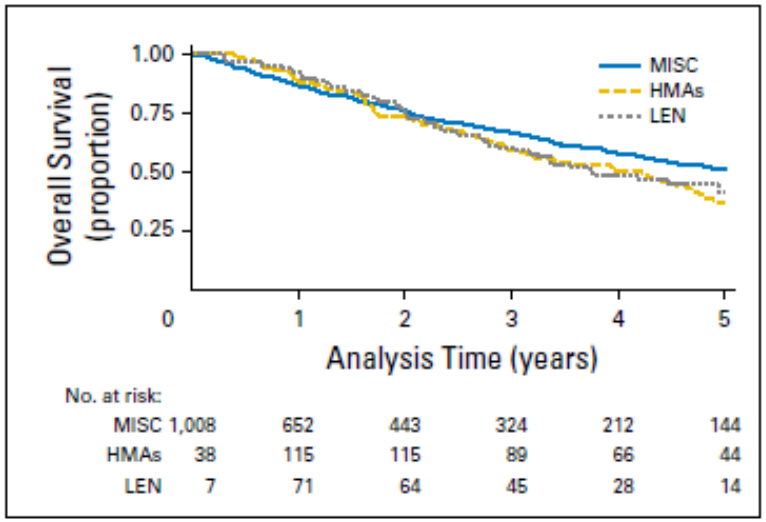


Fig 3. Simon-Makuch model (with treatment as a time-dependent variable) of overall survival in patients receiving lenalidomide (LEN) or hypomethylating agents (HMAs) at second-line treatment versus other treatments or RBC transfusion only (MISC; from erythropoiesis-stimulating agent failure; $P = 0.21$).

Park S et al, JCO 2017

Oral Azacitidine in lower-risk MDS patietns

ORIGINAL ARTICLE

Efficacy and safety of extended dosing schedules of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes

G Garcia-Manero[1], SD Gore[2], S Kambhampati[3], B Scott[4], A Tefferi[5], CR Cogle[6], WJ Edenfield[7], J Hetzer[8], K Kumar[8], E Laille[8], T Shi[8], KJ MacBeth[8] and B Skikne[8]

Table 2. Hematologic response and transfusion independence

Parameter	*Treatment schedule n responders/N evaluable (%)*		
	CC-486 300 mg once daily 14 days/cyde (n=28)	*CC-486 300 mg once daily 21 days/cycle (n=27)*	*Total (N=55)*
Overall response (CR, PR, any HI, TI)[a]	10/28 (36)	11/27 (41)	21/55 (38)
CR[b]	1/7(14)	0/5	1/12 (8.3)
PR	0/5	0/3	0/7
Any HI	7/28 (25)	10/27 (37)	17/55 (31)
HI-E	4/25 (16)	8/25 (32)	12/50 (24)
HI-P	4/18 (22)	3/15 (20)	7/33 (21)
HI-N	3/10 (30)	0/6	3/16 (19)
Marrow CR	0/7	3/5 (60)	3/12 (25)
RBC TI[c]			
Sustained for 56 days	5/16 (31)	6/16 (38)	11/32 (34)
Sustained for 84 days	2/16 (13)	5/16 (31)	7/32 (22)
Platelet TI[d]	0/4	0/2	0/6

Lenalidomide in RBC transfusion-dependent patients with IPSS Lower risk MDS with del(5q)

MDS-001 (PI–II; 2005)[1]

- Patients with all FAB subtypes (n=43)
- Erythroid response del(5q) = **83%**

MDS-003 (PII; 2006)[2]

- Patients with RBC-TD lower-risk MDS (n=148)
- Erythroid response = **76%**

MDS-004 (PIII; 2011)[3]

- Patients with RBC-TD lower-risk MDS (n=205)
- Placebo-controlled
- RBC-TI ≥26 weeks = **43–56%**

1.List A, et al. N Engl J Med 2005;352:549–57;
2. List A, et al. N Engl J Med 2006;355:1456–65;
3. Fenaux P, et al. Blood 2011 6;118(14):3765-76].

Lenalidomide in RBC transfusion-dependent patients with IPSS Lower risk MDS NO del(5q)

VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents

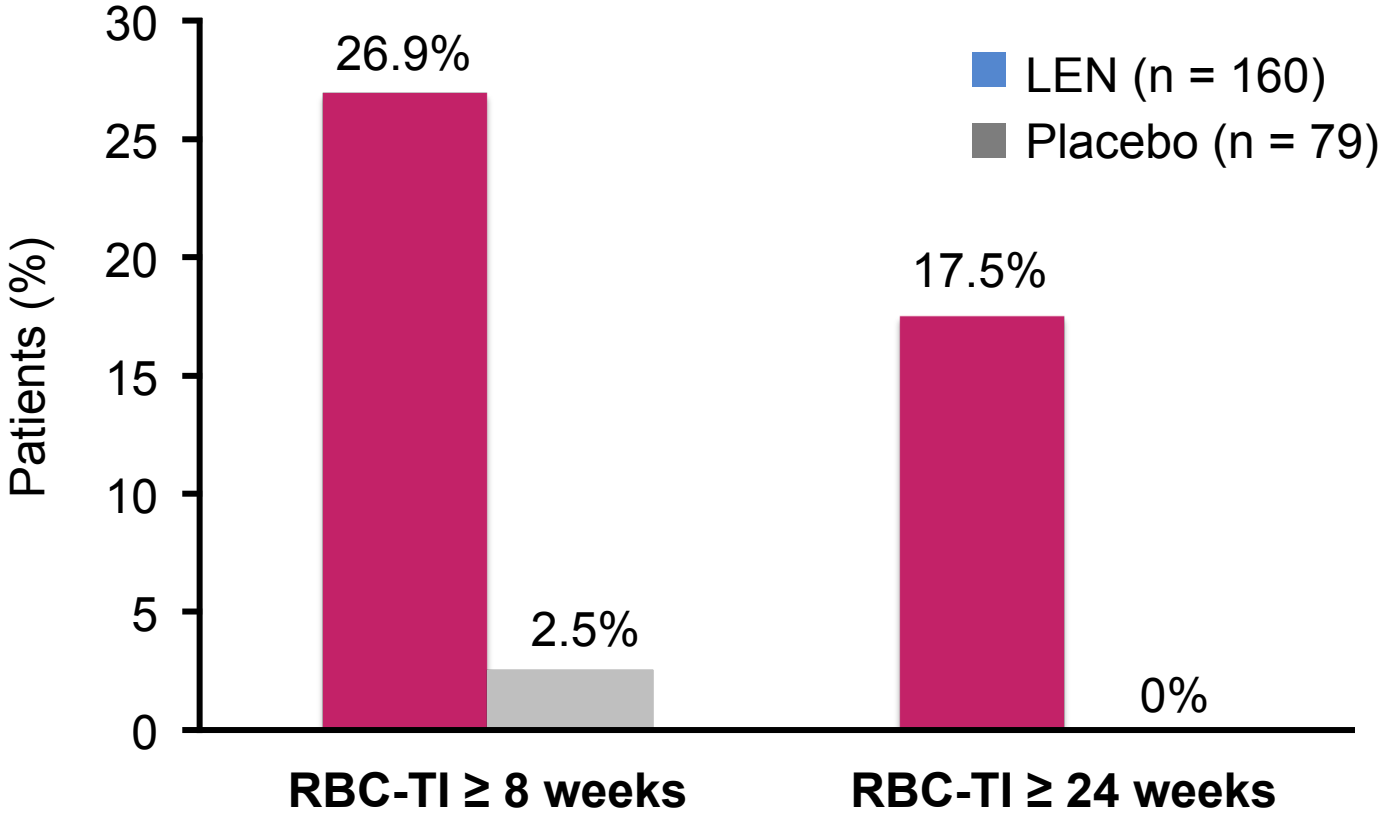
Valeria Santini, Antonio Almeida, Aristoteles Giagounidis, Stefanie Gröpper, Anna Jonasova, Norbert Vey, Ghulam J. Mufti, Rena Buckstein, Moshe Mittelman, Uwe Platzbecker, Ofer Shpilberg, Ron Ram, Consuelo del Cañizo, Norbert Gattermann, Keiya Ozawa, Alberto Risueño, Kyle J. MacBeth, Jianhua Zhong, Francis Séguy, Albert Hoenekopp, C.L. Beach, and Pierre Fenaux

IPSS low/int-1 MDS w/o del(5q);
refractory or unresponsive to ESA; w/ transfusion-dep anemia,
PLT > 50,000/µL, and ANC > 500/µL
(N = 239)

Treatment: Lenalidomide 10 mg/day/os on days 1-28
(5 mg if ClCr 40-60 ml/min)

Santini V et al JCO 2016

MDS-005: phase III trial of LEN vs placebo in patients with lower-risk RBC-TD non-del(5q) MDS

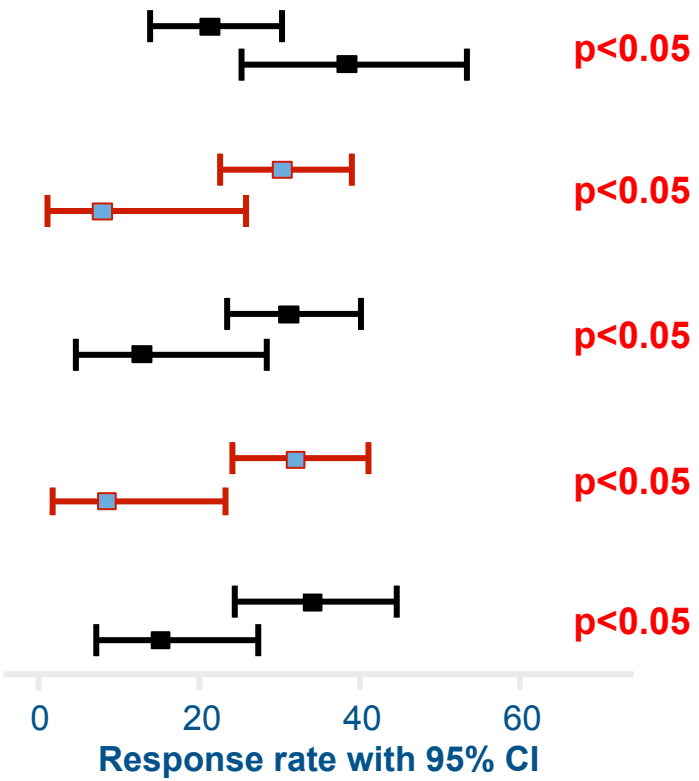


Santini V et al JCO 2016

MDS-005: phase III trial of LEN vs placebo in patients with lower-risk RBC-TD non-del(5q) MDS

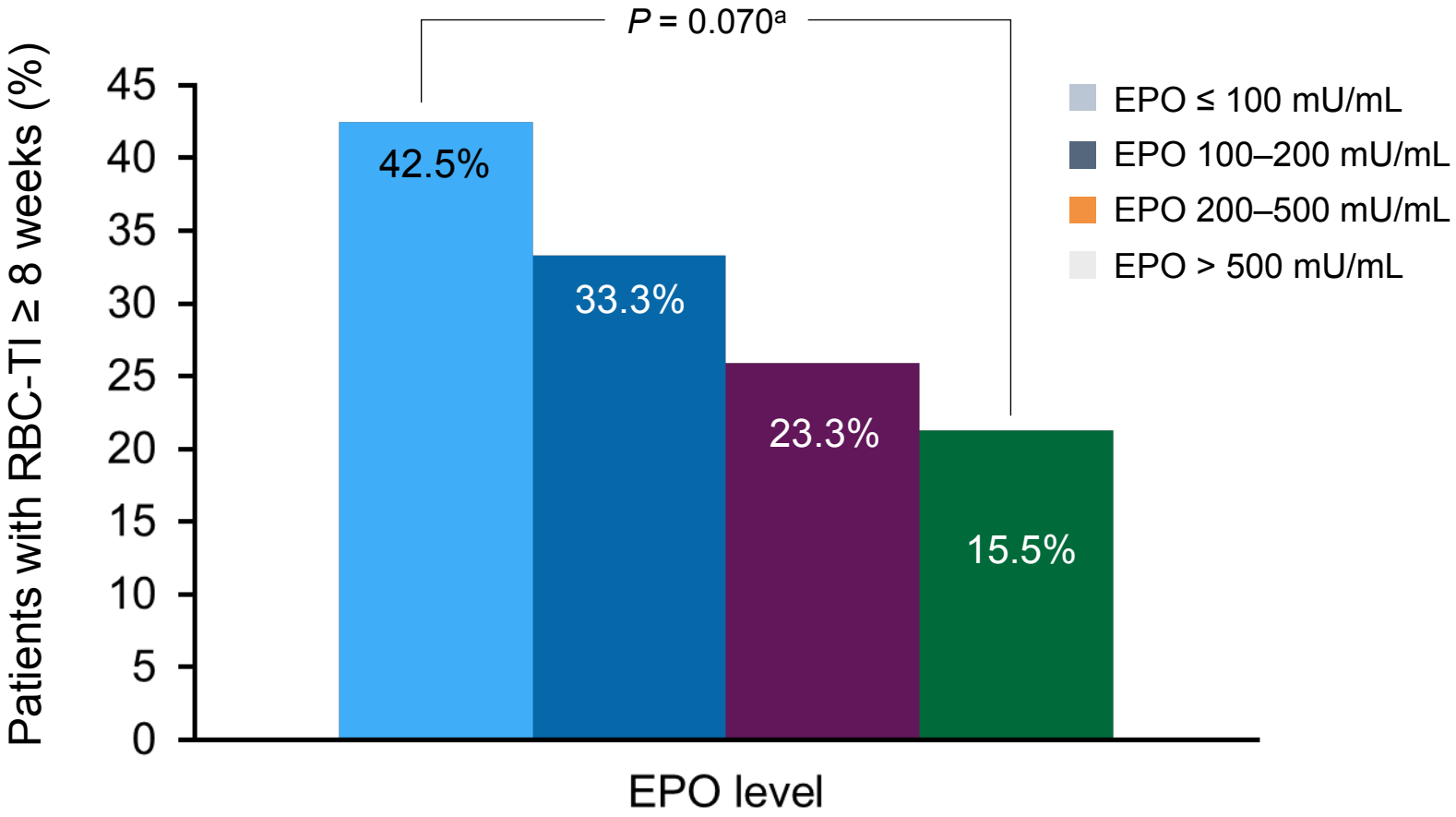
Baseline factors that had a significant impact on RBC-TI ≥8 weeks*

Baseline characteristic	RBC-TI ≥8 weeks, %
Gender	
male	21
female	39
Previous MDS therapy	
yes	30
no	8
Transfusion burden	
low†	31
high	13
Prior ESAs	
yes	32
no	9
Serum EPO	
≤500mU/mL	34
>500mU/mL	16



Santini V et al JCO 2016

MDS-005: phase III trial of LEN vs placebo in patients with lower-risk RBC-TD non-del(5q) MDS



[a] Linear trend test. Fisher exact test: *P* = 0.354.
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent;
RBC-TI, red blood cell transfusion independence.

Santini V et al JCO 2016

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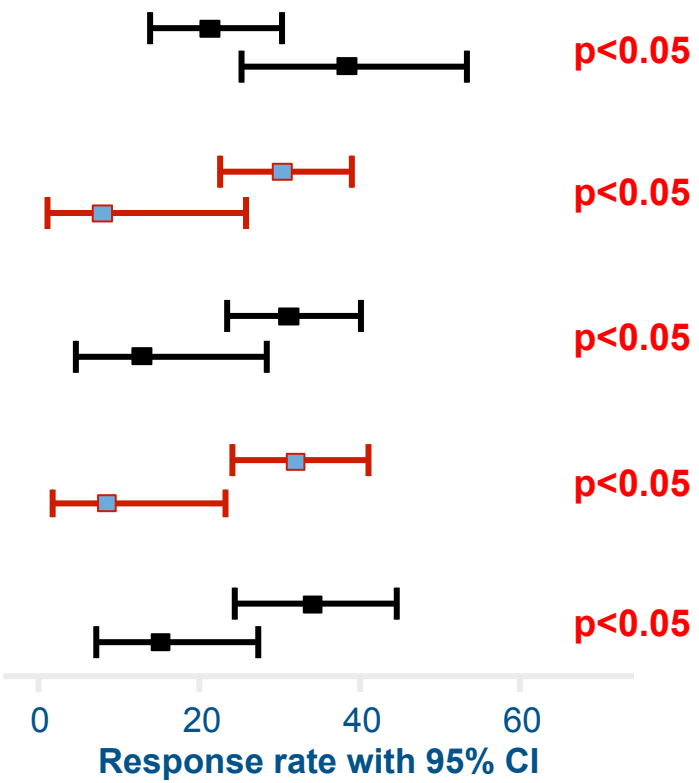
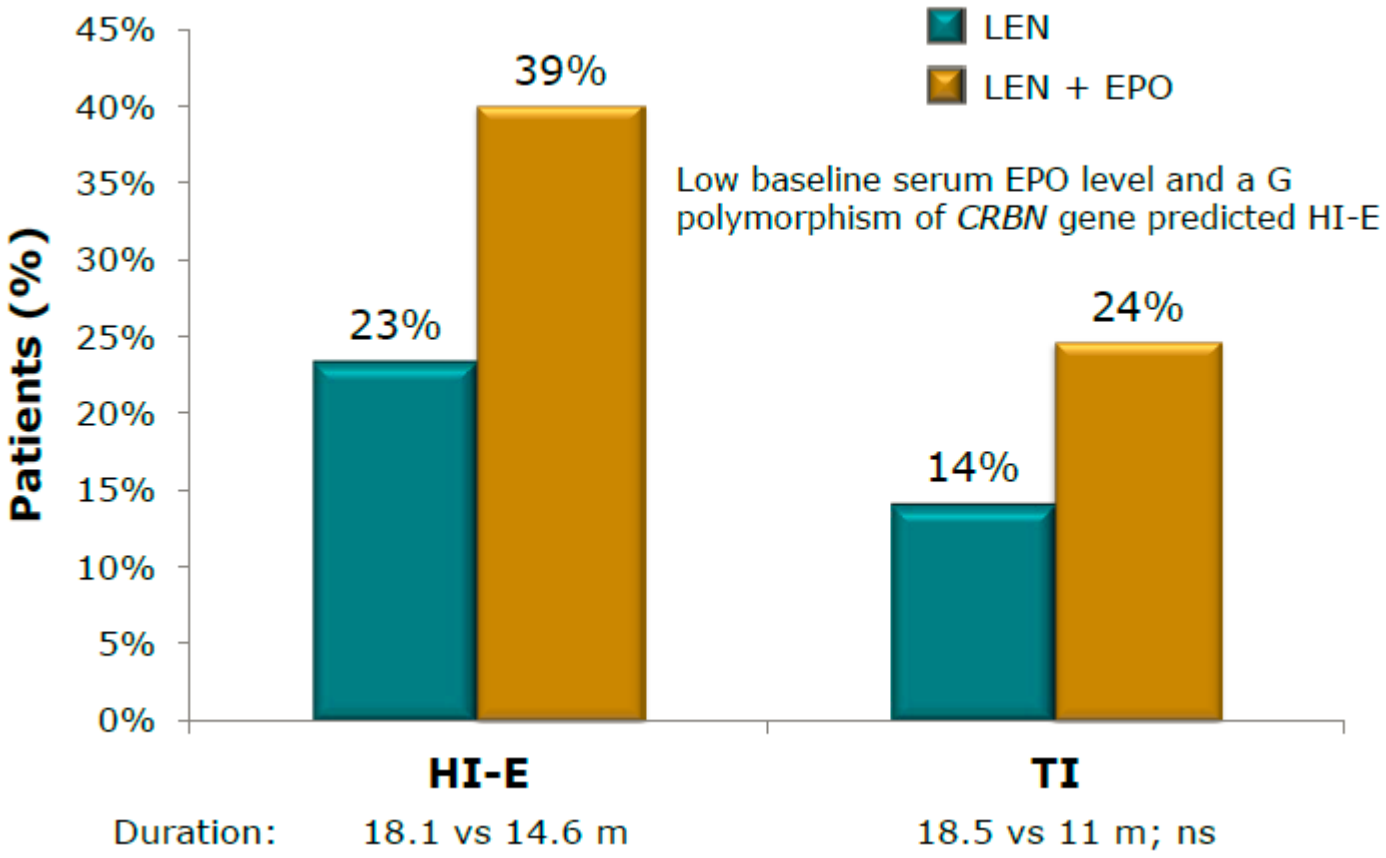


ASXL1 **mutant pts had a significantly lower LEN response rate vs wildtype pts, whereas *DNMT3A* mutant pts had a trend for improved LEN response**

Santini V, et al. JCO 2016

Addition of EPO to lenalidomide may further improve response rates



Toma A, et al. Leukemia 2016;

Azacitidine in patients with lower-risk MDS: results from an Italian named patient programme

Patient characteristics (n=74)

- IPSS low- or int-1-risk
- Transfusion dependent at diagnosis: 83.8%
- Previous therapy: 73.0%
- Median age: 68yrs

Azacitidine

Median cycles: 7 (1–30)

Dose: 75mg/m^2 (60.8% patients)

Schedule: 7 days every 28 days (58.1% patients)

CR = complete response; PR = partial response
HI = haematological improvement
BM = bone marrow; OS = overall survival

Response to therapy

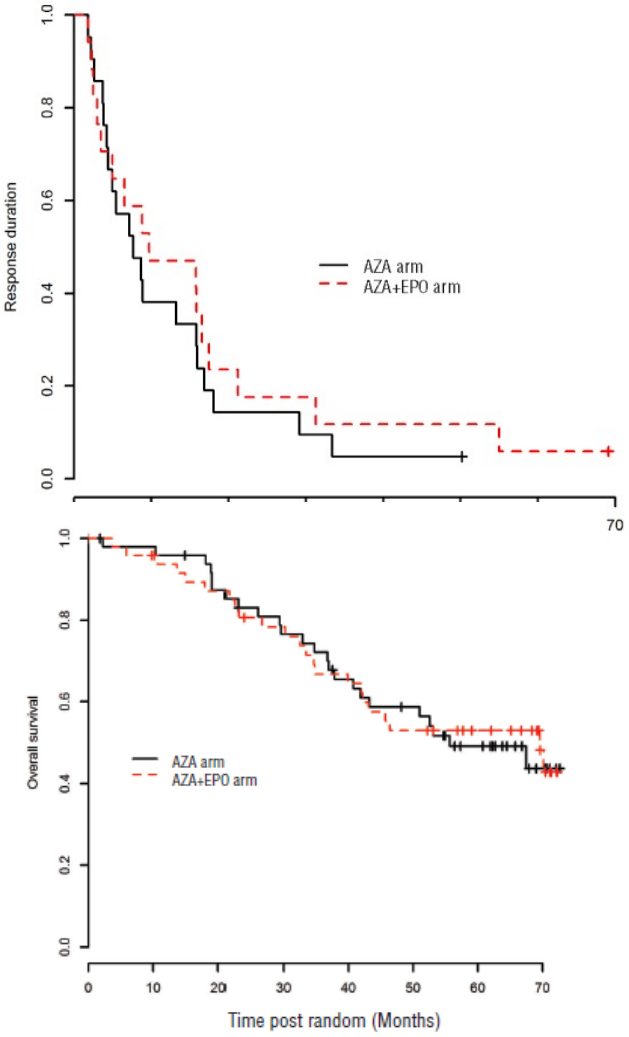
- 77% of responses occurred within the first 6 cycles
- Median duration of response = 6 months
- Projected OS at 30 months = 70.8% (median follow-up of 15 months)
- Projected OS was higher in responders than non-responders (93.9 vs 53.8%; p<0.0014)

Musto P, et al. Cancer 2010

azacitidine +/- epoetin-β in lower-risk MDS pts resistant to ESAs

A randomized phase II trial of azacitidine +/- epoetin-β in lower-risk myelodysplastic syndromes resistant to erythropoietic stimulating agents

Sylvain Thépot,[1*] Raouf Ben Abdelali,[2*] Sylvie Chevret,[3] Aline Renneville,[2] Odile Beyne-Rauzy,[4] Thomas Prébet,[5] Sophie Park,[6] Aspasia Stamatoullas,[7] Agnes Guerci-Bresler,[8] Stéphane Cheze,[9] Gérard Tertian,[10] Bachra Choufi,[11] Laurence Legros,[12] Jean Noel Bastié,[13] Jacques Delaunay,[14] Marie Pierre Chaury,[15] Laurence Sanhes,[16] Eric Wattel,[17] Francois Dreyfus,[6] Norbert Vey,[5] Fatiha Chermat,[18] Claude Preudhomme,[2] Pierre Fenaux[19] and Claude Gardin[1] on behalf of the Groupe Francophone des Myélodysplasies (GFM)



98 pts (49 vs 49)

Erythroid Response

24% AZA+EPO arm

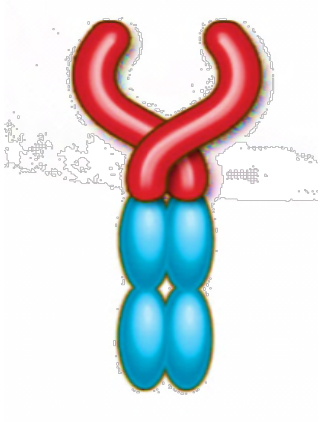
34% AZA arm (p=0.38)

Thepot S et al, Haematologica 2016

Luspatercept (ACE-536) Activity in MDS

- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 activation; increased Hb in healthy volunteers[1]
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia and increased Hb[2]

Luspatercept



Modified ECD of ActRIIB receptor

Fc domain of human IgG_1 antibody

1. Attie, K et al. Am J Hematol 2014;89:766

2. Suragani R et al., Nat Med 2014;20:408

PACE-MDS: Luspatercept in Lower-Risk, ESA-Refractory MDS

- Hematologic improvement (IWG HI-E) and reduced transfusion burden observed in pts with lower-risk MDS treated with luspatercept

Pt Group, n/n (%)	IWG HI-E	RBC-TI
Low transfusion burden	9/13 (69%)	3/3 (100%)
High transfusion burden	13/19 (68%)	8/19 (42%)

  - Of 22 pts transfused prior to study, 11 (50%) achieved RBC-TI for ≥ 8 wks (range: 9-50+ wks)
  - Responses observed for ≥ 50 pts who were ESA refractory or had serum EPO 200-500 U/L
- No serious AEs or grade 3/4 AEs related to luspatercept
  - AEs possibly related to study drug in ≥ 3 pts: bone pain, headache, nausea, myalgia, hypotonia (n = 1 each)

Platzbecker U et al. Haematologica 2016

sotatercept (ACE-011) in ESA refractory MDS pts

phase 2 dose-finding study

54 pts lower-risk MDS pts refractory to ESA or with lost response

Doses : 0.1- 0.3- 0.5- 1.0 mg/kg

53 evaluated for response (IWG 2006 modified criteria)

24 (45%) with hematologic improvement

most at the doses of 0.5 – 1.0 mh/kg(IWG HI-E)

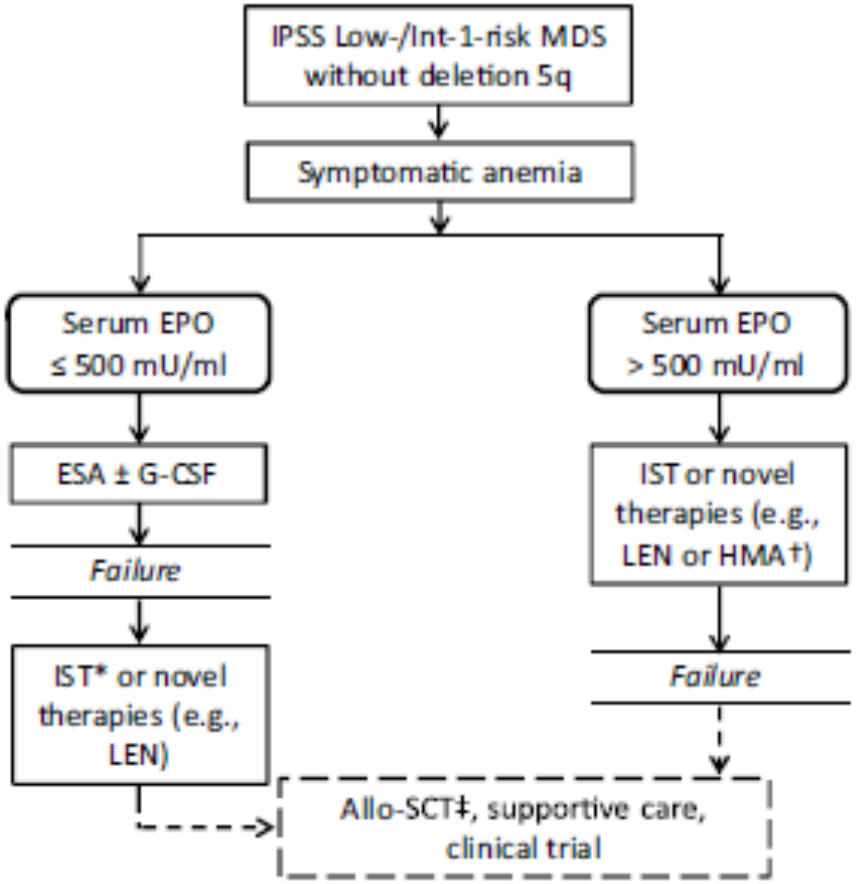
6 (11%) achieved RBC-TI for ≥ 8 wks

(range: 8-51+ wks)

- No serious AEs or grade 3/4 AEs related to sotatercept
  - AEs possibly related to study drug in 37% of pts: Fatigue 13% headache 9%, nausea 7%,

Komrokji et al, Leuk Res 2015 (abstr # 14)

Attuale algoritmo per l'uso dell'EPO nelle"lower-risk" MDS



Almeida et al, Leuk Res 2017

What can we conclude from the evidences?

- Response to EPO (and other ESAs) has a positive impact on both QoI and overall survival in MDS anemic pts;

However:

- It is observed in no more than ≈ 50-70% even in pts with a good probability to be responding
- The median duration of response is ≈ 1,5 - 2 y

new strategies of treatment need to be identified to increase both response-rate and duration of the response

OSPEDALE SAN MARTINO

Grazie per l'attenzione