FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

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

Napoli

Attualita' nel trattamento dell'anemia

Paolo Danise

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

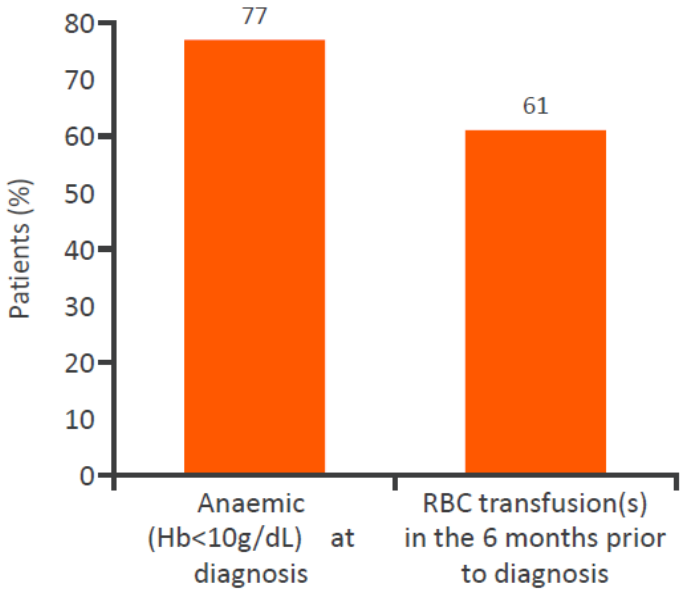
it is responsable for main morbidity and mortality

Santini V, Semin Hematol, 2015

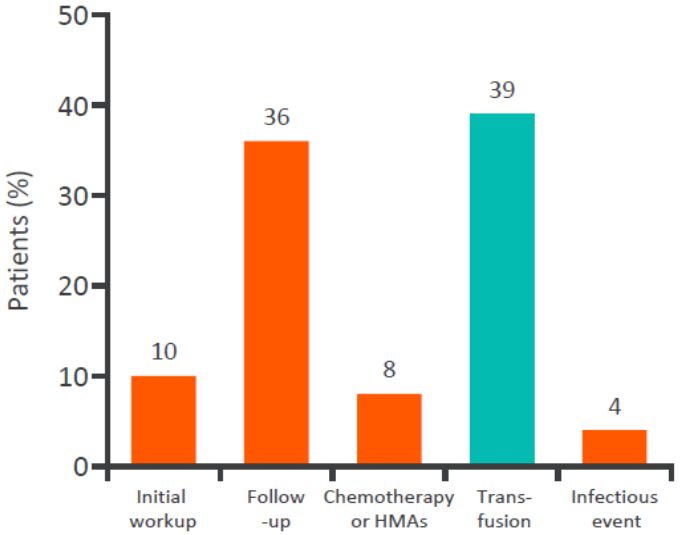
Incidenza e rilevanza clinica dell'anemia in corso di SMD

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*

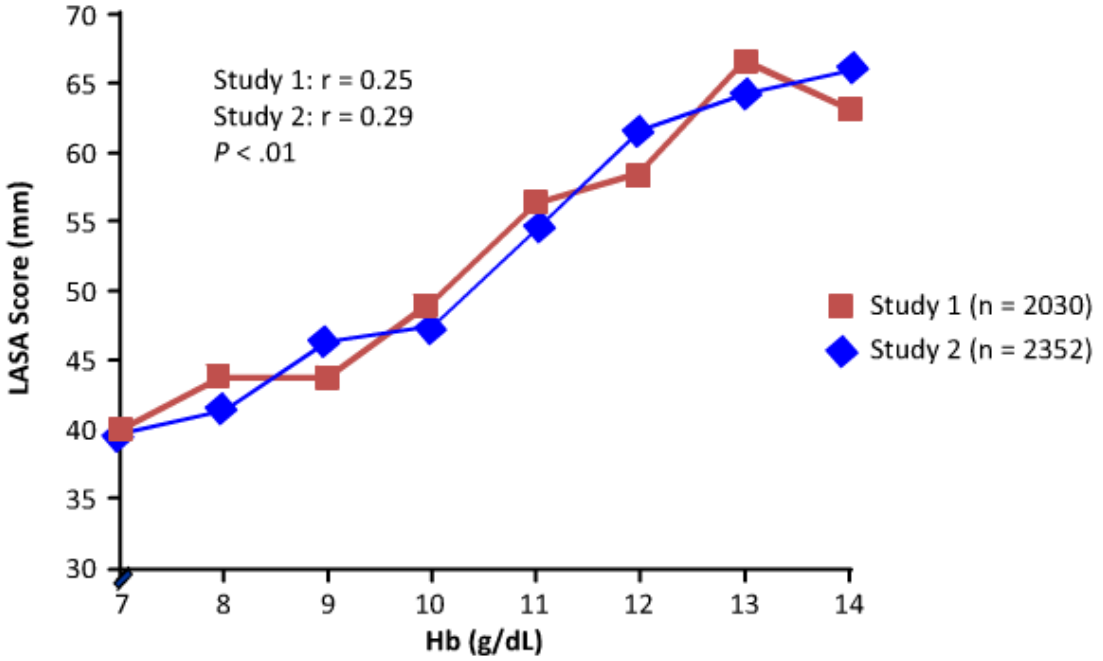


*based on a cross-sectional study of 907 patients with MDS who attended one of 74 French centres over a 1-week period
Hb = haemoglobin; HMA = hypomethylating agent
MDS = myelodysplastic syndromes; RBC = red blood cell

Kalaeidi et al Hematologica , 2010

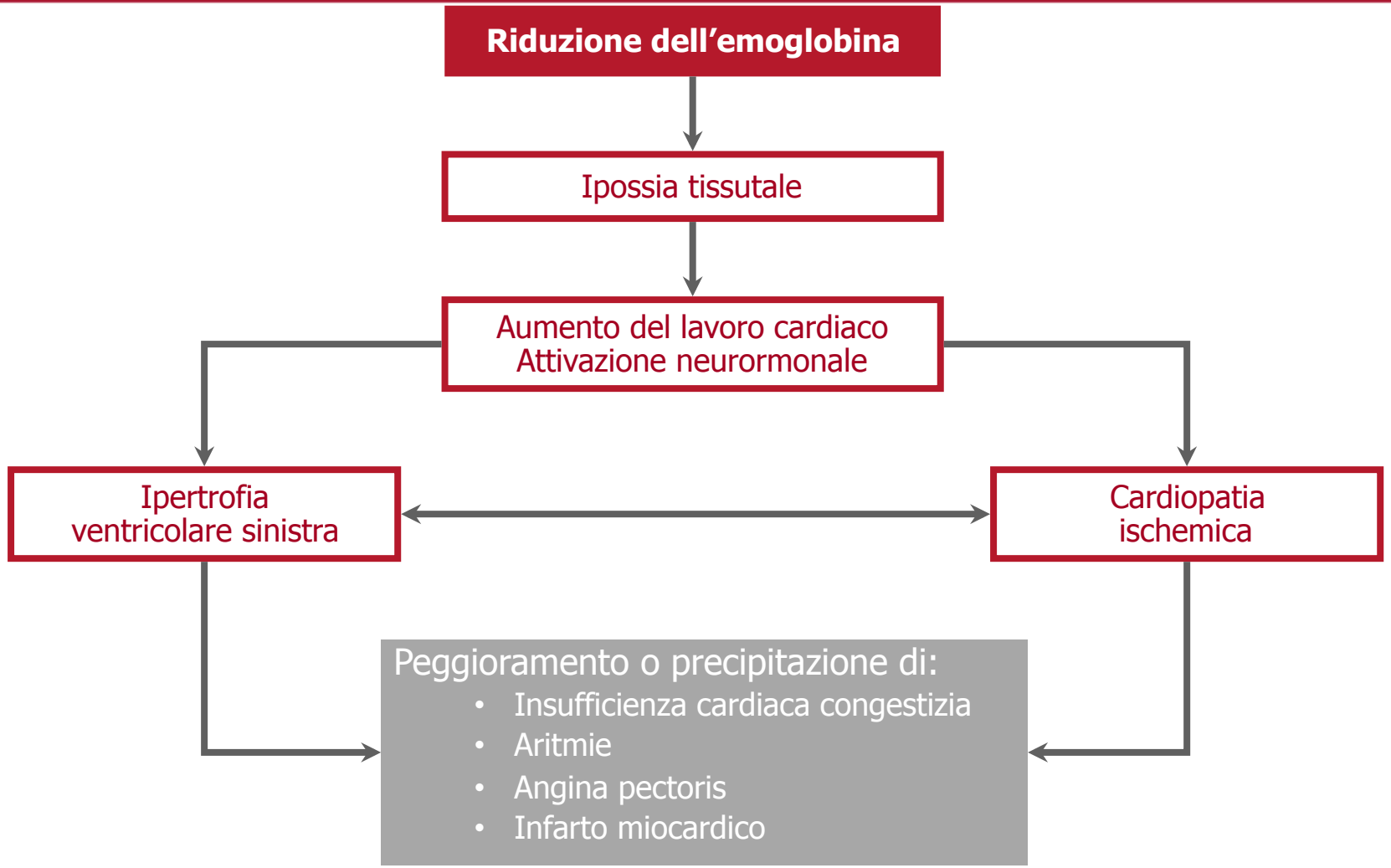
Incidenza e rilevanza clinica dell'anemia in corso di SMD

Relation between Hb level and QoL



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

Anemia e malattie cardiovascolari



Conseguenze a livello cardiaco di bassi valori di Hb

Anemia in MDS pts is associated with cardiac remodeling:

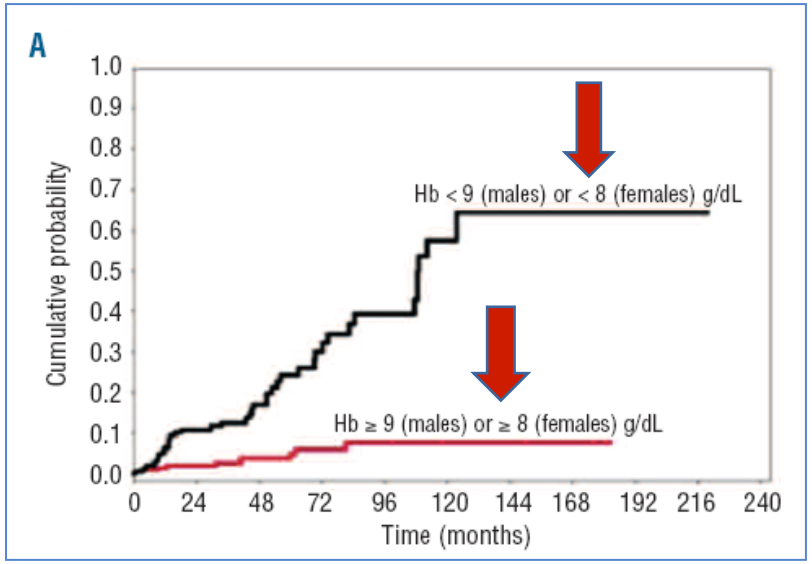
– 11 of 12 of transfusion-dependent vs 13 of 27 transfusion independent patients (92% vs 48%; *P* = 0.017)

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

Relazione tra grado di anemia e comorbidità e mortalità cardiaca in pazienti trasfusione dipendenti

- 25% dei pazienti con MDS è affetto da patologie cardiache
- 63% delle morti per cause non leucemiche sono per cause cardiache

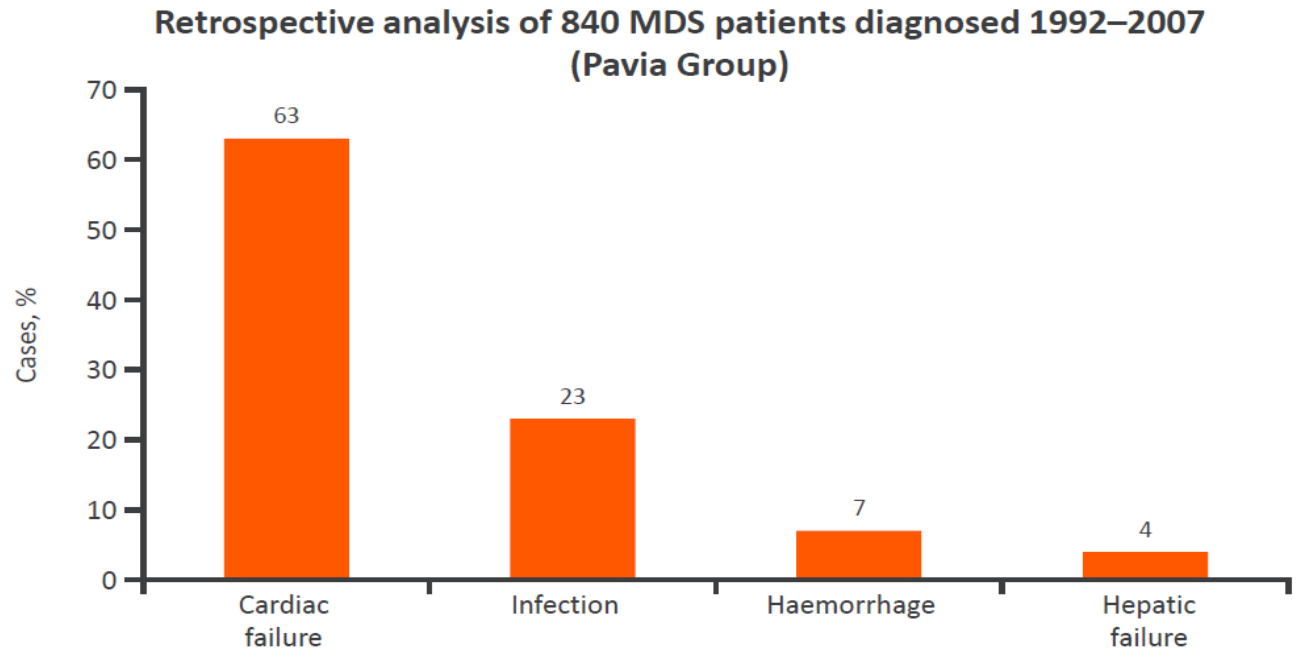


Pazienti con anemia severa (8-9 g/dl) o che sviluppano anemia severa nel corso del follow up hanno:

- una maggior probabilità di rischio di morte per cause cardiache (HR.3.62, p< 0.001)
- una maggiore probabilità di sviluppare malattie cardiache (HR.3.85, p< 0.001)

Malcovati, Hematologica 2011

The main cause of NLD in patients with MDS is cardiac failure

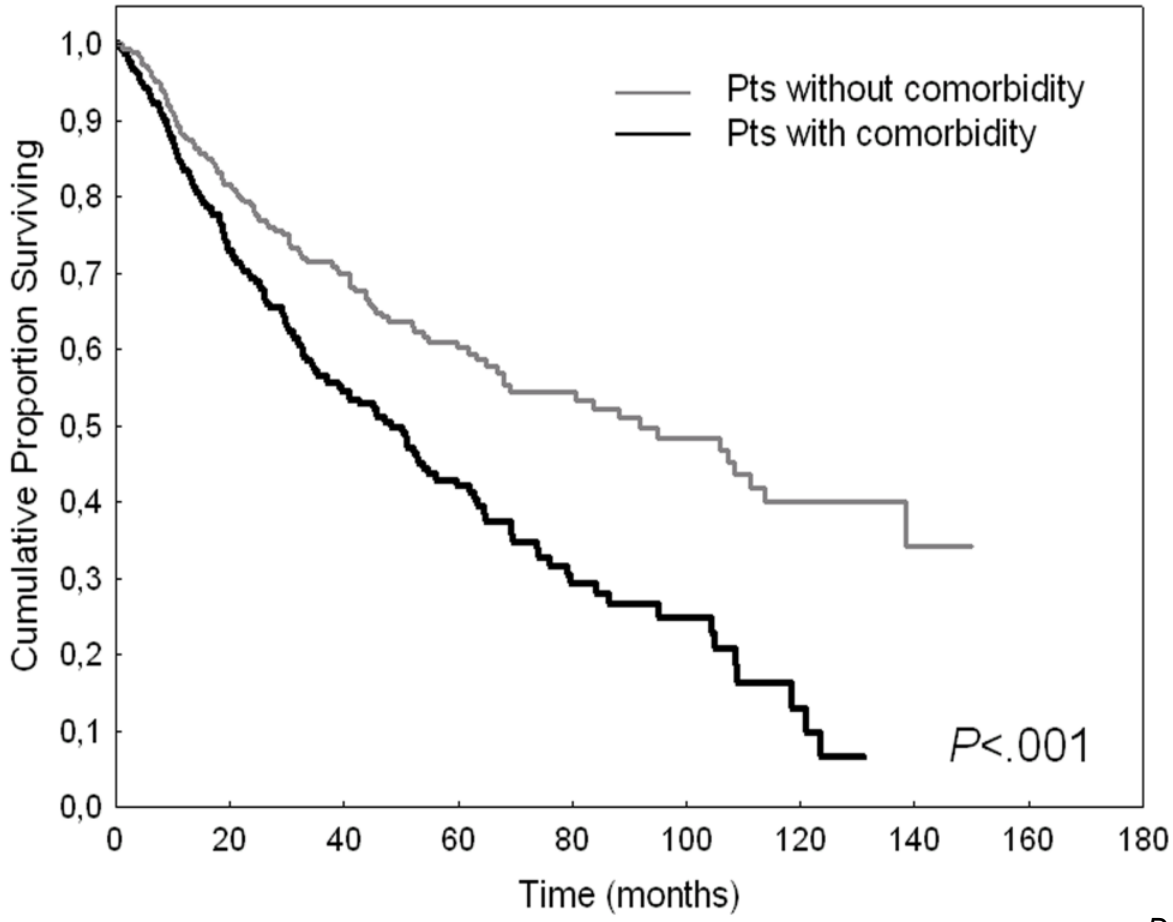


*36% of evaluable patients were IPSS low risk, 41% were IPSS int-1 risk and 33% were int-2/high risk
IPSS = International Prognostic Scoring System
MDS = myelodysplastic syndromes; NLD = non-leukaemic death

Della Porta MG, et al. Haematologica 2011;96:441–9

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

Overall survival



Dalla Porta et al Haematologica 2011

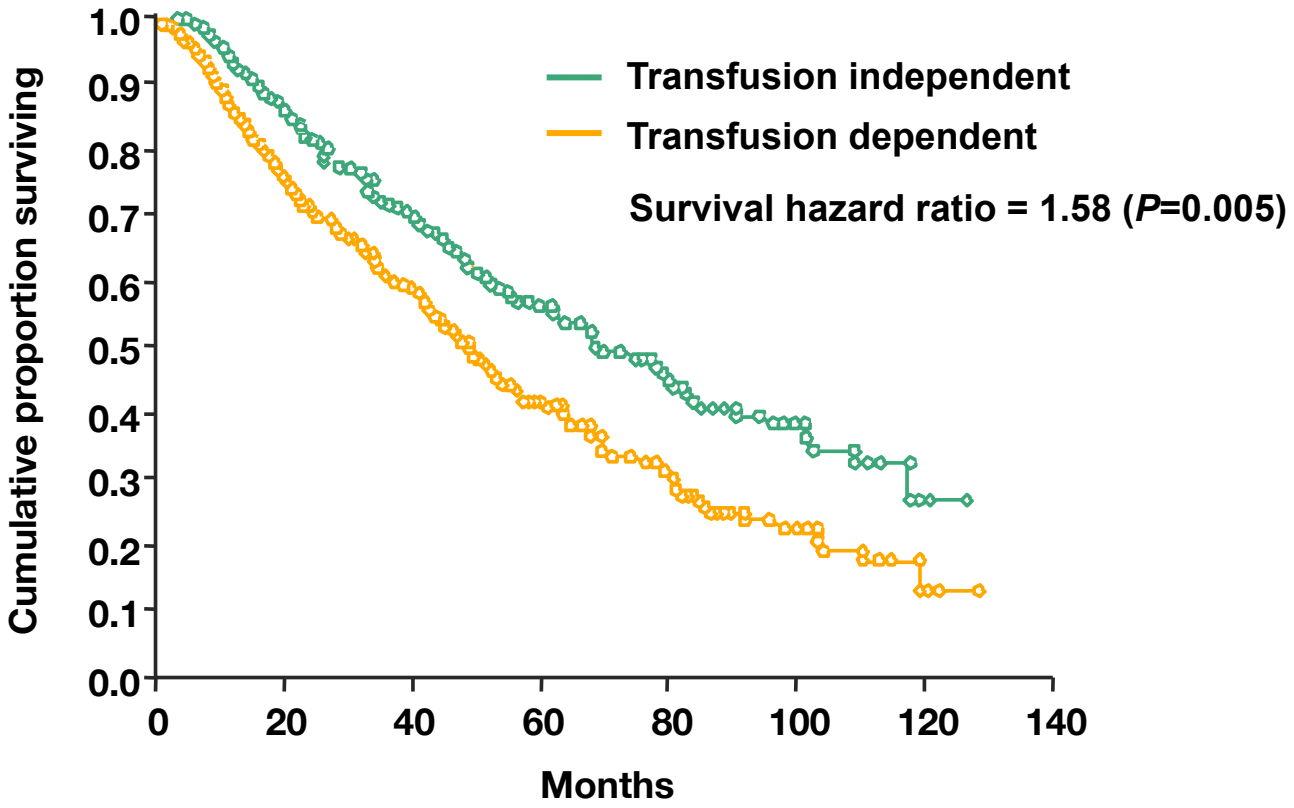
trasfusione

- Procedura costosa
- Procedura inevitabile
- Abbassa la qol
- Livello decisionale spesso legato a contingenze e non alla reale necessità del singolo paziente
- “Fiscalizzazione" del livello di hb pre-trasfusione

Il supporto trasfusionale spesso non è ottimale

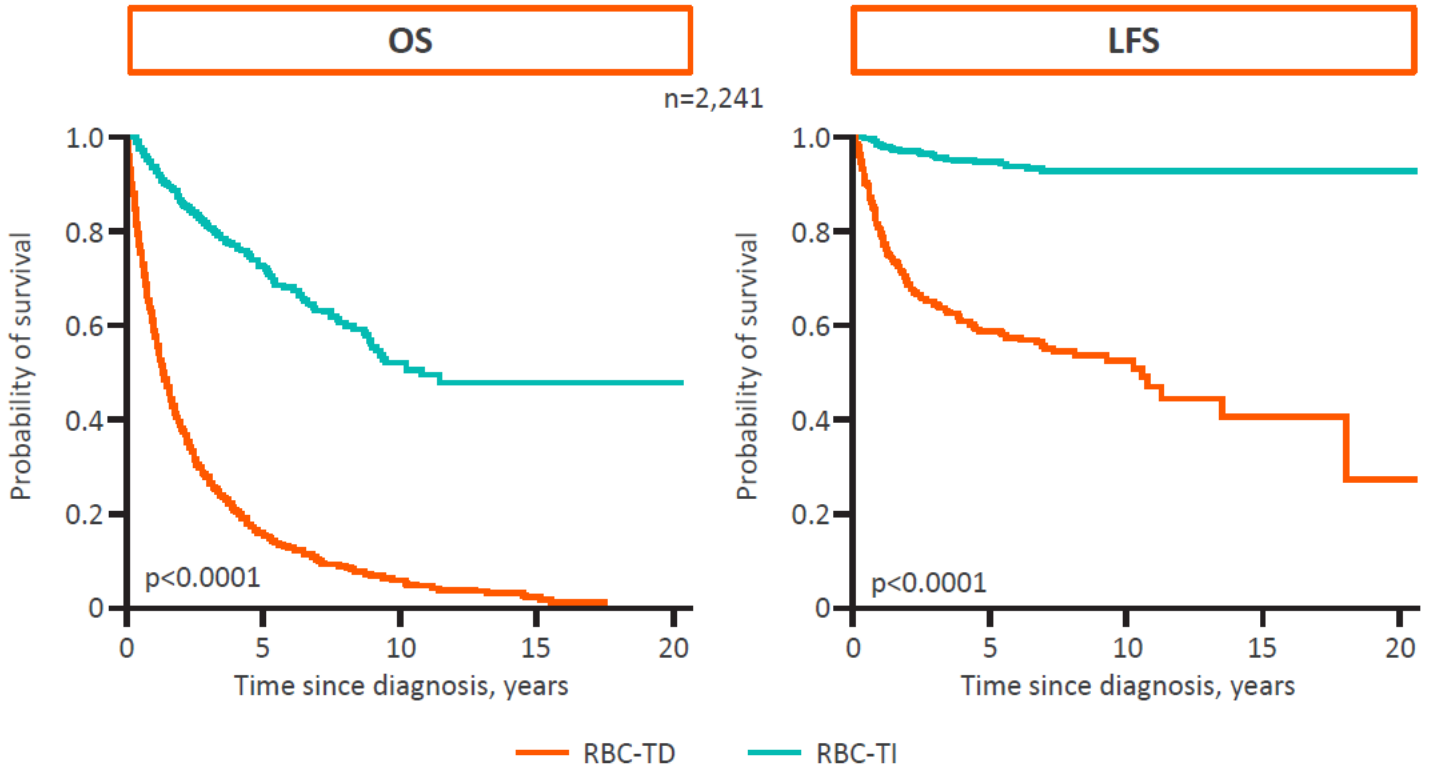
- Controlli meno frequenti del necessario
- Scarsa disponibilità di sangue
- Difficoltà di accesso rapido alle strutture in grado di erogare emotrasfusione
- Divergenze “analitiche” sul valore di Hb portano a considerare valido a livello decisionale il dato migliore

La trasfusione-dipendenza aumenta significativamente la mortalità nelle SMD



Cazzola M & Malcovati L. N Engl J Med 2005

RBC-TD* has a negative impact on survival in patients with MDS, independently from IPSS

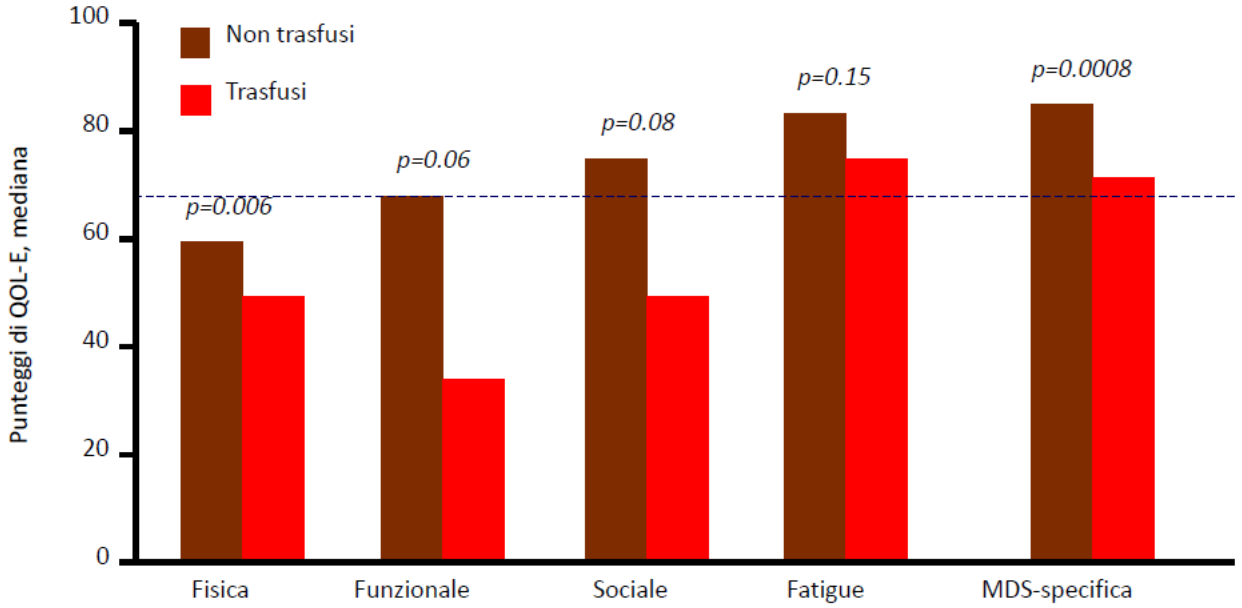


*Defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months
LFS = leukaemia-free survival; MDS = myelodysplastic syndromes; OS = overall survival
RBC-TD = red blood cell transfusion-dependent; TI = transfusion independent

Sanz G, et al. Blood 2008;112:abstract 640

La trasfusione dipendenza peggiora tutti gli aspetti della QOL

Studio Italiano, N= 147
QoL valutato con strumento QOL-E; paz stratificati per trasfusione-dip



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

Raccomandazioni ELN sulla trasfusione

blood

Prepublished online August 26, 2013;
doi:10.1182/blood-2013-03-492884

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

the objective of RBC transfusion therapy is to improve quality of life and to avoid anemia-related symptoms and ischemic organ damage (Recommendation level D)

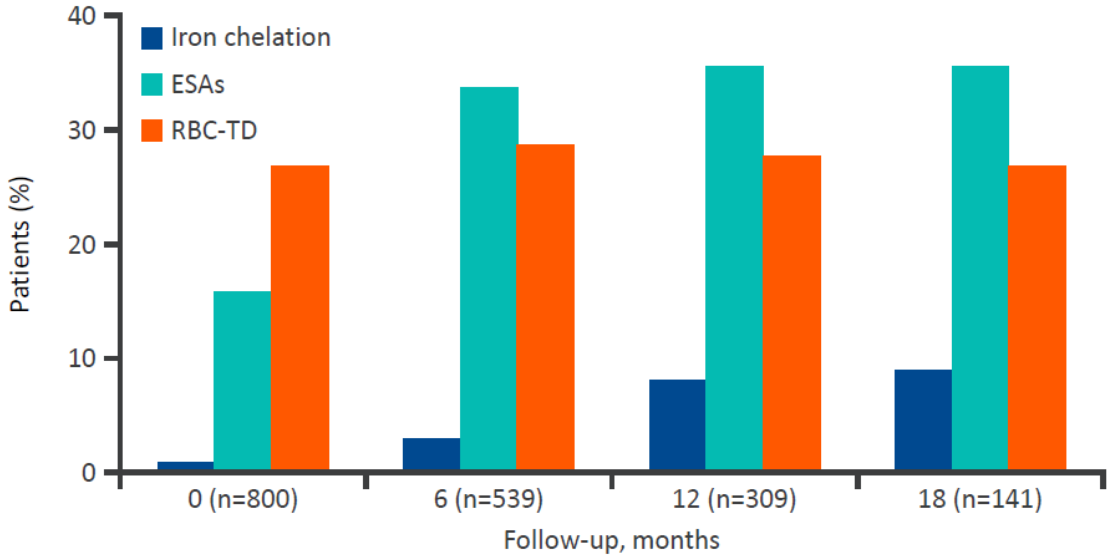
No single hemoglobin concentration can be recommended as being the optimal level below which red cell support should be given

all patients with severe anemia (Hb lower than 8 g/dL) and those with symptomatic milder anemia should receive RBC cell transfusion (Recommendation level D)

La percentuale di pazienti trasfusione dipendenti tende a restare costante nel tempo

Disease management in patients with lower-risk MDS: RBC-TD is difficult to overcome

Data from the ELN Registry of 800 patients with lower-risk MDS from 11 European countries



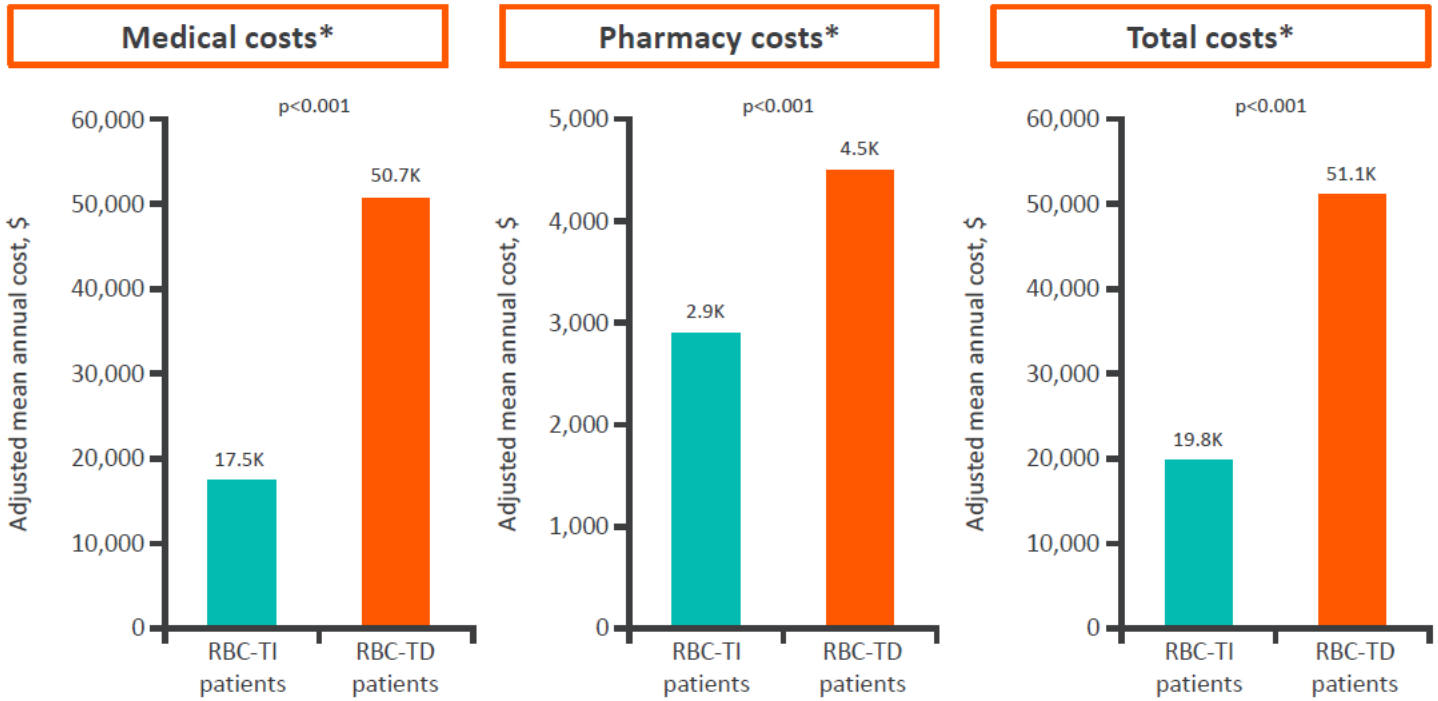
The proportion of patients who are RBC-TD remains largely unchanged over time

ELN = European Leukemia Network; ESA = erythropoietin stimulating agent
MDS = myelodysplastic syndromes; RBC-TD = red blood cell transfusion-dependent

De Swart L, et al. Blood 2010;116:abstract 2917

Annual healthcare costs are significantly higher for RBC-TD patients versus RBC-TI patients

Study of 3,200 MDS patients (2,864 RBC-TI, 336 RBC-TD) from the retrospective claims database of a large US health plan (May 2000–Sept 2003)



*Adjusted for demographics and comorbidity via gamma regression with a log link
MDS = myelodysplastic syndromes; RBC-TD = red blood cell transfusion-dependent
TI = transfusion independent; US = United States

Frytak JR, et al. Curr Med Res Opin 2009;25:1941–51

Impatto degli ESAs nella pratica clinica e nella MDS

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

EPO induces erythroid response in "lower-risk" MDS

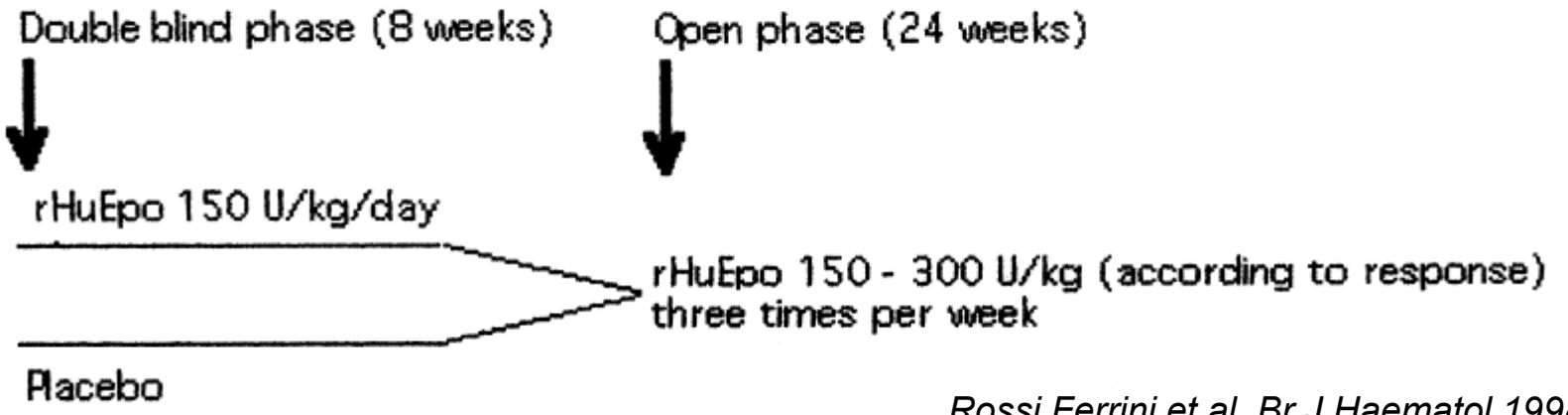
a Multicenter Italian Study

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

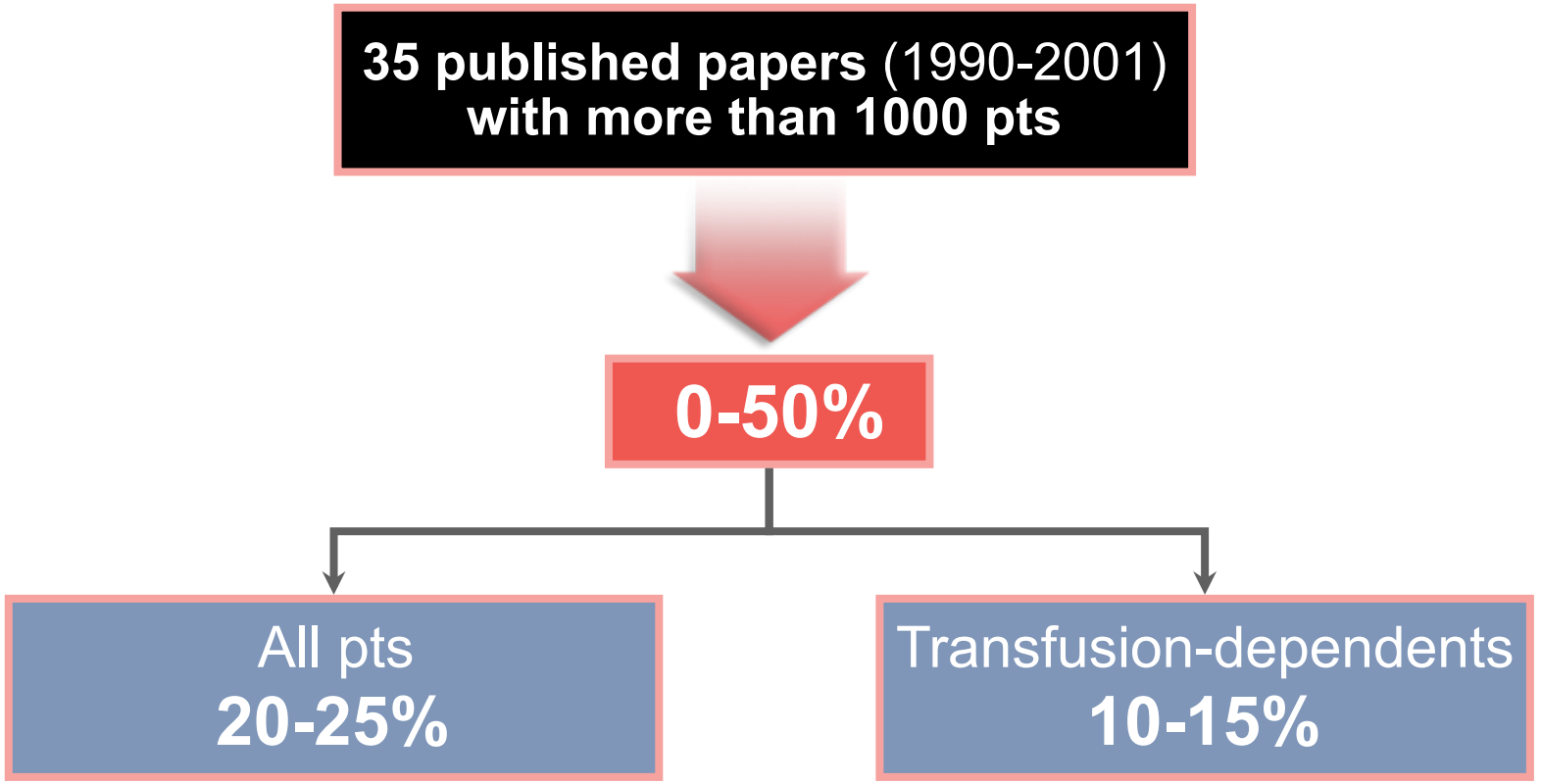
Epoetin alfa 150 IU/kg daily (n=44) or placebo (n=43)

- 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

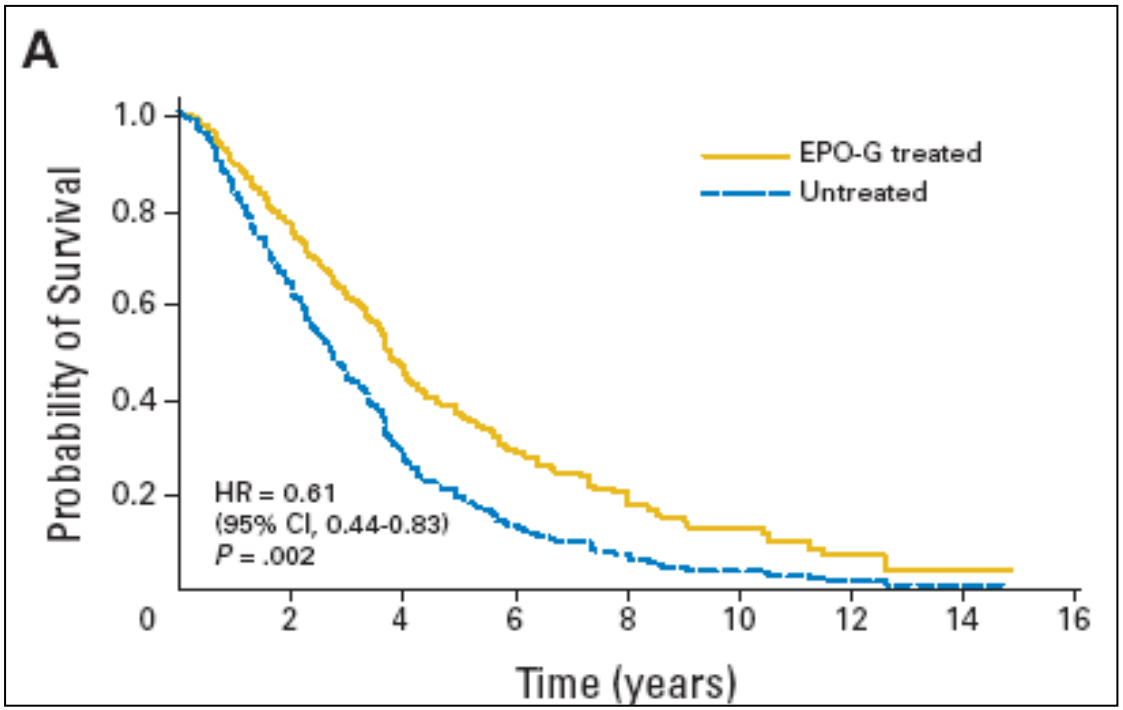
Rossi Ferrini et al, Br J Haematol 1998

Risposta all'EPO nei primi studi ('90)



Hellstrom-Lindberg et al. Semin Hematol 2002

terapia con ESAs: impatto sulla sopravvivenza



Jadersten et al, JCO 2008

Pt treated with EPO+G-CSF

for 12-18 months

(n=121)

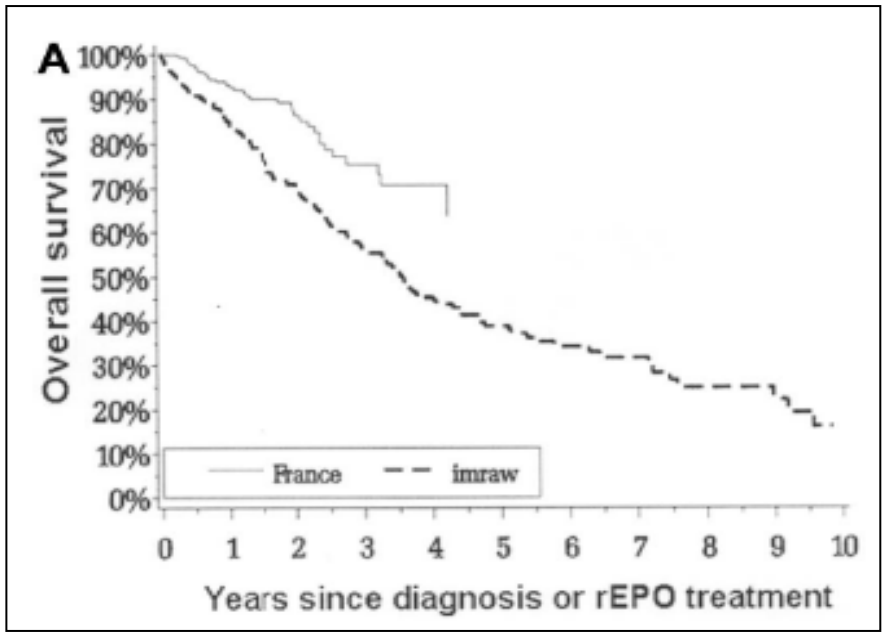
Pt Not treated

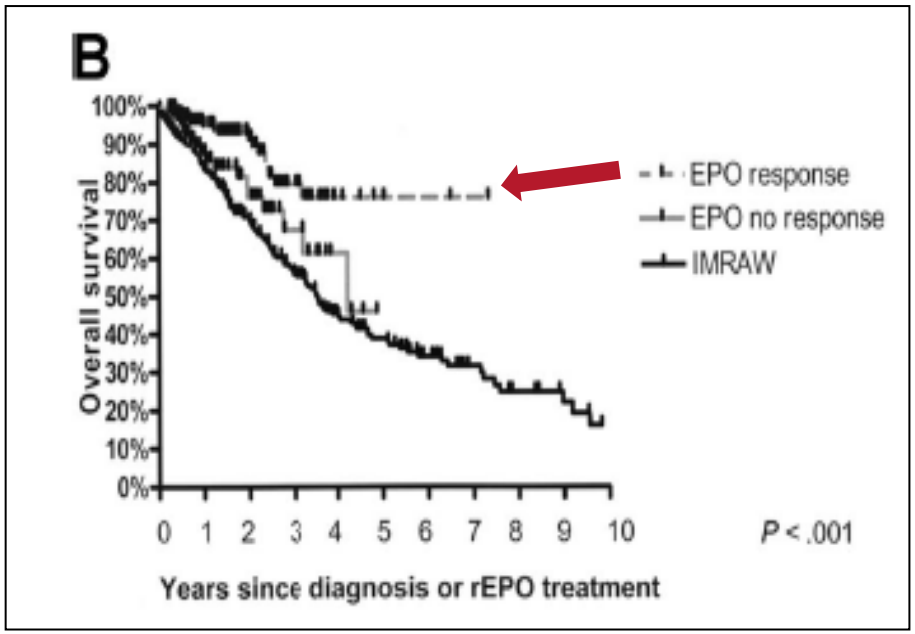
(n=237)

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

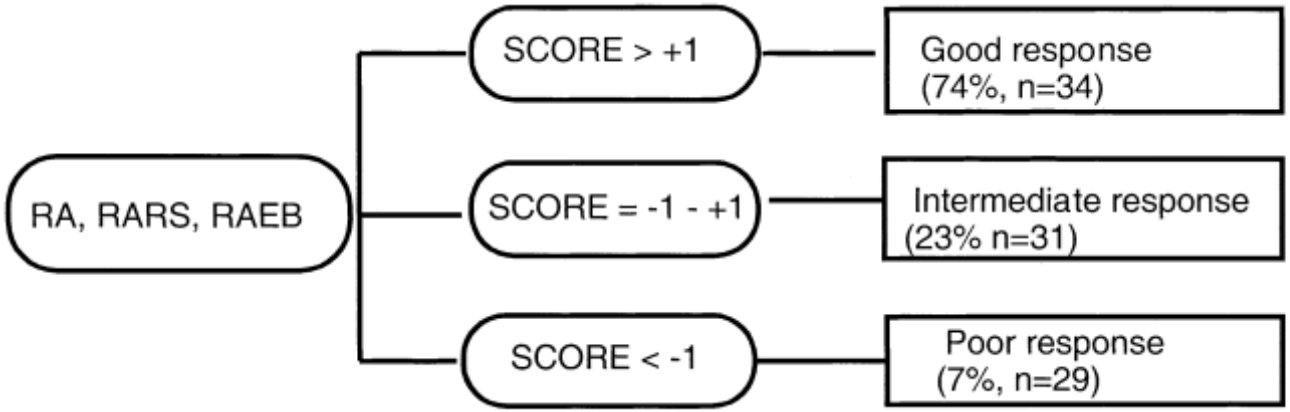
HR: 0.43 [CI 95% 0.25-0.72]

The advantage in survival is limited to patients responding to rEPO

Park S. et al, Blood 2008

Valutazione predittiva di risposta ad ESAs

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

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

"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

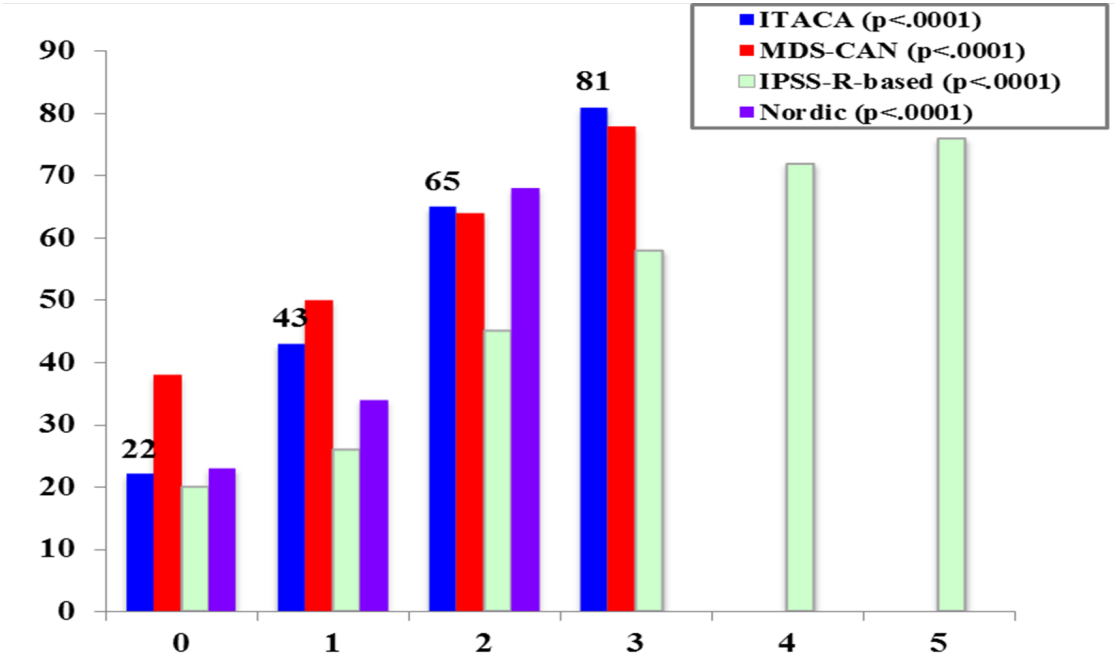
“EPO transatlantic venture ”
To validate Canadian ESA Score using FISM and GROM Cases

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

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

Le mutazioni somatiche sono predittive di risposta nelle MDS a basso rischio

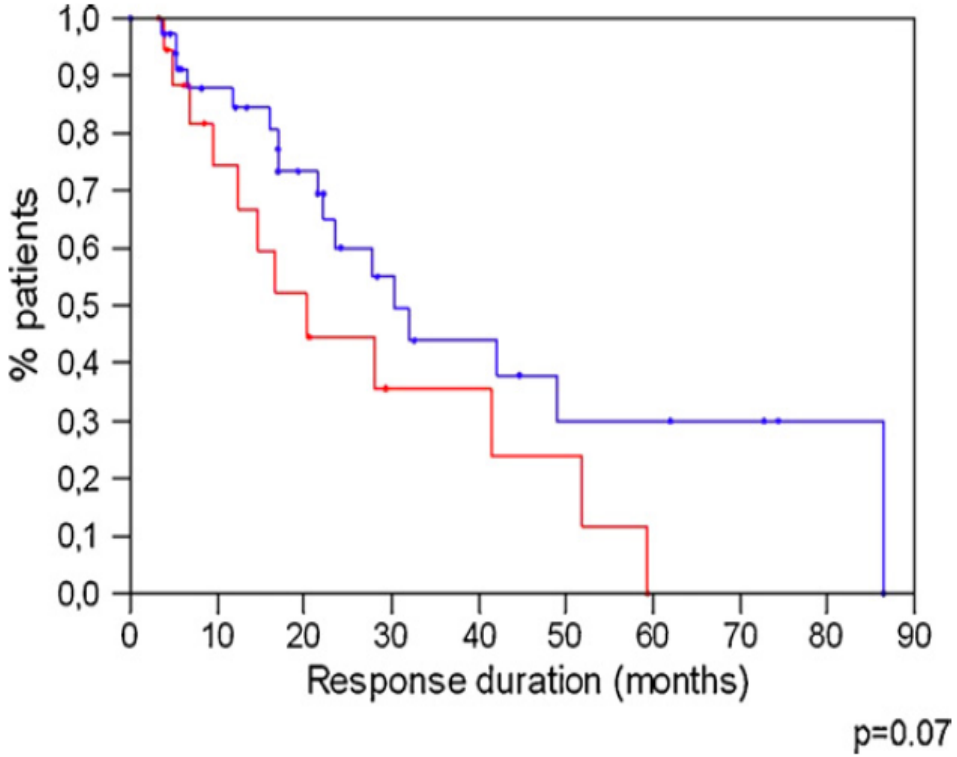
>2 somatic mutations predict for no response to ESAs in LR-MDS

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

Avvio precoce del trattamento con Epo e durata della risposta



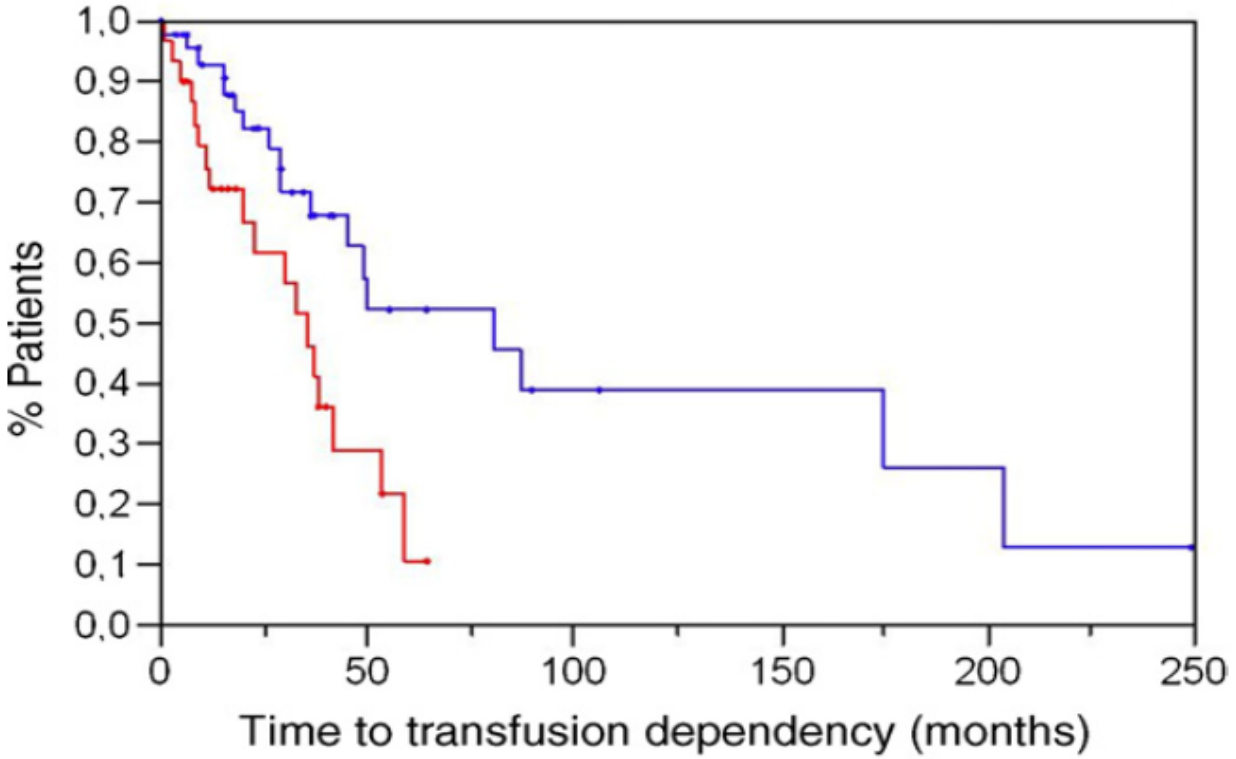
- Durata risposta media: 28.2 mesi
- **Early onset con ESA vs Late onset con ESA: 30 mesi vs 20 mesi (p=0.07)**

All' analisi multivariata i fattori che *influenzano la durata della risposta* sono:

- **Early onset con ESA (p=0.01)**
- Bassi livelli epo sierica (p=0.04)
- RCMD-RS (p=0.03)

Park, Leukemia Research 2010

Avvio precoce del trattamento con Epo e tempo alla dipendenza trasfusionale



Tempo medio alla dipendenza trasfusionale ***Early onset*** ***ESA vs*** ***Late onset*** ESA:

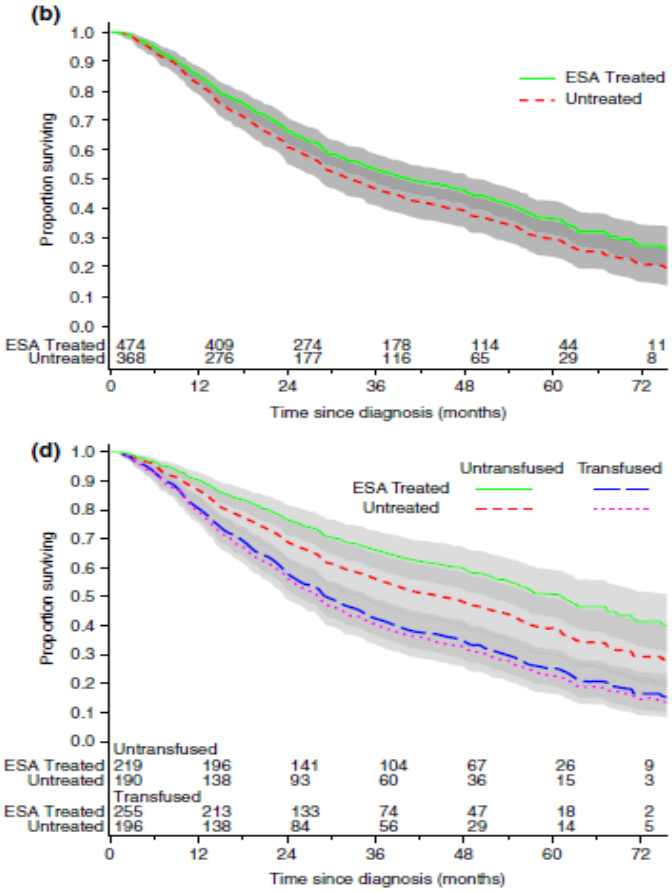
80 mesi vs 35 mesi (p=0.007)

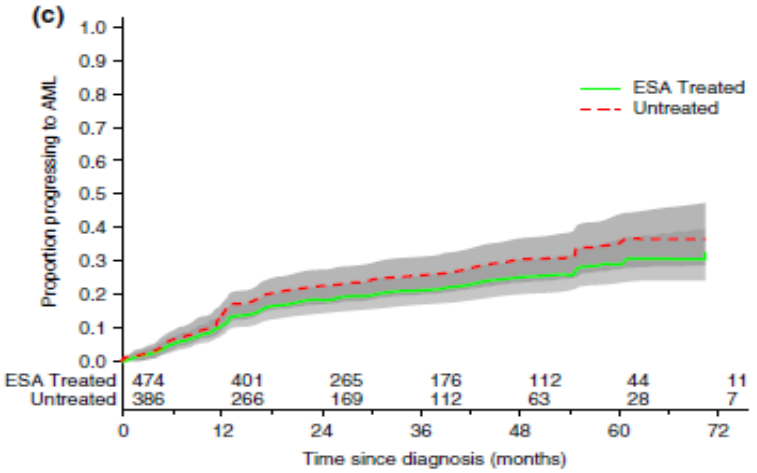
Park, Leukemia Research 2010

Original Article | Journal of INTERNAL MEDICINE
doi: 10.1111/joim.12579

Erythropoiesis-stimulating agents significantly delay the onset of a regular transfusion need in nontransfused patients with lower-risk myelodysplastic syndrome

H. K. G. Garelius[1], W. T. Johnston[2], A. G. Smith[2], S. Park[3], L. de Swart[4], P. Fenaux[5], A. Symeonidis[6], G. Sanz[7], J. Cermák[8], R. Stauder[9], L. Malcovati[10], M. Mittelman[11], A. A. van de Loosdrecht[12], C. J. van Marrewijk[4], D. Bowen[13], S. Crouch[2], T. J. M. de Witte[14] & E. Hellström-Lindberg[15]





- 539 patients
- median time to first post-ESA treatment transfusion was 6.1 months (IQR: 4.3-15.9 months) in transfused pts before ESA treatment vs 23.3 months (IQR: 7.0-47.8 months) in patients without prior transfusions (HR 2.4, 95% CI: 1.7-3.3, P < 0.0001).
- Responding patients had a better prognosis in terms of a lower risk of death (HR 0.65, 95% CI: 0.45-0.893, P = 0.018),
- there was no significant effect on the risk of progression to AML (HR 0.71, 95% CI: 0.39-1.29, P = 0.27).

Garelius et al., 2017J Intern Med

Effetti del prolungamento della terapia

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?

Meta-analysis of erythroid response to EPO alpha

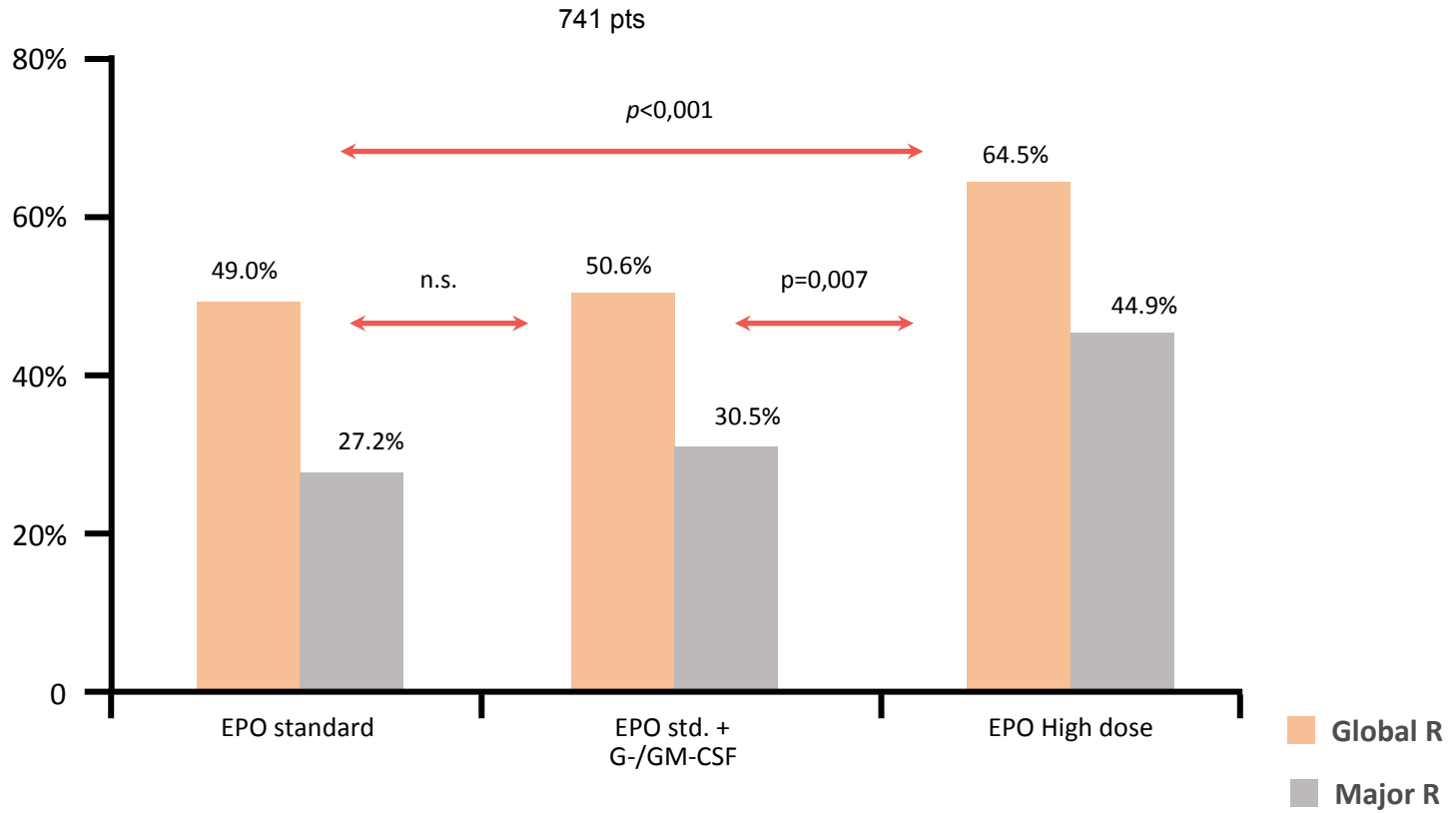
Acccording to EPO alpha dosage

•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

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)

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

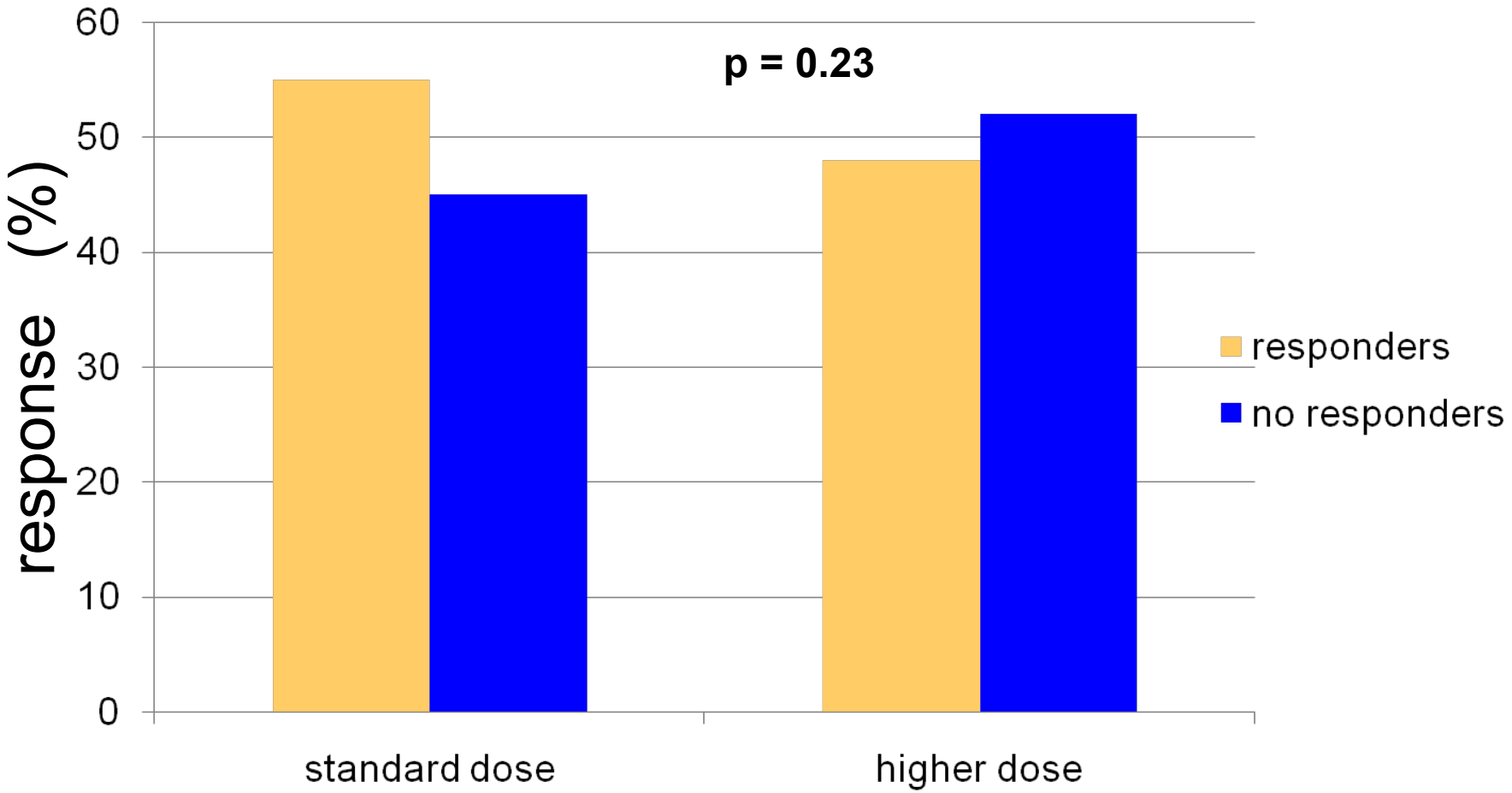
Balleari et al, ASH 2016 abstr 1387

Higher Versus Standard EPO Doses in MDS

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

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

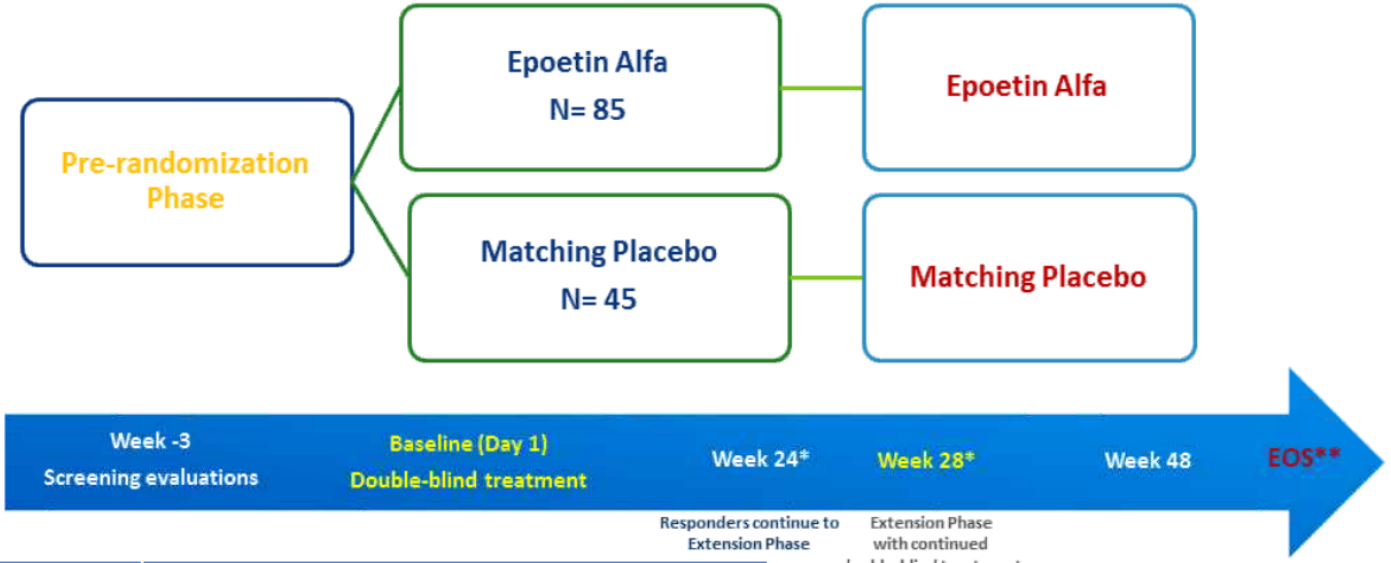
Erythroid response to EPO



Balleari et al, ASH 2016 abstr 1387

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

Primary Endpoint IWG 2006 ER by Response Review Committee

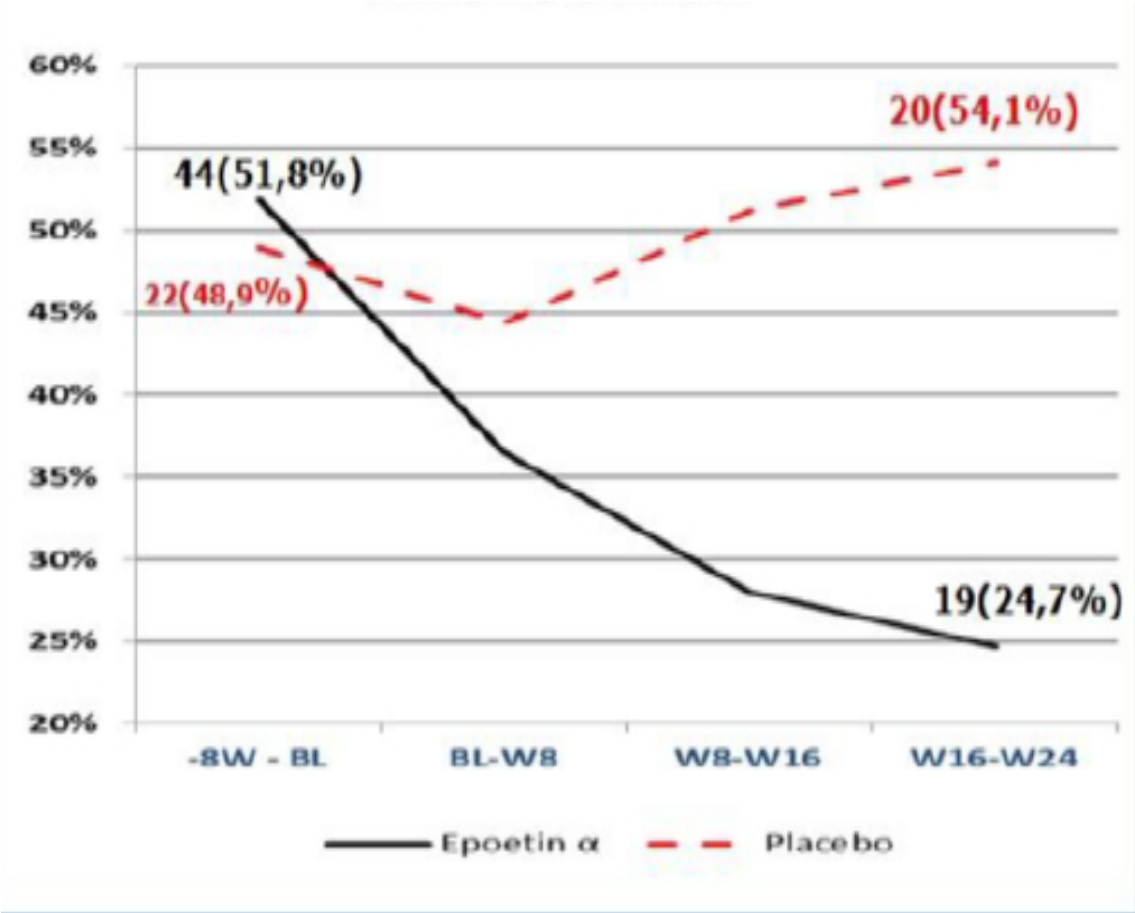
Epoetin alfa MDS
(EPOANE3021 Study)

	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.

Secondary Endpoint
% of patients receiving transfusions

Epoetin alfa MDS
(EPOANE3021 Study)



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*

Epo zeta in MDS e in MDS/MPN

Studio osservazionale, retrospettivo, multicentrico

- **80 pazienti (età mediana: 76 anni)**
- 40.000 UI, alla settimana in 70 pz (87.5%).
- 30.000 UI, alla settimana in 4 pz (5%)
- 80.000 UI, alla settimana in 6 pz (7.5%)

30/80 pz trasfusione dipendenti **(37.5%), con fabbisogno trasfusionale mediano di 2 U/mese**

➡ **Il 79% dei pazienti(50/63) aveva livelli di EPO sierica <200 U/L.**
valore mediano di EPO sierica = 60 U/L.

➡ **Nel 40% dei pz (33/80) è stato necessario aumentare il dosaggio di epo a 80.000 U/L.**

→ **OS mediana: 64 mesi**

➡ *Differenza stat. significativa (p=0.02) tra responder vs non-responders (**not reached vs 56 mesi)***

Pellizzari et al. 2015. *International Symposium on MDS, 2015*

Refrattarietà – perdita di risposta ad ESAs

Non più del 50 – 70% dei pazienti , compresi quelli con buona probabilità di risposta, risponde nella realtà

La durata media della risposta è di circa 1,5 – 2 anni

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

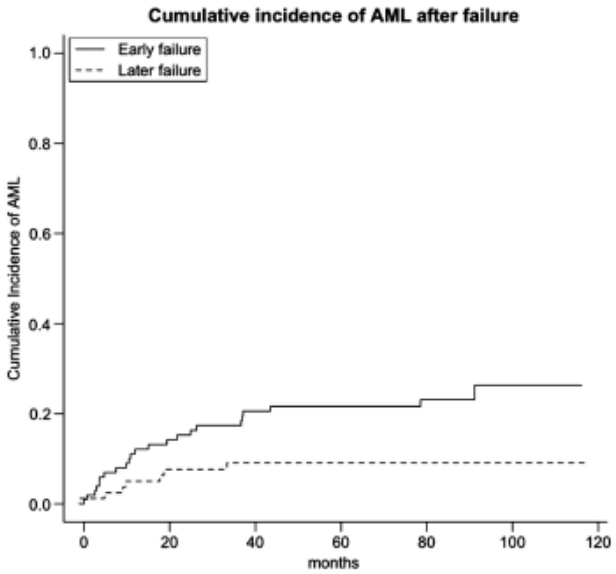


Figure 1. Cumulative incidence of AML after failure in patients with early and later failure.

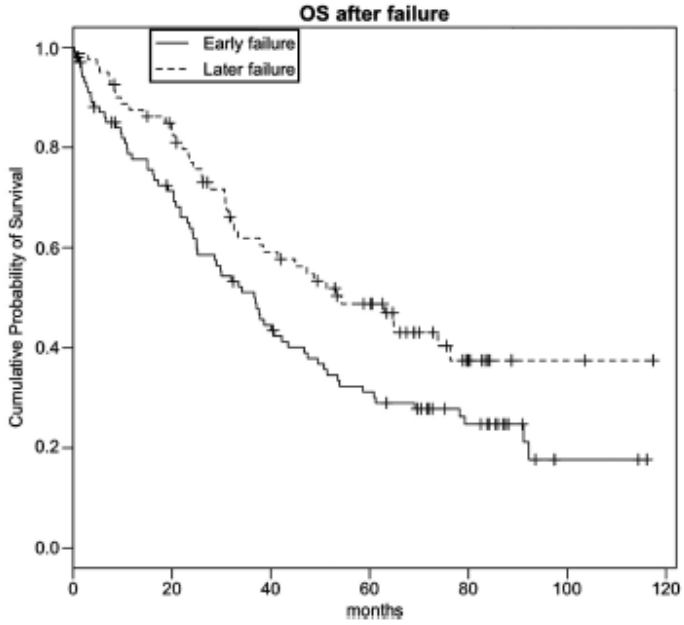


Figure 2. OS after failure in patients with early and later failure.

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

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

Median OS
Refractory 52.2 months
Relapsing 60.4 months

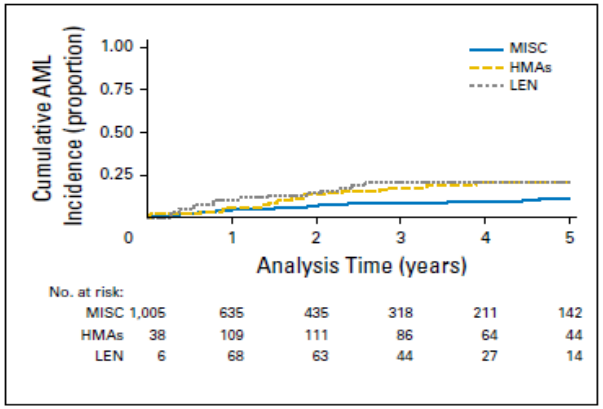


Fig 2. Simon-Makuch model (with treatment as a time-dependent variable) of cumulative acute myeloid leukemia (AML) incidence in patients receiving lenalidomide (LEN) or hypomethylating agents (HMAs) versus other treatments or RBC transfusion only (MISC) as second-line treatment (from erythropoiesis-stimulating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

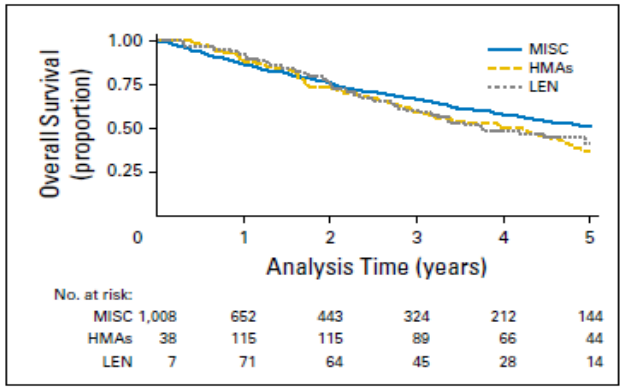


Fig 3. Simon-Makuch model (with treatment as a time-dependent variable) of overall survival in patients receiving lenalidomide (LEN) or hypomethylating agents (HMAs) at second-line treatment versus other treatments or RBC transfusion only (MISC; from erythropoiesis-stimulating agent failure; $P = 0.21$).

Park S et al, JCO 2017

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

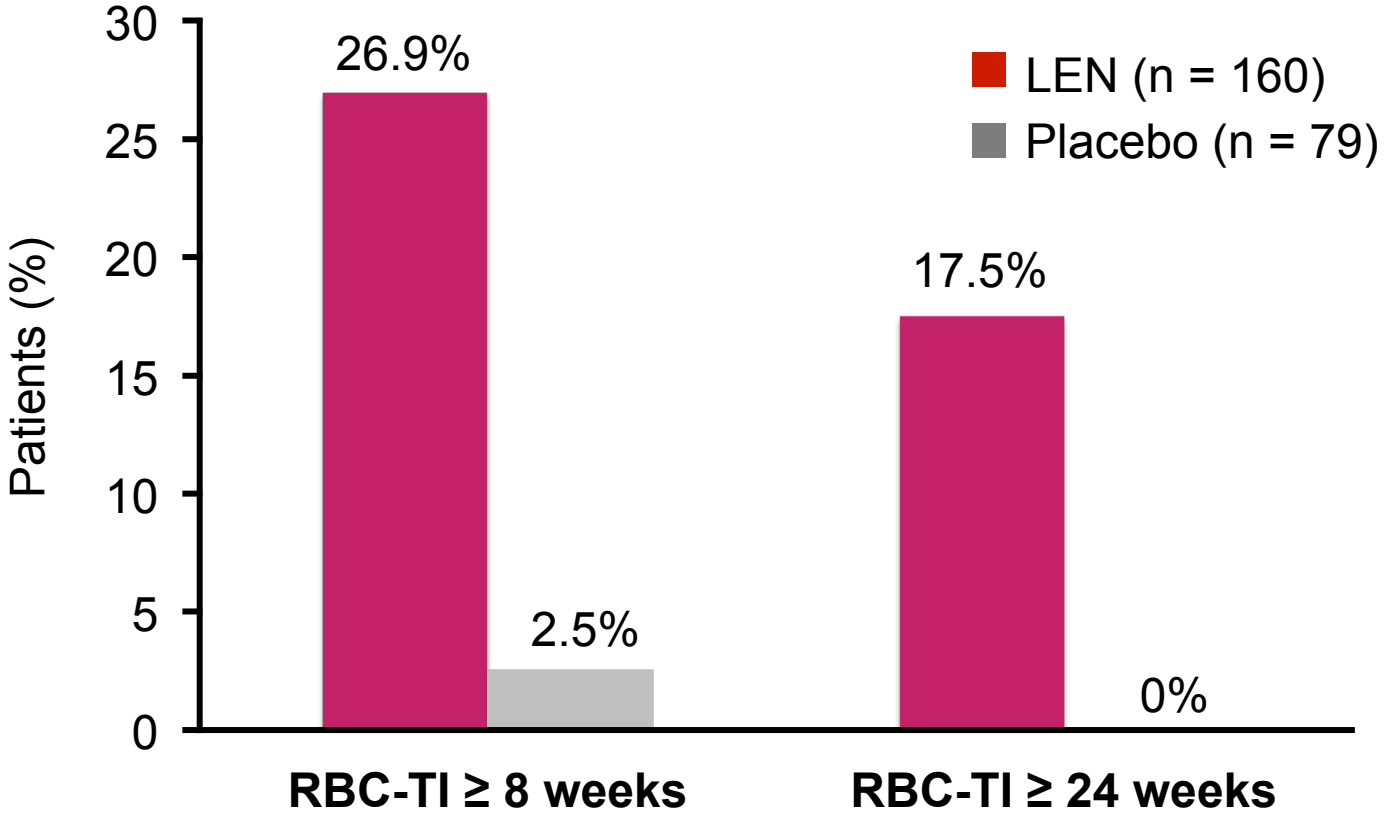
Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents

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)

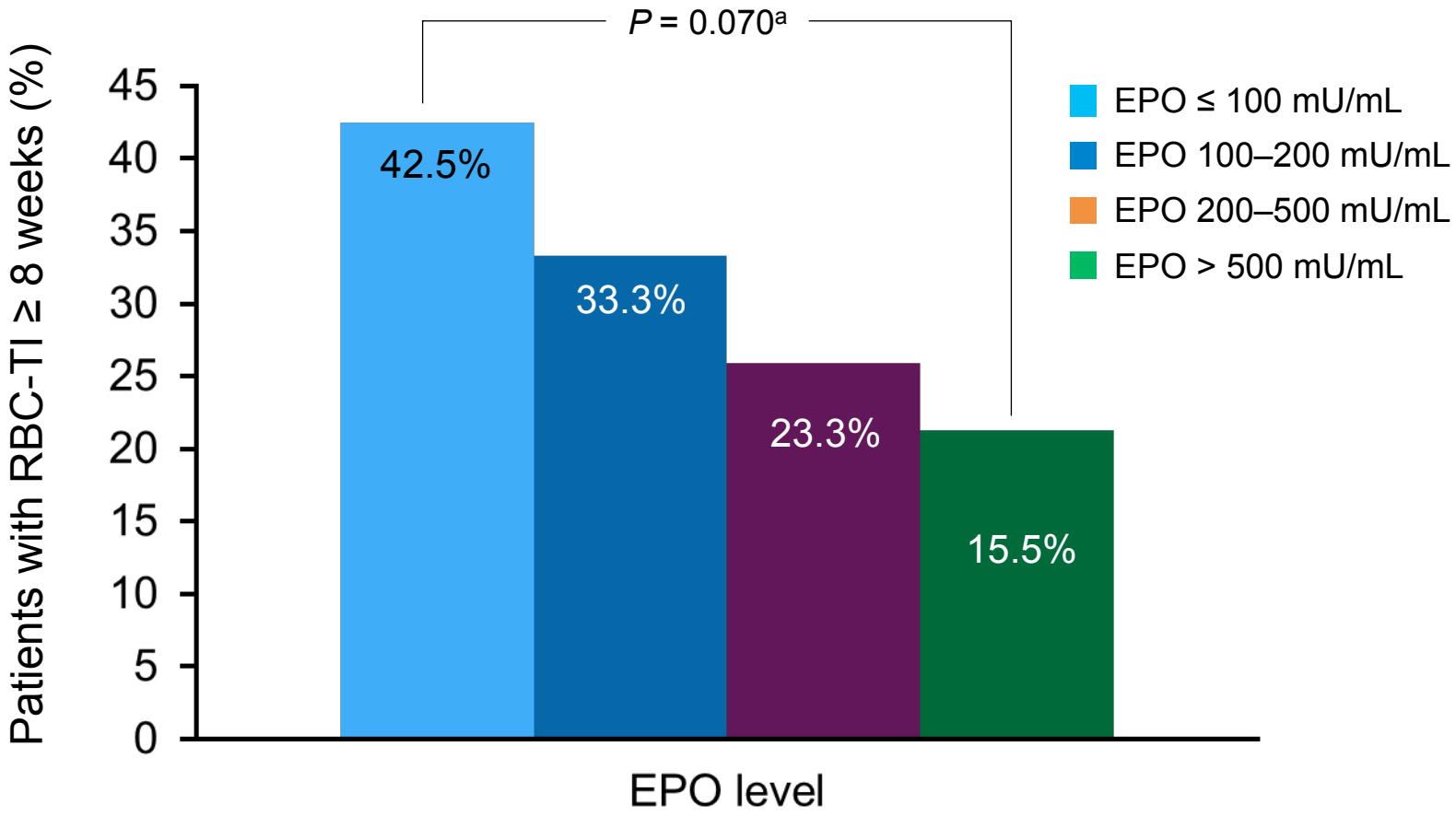
Treatment: Lenalidomide 10 mg/day/os on days 1-28
(5 mg if ClCr 40-60 ml/min)

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

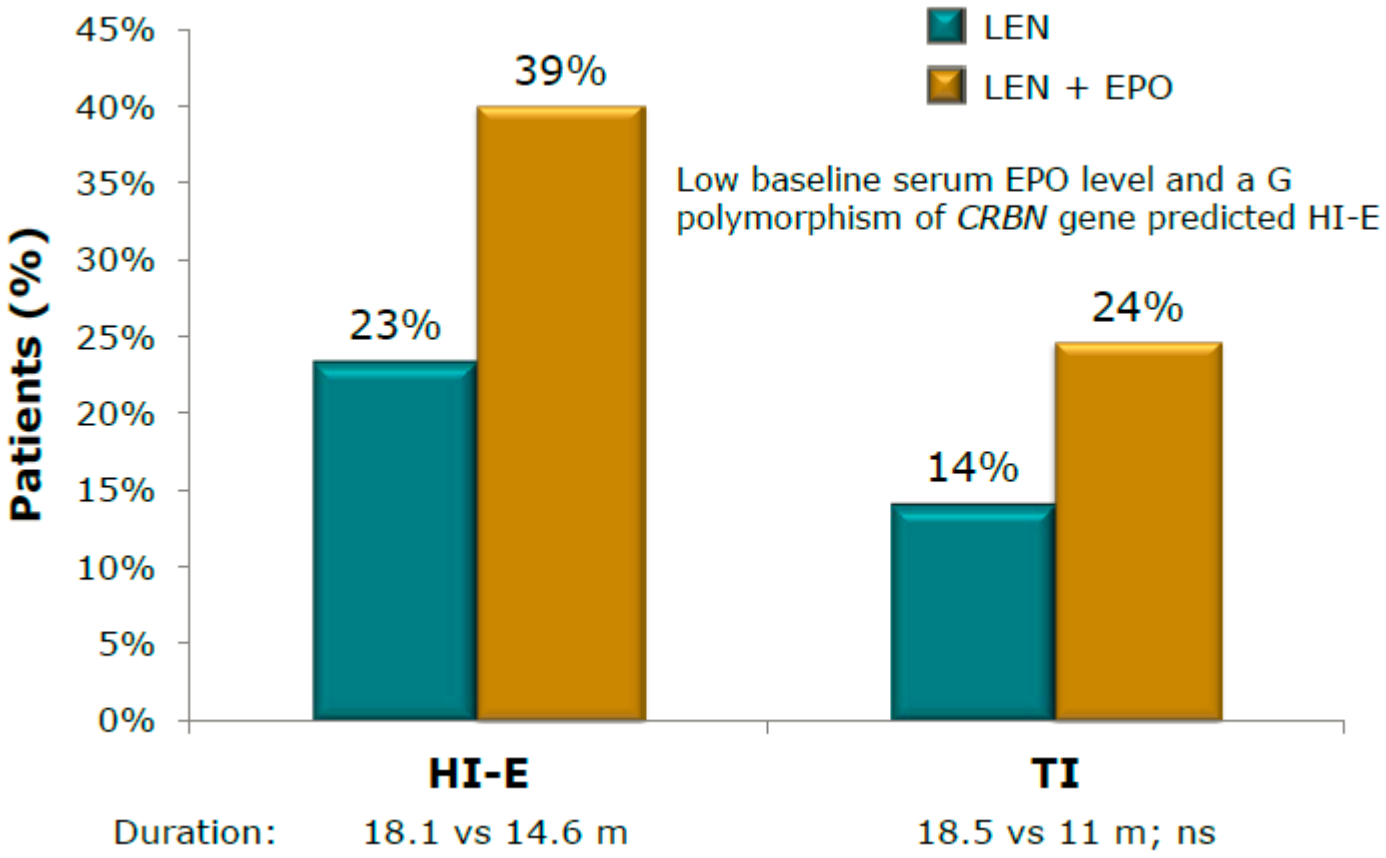
MDS-005: phase III trial of LEN vs placebo in patients with lower-risk RBC-TD non-del(5q) MDS



[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

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

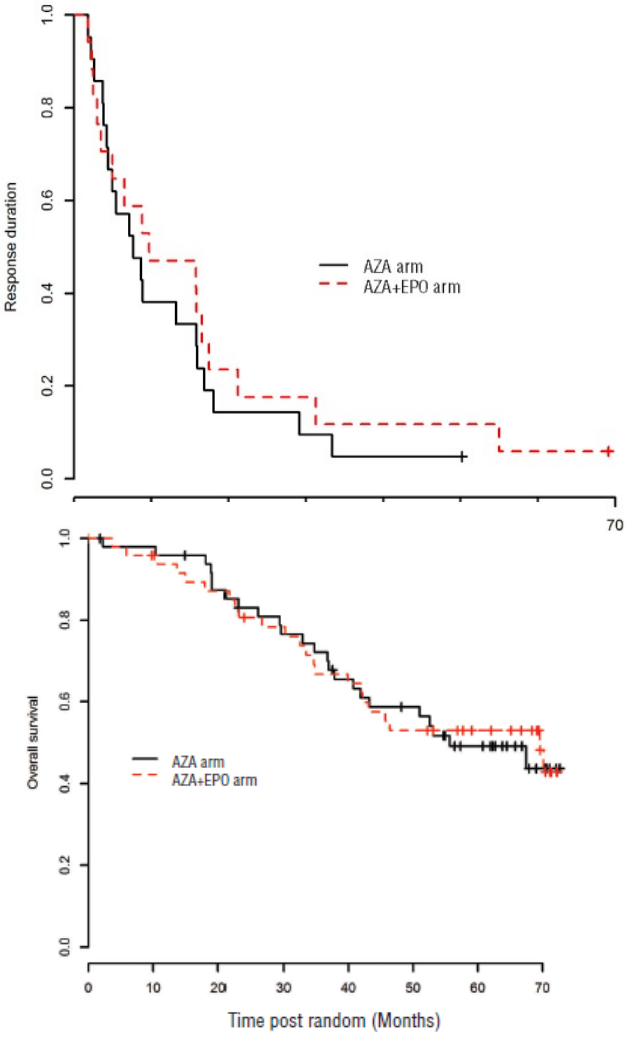
- 77% of responses occurred within the first 6 cycles
- Median duration of response = 6 months
- Projected OS at 30 months = 70.8% (median follow-up of 15 months)
- Projected OS was higher in responders than non-responders (93.9 vs 53.8%; p<0.0014)

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

CONCLUSIONI

Il trattamento dell'anemia deve essere precoce ed efficiente

La terapia trasfusionale va basata sulle condizioni del paziente e non sulle condizioni degli analizzatori ematologici e delle strutture deputate ad effettuarla

La terapia con Epo va iniziata non appena le condizioni la rendano necessaria e protratta per un tempo adeguato

…speriamo di non avere fattori predittivi sfavorevoli per risposta ad Epo….

…capisco che ho bisogno di una trasfusione quando gli scalini di casa diventano più alti….