Attualità nel trattamento dell'anemia

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SISTEMA SANITARIO REGIONALE
ASL ROMA 2

Incidence and clinical relevance of anemia in MDS

Anemia is present in 2/3 patients at diagnosis and in almost all during the MDS course. It is responsable for main morbidity and mortality

Cognitive impairment, falls, reduced QoL….

Anemia associated with cardiac remodeling and hypertrophy

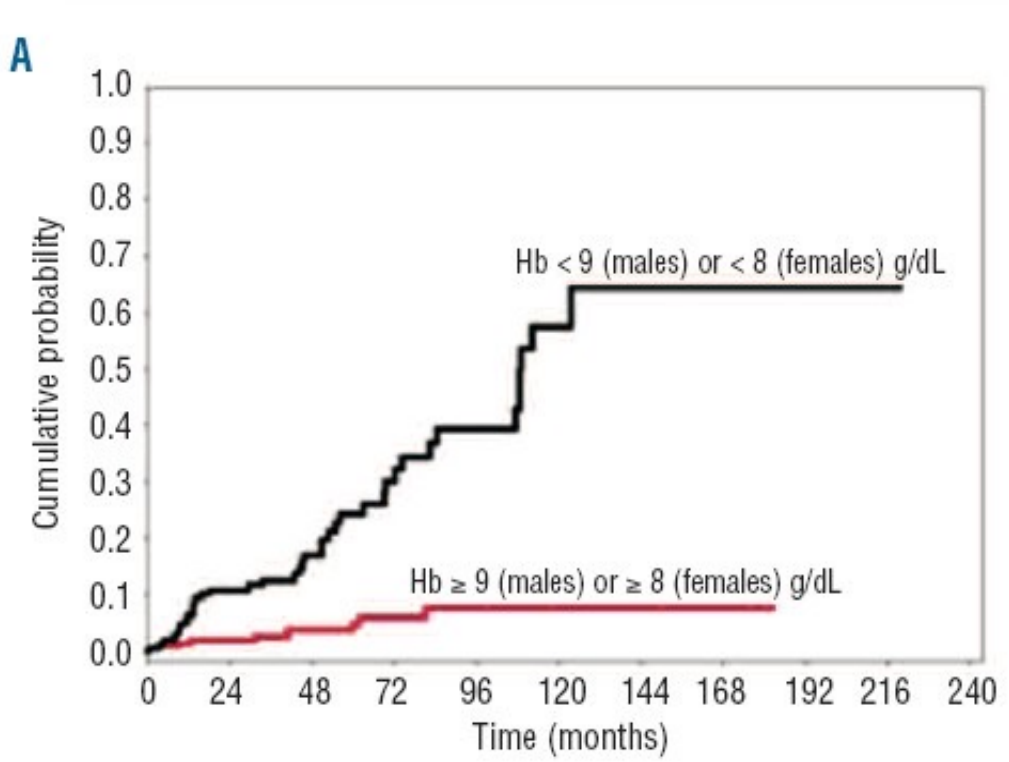
92% of transfusion--dependent vs 48% transfusion independent patients (*P* = 0.017)

Each 1 g/dL Hb increase predicted a 49% reduction in risk of cardiac remodeling (*P* < 0.0001)

…for Hb <10.7 g/dL, QoL was poorer…

Oliva EN, et al. Leuk Res 2005

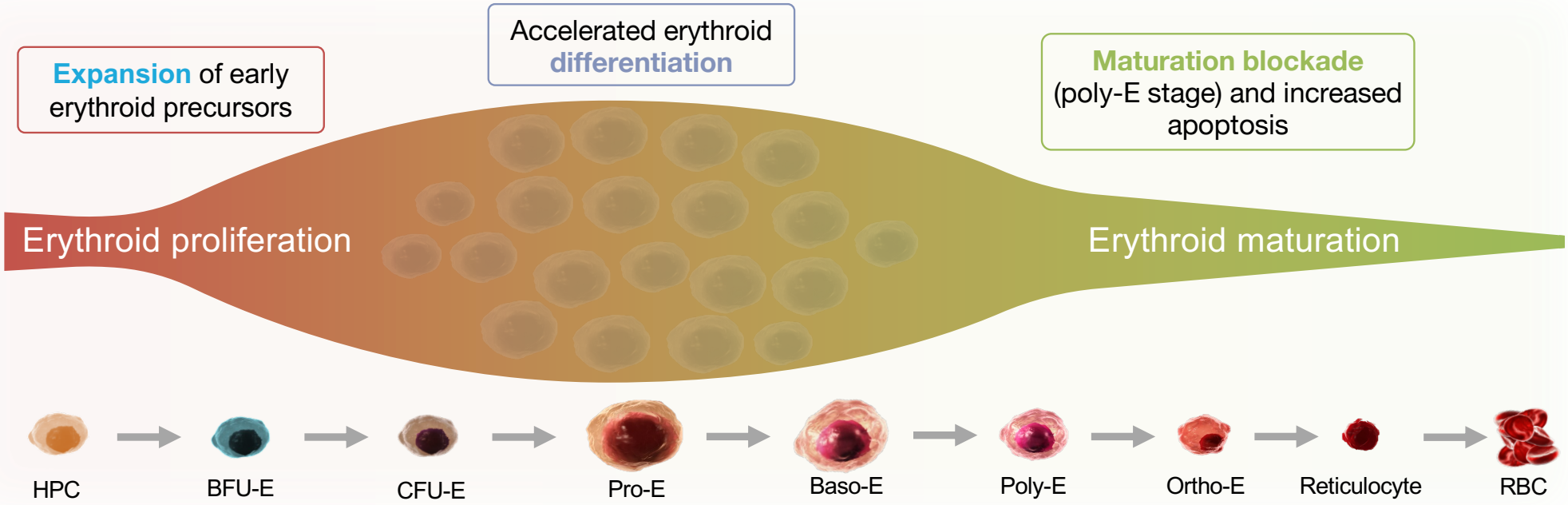
Relazione tra grado di anemia e comorbidità e mortalità cardiaca



Malcovati et al, Hematologica 2011

Ineffective Erythropoiesis

Defects in erythropoiesis, as seen with MDS, may lead to accelerated differentiation and apoptosis of erythroid precursors, resulting in decreased RBC output



» 1. Zivot et al. *Mol Med* 2018;24:11. 2. Valent et al. Haematologica 2018;103:1593–603. 3. Nandakumar et al. Br J Haematol 2016;173:206-218. 4. Fontenay-Roupie et al. Br J Haematol 1999;106:464-73.

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], P Mary Cotes [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

Multicenter Italian Study

44 patients were assigned to epoetin alpha (150 U/kg/d s.c. for 8 weeks) and 43 to placebo arms…

14/38 evaluable patients responded to epoetin alpha versus 4/37 to placebo (P=0.007).

….60% of non-pretransfused patients responded to epoetin alpha.

Basal erythropoietin (Epo) serum levels > 200 mU/l predicted for a non-response.

rHuEpo was effective in the treatment of low-risk MDS.

RA subtype, no transfusions prior to rHuEpo, and low basal Epo levels

were associated with higher probability of response.

Italian Cooperative Study Group, *Rossi Ferrini et al, Br J Haematol 1998*

EPOANE ad hoc analysis

	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.*

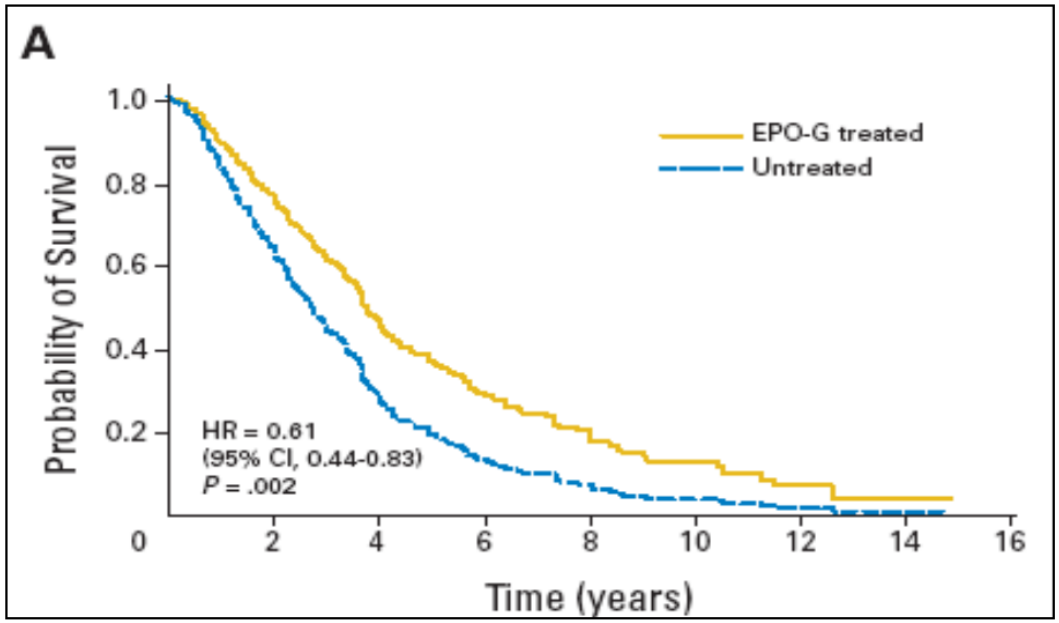
	Placebo	Epoetin Alfa
	45	85
Strata 1: Transfusion='No' and serum erythropoietin level <200 mU/mL	1 (5.0%)	18 (47.4%)
Strata 2: Transfusion='Yes' and serum erythropoietin level <200 mU/mL	1 (5.3%)	9 (27.3%)
Strata 3: Transfusion='No' and serum erythropoietin level ≥200 mU/mL	0	0
Strata 4: Transfusion='Yes' 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., Leukemia, 2018

Terapia con ESAs: impatto sulla sopravvivenza

Jadersten et al, JCO 2008



Pt treated with EPO+G-CSF

for 12-18 months

(n=121)

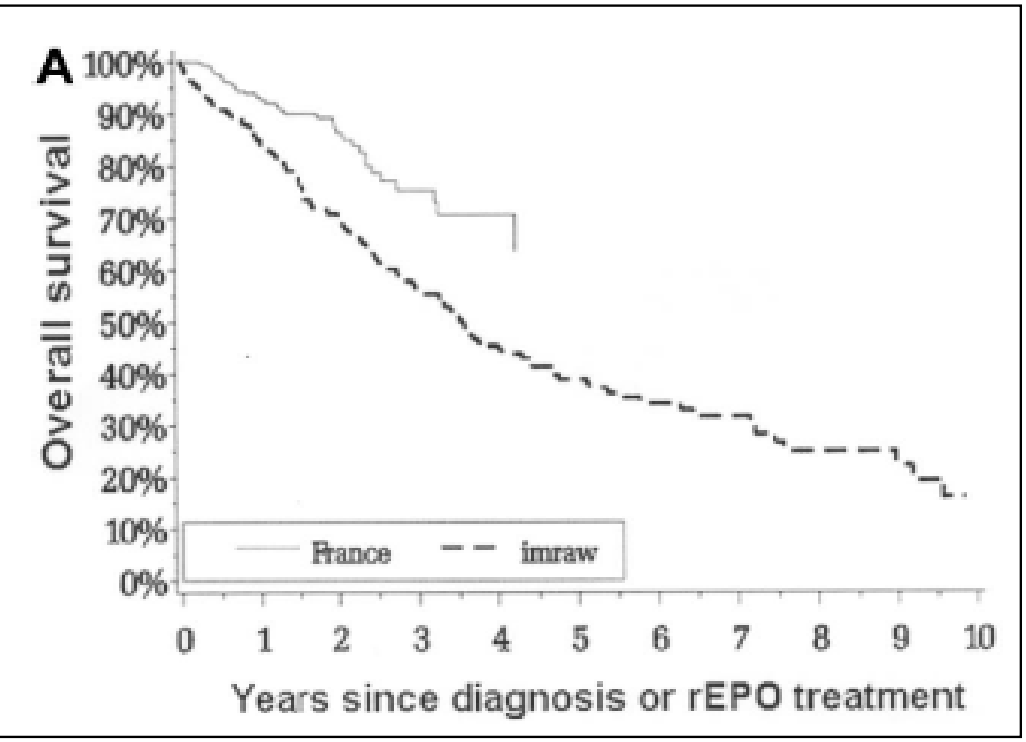
Pt Not treated

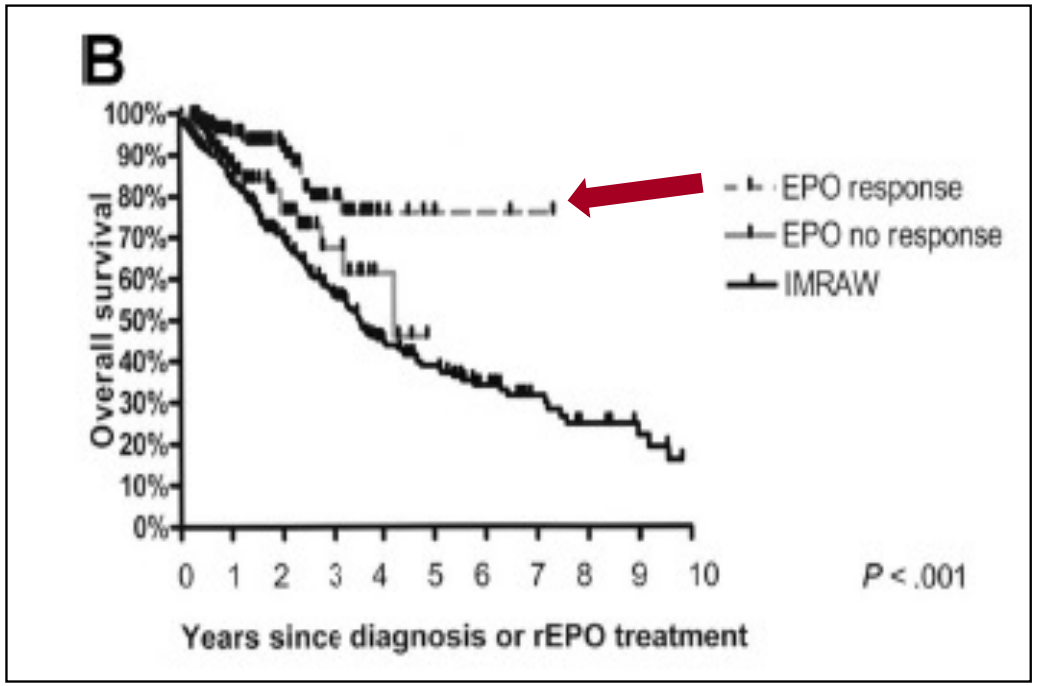
(n=237)

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

The first choice of treatment of anemic lower risk MDS patients should be ESAs…

…although used for decades,
are still not yet managed optimally…

Selection criteria

Optimal treatment doses

Periods of treatment

Esa failure

Santini V, Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):462-469.

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

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

15% di risposte

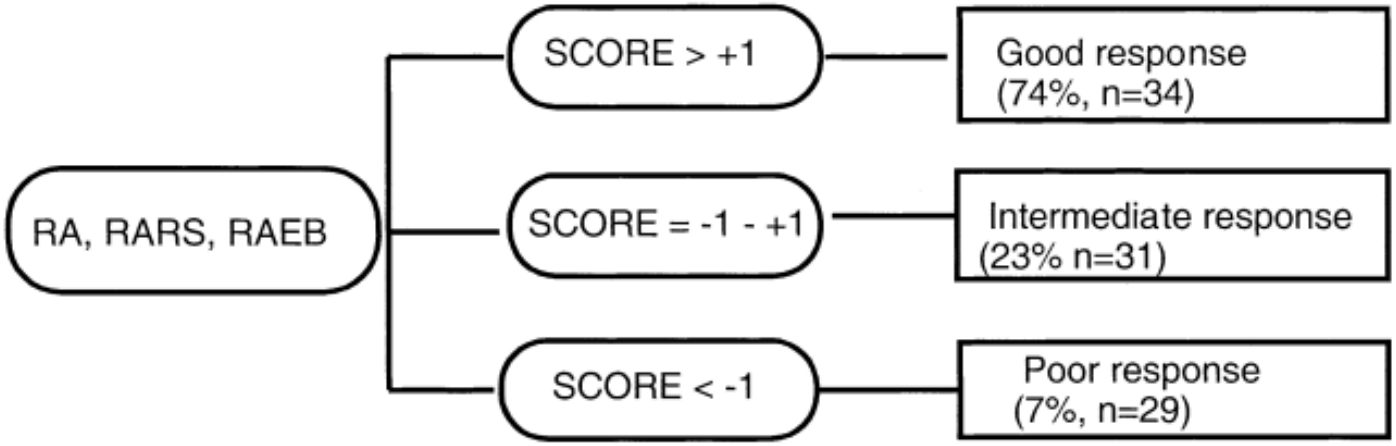
Pazienti SMD non selezionati.

>60% di risposte

Pazienti SMD selezionati per

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

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

Hellstrom-Lindberg et al. Br J Haematol 1997

"European" ESA score for predicting response to EPO

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

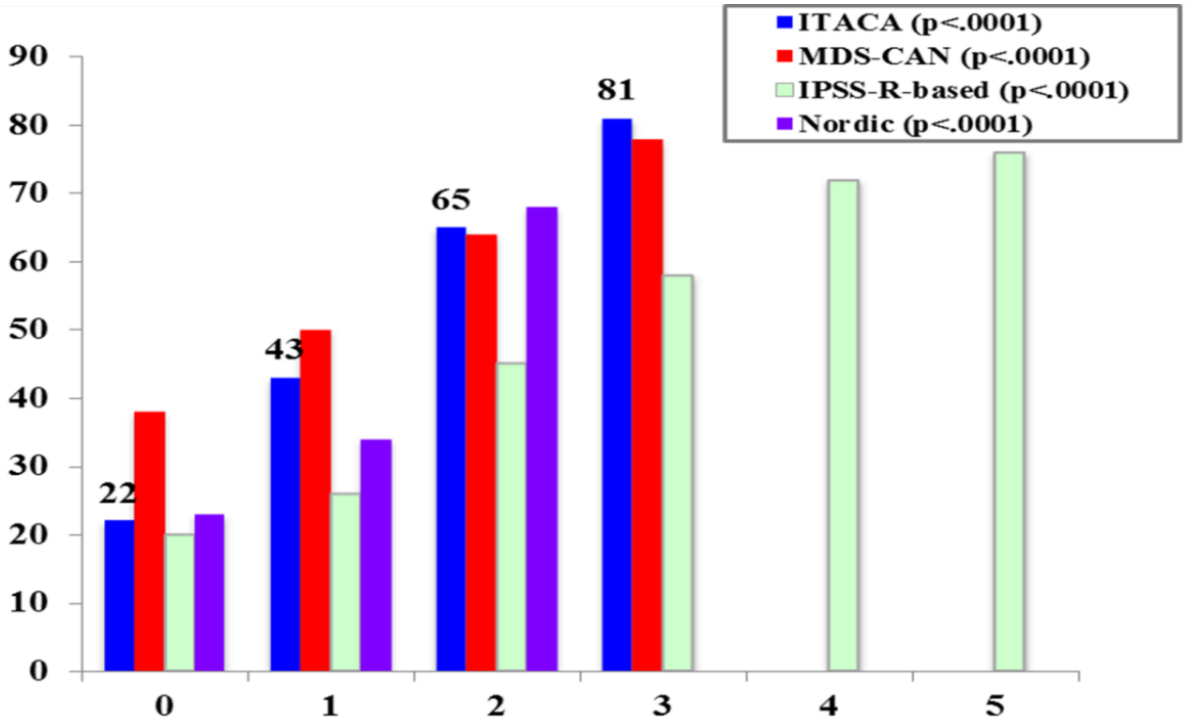
Score	Response Rate
0	85%
1	80%
2	64%
3	40%
>4	20%

Courtesy of Enrico Balleari

Santini V, et al. Blood. 2013.

ITACA: A New Validated International ESA-Response Score

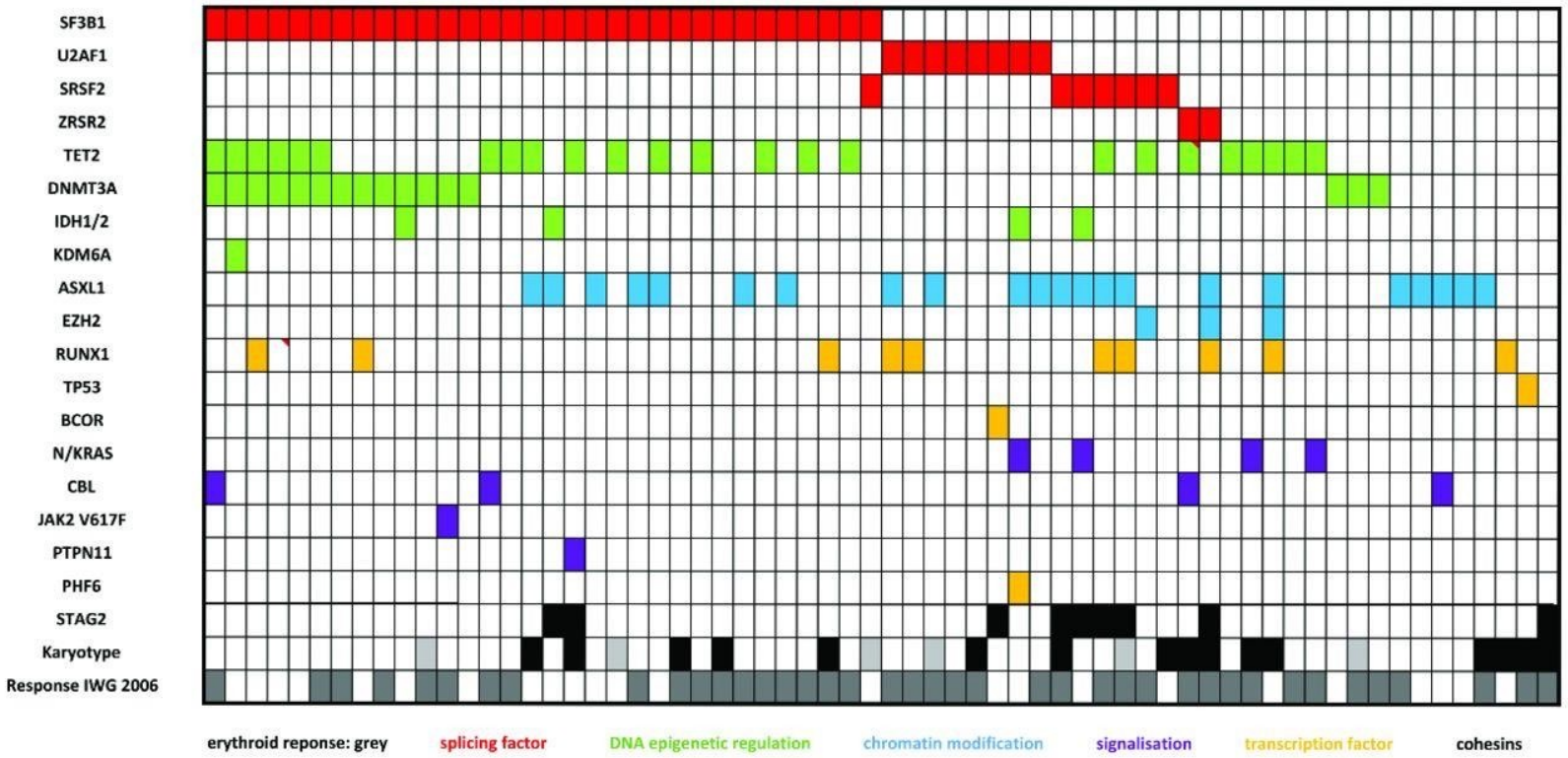
- **EPO**
  - > 100 = 0
  - < 100 = 1
- **Transfusion**
  - dependent =0
  - independent =1
- **IPSS**
  - INT-1 or Higher = 0
  - Low =1



- 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.

Buckstein et al. Am J Hematol 2017

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

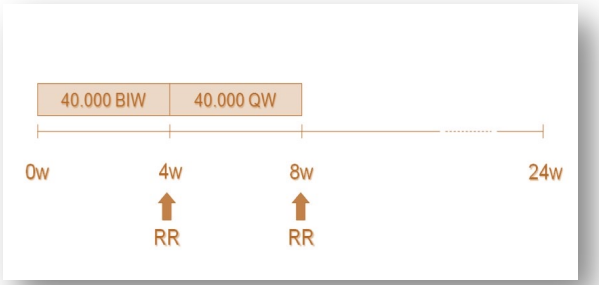


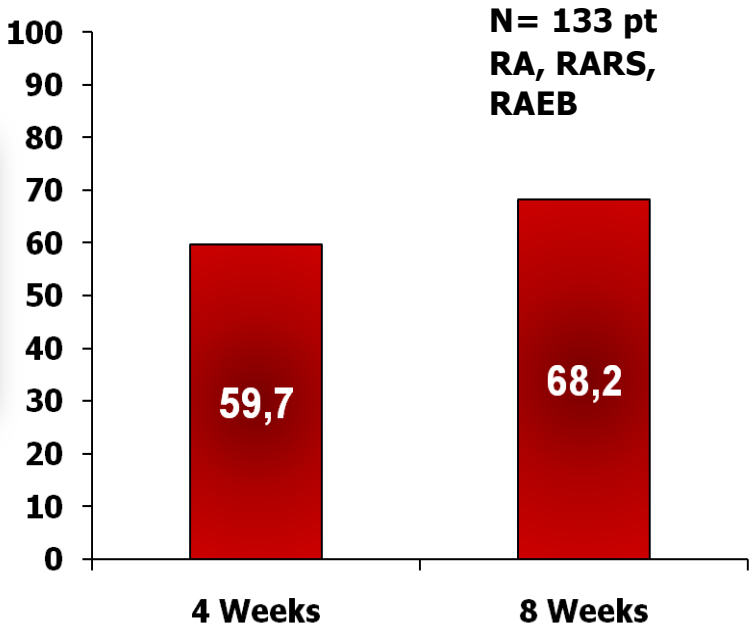
>2 somatic mutations predict for no response to ESAs in LR- MDS

≤ 2 mutations: 74% vs 46% >2 mutations (P=0.01)

Kosmider O et al, Haematologica 2016

Risposta ematologica Epo alfa: 40.000 UI BIW



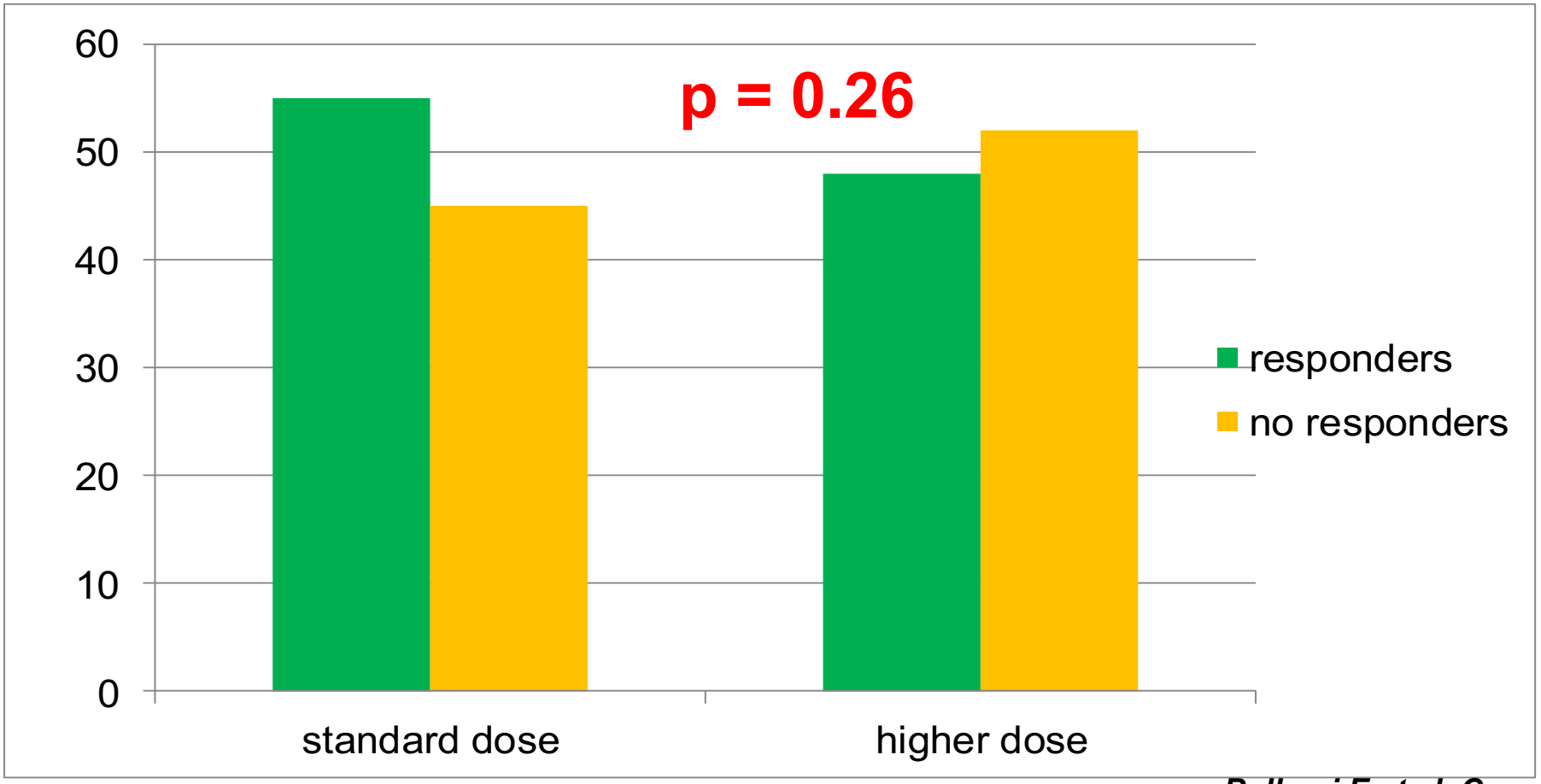


Epo alfa 80.000 UI: 68% di risposta

Aloe-Spiriti, Annals of Hematology 2005

Higher Versus Standard EPO Doses in MDS

Erythroid response to EPO



Balleari E et al, Cancer Medicine 2019

Higher Versus Standard EPO Doses in MDS

Overall survival of propensity-score matched patients according to rhEPO doses

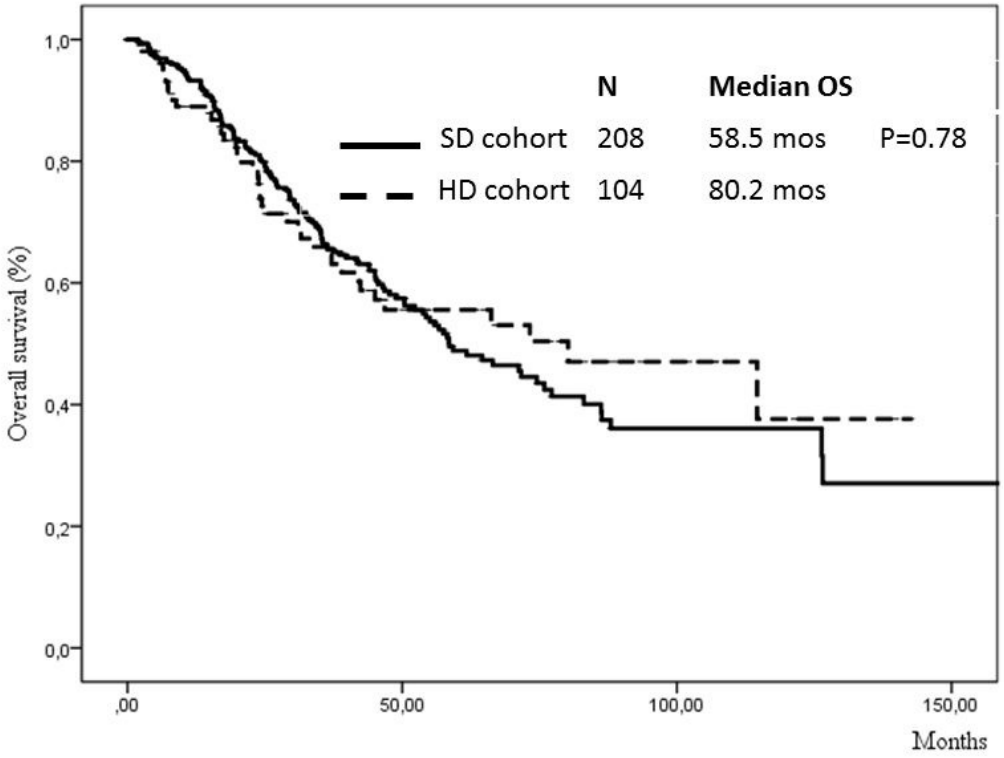


Figure 1

Balleari E et al, Cancer Medicine 2019

Response to EPO has a positive impact on both QoI and OS in MDS anemic pts;

However:

It is observed in no more than ≈ 50-70%; the median duration of response is ≈ 1,5 - 2 y.

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

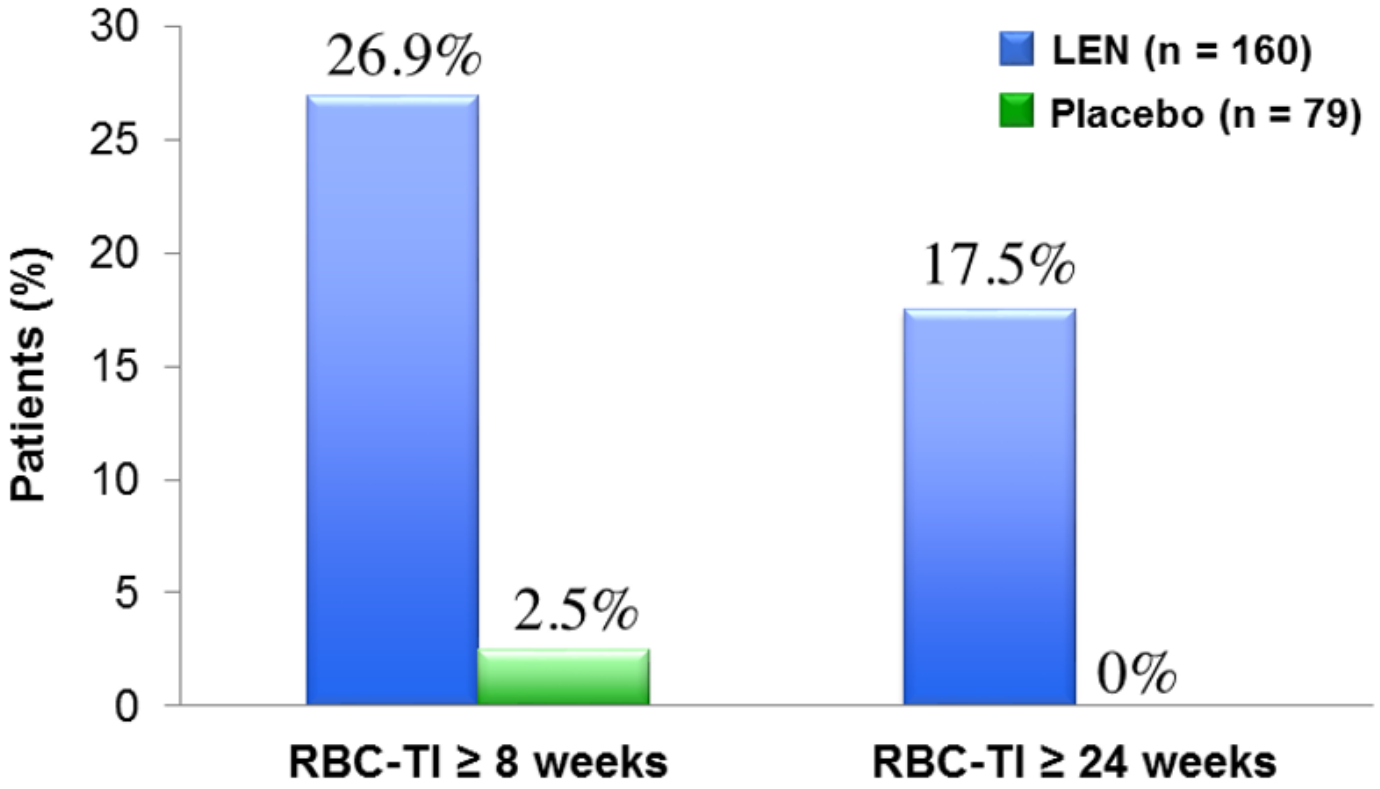
1147 (67,6%) % pts with failure
-654 refractory
-494 relapsing

2nd line treatment

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

Park S et al, JCO 2017

LENALIDOMIDE IN MDS NON DEL5q: PROTOCOLLO MDS-005



Santini V et al. JCO 2016;34:2988-96

Luspatercept for lower risk MDS: the phase 2 study

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Summary

Background Myelodysplastic syndromes are characterised by ineffective erythropoiesis. Luspatercept (ACE-536) is a novel fusion protein that blocks transforming growth factor beta (TGF-β) superfamily inhibitors of erythropoiesis, giving rise to a promising new investigative therapy. We aimed to assess the safety and efficacy of luspatercept in patients with anaemia due to lower-risk myelodysplastic syndromes.

Methods In this phase 2, multicentre, open-label, dose-finding study (PACE-MDS), with long-term extension, eligible patients were aged 18 years or older, had International Prognostic Scoring System-defined low or intermediate-1 risk myelodysplastic syndromes or non-proliferative chronic myelomonocytic leukaemia (white blood cell count <13 000/μL), and had anaemia with or without red blood cell transfusion support. Enrolled patients were classified as having low transfusion burden, defined as requiring less than 4 red blood cell units in the 8 weeks before treatment

29/42 (69%) HI-E in RARS

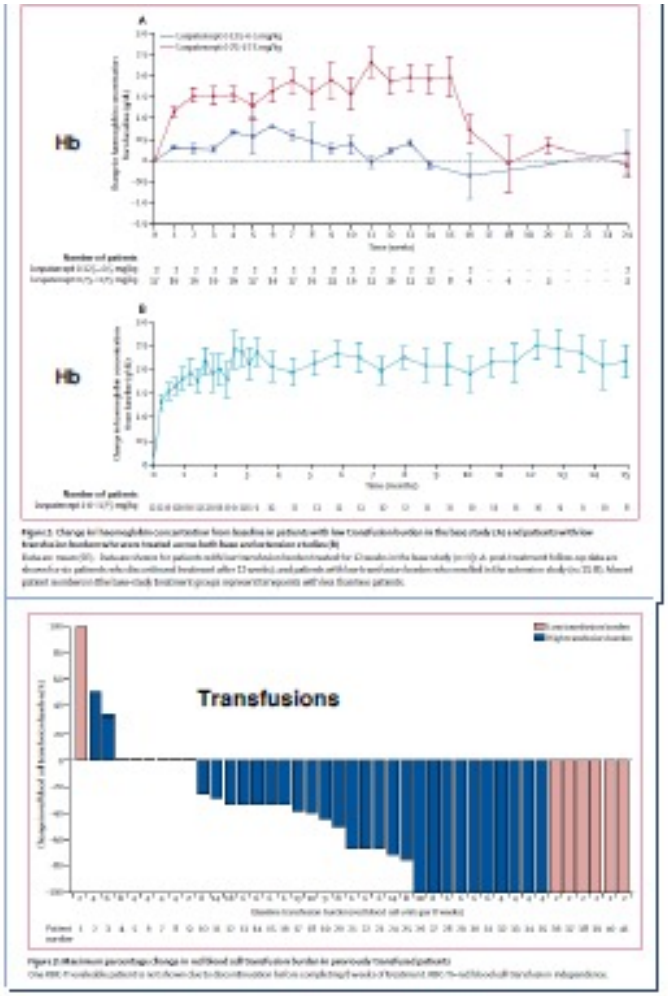
24/31 (77%) HI-E with SF3B1 mutation

proportion of patients achieving modified International Working Group-defined haematological improvement-erythroid (HI-E), defined as a haemoglobin concentration increase of 1·5 g/dL or higher from baseline for 14 days or longer in low transfusion burden patients, and a reduction in red blood cell transfusions of 4 or more red blood cell units or a 50% or higher reduction in red blood cell units over 8 weeks versus pre-treatment transfusion burden in high transfusion burden patients. Patient data were subcategorised by: luspatercept dose concentration (0·125–0·5 mg/kg vs 0·75–1·75 mg/kg); pre-study transfusion burden (high transfusion burden vs low transfusion burden, defined as ≥4 vs <4 red blood cell units per 8 weeks); pre-study serum erythropoietin concentration (≤200 U/L, 200–500 U/L, and >500 U/L); presence of 15% or more ring sideroblasts; and presence of SF3B1 mutations. Efficacy analyses were carried out on the efficacy evaluable and intention-to-treat populations. This trial is currently ongoing. This study is registered with ClinicalTrials.gov, numbers NCT01749956 and NCT02631083.

Findings Between Jan 21, 2013, and Feb 12, 2015, 58 patients with myelodysplastic syndromes were enrolled in the 12 week base study at nine treatment centres in Germany; 27 patients were enrolled in the dose-escalation cohorts (0·125–1·75 mg/kg) and 31 patients in the expansion cohort (0·0–1·75 mg/kg). 32 (61%; 95% CI 48–74) of 53 patients receiving higher dose luspatercept concentrations (0·75–1·75 mg/kg) achieved HI-E versus two (12%; 95% CI 3–40) of nine receiving lower dose concentrations (0·125–0·5 mg/kg). Three treatment-related grade 3 adverse events occurred in one patient each: myalgia (one [2%]), increased blast cell count (one [2%]), and general physical health deterioration (one [2%]). Two of these treatment-related grade 3 adverse events were reversible serious grade 3 adverse events: one patient (2%) had myalgia and one patient (2%) had general physical health deterioration.

Interpretation Luspatercept was well tolerated and effective for the treatment of anaemia in lower-risk myelodysplastic syndromes and so could therefore provide a novel therapeutic approach for the treatment of anaemia associated with lower-risk myelodysplastic syndromes; further studies are ongoing.

Funding Acceleron Pharma.

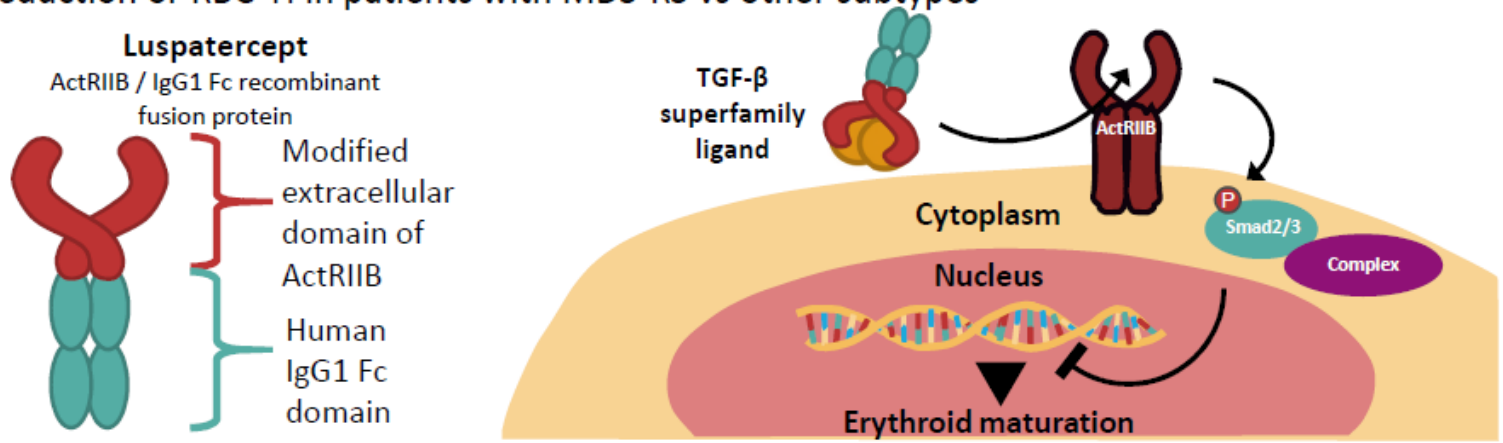


Platzbecker U et al,Lancet Hematology 2017

Luspatercept for lower risk MDS

Luspatercept

- Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes[2]



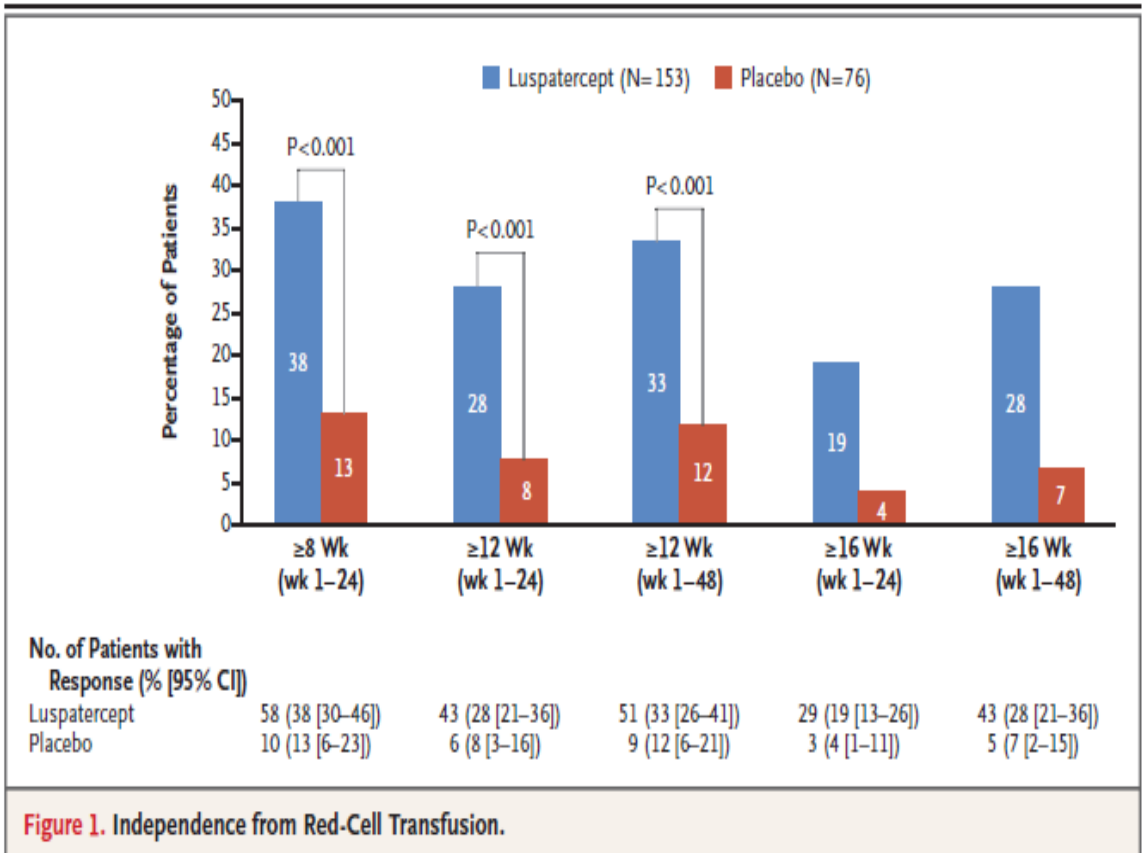
ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor beta.

1. Suragani RN, et al. Nat Med. 2014;20:408-414;
2. Platzbecker U, et. A. Lancet Oncol. 2017; 18:1338.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

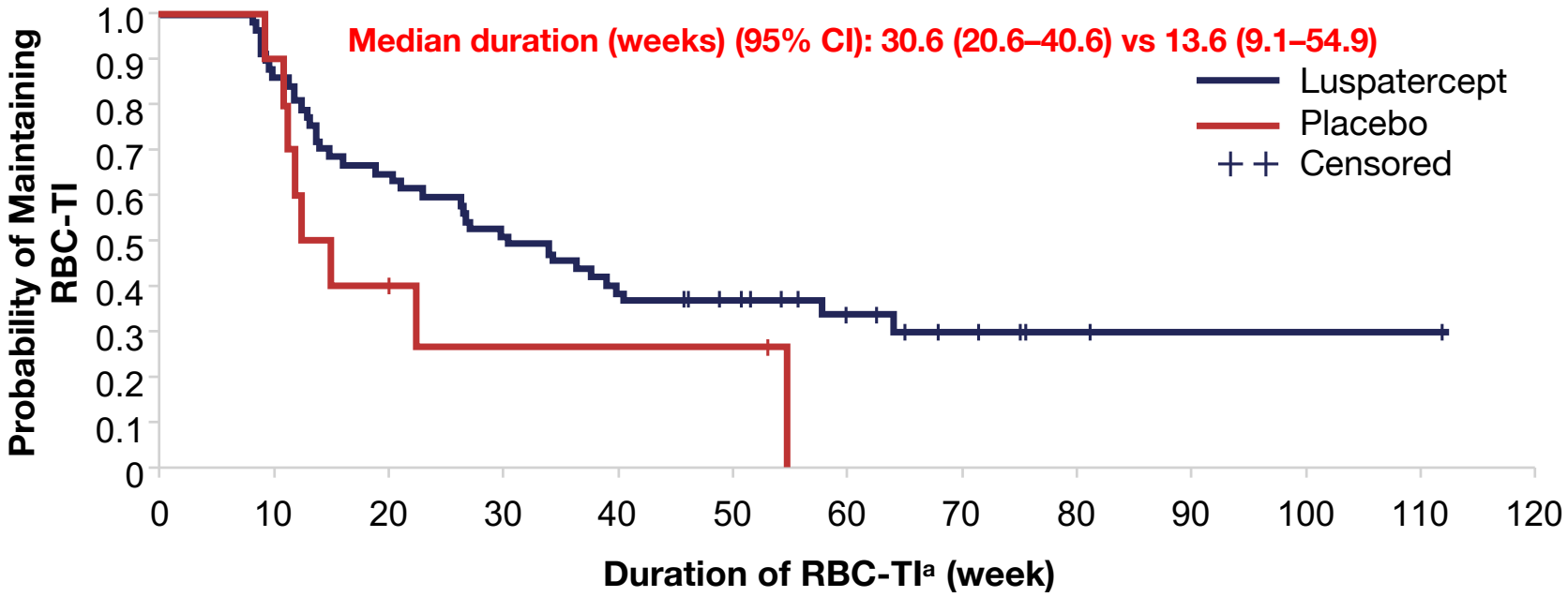


No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Figure 1. Independence from Red-Cell Transfusion.

Feanux P. et al NEJM 2020

MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders



Number of patients

Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

1. Fenaux et al. ASH 2018

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Grazie per l'attenzione

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