MDS a basso rischio

- No conflitti di interesse

Slow Medicine in Ematologia: le Patologie Mieloidi in Geriatria

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Aula Magna Nuove Patologie

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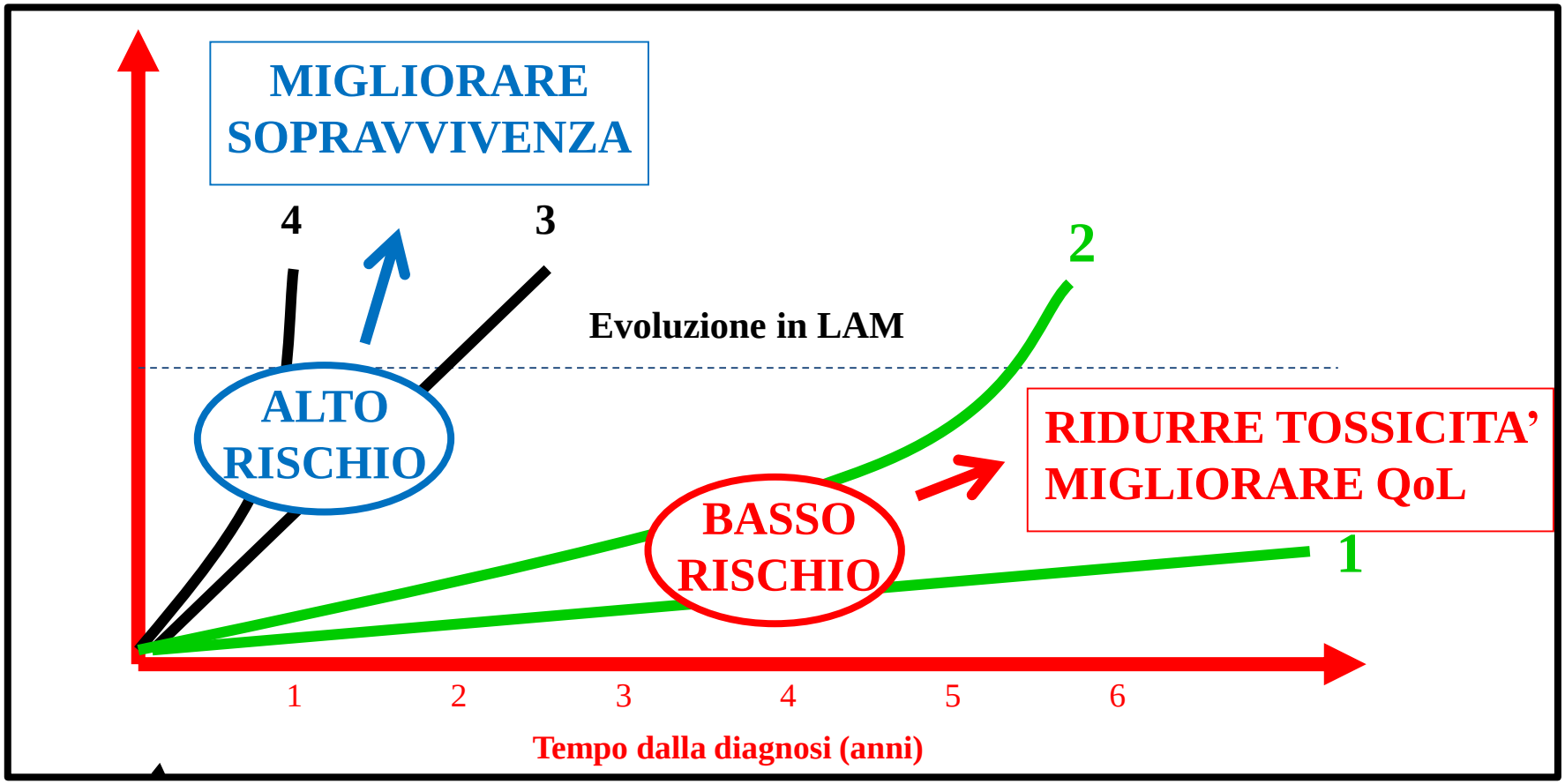
MDS a basso rischio

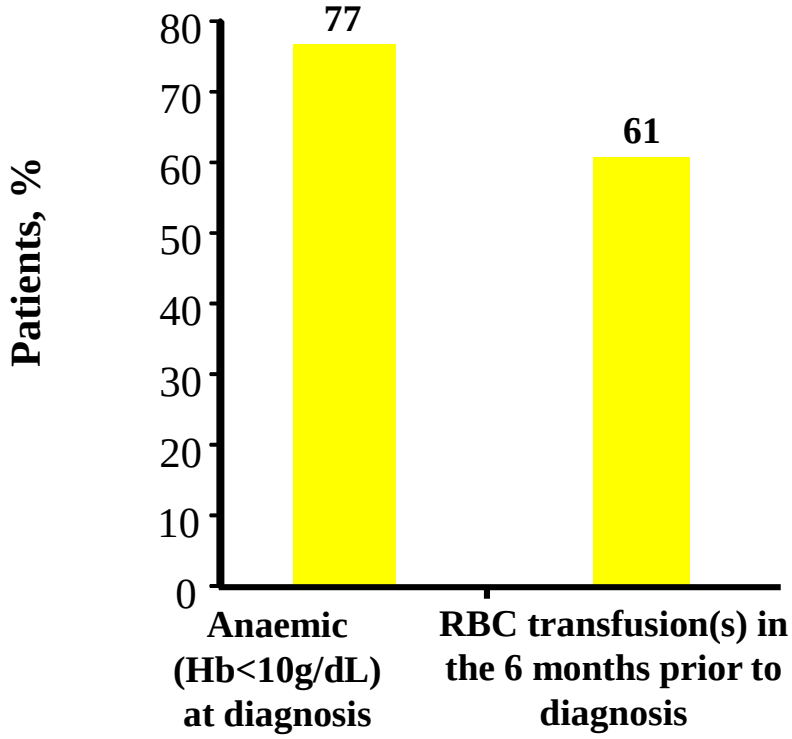
"…lower-risk myelodysplastic syndromes (MDSs) are defined as having low or intermediate-1 risk by the International Prognostic Scoring System. …"



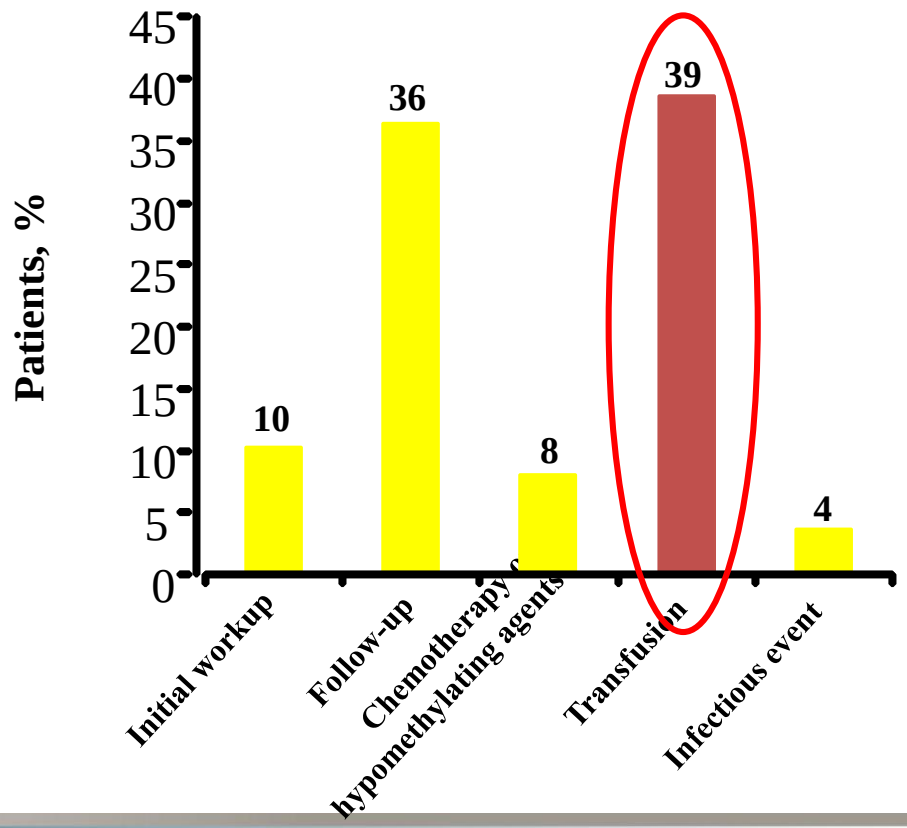
1 Decorso cronico protratto (low), 2 Decorso cronico progressivo (int-1), 3 Decorso subacuto (int-2), 4 Decorso acuto (high)

Anemia is a major clinical burden in patients with MDS

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



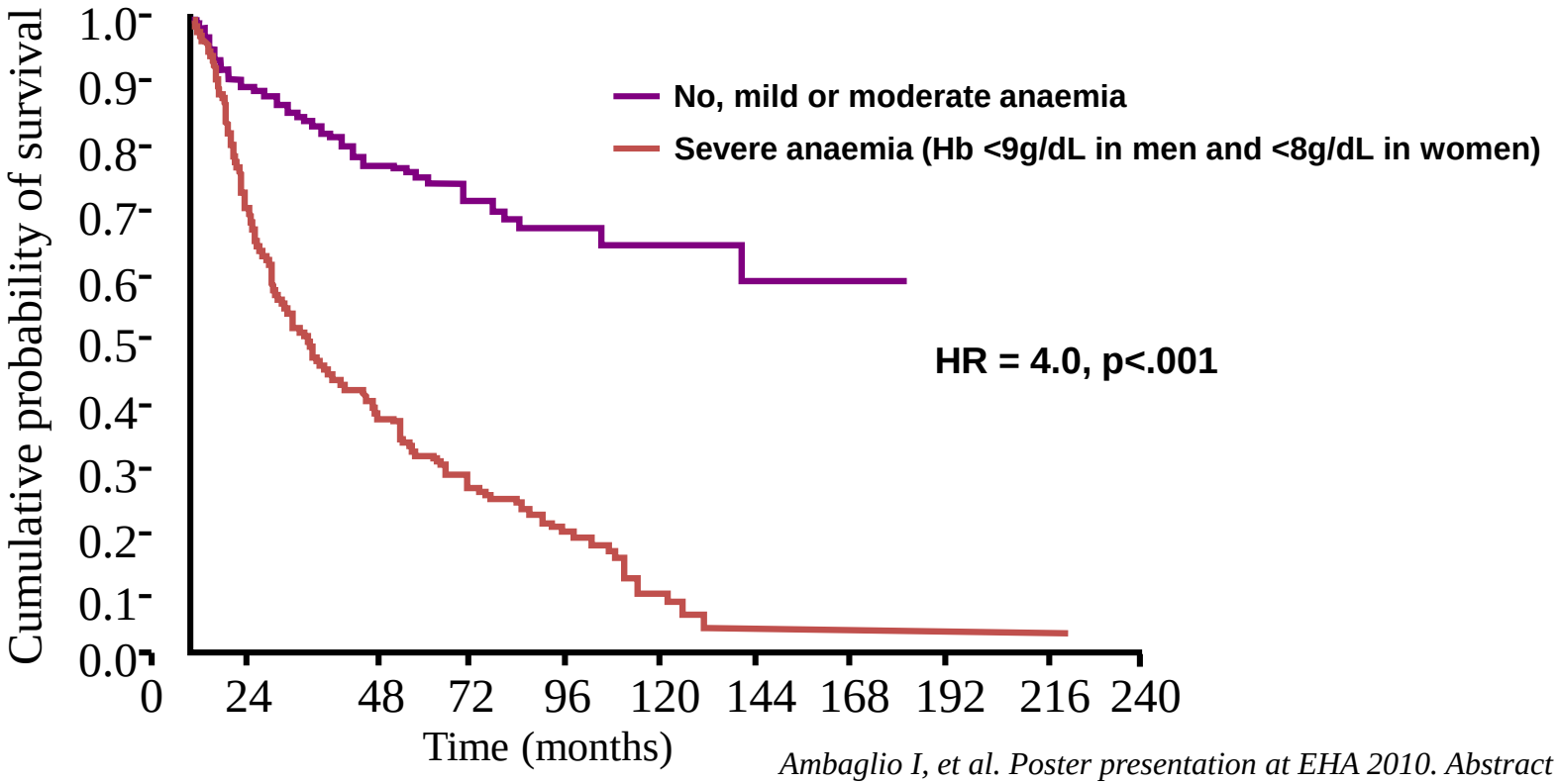
The most common reason for patients with MDS to attend a clinic: transfusion requirement*



Kelaidi C, et al. Haematologica 2010;95:892–9

Anemia has a negative impact on survival in patients with MDS

A single-centre study of 920 patients with MDS demonstrated that severe anaemia (measured before patients became RBC-TD) is an independent unfavourable prognostic indicator of survival



Ambaglio I, et al. Poster presentation at EHA 2010. Abstract 0310

RBC transfusions or drugs?

RBC-TD has many disadvantages

...in most patients with MDS symptomatic anaemia is managed with blood transfusions...

The role of RBC transfusions in patients with MDS

- **According to NCCN guidelines RBC transfusions should be used as an adjunct to treatment for symptomatic anaemia[1]**

Many patients with MDS become RBC-TD

- **Up to 90% of patients with MDS will receive transfusions[2]**
- **Many (~39–79%) will become RBC-TD[2]**

- Iron overload
  associated with hepatic, pituitary, pancreatic and cardiac dysfunction[4]
- Potential for infection
- Volume overload
- Acute/delayed reactions
- Possible immunosuppression
- Alloimmunisation
- Expensive

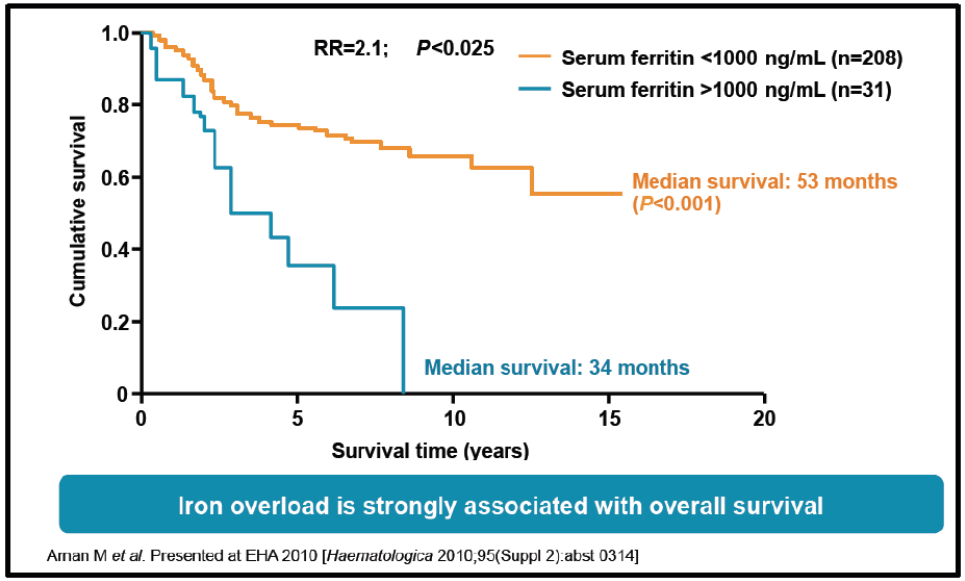
1. NCCN Guidelines on Myelodysplastic Syndromes V.2.2011; 2. Jabbour E, et al. Cancer 2008;112:1089–95
3. Spano J-P, Khayat D. The Oncologist 2008;13(Suppl. 3):27–32; 4. Dreyfus F. Blood Rev 2008;22(Suppl. 2):S29–34

RBC-TD can lead to iron overload in patients with MDS

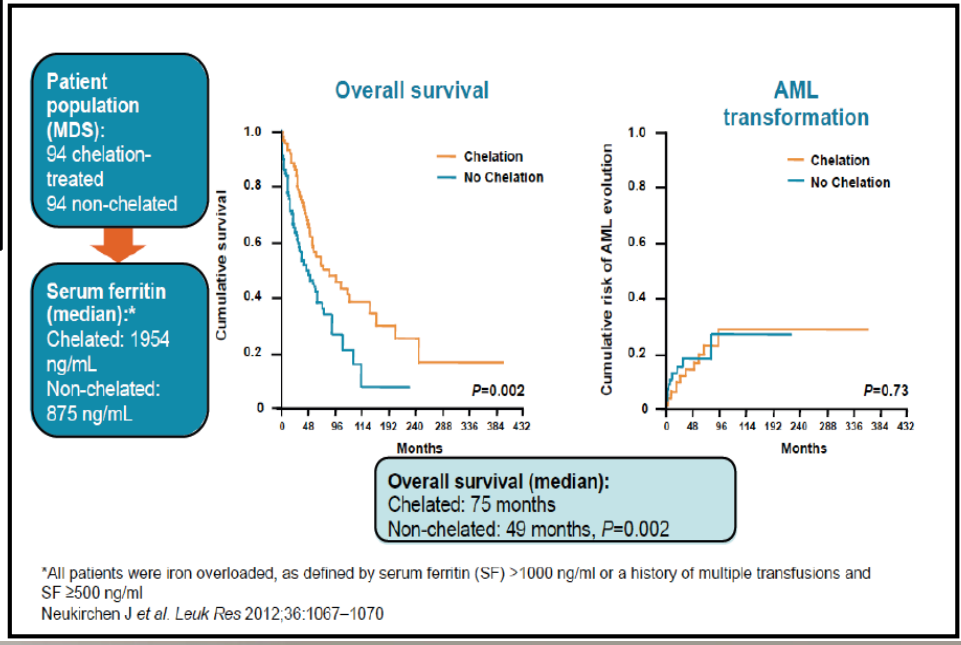
- The average adult can only store ~7g total body iron
- 1U of RBC contains ~200–250 mg of iron
- The body has no physiologic mechanism for secreting iron
- Patients who are transfused with 4 RBC units per month will accumulate ~9.6g of iron per year which exceeds storage capacity
- Patients can become overloaded with iron after ~20 transfusions

List A. Cancer Control 2010;17 (Suppl 1):1–8

Iron overload and chelation therapy



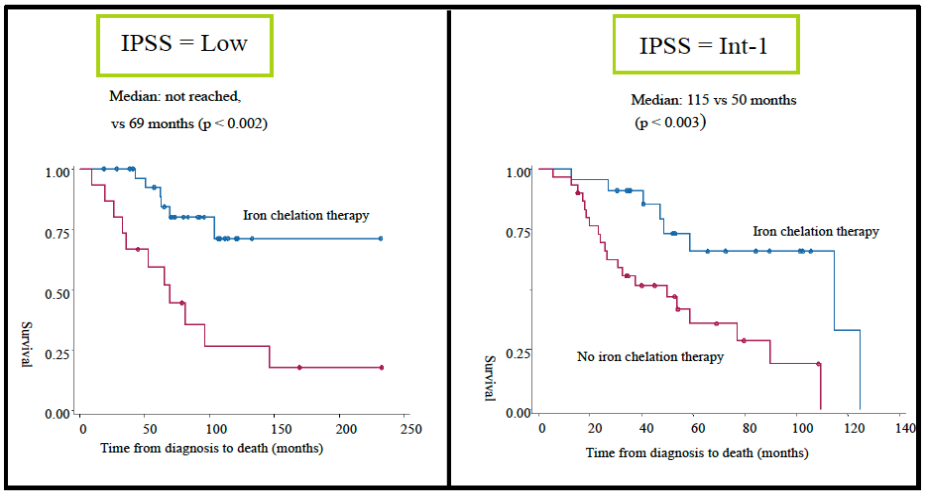
Aman M *et al.* Presented at EHA 2010 [*Haematologica* 2010;95(Suppl 2):abst 0314]

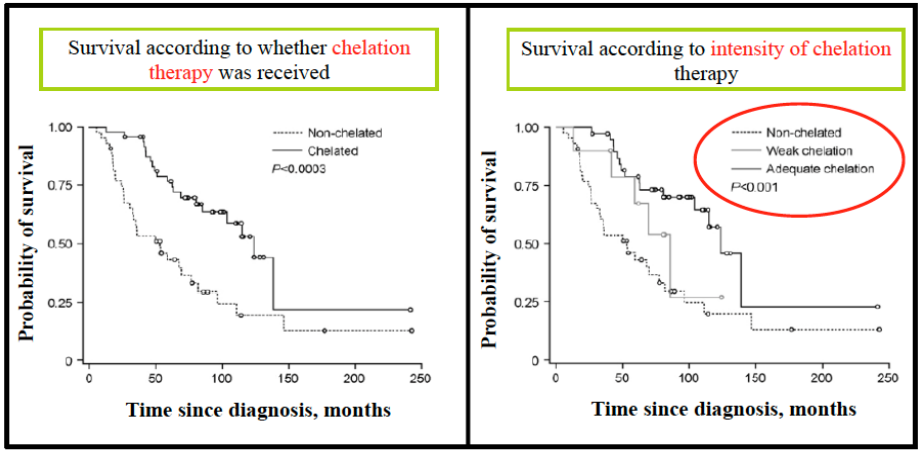


*All patients were iron overloaded, as defined by serum ferritin (SF) >1000 ng/ml or a history of multiple transfusions and SF ≥500 ng/ml

Neukirchen J *et al. Leuk Res* 2012;36:1067–1070

Impact of iron chelation therapy on survival in pts with MDS





Rose C, et al. Leuk Res 2010;34:864–70

Linee guida italiane

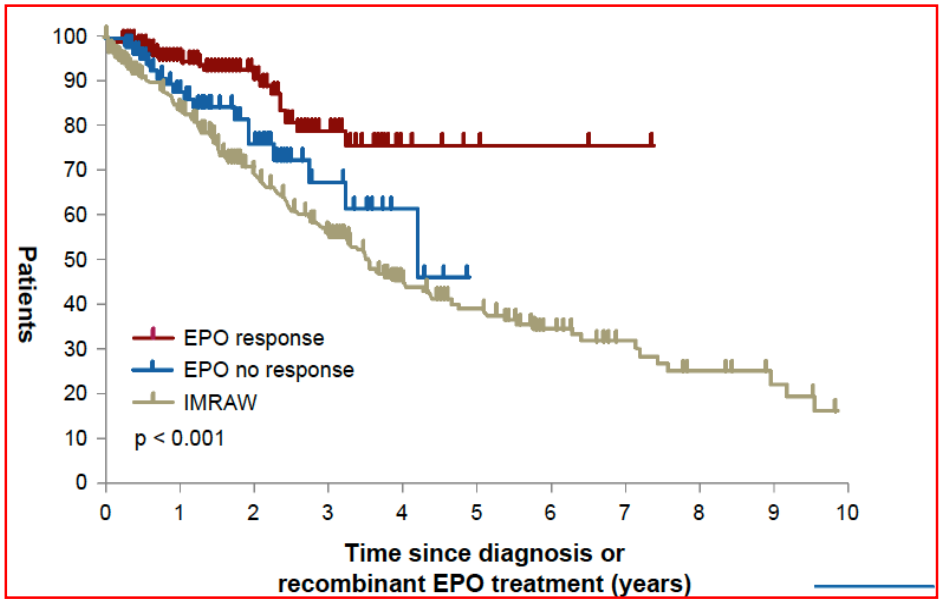
- Low-Int-1, TD, > 20 packed RBC unit
- Int1-High, TD, therapy-responsive
- Candidate to HSCT
- Iron chelation not only on the basis of ferritin level
- Deferasirox > Deferoxamine

Santini V *et al*. *Leuk Res* 2010

What is the first-line treatment of anemia in LR MDS?

Patients without del(5q): ESA

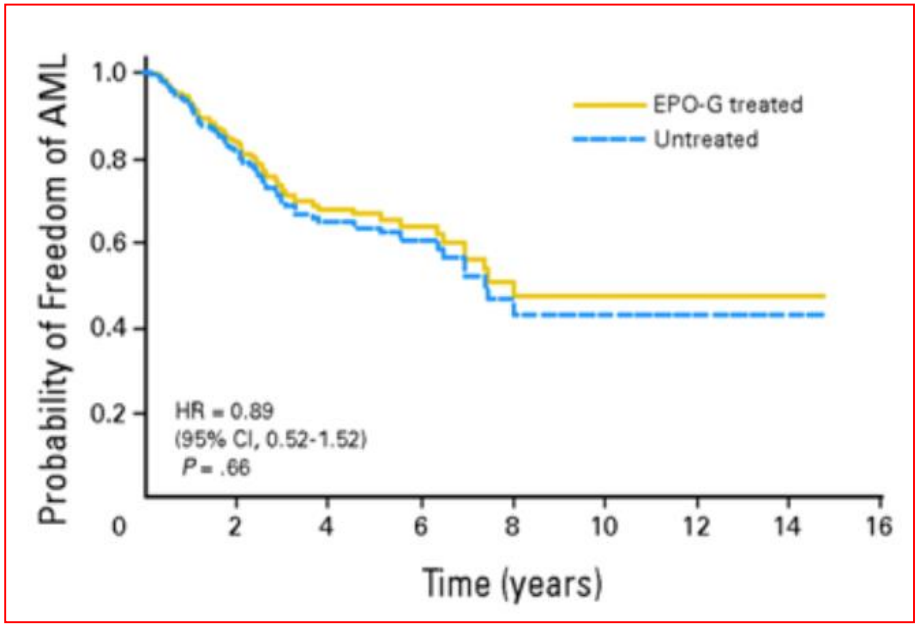
Impact of ESA on OS and AML risk progression



ESA and OS

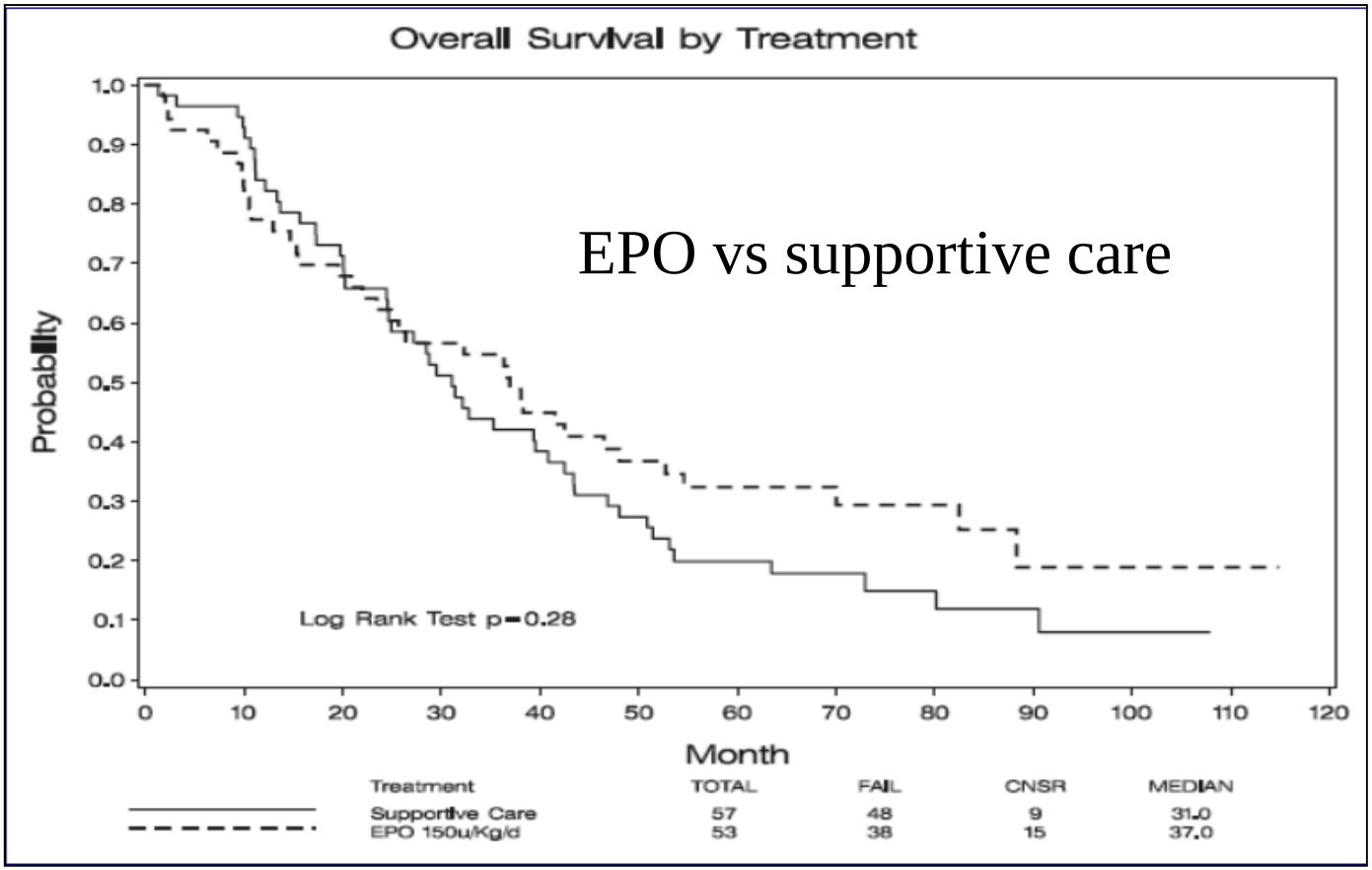
Park S, et al. Blood, 2008

ESA therapy and AML risk progression



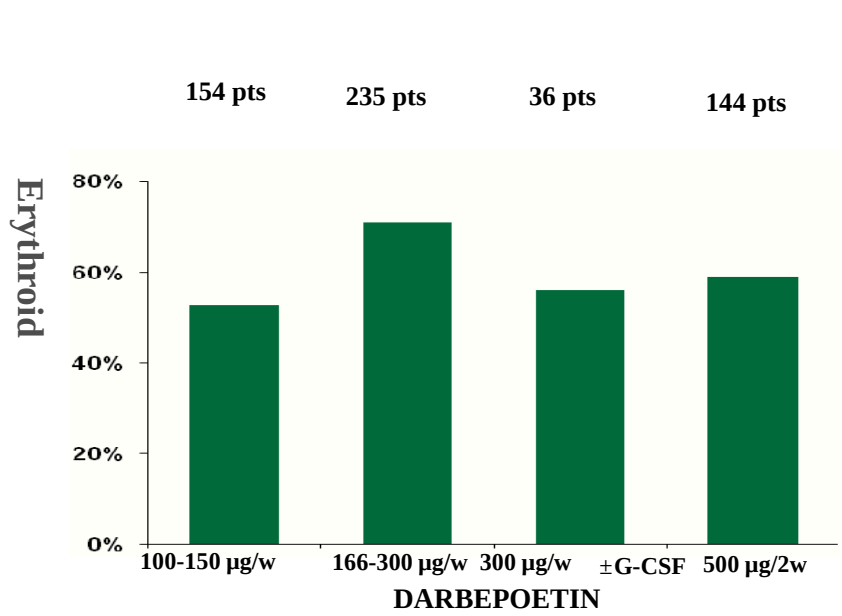
Jadersten, M. et al. J Clin Oncol; 2008

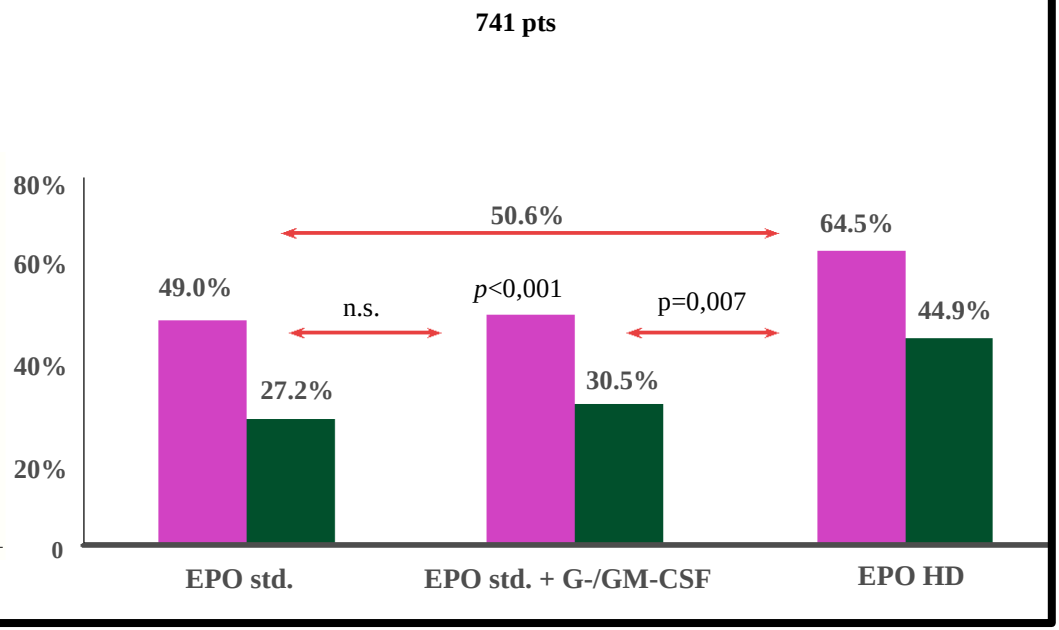
Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group



Greenberg et al, Blood. 2009 Sep 17; 114(12): 2393–2400.

Meta analisi della risposta eritroide dopo ESA





Dosi più elevate sia di EPO alfa (dose 60–80 K U/w) che di darbepoetin alfa (dose 150–300 mcg/w) correlano con percentuali di risposta più elevati

Santini V Semin Haematol 2012; 49(4):295-303

Modified from Moyo V et al *Ann Hematol* 2008 87:527–536

Santini V Oncologist 2011; 16 Suppl 3:35-42;

and Mundle S, et al. *Cancer* 2009;115:706-715.

ESA Treatment

- ESA (erythropoietin alfa/beta and darbepoetin) increase hemoglobin level and abolish trasfusion dependence in 19-68% of MDS cases (non 5q-)
- Wide range of responses depends on biological, clinical and drug variables
- Responsive MDS-patients treated with ESAs (w/wo G-CSF) have an advantage in terms of OS, with no TE events and no impact on AML progression
- 2 years median duration
- After failure… II line therapy or GRC trasfusion

Santini V, Oncologist, 2011; Smith SW, Haematologica, 2012

Variabili predittive di risposta ad ESA

Biological
Endogenous erythropoietin levels <500 U/L
Marrow blast <10%
IPSS low-INT-1
Diagnosis of refractory anemia
Normal karyotype
Clinical
Transfusion independence
Short duration of disease

Abbreviations: ESA, erythropoietic stimulating agents; INT-1, intermediate-1; IPSS, International Prognostic Score System; MDS, myelodysplastic syndromes.

The Oncologist

Santini V The Oncologist 2011

TRATTAMENTO CON ESA NELLE MDS

Linee Guida Italiane

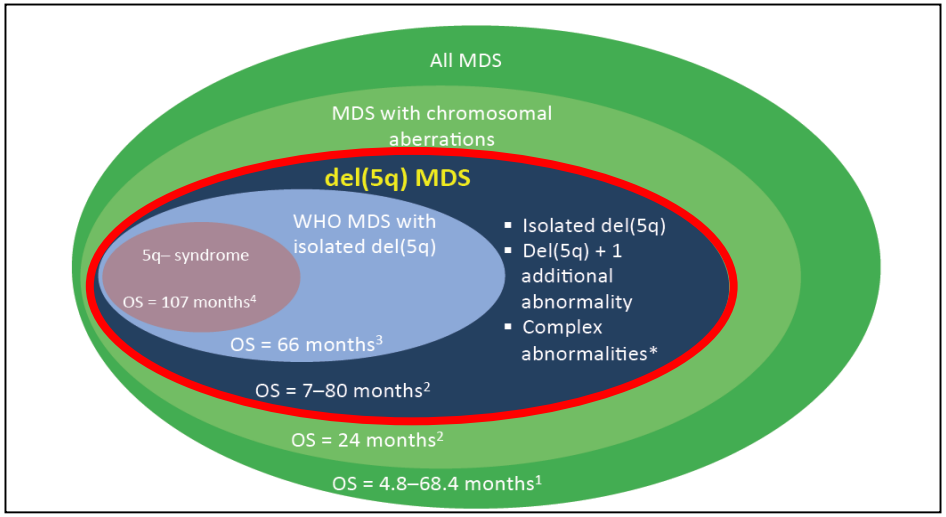
- Rischio IPSS basso/INT-1
- Hb < 10 g/dl
- Epo endogena < 500 mU/mL
- Dosi:
  - Epo 60.000-80.000 UI s.c. qW o divise in due dosi sett. (grado A)
- Durata del tratt.: almeno 12 sett., possibilmente > 20 settimane (grado B)
- Supplementazione Ferro se Tsat < 20% (grado D)
- Modifica della dose: al raggiungimento della risposta il livello di Hb deve essere mantenuto tra 10-12 g/dl (grado D)

Santini V *et al*. *Leuk Res* 2010

What is the first-line treatment of anemia in LR MDS?

Patients with del(5q): Lenalidomide

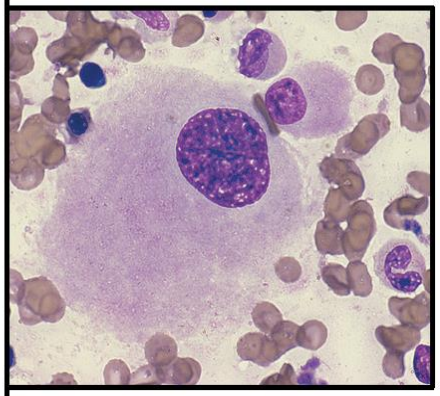
Del(5q) MDS is not only "5q– syndrome"



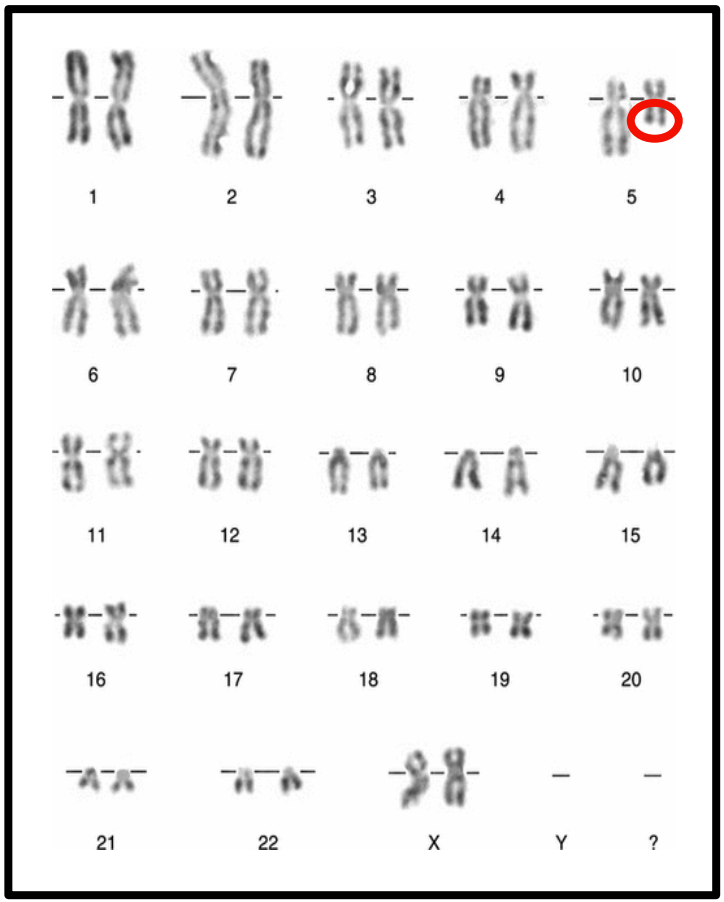
1. Greenberg P, et al.,Blood 1997;89:2079–88;
2. Haase D, et al., Blood 2007;110:4385–95;
3. Mallo M, et al., Leukemia 2011;25:110–2;
4. Giagounidis A, et al.,Hematology2004;9:271–7

van Den Berghe, *Nature*, **251**, 437-438 (1974)

- Female preponderance
- 5q- sole karyotypic abnormality
- Macrocytic anemia (MCV>100 fL)
- High platelet count
- Increased megakaryocytes with monolobulated nuclei
- Prolonged survival

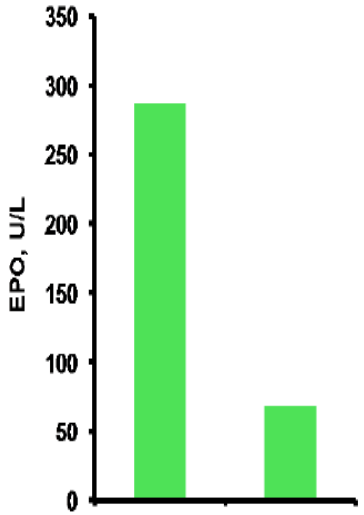


5q-



La scarsa risposta ad ESA si può attribuire ad alti livelli endogeni di EPO alla diagnosi nei pazienti con del(5q) MDS

Endogenous EPO level



Algoritmo di predizione risposta ad ESA

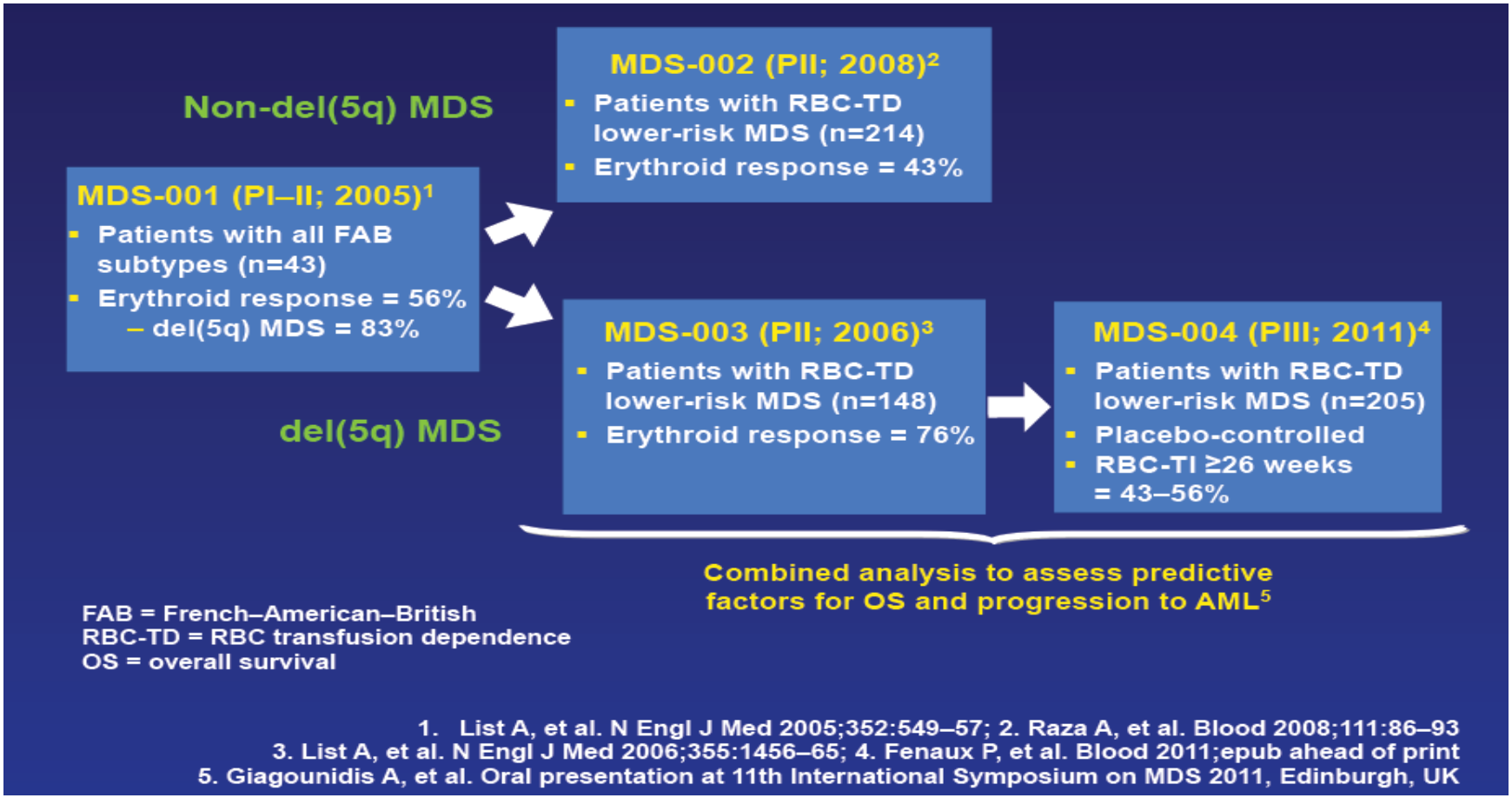
Factor	Value	Score	Value	Score
Transfusion requirement*	<2 U/month	0	≥2 U/month	1
Serum EPO*	<500 U/L	0	≥500 U/L	1

Predicted response

Score = 0: 74%
Score = 1: 23%
Score = 2: 7%

1. Kelaidi C et al Blood 2006;108 (Suppl 1.):757a 2. Hellström-Lindberg E, et al. Br J Haematol 2003;120:1037–46

Clinical Trials of Lenalidomide in MDS



MDS-003: study design

Patient characteristics (n=148)

- Age range, years: 37–95
- IPSS risk category, %
  - low: 37
  - int-1: 44
  - int-2/high: 5
  - unclassified: 14
- RBC-TD, %: 100
- Karyotype (in 85 patients with sufficient metaphases), %
  - del(5q): 75
  - del(5q) + 1: 18
  - del(5q) + ≥2: 7
- Prior treatment, %†
  - EPO: 73
  - chemotherapy: 39

Lenalidomide, 24 weeks

- 10 mg/day for 21/28-day cycles

If patients responded after 24 weeks they could continue on lenalidomide

Endpoints

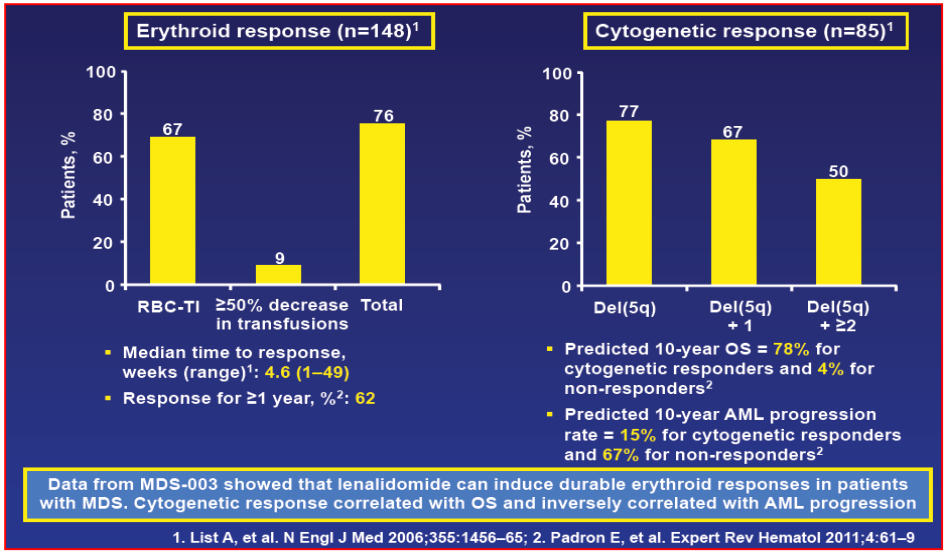
- Primary:
  - erythroid response*
  - RBC-TI (for ≥56 consecutive days)
- Secondary
  - RBC-TI duration
  - cytogenetic response
  - tolerability

MDS-003 was restricted to patients with RBC-TD del(5q) MDS. Only 26% of patients had 5q– syndrome

*As defined by the IWG 2000 criteria
†Patients could receive >1 prior treatment
EPO = erythropoietin

List A, et al. N Engl J Med 2006;355:1456–65

MDS-003: high response rate and toxicities



High response rate

Grade 3/4 AEs

Grade 3/4 AE	Patients, %
Thrombocytopenia	44
Neutropenia	55
Anaemia	7
Rash	6
Pruritus	3
Fatigue	3

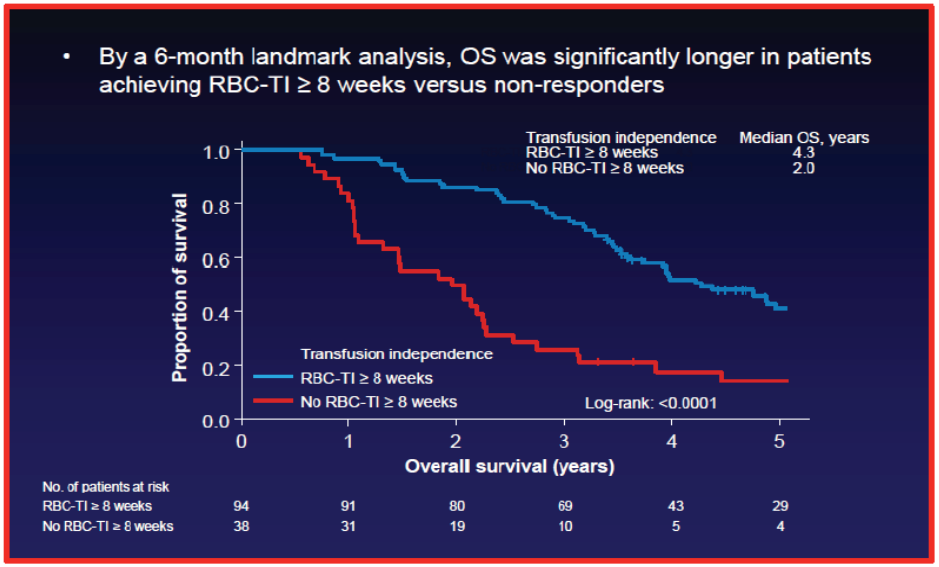
- 62% of haematologic AEs occurred within the initial 8 weeks of treatment
- Dose adjustment due to AEs was required in 84% of patients; 20% of patients discontinued lenalidomide due to AEs
- Three deaths due to neutropenic infection were judged to be possibly treatment-related

Myelosuppression generally occurred early on in the course of treatment; close laboratory monitoring and consideration of myeloid growth factors should be considered during the initial weeks of treatment

List A, et al. N Engl J Med 2006;355:1456–65

Long-term outcomes: OS

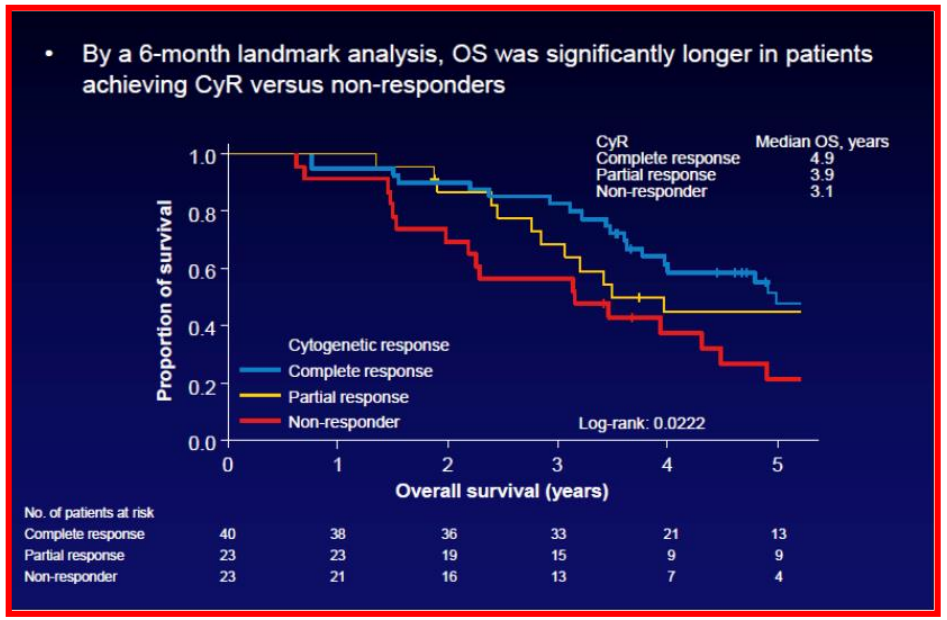
- By a 6-month landmark analysis, OS was significantly longer in patients achieving RBC-TI ≥ 8 weeks versus non-responders



OS by RBC-TI

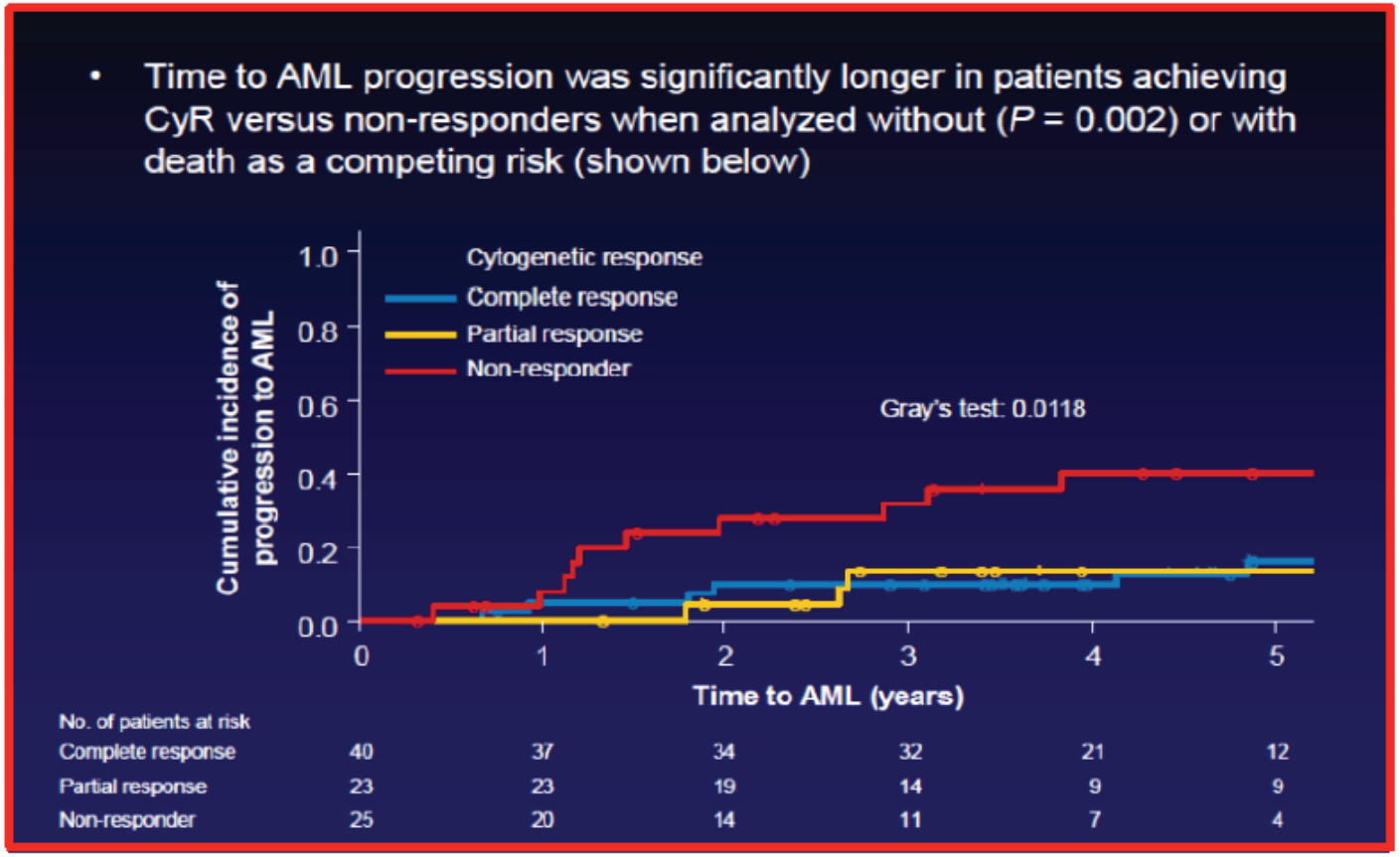
OS by CyR

- By a 6-month landmark analysis, OS was significantly longer in patients achieving CyR versus non-responders



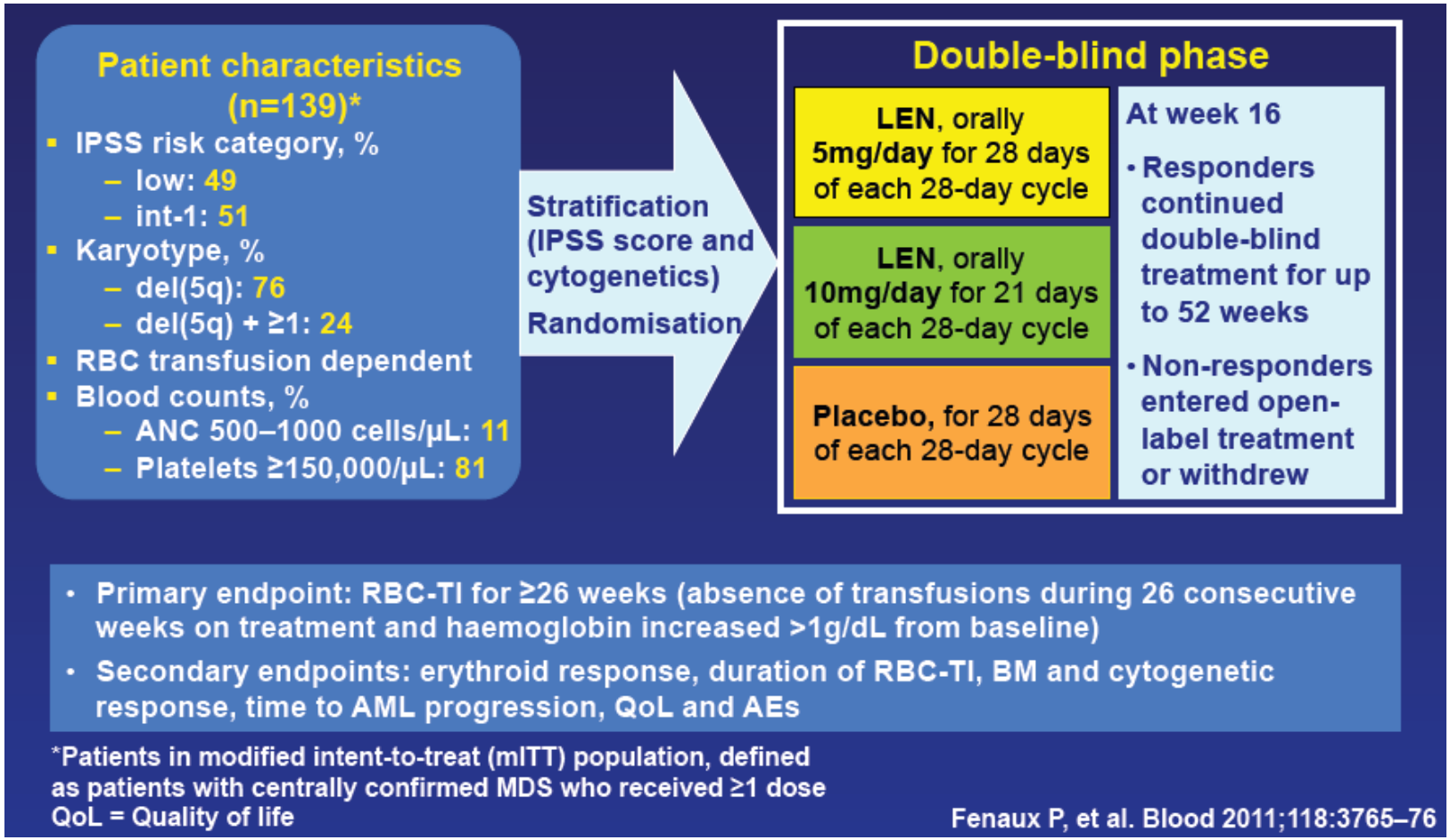
Results: AML progression by CyR

- Time to AML progression was significantly longer in patients achieving CyR versus non-responders when analyzed without (P = 0.002) or with death as a competing risk (shown below)

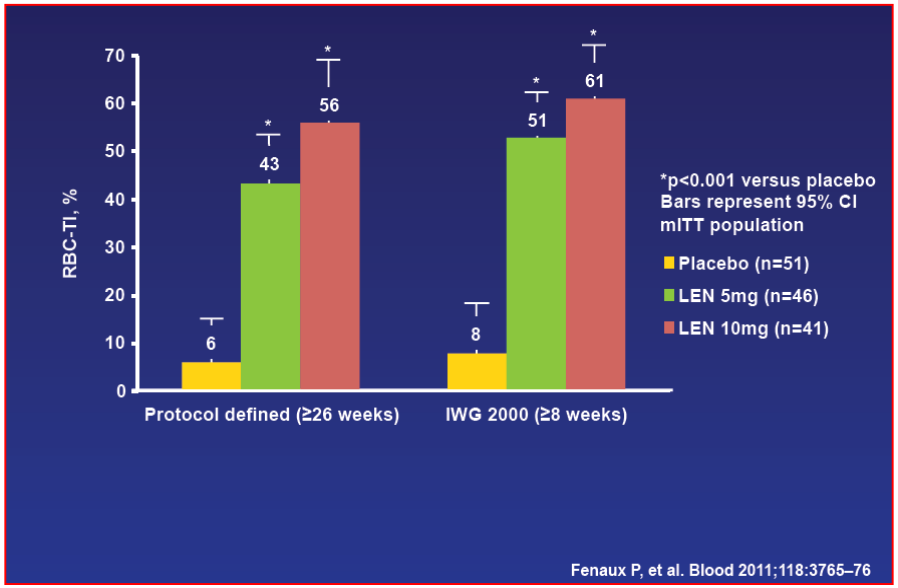


List AF, Leukemia 2014

MDS-004: study design

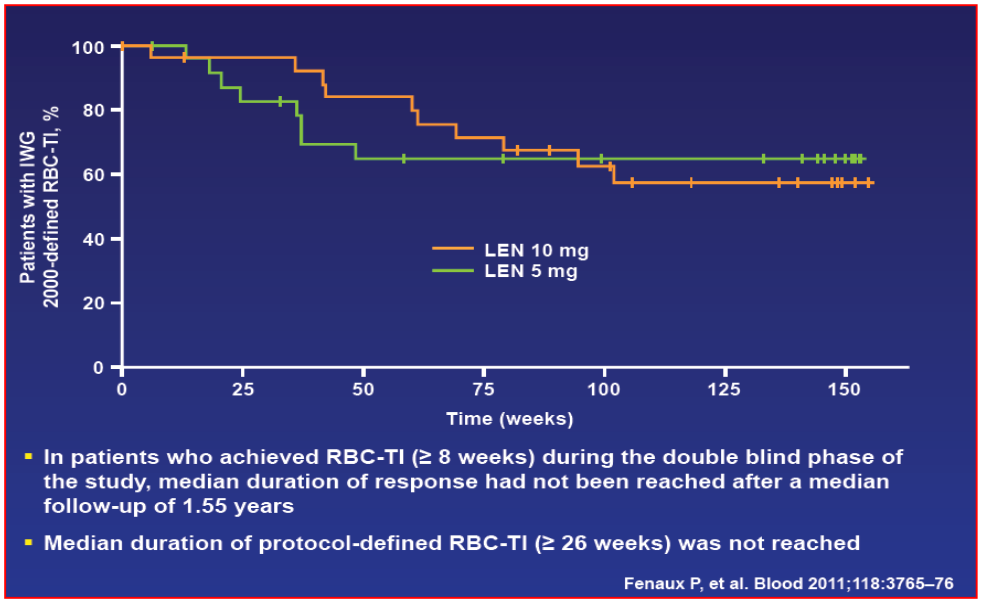


MDS-004: results

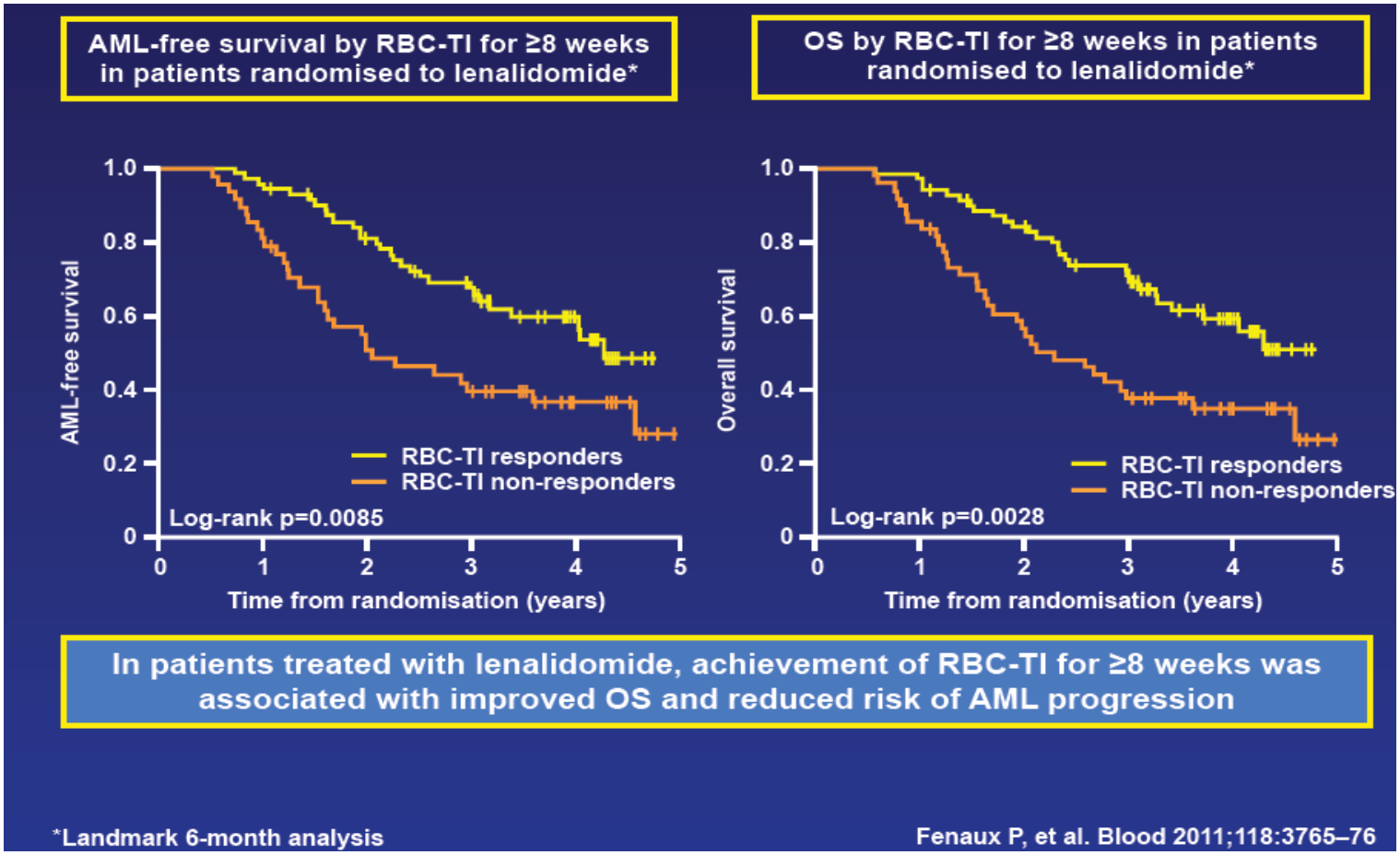


Significant improvements in RBC-TI in patients randomised to lenalidomide vs placebo

Durable response to lenalidomide



MDS-004: OS and progression to AML in patients who achieve RBC-TI



MDS-004: side effects

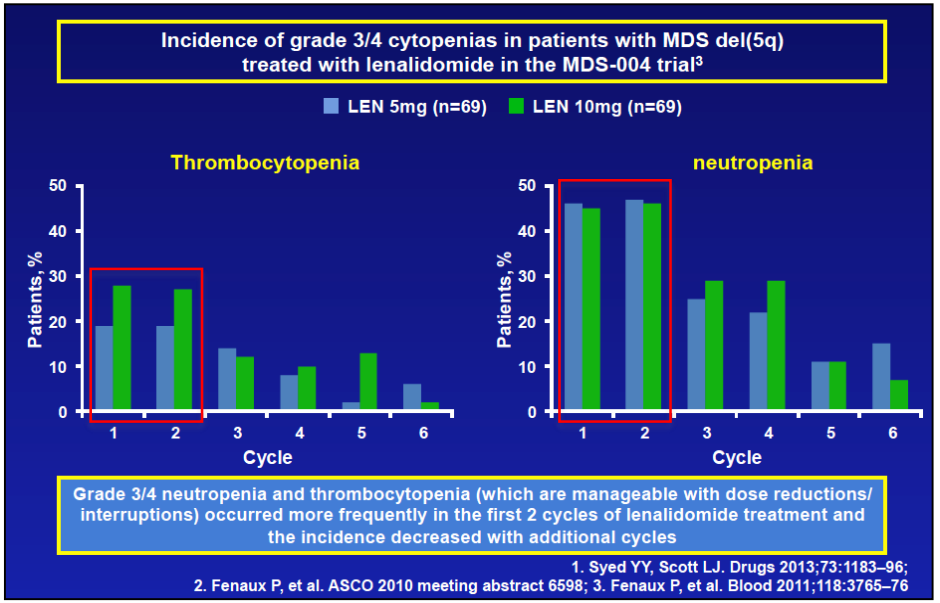
Grade 3 or 4 AEs (≥ 5% of patients), n(%)	Placebo (n = 67)	LEN 5 mg (n = 69)	LEN 10 mg (n = 69)
Patients with ≥ 1 AE	29 (43)	62 (90)	65 (94)
Neutropenia	10 (15)	51 (74)	52 (75)
Thrombocytopenia	1 (2)	23 (33)	28 (41)
Leukopenia	0	9 (13)	6 (9)
Anemia	6 (9)	4 (6)	2 (3)
DVT	1 (2)	1 (1)	4 (6)
AEs leading to			
Discontinuation	3 (5)	12 (17)	6 (9)
Dose reduction	–	36 (52)	38 (55)
Dose interruption	–	20 (29)	32 (46)

The AE profile of both doses of lenalidomide was predictable. Some patients experienced early myelosuppression. Otherwise, lenalidomide was generally well tolerated

Fenaux P, et al. Blood 2011;118:3765–76

Grade 3/4 AEs

LEN-related cytopenias in early cycles of treatment in patients with MDS del(5q)



What is the second-line treatment of anemia in LR MDS?

Patients without del(5q)

- Approximately 70% of the relapses of anemia after initial response to ESAs are not associated with progression to higher-risk MDS but simply to loss of sensitivity of erythroid progenitors to ESAs

- Early ESA failure (no response or relapse within 6 months) is a marker of disease severity associated with AML progression (Kelaidi C, Leukemia 2013)

- Second line treatment may be different (progression to HR MDS or not):
  - . long-term RBC transfusions
  - . *antithymocyte globulin (ATG)*
  - . HMAs (30%, Silverman, JCO 2006),
  - . Lenalidomide (43%, Raza, Blood 2008, 26,9%, Santini, ASH 2014)

Patients with del(5q)

- MDS 003 and MDS 004 trials: resistance to LEN in lower-risk MDS with del 5q is associated with poor prognosis even if no immediate progression to HR MDS is observed

- Patients with TP53 gene mutation may have a poor outcome

- Those patients should probably be candidates to approaches having demonstrated a survival benefit in MDS HMAs, and whenever possible allogeneic SCT

How do we treat cytopenias in lower-risk MDS?

Neutropenia

- Less frequent than anemia (WBC < 1.500/mm3 in only 7% of lower-risk MDS)

- Infrequently isolated or profound

- Rarely associated with life-threatening infection

- GCSF: - can improve neutropenia (50-70%)
  - their prolonged use has not demonstrated an impact on survival
  - risk of stimulating progression to HR MDS or AML has not been excluded
  - they may be used for transient periods

Thrombocytopenia

- Less frequent than anemia, infrequently isolate or profound (mainly accompanying anemia)

- Platelets < 50 000/mm3 are seen 30% of LR MDS

- Severe bleeding is relatively rare, but hemorrage represents the third cause of death in LR-MDS patients (Dayyani, Cancer, 2010)

- TPO receptor agonists (romiplostim and eltrombopag): are unavailable for routine practice.

(in a randomized phase II study vs placebo in LR MDS with thrombocytopenia, romiplostim reduced the incidence of severe bleeding and platelet transfusions, but there was a suspected increase of blast count, but similar AML rates)

Grazie