CESENA 28 maggio 2016
Sala Malatesta, Unaway Hotel

Con il supporto non condizionato di NOVARTIS ONCOLOGY

La ferrochelazione nella gestione della mielodisplasia 10 anni dopo

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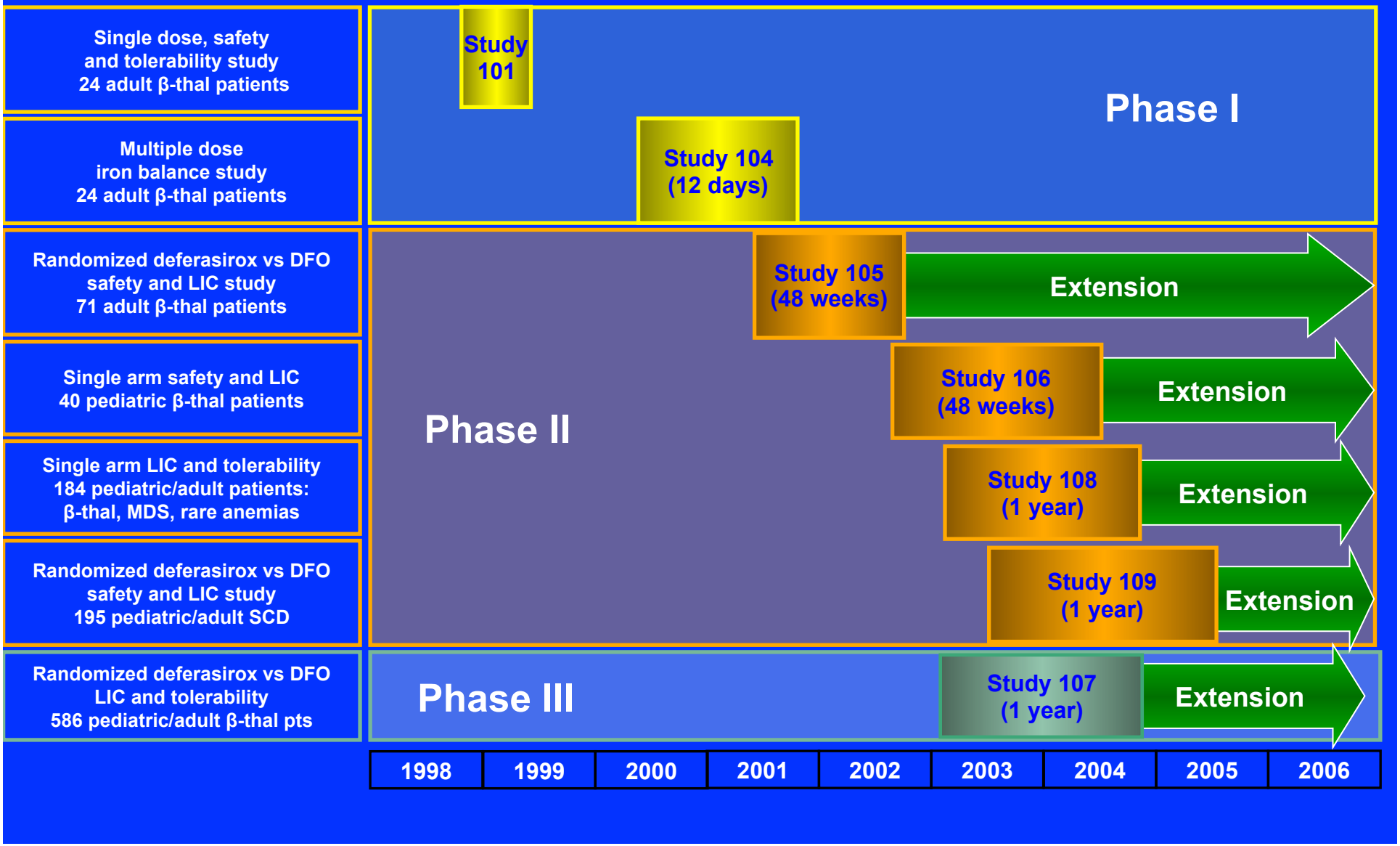
Comparison of chelators

Property	DFO	Deferiprone	Deferasirox
Usual dose (mg/kg/day)	25–60	75–100	20–30
Route	Sc, iv (8–12 hours, 5 days/week)	Oral 3 times daily	Oral Once daily
Half-life	20–30 minutes	3–4 hours	8–16 hours
Excretion	Urinary, fecal	Urinary	Fecal
Main adverse effects in prescribing information	Local reactions, ophthalmologic, auditory, growth retardation, allergic	Gastrointestinal disturbances, agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes	Gastrointestinal disturbances, rash, renal impairment, hepatic impairment, ophthalmologic, auditory
Status	Licensed	Licensed	Licensed

Deferasirox clinical development



Guidelines for treatment of iron overload in patients with MDS (1)

	UK Guidelines, 2003[1]	Nagasaki Consensus, 2005[2]	NCCN Guidelines, 2012[3]	Canadian Guidelines, 2008[4]
	Recommended that chelation therapy should be considered:			
Transfusion status	• Received ~25 RBC units	• Transfusion dependent	• Received >20–30 RBC units • To continue transfusions	• Transfusion dependent
Serum ferritin level	–	• >1000–2000 ng/mL	• >2500 ng/mL	• >1000 ng/mL
Patient profile	• Long-term survival likely (eg, pure sideroblastic anemia, del(5q) etc)	• IPSS Low or Int-1 • RA, RARS, del(5q)	• IPSS Low or Int-1 including potential transplant patients • IPSS Int-2 or High who do not respond to treatment or who relapse	• IPSS Low or Int-1 • RA, RARS, del(5q) • (IPSS Int-2 or High)

[1]Bowen D *et al*. *Br J Haematol* 2003;120:187–200; [2]Gattermann N *et al*. *Hematol Oncol Clin North Am* 2005; 19(Suppl 1):18–25; [3]NCCN Practice Guidelines for MDS V1 2012; [4]Wells RA *et al*. *Leuk Res* 2008;32:1338–1353

Guidelines for treatment of iron overload in patients with MDS (2)

	Spanish Guidelines, 2008[1]	Italian Guidelines, 2010[2]	Japanese Guidelines, 2008[3]	MDS Foundation Guidelines, 2008[4]	South African Guidelines, 2011[5]
	Recommended that chelation therapy should be considered:				
Transfusion status	• Transfusion dependent	• Received ≥20 RBC units (4 g iron)	• Received >40 Japanese units	• Received 2 RBC units/month for ≥1 year	• Received ≥ 2 RBC units/ month for >1 year
Serum ferritin level	• >1000 ng/mL	–	• >1000 ng/mL	• >1000 ng/mL	• >1000 ng/mL
Patient profile	• IPSS Low or Int-1 • Very low, Low or Int (WPSS) • Low risk (Spanish prognostic index)	• Regularly transfused • IPSS Low or Int-1 • IPSS Int-2 or High responding to life-extending therapy or HSCT	• Life-expectancy >1 year	• Life-expectancy >1 year	• IPSS Low or Int-1 • Life-expectancy >1 year • HSCT candidate

[1]Arrizabalaga B *et al*. *Haematologica* 2008;93(Suppl 1):3–10; [2]Santini V *et al*. *Leuk Res* 2010;34:1576–1588; [3]Suzuki T *et al*. *Int J Hematol* 2008;88:30–35; [4]Bennett JM. *Am J Hematol* 2008;83:858–861;[5]Louw V *et al*. *S Afr Med J* 2011;101:900–966

Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet
(Malcovati L et al, Blood 2013)

- The Expert Panel agreed that iron chelation should be considered in transfusion-dependent patients with RA, RARS, or MDS with isolated 5q deletion and a serum ferritin level higher than 1000 ng/mL after approximately 25 units of red cells **(recommendation level D)**.

- MDS patients who are potentially candidates for allo-SCT can be considered for appropriate iron chelation therapy prior to the conditioning regimen for transplantation **(recommendation level D)**.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes Version 1.2016 (1)

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The NCCN Panel Members recommend **monitoring serum ferritin levels and number of RBC transfusions** received as a practical means to determine iron stores and assess iron overload. Monitoring serum ferritin may be useful, **aiming to decrease ferritin levels to less than 1000 mcg/L**. It is recognized that such measurements, though useful, are less precise than SQUID (Superconducting Quantum Interference Device), or more recently **T2* MRI**, to provide a specific measurement of hepatic iron content.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes Version 1.2016 (2)

The NCCN Guidelines Panel recommends consideration of once-daily deferoxamine SC or deferasirox/ICL670 orally to decrease iron overload (aiming for a target ferritin level less than 1000 ng/mL) in the following IPSS Low- or Intermediate-1–risk patients:

1) patients who have received or are anticipated to receive greater than 20 RBC transfusions;

2) patients for whom ongoing RBC transfusions are anticipated;

3) patients with serum ferritin levels greater than 2500 ng/mL.

It is recommended that patients on deferasirox therapy be closely monitored. Monitoring should include measurement of serum creatinine and/or creatinine clearance and liver function tests prior to initiation of therapy and regularly thereafter. Deferasirox should be avoided in patients with creatinine clearance less than 40 mL/min.[211]

Review

Updated recommendations on the management of gastrointestinal disturbances during iron chelation therapy with Deferasirox in transfusion dependent patients with myelodysplastic syndrome – Emphasis on optimized dosing schedules and new formulations

Florian Nolte[a,*], Emanuele Angelucci[b], Massimo Breccia[c], Norbert Gattermann[d], Valeria Santini[e], Norbert Vey[f], Wolf-Karsten Hofmann[a]

[a] Department of Hematology and Oncology, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Germany
[b] Hematology and Bone Marrow Transplant Unit, and Medical Oncology Department, Ospedale Oncologico "Armando Businco", Cagliari, Italy
[c] Department of Cellular Biotechnologies and Hematology, "La Sapienza" University, Rome, Italy
[d] Comprehensive Cancer Center and Department of Hematology, Oncology, and Clinical Immunology, Heinrich Heine University, Düsseldorf, Germany
[e] Division of Hematology, University of Florence, Florence, Italy
[f] Department of Hematology, Institute Paoli Calmettes, Marseille, France

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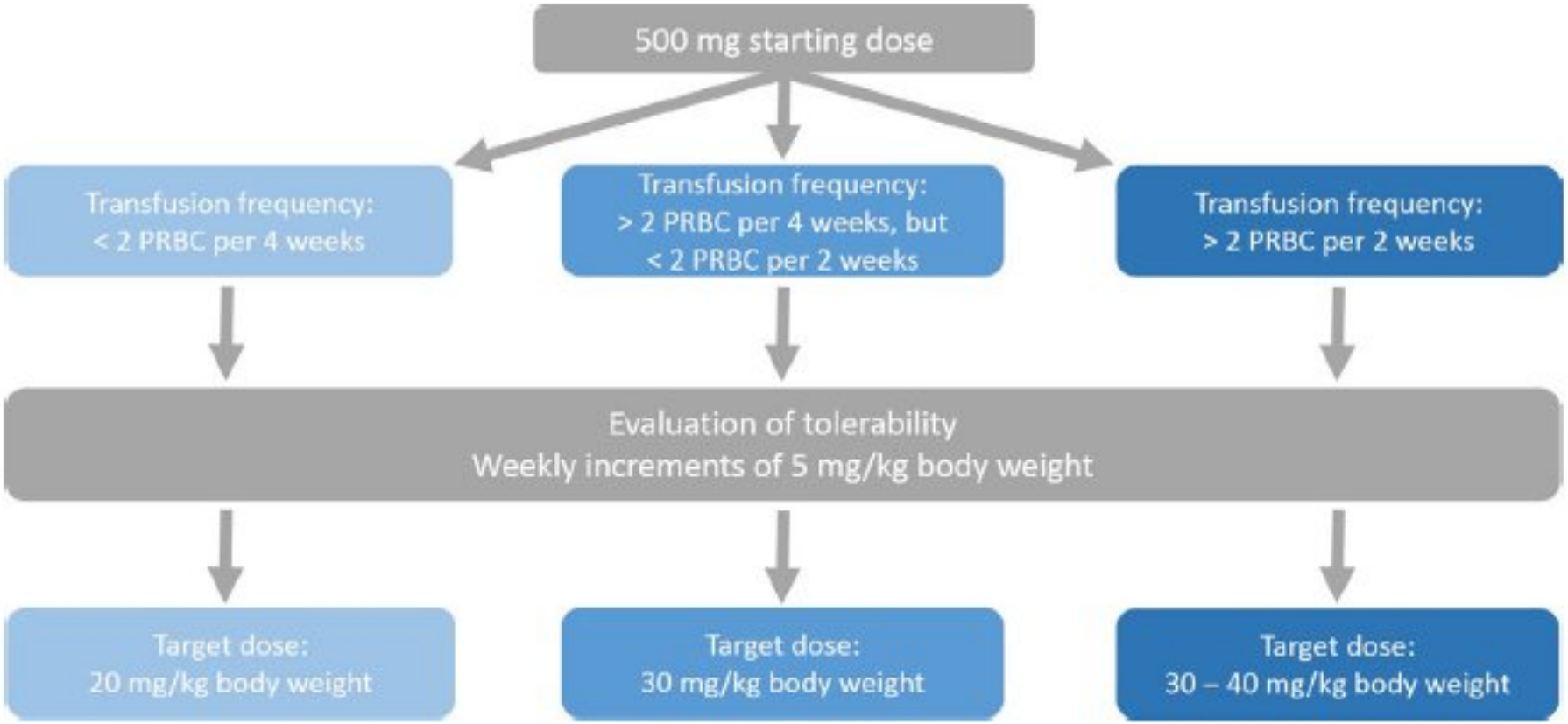
Nolte, Leuk Res 2015



Nolte, Leuk Res 2015

Deferasirox for managing iron overload in people with myelodysplastic syndrome (Review)

Meerpohl JJ et al, Cochrane Database of Systematic Reviews 2014,

Key results:

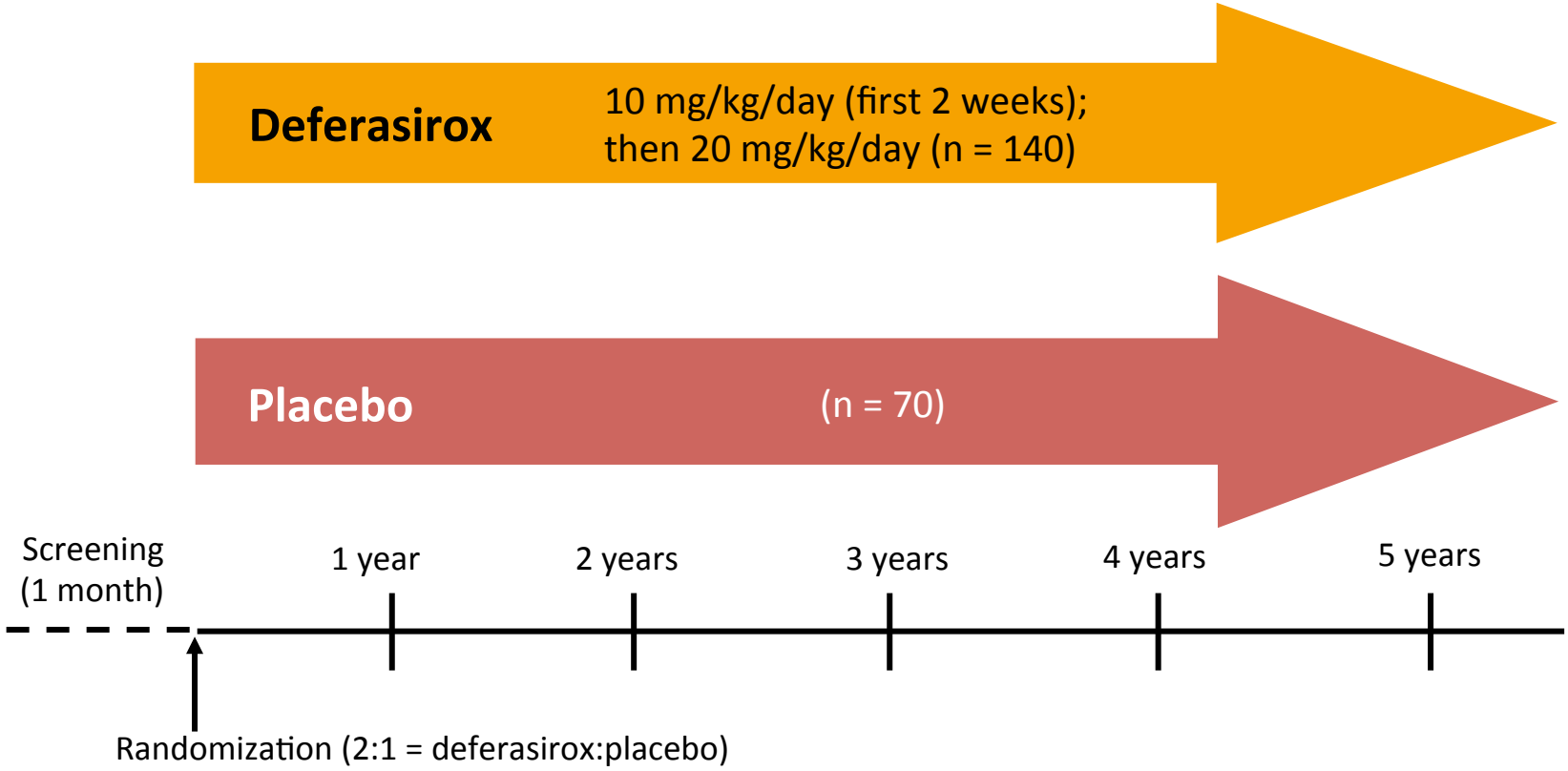
We searched the available literature up to 03 April 2014. We could not include any data in this review that answered our question.

However, we found three ongoing trials and one completed trial investigating deferasirox in people with MDS of lower risk groups (low

and intermediate-1 risk MDS). As the completed trial has only been reported in insufficient detail (in abstract format), we were unable to definitively decide on inclusion of this study or draw any conclusions from this. Once available, these results will be important to inform physicians and patients on the comparative advantages and disadvantages of this treatment option.

TELESTO: ongoing prospective study of deferasirox in MDS

- Prospective, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in **210** MDS patients
- Primary study end-point: EFS (death, cardiac, and hepatic non-fatal events)



Angelucci E, et al. Blood. 2009;114:abstract 4854.

TELESTO (Clinical trials.gov: NCT00940602)

Phase 3 trial

Descriptive Information	
Brief Title ICMJE	Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy Study
Official Title ICMJE	A Multi-center, Randomized, Double-blind, Placebo-controlled Clinical Trial of Deferasirox in Patients With Myelodysplastic Syndromes (Low/Int-1 Risk) and Transfusional Iron Overload
Brief Summary	The primary purpose of this study is to prospectively assess the efficacy and safety of iron chelation therapy with deferasirox compared to placebo in patients with myelodysplastic syndromes (low/int-1 risk) and transfusional iron overload.

Recruitment Information	
Recruitment Status ICMJE	Recruiting
Estimated Enrollment ICMJE	210
Estimated Completion Date	December 2017
Estimated Primary Completion Date	December 2017 (final data collection date for primary outcome measure)

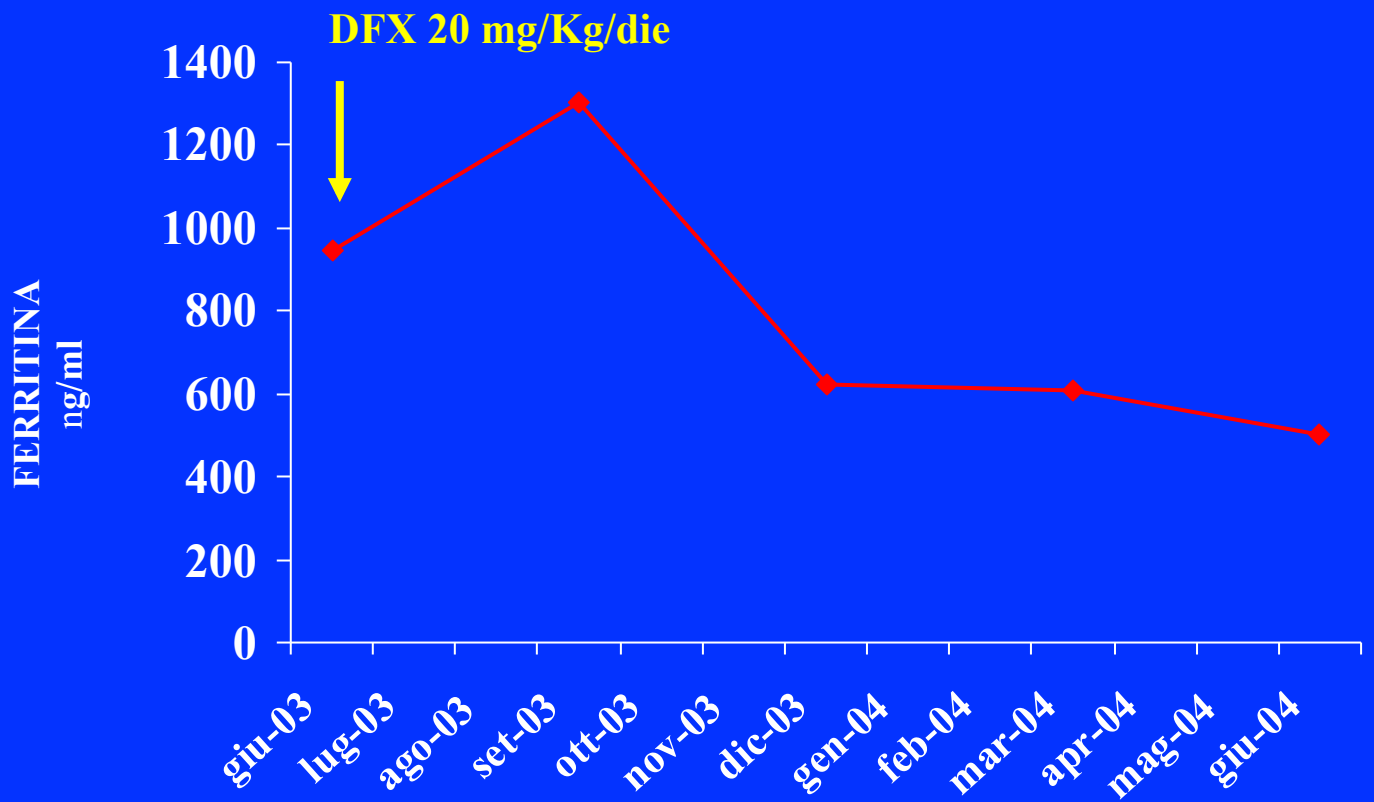
CASO CLINICO N° 1 (1)

- Femmina, 55 anni
- **Giugno 1996 :** Hb 6.5 MCV 126 reticolociti 0.2 %, WBC 4.2 (formula normale), Plts 187
- Aspirato e BOM: midollo ipocellulato, EP ridotta e displastica, MKC numerosi e displastici (ploidia ridotta), GP normale, moderato disomogeneo ↑ linfociti
- Cariotipo: N.V. (materiale scarso)
- EPO: 39
- Diagnosi presuntiva di PRCA , trattata con cortisone e poi ciclosporina , senza risposta (**ottobre 1996:** ancora trasfusione-dipendente)
- **Novembre 1996:** ripete aspirato + cariotipo: quadro morfologico invariato, 8/9 metafasi: **del(5q)(q13q33)**; assenza di piastrinosi (plts 210), WBC normali

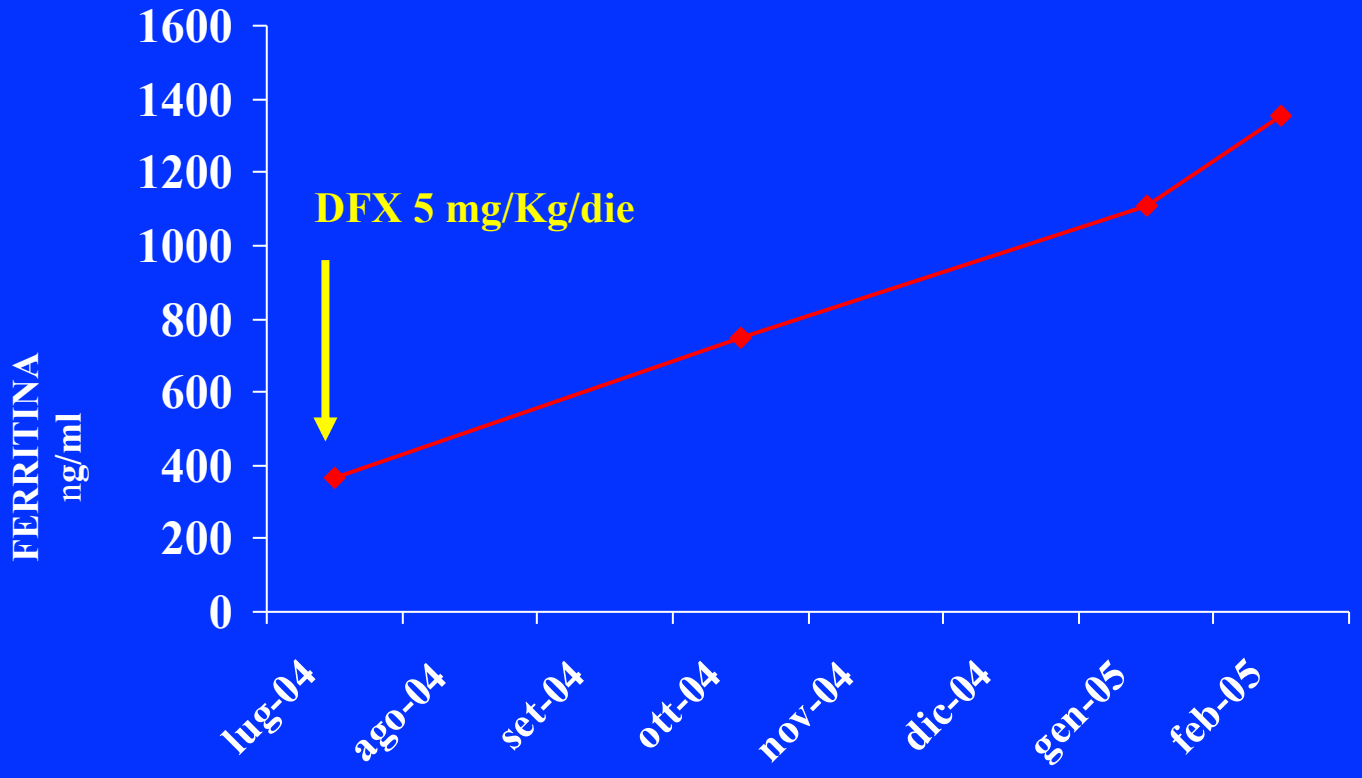
CASO CLINICO N° 1 (2)

- **Ottobre 1996:** inizia EPO, con beneficio solo parziale e transitorio
- **Aprile 1997:** ancora trasfusione-dipendente
- **Maggio 1998:** Inizio DFO (2 g/die i.c., pompa): ferritina 2.200, Ritmo Trasf : 2 GRC/10-14 gg
- **Febbraio 2003:** ferritina 1.100
- **Giugno 2003:** inizia Deferasirox (20 mg/Kg/die) (prot. 108): ferritina: 946 ng/ml; LIC (biopsia epatica): 13
- **Giugno 2004:** ferritina 504 ng/ml; LIC (biopsia epatica): 2.3

CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (A)

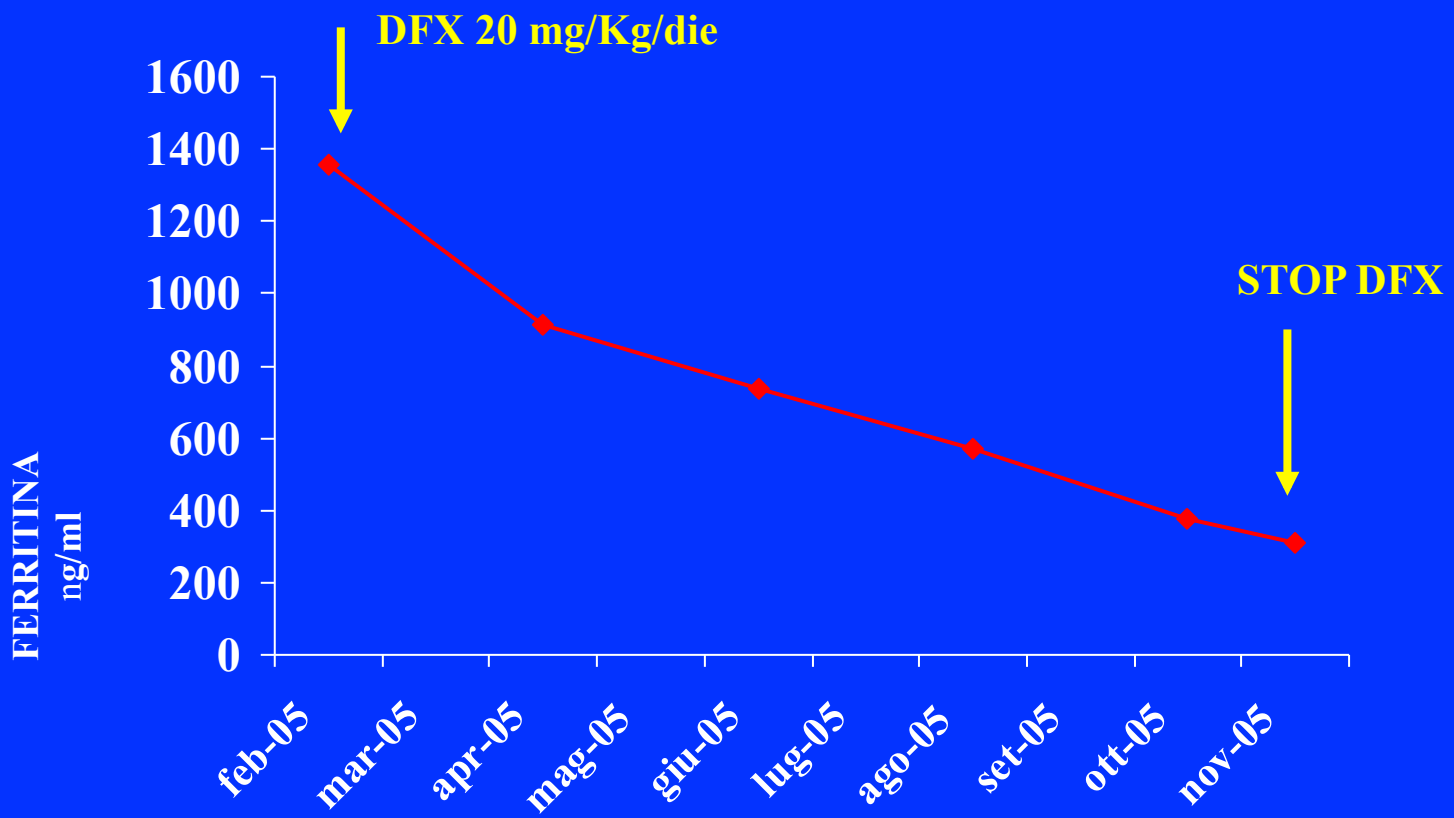


CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (B)



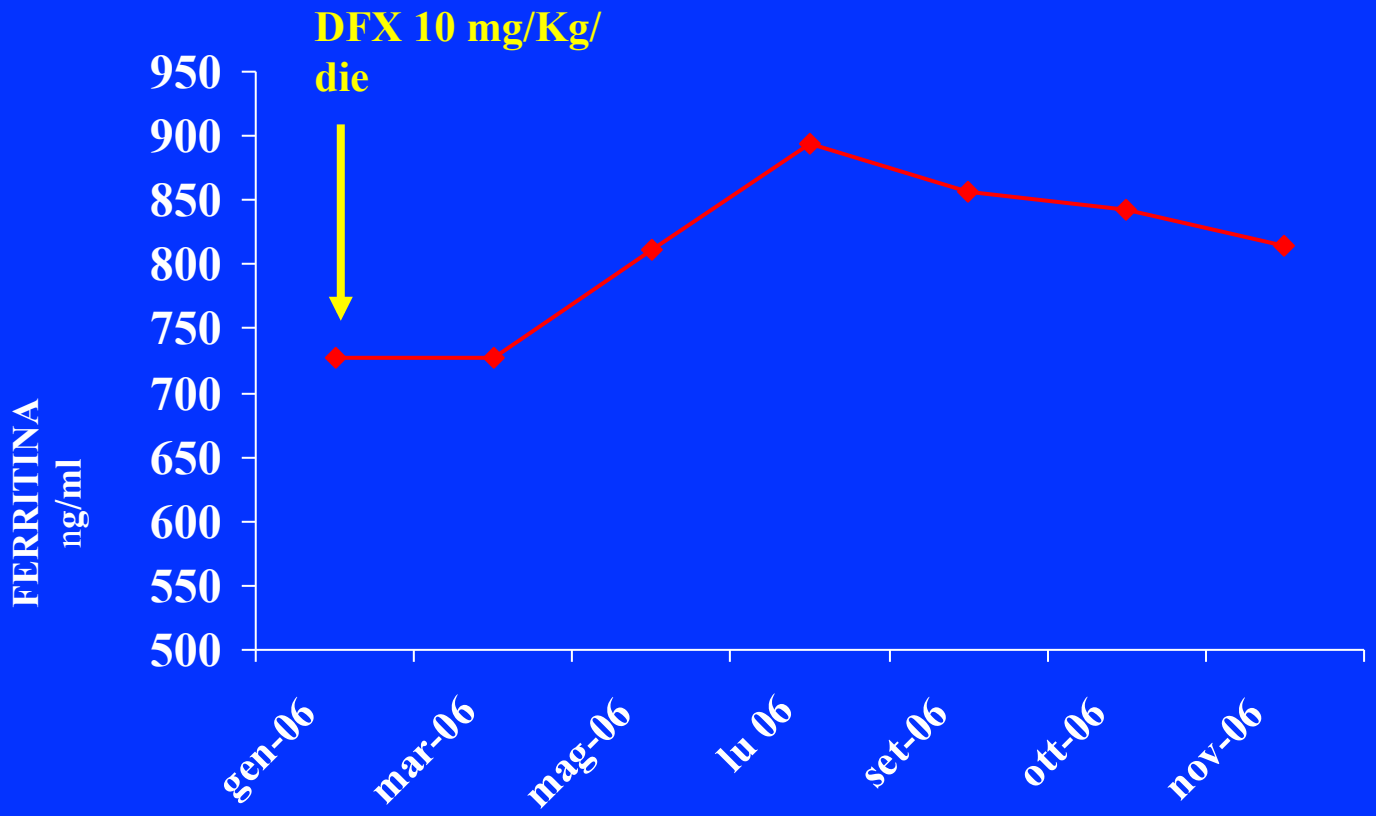
Da luglio 2004 prosegue Deferasirox con riduzione della dose (5 mg/Kg/die) sulla base della LIC (2.3) e della ferritinemia (364 ng/ml): Costante e progressivo incremento della ferritinemia (fino a 1354 ng/ml nel febbraio 2005)

CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (C)



Da febbraio 2005: nuovo incremento della posologia (20 mg/Kg/die). Progressivo decremento della ferritinemia fino a 311 ng/ml (novembre 2005) : sospende temporaneamente Deferasirox

CASO CLINICO N° 1: RISPOSTA AL DEFERASIROX (D)



Dal gennaio 2006 (ferritina 727 ng/ml) riprende Deferasirox alla posologia intermedia di 10 mg/Kg/die (prot. 108E). Da allora la ferritina si assesta a 700-900 ng/ml (bilancio marziale in pareggio) (ottobre 2006: 842 ng/ml)

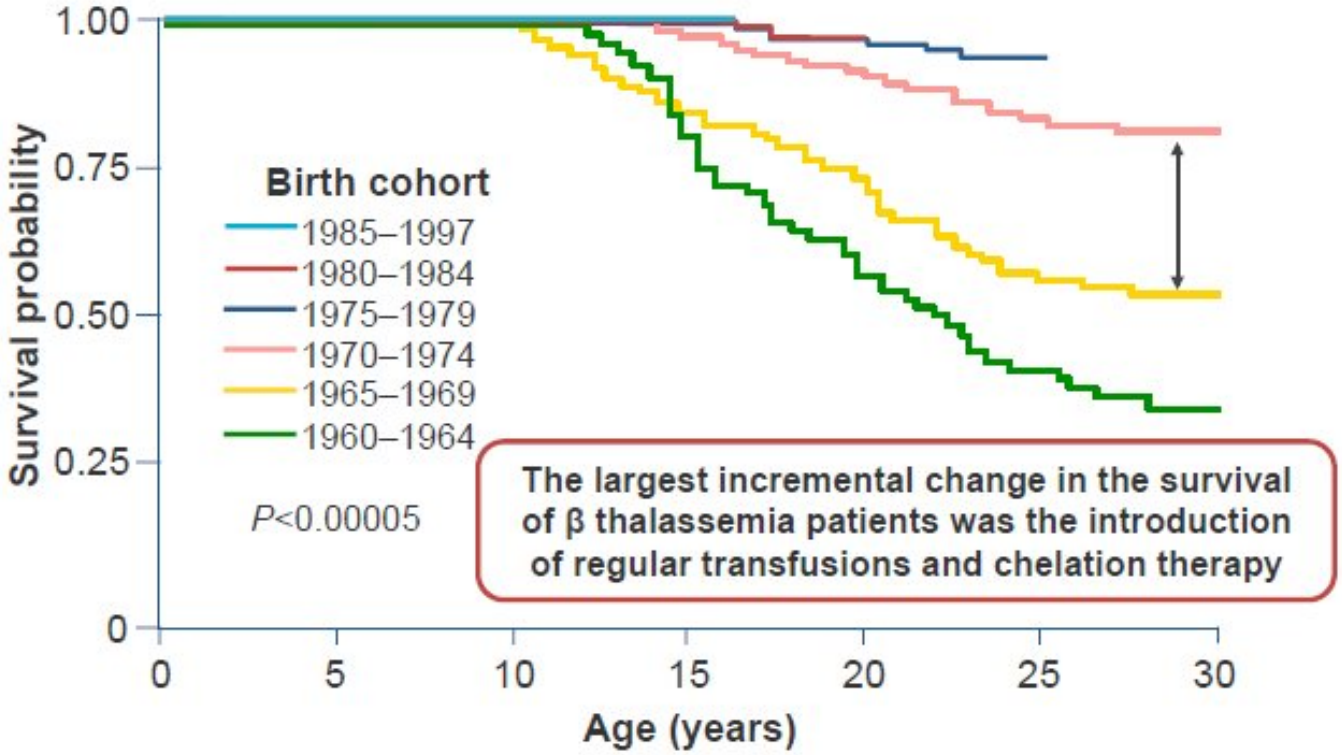
CASO CLINICO N° 1 (3)

- **giugno 2009:** Inizia terapia con **LENALIDOMIDE;**
  CARATTERISTICHE PRE-TERAPIA: Cariotipo: de(5q), +8; Blasti midollari < 2%; N° di citopenie: 1 (anemia); Rischio IPSS: basso (score 0); Ritmo trasfusionale: 4 unità/4 settimane; **ferritina (4/2009): 823 ng/ml**
- **ottobre 2009: 1° RISPOSTA (Hb 12,2);** TIPO DI RISPOSTA (IWG, Cheson 2006): RC; TEMPO ALLA 1° RISPOSTA : 3° mese; DURATA DELLA RC EMATOLOGICA: 76 mesi (ottobre 2009- febbraio 2013); DURATA DELLA CCR: : 18 mesi (luglio 2010-gennaio 2012)
- **ottobre 2009:** sospensione di DFX (cessazione delle trasfusioni, ferritina 791 ng/ml)
- **luglio 2010:** (dopo 12 mesi di terapia): remissione citogenetica completa (CCR)
- **luglio 2011:** sospensione della lenalidomide
- **aprile 2016 :** relapse (Hb 8,8): ripresa della lenalidomide
- **SOPRAVVIVENZA: 239 mesi dalla diagnosi**

CASO CLINICO N° 2

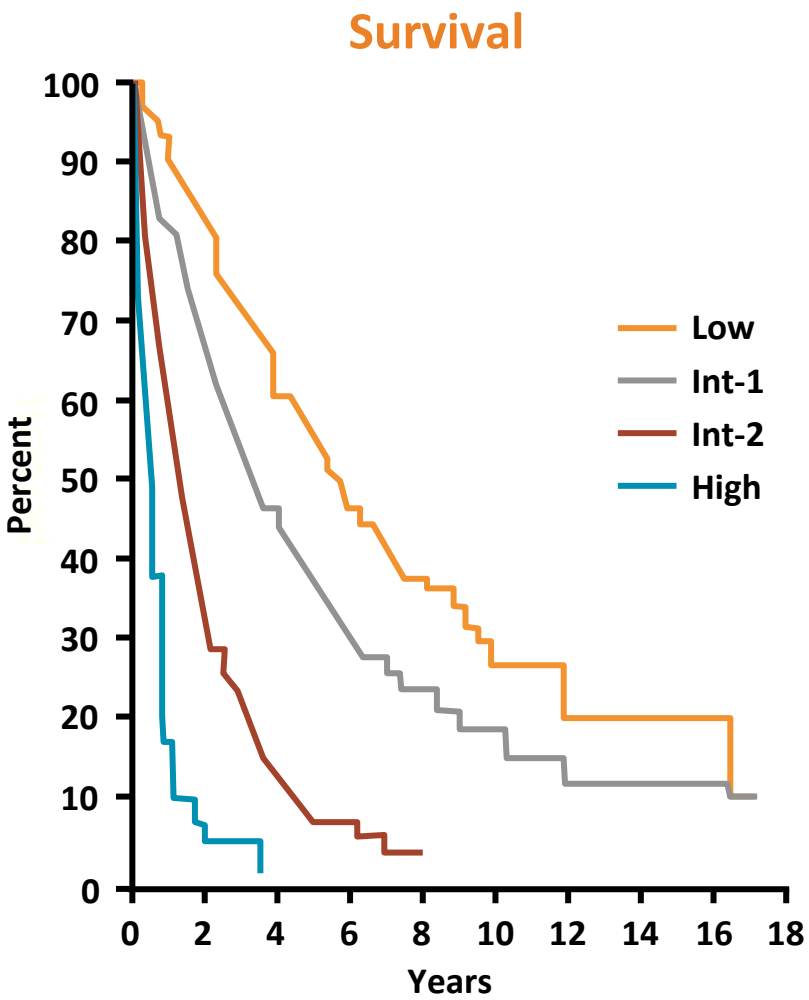
- Femmina, 48 anni
- **Ottobre 1991:** Hb 9.3 MCV 110 reticolociti 2.3 %, WBC 3.8 (PMN: 2.4), Plts 273; Ferritina : 203; Aspirato Midollare: **RARS** (blasti < 2%) ; Cariotipo: nomale; **rischio IPSS: basso; IPSS-R: basso**
- **Aprile 1994:** Hb 9, terapia con EPO e poi con androgeni: inefficace
- **Luglio 1997:** inizia terapia trasfusionale (Hb 7.4)
- **Ottobre 1997:** inizia DFO i.c. : scarsa tolleranza e scarsa compliance (3 volte/ settimana)
- **Marzo 2006:** sospende DFO e inizia DFX: 20 mg/Kg/die; emocromo e aspirato midollare: malattia stabile; ritmo trasfusionale: 1 GRC/7 gg; ferritina: 1936 ng/ml
- **Settembre 2006:** riduce DFX a 10 mg/Kg/die
- **Marzo 2007:** DFX 10 mg/Kg/die, malattia stabile, 4 GRC/7 gg; ferritina 725 ng/ml
- **Aprile 2016:** malattia e ritmo trasfusionale invariati, DFX 20 mg/Kg/die, ferritina 568 ng/ml, non segni di danno d'organo (eco di cuore e fegato)
- **SOPRAVVIVENZA: 294 mesi dalla diagnosi, 225 mesi dall'inizio delle trasfusioni**

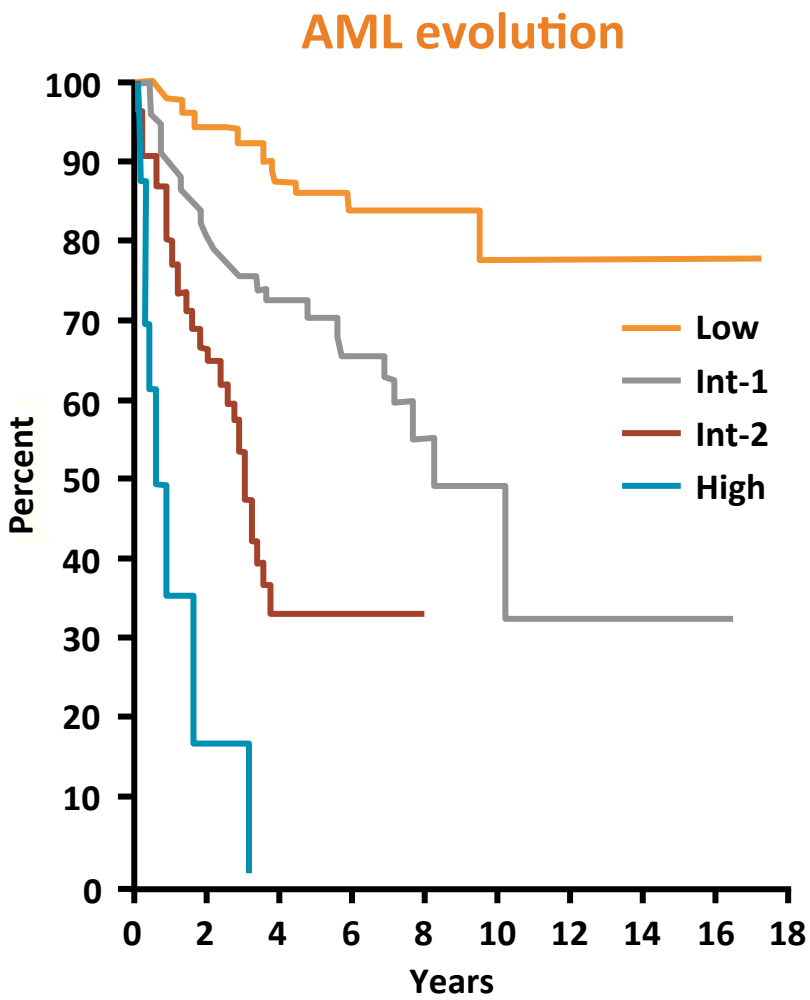
Regular transfusions and chelation therapy significantly improve survival of β thalassemia patients



1. Borgna-Pignatti C *et al. Haematologica* 2004;89:1187–1193.
Multicenter retrospective cohort study; n=977.

Cumulative survival of patients with MDS by IPSS





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

IPSS: Median Survival (yrs)

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

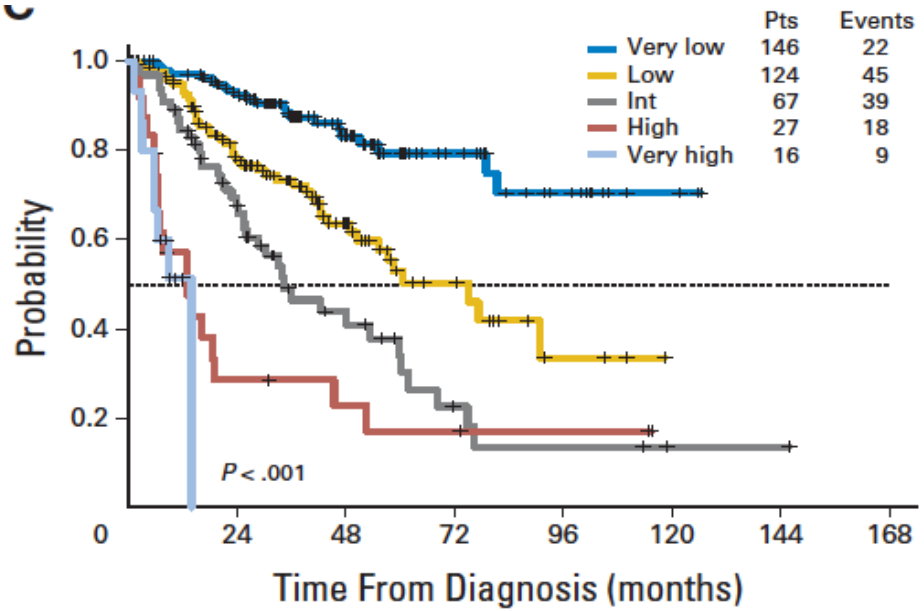
IPSS risk group (pts)	Age < 60	Age > 60	Age > 70
Low (0)	11.8	4.8	3.9
Int-1 (0.5-1.0)	5.2	2.7	2.4
Int-2 (1.5-2.0)	1.8	1.1	1.2
High (2.5-3.5)	0.3	0.5	0.4

Revised IPSS

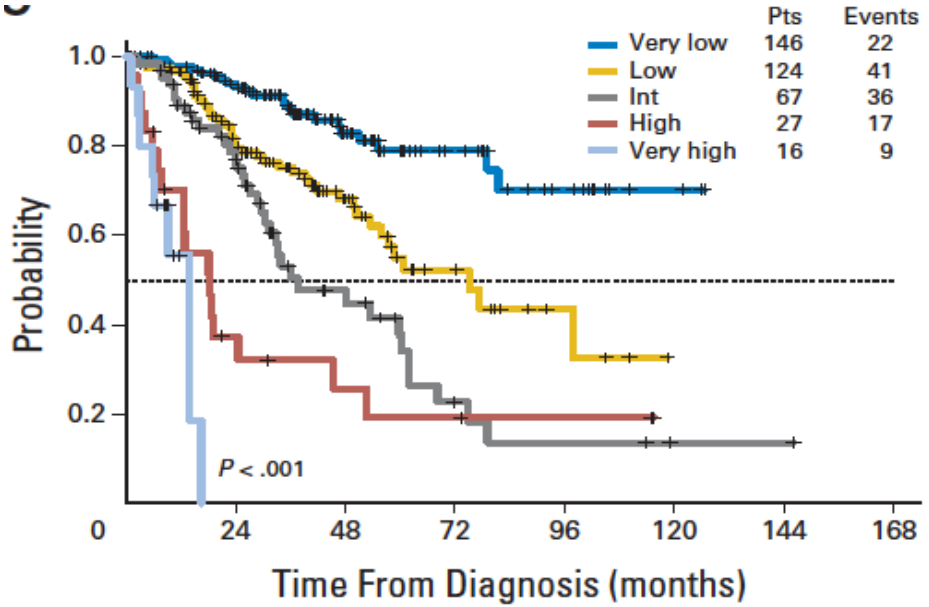
Categoria di rischio	Rischio	Sopravvivenza (mesi)	Evoluzione leucemica (25%, anni)
Molto basso	≤ 1.5	8.8	NR
Basso	> 1.5–3	5.3	10.8
Intermedio	> 3–4.5	3.0	3.2
Alto	> 4.5–6	1.6	1.4
Molto alto	> 6	0.8	0.7

Greenberg et al. Blood 2012

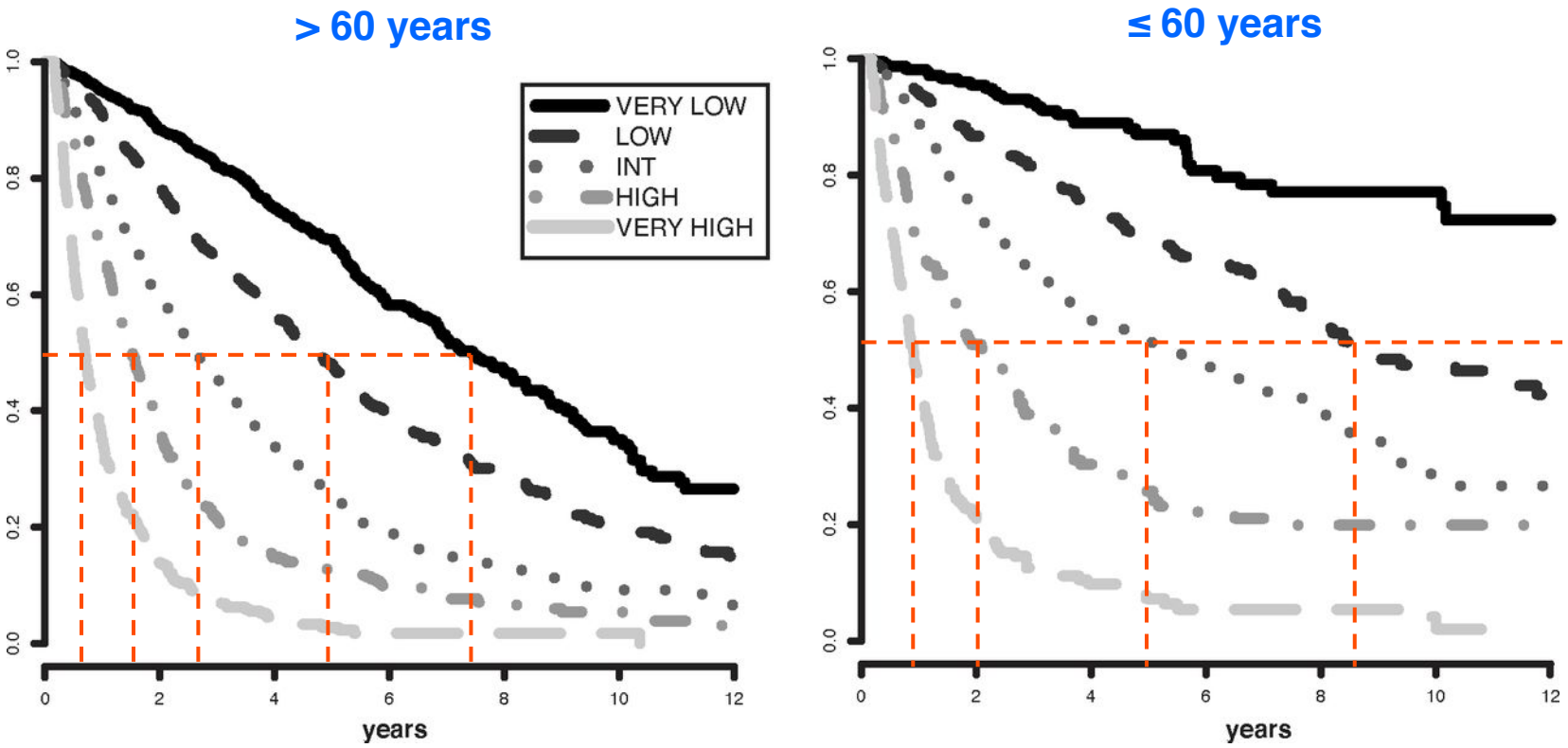
Leukemia-free Survival



Overall Survival



Survival based on Patient Ages

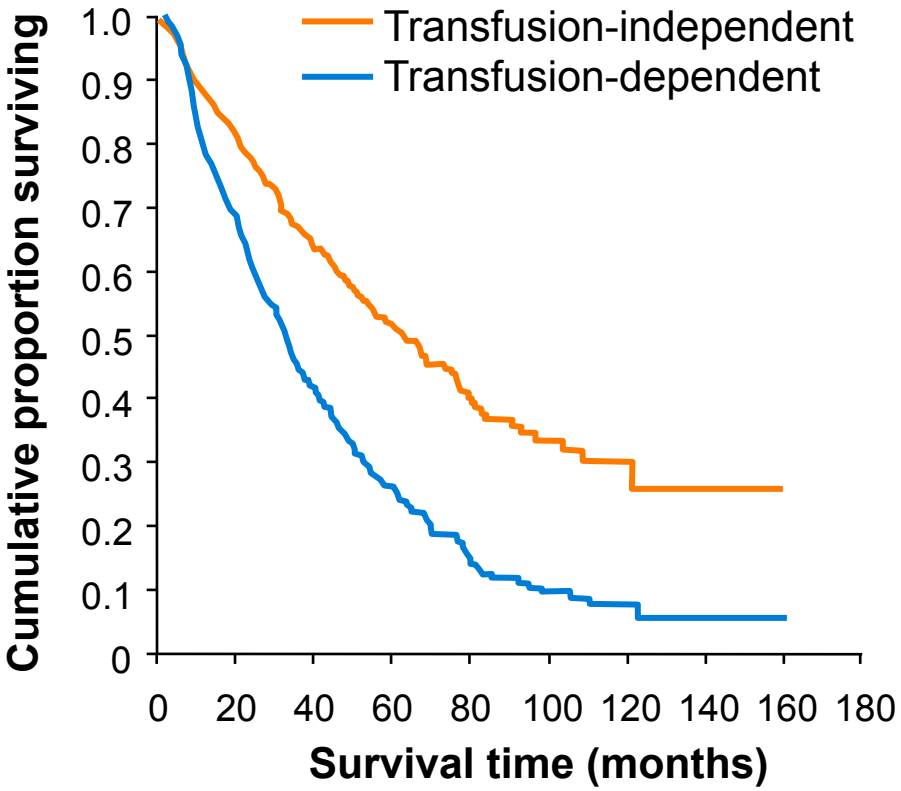


Greenberg P et al. Blood. 2012;120(12):2454.

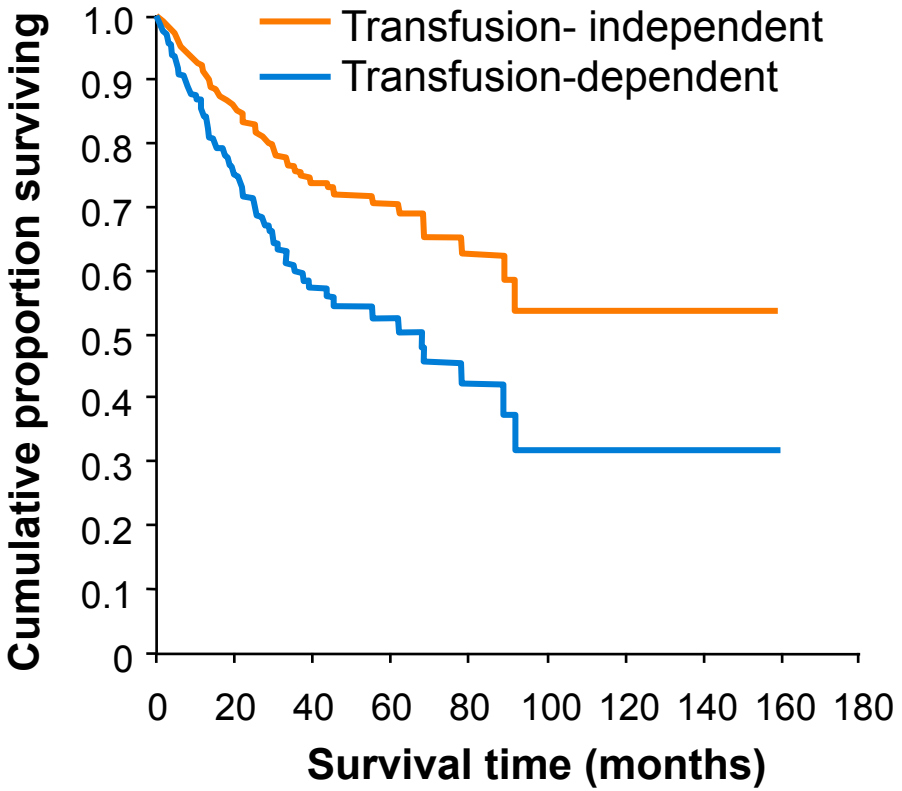
blood

Survival of MDS patients by transfusion dependence (N = 467)

Overall survival
(HR = 1.91; p < 0.001)



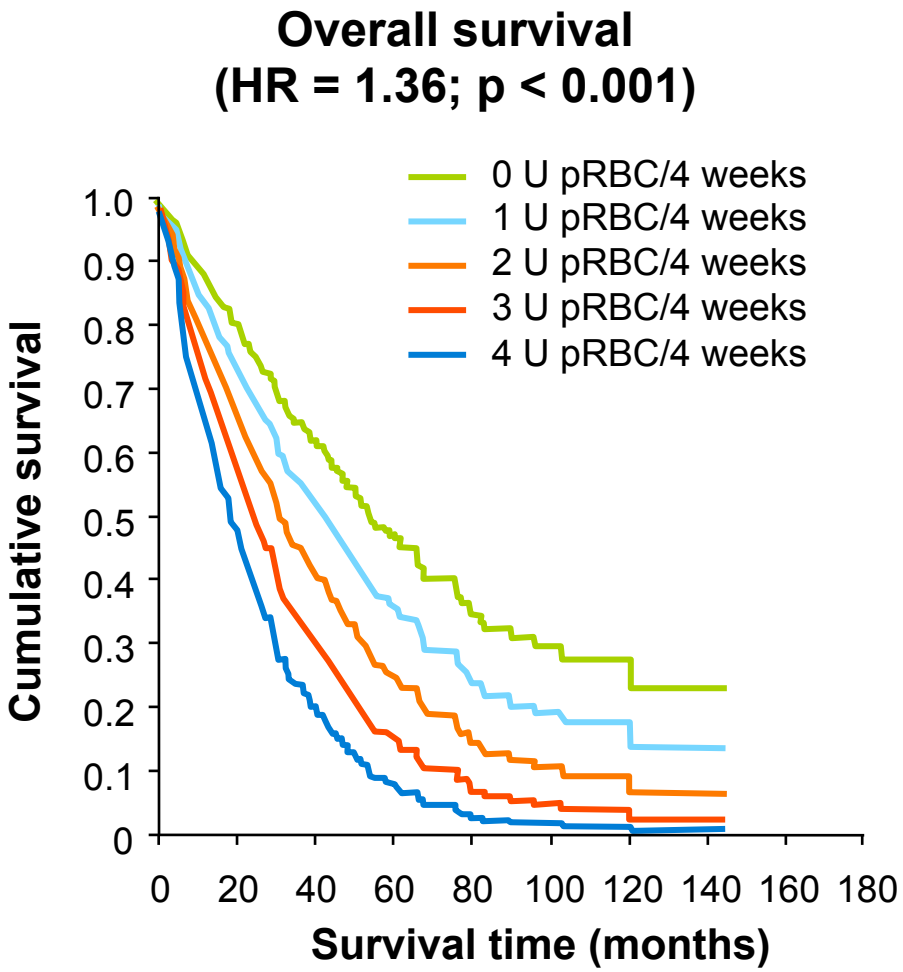
Leukaemia-free survival
(HR = 1.84; p = 0.001)

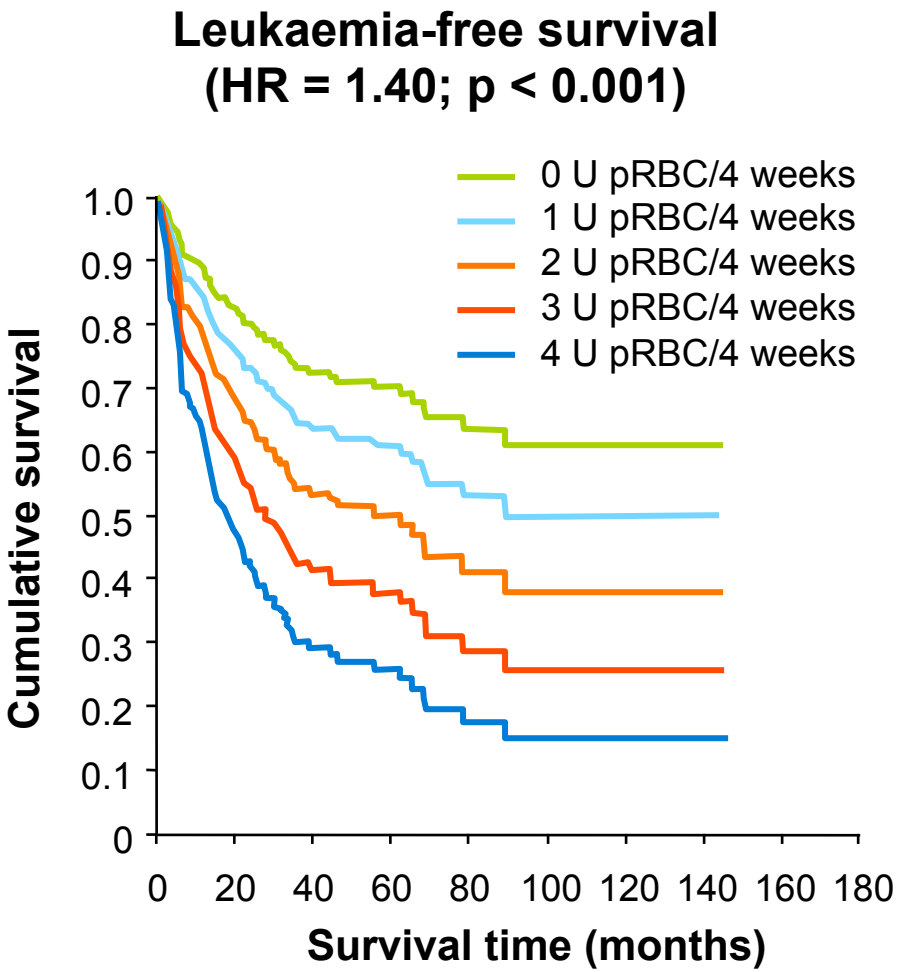


HR = hazard ratio.

Updated data from Malcovati L, et al. J Clin Oncol. 2005;23:7594-603.

Survival of MDS patients by severity of transfusion requirement

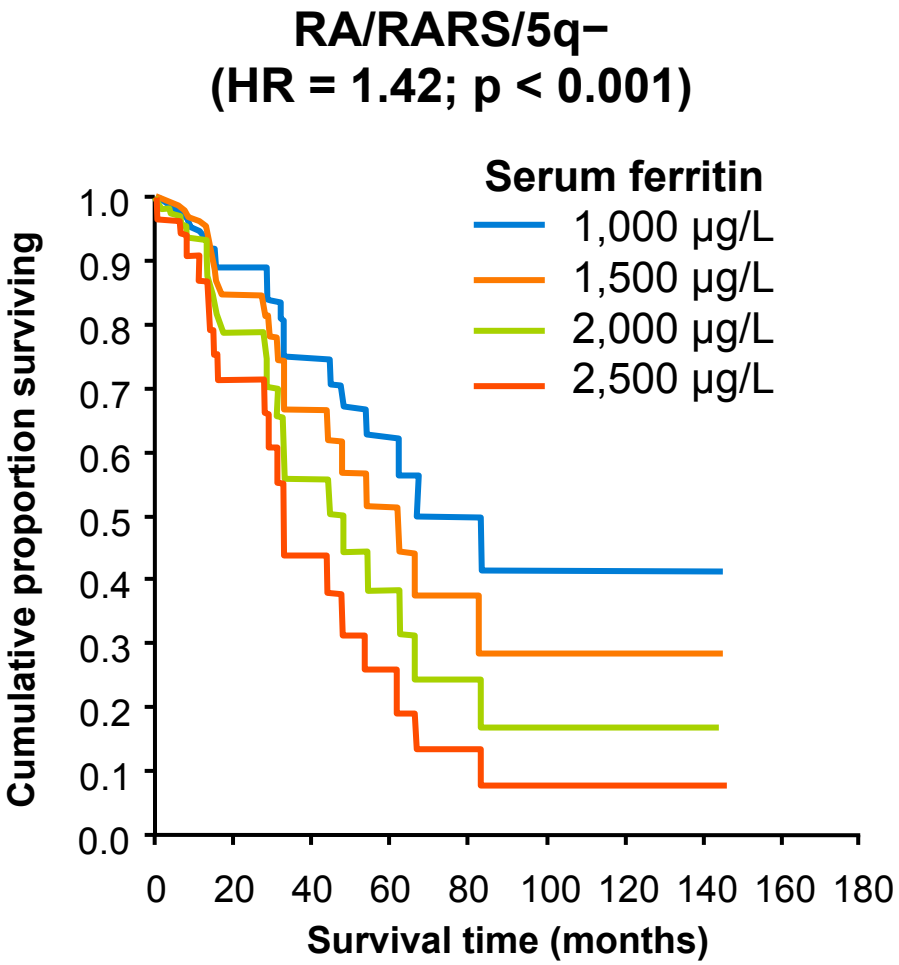


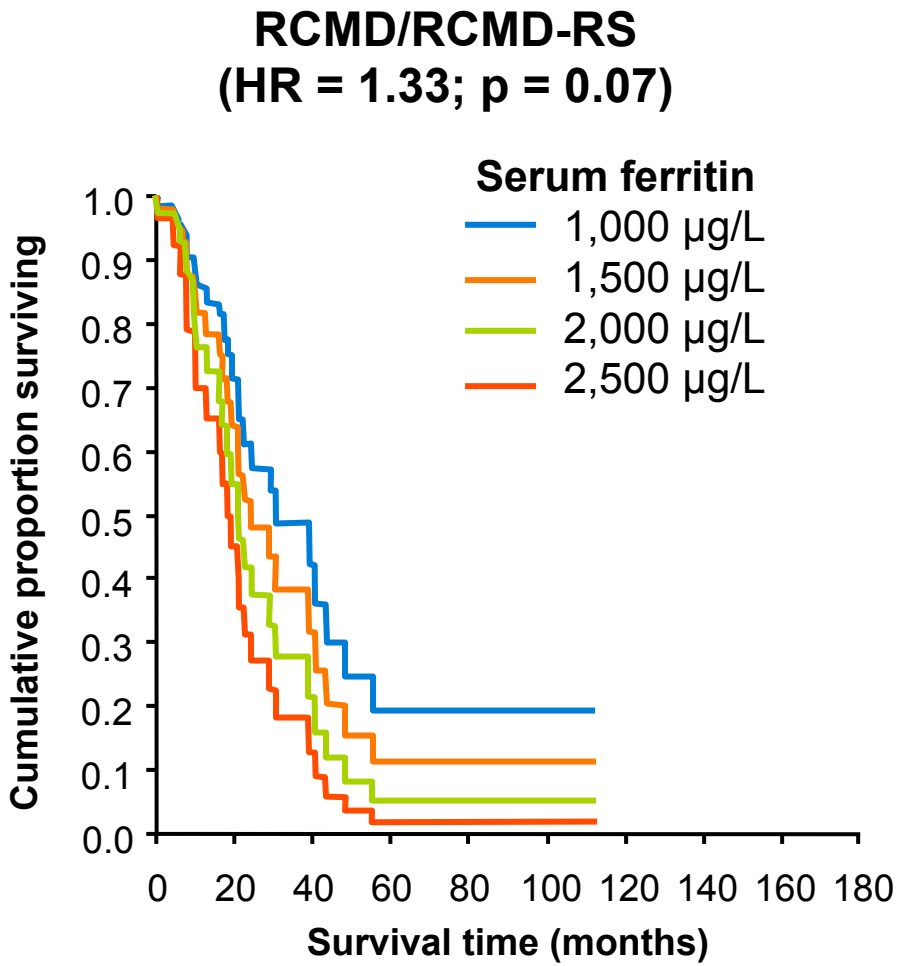


pRBC = packed red blood cells.

Updated data from Malcovati L, et al. Haematologica. 2006;91:1588-90.

Overall survival of transfusion-dependent patients by serum ferritin level





RA = refractory anaemia; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = RCMD with ringed sideroblasts..

Malcovati L, et al. Haematologica. 2006;91:1588-90.

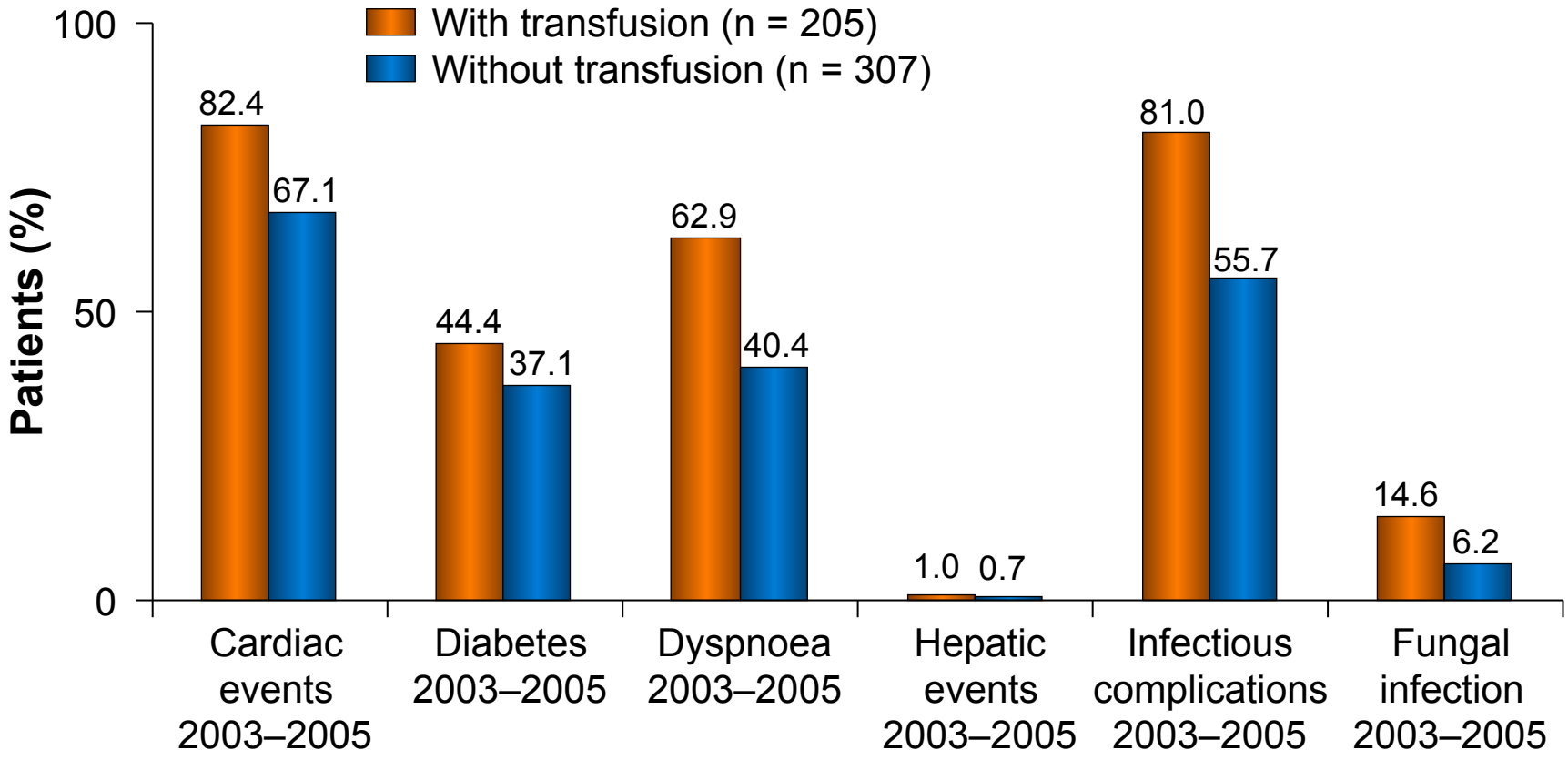
Impact of iron overload and transfusion dependency on cardiac disease and survival in patients with MDS

- Analysis of 455 patients with MDS:
  - Cardiac disease was the most frequent extra-hematological morbidity (25%)
  - Cardiac disease was the main cause (63%) of non-leukemic death
  - Serum ferritin level was significantly associated with the risk of cardiac disease and death (*P*=0.001)

Della Porta MG *et al*. *Blood* 2008;112(11):abst 2677

Prevalence of comorbidities in transfusion-dependent MDS

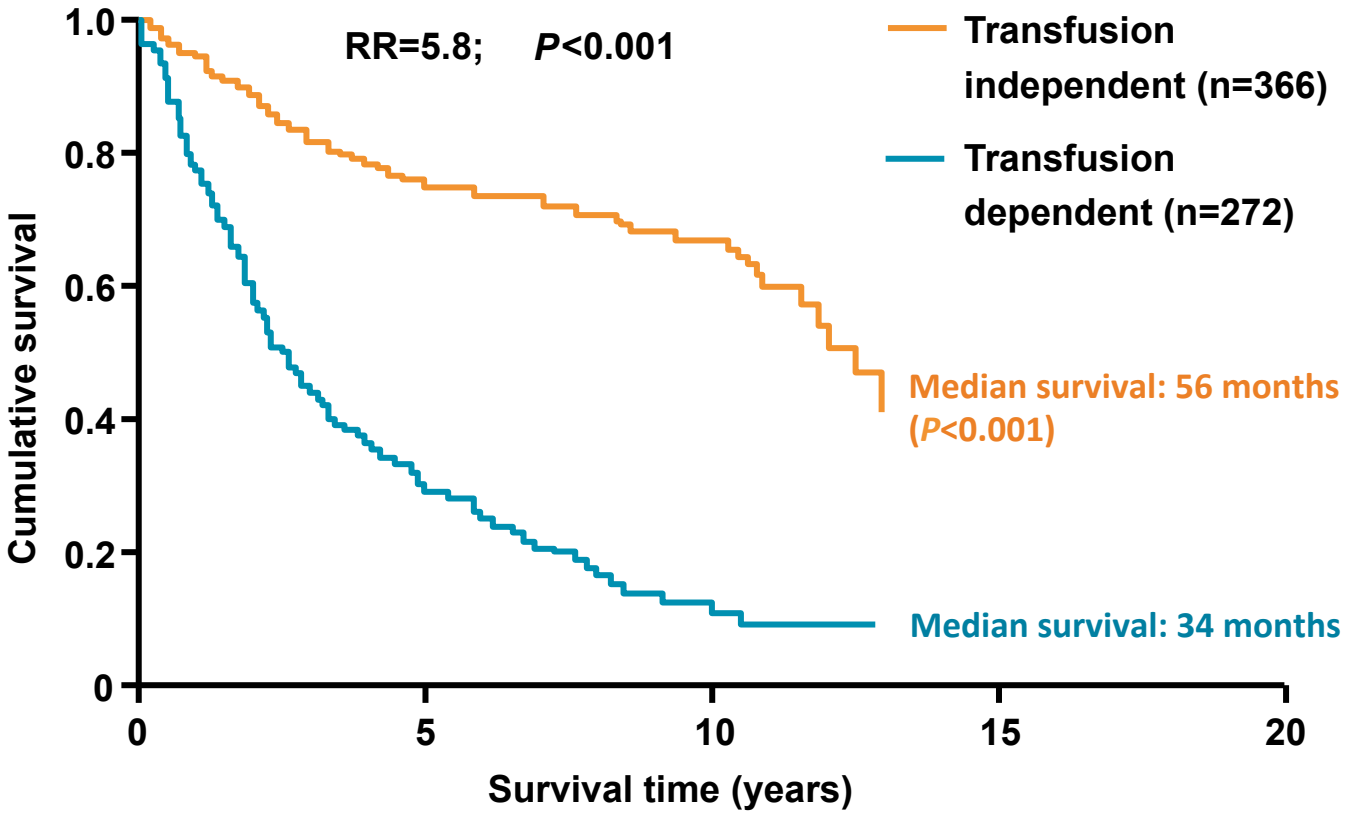
(retrospective review of 2003 Medicare Files: new MDS pts with 3-year follow-up)



Transfused MDS patients have a higher prevalence of cardiac events, diabetes mellitus, dyspnoea, and hepatic and infectious diseases than non-transfused MDS patients

Goldberg SL. J Clin Oncol. 2010;28:2847-52.

Independent impact of transfusion dependency on survival



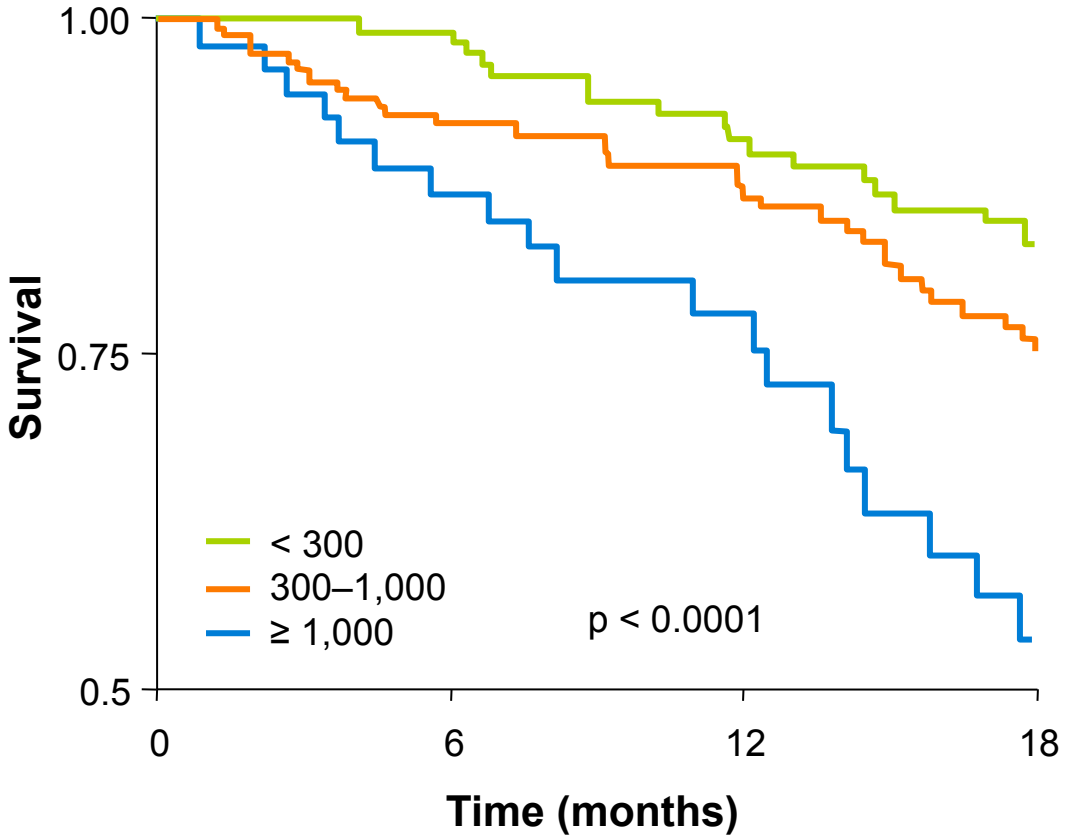
Transfusion dependency is strongly associated with overall survival

Arnan M *et al.* Presented at EHA 2010 [*Haematologica* 2010;95(Suppl 2):abst 0314]
Slide used with the permission of Montse Arnan, Hospital Duran i Reynals, Barcelona, Spain

RR, relative risk

LeukemiaNet prospective registry: mortality increased as serum ferritin increased in 1,000 MDS patients

Overall survival of transfusion-dependent patients by baseline serum ferritin status



- Significantly greater mortality was noted in MDS patients who were
  - transfusion-dependent patients ($p < 0.0001$)
  - patients with baseline serum ferritin ≥ 1,000 µg/L ($p < 0.0001$)
  - transfusions > 20 units ($p < 0.0001$)

de Swart L, et al. Blood. 2011;118:[abstract 2775].

Iron Overload in MDS Prognostic for OS and Risk of AML Transformation

- Transfusion dependency is a known prognostic factor in MDS[1]
- Development of iron overload may influence outcome
- Study of large series (N = 2994) of patients with de novo MDS (FAB criteria)[2]
- Median OS significantly worse with baseline transfusion dependency (*P* < .001)
  - Transfusion-dependent at diagnosis: 19 mos
  - Transfusion-dependent during evolution: 60 mos
  - Not transfusion dependent: 96 mos

Prognostic Factor	HR*	*P* Value
OS		
▪ Iron overload	2.1	< .0001
▪ Transfusion dependency	7.2	< .0001
LFS		
▪ Iron overload	1.6	.04
▪ Transfusion dependency	2.9	< .0001

*Multivariate analysis on cases with complete transfusion and serum ferritin records (n = 731).

1. Malcovati L, et al. J Clin Oncol. 2007;25:3503
2. Sanz G, et al. ASH 2008. Abstract 640.

Prognostic impact of iron overload is independent of WPSS score

Overall survival

Variable*	HR	p value
Iron overload	4.34	< 0.001
WPSS	1.60	< 0.001

Leukemia-free survival

Variable*	HR	p value
Iron overload	2.13	< 0.001
WPSS	2.24	< 0.001

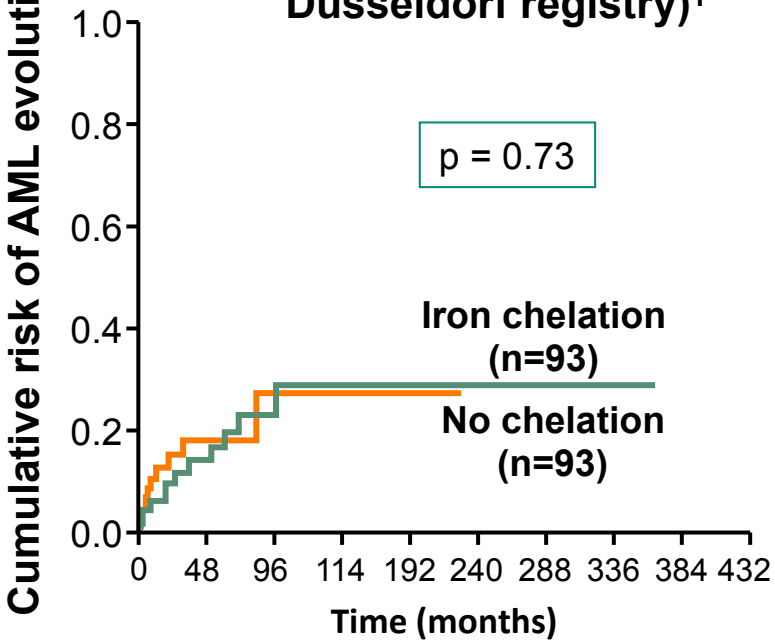
* Multivariate analyses including WPSS and development of iron overload (time-dependent) (n = 580). Cases with less than 3 serum ferritin measurements were excluded.

WPSS = WHO-classification-based Prognostic Scoring System.

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

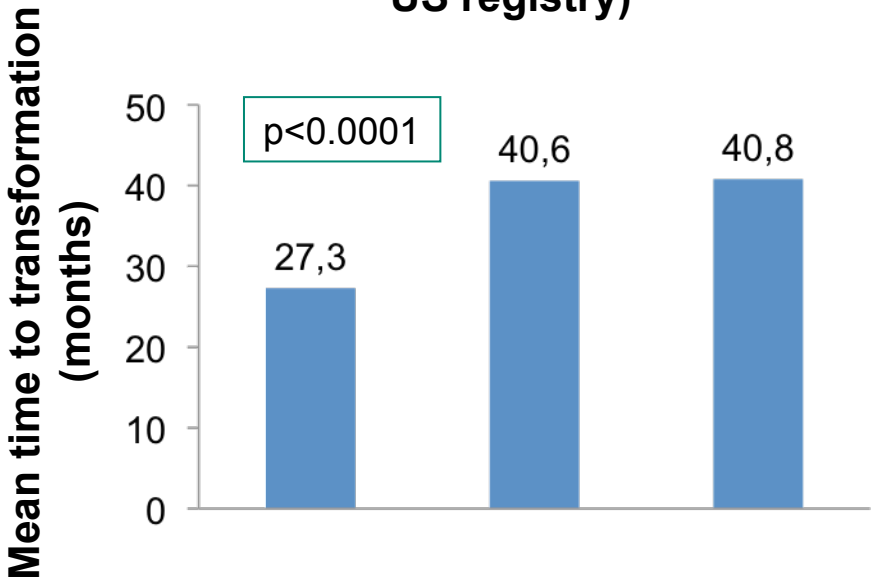
Iron Chelation and AML Transformation: Clinical Data

Iron chelation does not delay AML transformation (Matched-pair analysis from Dusseldorf registry)[1]



AML risk	2 years	5 years
Chelation	10%	19%
No chelation	12%	18%

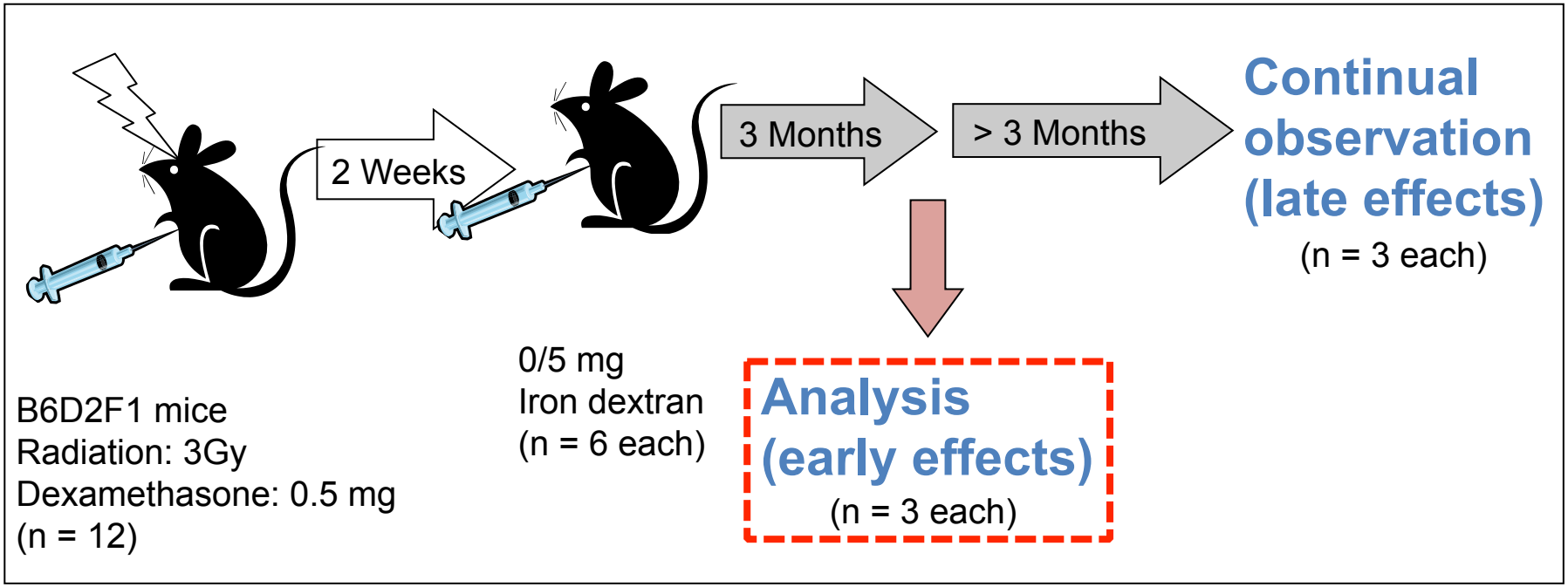
Iron chelation delays AML transformation (Multi-center analysis from US registry)[2]



	Non-chelated n=337	All Chelated n=263	Chelated ≥6 months n=191
AML transformation n (%)	30 (8.9)	12 (4.6)	10 (5.2)

[1]Fox *et al. Blood*. 2009;114:[abstract 1747]. [2]Lyons *et al. Blood*. 2011;118:[abstract 2800].

Iron Overload Accelerates Leukemogenesis in MDS Mouse Model



- Well-established radiation-induced AML model
- CBA/H and SJL/J strains (50–70%, 12 months)

Chan LSA, *et al. Blood*. 2010;116:[abstract 122].

Summary of the mouse model data

- Iron is mutagenic in haemopoietic cells (through increased intracellular ROS)
- Iron is not itself leukaemogenic; but in the context of the genomic instability of the MDS clone, iron overload may promote clonal evolution and thus accelerate progression of MDS to AML
- Further evaluation in animal models and in clinical trials is necessary to elucidate the clinical implications of these observations, especially in regard to the deployment of iron chelation therapy

Chan L, et al. Presented at ASH 2010. Blood. 2010;116:[abstract 122].

Iron Overload Accelerates Leukemogenesis in MDS Mouse Model Conclusions

- **Iron is mutagenic in hematopoetic cells (through increased intracellular ROS)**
- **Iron is not itself leukemogenic;**
  - but in the context of the genomic instability of the MDS clone, iron overload may promote clonal evolution and thus accelerate progression of MDS to AML.
- **Further evaluation in animal models and in clinical trials is necessary to elucidate the clinical implications of these observations, especially in regard to the deployment of iron chelation therapy.**

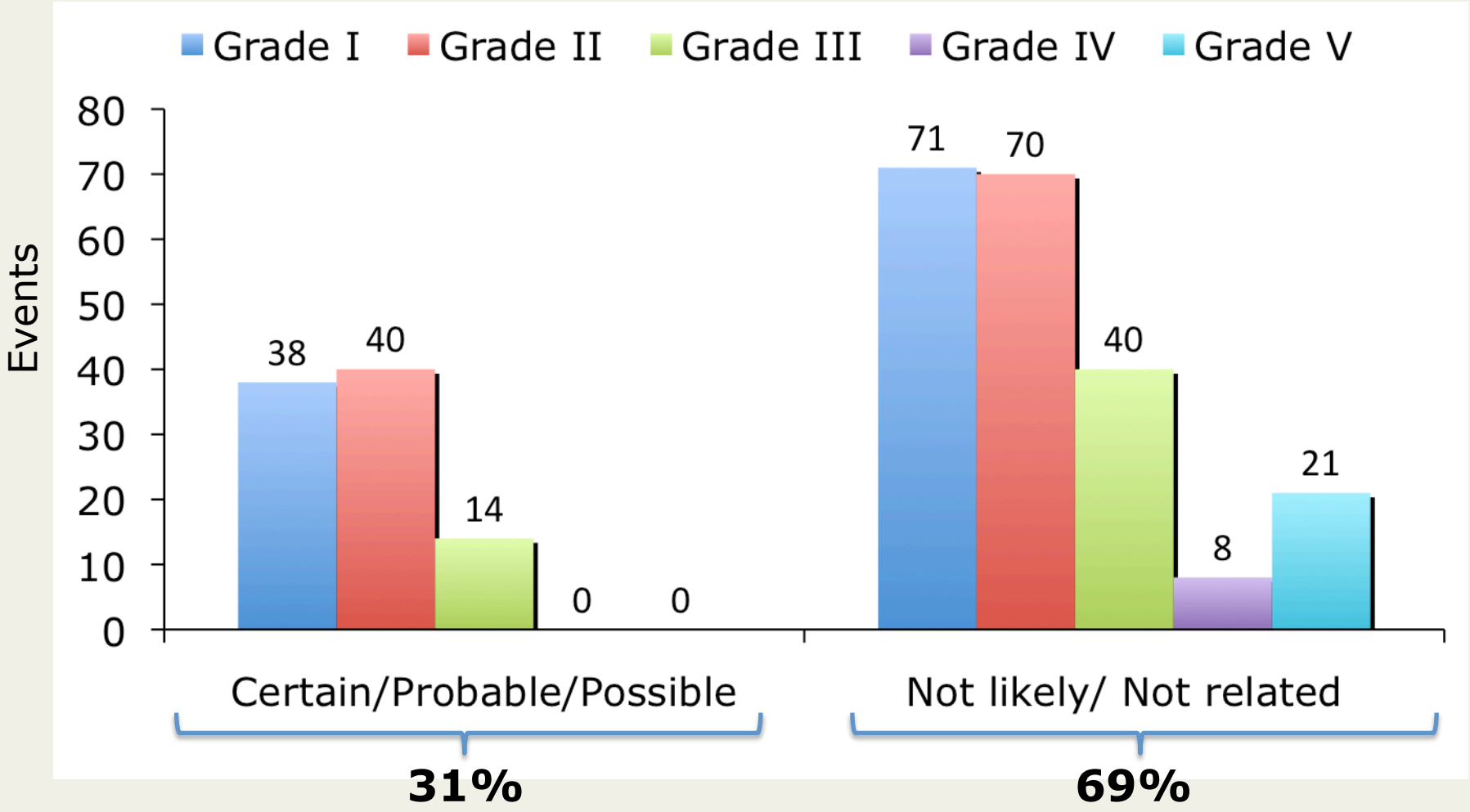
Chan L *et al.* Presented at ASH 2010 *[Blood* 2010;116(21):abst 122]

Principal clinical studies on DFX in MDS patients

	Study Type	No. pts	Inclusion criteria	Dose (mg/ kg/d)	Adverse effects	Efficacy
Porter, 2008	Phase II prospective multicenter	47	life expect >1 yr ≥8 transf/yr LIC[1]≥2 mg Fe/g dw	5-30	GI[5] events skin rash ↑ creatinine	↓ IOL[6] (SF[2],LIC[1])
List, 2009 (US03)	Phase II prospective multicenter open-label single-arm	176	IPSS[4] low/INT-1 ≥20 transfusions SF[2]≥1000 ng/mL	20	GI[5] events, ↑ creatinine	↓ IOL[6] (SF[2]) ↓ LPI[6] HI[9] (15-22%)
Gattermann, 2010 (EPIC)	Phase IIIb prospective multicenter open-label single-arm	341	life expect>1 yr >20 transfusions, SF[2]1000 ng/mL LIC[1]≥2 mg Fe/g dw	10-30	GI[5] events skin rash	↓ IOL[6] (SF[2]) ↓ LPI[8] HI[9] (13-22%)
Greenberg, 2010 (US02)	Prospective multicenter open-label single-arm	24	IPSS[4] low/INT-1 ≥20 transfusions SF[2]≥1000 ng/mL	20	GI[5] events ↑ creatinine skin rash	↓ IOL[6] (SF[2], LIC[1]) ↓ LPI[8]
Gattermann, 2012 (eXtend, eXjange)	Prospective observational multicenter open-label	167	SF[2]>1000 ng/mL ≥20 transfusions	10-30	GI[5] events ↑ creatinine skin rash	↓ IOL[6] (SF[2])
Angelucci, 2014 (GIMEMA MDS0306)	Prospective multicenter open-label single arm	150	IPSS[4] low/INT-1 ≥20 transfusions SF[2]≥1000 ng/mL	10-30	GI[5] events ↑ creatinine skin rash	↓ IOL[6] (SF[2)] HI[9] (13-22%)

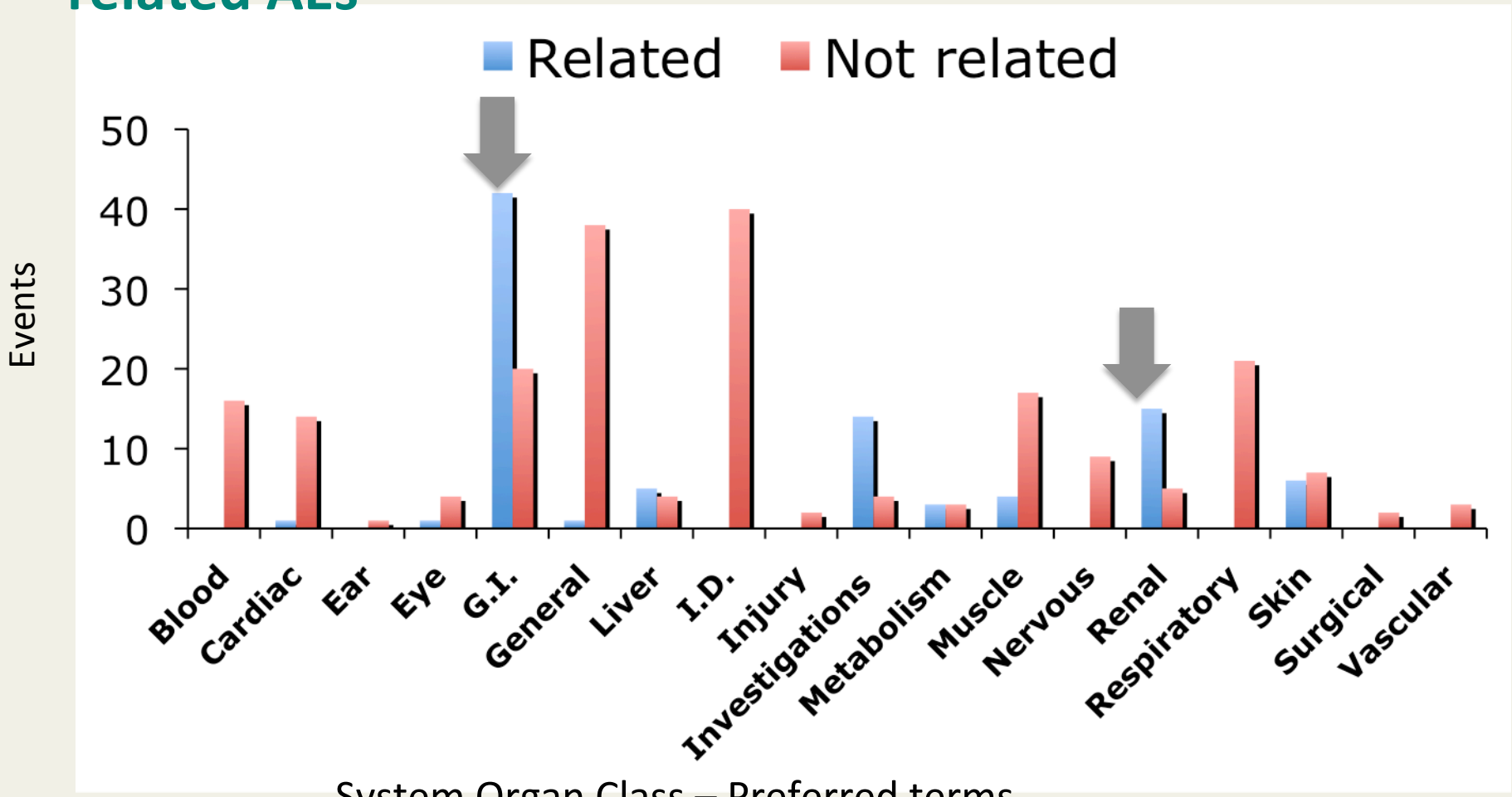
Adverse events

Severity and relationship to Deferasirox.

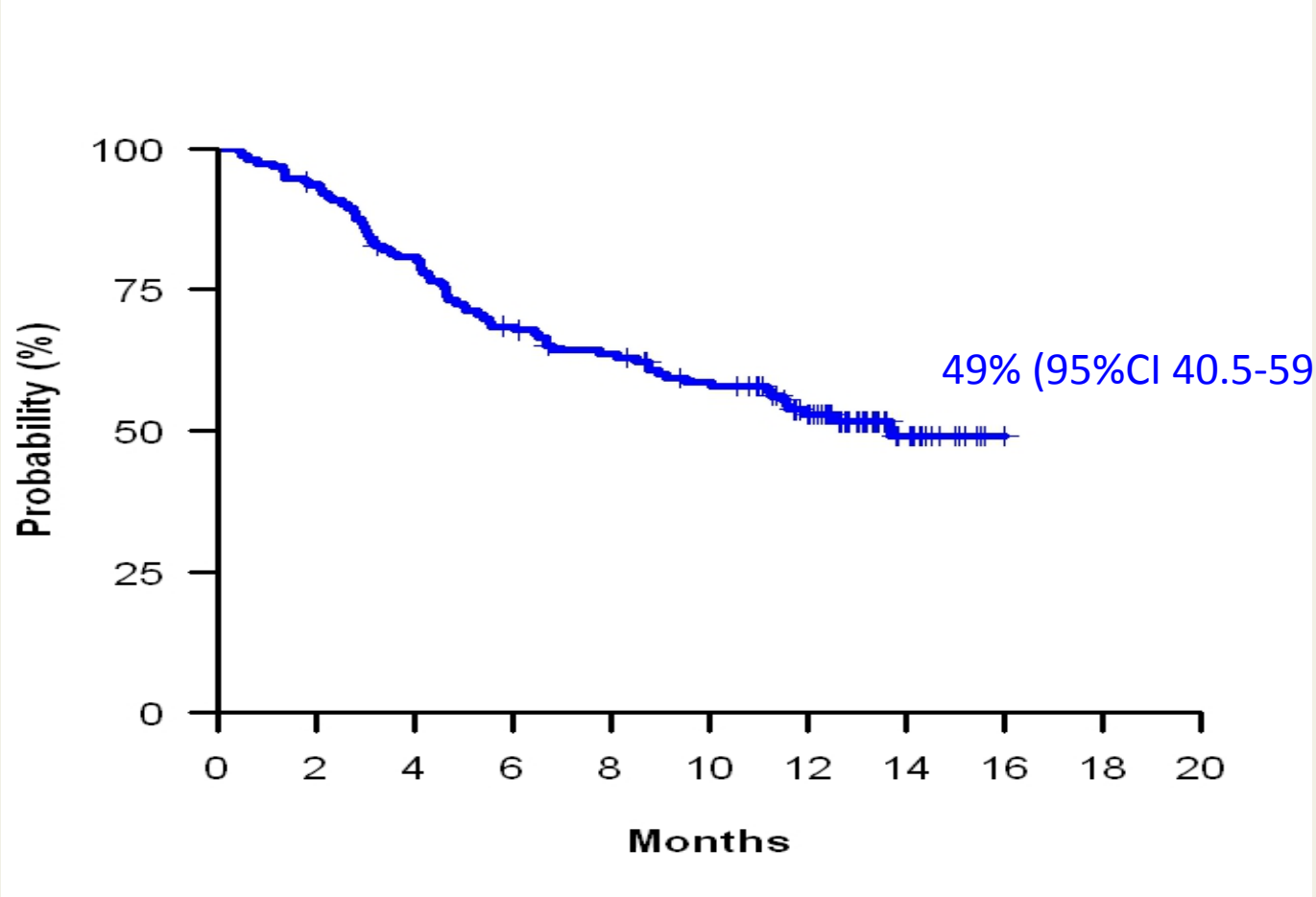


Adverse events

System Organ Class classification of related and not related AEs



K-M probability of continuing therapy



Causes of therapy discontinuation

Cause	Patients	%	
Adverse Event	28	33.3	33%
Death	22	26.2	36%
Disease progression	8	9.5	
Consent withdrawal	9	10.7	31%
Lost at follow up	8	9.5	
No response	2	2.4	
Serum ferritin < 500 ng/ml (no PRBC)	2	2.4	
Medical decision	5	6.0	
Total	84	100	

Multiple lines of evidence suggest ICT may improve OS in transfusion-dependent MDS

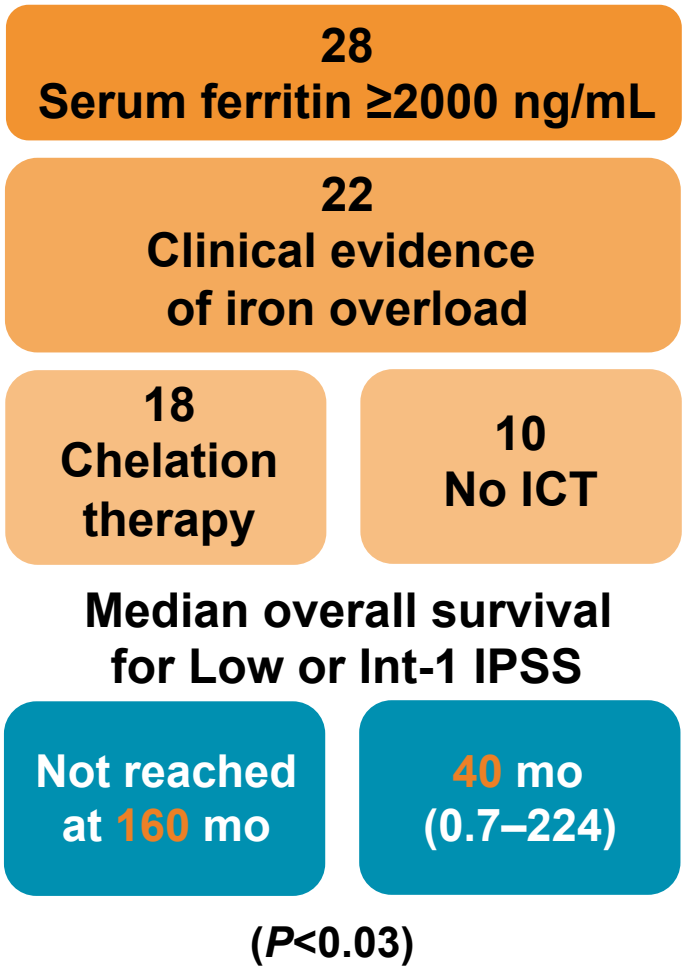
Study	N	Design	Survival	Non-chelated patients	Chelated patients	p value
Leitch 2008	36	Retrospective	Median OS	40 mo	Not reached	0.003
			4-year survival rate	43%	64%	0.003
Rose 2010	97	Prospective follow-up	Median OS from diagnosis	53 mo	124 mo	< 0.0003
			Median OS with adequate vs weak chelation	NA	124 vs. 85 mo	< 0.001
Neukirchen 2012[a]	188	Matched pair analysis	Median OS	49 mo	75 mo	0.002
Neukirchen 2012[b]	417	Retrospective, registry	Median time to death in TD patients	30 mo	67 mo	NR
Komrokji 2011	97	Retrospective	Median OS	34 mo	59 mo	0.013
Delforge 2012	186	Retrospective	Median OS in Low/Int-1	37 mo	126 mo	< 0.001
Zeidan 2012	4,226	Retrospective, registry	Median survival	47 wk	110 wk	0.003
			HR for 27-52 wks on DFX	1	0.77	NR
			HR for ≥ 53 wk on DFX	1	0.34	NR
Remacha 2012	228	Retrospective	Median OS	105 mo	133 mo	0.009
Lyons 2013	600	Prospective, registry	Median OS from diagnosis	48.7 mo	All 96.8 mo ICT > 6 mo 102.5 mo	< 0.0001
de Witte T 2012	1,000	Prospective, registry	Adjusted HR	1	0.51 (0.19-1.32)	NS

Delforge M, et al. Haematologica. 2012;97 Suppl 1:abstract 0898. Komorokji RS, et al. Blood. 2011;118:abstract 2776. Leitch H, et al. Clin Leuk. 2008;2:205-11. Lyons RM, et al. Blood. 2013;122:abstract 2775. [a] Neukirchen J, et al. Leuk Res. 2012;36:1067-70. [b] Neukirchen J, et al. Haematologica. 2012;97 Suppl 1: abstract 0359. Remacha A, et al. Blood. 2012;120:abstract 1723. Rose C, et al. Leuk Res. 2010;34:864-70. de Witte T, et al. EUMDS Registry. Presented at ELN 2012. Zeidan AM, et al. Blood. 2012;120:abstract 426.

Improved survival in patients with MDS receiving chelation therapy

Retrospective review of 178 patients

(36 RA, 42 RARS, 28 RAEB, 16 RAEB-T or AML, 25 CMML, 31 other)



ICT, iron chelation therapy

Leitch HA. *Clin Leukemia* 2008;2:205–211

Vancouver: the association between iron chelation therapy and overall survival in non-RARS is stronger than in RARS MDS patients

Retrospective analysis of 268 patients with lower-risk MDS receiving iron chelation therapy

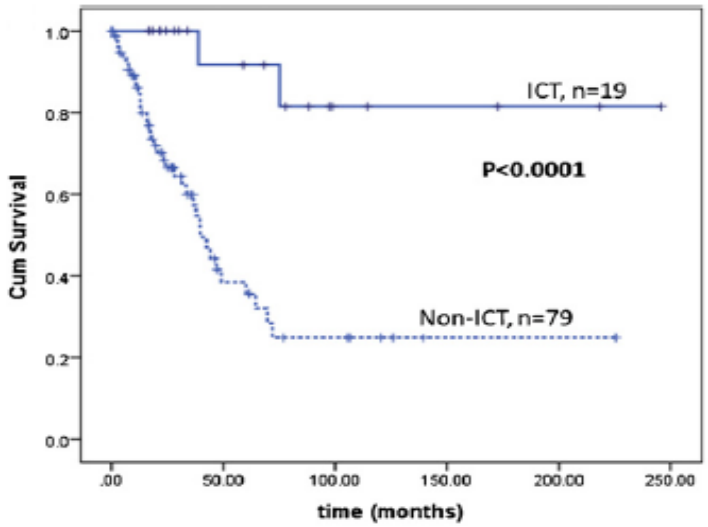
	Non-RARS (n = 129)			RARS (n = 53)		
	No ICT	ICT	p value	No ICT	ICT	p value
Projected median overall survival, months	44	NR	< 0.0001	99	134.4	< 0.0001
5-year overall survival, %	39.2	91.7	0.04	72.4	76.3	NS

Leitch H, et al. Blood. 2011;118:[abstract 1732].

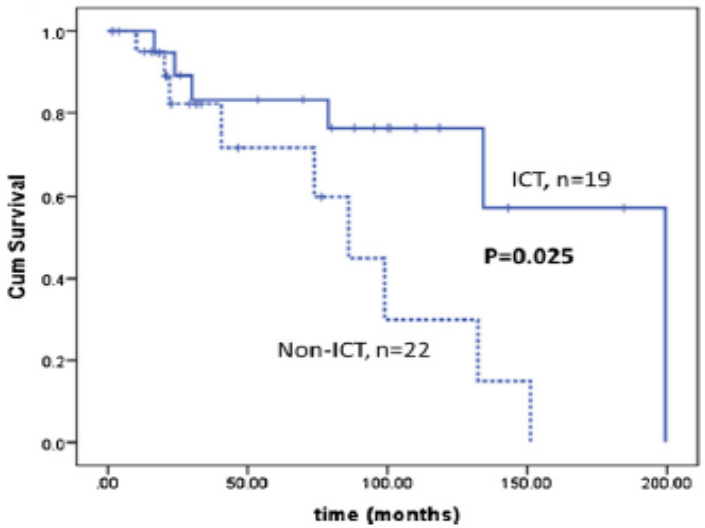
Impact of ICT on OS in non RARS MDS pts

Iron chelation therapy	38(21)
DFX	19(10)
DFO	9(5)
DFO followed by DFX	9(5)
DFX followed by DFO	1(0.5)

Non RARS MDS pts



RARS MDS pts

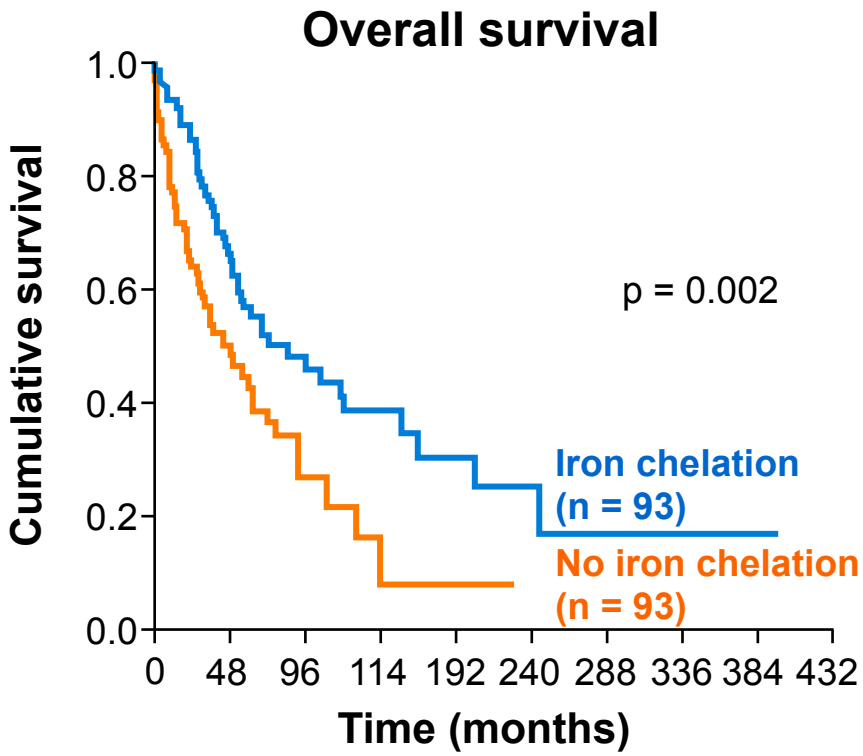


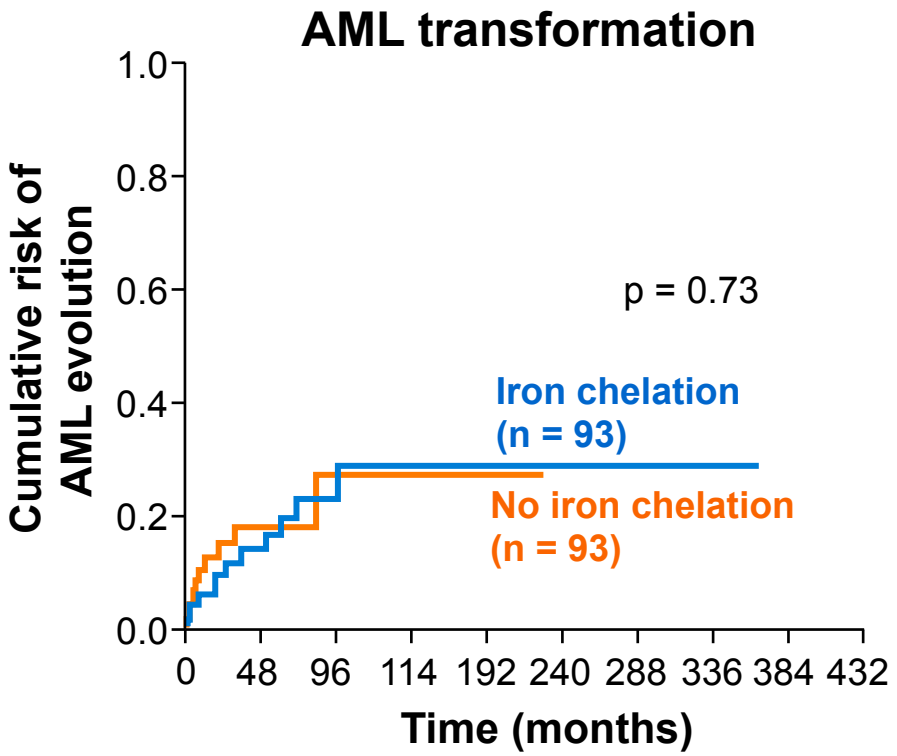
Significant survival improvement in non RARS pts who received ICT
(median OS not reached vs 44 mos of pts without ICT, P<0.0001)

Median OS of RARS pts with ICT was 134.4 mos versus 73.8 mos in pts without ICT (P<0.025)

Leitch HA. Leukemia Research 2012;36(11):1380-6

Iron chelation therapy improves survival in MDS patients: matched-pair analysis (n = 186)





Median cumulative survival
Chelation: 75 months
No chelation: 49 months

AML risk	2 years	5 years
Chelation	10%	19%
No chelation	12%	18%

Fox F, et al. Blood. 2009;114:[abstract 1747].

Iron chelation therapy improves survival in heavily transfused lower-risk MDS

- 165 patients with MDS in France, 97 of whom had Low- or Int-1 MDS
- 53 patients (55%) received chelation therapy for at least 6 months:
  - 28 overnight sc DFO, 5 deferiprone alone, 4 deferiprone + DFO, 4 deferasirox, 7 bolus DFO, 5 iv DFO
- Mean serum ferritin levels were 541, 1491 and 2788 ng/mL at diagnosis, onset of chelation and last evaluation, respectively
- No significant differences between the two groups in total number of comorbidities or the number of patients with iron-related comorbidities

	No iron chelation therapy (n=44)	Iron chelation therapy (n=53)	Total (n=97)	*P*-value
WHO classification				ns
IPSS, n(%)				
Low	15 (34.1)	30 (56.6)	45 (46.4)	0.044
Int-1	29 (65.9)	23 (43.4)	52 (53.6)	

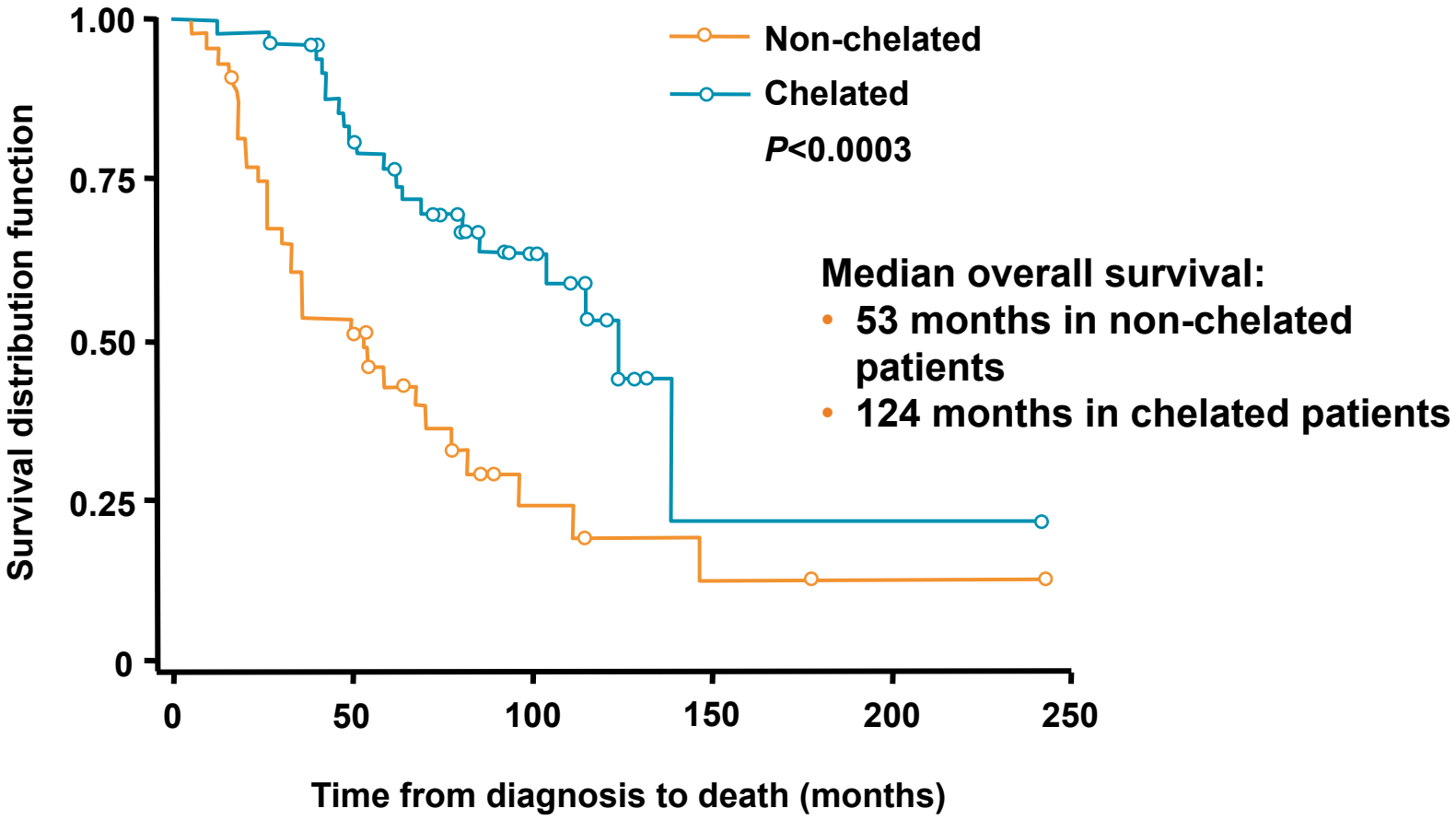
Rose C *et al*. *Leuk Res* 2010;34:864–870

Iron Chelation Therapy and Survival in MDS

- Survey of 170 patients with MDS referred for RBC transfusion at 18 French treatment centers during 1-month period in 2005
  - Assessments: hematologic data, RBC transfusion requirement, iron chelation therapy, and iron overload
  - Cohort survival prospectively followed and reanalyzed on May 15, 2007
- Standard iron chelation therapy
  - Subcutaneous deferoxamine 40 mg/kg/day for 3-5 days/week: n = 41
  - Deferiprone 30-75 mg/kg/day: n = 5
  - Subcutaneous deferoxamine + deferiprone: n = 5
  - Deferasirox 20-30 mg/kg/day: n = 6
- Low-dose iron chelation therapy
  - Subcutaneous deferoxamine bolus 2-3 g/week: n = 12
  - Intravenous deferoxamine 50-100 mg/kg once after RBC transfusion: n = 7

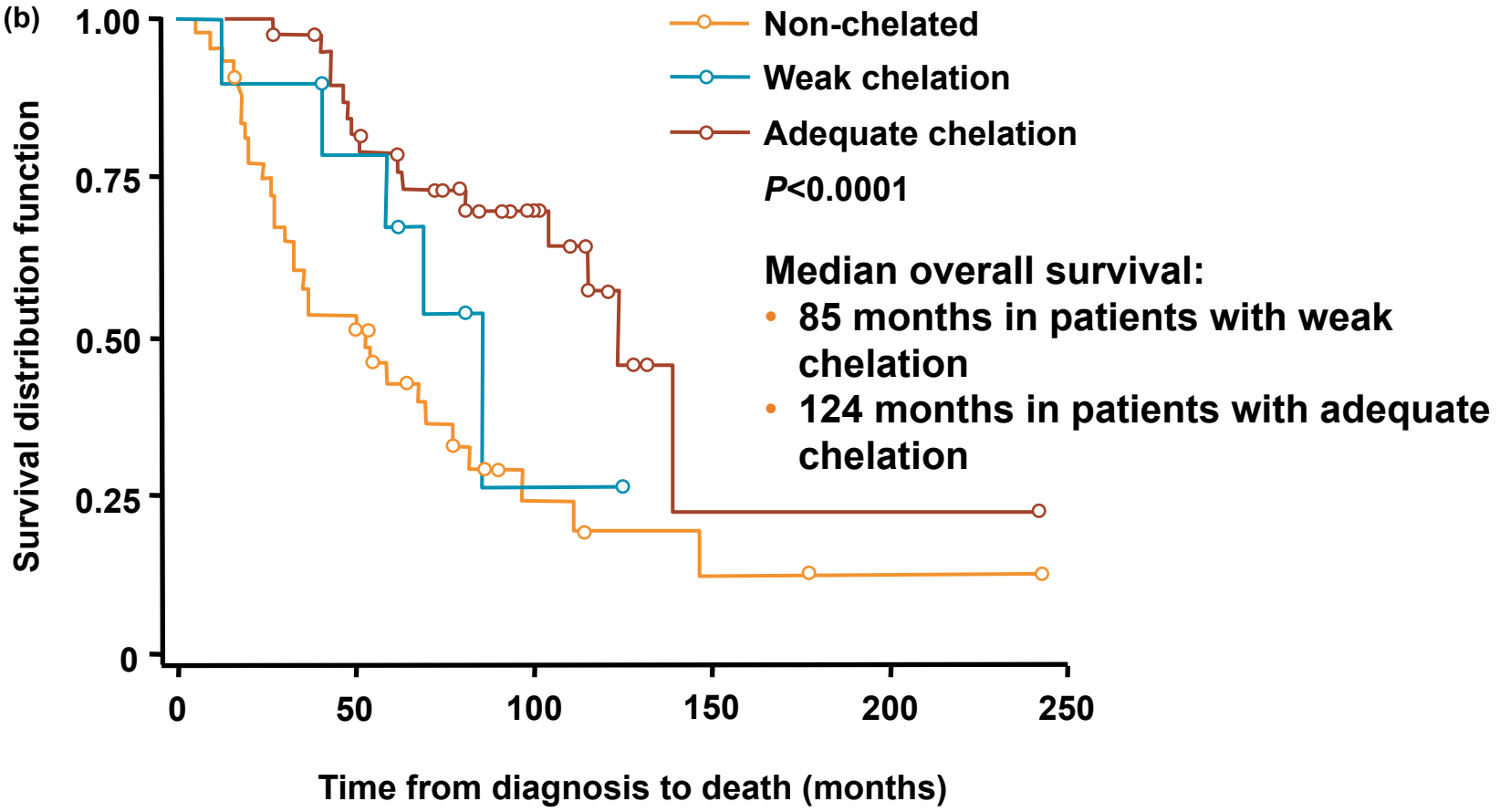
Rose C *et al. Leuk Res* 2010;34:864–870

Improved survival in patients with MDS receiving chelation therapy: Kaplan-Meier survival



Rose C *et al*. *Leuk Res* 2010;34:864–870

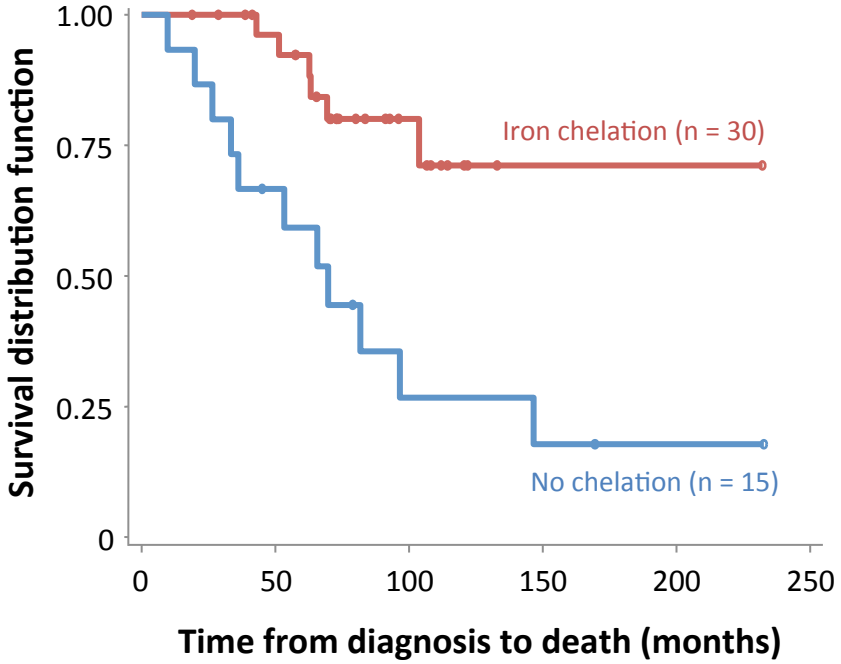
Improved survival in adequately chelated patients with MDS



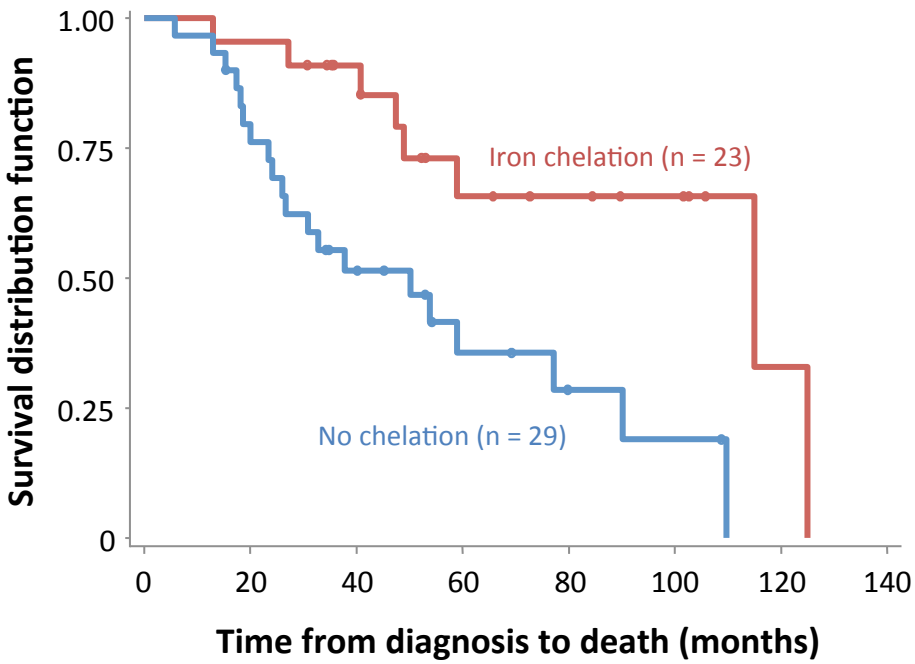
Rose C *et al*. *Leuk Res* 2010;34:864–870

Multiple lines of evidence suggest ICT may improve OS in MDS: GFM study

IPSS = Low
Median: not reached vs 69 months ($p < 0.002$)



IPSS = Int-1
Median: 115 vs 50 months ($p < 0.003$)



Results were the same regardless of sex and age.

GFM, Groupe Francophone des Myélodysplasies;
IPSS, International Prognostic Scoring System.

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

Moffitt Cancer Center: impact of iron chelation therapy on overall survival and AML transformation in lower-risk MDS patients

Retrospective assessment of IPSS Low/Int-1 risk MDS patients with serum ferritin ≥ 1,000 µg/L

	ICT (n = 45)	No ICT (n = 52)	p value
Mean serum ferritin, µg/L	2,680	3,038	0.77
WHO subtype , n (%)			
RARS	11 (24.4)	10 (19.2)	
non-RARS	34 (75.5)	42 (80.8)	
IPSS risk group, n (%)			
Low	15 (33)	9 (17.3)	0.07
Int-1	30 (66.7)	43 (82.7)	
Median overall survival, months	**59**	**34**	**0.013**
AML transformation rate (%)*	**15.6**	**21.2**	**0.33**

*Following adjustment for age > 60 years and MDS Anderson risk score.

Iron chelation therapy was associated with improved overall survival and a trend to lower AML transformation in patients with Low-/Int-1-risk MDS and serum ferritin ≥ 1,000 µg/L

ICT = iron chelation therapy.

Komrokji RS, et al. Blood. 2011;118:[abstract 2776].

Düsseldorf registry: impact of ICT on clinical outcomes in lower-risk MDS patients

- **Methods. Lower risk MDS diagnosed since 1990**, with serum ferritin measurements, who were not chelated or who had received deferasirox and/or deferoxamine (DFO). Transfusion-dependent patients were considered to be **chelated if they received ≥6 months of chelation therapy**, cumulatively. Data were evaluated **up to 30 June 2011**
- **Results.** Data from **417 patients** were analyzed in the three groups: transfusion-independent patients (n=43); and transfusion-dependent, non-chelated (n=289) and chelated patients (n=85). Overall 28 patients received deferasirox; 43 received DFO; 14 received deferasirox and DFO. Data on **comorbidities** were collected only at patient entry; cardiac (34.9, 23.2, 22.4%), hepatic (16.3, 4.2, 7.1%) and renal (7.0, 11.8, 8.2%) conditions were present among transfusion-independent, non-chelated and chelated patients, respectively.
- **In non-chelated patients, time to death was 30.0 months , compared with 67 months in chelated patients.**
- Overall, 4.7% of transfusion-independent patients **progressed to acute myeloid leukemia (AML)**. Among transfusion-dependent patients, **16.6% of non-chelated patients and 14.1% of chelated patients** had progressed.

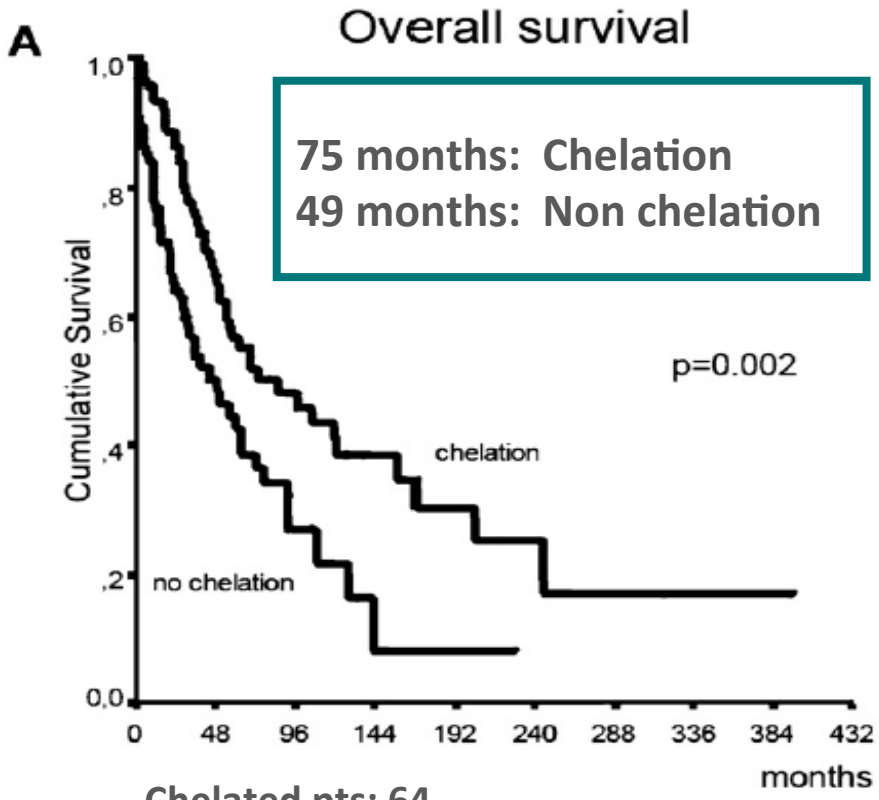
Neukirchen J, et al. Haematologica 2012;97 Suppl 2:abstract 0359

Improved survival in MDS patients receiving iron chelation therapy – A matched pair analysis of 188 patients from the Düsseldorf MDS registry

- **Methods. Matched-pair analysis : 94 patients on long-term chelation therapy and 94 matched patients without it.** All patients had iron overload, defined as serum ferritin (SF) above 1000 ng/ml or a history of multiple transfusions and SF ≥ 500 ng/ml.
- **Results.** Median SF was 1954 ng/ml in chelated and 875 ng/ml in non-chelated patients.
- The difference in **median survival (74 vs. 49 months, respectively; p = 0.002)** supports the idea that iron chelation therapy is beneficial for MDS patients.

Neukirchen J, et al Leuk Res: 36 1067-1070; 2012

Dusseldorf MDS Registry: impact of Deferasirox on OS in MDS pts

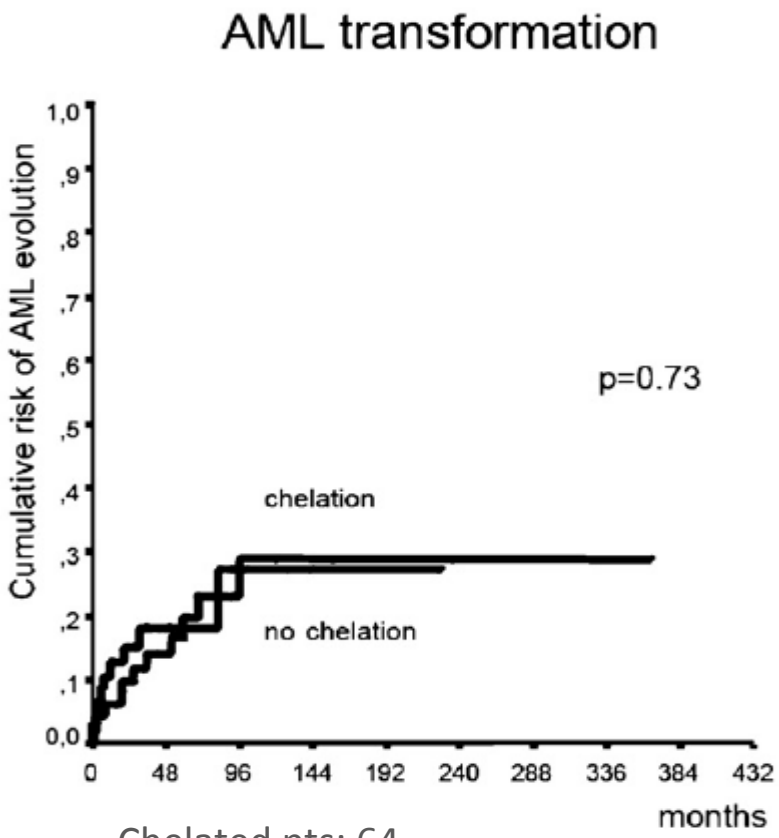


Chelated pts: 64
Not chelated pts: 67
Deferasirox: 47/64 pts
Mean duration Deferasirox tp: 28 months

There was **no significant difference** in median survival between chelated and non-chelated individuals in the cohort of patients with **higher-risk** MDS, whereas a **significant difference was found in the lower-risk** group (p = 0.008).

Neukirchen J. Leuk Res 2012:36(8):1067-70

Dusseldorf MDS Registry: impact of Deferasirox on LFS in MDS pts



Chelated pts: 64
Not chelated pts: 67
Deferasirox: 47/64 pts
Mean duration Deferasirox tp: 28 months

No significant difference regarding risk of AML evolution

Neukirchen J. Leuk Res 2012:36(8):1067-70

RETROSPECTIVE ANALYSIS ON THE IMPACT OF IRON CHELATION THERAPY ON SURVIVAL AND LEUKEMIA PROGRESSION IN TRANSFUSION DEPENDENT MDS PATIENTS IN BELGIUM

- **Methods.** A **Belgian cross-sectional analysis**, performed in Oct-Dec 2008, identified a **cohort of 193 TD MDS patients. Two years later**, this non interventional, retrospective study allowed to collect and analyze follow-up data from **186 patients of the original cohort.**
- **Results**. Of 186 patients, 38% still alive . MDS patients with low-intermediate1 IPSS scores at diagnosis had a median survival of 87 months. Patients from this group who received **ICT for at least 6 months had a significantly longer median survival than non-chelated patients (126 *vs.* 37 months; *p<0.001*).** This survival difference remained significant when looking only at low IPSS patients (171 *vs.* 37 months; *p<0.001*) or only at intermediate1 patients (126 *vs.* 37 months; *p=0.002*). **AML-free survival was similarly different** between the two groups. In **Cox Proportional Hazard models the use of iron chelation therapy appeared to be the most prominent factor impacting survival**, followed by calculated "transfusion intensity"

Delforge et al, Haematologica 2012 (EHA abstr.)

Multiple lines of evidence suggest ICT may improve OS in MDS: Belgian study

	Chelated ≥ 6 months (n = 62)	No ICT (n = 47)	p value
Total RBC units	144	70	< 0.001
Overall median survival (months)	126	37	< 0.001
Low IPSS	171	37	< 0.001
Int-1	126	37	0.002
Patients died – n (%)	20 (32)	33 (70)	< 0.001

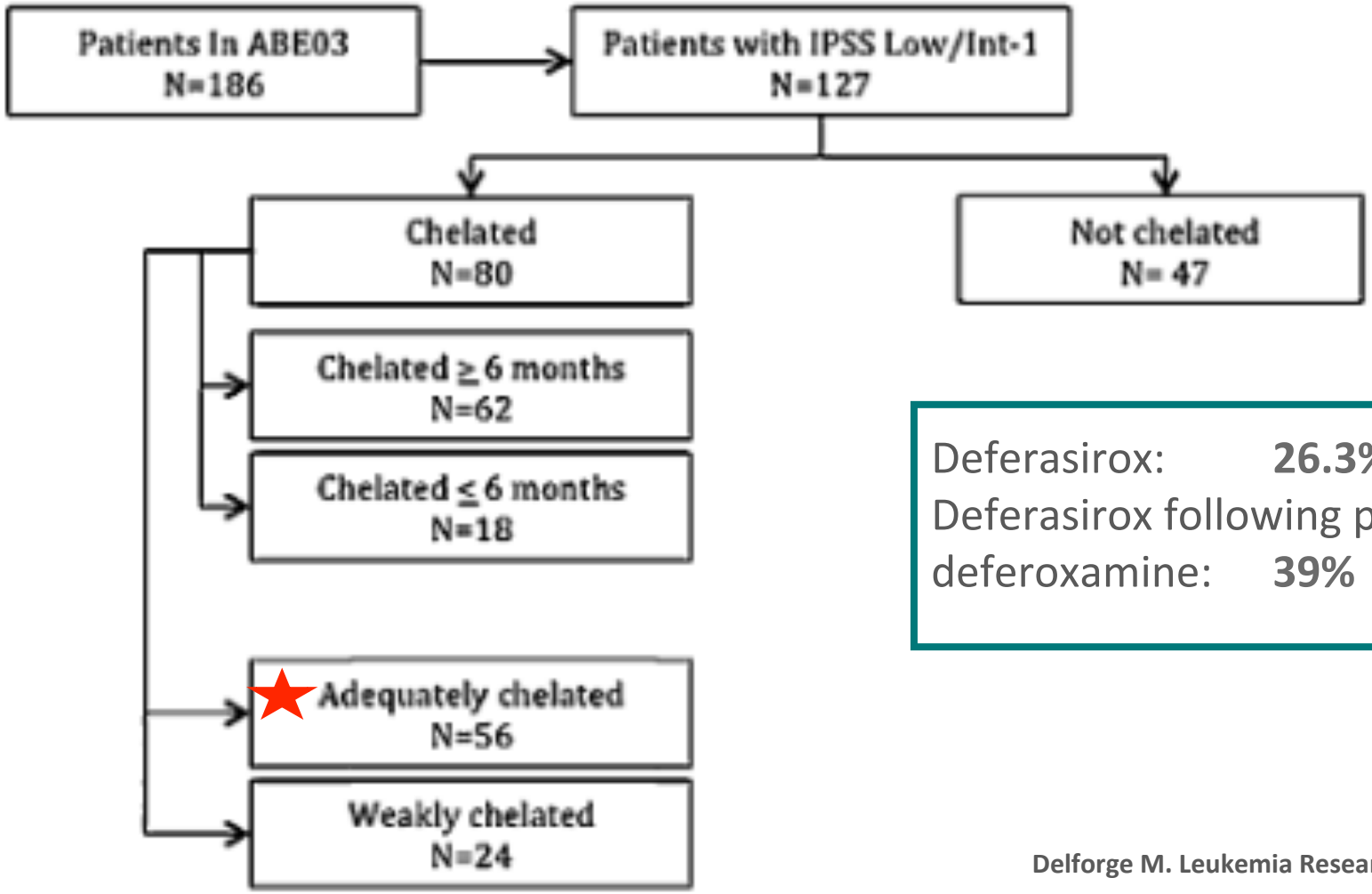
Delforge M, et al. Haematologica. 2012;97 Suppl 1:abstract 0898.

Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes *(Delforge et al, 2014)*

- **Methods: Follow-up of a retrospective study**. 127 Low/Int-1 MDS patients from 28 centers in Belgium. Statistical analysis stratified by duration (≥6 versus <6 months) and quality of chelation (adequate versus weak).
- **Results:** Crude **chelation rate was 63% but 88% among patients with serum ferritin ≥1000 g/L.** Of the 80 chelated patients, 70% were chelated adequately mainly with deferasirox (26%) or deferasirox following deferoxamine (39%). **Mortality was 70% among non-chelated, 40% among chelated, 32% among patients chelated ≥6 m, and 30% among patients chelated adequately;** with a trend toward reduced cardiac mortality in chelated patients. Overall, **median overall survival (OS) was 10.2 years for chelated and 3.1years for non-chelated patients (p < 0.001)**. For **patients chelated ≥6 m** or patients classified as adequately chelated, **median OS was 10.5 years**. Mortality increased as a function of average monthly transfusion intensity (HR = 1.08, p = 0.04) but was lower in patients receiving adequate chelation or chelation ≥6 m(HR = 0.24, p < 0.001).

Delforge et al, Leuk Res 38 (2014) 557-563

Adequate ICT ≥ 6 m in TD lower risk MDS pts: impact of Deferasirox on OS

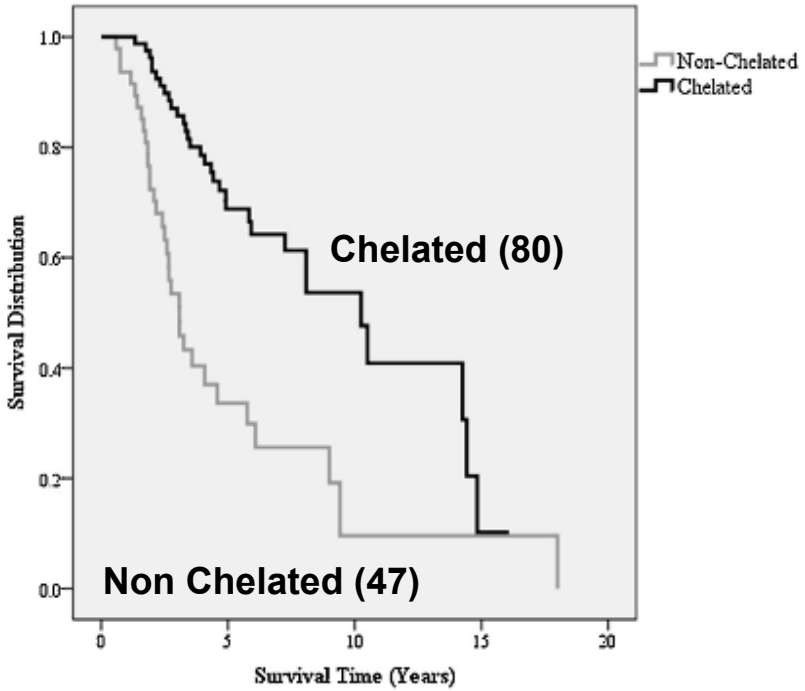


Deferasirox: **26.3%**
Deferasirox following prior deferoxamine: **39%**

Delforge M. Leukemia Research 2014;38:557-563

★ **s.c. deferoxamine infusion on multiple days /week or deferasirox at any dose**

Impact of Deferasirox on OS in MDS pts

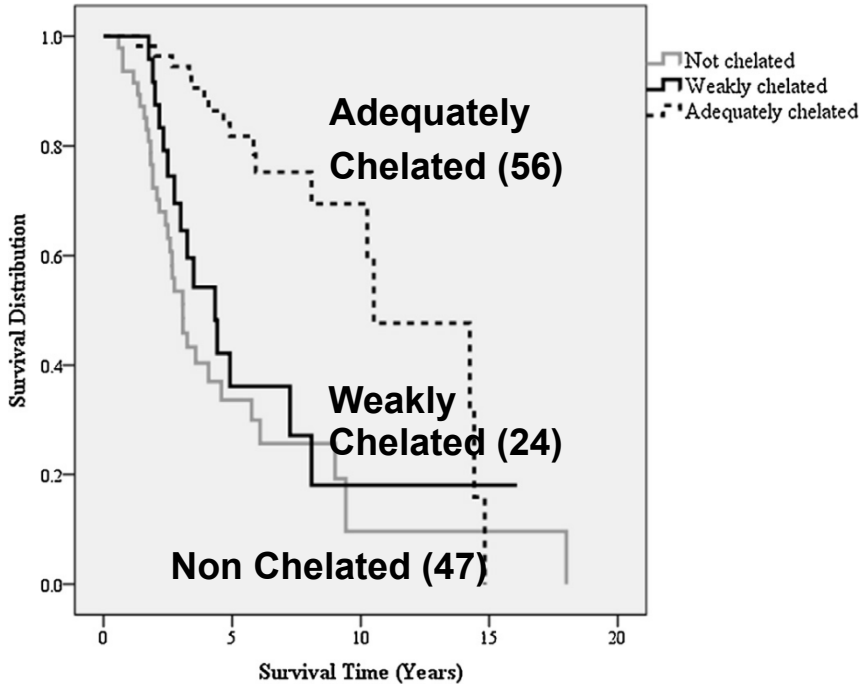


Median OS:

3.1 years: non chelated

10.2 years: chelated

P: < 0.001.



Median OS:

3.1 years: non chelated

4.3 years: weakly chelated

10.5 years: adequately chelated

P: <0.001

Delforge M. Leukemia Research 2014;38:557-563

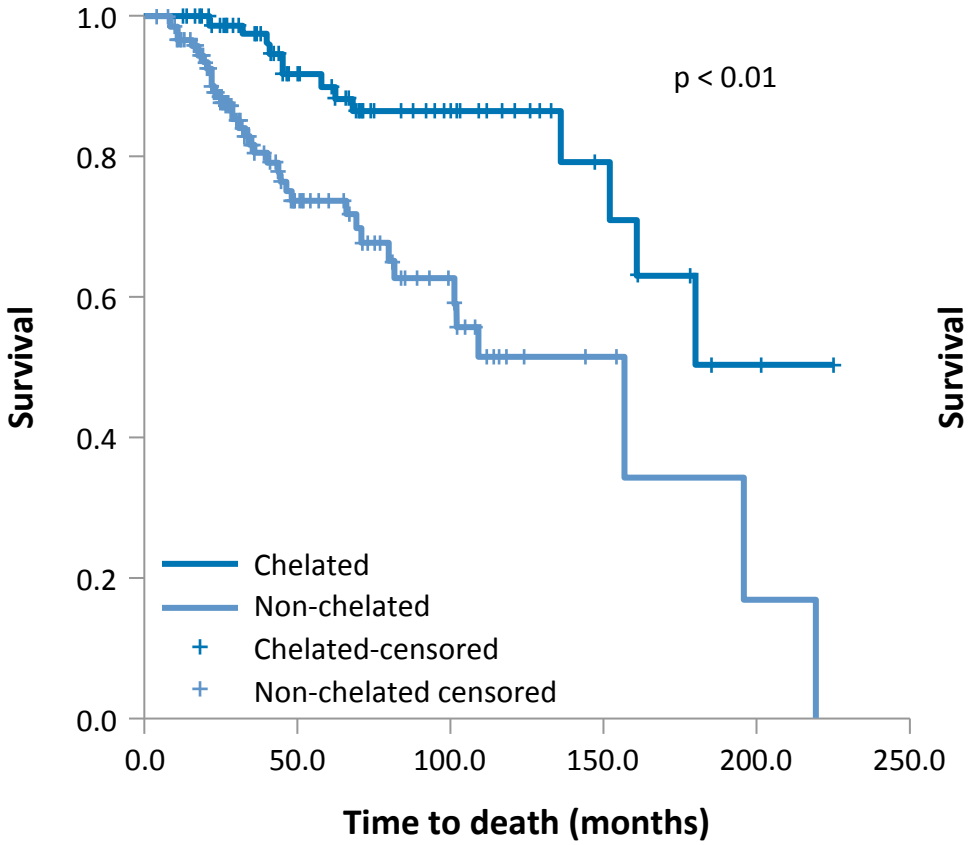
Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications

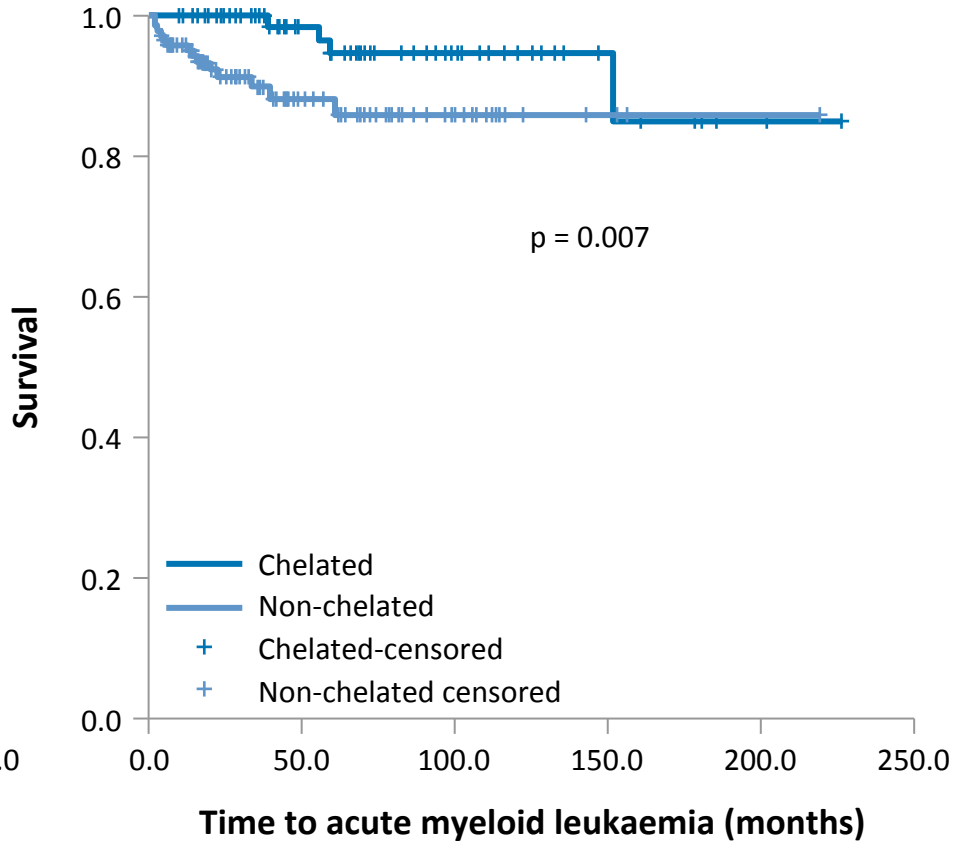
Remacha et al (IRON-2 STUDY GROUP) Ann Hematol 2015

- **Methods.** **Observational retrospective study** (March 2010- March 2011); 47 Spanish hospitals. **263 patients with lower risk MDS), transfusion-dependent, ≥10 PRBC** .
- **Results.** **Cardiac, hepatic, endocrine, or arthropathy complications** appeared/worsened in 20.2, 11.4, 9.9, and 3.8 % of patients, respectively.
- **96 (36.5 %) pts received iron chelation therapy for ≥6 months, (deferasirox: 71.9 %).** **Chelation-treated patients showed longer**
- **overall survival (p<0.001), leukemia-free survival (p=0.007), and cardiac event-free survival (p=0.017) than non-chelated patients.** **In multivariable analyses, age (p=0.011), IPSS (p<0.001), and chelation treatment (p=0.015)were predictors for overall survival**; IPSS (p=0.014) and transfusion frequency (p=0.001) for leukemia-free survival; and **chelation treatment (p=0.040) and Sorror comorbidity index (p=0.039) for cardiac event-free survival.**

Remacha et al, Ann Hematol 2015

IRON2: survival improves with ICT





Remacha AF, et al. Ann Hematol. 2014

EUMDS prospective registry: ICT halves the HR for early mortality in transfused MDS patients with SF > 1,000 µg/L

	Patients, n	Median SF levels	HR (95% CI)	Adjusted HR[a] (95% CI)
Chelation				
No	945	281	1	1
Yes	55	1,779	2.05 (1.15–3.64)	0.36 (0.15–0.88)
Mean number of units				
No chelation	4.6	–	–	–
Chelation	28.9	–	–	–
Chelation and transfusion status				
No transfusion/no chelation	570	345	1	1
Transfusion/no chelation	375	377	4.71 (3.01–7.36)	3.61 (1.96–6.66)
Transfusion/chelation	52	1,838	5.27 (2.71–10.26)	1.47 (0.50–4.31)
Transfusion and SF > 1,000 µg/L	134	–	–	–
No chelation	94	–	1	1
Chelation	40	–	0.75 (0.38–1.51)	0.51 (0.19–1.32)

[a] Adjusted for age at diagnosis, sex, country, WHO category, cytogenetics, number of cytopenia, % blasts, number of transfusions, and SF levels (at registration or start of chelation.

CI, confidence interval.

de Witte T, et al. EUMDS Registry. Presented at ELN 2012.

Impact of Deferasirox on mortality in MDS

Medicare population: DFX associated with reduced mortality risk in MDS patients

- Chelated pts: 544 (Deferasirox: 100%)
- Non chelated pts: 3.682

Risk of death reduced by:

23%: 14-26 weeks of Deferasirox

66%: ≥53 weeks of Deferasirox

Zeidan AM. Blood 2012;120(21):426

Deferasirox therapy is associated with reduced mortality risk in a medicare population with myelodysplastic syndromes

Journal of Comparative Effectiveness Research

Aims: Iron overload adversely affects patients with myelodysplastic syndromes (MDS), but benefits of iron chelation therapy have not been clearly demonstrated. We examined the association between deferasirox (DFX) therapy and mortality in transfusion-receiving Medicare patients. **Patients & methods:** MDS patients from 2005 to 2008 were identified using ICD-9 codes from 100% Medicare claims. Patients receiving ≥20 blood units were observed until death or end of study. Marginal structural models were used for estimation. **Results:** 3926 patients (10.1% used DFX) were observed for a mean of 48.8 weeks. Each incremental week of DFX was associated with a significant reduction in mortality risk (hazard ratio [HR]: 0.989; 95% CI: 0.983–0.996; p = 0.001). **Conclusion:** DFX therapy is associated with a reduced mortality risk among older MDS patients who received a minimum transfusion threshold.

Keywords: deferasirox • iron chelation therapy • iron overload • mortality • myelodysplastic syndromes

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J. Comp. Eff. Res. **(2015) 4(4), 327–340**

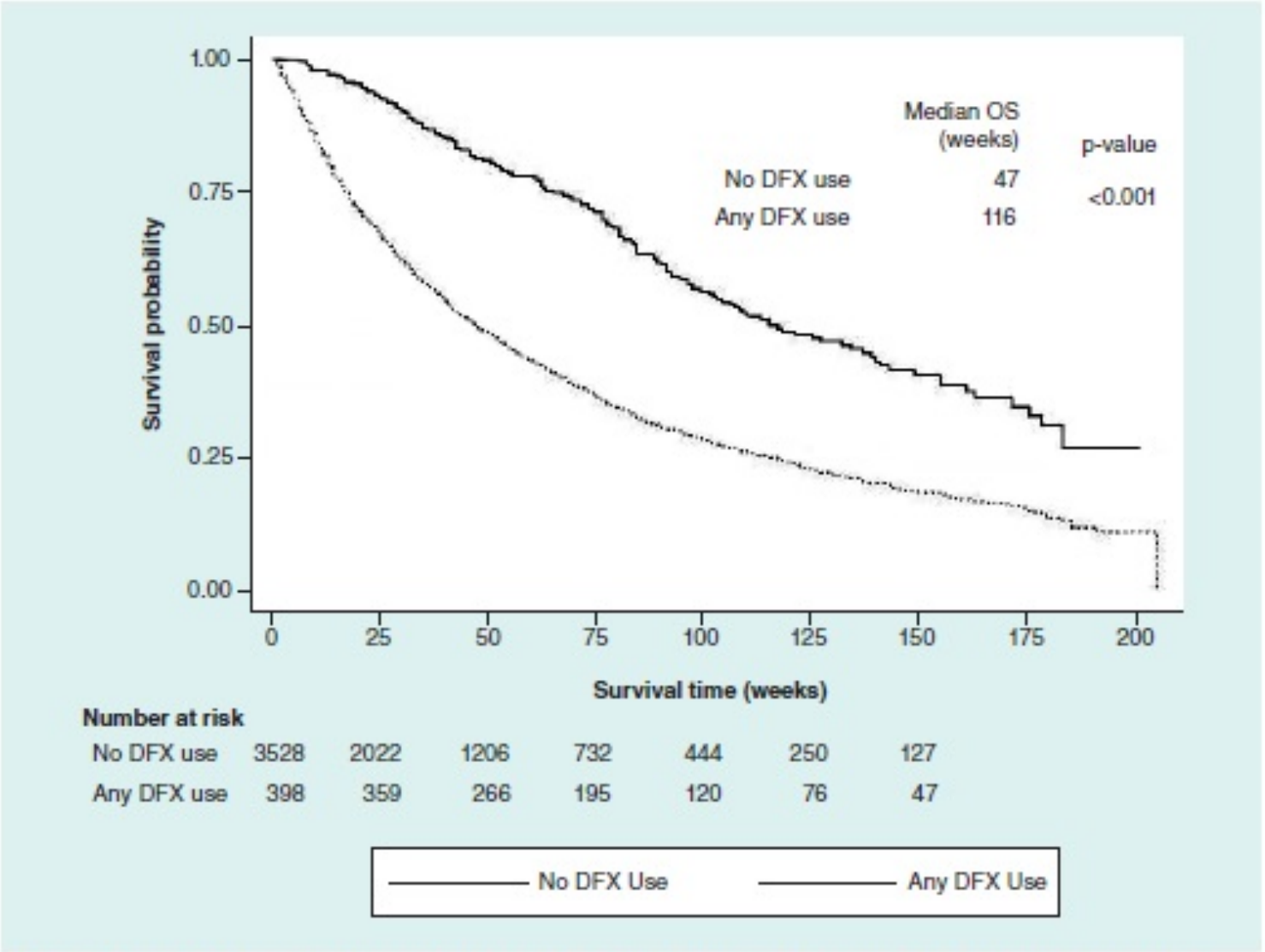


Figure 3. Kaplan–Meier overall survival estimates for patients with myelodysplastic syndromes who received deferasirox therapy and those who did not.

DFX: Deferasirox; OS: Overall survival.

***J. Comp. Eff. Res.* (2015) 4(4), 327–340**

Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry

Lyons et al, Leuk Res 38 (2014) 149-154

- **Methods**. **5-year, prospective registry** . Enrolled **600 lower-risk MDS pts with transfusional iron overload.** Clinical outcomes were compared between chelated and non-chelated pts.
- **Results**. **At baseline, cardio-vascular comorbidities more common in non-chelated pts**, and MDS therapy was more common in chelated pts.
- **At 24 months, chelation was associated with longer median overall survival (52.2 months vs. 104.4 months; p < .0001) and a trend toward longer leukemia-free survival and fewer cardiac events.**
- No differences in safety between groups.
- Limitations: 1) varying time from diagnosis and duration of chelation; 2) the decision to chelate may have been influenced by pt clinical status.

Lyons et al, Leuk Res 38 (2014) 149-154

Iron chelation and clinical outcomes in patients with lower-risk MDS: registry analysis at 5 years

Objective

- To evaluate the association between chelation and clinical outcomes and also between chelation and OS in lower-risk MDS patients for 5 years

Methods

- Multicentre, prospective study in patients (N = 600, ≥ 18 years of age) with lower-risk MDS and TIO
- Patients were categorized as non-chelated, chelated, and chelated ≥ 6 months, and followed for 5 years

Results

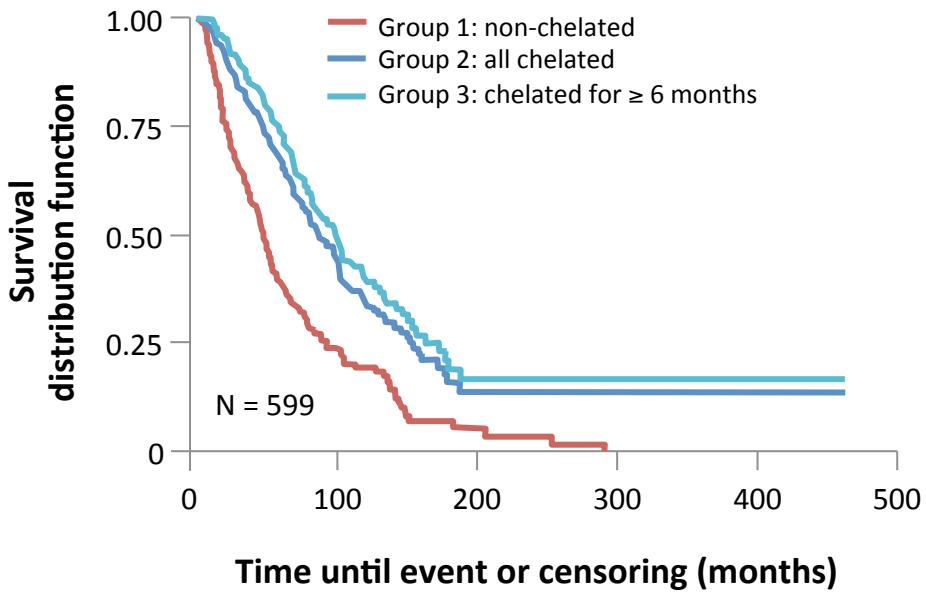
- 599 patients were evaluated (57.8% male) with a median age of 76 (range 21–99) years
  - 61 patients continue in the registry (May 2014); 538 discontinued (400 died, 66 were lost to follow-up, 46 completed study, and 26 discontinued for other reasons)
- At baseline
  - cardiac and vascular comorbidities (CVC) were significantly more common in non-chelated vs chelated patients (52.4% vs 34.3%, $p < 0.0001$, and 59.8% vs 48.0%, $p = 0.0039$, respectively)
  - ECs were numerically greater in non-chelated than in ≥ 6-mo-chelated patients (44.2% vs 35.6%)
- 271/599 patients were chelated
  - deferasirox 69.0% (n = 187)
  - deferoxamine 11.8% (n = 32)
  - deferoxamine and deferasirox 14.8% (n = 40)
  - unknown chelator or chelator name not provided 4.5% (n = 12)

EC, endocrine comorbidities; TIO, transfusional iron overload.

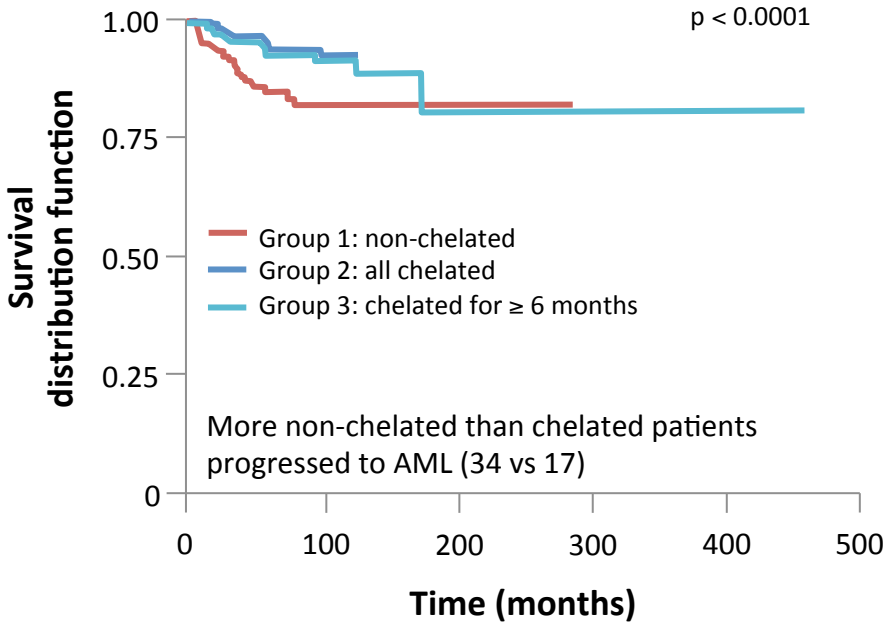
Lyons R, et al. Presented at ASH 2014. Blood. 2014;124:abstract 1350.

US22 prospective registry: OS and AML-free survival significantly greater in chelated patients

Overall survival



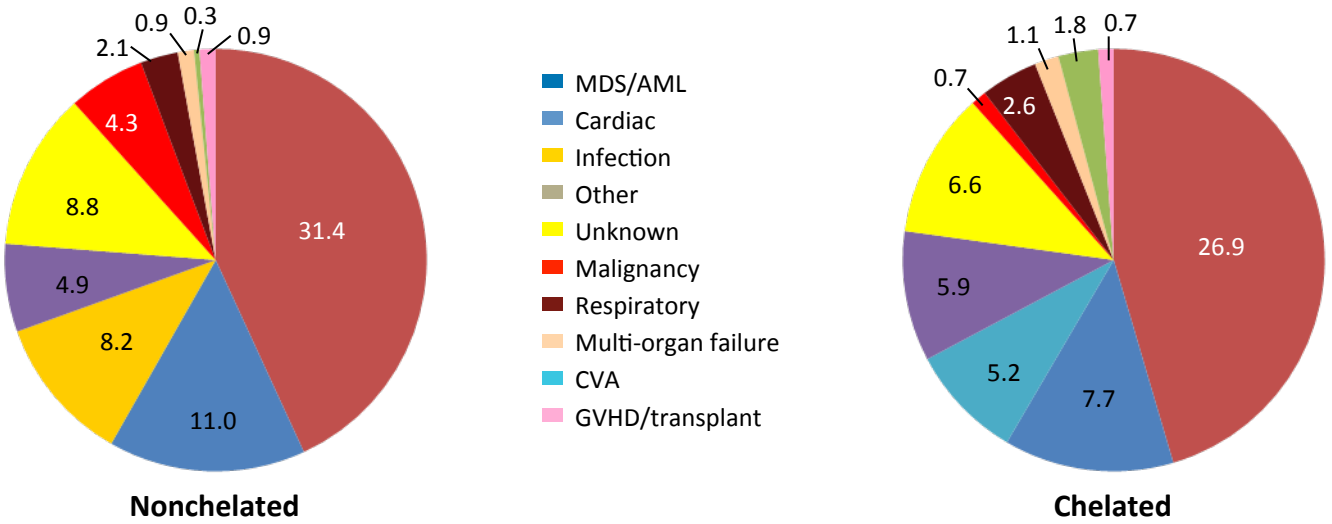
Time to progression to AML



Significantly greater OS and time to AML progression (from date of diagnosis) in chelated than in non-chelated patients (p < 0.0001)

Lyons RM, et al. Blood. 2014;124:abstract 1350.

US22 prospective registry: MDS patients receiving ICT have lower all-cause mortality



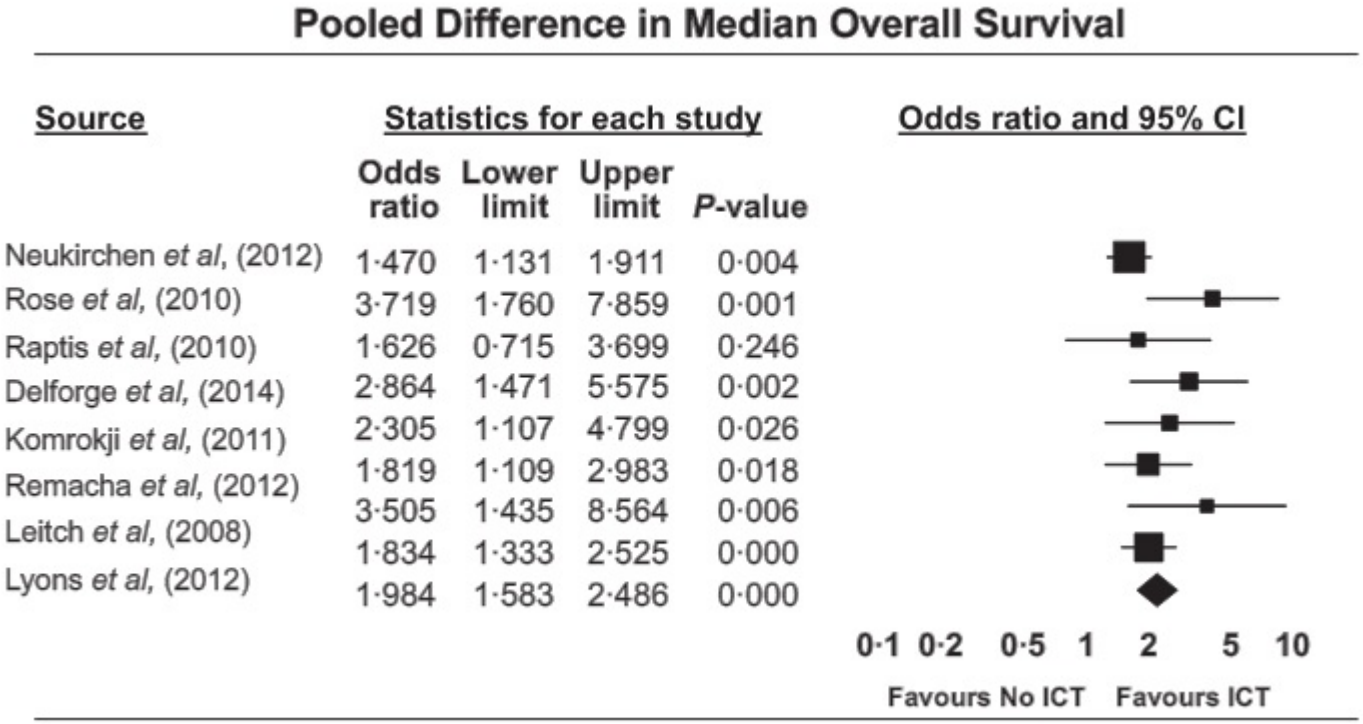
Patient characteristic	Non-chelated (N = 328)	Chelated (N = 271)	Chelated ≥ 6 months (N = 202)
Time to death, median (min, max), months	**47.8** (43.4, 53.1)	**88.0** (78.4, 103.0)[a,*]	**100.0** (83.4, 118.2) *
Deaths, n (%)	239 (72.9)	161 (59.4) [a,***]	115 (56.9) [a,**]
Cause of death, n (%)			
MDS/AML	103 (31.4)	73 (26.9)	53 (26.2)
Cardiac	36 (11.0)	21 (7.7)	15 (7.4)
Infection	27 (8.2)	14 (5.2)	14 (6.9)
Other	16 (4.9)	16 (5.9)	10 (5.0)
Unknown	29 (8.8)	18 (6.6)	12 (5.9)
Malignancy	14 (4.3)	2 (0.7)	0 (0.0)
Respiratory	7 (2.1)	7 (2.6)	4 (2.0)
Multi-organ failure	3 (0.9)	3 (1.1)	3 (1.5)
CVA	1 (0.3)	5 (1.8)	3 (1.5)
GVHD/transplant	3 (0.9)	2 (0.7)	1 (0.5)

[a] Versus non-chelated. * p < 0.0001; ** p = 0.0002; *** p = 0.0005.

Lyons RM, et al. Blood. 2014;124:abstract 1350.

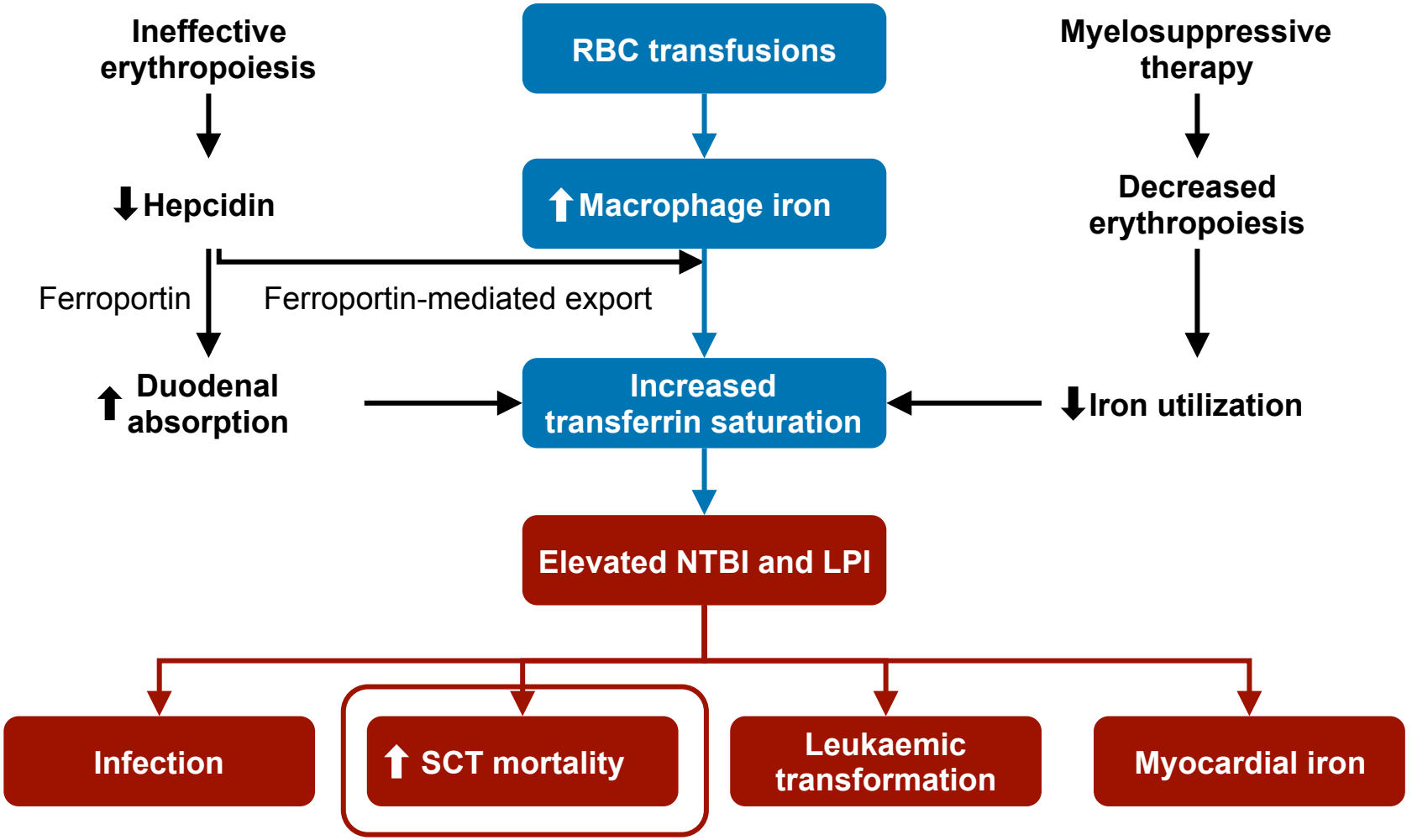
THE IMPACT OF CHELATION THERAPY ON SURVIVAL IN TRANSFUSIONAL IRON OVERLOAD: A META-ANALYSIS OF MDS (Mainous A et al, Br J Hematol, 2014, 167, 697-726)

- **Methods:** 8 observational studies, , 1562 pts, median sample size: 153 (78-534)
- **Results:** ICT associated with longer survival (mean difference: 61.2 months)



Mainous A et al, Br J Hematol 2014, 167, 697-726

Why ICT might improve survival in transfusion-dependent MDS patients?



Pullarkat V. Blood. 2009;114:5251-5.

CASO CLINICO N° 3

- maschio, 37 anni
- **Marzo 2007:** linfoma linfoplasmocitico nel 2007, con interessamento midollare, trattato con R-FC, in altra sede, con raggiungimento della RC, PET negativa
- **Marzo 2008:** comparsa di anemia trasfusione-dipendente, resistente a ESAs + CSF
- **Maggio 2009:** diagnosi di **MDS therapy-related**; Hb 7.5; PLTS 58; WBC: 1.8 (PMN 432); BOM: blasti 2%; cariotipo normale; **rischio IPSS: intermedio-1; IPSS-R: intermedio; ritmo trasfusionale: 1 GRC/7 gg**; emocromatosi eterozigote (H63); **ferritina 2000**; ALT 112 AST 57; fegato: NASH (steatosi colestatica non alcoolica); Fibroscan: fibrosi F1-F2; diabete mellito
- **Ottobre 2009: inizia DFX 20 mg/Kg/die**
- **Settembre 2010:** inizia azacitidina IC
- **Dicembre 2010:** cessazione delle trasfusioni
- **Febbraio 2011:** (dopo 4 cicli di azacitidina): RC ematologica, ferritina 1419 ng/ml, AST 96, ALT 41; continua DFX
- **Aprile 2011: SCT allogenico** (dopo5 cicli di azacitidina): AST 31; ALT 43; ferritina 1378; saturaz transferrinica 45%
- **Maggio 2016: vivo in RC (SOPRAVVIVENZA: 84 mesi dalla diagnosi di MDS)**

Pre-transplantation SF level and outcome after allo-SCT (selected trials)

Author	n	HSCT	Results
Armand et al. 2007	590 (AML,CML, MDS)	Myeloablative allogeneic	SF ↑ → NRM ↑ (OS and DFS ↓)
Pullarkat et al. 2008	190 (myeloid and lymphoid)	Myeloablative allogeneic	SF ↑ (≥ 1,000 µg/L) NRM ↑ → DFS/OS ↓ + GVHD ↑; blood stream infection ↑
Platzbecker et al. 2008	172 (MDS)	Myeloablative allogeneic	OS↓ (SF ↑) acute GVHD ↑ (SF ↑)
Kataoka et al. 2009	264 (haematological disease)	Myeloablative allogeneic	SF ≥ 599 µg/L: NRM ↑; OS↓, no impact on GVHD
Lee et al. 2009	101 (paediatric patients)	Myeloablative allogeneic	SF ≥ 1,000 µg/L OS ↑; DFS↓
Alessandrino et al. 2010	357 MDS	RIC/ myeloablative allogeneic	Transfusion dependence and SF ↑: NRM ↑; OS↓; DFS↓ (only myeloablative)

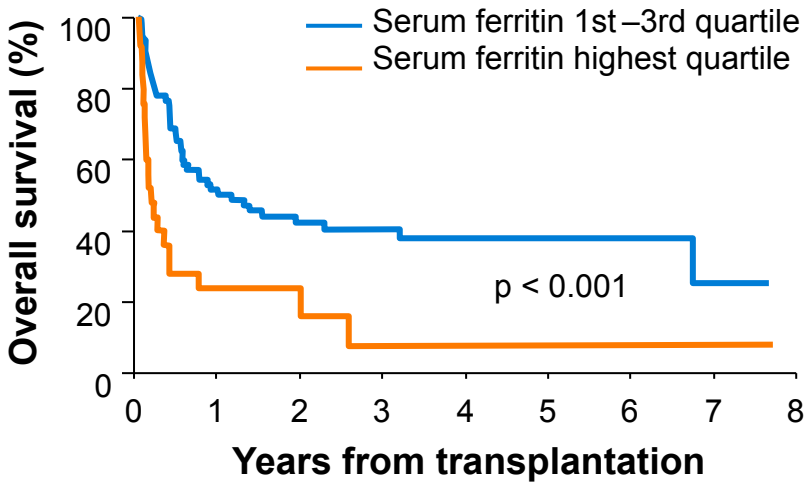
AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; RIC, reduced-intensity conditioning.

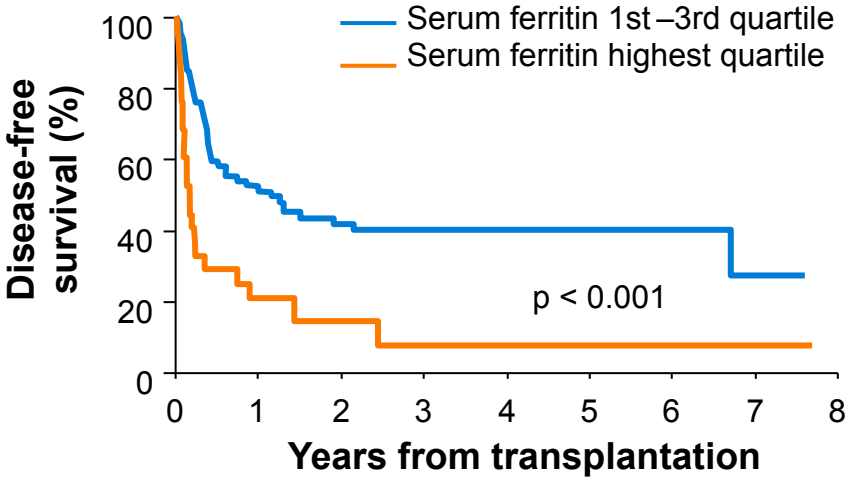
Alessandrino EP, et al. Haematologica. 2010;95:476-84. Armand P, et al. Biol Blood Marrow Transplant. 2007;13:655-64. Kataoka K, et al. Biol Blood Marrow Transplant. 2009;15:195-204. Lee JW, et al. Bone Marrow Transplant. 2009;44:793-7.Platzbecker U, et al. Biol Blood Marrow Transplant. 2008;14:1217-25. Pullarkat V, et al. Bone Marrow Transplant. 2008;42:799-805.

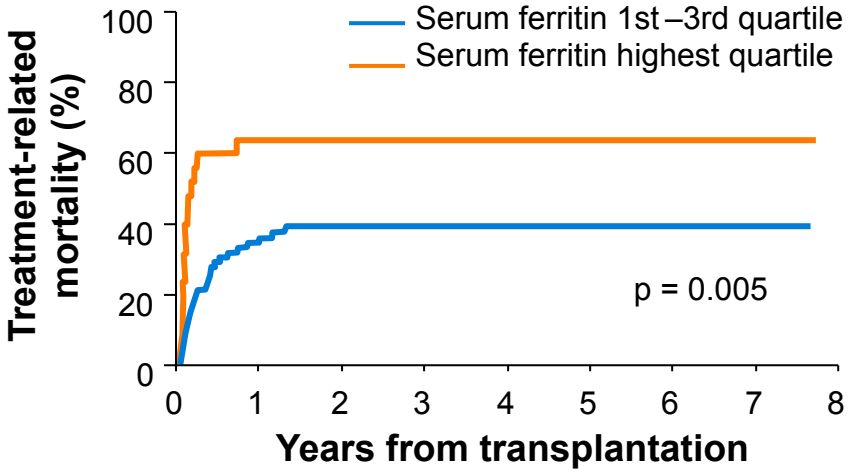
Outcome according to serum ferritin level

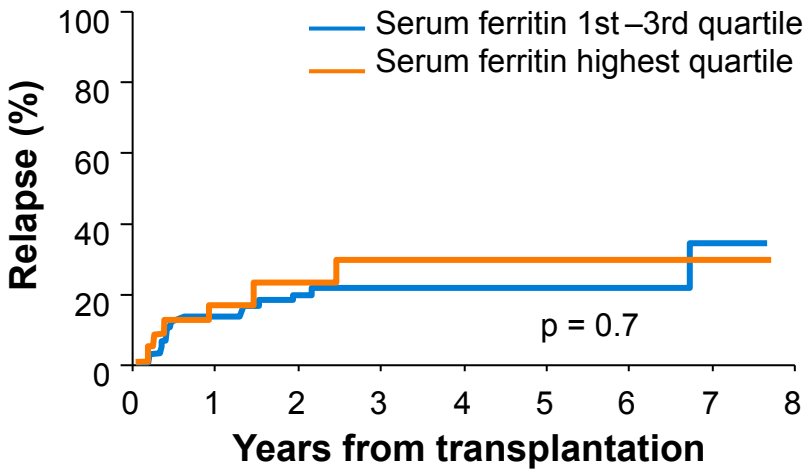
(590 pts: 154 CML, 144 AML, 103 MDS, 74 ALL, 115 other)

Armand P, et al. Blood. 2007;109:4586-8.

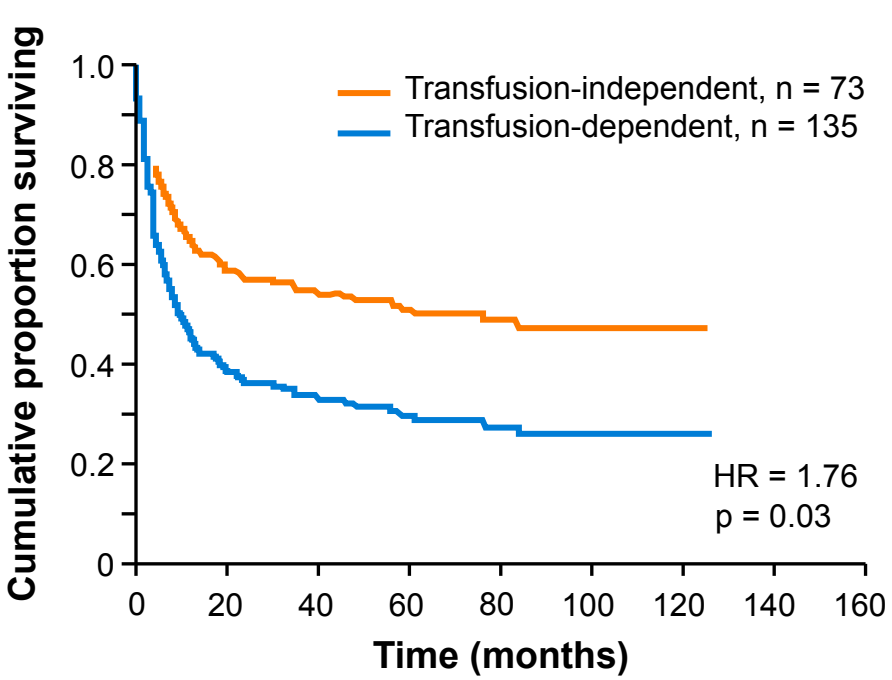


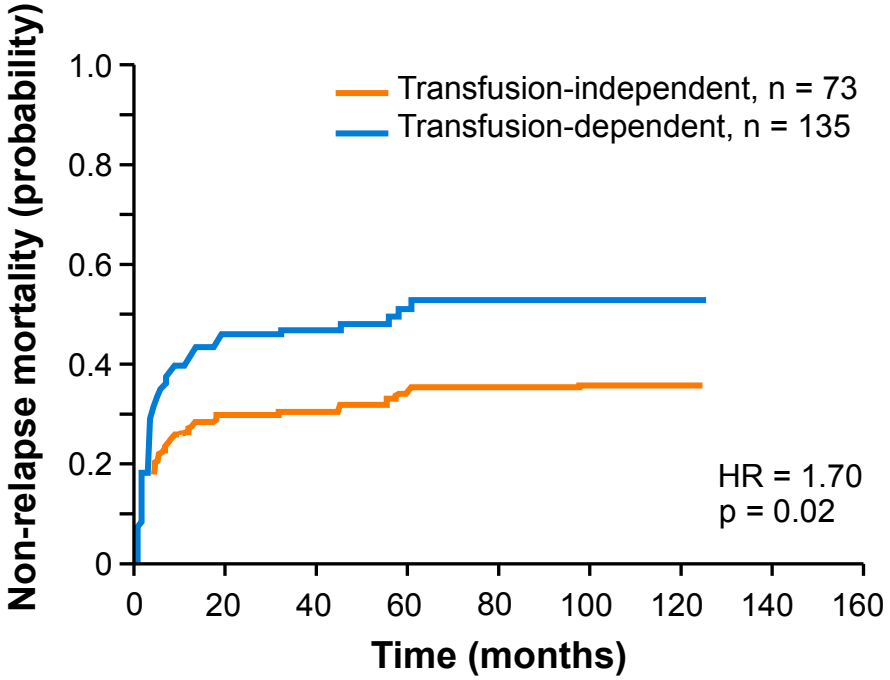






Impact of transfusion dependence on overall survival and non-relapse mortality in myeloablative SCT*





Lower overall survival in transfusion-dependent patients

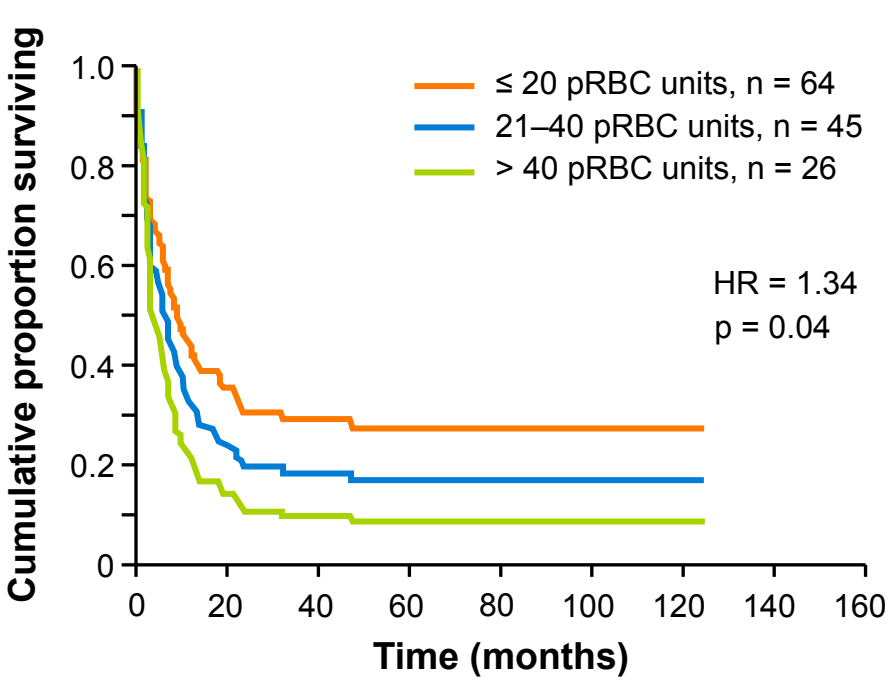
Higher non-relapse mortality in transfusion-dependent patients

*Multivariate analysis adjusted for other prognostic factors

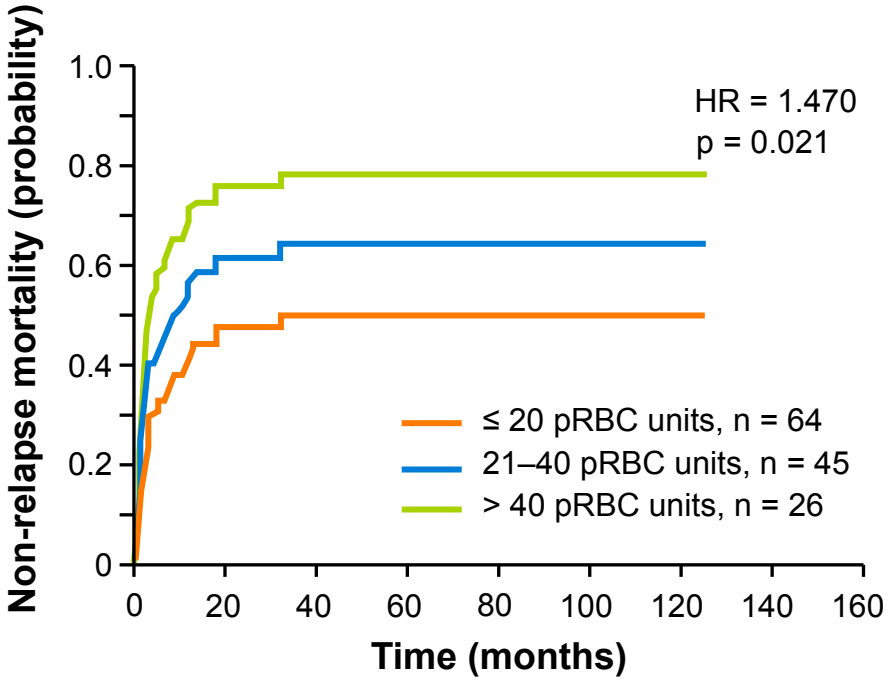
HR = hazard ratio;
SCT = stem cell transplantation.

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Impact of transfusion burden prior to SCT on overall survival and non-relapse mortality post-SCT



Overall survival by transfusion burden prior to SCT



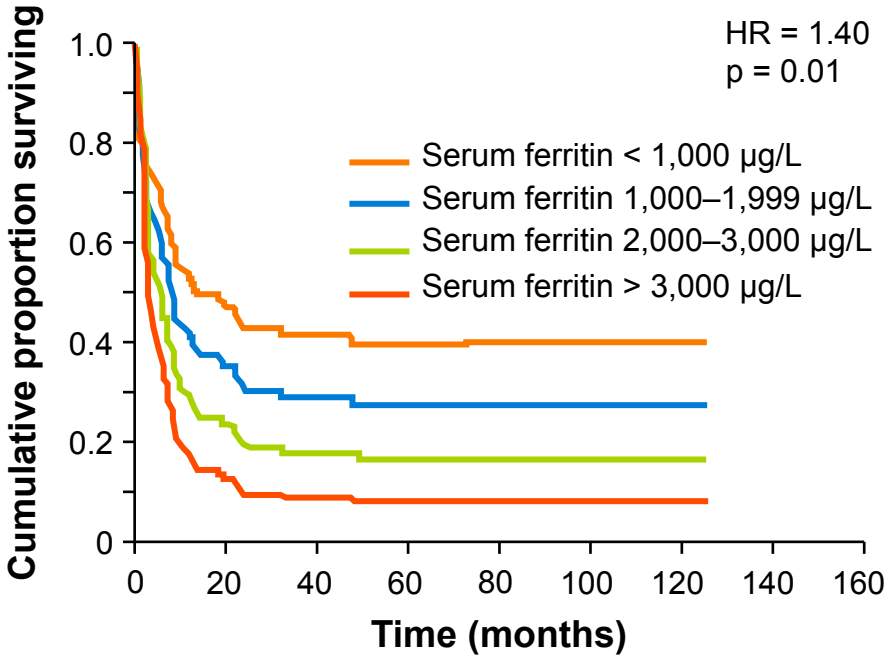
Non-relapse mortality by transfusion burden prior to SCT

Overall survival and non-relapse mortality for < 20 units were not significantly different compared with transfusion-independent patients

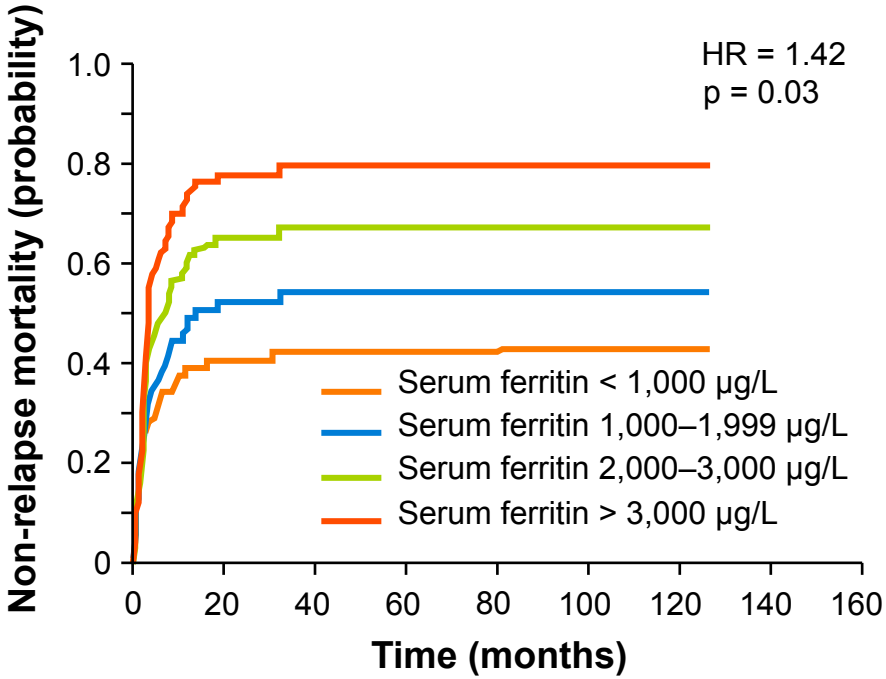
pRBC = packed red blood cells.

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Impact of serum ferritin level prior to SCT on overall survival and non-relapse mortality post-SCT (n = 129)



Overall survival by serum ferritin level prior to SCT



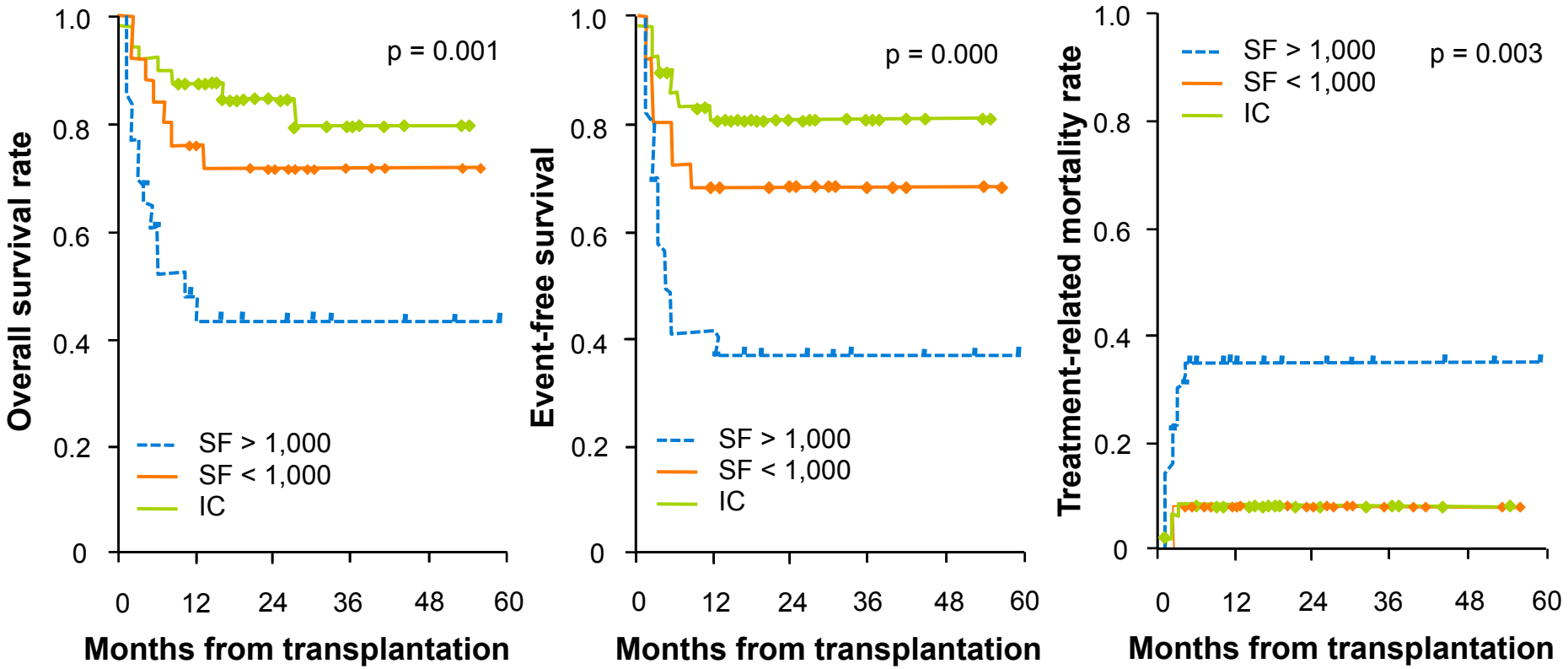
Non-relapse mortality by serum ferritin level prior to SCT

The impact of serum ferritin remained unchanged when the model was adjusted for albumin level

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

Iron chelation prior to HSCT improves survival

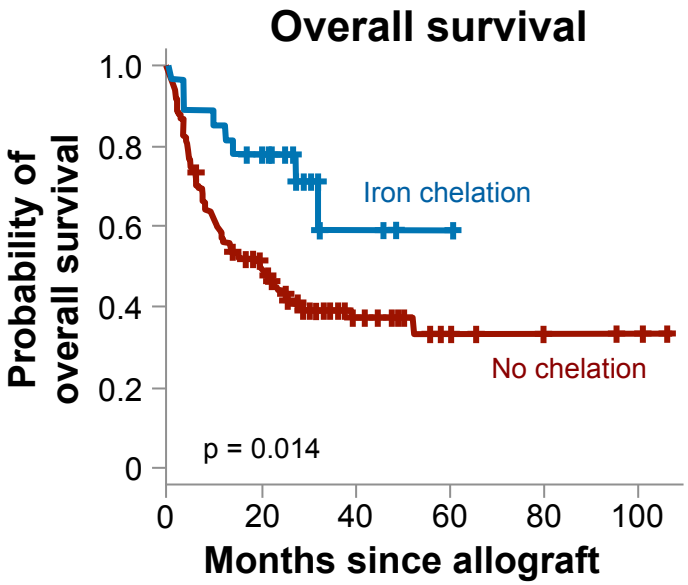
(retrospective study, 101 pediatric pts)



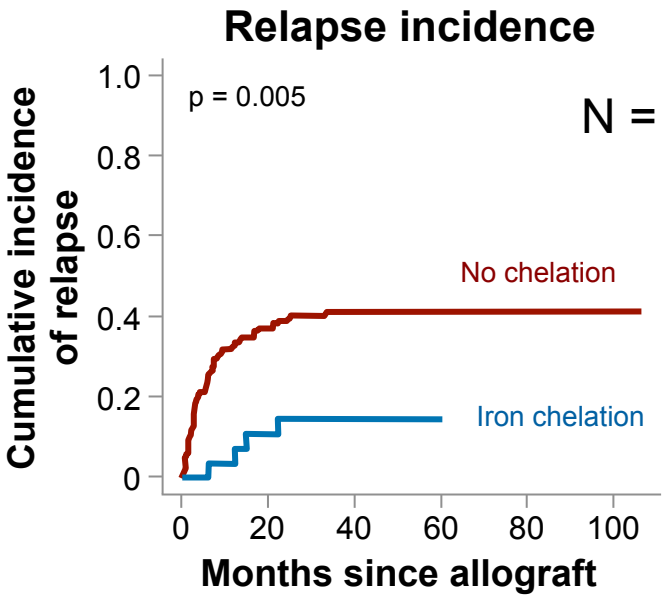
IC = patients with serum ferritin decreased to < 1,000 µg/L with ICT before HSCT;
ICT = iron chelation therapy;
SF > 1,000 = patients with serum ferritin ≥ 1,000 µg/L at the time of HSCT;
SF < 1,000 = patients with serum ferritin < 1,000 µg/L at the time of HSCT, without ICT.

Lee JW, et al. Bone Marrow Transplant. 2009;44:793-7.

ICT following allogeneic HSCT



HR 0.34 (0.15–0.76), p = 0.008



HR 0.22 (0.07–0.73), p = 0.012

- Conclusions: IOL at HSCT has a negative impact on TRM and overall survival; the use of iron chelation following HSCT was associated with a reduced risk of relapse, possibly by depriving leukaemic cells of iron

Michallet M, et al. Blood. 2013;122:abstract 180.

Which MDS patients undergoing allo-SCT could benefit from treatment of iron overload ?

GITMO working conference on iron chelation in MDS

- "...all MDS patients who are transfusion-dependent and are potential candidates for allo-SCT should receive ICT to prevent iron accumulation"
- "If iron overload has occurred in patients for whom a myeloablative allo-SCT has been planned, ...an attempt should be performed to reduce body iron stores. However, ...the accomplishment of the reduction of iron overload should not cause a delay in transplantation"
- "The Expert Panel recommendation for peri-transplantation ICT in MDS patients with iron overload is to offer IV deferoxamine infusion (40 mg/kg/day as a 24-hour i.v. infusion)"
- "In patients with MDS and iron overload after SCT, iron removal through phlebotomy is the first-choice therapy (6 mL/kg blood withdrawal at 14-day intervals). For those patients who cannot be phlebotomized due to low Hb level or cardiac impairment, deferoxamine or deferasirox should be considered. The optimal strategy, however, remains to be defined"

Alessandrino EP, et al. Am J Hematol. 2011;86:897-902.

CASO CLINICO N° 4

- maschio, 58 anni
- **Dicembre 2005:** anemia trasfusione-dipendente; **Novembre 2006: diagnosi di MDS**; Hb 7.5; PLTS 348; WBC 5.1 (PMN 3.1); WHO: anemia refrattaria; cariotipo: normale; rischio IPSS: basso; IPSS-R: basso; ritmo trasfusionale 2 GRC/mese; ferritina 689; EPO: 25
- **Gennaio 2007:** inizia EPO; aprile 2007: cessazione temporanea delle trasfusioni, Hb 10.4;
- **Gennaio 2008:** anemizzazione, ripresa delle trasfusioni (2 GRC/mese) , Hb 8, continua EPO
- **Dicembre 2008:** 2-3 GRC/mese, Hb 7, midollo: malattia stabile, cariotipo normale, blasti < 2%, ferritina 4.623 , PCR 3.66; **inizia DFX 20 mg/Kg/die**, continua EPO
- **Marzo 2009: riduzione ≥ 50% del ritmo trasfusionale**, Hb 8.4, ferritina 3.461 , PCR 1,22, continua EPO; Dicembre 2009: Hb 7.9, midollo invariato, ferritina 2.749, 8 GRC negli ultimi 10 mesi , continua DFX + EPO
- **Febbraio 2011: cessazione completa delle trasfusioni;** Hb 9.6; ferritina 733; **riduce Exjade: 10 mg/Kg/die**; **luglio 2011:** Hb 10, ferritina 516; **riduce DFX 5 mg/Kg/die**; **ottobre 2011:** Hb 10.3; ferritina 572: **sospende DFX**, continua EPO; **Maggio 2016:** Hb 10.6, ferritina 422, continua EPO
- **SOPRAVVIVENZA: 114 mesi dalla diagnosi, 125 mesi dall'inizio delle trasfusioni**

TERAPIA CHELANTE NELLE MDS: RIDUZIONE DEL FABBISOGNO TRASFUSIONALE *(Jensen, Br J Haematol, 1996)*

- 11 paz. con MDS trattati con DFO (standard in 4 paz., bolo i.c. in 7 paz) (+ vit C) (fino a 60 mesi)
- 7/11 paz (64%): ↓ del fabbisogno trasfusionale > 50%, 5/11 : miglioramento trilineare
- 7 paz: aumento delle piastrine e dei PMN
- 5/11 (46%): trasfusione-indipendenti,
- efficacia clinica (↓ ferro epatico con RMN) associata ad aumento del recettore della transferrina e dell'attività eritropoietica (b.ossea)
- **max risposta dopo almeno 18 mesi**, correlata all'efficacia della ferro-chelazione

Nei pazienti affetti da MDS deferasirox può migliorare l'emopoiesi: prime evidenze aneddotiche

Pubblicazione	n	Rischio IPSS	Risposta GR*	Risposta neutrofili*	Risposta PLT*
Breccia et al., 2010[1]	1	Basso	Maggiore	NR	NA
Capalbo et al., 2009[2]	1	Basso	Maggiore	NA	NA
Messa et al., 2008[3]	3	Intermedio 1 Intermedio 1 Alto	Minore Maggiore Maggiore	NA NA Maggiore	NA NA NR
Okabe et al., 2009[4]	1	NR	Maggiore	Maggiore	NR
Oliva et al., 2010[5]	1	Basso	Maggiore	NA	NA

***Le risposte di globuli rossi, piastrine e neutrofili sono valutate in base ai criteri IWG 2000.**

1. Breccia M, et al. Acta Haematol. 2010;124:46-8; 2. Capalbo S, et al. Acta Haematol. 2009;121:19-20.
3. Messa E, et al. Acta Haematol. 2008;120:70-4; 3. Okabe H, et al. Rinsho Ketsueki. 2009;50:1626-9.
5. Oliva EN, et al. Transfusion. 2010;50:1568-70; Tabella adattata da Guariglia R, et al. Leuk Res. 2011;35:566-70.

Pubblicazione	n	Rischio IPSS	Risposta GR*	Risposta neutrofili*	Risposta PLT*
Guariglia et al., 2011[1]	1	Intermedio 1	Maggiore	Maggiore	NA
List et al., 2009[2]	6	Basso/Int-1	2 maggiori 1 minore†	1 maggiore 1 maggiore‡	1 maggiore 1 maggiore‡
Badawi et al., 2010[3]	1	Intermedio 1	Maggiore§	NA	NA
Nishiuchi et al., 2010[4]	1	Intermedio 1	Maggiore‖	Maggiore‖	NA
Molteni et al., 2010[5]	6	NR	5 minori	1 maggiore	NA

*** Le risposte di globuli rossi, piastrine e neutrofili sono valutate in base ai criteri IWG 2000.**
† Il paziente ha ricevuto anche darbopoietina.
‡ Il paziente ha ricevuto anche G-CSF e decitabina.
§ La durata della risposta era 38 mesi; è stata osservata infiltrazione leucemica cutanea.
‖ La durata della risposta è stata > 12 mesi.

Tabella adattata da 1. Guariglia R, et al. Leuk Res. 2011;35:566-70.
2. List AF, et al. Blood. 2009;114:[abstract 3829]; 3. Badawi MA, et al. Adv Hematol. 2010;2010:164045.
4. Nishiuchi T, et al. Int J Hematol. 2010;91:333-5; 5. Molteni A, et al. Haematologica. 2010;95 Suppl 2:[abstract 1410].

Deferasirox can Improve Hematopoiesis in MDS: Recent data

Study	n	Risk IPSS	RBC response	Neutrophil response	PLT response
Cilloni D et al. 2011[1]	57	Low/Int-1	45.6%	NR	NR
List A et al. 2012[2]	173 52 77	Low/Int-1	15%	15%	22%
Gattermann N et al. 2012[3]	247 50 100	Low/Int-1	21.5%	22%	13%
Nolte F et al. 2012[4]	50	Low/Int-1	11%	NR	NR
Angelucci E et al. 2012[5]	152	Low/Int-1	Transfusion independence in 14.5%	NR	NR

RBC, PLT and neutrophil responses are asses 2006 criteria (1-3); NR, not reported

[1]CIlloni D *et al*. *Blood* 2011;118:abst 611. [2]List A *et al. J Clin Oncol*. 2012;30:2134-9. [3]Gattermann N *et al. Haematologica* 2012;97:1364-71; [4]Nolte *F et al. Ann Hematol*. 2012 Oct 17. [Epub ahead of print]; [5]Angelucci E *et al*. *Blood* 2012;118:abst 425.

Table 1 Major features indicated in the clinical studies reporting hematologic improvement (HI) during deferasirox treatment

Reference	No. pts	HI-E	HI-plts	HI-PMN	Biological parameters
EPIC [22]	247	53 (21.7 %) 11.8 % TI 8.9 % ↑ Hb	13 (13 %)	50 (22 %)	No significant changes in SF and LIP between responders and non-responders
US03 [23]	173	26 (15 %)	17/77 (22 %)	8/52 (15 %)	No significant changes in SF and LIP between responders and non-responders
German [24]	50	2/33 (6 %)	3/10 (30 %)	–	–
GIMEMA [25]	152	16/152 (11 %)	18/125 (15 %)	1/41 (3 %)	No significant changes in SF between responders and non-responders
Italian cooperative group [26]	105	41/105 (44.5 %)	nr	nr	HI not related to SF changes
REL [27]	53	19 (35.1 %)	8/13 (61 %)	13/17 (76.4 %)	No correlations

TI transfusion independence, *SF* serum ferritin, *Hi-E* erythroid improvement, *HI-Plts* platelet improvement, *HI-PMN* neutrophil improvement, *LIP* labile iron pool

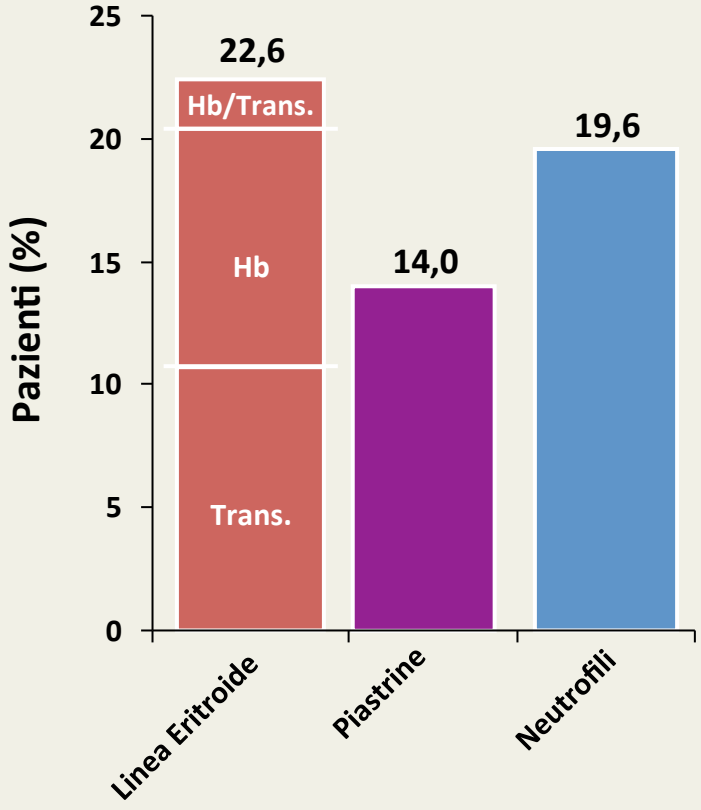
Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes

Norbert Gattermann,[1] Carlo Finelli,[2] Matteo Della Porta,[3] Pierre Fenaux,[4] Michael Stadler,[5] Agnes Guerci-Bresler,[6] Mathias Schmid,[7] Kerry Taylor,[8] Dominique Vassilieff,[9] Dany Habr,[10] Andrea Marcellari,[10] Bernard Roubert,[11] and Christian Rose[12]

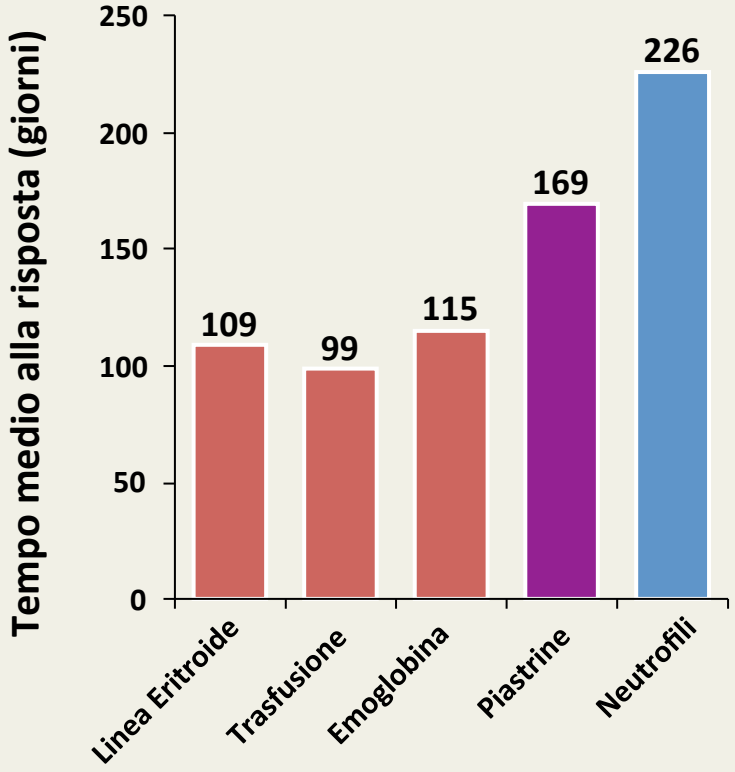
[1]Heinrich-Heine-Universität, Düsseldorf, Germany; [2]Policlinico S. Orsola-Malpighi, Bologna, Italy; [3]IRCCS Policlinico S. Matteo, Pavia, Italy; [4]Service d'hématologie Clinique, Hôpital Avicenne/Université Paris, Bobigny, France; [5]Medizinische Hochschule Hannover, Hannover, Germany; [6]CHU Brabois, Vandoeuvre Cédex, France; [7]Stadtspital Triemli, Zurich, Switzerland; [8]Mater Hospital, Brisbane, Australia; [9]Assistance Publique-Hôpitaux de Paris, Hôpital Cochin, Paris, France; [10]Novartis Pharmaceuticals, East Hanover, NJ, USA; [11]Novartis Pharma AG, Basel, Switzerland, and [12]Hôpital Saint-Vincent de Paul, Lille, France

Citation: Gattermann N, Finelli C, Della Porta M, Fenaux P, Stadler M, Guerci-Bresler A, Schmid M, Taylor K, Vassilieff D, Habr D, Marcellari A, Roubert B, and Rose C. Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. Haematologica 2012;97(9):1364-1371. doi:10.3324/haematol.2011.048546

Risposta ematologica



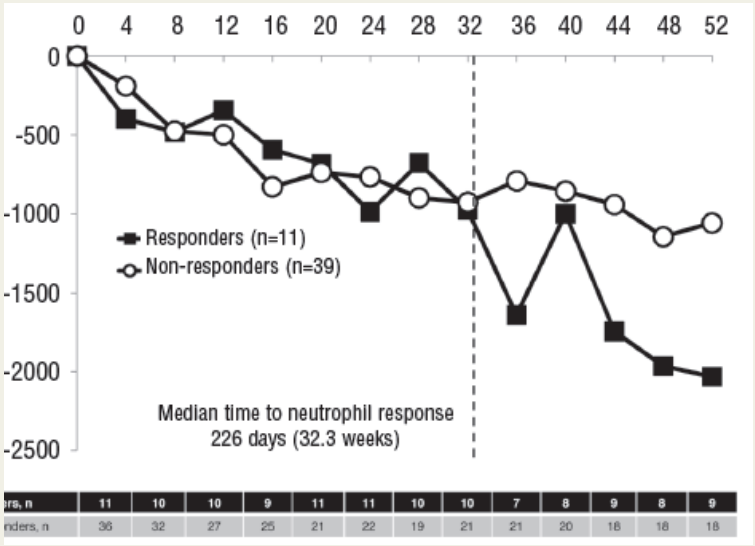
Tempo alla risposta ematologica



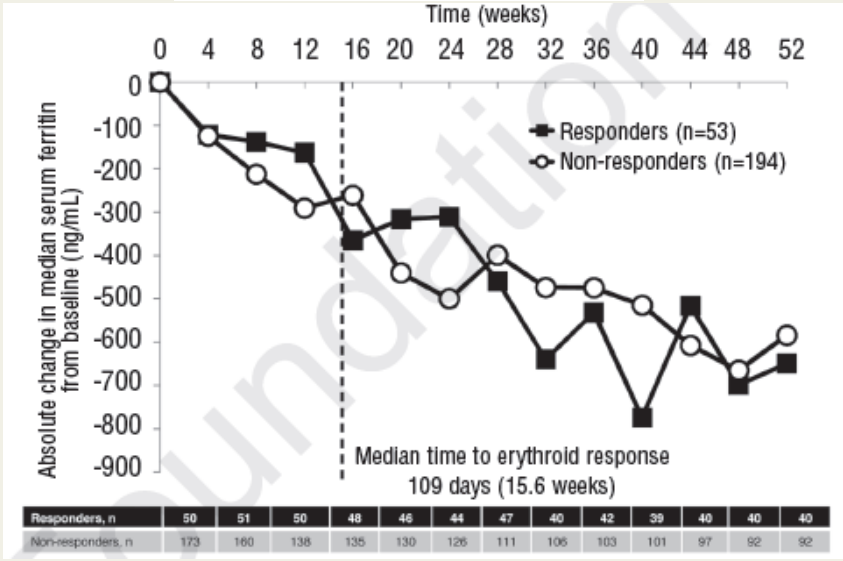
Gattermann N, et al. Haematologica 2012

Ferritina Serica

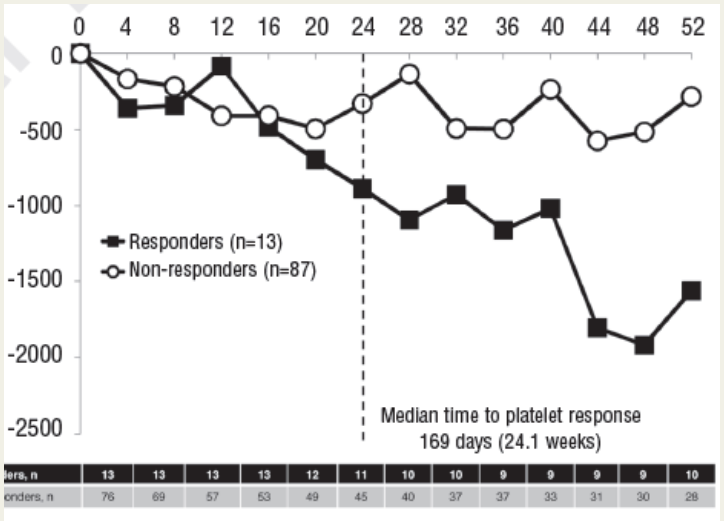
Risposta Neutrofila



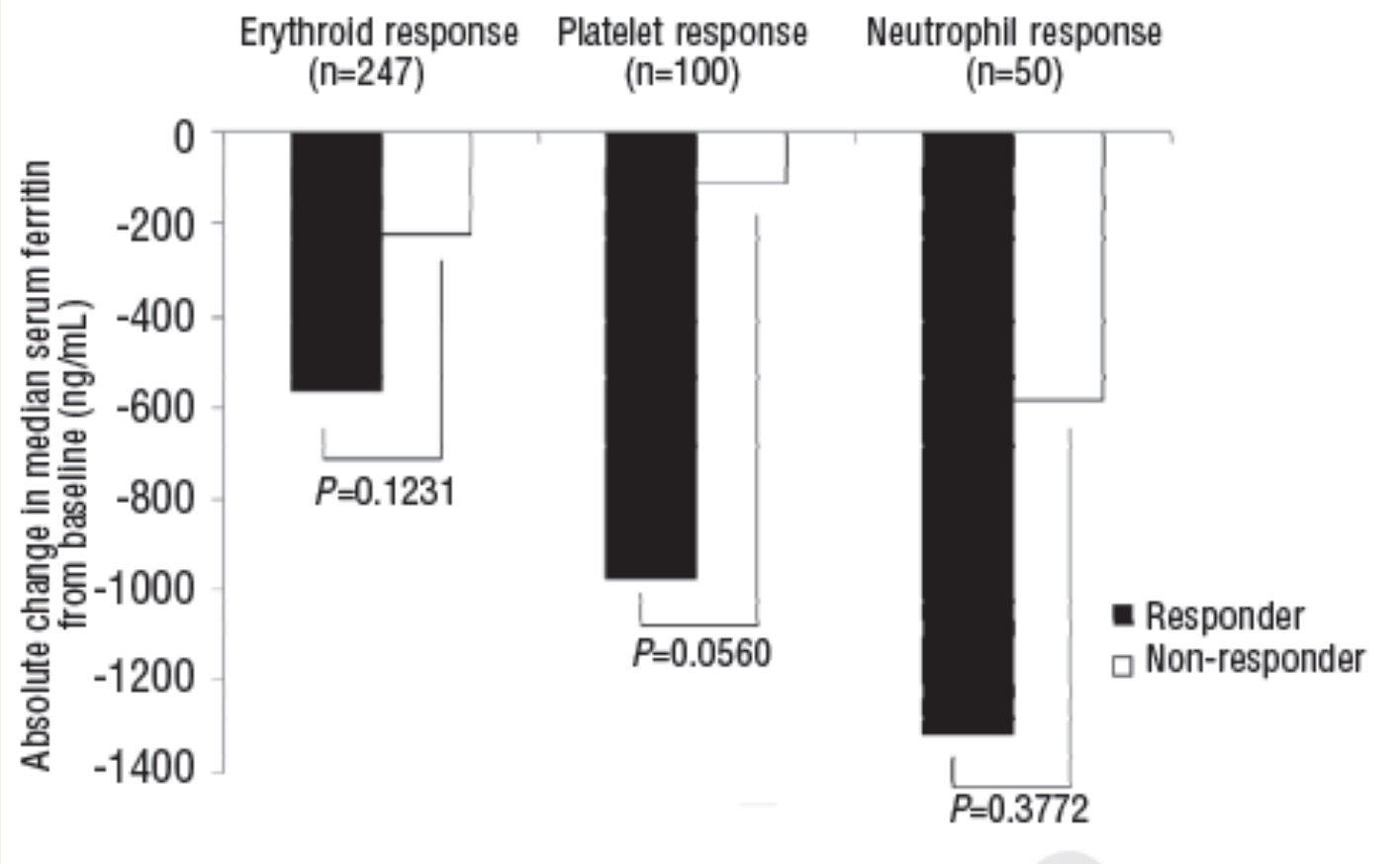
Risposta Eritroide



Risposta Piastrinica



Gattermann et al, Hematologica 2012



La risposta ematologica non correla direttamente con la riduzione della ferritina sierica

Gattermann et al, Hematologica 2012

VOLUME 30 · NUMBER 17 · JUNE 10 2012

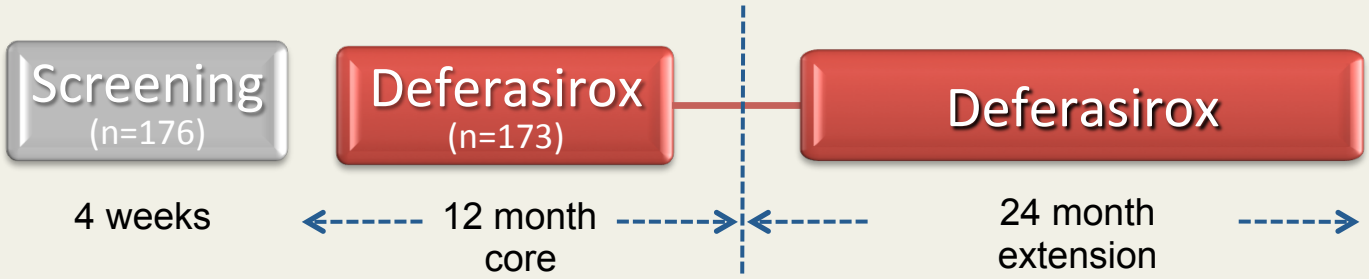
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Deferasirox Reduces Serum Ferritin and Labile Plasma Iron in RBC Transfusion–Dependent Patients With Myelodysplastic Syndrome

Alan F. List, Maria R. Baer, David P. Steensma, Azra Raza, Jason Esposito, Noelia Martinez-Lopez, Carole Paley, John Feigert, and Emmanuel Besa

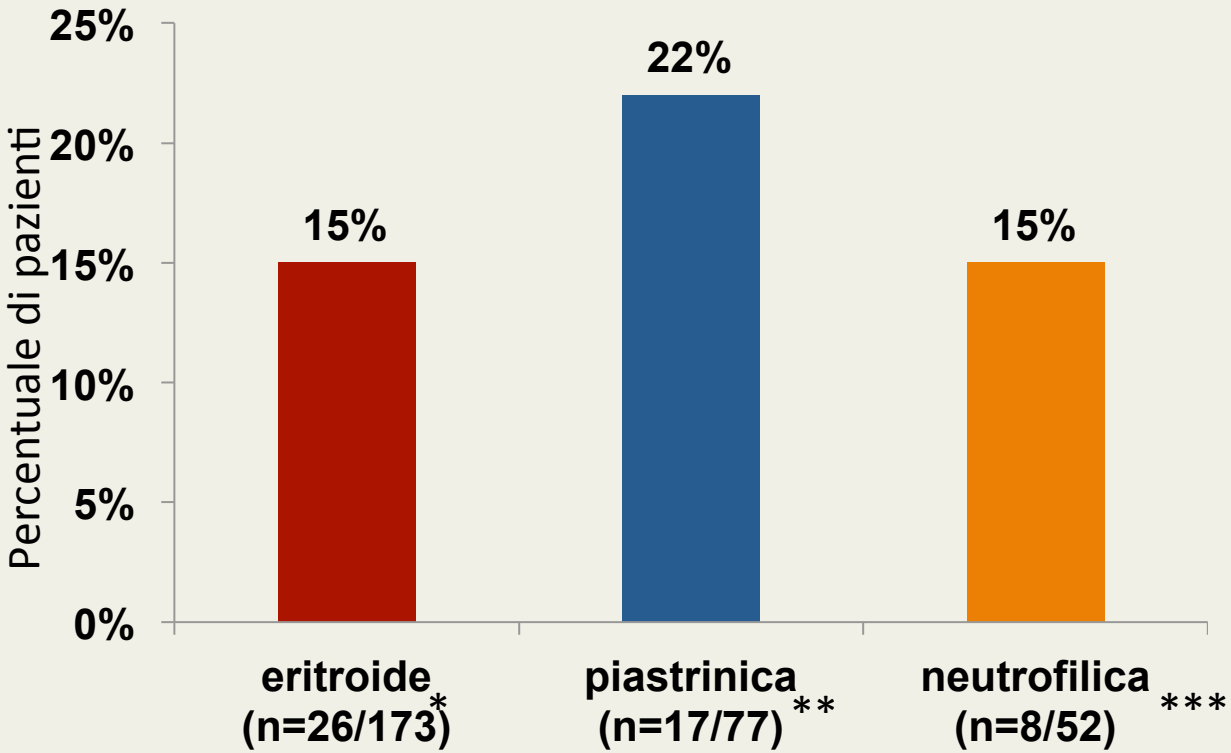
- Studio prospettico, multicentrico, di 3-aa, per stabilire sicurezza ed efficacia del deferasirox in 173 pazienti, con MDS a rischio basso o intermedio-1 (72%)
- Criteri di inclusione: almeno 20 unita' RBC, ferritina serica > 1,000 ng/mL.
- Accettabile creatinina aumentata fino a 2 volte il valore normale



Pazienti analizzati per risposta ematologica secondo criteri IWG 2006

N= 173

Durata risposta ≥8 settimane



Risposta ematologica

Tempo mediano alla risposta 169 gg (range 84-382)

*1pz assumeva anche lenalidomide, 2 EPO

** 1 pz assumeva EPO+ AZA

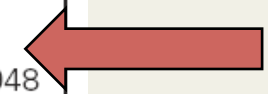
*** 1 pz assumeva EPO, 1 EPO+decitabina, 1 lenalidomide

List AF, et al. J Clin Oncol 2012;30(17):2134-9

Variazioni assolute della ferritinemia maggiori nei pazienti con risposta ematologica

Table 3. Change in Serum Ferritin From Baseline to End of Study in Patients With and Without Hematologic Response

Serum Ferritin Level	Patients Without Hematologic Improvement (n = 123)	Patients With Hematologic Improvement (n = 41)
Baseline serum ferritin, μg/L		
Median	2,751	3,045
Range	863-9,238	1,160-36,280
Change in serum ferritin from baseline to end of study, μg/L		
Median	−228	−693
Range	−4,227 to 5,317	−30,313 to 5,948



- Ferritinemia mediana ridotta in entrambi i gruppi, ma variazioni maggiori nel gruppo dei pazienti che ottenevano anche risposta ematologica
- Riduzione del LPI medio sia nei pazienti con HI, che in quelli che non ottenevano HI (media 0.47 mol/L v 0.32mol/L, rispettivamente).
- Vi era un trend per un miglioramento della sopravvivenza nei pazienti responsivi.

List AF, et al. J Clin Oncol 2012;30(17):2134-9

Hematological Response with Deferasirox: Retrospective Italian Study
Hematological Response (RBC)

	DFO	DFX	DFO---DFX	Total
Patients	**29**	**57**	**6**	**92**
RBC transfusion independence	**5** (17,2%)	**12** (21%)	**1** (16%)	18 (19,5%)
HI-e (reduction of 4 U /8 weeks)	**4** (13,7%)	**9** (15,7%)	**3** (50%)	16 (17,3%)
HI-e (increase of 1,5 g/dL)	**2** (6,8%)	**5** (8,7%)	**0**	7 (7,6%)
TOTAL	**11 (37%)**	**26 (45,6%)**	**4 (66%)**	**41 (44,5%)**

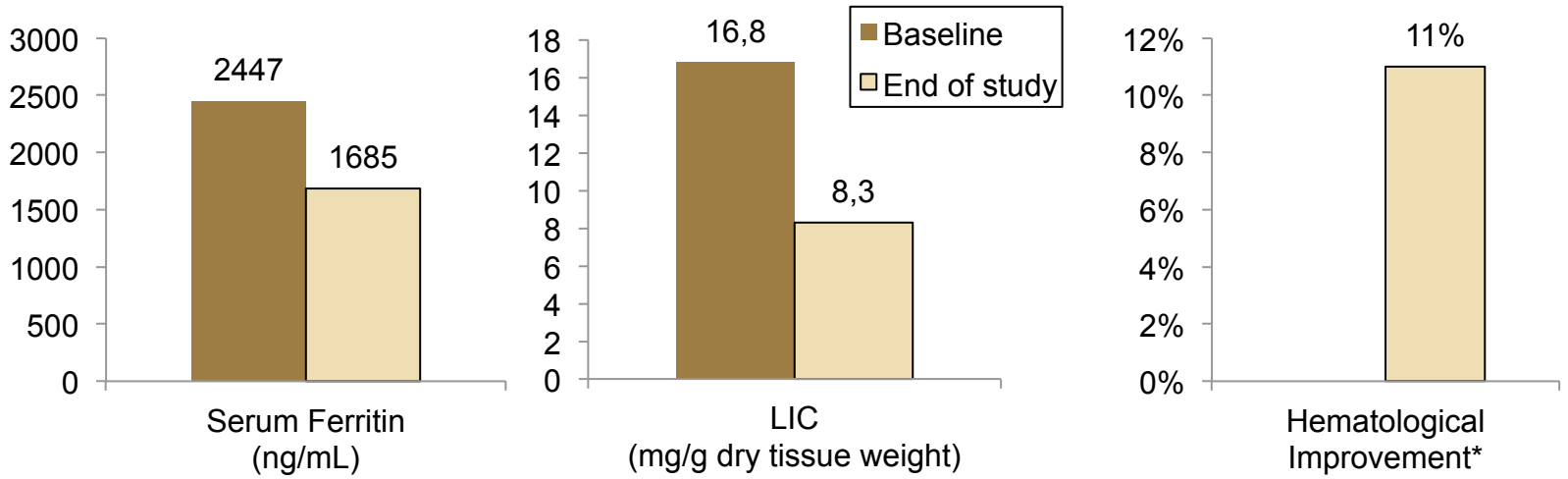
3 patients achieving complete erythroid response (2 with DFO and 1 with DFX) were receiving concomitant Epo from 15, 17 and 53 months with stable transfusion requirement at the time of ICT

IWG response criteria: Cheson et al. Blood 2006

Cilloni D *et al. Blood* 2011;118;abst 611.

1-year, Open-label, Single Arm, German Multi-center Trial: Hematological improvement in 11% Patients

- Multi-center trial evaluating the efficacy and safety of deferasirox (DFX) in low and intermediate-1 risk MDS patients with transfusion-dependent IOL.
- Mean daily dose of DFX was 19 mg/kg/day.
- The intention to treat population consisted of 50 MDS patients (28 male; 22 female) with a median age of 69 years who were treated with DFX for a median duration of 354 days.



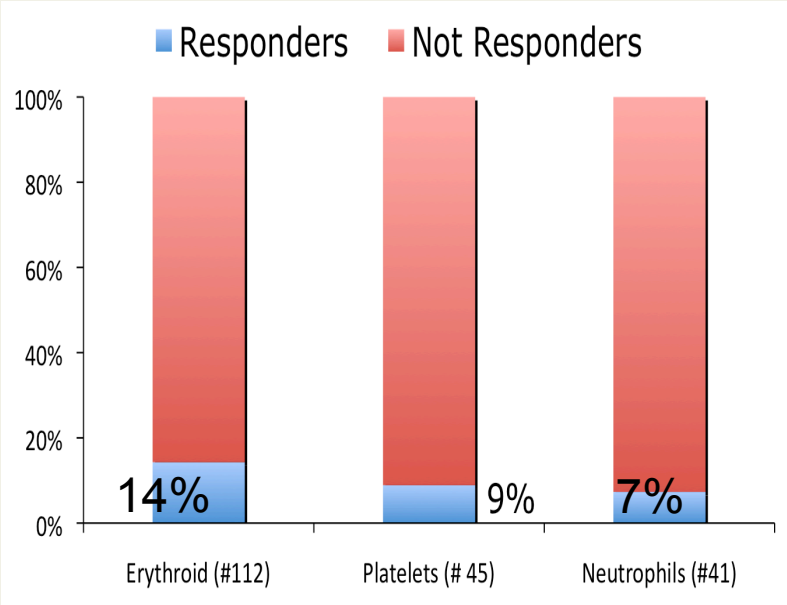
*Hematologic improvement according to IWG criteria (2006)

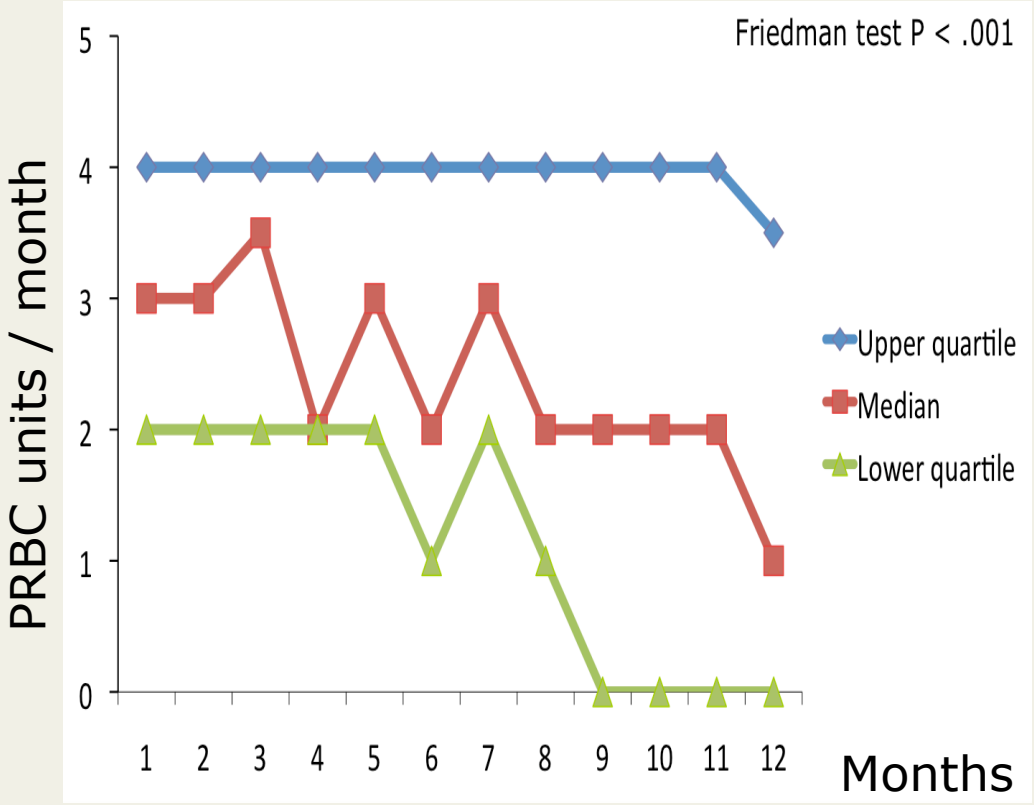
Nolte et al., *Ann Hematol*. 2013 Jan;92(2):191-8.

Risposta Ematologica

PRBC Units

In 68 pts dopo 1 anno di trattamento

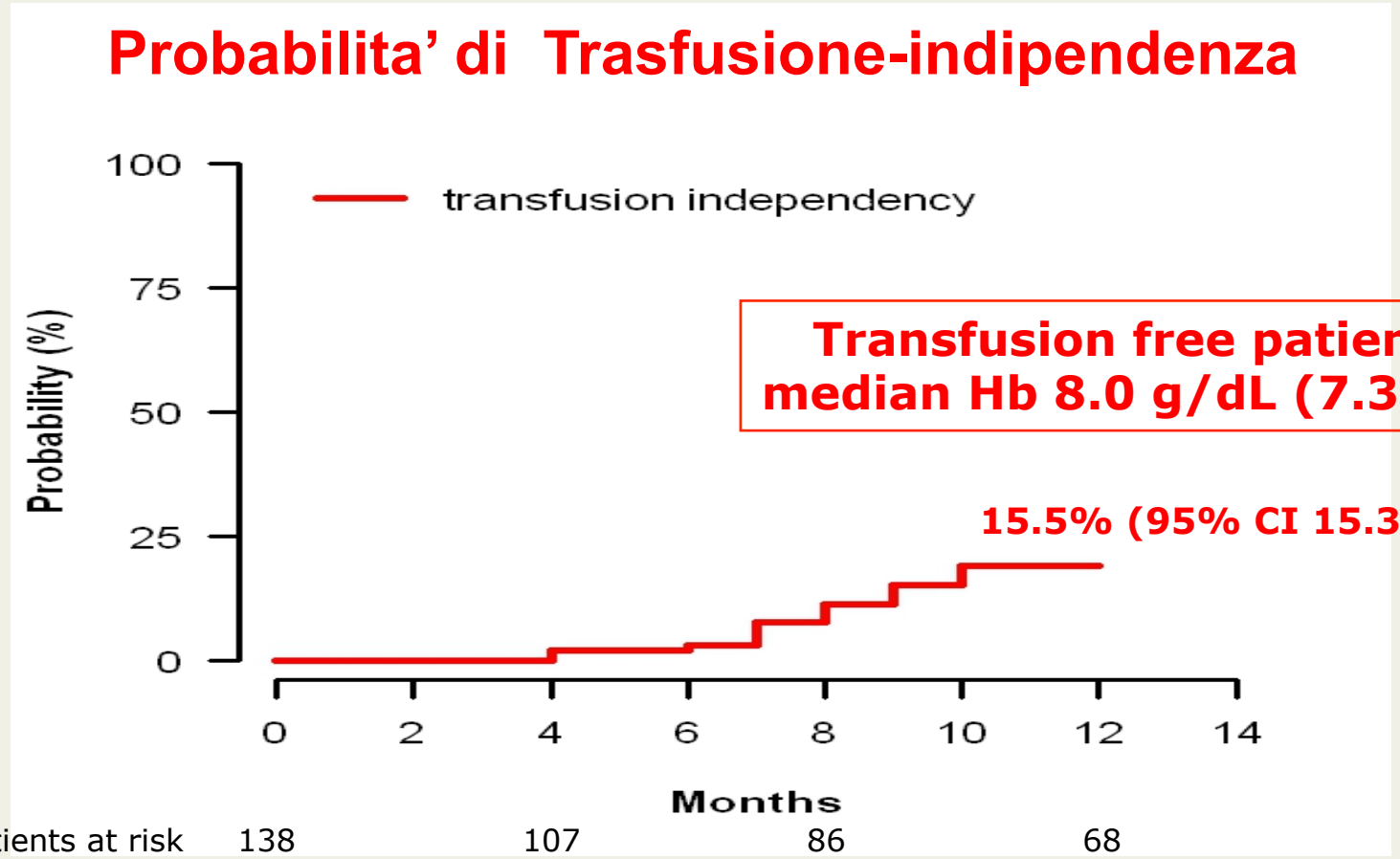




- Partendo da livelli paragonabili di Emoglobina pre-trasfusione, il fabbisogno trasfusionale si riduceva durante il trattamento [mediana PRBC/mese 3 (2-5) vs 1 (0-4) dopo 1 anno (P= 0.0001)]

Angelucci E et al. Eur J Haematol, 2014.

Probabilita' di Trasfusione-indipendenza



Transfusion free patients: median Hb 8.0 g/dL (7.3-8.6)

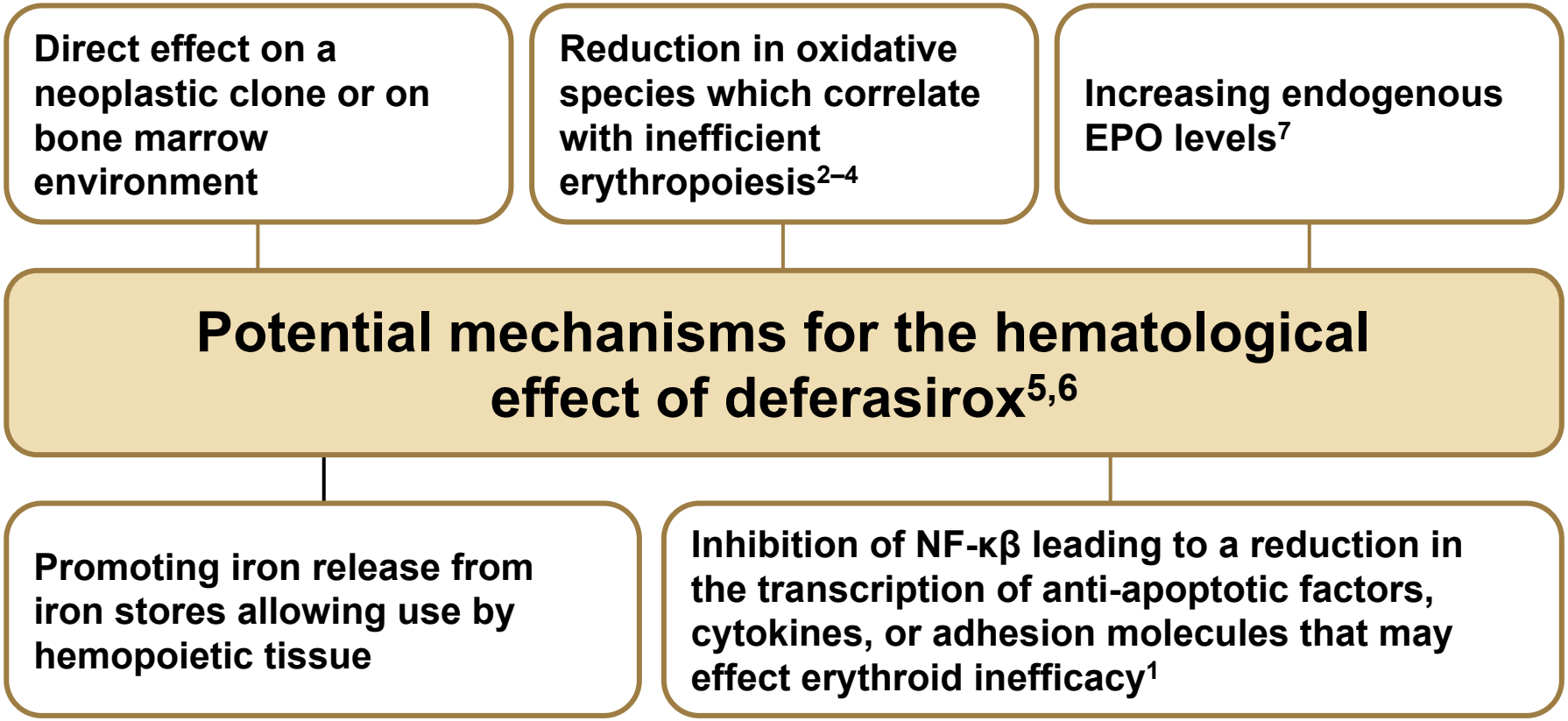
15.5% (95% CI 15.3–15.8)

- 22 pz TI, con una probabilita' del 5.5% (95%CI 5.4-5.6), 15.7% (95%CI 15.4-15.9) e 19.7% (95% CI 19.4-20) dopo 6, 9 e 12 mesi di trattamento.

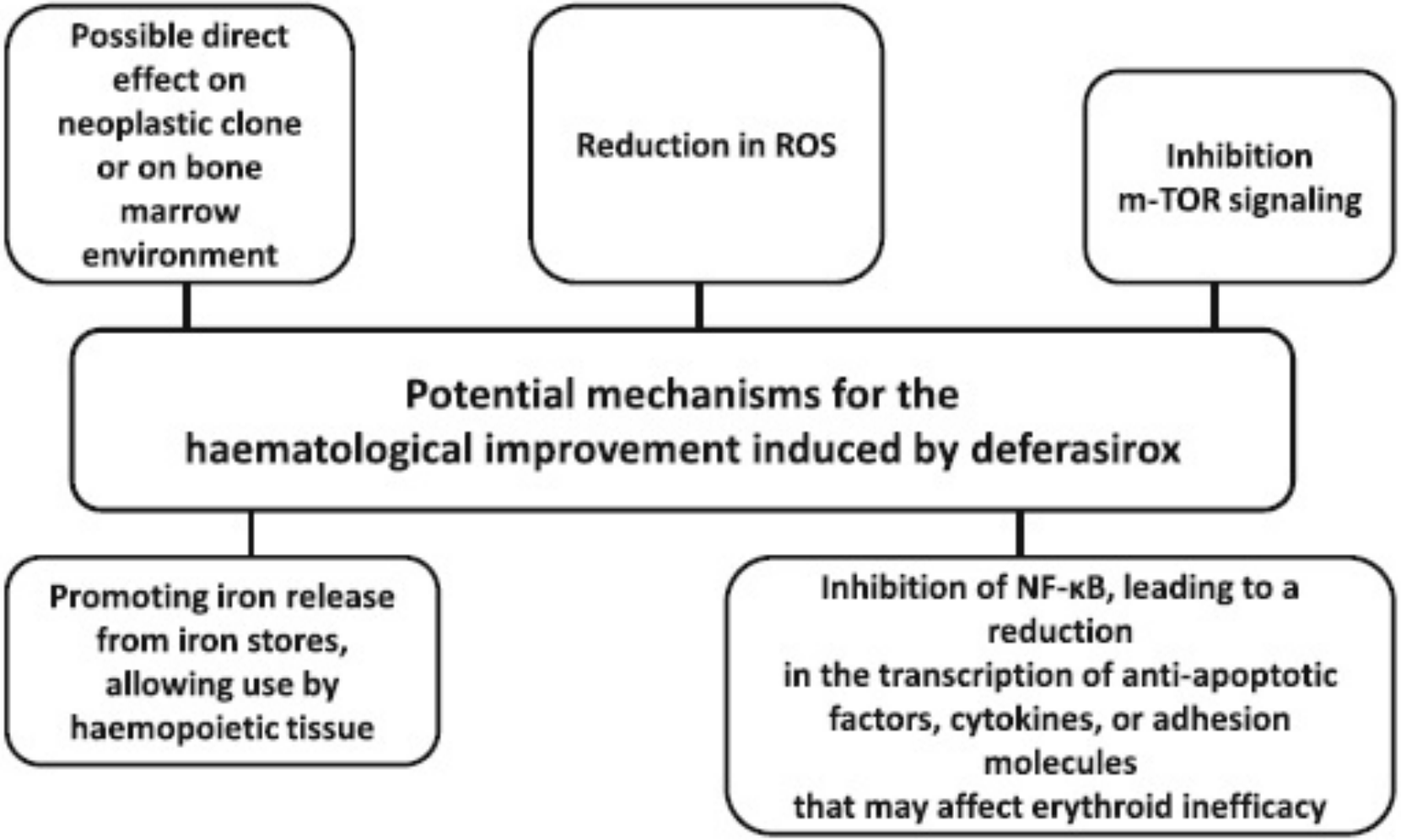
Non parametric cumulative incidence estimator.
Drop out, progression and death were considered competitive risks

Angelucci E et al. Eur J Haematol, 2014.

Potential Mechanisms for the Hematologic Effect of Deferasirox



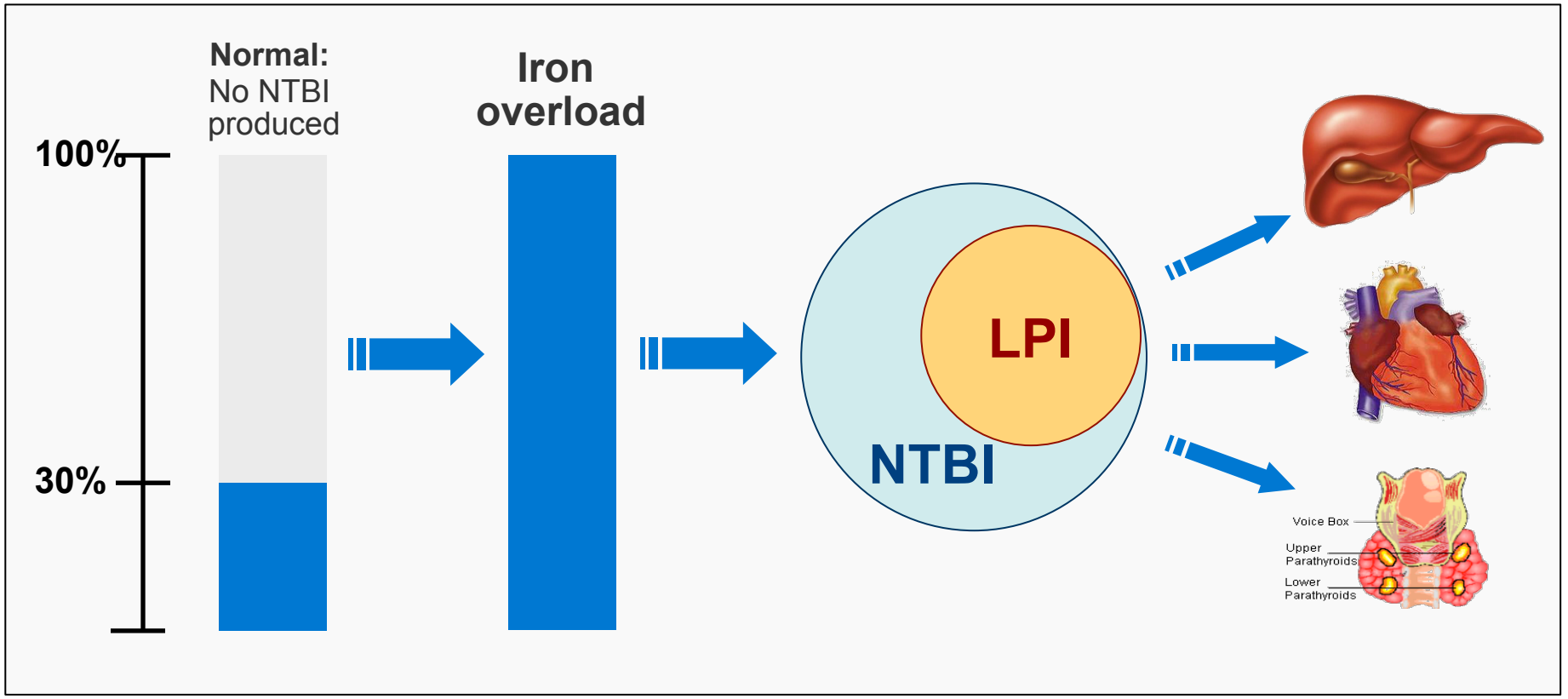
1. Messa E, et al. *Haematologica*. 2010;95:1308-16. 2. Ghoti H, et al. *Eur J Haematol*. 2007;79:463-7.
3. Hartmann J, et al. *Blood*. 2008;112:[abstract 2694]. 4. Chan LSA, et al. *Blood*. 2008;112:[abstract 2685].
5. Breccia M, et al. *Acta Haematol*. 2010;124:46-8. 6. Guariglia R, et al. *Leuk Res*. 2011;35:566-70.
7. Ren X, et al. *J Appl Physiol*. 2000;89(2):680-6.



NF-κB, nuclear factor kappa B
ROS= reactive oxygen species

Fig. 1 Potential mechanisms for the hematological effect of deferasirox

Non-Transferrin-Bound Iron (NTBI)



NTBI appears when plasma iron exceeds transferrin binding capacity (saturation > 60–70%)

LPI = labile plasma iron:

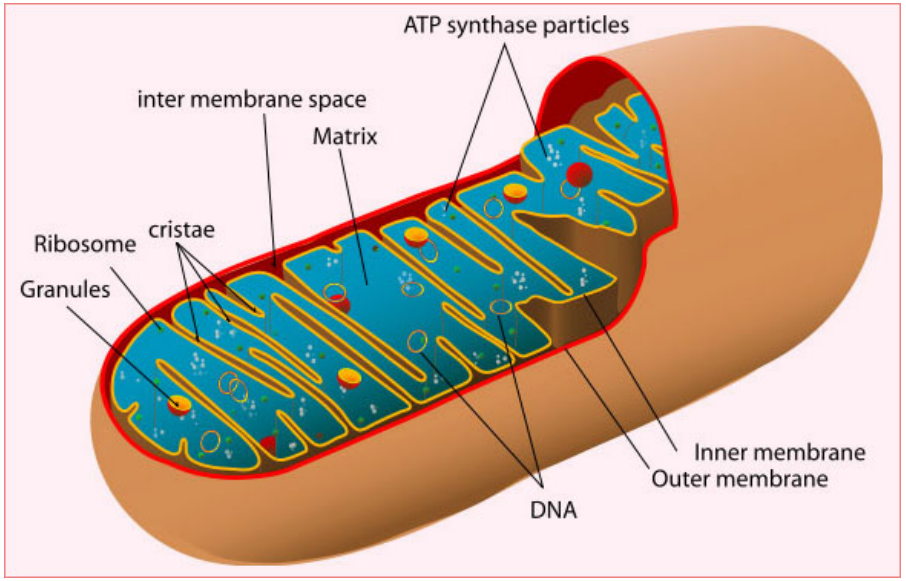
- **redox-active**
- **chelatable**
- **membrane-permeant**

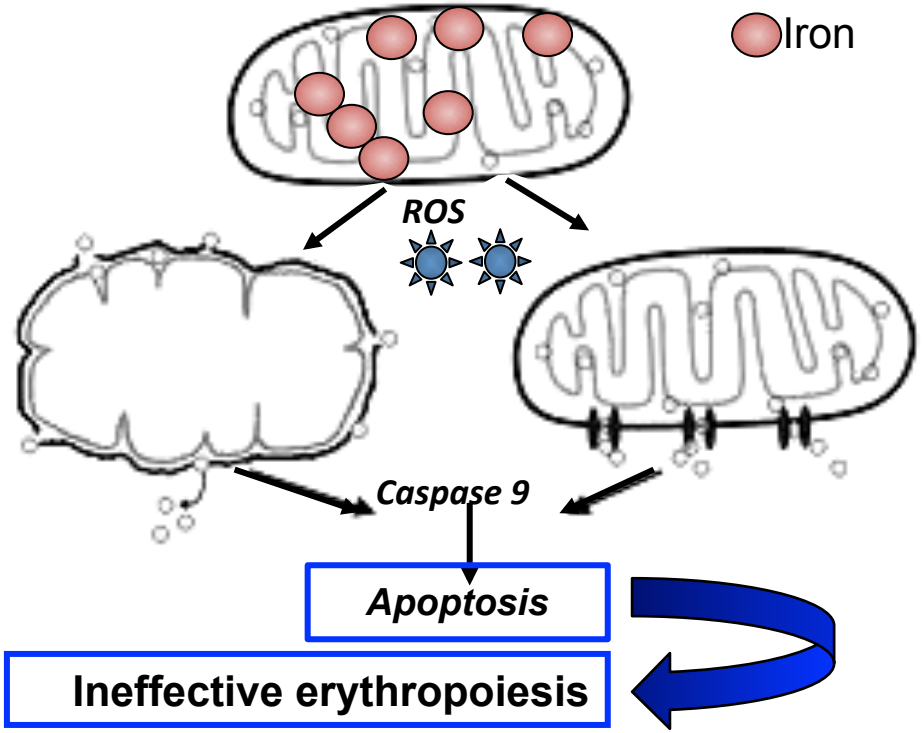
ROS Promote Apoptosis through Activation of the Caspase Cascade

Iron is also a potentially toxic metal

Labile iron can catalyze the production of toxic radicals:

$$O_2^{\bullet -} + H_2O_2 \xrightarrow{Fe(II)} O_2 + OH^- + OH^{\bullet}$$ that can damage the cells





Zuo Y, *et al. Cell Res*. 2009;19:449-57.

Increased Oxidative Stress in MDS

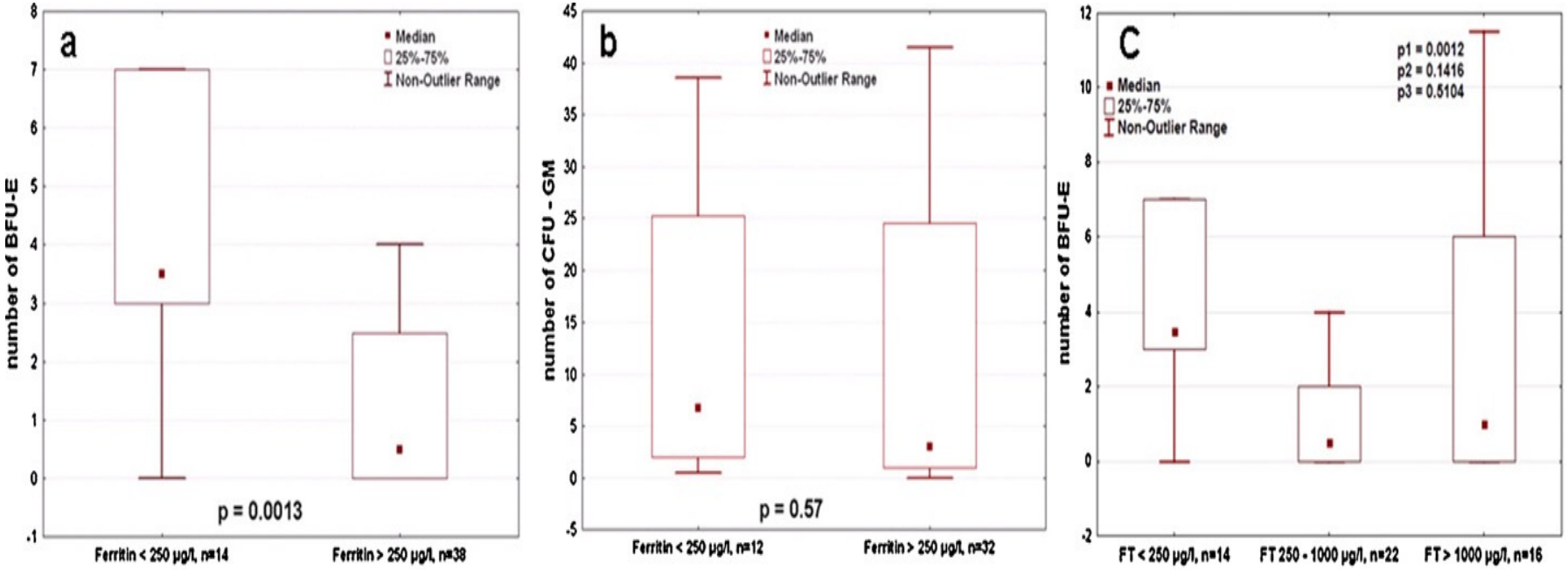
Bowen D, Wang L, Frew M, Kerr R, Groves M (2003)
Antioxidant enzyme expression in myelodysplastic and acute myeloid leukemia bone marrow: Further evidence of a pathogenetic role for oxidative stress?
Haematologica 88:1070-1072

Ghoti H, Amer J, Winder A, Rachmilewitz EA, Fibach E (2007)
Oxidative stress in red blood cells, platelets and polymorphonuclear leukocytes from patients with myelodysplastic syndrome.
Eur J Haematol 79:463-467

Novotna B, Bagryantseva Y, Siskova M, Neuwirtova R (2009)
Oxidative DNA damage in bone marrow cells of patients with low-risk myelodysplastic syndrome.
Leukemia Research 33:340-343

Ghoti H, Fibach E, Merkel LD, Perez-Avraham G, Grisariu S, Rachmilewitz E (2010)
Changes in parameters of oxidative stress and free iron biomarkers during treatment with deferasirox is iron-overloaded patients with myelodysplastic syndromes.
Haematologica 95:1433-1434

Iron overload suppresses the proliferation of erythroid progenitors cells (BFU-E)



"We demonstrate that iron overload suppresses the proliferation of erythroid progenitors cells (BFU-E), while the myeloid compartment (CFU-GM) was not found to be affected. Even patients with slightly elevated ferritin values show an impaired proliferation capacity in comparison to patients with normal ferritin levels. Furthermore, we show that this negative impact is reversible by sufficient iron chelation therapy."

J. Hartmann et al. / Leukemia Research *37 (2013) 327– 332*

bjh research paper

The oral iron chelator deferasirox inhibits NF-κB mediated gene expression without impacting on proximal activation: implications for myelodysplasia and aplastic anaemia*

Ashish Banerjee,[1,2] Nicole A. Mifsud,[3] Robert Bird,[4,5] Cecily Forsyth,[6] Jeff Szer,[7] Constantine Tam,[8] Sybil Kellner,[9] Andrew Grigg,[10] Penelope Motum,[11] Mark Bentley,[12] Stephen Opat[13] and George Grigoriadis[1,2,13,14]

[1]*Centre for Cancer Research, MIMR PHI Institute of Medical Research,* [2]*Centre for Inflammatory Diseases, Monash University,* [3]*Departments of Medicine and Allergy, Immunology and Respiratory Medicine, Monash University, Clayton, Vic.,* [4]*Haematology, Princess Alexandra Hospital,* [5]*School of Medicine, Griffith University, Brisbane, Qld,* [6]*Haematology, Jarrett Street Specialist Centre, North Gosford, NSW,* [7]*Clinical Haematology, Royal Melbourne Hospital, Melbourne,* [8]*Haematology, Peter MacCallum Cancer Centre, East Melbourne, Vic.,* [9]*Haematology, Cotton Tree Specialist Centre, Cotton Tree, Qld,* [10]*Department of Clinical Haematology, Austin Hospital, Heidelberg, Vic.,* [11]*Haematology Department, Liverpool Hospital, Liverpool, NSW,* [12]*Haematology, Queensland Haematology and Oncology Group, Brisbane, Qld,* [13]*Clinical Haematology, Monash Health, Clayton, Vic., and* [14]*Department of Haematology, Alfred Health, Melbourne, Australia*

Summary

The myelodysplastic syndromes (MDS) are a group of disorders characterized by ineffective haematopoiesis, bone marrow dysplasia and cytopenias. Failure of red cell production often results in transfusion dependency with subsequent iron loading requiring iron chelation in lower risk patients. Consistent with previous reports, we have observed haematopoietic improvement in a cohort of patients treated with the oral iron chelator deferasirox (DFX). It has been postulated that MDS patients have a pro-inflammatory bone marrow environment with increased numbers of activated T cells producing elevated levels of tumour necrosis factor (TNF), which is detrimental to normal haematopoiesis. We demonstrate that DFX inhibits nuclear factor (NF)-κB dependent transcription without affecting its proximal activation, resulting in reduced TNF production from T cells stimulated *in vitro*. These results suggest that the haematopoietic improvement observed in DFX-treated patients may reflect an anti-inflammatory effect, mediated through inhibition of the transcription factor NF-κB and support the therapeutic targeting of this pathway, which is aberrantly activated in a large proportion of haematological malignancies.

Keywords: aplastic anaemia, biochemistry, blood diseases, chelation, myeloid function and development.

Banerjee, Br J Haematol 2015