Low Risk Myelodysplastic Syndrome

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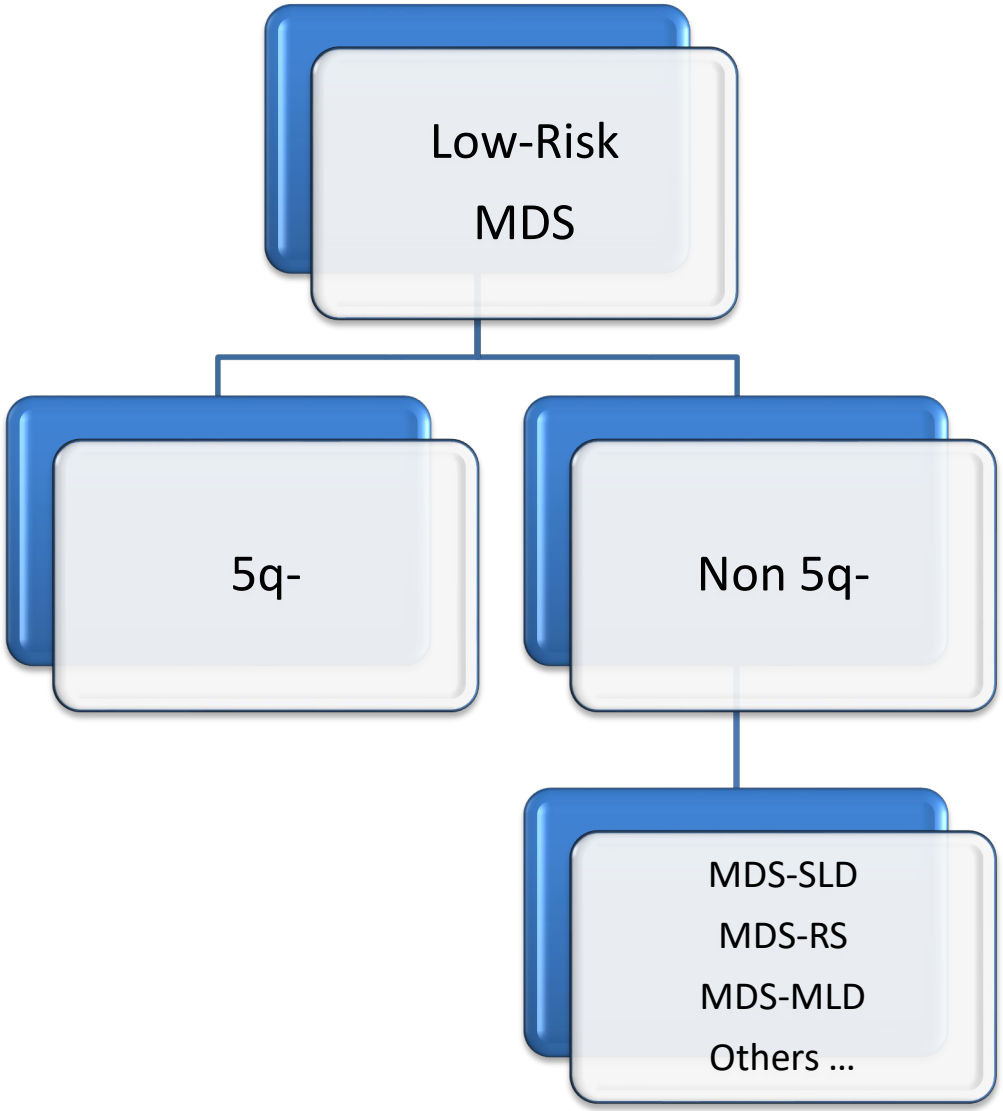
Icon Cancer Care

GET Weekend 2019

Classification … based on therapy paradigms



Goals of Therapy in Low-Risk MDS

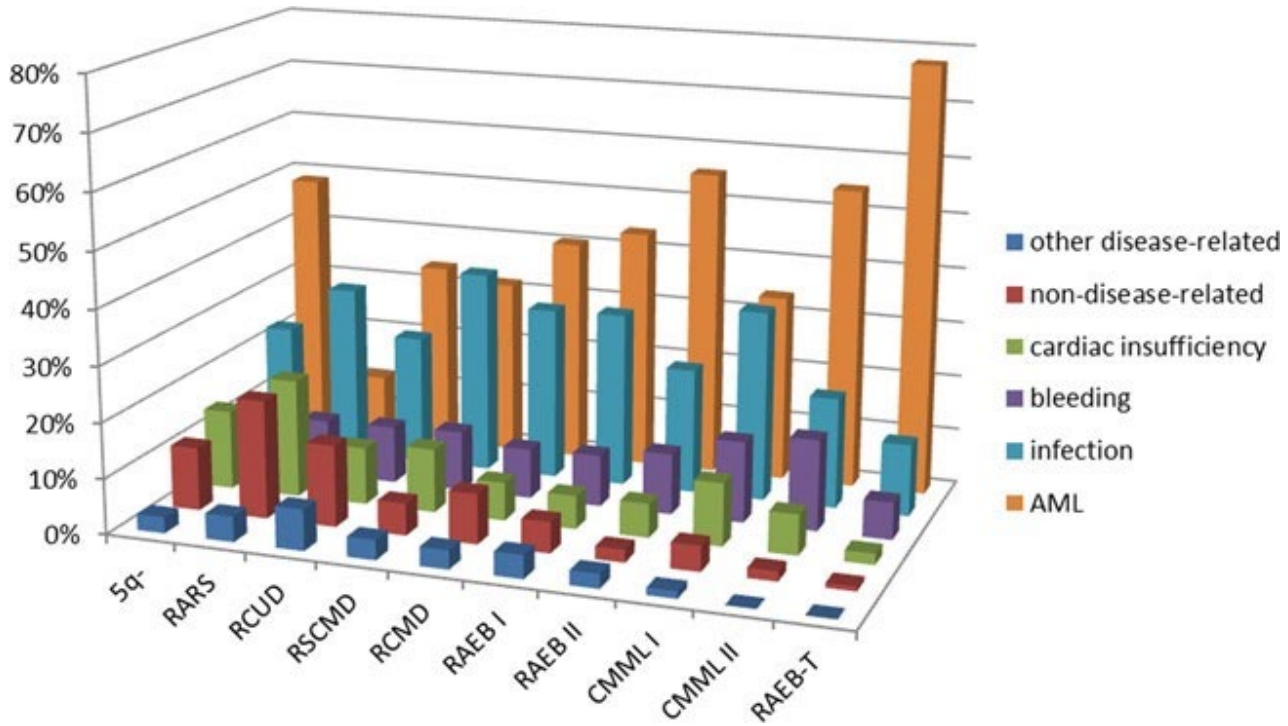
- Quality of Life
- Improve anaemia
  - Reduce fatigue
- Minimise transfusion requirements
- Minimise bleeding risk

- Remember: up to half of patients may die from causes other than MDS [1]

Nachtkamp K (2016) Ann Hematol; 95: 937-944

Cause of death

- Overall:
  - Leukaemic transformation (46.6%
  - Infection (27.0%)
  - Haemorrhage (9.8%)



Nachtkamp K (2016) Ann Hematol; 95: 937-944

Cause of death varies by MDS subtype

	AML	Infection	Bleeding	Cardiac insufficiency	Non-disease-related	Other disease-related	*P* value
	46.6 %	27.0 %	9.8 %	7.9 %	6.0 %	2.7 %	
RCUD ($n=68$)	33.8 %	23.5 %	10.3 %	10.3 %	14.7 %	7.4 %	<0.00005
RARS ($n=89$)	11.2 %	31.5 %	10.1 %	21.3 %	21.3 %	4.5 %	
RCMD ($n=321$)	40.5 %	31.2 %	9.0 %	6.9 %	9.0 %	3.4 %	
RSCMD ($n=139$)	31.7 %	36.7 %	10.8 %	11.5 %	5.8 %	3.6 %	
5q− ($n=35$)	48.6 %	22.9 %	0.0 %	14.3 %	11.4 %	2.9 %	
RAEB I ($n=216$)	43.5 %	31.5 %	9.3 %	6.0 %	5.6 %	4.2 %	
RAEB II ($n=310$)	55.5 %	22.6 %	11.0 %	6.1 %	2.3 %	2.6 %	
CMML I ($n=151$)	33.8 %	34.4 %	14.6 %	11.3 %	4.6 %	1.3 %	
CMML II ($n=55$)	54.5 %	20.0 %	16.4 %	7.3 %	1.8 %	0.0 %	
RAEB-T ($n=254$)	77.6 %	13.0 %	6.7 %	2.0 %	0.8 %	0.0 %	
Unclassifiable ($n=5$)	60.0 %	40.0 %	0.0 %	0.0 %	0.0 %	0.0 %	
RARS-T ($n=22$)	22.7 %	45.5 %	4.5 %	22.7 %	4.5 %	0.0 %	

Nachtkamp K (2016) Ann Hematol

Prognostic Scoring Systems - IPSS

Variable	Score				
	0	**0.5**	**1**	**1.5**	**2**
Blasts in BM(%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Risk	Total Score	AML	Survival
Low	0	9.4	5.7
Int-1	0.5-1.0	3.3	3.5
Int-2	1.5-2.0	1.1	1.2
High	≥ 2.5	0.2	0.4

Greenberg P (1997) Blood; 89: 2079-2088

The IPSS is relatively insensitive to prognosis in low-risk MDS

What other factors influence prognosis?

- Transfusion requirements [1]
- Severity of thrombocytopenia [2]
- Severity of neutropenia [2]
- Molecular phenotype e.g. *TP53, EZH2, ETV6, RUNX1, ASXL1, SF3B1* [3,4]
- Therapy-resistance [5]

1. Malcovati JCO 2007; 25: 3503-3510
2. Greenberg P (2012) Blood; 120: 2454-2465
3. Bejar R (2015) Blood; 126-907
4. Bejar R (2017) JNCCN; 15: 131-135
5. Kelaidi (2013) Leukemia; 271: 1283-90

Prognostic Scoring Systems – IPSS-R

Variable	Score						
	0	0.5	1	1.5	2	3	4
Cytogenetics	V. Good		Good		Intermediate	Poor	V.Poor
BM Blast%	≤ 2		> 2 - < 5		5-10	> 10	
Haemoglobin	≥ 10		8 - <10	<8			
Platelets	≥100	50-<100	<50				
Neutrophils	≥ 0.8	<0.8					

Group	Total Score	OS (yrs)	AML (yrs)
Very Low	≤ 1.5	5.4	NR
Low	> 1.5 -3	4.8	9.4
Intermediate	> 3- 4.5	2.7	2.5
High	> 4.5 – 6	1.5	1.7
Very High	> 6	0.7	0.7

Prognostic Group	Cytogenetic Abnormalities
Very Good	-Y, del(11q)
Good	Normal, del (5q), del (12p), el(20q), double inc del(5q)
Intermediate	Del(7q), +8, +10, iso(17q), any other single or double
Poor	-7, inv(3)/t(3q)/del(3q),double inc -7/del(7q), complex: 3 abnormalites
Very Poor	Complex: >3 abnormalities

Greenberg P (2012) Blood; 120: 2454-2465

Prognostic Scoring Systems – WPSS

Variable	Score			
	0	1	2	3
WHO Category	RA,RARS, 5q-	RCMD, RCMD-RS	RAEB-I	RAEB-II
Karyotype	Good	Intermediate	Poor	
Transfusion Req	No	Regular		

	OS (months)	AML
Very Low (0)	141	3%
Low (1)	66	6%
Intermediate (2)	48	21%
High (3-4)	26	38%
Very High (5-6)	9	80%

≥ 1 RBC transfusion every 8 weeks over period of 4 months

Good: normal, -Y, del(5q), del(20q)
Intermediate: other
Poor: Complex (≥ 3 abnormalities), chromosome 7 abnorm

Malcovati JCO 2007; 25: 3503-3510

Low-Risk Scoring System (LRSS) – MDACC

Variable	Score
Unfavourable Cytogenetics*	1
Age ≥ 60	1
Hb < 100	1
Plat < 50	2
Plat 50-200	1
BM Blasts ≥ 4%	1

*All except diploid and 5q considered unfavourable

Score	Median OS (mths)	4 YRS OS (%)	Group
0	NR	78	1
1	83	82	
2	51	51	
3	36	40	2
4	22	27	
5	14	9	3
6	16	7	
7	9	NA	

Garcia-Manero (2008) Leukemia; 22: 538-543

Are the newer scores better at finding a “high-risk” group?

- 27% of Low, Int-1 IPSS reclassified as intermediate or higher R-IPSS [1]

- Spanish retrospective [2]
  - Compared IPSS with IPSS-R, LRSS, WPSS

  - 1290 patients with low-risk MDS
    - No score able to pick out high risk group (OS < 30 months)
  - 1083 patients with Int-1 risk
    - WPSS-R 30% - higher risk
    - IPSS-R 30% – higher risk
    - LRSS 47% - higher risk

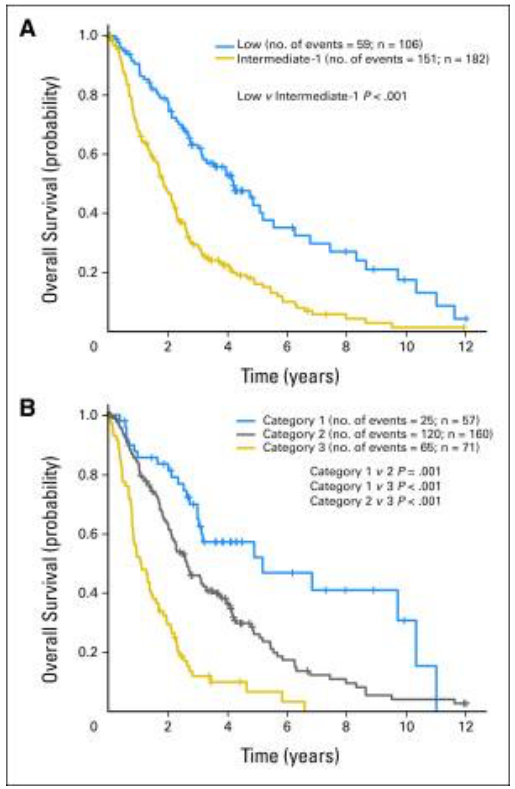
1. Greenberg P (2012) Blood; 120: 2454-2465 2. Valcarcel D (2015) Lancet Haematol; 2: e260-66

Molecular Milieu

- Signaling molecules (*NRAS, KRAS, CBL, JAK2, FLT3*)
- Epigenetic Regulators (*TET2, ASXL1, EZH2, UTX, IDH1, IDH2, DNMT3A, SETBP1*)
- Splicing (*SF3B1, SRSF2, ZRSF2, U2AF1*)
- Transcription regulators (*RUNX1,NPM1, TP53*)
- Hypermethylation

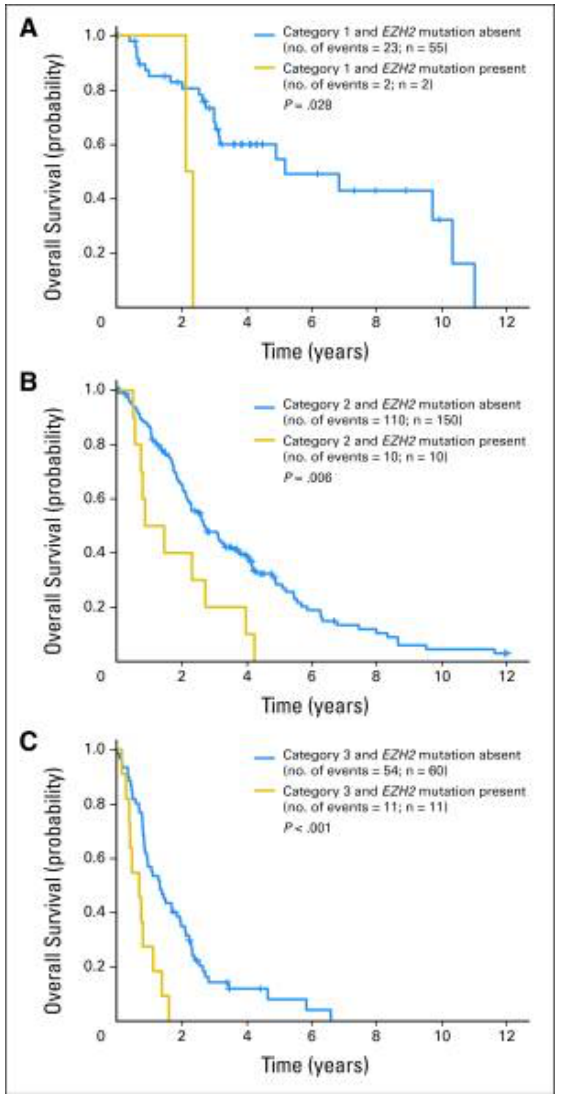
Bejar R (2011) NEJM 364: 2496-2506
Paquette R (1993) Blood; 82: 590-599
Delhommeau F (2009) NEJM; 360: 2289-2301
Kosmider O (2009) Blood; 114: 3285-3291
Gelsi-Boyer V (2009) BJH; 145: 788-800
Kosmider O (2010) Leukemia; 24: 1094-1096
Thol F (2010) Haematologica; 95: 1668-1674
Damm F (2013) Leukemia; 27: 1401-1403
Yoshida K (2011) Nature; 478: 64-69
Papaemmanuil E (NEJM) 2011; 365: 1384-1395
Malcovati L (2011) Blood; 118: 6239-6246
Patnaik M (2012); Blood: 569-572
Christiansen D (2004) Blood; 104: 1474-1481
Harada H (2004) Blood; 103: 2316-2324
Kaneko H (1995) Blood; 85: 2189-2193

Mutation-assisted Prognostic scores



TET2
SF3B1
ASXL1
U2AF1
SRSF2
DNMT3A
RUNX1
EZH2
JAK2
NRAS
TP53
ETV6
CBL
NPM1
IDH1

TET2
SF3B1
ASXL1
U2AF1
SRSF2
DNMT3A
RUNX1
EZH2
JAK2
NRAS
TP53
ETV6
CBL
NPM1
IDH1



Bejar (2012) JCO 30: 3376-3382

Other Prognostic Factors

- Immune system alterations [1,2]
- Activation of Inflammation [3]
- Marrow Fibrosis [4]
- Flow Cytometry [5]

1. Ganan-Gomez I (2015) Leukemia 29:1458-1469 2. Kordasti S (2009) BJH 145: 64 3. Kittang A (2015) OncoImmunology 5:e1062208
4. Della Porta M (2009) JCO; 27: 754-762 5. van de Loosdrecht A (2008) Blood 111: 1067-1077

Anaemia

- 89% of patients – Italian Registry (FISMonlus) [1]

- Major determinant of symptoms OF MDS [2,3,4]
  - Cardiac dysfunction
  - Cognitive dysfunction
  - Increased falls risk
  - Decline in functional status

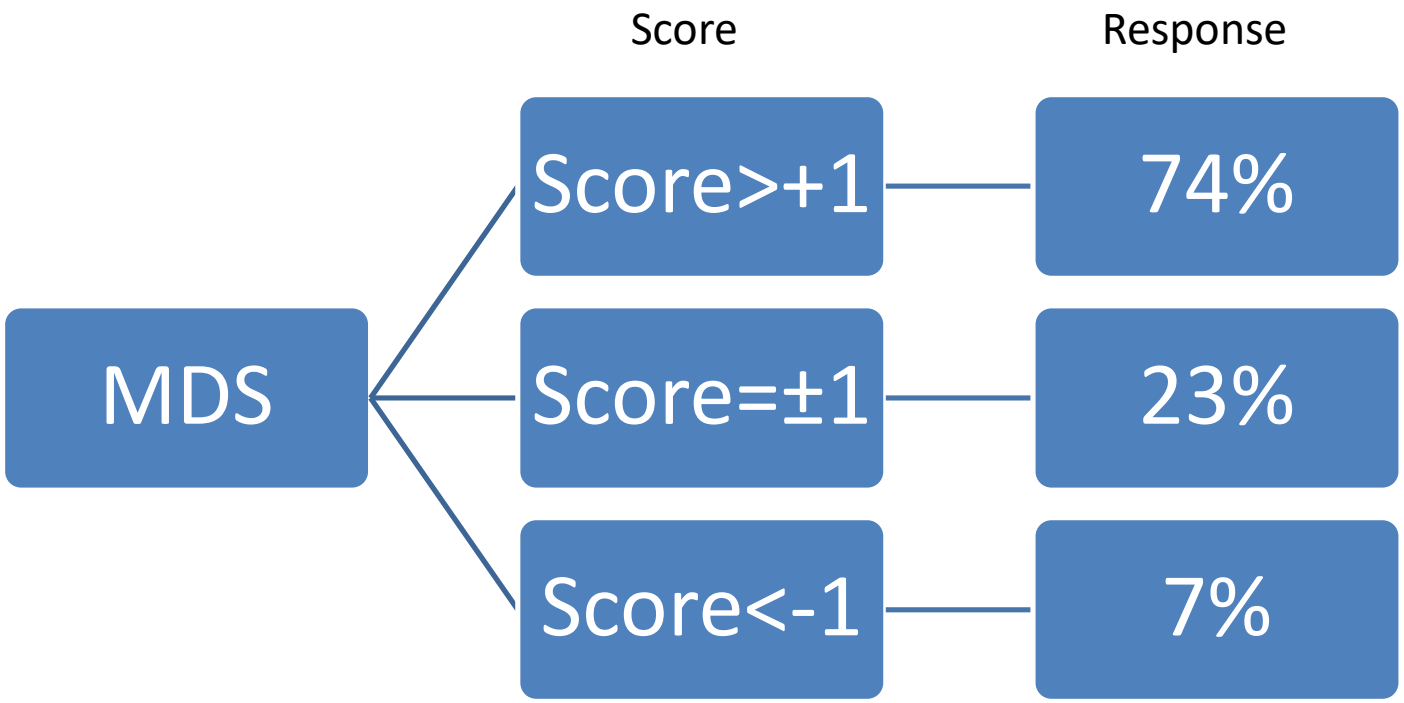
1. www.fismonlus.it 2. Santini V (2015) Semin Hematol; 52: 348-356 3. Kelaidi C (2013) Ann Hematol; 92: 621-631
4. Nilsson-Ehle H (2011) Eur J Haenatol; 87: 244-252

Erythroid Stimulating Agents

- Consensus that represents Standard of Care for first-line therapy of low-risk MDS

- Availability variable based on registration / reimbursement in health jurisdictions

Nordic MDS Study Group



CR Hb> 115

PR Increase in Hb of >15g/L or elimination of transfusion

Epo	<100	+2
	100-500	+1
	>500	-3
RBC need	<2 units / mth	+2
	≥ 2 units / mth	-2

Hellstrom-Lindberg (1997) BJH, 99: 344-351

R-IPSS may predict for response

VARIABLES

1. EPO > 200 — 1
2. Ferritin > 350ng/mL — 1
3. IPSS-R
   - Very Low — 0
   - Low — 1
   - Intermediate — 2
   - High — 3

Score	Probablity of Response
0	85%
1	80%
2	64%
3	40%
4	20%

Santini (2013 Blood: 122: 2286-2288

EPOANE3021 Study

- IPSS Low- or intermediate-1 risk
- Hb < 100, Epo < 500
- No or moderate RBC dependence (<=4U every 8 wks)

- Double-blind, placebo-controlled
- 2:1 randomization to active arm
- 24 weeks of treatment, with extension in responders
- Independent review of IWG-2006 criteria

- Primary endpoint: erythroid response by Week 24

Fenaux, P (2018) Leukemia; 32: 2648-2658

EPOANE3021 Study

- EPO commenced at 450 IU / kg / week, titrated up to 40,000 IU
- Weekly Hb measurements

- At week 8, increased to 1050IU/kg/week (max 80000)

Fenaux, P (2018) Leukemia; 32: 2648-2658

Results from EPOANE Study

ER	miTT analysis		PP analysis	
	Placebo *n* = 45	Epoetin-α *n* = 85	Placebo *n* = 21	Epoetin-α *n* = 32
ER during first 24 wks	2 (4.4%)	27 (31.8%)	0	11 (34.4%)

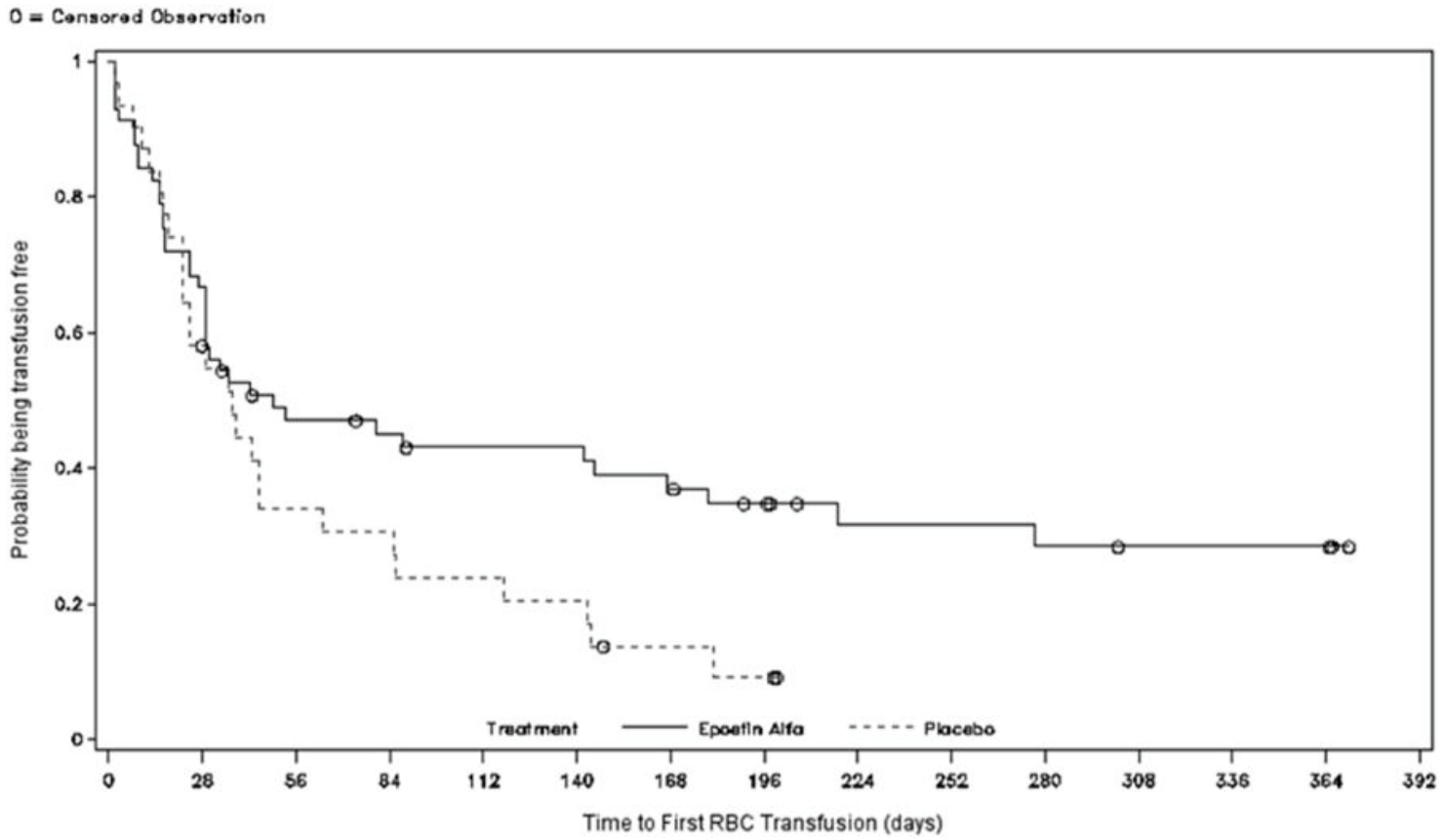
Patients with erythroid response by IPSS risk category				
Low = 0[e]	2 (8.7%)	16 (45.7%)	0	7 (58.3%)
Intermediate-1 = 0.5–1.0[e]	0	10 (20.4%)	0	4 (20.0%)
P value[d]		<0.001		0.001

ER according to Nordic Score Classification	**High**	**Intermediate**	**Low**
Responders	21 (44.7%)	6 (16.7%)	
Nonresponders	26 (55.3%)	30 (83.3%)	1 (100%)

ER according to RA/RCMD and RARS/RCMD-RS MDS subtypes		
MDS Subtypes	***RA/RCMD***	***RARS/RCMD-RS***
Responders	13 (30.2%)	8 (38.1%)
Nonresponders	30 (69.8%)	13 (61.9%)

Fenaux, P (2018) Leukemia; 32: 2648-2658

EPOANE Study – Time to First RBC Transfusion



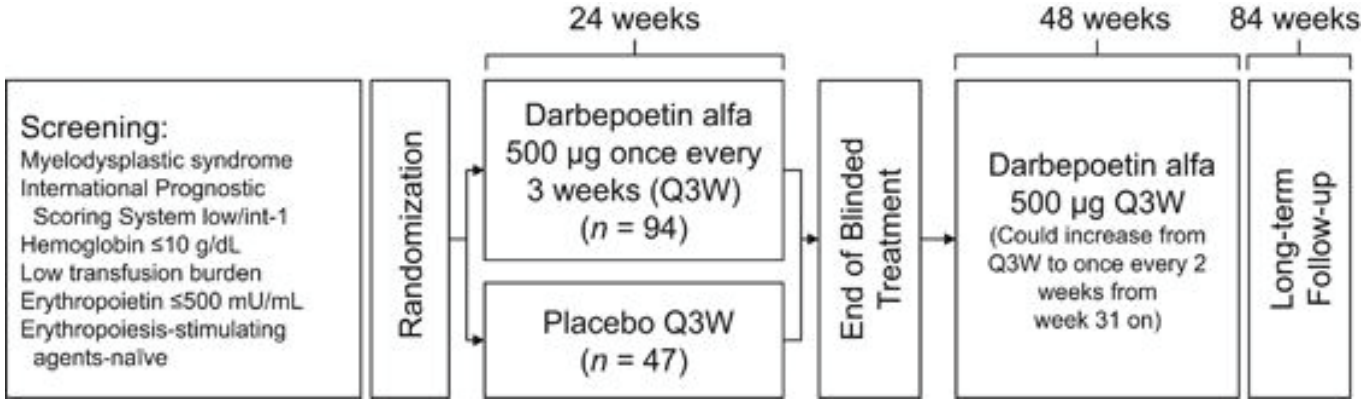
Fenaux, P (2018) Leukemia; 32: 2648-2658

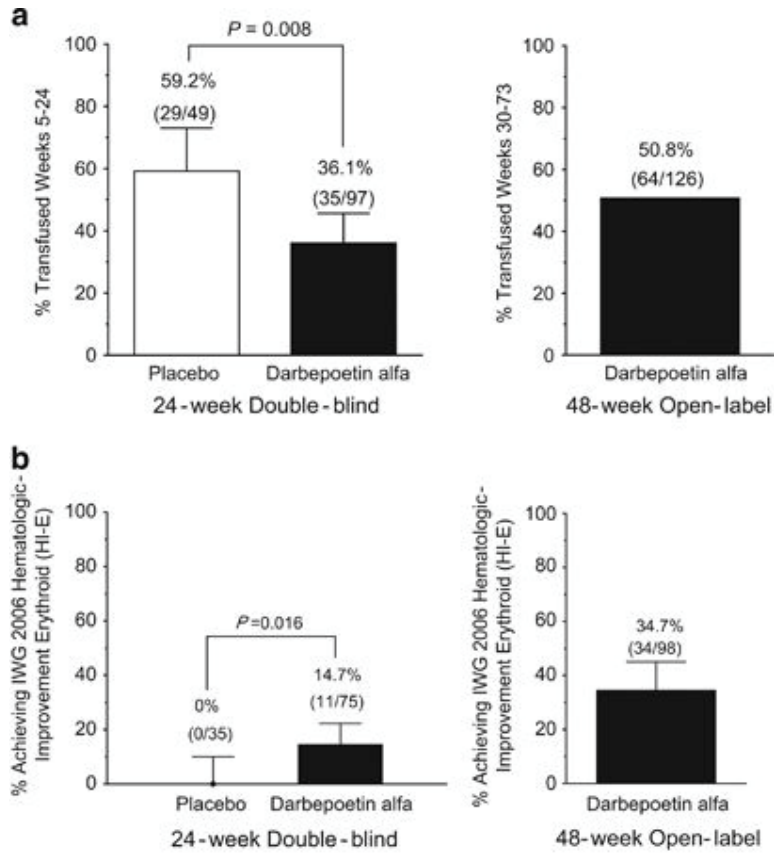
EPOANE Prediction

Transfusion Requirements / 8 wks	EPO Level	Likelihood of response
0	<200	67%
0-4	<200	25%
0-4	>200	0%

Fenaux, P (2018) Leukemia; 32: 2648-2658

ARCADE Study





147 patients randomized
- 49 Placebo
- 98 Darbo (97 received)

No safety issues identified

Platzbecker, U (2017) Leukemia 31:1944-1950

ESA Dosing

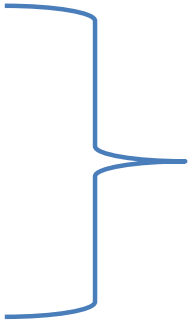
- Check Epo level
  - If Epo < 500, start ESA
- Commencing dose:
  - 30,000 – 80,000 IU Erythropoietin
  - 150-300 mcg Darbopoietin
- Ideally start before transfusion dependence
- Response typically by 12/52 – do not cease if no response prior
- Target Hb ?100-120 g/dL

My Opinion

Iron Overload

- Once transferrin sats > 80%, non transferrin bound iron appears in PB

- Reactive oxygen species →
  - Haematopoietic insufficiency
  - Increase DNA mutation rate
  - Anti-apoptosis



Damage to HSC's

1. Pullarkat V (2012) Leuk Res; 36: 966-973 2. Hartmann J (2013) Leuk Res; 37: 327-332 3. Taoka K (2012) Int J Hematol; 95: 149-159

Iron Chelation Therapy

- Recommend if ferritin 1000-2500
  - ELN [1] and NCCN Guidelines [2]

- 4 prospective Phase 2 studies of deferasirox
  - EPIC
  - US Multicentre
  - ICL670
  - GIMEMA MDS0306 Trial

- Randomised & Long-term follow-up data: TELESTO

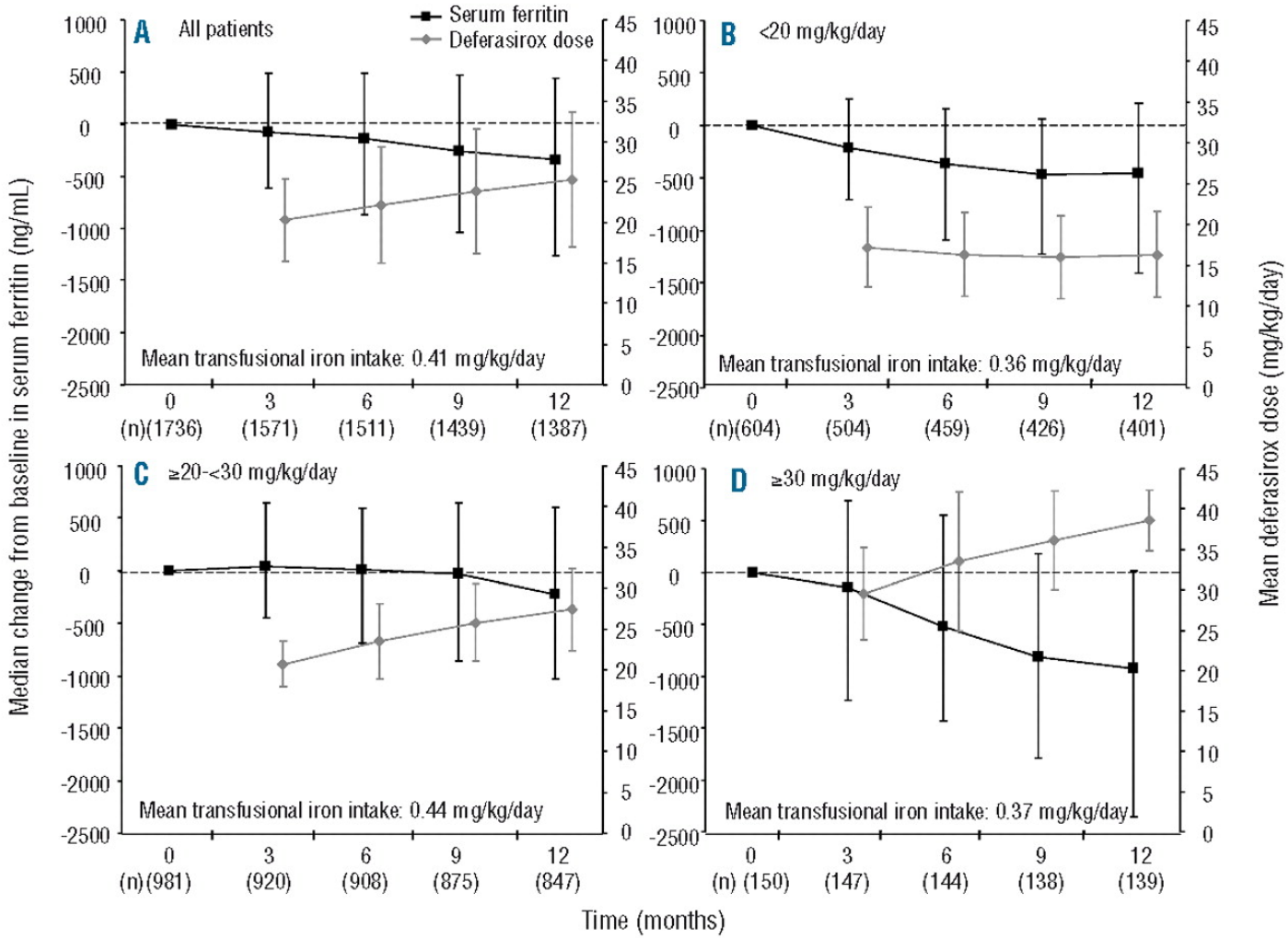
1. HTTPS://WWW.NCCN.ORG (MDS, 2016) 2. Malcovati L (2013) Blood; 22: 2943-2964

Iron Chelation Trials

	n		
EPIC [1,2]	341	Ferritin > 1000, or < with 20U RBCS, RD MRI confirmed LIC>2	Decrease in baseline by median of 264, at mean dose of 22.2 mg/kg
US Multicenter [3]	176	Ferritin > 1000 AND 20U RBC's, ongoing transfusions	53% completed 12 months -> 23% decrease in ferritin 28% completed 24 months -> 36.7% decrease in ferritin 38% discontinued due to adverse events
ICL670 [4]	47	>= 8 transfusions per year, LIC .= 2mg Fe/dry weight Starting dose based on LIC	78.6% reduction in LIC Changes in ferritin correlated with LIC
GIMEMA MDS0306 [5]	159	>= 1 unit in <= 8wks averaged over months; minimum 20U; ferritin >=1000	Median ferritin 1966-> 1476ng/ML; improvement in LFT's

1. Cappellini,M (2010) Haematologica 95: 557-566
2. Gatterman N 2012 Haematologica 97: 1364-1371
3. List A 2012 JCO 30: 2134-2139
4. Porter J 2008 Eur J Haem, 80: 168-176
5. Angelucci E 2014 Eur J Haem 92: 527-536

Mean actual deferasirox dose±SD (mg/kg/day) and median change in serum ferritin±25th and 75th percentiles (ng/mL) during the study by average actual dose categories in the full analysis set of patients.



Maria Domenica Cappellini et al. Haematologica 2010;95:557-566

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Safety and Efficacy, Including Event-free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients with Low- and Int-1-Risk Myelodysplastic Syndromes (MDS): Outcomes from the Randomized, Double-Blind TELESTO Study

Emanuele Angelucci,[1] Junmin Li,[2] Peter Greenberg,[3] Depei Wu,[4] Ming Hou,[5] Efreen Horacio Montaño Figueroa,[6] Maria Guadalupe Rodriguez,[7] Xunwei Dong,[8] Jagannath Ghosh,[8] Miguel Izquierdo,[9] and Guillermo Garcia-Manero[10]

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TELESTO study design

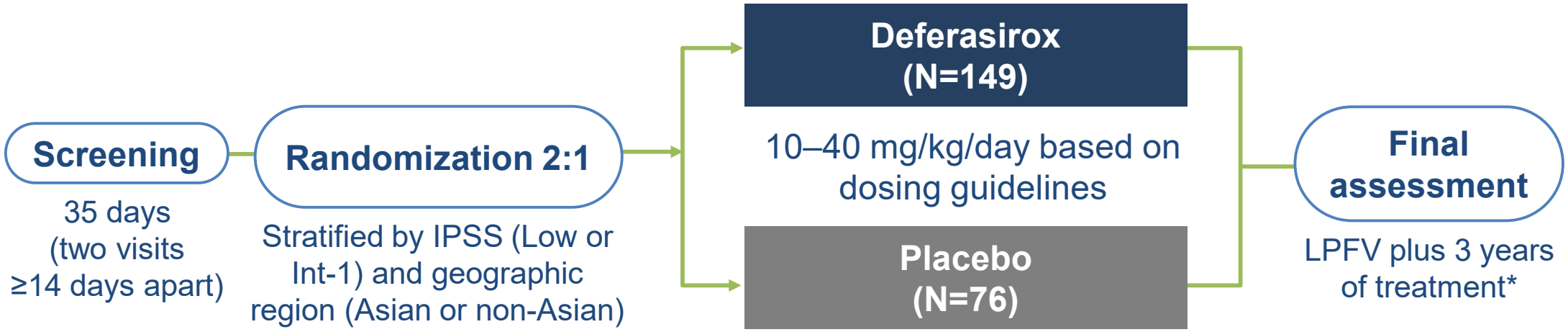
Designed as a **Phase III trial** with a target enrolment of **630** patients

Because of low enrolment, the target sample size was reduced, based on the feasibility of enrolling patients and consultations with the health authorities

Changed a to **Phase II trial** with target enrolment of **210** patients

Trial was therefore not designed to make statistical comparisons

TELESTO – a Phase II, randomized, double-blind study



*Patients who experienced a non-fatal event were discontinued and followed up for 28 days; patients were then followed up every 3–6 months (for evaluation or survival)

Key inclusion criteria:

- Hematologically stable IPSS Low or Int-1-risk MDS, confirmed by bone marrow within 6 months prior to study entry
- Serum ferritin >1000 ng/mL
- History of transfusion of 15–75 pRBC units
- No history of hospitalization due to congestive heart failure and LVEF ≥50% by echocardiography
- ALT or AST ≤3.5×ULN, total bilirubin ≤1.5×ULN, no previous diagnosis of liver cirrhosis; CrCl ≥40 mL/min
- ECOG performance status ≤2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; LPFV, last patient first visit; LVEF, left ventricular ejection fraction; pRBC, packed red blood cell; ULN, upper limit of normal

TELESTO – study objectives

Primary

To evaluate event-free survival (composite endpoint)

- Defined as the time from randomization to first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an **independent adjudication committee**, or death, whichever occurred first

Key secondary

To assess:

- Overall survival
- Change in serum ferritin level
- Hematologic improvement in terms of erythroid response (based on International MDS Working Group criteria[1])
- Change in endocrine function (thyroid and glycemic control)
- Safety

1. Cheson BD *et al. Blood* 2006;108:419–425

Non-fatal components of the composite primary endpoint adjudicated by the EAC

Component	Criteria
1. Echocardiographic evidence of worsening cardiac function	• At least 15% absolute decrease in LVEF from screening value at two consecutive assessments at least 2 weeks apart OR • LVEF below institutional limits of normal and at least 10% absolute decrease from LVEF screening value at two consecutive assessments at least 2 weeks apart
2. Hospitalization for congestive heart failure (CHF)	• Overnight stay (ie change in calendar day) due to CHF confirmed by the presence of the following: – At least one of the following symptoms: paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion AND – Two or more of the following signs consistent with heart failure: pulmonary edema by radiography, rales, enlarged heart by radiography, peripheral edema, S3 gallop, hepatojugular reflux, neck vein distention, rapid weight gain, elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP AND – Treatment with intravenous diuretics, intravenous vasodilators, or intravenous inotropes, mechanical fluid removal (eg ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump for hemodynamic compromise. Initiation of oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify
3. Liver function impairment	• ALT or AST >2 times the baseline value and >3 times the ULN at two consecutive visits AND • Total bilirubin >2 mg/dL at two consecutive visits
4. Liver cirrhosis	• Presence of at least one of the following symptoms/signs: cirrhosis-related ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding due to portal hypertension OR • Abdominal ultrasonography OR • Liver biopsy (if clinically indicated)
5. AML transformation	• Confirmed by bone marrow biopsy

EAC, Endpoint Adjudication Committee

Key demographic and baseline characteristics

Demographic variable	Deferasirox (N=149)	Placebo (N=76)	All patients (N=225)
Age, years			
Mean (SD)	61.2 (16.1)	60.7 (15.1)	61.0 (15.7)
Median (range)	66 (21–88)	65 (20–80)	65 (20–88)
Age category (years), n (%)			
<50	37 (24.8)	20 (26.3)	57 (25.3)
50–<65	34 (22.8)	17 (22.4)	51 (22.7)
65–<75	40 (26.8)	26 (34.2)	66 (29.3)
≥75	38 (25.5)	13 (17.1)	51 (22.7)
Male, n (%)	93 (62.4)	44 (57.9)	137 (60.9)
Race, n (%)			
Caucasian	68 (45.6)	36 (47.4)	104 (46.2)
Asian	66 (44.3)	34 (44.7)	100 (44.4)
Other	15 (10.1)	6 (7.9)	21 (9.3)
MDS risk category (IPSS), n (%)			
Low	41 (27.5)	21 (27.6)	62 (27.6)
Int-1	108 (72.5)	55 (72.4)	163 (72.4)
Prior chelation therapy, n (%)			
Yes	35 (23.5)	14 (18.4)	49 (21.8)
	114 (76.5)		

SD, standard deviation

Exposure to study drug

Variable	Deferasirox (N=148)	Placebo (N=76)	All patients (N=224)
Time on treatment, days			
Mean (SD)	718.2 (598.4)	488.1 (362.8)	640.1 (540.6)
Median (range)	587.5 (1–2599)	370.5 (12–1708)	484.0 (1–2599)
Exposure category (days), n (%)			
<1 year (379 days)	58 (39.2)	39 (51.3)	97 (43.3)
1–<2 years (743 days)	25 (16.9)	18 (23.7)	43 (19.2)
2–<3 years (1107 days)	25 (16.9)	12 (15.8)	37 (16.5)
3–<4 years (1471 days)	24 (16.2)	6 (7.9)	30 (13.4)
4–<5 years (1835 days)	8 (5.4)	1 (1.3)	9 (4.0)
≥5 years	8 (5.4)	0	8 (3.6)

Exposure excluding interruption (days) = date of last dose – date of first dose – days with 0 dose + 1

Median time on treatment was **217** days longer with deferasirox (587.5 days) than with placebo (370.5 days)

Mean dose was lower with deferasirox (**14.9** mg/kg/day) than with placebo (**23.5** mg/kg/day), reflecting dose adjustments for SF level changes

SF, serum ferritin

Primary endpoint EFS: Stratified log-rank test and Cox regression model

All patients*	Log-rank test			Cox model
	Event/N (%)	Median time to event (95% CI), days†	*P* value‡	HR (95% CI)§
Deferasirox	62/149 (41.6)	1440 (1167, 1559)	0.015	0.636 (0.42, 0.96)
Placebo	37/76 (48.7)	1091 (820, 1348)		

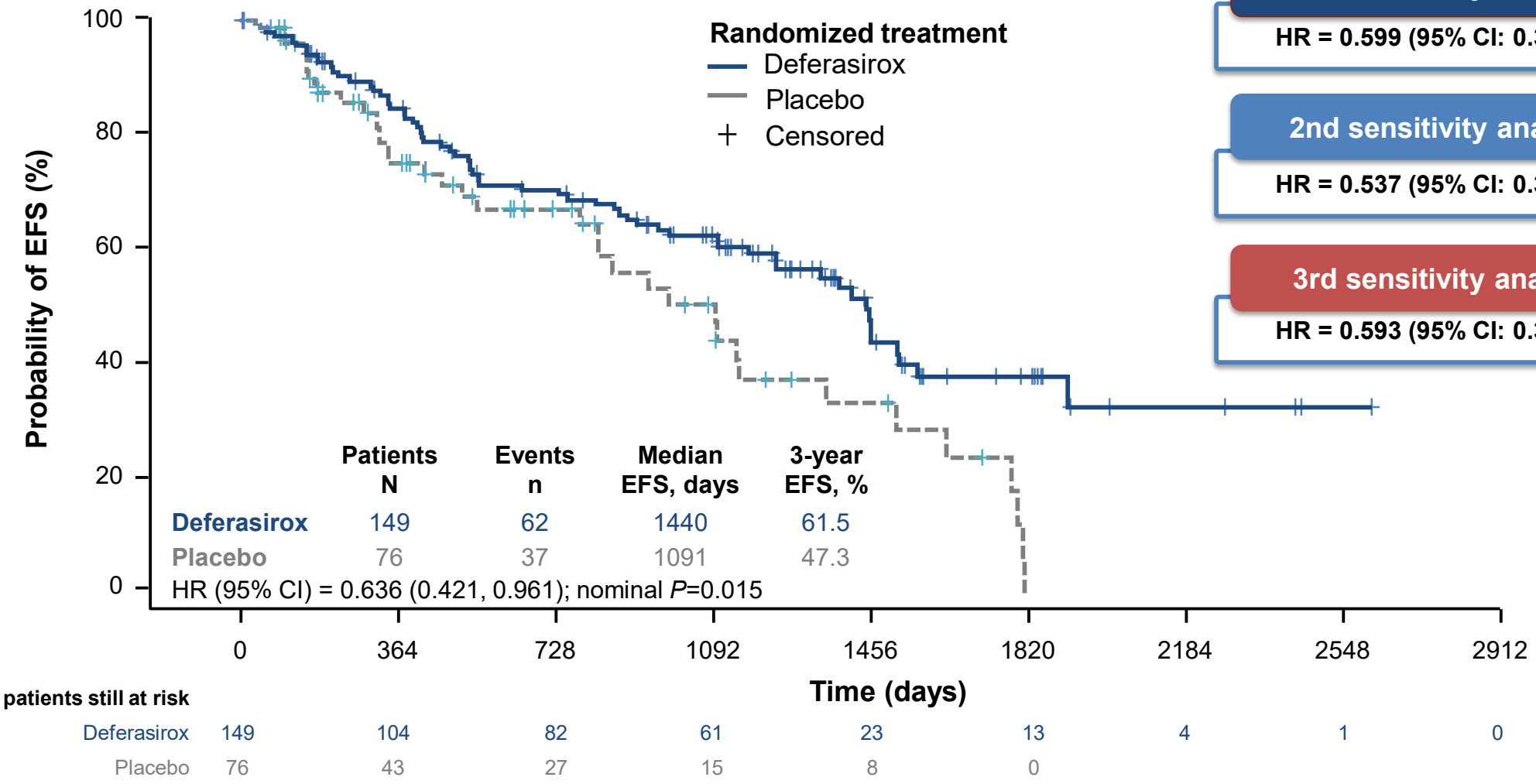
*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)

CI, confidence interval; HR, hazard ratio

Kaplan–Meier plot of EFS

Stratification: All patients



1st sensitivity analysis

HR = 0.599 (95% CI: 0.38, 0.95)

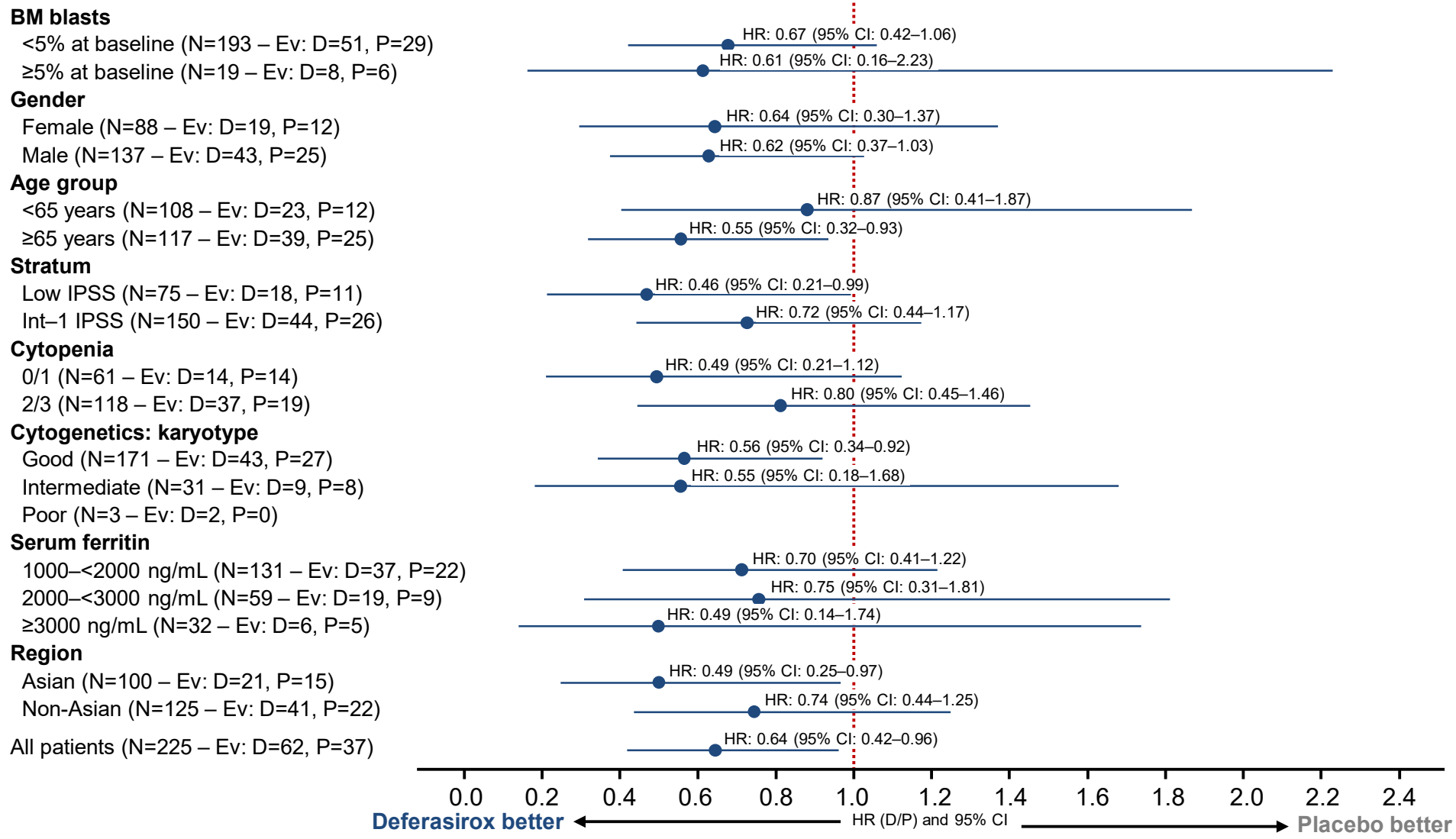
2nd sensitivity analysis

HR = 0.537 (95% CI: 0.30, 0.97)

3rd sensitivity analysis

HR = 0.593 (95% CI: 0.39, 0.91)

Forest plot for EFS

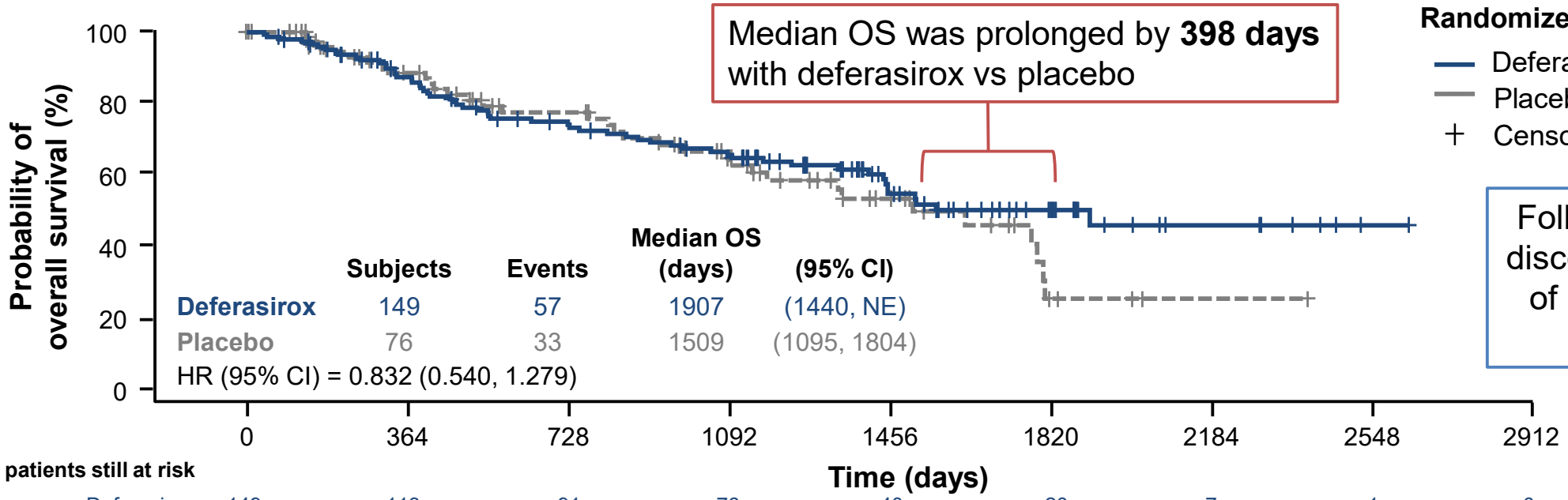


BM, bone marrow; D, deferasirox; Ev, event; Int-1, Intermediate-1; P, placebo

Summary of overall survival

All patients*	Log-rank test		Cox model	
	Event/N (%)	Median time (95% CI), days†	*P* value‡	Hazard ratio (95% CI)§
Deferasirox	57/149 (38.3)	1907 (1440, NE)	0.200	0.832 (0.54, 1.28)
Placebo	33/76 (43.4)	1509 (1095, 1804)		

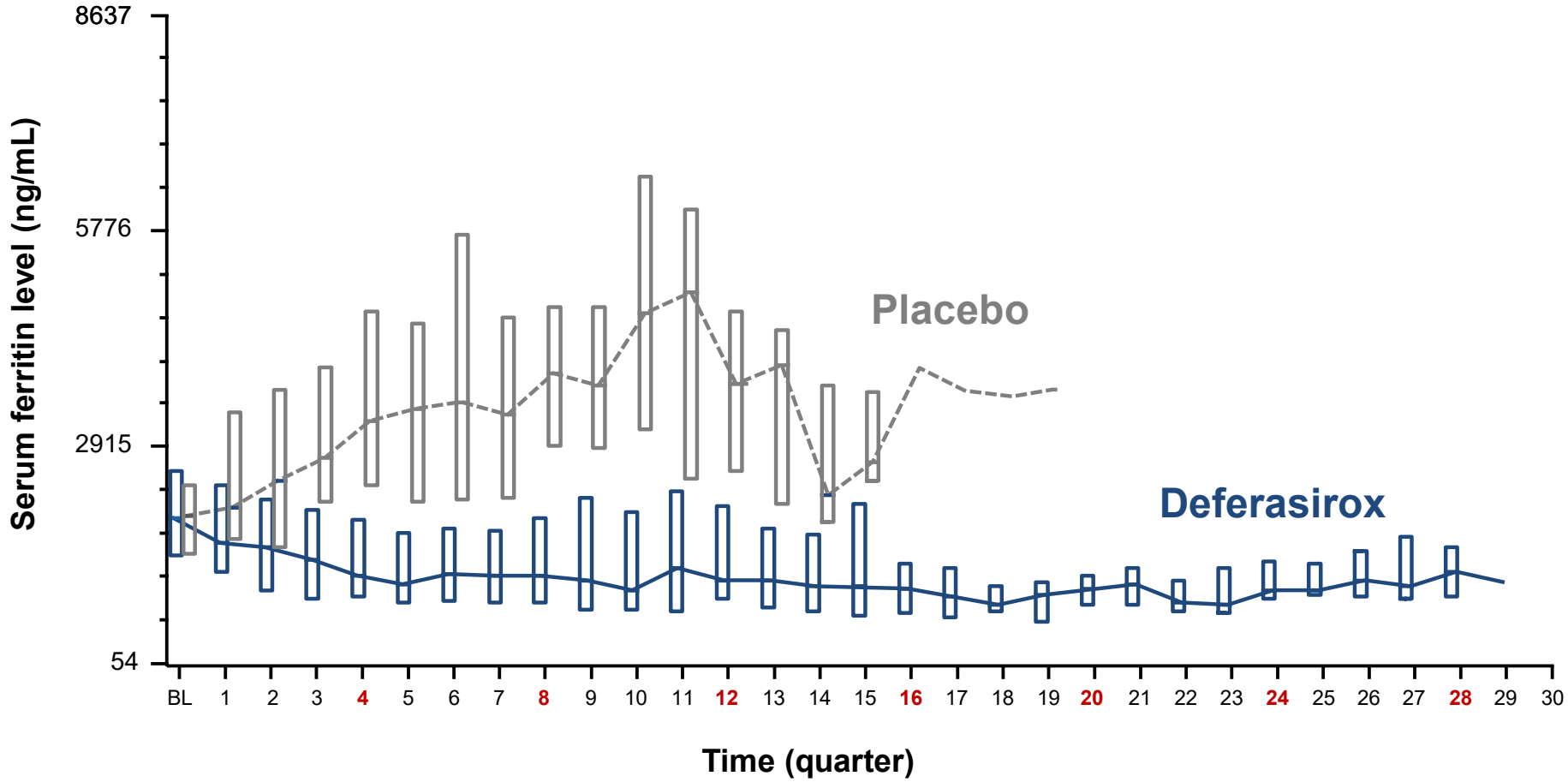
*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model



Following study drug discontinuation 52.1% of placebo patients started ICT

NE, not evaluable

Serum ferritin trends



Deferasirox	146	141	123	108	94	89	83	76	70	63	60	55	49	39	29	26	22	16	12	10	8	8	4	4	4	4	3	3	2	1
Placebo	76	76	69	56	49	37	30	24	24	18	11	10	9	5	3	3	1	1	1	1										

Boxes show lower and upper quartiles, horizontal line shows the median

Exposure-adjusted AEs (>10% in either arm)

Preferred term	Deferasirox (N=148)			Placebo (N=76)		
	All AEs, n (IR per 100 STY)	Severe AEs, n (IR per 100 STY)	Serious AEs, n (IR per 100 STY)	All AEs, n (IR per 100 STY)	Severe AEs, n (IR per 100 STY)	Serious AEs, n (IR per 100 STY)
Diarrhea	53 (24.7)	4 (1.3)	5 (1.7)	20 (23.9)	2 (1.9)	4 (3.8)
Pyrexia	51 (21.8)	11 (3.8)	14 (4.9)	17 (18.7)	3 (2.9)	5 (4.9)
Increased blood creatinine	**38 (15.9)**	1 (0.3)	1 (0.3)	**1 (0.9)**	0	0
Upper RTI	**37 (16.7)**	4 (1.3)	4 (1.3)	**20 (22.7)**	2 (1.9)	2 (1.9)
Cough	32 (12.6)	1 (0.3)	2 (0.7)	11 (11.3)	0	0
Nausea	26 (10.7)	2 (0.7)	3 (1.0)	10 (10.4)	0	0
Peripheral edema	22 (8.2)	0	0	11 (10.9)	2 (1.9)	2 (1.9)
Fatigue	**21 (8.0)**	1 (0.3)	0	**13 (13.5)**	1 (0.9)	1 (0.9)
Constipation	**19 (7.0)**	2 (0.7)	3 (1.0)	**12 (12.9)**	1 (0.9)	0
Headache	**17 (6.3)**	0	0	**13 (14.6)**	2 (1.9)	0
Abdominal pain	**14 (4.9)**	1 (0.3)	1 (0.3)	**10 (10.1)**	1 (0.9)	1 (0.9)

IR = exposure-adjusted incidence rate: number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in subject treatment years (STY) is counted up to the first event (or EOT for subjects without an event)

AEs occurring more frequently in one group (with ≥5% difference relative to the other) are highlighted in bold

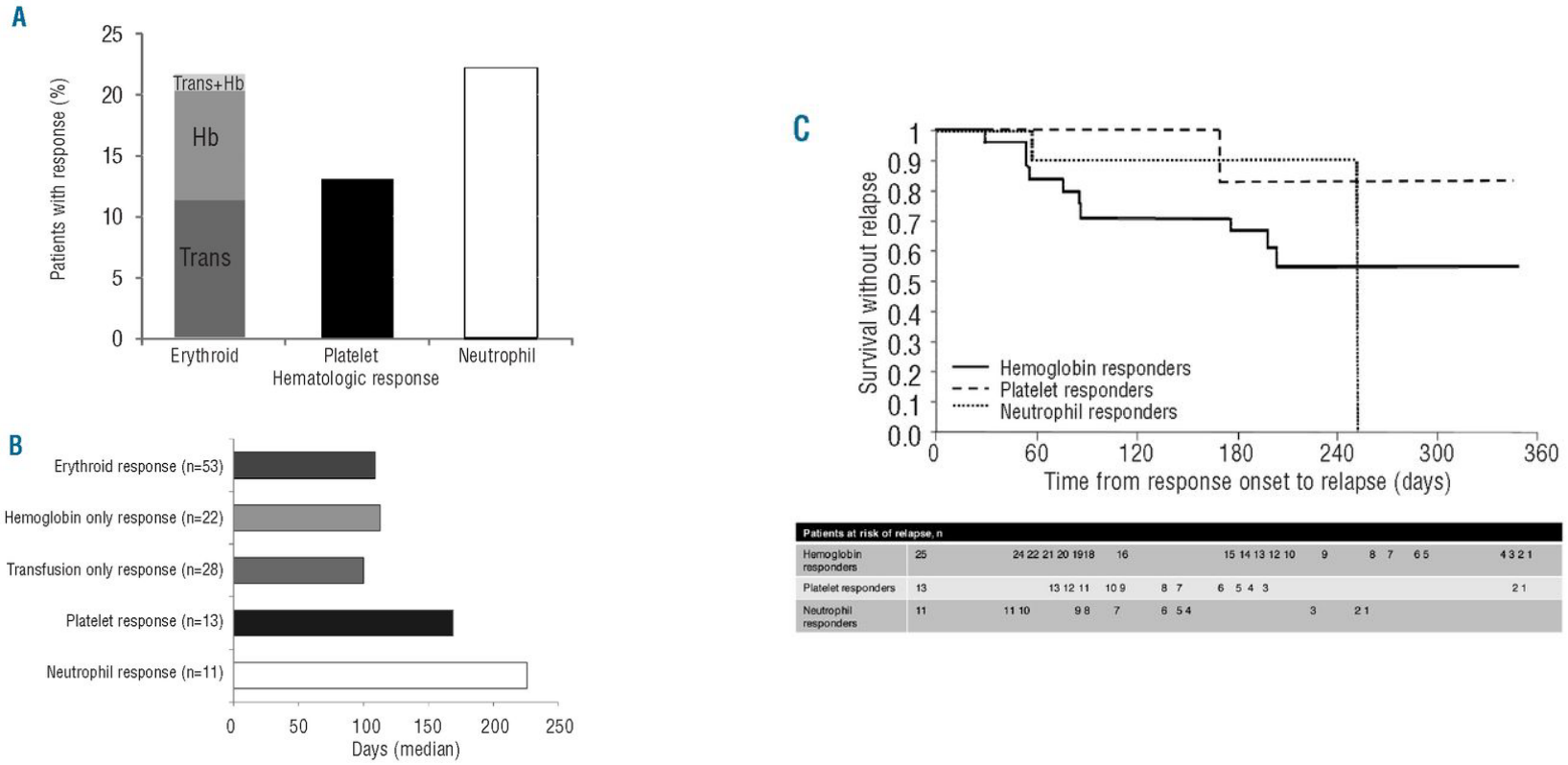
Does Deferasirox have Disease-Modifying Activity?

- US Multicentre study- 28% of patients experienced IMWG-2006 haematologic improvement [1]

- GIMEMA [2]– progressive increase in cumulative incidence of transfusion independence
  - 6 months 2.6%
  - 9 months 12.3%
  - 12 months 15.5%

1. List A 2012 JCO 30: 2134-2139 2. Angelucci E 2014 Eur J Haem 92: 527-536

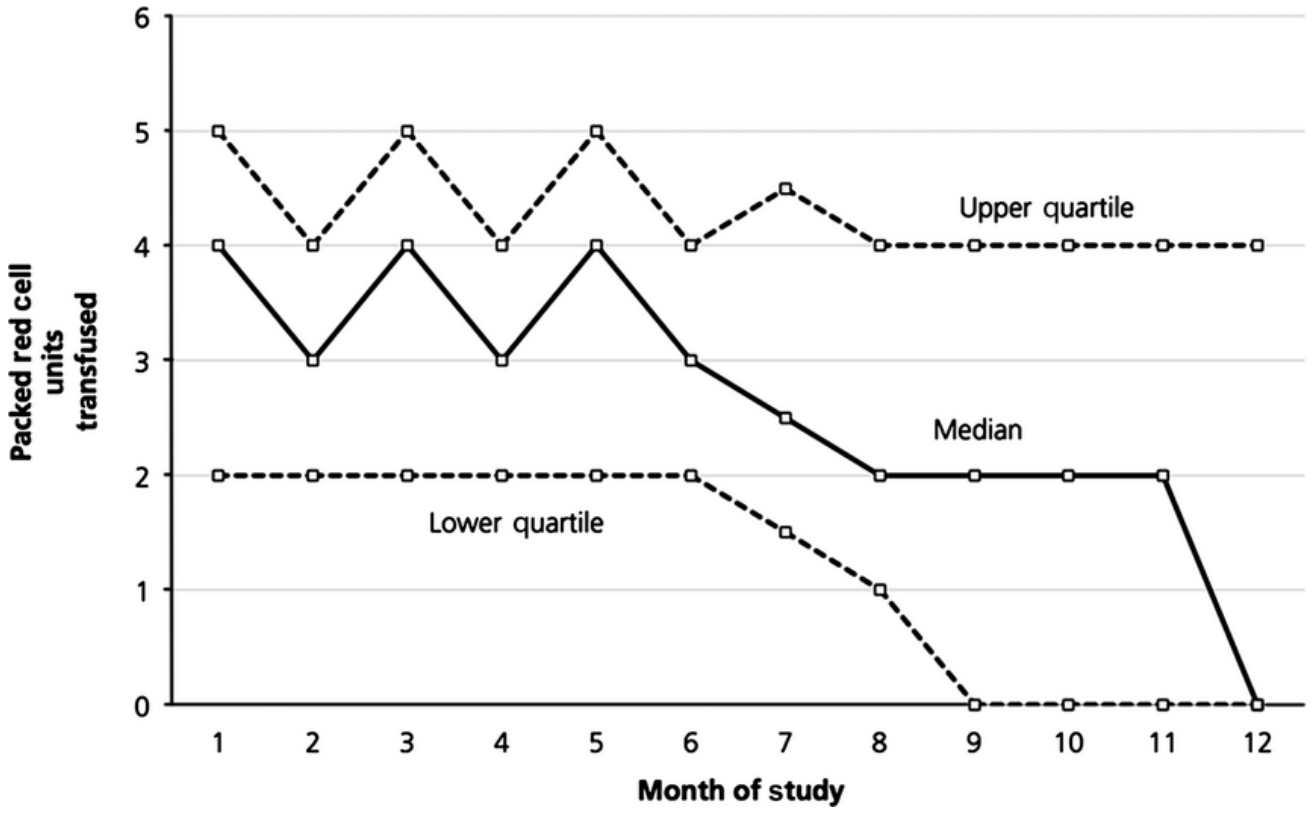
(A) Percentage of patients experiencing hematologic responses, (B) median time to hematologic responses during deferasirox treatment and (C) time from response onset to relapse in patients with hemoglobin, platelet and neutrophil hematologic responses.



Norbert Gattermann et al. Haematologica 2012;97:1364-1371

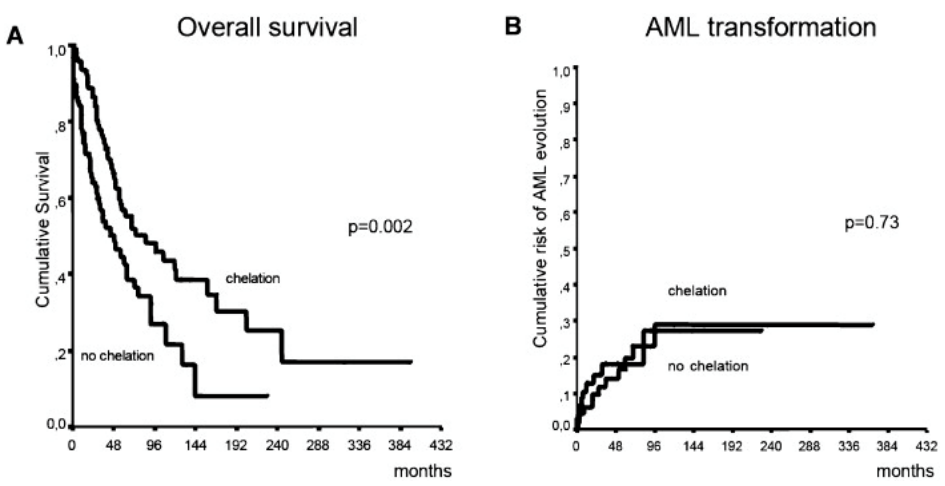
haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Deferasirox for transfusion-dependent patients with myelodysplastic syndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial)

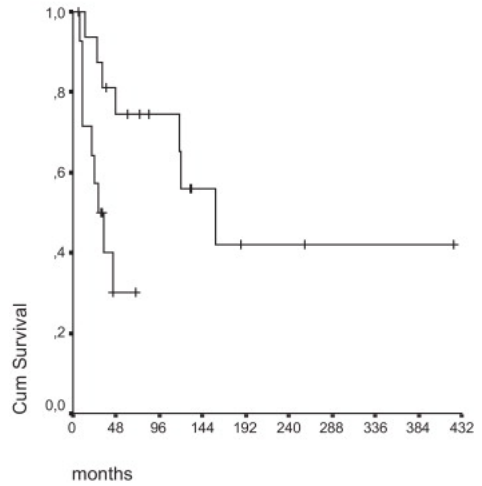


European Journal of Haematology, Volume: 92, Issue: 6, Pages: 527-536, First published: 03 March 2014, DOI: (10.1111/ejh.12300)

Dusseldorf Retrospective



Impact of iron chelation therapy on OS and AML transformation (n = 188)



Cumulative survival of patients who responded
to chelation therapy in comparison to those with increasing ferritin levels (n=31)

Neukirchen J (2012) Leukemia Research; 36: 1067-1070

Dosing of Deferasirox Formulations

- Start at low dose - 5mg/kg Exjade = 3.5mg/kg Jadenu
- Build to 20-30mg / kg Exjade = 14-21mg / kg Jadenu

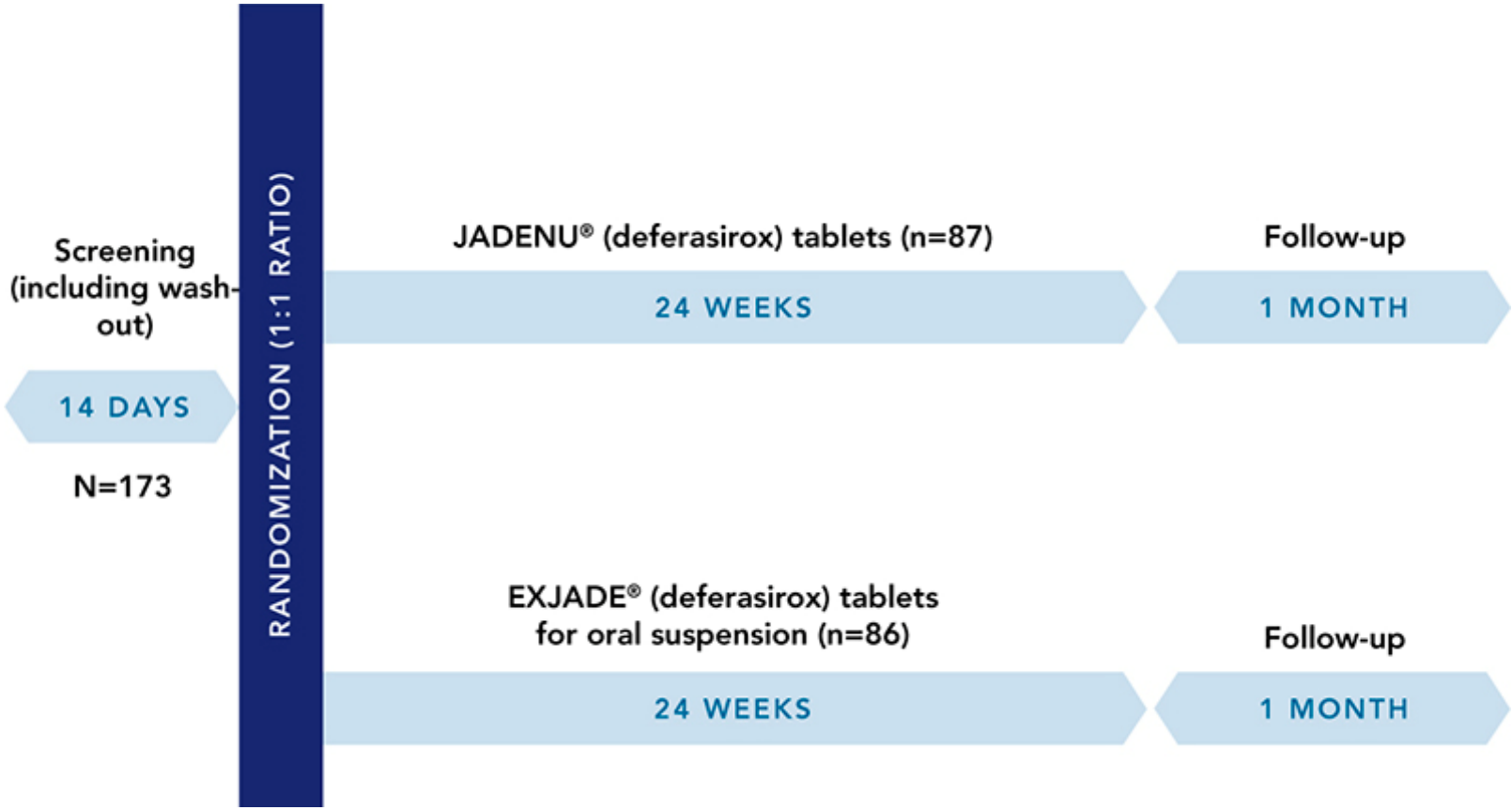
- 25% reduction in GFR
  - Occurs early, then stabilizes
  - Reversible

- GIT toxicity is mostly dose-dependent but can be troublesome

Renal and Hepatic Effects of ICT

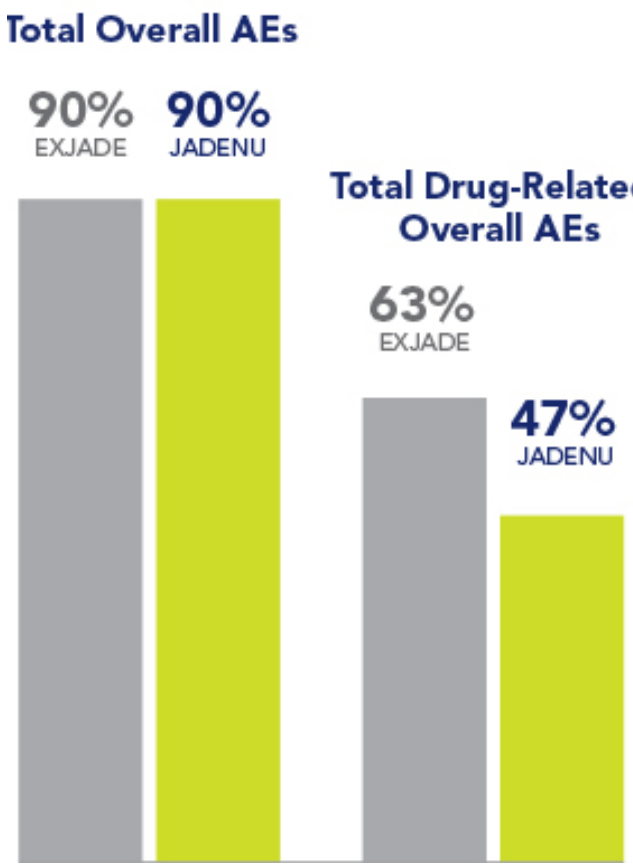
	Beta-thal		SCD		Low-Risk MDS
	Deferasirox (n=296) n (%)	**DFO (n=290) n (%)**	**Deferasirox (n=132) n (%)**	**DFO (n=63) n (%)**	**Deferasirox (n=627) n (%)**
Serum creatinine increase > 33% at 2 consecutive postbaseline visits	113 (38)	41 (14)	48 (36)	14 (22)	229 (37)
Serum creatinine increase > 33% and >ULN at 2 consecutive postbaseline visits	7 (2)	1 (0)	3 (2)	2 (3)	126 (20)
AST/ALT > 5× ULN at 2 postbaseline visits	25 (8)	7 (2)	2 (2)	0	9 (1.4)
AST/ALT >5× ULN at 2 consecutive postbaseline visits	17 (6)	5 (2)	5 (4)	0	5 (0.8)

Jadenu in Low-Risk MDS – ECLIPSE II Study



Taher, A (2017) Am J Hematol; 95: 420-428

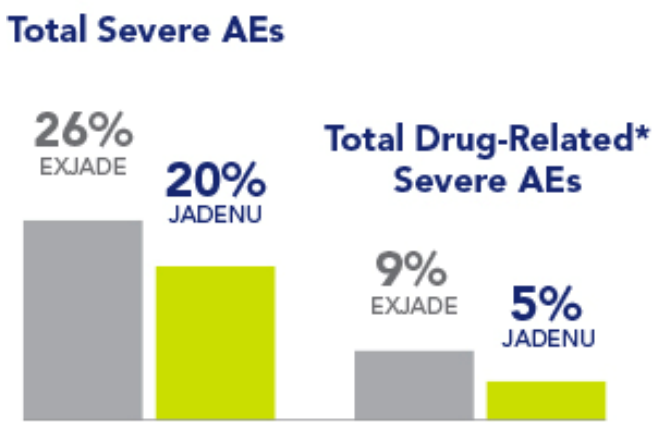
ECLIPSE II – Adverse Events



	Overall AEs		Drug-Related Overall AEs*	
	EXJADE (n=86)	JADENU (n=87)	EXJADE (n=86)	JADENU (n=87)
Diarrhea	35%	33%	20%	14%
Nausea	27%	28%	13%	9%
Abdominal pain	27%	26%	16%	8%
Urine protein/ creatinine ratio increased	13%	21%	11%	17%
Vomiting	22%	17%	15%	5%
Constipation	15%	8%	4%	1%
Headache	14%	6%	0%	1%

Taher, A (2017) Am J Hematol; 95: 420-428

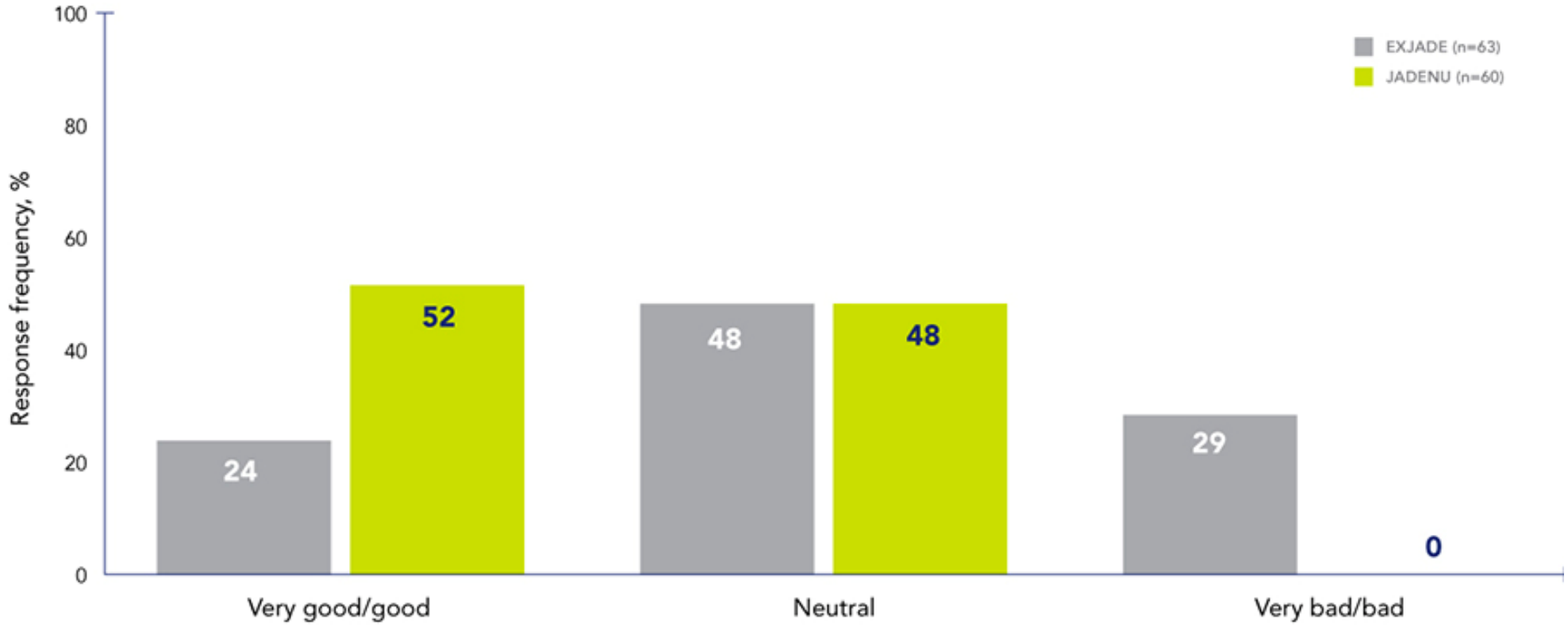
ECLIPSE II – Severe Adverse Events



	Severe AEs		Drug-Related Severe AEs*	
	EXJADE (n=86)	JADENU (n=87)	EXJADE (n=86)	JADENU (n=87)
Diarrhea	7%	1%	4%	1%
Nausea	2%	1%	1%	1%
Abdominal pain	5%	2%	2%	0%
Urine protein/ creatinine ratio increased	2%	0%	1%	0%
Vomiting	1%	0%	0%	0%
Constipation	2%	0%	1%	0%
Headache	2%	0%	0%	0%

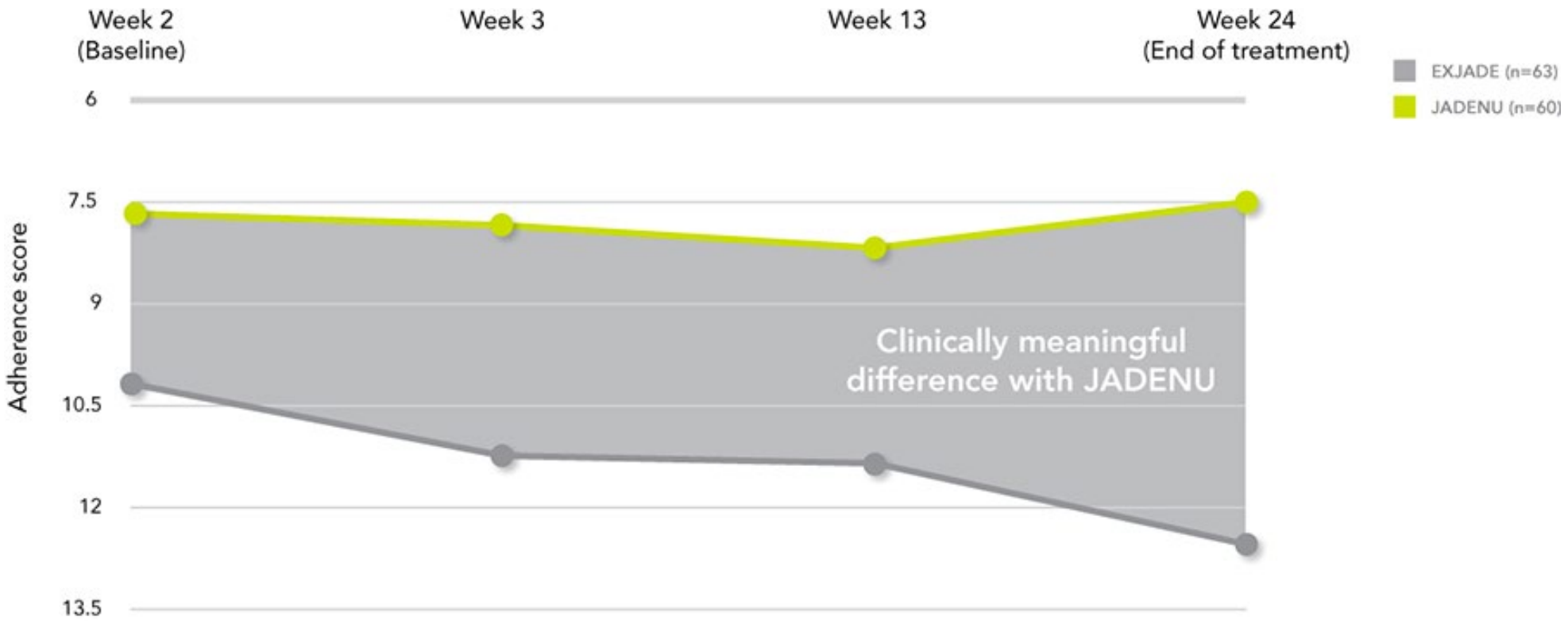
Taher, A (2017) Am J Hematol; 95: 420-428

Patient-Reported Palatability



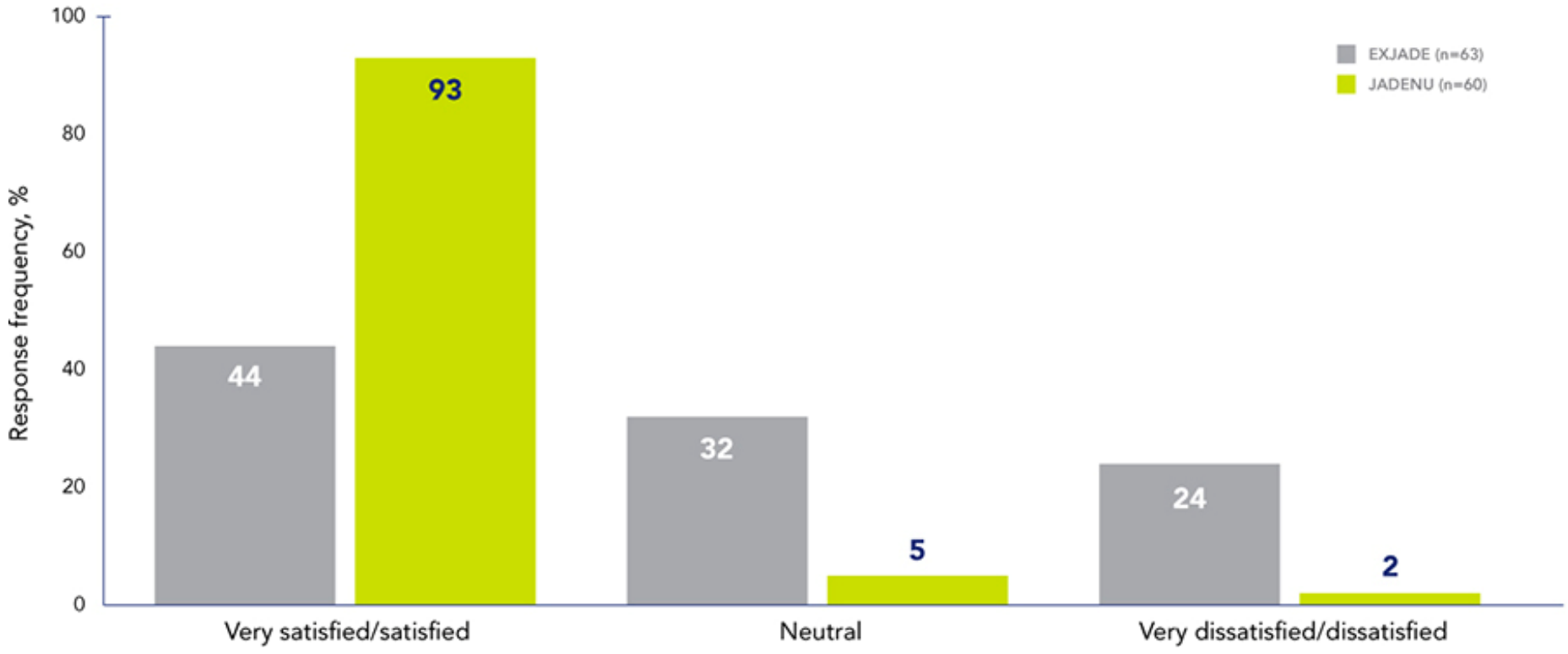
Taher, A (2017) Am J Hematol; 95: 420-428

Patient-Reported Adherence



Taher, A (2017) Am J Hematol; 95: 420-428

Patient Satisfaction



Taher, A (2017) Am J Hematol; 95: 420-428

Lenalidomide

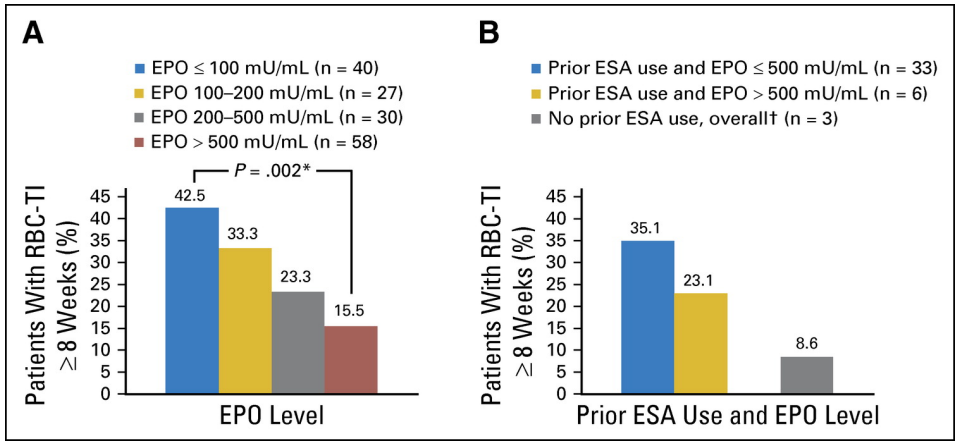
Double-blinded comparison of Lenalidomide and Placebo

Transfusion dependent IPPS Low and Int-1 (at least 2 units / 8 weeks

Refractory / ineligible for ESA's

Lenalidomide 10mg daily

Response	Lenalidomide, No. (%)	Placebo, No. (%)
No. of patients	160	79
RBC-TI ≥ 8 weeks	43 (26.9)*	2 (2.5)
Median duration of RBC-TI ≥ 8 weeks, weeks (95% CI)†	30.9 (20.7 to 59.1)	NE‡
Median time to RBC-TI ≥ 8 weeks, weeks (range)†	10.1 (0.3 to 23.6)	0.3 (0.3 to 0.3)
RBC-TI ≥ 24 weeks	28 (17.5)*	0
Erythroid response (IWG 2006)§		
≥ 4 pRBC units transfusion reduction	57 (36.5)	15 (19.5)
≥ 1.5 g/dL hemoglobin increase	31 (19.4)	2 (2.5)
≥ 4 pRBC units transfusion reduction (112-day assessment period‖)	34 of 156 (21.8)	0 of 77 (0)



Santini V (2016) JCO 34: 2988-2996

Lenalidomide - Treatment-Emergent Adverse Events

Adverse Event	Any Grade, No.(%)		Grade 3 or 4, No. (%)	
	Lenalidomide	Placebo	Lenalidomide	Placebo
No. of patients	**160**	**79**	**160**	**79**
Hematologic				
Neutropenia	103 (64.4)	10 (12.7)	99 (61.9)	10 (12.7)
Thrombocytopenia	63 (39.4)	6 (7.6)	57 (35.6)	3 (3.8)
Infection	83 (51.9)	34 (43.1)	23 (14.4)	3 (3.8)
Bleeding	33 (20.6)	8 (10.1)	3 (1.9)	0
Nonhematologic				
Venous thromboembolism	5 (3.1)	0	3 (1.9)	0
Arterial thromboembolism	4 (2.5)	2 (2.5)	2 (1.3)	1 (1.3)
Hepatic disorder	23 (14.4)	4 (5.1)	8 (5.0)	2 (2.5)
Renal failure	6 (3.8)	0	2 (1.3)	0
Peripheral neuropathy	4 (2.5)	1 (1.3)	0	0
Cardiac failure	8 (5.0)	4 (5.1)	3 (1.9)	1 (1.3)
Cardiac arrhythmia	18 (11.3)	7 (8.9)	2 (1.3)	4 (5.1)
Ischemic heart disease	3 (1.9)	3 (3.8)	3 (1.9)	1 (1.3)
Interstitial lung disease	4 (2.5)	0	0	0
Cutaneous reactions	16 (10.0)	1 (1.3)	2 (1.3)	0
Angioedema	7 (4.4)	1 (1.3)	1 (0.6)	0
Diarrhea	68 (42.5)	18 (22.8)	4 (2.5)	0
Constipation	36 (22.5)	10 (12.7)	0	2 (2.5

Santini V (2016) JCO 34: 2988-2996

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Hepatic disorder	23 (14.4)	4 (5.1)	8 (5.0)	2 (2.5)
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Peripheral neuropathy	4 (2.5)	1 (1.3)	0	0
Cardiac failure	8 (5.0)	4 (5.1)	3 (1.9)	1 (1.3)
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Interstitial lung disease	4 (2.5)	0	0	0
Cutaneous reactions	16 (10.0)	1 (1.3)	2 (1.3)	0
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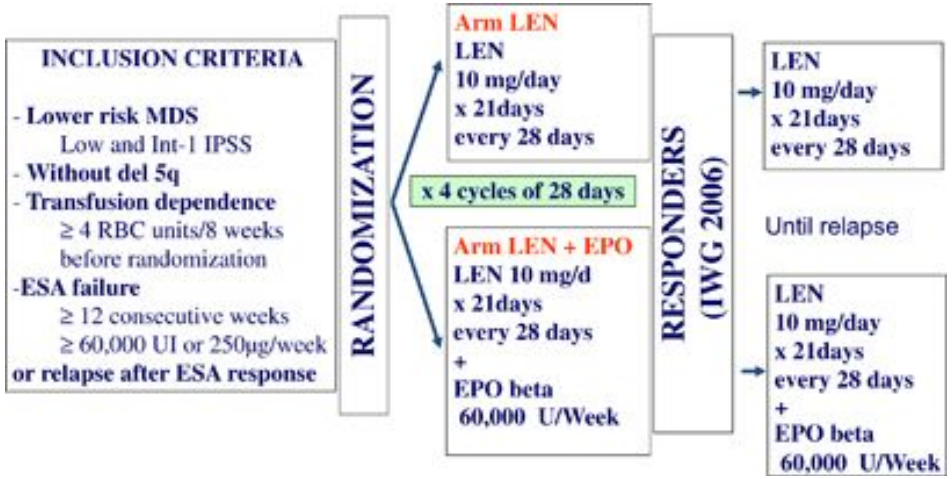
Constipation	36 (22.5)	10 (12.7)	0	2 (2.5

Santini V (2016) JCO 34: 2988-2996

Lenalidomide + Growth Factors

- GFM-LENEPO 2008



	Len	Len+Epo	p
HI-E after 4 cycles	23.1%	39.4%	0.044
Transfusion Independence	13.8%	24.2%	0.13
Median response duration	18.1 mths	15.1 mths	0.64

Toma A (2016) Leukemia 30: 897-905

Lenalidomide + Growth Factors

- HOVON89 [1]
  - ESA-refractory (or deemed unlikely to respond)
  - Randomised to lenalidomide (10mg D1-21), or Len + Epo
    - G-CSF added at 8 months if no haematological improvement
  - 33% patient achieved sustained improvement; Epo / G-CSF did not improve outcomes
  - Responders had improvement in PFS and OS

- ECOG E2905 (NCT00843882)
  - LEN v LEN+Epo – recruitment completed

1. Van de Loosdrecht A (2016) Blood 128: 224

Immunosuppressive Therapy

ATGAM

- Haem improvement reported in 20-60% patients

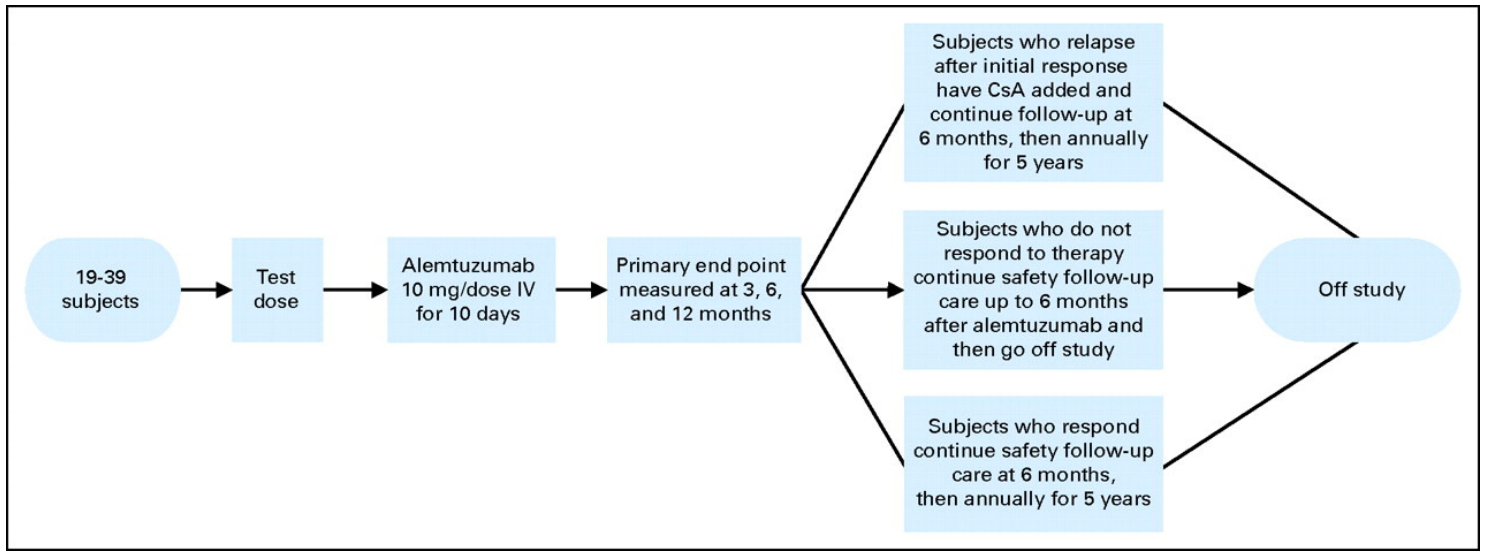
  Blood 102:3025, Leukemia 17:2101, BJH 99:699, JCO 26:2505, Leukemia 21:1436

- SAKK 33/99 study Equine ATG 15mg/kg x 5 days and oral CSA compared with Best Supportive Care (BSC)

	ATG+CSA	BSC
Total number	45	43
Low and INT-1	32	33
Hypoplastic	9	4
Haematologic Response	13	4 (p=0.0156)
2 yr Transformation Free	46%	55% (NS)
2 YR OS	49%	64% (NS

Passweg, J 2(2011) JCO; 29: 303-309

Alemtuzumab



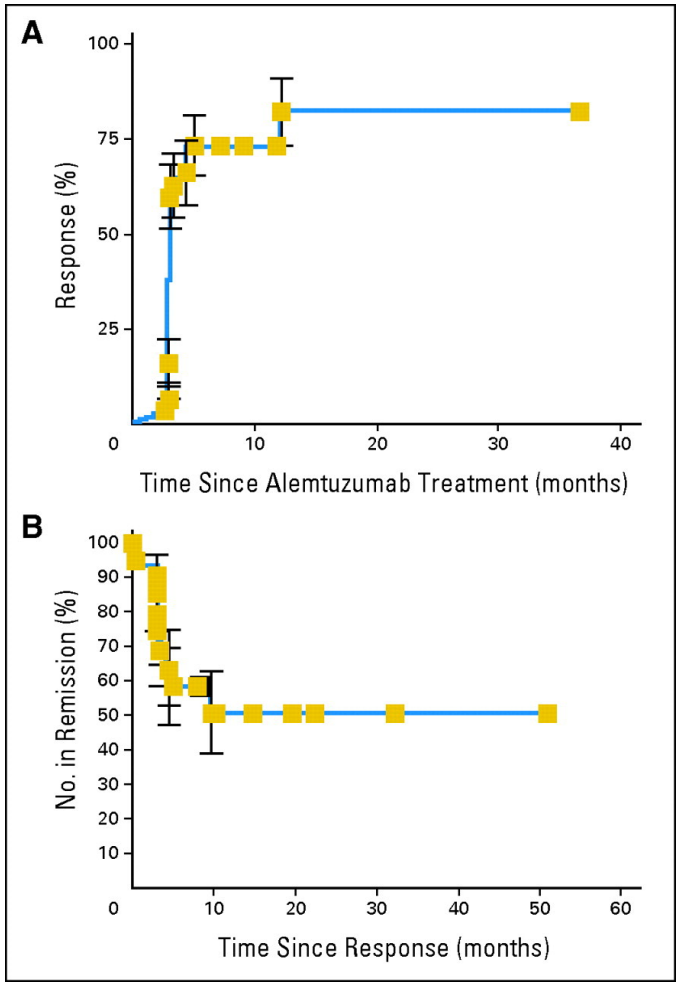
n= 31
68% - Haematological Improvement at median of 3 months
40% - Transfusion independent at 3 months
4/7 responding patients had karyotypic CR by 1 year

1. Saunthararajah Y (2003) Blood 102: 3025-3027
2. Sloand E (2010) JCO 28: 5166-5173

Alemtuzumab

Patients age, y + duration of TD, mo		
DR15-	**DR15+**	**PPR**
> 57	> 71	Low (0-40%)
≤ 57	≤ 71	High (41-100%)

PPR	No Response	Response
Low (0-40%)	13	1
High (41-100%)	3	6



1. Saunthararajah Y (2003) Blood 102: 3025-3027
2. Sloand E (2010) JCO 28: 5166-5173

Hypomethylating Agents

- Retrospective data suggest variable response:
  - 30-40% RBC transfusion independence
  - 25-55% haematological improvements

JCO 27: 1850, CANCER 116: 1485, JCO 31: 2548,

- 2 trials in ESA-refractory patients:
  - Nordic NMDSG08A Phase II trial [1]
  - GFMAzaEpo-2008-1 [2]
- 1 trial in front-line setting
  - MDACC: Decitabine v Azacytidine [3]
- Ongoing clinical trials of oral azacytidine
  - (QUAZAR MDS-003) [4]

1. Tobiasson (2014) Blood Cancer J; 4: e1893. 2. Boehrer Blood 2010 116: 1880 3. Jabbour Blood 2014 124: 4640 4. Garcia-Menero G (2016) BMC Hematol 16:12

Hypomethylating Agents

NMDSG08A [1]	Low or Int-risk IPSS*	AZA 75.m2 x 5 days x 6 cycles	30 patients: 1 cycle 22 patients: 6 cycles 17% -> Transfusion independence 3 patients – erythroid improvement
GFMAzaEPO-2008-1 [2]	ESA-resistant, Low or Int-risk IPSS	AZA 75mg/m2 x 5 days x 6cyles +/- EPO 60000IU/wk	HI-E: 40 v 36.5% HI-E Major: 13 v 32%
MDACC [3]	Untreated Low or Int-I risk	DAC 20mg/m2 x 3 days AZA 75mg/m2 x 3 days	68 patients Overall improvement: 54% v 56% RBC-TI 7% v 27%

*Patients with intermediate / high Nordic response required prior treatment with EPO and EPO+G-CSF
Patients with low probability of response to EPO could be untreated

1. Tobiasson (2014) Blood Cancer J; 4: e1893. 2. Boehrer Blood 2010 116: 1880 3. Jabbour Blood 2014 124: 4640

Novel Therapeutic Options

- TGF-β
  - Activin receptor inhibition (Ligand Traps)
    - Luspatercept Phase II PACE-MDS [1]
      Relapsed MEDALIST study [2]
      Front-line COMMANDS study
  - Galunisertib [1]

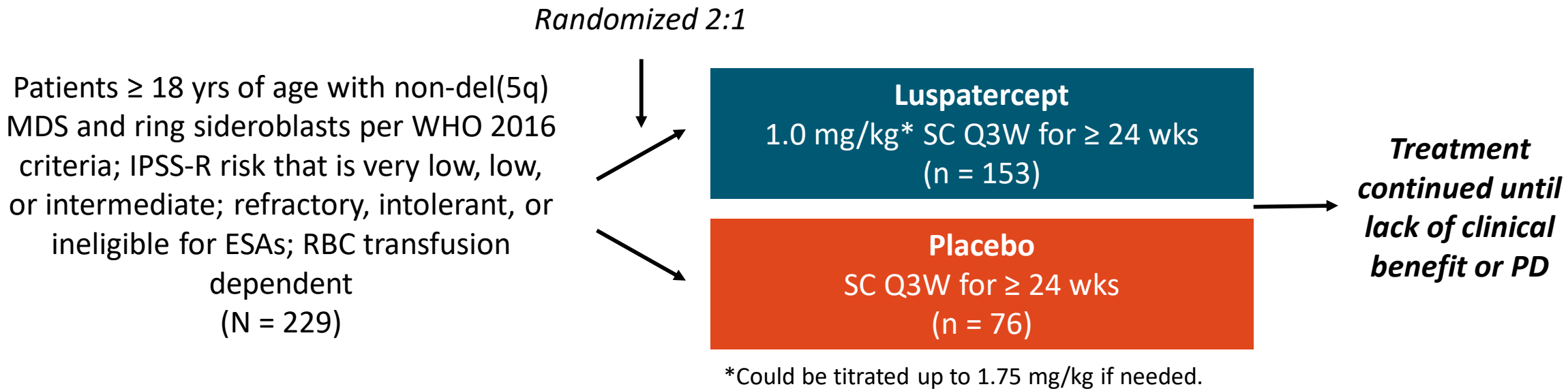
- Oral splicing modulator – H3B-8800
  - SF3B1, SRSF2, U2AF1, ZRSR2

- Telomerase Inhibitor – Imetelstat [3]

1. Giagounidis A, (2015) Blood 126: 92 2. Fenaux P, ASH2018: Abstr 1 3. Fenaux P (2017) Blood; 130: 4256

MEDALIST: Study Design

- International, randomized, double-blind, placebo-controlled phase III trial



- Primary endpoint: RBC TI for ≥ 8 wks between Wk 1 and Wk 24
- Secondary endpoints: RBC TI for ≥ 12 wks between Wk 1 and Wk 24, modified hematologic improvement–erythroid response per IWG 2006 criteria, DoR, Hb change from baseline

Fenaux. ASH 2018. Abstr 1. NCT02631070.

MEDALIST: Efficacy

Outcome, %	Luspatercept (n = 153)	Placebo (n = 76)	*P* Value
RBC TI ≥ 8 wks in Wks 1-24	37.9	13.2	< .0001
RBC TI ≥ 12 wks in Wks 1-24	28.1	7.9	.0002
RBC TI ≥ 12 wks in Wks 1-48	33.3	11.8	.0003
mHI-E* ≥ 8 wks in Wks 1-24	**52.9**	**11.8**	**< .0001**
▪ Reduction of ≥ 4 RBC units/8 wks	48.6	14.3	
▪ Hb increase of ≥ 1.5 g/dL	63.0	5.0	
mHI-E* ≥ 8 wks in Wks 1-48	**58.8**	**17.1**	**< .0001**
▪ Reduction of ≥ 4 RBC units/8 wks	54.2	21.4	
▪ Hb increase of ≥ 1.5 g/dL	69.6	5.0	

*Defined as transfusion reduction of ≥ 4 units/8 wks or mean hemoglobin increase ≥ 1.5 g/dL/8 wks in absence of transfusions

- Among primary endpoint responders, the median duration of RBC TI response was 30.6 wks in the luspatercept arm vs 13.6 wks in the placebo arm

Fenaux. ASH 2018. Abstr 1.

MEDALIST: Safety

TEAE of Any Grade, %	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	26.8	13.2
Diarrhea	22.2	9.2
Asthenia	20.3	11.8
Nausea	20.3	7.9
Dizziness	19.6	5.3
Back pain	19.0	6.6
Cough	17.6	13.2
Peripheral edema	16.3	17.1
Headache	15.7	6.6
Dyspnea	15.0	6.6
Bronchitis	11.1	1.3
Constipation	11.1	9.2
UTI	11.1	5.3
Fall	9.8	11.8

TEAE, %	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE	98.0	92.1
▪ ≥ 1 serious TEAE	31.4	30.3
▪ ≥ 1 grade 3/4 TEAE	42.5	44.7
▪ TEAEs leading to death	3.3	5.3
▪ ≥ TEAE causing discontinuation	8.5	7.9

- 4 patients progressed to acute myeloid leukemia: 3 in luspatercept arm, 1 in placebo arm
- The most common grade 3/4 TEAEs in luspatercept arm were anemia (6.5%), fatigue (4.6%), and fall (4.6%)

Fenaux. ASH 2018. Abstr 1.

Managing thrombocytopenia

- 30% of patient have platelet counts < 50
- 15-20% of patients have platelet counts < 20

- Remember: Haemorrhage is 3rd most common cause of death

1. www.fismonlus.it 2. Nachtkamp K (2016) Ann Hematol; 95: 937-944

Managing Thrombocytopenia

- ?? Role of prophylactic platelet support

- Romiplostin
- Eltrombopag
- Combination studies
  - Azacitidine Kantarjian H (2010) Blood 116: 3163-3170
  - Decitabine Greenberg P (2013) Leuk Lymphoma 54: 321-328
  - Lenalidomide Wang E (2012) J Haematol Oncol 5: 71

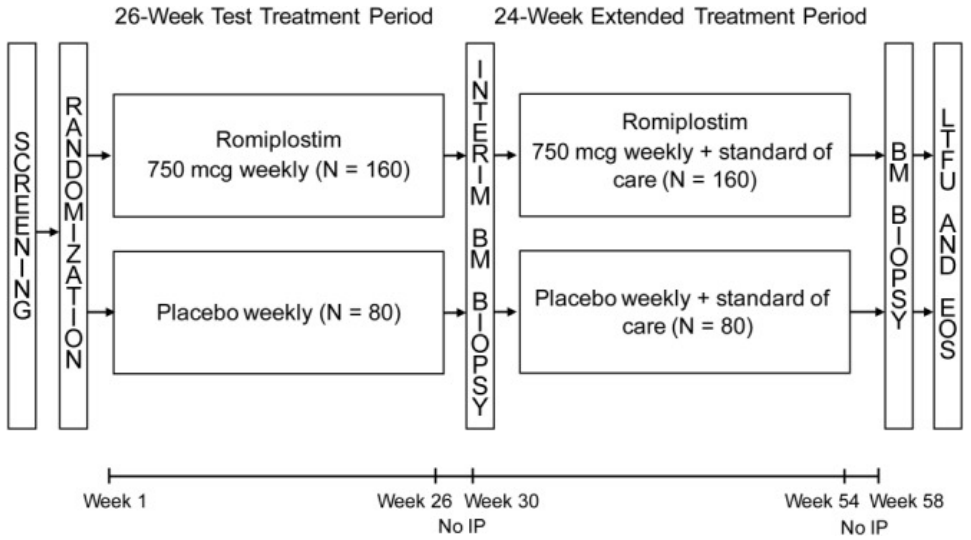
Romiplostin in Low-Risk MDS

Phase 2 randomised (2:1), double-blind study

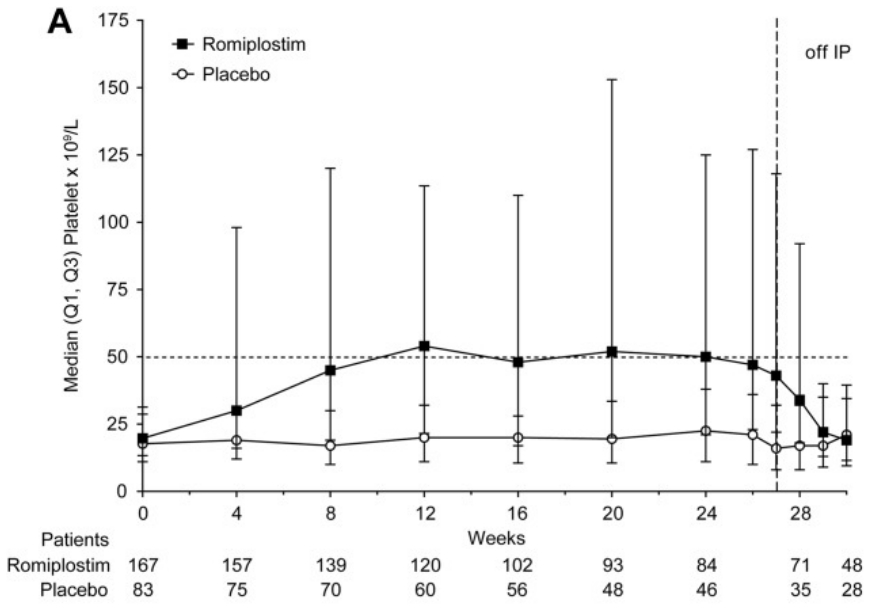
Platelets < 20 or ≥ 20 with hx of bleeding
Low or Int-1 IPSS risk
Starting dose 750mcg

Primary endpoint: clinically significant bleeding events

N = 167 v 83



Romiplostin in Low-Risk MDS

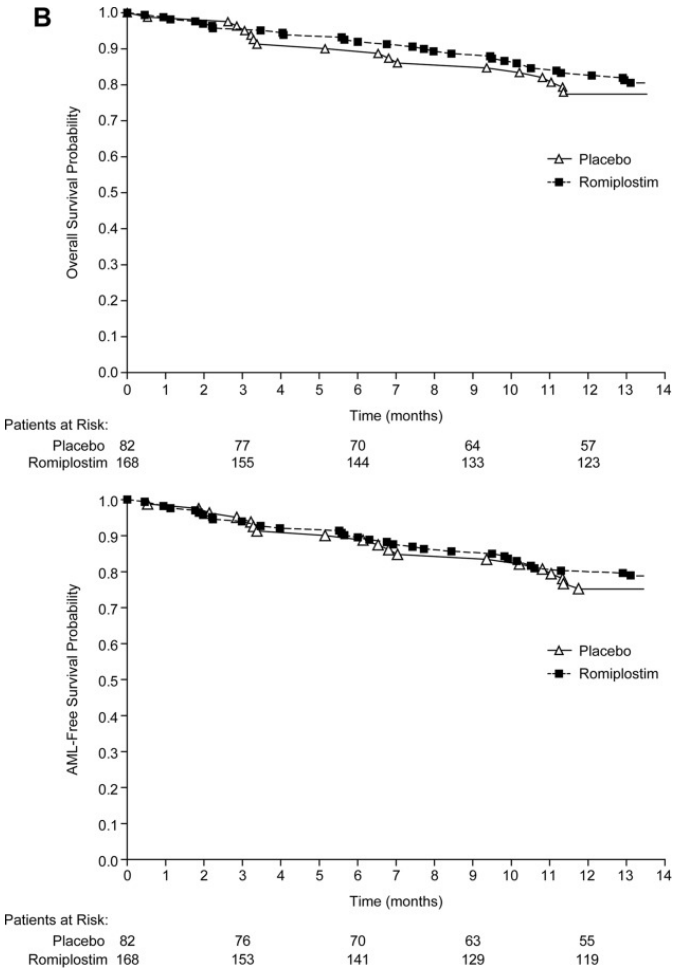


Variable[b]	Placebo	Romiplostim	Ratio (95% CI)	*P*
All patients[c]				
CSBE: Mean no. of events per patient at week 26	1.94	1.47	HR, 0.83 (0.66-1.05)	.13
All bleeding events per 100 pt-yrs	3786.4	3459.9	RR, 0.922 (0.86-0.99)	.026
Baseline platelets <20 × 10^9/L[d]				
CSBE rate per 100 pt-yrs	501.2	514.9	RR, 1.03 (0.79-1.35)	
Baseline platelets ≥20 × 10^9/L[e]				
CSBE rate per 100 pt-yrs	226.4	79.5	RR, 0.35 (0.21-0.59)	< .0001

Giagounidis A (2014) Cancer 120: 1838-1846

Romiplostin in Low-Risk MDS

Variable	No. of Patients (%)		
	Placebo, N = 82	Romiplostim, N = 168	Total, N = 250
Total no. with study-defined AML	4	10	14
Baseline WHO classification			
RAEB-1 or RAEB-2	3 (75)	6 (60)	9 (64)
Non-RAEB	1 (25)	4 (40)	5 (36)
AML diagnosis by			
Bone marrow/peripheral blasts ≥20%	2 (50)	7 (70)[a]	9 (64)
Anti-AML therapy alone	2 (50)	3 (30)	5 (36)



Giagounidis A (2014) Cancer 120: 1838-1846

Eltrombopag in Low-Risk MDS – EQoL-MDS

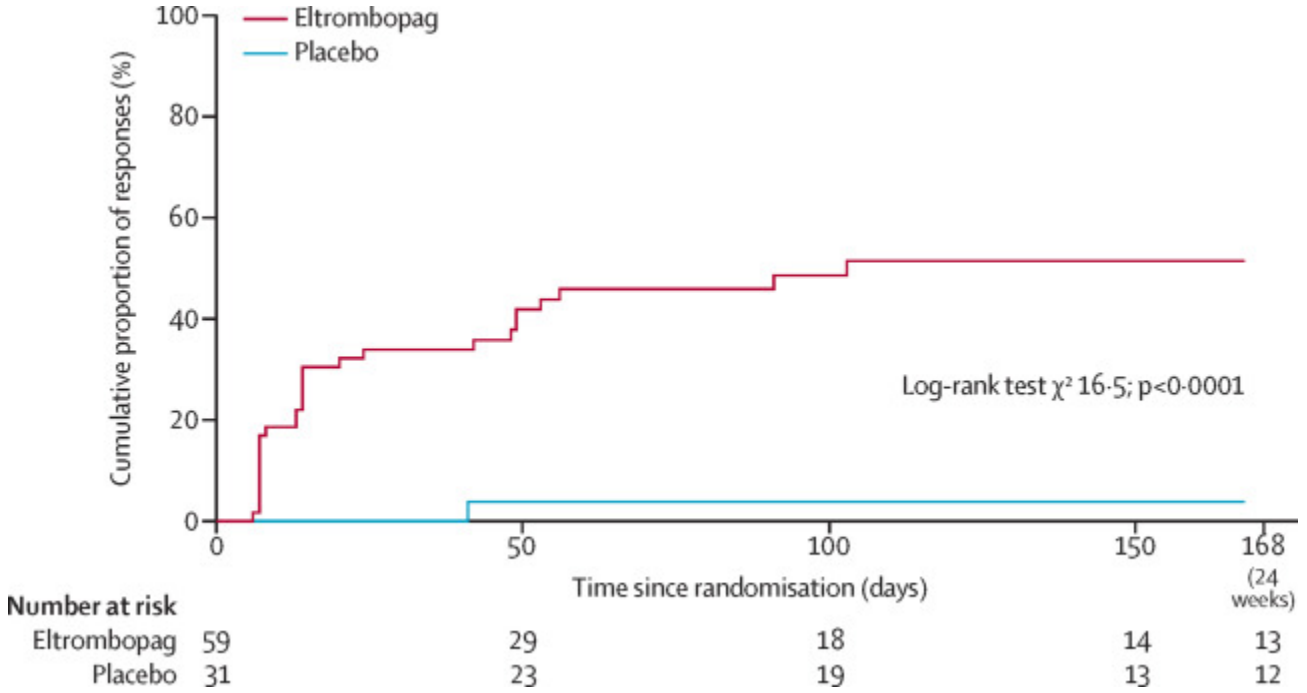
Randomised Phase 2 single-blind, placebo-controlled

Stable platelets < 30
Low or INT-1 IPSS risk MDS

2:1 randomisation (n = 59 v 31)

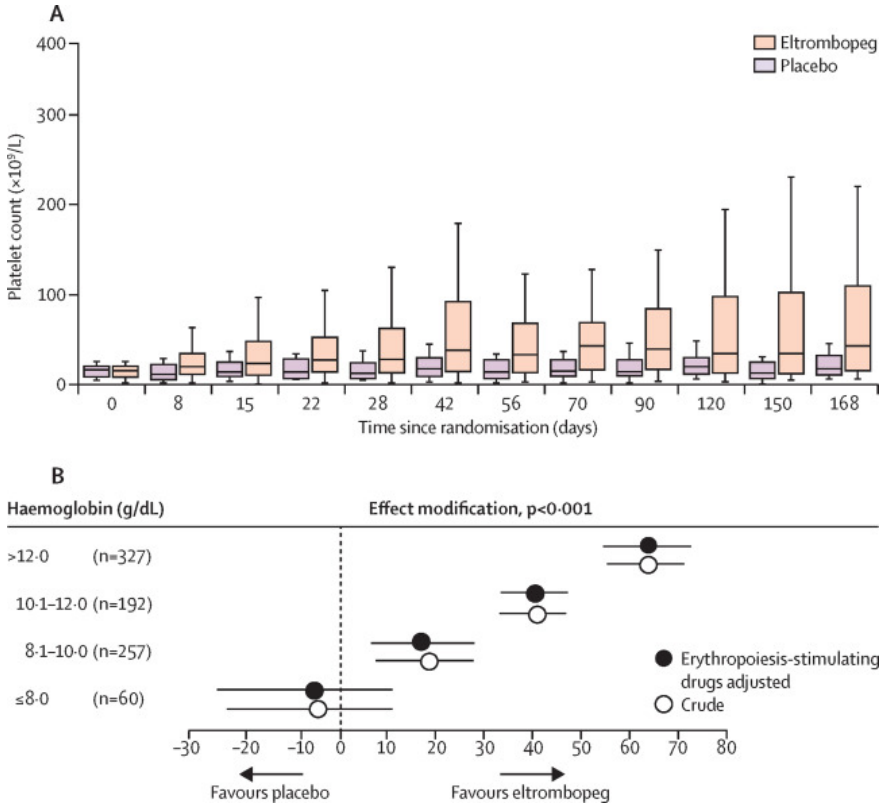
50mg daily starting dose -> titrated to max 300mg per day

Complete response = plat > 100
Partial response: Absence of bleeding & plats > 30 (if baseline 20-30) or > 20 (if baseline <20)



Oliva E (2017) Lancet Haematology; 4: e127-e136

EQoL-MDS Study



Median dose at response = 50mg

No increase in PB blasts
No leukaemic risk

47% overall response (v 3%)
29% complete response

13 / 23 anaemic patients had erythroid Haematological improvement

Oliva E (2017) Lancet Haematology; 4: e127-e136

Neutropenia

- Rarely found in isolation
  - Generally good prognosis, low leukaemic transformation risk [1]
- No data regarding G-CSF
  - OS, infection prevention, leukaeima ransfromation [2]

1. Gyan E (2016) BJH; 175: 975-979
2. Hutzschenreuter F Cochrane Review (2016): CD009310

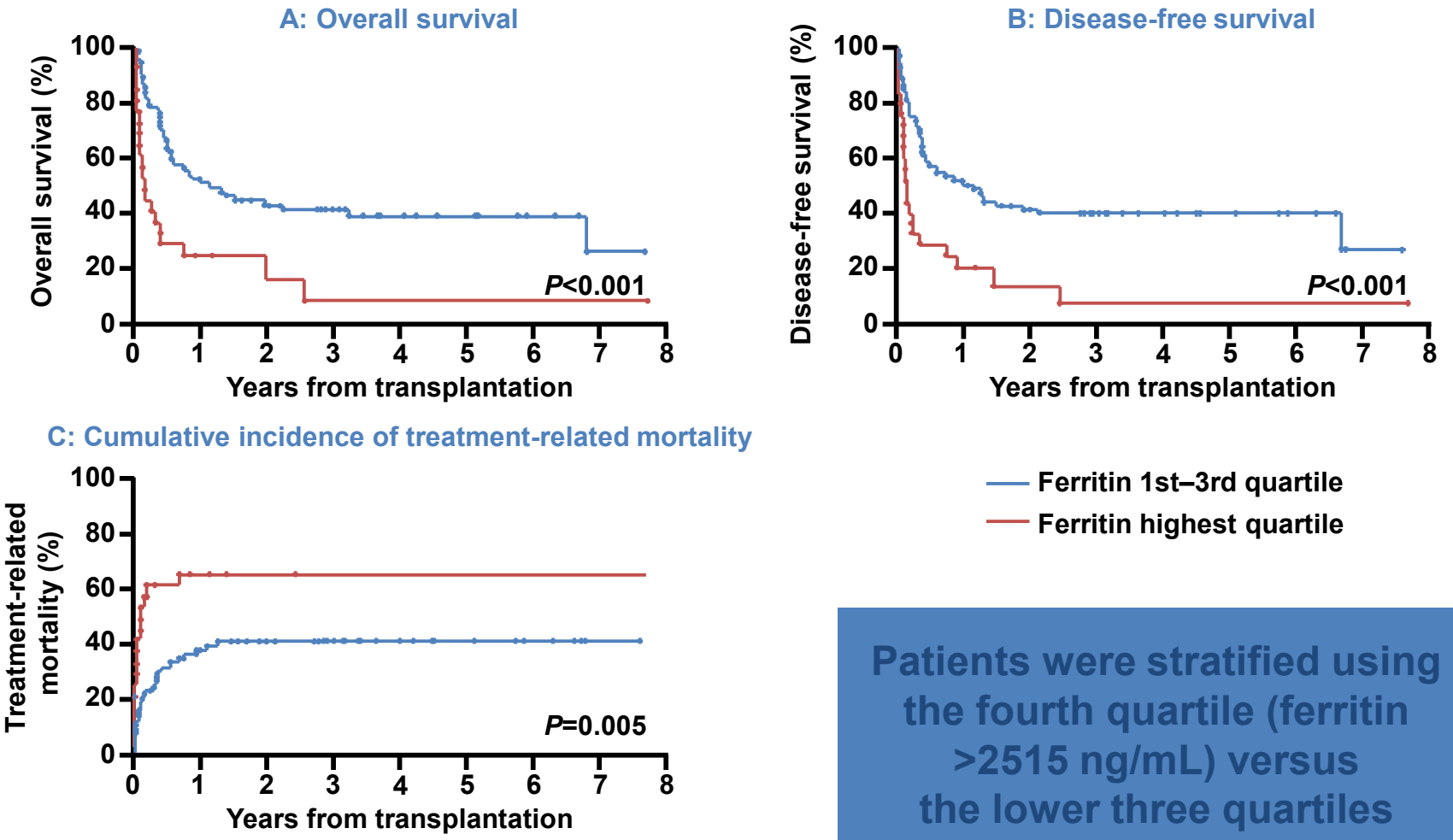
Allogeneic Stem Cell Transplantation

- Timing optimal if disease progression but prior to leukaemic transformation

- Highly symptomatic disease
- Refractory to available therapeutic options

- Effects of pre-transplant ferritin on allo-transplantation outcomes highly prognostic

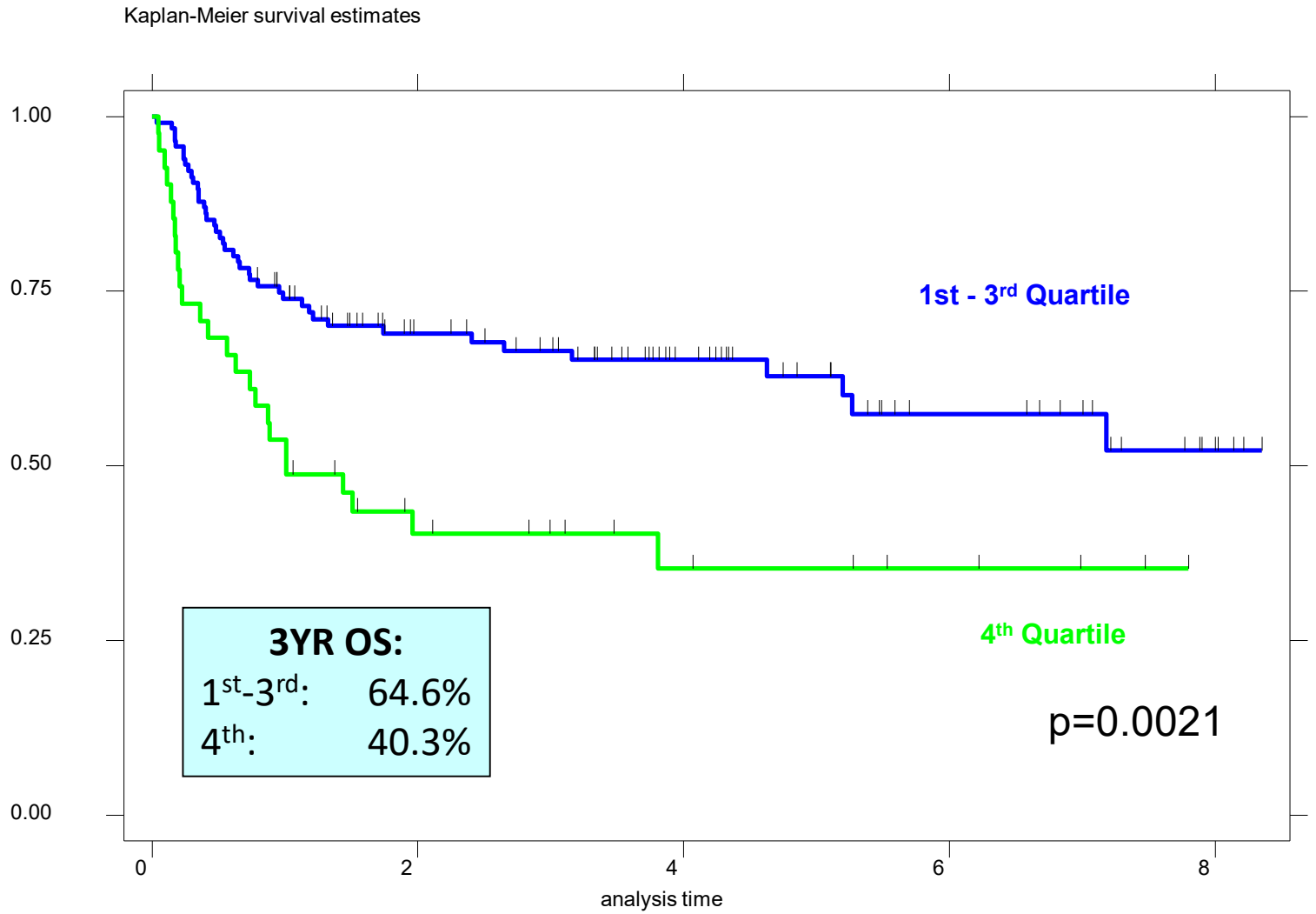
Pre-transplant serum ferritin is a prognostic factor for the success of HSCT



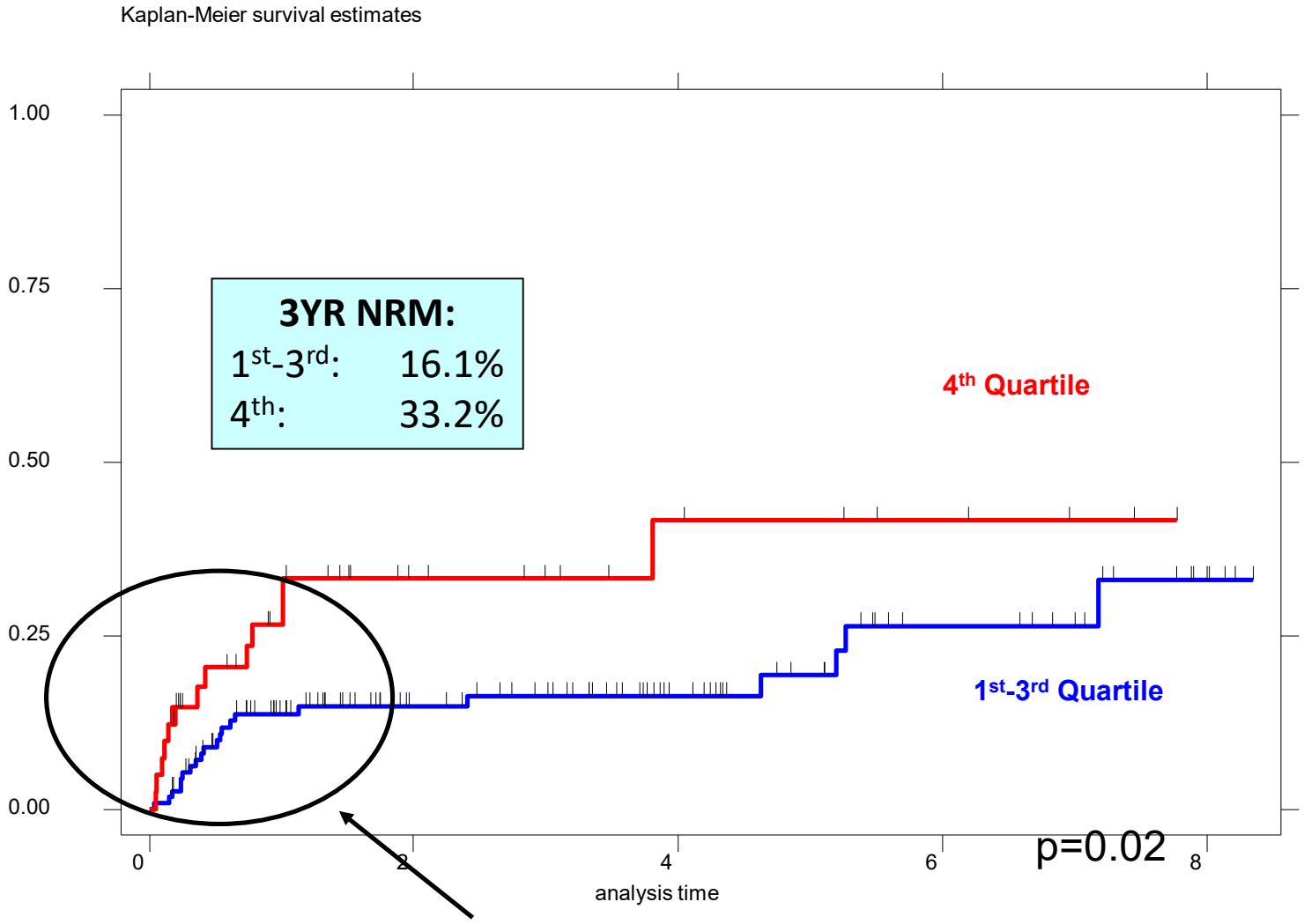
Patients were stratified using the fourth quartile (ferritin >2515 ng/mL) versus the lower three quartiles

Armand P *et al*. *Blood* 2007;109:4586–4588

OS – 1st-3rd versus 4th quartile



NRM – 1st-3rd versus 4th quartile



5q- MDS

5q- MDS

- Classical presentation with macrocytic anaemia and thrombocytosis
- May have ring sideroblasts – often with SF3B1 and / or JAK2 mutations
- High EPO levels – tend to be lower and more short-lived responses to ESA
- TP53 mutations associated with poor outcome
  - Found in perhaps 10-20% of patients

MDS-003

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

* The daily dose was 10 mg.
† The baseline hemoglobin concentration was the minimum value during the baseline period.
‡ The response hemoglobin concentration was the maximum value during the transfusion-independent response period.

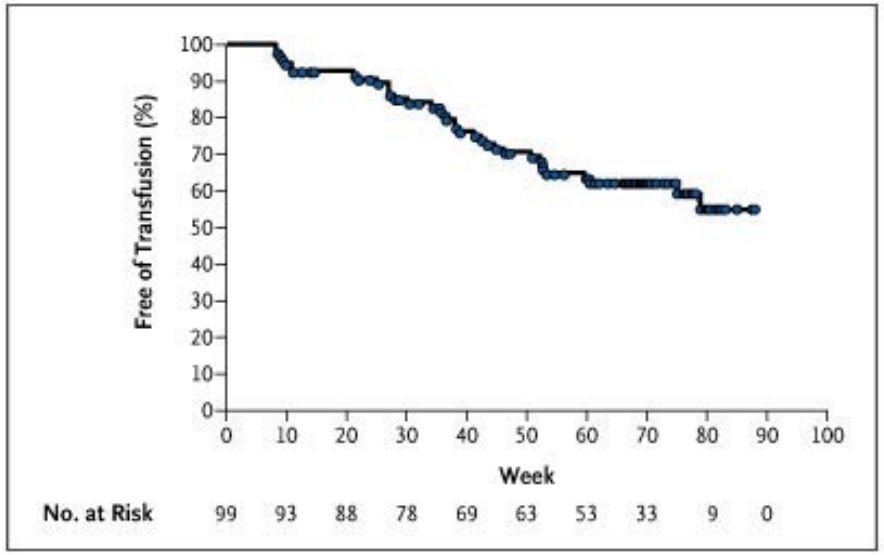


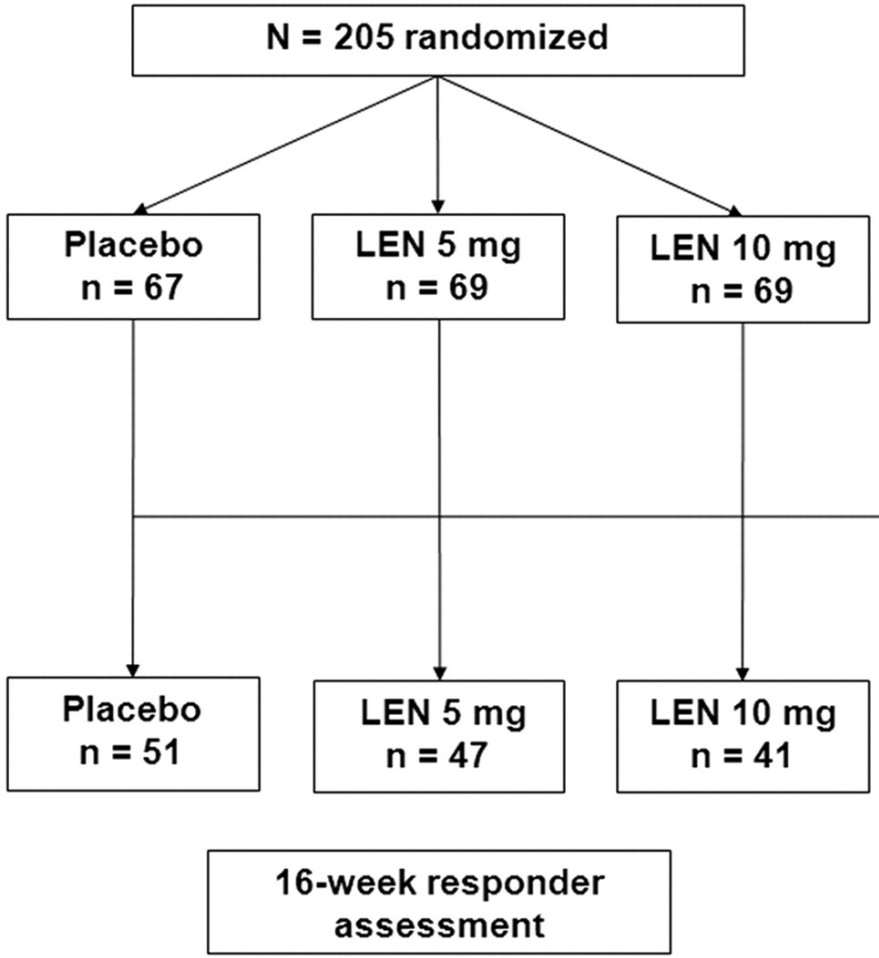
Table 3. Frequency of Cytogenetic Response According to Karyotype Complexity.

Complexity	Patients Who Could Be Evaluated*	Cytogenetic Response	Complete Cytogenetic Remission
Isolated 5q deletion — no. (%)	64	49 (77)	29 (45)
5q deletion + 1 additional abnormality — no. (%)	15	10 (67)	6 (40)
Complex (≥3 abnormalities) — no. (%)	6	3 (50)	3 (50)
P value		0.27	0.93

* Patients who could be evaluated were those with at least 20 analyzable cells in metaphase at baseline and at least one follow-up assessment. P values are for the association between karyotypic complexity and a cytogenic response or complete cytogenetic remission.

List A (2006) NEJM; 355: 1456-1465

MDS-004



ITT population (N = 205)
Patients who were randomized

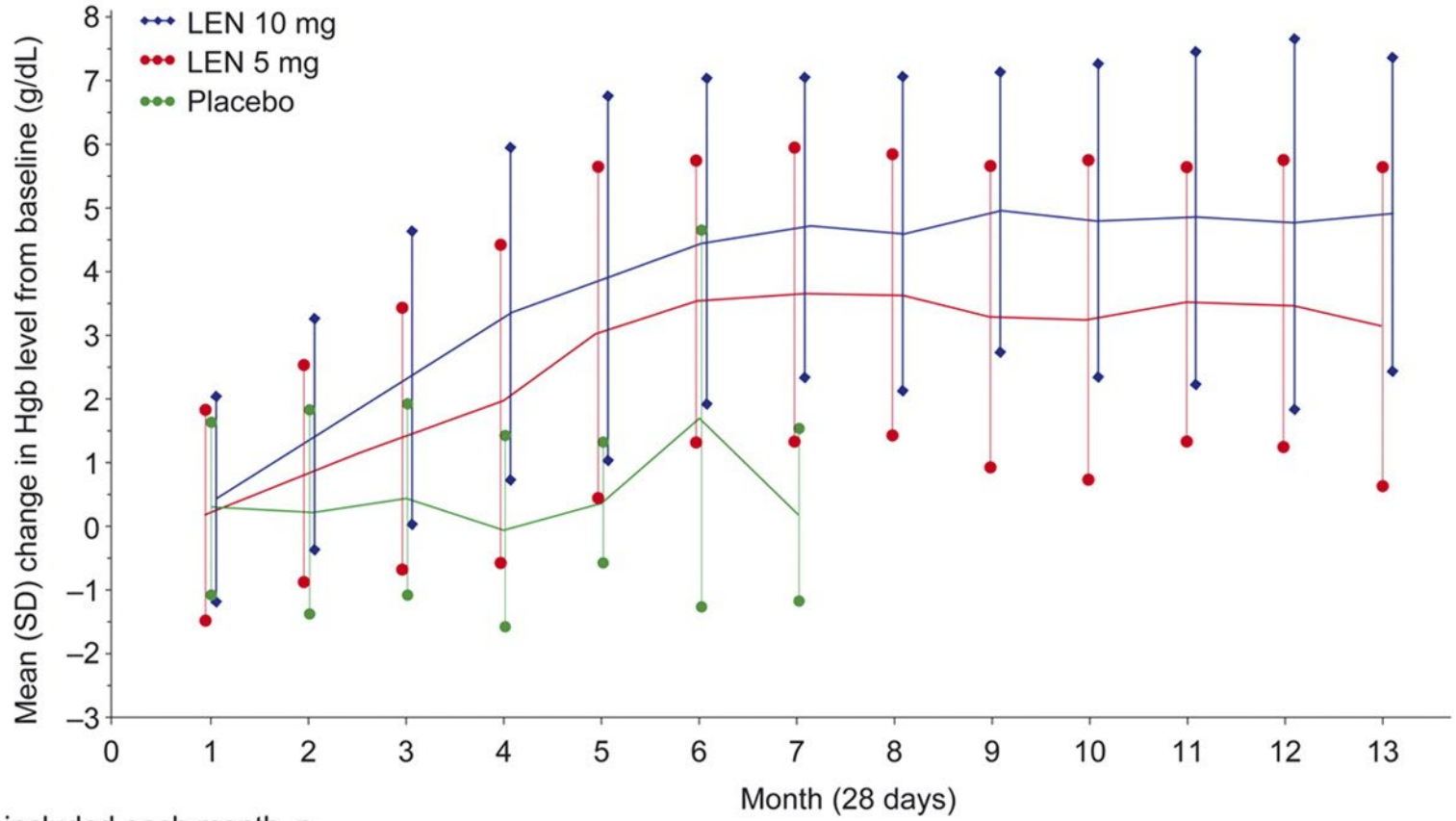
Safety population (N = 205)
Patients who were randomized and received ≥ 1 dose

Reasons for exclusion from mITT(n = 66)
- Inadequate BM sample (n = 40)
- IPSS Int-2-/High-risk (n = 11)
- Insufficient IPSS information (n = 4)
- No del5q31 by central review (n = 9)
- TI prior to randomization (n = 2)

mITT population (N = 139)
Patients with centrally-confirmed Low-/Int-1-risk MDS with del5q31 and RBC transfusion dependence who received ≥ 1 dose

Pierre Fenaux et al. Blood 2011;118:3765-3776

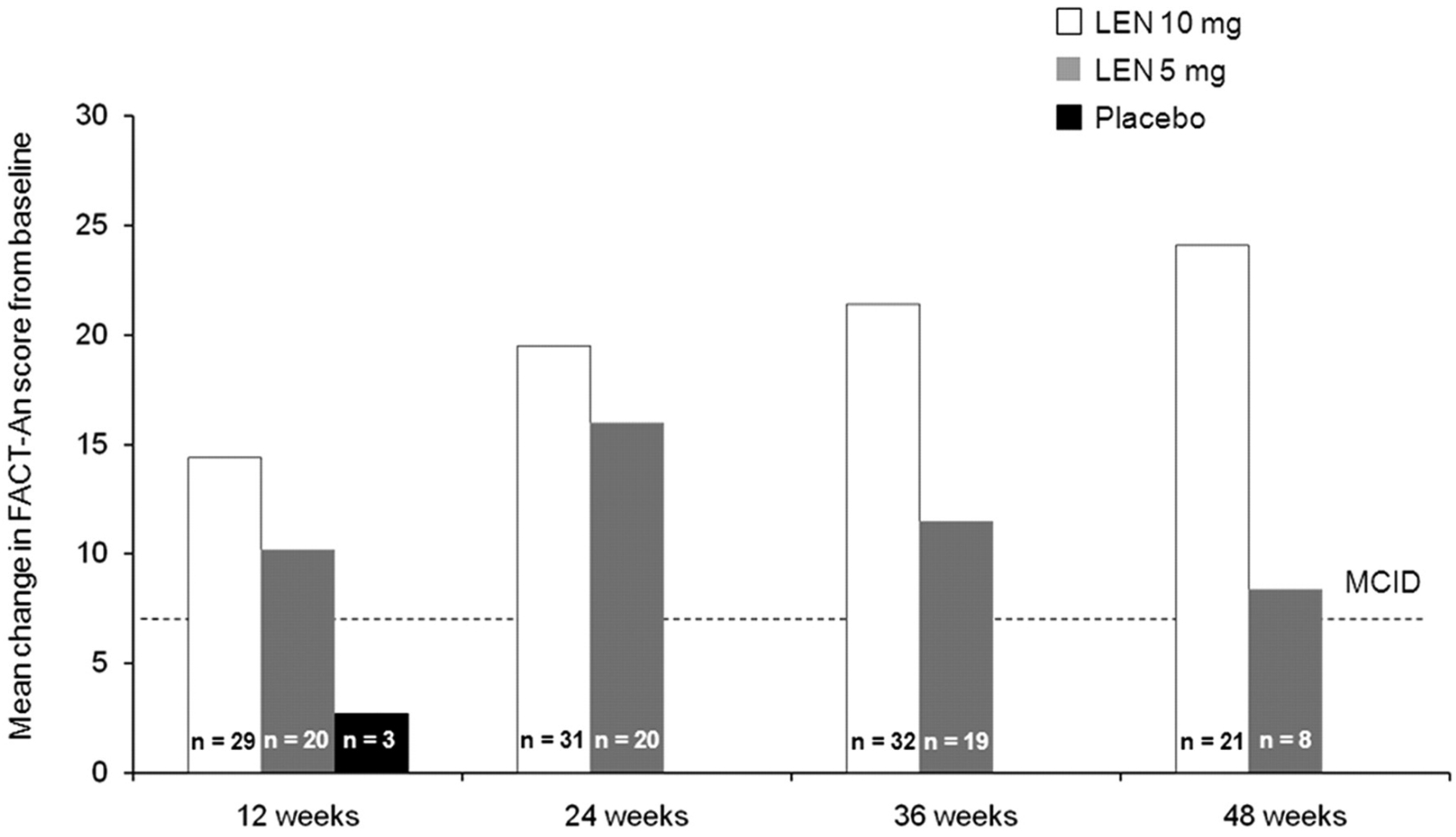
Mean hemoglobin (Hgb) change from baseline over time by randomized treatment group (mITT population).



Patients included each month, n													
LEN 10 mg	40	38	38	36	29	26	24	24	24	24	23	23	18
LEN 5 mg	47	46	43	42	29	24	24	24	23	22	20	18	11
Placebo	51	50	49	47	7	5	4						

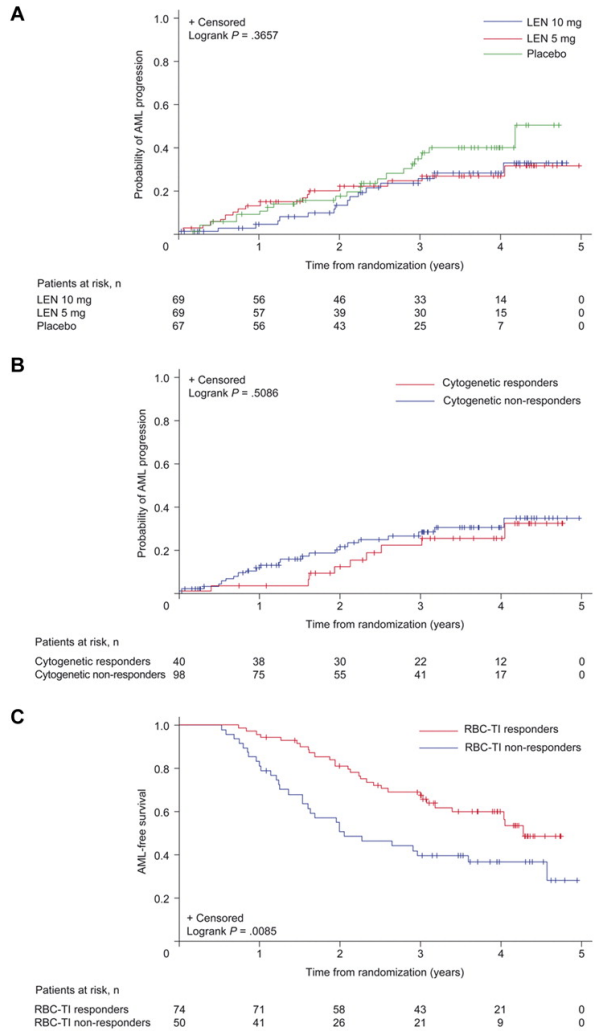
Pierre Fenaux et al. Blood 2011;118:3765-3776

Absolute change in FACT-An scores from baseline among patients who achieved RBC-TI for ≥ 26 weeks in the placebo group at week 12 (before crossover) and the lenalidomide (LEN) 5 mg and 10 mg treatment groups at weeks 12, 24, 36, and 48 (safety population).



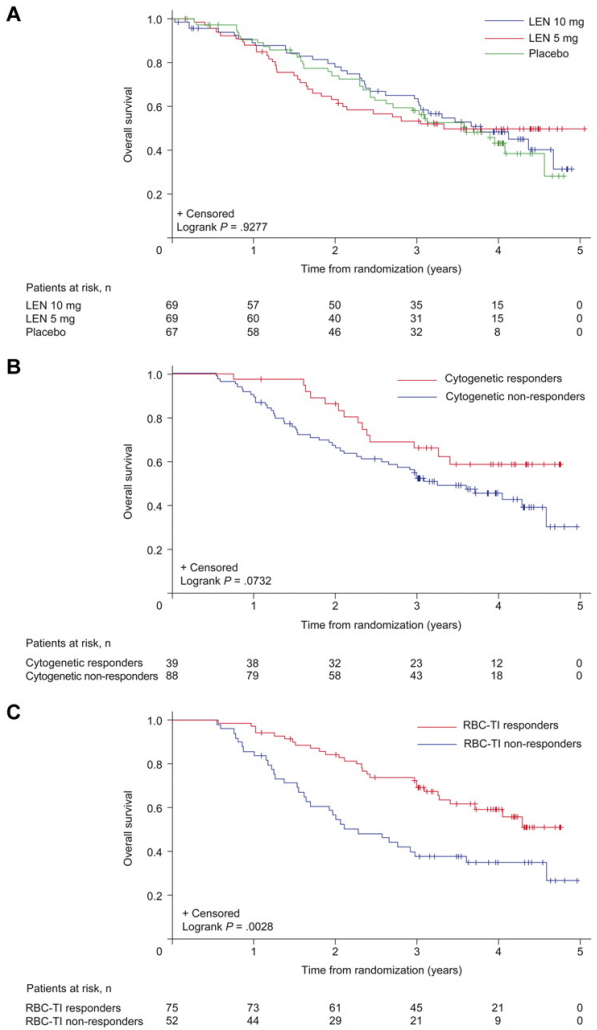
Pierre Fenaux et al. Blood 2011;118:3765-3776

Time to AML progression.



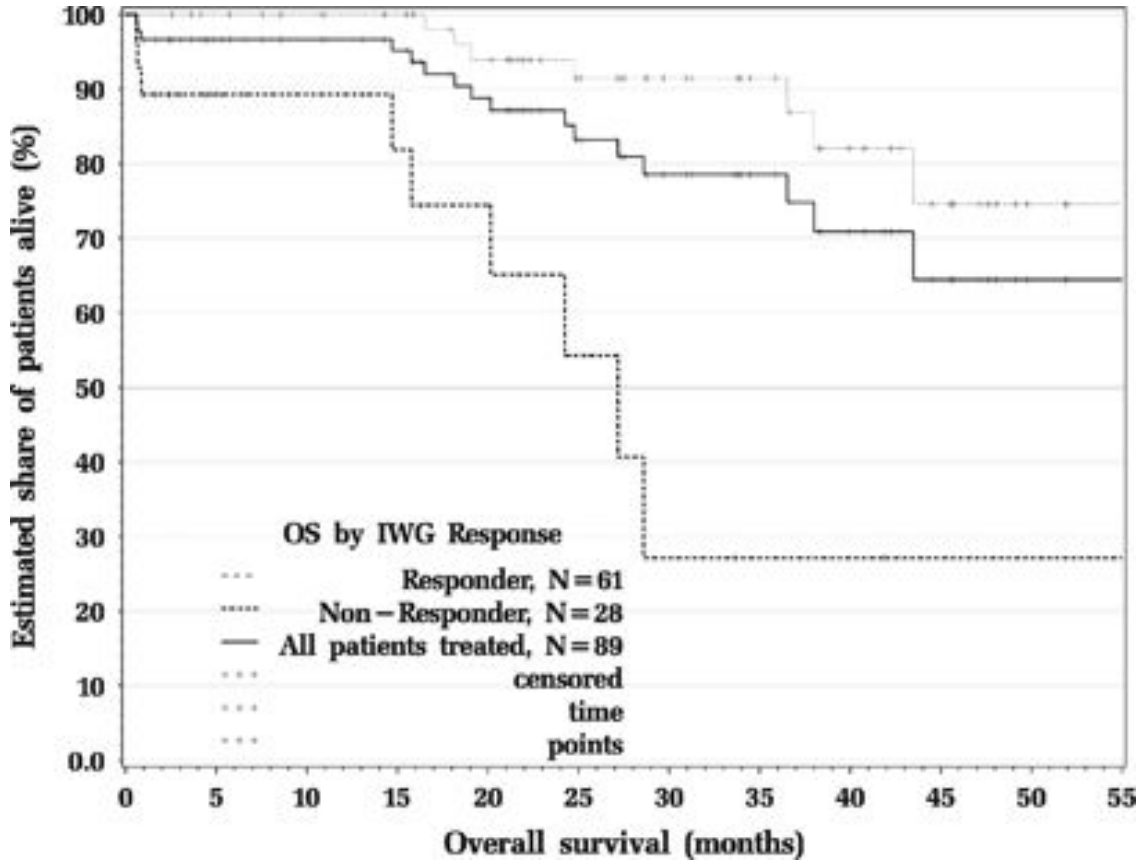
Pierre Fenaux et al. Blood 2011;118:3765-3776

Duration of OS. Results are presented for the safety population: (A) by randomized treatment group, by 6-month landmark analyses of OS, (B) by cytogenetic response (complete + partial), and (C) by RBC-TI (≥ 8 weeks) in patients randomized to lenalidomide (L...



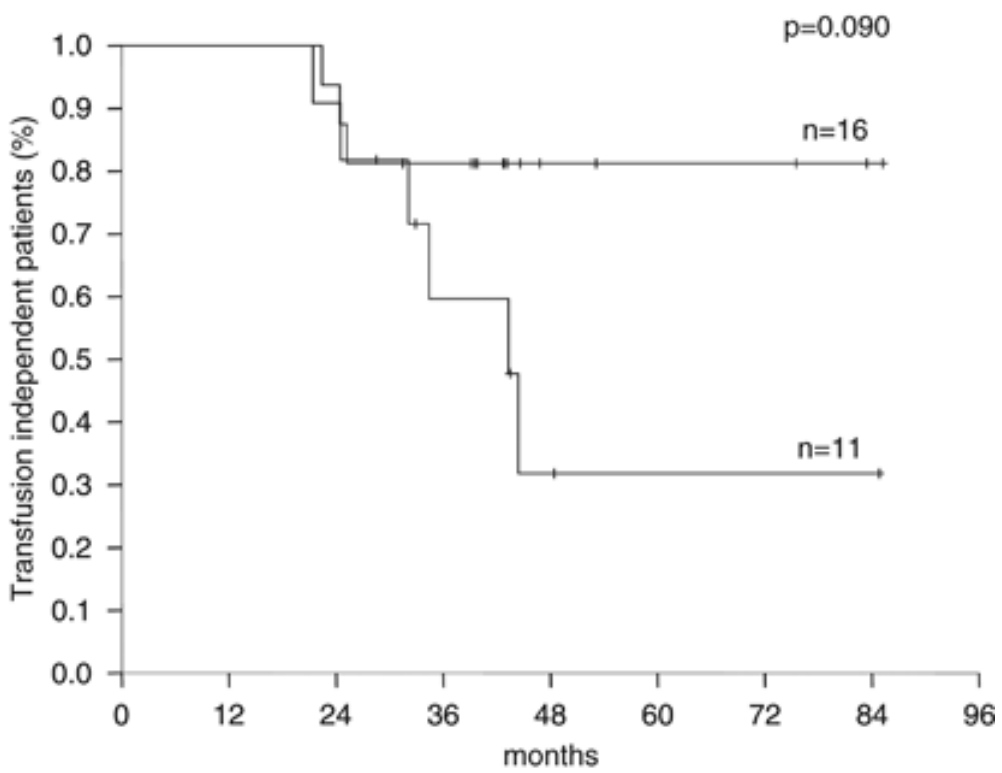
Pierre Fenaux et al. Blood 2011;118:3765-3776

LeMON-5 Study

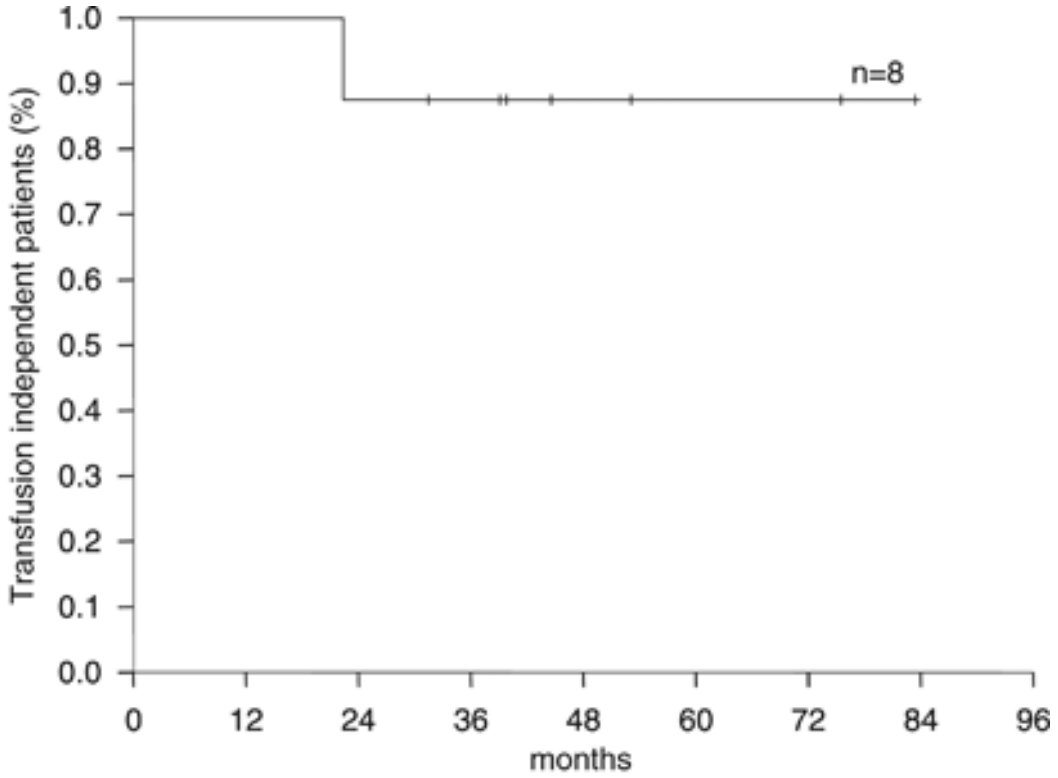


Schuler E (2016) Leukemia; 30: 1580-1582

Lenalidomide Drug Holiday



Long-term transfusion independence in patients achieving CCyR or not



Transfusion independence in 8 patients who continued lenalidomide for 6 months after achievement of CCyR

Giagounidis A (2012) Leukemia; 26: 855-858

Thank-You!