MDS a basso rischio: un caso clinico

D.ssa Giulia Daghia,
U.O. Ematologia
Ospedale S.M. delle Croci

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna
RAVENNA

Nessun conflitto di interesse da dichiarare

Marzo 2011

MP, femmina, 72 anni, ECOG 1:

- GB 3450/µl, **Hb 11 g/dl, MCV 105 fl**, PLT 315000/µl, neutrofili 1670/µl, monociti 760/µl, linfociti 1010/µl, reticolociti

- Anamnesi negativa per esposizione a tossici, RT o CHT;
- Comorbidità: ipertensione arteriosa, coxartrosi dx, osteoporosi, insufficienza venosa AAII;
- Terapia cronica: sotalolo 80 mg ½ cp die; calcio carbonato e colecalciferolo, etoricoxib 60 mg die a cicli;
- Nessuna allergia riferita.

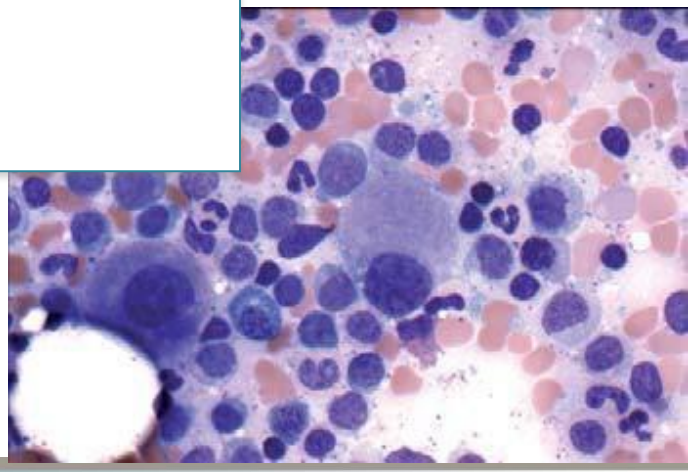
Marzo 2011

- **Creatinina** 0.86 mg/dl, AST 14 U/l, ALT 9 U/l, sodio 134 mmol/l, potassio 4 mmol/l, calcio 9.6 mg/dl;
- **B12** 250 pmol/l , **acido folico** 9.8 mmol/l ;
- **Test di Coombs** diretto e indiretto negativi, aptoglobina 1.27 g/l, **LDH** 135 U/l;
- Ferro 75 µg/dl, transferrina 2.5 g/l, **ferritina** 250 µg/l;
- **Eco addome**: lieve epatomegalia con note steatosiche, milza regolare con diametro bipolare 10.6 cm, reni in sede, cisti corticale a dx diam. max 2.3 cm;
- Striscio SP: macrocitosi e anisopoichilocitosi delle emazie, **non blasti**.

Marzo 2011

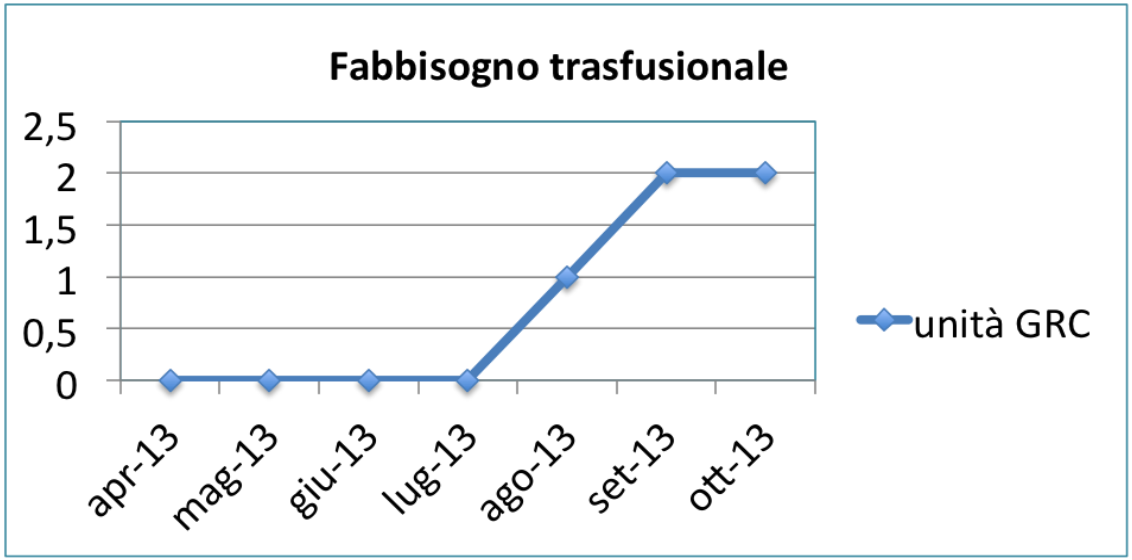
- BM: cellularità buona, rapporto mielo-eritroide 3:1. **Megacariociti** …menti **monolobati** e … e depressa con note di **m**
- Perls: non sid…
- Cariotipo: **46,**…
- BOM: sindron…
  citopenia refr…
  plurilineare, cellule CD34+<5%,
  non segnalata fibrosi.

MDS con del(5q) isolata
IPSS 0 (low)



Aprile 2013

- GB 3120/µl, Hb 9.5 g/dl, MCV 102 fl, PLT 265000/µl, neutrofili 1350/µl;
- B12 236 pmol/l, acido folico 9.4 mmol/l Ferro 68 µg/dl, transferrina 2.3 g/l, ferritina 258 µg/l;
- **EPO 287 U/l**.



Epoetina alfa
40000-80000 UI/wk

Ottobre 2013

- ECOG 2;
- GB 3000/µl, **Hb 5.6 g/dl**, PLT 247000/µl, neutrofili 1450/µl;
- **BM:** citologia compatibile con **MDS associata a del(5q) isolata, blasti<5%**;
- Cariotipo: 46,XX,del(5)(q15)[13]/46,XX[7].
- FISH: **Del 5q31 nel 65% dei nuclei esaminati**.
- Creatinina 0.66 mg/dl, ClCr 89 ml/min, TSH 1.96 mUI/l.

Lenalidomide 10 mg die per 21 giorni/28

Novembre 2013, g 15 ciclo 1

- **ECOG 3**, **TC 37.8° C**, riferisce **astenia marcata**, **dolori muscolari**, stipsi ostinata e una emissione di feci picee;
- GB 3020/µl, Hb 7.1 g/dl, PLT 223000/µl, MCV 113 fl, neutrofili 1170/µl, linfociti 1240/µl, monociti 290/µl, creatinina 0.97 mg/dl, ferritina 461µ/l, bilirubina totale 2,2 mg/dl, indiretta 1.72 mg/dl, PCR 5 mg/l, TSH 1.91 mUI/l.

Ricovero:

✓Trasfusa con 3 unità di GRC;
✓RSO, PCS e EGDS negativi.

D1. Alla luce dell'aumentato fabbisogno trasfusionale nelle prime settimane del trattamento e della flu-like syndrome di grado 3, la terapia:

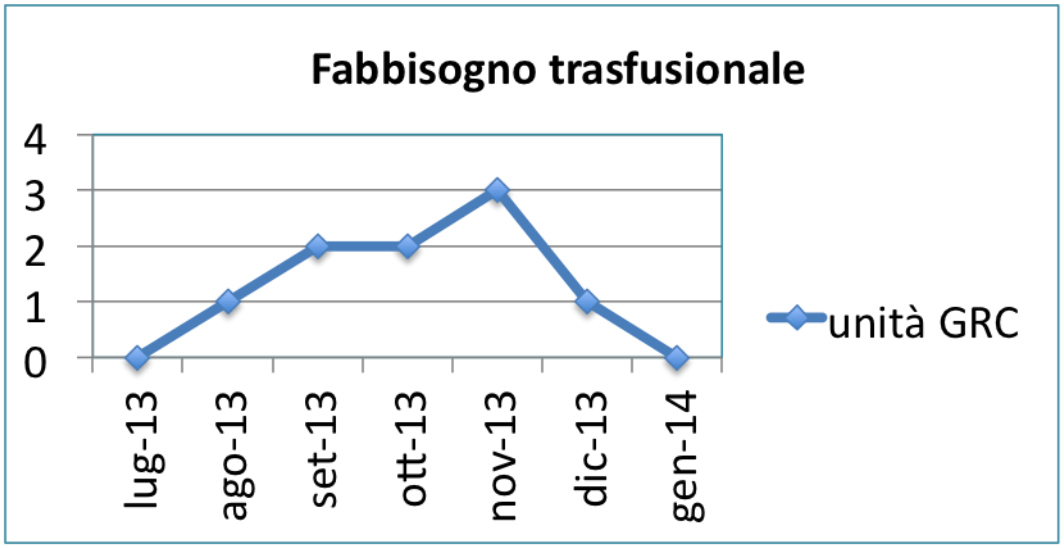
1. **Va sospesa per inefficacia**

2. **Va proseguita, ma solo dopo ripetizione di un aspirato midollare per escludere una progressione**

3. **Va proseguita, intensificando il supporto e valutando una eventuale riduzione del dosaggio**

Gennaio 2014, len10 mg, ciclo 3

- GB 3000/µl, **Hb 9.7 g/dl**, PLT 260000/µl, MCV 103 fl, neutrofili 1210/µl;



Caduta accidentale al domicilio con frattura del collo del femore destro trattata chirurgicamente con endoprotesi

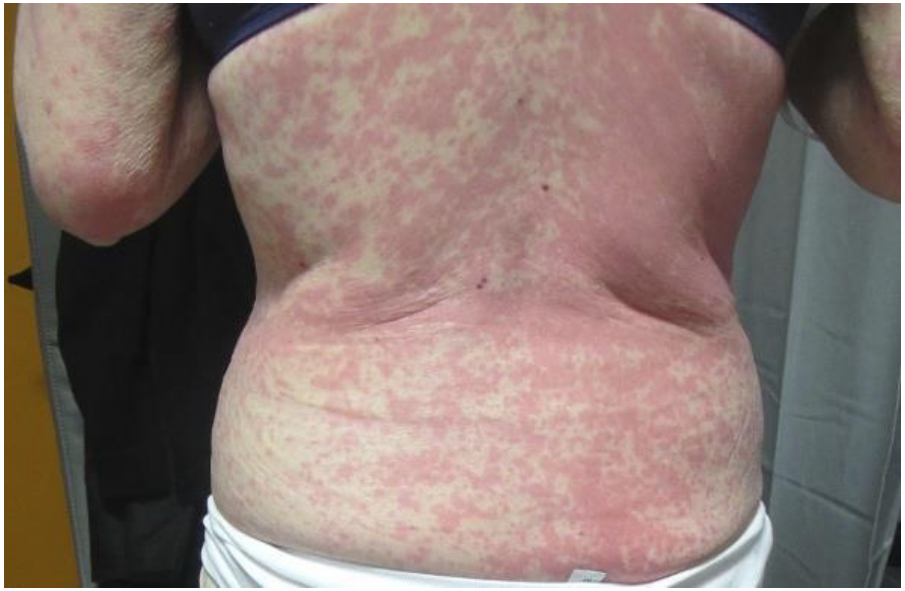
D2. Considerando il rischio trombotico secondario ad allettamento, intervento di chirurgia ortopedica e trattamento con lenalidomide, la terapia va sospesa?

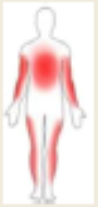
1. **Si, e ripresa solo ad avvenuta mobilizzazione**

2. **No, se in corso profilassi con LMWH**

Marzo 2014, len10 mg, ciclo 5

- GB 5970/µl, **Hb 11.9 g/dl**, PLT 237000/µl, PMN 1990/µl;
- Rash maculopapulare di grado 3 (CTACAE 3.0)



>30% of BSA	

Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Real-world analysis of the Celgene Global Drug Safety database: early discontinuation of lenalidomide in patients with myelodysplastic syndromes due to non-serious rash

Table 2 Actions taken with lenalidomide in the real world versus clinical trials for rash

Action taken with lenalidomide	Global Drug Safety database			MDS-003 clinical trial			MDS-004 clinical trial		
	Non-serious[a] (n=1,444)	Serious[a] (n=149)	Total (n=1,593)	Grade 1/2 (n=84)	Grade 3/4 (n=13)	Total (n=97)	Grade 1/2 (n=53)	Grade 3/4 (n=4)	Total (n=57)
Permanent discontinuation	378 (26.2)	79 (53.0)	457 (28.7)	0	3 (23.1)	3 (3.1)	1 (1.9)	0	1 (1.8)
Dose interruption	352 (24.4)	37 (24.8)	389 (24.4)	2 (2.4)	5 (38.5)	7 (7.2)	1 (1.9)	0	1 (1.8)
Dose reduction	191 (13.2)	11 (7.4)	202 (12.7)	1 (1.2)	3 (23.1)	4 (4.1)	0	2 (50.0)	2 (3.5)
No action taken	523 (36.2)	22 (14.8)	545 (34.2)	81 (96.4)	2 (15.4)	83 (85.6)	51 (96.2)	2 (50.0)	53 (93.0)

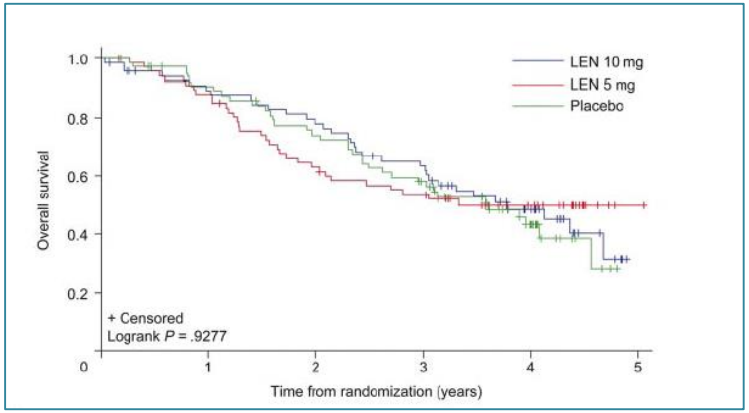
Notes: Data are presented as n (%). [a]Serious rash was defined as requiring hospitalization or intervention, disabling, an important medical event, life-threatening, or fatal; non-serious rash was defined as all other rash events.

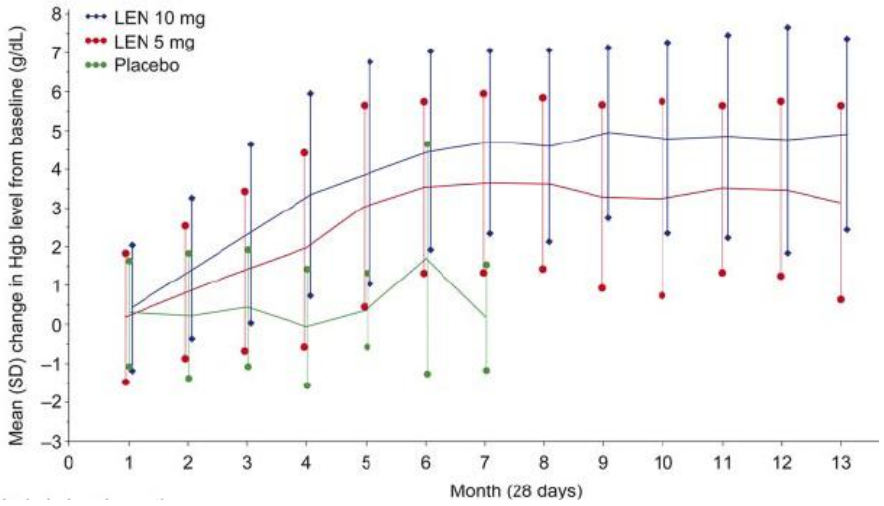
Weiss L et al, 2015

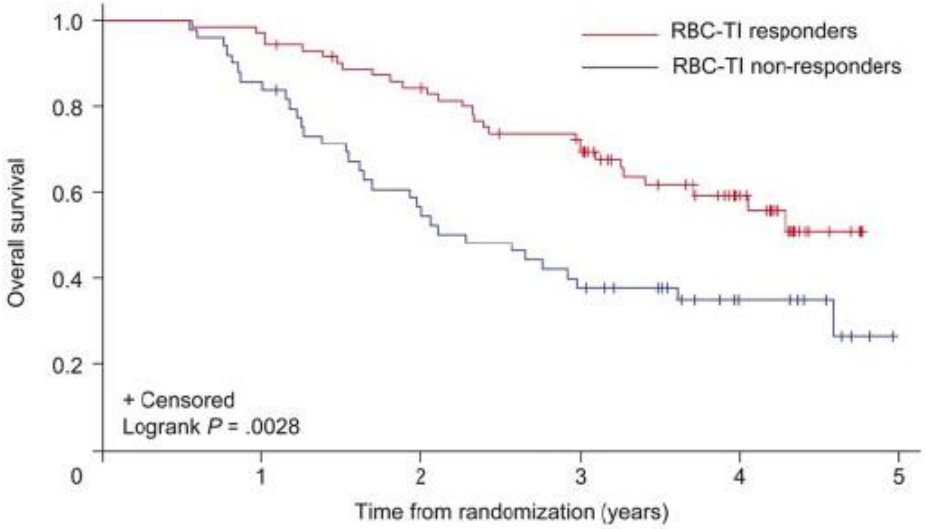
Plenary paper

A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q

Pierre Fenaux,[1] Aristoteles Giagounidis,[2] Dominik Selleslag,[3] Odile Beyne-Rauzy,[4] Ghulam Mufti,[5] Moshe Mittelman,[6] Petra Muus,[7] Peter te Boekhorst,[8] Guillermo Sanz,[9] Consuelo del Cañizo,[10] Agnes Guerci-Bresler,[11] Lars Nilsson,[12] Uwe Platzbecker,[13] Michael Lübbert,[14] Bruno Quesnel,[15] Mario Cazzola,[16] Arnold Ganser,[17] David Bowen,[18] Brigitte Schlegelberger,[17] Carlo Aul,[2] Robert Knight,[19] John Francis,[19] Tommy Fu,[19] and Eva Hellström-Lindberg,[20] for the MDS-004 Lenalidomide del5q Study Group







D3. Alla comparsa di tossicità cutanea severa (G3):

1. **Si prosegue lenalidomide, associando antistamici e steroidi topici**

2. **Si sospende lenalidomide, associando antistamici e steroidi topici e/o sistemici, e si riprende alla risoluzione del sintomo a dosaggio ridotto**

3. **Si sospende lenalidomide definitivamente**

4. **Si sospende lenalidomide temporaneamente, somministrando eritropoetina per mantenere la risposta ematologica**

Marzo 2014, STOP lenalidomide, Epoetina alfa 40000 U/w

- GB 4180/µl, **Hb 13.7 g/dl**, PLT 234000/µl, PMN 1970/µl;

PLOS | ONE

RESEARCH ARTICLE

Lenalidomide Induces Lipid Raft Assembly to Enhance Erythropoietin Receptor Signaling in Myelodysplastic Syndrome Progenitors

Kathy L. McGraw[1], Ashley A. Basiorka[2], Joseph O. Johnson[3], Justine Clark[1], Gisela Caceres[4], Eric Padron[1], Ruth Heaton[5], Yukiyasu Ozawa[6], Sheng Wei[7], Lubomir Sokol[1], Alan F. List[1]*

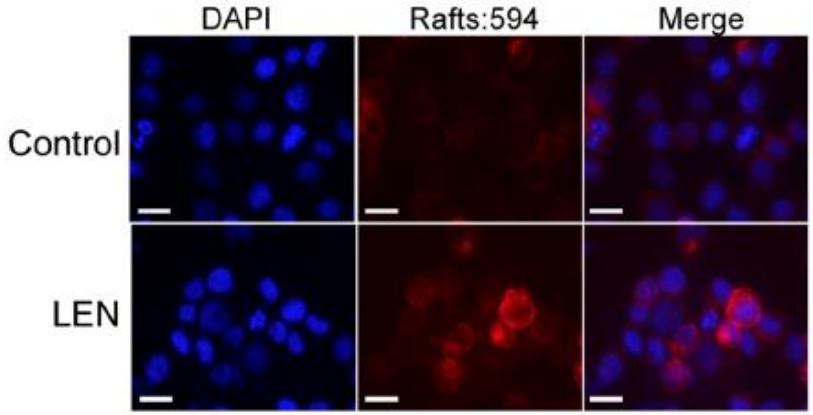
1. Department of Malignant Hematology, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, United States of America, 2. Department of Malignant Hematology, H. Lee Moffitt Cancer Center-Cancer Biology Ph.D. Program, University of South Florida, 12902 Magnolia Drive, Tampa, FL, 33612, United States of America, 3. Analytic Microscopy Core Facility, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL, 33612, United States of America, 4. Morsani Molecular Diagnostic Laboratory, H. Lee Moffitt Cancer Center, 10902 N. McKinley Drive, Tampa, FL, 33612, United States of America, 5. Department of Pathology, University of Arizona, 1501 N Campbell Ave, Tucson, AZ, 85724, United States of America, 6. Department of Hematology, Japanese Red Cross Nagoya First Hospital, 3-35 Michishita-cho, Nakamura-ku, Aichi, 453-8511, Japan, 7. Department of Immunology, H. Lee Moffitt Cancer Center, 12902 Magnolia Drive Tampa, FL, 33612, United States of America

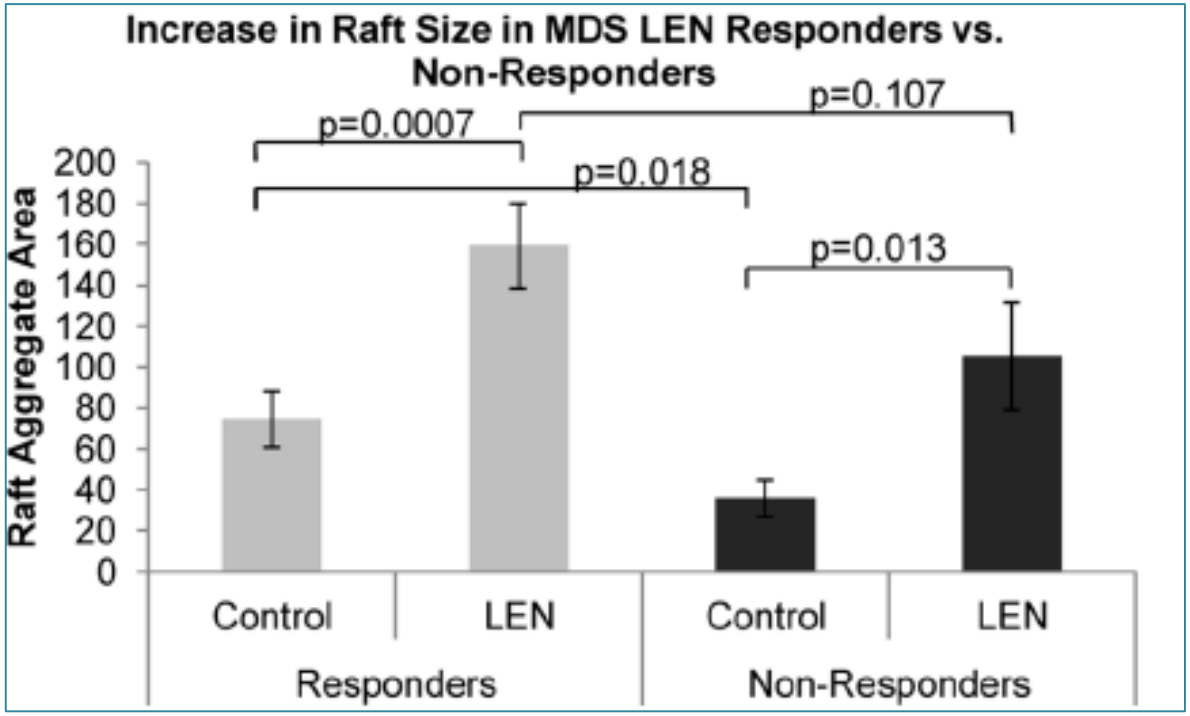
*Alan.List@moffitt.org

CrossMark click for updates

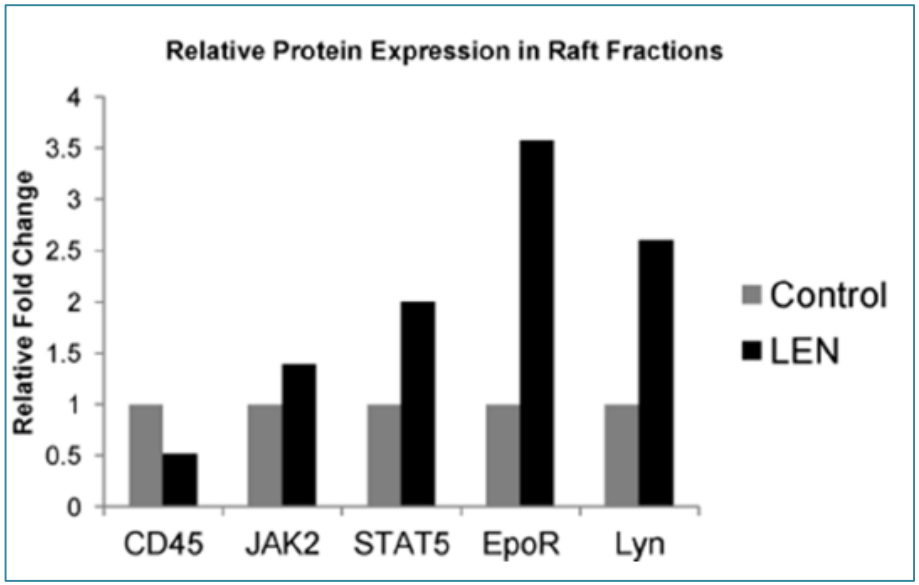
OPEN ACCESS

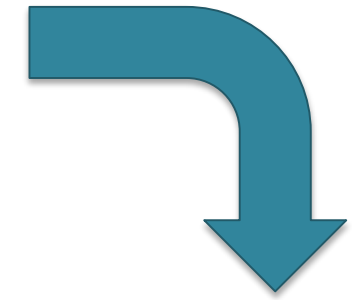
Citation: McGraw KL, Basiorka AA, Johnson JO, Clark J, Caceres G, et al. (2014) Lenalidomide Induces Lipid Raft Assembly to Enhance Erythropoietin Receptor Signaling in Myelodysplastic Syndrome Progenitors. PLoS ONE 9(12): e114249. doi:10.1371/journal.pone.0114249

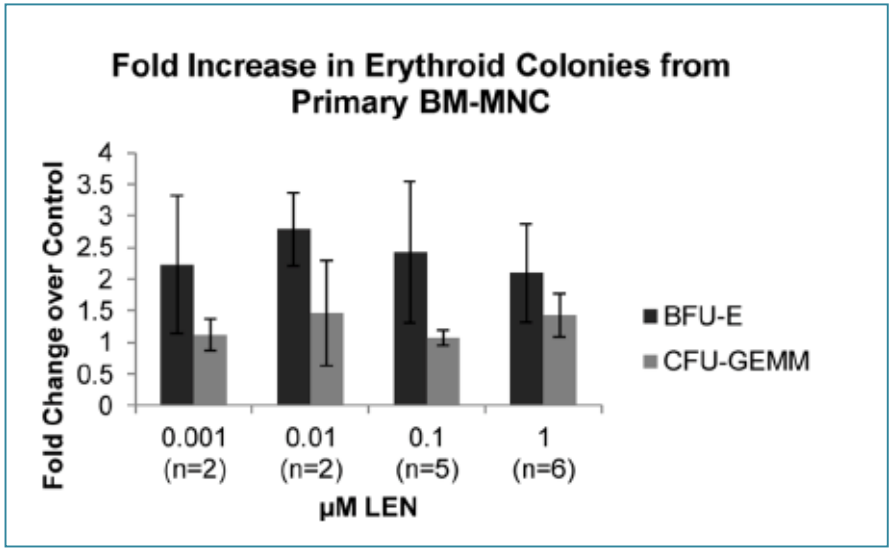




McGraw K et al,2014







McGraw, K et al, 2014

Aprile 2014, len5mg, ciclo 6

- GB 5200/µl, **Hb 12.8 g/dl**, PLT 230000/µl, PMN 2080/µl; creatinina 0.82 mg/dl;
- **BM:** cellularità discreta, rapporto M:E 1:1, **ritardo maturativo mieloide** con scarsa presenza di elementi segmentati, filiera eritroide ridondante con **megaloblastosi**, **megacariociti** presenti e **displastici**, **blasti<5%**;
- Cariotipo: non metafasi esaminabili;
- **FISH: del5q31 nel 53% dei nuclei esaminati**

D4. La paziente non ha ottenuto, al ciclo 6, una risposta citogenetica, pertanto:

1. La terapia va sospesa per inefficacia

2. La terapia va proseguita perché c'è stata comunque una risposta ematologica con ottenimento dell'indipendenza trasfusionale

3. La terapia va proseguita e il dosaggio di lenalidomide può essere nuovamente aumentato a 10 mg se non ricompare rash o altra tossicità

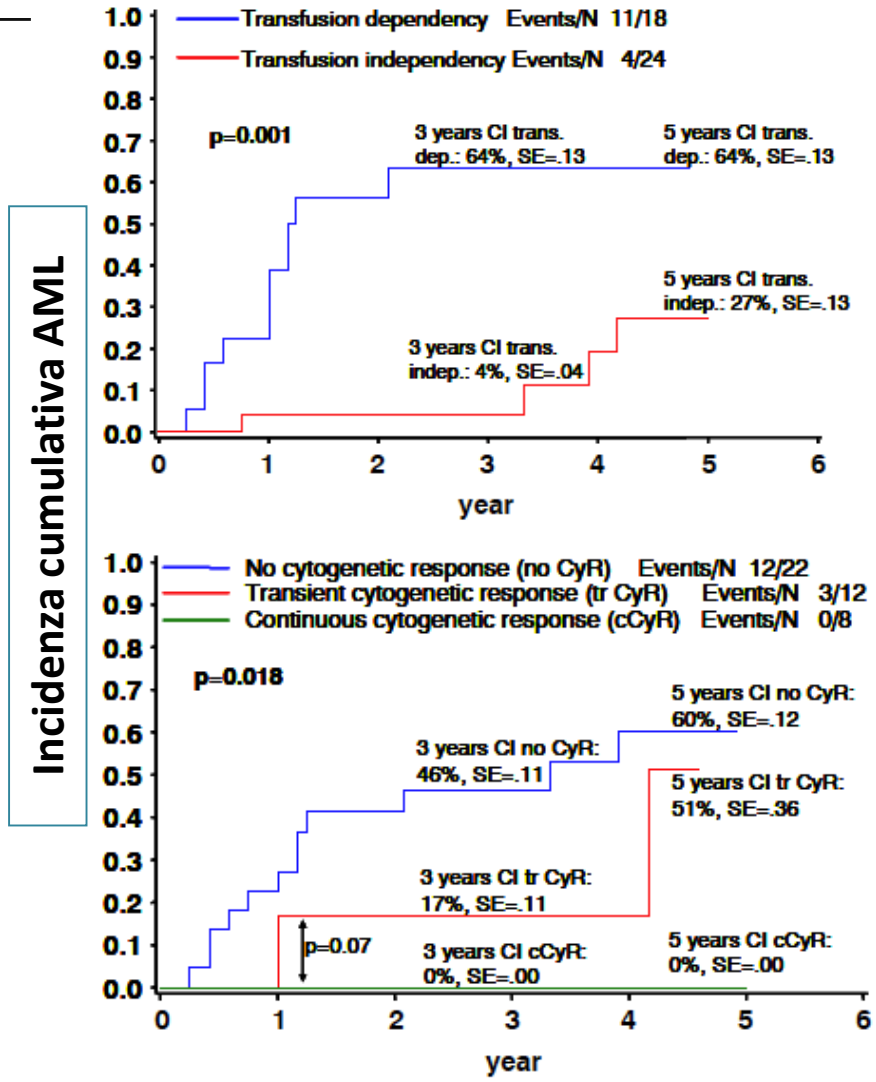
Ann Hematol (2010) 89:365–374
DOI 10.1007/s00277-009-0846-z

ORIGINAL ARTICLE

Patients with del(5q) MDS who fail to achieve sustained erythroid or cytogenetic remission after treatment with lenalidomide have an increased risk for clonal evolution and AML progression

Gudrun Göhring · Aristoteles Giagounidis · Guntram Büsche · Hans Heinrich Kreipe · Martin Zimmermann · Eva Hellström-Lindberg · Carlo Aul · Brigitte Schlegelberger

- Nello studio MDS-004 la probabilità di ottenere una TI e la CyCR era dose-dipendente (50% nel braccio 10 mg e 25% nel braccio 5 mg);
- 42 pazienti arruolati nello studio MDS-003 e seguiti per FU mediano di 40 mesi.



OPEN

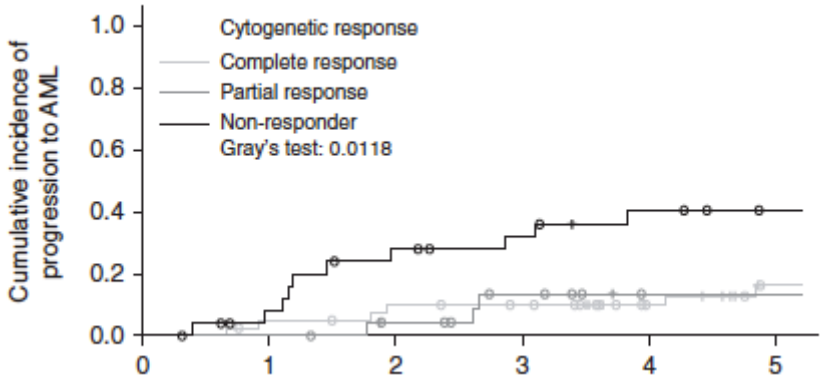
Leukemia (2014) **28**, 1033–1040

www.nature.com/leu

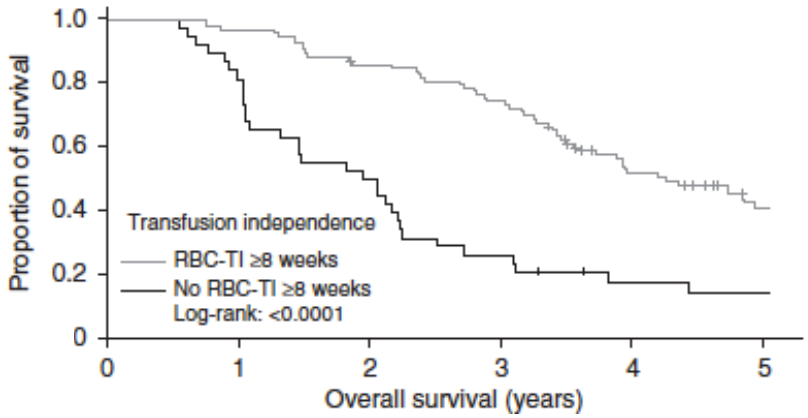
ORIGINAL ARTICLE

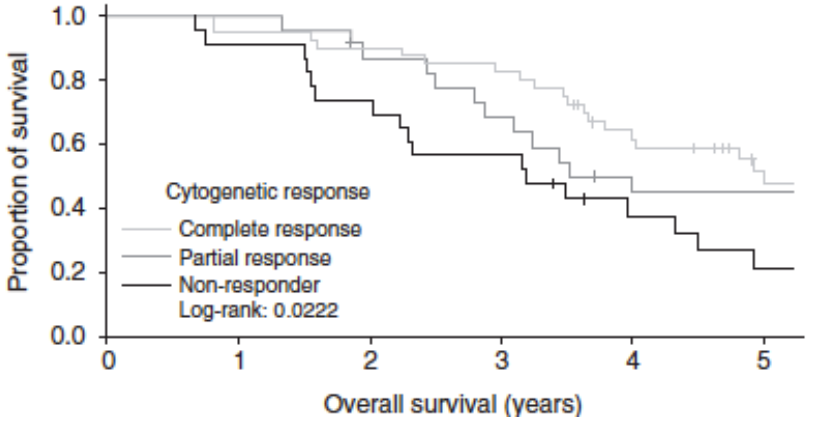
Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS

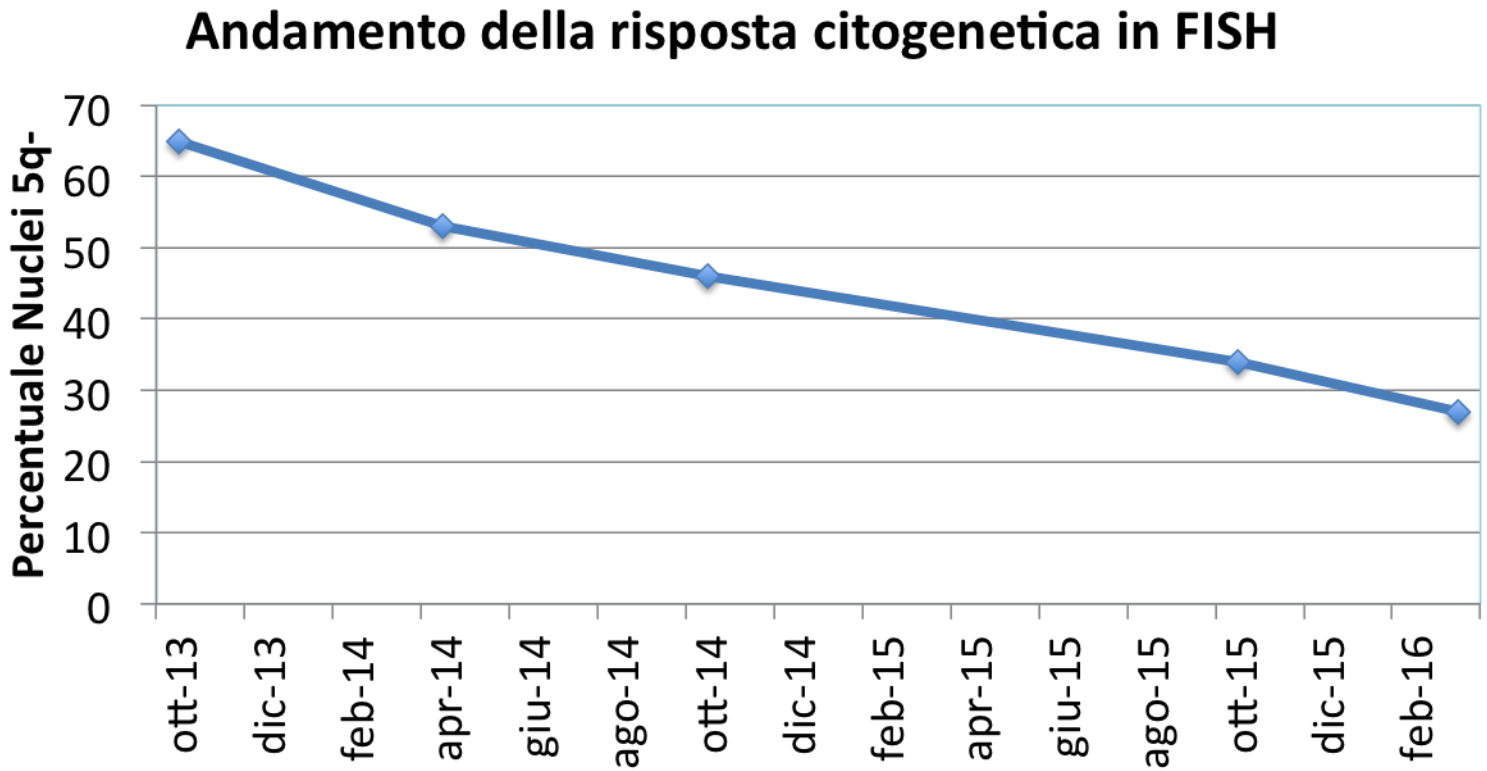
AF List[1], JM Bennett[2], MA Sekeres[3], B Skikne[4], T Fu[4], JM Shammo[5], SD Nimer[6], RD Knight[4] and A Giagounidis[7] on behalf of the MDS-003 Study Investigators[8]

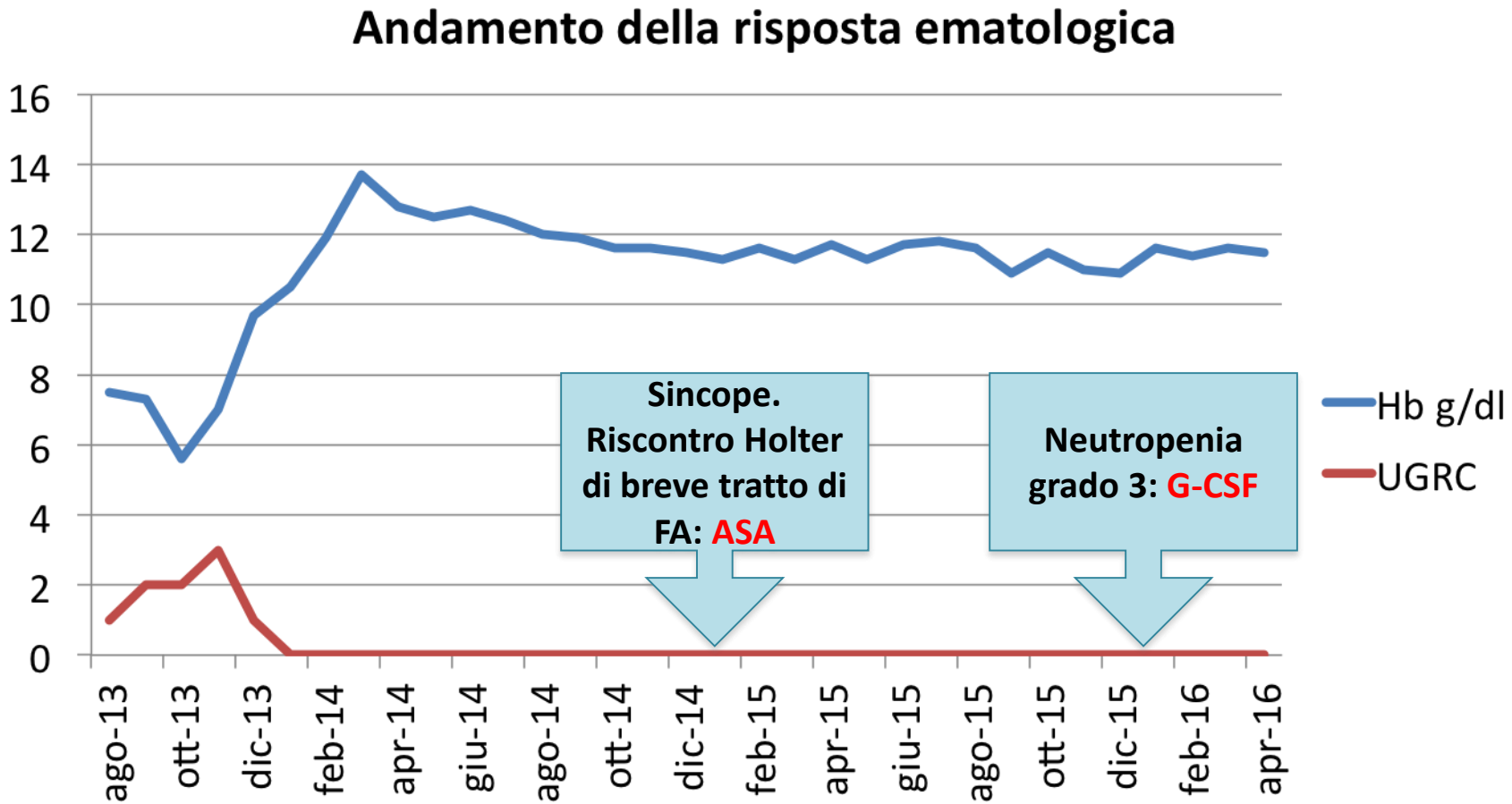


"Optimizing RBC-TI and cytogenetic response may, therefore, maximize the disease-modifying potential of lenalidomide".






Andamento della risposta citogenetica in FISH
Percentuale Nuclei 5q-
70
60
50
40
30
20
10
0
ott-13
dic-13
feb-14
apr-14
giu-14
ago-14
ott-14
dic-14
feb-15
apr-15
giu-15
ago-15
ott-15
dic-15
feb-16


Andamento della risposta ematologica
16
14
12
10
8
6
4
2
0
ago-13
ott-13
dic-13
feb-14
apr-14
giu-14
ago-14
ott-14
dic-14
feb-15
apr-15
giu-15
ago-15
ott-15
dic-15
feb-16
apr-16
Sincope. Riscontro Holter di breve tratto di FA: ASA
Neutropenia grado 3: G-CSF
Hb g/dl
UGRC

Grazie

Comprehensive Geriatric Assessment (GCA) in oncoematologia

Scala	FIT	UNFIT	FRAIL
ADL	6	5 funzioni residue	<=4 funzioni residue
IADL	8	7-6 funzioni residue	<=5 funzioni residue
CIRS	Score 3-4: 0 Score 2: <=5	Score 3-4: 0 Score 2: 5-8	Score 3-4: 1 Score 2: >8
Età		>=80 aa	>=80 aa

haematologica | 2011; 96(3)

DECISION MAKING AND PROBLEM SOLVING

Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome

Matteo G. Della Porta,[1] Luca Malcovati,[1] Corinna Strupp,[2] Ilaria Ambaglio,[1] Andrea Kuendgen,[2] Esther Zipperer,[2] Erica Travaglino,[3] Rosangela Invernizzi,[3] Cristiana Pascutto,[1] Mario Lazzarino,[1] Ulrich Germing,[2] and Mario Cazzola[1]

[1]Department of Hematology Oncology, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine-University, Dusseldorf, Germany; and [3]Department of Medicine, University of Pavia & Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Comorbidity	HR obtained through a multivariable Cox's survival analysis with NLD as an outcome	Variable weighted score (to be taken into account if the specific comorbidity is present)
Cardiac disease	3.57 (P<0.001)	2
Moderate-to-severe hepatic disease	2.55 (P=0.01)	1
Severe pulmonary disease	2.44 (P=0.005)	1
Renal disease	1.97 (P=0.04)	1
Solid tumor	2.61 (P<0.001)	1

MDS-CI risk	Sum of individual variable scores	Proportion of patients in the learning cohort belonging to the risk group (%)
Low risk	0	546/840 (65%)
Intermediate risk	1-2	244/840 (29%)
High risk	>2	50/840 (6%)

NLD: non-leukemic death.

Leukemia Research 39 (2015) 846–852

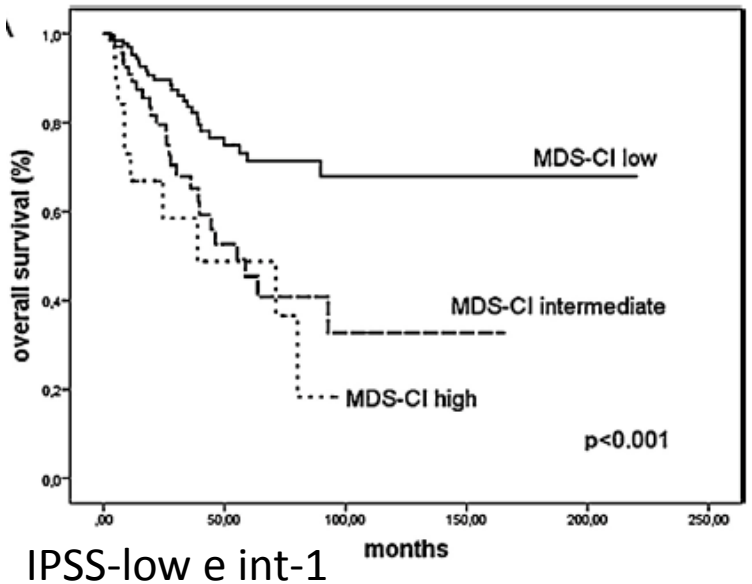
Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Age and comorbidities deeply impact on clinical outcome of patients with myelodysplastic syndromes

E. Balleari[a,*], C. Salvetti[a], L. Del Corso[a], R. Filiberti[b], A. Bacigalupo[a], A. Bellodi[a], G. Beltrami[a], M. Bergamaschi[a], G. Berisso[c], T. Calzamiglia[d], A.M. Carella[a], M. Cavalleri[e], A. Da Col[a], S. Favorini[a], G.L. Forni[f], R. Goretti[g], M. Miglino[a], L. Mitscheuning[a], E. Molinari[a], O. Racchi[h], M. Scudeletti[e], R. Tassara[i], M. Gobbi[a], R. Lemoli[a], M. Clavio[a]



IPSS-low e int-1

- La presenza di **comorbidità** impatta negativamente sulla sopravvivenza dei pazienti con MDS, indipendemente da IPSS e IPSS-R;
- I pazienti con **età** superiore a 75 anni, adjusted per IPSS, IPSS-R e comorbidity score, hanno un rischio di morte del 40% maggiore rispetto ai pazienti più giovani;
- L'incidenza complessiva degli eventi avversi nei pazienti trattati con lenalidomide non aumenta nei pazienti>65 aa, ma i **SAE** sono **più frequenti** (54% vs. 33%);
- I dati clinici mostrano che **ORR** a lenalidomide è simile in tutti i gruppi di età (List, 2005);
- E' cruciale considerare età e comorbidità nella pianificazione del trattamento.

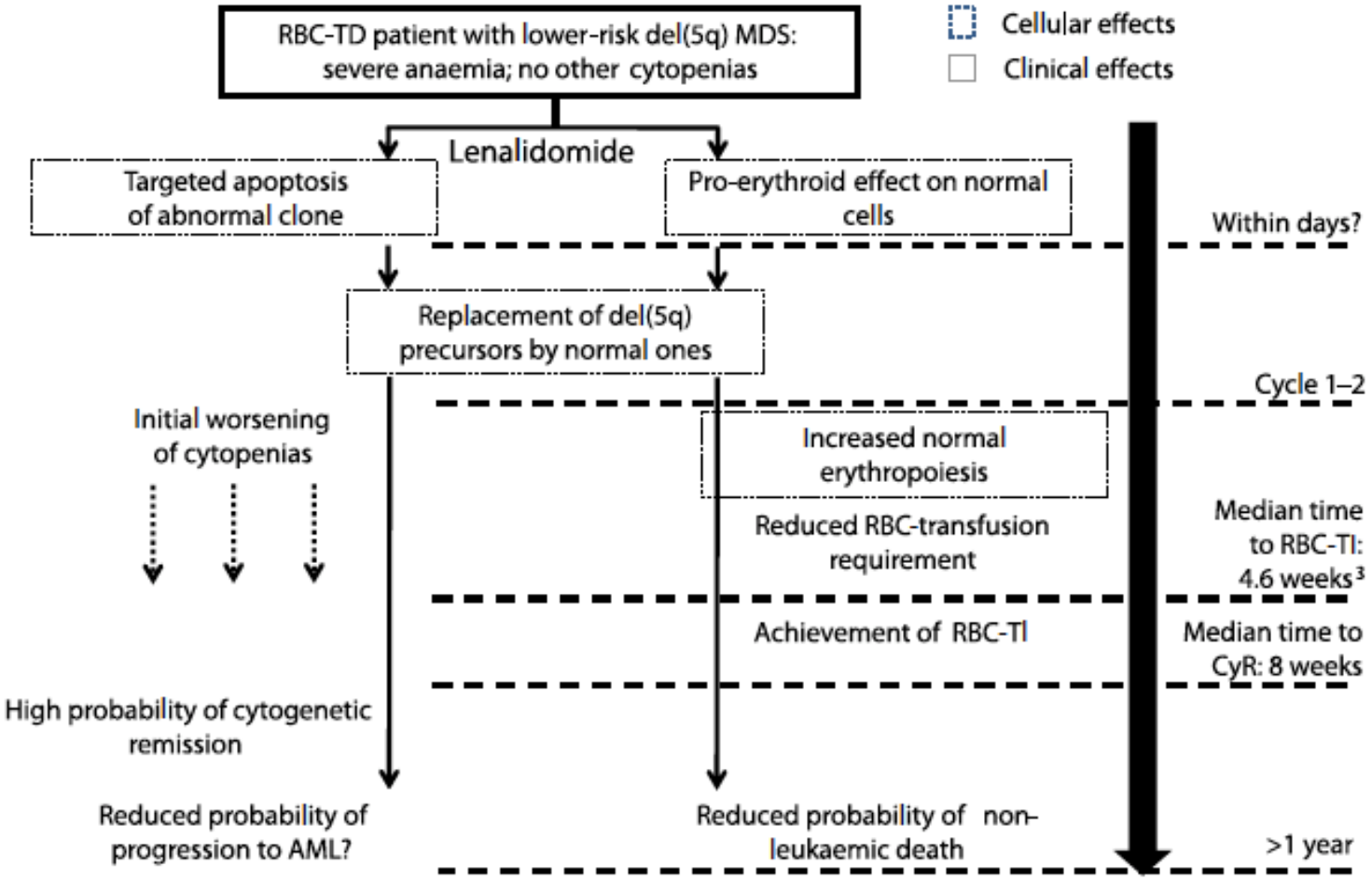
Ann Hematol (2014) 93:1–11
DOI 10.1007/s00277-013-1863-5

REVIEW ARTICLE

Lenalidomide as a disease-modifying agent in patients with del(5q) myelodysplastic syndromes: linking mechanism of action to clinical outcomes

Aristoteles Giagounidis · Ghulam J. Mufti · Pierre Fenaux · Ulrich Germing · Alan List · Kyle J. MacBeth

Gene		Effect of lenalidomide		Functional effect
SPARC	→	Increased expression in MDS CD34+ cells ex vivo	→	Inhibits proliferation and adhesion
EGR1	→	Increased expression in an MDS-derived del(5q) cell line	→	Reduced proliferation
CDC25c PP2A	→	Direct inhibition of CDC25c, indirect inhibition of PP2A	→	G_1 and G_2M arrest and apoptosis
RPS14	→	Increased in patients with del(5q)	→	Erythroid response
miR-145 miR-146a	→	Increased in patients with del(5q)	→	Anti-inflammatory?
DIAPH	→	To be determined	→	Immunomodulatory? Antiproliferative?



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ORIGINAL RESEARCH

Early lenalidomide treatment for low and intermediate-1 International Prognostic Scoring System risk myelodysplastic syndromes with del(5q) before transfusion dependence

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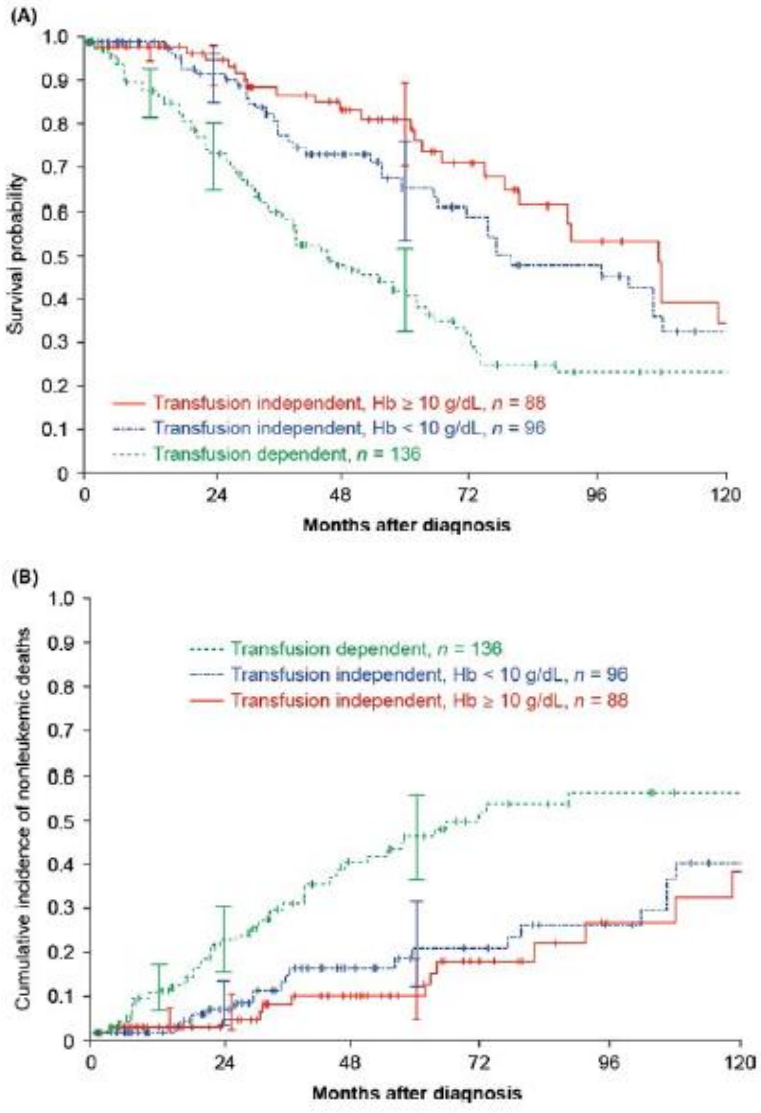

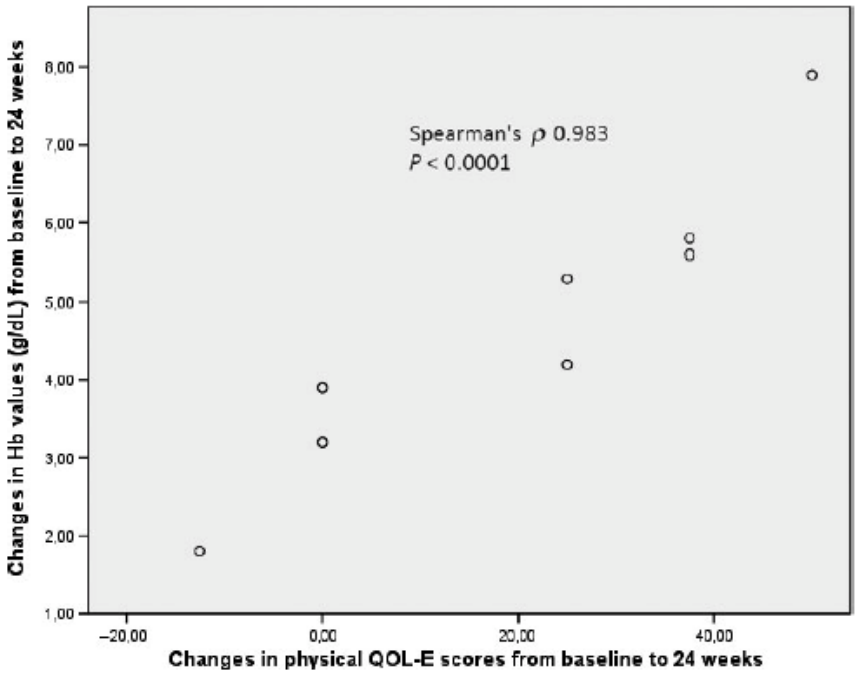

TI con Hb<10 g/dl