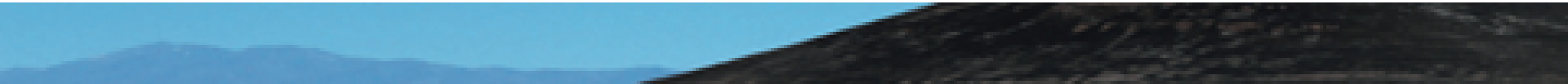
9th EDITION
Highlights from EHA

NOVITA' DALL'EHA: LE MIELODISPLASIE

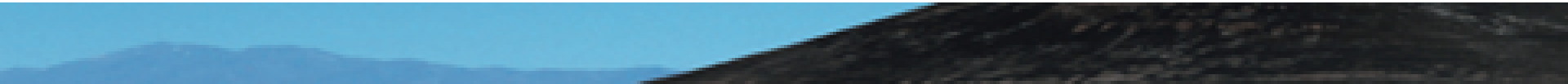
Dott. Roberto Latagliata

Ematologia – Università "Sapienza", Roma



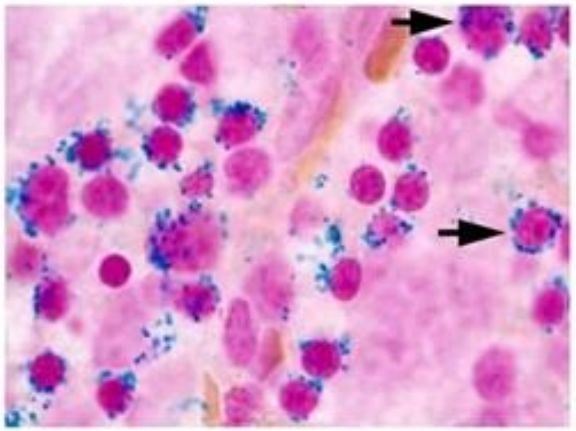
SINDROMI MIELODISPLASTICHE: IN QUALI ASPETTI LE PIU'IMPORTANTI NOVITA' DALL'EHA?

- **CLASSIFICAZIONE (WHO 2016)**
- **PROGNOSI (le alterazioni molecolari servono?)**
- **TERAPIA (bassi rischi/alti rischi)**



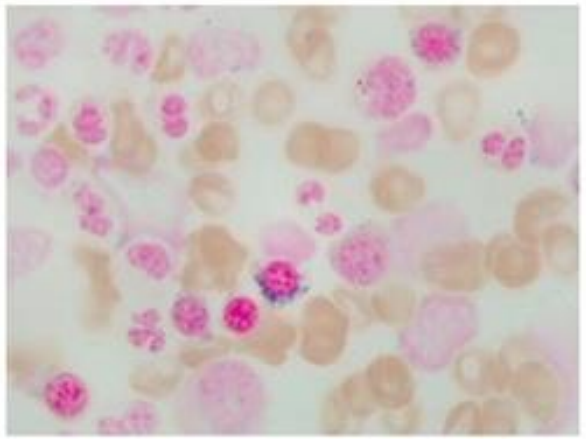
CLASSIFICAZIONE WHO 2008

Sideroblasti ad anello ≥ 15%



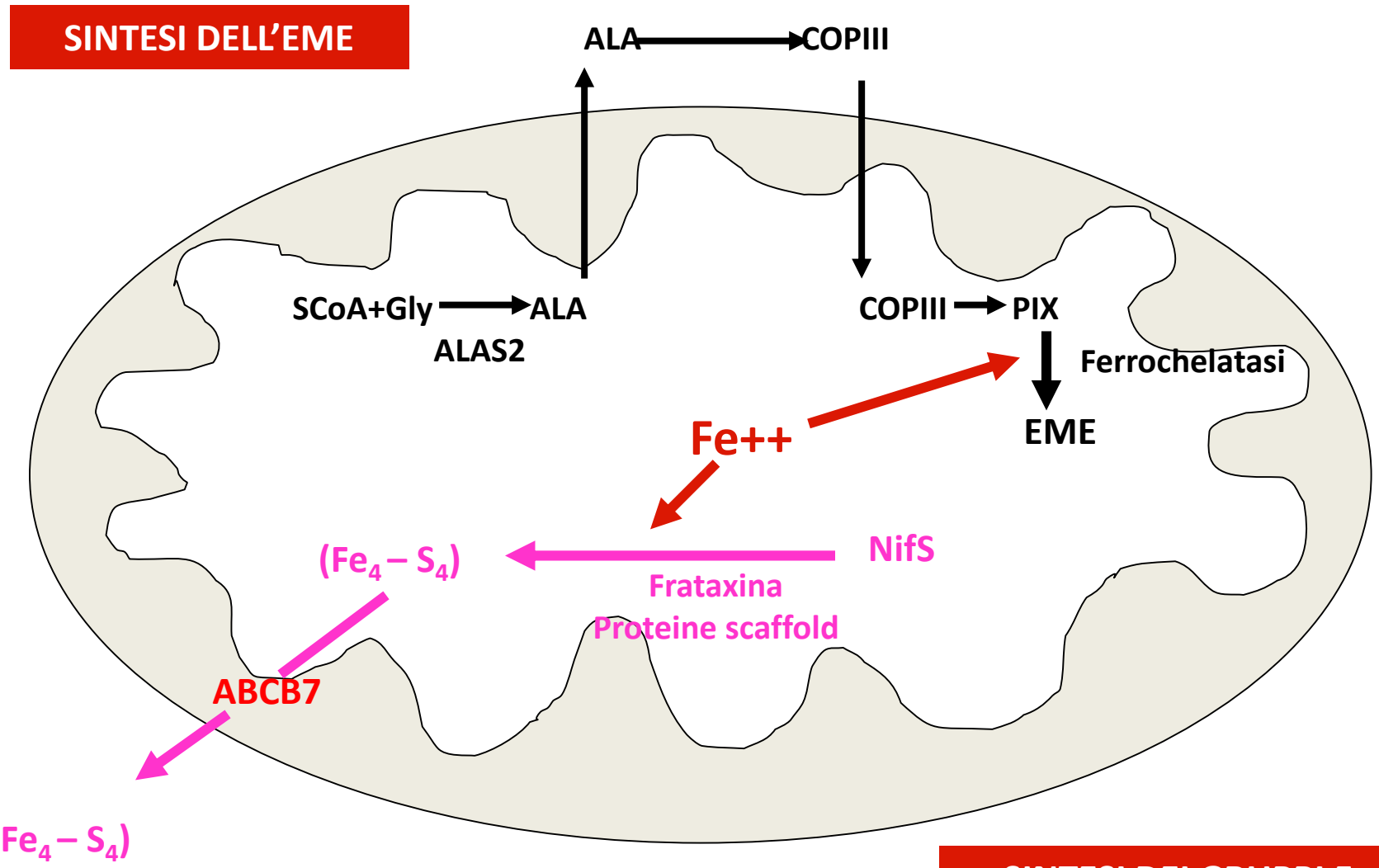
RARS

Sideroblasti ad anello 5 -14%

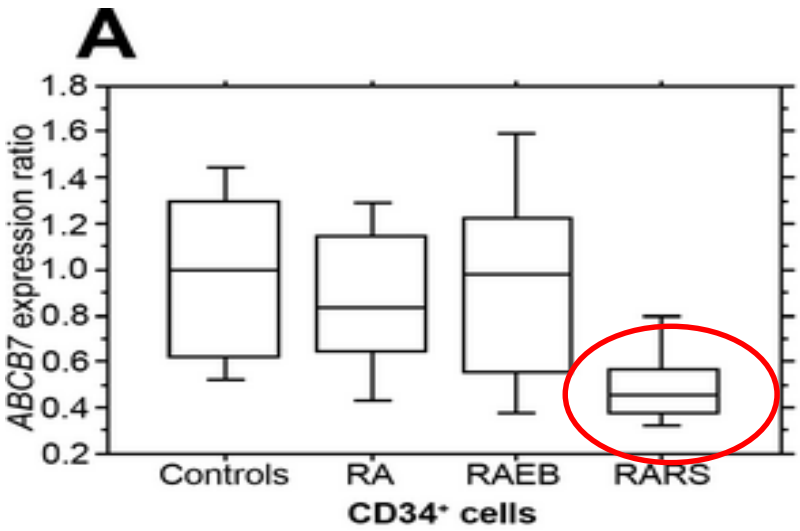


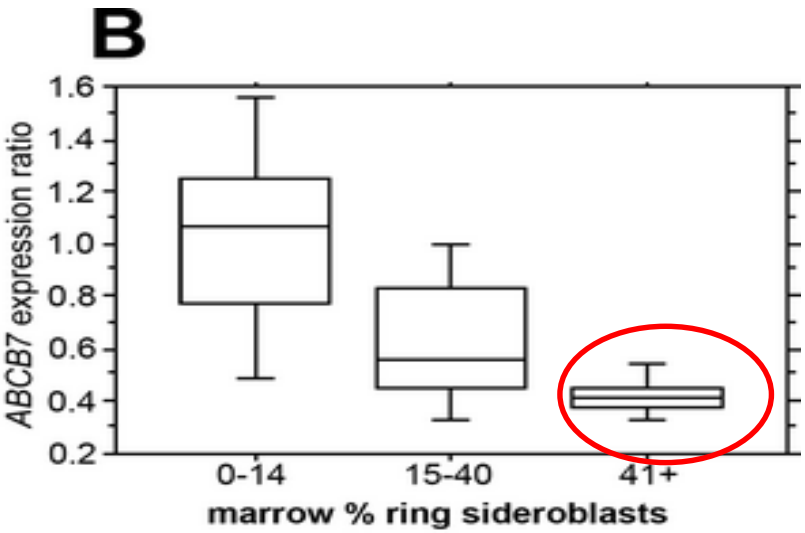
RA/ICUS

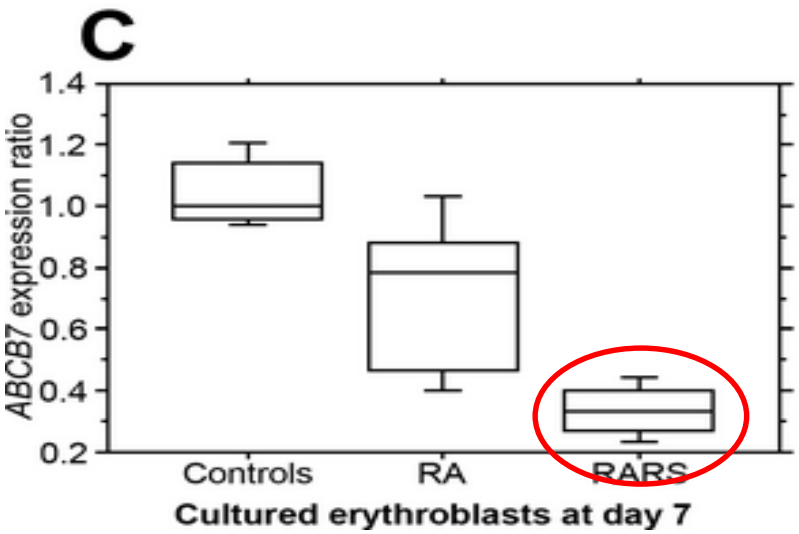
METABOLISMO MITOCONDRIALE DEL FERRO



DEREGOLAZIONE PRIMITIVADEL FERRO NELLE MIELODISPLASIE: ALTERATA ESPRESSIONE DI ABCB7



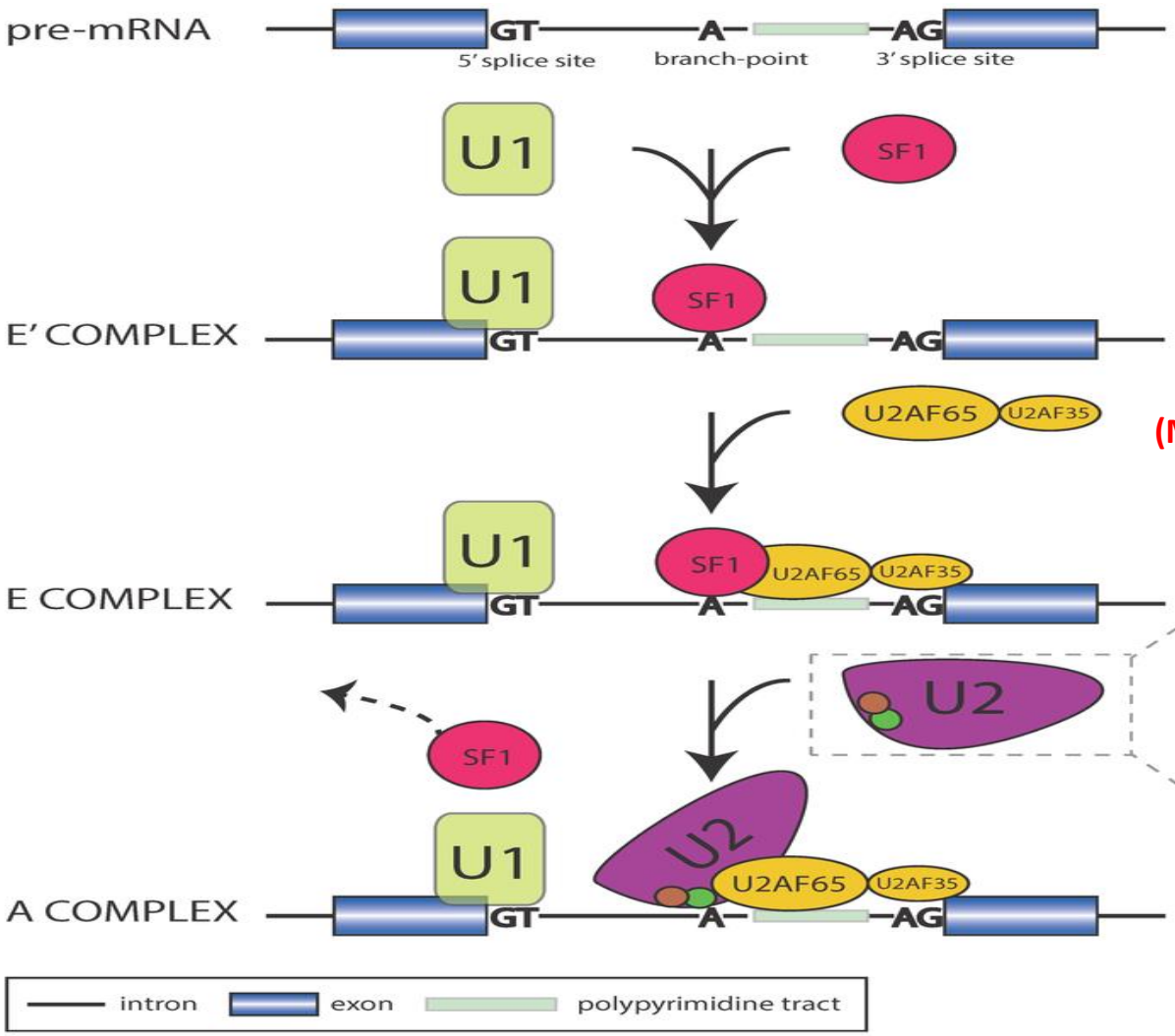




Boultwood J, et al. PLoS One. 2008 Apr 9; 3(4):e1970.

LO SPLICEOSOMA: COSA E' E COME FUNZIONA

LO SPLICEOSOMA: COSA E' E COME FUNZIONA (2)



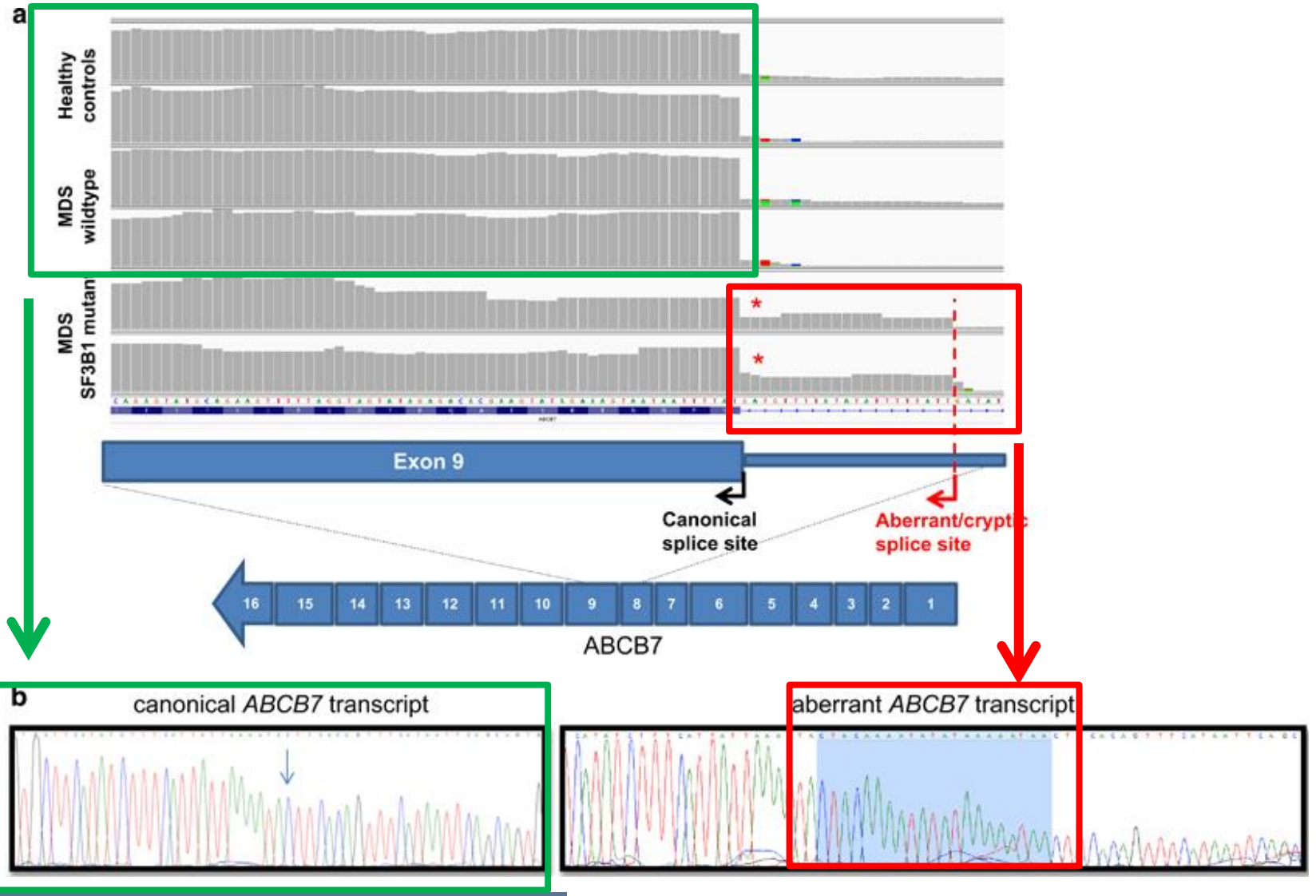
Riduzione quantitativa e/o qualitativa di ABCB7?

Mutato nell'81% delle RARS

(Malcovati et al, Blood 2015, 126:233-41)

Fredericks AM, et al. Biomolecules 2015, 5(2), 893-909

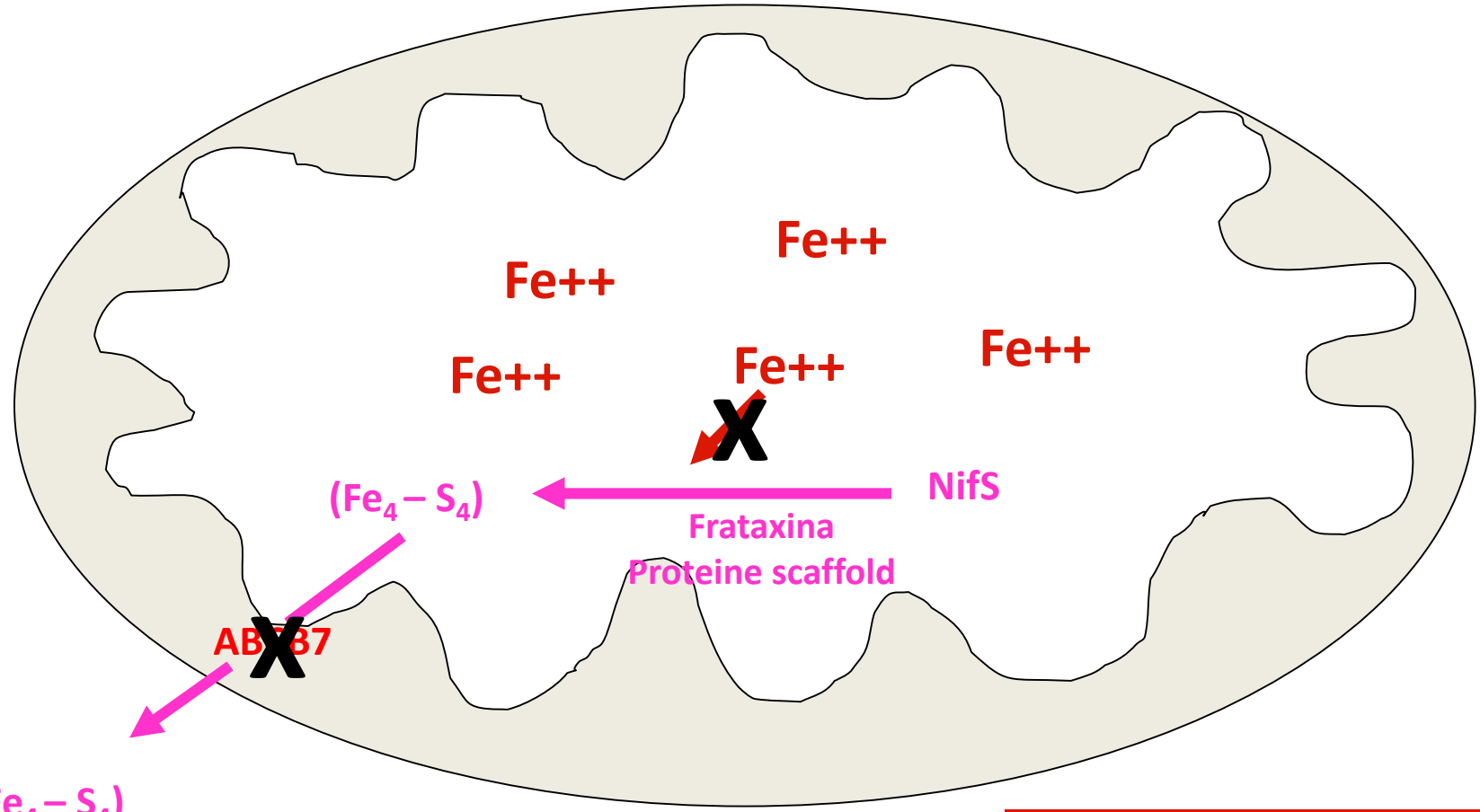
DALLA MUTAZIONE DI SF3B1 ALL'ALTERAZIONE DI ABCB7



Boultwood J, EHA 2016, SWG - MDS

Dolatshad H et al, Leukemia 2016 [Epub ahead of print]

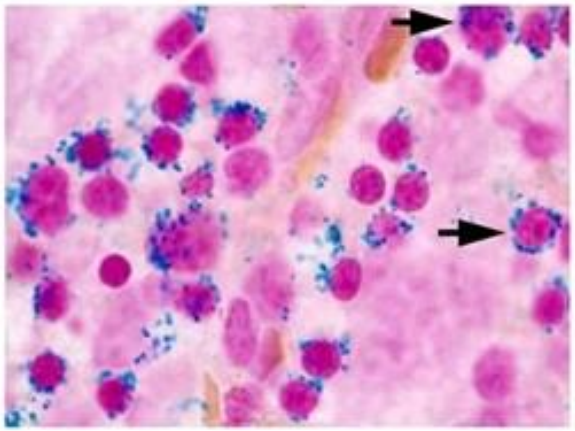
METABOLISMO MITOCONDRIALE DEL FERRO



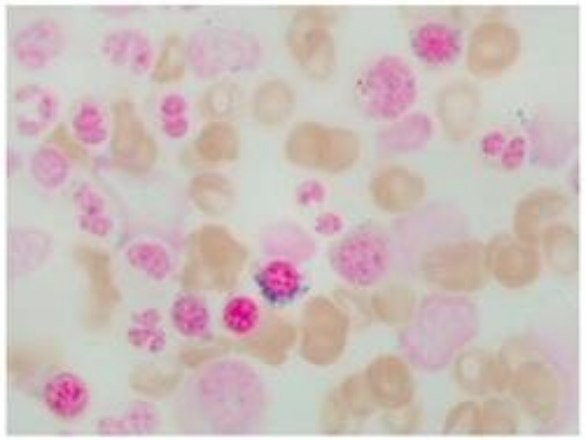
SINTESI DEI GRUPPI Fe-S

CLASSIFICAZIONE WHO 2016

Sideroblasti ad anello ≥ 15%



Sideroblasti ad anello 5 -14%



MDS-RS

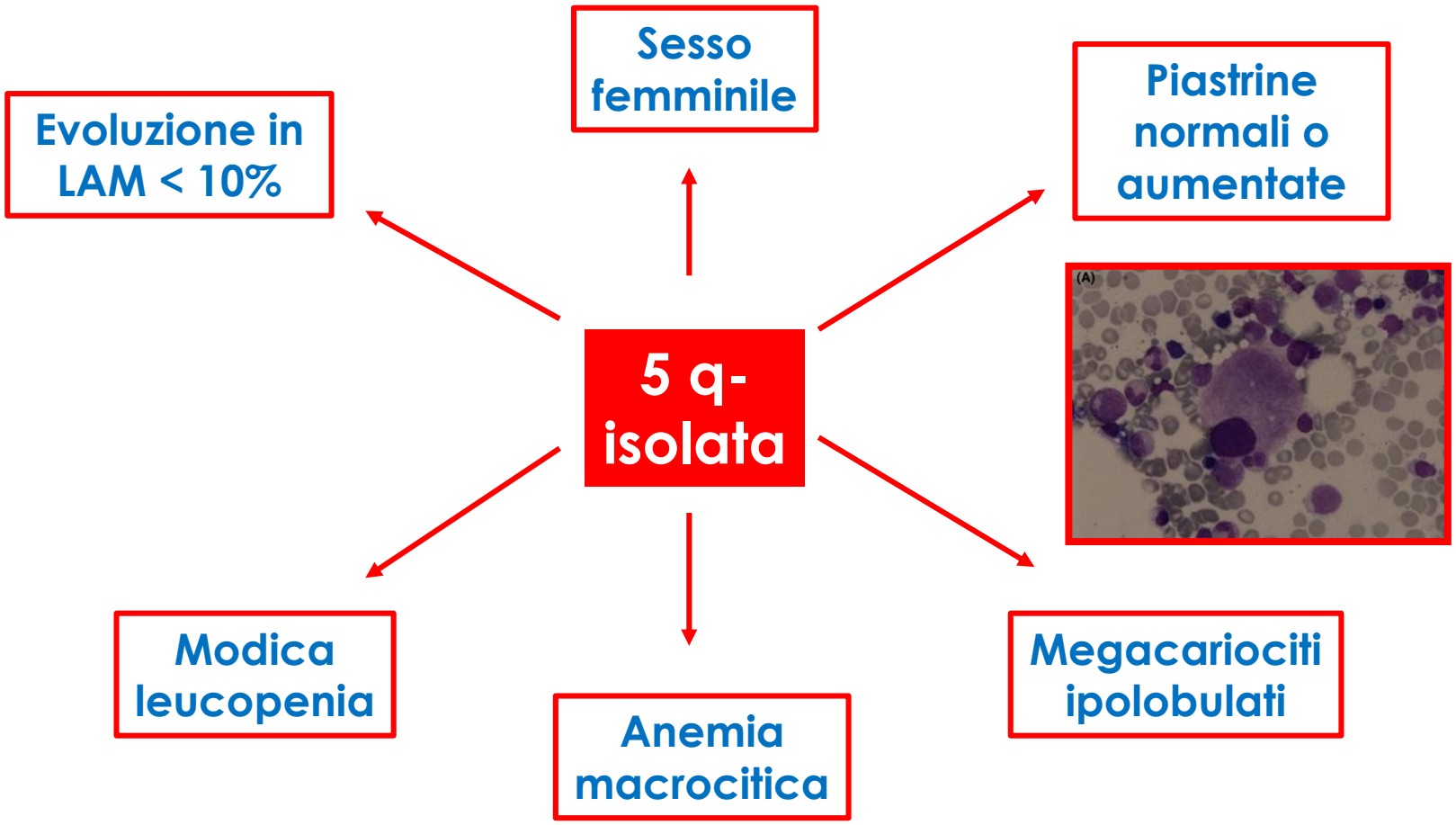
RA/ICUS

+ mutazione SF3B1

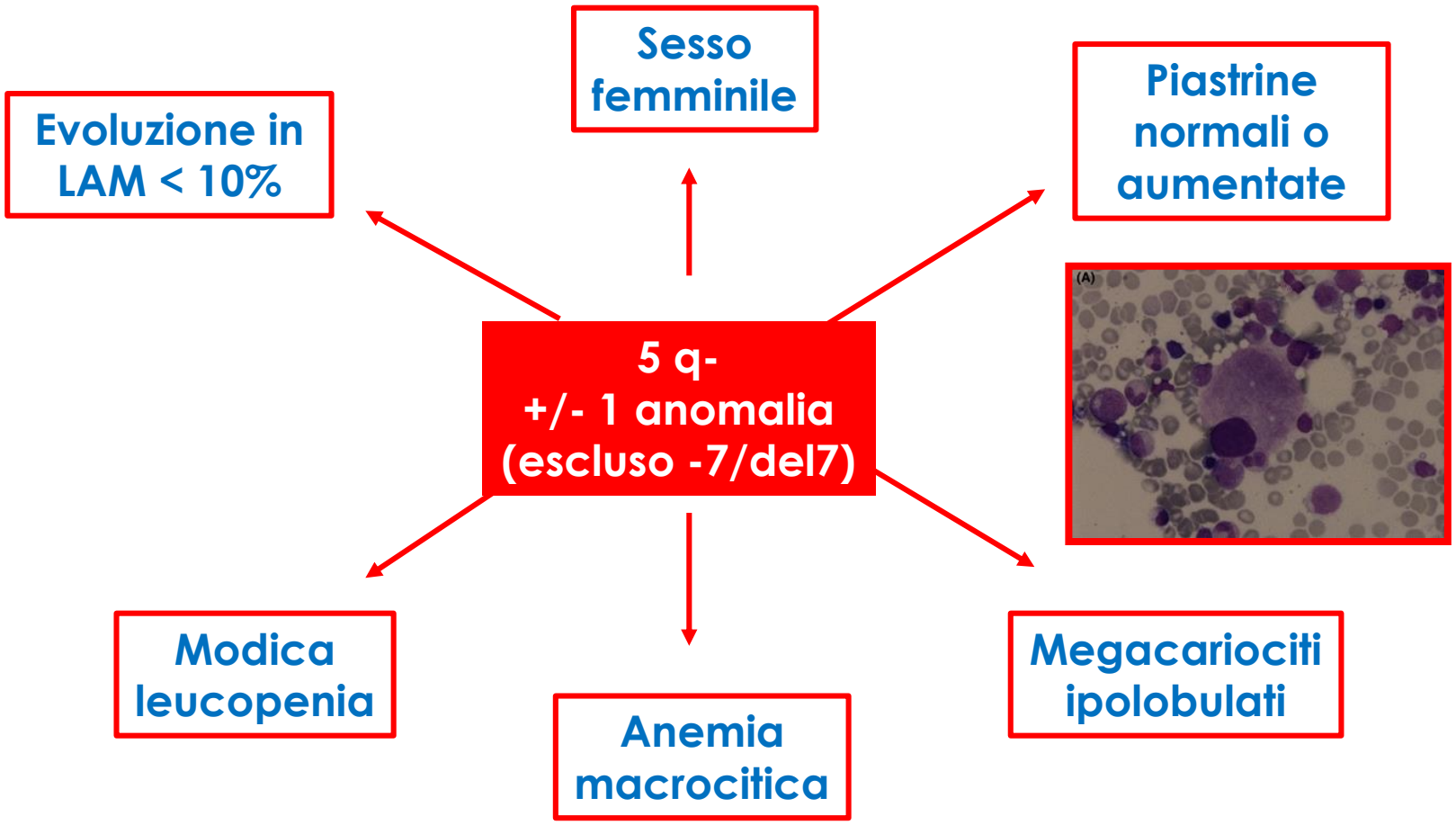
Bejar R, EHA 2016, educational session

Arber et al, Blood 2016:127;2391-405

SINDROME DEL 5q- (WHO 2008)
CARATTERISTICHE CLINICO-MORFOLOGICHE



SINDROME DEL 5q- (WHO 2016)
CARATTERISTICHE CLINICO-MORFOLOGICHE



Bejar R, EHA 2016, educational session

Arber et al, Blood 2016:127;2391-405

SMD ED ERITROLEUCEMIA:COSA CAMBIA?

SE ERB > 50%
NEL MIDOLLO....

WHO 2008

....I BLASTI SI CONTANO SOLO SULLE CELLULE NON ERITROIDI

↓

LAM-M6

WHO 2016

....I BLASTI SI CONTANO SU TUTTE LE CELLULE COME QUANDO ERB < 50%

↓

MDS-EB

....paziente con ERB 55% e blasti 12%....

Saft L, EHA 2016, SWG - MDS

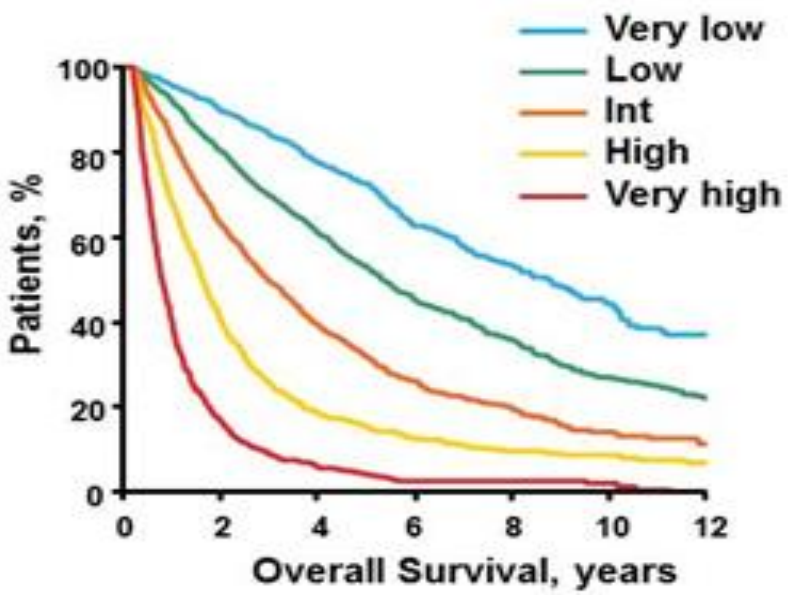
Arber et al, Blood 2016:127;2391-405

LA PROGNOSI: E'POSSIBILE ANDARE OLTRE L'r-IPSS?

Risk group	Included karyotypes (19 categories)	Median survival, months	Proportion of patients in this group
Very good	del(11q), -Y	60.8	2.9%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	48.6	65.7%
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones	26.1	19.2%
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities	15.8	5.4%
Very poor	Complex with > 3 abnormalities	5.9	6.8%

Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



- L'r-IPSS non considera le mutazioni somatiche
- Le mutazioni somatiche sono comuni nelle MDS
- Molte mutazioni somatiche hanno un significato prognostico indipendente dall'r-IPSS
- Non è ancora chiaro come impiegare le mutazioni somatiche nella pratica clinica

Bejar R, EHA 2016, educational session

International Working Group for MDS-Molecular Prognosis Committee

Prelievi di pazienti con MDS da 19 Centri in Europa, Stati Uniti ed Asia

3652 MDS

Rafael Bejar, MD,
Elli Papaemmanu
Torsten Haferlach
Seishi Ogawa, MD, PhD
Guillermo Garcia-Manero, MD
Jaroslaw P. Maciejewski, MD, PhD
Mikkael A. Sekeres, MD, MS
Matthew J. Walter, MD
Timothy A. Graubert, MD
Mario Cazzola, MD
Luca Malcovati, MD
Pierre Fenaux, MD, PhD
Eva Hellstrom-Lindberg, MD, PhD
Wolfgang Kern, MD
Lionel Adès, MD, PhD
Jacqueline Boultwood, PhD

Michael Groves, PhD
Paresh Vyas, MD, PhD
Lynn Quek, MD
Christine Ganster, PhD
Yusuke Okuno, MD, PhD
Eric Padron, MD
David Sallman, MD

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se, MD, PhD
Julie Schanz, MD
Valeria Santini, MD
Michaela Fontenay, MD, PhD
Peter J Campbell, MD, PhD
Heinz Tüchler
Kristen Stevenson, MS
Donna S Neuberg, ScD
Peter Greenberg, MD
Benjamin L Ebert, MD, PhD

mds foundation
the myelodysplastic syndromes foundation, inc.

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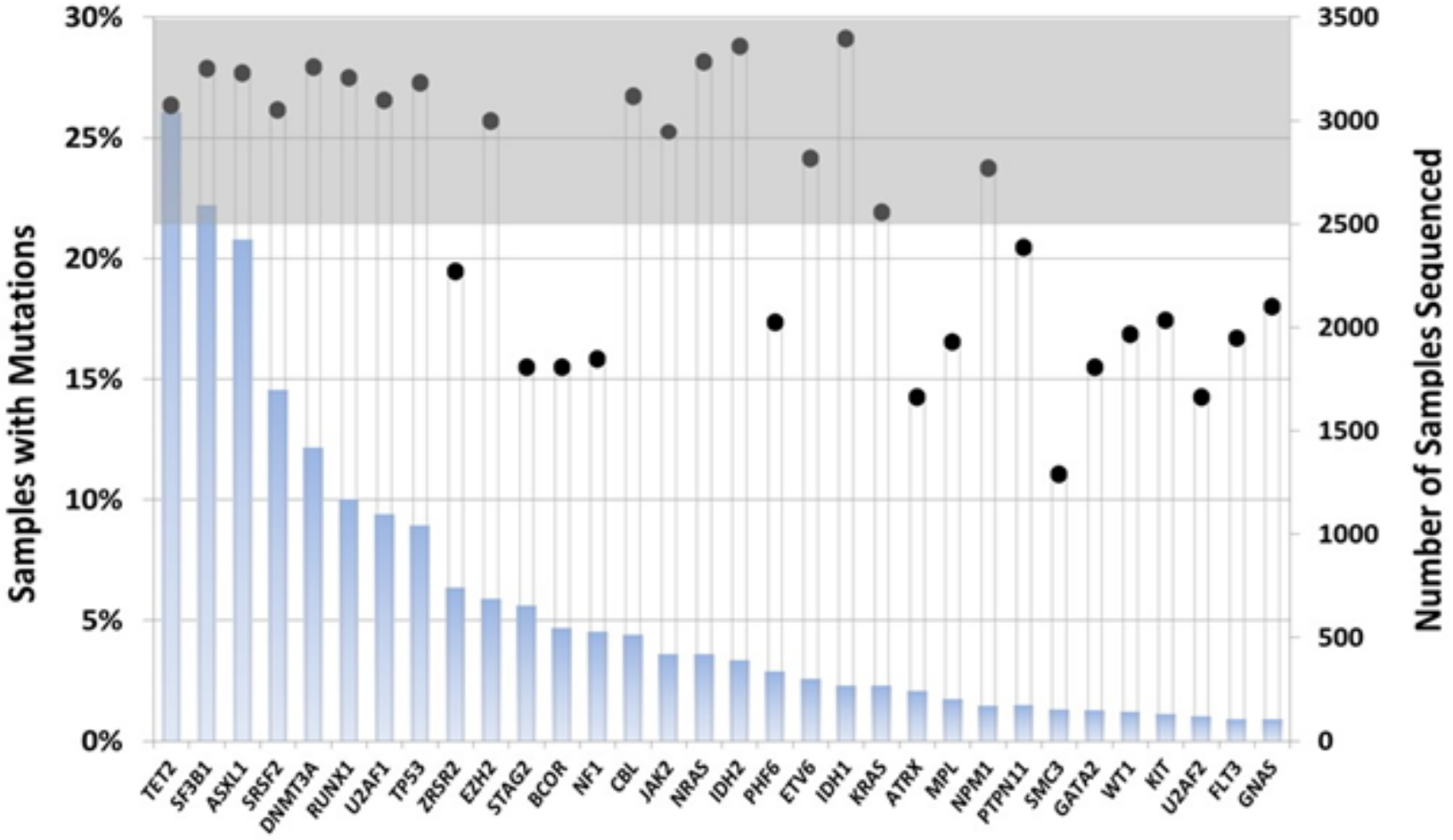
INCIDENZA COMPLESSIVA DELLE MUTAZIONI

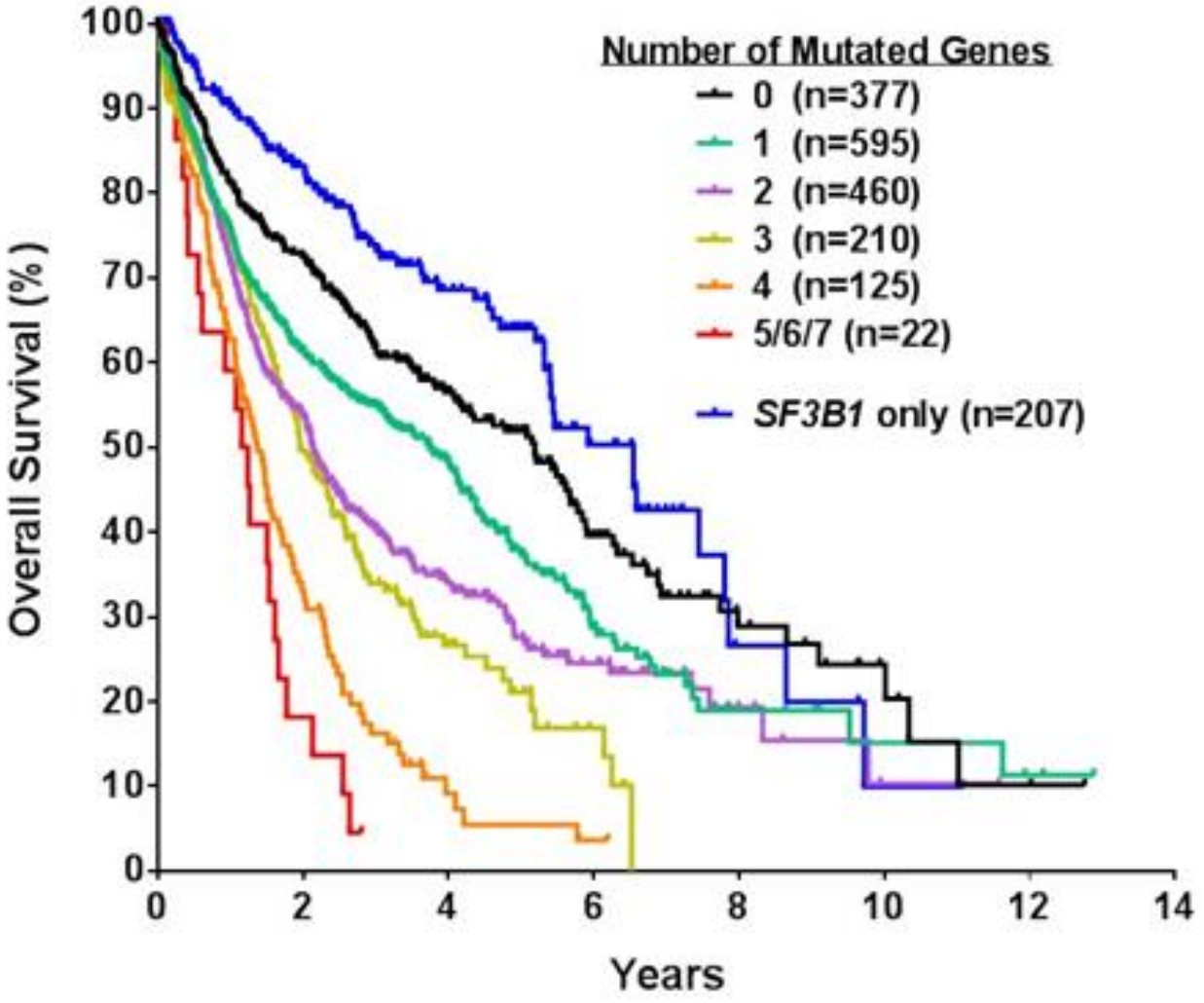


Bejar R, EHA 2016, educational session

SOPRAVVIVENZA GLOBALE IN BASE AL NUMERO DELLE MUTAZIONI

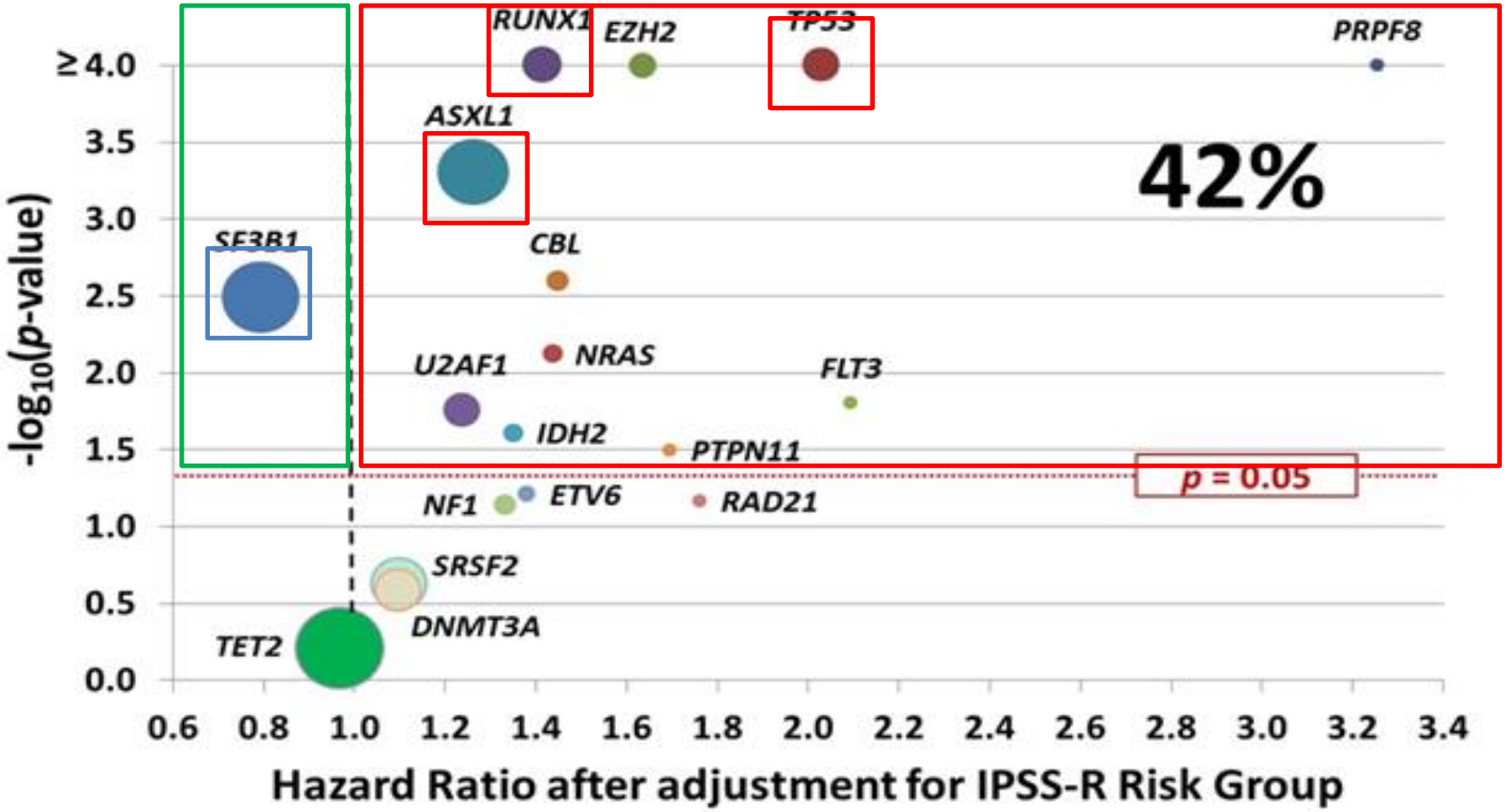
ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1

SF3B1



Bejar R, EHA 2016, educational session

PROGNOSI E MUTAZIONI: CASISTICA GLOBALE



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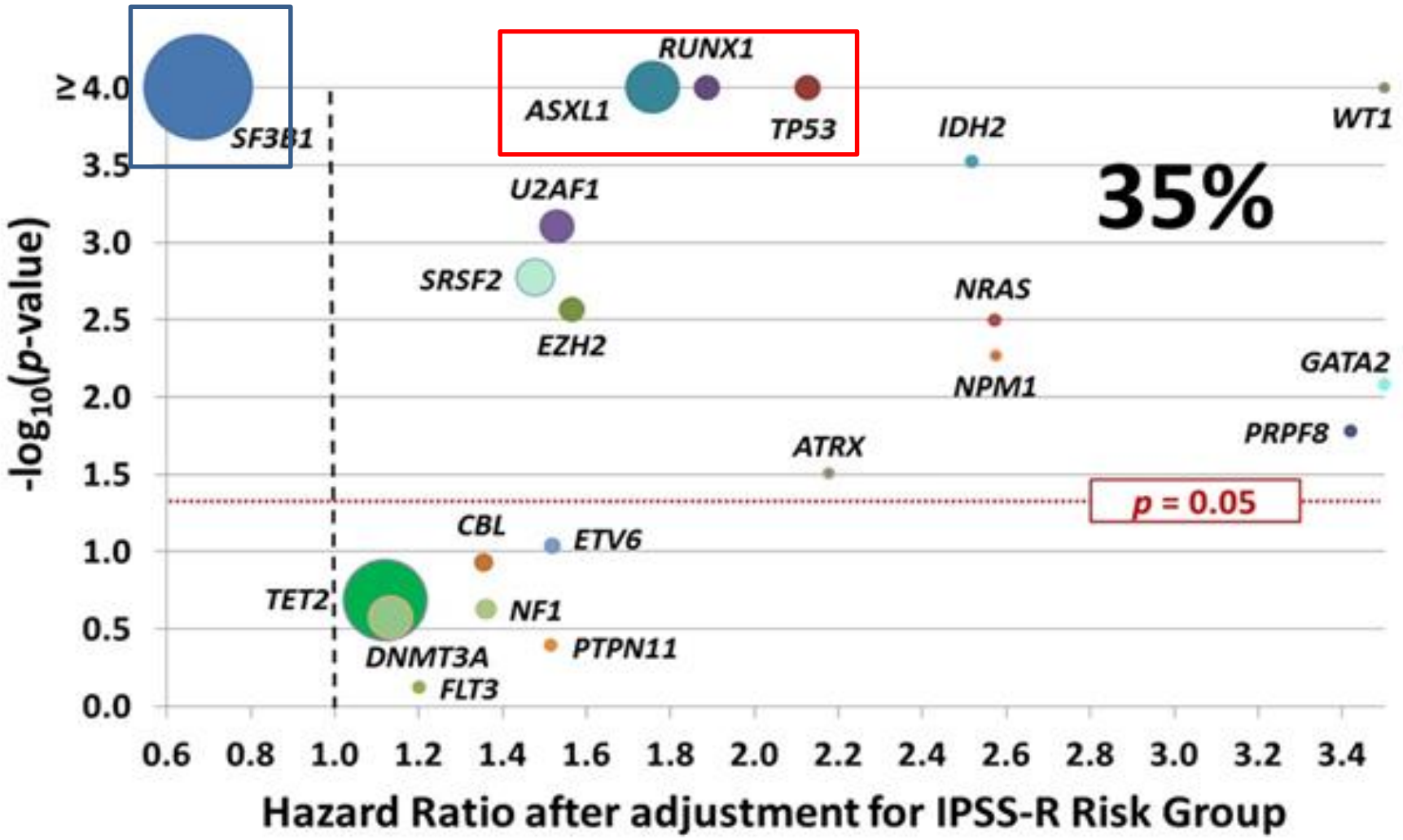
PROGNOSI E MUTAZIONI: BLASTI MIDOLLARI < 5%



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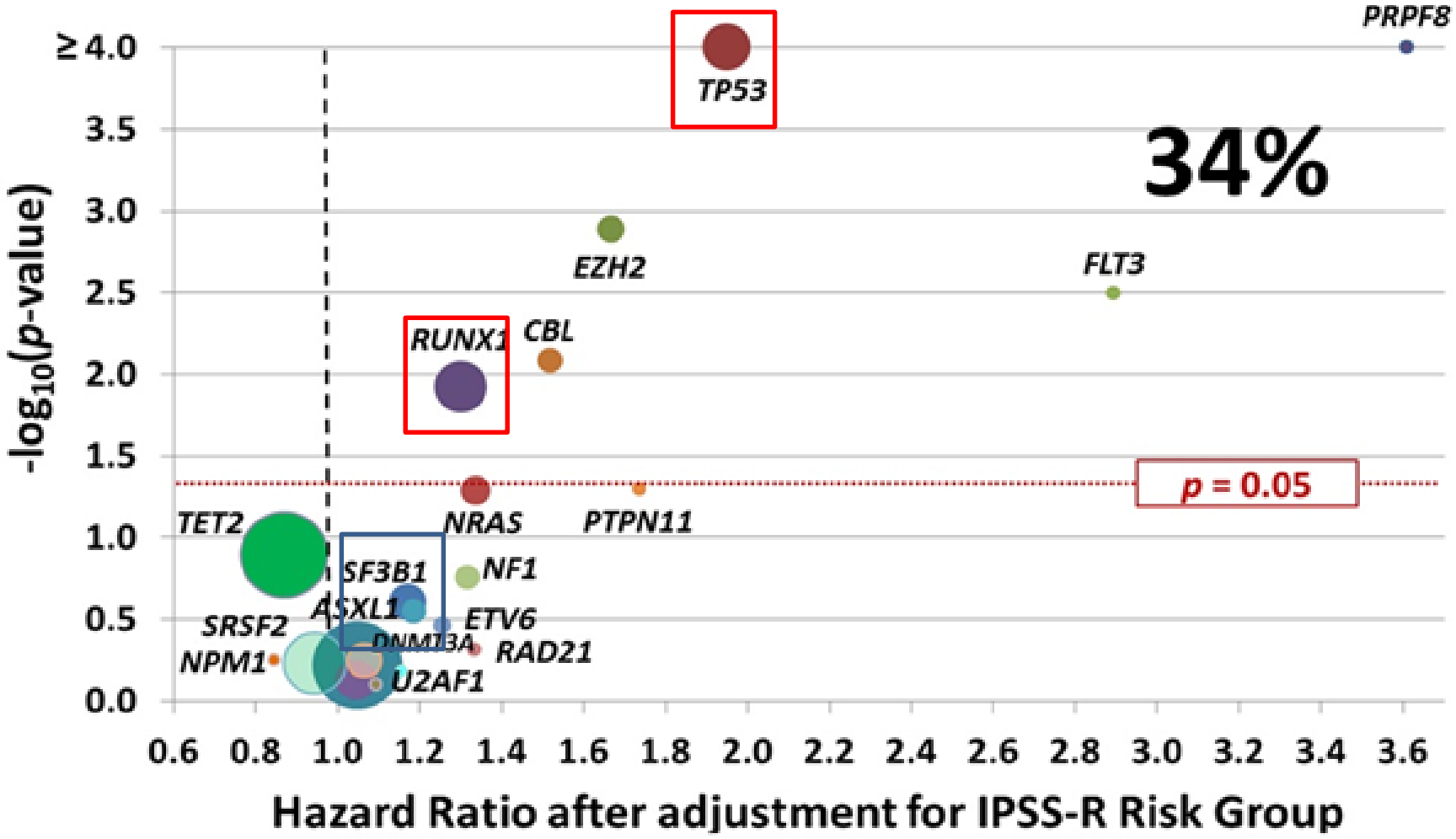
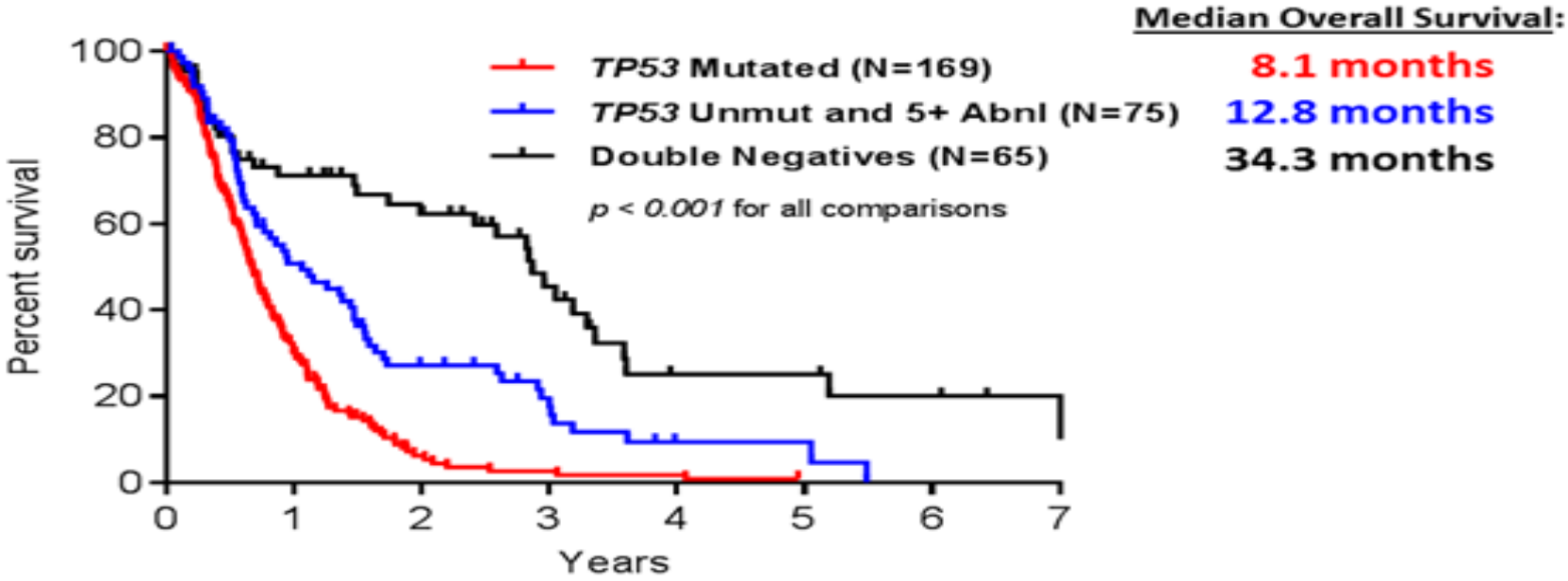
PROGNOSI E MUTAZIONI: BLASTI MIDOLLARI > 5%



Bejar R, EHA 2016, educational session

PROGNOSI E SOPRAVVIVENZA IN 309 PAZIENTI CON CARIOTIPO COMPLESSO

	Univariate		Multivariable	
Three element model	HR [95% CI]	p-value	HR [95% CI]	p-value
Monosomal Yes vs. No	2.01 [1.48-2.74]	<0.001	1.34 [0.95-1.89]	0.092
Number of Abnormalities 5+ vs. 3 or 4	2.33 [1.71-3.17]	<0.001	1.58 [1.11-2.25]	0.011
TP53 Mutation vs. No mutation	2.55 [1.93-3.35]	<0.001	2.08 [1.56-2.77]	<0.001



Bejar R, EHA 2016, educational session

PROGNOSI E MUTAZIONI NELLE MDS: QUALCHE CONSIDERAZIONE DALL'EHA 2016

- **Le mutazioni somatiche di molti geni hanno un significato prognostico indipendente dall' r-IPSS**

BISOGNA INIZIARE AD ORGANIZZARSI PER FARLE NELLA PRATICA CLINICA

QUALI ED IN CHI?

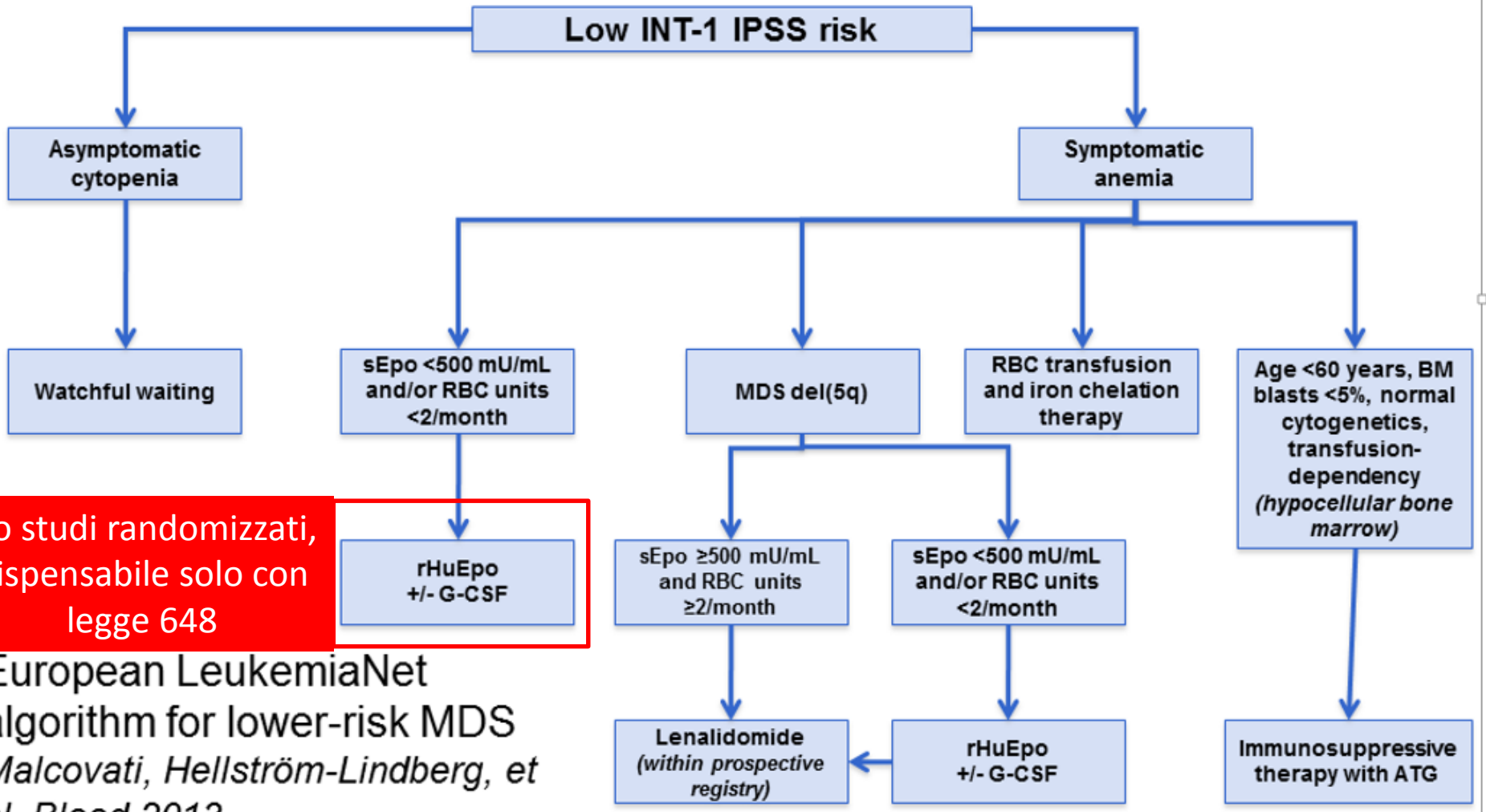
TP53 (RUNX1)
Tutte le MDS
Prognosi sfavorevole

ASXL1
Prognosi sfavorevole

SF3B1
Prognosi favorevole

MDS a basso rischio

TERAPIA DELLE MDS A BASSO RISCHIO: DA DOVE PARTIVAMO PRIMA DELL'EHA 2016?



No studi randomizzati, dispensabile solo con legge 648

European LeukemiaNet algorithm for lower-risk MDS
Malcovati, Hellström-Lindberg, et al, Blood 2013

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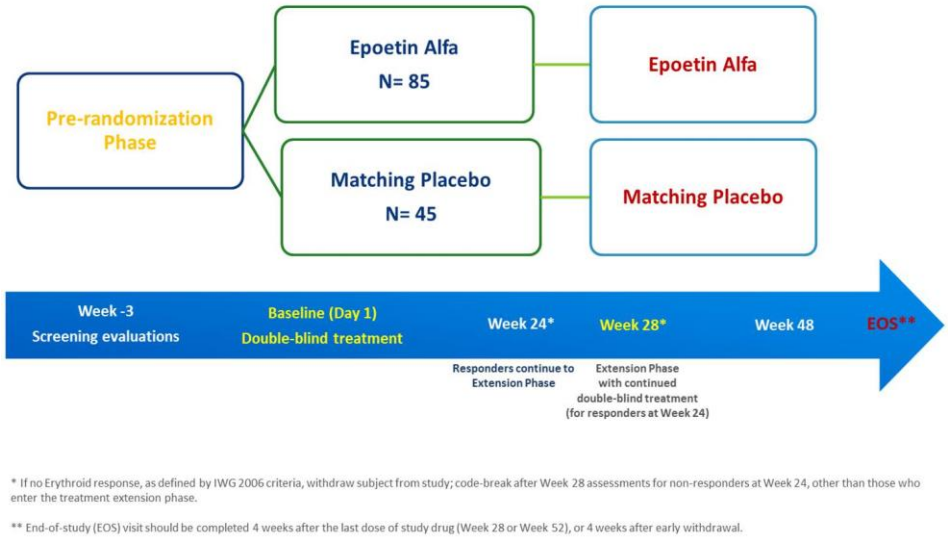
Hellstrom E, EHA 2016, educational session

TERAPIA DELLE MDS A BASSO RISCHIO: STUDI RANDOMIZZATI EPO vs PLACEBO

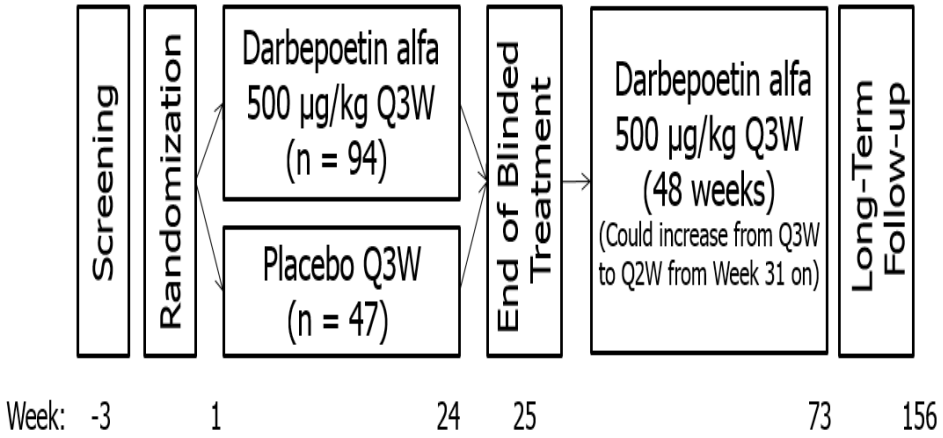


* If no Erythroid response, as defined by IWG 2006 criteria, withdraw subject from study; code-break after Week 28 assessments for non-responders at Week 24, other than those who enter the treatment extension phase.

** End-of-study (EOS) visit should be completed 4 weeks after the last dose of study drug (Week 28 or Week 52), or 4 weeks after early withdrawal.

EPO-ANE
(Epo alfa vs placebo)
Fenaux et al, EHA 2016, P248

ARCADE
(Darbepoietin alfa vs placebo)
Platzbecker et al, EHA 2016, S128



STUDI RANDOMIZZATI EPO vs PLACEBO: LE CASISTICHE

EPO-ANE

	Placebo	Epoetin Alfa	Total
	45	85	130
Age (years)			
Mean (SD)	74.1 (9.2)	74.3 (8.6)	74.2 (8.8)
Median	75.0	75.0	75.0
Range	(36, 87)	(40, 94)	(36, 94)
(Lower 95% CI, Upper 95% CI for the mean)	(71.3,76.8)	(72.4,76.1)	(72.7,75.7)
Sex			
Male	25 (55.6%)	46 (54.1%)	71 (54.6%)
Female	20 (44.4%)	39 (45.9%)	59 (45.4%)
IPSS Risk Category			
Low = 0	23 (51.1%)	35 (41.2%)	58 (44.6%)
Intermediate 1 = 0.5 to 1.0	22 (48.9%)	49 (57.6%)	71 (54.6%)

Fenaux et al, EHA 2016, P248

ARCADE

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Total (N = 146)
Male	29 (59.2)	51 (52.6)	80 (54.8)
Race, white	49 (100.0)	97 (100.0)	146 (100.0)
Age, years, median (Q1, Q3)	73 (55, 80)	74 (68, 79)	74 (67, 79)
IPSS risk category – Low	25 (51.0)	49 (50.5)	74 (50.7)
- Intermediate-1	24 (49.0)	48 (49.5)	72 (49.3)

Platzbecker et al, EHA 2016, S128

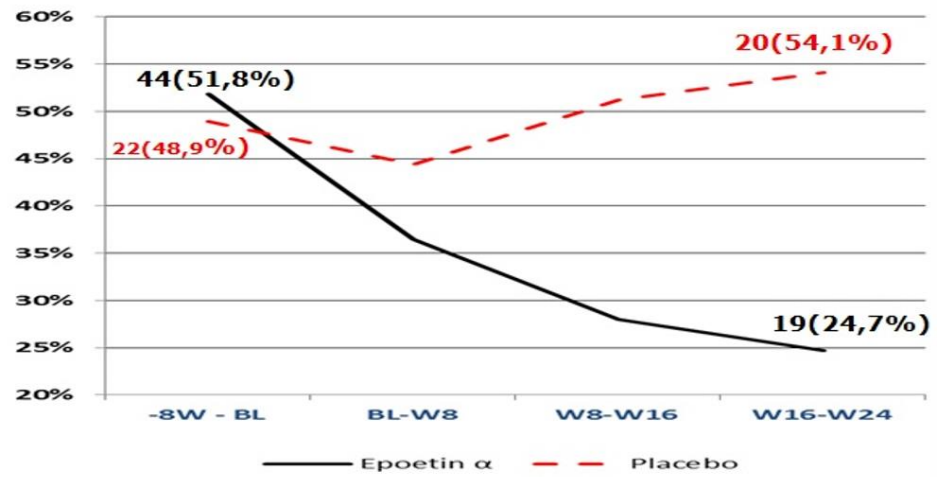
STUDO EPO-ANE: RISPOSTA ERITROIDE (IWG 2006)

	Placebo	Epoetin Alfa
	45	85
Subjects with Erythroid Response at 24 weeks	2 (4.4%)	27 (31.8%)
	p-value <.001	
Subjects with Erythroid Response at any time during the first 24 weeks of study	2 (4.4%)	39 (45.9%)
	p-value <.001	

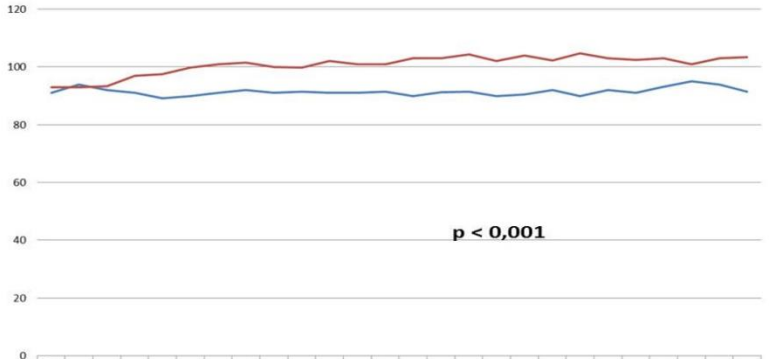
Fenaux et al, EHA 2016 P248

STUDO EPO-ANE: ALTRI RISULTATI

PAZIENTI TRASFUSIONE-DIPENDENTI



INCREMENTO Hb MEDIANA

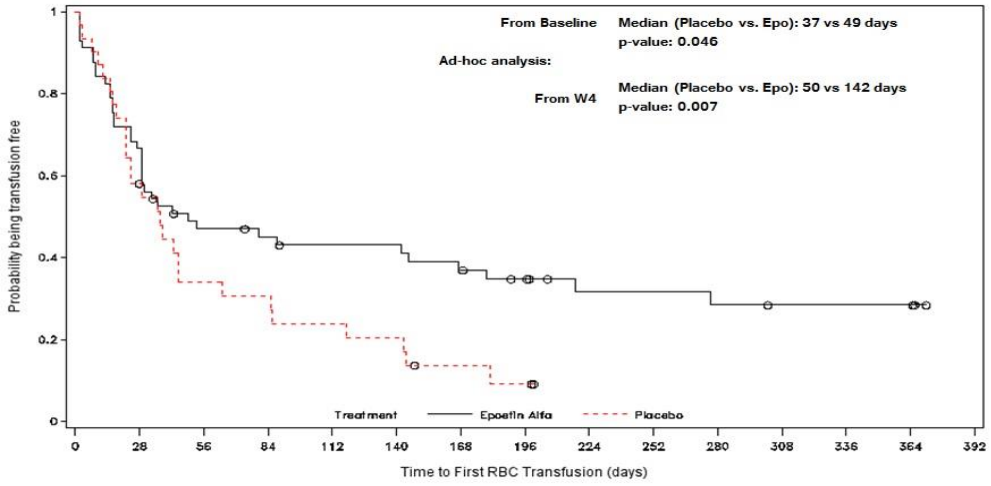


	Screening	Baseline	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23	W24
#Hb measurments Epoetin alpha	85	85	83	83	82	83	80	82	81	82	75	75	75	75	73	74	74	75	70	71	70	70	69	69	70	70
# Hb measurments placebo	45	45	45	45	45	45	41	41	41	40	39	40	40	40	36	36	36	36	33	32	33	35	34	33	33	34
Median Hb Placebo (g/L)	91	94	92	91	89,2	90	91	92	91,1	91,5	91	91	91,5	90	91,3	91,5	90	90,5	92	90	92	91	93,2	95	94	91,5
Median Hb Epoetin alpha (g/L)	93	93	93,43	97	97,5	99,88	101	101,5	100	99,88	102	101	101	103	103	104,4	102	104	102,2	104,7	103	102,5	103	101	103	103,5

placebo — Median Hb Placebo (g/L)

rments Epoetin alpha)

SOPRAVVIVENZA LIBERA DA TRASFUSIONI



0 = Censored Observation

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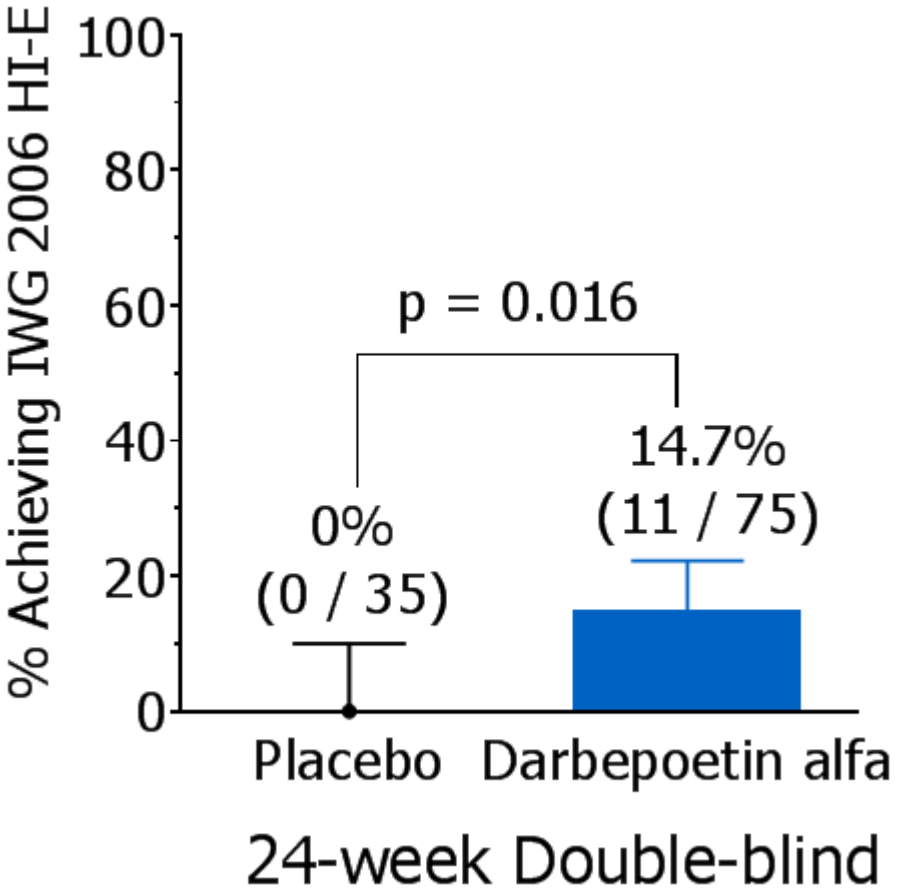
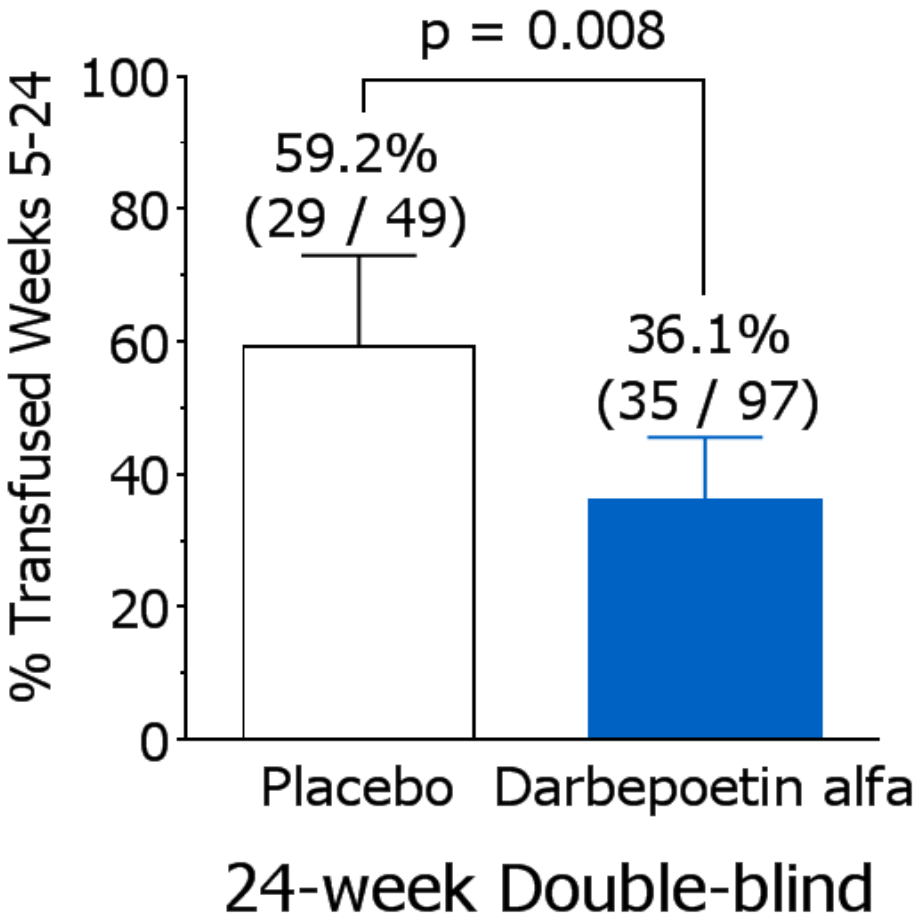
Fenaux et al, EHA 2016, P248

STUDO ARCADE: RISULTATI





Platzbecker et al, EHA 2016, S128

STUDI RANDOMIZZATI EPO vs PLACEBO: CONCLUSIONI

EPO-ANE

"Epoetin-a significantly improved anemia by increasing Hb and reducing transfusion requirement in patients with Low or Int-1 MDS. Improved QoL was observed in responders. No new safety signals were detected in this study. These results confirm experience from clinical practice"

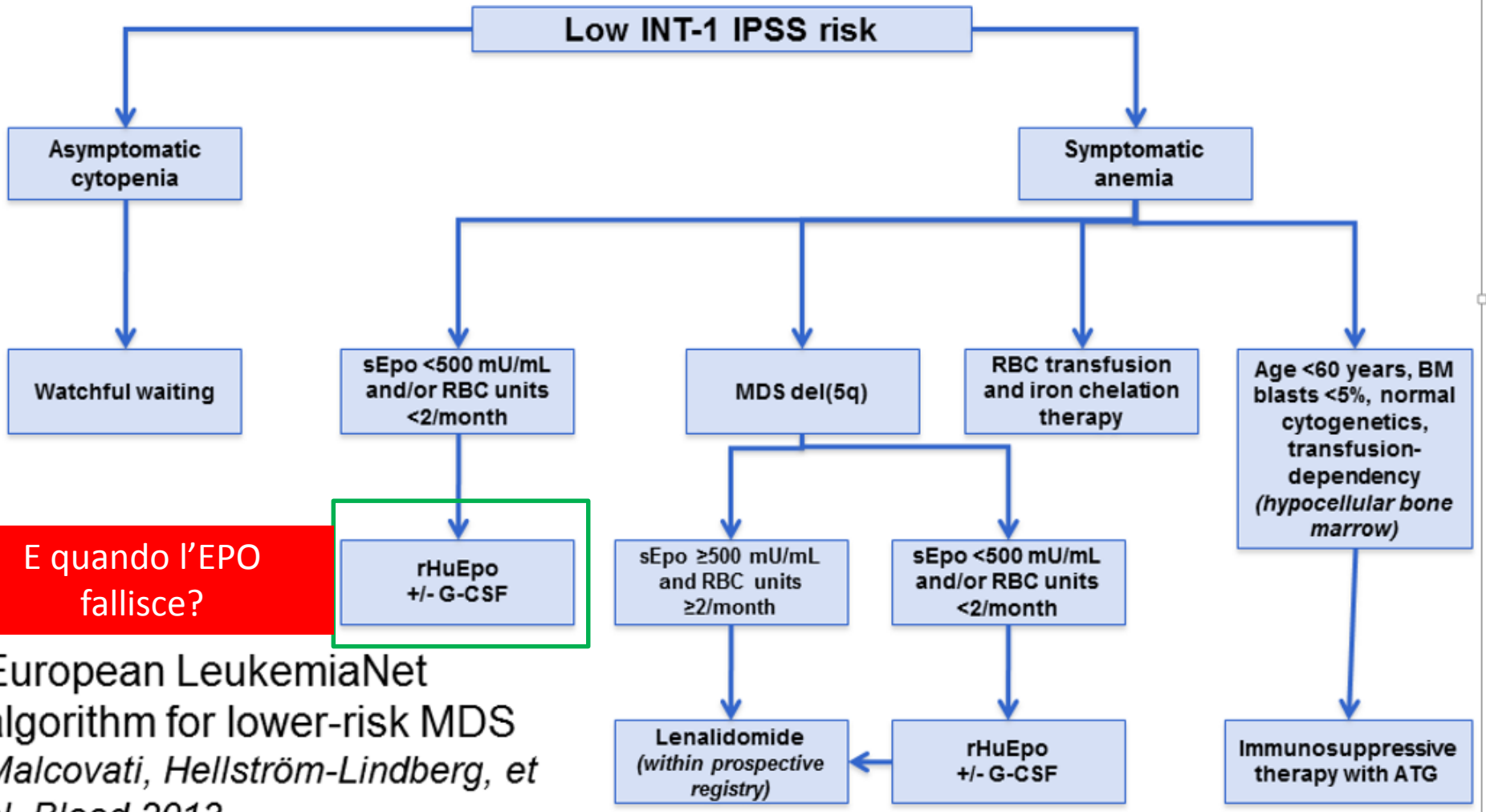
Fenaux et al, EHA 2016, P248

ARCADE

"In this phase 3, randomized, double-blind, PBO-controlled trial in low/int-1 MDS patients with anemia, 24 weeks of darbepoietin alfa Q3W significantly reduced transfusions and increased rates of erythroid response compared with placebo with no new safety signals"

Platzbecker et al, EHA 2016, S128

TERAPIA DELLE MDS A BASSO RISCHIO: DA DOVE PARTIVAMO PRIMA DELL'EHA 2016?



E quando l'EPO fallisce?

European LeukemiaNet algorithm for lower-risk MDS
Malcovati, Hellström-Lindberg, et al, Blood 2013

9th EDITION Highlights from EHA

Hellstrom E, EHA 2016, educational session

TERAPIA DELLE MDS A BASSO RISCHIO: CHE NOVITA' DALL'EHA 2016 QUANDO L'EPO FALLISCE?

LENALIDOMIDE in MDS non-del5q

Hellstrom E, EHA 2016, educational session

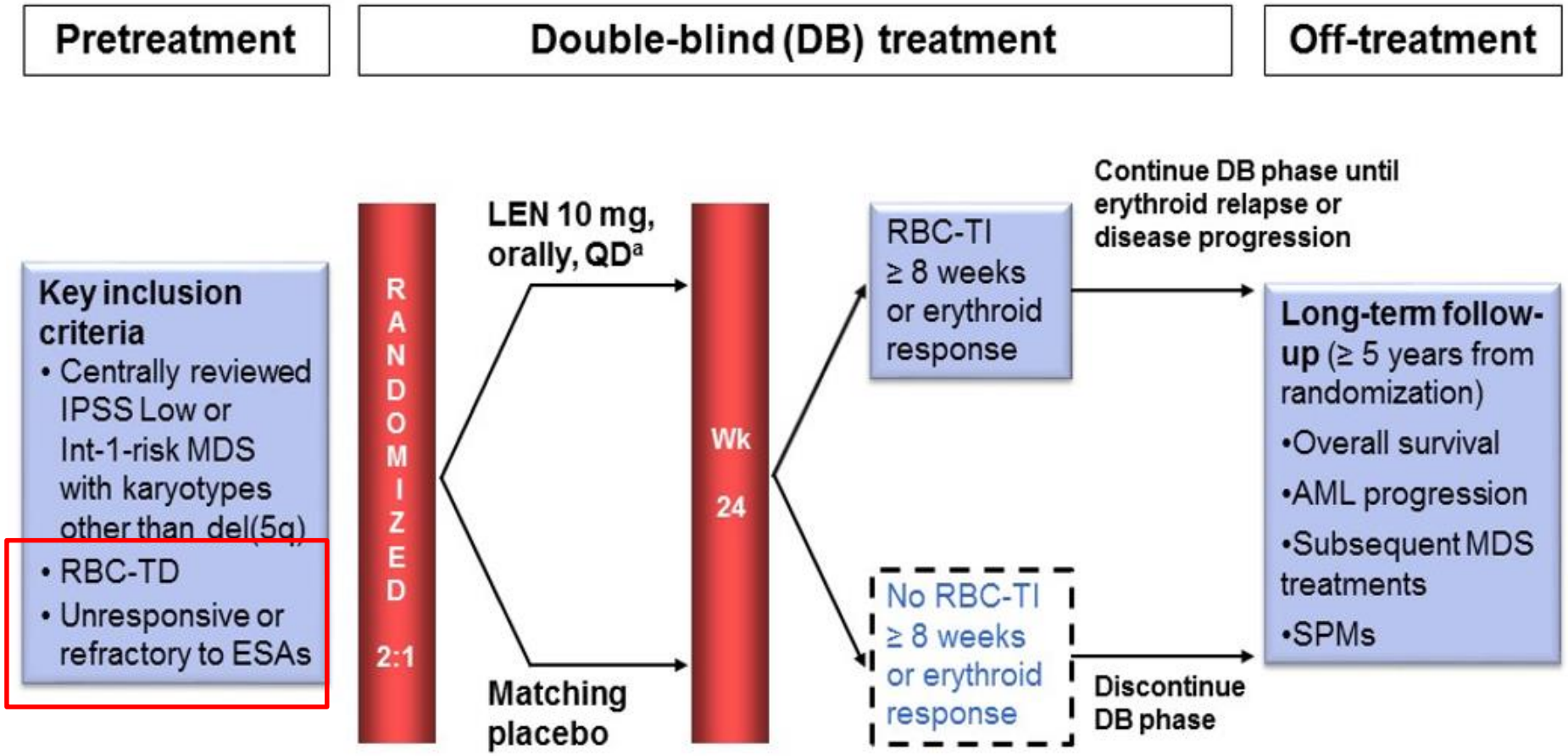
AZACITIDINA ORALE (CC-486)

Garcia-Manero et al, EHA 2016, S129

LUSPATERCEPT

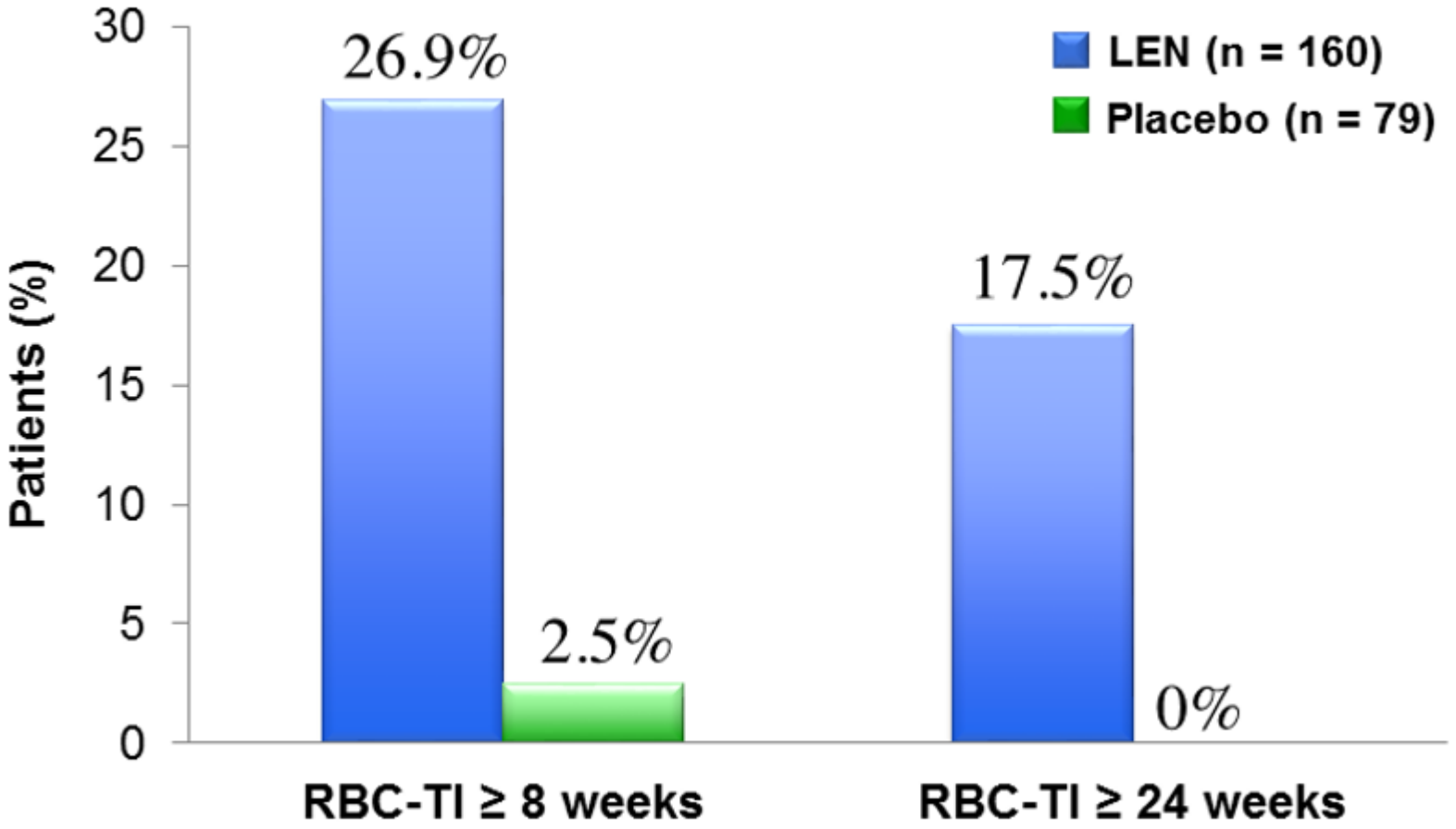
Platzbecker et al, EHA 2016, S131

LENALIDOMIDE IN MDS NON DEL5q: DISEGNO DEL PROTOCOLLO MDS-005



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

LENALIDOMIDE IN MDS NON DEL5q: RISULTATI DEL PROTOCOLLO MDS-005



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

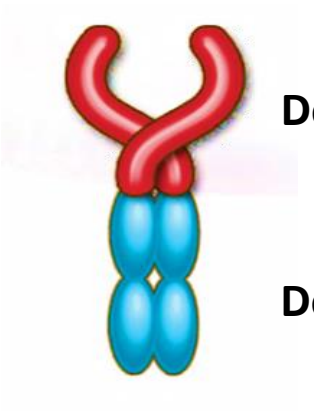
AZACITIDINA ORALE: RISULTATI

Hematologic Response	LowPlt ≤75x10^9/L (n=72) n/N (%)	HiPlt >75x10^9/L (n=64)* n/N (%)	All patients (n=136)* n/N (%)
Overall Response Rate (CR + PR + Any HI + Any TI)	30/72 (42)	27/64 (42)	57/136 (42)
CR†	8/36 (22)	2/29 (7)	10/65 (15)
PR†	0/24	0/28	0/52
Any HI	24/72 (33)	21/62 (34)	45/134 (34)
HI-E	12/65 (18)	16/55 (29)	28/120 (23)
HI-P	17/72 (24)	6/13 (46)	23/85 (27)
HI-N	4/37 (11)	4/21 (19)	8/58 (14)
Any TI	9/32 (28)	14/33 (42)	23/65 (35)
RBC TI	7/27 (26)	14/33 (42)	21/60 (35)
Platelet TI	2/14 (14)	0/0	2/14 (14)

n = number of pts with response / N = number of pts eligible for response
*No response assessment available for 1 pt
†CR and PR were investigator-assessed for 19 patients (1 CR, 0 PR)

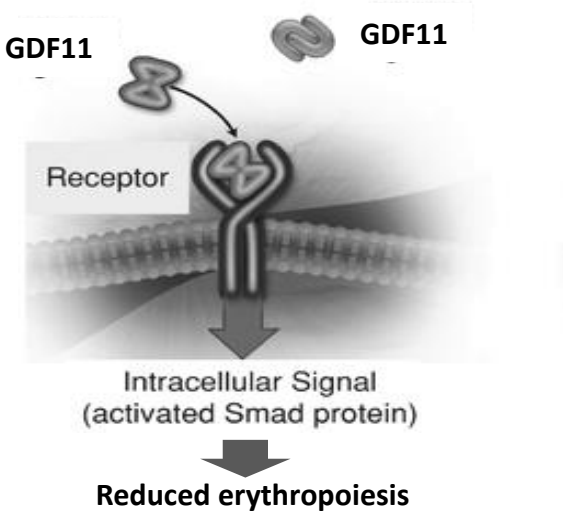
Garcia-Manero et al, EHA 2016, S129

TERAPIA DELLE MDS A BASSO RISCHIO: COS'E' IL LUSPATERCEPT E COME FUNZIONA?

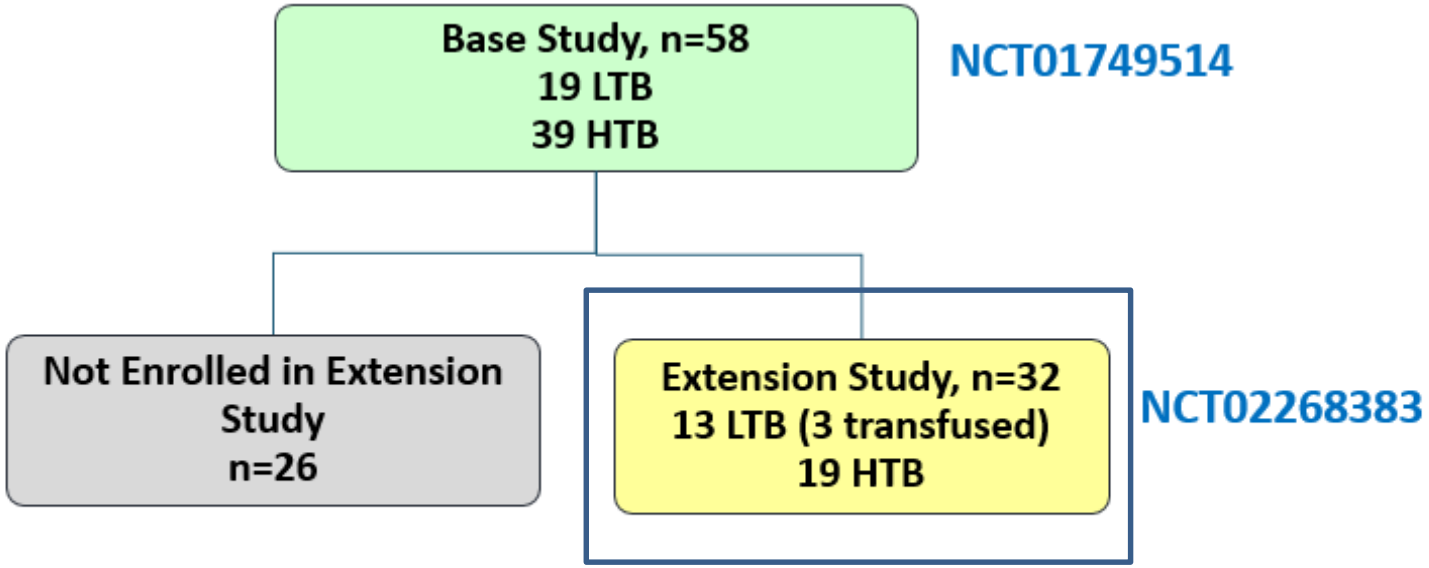


Dominio extracellulare modificato del recettore ActRIIB

Dominio Fc di IgG_1 umana



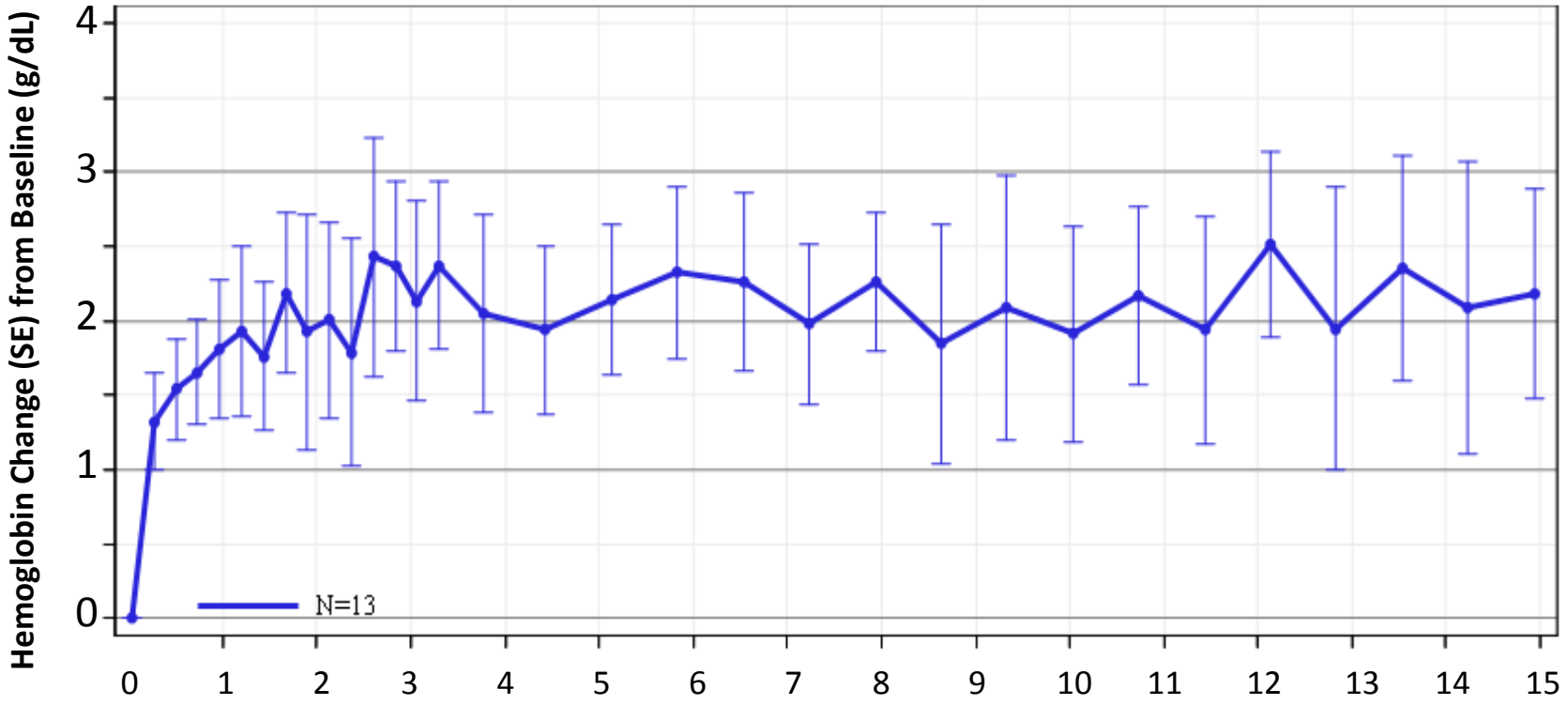
IL LUSPATERCEPT NELLE MDS A BASSO RISCHIO: LO STUDIO PACE-MDS



Parameter	Base Study N=58	Extension Study N=32
Age, yr, median (range)	71.5 (27-90)	71.5 (29-90)
Sex, male, n (%)	34 (59%)	22 (69%)
Time since diagnosis, yr, median (range)	2.4 (0-14)	2.9 (0-14)
Prior lenalidomide treatment, n (%)	10 (17%)	6 (19%)
Prior ESA treatment, n (%)	38 (66%)	19 (59%)
Baseline EPO		
<200 U/L	28 (48%)	19 (59%)
200-500 U/L	13 (22%)	7 (22%)
>500 U/L	17 (29%)	6 (19%)
RS+ (ring sideroblast ≥ 15%)	45 (78%)	29 (91%)
SF3B1 mutation	33 (57%)	23 (72%)

Platzbecker et al, EHA 2016, S131

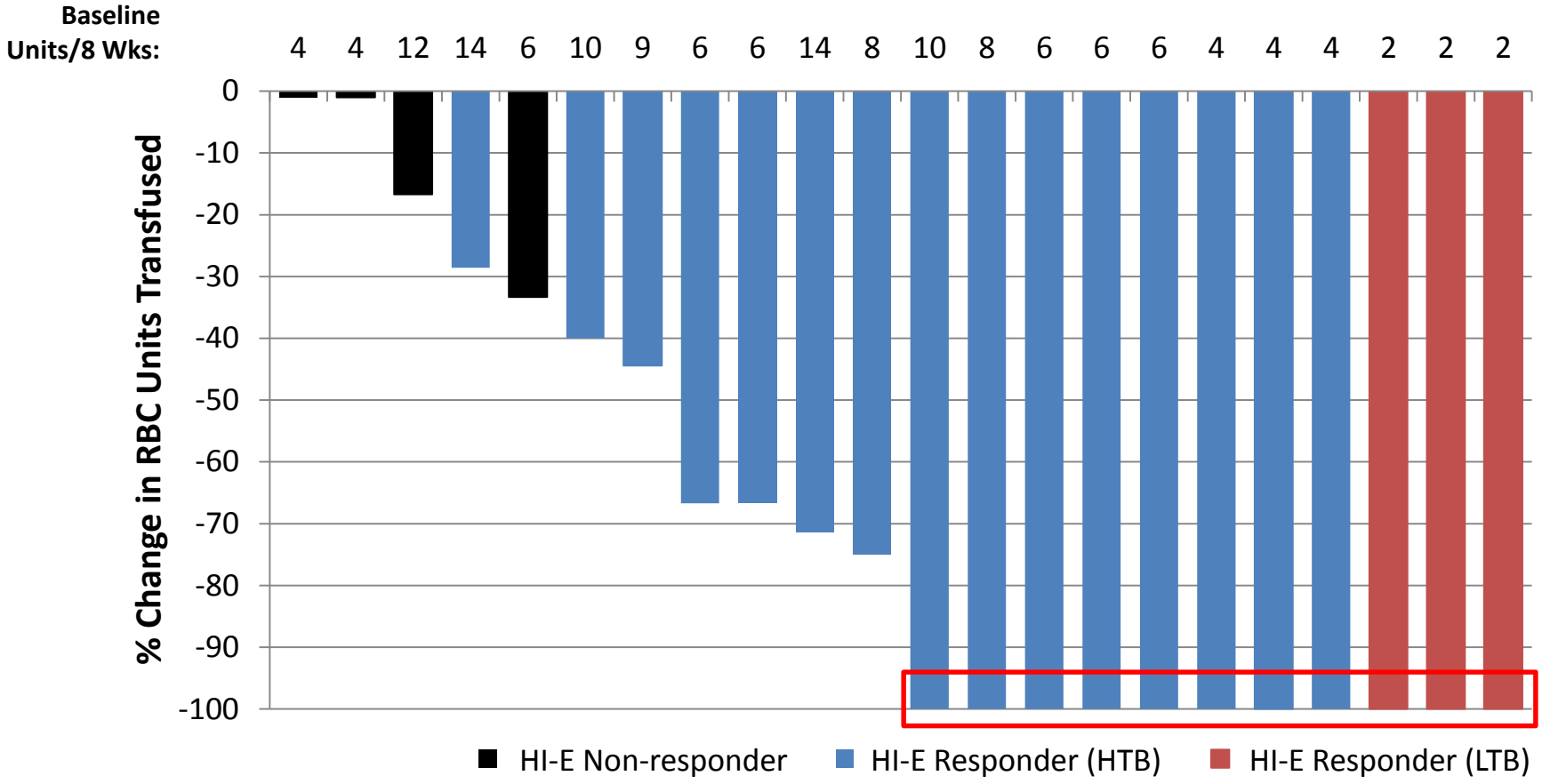
LUSPATERCEPT:
INCREMENTO MEDIANO DELL'Hb NEI PAZIENTI LTB



- 11/13 (85%) HI-E responders; median time to response: 6 weeks

Platzbecker et al, EHA 2016, S131

LUSPATERCEPT:
% DI RIDUZIONE DEL FABBISOGNO TRASFUSIONALE

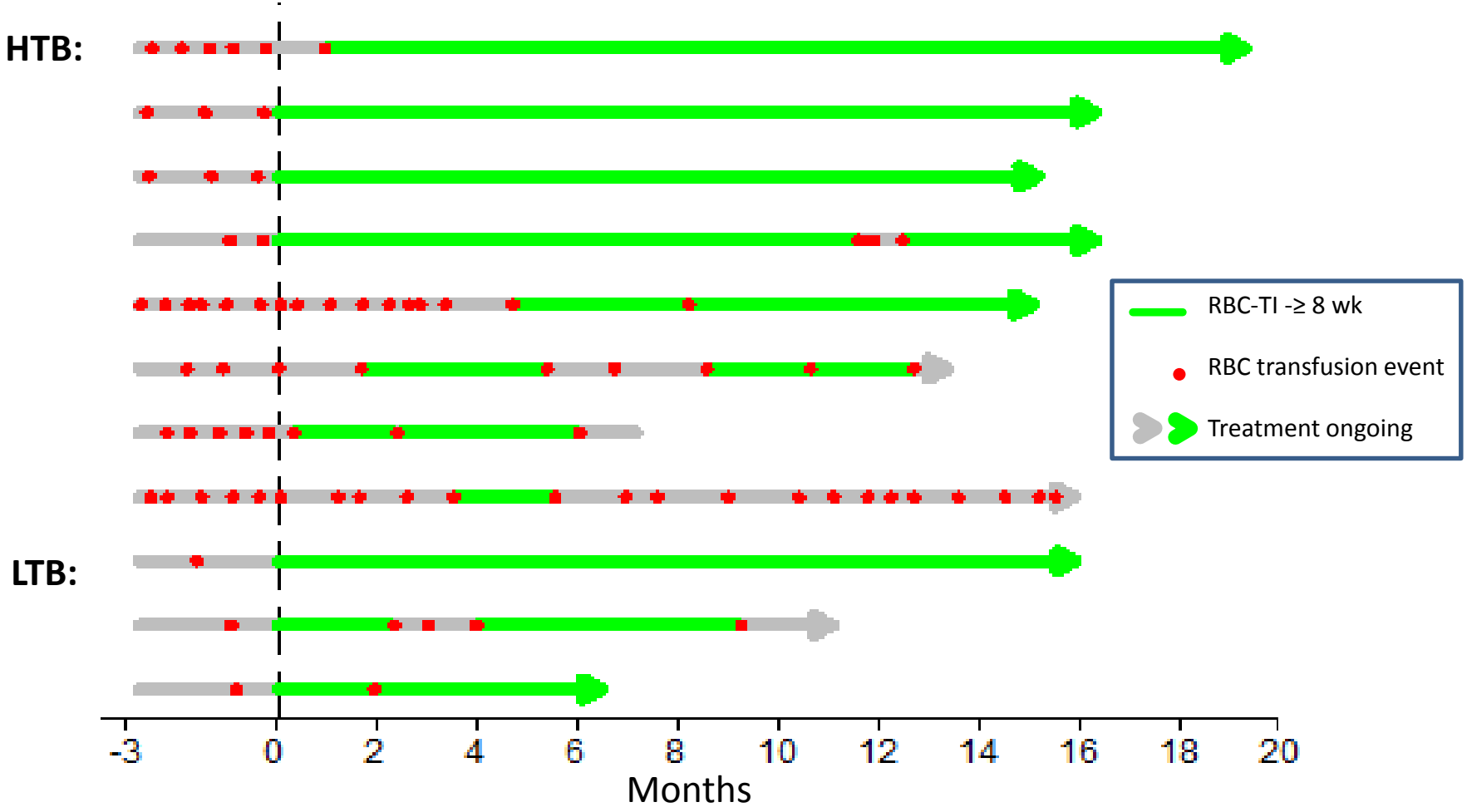


- 15/19 (79%) HTB patients were HI-E responders (≥ 4 unit decrease /8 wk)

Platzbecker et al, EHA 2016, S131

LUSPATERCEPT: DURATA DELLA TI

- 50% (11/22*) patients who were transfused prior to study achieved RBC transfusion independence (TI) ≥ 8 weeks (range 9-80+ weeks)



* Includes 19 HTB patients and 3 LTB patients evaluable for transfusion independence

Platzbecker et al, EHA 2016, S131

The MEDALIST Study

Phase 3 Study of Luspatercept in MDS: NOW ENROLLING

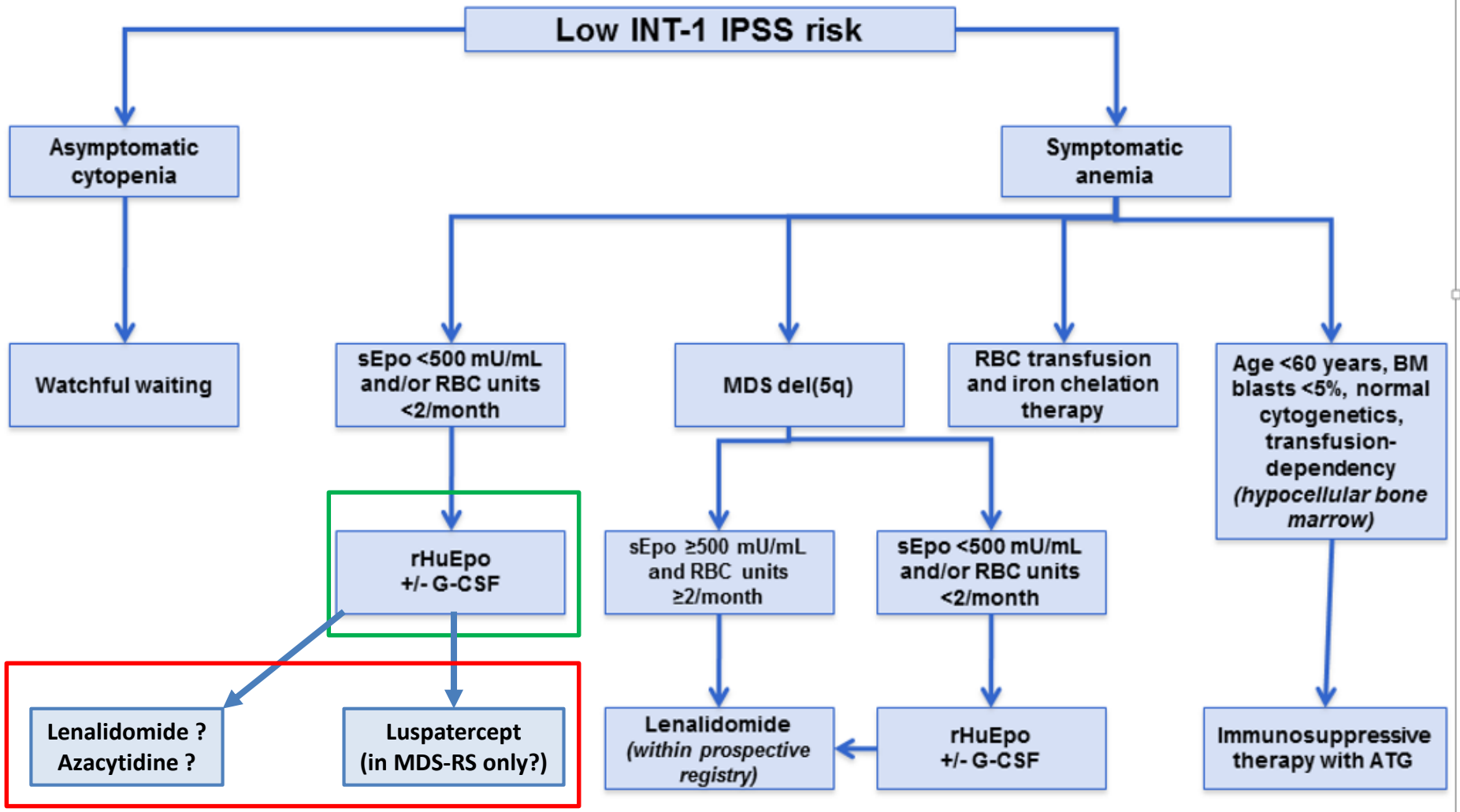
MEDALIST

Patient Population / Study Design	Randomized, double-blind, placebo-controlled study in very low, low or intermediate risk (IPSS-R) MDS patients with ring sideroblasts (RS+) who require RBC transfusion 210 patients randomized 2:1; luspatercept 1 mg/kg SC every 3 weeks, titration up to 1.75 mg/kg possible
Key Inclusion Criteria	Refractory / intolerant to prior ESA *or* EPO > 200 U/L RS+; <5% blasts; no prior HMA or lenalidomide ≥ 2 units RBCs transfused / 8 weeks Excluded: del(5q), secondary MDS
Primary Efficacy Endpoint	Proportion of patients that become RBC-transfusion independent (≥ 8 weeks) during the first 24 weeks

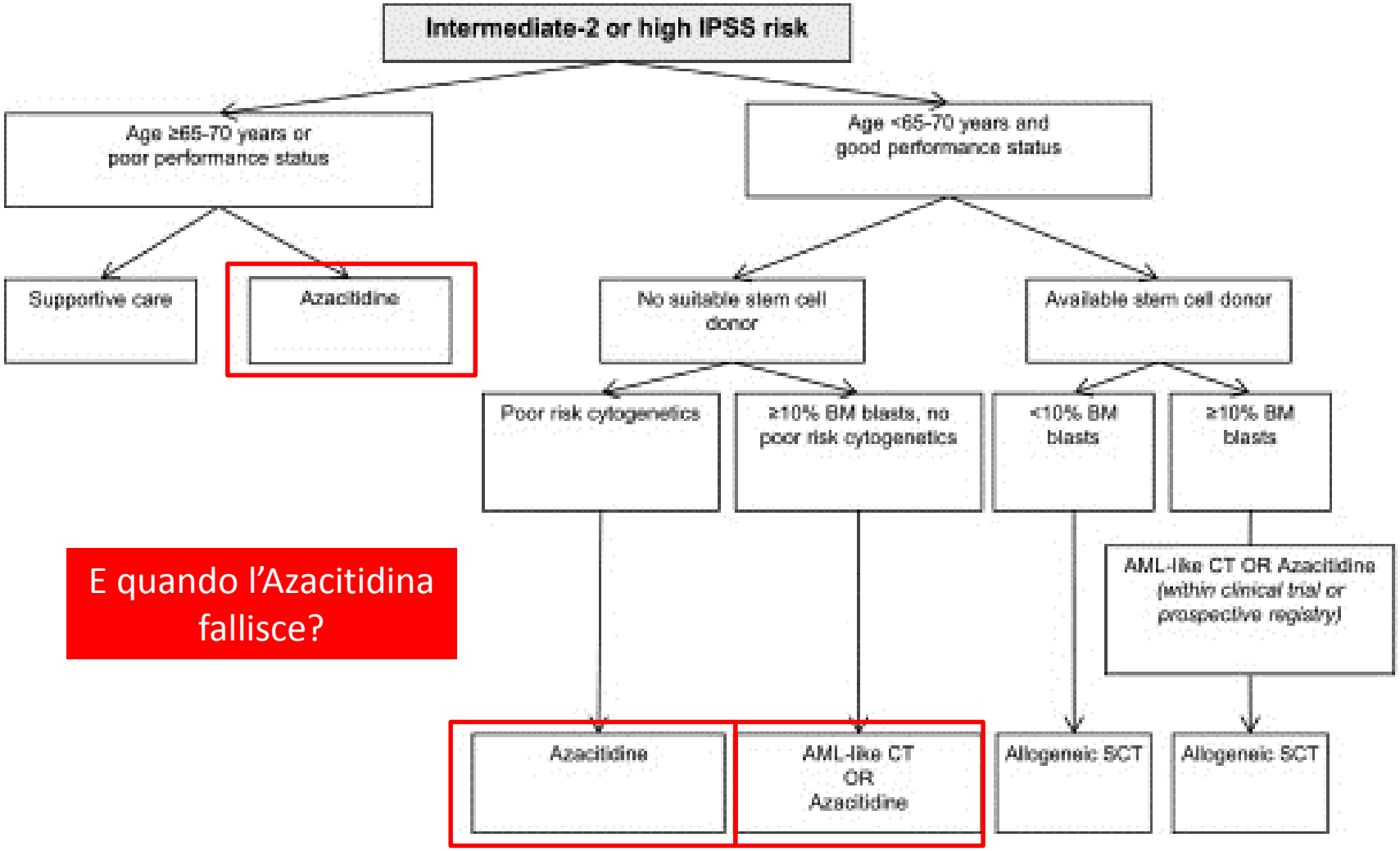
Sponsored by Celgene

NCT02631070

TERAPIA DELLE MDS A BASSO RISCHIO: UN NUOVO ALGORITMO DOPO L'EHA 2016?



TERAPIA DELLE MDS AD ALTO RISCHIO: DA DOVE PARTIVAMO PRIMA DELL'EHA 2016?



E quando l'Azacitidina fallisce?

TERAPIA DELLE MDS AD ALTO RISCHIO: CHE NOVITA' DALL'EHA 2016 QUANDO L'AZACITIDINA FALLISCE? (O PER PREVENIRNE IL FALLIMENTO)

FARMACI ALTERNATIVI → **GUADECITABINA**

Garcia-Manero et al, EHA 2016, P249

ASSOCIAZIONE DI AZACITIDINA CON ALTRI FARMACI

- **AZACITIDINA + GLASDEGIB**
  Borate U et al, EHA 2016, P255
- **AZACITIDINA + RIGOSERTIB**
  Navada S et al, EHA 2016, P256

TERAPIA DELLE MDS AD ALTO RISCHIO: MECCANISMI DI AZIONE DEI NUOVI FARMACI

GUADECITABINA

↓

Dinucleotide (decitabina + deossiguanina)

↓

Resistente alla citidina-deaminasi (CDA)

GLASDEGIB

↓

Inibitore di SMO

↓

Inibizione della pathway di Hedgehog

RIGOSERTIB

↓

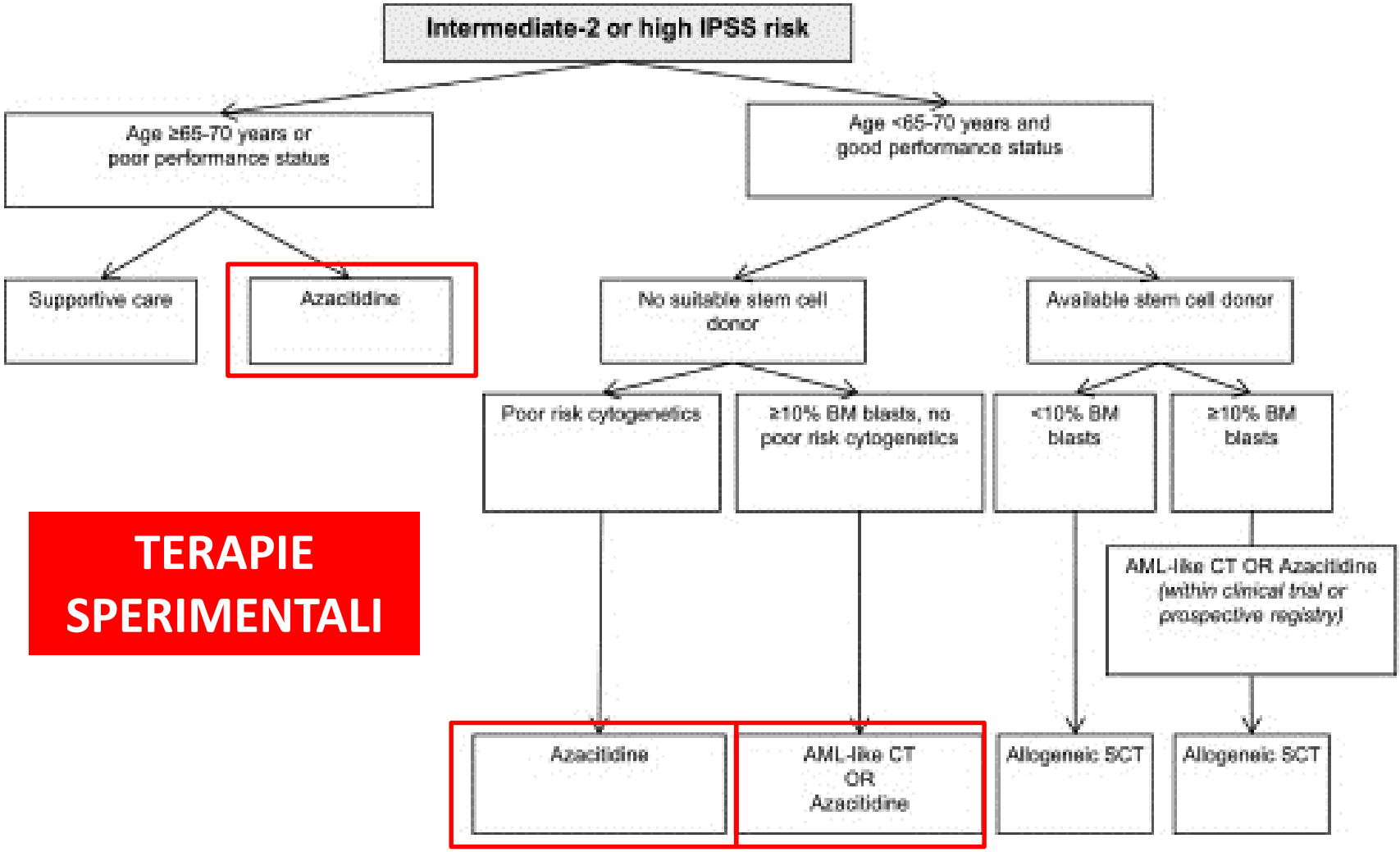
Inibitore di PI3K

TERAPIA DELLE MDS AD ALTO RISCHIO: RISULTATI DEI NUOVI FARMACI

	GUADECITABINA	AZACITIDINA + GLASDEGIB	AZACITIDINA + RIGOSERTIB
N° pazienti: AZA naive AZA refrattari	53 / 53	7 7 /	30 19 11
Dose e schedula	60 – 90 mg/m^2 sc gg 1-5	AZA 75 mg/m^2 gg 1-7 sc GLA 100 mg po gg 1-28	AZA 75 mg/m^2 gg 8-15 sc RIG 840 mg bid po gg 1-21
Risposte globali: RC mRC HI	28/53 (52%) 2 15 11	2/7 1 1 /	23/30 (77%) 6 16 1
Sopravvivenza	11.7 mesi (mediana)	70.7% a 6 mesi	NR

Dati molto preliminari, sui quali si può dire poco

TERAPIA DELLE MDS AD ALTO RISCHIO: NESSUN NUOVO ALGORITMO DOPO EHA 2016!



TERAPIE SPERIMENTALI

IN CONCLUSIONE…

…ABBIAMO UNA LUNGA STRADA DA FARE!