27-28 OTTOBRE 2008

BORGO SAN LUIGI

MONTERIGGIONI, SIENA

A PHASE II STUDY OF OUTPATIENT ADMINISTRATION OF DECITABINE FOR 5 DAYS EVERY 4 WEEKS TO ADULTS WITH MYELODYSPLASTIC SYNDROMES MYELODYSPLASTIC SYNDROMES

Steensma et al, abstract 225 (poster)

Confirmatory US Phase II study: decitabine administered on a 5-day schedule in MDS

Objective

- Evaluation of IV dosing of decitabine over 1 hour once daily for 5 days

Patients

- Median age 72 years; 72% male; 89% de novo MDS, median time from diagnosis 154 days, and 27% received prior therapy
- Low 1%; Int-1 53%; Int-2 23%; High 23%

Results: (ITT: 99 patients; 87 patients evaluable for efficacy; 99 for safety)

Best response	ITT	Eval
CR + mCR	32%	38%
Overall Improvement rate (CR + PR + HI)	51%	60%
Stable disease (SD)	24%	29%
Progressive disease (PD)	10%	12%

mCR: marrow CR

Median of 5 cycles of decitabine (range 1-20), 38% of patients receiving ≥8 cycles

Azacitidine in patients with lower-risk MDS: results from an Italian named patient programme

Patient characteristics (n=74)

- IPSS low- or int-1-risk
- Transfusion dependent at diagnosis: 83.8%
- **Previous therapy: 73.0%**

Azacitidine

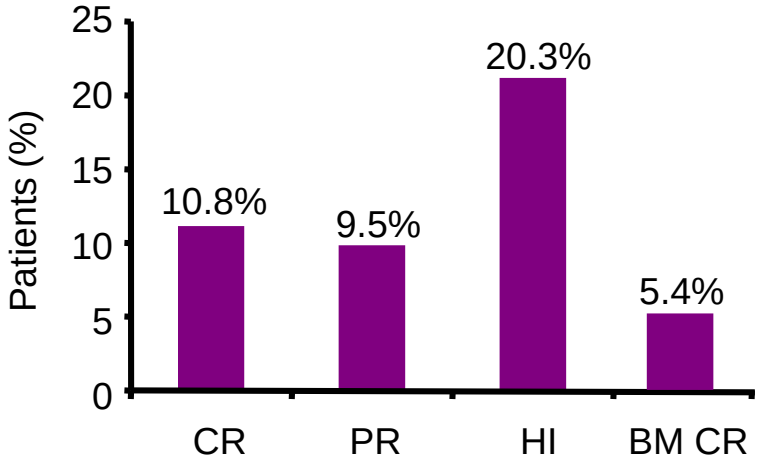
Median cycles: 7 (1–30)

Dose: 75mg/m^2 (60.8% patients)

Schedule: 7 days every 28 days (58.1% patients)

CR = complete response; PR = partial response
HI = haematological improvement
BM = bone marrow; OS = overall survival

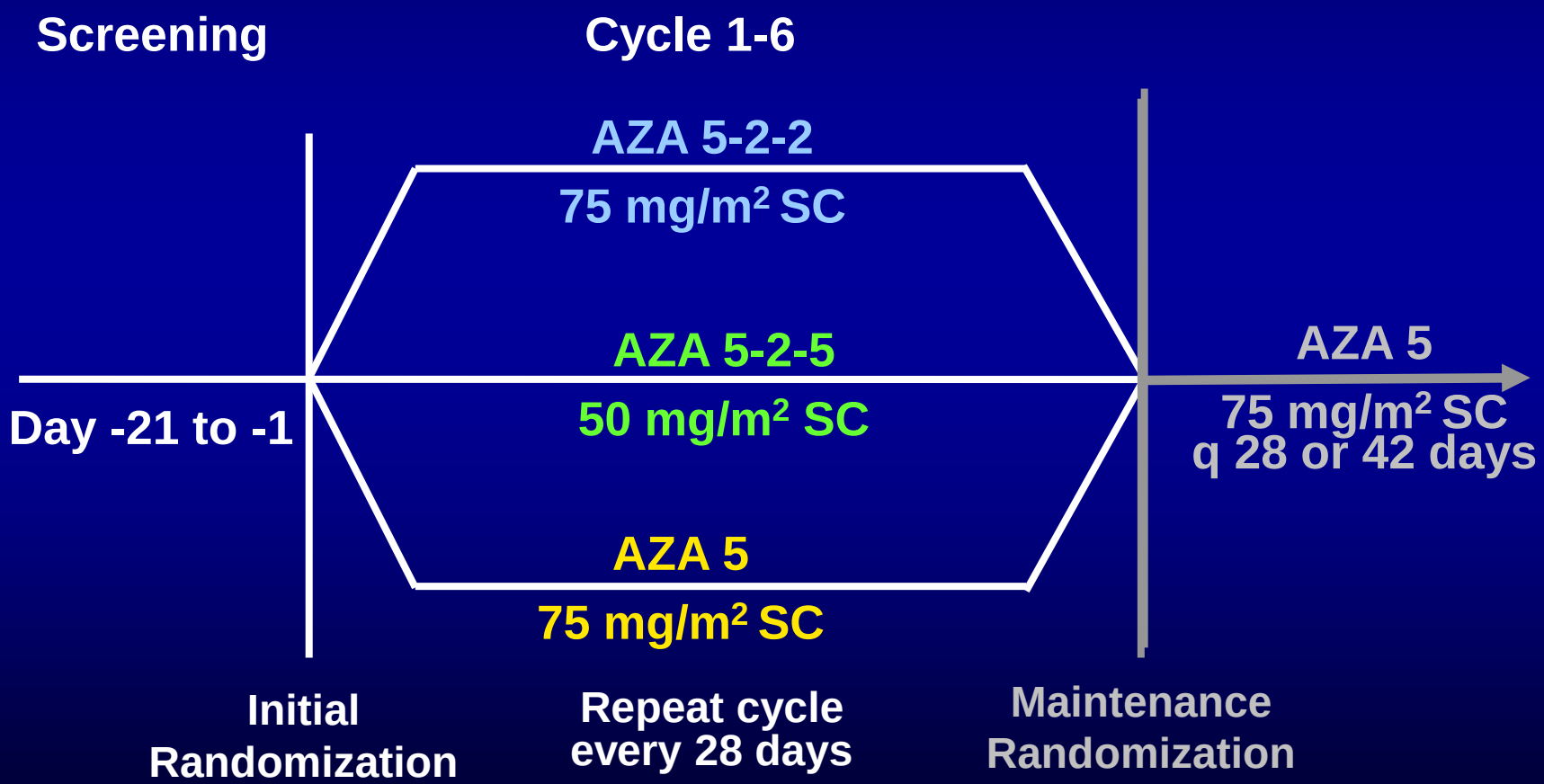
Response to therapy



- 77% of responses occurred within the first 6 cycles
- Median duration of response = 6 months
- Projected OS at 30 months = 70.8% (median follow-up of 15 months)
- Projected OS was higher in responders than non-responders (93.9 vs 53.8%; p<0.0014)

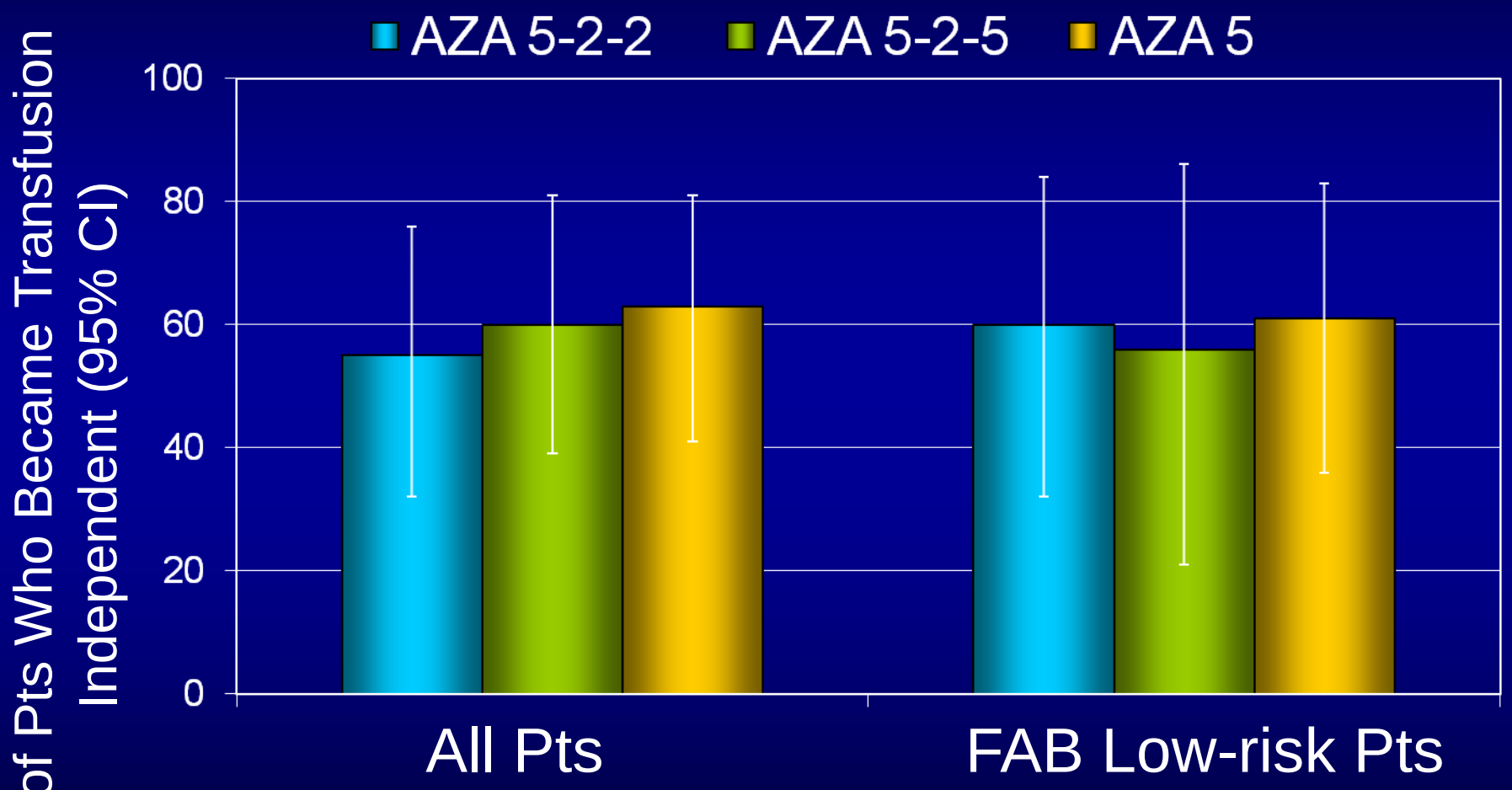
Musto P, et al. Cancer 2010

Phase II, prospective, multicenter, randomized, open-label, 3-arm trial azacitidine in community hospitals

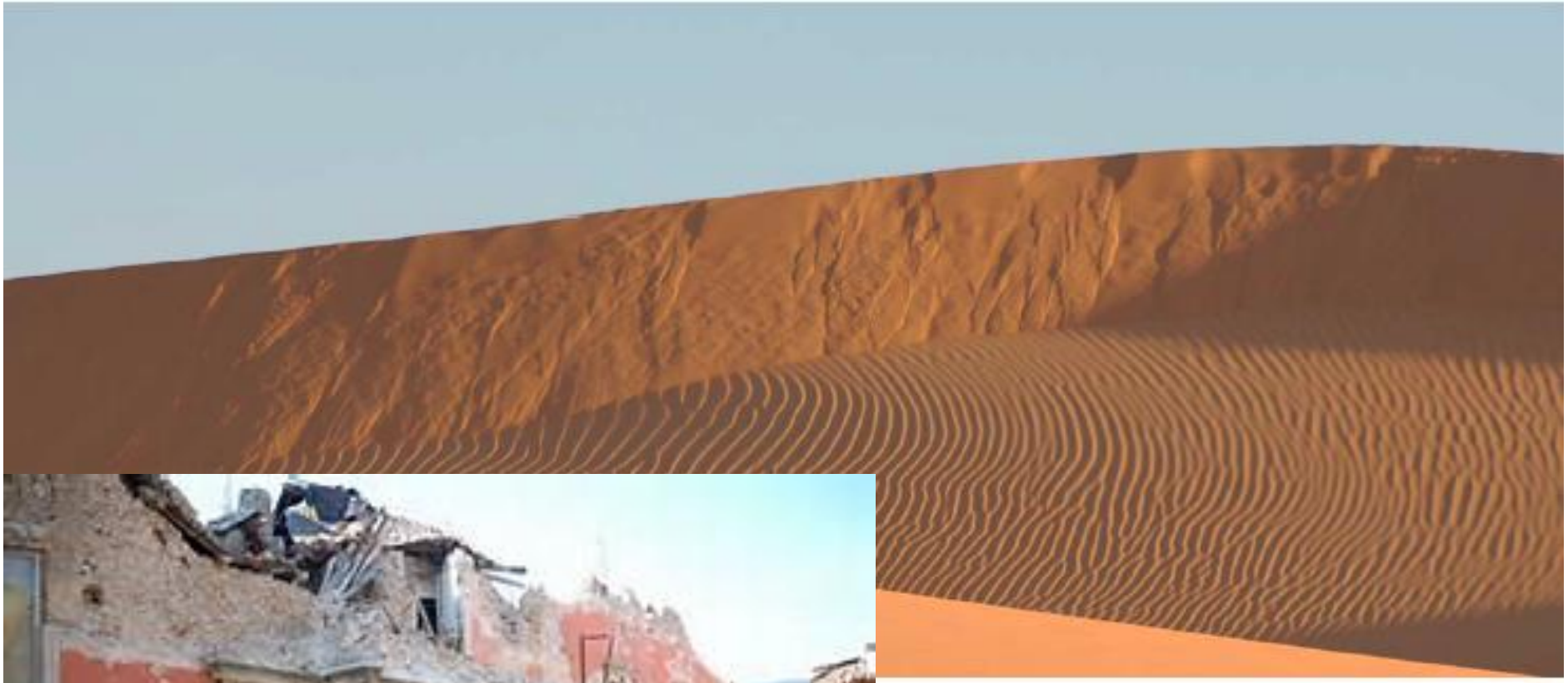


Lyons, 2009

RBC Transfusion Independence in Baseline-Dependent Pts



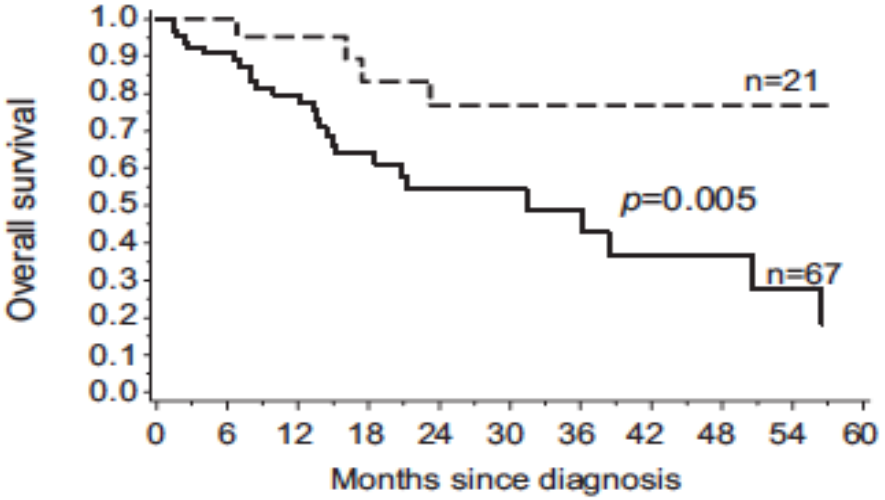
Lyons, 2009



Coordinamento Scientifico
Robin Foà

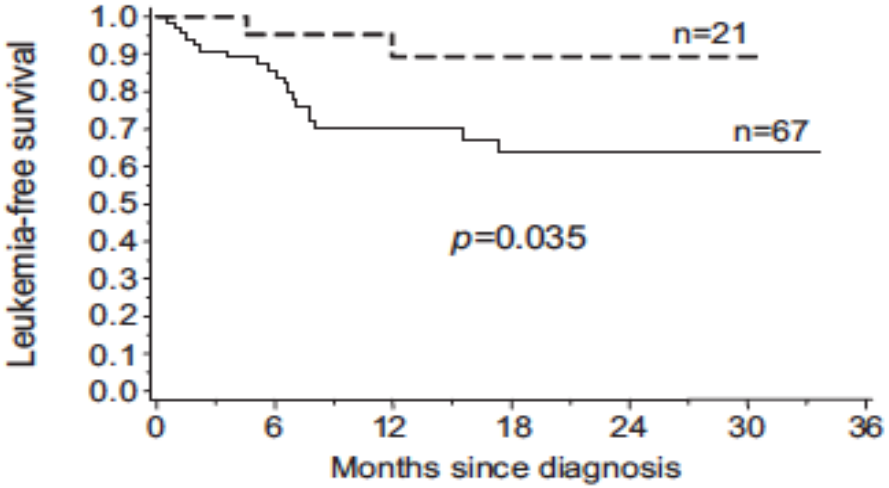
18-19 SETTEMBRE 2009
PARK HOTEL AI CAPPUCCINI
GUBBIO

TET2 Mutations are independent favorable prognostic variable in MDS



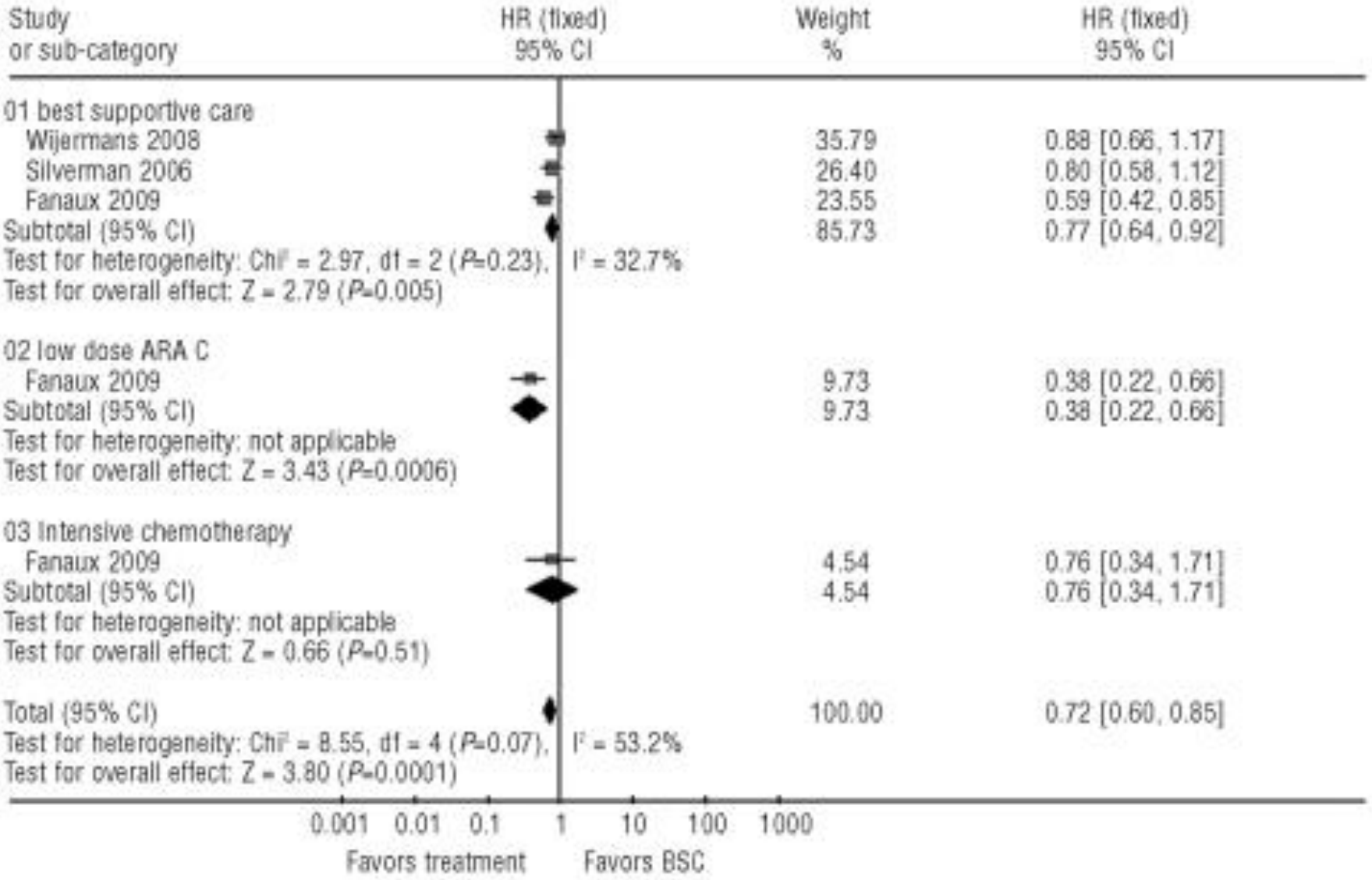
Number at risk

Months since diagnosis	0	12	24	36	48	60
Mutated (n)	21	16	12	11	8	3
Unmutated (n)	67	38	14	8	4	2

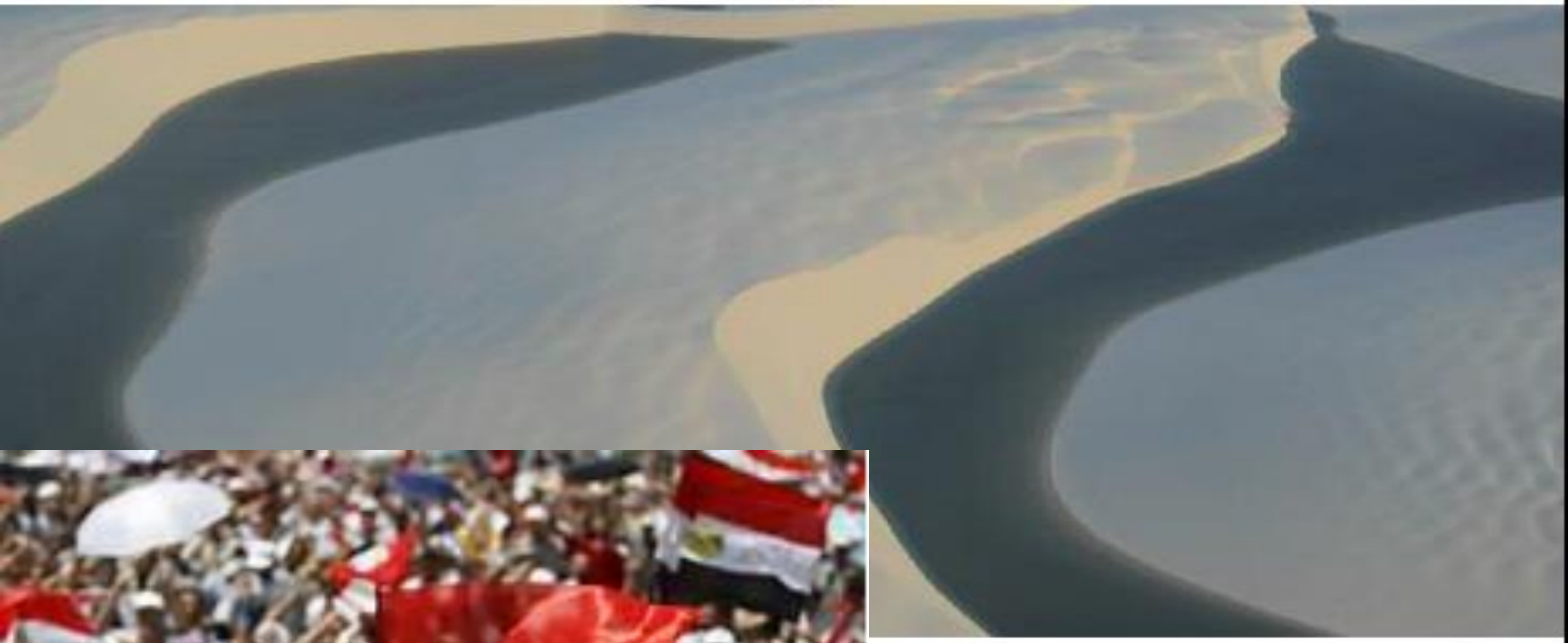


Kosmider et al Blood. 2009 Oct 8;114(15):3285-91

Metanalysis of efficacy of azacitidine and decitabine in MDS



Shpilberg et al Haematologica. 2010 Feb; 95(2): 303–310.



Coordinamento Scientifico
Robin Foà

17-18 SETTEMBRE 2010
HOTEL REGINA PALACE
STRESA

New classification of cytogenetic risk

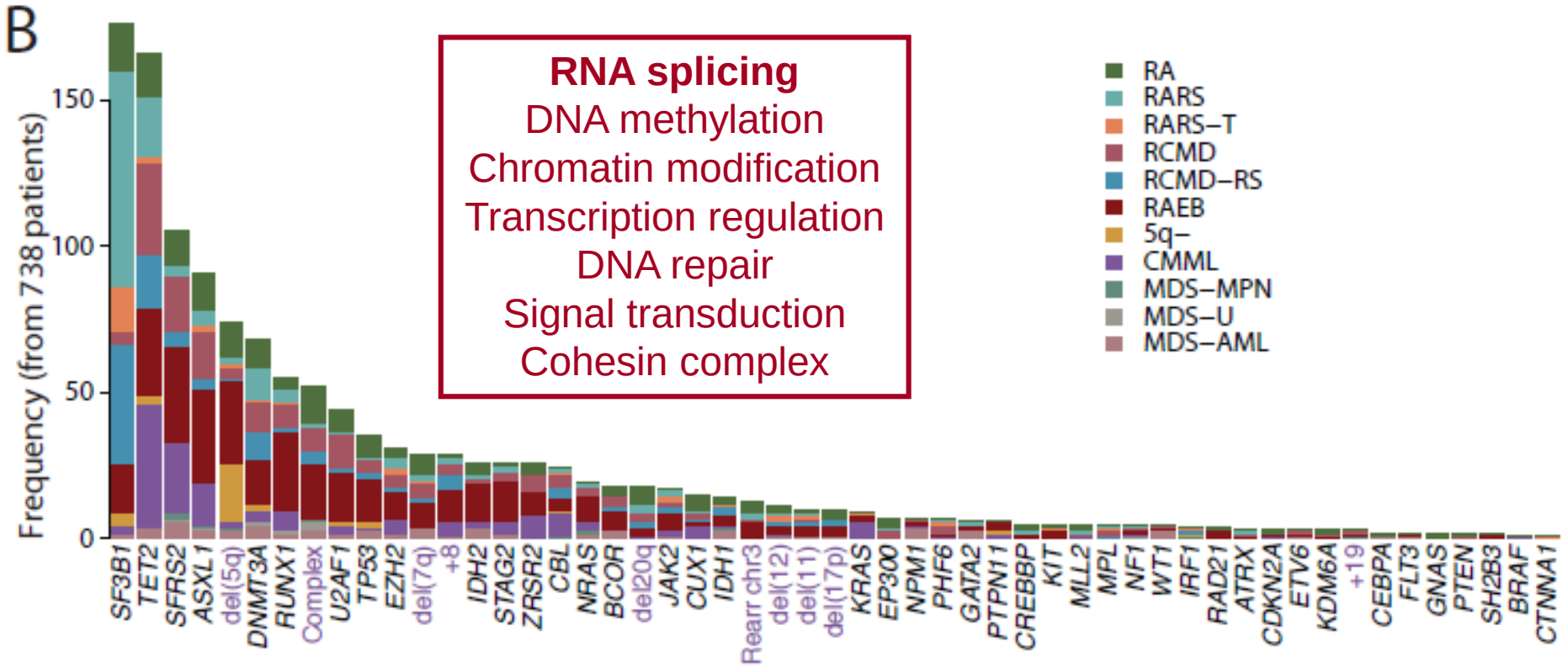
Very good	Good	Intermediate	Poor	Very poor
Isolated: del(11q) -Y	Normal **Isolated:** der(1;7) del(5q) del(12p) del(20q)	**Isolated:** 7q- +8 i(17p) +21 +19 Other single	**Isolated:** der(3)(q21q26) -7	**Complex** >3 anomalies
	Double with 5q-	Other double	**Complex** 3 anomalies	
			Double with –7/7q-	

Schanz J et alJ Clin Oncol. 2012 Mar 10;30(8):820-9.

Coordinamento Scientifico
Robin Foà

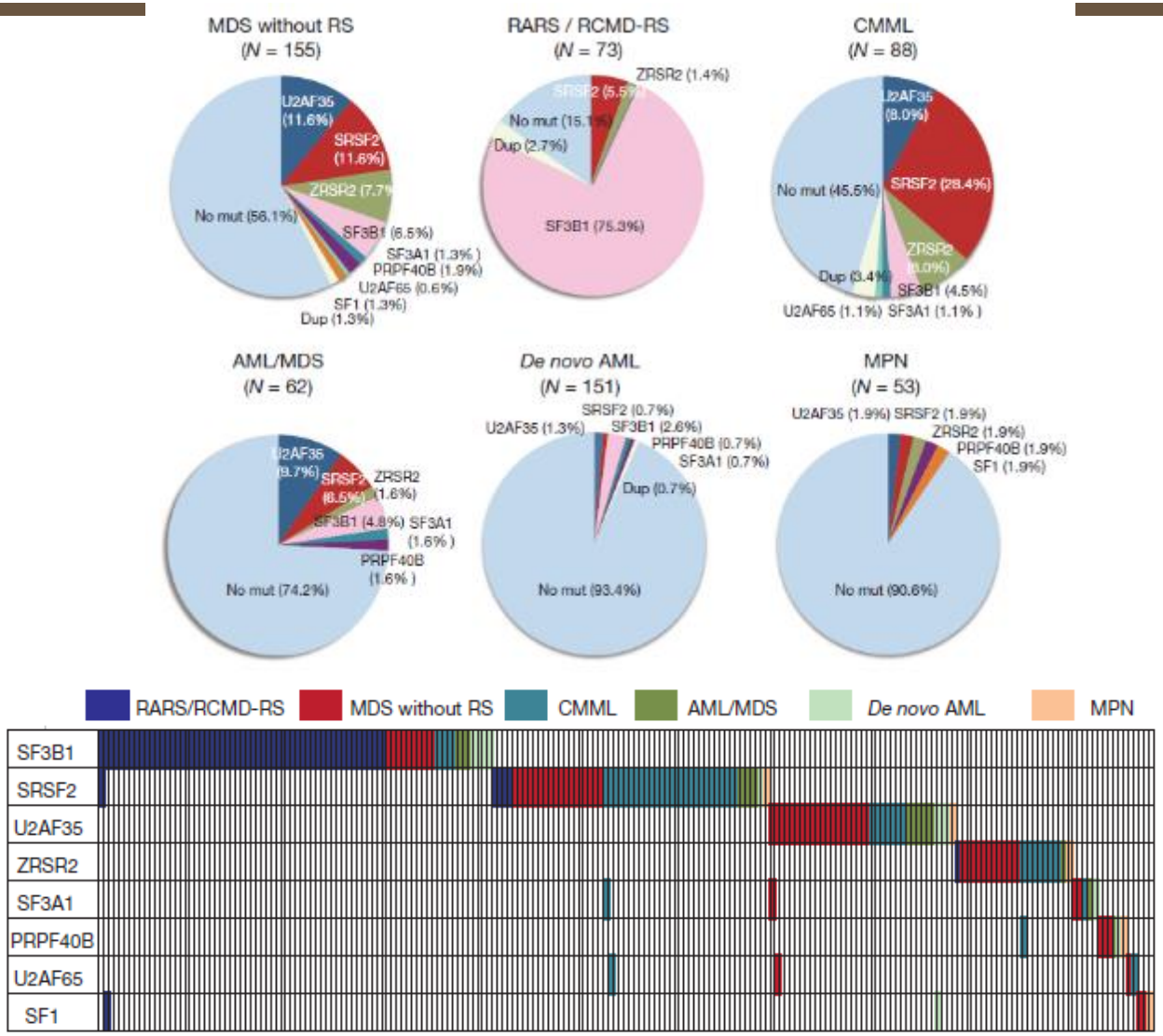
23-24 Settembre 2011
PARK HOTEL AI CAPPUCCINI
Gubbio

Clinical Effect of Point Mutations in Myelodysplastic Syndromes



Papaemmanuil E et al. Blood. 2013;122:3616-27
Cazzola M, Della Porta MG, Malcovati L. Blood 2013;122:4021-34
Della Porta MG et al. Leukemia 2015;29:1502-13

Frequent pathway mutations of splicing machinery in myelodysplasia



N Engl J Med 2011; 365:1384-1395

Nature. 2011 Sep 11;478(7367):64-9

Combined analysis MDS-003/004: Conclusions

Predictive factors* associated with:

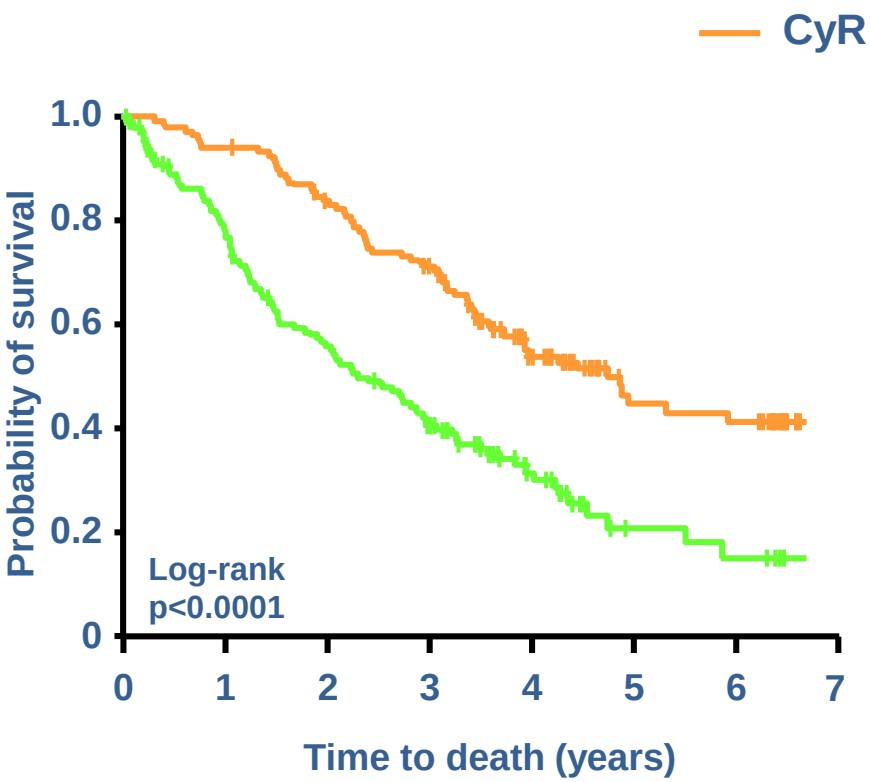
↑ risk of AML progression	→	– del(5q) plus ≥ 2 abnormalities – higher transfusion burden
↑ risk of death	→	– older age – higher FAB subtype – del(5q) plus ≥ 2 abnormalities – higher transfusion burden
↓ risk of AML progression	→	– CyR
↓ risk of death	→	– CyR – RBC-TI for ≥ 26 weeks – higher platelet count

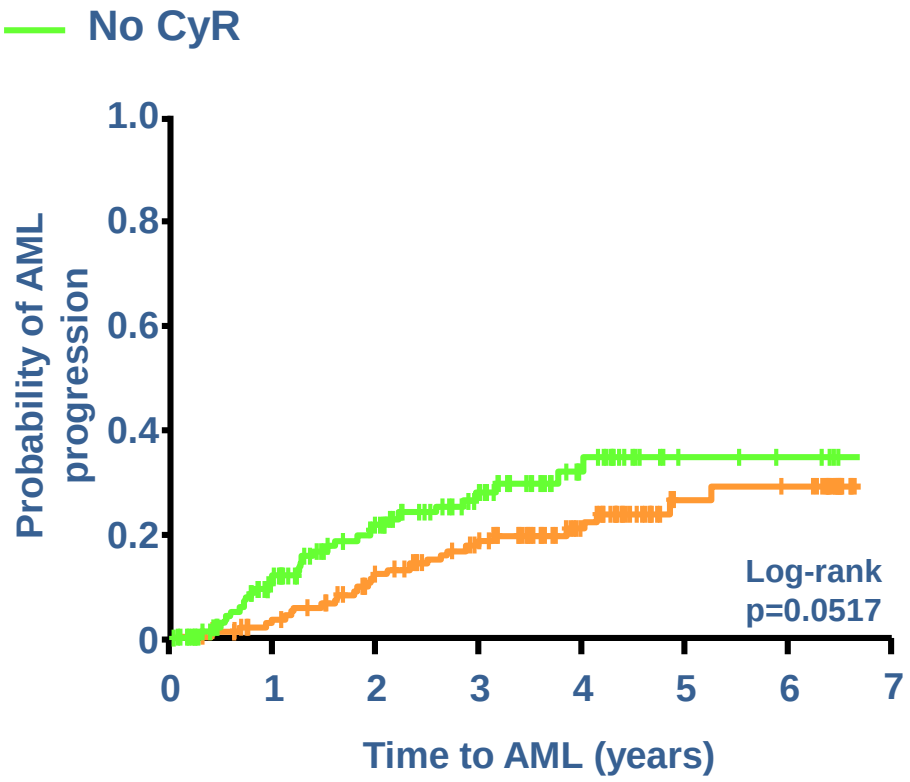
Giagounidis A, et al. Oral presentation at EHA 2011. Abstract 0481

Combined analysis of MDS-003 and MDS-004: impact of cytogenetic response on OS and progression to AML in lower risk MDS patients with del(5q) treated with lenalidomide (n=286)

Achievement of CyR was associated with significantly longer OS

Risk of AML progression appeared to be higher in patients without CyR





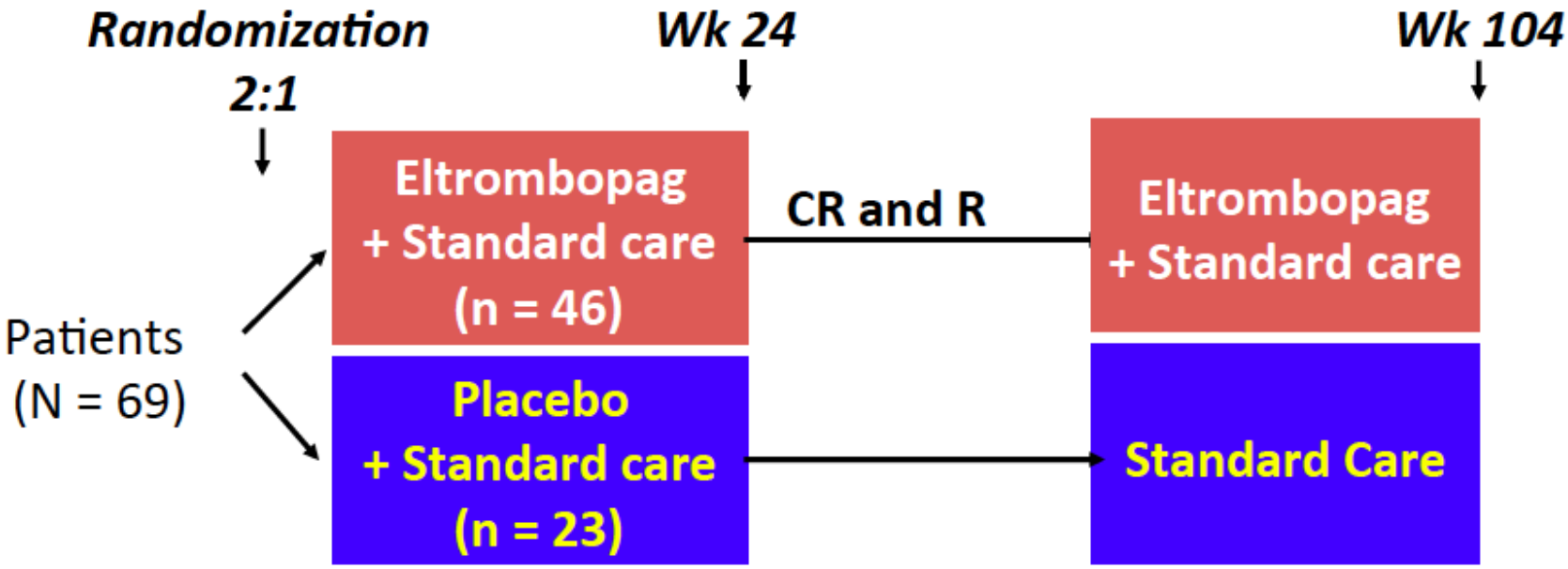
Giagounidis A, et al. Oral presentation at 11th International Symposium on MDS 2011, Edinburgh, UK. Abstract 58

Coordinamento Scientifico
Robin Foà

14-15 SETTEMBRE 2012

CENTRO CONVEGNI LE MONACELLE
MATERA

Eltrombopag vs Placebo in Low- or Intermediate-1 IPSS risk MDS and low PLT count (< 30.000/mm^3) receiving supportive care



Dose start: 50 mg/d p.o. with increases every 2 weeks up to 300 mg daily

Oliva et al, Oral 1138

Results: PLT responses and Bleeding within first 8 weeks

Response	Eltrombopag N= 9	Placebo N=4
R, n	1	1
CR, n	5	0
NR	3§	3
Total, n (%)	6 (67)	1 (25)
WHO bleeding grade ≥ 2, events	0	8*

§ 1 NR reached study completiona at 300 mg dosing
*** One case with WHO bleeding grade 2 events (n=8)**

Eltrombopag:
- Day +8, 4 patients in R and 1 patient in CR
- Day +14, 1 patient in R and 4 in CR

Median dose for response 50 mg daily

Complete Response (CR):
PLT count ≥ 100,000/mm^3 and absence of bleeding
Response (R):
Baseline > 20 ,000/mm^3: absence of bleeding + absolute increase in PLT ≥ 30,000/mm^3
Baseline < 20,000/mm^3 : PLT > 20,000/mm^3 and increase by at least 100%, not due to PLT transfusion.
Durable PLT response = continuous PLT response of at least 4 weeks

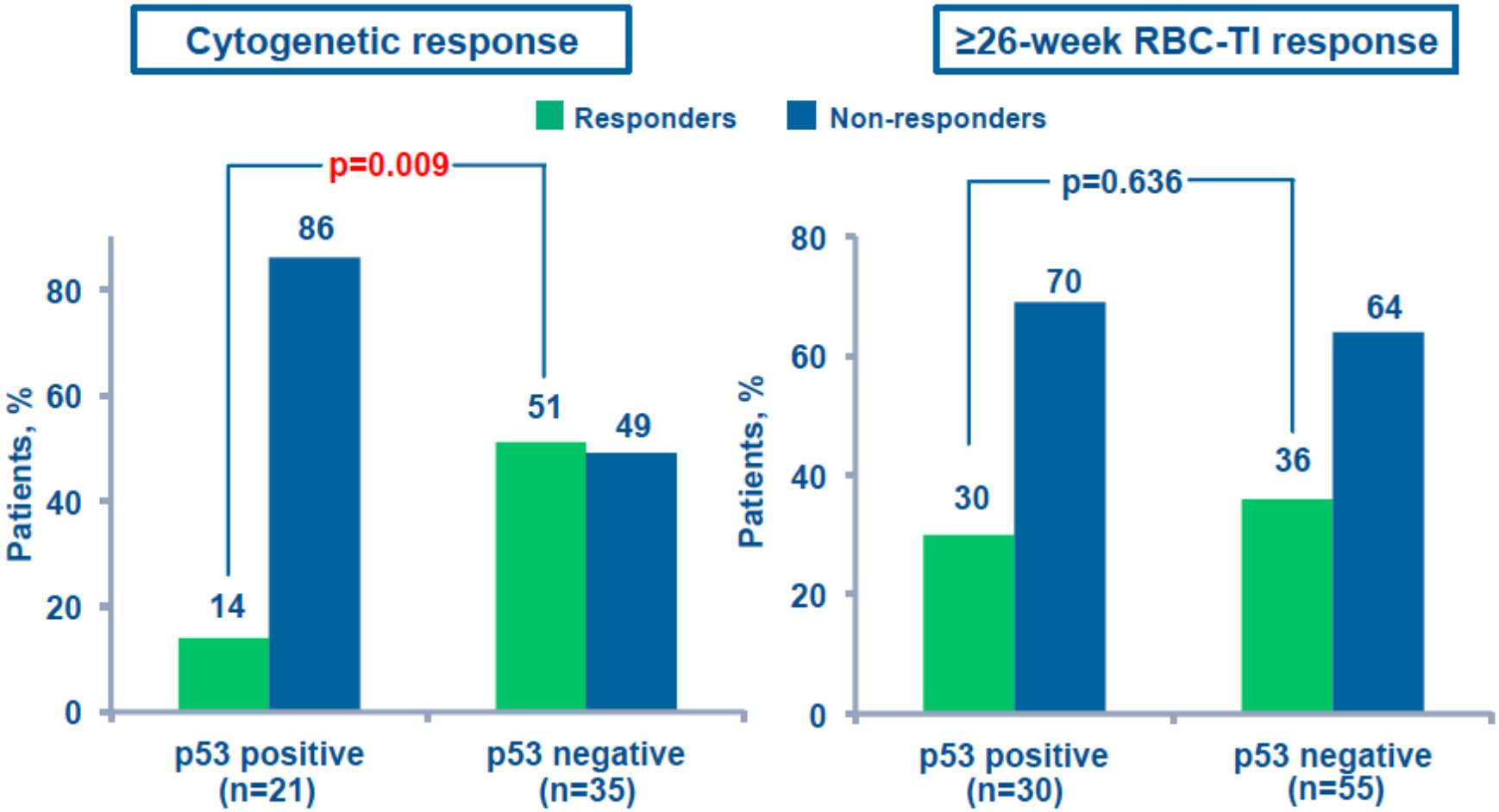
Oliva et al, Oral 1138

Coordinamento Scientifico
Robin Foà

20-21 SETTEMBRE 2013

GRAND HOTEL BAGLIONI
FIRENZE

Prognostic value of p53 expression in patients with low-/int-1-risk del5q



Strong p53 protein expression* was associated with poor cytogenetic response but had no effect on achievement of RBC-TI

*Correlated with presence of *TP53* mutations

Saft L, et al. Oral presentation at EHA 2013. Abstract S-1165

Azacitidine as bridging therapy before allo-HSCT in patients with higher-risk MDS

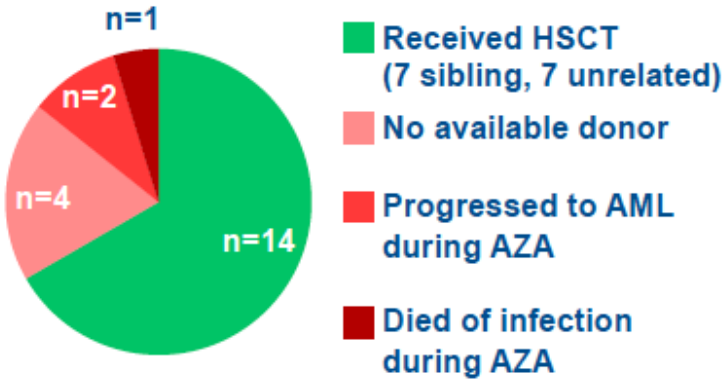
Phase II study evaluating the efficacy and safety of azacitidine (75mg/m²/d, d1–7, q28d) as bridging therapy in patients with higher-risk MDS eligible for allo-HSCT

Patient characteristics (n=21)	
Median age, years (range)	50 (18–63)
Male/female, %	67/33
WHO diagnosis, % RCMD/RAEB-1/RAEB-2	14/14/72
IPSS risk, % int-2/high	52/48
IPSS-R risk, % int/high/very high	33/24/43
Karyotype (by IPSS), % good/int/poor	19/38/43
WPSS risk, % high/very high	48/52

AZA

- Median cycles, n (range): 4 (1–9)
- ORR*: 62%
- CR: 10%
- PR: 5%
- HI: 48%
- SD: 24%

Details of HSCT



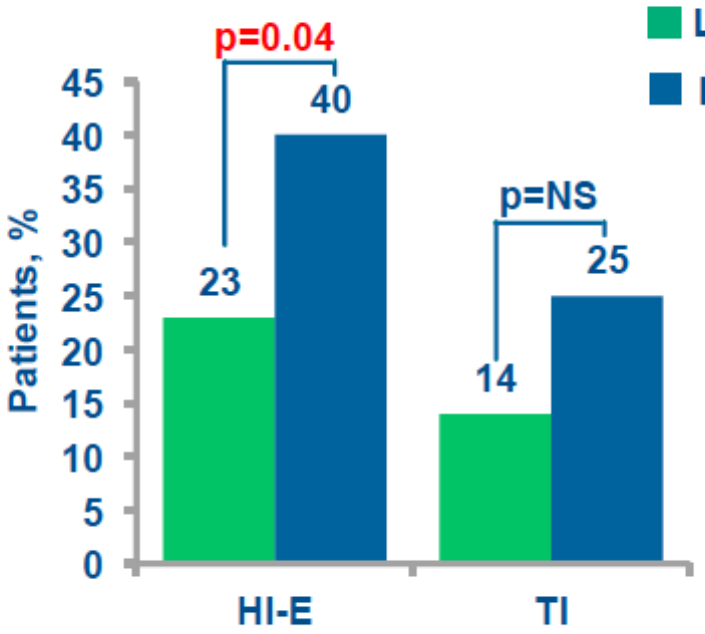
- PBSC: 100%
- Non-myeloablative conditioning: fludarabine + busulphan
- Immunosuppression:
  - sibling: cyclosporin + methotrexate
  - unrelated: anti-thymocyte globulin + FK 506

*CR+PR+HI

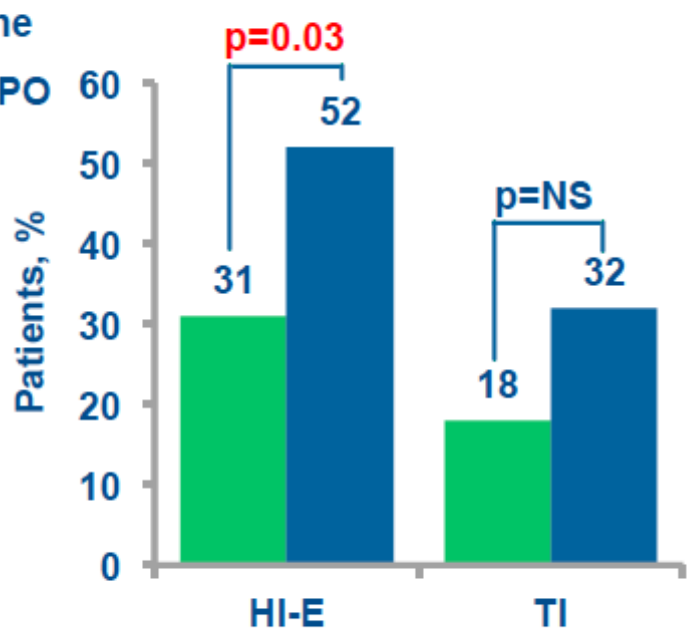
Ahn JS, et al. Poster presentation at EHA 2013. Abstract P-191

LEN +/– EPO as salvage therapy for lower-risk patients with MDS non-del(5q): response

Erythroid response, ITT population (n=129)



Erythroid response after 4 cycles (n=99)



- A gene promoter polymorphism in the *CRBN* gene significantly correlated with HI-E in both treatment arms (p=0.034)

LEN + EPO salvage therapy yielded a significantly better erythroid response than LEN alone in lower-risk MDS patients with anaemia following first-line ESA

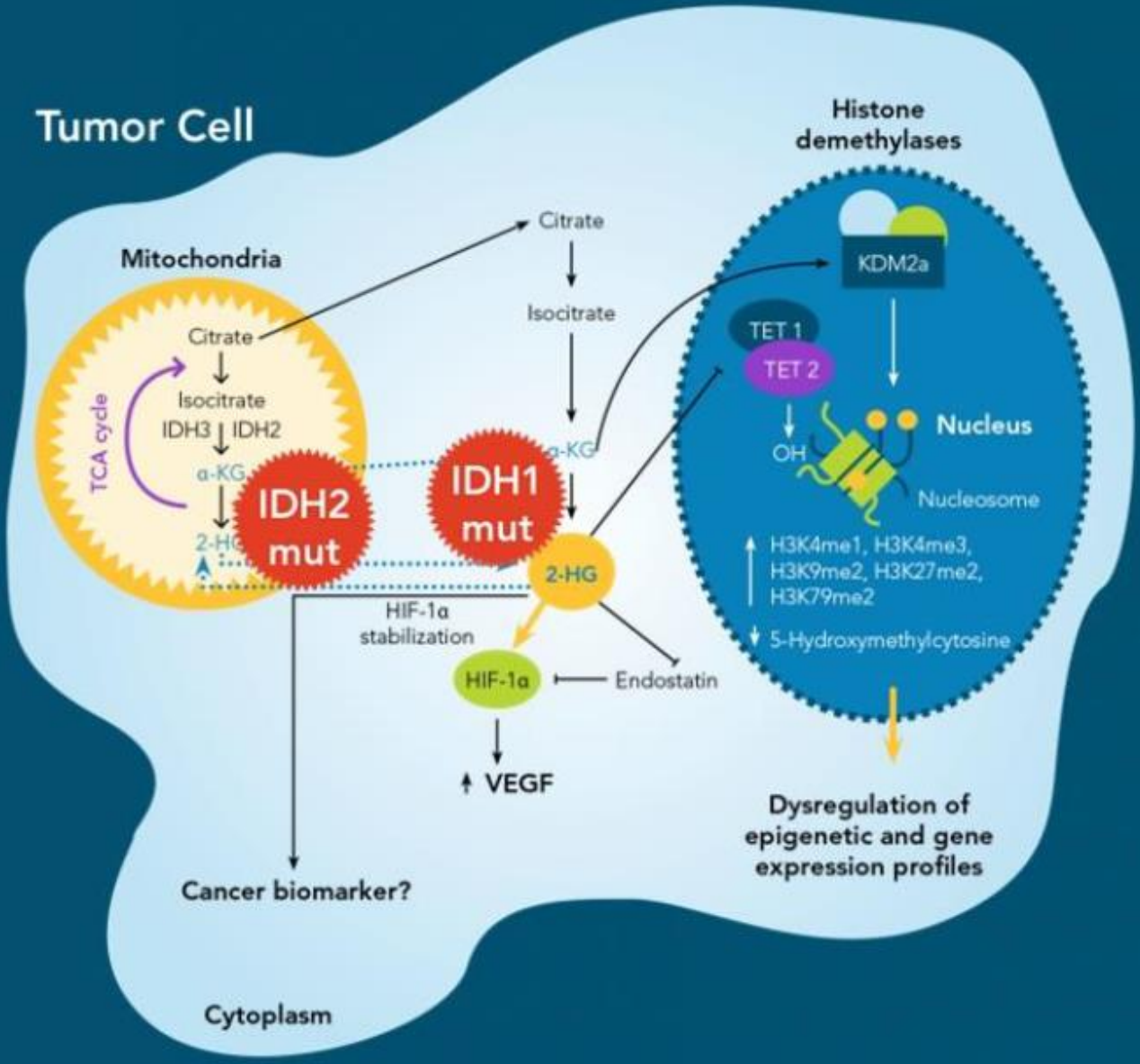
Toma A, et al. Oral presentation at EHA 2013. Abstract S-1107

Coordinamento Scientifico
Robin Foà

19-20 SETTEMBRE 2014

GRAND HOTEL BAGLIONI
FIRENZE

IDH Mutations Represent Important Cancer Metabolism Targets



- **IDHwt: catalyzes oxidative decarboxylation of isocitrate to produce CO_2 and α-KG**
- **3 isoforms exist: IDH1, IDH2, IDH3**
  - **IDH1: cytoplasm**
  - **IDH2: mitochondria**
- **IDH mutations have neomorphic activity:**
  - **Produce high levels of "oncometabolite" 2-HG (gain of function)**
  - **2HG leads to differentiation block via epigenetic alterations**

Adapted from: Prensner JR, Chinnaiyan AM. *Nat Med.* 2011;17(3):291-293.

agios

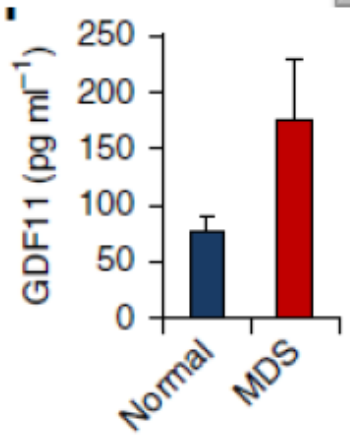
Best Response: IWG Criteria per Investigator

Overall Response Rate: 14 of 25 Evaluable Subjects

	30 mg BID N=7	50 mg BID N=7	75 mg BID N=6	100 mg QD N=5	100 mg BID N=5	150 mg QD N=5	Total N=35
CR	2	3	-	1	-	-	6
CRp	1	-	-	-	1	-	2
CRi	-	1	-	-	-	-	1
PR	1	1	1	-	1	1[a]	5
SD	-	1	2	1	-	1	5
PD	-	1	1	3	1	-	6[b]
ORR	*4/4*	*5/7*	*1/4*	*1/5*	*2/3*	*1/2*	*14/25*
NE	3[c]	-	2[c]	-	2[c]	3[d]	10

[a] *PR at C1D15*
[b] *3 Subjects with Clinical PD/Clinical Deterioration (No Day 28 Marrow Assessment).*
[c] *Subjects did not have a Day 28 Marrow Assessment (Off Study).*
[d] *Subjects on study (<28 days at data cut).*

CR = Complete Response
CRp = Complete Response, Incomplete Platelet Recovery
CRi = Complete Response, Incomplete Hematologic Recovery
PR = Partial Response (>50% Decrease in Bone Marrow Blasts)
SD = Stable Disease
PD = Progressive Disease
NE = Not Evaluable
ORR = CR + CRp + CRi + PR



TGF-ß Superfamily Signaling

GDF11, Others

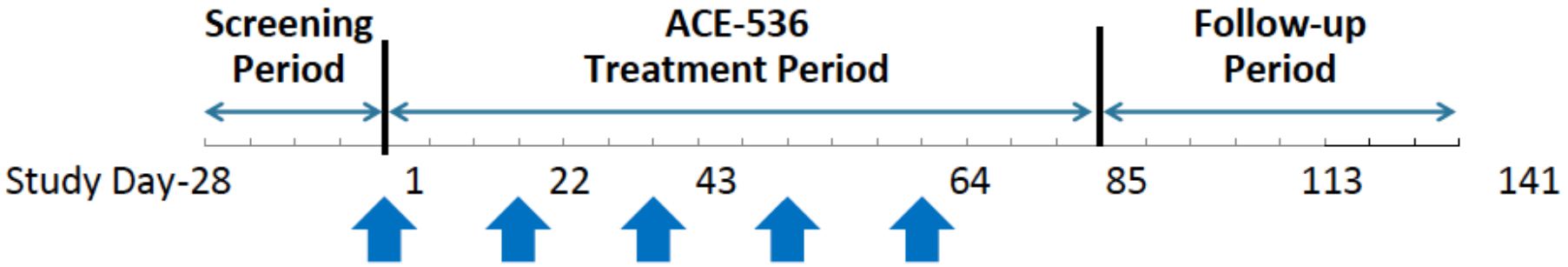
ACE-536

Erythropoiesis

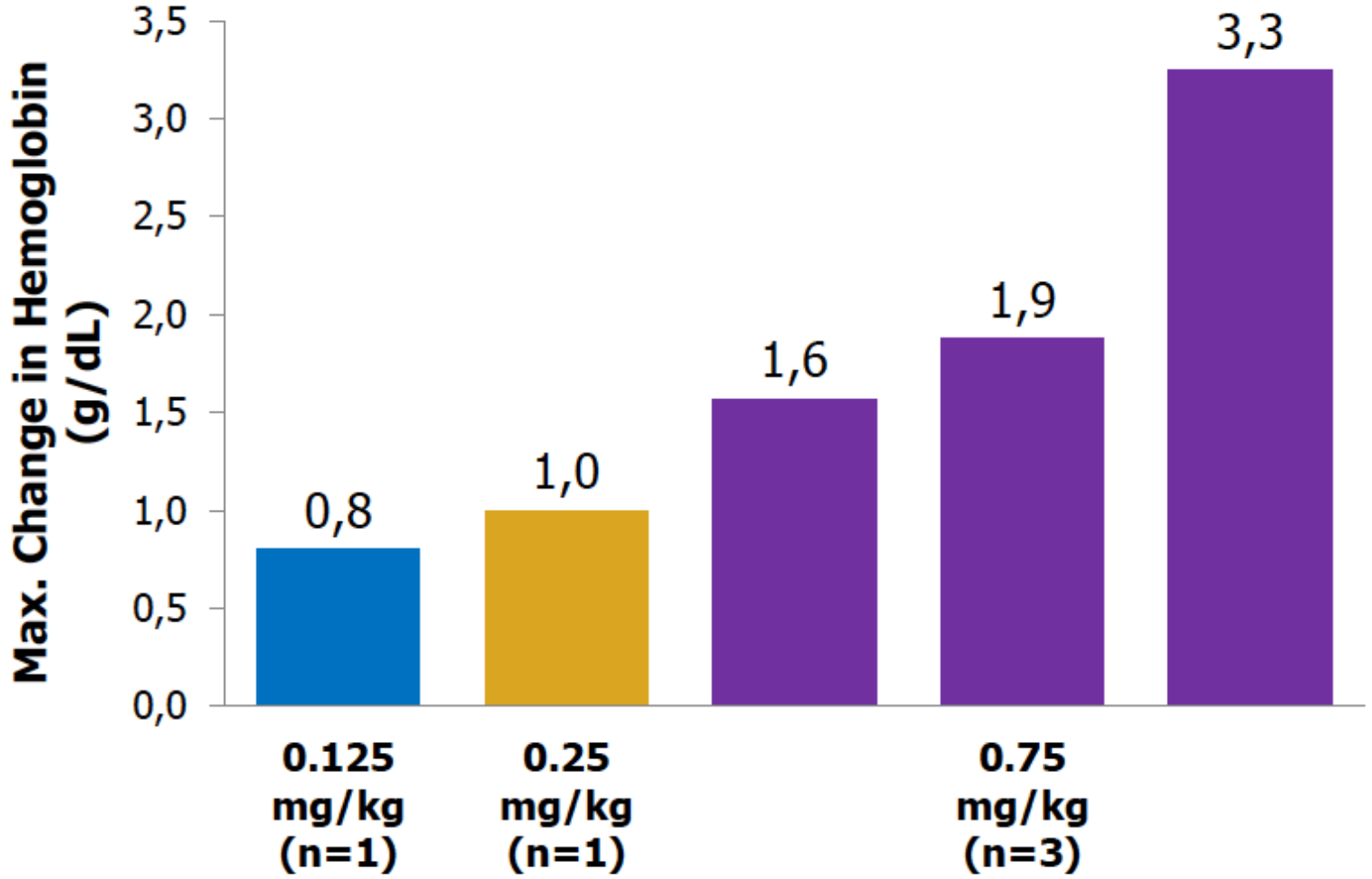
Fusion protein containing modified activin receptor IIB (ActRIIB)

Suragani et al. Nature Medicine 2014

- Phase 2, multicenter, open-label, dose-finding
- IPSS Low/Int-1
  - Transfusion-dependent (TD), or
  - Non-transfusion dependent (NTD, Hgb <10 g/dL)
- EPO >500 U/L or nonresponsive/refractory to ESAs
- No prior azacitidine or decitabine
- Schedule: ACE-536 SC every 3 weeks for 3 months (up to 5 doses)
- Preliminary data as of 28 April 2014



Maximum Hemoglobin Increase in NTD Patients



NTD, non-transfusion dependent

ICH BIN CHARLIE

انا شارلي

YO SOY CHARLIE

JE SUIS CHARLIE

من چارلی هستیم

SOM CHARLIE HEBDO

Я ШАРЛИ ЭБДО

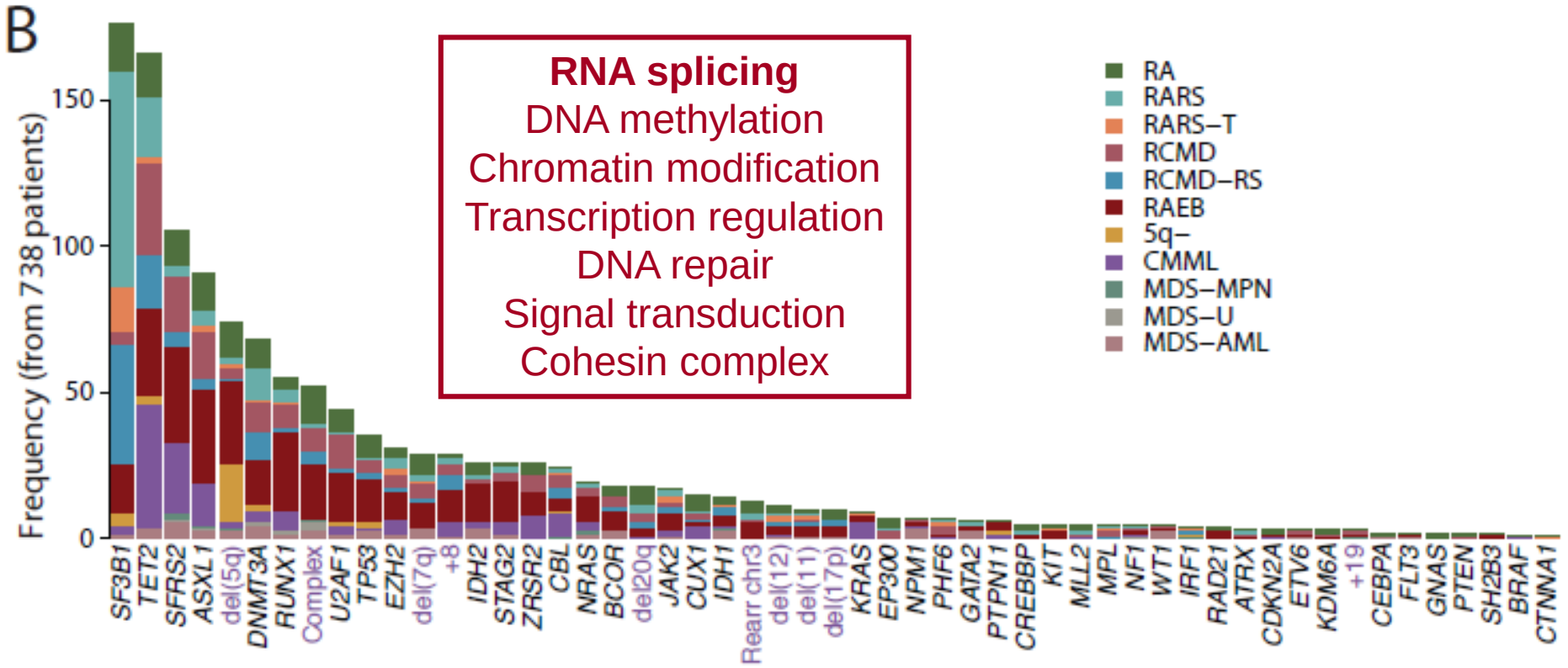
JSEM CHARLIE HEBDO

Coordinamento Scientifico
Robin Foà

18-19 SETTEMBRE 2015

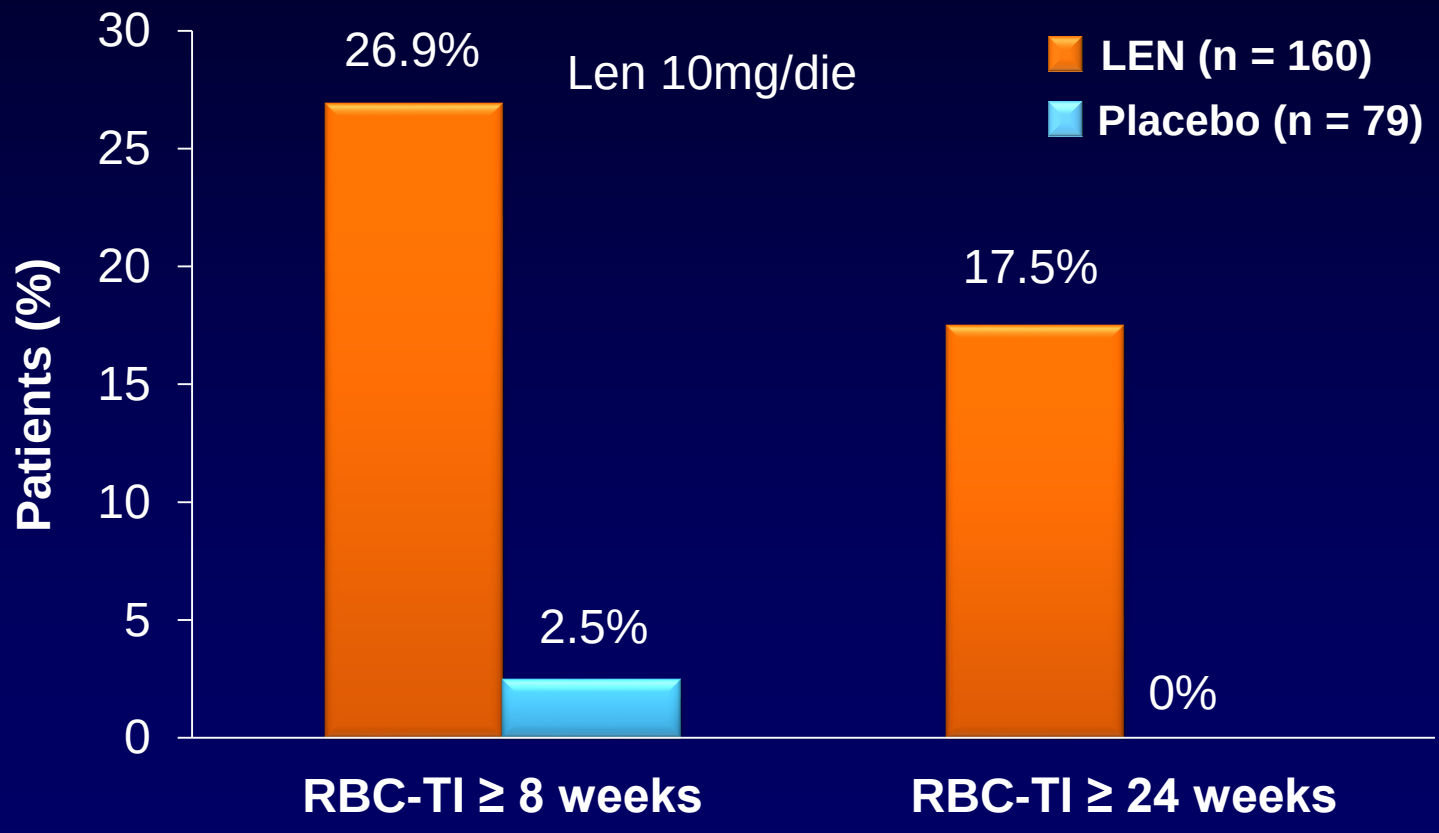
GRAND HOTEL BAGLIONI
FIRENZE

Clinical Effect of Point Mutations in Myelodysplastic Syndromes



Papaemmanuil E et al. Blood. 2013;122:3616-27
Cazzola M, Della Porta MG, Malcovati L. Blood 2013;122:4021-34
Della Porta MG et al. Leukemia 2015;29:1502-13

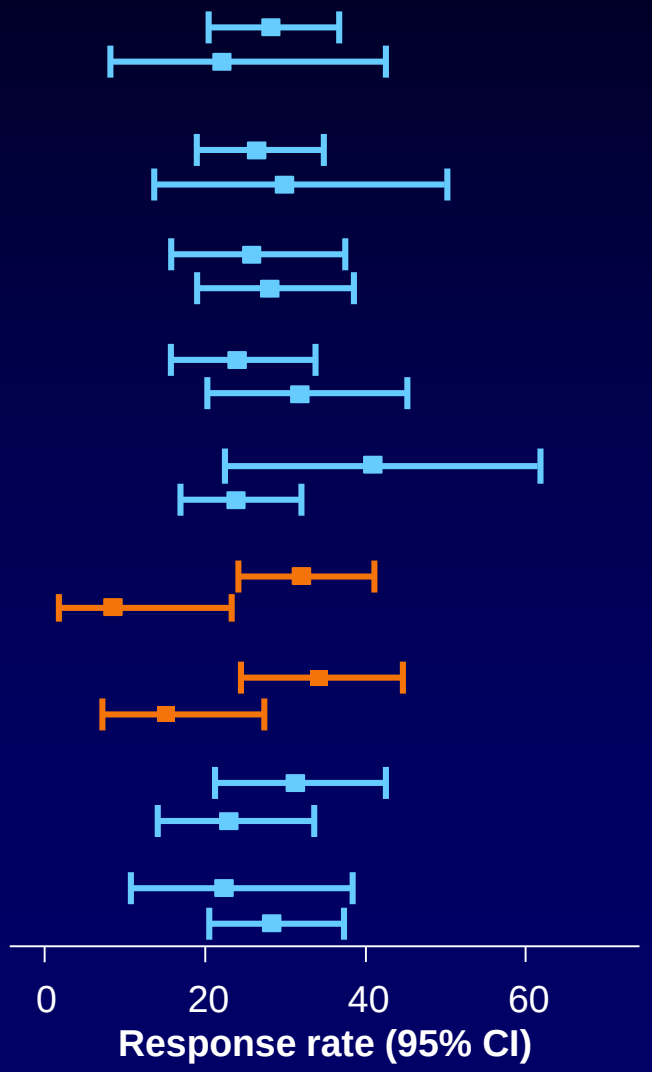
Lenalidomide in nondel5q MDS (MDS-005): RBC-TI ≥ 24 Weeks



Santini V et al JCO 2015

MDS-005: Subgroup Analysis of RBC-TI ≥ 8 Weeks in LEN-Treated Patients

Baseline characteristic	RBC-TI ≥ 8 weeks, n/N (%)
IPSS karyotype (central review)	
Good	37/132 (28.0)
Intermediate	6/27 (22.2)
BM blasts	
< 5%	35/133 (26.3)
≥ 5%	8/27 (29.6)
IPSS category (central review)	
Low	18/70 (25.7)
Int-1	25/89 (28.1)
Number of cytopenias	
0–1	24/100 (24.0)
2–3	19/60 (31.7)
Prior G-CSF use	
Yes	11/27 (40.7)
No	32/133 (24.1)
Prior ESA use*	
Yes	40/125 (32.0)
No	3/35 (8.6)
Serum EPO level*	
≤ 500 mU/mL	33/97 (34.0)
> 500 mU/mL	9/58 (15.5)
ECOG performance status score	
0	24/77 (31.2)
1–2	19/83 (22.9)
Creatinine clearance	
< 60 mL/min	9/40 (22.5)
≥ 60 mL/min	34/120 (28.3)



*Indicates a statistically significant difference in rates within this subgroup ($P < 0.05$).
ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor.

Overall survival and baseline disease characteristics in MDS pts with primary HMA failure in a randomized, controlled, phase III study of rigosertib

- ONTIME trial: **rigosertib (inibizione di PI3K e PLK) vs BSC** (2:1) in 299 pts alto rischio non rispondenti o in failure post HMA
- 69% maschi, età mediana 73 anni
- **Riscontrato un vantaggio di OS per i pts trattati con rigosertib**

Median (months) OS by Baseline Disease Characteristics in Pts with Primary HMA Failure

Characteristic	RIG		BSC		Log-rank p-value	Hazard ratio (RIG/BSC) (95% CI)
	N	OS	N	OS		
All patients with Primary HMA Failure	117	8.6	52	4.5	0.011	0.63 (0.44-0.90)
IPSS-R category of high or very high	97	8.6	38	4.1	0.0015	0.52 (0.35-0.79)
Bone marrow blast = 5%-19%	93	10.1	36	4.7	0.0079	0.58 (0.39-0.87)
Duration of prior HMA treatment < 9 months	79	8.6	37	4.5	0.0014	0.49 (0.31-0.76)

- Aes più frequenti con rigosertib: anemia, neutropenia febbrile, polmonite

Clinical and molecular predictors of response to erythropoiesis stimulating agents (ESA) in lower risk MDS

- **Fattori prognostici per la risposta eritroide all'ESA in 90 pts** basso rischio (FISM, GFM, GMDS)
- Età mediana 74 anni, 26% trasfusione dipendenti
- WHO: 21% RA 24% RAEB-1 24.6% RARS 24% RCMD
  2% del (5q) 3.6% MDS-U
- **86% dei pazienti con almeno 1 mutazione**
- SF3B1, DNMT3A, TET2 possono essere concomitanti; ASXL1 e DNMT3A sono mutualmente esclusive come anche SRSF2 E SF3B1. **Il no. di mutazioni non correla con il grado di displasia**
- **Più di 2 mutazioni sono predittive di cattive risposte eritroidi**
- In multivariata, mutazioni, età, cariotipo e displasia non hanno impatto su HI-E

Coordinamento Scientifico
Robin Foà

16-17 SETTEMBRE 2016

GRAND HOTEL BAGLIONI
FIRENZE

WHO 2016 classification

Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood

Blood , April 2016

WHO proposal – MDS 2016

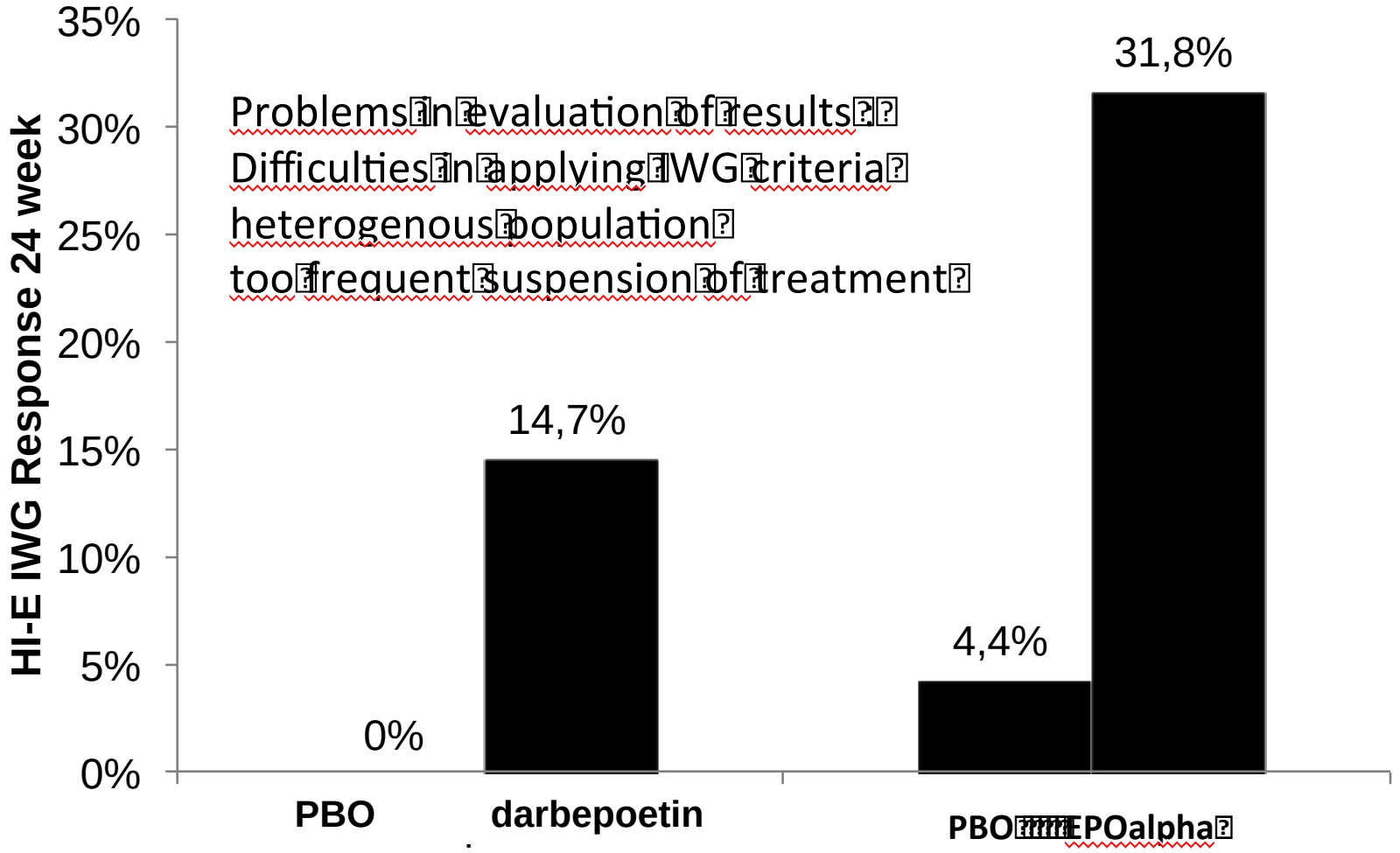
Old WHO	Marrow	WHO 2016
MDS with single del(5q)	< 5% blasts	▪ del(5q) ±1 apart Chr7
RARS	< 5% blasts	▪ MDS-RS with single lineage dysplasia (MDS-RS-SLD) ▪ MDS-RS with multilineage dysplasia (MDS-RS-MLD)
RA, RT, RN	< 5% blasts	▪ MDS with single lineage dysplasia (MDS-SLD)
RCMD (± RS)	< 5% blasts	▪ MDS with multilineage dysplasia (MDS-MLD)
RAEB-1	5–9% blasts	▪ MDS with excess blasts (MDS-EB1)
RAEB-2	10–19% blasts	▪ MDS with excess blasts (MDS-EB2)

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

ESAs in MDS

IWG responses in registration studies

IPSS Lower risk



Platzbecker et al. Haematologica 2016; 101: s1, abs 128

Fenaux et al. Haematologica 2016; 101: s1, abs P248

Epoetin-a vs placebo in Low and Int-1 MDS, a Multicenter, randomized, double blind, placebo controlled phase 3 study

Key eligibility criteria

- ✓De novo IPSS Low or Int-1 MDS
- ✓Hb ≤10.0 g/dl
- ✓Transfusions ≤4 RBC units within 8 weeks before randomization
- ✓Baseline serum EPO level <500 mU/mL
- ✓Adequate iron and B9 & B12 vitamin stores

RANDOMIZE

2:1

Epoetin-a (n= 85)

- **First administration and up to week 8: 450 IU/kg SQ once weekly (max. 40K IU)**
- **If no response at wk 8 and Hb level <11 g/dL: 1050 IU/kg SQ once weekly (max. 80K IU)**
- **If no response at wk 8 and Hb level 11-12 g/dL: 787.5 IU/kg SQ once weekly (max. 80K IU)**

Placebo (n= 45)

Matching placebo

Primary endpoint

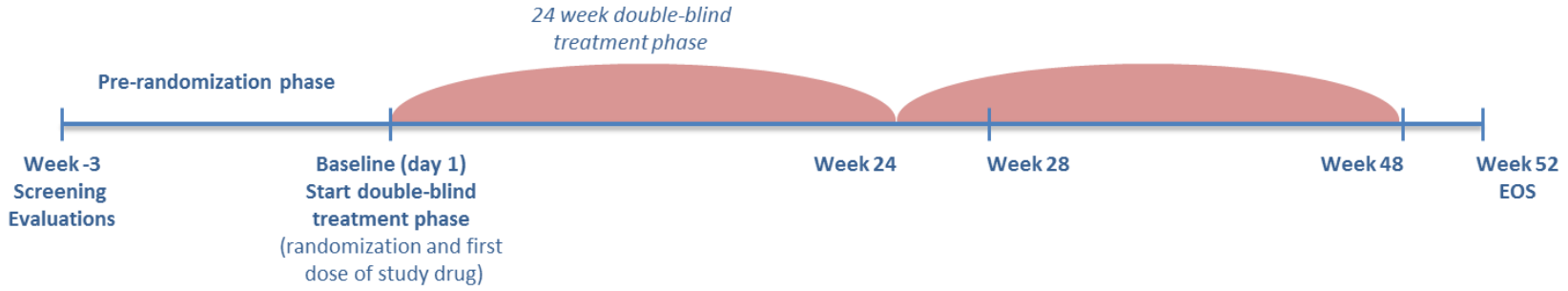
Erythroid Response (IWG 2006 criteria) at any point during 24 weeks

Secondary endpoints

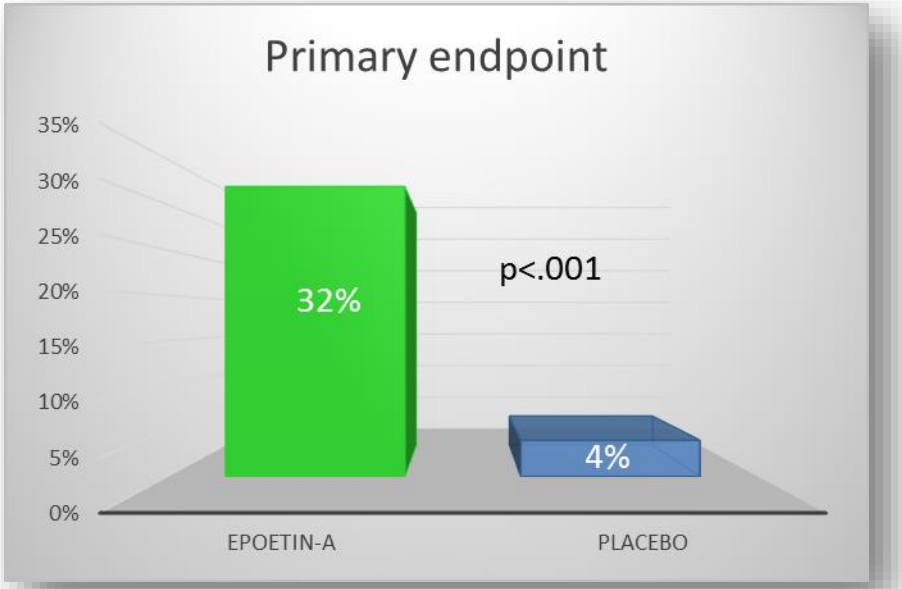
- Erythroid response at wk 24
- Duration of the response
- Time to first RBC
- Transfusion free interval
- QoL

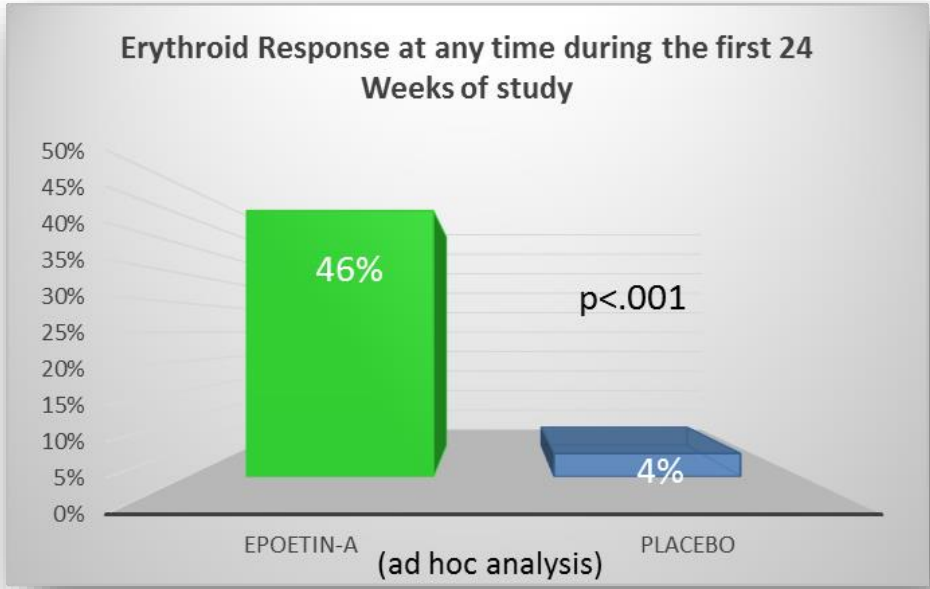
Stratification:

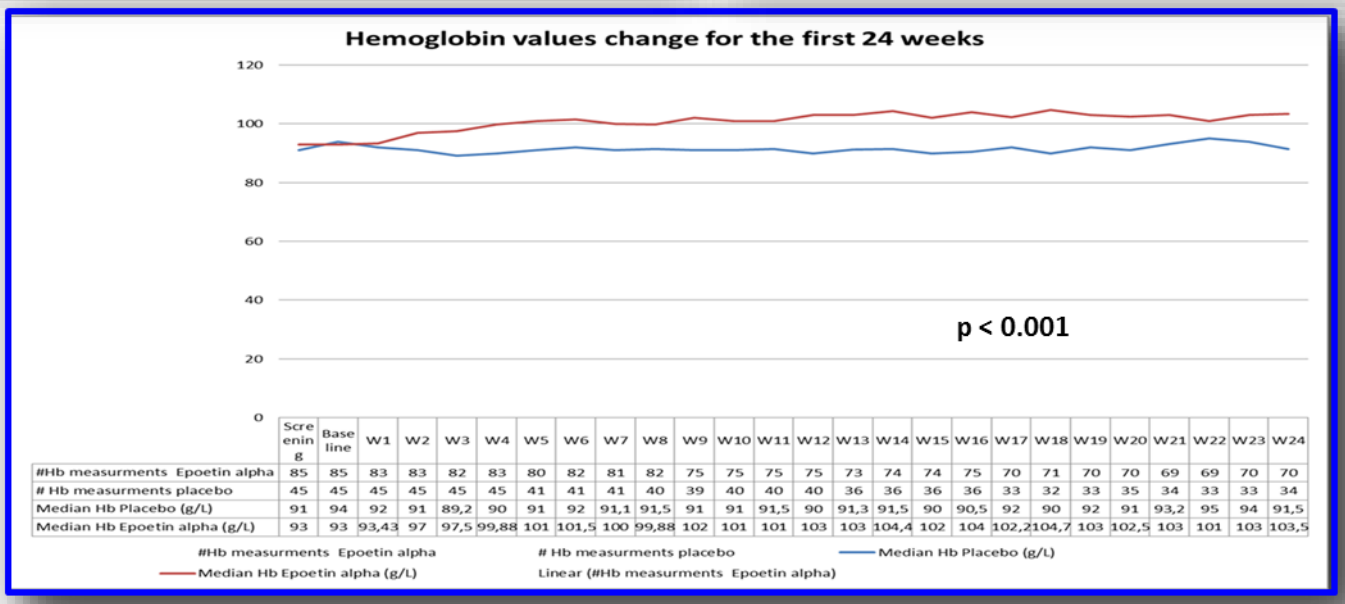
- Transfusion requirements (yes/no) in the 8 weeks prior to baseline
- Serum erythropoietin levels (≥200 mU/mL or <200 mU/mL) during screening



Efficacy results

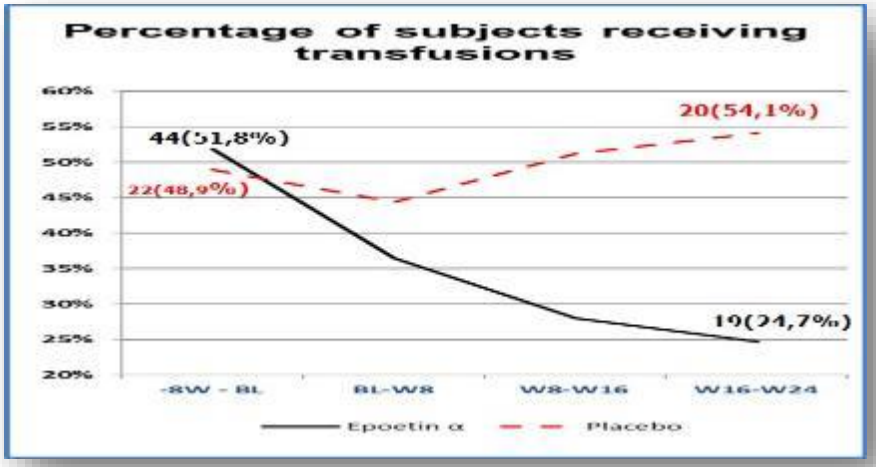


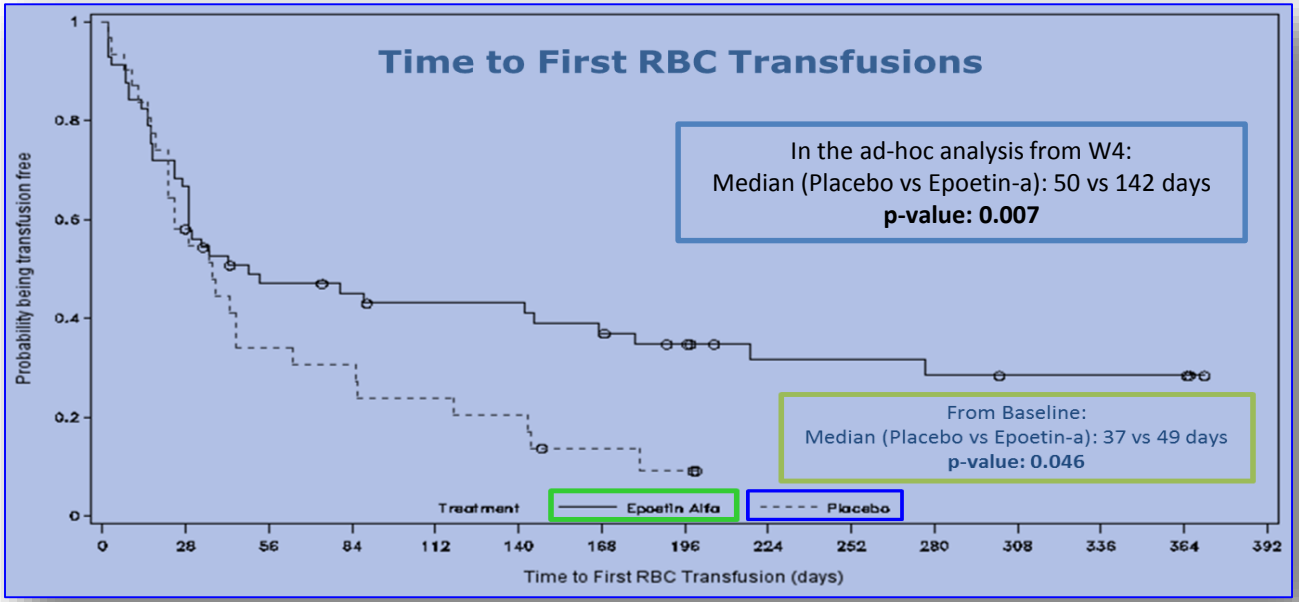




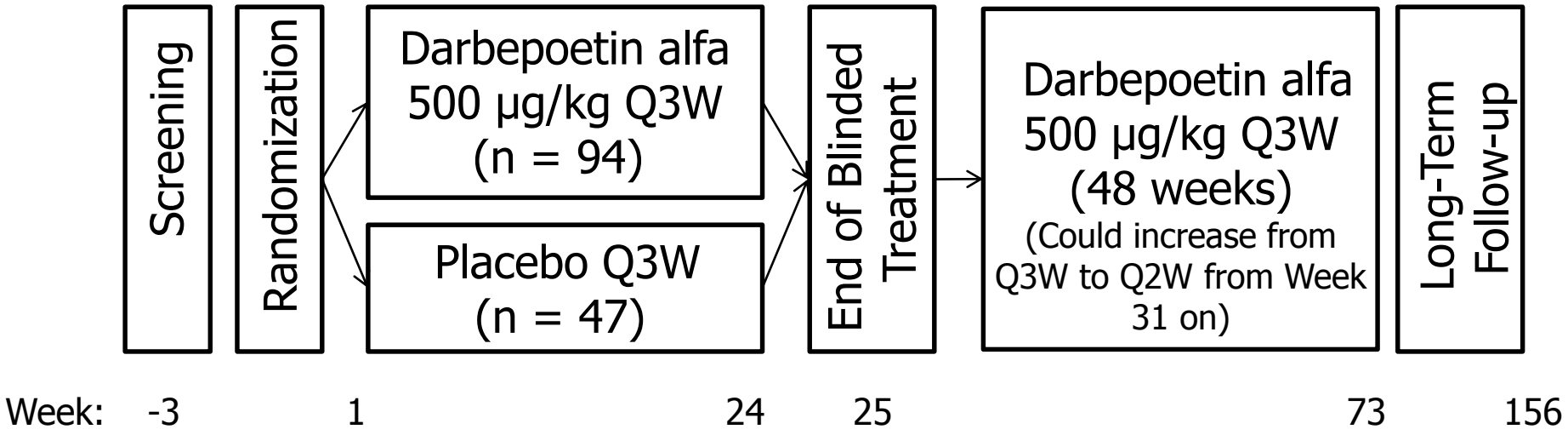
	Screening	Baseline	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23	W24
#Hb measurments Epoetin alpha	85	85	83	83	82	83	80	82	81	82	75	75	75	75	73	74	74	75	70	71	70	70	69	69	70	70
# Hb measurments placebo	45	45	45	45	45	45	41	41	41	40	39	40	40	40	36	36	36	36	33	32	33	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

Efficacy results





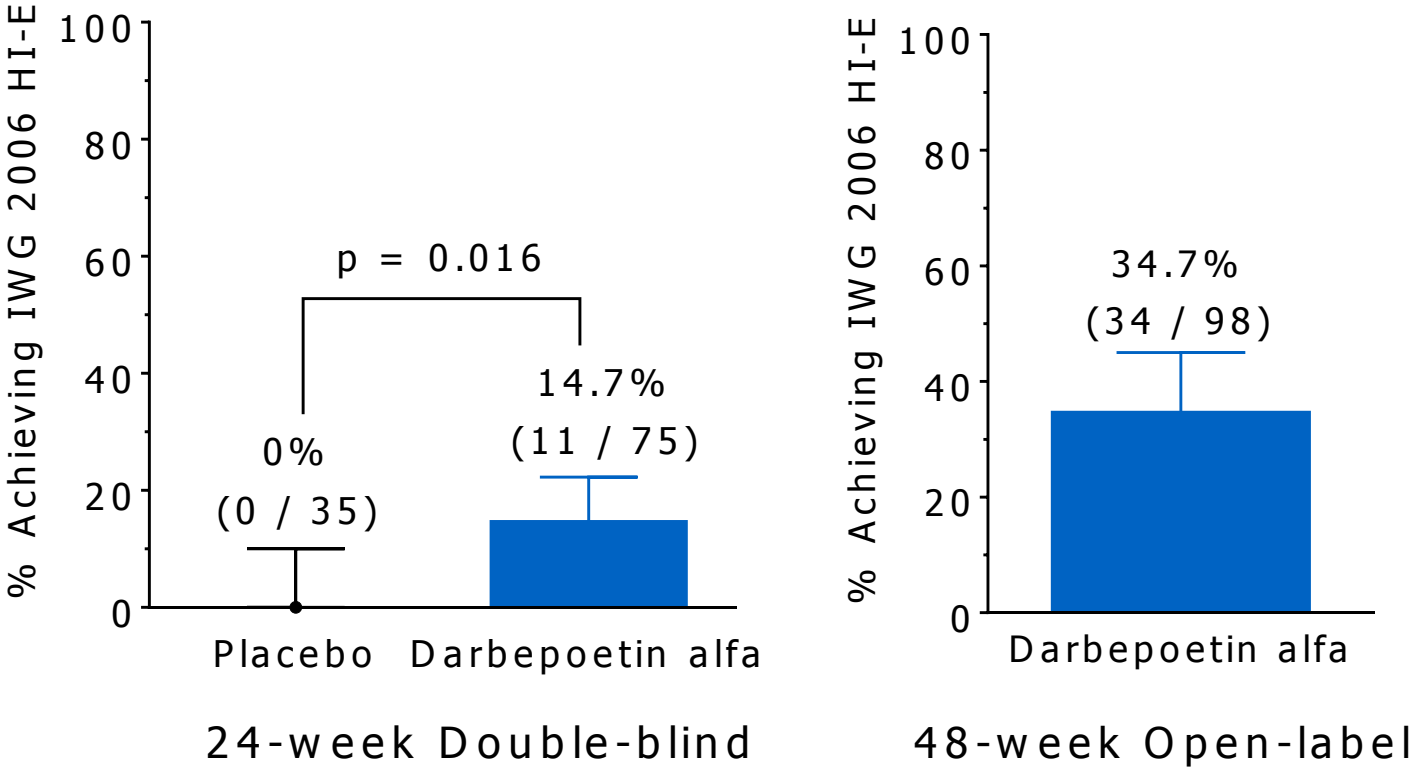
ARCADE (20090160): A Phase 3 Randomized Placebo-Controlled Double-Blind Trial of Darbepoetin Alfa in the Treatment of Anemia in Patients With Low or Intermediate-1 Risk Myelodysplastic Syndromes



- Patients were stratified by screening IPSS status (low or int-1) for randomization.
- The dose was reduced if Hgb was >12.0 g/dL or if Hgb increased by >1.5 g/dL in 3 weeks without transfusion.
- Investigational product (IP) was discontinued and the patient entered follow-up if >3 dose reductions were needed.

Platzbecker et al , EHA 2016

Results: HI-E Rates



- 24-week Double-blind Period:
  - All patients with HI-E (n = 11) had a baseline serum EPO level <100 mU/mL.
- 48-week Open-label Period: HI-E rate of 34.7%
  - 81% (102/126) of patients increased dose frequency (from Q3W to Q2W) over the 48 weeks (twice as long as the blinded period)

Platzbecker et al , EHA 2016

1) Quale è la reale possibilità di valutare la presenza di mutazioni somatiche in corso di accertamenti diagnostici/prognostici ??

Al momento emerge che la necessità maggiore viene percepita per il paziente giovane, in cui in casi selezionati si avviano già le analisi mutazionali.
Difficoltà per i centri piccoli nel gestire questo tipo di studi molecolari.

Interpretazione del dato di mutazione somatica nel contesto clinico. Problema della emopoiesi clonale e VAF.

Se lo studio delle mutazioni può portare ad una scelta terapeutica mirata (luspatercept o altro) deve essere organizzata o sviluppata una rete di laboratori nazionali che possano
sostenere e ottimizzare la valutazione molecolare.

2) Diagnosi di RARS fatta con morfologia e Perls.

Ancora non viene studiato SF3B1 mutato

3) ARCH è una predisposizione come MGUS???

Dobbiamo effettuare valutazioni periodiche di questi pazienti?
E come possiamo individuarli?

Ancora approccio molto iniziale.
Aspettiamo i dati ulteriori di studi in atto.