

Highlights from EHA

Novità dall'EHA >> [Mielodisplasie]

Relatore: **P. MUSTO**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

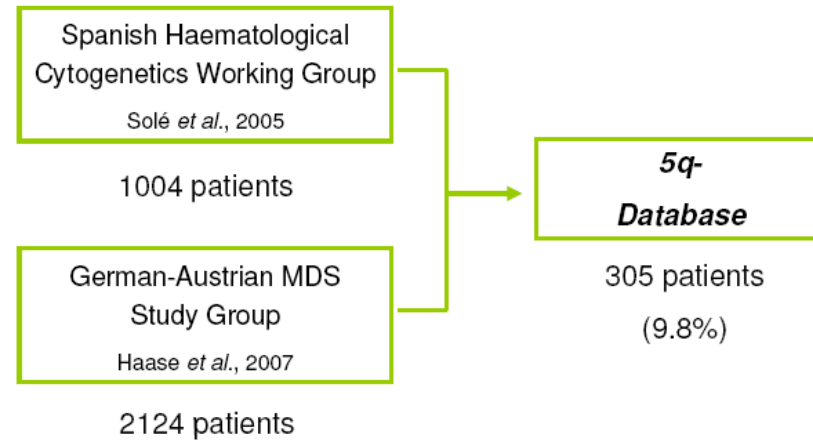
Abstract 906, Oral Communication

Prognostic impact of additional chromosomal aberrations to 5q- in patients with primary myelodysplastic syndromes

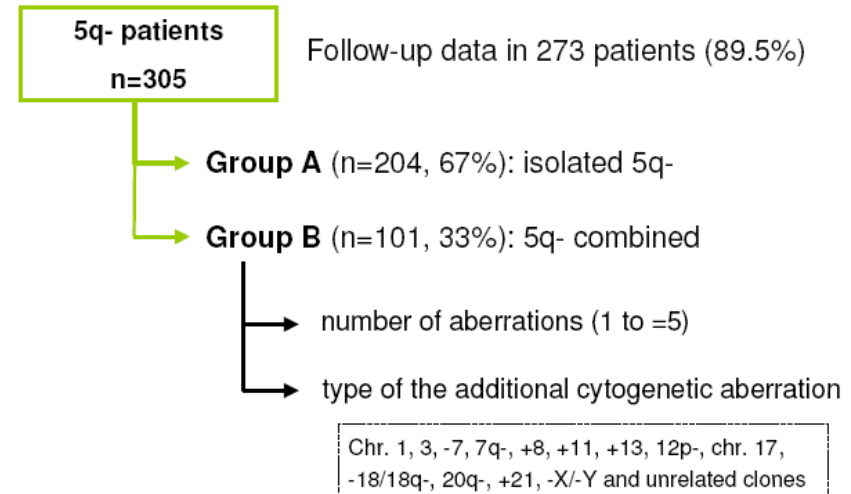
M. Mallo, J. Cervera, J. Schanz, B. Espinet, E. Such, E. Luño, C. Steidl, ML. Martín, U. Germing, I. Granada, M. Pfeilstöcker, JM. Hernández, T. Noesslinger, MJ. Calasanz, P. Valent, R. Collado, C. Fonatsch, E. Bureo, M. Lübbert, R. Ríos, R. Stauder, E. Arranz, B. Hildebrandt, JC. Cigudosa, C. Pedro, M. Salido, L. Arenillas, GF. Sanz, MA. Sanz, A. Valencia, L. Florensa, D. Haase, F. Solé

Spanish Haematological Cytogenetics Working Group
German-Austrian MDS Study Group
International Working Group on MDS Cytogenetics

PATIENTS AND METHODS

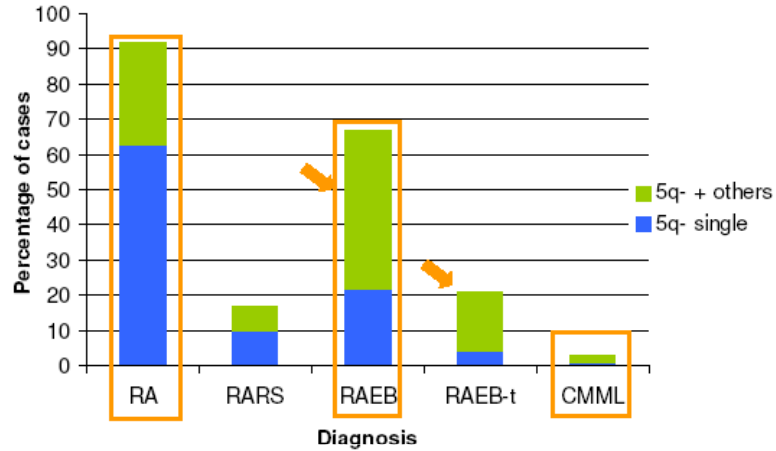


PATIENTS AND METHODS



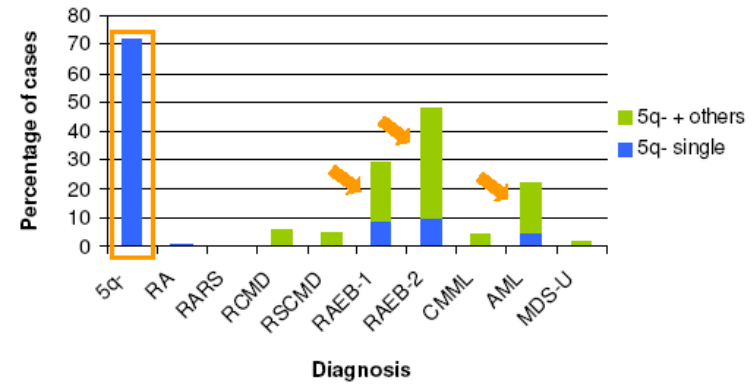
RESULTS

• FAB diagnoses (n=294)



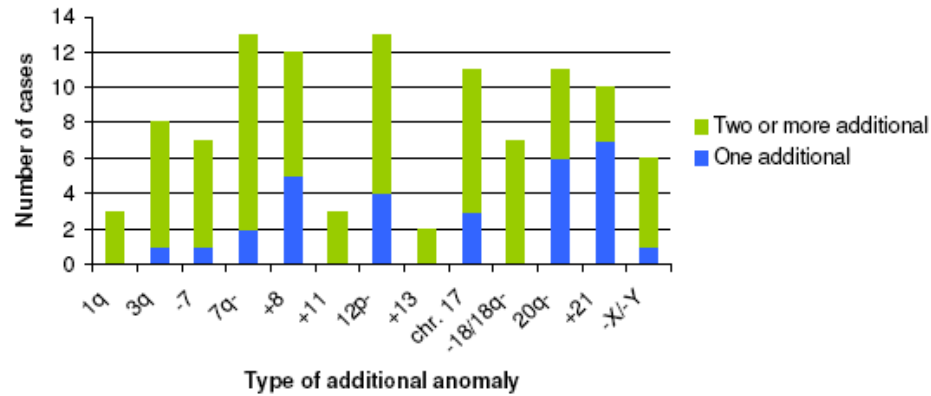
RESULTS

• WHO diagnoses (n=217)



RESULTS

• Distribution according to the type of aberration (n=101)



RESULTS

- Survival curves: Additional cytogenetic abnormalities

Cytogenetic group	n	Median survival time
5q-	179	69 months
5q- + 1	45	55 months
5q- + 2	10	8 months
5q- + 3	6	6 months
5q- + 4	7	8 months
5q- + =5	26	7 months

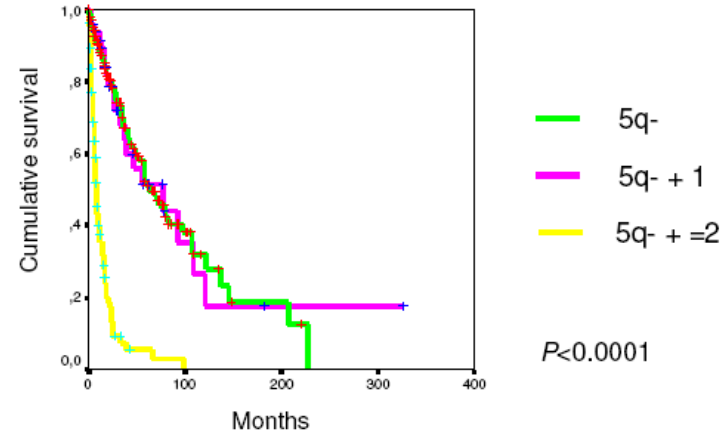
Global MS time (n=305): 48 months

RESULTS

<i>Univariate analysis</i>	Overall survival	Leukemic transformation
Age groups	$P=0.0009$	$P=0.7550$
Sex	$P=0.0008$	$P=0.0035$
BM blasts groups (%)	$P=0.009$	$P<0.0001$
FAB diagnoses groups	$P<0.0001$	$P<0.0001$
WHO diagnoses groups	$P<0.0001$	Not evaluated
Cytogenetic complexity	$P<0.0001$	$P<0.0001$
Type of additional aberration	Not evaluated	Not evaluated

RESULTS

- Survival curves: Additional cytogenetic abnormalities (n=273)



RESULTS

- Overall survival (multivariate analysis) (n=76)

Variables	
Age	
Sex: male/female	
Number of cytopenias	
FAB/WHO diagnoses	
Bone marrow (BM) blasts (5% / 10%)	
High and low risk (FAB)	
Karyotype complexity	

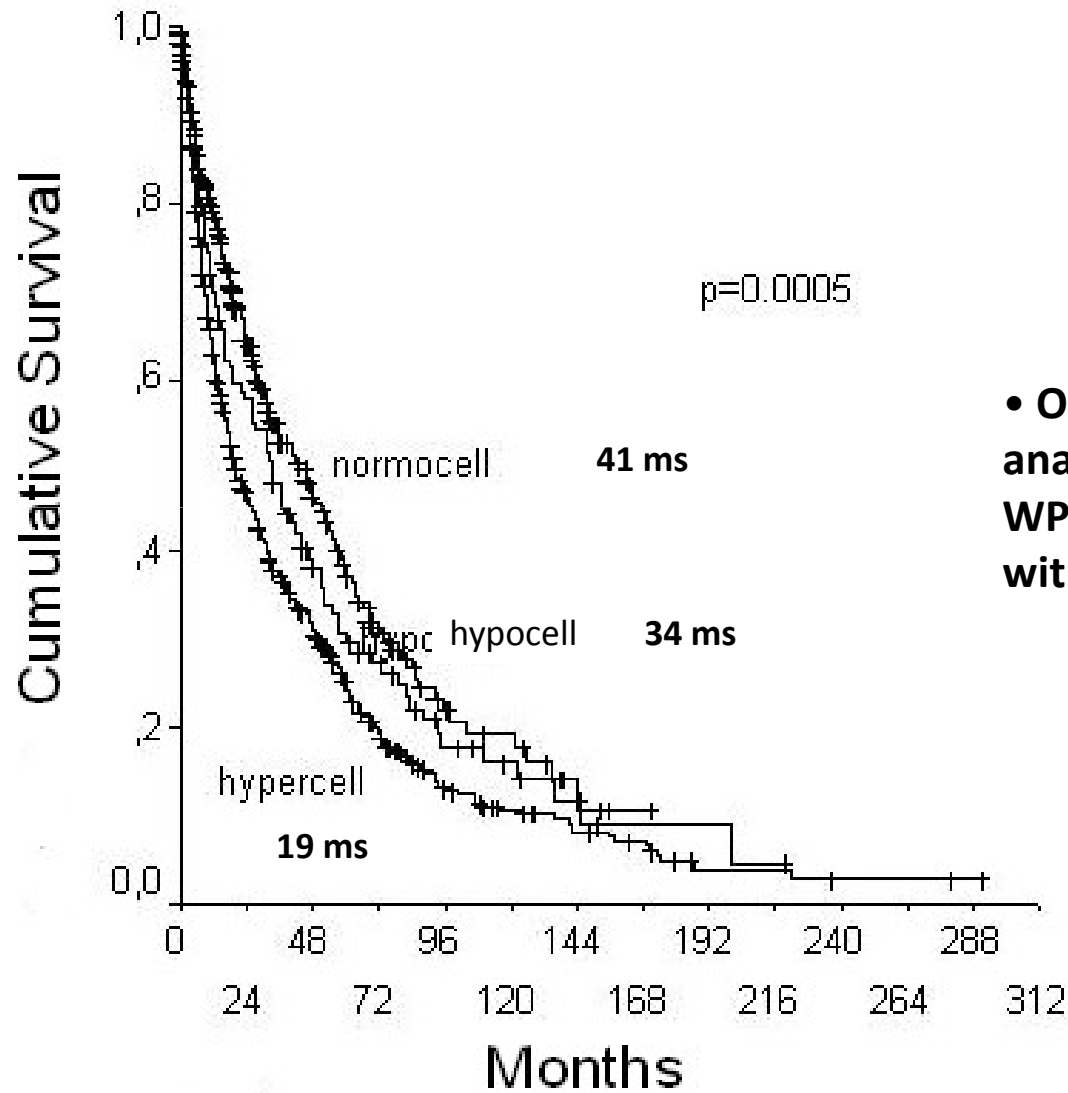
Karyotype complexity → Cytopenias → Age

INFLUENCE OF HISTOLOGICAL BONE MARROW FINDINGS ON OUTCOME IN 1175 PATIENTS SUFFERING FROM MYELOYDYSPLASTIC SYNDROME

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Blum et al, abstract 709 (poster)

- **1175** patients with MDS (mean age 69 years, range 14-96), from the registries in Düsseldorf and Lausanne collected between 1975 and 2007
- BM was hypocellular in **13%**, normocellular in **34%**, hypercellular in **53%**
- Hypocellular MDS showed significantly **lower white blood cell** and neutrophil counts and **lower platelet counts**
- There was **no difference** in hemoglobin level, BM blasts, risk of transformation to AML or distribution to FAB and WHO classification, IPSS or WPSS
- **Fibrosis** was **more frequent in hypercellular BM (22%)** as compared to hypocellular (9%) and normocellular BM (6%) (p=0.003)



- OS remained significant when analysed for FAB, WHO, IPSS and WPSS, and also if CMML was withdrawn

- 150 initial BM biopsies: **14.5%** with fibrosis
- Median survival: **14 months** with fibrosis, **28 months** without fibrosis ($p < 0.000005$), not related to AML-transformation
- Cytogenetic aberrations: **more frequent with fibrosis** (abnormal non complex karyotype 60 vs. 45% ($p = 0.03$), complex karyotype 27 vs. 13% ($p = 0.002$))
- **Survival difference** remained significantly different in IPSS cytogenetic low and intermediate risk groups, but **not within the cytogenetic high risk group**
- In a multivariate testing, chromosomal risk group, medullary blast count as well as **cellularity** were **independent risk factors** for survival

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

Time to Response

Patients with CR/mCR/PR/Hi (%)

100
80
60

N = 50

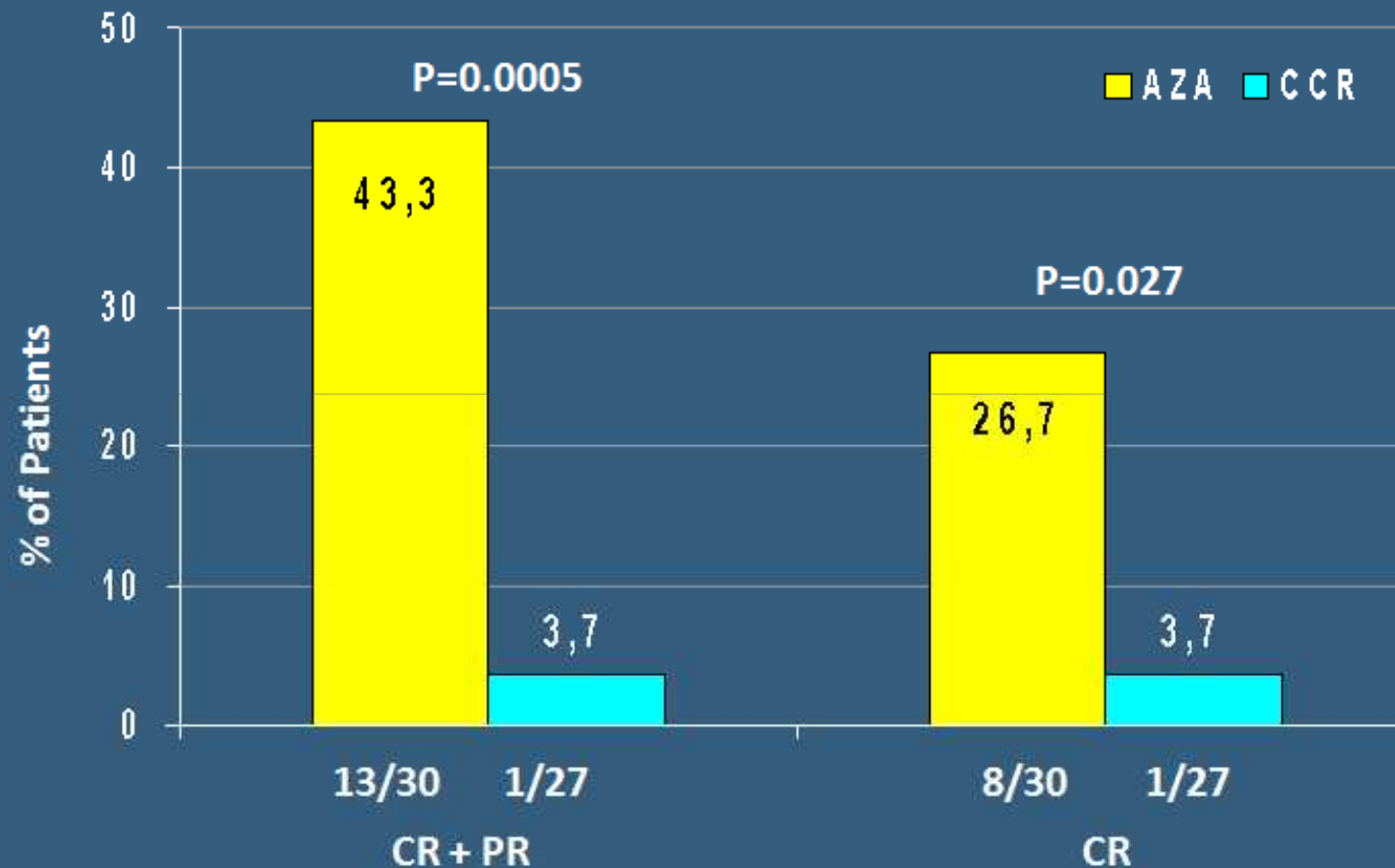
82% of improvement was demonstrated by cycle 2

- Median survival was 19.6 months and the 1-year survival rate was 66%

- Most frequent grade 3 or higher adverse events: neutropenia (31%), thrombocytopenia (18%), febrile neutropenia (14%), anemia (12%), pneumonia (11%), and fatigue (5%)

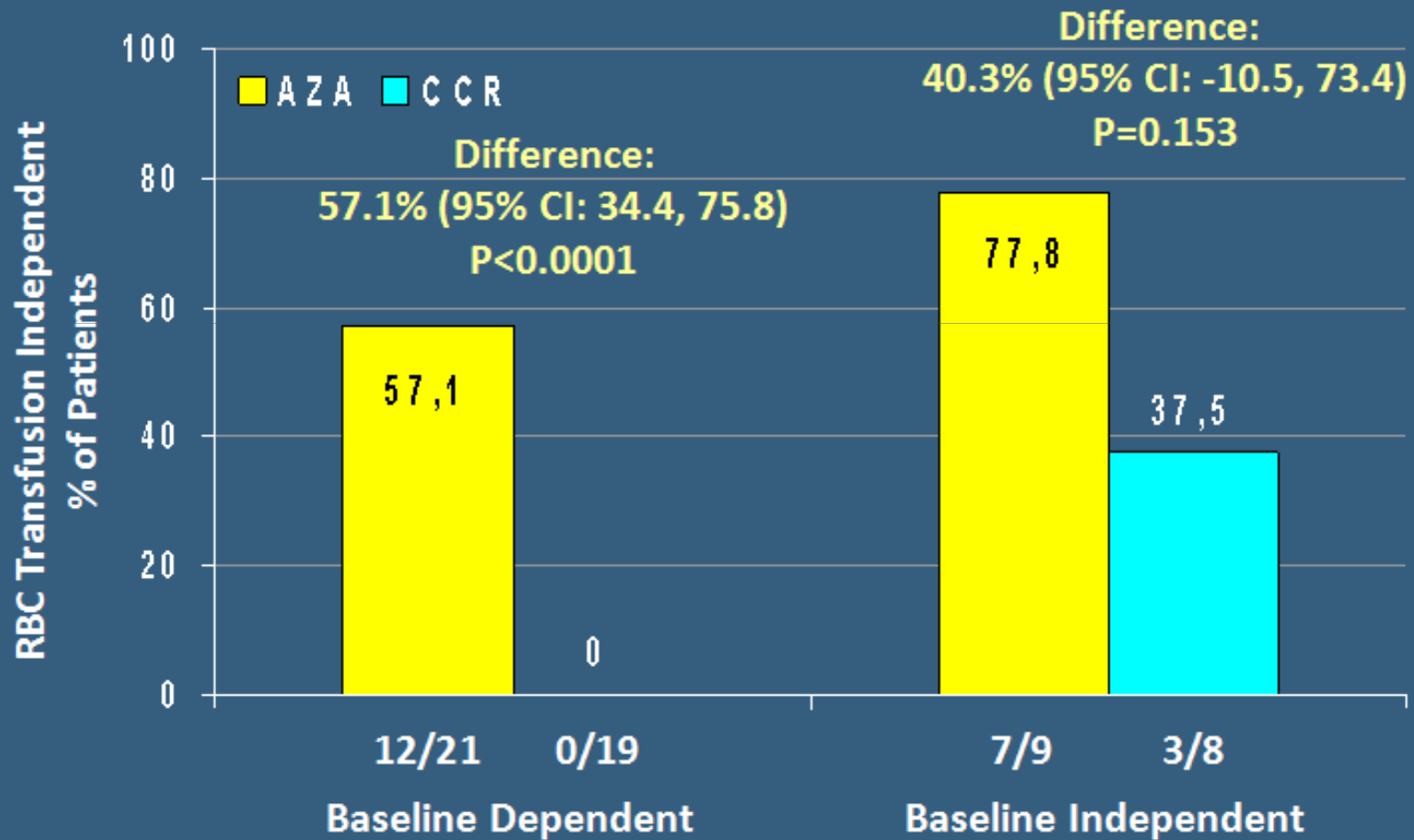
- Median time to initial improvement (CR+mCR+PR+HI) was 1.7 months

PROLONGED SURVIVAL IN HIGHER-RISK MYELODYSPLASTIC SYNDROME PATIENTS WITH -7/del 7q TREATED WITH AZACITIDINE Mufti et al, abstract 928 (oral communication)

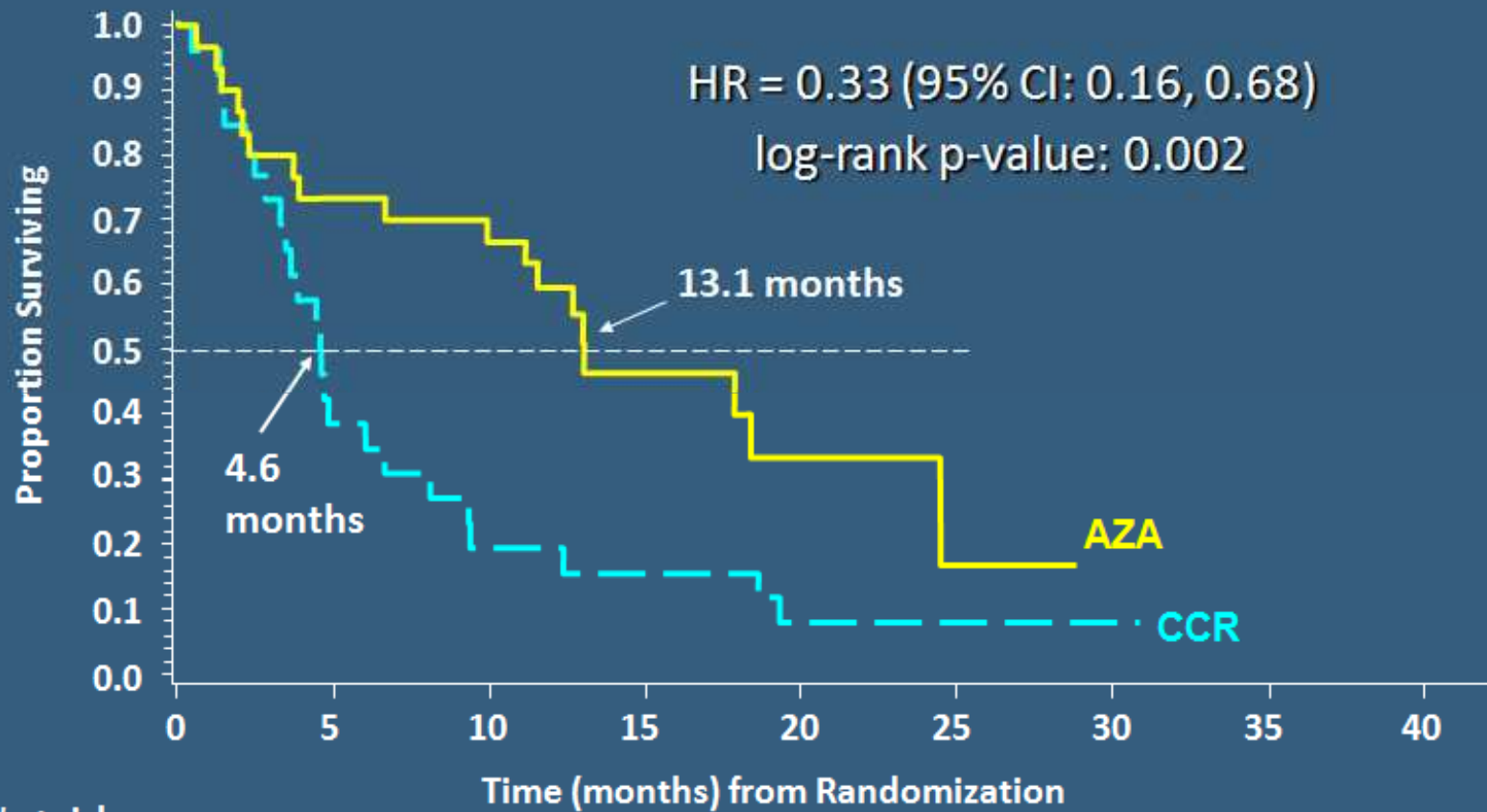


Response Rates (IWG 2000) in MDS Patients with -7/del(7q) AZA vs CCR (AZA-001)

RBC Transfusion Independence in MDS Patients with -7/del(7q) AZA vs CCR (AZA-001)



Overall OS in MDS Patients with -7/del(7q) AZA vs CCR (AZA-001)



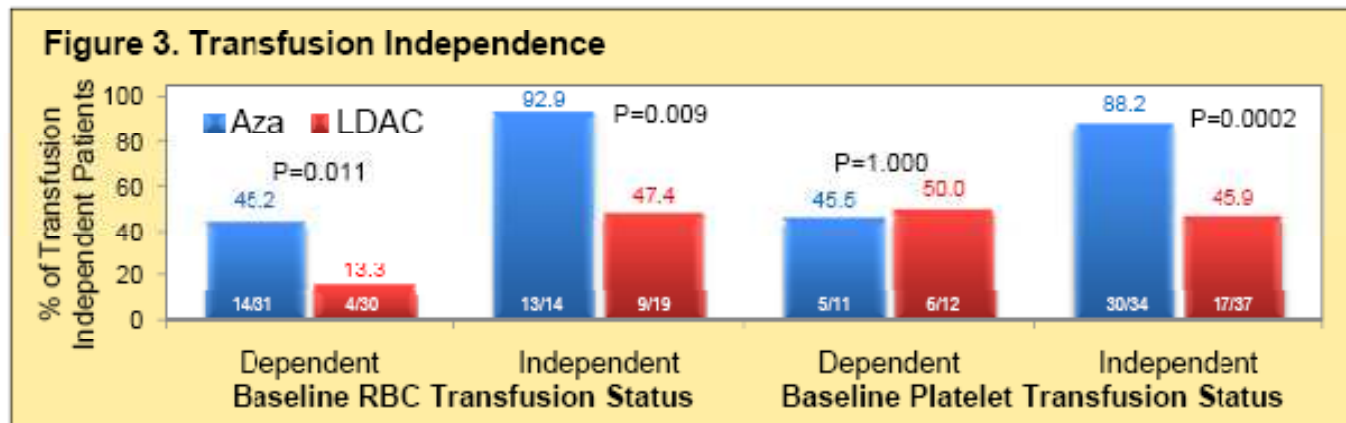
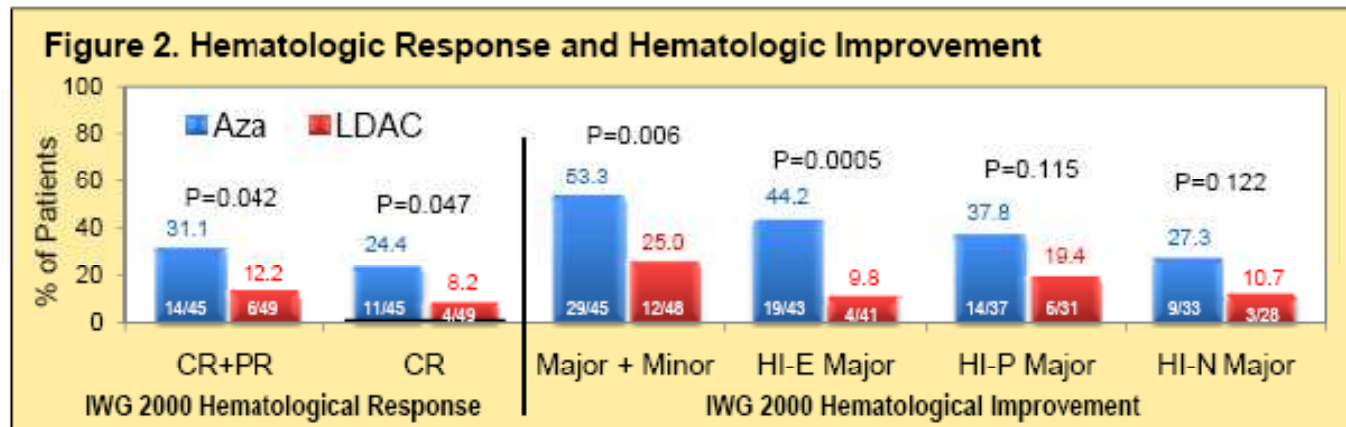
at risk

AZA	30	22	20	9	5	1	0	0	0
CCR	27	10	5	4	2	1	1	0	0

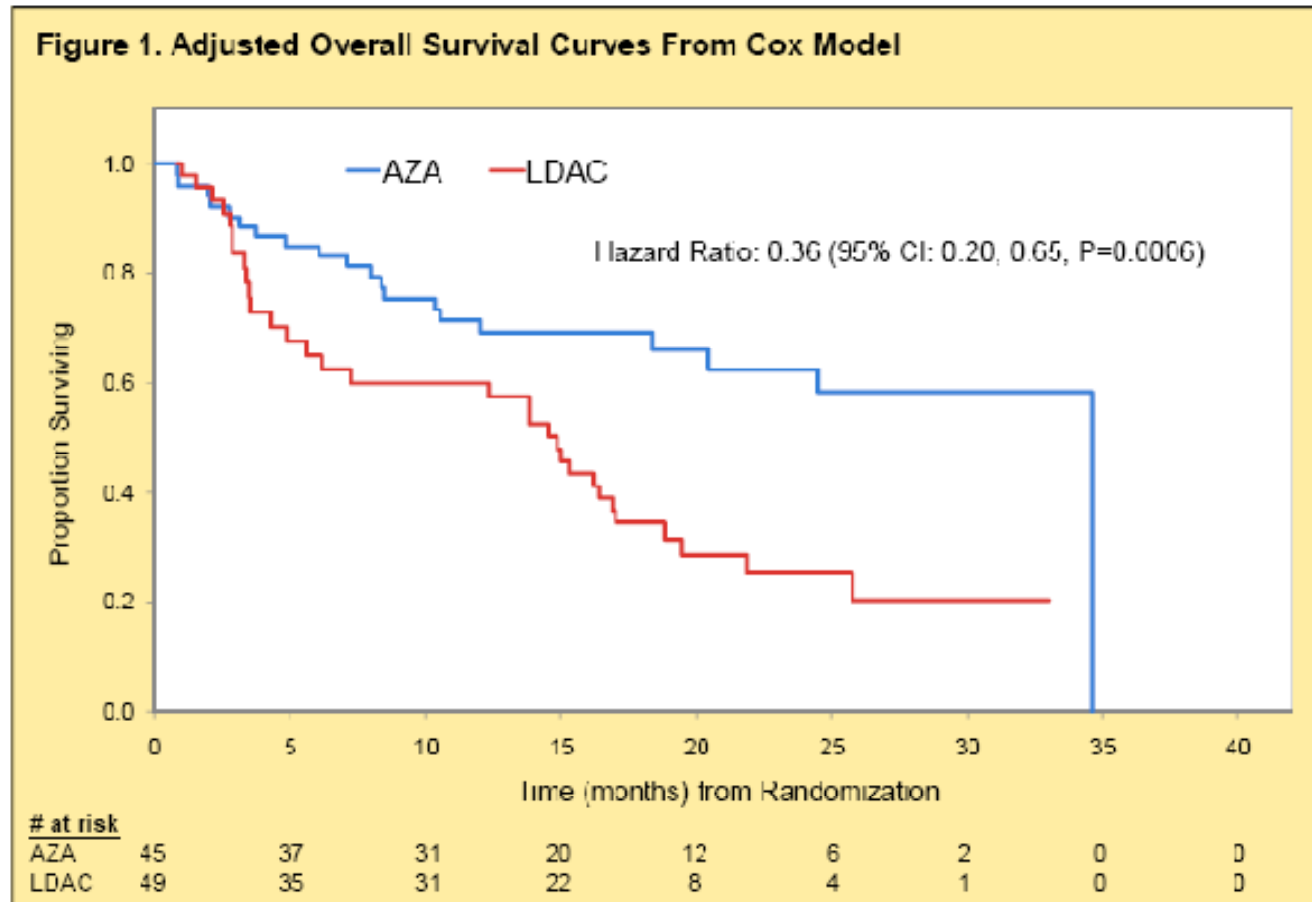
EFFECT OF AZACITIDINE (AZA) VERSUS LOW-DOSE ARA-C (LDAC) ON OVERALL SURVIVAL, HEMATOLOGIC RESPONSE, TRANSFUSION INDEPENDENCE, AND SAFETY IN PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES (MDS)

P. Fenaux,¹ N. Gattermann,² J. Seymour,³ E. Hellström-Lindberg,⁴ G. Muftic,⁵ U. Diehrsen,⁶ S. Gore,⁷ F. Ramos,⁸ O. Beyne-Rauzy,⁹ H. Dombret,¹⁰ A. List,¹¹ D. McKenzie,¹² J. Backstrom,¹² A. Allen,¹² C.L. Beach¹²
 1. Hôpital Avicenne, Bobigny, France; 2. Heinrich-Heine-University, Düsseldorf, Germany; 3. Peter MacCallum Cancer Centre, East Melbourne, Australia; 4. Karolinska University Hospital, Stockholm, Sweden; 5. King's College London, London, United Kingdom;
 6. University Hospital Essen, Essen, Germany; 7. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 8. Hospital de León, León, Spain; 9. Chu Purpan, Toulouse, France;
 10. Hôpital Saint-Louis (AP-HP), Paris, France; 11. Moffitt Cancer Center, Tampa, FL, USA; 12. Celgene Corporation, Summit, NJ, USA

Poster n. 224



ITT population



AZA significantly prolonged OS with a 62% reduced risk of death versus LDAC.

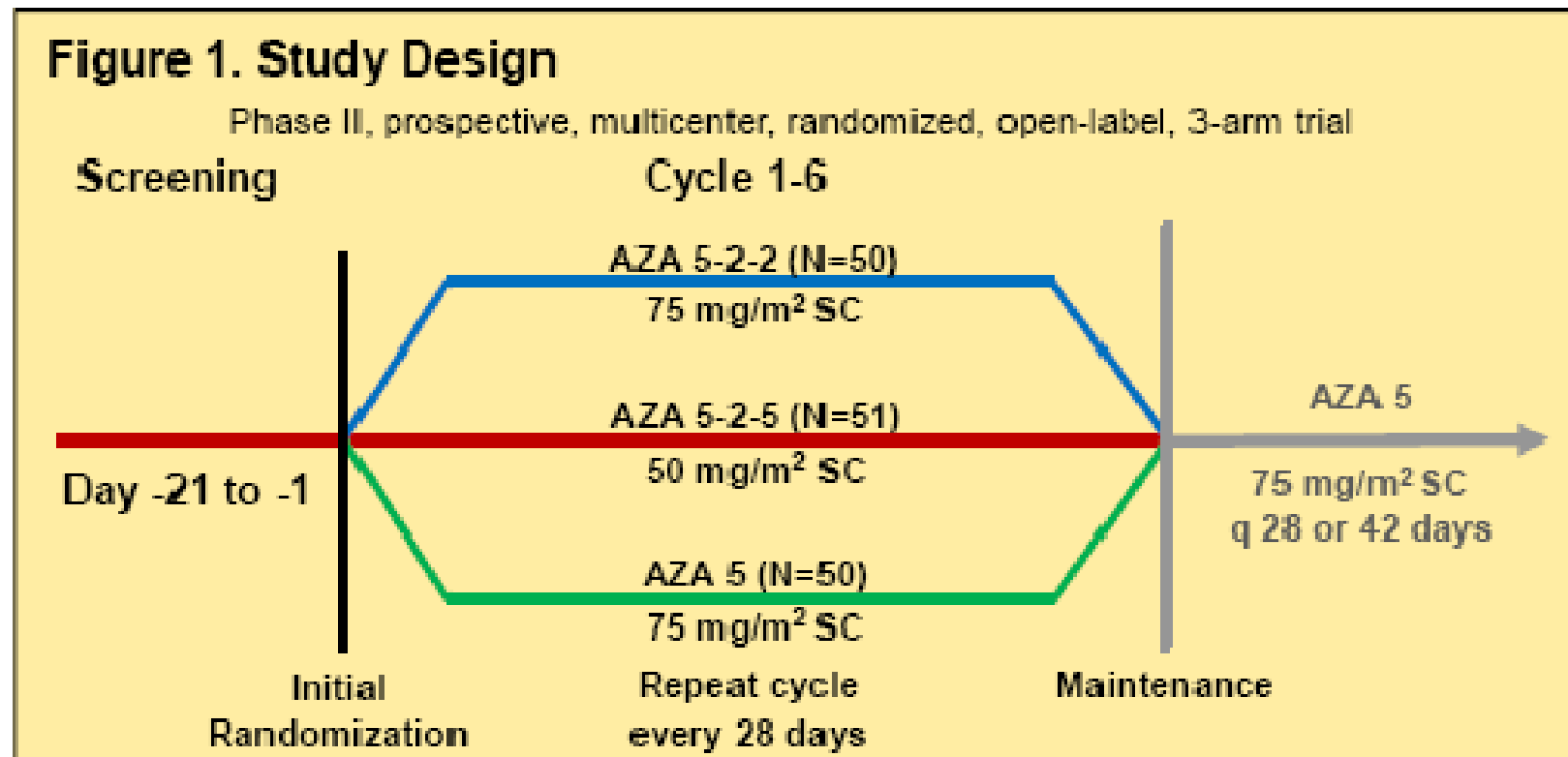
RAPID ONSET OF EFFECTIVENESS WITH THREE ALTERNATIVE AZACITIDINE (AZA) DOSING REGIMENS IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES (MDS)

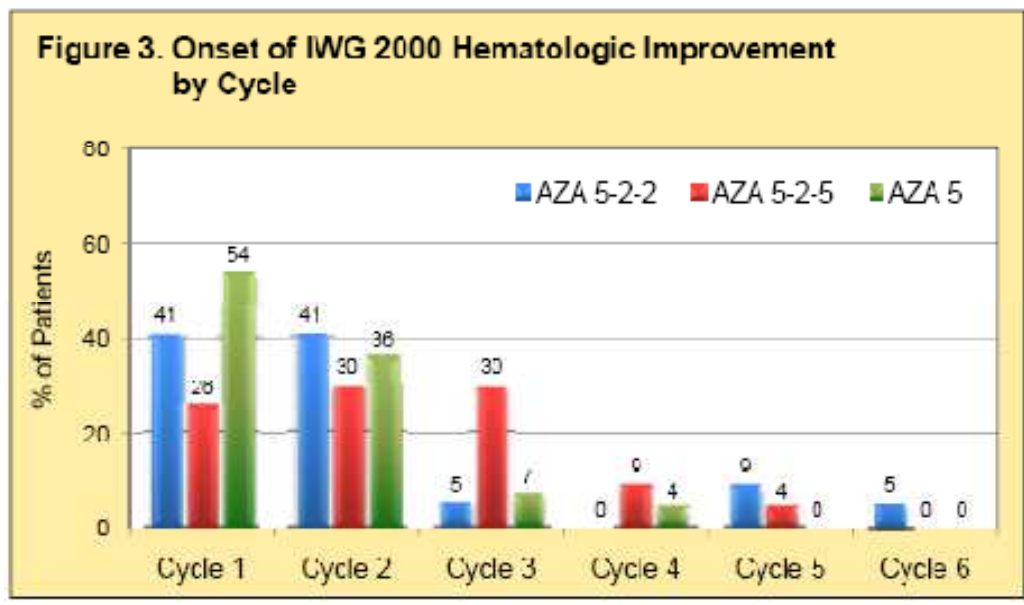
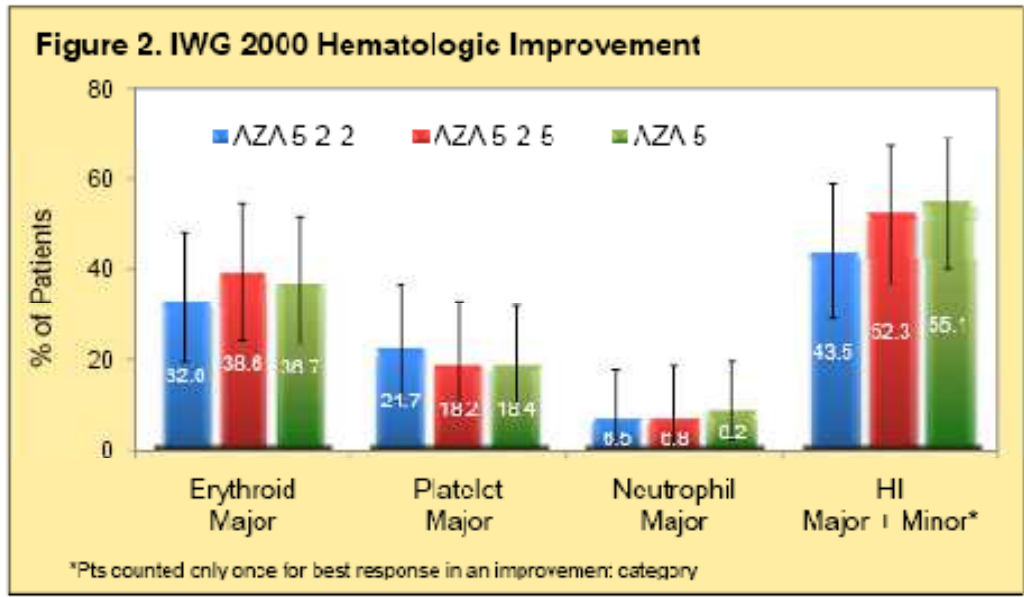
R. Lyons,¹ T. Cosgriff,² S. Modi,³ H. McIntyre,⁴ I. Fernando,⁴ J. Backstrom,⁴ C.L. Beach⁴

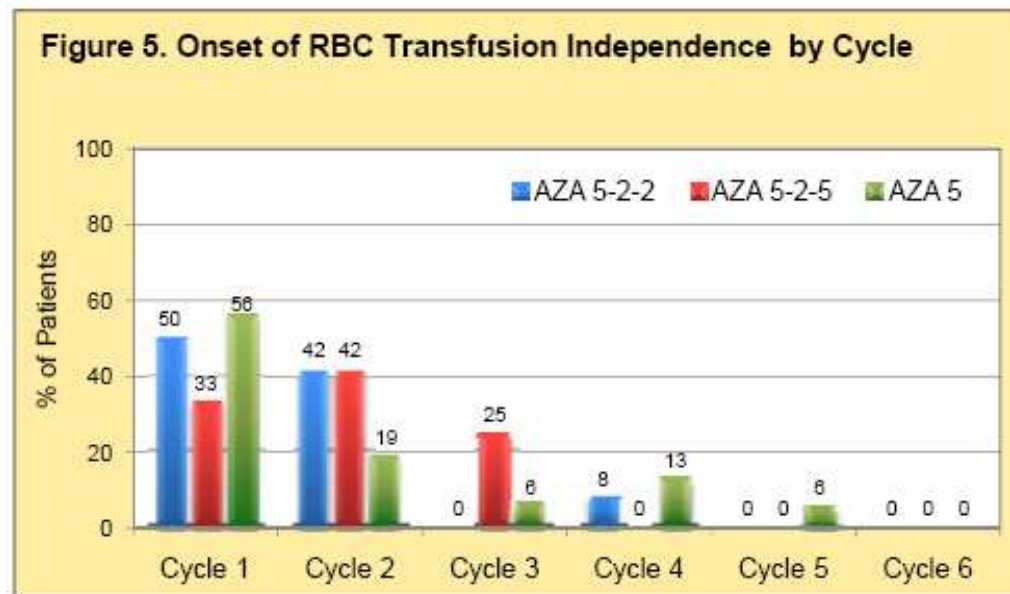
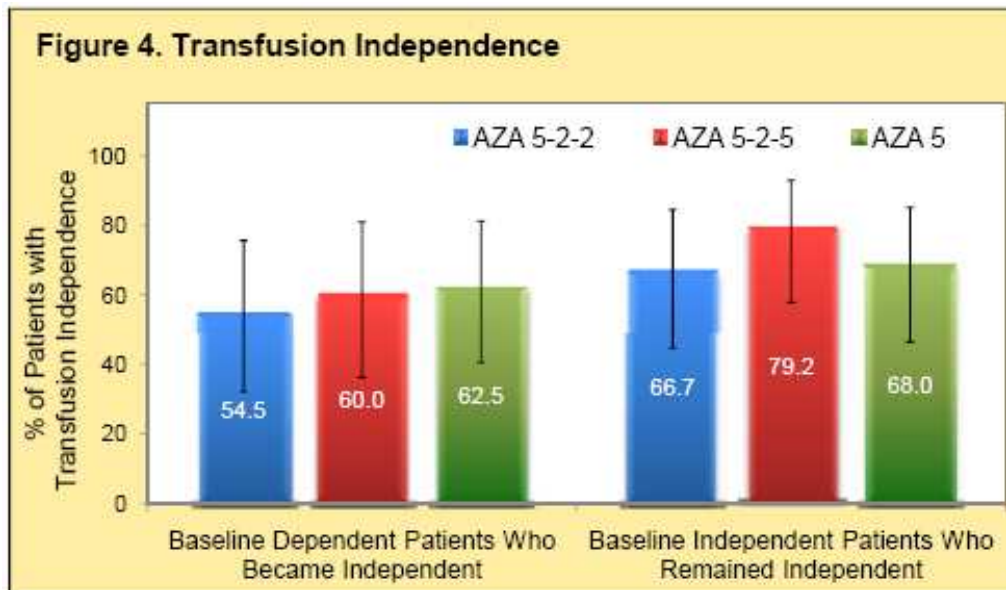
1. Cancer Care Centers of South Texas/US Oncology, San Antonio, TX, USA; 2. Hematology and Oncology Specialists, Metairie, LA, USA;

3. Joliet Oncology-Hematology Associates, Joliet, IL, USA; 4. Celgene Corporation, Summit, NJ, USA

Poster n. 232







5-Azacytidine for the Treatment of Low/Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Results in 82 Patients from the Italian Patient Named Program

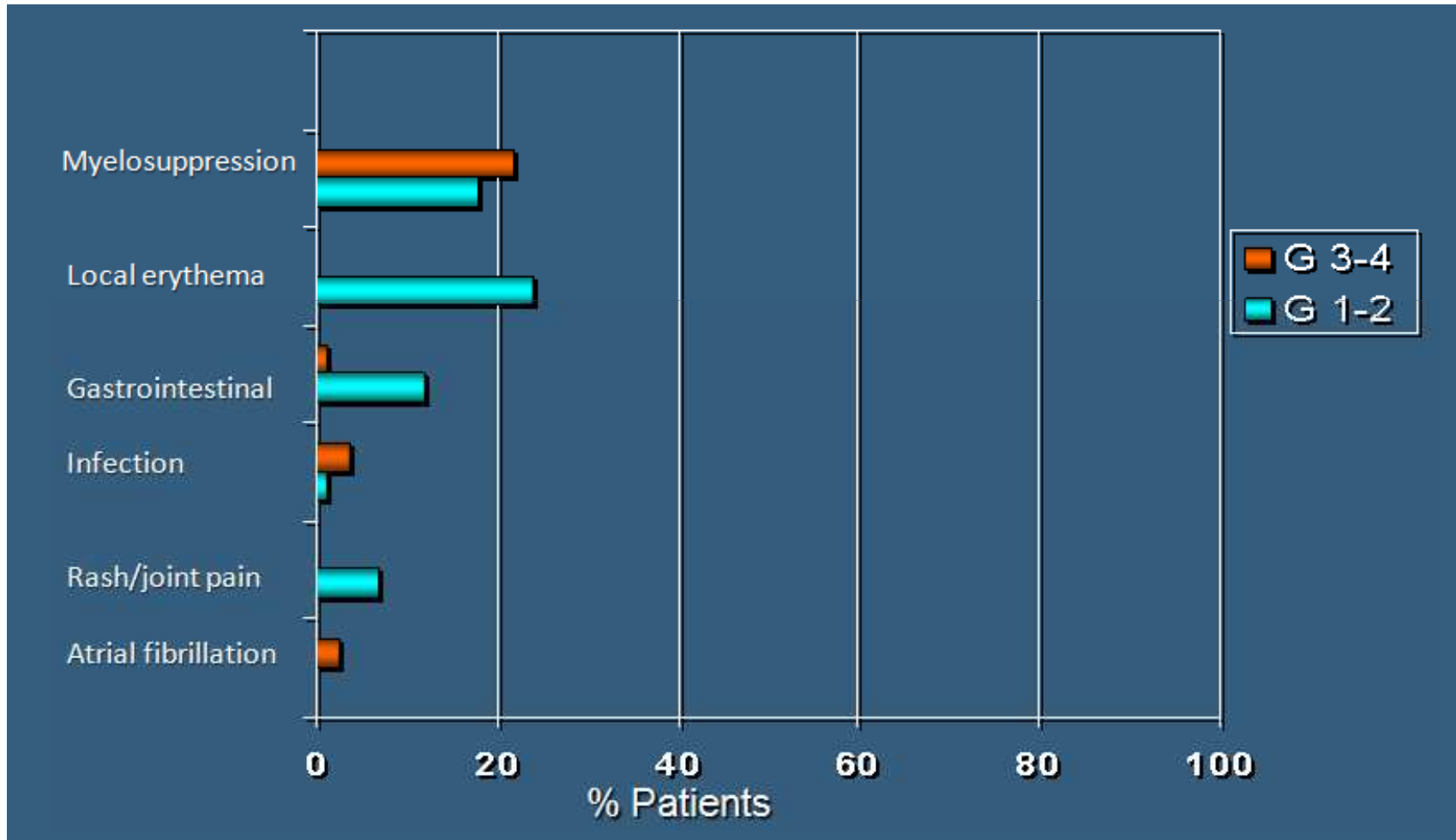
Musto et al, abstract 925 (oral communication)

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- **Retrospective, multicenter study started on Sept. 2007, to evaluate patients with MDS or AML treated with AZA outside of clinical trials**
- **31 Italian Institutions**
- **218 patients registered since 2005**
- **82 patients were Low/Int-1 IPSS risk MDS**

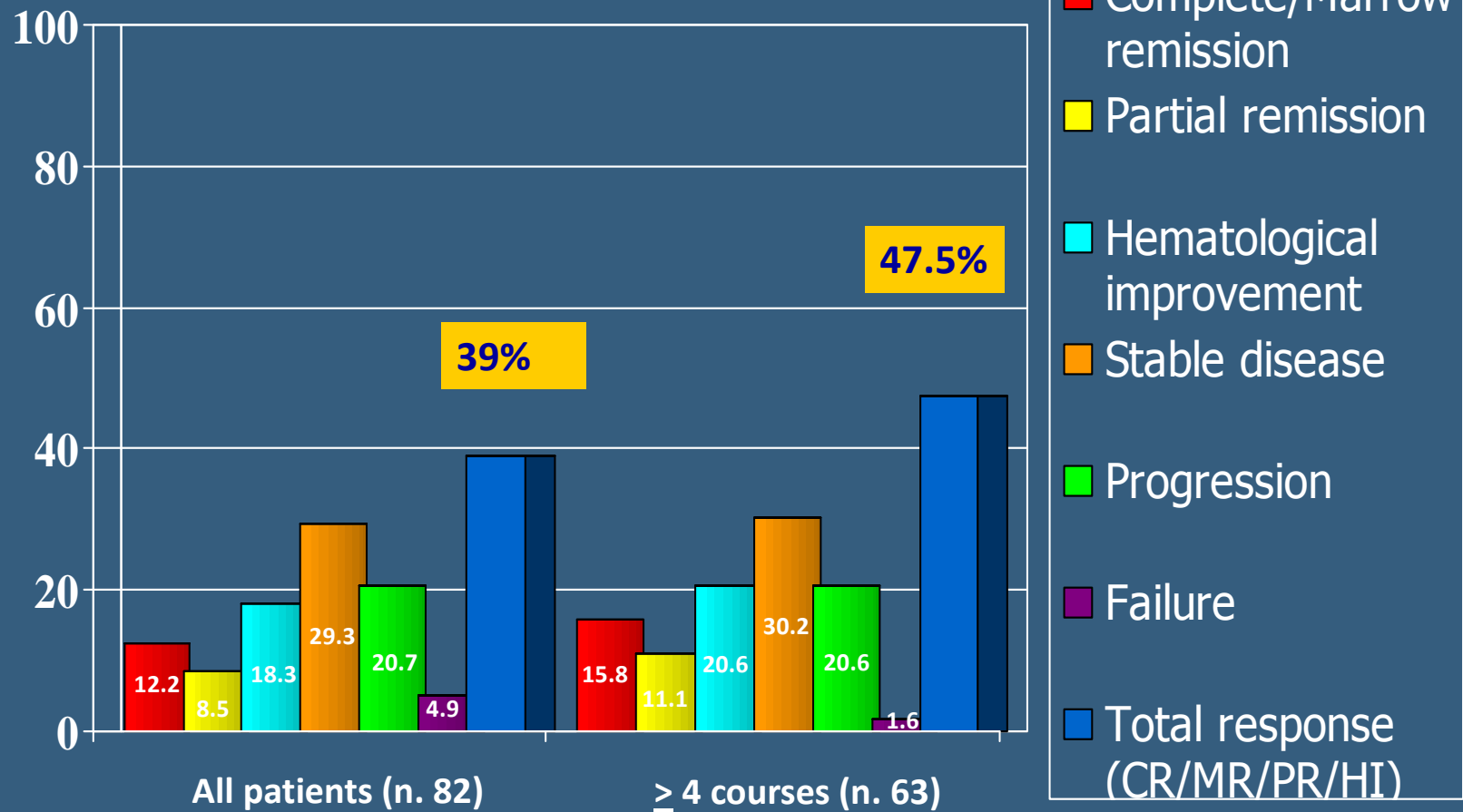
TREATMENT RELATED TOXICITY

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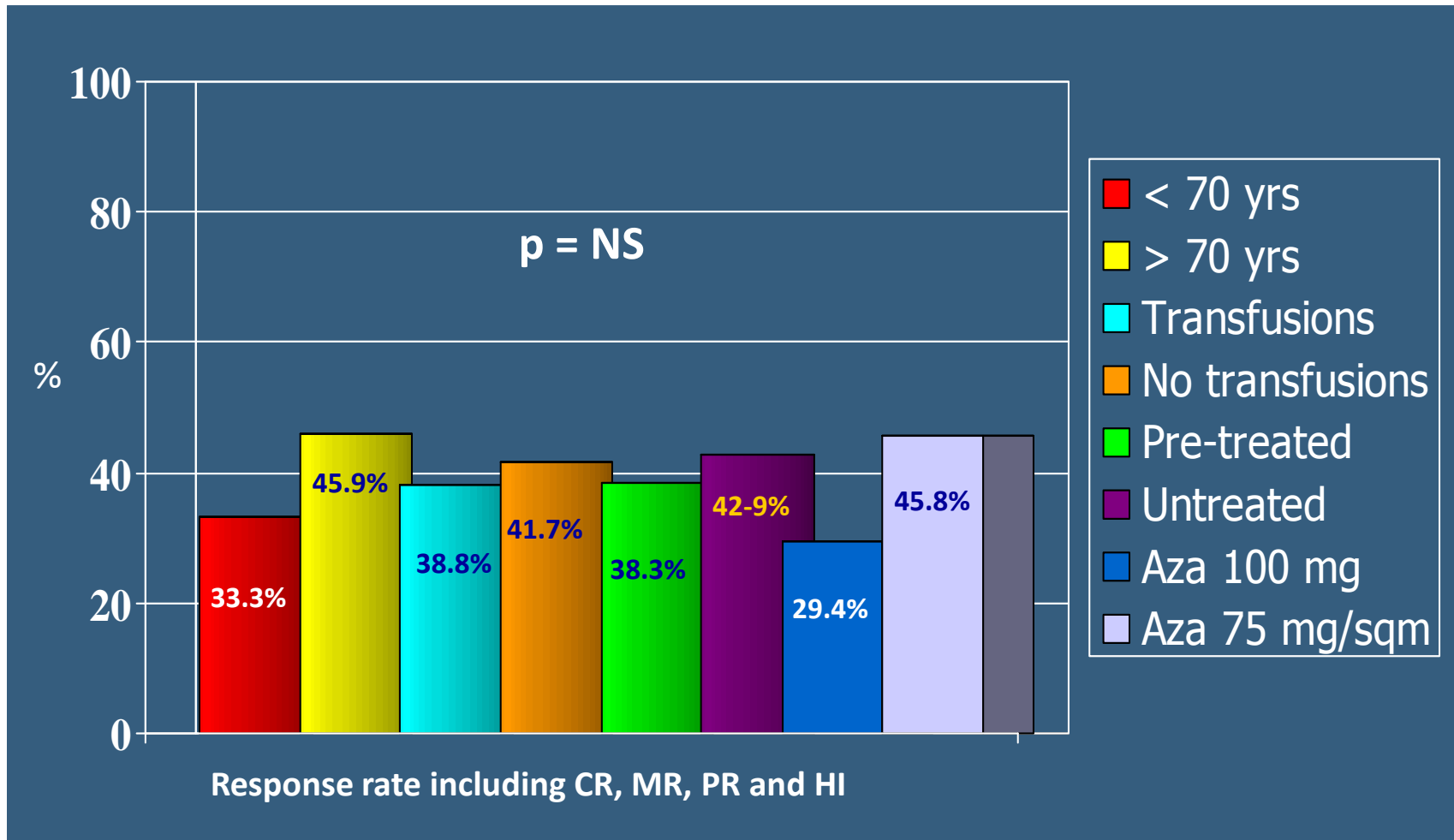
ANALYSIS OF RESPONSE ACCORDING TO IWG CRITERIA (2006)

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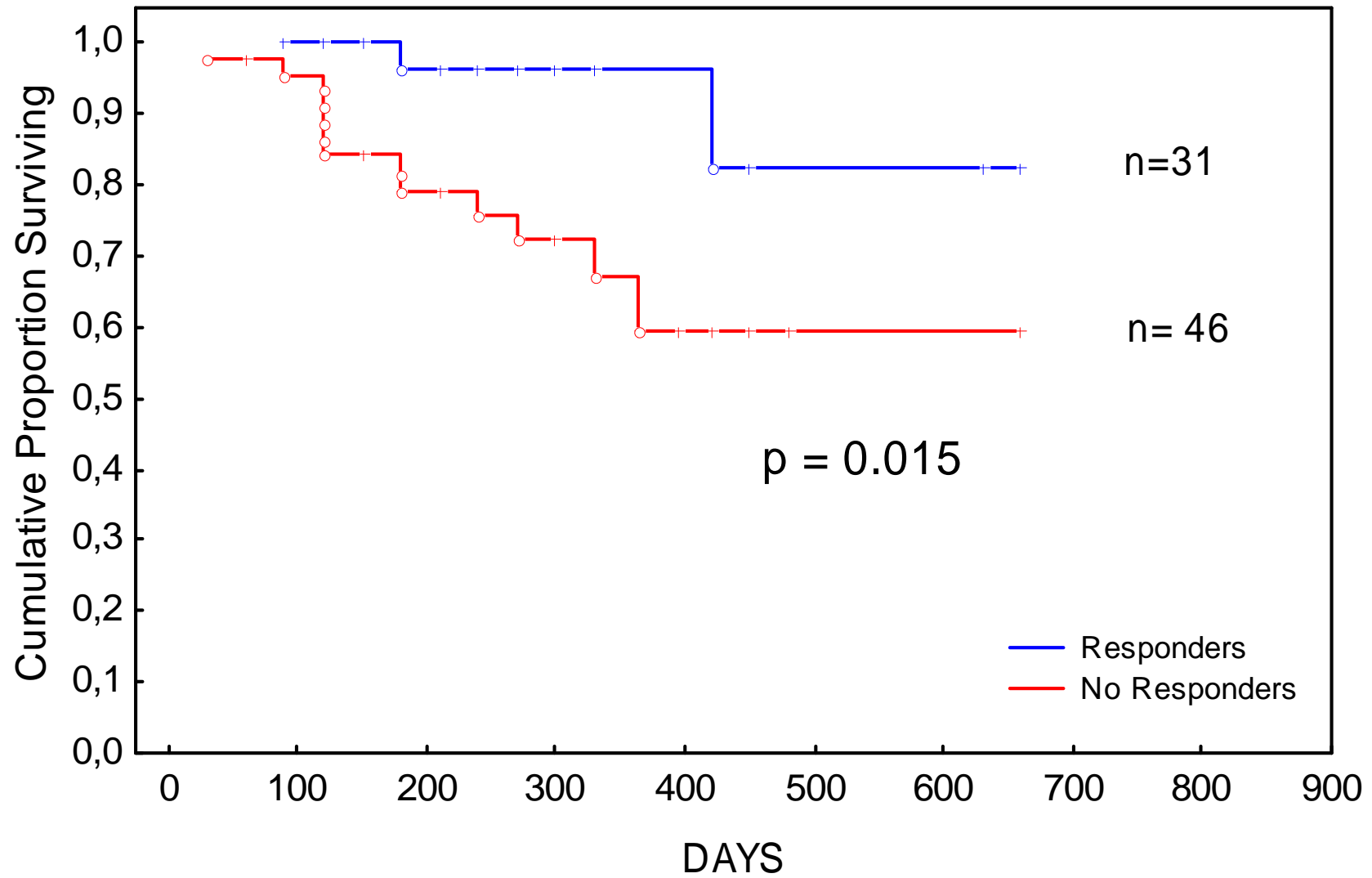
CORRELATIONS WITH RESPONSE

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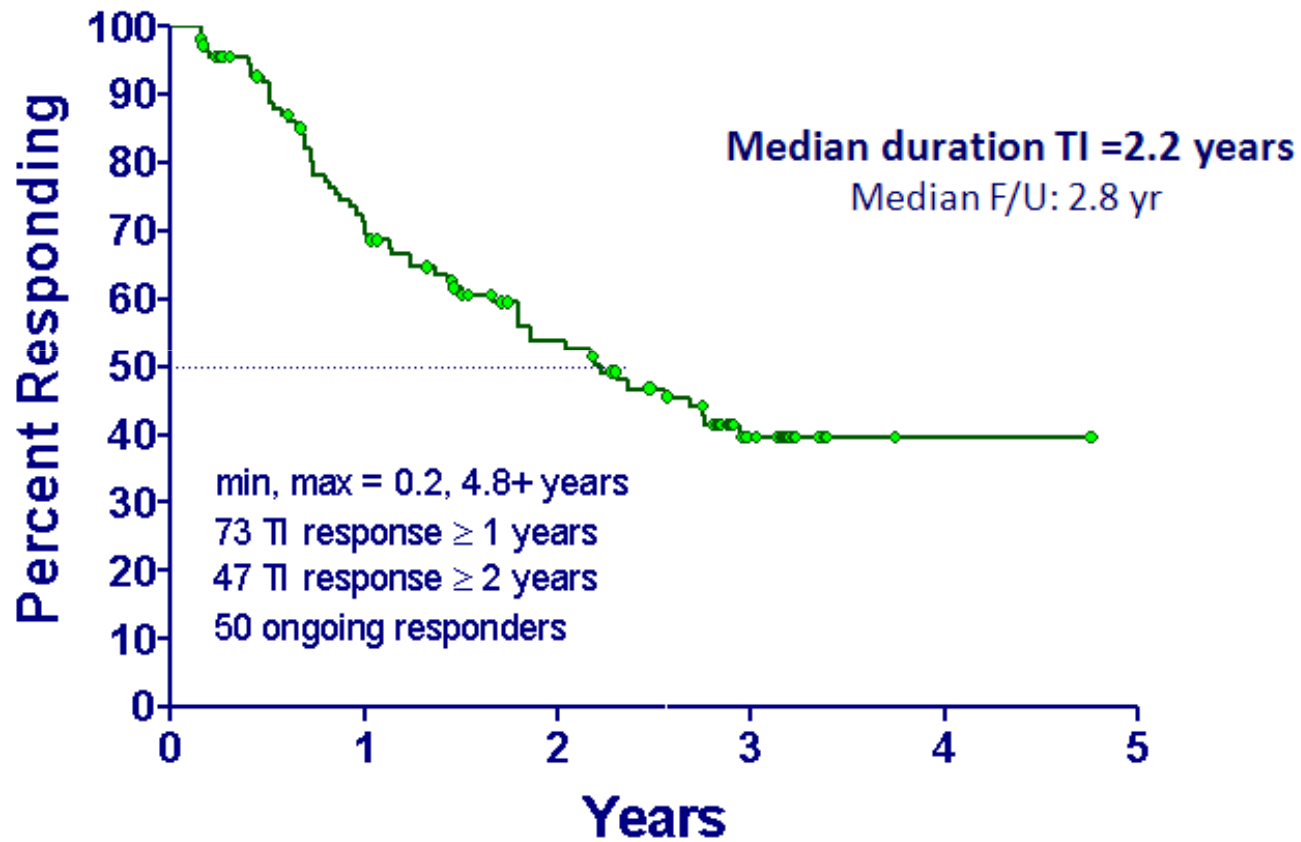
OS BY RESPONSE

N°77 patients



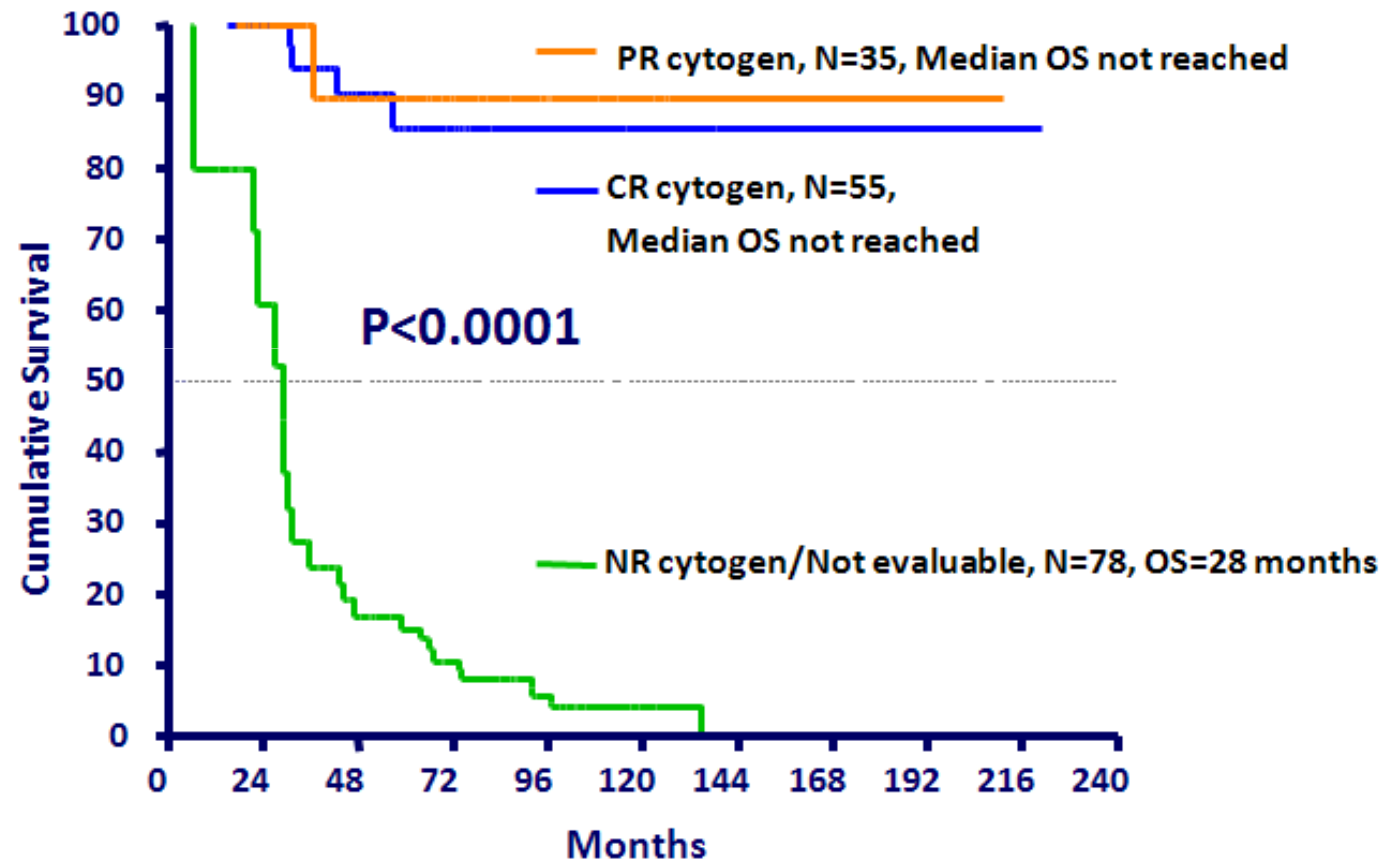
Lenalidomide in del5q MDS

Transfusion-independence duration MDS001 and MDS003 studies



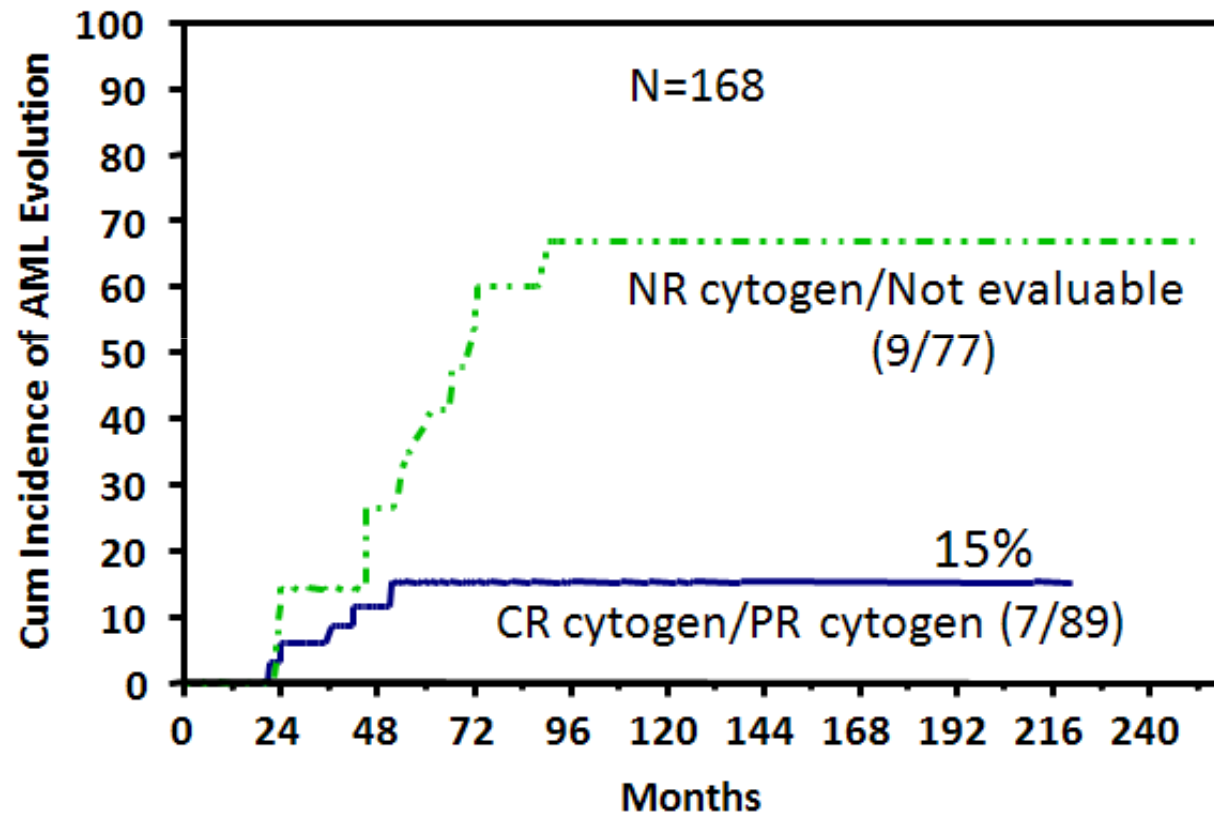
Unpublished data, courtesy of Alan List

Survival correlates to cytogenetic response to lenalidomide



Unpublished data, courtesy of Alan List

AML evolution correlates to cytogenetic response to lenalidomide



Unpublished data, courtesy of Alan List

Risk Factors for Acute Myeloid Leukemia Transformation and Mortality in Transfusion-dependent Deletion 5q Myelodysplastic Syndromes

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¹University of South Florida, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; ²St. Johannes Hospital, Düsseldorf, Germany; ³Celgene Corporation, Summit, NJ, USA; ⁴Celgene Germany GmbH, Munich, Germany; ⁵Heinrich Heine University, Düsseldorf, Germany

Table. Baseline patient characteristics.

Characteristic	Quantity	
	MDS-003	Registry
Patients, n	116	34
Median age, years (range)	71 (37–95)	66 (33–83)
Male, %	32	29
Median MDS duration, years (range)	2.5 (0.1–20.7)	N/A
Median RBC units/8 weeks (range)	5 (1–18)	4 (1–10)
Patients receiving ≥ 2 RBC units/month, n (%)	85 (73)	20 (59)
Hemoglobin at baseline (g/dL), median (range)	7.8 (3.6–11.8)	7.8 (3.0–11.6)
IPSS risk category, n (%)		
Low	53 (46)	16 (48)
Intermediate-1	63 (54)	17 (52)
FAB RA/RARS, n (%)	91 (78)	32 (94)

Figure 1. The 4-year cumulative incidence of AML transformation and mortality.

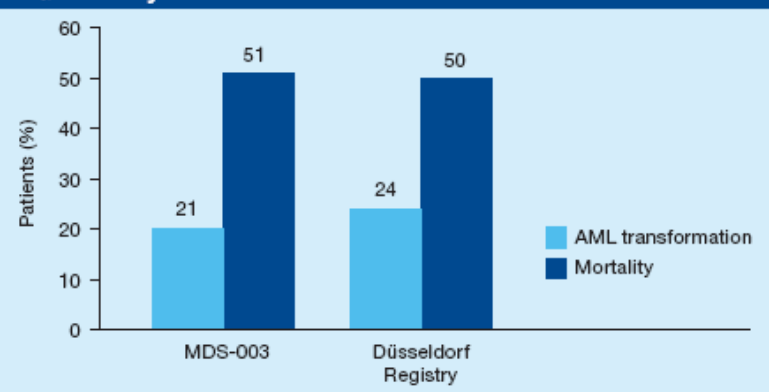
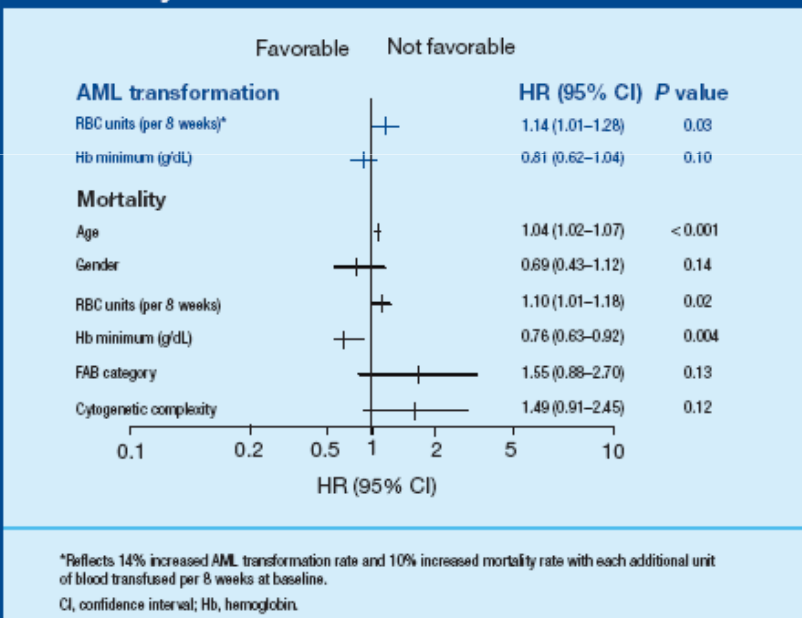


Figure 2. Cox proportional hazards model for AML transformation and mortality.



**IMMUNOSUPPRESSION FOR PATIENTS WITH LOW AND INTERMEDIATE RISK
MYELOYDYSPLASTIC SYNDROME: A PROSPECTIVE RANDOMIZED MULTICENTER
TRIAL COMPARING ANTI-THYMOCYTE GLOBULIN AND CYCLOSPORINE WITH BEST
SUPPORTIVE CARE: SAKK 33/99**

Ramirez et al, abstract 908 (oral communication)

- Eighty-eight transfusion dependent patients were randomized to receive ATG+CSA (15mg/kg of horse ATG (Lymphoglobuline, Genzyme) for 5 days and oral CSA for 180 days) or best supportive care (BSC),
- Stratification by treatment center and IPSS risk score between November 2000 and October 2006.

	ATG+CSA	BSC
Patients: n	45	43
Age: median years (range)	62 (23-75)	65 (24-76)
Sex: n male (%)	25 (56)	35 (81)
IPSS score: n (low/int-1/int-2/high/na)	(8/24/7/1/4)	(8/25/5/0/5)
MDS type: n (RA/RAS/RAEB-I/RAEB-II/hypoplastic)	(21/6/9/0/9)	(18/8/11/2/4)

- At 6 months hematologic response (CR + PR) occurred in **31%** in the ATG+CSA arm, compared to **12%** in the BSC arm (**p = 0.04**)
- Response duration in the ATG arm was **1.4 (0.6-2.8) years**
- Transformation-free survival probability estimates at 2 years were **39%** for ATG+CSA and **43%** for BSC (**p n.s**)
- Overall survival probability estimates at 2 years were **46%** for ATG+CSA and **60%** for BSC (**p n.s**)
- There were 23 SAEs (mainly infectious and inflammatory complications): 16 in the ATG+CSA arm and 7 in the BSC arm (**p 0.04**)

ANEMIA WITH RING SIDEROBLASTS ASSOCIATED WITH THROMBOCYTOSIS: CLINICAL AND ANALYTICAL FEATURES ACCORDING TO THE PRESENCE OR ABSENCE OF THE JAK2 V617F MUTATION

Raya et al, abstract 716 (poster)

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	RARS-T with JAK2 V617F mutation (n=17)	RARS-T without JAK2 V617F mutation (n=30)	p value
Age (years)	72.9 ± 11.1	73.6 ± 8.8	N.S.
Sex (M:F)	11:6	17:13	N.S.
Platelet count (x10 ⁹ /L)	845 ± 278	591 ± 239	<0.001
WBC count (x10 ⁹ /L)	9.2 ± 3.5	6.7 ± 2.2	0.018
Hemoglobin (g/L)	109.2 ± 16.6	97.7 ± 16.0	0.029
MCV (fL)	97.3 ± 8.7	102.4 ± 6.4	0.037
Basophil count (x10 ⁹ /L)	0.108 ± 0.082	0.063 ± 0.060	N.S.
Bone marrow blasts (%)	0.9 ± 1.2	1.2 ± 1.2	N.S.
Type III sideroblasts (%)	31 ± 27	32 ± 23	N.S.
Ringed sideroblasts (%)	48 ± 21	48 ± 19	N.S.
Uric acid	5.3 ± 2.4	5.8 ± 1.8	N.S.
Lactate-dehydrogenase (U/L)	429 ± 191	324 ± 106	N.S.
Ferritin	656 ± 674	560 ± 984	N.S.
Vitamin B ₁₂	579 ± 391	677 ± 577	N.S.
Splenomegaly	4/14 (29%)	3/23 (13%)	N.S.
Karyotype aberrations	2/15 (13%)	2/22 (9%)	N.S.
BM Megakaryocytic hyperplasia	7/8 (87%)	4/5 (80%)	N.S.
BM reticulin fibrosis	5/7 (71%)	2/5 (40%)	N.S.
Transfusional dependence	1/14 (7%)	8/27 (29%)	N.S.

A retrospective study of 47 patients with diagnosis of RARS-T (platelet count above 400x10⁹/L), taking into account the presence or absence of the JAK2 V617F mutation.

There were no differences in terms of survival (p=0.38)

Published with 76 patients

Int J Hematol. 2008 Sep 27. [Epub ahead of print]

TREATMENT-RELATED MYELOYDYSPLASIA AND SECONDARY AML FOLLOWING FLUDARABINE COMBINATION CHEMOTHERAPY

Carney et al, abstract 233 (poster)

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- 146 pts treated with fludarabine in combination (F+) (CLL, FL, WM/MZL, MCL)
- Median f.u. 40 months
- 17 sMDS/AML (11.6%) were diagnosed: (12 RCMD, 2 CMML, 1 RAEB, 2 AML)
- sMDS/AML occurred in **22.4% of FL**, 2.9% of CLL, 21.1% of WM/MZL (21.1%) at a median time of 46 months following commencement of F+ treatment
- Karyotypic analysis was typically complex
- MDS-free rate at 6 years was 100% for CLL and MCL, 75% for WM/MZL, **69% for FL (p=0.029)**
- The MDS-free rate at 6 years was 54% for **F+Mitoxantrone** compared to 86% without Mitoxantrone (**p<0.001**)

IMPROVEMENT OF HEMOGLOBIN LEVEL AND REDUCTION OF TRANSFUSION REQUIREMENT IN 4 PATIENTS AFFECTED BY MYELOYDYSPLASTIC SYNDROMES AND PRIMARY MYELOFIBROSIS RECEIVING DEFERASIRO TREATMENT

Messa et al, abstract 63 (poster)

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Case Report

*Acta
Haematologica*

Acta Haematol 2008;120:70–74
DOI: [10.1159/000158631](https://doi.org/10.1159/000158631)

Received: April 10, 2008
Accepted after revision: July 3, 2008
Published online: October 1, 2008

Deferasirox Treatment Improved the Hemoglobin Level and Decreased Transfusion Requirements in Four Patients with the Myelodysplastic Syndrome and Primary Myelofibrosis

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Division of Hematology and Internal Medicine, Department of Clinical and Biological Sciences, University of Turin, Orbassano, Italy

EHA 2008: A call for morphology and karyotype standards

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- EUROPEAN LEUKEMIANET (ELN) PLATFORM (WP10): PRELIMINARY RESULTS OF THE EUROPEAN MORPHOLOGY CONSENSUS PANEL
Zini et al, abstract 707 (poster)
- A STANDARDIZED APPROACH FOR THE ASSESSMENT OF BONE MARROW DYSPLASIA IMPROVES THE ACCURACY OF THE WHO CLASSIFICATION IN MYELOYDYSPLASTIC SYNDROMES.
Invernizzi et al, abstract 715 (poster)
- MAJOR DIFFERENCES WITH SCORING KARYOTYPE RESULTS FOR PATIENTS WITH MYELOYDYSPLASTIC SYNDROMES: A CALL FOR INTERNATIONAL STANDARDIZATION.
Hagemeyer et al, abstract 711 (poster) Leuk Res. 2008 Sep;32(9):1329-32. International Working Group on MDS cytogenetics: October 2007 meeting report.
- FISH IMPROVES THE DETECTION OF 5q31 DELETION IN MYELOYDYSPLASTIC SYNDROMES WITHOUT CITOGNETIC EVIDENCE OF 5q-
Mallo et al, abstract 166 (poster) Mallo, M. et al. Haematologica 2008;93:1001-1008
- PRIMARY MYELOYDYSPLASTIC SYNDROMES WITH NORMAL CYTOGENETICS: VALUE OF INTERPHASE FISH FOR THE DETECTION OF CRYPTIC CHROMOSOME 7 ABNORMALITIES
Stevens-Kroef et al, abstract 1035 (only publication)
- REDFINING MONOSOMY 20 BY MOLECULAR CYTOGENETICS IN 10 MDS/AML PATIENTS
Bernasconi et al, abstract 680 (poster)