37 Diada Internacional
Societat Catalana d'Hematologia i Hemoteràpia (SCHH)
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Agents Hipometilants en les SMD

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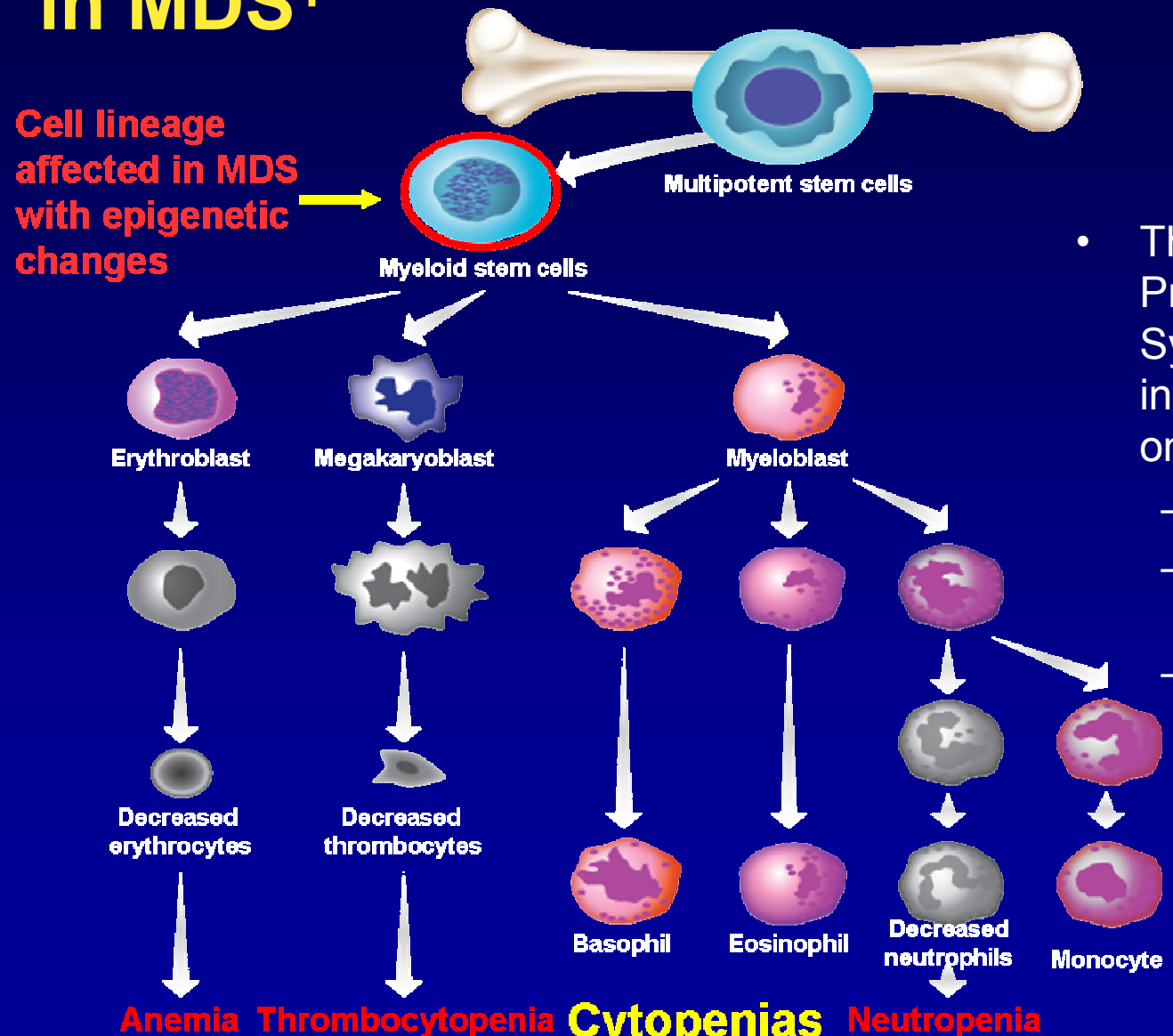
Ineffective hematopoiesis and cytopenias in MDS[1]



- The International Prognostic Scoring System categorizes MDS into 4 risk groups based on[2]:
  - Number of cytopenias
  - Percentage of abnormal marrow blasts
  - Cytogenetics

MDS, myelodysplastic syndromes.

1. Adapted from Bondurant MC, Koury MJ. Wintrobe's Clinical Haematology: 1999:145–69.
2. Greenberg P, et al. Blood 1997;89:2079–88.

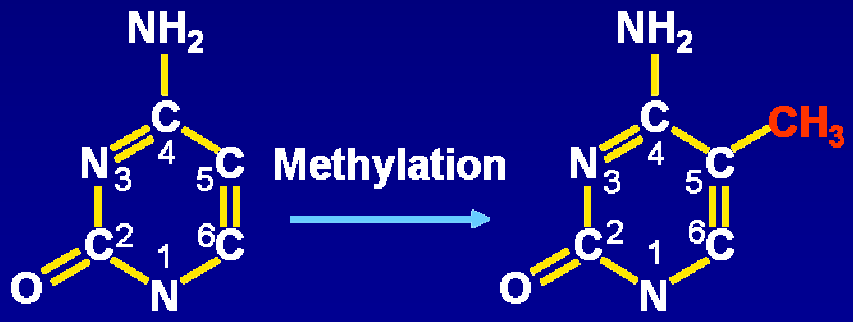
Epigenètica i càncer

- La expressió dels gens pot ser regulada per:
  - Alteracions genètiques (delecions, amplificacions o mutacions)
  - Alteracions epigenètiques (metilació del DNA o modificació de histones, microRNAs)
- La hipermetilació del DNA pot produir silenciament de gens
- El silenciament de gens supressors de tumors pot permetre desenvolupament i progressió del càncer

DNA methylation

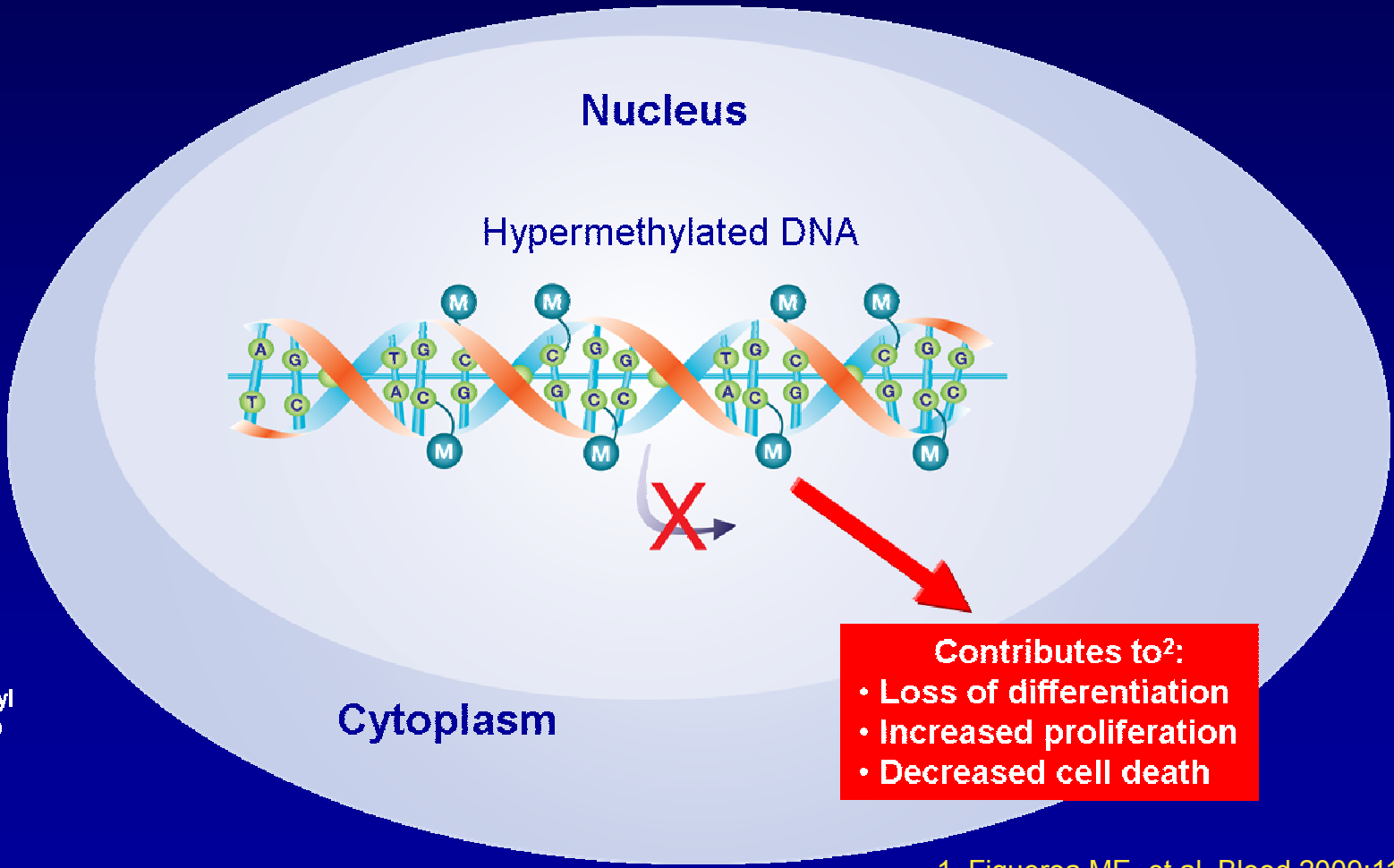
- A covalent modification of cytosine residues catalyzed by DNA methyltransferases
- Occurs at CpG dinucleotides and is enriched at noncoding regions and gene promoter regions

Cytosine



Untreated MDS

Tumor suppressor genes are silenced by hypermethylation in cancer, including MDS[1]



MDS, myelodysplastic syndromes.

1. Figueroa ME, et al. Blood 2009;114:3448–58.
2. DeVita VT, et al, eds. Cancer Principles and Practice of Oncology 2008:2292–304.

Genes commonly hypermethylated in MDS

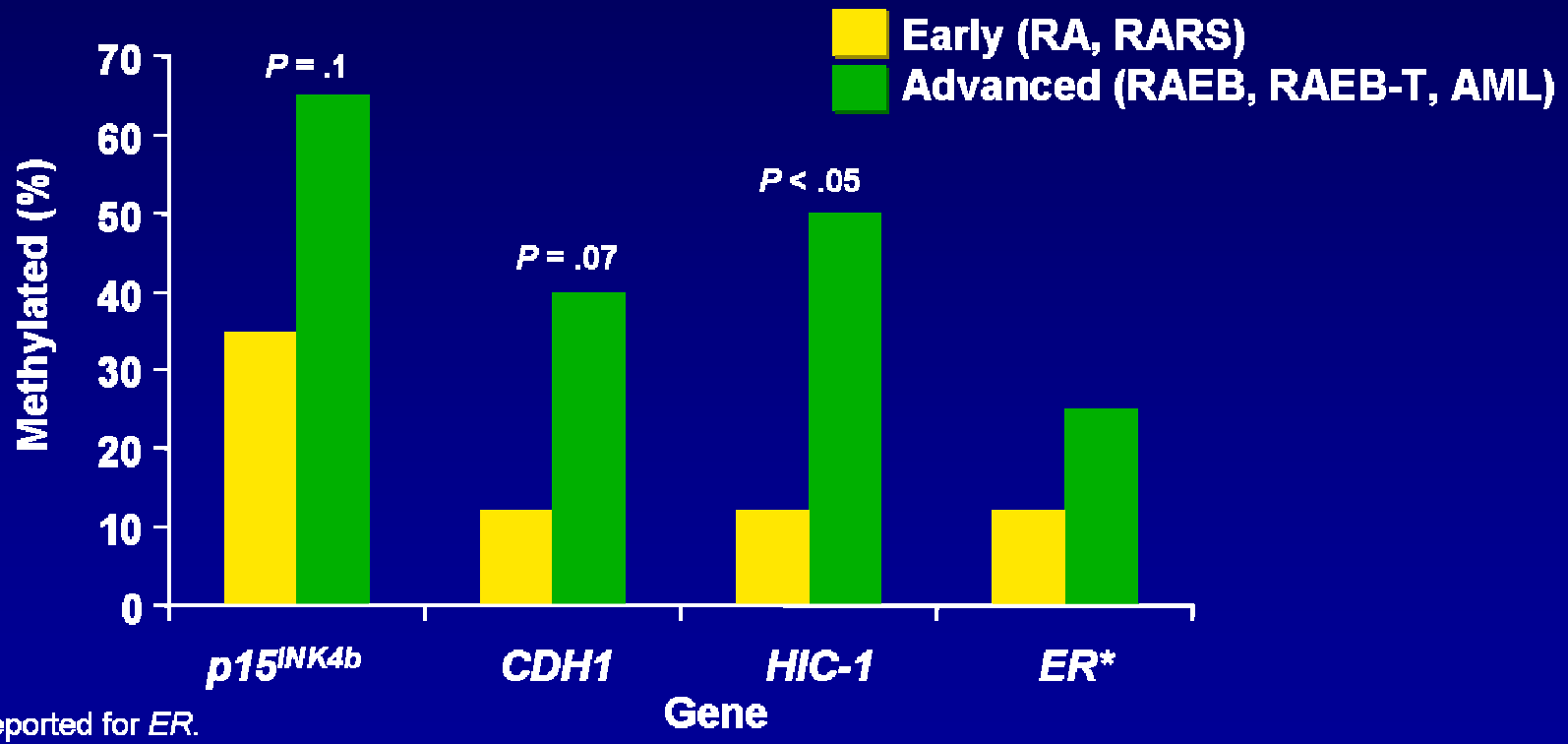
Gene	Function	Prevalence of methylation in patients with MDS
Calcitonin	Calcium and phosphorus metabolism	≈ 90%[1]
Death-associated protein kinase-1 (DAPK-1)	Apoptosis	≈ 60%[2]
$p15^{INK4b}$	Cell cycle regulation	≈ 50%[3]
Suppressor of cytokine signaling-1 (SOCS-1)	Regulation of cytokine signaling	≈ 50%[4]
E-cadherin (CDH1)	Cell adhesion	≈ 30%[3]
Hypermethylated in cancer-1 (HIC-1)	Tumor suppressor gene	≈ 30%[3]
Estrogen receptor (ER)	Hormone receptor	≈ 20%[3]

MDS, myelodysplastic syndromes.

1. Ihalainen J, et al. Leukemia 1993;7:263–67.
2. Qian J, et al. Int J Lab Hematol 2010; 32:74–81.
3. Aggerholm A, et al. Eur J Haematol 2006;76:23–32.
4. Wu SJ, et al. Br J Haematol 2006;135:317–23.

Hypermethylation in MDS/AML increases with advanced disease

Frequency of Tumor Suppressor Gene Promoter Hypermethylation in Bone Marrow Mononuclear Cells

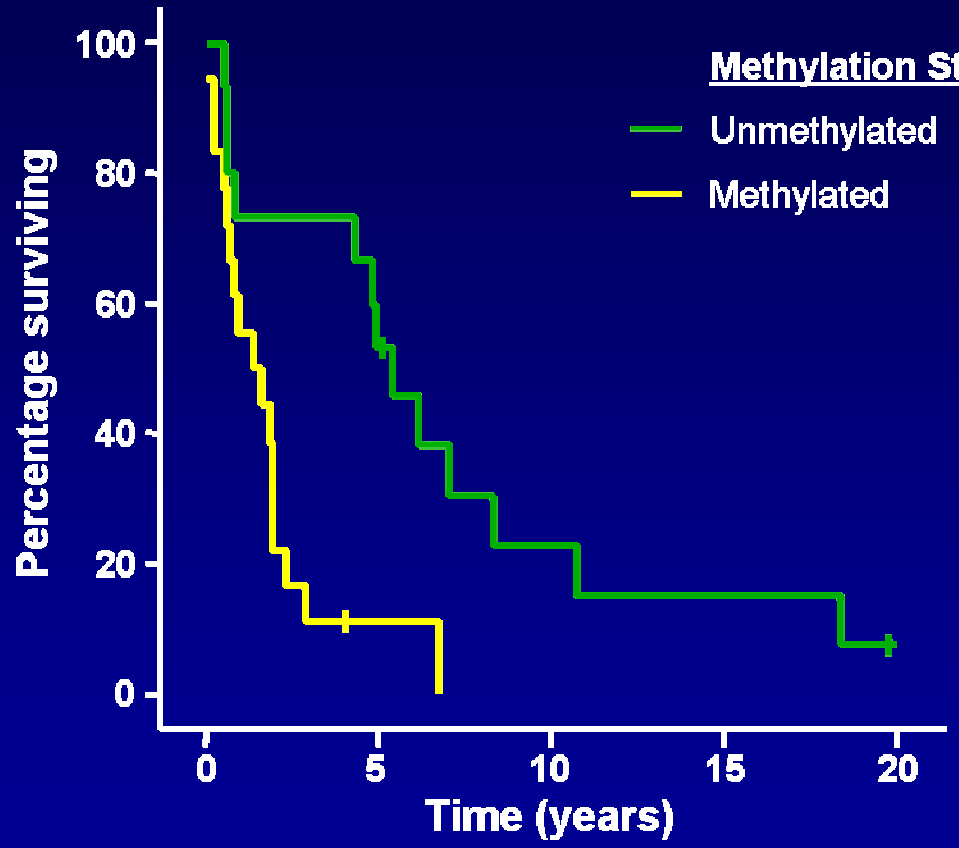


* *P* value not reported for *ER*.

AML, acute myeloid leukemia; *CDH1*, E-cadherin; *ER,* estrogen receptor; *HIC-1,* hypermethylated in cancer-1; MDS, myelodysplastic syndromes; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-T, RAEB in transformation.

Aggerholm A, et al. Eur J Haematol 2006;76:23–32.

Hypermethylation in MDS/AML is a poor prognostic factor



Methylation Status	n	Median OS*
Unmethylated	15	67 months
Methylated	18	17 months

P = .002

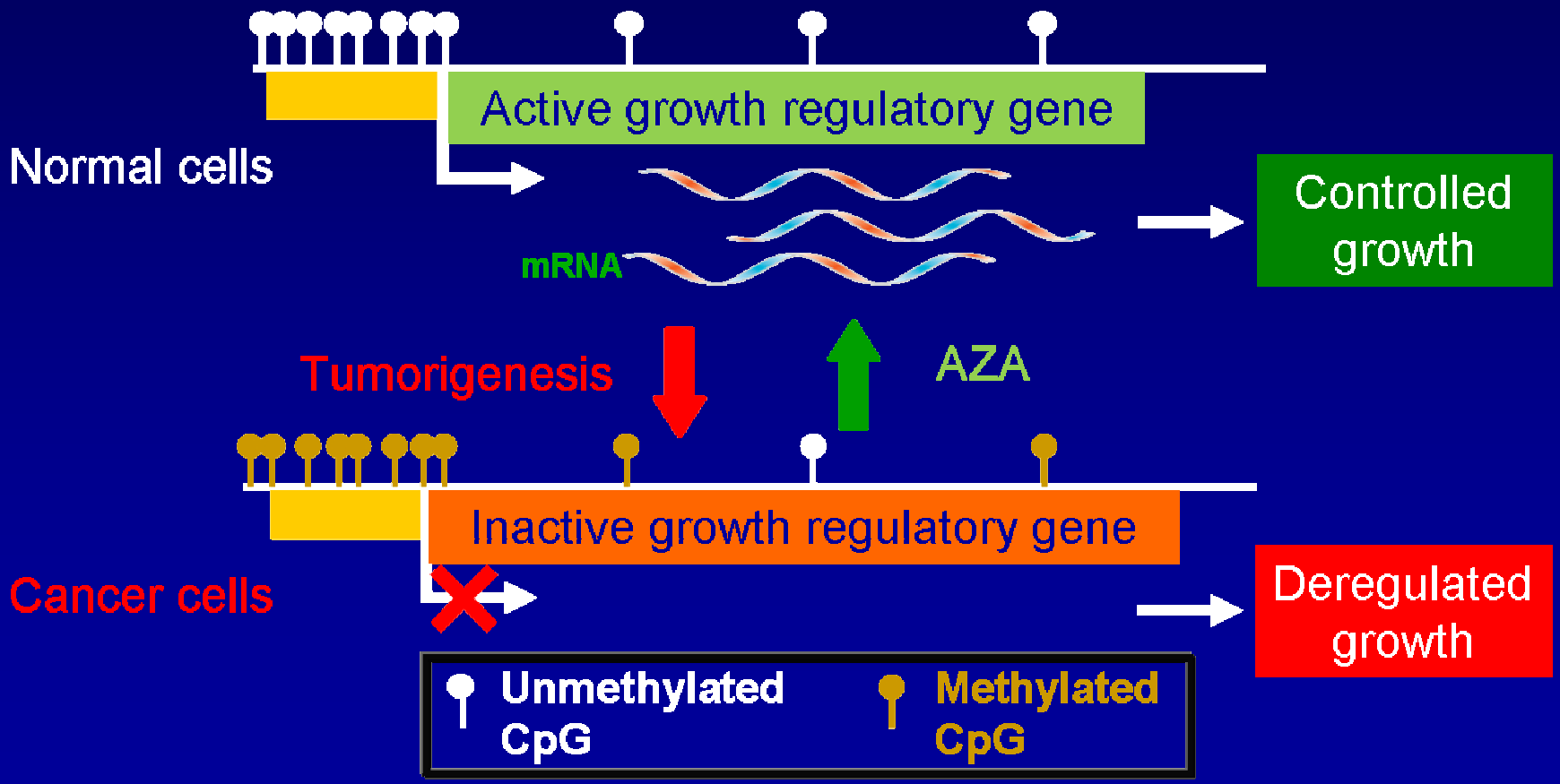
- **Patients with hypermethylation of at least 1 tumor suppressor gene have significantly shorter survival**

* Overall survival data available for 33 of 37 patients.
AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; OS, overall survival.

Aggerholm A, et al. Eur J Haematol 2006;76:23–32.

Tumorigenic epigenetic changes are reversible

Hypomethylating agents (eg, AZA) can reduce hypermethylation, re-expressing tumor suppressor genes



AZA, azacitidine; mRNA, messenger RNA.

Yoo CB, Jones PA. *Nat Rev Drug* Discovery. 2006;5: :37–50.

Metilació del DNA i Càncer. Resum

- La metilación del DNA es un mecanisme important en la regulació epigenètica dels gens
- Els gens supressors de tumors poden ser silenciats per una hipermetilació aberrant en les cèl·lules canceroses
- En les SMD i LMA la hipermetilació augmenta en la malaltia avançada i constitueix un factor de mal pronòstic
- Els tractaments epigenètics poden revertir la metilació aberrant, potencialment restaurant la funció cel·lular normal

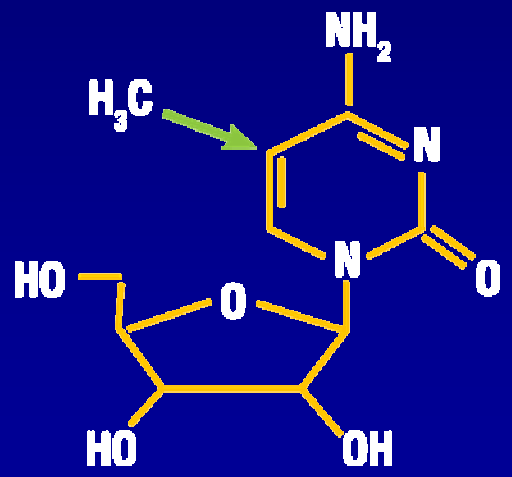
Agents demetilans

- AZACITIDINA
- DECITABINA

Structure of azacitidine

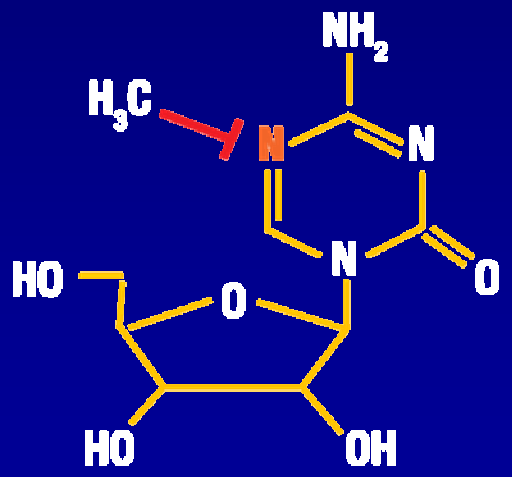
- AZA is 5-azacitidine, a cytidine nucleoside analog[1]
- Substitution of the carbon (C) at position 5 with nitrogen (N) prevents DNA methylation[2]

Nucleoside



Cytidine

Nucleoside Analog



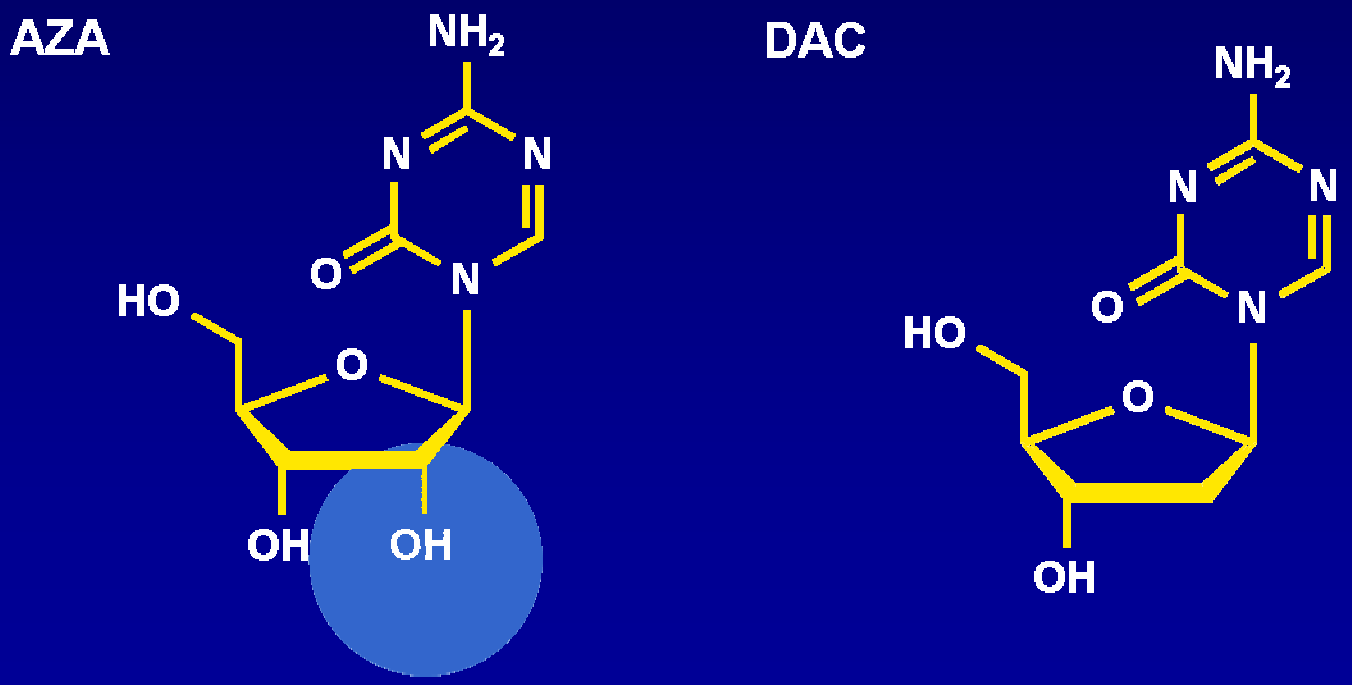
Azacitidine

AZA, azacitidine.

1. Vidaza [package insert]. Summit, NJ: Celgene Corp; 2008.
2. Raj K, Mufti GJ. Ther Clin Risk Manag 2006;2:366–88.

Decitabine: another hypomethylating agent

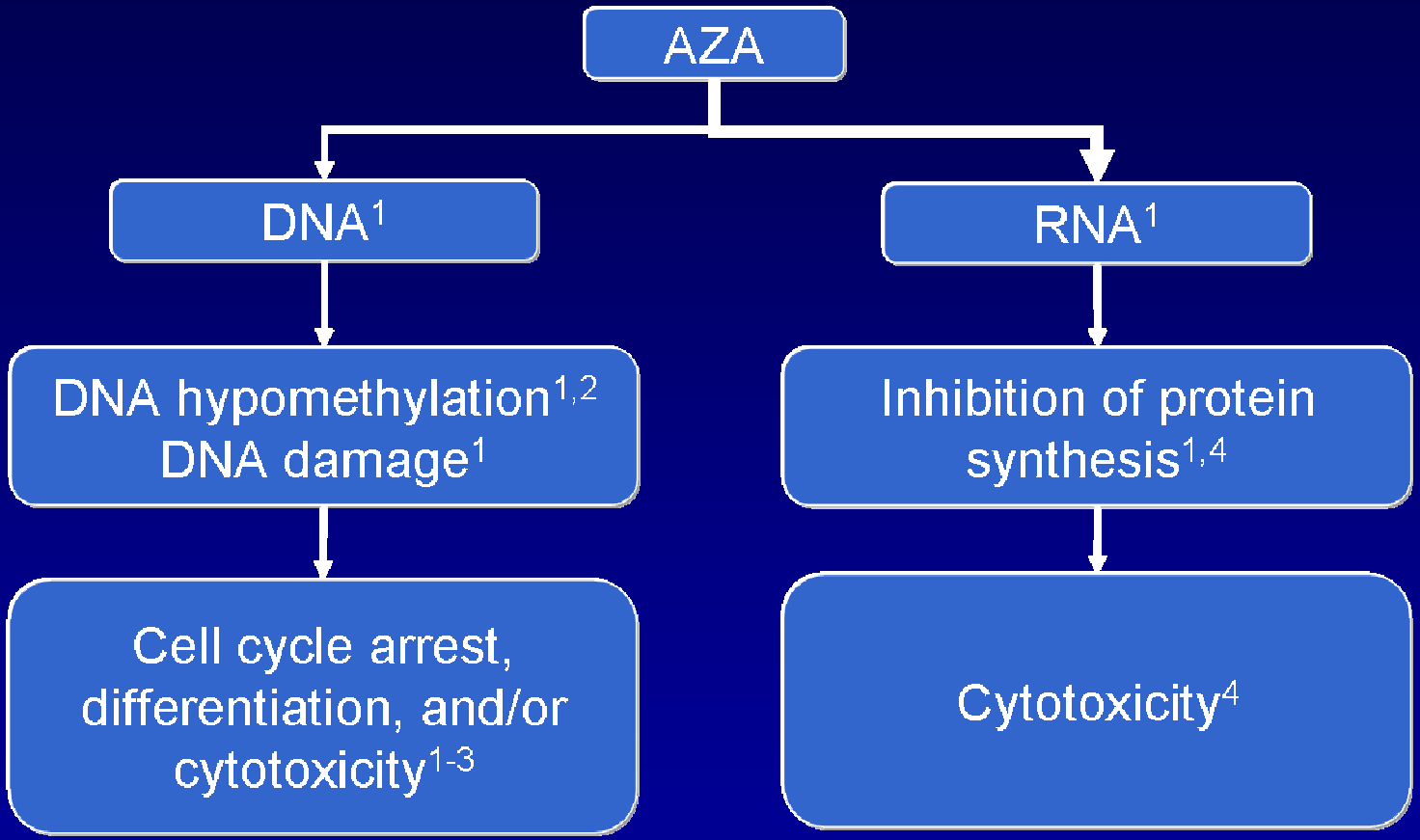
The structure of decitabine differs from azacitidine by one hydroxyl-group (OH) in the ribose sugar



AZA, azacitidine; DAC, decitabine.

Raj K, Mufti GJ. Ther Clin Risk Manag 2006;2:377–88.

Azacitidine is incorporated into DNA and RNA



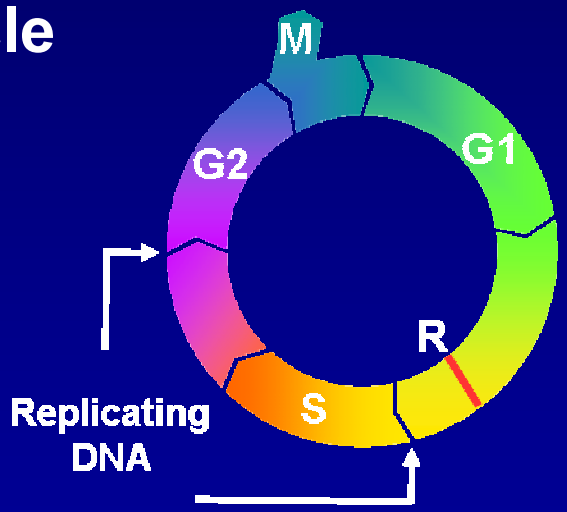
- **AZA incorporation is greater in RNA compared with DNA[1]**

1. Hollenbach PW, et al. PLoS One 2010;5:1–10.
2. Vidaza [package insert]. Summit, NJ: Celgene Corp; 2008.
3. Poirier F, et al. Cancer Cell Int 2001;1:1–12.
4. Murakami T, et al. Cancer Res 1995;55:3093–8.

AZA, azacitidine.

Azacitidine vs decitabine: differences in incorporation into genetic material

- AZA incorporates into both RNA and DNA[1-5]; DAC incorporates into DNA only[5,6]
- AZA and DAC incorporate into replicating DNA during S phase of the cell cycle (S-phase restricted)[1-3,6]
- AZA incorporation into newly synthesized RNA can occur during all cell cycle phases[2-4]

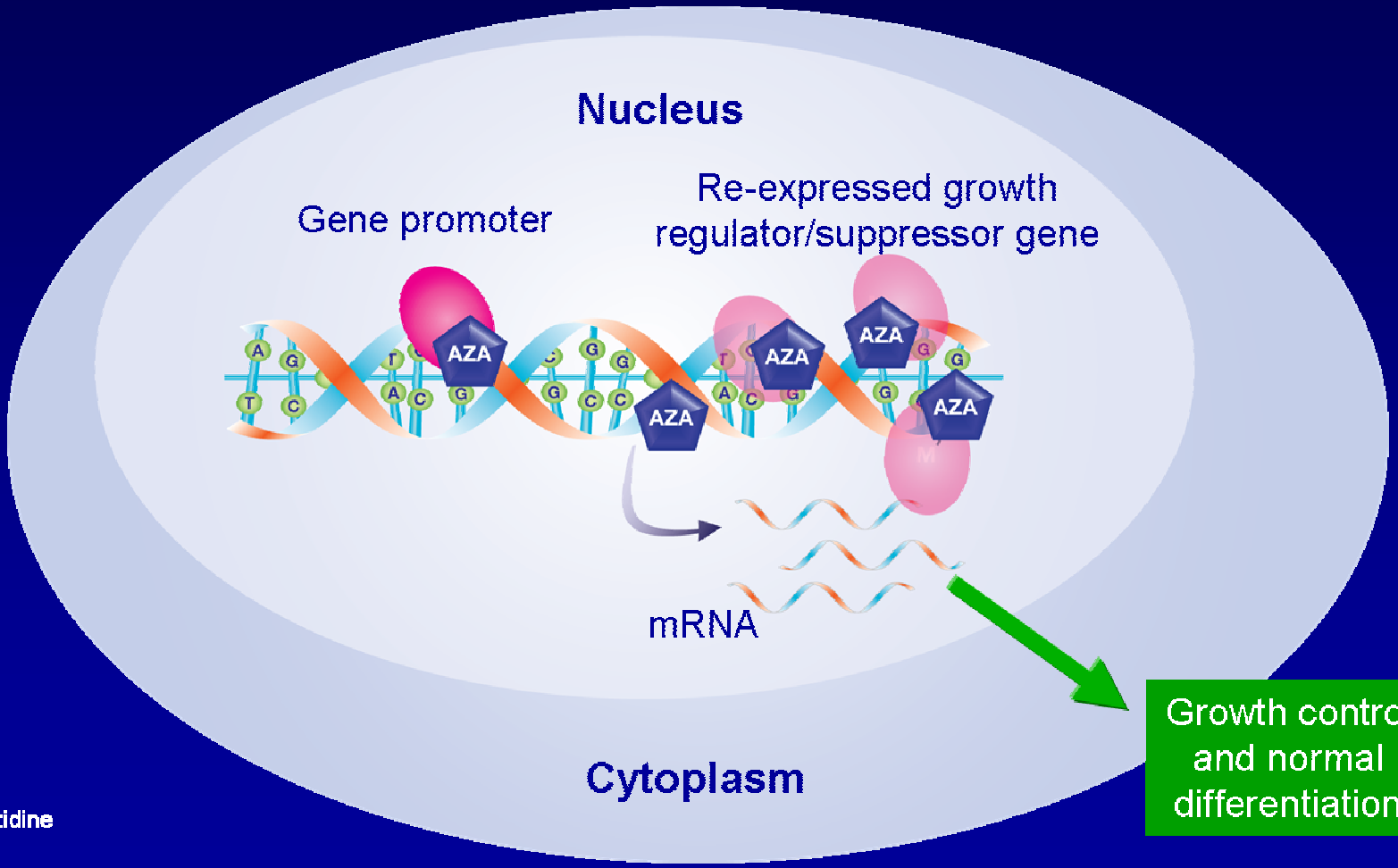


1. Vidaza. [package insert]. Summit, NJ: Celgene Corp; 2008.
2. Hollenbach PW, et al. PLoS One 2010;5:1–10.
3. Kaminskas E, et al. Oncologist 2005;10:176–82.
4. Glover AB, Leyland-Jones B. Cancer Treat Rep 1987;71:959–64.
5. Yoo CB, Jones PA. Nat Rev Drug Discov 2006;5:37–50.
6. Dacogen [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2008.

AZA, azacitidine; DAC, decitabine.

Re-expression of silenced genes

Hypometilating agents results in depletion of DNMTs, reduced DNA methylation, and re-expression of silenced genes



AZA, azacitidine

DNMT, DNA methyltransferase

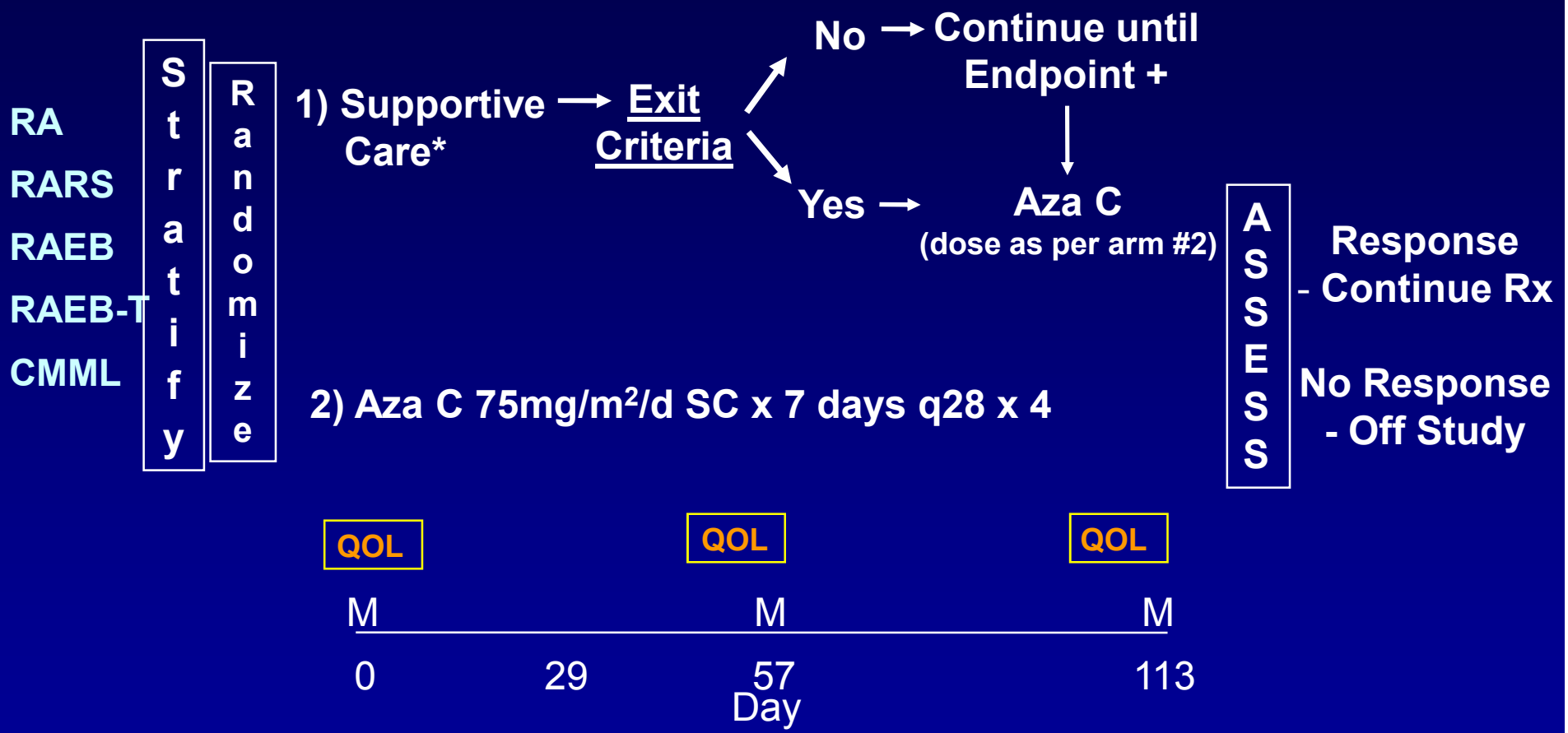
Hollenbach PW, et al. PLoS One 2010;5:1–10.

SMD
Azacitidina

Reference	Disease	Dose/Schedule	N	CR (%)	PR (%)
Karon M, 1973	Refractory AML (pediatric)	2-268 mg/m^2/d	15	5 (33)	1 (7)
Levi JA, 1976	Refractory/relapsed AML	200-250 mg/m^2/d	18	5 (28)	1 (6)
Saiki JH, 1978	Refractory/relapsed AML/ALL	300 mg/m^2/d	72	17 (24)	NA
Saiki JH, 1981	Refractory/relapsed leukemia	100-300 mg/m^2/d	120	9 (8)	2 (2)
Chitambar CR, 1991	High-risk MDS	10-35 mg/m^2/d	15	NA	4 (24)
Silverman LR, 1993	GALGB RAEB, RAEB-t	75 mg/m^2/d (IV)	49	6 (12)	12 (25)
Silverman LR, 2004	GALGB phase II, RAEB, RAEB-t	525 mg/m^2 (SQ)	70	50% total response	
Gryn J, 2002	Elderly high-risk MDS	75 mg/m^2/d (SQ)	57	39% transf. independence	
Silverman LR, 2002	GALGB phase III, high-risk MDS	75 mg/m^2/d (SQ)	99	60% total response	

CALGB 9221

A Randomized Phase III Controlled Trial of Azacitidine in MDS



* Minimum duration of supportive care = 4 months unless transform to AML; death or plts š 20 x 10^9/L at week 8 or later

QOL – Quality of Life Assessment
M = Bone Marrow Aza C – Azacitidine S.C.

Silverman L et al. J Clin Oncol 2002. 18:2414-26

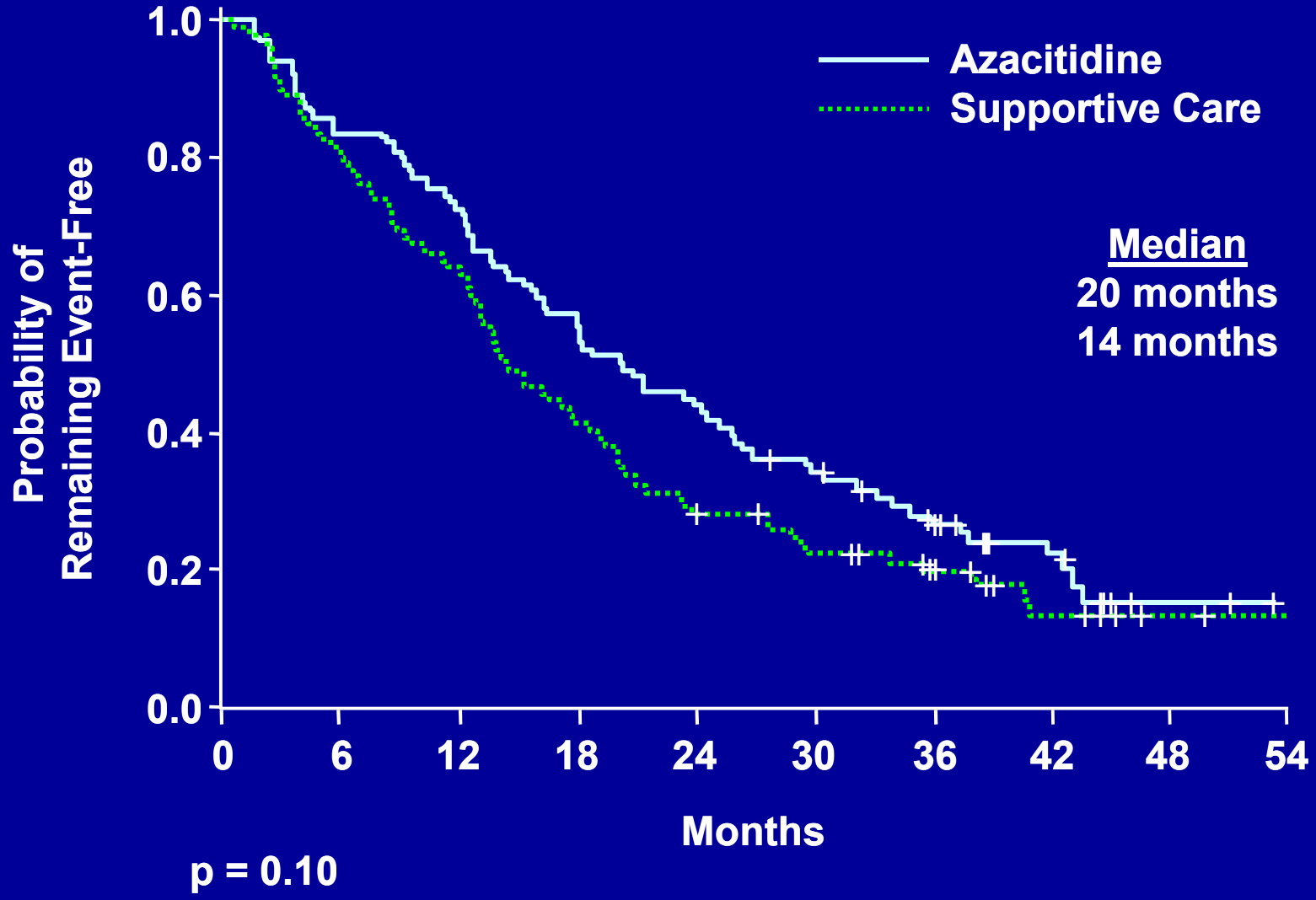
Azacitidina versus Tractament de Suport
Resposta hematològica

SC	AZA	Crossover	
No. Evaluated	**92**	**99**	**49**
CR	0 (0%)	7 (7%)*	5 (10%)
PR	0 (0%)	15 (16%) **	2 (4%)
Improved	5 (5%)	38 (37%) **	16 (36%)
Total	5 (5%)	60 (60%) **	23 (47%)

P value * < 0.01 **<0.001

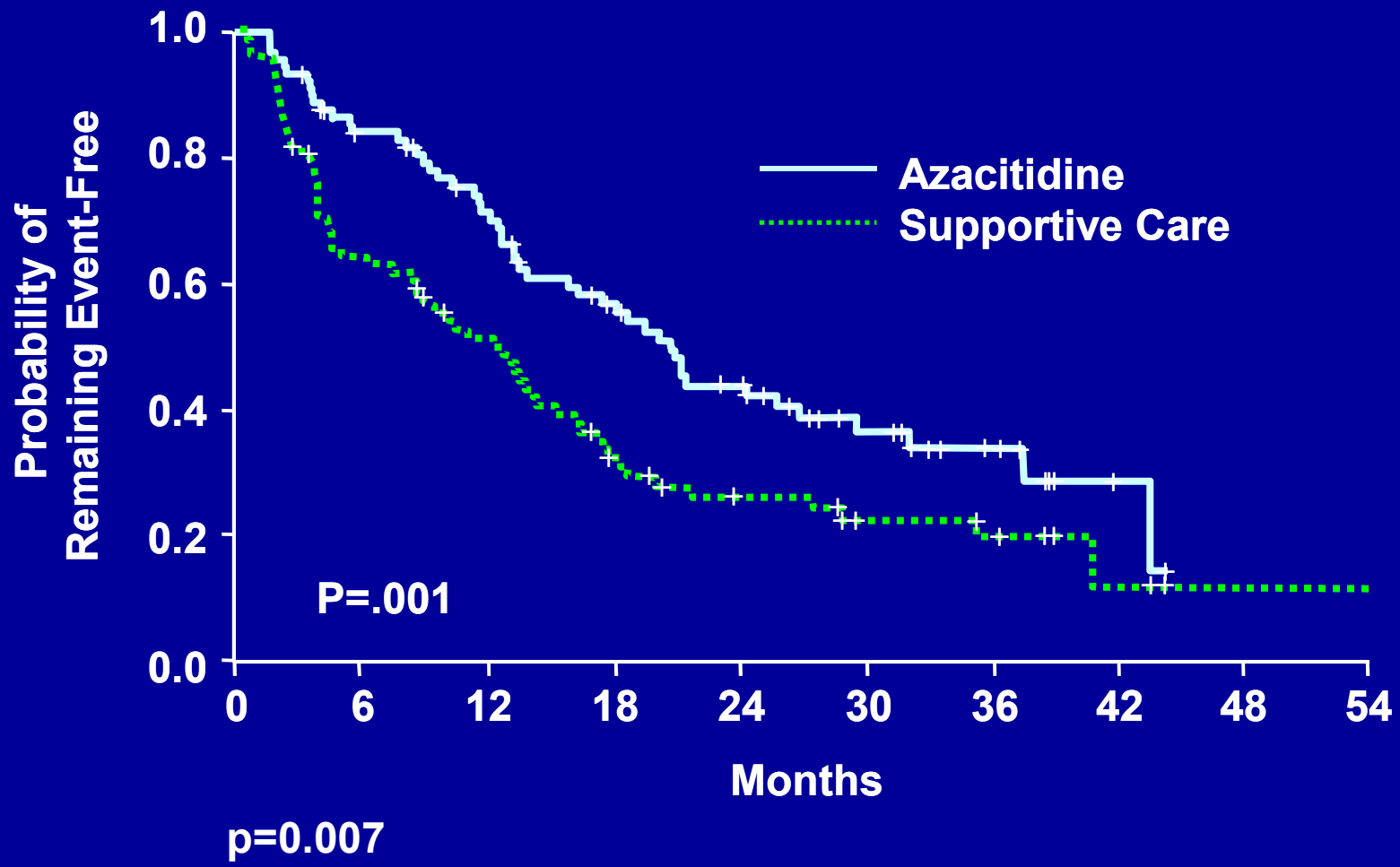
Silverman L et al. J Clin Oncol 2002. 18:2414-26

Overall Survival



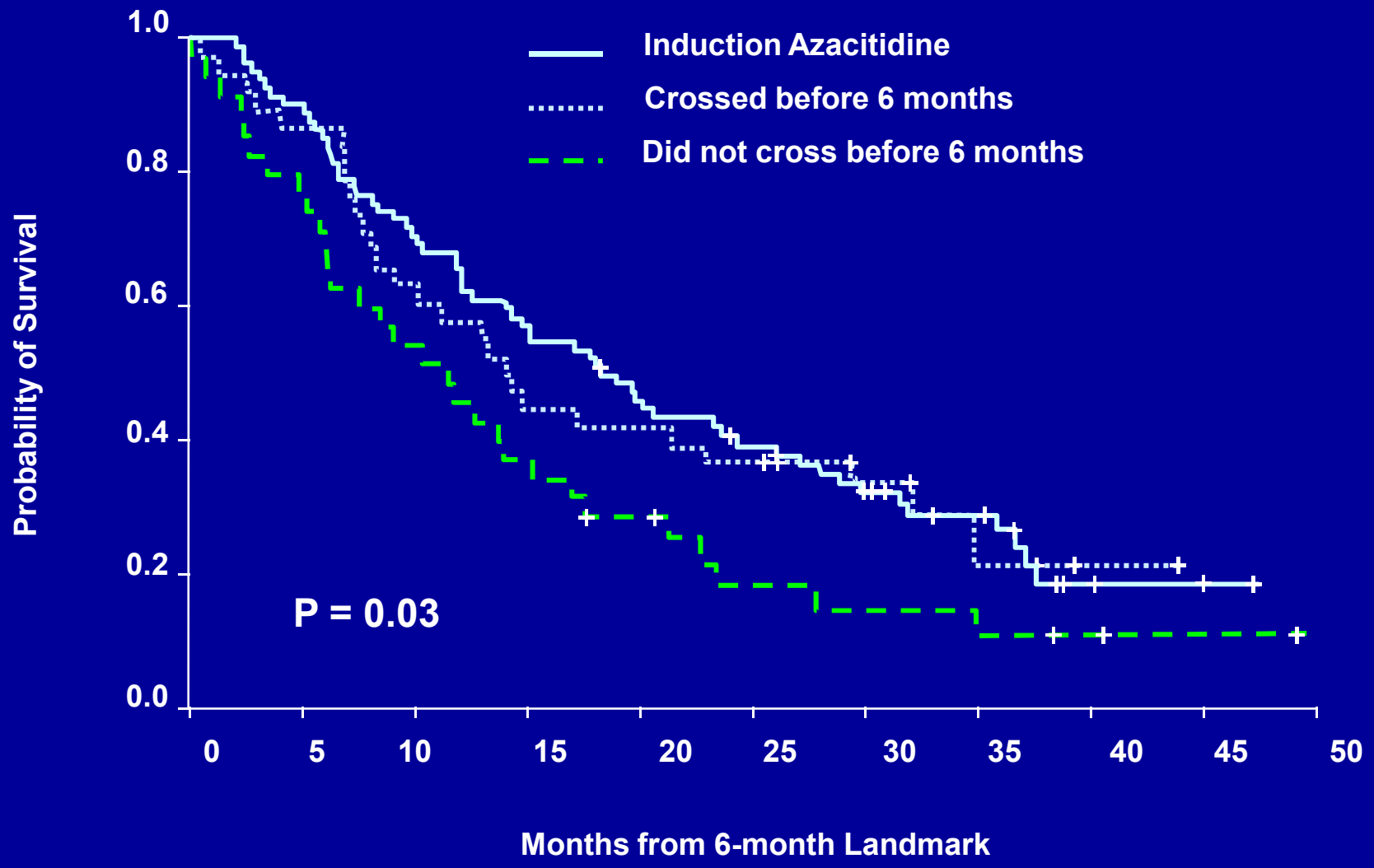
Silverman L, et al. Randomized Controlled Trial of Azacitidine in Patients with MDS: A Study of the CALGB
J Clin Oncol 2002. 18:2414-26. Reprinted with permission from the American Society of Clinical Oncology.

Time to AML Transformation



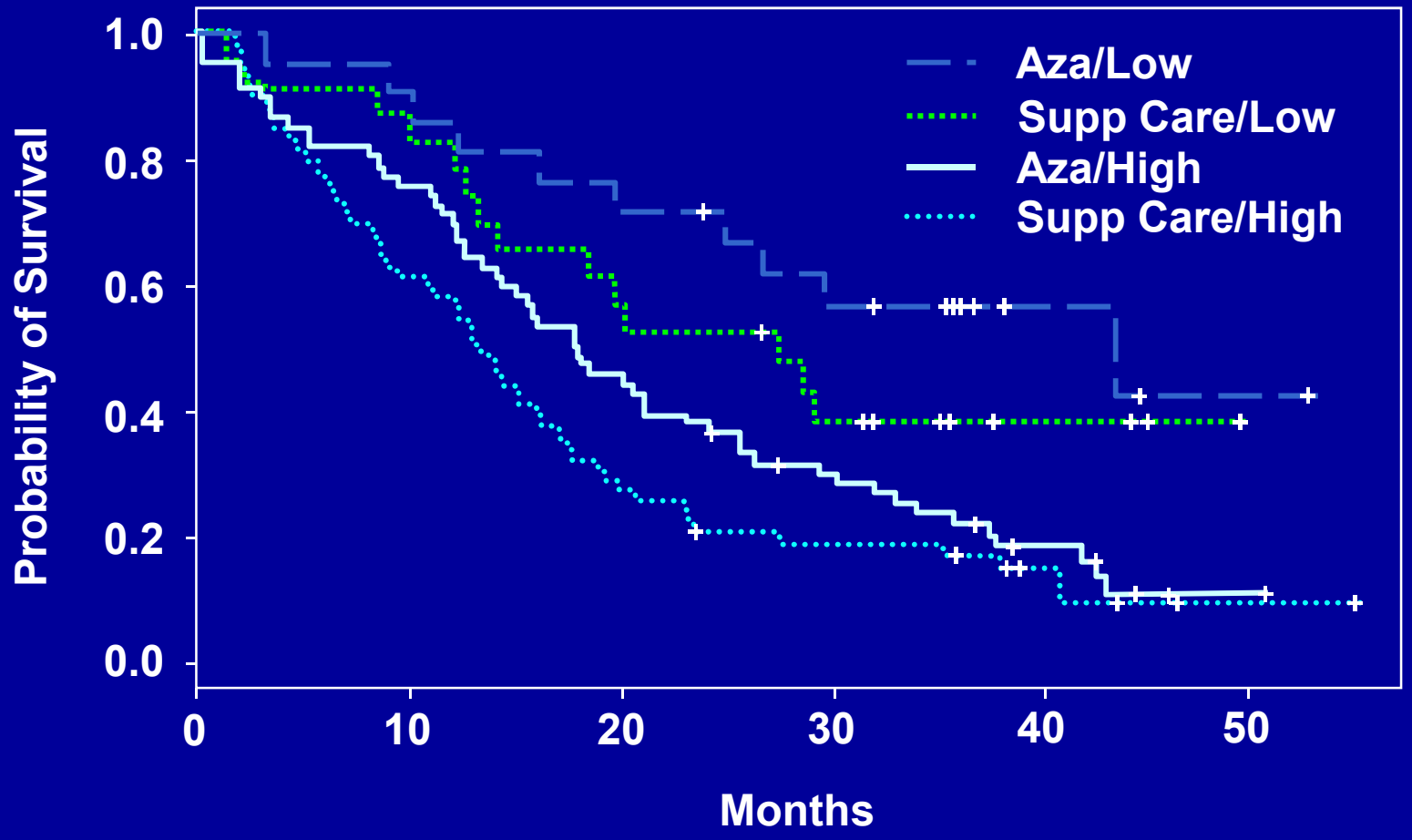
Silverman L, et al. Randomized Controlled Trial of Azacitidine in Patients with MDS: A Study of the CALGB *J Clin Oncol* 2002. 18:2414-26. Reprinted with permission from the American Society of Clinical Oncology.

Azacitidina versus Tractament de Suport
Supervivència segons mètode de la fita



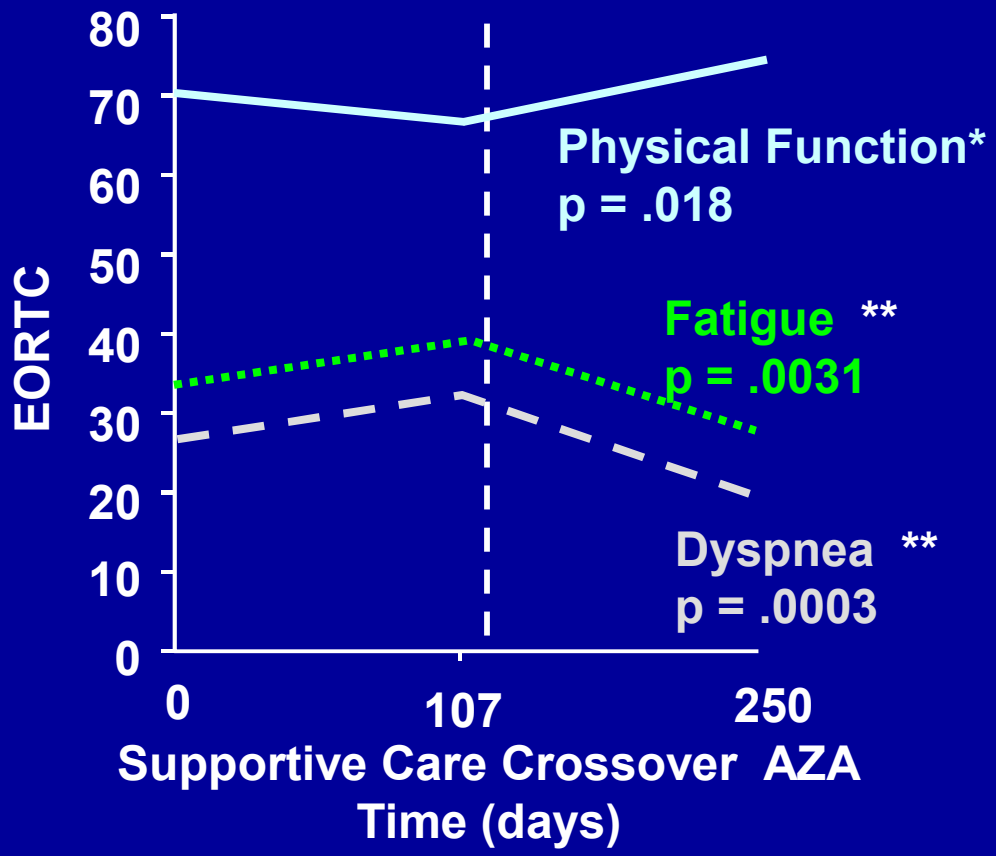
Silverman L et al. *J Clin Oncol* 2002. 18:2414-26

Azacitidina versus Tractament de Suport
Supervivència segons subtipus FAB



Silverman L et al. J Clin Oncol 2002. 18:2414-26

Azacitidina versus Tractament de Suport
Efecte en la qualitat de vida

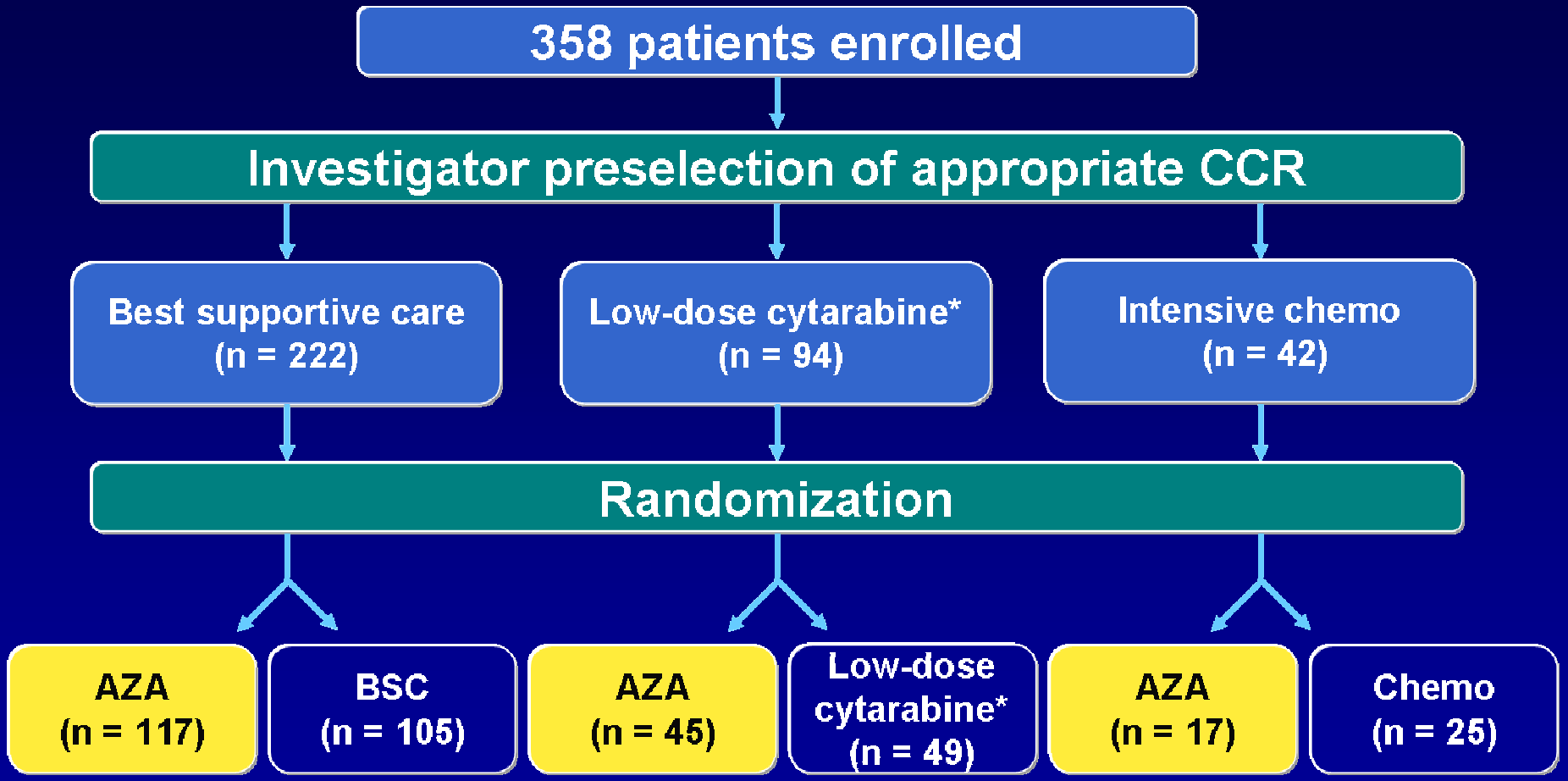


* Higher Scores = Better Functioning

** Lower Scores = Symptom Improvement

Kornblith et al. J Clin Oncol 2002; 20: 2441-52.

AZA-001: phase III trial study design

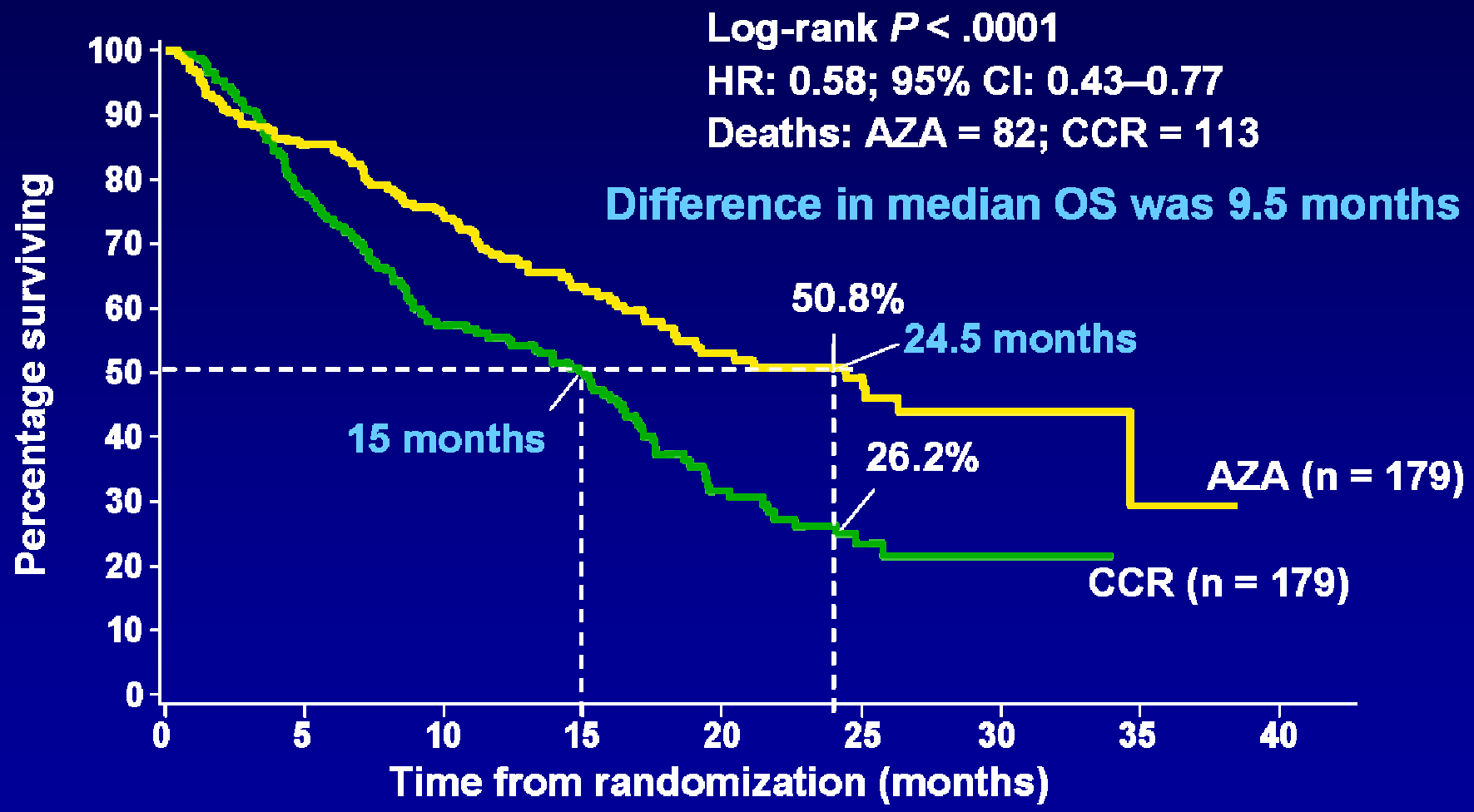


- Treatment continued until relapse, unacceptable adverse events, or disease progression
- Primary endpoint: overall survival

* 20 mg/m^2/day for 14 days every 28-42 days.
AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimen; chemo, chemotherapy.

Fenaux P, et al. Lancet Oncol 2009;10:223–32.

Azacitidine is the only hypomethylating agent that significantly prolongs OS

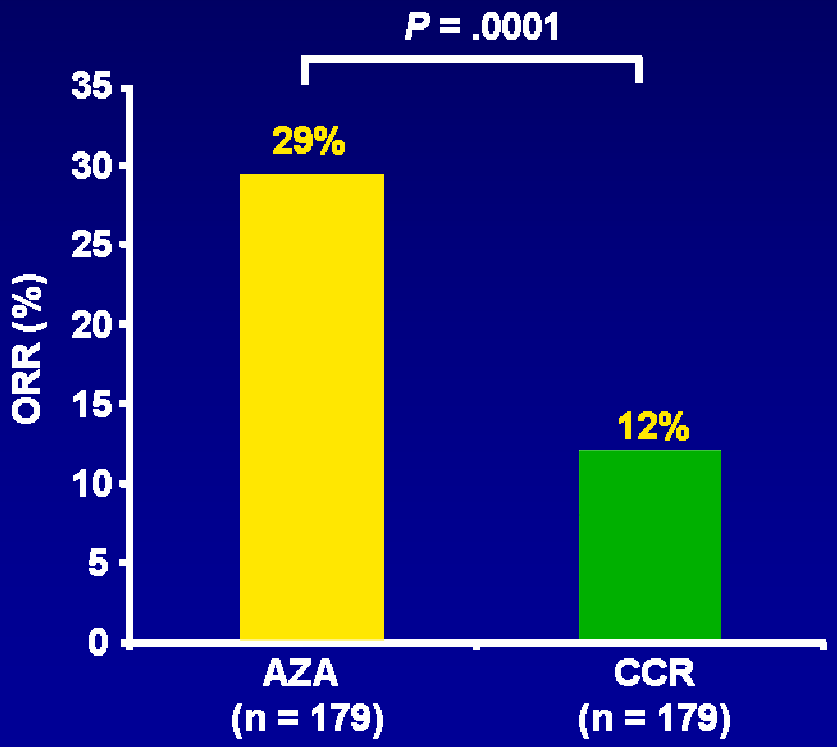


AZA, azacitidine; CCR, conventional care regimen; CI, confidence interval; HR, hazard ratio; OS, overall survival.

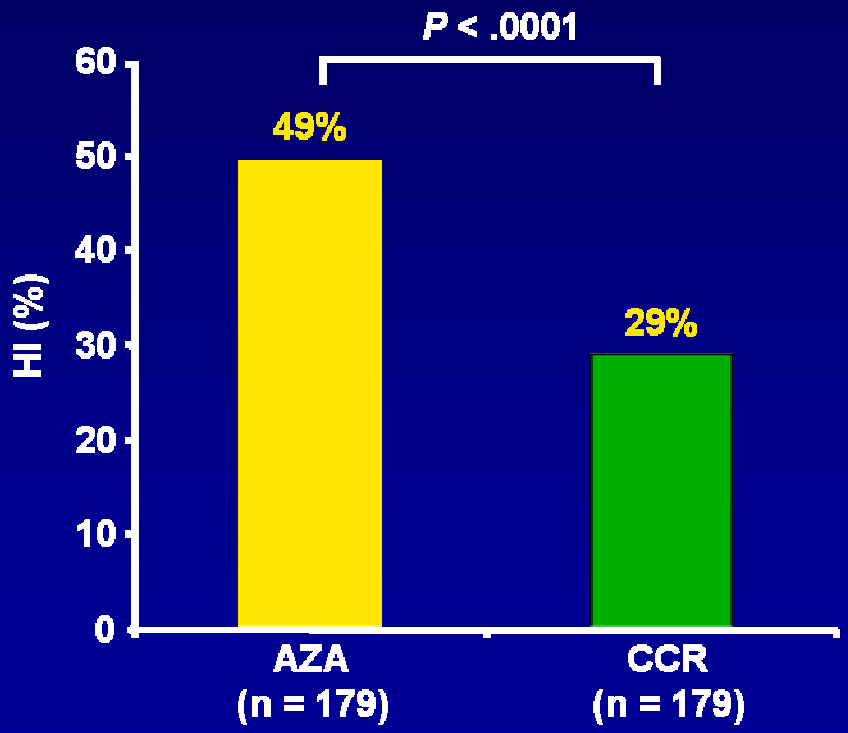
Fenaux P, et al. Lancet Oncol 2009;10:223–32.

Azacitidine provides significant clinical benefits

ORR (CR+PR)*,†



HI (Major + Minor)†

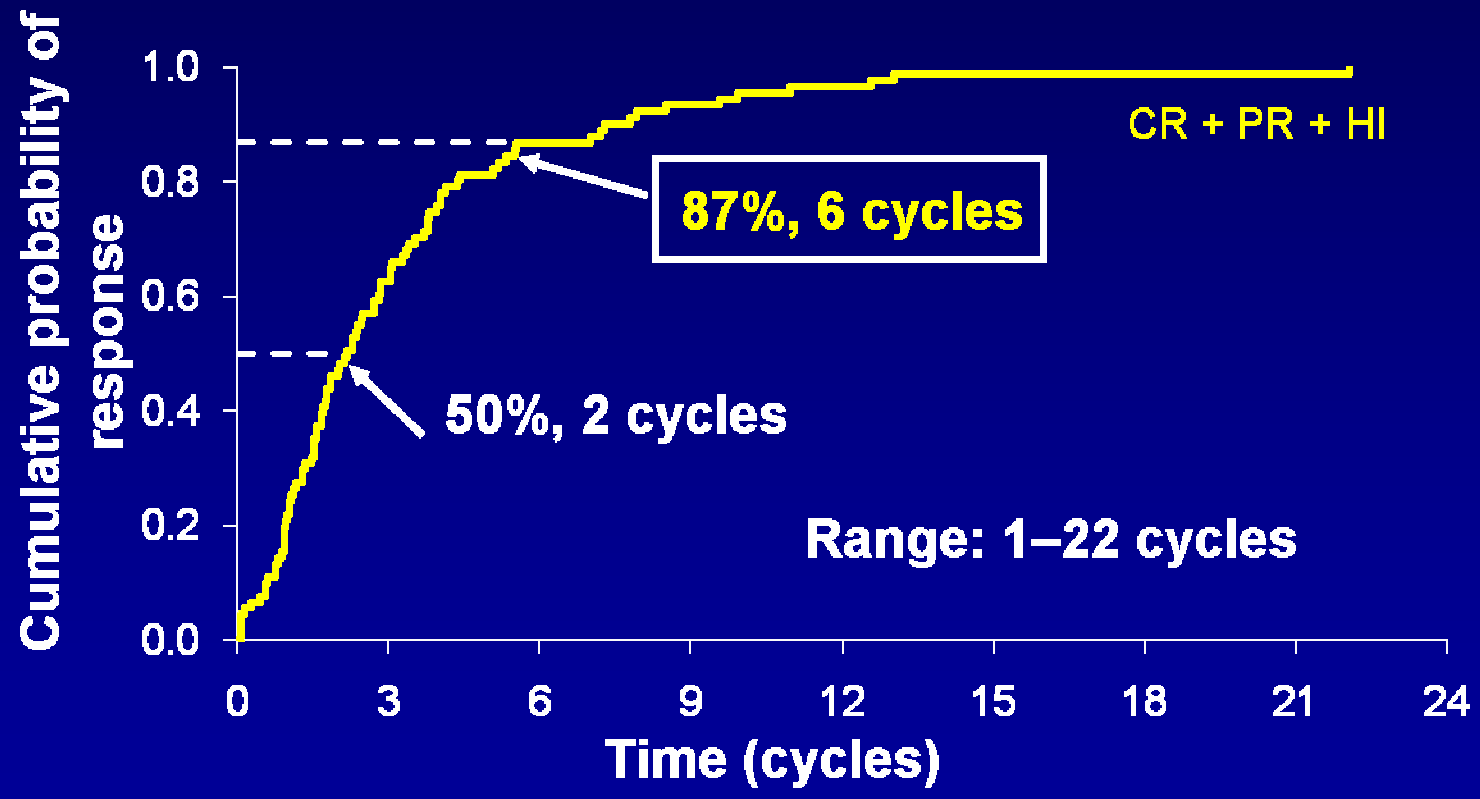


*Evaluated by investigator; †Evaluated according to IWG 2000 criteria.
AZA, azacitidine; CCR, conventional care regimen; CR, complete remission; HI, hematologic improvement; IWG, International Working Group; ORR, overall response rate; PR, partial remission.

Fenaux P, et al. Lancet Oncol 2009;10:223–32.

Continued azacitidine treatment increases probability of response

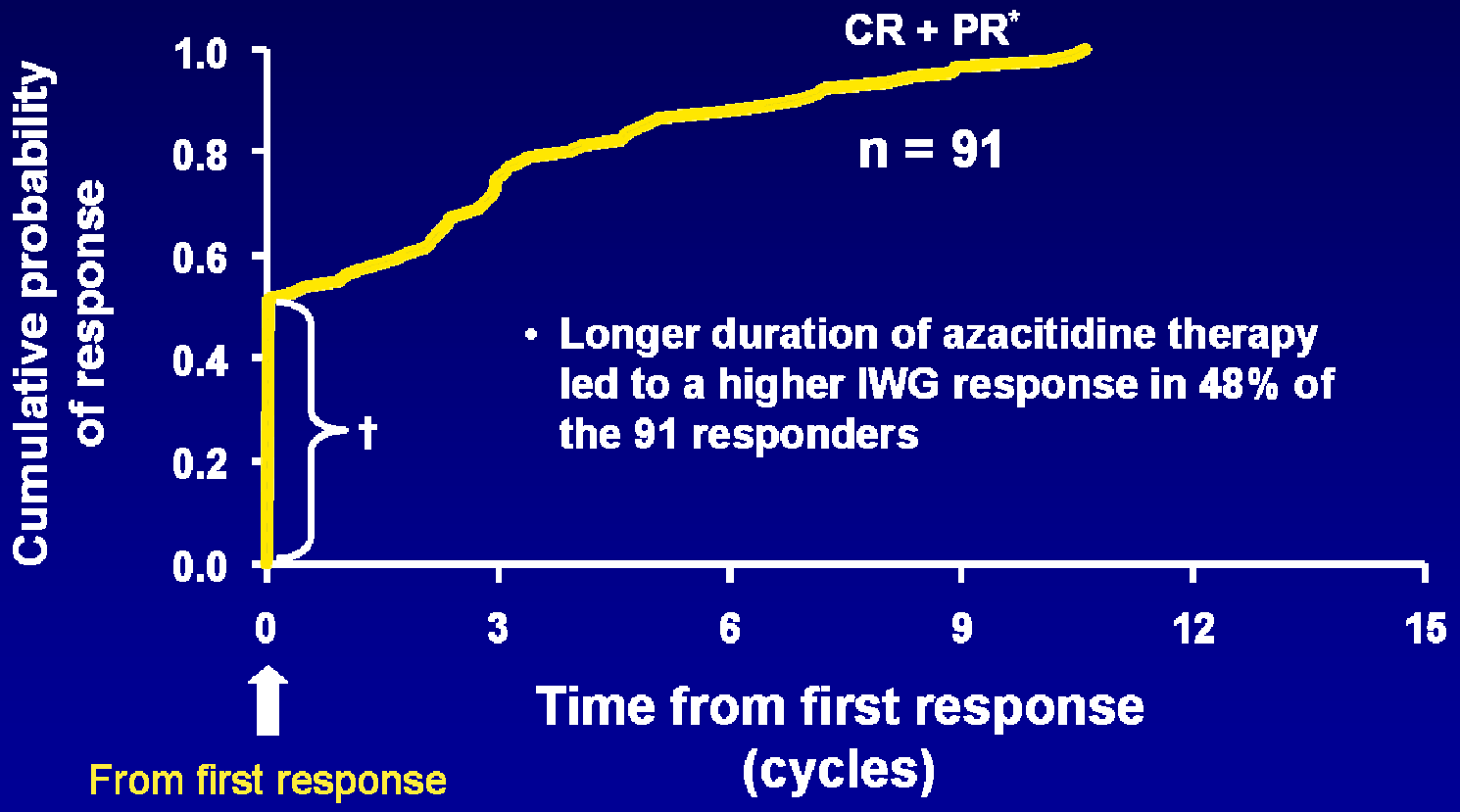
Median time to first response is 2 cycles



CR, complete remission; HI, hematologic improvement; PR, partial remission.

Silverman LR, et al. Blood 2008;112: abstract and presentation:227.

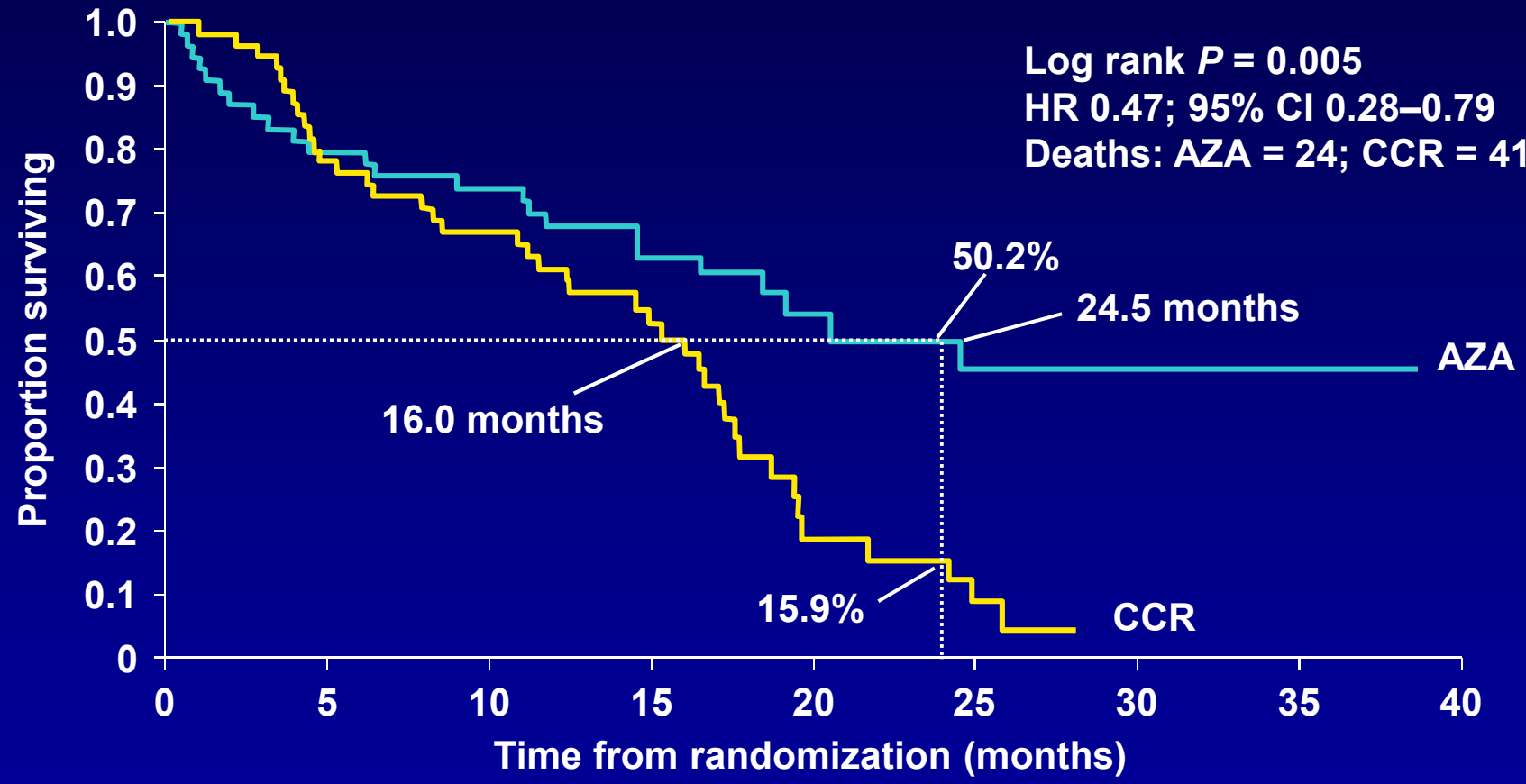
Continued azacitidine therapy improves quality of response



*CR and PR per IWG 2000 response criteria.[2]
†The vertical line on the y-axis represents the 52% of patients whose first response was their best response.
CR, complete response; IWG, International Working Group; PR, partial response.

1. Silverman LR, et al. Blood 2008;112: abstract and presentation:227.
2. Cheson BD, et al. Blood 2000;96:3671–74.

AZA-001: WHO AML (20–30% BM blasts) OS

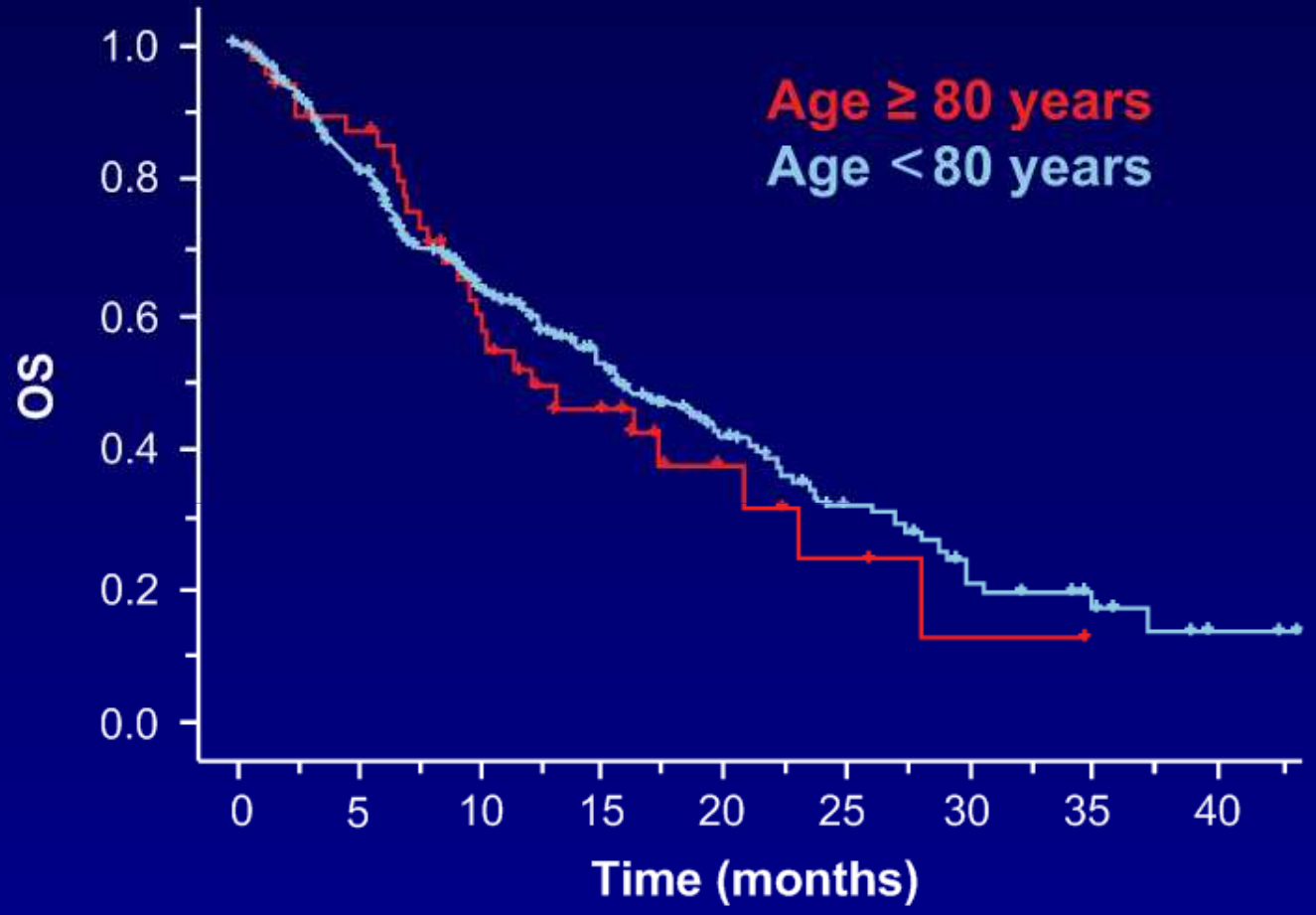


AZA significantly prolonged OS compared with CCR

Fenaux P, et al. J Clin Oncol. 2010;28:562-569.

Main

Results: Overall Survival



- OS similar in patients aged < 80 and ≥ 80 years (*P* = .6)
- Median OS 12.1 months; 1- and 2-year OS: 50% and 23.2%

OS, overall survival.

Itzykson, R., et al. *Blood*. 2009;114(22):705.

Azacitidina i Decitabina en SMD de risc alt

Table 1. Principal clinical studies with hypomethylating agents in IPSS higher-risk MDS patients

Drug	Dose/schedule	N	ORR, %	OS, mo	RD, mo	Reference
Decitabine	15 mg/m^2/TID IV × 3 d	177	49	15	9	2
	15 mg/m^2/TID IV × 3 d	180	36	10	6.6	5
	20 mg/m^2/d IV × 5 d	46	52	13.4	NR	8
	20 mg/m^2/d IV × 5 d					4
	20 mg/m^2/d SC × 5 d	51	43 (CR)	22	NR	
	10 mg/m^2/d IV × 10 d					
	15 mg/m^2/TID IV × 3 d	61	18	14	12	3
Azacitidine	75 mg/m^2/d SC × 7 d	179	51	24.4	26.1	1
	75 mg/m^2/d SC × 7 d	99	47	19.3	21	6
	75 mg/m^2/d SC × 7 d	72	40	NR	NR	7
	75 mg/m^2/d IV × 7 d	48	44	13.3	14.7	7

N indicates number of patients; ORR, overall response rate; OS, overall survival; RD, response duration; TID, 3 times/d; SC, subcutaneous; NR, not reported; and CR, complete response.

Santini V, ASH 2012

Azacitidina i Decitabina en SMD de risc baix

Table 2. Clinical studies with hypomethylating agents in IPSS lower-risk MDS patients

Drug	Dose/schedule	N	ORR	Reference
Decitabine	15 mg/m²/TID IV × 3 d	28	30%	3
	20 mg/m²/d IV × 5 d 20 mg/m²/d SC × 5 d 10 mg/m²/d IV × 10 d	19	47%	4
	20 mg/m²/d IV × 5 d	53	50%	8
Azacitidine	75 mg/m²/d SC × 7 d	23	60%	6
	75 mg/m²/d SC × 5/7 d	74	45.9%	25
	75 mg/m²/d SC/IV 5-2-2 75 mg/m²/d SC/IV × 5 d 75 mg/m²/d SC/IV × 7 d	228	61%	26
	75 mg/m²/d SC 5-2-2 75 mg/m²/d SC × 5 d 50 mg/m²/d SC 5-2-5	95	44%-46%	27

N indicates number of patients; ORR, overall response rate; TID, 3 times/d; and SC, subcutaneous.

Santini V, ASH 2012

Main

AZACITIDINE VS DECITABINE IN MDS

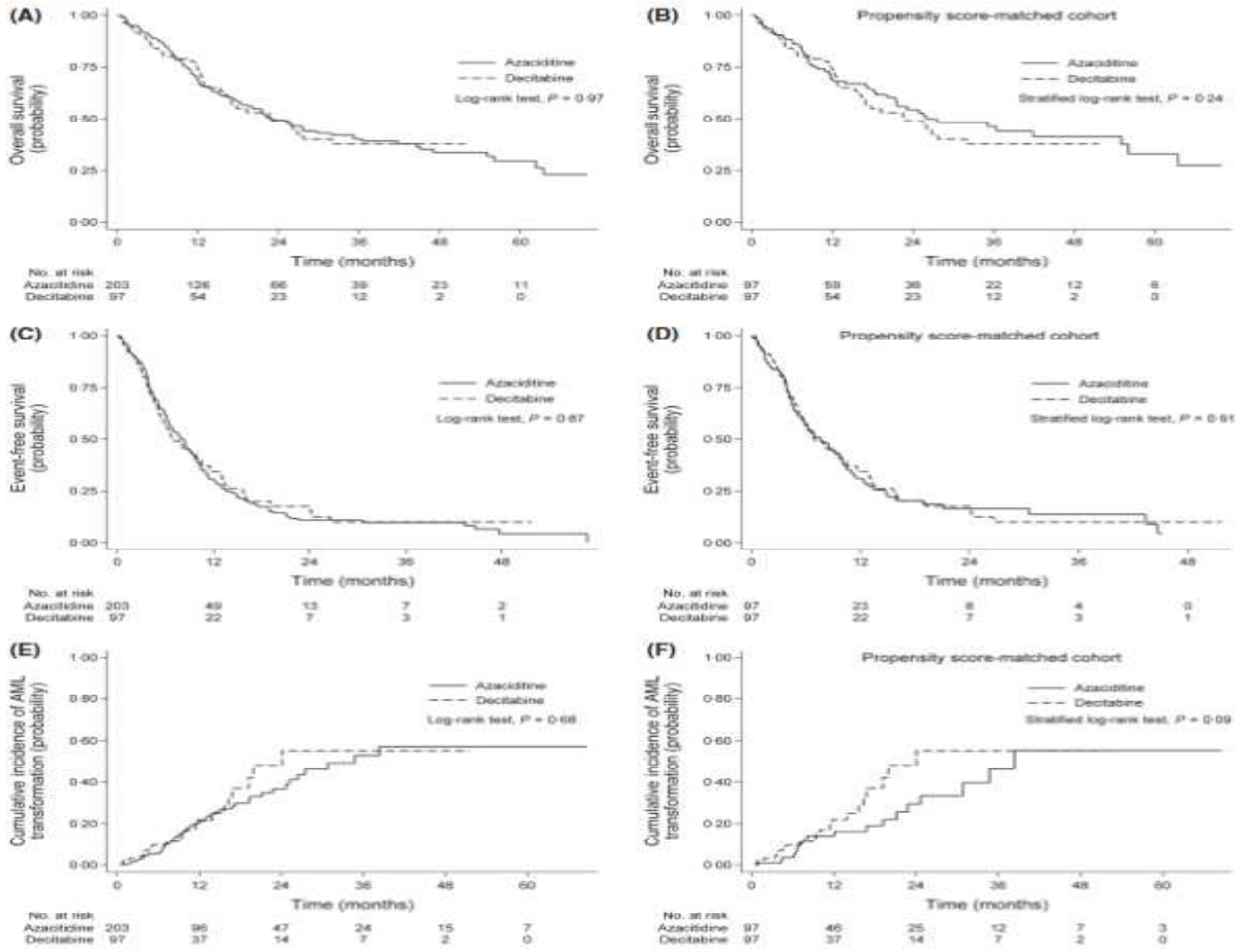


Fig 1. Analyses of the efficacy endpoints (A) Overall survival (OS) by the hypomethylating agents (HMAs) in the overall cohort. (B) OS by HMA in the propensity score-matched cohort. (C) Event-free survival (EFS) by HMA in the overall cohort. (D) EFS by HMA in the propensity score-matched cohort. (E) Cumulative incidence of acute myeloid leukaemia (AML) transformation in the overall cohort. (F) Cumulative incidence of AML transformation in the propensity score-matched cohort.

Lee YG, Kim I, Park S et al. Br. J. Hematol 2013

AZACITIDINE VS DECITABINE IN MDS

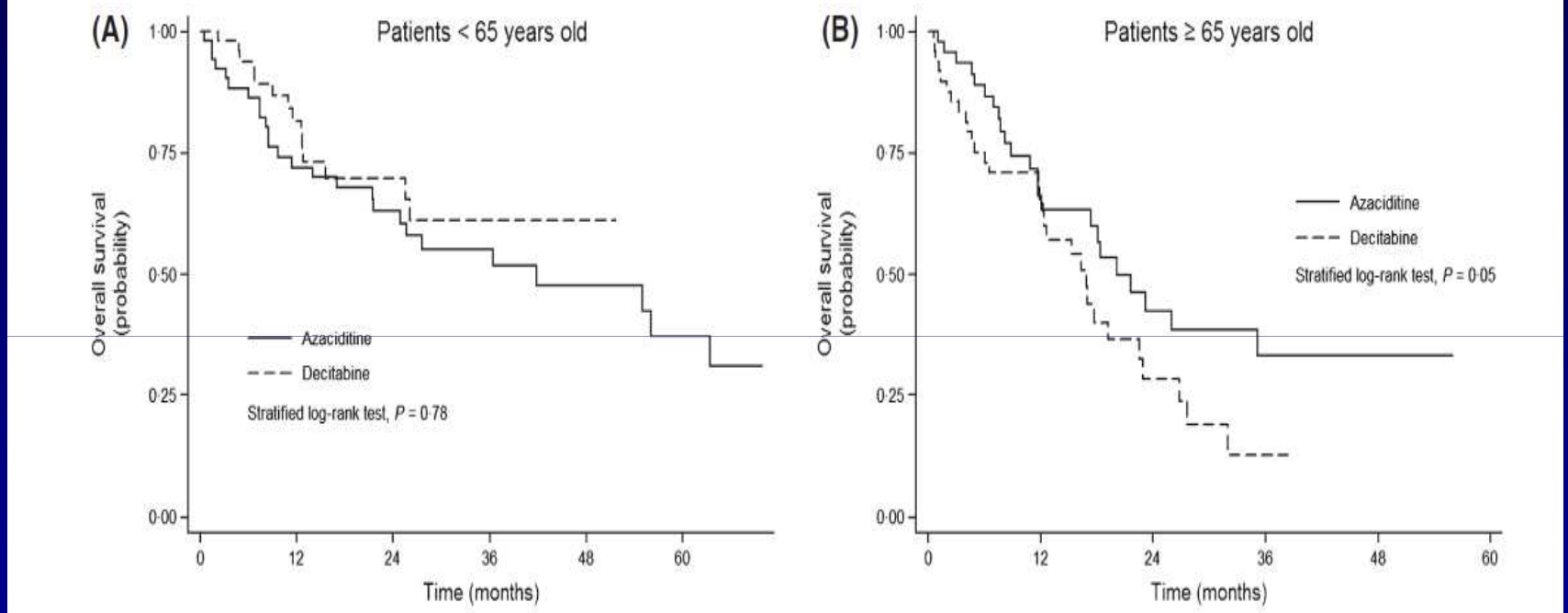


Fig 2. Comparison of overall survival between azacitidine and decitabine in the propensity score-matched cohort among patients <65 years of age (A) and ≥65 years of age (B).

Lee YG, Kim I, Park S et al. Br. J. Hematol 2013

Hypomethylating agents in combination

Table 4. Combination therapies with hypomethylating agents in patients with MDS

Drugs	N	ORR
Azacitidine + phenylbutyrate	32	34%
Azacitidine + valproic acid + all-*trans* retinoic acid	62	46%
Azacitidine + entinostat	136	43%
Azacitidine + lenalidomide (phase 1)	18	67%
Azacitidine + lenalidomide (phase 2)	18	71%
Azacitidine + thalidomide	36	58%
Decitabine + gentuzumab ozogamicin	33	42%
Azacitidine + etanercept	32	72%
Azacitidine + erythropoietin	32	44%
Azacitidine + romiplostim	40	23%*
Decitabine + romiplostim	29	16

Combination studies were reviewed in Ornstein and Sekeres.[54]
N indicates number of patients; and ORR, overall response rate.
*Decrease in hemorrhagic events.

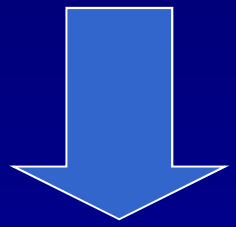
Santini V, ASH 2012

Azacitidine after allo-SCT

*Upregulates expression of tumor Ags on leukemic blasts

Expands the number of immunomodulatory T regulatory cells (Tregs)

Aza migth selectively augment a GVL effect without GVHD



**Aza + donor lymphocyte infusions (DLI) as a salvage therapy for relapse of AML and MDS after allo-SCT

*Goodyear OC, et al. Blood 2012

**Schroeder T, et al. Leukemia 2013

Main

Factores Predictius de la Resposta als Agents Hipometilants

blood

2011 117: 403-411
Prepublished online October 12, 2010;
doi:10.1182/blood-2010-06-289280

Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine

Raphael Itzykson, Sylvain Thépot, Bruno Quesnel, Francois Dreyfus, Odile Beyne-Rauzy, Pascal Turlure, Norbert Vey, Christian Recher, Caroline Dartigeas, Laurence Legros, Jacques Delaunay, Célia Salanoubat, Sorin Visanica, Aspasia Stamatoullas, Francoise Isnard, Anne Marfaing-Koka, Stephane de Botton, Youcef Chelghoum, Anne-Laure Taksin, Isabelle Plantier, Shanti Ame, Simone Boehrer, Claude Gardin, C. L. Beach, Lionel Adès, Pierre Fenaux and on behalf of the Groupe Francophone des Myelodysplasies (GFM)

Itzykson et al. Blood 2011

Table 2. Response to azacitidine according to IWG 2006 criteria in the intent-to-treat cohort (n = 282)

	Response achievement		Duration (mo)	
IWG 2006 response	n	%	Median	Range
Complete response (CR)	38	14	10.4	1-24+
Partial response (PR)	9	3	9.8	1-13
Marrow CR (mCR)	32	11	8.0	2-38+
Stable disease with hematological improvement	43	15	7.9	2-28+
Stable disease without hematological improvement	61	22		
Progressive disease	52	18		
Failure to achieve 4 cycles of AZA	47	17		
Overall response rate (CR + PR + mCR + SD with HI)	122	43	9.5	1-38+

Prognostic Factors of Response High Risk MDS treated with Azacitidine

(multivariate analysis)

Response Achievement (n=282)

Prior LD AraC	P= .009
Abnormal Karyotype	P = .003
Marrow Blast ≥ 15%	P =.004

Response Duration (n= 122)

Complex Karyotype	P= .0003

Itzykson et al. Blood 2011

Itzykson et al. Blood 2011

Prognosis Factors for Overall Survival
(multivariate analysis)

ECOG PS 0-1 vs ≥ 2	P < 0.0001
CYtogenetic Risk (IPSS) (favorable vs intermediate/unfavorable)	P < 0.0001
Transfusion dependence 0-3 units/ 8 weeks vs >	P < 0.0001
PB blasts present vs absent	P < 0.0001

Itzykson et al. Blood 2011

Prognostic Score for Overall Survival

ECOG ≥ 2	1 point
Circulating blasts	1 point
RBCT dependency ≥ 4 units/8 weeks	1 point
Cytogenetic Risk bt IPSS (1997)	
intermediate	1 point
high	2 points

Low: 0 ; Intermediate: 1-3 ; High: 4-5

Itzykson et al. Blood 2011

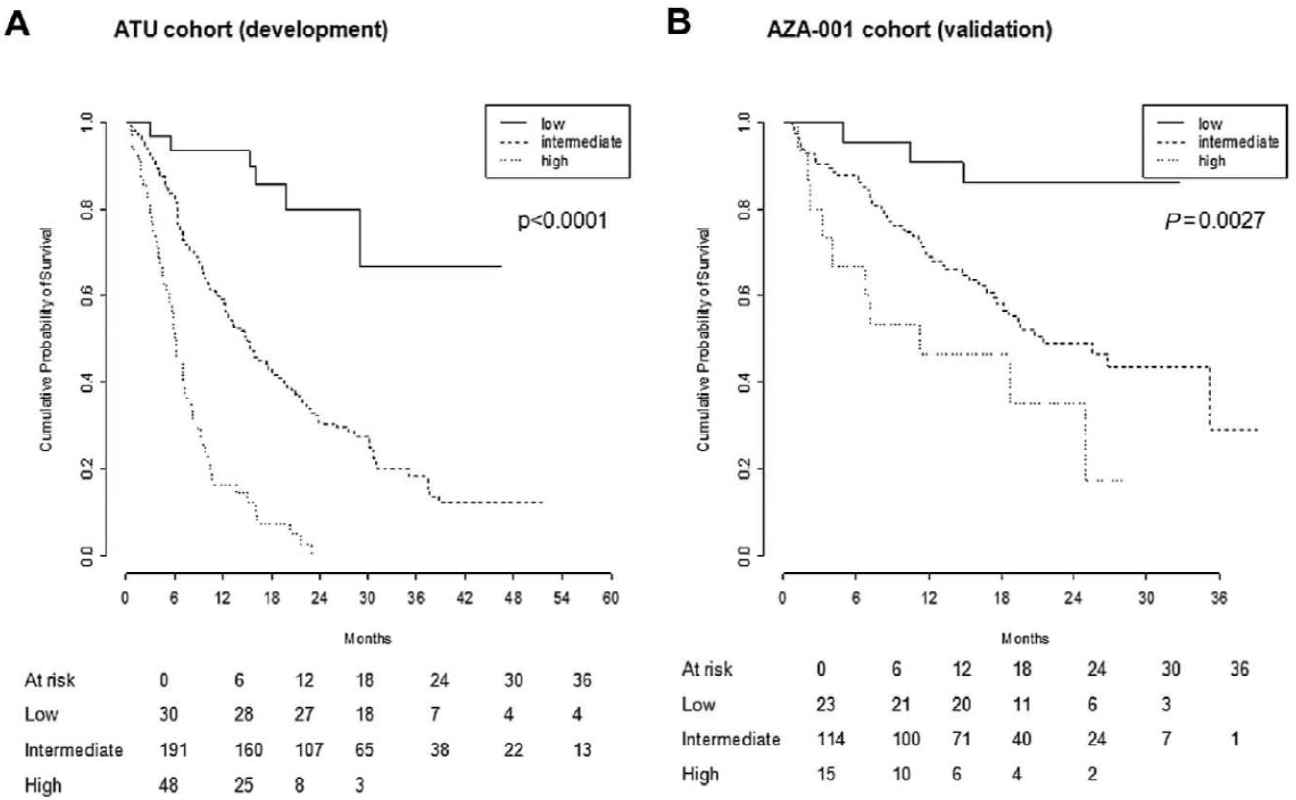


Figure 2. Prognostic score for overall survival. The score was computed (for each patient) based on the presence of PS ≥ 2 (1 point), presence of circulating blasts (1 point), RBC TD ≥ 4 RBC units/8 weeks (1 point), and intermediate- and high-risk cytogenetics (1 and 2 points, respectively). Kaplan-Meier curves of OS for low (score = 0), intermediate (score = 1-3), and high (score = 4-5) risk patients in the development (ATU) and validation (AZA-001) cohorts

Itzykson et al. Blood 2011

Table 5. Time-dependent Cox model of OS in stable disease or marrow CR patients according to the achievement or not of hematological improvement

	Evaluable	n (%)	HR (95% CI)	*P*
Any HI	151	62 (41%)	0.54 [0.34-0.87]	.02
HI-E	131	33 (25%)	0.56 [0.38-0.83]	.004
HI-N	88	31 (27%)	0.65 [0.40-1.00]	.07
HI-P	114	18 (20%)	0.67 [0.45-1.00]	.05

Itzykson et al. Blood 2011

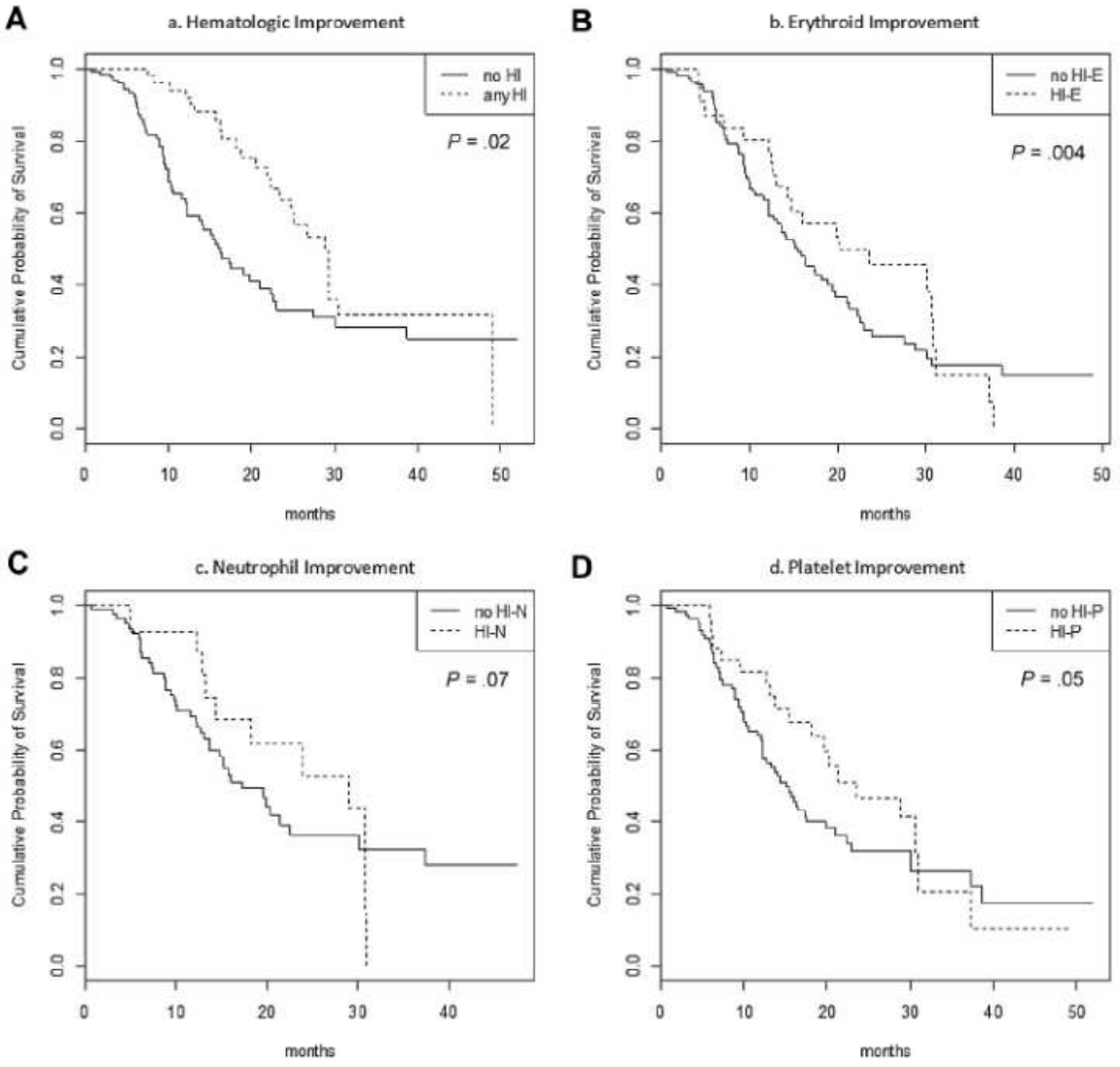


Figure 3. Impact of hematological improvement on OS in a time-dependent model in patients with baseline cytopenia(s) who achieved SD or mCR (n = 151). (A) Achievement of any HI. (B) Achievement of HI-E in patients with baseline Hb < 11 g/dL or RBC transfusion dependency (n = 131). (C) Achievement of HI-P in patients with baseline platelets < 100 G/L (n = 114). (E) Achievement of HI-P in patients with baseline ANC < 1.0 G/L (n = 88).

Mufti GJ, Gore SD, Santini V,et al. Blood (ASH 2009; Abstract 1755)

Table. Overall Survival in Pts with Common Cytogenetic Abnormalities as Part of a Non-complex (<3 Abnormalities) or Complex (≥3 Abnormalities) Karyotype

Cytogenetic Abnormality	AZA		CCR		AZA - CCR	AZA vs CCR
	N	Median OS mos (95% CI)	N	Median OS mos (95% CI)	Difference in Median OS mos	Hazard Ratio (95% CI)
Del 5/5q-						
Non-complex	5	25.1 (2.7 – 25.1)	10	17.3 (13.2 - 21.5)	**7.9**	**0.43** (0.05 – 3.80)
Complex	29	9.9 (3.9 – 19.2)	30	4.9 (3.5 - 7.3)	**5.1**	0.55 (0.29 - 1.05)
Del 7/7q-						
Non-complex	16	24.5 (13.0 – NR)	11	8.1 (2.9 - 19.3)	**16.3**	**0.33** (0.10 – 1.13)
Complex	14	5.3 (2.1 - 12.7)	16	3.9 (3.3 - 4.7)	**1.4**	0.45 (0.17 – 1.22)
Del 5/5q- WITHOUT Del 7/7q-						
Non-complex	5	25.1 (2.7 – 25.1)	9	17.6 (15.3 – 21.5)	**7.5**	**0.51** (0.05 - 4.74)
Complex	16	15.3 (6.2 – 34.7)	17	7.3 (2.9 – 8.8)	**8.0**	0.53 (0.20 – 1.39)
Del 7/7q- WITHOUT Del 5/5q-						
Non-complex	16	24.5 (13.0 – NR)	10	10.3 (2.9 – 19.3)	**14.2**	**0.38** (0.11 – 1.32)
Complex	1	--	3	2.1 (0.5 – 3.6)	--	--
Del 5/5q- AND Del 7/7q-						
Non-complex	0	--	1	--	--	--
Complex	13	6.7 (2.3 – 12.7)	13	4.5 (3.3 – 4.9)	**2.2**	**0.44** (0.15 – 1.29)
Trisomy 8						
Non-complex	16	26.3 (16.2 – NR)	12	8.7 (4.3 - 16.6)	**17.6**	**0.20** (0.06 – 0.65)
Complex	9	17.3 (7.1 – NR)	9	4.9 (3.6 – 7.6)	**12.4**	**0.42** (0.10 – 1.69)

Mos = months; NR = Not reached; Non-complex: <3 cytogenetic abnormalities; Complex: ≥3 cytogenetic abnormalities

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.

Della Porta hematologica 2011

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]

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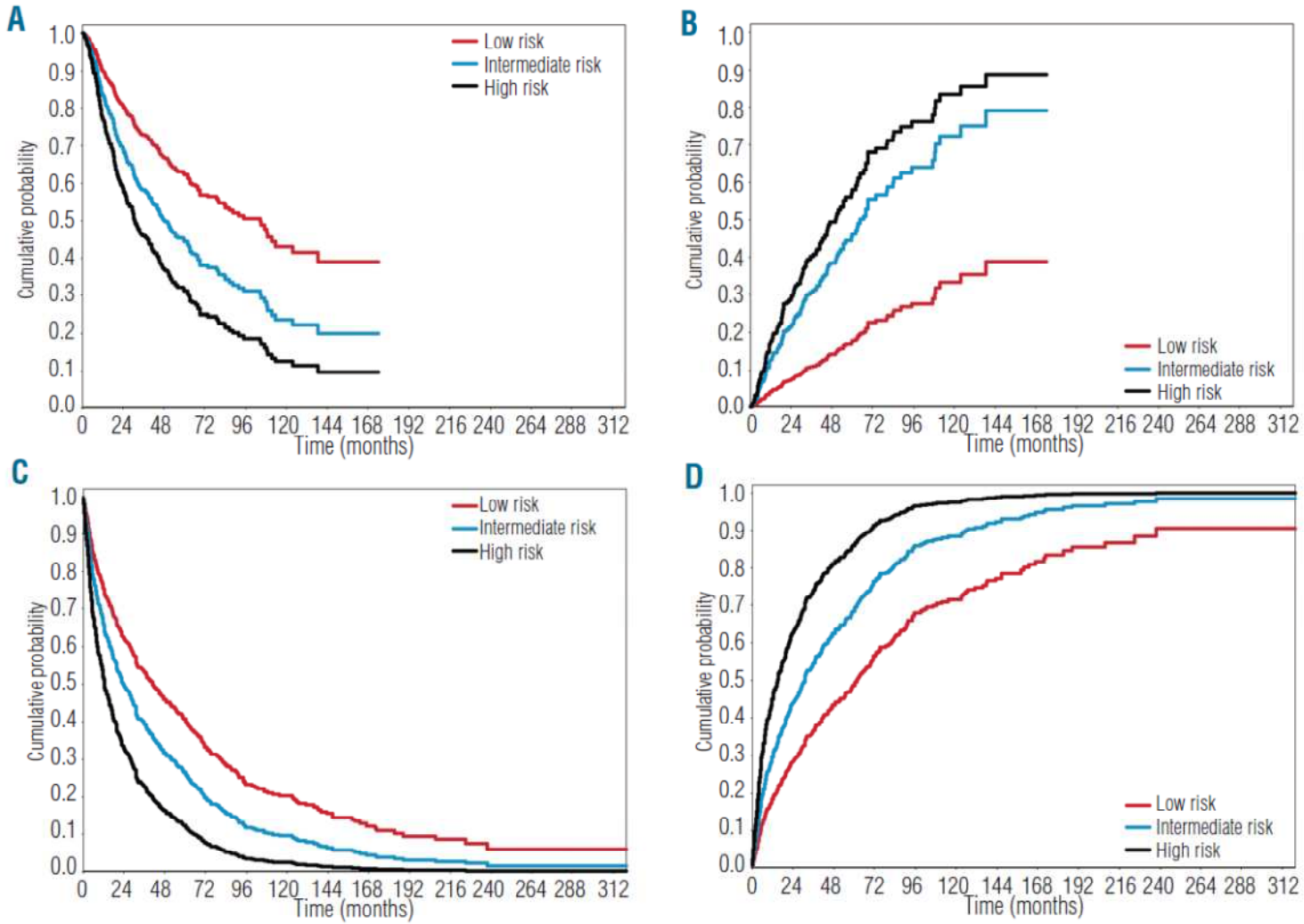


Breccia M et al

Haematologica 2012

Application of MDS –CI (Della Porta)

Pts Treated with azacitidine (n=60)

Low Risk	32	21 m.
Intermediate R.	14	11.9 m.
High Risk	13	8 m.

P= 0.01

Patients still alive at 1 year (n=44)

Low Risk	23 m.
Intermediate R	9.5 m.
High Risk	6 m.

P=0.01

MDS-CI in patients treated with hypomethylating agents could be useful to identify at baseline subjects with greater chance of benefit from this type of treatment

bjh research paper

Platelet doubling after the first azacitidine cycle is a promising predictor for response in myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML) patients in the Dutch azacitidine compassionate named patient programme

Lieke H. van der Helm,[1] Canan Alhan,[2] Pierre W. Wijermans,[3] Marinus van Marwijk Kooy,[4] Ron Schaafsma,[5] Bart J. Biemond,[6] Aart Beeker,[7] Mels Hoogendoorn,[8] Bastiaan P. van Rees,[9] Okke de Weerdt,[10] Jurgen Wegman,[11] Ward J. Libourel,[12] Sylvia A. Luykx-de Bakker,[13] Monique C. Minnema,[14] Rolf E. Brouwer,[15] Fransien Croon-de Boer,[16] Matthijs Eefting,[17] Kon-Siong G. Jie,[18] Arjan A. van de Loosdrecht,[2] Jan Koedam,[19] Nic J. G. M Veeger,[1] Edo Vellenga[1] and Gerwin Huls[1]

Summary

The efficacy of azacitidine in the treatment of high-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML) (20–30% blasts) has been demonstrated. To investigate the efficacy of azacitidine in daily clinical practice and to identify predictors for response, we analysed a cohort of 90 MDS, CMML and AML patients who have been treated in a Dutch compassionate named patient programme. Patients received azacitidine for a median of five cycles (range 1–19). The overall response rate (complete/partial/haematological improvement) was 57% in low risk MDS, 53% in high risk MDS, 50% in CMML, and 39% in AML patients. Median overall survival (OS) was 13·0

Van der Helm et al.
B J Haematol 2011

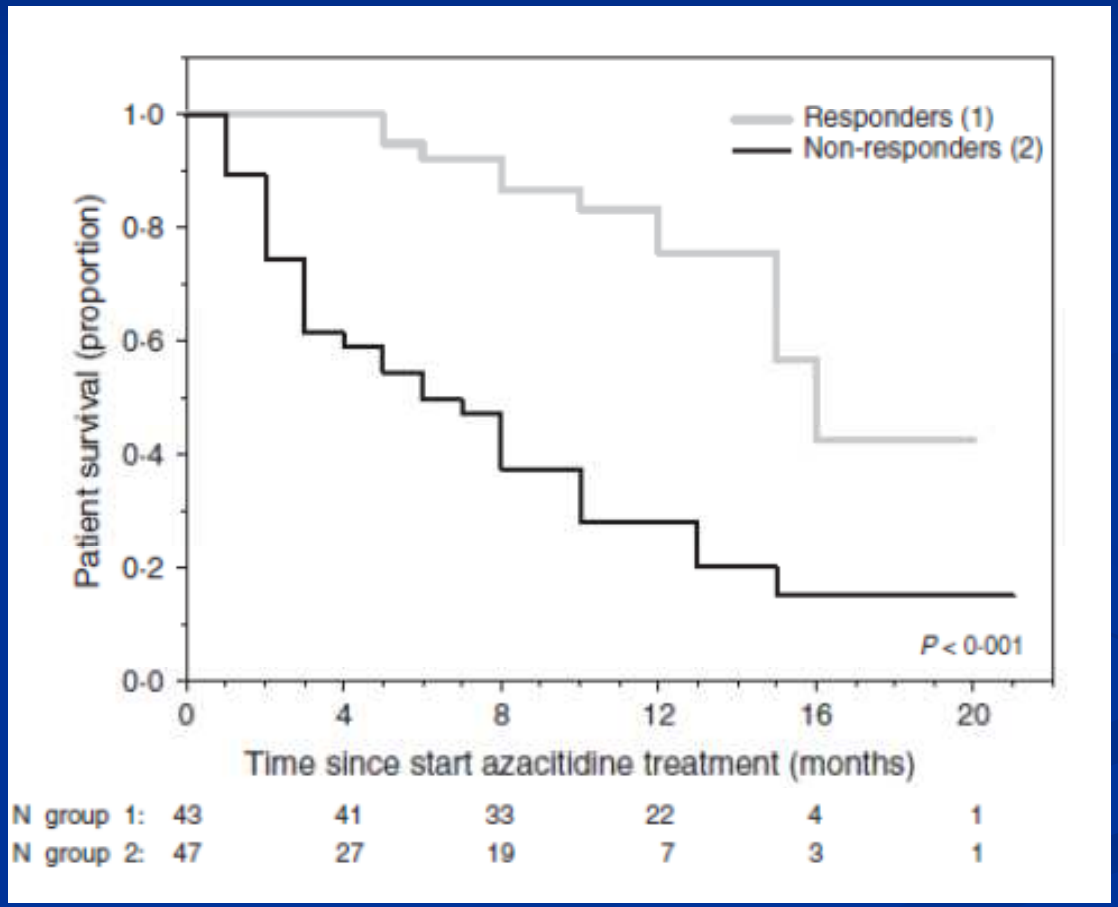
Van der Helm et al. BJH 2011

Pts n= 90

RARS or RCMD 10 (11%); AREB-1 9 (10%); AREB-2 20 (31%); CMML 12 (13%); AML 31 (34%)

IPSS Intermediate-1	**9 (14%)**	**57% Response**
IPSS-Intermediate-2	**31 (46%)**	
IPSS High Risk	**27 (40%)**	**50% Response**
CMML		**50% Response**
AML		**39% Response**
Median Overall Survival (OS)		**13.0 (9.8-16.2) m.**

Van der Helm et al. BJH 2011



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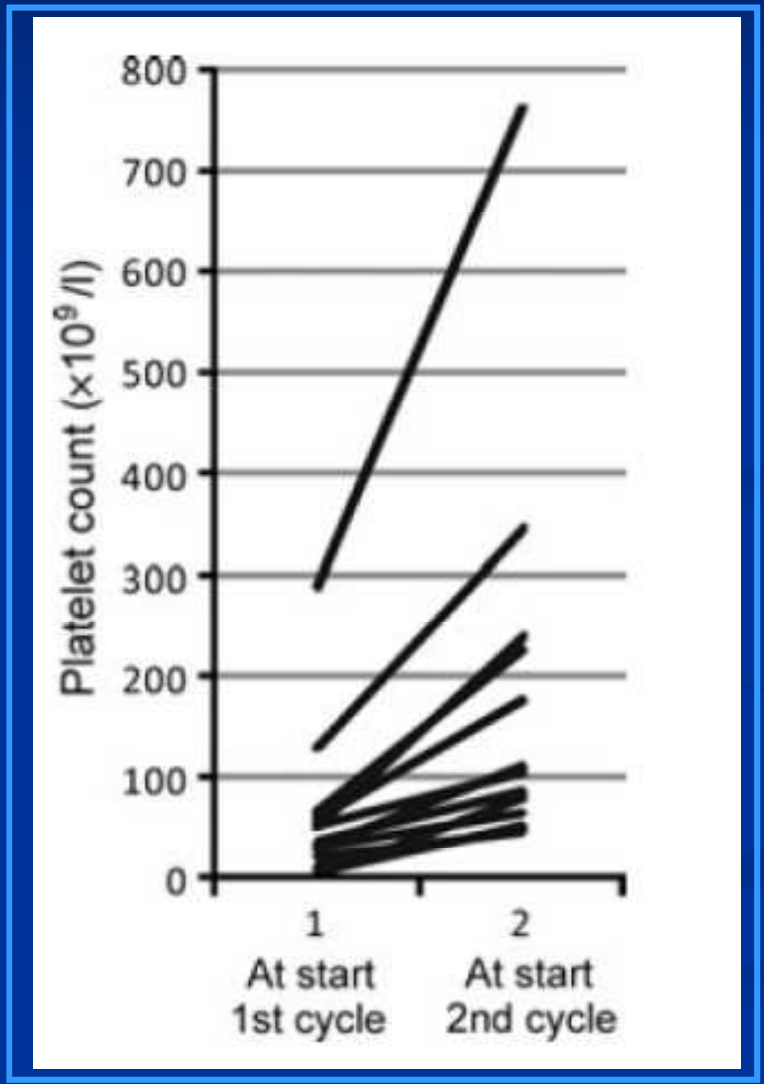
Factors Predicting	median OS (months)	HR (95% CI)	P value
(b) Multivariate analysis			
Cirulating blasts		0·48 (0·24–0·99)	0·05
Present	8·0 (4·3–11·6)		
Absent	15·0 (11·3–18·7)		
Cytogenetic risk		0·45 (0·22–0·91)	0·03
Good/intermediate	15·0 (9·1–20·9)		
Poor	8·0 (5·0–11·0)		
Platelet ratio second and first cycle*		5·4 (0·73–39·9)	0·10
≥2-fold increase	Not reached		
<2-fold increase or decrease	13·0 (10·0–16·0)		

Van der Helm et al. BJH 2011



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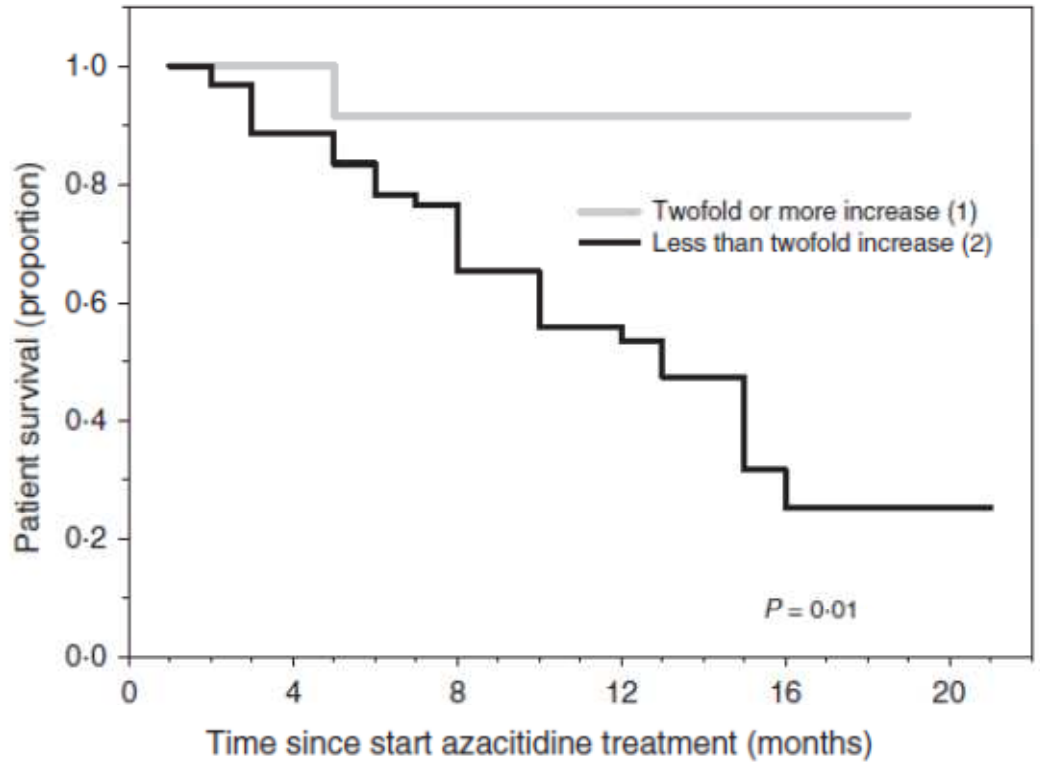
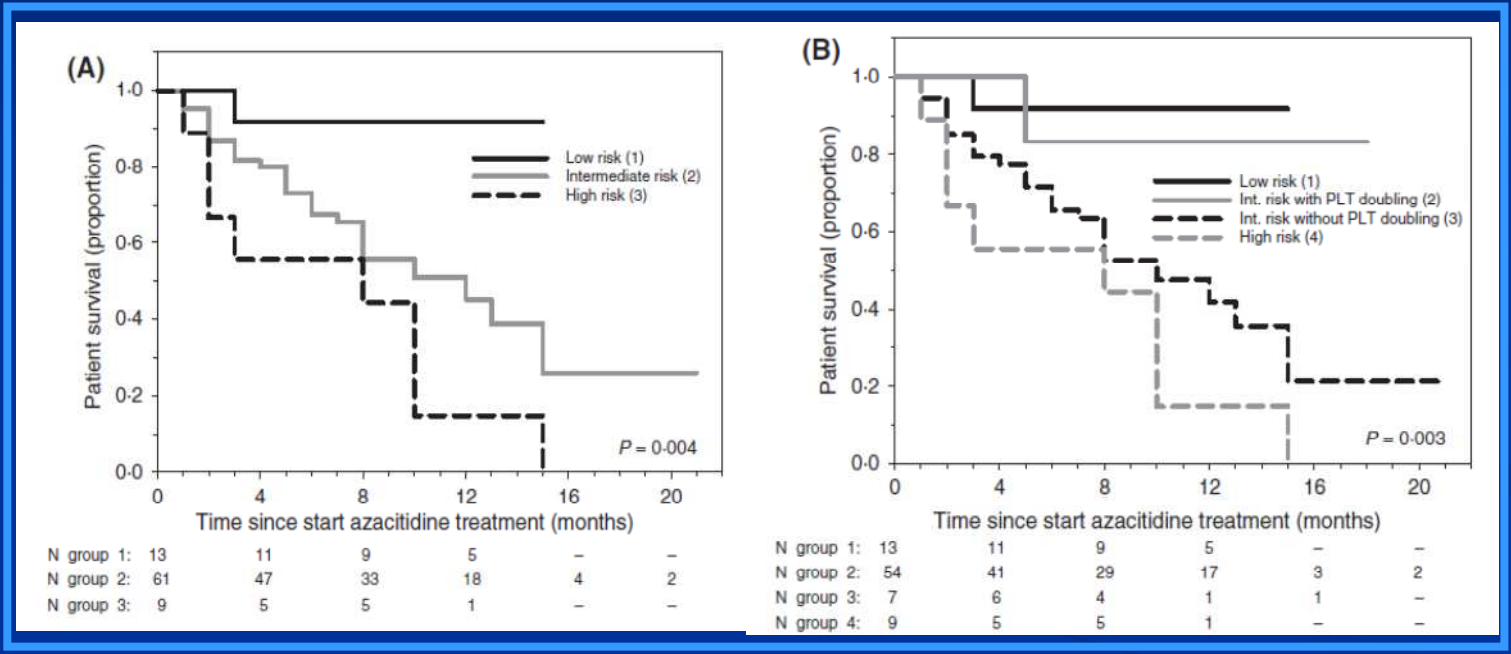


Fig 3. Overall Survival in patients with and without a two-fold platelet increase. An at least two-fold increase in platelet count at the start of

Van der Helm et al. BJH 2011



Validation for Itzykson's Prognostic Score

A: All three groups using Itzykson criteria

B: Intermediate Risk divided into patients with or without at least two-fold increase in platelet count after 1st cycle of Azacitidine

VOLUME 28 · NUMBER 4 · FEBRUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

DNA Methylation Predicts Survival and Response to Therapy in Patients With Myelodysplastic Syndromes

Lanlan Shen, Hagop Kantarjian, Yi Guo, E Lin, Jianqin Shan, Xuelin Huang, Donald Berry, Saira Ahmed, Wei Zhu, Sherry Pierce, Yutaka Kondo, Yasuhiro Oki, Jaroslav Jelinek, Hussain Saba, Eli Estey, and Jean-Pierre J. Issa

From the Departments of Leukemia and Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX; and H. Lee Moffitt Cancer Center, Tampa, FL.

ABSTRACT

Purpose

The current classification systems of myelodysplastic syndromes (MDS), including the Interna-

Shen L. et al.

JCO 2010

E-Cadherin (CDH-1)
N-Cadherin (CDH 13)
Estrogen Receptor α (ERα)
NOR1
NPM2
OLIG2
$P15^{INK4\beta}$
PGRA
PGRB
RIL

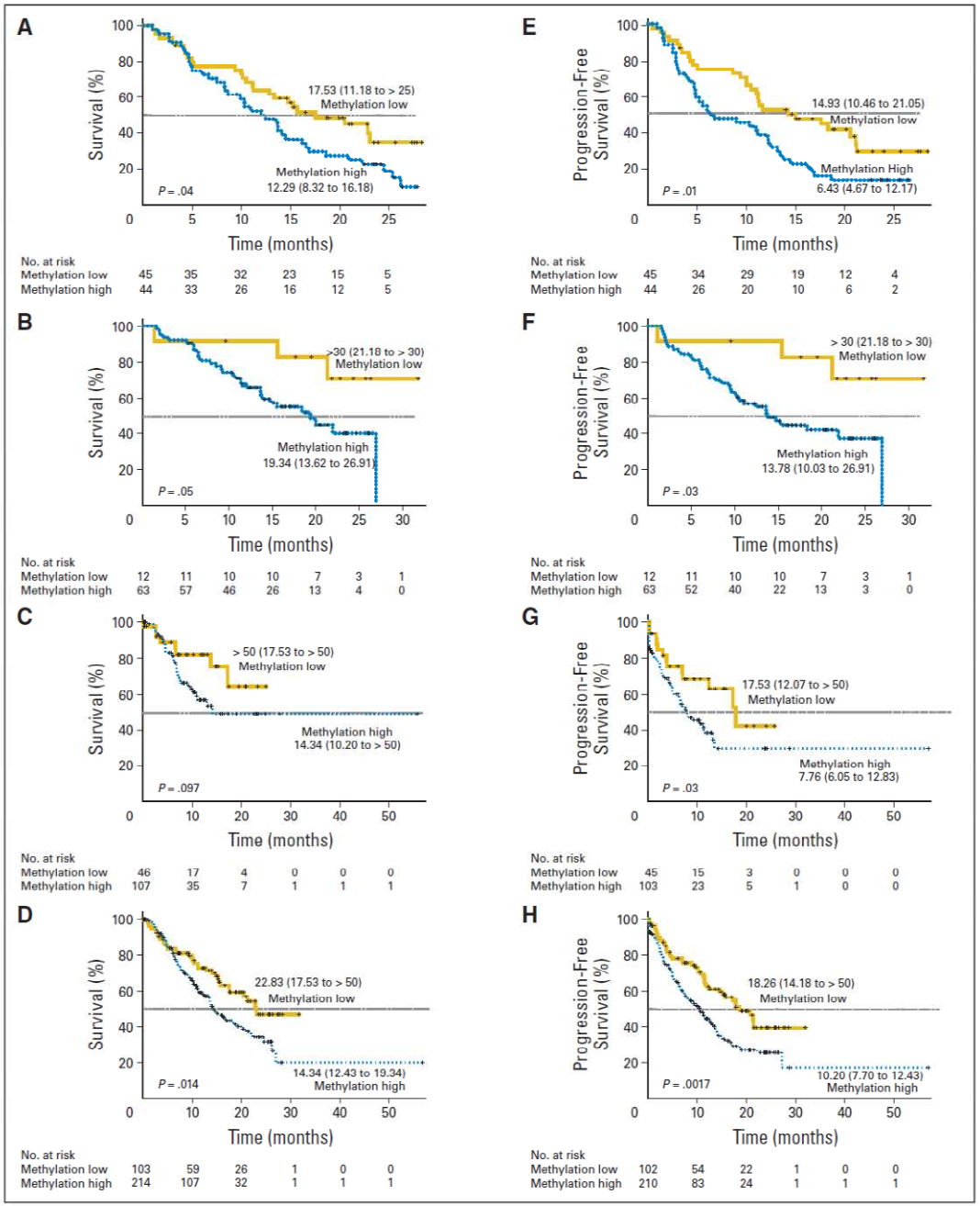


Fig 1. Kaplan-Meier survival estimates of overall and progression-free survival in patients with myelodysplastic syndromes. Overall survival in (A) training cohort, (B) first validation cohort, (C) second validation cohort, and (D) all patients. Progression-free survival in (E) training cohort, (F) first validation cohort, (G) second validation cohort, and (H) all patients. In each panel, patients are grouped into methylation low (gold) or methylation high (blue) groups according to their combined methylation *z* scores. Median survival (95% CI) of each group in each panel is shown. *P* values are based on the log-rank test.

Shen L, et al. JCO 2010

OS (left) and Progression-free Survival (right)in MDS patients
A and E: training cohort
B and F: first validation cohort
C and G: second validation cohort
D and H: all patients

Orange: methylation Low
Blue: methylation High

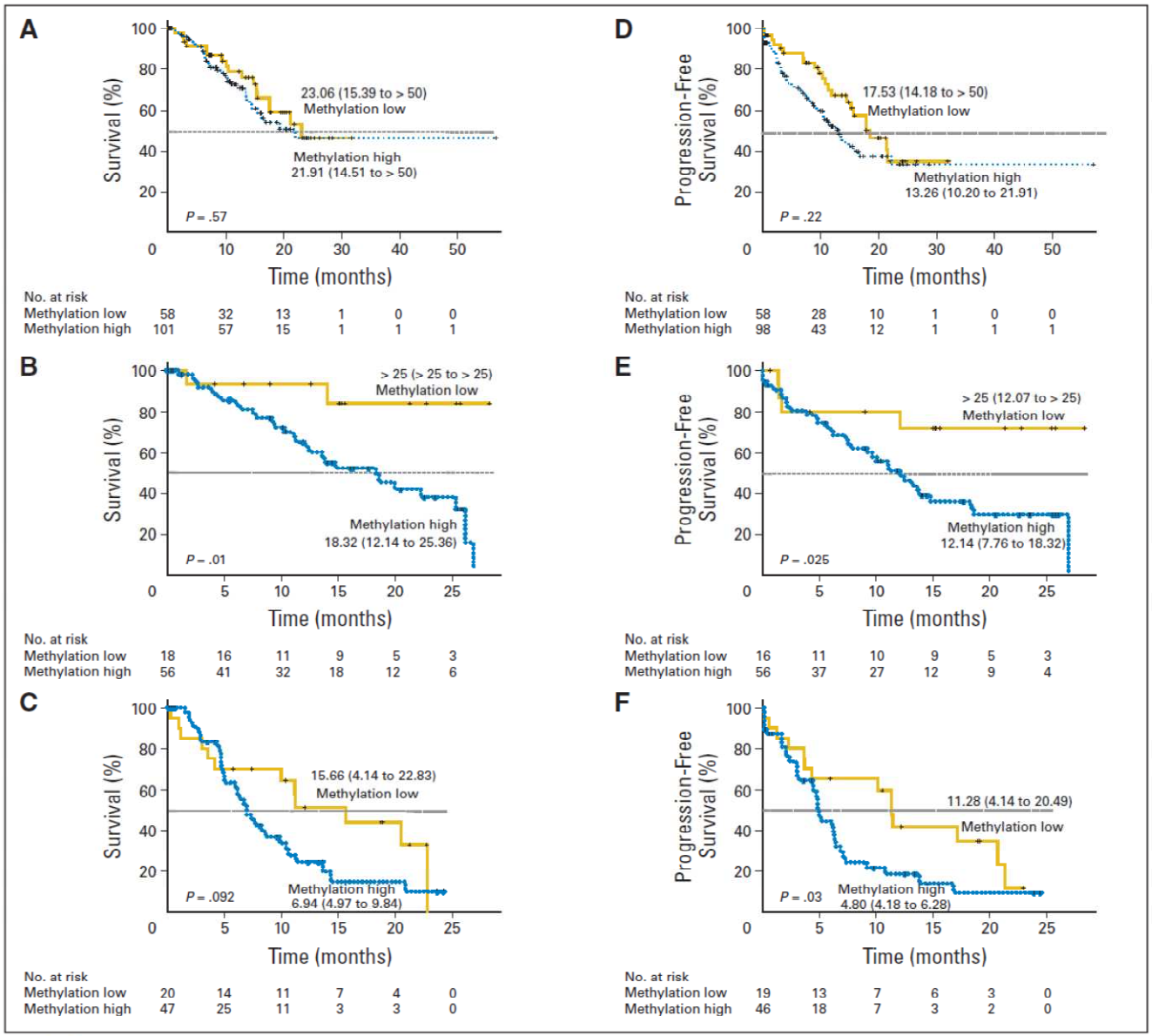


Fig 2. The DNA methylation prognostic model and cytogenetic risk groups. The Kaplan-Meier estimates show survivals for groups of patients with cytogenetic good risk (A: overall survival; D: progression-free survivals), intermediate risk (B: overall survival; E: progression-free survival), and high risk (C: overall survival; F: progression-free survival).

Shen L. et al. JCO 2010

Cytogenetics Groups for IPSS

left: Overall Survival (OS)
Right: progression-free S (PFS)

Good Risk : A and D
Intermediate Risk: B and E
High Risk: C and F

Orange: methylation Low
Blue: methylation High

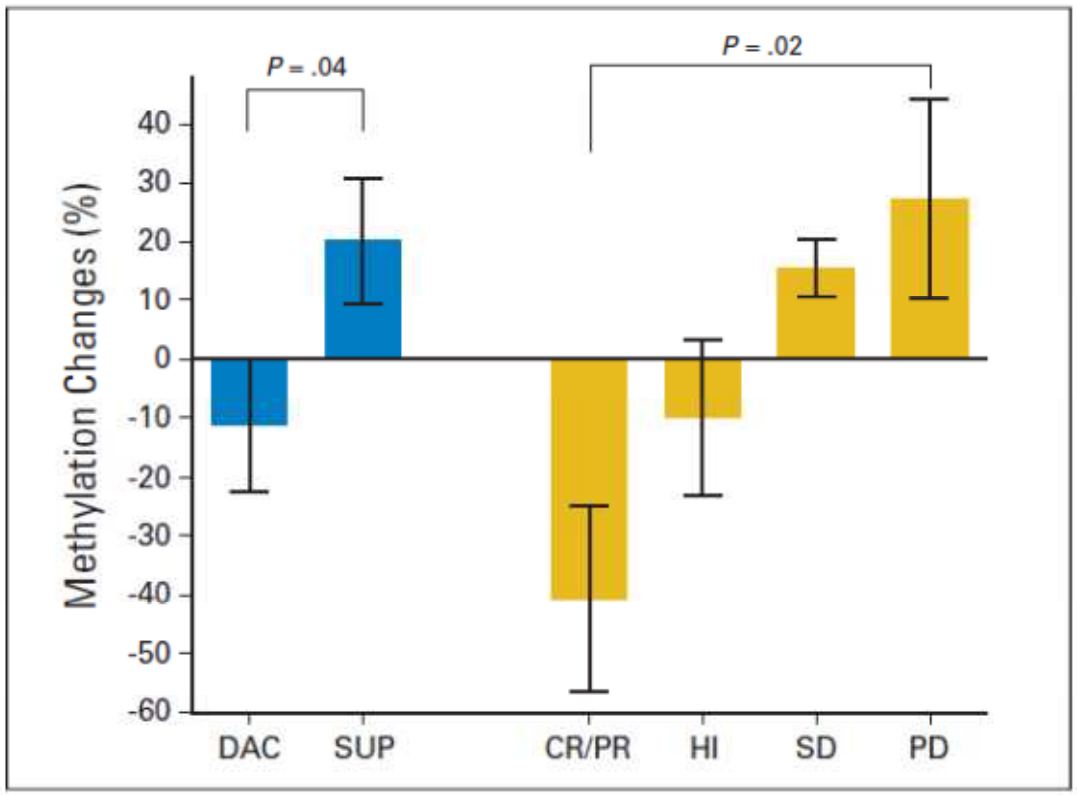


Fig 3. Methylation changes at multiple time points after treatment. Average methylation changes (before and after 4 months on therapy) were compared between patients treated with decitabine (DAC) and supportive care (SUP). Methylation decreased by 11.2% in patients on DAC but increased by 20.1% in patients on SUP ($P = .04$ by Mann-Whitney U test). These methylation changes were then analyzed for correlation with response in 34 patients (DAC arm: two patients with complete remission [CR], three patients with partial remission [PR], four patients with hematologic improvement [HI], four patients with stable disease [SD], and one patient with progressive disease [PD]; supportive care arm: two patients with HI, six patients with SD, and 12 patients with PD). A greater decrease was observed in patients with CR or PR (40.6% ± 15.7%) compared with HI (9.8% ± 13.2%). Methylation increased by 15.4% in patients with SD and by 27.2% in patients with PD ($P = .02$ by Kruskal-Wallis test).

Shen L. et al. JCO 2010

Metilation and Response to Treatment

DAC: Decitabine
SUP: Suportive Care

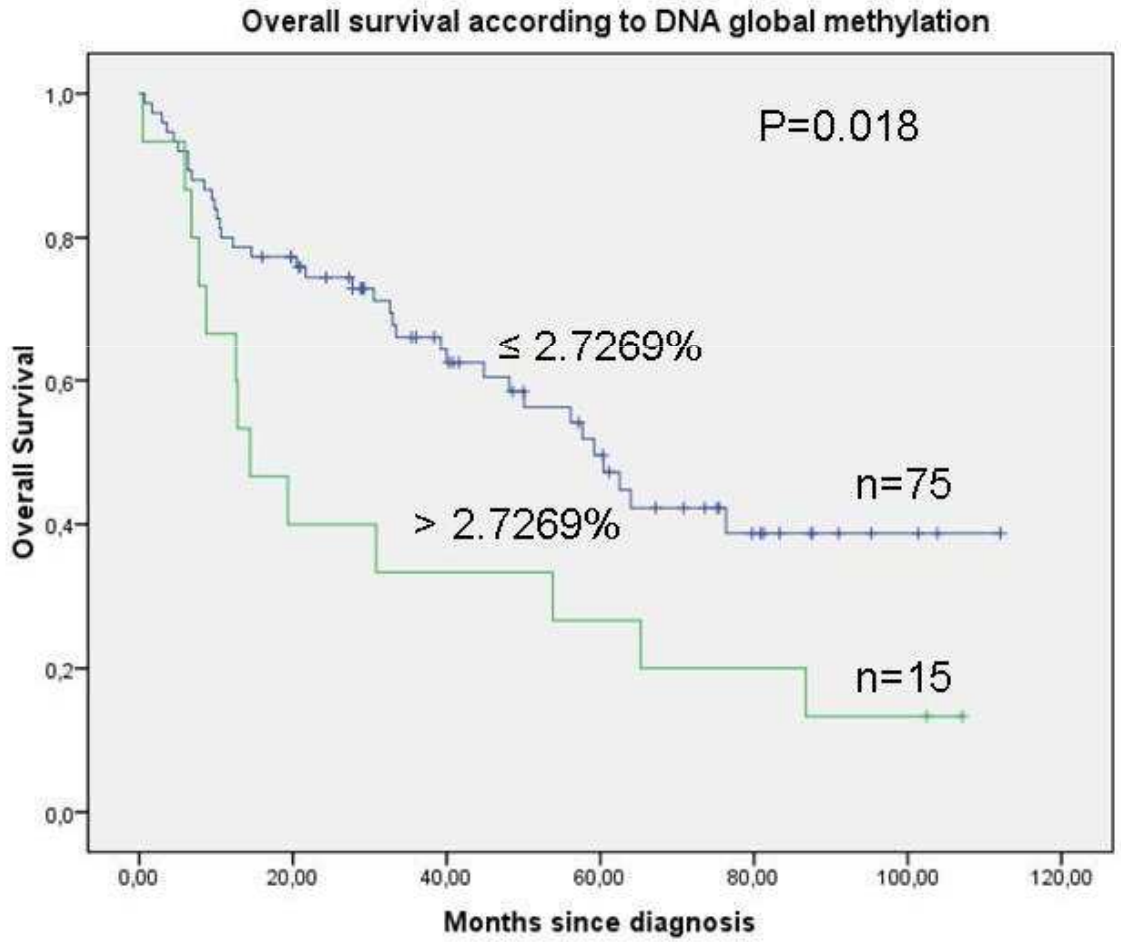
CR/PR, HI, SD, PD: response items for IWG

HIGH LEVELS OF GLOBAL DNA METHYLATION ARE AN INDEPENDENT ADVERSE PROGNOSTIC FACTOR IN A SERIES OF 90 PATIENTS WITH DE NOVO MYELODYSPLASTIC SYNDROME (MDS)

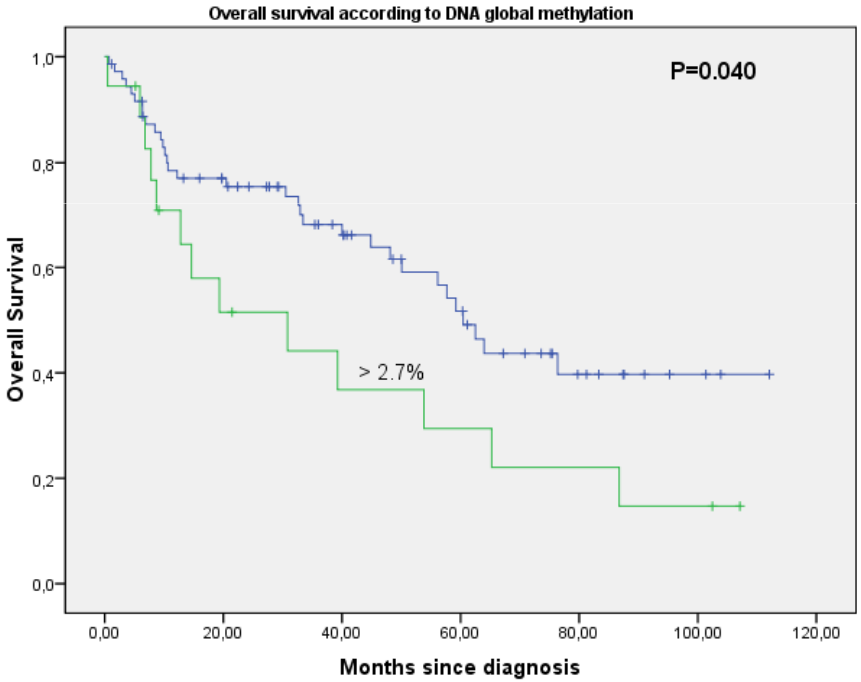
Calvo X[1], Nomdedeu M[1], Costa D[3], Navarro A[2], Pereira A[5], Tejero R[2], Muñoz C[3], Cobo F[4], Rovira J[1], Díaz-Beyá M[1], Monzó M[2], Esteve J[1], Nomdedeu B[1]

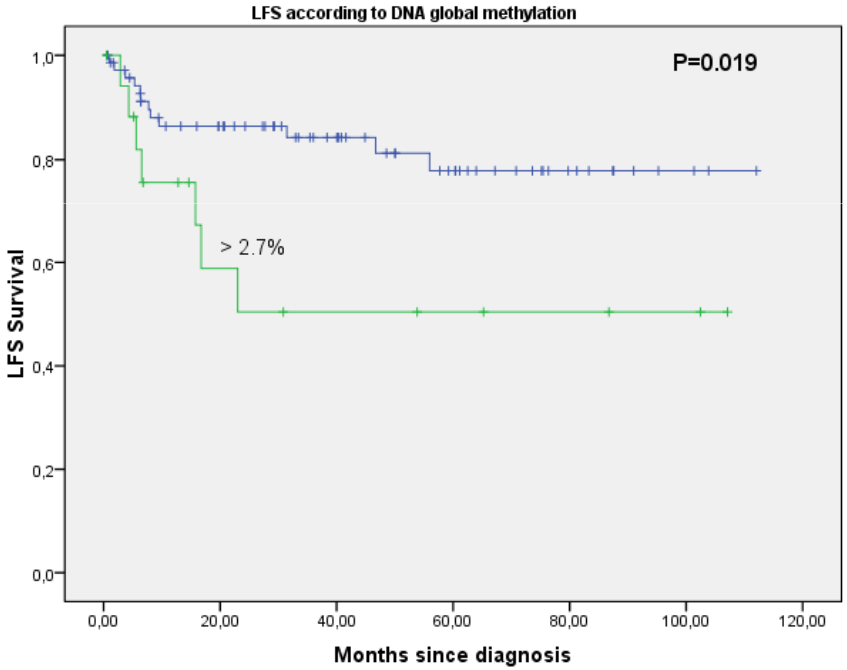
[1]Department of Hematology. Hospital Clínic de Barcelona; [2]Molecular Oncology and Embryology Laboratory, Human Anatomy Unit. School of Medicine. University of Barcelona. IDIBAPS; [3]Department of Pathology. Cytogenetics. Hospital Clínic de Barcelona; [4]Department of Hematology. Clínica Teknon Barcelona; [5]Department of Hemotherapy and Hemostasis. Hospital Clínic de Barcelona.

OS of de novo MDS according to DNA Global Methylation



OS and LFS after censoring patients at time of allo-SCT and at time of receiving azacitidine or intensive chemotherapy (9 patients)





Multivariate Analysis

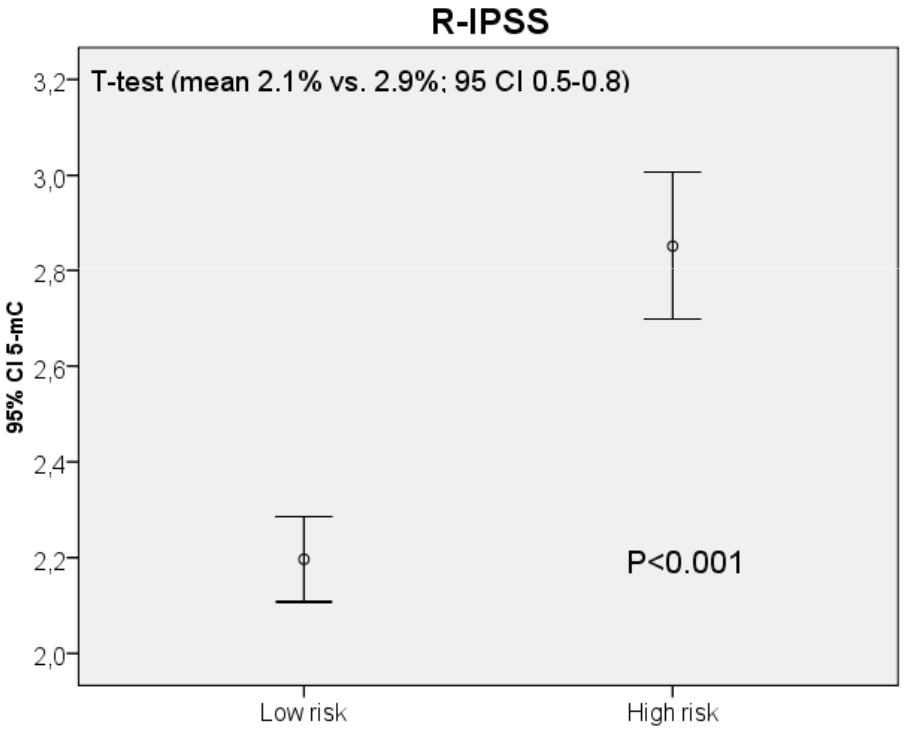
Cox Regression analysis for OS

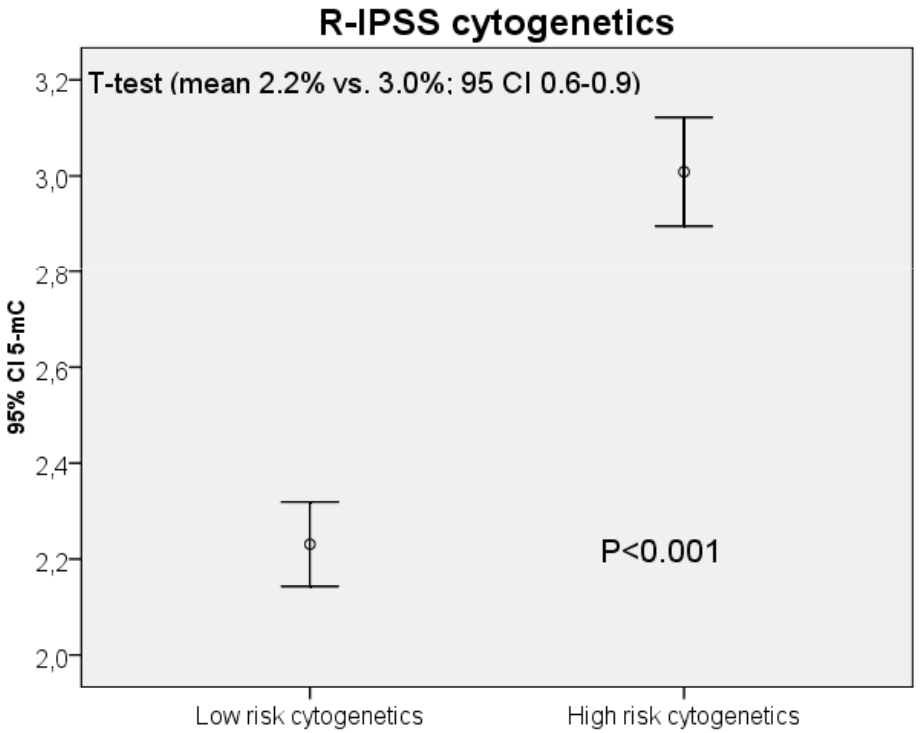
	P	ORR	95,0% CI for ORR	
			Lower	Upper
Age	,002	1,063	1,023	1,105
Sex	,344	-	,724	2,523
5-mC%>2.7	,042	2,042	1,025	4,070
Transfusional requirement	,098	-	,905	3,267
IPSS (INT-2/high)	,001	4,439	1,916	10,287

Cox Regression analysis for LFS

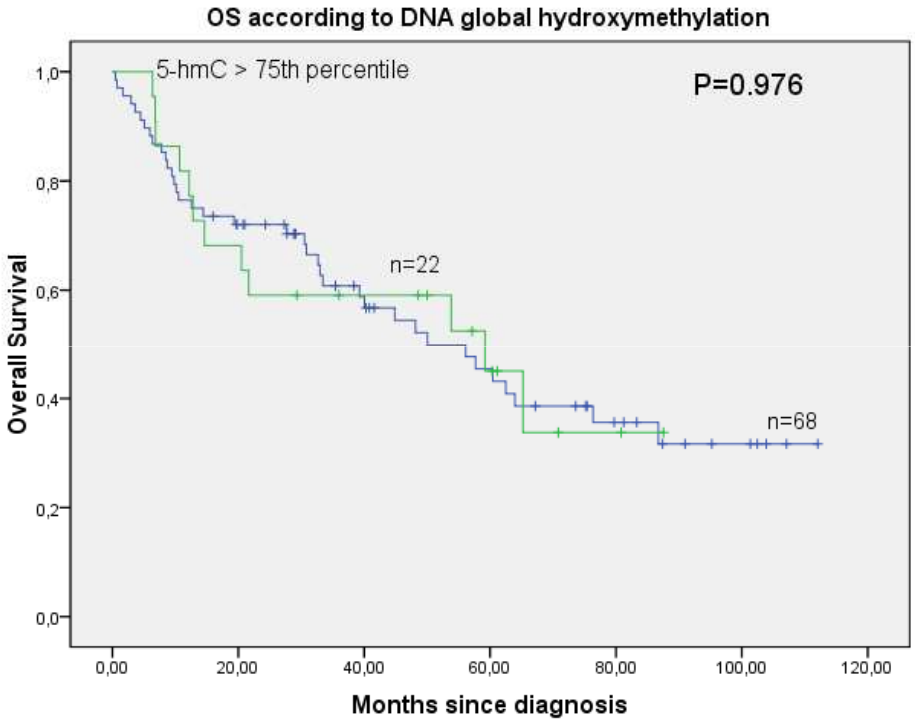
	P	ORR	95,0% CI for ORR	
			Lower	Upper
Age	,346	-	,973	1,083
Sex	,106	-	,176	1,181
5-mC%>2.7	,007	3,883	1,443	10,450
Transfusional requirement	,708	-	,446	3,286
IPSS (INT-2/high)	,000	7,993	2,526	25,287

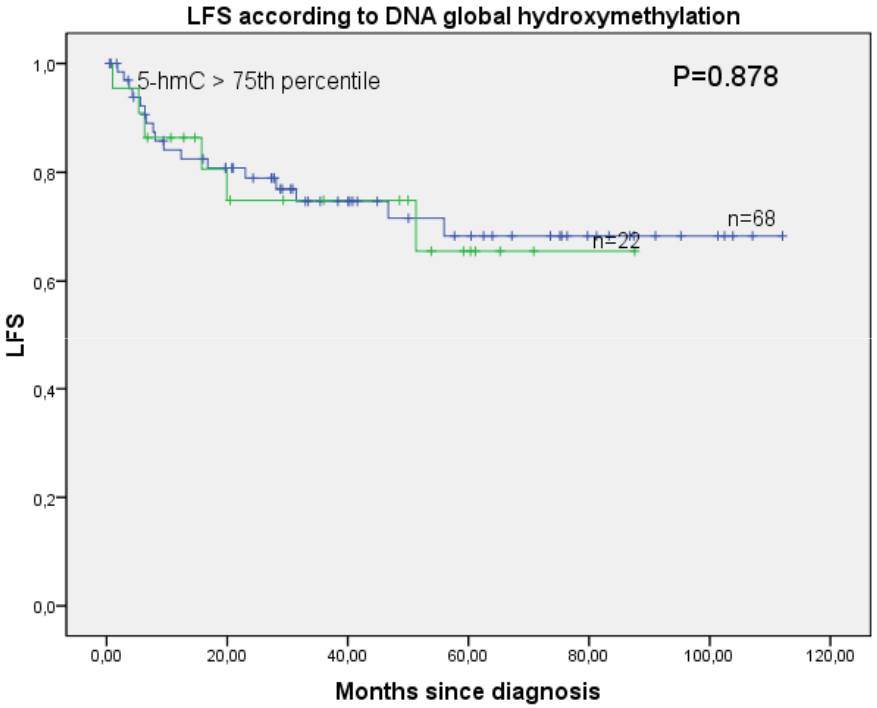
Association of classical prognostic factors with 5-mC levels





OS and LFS of de novo MDS according to DNA Global Hydroxymethylation





We could not obtain an optimal cutpoint for the 5-hmC percentage with statistical significance for OS or LFS

Leukemia (2011) 25, 1147–1152

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ORIGINAL ARTICLE

Impact of *TET2* mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias

R Itzykson[1,12], O Kosmider[2,12], T Cluzeau[3], V Mansat-De Mas[4], F Dreyfus[5], O Beyne-Rauzy[6], B Quesnel[7], N Vey[8], V Gelsi-Boyer[9], S Raynaud[10], C Preudhomme[11], L Adès[1], P Fenaux[1] and M Fontenay[2] on behalf of the Groupe Francophone des Myelodysplasies (GFM)

Table 3 Response to azacitidine and response duration, according to *TET2* gene status

	Overall	*TET2 mutated*	*TET2 WT*	P[a]
Patients (*n*)	86	13	73	
CR	20 (23%)	5 (38%)	15 (21%)	0.17
PR	1 (1%)	0 (0%)	1 (1%)	
mCR	11 (13%)	4 (31%)	7 (10%)	
SD with HI	13 (15%)	2 (15%)	11 (15%)	
SD without HI	23 (27%)	1 (8%)	22 (31%)	
Progression	15 (17%)	1 (8%)	14 (19%)	
Early death (<4 cycles)	3 (4%)	0 (0%)	3 (4%)	
Overall response (CR, PR, mCR)	32 (37%)	9 (69%)	23 (31%)	0.01
Overall response including SD with HI	45 (52%)	11 (85%)	34 (47%)	0.01
Response duration, mos	9.3 (1.7–29.0)	9.2 (2.0–28.2)	7.1 (1.7–29.0)	0.7

Abbreviations: CR, complete remission; HI, hematological improvement; mCR, marrow CR; mos, months; PR, partial remission; SD, stable disease; TET2, ten-eleven-translocation 2.
Results are reported as *n* (%) or median.

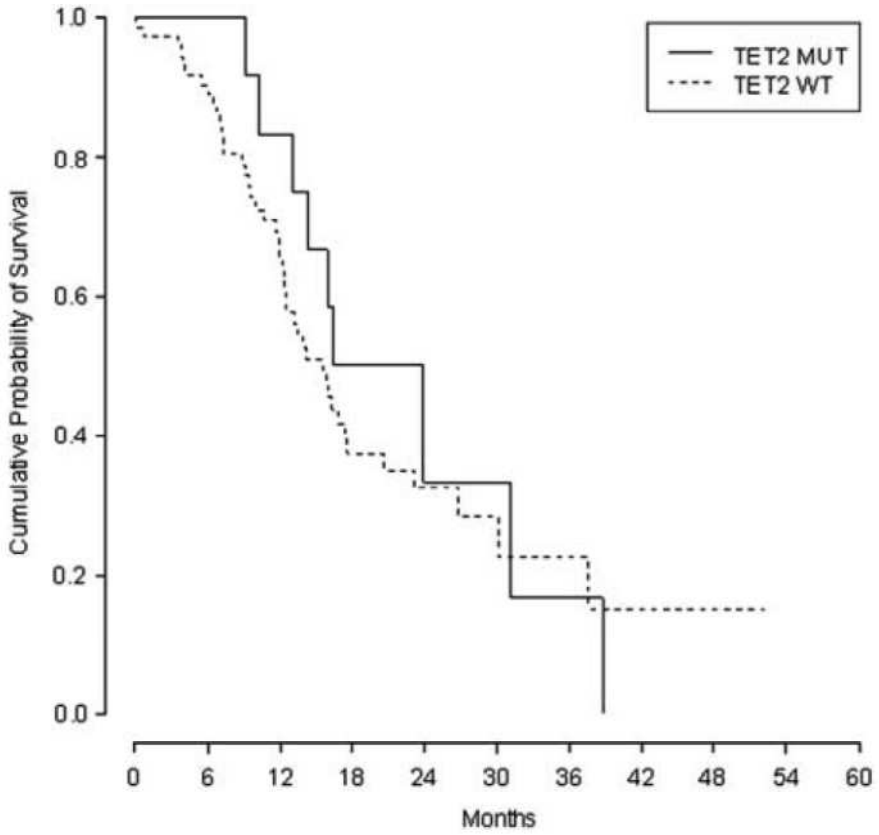

Figure 1 Overall survival according to *TET2* status. Kaplan–Meier plot of OS in the 86 patients depending on *TET2* status. Curves of *TET2* mutated (MUT) patients are given as a plain line and *TET2* WT patients as a dotted line (log-rank test: $P = 0.6$).

Itzykson R et al.
Leukemia 2011

Traina F, Jankowska AM, Visconte V, et al
Blood (ASH 2011; Abstract 461)

Aberrant DNA methylation in MDS→Rationale for treating with hypomethylating agents (AZA, DCA)

Gene Mutations ?

DNMT3A, TET2, IDH1/IDH2, EZH2, ASXL1, UTX, KRAS, NRAS, CBL, RUNX1, TP53, SF3B1 were sequenced

88 pts (RCUD=2; RARS=6; RCMD=11, MDS-U=3; AREB1/2=29; LMMC 1/2=16; MDS/MPN-U=5; RARS-T=5; AML from MDS=11)

Treatment: AZA=53; DAC= 24; both= 11

Median cycles 7(1-35); Median age 69 (42-82); Median follow up= 18 m (0-76)

Traina F, Jankowska AM, Visconte V, et al.

Blood (ASH 2011; Abstract 461)

Gene Mutations

SF3B1	6/11	(55%)
ASXL	13/50	(26%)
TET2	18/88	(20%)
KRAS	3/34	(9%)
DNMT3A	7/88	(8%)
EZH2	2/43	(5%)

TP53	1/23	(4%)
IDH1	4/88	(5%)
IDH2	3/88	(3%)
UTX	1/36	(3%)

CBL, NRAS, RUNX1

No Mutations

DNMT3A (86% vs 41%) , ASXL1 (85% vs 38%) and TET2 (67% vs 39%) MUTATIONS ARE INDEPENDENTLY ASSOCIATED WITH BETTER RESPONSE TO HYPOMETHYLATING AGENTS

Conclusions (1)

- El tractament del les SMD s'ha beneficiat en els últims anys de la introducció dels agents hipometilants (azacitidina i decitabina)
- Les SMD de baix risc es beneficien dels agents hipometilants en el tractament de les citopènies usualment una vegada perduda la resposta als ESA, lenalidomida i/o immunosupressió
- En les SMD d'alt risc els tractament amb hipometilants permeten tractar persones grans i fràgils i obtenir millores de les citopènies, de la supervivència i de la qualitat de vida en un alt percentatge dels pacients
- En les SMD d'alt risc en persones joves amb una expectativa de vida prolongada els hipometilants només son una opció intermèdia cap a la única opció curativa, l'al·lotrasplantament de progenitors

Conclusions (2)

- Els factors predictius de la resposta als agents hipometilants son de tipus clínic i biològic
- Els factors predictius de tipus clínic semblen ben caracteritzats però els biològics (metilació, estat mutacional i funcional de determinats gens) estan per establir en forma definitiva
- Una millor identificació d'aquests factors permetrà l'elecció del tractament òptim per a les SMD d'alt risc, especialment en pacients amb escasses perspectives de resposta i amb disponibilitat de tractaments alternatius
- El tractament de primera línia de les SMD d'alt risc pot millorar, possiblement per la combinació dels agents hipometilants amb altres fàrmacs (lenalidomida, inhibidors de les histonadesacetilases, etc) però els avenços estan encara en la fase dels assajos clínics
- La recerca de tractaments alternatius als hipometilants es necessària en el camí de la millora en el tractament de les SMD

Gràcies per la seva atenció