

Hypomethylating agents in MDS



Pierre Fenaux

Department of hematology and immunology

Hôpitaux St Louis, R Debré, Avicenne

Université de Paris

GFM



Hypomethylating agents in MDS

- Practical use of HMAs in MDS
- Perspectives

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Practical use of HMAs in higher risk MDS

- **Azacitidine or Decitabine ?**
- **In what MDS (AML), and when to start?**
- **Until what age ?**
- **Prognostic factors of response and survival?**
- **What regimen? For how long ?**
- **How to evaluate response ?**
- **How to prevent and treat side side effects?**

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Comparative analysis between azacitidine and decitabine for the treatment of myelodysplastic syndromes

- **300 patients, 203 azacitidine and 97 decitabine.**
- **Propensity-score matching yielded 97 patient pairs**

Yun-Gyoo Lee,¹ Imho Kim,¹ Sung-Soo Kim,¹ Summary

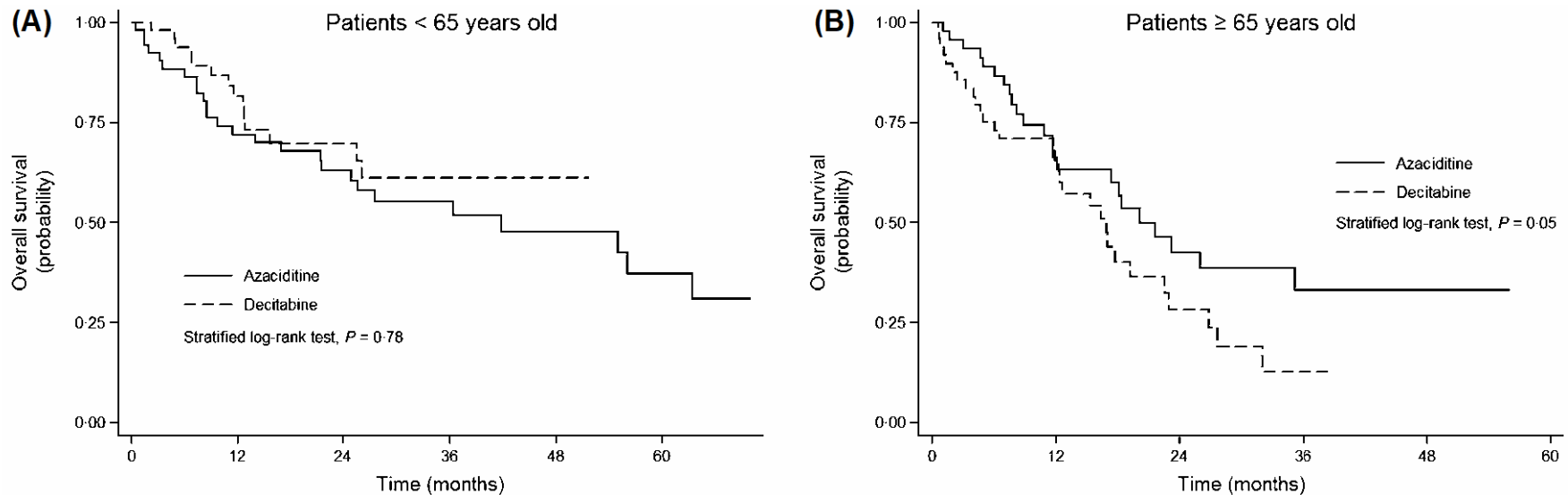


Fig 2. Comparison of overall survival between azacitidine and decitabine in the propensity score-matched cohort among patients <65 years of age (A) and ≥ 65 years of age (B).

Comparison of 7-day azacitidine and 5-day decitabine for treating myelodysplastic syndrome

Je-Hwan Lee • Yunsuk Choi • Sung-Doo Kim •
Dae-Young Kim • Jung-Hee Lee • Kyoo-Hyung Lee •
Sang-Min Lee • Su-Hee Cho • Won-Sik Lee •
Young-Don Joo

- **75 DEC 5 days, 74 AZA 7 days**
- **Same response and OS**
- **Grade 3 or higher neutropenia occurred more frequently with DEC-5d (79.6 %) than with AZA-7d (72.2 %) (P=0.040)**
- **AZA-7d associated with higher survival rates than DEC-5d in patients with poor performance status.**

Comparison Between Decitabine and Azacitidine for the Treatment of Myelodysplastic Syndrome: A Meta-Analysis With 1392 Participants

Mixue Xie,¹ Qi Jiang,^{2,3} Yanhui Xie¹

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 1, 22-8 © 2015

- **1392 MDS (decitabine, 768; azacitidine, 624)**
- **no differences regarding CR, RBC-TI**
- **When compared with BSC , azacitidine significantly improved OS and time to AML , but not decitabine**
- **In patients with high IPSS or older than 75 years, treatment with azacitidine was a favorable factor, whereas decitabine showed no advantage.**

Long-term survival of older patients with MDS treated with HMA therapy without subsequent stem cell transplantation

Amer M. Zeidan,^{1,2} Maximilian Stahl,^{1,2} Xin Hu,² Rong Wang,^{2,3} Scott F. Huntington,^{1,2} Nikolai A. Podoltsev,^{1,2} Steven D. Gore,^{1,2} Xiaomei Ma,^{2,3} and Amy J. Davidoff^{2,4}

B

AZA
DEC

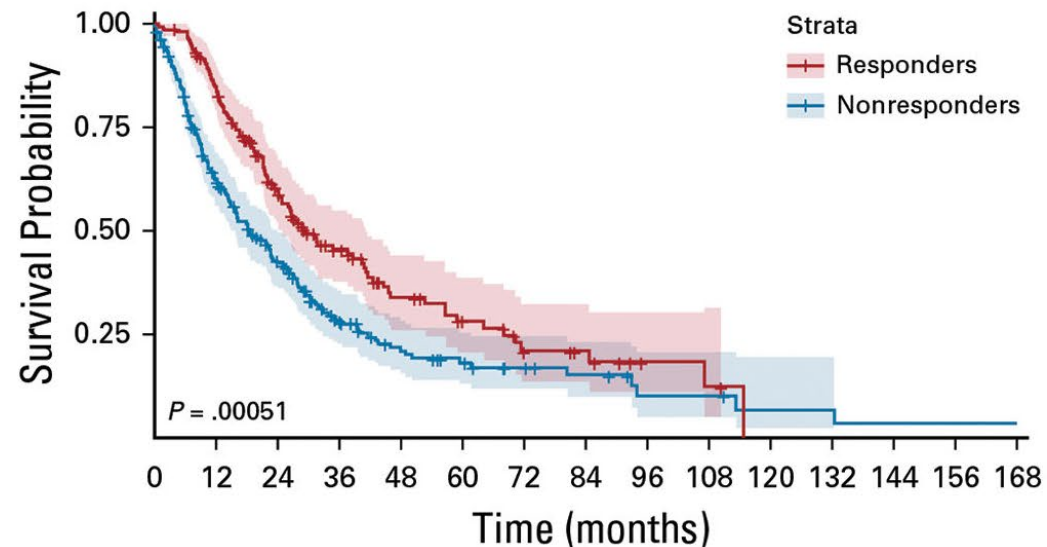
JCO Precis Oncol. 2019

Genomic Biomarkers to Predict Resistance to Hypomethylating Agents in Patients With Myelodysplastic Syndromes Using Artificial Intelligence

Aziz Nazha, MD¹, Mikkael A. Sekeres, MS, MD¹, Rafael Bejar, MD, PhD², Michael J. Rauh, MD, PhD³, Megan Othus, PhD⁴, Rami S. Komrokji, MD⁵, John Barnard, PhD¹, Cameron B. Hilton¹, Cassandra M. Kerr, MS¹, David P. Steensma, MD⁶, Amy DeZern, MD⁷, Gail Roboz, MD⁸, Guillermo Garcia-Manero, MD⁹, Harry Erba, MD, PhD¹⁰, Benjamin L. Ebert, MD, PhD¹¹, Jaroslaw P. Maciejewski, MD, PhD¹

JCO Precis Oncol. 2019

N=433



TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

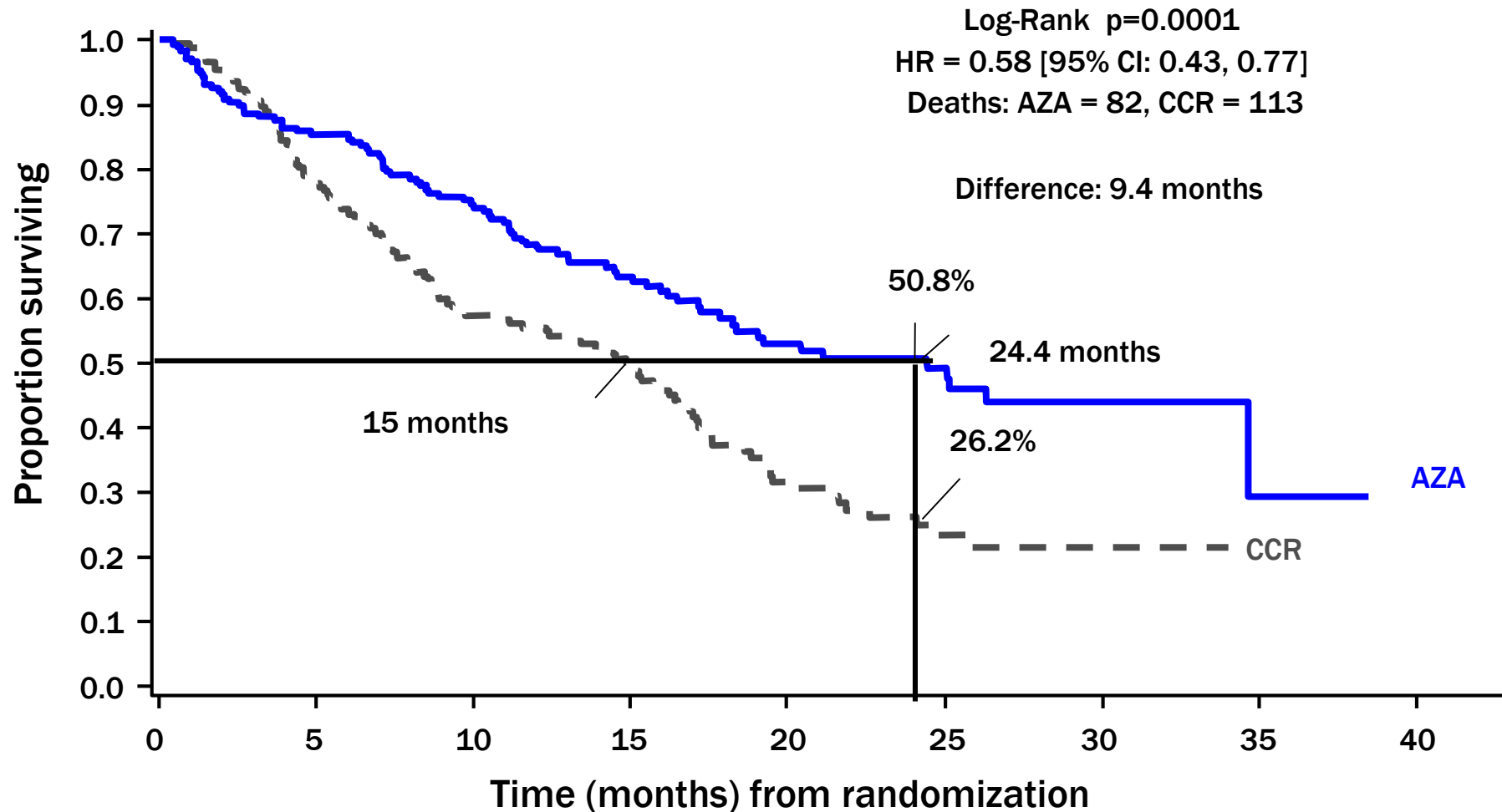
J.S. Welch, A.A. Petti, C.A. Miller, C.C. Fronick, M. O'Laughlin, R.S. Fulton, R.K. Wilson, J.D. Baty, E.J. Duncavage, B. Tandon, Y.-S. Lee, L.D. Wartman, G.L. Uy, A. Ghobadi, M.H. Tomasson, I. Pusic, R. Romee, T.A. Fehniger, K.E. Stockerl-Goldstein, R. Vij, S.T. Oh, C.N. Abboud, A.F. Cashen, M.A. Schroeder, M.A. Jacoby, S.E. Heath, K. Lubner, M.R. Janke, A. Hantel, N. Khan, M.J. Sukhanova, R.W. Knoebel, W. Stock, T.A. Graubert, M.J. Walter, P. Westervelt, D.C. Link, J.F. DiPersio, and T.J. Ley

- **Response rates higher with *TP53* mutations than with wild-type *TP53***
- **Median survival 12.7 months with *TP53* mutations and 15.4 months with wild-type *TP53* (P=0.79)**

Practical use of HMAs in higher risk MDS

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AZA 001 trial in higher risk MDS : Overall survival: azacitidine vs CCR (ITT population) (Lancet Oncol, 2009)

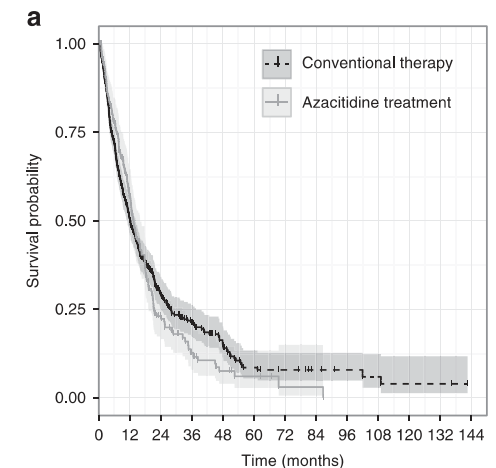


ORIGINAL ARTICLE

Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry

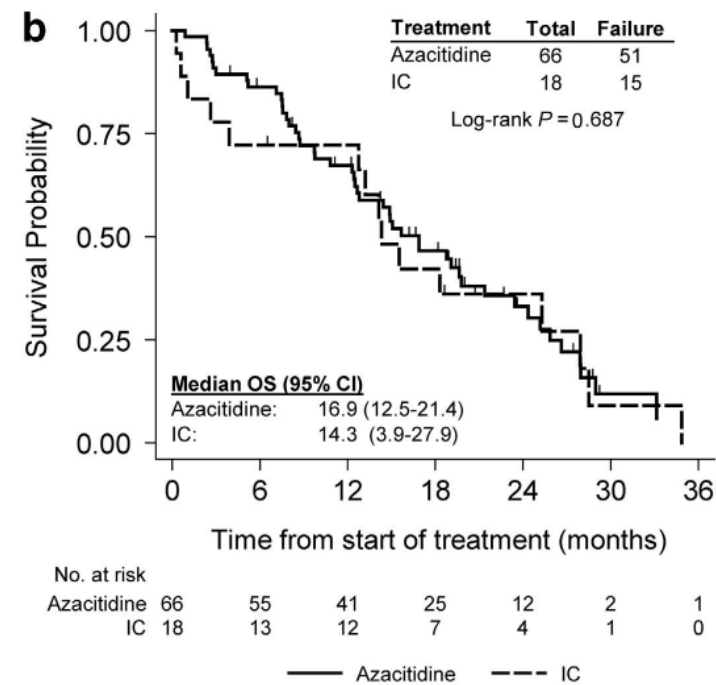
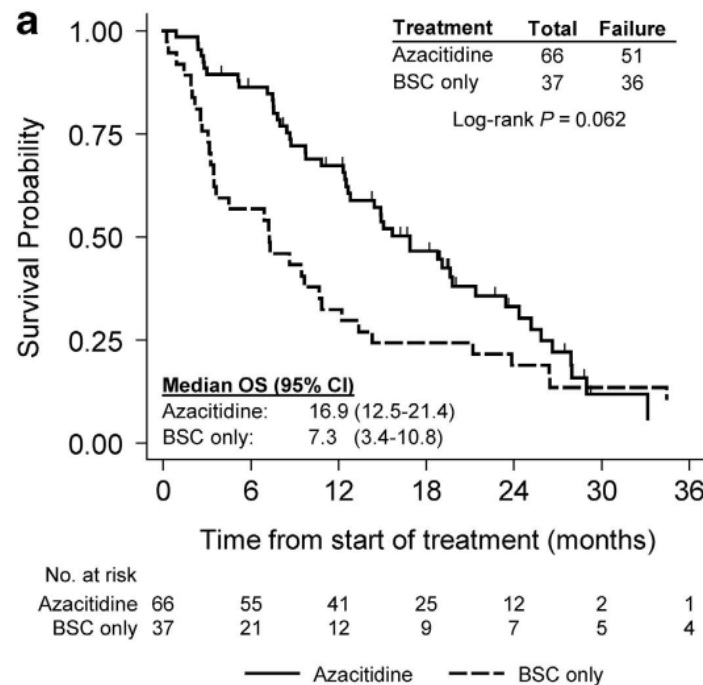
T Bernal¹, P Martínez-Camblor^{1,2}, J Sánchez-García³, R de Paz⁴, E Luño¹, B Nomdedeu⁵, MT Ardanaz⁶, C Pedro⁷, ML Amigo⁸, B Xicoy⁹, C del Cañizo¹⁰, M Tormo¹¹, J Bargay¹², D Valcárcel¹³, S Brunet¹⁴, L Benlloch¹⁵ and G Sanz¹⁶ on behalf of The Spanish Group on Myelodysplastic Syndromes and PETHEMA Foundation, Spanish Society of Hematology

- Median survival 13.4 months for azacitidine- treated patients and 12.2 for patients under CCT (P = 0.41)
- in patients with chromosome 7 abnormalities, trend toward a better survival was observed in azacitidine-treated patients (median survival 13.3 compared with 8.6 for CCT (P = 0.08))



CORRESPONDENCE

Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: results from the Dutch population-based PHAROS MDS registry



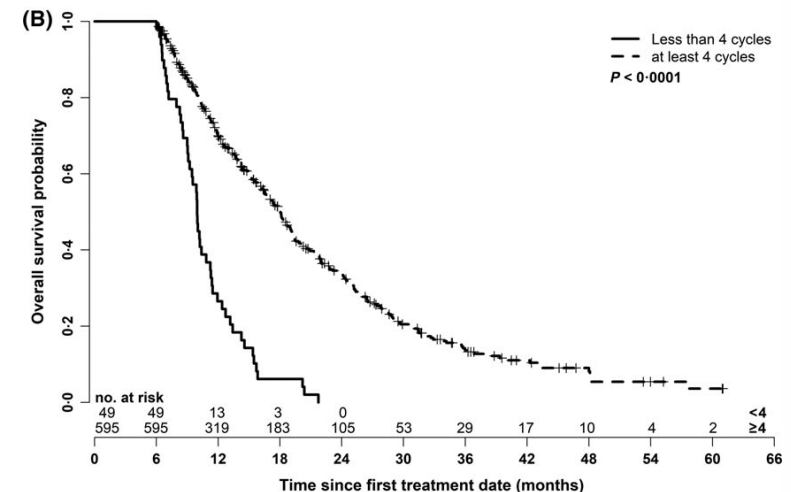
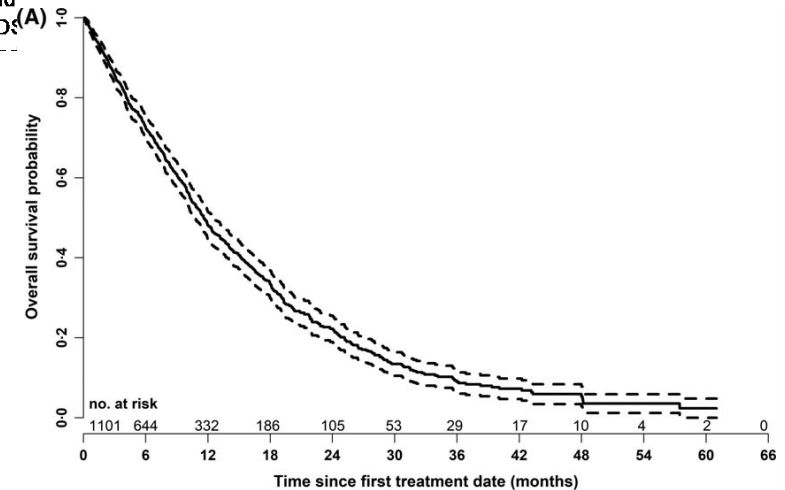
Azacitidine in the 'real-world': an evaluation of 1101 higher-risk myelodysplastic syndrome/low blast count acute myeloid leukaemia patients in Ontario, Canada

Lee Mozessohn,¹ Matthew C. Cheung,¹ Saber Fallahpour,² Tripat Gill,² Asmaa Maloul,² Liying Zhang,¹ Olivia Lau¹ and Rena Buckstein¹

Summary

The outcome of myelodysplastic syndrome (MDS) patients with uniformly higher-risk disease treated with azacitidine (AZA) in the 'real-world' remains largely unknown. We evaluated 1101 consecutive higher-risk MDS

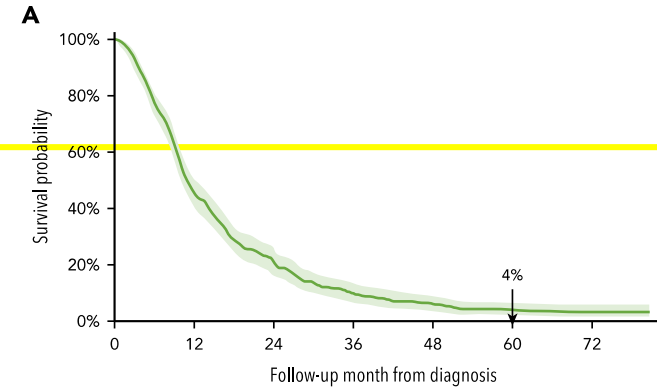
- 24.7% received AZA for seven consecutive days, 12.4% for six consecutive days and 62.9% by 5-2-2
- actuarial median survival 11.6 months for the entire cohort and 18.0 months for those receiving at least 4 cycles



Long-term survival of older patients with MDS treated with HMA therapy without subsequent stem cell transplantation

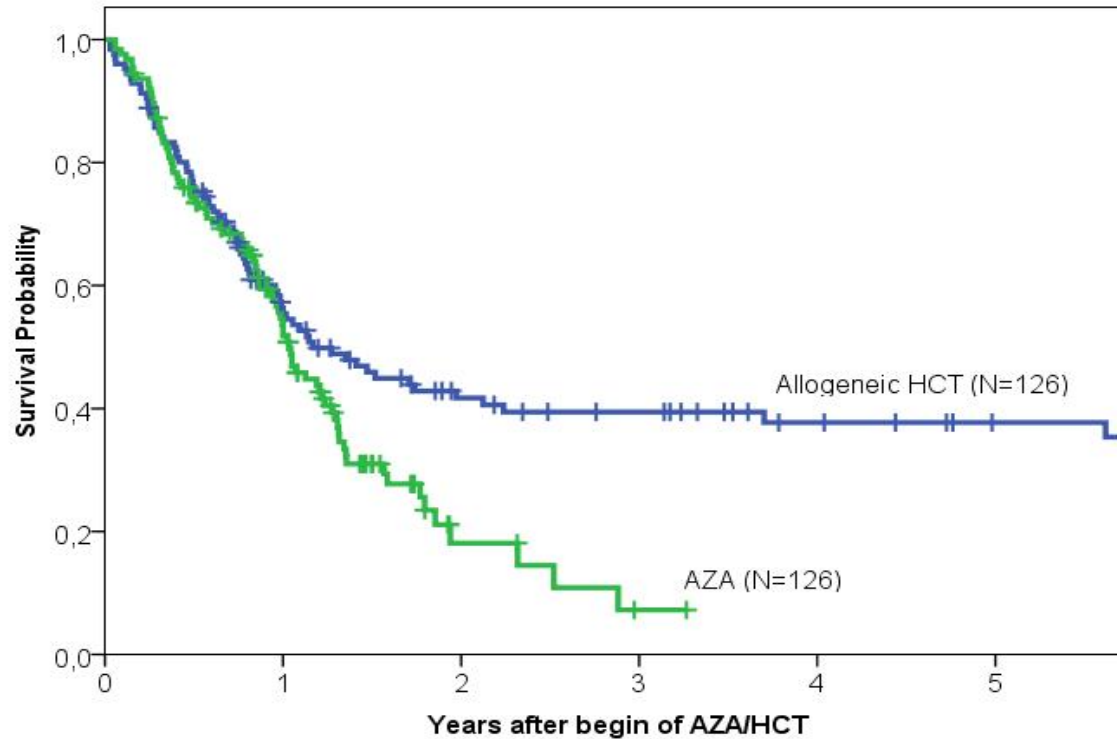
Amer M. Zeidan,^{1,2} Maximilian Stahl,^{1,2} Xin Hu,² Rong Wang,^{2,3} Scott F. Huntington,^{1,2} Nikolai A. Podoltsev,^{1,2} Steven D. Gore,^{1,2} Xiaomei Ma,^{2,3} and Amy J. Davidoff^{2,4}

- **n= 1187 HMA**
- **median OS for the 1187 patient cohort 14 months**
- **5-year OS probability was 8% (95% CI, 7%-10%).**



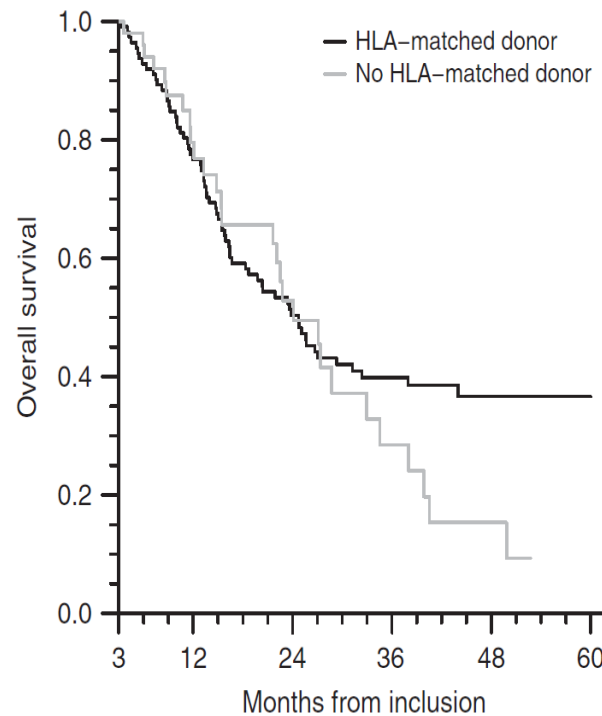
Allo SCT remains the only curative treatment in higher risk MDS

(Platzbecker, BBMT, 2012)



Median follow-up of 20 months
3-year OS was 39% for HCT and 7% for 5-aza

Survival gain in higher risk patients with a donor

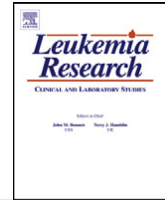


No. at risk:

HLA-matched donor	112	85	63	50	39	33	23	14	8	5
No matched donor	50	29	21	15	8	6	3	2	0	0

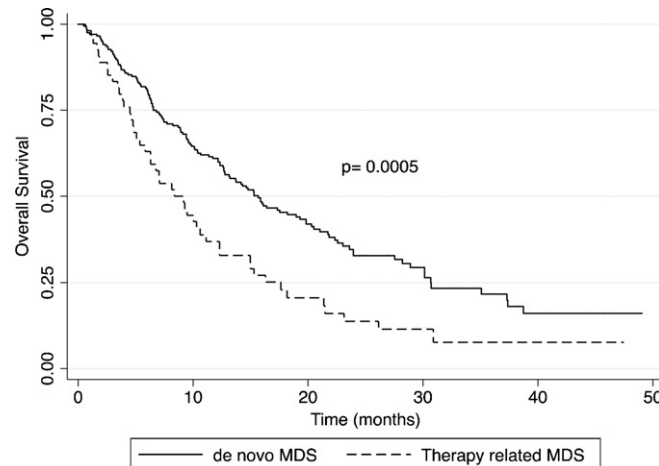
AZA in MDS/AML post MPD (S Thépot, Blood, 2010)

- 54 patients with MDS or AML post myeloproliferative disorder (in the French ATU program)
- 52% responses, with reversal to features of MPD (polycythemia, thrombocythemia) in one half of responders



Azacitidine in the treatment of therapy related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML): A report on 54 patients by the Groupe Francophone Des Myelodysplasies (GFM)

Cecile Bally^{a,b}, Sylvain Thépot^{a,b}, Bruno Quesnel^{a,c}, Norbert Vey^{a,d}, Francois Dreyfus^{a,e}, Jehane Fadlallah^b, Pascal Turlure^{a,f}, Stephane de Botton^{a,g}, Caroline Dartigeas^{a,h}, Benoit de Renzis^{a,i}, Raphael Itzykson^a, Pierre Fenaux^{a,b,*}, Lionel Adès^{a,b,*}



marrow blast percentage had no significant impact. By comparison with de novo MDS/AML treated in the same program, t-MDS/AML had a similar response rate (38% vs 45% in de novo MDS/AML, $p=0.53$), but significantly shorter OS (2 year OS of 14% vs 33.9%, $p=0.0005$). However, in a multivariate analysis performed in all patients (de novo and therapy related cases), only complex karyotype and high IPSS, and not etiology (i.e. de novo versus therapy related), had a significant impact on OS. Nine (15%) patients received allogeneic stem cell transplantation, 4 of whom were still alive.

AZA in lower risk MDS

(S Thépot C Gardin, Haematologica, 2016)

- 93 pts
- Mainly “purely anemic patients”
- Randomized phase II trial AZA+/- EPO beta *In patients CLEARLY resistant to ESAs (at least 12 weeks using 60000 U/ w EPO or 250ug/w Darbepoetin)*
- Transfusion independence in 19% of patients
- AZA+EPO= AZA

Efficacy of Azacitidine in autoimmune and inflammatory disorders associated with myelodysplastic syndromes and chronic myelomonocytic leukemia



Jean-Baptiste Fraison^{a,*,1}, Arsène Mekinian^{b,1}, Eric Grignano^c, Jean-Emmanuel Kahn^d, Jean-Benoit Arlet^e, Olivier Decaux^f, Guillaume Denis^g, Anne-Laure Buchdahl^h, Mohamed Omouriⁱ, Gwenola Maigne^j, Achille Aouba^j, Nathalie Leon^k, Sabine Berthier^l, Eric Liozon^m, Sophie Parkⁿ, Claude Gardin^o, Olivier Lortholary^p, Julien Rossignol^c, Pierre Fenaux^q, Olivier Fain^{b,1}, Thorsten Braun^{o,1}



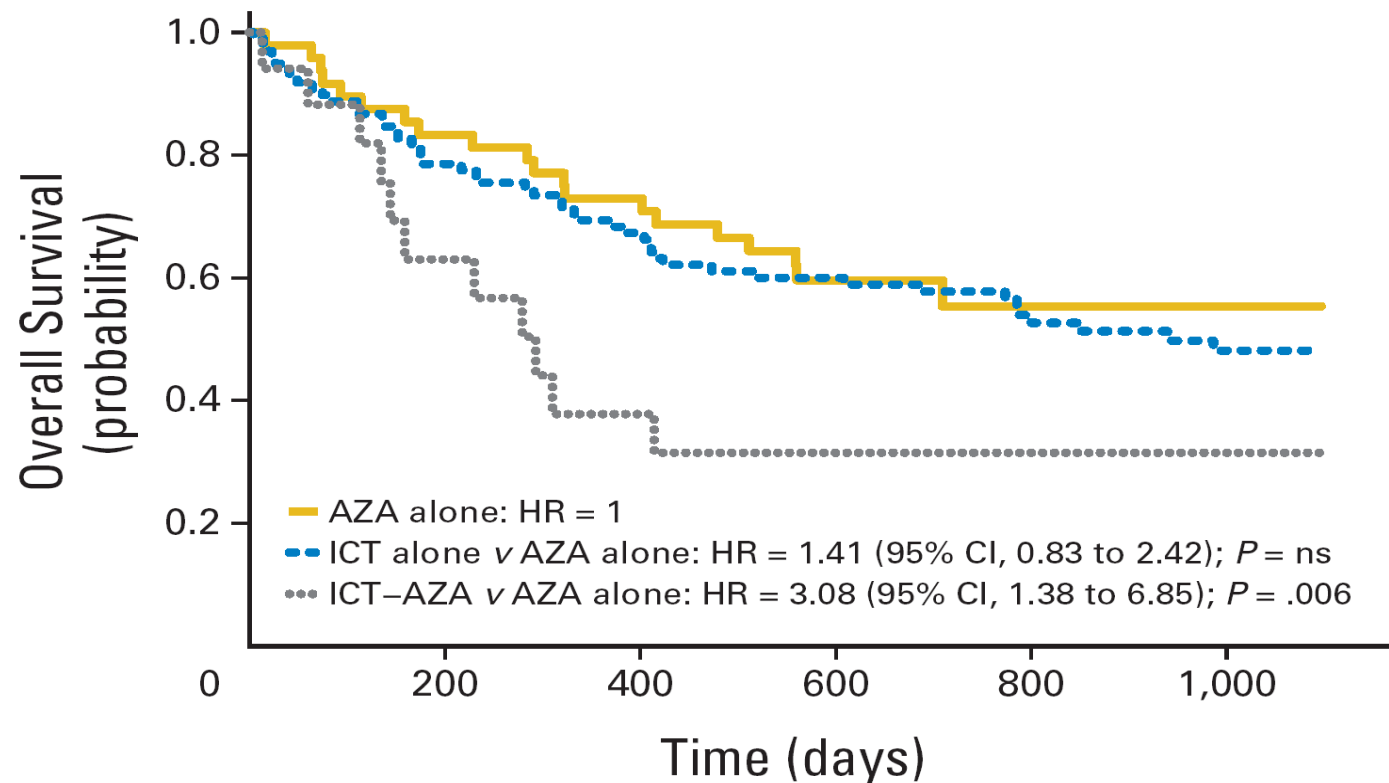
- **22 patients treated with AZA for autoimmune disorders (AID) associated with MDS/CMML**
- **Response of AID to Azacitidine in 19 patients (86%)**
- **Reduction or discontinuation of steroids and/or immunosuppressive therapy possible in 16 cases (73%).**

Treatment prior to allo HSCT: Azacitidine versus intensive chemotherapy

- 163 pts (AZA, 48; ICT, 98; AZA-ICT, 17)
- Donors: siblings, 75; MUD, 88
- Conditioning: RIC, 130; MAC, 33



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ORIGINAL ARTICLE

Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation

T Schroeder^{1,8}, A Czibere^{1,8}, U Platzbecker², G Bug³, L Uharek⁴, T Luft⁵, A Giagounidis⁶, F Zohren¹, I Bruns¹, C Wolschke⁷, K Rieger⁴, R Fenk¹, U Germing¹, R Haas¹, N Kröger⁷ and G Kobbe¹

- N= 30
- up to 8 cycles azacitidine followed by DLI after every second azacitidine cycle.
- A median of three courses azacitidine (range 1–8) were administered, and 22 patients (73%) received DLI.
- Overall response rate 30%, including 7 CR (23%) and 2 PR (7%).
- 5 patients remained in CR for a median of 777 days

“Preventive” Post-transplant ASTX 727 in very high risk MDS patients: a phase II prospective study

(M Robin)

Inclusion criteria

Patients aged from 18 to 70 years

MDS according to WHO with a very complex cytogenetic (according to IPSS-R) or TP 53 gene mutation

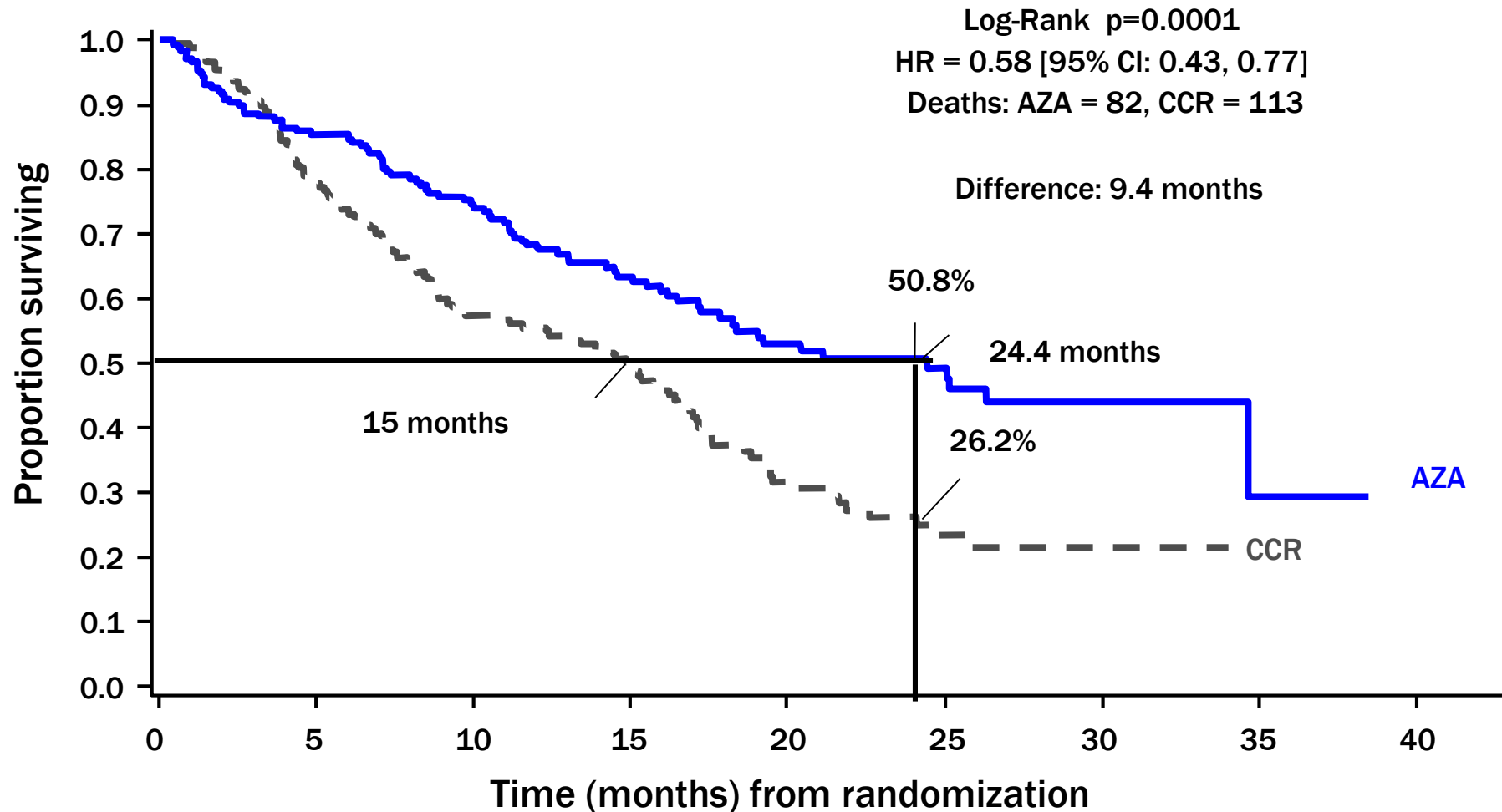


- **ASTX 727 (decitabine + cedazuridine) started on day 40**
- **Immunosuppression stopped on day 70**
- **DLI started on day 100**

Practical use of HMAs in higher risk MDS

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AZA 001 trial: Overall survival: azacitidine vs CCR (ITT population) (Lancet Oncol, 2009)



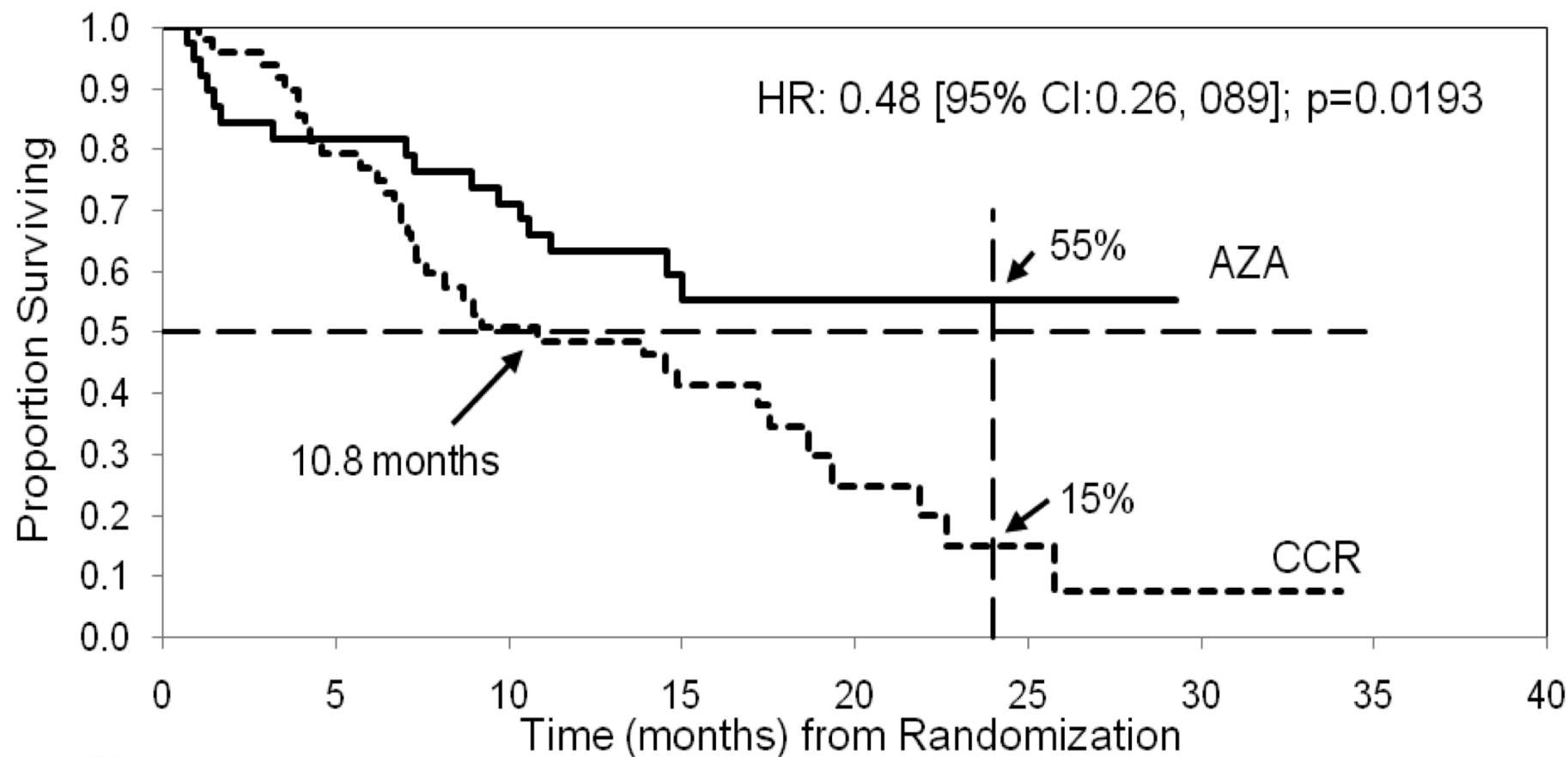
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AZA 001 trial in patients older than 75 years

(Seymour J, Crit Rev Oncol Hematol. 2010)

Figure 2. Overall Survival in Patients ≥ 75 Years of Age: AZA vs CCR

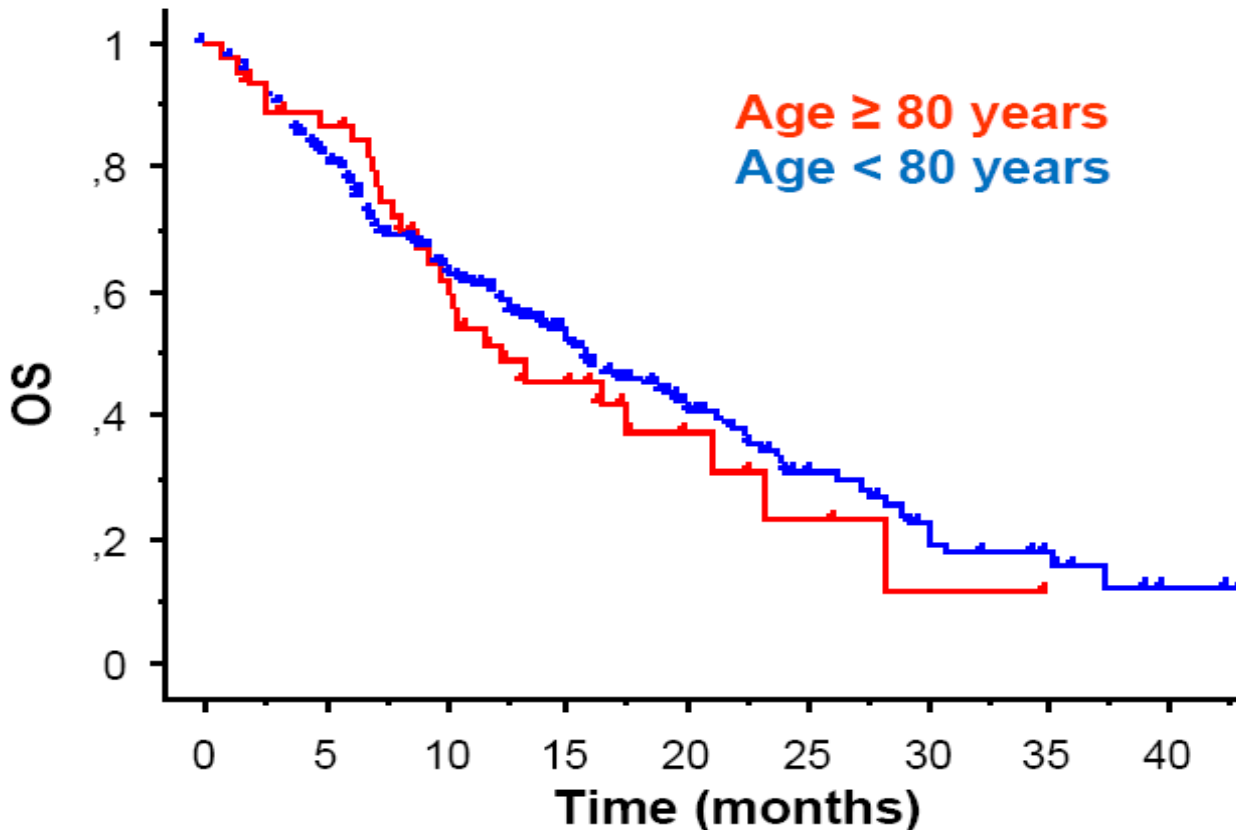


at Risk

AZA	38	31	27	14	9	3	0	0	0
CCR	49	37	23	16	5	3	1	0	0

French patient named program of AZA (ATU)

OS did not differ from pts <80 years ($p=0.6$)



Median OS was 12.1 months

1 year-OS was of 50.0%

2-year-OS was of 23.2%



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Results of treatment with azacitidine in patients aged ≥ 75 years included in the Spanish Registry of MDS Leuk Lymphoma. 2013

- 107 patients ≥ 75 years from the **Spanish Registry of MDS** treated with AZA.
- median age 78
- 38/ 94 (40%) patients achieved TI
- **median OS 18 months and 2 year OS 34%**

Practical use of HMAs in higher risk MDS

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Specific molecular signatures predict decitabine response in chronic myelomonocytic leukemia

Kristen Meldi,¹ Tingting Qin,¹ Francesca Buchi,² Nathalie Droin,³ Jason Sotzen,¹ Jean-Baptiste Micol,^{3,4} Dorothée Selimoglu-Buet,³ Erico Masala,² Bernardino Allione,^{5,6} Daniela Gioia,^{6,7} Antonella Poloni,^{6,8} Monia Lunghi,^{6,9} Eric Solary,³ Omar Abdel-Wahab,⁴ Valeria Santini,^{2,6} and Maria E. Figueroa¹

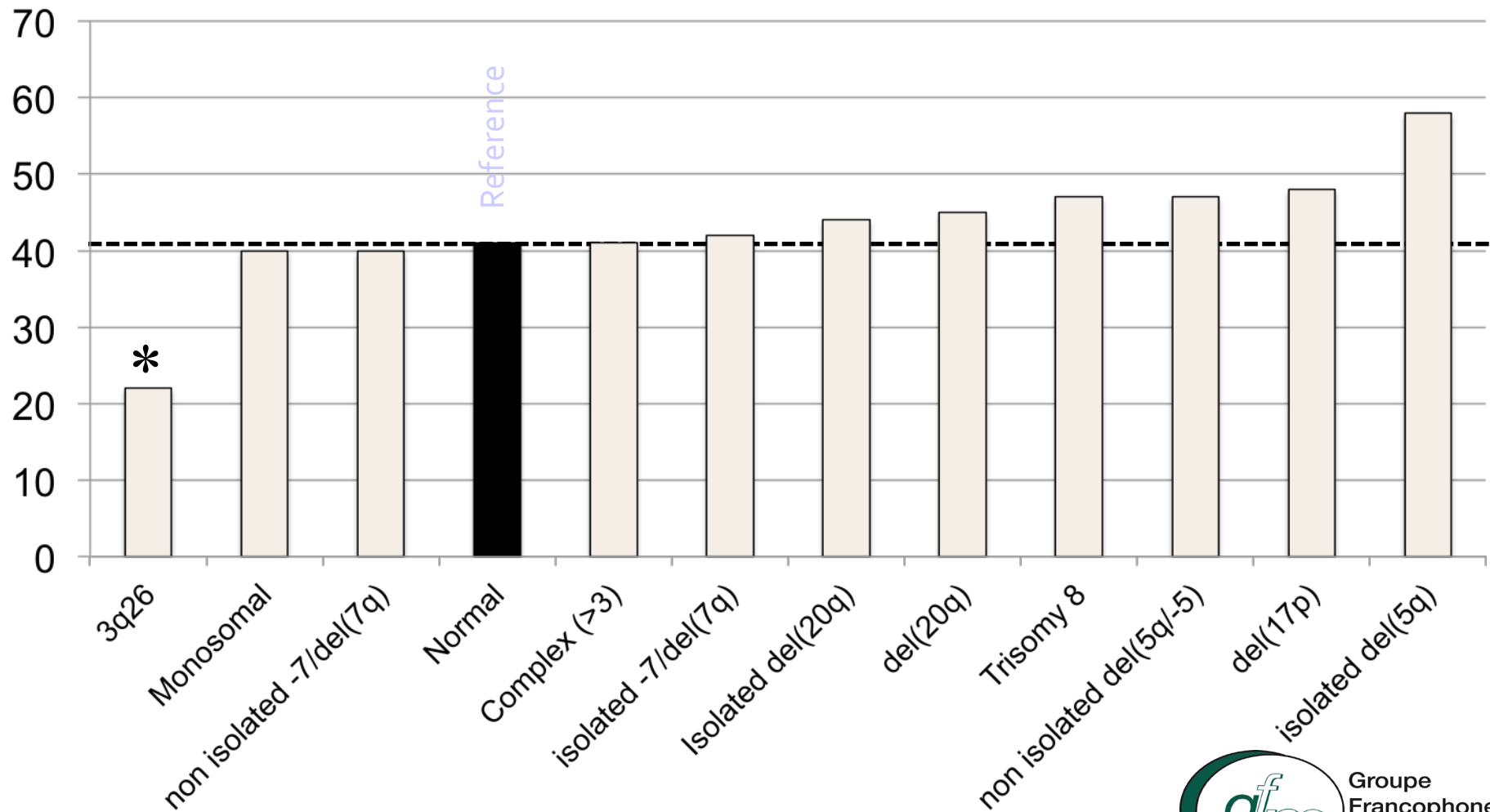
167 differentially methylated regions (DMRs) of DNA at baseline distinguished responders from nonresponders using NGS .

These DMRs were primarily localized to nonpromoter regions and overlapped with distal regulatory enhancers

Impact Of Cytogenetics and Cytogenetic Response On Outcome In Myelodysplastic Syndromes (MDS) treated With Azacitidine (AZA). A Collaborative Study In 878 Patients

Marie Sebert^{1*}, Rami S Komrokji, MD², Mikkael A. Sekeres, MD, MS³, Thomas Prebet, MD PhD⁴, Thomas Cluzeau, MD, PhD^{5*}, Valeria Santini, MD^{6*}, Alessandro Sanna^{7*}, Najla H Al Ali^{2*}, Sean Hobson^{8*}, Virginie Eclache, MD^{9*}, Alan List, MD², Pierre Fenaux, MD, PhD¹⁰ and Lionel Ades, MD, PhD¹¹

ASH 2014

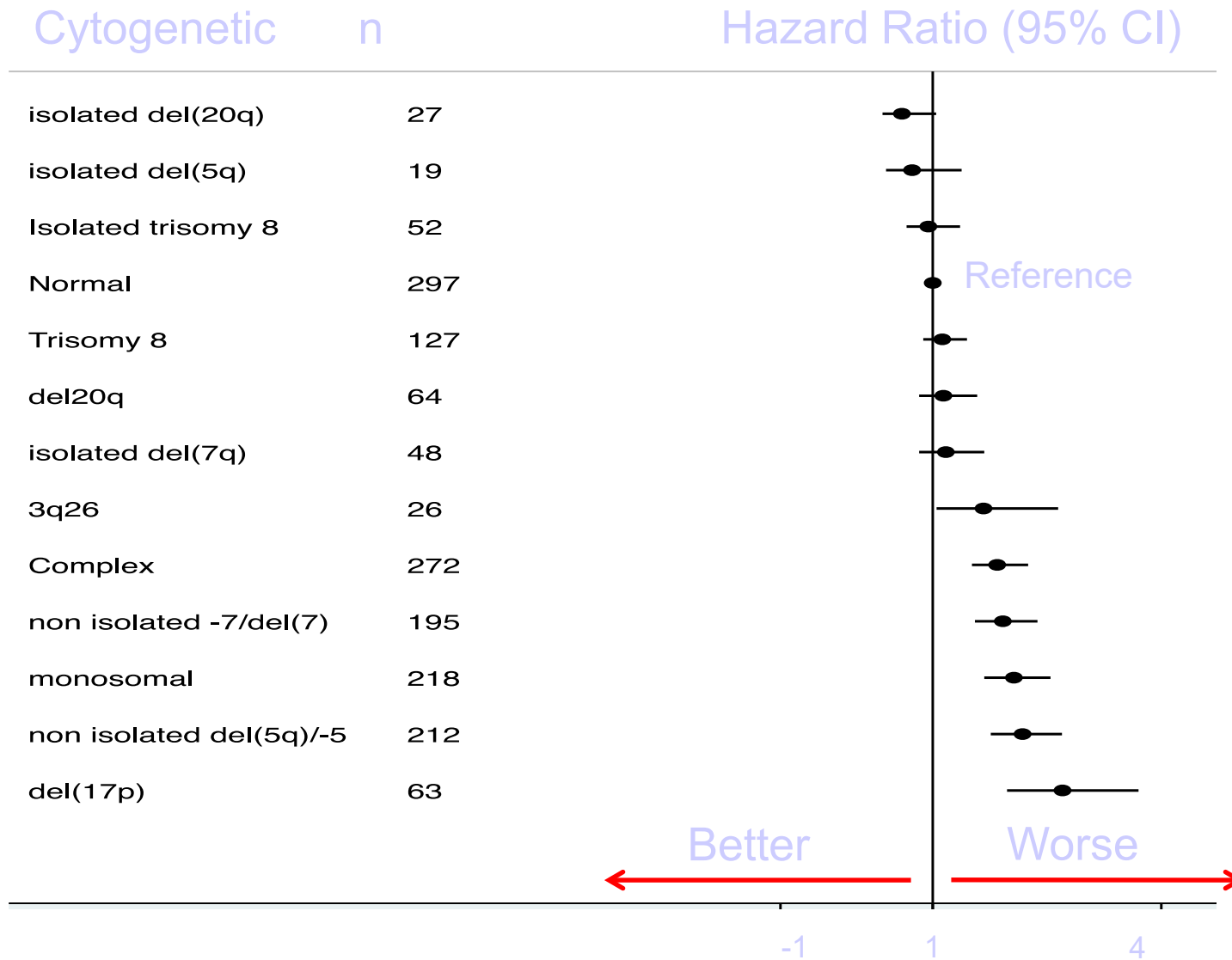


* : $p < 0.05$ compared to Normal



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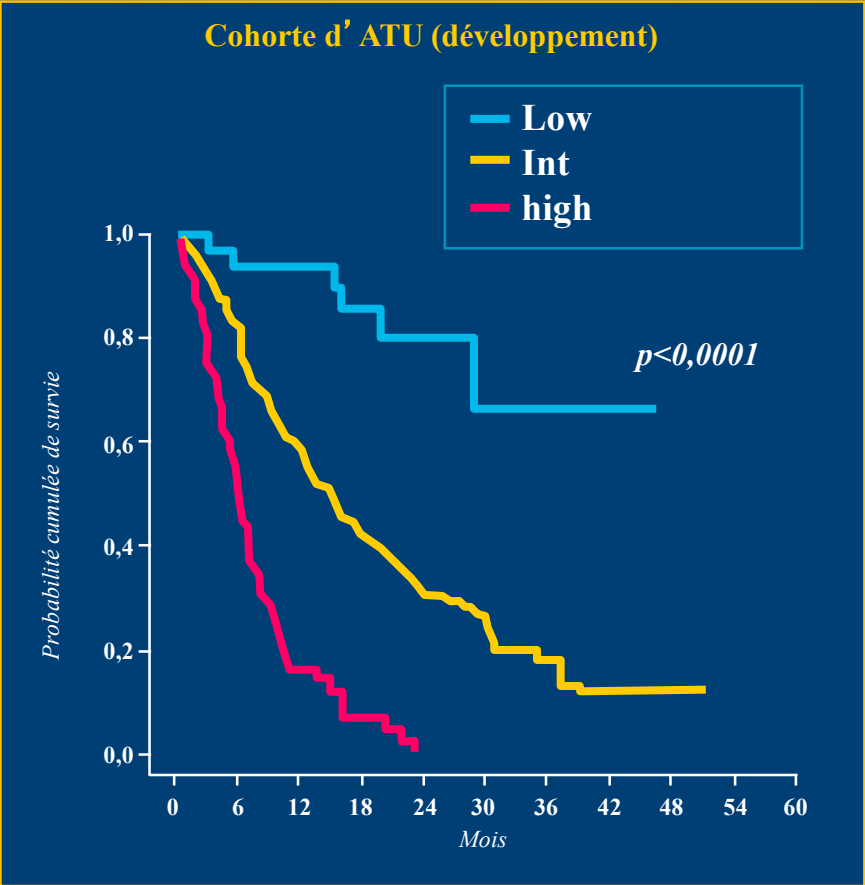
Impact of Cytogenetics on OS (compared to NK)



Prognostic factors of treatment with AZA ?



- French ATU program 282 patients
- Validation with AZA-001 patients (n=161)



Multivariate Analysis		HR [95% CI]	p	puntuacion	
Performance status		2,0 [1,4-2,9]	<10 ⁻⁴	1	
≥ 4 units RBC transfused /8w		1,9 [1,4-2,6]	<10 ⁻⁴	1	
Presence of circulating blasts		2,0 [1,5-2,7]	<10 ⁻⁴	1	
Cytogenetics (IPSS)			<10 ⁻⁴		
intermediate risk		1,4 [0,8-2,3]		1	
unfavorable		3,0 [2,0-4,3]		2	
Grupo, de riesgo	Score	ATU (n=269)		AZA-001 (n=152)	
		(N,%)	Survie médiane globale (mois)	(N,%)	Survie médiane globale (mois)
low	0	30 (11%)	NR	23 (15%)	NR
Intermediate	1-3	191 (71%)	15,0	114 (75%)	21,4
high	4-5	48 (18%)	6,1	15 (10%)	9,3

R. Itzykson et al.,Blood , 2011

Long-term outcome of higher-risk MDS patients treated with azacitidine: an update of the GFM compassionate program cohort

Raphael Itzykson, Sylvain Thépot, Bruno Quesnel, Francois Dreyfus, Christian Recher, Eric Wattel, Claude Gardin, Lionel Adès and Pierre Fenaux

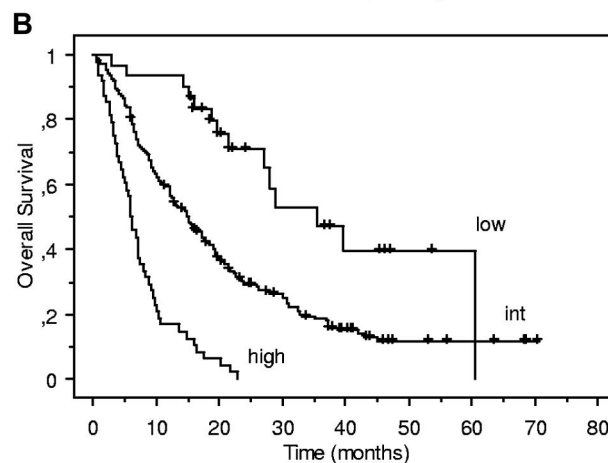


Figure 1. Updated Kaplan-Meier estimates of overall survival (OS) of our previously reported cohort of 282 higher-risk myelodysplastic syndromes (MDS) patients treated with azacitidine, with a median follow-up of 41.3 months. (A) Global cohort (n = 282).¹ (B) Cohort according to our risk stratification: low (n = 30, median OS: 32.1 month); intermediate (int; n = 191, median OS: 15.0 months); high (n = 48; median OS: 6.1 month; log-rank test: $P < 10^{-4}$).

The revised IPSS is a powerful tool to evaluate the outcome of MDS patients treated with azacitidine: the GFM experience

Mathilde Lamarque, Sophie Raynaud, Raphael Itzykson, Sylvain Thepot, Bruno Quesnel, Francois Dreyfus, Odile Beyne Rauzy, Pascal Turlure, Norbert Vey, Christian Recher, Caroline Dartigeas, Laurence Legros, Jacques Delaunay, Sorin Visanica, Aspasia Stamatoullas, Pierre Fenaux and Lionel Adès

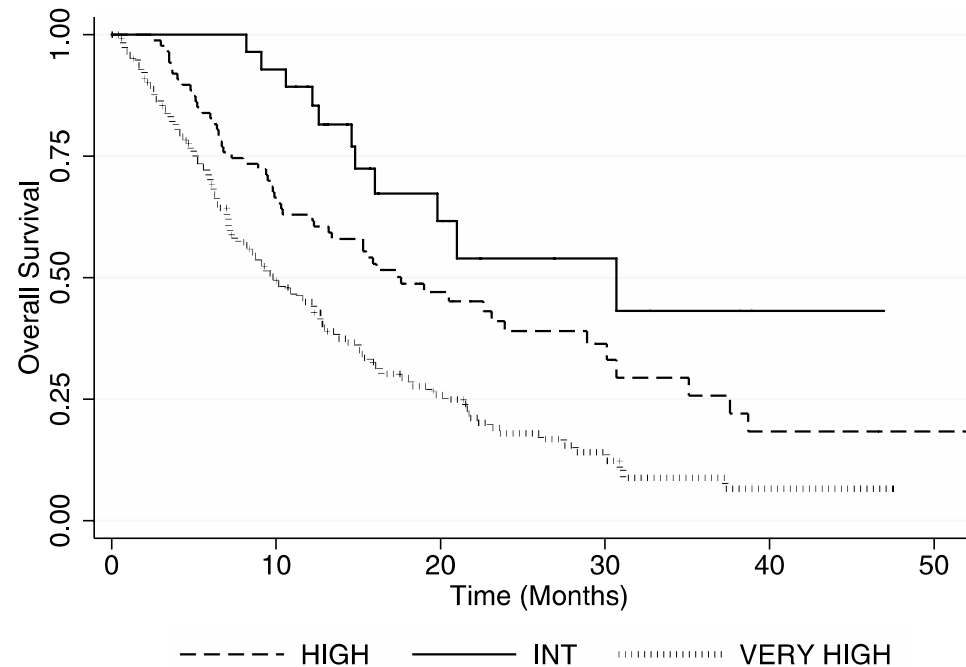


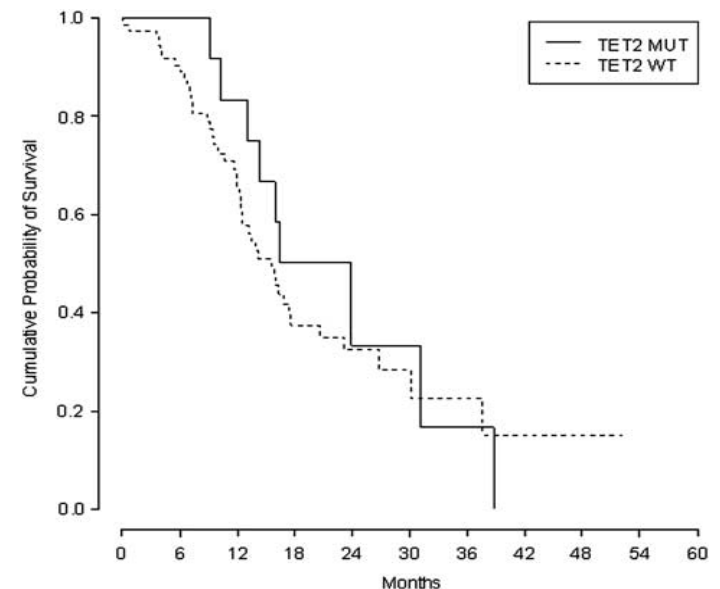
Figure 1. OS according to IPSS-R score in MDS patients treated with AZA with a median follow-up time of 41.4 months.

ORIGINAL ARTICLE

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

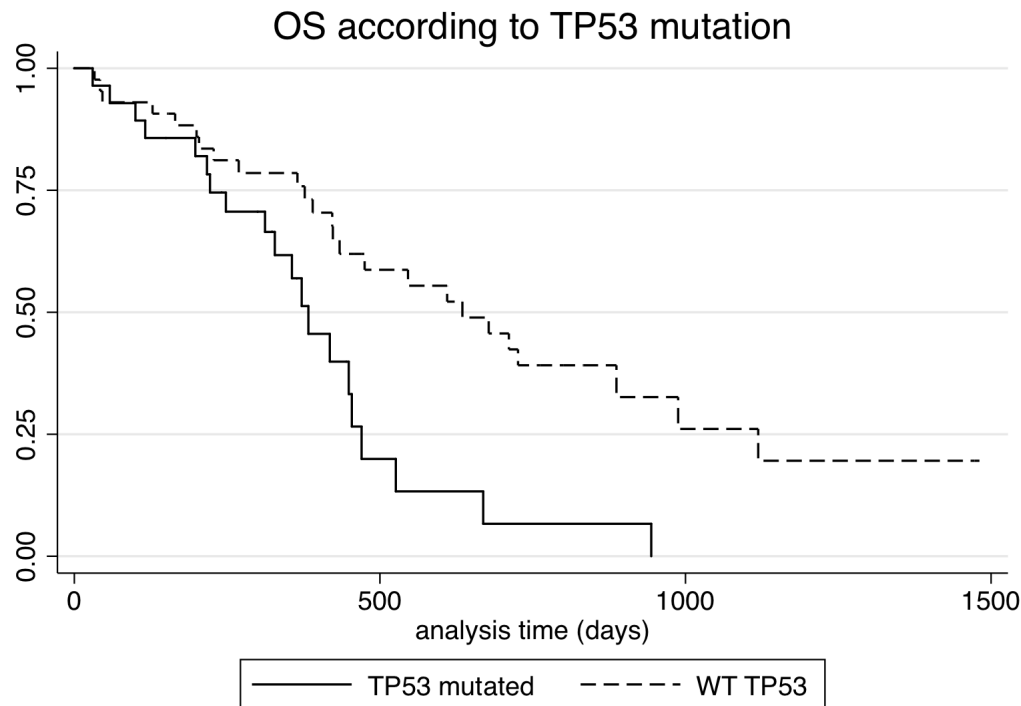
R Itzykson^{1,12}, O Kosmider^{2,12}, T Cluzeau³, V Mansat-De Mas⁴, F Dreyfus⁵, O Beyne-Rauzy⁶, B Quesnel⁷, N Vey⁸, V Gelsi-Boyer⁹, S Raynaud¹⁰, C Preudhomme¹¹, L Adès¹, P Fenaux¹ and M Fontenay² on behalf of the Groupe Francophone des Myélodysplasies (GFM)

- **Mutated *TET2* (p=0.04) and favorable cytogenetic risk predicted higher response rate**
- **Response duration and overall survival however, comparable in the MUT and WT groups.**



otted line (log-rank test: $P=0.6$).

TP53 mutations are associated with poorer survival with azacitidine in high risk MDS (Bally, Leuk Res , 2013)



Guillermo Montalban-Bravo, M.D.
Koichi Takahashi, M.D.
Guillermo Garcia-Manero, M.D.

Table 1. Outcomes of Patients with Acute Myeloid Leukemia and Myelodysplastic Syndromes (MDS) Treated with Hypomethylating Agents in Four Studies, According to *TP53* Mutation Status.*

Study	No. of Patients	Patients with Mutated <i>TP53</i>	Overall Response			Complete Response			Overall Survival		
			Mutated <i>TP53</i>	Wild-Type <i>TP53</i>	P Value	Mutated <i>TP53</i>	Wild-Type <i>TP53</i>	P Value	Mutated <i>TP53</i>	Wild-Type <i>TP53</i>	P Value
			no. of patients (%)			no. (%)					
Bally et al.†	62 (44 MDS)	23 (37)	10 (43)	20 (51)	0.60	5 (22)	15 (38)	0.26	Median of 12.4 mo	Median of 23.7 mo	<0.001
Bejar et al.‡	213 MDS	39 (18)	20 (51)	80 (46)	NS	NA	NA	NA	Hazard ratio for death, 2.01 (95% CI, 1.29–3.14)		0.002
Takahashi et al.§	168 MDS	38 (23)	15 (39)	41 (32)	0.13	13 (34)	35 (27)	0.38	Median of 9.4 mo	Median of 20.7 mo	<0.001
Jung et al.¶	107 MDS	13 (12)	10 (77)	47 (50)	0.08	NA	NA	NA	31% at 2 yr	67% at 2 yr	0.003

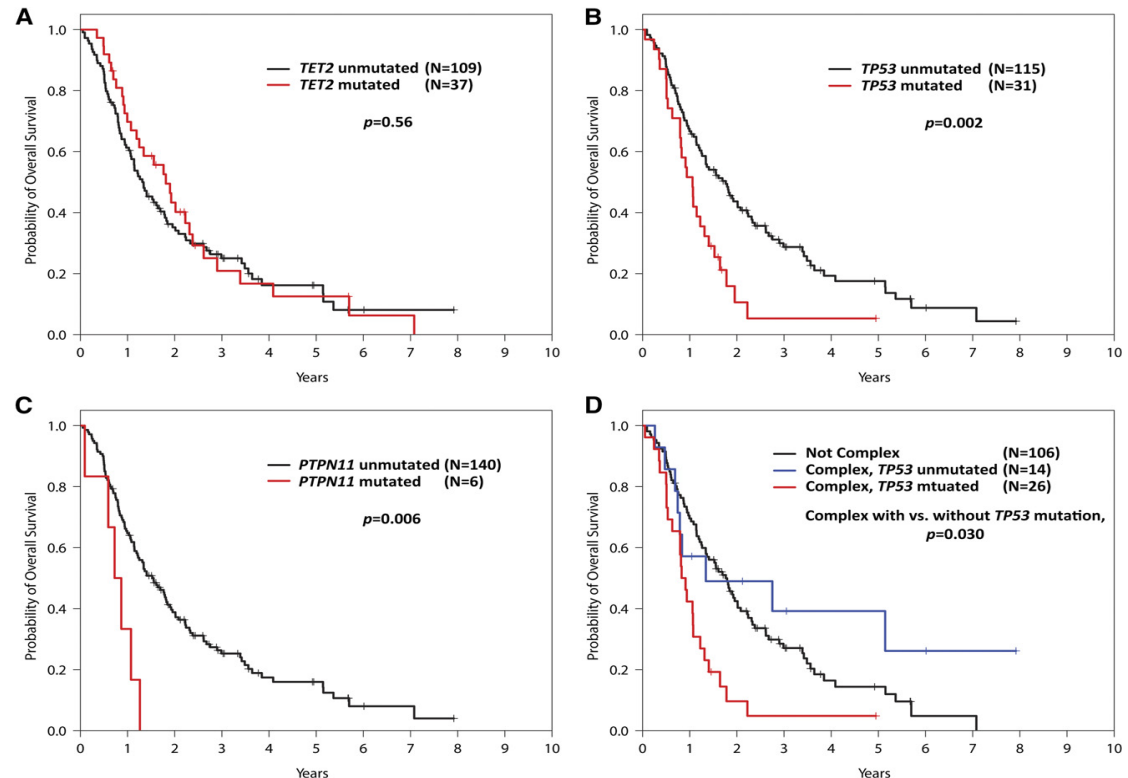
Regular Article

MYELOID NEOPLASIA

TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients

Rafael Bejar,¹ Allegra Lord,² Kristen Stevenson,³ Michal Bar-Natan,⁴ Albert Pérez-Ladaga,¹ Jacques Zaneveld,⁵ Hui Wang,⁵ Bennett Caughey,¹ Petar Stojanov,⁶ Gad Getz,⁶ Guillermo Garcia-Manero,⁷ Hagop Kantarjian,⁷ Rui Chen,⁵ Richard M. Stone,⁴ Donna Neuberg,³ David P. Steensma,⁴ and Benjamin L. Ebert^{2,6}

- Higher abundance *TET2* mutations are associated with increased response to hypomethylating agents, particularly when *ASXL1* is not mutated.
- *TP53* and *PTPN11* mutations are associated with shorter overall survival after hypomethylating agent treatment, but do not predict response.



JCO Precis Oncol. 2019

Genomic Biomarkers to Predict Resistance to Hypomethylating Agents in Patients With Myelodysplastic Syndromes Using Artificial Intelligence

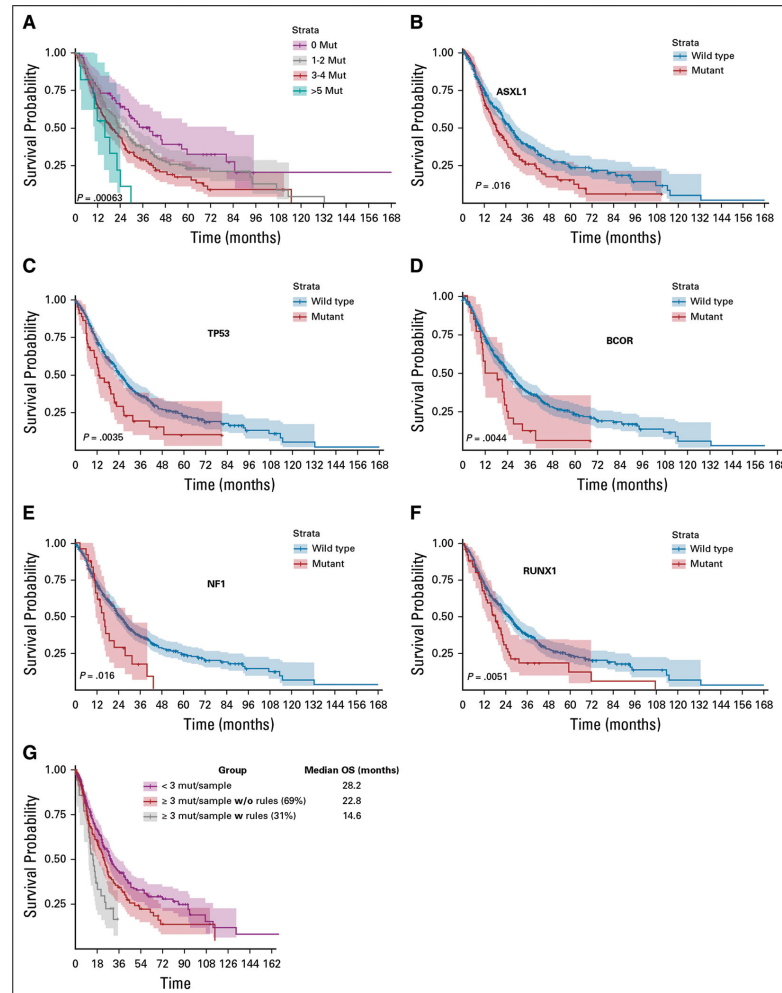
Aziz Nazha, MD¹, Mikkael A. Sekeres, MS, MD¹, Rafael Bejar, MD, PhD², Michael J. Rauh, MD, PhD³, Megan Othus, PhD⁴, Rami S. Komrokji, MD⁵, John Barnard, PhD¹, Cameron B. Hilton¹, Cassandra M. Kerr, MS¹, David P. Steensma, MD⁶, Amy DeZern, MD⁷, Gail Roboz, MD⁸, Guillermo Garcia-Manero, MD⁹, Harry Erba, MD, PhD¹⁰, Benjamin L. Ebert, MD, PhD¹¹, Jaroslaw P. Maciejewski, MD, PhD¹

JCO Precis Oncol. 2019

N=433

Association Rules for Resistance to HMAs

ASXL1, NF1
ASXL1, EZH2, TET2
ASXL1, EZH2, RUNX1
EZH2, SRSF2, TET2
ASXL1, EZH2, SRSF2
ASXL1, RUNX1, SRSF2
ASXL1, TET2, SRSF2
ASXL1, BCOR, RUNX1

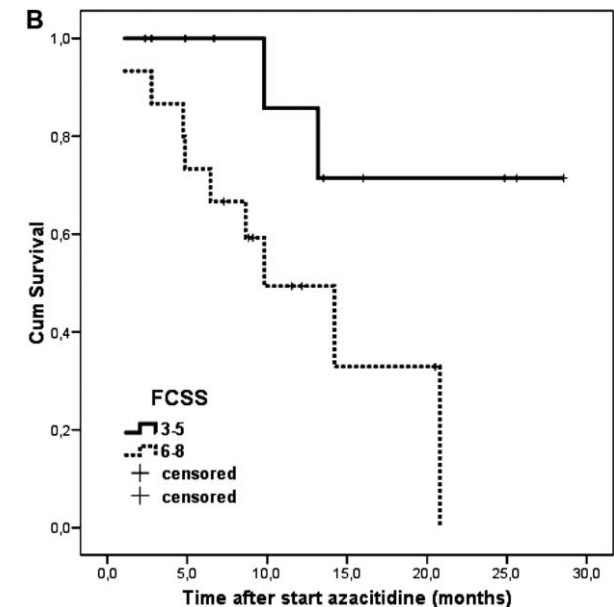
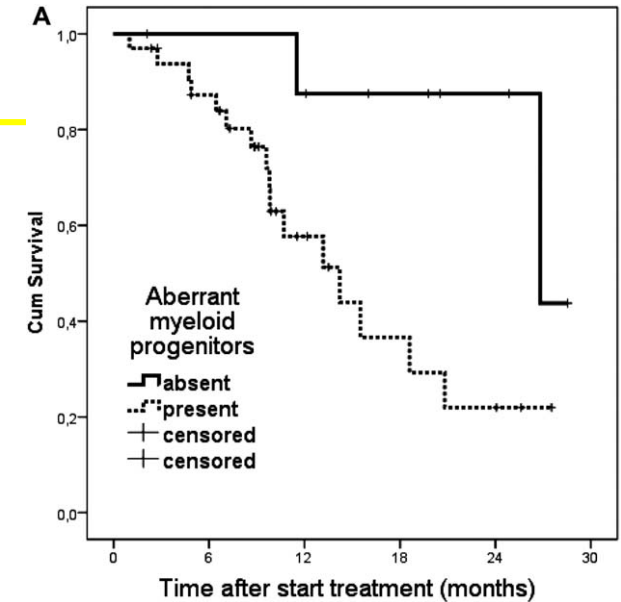


Original Article

Absence of Aberrant Myeloid Progenitors by Flow Cytometry is Associated with Favorable Response to Azacitidine in Higher Risk Myelodysplastic Syndromes

Canan Alhan,¹ Theresia M. Westers,¹ Lieke H. van der Helm,² Corien Eeltink,¹
Gerwin Huls,³ Birgit I. Witte,⁴ Francesca Buchi,⁵ Valeria Santini,⁵
Gert J. Ossenkoppele,¹ and Arjan A. van de Loosdrecht^{1*}

- presence of myeloid progenitors with aberrant immunophenotype associated with lack of response ($p < 0.02$).
- low pretreatment FCSS associated with better OS ($p < 0.03$).
- significant decrease in FCSS in patients with CR after three cycles ($p < 0.006$).

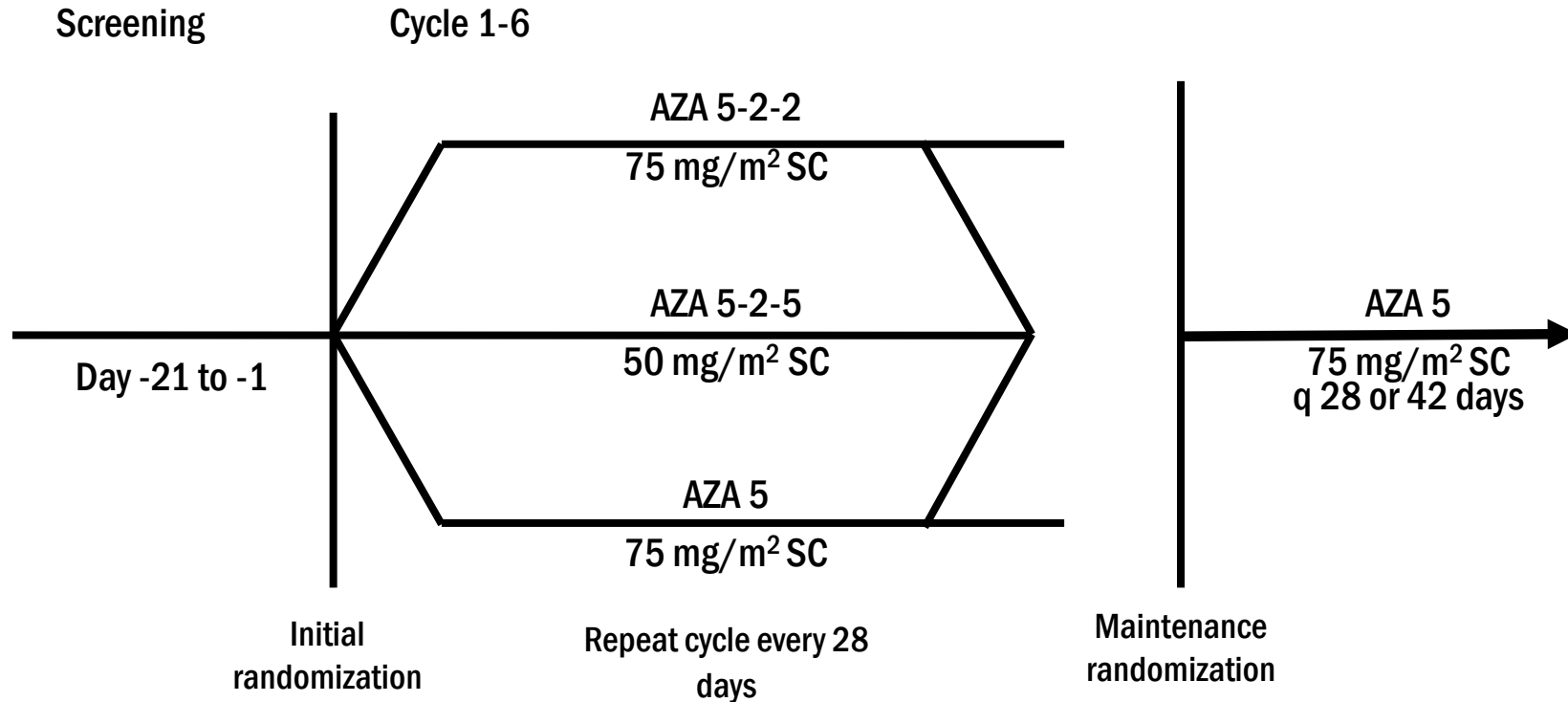


Practical use of HMAs in higher risk MDS

- Azacitidine or Decitabine ?
- In what MDS (AML), and when to start?
- Until what age ?
- Prognostic factors of response and survival?
- **What regimen?** For how long ?
- How to evaluate response ?
- How to prevent and treat side side effects?

Study of three alternative dosing schedules of azacitidine in MDS (Lyons, JCO, 2009)

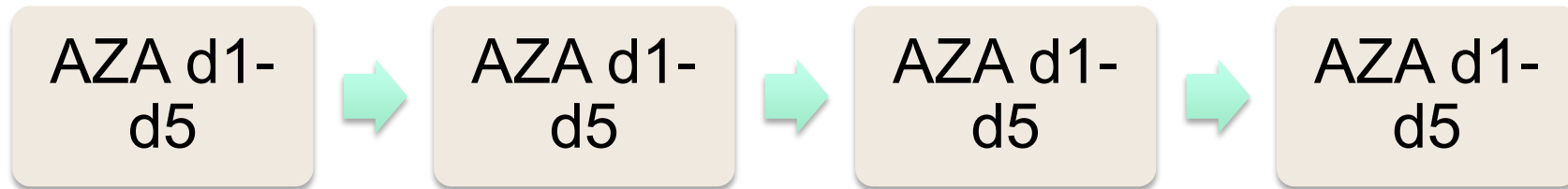
Phase II, prospective, multicenter,
randomized, open-label, 3-arm trial



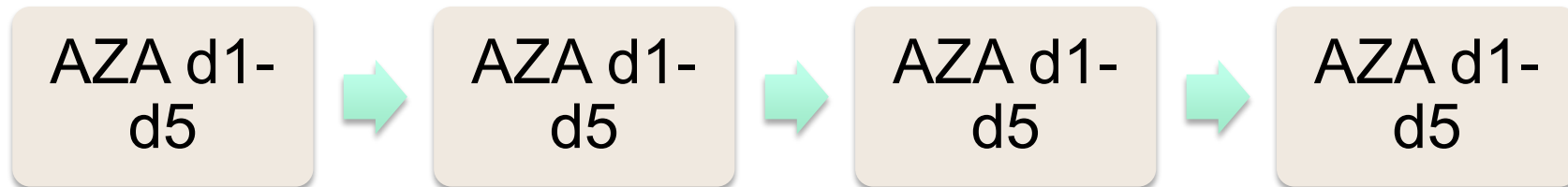
Intensified schedule of AZA (Adès, BJH 2016)

AZA 75 mg/m²/d 5 days every second week

- Cycle 1-4 every 2 weeks



- Cycles 5-8 every 3 weeks



- N=21

Intensified schedule of AZA

- **After 4 cycles**

- 1 achieved CR
- 5 PR 5 marrow CR
- 8 stable disease without HI
- and 1 progression

ORR 55%

- **After 8 cycles**

- 1 PR patient at 4 cycles achieved CR
- 5 additional responses
 - 3 marrow CR
 - 2 CR

ORR 70%

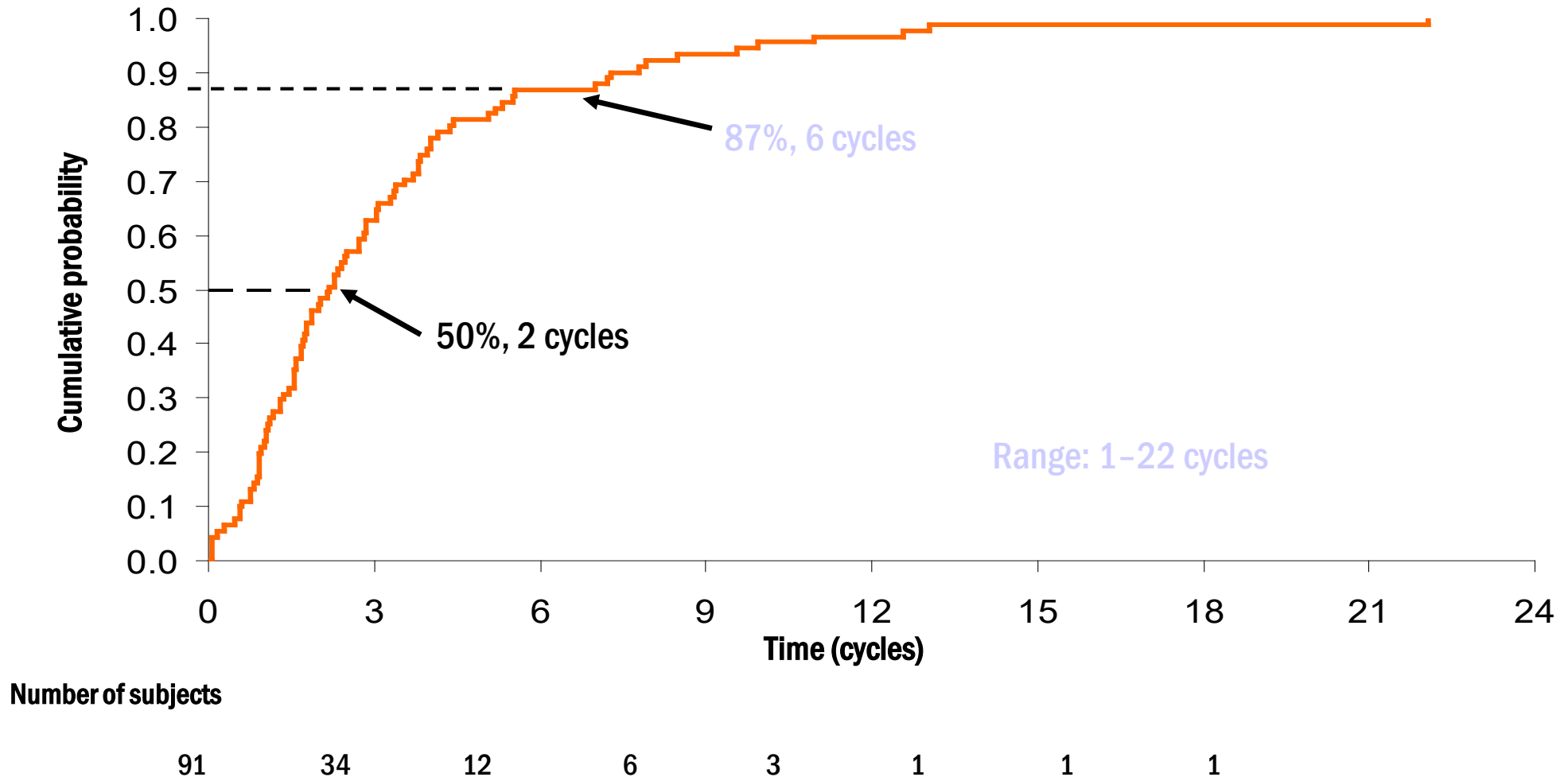
A randomized phase II trial of 5-day versus 10-day schedules of decitabine in older patients with newly diagnosed AML (Short; Lancet Hematol, 2019)

- **N= 71**
- **ORR similar in the 5-day and 10-day arms (43% versus 40%, $P=0.78$).**
- **Median OS in the 5-day and 10-day decitabine arms was 5.5 months and 6.0 months 1-year OS 25% in both arms ($P=0.47$)**

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AZA-001: number of cycles of azacitidine to first response (CR, PR or HI)



**Discontinuation of Hypomethylating Agent Therapy in Patients
with Myelodysplastic Syndromes or Acute Myelogenous
Leukemia in Complete Remission or Partial Response:
Retrospective Analysis of Survival after Long-term Follow-up**

Monica Cabrero, Elias Jabbour, Farhad Ravandi, Zach Bohannon, Sherry Pierce, Hagop M. Kantarjian, and Guillermo Garcia-Manero

**-16 higher-risk MDS or AML who achieved PR
(n=1) or CR (n=15) and stopped HMA therapy
while in response**

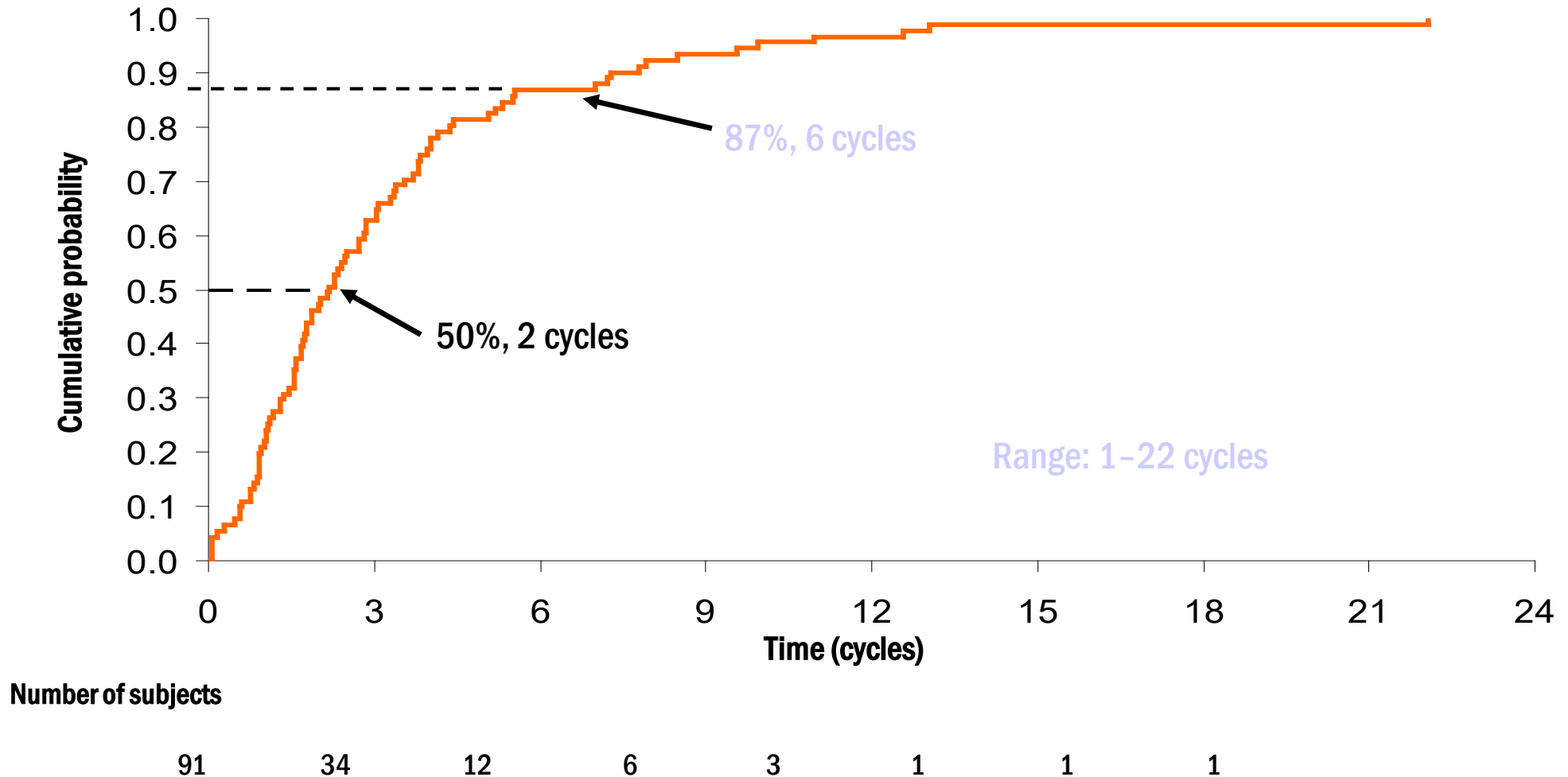
- median of 12 courses (range 1–24)

**-Loss of response after discontinuation of
therapy was rapid, with a median PFS of 4
months**

Practical use of HMAs in higher risk MDS

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AZA-001: number of cycles of azacitidine to first response (CR, PR or HI)

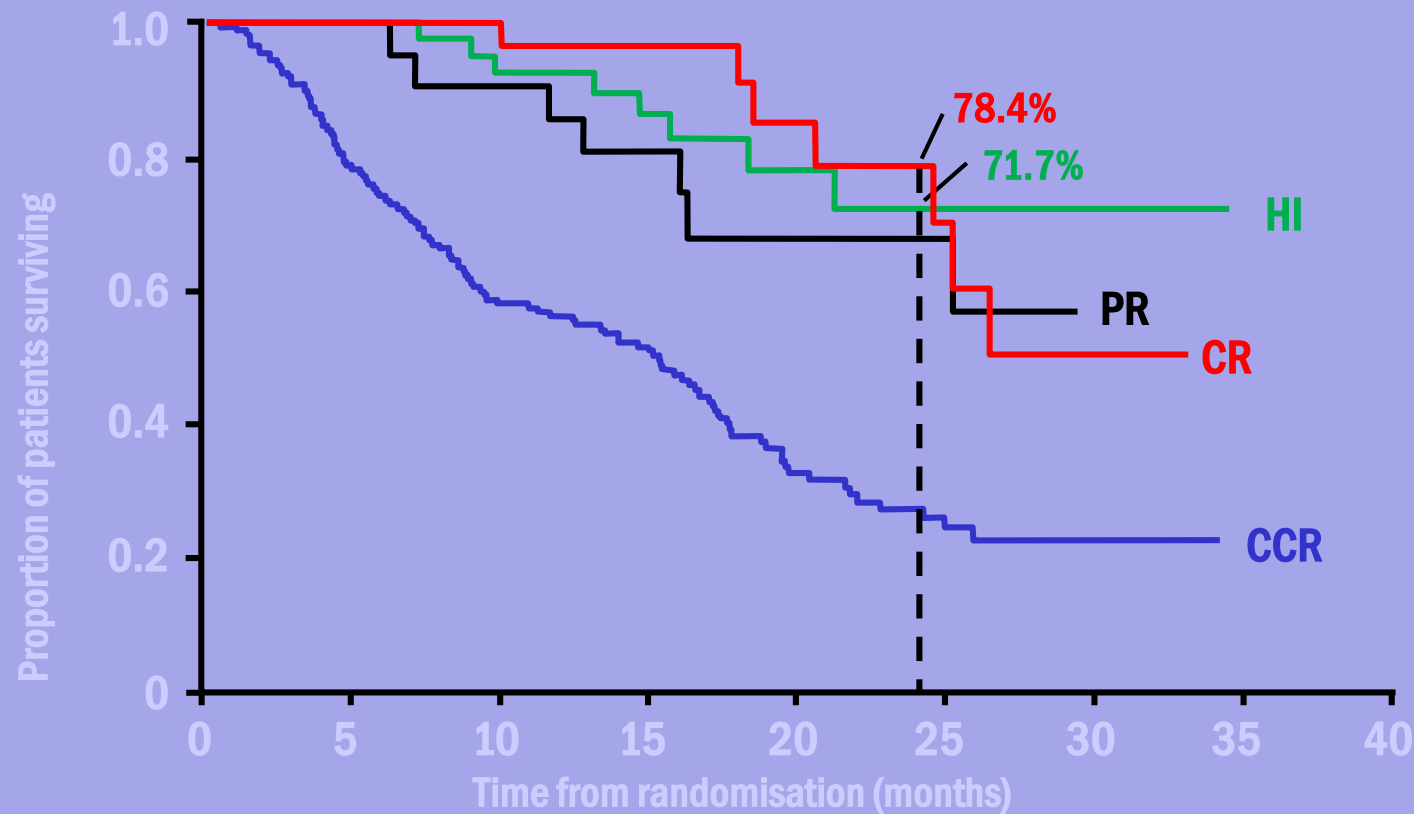




AZA 001 trial: Secondary endpoints: IWG (2000) CR, PR and HI

	AZA n=179 (%)
Overall (CR+PR)	29
CR	17
PR	12
IWG HI	
Major+minor	49
HI-E major	40
HI-P major	33
HI-N major	19

AZA-001: hematological improvement without CR or PR associated with better survival (Gore, Haematologica, 2013)

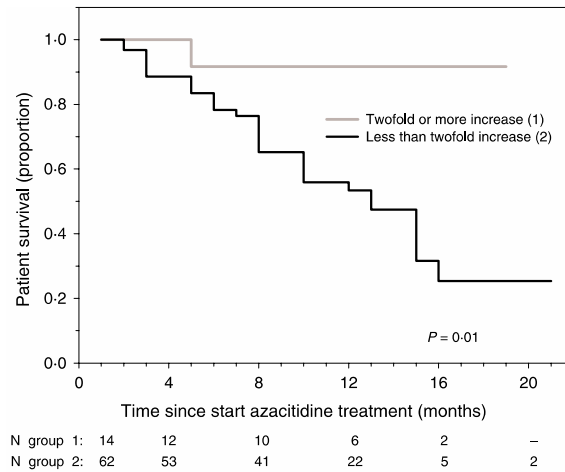


IWG = International Working Group; HI = haematological improvement
PR = partial response; CR = complete response

Adapted from List AF, et al. Oral presentation at
ASCO 2008, Chicago, IL [abstract 7006]

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

Van der Helm, BJH, 2011



Platelet response during the second cycle of decitabine treatment predicts response and survival for myelodysplastic syndrome patients

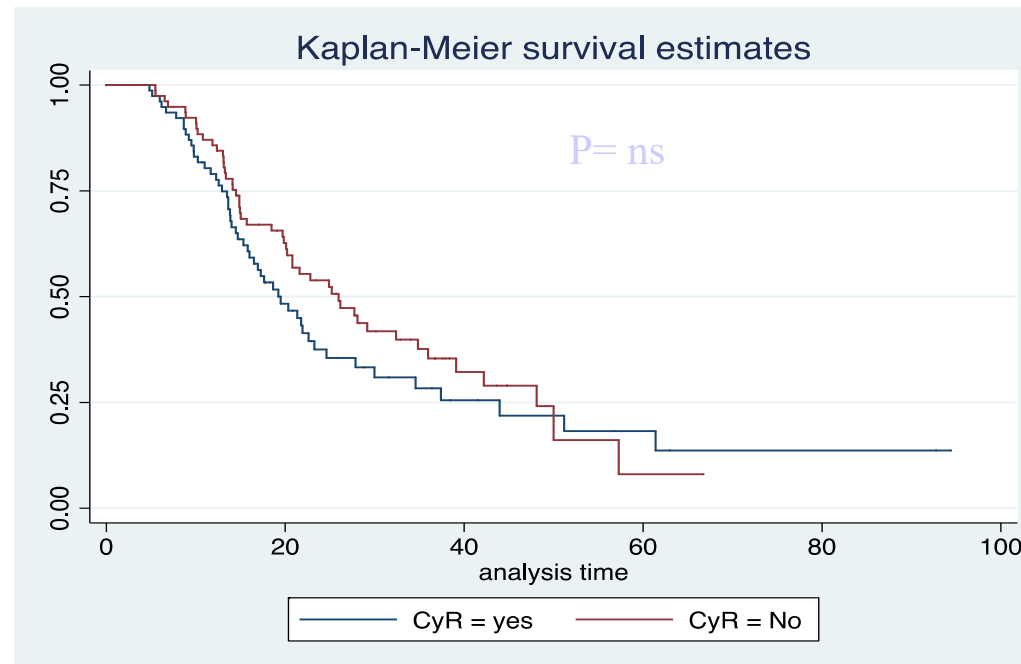
Hyun Ae Jung^{1,2}, Chi Hoon Maeng³, Moonjin Kim¹, Sungmin Kim¹, Chul Won Jung¹, and Jun Ho Jang¹

Impact Of Cytogenetics and Cytogenetic Response On Outcome In Myelodysplastic Syndromes (MDS) treated With Azacitidine (AZA). A Collaborative Study In 878 Patients

Marie Sebert^{1*}, Rami S Komrokji, MD², Mikkael A. Sekeres, MD, MS³, Thomas Prebet, MD PhD⁴, Thomas Cluzeau, MD, PhD^{5*}, Valeria Santini, MD^{6*}, Alessandro Sanna^{7*}, Najla H Al Ali^{2*}, Sean Hobson^{8*}, Virginie Eclache, MD^{9*}, Alan List, MD², Pierre Fenaux, MD, PhD¹⁰ and Lionel Ades, MD, PhD¹¹

• CYTOGENETIC RESPONSE AND SURVIVAL

- Landmark analysis at 3 months
- Comparing achievement of Cytogenetic responses or not
 - in pts with IWG 2006 response
 - in pts without IWG 2006 response



ARTICLE

Received 12 Jun 2015 | Accepted 19 Jan 2016 | Published 24 Feb 2016

DOI: 10.1038/ncomms10767

OPEN

Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents

Jane Merlevede^{1,2,*}, Nathalie Droin^{1,2,3,*}, Tingting Qin⁴, Kristen Meldi⁴, Kenichi Yoshida⁵, Margot Morabito^{1,2}, Emilie Chautard⁶, Didier Auboeuf⁷, Pierre Fenaux⁸, Thorsten Braun⁹, Raphael Itzykson⁸, Stéphane de Botton^{1,2}, Bruno Quesnel¹⁰, Thérèse Combes¹¹, Eric Jourdan¹², William Vainchenker^{1,2}, Olivier Bernard^{1,2}, Noemie Pata-Merci³, Stéphanie Solier^{1,2}, Velimir Gayevskiy¹³, Marcel E. Dinger¹³, Mark J. Cowley¹³, Dorothée Selimoglu-Buet^{1,2}, Vincent Meyer¹⁴, François Artiguenave¹⁴, Jean-François Deleuze¹⁴, Claude Preudhomme¹⁰, Michael R. Stratton¹⁵, Ludmil B. Alexandrov^{15,16,17}, Eric Padron¹⁸, Seishi Ogawa⁵, Serge Koscielny¹⁹, Maria Figueroa⁴ & Eric Solary^{1,2,20}

Serial sequencing demonstrates that the response to hypo- methylating agents is associated with changes in DNA methylation and gene expression, without any decrease in the mutation allele burden, nor prevention of new genetic alteration occurrence.

Our findings indicate that cytosine analogues restore a balanced haematopoiesis without decreasing the size of the mutated clone, arguing for a predominantly epigenetic effect.

Practical use of HMAs

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- What regimen? For how long ?
- How to evaluate response ?
- **How to prevent and treat side side effects?**

Side effects of hypomethylating agents

- **Cytopenias**
 - Anemia : transfusions
 - thrombocytopenia: transfusions
 - Neutropenia
 - G-CSF?
 - Treatment of febrile neutropenia
- **Local side effects (AZA subcutaneously)** (do not purge syringe, local treatments...)

Side effects of hypomethylating agents

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 - Infection prophylaxis ?
- **Local side effects (AZA subcutaneously)** (do not purge syringe, local treatments...)

Predicting infections in high-risk patients with MDS/AML treated with azacitidine: A retrospective multicenter study

D Merkel Am J Hemat, 2013

- **153 infectious events during 928 treatment cycles (16.5%) administered to 100 patients**
- **114/153 (75%) events required hospitalization and 30 (19.6%) were fatal**
- **In multivariate analysis, only low Hb level, low PLT count, and unfavorable cytogenetics remained predictive of infection**

Prognostic Factors of Severe Infections, and Effect of Primary Anti-Infectious Prophylaxis in MDS Patients Treated with Azacitidine (AZA). A Single Center Study On 144 Patients

Valérie Vidal^{1*}, Marie Sebert^{2*}, Sylvain Thepot^{3*}, Thorsten Braun^{4*}, Claude Gardin^{5*}, Sabine Brechignac^{6*}, Pierre Fenaux, MD, PhD⁷ and Lionel Ades, MD, PhD⁷

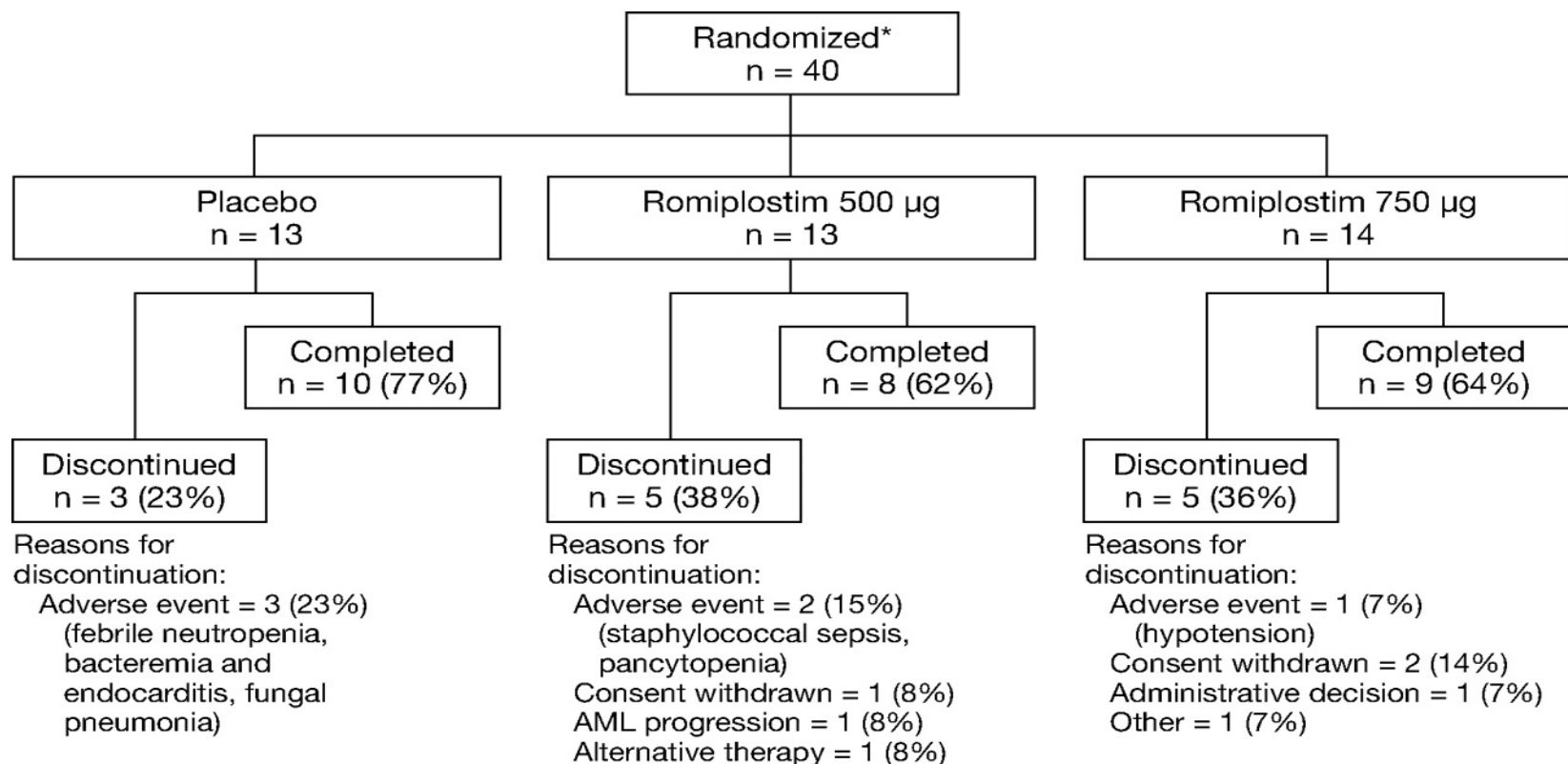
- Prophylactic treatment with **levofloxacin-posaconazole**
- During the 6 first cycles
- Prospective studies needed

Side effects of hypomethylating agents

- **Cytopenias**
 - Anemia : transfusions
 - thrombocytopenia: transfusions (+TPO agonists ?)
 - Neutropenia
 - G-CSF?
 - Treatment of febrile neutropenia
 - Infection prophylaxis ?
- **Local side effects (AZA subcutaneously)** (do not purge syringe, local treatments...)

Phase 2 study of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving azacitidine therapy

Hagop M. Kantarjian, Francis J. Giles, Peter L. Greenberg, Ron L. Paquette, Eunice S. Wang, Janice L. Gabrilove, Guillermo Garcia-Manero, Kuolung Hu, Janet L. Franklin and Dietmar P. Berger



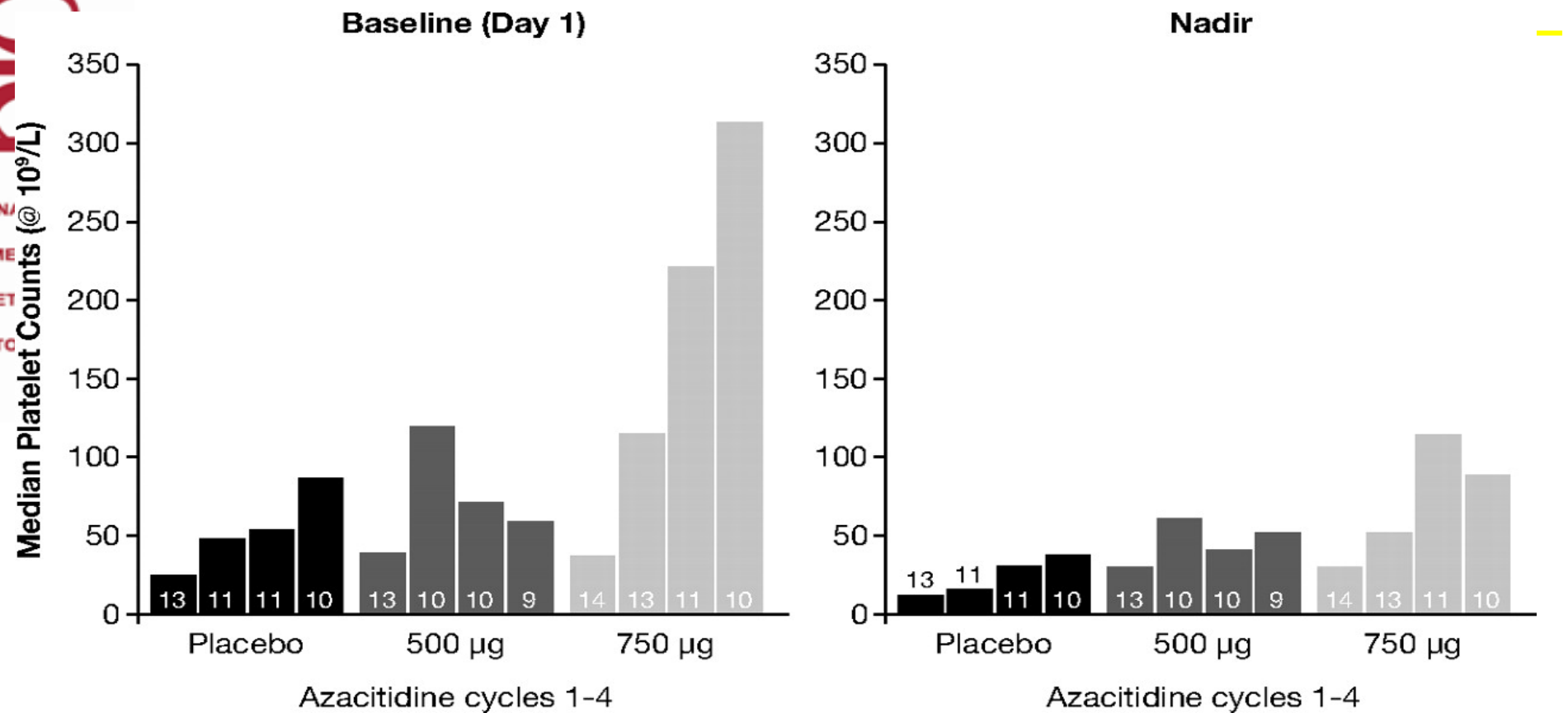
Kantarjian H M et al. Blood 2010;116:3163-3170



Blood

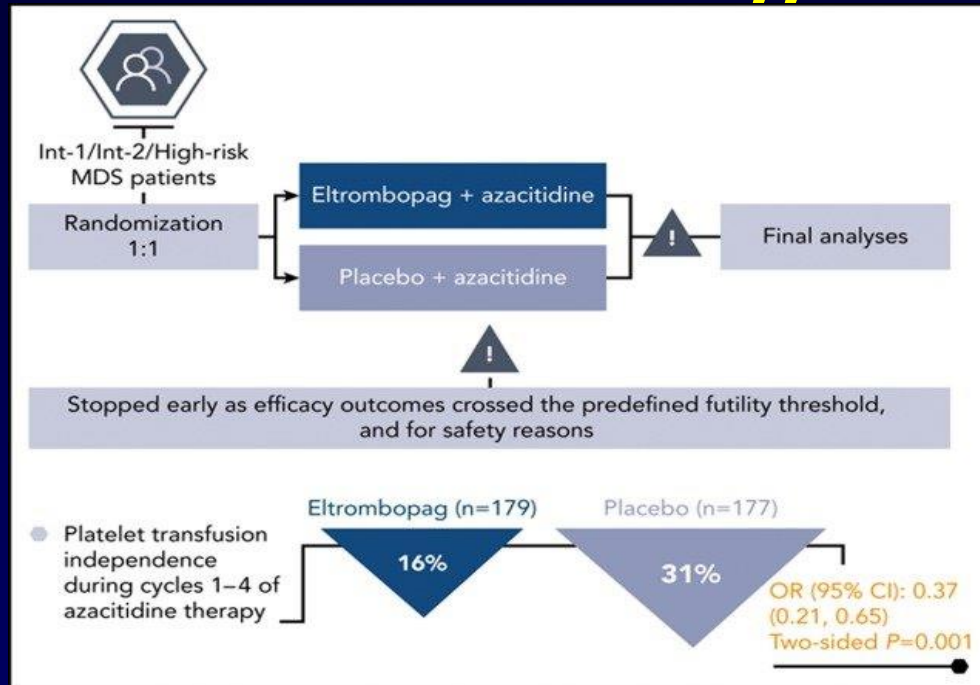
JOURNAL
OF THE
AMERICAN
SOCIETY
OF
HEMATOLOGY

omiplostim on median platelet counts on day 1 of each treatment cycle (left panel) and on median platelet counts at nadir during each treatment cycle (right panel).



Kantarjian H M et al. Blood 2010;116:3163-3170

Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia (Dickinson, Blood, 2018)



- Overall response in 20% and 35% of eltrombopag and placebo patients, respectively

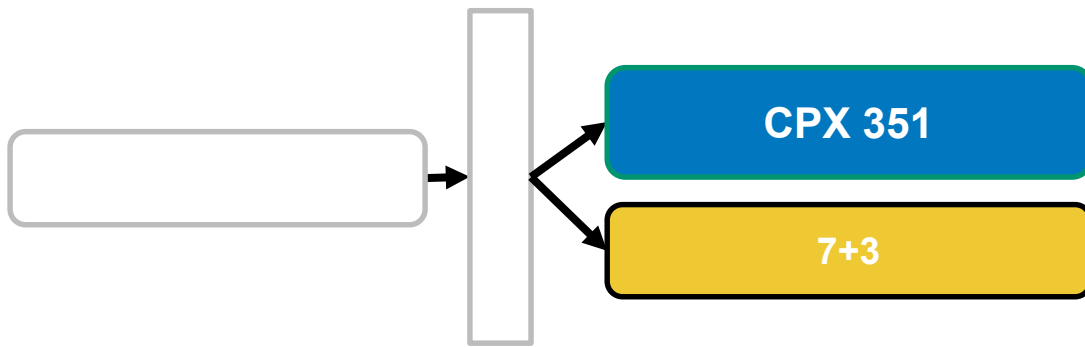
Hypomethylating agents in MDS

- Practical use of HMAs in MDS
- Perspectives

Perspectives

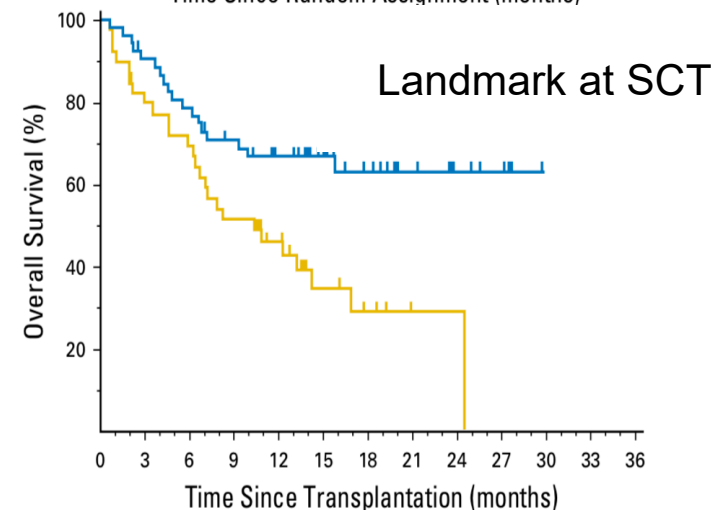
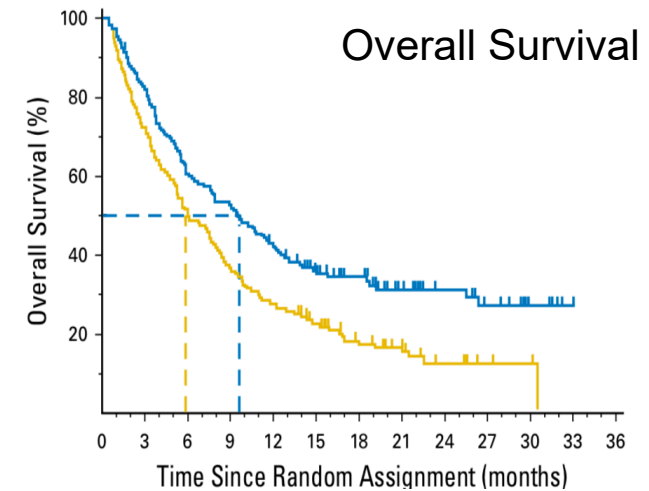
- **A new competitor to HMAs ?**
- **New HMAs ?**
- **Combinations ?**

CPX-351 (cytarabine and daunorubicin) Liposome 7+3 in Older Patients With sAML



CPX-351 significantly improves :

- Median overall survival versus 7+3 (9.56 v 5.95 months)
- Remission rate (47.7% v 33.3%; $P = .016$)
- Outcome after SCT



ORIGINAL ARTICLE

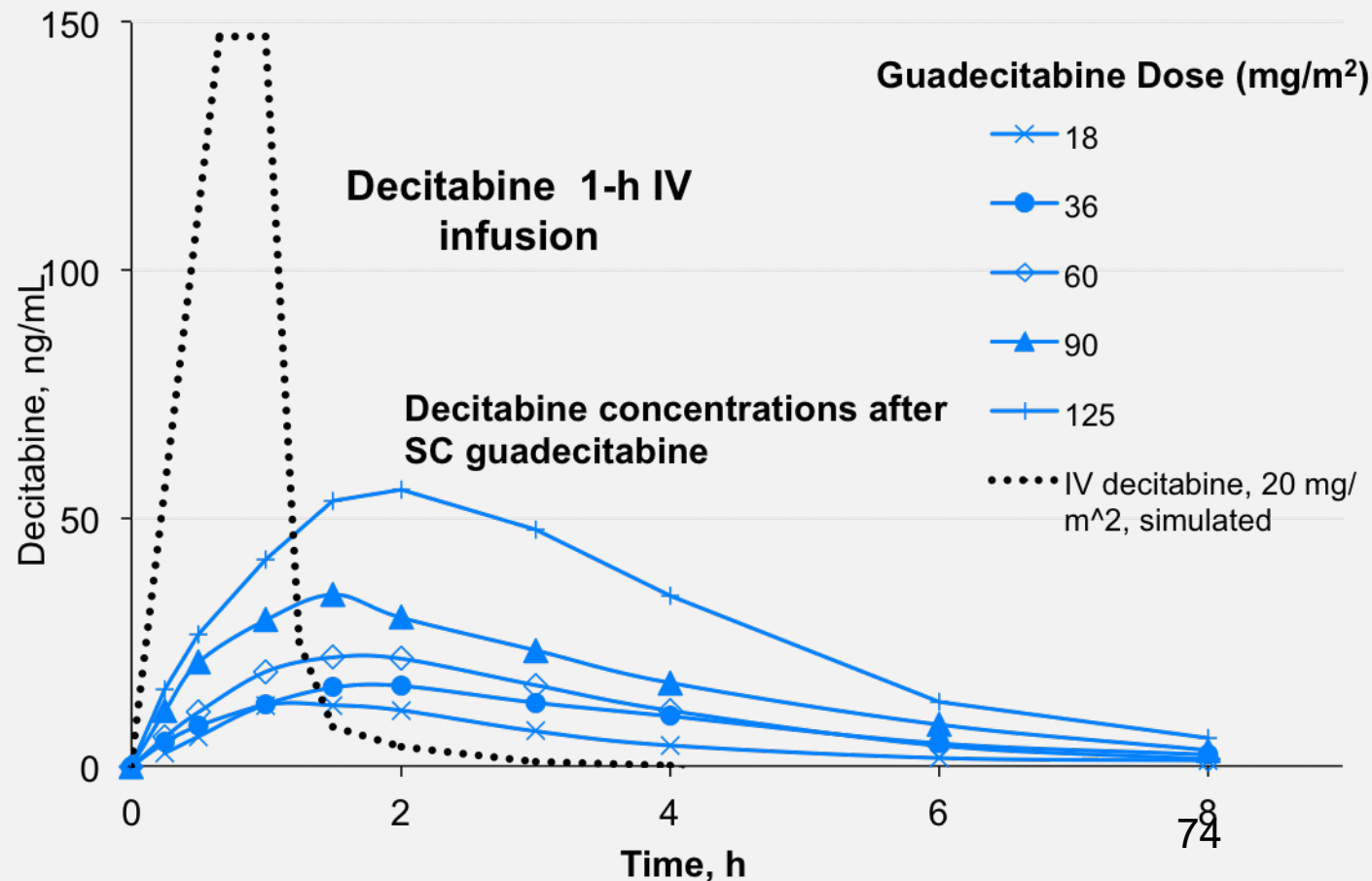
Efficacy and safety of extended dosing schedules of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes

G Garcia-Manero¹, SD Gore², S Kambhampati³, B Scott⁴, A Tefferi⁵, CR Cogle⁶, WJ Edenfield⁷, J Hetzer⁸, K Kumar⁸, E Laille⁸, T Shi⁸, KJ MacBeth⁸ and B Skikne⁸

- **Patients with lower-risk myelodysplastic syndromes (MDS) received 300 mg CC-486 once daily for 14 days (n = 28) or 21 days (n = 27) of repeated 28-day cycles**
- **Median number of CC-486 treatment cycles was 7 (range 2–24) for the 14-day dosing schedule and 6 (1–24) for the 21-day schedule.**
- **Overall response 36% of patients receiving 14-day dosing and 41% receiving 21-day dosing.**

Guadecitabine (SGI-110): A Next Generation Hypomethylating Agent

- Guadecitabine is a dinucleotide of decitabine and deoxyguanosine resistant to deamination by cytidine deaminase, prolonging *in vivo* exposure to active metabolite decitabine (8-12 h decitabine exposure vs 3-4 h for decitabine IV)



ASTRAL-1, a Phase 3 Randomized Trial of Guadecitabine vs Treatment Choice (TC) in Treatment-Naïve Not Eligible for Intensive Chemotherapy (EHA 2019)

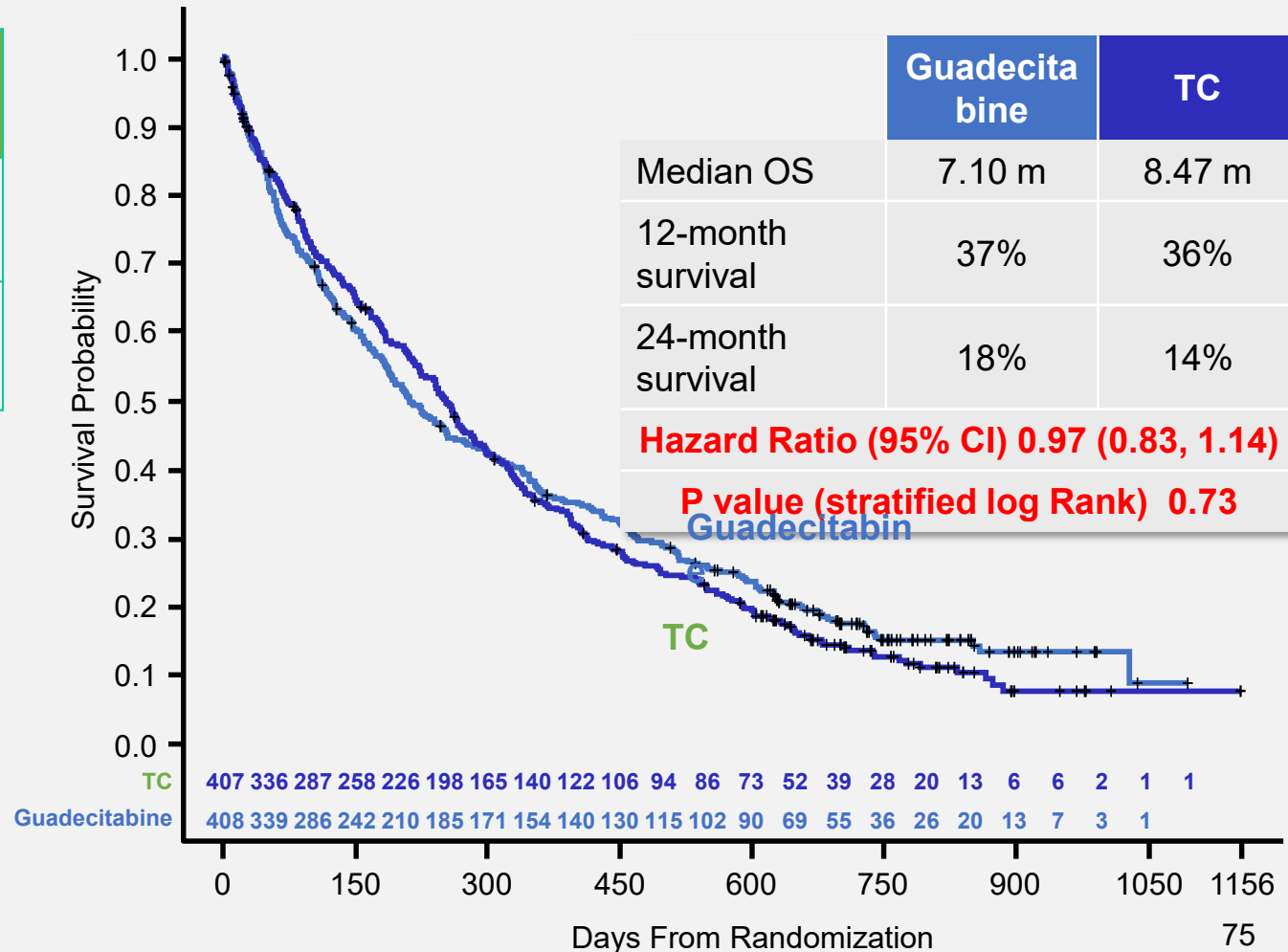
Complete Response (CR)

Guadecitabine	TC
79 (19.4%)	71 (17.4%)
Stratified p value	0.48

Median Time to CR (min, max): months

Guadecitabine	TC
4.5 (1.9, 19.1)	4.4 (1.9, 15.1)

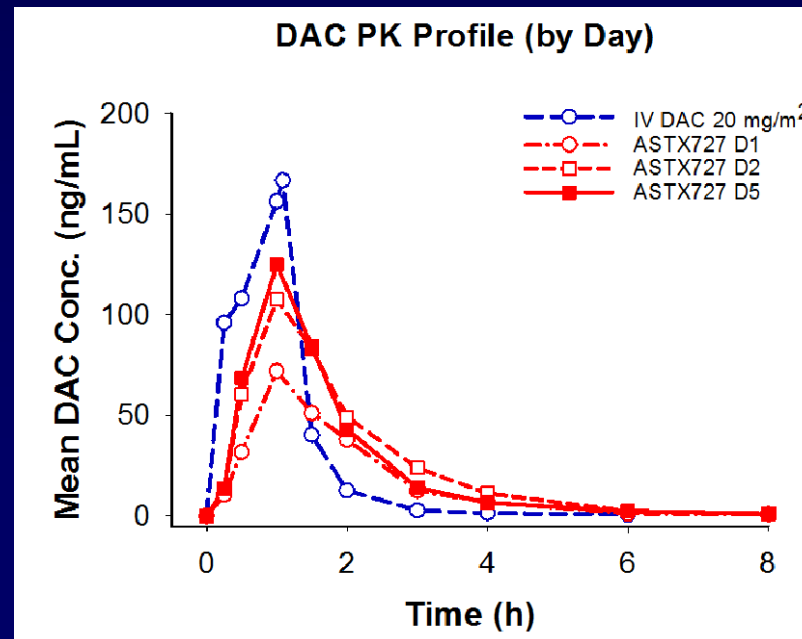
Overall Survival



ASTX 727: An oral fixed-dose combination of decitabine and cedazuridine in MDS : a multicentre, open-label, dose-escalation, phase 1 study

Savona MR, Lancet Hematol, 2019

- 43 patients
- Decitabine 30 mg and 40 mg plus cedazuridine 100 mg produced mean day-5 decitabine AUCs closest to the mean intravenous-decitabine AUC



HMAAs + other drugs

- « not targeted »
 - Venetoclax
 - Pevonidostat
 - Glasdegib
- « targeted »
 - IDH1 and IDH 2 inhibitors
 - APR 246
- Triple associations ?
- Myelosuppression a key factor

Conclusion

- **An HMA alone probably not sufficient except in older patients**
- **Combinations especially before HSCT?**
- **CPX 351 a strong competitor of HMAs except in patients with complex monosomal karyotype ?**

Department of hematology and immunology, St Louis, R Debré, Avicenne hospitals (APHP and Paris University)

Hôpital St Louis

- 7 servicios de hematología (H Dombret, N Boissel, G Socié, B Arnulf, E Oksenhendler, P Fenaux, C Thiéblemont)
- Servicio de reanimación (E Azoulay)
- Servicio de neumología (A Tazi)

Hôpital Robert Debré

- Servicio de pediatría hematológica (A Baruchel)
- Unidad de tratamiento de anemia falciforme (M Benkerrou)

Hospital Avicenne

- Servicio de hematología (C Gardin)



Groupe Francophone des Myélodysplasies

- Activates clinical trials in MDS (35 centers in France and Belgium + Switzerland,)
- Website: www.gfmgroup.org
- Online registry of French MDS cases
- Close cooperation with:
 - a patient support group
 - the International MDS Foundation
 - the European Leukemia Net

