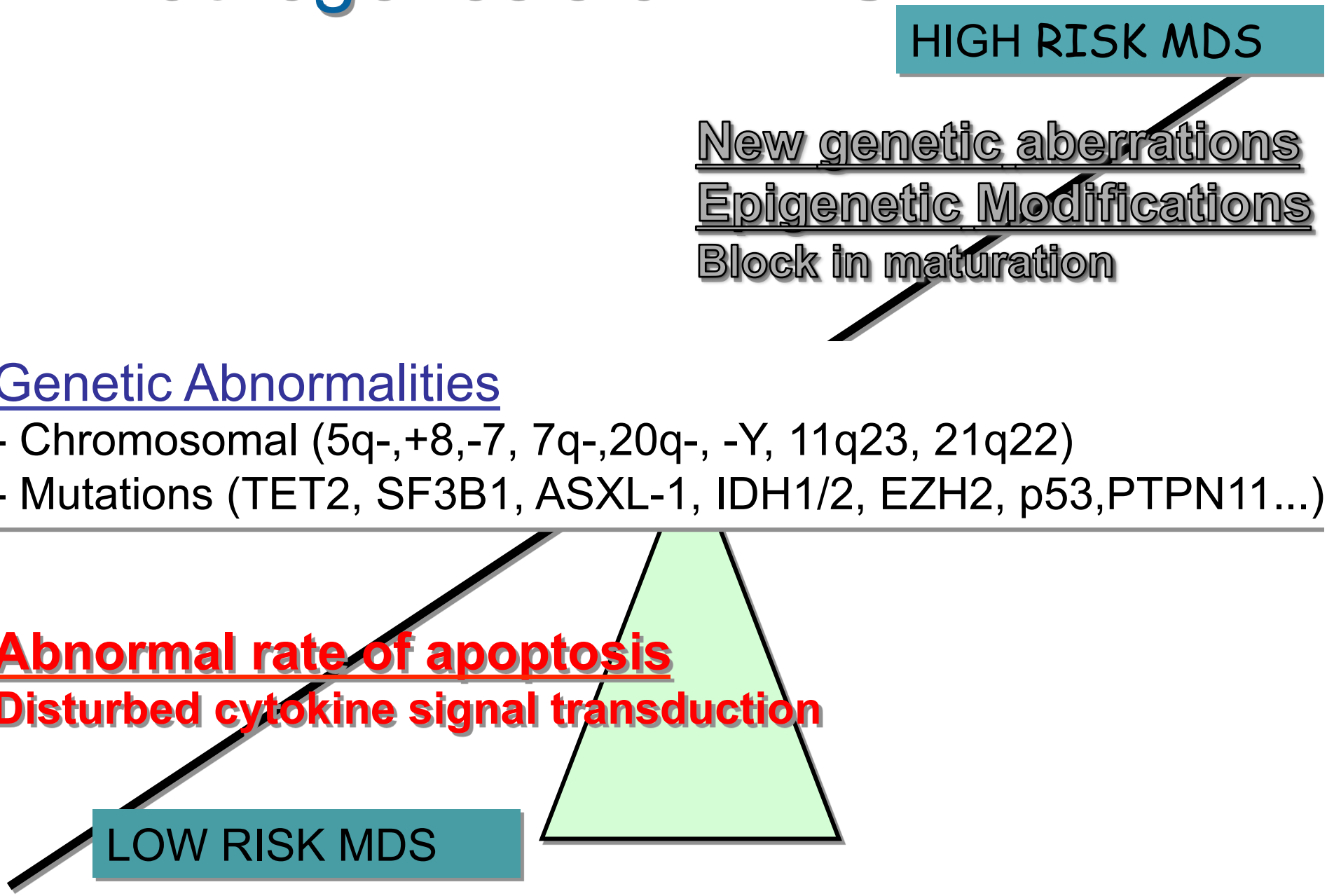
Opzioni terapeutiche per il paziente ad alto rischio

Impossibile visualizzare l'immagine. La memoria del computer potrebbe essere insufficiente per aprire l'immagine oppure l'immagine potrebbe essere danneggiata. Riavviare il computer e aprire di nuovo il file. Se viene visualizzata di nuovo la x rossa, potrebbe essere necessario eliminare l'immagine e inserirla di nuovo.

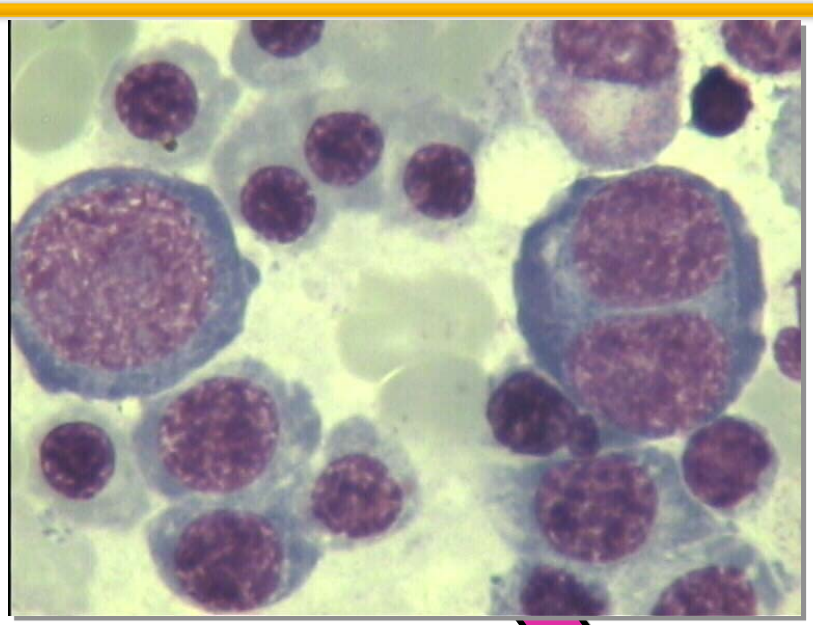
Valeria Santini

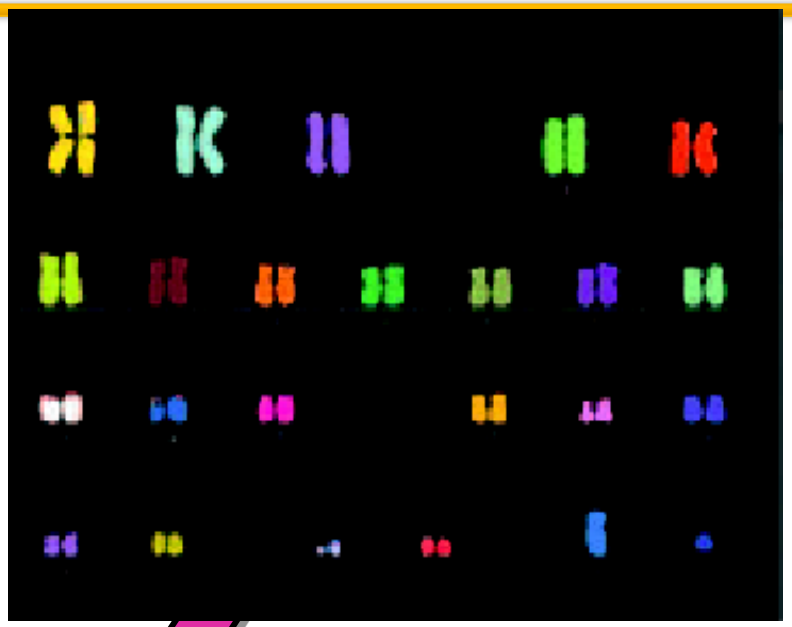
UF Ematologia, Università di Firenze

Pathogenesis of MDS



Myelodysplastic syndromes are a constellation of cytopenias with difficult diagnosis

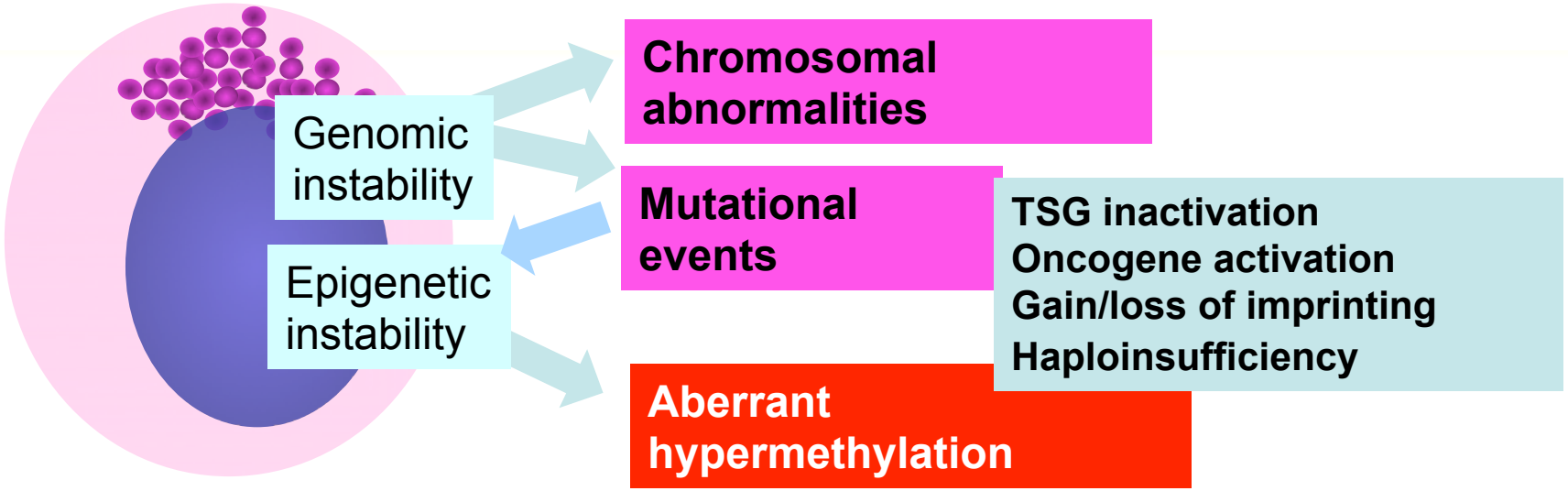


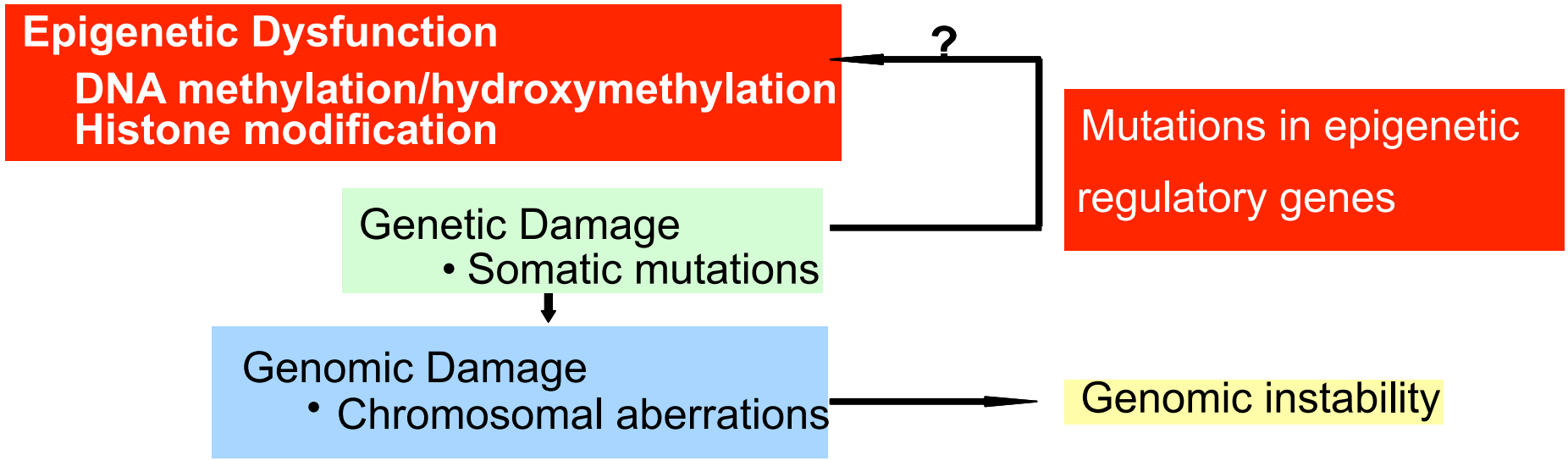


An accurate diagnosis is the basis for successful prognostic stratification (and treatment) of MDS

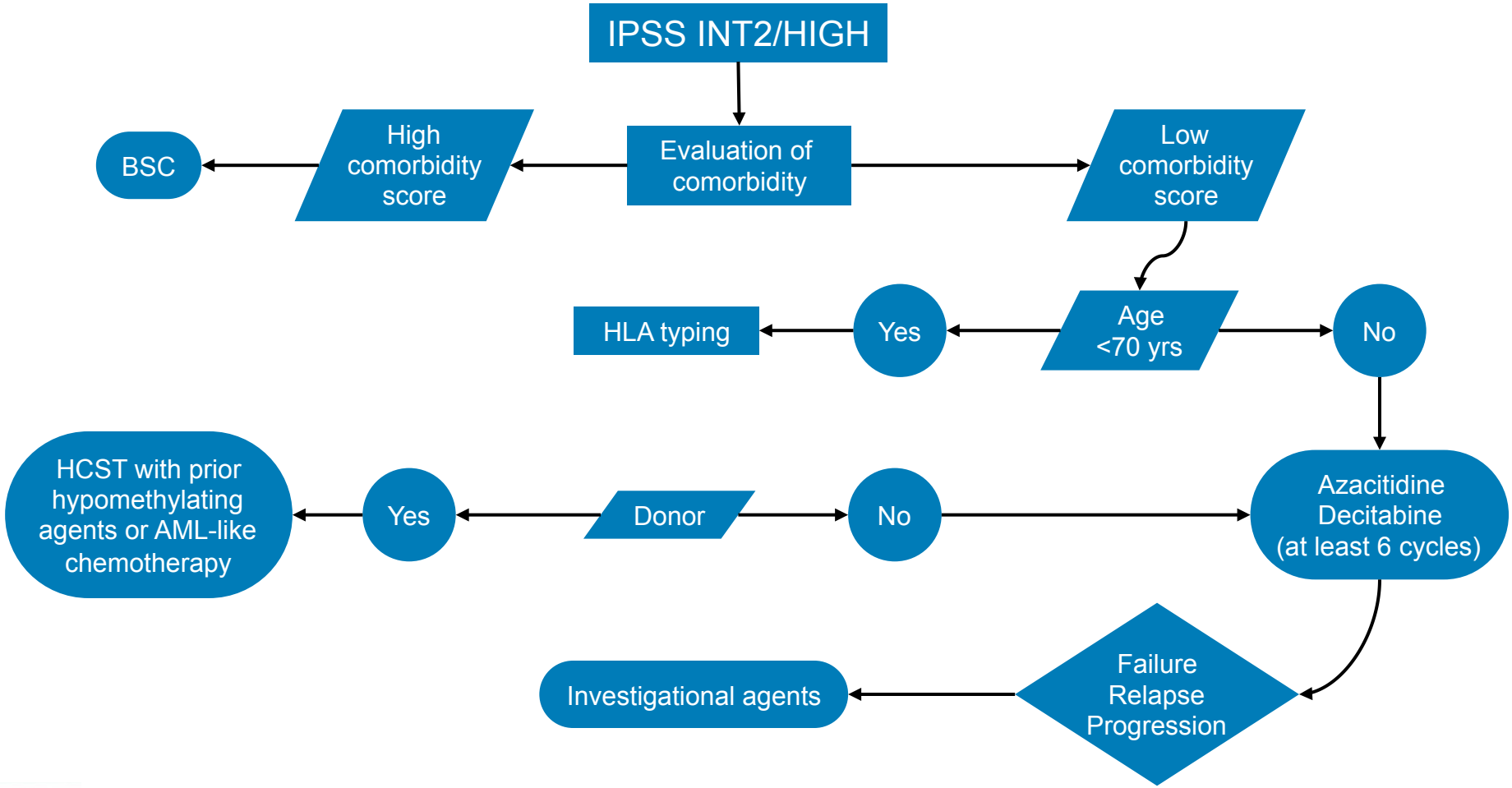
Criteria: presence and number of dysplastic lineages , percentage of bone marrow blasts, cytogenetic abnormalities, somatic mutations

MOLECULAR PATHOGENESIS OF MDS

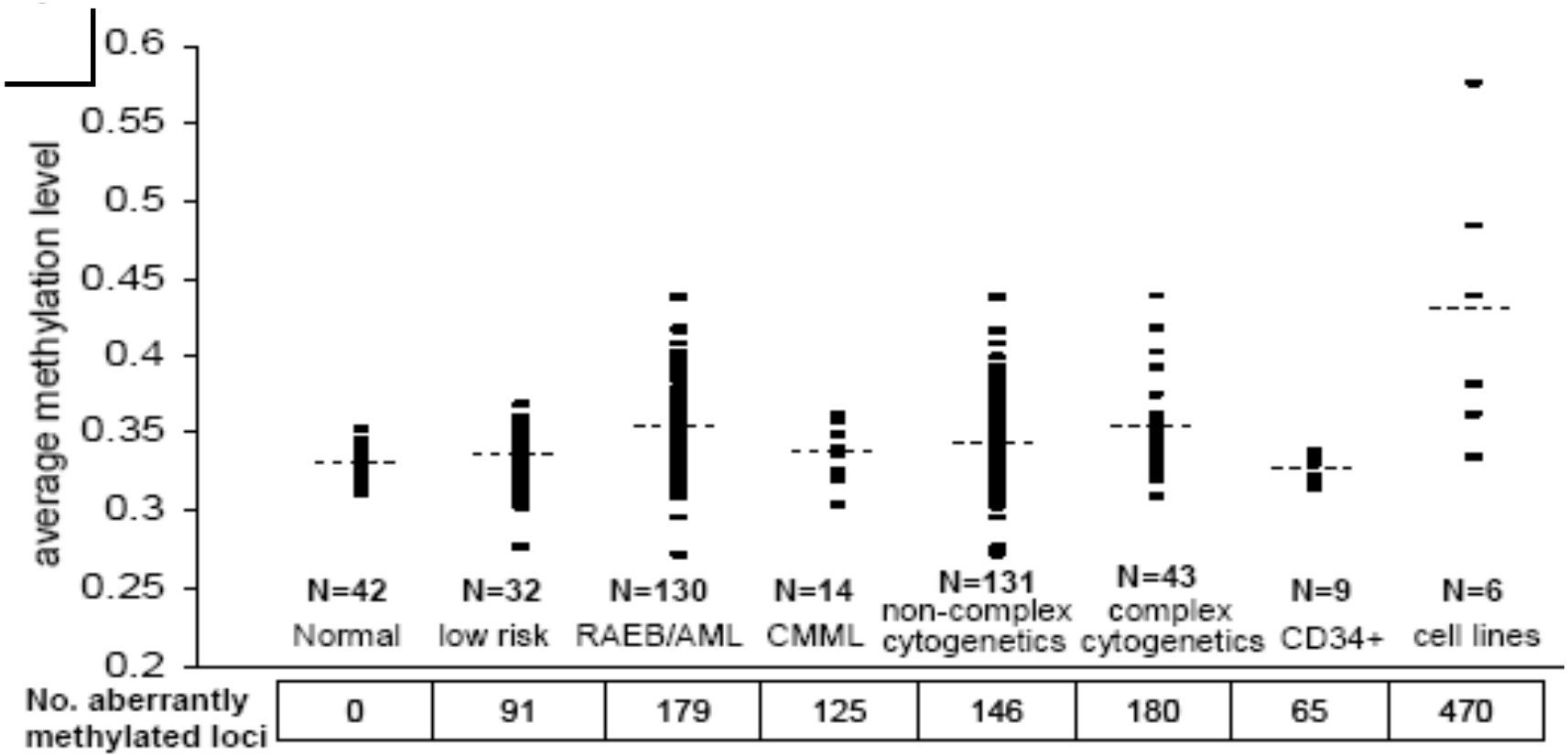




Therapeutical options

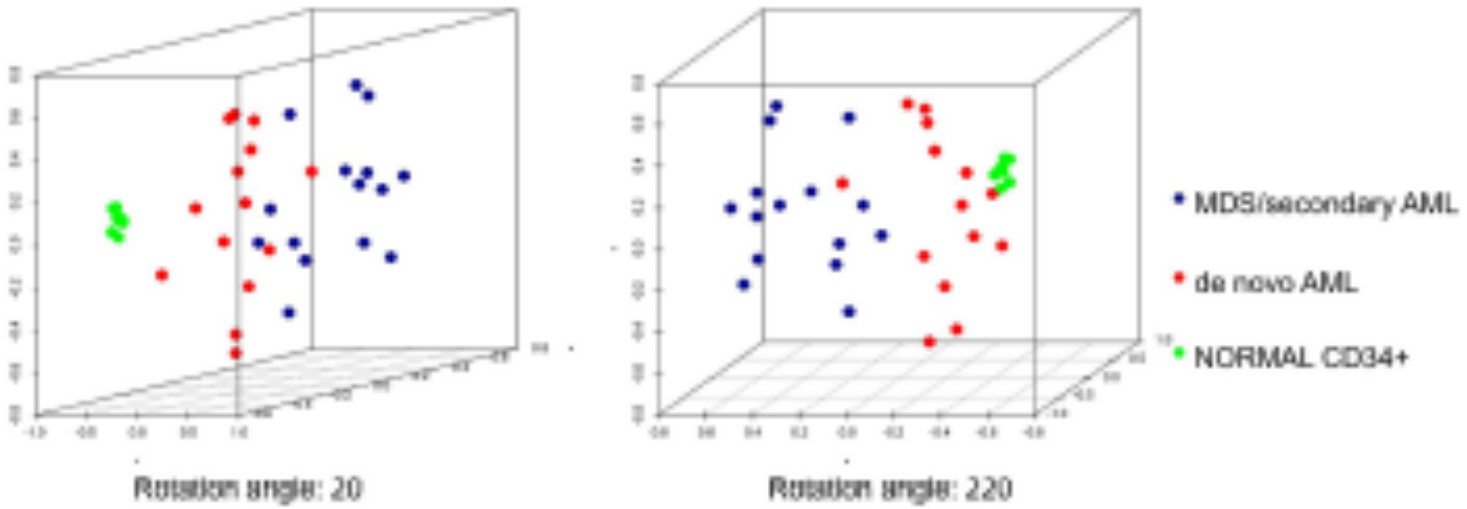


Aberrant promoter methylation correlates with disease evolution (methylation array)



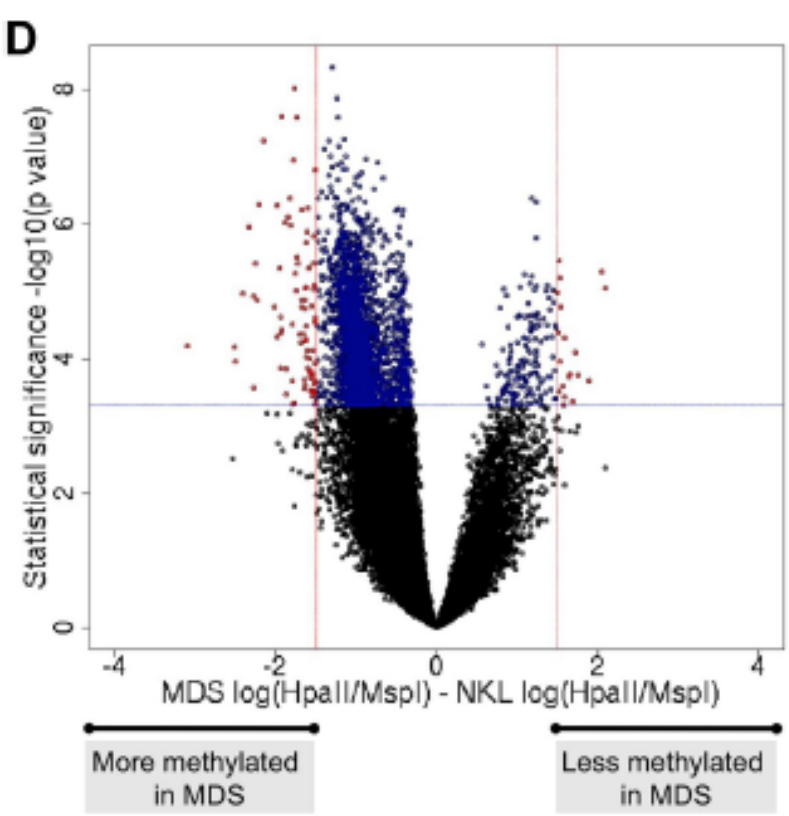
Jiang Y, et al. Blood 2009;113: 1315–25

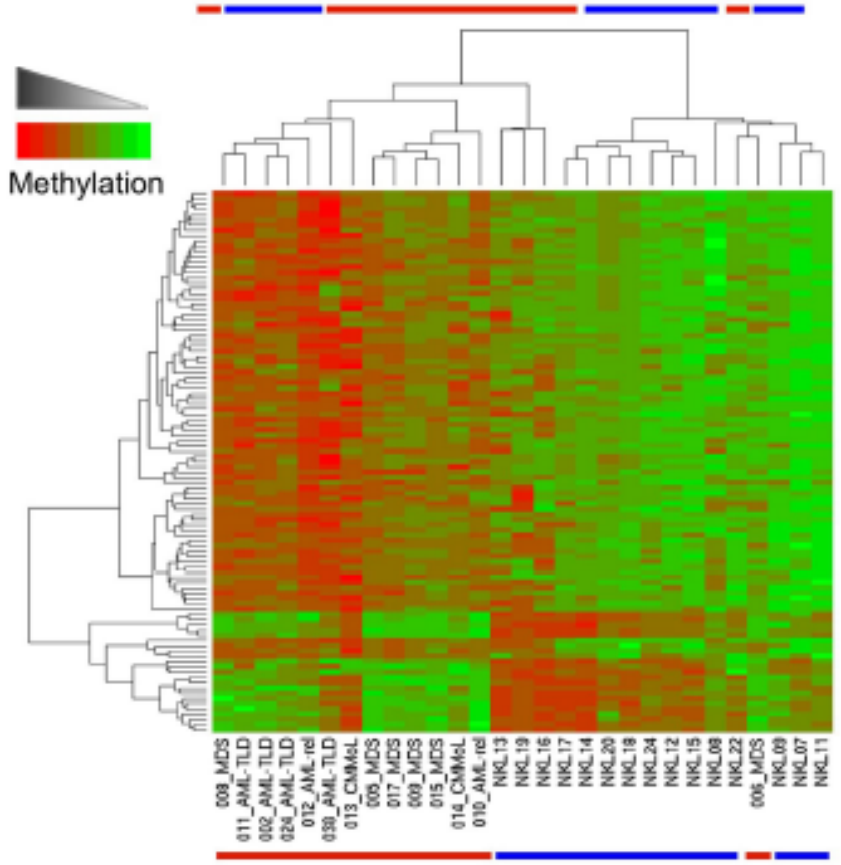
Methylation is more abundant in MDS cells than in AML



Figueroa ME et al; Blood 2009 114: 3448-3458

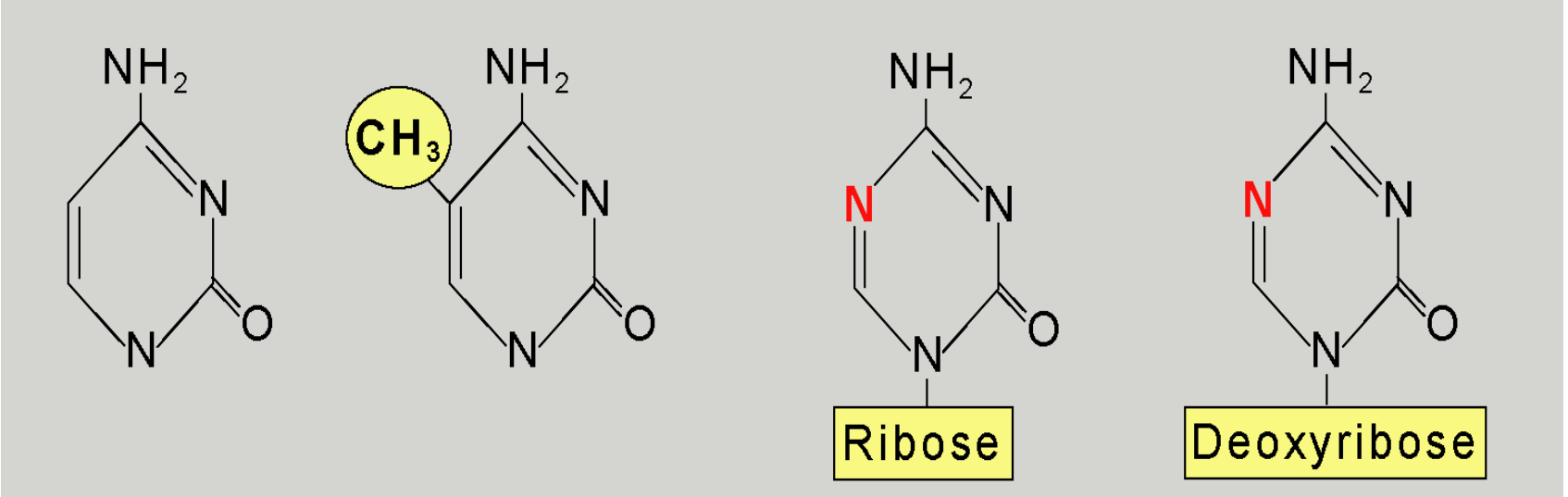
Methylation is more abundant in MDS cells than in AML





Figueroa ME et al; Blood 2009 114: 3448-3458

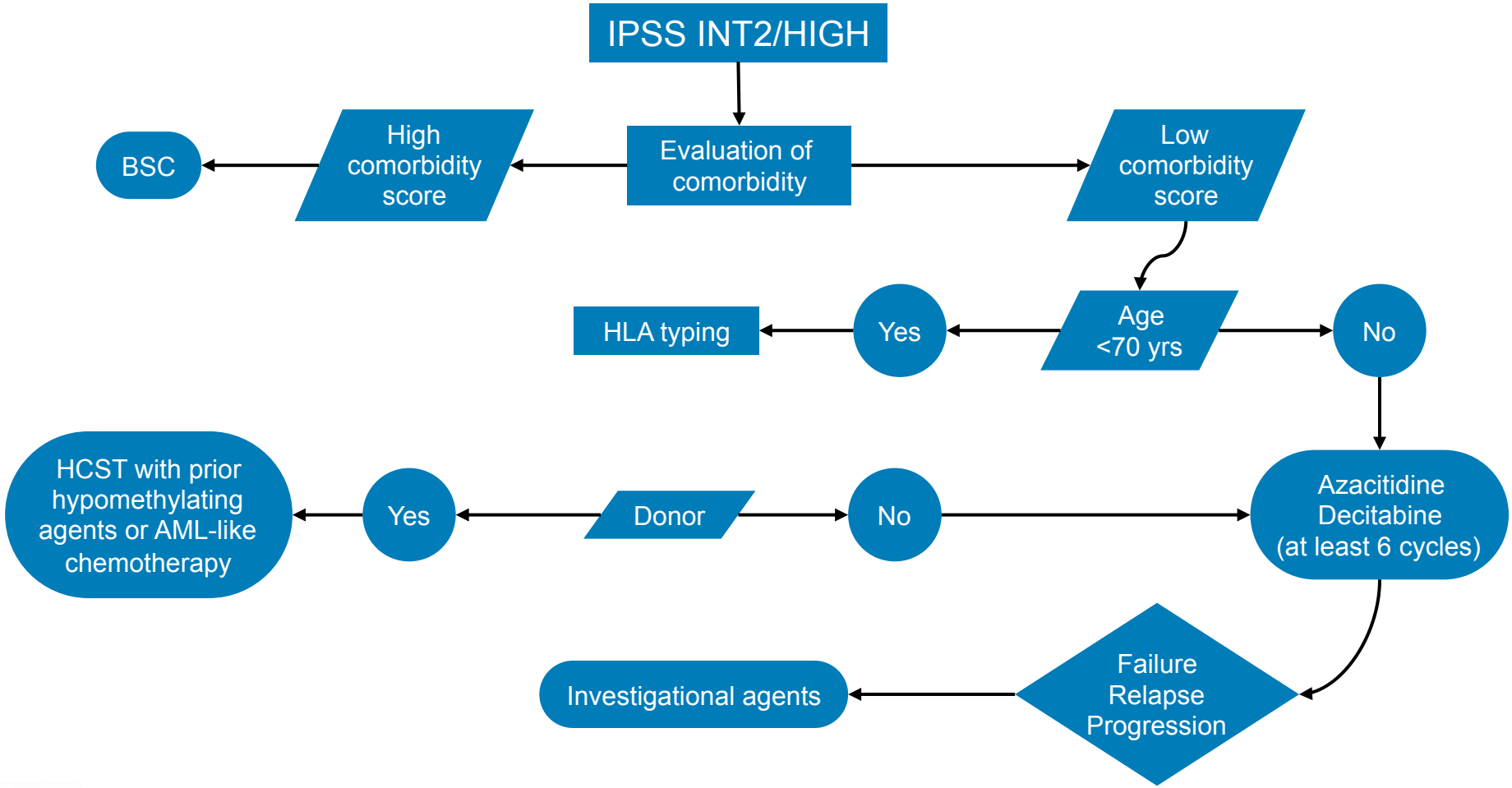
Azanucleosides, Cytosine Analogues with hypomethylating properties



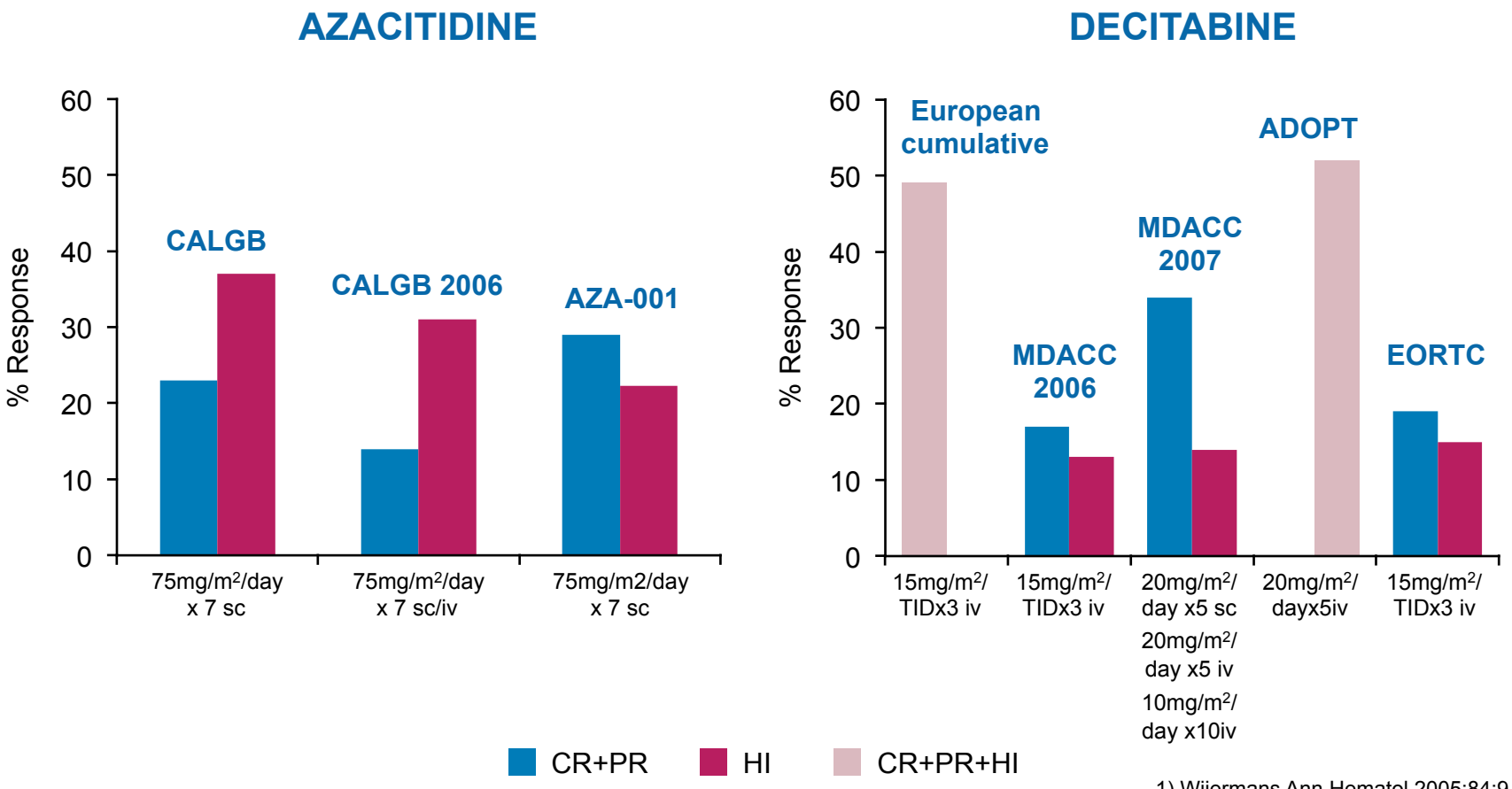
Cytosine	5-methyl-cytosine	5-aza-cytidine	5-aza-2'-deoxy-cytidine
		Azacitidine	Decitabine

Santini et al, Ann Int Med 2001

Therapeutical options



Hypomethylating agents in higher risk MDS: response

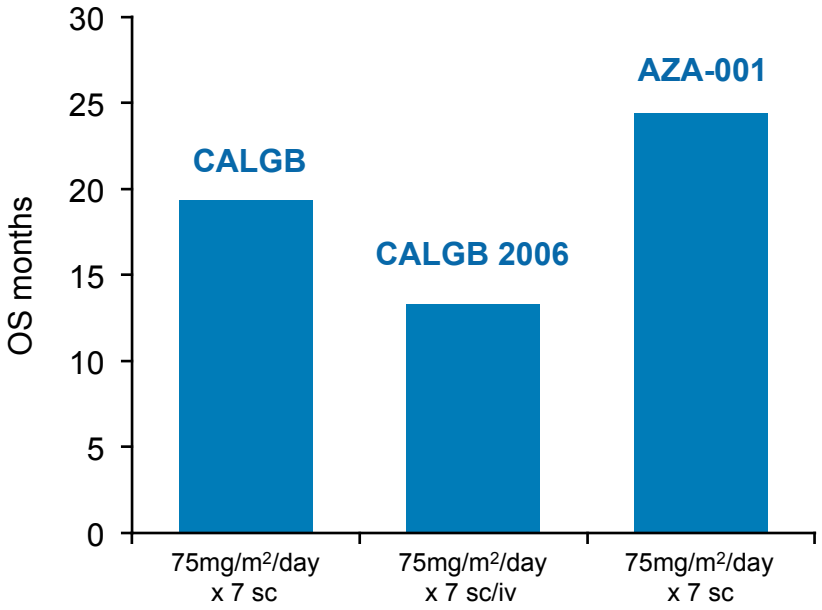


1) Silverman JCO 2002;20:2429
2) Silverman JCO 2006;24:3895
3) Fenaux Lancet Oncol 2009;10:223.

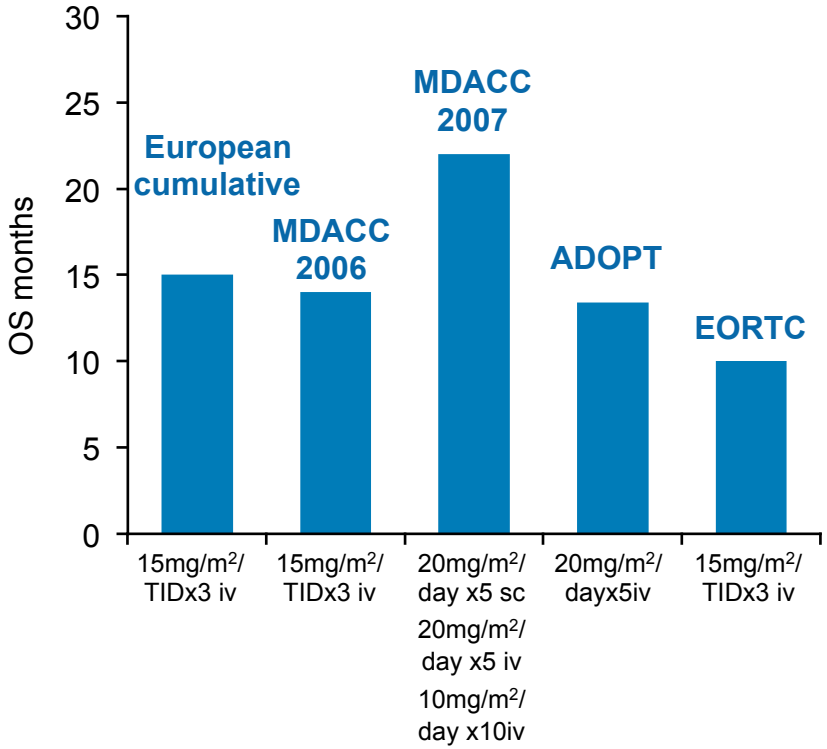
1) Wjiermans Ann Hematol 2005;84:9
2) Kantarjian Cancer 2006;106:1794
3) Kantarjian Blood 2007;109:52
4) Steensma JCO 2009;24:3842
5) Luebbert JCO 2011;29:1987

Hypomethylating agents in higher risk MDS: Overall survival

AZACITIDINE



DECITABINE



1) Silverman JCO 2002;20:2429
2) Silverman JCO 2006;24:3895
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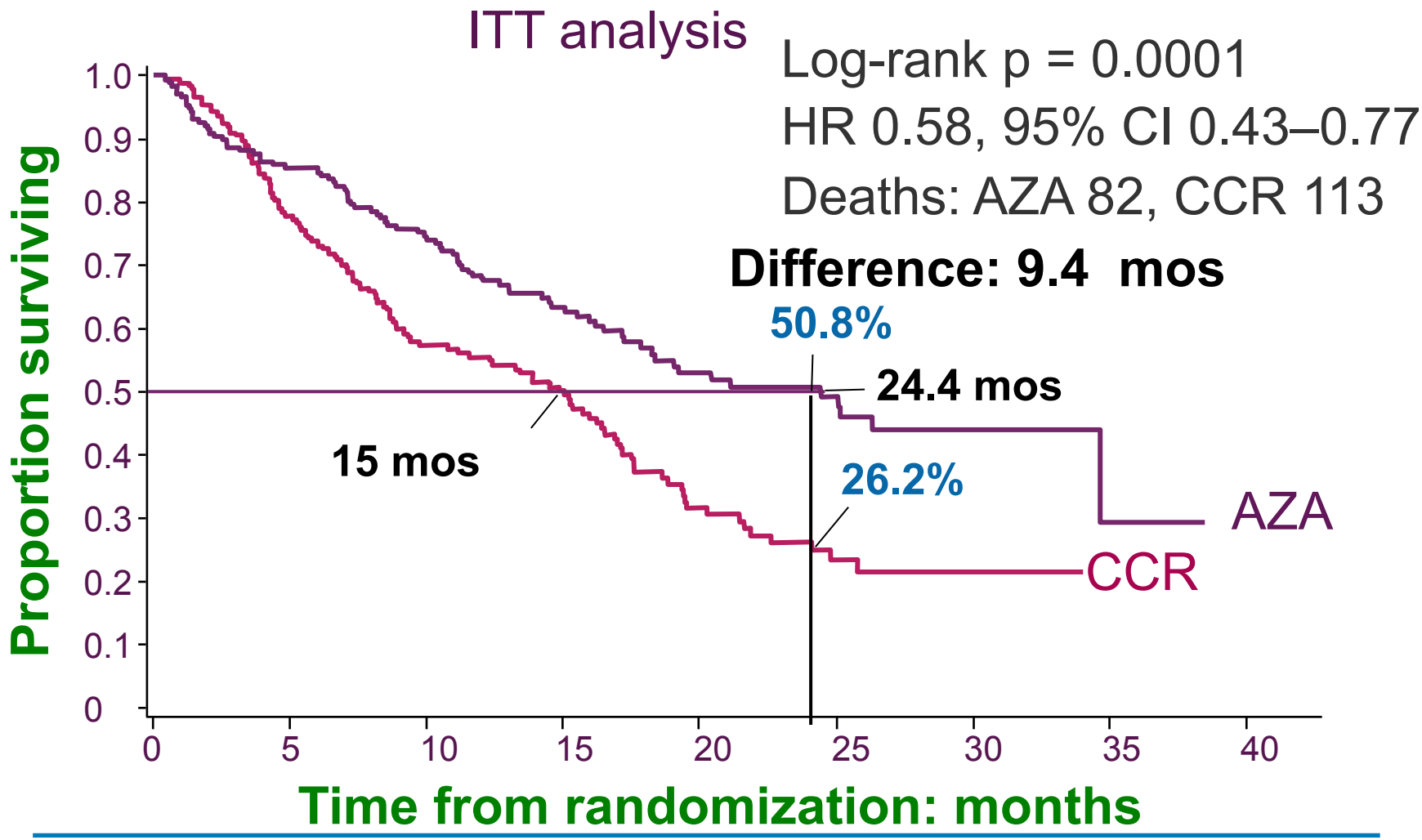
1) Wjiermans Ann Hematol 2005;84:9
2) Kantarjian Cancer 2006;106:1794
3) Kantarjian Blood 2007;109:52
4) Steensma JCO 2009;24:3842
5) Luebbert JCO 2011;29:1987

Response duration with decitabine or azacitidine therapy ranges from 6 to 26 months

Overall survival: AZA vs CCR



CI, confidence interval; ITT, intention-to-treat.

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

Cosa sappiamo degli agenti ipometilanti

I loro effetti si notano dopo 2-4 cicli di terapia

Anche solo il raggiungimento del miglioramento ematologico garantisce prolungamento della sopravvivenza

I pazienti con cariotipo complesso possono avere risposta, ma di breve durata

L'interruzione della terapia provoca perdita della risposta MA…

I pazienti ricaduti or esistenti hanno una sopravvivenza estremamente breve

References: JCO 201129: 1987;Lancet Oncol 2009 10:223; JCO 2009 27:3842; Blood 2007 109:52; Cancer 2006 106:1794; JCO 2002; Cancer 2010 116:3830; JCO 2011 29:3322; Leukemia 2011 25:1207)

MDS: treatment with HMT

Advantages:

prolonged survival

high rate hematologic improvement

no need of hospitalization

low toxicity

feasible in very elderly patients

Disadvantages:

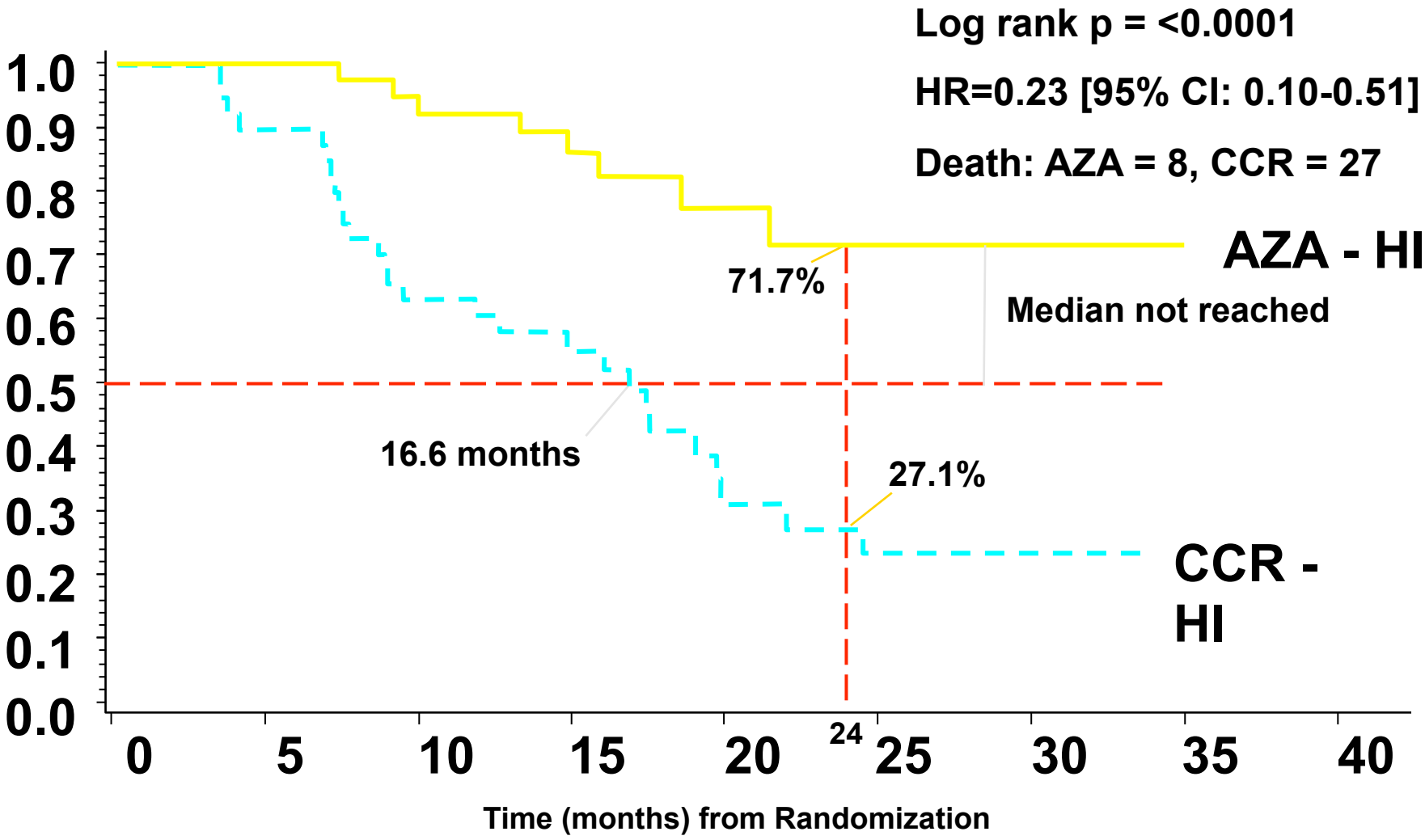
prolonged treatment

retarded effect

relapse/resistance

no eradication of the clone

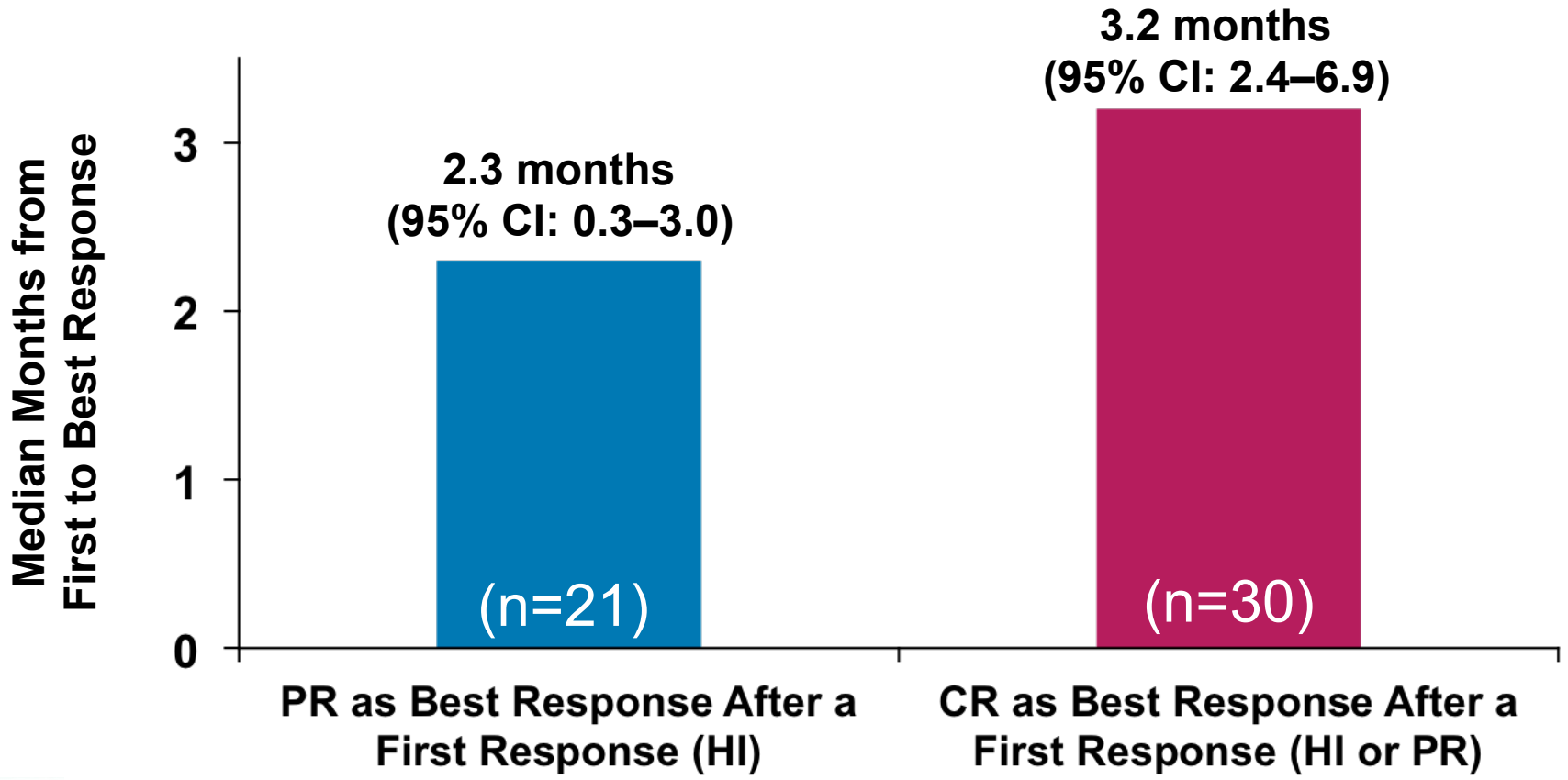
AZA vs CCR: OS in Pts with Best Response of HI



Gore S, et al, Haematologica. 2013 Jul;98(7):1067-72.

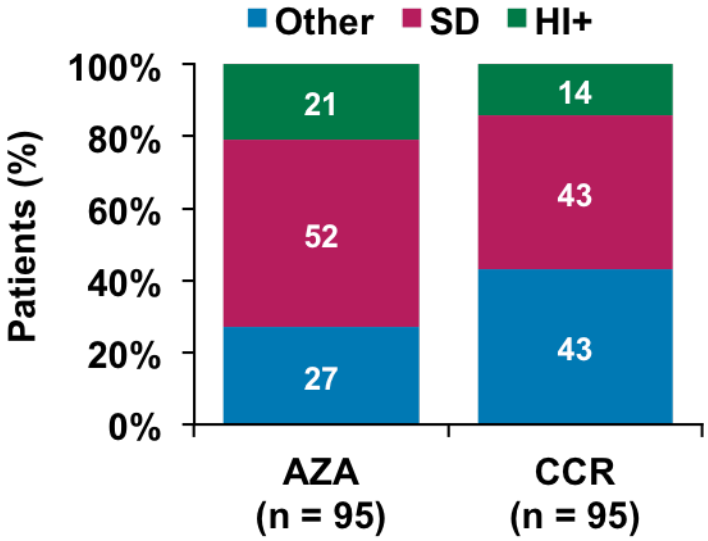
AZA-001: time from first to best response

Continued azacitidine dosing led to a higher IWG response category in **48%** of patients

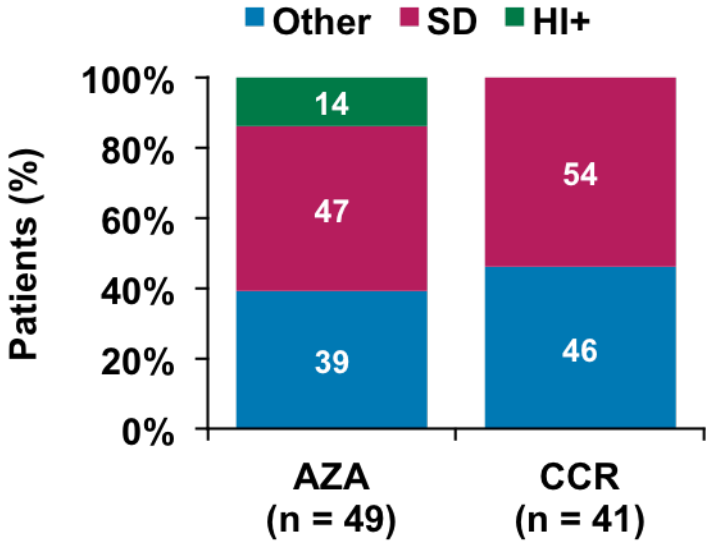


AZA-001 – Multivariate Analysis: Continued AZA Improved Responses Beyond Stable Disease

Response at 6 months for patients with SD at 3 months



Response at 9 months for patients with SD at 6 months



- 21% of AZA-treated patients compared with 14% of CCR-treated patients with SD at 3 months achieved an HI+ by 6 months
- 14% of AZA-treated patients compared with 0% of CCR-treated patients with SD at 6 months achieved an HI+ by 9 months

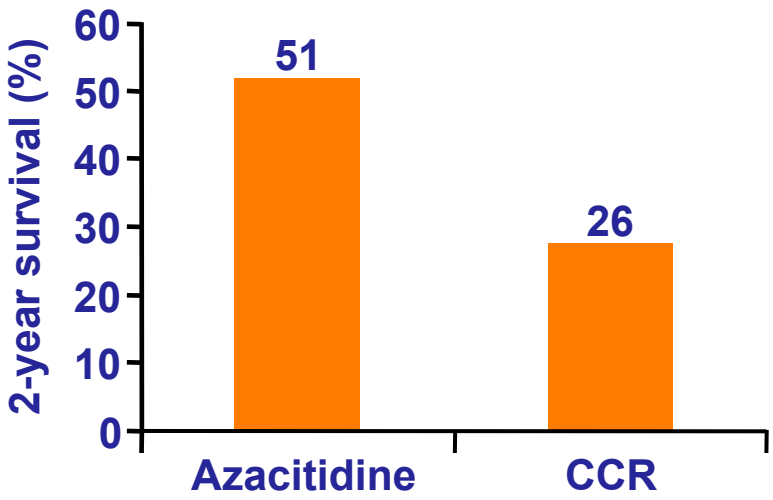
AZA, azacitidine; CCR, conventional care regimen; CR, complete response/remission; HI, hematologic improvement; HI+, CR, PR, and/or HI; OS, overall survival; PR, partial response/remission; SD, stable disease.

Gore S, et al. *J Clin Oncol.* 2010;28:abstract 6503.

Elderly MDS patients respond to azacitidine treatment

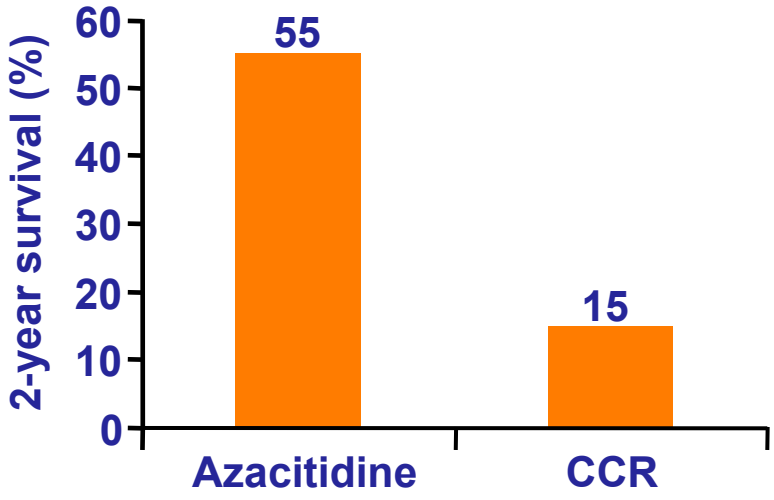
2-year survival (all patients)[1]

p<0.0001



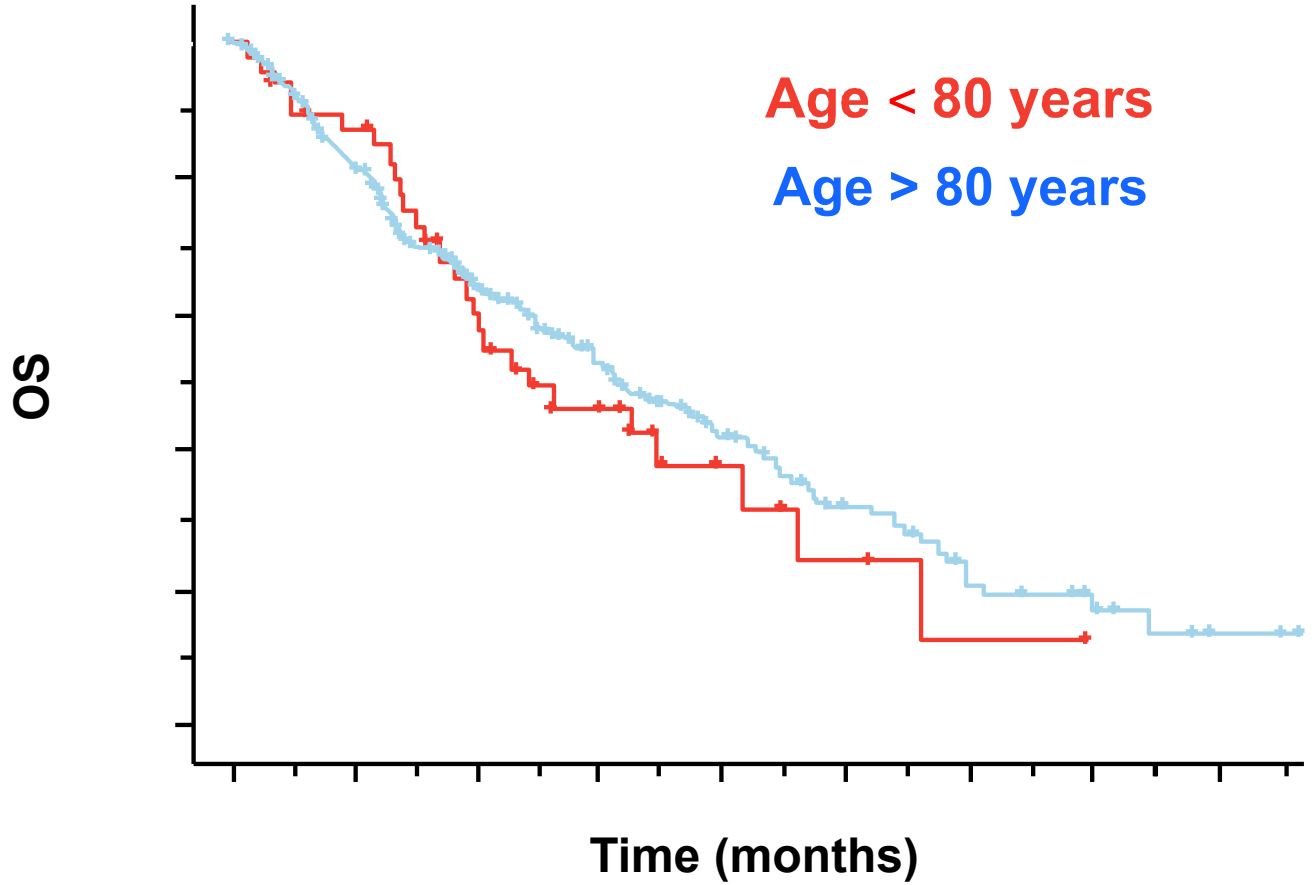
2-year survival (patients aged >75 years)[2]

p<0.0003



1. Fenaux P, et al. Lancet Oncol 2009;10:223–32
2. Seymour JF, et al. Poster presented at ASH 2008, San Francisco, CA, USA

Azacitidine (AZA) in Higher Risk MDS Patients (pts) Aged ≥ 80 Years : OS

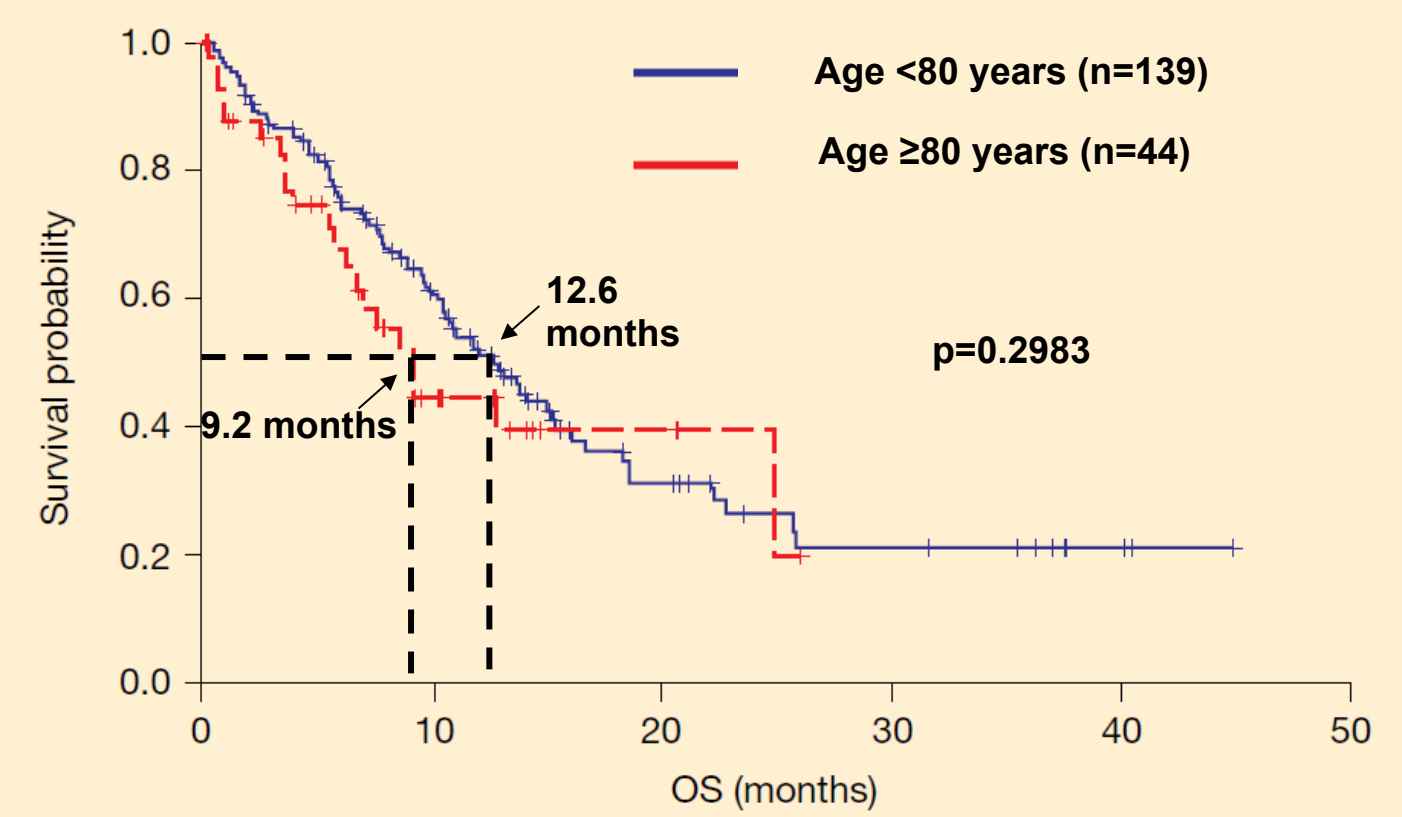


- OS similar in patients aged < 80 and ≥ 80 years (*P* = .6)
- Median OS 12.1 months; 1- and 2-year OS: 50% and 23.2%

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

‘Real-world’ experience with azacitidine in patients with MDS, AML or CMML: Austrian Registry

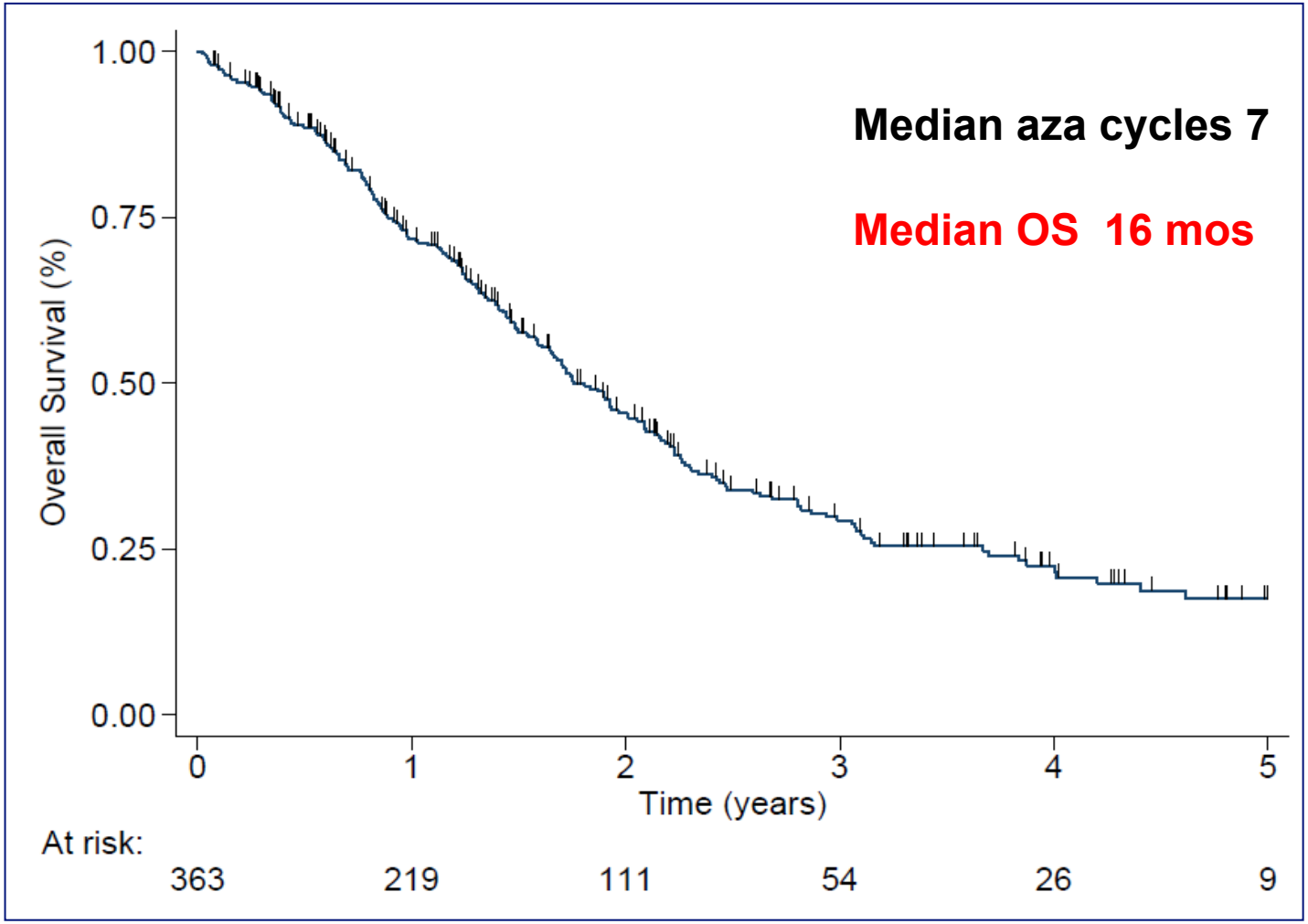
OS was similar in patients aged <80 years old and patients aged ≥80 years old



Pleyer L, et al. Poster presentation at 11th International Symposium on MDS 2011, Edinburgh, UK. Abstract 101

What happens in real life?

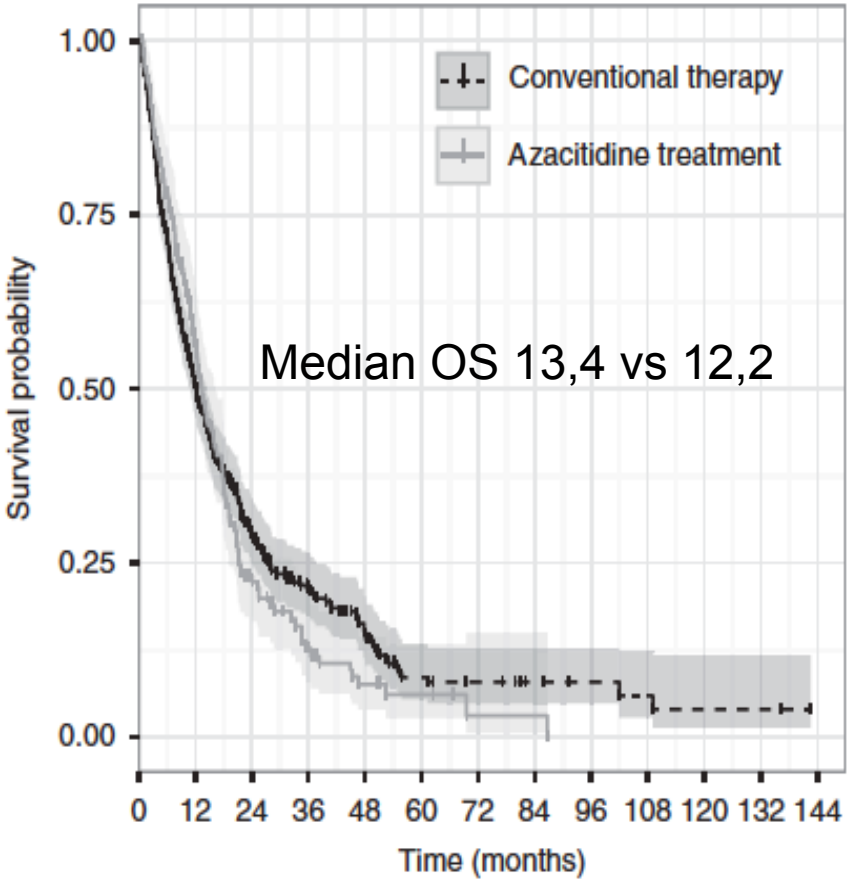
370 higher risk MDS pts treated with AZA

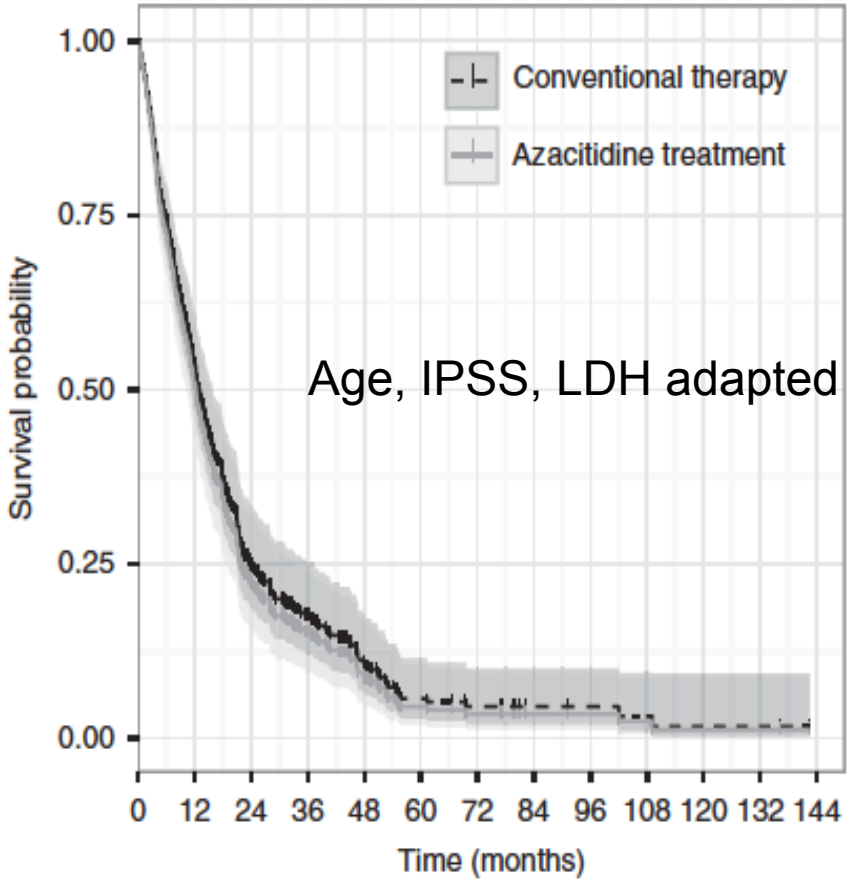


FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

What happens in real life?

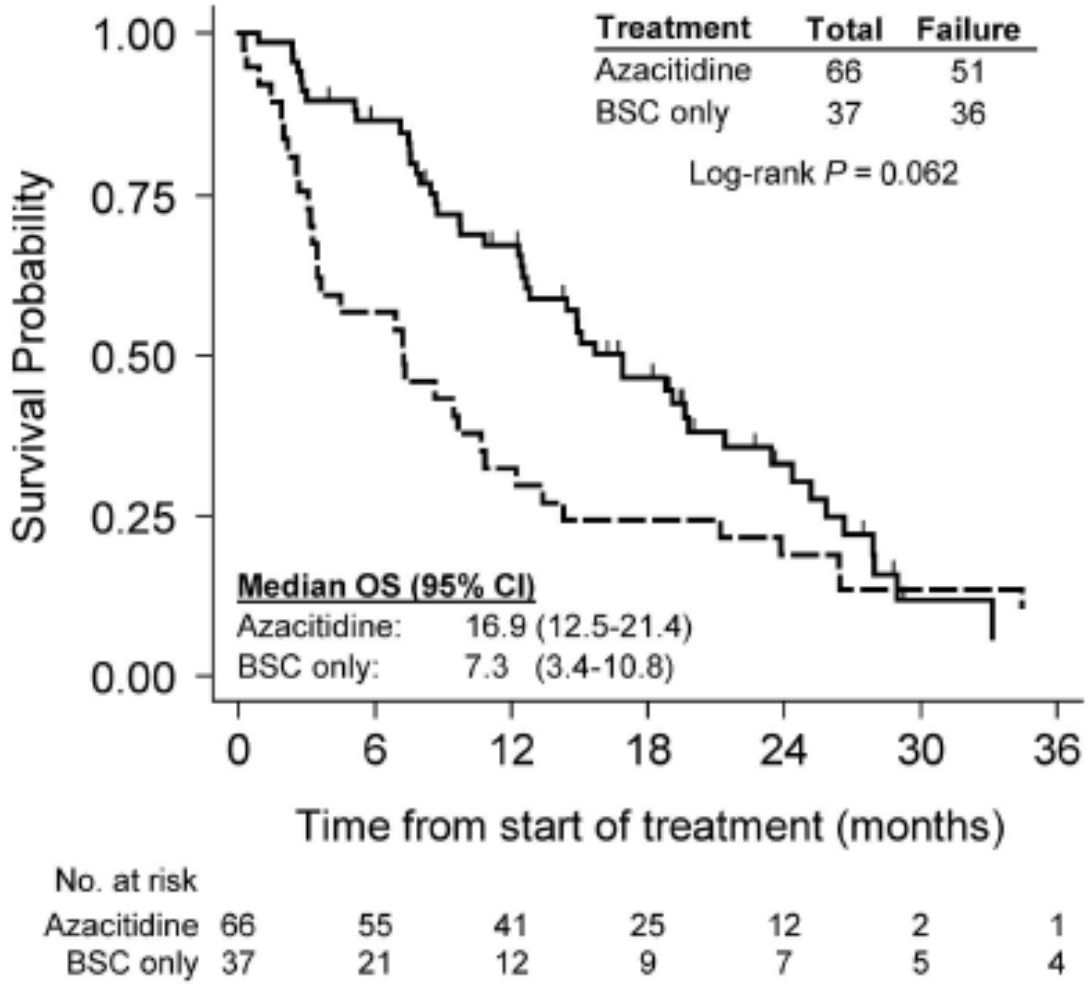
AZA treatment/Spanish experience





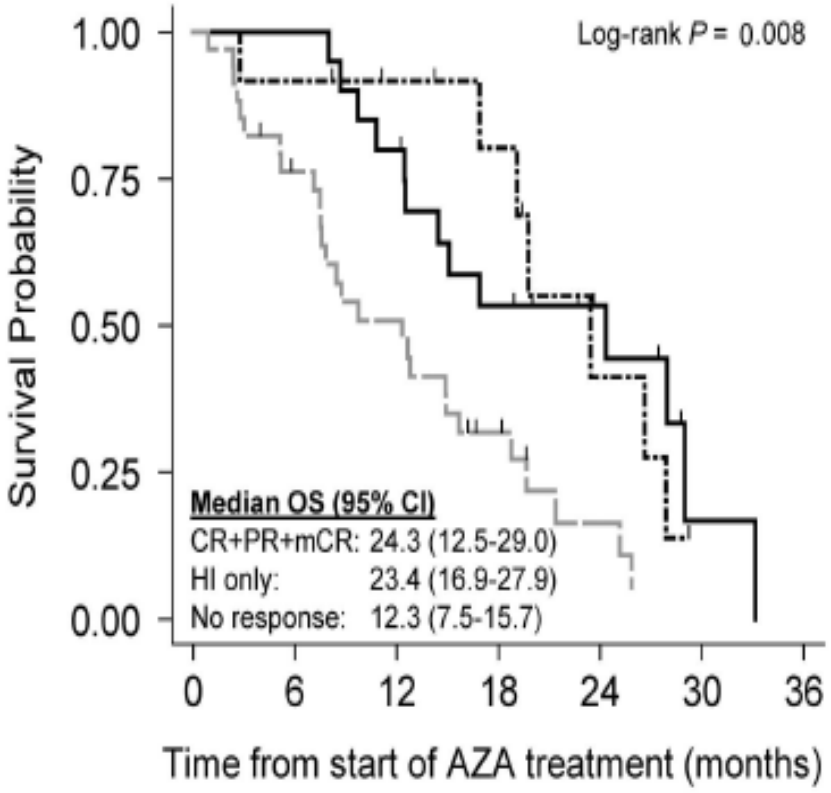
Bernal et al, Leukemia (2015) 29, 1875–1881

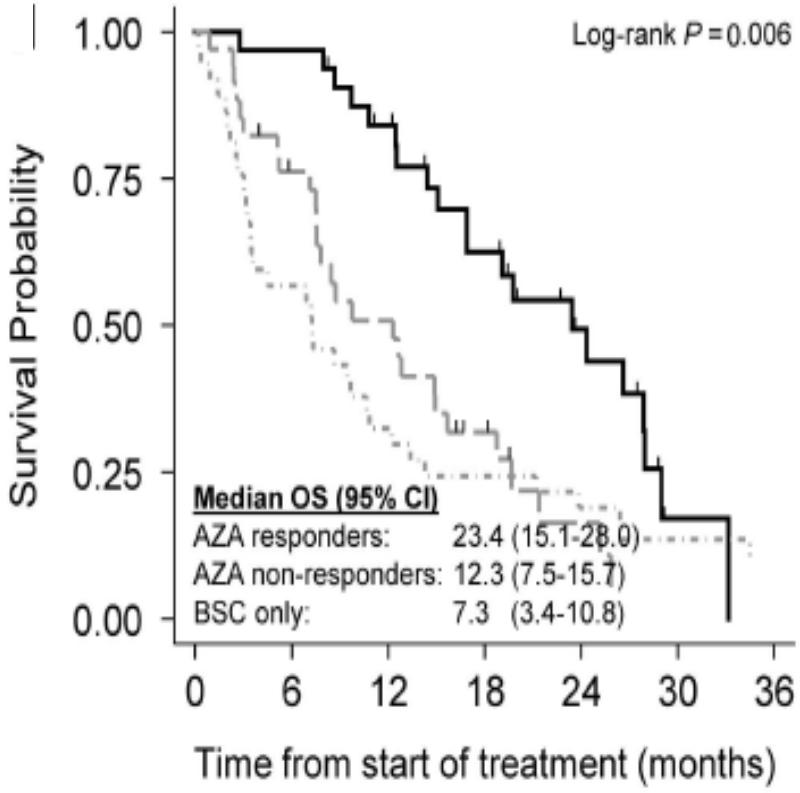
What happens in real life?
AZA treatment Dutch experience



Dinmohamed et al. Leukemia (2015) 29, 2449–2451

What happens in real life?
AZA treatment/Dutch experience

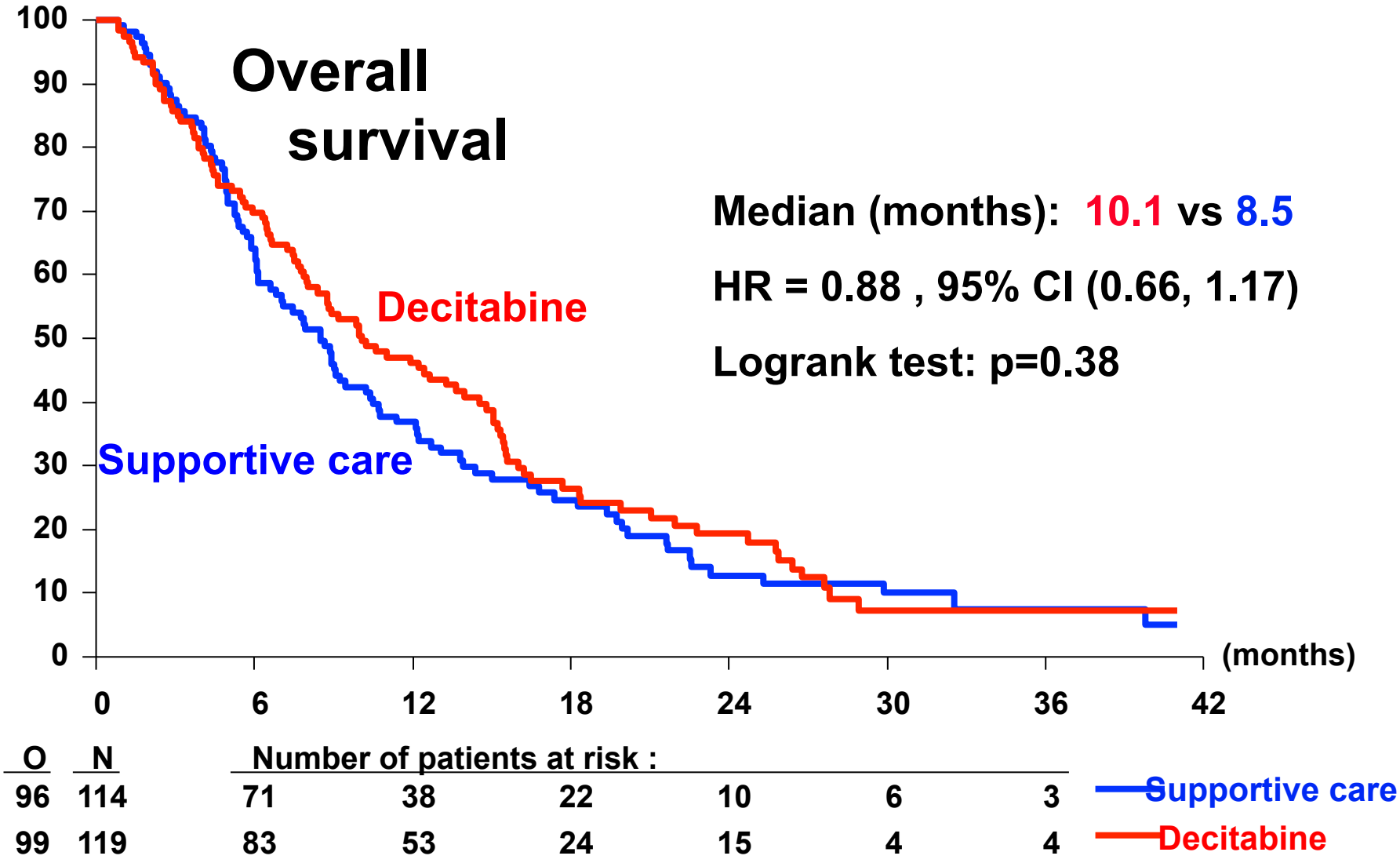




Dinmohamed et al. Leukemia (2015) 29, 2449–2451

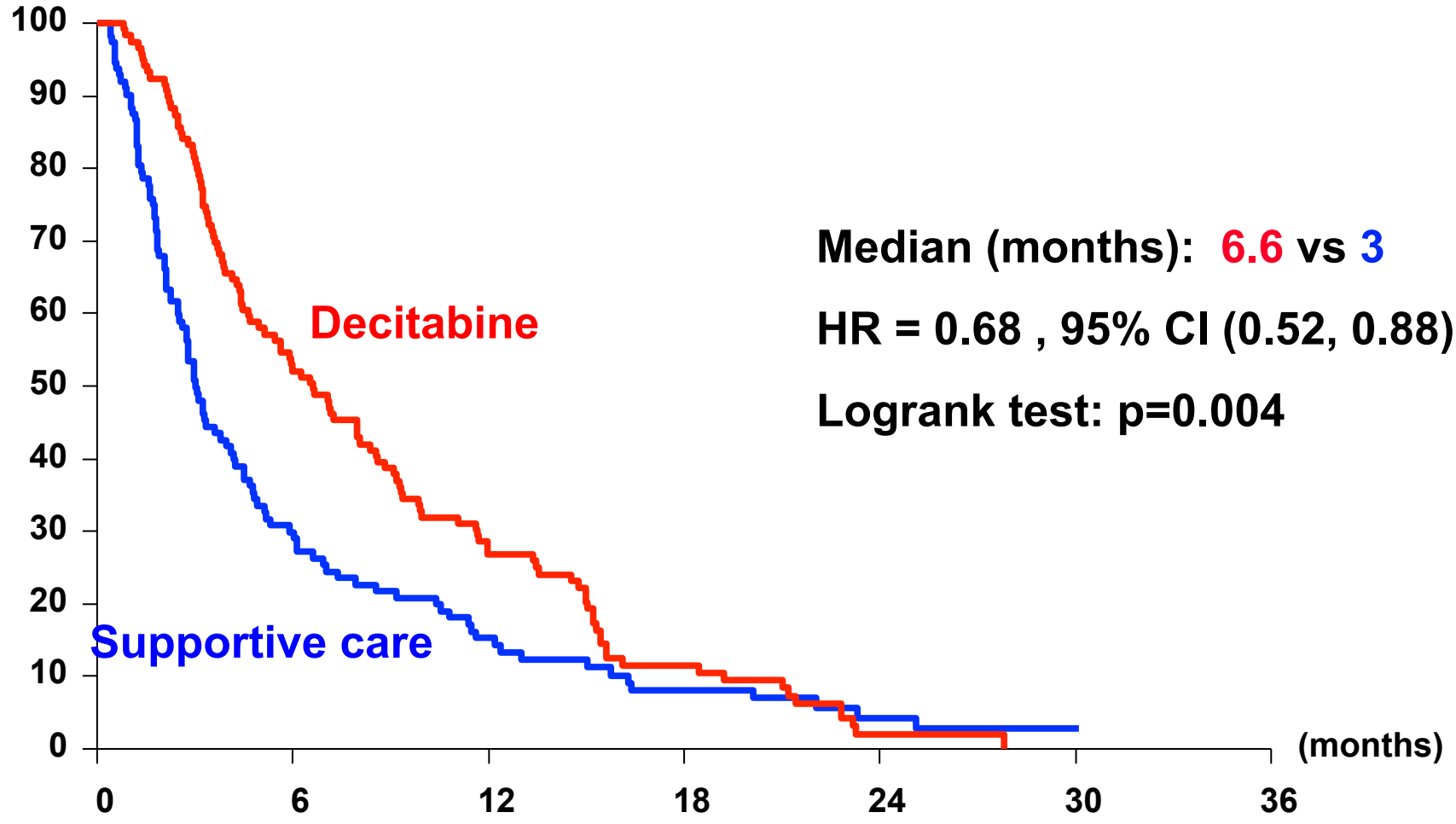
EORTC
European Organization for Research and Treatment of Cancer

Low dose decitabine vs. BSC in elderly patients with intermediate or high risk MDS not eligible for chemotherapy: Randomized Phase 3 Study



EORTC
European Organization for Research and Treatment of Cancer

Progression-Free Survival



Median (months): 6.6 vs 3

HR = 0.68 , 95% CI (0.52, 0.88)

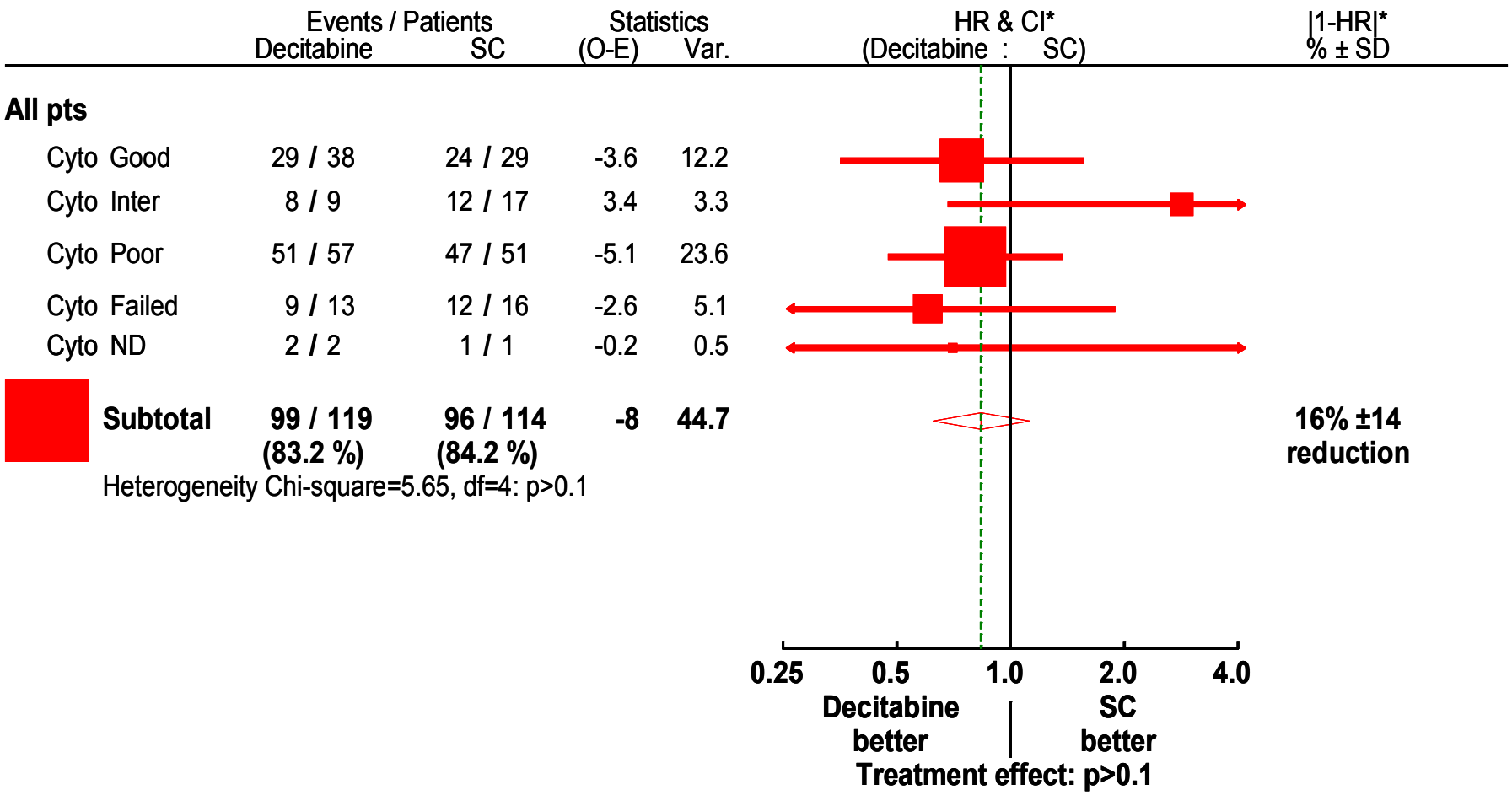
Logrank test: p=0.004

O	N	Number of patients at risk :				
105	114	33	15	7	3	1
113	119	62	32	11	2	0

Supportive care

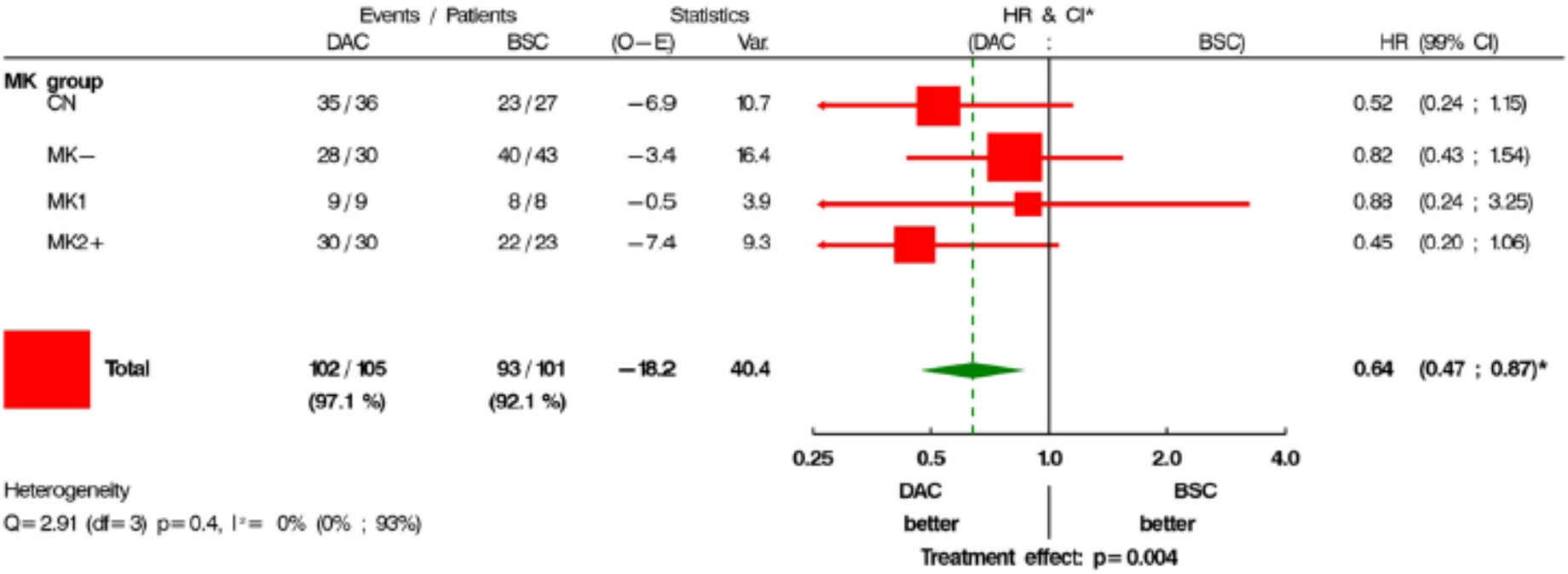
Decitabine

Forest plot by Cytogenetics



*95% CI for totals and subtotals, 99% CI elsewhere

Progression-free survival after decitabine is strikingly prolonged in the presence of 2 or more monosomies



Lübbert, Suciu et al., 2016

Resistance/sensitivity to HMT:

40-60% of MDS patients fail to achieve a response to HMTs

Silverman LR et al JCO 2002;20:2429-40
Silverman LR et al Leukemia 1993;7 Suppl 1:21-9
Itkynson R et al Blood 2011;117:403-11
Kadia tm et al Semin Oncol 2011;38:682-92

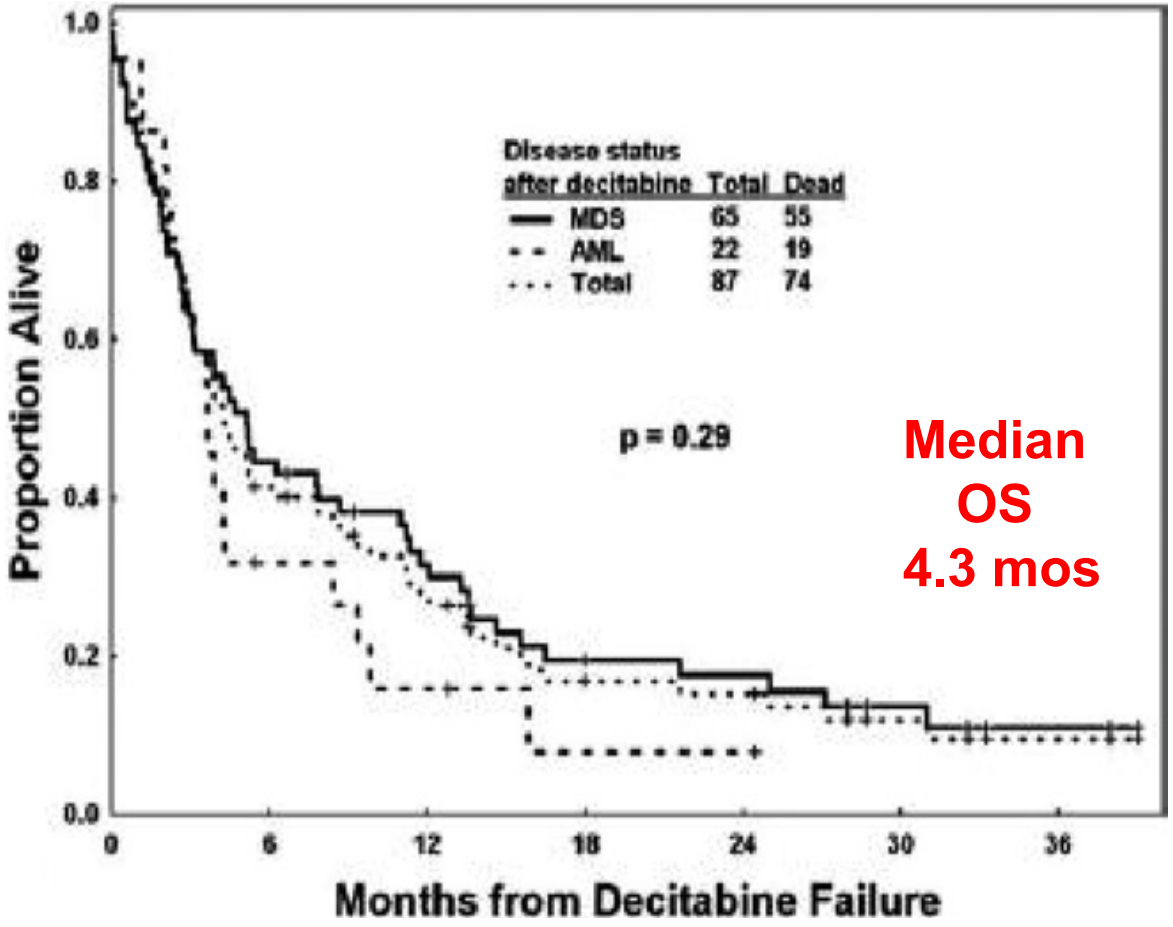
Resistance/sensitivity to HMT:

Clinical/individual

Disease related

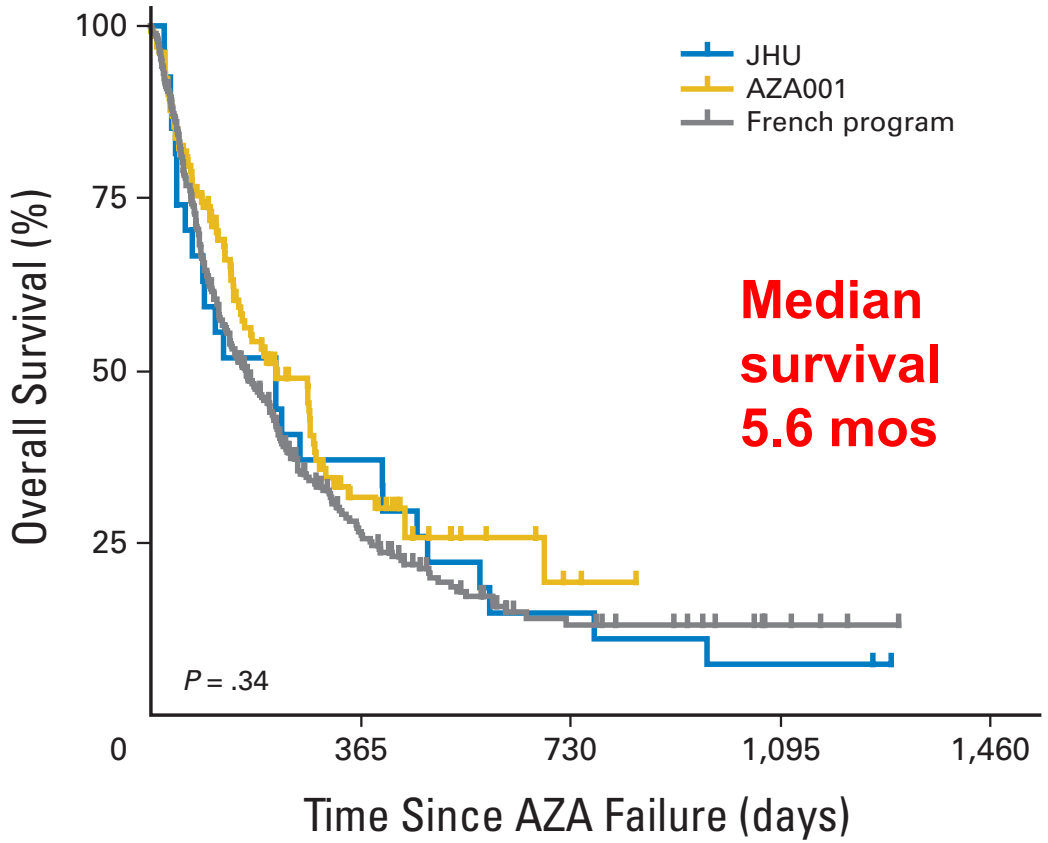
- cytogenetics
- somatic mutations
- drug metabolizing enzyme expressior
- DNA methylation pattern baseline

Survival after decitabine failure in MDS/AML patients



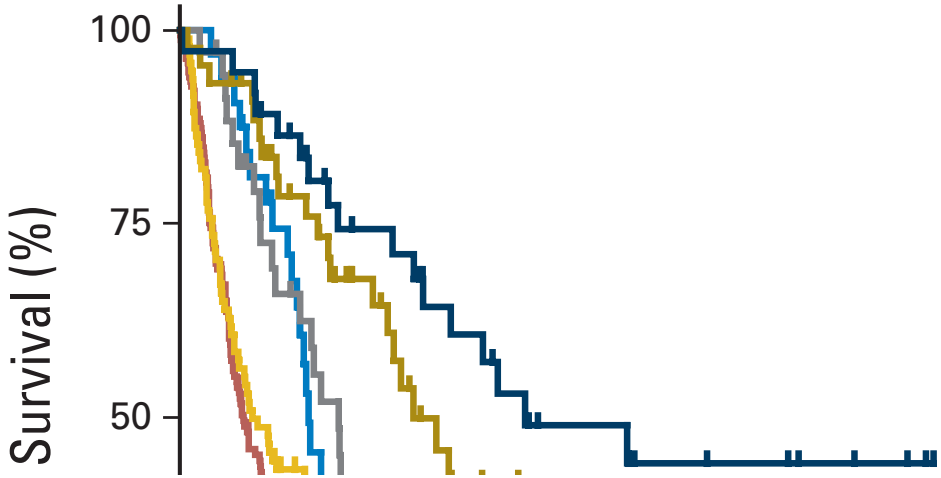
Jabbour et al, Cancer 116:3830(2008)

Survival after azacitidine failure in MDS/AML patients



Prebet et al, JCO 29:3322 (2011)

Survival according to salvage therapy



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*

The difference between IT and HSCT did not reach significance (P .09).

Prebet et al, JCO 29:3322 (2011)

Can we predict response to HMTs?

Resistance/sensitivity to HMT:

Clinical/individual

Disease related

- cytogenetics
- somatic mutations
- drug metabolizing enzyme expressior
- DNA methylation pattern baseline

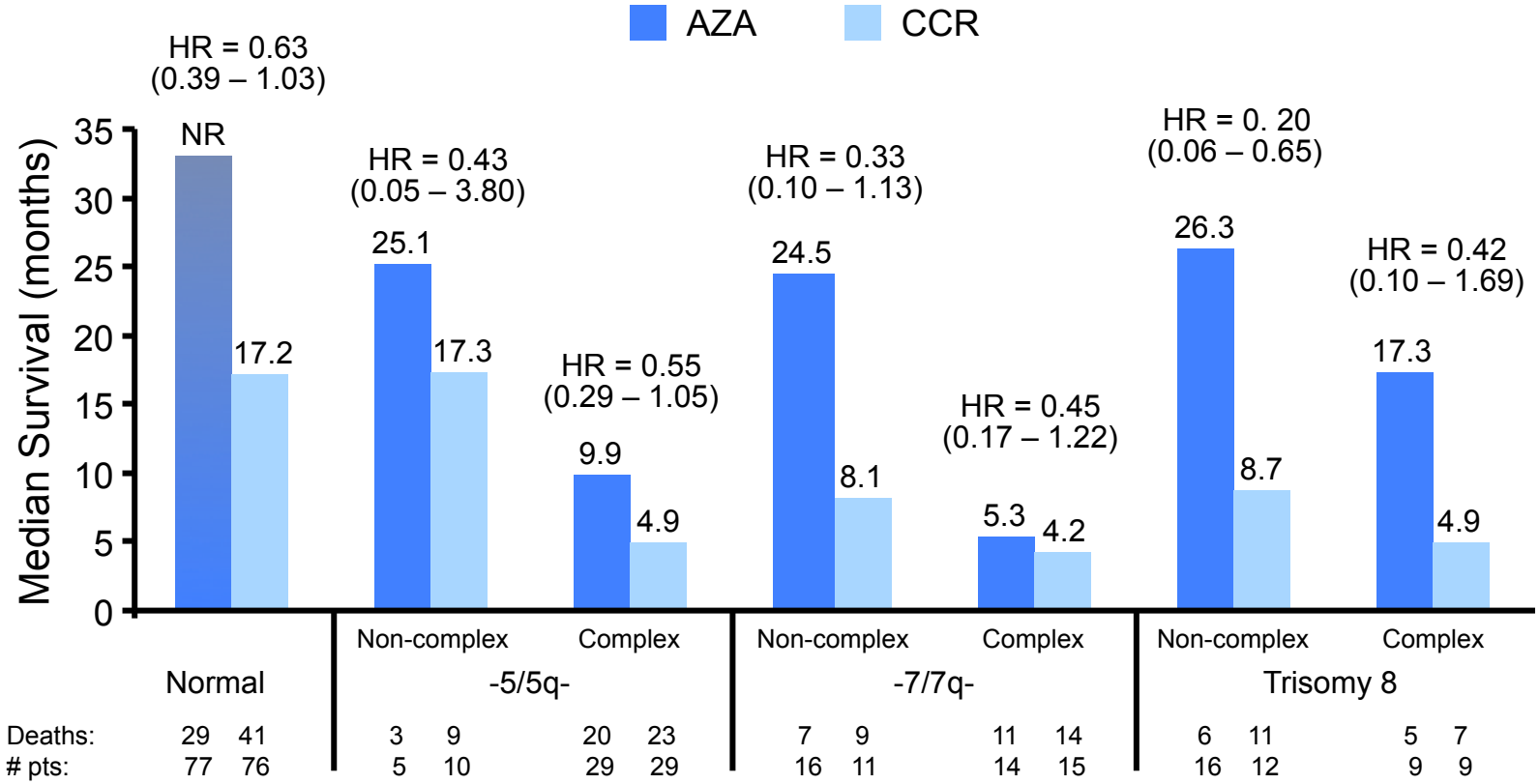
Parameters predictive of HMT response

Clinical	Positive	Negative
	Doubling of platelets	BM blasts > 15%
		Previous therapy
		Transfusion dependency
		Marrow fibrosis grade 3

Molecular	Positive	Negative
	Mutated TET2	Mutated p53
	Mutated DNMT3a	Abnormal/complex Karyotype
		Low expression of UCK1
		Mutated ASXL1
		Overexpression of CXCL7 and CXCL4

Wjiermans et al Ann Haematol 2005; Itkynson et al Leukemia 2011; Kulasekararaj et al Blood 2010; Itkynson et al Leukemia 2011; Itkynson et al Blood 2011; Sanna et al Leuk Res 2011; Sekeres et al Blood 2012, Meldi, et al, JCI 2015

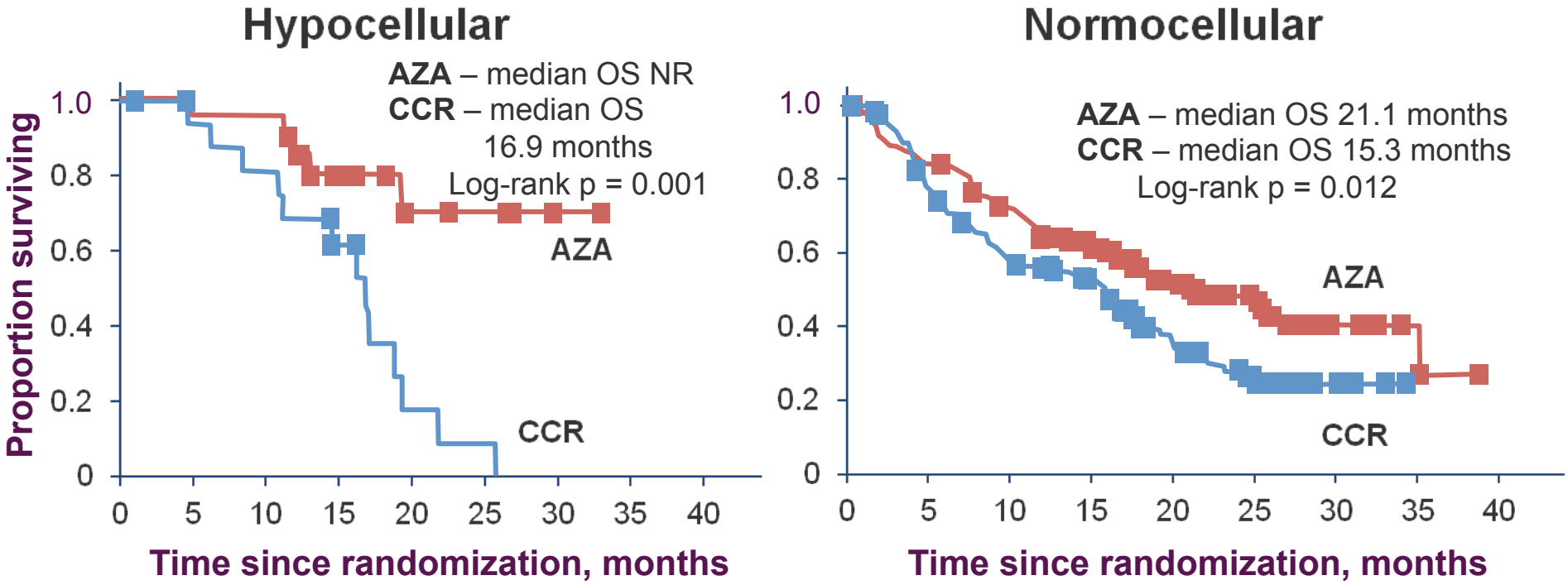
Effect of Cytogenetic Abnormalities on Overall Survival after azacitidine



- There was a trend for a survival advantage with AZA vs CCR in pts with normal karyotype
- Patients with non-complex karyotypes had a substantially longer OS than patients with complex karyotypes, regardless of treatment

AZA, azacitidine; CCR, conventional care regimen; HR, hazard ratio; NR, not reached; OS, overall survival.

Impact of bone marrow cellularity on efficacy and tolerance of AZA



- No difference in HI rate (hypocellular 52.5% vs normocellular 48%)
- Median cycle duration (hypocellular 35.5 days vs normocellular 33 days)
- No difference in grade ≥ 3 haematological AEs

AE, adverse event.

Seymour JF, et al Br J Haematol. 2014 Apr;165(1):49-56..

Prognostic factors for response and OS in Int-2/High-risk MDS patients treated with AZA

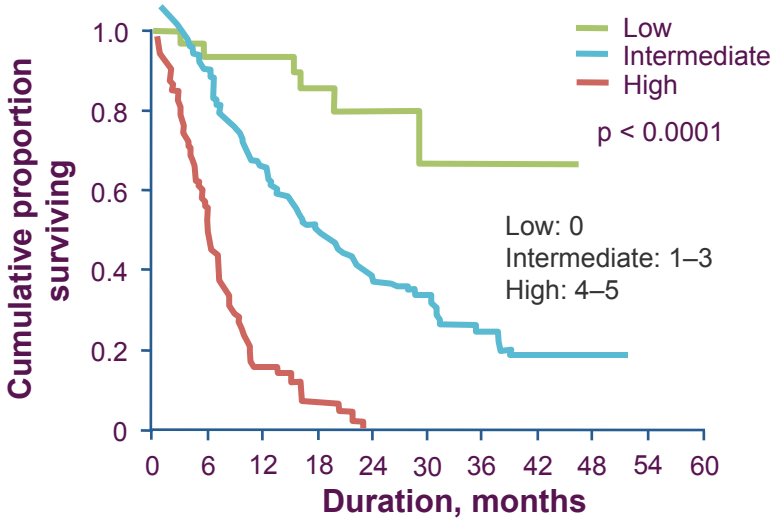
GFM ATU compassionate use study (n = 282)

AZA response score

Variable	Response rate, yes/no %	p value*
Prior LD ARA-C	24/46	0.009
Normal karyotype	51/39	0.003
Marrow blasts > 15%	35/50	0.004
Response duration		
Complex karyotype	4.6 vs 10.3 months	0.0003

OS prognostic score

Variable	Score
Performance status ≥ 2	1
Circulating blasts	1
RBC transfusion dependence ≥ 4 U/8 wks	1
Intermediate karyotype	1
High-risk karyotype	2

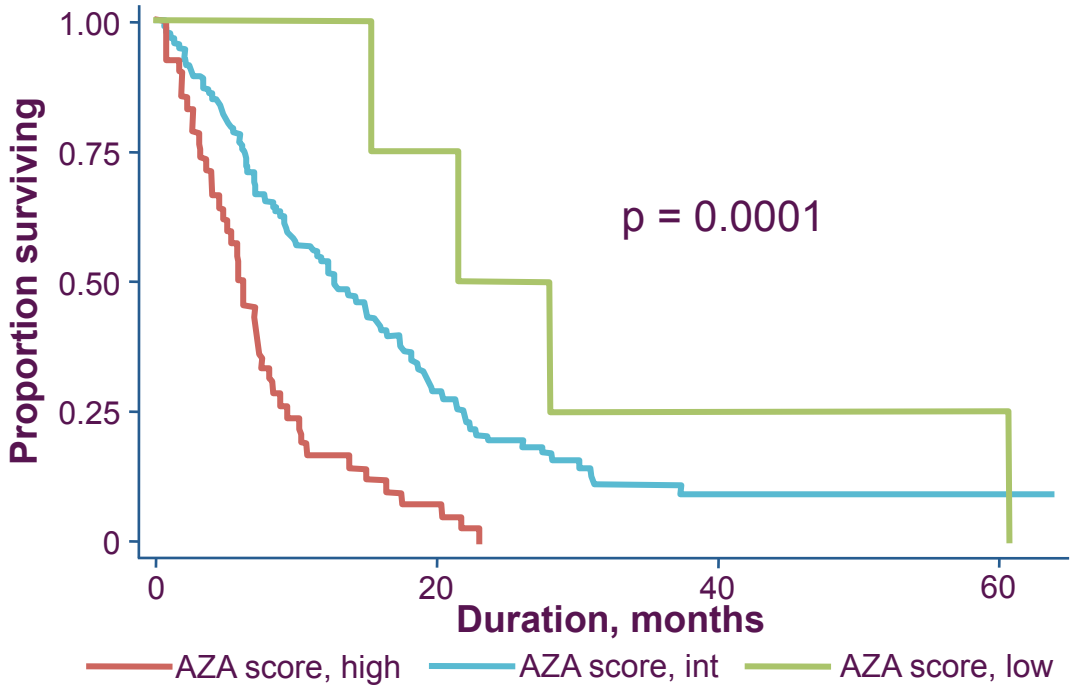


* Multivariate analysis.
ATU, authorization for temporary use.

Itzykson R, et al. Blood. 2011;117:403-11.

OS in IPSS-R very poor-risk group according to French AZA scoring system

IPSS-R very poor-risk MDS



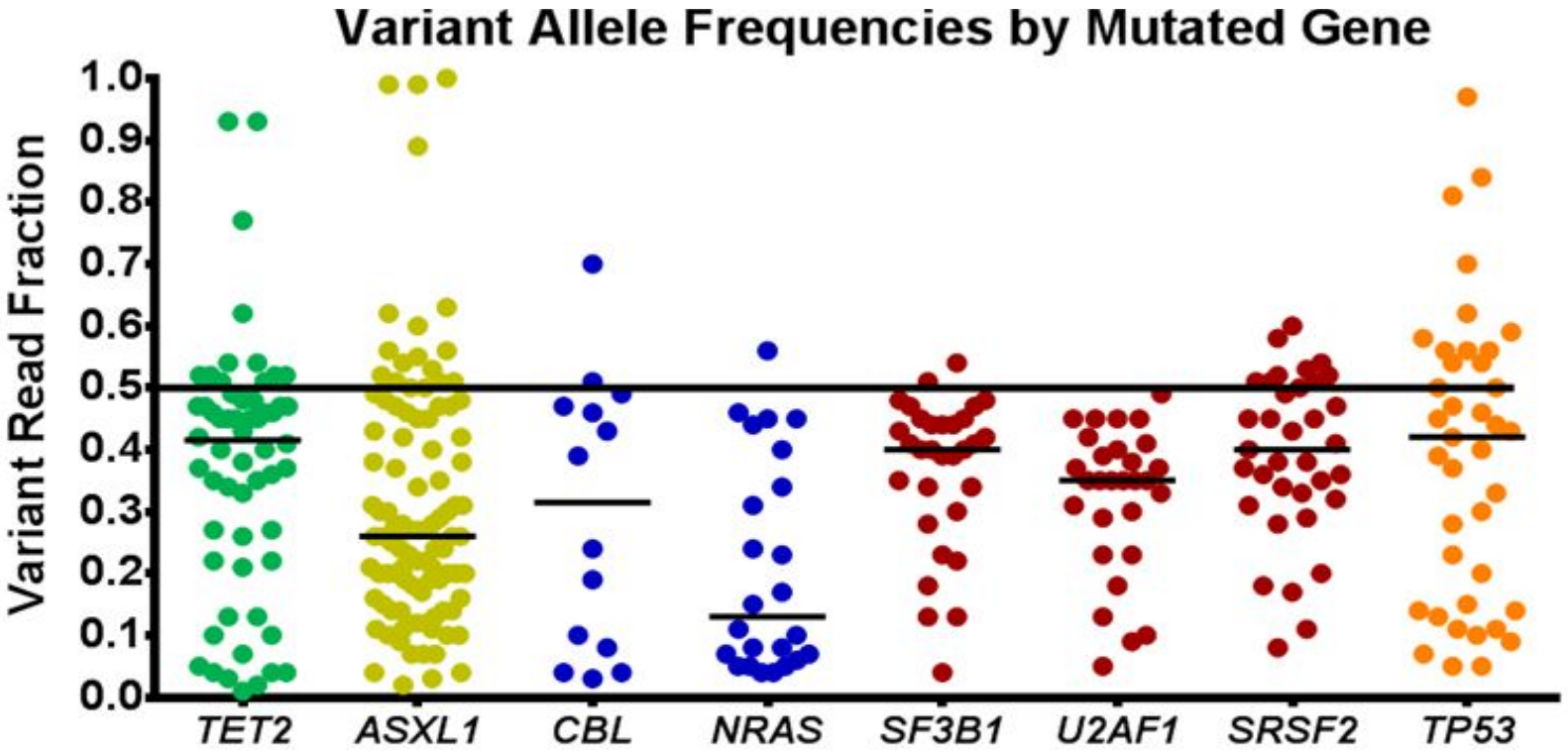
French AZA scoring system

Risk factor	Score
ECOG performance status ≥ 2	1
Intermediate-risk cytogenetics	1
Poor-risk cytogenetics	2
Transfusion dependence ≥ 4 U/8 wks	1
Peripheral blood blasts present	1

ECOG, Eastern Cooperative Oncology Group.

Ades L, et al. Blood. 2012;120:abstract 422 and data presented at ASH 2012.
Itzykson R, et al. Blood. 2011;117:403-11.

TET2 mutations predict response to hypomethylating agents



Gene (n) *VAF ≥ 0.1*	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
***TET2* (50)**	**1.99** (1.05, 3.80)	**0.036**	**1.98** (1.02, 3.85)	**0.044**
***TET2* mut + *ASXL1* wt (23)**	**3.65** (1.38, 9.67)	**0.009**	**3.64** (1.35, 9.79)	**0.011**

Bejar R et al; Blood 2014; 124:2705

Risk stratification in MDS patients treated with hypomethylating agents

Response to HMT

Feature	Category	Score
Platelets, x10⁹/L	≥100 < 100	0 1
WBC , x10⁹/L	<3.0 ≥3.0	0 1
TET2/DNMT3A mutation	One or both genes mutated Both genes wild type	0 1

Total Score	Risk Group	N (%)	N (%) Response	p^3
0 or 1	Favorable	23 (25%)	10 (43%)	
2	Intermediate	52 (57%)	12 (23%)	
3	Unfavorable	16 (18%)	-0-	***0.002***

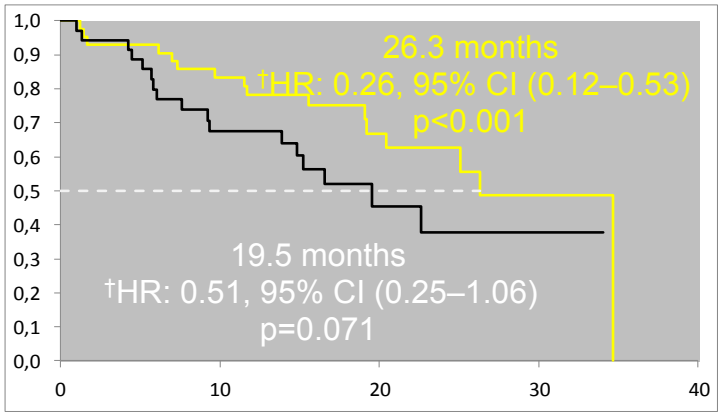
OS after HMT

Feature	Category	Score
Cytogenetic Risk	Good Intermediate or no growth Poor	0 2 5
ASXL1	Wild type Mutated	0 3
Hemoglobin, g/dL	≥10 <10	0 2
Age	< 60 ≥ 60	0 4
SF3B1	Mutated Wild type	0 8

Total Score	Risk Group	N (%)	Median Survival (months)	p^3
<12	Favorable	49 (53%)	30.7	
≥12	Unfavorable	43 (47%)	7.9	***<0.0001***

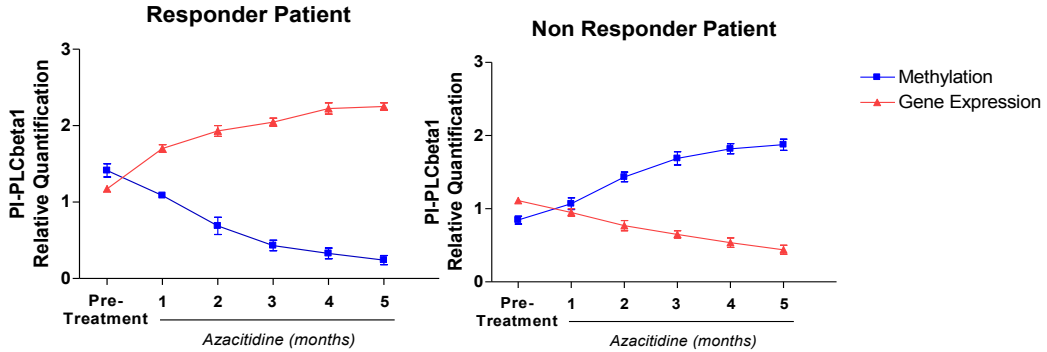
Traina F et al, Leukemia 2013

Methylation pattern and response to therapy

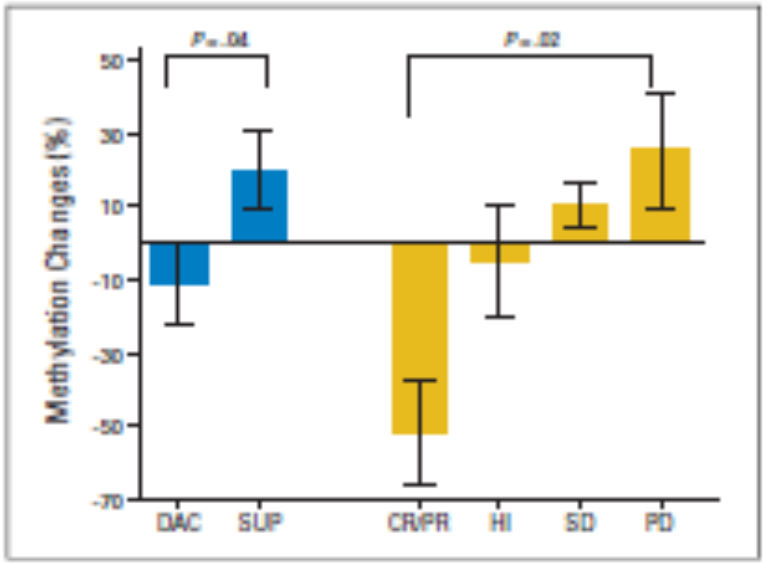


OS after AZA according to CDH1 methylation levels

Herman JG, et al. Presented at AACR 2009 [Abstract 4746]



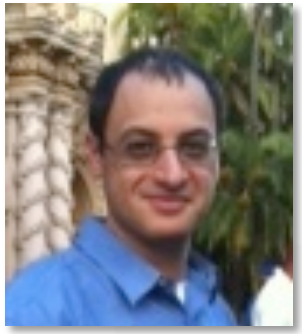
PI-PLCbeta1 promoter methylation and gene expression correlate with response to azacitidine
Follo et al PNAS 2009 29;106(39):16811-6



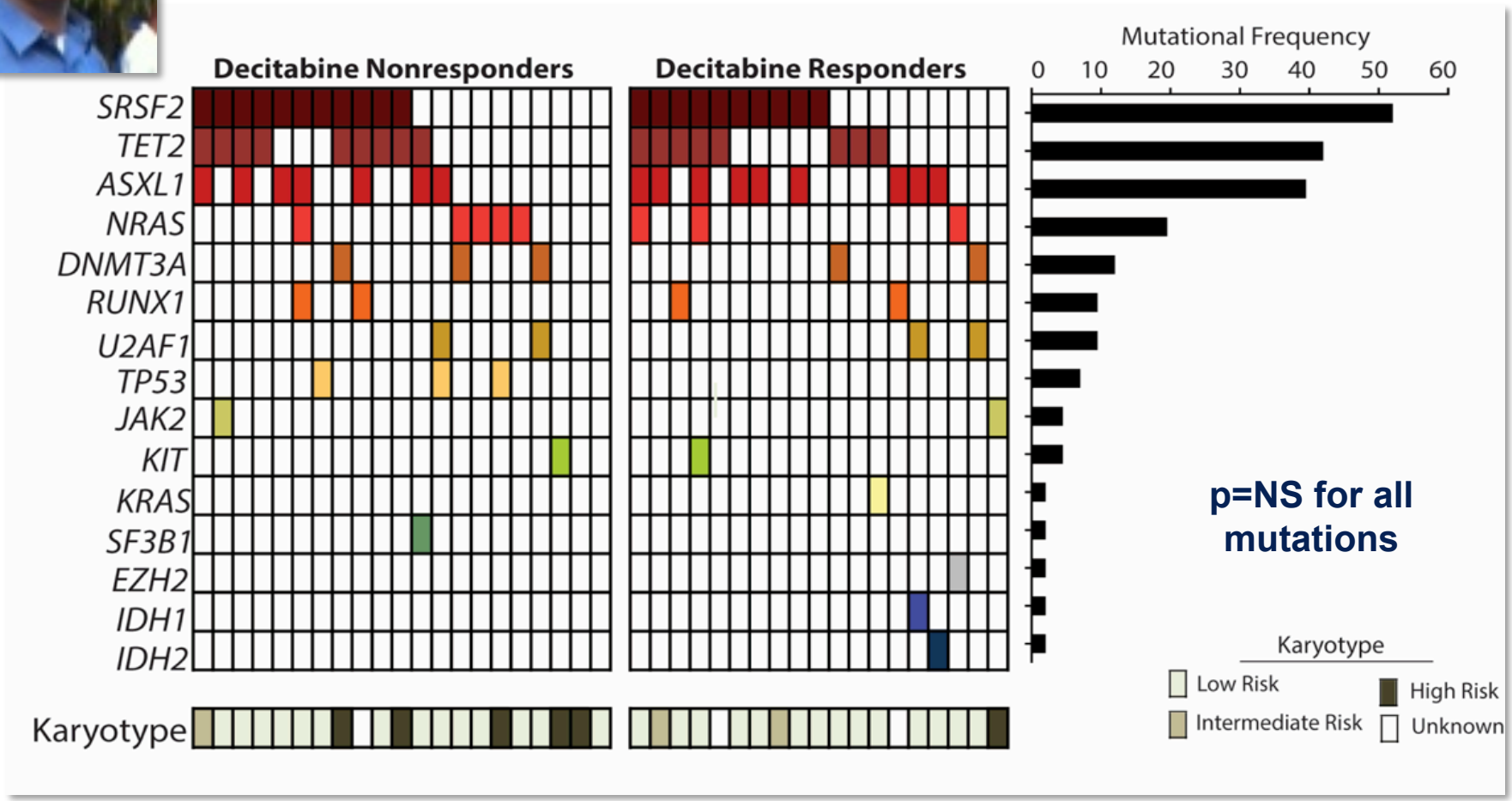
Global methylation and response to Decitabine

Shen, J Clin Oncol. 2010 1;28(4):605-13

Mutational profiles do not correlate with response to DAC

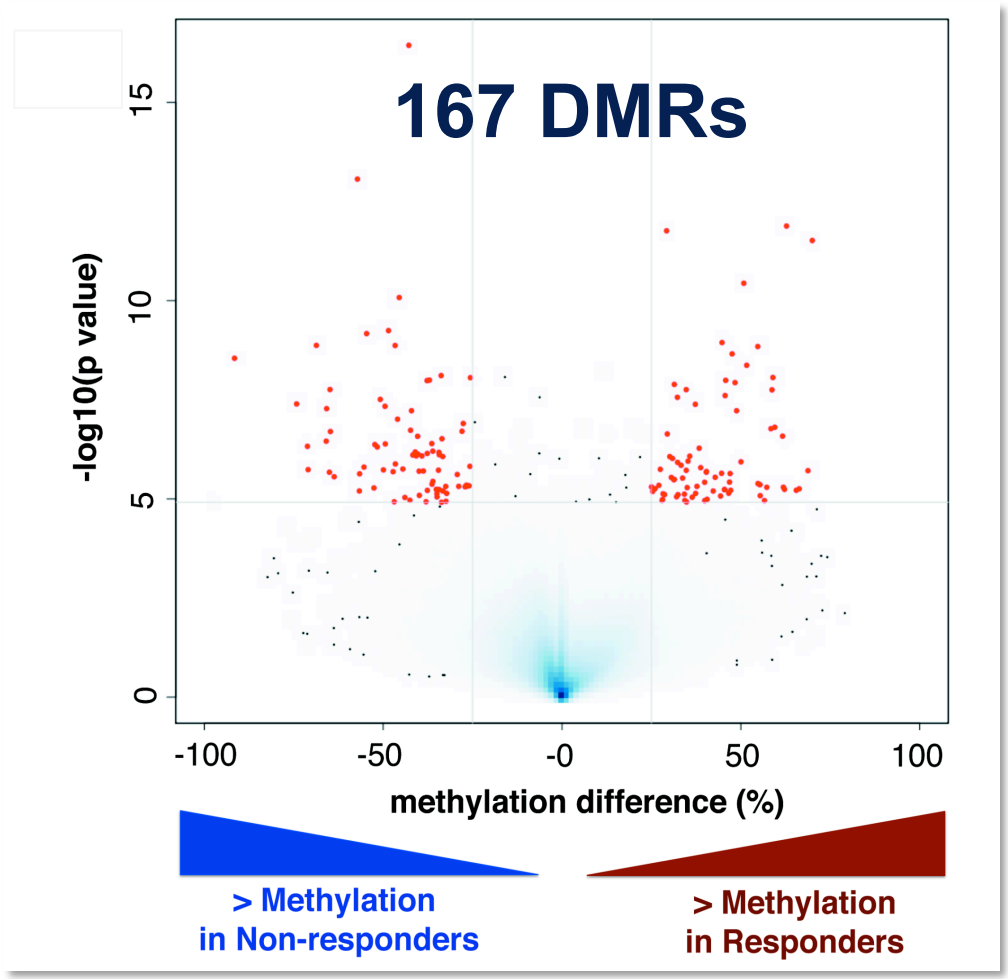


Responders **Non-Responders**



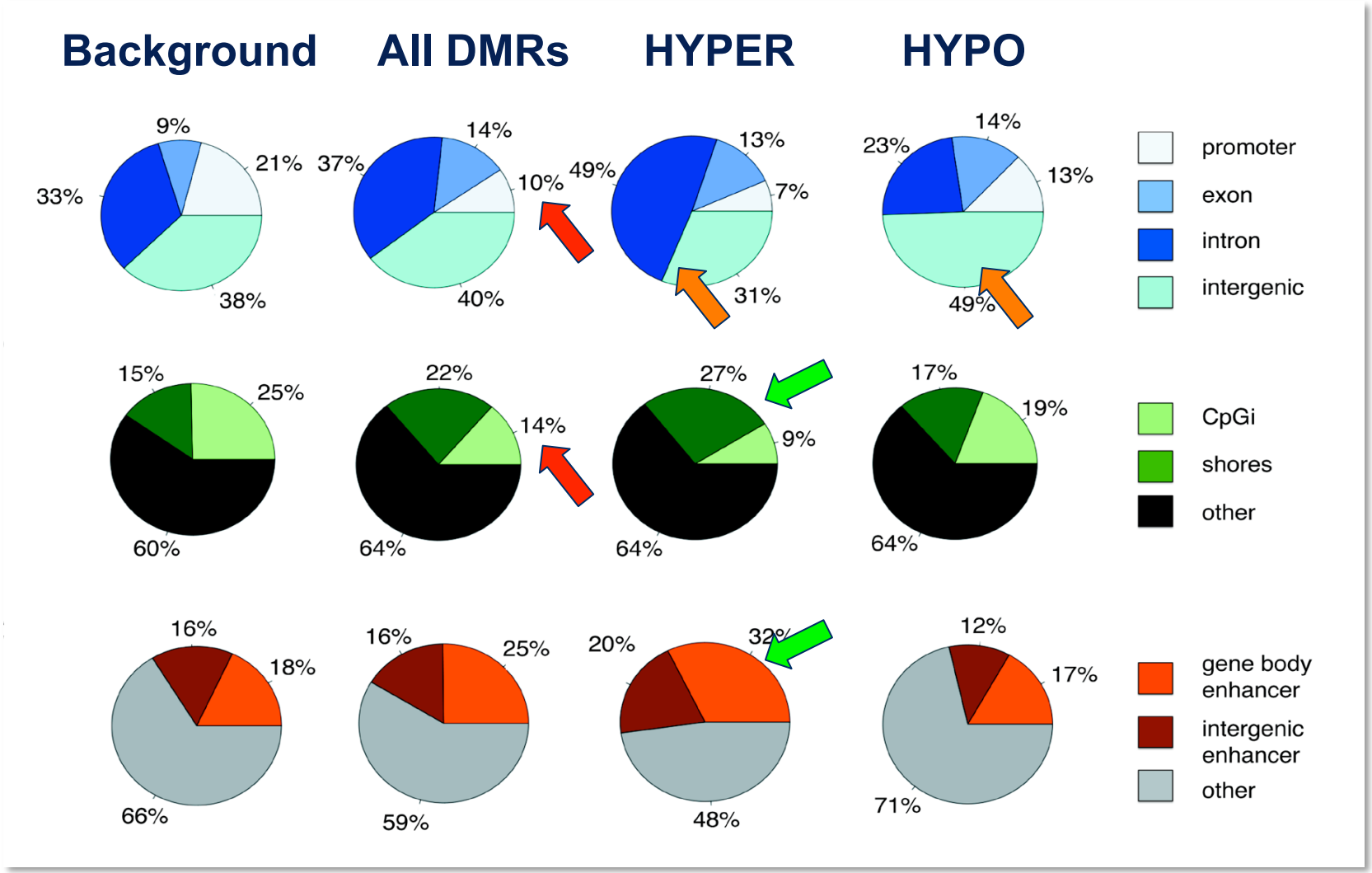
Meldi et al; J Clin Invest. 2015 May;125(5):1857-72.

Distinct DNA methylation profiles at diagnosis of CMML is associated with response to decitabine



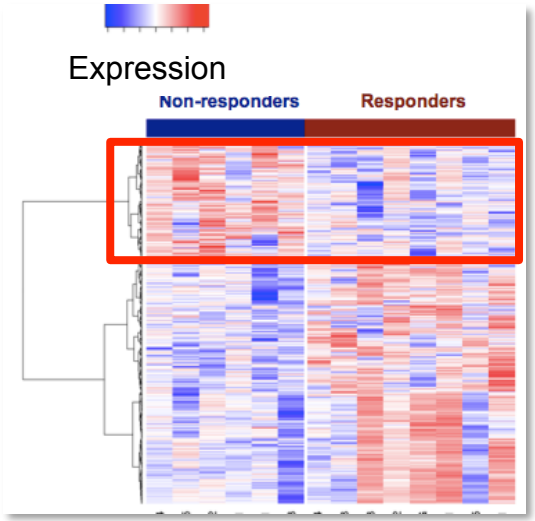
Meldi, et al. JCI 2015

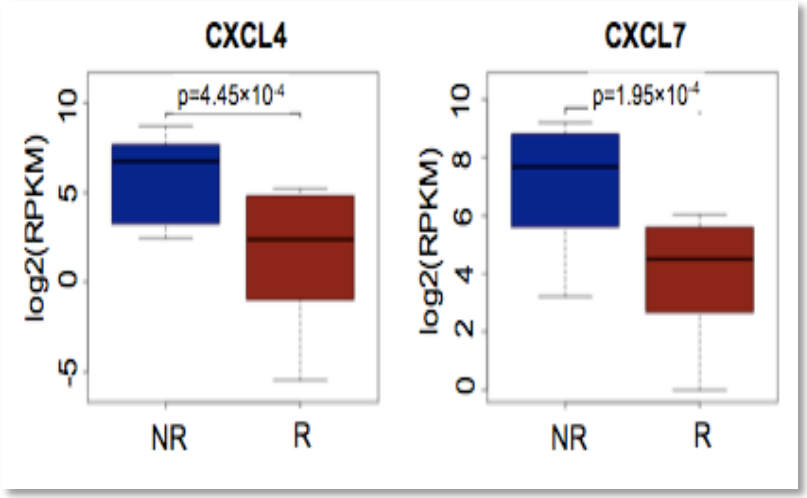
Differentially methylated regions are enriched at distal intergenic regions and enhancers

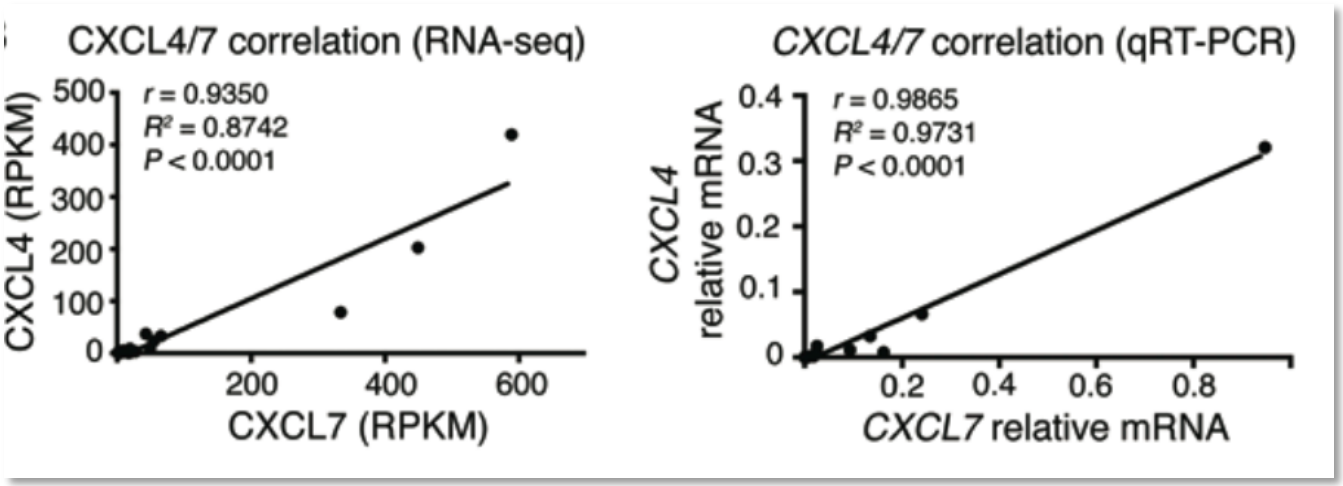


Meldi, et al. JCI 2015

CXCL4 and CXCL7 are up-regulated in the bone marrow of non-responders



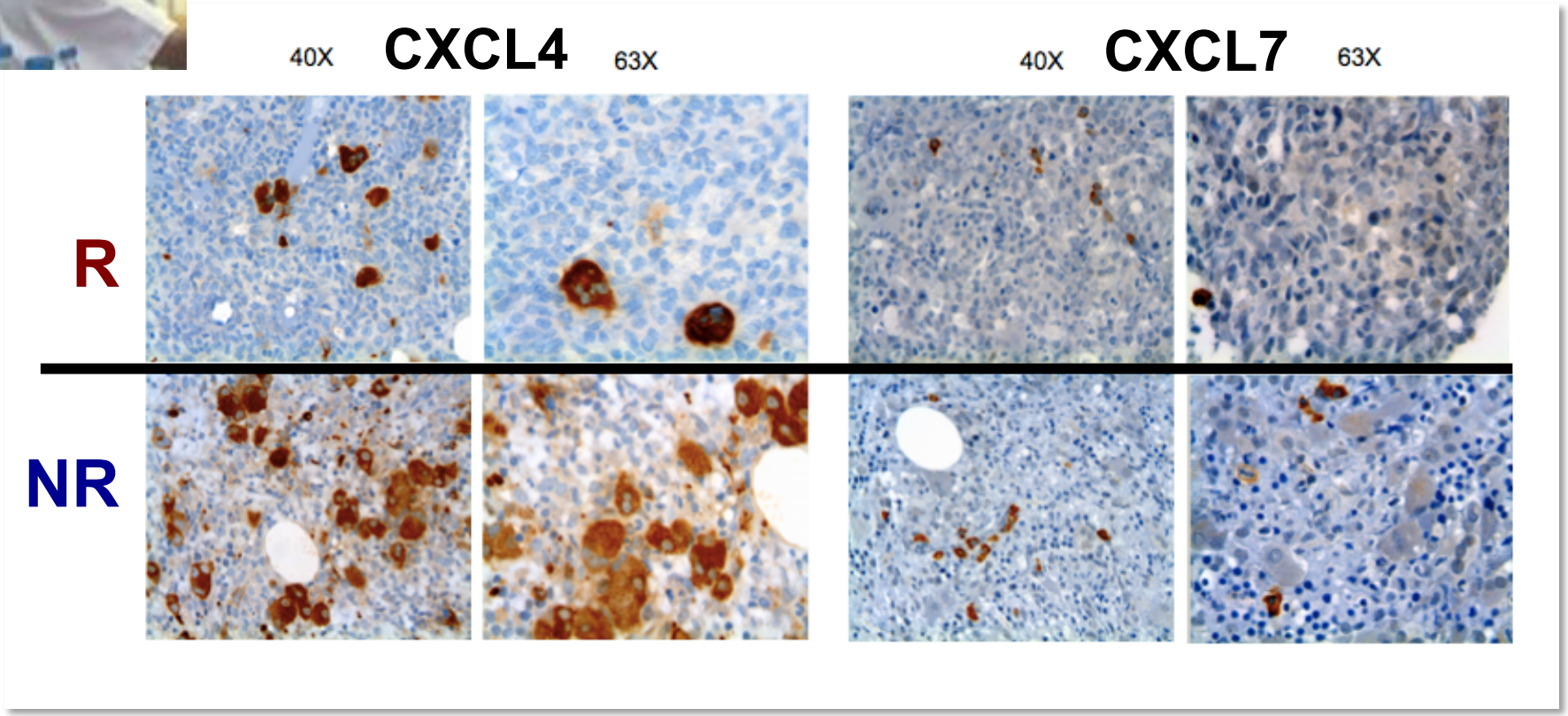




Meldi, et al. JCI 2015

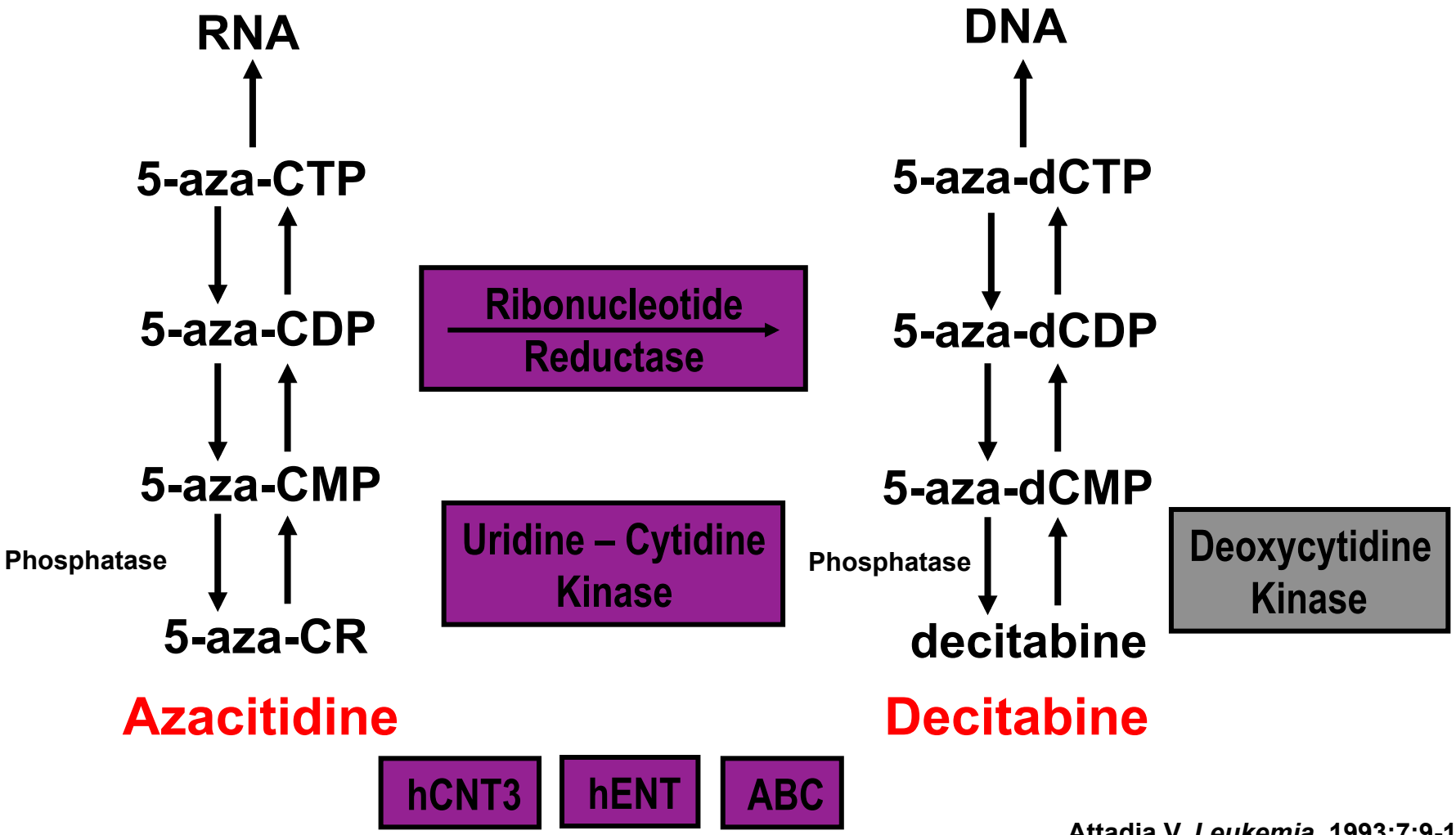
CXCL4 and CXCL7 are up-regulated in the bone marrow of non-responders

Francesca Buchi



Meldi, et al. JCI 2015

RNA/DNA uptake of hypomethylating agents



Attadia V. *Leukemia.* 1993;7:9-16.

UCK1 hyperexpression modulates response to Azacitidine in HR-MDS

Ana Valencia et al, Leukemia 2013

57 MDS pts

↓

Azacitidine

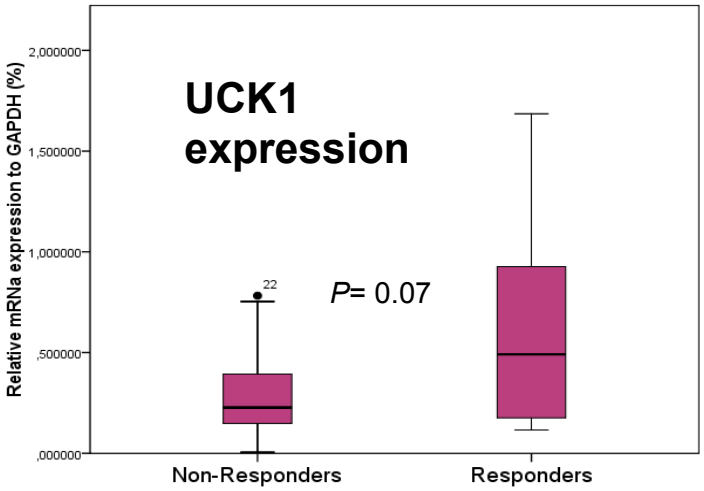
75mg/m^2/7 days
every 28 gg

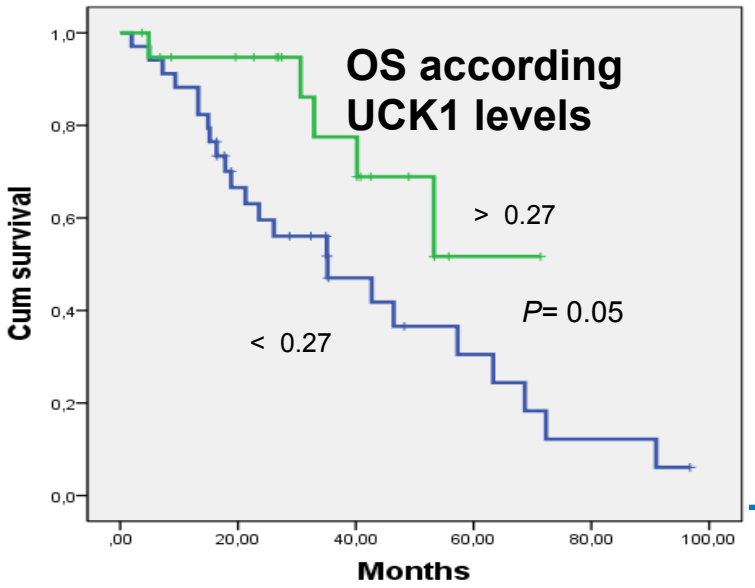
UCK1/2

Gene expression

Promoter methylation

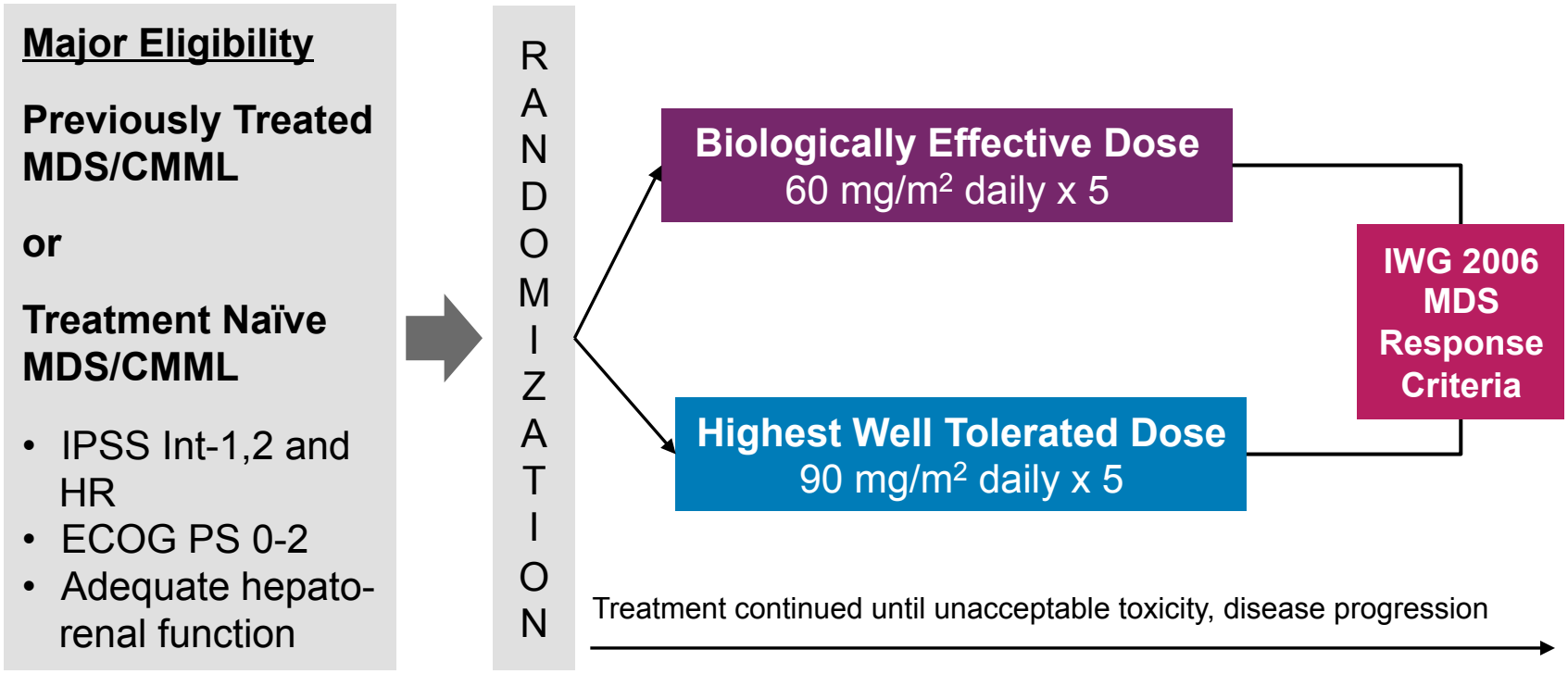
Gene sequence





Use new drugs?

“Long acting “ Hypomethylating Agent : SGI-110



- Primary Endpoint: Overall Response Rate (CR, PR, mCR, HI)
- Secondary Endpoints: Transfusion independence, LINE-1 demethylation, time to AML, overall survival

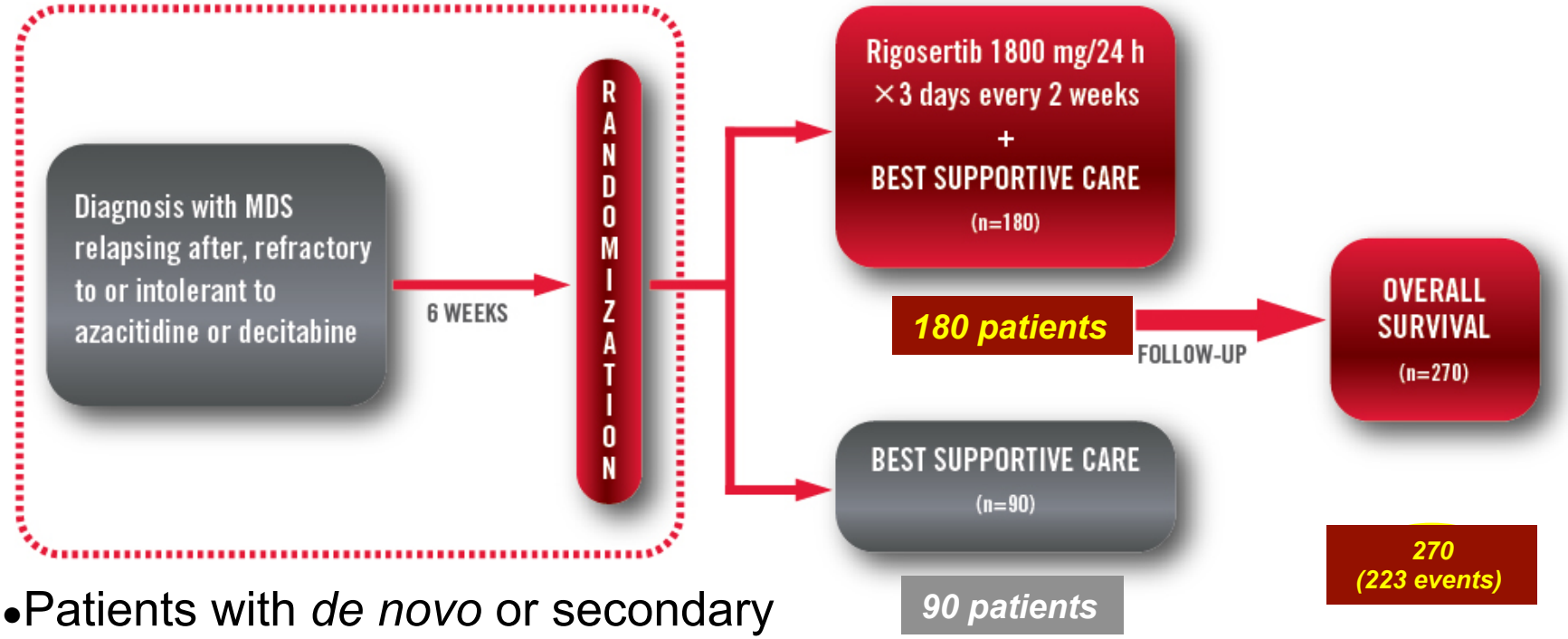
Guadecitabine (Clinical Responses in Tx naïve MDS/ CMML) 60 and 90 mg/m^2 SC Dailyx5 combined

Response Category[1]	Tx Naïve (n=49)
	Response rate n (%)
CR	7 (14.3)
mCR	3 (6.1)
HI	9 (18.4)
CR+mCR	10 (20.4)
Overall Response Rate	19 (38.8)

[1]International Working Group 2006 MDS Response Criteria

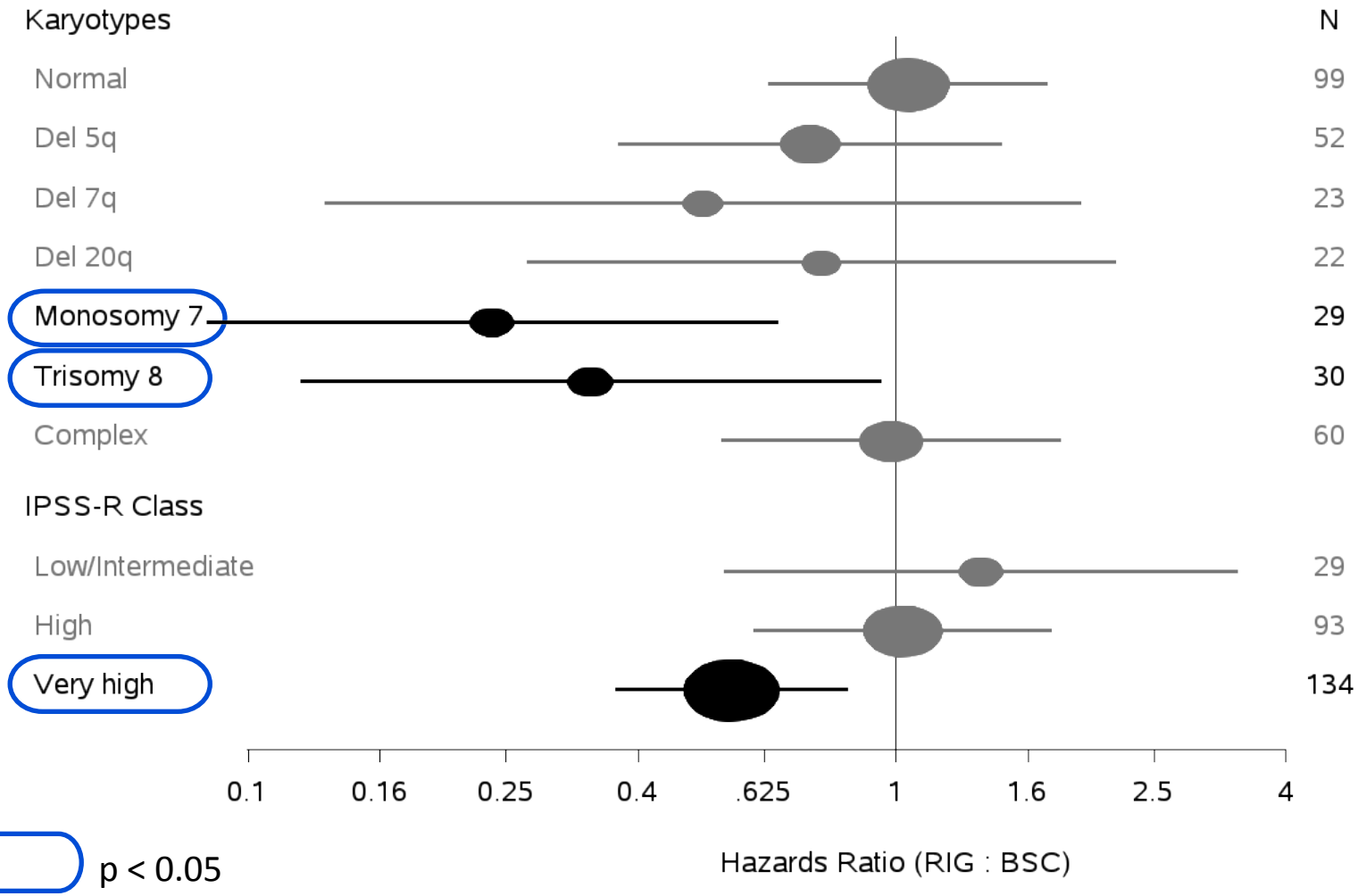
Garcia-Manero et al – American Society of Hematology 2014

Rigosertib
Multicenter International Phase III ongoing Trial



- Patients with *de novo* or secondary MDS who **relapse** after, progress, are **refractory to azacitidine or decitabine**
- Higher risk MDS, or chronic myelomonocytic leukemia (CMML)

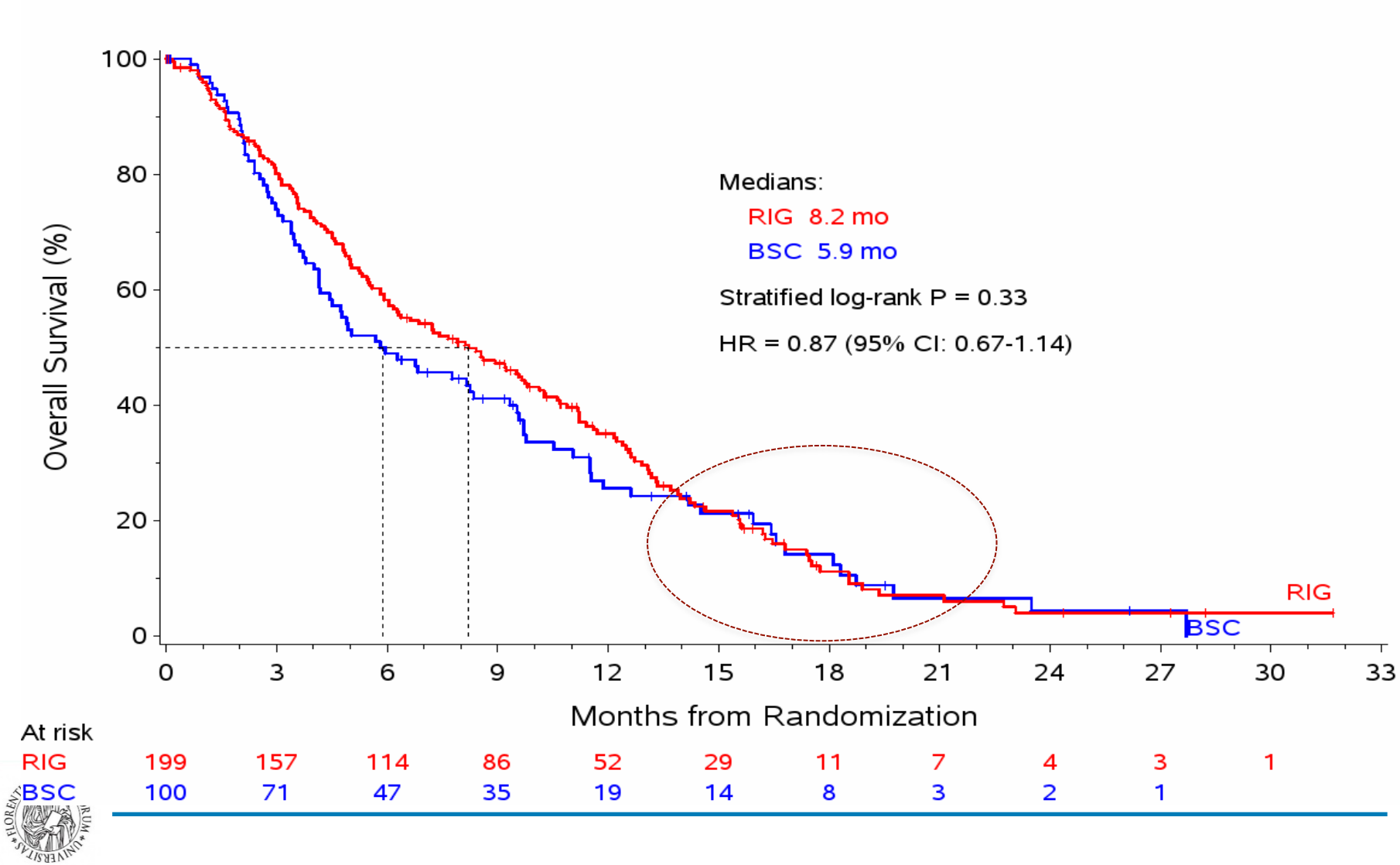
ONTIME Trial: Subgroups Correlated with Longer Median OS - ITT



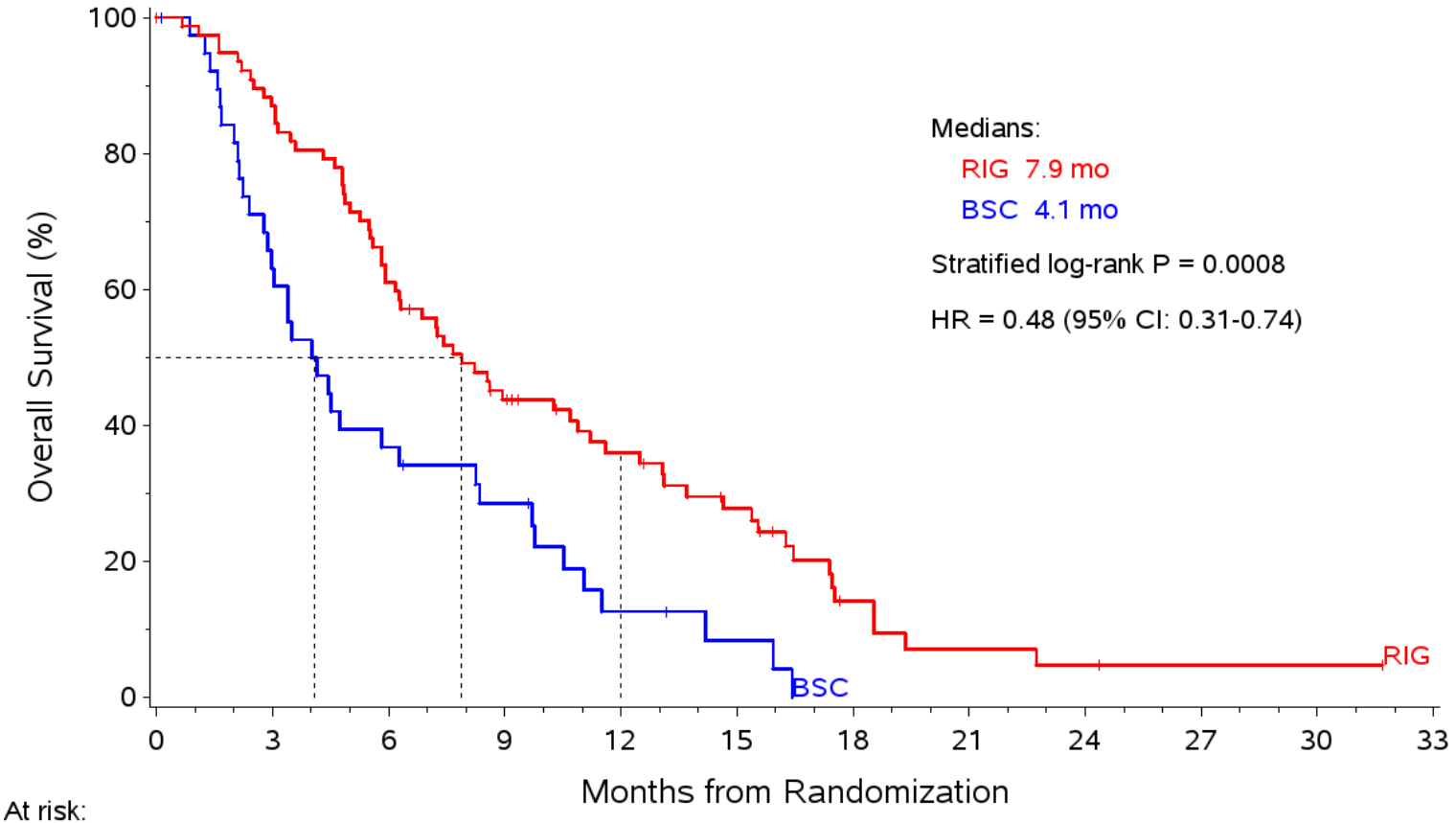
p < 0.05

Additional information on the relationship between rigosertib and karyotype mutations is available in Poster #3258

Study 04-21: Primary Efficacy Results – ITT



04-21: Proposed Patient Population (≤9 HMA DoT; <80 yrs; <6 Month from HMA)



IDH1/2 mutations in MDS

Present in ~4-12% of patients with MDS

Missense mutations: heterozygous; target highly conserved Arginine residues

IDH1: R132H mutations

IDH2: R172K or R140Q mutations

All variants produce 2-hydroxyglutarate (2-HG)

Mutations in IDH1/2 are associated with increased 5-methylcytosine

Initial reports: Unfavorable prognosis for IDH-mut MDS

Response to AG221(IDH2m-inhibitor) in IDH2m AML and MDS patients

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
CR	29 (18%) [95%CI: 13%, 25%]	4 (17%) [5%, 37%]	3 (21%) [5%, 51%]	37 (18%) [13%, 24%]
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (46%)	9 (38%)	6 (53%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)
Overall Response (CR, PR, CRp, CRi, mCR)	59 (37%) [95%CI: 30%, 45%]	10 (42%) [22%, 63%]	7 (50%) [23%, 77%]	79 (38%) [31%, 45%]

Stein EM, et al. Oral Presentation at ASH 2015. Abstract 323

In MDS, upfront HSCT will cure 20-30% of eligible patients

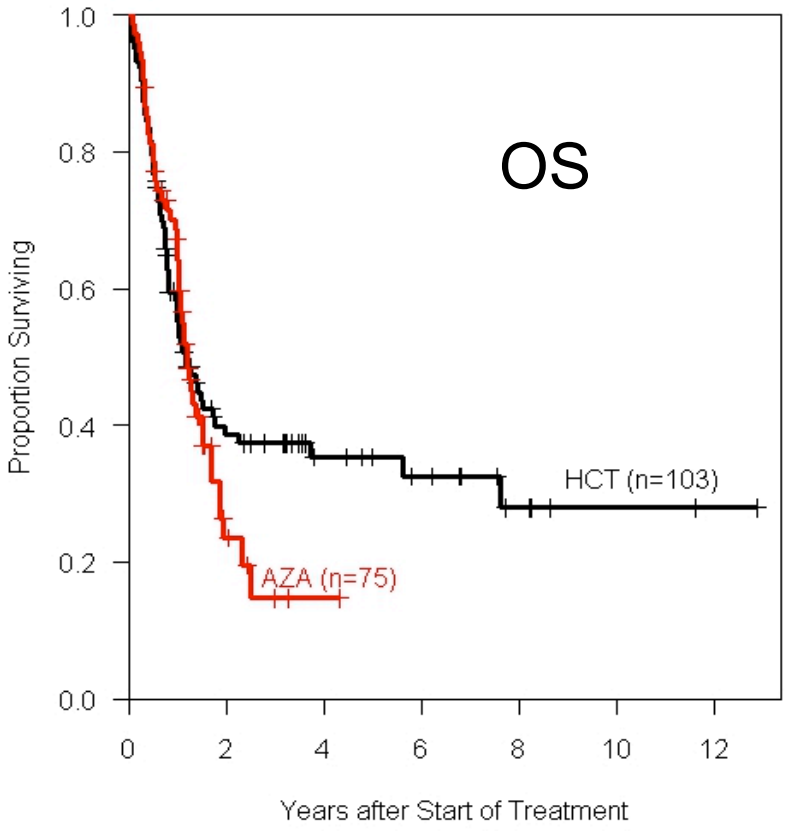
How many of these MDS patients are really fit to undergo HSCT ???

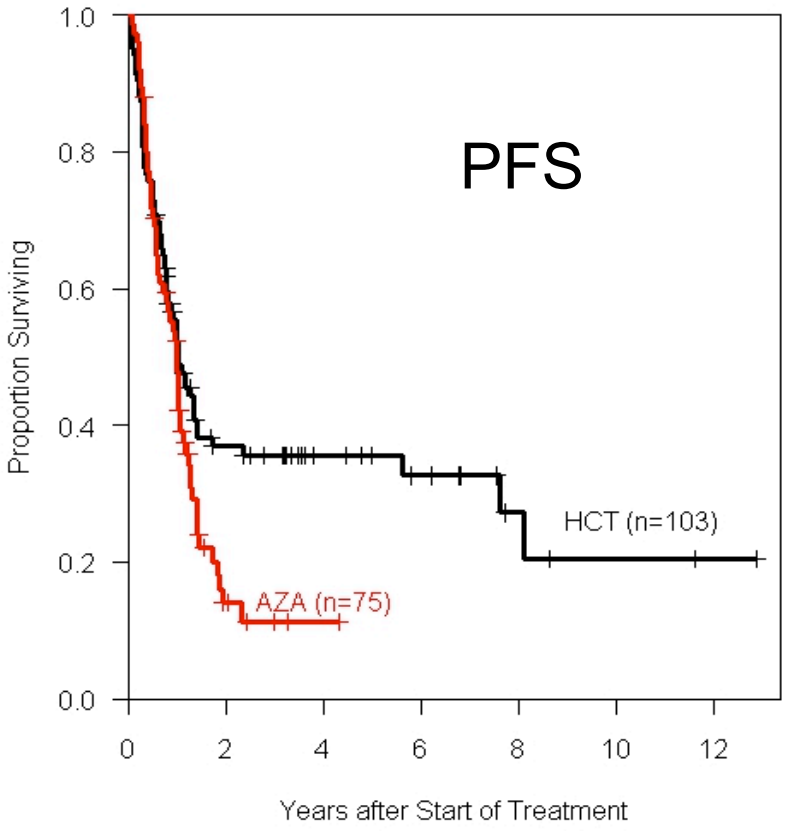
37/270 in Prebet survey (14%)

28/37 with prior intensive therapy

19/37 evaluable

Allogeneic HSCT vs AZA in MDS patients 60-70 years of age





Platzbecker et al. BBMT 2012

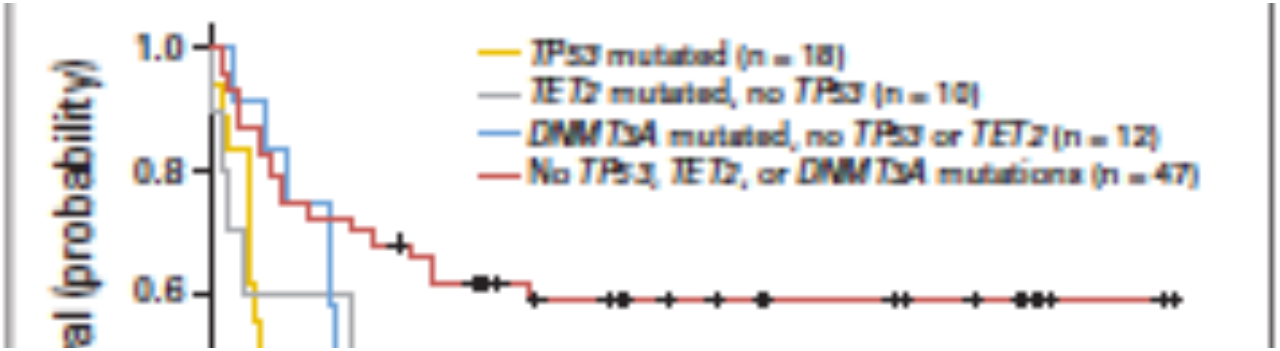
Azacitidine as a bridge to HSCT

Study	Drug	M Age	Pts	ORR prior to HSCT	Outcome after allo HSCT
Mc Carty BMT 2008	AZA	58	25	52 %	nr
Field BMT 2010	AZA	56	30	45%	OS (1 yr) 47% RR 20%
Kim BMT 2012	AZA/ DAC	54	19	59%	OS (1yr) 90% RR 25%
Gerd BBMT 2012	AZA	60	68	nd	OS (1 yr) 57% RR 29%
Damaj JCO 2012	AZA	57	163	nd	OS (3yrs) 55% RR 40%

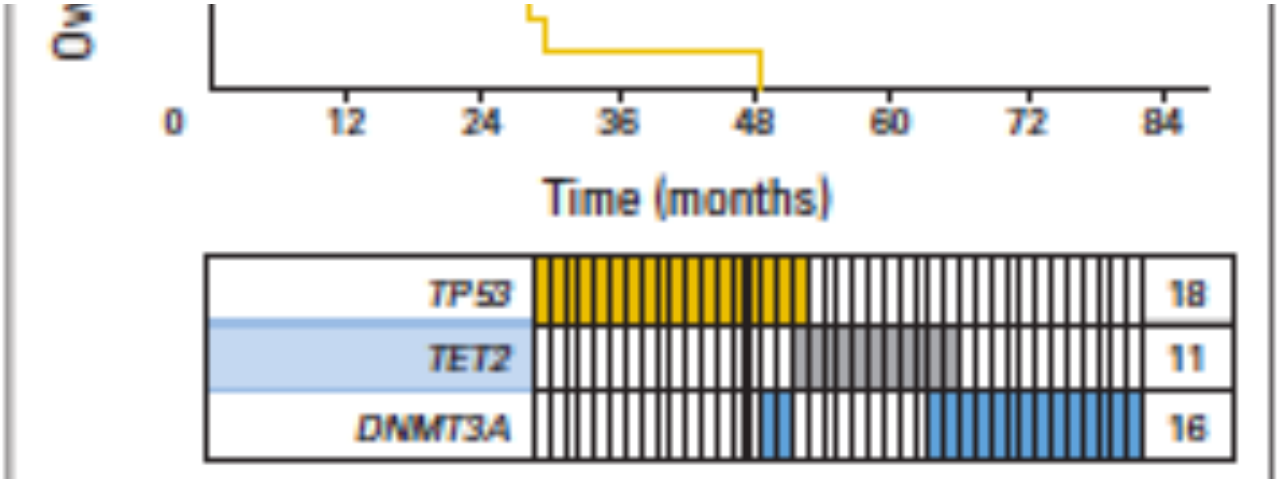
No broad analysis of pre-transplant conditioning regimens was undertaken in patients who received HSCT after hypomethylating agents (all RIC?)

What about QoL, GVHD and EFS?

HSCT is curative , but outcome is influenced by *some* mutations



Mutated RUNX1, ASXL1, SRSF2, and U2AF1 are not associated with shorter OS



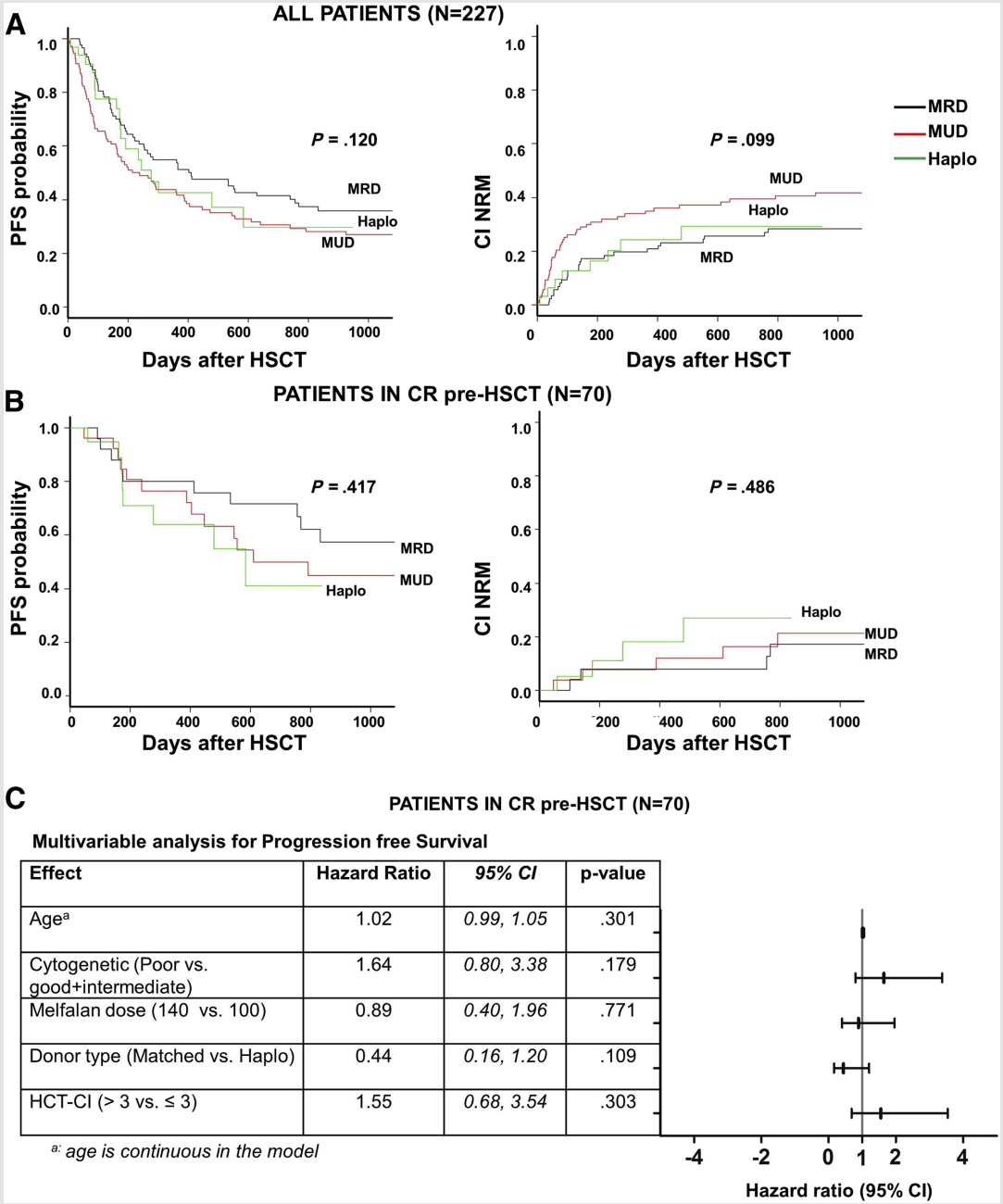
Bejar R et al , JCO 2014; 32: 25

Is haploidentical transplant our future for MDS?

Similar Transplantation Outcomes for Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients with Haploidentical versus 10/10 Human Leukocyte Antigen–Matched Unrelated and Related Donors

Antonio Di Stasi, Denái R. Milton, L.M. Poon, Amir Hamdi, Gabriela Rondon, Julianne Chen, Sai R. Pingali, Marina Konopleva, Piyanuch Kongtim, Amin Alousi, Muzaffar H. Qazilbash, Sairah Ahmed, Qaiser Bashir, Gheath Al-atrash, Betul Oran, Chitra M. Hosing, Partow Kebriaei, Uday Popat, Elizabeth J. Shpall, Dean A. Lee, Marcos de Lima, Katayoun Rezvani, Issa F. Khouri, Richard E. Champlin, Stefan O. Ciurea

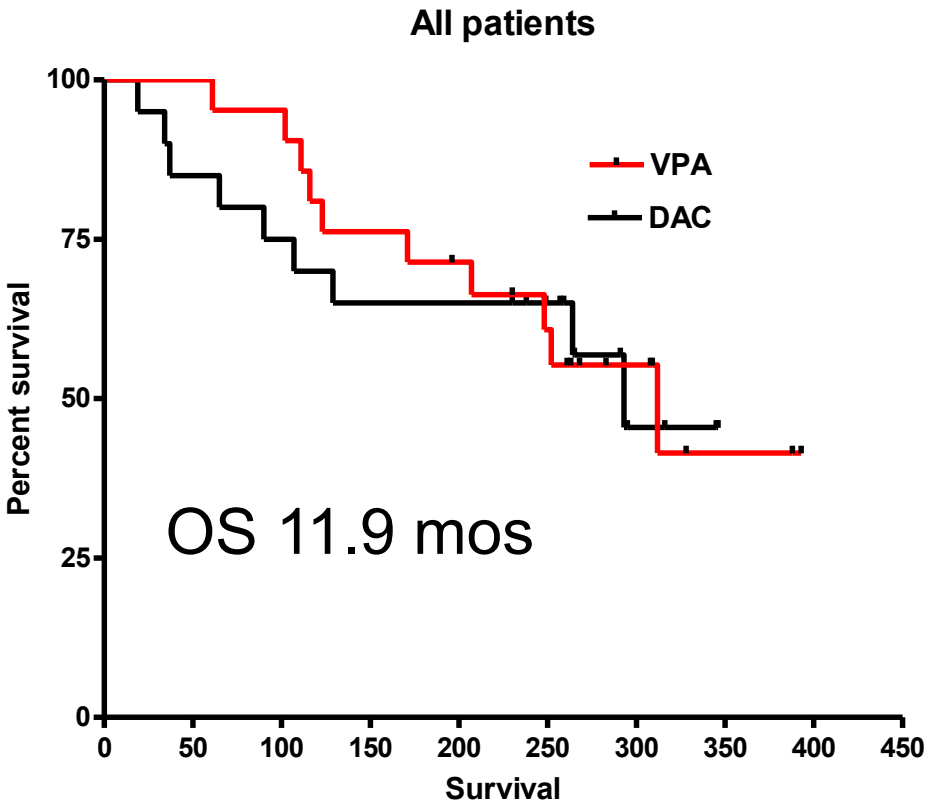
Biology of Blood and Marrow Transplantation
Volume 20, Issue 12, Pages 1975-1981 (December 2014)
DOI: 10.1016/j.bbmt.2014.08.013

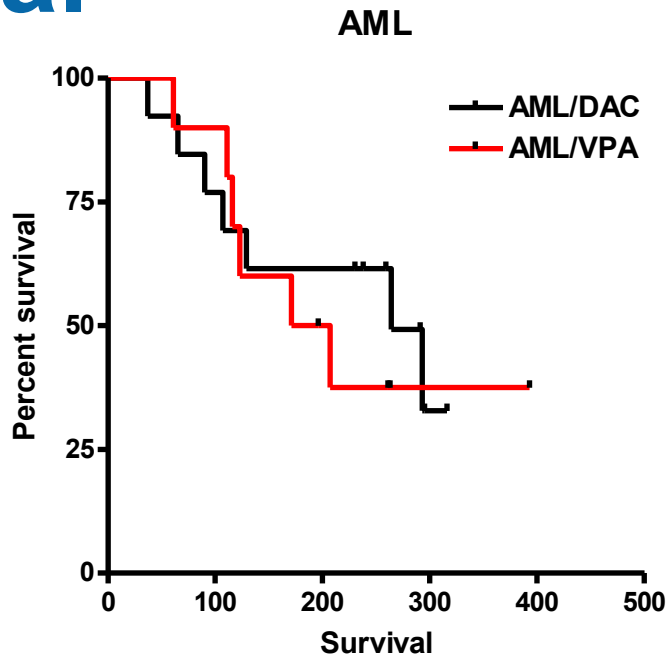


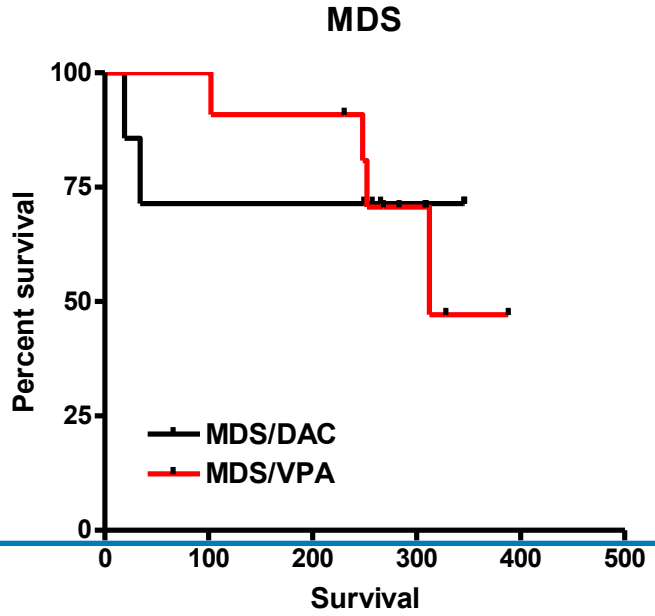
Biology of Blood and Marrow Transplantation 2014 20, 1975-1981DOI: (10.1016/j.bbmt.2014.08.013)

Is there still hope for combination therapy?

DAC +/- VPA Survival







Issa et al., Cancer. 2015 Feb 15;121(4):556-61.

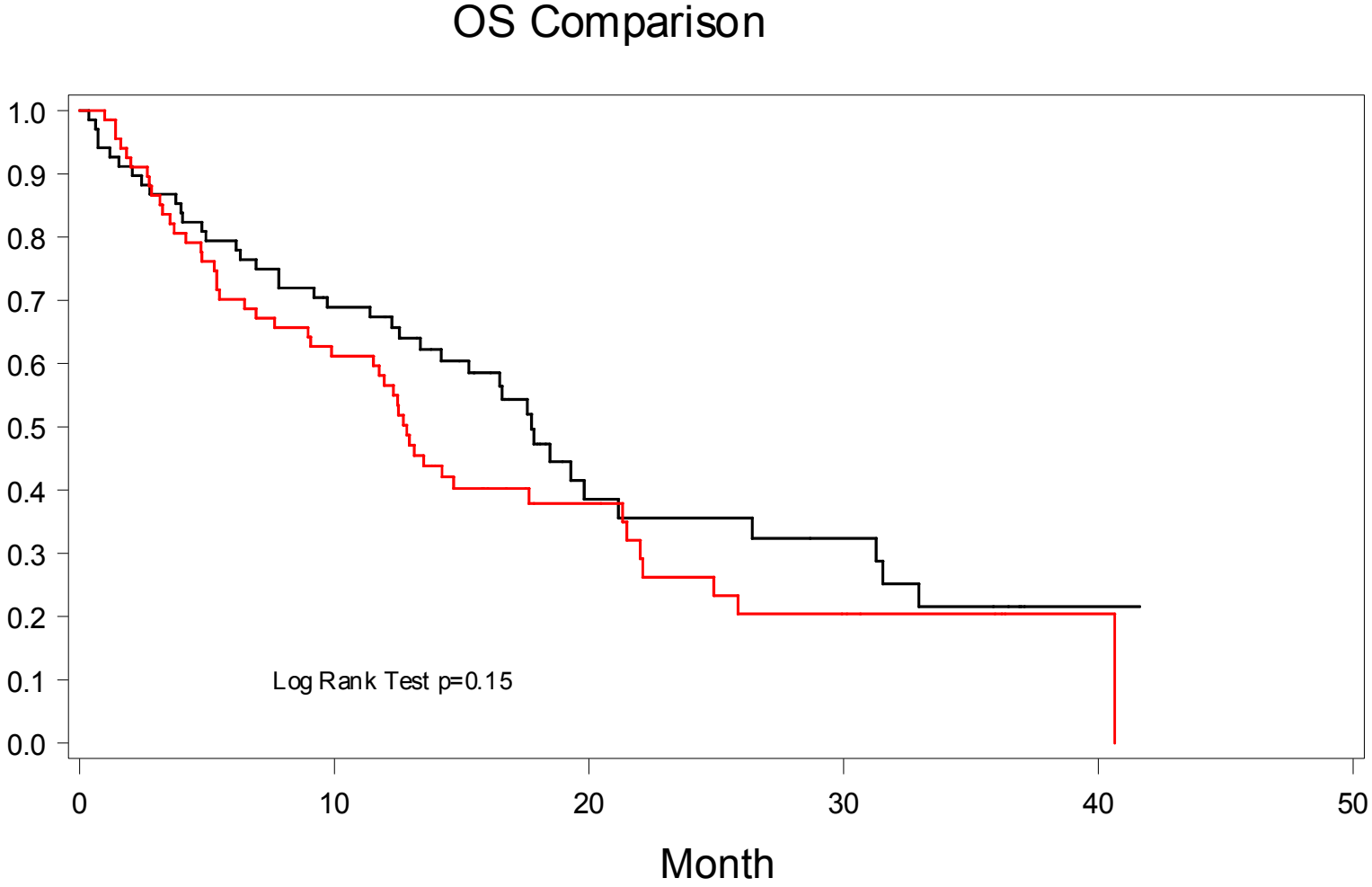
Azacitidine with or without Entinostat

Response evaluation (IWG 2000)

	Arm A AZA alone	Arm B AZA+ Entinostat
Complete Remission	Trilineage Response: 31%	Trilineage Response: 24%
Partial Remission		
Trilineage HI		
HI not trilineage	12%	19%
No response	57%	56%

Prebet et al 2012

Analysis of overall survival



Treatment	TOTAL	FAIL	CNSR	MEDIAN
Azacitidine	68	40	28	17.7
Azacitidine+Entinostat	68	47	21	12.8

AZA vs AZA + vorinostat in patients with MDS/AML and poor PS: phase II study

Phase II randomised* study of AZA vs AZA + V in patients with higher-risk MDS or newly diagnosed AML† usually ineligible for clinical trials due to comorbidities, organ dysfunction or poor PS

Patient baseline characteristics (n=79)	
Median age, years (range)	70 (30–90)
Median BM blasts, % (range)	8 (1–89)
Median WBC, x10^9/L (range)	2.8 (0.2–102)
Median PB blasts, % (range)	0 (0–78)
Cytogenetic risk, % normal favourable intermediate adverse missing	 25 1 16 52 5
Factors that precluded enrolment in other studies, % history of other malignancy ECOG PS ≥2 comorbidities‡/HIV positive other pts were higher priority	 46 11 22 22

AZA arm (n=27)
75mg/m^2 on days 1–5

Median cycles, n (range): 1 (1–12)

Median cycles, n (range): 3 (1–12)

AZA + V arm (n=52)
- AZA: 75m/mg^2 on days 1–5
- V: 200mg 3x daily on days 1–5

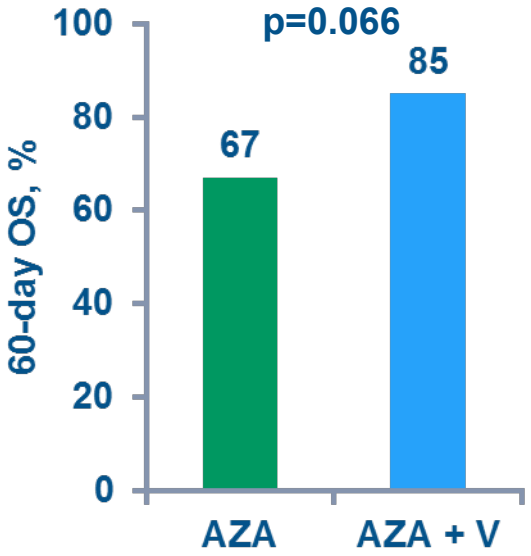
Outcomes
- Survival
  - 60-day OS (primary objective)
  - median OS
  - RFS
- Response
  - CR + CRp
- Safety

Garcia-Manero G, et al. Poster presentation at ASH 2014. Abstract 3277

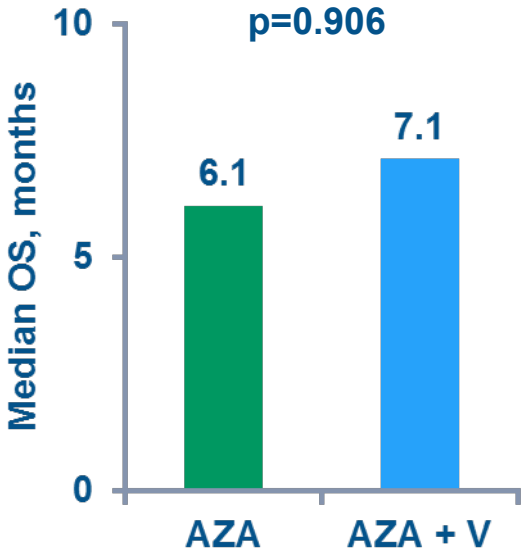
AZA vs AZA + vorinostat in patients with MDS/AML and poor PS: phase II study

- Median follow-up: **9.5 months**
- Patients alive at last follow up, n (%): **23 (29)**

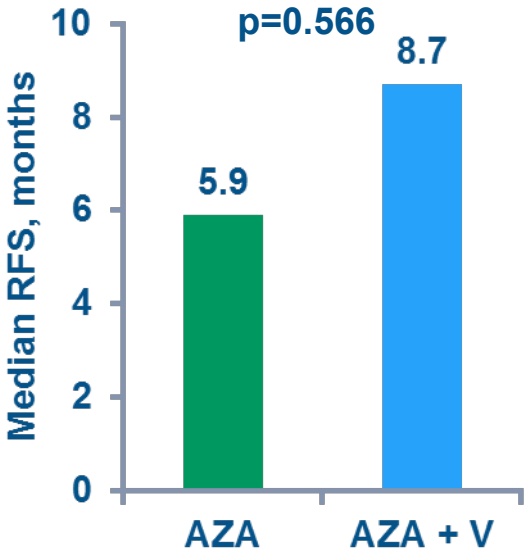
60-day OS



Median OS

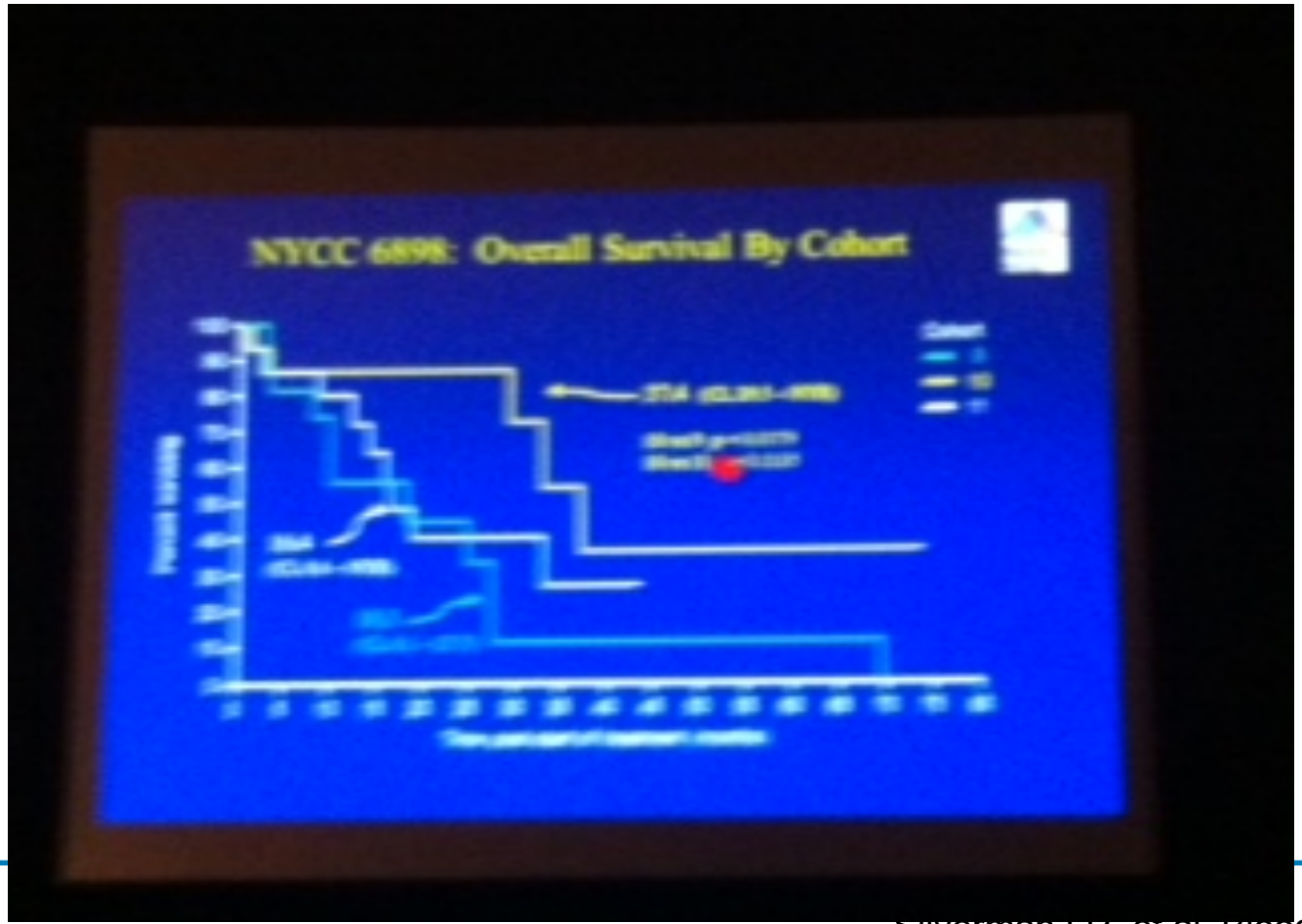


RFS



Garcia-Manero G, et al. Poster presentation at ASH 2014. Abstract 3277

Combination of azacitidine and vorinostat in high risk MDS patients aza 75mg/m2/die plus vorinostat 600mg/die for 7 days

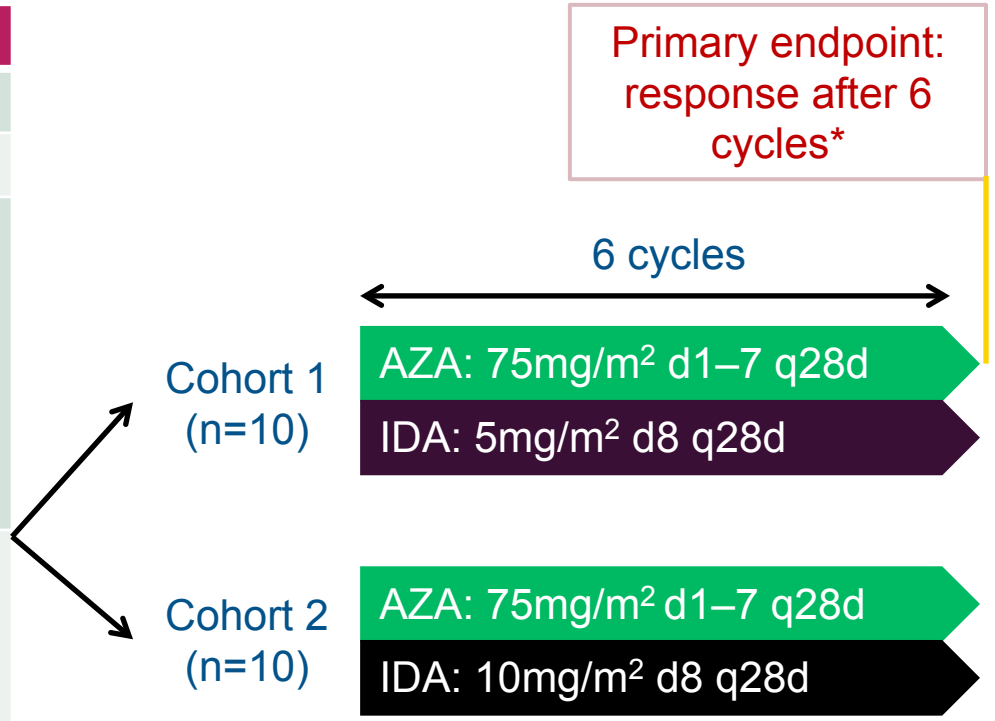


Silverman LR, et al. Blood. 2013 abs ASH

Azacitidine + idarubicin combination therapy in patients with high-risk MDS or AML

Phase I/II trial of azacitidine (AZA) combined with idarubicin (IDA) in untreated patients with high-risk MDS or WHO-AML (20–30% blasts)

Patient characteristics (N=20)	
Median age, years	75
Male/female, %	65/35
WHO diagnosis, %	
RCMD	5
CMML	5
RAEB-1	30
RAEB-2	35
AML (20–30% blasts)	15
MDS unknown	10
IPSS cytogenetics, %	
Favourable	35
Intermediate	15
Unfavourable	40
NA	10
Performance status, %	
0	28
1	50
2	22

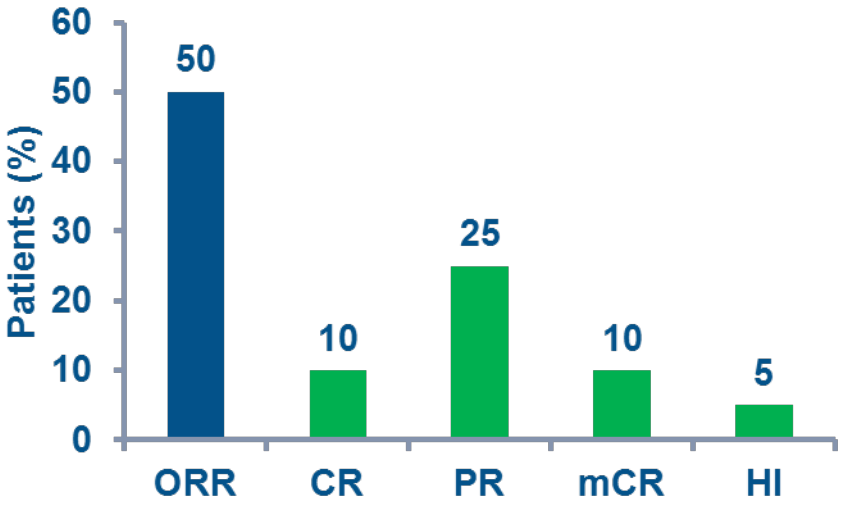


*Responding patients could continue AZA + IDA treatment for a further 3 cycles then continue AZA therapy

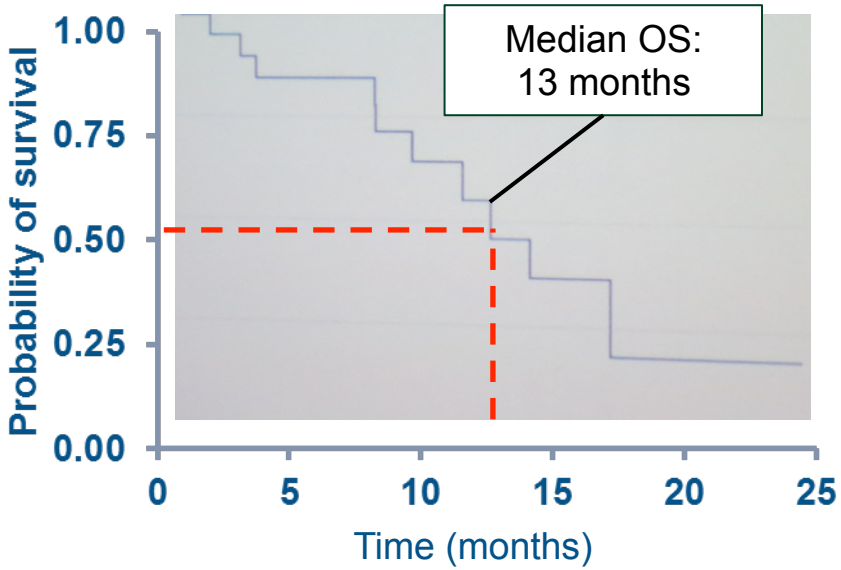
Ades L, et al. Oral presentation at MDSF 2013. Abstract O-011

Azacitidine + idarubicin combination therapy in patients with high-risk MDS or AML

Response after 6 cycles

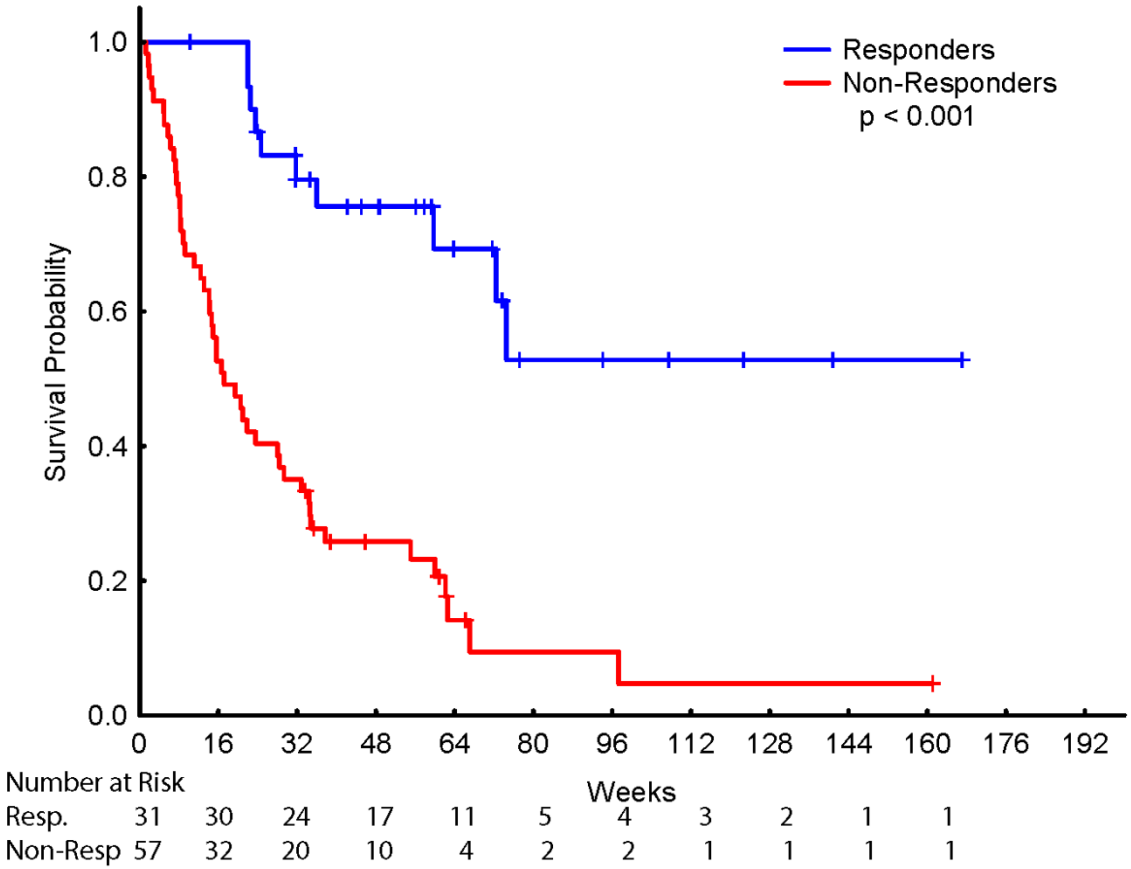


Overall survival

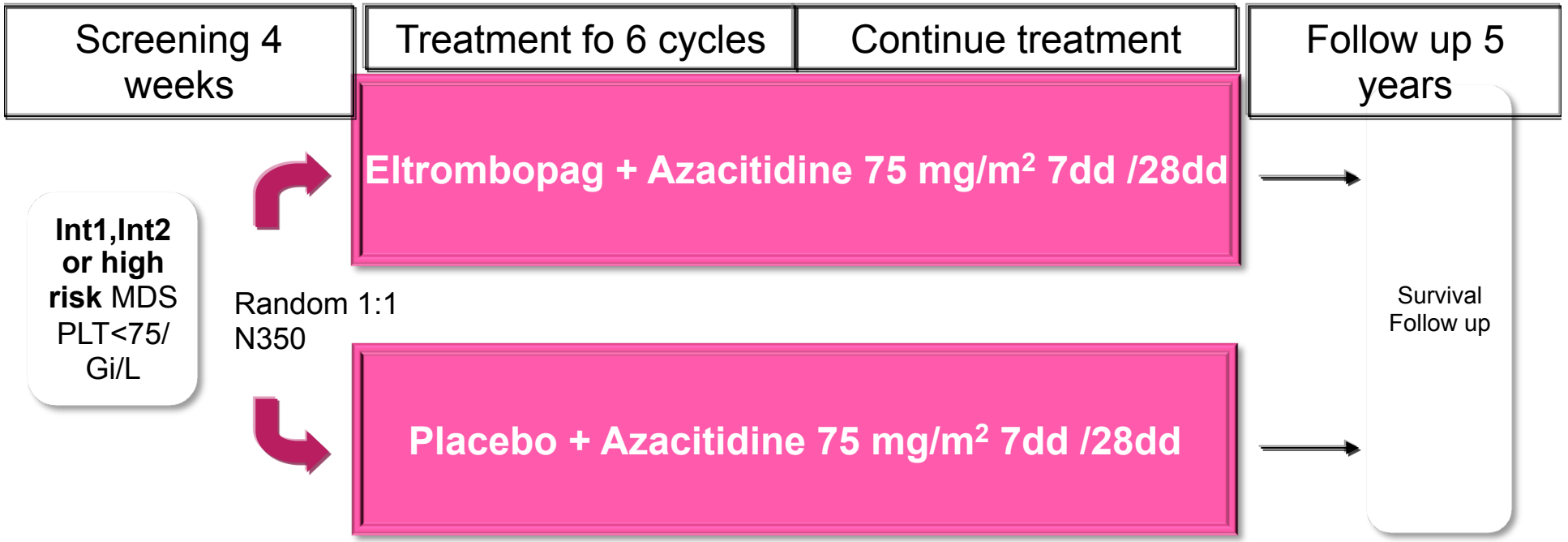


- Ten patients responded, six are still on study

AZA + LEN. OS by Response



Eltrombopag plus azacitidine: TRC112121 Support



Eltrombopag plus azacitidine: TRC112121 Support

- On December 16° recommendation from the IDMC **to stop** the SUPPORT study based on a risk/benefit assessment:
- Primary reason: due to futility analysis
- Secondary reason: due to safety
- The results show that **the futility criterion has been met**. The observed p-value is >0.9 and the estimated treatment effect favor to placebo.
- The IDMC noted that while there was no difference in overall deaths that would indicate harm, there is **a trend towards disease progression, favoring placebo**

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