Treatment of high risk MDS

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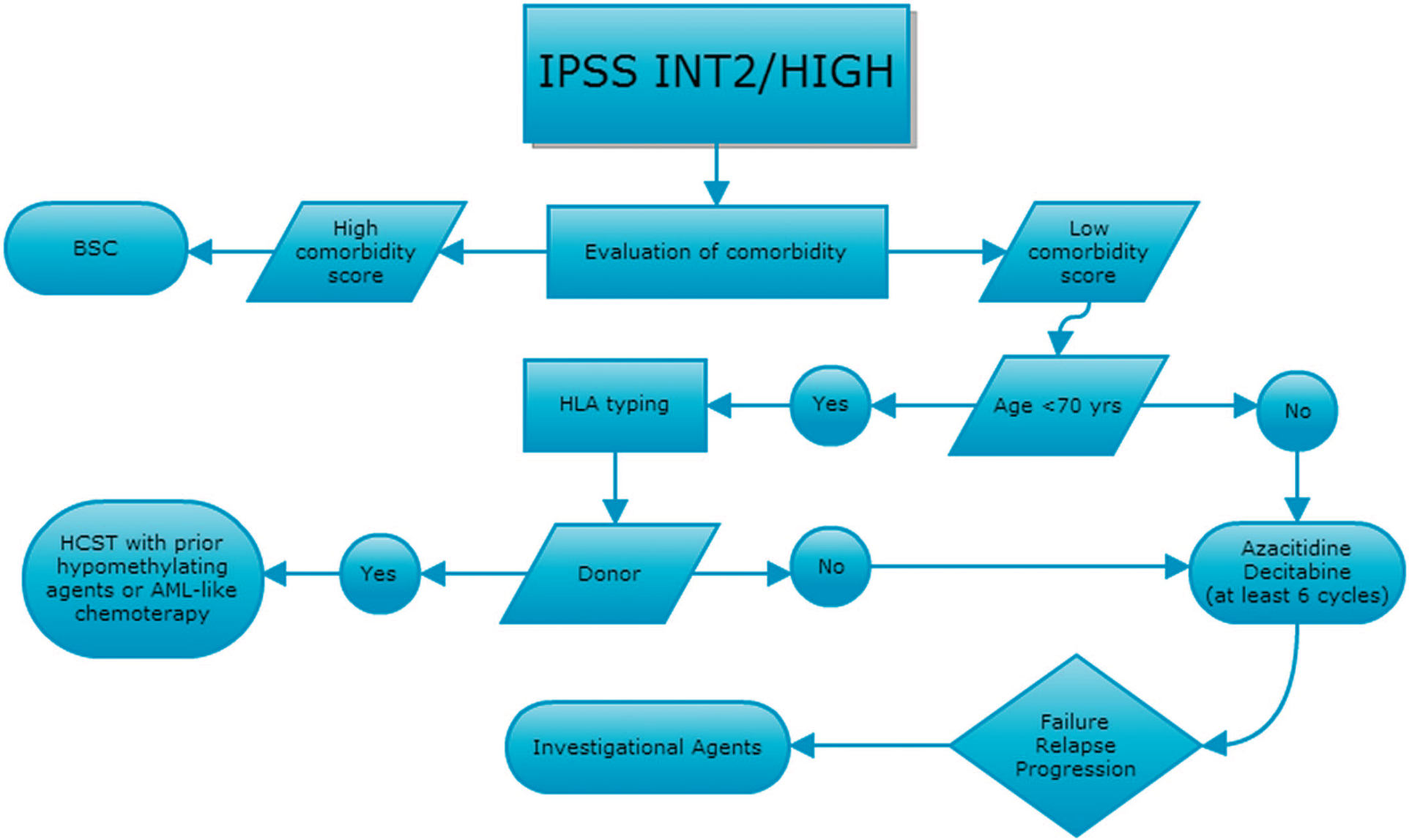
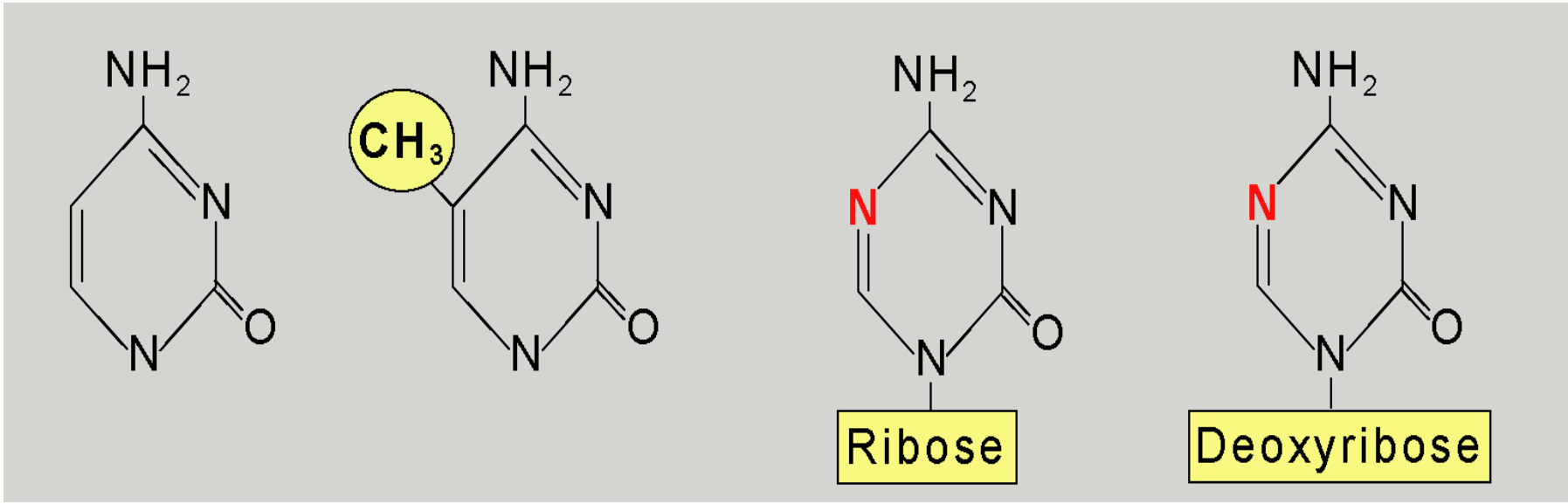
Therapeutical options



Azanucleosides, Cytosine Analogues with hypomethylating properties



Cytosine

5-methyl-cytosine

5-aza-cytidine

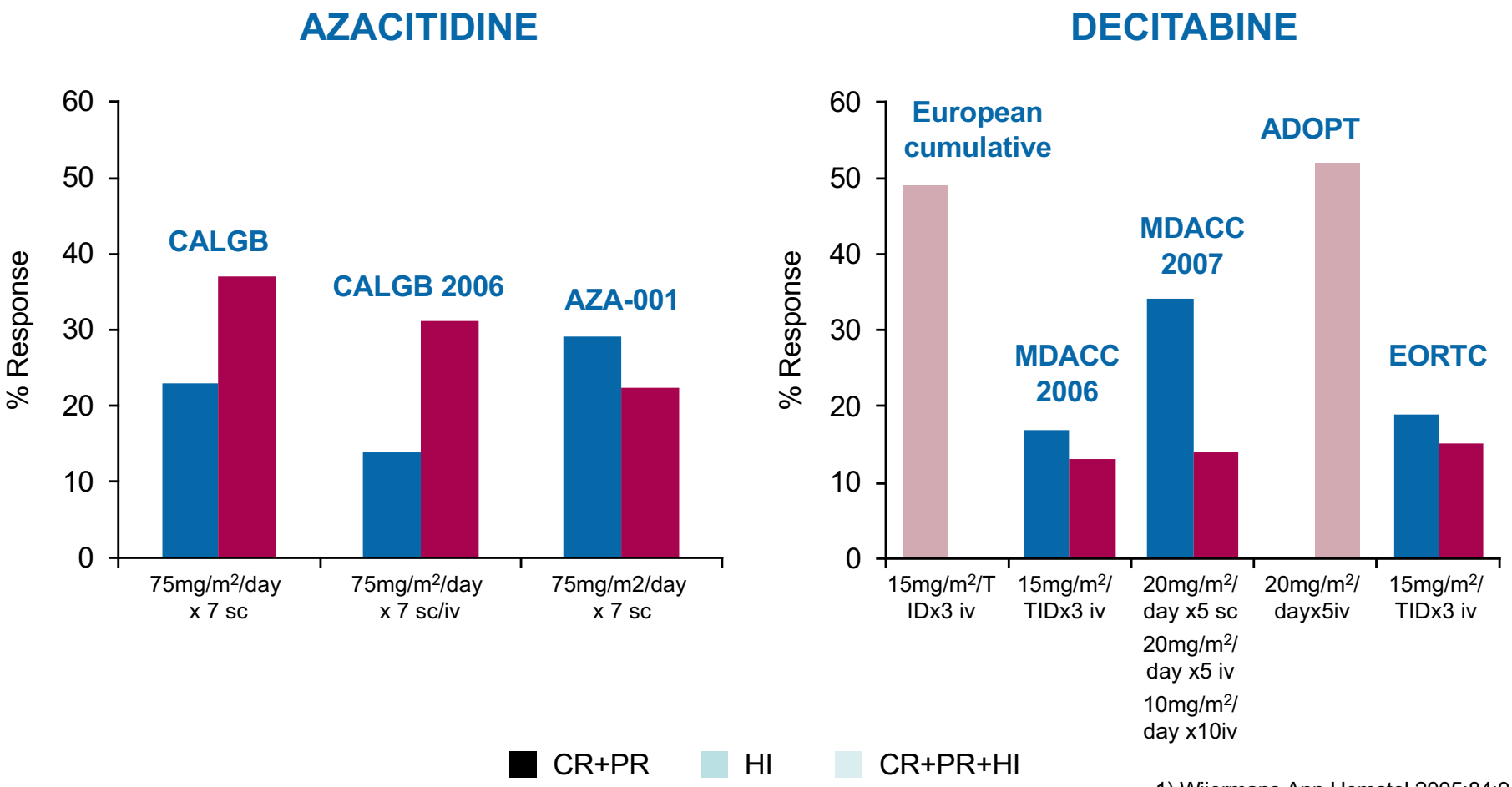
Azacitidine

5-aza-2'-deoxy-cytidine

Decitabine

Santini et al, Ann Int Med 2001

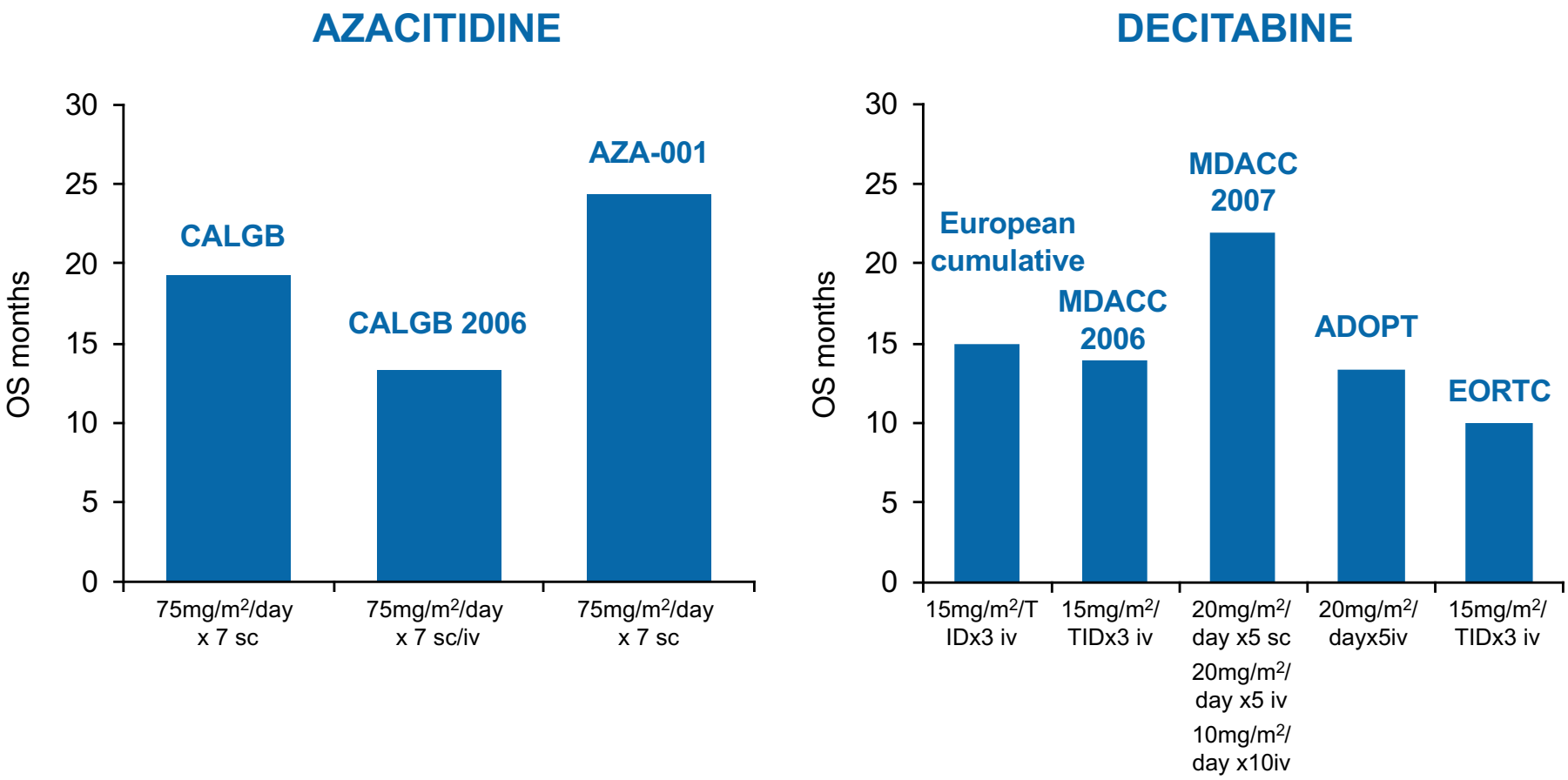
Hypomethylating agents in higher risk MDS: response



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



1) Silverman JCO 2002;20:2429
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3) Kantarjian Blood 2007;109:52
4) Steensma JCO 2009;24:3842
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Response duration with decitabine or azacitidine therapy ranges from 6 to 26 months

FACTS OF HYPOMETHYLATING AGENTS

Beneficial effects of hypomethylating agents are noted generally after 2-4 cycles of therapy

Achievement of sole hematological improvement may assure prolonged survival

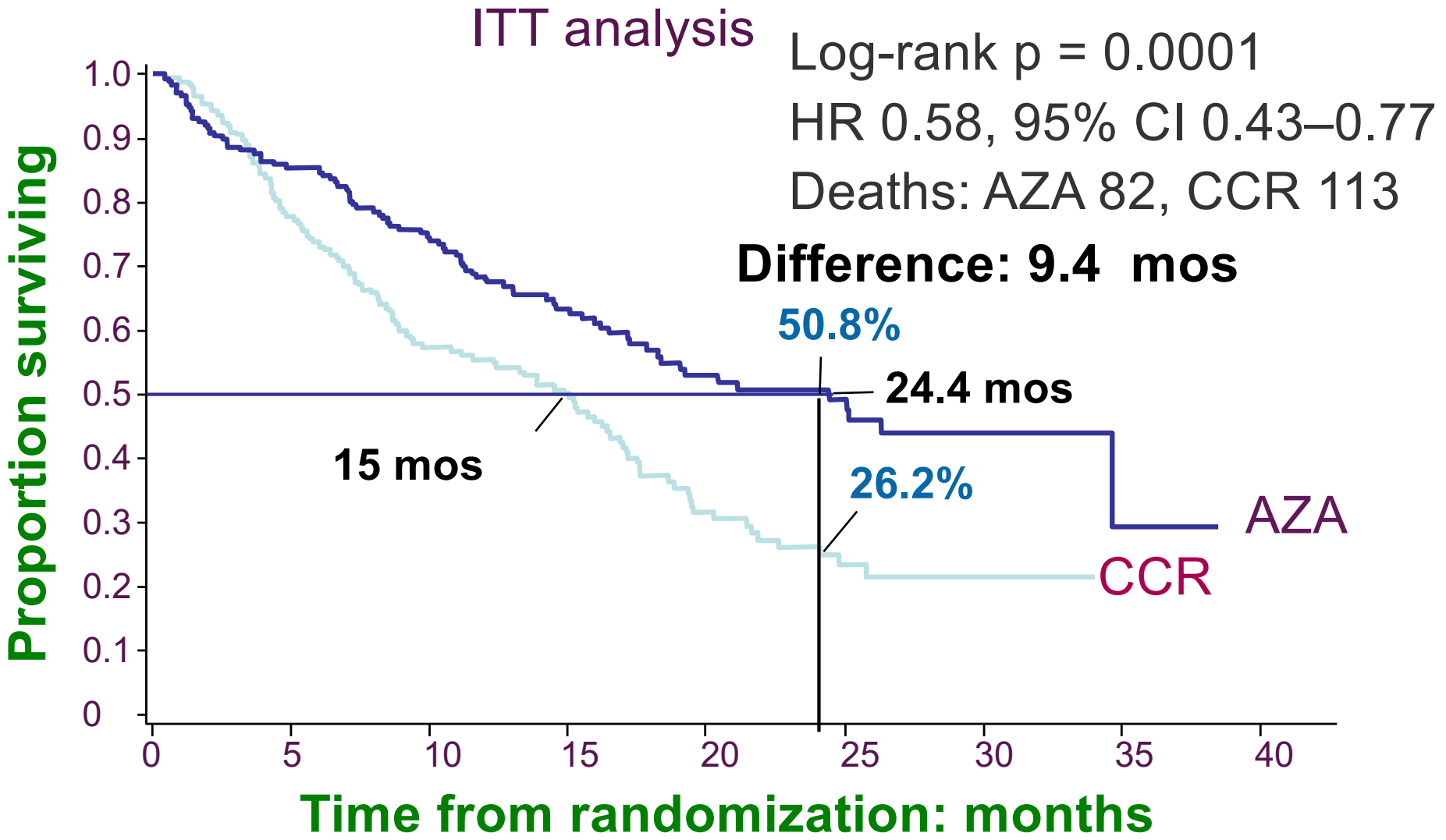
Patients with complex karyotype may achieve response although not durable

Interruption of treatment provokes loss of response

BUT…
Patients resistant or relapsed have an extreme short survival irrespective of further treatment

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)

Overall survival: AZA vs CCR



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

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

MDS: treatment with HMT

Advantages:

prolonged survival

high rate hematologic improvement

no need of hospitalization

low toxicity

feasible in very elderly patients

Disadvantages:

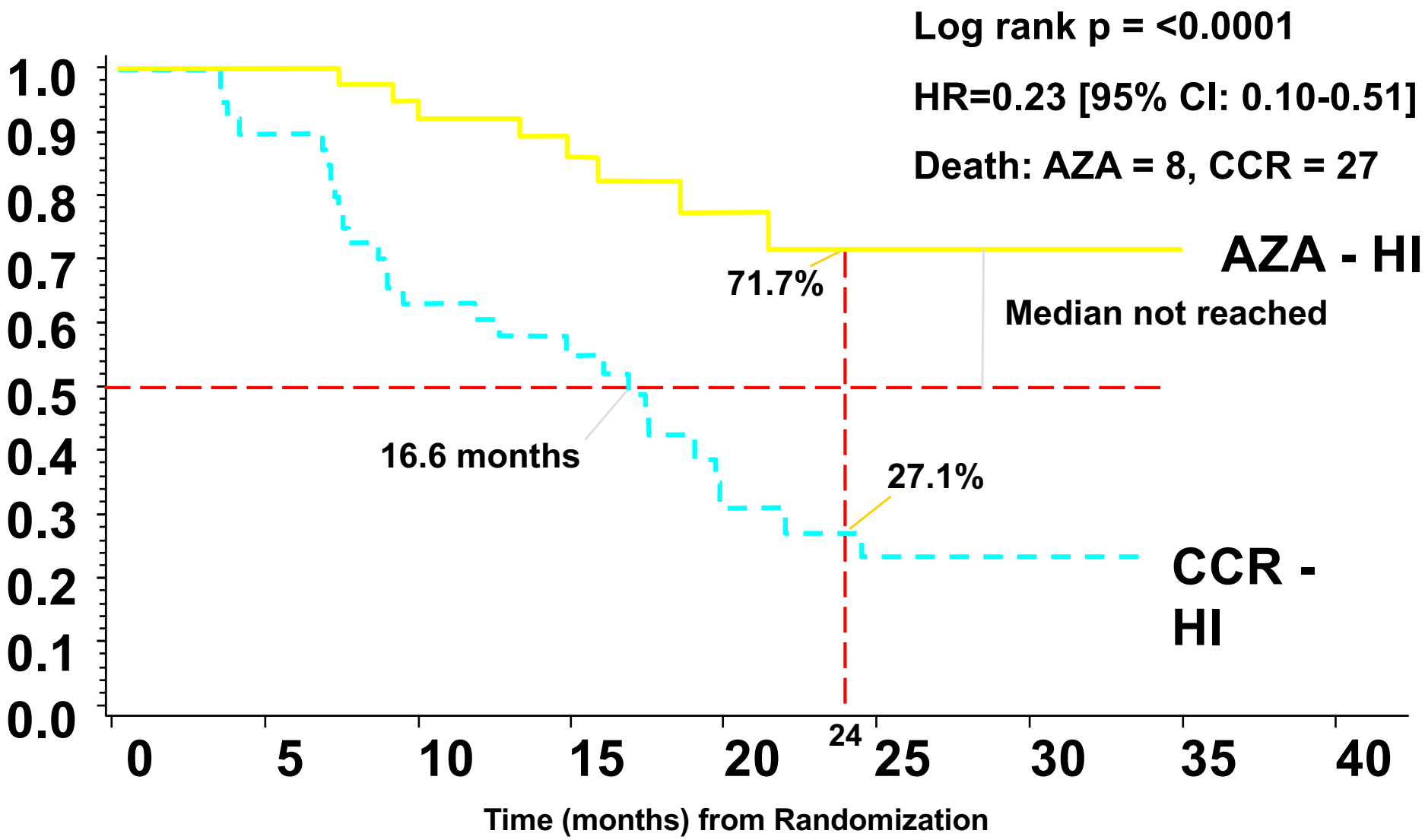
prolonged treatment

retarded effect

relapse/resistance

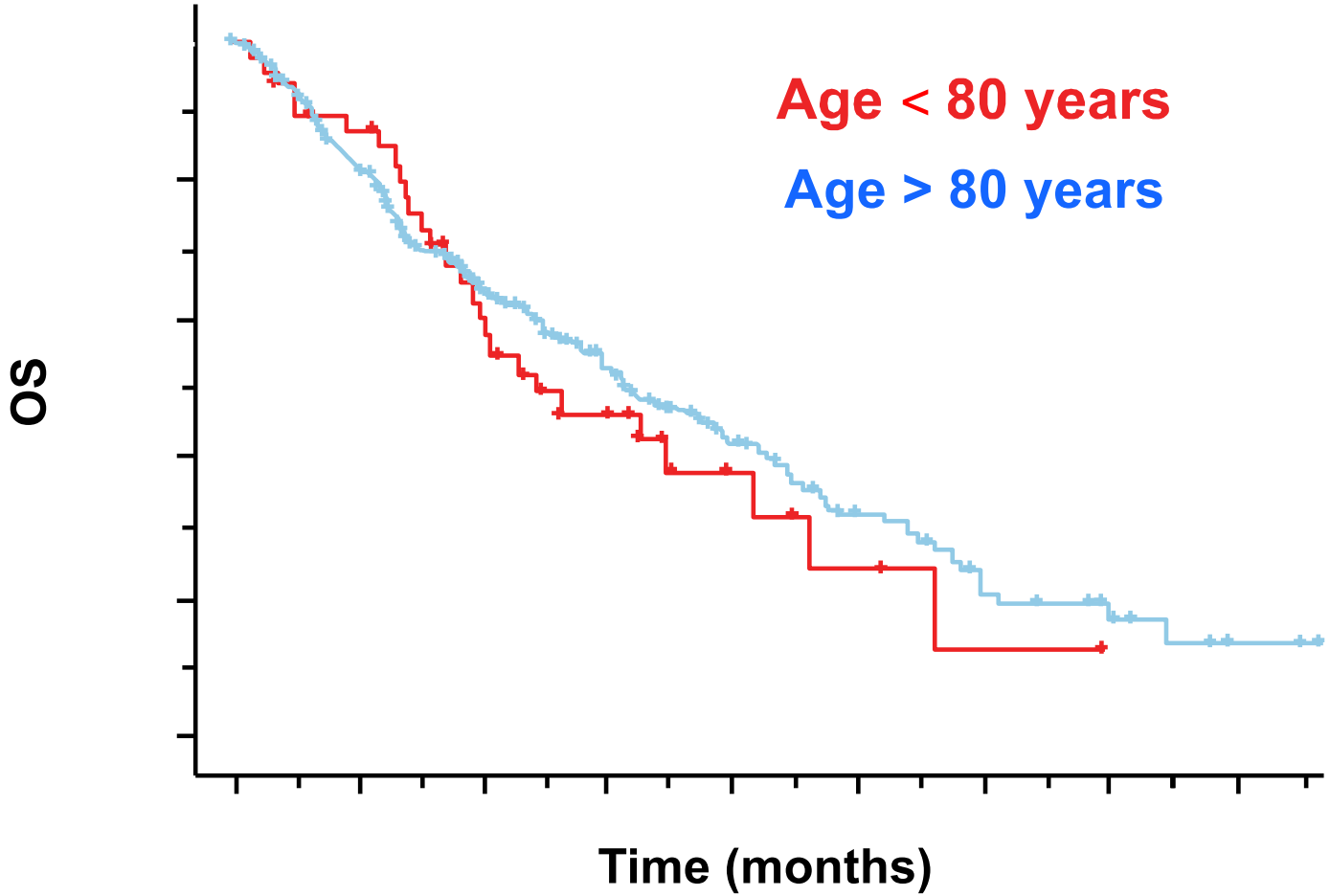
no eradication of the clone

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



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

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

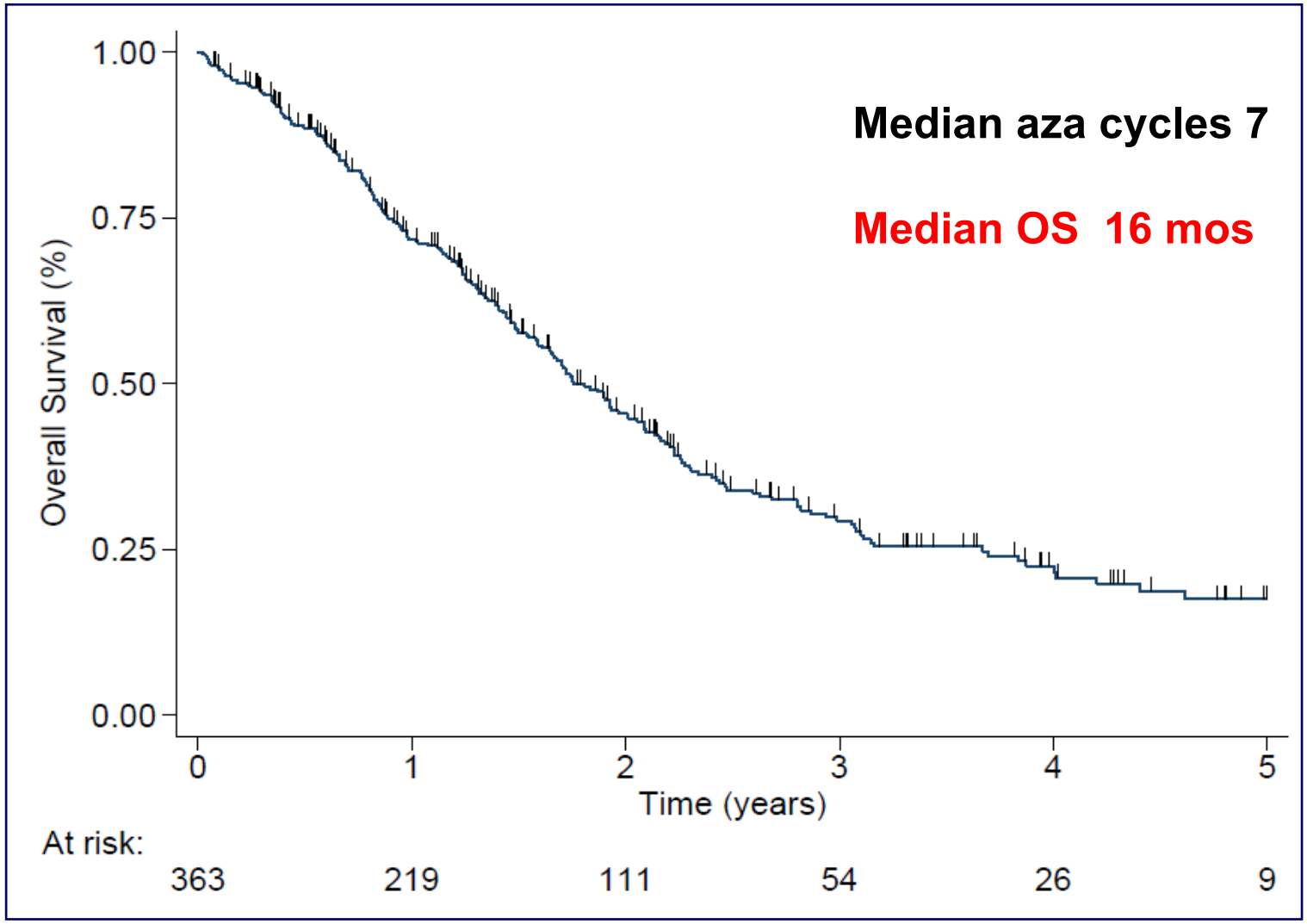


- OS similar in patients aged < 80 and ≥ 80 years (*P* = .6)
- Median OS 12.1 months; 1- and 2-year OS: 50% and 23.2%

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

What happens in real life?

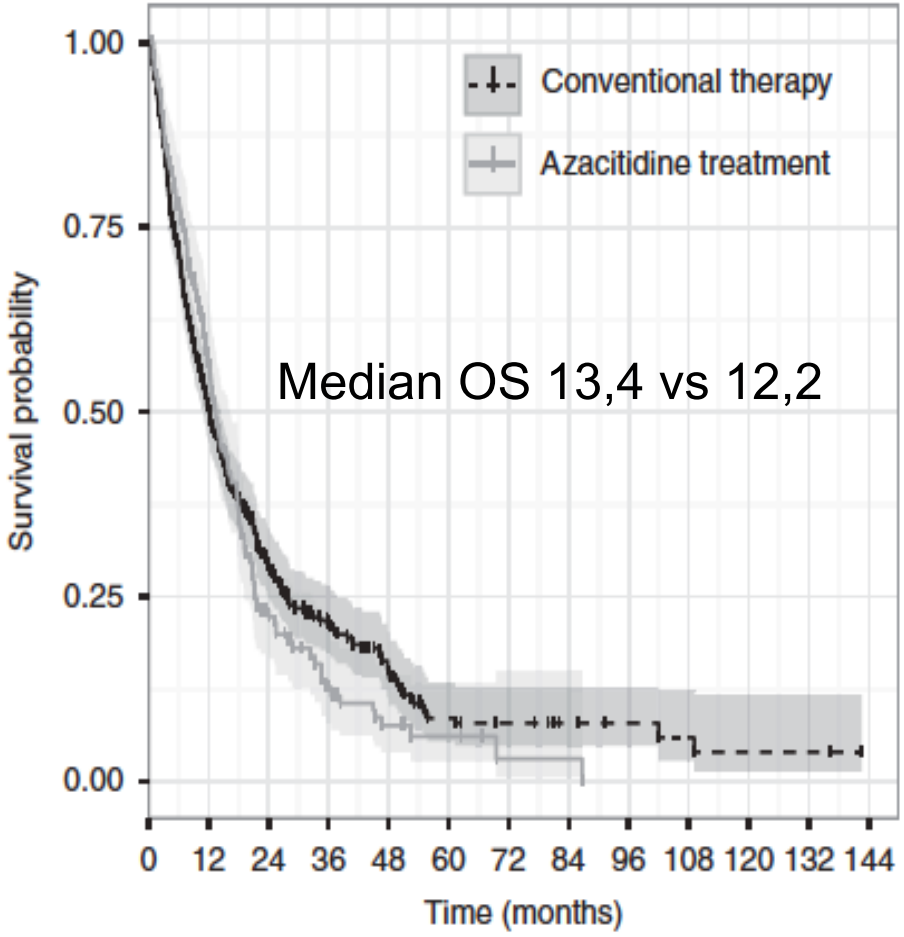
370 higher risk MDS pts treated with AZA

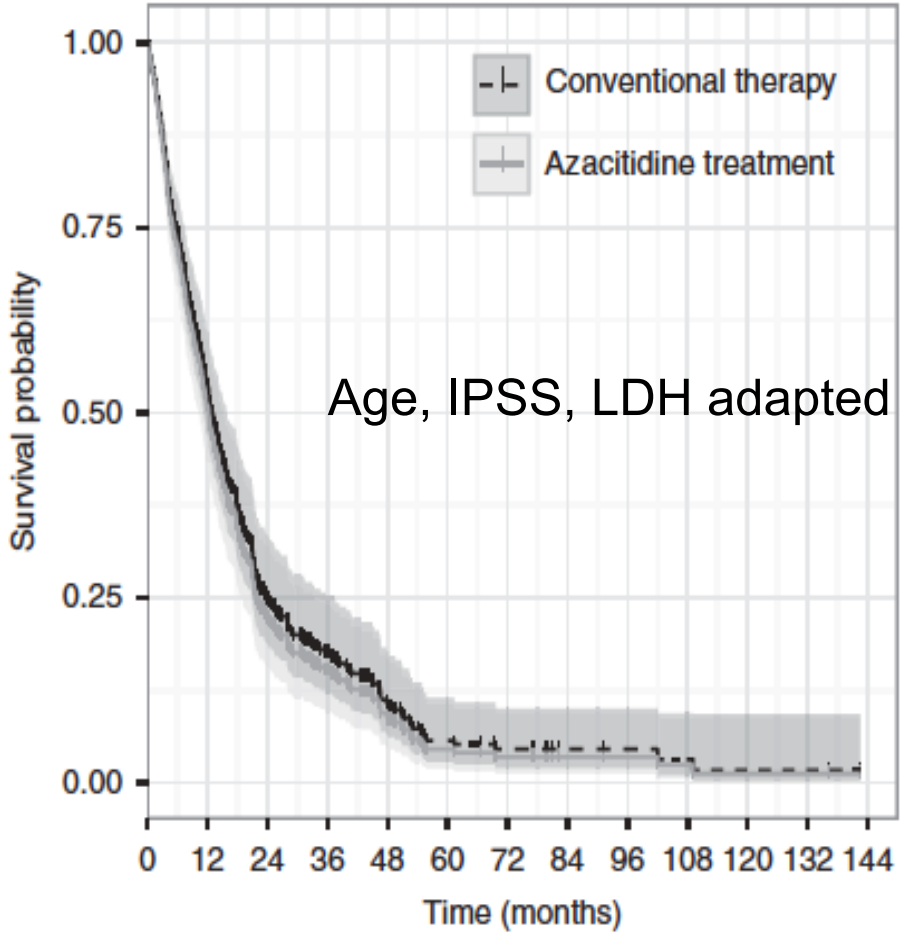


FISM
FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

What happens in real life?

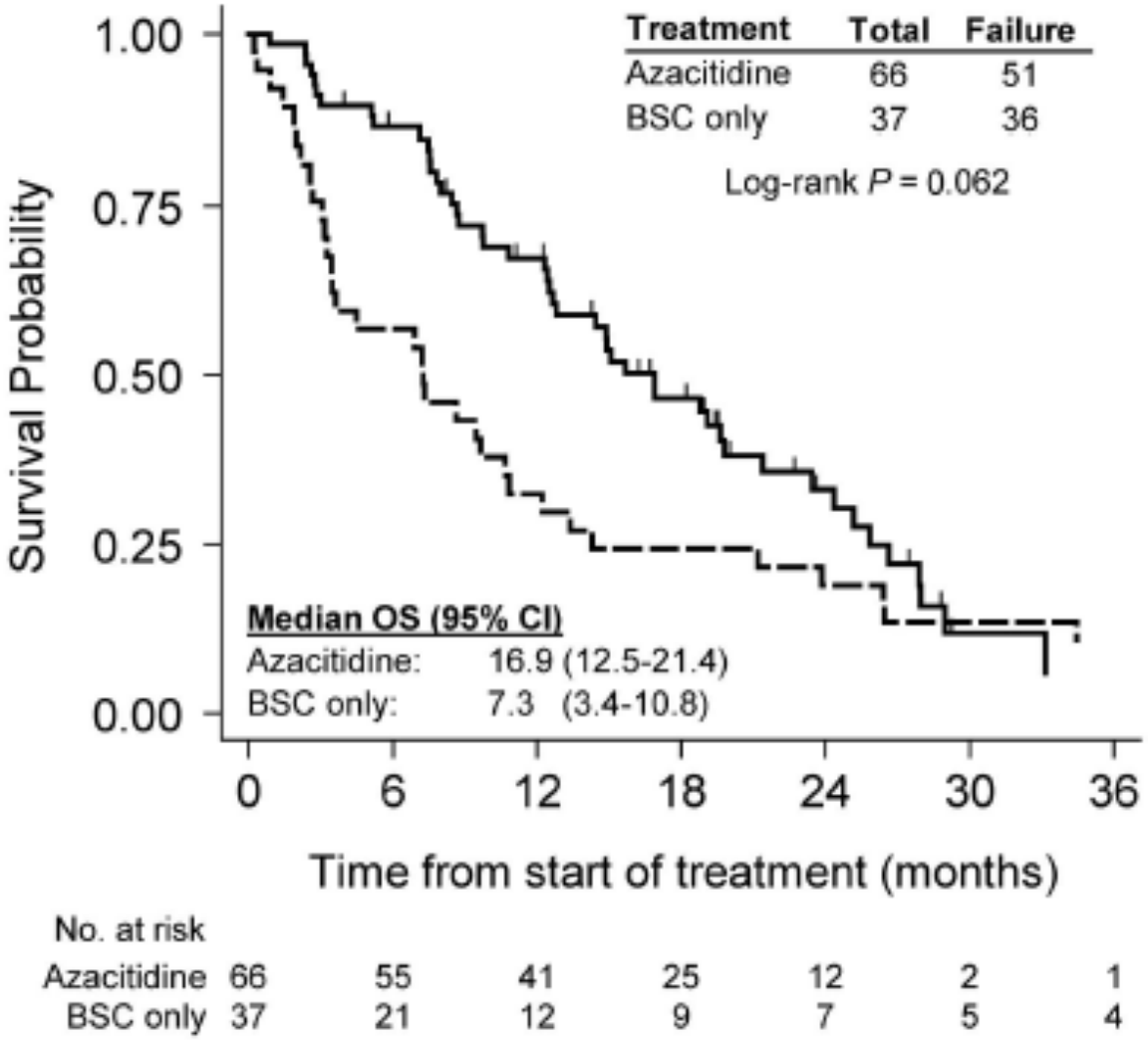
AZA treatment/Spanish experience





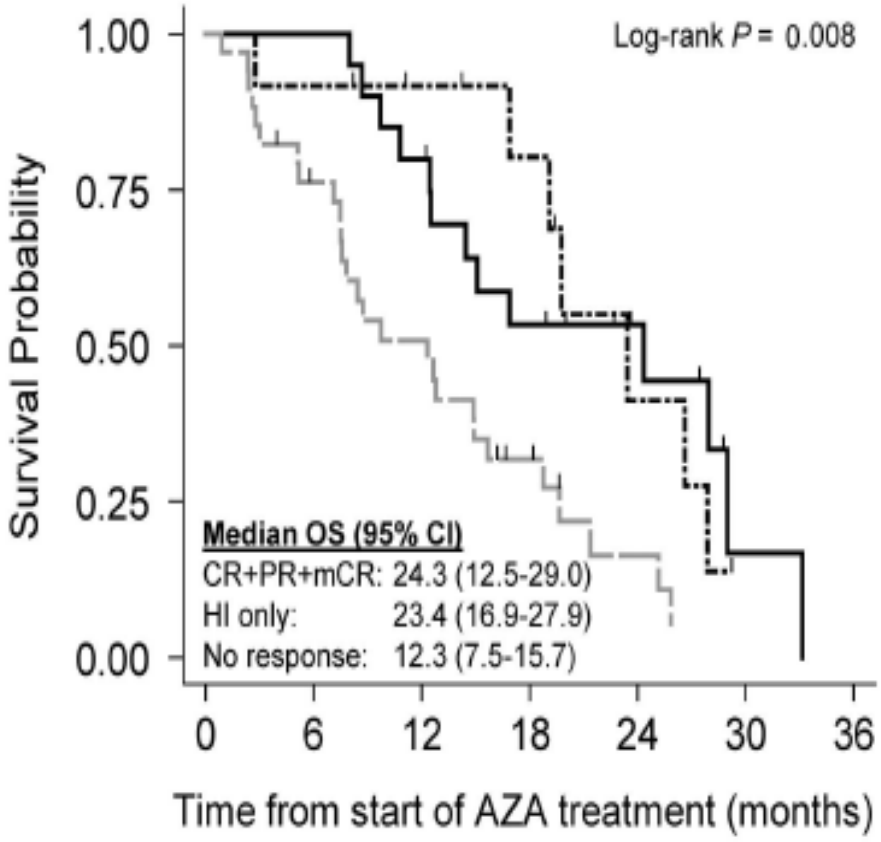
Bernal et al, Leukemia (2015) 29, 1875–1881

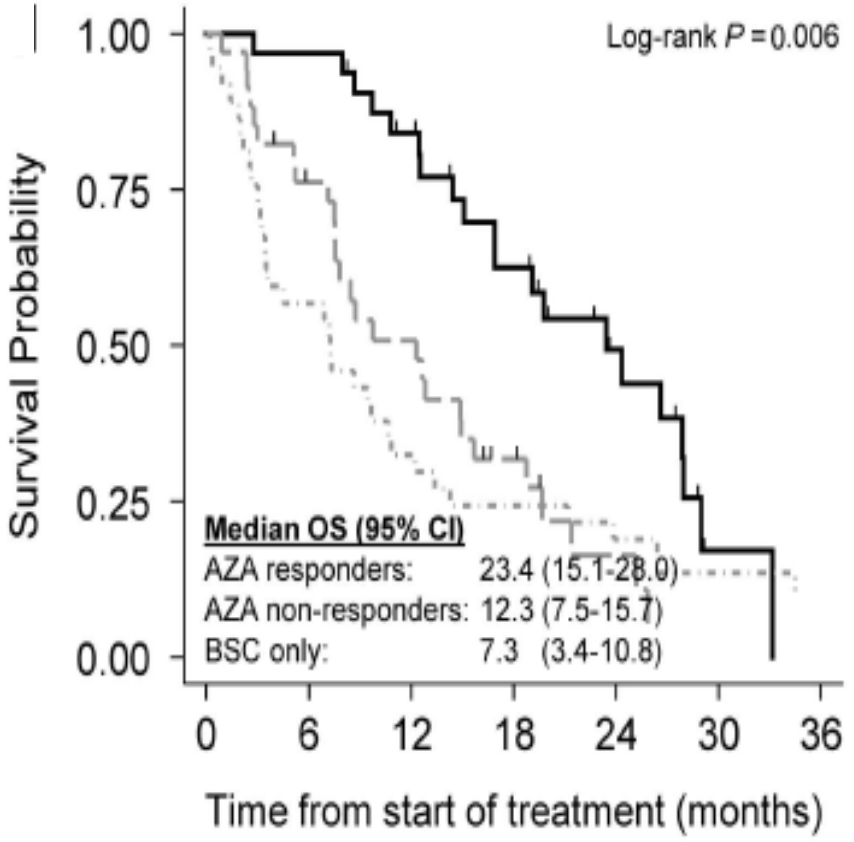
What happens in real life?
AZA treatment Dutch experience



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

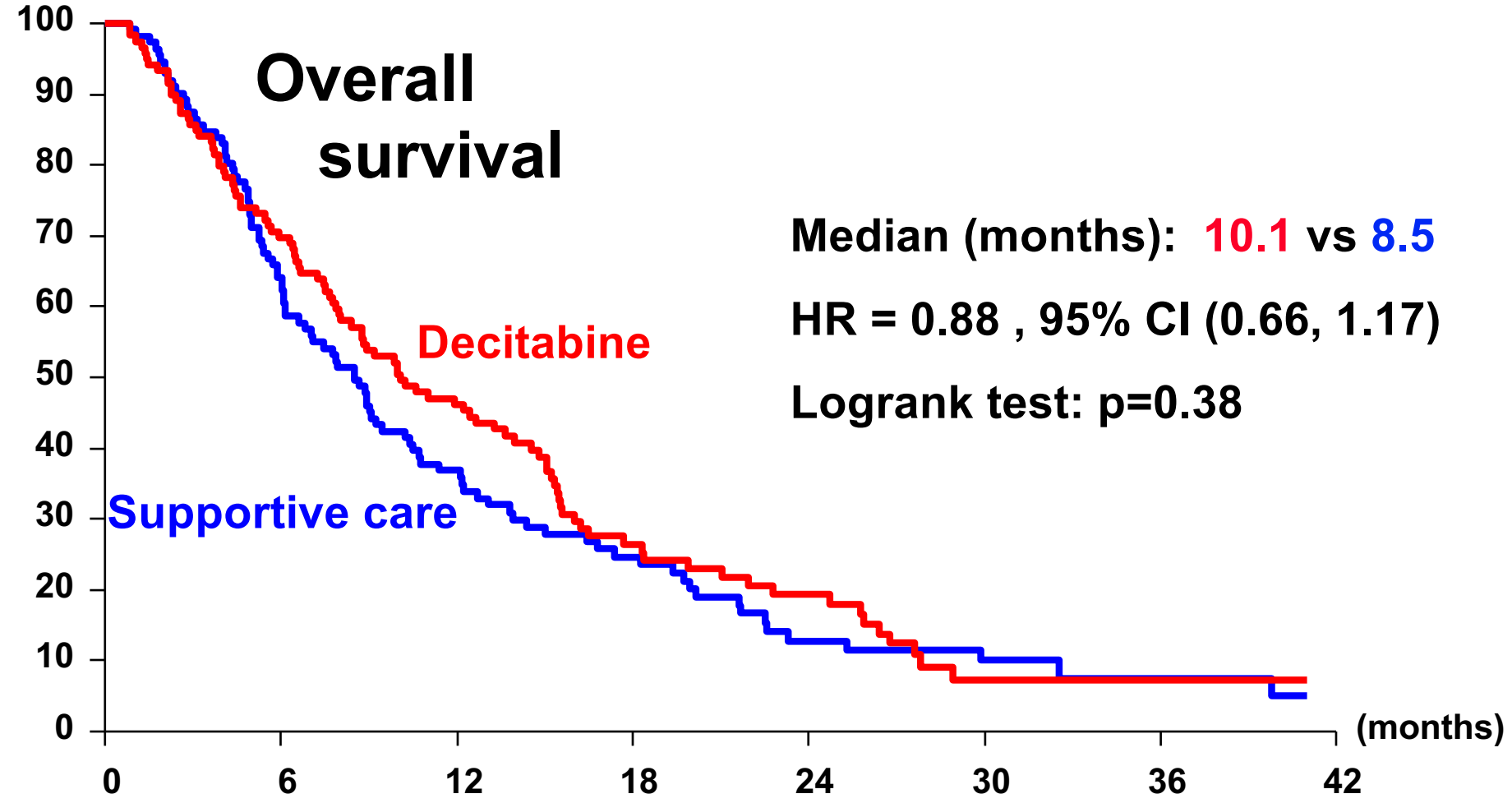
What happens in real life?
AZA treatment/Dutch experience





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

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

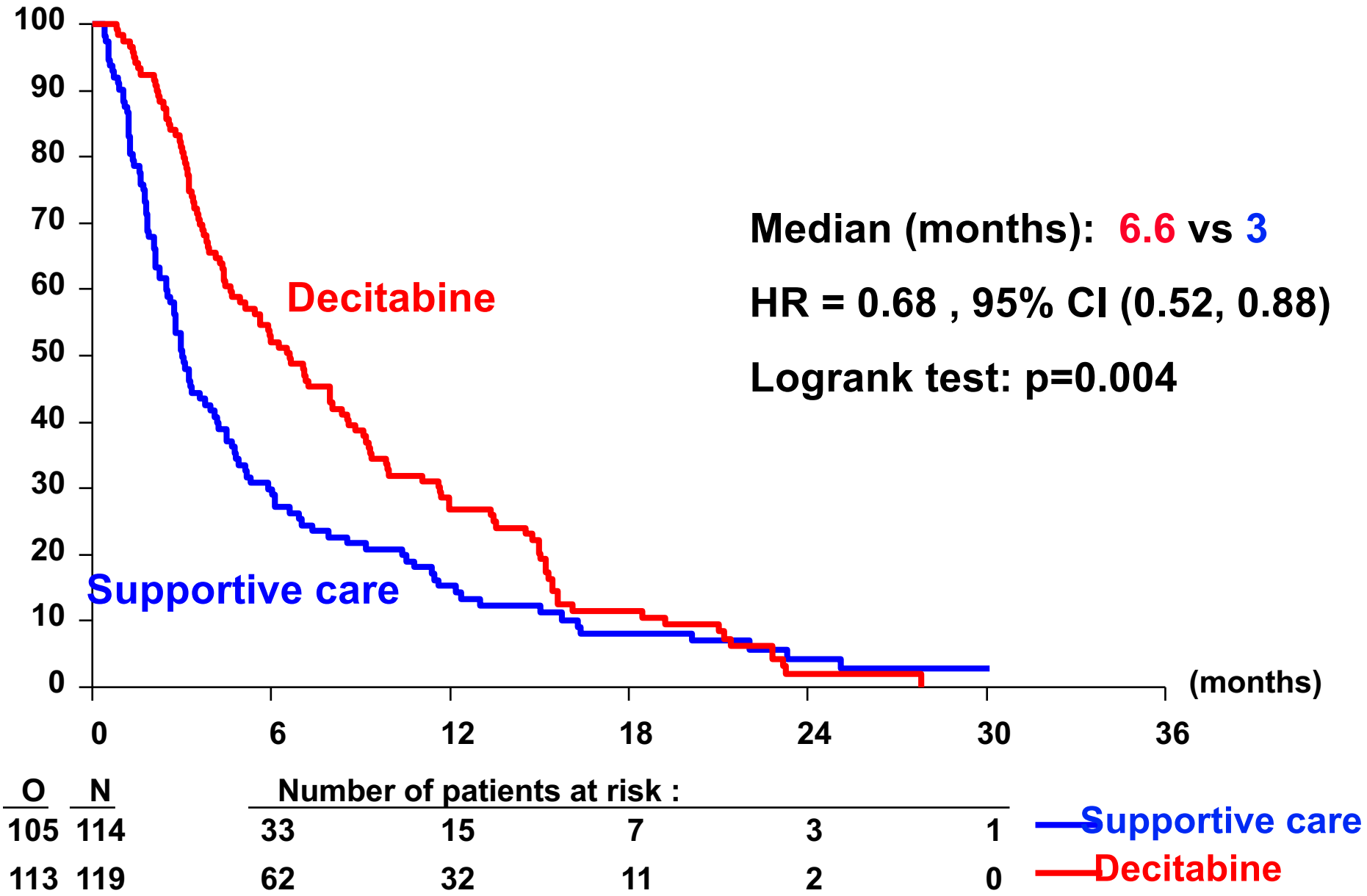


O	N	Number of patients at risk :					
96	114	71	38	22	10	6	3
99	119	83	53	24	15	4	4

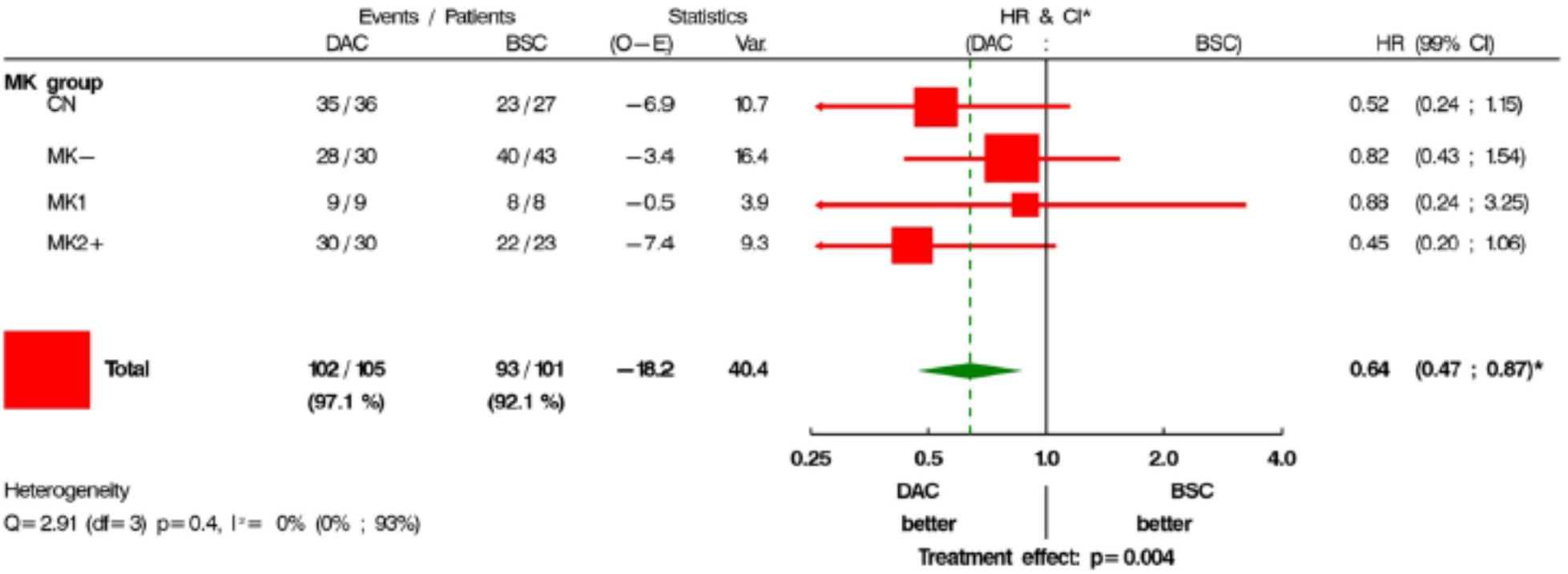
Supportive care

Decitabine

Progression-Free Survival



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



Lübbert, Suciu et al., 2016

Resistance to HMA:

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

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

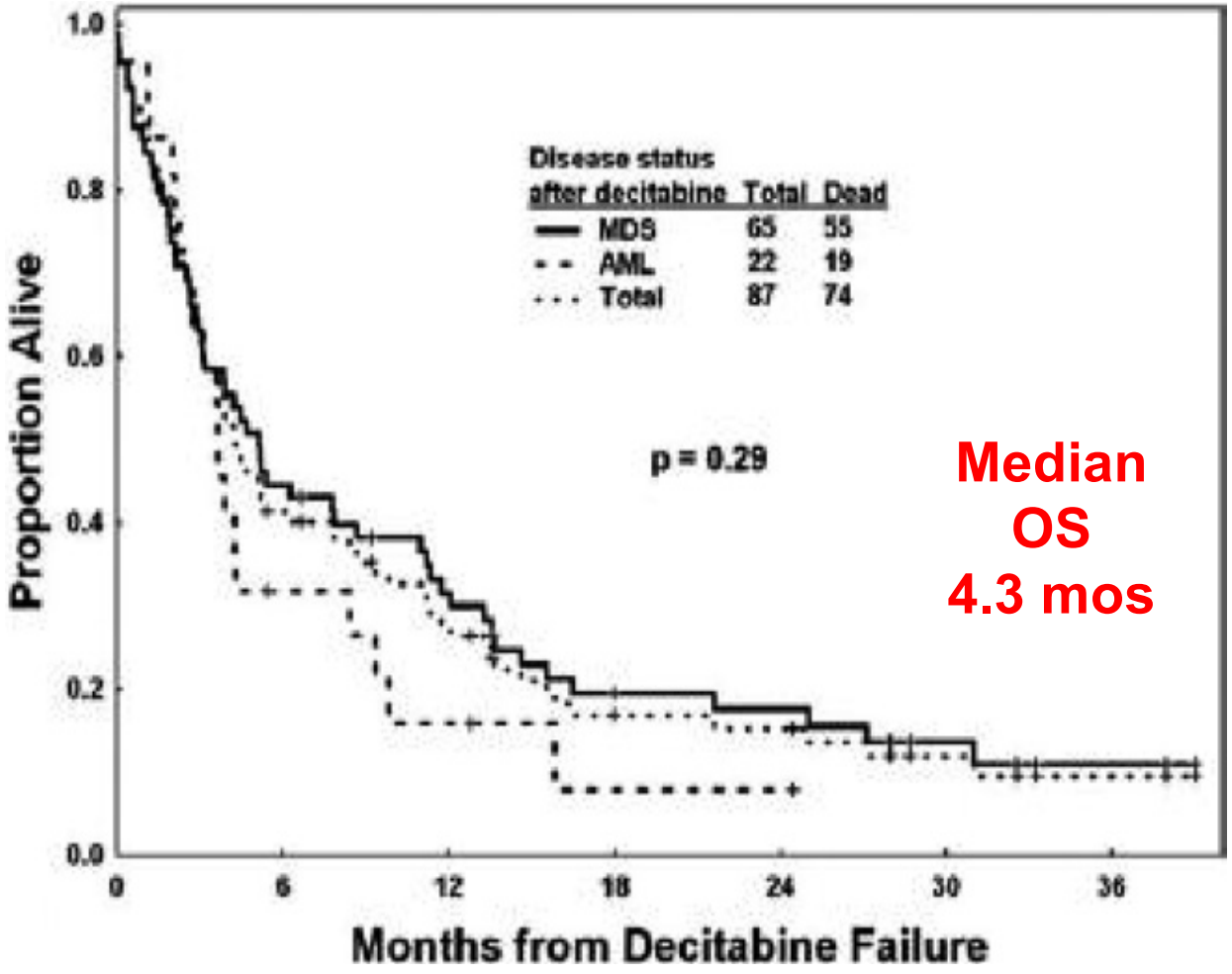
Resistance/sensitivity to HMAs:

Clinical/individual

Disease related

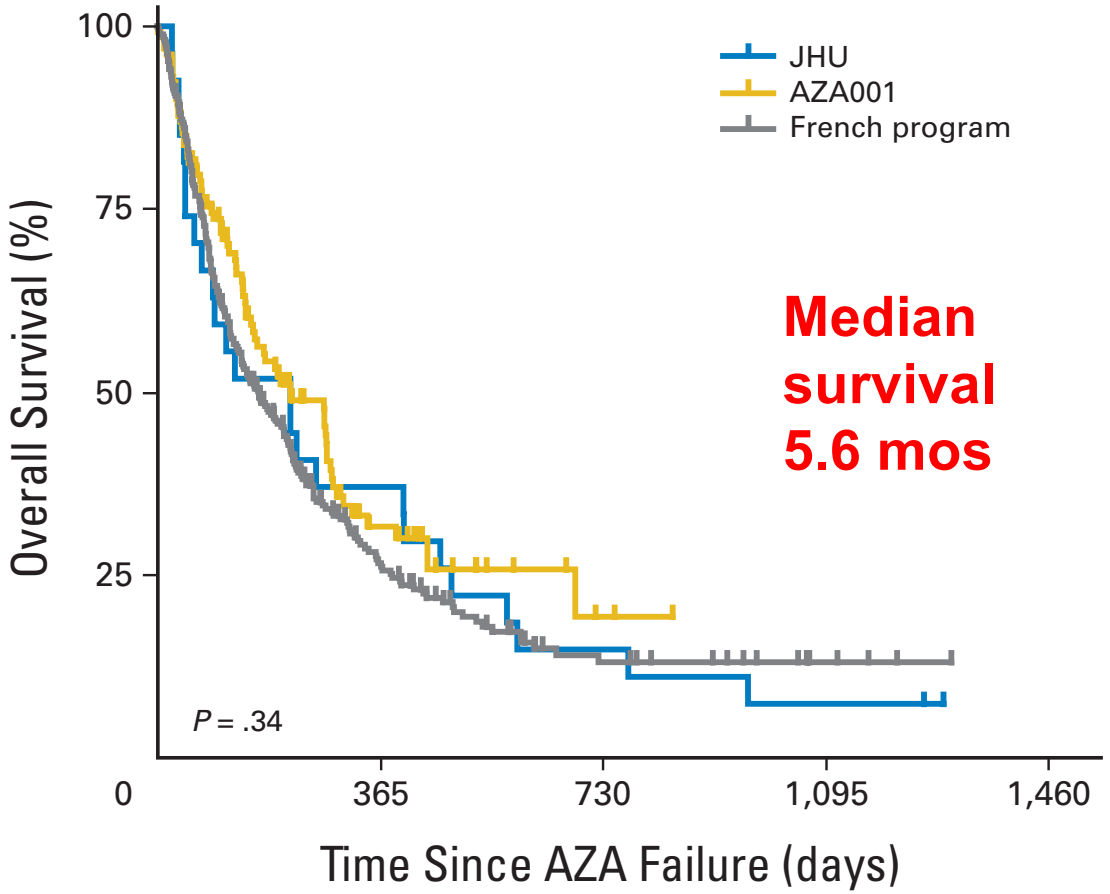
- cytogenetics
- somatic mutations
- drug metabolizing enzyme expression
- DNA methylation pattern baseline

Survival after decitabine failure in MDS/AML patients



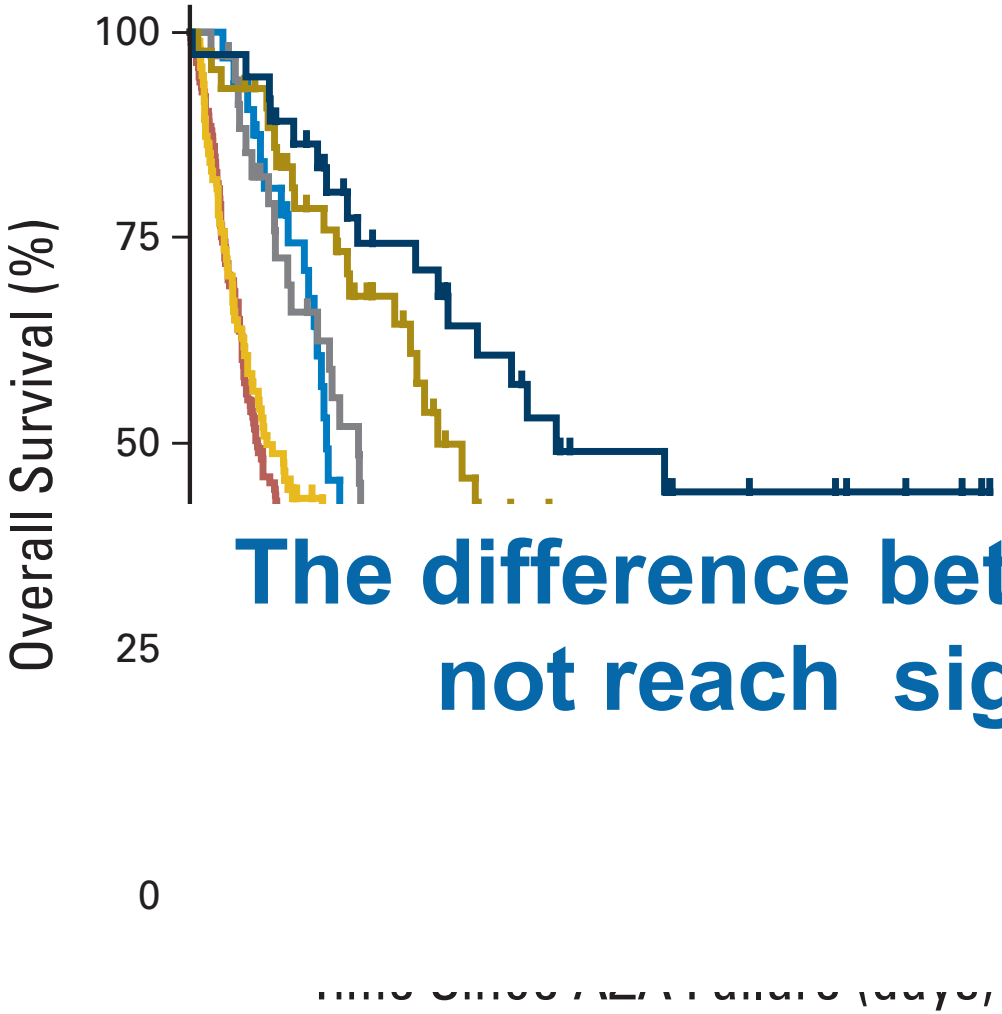
Jabbour et al, Cancer 116:3830(2008)

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)

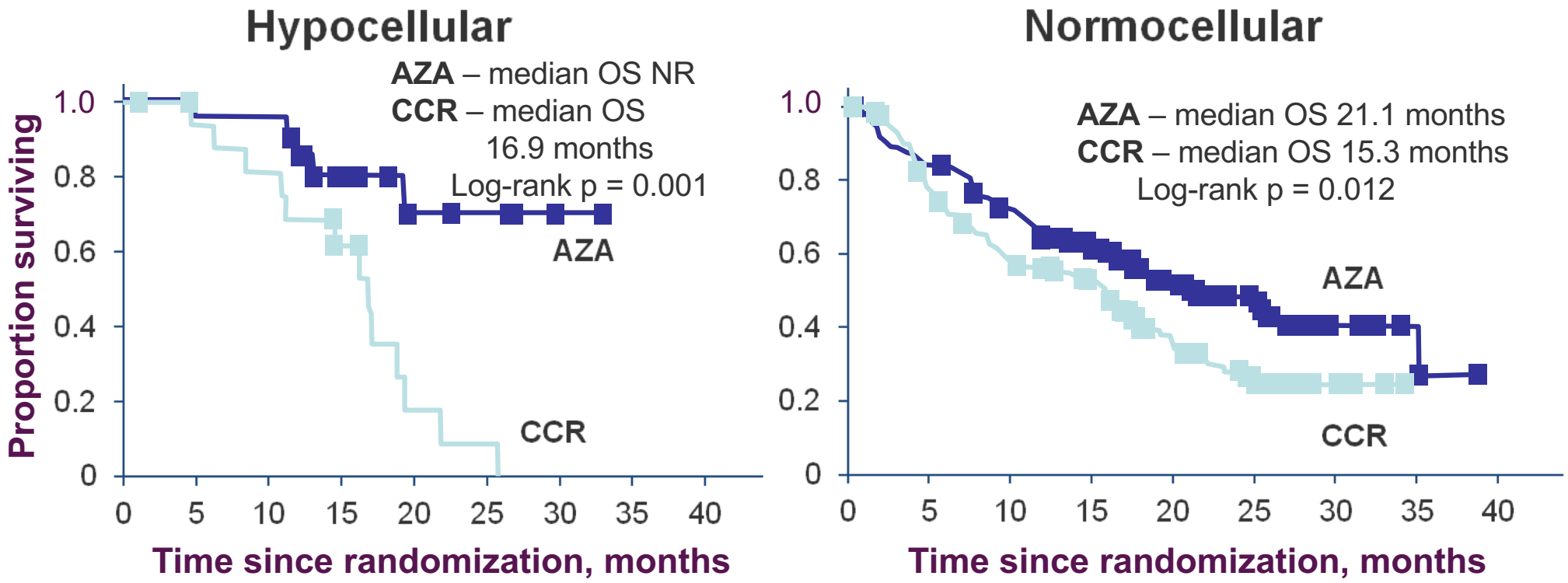
Can we predict response to HMAs?

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

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)

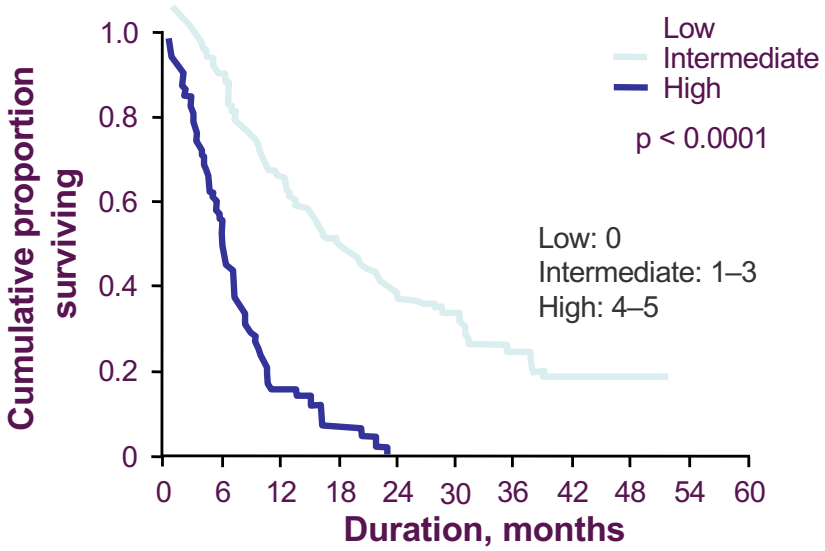
AZA response score

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

* Multivariate analysis.
ATU, authorization for temporary use.

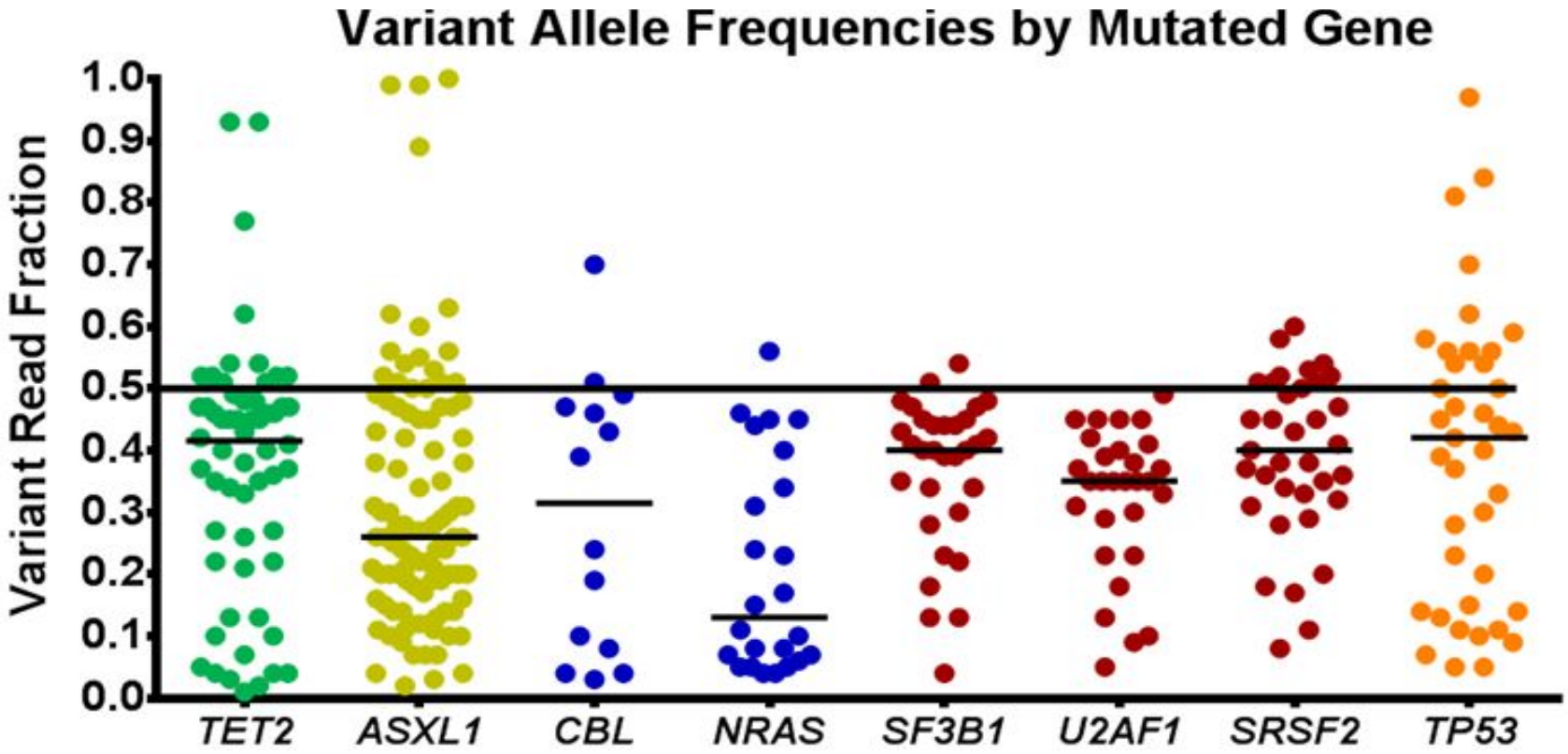
OS prognostic score

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



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***

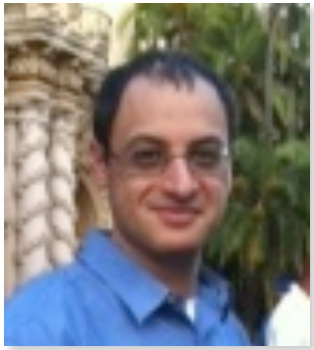
OS after HMT

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

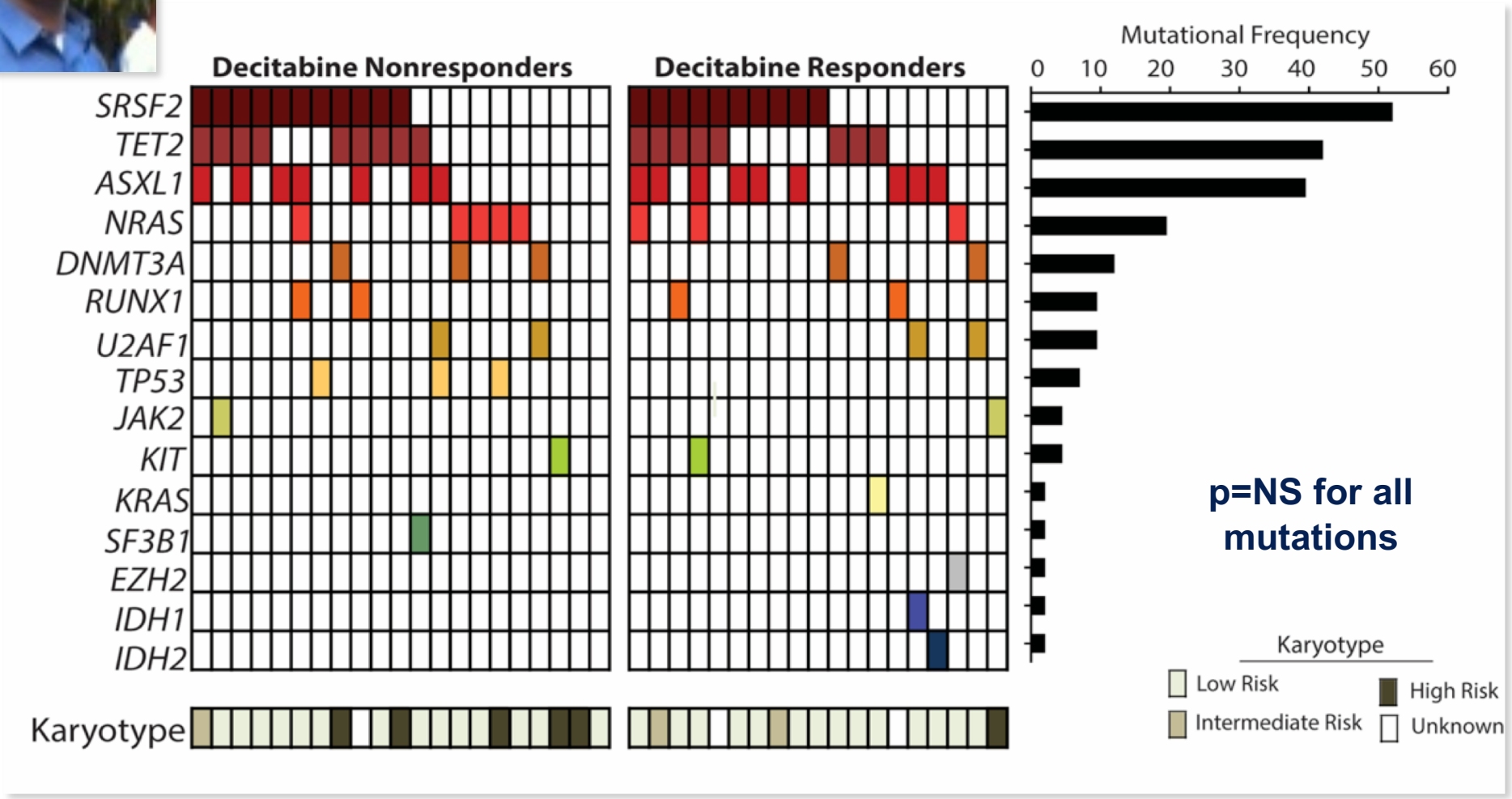
Total Score	Risk Group	N (%)	Median Survival (months)	p^3
<12	Favorable	49 (53%)	30.7	
≥12	Unfavorable	43 (47%)	7.9	***<0.0001***

Traina F et al, Leukemia 2013

Mutational profiles do not correlate with response to DAC

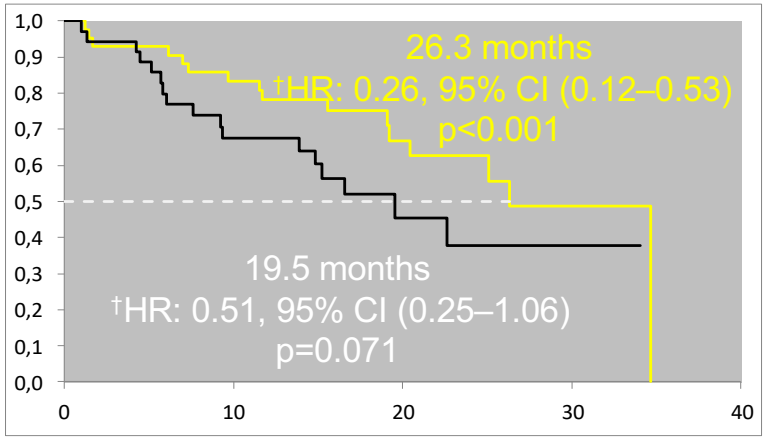


Responders **Non-Responders**



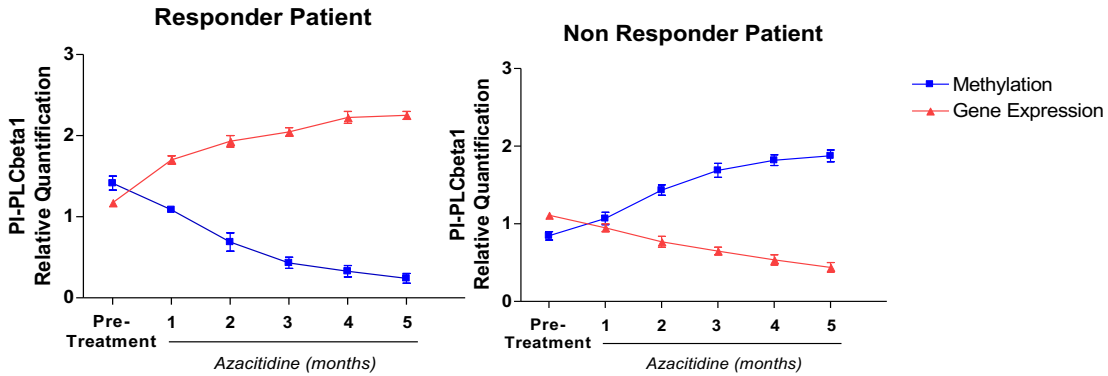
Meldi et al; J Clin Invest. 2015 May;125(5):1857-72.

Methylation pattern and response to therapy

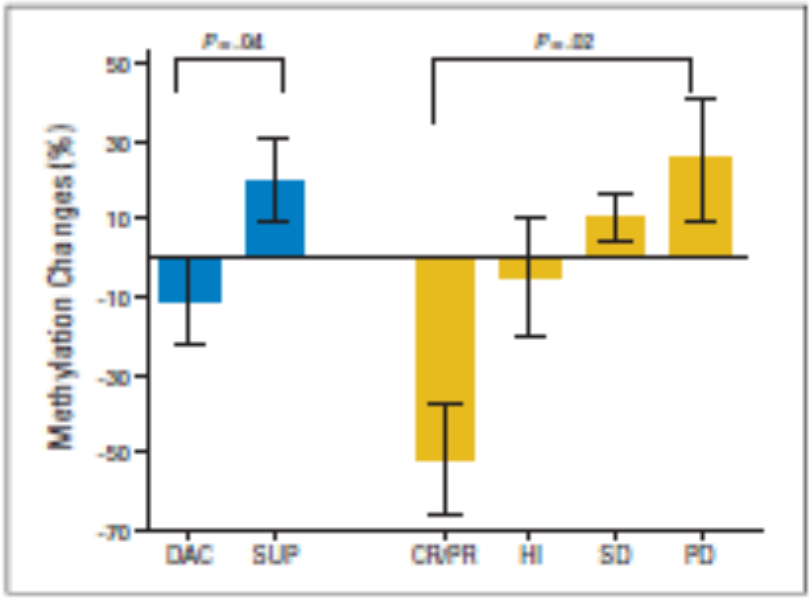


OS after AZA according to CDH1 methylation levels

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



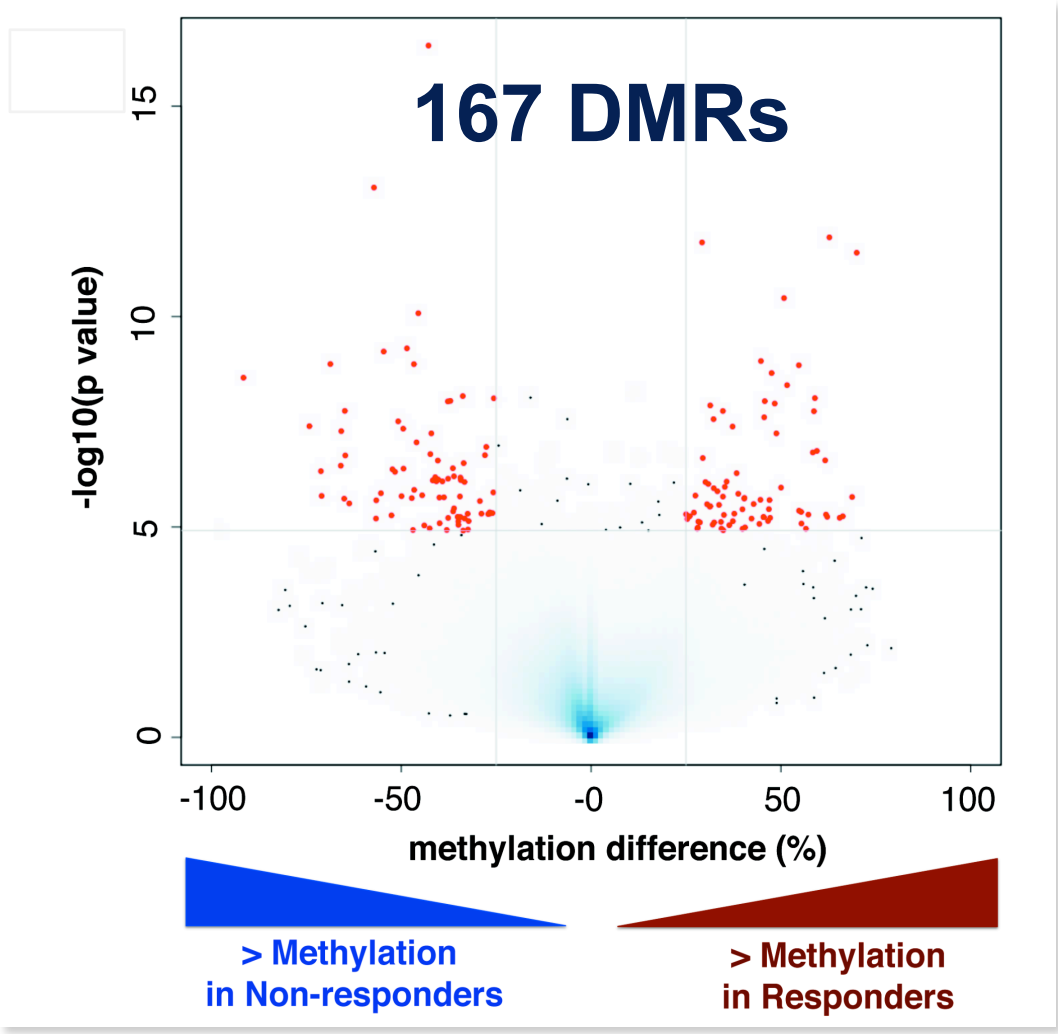
PI-PLCbeta1 promoter methylation and gene expression correlate with response to azacitidine
Follo et al PNAS 2009 29;106(39):16811-6



Global methylation and response to Decitabine

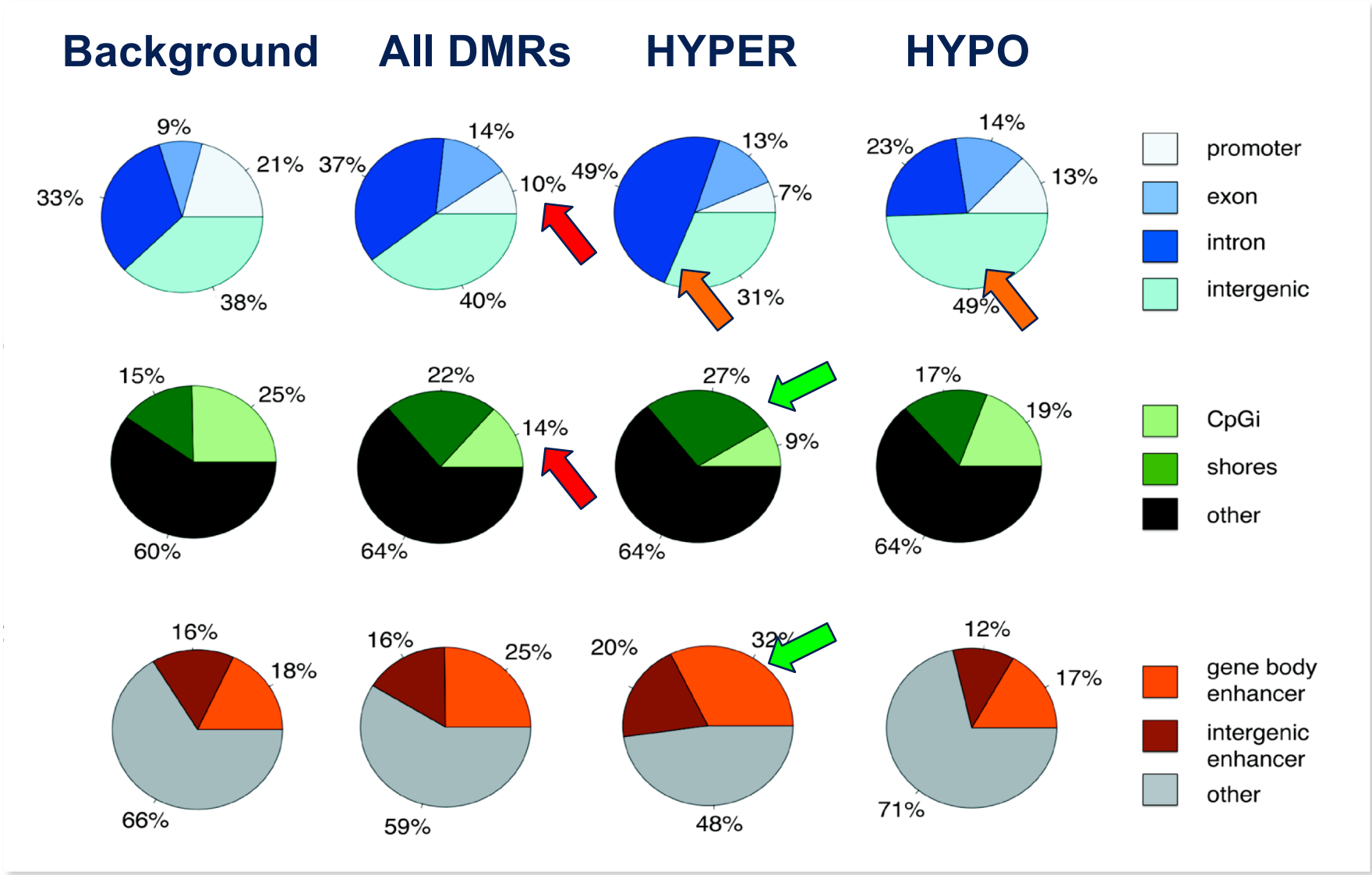
Shen, J Clin Oncol. 2010 1;28(4):605-13

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



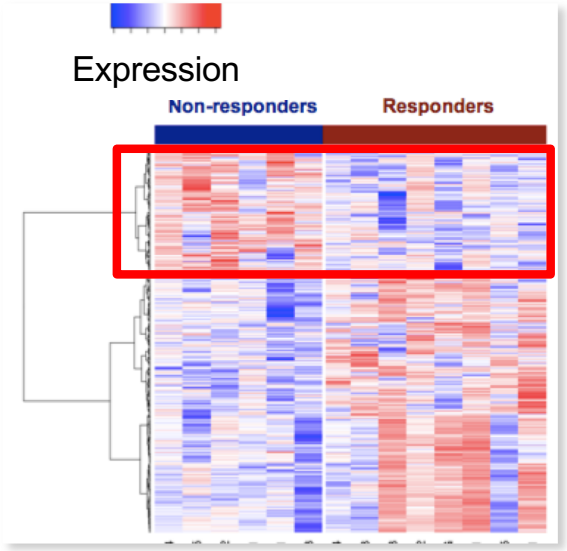
Meldi, et al. JCI 2015

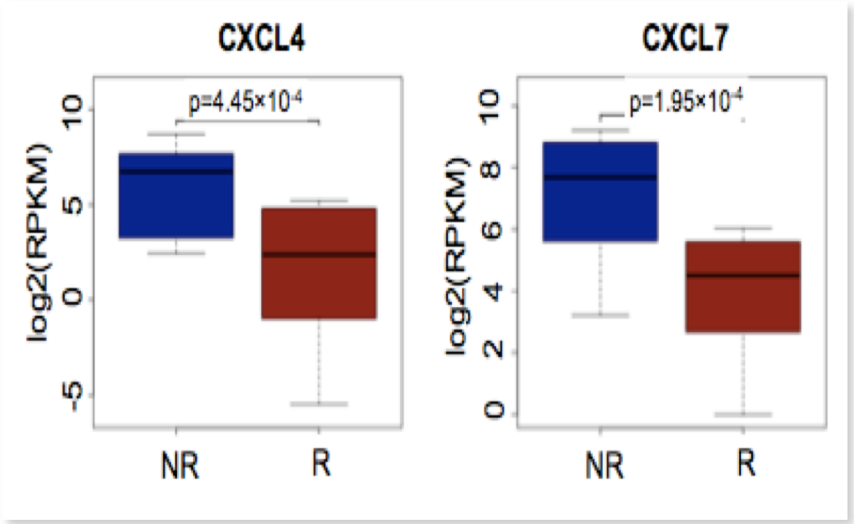
Differentially methylated regions are enriched at distal intergenic regions and enhancers

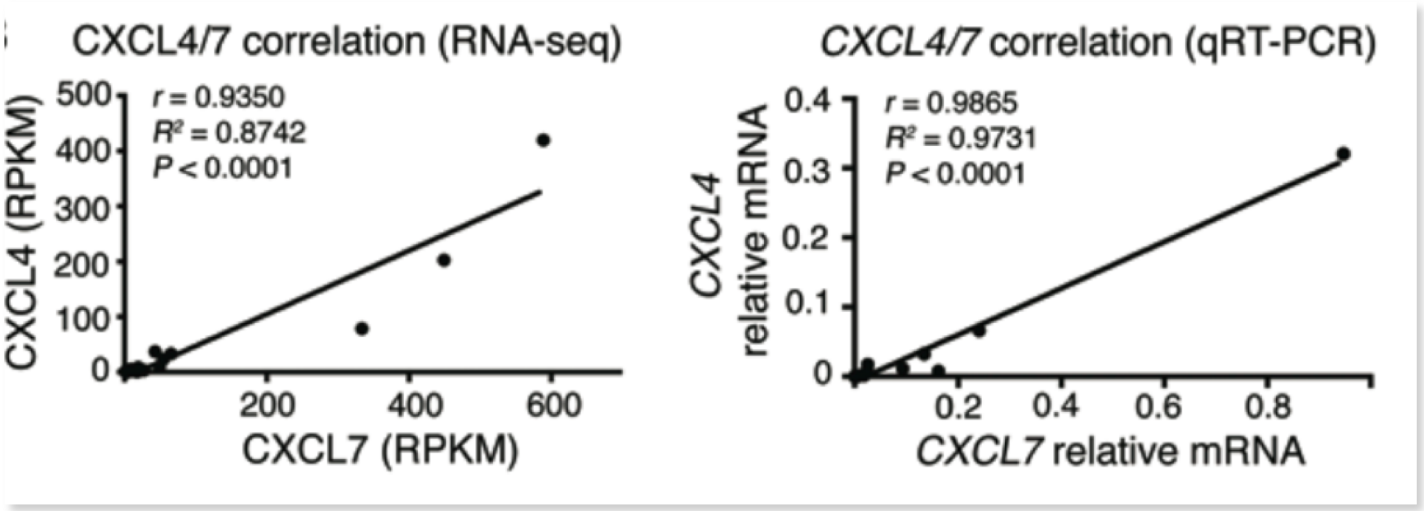


Meldi, et al. JCI 2015

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







Meldi, et al. JCI 2015

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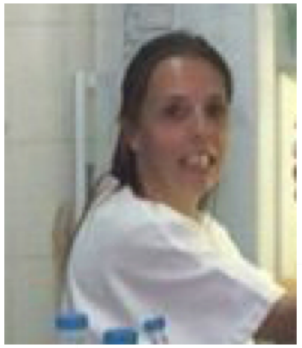
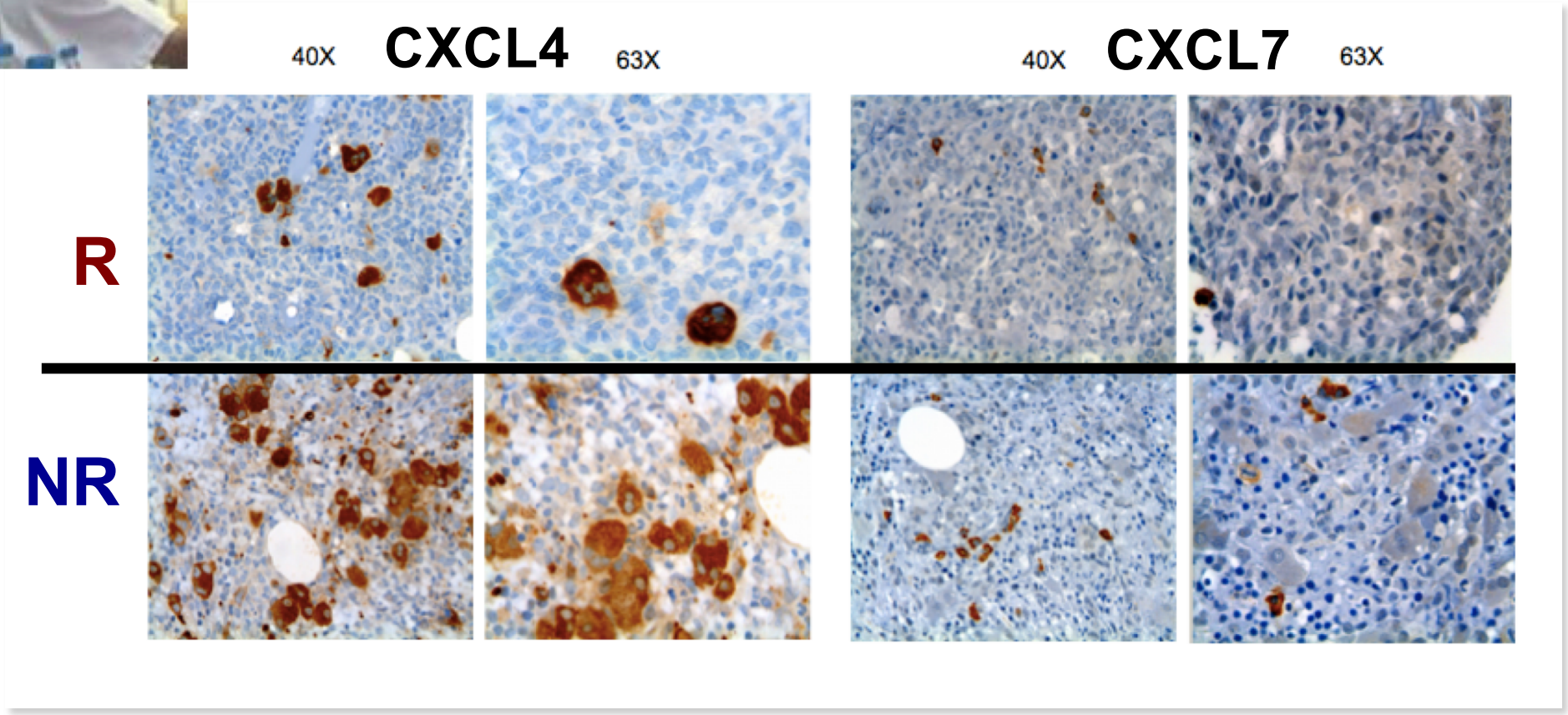
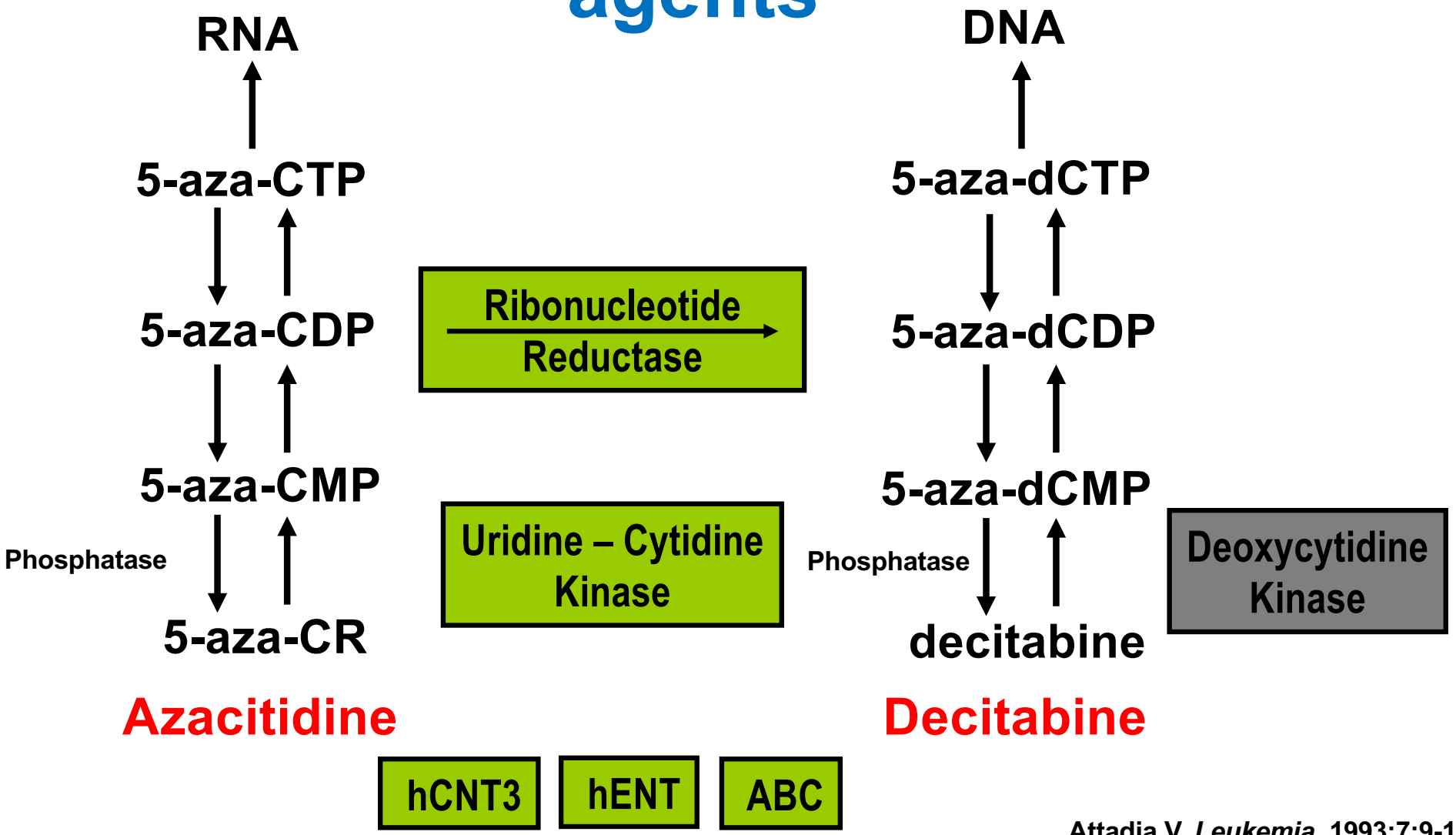


Francesca Buchi



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

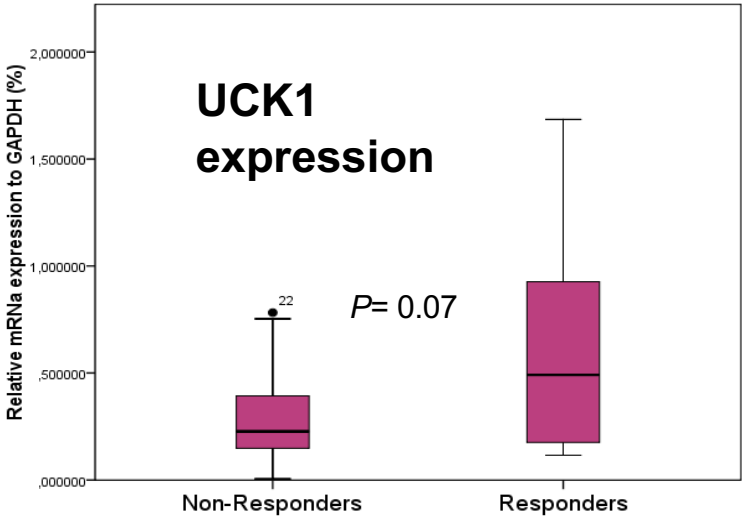
75mg/m^2/7 days
every 28 gg

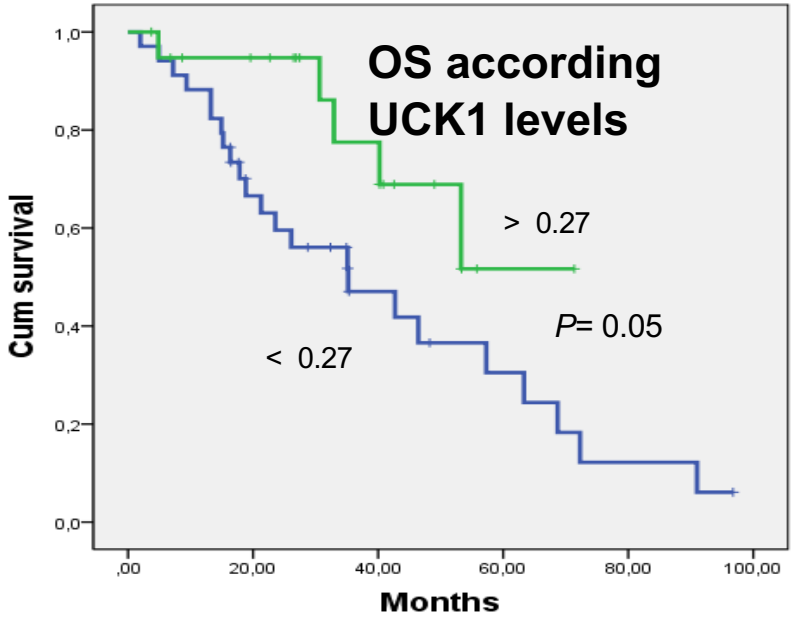
UCK1/2

Gene expression

Promoter methylation

Gene sequence





Use new drugs or use in a selective way traditional drugs?

Myelodysplastic syndromes

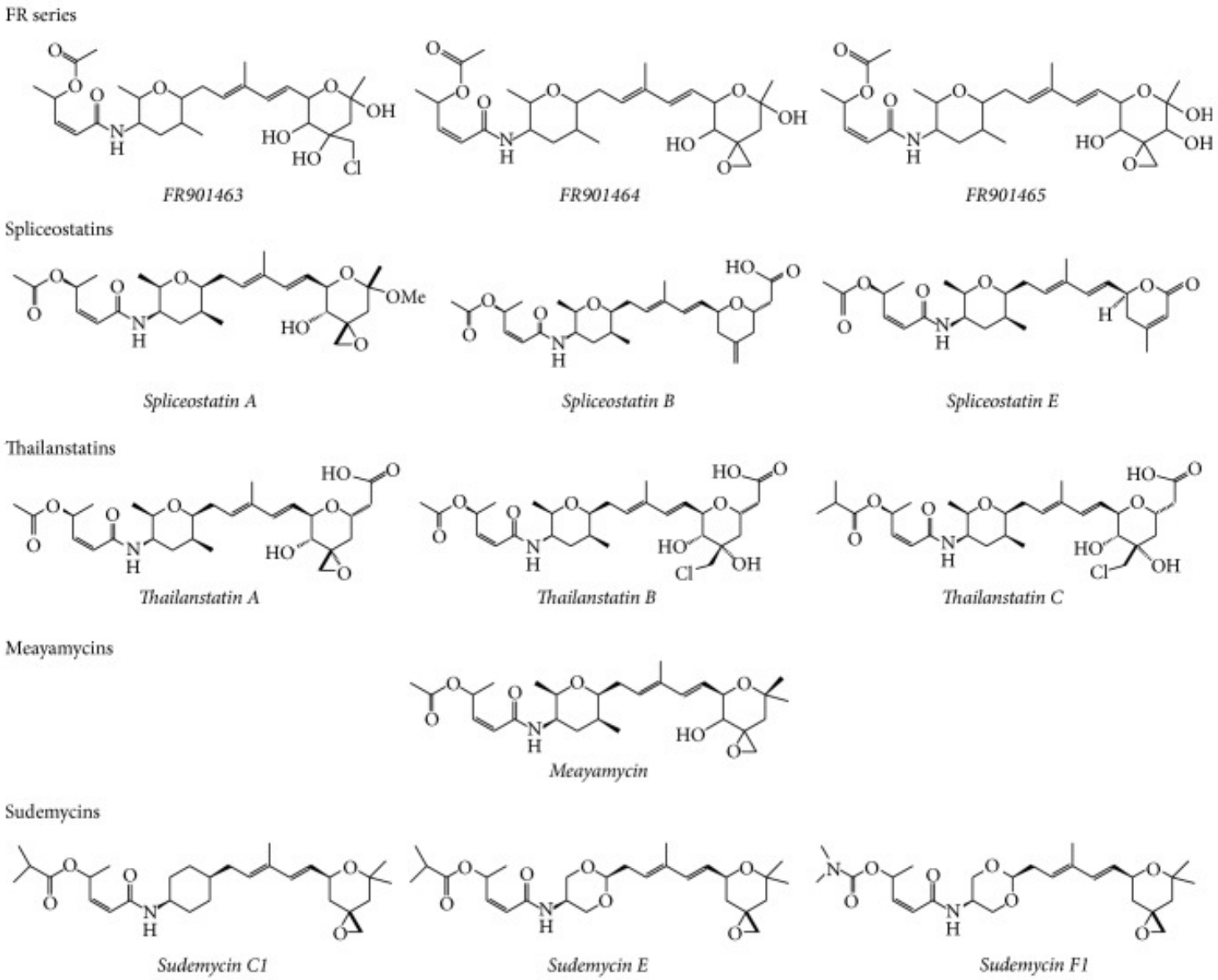
Targeted sequencing of a limited number of genes can detect mutations in 80-90% of MDS patients;

the most commonly mutated genes in MDS are

SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2.

Arber DA et al Blood April 2016

Spliceosome inhibitors

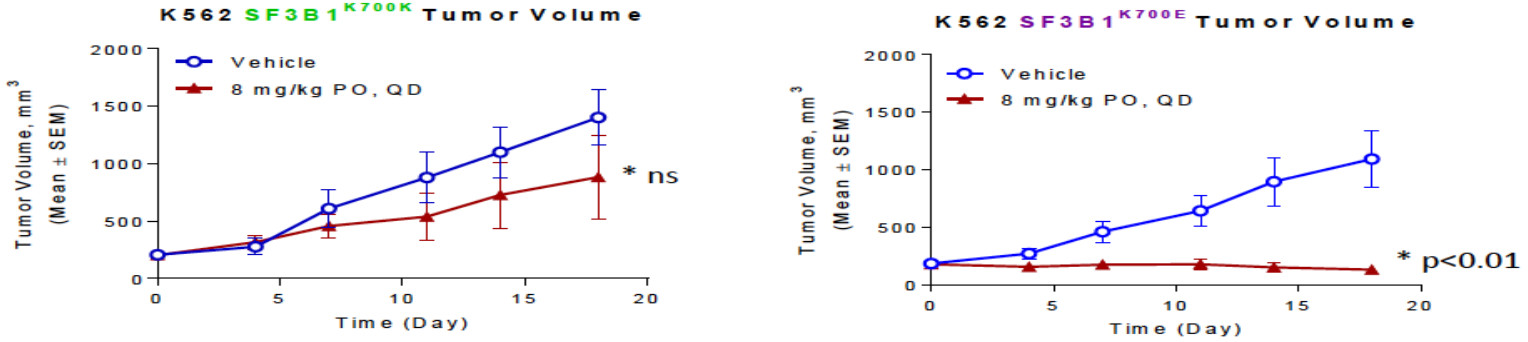


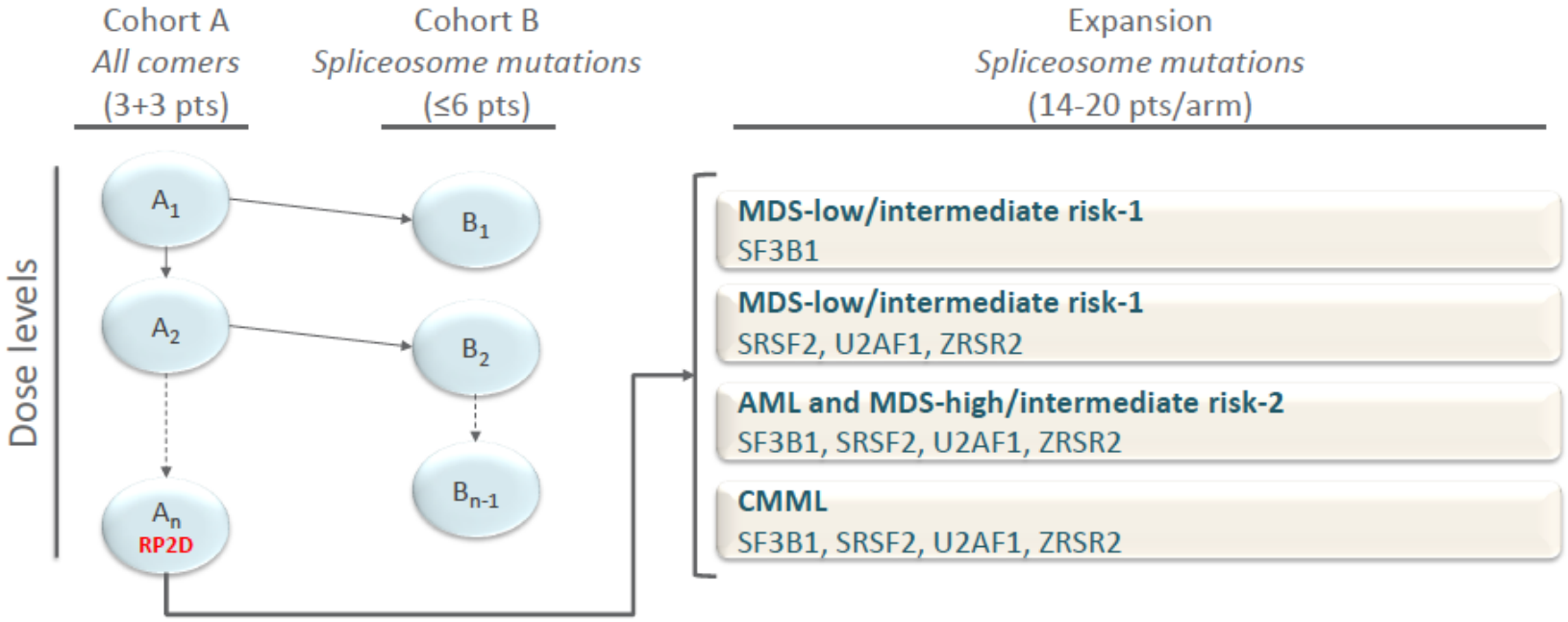
Martines-Montiel et al; BioMed Research International 2016

Splicesome inhibitor oral H3B-8800 for MDS carrying mutations in spliceosome genes

Buonamici et al, ASH 2017 (ClinicalTrials.gov **NCT02841540)**

Xenografts of AML cells with or without SF3B1^{K700E} mutation treated with vehicle or **oral** H3B-8800 *in vivo*





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 mIDH2 and mIDH1 inhibitors in R/R AML (……and few MDS)

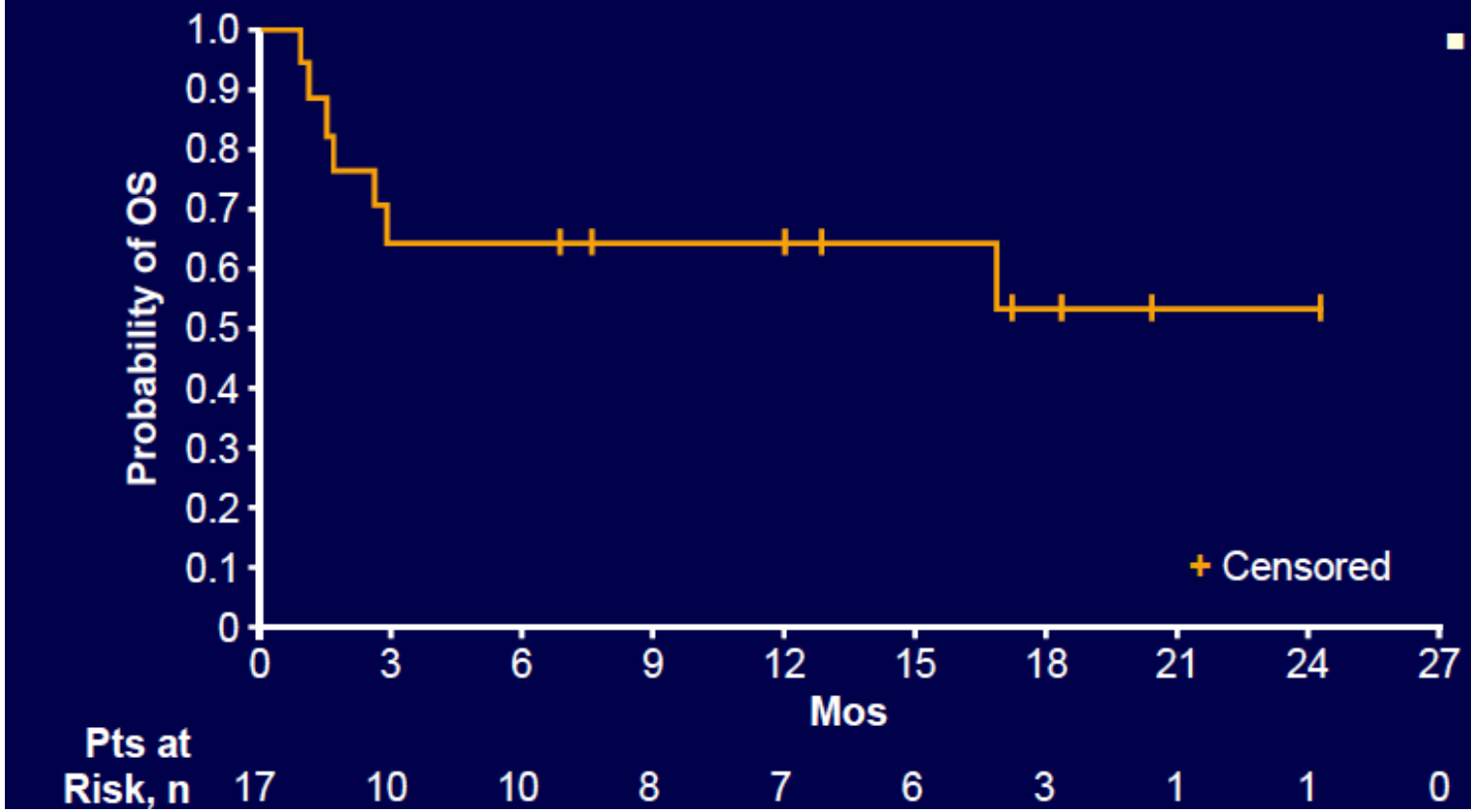
	AG-221 (Enasedinib)	AG-120 (Ivosedinib)
Clinical trial	NCT01915498. (Stein et al-Blood. 2017;130(6):722-731)	NCT02074839.(DiNardo et al NEJM June 2, 2018 DOI: 10.1056/NEJMoa1716984), Pollyea ASCO 2018
Pts dosed	258	239
Overall Response Rate	40.3%	39.1%

ONGOING:
HMA-naïve high risk MDS in combination with azacitidine (NCT03383575).

Median time to response	1.9 months	1.9 months
Overall survival	9.3 months	9.0 months
Duration of response if CR	8.8 months	10.1 months
Toxicity	-Indirect hyperbilirubinemia (inhibiting UGT1A1) -nausea -leukocytosis	-QT prolongation -diarrhea -nausea -leukocytosis

MDS pts 50% ORR
21% CR

Enasidenib in m*IDH2* MDS: OS



- Median OS not reached at median follow-up of 7.5 mos

Stein EM, ASH 2016 abs 343

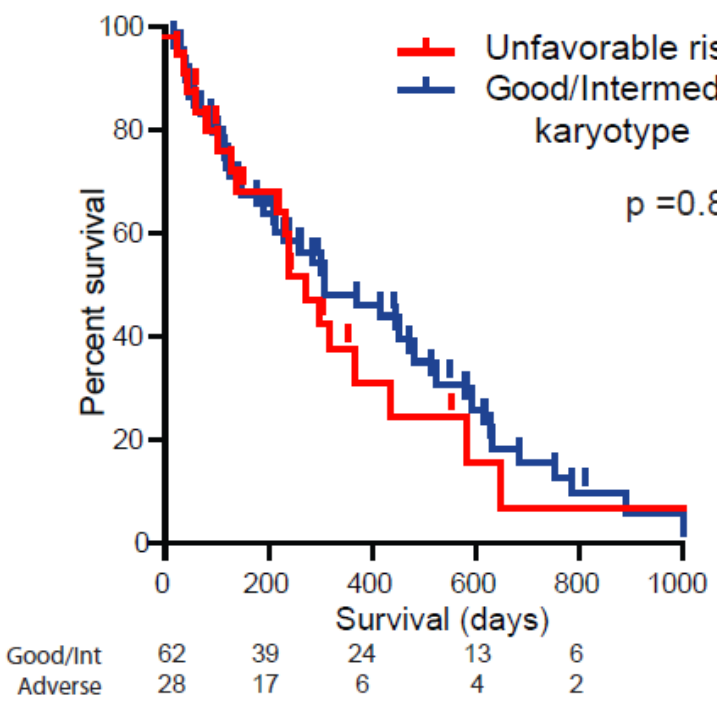
Enasidenib has been approved 2017 by FDA for treatment of IDH2mut AML

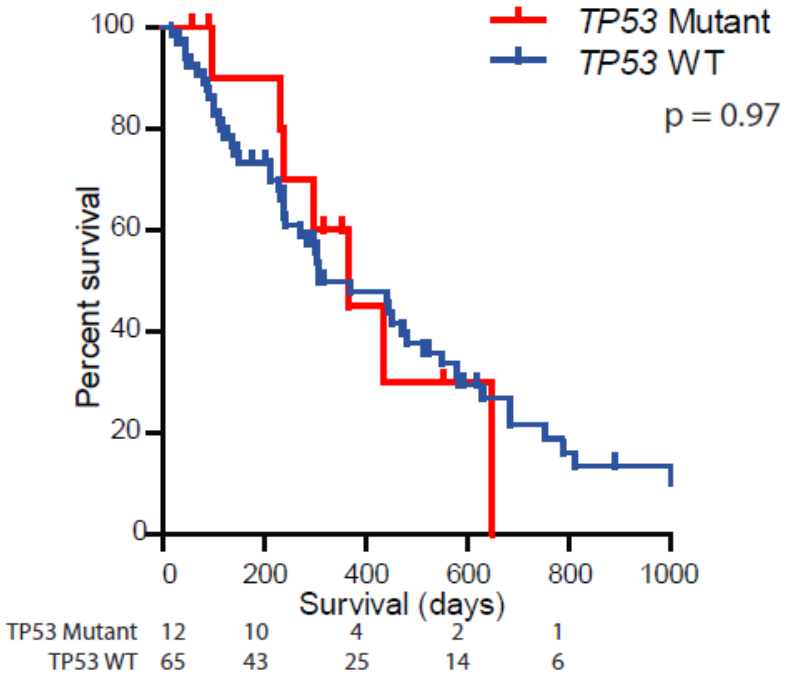
100% patients with *TP53* mutations respond to 10day-Decitabine

Characteristic	All Patients (N=116)	*TP53* Mutations (N=21)	Wild-Type *TP53* (N=78)	*TP53* Not Evaluated (N=17)	P Value†
Response — no. (%)					
Bone marrow blast clearance <5% blasts	53 (46)	21 (100)	32 (41)	0	<0.001
Complete remission					
With recovery of peripheral-blood counts	15 (13)	4 (19)	11 (14)	0	0.73
With incomplete count recovery	24 (21)	9 (43)	15 (19)	0	0.04
Morphologic complete remission					
With hematologic improvement	6 (5)	5 (24)	1 (1)	0	0.002
Without hematologic improvement	8 (7)	3 (14)	5 (6)	0	0.36
No bone marrow blast clearance	63 (54)	0	46 (59)	5 (29)	<0.001
Partial response	9 (8)	0	9 (12)	0	0.05
Stable disease	23 (20)	0	18 (23)	5 (29)	0.006
Progressive disease	19 (16)	0	19 (24)	0	0.003
Samples not available for evaluation	12 (10)	0	0	12 (71)	

Welch JS et al. N Engl J Med 2016;
375:2023-2036

OS according to risk karyotype and TP53 profile with decitabine

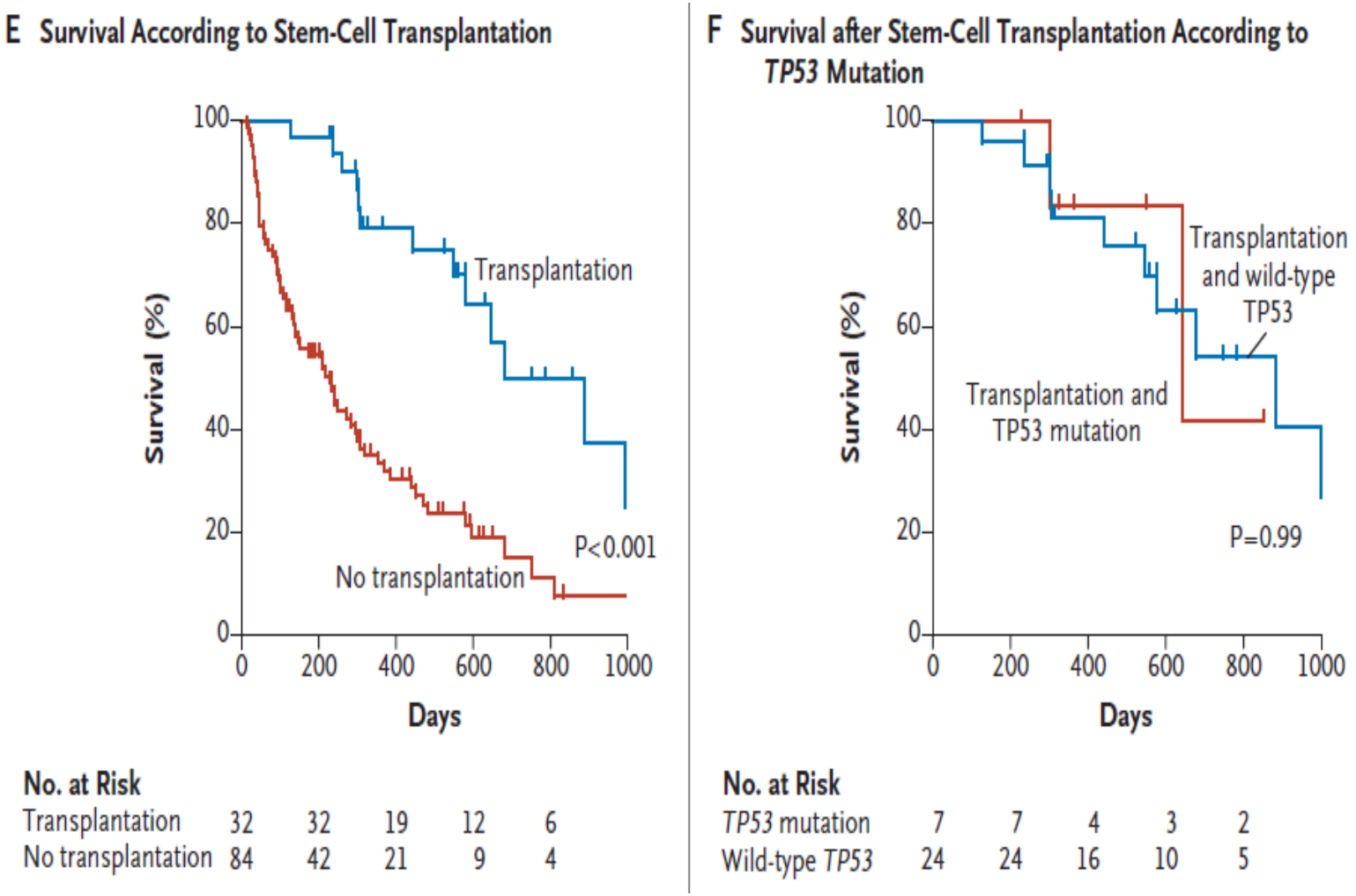




No differences between unfavourable and favourable risk karyotype
No differences between per status TP53 mutant and wild type

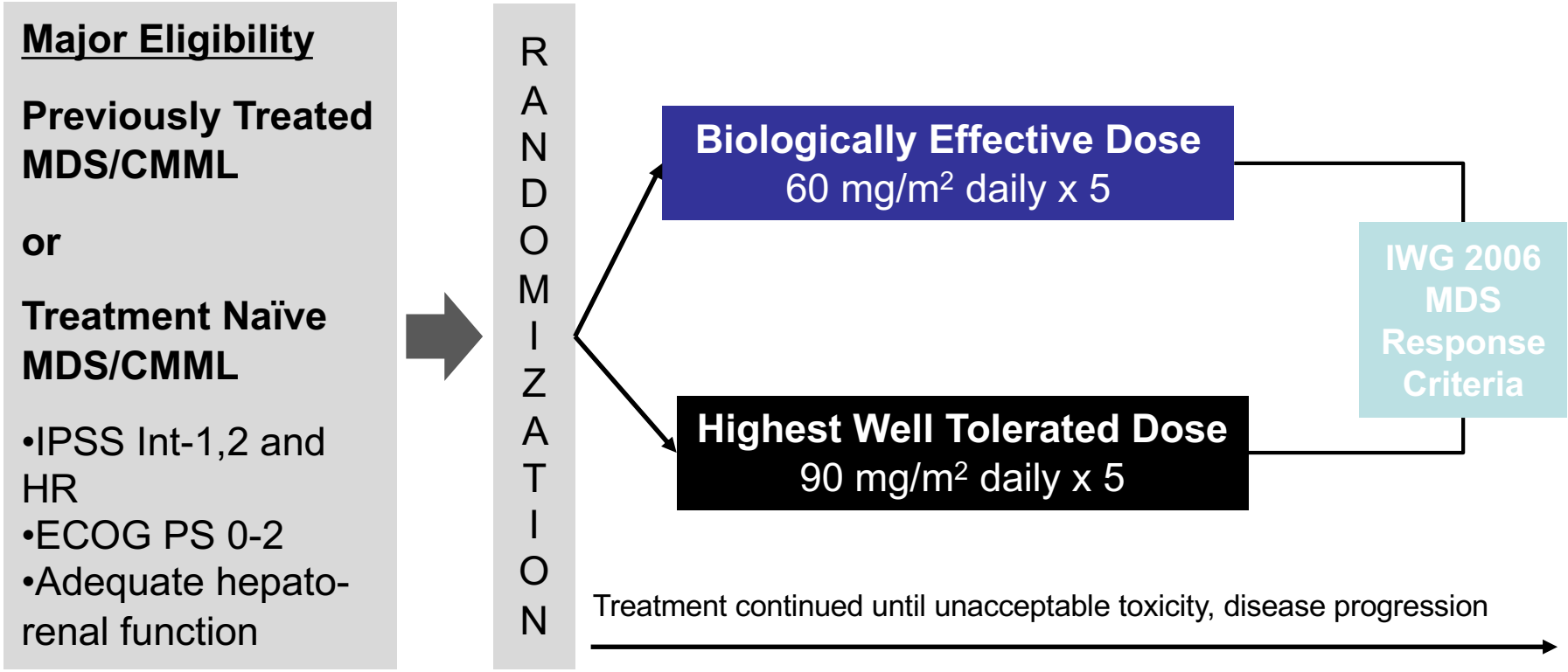
Welch et al. NEJM 2016;375:2023–36

Survival after transplant not adversely affected by *TP53* status



Welch JS et al. N Engl J Med 2016; 375:2023-2036

“Long acting “ Hypomethylating Agent : SGI-110



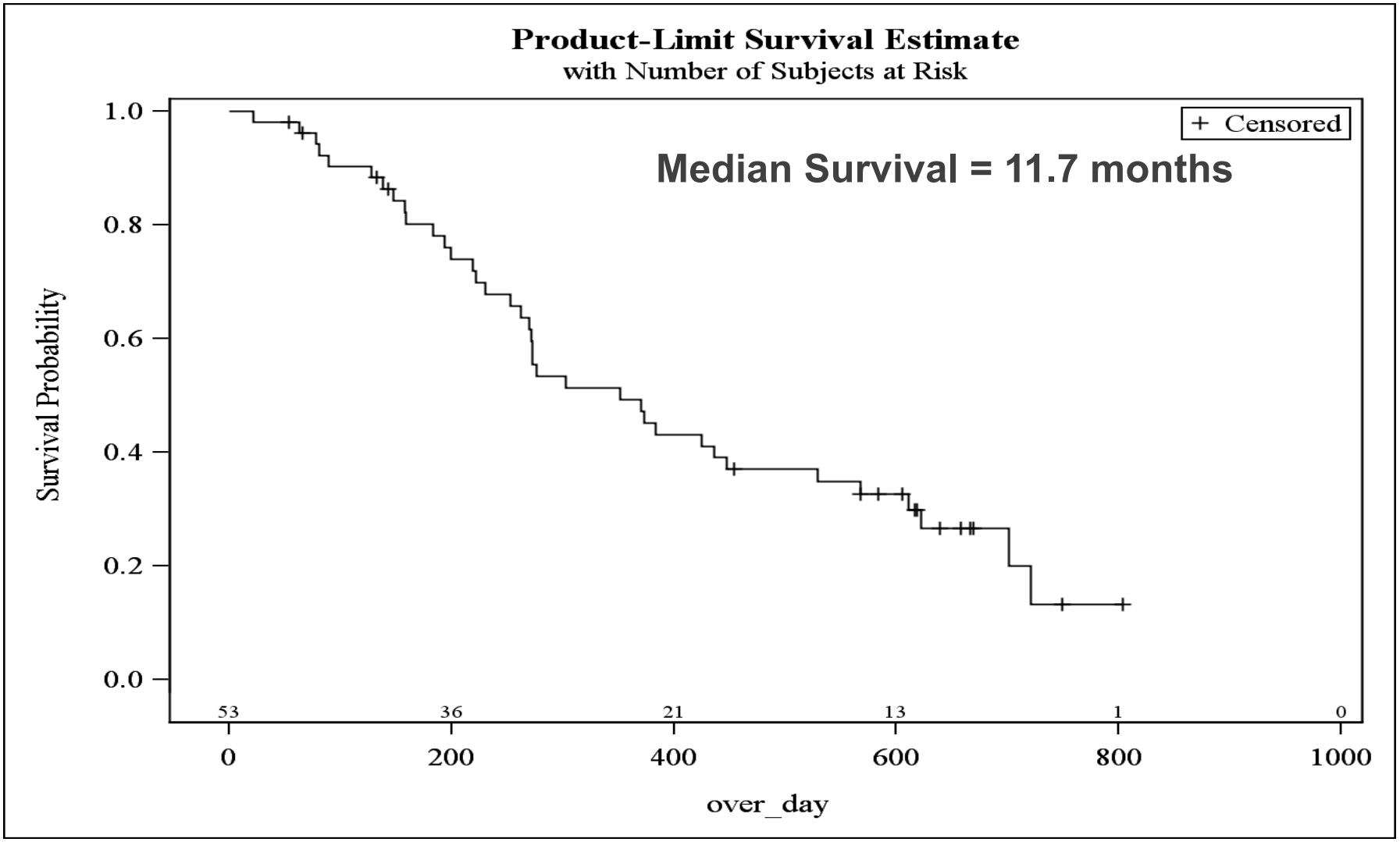
- Primary Endpoint: Overall Response Rate (CR, PR, mCR, HI)
- Secondary Endpoints: Transfusion independence, LINE-1 demethylation, time to AML, overall survival

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

Phase 2 – r/r MDS
Overall Survival – Combined Data



Guadecitabine 60 and 90 mg/m^2 SC 10 or 5 days in R/R AML

	Response Rate					
	5-d Regimens[b]					
Response Category[a]	60 mg/m^2 (n = 24)	90 mg/m^2 (n = 26)	Total (n = 50)	10-d Regimen at 60 mg/m^2 (n = 53)	Total (n = 103)	*P*[c]
CR, No. (%)	2 (8.3)	2 (7.7)	4 (8.0)	10 (18.9)	14 (13.6)	.1515[d]
CRi, No. (%)	1 (4.2)	3 (11.5)	4 (8.0)	2 (3.8)	6 (5.8)	NS
CRp, No. (%)	0	0	0	4 (7.5)	4 (3.9)	NS
CRc rate (CR + CRi + CRp)						
No. (%)	3 (12.5)	5 (19.2)	8 (16.0)	16 (30.2)	24 (23.3)	.1061[d]
95% CI, %	2.7-32.4	6.6-39.4	7.2-29.1	18.3-44.3	15.5-32.7	

Roboz et al; Cancer 2018

CD33-targeted therapeutics are back for MDS ???

Highly Potent CD33xCD3 T-Cell Engager Targeting $CD33^{Hi}$ Cells in MDS

- **AMV564 is a bispecific, bivalent, 2X2 T-cell engager**
  - **Composed of human antibody variable fragments (scFv)**

Fc-engineered unconjugated antibodies (BI 836858 [mAb 33.1]),
ADCs (SGN-CD33A [vadastuximab talirine], IMGN779),
radioimmunoconjugates (^{225}Ac-lintuzumab),
bi- and trispecific antibodies (AMG 330, AMG 673, AMV564, 161533 TriKE fusion protein),
and chimeric antigen receptor (CAR)-modified immune effector cells

- proliferation of $CD4^+$ and $CD8^+$ T-cells more than doubled with AMV564 treatment
- IFN-γ secretion markedly increased in AMV564-treated cells

- Suppression of MDSCs by AMV564 reduced DNA damage in HSPC and improved colony-forming capacity
- AMV564 depletion of MDSC enhances CD4/CD8 T-cell response to PD-1 blockade which warrants clinical investigation in patients with lower risk MDS

Eksioglu EA et al. Leukemia. 2017 Oct;31(10):2172-2180.

A phase II study evaluating the efficacy and safety of bemcentinib BGB324 in patients with MDS or AML failing therapy with hypomethylating agents – BERGAMO trial

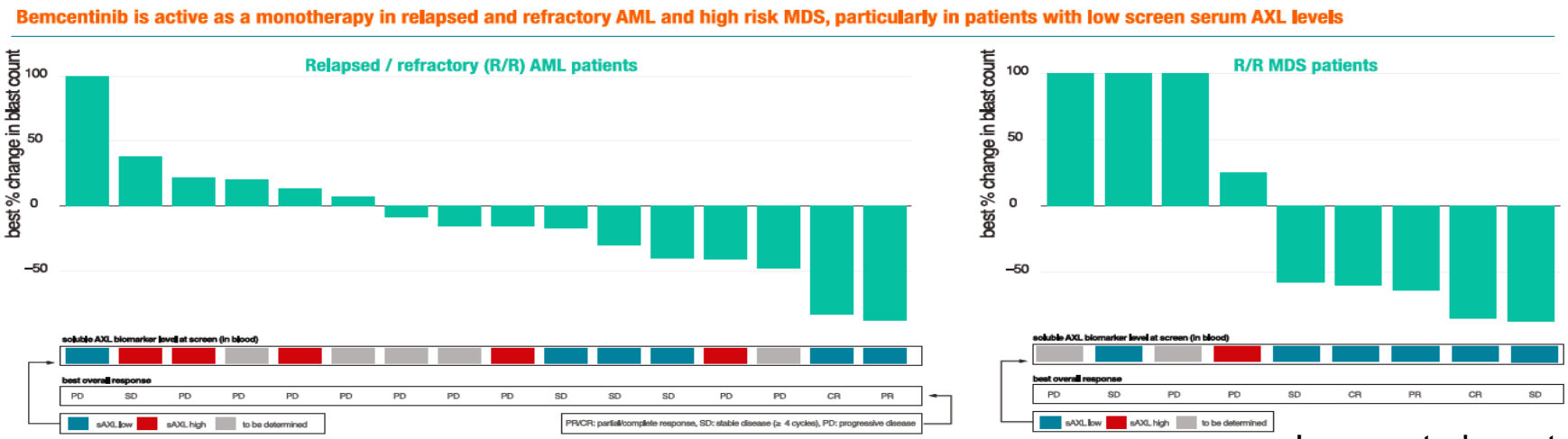
43 patients- bemcentinib is a selective oral Axl inhibitor

Axl: potential new target in higher-risk MDS and AML

- member of the Tyro3, Axl, Mer (TAM) receptor family
- mediates proliferation and survival of leukemic cells
- upregulated upon cytostatic treatment
- leukemic cells induce expression of Gas6* in bone marrow stroma cells
    - which further amplifies their growth and therapy resistance

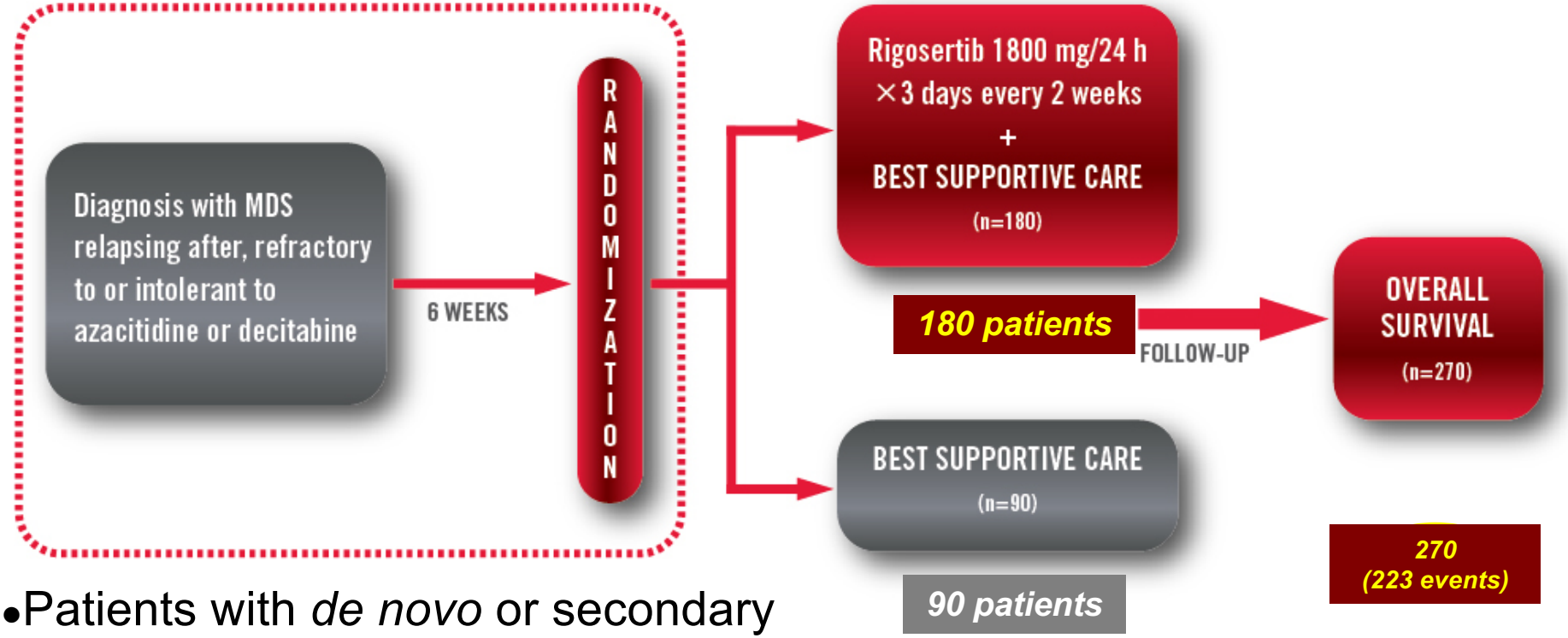
in-vitro and mouse models showed:

- BGB324 inhibited leukemic proliferation
- blockade of Gas6/Axl signaling axis by BGB324 impaired MDS growth in patient material-derived cells cultures
- Effect especially prominent in CD34+ MDS stem cell fraction



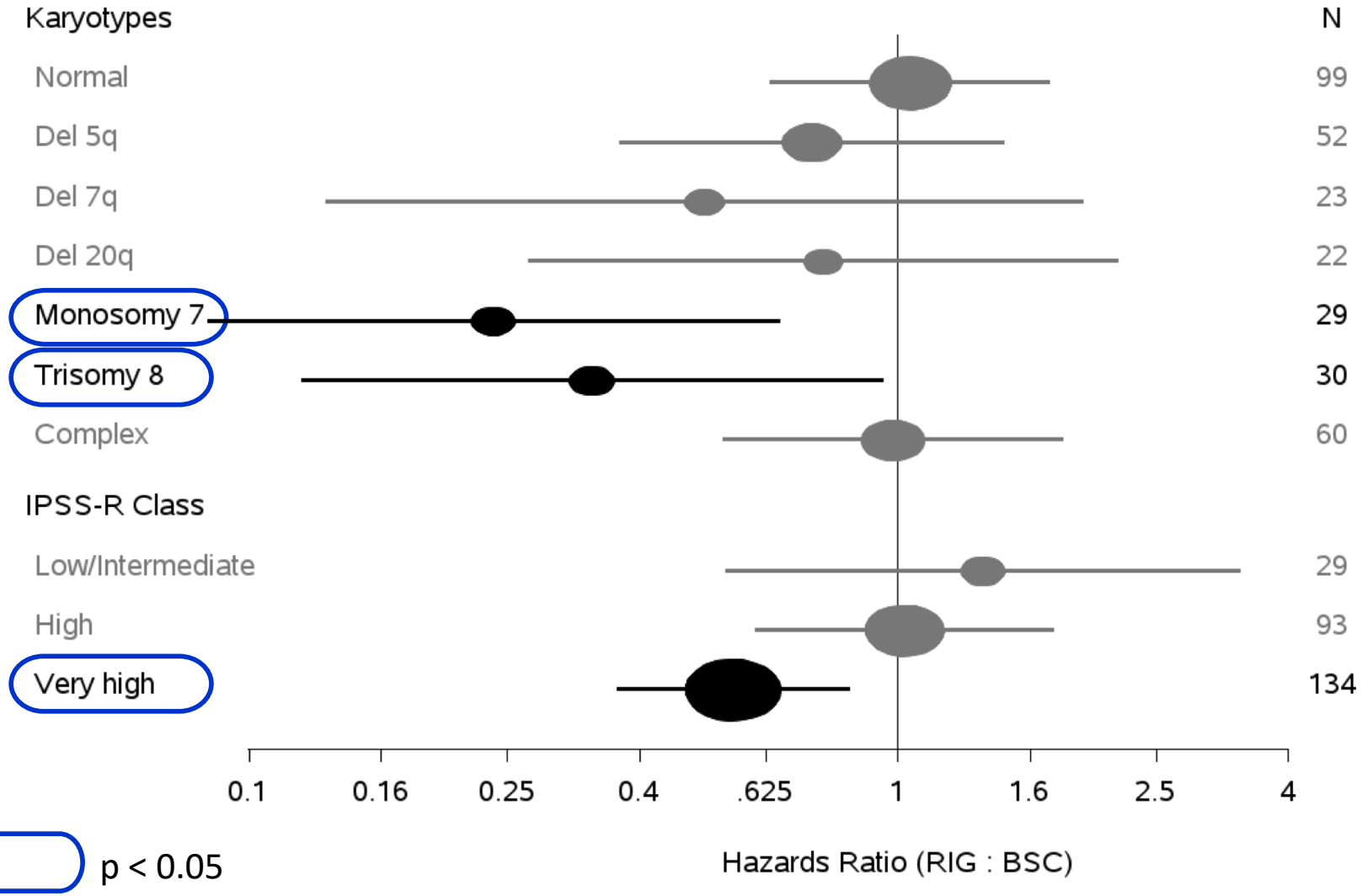
Loges at al, poster EHA 2018

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)

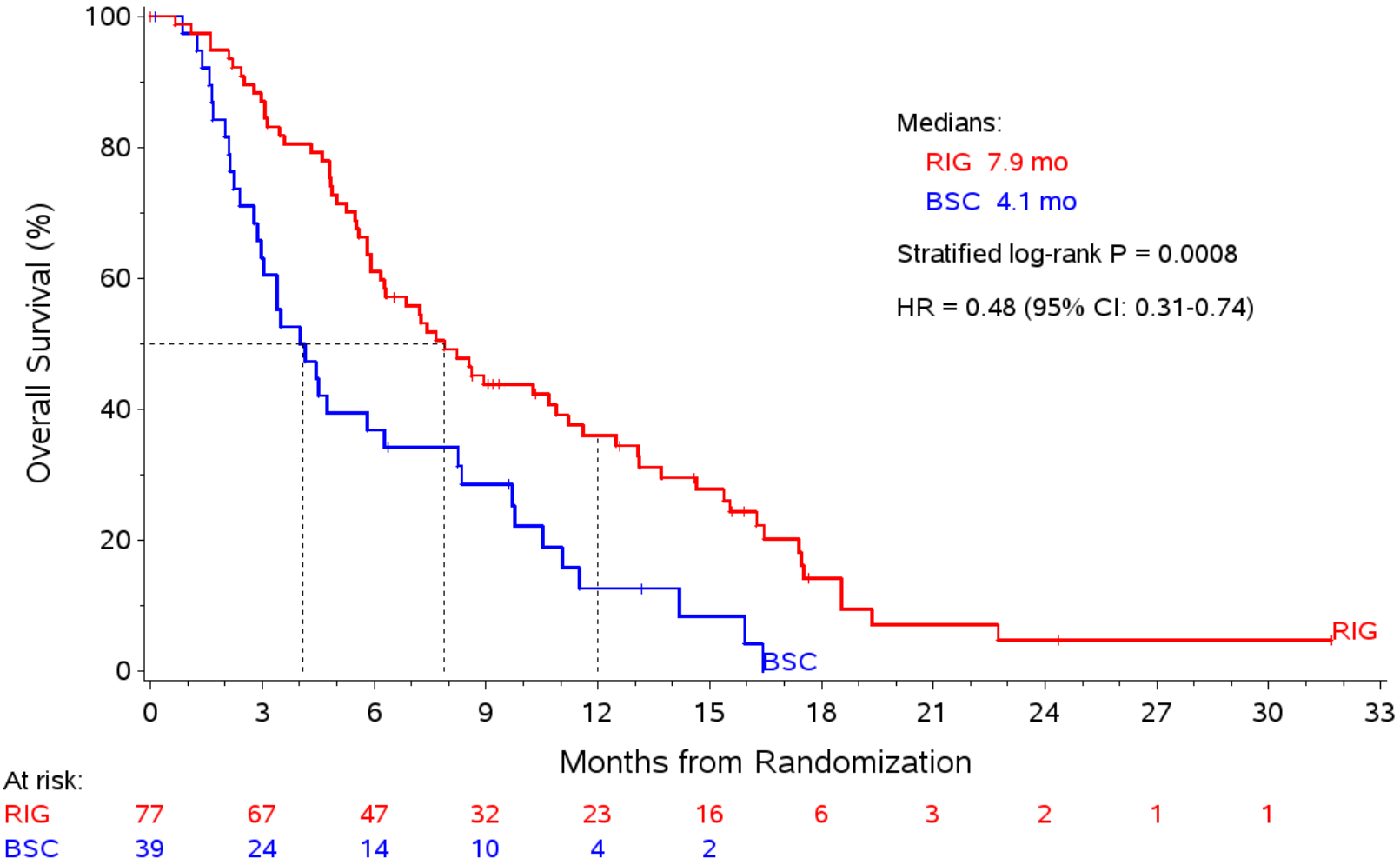
ONTIME Trial: Subgroups Correlated with Longer Median OS - ITT



p < 0.05

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

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



Is there still hope for combination therapy?

Combination therapy in MDS:

The addition of HDAC inhibitors
to HMTs does not seem to increase CR or OS

New **HDAC inhibitors**

- **Tenfinostat (CHR-2845)**
  - **cleaved by an enzyme found only in cells on monocytoid lineage**
- **Mocetiostat/Pracinostat**
- **Pevonedistat**

The addition of eltrombopag, vosaroxin, volasertib
not additional to activity of HMTs

BCL2 directed therapy (ABT-199 Venetoclax)
ABT199 effectively induces apoptosis in MDS

Anti-CD33 directed therapies (?)
SGN-CD33a, BI agent

Anti PD-1 anti PDL-1 antibodies

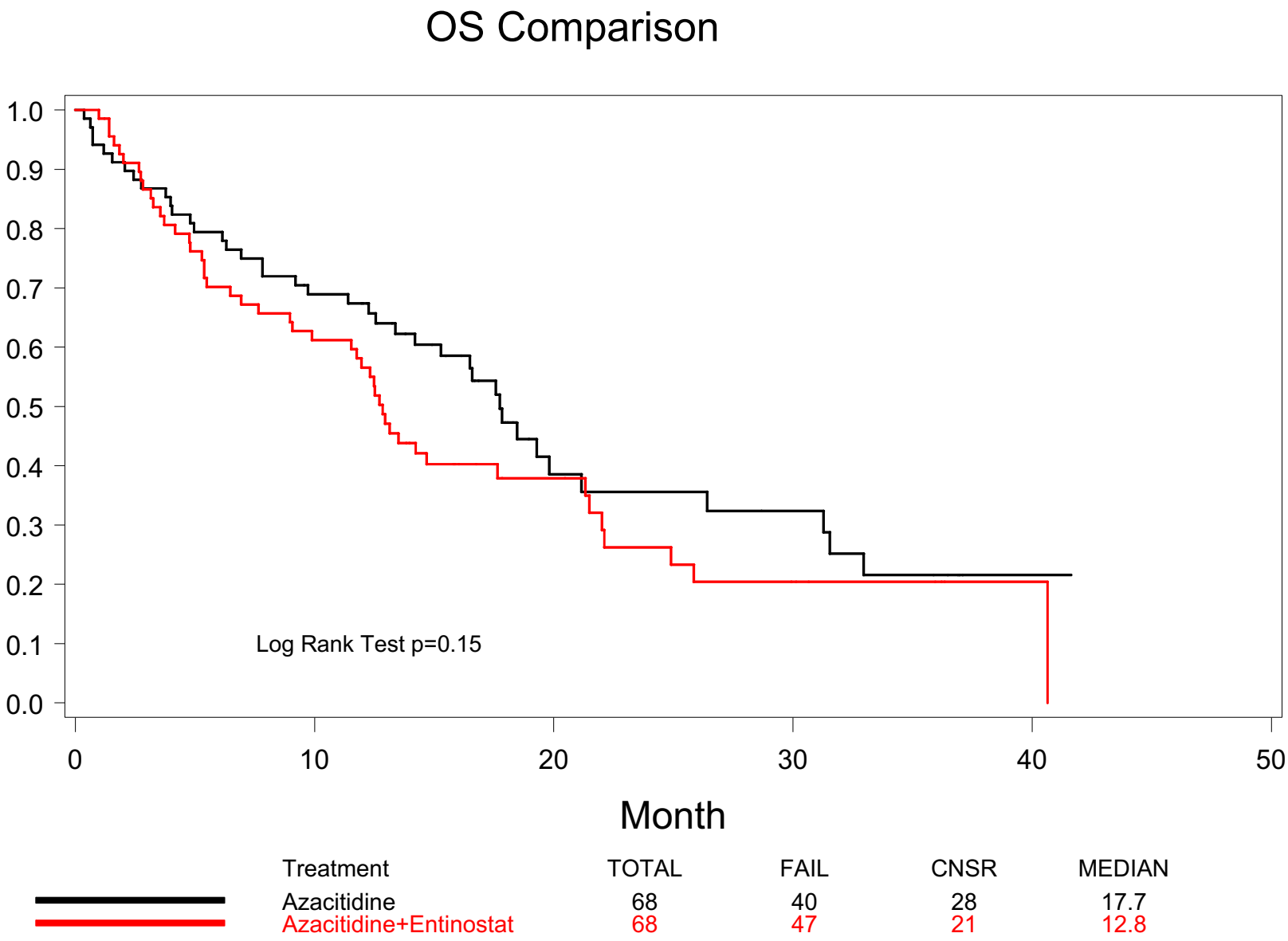
Azacitidine with or without Entinostat

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

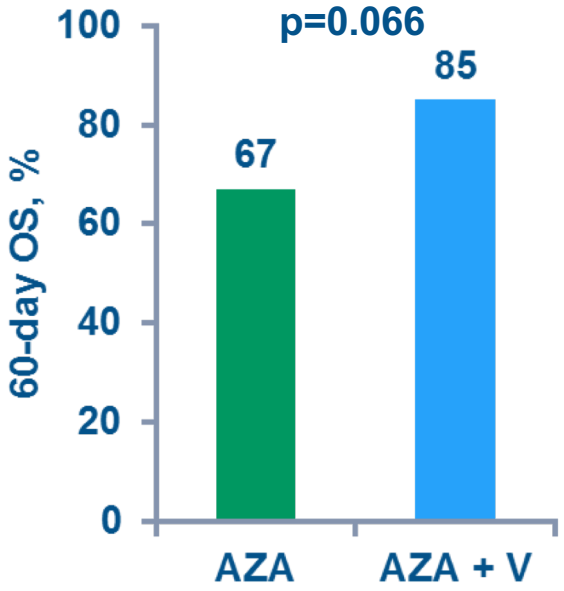
Analysis of overall survival



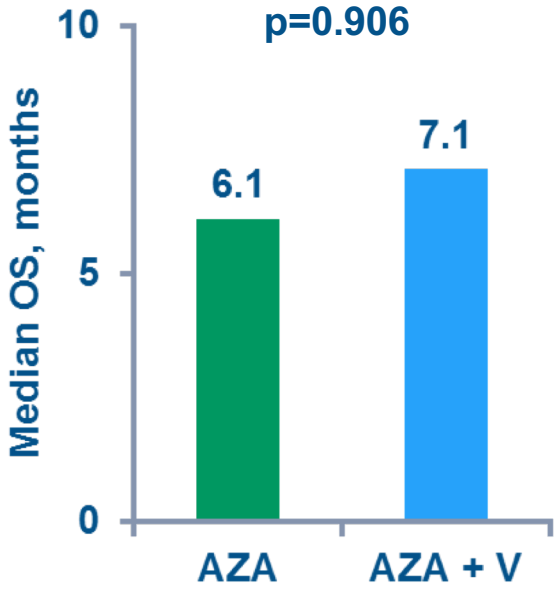
AZA vs AZA + vorinostat in patients with MDS/AML and poor PS: phase II study

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

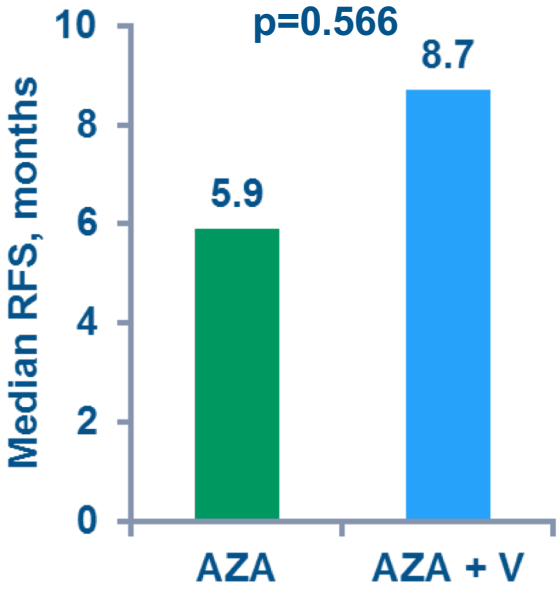
60-day OS



Median OS

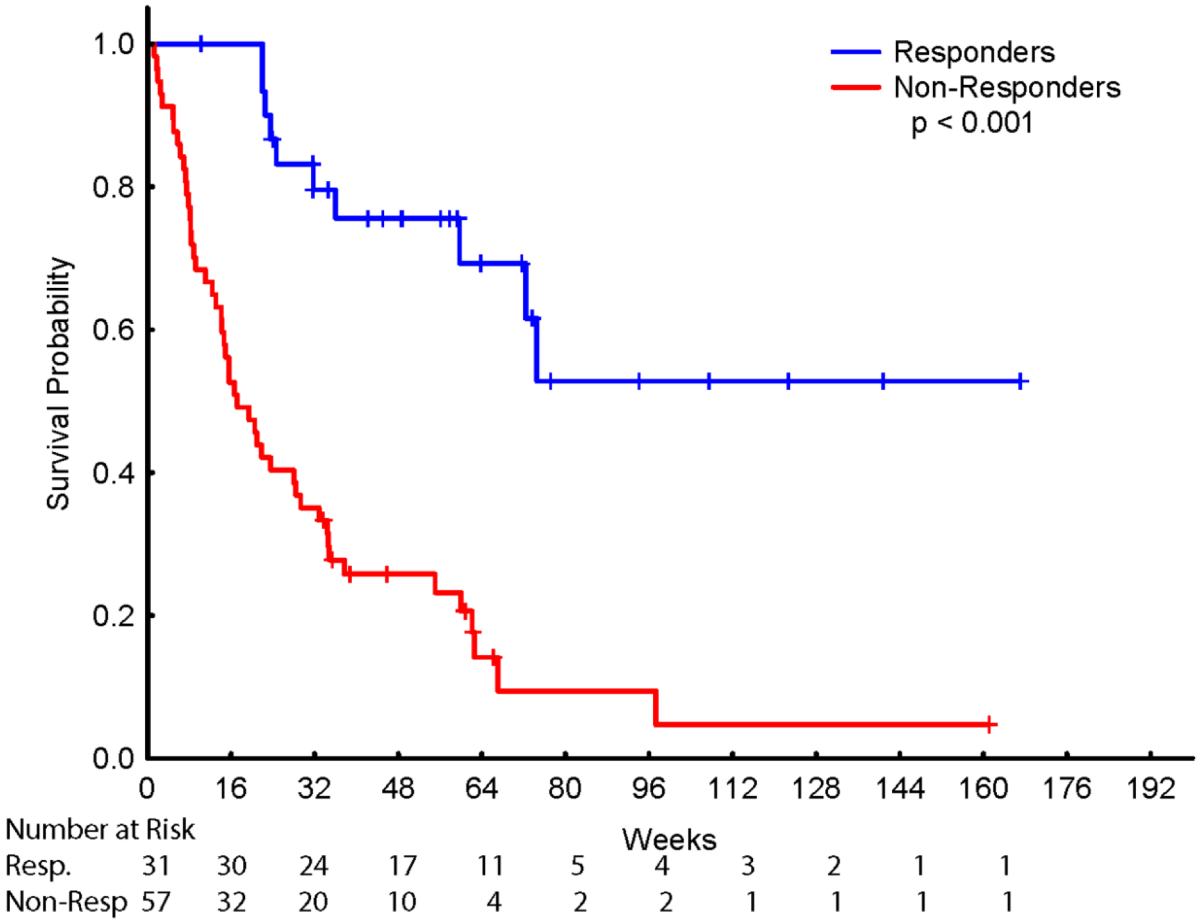


RFS



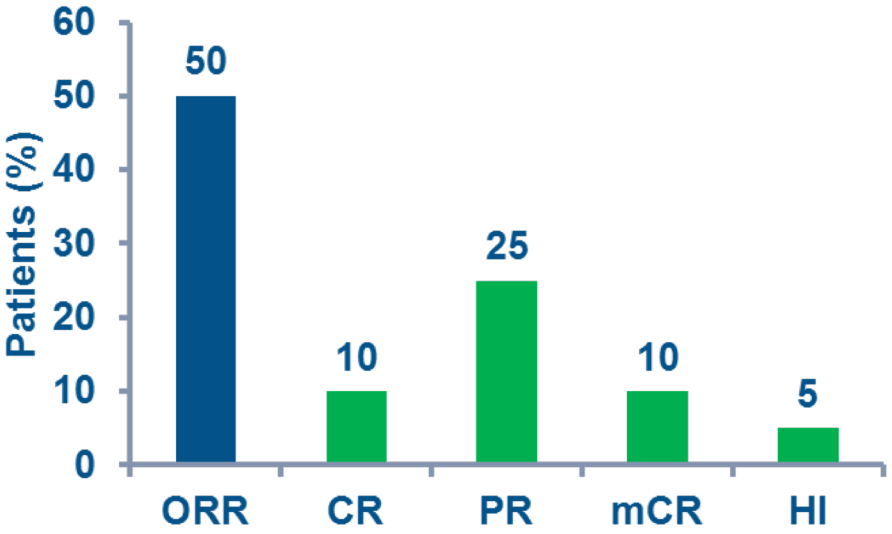
Garcia-Manero G, et al. Poster presentation at ASH 2014. Abstract 3277

AZA + LEN. OS by Response

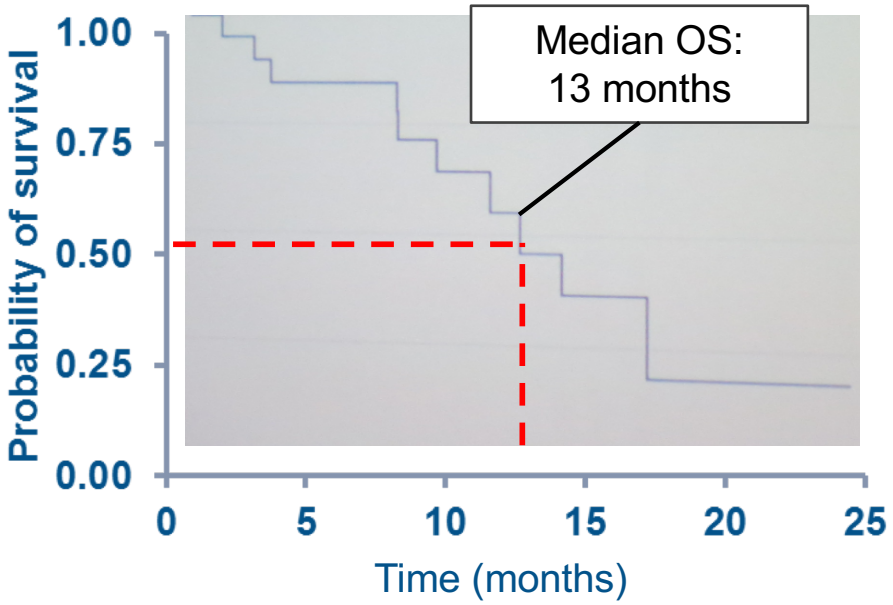


Azacitidine + idarubicin combination therapy in patients with high-risk MDS or AML

Response after 6 cycles



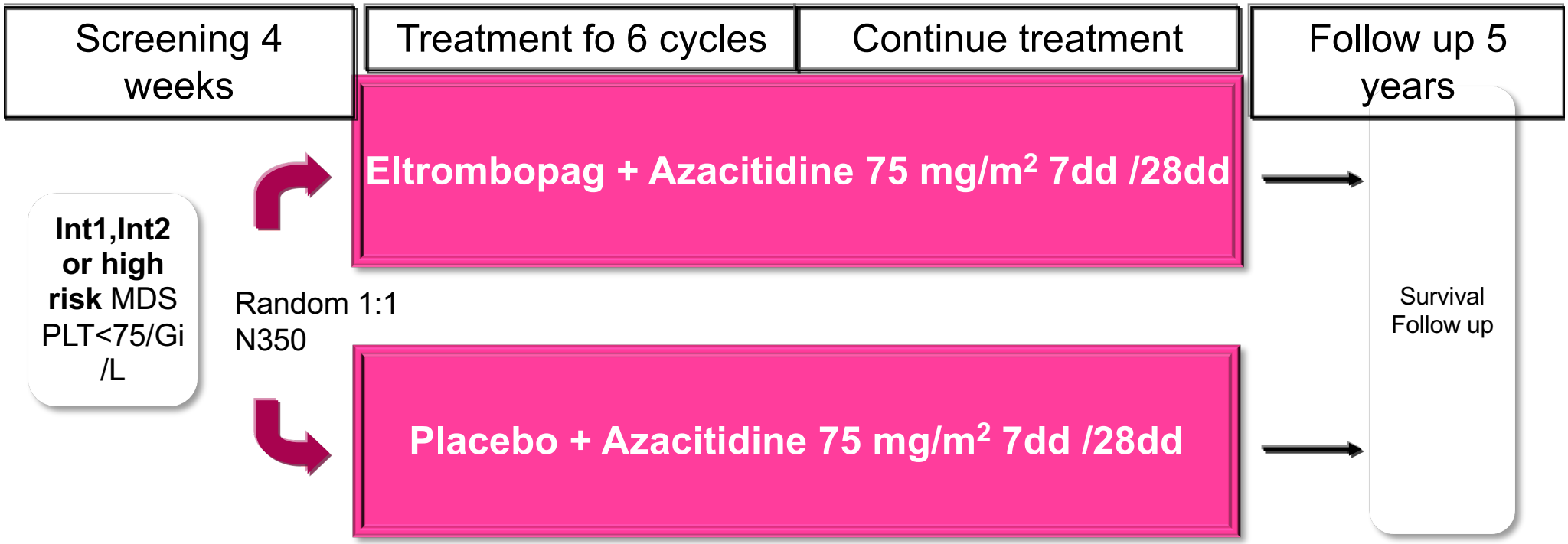
Overall survival



- Ten patients responded, six are still on study

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

Eltrombopag plus azacitidine: TRC112121 Support



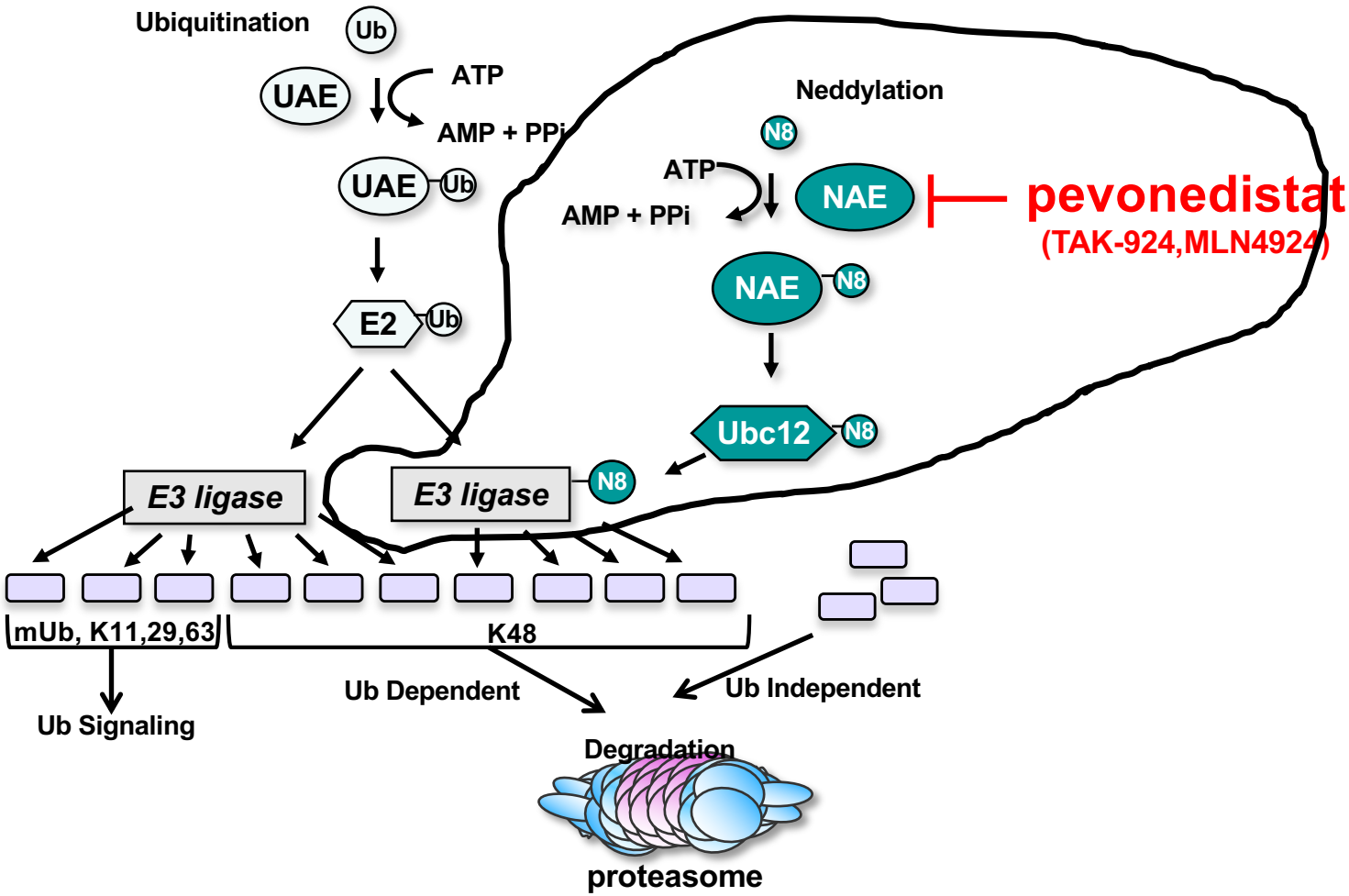
Eltrombopag plus azacitidine: TRC112121 Support

- 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**

The Ubiquitin System and the Proteasome

Substrate proteins

Regulatory pathway	Ex. of CRL substrates
Cell cycle	p21, p27, cyclin E, Wee1, CDC25A, Emi1
DNA replication	Cdt1, ORC1
NFκB signaling	IκBα
Hypoxia sensing	HIF-1α
Oxidative stress response	Nrf-2
mTOR signaling	Redd1, DEPTOR



Evaluating an inhibitor of the NEDD-8 activating enzyme: Pevonedistat

Phase 2, Randomized, Open-label, Global, Multicenter Study Comparing Pevonedistat Plus Azacitidine vs. Azacitidine in Patients with Higher Risk MDS, CMML, or Low-Blast AML

Stratification:
- Low-Blast AML
- MDS
  - -very high risk
  - -high risk
  - - intermediate risk
- CMML

Evaluated by IPPS-R

Primary Endpoint: Event Free Survival
- For higher risk MDS or CMML, an event is death or transformation to AML.
- For low-blast AML, an event is death or disease progression.

Venetoclax (ABT-199) with HMAs in R/R MDS

Characteristic	N = 43 (%)
VEN combination cycles received[a]—no. (%)	
1	17 (40)
2	18 (42)
≥3	8 (19)
Response—no. (%)	
ORR	9 (21)
CR	2 (5)
CRi	3 (7)
MLFS	4 (9)
NR	34 (79)
Early death (within 30 days)	5 (12)
Median overall survival[a] (range), *months*	3.0 (0.5–8.0)

Di Nardo et al, Am J Hematol 2017

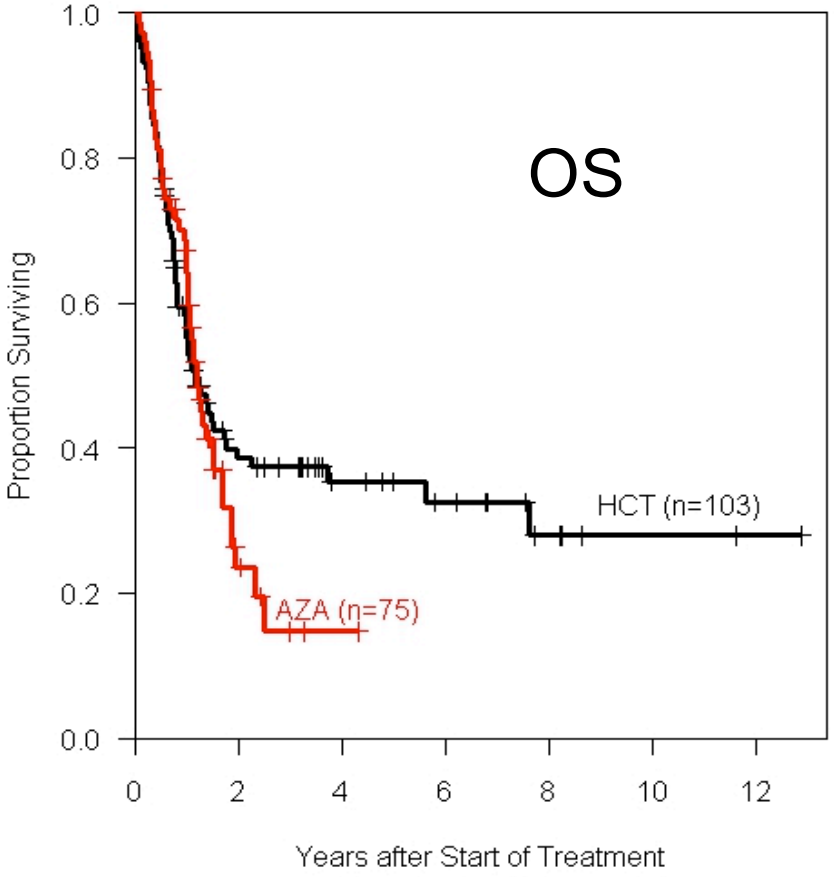
In MDS, upfront HSCT will cure 20-30% of eligible patients

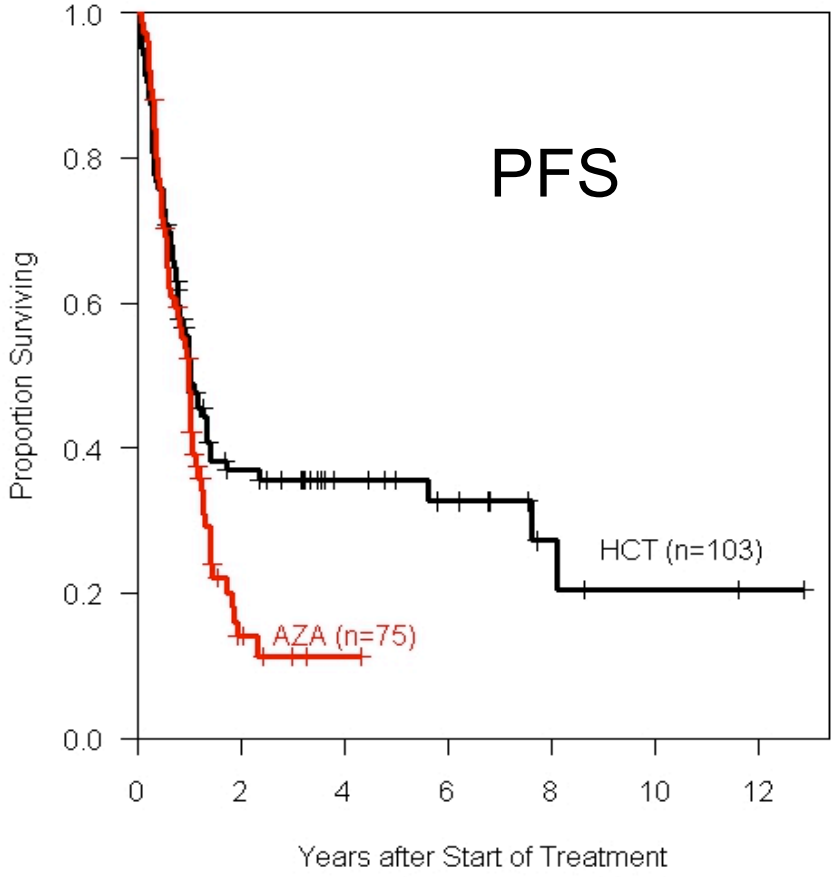
How to minimize relapse and prolong survival .

Role of azacitidine *versus*, pre- and post-HSCT

Role of azacitidine *versus* HSCT

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





Platzbecker et al. BBMT 2012

UNIVERSITÀ DEGLI STUDI FIRENZE

DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

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