FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

L'attuale approccio clinico al paziente con **Sindrome Mielodisplastica**

Napoli

Il trattamento dei pazienti ad alto rischio

Ottimizzazione del trattamento con ipometilanti

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Lecce

Treatment of MDS General comments

- Advanced age
- Comorbidity and associated diseases frequent
- Great prognostic heterogeneity
- Curative modalities (i.e. allo-SCT) high morbidity and mortality

Risk-adapted treatment essential

MDS: Management Goals by Risk-group

	Low risk	High risk
Treatment Goal	Hematopoiesis	Survival
Clinical Endpoint	▪ HI ▪ QOL	▪ Alter natural history ▪ Delay AML
Management Considerations	▪ ESA ▪ IMiD ▪ IST ▪HMA	▪ HMA ▪ AlloSCT ▪ Chemotherapy

Is IPSS the better prognostic score to select high-risk patients?

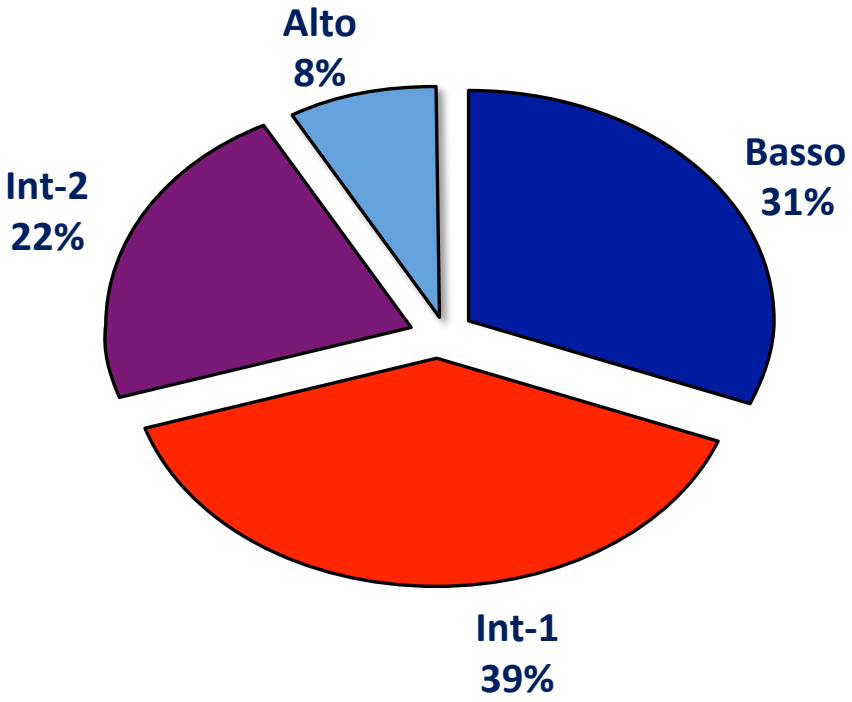
Categorie di rischio IPSS - Distribuzione dei pazienti

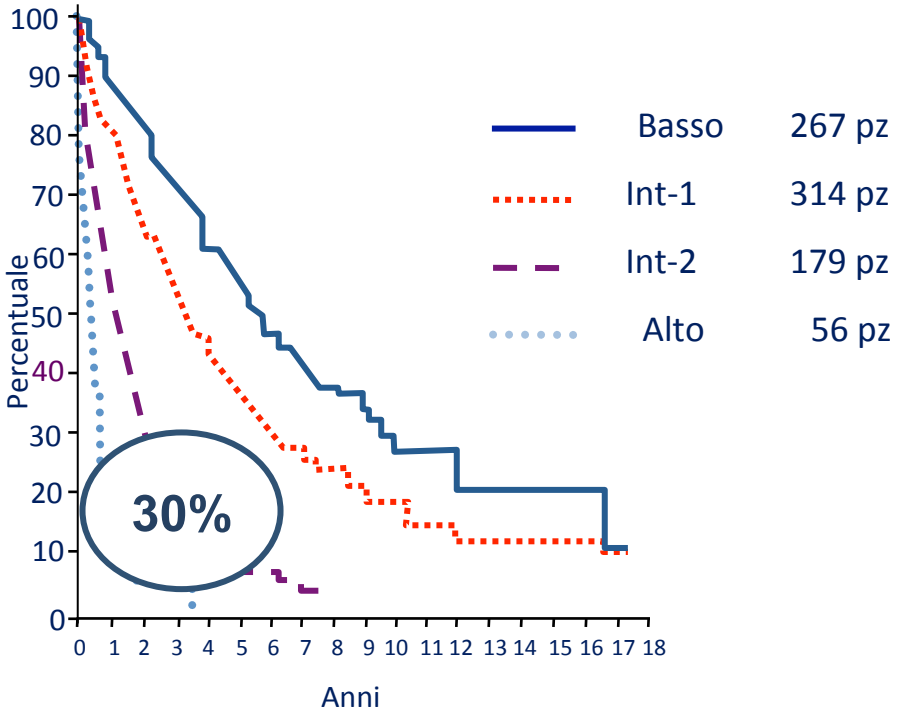
	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

* Good, normal, −Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

- **Blasti midollari %**
- **Citogenetica**
- **Citopenie**





Semplice, universalmente accettato, stratificazione prognostica per l'accesso ai farmaci

Greenberg P et al. Blood. 1997;89:2079

WHO classification-based Prognostic Scoring System (WPSS)

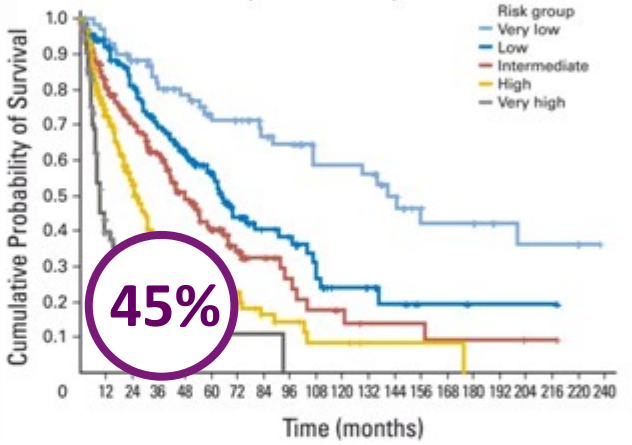
Variable	*Points*			
	0	*1*	*2*	*3*
WHO category	RA, RARS, MDS with isolated deletion (5q)	RCMD	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	-
Severe anemia**	Absent	Present	-	-
Bone marrow fibrosis	The presence of grade 2-3 bone marrow fibrosis involves a shift to a one-step more advanced risk group after accounting for WHO category, karyotype, and transfusion requirement			

* Good: normal, del(5q) only, del(20q) only, -Y only; Poor: very complex (>2) abnormalities, chromosome 7 anomalies; Intermediate: other abnormalities.

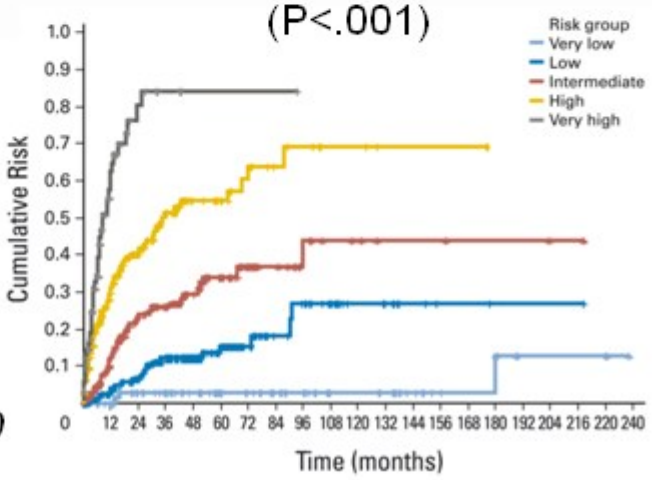
** Severe anemia: Hemoglobin <9 g/dL in males or <8 g/dL in females.

***Risk groups*: very low (0), low (1), intermediate (2), high (3-4), very high (5-6)**

Overall survival (P<.001)



Risk of AML evolution (P<.001)



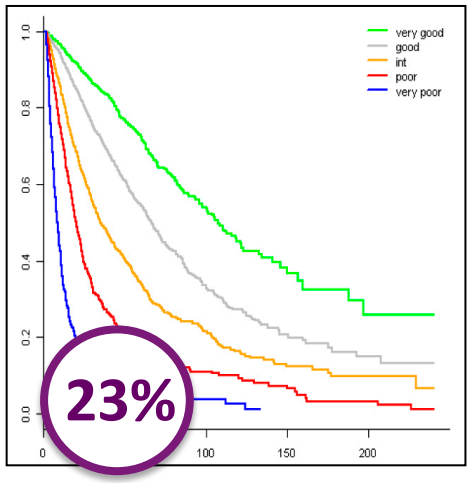
Simple, reproducible, dynamic (applicable during evolution)

J Clin Oncol 2007;25:3503-10; Haematologica. 2011;96:1433-40

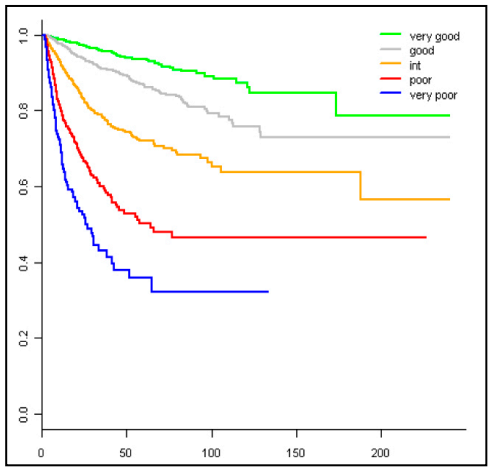
IPSS-R: Prognostic Risk Groups/Scores

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Inter-mediate	Poor	Very poor
BM blasts	<2%	-	>2%<5%	-	5%-10%	>10%	-
Hemoglobin, g/dL	>10	-	8 <10	<8	-	-	-
Platelets	>100	50<100	<50	-	-	-	-
ANC	>0.8	<0.8	-	-	-	-	-

IPSS-R Survival n=7012



Freedom from AML



Risk group	Score	%
Very low	0-2	19
Good	>2 -3.5	38
Intermediate	>3.5-5	20
High	>5-6	13
Very hjgh	>6	10

	Very Low	Good	Inter-mediate	Poor	Very High
Med. OS	8.7	5.3	3.0	1.6	0.8
AML 25%	NR	10.7	4.0	1.4	0.8

Using IPSS-R compared with IPSS
- 27% of IPSS lower-risk “upstaged”
- 18% of IPSS higher-risk “downstaged”

Greenberg PL et al. Blood. 2012;120(12): 2454-2465

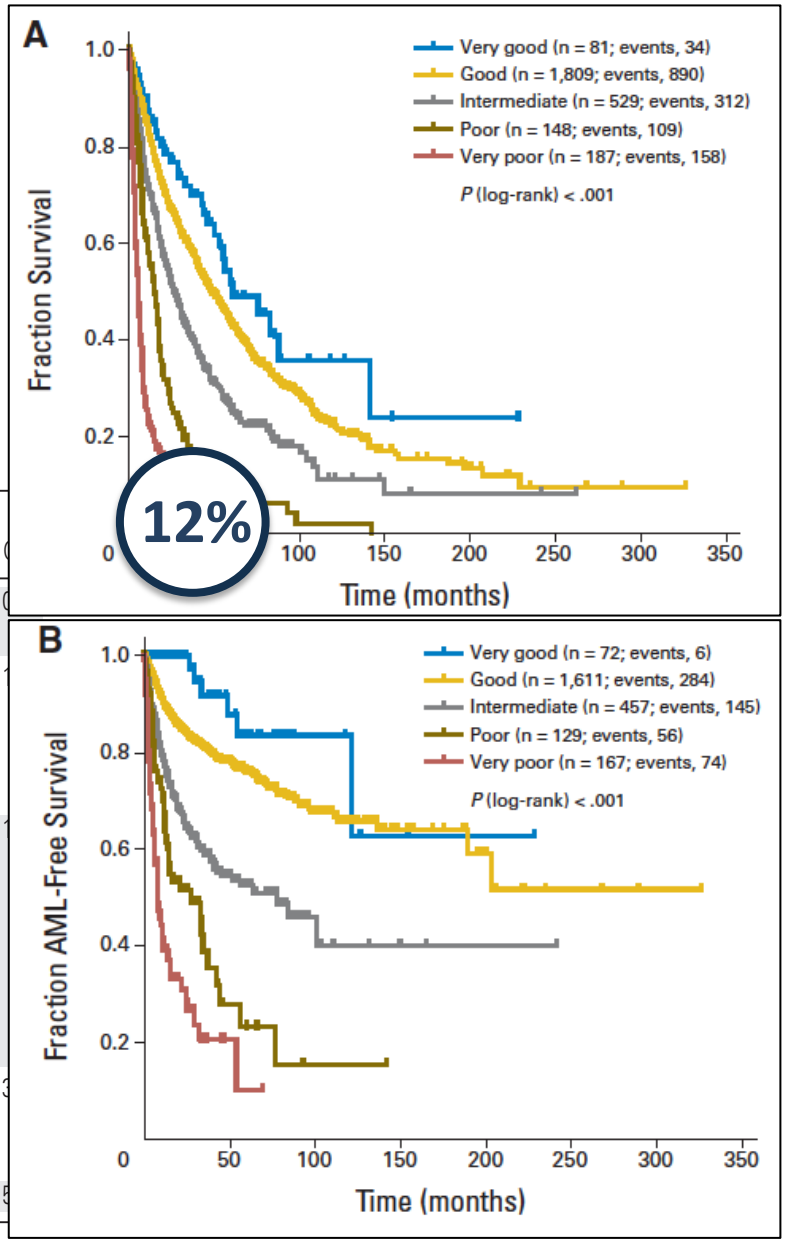
New Comprehensive Cytogenetic Scoring System for Primary Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia After MDS Derived From an International Database Merge

Karyotype	N=	%
Normal	1.543	55.1
Abnormal	1.258	44.9

New Cytogenetic Scoring System (n 2,754)

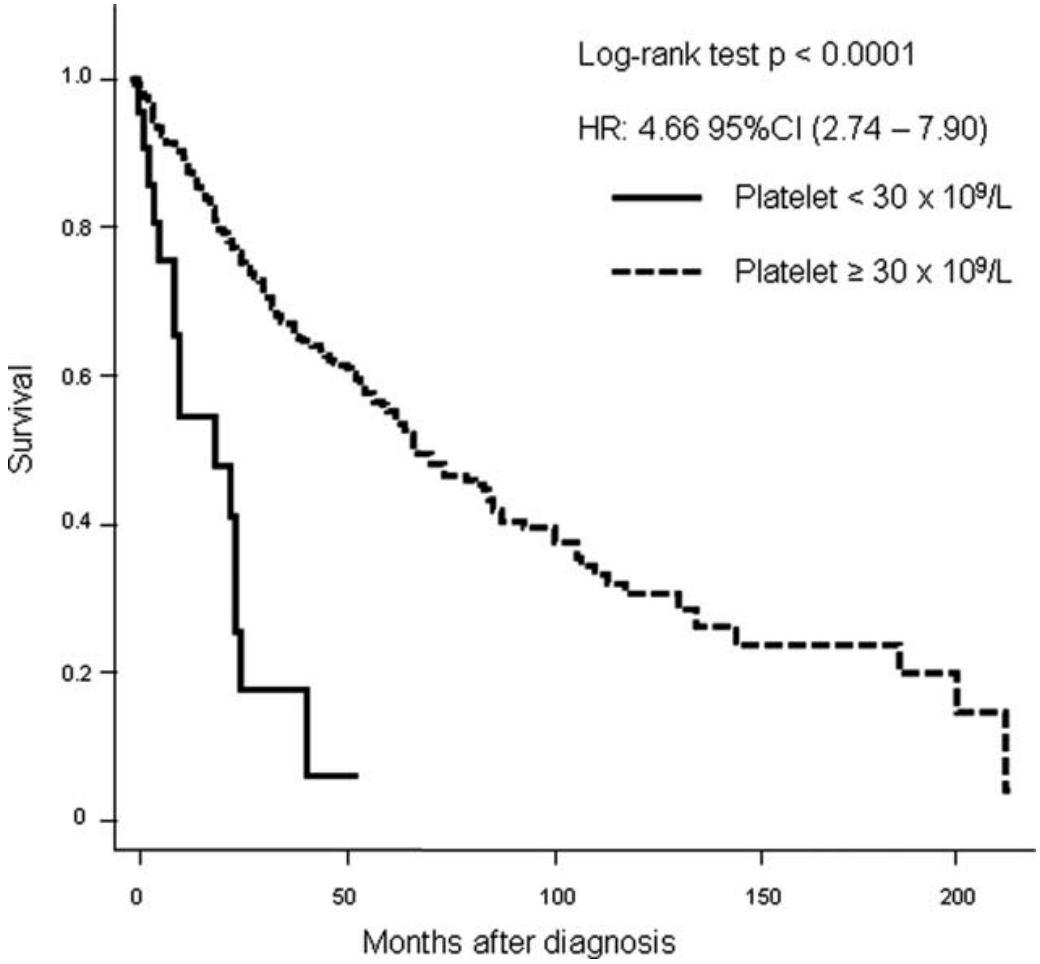
Prognostic Subgroup	No. of Patients	%	Abnormality: Single	Abnormality: Double	Abnormality: Complex	Overall Survival: Median (months)†	Overall Survival: 95% CI	Overall Survival: HR	Overall Survival: 95%
Very good	81	2.9	del(11q) −Y	—	—	60.8	50.3 to NR	0.5†	0.3 to
Good (reference)	1,809	65.7	Normal del(5q) del(12p) del(20q)	Including del(5q)	—	48.6	44.6 to 54.3	1.0	0.9 to
Intermediate	529	19.2	del(7q) +8 i(17q) +19 Any other Independent clones	Any other	—	26.0	22.1 to 31.0	1.6†	1.4 to
Poor	148	5.4	inv(3)/t(3q)/ del(3q) −7	Including −7/del(7q)	3	15.8	12.0 to 18.0	2.6†	2.1 to
Very poor	187	6.8	—	—	> 3	5.9	4.9 to 6.9	4.2†	3.4 to

Abbreviations: AML, acute myeloid leukemia; HR, hazard ratio; NR, not reached.
*Patients with complete data.
†$P < .01$.



Schanz J et al. J Clin Oncol 2012; 30:820-829

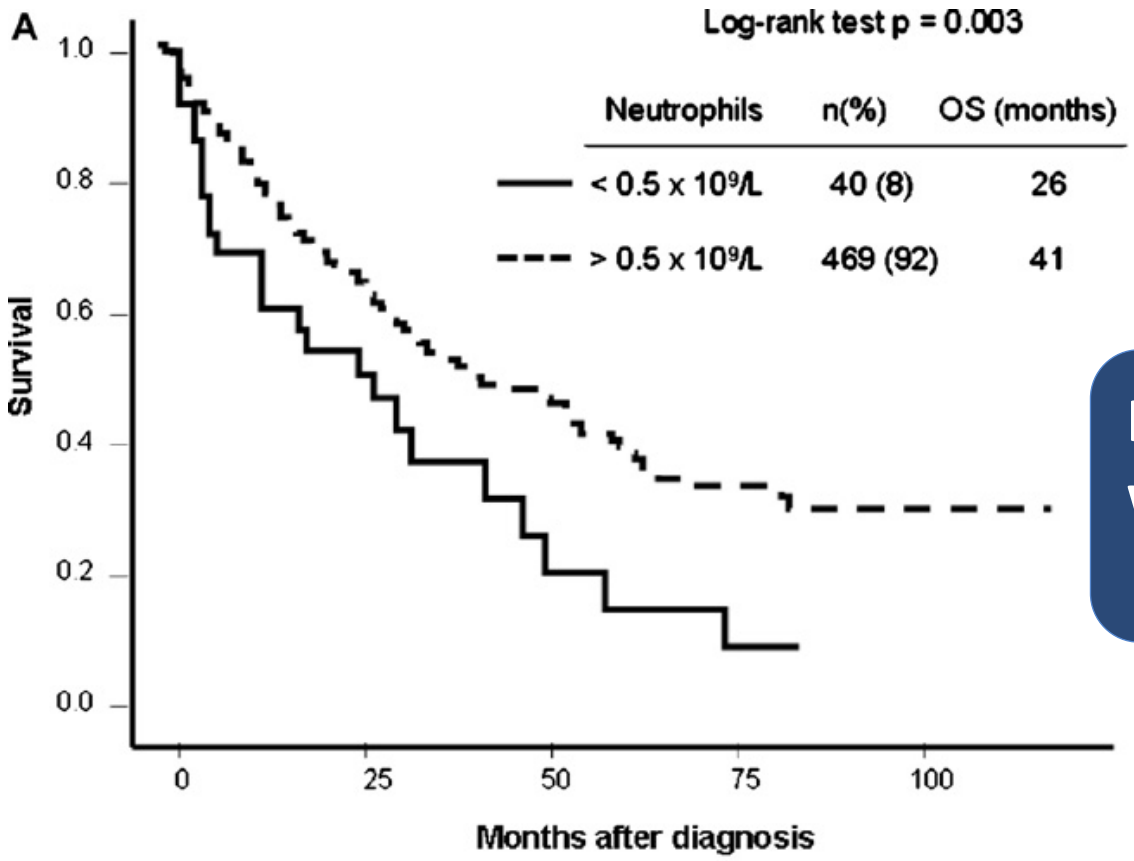
Overall survival by platelet count in lower risk MDS (IPSS low and intermediate-1)



Independent association with OS in multivariate analysis

Gonzalez-Porras JR et al Cancer 2011;117:5529–37

Overall survival by neutrophil count in IPSS low-risk MDS

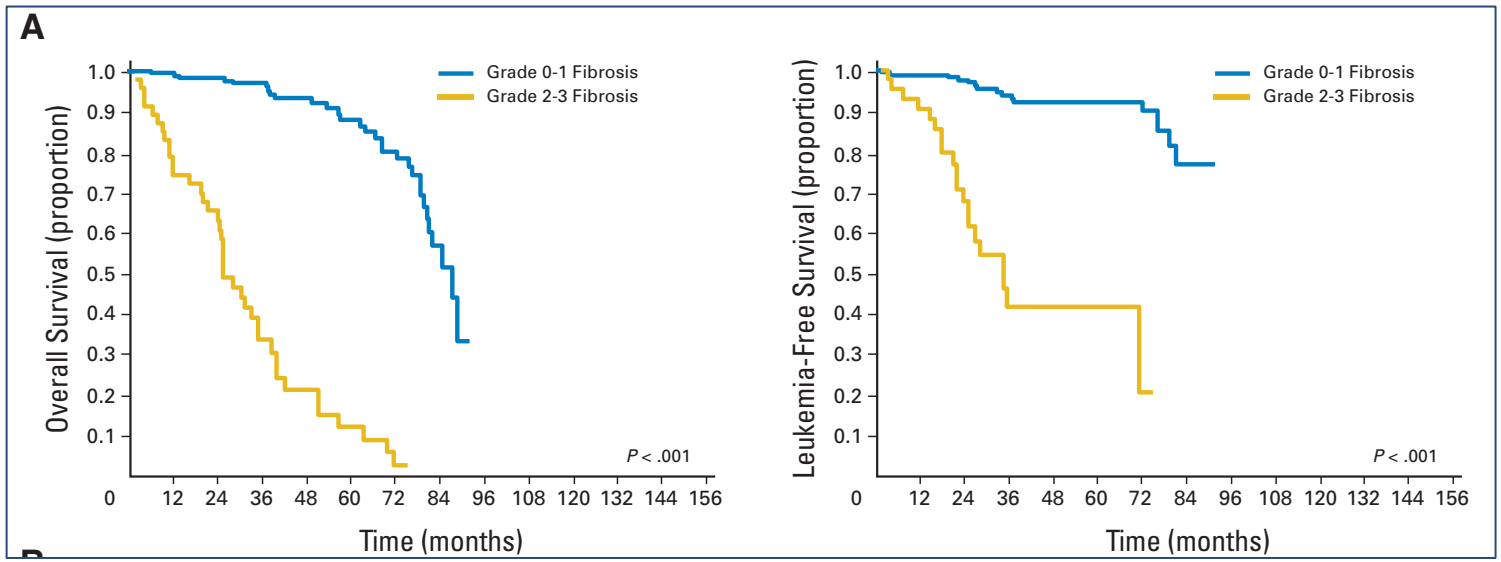


Independent association with OS and AML risk in multivariate analysis

Cordoba I et al. Leukemia Research 2011

Overall Survival and Leukemia-free survival by extent of bone marror fibrosis in MDS

RA,RARS, RCMD ± RS



Patients with grade 2-3 fibrosis had reduced OS and LFS compared to patients with grade 0-1

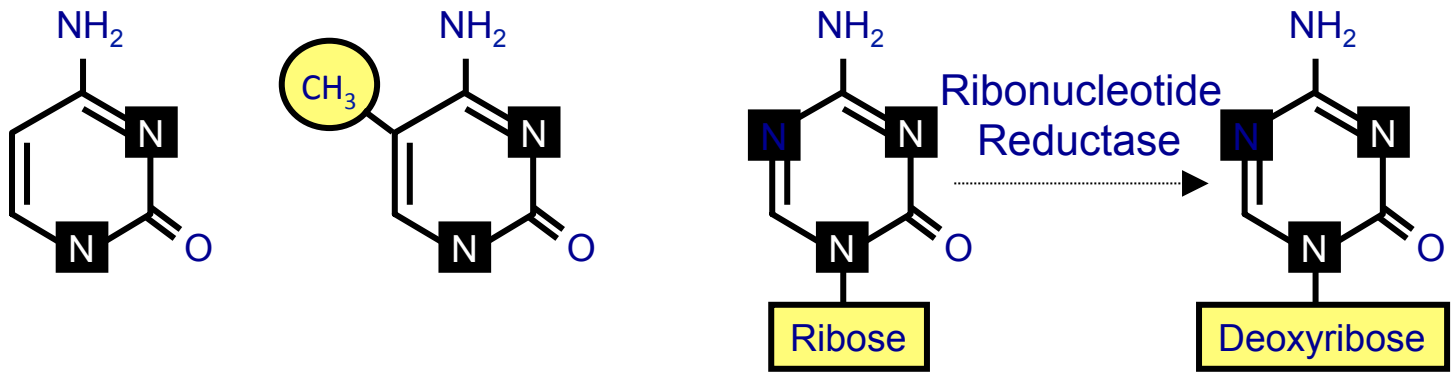
Della Porta MG et al . J Clin Oncol 27:754-762. 2008

Risk-adapted treatment of MDS definition of higher risk patients

- IPSS int-2 or high and/or WPSS high or very high and /or IPSS-R high or very high
- IPSS int-1 and/or WPSS or IPSS-R intermediate with one or more of the following features
  - High or very high risk cytogenetics (by IPSS-R)
  - Severe neutropenia (<0.5 x 10^9 PMN/L)
  - Severe thrombocytopenia (<30 x 10^9 platelets/L)
  - Moderate/severe BM fibrosis (grade2-3)

Symptomatic anemia should be the only remaining reason for treatment in patients with lower-risk MDS

Hypomethylating Cytosine Analogs



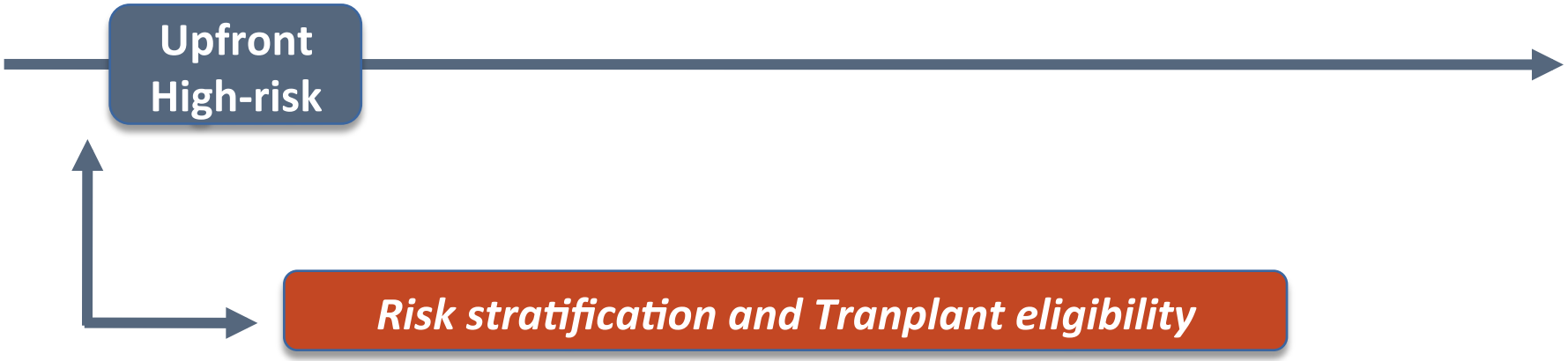
Cytosine 5-methyl-cytosine 5-aza-cytidine 5-aza-2′-deoxy-cytidine

90% RNA, 10% DNA incorporation

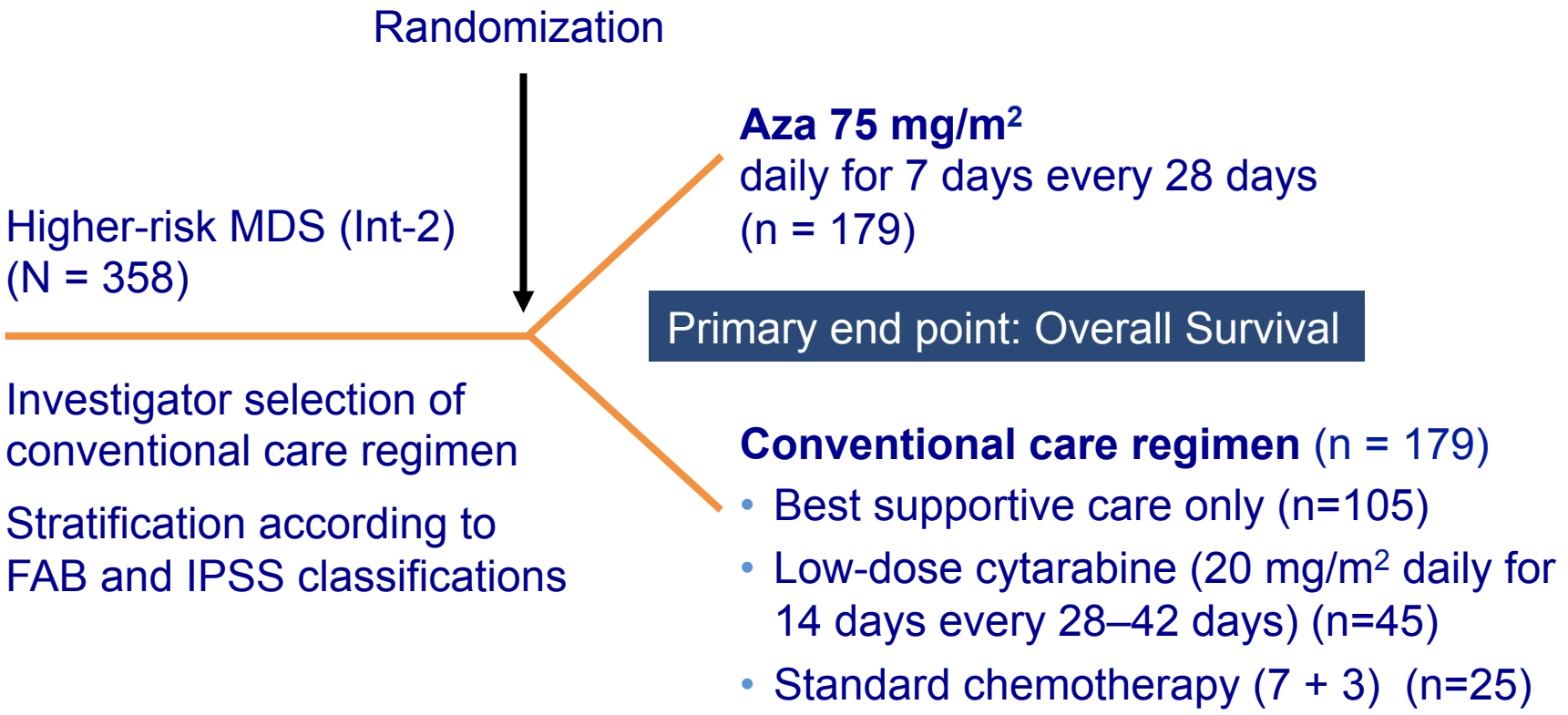
DNA specific

High-dose decitabine causes DNA synthesis arrest, leading to cytotoxicity.
Low-dose decitabine induces DNMT inhibition with minimal cytotoxicity

Hypomethylating agents in MDS



Azacitidine phase III survival study (AZA-001): design



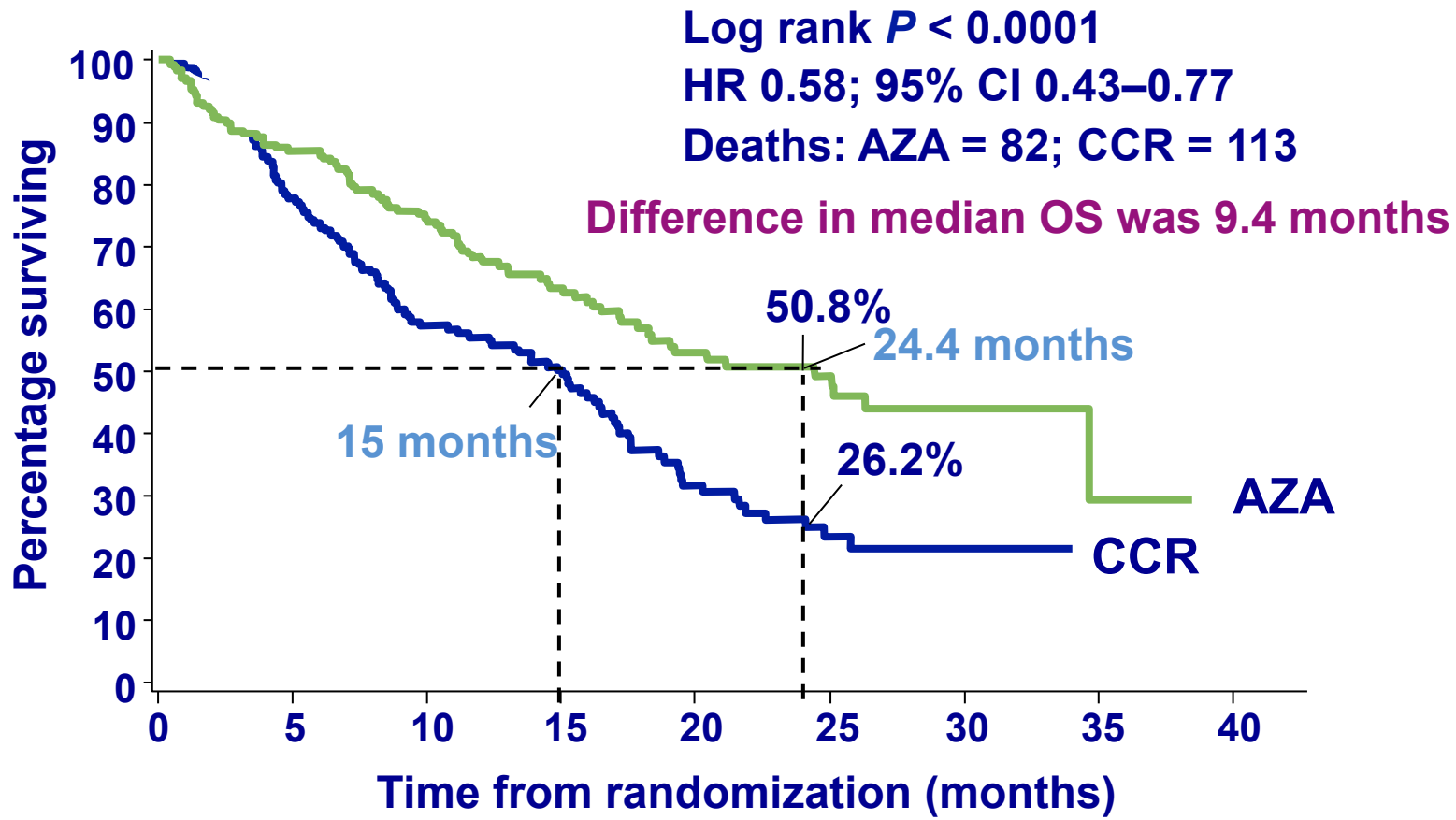
Treatment continued until unacceptable adverse events or transformation to AML or disease progression

Azacitidine vs CCR: IWG 2000 Response and HI

Response	AZA N=179 (%)	CCR N=179 (%)	BSC N=105 (%)	LDAC N=49 (%)	Std Ind N=25 (%)	P-Value AZA vs CCR
Overall (CR+PR)	**29**	**12**	5	12	40	**0.0001**
CR	**17**	**8**	1	8	36	**0.02**
PR	**12**	**4**	4	4	4	**0.009**
IWG HI						
Major+Minor	**49**	**29**	31	25	28	**<0.0001**
HI-E Major	**40**	**11**	8	10	22	**<0.0001**
HI-P Major	**33**	**14**	10	19	20	**0.0003**
HI-N Major	**19**	**18**	20	11	24	**0.87**

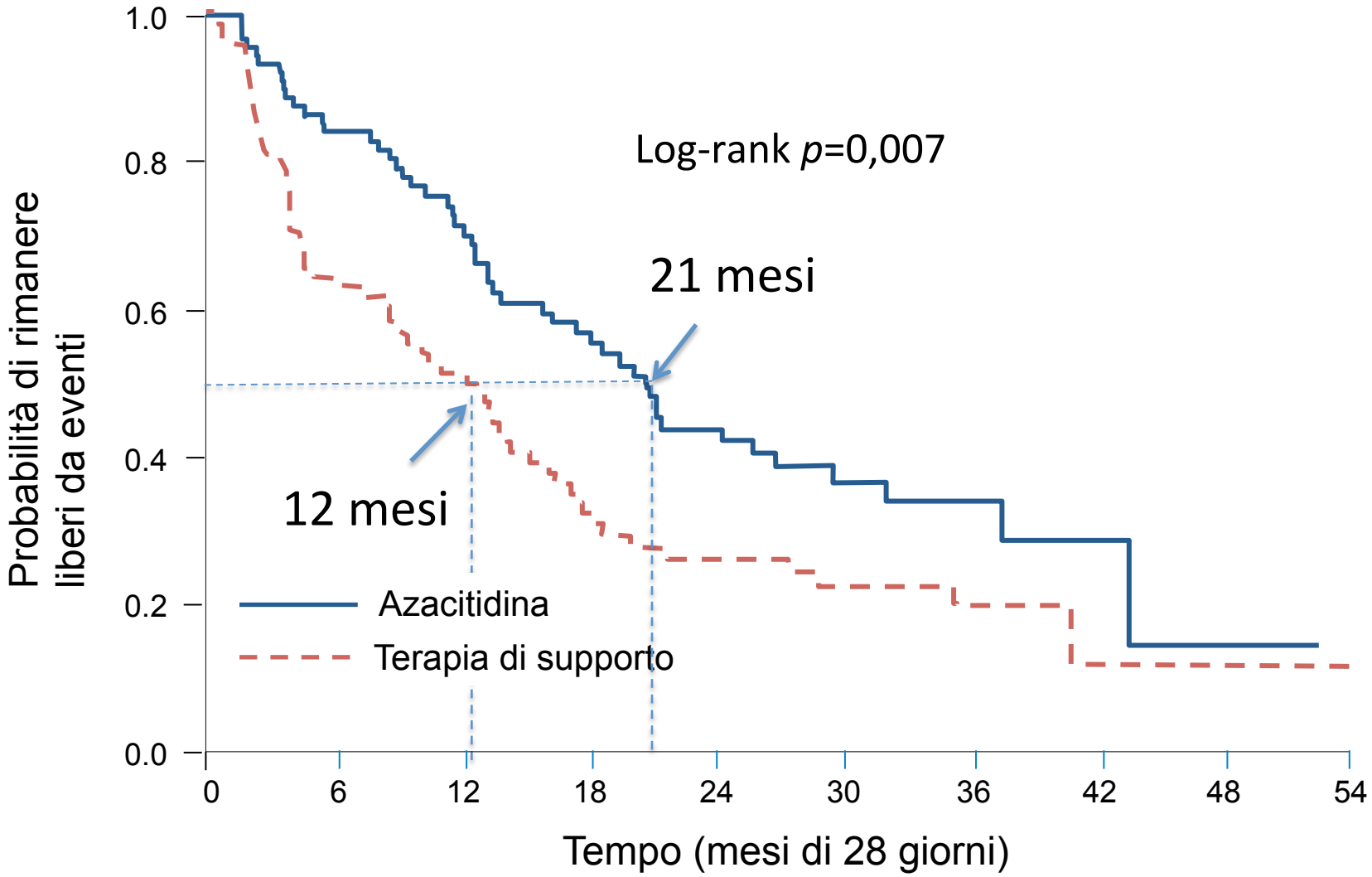
Fenaux P, et al. Lancet Oncol. 2009;10:223-32.

Azacitidine prolongs overall survival in patients with IPSS Int-2- or High-risk MDS



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat.

Azacitidina: tempo alla trasformazione in AML o al decesso per tutti i pazienti



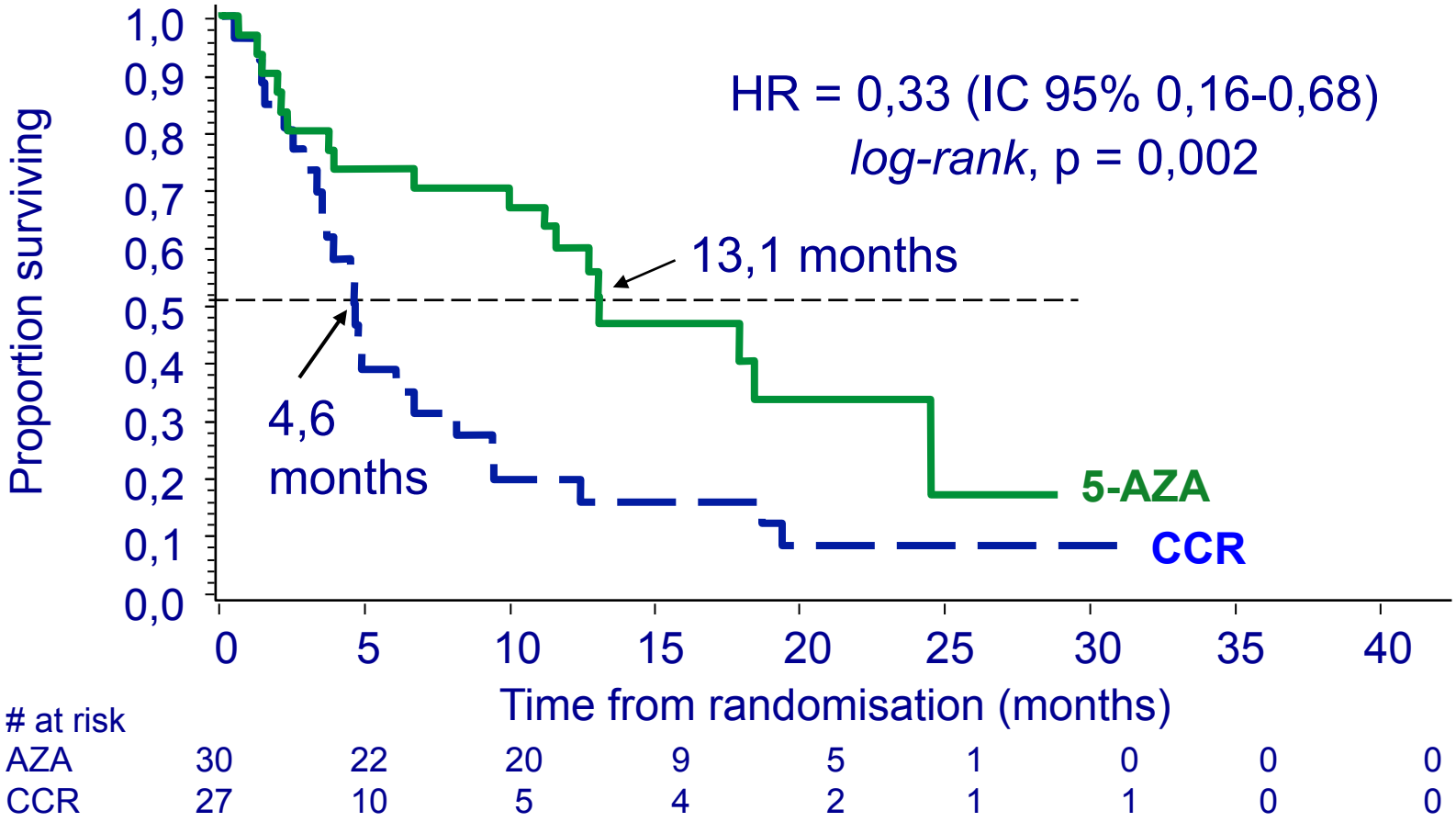
Silverman et al. J Clin Oncol 2002;20:2429–2440

AZA vs CCR
Survival According to CCR and Cytogenetics

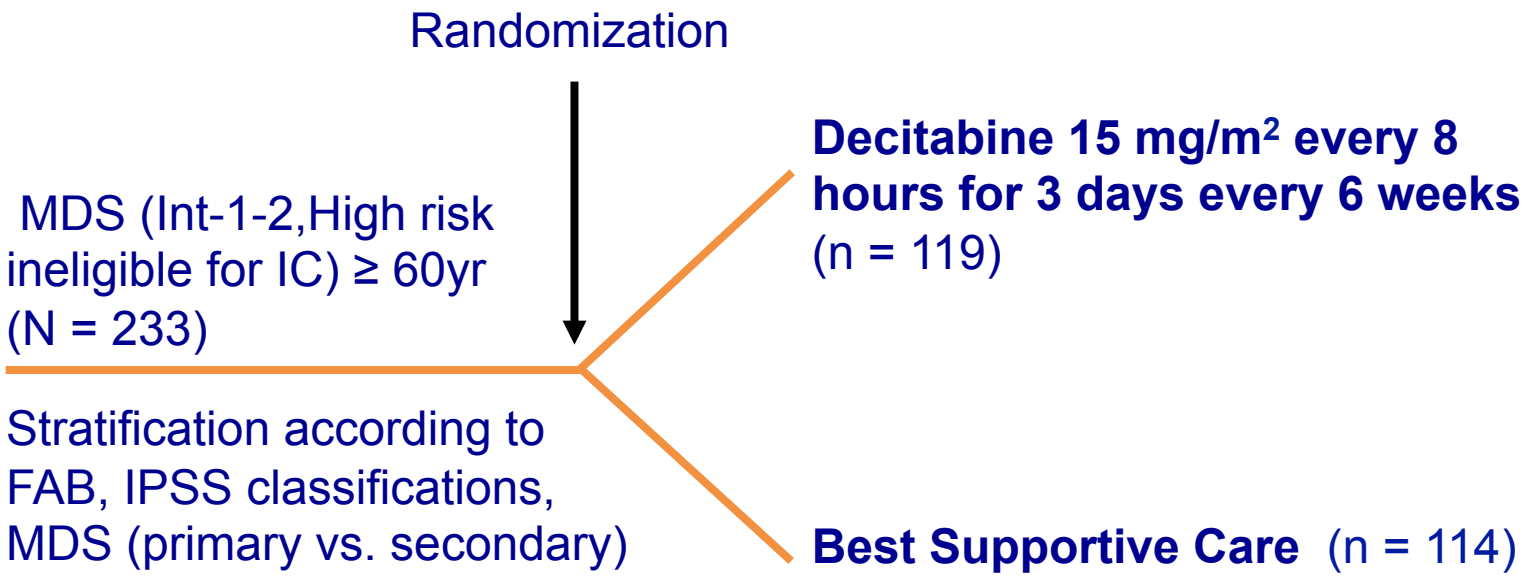
Patient Groups	AZA Med. OS [mos]	CCR Med. OS [mos]	*P* value Log rank
All Patients	24.4	15	0.0001
CC Regimen	24.4	BSC 11.5 LDAC 15.3 Std CT 15.7	0.0003 0.016 0.19
IPSS Cytogenetics **Good** **Intermediate** **Poor**	 NR 26.3 17.2	 17.1 17.0 6.0	 0.030 0.017 0.011

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

Patients with 7/del(7q) cytogenetic abnormality AZA *vs* CCR



Low-dose Decitabine vs Best Supportive Care Phase III study design (EU Study)



Study end points:

- Overall Survival
- AML-Free Survival
- PFS
- Relapse after CR/PR

Lubbert M, et al. J Clin Oncol. 2011;29:1987-96

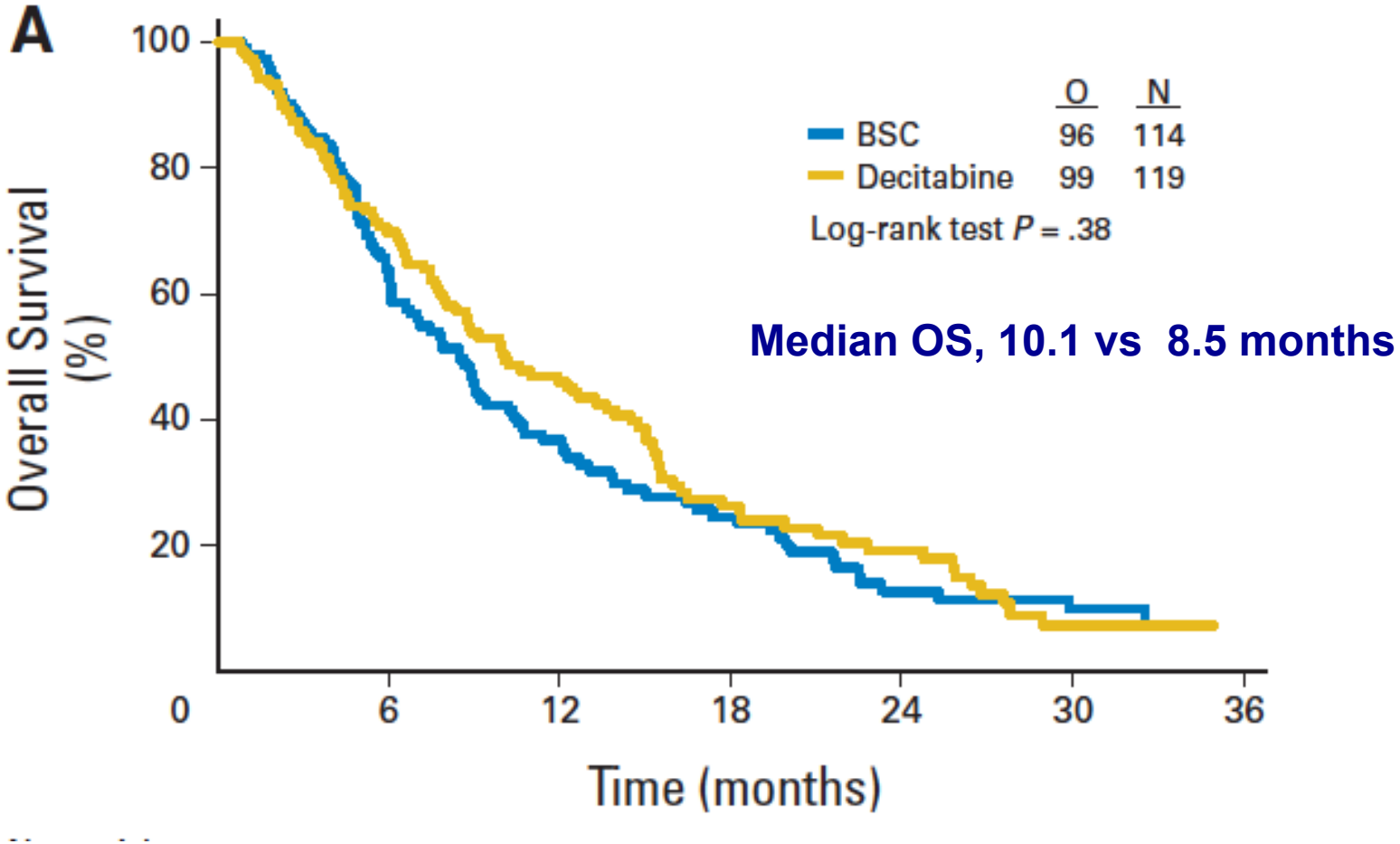
Low-dose Decitabine vs BSC
Best response to treatment

	BSC N=114 (%)	Decitabine N=119 (%)
Complete Remission	0 (0.0)	
Partial Remission	0 (0.0)	
Hematologic Improvement	2 (1.8)	18 (15.1)
Stable Disease	25 (21.9)	17 (14.3)
Progressive Disease	78 (68.4)	35 (29.4)
Hypoplasia	0 (0.0)	17* (14.3)
Response inevaluable	9 (7.9)	9 (7.6)

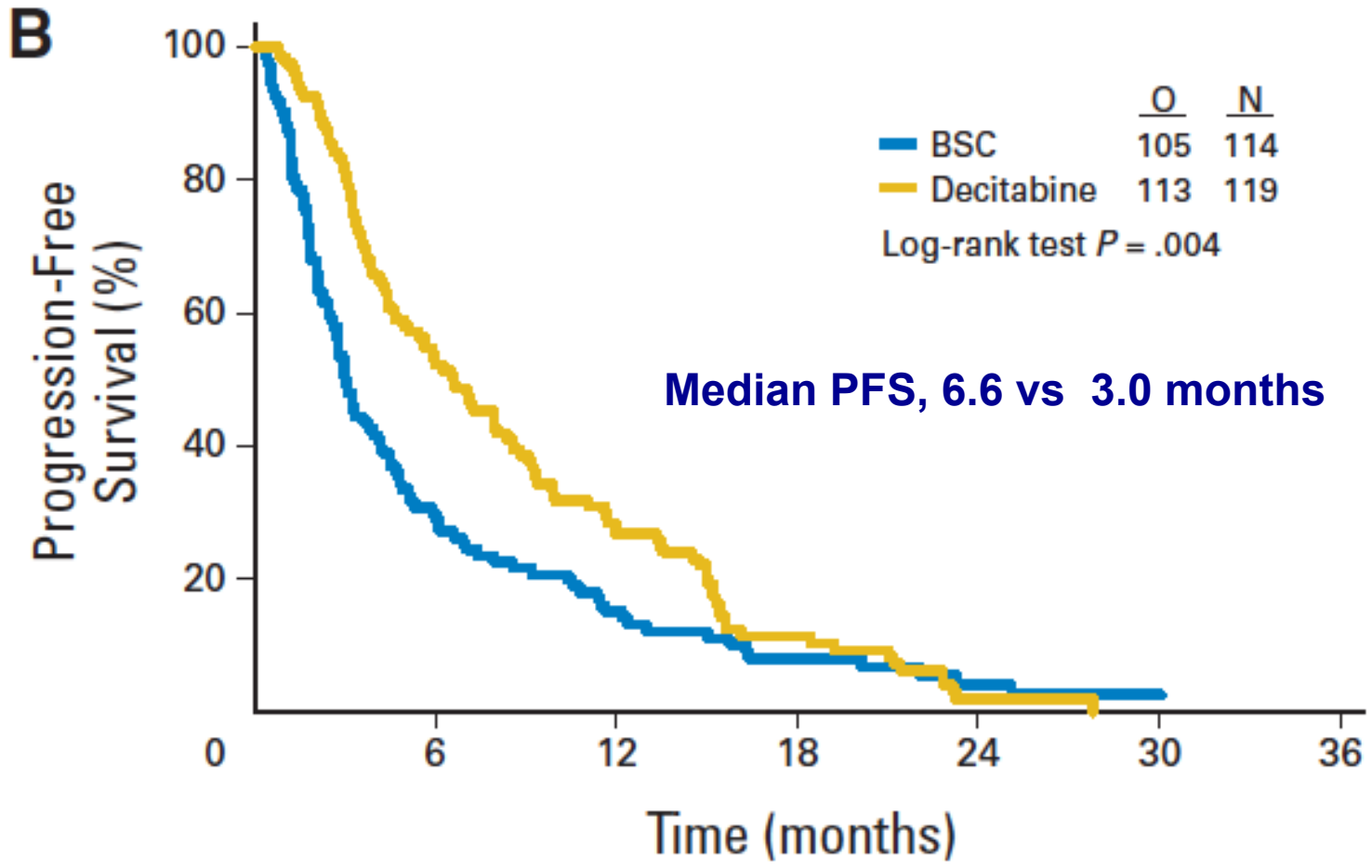
CR + PR
19.3%

Lubbert M, et al. J Clin Oncol. 2011;29:1987-96

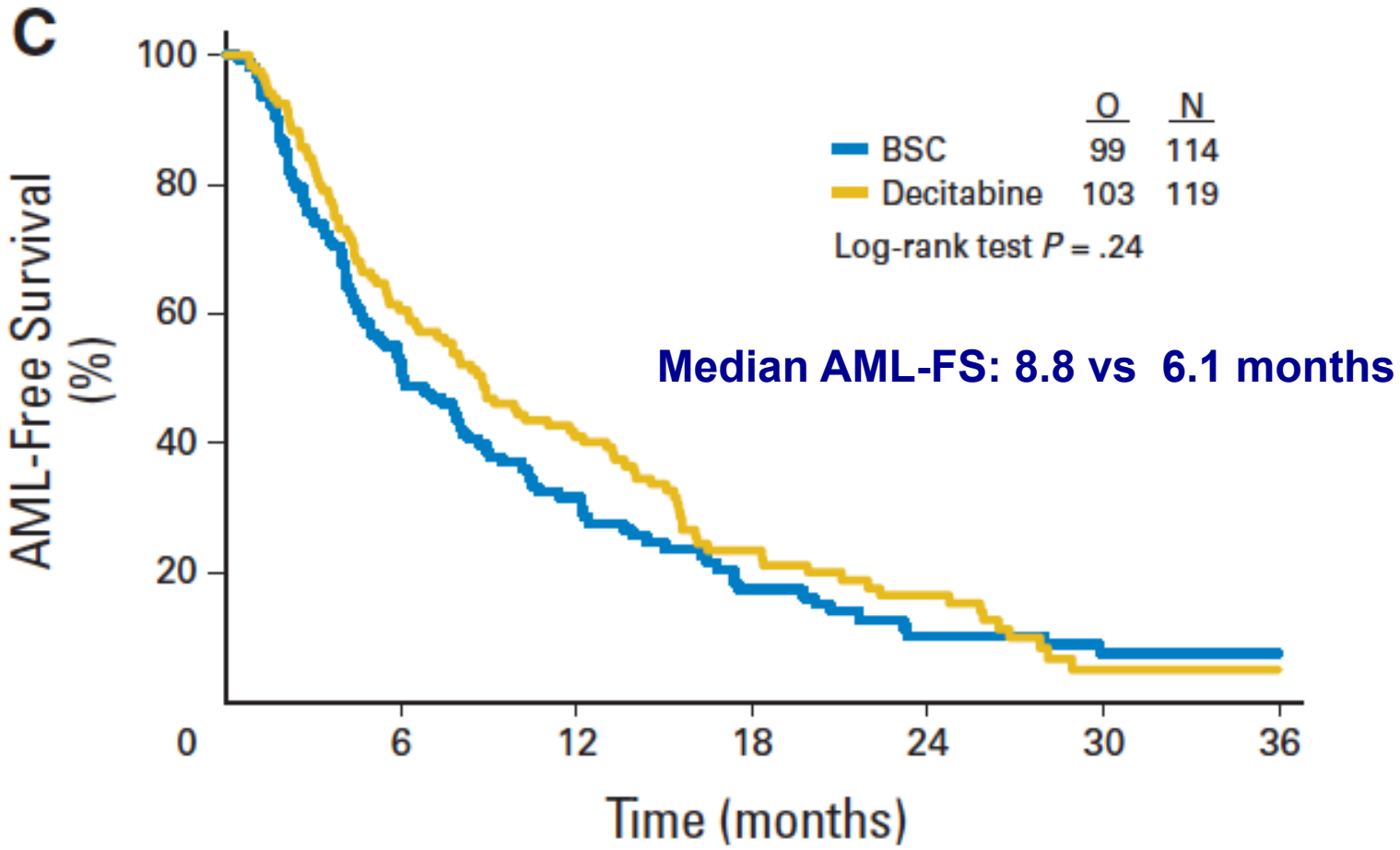
Decitabine do not prolong overall survival compared with BSC



Decitabine *prolongs Progression-free survival* compared with BSC



Decitabine do not prolong AML-free survival compared with BSC



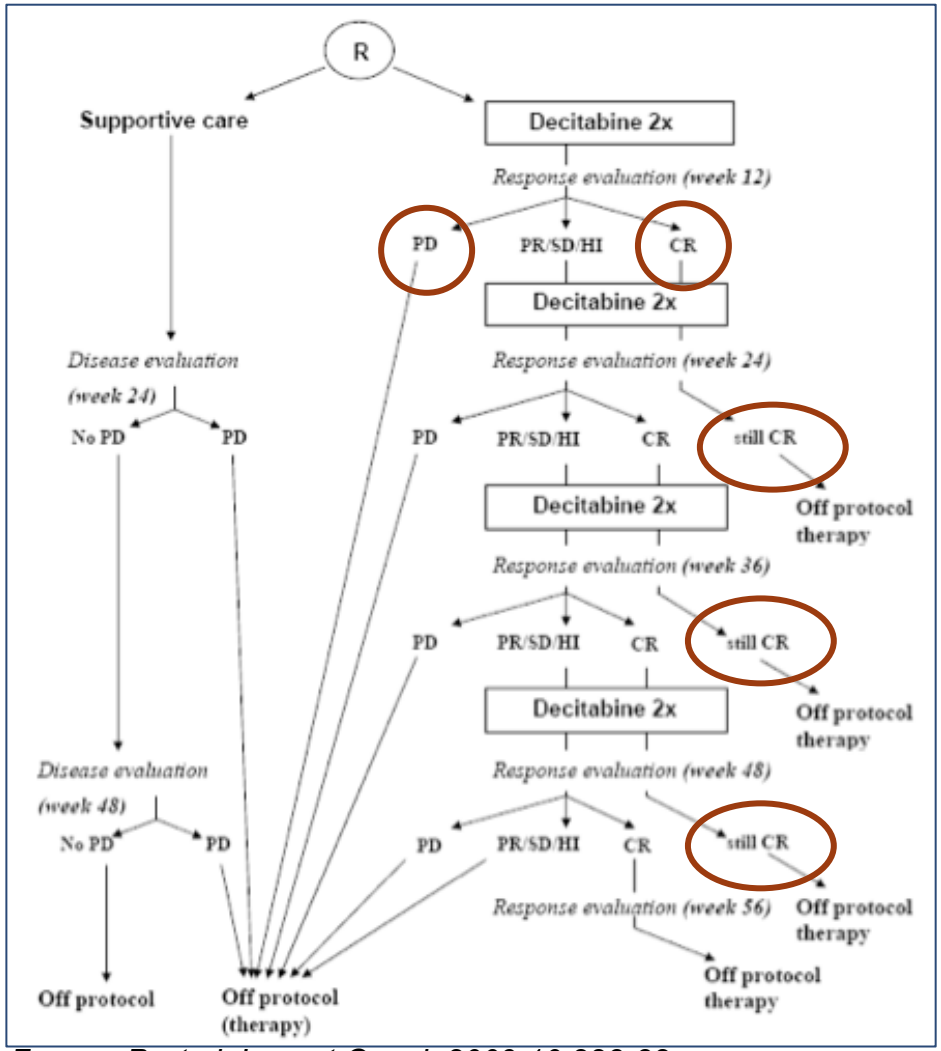
Comparison between AZA and DAC Studies

	5-AZA %	DAC %
Median age (year)	69	69
IPSS Int-1 Int-2 High	3 43 46	7 54 39
Cytogenetic good Intermediate Poor	46 21 28	32 7 48
Time from diagnosis ≥ 3 months	17	50
CR	17	13.4
CR + PR	29	19.3
Median OS (months)	24.4	10.1

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

Lubbert M, et al. J Clin Oncol. 2011;29:1987-96

Why so poor results with Decitabine compared to 5-Azacitidine



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

- **DAC given up to 8 cycles, depending on clinical response or toxicity**
- **Only 26% of patients received all eight courses of DAC**
- **5-Aza given until PD or toxicity**
- **5-Aza given for a median of 9 cycles**
- **86% of patients receiving 5-AZA remained on 75 mg/m^2 per day with no dose adjustments**
- **The median 5-AZA cycle-length was 28 days**

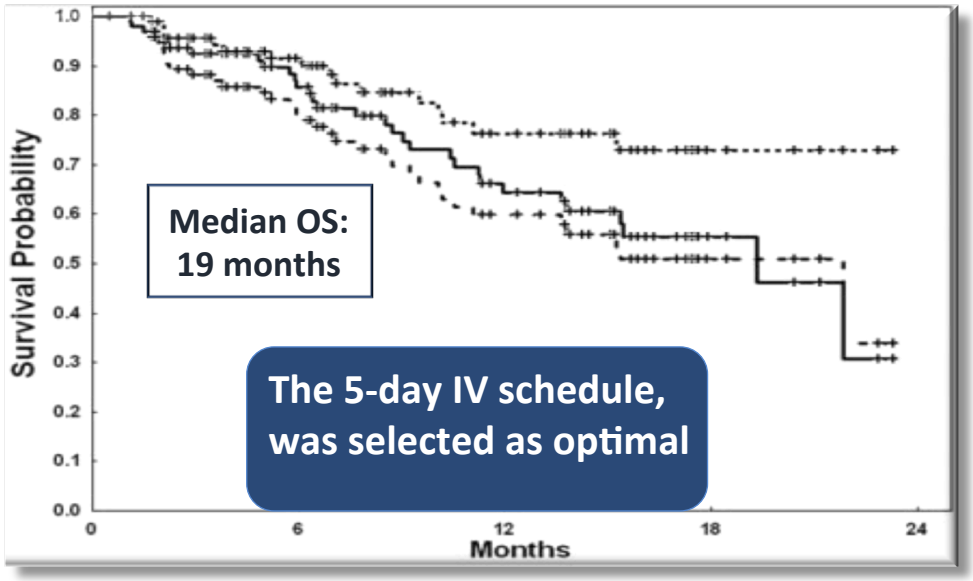
Lubbert M, et al. J Clin Oncol. 2011;29:1987-96

Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia

- 20 mg/m^2 IV daily for 5 days
- 20 mg/m^2 daily for 5 days;
- 10 mg/m^2 IV daily for 10 days

Response data (95 patients) by the Modified IWG Criteria

Response	No. of patients (%)	5-day IV	5-day SC	10-day IV
Complete response	32 (34)	39%	21%	24%
Partial response	1 (1)			
Marrow CR	10 (11)			
Marrow CR + other HI	13 (14)			
Hematologic improvement				
Single lineage	9 (9)			
2 or 3 lineages	4 (4)			
Objective response	**69 (73)**			



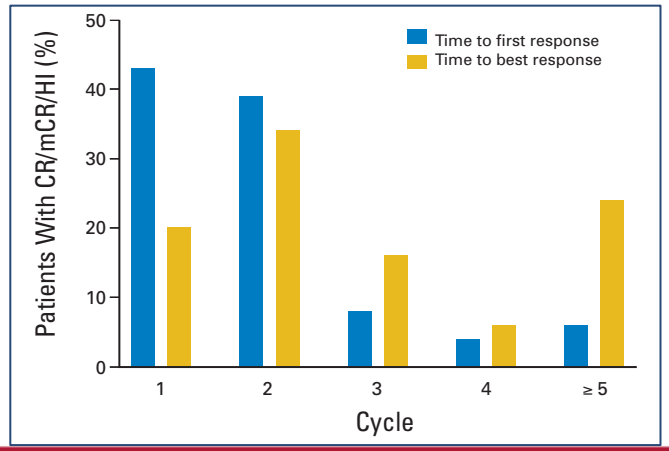
The 5-day IV schedule, was selected as optimal

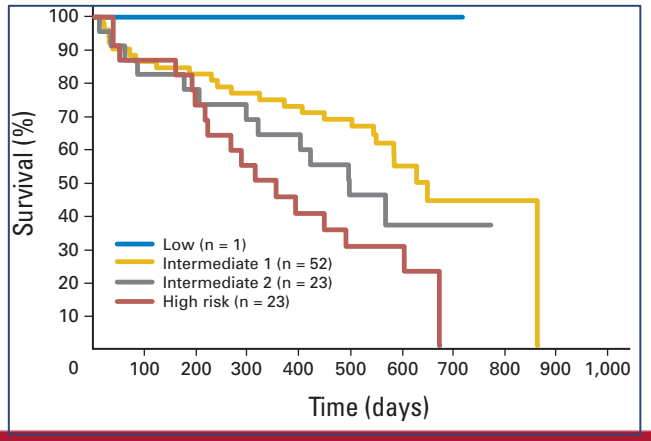
Decitabine: The Alternative Dosing for Outpatient Treatment (ADOPT Trial)

N=99 de novo or s-MDS of any FAB subtype and IPSS score ≥ 0.5

Decitabine 20 mg/m^2 IV for 5 days

Response (IWG 2006 Criteria), n (%)	Patients (N = 99)
Overall complete response rate (CR + marrow CR)	32 (32)
Overall response rate (CR + marrow CR + PR)	32 (32)
Overall improvement rate (CR + marrow CR + PR +HI)	50 (51)
HI	18 (18)
Rate of SD or better (CR +mCR + PR + HI + SD)	**74 (75)**





1-year OS: 66%
Median OS: 19.4 mos.

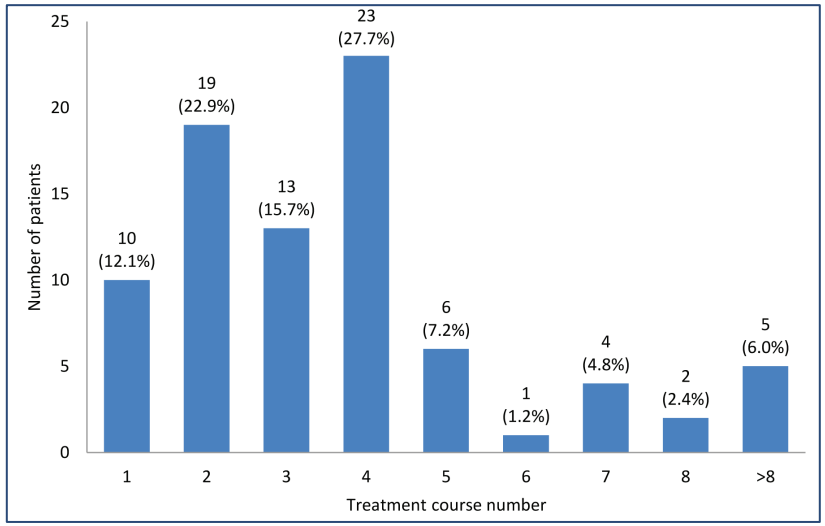
A prospective, multicenter, observational study of long-term decitabine treatment in patients with MDS

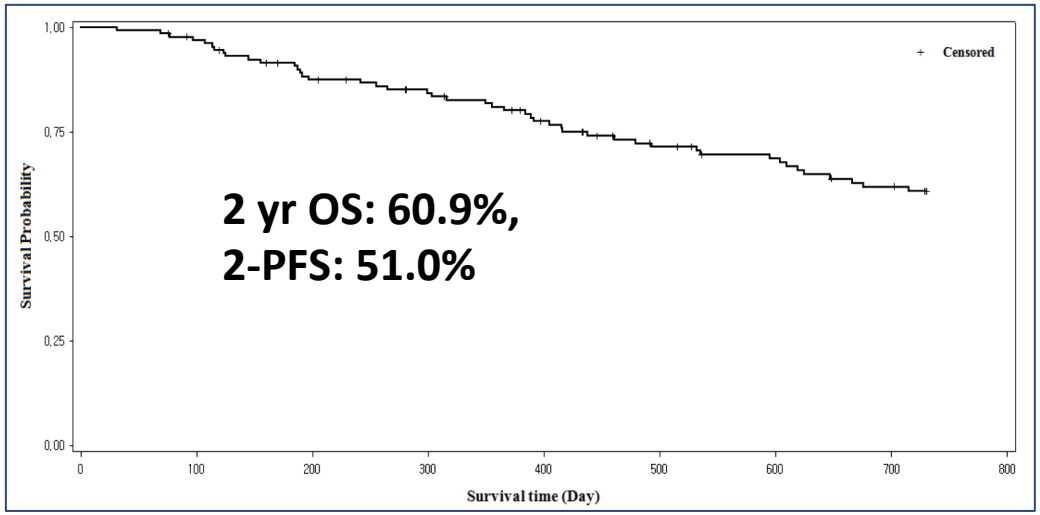
N=132

WHO subtype		
RCUD	4	(3.03%)
RARS	3	(2.27%)
RCMD	40	(30.30%)
RAEB-1	30	(22.73%)
RAEB-2	36	(27.27%)
MDS-U	6	(4.55%)
Del(5q)	1	(0.76%)
CMML-1	7	(5.30%)
CMML-2	4	(3.03%)
Unclassified	1	(0.76%)
IPSS risk categc		
Intermediate·	86	(65.15%)
Intermediate·	36	(27.27%)
High	10	(7.58%)

Decitabine 20 mg/m²/IV day IV d1-5 every 4 weeks

Response	n (%)	
CR	36	(27.27%)
PR	3	(2.27%)
mCR with HI	8	(6.06%)
mCR without HI	11	(8.33%)
HI only*	25	(18.94%)
Patient experienced HI	72	
SD#	48	(36.36%)
ORR (CR + PR + mCR + I	83	(62.88%)
95% CI+	(54.04%	-71.12%)
CR + PR + mCR + HI + SI	131	(99.24%)



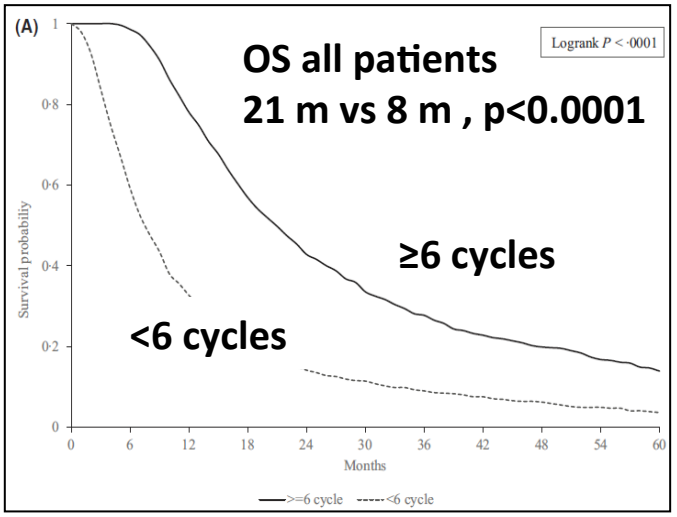


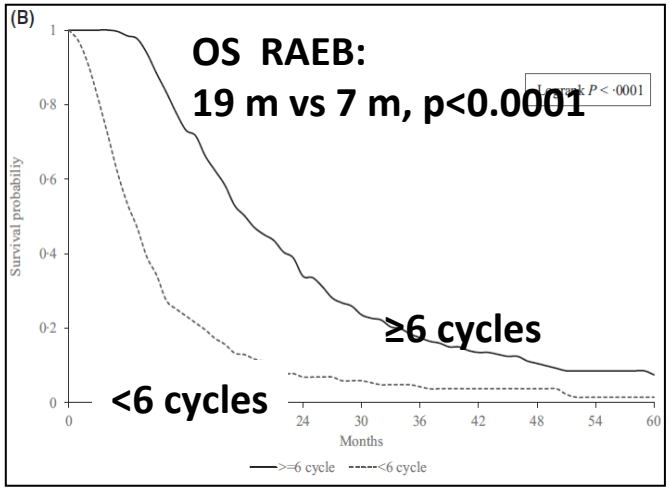
Seong Hyun Jeong et al. Oncotarget, Vol. 6, No. 42. 2015

HMAs in real life: overall survival

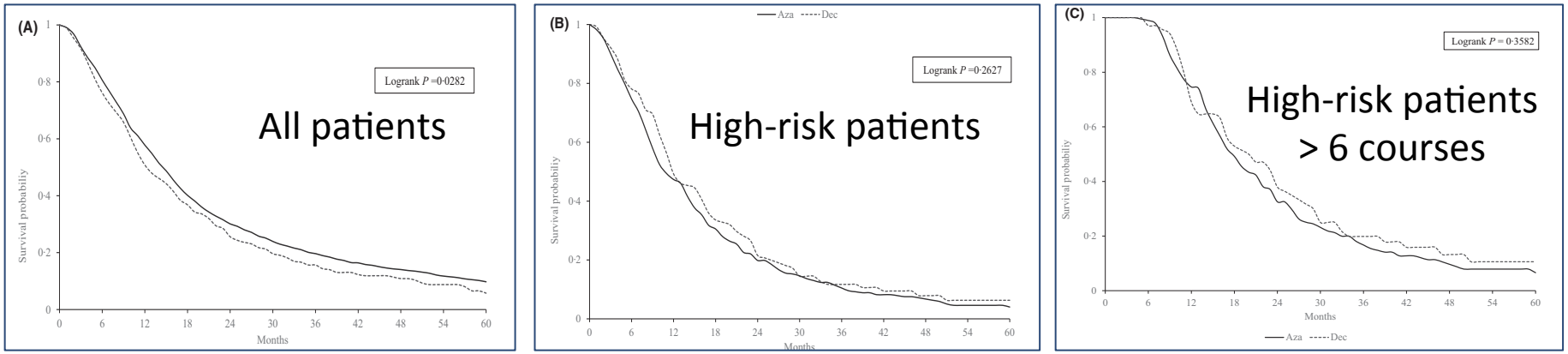
- **2025 eligible MDS patients diagnosed between 2004 and 2011 who received ≥ 10 doses of HMA identified from SEER Registry**
- **Higher-risk patients (n = 523)**

Caratteristiche	AZA(%)	DEC (%)
Totali	1580 (78)	445 (22)
Età: 66-69 70-74 75-79 80+	 207 (13,1) 357 (22,6) 450 (28,5) 566 (35,8)	 74 (16,6) 139 (31,2) 109 (24,5) 123 (27,6)
Mediana cicli HMA	6 [3-10]	6 [4-10]
Cicli HMA ≥ 4 Cicli HMA ≥ 6	1163 (73,6) 825 (52,2)	339 (76,2) 227 (51,0)
MDS risk group: Lower risk High risk Other (MDS-NOS, t-MDS)	 406 (25,7) 395 (25,0) 779 (49,3)	 94 (21,1) 128 (28,8) 223 (50,1)





HMAs in real life: AZA vs DAC



- No significant survival difference was found between azacitidine and decitabine in patients with MDS, including RAEB.
- Population-based survival of azacitidine-treated RAEB patients was substantially shorter than in the AZA-001 clinical trial (11 versus 24.5 months)

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

*Raphael Itzykson,[1] *Sylvain Thépot,[1,2] Bruno Quesnel,[3] Francois Dreyfus,[4] Odile Beyne-Rauzy,[5] Pascal Turlure,[6] Norbert Vey,[7] Christian Recher,[8] Caroline Dartigeas,[9] Laurence Legros,[10] Jacques Delaunay,[11] Célia Salanoubat,[12] Sorin Visanica,[13] Aspasia Stamatoullas,[14] Francoise Isnard,[15] Anne Marfaing-Koka,[16] Stephane de Botton,[17] Youcef Chelghoum,[18] Anne-Laure Taksin,[19] Isabelle Plantier,[20] Shanti Ame,[21] Simone Boehrer,[1,2] Claude Gardin,[1] C. L. Beach,[22] Lionel Adès,[1,2] and Pierre Fenaux,[1,2] on behalf of the Groupe Francophone des Myelodysplasies (GFM)

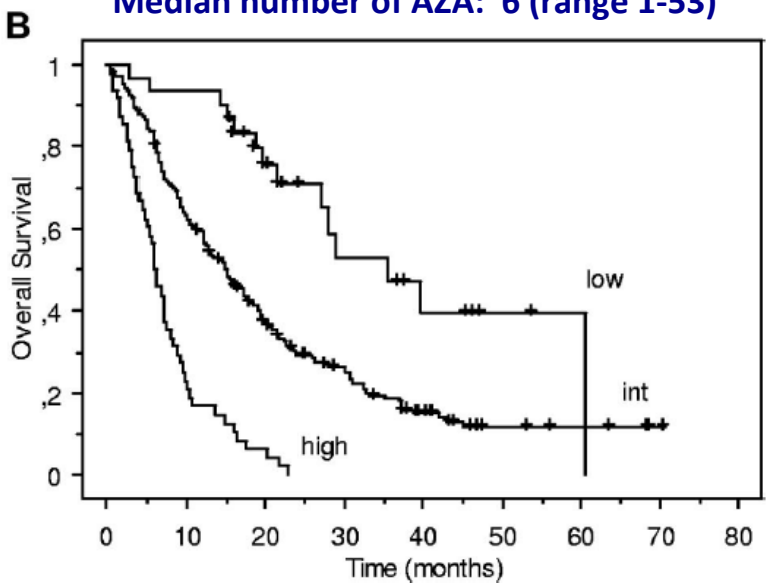
French Patient Name Program

282 patients with MDS IPSS int-2 or High
without previous high dose CT or SCT
who received at least 1 cycle of AZA

Variable	Point
PS ECOG > 2	1
Intermediate-risk cytogenetics	1
Poor-risk cytogenetics	2
Presence of circulating blasts ≥ 15%	1
RBC transfusion dependency 4 units/8 weeks	1

Score	Risk-group	Median OS (months)
0	Low (n=30)	32.1
1-3	Intermediate (n=191)	15
4-5	High (n=48)	6.1

Median follow-up: 41.3 months,
Median number of AZA: 6 (range 1-53)



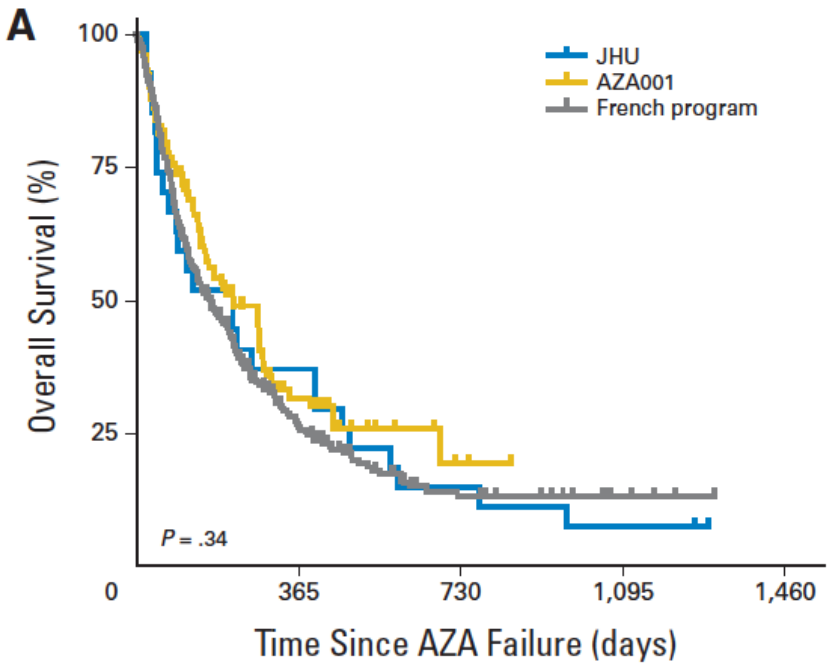
BLOOD, 2011; 117:403-411
BLOOD, 2012; 119:6172-6173

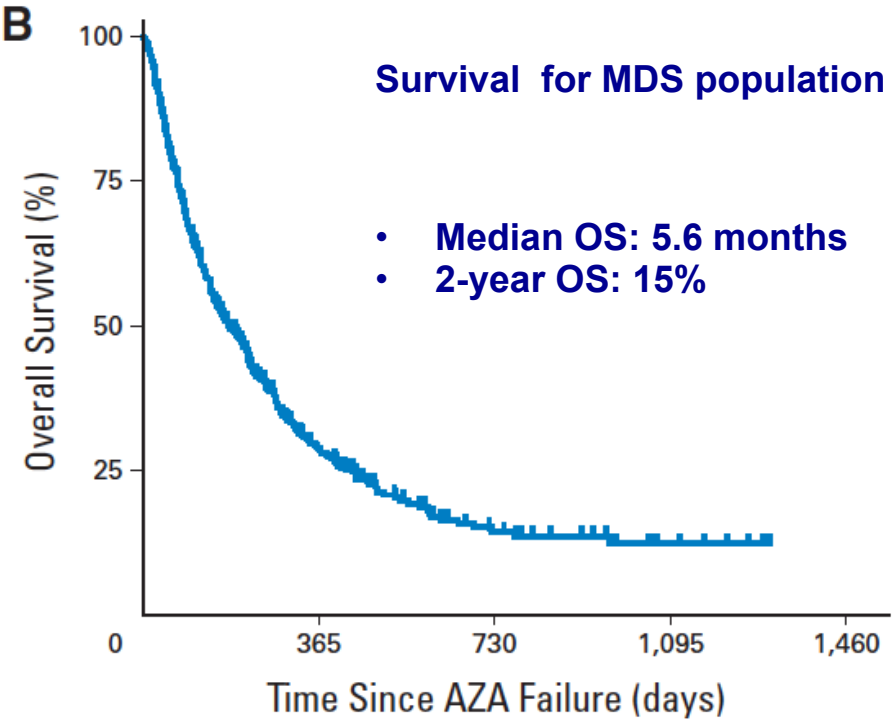
Outcome of High-Risk Myelodysplastic Syndrome After Azacitidine Treatment Failure

Thomas Prébet, Steven D. Gore, Benjamin Esterni, Claude Gardin, Raphael Itzykson, Sylvain Thepot, François Dreyfus, Odile Beyne Rauzy, Christian Recher, Lionel Adès, Bruno Quesnel, C.L. Beach, Pierre Fenaux, and Norbert Vey

435 patients with high-risk MDS and RAEB-T evaluated for outcome after AZA failure

Survival estimates for the different data sets

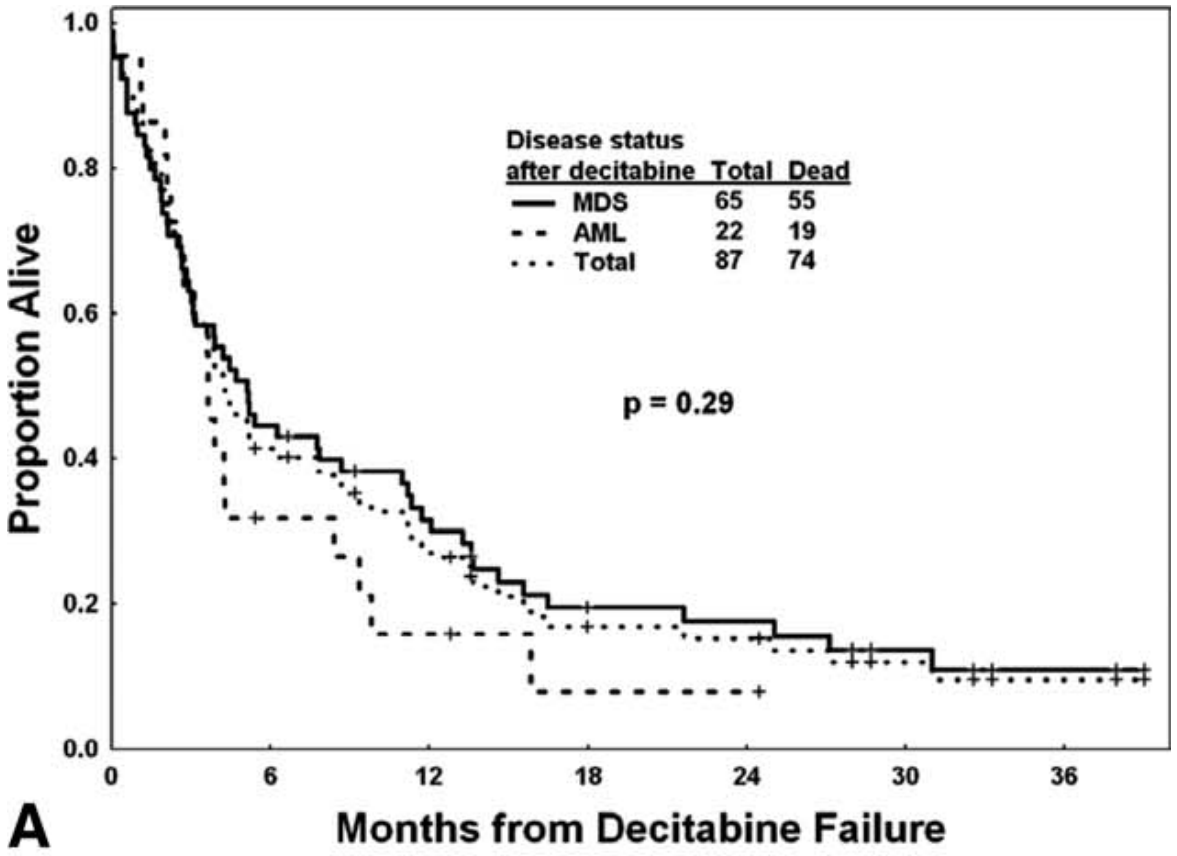




Survival for MDS population

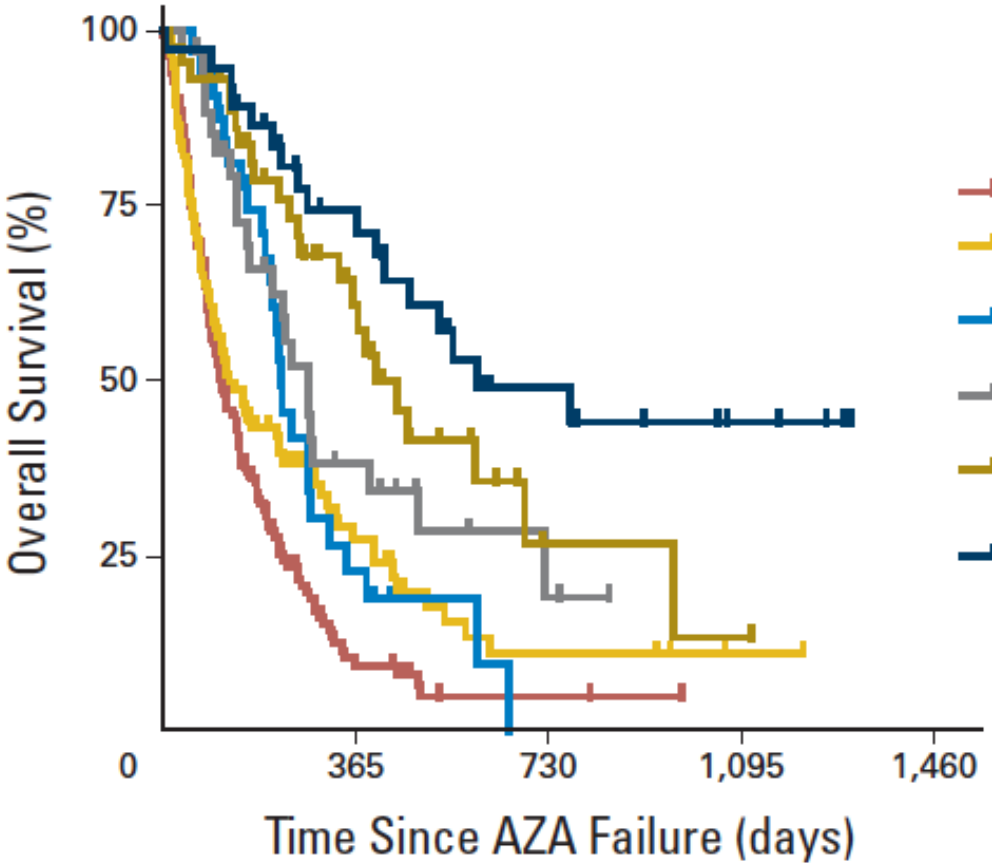
- **Median OS: 5.6 months**
- **2-year OS: 15%**

Outcome of patients failing HMA is poor: Decitabine



Jabbur E. et al . Cancer 2010

Outcome of patients failing HMA is poor: 5-AZA



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*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

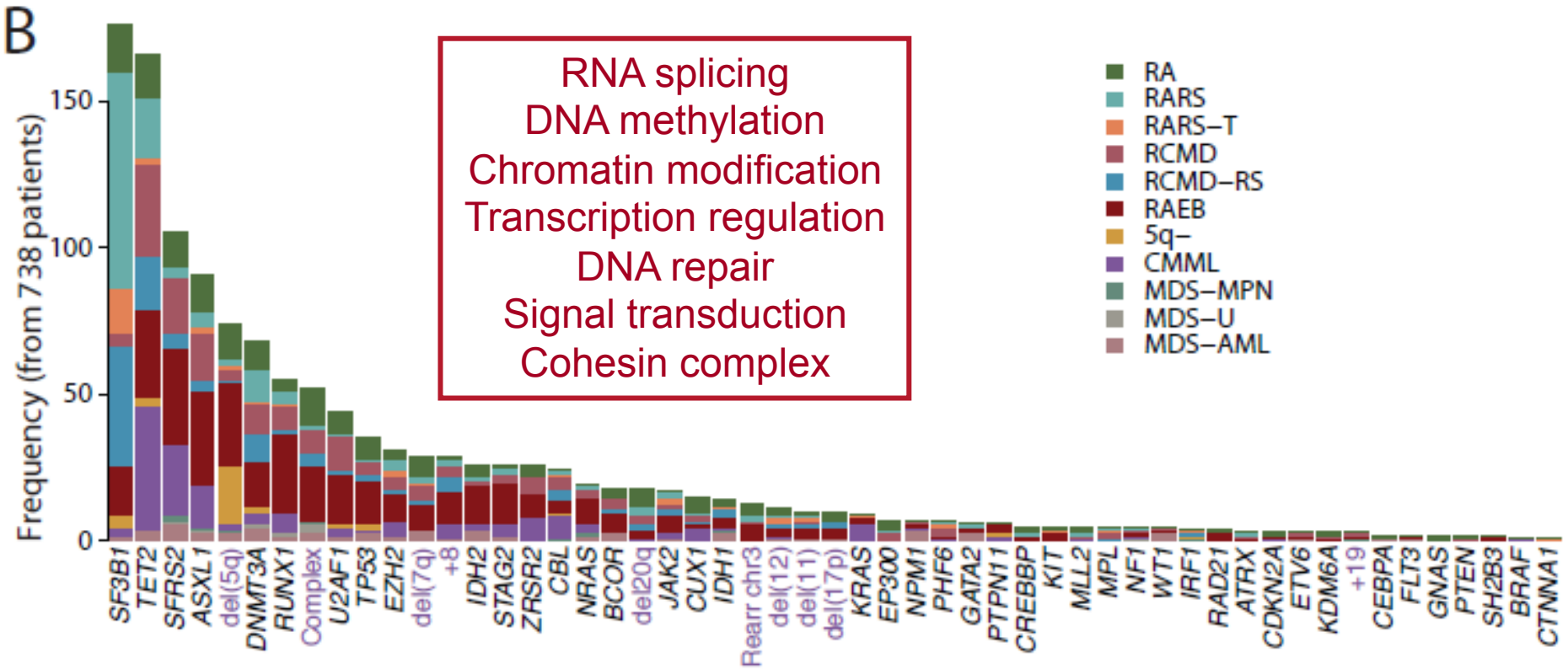
Prebet T et al. J Clin Oncol 2011; 29:3322-3327

Sequential treatment with HMA could be an alternative approach in patients failing first line HMA

Enrollment in clinical trial should be the strongly encouraged in HMA failure
Sequential use of HMA is a common practice given limited alternatives

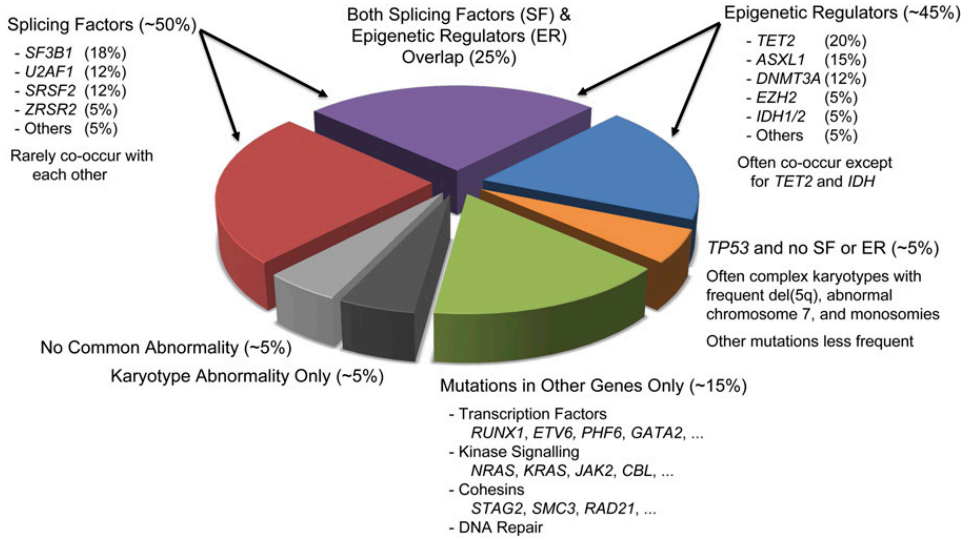
		DAC after AZA (n=21)	AZA after DAC (n=10)
Time to first line from Diagnosis	Median (months)	10	2.4
1 st line cycles	mean	8	4
1 st line best response (HI+)	%	63	50
2 nd line cycles		4	6
2 nd line best response (HI+)	%	19	40
Median OS Start of 2 nd line	**months**	**17.8**	**22**
AML transformation	%	29	20

Clinical Effect of Point Mutations in Myelodysplastic Syndromes



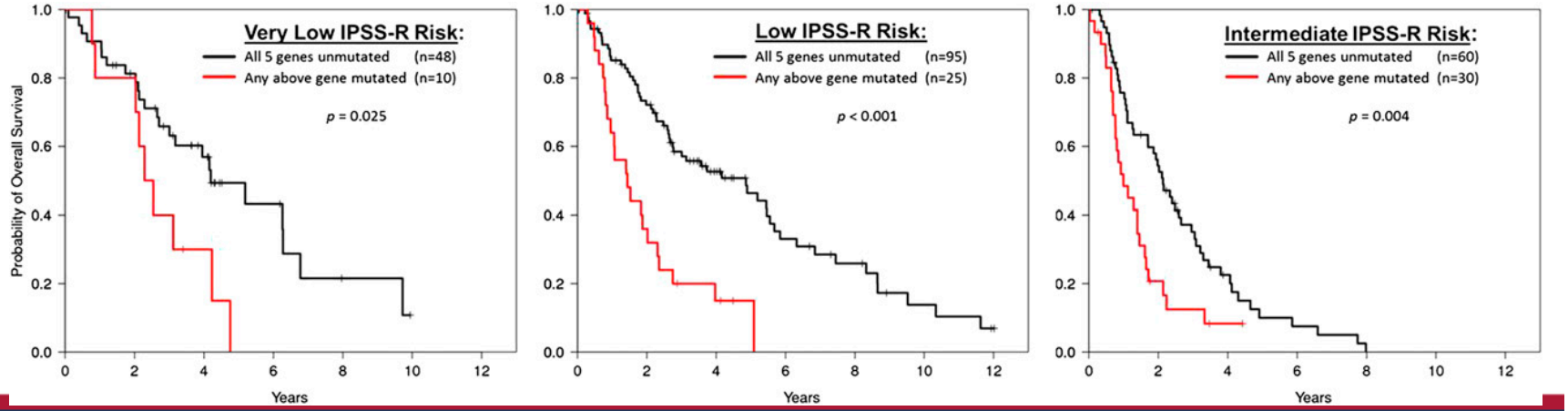
Papaemmanuil E et al. Blood. 2013;122:3616-27
Cazzola M, Della Porta MG, Malcovati L. Blood 2013;122:4021-34
Della Porta MG et al. Leukemia 2015;29:1502-13

Distribution of recurrent mutations and karyotypic abnormalities in MDS

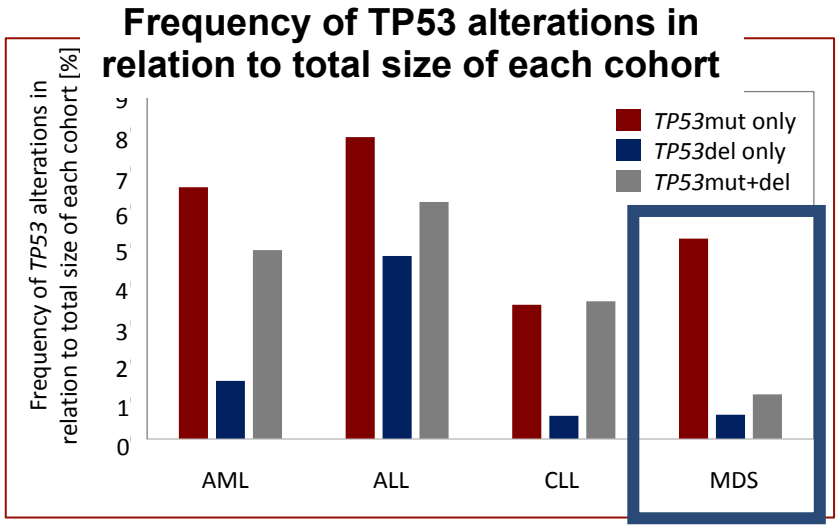


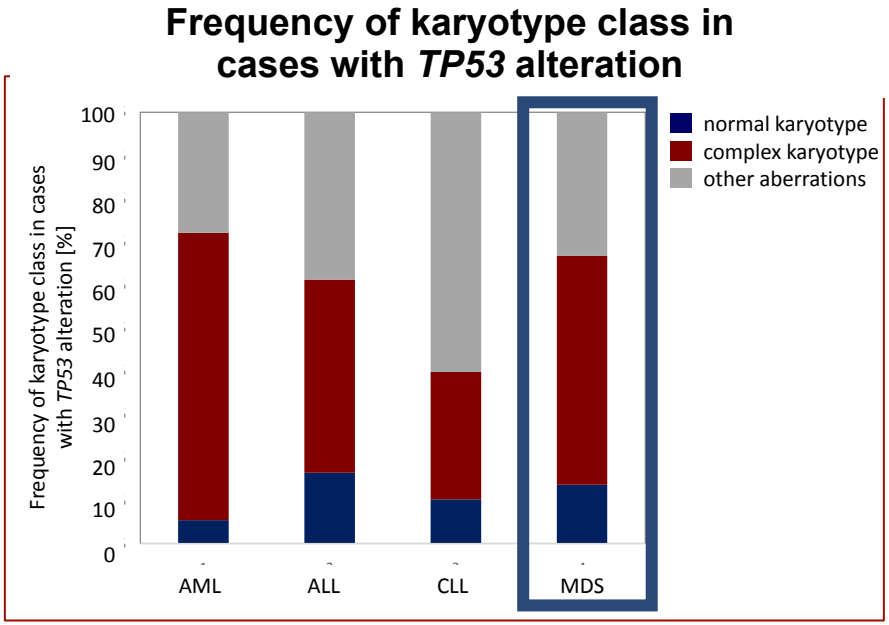
Any mutation have prognostic significance independent of IPSS-R

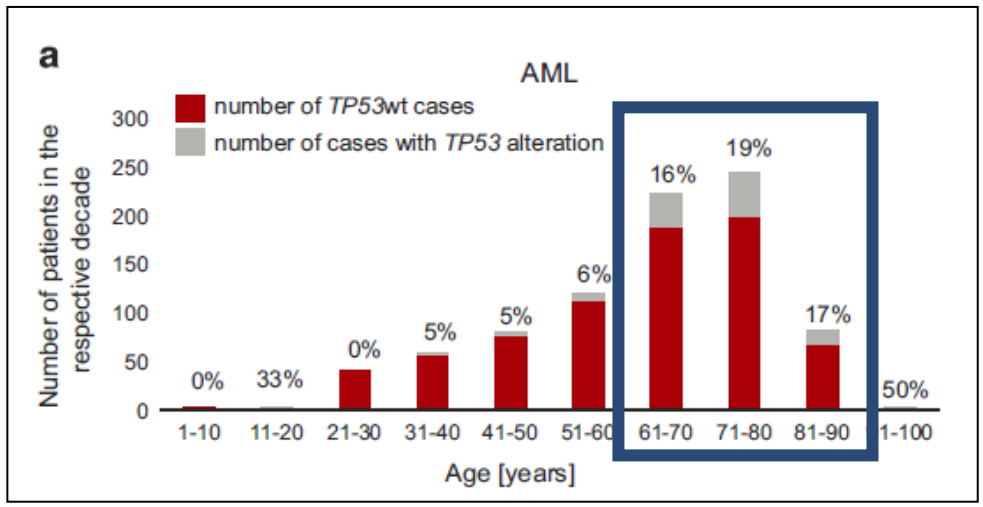
TP53
EZH2
RUNX1
ASLX1
ETV6



Frequency of TP53 alterations in hematological malignancies and correlation with cytogenetic aberrations

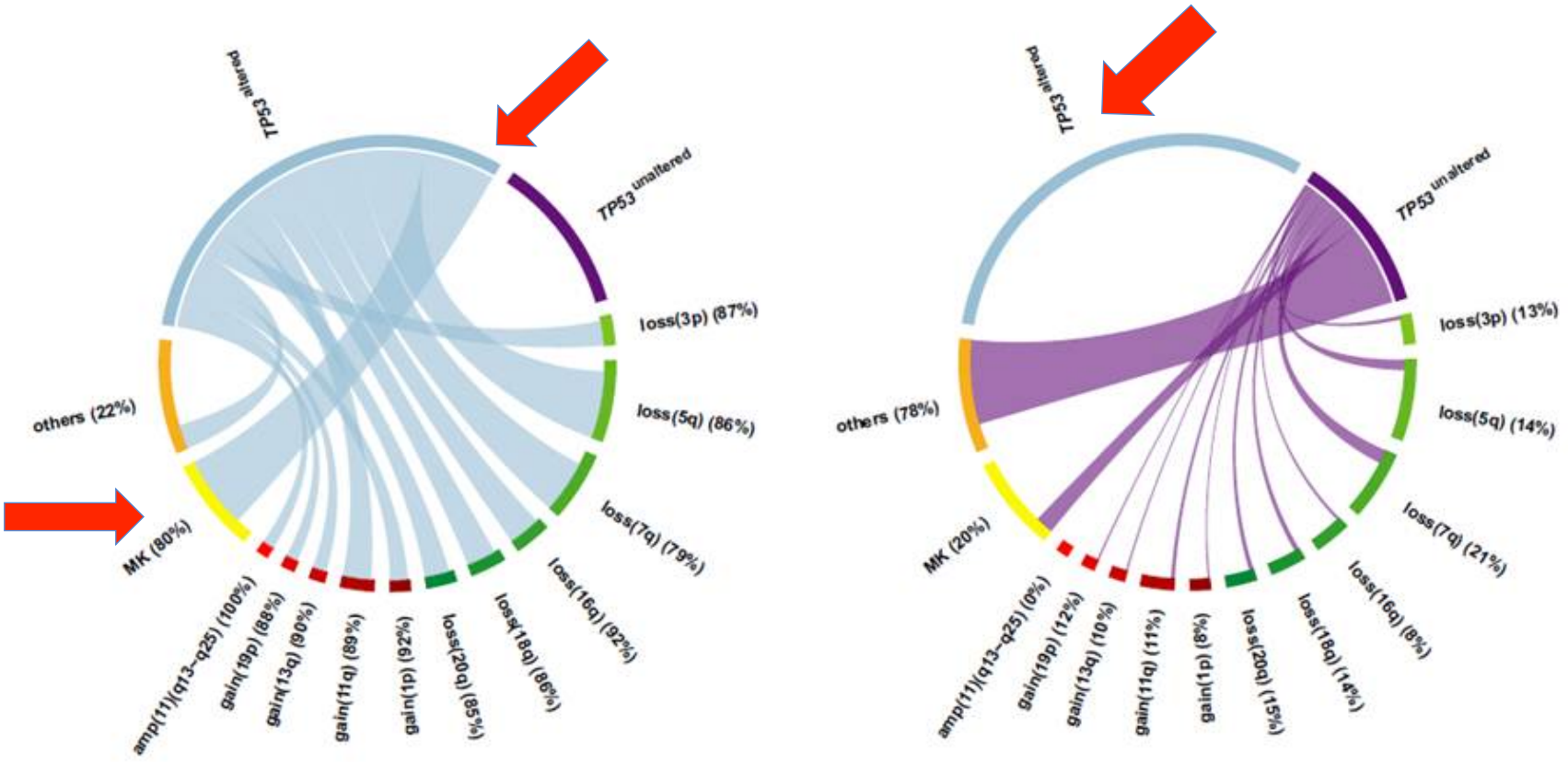






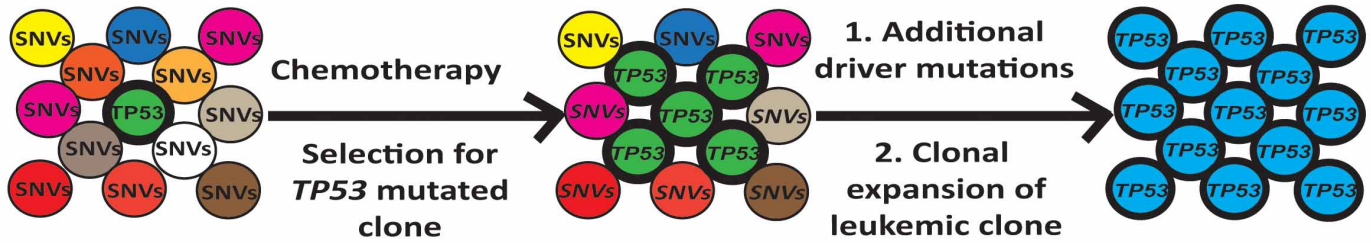
In the age range 60-80, the TP53 mutation occurs on average in 15% of cases

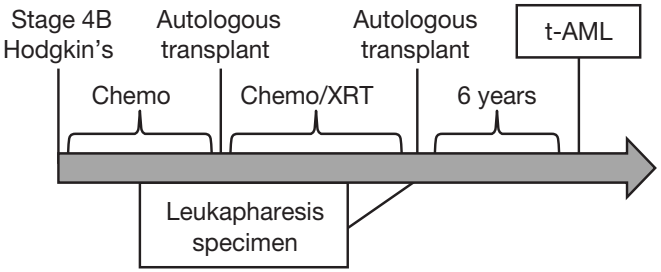
TP53 mutation correlates with a monosomal or complex karyotype

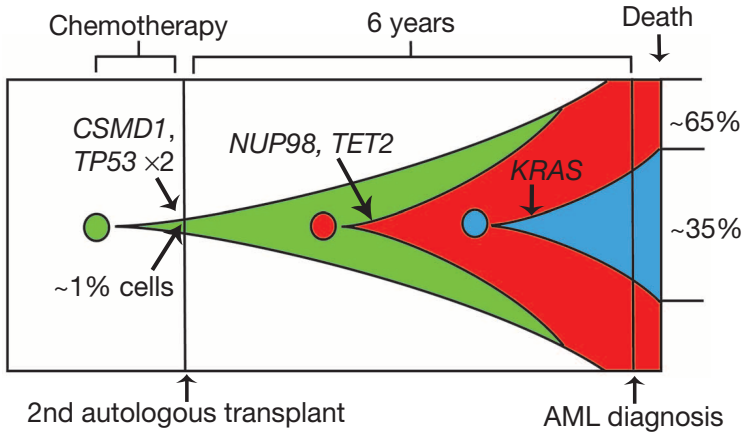


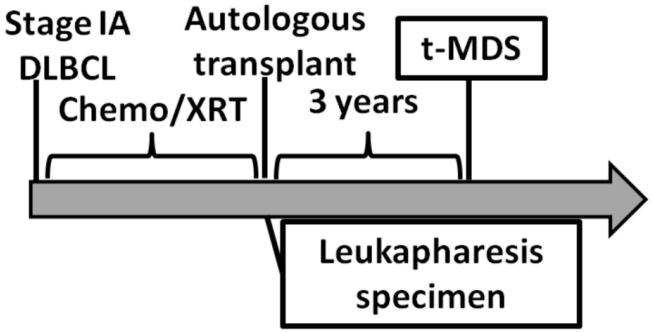
***P53* alterations are associated with resistance to chemotherapy**

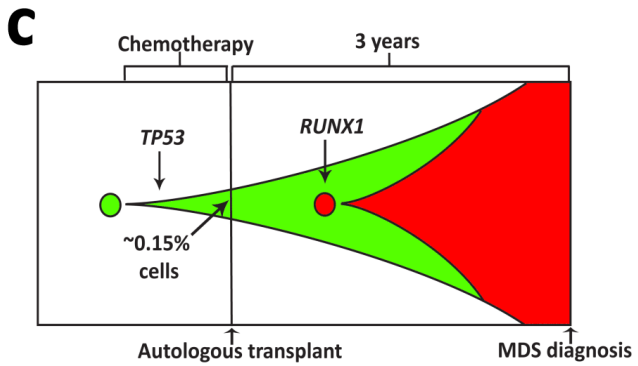
Model of how cytotoxic therapy shapes clonal evolution in t-AML/t-MDS



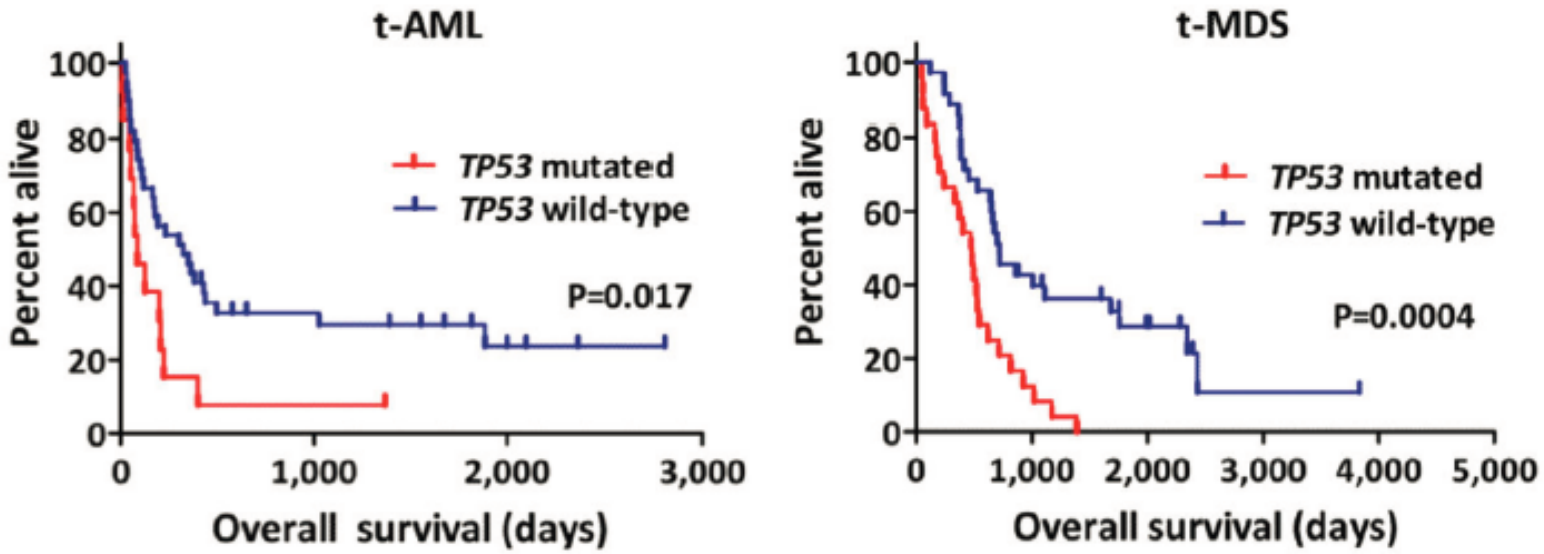








TP53 mutations are associated with decreased overall survival in t-AML/t-MDS



- **The TP53 mutation is closely related to complex karyotype and further deteriorates the prognosis**
- **The TP53 mutation is an independent prognostic factor and is the one weigh most in a complex karyotype**

Wong N T et al. Nature 2014

The NEW ENGLAND JOURNAL of MEDICINE

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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. Luber, 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

Decitabine 20 mg/m^{2}per day for 10 days in monthly cycles

Characteristics of the Patients

AML n=54
Relapsed AML n=39
MDS n=26

Characteristic	All Patients (N=116)	*TP53* Mutations (N=21)	Wild-Type *TP53* (N=78)	*TP53* Not Evaluated (N=17)	P Value†
Sequencing performed — no. (%)					
Any type	99 (85)	21 (100)	78 (100)	0	
Exome	39 (34)	7 (33)	32 (41)	0	
264-gene panel	15 (13)	7 (33)	8 (10)	0	
8-gene panel	45 (39)	7 (33)	38 (49)	0	
Male sex — no. (%)	68 (59)	9 (43)	47 (60)	12 (71)	0.21
Age at diagnosis — yr					0.90
Median	74	71	72	76	
Range	29–88	47–86	29–88	50–85	
Disease — no. (%)					
AML	54 (47)	9 (43)	34 (44)	11 (65)	1.00
Relapsed AML	36 (31)	3 (14)	31 (40)	2 (12)	0.04
MDS	26 (22)	9 (43)	13 (17)	4 (24)	0.02
IPSS in patients with MDS — no./total no. (%)‡					
Low	1/26 (4)	0	0	1/4 (25)	
Intermediate 1	8/26 (31)	1/9 (11)	4/13 (31)	3/4 (75)	0.40
Intermediate 2	8/26 (31)	1/9 (11)	7/13 (54)	0	0.08
High	9/26 (35)	7/9 (78)	2/13 (15)	0	0.007
Cytogenetic risk group — no. (%)					
Favorable	5 (4)	0	4 (5)	1 (6)	0.58
Intermediate	66 (57)	1 (5)	54 (69)	11 (65)	<0.001
Unfavorable	43 (37)	20 (95)	19 (24)	4 (24)	<0.001
Not performed	2 (2)	0	1 (1)	1 (6)	

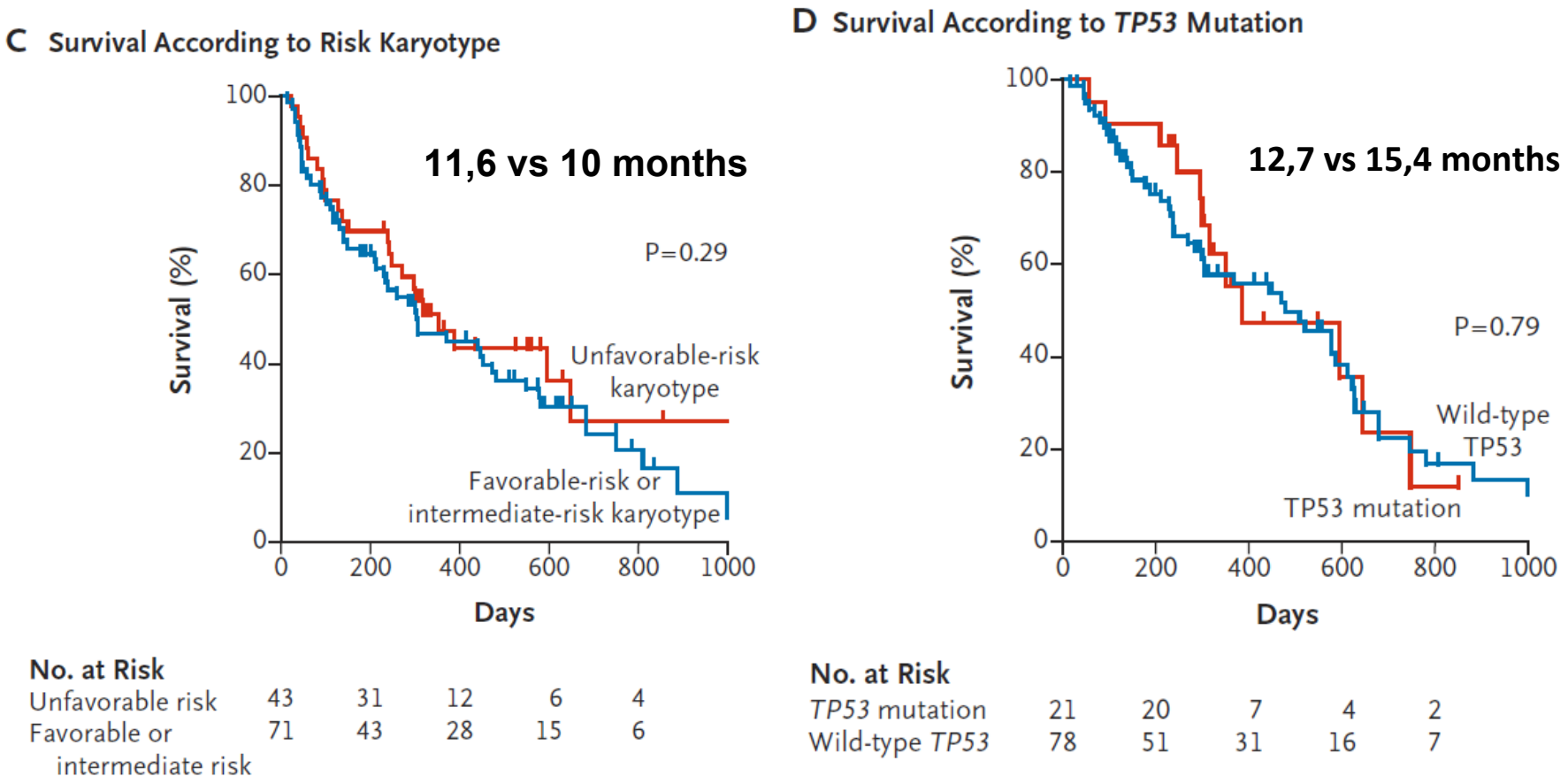
TP53 and Decitabine in AML and MDS Response

Median nunber of cycles: 2

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
Samples not available for evaluation	12 (10)	0	0	12 (71)	

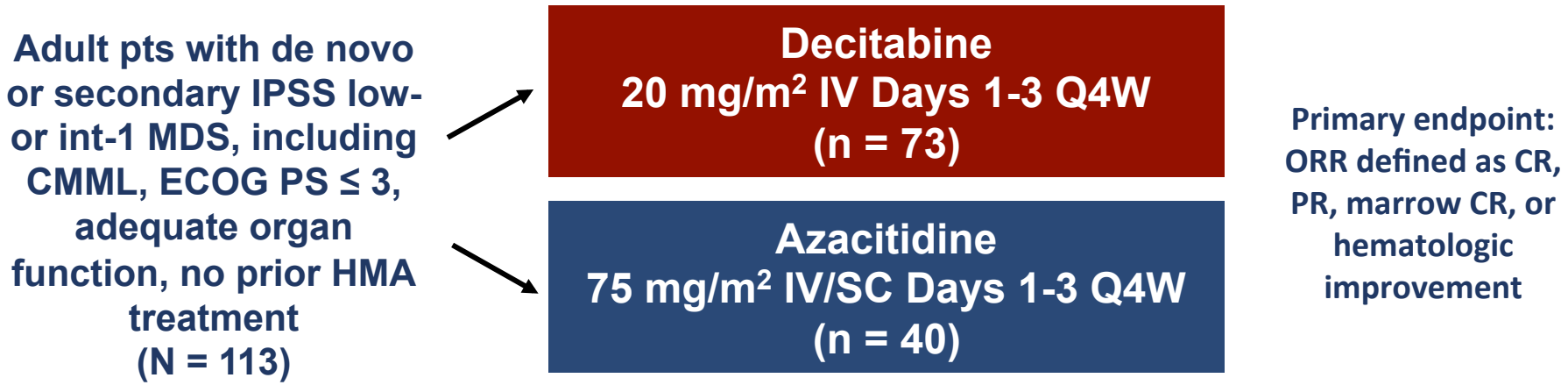
- **ORR= 67% (29/43) unfavorable-risk karyotype**
- **ORR= 34% (24/71) favorable/intermediate-risk karyotype**

Overall survival according to risk karyotype and TP53 mutation



Hypomethylating agents in MDS

Low-Dose HMAs in LR MDS



- Open-label phase II study
  - Randomized by Bayesian adaptive design; pts more likely to be assigned to better-performing treatment arm
  - Median follow-up: 20 mos

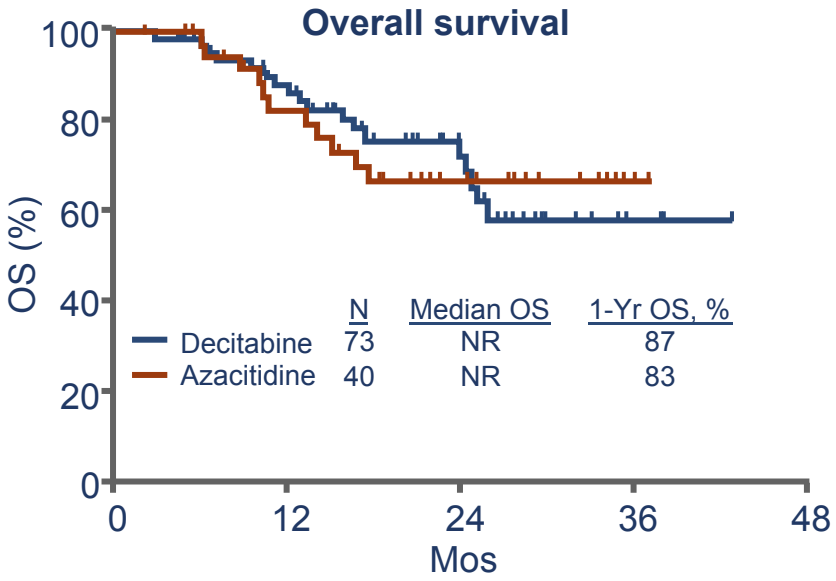
Low-Dose HMAs in LR MDS: Response Rates

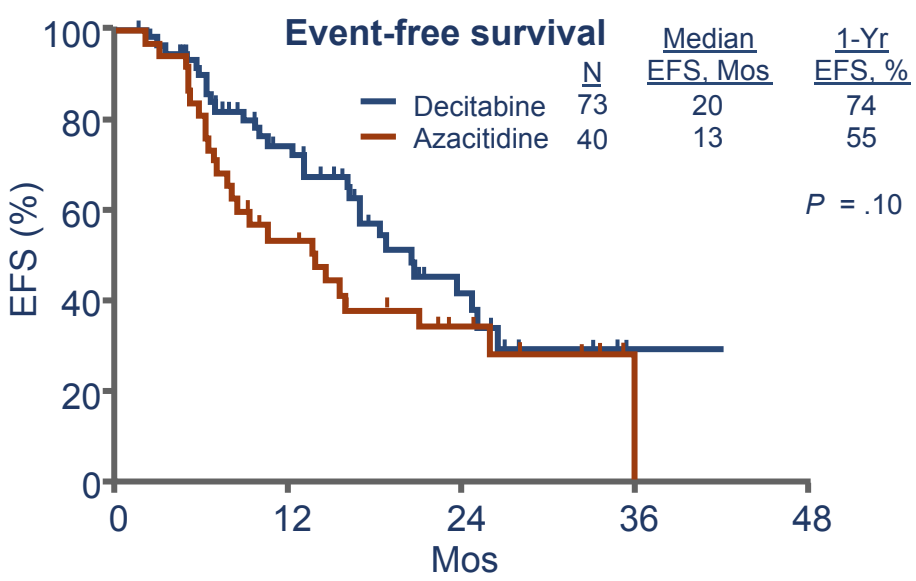
Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	P Value
ORR	**70**	**49**	**.03**
▪ CR	37	36	.90
▪ mCR	9	5	NR
▪ HI	24	8	NR
▪ SD	26	44	NR
▪ PD	4	8	NR
CCyR	25	6	.12
PCyR	36	19	
▪ **CCyR + PCyR**	**61**	**25**	**.02**

Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	P Value
Blasts ≥ 5%	(n = 21)	(n = 11)	
▪ ORR	100	36	< .001
▪ CR	52	18	.06
Blasts < 5%	(n = 45)	(n = 27)	
▪ HI - ≥ 1 lineage	36	48	.29
▪ HI - all lineages	22	26	.72
TI at response	32	16	.20

→ Strongest predictors of response included BM blasts ≥ 5%, MDS/MPN or CMML diagnosis, high MDA LR MDS score, and IPSS intermediate-1 risk

Low-Dose HMAs in LR MDS



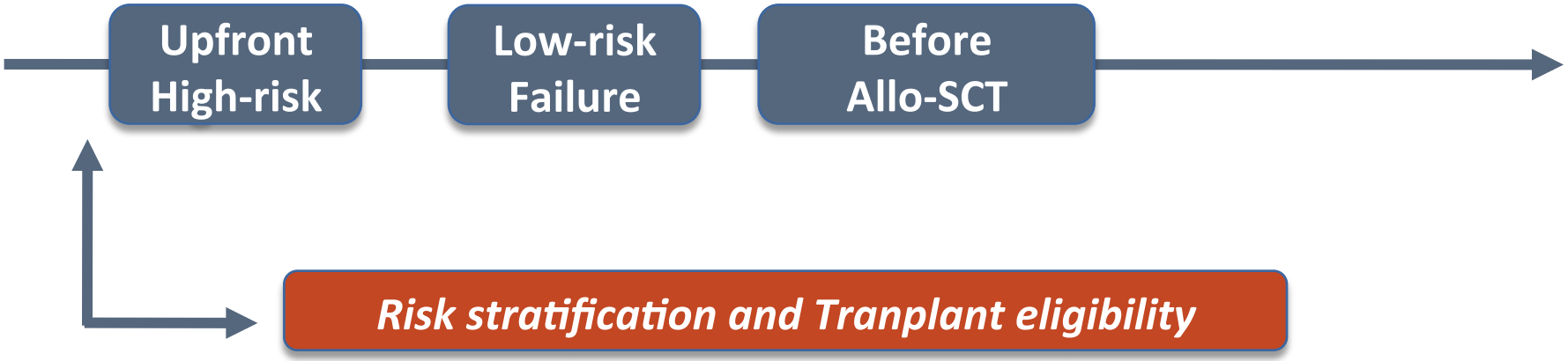


- **Strongest predictors of EFS included BM blasts ≥ 5%, MDS/MPN or CMML diagnosis, high MDA LR MDS score, and adverse mutation risk**
- Among pts in both arms (N = 113): 1-yr EFS 65%, 1-yr OS 85%

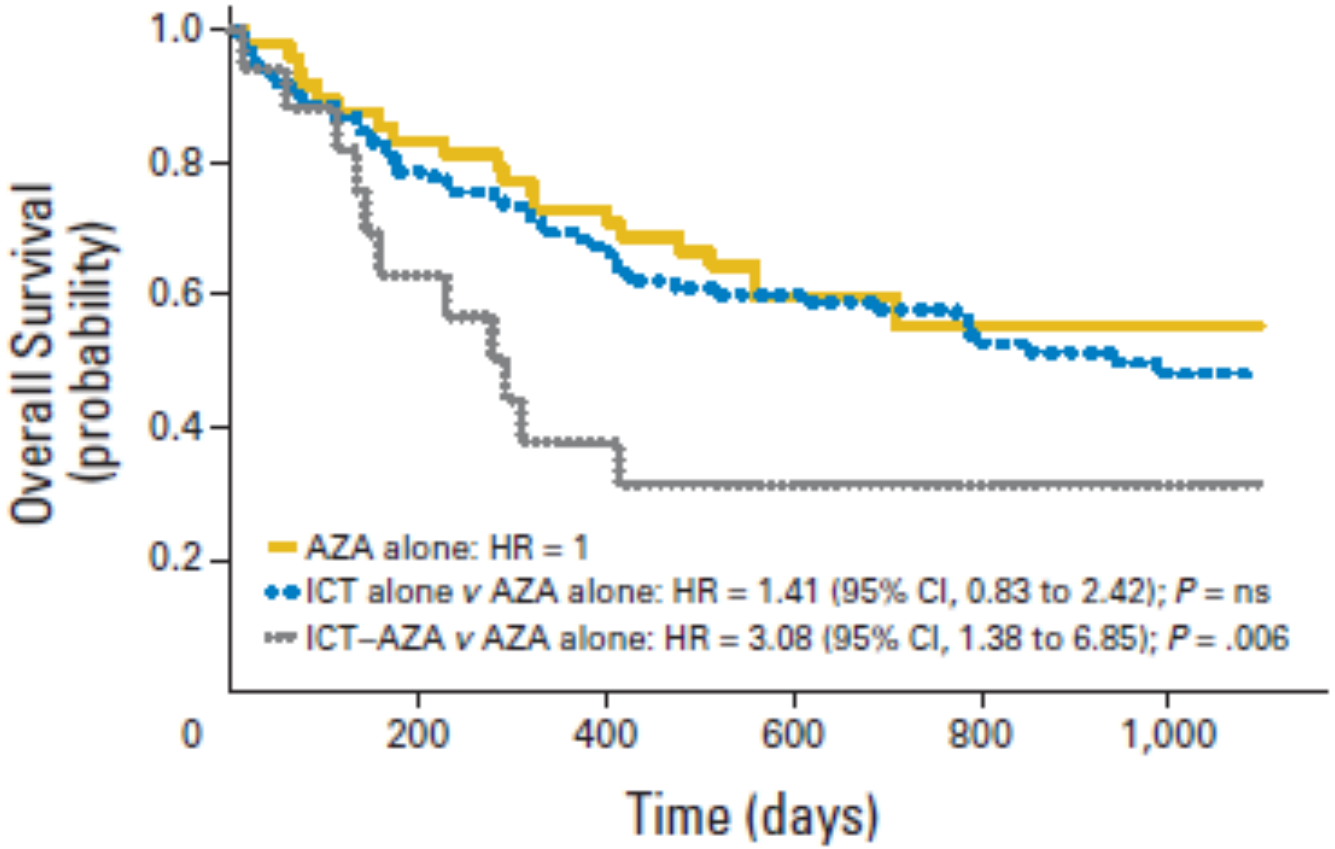
Nonhematologic AEs,* n (%)	Decitabine (n = 73)	Azacitidine (n = 40)
Nausea	11 (15)	6 (15)
Fatigue	6 (8)	4 (10)
Constipation	3 (4)	6 (15)
Infection/neutropenic fever	5† (7)	2 (5)
Diarrhea	2 (3)	3 (8)

Jabbour EJ, et al. ASH 2016. Abstract 226.

Hypomethylating agents in MDS



AZA alone led to outcomes similar to those for standard ICT



Damaj G et at. J Clin Oncol 2012;30:4533-4540

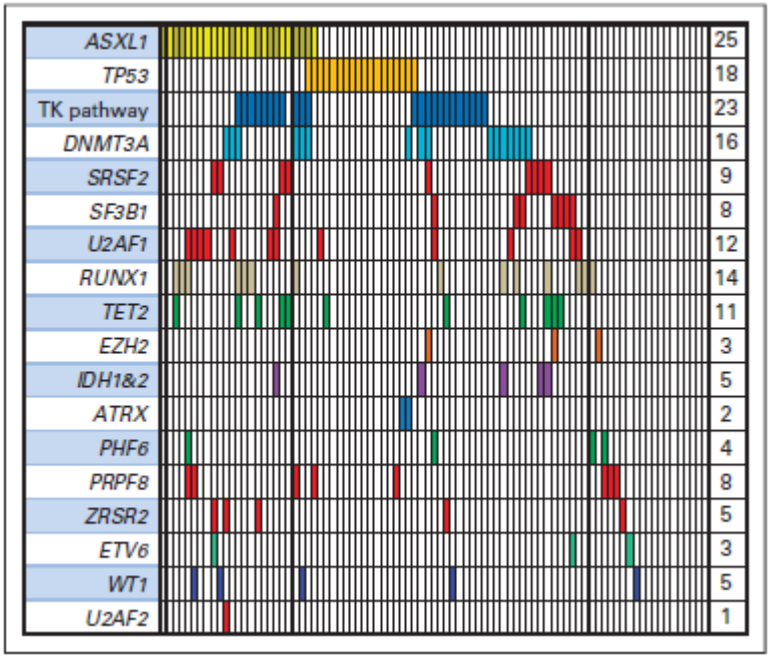
Prior decitabine before BMT (RAEB/RAEB-t) did not increase toxicity and may improve the outcome

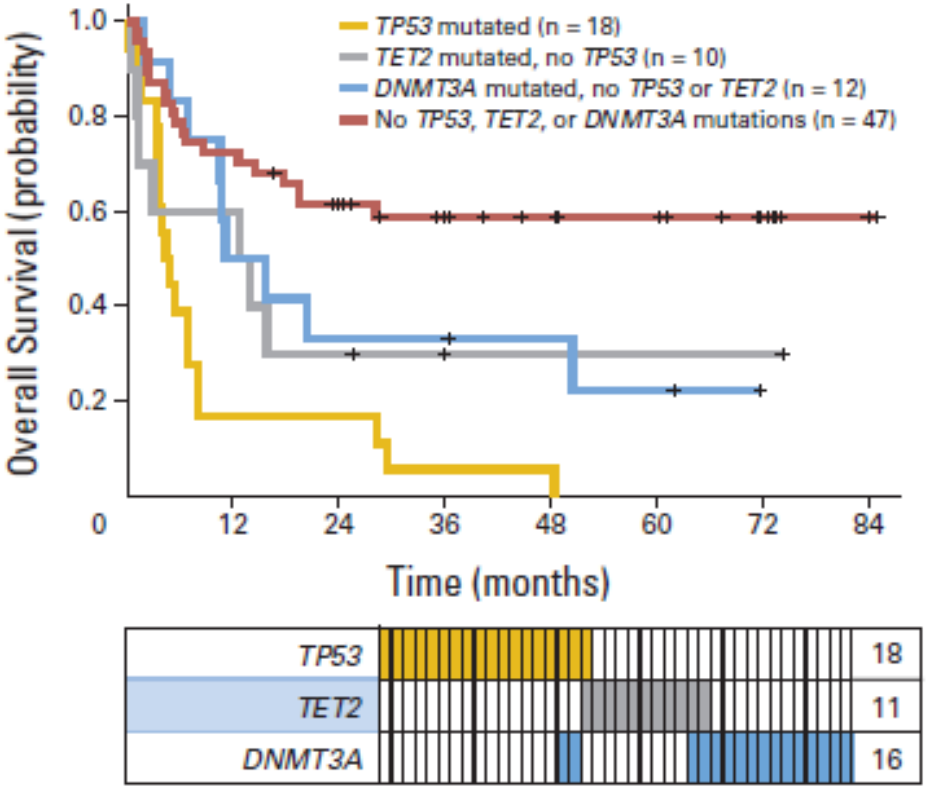
- **17 patients with MDS with a median age of 55.5 years (range, 36–66 years)**
- **decitabine 20mg/m^2 i.v. daily for 5 days for a median of five cycles**

UPN	*Days to ANC> 500/mm^3*	*Days to plt >20K/mm^3*	*Chimerism (%) on SCT day 30/100*	*Toxicity (grade)*	*Acute GVHD (grade)*	*Chronic GVHD*	*Best hematologic response after SCT*	*Relapse after SCT*	*EFS (mo)*	*Status last follow up*	*Overall survival (mo)*
1	15	23	100/100	No	Skin (2)	LIM	CR	Yes	33	Alive	35+
2	12	7	100/100	M/N/V (2)	Skin (2) Eye (1)	No	CR	No	24	Alive	24+
3	11	13	100/100	No	GI (2) Skin (1)	No	CR	Yes	7	Dead	8
4	13	17	100/67	N/D/V(1)	Skin (3)	No	CR	Yes	3	Dead	5
5	13	16	100/100	D(2)	Skin (2)	LIM	CR	No	18	Alive	18+
6	12	14	100/100	N/D(1)	Skin (3)	EXT	CR	No	9	Alive	9+
7	30	N	100/100	N/V/M/NF(2)	Skin (1)	No	HI	Yes	3	Dead	7
8	12	14	100/100	No	GI (2) Skin (1)	No	HI	No	5	Dead	5
9	11	12	100/100	N (1)	GI (1)	LIM	CR	No	8	Alive	8+
10	13	15	100/100	N/M (1)	No	EXT	CR	No	9	Alive	9+
11	12	13	94/95	N/M (1)	GI (1)	No	CR	Yes	5	Alive	9+
12	10	10	100/100	D/arrhythmia (1)	GI (1) Skin (1)	No	HI	No	4	Alive	4+
13	14	N	NA	MOF (4)	No	NA	ED	NA	1	Dead	1
14	13	10	84/100	M/N/liver (1)	No	NA	CR	No	3	Alive	3+
15	10	11	100/100	D/M (4)	No	N	CR	Yes	17	Alive	22+
16	Failed	Failed	Failed	N (1)	No	NA	NA	NA	2	Dead	6
17	19	35	100100	N/V/M (2)	No	LIM	HI	No	8	Alive	8+

- Median follow-up: 12 months
- Overall Survival : 67%
- Complete Continue Response: 47%

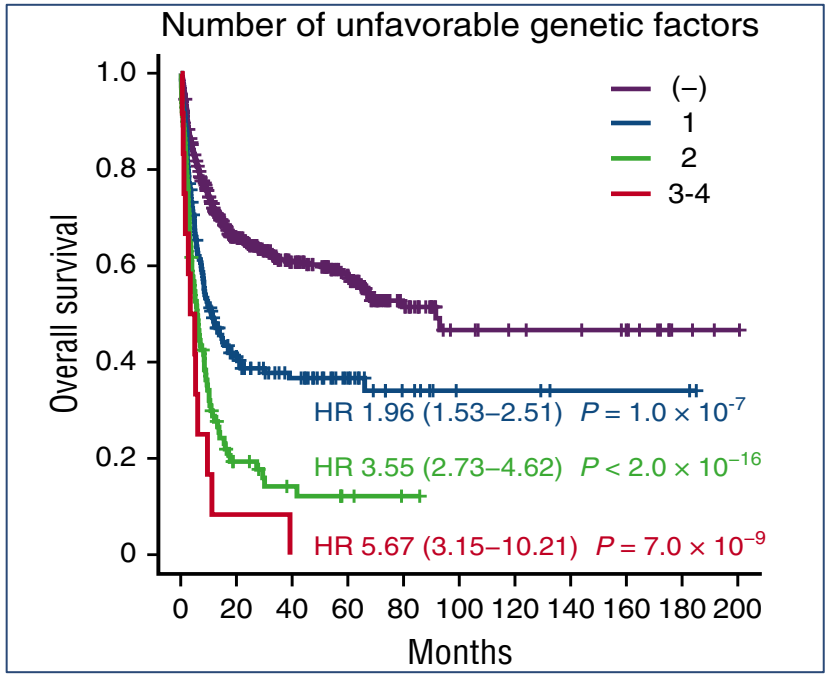
Somatic Mutations Predict Poor Outcome in Patients With MDS After Hematopoietic Stem-Cell Transplantation

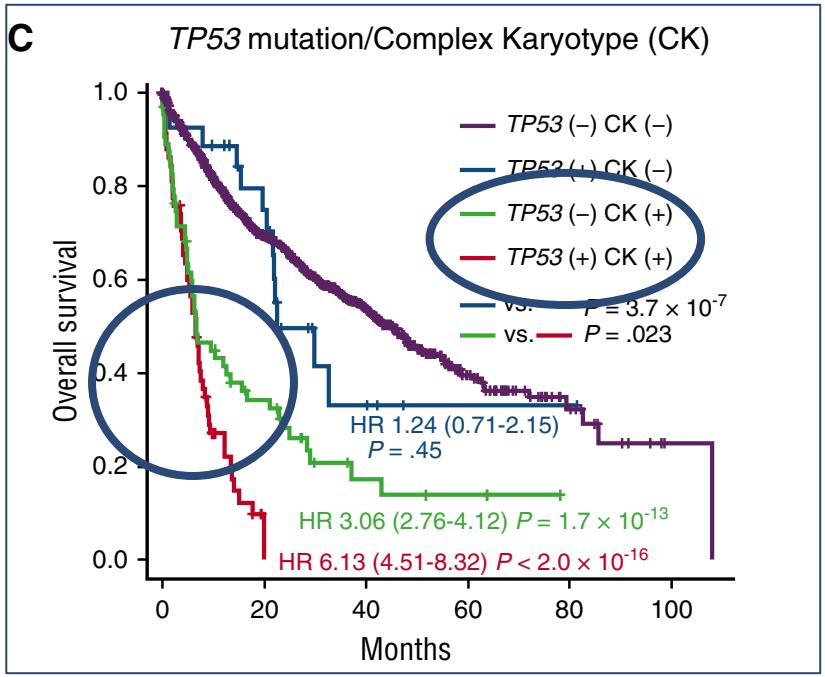




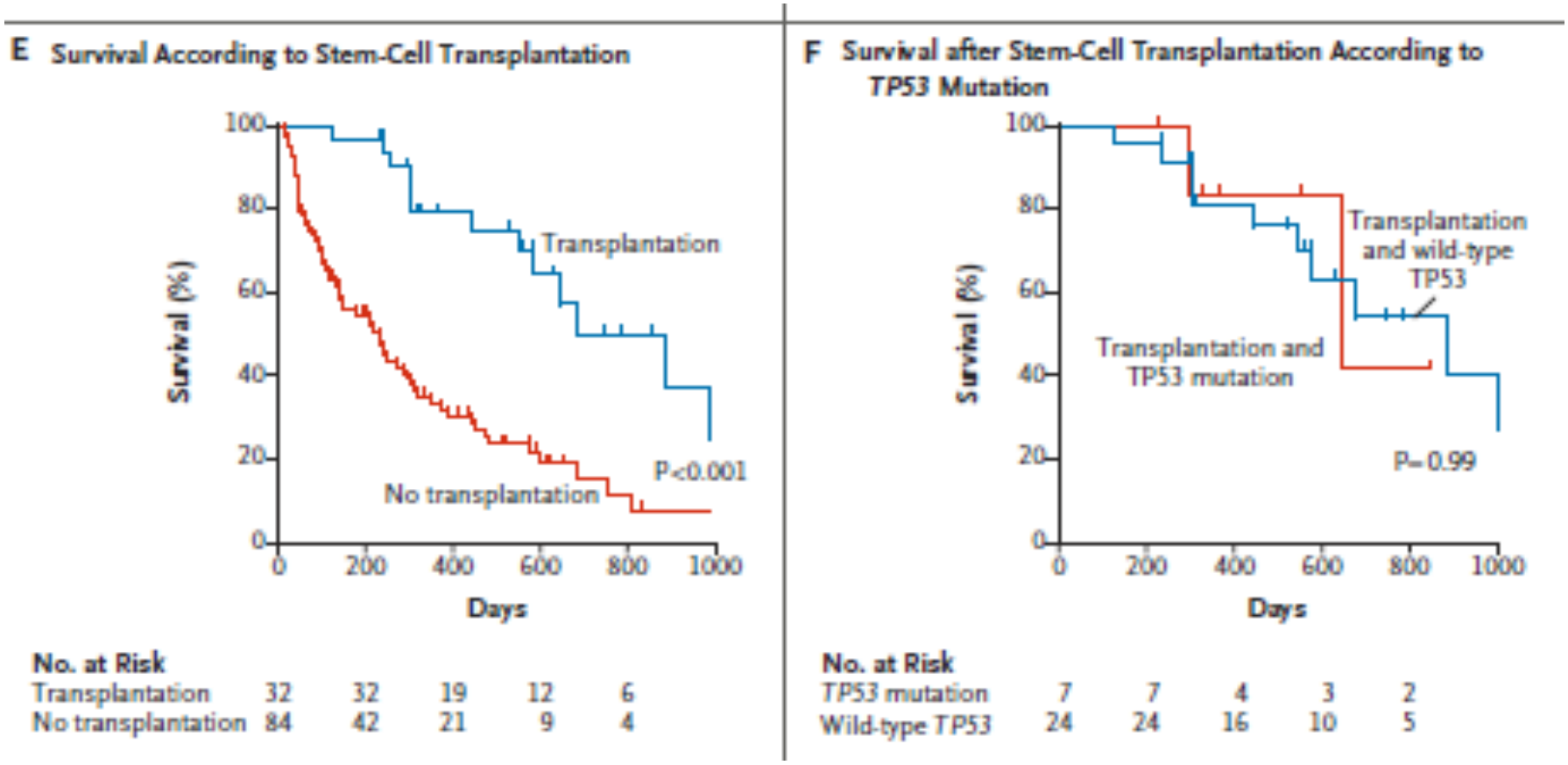
Bejar R et al. J Clin Oncol 2014;32:2691-2698.

Impact on outcome of stem cell transplantation of genetic abnormalities and *TP53* mutation/Complex Karyotype in MDS

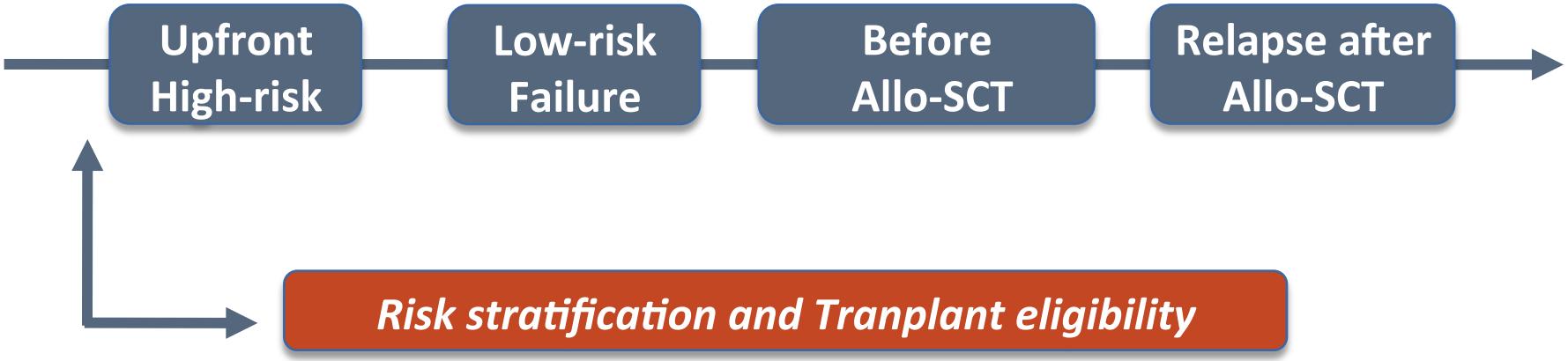




Decitabine 20 mg/m^2 d1-10 in AML and MDS
Overall survival according to transplant and TP53 mutation

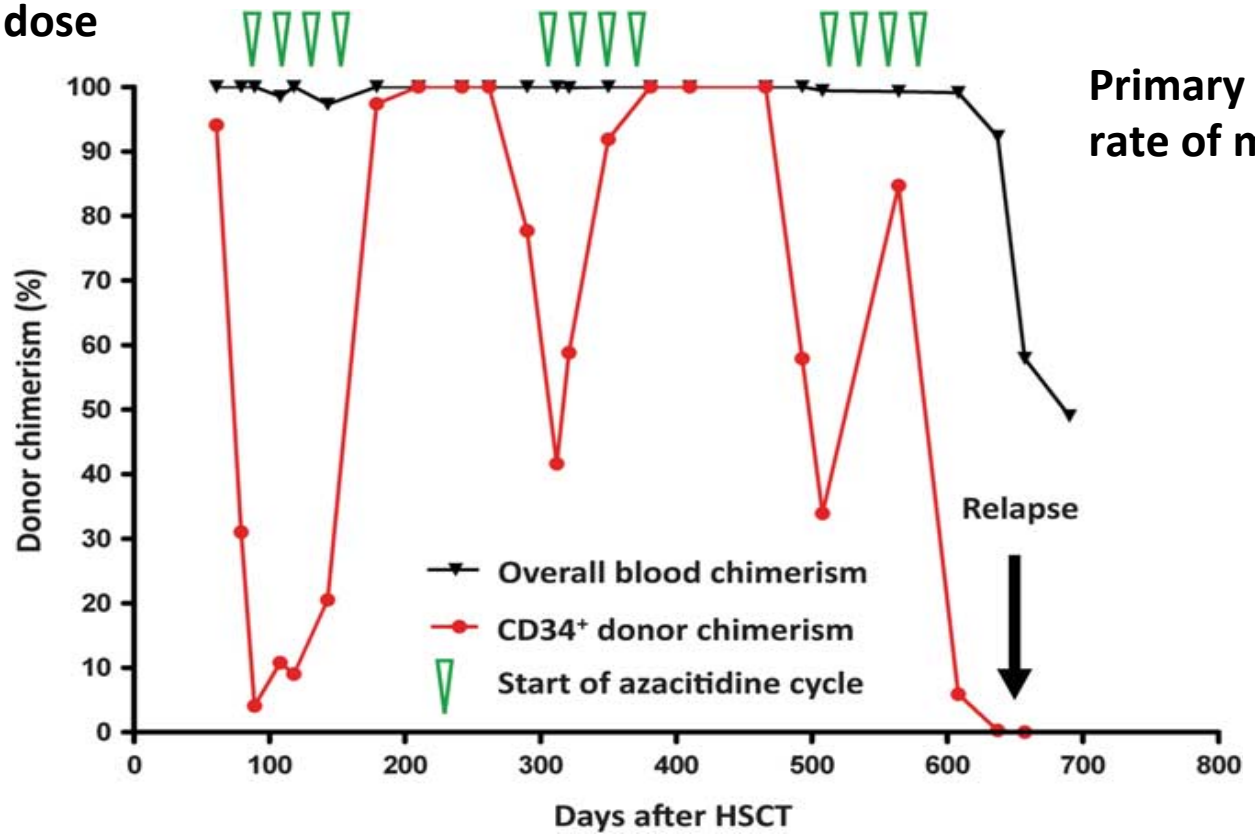


Hypomethylating agents in MDS



5-Aza for non hematologic relapse after allo-HSCT in MDS or AML: RELAZA trial (n=20)

Four dose of 5-aza at standard dose



Primary end point: rate of major response

MRD- triggered treatment may be effective strategy for preventing or delaying hematologic relapse

Aza and DLI as first salvage therapy for relapse of AML or MDS after allo-SCT

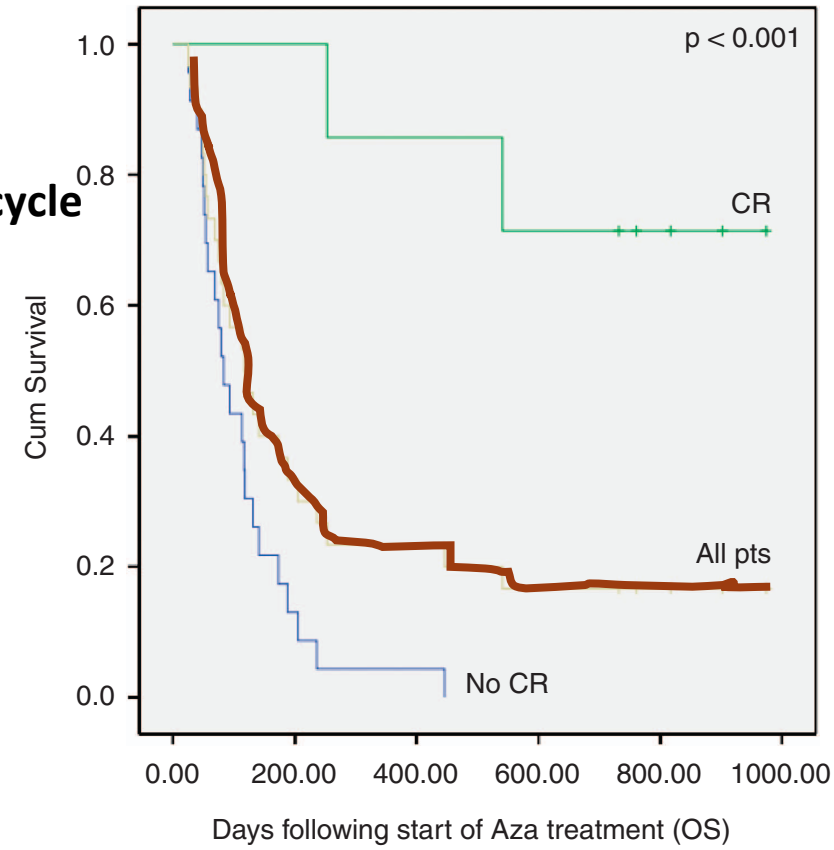
- **Hematological relapse defined as BM blasts > 5%, reappearance of blasts in peripheral blood and/or extramedullary disease**

- **Six cycles Aza 100 mg/m²/day sc d1–5 4QW**
- **DLI given on the sixth day of every second Aza cycle**

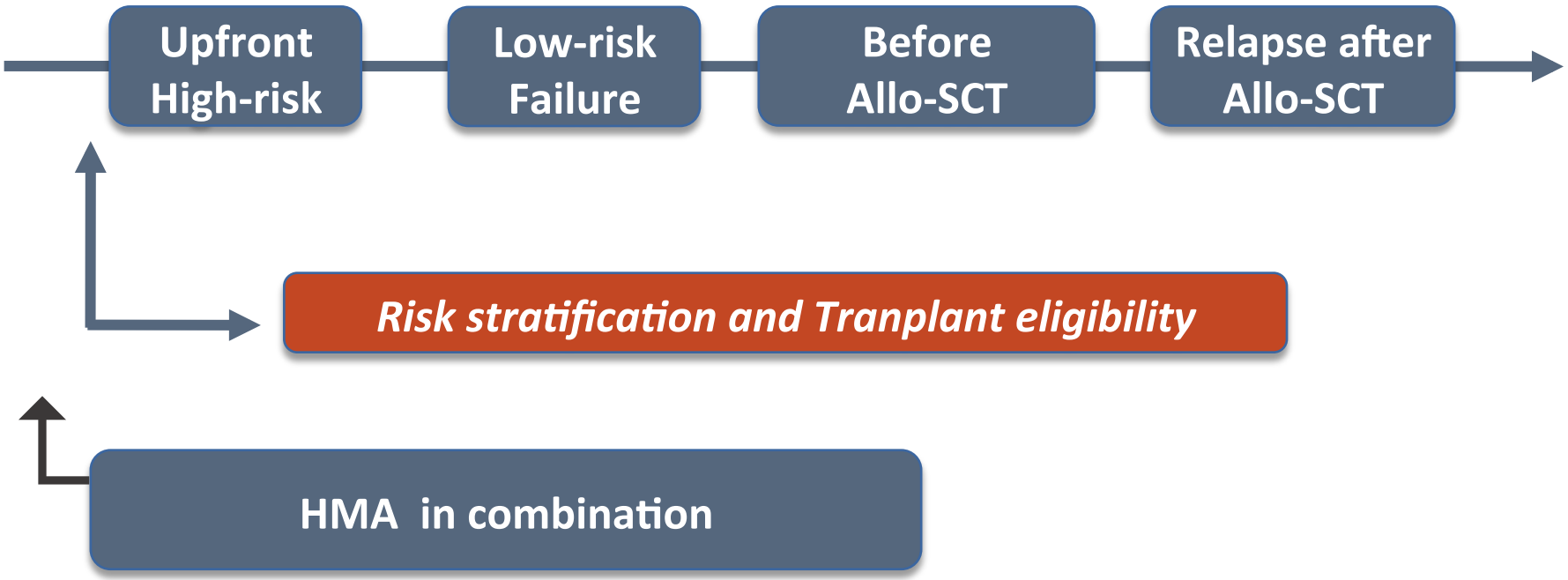
Response

ORR 30%
CR 23%
PR 7%
SD 17%

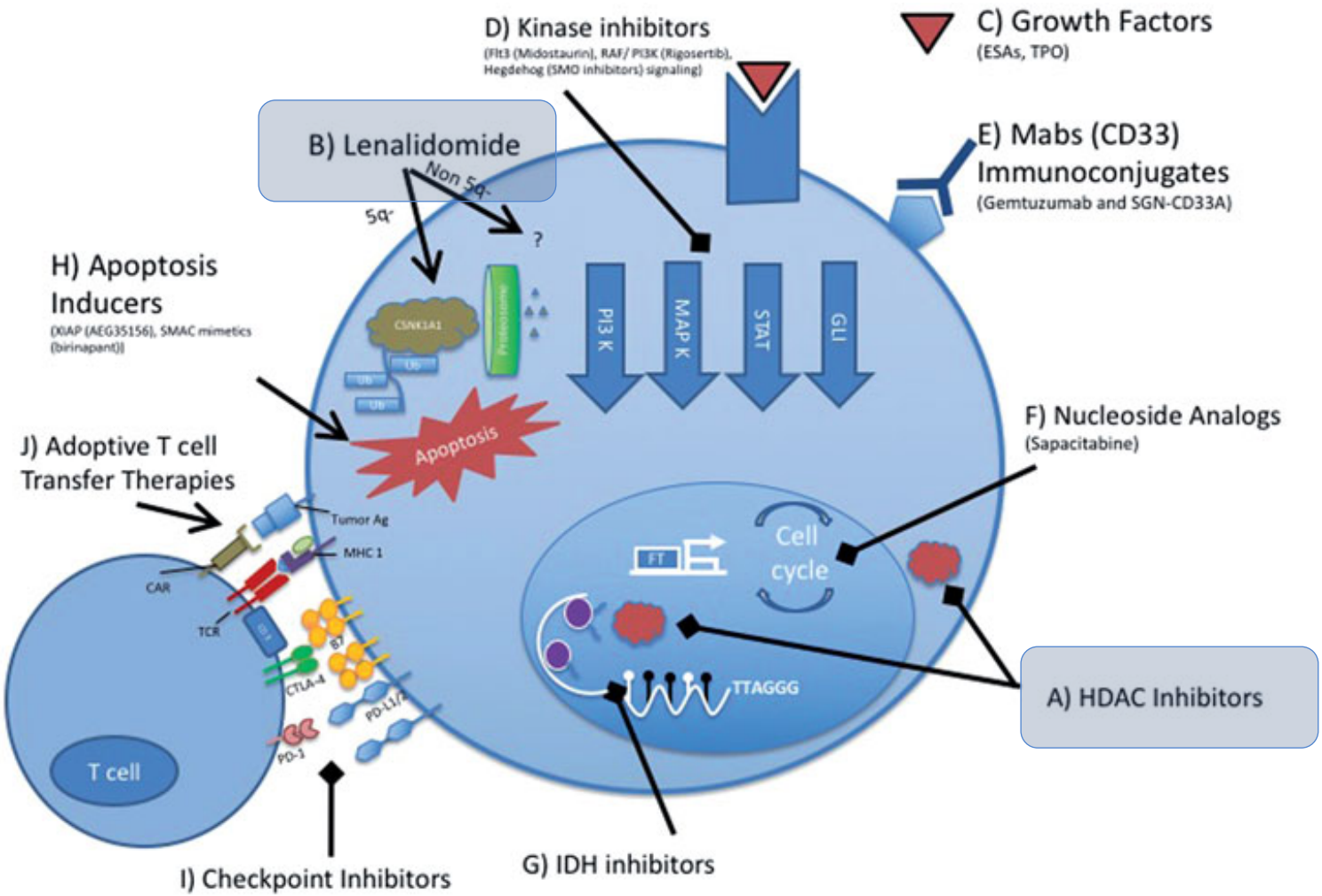
- **Median follow-up 817 days (range 732–974)**
- **17% alive and free of disease.**



Hypomethylating agents in MDS



Overview of current therapies used in combination with hypomethylating agents in MDS



Selected clinical trials of HDAC inhibitors in combination with hypomethylating agents in MDS

HDAC inhibitor	Targets	Selected study	Study intervention	*N* % MDS	ORR %* CR/PR/HI %*	Survival
Phenylbutyrate	Class I and IIa	Gore et al. [25]	PB + AZA Phase I	*n* = 29 36%	38 14/3/21	–
Valproic acid	Class I and IIa	Issa et al. [28]	VPA + DAC Phase II, RCT	*n* = 149 58% DAC, *n* = 70 VPA + DAC, *n* = 79	DAC 51 31/−/− VPA + DAC 58 [*p* vs. DAC= 0.4] 37/−/− [*p* vs. DAC = 0.5]	Median OS (Mos) DAC 11.9 VPA + DAC 11.2 [*p* vs. DAC= 0.92)
Vorinostat	Class I, II, IV	Sekeres et al. [33]	VOR + AZA Phase II, RCT	*N* = 276 82% AZA, *n* = 92 VOR + AZA, *n* = 91	AZA 37 24/0/13 VOR + AZA 27 [*p* vs. AZA =0.16] 17/1/9 [CR *p* vs. AZA 0.36]	Median OS (Mos) AZA 15 AZA + VOR 17 [log-rank *p* = .17]
Panobinostat	Class I, II, IV	Garcia-Manero et al. [35]	PAN + AZA Phase IIb, RCT	*N* = 82 57% AZA, *n* = 42 PAN + AZA, *n* = 40	AZA 38 10/−/− PAN + AZA 38 15/−/−	Probability of 1 year Survival AZA 70% PAN + AZA 60% [*p* vs. AZA = NS]
Pracinostat	Class I, II, IV	Garcia-Manero et al. [36]	PRA + AZA Phase II, RCT	*N* = 1-2 100% AZA, *n*= PRA + AZA, *n*=	AZA – 31/−/55 PRA + AZA – 18/−/35	Median OS (Mos) AZA 18.8 PRA + AZA 15.7 [HR =1.21, *p*=NS]
Entinostat	Class I	Prebet et al. [37]	ENT + AZA Phase II, RCT	*n* = 149 62% AZA, *n* = 74 AZA + ENT, *n* = 75	AZA 33 12/8/12 AZA + ENT 27 [*p* vs. AZA = NS] 8/7/12	Median OS (Mos) AZA 18 ENT + AZA 13
Mocetinostat	HDAC 1, 2, 3, 11	Luger et al. [39]	MOC + AZA	*N* = 22 100%	MOC + AZA CR + CRi rate 59%	–

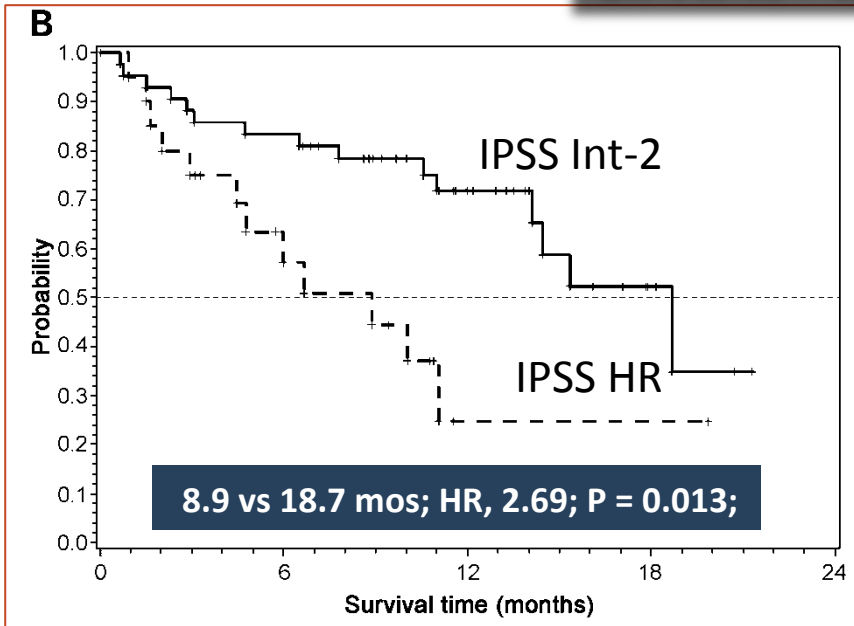
Valproic Acid and 5-Azacytidine in Higher Risk Myelodysplastic Syndromes

	n (%)
Sex	
Male	43 (69.4)
Female	19 (30.6)
Age	
Median (range)	69.6 (52.9-83.2)
Diagnosis	
RAEB	39 (62.90)
RAEBT	19 (30.65)
CMML	4 (6.45)
MDS history	
De novo	60 (97)
Therapy-related	2 (3)
IPSS score	
Intermediate-2	42 (67.74)
High	20 (32.26)
Karyotype	
Chromosome 7	8
Chromosome 5	3
Complex	11
Normal	15
Other	25
Bone marrow blasts (%)	
Median (range)	16 (6.0-32.5)
Hemoglobin (g/dL)	
Median (range)	9.0 (5.9-14.5)
Platelets (10^9/L)	
Median (range)	54.0 (4.0-653.0)
WBC (10^9/L)	
Median (range)	2.7 (0.7-34.0)

Table 2. Treatment response

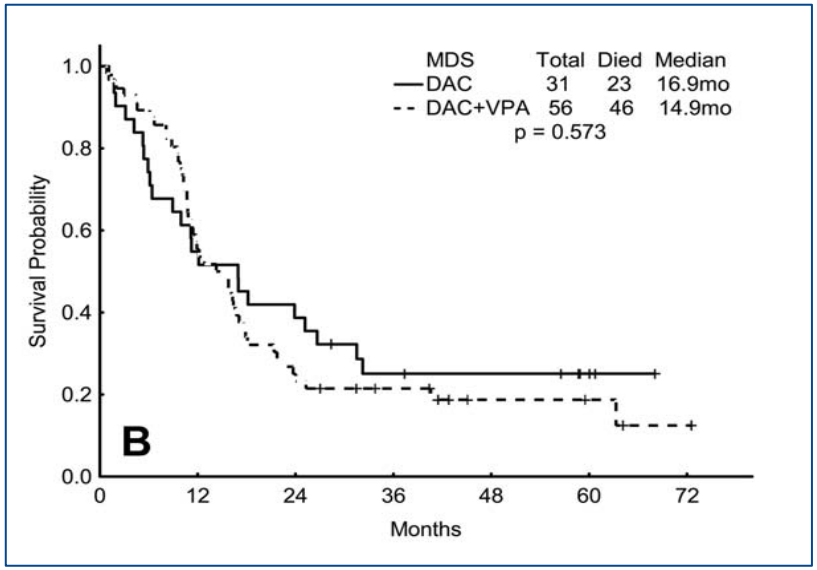
	After four cycles (*n* = 41)	After eight cycles (*n* = 26)
Hematologic improvement	12 (29.3%)	4 (15.4%)
Stable disease	20 (48.9%)	10 (38.5%)
Failure	4 (9.7%)	4 (15.4%)
CR	1 (2.4%)	3 (11.5%)
PR	4 (9.7%)	5 (19.2%)

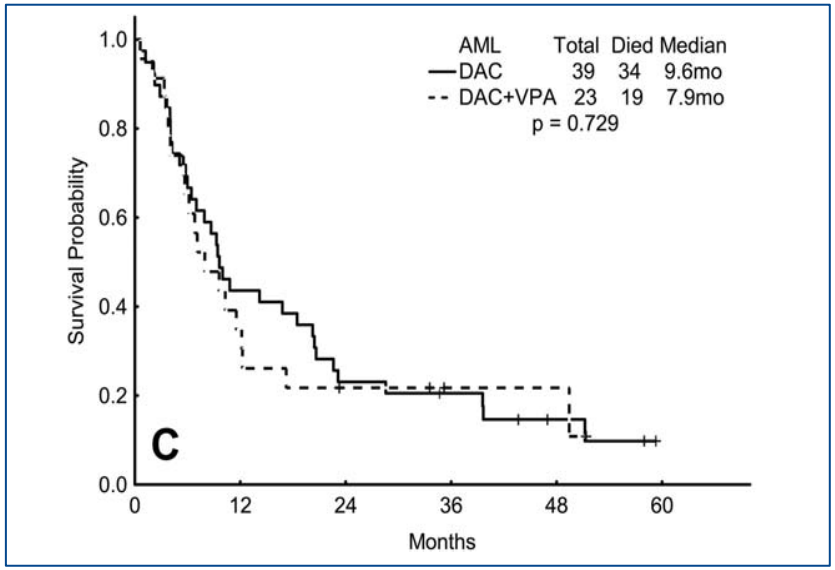
CR+PR+HI = 46%



DAC ± Valproic Acid in MDS and AML
Phase 2 Randomized Study

	DAC (%) (n=70)	DAC + VPA (%) (n=79)	p.
No. CR	**22 (31)**	**29 (37)**	**.479**
BM Cr + HI + PR	**14 (20)**	**17 (27)**	**.818**
ORR	**36 (51)**	**46 (58)**	**.407**

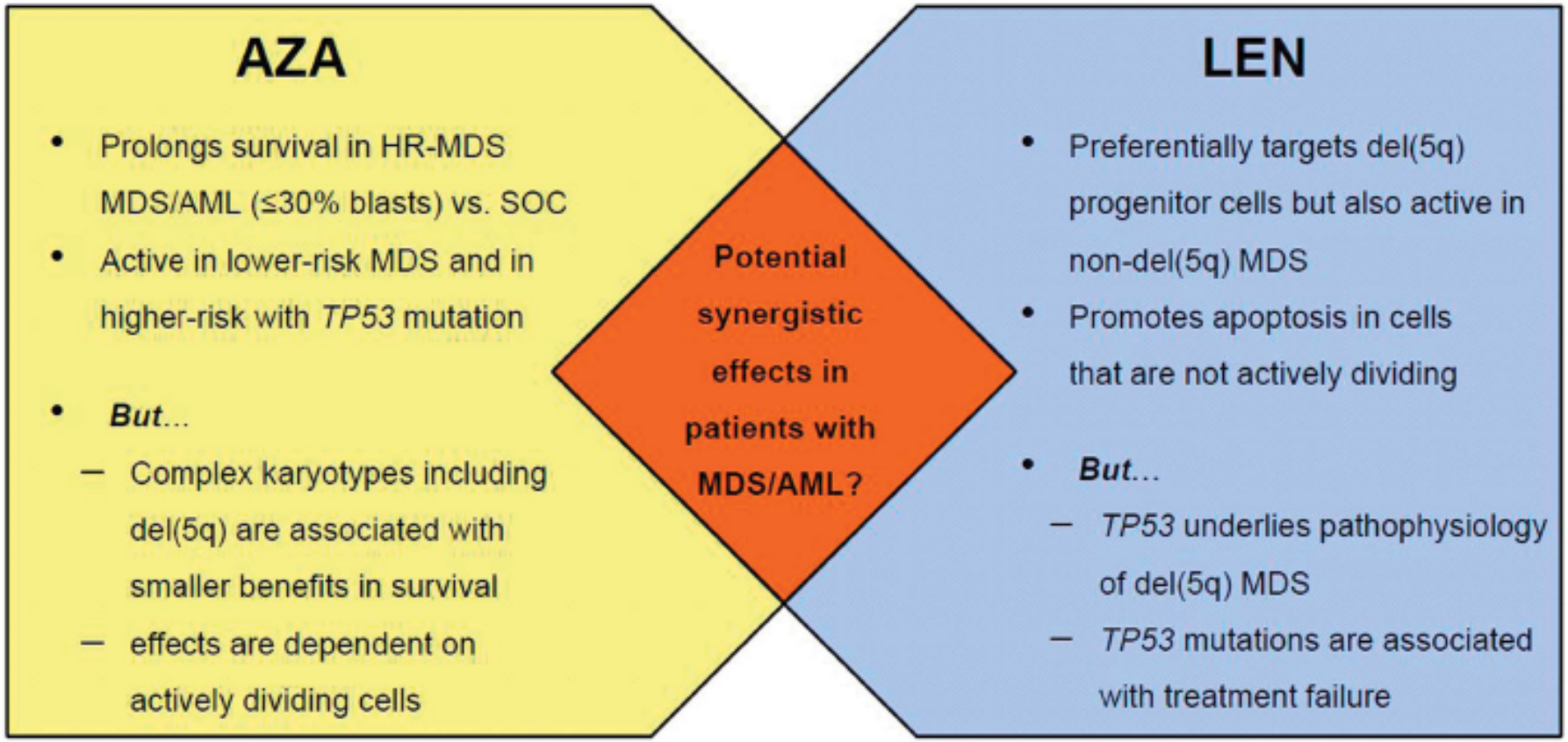




Selected clinical trials of non-HDAC inhibitor combination therapies with hypomethylating agents in MDS

Study	Intervention	Design	*N*	Med Age	% MDS	ORR%*	CR%*	Med OS (ms)
Sekeres et al. [49]	AZA + LEN	Phase II	36	68	100%	72%	44%	13.6
Narayan et al. [50]	AZA + LEN	Phase II	32	73.5	19%	25%	12.5%	5
DiNardo et al. [51]	AZA + LEN	Phase I/II	88	67	51%	35%	17%	8.2
Sekeres et al. [33]	AZA AZA + LEN	Phase II, RCT	Total, $n = 277$ AZA, $n = 92$ AZA + LEN, $n = 93$	70	82%	AZA 37% AZA + LEN 45% [p vs. AZA= 0.45]	AZA 24% AZA + LEN 21% [p vs. AZA = 0.73]	AZA 15 AZA + LEN 18 [p vs. AZA = 0.38]
Mittelman et al. [46]	AZA + LEN	Phase II	18	–	100% HR and LR MDS Selected for 5q-	78%	44%	–
Platzbecker et al. [47]	AZA + LEN	Phase I	19	69	65% Selected for 5q-	42%	11%	
Ades et al. [48]	AZA + LEN	Phase I-II	49	69	63% IPSS-2 or high risk MDS Selected for 5q-	24%	8%	–
Itzykson et al. [55]	AZA + ESA	Retro.	Total, $n = 282$ AZA, $n = 239$ AZA + ESA, $n = 32$	72	Total 77% AZA 84% AZA + ESA 76%	AZA 43% AZA + ESA 53% [p vs. AZA= 0.34]	AZA 13% AZA + ESA 19%	AZA 11.9 AZA + ESA 19.6 [p vs. AZA = 0.04]
Tobiasson et al. [58]	AZA + ESA	Phase II	Total, $n = 30$ AZA, $n = 30$ Non-responders to AZA monotherapy received AZA + ESA, $n = 16$	69	100% IPSS low and Int-1 refractory to ESA	AZA 23% AZA + ESA 7%	–	–
Kantarjian et al. [60]	AZA + ROM	Phase II, RCT	Total, $n = 40$ AZA, $n = 13$ AZA + ROM (500 μg), $n = 13$ AZA + ROM (750 μg), $n = 14$	71	100% IPSS Low, Int-1, Int-2	AZA 15% AZA + ROM (500μg) 8% AZA + ROM (750μg) 14%	–	
Greenberg et al. [59]	DAC + ROM	Phase II, RCT	Total, $n = 29$ DAC, $n = 14$ DAC + ROM, $n = 15$	68	100% IPSS low, Int, high risk MDS	DAC 21% DAC + ROM 33% p = NS	DAC 7% DAC + ROM 13% p = NS	–
Svensson et al. [62]	AZA + ELT	Phase I	12	74	100%	67%	33%	–
Strati et al. [64]	AZA + MID	Phase I/II	54	65	5%	26%	2%	5.5
Daver et al. [68]	AZA + GEM	Phase II	110	70	22%	–	35%	7.2
Fathi et al. [70]	HMA + SGN-33A	Phase 1	23	77	0% MDS 100% AML	65%	22%	–
Ravandi et al. [72]	DAC + SAP	Phase I/II/III	33	77	0% MDS 100% AML	37%	30%	7.8
Nevada et al. [75]	AZA + RIG	Phase I/II	12	71	61%	50%	8.3%	–
Tibes et al. [79]	AZA + SON	Phase I/Ib	29	72	31%	–	40% or 2/5 untreated MDS	–
Ritchie et al. [98]	AZA + BIR	Phase II	6	≥60	100%	83%	50%	–

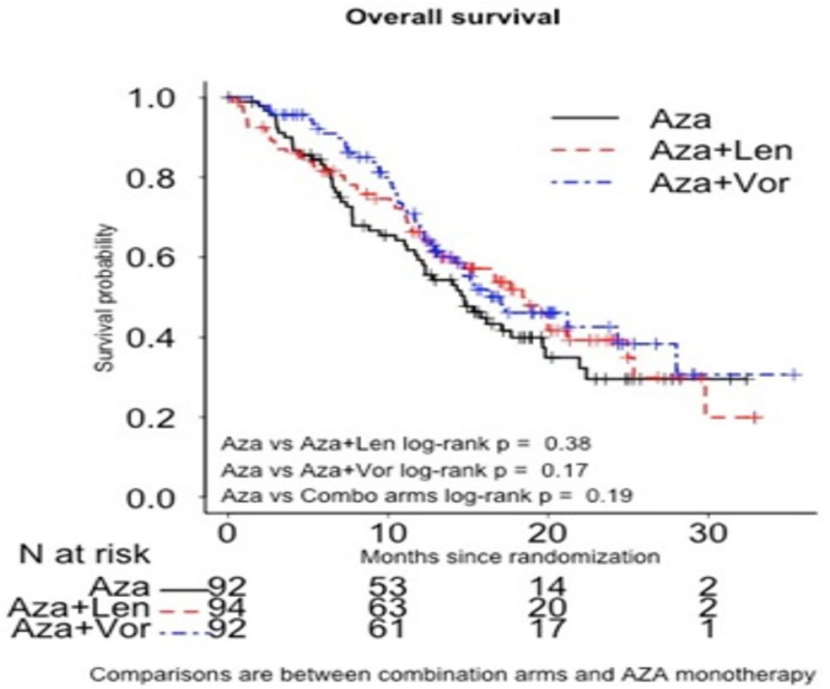
Rationale for a combination of azacitidine (AZA) and lenalidomide (LEN) in MDS or AML



Platzbecker U, et al; Leukemia (2013) 27, 1813–1819

SWOG-S1117 Trial: AZA vs AZA/LEN vs AZA/VOR in MDS and CMML

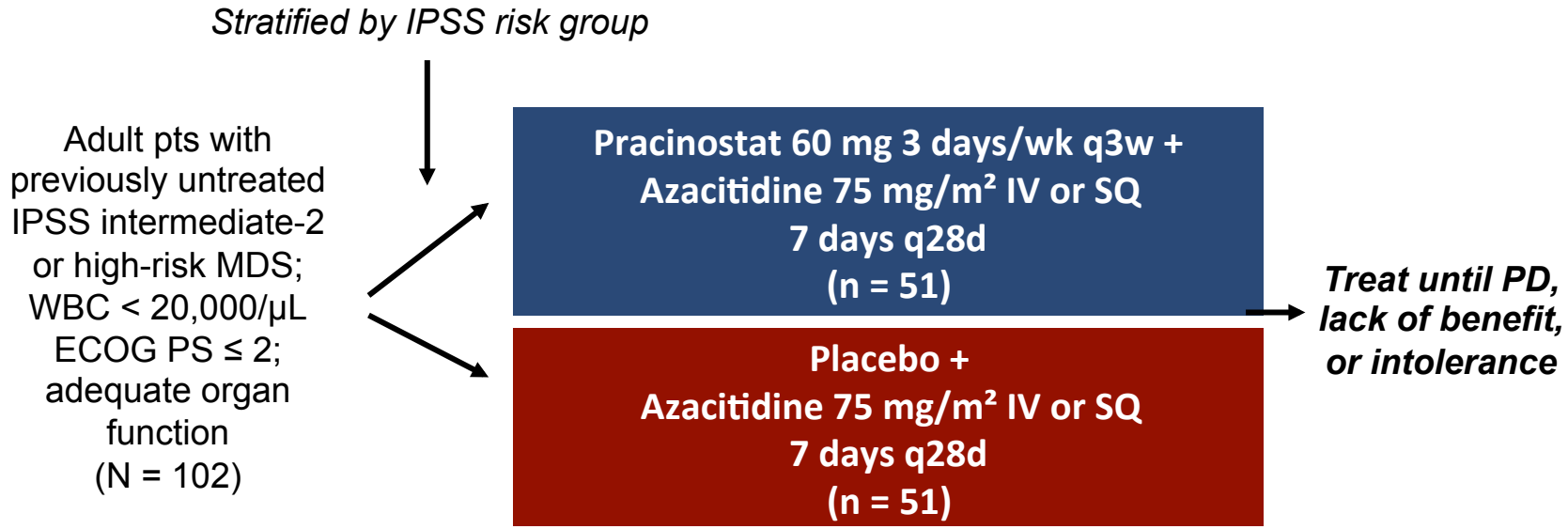
- **Primary endpoint:** overall response rate
- No significant difference in ORR between AZA and the combination regimens:
- AZA versus AZA/LEN $p = 0.38$
- AZA versus AZA/VOR $p = 0.17$
- AZA versus combinations $p = 0.19$
- Subgroup analyses:
- – Higher-risk MDS: Similar ORR and OS
- – CMML: ORR significantly higher with AZA/LEN compared to AZA (63% vs 29%; $p = 0.04$)



AZA (n=92), AZA+LEN (n=94), AZA+VOR (n=92)

Pracinostat + Azacitidine in MDS: Study Design

- Randomized, multicenter phase II trial (24 sites in US)



- Primary endpoint: confirmed CR by IWG criteria within 6 cycles
- Secondary endpoints: ORR, hematologic improvement, CBR, duration of response, PFS, rate of leukemic transformation, OS, safety and tolerability

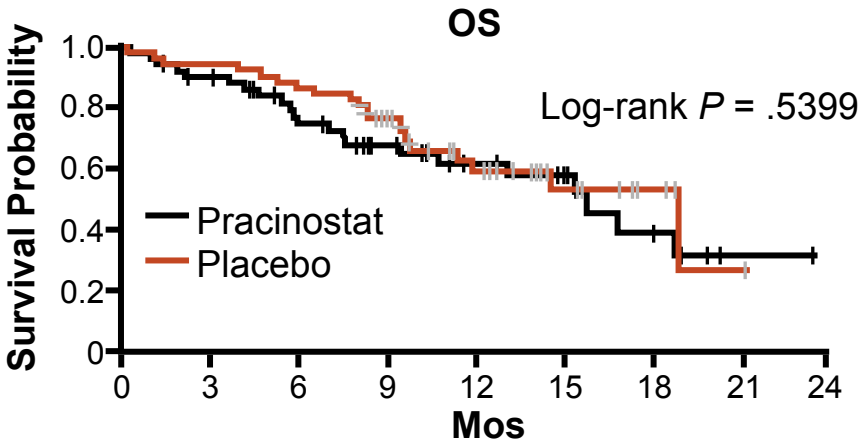
Pracinostat + Azacitidine in MDS: Response

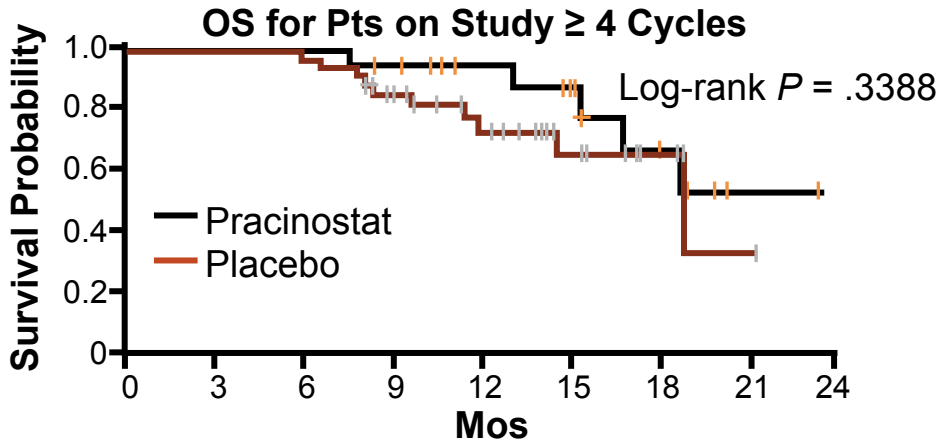
Endpoint, %	Pracinostat + Azacitidine (n = 51)	Placebo + Azacitidine (n = 51)
CR within 180 days	18	33
Best response ▪ CR ▪ PR ▪ SD ▪ PD	 20 0 26 6	 33 0 29 6
Hematologic improvement ▪ Erythroid ▪ Platelet ▪ Neutrophil	35 28 31 26	55 45 53 39
Clinical benefit rate*	53	63
Cytogenetic response ▪ Cytogenetic CR ▪ Cytogenetic PR	42 24 18	55 29 26

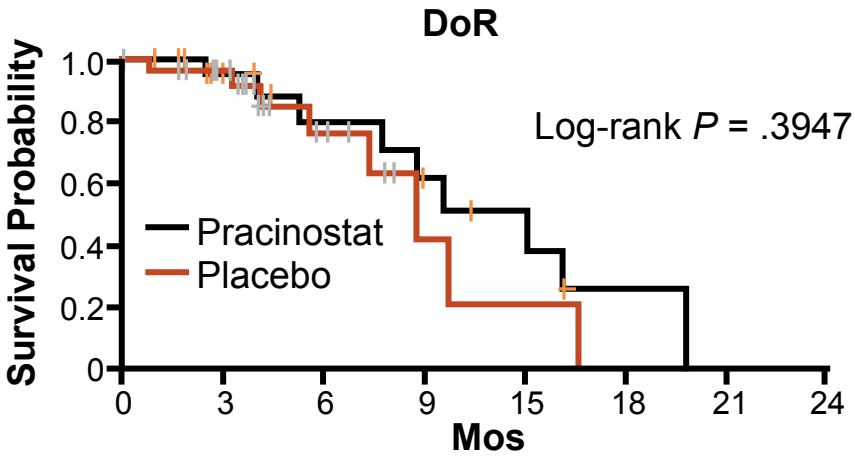
***CR + PR + hematologic improvement + molecular CR**

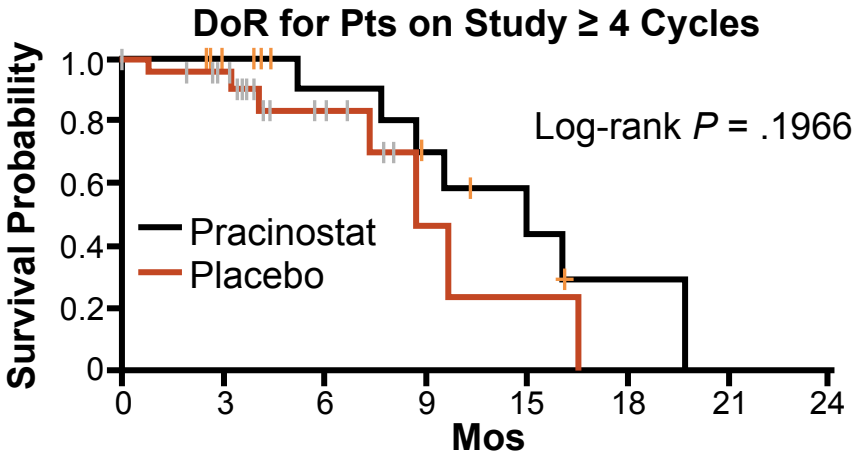
Pracinostat + Azacitidine in MDS: Overall Survival and Duration of Response

- Median follow-up: 15.4 mos
- 1-yr OS: Pracinostat 57.1%; Placebo 57.4%









Garcia-Manero G, et al. ASH 2015. Abstract 911

Rigosertib (Kinase Inhibitor) + Azacitidine in MDS: Study Design

Phase I study of rigosertib + azacitidine suggested clinical activity in MDS post-HMA failure with toxicity similar to single-agent azacitidine

Navada SC, et al. ASH 2014

- Open-label, multicenter phase II study[1]

Bone marrow aspiration/ biopsy: Wk 4, every 8 wks after

4-wk cycles

- Adult pts with MDS or CMML; IPSS int-1, int-2, or high; ECOG PS 0-2; adequate organ function; **untreated or relapsed/failed prior HMA**; no prior rigosertib (N = 37)*

→ **Rigosertib 560 mg qAM/280 mg qPM† PO Wk 1-3 + Azacitidine 75 mg mg/m2/day SC or IV Wk 2 No treatment Wk 4**

- Endpoints: CR, PR, bone marrow response, improvement in neutrophil, platelet, and erythroid counts, safety and tolerability

Navada SC, et al. ASH 2015. Abstract 910.

Rigosertib + Azacitidine in MDS

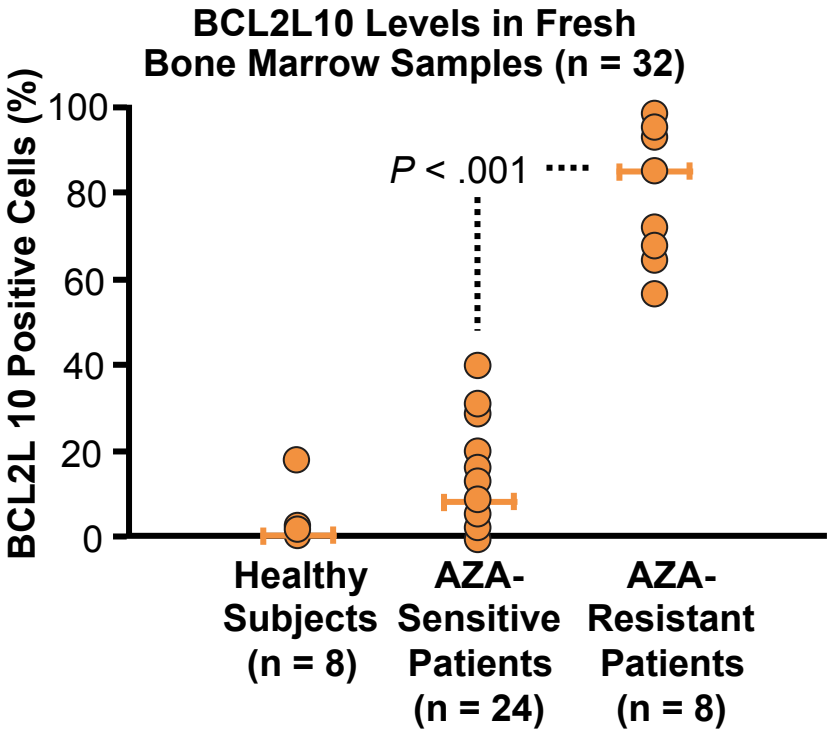
Characteristic	MDS Pts (N = 37)
Age, median yrs (range)	64 (25-85)
Male, %	73
Earlier HMA therapy, % ▪ Azacitidine ▪ Decitabine ▪ Both ▪ None	 27 8 3 62
IPSS risk group, % ▪ Intermediate-1 ▪ Intermediate-2 ▪ High	 27 41 32

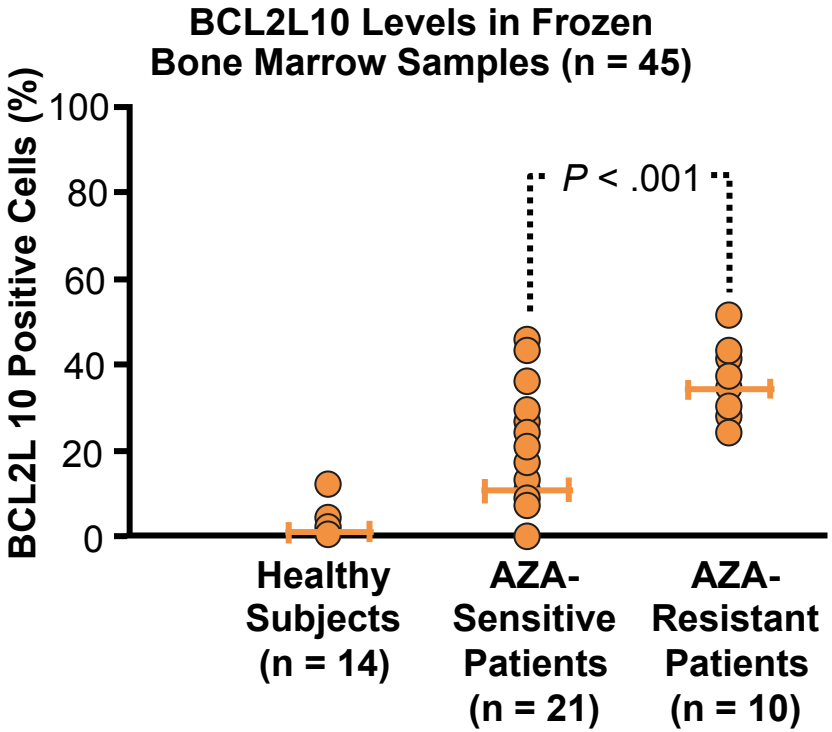
Parameter	MDS Pts (N = 37)
Evaluable for response,* n	30
Duration of treatment, median mos (range)	4 (1 to ≥ 27)
Overall response, %	**77**
Hematologic response,† % ▪ CR ▪ PR ▪ Bone marrow response ▪ SD ▪ PD	 20 0 53 20 3

Navada SC, et al. ASH 2015. Abstract 910.

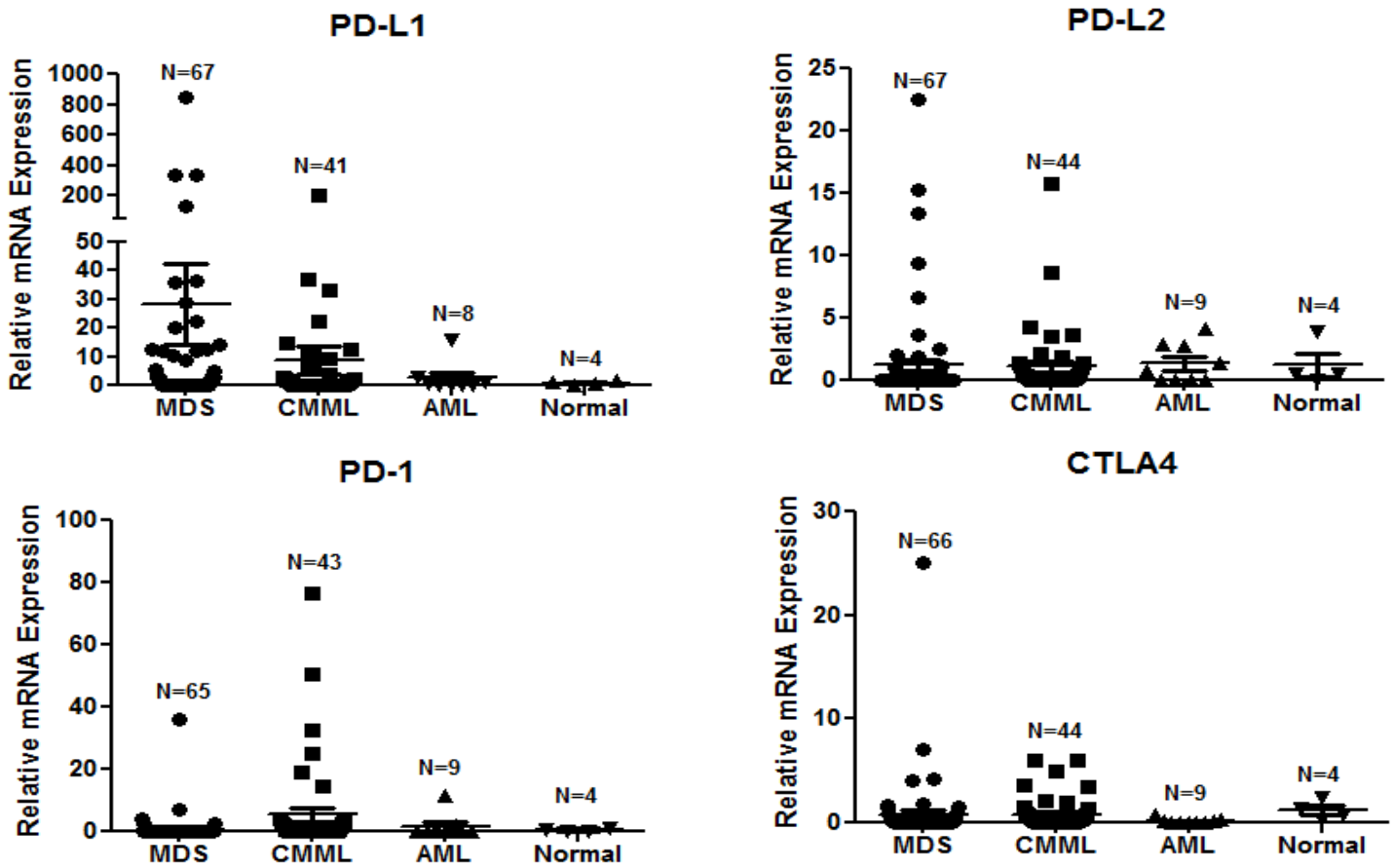
Inhibition of BCL2L10 by ABT-737 reverses AZA resistance

- Percentage of BCL2L10-positive cells in bone marrow significantly higher in AZA-resistant patients ($P < .0001$, all comparisons)





Aberrant up-regulation of PD-L1, PD-L2, PD-1 and CTLA4 in CD34+ cells from MDS, CMML and AML



Yang et al. Leukemia 2014

MDS treatment algorithm