CORSO EDUCAZIONALE GITMO

GITMO

AULA MAGNA KOLBE, UNIVERSITÀ DI UDINE
21-22 Gennaio 2016

Agenti ipometilanti e trapianto nelle sindromi mielodisplastiche e nelle leucemie mieloidi acute

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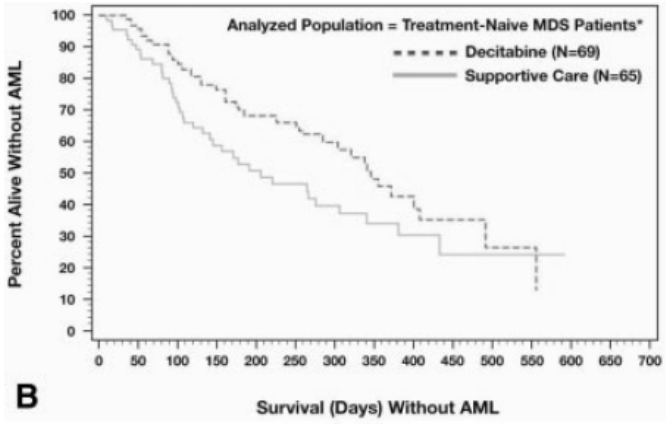
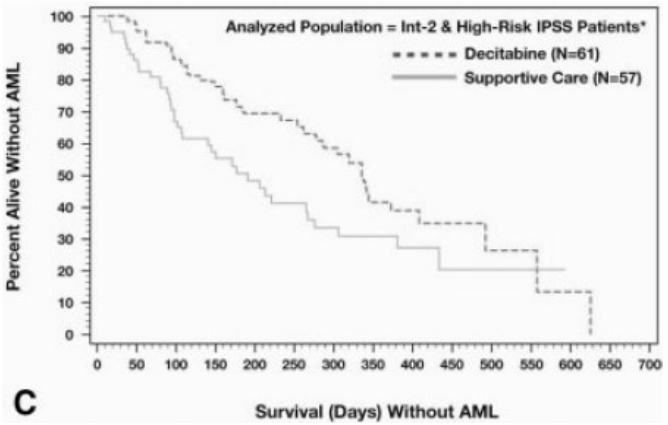
Decitibine in MDS

Intent-to-Treat Analysis of Response to Decitabine

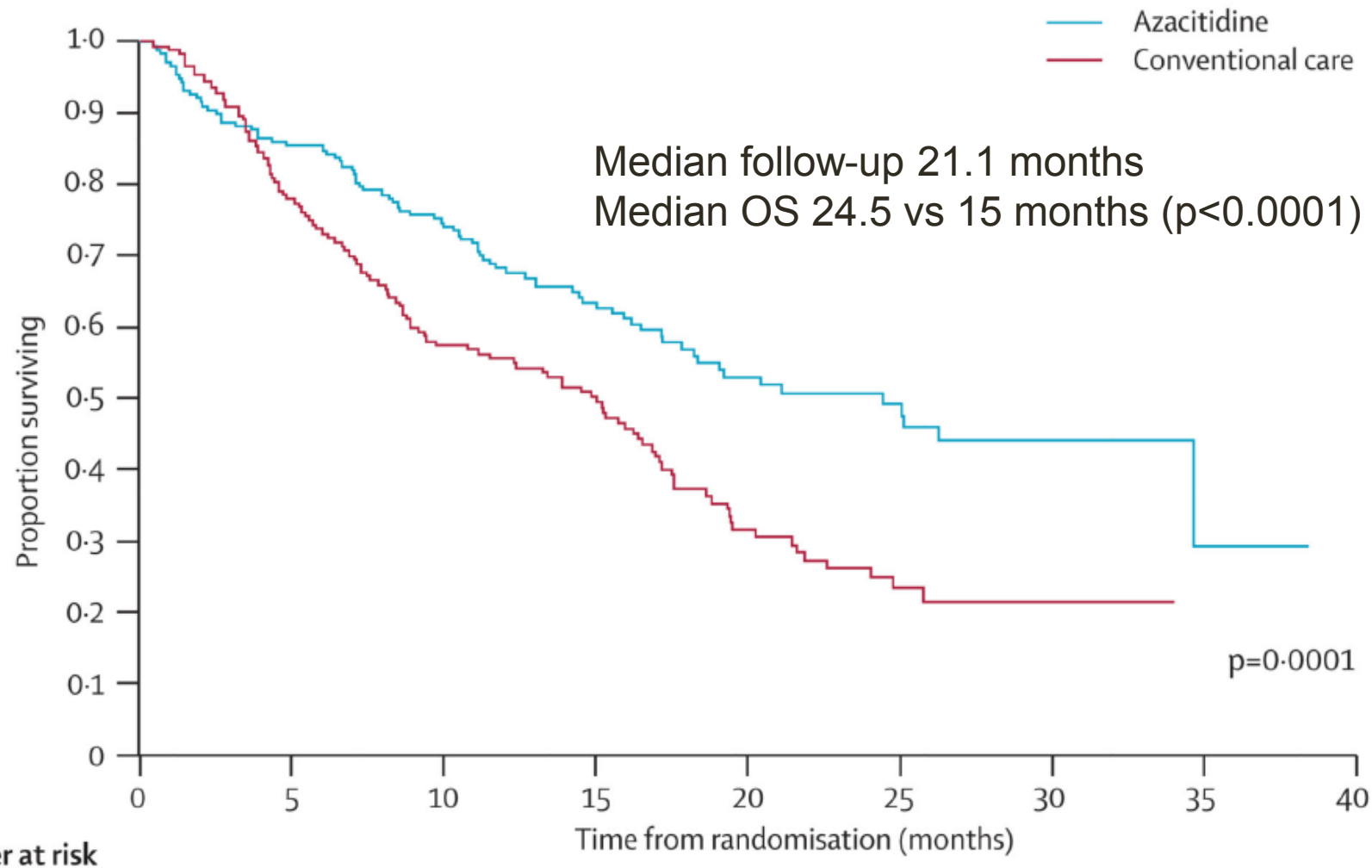
	Decitabine (n = 89) (%)	Supportive care (n = 81) (%)	P value*
Clinical response			
Overall response (CR + PR)	15 (17)	0	< .001
CR	8 (9)	0	
PR	7 (8)	0	
Clinical improvement			
Overall Improvement (CR + PR + HI)	27 (30)	6 (7)	< .001
HI	12 (13)	6 (7)	
Major	12 (13)†	5 (6)‡	
Minor	0 (0)	1 (1)	





Kantarjian et al. Cancer 2006

5-azacitidine in higher-risk MDS



Number at risk

Azacitidine	179	152	130	85	52	30	10	1	0
Conventional care	179	132	95	69	32	14	5	0	0

Fenaux et al. Lancet Oncol 2009

HMAs in MDS

Study	Drug (schedule)	Patients (*n*)	IPSS-RISK (*n*: patients)	Median age (range)	ORR (%)	Median OS (months)
Voso *et al.* [5▪▪]	AZA (StD: 163 pts, 100 mg/day 5–7 days: 33 pts)	196	Evaluable in 159 pts: Low: 7 (4%) Int-1: 36 (23%) Int-2: 99 (62%) High: 17 (11%) AML: 12	65 (55–74)	56%	17 months
Hwang *et al.* [6▪▪]	AZA (StD)	243	Int-2: 168 (69%) High: 75 (31%)	65 (43–76)	57%	24 months
Falantes *et al.* [7]	AZA (StD: 26%, 75 mg/m^2/d 5 d: 37%, 5–2–2: 30%)	27	Int-1: 27	74 (62–83)	40.7%	18 months
Oshikawa *et al.* [8]	AZA + allo-BMT	15	Low/Int-1: 5 Int-2/ High: 10	62 (25–70)	40%	1 yr OS: 79.0%
Jung *et al.* [9]	DAC 20 mg/m^2/d, 5 days every 28 days	101	Low: 7 Int-1: 45 Int-2: 38 High: 11	65 (18–84)	50.5%	17 months
Harel *et al.* [10▪▪]	DAC 20 mg/m^2/d, 5 days, every 28 days	36	Int-2: 10 High: 10 NA: 16	70.5 (53–84)	19.4%	7 months

5. Eur J Hematol 2015./ 6. Blood Res 2014 / 7. Clin Lym Myel Leuk 2013 / 8. Pathol Oncol Res 2015 / 9. Oncotarget 2015 / 10. Leuk Res 2015

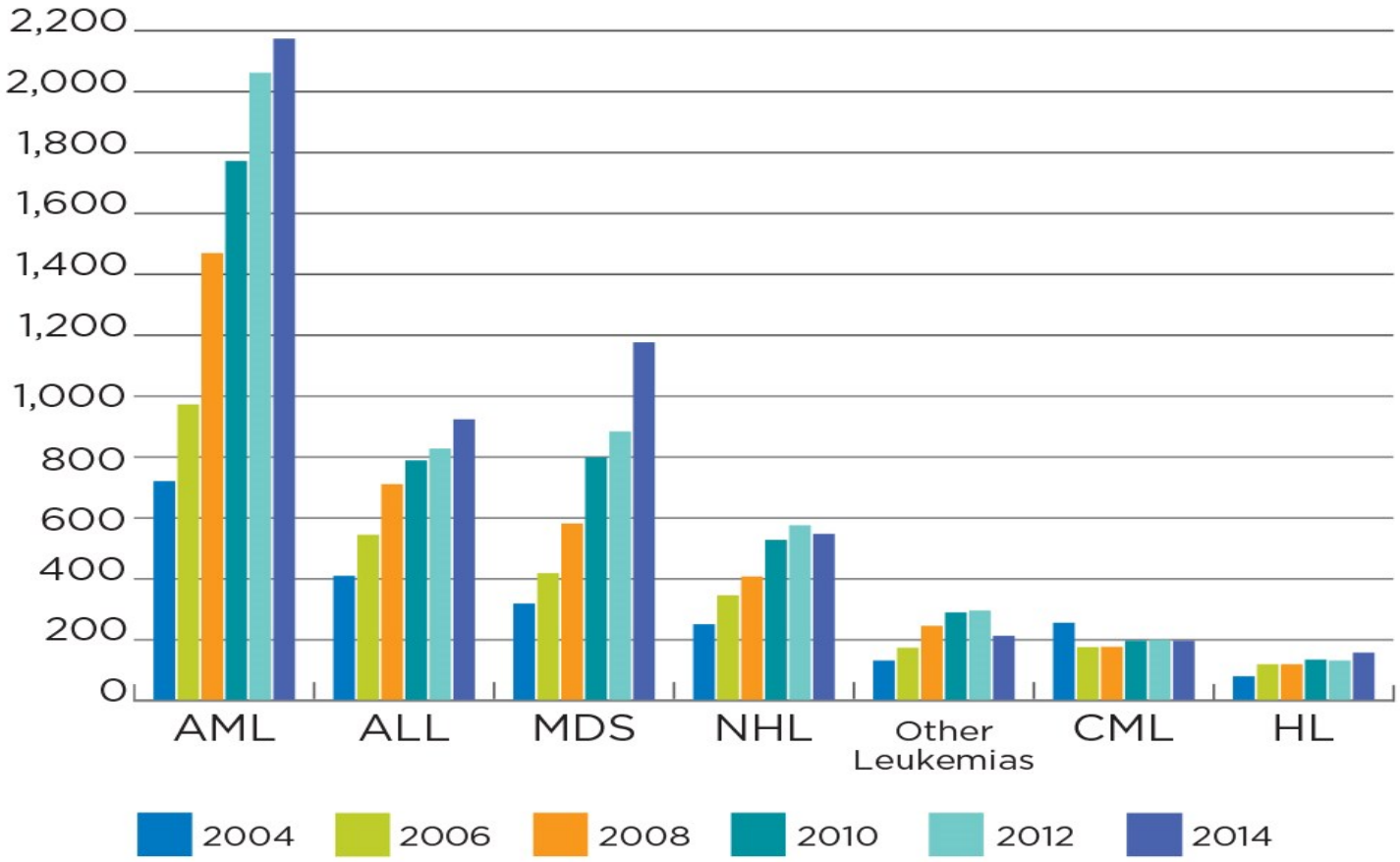
Voso MT et al. Curr Opin Hematol 2015

Allogeneic SCT in the HMA era

- In the HMA era, allogeneic SCT stil represents the only curative treatment option for patients with MDS
- Risk-benefit ratio of allo-SCT is strongly determined by the selection of patients and optimal timing of transplantation
- **Who** to transplant and **when** to transplant are the key questions

Adès L et al. *Lancet.* 2014;383:2239-2252; Garcia-Manero G. Am J Hematology. 2014;89:97-108.; Malcovati L et al. Blood. 2013;122:2943-2964. Vaughn JE, Scott BL, Deeg HJ. Curr Opin Hematol. 2013;20:494-500.

Unrelated Donor Transplants

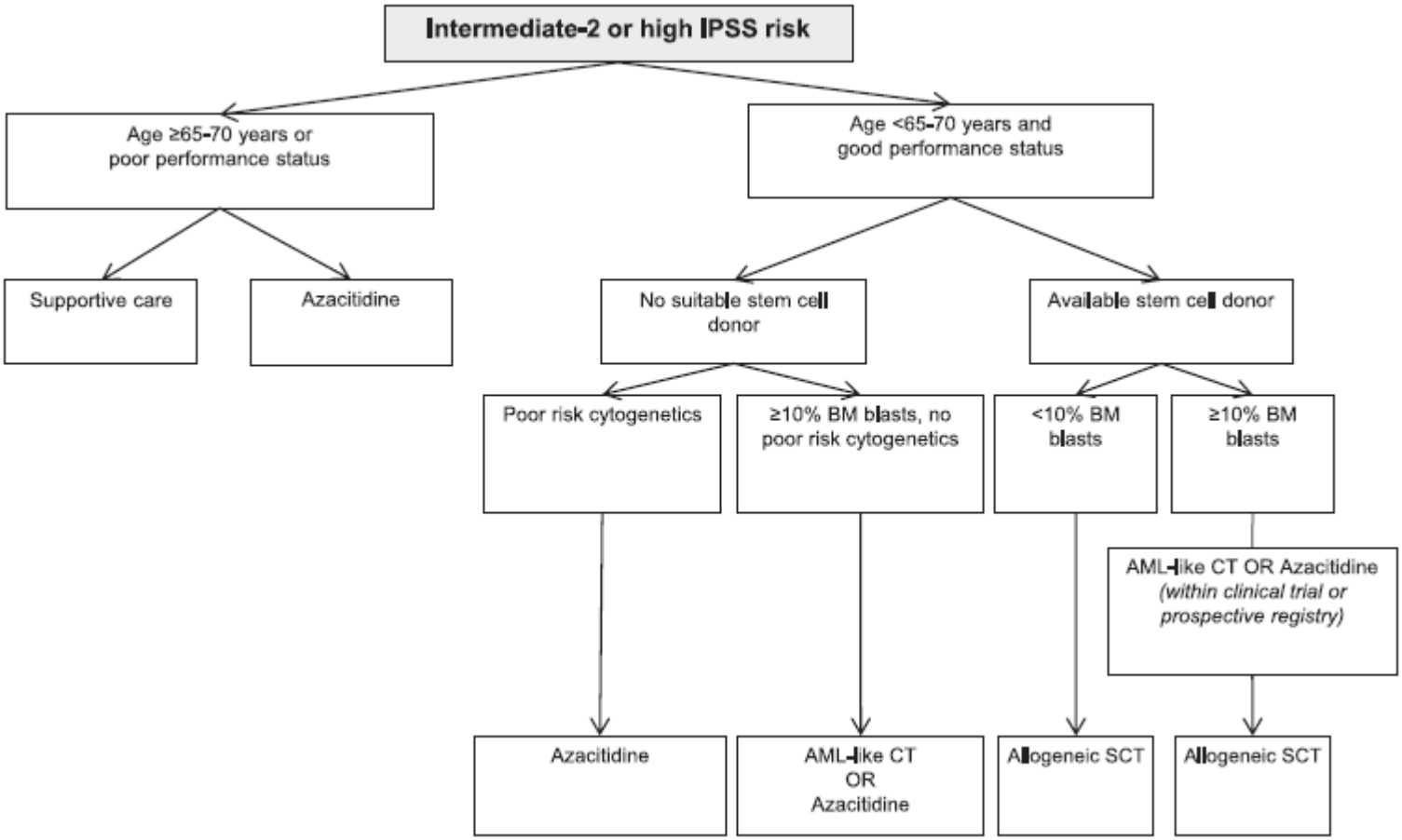


Source: National Marrow Donor Program/Be The Match FY 2014

NATIONAL MARROW DONOR PROGRAM®

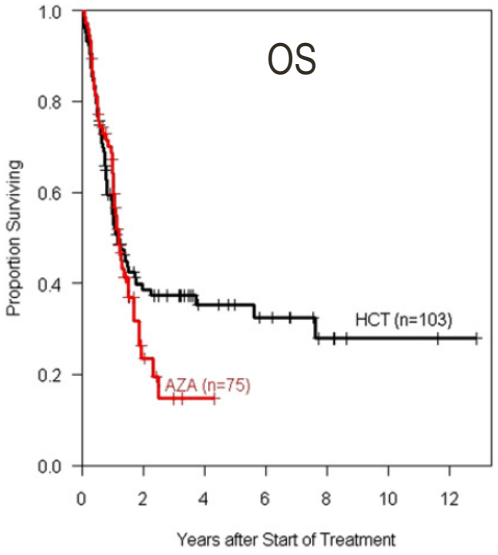
BE THE MATCH®

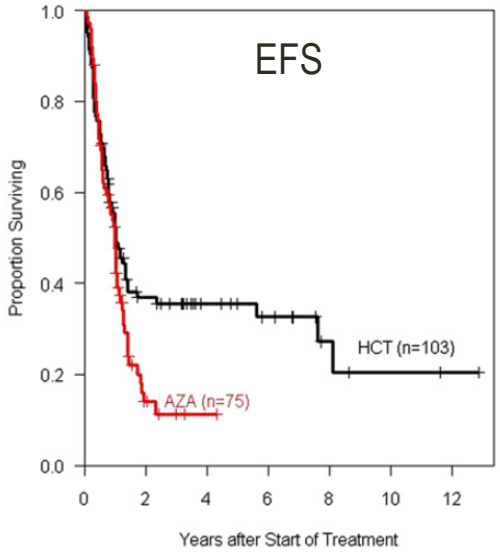
ELN therapeutic algorithm for MDS and Int-2 or high IPSS score

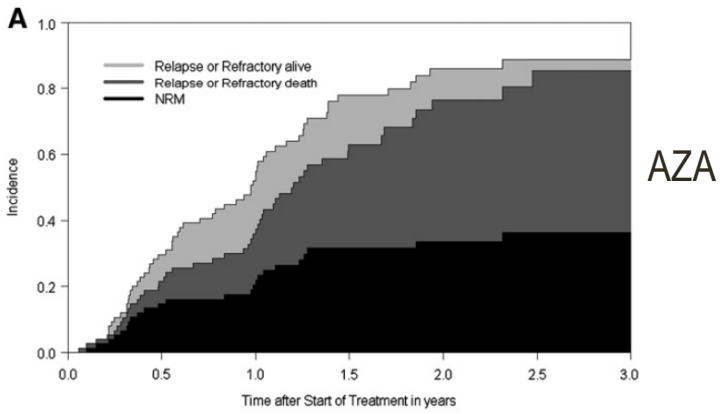


Malcovati L et al. Blood 2013

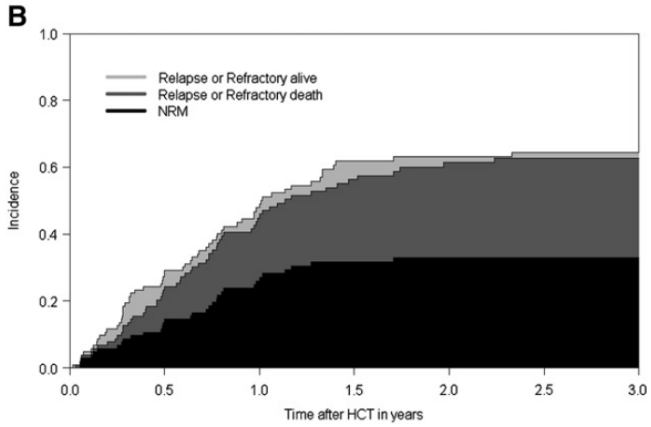
Allo-HSCT vs 5-Aza in pts with MDS or sAML aged 60 to 70







AZA



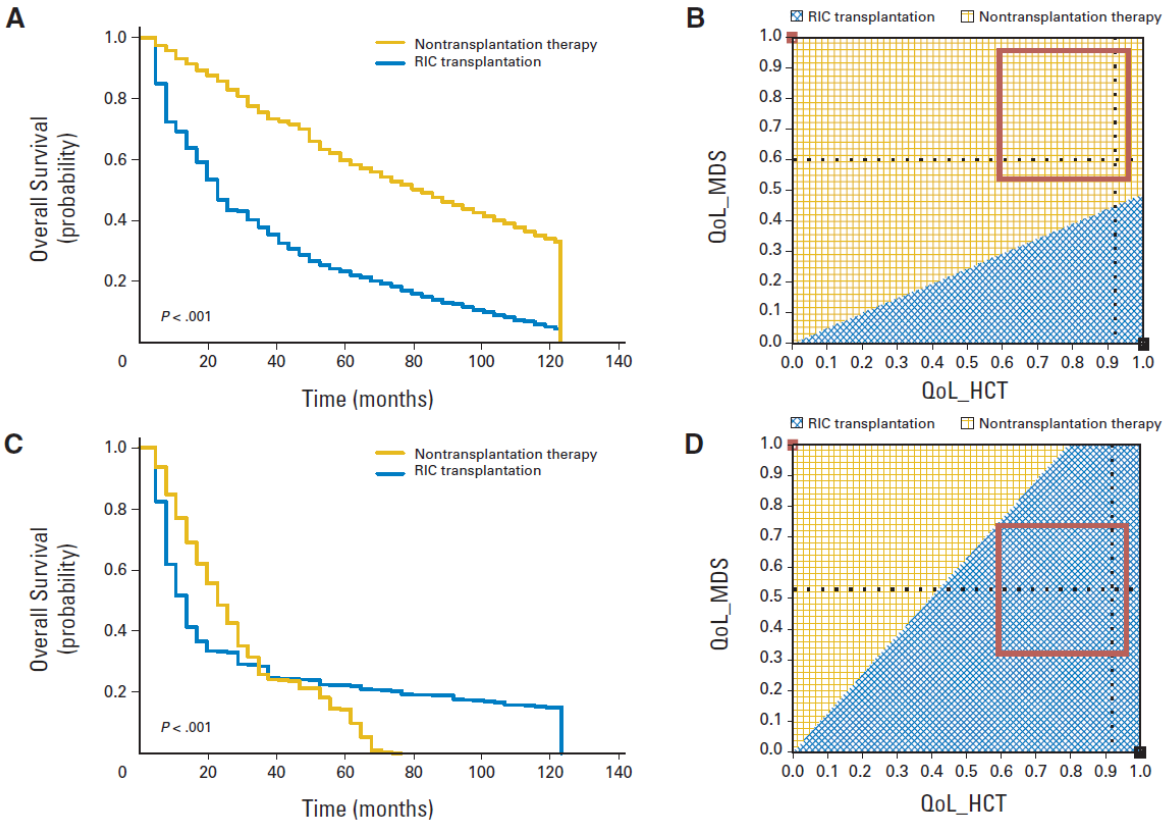
SCT

Platzbecker et al. BBMT 2012;18:1415-1421

RIC-allo SCT in older patients with de novo MDS

IPSS Low/Interm-1

IPSS Interm-2/High



Koreth J et al. JCO 2013;31:2662-2670

Allo-SCT vs non-transplant approaches in older pts with MDS

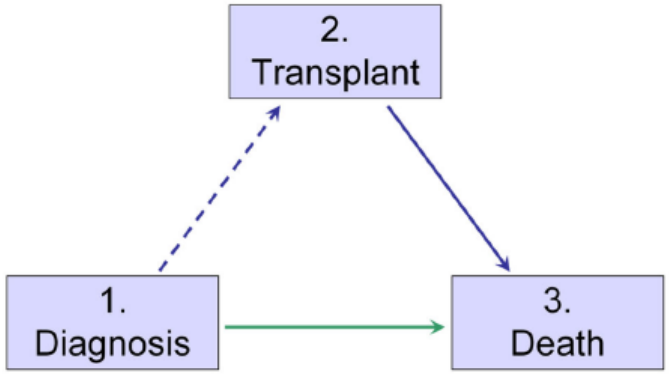
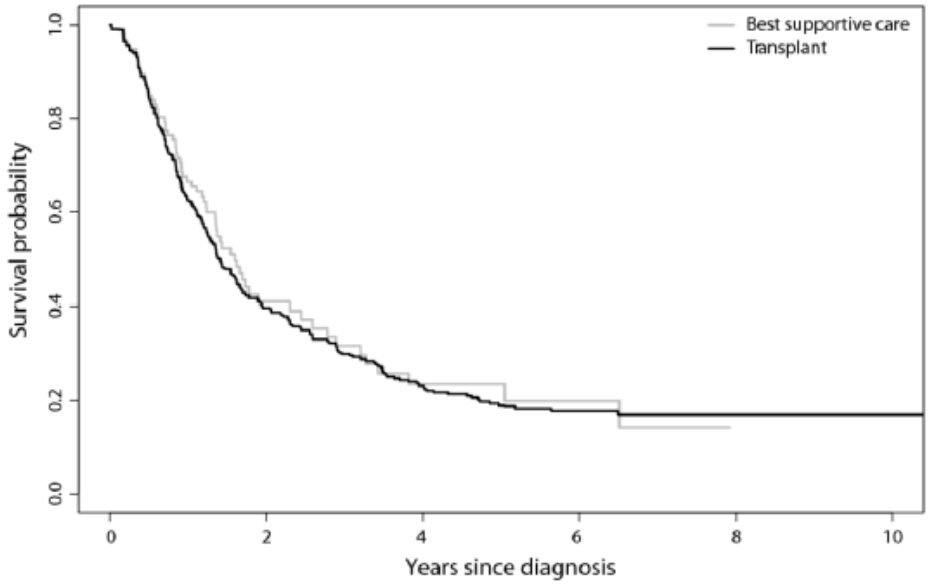


Figure 1. Multi-state model comparing transplant vs. non-transplant approach in elderly (55-69y) MDS patients.

HSCT = 247 pts (EBMT)

Vs

BSC = 137 pts (Dűsseldorf)



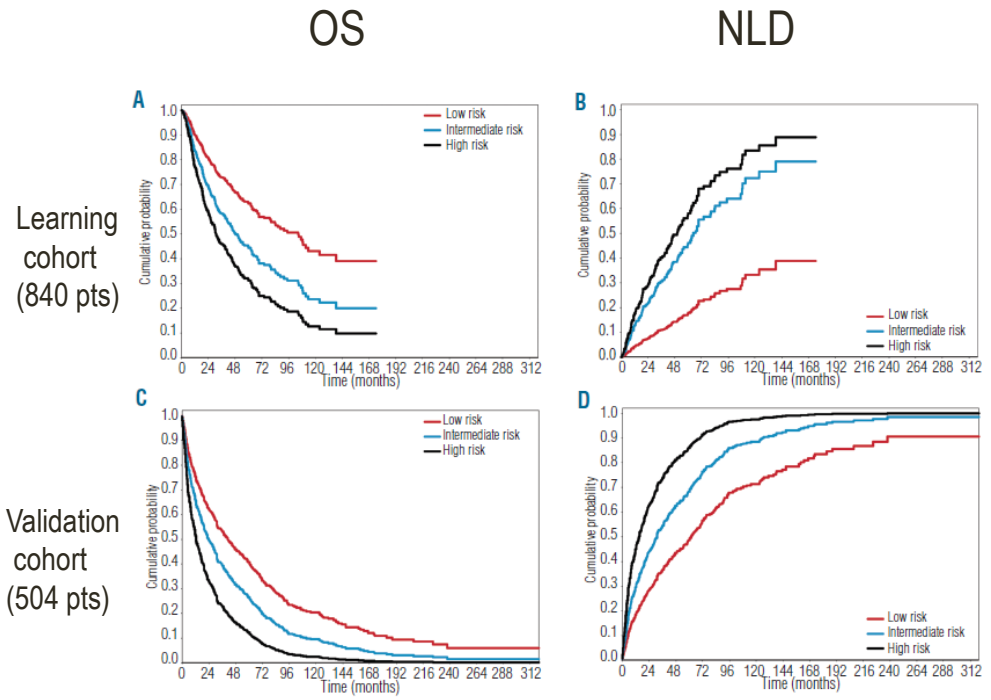
Brand R et al. Plos One 2013;8:e74368

Time-dependent MDS-specific Comorbidity Index

Comorbidity	HR obtained through a multivariable Cox's survival analysis with NLD as an outcome	Variable weighted score (to be taken into account if the specific comorbidity is present)
Cardiac disease	3.57 (P<0.001)	2
Moderate-to-severe hepatic disease	2.55 (P=0.01)	1
Severe pulmonary disease	2.44 (P=0.005)	1
Renal disease	1.97 (P=0.04)	1
Solid tumor	2.61 (P<0.001)	1

MDS-CI risk	Sum of individual variable scores	Proportion of patients in the learning cohort belonging to the risk group (%)
Low risk	0	546/840 (65%)
Intermediate risk	1-2	244/840 (29%)
High risk	>2	50/840 (6%)

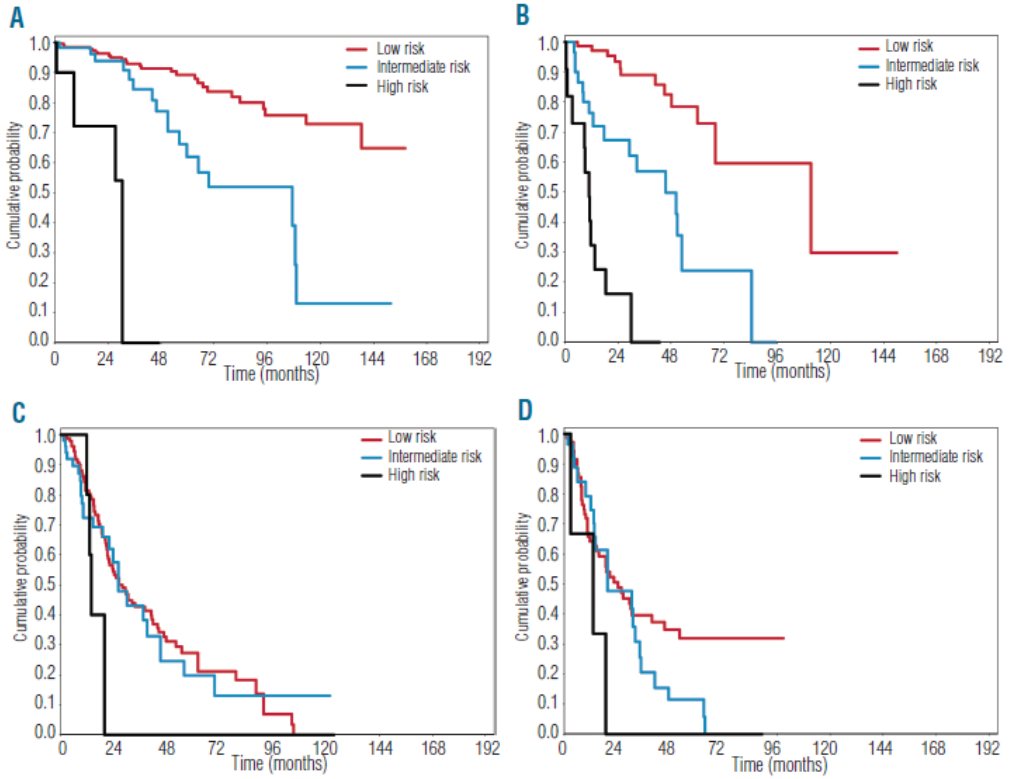
NLD: non-leukemic death.



Della Porta M et al. Haematologica 2011;96:441-449

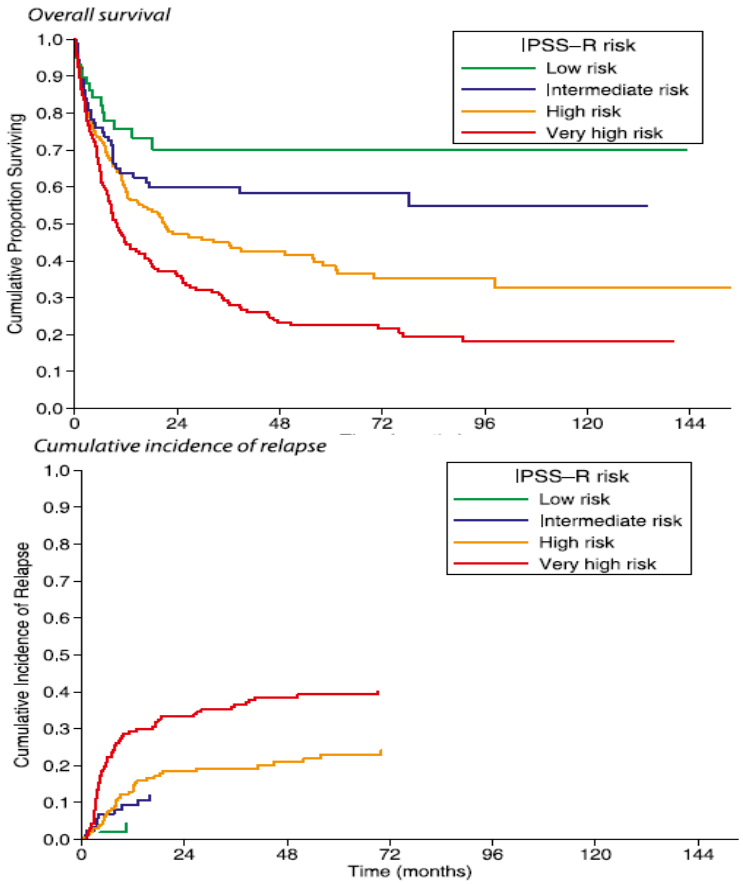
Impact of the MDS-CI in the WPSS risk groups

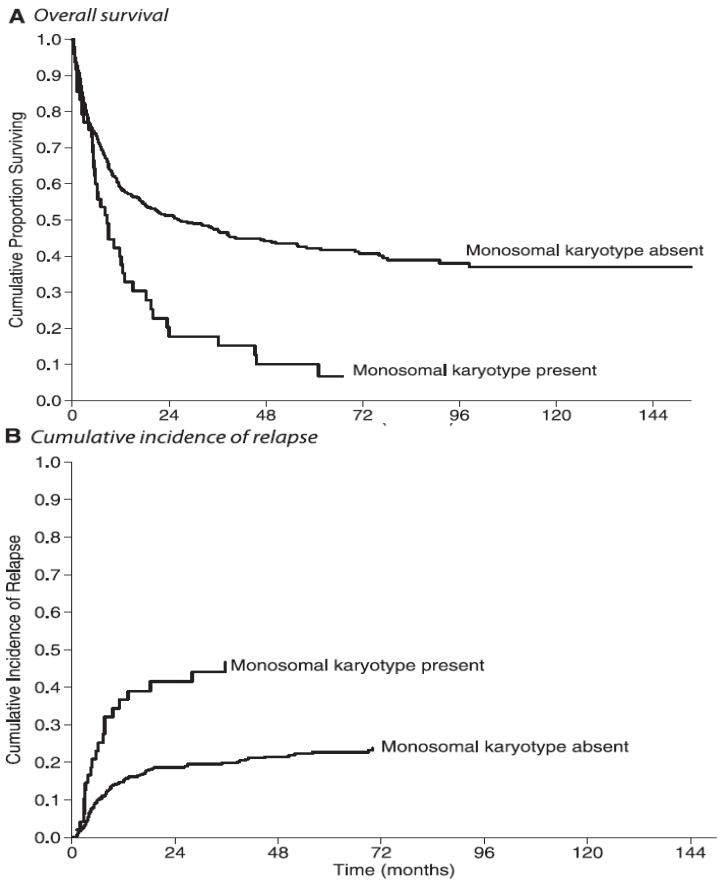
A. Very Low / Low-risk
B. Intermediate-risk
C. High-risk
D. Very High-risk



Della Porta M et al. Haematologica 2011;96:441-449

Survival and cumulative incidence of relapse following allogeneic HSCT in MDS patients stratified according to IPSS-R risk





Della Porta M G et al. Blood 2014;123:2333-2342

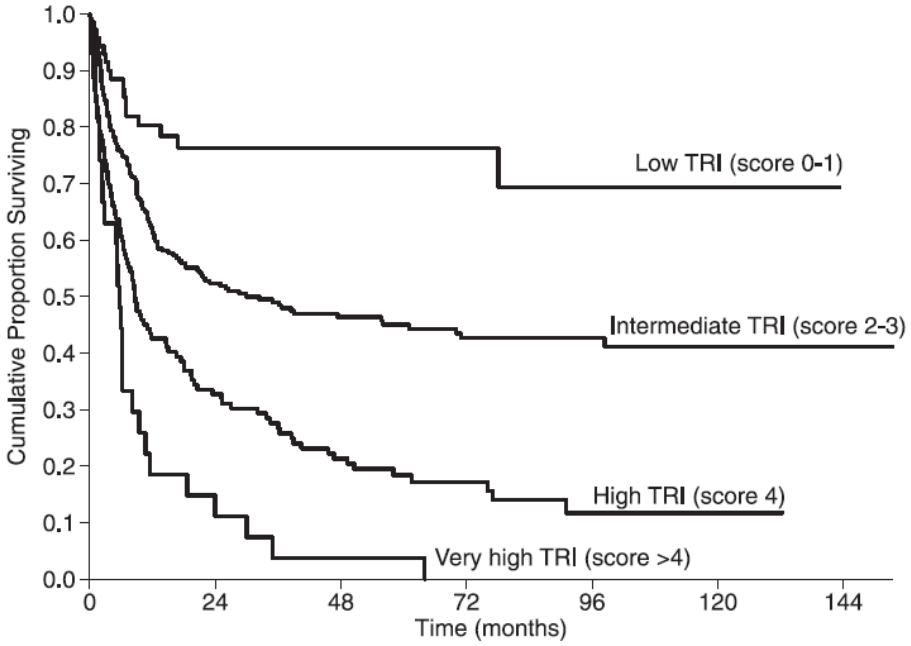
Patient-based and disease status–based risk stratification of outcome among MDS patients receiving allogeneic HSCT

A *MDS transplantation risk index (TRI) calculation*

Prognostic variable	Score values			
	0	1	2	3
Age, yr	<50	≥50	-	-
IPSS-R	low	intermediate	high	very high
Monosomal karyotype	no	yes	-	-
HCT-CI	low/intermediate	high	-	-
Refractoriness to induction chemotherapy	no	yes	-	-

TRI is calculated as the sum of individual score values

B *Posttransplantation outcome according to TRI*



Matteo G. Della Porta et al. Blood 2014;123:2333-2342

Risk factors associated to transplantation delay

- **Disease progression**
- Infectious complications
- Transfusion refractoriness
- Iron overload (secondary to transfusions)
- Performance status decline
- Additional comorbidities
- Older age

Higher risk of nonrelapse mortality

Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. A GITMO study.

TABLE II. Estimated Gains or Losses in Life Expectancy (Years) According to Different Transplantation Policies and Variable Patient's Age

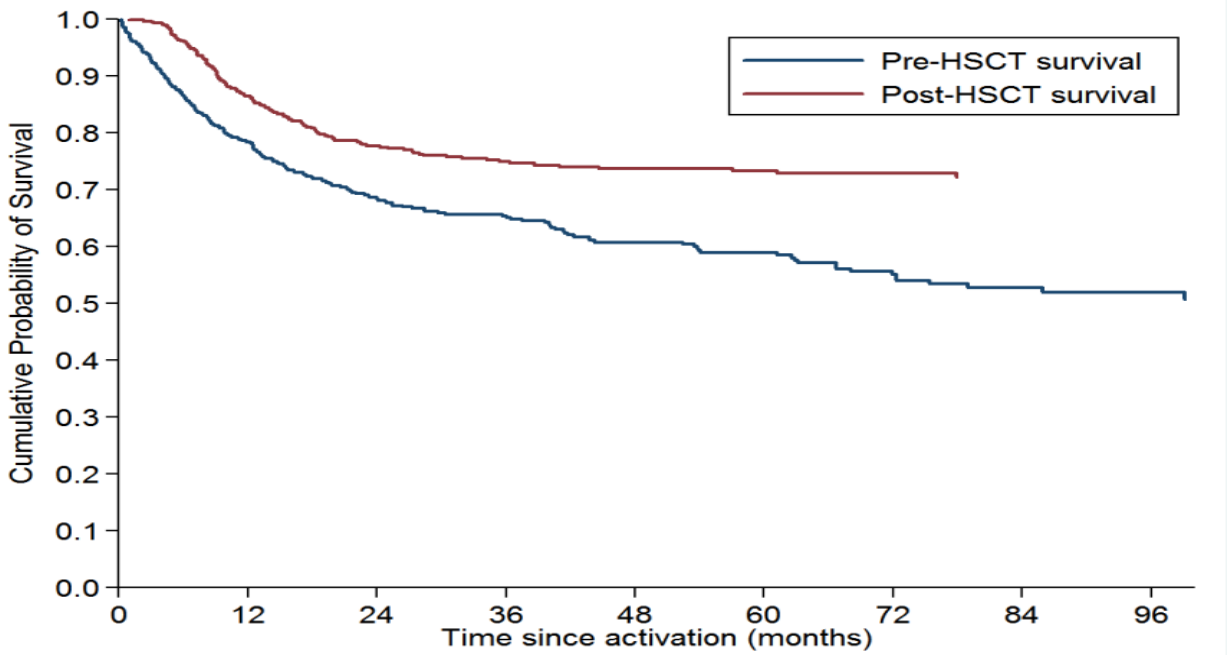
IPSS-based transplantation policies	Delay time (months)	Patient's age (years) 40	50	60	WPSS-based transplantation policies	Delay time (months)	Patient's age (years) 40	50	60
Policy 1: transplantation in low IPSS risk	0	−0.60	−0.60	−0.60	Policy 1: transplantation in low WPSS risk	0	7.05	6.53	3.97
	12	0.09	0.09	0.09		12	7.82	7.16	3.88
	24	0.71	0.71	0.71		24	8.44	7.64	3.68
	48	1.80	1.80	1.80		48	9.34	8.27	3.05
	60	2.27	2.27	2.65		60	9.67	8.48	2.67
Policy 2: transplantation in intermediate-1 IPSS risk	0	6.37	5.38	2.67	Policy 2: transplantation in intermediate WPSS risk	0	10.77	8.66	2.67
	12	5.11	4.25	1.82		12	7.29	5.67	1.33
	24	4.18	3.41	1.21		24	5.15	3.88	0.68
	48	2.95	2.32	0.51		48	3.04	2.18	0.28
	60	2.58	2.00	0.32		60	2.55	1.81	0.25
Policy 3: transplantation in intermediate-2 IPSS risk	0	1.44	1.09	0.32	Policy 3: transplantation in high WPSS risk	0	2.24	2.18	0.73
	12	1.08	0.79	0.19		12	1.63	1.30	0.20
	24	0.96	0.69	0.16		24	1.39	1.00	0.09
	48	0.91	0.65	0.16		48	1.28	0.87	0.10
	60	0.90	0.65	0.15		60	1.26	0.86	0.09

Alessandrino EP et al. Am. J. Hematol. 2013;88:581–588.

Impact of time spent waiting for a suitable unrelated donor on the outcome of patients with MDS candidate to allogeneic SCT

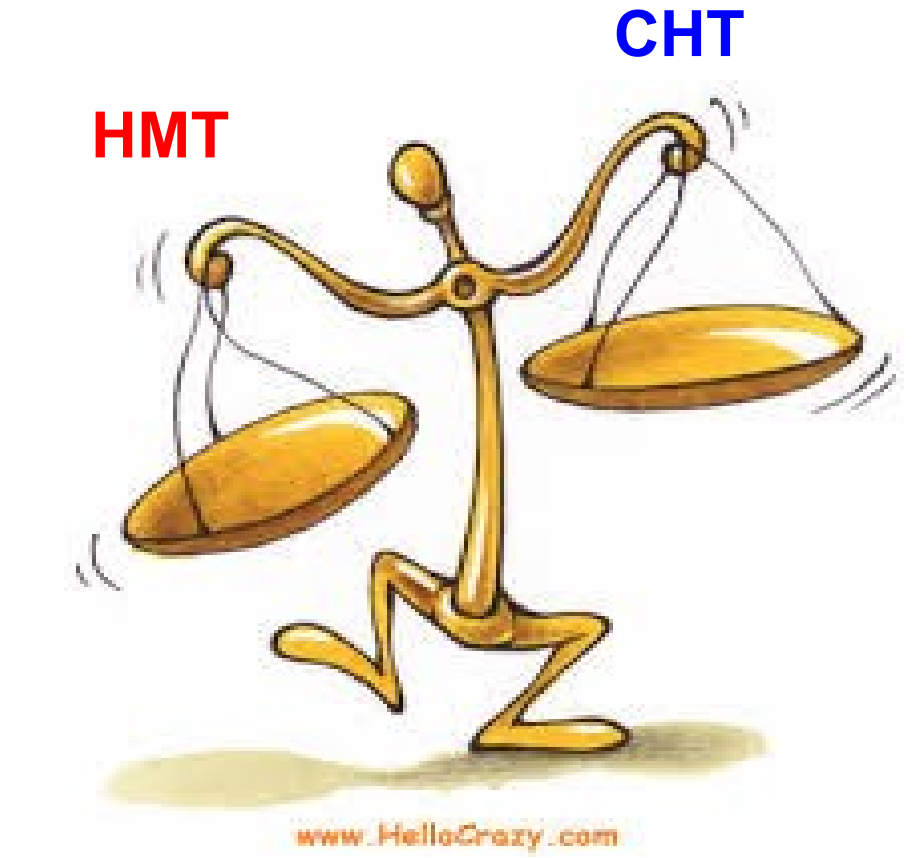
Cumulative probability of surviving while waiting for a suitable unrelated donor, UD

Cumulative probability of surviving after receiving allo-SCT



Della Porta M. et al. - Submitted

The challenge of pre-transplant induction



- Better Tolerability
- Disease control, with less CR

- More CR
- Significant side effects

Courtesy of MT Voso

Should cytoreductive treatment be performed before transplantation in patients with high-risk myelodysplastic syndrome?

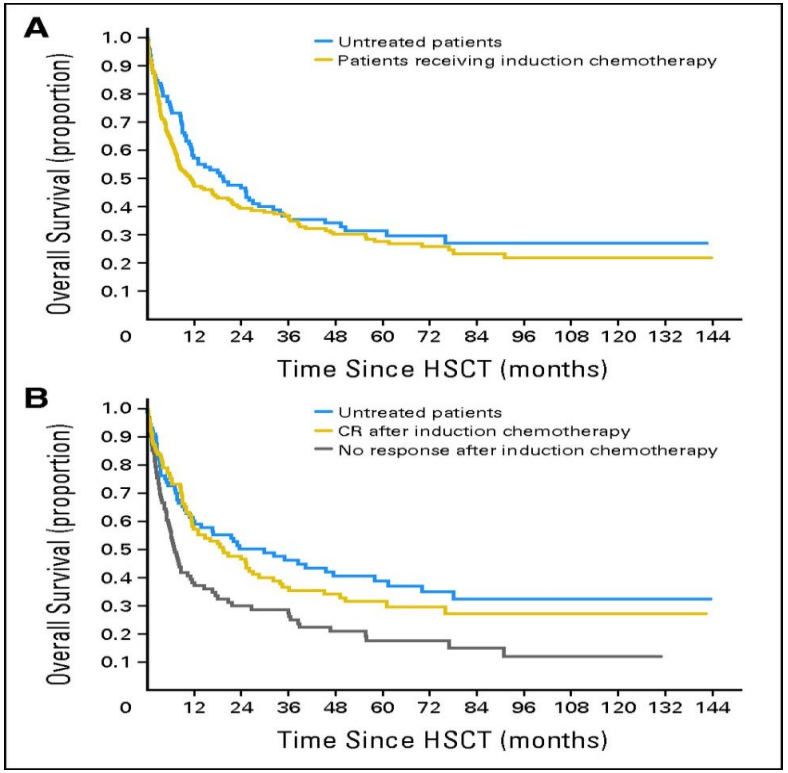
-457 pts with Int-2 and high-risk [GITMO registry]

-CR 99/209 patients (47%)

-multivariate: ICT no benefit on outcome

<u>CR vs no Response</u>:
sAML p=0.007
RAEB1 + RAEB 2 p= ns

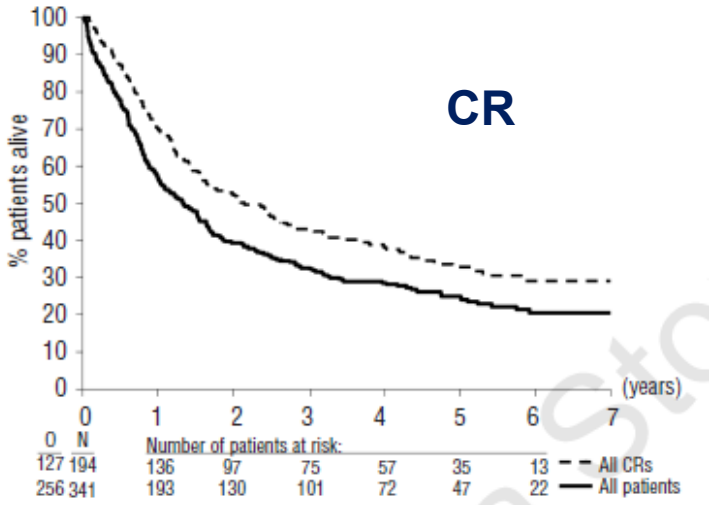
Do not delay SCT to perform a cytoreductive treatment



Alessandrino EP et al. JCO 2013;31:2761-2762

Intensive CHT: CRIANT Study (1-2 ICE, 1 HDARAC/Ida)

- 341 evaluable patients, median age: 51 years (range, 16-67 years).
- FAB: 7 RA, 2 RARS, 104 RAEB, 131 RAEB-t, 20 CMML, 77 sAML
- CR was achieved in 173 patients (51%) after 1 course and in 194 (57%) after 1-2 courses. The remaining patients had either resistant disease, persistent hyperplasia or died before hematopoietic recovery.
- Allo-SCT was administered to 56 pts (16%).
- The median survival was 1.3 years (95% CI, 1.0 - 1.7 years) and the 4-year survival rate was 28%
- CGs were the most significant disease-associated prognostic factor



4-yr survival rate according to CGs:

- Good-risk = 44%
- Interm-risk = 28%
- High-risk = 9%

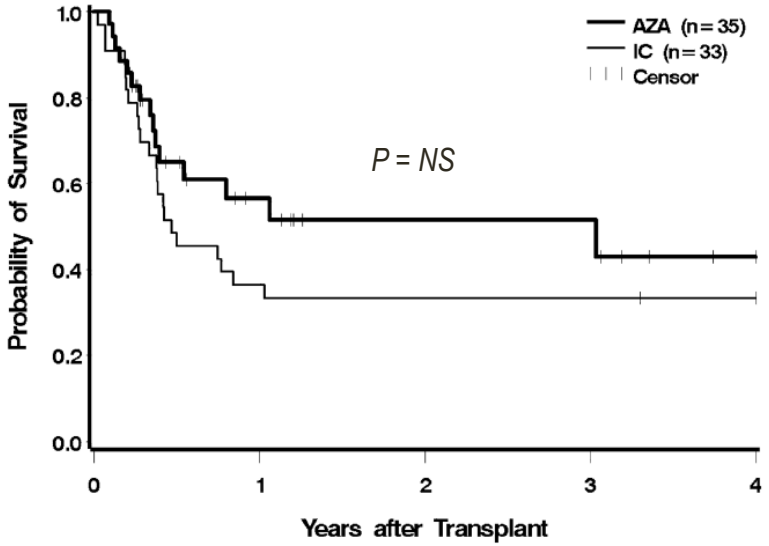
De Witte et al, Haematologica 2010

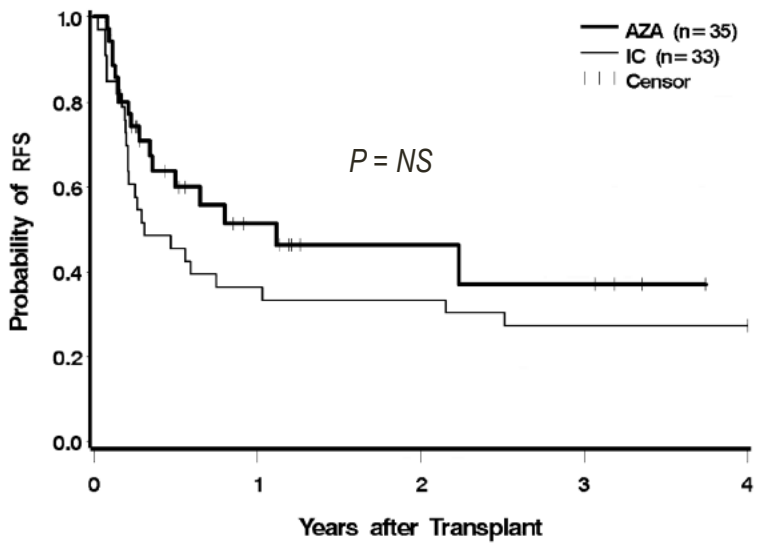
Pre-Transplant Therapy with Azacitidine Versus Induction Chemotherapy and Post-Transplant Outcome in Patients with MDS

Aaron T. Gerds, M.D.[1,2], **Ted A. Gooley, Ph.D.**[1,2], **Elihu H. Estey, M.D.**[1,2], **Frederick R. Appelbaum, M.D.**[1,2], **H. Joachim Deeg, M.D.**[1,2], and **Bart L. Scott, M.D.**[1,2]

[1]Fred Hutchinson Cancer Research Center, Seattle, Washington

[2]University of Washington School of Medicine, Seattle, Washington



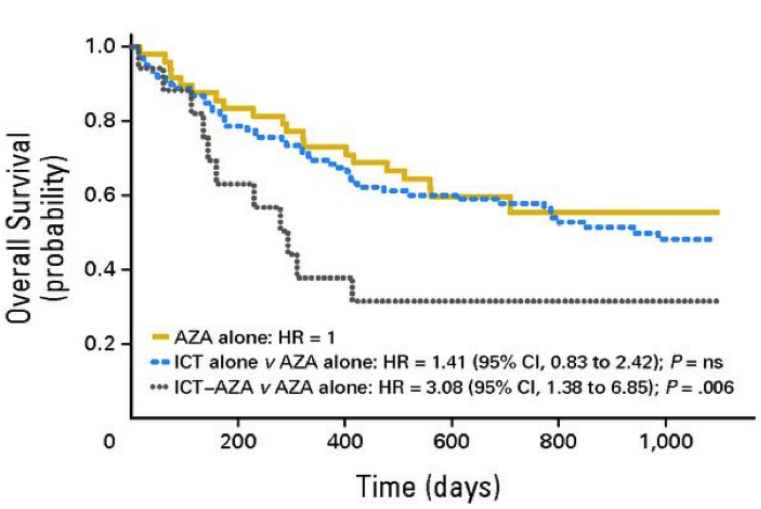


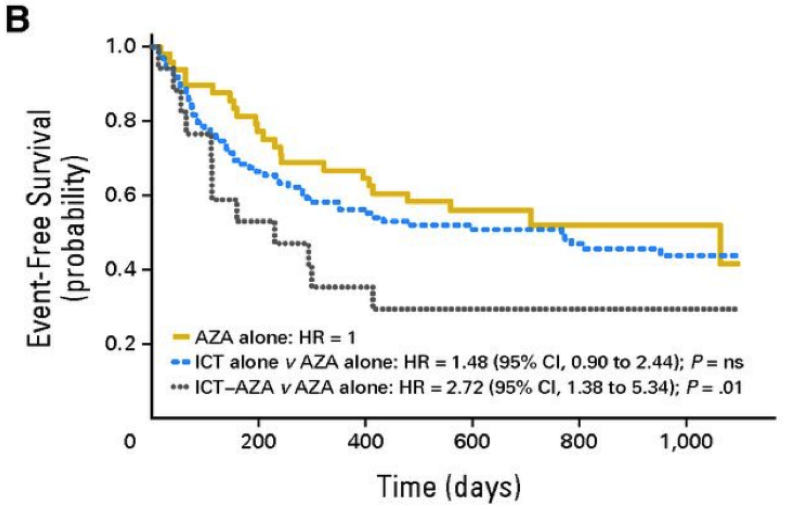
Gerds AT et al. BBMT 2012;18(8):1211-1218

Choice of therapy prior to allogeneic HSCT in MDS patients

2005-2009: 163/265 received cytoreductive treatment prior to allo-SCT

- ICT = 98
- 5-AZA = 48
- AZA-ICT = 17





Multivariate analysis: no differences between the AZA and the ICT groups in terms of OS, EFS, relapse, and NRM

Damaj G et al. JCO 2012;30:4533-4540

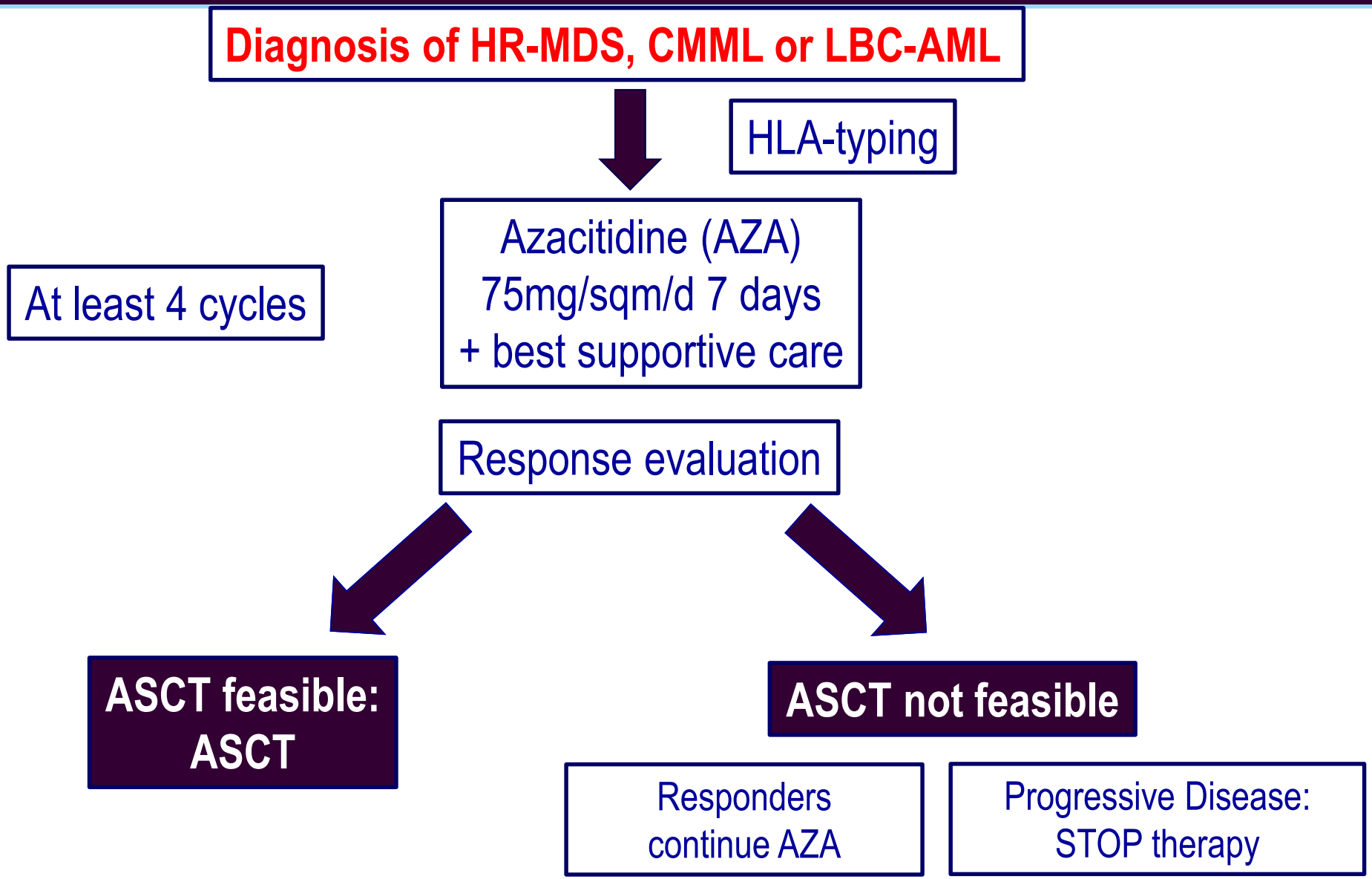
BMT-AZA Protocol

Feasibililty of Azacitidine As Bridge to Allogeneic Stem Cell Transplantation in Patients with Higher-Risk MDS or Low-Blast Count AML (LBC-AML): Results of the BMT-AZA Multicenter Prospective Study

Maria Teresa Voso, Giuseppe Leone, Alfonso Piciocchi, Luana Fianchi, Paolo Di Bartolomeo, Anna Candoni, Marianna Criscuolo, Arianna Masciulli, Elisa Cerqui, Alfredo Molteni,
Carlo Finelli, Matteo Parma, Flavia Rivellini, Nicola Cascavilla, Francesco Spina,
Agostino Cortelezzi, Flavia Salvi, Mauro Montanari, Emilio Paolo Alessandrino,
Alessandro Rambaldi, and Simona Sica
On behalf of GITMO ONLUS

Courtesy of M.T. Voso

BMT-AZA Protocol



Study Endpoints

Primary

- Rate of ASCT after first-line AZA

Secondary

- OS, DFS at 1 year
- Time to AML progression at 1 year
- Rate of transplant-related mortality (TRM)

Baseline patient characteristics (n=97)

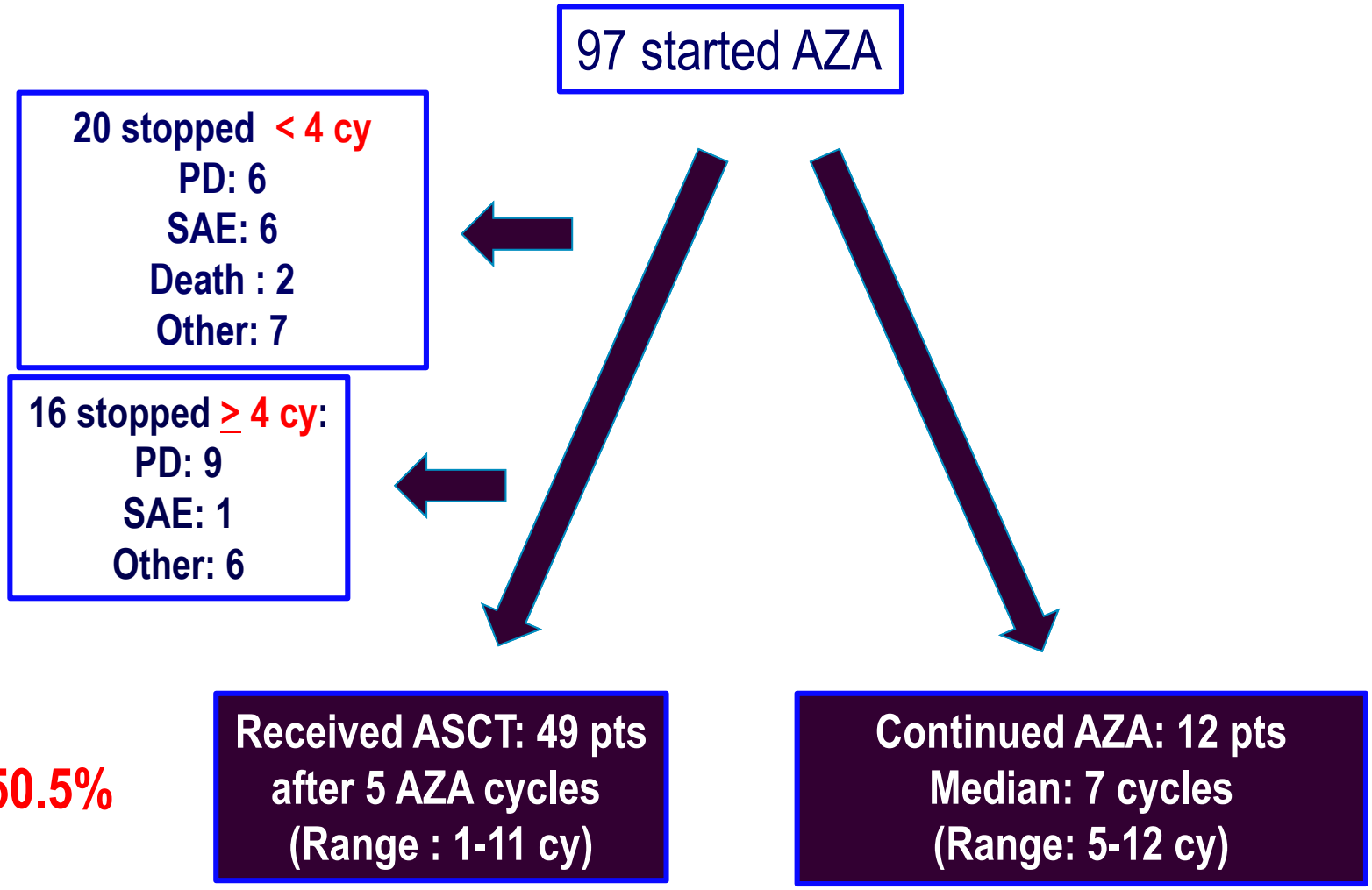
		n (median, range)
Age		59.1 (21-66)
Disease duration (months)		0.87 (0-105)
Blast BM		15 (0-30)
ECOG	0 1 2	70 (72%) 17 (17.5%) 10 (10%)
WHO	RA/RCMD RAEB AML (20-30%) CMML	6 (6%) 67 (69%) 16 (16.5%) 8 (8%)
Karyotype (n=90)	Normal Abnormal	33 (37%) 57 (63%)

Risk Scores

		n (%)
IPSS (n=90)	Low/Int-1 Int-2 High	2 (2%) 44 (49%) 44 (49%)
WPSS (n=73)	Low/Interm. High Very high	9 (12%) 43 (59%) 21 (29%)
R-IPSS (n=68)	Very low/low Intermediate High Very high	4 (6%) 10 (15%) 22 (32%) 32 (47%)
HCT-CI*	Low (0) Intermed. (1-2) High (≥3)	46 (47%) 41 (42%) 10 (10%)

Sorror et al, Blood 2005

Patient Flow



50.5%

Response to AZA

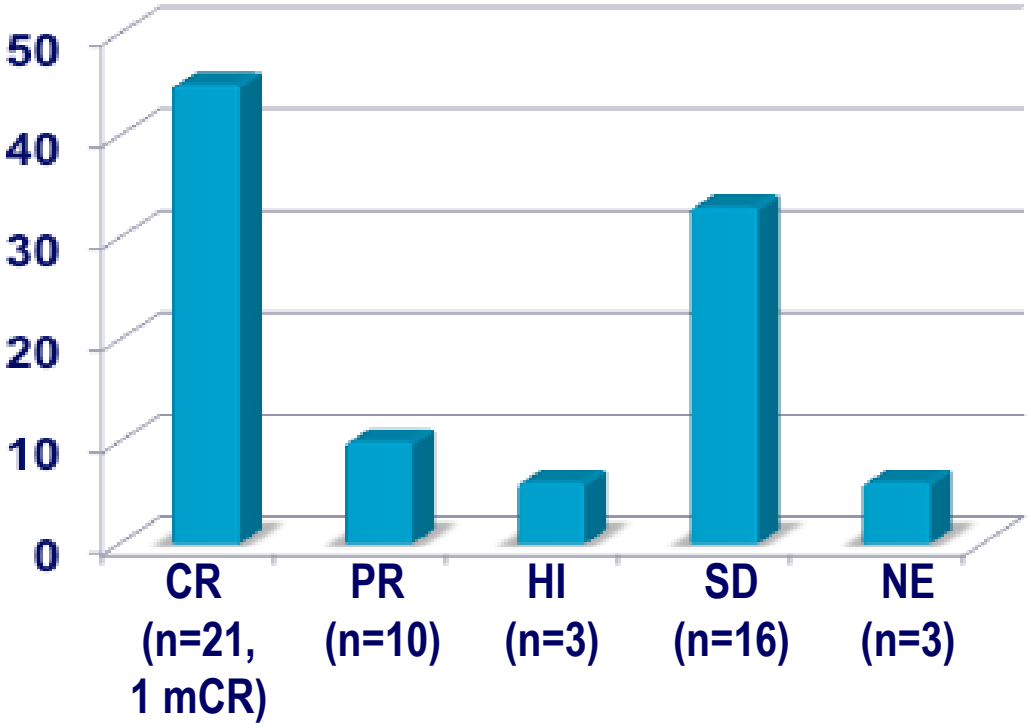
After at least 4 Cycles (range 4-11)

	76 pts	%
Complete Remission (CR)	21	28
Partial Remission	11	14.5
Hematologic Improvement	7	9
Stable Disease	27	35.5
Progressive Disease	10	13

ORR: 51%

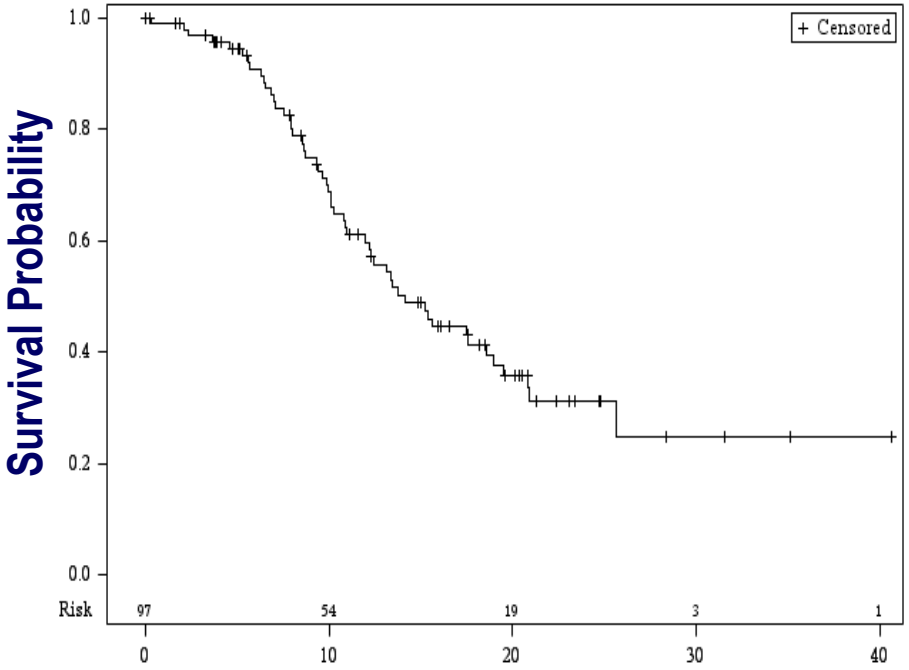
Status at ASCT

ASCT was performed in 49 patients (50.5%),
after a median of 5.0 (range: 1-11) azacitidine cycles



Survival Analysis 1.

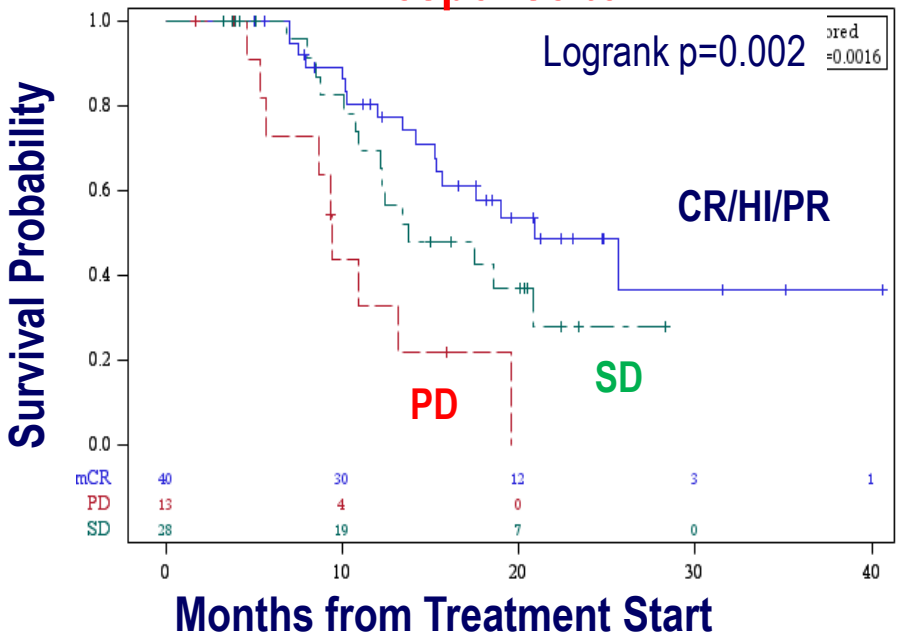
Overall Survival (ITT analysis)
Median Follow-up: 20.3 months (1.0-40.6)



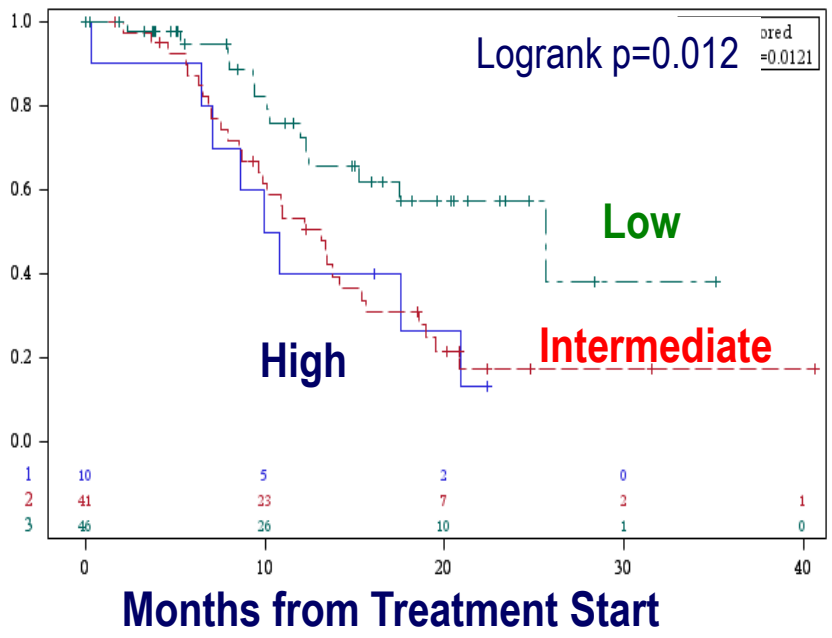
Months	OS (%)	95% CI
12	61.0	51.3-72.6
24	31.2	21.5-45.2

Survival Analysis 2.

Response to AZA



HCT-CI Index



- In the multivariable analysis, treatment response and HCT-CI index were independent prognostic factors for survival
- ASCT considered as time-dependent covariate is associated to significantly longer survival (p=0.018, HR 0.47, 95% C.I. 0.25-0.88)

→ Median OS for ASCT: 20.8 months (6.8-40.6) vs 9.7 months (0.23-21.3)

Conclusions

- ASCT is feasible after AZA treatment in HR-MDS or LBC-AML, with 50% of patients undergoing ASCT
- Independent factors for OS and PFS were response to azacitidine and HCT-CI
- ASCT as time-dependent variable was associated with prolonged survival
- Relapse was the most frequent cause of death in pts not receiving ASCT
- Biologic ancillary studies are ongoing

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

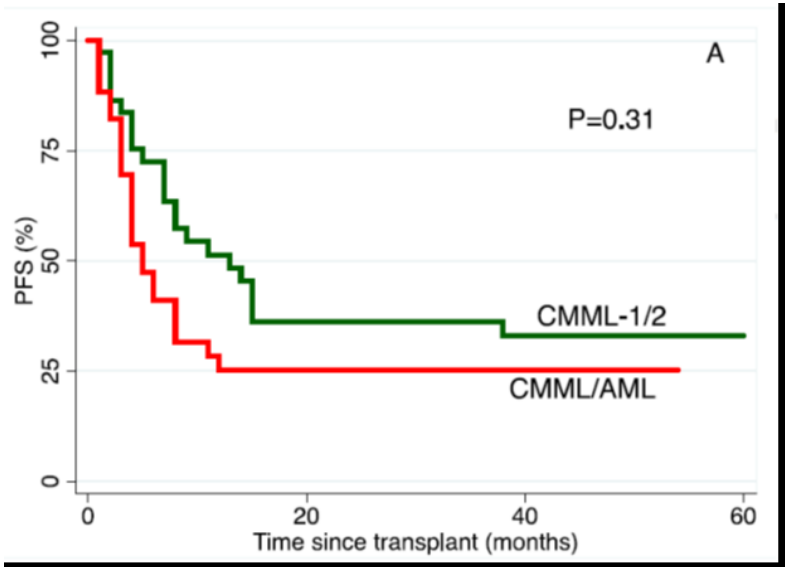
Clinical Research: Adult

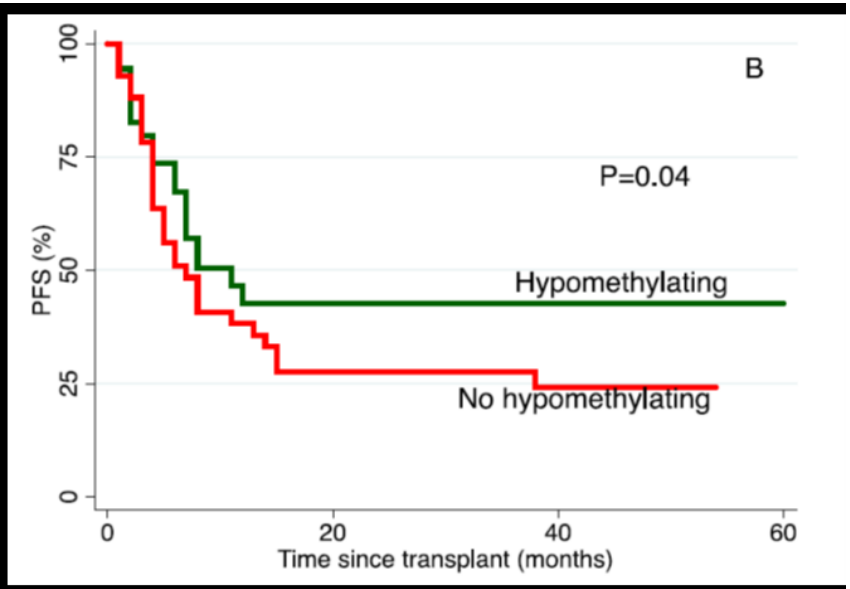
Treatment with Hypomethylating Agents before Allogeneic Stem Cell Transplant Improves Progression-Free Survival for Patients with Chronic Myelomonocytic Leukemia

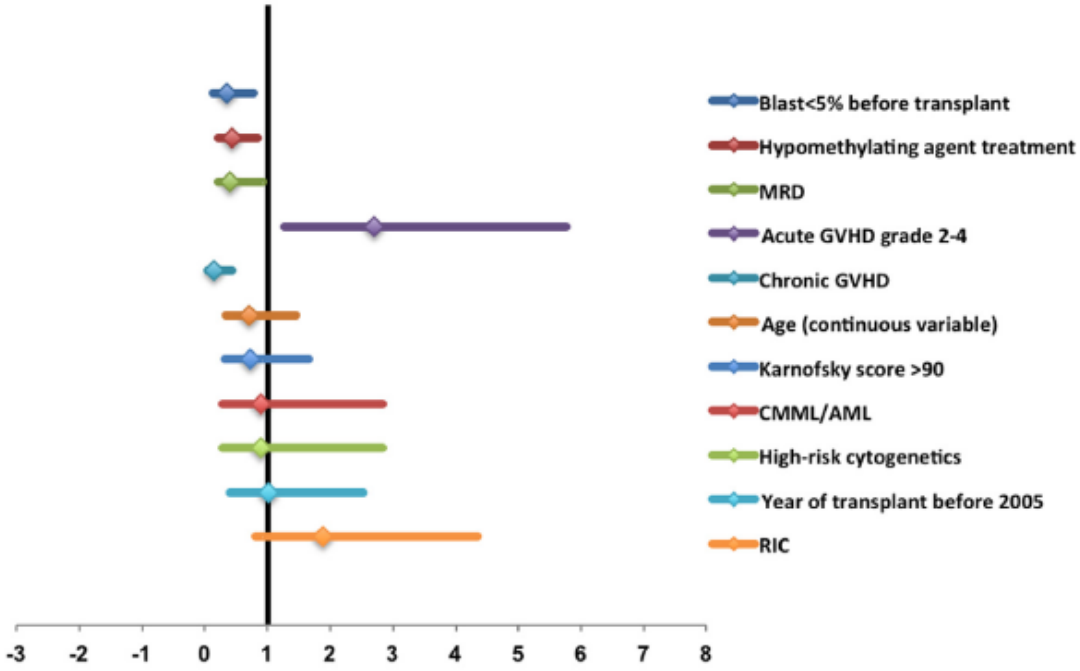
83 consecutive pts (1991-2013): 47 CMML1/2 (57%) / 36 AML from CMML (43%)
Median age 57 (range 18-78), >60 yrs in 40%
78 (94%) received «induction» treatment: 37 HMAs, 41 CHT (mostly 1-2 courses of 3+7 Ida+Ara-C or CIA)

Outcome	All pts	CMML 1-2	AML post CMML	p	HMA	CHT	p
Relapse	33%	35%	27%	NS	**22%**	**35%**	**0.03**
1-yr NRM	31%	29%	35%	NS	27%	30%	NS
3-yrs OS	35%	36%	32%	NS	45%	39%	NS
3-yrs PFS	34%	35%	27%	NS	**43%**	**27%**	**0.04**

Kongtim P et al. BBMT 2016







Kongtim P et al. BBMT 2016

HMAs in AML

- Epigenetic changes are frequent in AML (aberrant DNA methylation and mutations of epigenetic modifiers such as DNA methyltransferase 3A)

- DNA methylation an attractive therapy target in myeloid disorders

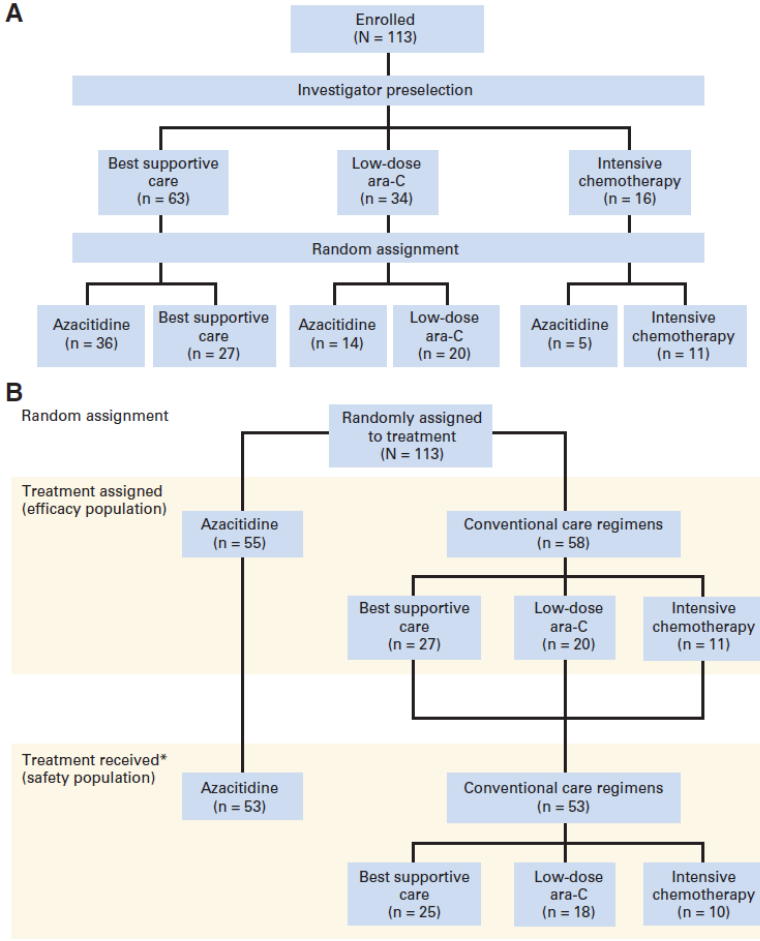
Table 1. Clinical outcome of phase 3 trials of azacitidine and decitabine in acute myeloid leukemia (AML).

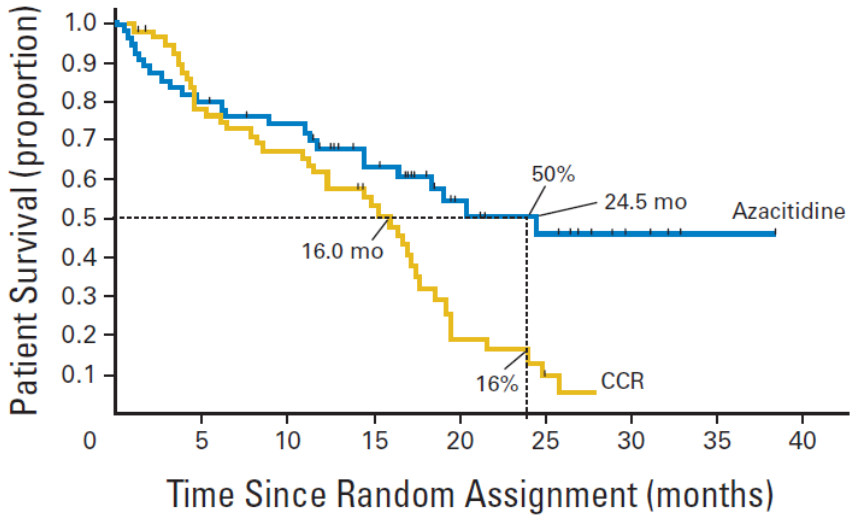
Azacitidine (7 Days 75 mg/m² SC; Every 4 Weeks)				
Study	**Competitors**	**CR (%)**	**Median OS**	**1/2-Year OS**
Post hoc analysis CALGB 9221 (AML 20%–30% blasts) [11]	AZA (n = 27) *vs.* Observation (n = 12)	7% *vs.* 0%	19.3 months *vs.* NA; Combining CALGB 8421, 8921, 9221: 12.9 months (n = 25; p = NA)	NA
Post hoc analysis AZA001 study (AML 20%–30% blasts) [12]	Aza (n = 55) *vs.* CCR (n = 58) (BSC = 27/LDAC = 20/IC = 11)	18% *vs.* 16%	24.5 months *vs.* 16 months (p = 0.005)	50% *vs.* 16% (p = 0.001) (2-year C
AML001 study (AML >30% blasts) [13]	Aza (n = 241) *vs.* CCR (n = 247) (BSC = 45/LDAC = 158/IC = 44)	20% *vs.* 22%	10.4 months *vs.* 6.5 months (p = 0.08). Analysis censored for subsequent Tx: 12.1 months *vs.* 6.9 months (p = 0.01)	46.5% *vs.* 34.2% (p = NA) (1-year O
Decitabine (5 Days 20 mg/m² IV; Every 4 Weeks)				
DACO-016 (AML >20% blasts; only intermediate and poor risk) [19]	Decit (n = 242) *vs.* TC (n = 243) (BSC = 28/LDAC = 215)	15.7% *vs.* 7.4%	7.7 months *vs.* 5.0 months (p = 0.11). Analysis censored for subsequent Tx: 8.5 months *vs.* 5.3 months (p = 0.04). Unplanned analysis after 446 deaths: 7.7 months *vs.* 5.0 months (p = 0.04)	NA

Cruijsen M et al. J Clin Med 2015,4:1-17

Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia

Pierre Fenaux, Ghulam J. Mufti, Eva Hellström-Lindberg, Valeria Santini, Norbert Gattermann, Ulrich Germing, Guillermo Sanz, Alan F. List, Steven Gore, John F. Seymour, Hervé Dombret, Jay Backstrom, Linda Zimmerman, David McKenzie, C.L. Beach, and Lewis R. Silverman





No. of patients at risk

Azacitidine	55	43	38	26	15	10	4	1	0
CCR	58	43	36	22	6	3	0	0	0

Fenaux et al. JCO 2010, 28: 562-569

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

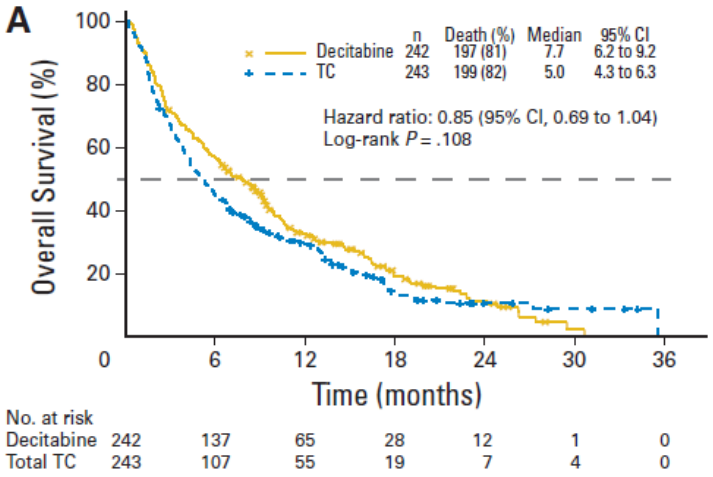
Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia

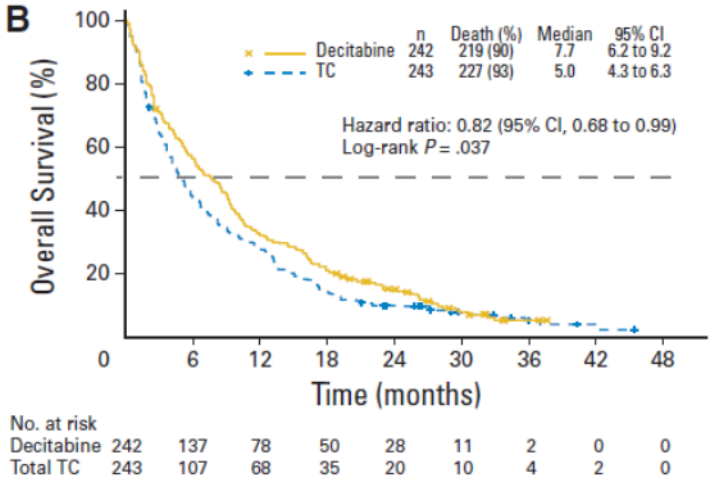
Hagop M. Kantarjian, Xavier G. Thomas, Anna Dmoszynska, Agnieszka Wierzbowska, Grzegorz Mazur, Jiri Mayer, Jyh-Pyng Gau, Wen-Chien Chou, Rena Buckstein, Jaroslav Cermak, Ching-Yuan Kuo, Albert Oriol, Farhad Ravandi, Stefan Faderl, Jacques Delaunay, Daniel Lysák, Mark Minden, and Christopher Arthur

485 pts, median age 73 yrs (65-91)
randomized 1:1

→ decitabine 20 mg/m^2/day x 5 days q28

→ supportive care or ara-C 20 mg/m^2/day sc x 10 days q28





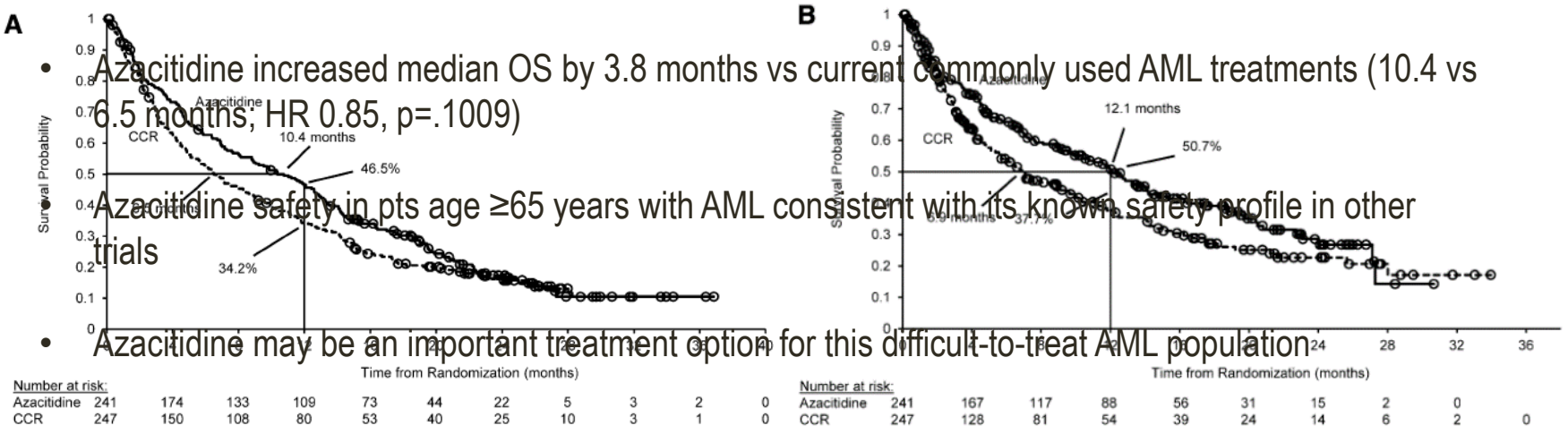
International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Hervé Dombret,[1] John F. Seymour,[2] Aleksandra Butrym,[3] Agnieszka Wierzbowska,[4] Dominik Selleslag,[5] Jun Ho Jang,[6] Rajat Kumar,[7] James Cavenagh,[8] Andre C. Schuh,[9] Anna Candoni,[10] Christian Récher,[11] Irwindeep Sandhu,[12] Teresa Bernal del Castillo,[13] Haifa Kathrin Al-Ali,[14] Giovanni Martinelli,[15] Jose Falantes,[16] Richard Noppeney,[17] Richard M. Stone,[18] Mark D. Minden,[9] Heidi McIntyre,[19] Steve Songer,[19] Lela M. Lucy,[19] C. L. Beach,[19] and Hartmut Döhner[20]

488 patients age ≥ 65 yrs
(median age 75, range 65-91)

→ Azacitidine 75 mg/m^2/day x 7 days q28 (at least 6 cycles)

→ CCRs (ICT or LD-Ara-C or BSC)



- Azacitidine increased median OS by 3.8 months vs current commonly used AML treatments (10.4 vs 6.5 months; HR 0.85, p=.1009)
- Azacitidine safety in pts age ≥65 years with AML consistent with its known safety profile in other trials
- Azacitidine may be an important treatment option for this difficult-to-treat AML population

Dombret H et al. Blood 2015, 126(3): 291-299

Rationale for combination of HMAs and Ara-C

- DNA methytransferase inhibitors azacitidine and decitabine may lead to clinical benefit but are not curative
- Inactivation of deoxycitidine kinase, which phosphorylates cytarabine to its active compound ara-CTP, has been reported as a possible mechanism of cytarabine resistance in AML
- Cytarabine sensitivity could be restored by 5-Aza *in vitro* in deoxycidine kinase-deficient leukemic cell lines
- A sinergistic effect of cytarabine and azacitidine could be anticipated when azacitidine is administered before cytarabine treatment

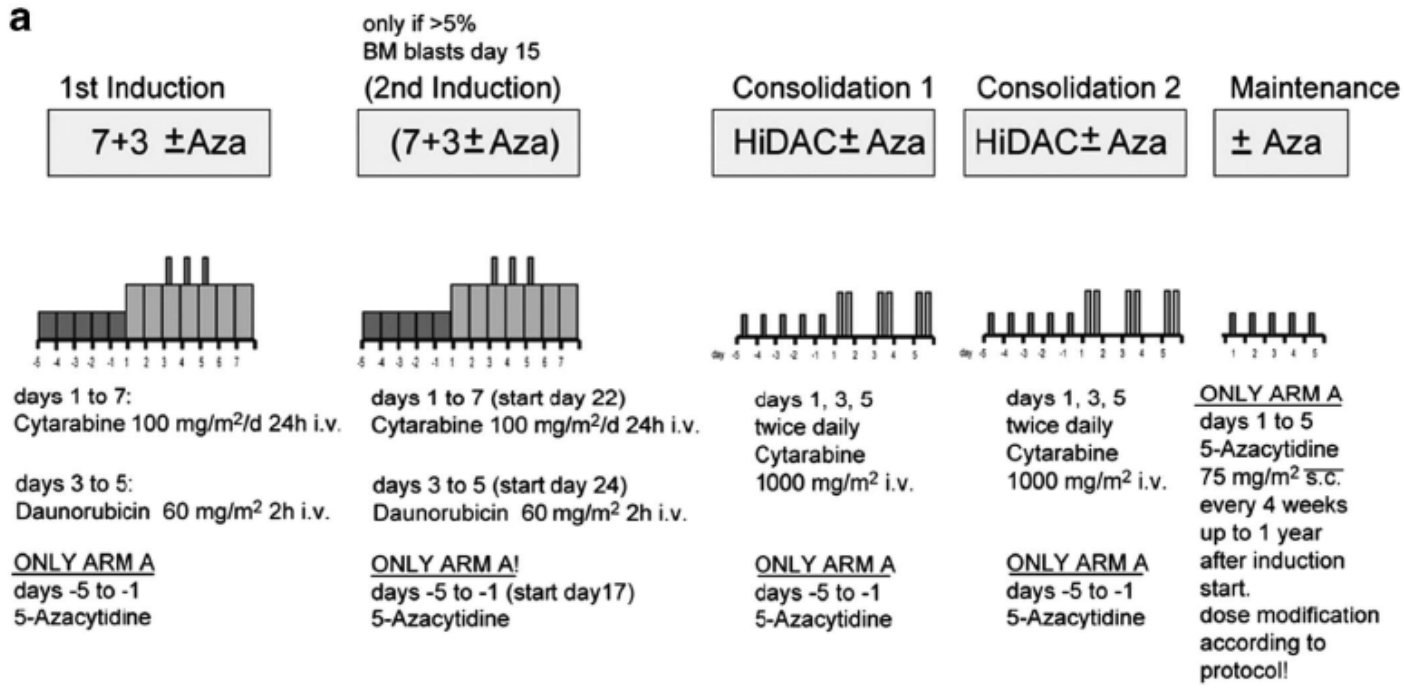
Leukemia (2015), 1–7

www.nature.com/leu

ORIGINAL ARTICLE

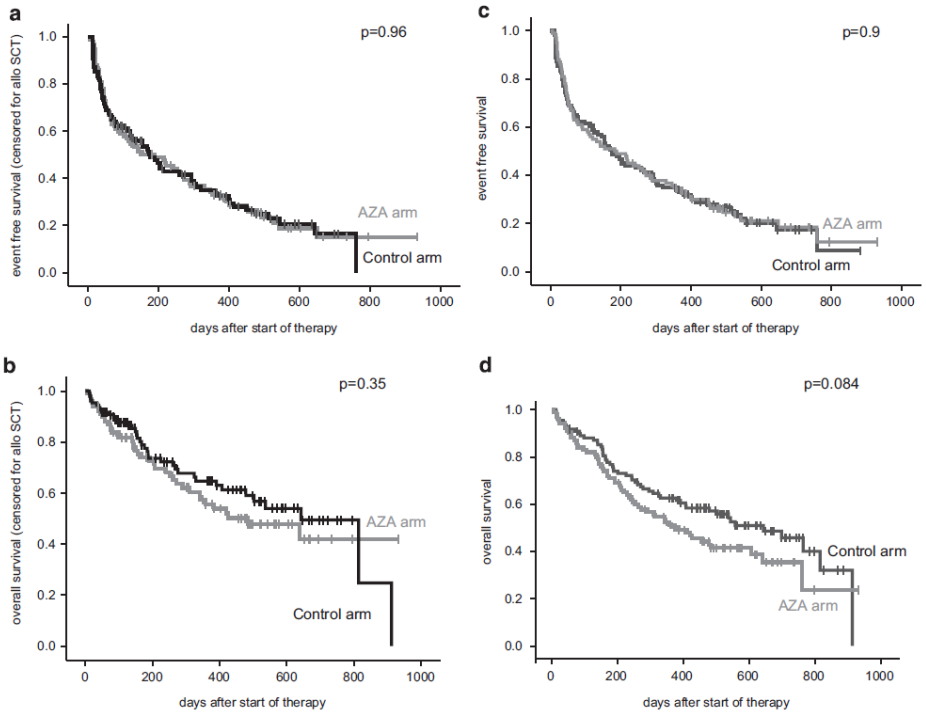
Azacitidine in combination with intensive induction chemotherapy in older patients with acute myeloid leukemia: The AML-AZA trial of the study alliance leukemia

C Müller-Tidow[1,2,32], P Tschanter[1,2,32], C Röllig[3], C Thiede[3], A Koschmieder[2,4], M Stelljes[2], S Koschmieder[2,4], M Dugas[5], J Gerss[6], T Butterfaß-Bahloul[7], R Wagner[7], M Eveslage[6], U Thiem[8], SW Krause[9], U Kaiser[10], V Kunzmann[11], B Steffen[12], R Noppeney[13], W Herr[14], CD Baldus[15], N Schmitz[16], K Götze[17], A Reichle[14], M Kaufmann[18], A Neubauer[19], K Schäfer-Eckart[20], M Hänel[21], R Peceny[22], N Frickhofen[23], M Kiehl[24], A Giagounidis[25], M Görner[26], R Repp[27], H Link[28], A Kiani[29], R Naumann[30], TH Brümmendorf[4], H Serve[12], G Ehninger[3], WE Berdel[2] and U Krug[2,31] for the Study Alliance Leukemia Group



- 214 pts randomized, median age 70 yrs
- Median EFS = 6 months in both arms

	Azacitidine		Control	
	Number (n = 100)	Percent	Number (n = 109)	Percent
Complete remission	48	48%	57	52%
Leukemia-free state	10	10%	11	10%
Total response	58	58%	68	62%
Resistant disease	24	24%	28	26%
Indeterminate cause	15	15%	12	11%
Death in aplasia	0	0%	1	1%
Unknown induction result	3	3%	0	0%



Conclusions: **azacitidine added to standard CT increases toxicity in older pts with AML providing no additional benefit for <u>unselected</u> patients**

Rationale for HMAs post-allo HSCT

- Host regulatory T cells (T_{regs}) and donor NK cells play key roles in the regulation of GvHD/GvL
- T_{regs} cells appear to suppress GvHD without decreasing GvL effect
- T_{regs} cells function is modulated by *FOXP3* gene, which is regulated by epigenetic modifications (unmethylated in normal active T_{regs})
- NK cell activity is regulated by inhibitory and activating KIR (killer-cell-immunoglobulin-like receptors), which interact with MCH class 1 molecules on target cells
- As KIR expression and variability is regulated by methylation in NK cells, treatment with HMAs may induce GvL effect by enhancing KIR expression and variability

Martino M et al. Curr Cancer Drug Targets 2013

Azacitine after allogeneic SCT

Ref	Pts (dx)	Aim	Regimen	Schedule	Median cycles	Efficacy	safety
De Lima M et al Cancer 2010	45 (AML,MDS)	MAINT	Aza	8,16,24, 32 mg/mq for 5 d starting +42 (1-4 30 day cycles)	n/r	1-yr EFS 58% 1-yr OS 77%	Grade 2-3 GvHD in 36%
Platzbecker et al, Leukemia 2012	20 (AML,MDS)	Prehen	Aza	75 mg/mq for 7 d (28 day cycles)	4	Donor CD34+ chimerism >80% in 16/20 pts	No GvHD if no previous GvHD
Craddock et al, BBMT 2016	51 [37] (HR AML)	MAINT	Aza	36 mg/mq for 5 d up to 1 y to HSCT (28 day cycles)	31 (84%) ≥3 cycles	2-yr RFS 49% CD8+ T-cell induction associated with lower RR	Grade 2 GvHD in 31% No Ext GvHD
Czibere et al, BMT 2010	22 (MDS,AML)	SALV	Aza +DLI	100 mg/mq for 5 d every 28 days. DLI in 18/22 pts	2	ORR 72%, CR 32%,	aGvHD in 6/22 pts, 4 of whom developed cGvHD
Lubbert et al, BMT 2010	23 (AML, CMML)	SALV	Aza +DLI	100 mg/mq for 3 d every 22 days. DLI on d 10 of every cycle	2	CR in 66%	GvHD in 2/23 pts
Schroeder et al, Leukemia 2013	30 (rel AML/MDS)	SALV	Aza +DLI	100 mg/mq for 5 d every 28 days. DLI after every second cycle	3 Aza 11 DLI	ORR 30% CR 23%	GvHD more common in pt achieved CR (a37%,c17%)

Conclusions and take home messages

- In MDS accurate assembling of several disease-, patient- and transplant characteristics is mandatory for individual decision making on allo-SCT and for the optimization of timing
- Allo-SCT is recommended for fit patients with high-risk MDS but also for carefully selected patients with the intermediate risk category (IPSS-R).
- Hypomethylating treatment pre-SCT is feasible, with most probable benefit in patients with less aggressive diseases
- In the absence of data from prospective trials, no definitive recommendation should be formulated about delaying allo-SCT to perform a cytoreductive treatment.
- In MDS and AML, HMAs +/- DLI post-SCT showed promising results and should be further explored in clinical trial
- Genetic profile may help patient stratification for best treatment allocation

Acknowledgements

- Matteo Della Porta, Paolo Emilio Alessandrino and the “GITMO” Group

- Maria Teresa Voso, Università Tor Vergata, Roma