ALLOGENEIC STEM CELL TRANSPLANTATION FOR MYELOID MALIGNANCIES

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PAOLI-CALMETTES
PROVENCE-ALPES-CÔTE D'AZUR

ALLOGENEIC ACTIVITY IN EUROPE

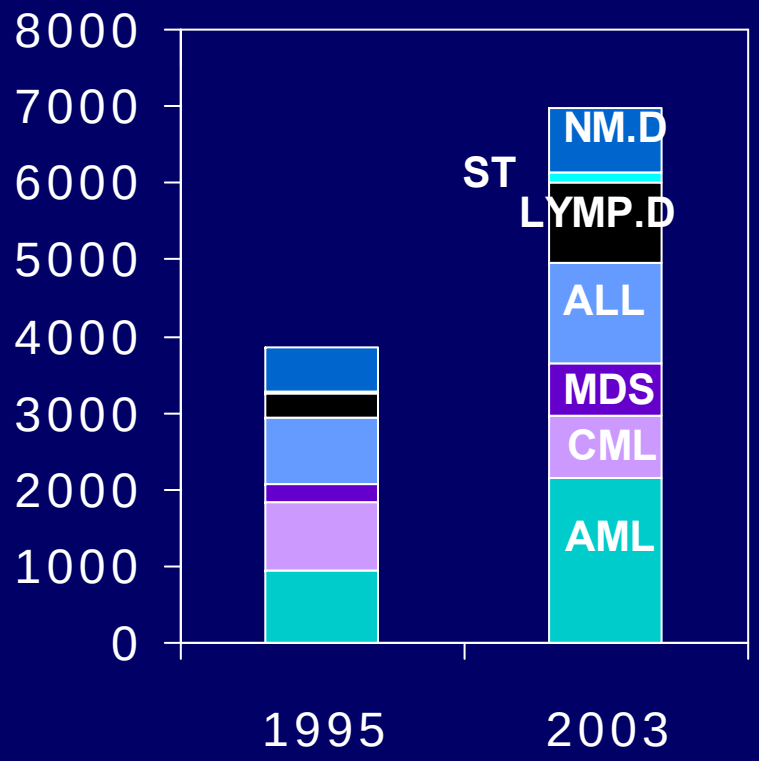
Table 1 Proposed classification of transplant procedures for adults – 2005: (a) leukaemias, (b) lymphomas, (c) other diseases

Disease	*Disease status*	*Allo*			*Auto*
		Sibling donor	*Well-matched unrelated/1 ag related*	*Mm unrelated/ >1 ag related*	
(*a*)					
AML	CR1 (low risk[a])	CO	D	GNR	CO
	CR1 (intermediate or high risk[a])	S	CO	D	S
	CR2	S	CO	D	S
	CR3, incipient relapse	S	CO	D	GNR
	M3 Molecular persistence	S	CO	GNR	GNR
	M3 Molecular CR2	S	CO	GNR	S
	Relapse or refractory	CO	D	GNR	GNR
ALL	CR1 (low risk[a])	D	GNR	GNR	D
	CR1 (high risk[a])	S	S	CO	D
	CR2, incipient relapse	S	S	CO	GNR
	Relapse or refractory	CO	GNR	GNR	GNR
CML	First chronic phase (CP)	S	S	GNR	D
	Accelerated phase or >first CP	S	S	CO	D
	Blast crisis	GNR	GNR	GNR	GNR
Myeloproliferative disorders		CO	CO	D	CO
Myelodysplastic syndrome	RA, RAEB	S	S	CO	CO
	RAEBt, sAML in CR1 or CR2	S	CO	CO	CO
	More advanced stages	S	CO	D	GNR
CLL	Poor risk disease	S	S	D	CO

Bone Marrow Transplantation (2005) 36, 575–590

Bone Marrow Transplantation (2006), 1–11

CHRONIC MYELOID LEUKEMIA



CHRONIC MYELOID LEUKEMIA

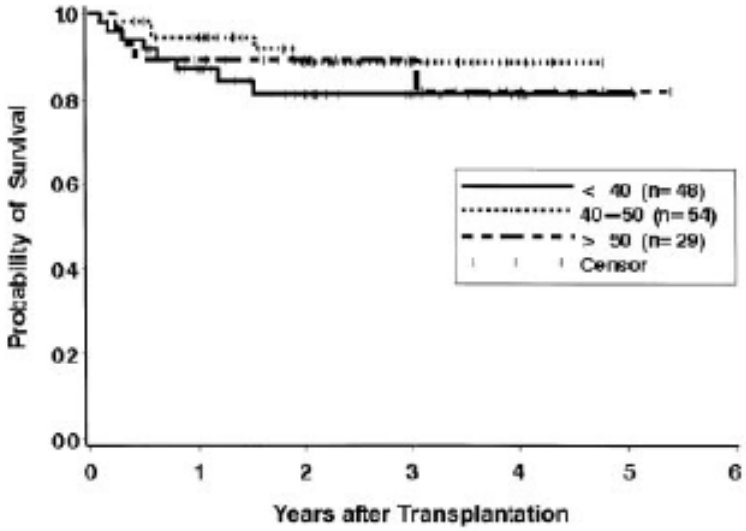
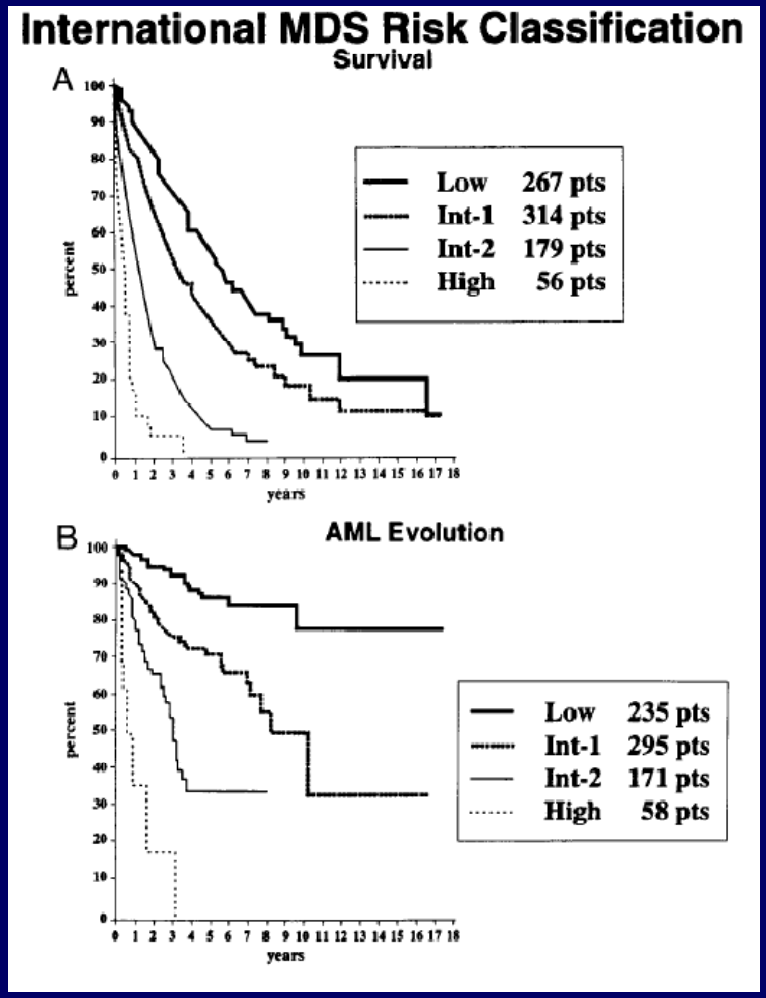
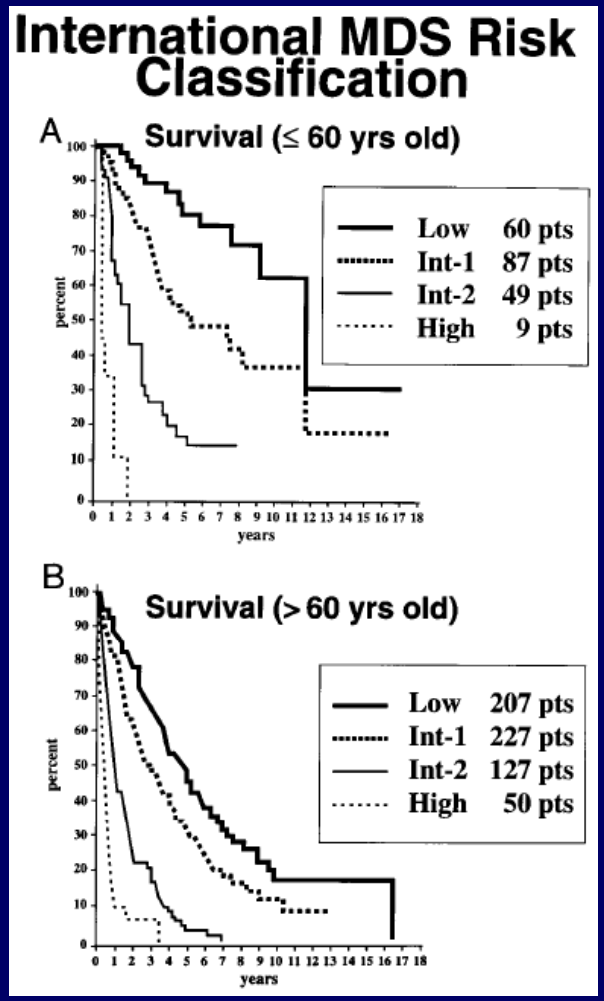


Figure 2. Effect of age on survival. There are no statistically significant differences in survival of patients aged younger than 40 years, 40 to 50 years, and older than 50 years ($P = .55$).

MYELODYSPLASIC SYNDROMES





Greenberg et al, 1997

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES

Evidences for an allogeneic graft-vs-MDS effect?

Table 2. Characteristics of patients with and without GVHD, defined as acute grade II-IV or chronic GVHD

	Developed GVHD	Did not develop GVHD
No. of patients	24	13
Median age (range)	57 (35-63)	58 (22-64)
Male sex (%)	15 (62)	5 (38)
AML/MDS	9/15	8/5
Early disease phase* (%)	7 (29)	8 (61)
Sex mismatch (%)	9 (37)	6 (46)
100% donor chimerism in PB on d +30 (%)	15 (62)	9 (69)
Achieved > 95% donor chimerism (%)		
before d +100*	18/20 (90)	7/11 (64)
TRM (%)	2 (8)	1 (8)
Follow-up, in d* (range)	330 (69-1156)	124 (61-489)

*All *P* values are > .2 except for early disease phase (*P* = .08), having achieved greater than 95% donor chimerism before day − 100 (*P* = .07) and follow-up (*P* = .04).

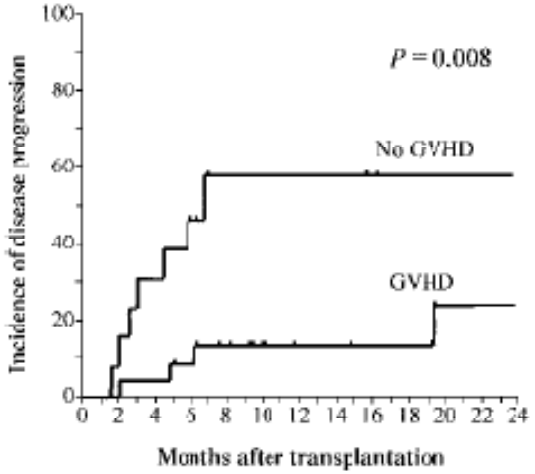


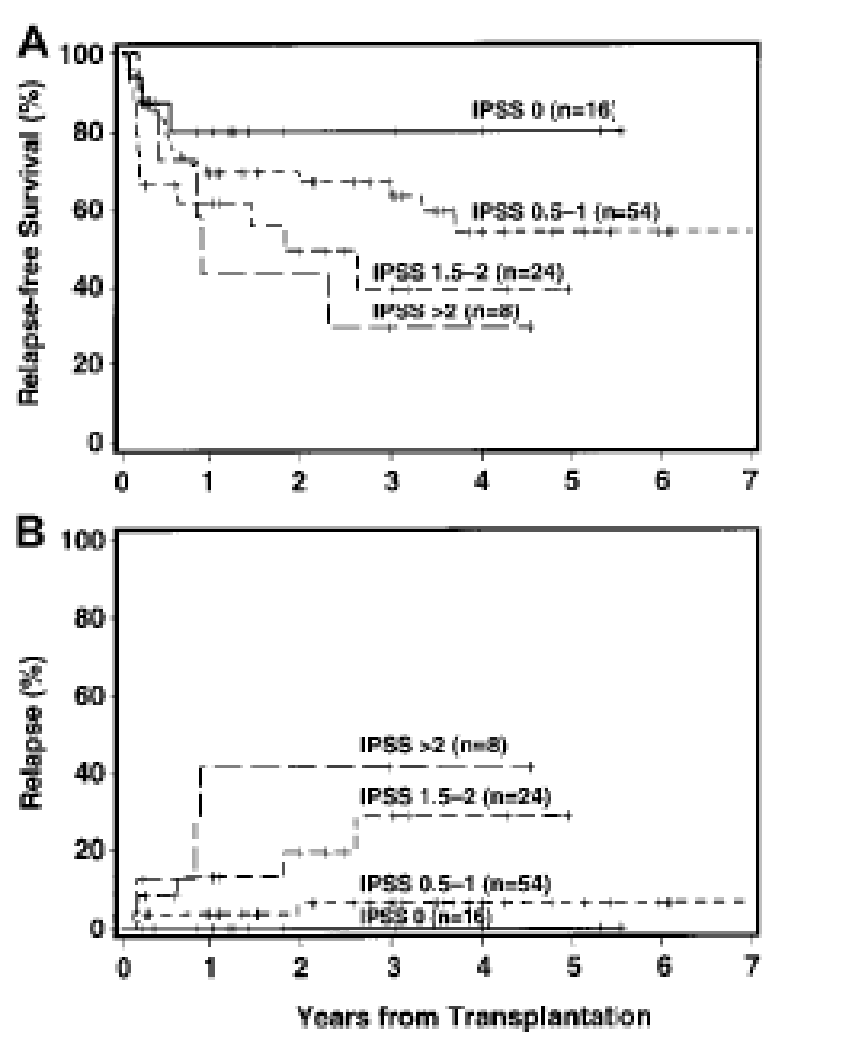
Figure 1. Disease progression after PBSCT. Cumulative incidence of disease progression after allogeneic PBSCT with RIC in patients with (n = 24) and without (n − 13) GVHD (acute grade II IV or chronic GVHD). The 1 year incidence of disease progression in patients with and without GVHD was 13% (95% CI, 4%-34%) and 58% (95% CI, 35%-96%), respectively (*P* = .008).

Martino et al, 2002

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES

- **CLINICAL EXPERIENCE OF ALLO SCT?**
  - Toxicity : too high for low risk patients
  - Efficacy: too low for high risk patients
  - Scope (age < 50): not adapted to the real population

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES



Deeg et al, 2002

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES

TIMING FOR TRANSPLANT?

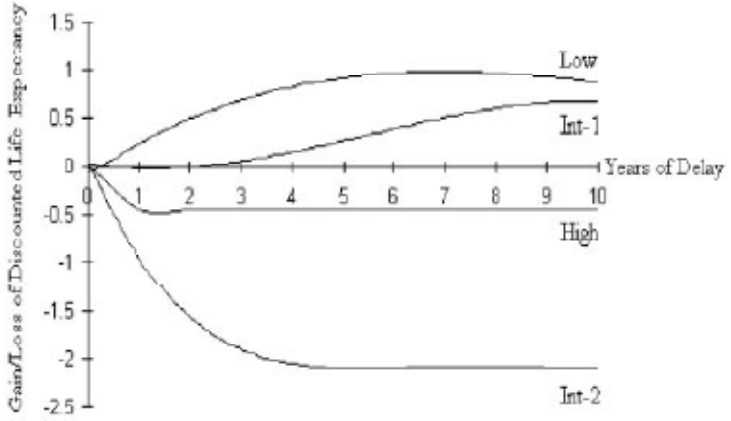


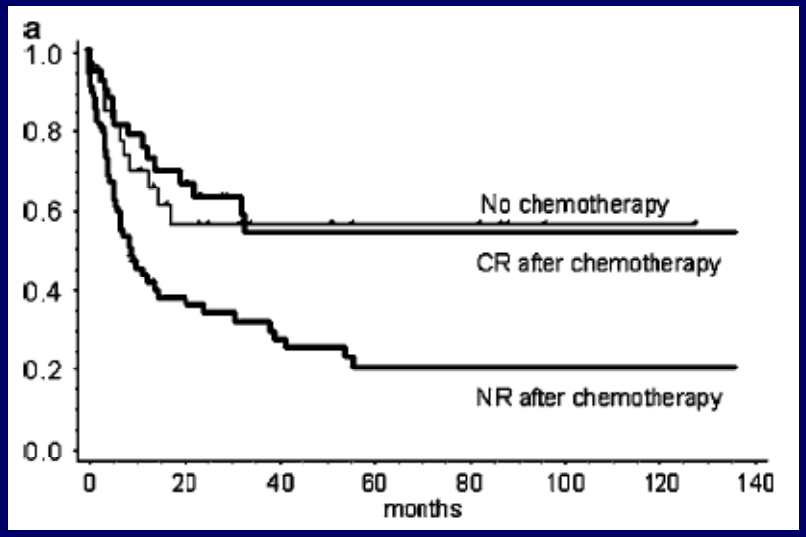
Figure 3. Net benefit or loss of overall discounted life expectancy for the 4 IPSS risk groups are shown above and below the x-axis. A net benefit for delaying transplantation is noted for low and int-1 risk groups, whereas any delay in the time to transplantation is associated with a loss in survivorship in the higher risk groups.

Table 3. Discounted life expectancy, in years, for alternative transplantation strategies

Patients, by IPSS risk group	Transplantation at diagnosis	Transplantation at a fixed time point				Transplantation at AML progression
		2 y	4 y	6 y	8 y	
All patients						
Low	6.51	6.66	7.47	7.46	7.49*	7.21
Int-1	4.61	4.74	4.72	5.02	5.20*	5.16
Int-2	4.93*	3.21	2.94	2.85	2.84	2.84
High	3.20*	2.75	2.75	2.75	2.75	2.75
Patients younger than 40 y						
Low	5.62	6.63	7.53	8.32	9.00	10.21*
Int-1	2.48	4.04	5.37	6.53	7.49	10.21*
Int-2	1.65*	1.48	1.51	1.52	1.53	1.53
High	—	—	—	—	—	—

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES

- **CHEMOTHERAPY PRE-TRANSPLANT?**



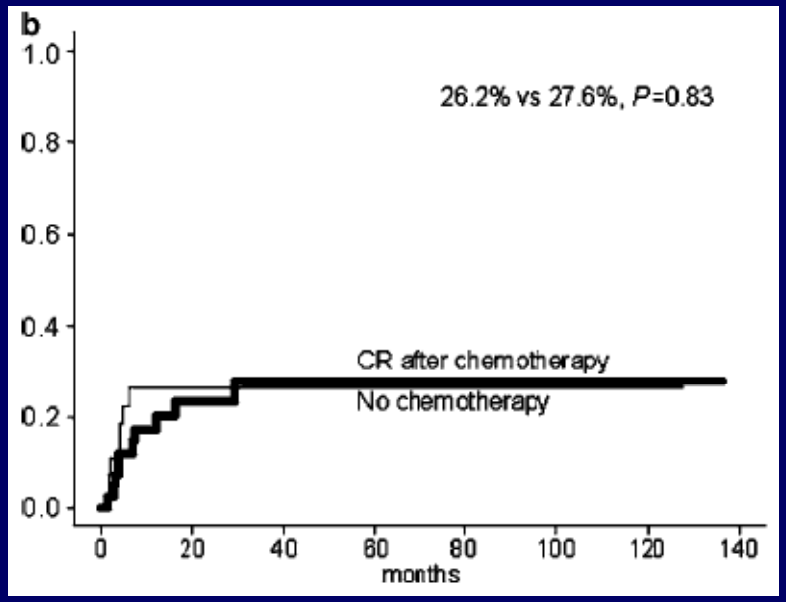
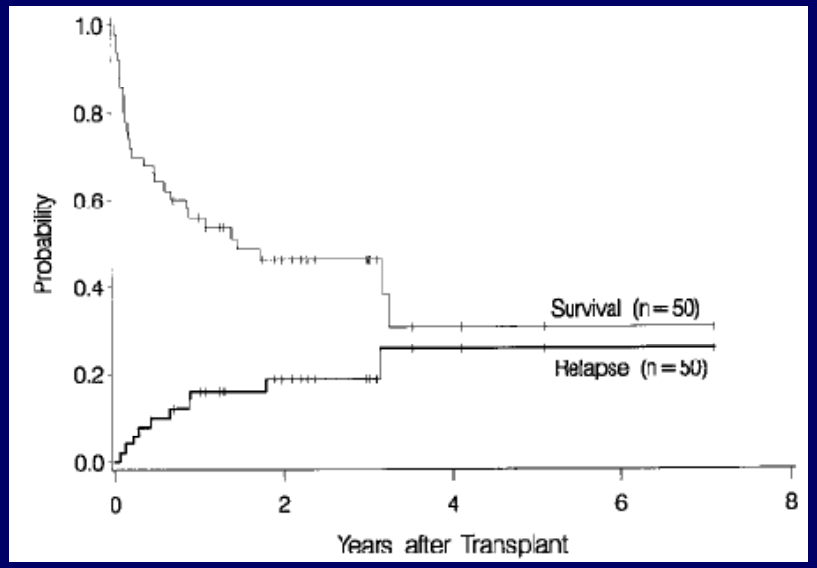


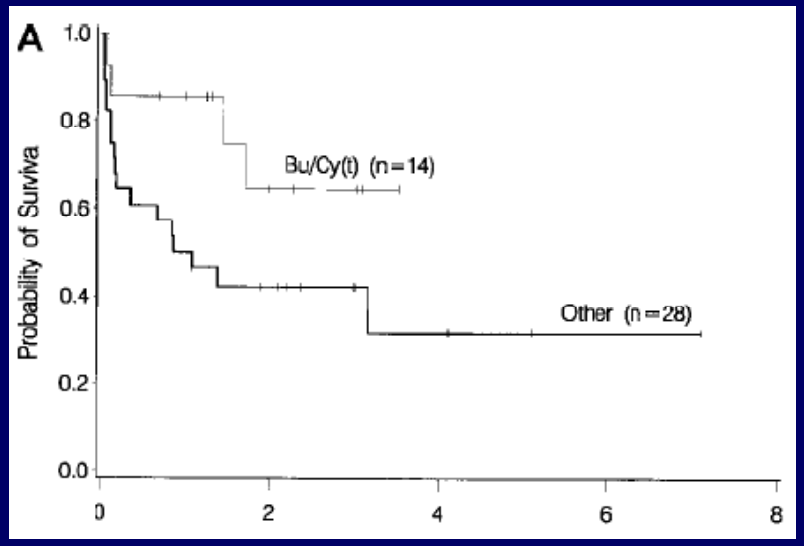
Figure 3 Overall survival (a) and cumulative incidences of relapse (b) and nonrelapse mortality (c) grouped according to the presence or absence of previous history of chemotherapy. These are compared between patients who achieved remission after chemotherapy and those who did not undergo chemotherapy. Only patients with RAEB-t or LT were included in the analyses.

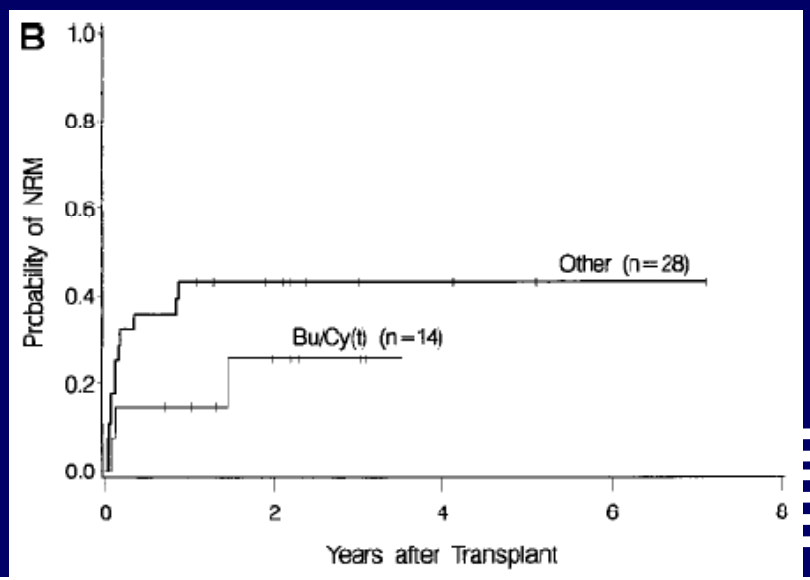
Nakai et al, 2005

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES

TRANSPLANT POSSIBLE IN ELDERLY?







Patients above the age of 55
Deeg et al, 2000

ALLO STEM CELL TRANSPLANTATION FOR MYELODYSPLASIC SYNDROMES

- **CLINICAL EXPERIENCE WITH STD ALLO SCT?**
  - Toxicity : too high for low risk patients
    - ✓ Delayed transplant
  - Efficacy: too low for high risk patients
    - ✓ Not increased by pre-transplant chemotherapy
  - Scope (age < 50): not adapted to the real population
    - ✓ Transplant possible in elderlies if adapted

- **POTENTIAL GOALS FOR ALLO IMMUNOTHERAPY**
  - To decrease toxicity
  - To increase efficacy
  - To widen scope

Retrospective Comparison Of Reduced Intensity Conditioning And Conventional High Dose Conditioning For Allogeneic Stem Cell Transplantation Using HLA Identical Sibling In Myelodysplastic Syndromes

Blood First Edition Paper, prepublished online April 4, 2006;

Table 1. Patient characteristics (percentage in parentheses)

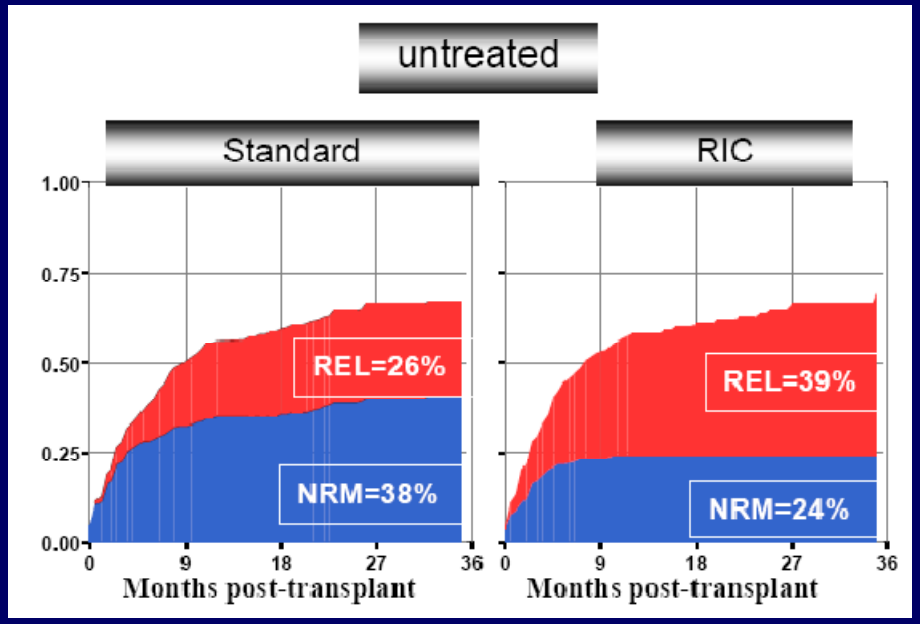
	Standard myeloablative conditioning	Reduced-intensity conditioning	P
Number	621 (74.3)	215 (25.7)	
Period of transplant			
1997-1998	268 (43.2)	30(14)	
1999-2001	353 (56.8)	185 (86)	
Male sex	340 (54.8)	121 (56.3)	
Median age [range]	45 [18-67]	56 [27-72]	<0.0001
Age ≤ 35 years	135 (21.7)	5 (2.3)	
Age 36-50	315 (50.7)	54 (25.1)	
Age > 50	171 (27.5)	156 (72.6)	
Last FAB disease classification			0.007
Secondary or therapy-related AML	198 (37.4)	75 (41.4)	
RA or RARS	72 (13.6)	20 (11.1)	
RAEB	126 (23.8)	59 (32.6)	
RAEB-t	134 (25.3)	27 (14.9)	
Unclassified MDS	91 (14.7)	34 (15.8)	
Response to chemotherapy at transplant (disease status)			0.02
Untreated	234 (37.7)	90 (41.9)	
First complete remission (CR-1)	211 (34)	66 (30.7)	
Non-CR-1	176 (28.3)	59 (27.4)	
> 10% blasts in BM at transplant	73 (11.8)	31 (14.4)	0.04

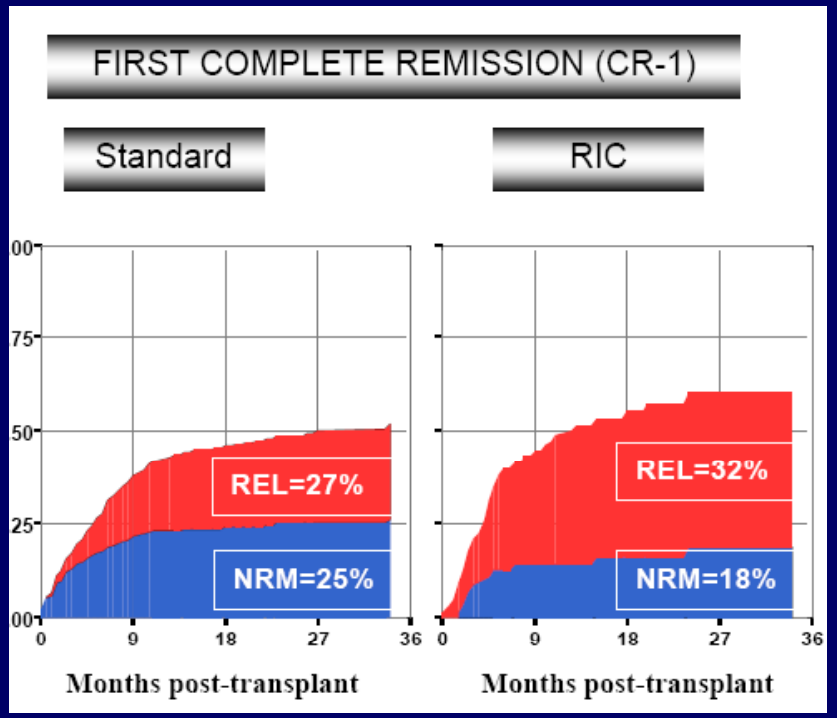
Martino et al, 2006

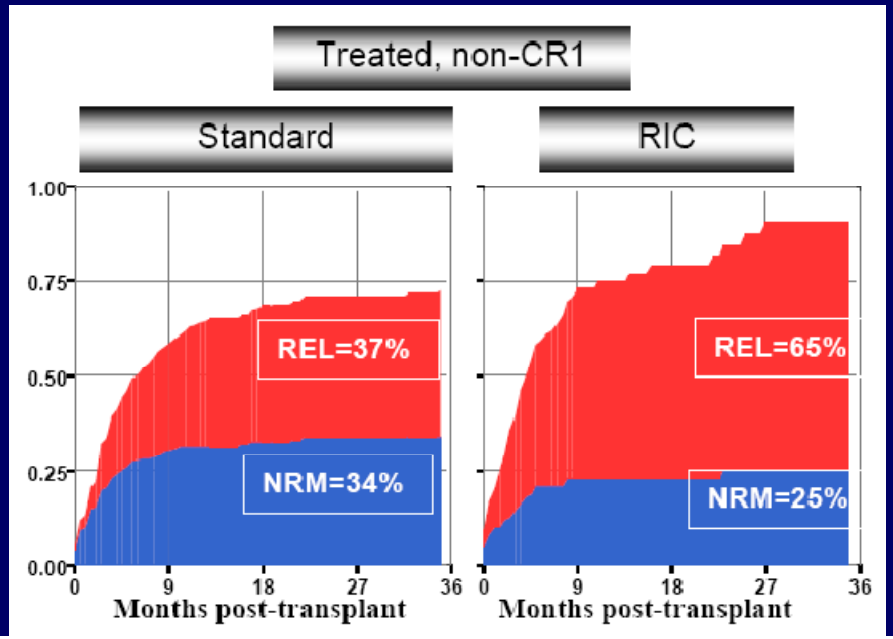
Table 6. Multivariate analysis of 36 month progression-free survival (PFS) in a COX model

Variable	Num. evaluable	Hazard Ratio of PFS (95% Confidence Interval) **	P value (overall)$ contrast
Transplant Group (main study variable)			
Standard myeloablative conditioning*	621	(1)	
Reduced-intensity conditioning	215	1.1 (0.8-1.4)	0.9
Disease group			(0.088)
Secondary acute leukemia *	463	(1)	
Myelodysplasia	276	0.78 (0.6-0.98)	0.03
Response to AML-type chemotherapy			(<0.001)
First complete remission *	235	(1)	
Untreated	276	1.3 (1.01-1.7)	0.04
Treated, but not in CR1	241	2 (1.6-2.5)	<0.001
Patient age			
≤ 50 years*	508	(1)	
> 50 years	326	1.2 (1-1.5)	0.053
Cytogenetics (see text for details)			(0.02)
Non-poor risk *	122	(1)	
Poor-risk	188	1.1 (0.79-1.5)	0.64

Martino et al, 2006







Martino et al, 2006

WHERE TO GO?

- **RICs:**
  - Decrease TRM
  - Allow allogeneic effect
- **How to take advantage from this?**
  - By widening the scope to older population? to be prospectively assessed
  - By improving results in younger population? RIC approach should be prospectively assessed against « NON-STANDARD » myelo-ablative regimen in younger patients

ACUTE MYELOBLASTIC LEUKEMIA

- **Rare and acute and serious disease**
- **Initially allo SCT as rescue of refractory diseases**
  - 10 to 15% durable remission
- **Progressively, switch towards CR consolidation**
  - Long term results with survival > 50%
  - Cure achievable
- **For many years: large debate (religious war!!!)**
  - **Allo** Against **Auto** Against **chemotherapy**
- **The 2 main real problems for allo**
  - Age limitation
  - Donor limitation
- **Progressive advances in the field**
  - **Chemotherapy**: New drugs (retinoic acid…), High dose aracytine,…
  - **SCT**: Conditioning regimen, graft source, Donor choice, antiviral treatment,…
  - **AML**: Cytogenetics and prognosis factors,…

Donor
- Match sibling
- Match unrelated / MM unrelated
  - Typing resolution
  - 6/6 vs 10/10
- MM Sibling

Stem Cell Source
- Bone Marrow
- PBSC
- Cord Blood

Allo SCT

Disease Status
- CR1
- CRn
- more advanced

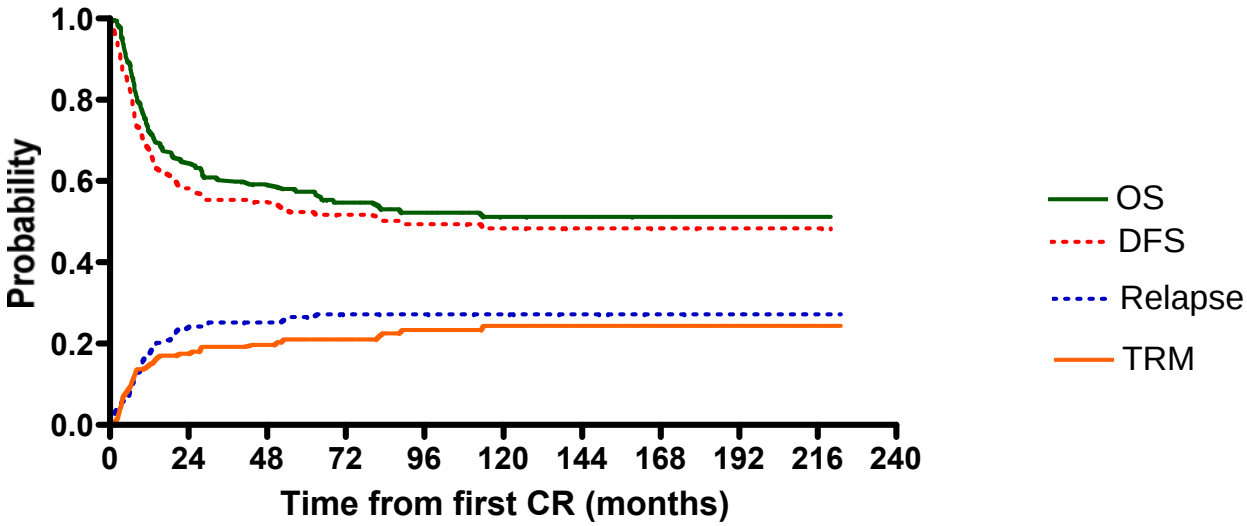
Conditioning
- Standard Myeloablative
  - TBI
  - No TBI
- Reinforced Myeloablative
- Reduced intensity
- Non Myeloablative

GVHD prophylaxis
- CSA
- CSA + MTX
- others
- Ex vivo T Cell depletion
- ATG

ALLO *VS* AUTO *VS* CT

- **5 prospective randomized trials**
  - EORTC AML-8 — Zittoun N Engl J Med 1995
  - GOELAMS — Harousseau, Blood 1997
  - Intergroup US — Cassileth, N Engl J Med 1998
  - MRC AML-10 — Burnett BJH 2002
  - EORTC AML-10 — Suciu , Blood 2003

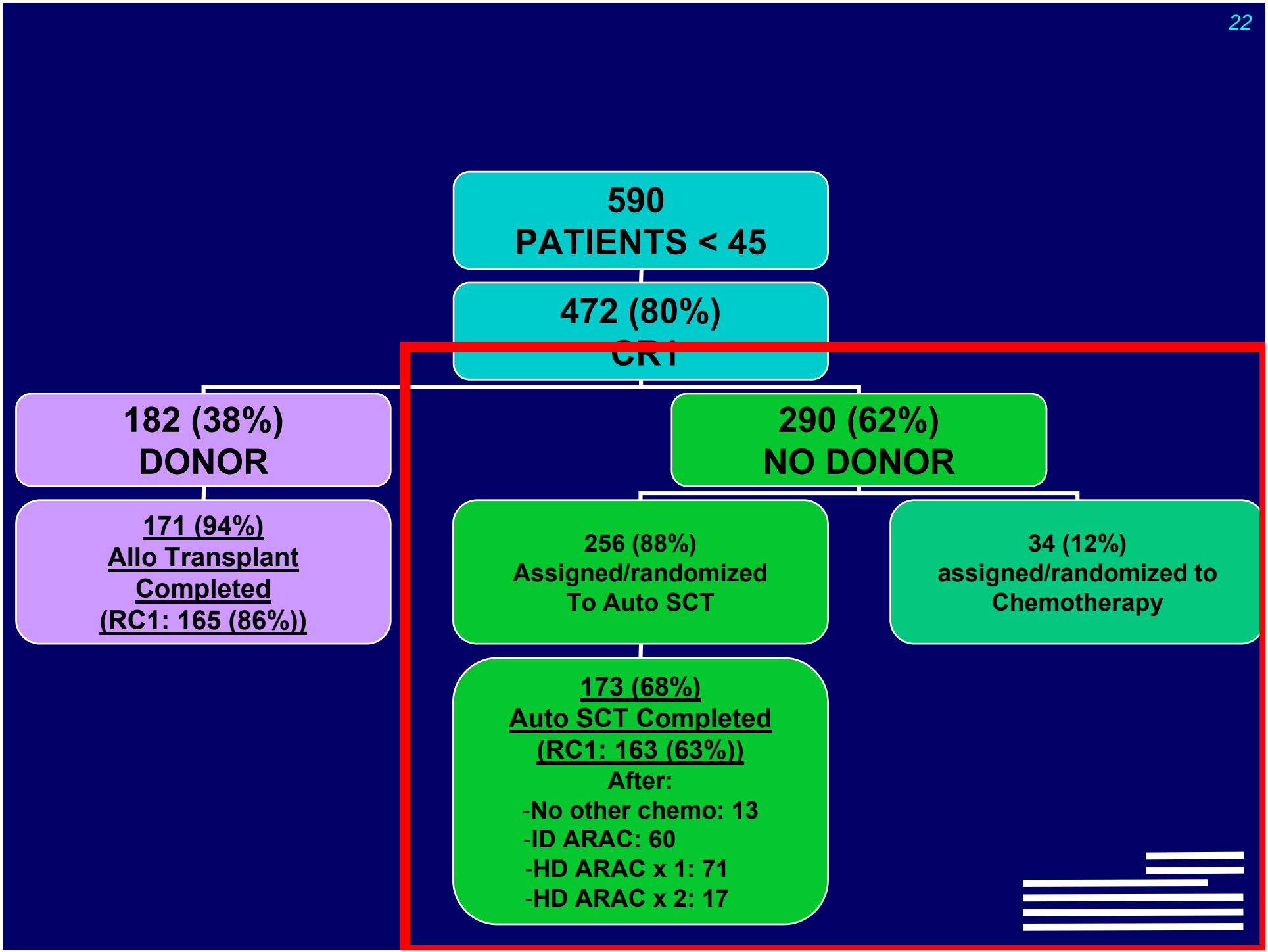
RESULTS « STANDARD » ALLO SCT



- **Relapse : 20 to 30 %**
- **TRM : 20 à 30 %**
- **LFS et OS : 50 à 60 %**

ALLOGENEIC STEM CELL TRANPLANT for CR1 AML 17 YEAR EXPERIENCE OF BGMT

- **To evaluate** survival **after allo SCT as compared to no allo SCT** after achieving CR1
  - In an intent to treat manner
  - Taking opportunity of
    - ✓ Large cohort of patients: N=472
    - ✓ Long Follow-up: 10 years (3-18)
    - ✓ High completion of Allo SCT: 94%
    - ✓ Large documentation of cytogenetics: 77%
- **To more precisely determine the risk for survival**


590
PATIENTS < 45
472 (80%)
182 (38%)
DONOR
290 (62%)
NO DONOR
171 (94%)
Allo Transplant
Completed
(RC1: 165 (86%))
256 (88%)
Assigned/randomized
To Auto SCT
34 (12%)
assigned/randomized to
Chemotherapy
173 (68%)
Auto SCT Completed
(RC1: 163 (63%))
After:
-No other chemo: 13
-ID ARAC: 60
-HD ARAC x 1: 71
-HD ARAC x 2: 17

CYTOGENETICS	• 0 • 1 • 2 • 3	• FAVORABLE • INTERMEDIATE • NE • UNFAVORABLE
FAB	• 0 • 1	• M1-M5 • M0, M6, M7

COMPLETE REMISSION	• 0 • 1	• 1 COURSE • 2 COURSES
INITIAL WBC	• 0 • 1	• <= 30 • > 30

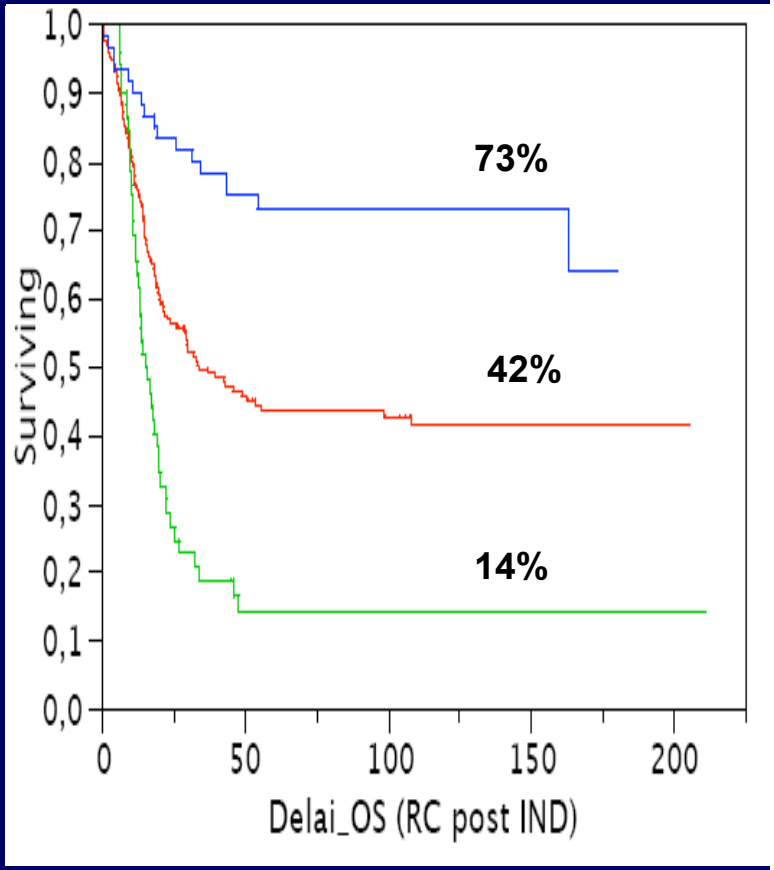
cytogenetics	FAB	CR	WBC	Risk	exp(risk)	Score
cyto high risk	FAB MO-M6-M7	CR 2 courses	WBC >30	3,353	28,5883702	6
cyto high risk	FAB MO-M6-M7	CR 1 course	WBC >30	2,888	17,9573589	5
cyto NE	FAB MO-M6-M7	CR 2 courses	WBC >30	2,845	17,2015587	5
cyto NE	FAB MO-M6-M7	CR 1 course	WBC >30	2,38	10,8049029	4
cyto high risk	FAB MO-M6-M7	CR 1 course	WBC<=30	2,373	10,7295326	4
cyto intermediate risk	FAB MO-M6-M7	CR 2 courses	WBC >30	2,337	10,3501395	4
cyto NE	FAB other	CR 1 course	WBC >30	1,531	4,62279731	3
cyto high risk	FAB other	CR 1 course	WBC<=30	1,524	4,59055072	3
cyto intermediate risk	FAB other	CR 2 courses	WBC >30	1,488	4,4282302	3
cyto low risk	FAB MO-M6-M7	CR 2 courses	WBC<=30	1,314	3,7210281	2
cyto intermediate risk	FAB other	CR 1 course	WBC >30	1,023	2,78152684	2
cyto low risk	FAB other	CR 1 course	WBC >30	0,515	1,6736385	1
cyto intermediate risk	FAB other	CR 1 course	WBC<=30	0,508	1,66196394	1
cyto low risk	FAB other	CR 1 course	WBC<=30	0	1	0

RISK FACTOR GROUPS

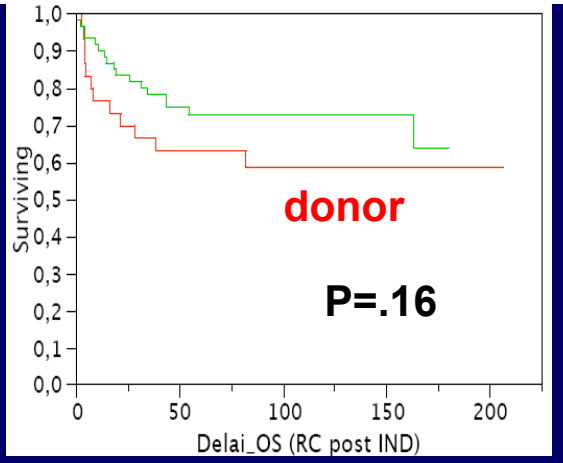
- Low Risk: N=47 (16%)
  - **Favorable Cytogenetics**
  - **No other adverse factor**

- Intermediate Risk: N=163 (56%)
  - **No adverse Cytogenetics**
  - **Favorable Cytogenetics +1-2 OAF**
  - **Intermediate cytogenetics + 0-1 OAF**
  - **NE cytogenetics + 0 OAF**

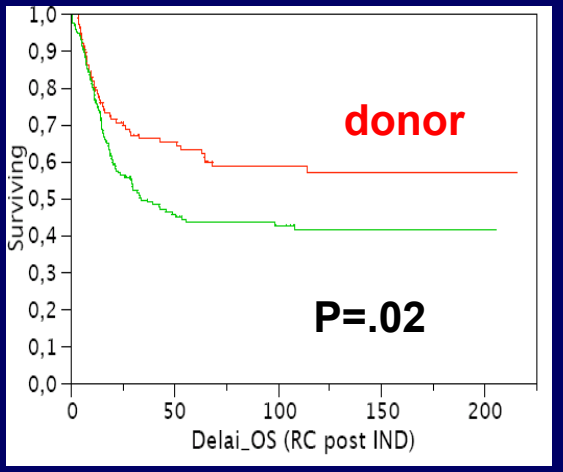
- Poor Risk: N=80 (28%)
  - **Adverse Cytogenetics***
  - **Intermediate Cytogenetics + 2-3 OAF**
  - **NE Cytogenetics + 1-3 OAF**



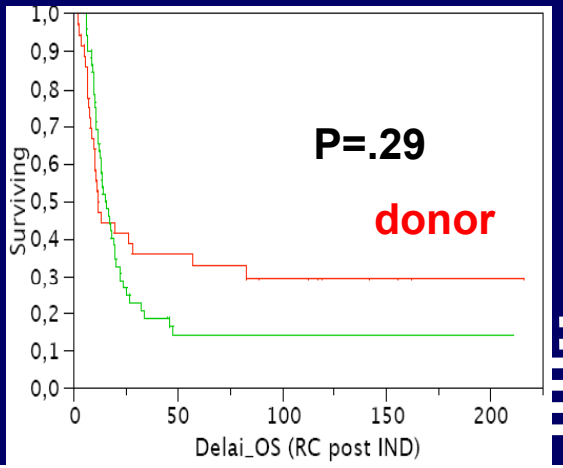
LOW RISK GROUP
PROGNOSTIC INDEX= 0

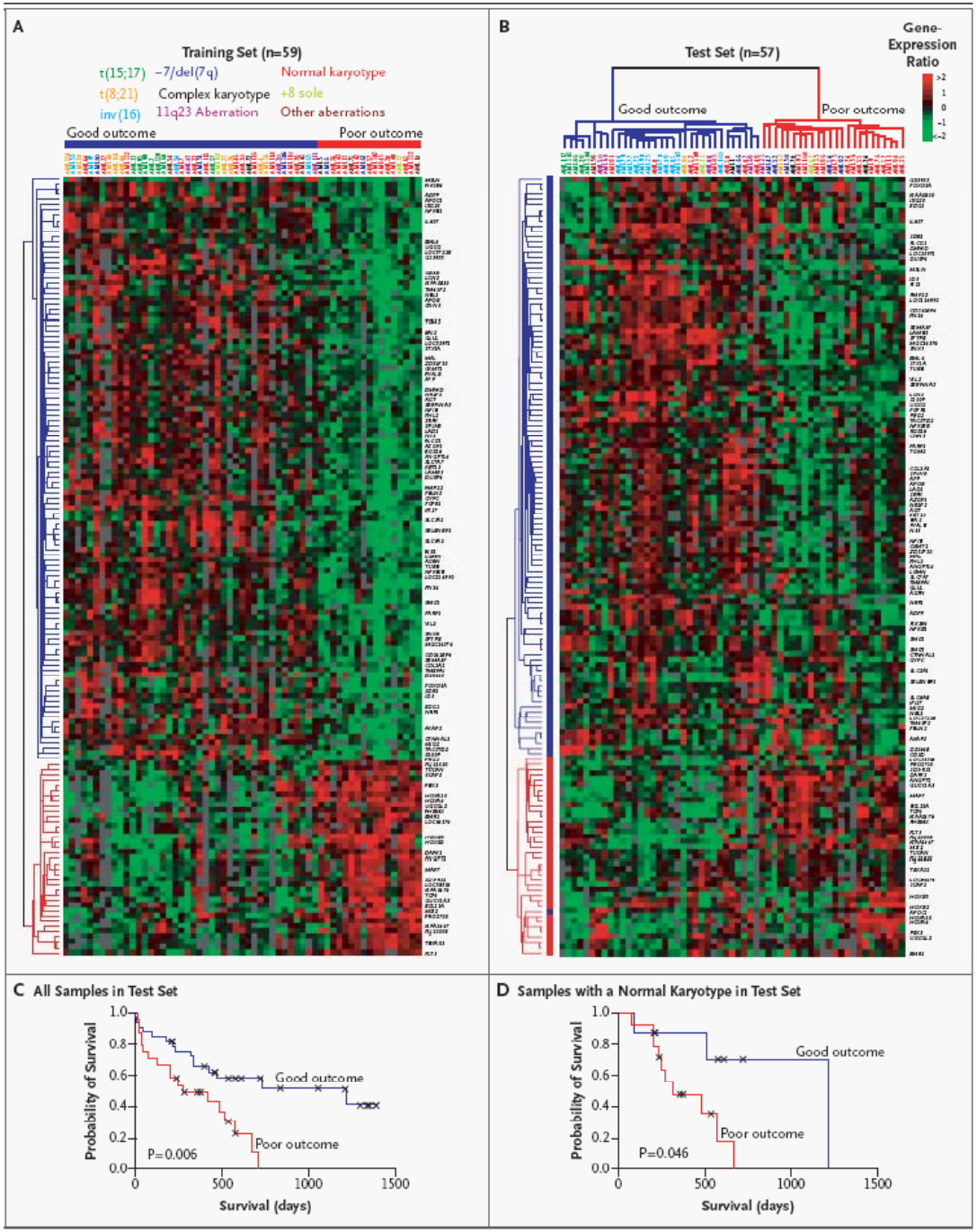


INTERMEDIATE RISK GROUP
PROGNOSTIC INDEX= 1 or 2



POOR RISK GROUP
PROGNOSTIC INDEX > 2





Bullinger et al, 2004

RIC FOR AML
PRESENT KNOWLEDGE?

- **FEW PUBLISHED DATA**
- **FEW SPECIFIC REPORTS**
- **PILOT STUDIES**
  - LIMITED NUMBERS WITH MIXED INFORMATIONS
    - ✓ AML +/- MDS
    - ✓ GENO +/- MUD
  - SHORT FOLLOW-UP
  - MULTIPLE REGIMENS AND APPROACHES
- **DIFFERENT POPULATIONS THAN IN PREVIOUS EXPERIENCE**
  - OLDER PATIENTS
  - PATIENTS WITH COMORBIDITIES

Treatment for Acute Myelogenous Leukemia by Low-Dose, Total-Body, Irradiation-Based Conditioning and Hematopoietic Cell Transplantation From Related and Unrelated Donors

Ute Hegenbart, Dietger Niederwieser, Brenda M. Sandmaier, Michael B. Maris, Judith A. Shizuru, Hildegard Greinix, Catherine Cordonnier, Bernard Rio, Alois Gratwohl, Thoralf Lange, Haifa Al-Ali, Barry Storer, David Maloney, Peter McSweeney, Thomas Chauncey, Ed Agura, Benedetto Bruno, Richard T. Maziarz, Finn Petersen, and Rainer Storb

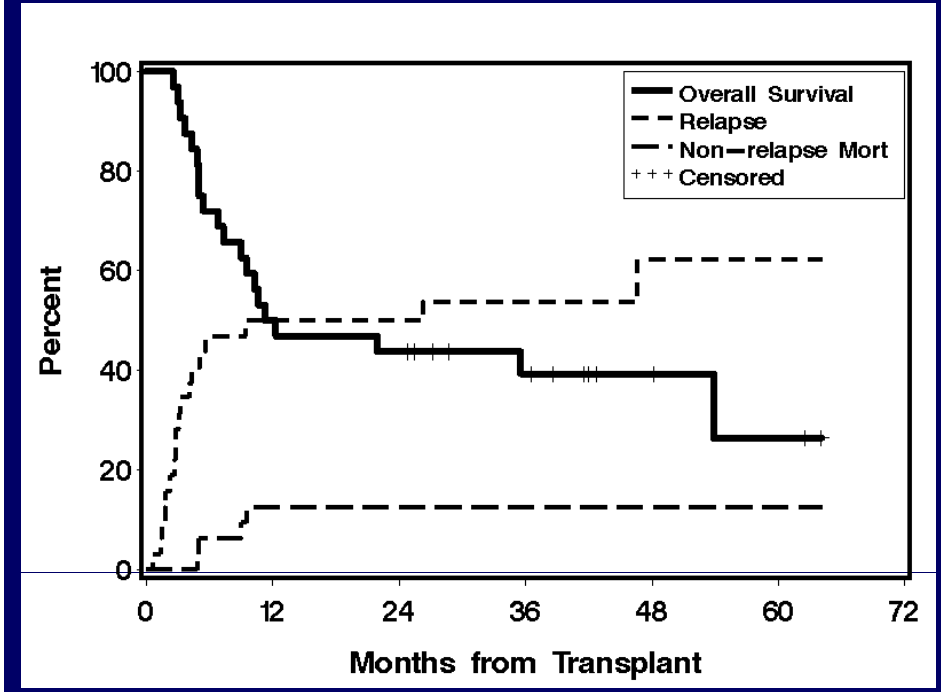
JCO, 2006

- **N: 122**
- **Status**
  - CR1: 42%
  - CR2 : 32%
  - Advanced: 26%
- **DONOR**
  - MRD: 48%
  - MUD: 52%
- **Not Eligible for STD ASCT**
- **AGE: 57 (17-74)**
- **TBI 2 Gy +/- FLUDA**
- **CSA + MMF**
- **Fup: 17 mths**

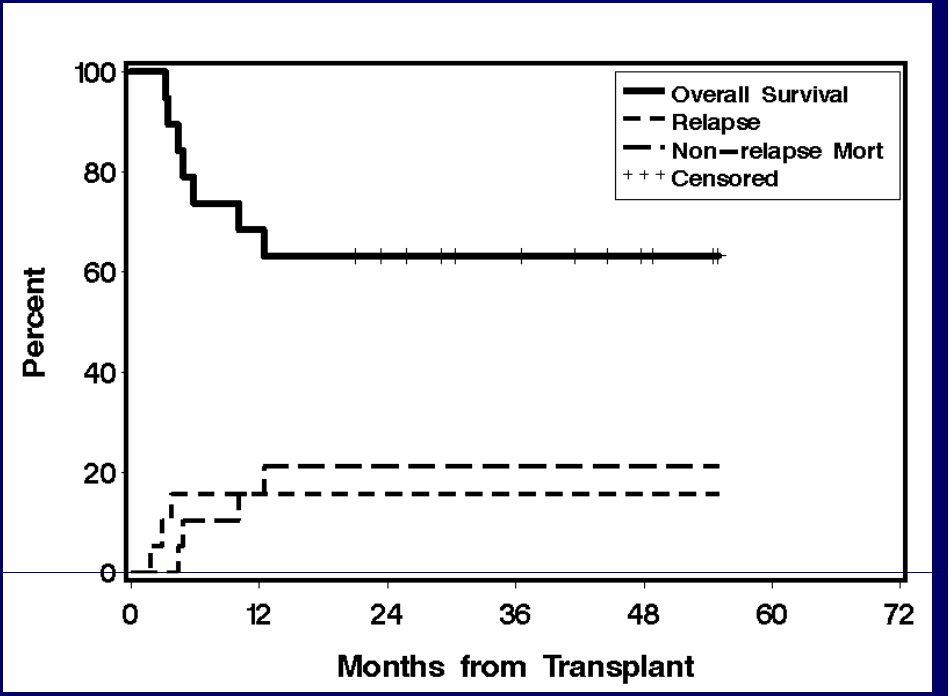
- **NRD: 3% at 100d; 16% at 2 years**
- **Relapse: 39% at 2 years**
- **OS: 48% at 2 years**
- **LFS: 44% at 2 years**

OUTCOME OF PATIENTS WITH AML CR1 AFTER HCT WITH MINIMAL CONDITIONING

related

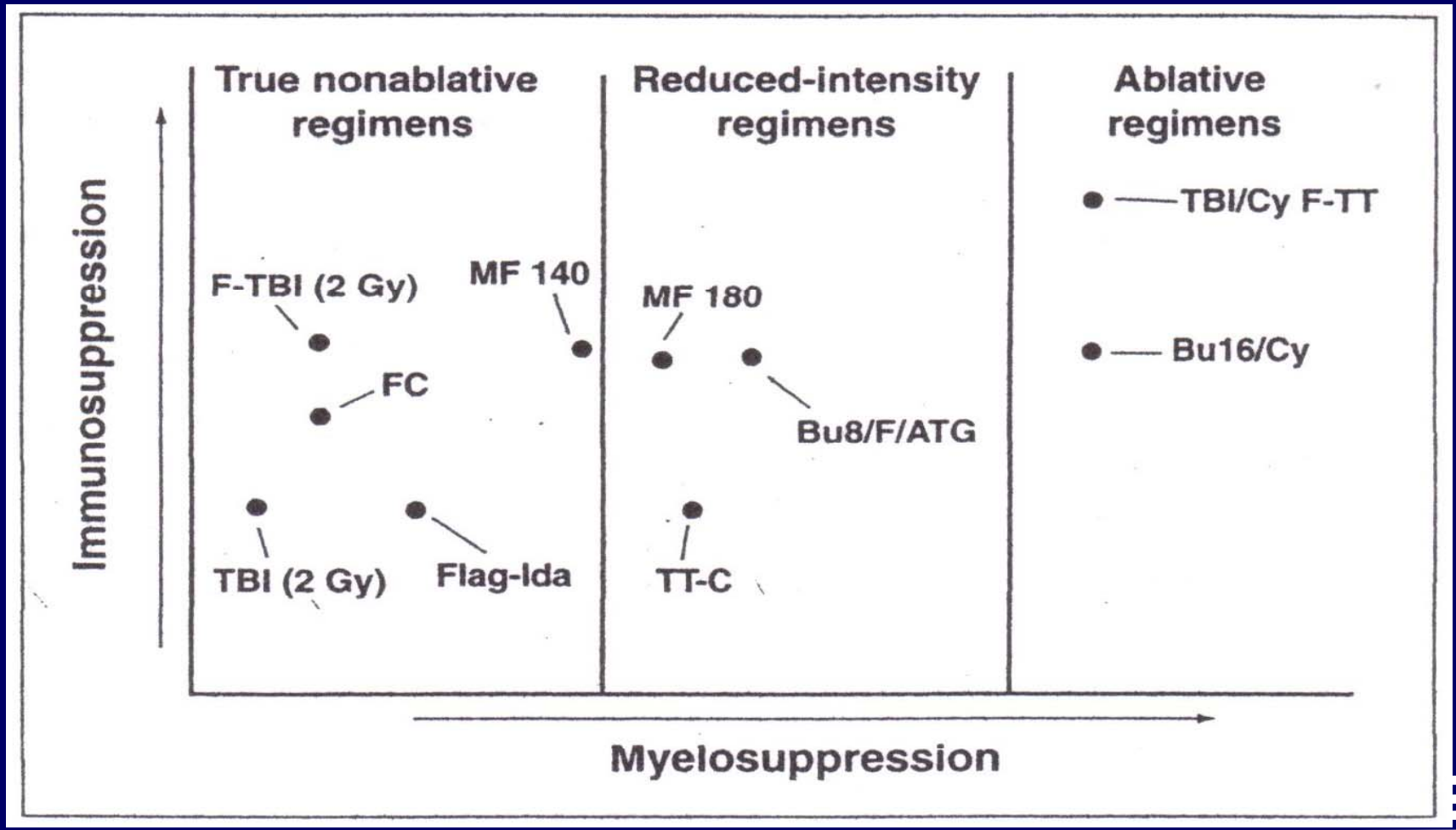


unrelated



Courtesy from Dietger Niederwieser

IS A RIC ALLO-SCT BETTER THAN ANOTHER?



Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation

Marcos de Lima, Athanasios Anagnostopoulos, Mark Munsell, Munir Shahjahan, Naoto Ueno, Cindy Ippoliti, Borje S. Andersson, James Gajewski, Daniel Couriel, Jorge Cortes, Michele Donato, Joyce Neumann, Richard Champlin, and Sergio Giralt

- **FAI:**
  - FLUDA: 120 mg/m²
  - CYTARABINE: 4 g/m²
  - IDARUBICINE: 36 mg/m²
- **FM**
  - FLUDA: 100-150 mg/m²
  - MELPHALAN: 140 mg/m²

Table 1. Characteristics of patients treated with FAI or FM

Characteristics	FAI	FM	*P*
No. patients	32	62	
Average age, y (range)	61 (27-74)	54 (22-75)	.001
No. female (%)/no. male (%)	18 (56)/14 (44)	29 (47)/33 (53)	.514
Average mos. from diagnosis to treatment (range)	10 (1.1-48.6)	12 (0.9-173.6)	.662
No. prior therapies (range)	2 (0-4)	2 (0-8)	.399
Diagnosis, no. (%)			
AML	26 (81)	42 (68)	
MDS	6 (19)	20 (32)	.253
Stage at transplantation, no. (%)			
Remission	14 (44)	10 (16)	.006
Not in remission	18 (56)	52 (84)	
First remission at transplantation, no. (%)	9 (28)	2 (3)	.0008
Donor type, no. (%)			
Matched sibling	26 (81)	25 (40)	
Mismatched related	6 (19)	8 (13)	<.001
Matched unrelated	0 (0)	29 (47)	
Stem cell source, no. (%)			
Bone marrow	27 (84)	26 (42)	<.001
Peripheral blood	5 (16)	36 (58)	

FAI indicates fludarabine, araC, and idarubicin; FM, fludarabine and melphalan.

Table 2. Engraftment and chimerism according to preparative regimen

	FAI	FM	*P*
No. of patients	32	62	NS
Median d to ANC 0.5 × 10^9/L (range)	14.5 (10-38)	14 (11-100)	NS
Median d to platelet 20 × 10^9/L (range)	17 (10-78)	20 (6-49)	NS
Mean % donor cells on d 30 (no. patients)	79.6 (29)	95 (50)	.015
% donor cells on d 90 (no. patients)	66 (24)	89 (40)	.009
% donor cells on d 360 (no. patients)	71 (7)	95 (23)	.08
% autologous reconstitution or graft failure (no. patients)	19 (6)	3 (2)	.03

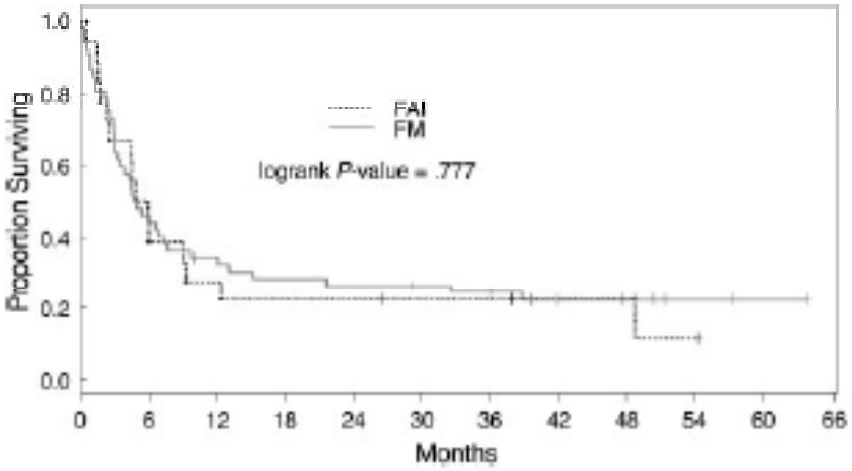


Figure 2. Overall survival of patients with active disease at transplantation. Overall survival of patients with active disease at transplantation was similar in both treatment groups. FM indicates fludarabine and melphalan; FAI indicates fludarabine, araC, and idarubicin.

Table 5. Estimates of cumulative incidence of mortality at 3 years

Outcome and treatment	Cumulative incidence	95% confidence interval	
		Lower bound	Upper bound
Relapse-related mortality			
FAI	0.534	0.343	0.725
FM	0.260	0.149	0.371
Non–relapse-related mortality			
FAI	0.156	0.028	0.285
FM	0.392	0.267	0.517

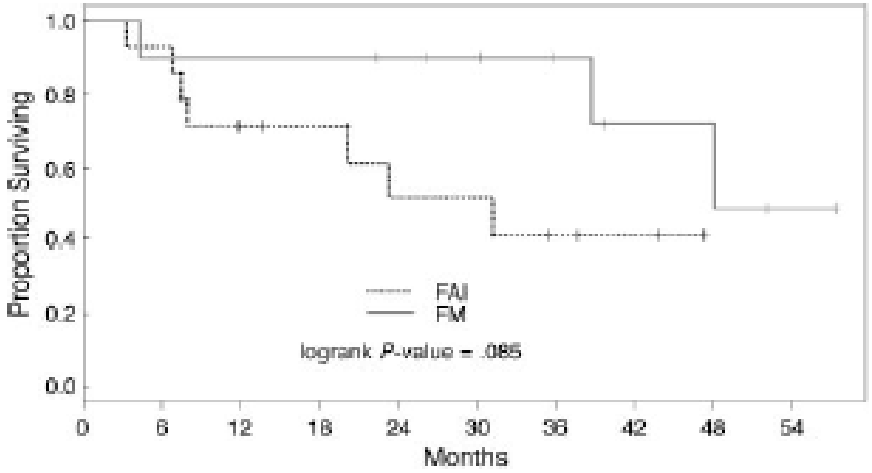


Figure 1. Overall survival of patients in remission at transplantation. Survival of patients in remission at transplantation after conditioning with FM or FAI. FM indicates fludarabine and melphalan; FAI indicates fludarabine, araC, and idarubicin.

IS THERE AN ALTERNATIVE TO THE TOXICITY-EFFICACY DILEMMA?

- PRE ASCT CHEMOTHERAPY

Induction | Consolidation | Intensive consolidation* | **RIC**

*** HIDAC Dauno (60 mg/m²) day 1 and 2; ARAC: 3 g/m² x 2/d over 3 H for 4 days**
Or HIDAC + HDM: Melphalan 140 mg/m²

- ALLOGENEIC TRANPLANT

FBA (High ATG)	- 12	- 11	- 10	- 9	- 8	- 7	- 6	- 5	- 4	- 3	- 2	- 1
Fludarabine 30 mg/m²	X	X	X	X	X	X						
Busulfan4 mg/kg							X	X				
ATG * 2,5 mg/kg									X	X	X	(X)

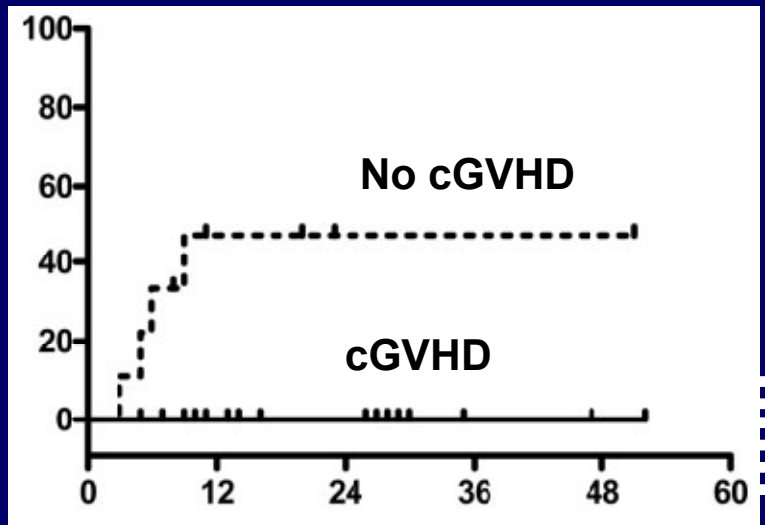
FBA (Low ATG)	- 12	- 11	- 10	- 9	- 8	-7	- 6	- 5	- 4	- 3	- 2	- 1
Fludarabine 30 mg/m²							X	X	X	X	X	X
Busulfan 4 mg/kg									X	X		
ATG * 2,5 mg/kg										X		

*: *THYMOGLOBULINE*

RIC AML for Patients with CR1 AML

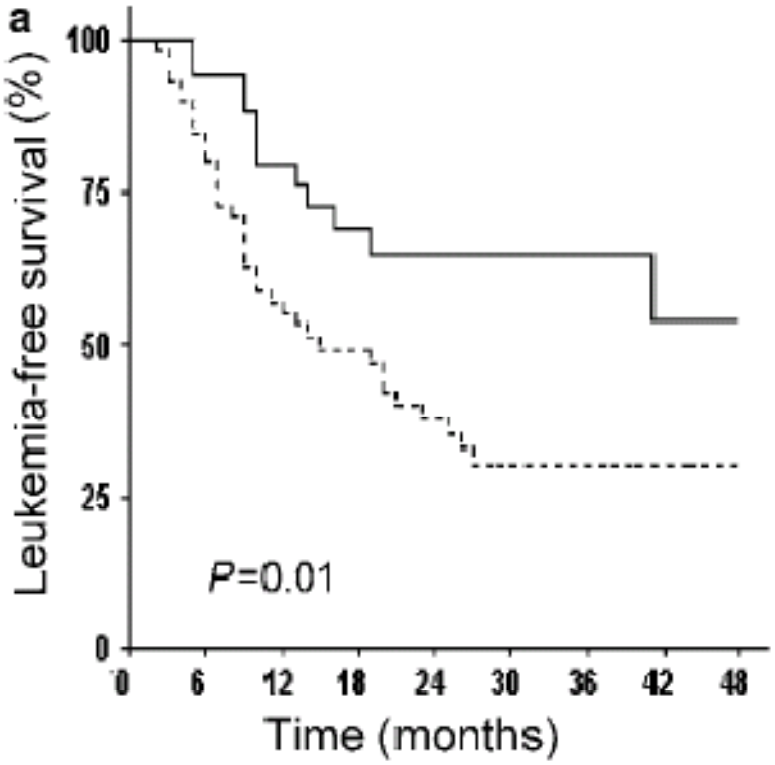
	N=33
Patient Age	52 (26-60)
Pts with poor leukemic risk • poor risk cytogen. • 2 induction courses • WBC ≥ 30 x 10^9/l • M0-M6-M7 FAB • Secondary leukemia	21 (64) 11 (33) 8 (24) 4 (12) 3 (9) 3 (9)
Pts with high clinical risk • Age > 55 • Serious comorbidities	15 (45) 8 (24) 8 (24)

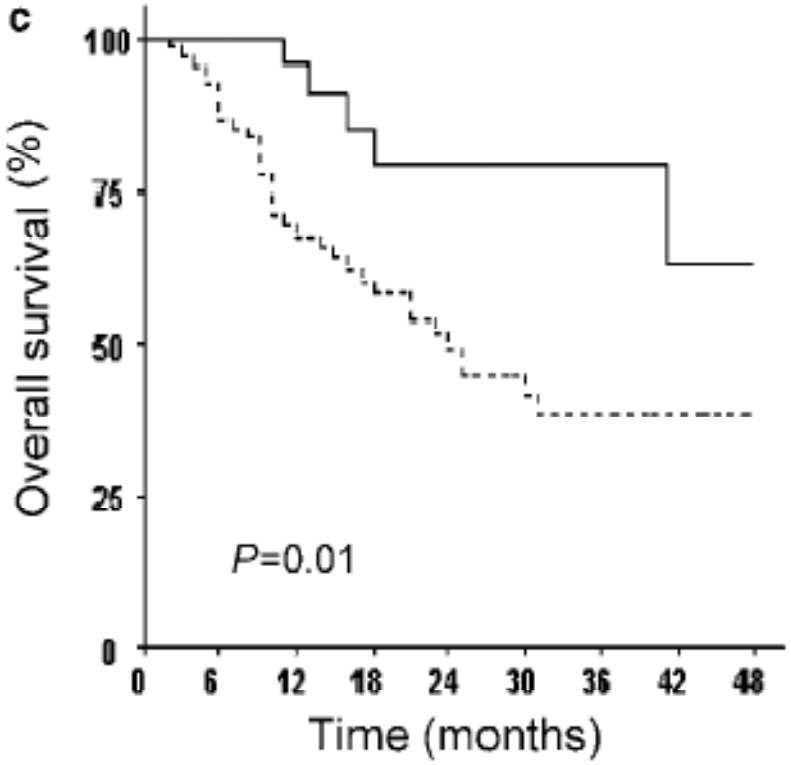
Follow-up: months	18 (6-51)
Non relapse deaths Days	9% (0-19) 89,176,1067
Relapse Days	18% (5-31) 143 (71-304)
2 Y Overall Survival CR1/CR2	79% (60-90) 23/3
2 Year LFS	75% (58-87)



CANCER November 1, 2005 / Volume 104 / Number 9

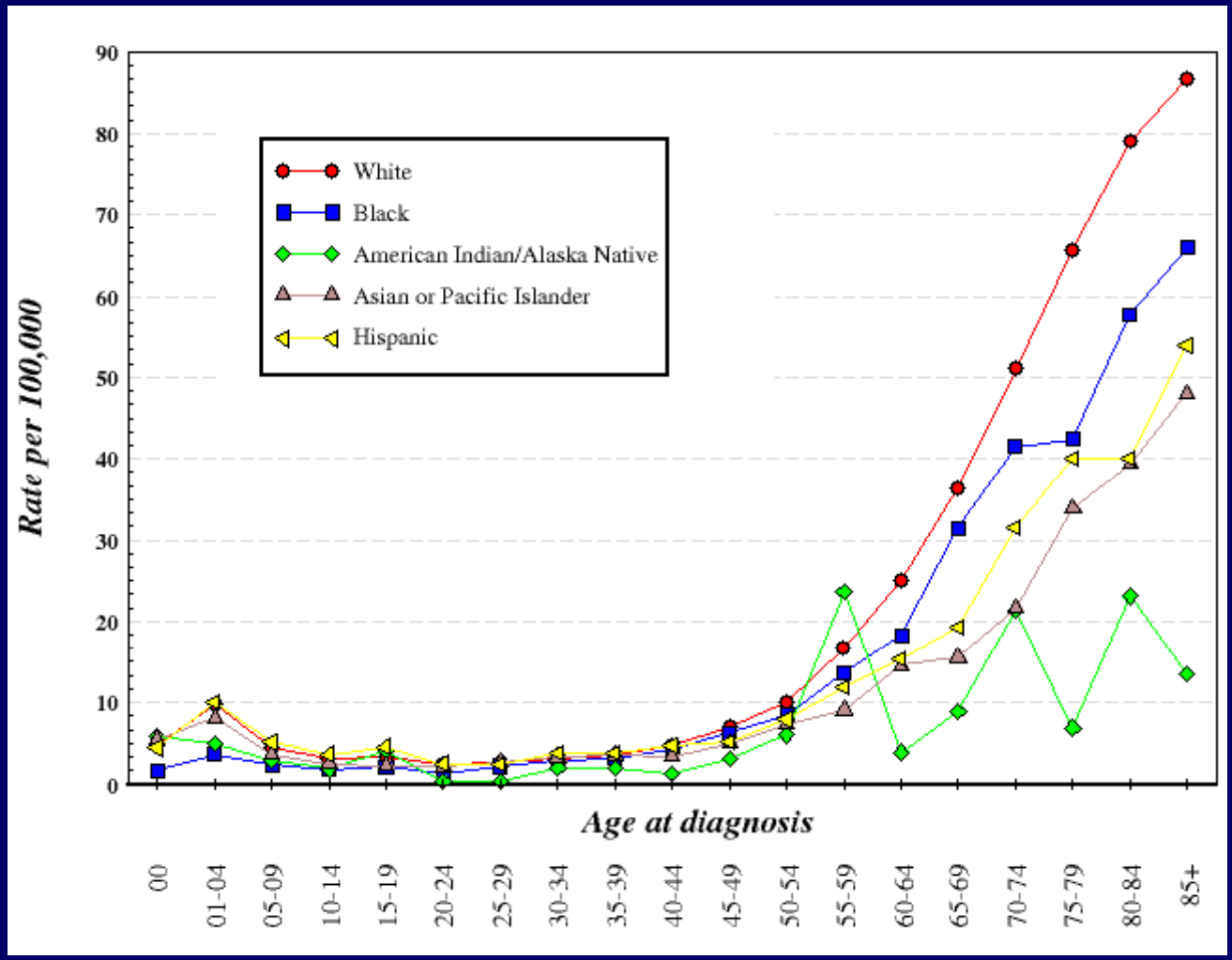
	No donor group N=60 (%)	Donor group N=35 (%)	P
Relapse	32 (53)	9 (26)	0,01
Median time (range) to relapse (from CR)	250 (82-784)	246 (108-518)	NS
% LFS (from CR) at 4 years	30.4	54	0,01
% OS (from CR) at 4 years	39,3	54,4	0,01





CONCLUSIONS

- **Individual prognosis is still to be determined**
- **Allo SCT affords long term cure**
- **Debate remains open**
  - Goal of RIC approach: SCT → Immunotherapy
    - ✓ Can complete chemotherapy approach
  - 75% patients have no sibling donor
    - ✓ RIC and MUD/CB: will NRD be decreased enough?
  - The real challenge is the elderly population



SEER Crude Incidence Rates Leukemia
SEER 13 Registries for 1998-2002

ELSEVIER

EXPERIMENTAL HEMATOLOGY

Experimental Hematology 31 (2003) 1–10

Allogeneic hematopoietic stem cell transplantation—Yesterday, today, and tomorrow

Rainer Storb

Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, Wash., USA

ALLOGENEIC IMMUNOTHERAPY?


Sabine Fürst, MD
Catherine Faucher, MD
Mohamad Mohty, MD
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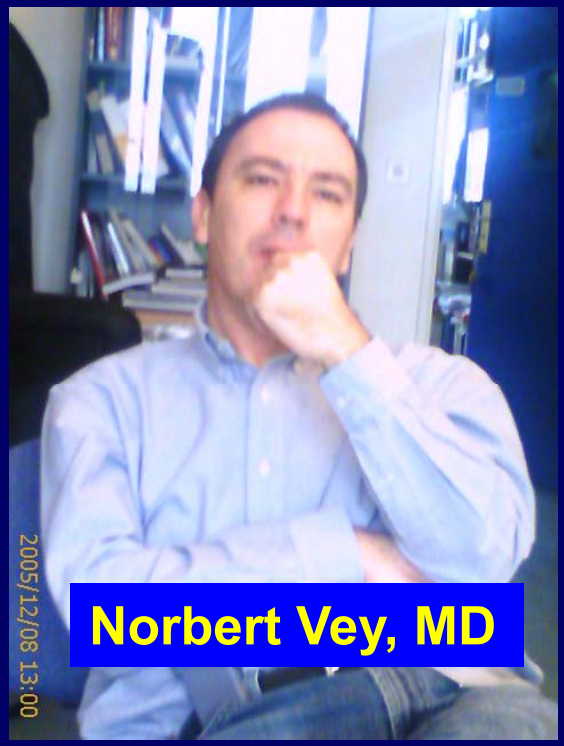
Norbert Vey, MD
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