Allogreffe dans les LAM

AGADIR

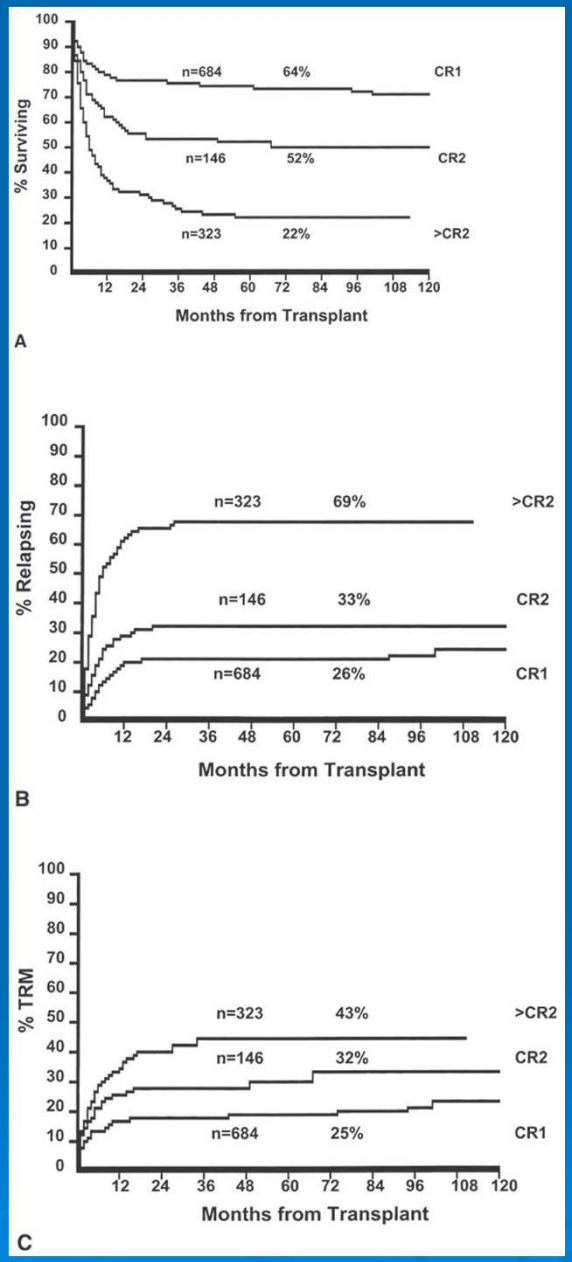
Mai 2014

JP Vernant

Actuarial survival

Relapse rate

TRM



AML from 1991 to 2001

EBMT

Figure 95-03

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- Comment greffer les LAM
  - - avec quel donneur ?
  - - avec quel conditionnement?
  - -avec quel greffon?
  - -avec quelle prophylaxie de la GVHD ?
- Quand greffer les LAM
- Quelques problèmes en plus

- Comment greffer les LAM
  - - avec quel donneur ?
  - - avec quel conditionnement?
  - -avec quel greffon?
  - -avec quelle prophylaxie de la GVHD ?
- Quand greffer les LAM

DONNEURS en 2014

- 1970 : - germain HLA-identique
- 1990 : - donneur non apparenté → phéno 6/6 (générique) → fichier (> 20 M)
  → phéno 10/10 (allélique)

- membres de la famille haplo-identiques (GVL – NK-dépendante)

- sang placentaire (enfants) → banque de sang placentaire (> 700 000 unités)

- 2000 : - double sang placentaire (adultes)

Il n'y a plus de malades sans donneur même si la greffe est difficile

On n'a plus à « attendre un donneur »

DONNEURS DES FICHIERS

Allogeneic Marrow Stem-Cell Transplantation From Human Leukocyte Antigen–Identical Siblings Versus Human Leukocyte Antigen–Allelic–Matched Unrelated Donors (10/10) in Patients With Standard-Risk Hematologic Malignancy: A Prospective Study From the French Society of Bone Marrow Transplantation and Cell Therapy

Table 1. Main Initial Characteristics of the Patients and Donors (N = 236)

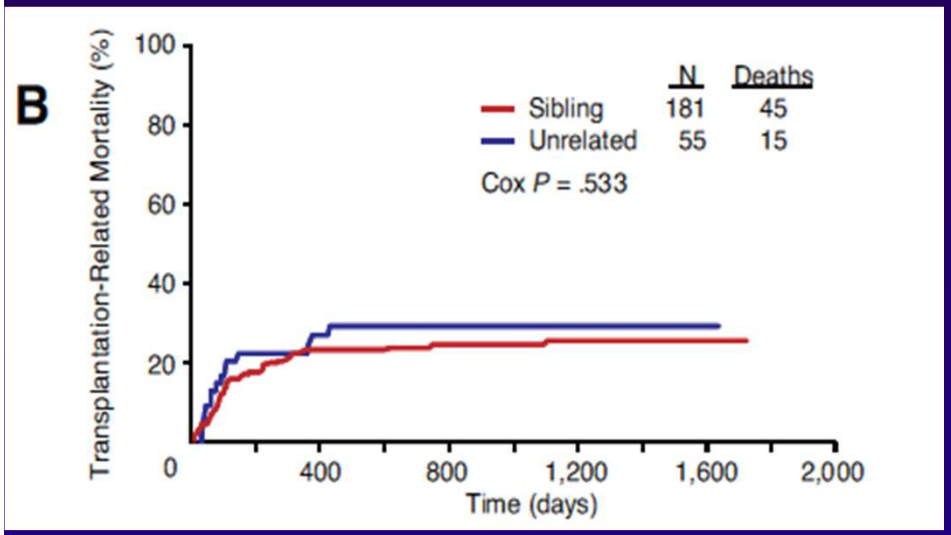
Characteristic	All Patients (N = 236)		Sibling Group (n = 181)		Unrelated Group (n = 55)		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Recipient age, years							.045
< 36.7	118	50	84	46	34	62	
≥ 36.7	118	50	97	54	21	38	
Underlying disease							
AL	175	74	141	78	34	62	.02
CML	43	18	30	17	13	24	NS
MDS	18	8	10	5	8	14	.039
Disease status							
AL in first complete remission or CML in chronic phase	167	71	134	74	33	60	.045
Other situations	69	29	47	26	22	40	

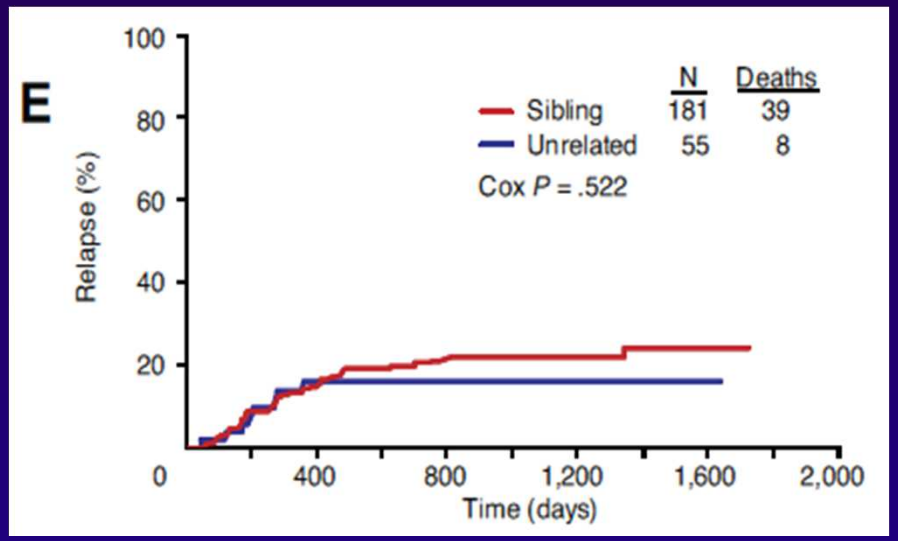
JOURNAL OF CLINICAL ONCOLOGY

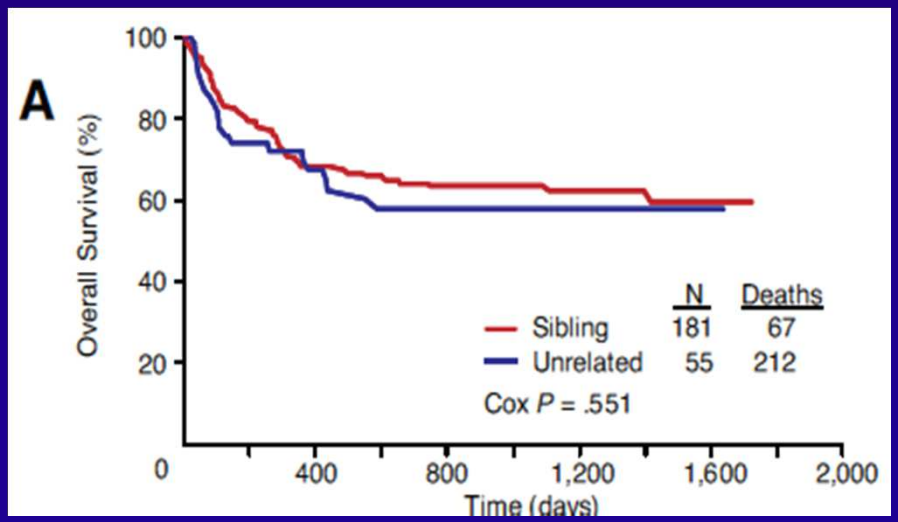
DECEMBER 20 2006

Ibrahim Yakoub-Agha, Florence Mesnil, Mathieu Kuentz, Jean Michel Boiron, Norbert Ifrah, Noel Milpied, Sami Chehata, Helene Esperou, Jean-Paul Vernant, Mauricette Michallet, Agnes Buzyn, Nicole Gratecos, Jean Yves Cahn, Jean Henri Bourhis, Zina Chir, Colette Raffoux, Gerard Socié, Jean Louis Golmard, and Jean-Pierre Jouet

Sibling *v* HLA-Matched Unrelated Allo-SCT







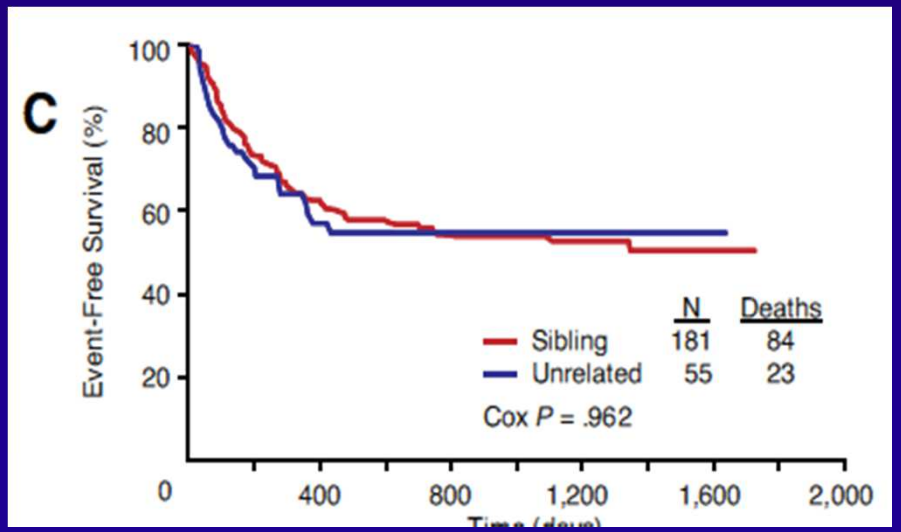


Table 2. Comparative outcomes of various donor sources for HCT in AML

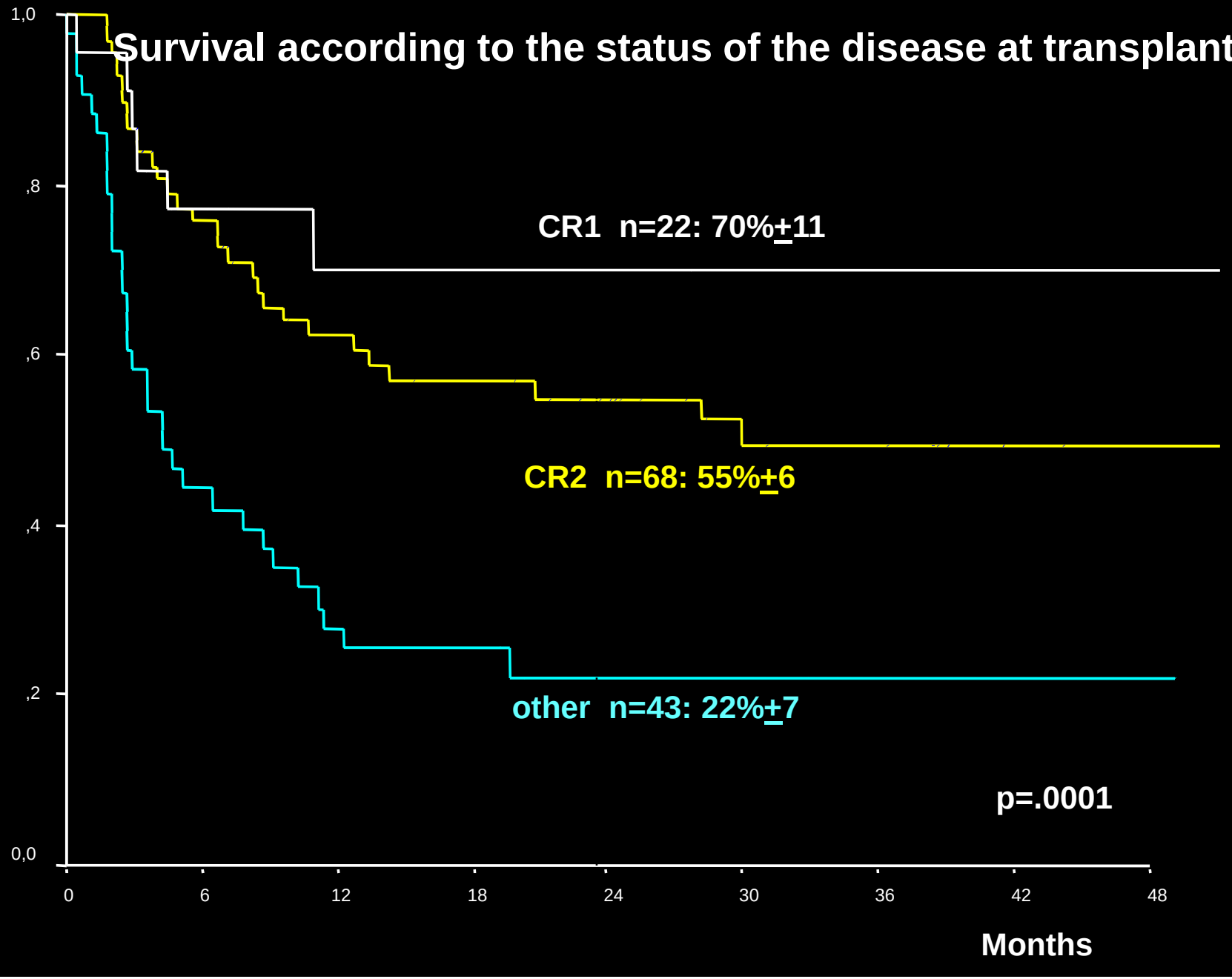
Study	Sample size and patient population	Disease status	Main comparison	LFS and OS	Additional comments
Hegenbert et al, 2006,[57] Multicenter, Seattle Consortium	122, age 17-74 y, using NMA conditioning only	CR1 (n = 51), CR2 (n = 39), advanced (n = 32)	MRD (n = 58) vs MUD (n = 64)	No difference between MRD and MUD	Disease status at HCT and cytogenetics most important factors for LFS and OS
Moore et al, 2007,[58] Multicenter, Australasian Registry	210, age 16-59 y, using MAC only	CR1 (n = 36), > CR1/others (n = 174)	MSD (n = 105) vs URD (n = 105)	No difference between MSD and URD	Matched case-controlled study
Schetelig et al, 2008,[59] Multicenter, Germany	368, age 50-73 y, both MAC and RIC	CR1 (n = 136), advanced, (n = 228), others (n = 4)	MSD (n = 168) vs M/MRD (n = 12) vs MUD (n = 51) vs possibly MUD (n = 68) vs partially MUD (n = 45) vs poorly MUD (n = 24)	No difference between different donor types	Advanced disease at HCT, secondary AML, and high risk cytogenetics associated with poor outcomes
Atsuta et al, 2009,[54] Multicenter, JMDP/JCBBN	484, age 16-69 y, using MAC only	CR1 (n = 180), Others (n = 304)	MUD (n = 311) vs UCB-HCT (n = 173)	Inferior outcomes in UCB-HCT attributable to increased TRM	No difference in risk of relapse
Walter et al, 2010,[49] single center, Seattle	220, age 18-69 y, using MAC only	CR1, Intermediate cytogenetics (n = 141), high risk cytogenetics (n = 60), others (n = 19)	MRD (n = 135) vs 10/10 MUD (n = 62) vs 9/10 URD (n = 23)	No difference between MRD vs 10/10 MUD vs 9/10 URD	Unfavorable cytogenetics and high HCT-CI score associated with worse outcomes
Gupta et al, 2010,[48] Multicenter, CIBMTR	584, age <1-74 y, Both MAC and RIC	AML in CR1 with adverse cytogenetics	MSD (n = 226) vs well-matched URD (n = 254) vs Partially matched URD (n = 104)	Similar between MSD and well-matched URD, inferior for partially matched URD	Lower risk of relapse in patients with chronic GVHD
Schlenk et al, 2010,[46] Multicenter, Germany and Austria	162, age 19-61 y, Both MAC and RIC	High-risk AML in CR1, patients refractory to induction therapy	MRD (n = 62) vs MUD (n = 89) vs CB/HaploHCT (n = 11)	Similar between MSD and MUD	Prospective study, also compared with patients who could not get transplant, benefit of HCT seen in comparison with non-HCT patients in landmark analysis

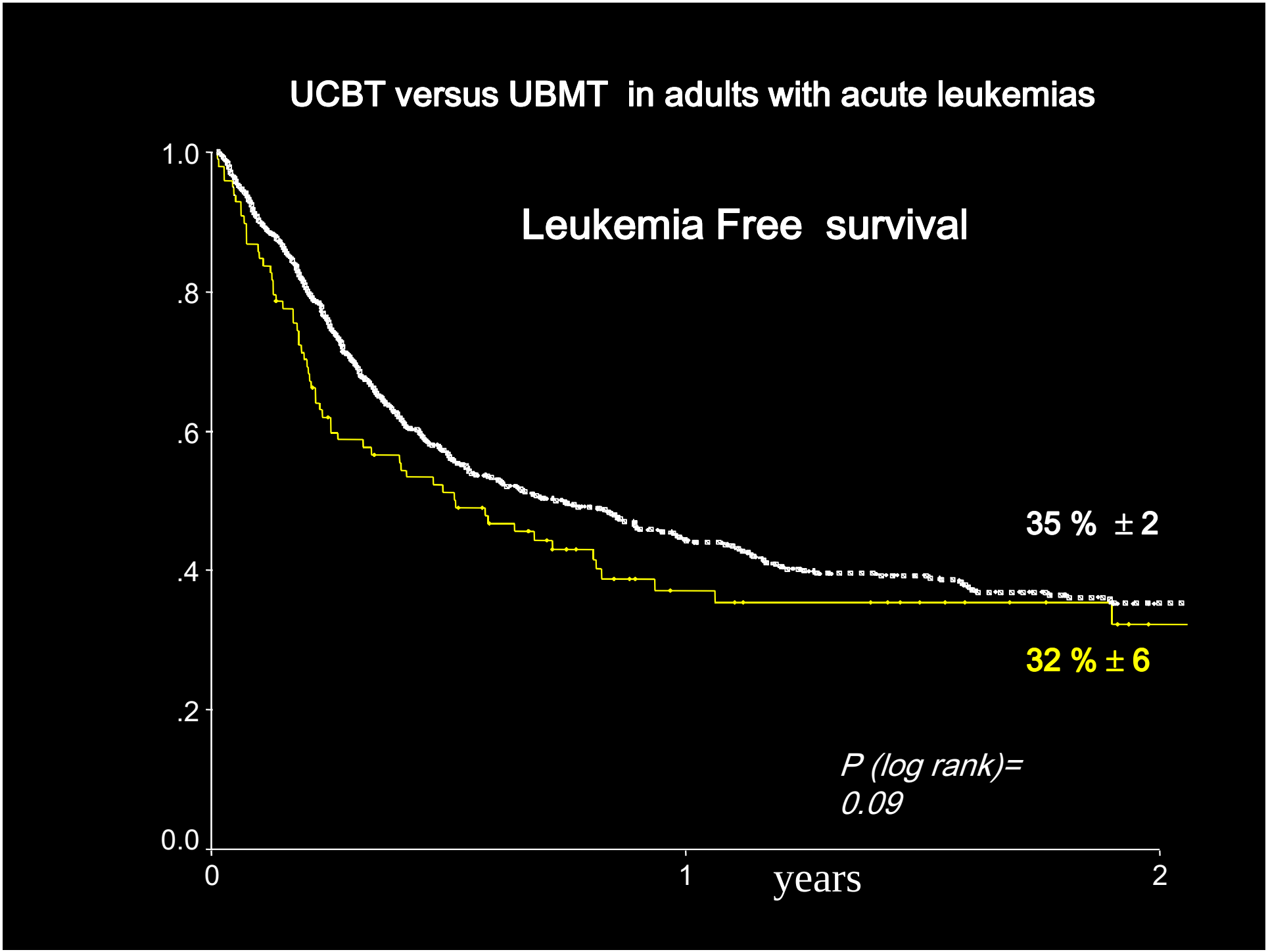
CIBMTR indicates Center for International Blood and Marrow Transplant Research; CR1, first complete remission; CR2, second complete remission; GVHD, graft versus host disease; haploHCT, haplo-identical cell transplantation; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; JCCBN, Japanese cord blood bank network; JMDP, Japanese Marrow Donor Program; LFS, leukemia-free survival; MAC, myeloablative conditioning; NMA, nonmyeloablative; OS, overall survival; M/MRD, mismatched related donor; MRD, matched related donor; MSD, matched sibling donor; MUD, matched unrelated donor; RIC, reduced-intensity conditioning; TRM, treatment-related mortality; UCB, umbilical cord blood; and URD, unrelated donor.

Géno (MSD) versus Phéno (MUD) lors d'allogreffe pour LAM

GREFFES DE SANG PLACENTAIRE

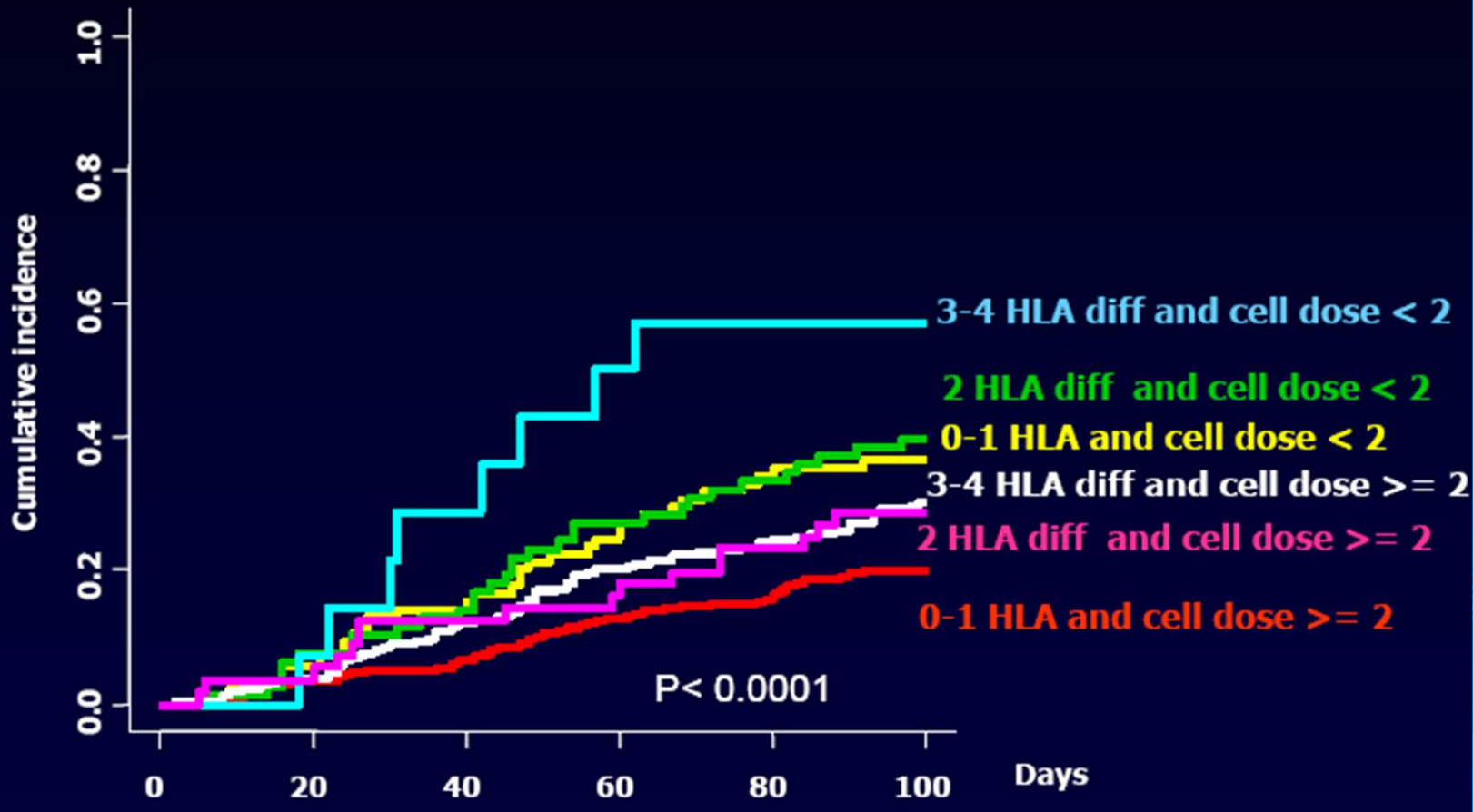
UCBT in children with AML (n=133)




UCBT versus UBMT in adults with acute leukemias
Leukemia Free survival
1.0
.8
.6
.4
.2
0.0
0
1
2
years
35 % ± 2
32 % ± 6
P (log rank)= 0.09

UCBT malignant disorders (n=929)

TRM according to number of HLA and cell dose



UNRELATED CORD BLOOD TRANSPLANTATION IN ADULTS

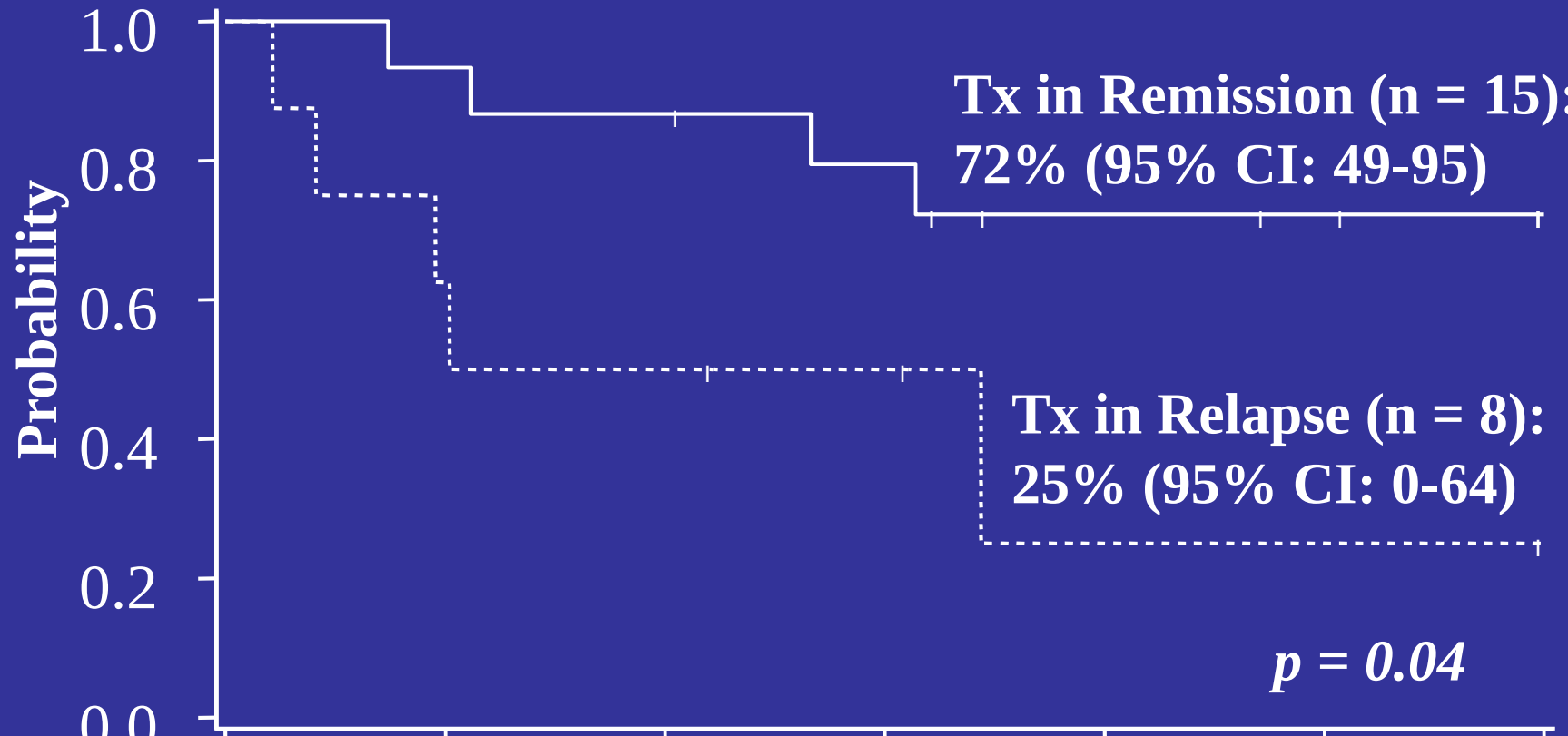
Problem :

- few stem cells in the graft

- solutions :
  - expansion ?
  - co-transplantation of mesenchymal cells of a third party ?
  - transplantation of 2 cord blood units of 2 donors ?

Disease-Free Survival

Adults transplanted with 2 Cord Blood



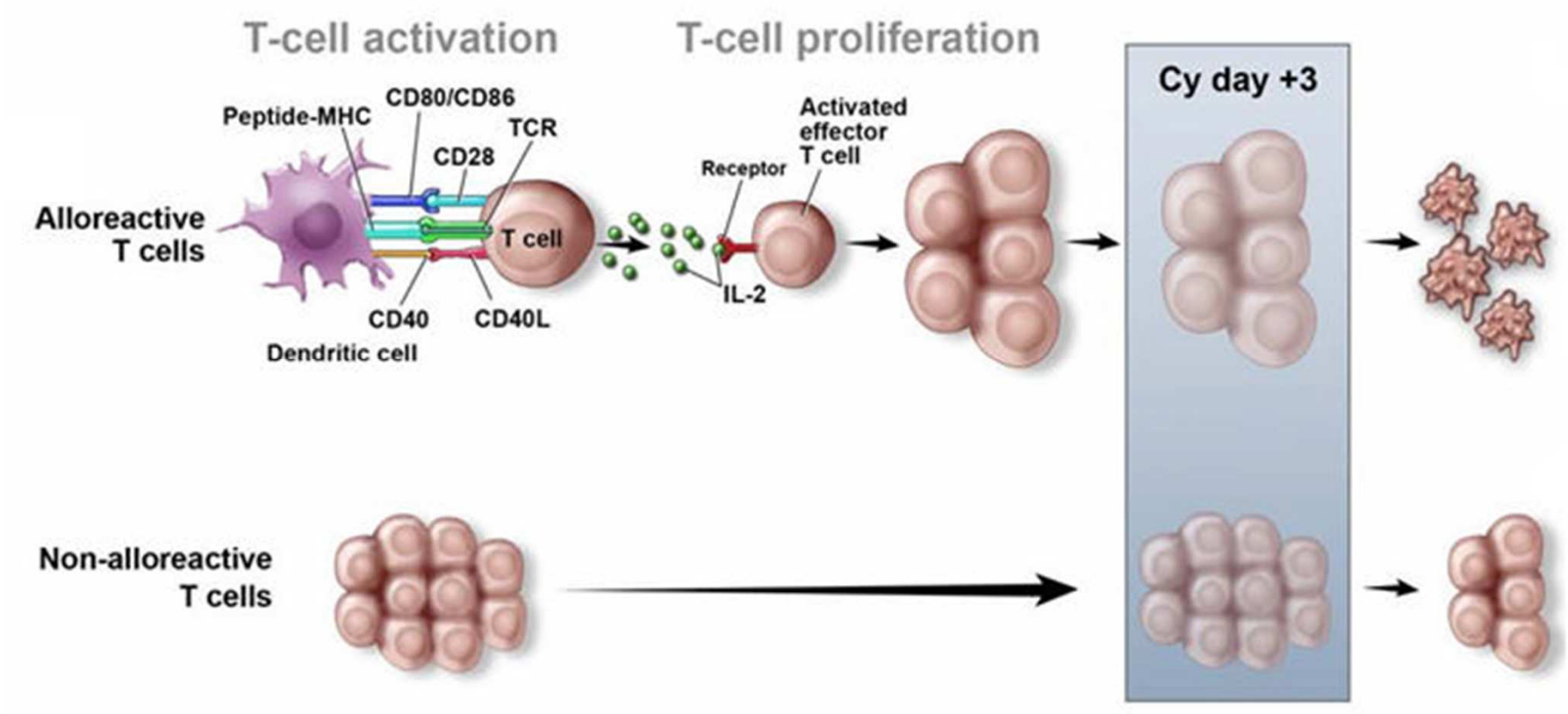
(Minneapolis)

DONNEURS HAPLO-MISMATCH

Caractéristiques des patients et des greffons

N°	Age	disease	selection	CD34+ 10^6/Kg	**CD3+ 10^4/Kg**	MM	GvHD	infection	outcome
Groupe pTCD									
#1	17	LAM/rec3	cellpro	14	120	no	II	CMV++	vivant RC à 17ans
#2	24	LNH/ RC2	cellpro	16	230	yes	III	CMV++	dcd GvH j161
#3	30	LAM/ ref	cellpro	2.37	18	no	IV		dcd GvH j42
#4	31	LAM/ RC2	cellpro	5.2	26	yes	II	VZV	vivant RC à 17ans
#5	46	AREBt/rec3	cellpro	5	54	no	Ext	HSV	dcd infection j168
#6	34	LAL/RC3	cellpro	3.8	15	no	II	PNC	dcd infectionj356
#7	34	LAM/RC2	cellpro	3.9	30	no	IV		dcd GvH j40
#8	14	LAM/rec 3	cellpro	9.4	67	ND	II		dcd rechute d50
#9	40	LAL/RC2	cellpro	3.9	83	ND	III-IV	aspergillus	dcd GvH j84
#10	20	LAM/rec2	cellpro	4	100	yes	IV		dcd GvH j20
#11	37	LMC/PC2	Milteny	4.45	14.4	yes	II	EBV nocardia	vivant RC à 9 ans
					10x10^4/Kg				
Groupe eTCD									
#12	24	LAM/ref	Milteny	11.1	1	yes	0	toxo	dcd infection j31
#13	24	LAM/ ref	Milteny	5.65	1.03	yes	0		dcd TRM j210
#14	19	LAM/ ref	Milteny	17.6	6.07	no	0		dcd rechute j120
#15	21	LAM/ ref	Milteny	14.5	0.86	yes	0		dcd rechute j124
#16	35	LAM/ ref	Milteny	7.7	4.39	yes	0		dcd rechute j59
#17	38	LAM/rel2	Milteny	7.3	1.5	yes	0		dcd rechute j93
#18	23	LAM/rel2	Milteny	7.88	8.94	yes	0		dcd rechute j87
#19	15	LAM/ ref	Milteny	8.61	3.3	yes	0		dcd rechute j185
#20	20	LAM/ ref	Milteny	18.81	4.65	yes	0		dcd TRM j130
#21	25	LAM/RC2	Milteny	8.04	4.07	yes	0		dcd rechute j138

Mécanismes d'action de l'ENDOXAN forte dose post greffe

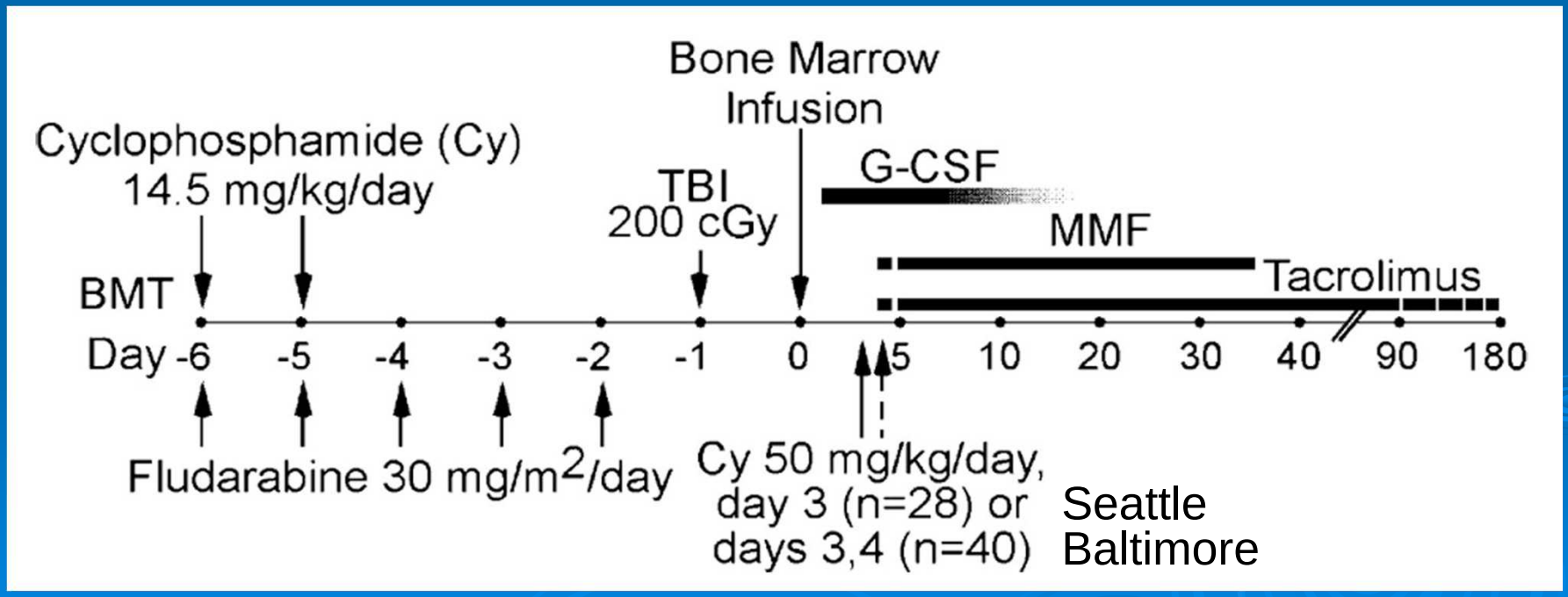


Déplétion des T alloréactifs

Préservation des clones quiescents

HLA haploidentical BMT for hematological malignancies using non myeloablative conditioning and high-dose post Tx cyclophosphamide

68 pts with poor risk hematological malignancies



Luznik, BBMT 2008

MAC-Haplo Atlanta, Bashey JCO 2013

Comparaison Haplo/ MRD/MUD

Haplo: n= 53: 40% LAM/MDS, 20% LAL, 40% autres (SMP, LNH, LH)

N=18 MAC
Fluda 25mg/m2 de J-6 à J-2
Bu 110 à 130mg/m2 J-7 à J-4
EDX 14,5mg/Kg/j J-3 et J-2
Greffe de ***CSP non T déplétée***

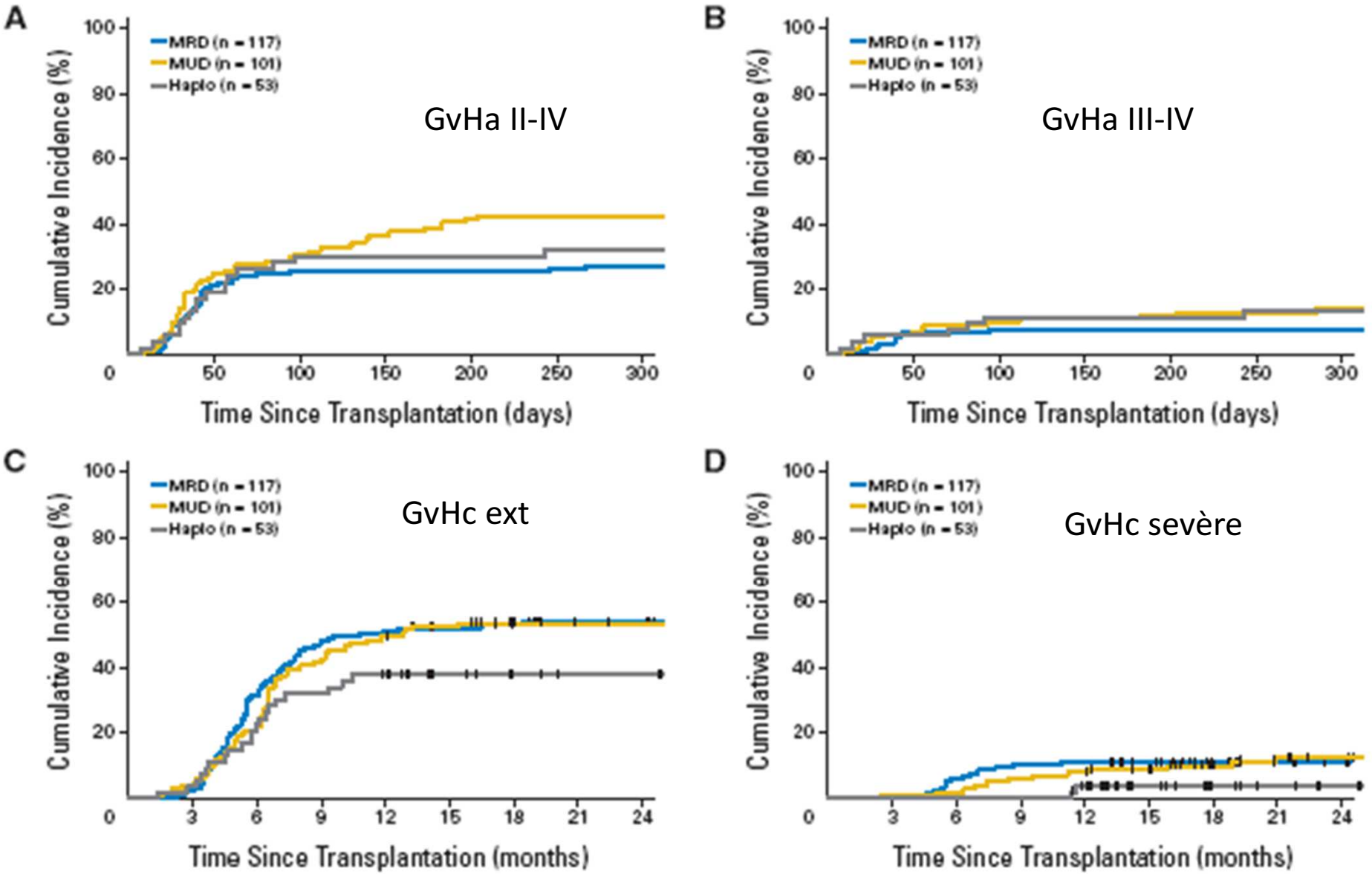
EDX 50mg/Kg J+3 et J+4

N=35 RIC
Fluda 30mg/m2 J-6 à J-2
TBI 2Gy J-1
EDX 14,5mg/Kg/j J-6 et J-5
Greffe de ***MO non T déplétée***

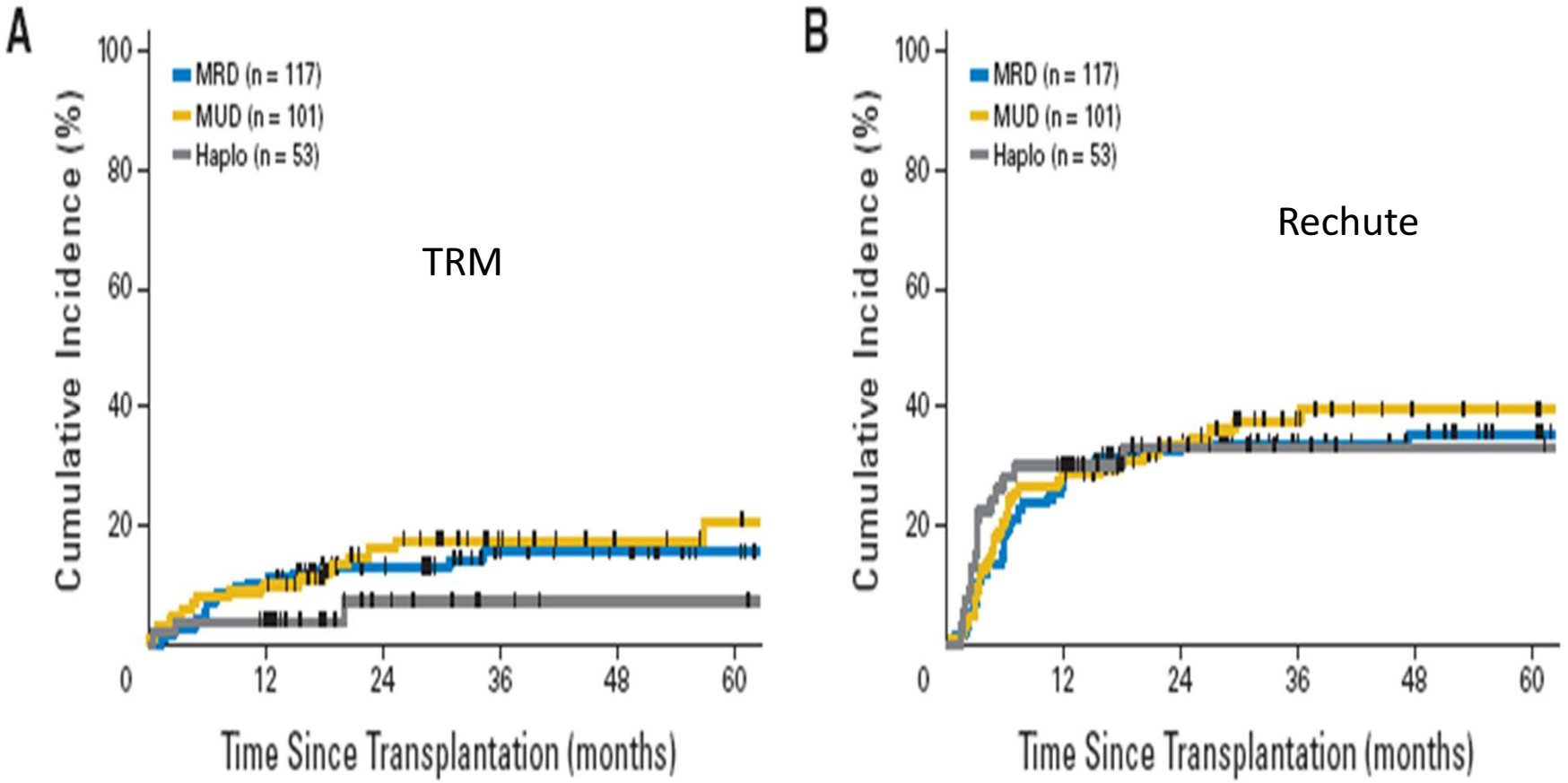
Génoid:n=117
CDT RIC et NMA

Fichier 10/10 ou 9/10: n=101
CDT RIC et NMA, ATG ou Campath

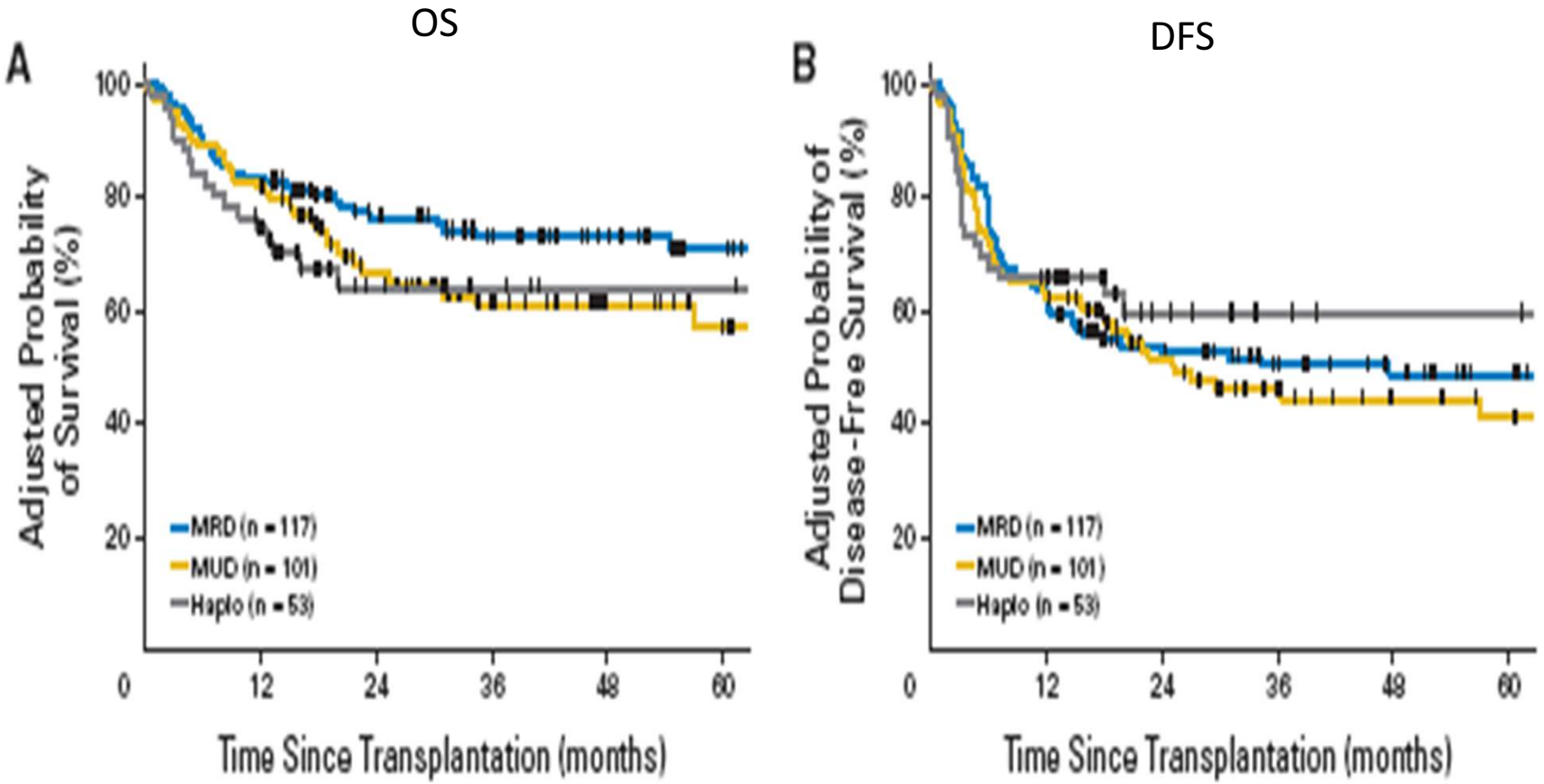
MAC-Haplo Atlanta, Bashey JCO 2013



MAC-Haplo Atlanta, Bashey JCO 2013



MAC-Haplo Atlanta, Bashey JCO 2013



AUTRE TECHNIQUE DE GREFFE HAPLO MISMATCH

The superiority of haploidentical related stem cell transplantation over chemotherapy alone as postremission treatment for patients with intermediate- or high-risk acute myeloid leukemia in first complete remission

Xiao-Jun Huang,[1] Hong-Hu Zhu,[1] Ying-Jun Chang,[1] Lan-Ping Xu,[1] Dai-Hong Liu,[1] Xiao-Hui Zhang,[1] Bin Jiang,[1] Qian Jiang,[1] Hao Jiang,[1] Yu-Hong Chen,[1] Huan Chen,[1] Wei Han,[1] Kai-Yan Liu,[1] and Yu Wang[1]

[1]Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Peking University People's Hospital and Peking University Institute of Hematology, Beijing, China

BLOOD, 7 JUNE 2012 • VOLUME 119, NUMBER 23

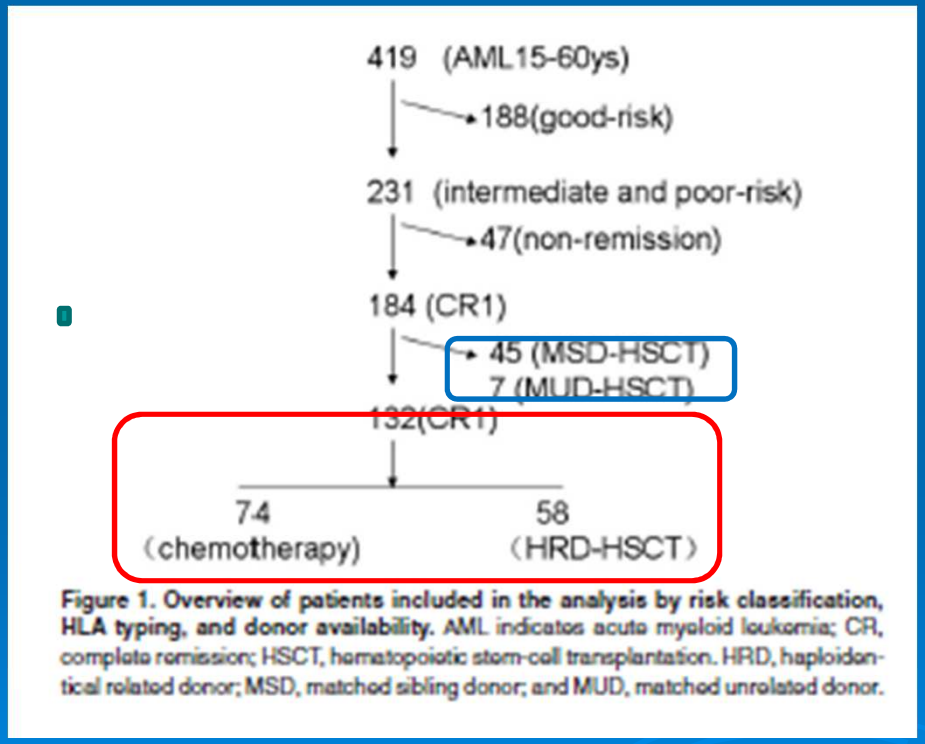


Figure 1. Overview of patients included in the analysis by risk classification, HLA typing, and donor availability. AML indicates acute myeloid leukemia; CR, complete remission; HSCT, hematopoietic stem-cell transplantation. HRD, haploidentical related donor; MSD, matched sibling donor; and MUD, matched unrelated donor.

For HRD-HSCT patients, as described previously,[11,12,18] G-CSF–mobilized BM and peripheral blood stem cells were used as a graft resource. The conditioning regimen was a modification of BU/CY (busulfan/cyclophosphamide) and antithymocyte globulin (ATG), which consisted of the following: cytosine arabinoside (4 g/m^2/d IV) on days −10 and −9; busulfan (12 mg/kg orally in 12 doses) on days −8, −7, and −6; cyclophosphamide (1.8 g/m^2/d IV) on days −5 and −4; semustine (250 mg/m^2, orally) on day −3, and thymoglobulin (rabbit ATG [Sangstat-Genzyme] 2.5 mg/kg/d IV or porcine ATG [Bioproduct Inc] 20 mg/kg/d) through days −5 to −2. All transplantation recipients received cyclosporine A (CsA), mycophenolate mofetil (MMF), and short-term methotrexate (MTX) as GVHD prophylaxis. The dosage of CsA was 2.5 mg/kg/d IV from day −9 until bowel function returned to normal, at which point, patients were switched to oral CsA. Every 12 hours, 0.5 g of MMF was administered orally from day −9 to day +30 after transplantation; after that time, the MMF dose was tapered to half until day 160 and discontinued thereafter.

Patients non randomisés: greffe haplo ou non après « discussion » (haplo plus jeunes : 30 vs 47)

Risque de rechute

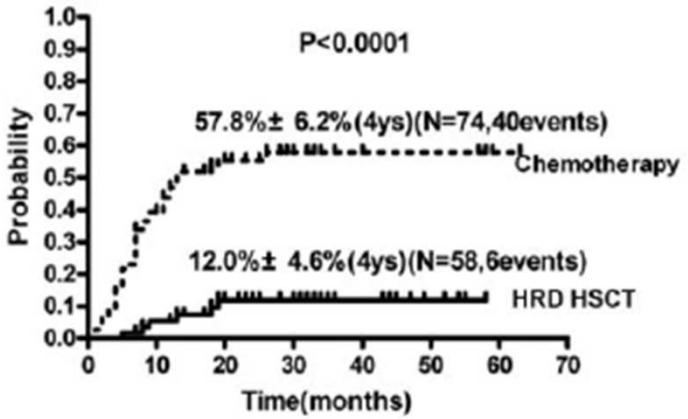


Figure 4. CIR of the HRD-HSCT group and the chemotherapy-alone group of patients with intermediate- and high-risk AML.

dfs

os

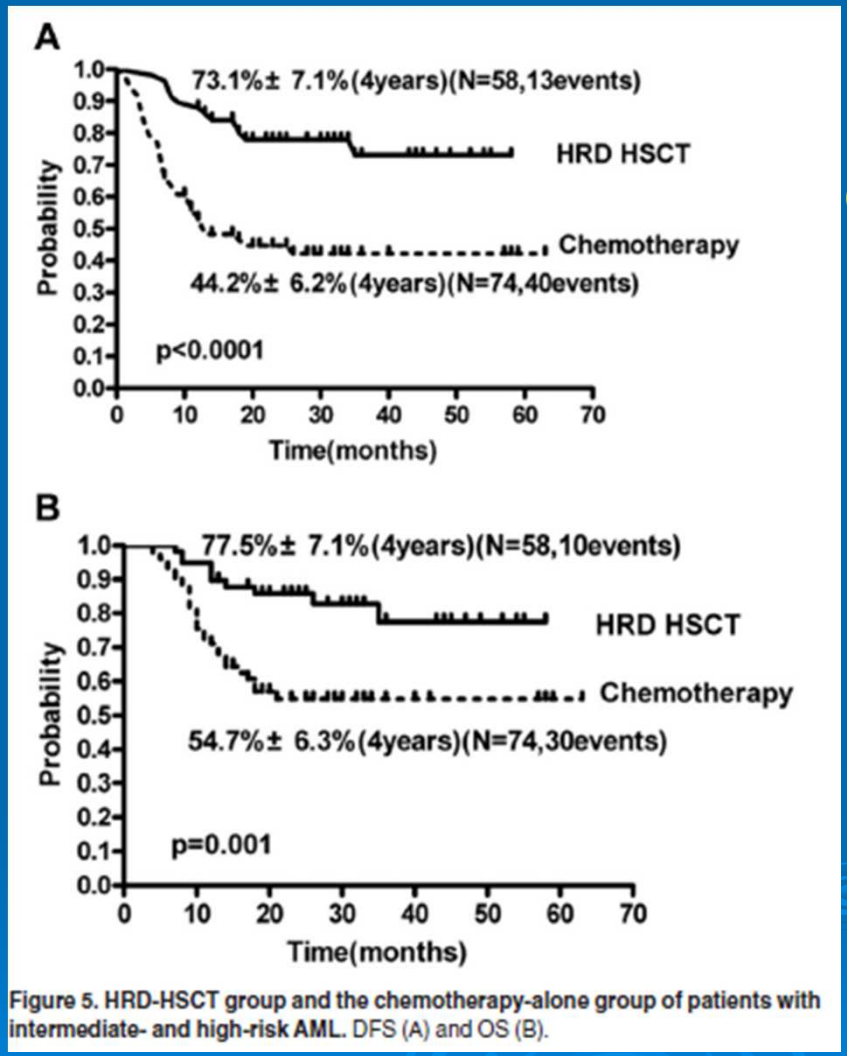


Figure 5. HRD-HSCT group and the chemotherapy-alone group of patients with intermediate- and high-risk AML. DFS (A) and OS (B).

Malheureusement pas de comparaison entre greffes haplo et greffes géno et phéno identiques

BLOOD, 7 JUNE 2012 • VOLUME 119, NUMBER 23

DONNEURS en 2014

- 1970 : - germain HLA-identique
- 1990 : - donneur non apparenté → phéno 6/6 (générique) → fichier (> 20 M)
  → phéno 10/10 (allélique)

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- sang placentaire (enfants) → banque de sang placentaire (> 700 000 unités)

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Il n'y a plus de malades sans donneur même si la greffe est difficile

On n'a plus à « attendre un donneur »

- Comment greffer les LAM
  - - avec quel donneur ?
  - - avec quel conditionnement?
  - -avec quel greffon?
  - -avec quelle prophylaxie de la GVHD ?
- Quand greffer les LAM

CONDITIONNEMENT

Endoxan – TBI
Seattle 70

10 Gy en single dose

Débit de dose

fractionnement

BU-Cy
Baltimore 80

Adjonction d'autres Drogues

Endoxan

Bu injectable

Non myélo-ablatif
Fin années 90

-BU
-Cy
-TLI
- TBI 2 Gy
- Fluda
- SAL
-Campath
-…

ATTENUE
(1970 – …..)

…

Les vieux supportent mieux

Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation in Patients With Acute Myeloid Leukemia

Boglarka Gyurkocza, Rainer Storb, Barry E. Storer, Thomas R. Chauncey, Thoralf Lange, Judith A. Shizuru, Amelia A. Langston, Michael A. Pulsipher, Christopher N. Bredeson, Richard T. Maziarz, Benedetto Bruno, Finn B. Petersen, Michael B. Maris, Edward Agura, Andrew Yeager, Wolfgang Bethge, Firoozeh Sahebi, Frederick R. Appelbaum, David G. Maloney, and Brenda M. Sandmaier

VOLUME 28 · NUMBER 17 · JUNE 10 2010

JOURNAL OF CLINICAL ONCOLOGY

Conditionnement par TBI 2 Gy + ou - Fluda
LAM de novo ou secondaires
Prophylaxie GVHD : Ciclo + MMF
Age médian : 60 ans (5-74)
117 donneurs géno id ,123 MUD et 34 mismatch

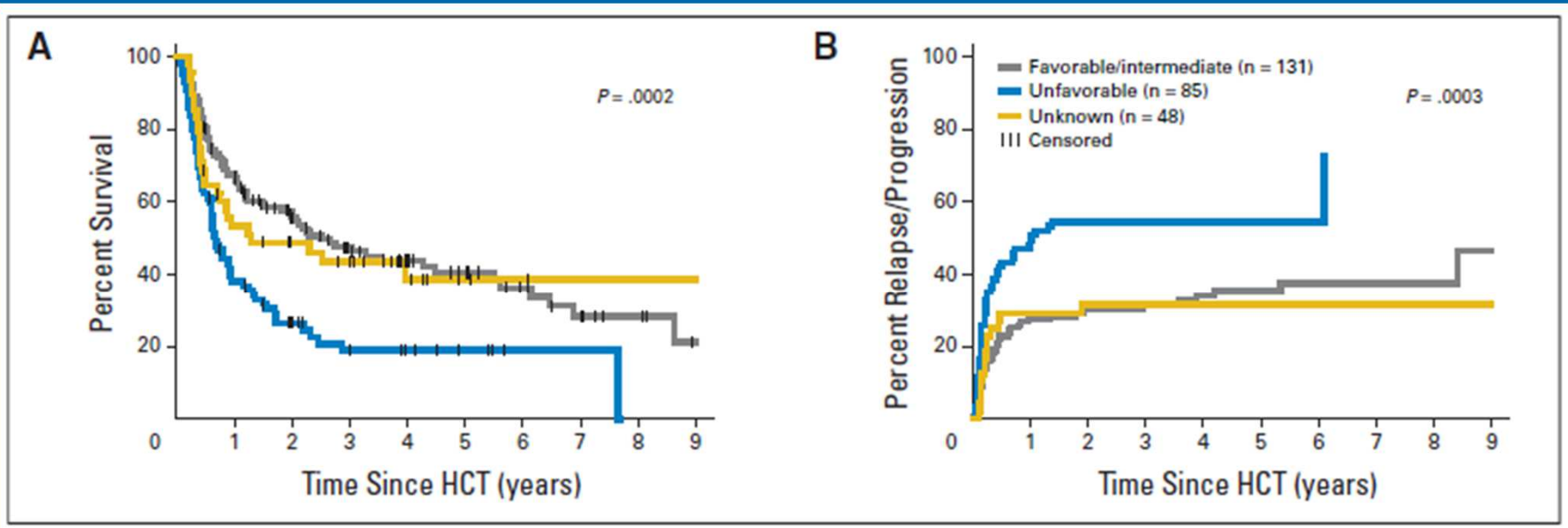


Fig 2. (A) Overall survival and (B) relapse/progression stratified by cytogenetic risk before hematopoietic cell transplantation (HCT). Total number of patients was 264 because cytogenetic data were not available in 10 patients.

VOLUME 28 · NUMBER 17 · JUNE 10 2010
JOURNAL OF CLINICAL ONCOLOGY

MAC versus RIC (et NMA)

BLOOD, 24 FEBRUARY 2011 • VOLUME 117, NUMBER 8

(Comparaison de séries rétrospectives)

Table 5. Comparisons of myeloablative and reduced intensity or nonmyeloablative conditioning in adult patients with AML

Study	Patient population	Sample size	LFS	OS	Other comments
Aoudjhane et al, 2005[104]; Multicenter, EBMT	AML, > 50 y, MSD only	722, RIC = 315, MAC = 407	Similar	Similar	Decreased acute GVHD, chronic GVHD, and TRM, but increased relapse with RIC
Alyea et al, 2006[70]; single center, Boston	AML/MDS, 21-70 y, MRD and URD donors	136, (AML, 82) RIC = 39, MAC = 97	Similar	Similar	Decreased TRM, and increased relapse with RIC
Scott et al, 2006[102]; single center, Seattle	MDS/sAML with previous MDS, 40-72 y, MRD and URD	150, (AML, 55) NMA = 38, MAC = 112	Similar	Similar	No difference in relapse/TRM
Shimoni et al, 2006[72]; single center, Tel-Hashomer	AML/MDS, 17-70 y, MRD and URD	112, (AML, 56) RIC = 67, MAC = 45	Similar	Similar	Similar outcomes for patients in remission at HCT, inferior outcomes of patients with active disease treated with RIC
Flynn et al, 2007[103]; single center, Minnesota	AML/MDS, 19-69 y, MRD and URD (included UCB grafts)	219, (AML, 160) RIC = 32, MAC = 187	Similar	Similar	Similar TRM, but increase in relapse with RIC
Ringden et al, 2009[101]; EBMT multicenter	AML, 16-76 y, URD transplants only	1555, RIC = 401, MAC = 1154	Similar	Not reported	Reduced NRM in ≥50 y, and increased relapse in patients <50 y with RIC.
Lim et al, 2010[106]; EBMT, multicenter	MDS/sAML with previous MDS, ≥ 50 y, MRD and URD	1333, (AML, 334), RIC = 833, MAC = 500	Not reported	Similar	Increased relapse, and decreased TRM with RIC
Khabori et al, 2010[99]; single center, Toronto	AML/MDS, 40-60 y, MRD and URD transplants	101, (AML, 77), RIC = 39, MAC = 62	Similar	Similar	Poor outcome in patients with high-risk disease biology attributable to higher relapse rate
Luger et al, CIBMTR[105], multicenter	AML/MDS, 18-70 y, MRD and URD	5179, RIC/NMA = 1448, MAC = 3731	Similar between MAC vs RIC, inferior for NMA	Similar between MAC vs RIC, More relapse with NMA	Late TRM negated any advantage offered by RIC or NMA

CIBMTR indicates Center for International Blood and Marrow Transplant Research; EBMT, European Group for Blood and Marrow Transplantation; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation; LFS, leukemia-free survival; MAC, myeloablative conditioning; MRD, matched related donor; MUD, matched unrelated donor; NMA, nonmyeloablative, NRM, nonrelapse mortality; OS, overall survival; RIC, reduced-intensity conditioning; sAML, secondary AML; TRM, treatment-related mortality; UCB, umbilical cord blood; and URD, unrelated donor.

ET POUR LES MAC :
TBI- EDX ou BU- CY ?

TBI-CY vs. BuCY in AML CR1

Blaise et al., Blood, 10: 2578, 1992

- Phase III randomized trial – 101 patients
- TBI
  - Most FTBI
  - 79% 12 Gy at 2 Gy BID
  - Few 10 Gy single fx
- CY 120 mg/kg
- BU 16 mg/kg

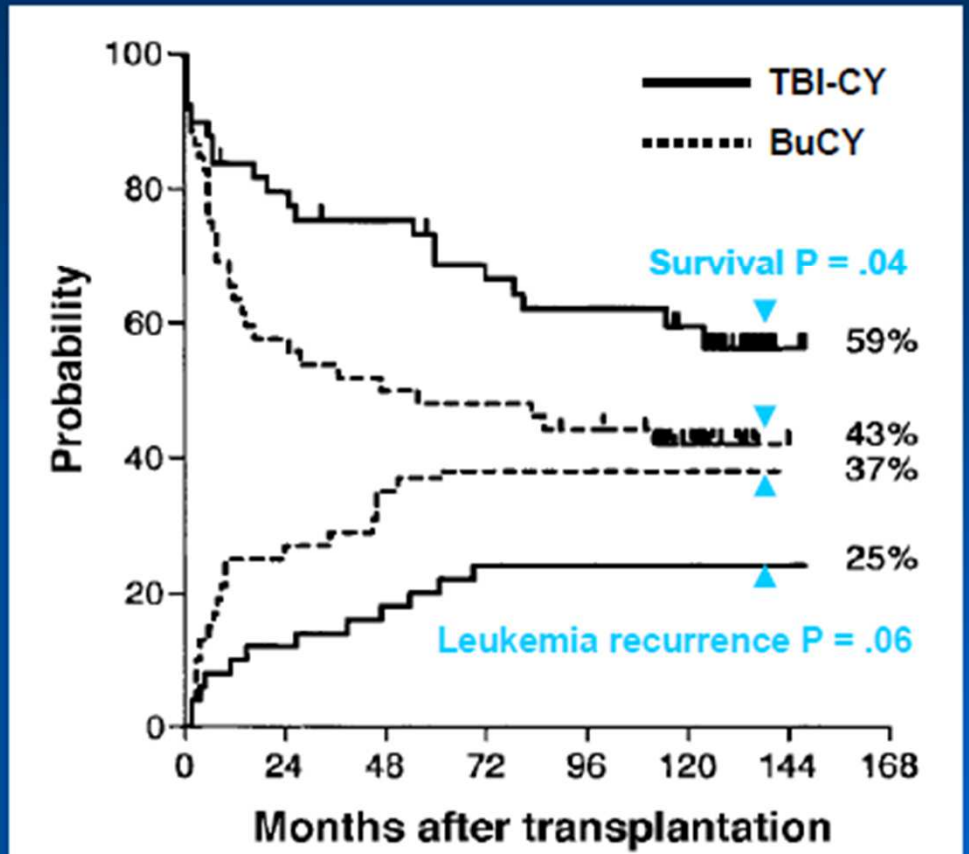
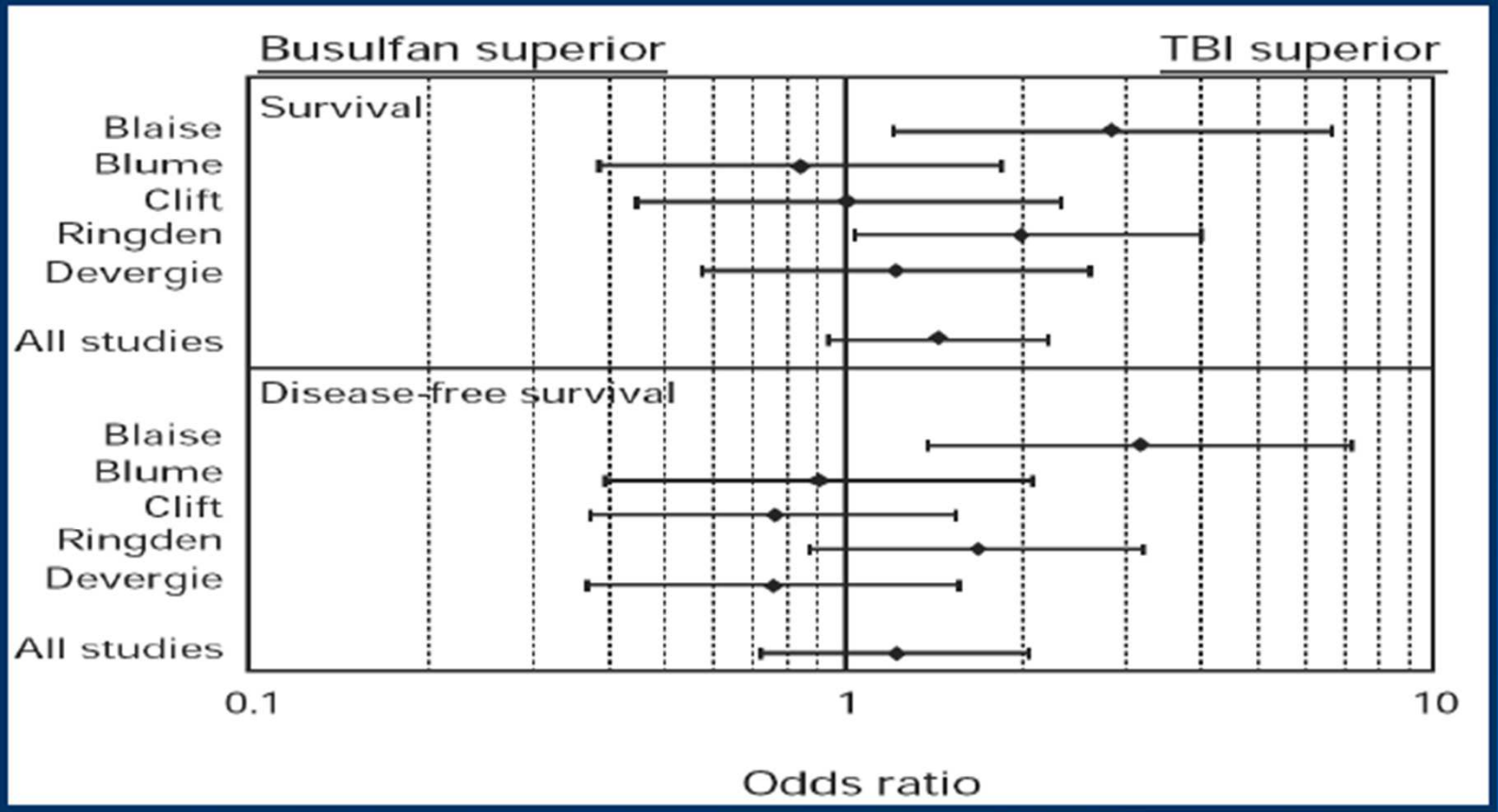


Figure 1. Kaplan-Meier estimate of survival and cumulative incidence of leukemia recurrence. Kaplan-Meier estimates ($P = .04$) are represented by the top 2 curves; cumulative incidences ($P = .06$), by the bottom 2 curves; BUCY estimates, by the dotted lines; CYTBI estimates, by the solid lines.

Blaise et al, 97: 3669, 2001 update
Median 10.8 year follow-up

Meta-analysis of 5 Trials: CY-TBI or E-TBI vs. BuCy



Hartman et al, BMT 1998; 22: 439-43

Mais apport du Busulfan IV (Busilvex)

Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI

Edward A. Copelan,[1] Betty K. Hamilton,[2] Belinda Avalos,[1] Kwang Woo Ahn,[3] Brian J. Bolwell,[2] Xiaochun Zhu,[3] Mahmoud Aljurf,[4] Koen van Besien,[5] Christopher Bredeson,[6] Jean-Yves Cahn,[7] Luciano J. Costa,[8] Marcos de Lima,[9] Robert Peter Gale,[10] Gregory A. Hale,[11] Joerg Halter,[12] Mehdi Hamadani,[13] Yoshihiro Inamoto,[14] Rammurti T. Kamble,[15] Mark R. Litzow,[16] Alison W. Loren,[17] David I. Marks,[18] Eduardo Olavarria,[19] Vivek Roy,[20] Mitchell Sabloff,[6] Bipin N. Savani,[21] Matthew Seftel,[22] Harry C. Schouten,[23] Celalettin Ustun,[24] Edmund K. Waller,[25] Daniel J. Weisdorf,[24] Baldeep Wirk,[26] Mary M. Horowitz,[3] Mukta Arora,[24] Jeff Szer,[27] Jorge Cortes,[28] Matt E. Kalaycio,[2] Richard T. Maziarz,[29] and Wael Saber[3]

Table 1. Characteristics of patients who underwent first allogeneic transplantation with an HLA-identical sibling or unrelated donor for AML in CR1 and received preparation with Cy/TBI, oral or IV BuCy, reported to CIBMTR from 2000 to 2006

Characteristics of patients	Cy/TBI	Oral BuCy	IV BuCy
Number of patients	586	408	236
Number of centers	117	86	80
Patient-related			
Age, median (range), years	37 (2-63)	34 (2-62)	40 (2-64)
10 y or less	17 (3)	26 (6)	27 (11)
11-20	66 (11)	65 (16)	35 (15)
21-30	110 (19)	88 (22)	29 (12)
31-40	144 (25)	80 (20)	31 (13)
41-50	159 (27)	97 (24)	65 (28)
Older than 50	90 (15)	52 (13)	49 (21)

Etude rétrospective

BLOOD, 5 DECEMBER 2013 • VOLUME 122, NUMBER 24

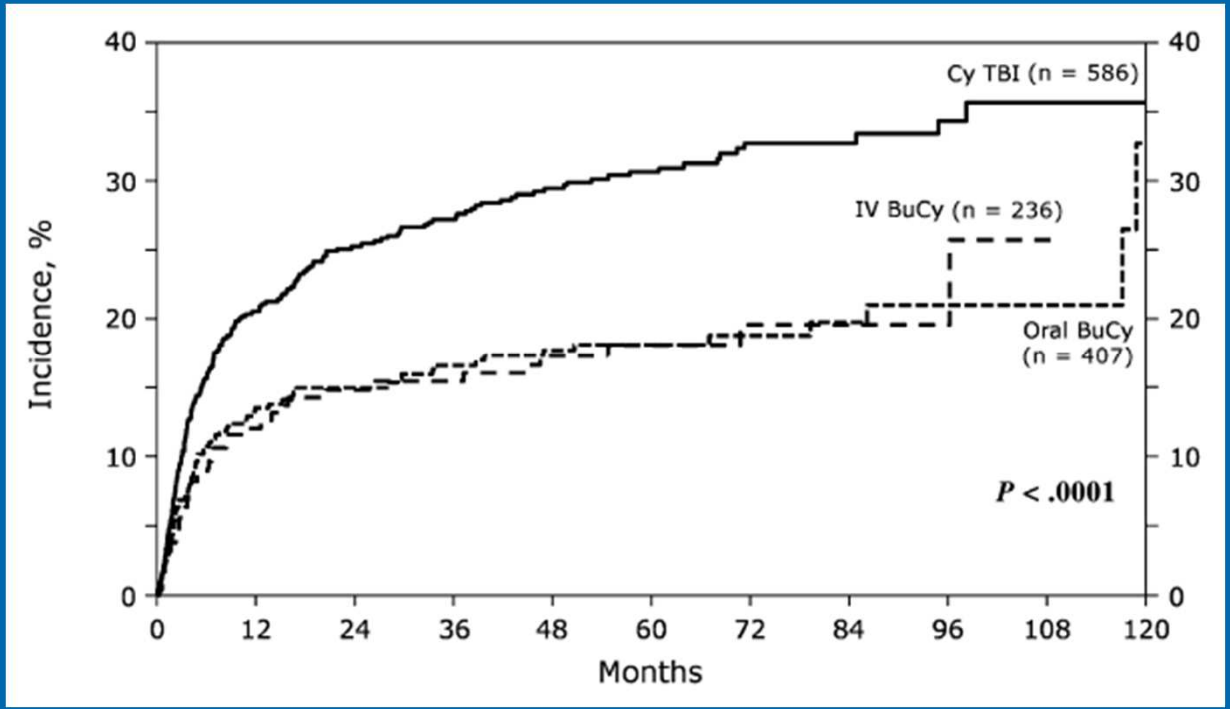


Figure 1. Univariate cumulative incidence for non-relapse mortality according to preparative regimen.

BLOOD, 5 DECEMBER 2013 • VOLUME 122, NUMBER 24

LFS

OS

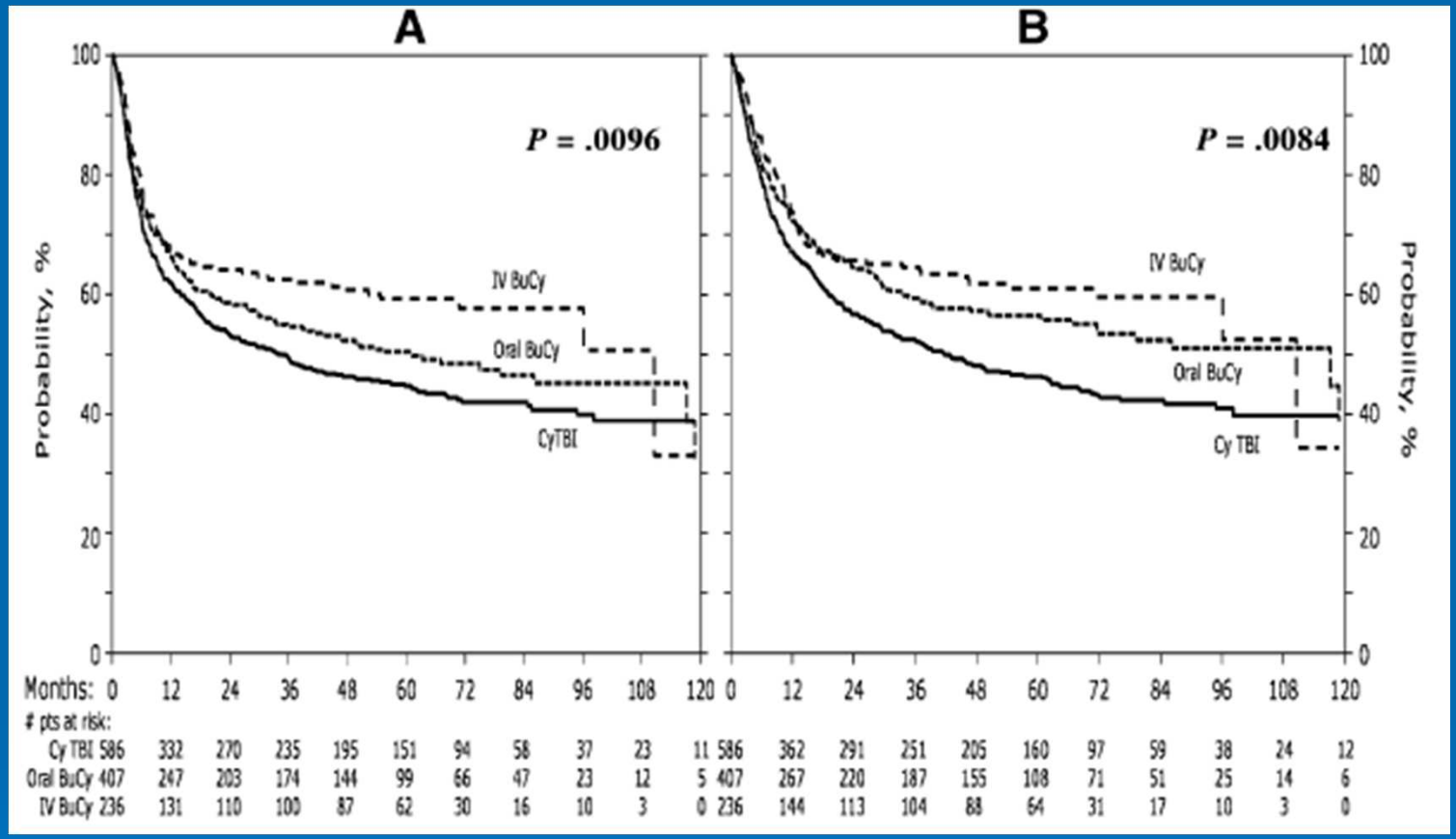


Figure 2. Adjusted probabilities of LFS and OS for all patients according to preparative regimen. LFS is represented in panel A. OS is represented in panel B.

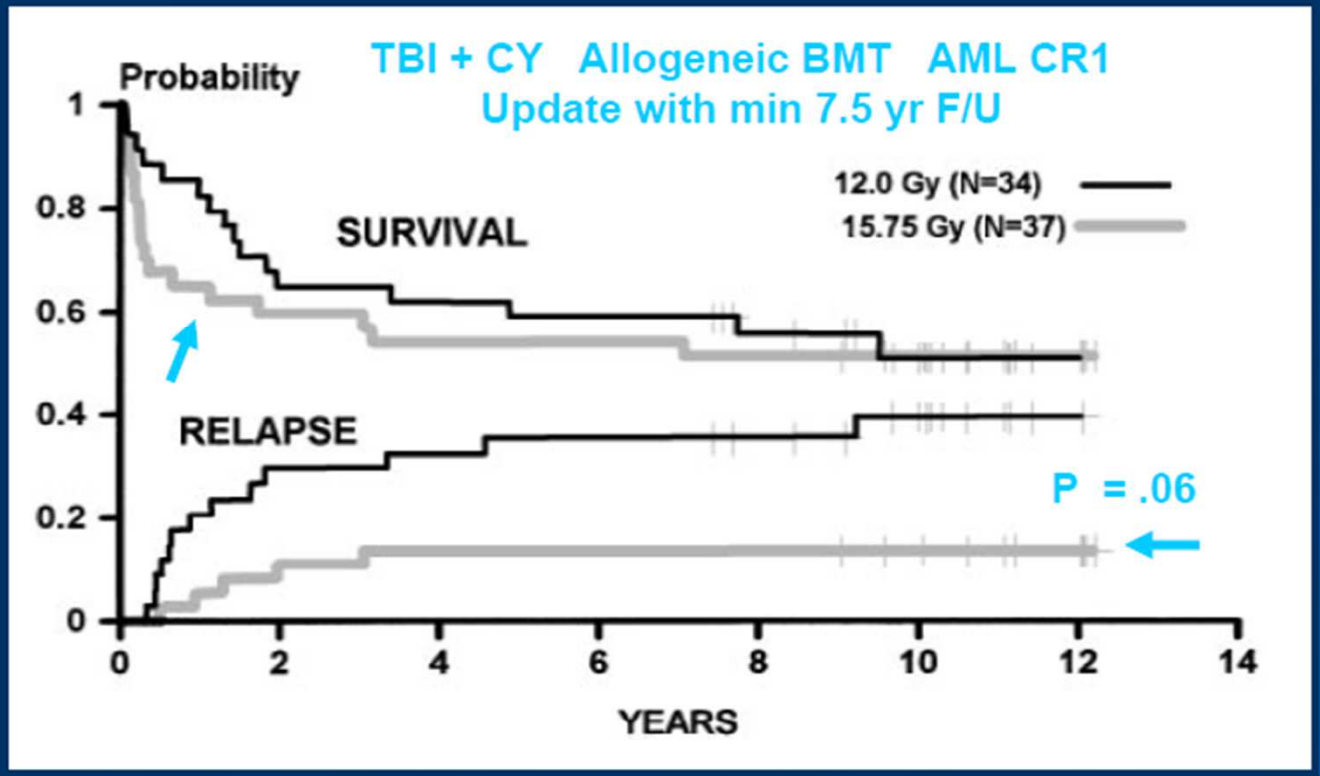
BLOOD, 5 DECEMBER 2013 • VOLUME 122, NUMBER 24

In haematopoietic SCT for acute leukemia TBI impacts on relapse but not survival: results of a multicentre observational study

C Aristei[1], A Santucci[2], R Corvò[3], G Gardani[4], U Ricardi[5], G Scarzello[6], SM Magrini[7], V Donato[8], L Falcinelli[9], A Bacigalupo[10], F Locatelli[11], F Aversa[12], E Barbieri[13] and Italian TBI working group[14]

Bone Marrow Transplantation (2013) **48,** 908–914

Rationale: TBI Dose Response
12 Gy vs. 15.75 Gy



Clift et al, Blood 1998; 92: 1455-6

Quel avenir pour la radiothérapie :
la TMI ???

Dose Escalation of Total Marrow Irradiation With Concurrent Chemotherapy in Patients With Advanced Acute Leukemia Undergoing Allogeneic Hematopoietic Cell Transplantation

Jeffrey Y.C. Wong, MD,* Stephen Forman, MD,† George Somlo, MD,†
Joseph Rosenthal, MD,†,‡ An Liu, PhD,* Timothy Schultheiss, PhD,*
Eric Radany, MD, PhD,* Joycelynne Palmer, PhD,§ and Anthony Stein, MD†

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Received Feb 5, 2012, and in revised form Mar 10, 2012. Accepted for publication Mar 19, 2012

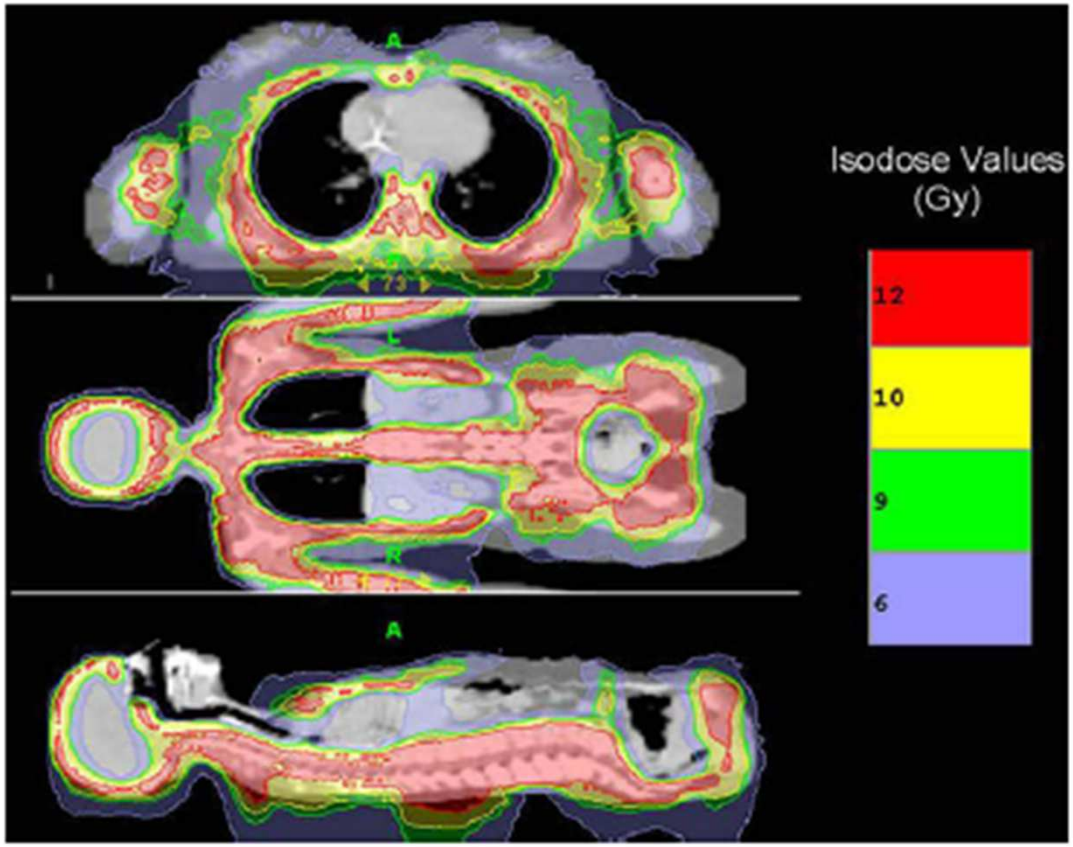


Fig. 1. Color wash shows dose distribution of the first patient treated with targeted total-body irradiation (TBI) using Tomotherapy. The target structure is skeletal bone. Reprinted from Biol Blood Marrow Transplant, vol. 12, Wong JYC, Liu A, Schultheiss T, et al. Targeted total marrow irradiation using three-dimensional image-guided tomographic intensity-modulated radiation therapy: An alternative to standard total body irradiation, pages 306–315. Copyright 2006, with permission from American Society for Blood and Marrow Transplantation.

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 1, pp. 273–279, 2009

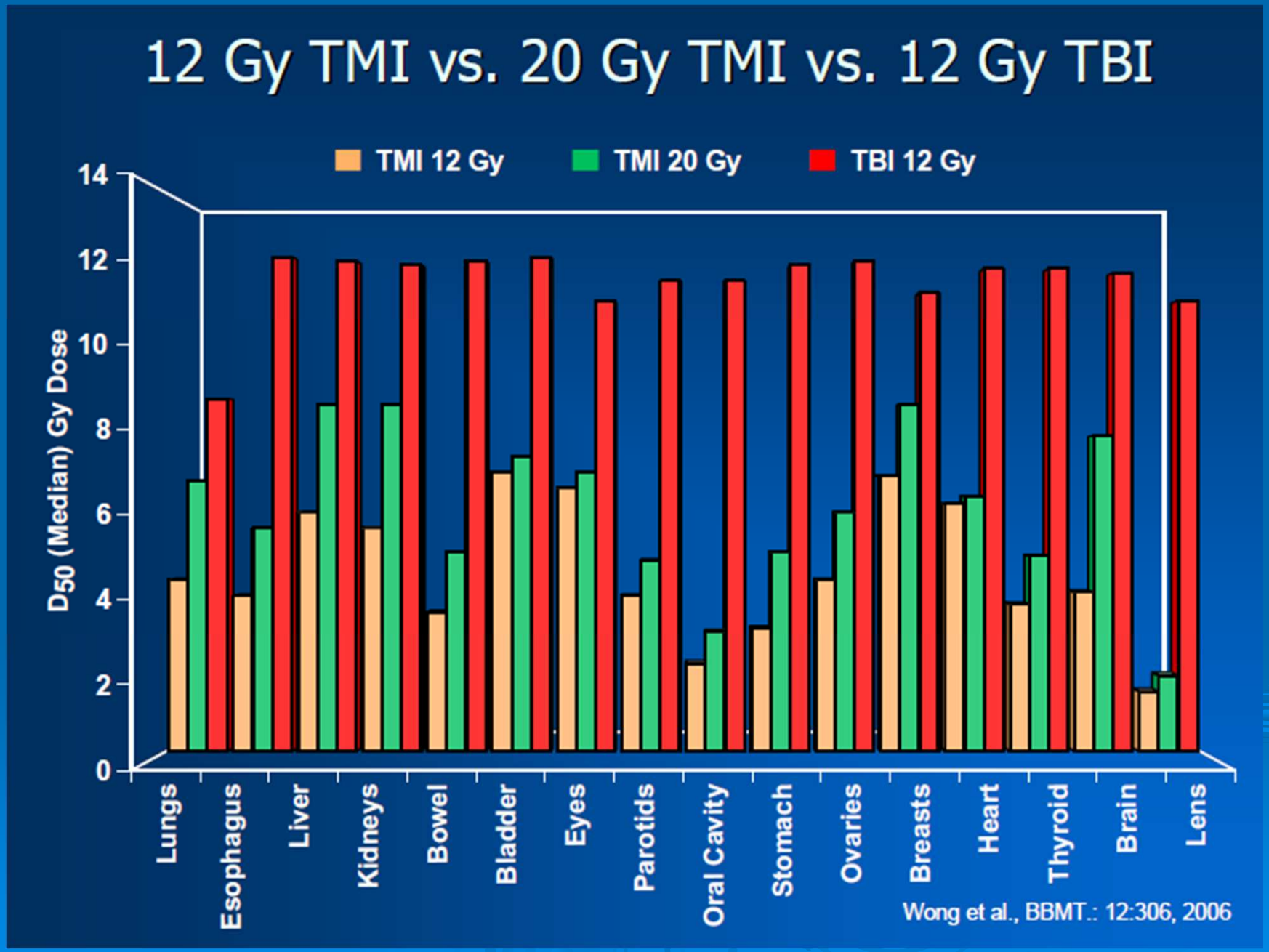

12 Gy TMI vs. 20 Gy TMI vs. 12 Gy TBI
TMI 12 Gy
TMI 20 Gy
TBI 12 Gy
D50 (Median) Gy Dose
0
2
4
6
8
10
12
14
Lungs
Esophagus
Liver
Kidneys
Bowel
Bladder
Eyes
Parotids
Oral Cavity
Stomach
Ovaries
Breasts
Heart
Thyroid
Brain
Lens
Wong et al., BBMT.: 12:306, 2006

Table 3 Trial 1 clinical summary

Patient	Age/sex	TMI dose (Gy)	Dx	Status	Type of transplant	% peripheral blasts
1	44/F	12	ALL	IF	MR	51
2	21/M	12	ALL	1RL	MR	0
3	34/M	12	Mixed lineage	IF	MR	0 (chloromas)
4	20/M	13.5	ALL	1RL	MR	0
5	24/F	13.5	ALL	1RL	MR	0
6	53/M	13.5	AML	IF	MMU	85
7	35/M	15	ALL	1RL	MR	0
8	54/F	15	AML	1RL	MMU	70
9	31/F	15	AML	IF	MMU	24
10	31/F	15	ALL	IF	MR	0
11	22/F	15	AML	1RL	MR	0 (chloromas in CNS)
12	50/F	15	AML	IF	MMU	58

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; AWD = alive with disease; BM = bone marrow; CNS = central nervous system; CR = complete remission; cGVHD = chronic graft versus host disease; DOD = dead of disease; IF = induction failure; MMU = mismatched unrelated; MR = matched related; MU = matched unrelated; NA = not available; NE = not evaluable; NRM = nonrelapse mortality; 1RL = first relapse; 2RL = second relapse.

Table 1 Doses to critical organs at risk and target structures in trial 1

	Mean D80 (range)		
Organ at risk	12 Gy (n=3)	13.5 Gy (n=3)	15 Gy (n=6)
Esophagus	4.1 (4.0-4.3)	4.1 (3.8-4.2)	4.2 (3.6-4.8)
Oral cavity	2.6 (2.3-2.8)	4.1 (2.0-5.3)	3.4 (2.1-6.3)
Lungs	5.1 (4.7-5.6)	4.8 (4.4-5.5)	4.6 (3.8-5.0)
Small intestine	4.8 (4.0-5.8)	4.7 (4.1-5.6)	4.7 (3.9-5.1)
Kidneys	6.0 (5.7-6.2)	4.2 (3.9-4.5)	5.1 (4.2-5.6)
Heart	6.0 (5.4-6.6)	6.0 (5.4-6.4)	4.7 (4.0-5.2)
Target organs			
Bone	12.1 (12.0-12.2)	12.5 (12.2-12.9)	13.1 (12.5-14.0)
Lymph nodes	12.1 (12.0-12.1)	12.6 (12.2-13.0)	13.1 (12.5-13.9)
Spinal cord	12.1 (11.8-12.5)	12.8 (12.2-13.6)	13.3 (12.6-14.1)
Liver	12.3 (11.9-12.7)	12.8 (12.2-13.6)	13.3 (12.6-14.1)
Spleen	12.3 (12.0-12.7)	12.7 (12.2-13.4)	13.2 (12.6-14.1)
Ribs/sternum	11.8 (11.2-12.3)	12.5 (12.2-12.8)	13.1 (12.7-13.8)
Brain	11.9 (11.8-11.9)	12.1 (12.0-12.2)	12.3 (12.2-12.5)
Skull	11.9 (11.7-12.1)	12.0 (12.0-12.1)	12.3 (12.1-12.4)

- Comment greffer les LAM
  - - avec quel donneur ?
  - - avec quel conditionnement?
  - -avec quel greffon?
  - -avec quelle prophylaxie de la GVHD ?
- Quand greffer les LAM

GREFFONS

Années 1970 : MOELLE « BMT »

et éventuellement (1980)

- T-déplétion ex vivo : sélection négative
  : sélection positive
  +/- Add back
- T-déplétion in vivo

Années 1990 : CSP :

- prise plus rapide
- modifications de l'histoire de la GVH
- permet la prise - malgré des conditionnements moins lourds
  - malgré une T-déplétion l

Sang placentaire :

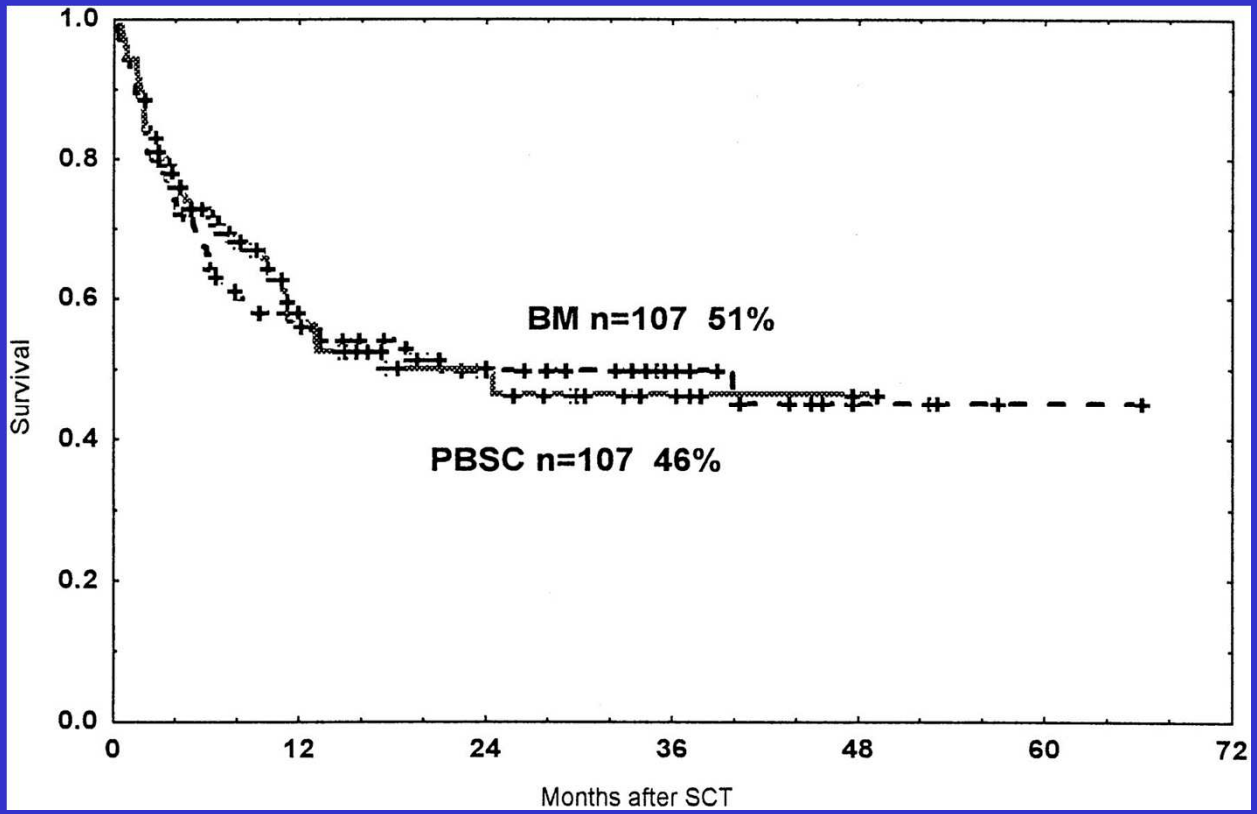
- exigence HLA moindre
- mais problème quantitatif : expansion ?
  2 sangs placentaires ?

GREFFONS

Possibilité d'adjoindre au greffon (T-déplété ou non) :

- lymphocytes du donneur (contrôle du chimérisme)
- lymphocytes modifiés :
  - Transduits par un gène suicide (HsTK)
  - CTL anti-CMV, EBV …
  - Cellules mésenchymateuses
  - T reg (CD4+ CD25+)
  - NK cultivés et activés
  - …

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



CSP (107) vs BMT(107) in MUD

Remberger, M. et al. Blood 2001;98:1739-1745

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Mobilized Peripheral Blood Stem Cells Compared with Bone Marrow as the Stem Cell Source for Unrelated Donor Allogeneic Transplantation with Reduced-Intensity Conditioning in Patients with Acute Myeloid Leukemia in Complete Remission: An Analysis from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

Arnon Nagler,[1] Myriam Labopin,[2] Avichai Shimoni,[1] Dietger Niederwieser,[3] Ghulam J. Mufti,[4] Axel R. Zander,[5] Renate Arnold,[6] Hildegard Greinix,[7] Jan J. Cornelissen,[8] Graham H. Jackson,[9] Charles Craddock,[10] Donald W. Bunjes,[11] Arnold Ganser,[12] Nigel H. Russell,[13] Slawomira Kyrcz-Krzemien,[14] Vanderson Rocha,[15,] Mohamad Mohty[16,*]*

Biol Blood Marrow Transplant 18:1422-1429, 2012

Etude rétrospective EBMT

Table 1. Patient and Disease Characteristics

Patient Characteristics	PBSC	BM	*P* Value
Number of patients	508	94	
Median age in years (range)	57 (17-77)	51 (17-76)	<.0001
Gender	M: 281 (55.4%)	M: 63 (69.2%)	.72
	F: 226 (44.6%)	F: 28 (30.8%)	
CMV status	Neg = 111 (33.9%)	Neg = 19 (29.7%)	.51
	Pos = 216 (66.1%)	Pos = 45 (70.3%)	
Transplantation year	2006 (2000-2007)	2005 (2000-2007)	.001
Disease status*	CR1 = 310 (61%)	CR1 = 56 (60%)	.79
	CR2 = 198 (39%)	CR2 = 38 (40%)	
WBC† (10^9/L) median (range)	10.0 (0.5-461)	10.9 (0.7-145)	.79
FAB classification	M1 M2-M3 = 51.5%	M1 M2-M3 = 47.1%	.33
	M4-M5 = 34.2%	M4-M5 = 42.9%	
	M0 M6 M7 = 14.3%	M0 M6 M7 = 10%	

PBSC indicates peripheral blood stem cells; BM, bone marrow; CMV, cytomegalovirus; CR1, first complete remission; CR2, second complete remission; Neg, negative; Pos, positive; FAB, French, American, British.
*At transplantation.
†At diagnosis.

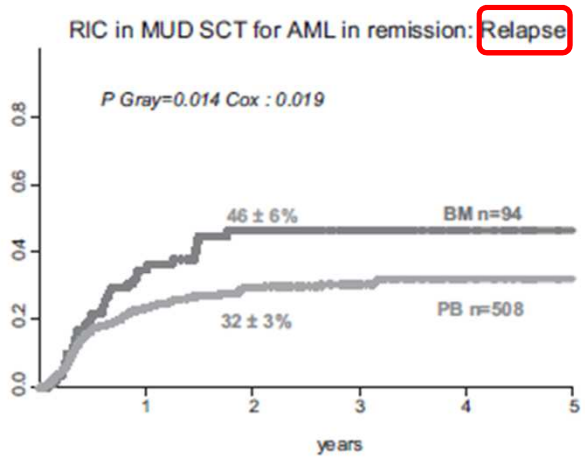


Figure 2. Probability of relapse after reduced-intensity conditioning (RIC) allogeneic stem cell transplant (alloSCT) with mobilized peripheral blood stem cell graft (PBSC; n = 508) versus bone marrow (BM) graft (n = 94; *P* Gray = .014; *P* Cox = .019).

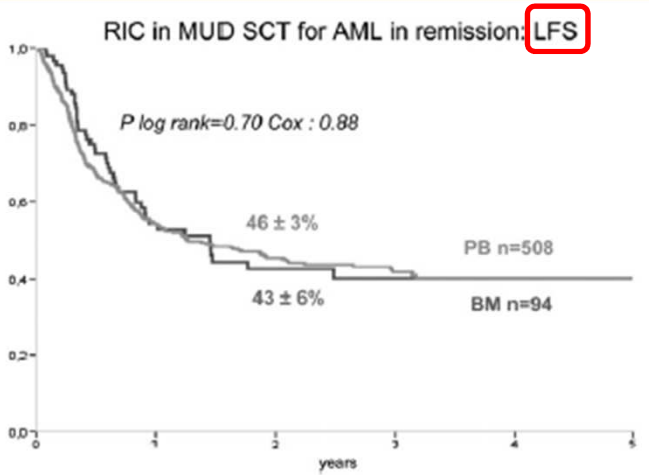


Figure 4. Probability of leukemia-free-survival (LFS) at 2 years after reduced-intensity conditioning (RIC) allogeneic stem cell transplant (alloSCT) with mobilized peripheral blood stem cell (PBSC) graft (n = 508) versus bone marrow (BM) graft (n = 94; *P* log-rank = .70; *P* Cox = .88).

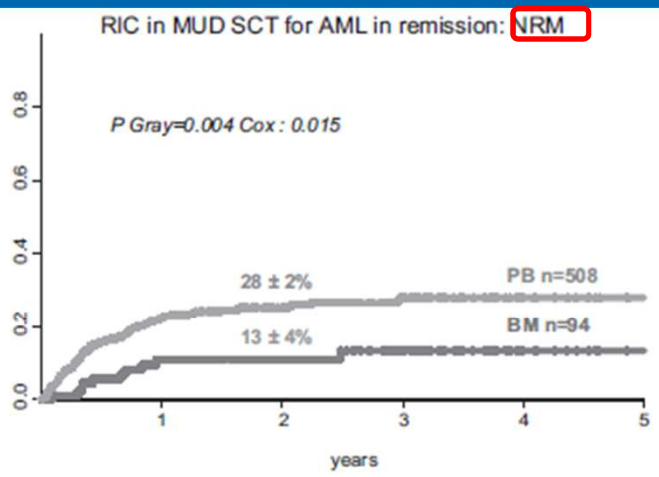


Figure 1. Probability of 2-year non-relapse mortality (NRM) after reduced-intensity conditioning (RIC) allogeneic stem cell transplant (alloSCT) with mobilized peripheral blood stem cell graft (PBSC; n = 508) versus bone marrow (BM) graft (n = 94; *P* Gray test = .004; *P* Cox = .015).

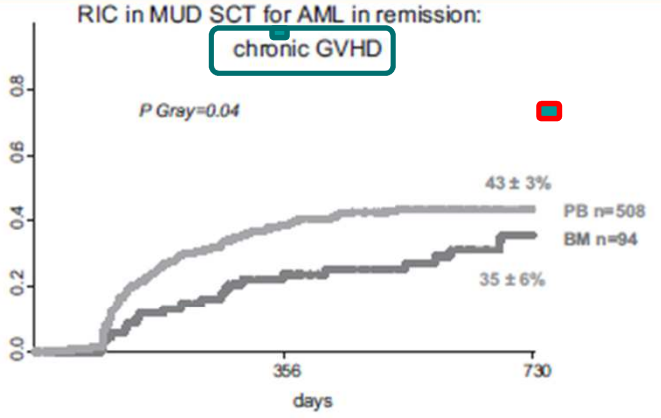
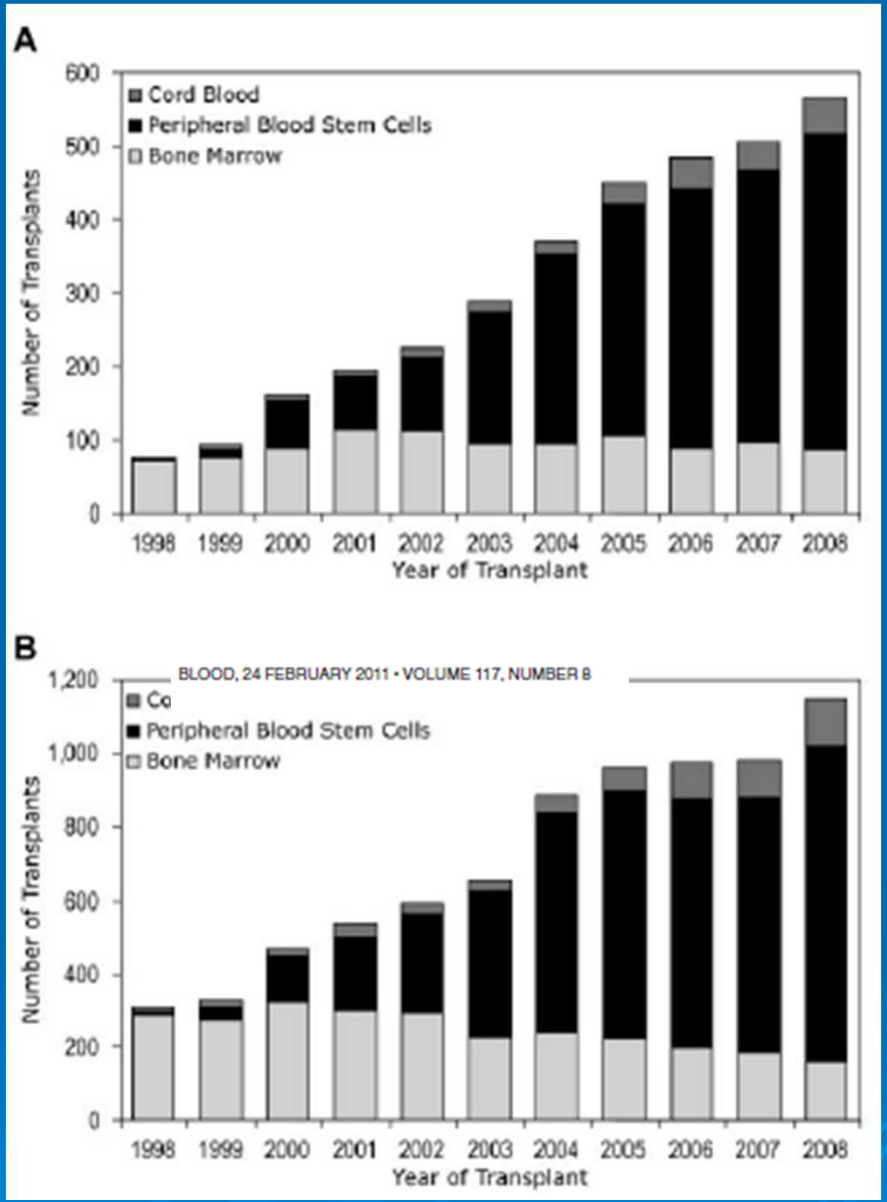


Figure 3. Probability of chronic graft-versus-host disease (cGVHD) at 2 years after reduced-intensity conditioning (RIC) allogeneic stem cell transplant (alloSCT) with mobilized peripheral blood stem cell (PBSC) graft (n = 508) versus bone marrow (BM) graft (n = 94; *P* Gray = .04).

Biol Blood Marrow Transplant 18:1422-1429, 2012

Greffes enregistrées
par l'IBMTR
de 1998 à 2008

CSP:
Solution de facilité ?



Adultes donneurs apparentés

Adultes donneurs non apparentés

BLOOD, 24 FEBRUARY 2011 • VOLUME 117, NUMBER 8

Figure 1. Trends in allogeneic HCT activity in adult AML patients (≥ 18 years) by the use of unrelated donors according to disease status at HCT: cases registered with CIBMTR from 1998 to 2008. (A) Adult AML patients (≥ 18 years), CR1, CR2, CR3, and not in remission, undergoing unrelated HCT. (B) Adult AML patients (≥ 18 years) undergoing unrelated HCT in CR1.

- Comment greffer les LAM
  - - avec quel donneur ?
  - - avec quel conditionnement?
  - -avec quel greffon?
  - -avec quelle prophylaxie de la GVHD ?
- Quand greffer les LAM

PROPHYLAXIE DE LA GVH

1970 : - MTX (Seattle) EDX (Baltimore)

1990 : - CSA
- MTX + CSA
- T-déplétion ex vivo (… + DLI : 2000)

1990 : - T-déplétion in vivo (ATG – CAMPATH)

2000 : - Tacrolimus
- Cellcept
- Rapamycine …
- Conditionnement atténué

Choix entre risque de GVH et risque de rechute

Ex Vivo T Cell–Depleted versus Unmodified Allografts in Patients with Acute Myeloid Leukemia in First Complete Remission

Ulas D. Bayraktar [1], Marcos de Lima [1], Rima M. Saliba [1], Molly Maloy [2], Hugo R. Castro-Malaspina [2], Julianne Chen [1], Gabriela Rondon [1], Alexander Chiattone [1], Ann A. Jakubowski [2], Farid Boulad [2,3], Nancy A. Kernan [2,3], Richard J. O'Reilly [2,3], Richard E. Champlin [1], Sergio Giralt [2], Borje S. Andersson [1], Esperanza B. Papadopoulos [2,*]

[1] *Department of Stem Cell Transplantation and Cellular Therapy, University of Texas M.D. Anderson Cancer Center, Houston, Texas*
[2] *Adult Bone Marrow Transplantation Service, Memorial Sloan-Kettering Cancer Center, Weill Medical College of Cornell University, New York, New York*
[3] *Pediatric Bone Marrow Transplantation Service, Memorial Sloan-Kettering Cancer Center, Weill Medical College of Cornell University, New York, New York*

Comparison of Demographic and Clinical Characteristics of Patients Who Underwent Transplantation with T Cell–Depleted (TCD) or Unmodified Grafts

Characteristics	TCD N = 115, n (%)	Unmodified N = 181, n (%)	*P* Value
Age, yr*	52 (19-71)	48 (18-63)	<.001
>50	66 (57)	76 (42)	.010
Female	58 (50)	90 (50)	NS
Time CR1 to transplantation, d*	83 (12-304)	97 (8-455)	.040
Etiology			<.001
de novo	60 (52)	144 (80)	
Secondary	38 (33)	24 (13)	
Therapy-related	17 (15)	13 (7)	
Cytogenetic risk status			NS
Good	1 (1)	2 (1)	
Intermediate	72 (63)	103 (57)	
Poor	42 (37)	76 (42)	
Donor type			<.001
Matched related	56 (49)	103 (57)	
Matched unrelated	32 (28)	64 (35)	
Mismatch	27 (23)	14 (8)	
Donor/recipient gender			NS
Match	54 (47)	89 (49)	
Mismatch	61 (53)	92 (51)	
Stem cell source			<.001
Bone marrow	8 (7)	57 (32)	
Peripheral blood	107 (93)	124 (68)	

CR1 indicates first complete remission; NS, not significant.
* Data presented as median (range).

Comparaison rétrospective de LAM greffées avec MAC

- à NY après T déplétion
- Houston sans T déplétion

Hétérogénéité des CDT

Les greffes avec MUD ont toutes reçus de l'ATG dans le CDT…

Biol Blood Marrow Transplant 19 (2013) 898–903

Biol Blood Marrow Transplant 19 (2013) 898–903

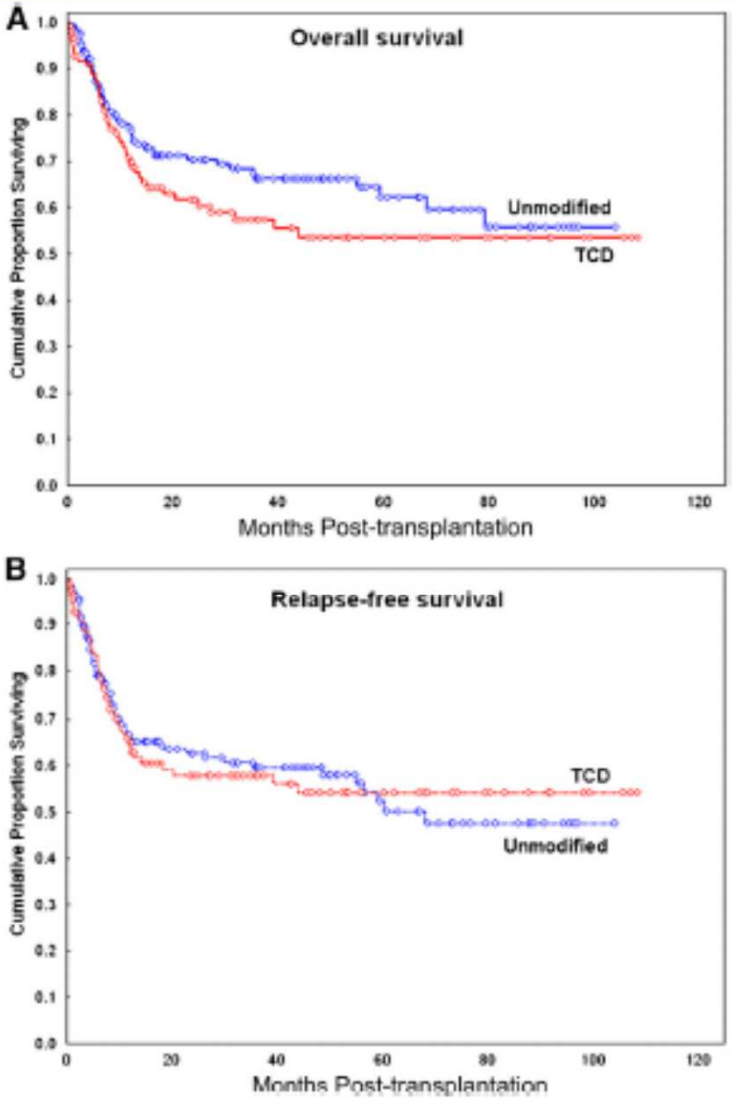


Figure 1. Probabilities of overall (top) and relapse-free (bottom) survival among recipients of T cell–depleted (TCD) and unmodified grafts.

Comparison of Outcomes in the T Cell–Depleted (TCD) and Unmodified Graft Groups Based on Univariate Analysis Using Cox's Proportional Hazards Regression

Outcome	TCD (95% CI)	Unmodified (95% CI)	PValue
Relapse-free survival			
1 yr	62% (51-70)	65% (57-72)	.6
3 yr	58% (47-67)	60% (51-67)	.7
Overall survival			
1 yr	68% (58-76)	74% (66-80)	.3
3 yr	57% (47-67)	66% (58-74)	.2
Relapse incidence			
1 yr	17% (11-26)	21% (15-28)	.4
3 yr	18% (12-27)	25% (19-33)	.3
Nonrelapse mortality			
100 d	8% (4-15)	3% (1-7)	.07
1 yr	18% (12-27)	13% (9-19)	.2
3 yr	24% (17-34)	16% (11-23)	.1
Acute GVHD (grade 2-4)			
100 d	5% (2-11)	18% (13-24)	.005
Chronic GVHD			
3 yr	13% (8-22)	53% (46-62)	<.001

GVHD indicates graft-versus-host disease.

Predictors of Overall Survival (OS) and Relapse-free Survival (RFS) Evaluated by Univariate Analyses

Value	RFS, HR at 3 years (95% CI)	OS, HR at 3 years (95% CI)
Age, yr		
≤50	Reference	
>50	1.0 (.7-1.4)	1.1 (.8-1.7)
Gender		
Male	Reference	
Female	1.1 (.7-1.7)	1.1 (.7-1.5)
Etiology		
de novo	Reference	
Secondary	1.4 (.9-2.2)	1.7 (1.1-2.8)*
Therapy-related	.9 (.4-1.7)	.9 (.4-2.0)
Cytogenetic risk		
Good/intermediate	Reference	
Poor	1.1 (.7-1.6)	.9 (.6-1.4)
Donor type		
Matched related	Reference	
Matched unrelated	1.1 (.8-1.7)	1.2 (.8-1.9)
Mismatch	1.0 (.5-1.7)	1.2 (.7-2.2)
Stem cell source		
Bone marrow	Reference	
Peripheral blood	1.4 (.8-2.5)	1.6 (.9-2.9)
Graft type		
T cell–depleted	Reference	
Unmodified	.9 (.6-1.4)	.7 (.5-1.1)

* $P = .02$.

Prophylaxie de base :

Après MAC et donneur géno-id : Ciclo + MTX court

Après RIC et donneur géno-id : Ciclo + MMF

et éventuellement surtout si CSP : ATG + Ciclo

Est-il nécessaire de faire ,de principe ,une T déplétion in vivo avec de l'ATG chez certains malades en particulier en cas de donneurs phéno-identiques ?

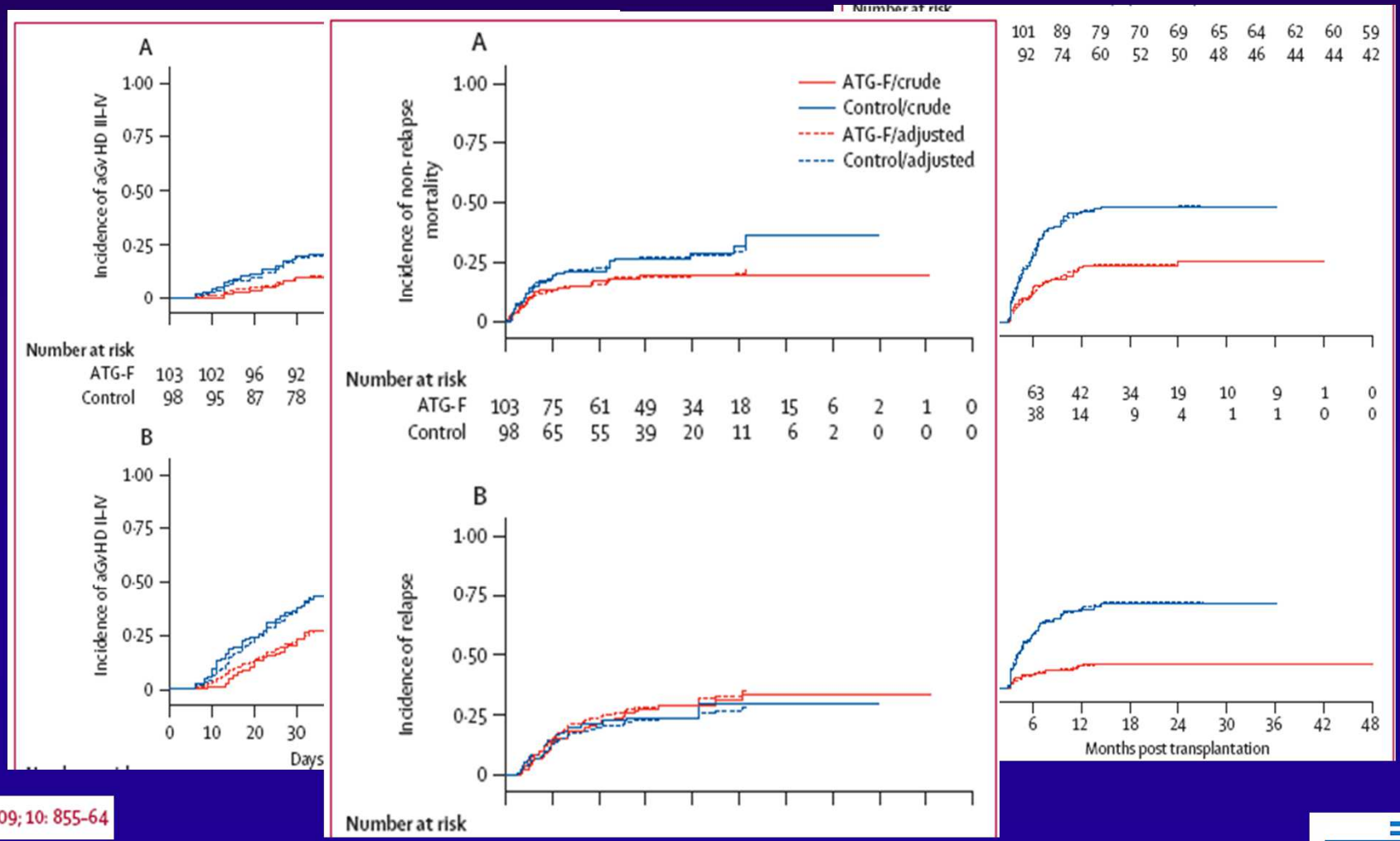
Essai randomisé:
CSA + MTX avec ou sans ATG chez des malades greffés pour hémopathies malignes avec des donneurs non apparentés

Characteristic	ATG-F (N = 103)	Control (N = 98)
Patient age (median, range)	40 (18-60)	39 (18-60)
<40 years	47	50
≥40 years	56	48
Donor age (median, range)	35 (20-58)	37 (18-56)
<40 years	62	64
≥40 years	32	30
Unknown	9	4
Patient/donor sex		
Patient male/donor female	14	13
Other	87	85
Unknown	2	0
Patient/donor CMV status		
Patient negative/donor negative	23	44
Other	80	54
Diagnosis		
ALL	37	33
AML	55	46
CML	6	11
MDS	5	5
OMF	0	3
Disease status		
Early	64	43
Advanced	39	55
Conditioning regimen		
TBI/Cy	54	48
Busulfan/Cy	26	26
TBI/etoposide/Cy	11	6
TBI/other	7	9
No TBI/other	5	9
Stem-cell source		
BM	21	16
PB	82	82

Lancet Oncol 2009 (10) 855

Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial

*Jürgen Finke, Wolfgang A Bethge, Claudia Schmoor, Hellmut D Ottinger, Matthias Stelljes, Axel R Zander, Liisa Volin, Tapani Ruutu, Dominik A Heim, Rainer Schwerdtfeger, Karin Kolbe, Jiri Mayer, Johan A Maertens, Werner Linkesch, Ernst Holler, Vladimir Koza, Martin Bornhäuser, Hermann Einsele, Hans-Jochem Kolb, Hartmut Bertz, Matthias Egger, Olga Grishina, Gérard Socié, for the ATG-Fresenius Trial Group**



Lancet Oncol 2009; 10: 855–64

MAIS :

No mismatch	67	65
Mismatch	26	21
2-digit match/4-digit mismatch	4	2
2-digit mismatch	22	19
Unknown	10	12

ATG pour les greffes avec MUD?

Dans ce papier l'avantage pour le groupe recevant de l'ATG pourrait être lié au fait :

- qu'un pourcentage important de donneurs n'étaient pas phéno-identiques 10/10 en allélique. (en effet l'identité HLA- C n'était pas contrôlée et l'identité HLA-A et B n'était contrôlée qu'au 2eme digit)
- que le nombre de patients à haut risque de rechute était plus élevé dans le groupe sans ATG.
- que plus de 80% de l'ensemble des patients avaient reçu des CSP.

Il n'est donc pas sûr qu'il faille faire de principe de l'ATG dans toutes les greffes avec MUD surtout avec un greffon médullaire.

- Comment greffer les LAM
  - - avec quel donneur ?
  - - avec quel conditionnement?
  - -avec quel greffon?
  - -avec quelle prophylaxie de la GVHD ?
- Quand et qui greffer

Qui greffer et quand ?

INDICATIONS

Table 3. Guidelines for indications for HCT in adult patients with AML

	MSD	MUD	UCB	Haplo-identical
First remission				
Favorable cytogenetics				
APL	No	No	No	No
CBF-AML*	No	No	No	No
With m*KIT*	Uncertain	Uncertain	Uncertain	Uncertain
Without m*KIT*	No	No	No	No
CN-AML*	Yes	Uncertain	Uncertain	Uncertain
"m*NPM1* without FLT3ITD"	No	No	No	No
"m*CEBPA*"†	No	No	No	No
Others than above	Yes	Uncertain	Uncertain	Uncertain
Intermediate risk with abnormal cytogenetics	Yes	Uncertain	Uncertain	Uncertain
Adverse	Yes	Yes	Yes‡	Yes‡
Second remission	Yes	Yes	Yes‡	Yes‡
Not in remission§	Yes	Yes	Uncertain	Uncertain

Uncertain implies insufficient published data for a recommendation.

APL indicates acute promyelocytic leukemia; CBF, core binding factor [t(8;21) or Inv(16)]; CN-AML, cytogenetically normal AML; FLT3ITD, FMS-related tyrosine kinase 3–internal tandem duplication; HCT, hematopoietic cell transplantation; m*CEBPA*, mutated *CEBPA*; m*KIT*, KIT mutations; MSD, matched sibling donor; m*NPM1*, mutated *NPM1*; MUD, matched unrelated donor; and UCB, umbilical cord blood.

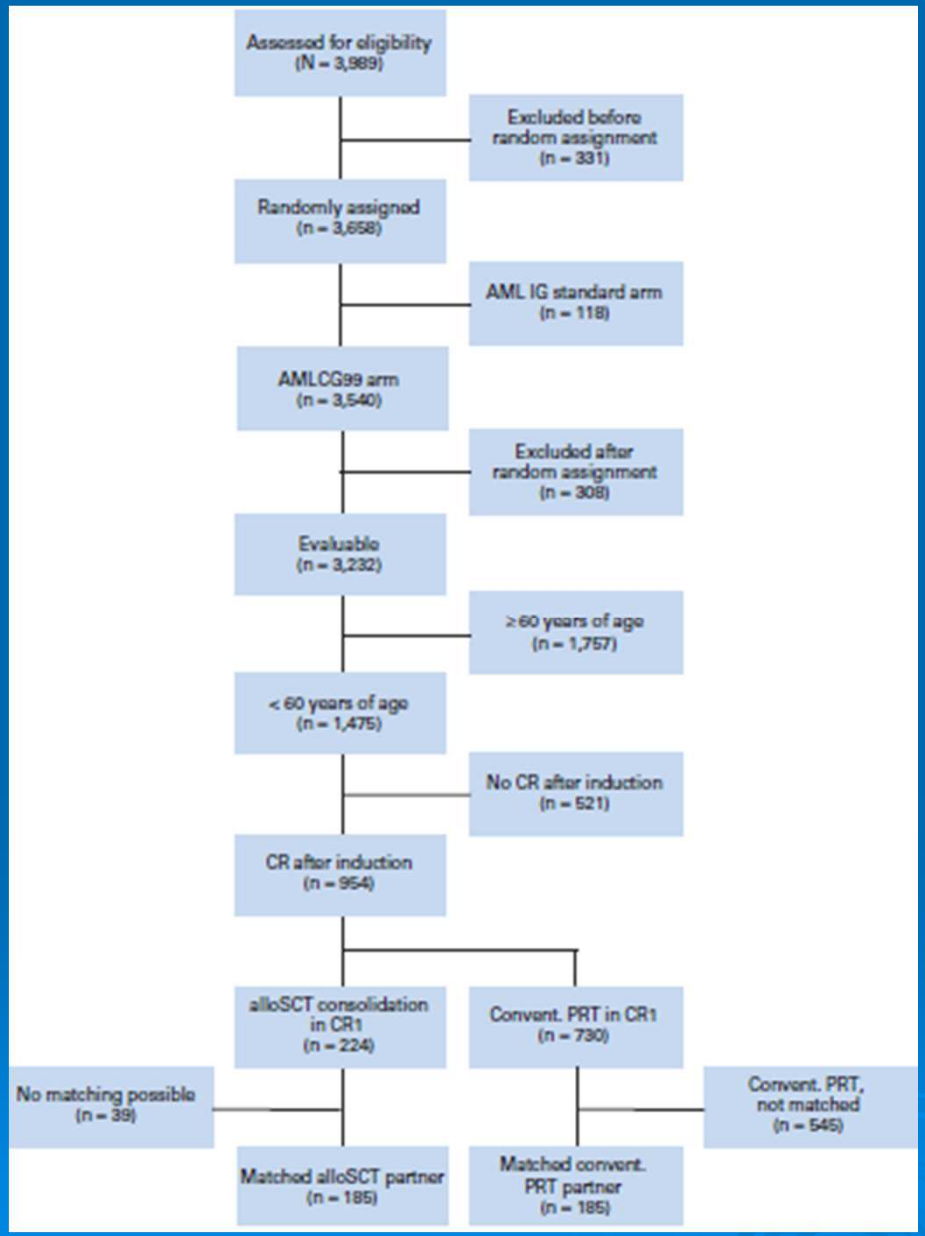
*If the data on molecular markers are not available.

†Increasing data show that the beneficial effect may be restricted only to patients with double mutations.

‡Only at experienced centers and in the absence of a timely available MUD.

§Carefully selected patients with good performance status and low disease burden; CIBMTR risk score may aid the patient selection.

BLOOD, 24 FEBRUARY 2011 • VOLUME 117, NUMBER 8



Allogeneic Transplantation Versus Chemotherapy as Postremission Therapy for Acute Myeloid Leukemia: A Prospective Matched Pairs Analysis

Matthias Stelljes, Utz Krug, Dietrich W. Beelen, Jan Braess, Maria C. Sauerland, Achim Heinecke, Sandra Ligges, Tim Sauer, Petra Tschanter, Gabriela B. Thoennissen, Björna Berning, Hans J. Kolb, Albrecht Reichle, Ernst Holler, Rainer Schwerdtfeger, Renate Arnold, Christoph Scheid, Carsten Müller-Tidow, Bernhard J. Woermann, Wolfgang Hiddemann, Wolfgang E. Berdel, and Thomas Büchner

Protocole AMLCG99 (> 16 ans) (1999-2011)

Double induction

185 patients (< 60 ans) en RC1 allo greffés(RIC) comparés avec 185 patients recevant conso +auto ou conso + maintenance (la majorité).

Matching tenant compte de :FAB ,,de novo/ secondaire ,âge ,risque cytogénétique , % de blastes à J 15 et temps d'obtention de la RC.

Pas de différence NPM / FLT3 ID

MRD (115),MUD (46) ,Mismatch (24)

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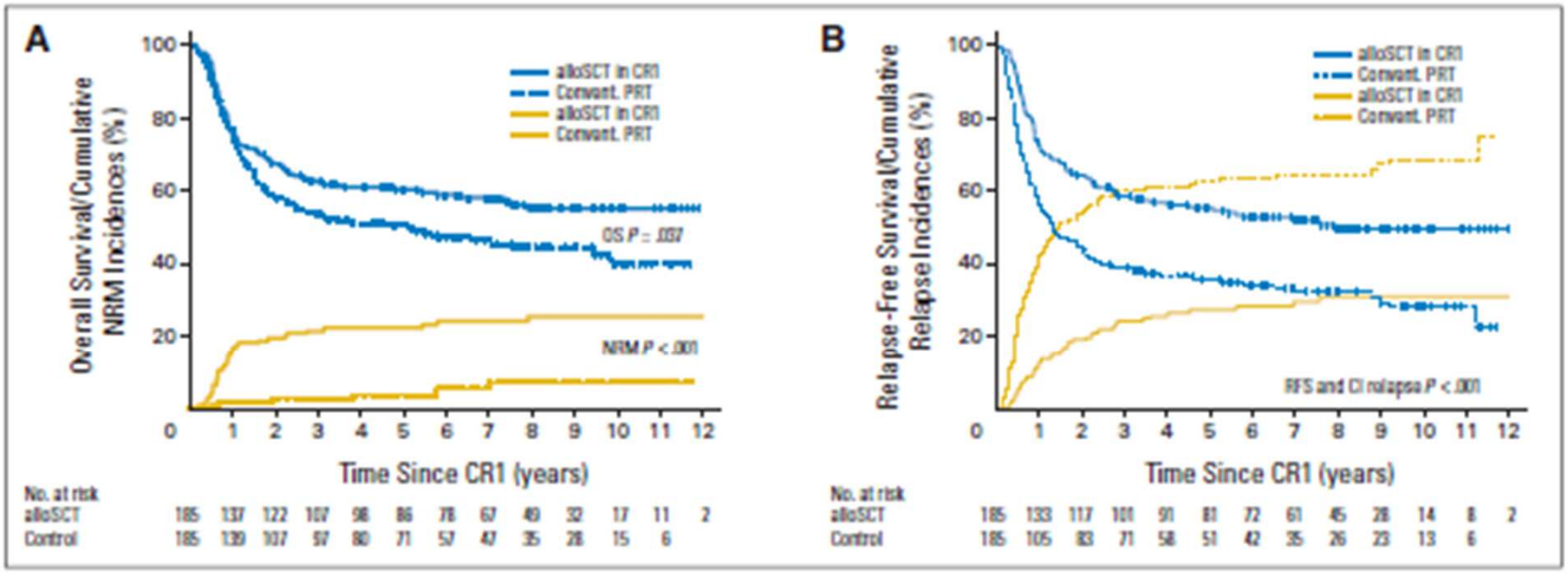

Fig 2. Kaplan-Meier survival estimates and cumulative incidences of nonrelapse mortality (NRM) and relapse according to postremission therapy. Data are shown for (A) overall survival (OS) and cumulative incidences of NRM and (B) relapse-free survival (RFS) and cumulative incidences (CI) of relapse. Gold lines depict cumulative incidences, blue lines survival curves. Tick marks represent (A) patients whose data were censored at the last time they were known to be alive or (B) whose data were censored at the last time they were known to be alive and in complete remission. NRM events for the postremission therapy (PRT) group were deaths in CR1 (first complete remission). alloSCT, allogeneic stem-cell transplantation; convent. PRT, conventional PRT.

ALLO VS NON-ALLO

ANALYSE GLOBALE

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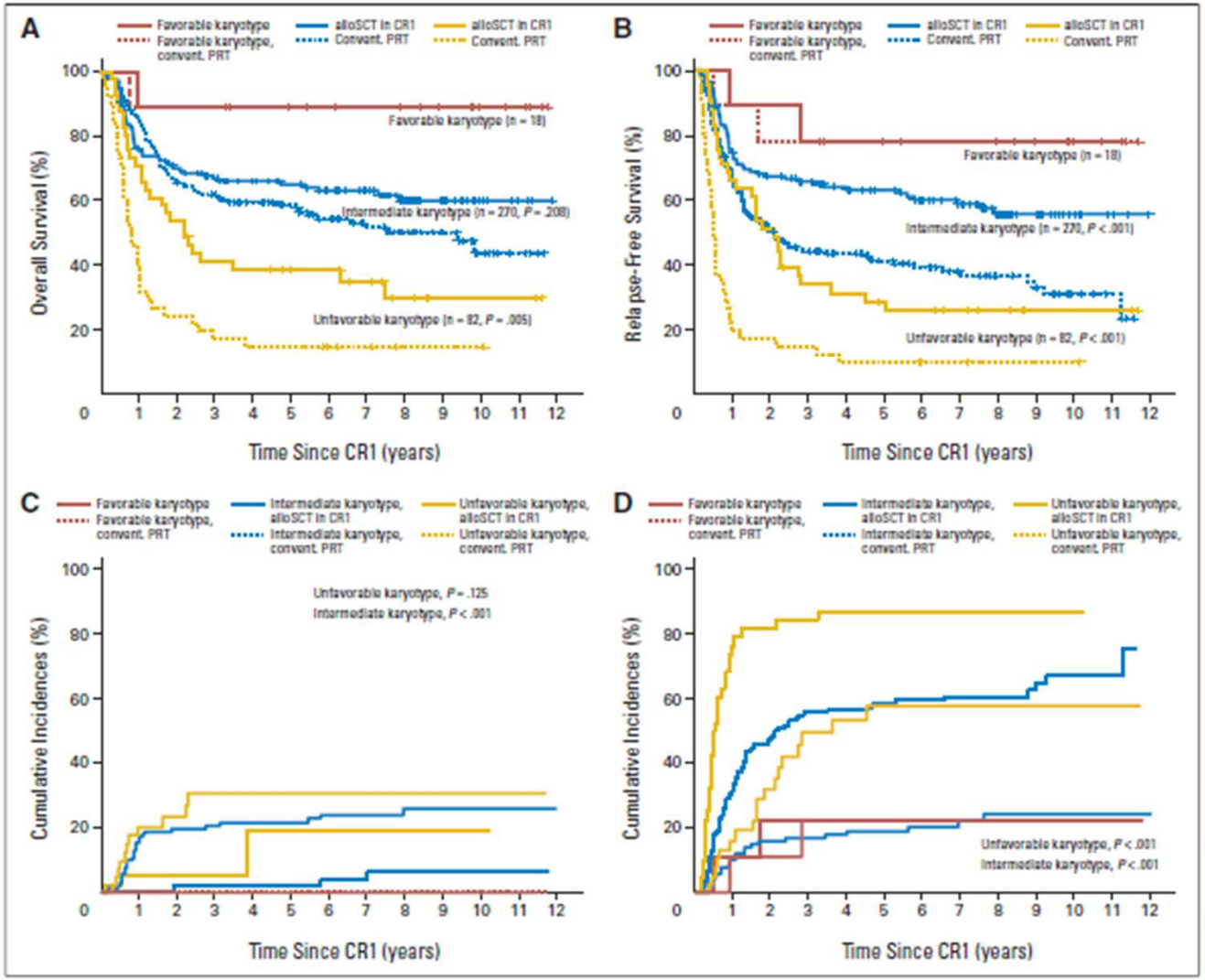

Fig 3. Kaplan-Meier survival estimates and cumulative incidences of nonrelapse mortality (NRM) and relapse according to postremission therapy (PRT) and cytogenetic risk categories. Data are shown for (A) overall survival (OS), (B) relapse-free survival (RFS), (C) cumulative incidences of NRM (NRM events for the PRT group were deaths in first complete remission [CR1]), and (D) cumulative incidences of relapse. Curves with dotted lines represent patients who received conventional PRT (convent. PRT); curves with continuous lines represent patients receiving allogeneic stem-cell transplantation (alloSCT) in CR1. Gold lines depict patients with unfavorable karyotype, blue lines with intermediate karyotype, and red lines with favorable karyotype. Tick marks represent (A) patients whose data were censored at the last time they were known to be alive or (B) whose data were censored at the last time they were known to be alive and in CR. Curves for the favorable karyotype subgroups overlap (A and B).

9 patients avec bon risque cytogénétique greffés car pour MRD défavorable en RC.

RISQUE CYTOGENETIQUE

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OS

RFS

NRM

Relapse

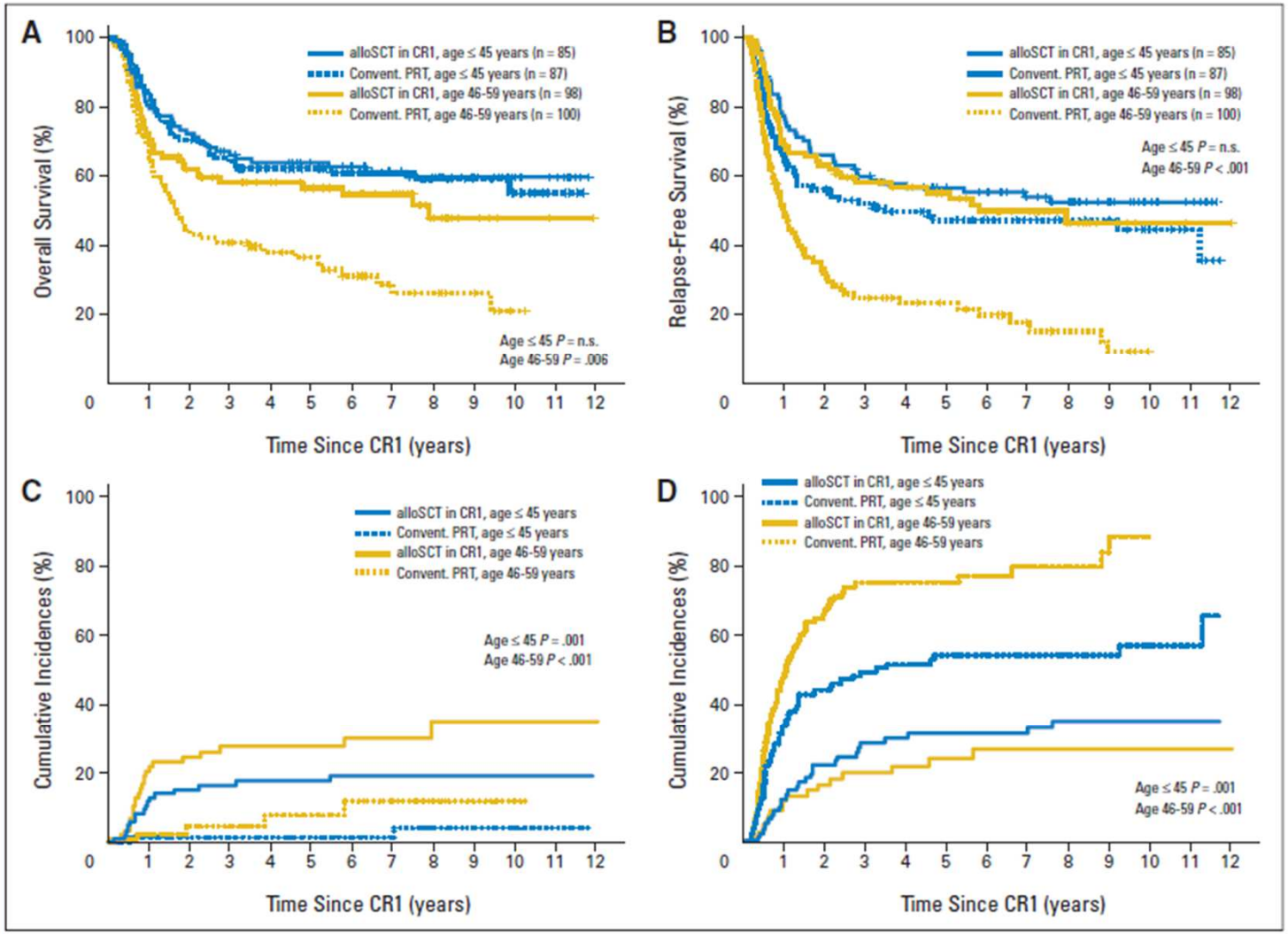

Fig 4. Kaplan-Meier survival estimates and cumulative incidences of nonrelapse mortality (NRM) and relapse according to postremission therapy (PRT) and patient age group (≤ 45 years *v* 46 to 59 years). Data are shown for (A) overall survival, (B) relapse-free survival, (C) cumulative incidences of NRM (NRM events for the PRT group were deaths in first complete remission [CR1]), and (D) cumulative incidences of relapse. Curves with dotted lines represent patients who received conventional PRT (convent. PRT); curves with continuous lines represent patients receiving allogeneic stem-cell transplantation (alloSCT) in CR1. Blue lines depict patients ≤ 45 years of age, red lines patients 46 to 59 years of age. Tick marks represent (A) patients whose data were censored at the last time they were known to be alive or (B) whose data were censored at the last time they were known to be alive and in CR. n.s., not significant.

PLUS OU MOINS DE 45 ANS

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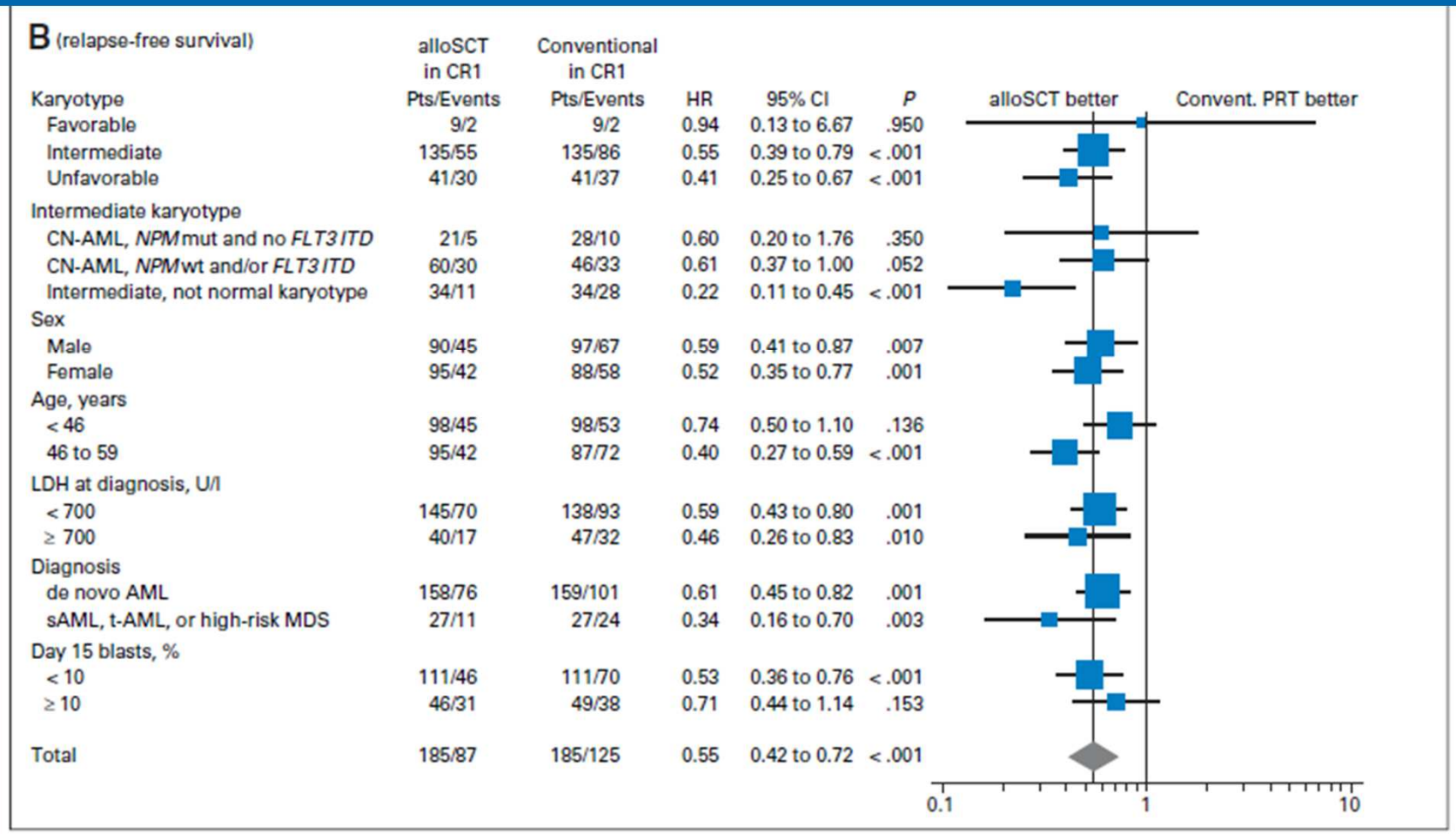

Fig 5. Forest plot of the effect of allogeneic stem-cell transplantation (alloSCT) versus conventional postremission therapy (convent. PRT) in subgroups. The effects are shown by proportional hazard risks of alloSCT versus convent. PRT for (A) overall survival (OS) from CR achievement and for (B) relapse-free survival (RFS), obtained by Cox proportional hazards regression. AML, acute myeloid leukemia; CN-AML, cytogenetically normal AML; CR1, first complete remission; day 15 blasts, bone marrow blast percentage in the early bone marrow assessment on day 15 after start of induction therapy; HR, proportional hazard risk; LDH, lactate dehydrogenase serum level; high-risk MDS, myelodysplastic syndrome with more than 10% bone marrow blasts at study entry; NPMmut, mutated Nucleophosmin 1 gene; NPMwt, no mutated Nucleophosmin 1 gene; pts, patients; sAML, AML evolving from myelodysplastic syndrome; t-AML, AML after cytotoxic treatment (chemotherapy or irradiation).

Results

In the overall pairwise compared AML population, the projected 7-year overall survival (OS) rate was 58% for the alloSCT and 46% for the conventional postremission treatment group ($P = .037$; log-rank test). Relapse-free survival (RFS) was 52% in the alloSCT group compared with 33% in the control group ($P < .001$). OS was significantly better for alloSCT in patient subgroups with nonfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome. For the entire patient cohort, postremission therapy was an independent factor for OS (hazard ratio, 0.66; 95% CI, 0.49 to 0.89 for alloSCT *v* conventional chemotherapy), among age, cytogenetics, and bone marrow blasts after the first induction cycle.

Conclusion

AlloSCT is the most potent postremission therapy for AML and is particularly active for patients 45 to 59 years of age and/or those with high-risk cytogenetics.

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INDICATIONS

Table 3. Guidelines for indications for HCT in adult patients with AML

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"m*NPM1* without FLT3ITD"	No	No	No	No
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APL indicates acute promyelocytic leukemia; CBF, core binding factor [t(8;21) or Inv(16)]; CN-AML, cytogenetically normal AML; FLT3ITD, FMS-related tyrosine kinase 3–internal tandem duplication; HCT, hematopoietic cell transplantation; m*CEBPA*, mutated *CEBPA*; m*KIT*, KIT mutations; MSD, matched sibling donor; m*NPM1*, mutated *NPM1*; MUD, matched unrelated donor; and UCB, umbilical cord blood.

*If the data on molecular markers are not available.

†Increasing data show that the beneficial effect may be restricted only to patients with double mutations.

‡Only at experienced centers and in the absence of a timely available MUD.

§Carefully selected patients with good performance status and low disease burden; CIBMTR risk score may aid the patient selection.

Nécessité de réévaluer les indications des greffes en haplo-mismatch dont les indications apparaissent très mouvantes.

BLOOD, 24 FEBRUARY 2011 • VOLUME 117, NUMBER 8

LAM de mauvais pronostic

Table 1. Patient, Disease, and Transplantation Characteristics According to FLT3/ITD Status

Characteristic	FLT3/ITD Negative (n = 861) No.	%	FLT3/ITD Positive (n = 120) No.	%	*P*
Patient					
Age, years					.31
Median	42		41		
Range	19-59		18-60		
Sex					.06
Male	50	58	54	45	
Female	36	42	66	55	
Disease					
FAB type					.07
M0	2	7	0	0	
M1	9	17	26	35	
M2	17	32	22	30	
M4	17	32	14	19	
M5	8	15	12	16	
WBC, $\times 10^9$/L	72		106		< .001
Median	21		59		
Range	0.8-240		0.7-373		
No. of courses to CR1					.6
1	49	77	76	80	
> 1	15	23	19	20	
Interval from CR1 to transplantation, days	77		104		.04
Median	99		87		
Range	26-219		17-241		

Impact of FLT3 Internal Tandem Duplication on the Outcome of Related and Unrelated Hematopoietic Transplantation for Adult Acute Myeloid Leukemia in First Remission: A Retrospective Analysis

Salut Brunet, Myriam Labopin, Jordi Esteve, Jan Cornelissen, Gerard Socié, Anna P. Iori, Leo F. Verdonck, Liisa Volin, Alois Gratwohl, Jorge Sierra, Mohamad Mohty, and Vanderson Rocha

Etude rétrospective de l'EBMT

VOLUME 30 · NUMBER 7 · MARCH 1 2012

JOURNAL OF CLINICAL ONCOLOGY

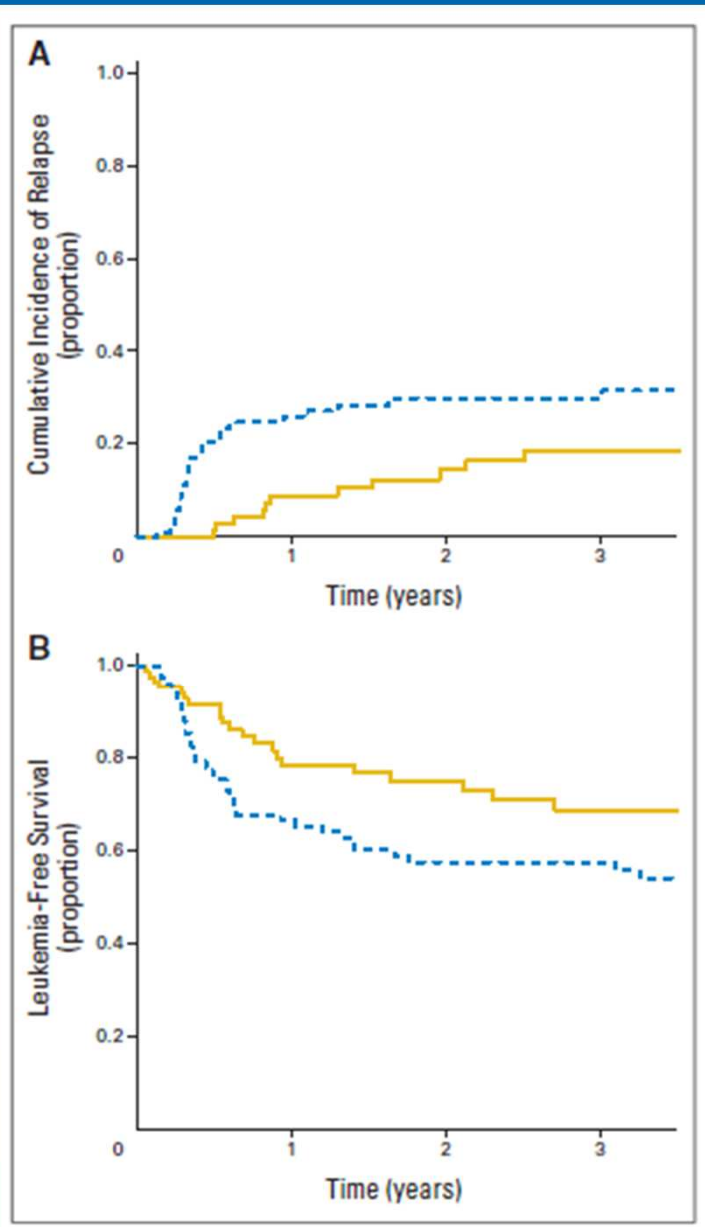

Fig 1. Outcome after allogeneic transplantation performed in first complete remission for patients with acute myeloid leukemia and normal cytogenetics according to the presence (dashed line) or absence (solid line) of internal tandem duplication of *FLT3* gene. (A) Estimated probability of 2 years of cumulative incidence of relapse; (B) leukemia-free survival after transplantation at 2 years.

Table 3. Results of Multivariable Analyses for LFS and RI (n = 158)

Outcome	HR	95% CI	P
LFS			
FLT3/ITD, positive *v* negative	0.37	0.19 to 0.73	.002
Age ≥ 42 years	0.54	0.3 to 0.99	.05
> One course to CR	0.26	0.14 to 0.48	< .001
RI			
FLT3/ITD, positive *v* negative	3.4	1.46 to 7.94	.005
Age ≥ 42 years	3.02	1.48 to 6.15	.002
Patient sex, female *v* male	2.61	1.23 to 5.55	.013
Interval from CR to transplantation > 93 days	0.46	0.21 to 0.98	.046
> One course to CR	3.72	1.71 to 8.09	< .001

Abbreviations: CR, complete remission; FLT3/ITD, internal tandem duplication of *FLT3* gene; HR, hazard ratio; LFS, leukemia-free survival; RI, relapse incidence.

Conclusion

FLT3/ITD adversely affected the outcome of HSCT in the same direction it does after chemotherapy; despite this, more than half of the patients harboring this mutation who received transplants were alive and leukemia free at 2 years. To further improve the results, use of FLT3 inhibitors before or after HSCT deserves investigation.

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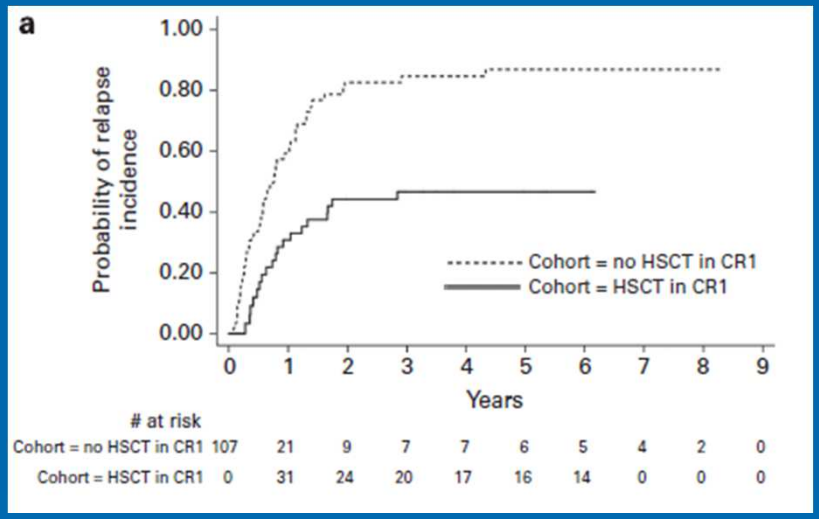
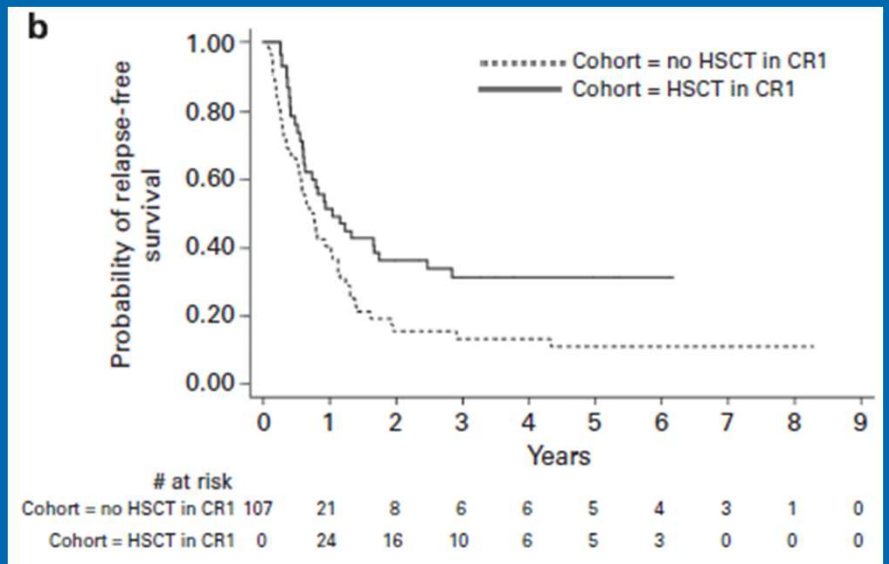
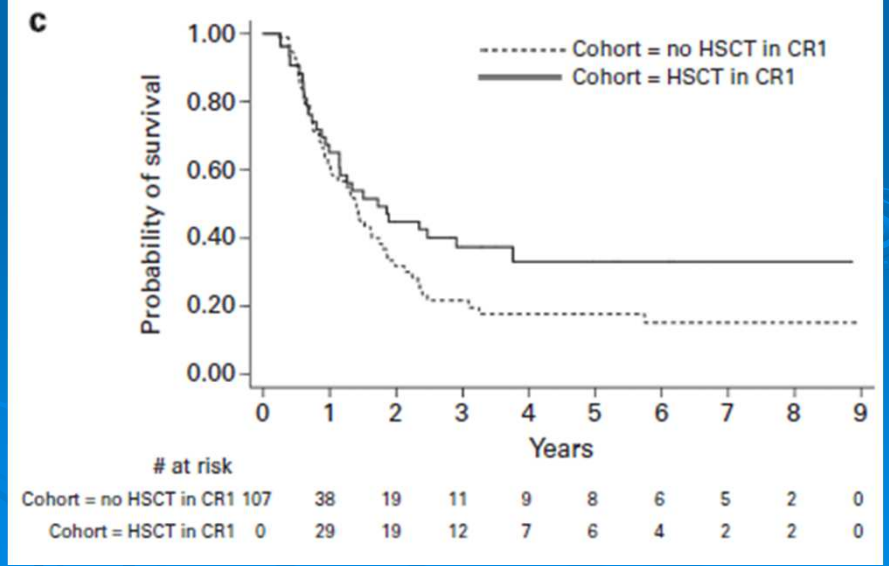
JOURNAL OF CLINICAL ONCOLOGY

Evaluation of allogeneic hematopoietic SCT in younger adults with adverse karyotype AML

MA Hospital[1], X Thomas[2], S Castaigne[3], E Raffoux[1], C Pautas[4], C Gardin[5], J-H Bourhis[6], O Reman[7], T de Revel[8], C Terré[9], C Preudhomme[10], P Fenaux[5], M Michallet[2], G Socié[1] and H Dombret[1]







Bone Marrow Transplantation (2012) **47**, 1436 - 1441

Comparative Analysis of the Value of Allogeneic Hematopoietic Stem-Cell Transplantation in Acute Myeloid Leukemia With Monosomal Karyotype Versus Other Cytogenetic Risk Categories

Jan J. Cornelissen, Dimitri Breems, Wim L.J. van Putten, Alois A. Gratwohl, Jakob R. Passweg, Thomas Pabst, Johan Maertens, H. Berna Beverloo, Marinus van Marwijk Kooy, Pierre W. Wijermans, Bart J. Biemond, Edo Vellenga, Leo F. Verdonck, Gert J. Ossenkoppele, and Bob Löwenberg

Présence d'au moins 2 monosomies ou d'une monosomie associée à d'autres anomalies structurales (exceptés les »ring »)

Table 3. Treatment Outcome After Consolidation Therapy by AlloHSCT or AutoHSCT/CT

Cytogenetic Subgroup	No. of Patients	Outcome After HSCT (% at 5 years) OS	RFS	Relapse	NRM
AlloHSCT					
CN	306	60	57	23	20
CA	87	58	53	26	20
CA-unfavorable	117	46	40	43	17
MK	45	19	17	68	15
AutoHSCT/CT					
CN	688	46	37	59	4
CA	168	36	31	67	2
CA-unfavorable	115	26	14	83	3
MK	62	8	7	91	2

Abbreviations: AlloHSCT, allogeneic hematopoietic stem-cell transplantation; AutoHSCT, autologous HSCT; CA, cytogenetically abnormal; CN, cytogenetically normal; CT, chemotherapy; HSCT, hematopoietic stem-cell transplantation; MK, monosomal karyotype; NRM, nonrelapse mortality; OS, overall survival; RFS, relapse-free survival.

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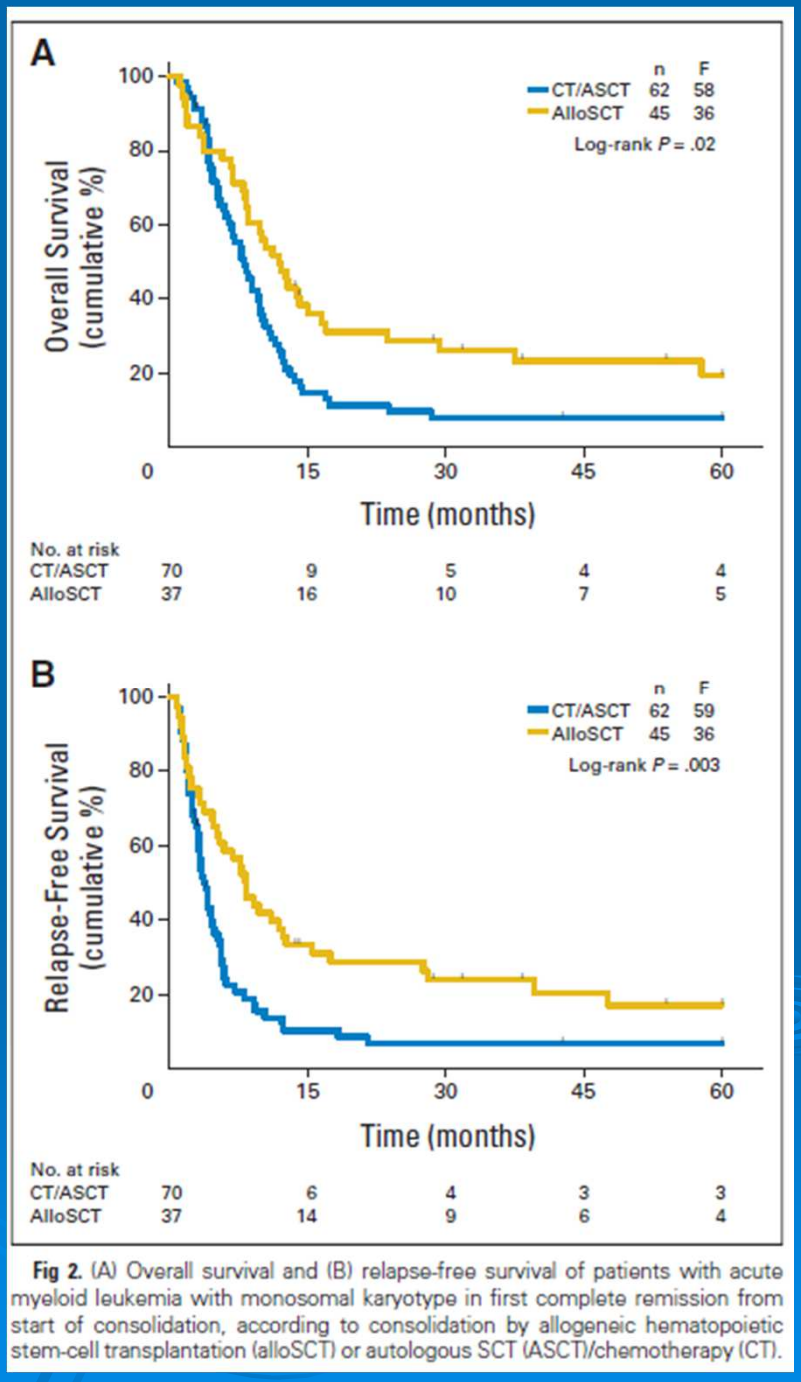


Fig 2. (A) Overall survival and (B) relapse-free survival of patients with acute myeloid leukemia with monosomal karyotype in first complete remission from start of consolidation, according to consolidation by allogeneic hematopoietic stem-cell transplantation (alloSCT) or autologous SCT (ASCT)/chemotherapy (CT).

Même si la greffe améliore la RFS de la plupart des LAM de mauvais pronostic , ces facteurs de mauvais pronostic ne sont pas gommés : que faire pour tenter d'améliorer les choses:

- **traitement spécifique ?**
- **alourdir le conditionnement (tomothérapie ?)**
- **immuno-intervention post greffe en se basant sur la MRD.**

Quelques problèmes supplémentaires

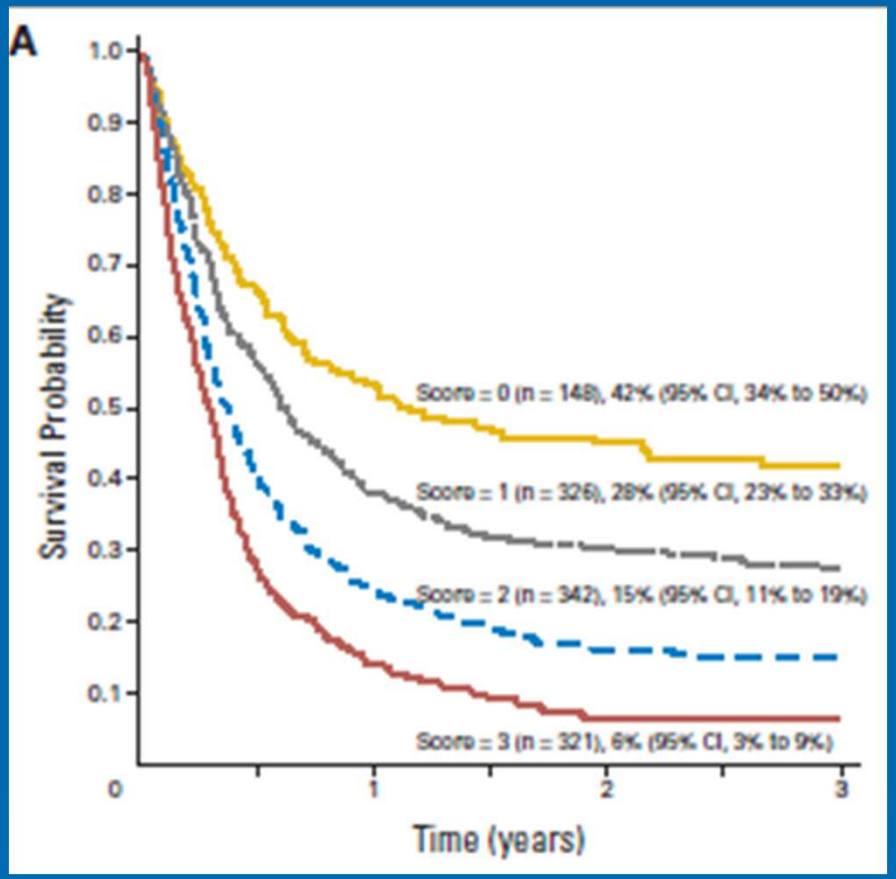
Est-il raisonnable d'allogreffer des patients blastiques qu'ils soient en échec primaire ou après rechute?

Hematopoietic Stem-Cell Transplantation for Acute Leukemia in Relapse or Primary Induction Failure

Michel Duval, John P. Klein, Wensheng He, Jean-Yves Cahn, Mitchell Cairo, Bruce M. Camitta, Rammurti Kamble, Edward Copelan, Marcos de Lima, Vikas Gupta, Armand Keating, Hillard M. Lazarus, Mark R. Litzow, David I. Marks, Richard T. Maziarz, David A. Rizzieri, Gary Schiller, Kirk R. Schultz, Martin S.Tallman, and Daniel Weisdorf

Table 5. Scoring System for Post-HSCT Outcome in AML and ALL

Outcome by Disease	Score	No. of Patients
AML		
Disease group		
PIF or duration of first CR ≥ 6 months	0	763
Duration of first CR < 6 months	1	374
Cytogenetics prior to HSCT		
Good or intermediate	0	901
Poor	1	236
HLA match group		
HLA identical sibling or well matched or partially matched unrelated	0	900
Mismatched unrelated	1	156
Related other than HLA identical sibling	2	81
Circulating blasts		
Absent	0	503
Present	1	634
Karnofsky or Lansky score		
90-100	0	604
< 90	1	533



1673 patients de l'IBMTR allogreffés en rechute ou en échec primaire entre 1995 et 2004 après MAC - 19% de survie à 3 ans et 16% à 5 ans.

VOLUME 28 · NUMBER 23 · AUGUST 10 2010
JOURNAL OF CLINICAL ONCOLOGY

Greffe dans les LAM réfractaires ou en rechute avec induction/conditionnement

Induction/conditionnement

Schmid – Blood 2006

- 103 malades - échec de 1ère induction : 37
  - en 1ère rechute (RC < 6 mois) : 53
  - en 1ère rechute réfractaire : 8
  - en 2ème rechute d'emblée : 5

- Modalités de la greffe :
  - Induction/conditionnement
  - Prophylaxie de la GVH : CSA + MMF
  - CSP : 93 Moelle : 10
  - HLA géno : 41 MUD : 62

Induction/conditionnement

Schmid – Blood 2006

	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
FLUDA 30 mg/m²	●	●	●	●									
ARA C 2 g/m²	●	●	●	●									
AMSA 10 mg/m²	●	●	●	●									
TBI 4 Gy								●					
EDX 40 à 60 mg/m²									●	●			
ATG									●	●	●		
Greffe													●
DLI > J120													

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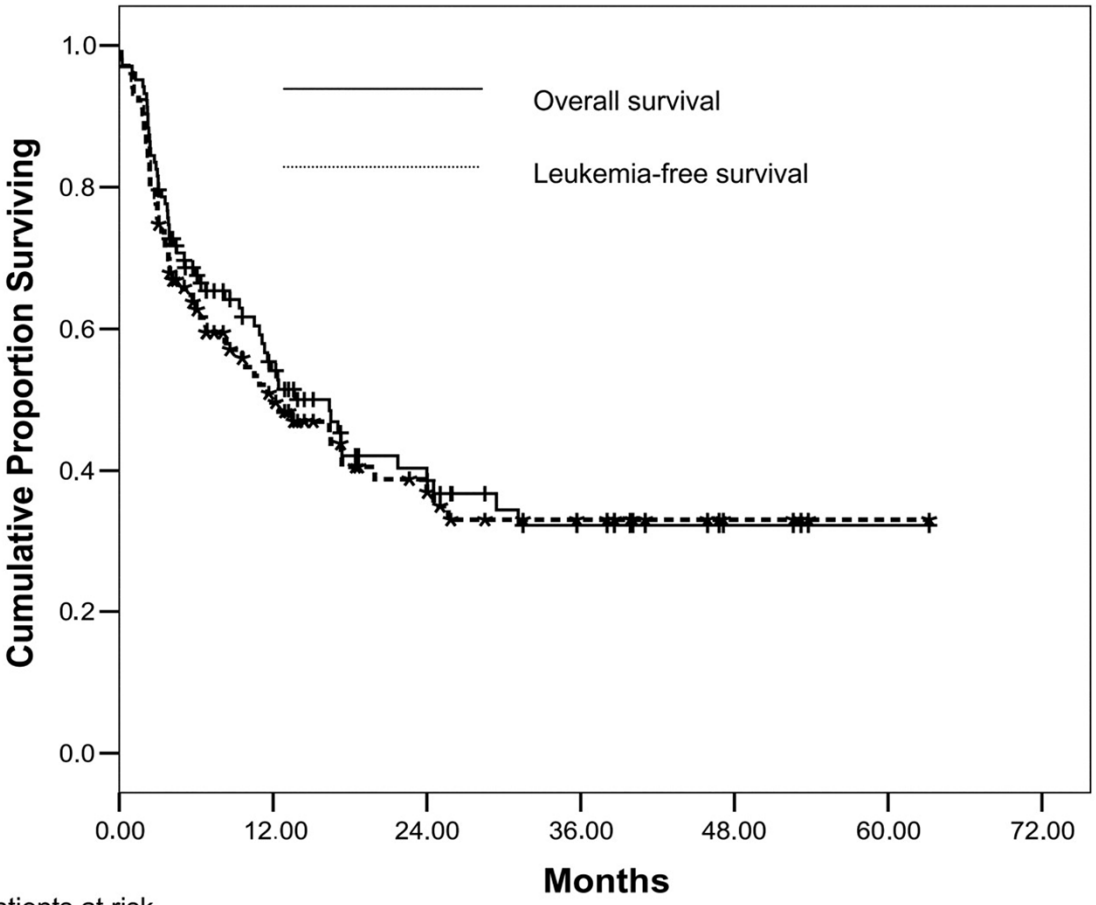
Figure 1. Overall survival and leukemia-free survival



Patients at risk

OAS	103	42	23	12	5	5
LFS	103	39	21	12	5	5

Schmid, C. et al. Blood 2006;108:1092-1099

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blood
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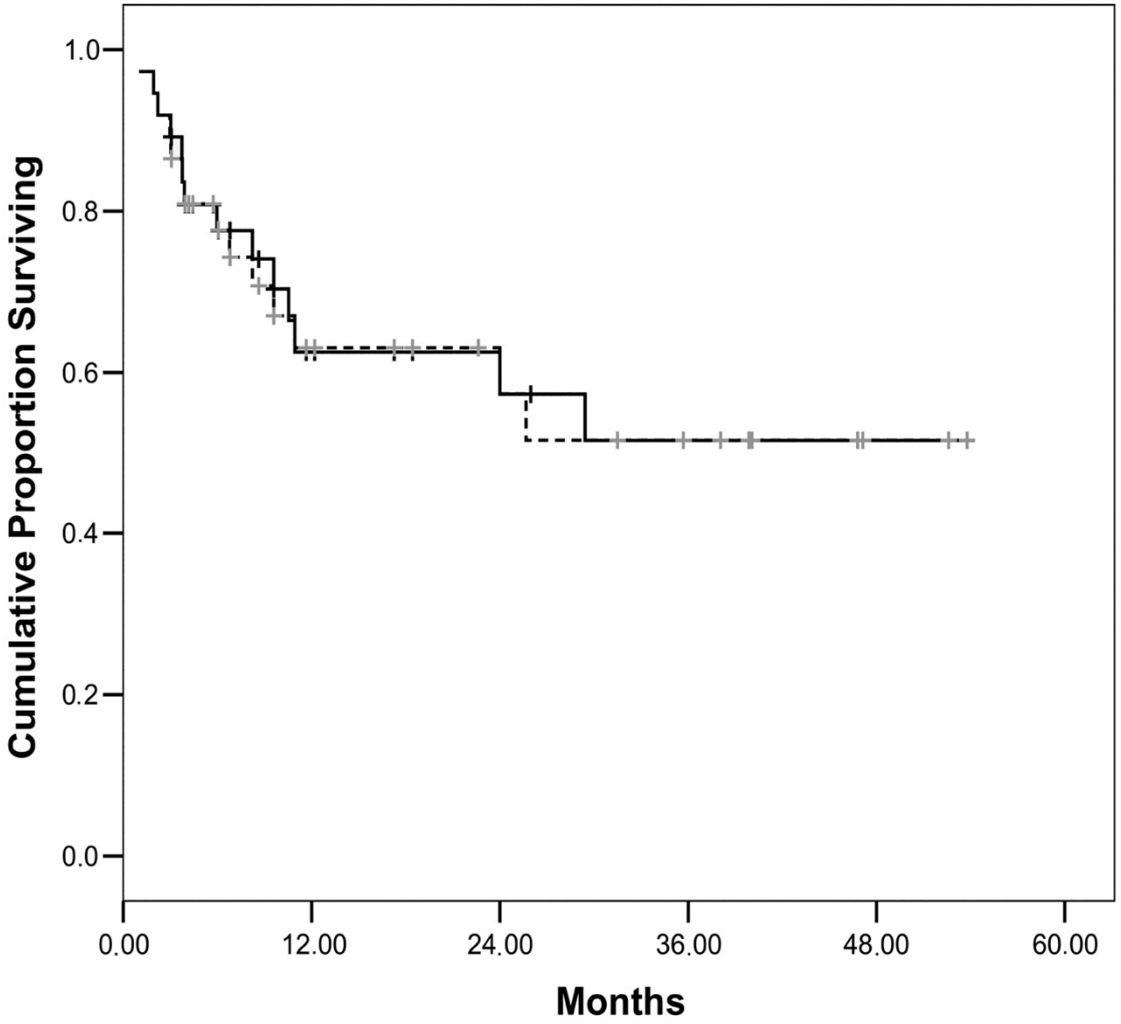
Figure 2. Overall survival (solid curve) and leukemia-free survival (dashed curve) in patients with primary induction failure (n = 37)



Schmid, C. et al. Blood 2006;108:1092-1099

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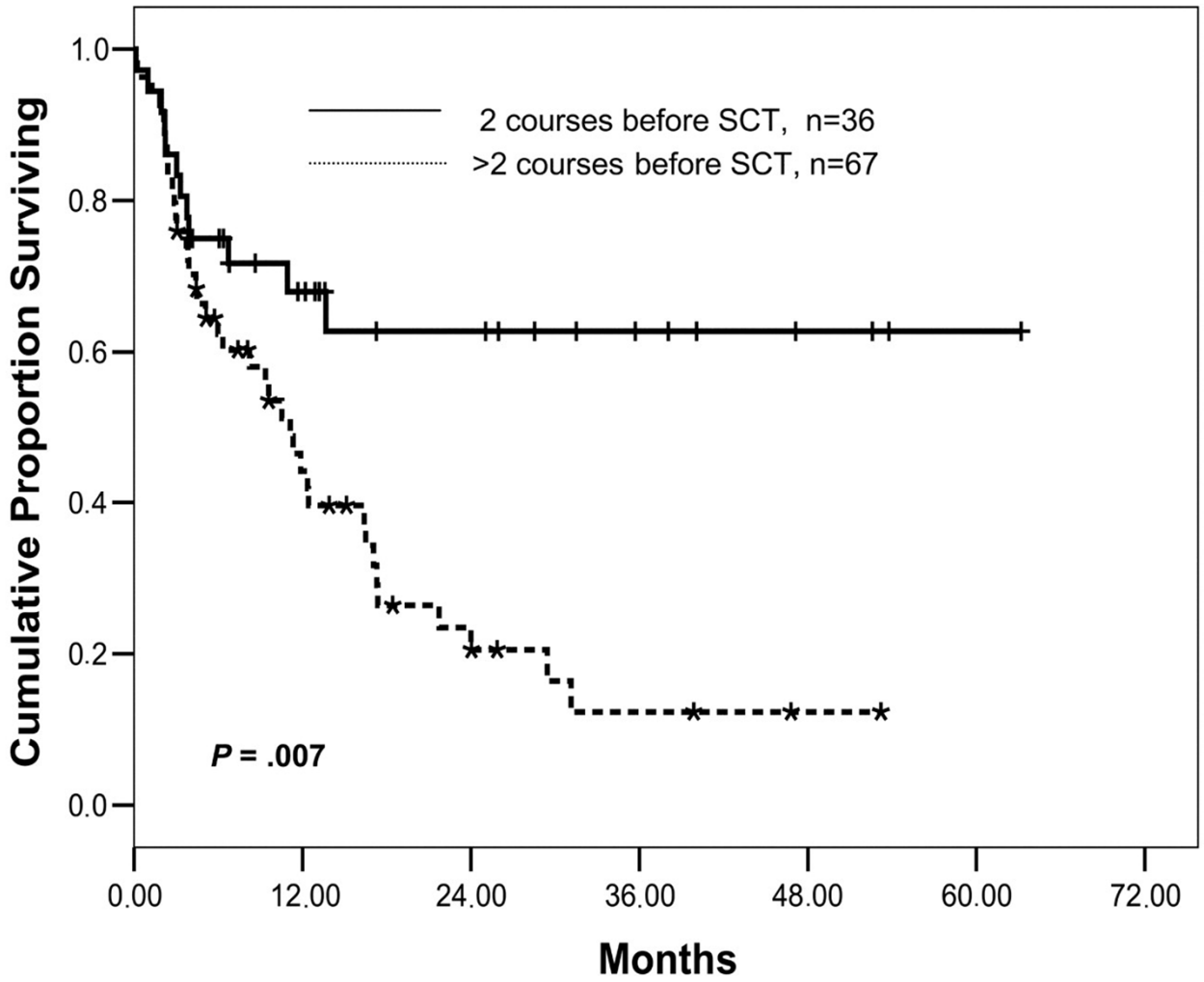
Figure 3. Overall survival as of number of chemotherapy cycles prior to conditioning for SCT



Schmid, C. et al. Blood 2006;108:1092-1099

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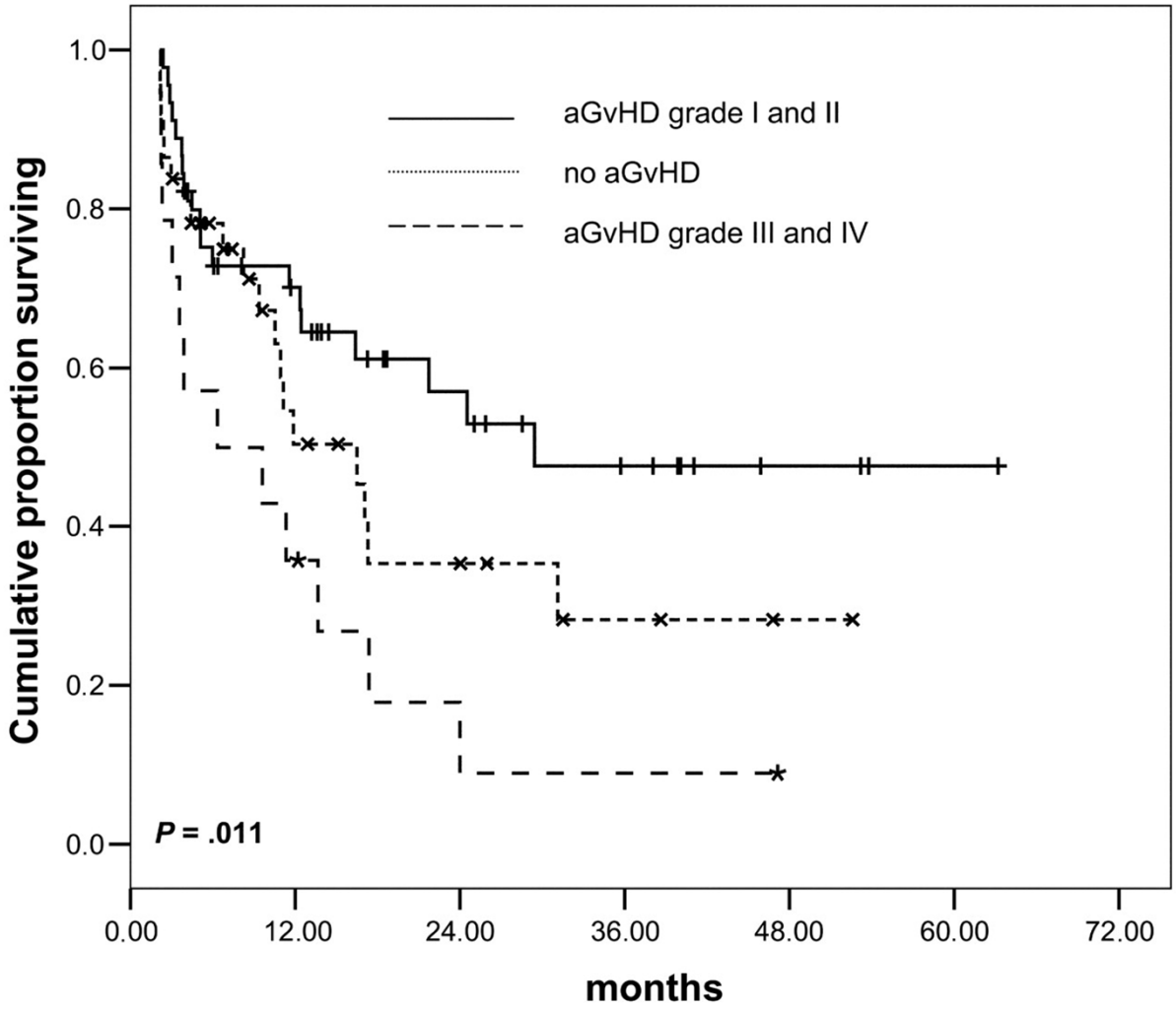
Figure 4. Influence of acute GvHD on overall survival, multigroup comparison



Schmid, C. et al. Blood 2006;108:1092-1099

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Rechute post-Allo :
DLI ou 2eme Allo ?

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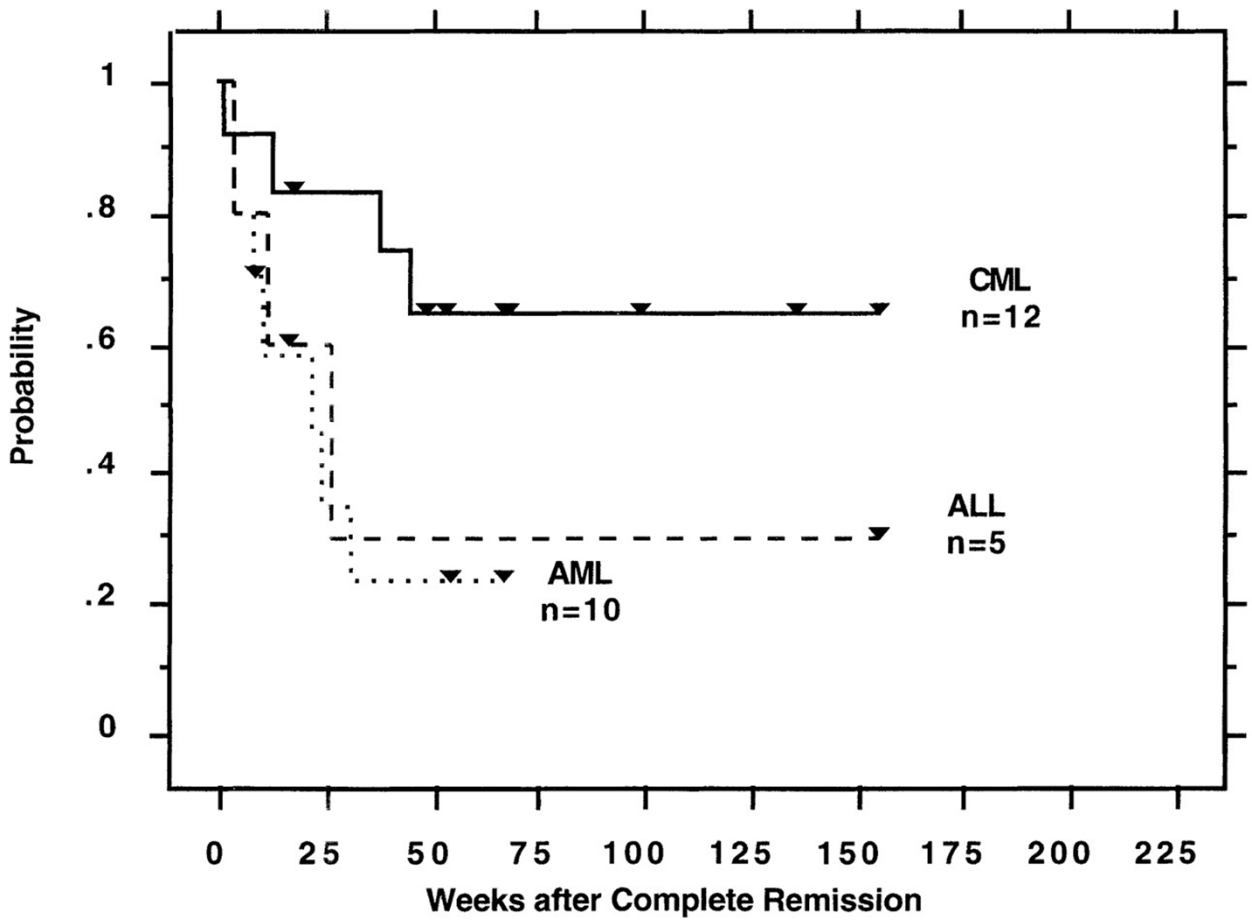
HEMATOLOGY

Treatment of relapse post BMT with MUD DLI



Porter, D. L. et al. Blood 2000;95:1214-1221

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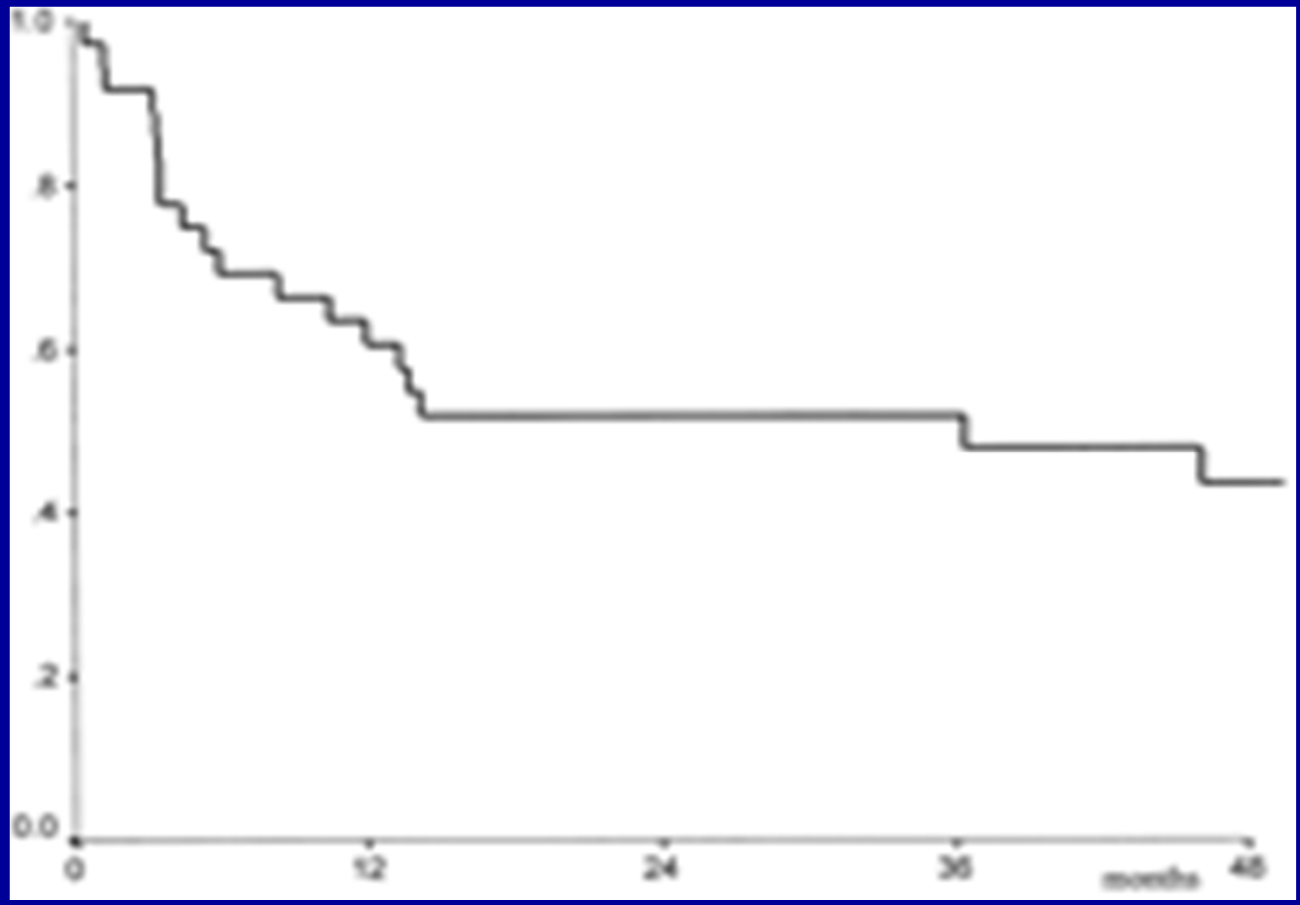
2 eme BMT

LFS chez patients en 2eme RC avec intervalle >300 jours entre 1ere BMT et rechute



Bosi – JCO- 2001

Eviter l’utilisation de G CSF

Eviter l'utilisation du G CSF post allogreffe

Olle Ringdén,[1] Myriam Labopin,[2] Norbert-Claude Gorin,[2] Liisa Volin,[3] Giovanni F. Torelli,[4] Michel Attal,[5] Jean P. Jouet,[6] Noel Milpied,[7] Gerard Socié,[8] Catherine Cordonnier,[9] Mauricette Michallet,[10] Arturo I. Atienza,[11] Olivier Hermine,[12] Mohamad Mohty[13] for the Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation

Growth factor-associated graft-versus-host disease and mortality 10 years after allogeneic bone marrow transplantation

Table II. Univariate and multivariate analysis of patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) treated or not treated with growth factors and results on acute GVHD grades II–IV, chronic GVHD, GVHD-free survival, non-relapse mortality (NRM), relapse and leukaemia-free survival (LFS).

	aGVHD ≥ grade II	2-year cGVHD	5-year GVHD-free survival	5-year NRM	5-year relapse	5-year LFS
AML						
Growth factor treatment						
No	37 ± 2	26 ± 2	25 ± 1	26 ± 1	26 ± 1	49 ± 2
Yes	46 ± 3	38 ± 4	16 ± 2	38 ± 3	23 ± 3	39 ± 3
P value	0·01	0·006	0·003	0·003	0·47	0·002
Multivariate (*P* value)	0·016	0·04	0·016	0·0004	0·69	<0·0001
ALL						
Growth factor treatment						
No	42 ± 2	34 ± 2	21 ± 2	25 ± 2	30 ± 3	45 ± 2
Yes	44 ± 4	36 ± 4	13 ± 2	36 ± 3	31 ± 3	33 ± 3
P value	0·82	0·91	0·012	0·008	0·83	0·003
Multivariate (*P* value)	0·94	0·88	0·04	0·03	0·87	0·04

±, Standard error.

Prophylaxis with growth factor increases the risk of GVHD, does not affect relapse, increases NRM and reduces LFS > 10 years after HSCT, regardless of conditioning with TBI.

Etude rétrospective EBMT

British Journal of Haematology, 2012, **157**, 220–229

Il y n’y probablement pas besoin de consolidations **systématiques** entre la RC et l’ allogreffe

Impact of Postremission Consolidation Chemotherapy on Outcome After Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation for Patients With Acute Myeloid Leukemia in First Complete Remission

A Report From the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

Moshe Yeshurun, MD[1,2]; Myriam Labopin, MD[3,4,5,6]; Didier Blaise, MD[7]; Jan J. Cornelissen, MD[8]; Henrik Sengeloev, MD[9]; Lars Vindelov, MD[9]; Juergen Kuball, MD[10]; Patrice Chevallier, MD[11]; Charles Craddock, MD[12]; Gerard Socie, MD[13]; Karin Bilger, MD[14]; Harry C. Schouten, MD[15]; Nathalie Fegueux, MD[16]; Hakan Goker, MD[17]; Johan Maertens, MD[18]; Donald Bunjes, MD[19]; Renate Arnold, MD[20]; Arnon Nagler, MD[21]; and Mohamad Mohty, MD[3,4,5,6]

Cancer March 15, 2014

TABLE 1. Patient-, Disease-, and Treatment-Related Characteristics of Patients Who Underwent Transplant Within the Median Time Frame Between Achievement of CR and alloSCT

Variable		No Consolidation Chemotherapy Cycles N = 151	1 or More Consolidation Chemotherapy Cycles N = 222	*P*
Median age (range), y		58 (30-76)	56 (19-70)	.03
Cytogenetic risk group	Good	4 (3%)	8 (4%)	.4
	Intermediate	102 (68%)	162 (73%)	
	Poor	28 (19%)	37 (17%)	
	Missing data	17 (11%)	15 (7%)	
No. of induction cycles before CR1	1	30 (20%)	144 (65%)	<0.001
	2	121 (80%)	78 (35%)	
Interval from CR1 to alloSCT (range), d		56 (11-119)	71 (10-121)	<0.001
Y of transplantation (range)		2008 (2001-2010)	2008 (2001-2010)	.11
Donor type	Sibling	111 (74%)	152 (68%)	.3
	MUD	40 (26%)	70 (32%)	
Patient sex	Male	75 (50%)	116 (52%)	.62
	Female	76 (50%)	106 (48%)	
Donor sex	Male	91 (60%)	128 (58%)	.62
	Female	60 (40%)	94 (42%)	
Female-to-male sex combination	No	126 (83%)	184 (83%)	.89
	Yes	25 (17%)	38 (17%)	
TBI-based conditioning regimen	No	65 (43%)	172 (77%)	<0.001
	Yes	86 (57%)	50 (23%)	
ATG for GVHD prevention	No	108 (71%)	129 (58%)	.008
	Yes	43 (29%)	93 (42%)	

Abbreviations: alloSCT, allogeneic stem cell transplantation; ATG, antithymocyte globulin; CR, complete remission; CR1, first CR; GVHD, graft-versus-host disease; MUD, matched unrelated donor; TBI, total body irradiation.

TABLE 3. Multivariate Analysis for Transplant Outcomes of Patients Who Underwent Transplant Within the Median Time Frame Between Achievement of CR and alloSCT

	Variable	HR	95% CI	*P*
RI	Consolidation vs no consolidation	1.29	0.84-1.97	.24
	Age >median	0.99	0.71-1.38	.95
	No. of induction cycles	1.12	0.76-1.64	.58
	Interval from CR1 to Tx	0.99	0.98-1.00	.01
	MUD vs sibling donor	1.38	0.91-2.1	.13
	Poor cytogenetics	6.65	2.76-16	<.0001
	TBI	1.39	0.95-2.03	.09
	ATG	0.78	0.51-1.18	.24
	Interaction between poor karyotype and interval from CR1 to Tx	0.98	0.96-0.99	.001
NRM	Consolidation vs no consolidation	0.59	0.32-1.09	.09
	Age >median	1.35	0.82-2.22	.24
	No. of induction cycles	0.65	0.36-1.18	.16
	Interval from CR1 to Tx	1.00	0.99-1.02	.70
	MUD vs sibling donor	1.09	0.57-2.1	.79
	Poor cytogenetics	0.62	0.1-3.75	.60
	TBI	0.78	0.44-1.39	.40
	ATG	0.70	0.38-1.30	.26
	Interaction between poor karyotype and interval from CR1 to Tx	1.01	0.99-1.03	.45
LFS	Consolidation vs no consolidation	1.00	0.71-1.42	.99
	Age >median	1.09	0.82-1.43	.56
	No. of induction cycles	0.94	0.68-1.3	.72
	Interval from CR1 to Tx	0.99	0.99-1	.03
	MUD vs sibling donor	1.33	0.94-1.89	.11
	Poor cytogenetics	3.60	1.67-7.74	.001
	TBI	1.15	0.84-1.58	.39
	ATG	0.75	0.53-1.06	.11
	Interaction between poor karyotype and interval from CR1 to Tx	0.99	0.97-1	.01
OS	Consolidation vs no consolidation	0.96	0.66-1.39	.82
	Age >median	1.22	0.92-1.63	.18
	No. of induction cycles	0.88	0.63-1.24	.47
	Interval from CR1 to Tx	0.99	0.99-1	.15
	MUD vs sibling donor	1.29	0.89-1.87	.18
	Poor cytogenetics	3.32	1.47-7.5	.004
	TBI	1.07	0.77-1.49	.69
	ATG	0.74	0.52-1.07	.11
	Interaction between poor karyotype and interval from CR1 to Tx	0.99	0.97-1	.03

Abbreviations: 95% CI, 95% confidence interval; alloSCT, allogeneic stem cell transplantation; ATG, antithymocyte globulin; CR, complete remission; CR1, first CR; HR, hazards ratio; LFS, leukemia-free survival; MUD, matched unrelated donor; NRM, nonrecurrence mortality; OS, overall survival; RI, recurrence incidence; TBI, total body irradiation; Tx, transplantation.

Valeur pronostique de la MRD avant la greffe

BLOOD, 5 SEPTEMBER 2013 • VOLUME 122, NUMBER 10

Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission

Roland B. Walter, Sarah A. Buckley, John M. Pagel, Brent L. Wood, Barry E. Storer, Brenda M. Sandmaier, Min Fang, Boglarka Gyurkocza, Colleen Delaney, Jerald P. Radich, Elihu H. Estey and Frederick R. Appelbaum

Seattle 253 patients consécutifs

en RC 1 (n=183) ou

RC 2 (n =70)

OS

DFS

Relapse

TRM

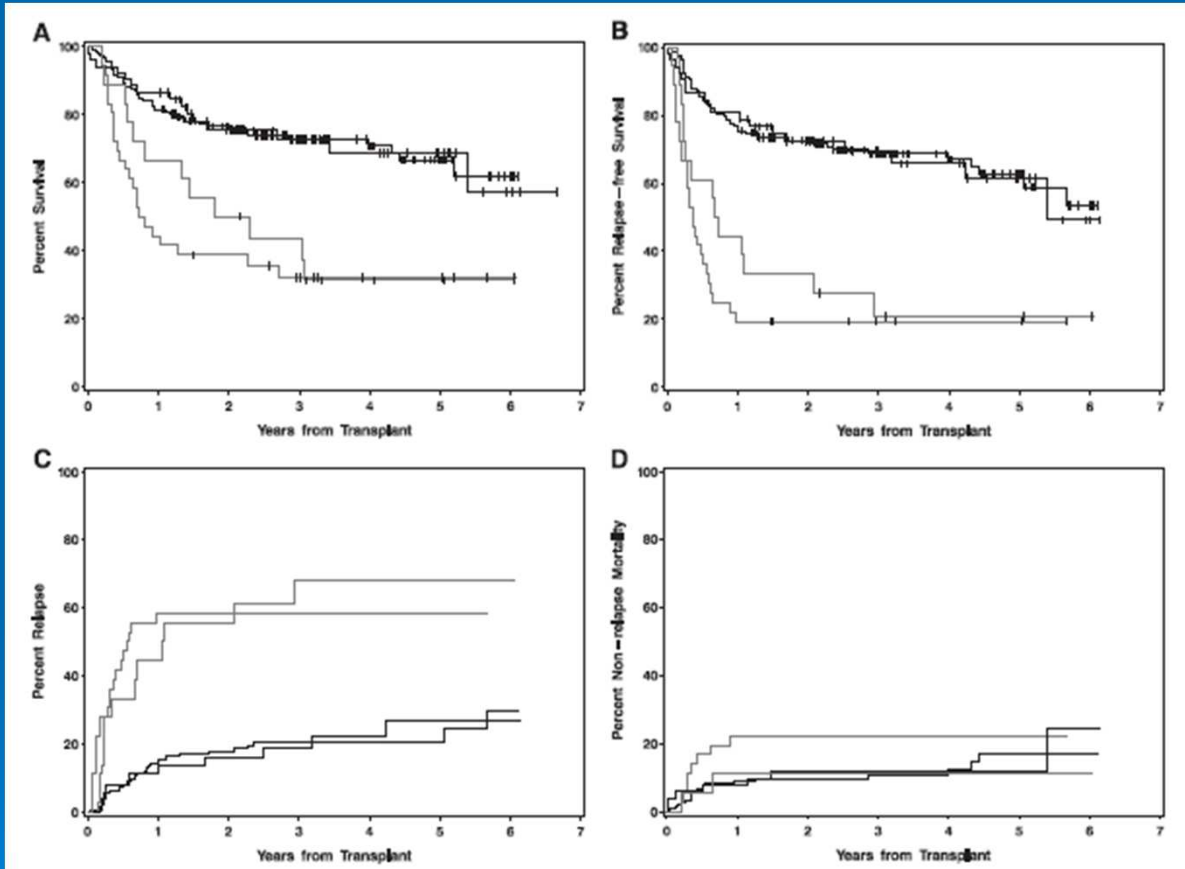


Figure 1. Association between pre-HCT MRD, as determined by multiparameter flow cytometry, and post-HCT outcome for AML patients in CR1 and CR2. Estimates of OS (A), DFS (B), cumulative incidence of relapse (C), and cumulative incidence of NRM (D) after myeloablative allogeneic HCT for AML in complete morphologic remission, shown individually for MRD^{neg} (n = 147; black solid line) and MRD^{pos} (n = 36; gray solid line) CR1 patients, as well as MRD^{neg} (n = 52; black dashed line) and MRD^{pos} (n = 18; gray dashed line) CR2 patients.

MRD + ou – (par cytométrie) gomme RC 1 ou 2

Wilms' tumor gene 1 expression: an independent acute leukemia prognostic indicator following allogeneic hematopoietic SCT

X-S Zhao, S Jin, H-H Zhu, L-P Xu, D-H Liu, H Chen, K-Y Liu and X-J Huang

Department of Bone Marrow Transplantation, People's Hospital, Peking University Institute of Hematology, Beijing, China

Bone Marrow Transplantation (2011), 1–9

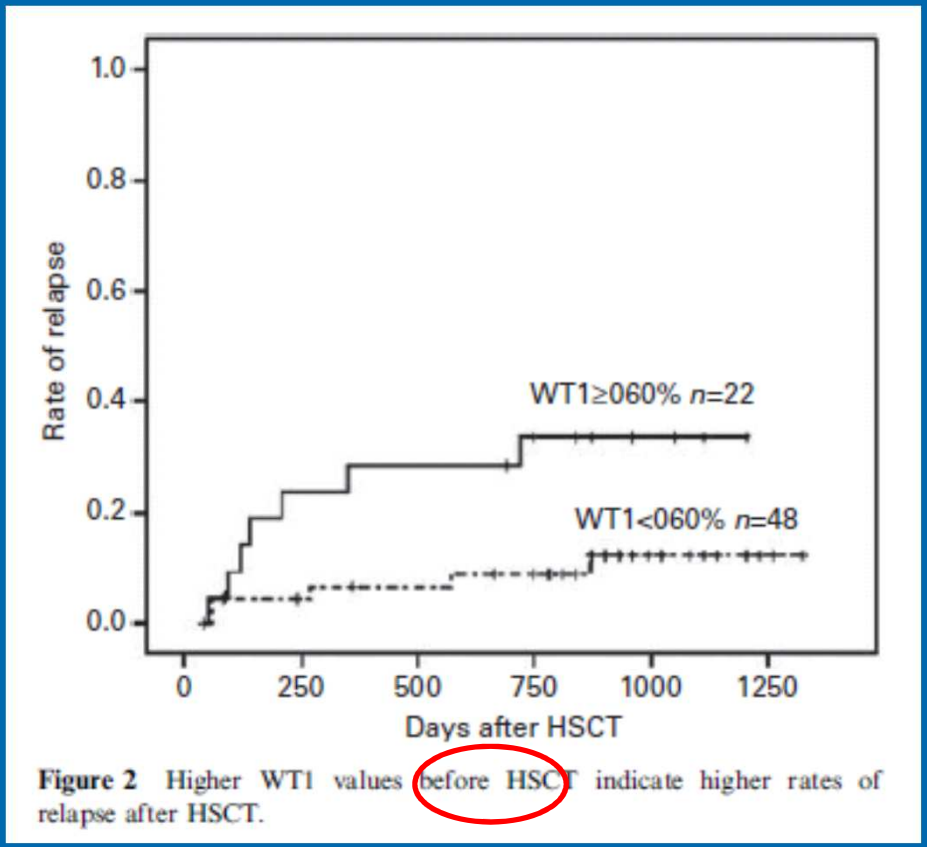


Figure 2 Higher WT1 values before HSCT indicate higher rates of relapse after HSCT.

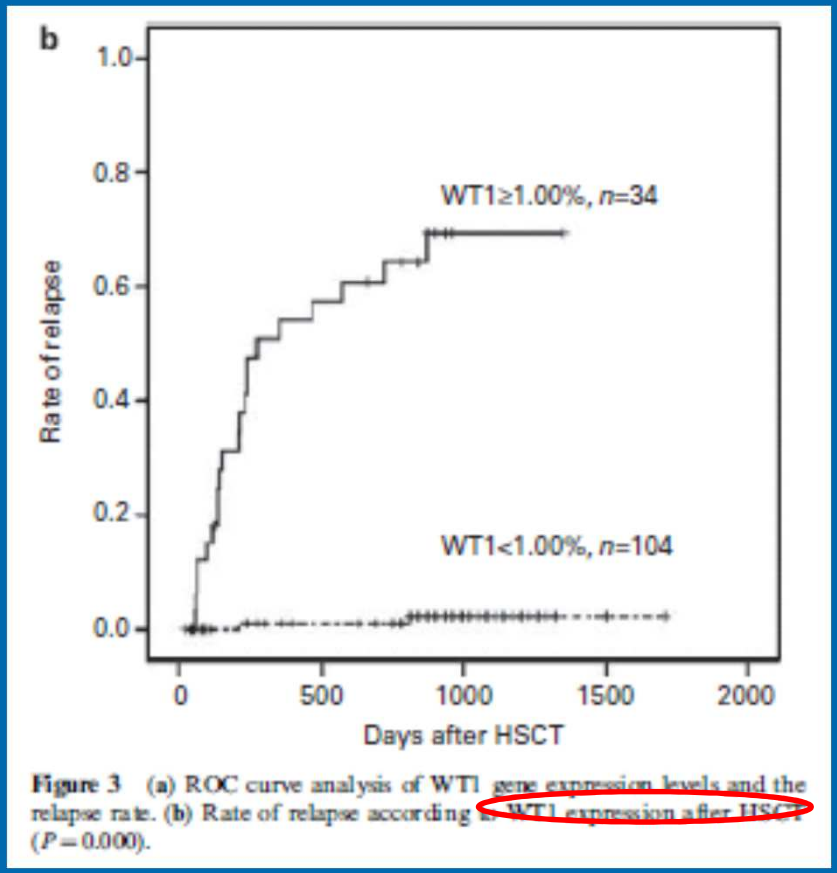


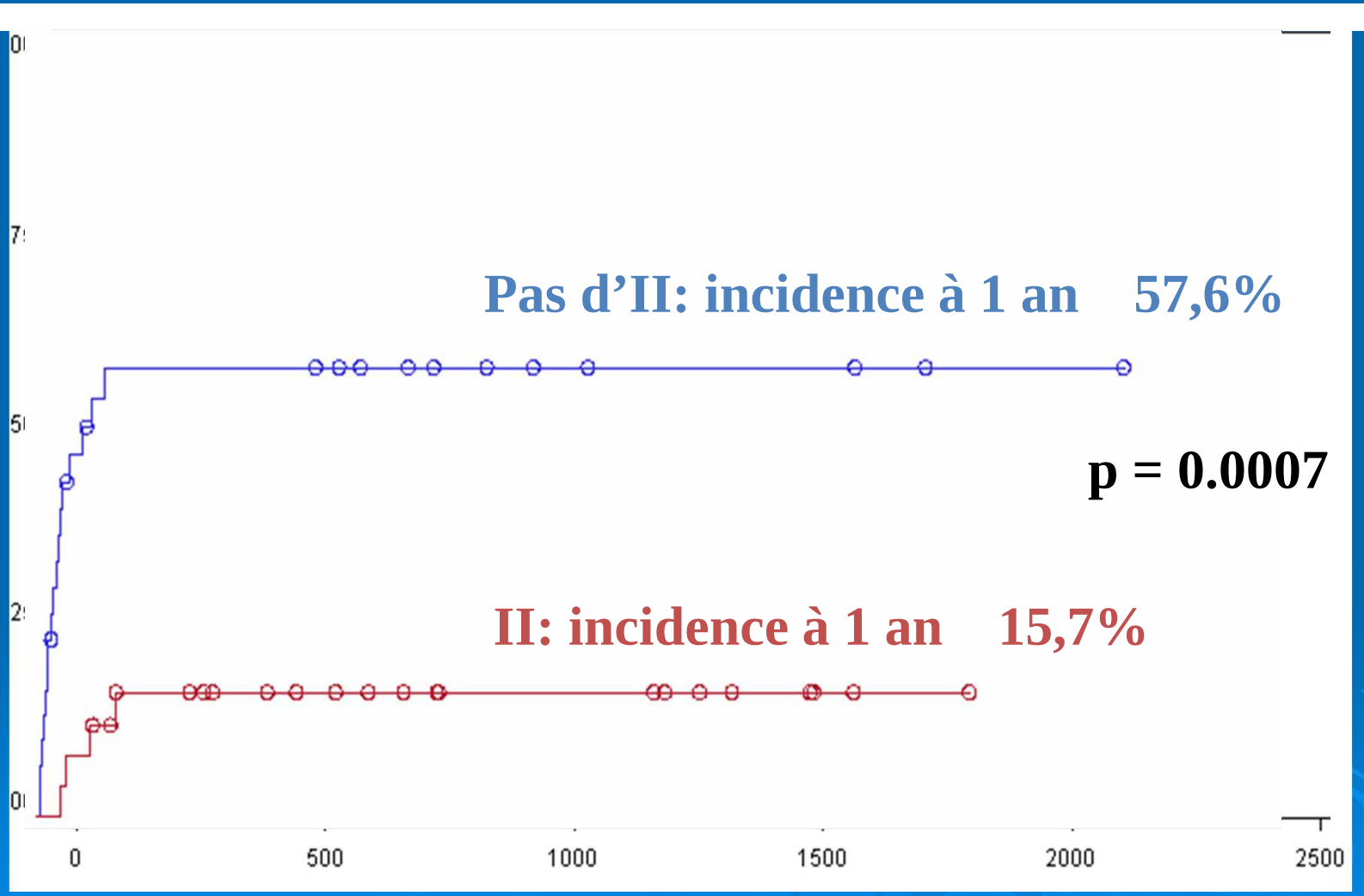
Figure 3 (a) ROC curve analysis of WT1 gene expression levels and the relapse rate. (b) Rate of relapse according to WT1 expression after HSCT ($P=0.000$).

Possibilité d'adapter le conditionnement, la prophylaxie de la GVHD et l'utilisation, de principe , de DLI à la MRD pré-greffe.

Bone Marrow Transplantation (2011), 1–9

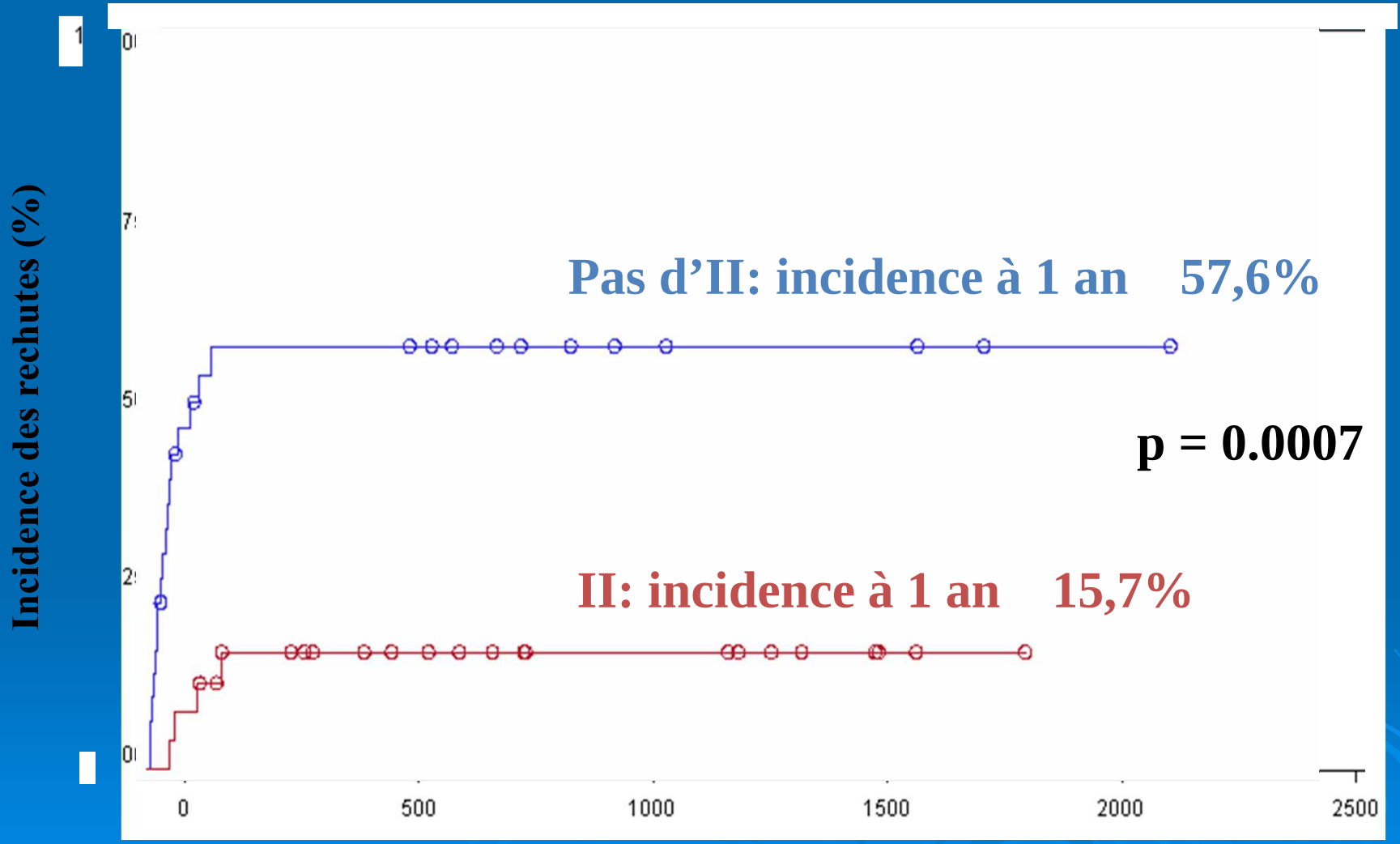
Immuno intervention post greffe

IMPACT DE L'IMMUNO-INTERVENTION SUR LA RECHUTE : après 1 CMA



e tude du chimerisme

IMPACT DE L'IMMUNO-INTERVENTION SUR LA RECHUTE : après 1 CMA



Etude du chimérisme

Greffes de CSH dans les LAM

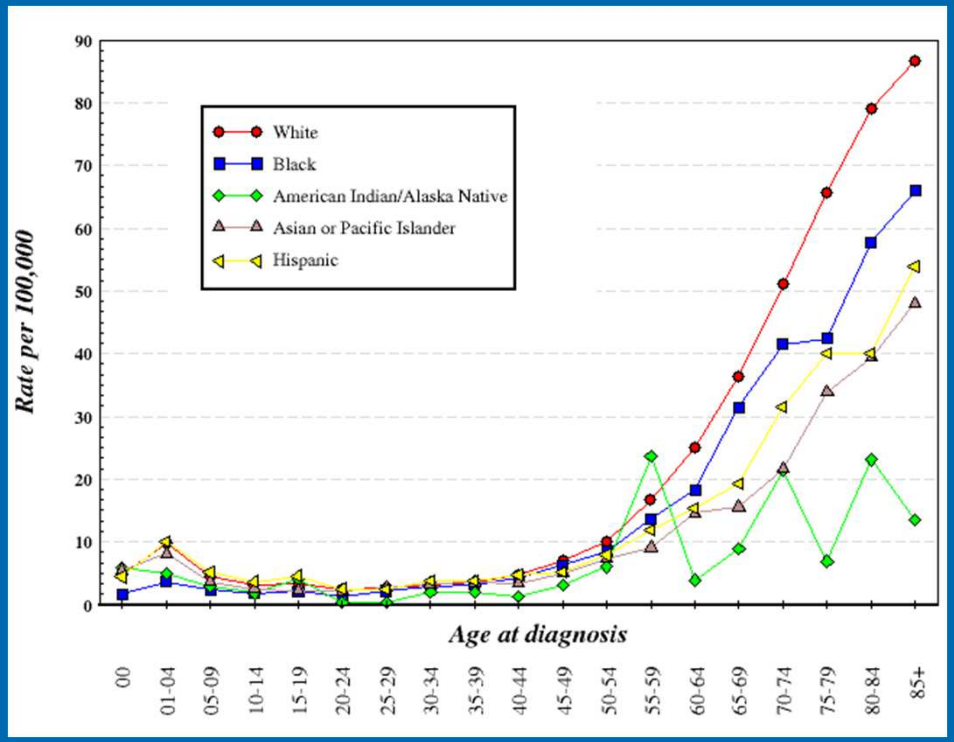
Au total 1) on pourrait proposer de principe en cas de donneur géno ou phéno identique :

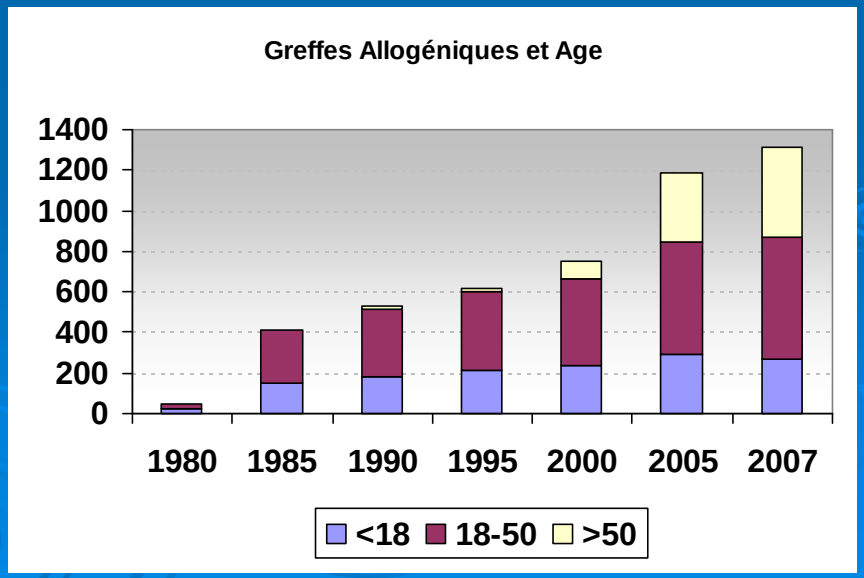
- chez les plus « jeunes » MAC sans ATG et greffon médullaire.
- chez les plus « âgés » RIC avec ATG et greffon de CSP

Il serait souhaitable de proposer :
pour les malades à risque de rechute élevé (réfractaires ou à MRD pré greffe élevée)

- un conditionnement alourdi ,sans ATG avec, chez ceux n'ayant pas fait de GVHD , un arrêt rapide de la prophylaxie
- un contrôle du chimérisme et de la MRD post greffe pour juger de l'opportunité de prescrire des DLI.

2) En l'absence de donneur pheno ou géno ,greffe mismatch-haplo


Rate per 100,000
Age at diagnosis
White
Black
American Indian/Alaska Native
Asian or Pacific Islander
Hispanic
0
10
20
30
40
50
60
70
80
90
00
01-04
05-09
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+


Greffes Allogéniques et Age
1400
1200
1000
800
600
400
200
0
1980
1985
1990
1995
2000
2005
2007
<18
18-50
>50

Merci !