Il Trapianto da donatore MUD

Alessandro Rambaldi

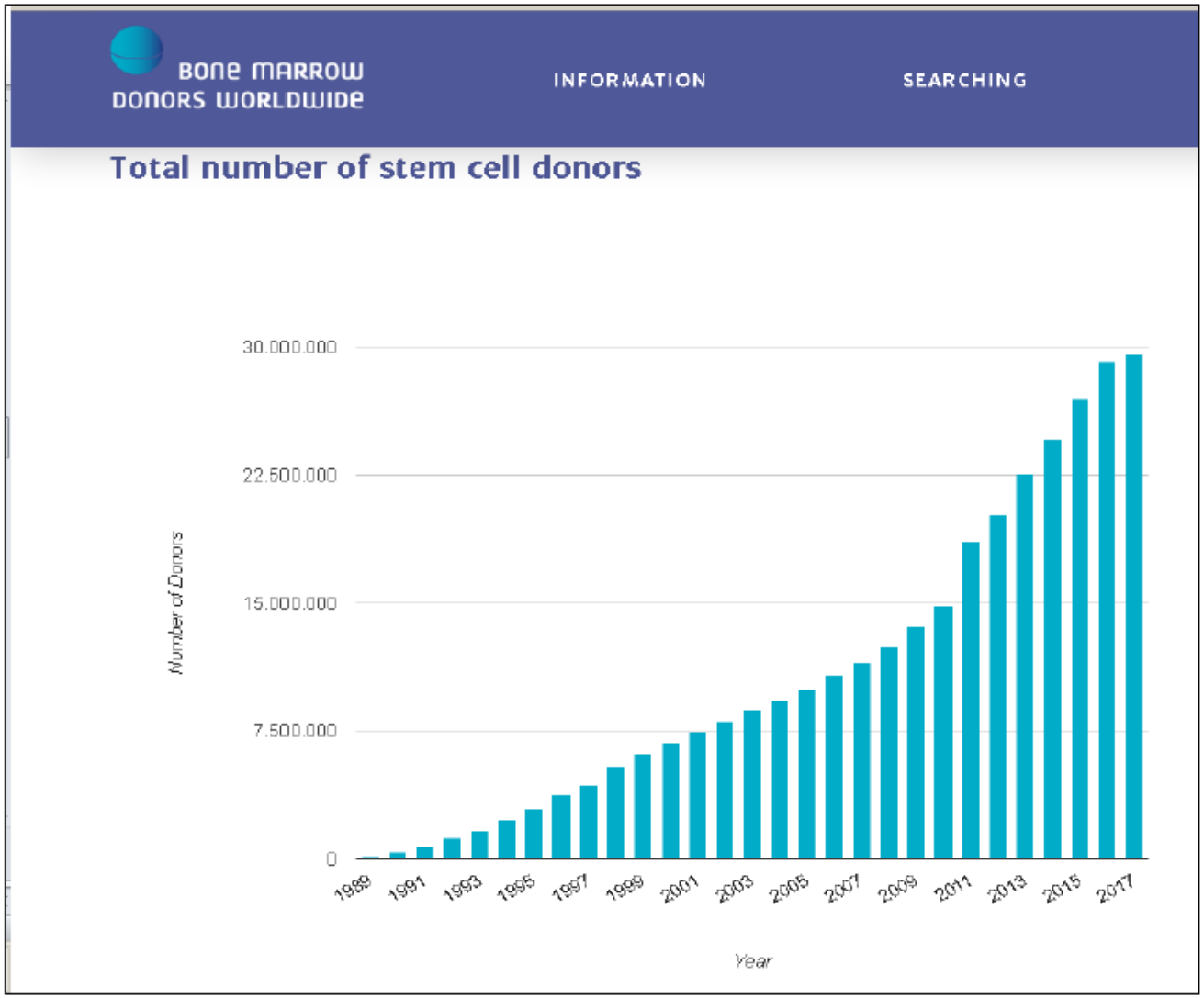
UNIVERSITÀ DEGLI STUDI DI MILANO

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

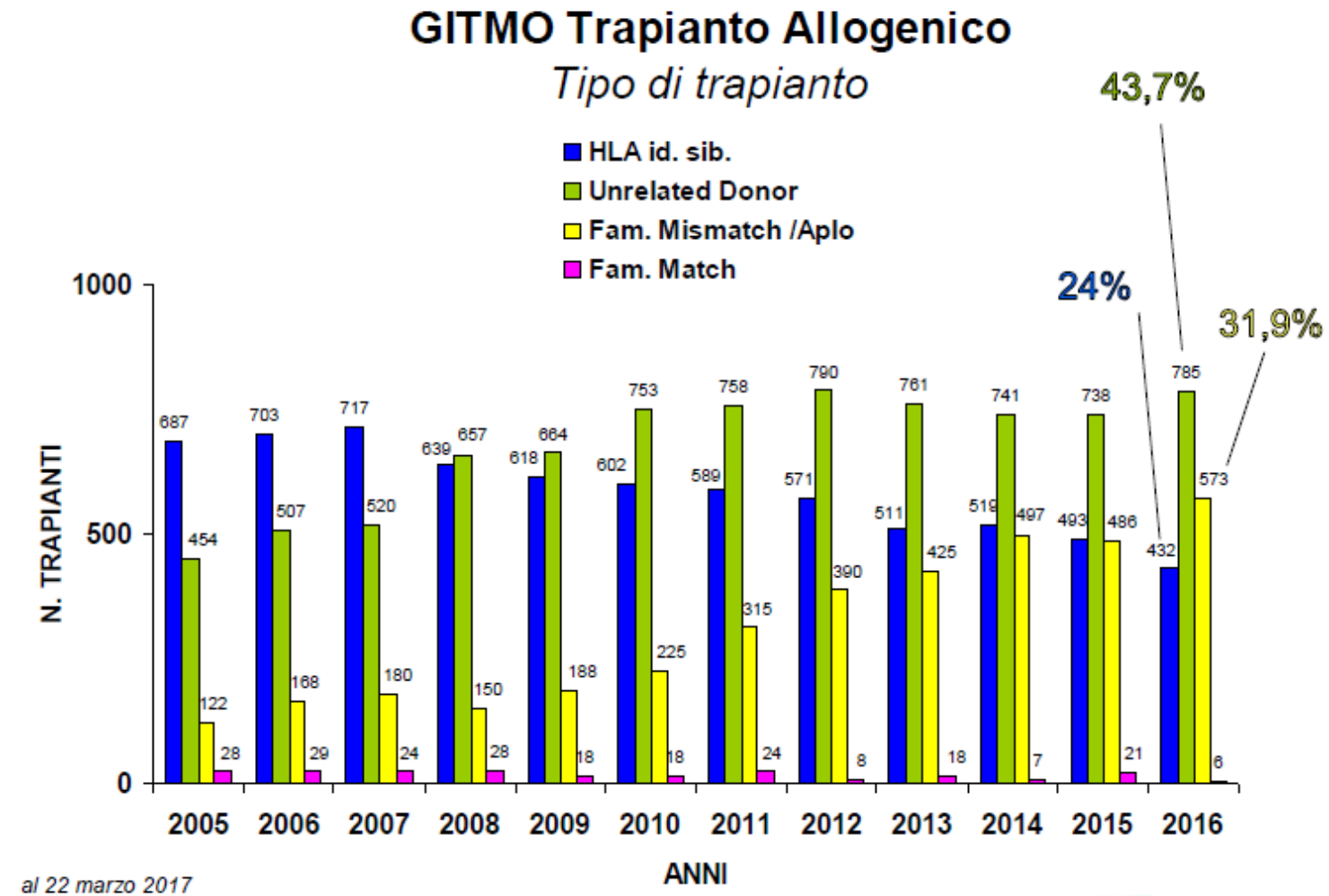
Overview

- **Comparison of outcomes of allo-HSCT from matched related and unrelated donors. We need evidence based results!**
- **Is the time needed to find an unrelated donor a real issue (in Europe and USA)?**
- **Is the Haplo donor the only available alternative donor? Should we abandon allo-HSCT from CB units??**

Bone Marrow Donors Worldwide

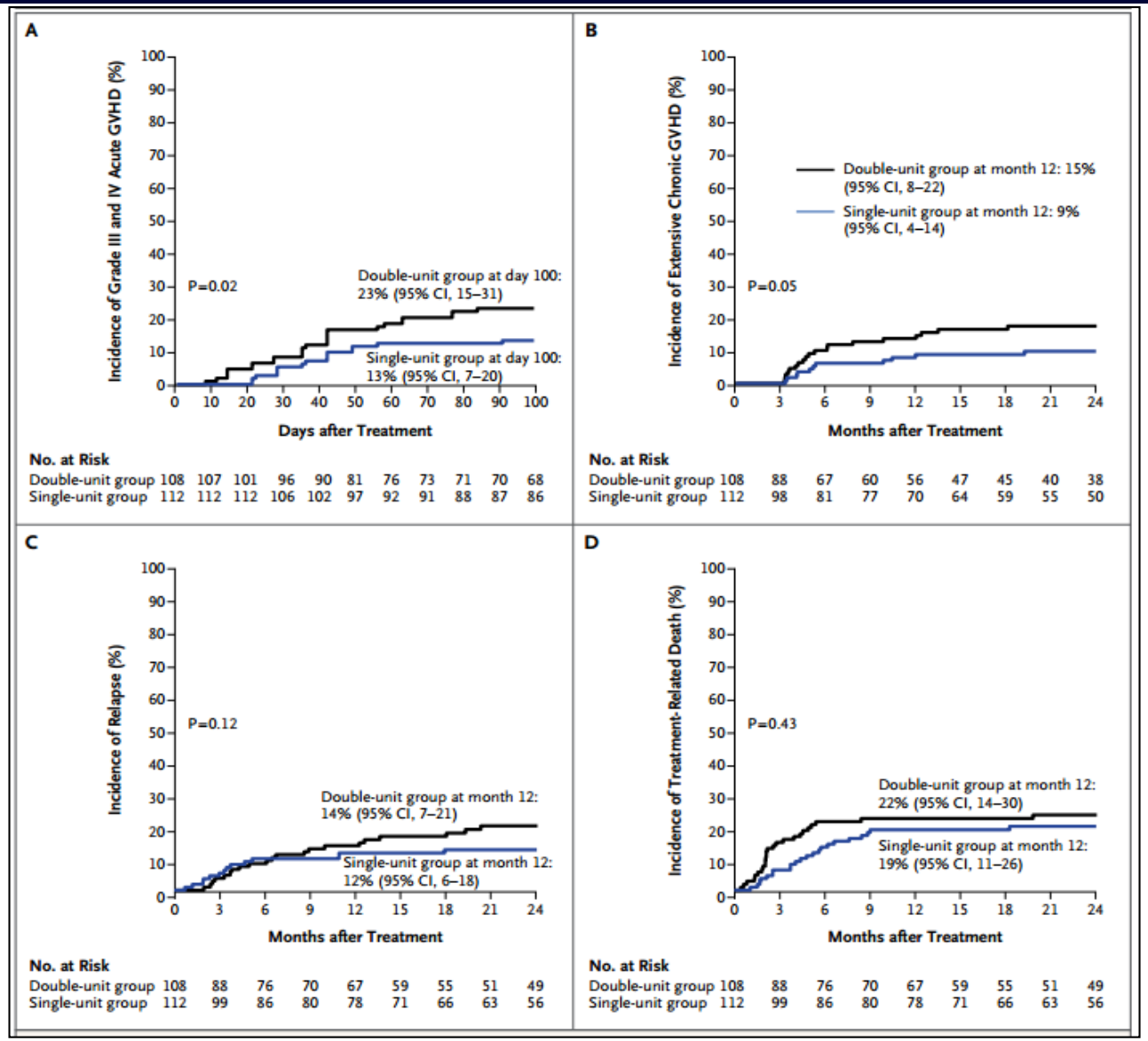


Types of Allogeneic transplants in Italy



Evidence Based or Emotional Driven Transplantation?

One vs Two Units Cord Blood Transplantation

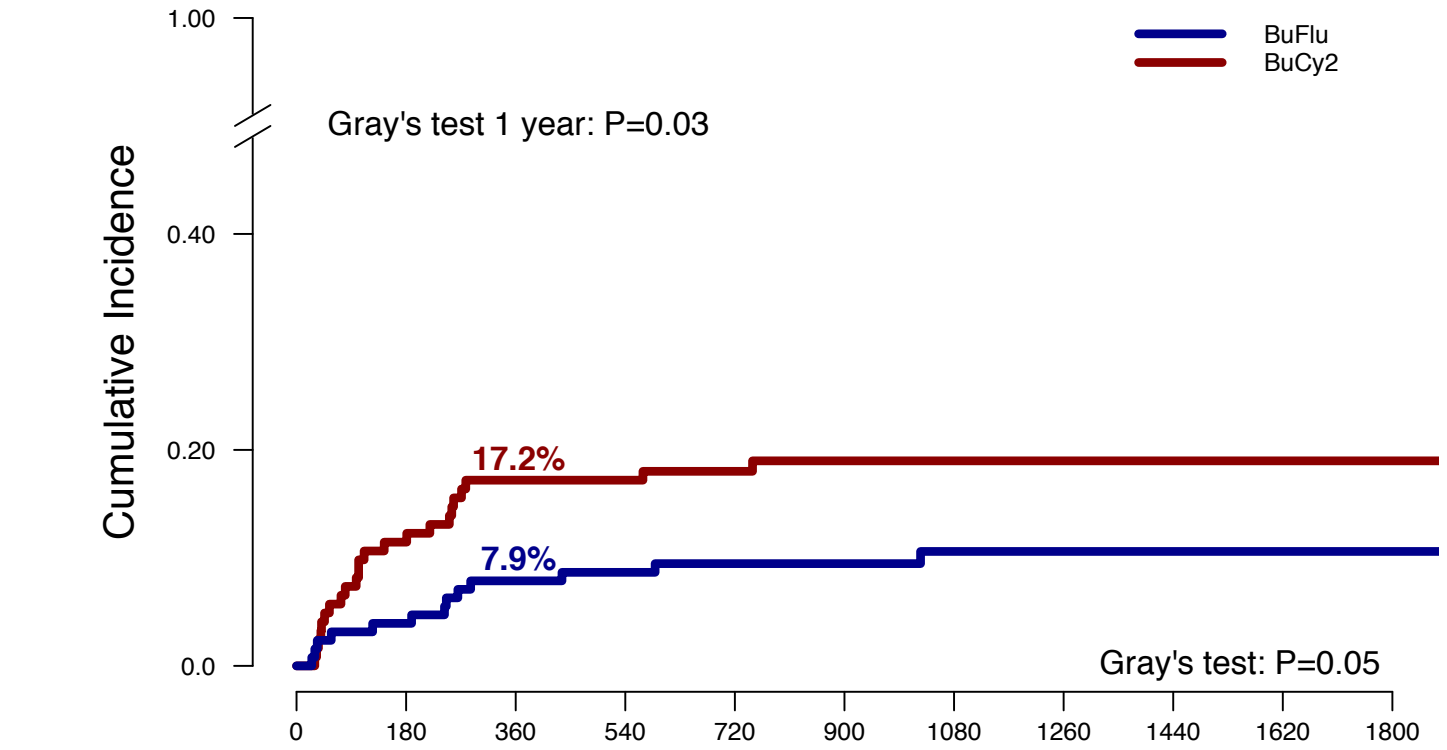


Wagner J et al.: N Eng J Med 2014; 371 , 1685-1694

Results of UD Transplant in AML

Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial

- **Non Relapse Mortality** **Median Age: 51**

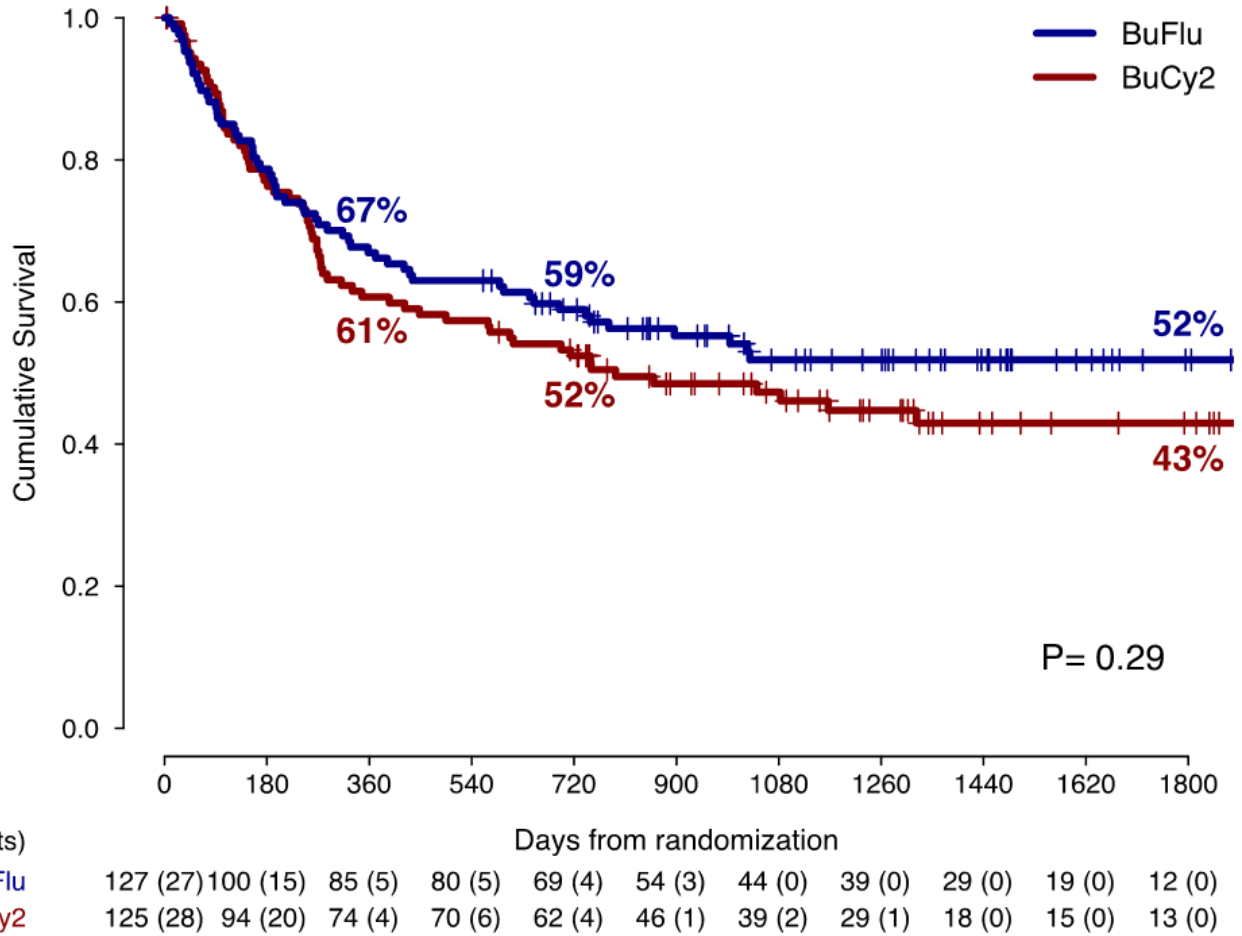


Pts (Events)											
BuFlu	127 (0)	100 (5)	85 (5)	80 (1)	69 (1)	54 (0)	44 (1)	39 (0)	29 (0)	19 (0)	12 (0)
BuCy2	125 (0)	94 (14)	74 (7)	70 (0)	62 (1)	46 (1)	39 (0)	29 (0)	18 (0)	15 (0)	13 (0)

A. Rambaldi et al.: The Lancet Oncology, 2015

Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial

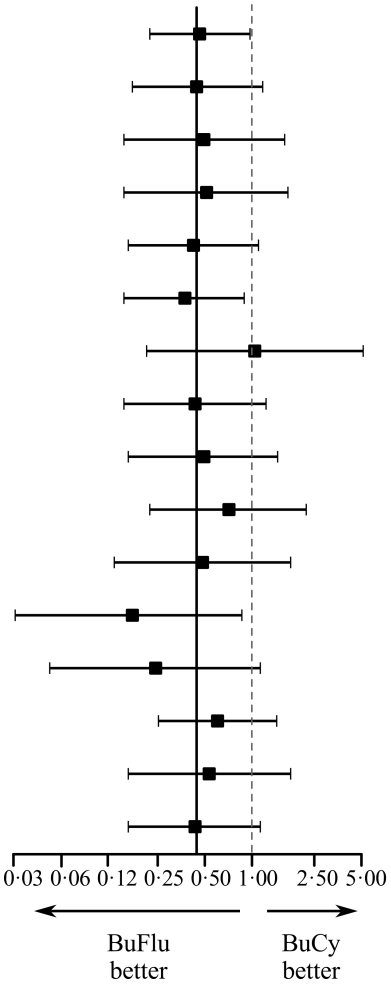
- **Leukemia Free Survival** **Median Age: 51**



A. Rambaldi et al.: The Lancet Oncology, 2015

Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial

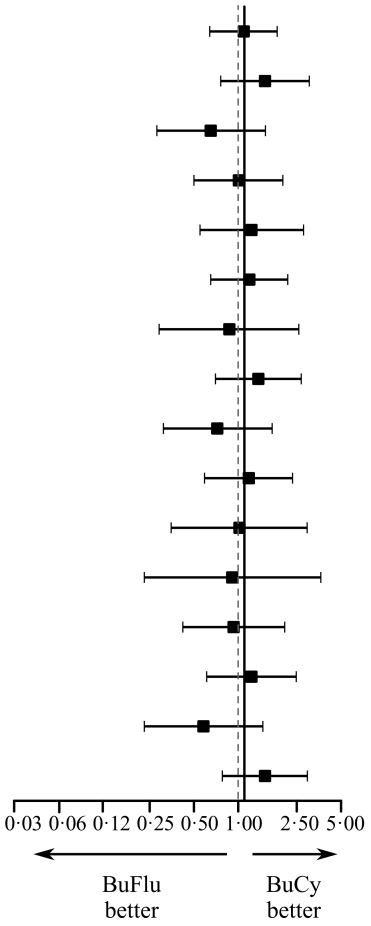
	BuCy n (events)	BuFlu n (events)	HR (95% CI)	p
Non relapse mortality				
All patients	121 (21)	124 (10)	0·46 (0·22–0·97)	0·04
Male	66 (13)	70 (6)	0·44 (0·17–1·17)	0·10
Female	55 (8)	54 (4)	0·49 (0·15–1·62)	0·24
Age <51 years	63 (8)	61 (4)	0·51 (0·15–1·70)	0·27
Age ≥51 years	58 (13)	63 (6)	0·42 (0·16–1·10)	0·08
Disease status: 1° CR	102 (18)	107 (7)	0·37 (0·15–0·89)	0·03
Disease status: ≥2° CR	19 (3)	17 (3)	1·04 (0·21–5·18)	0·96
ELN risk Good/Int-1	75 (12)	75 (5)	0·43 (0·15–1·23)	0·11
ELN risk Int-2/Adv	46 (9)	49 (5)	0·49 (0·16–1·46)	0·20
HCT-CI 0	67 (7)	71 (5)	0·71 (0·22–2·23)	0·55
HCT-CI 1-2	40 (9)	26 (3)	0·48 (0·13–1·77)	0·27
HCT-CI ≥3	14 (5)	27 (2)	0·17 (0·03–0·86)	0·03
Related donor	55 (8)	57 (2)	0·24 (0·05–1·13)	0·07
Unrelated donor	66 (13)	67 (8)	0·60 (0·25–1·44)	0·25
Bone Marrow graft	41 (8)	36 (4)	0·53 (0·16–1·77)	0·30
Peripheral blood graft	80 (13)	88 (6)	0·43 (0·16–1·13)	0·09



A. Rambaldi et al.: The Lancet Oncology, 2015

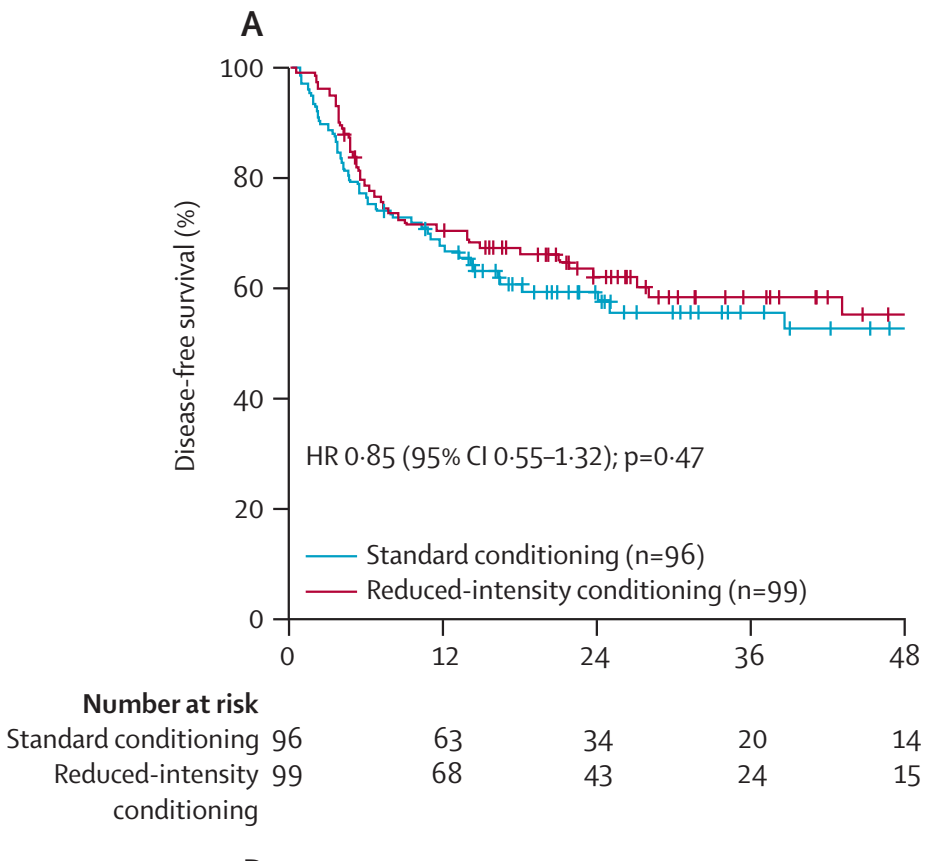
Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial

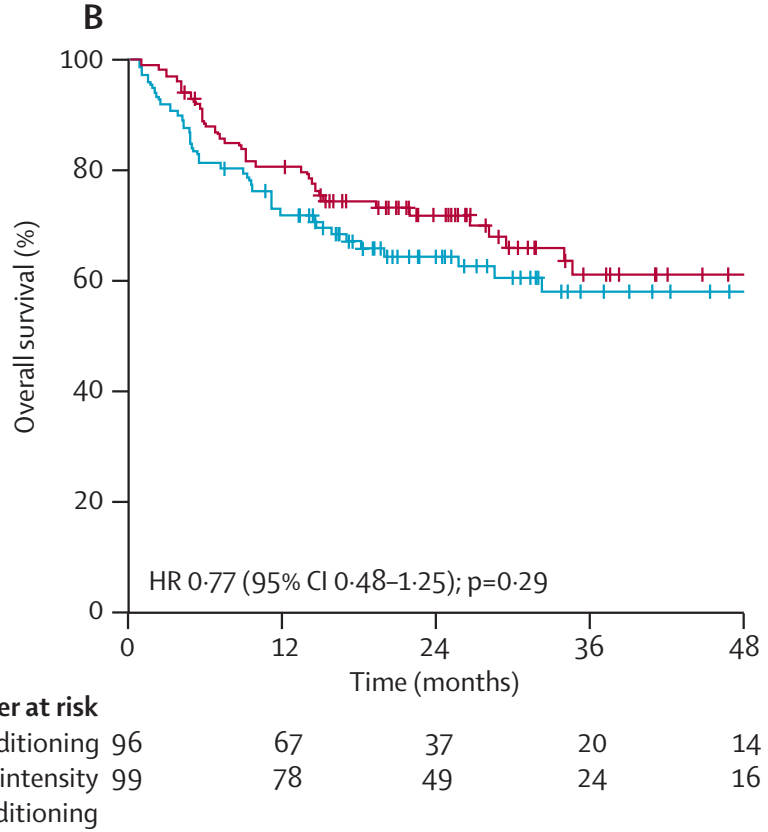
	BuCy n (events)	BuFlu n (events)	HR (95% CI)	p
Relapse				
All patients	121 (26)	124 (30)	1·09 (0·64–1·84)	0·75
Male	66 (13)	70 (21)	1·52 (0·76–3·04)	0·23
Female	55 (13)	54 (9)	0·65 (0·28–1·53)	0·33
Age <51 years	63 (16)	61 (16)	1·01 (0·50–2·01)	0·98
Age ≥51 years	58 (10)	63 (14)	1·23 (0·55–2·78)	0·61
Disease status: 1° CR	102 (19)	107 (24)	1·19 (0·65–2·17)	0·57
Disease status: ≥2° CR	19 (7)	17 (6)	0·87 (0·29–2·58)	0·80
ELN risk Good/Int-1	75 (15)	75 (20)	1·37 (0·70–2·68)	0·36
ELN risk Int-2/Adv	46 (11)	49 (10)	0·72 (0·31–1·70)	0·46
HCT-CI 0	67 (15)	71 (18)	1·18 (0·59–2·34)	0·64
HCT-CI 1-2	40 (8)	26 (6)	1·02 (0·35–2·94)	0·97
HCT-CI ≥3	14 (3)	27 (6)	0·91 (0·23–3·64)	0·89
Related donor	55 (12)	57 (12)	0·93 (0·42–2·07)	0·86
Unrelated donor	66 (14)	67 (18)	1:23 (0·61–2·48)	0·56
Bone Marrow graft	41 (12)	36 (7)	0·58 (0·23–1·47)	0·25
Peripheral blood graft	80 (14)	88 (23)	1·52 (0·78–2·95)	0·22



A. Rambaldi et al.: The Lancet Oncology, 2015

Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial



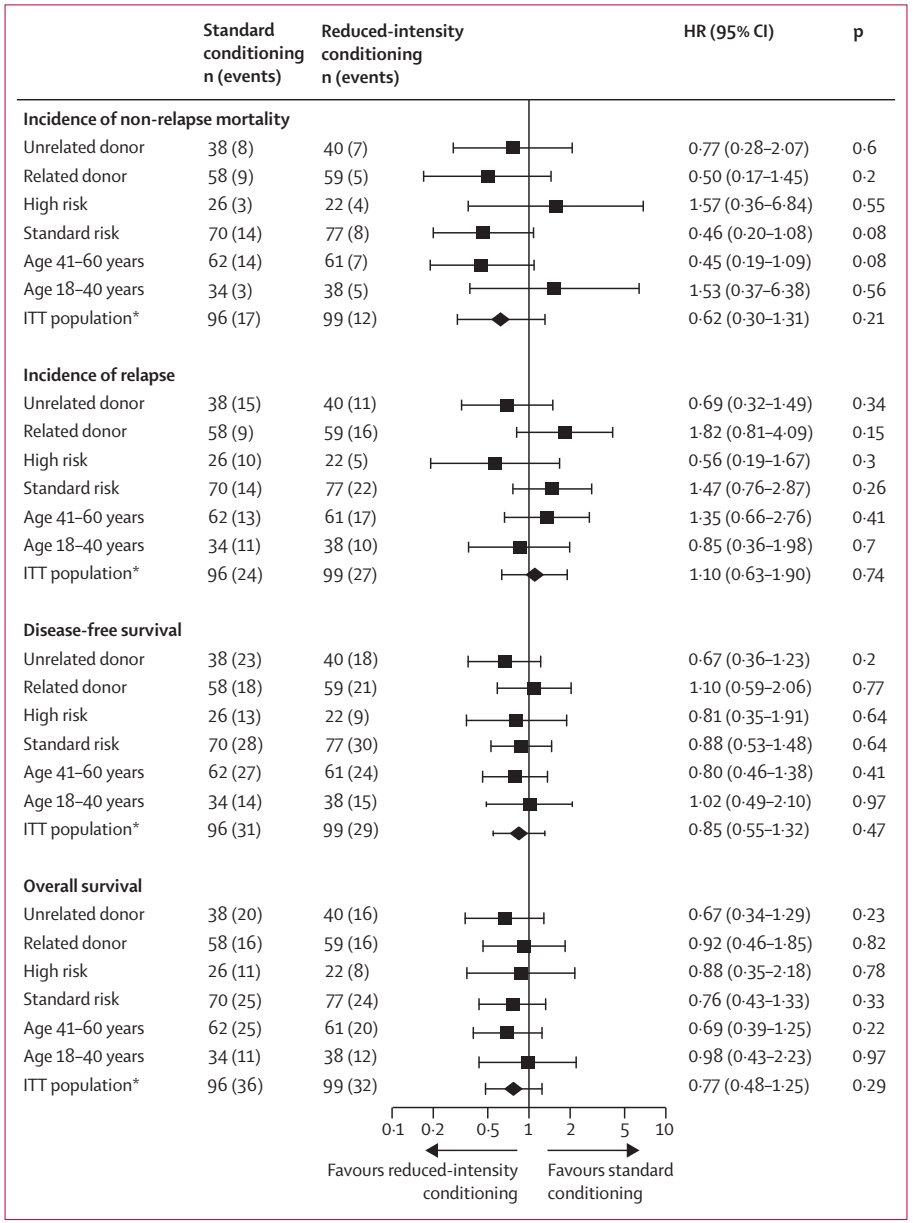


Median Age: 44 years

Bornhäuser M. et al.: , Lancet Oncol 2012; 13: 1035–44

Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial

Median Age: 44 years

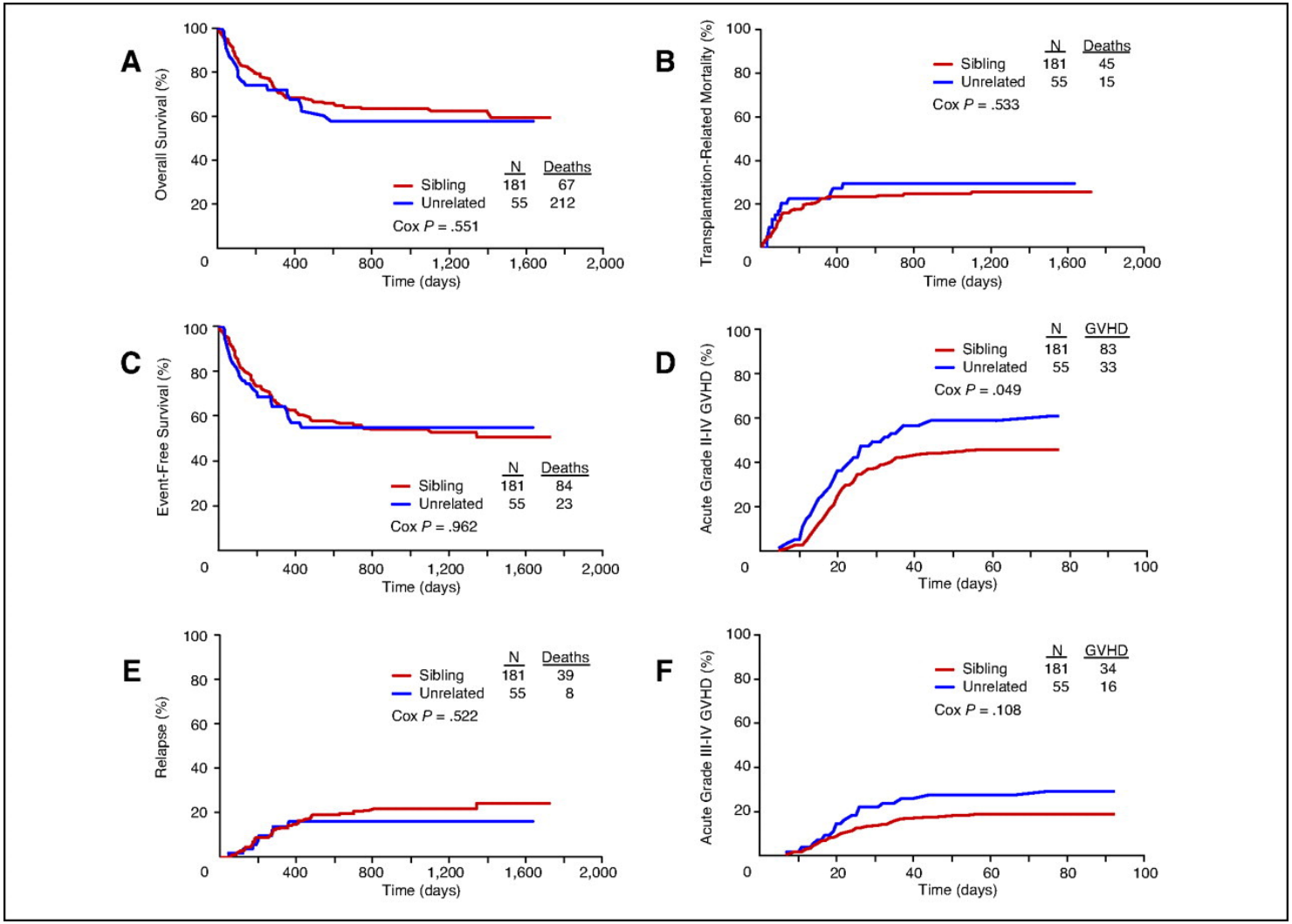


	Standard conditioning n (events)	Reduced-intensity conditioning n (events)	HR (95% CI)	p
Incidence of non-relapse mortality				
Unrelated donor	38 (8)	40 (7)	0·77 (0·28–2·07)	0·6
Related donor	58 (9)	59 (5)	0·50 (0·17–1·45)	0·2
High risk	26 (3)	22 (4)	1·57 (0·36–6·84)	0·55
Standard risk	70 (14)	77 (8)	0·46 (0·20–1·08)	0·08
Age 41–60 years	62 (14)	61 (7)	0·45 (0·19–1·09)	0·08
Age 18–40 years	34 (3)	38 (5)	1·53 (0·37–6·38)	0·56
ITT population*	96 (17)	99 (12)	0·62 (0·30–1·31)	0·21
Incidence of relapse				
Unrelated donor	38 (15)	40 (11)	0·69 (0·32–1·49)	0·34
Related donor	58 (9)	59 (16)	1·82 (0·81–4·09)	0·15
High risk	26 (10)	22 (5)	0·56 (0·19–1·67)	0·3
Standard risk	70 (14)	77 (22)	1·47 (0·76–2·87)	0·26
Age 41–60 years	62 (13)	61 (17)	1·35 (0·66–2·76)	0·41
Age 18–40 years	34 (11)	38 (10)	0·85 (0·36–1·98)	0·7
ITT population*	96 (24)	99 (27)	1·10 (0·63–1·90)	0·74
Disease-free survival				
Unrelated donor	38 (23)	40 (18)	0·67 (0·36–1·23)	0·2
Related donor	58 (18)	59 (21)	1·10 (0·59–2·06)	0·77
High risk	26 (13)	22 (9)	0·81 (0·35–1·91)	0·64
Standard risk	70 (28)	77 (30)	0·88 (0·53–1·48)	0·64
Age 41–60 years	62 (27)	61 (24)	0·80 (0·46–1·38)	0·41
Age 18–40 years	34 (14)	38 (15)	1·02 (0·49–2·10)	0·97
ITT population*	96 (31)	99 (29)	0·85 (0·55–1·32)	0·47
Overall survival				
Unrelated donor	38 (20)	40 (16)	0·67 (0·34–1·29)	0·23
Related donor	58 (16)	59 (16)	0·92 (0·46–1·85)	0·82
High risk	26 (11)	22 (8)	0·88 (0·35–2·18)	0·78
Standard risk	70 (25)	77 (24)	0·76 (0·43–1·33)	0·33
Age 41–60 years	62 (25)	61 (20)	0·69 (0·39–1·25)	0·22
Age 18–40 years	34 (11)	38 (12)	0·98 (0·43–2·23)	0·97
ITT population*	96 (36)	99 (32)	0·77 (0·48–1·25)	0·29

Bornhäuser M. et al.: , Lancet Oncol 2012; 13: 1035–44

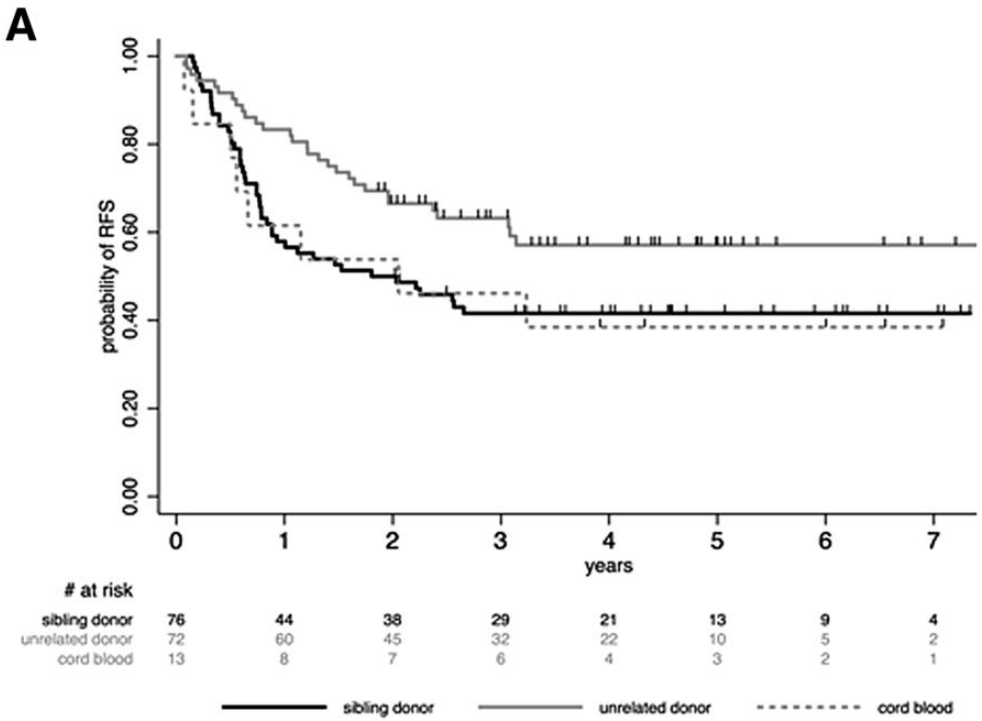
Results of UD Transplant in ALL

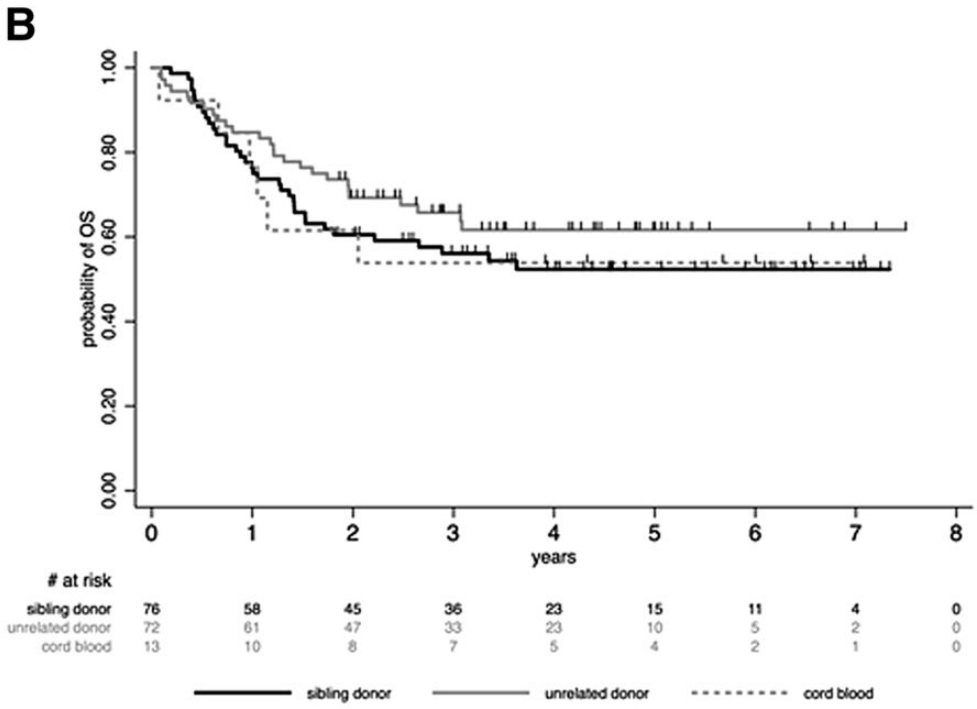
Sibling *v* HLA-Matched Unrelated Allo-SCT in Patients With Standard-Risk Hematologic Malignancy: A Prospective Study From the French Society of Bone Marrow Transplantation and Cell Therapy



Ibrahim Yakoub-Agha et al.: *J Clin Oncol 24:5695-5702. © 2006*

The GRAALL Study in Ph+ ALL: post-SCT outcome by stem cell source (allogeneic SCT cohort)





Yves Chalandon et al. Blood 2015;125:3711-3719

blood

Rabbit anti-thymocyte globulin to prevent GVHD

When using unrelated donors

- Thymoglobulin prevents cGvHD, chronic lung dysfunction, and late transplant-related mortality. *Bacigalupo A et al.: Biol Blood Marrow Transplant* 2006
- ATG-F added to GVHD prophylaxis resulted in decreased incidence of acute and chronic GVHD without an increase in relapse or non-relapse mortality, and without compromising overall survival. *Finke J.et al.: Lancet Oncology 2008*
- Thymoglobulin added to myeloblative and non-myeloblative preparative regimens decreases steroid use and the clinical benefit significant. *Walker I et al.: Lancet Oncology 2015*

When using HLA-identical sib donors and PBSC as stem cell source

- ATG-F resulted in a significantly lower rate of cGVHD and the composite end point of cGVHD–free survival and relapse-free survival was better with ATG. *Kroger N et al.: NEJM 2015*

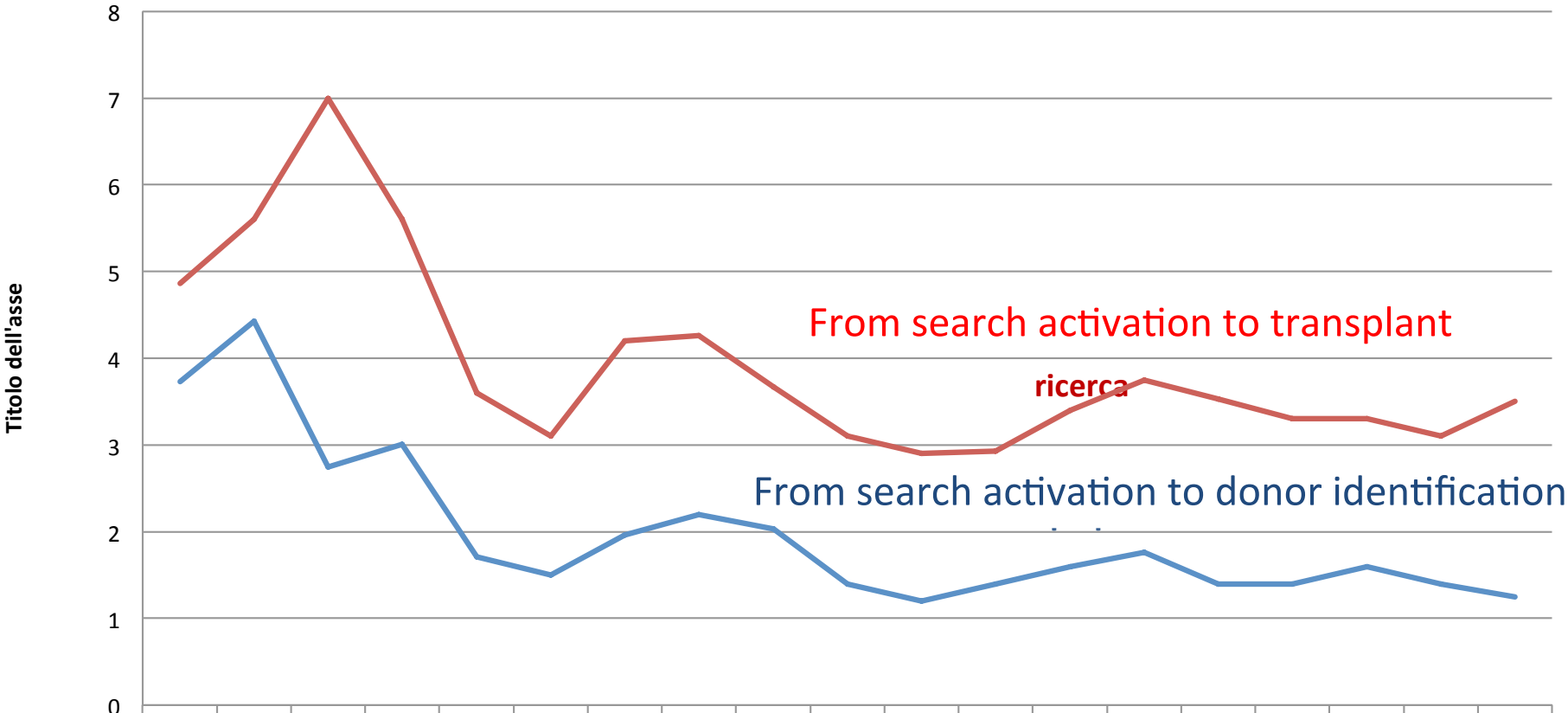
Rabbit anti-thymocyte globulin to prevent GVHD

- **The addition of ATG to the conditioning regimen of patients undergoing allogeneic transplantation from unrelated donors should always be advised**
- **It represents a standard of care for GVHD prophylaxis in particular when the stem cell source is represented by G-CSF mobilised peripheral blood stem cells**

Rambaldi A et al.: Lancet Onclogy 2015

Is the time needed to find an unrelated donor a real issue (in Europe and USA)?

Time to find an unrelated donor: Bergamo experience

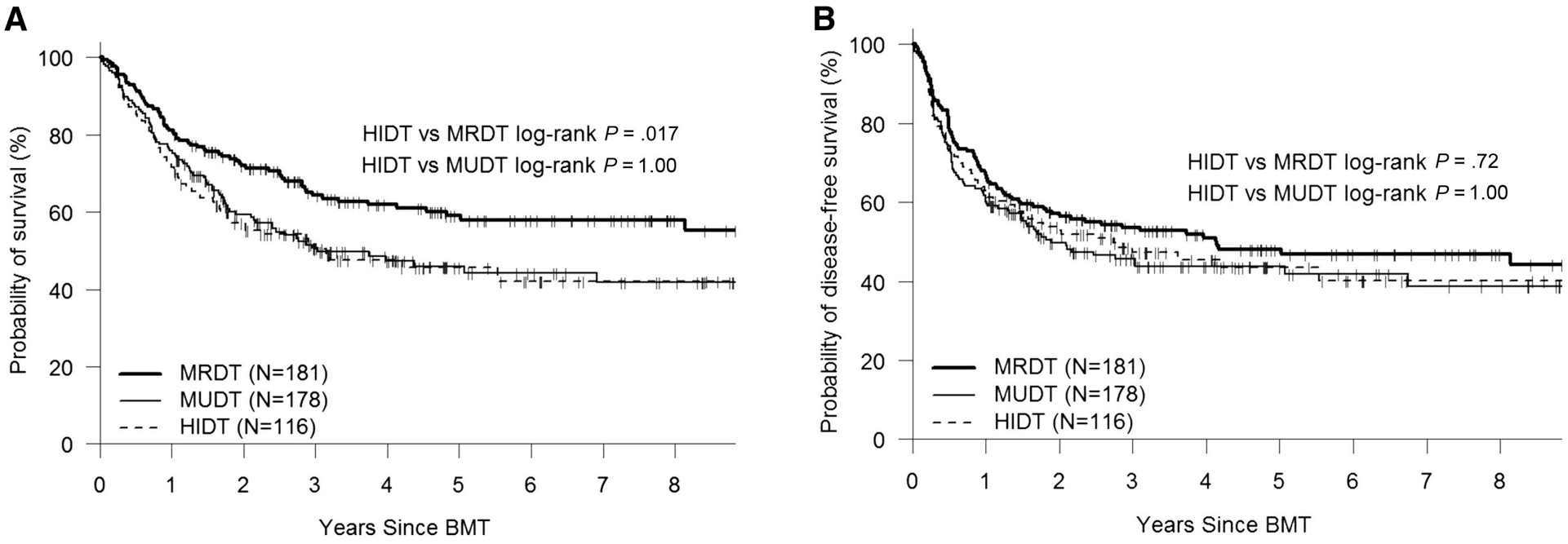


	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Serie1	3,73	4,43	2,75	3,01	1,71	1,5	1,96	2,2	2,03	1,4	1,2	1,4	1,6	1,76	1,4	1,4	1,6	1,4	1,25
Serie2	4,86	5,6	7	5,6	3,6	3,1	4,2	4,26	3,67	3,1	2,9	2,93	3,4	3,75	3,53	3,3	3,3	3,1	3,5

N transplants	1	3	6	10	8	4	15	18	13	21	21	28	28	36	27	30	37	39	36

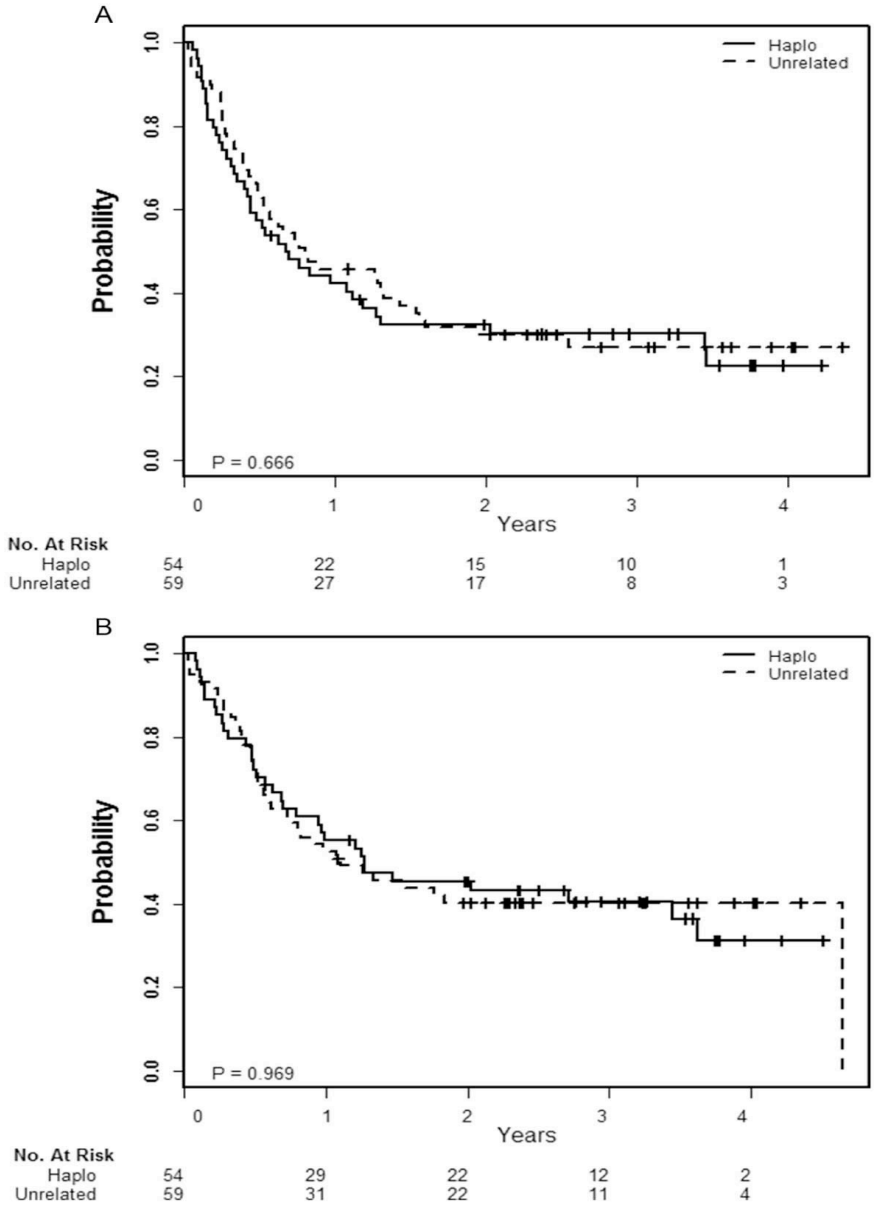
Comparison of Outcomes of Haploidentical Donors Using Post-Transplantation Cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 Allele-Matched Unrelated Donors and HLA-Identical Sibling Donors

Comparison of Outcomes of Hematopoietic Cell Transplants from T-Replete Haploidentical Donors Using Post-Transplantation Cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 Allele-Matched Unrelated Donors and HLA-Identical Sibling Donors: A Multivariable Analysis Including Disease Risk Index



Bashey A et al.: Biology of Blood and Marrow Transplantation Volume 22, Issue 1, Pages 125-133 (2016)

Comparative Outcomes after Haploidentical or Unrelated Donor Bone Marrow or Blood Stem Cell Transplantation in Adult Patients with Hematological Malignancies

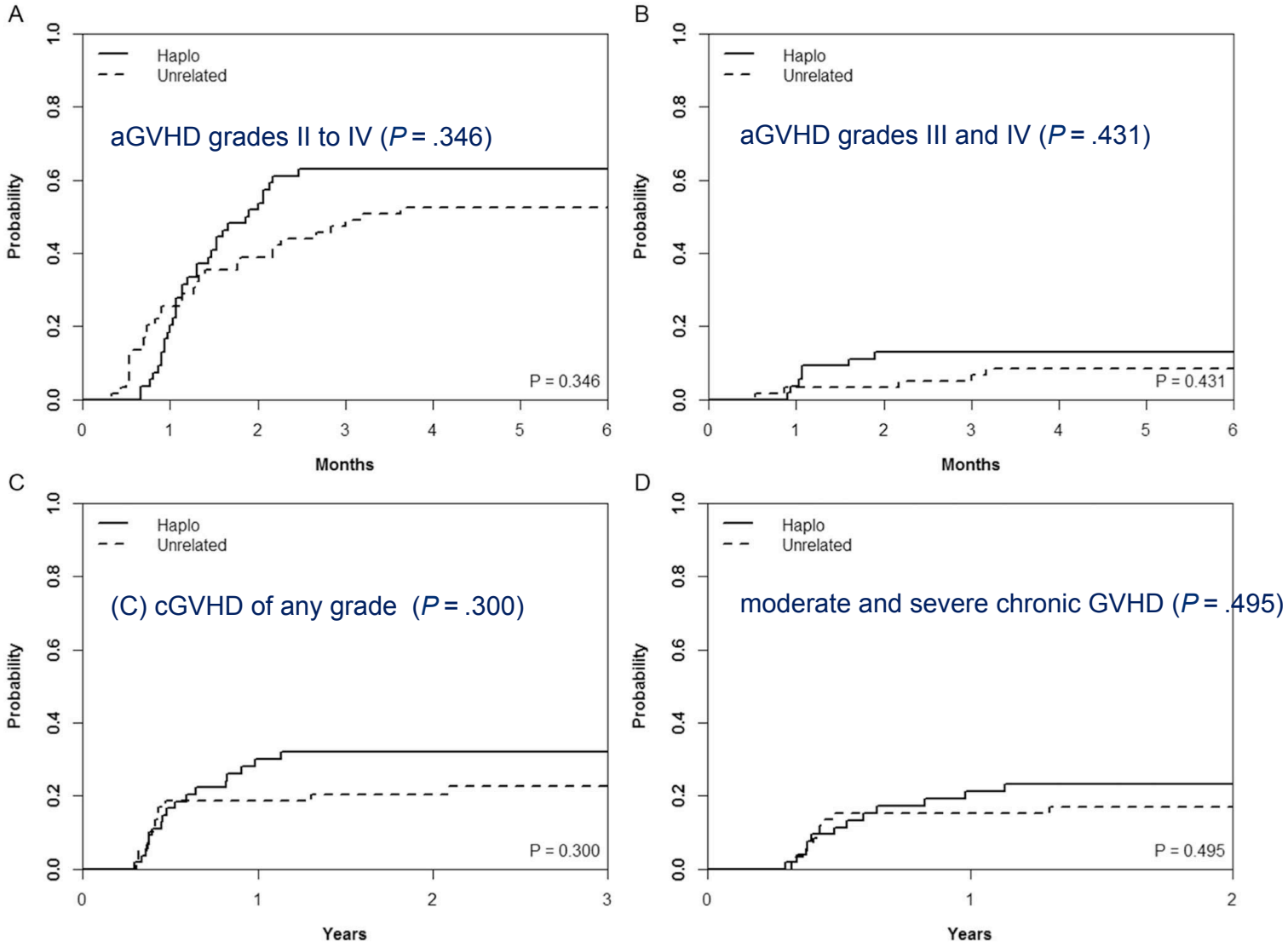


(A) progression-free survival (*P* = .666)

(B) overall survival (*P* = .969)

Baker , M et al.: Biology of Blood and Marrow Transplantation Volume 22, Issue 11, Pages 2047-2055 (November 2016)

Comparative Outcomes after Haploidentical or Unrelated Donor Bone Marrow or Blood Stem Cell Transplantation in Adult Patients with Hematological Malignancies



Baker , M et al.: Biology of Blood and Marrow Transplantation Volume 22, Issue 11, Pages 2047-2055 (November 2016)

Possible advantages of the haploidentical donor option

- A haploidentical donor can be found for nearly every patient that is referred for allo-HSCT
- Graft acquisition costs are modest compared with unrelated donor options
- The donor is readily available to donate more stem cells (or lymphocytes?) in the event of graft failure or relapse, respectively
- HLA disparity may account for a strong Graft versus Leukemia effect (NK and T mediated)

Matched unrelated vs. haploidentical donor for allogeneic stem cell transplantation in patients with acute leukemia – a randomized prospective European trial

EudraCT No.	2017-002331-41
Protocol No.	HaploMUDStudy
Version/Date	0.3 29-May-2017
Sponsor	University Medical Center Hamburg-Eppendorf Investor Initiated Trial (IIT) (financial support by DKMS)
Coordinating Investigator	Germany: N. Kröger The Netherlands: J. Cornelissen Finland: M. Itälä-Remes Czech Republic: M. Markova-Stástnà Poland: S. Giebel Italy: F. Bonifazi Spain: Carlos Solano United Kingdom: K. Raj Swiss: J Halter
Protocol writing committee	J. Cornelissen (The Netherlands) M. Itälä-Remes (Finland**)** M. Markova-Stástnà (Czech Republic) S. Giebel, W. Mendrek (Poland) A. Rambaldi, A. Bacigalupo , F. Bonifazi (Italy) D. Hölzer, N. Kröger (Germany) Jaime Sanz, C. Solano (Spain) K. Raj /D. Marks (United Kingdom) J Halter (Swiss)

Matched unrelated vs. haploidentical donor for allogeneic stem cell transplantation in patients with acute leukemia – a randomized prospective European trial

Primary Objectives	To compare anti-leukemic activity of allogenic stem cell transplantation for patients with acute leukemia in complete remission between a 10/10 HLA matched unrelated donor and a haploidentical donor. Hypothesis: Haploidentical stem cell transplantation with post cyclophoshamide induces a stronger anti-leukemic activity in comparison to 10/10 HLA matched unrelated donor and reduces the risk of relapse at 2 years after stem cell transplantation by 10%
Secondary Objectives	To assess and compare the safety and efficacy of study treatments therapy in both study arms on non-relapse mortality (NRM), relapse-free survival (RFS), Overall survival (OS),QOL, toxicity, development of acute and chronic GVDH as well as engraftment and chimerism.
Methodology:	Open label, two arm multicenter, multinational phase II trial. Treatment A: Allogeneic stem cell transplantation from 10/10 HLA matched unrelated donor Treatment B: Allogeneic stem cell transplantation from haplo-identical donor

Matched unrelated vs. haploidentical donor for allogeneic stem cell transplantation in patients with acute leukemia – a randomized prospective European trial

Sample size calculation:	A difference of 10% in relapse incidence at 2 years results in 74 patients for a power of 80% and a two-sided alpha of 5% based on a z-test on Kaplan-Meier rates (assuming a sigma of 0.15). To account for the potential occurrence of competing risks in the trial, the sample size is adjusted according to the method suggested by Suldigen et al., (2005) and Tai, Wee & Machin (2011). Assuming the probabilities of relapses are 20% for the treatment arm and 30% for the control arm, while 10% of competing events occur in each arm, with 1.5-year of accrual period, 2 years of follow-up period and an equal size of two treatment groups, after taking 10% drop-outs into account, an overall sample size of 402 patients for both arms is required (approximately 200 patients in each arm).
Number of patients:	402 patients will be enrolled in the study.
Diagnosis and main criteria for inclusion:	1. Acute Myeloid Leukemia (AML) intermediate 2 or high risk according ELN or Acute Lymphoblastic Leukemia (ALL) (high risk) in 1. complete remission (CR) or AML/ALL in 2. CR and high risk MDS in 1.or 2. CR with available 10/10 HLA matched unrelated donor and available haploidentical donor. 2. Patients age: 18 - 70 years at time of inclusion. 3. Patients understand and voluntarily sign an informed consent form.

Is the Haplo donor the only available alternative donor? Should we abandon allo-HSCT from CB units?

The EBMT retrospective study comparing CB vs. haplo

ORIGINAL ARTICLE

Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia

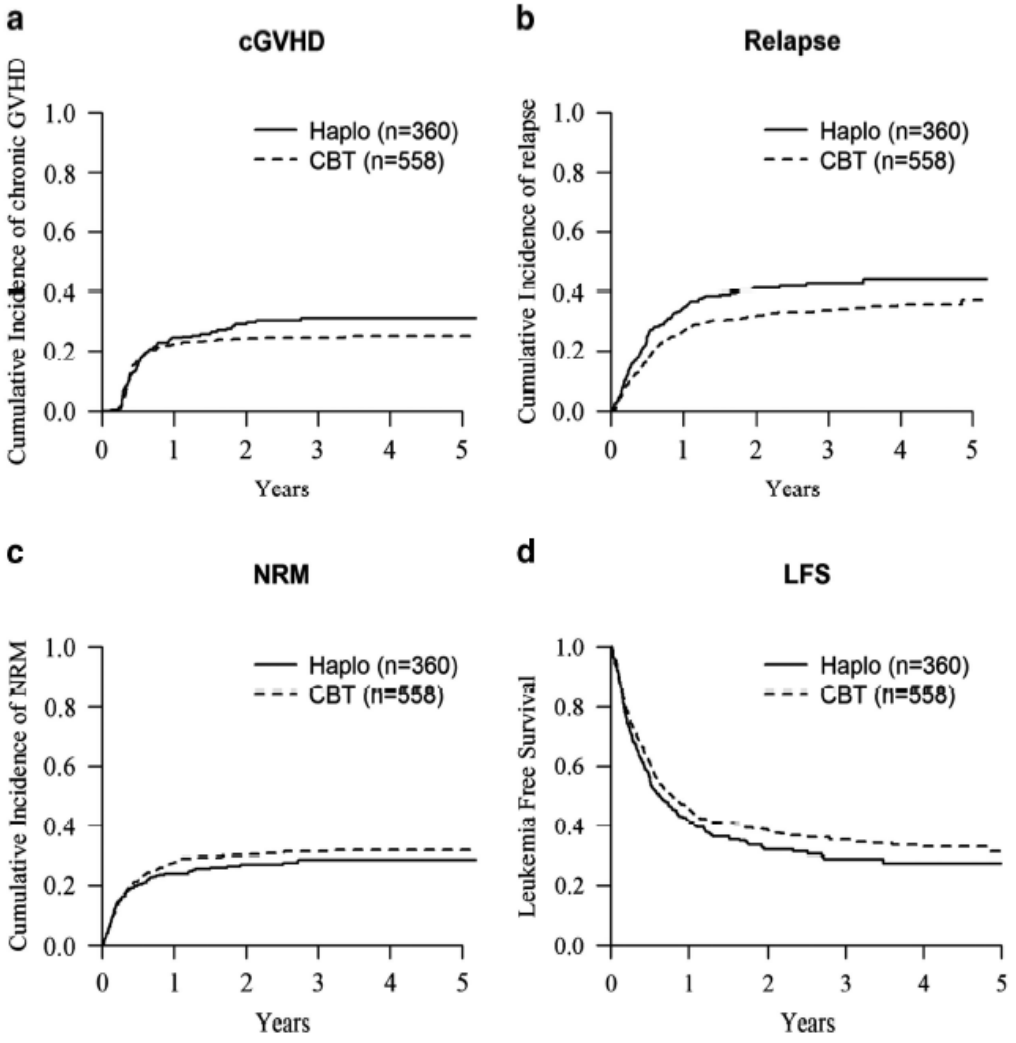
A Ruggeri[1,2,3], M Labopin[1,4], G Sanz[5], S Piemontese[6], W Arcese[7], A Bacigalupo[8], D Blaise[9], A Bosi[10], H Huang[11], D Karakasis[12], Y Koc[13], M Michallet[14], A Picardi[7], J Sanz[5], S Santarone[15], H Sengelov[16], J Sierra[17], L Vincent[18], F Volt[3], A Nagler[19,20], E Gluckman[3,21], F Ciceri[6], V Rocha[3,22] and M Mohty[1,2,4] on behalf of Eurocord, Cord Blood Committee of Cellular Therapy and Immunobiology working party-EBMT, ALWP-EBMT study

Population: Adults with *de novo* acute myeloid and lymphoblastic leukemia who underwent to a first allogeneic transplant between January 2007 and December 2012. Median follow-up 24 months

Ruggeri A et al.: Leukemia (2015) 29, 1891–1900

The EBMT retrospective study comparing CB vs. haplo

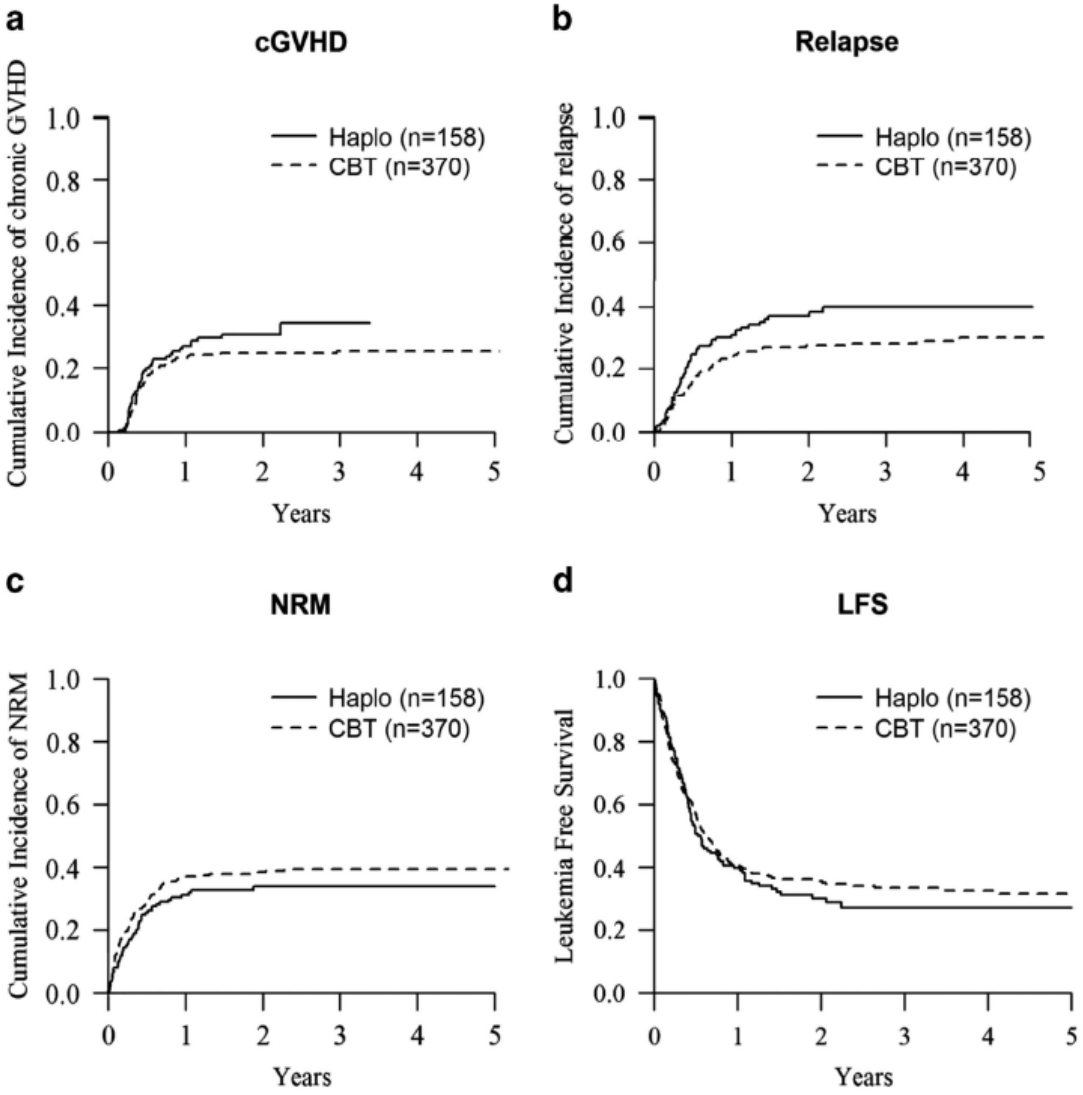
Haplo vs UCBT: AML



Ruggeri A et al.: Leukemia (2015) 29, 1891–1900

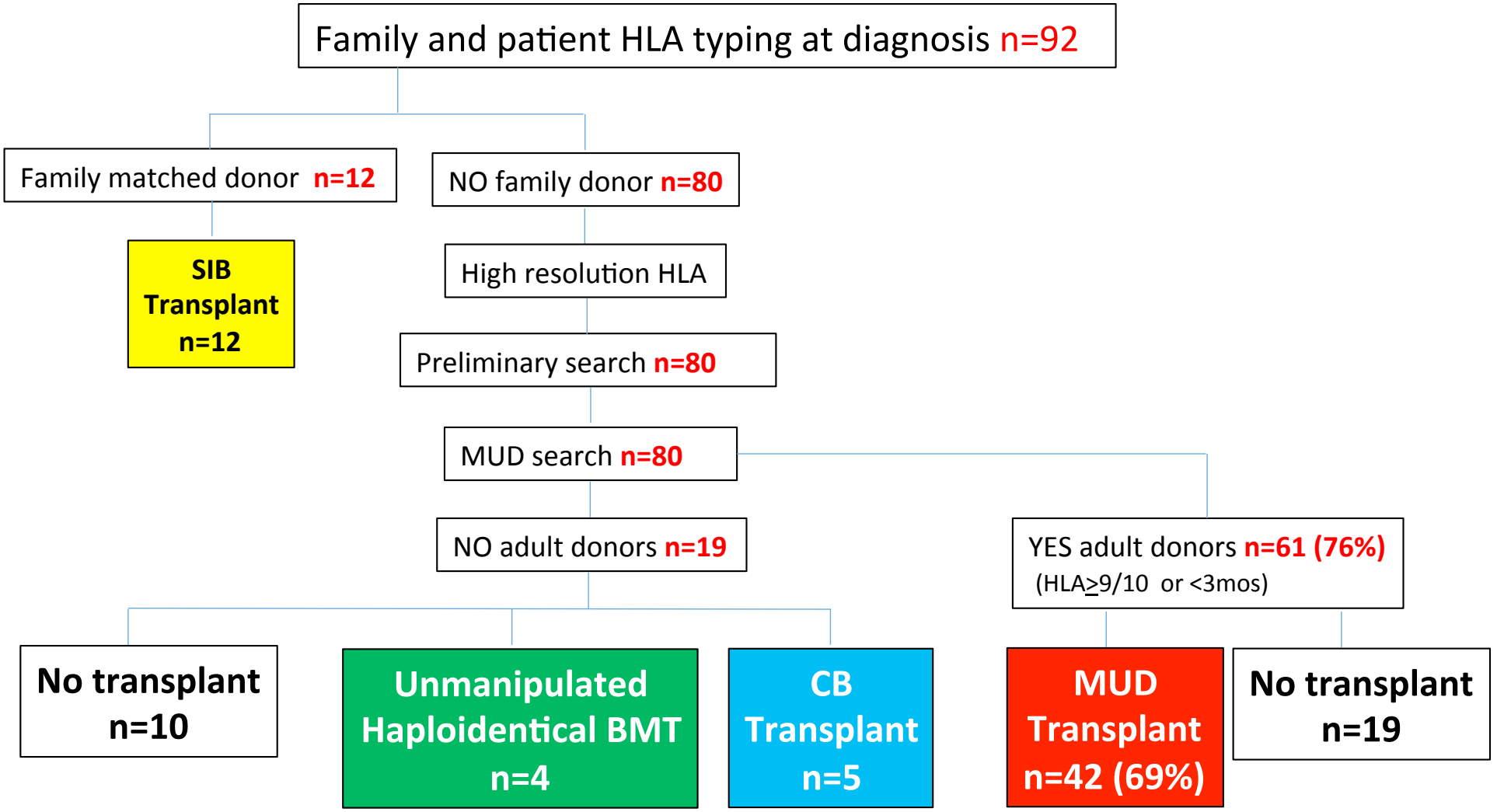
The EBMT retrospective study comparing CB vs. haplo

Haplo vs UCBT: ALL



Ruggeri A et al.: Leukemia (2015) 29, 1891–1900

Donor search in adults with Acute Leukemia during years 2014-2015 (Hematology-Bergamo)



Conclusions

- **An HLA identical SIB or 10/10 UD donor remain the optimal, first choice for an allo-HSCT in acute leukemia patients**
- **Most patients can find such a donor and perform an alloHSCT within 3 months from search activation**
- **CB and Haplo donors are reasonable alternatives when a donor is not available**
- **Prospective studies are needed to change such an algorythm**