Аллогенная ТГСК: Кому? Когда? Как?

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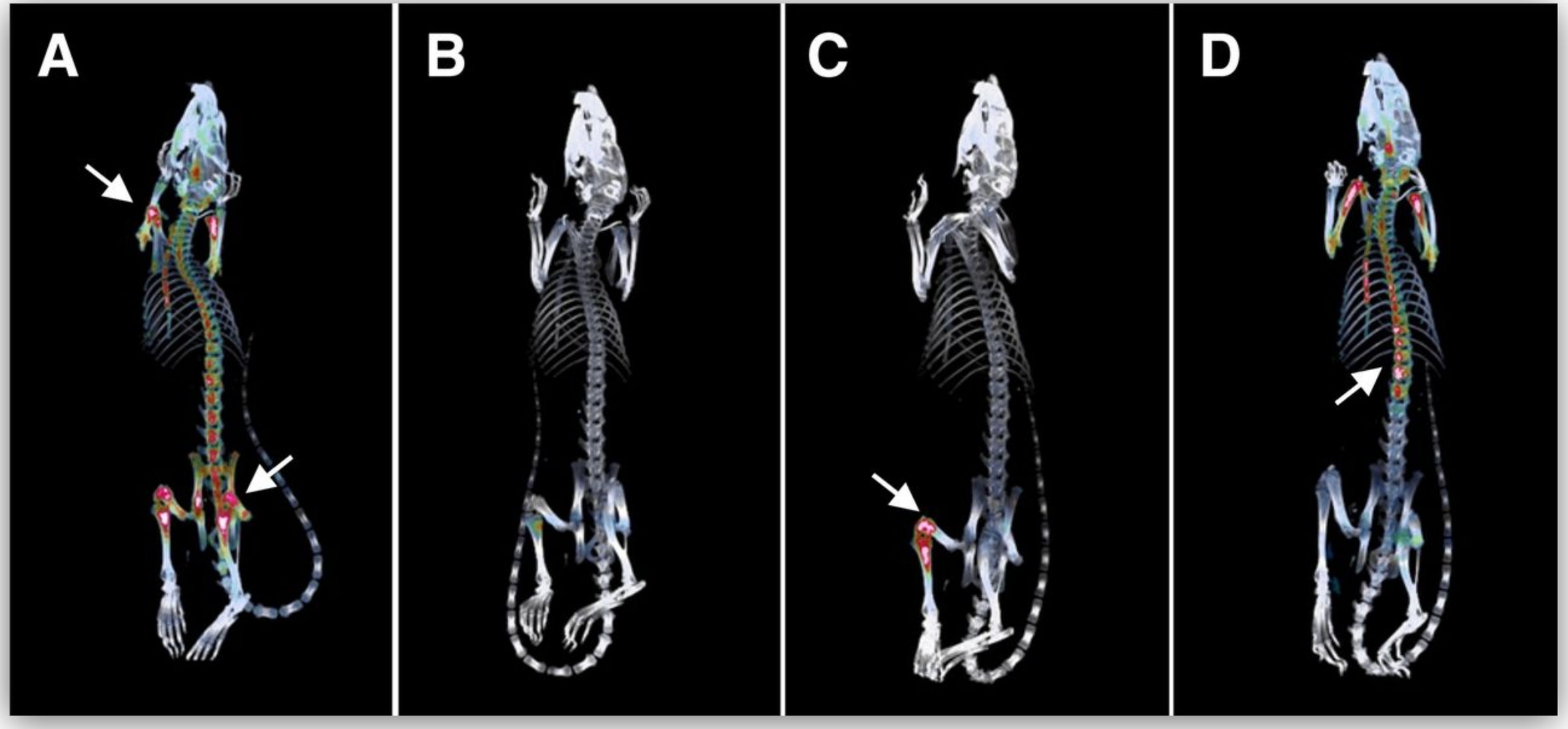
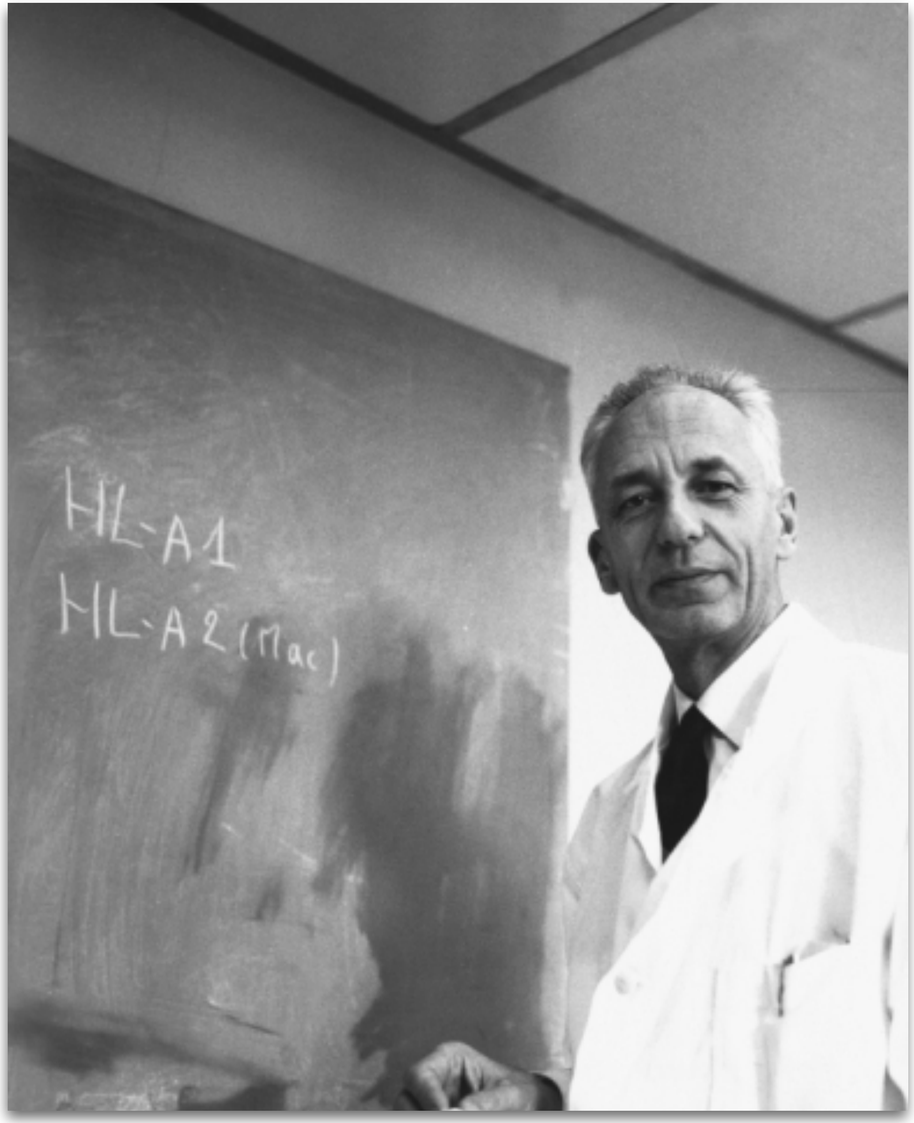
ФГБУ „НМИЦ им. В.А. Алмазова“ Минздрава России
Санкт-Петербург

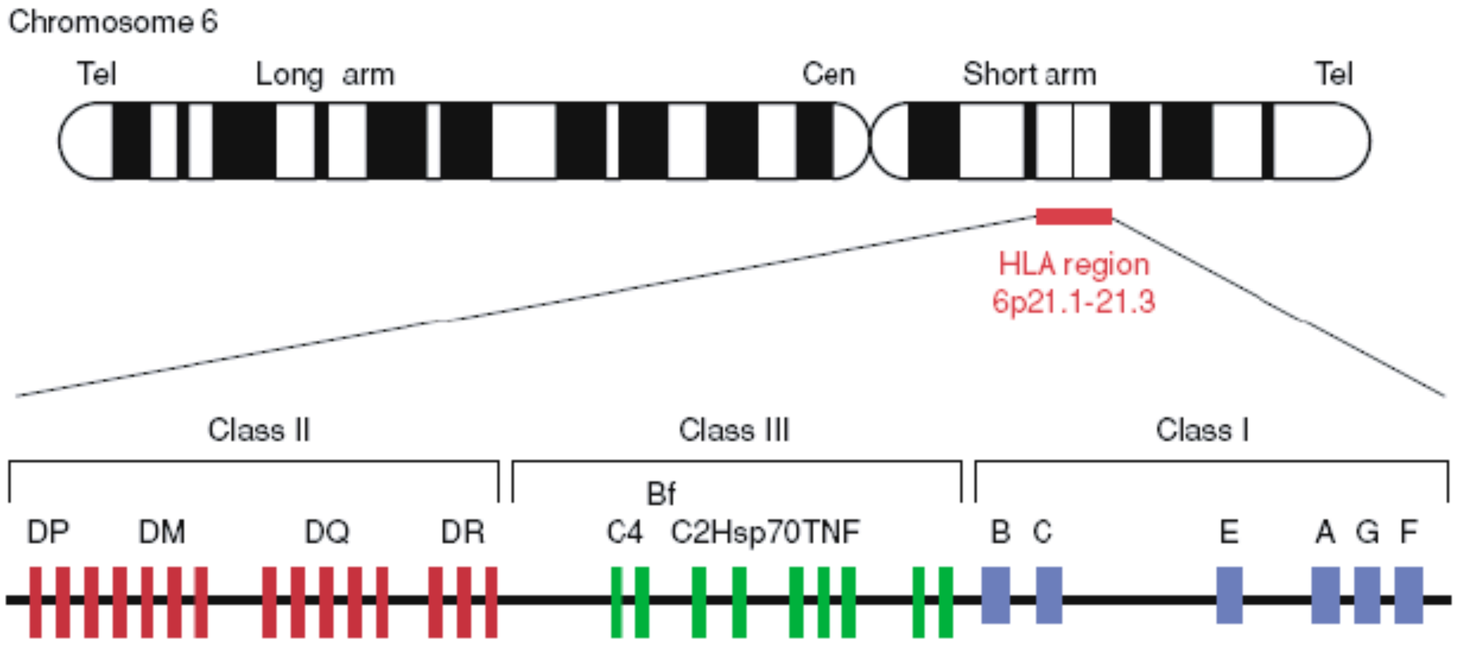


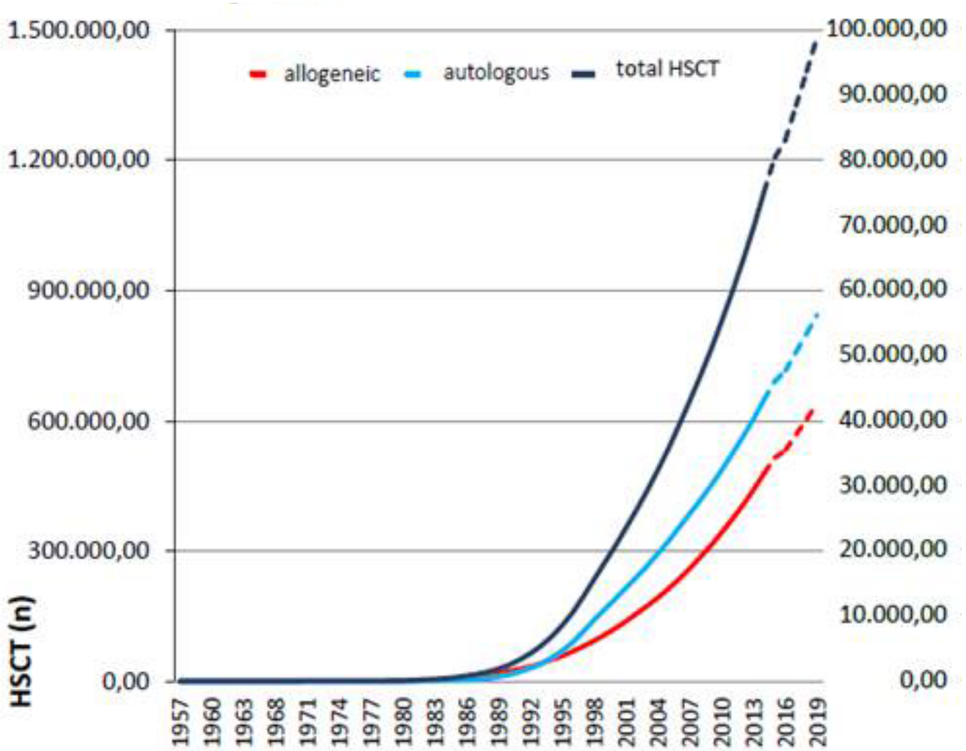
18F-FLT PET/CT imaging maps degree and location of radiation exposure.

JNM The Journal of NUCLEAR MEDICINE *David A. Rendon et al. J Nucl Med 2016;57:266-271*

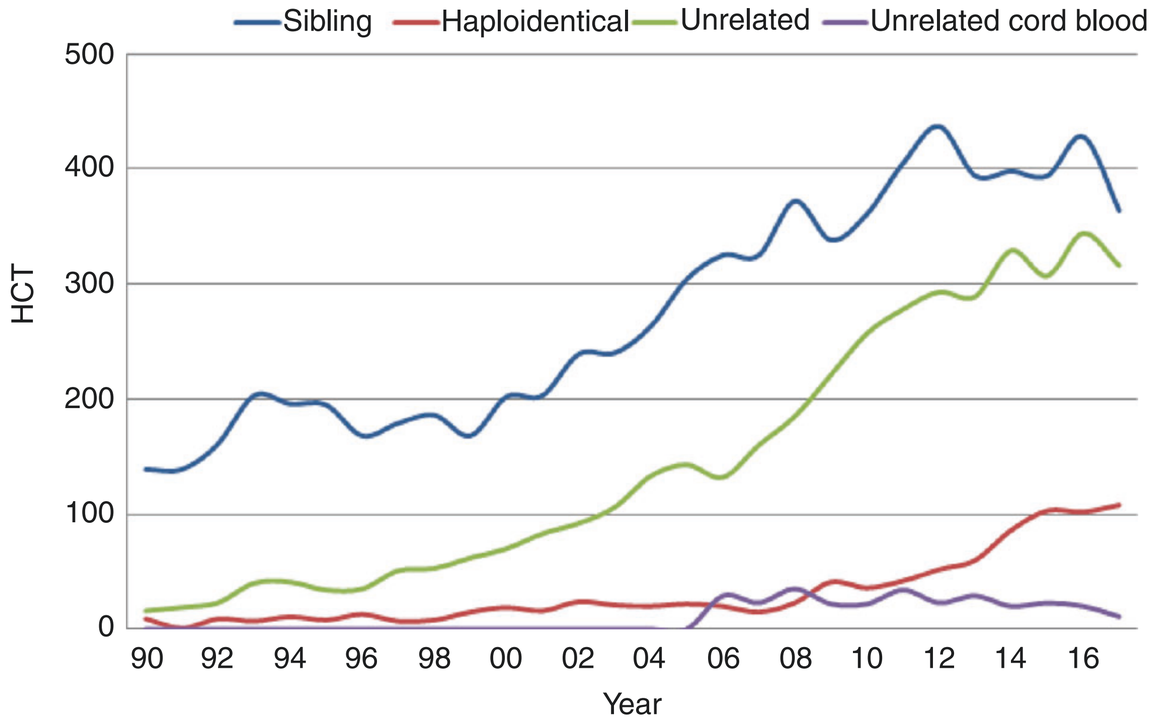


Jean Dausset
(1916 - 2009)





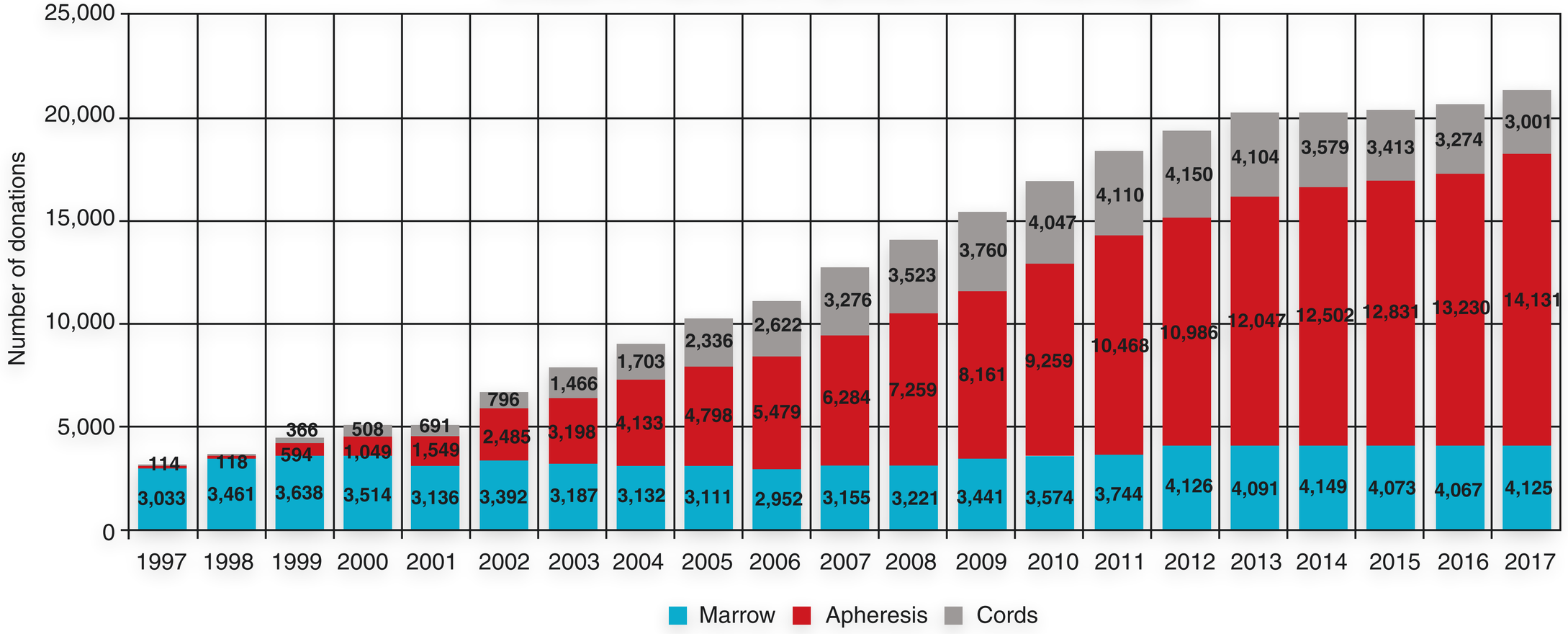
One and Half Million Hematopoietic Stem Cell Transplants (HSCT). Dissemination, Trends and Potential to Improve Activity By Telemedicine from the Worldwide Network for Blood and Marrow Transplantation (WBMT)

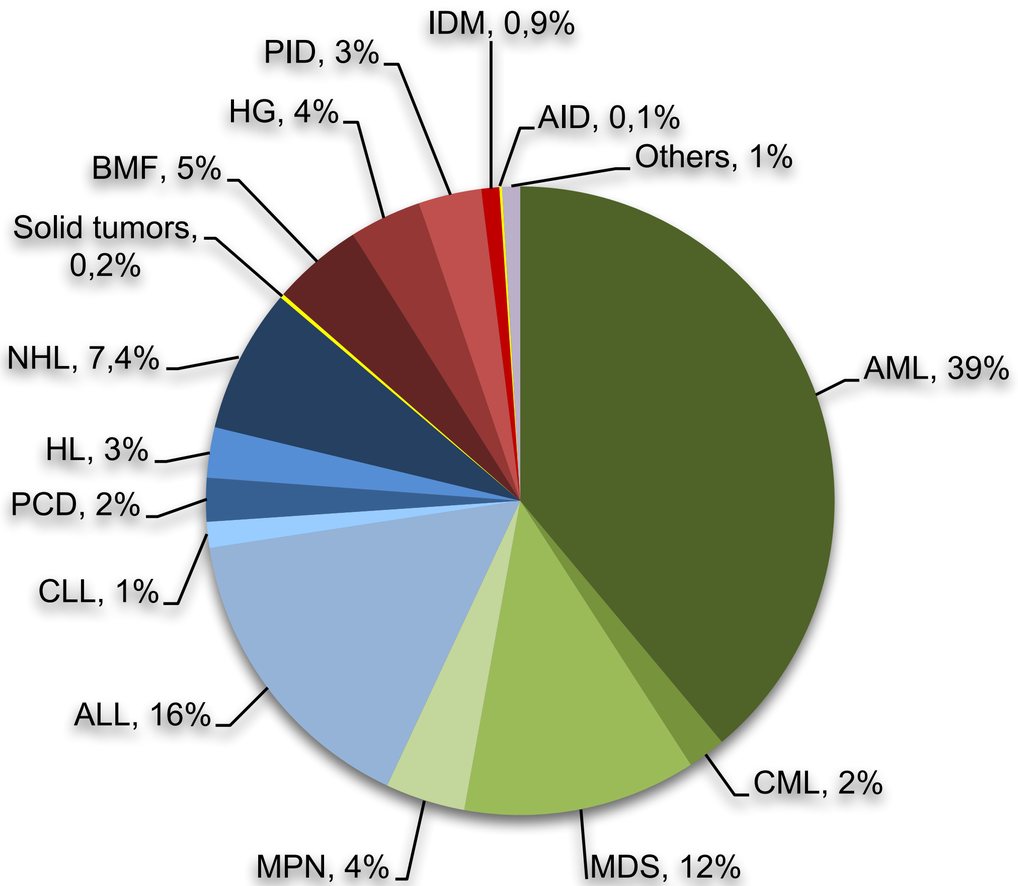


Changes in donor choice and stem cell source for bone marrow failure in Europe 1990–2017

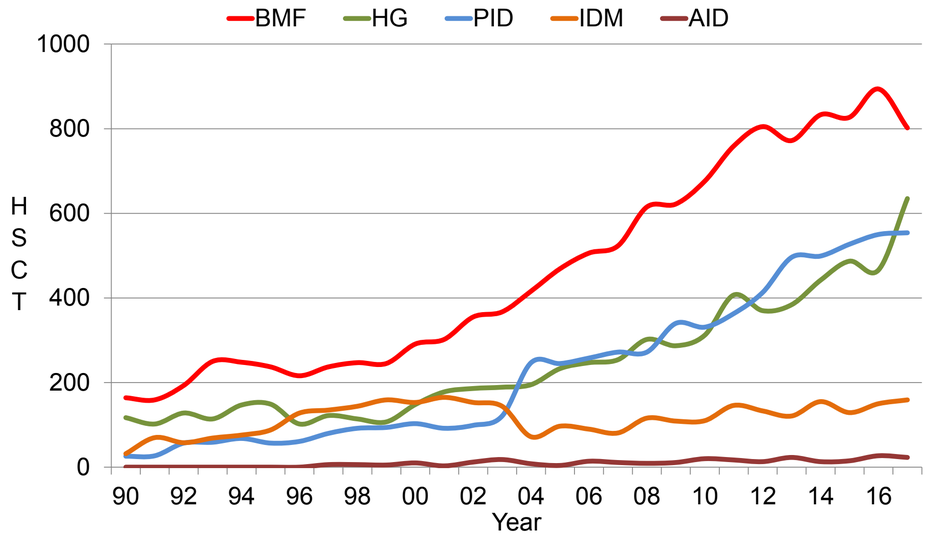
matching donors • serving patients

Unrelated HPC Marrow, HPC Apheresis and HPC Cords shipped





Allogeneic HSCT for non-malignant disorders in Europe 1990-2017



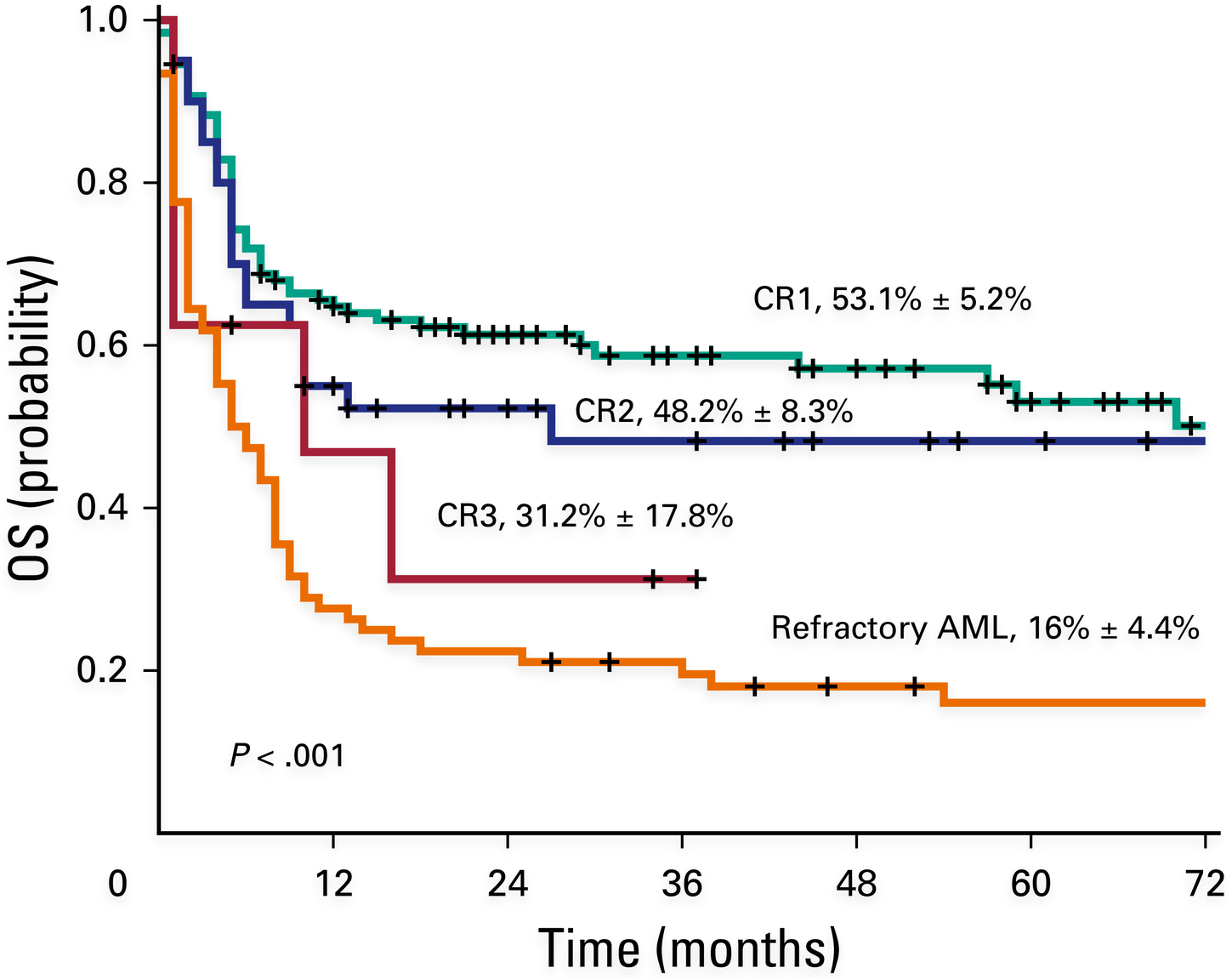
The EBMT activity survey report 2017: a focus on allogeneic HCT for nonmalignant indications and on the use of non-HCT cell therapies
Bone Marrow Transplantation (2019) 54:1575–1585

Risk-adapted post-remission treatment for patients with AML in first CR[a]

AML risk classification[b]	MRD status[c]	Preferred post-remission treatment
Favorable		
t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Negative	Chemotherapy/auto-HSCT
inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*		
Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}	Positive	Allo-HSCT[d], (unless excessive TRM can be predicted)
Biallelic mutated *CEBPA*		
Intermediate		
Mutated *NPM1* and *FLT3*-ITD^{high}	Negative	Allo-HSCT[d] (if acceptable risk of TRM; alternative, chemo/auto-HSCT)
Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse risk genetic lesions)		
t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*	Positive	Allo-HSCT[e]
Cytogenetic abnormalities not classified as favorable or adverse		
Adverse		
t(6;9)(p23;q34.1); *DEK-NUP214*	Negative	Allo-HSCT[e]
t(v;11q23.3); *KMT2A* rearranged		
t(9;22)(q34.1;q11.2); *BCR-ABL1*	Positive	Allo-HSCT[e]
inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM(EVI1)*		
−5 or del(5q); −7; −17/abn(17p)		
Complex karyotype, monosomal karyotype		
Wild-type *NPM1* and *FLT3*-ITD^{high}		
Mutated *RUNX1*		
Mutated *ASXL1*		
Mutated *TP53*		

nonAPL - AML

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel
BLOOD, 26 JANUARY 2017 x VOLUME 129, NUMBER 4



Allogeneic Stem Cell Transplant for Acute Myeloid Leukemia: Evolution of an Effective Strategy in India
Journal of Global Oncology . 773 Volume 3, Issue 6, December 2017

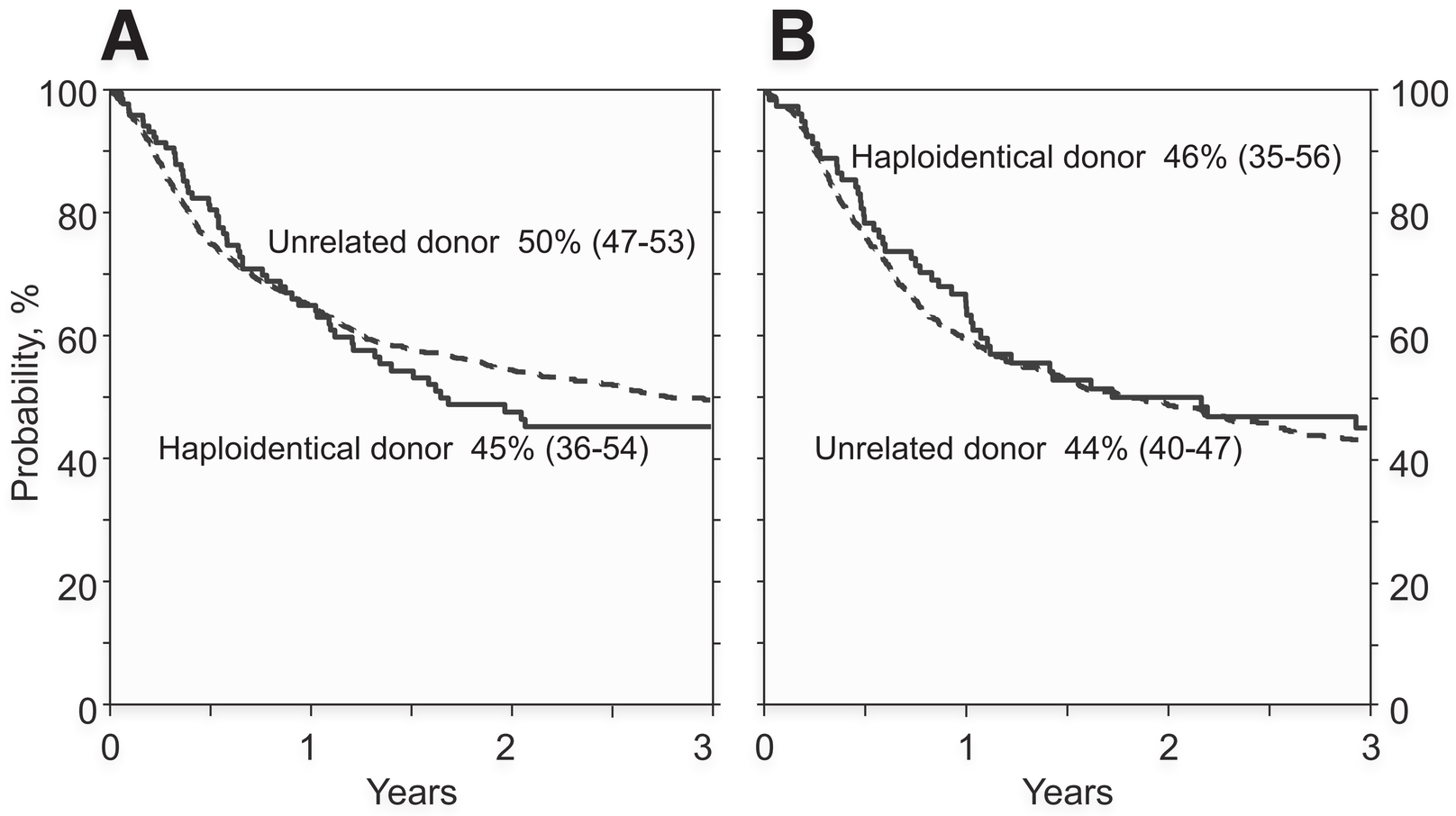


Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.

Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015;126:1033–40.

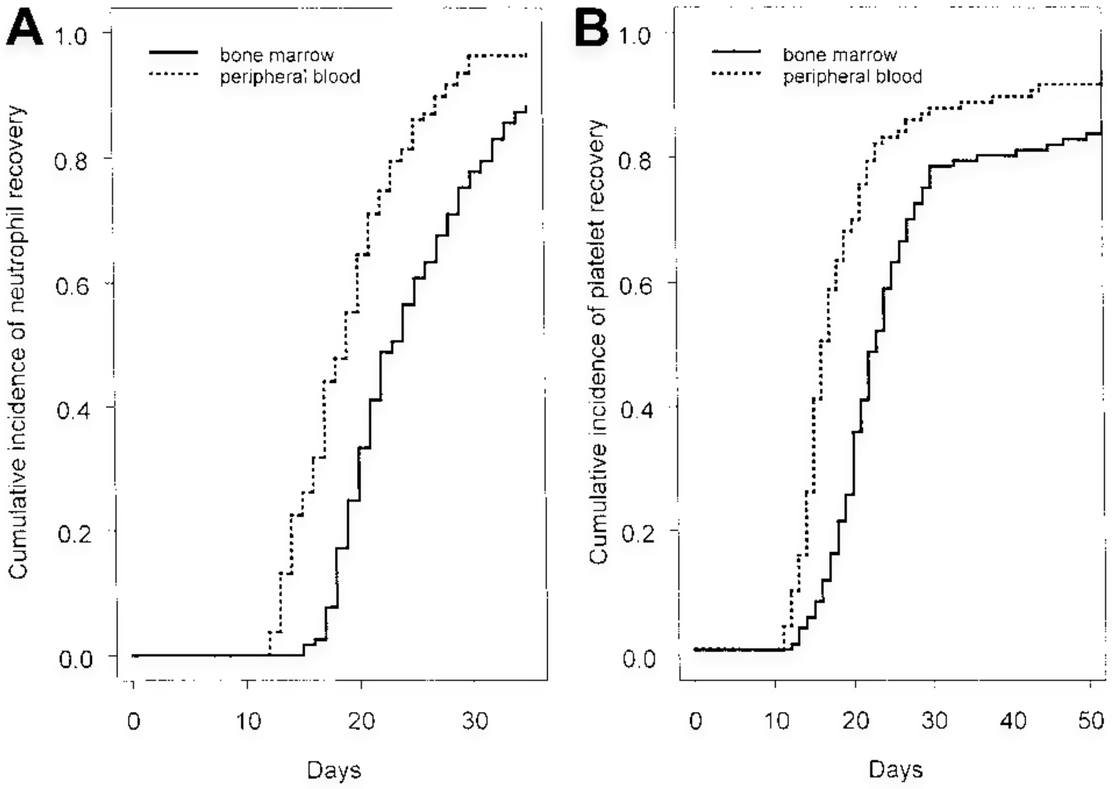


Figure 1. Hematologic recovery by transplantation arm. (A) Neutrophil recovery. (B) Platelet recovery.

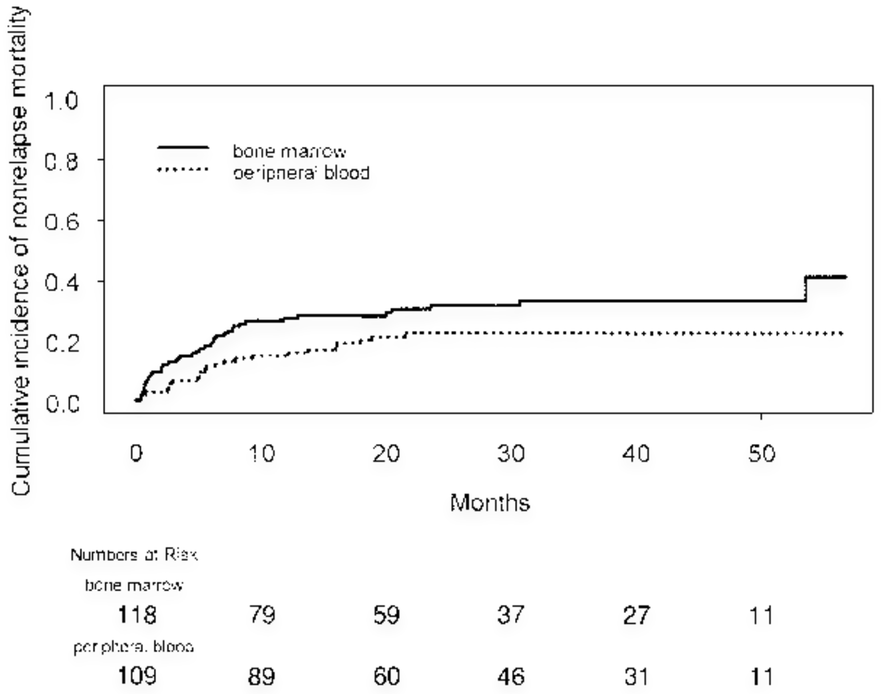


Figure 4. Nonrelapse mortality by treatment arm.

Couban S, Simpson DR, Barnett MJ, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood. 2002;100:1525–31.

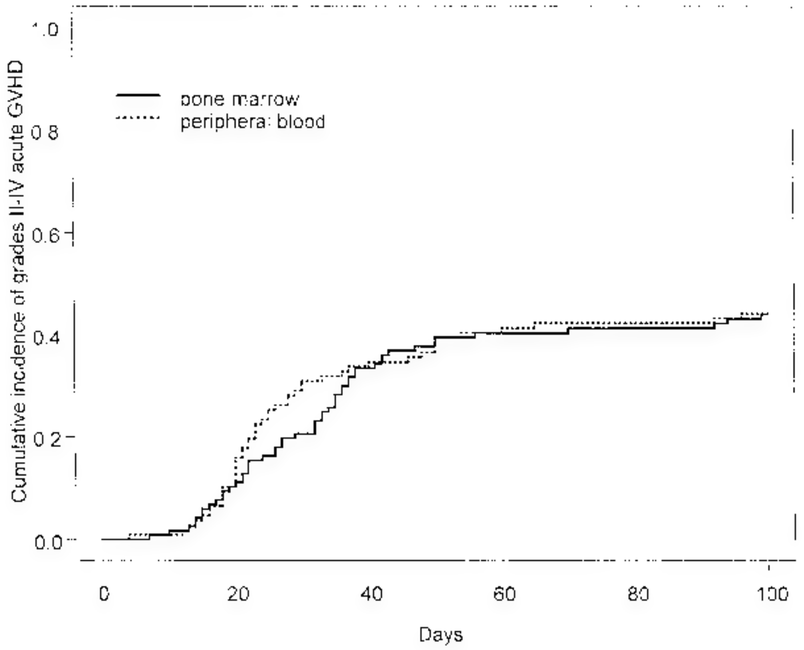


Figure 2. Grades II to IV acute GVHD by transplantation arm.

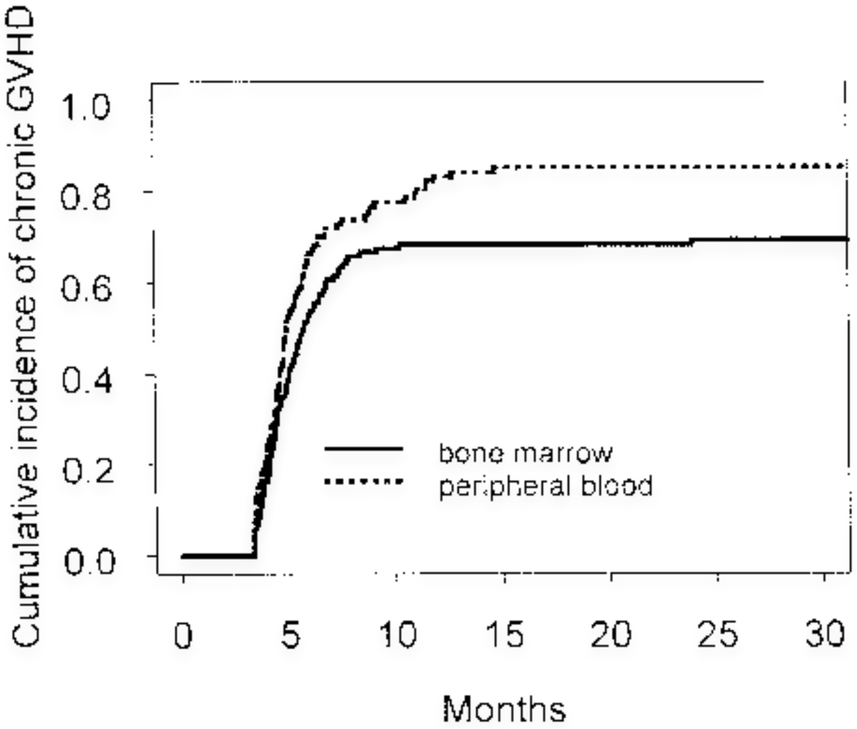


Figure 3. Rates of chronic GVHD by transplantation arm.

Couban S, Simpson DR, Barnett MJ, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood. 2002;100:1525–31.

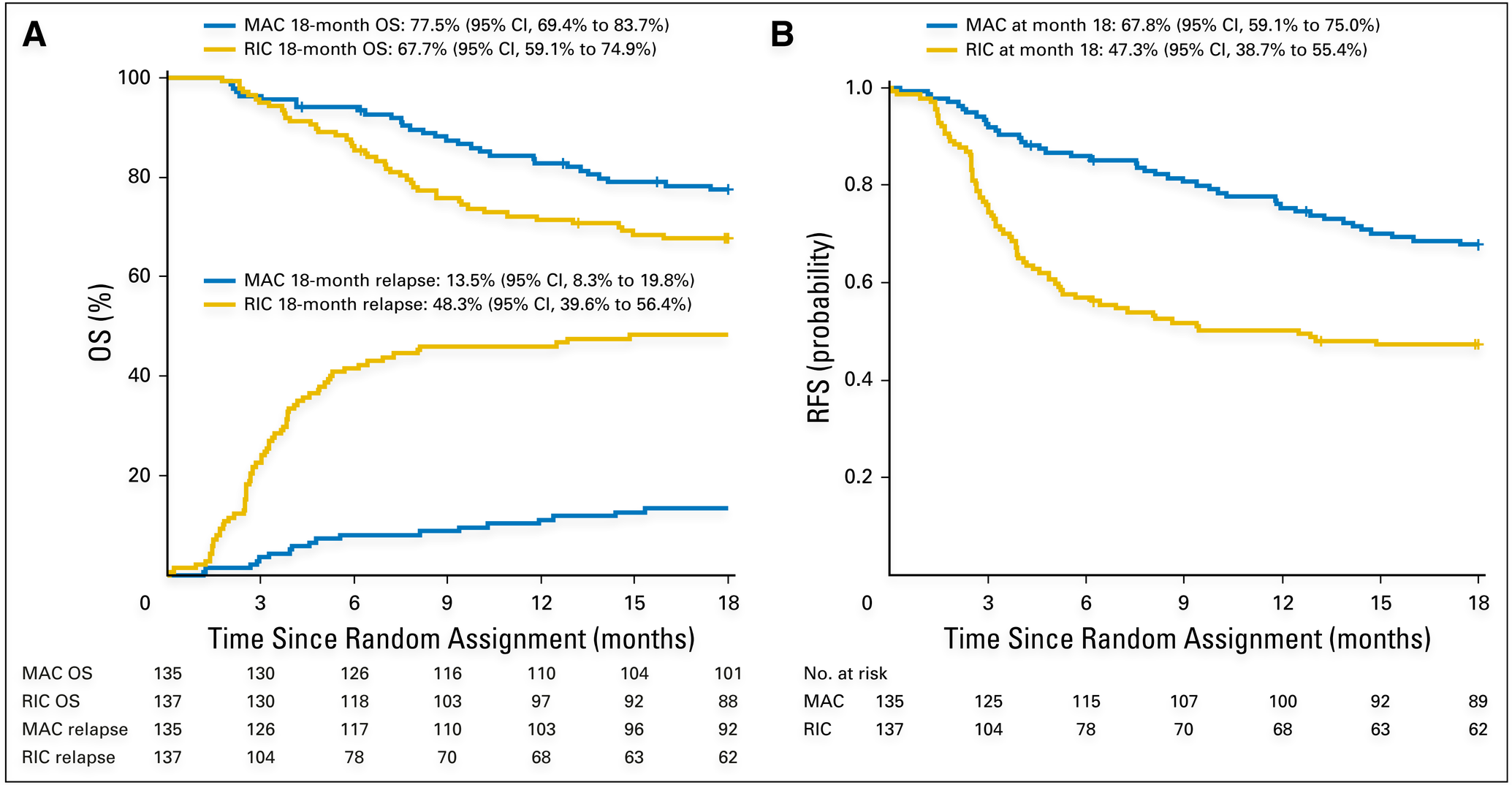


Fig 2. (A) Overall survival (OS) and incidence of relapse by treatment arm and (B) relapse-free survival (RFS). MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol. 2017;35:1154–61.

MDS

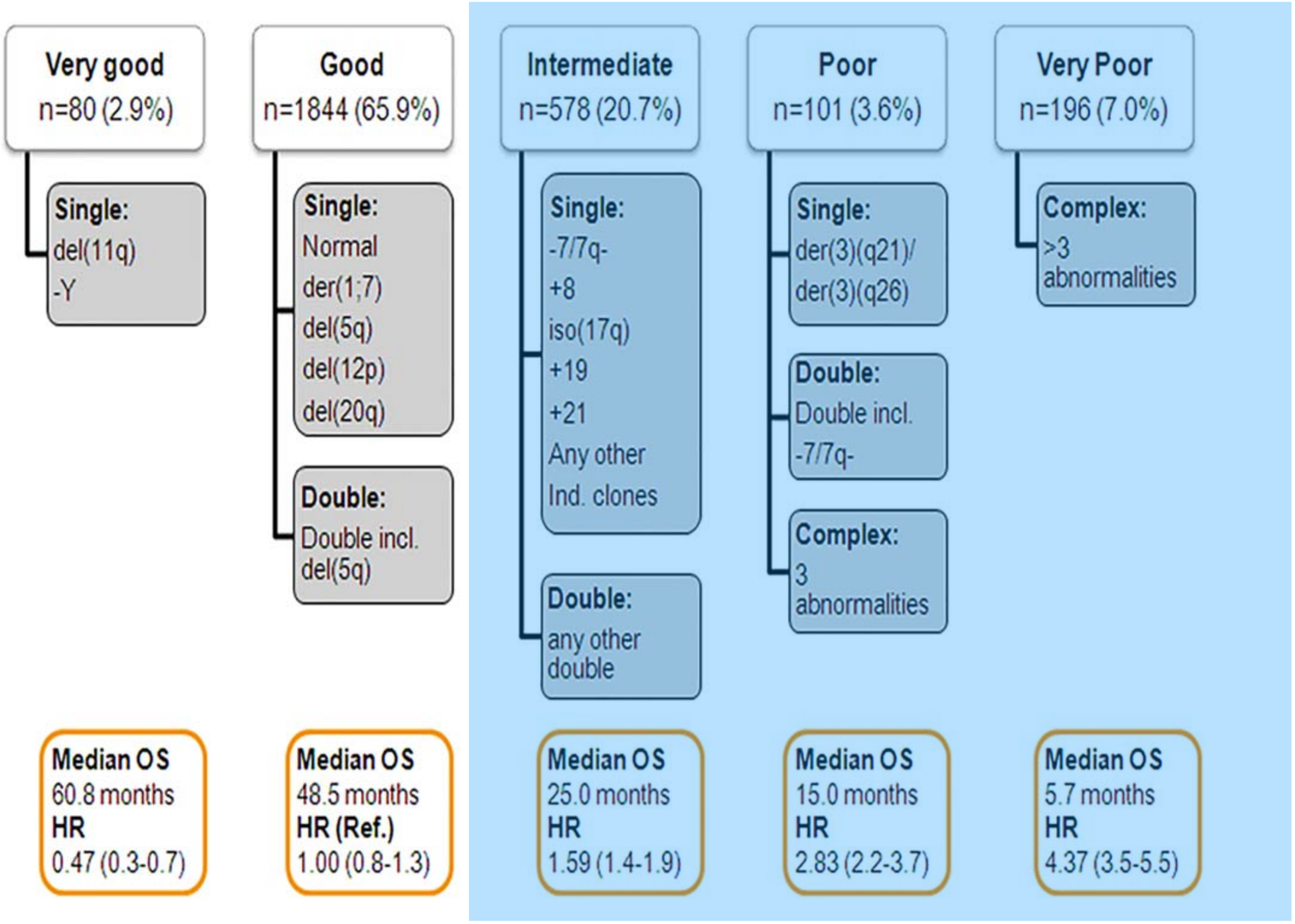
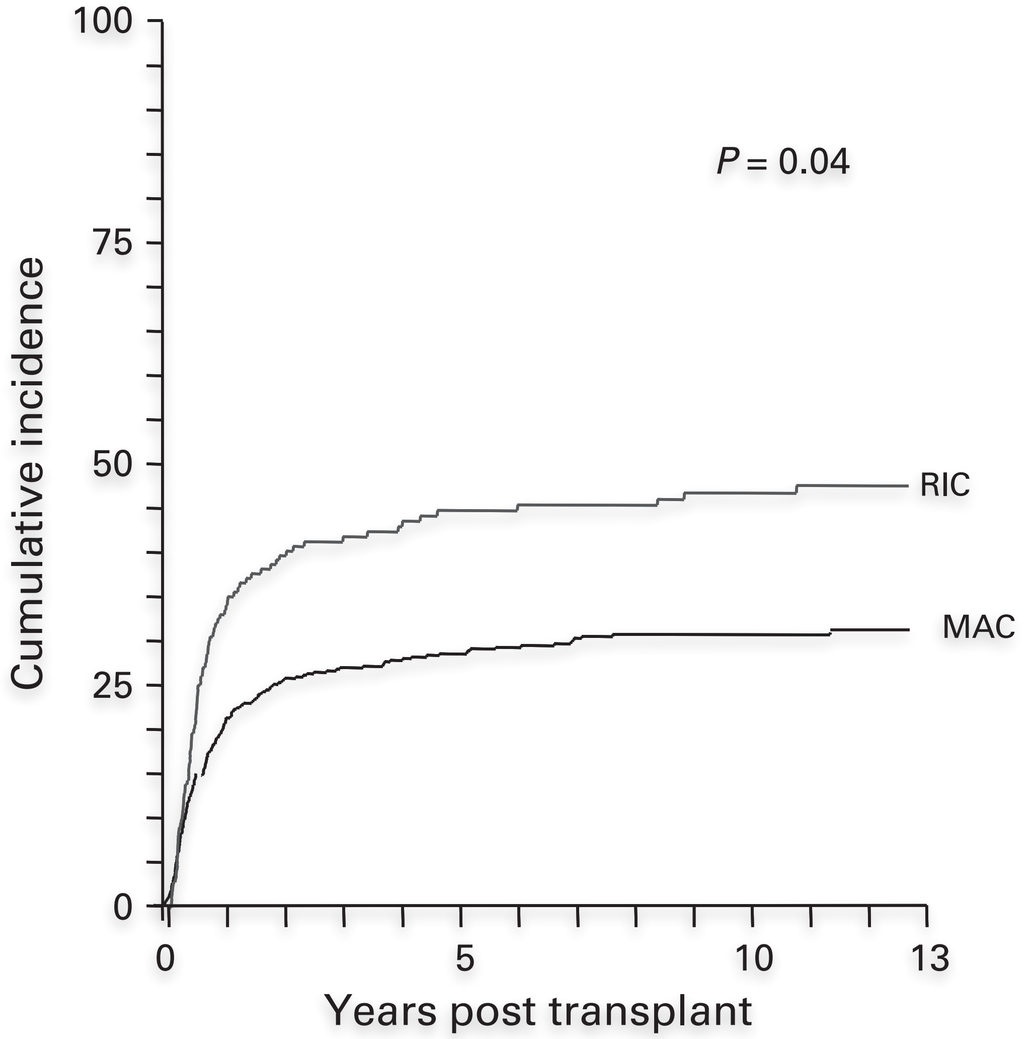
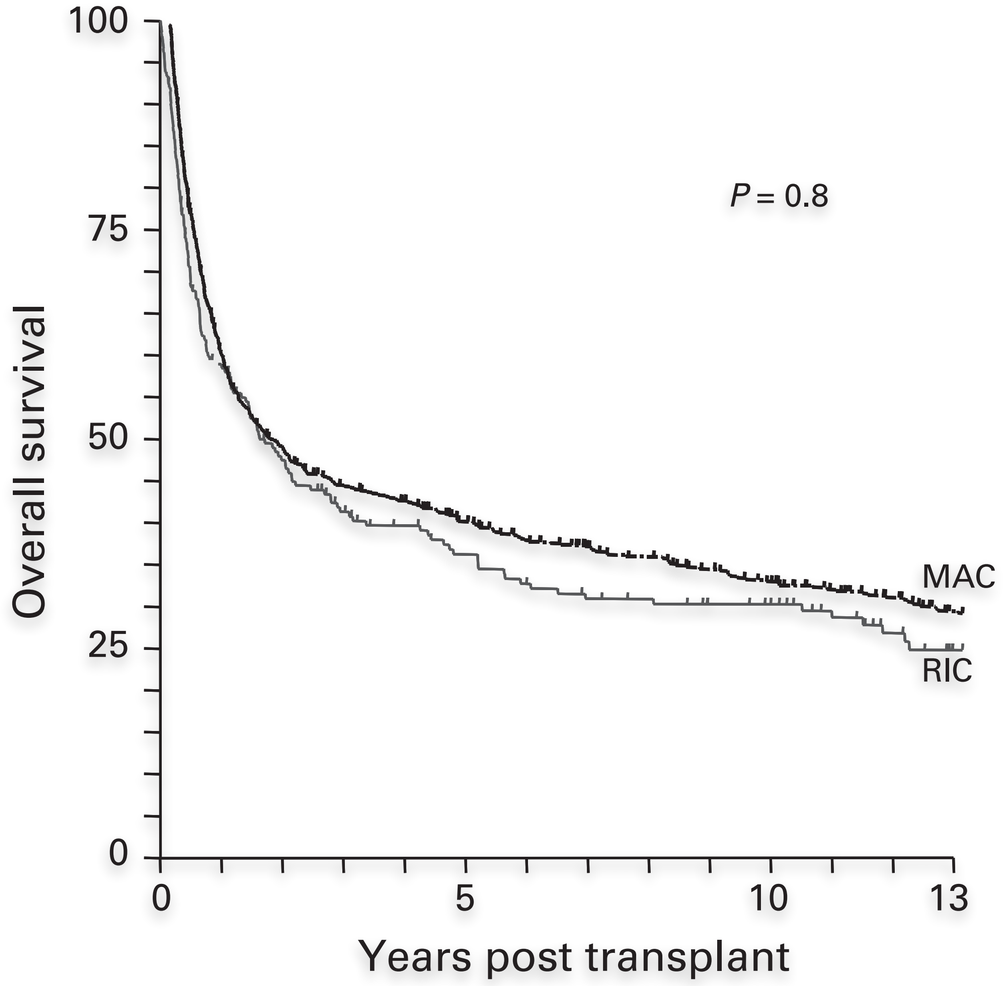


FIGURE 1 Cytogenetic classification of MDS. Adapted from Schanz et al[9] [Color figure can be viewed at wileyonlinelibrary.com]

Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management
Am J Hematol. 2018 Jan;93(1):129-147.





Long-term follow-up of a retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic transplantation from matched related donors in myelodysplastic syndromes. Bone Marrow Transplantation (2017) 52, 1107–1112

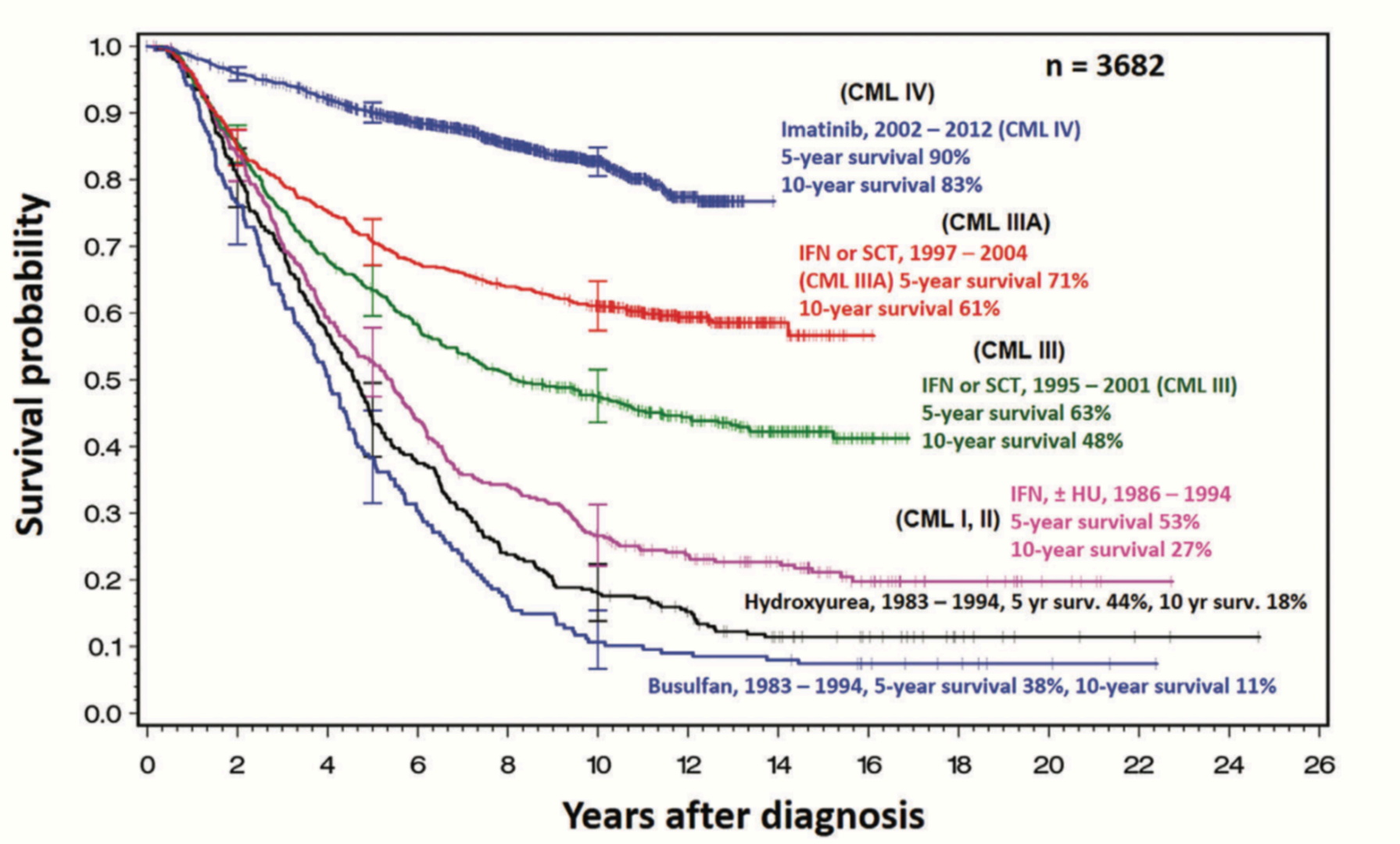


Figure 1. Survival with chronic myeloid leukemia in five consecutive randomized studies of the German CML Study Group since 1983; update 2016.

Innovation In Hematology. Perspectives: CML 2016
Haematologica June 2016 101: 657-659

Фазы хронического миелолейкоза (ELN)

Фаза ХМЛ	Классификация ELN
ХФ	Отсутствие признаков ФА или БК
ФА*	15–29 % бластных клеток в периферической крови и/или костном мозге; сумма бластных клеток и промиелоцитов ≥ 30 % (при этом бластных клеток < 30 %); количество базофилов в крови ≥ 20 %; персистирующая тромбоцитопения с числом тромбоцитов < 100 × 10^9/л, не связанная с терапией; обнаружение некоторых ДХА** в Ph-позитивных клетках на фоне терапии
БК*	Наличие в периферической крови и/или в костном мозге ≥ 30 % бластных клеток; появление экстрамедуллярных инфильтратов бластных клеток

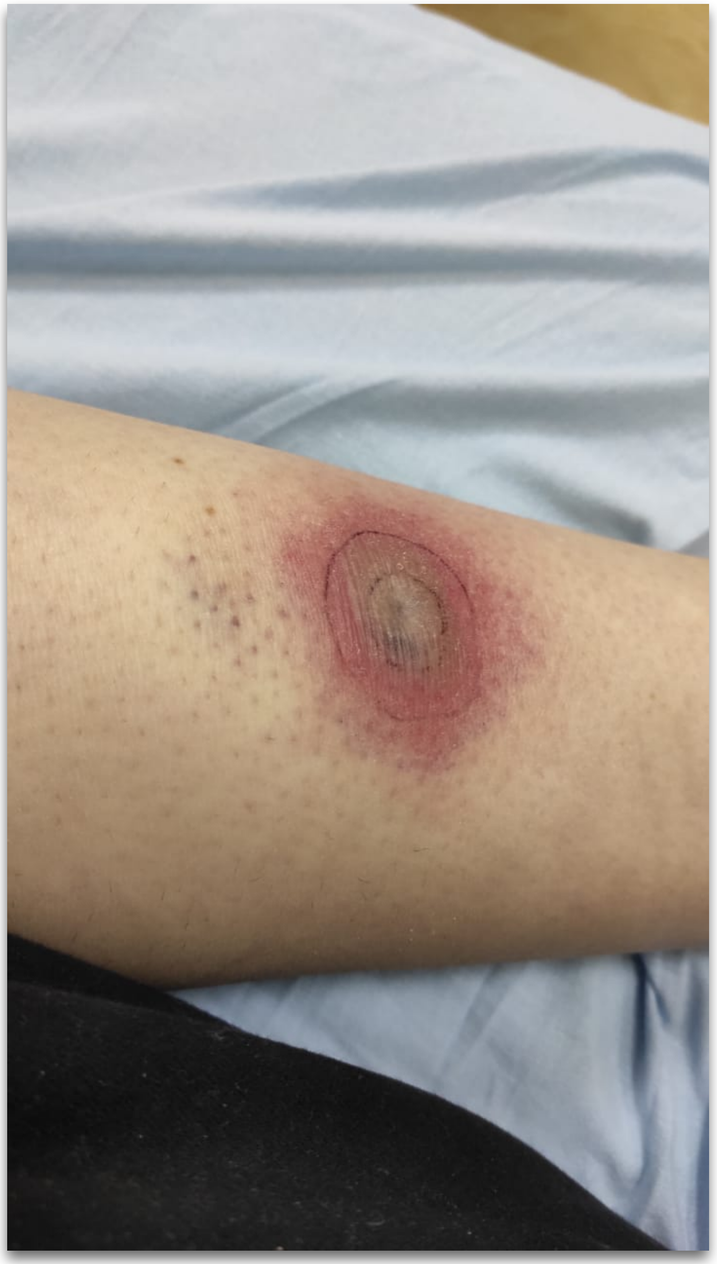
* ФА или БК устанавливают при наличии хотя бы одного критерия.
** Трисомия хромосом 8, 19; удвоение Ph-хромосомы [+der(22) t(9;22)(q34;q11)]; изохромосома 17 [i(17)(q10)]; –7/del7q и перестройки хромосомы 3(q26.2); –Y. Обозначенные выше дополнительные хромосомные аномалии (ДХА) выявляются на фоне терапии [37].

Рекомендации по лечению больных ХМЛ в фазе акселерации и бластном кризе

Фаза ХМЛ	Рекомендации по лечению
ФА	Нилотиниб — 400 мг 2 раза в сутки Дазатиниб — 140 мг 1 раз в сутки Иматиниб — 600 мг/сут АллоТГСК Клинические исследования
БК	**Лимфоидный вариант БК** Клинические исследования Терапия по программе лечения Ph-позитивного острого лимфобластного лейкоза Дазатиниб — 140 мг/сут как этап подготовки к аллоТГСК АллоТГСК (если возможно) с последующим продолжением ИТК (выбор ИТК в зависимости от предшествующего лечения, переносимости, результатов мутационного анализа) **Миелоидный вариант БК** Клинические исследования Терапия по программе лечения острых миелоидных лейкозов Дазатиниб — 140 мг/сут как этап подготовки к аллоТГСК (если возможно) с последующим продолжением ИТК (выбор ИТК в зависимости от предшествующего лечения, переносимости, результатов мутационного анализа)

ALL

Prognostic factor	Indication of allo-HSCT if
Age	>40 years
High WBC count at diagnosis	>30 × 10^9/L in BCP-ALL >100 × 10^9/L in T-ALL
Poor-risk cytogenetics	Ph chromosome t(4;11)(q21;q23) t(8;14)(q24.1;q32) Complex karyotype Low hypodiploidy/near triploidy
ALL subtypes with poor prognosis	Early T-cell precursor ALL (Ph-like ALL) (limited data, pending trials)
High-risk genetics	IKZF1 deletion in B precursor ALL (NOTCH1/FBXW7; N/K-RAS; PTEN genetics in T-ALL (Trinquand et al. 2013)) (limited data, pending trials)
Failure to attain CR	Within 4 weeks of therapy PPR
Minimal residual disease	>1 × 10^{-4} after two courses of therapy Reappearance of MRD marker (no MRD marker at initial diagnosis)



Подсчет риска по системе стратификации DIPSS+.

Признак	Количество баллов по системе стратификации риска
Возраст более 65 лет	1
Уровень гемоглобина менее 100г/л	2
Уровень лейкоцитов более $25x10^9$/л	1
Бласты в периферической крови равно или более 1%	1
Наличие симптомов опухолевой интоксикации	1
Тромбоциты $<100x10^9$/л	1
Необходимость переливания эрироцитов	1
Неблагоприятный кариотип: +8,-7/7q-, (17q),inv(3), -5/5q-, 12p-, перестройки 11q23	1
• 0 балов - низкий риск; • 1 балл - промежуточный 1; • 3 - 3 балла – промежуточный 2; • 4 балла или более – высокий риск.	

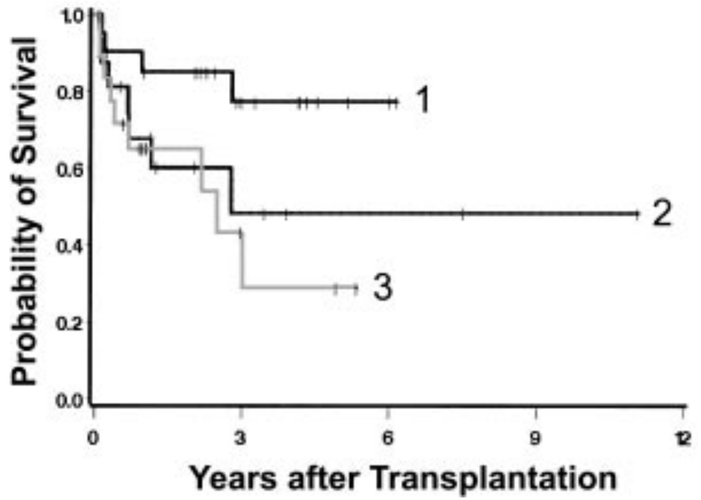
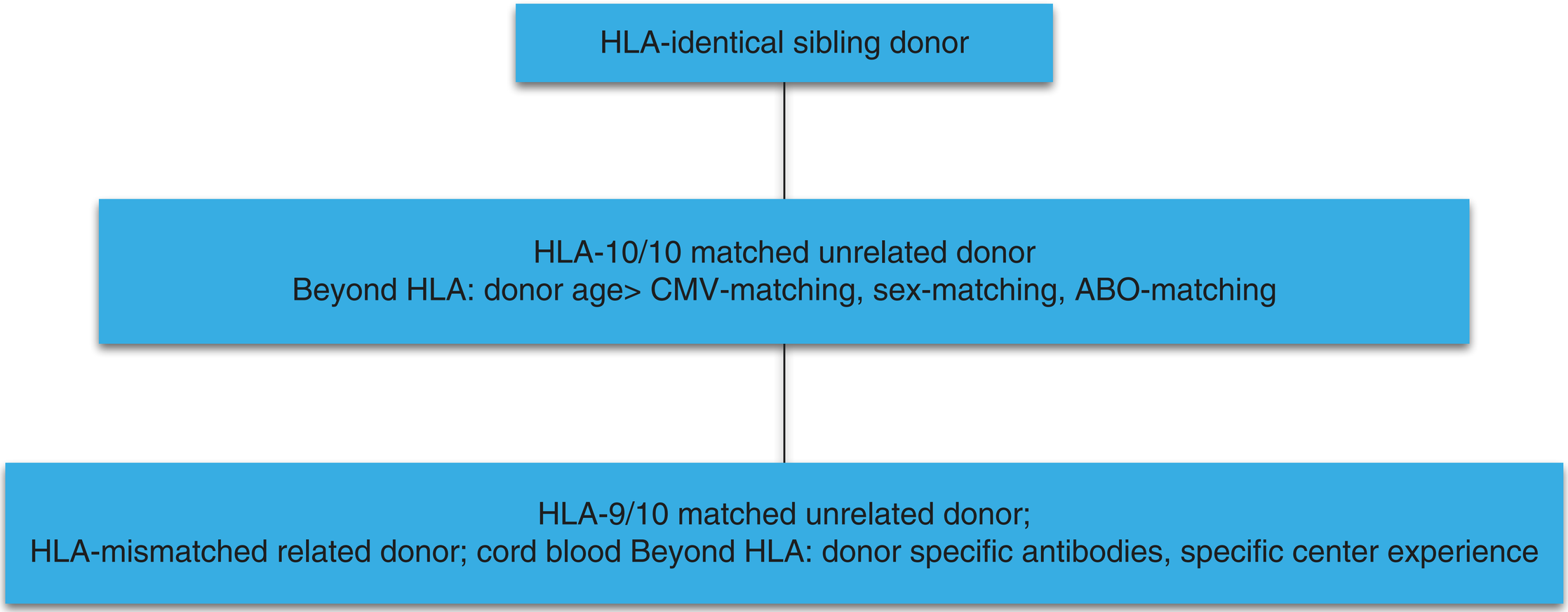


Figure 3. Survival by degree of marrow fibrosis. Group 3 includes patients who had evidence of osteosclerosis.

Deeg HJ, Gooley TA, Flowers ME, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. Blood. 2003;102:3912–8.

Algorithm for donor selection for adult patients with hematological malignancies

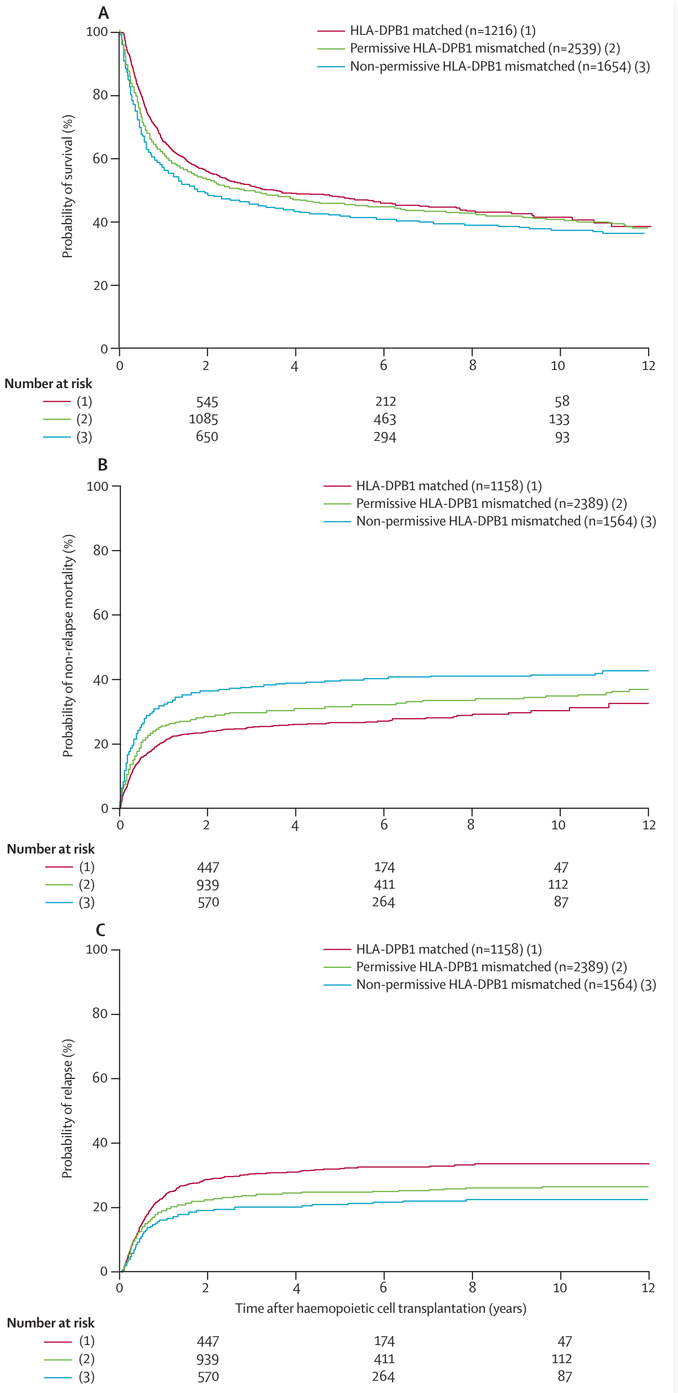


Impact of specific HLA locus or allele mismatches as reported in recent (2013-2016) multicenter studies of unrelated HSCT.

Ref.	N. of patients	Main conclusions
5	2,646	Single HLA-A,B,C,DRB1 MM (either antigen or allele) associated with increased mortality, additional risk with <9/10 matched (including DQB1) donors
13	8,539	Non-permissive DPB1 MM associated with increased mortality in 9-10/10 matched HSCT
30	3,853	In 7/8 matched HSCT : >2 MM at DRB3/4/5, DQB1 or DPB1 loci associated with lower survival
29	7,349	C*03:03/03:04 MM better tolerated, lower impact of C-locus MM explained by the high frequency of C*03:03/03:04 MM in the 7/8 matched group
12	8,003	Single HLA-A,B,C,DRB1 MM associated with increased mortality, DQB1 MM associated with increased acute GVHD, non-permissive DPB1 MM associated with increased mortality in 10/10 or 8/8 matched cases
15	7,898	Single HLA-A,B,C and double HLA-DRB1-DQB1 MM associated with increased mortality, HLA-A,B,C,DPB1 MM associated with higher risk of acute GVHD, reduced relapse only with C,DPB1 MM
30	2,588	Reduced intensity conditioning HSCT: increased mortality in 7/8 matched HSCT, no impact of C*03:03/03:04 or permissive DPB1 MM
16	803	Single HLA-A,B,C MM (9/10) associated with higher mortality, HLA-DRB1/DQB1 MM more permissive (high ratio of DRB1*11:01/11:04 and DQB1*03:01/03:02 MM)
50	2,029	In 11/12 matched HSCT: single nucleotide polymorphism in the regulatory region of DPB1 locus associated with acute GVHD
44	6,967	Patient and/or donor B*51:01 and patient C*14:02 associated with increased acute GVHD and mortality
16	11,039	Donor age (>32 years) and 7/8, 6/8 mismatched donors associated with lower overall survival

MM: mismatch.

How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica. 2016 Jun; 101(6): 680–687.

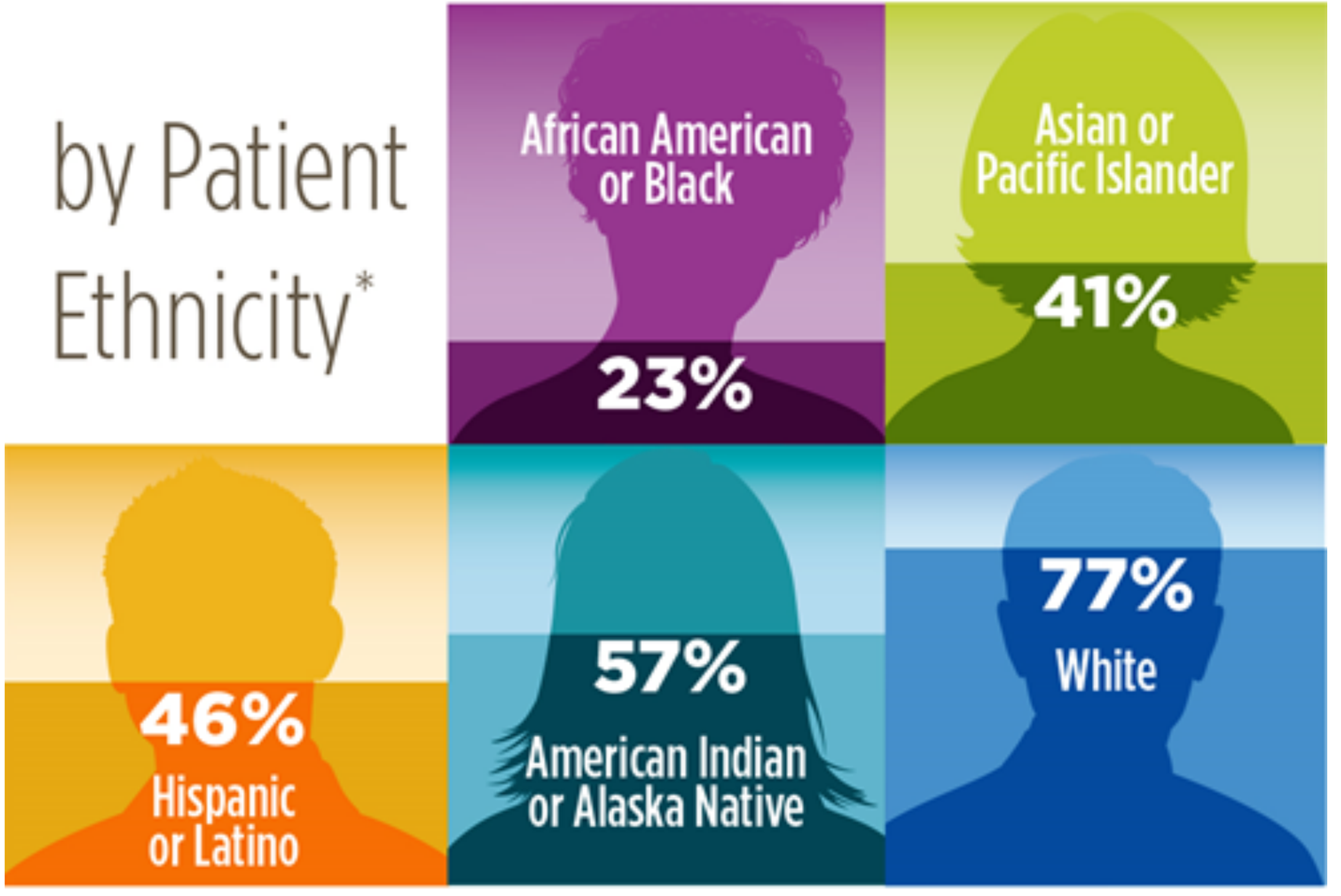


Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study

	HLA 10/10 match					HLA 9/10 match				
	Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch		Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch	
		HR or OR	p value	HR or OR	p value		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	0·96 (0·87–1·06)	0·40	1·15 (1·05–1·25)	0·002	1 (ref)	0·98 (0·85–1·13)	0·80	1·10 (1·00–1·22)	0·06
Non-relapse mortality	1 (ref)	0·86 (0·75–0·98)	0·03	1·28 (1·14–1·42)	<0·0001	1 (ref)	0·98 (0·82–1·17)	0·81	1·19 (1·05–1·36)	0·007
Relapse*	1 (ref)	1·34 (1·17–1·54)	<0·0001	0·89 (0·77–1·02)	0·10	1 (ref)	1·05 (0·84–1·31)	0·68	0·93 (0·78–1·11)	0·44
Grade 3–4 aGvHD	1 (ref)	0·84 (0·69–1·03)	0·09	1·31 (1·11–1·54)	0·001	1 (ref)	0·93 (0·71–1·21)	0·58	1·37 (1·13–1·66)	0·002

Likelihood of finding a Matched Adult Donor on the Be The Match Registry®

by Patient Ethnicity*



*Patients are most likely to match an adult donor of their own ethnic background.

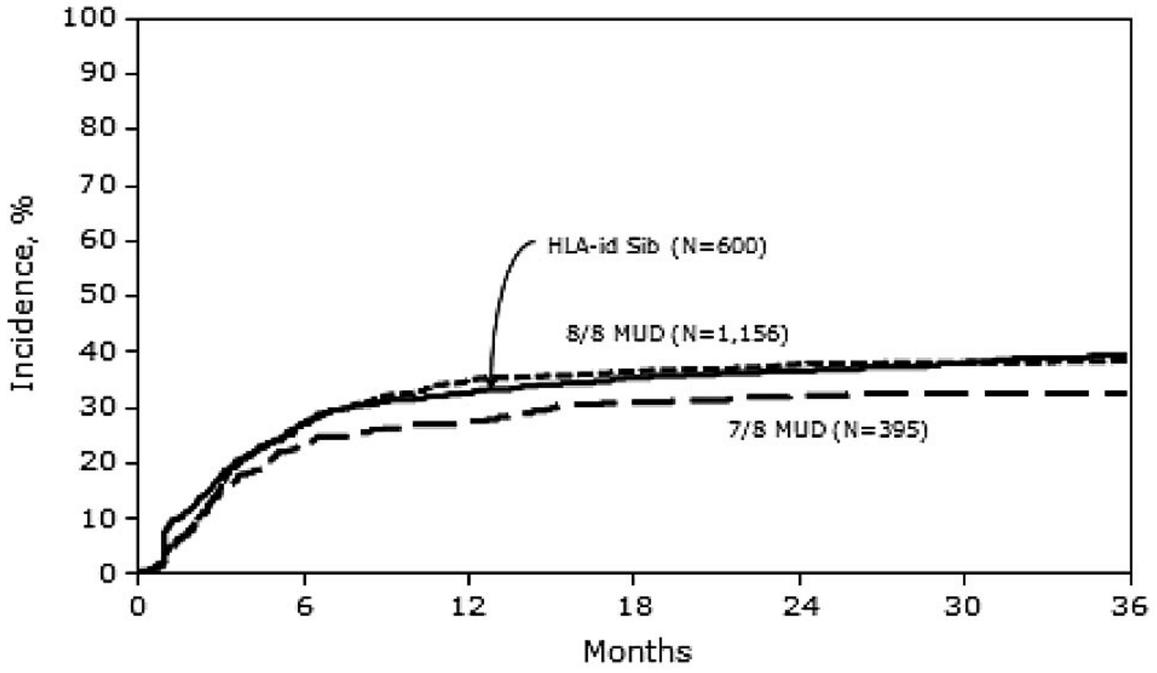


Figure 2. Adjusted probability of relapse in adult AML patients by donor type.

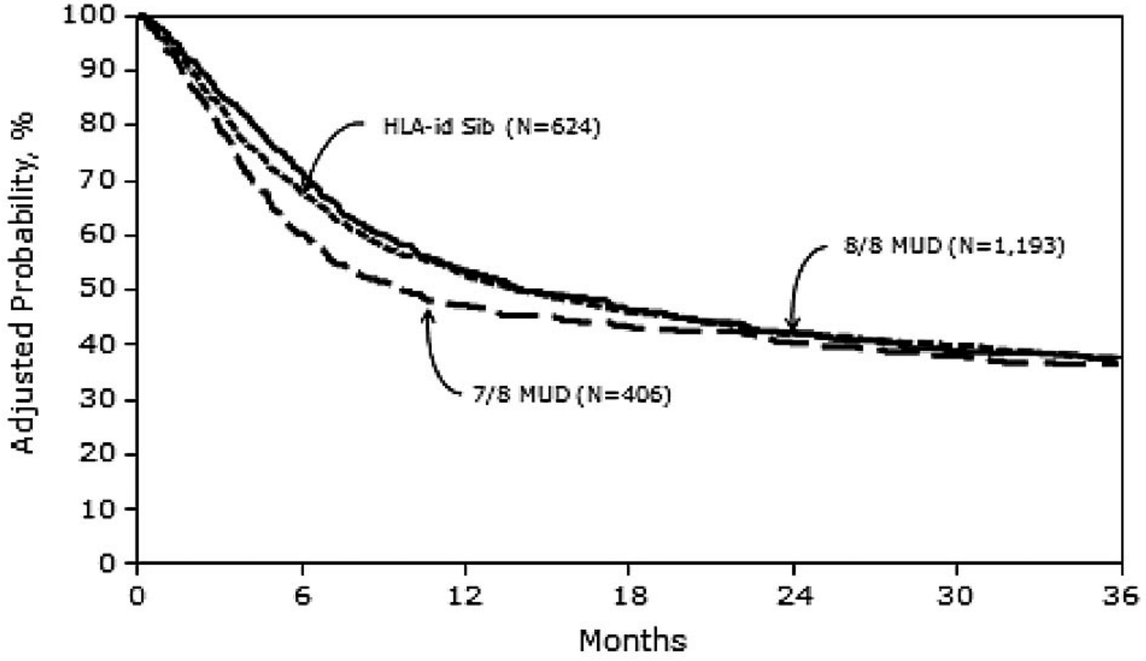


Figure 4. Adjusted probability of overall survival in 2223 adult AML patients by donor type.

Saber W, Opie S, Rizzo JD, et al. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. Blood. 2012;119:3908–16.

blood advances™

Related haploidentical donors are a better choice than matched unrelated donors: Point

Ephraim Joseph Fuchs

Division of Hematologic Malignancies, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Table 2. Retrospective comparisons of outcomes of haplo SCT plus posttransplantation cyclophosphamide vs MUD SCT

Reference	RIC or MAC	N		aGVHD II-IV (%)		cGVHD (%)		NRM (%)		Relapse (%)		Overall survival (%)		Event-free survival (%)	
AML ± MDS		Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD
19	MAC	104	1245	**16**	**33‡**	**30**	**53‡**	14	20	44	39	45	50	42	41
	RIC	88	737	**19**	**28***	**34**	**52†**	**9**	**23‡**	**58**	**42†**	46	44	33	35
20	RIC	32	108	–	–	–	–	24	25	33	23	–	–	43	42
21	Mix	52	88	40	36	10	9	27	27	29	43	42	37	44	30
22	Mix	62	21§	40	19	6	5	22	16	31	26	53	58	–	–
Hodgkin lymphoma															
23	RIC	28	38	43	50	35	63	9	8	40	63	58	58	**51**	**29***
Non-Hodgkin lymphoma															
24	RIC	185	491	52	60	**15**	**62‡**	17	22	36	28	60	62	47	49
25	RIC	26	28	–	–	15	29	15	27	19	7	77	71	65	68

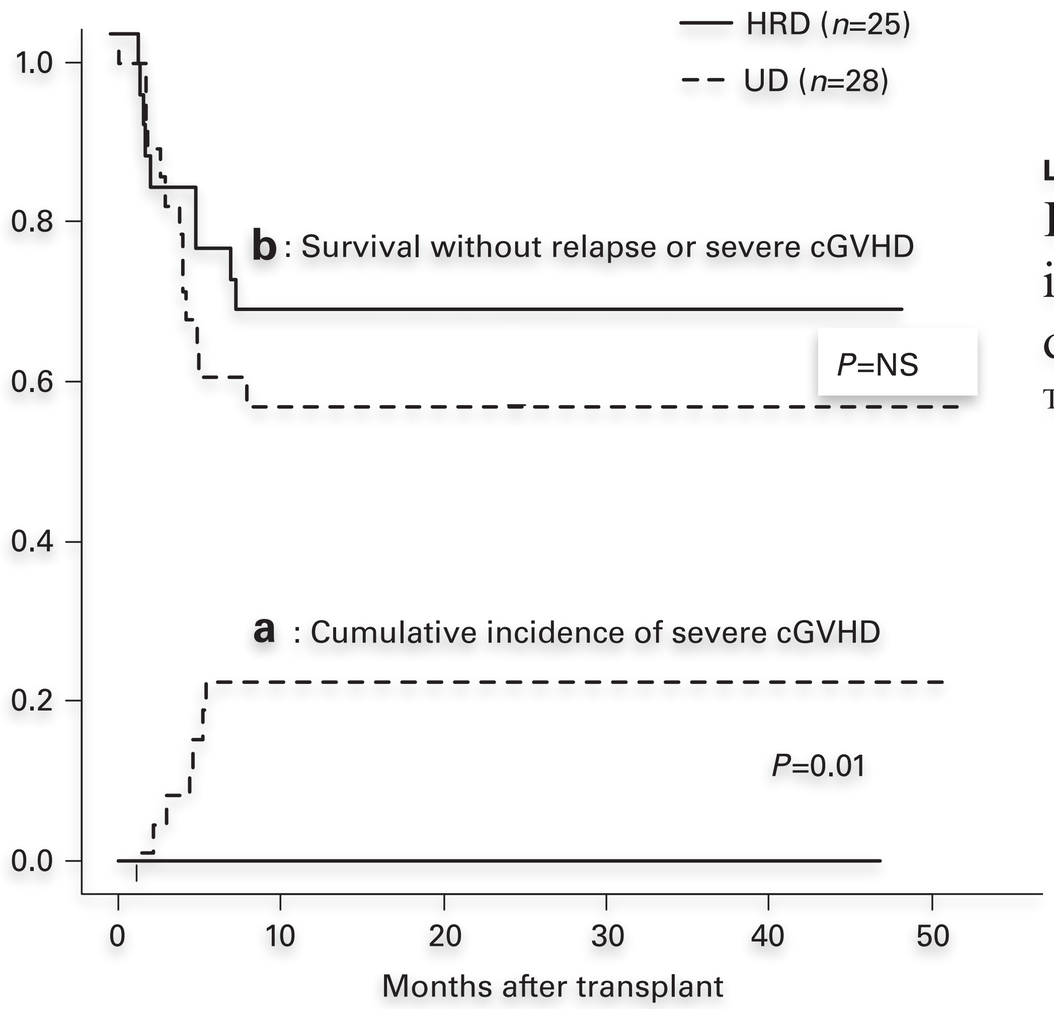


Figure 1. Cumulative incidence of severe chronic GVHD (**a**) ar survival without relapse or severe chronic GVHD (**b**) for HRD and U groups.

Bone Marrow Transplantation (2015) **50,** 865–867

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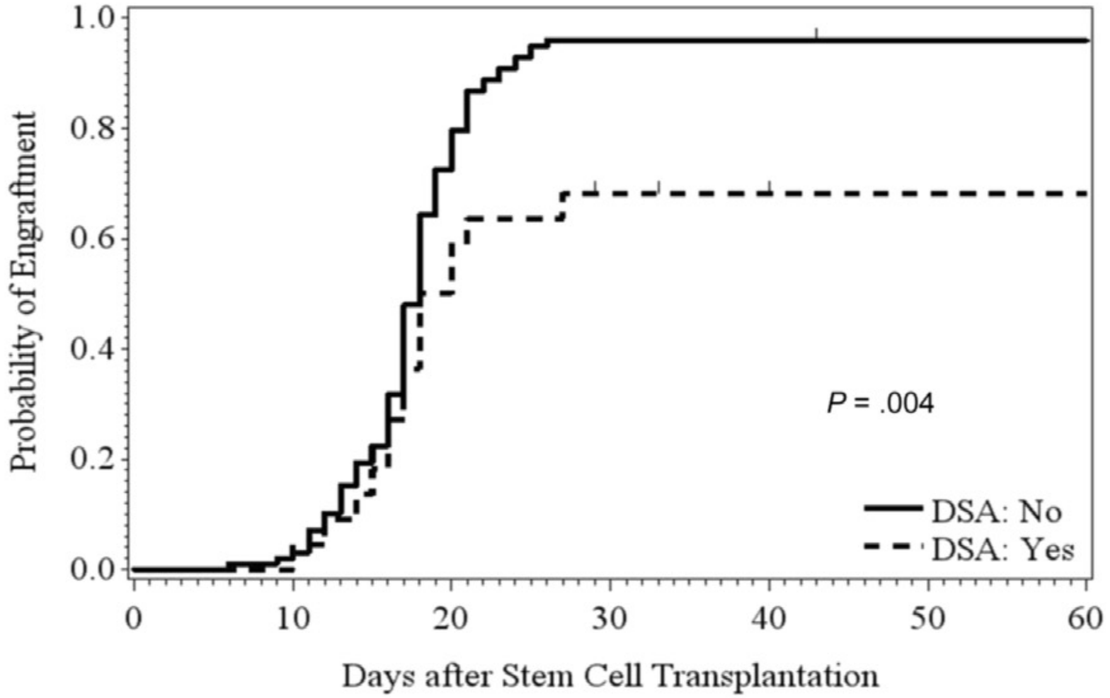
LETTER TO THE EDITOR

Familial haploidentical challenging unrelated donor Allo-SCT in advanced non-Hodgkin lymphomas when matched related donor is not available

This article has been corrected since Advance Online Publication and an erratum is also printed in this issue.

RFS	65% HDR vs 54% UD
NRM	15% vs 21% UD
cGvHD	15% HDR vs 29% UD

* The median follow-up was 27 months (range 9–67)

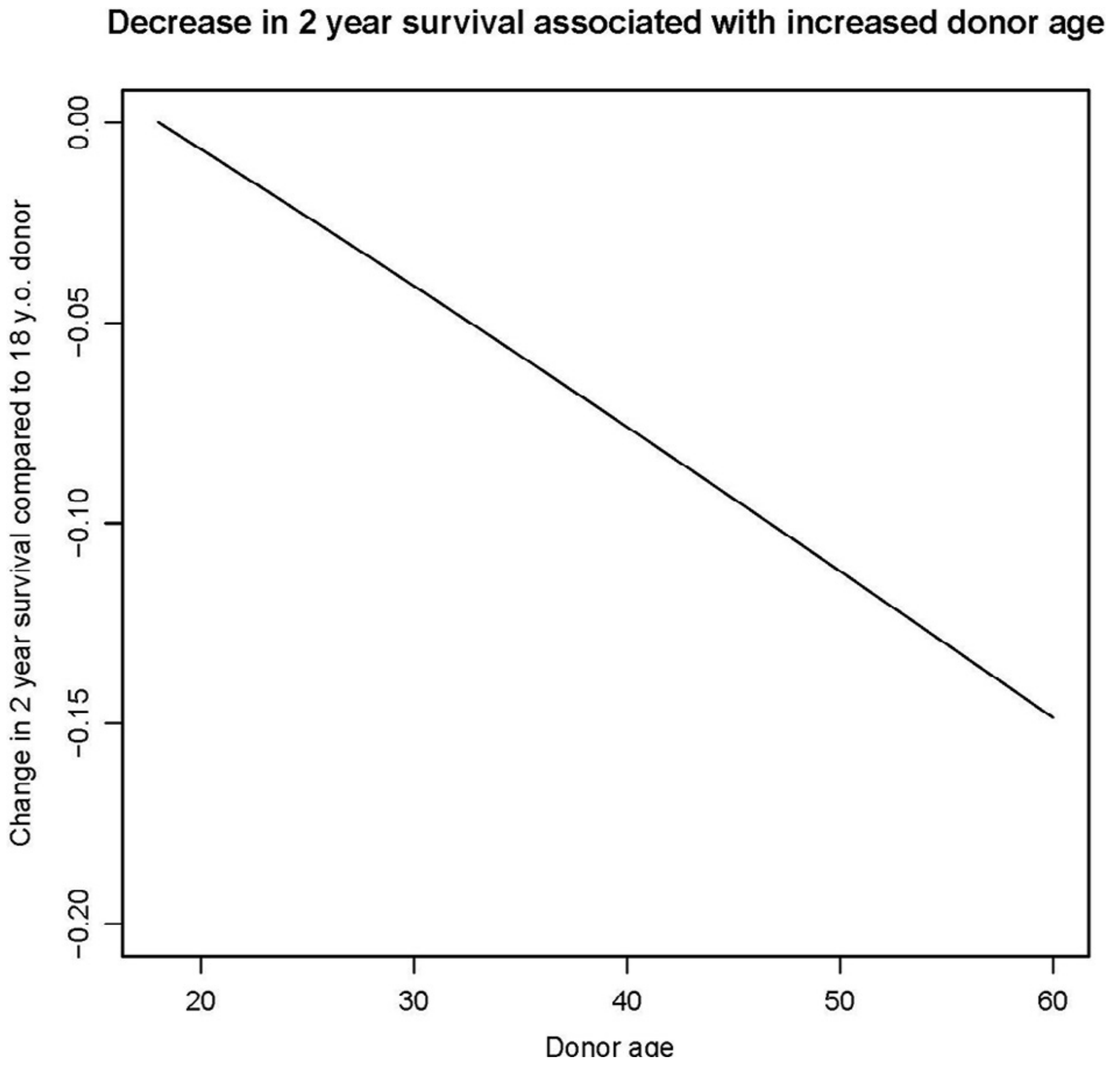


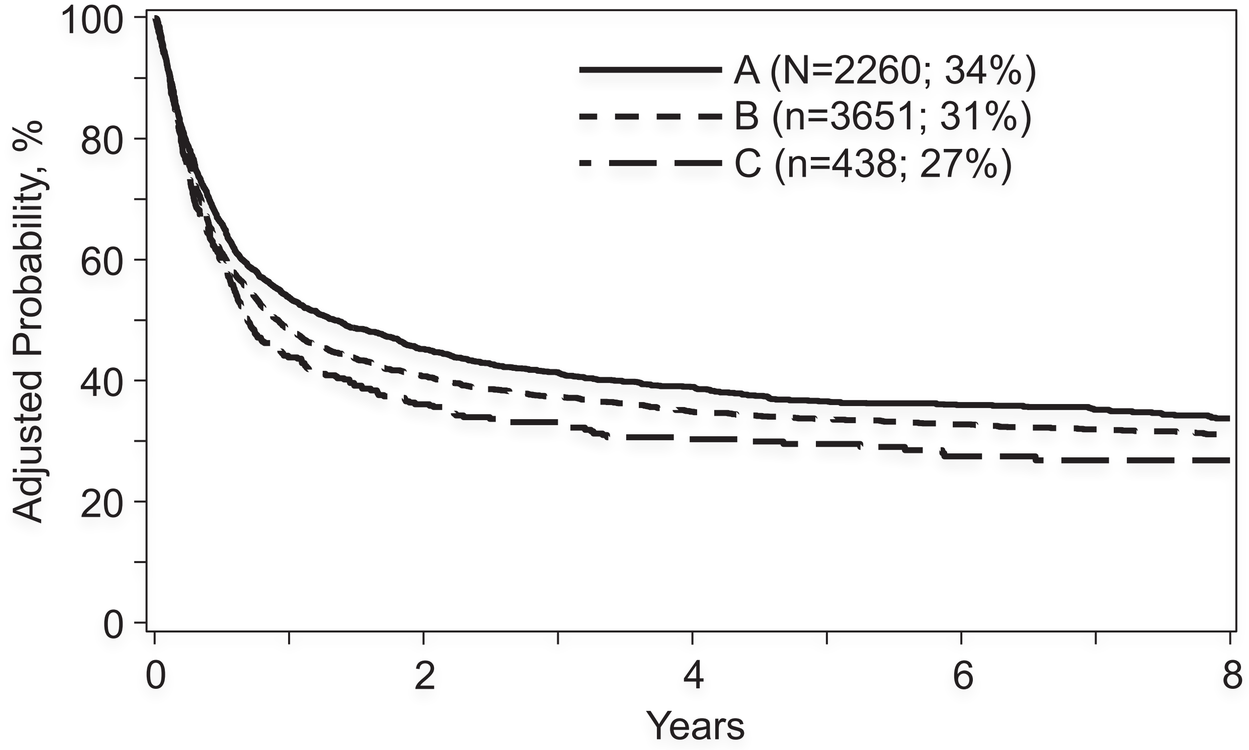
Various desensitization strategies employed to date

Strategy	Method
Antibody removal	Plasmapheresis
	Immunoadsorption
Antibody neutralization/enhance the clearance of anti-HLA antibodies	Intravenous immunoglobulin
	Donor platelets or "buffy coat" (white blood cells) infusion
Inhibition of antibody production	Anti-CD20+ B cells monoclonal antibody: rituximab
	Proteazome inhibition: bortezomib
	Splenectomy[a]
Complement cascade blockage	Anti-C5a: Eculizumab[a]
	Intravenous immunoglobulin

[a]Not used in hematopoietic stem cell transplantation to date

Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2015 Aug;21(8):1392-8.
The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. Bone Marrow Transplant. 2018 May;53(5):521-534.





Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most.
Biol Blood Marrow Transplant. 2018 May;24(5):1049-1056.
Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2016;127:260–7.

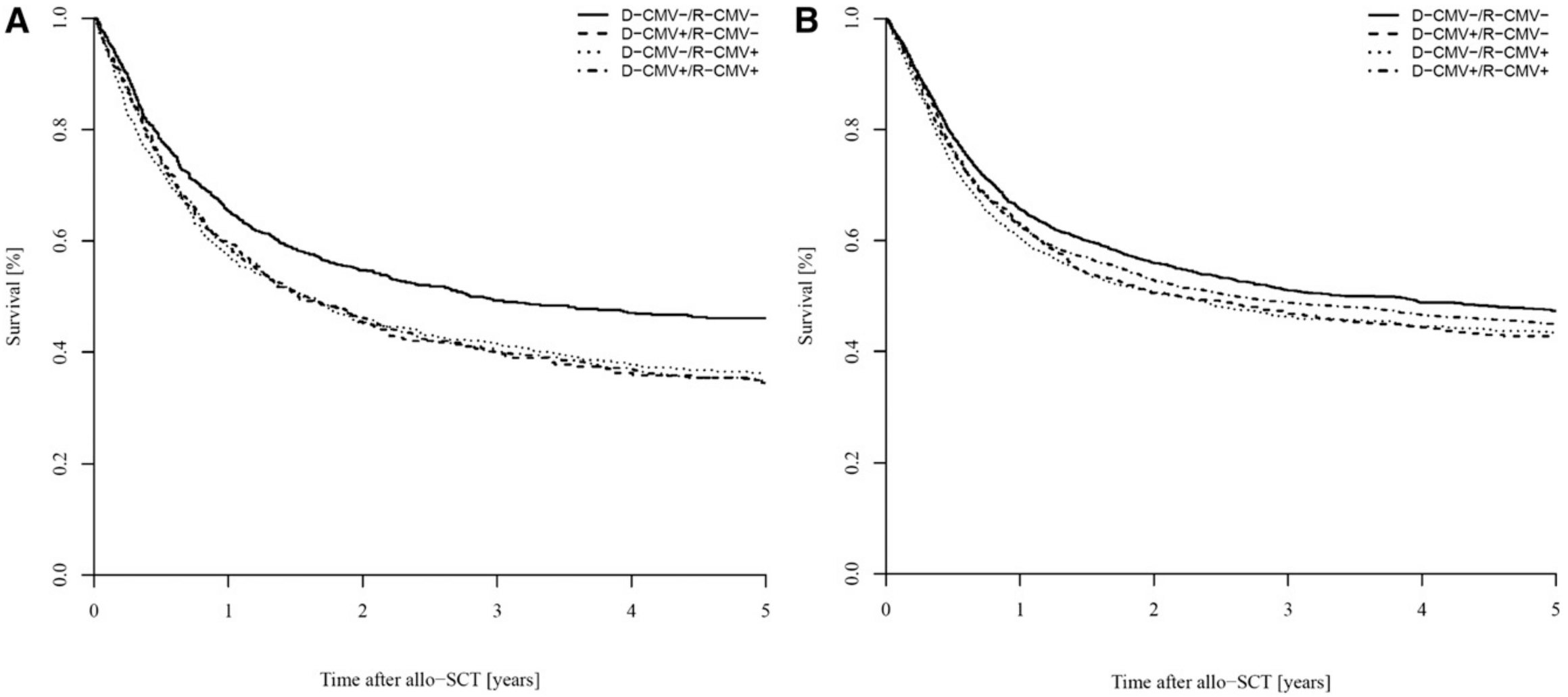
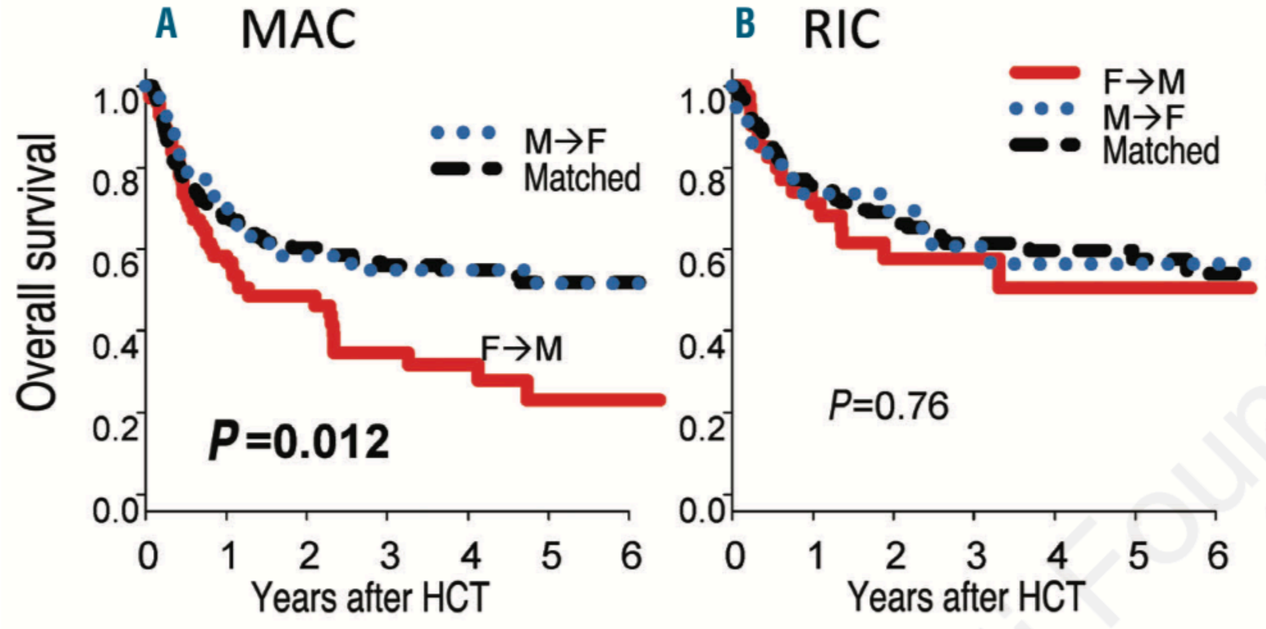
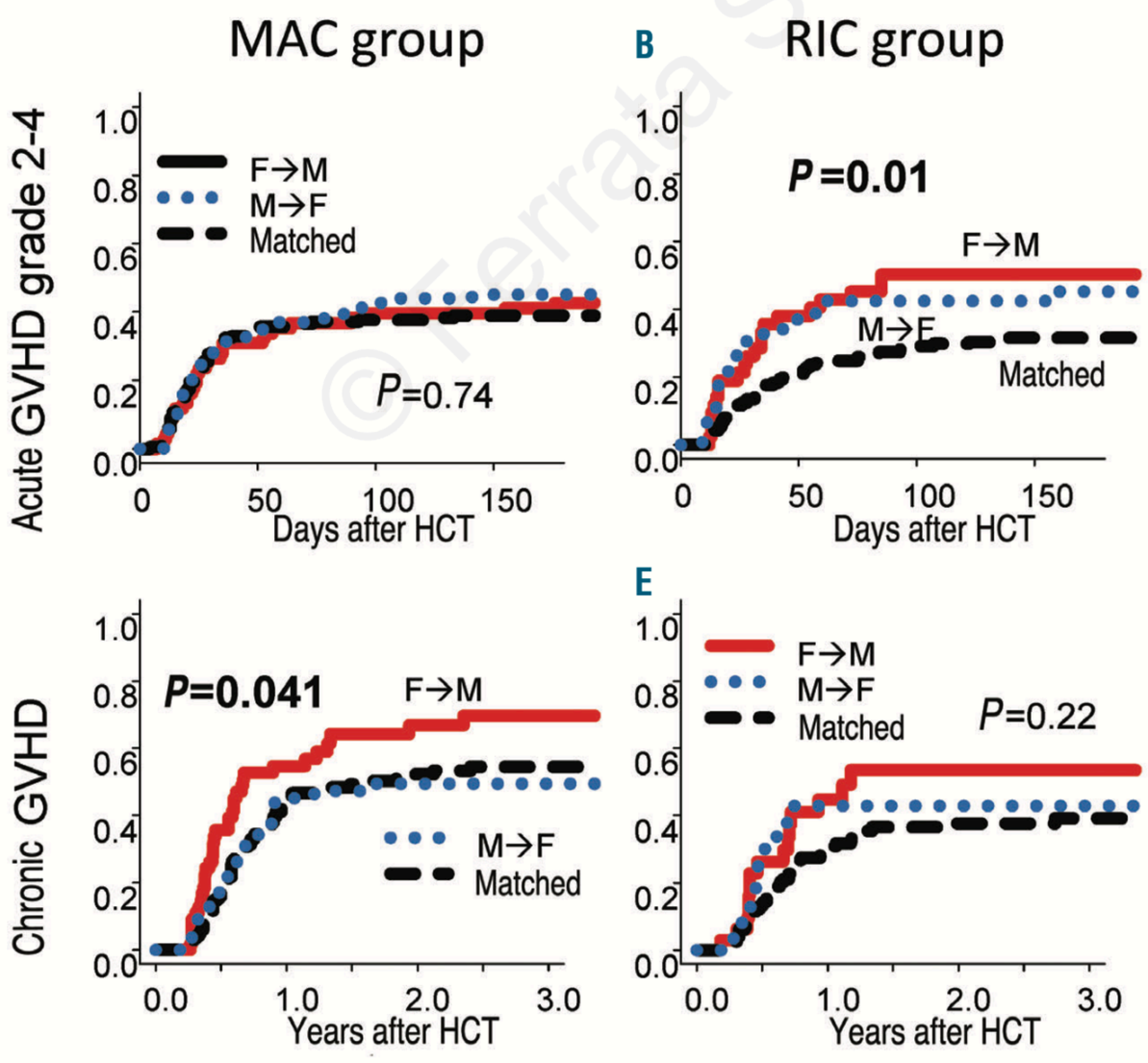


Figure 1. Impact of donor/recipient CMV serostatus on OS. Impact in (A) ALL vs (B) AML.

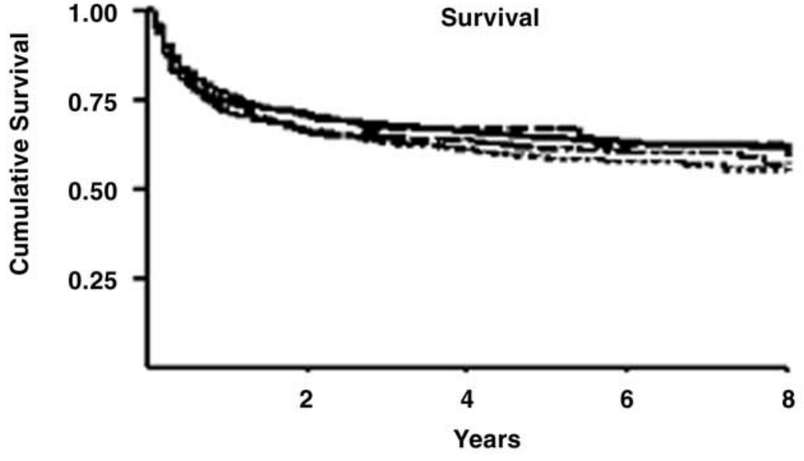
CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. Blood. 2013 Nov 7;122(19):3359-64.

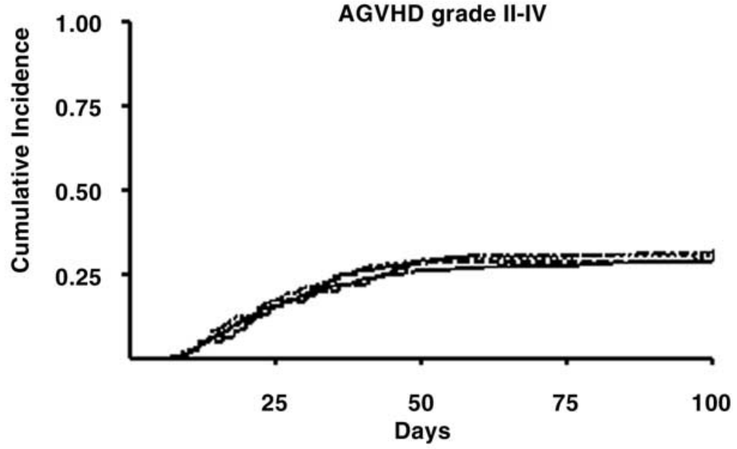


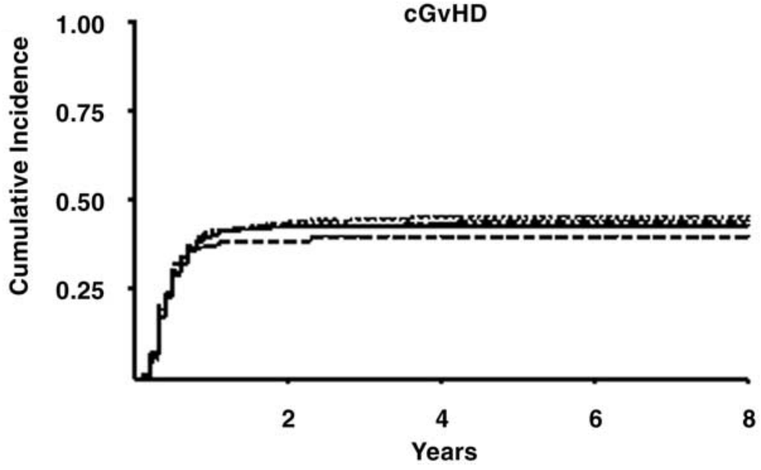


Risks And Benefits Of Sex-Mismatched Hematopoietic Cell Transplantation Differ According To Conditioning Strategy
Haematologica November 2015 100: 1477-1485

ABO Mismatch	Donor	Recipient	Known and Postulated Consequences
Minor	O	A, B or AB	Recipient hemolysis
	A, B	AB	Reports of increased GVHD
Major	A, B or AB	O	Posttransplantation pure red blood cell aplasia
	AB	A, B	Reports of impaired engraftment and increased GVHD
Bidirectional	A	B	Recipient hemolysis and red blood cell aplasia
	B	A	Reports of reduced overall survival
			Reports of impaired engraftment and increased GVHD







ABO blood group barrier in allogeneic bone marrow transplantation revisited.
Biol Blood Marrow Transplant. 2005 Dec;11(12):1006-13.

Заключение

Аллогенная трансплантация СК остается методом терапии с излечивающим потенциалом

Показания к аллогенной ТГСК гетерогенны и требуют индивидуального подхода на основании прогностических факторов, в т.ч. молекулярно-биологических

Раннее проведение ТГСК обеспечивает максимальные преимущества в показателях выживаемости

Продемонстрированы сопоставимые результаты при привлечении альтернативных доноров