La selezione del donatore nel 2026

l'importanza di HLA, epitopi, anticorpi e i modelli trapiantologici

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IRCCS Ospedale Pediatrico Bambino Gesù

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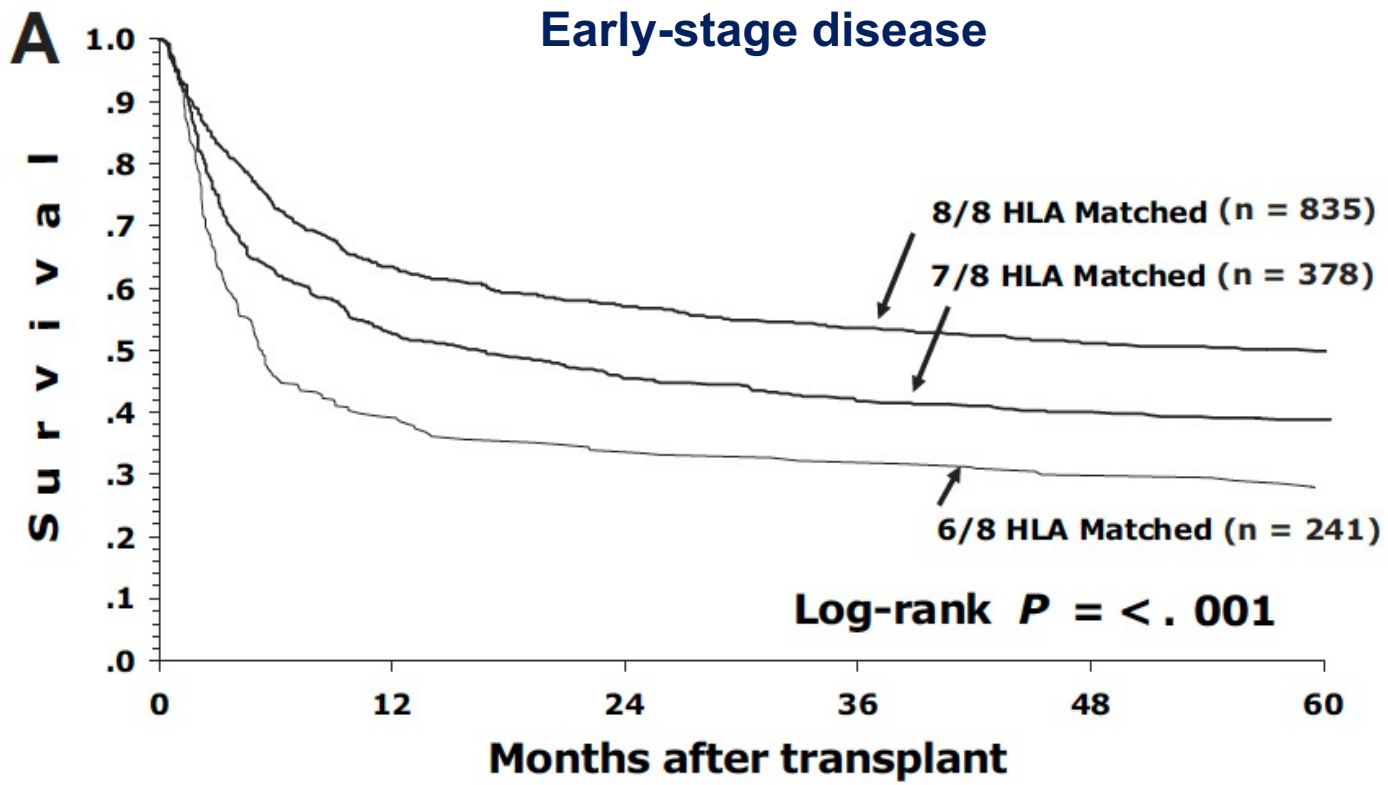
HLA matching between donor and recipient



Lee SJ et al. - 2007 Blood

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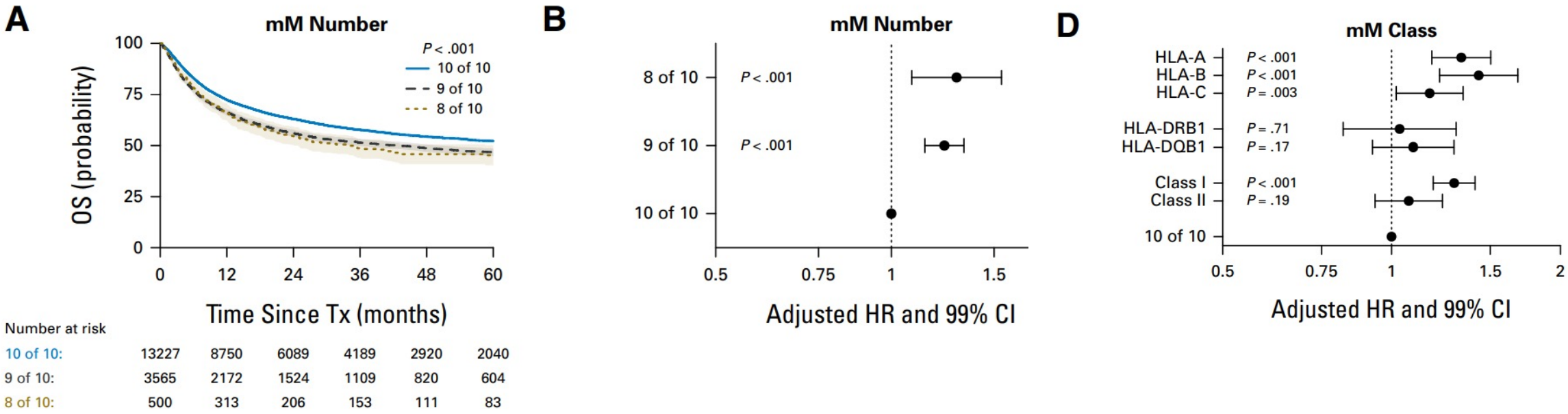
EBMT - study

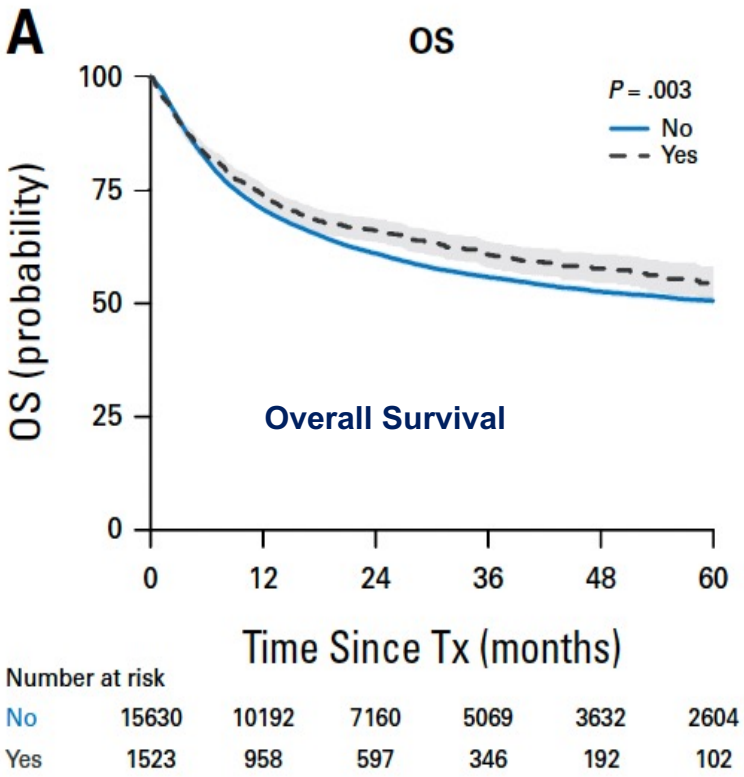
The study included **17,292 unrelated HCTs with 6-locus high-resolution HLA typing**, between 2016 and 2020, **including 1,523 transplants with PTCy**

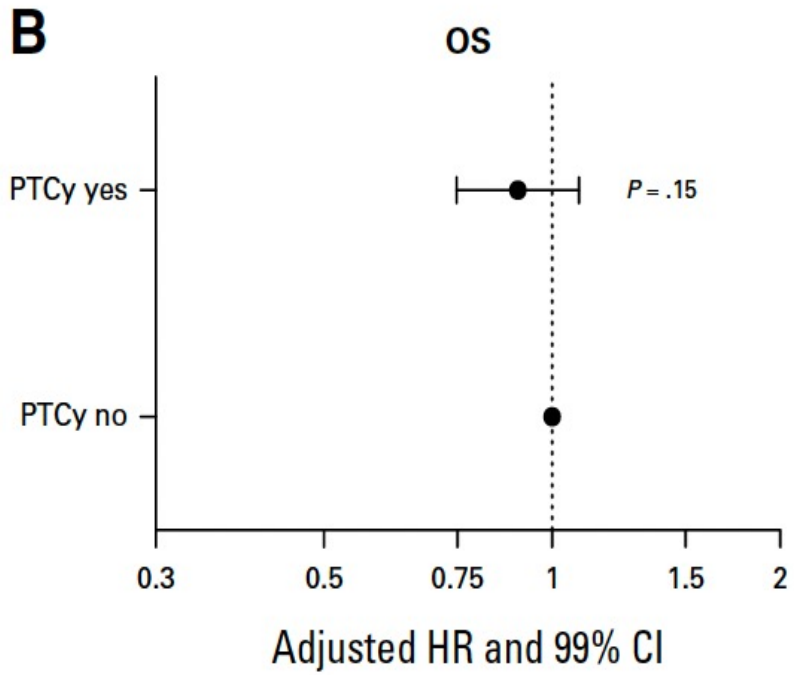


Does the use of PTCy improve the clinical outcome in matched settings…?

EBMT - study

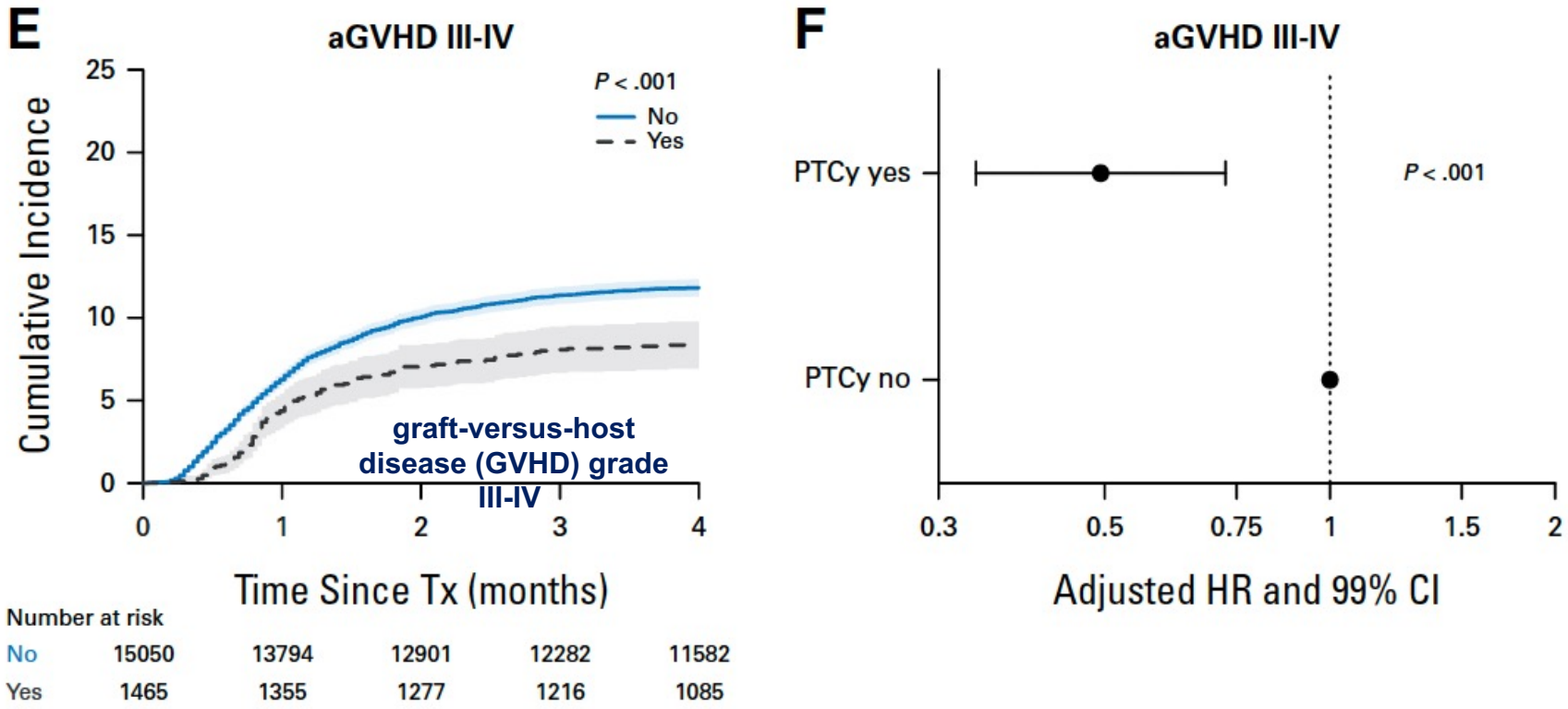
Comparison between MUD recipients: **15630 - NO PTCy** and **1523 - YES PTCy**





EBMT - study

Comparison between MUD recipients: 15630 - NO PTCy and 1523 - YES PTCy



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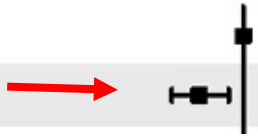
CIBMTR - study

The study included 10025 unrelated HCTs with HLA-A, -B, -C, and -DRB1 (8/8) HR typing for acute leukaemia (70.9%) or myelodysplastic syndromes (29.2%)

Comparator Group	No. of Patients	HR (95% CI)	P
Overall survival			
MUD-CNI	7272	Reference	
MUD-PTCy	1681	0.879 (0.8–0.96)	.004

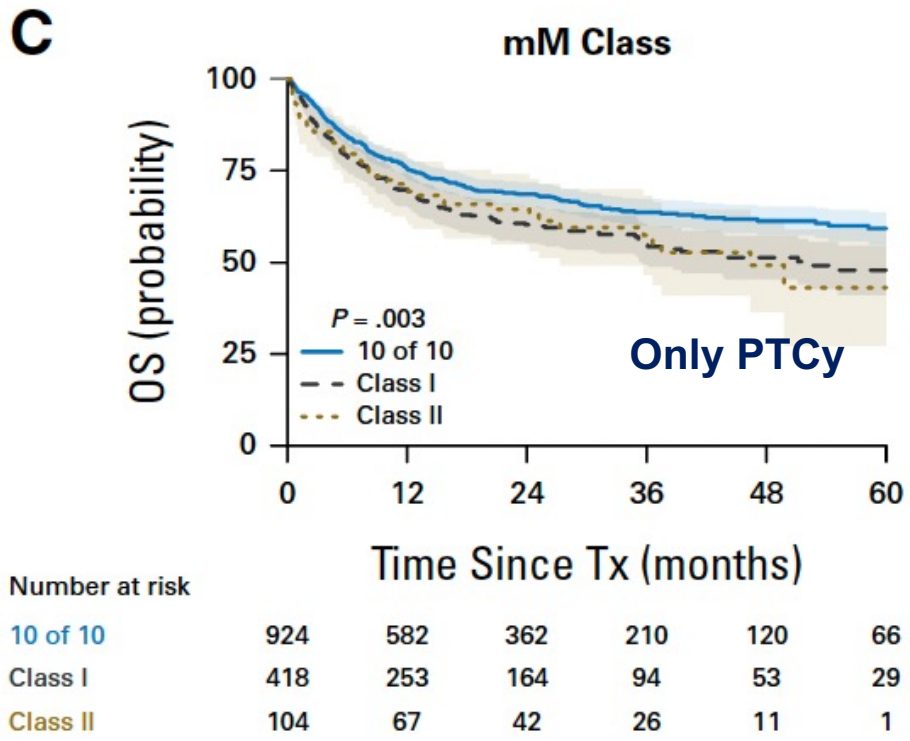


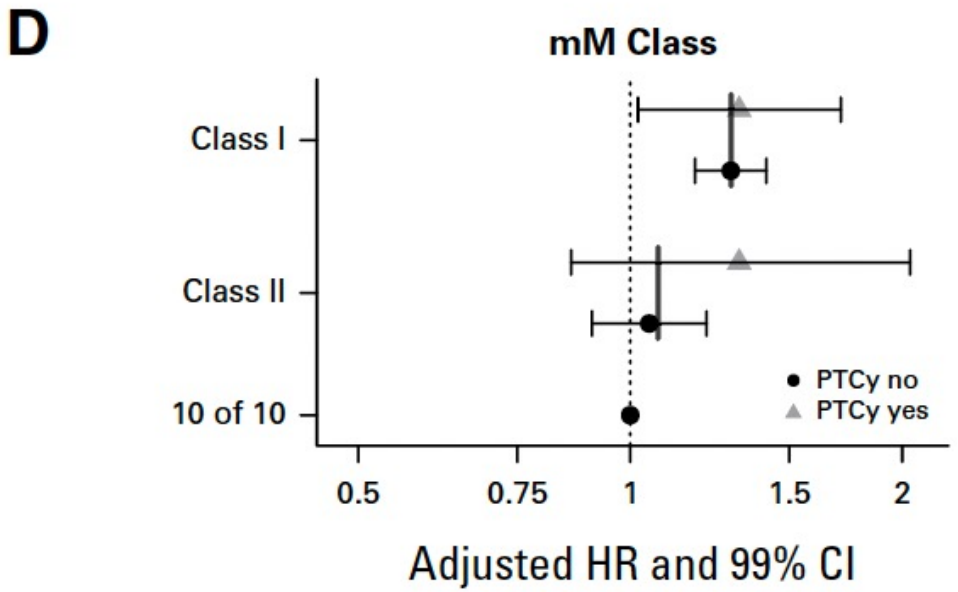
Posttransplant cyclophosphamide (PTCy)
Calcineurin inhibitor (CNI)

Does the use of PTCy reduce the importance of HLA compatibility in MUD HSCT mismatched settings…?

EBMT - study

The study included 1523 unrelated HSCTs with 6-locus high-resolution HLA typing only with PTCy





Arrieta-Bolaños E- 2024 by American Society of Clinical Oncology

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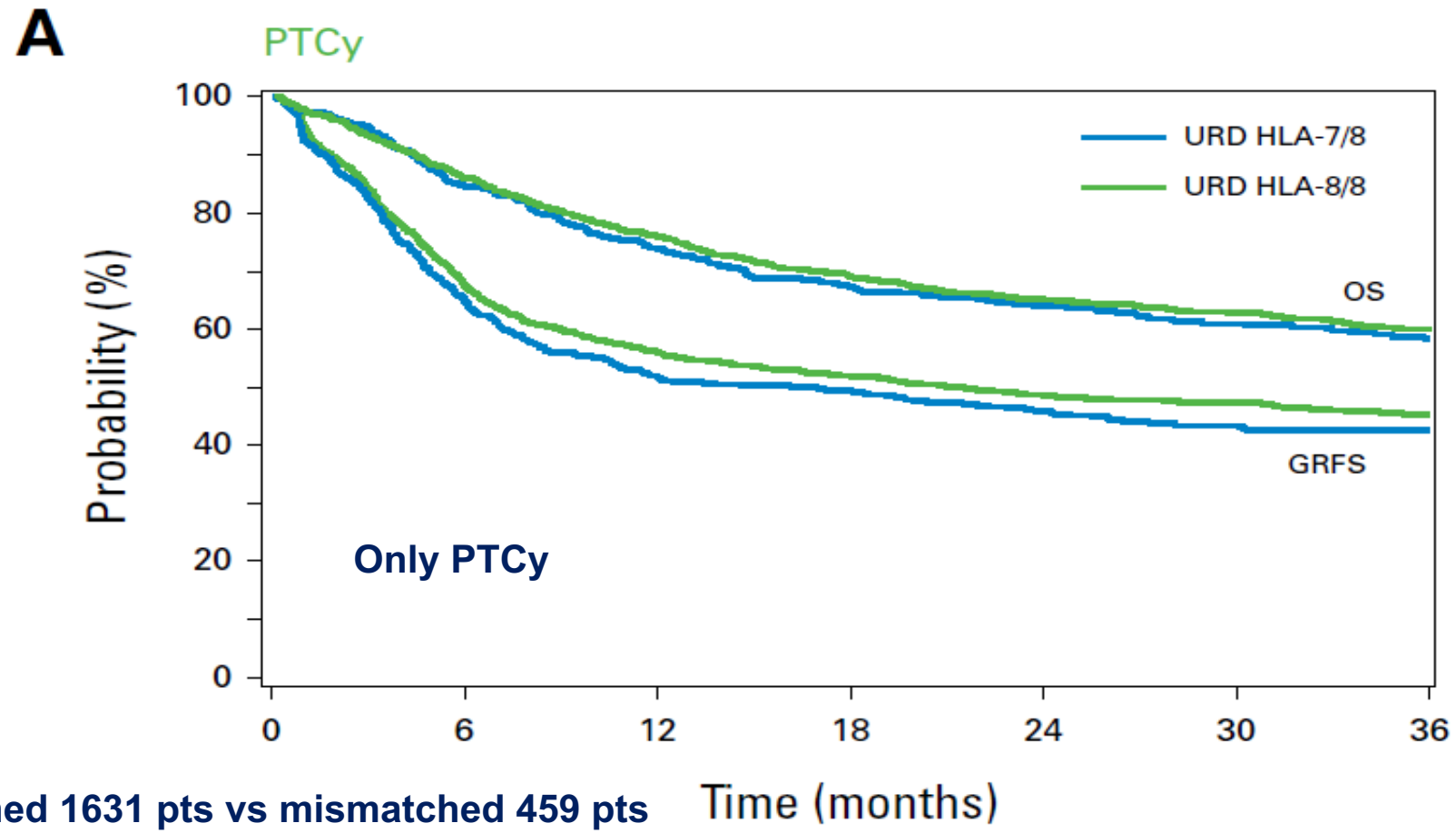
CIBMTR - study

The study included 2090 unrelated HCTs with 8/8 high-resolution HLA typing with PTCy



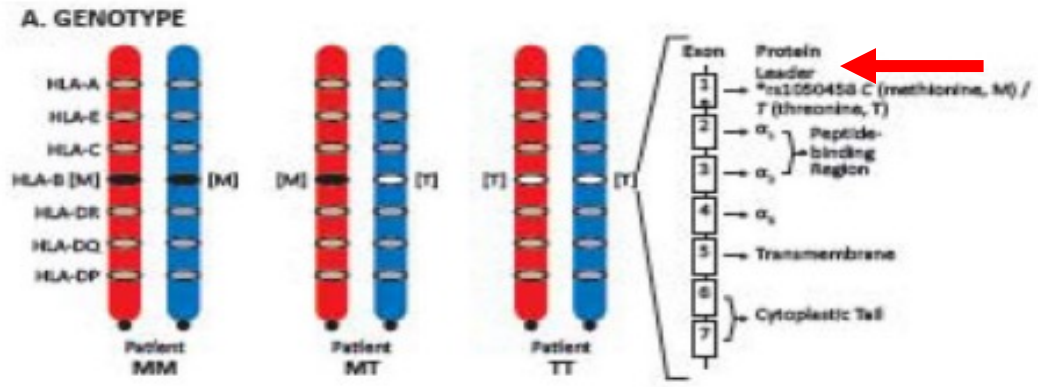
HLA-8/8 matched 1631 pts vs mismatched 459 pts

Models for HLA mismatch that should be considered permissive in transplantation

B Leader

B Leader

In exon 1 of HLA-B, the leader sequence codes for methionine (M) o threonine (T) in position -21, giving origin to 3 possible different potential genotypes: TT, MT, or MM



Petersdorf et al. 2020 Lancet Haematol

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B Leader

Survey of 17100 patients HLA-matched compared with 1457 HLA-B-mismatched

			Grades II-IV acute GVHD			Grades III-IV acute GVHD		
			Patients with endpoint/ evaluabl patients*	Odds Ratio (95% CI)	p value	Patients with endpoint/ evaluable patients*	Odds ratio (95% CI)	p value
Leader genotype	Patient	TT	264/503	1·0	..	111/503	1·0	..
		MT	198/371	1·11 (0·82–1·52)	0·50	114/366	1·64 (1·15–2·32)	0·0057
		MM	32/55	1·51 (0·78–2·94)	0·22	22/55	2·40 (1·20–4·78)	0·013
	Donor	TT	250/489	1·0	..	104/489	1·0	..
		MT	210/377	1·29 (0·94–1·76)	0·11	121/373	1·82 (1·28–2·59)	0·00094
		MM	34/63	1·27 (0·68–2·39)	0·45	22/62	2·06 (1·04–4·07)	0·038

In HLA-B-mismatched the presence of M in B-leader sequence in patients and/or in the donor increases the risk of aGvHD grade III-IV

Petersdorf et al. 2020 Lancet Haematol

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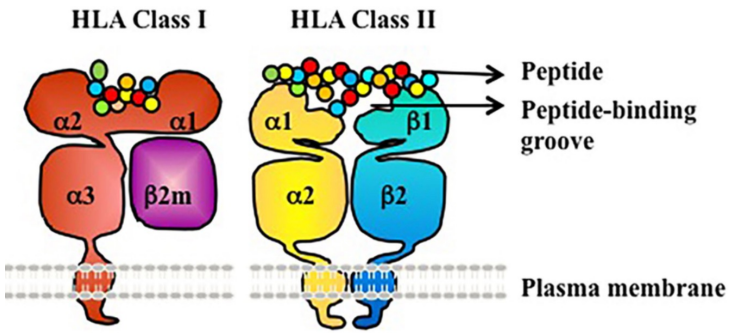
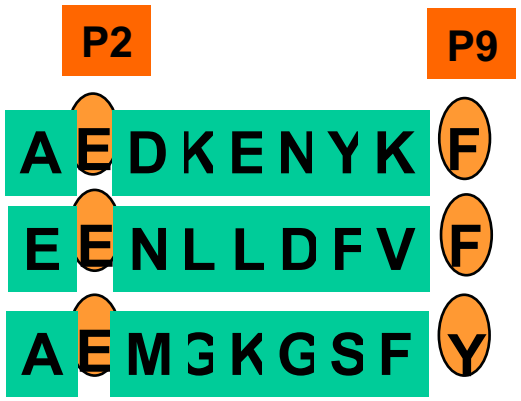
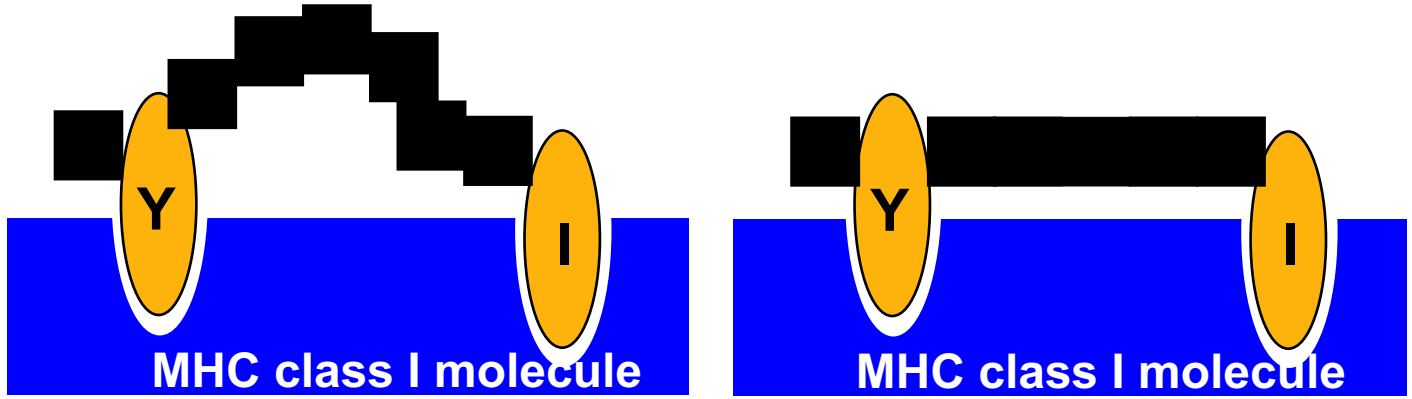
PBM in HLA-Class I

Immunopeptidome



The **immunopeptidome** is the collection of protein fragments derived from pathogens presented on the surface of the cells by HLA molecules to be "read" by T cells, acting as the crucial signal that defines "self" vs "non-self" for the immune system





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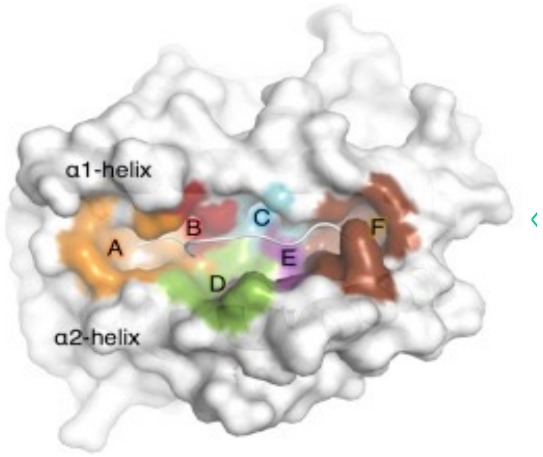
PBM in HLA-Class I

Polymorphism in peptide binding domain



Comparison between different PBM can serve as proxy for immunopeptidome divergence and prediction of T cell alloreactivity

Meurer et al Blood 2021;
Arrieta-Bolaños E. et al, Blood 2023

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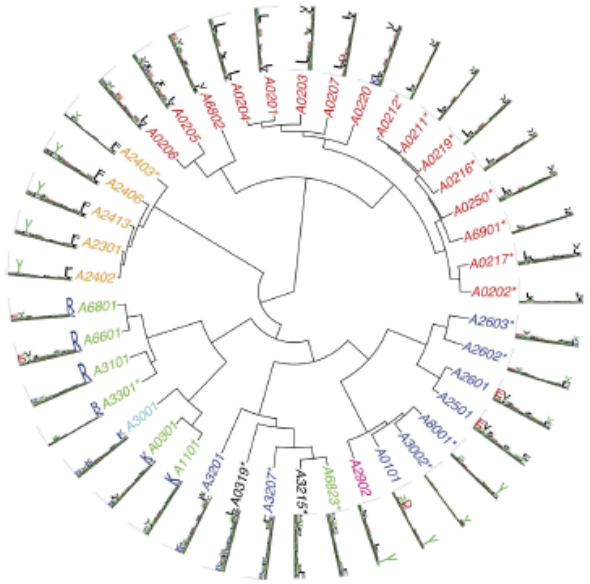
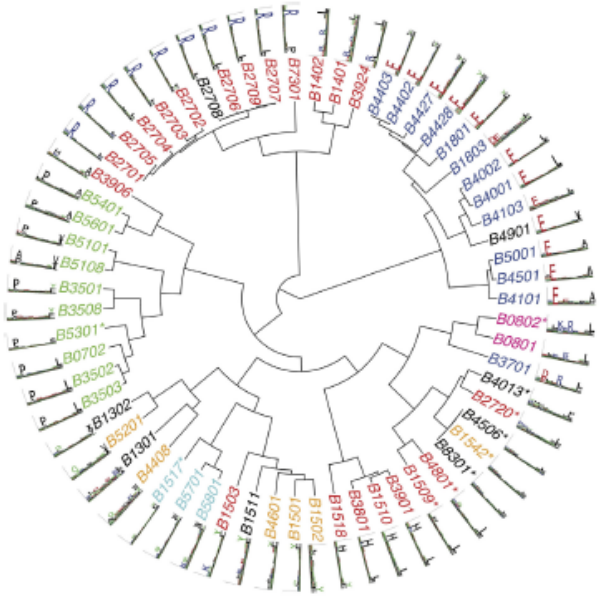
PBM in HLA-Class I

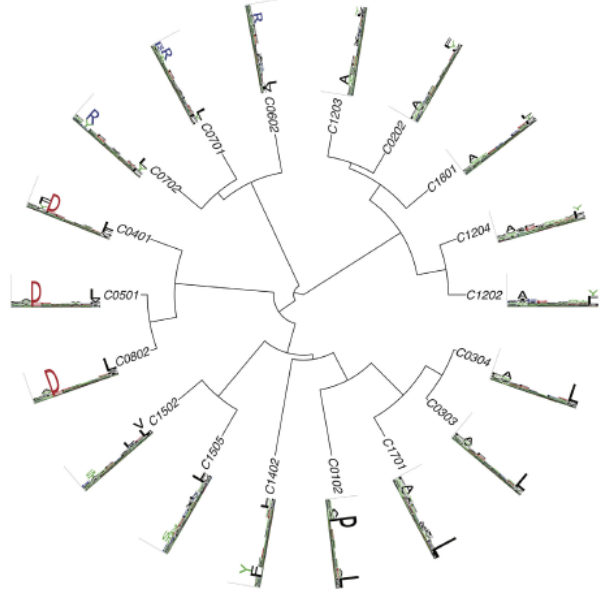
HLA-A (N=44)



HLA-B (N=63)



HLA-C (N=18)



Gfeller & Bassani-Sternberg Front Immunol 2018

- Alleles were grouped by clustering analysis of their PBM
- **21 PBM groups**: 7 HLA-A, 9 HLA-B, 5 HLA-C

PBM in HLA-Class I

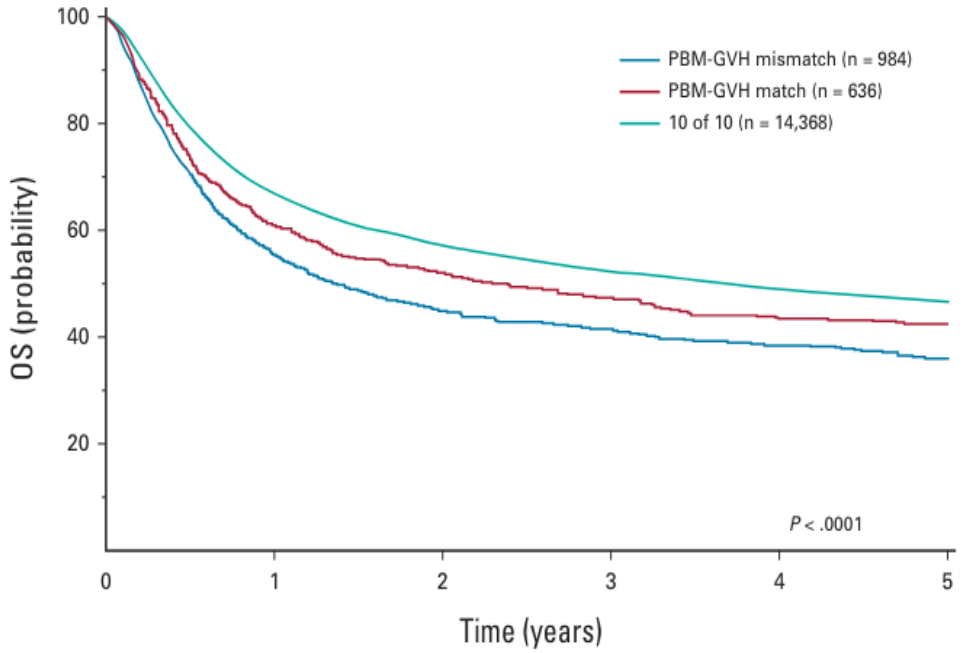
Study included 2391 patients receiving a MUD HSCT characterized by the presence of only a single HLA-mismatch class I (9/10) between 2008 and 2018

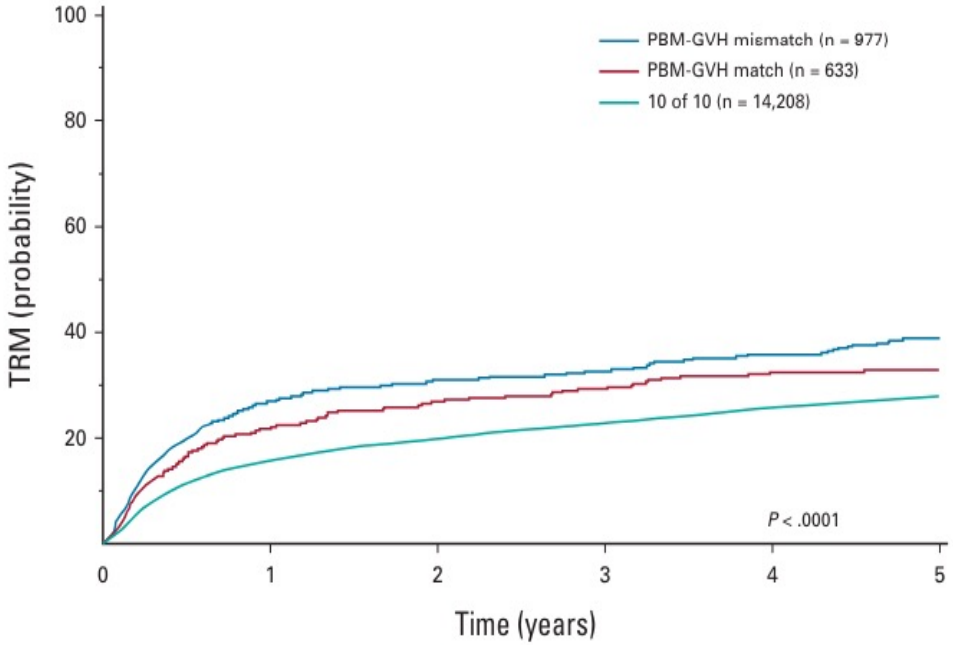
Example, No.	PBM Group			Immunopeptidome	PBM Status	Direction
	Shared	Donor	Recipient			
1	PBM-x	PBM-x	PBM-x	Low divergence	Match	None
2	PBM-x	PBM-y	PBM-y			
3	PBM-x	PBM-z	PBM-z			
4	PBM-x	PBM-y	PBM-z	High divergence	Mismatch	Bidirectional
5	PBM-x	PBM-x	PBM-y			Unidirectional GVH
6	PBM-x	PBM-y	PBM-x			Unidirectional HVG

Made a distinction between PBM with wide divergences (mismatched) and those characterized by lower divergences (matched) between donors and recipients

PBM in HLA-Class I

Crivello et al showed that after 9/10 UD-HSCT HLA mismatched, the presence of wide immunopeptidome divergences in the recipient (but not in the donor - graft-versus-host direction), was associated with a lower probability of survival





Crivello P et al. Journal of Clinical Oncology - 2023

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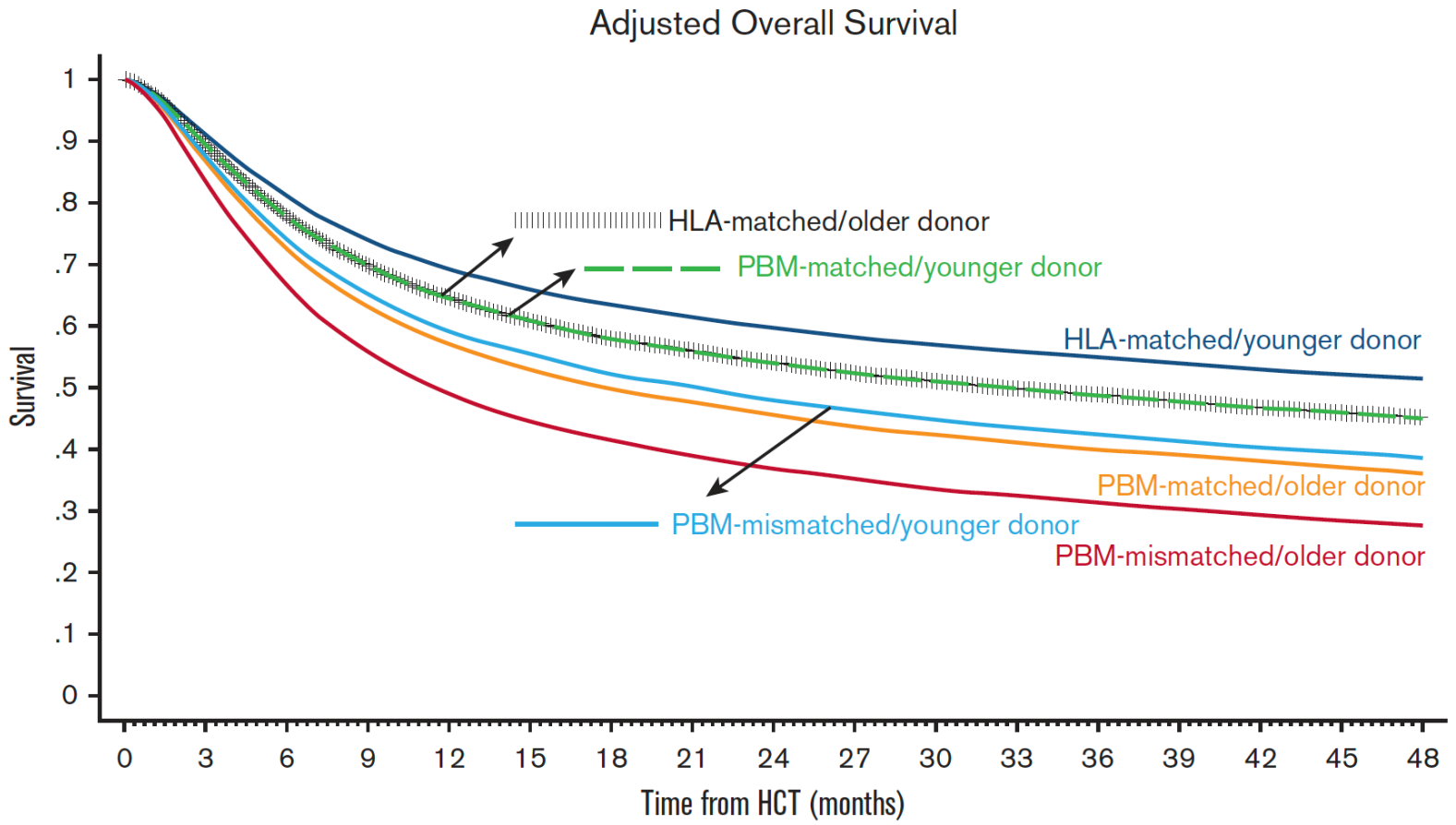
PBM in HLA-Class I



More than 15000 HSCT patients transplanted between 2008 and 2018 with no PTCy treatment confirmed Crivello's results, associating the younger age of the donor with PBM match

Mehta RS et al. Blood Advances - 2024

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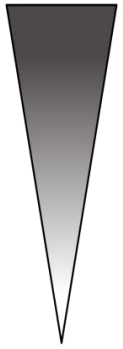
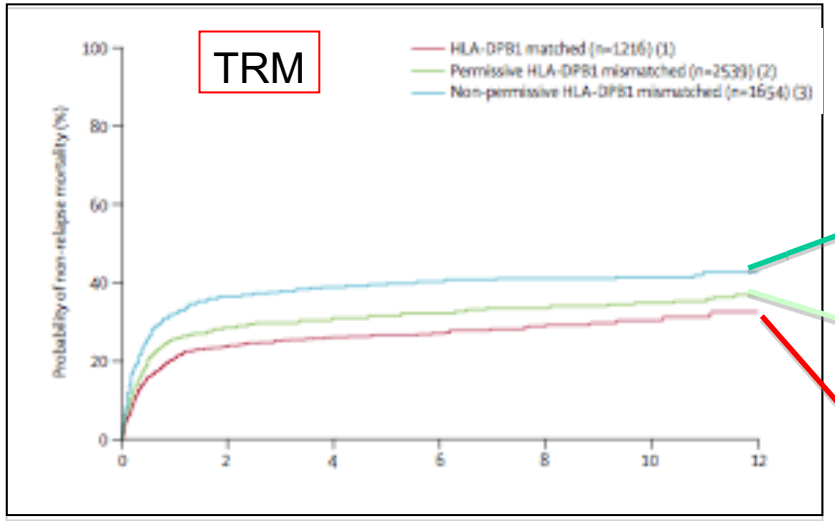
HLA-DPB1 mismatches

Permissive HLA Mismatched in MUD – **HLA-DPB1**

Locus DPB1 - Retrospective study on 5428 UD-HSCT (10/10)

DPB1* alleles	TCE3 group	Immunogenicity
0901 1001 1701	1	
0301 1401 4501	2	
Altre	3	

Donor \ Recipient	1/1	1/2	1/3	2/2	2/3	3/3
1/1	permissive			non-permissive (HvG)		
1/2						
1/3						
2/2	non-permissive (GvH)			permissive		
2/3						
3/3						permissive



Non-permissive TCE Mismatch

Permissive TCE Match

Allelic DPB1 Match

HLA-DPB1 (T-cell epitopes [TCE]) matching or permissive mismatching is associated with

- **less acute GVHD**
- **better survival**
- **higher relapse**

TCE Model

Fleishhauer et al., Lancet Oncol 2012

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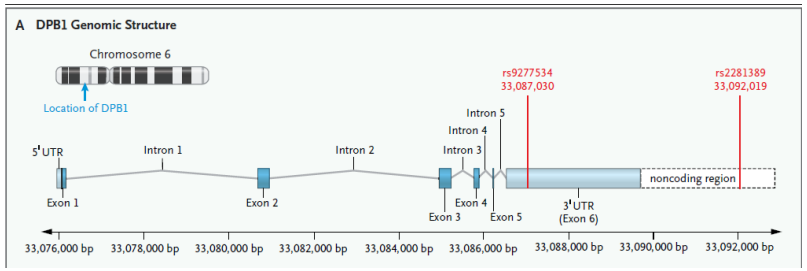
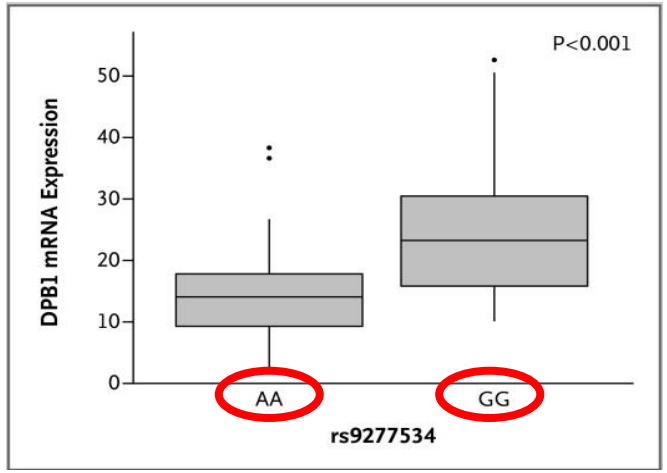
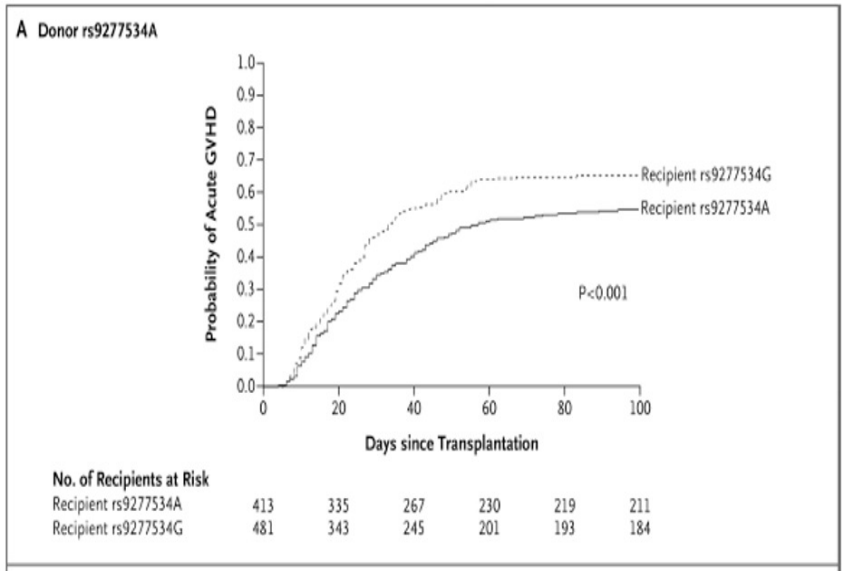
Permissive HLA Mismatched in MUD – **HLA-DPB1**





Polymorphism of A vs G in gene rs9277534 influence the expression of molecules produced by DPB1

Expression Model



Donor A - Recipient A: less incidence of aGvHD
Donor A - Recipient G: more incidence of aGvHD

Petersdorf et al – New Engl J Med 373:599, 2015

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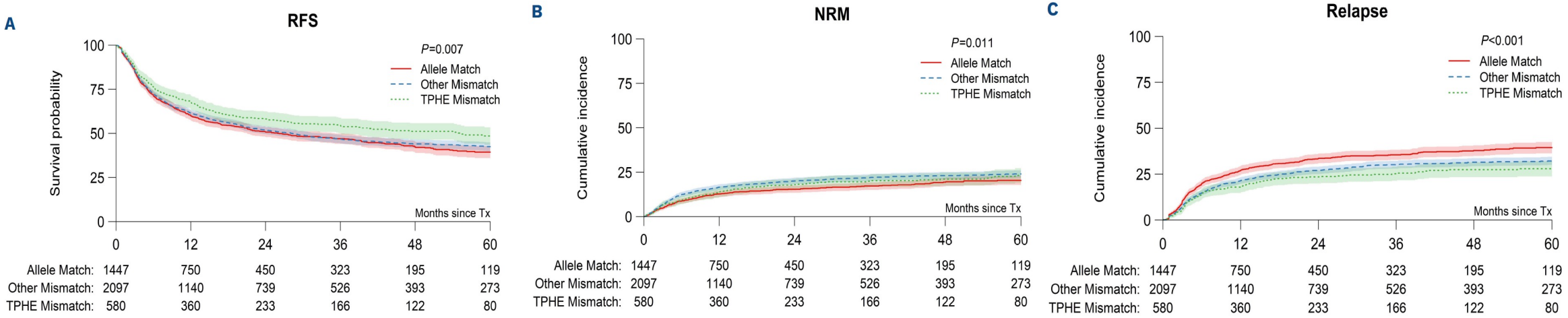
Permissive HLA Mismatched in MUD – **HLA-DPB1**

TPHE

Combination of TCE-Permissive and High Expression HLA-DPB1 mismatches improves clinical outcome



Petersdorf et al – Haematologica, 2023

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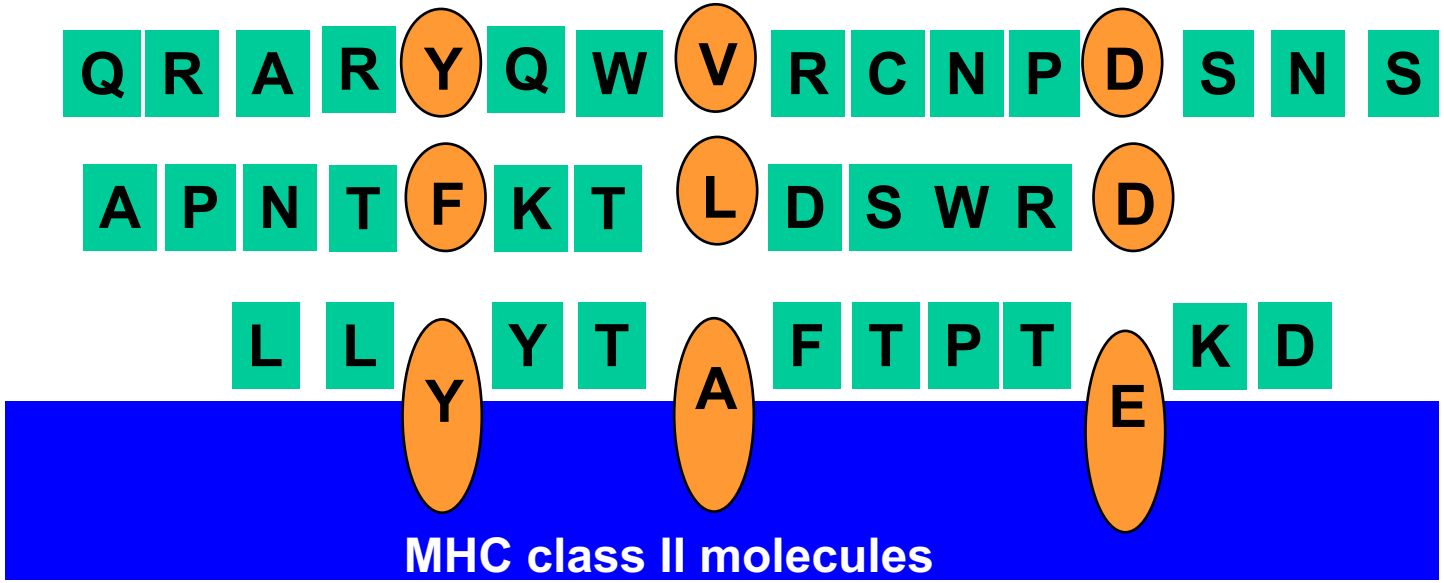
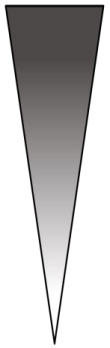
IMMUNOPEPTIDOME



Permissive HLA Mismatched in MUD – **Immunopeptidome in DPB1**

DPB1* alleles	TCE3 group	Immunogenicity
0901 1001 1701	1	
0301 1401 4501	2	
Altre	3	

	HLA-DPB1*	TCE-1 09:01	TCE-1 10:01	TCE-2 03:01	TCE-2 06:01	TCE-3 02:01	TCE-3 04:01	TCE-3 04:02
TCE-1	09:01							
	10:01	51,6						
TCE-2	03:01	5,1	3,9					
	06:01	3,3	2,3	13,9				
TCE-3	02:01	2,2	1,4	2,1	1,2			
	04:01	0,9	1,2	2,1	1,0	10,1		
	04:02	1,1	0,7	2,3	0,5	18,3	26,2	

60%

0%

Meurer's group **investigated the diversity of peptide repertoires** within the different TCE groups in a model of specific **permissive vs non-permissive HLA-DP allelic variant combinations**

Meurer et al Blood 2021

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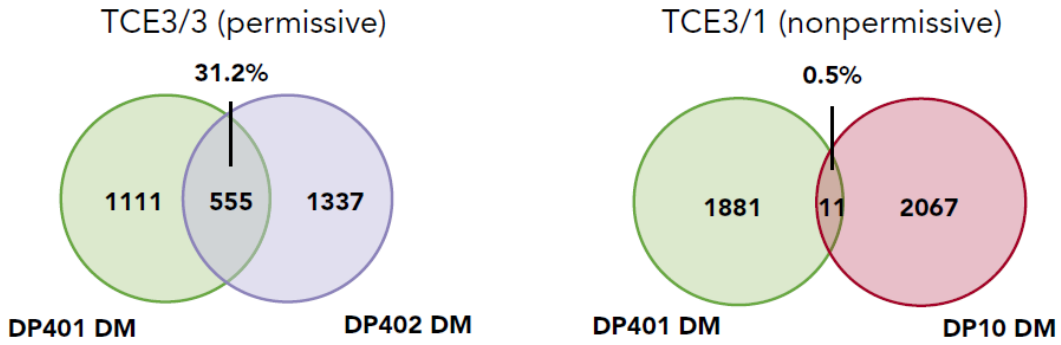
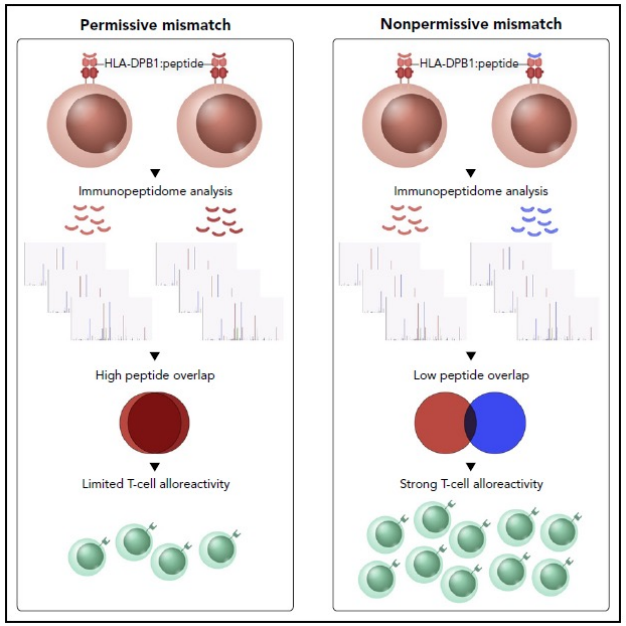
Permissive HLA Mismatched in MUD – **Immunopeptidome in DPB1**





High peptide overlapping in permissive DPB1 vs low peptides overlapping in non permissive DPB1

Resulting in different frequency and diversity of alloreactive TCR-β clonotypes in transplanted patients

Juliane Sarah Walz -Blood 2021

Meurer et al Blood 2021

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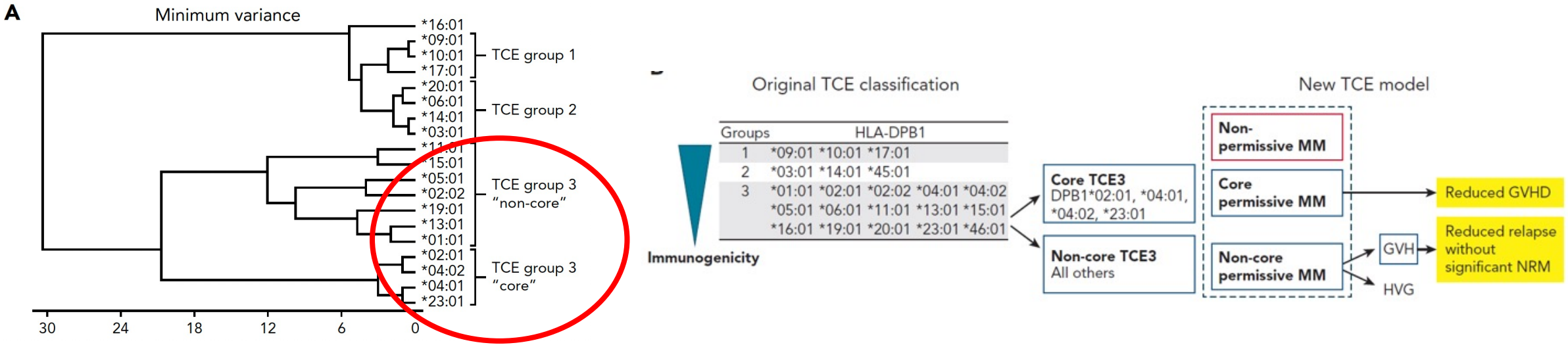
Permissive HLA Mismatched in MUD – **Immunopeptidome in DPB1**

Alleles of "core" TCE3 group showed to have a similar bound-peptide motifs (PBM) and immunopeptidome overlapping

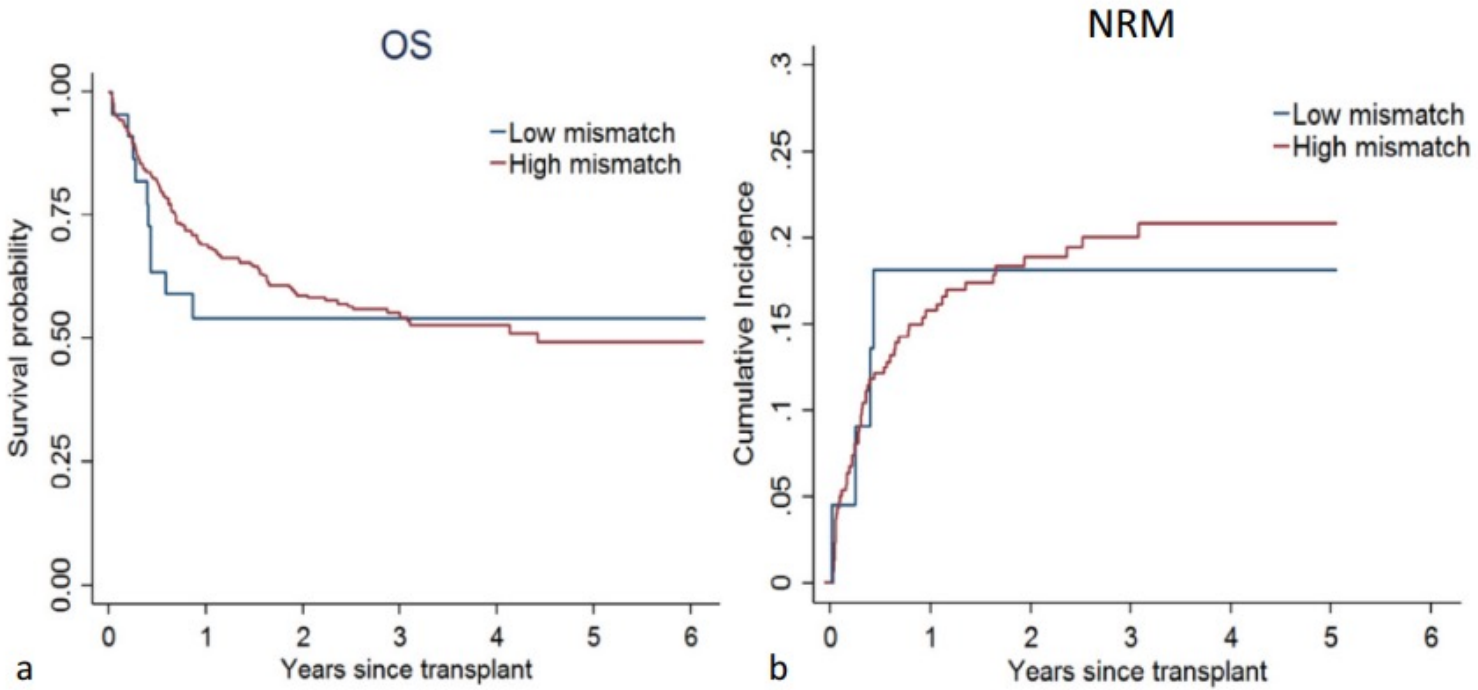


TCE3 "core" alleles showed a significantly weaker (18.5%) T-cell alloreactive response from permissive donors compared with common "non-core" alleles (29.2%); P .001; demonstrating the functional relevance of the clustering

Haploidentical HSCT

Is HLA compatibility still relevant in haploidentical settings…?

HLA Compatibility in Haploidentical



OS and NRM In univariate analysis having more HLA differences was not associated with worse OS or with increased NRM irrespective of whether they were analyzed as discrete (either 0 to 2 versus 3 to 4 and 0 to 3 versus 4 mismatches) or continuous variables.

Raiola AM et al. - Biol Blood Marrow Transplant - 2018

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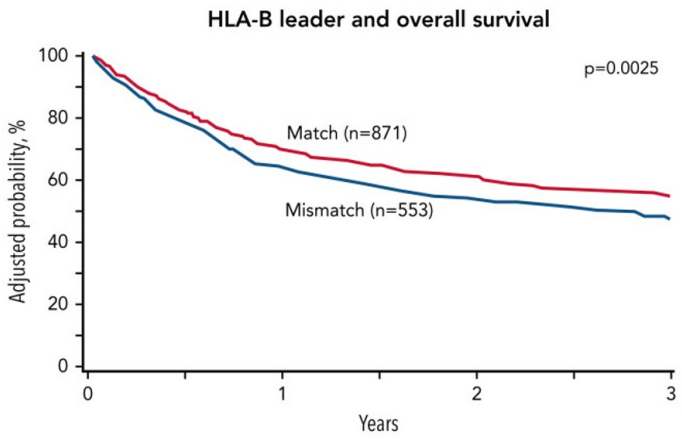
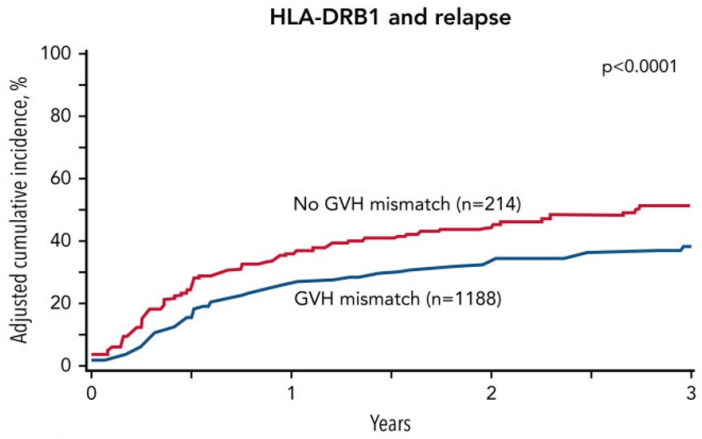
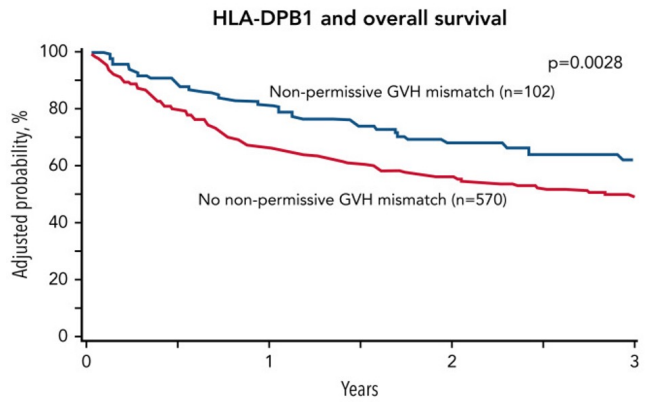
HLA Compatibility in Haploidentical

Mismatched 5/10 (928, 65%) or 6/10 (314, 22%) for HLA-A, -B, -C, -DRB1 and -DQB1







The clinical outcome has been associated in these patients with matched or mismatched condition for single loci, and not for the total of the mismatched loci

Fuchs E et al - Blood 2022

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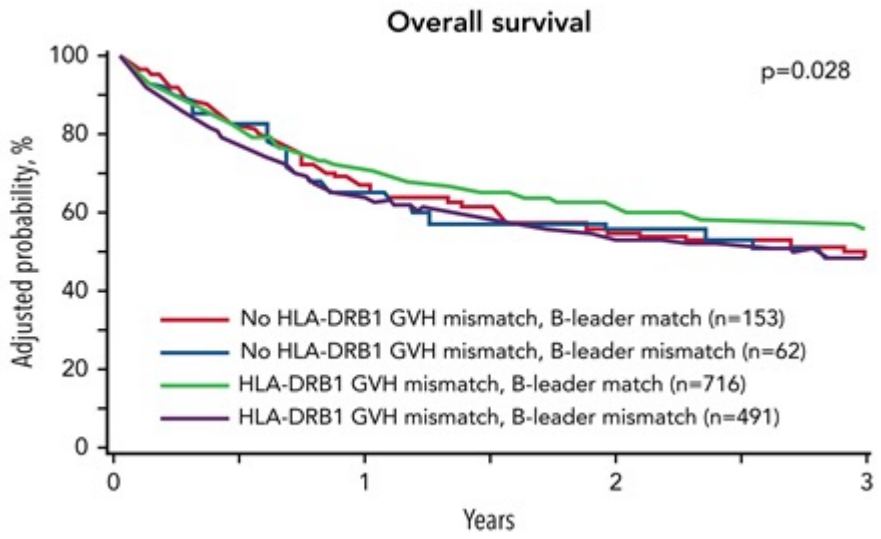
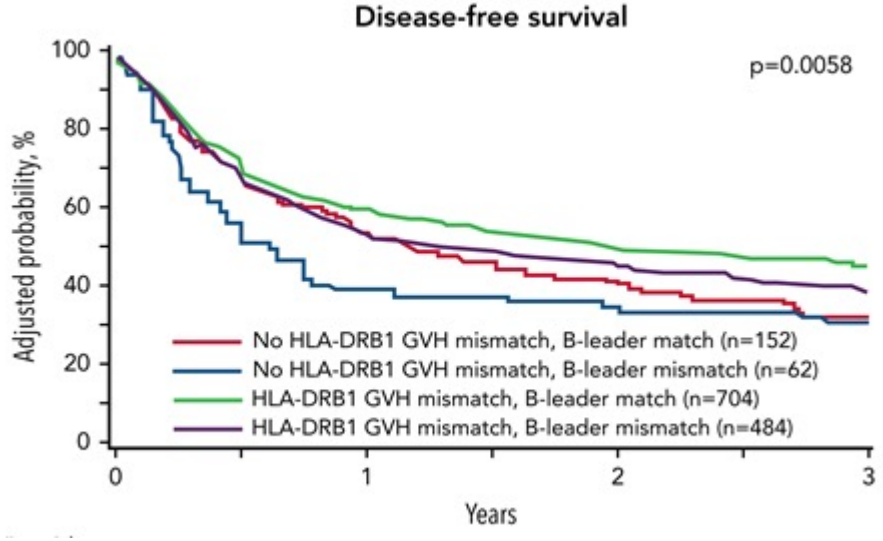
HLA Compatibility in Haploidentical

Mismatched 5/10 (928, 65%) or 6/10 (314, 22%) for HLA-A, -B, -C, -DRB1 and -DQB1





4 transplant groups by the presence of concurrent (mis)matching for the HLA-B leader and HLA-DRB1
Best combination: HLA-B leader match and HLA-DRB1GvH mismatch

Fuchs E et al - Blood 2022

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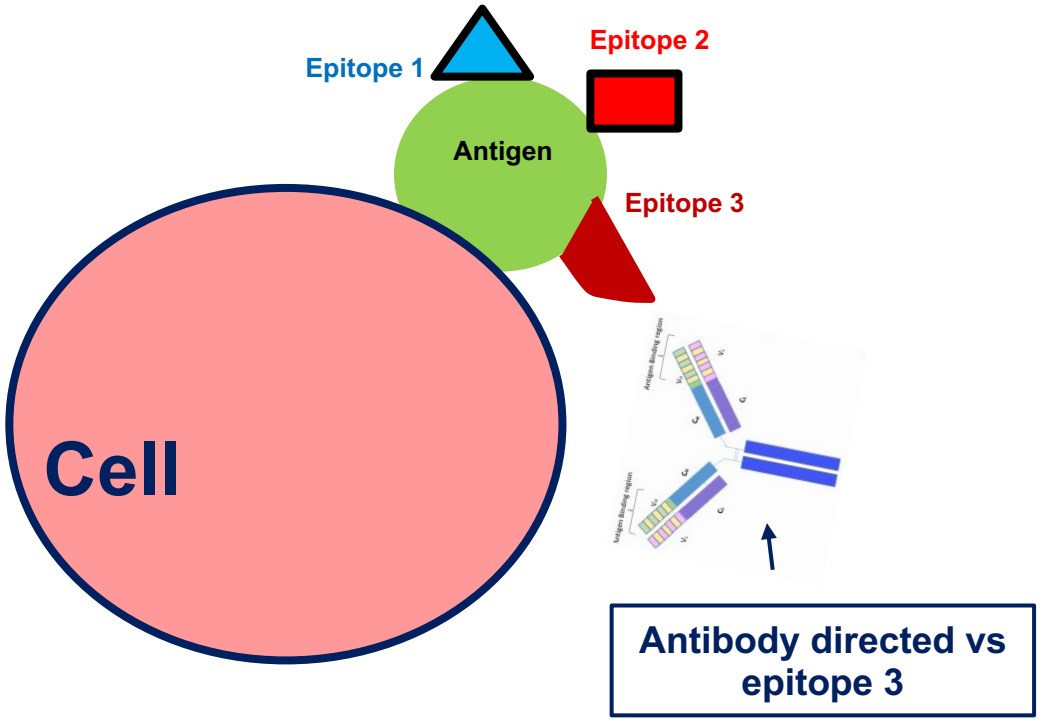
Eplet mismatches

Eplets mismatched

An antibody binds an epitope of an HLA antigen

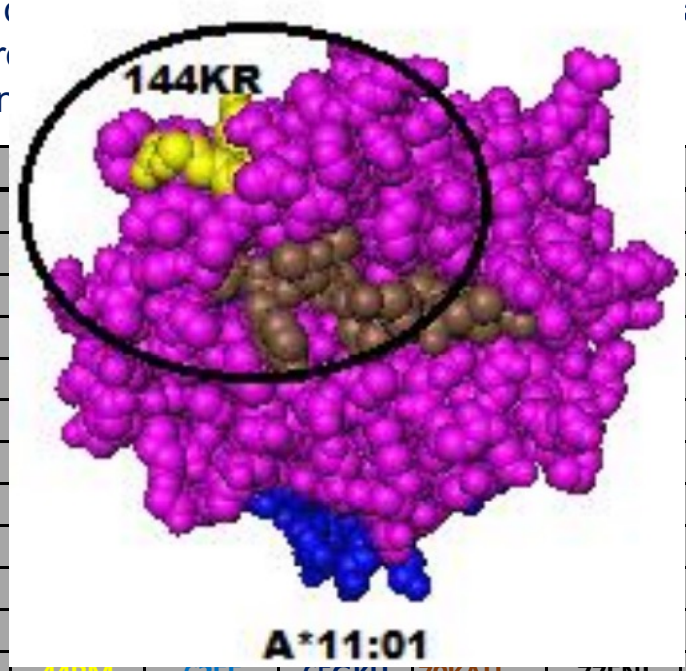


Antibody directed vs epitope 3

EPLETS

- Essential components of HLA epitopes recognized by antibody (“hot s
- Eplet
- Namir

within a 3-3.5 Amstr



Locus A						.....	248
*01:01						-	248VK
*02:01						-	248VK
*02:02						-	248VK
*02:03						-	248VK
*02:05						-	248VK
*03:01						-	248VK
*03:02						-	248VK
*11:01						-	248VK
*11:02						-	248VK
*23:01						-	248VK
*24:02						-	248VK
*24:03	44RM	62EE	65GKH	70KAH	77ENI	-	248VK

From: **Clinical Relevance of H&I in solid organ transplantation. ESHI (EuropeanSpecialisationin H&I) Diploma. EBTI.**
Sebastiaan Heidt. Leiden University Medical Center

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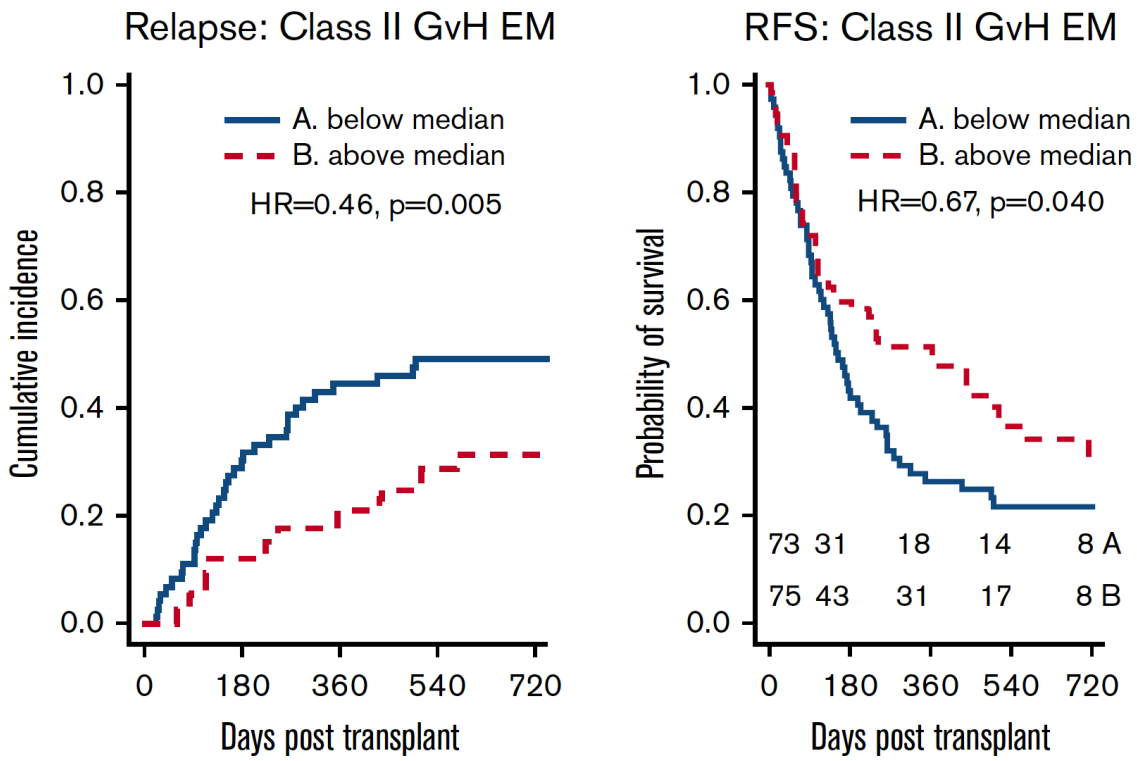
Eplets mismatched



Higher EM levels for HLA class II alleles have been associated with a reduced risk of relapse and relapse-free survival in 158 patients treated with HSCT haploidentical

Rimando J et al. – Blood Advances, 2018

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Eplets mismatched

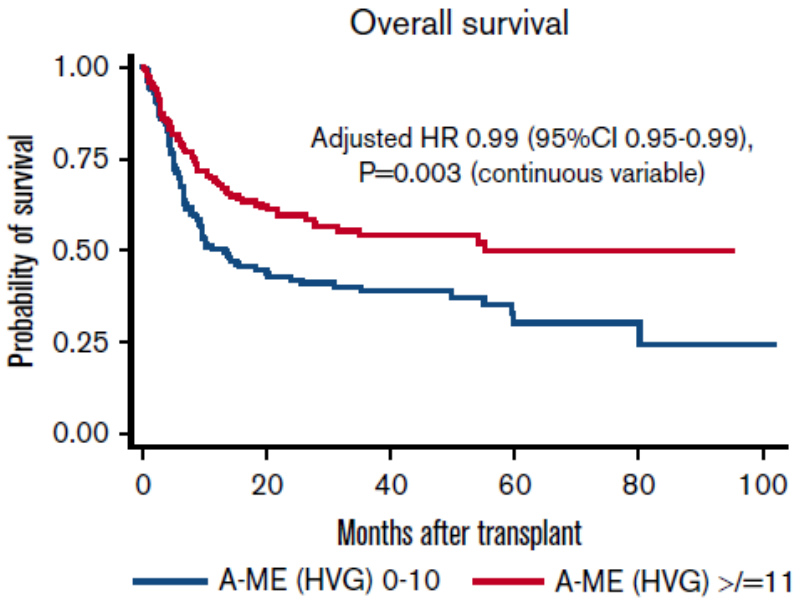
REGULAR ARTICLE

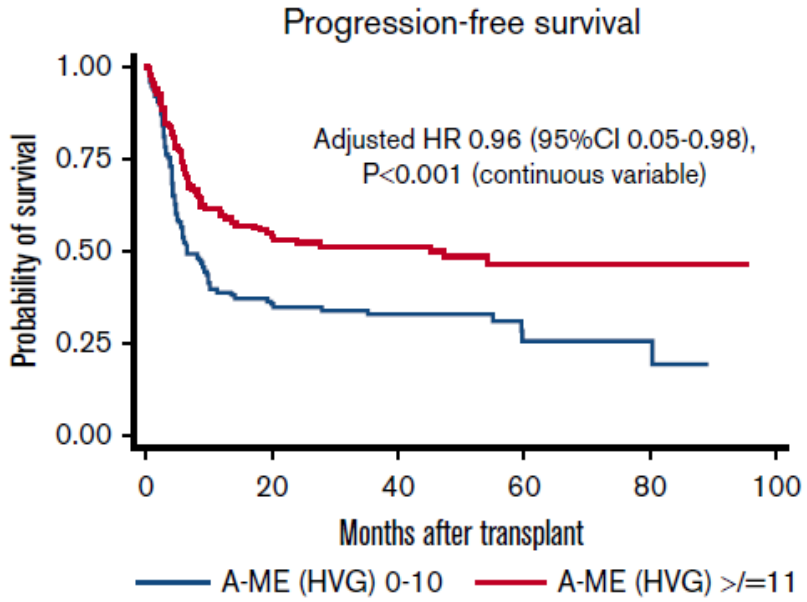
blood advances

Molecular disparity in human leukocyte antigens is associated with outcomes in haploidentical stem cell transplantation

Jun Zou,[1,*] Stefan O. Ciurea,[2,*] Piyanuch Kongtim,[3] Min Yi,[4] Yudith Carmazzi,[1] Gabriela Rondon,[3] Samer Srour,[2] David Partlow,[1] Richard E. Champlin,[2] and Kai Cao[1]

Impact of eplet mismatched in 278 haploidentical HSCT





Zou J et al. – Blood Advances, 2019

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Eplets mismatched

Published in final edited form as:
Transplant Cell Ther. 2022 February ; 28(2): 107.e1–107.e8. doi:10.1016/j.jtct.2021.11.001.

Number of HLA-Mismatched Eplets Is Not Associated with Major Outcomes in Haploidentical Transplantation with Post-Transplantation Cyclophosphamide: A Center for International Blood and Marrow Transplant Research Study

Jun Zou[1,*], Tao Wang[2,3], Meilun He[4], Yung-Tsi Bolon[4], Shahinaz M. Gadalla[5], Steven G.E. Marsh[6,7], Michelle Kuxhausen[4], Robert Peter Gale[8], Akshay Sharma[9], Amer Assal[10], Tim Prestidge[11], Mahmoud Aljurf[12], Jan Cerny[13], Sophie Paczesny[14], Stephen R. Spellman[4], Stephanie J. Lee[15,16], Stefan O. Ciurea[17]

Because this study **failed to demonstrate** the predictive value of ME from HLA molecules for clinical outcomes**, other molecular mismatch algorithms in haplo-HSCT settings should be tested.**

Zou J et al. – Transplant Cell Ther, 2022

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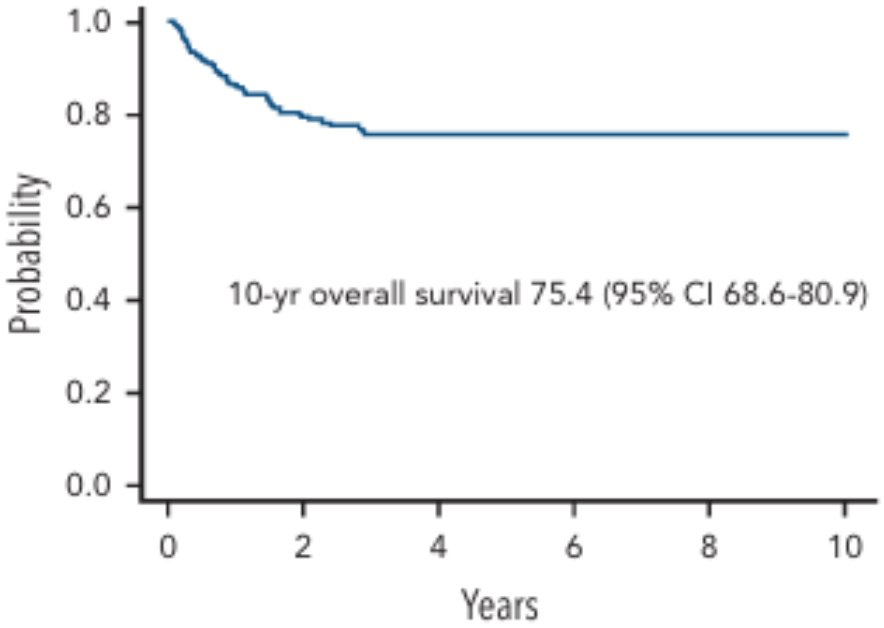
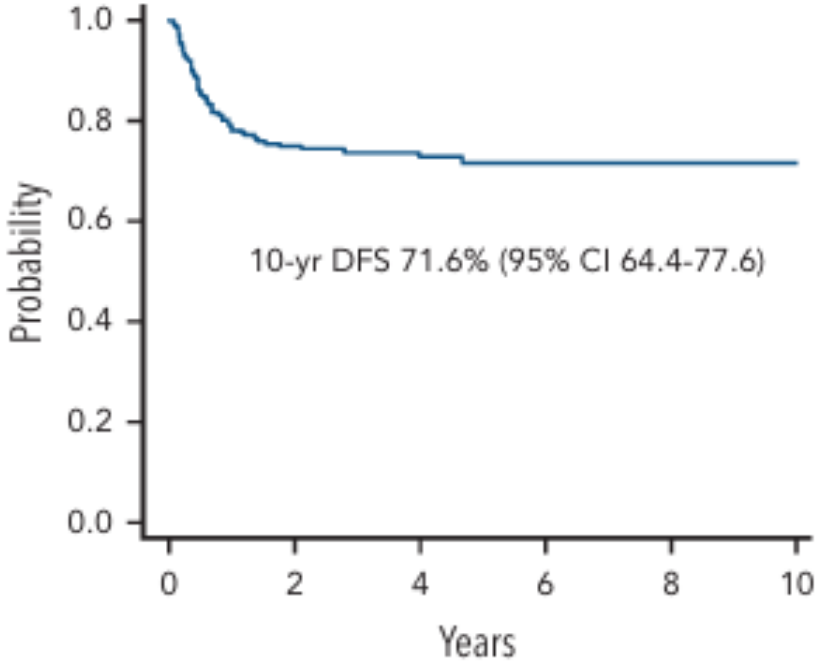
TCRαβ/CD19 cell–depleted HLA-haploidentical transplantation to treat pediatric acute leukemia: analysis on a cohort of 213 children





Merli P. et al - 2024 Blood

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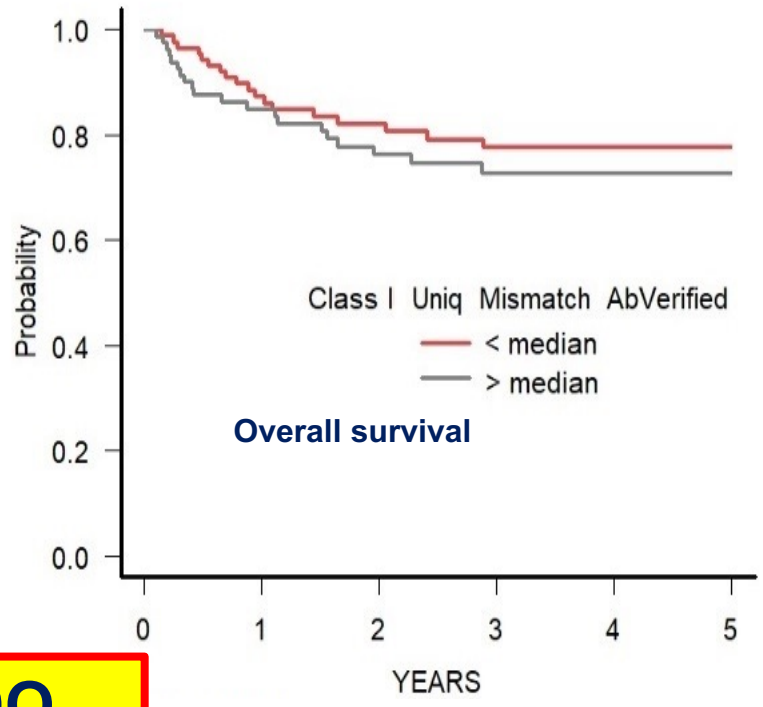
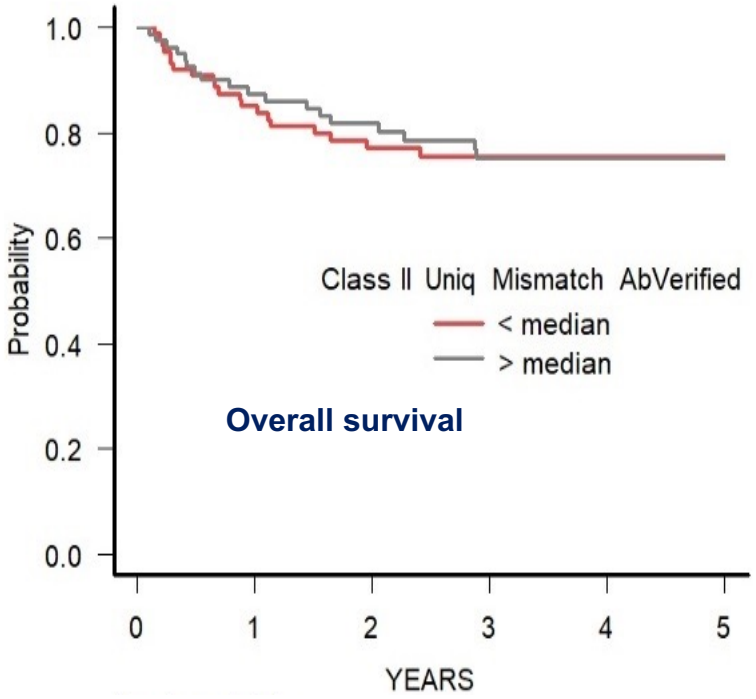
Eplets mismatched

Our experience in OPBG in a group of pediatric patients after haploidentical HSCT





PLEASE, DO NOT POST

Merli P, Crivello P., Andreani M., Fleishhauer K. and. Locatelli F. (Manuscript in preparation)

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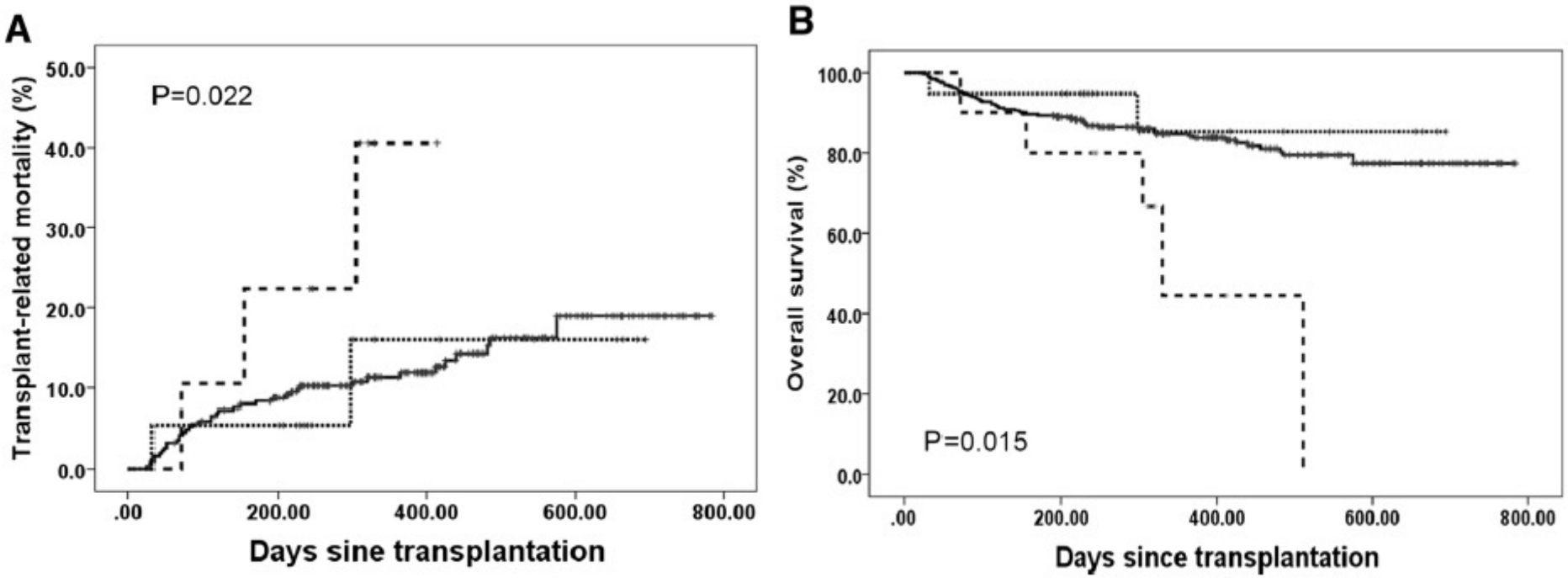
How should the presence of anti-HLA antibodies in the recipient influence donor selection?

Haploidentical HSCT and donor-specific anti-HLA antibodies (DSA)



- (n = 316, solid line) DSA negative and those with a DSA MFI <2000
- (n = 19, dotted line) DSA with 2000 ≤ MFI < 10,000
- (n = 10, dashed line) DSA with a MFI ≥10,000

Chang YJ - J Hematol Oncol. 2015

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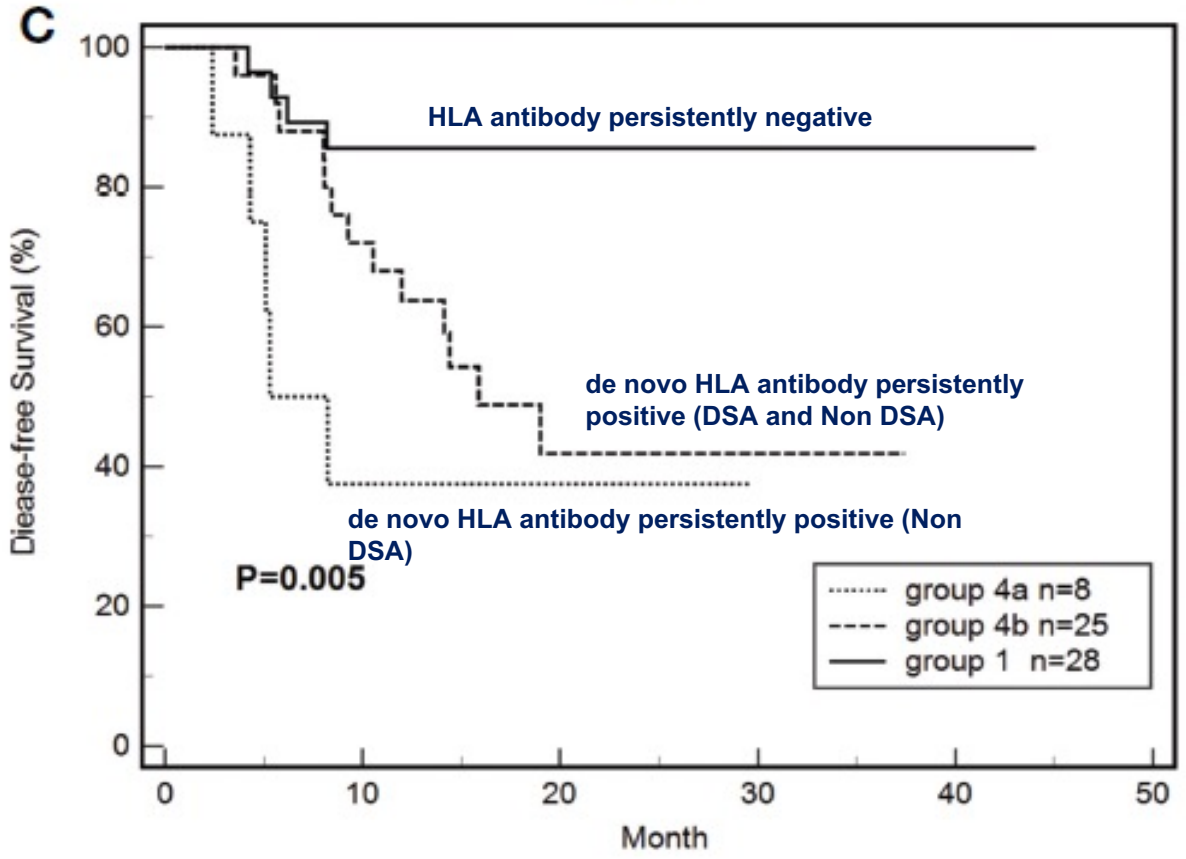
Haploidentical HSCT and donor-specific anti-HLA antibodies (DSA)

116 AML, ALL and MDS patients who were negative for pre-existing HLA antibodies



Wang L - 2022 - Frontiers in Immunology

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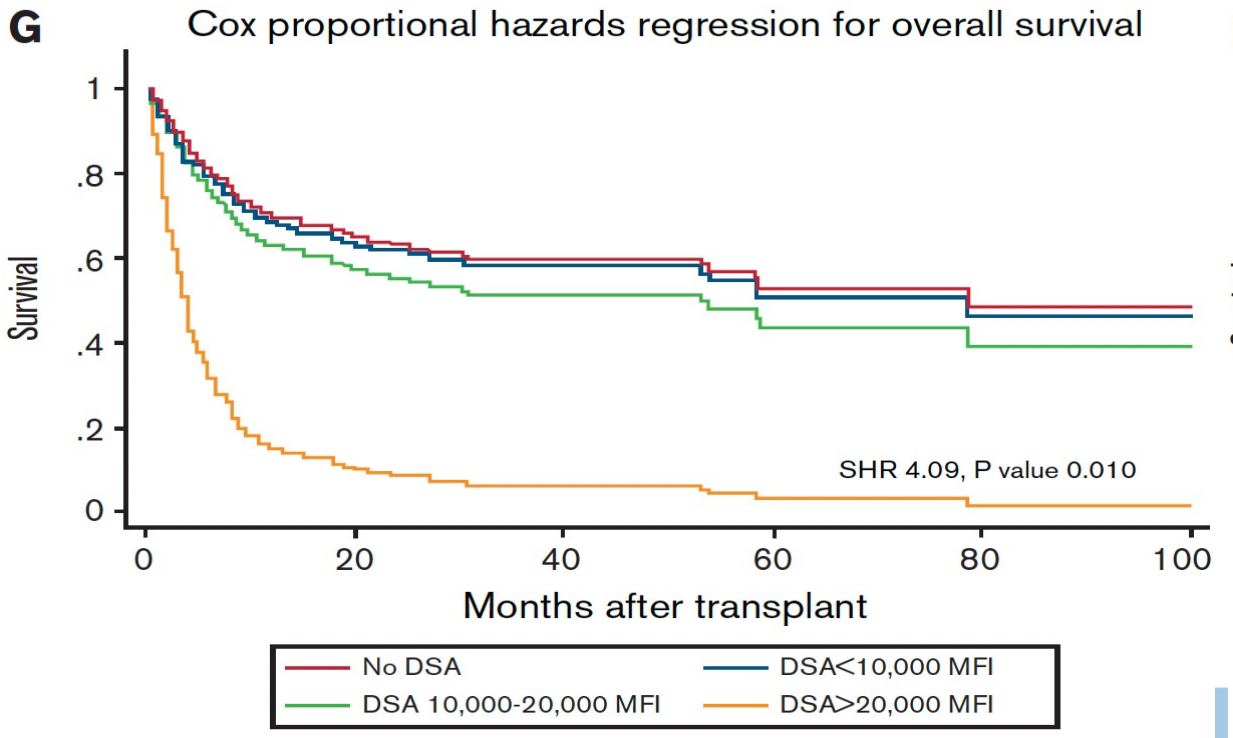
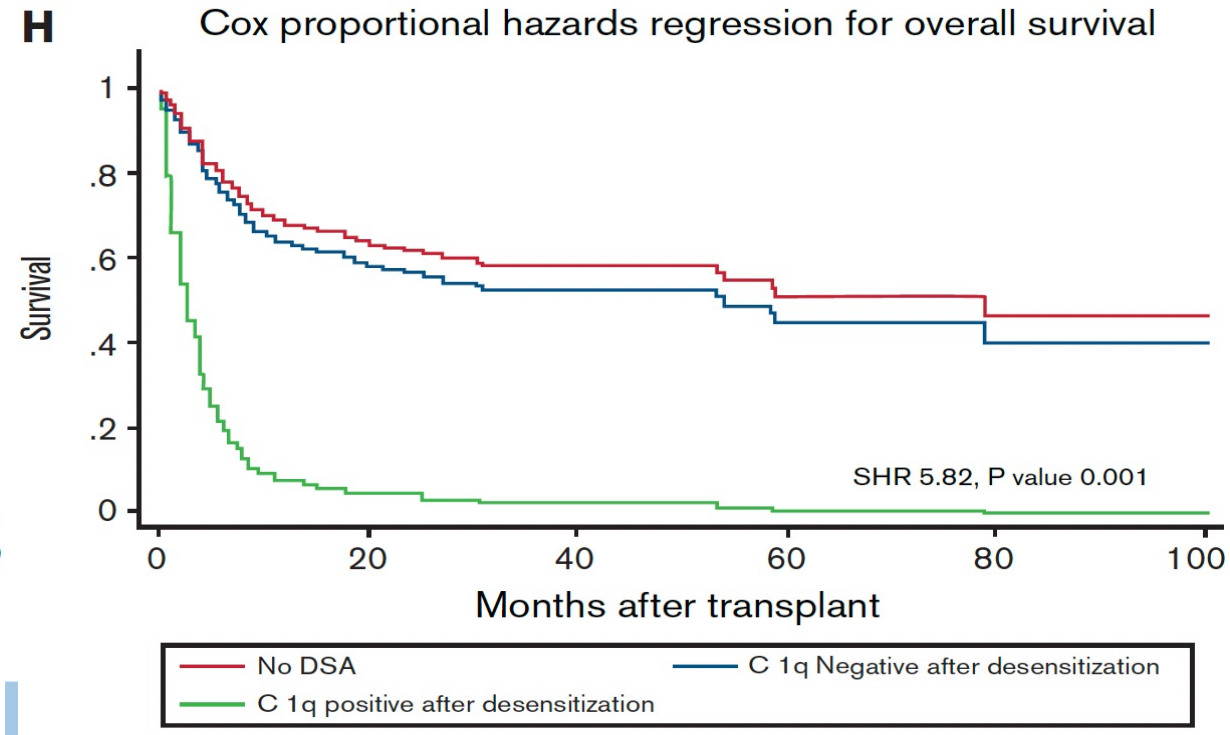
Haploidentical HSCT and donor-specific anti-HLA antibodies (DSA)

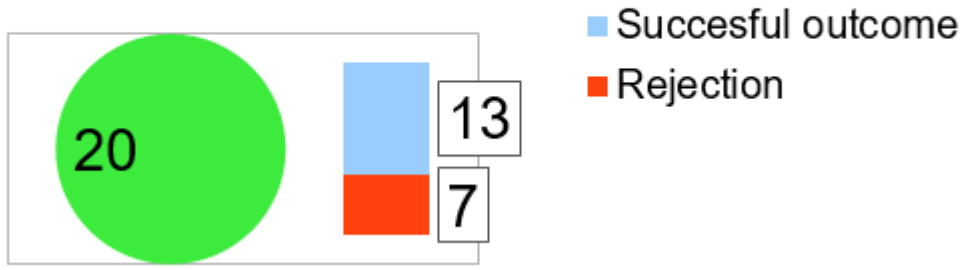
37 patients affected by malignancies with DSA were treated with a desensitization protocol before haplo-HSCT and compared with a group of 345 patients with no DSA

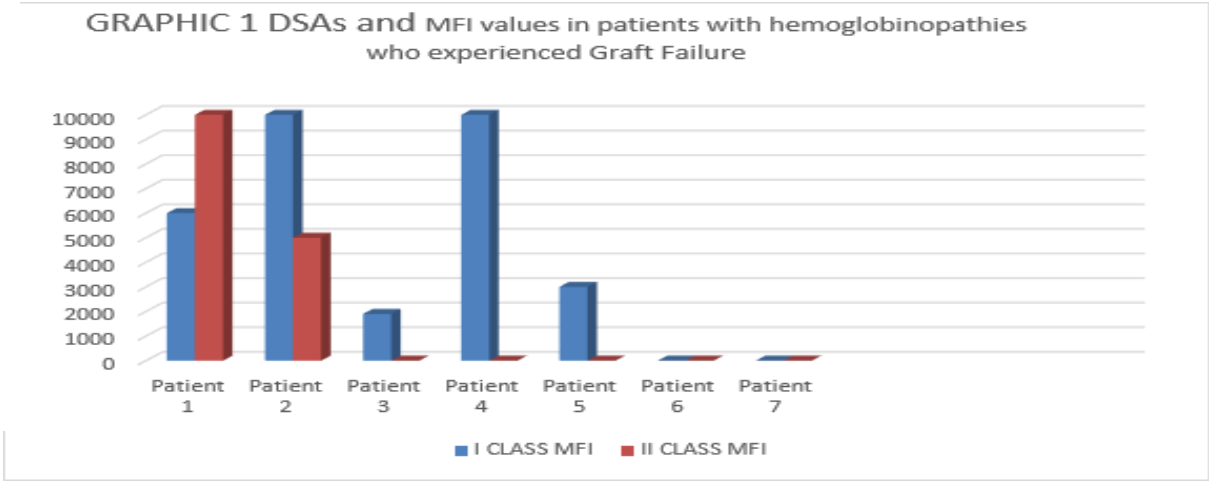




Haploidentical HSCT and donor-specific anti-HLA antibodies (DSA)

Rejection in 20 patients affected by hemoglobinopathies





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New EBMT recommendations

Title: HLA matching in contemporary haematopoietic cell transplantation: recommendations from the EBMT Practice Harmonisation and Guidelines Committee

Esteban Arrieta-Bolaños[1], Alberto Cardoso Martins Lima[2], Marco Andreani[3], Dianne De Santis[4], Florent Malard[5], Neema P. Mayor[6,7], Rohtesh S. Mehta[8], Roland Meisel[9], Simona Pagliuca[10], Effie Petersdorf[11], Simona Piemontese[12], Nicoletta Sacchi[13], Nicole Santoro[14], Jaime Sanz[15], Johannes Schetelig[16,17], Stephen R. Spellman[18], Francesco Onida[19], Isabel Sánchez-Ortega[20], Mohamad Mohty[5] Ibrahim Yakoub-Agha[21], Katharina Fleischhauer[1*], Annalisa Ruggeri[12, 22*]

Submitted to BMT

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Conclusions

- HLA compatibility, with 10/10 is better than 9/10
- Use of PTCy increases the probability of higher overall survival in MUD
- Still debating the importance of HLA matching in MUD after the use of PTCy
- Differences in the PBM need to be considered
- Role of eplet matching after haploidentical HSCT needs to be further investigated
- Presence of anti-HLA antibodies (DSA) and C1q is detrimental in haploidentical HSCT settings
- Use of artificial intelligence will probably help in the choice of the best donor for each patients

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Francesca Besi

Many thanks for the attention

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