

BMT MASTER CLASS

DONOR SELECTION beyond HLA

Dr Neeraj Sidharthan MD DNB DM

Professor and Head

Department of Clinical Haematology, Transplant and Cellular Therapy

Amrita Institute of Medical Sciences ,Kochi , India

Patient Scenario

A 32-year-old man with **AML with intermediate-risk Cytogenetics** achieved CR1 after standard 7+3 induction and HiDAC consolidation.

He **relapsed 9 months later** and achieved **CR2 after FLAG-IDA**.

He is planned for **allogeneic HSCT in CR2**.

HLA typing shows **no fully matched sibling donor**.

Four potential donors are available:

Patient Scenario

Option A

- **28-year-old HLA-matched unrelated donor (10/10)**
- **Female, multiparous (2 pregnancies)**
- **CMV seropositive**
- **Donor availability in 10–12 weeks**

Patient Scenario

Option B

- 55-year-old **haploidentical father**
- Male
- CMV seropositive
- No significant comorbidities
- Immediate availability

Patient Scenario

Option C

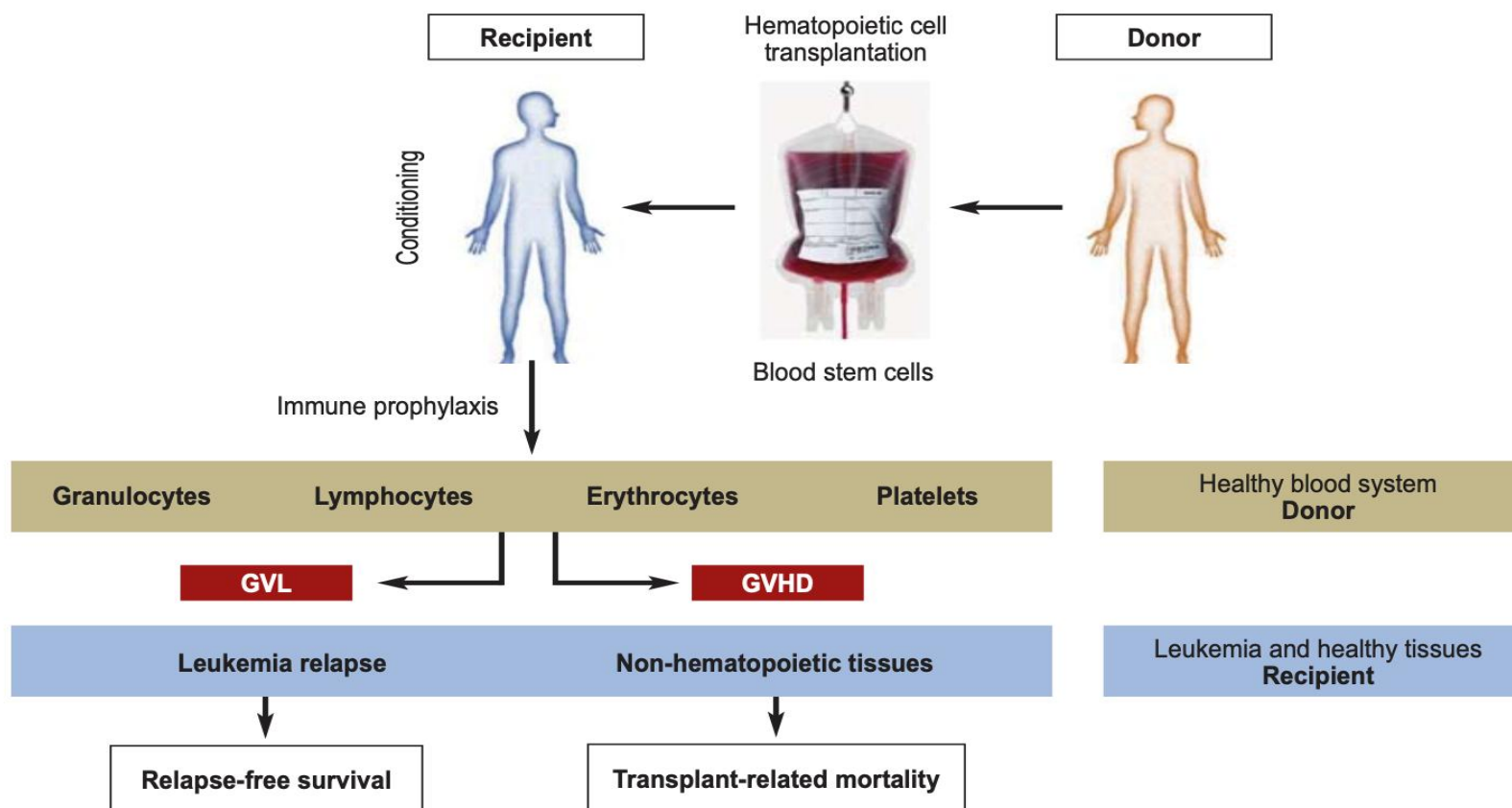
- 24-year-old **haploidentical younger brother**
- Male
- CMV seronegative
- **KIR B haplotype**, favorable NK alloreactivity
- ABO major mismatch
- Immediately available

Patient Scenario

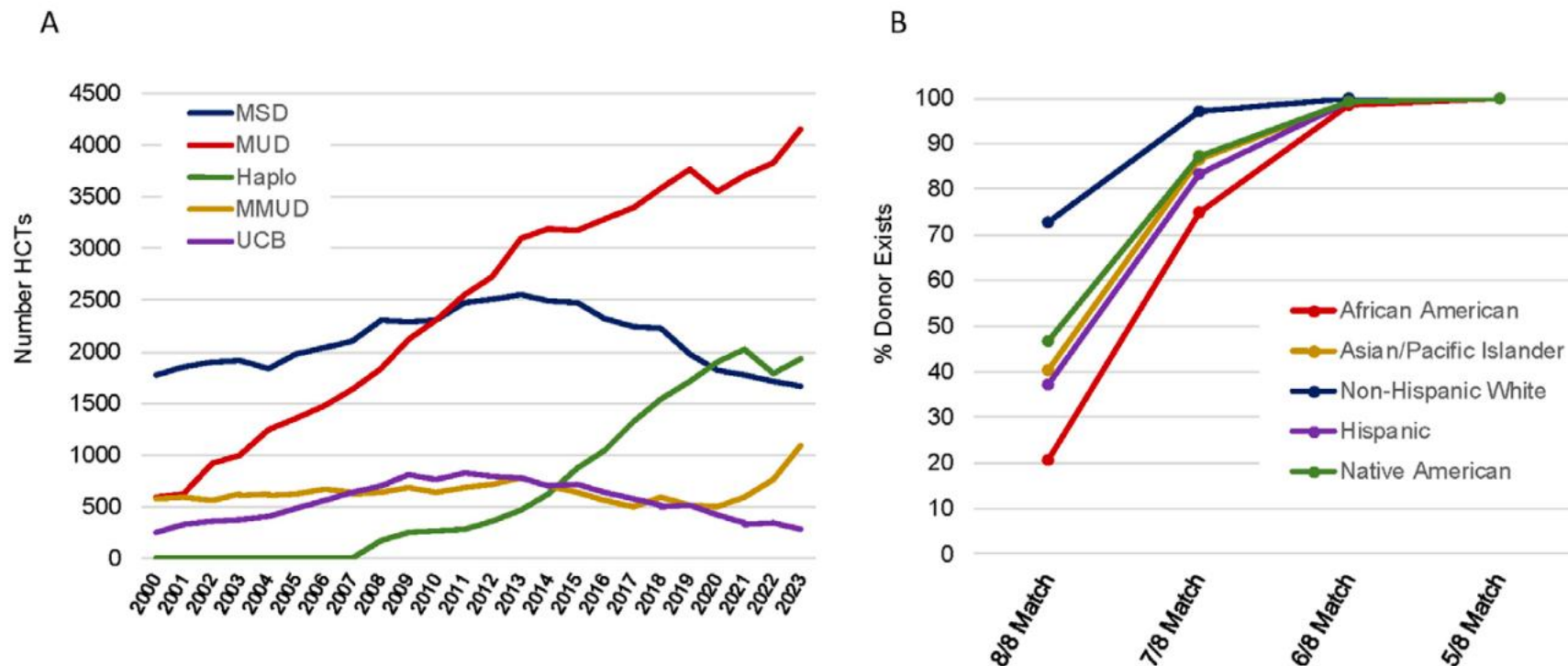
Option D

- 35-year-old **9/10 mismatched unrelated donor** (single DR mismatch)
- Male
- CMV seropositive
- Donor available in **4–5 weeks**

Donor selection for allogeneic hematopoietic cell transplantation. Dtsch Arztebl Int 2023; 120: 261–8. DOI: 10.3238/arztebl.m2023.0031



HLA mismatched transplants are rising



— · · A.M. Jimenez Jimenez et al. / Transplantation and Cellular Therapy 31 (2025) 973–988

NON HLA factors

Secondary Characteristic Considerations:

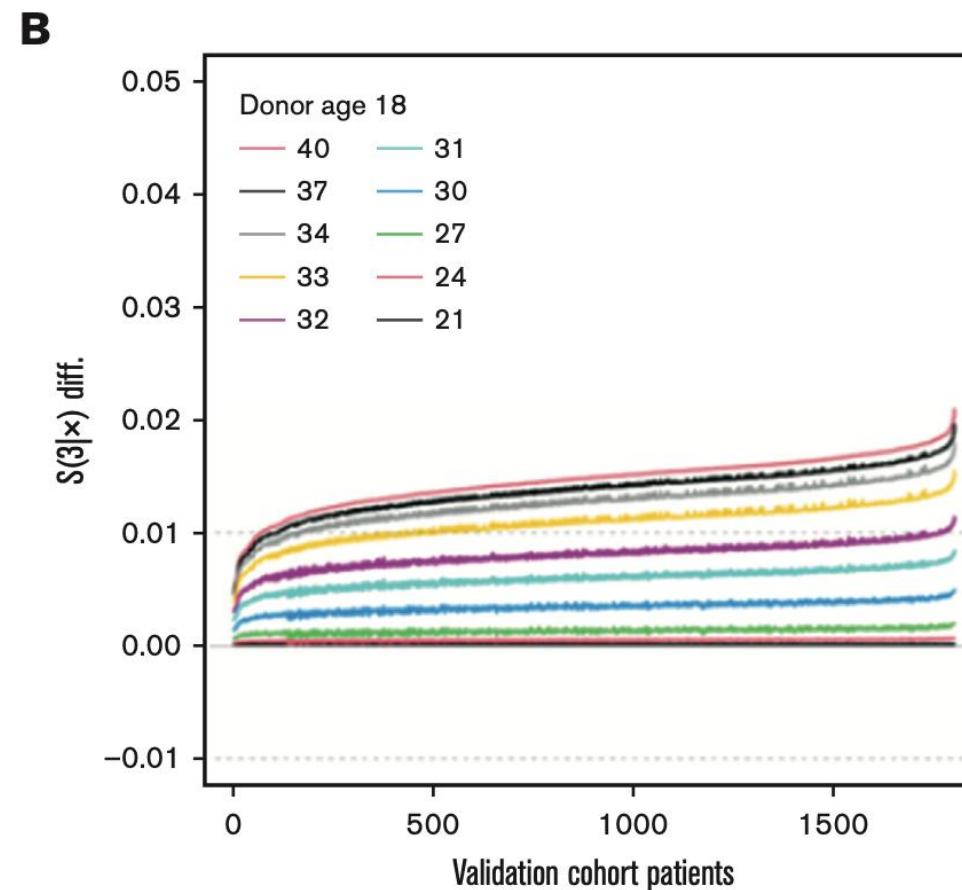
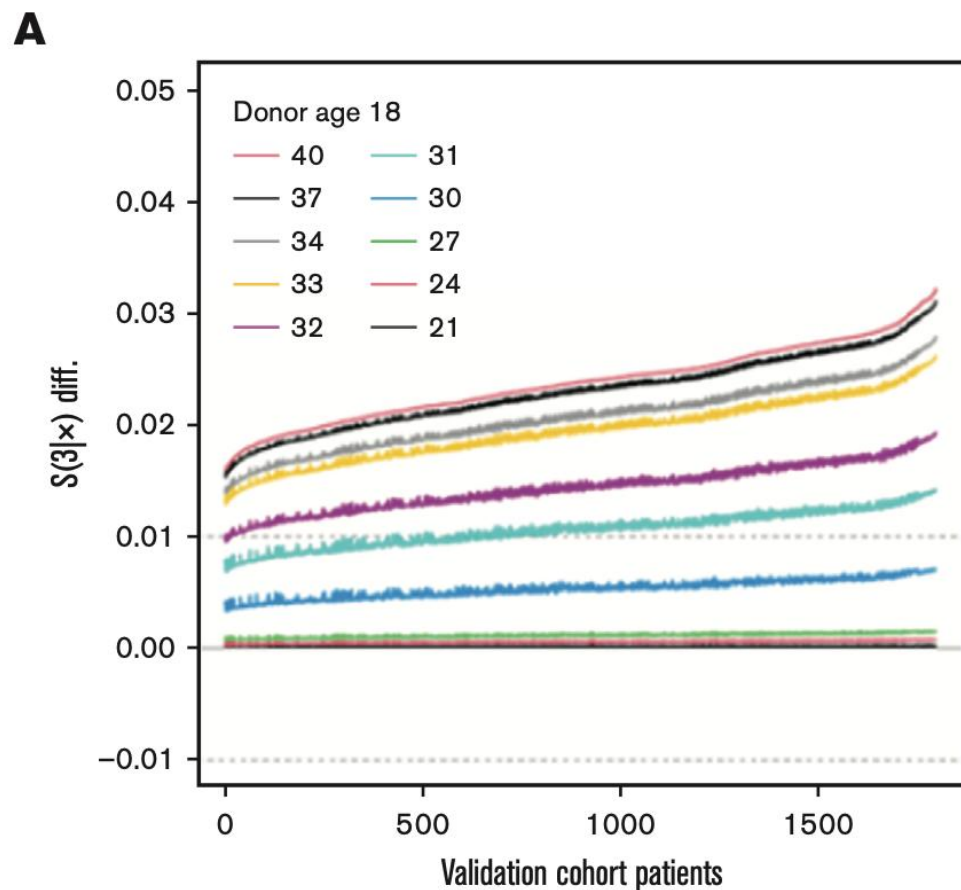
Recommendation	Evidence Level	References
<p>Donor age:</p> <ul style="list-style-type: none"> • Donors ≤ 30 years old should be prioritized to maximize OS. <p>Donor CMV, ABO, and sex:</p> <ul style="list-style-type: none"> • Donor/recipient ABO matching may reduce post HCT transfusion burden. • Major ABO mismatches should be avoided in haplo and when using BM grafts. • Donor CMV serostatus may be considered in specific clinical cases (e.g., SCID) <p>Donor weight:</p> <ul style="list-style-type: none"> • A large patient-donor weight discrepancy should be avoided in the setting of BM HCT. 	<p>+++ ++ ++ + +++</p>	<p>Dehn et al. [1] Ciurea et al. [39] Kollman et al. [61] Spellman et al. [68] Mehta et al. [69] Anthias et al. [88] Sanz et al. [94] Murthy et al. [98]</p>

A.M. Jimenez Jimenez et al. / Transplantation and Cellular Therapy 31 (2025) 973–988

Miles Apart, Hearts Together



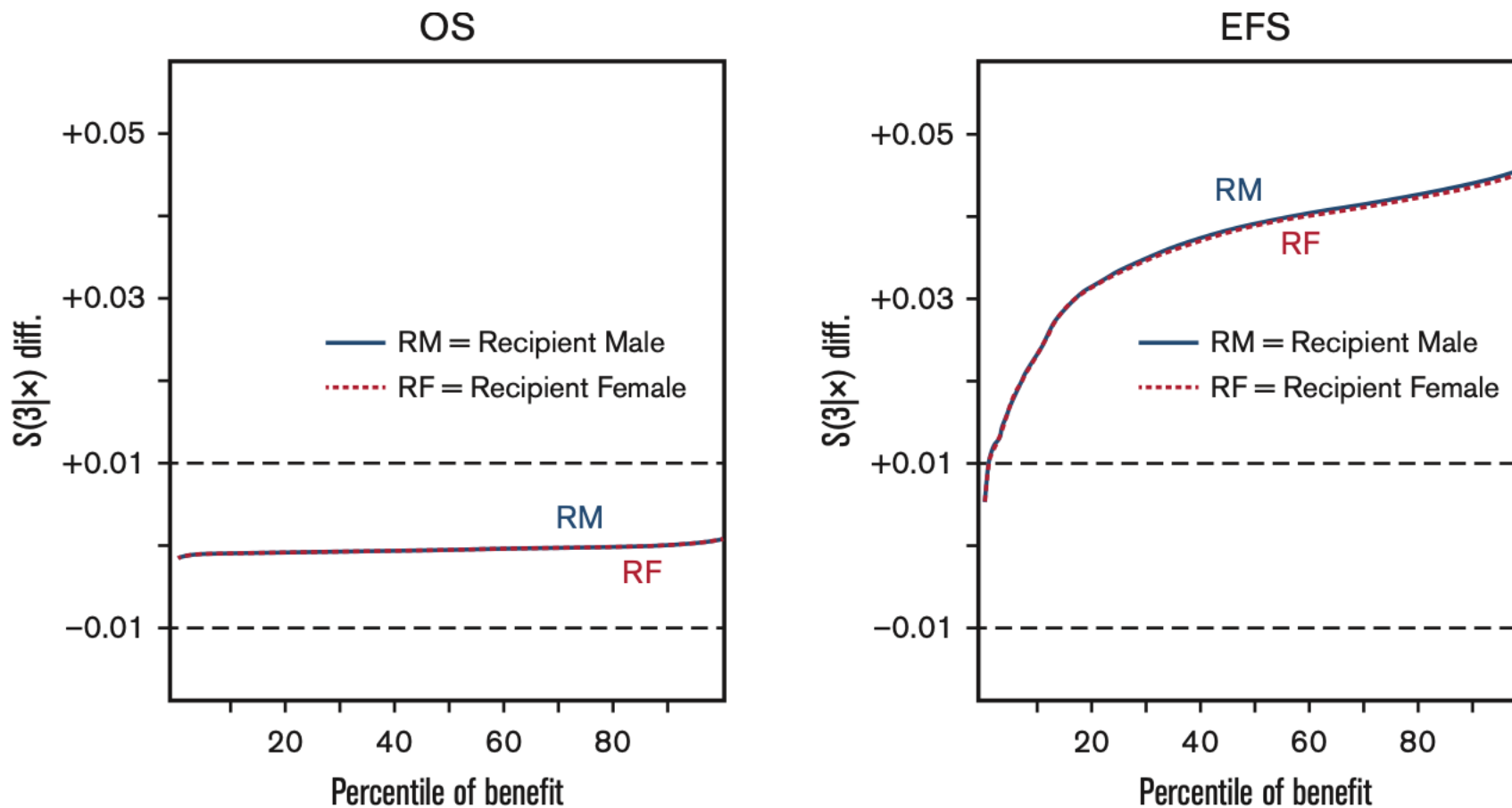
Donor Age- 18- 30 seem best



Donor Age- 18- 30 seem best

- Less acute and chronic GVHD
- Decreased Non Relapse Mortality
- Improved overall survival

Donor Gender- Male donor has EFS benefit



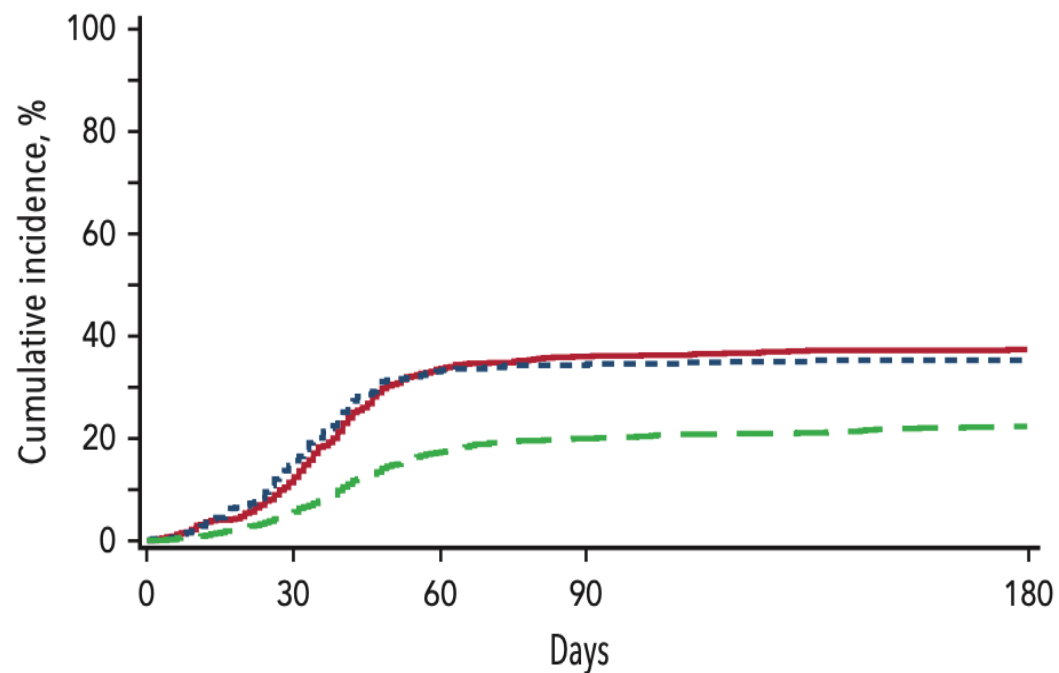
Donor Gender- Male donor has EFS benefit

- Female – Male transplants associated with Higher chronic GVHD
- Due to H- Y antigen sensitization

Parity

- Multiparous female donors – higher alloimmunization risk
- Nulliparous females are preferable if female donor is unavoidable

CMV status --



	N at Risk				
	0	30	60	90	180
— Haplo CY	755	632	438	402	345
- - - Sib CY	402	333	244	231	200
- - - Sib CNI	1603	1500	1282	1199	1046

CMV status

- CMV mismatch D+/R-
- Increased CMV disease
- Increased NRM
- Less critical with letermovir prophylaxis , but still relevant

ABO group and compatibility

- Major mismatch (O d ---- A r)
- --- Delayed RBC engraftment . Pure red cell Aplasia
- Minor mismatch – Passenger Lymphocyte syndrome
- Bidirectional mismatch --- Highest risk

Donor weight

- Important for PBSC grafts
- Adult recipient getting marrow from paediatric donor
- Target CD 34 dose – 4-5 million/kg of recipient weight

Donor Health and comorbidities

- Exclude donors with HBV HCV HIV active infections
- Autoimmune diseases are relative contraindications
- IBMFS – even if asymptomatic but having pathogenic mutation

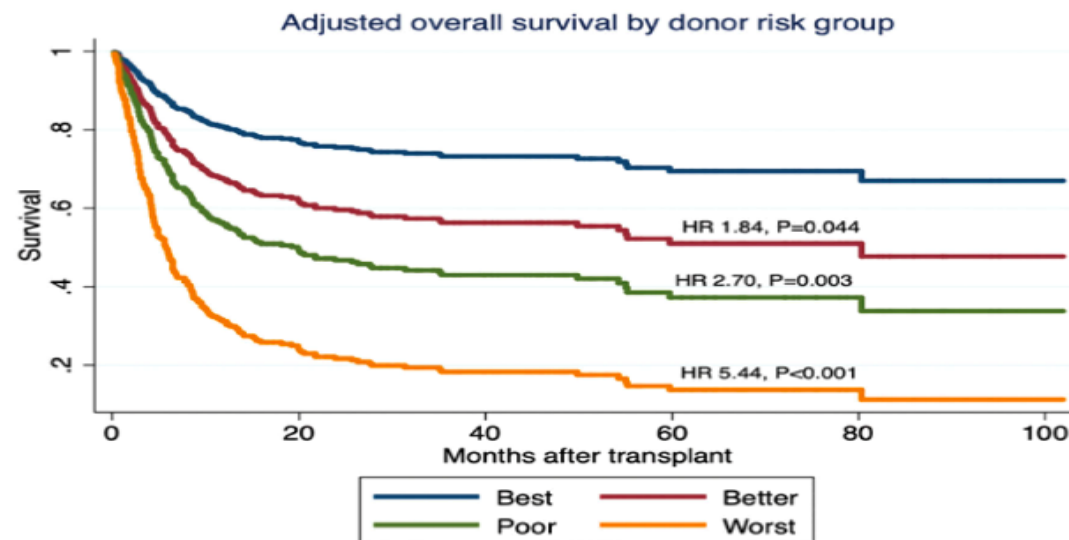
Non Inherited Maternal Antigens

- Relevant in Haplo BMT
- Maternal donors or siblings sharing NIMA – Decreased GVHD and increased tolerance
- Evidence strongest in PTCy platforms – T cell replete

Killer Immunoglobulin like Receptor Factors

- Relevant mainly in AML , Haploidentical or mismatched transplants
- Favourable features-
 - KIR ligand mismatch in GVH direction
 - Donor with KIR B haplotype
- Effects : decrease relapse in AML
- Possibly via increased NK cell mediated graft versus leukemia effect

Donor selection for KIR alloreactivity is associated with superior survival in haploidentical transplant with PTCy



Donor age <58

Recipient CMV

seronegative

Front. Immunol. 13:1033871.
doi: 10.3389/fimmu.2022.1033871

Calculating KIR alloreactivity

- **Step 1 — Identify Donor Inhibitory KIRs**
- Relevant inhibitory KIRs:
- **KIR2DL1** → ligand: **HLA-C2**
- **KIR2DL2 / KIR2DL3** → ligand: **HLA-C1**
- **KIR3DL1** → ligand: **HLA-Bw4**

Calculating KIR alloreactivity

- **Step 2 — Identify Recipient HLA Ligand Groups**
- Categorize based on high-resolution HLA:
- **C1 group:** HLA-C alleles with Asparagine at position 80
- **C2 group:** HLA-C alleles with Lysine at position 80
- **Bw4 epitope:** subclass of HLA-B alleles (and some HLA-A alleles)
-

Calculating KIR alloreactivity

- **Step 3 — Apply the Missing-Ligand Formula**
- For each inhibitory KIR:
- KIR-X alloreactivity

$$= \begin{cases} 1 & \text{if donor has KIR-X AND recipient lacks its ligand} \\ 0 & \text{otherwise} \end{cases}$$
- Combine:
- **Total Alloreactivity Score** = $DL1 + DL2/3 + 3DL1$
- Interpretation:
- **0 = No KIR alloreactivity**
- **≥ 1 = Alloreactive donor**

Stem cell source

- PBSC – faster engraftment , Higher C/C GVHD
- Marrow – less c/c GVHD
- Cord blood – HLA mismatch tolerance and cell dose important

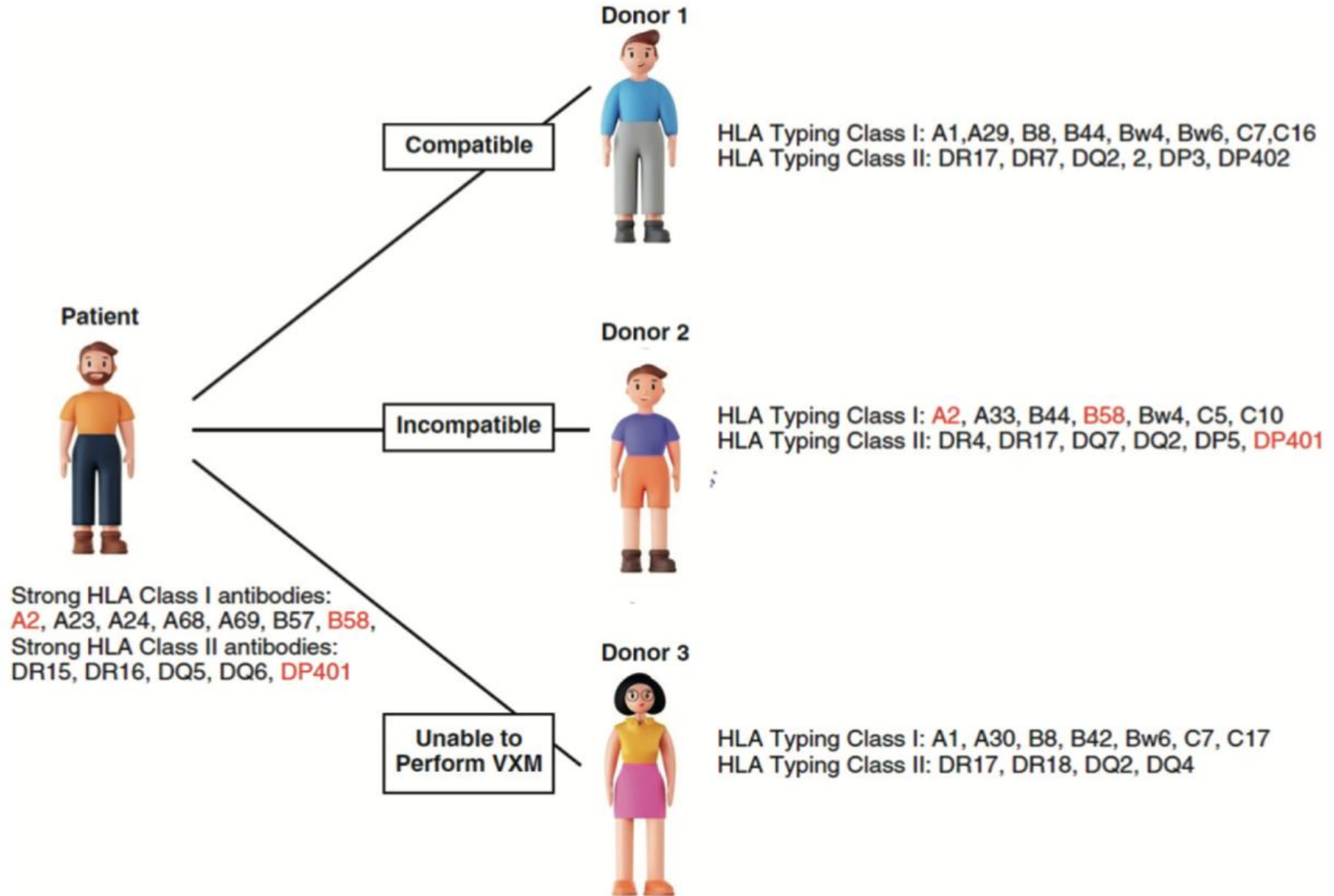
Stem cell source and dose

	Volume collected	Med CD34 content	Med CD3 content	Target cell dose
Bone marrow	10–20 mL/kg	$2-3 \times 10^6/\text{kg}^a$	$25 \times 10^6/\text{kg}$	$>2 \times 10^8 \text{ TNC}/\text{kg}$
Peripheral blood	150–400 mL	$8 \times 10^6/\text{kg}$	$250 \times 10^6/\text{kg}$	$5-10 \times 10^6 \text{ CD34}^+/\text{kg}$
Umbilical cord blood	80–160 mL	$0.2 \times 10^6/\text{kg}$	$2.5 \times 10^6/\text{kg}$	$>3 \times 10^7 \text{ TNC}/\text{kg}$

^aPer kilogram recipient body weight

Donor – Recipient Race /Ethnicity

- Minor Histocompatibility antigens
- Less relevant once a matched donor is identified

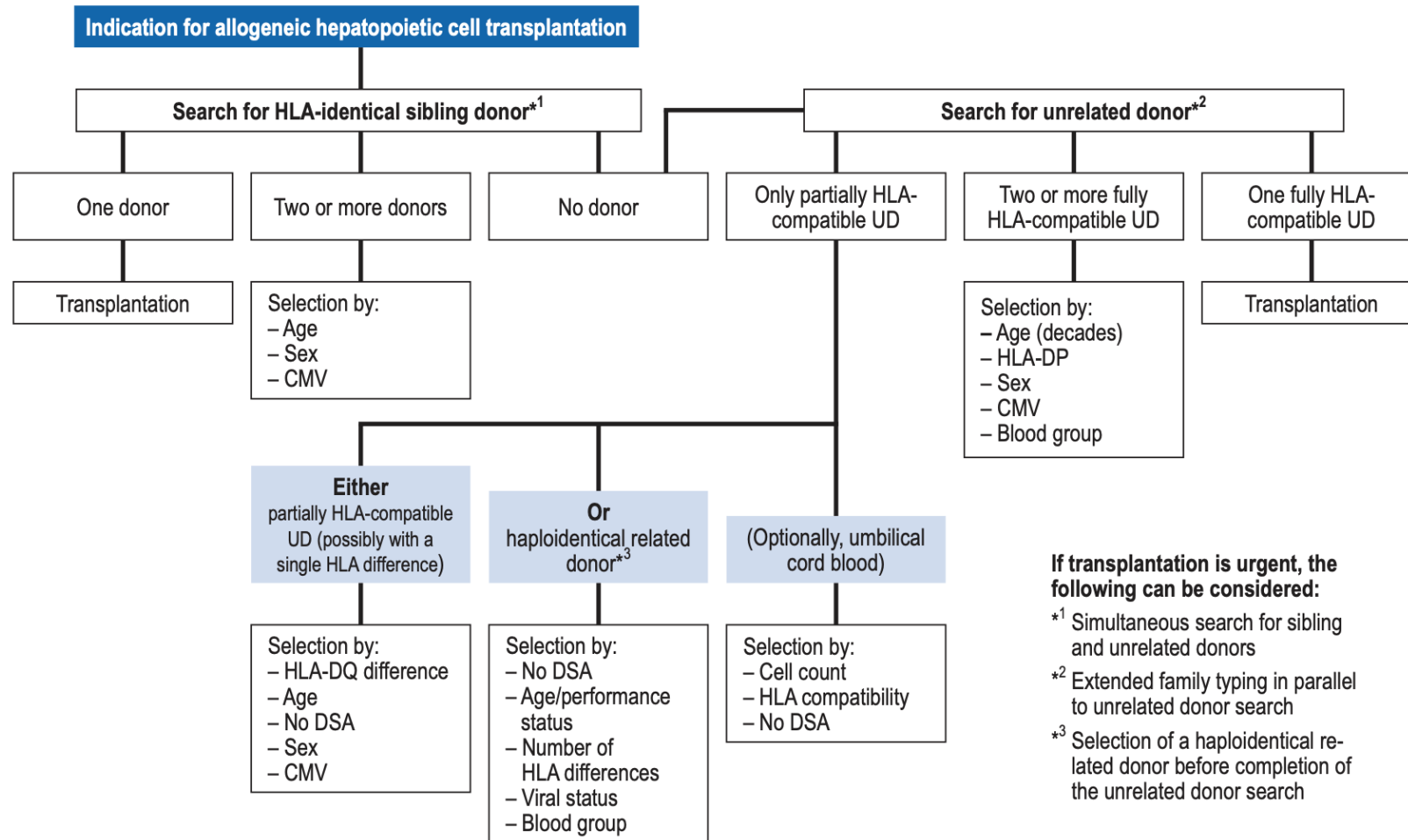


If donor change is feasible

- For very high MFI (>10,000/20,000) and/or persistent C1q+, a different donor usually outperforms any desensitization package.
Clinician checkpoint: Combine **antibody removal, production blockade**, and **time your checks**. Donor switch beats heroics when available.

GvHD Prophylaxis	PTCy		Conventional
Donor Types	Haploidentical	Unrelated	Unrelated
Latest consensus recommendation or guideline	EBMT 2020 [10]	Not published	NMDP/CIBMTR 2019 [7]
HLA factors			
Donor-specific antibody	Risk [26]	Risk	Risk [24]
HLA mismatch degree	No impact [39–43]	No impact [46–48]	
Class I mismatch	Potential risk HLA-A [44,49]; HLA-C [41]	Potential risk [50]	Risk (HLA-A, B, C, DRB1) [4,6]
Class II mismatch	Potential benefit [41,44,45] No impact [39] Potential risk [43]	No impact [50]	
B-leader match	Potential benefit [41,49]	Insufficient data	Potential benefit [52]
Non-HLA factors			
Older donor	Risk [19,60–62,65–67]	Risk [65–67]	Risk [6,65–67]
Offspring/sibling vs. parent	Offspring/sibling is better [45,60,63,64]	Not applicable	Not applicable
Father vs. mother	Father better [69,70] No difference [39,60]	Not applicable	Not applicable
NIMA-M vs. NIPA-M	Potential benefit of NIMA-M [49]	Not applicable	Not applicable
Female-to-Male	Potential risk [40,41,43,63] No impact [41,42,60]	No impact [48]	No impact [6]
Donor CMV serostatus	No impact [64,76,77]	Insufficient data	No impact [6]
ABO match	No impact [39,45,64]	Insufficient data	No impact [6]

Shike, H.; Zhang, A. HLA and Non-HLA Factors for Donor Selection in Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide GvHD Prophylaxis. *Cells* **2024**, *13*, 2067. <https://doi.org/10.3390/cells13242067>



Donor selection for allogeneic hematopoietic cell transplantation. Dtsch Arztebl Int 2023; 120: 261–8. DOI: 10.3238/arztebl.m2023.0031

Donor Options

Option A

- 28-year-old **HLA-matched unrelated donor (10/10)**
- Female, **multiparous (2 pregnancies)**
- CMV seropositive
- Donor availability in **10–12 weeks**

Option C

- 24-year-old **haploidentical younger brother**
- Male
- CMV seronegative
- **KIR B haplotype**, favorable NK alloreactivity
- ABO major mismatch
- Immediately available

Option B

- 55-year-old **haploidentical father**
- Male
- CMV seropositive
- No significant comorbidities
- Immediate availability

Option D

- 35-year-old **9/10 mismatched unrelated donor** (single DR mismatch)
- Male
- CMV seropositive
- Donor available in **4–5 weeks**

**Thank
you**

