Höhepunkte des Europäischen Kongresses für Stammzelltransplantation und Zelltherapie EBMT 2026

Tim Flaadt, Kinderklinik Abt. 1

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REGISTRY-BASED, PAIR-MATCHED ANALYSIS COMPARING A/B T-/CD19-CELL DEPLETION AND POST-TRANSPLANT CYCLOPHOSPHAMIDE IN HLA-HAPLOIDENTICAL HSCT FOR CHILDREN WITH ACUTE LEUKEMIA: AN EBMT PDWP STUDY

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Study background and rationale

- HLA-haploidentical stem cell transplantation (haplo-HSCT) has emerged as a suitable alternative for pediatric patients with acute leukemia (AL) when a HLA-matched donor is unavailable;
- The two most employed approaches for T-cell depletion/modulation are:

✓ *in vitro* selective depletion of CD3+ T-cell receptor (TCR)αβ/CD19+ (TCRαβ) lymphocytes from peripheral blood stem cells **(TCR αβ-HSCT)**
✓ *in vivo* depletion of alloreactive T cells in unmanipulated grafts using post-transplant cyclophosphamide **(PTCY-HSCT)**

- No large comparative study focused on these two platforms in children with AL given haplo-HSCT has been conducted so far;

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Study design and population

Aim: to compare the leukemia-free survival (LFS) and other outcomes between TCR αβ and PTCY approaches in pediatric haplo-HSCT recipients treated in EBMT centers.

Retrospective, multicentric, registry-based study on behalf of the EBMT Pediatric Disease Working Party

Inclusion criteria

- First allogeneic HSCT for ALL or AML
- Age at HSCT<18 ys
- Haploidentical related donor with αβ-TCD or PTCY as T-cell depletion approach
- Year of HSCT: January 2010-December 2022

Exclusion criteria

- Haplo-HSCT with a T-cell depletion strategy other than αβ-TCD or PTCY
- Graft from multiple donors
- Haplo-HSCT as a second allograft

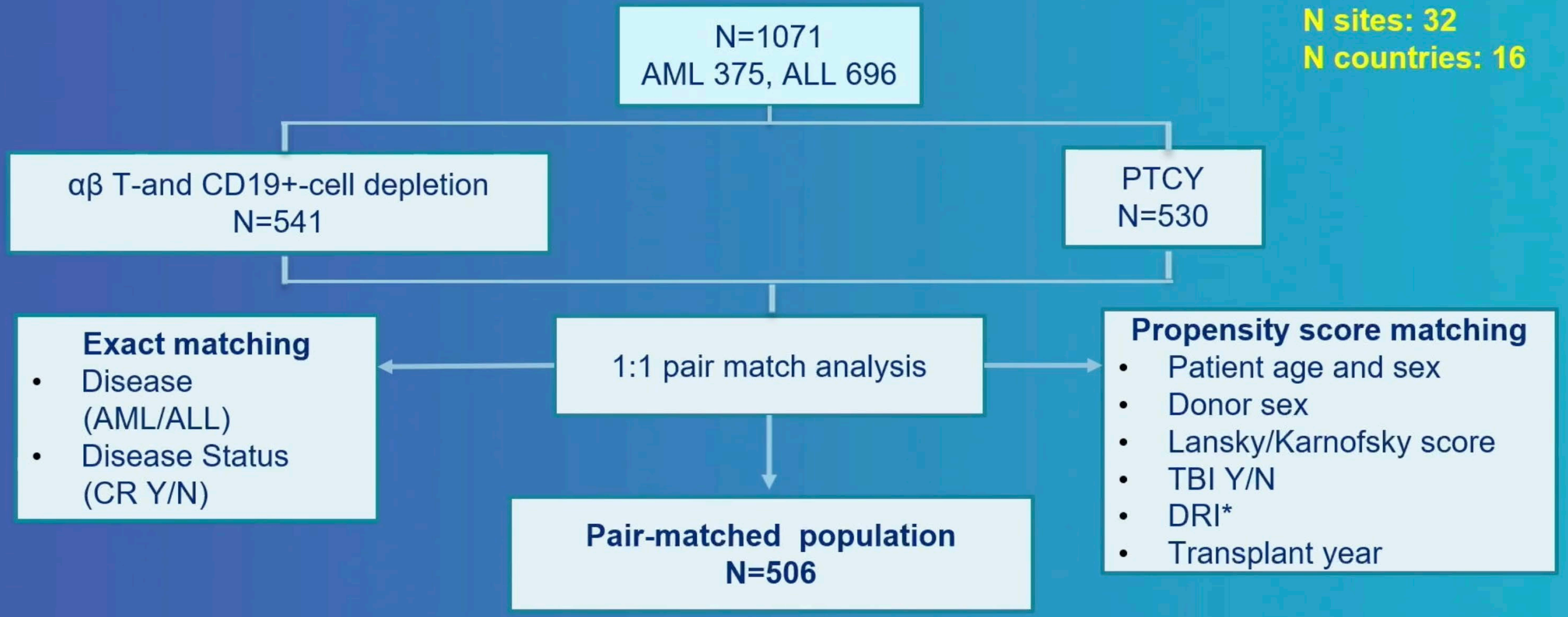
Primary objective

To compare the 4-year leukemia-free survival (LFS)

Main secondary objective

- 4-y overall survival (OS)
- 4-y GvHD-free/relapse-free survival (GRFS)
- 4-y cumulative incidence of relapse (CIR)
- 4-y cumulative incidence of non-relapse mortality (NRM)
- Time to neutrophil and platelet recovery
- Incidence and severity of acute GvHD (aGvHD)
- Incidence and severity of chronic GvHD (cGvHD

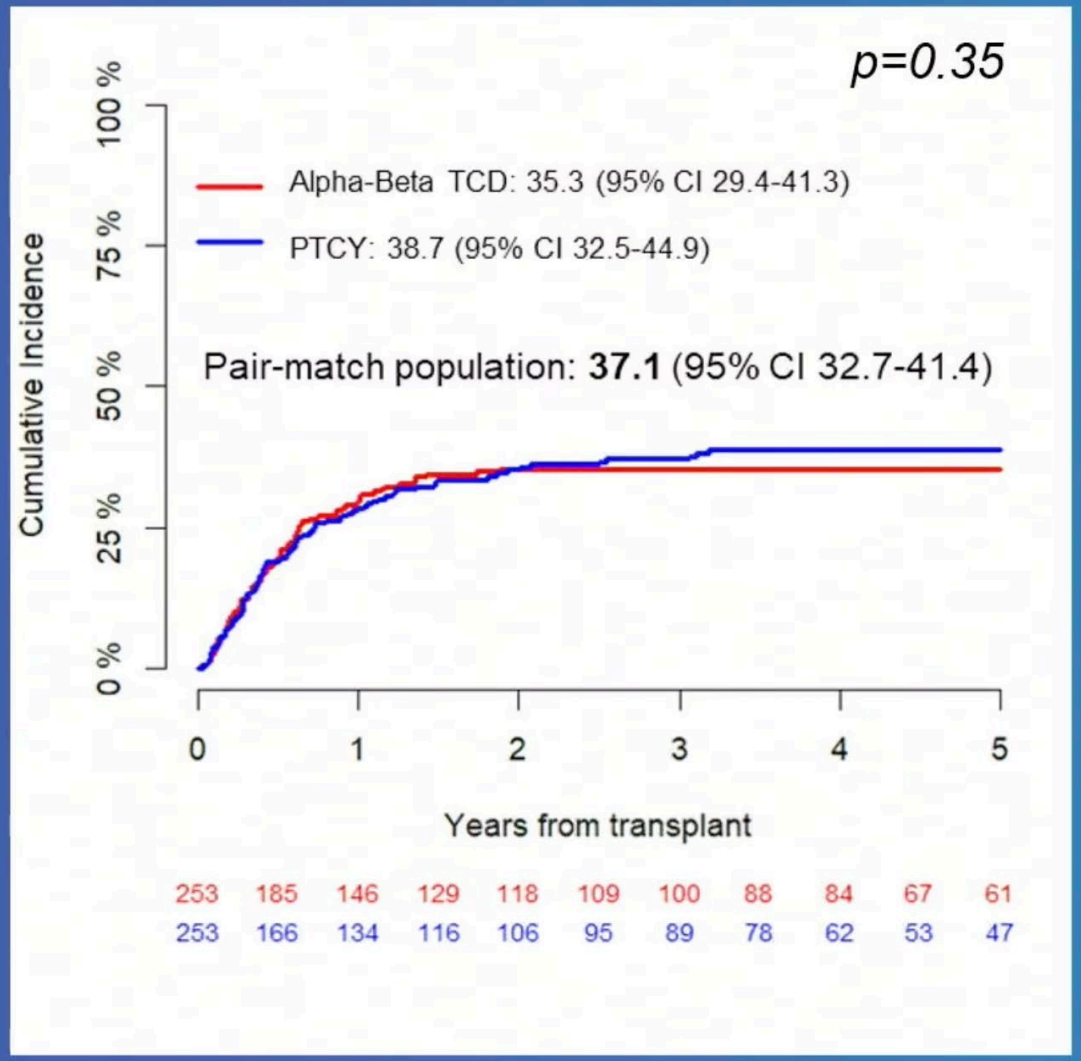
Patients and methods



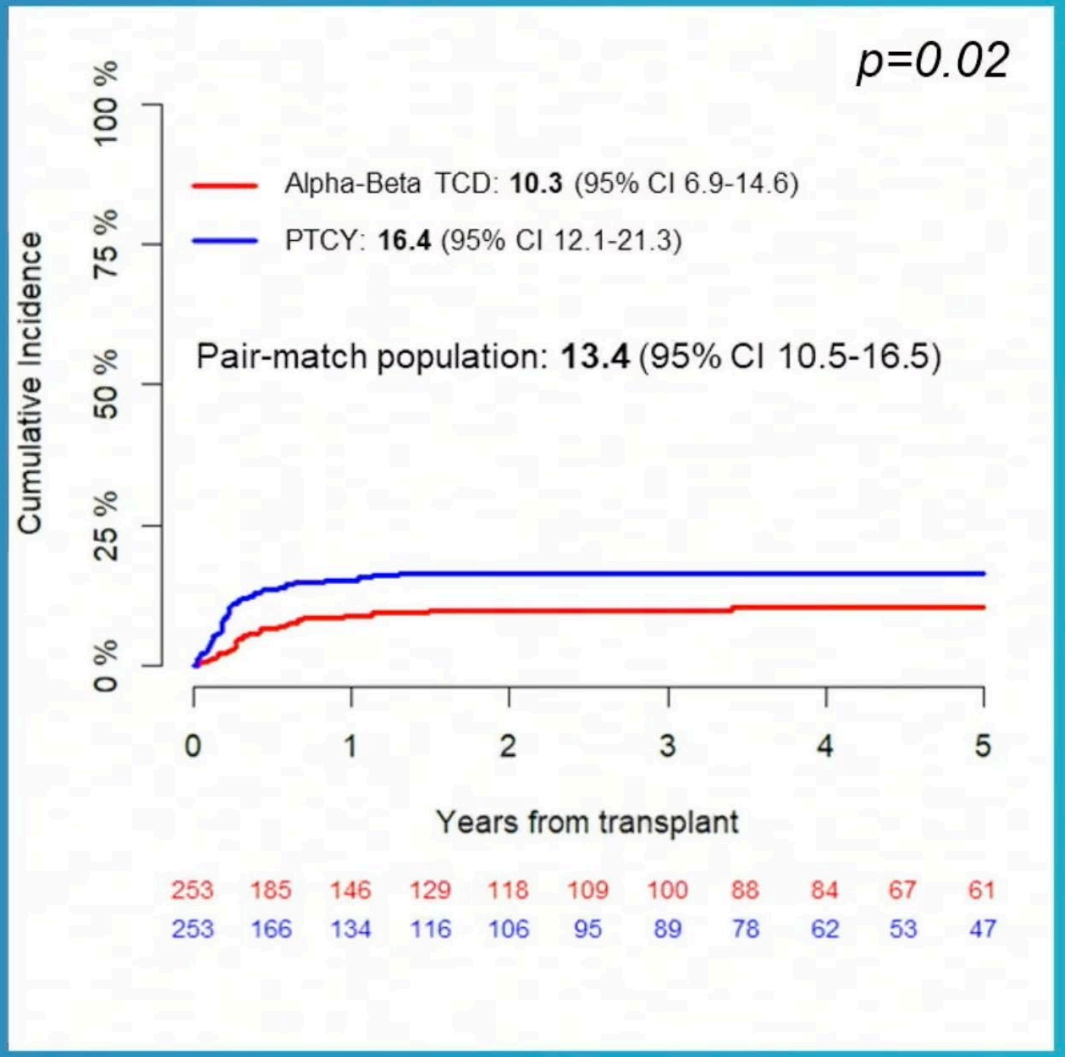
Disease Risk Index, (Armand P, Blood 2012)

Relapse and non-relapse mortality incidence

4-y relapse incidence

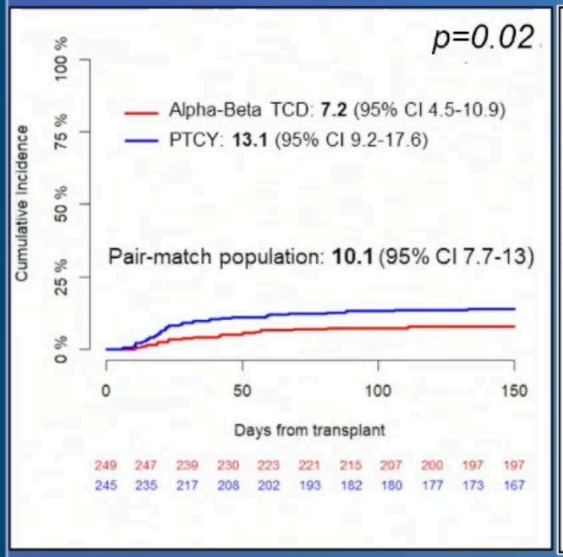


4-y non-relapse mortality

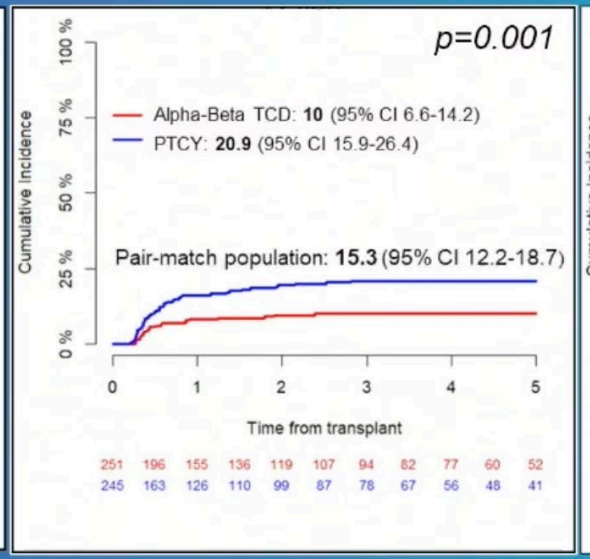


Acute, chronic and extensive-chronic GvHD incidence

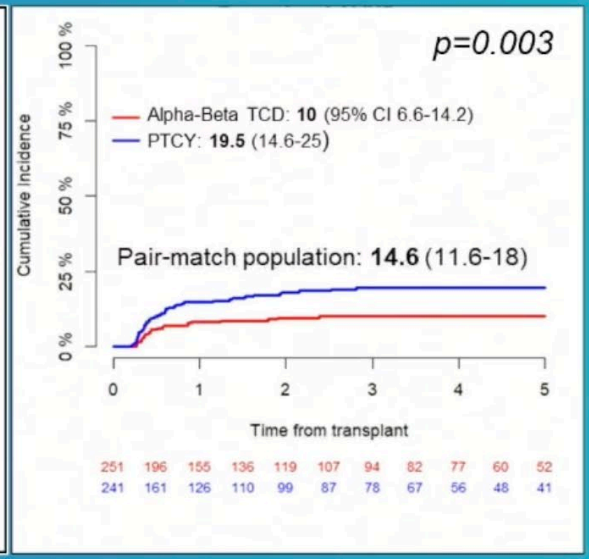
Day 100 grade III-IV aGvHD



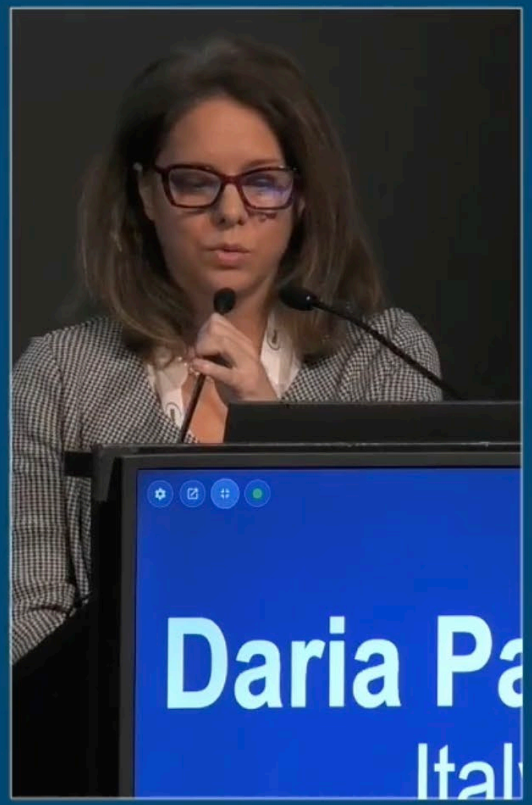
4-y cGvHD



4-y extensive cGvHD

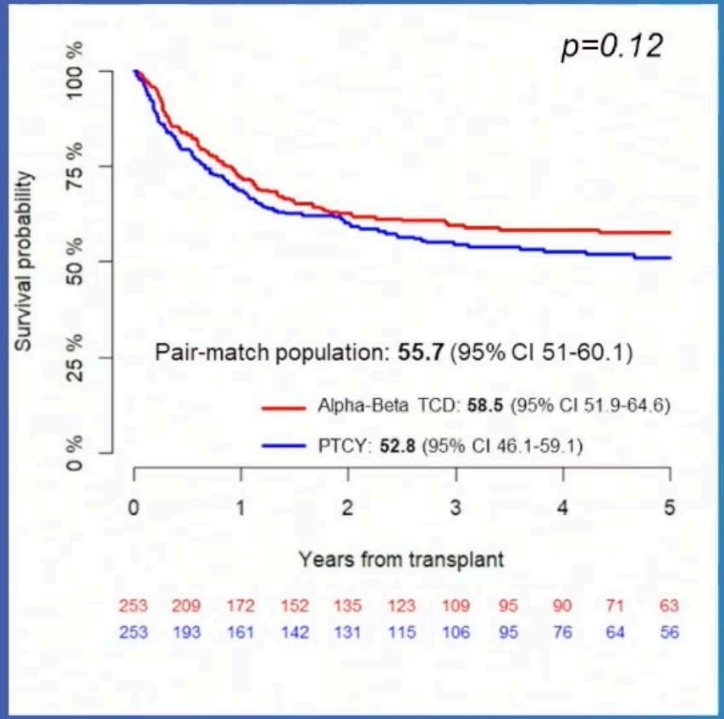


EBMT

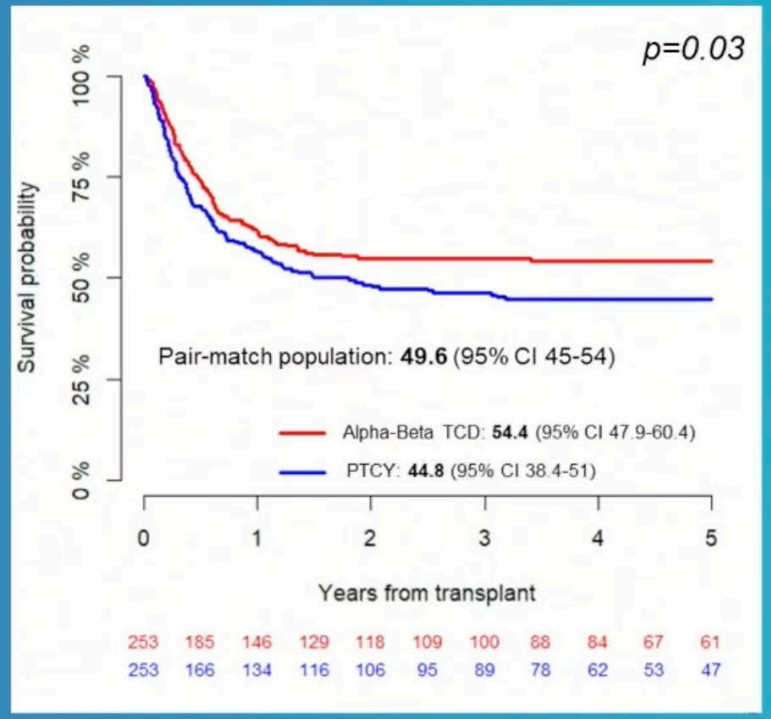


Overall and leukemia-free survival

4-y overall survival



4-y leukemia-free survival



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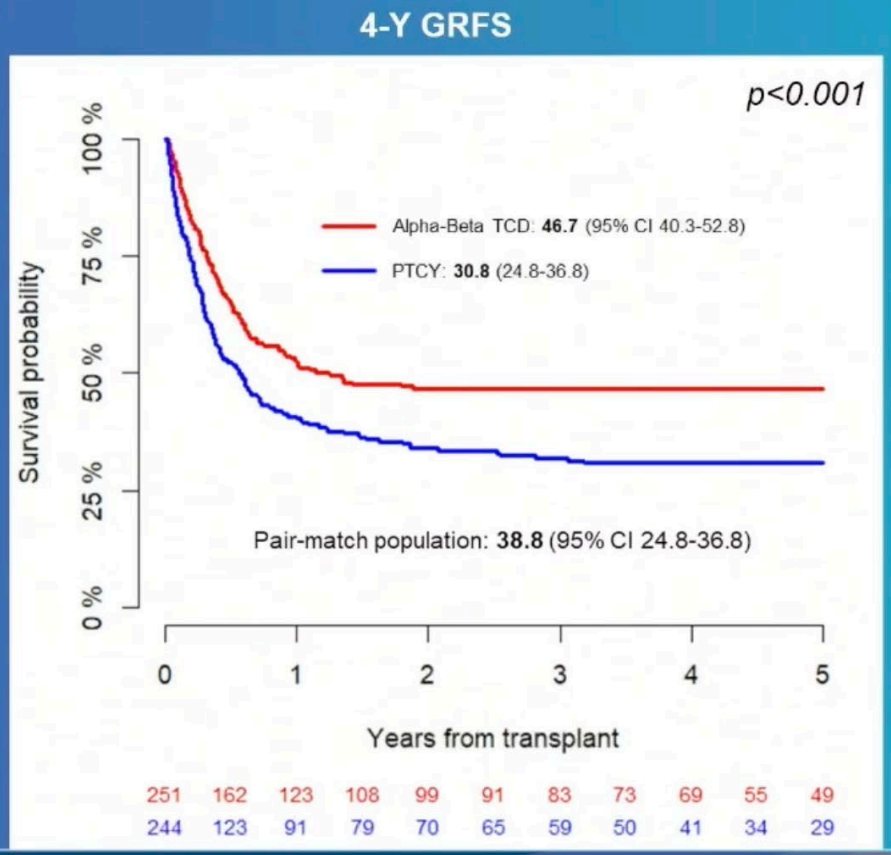
Graft and relapse-free survival



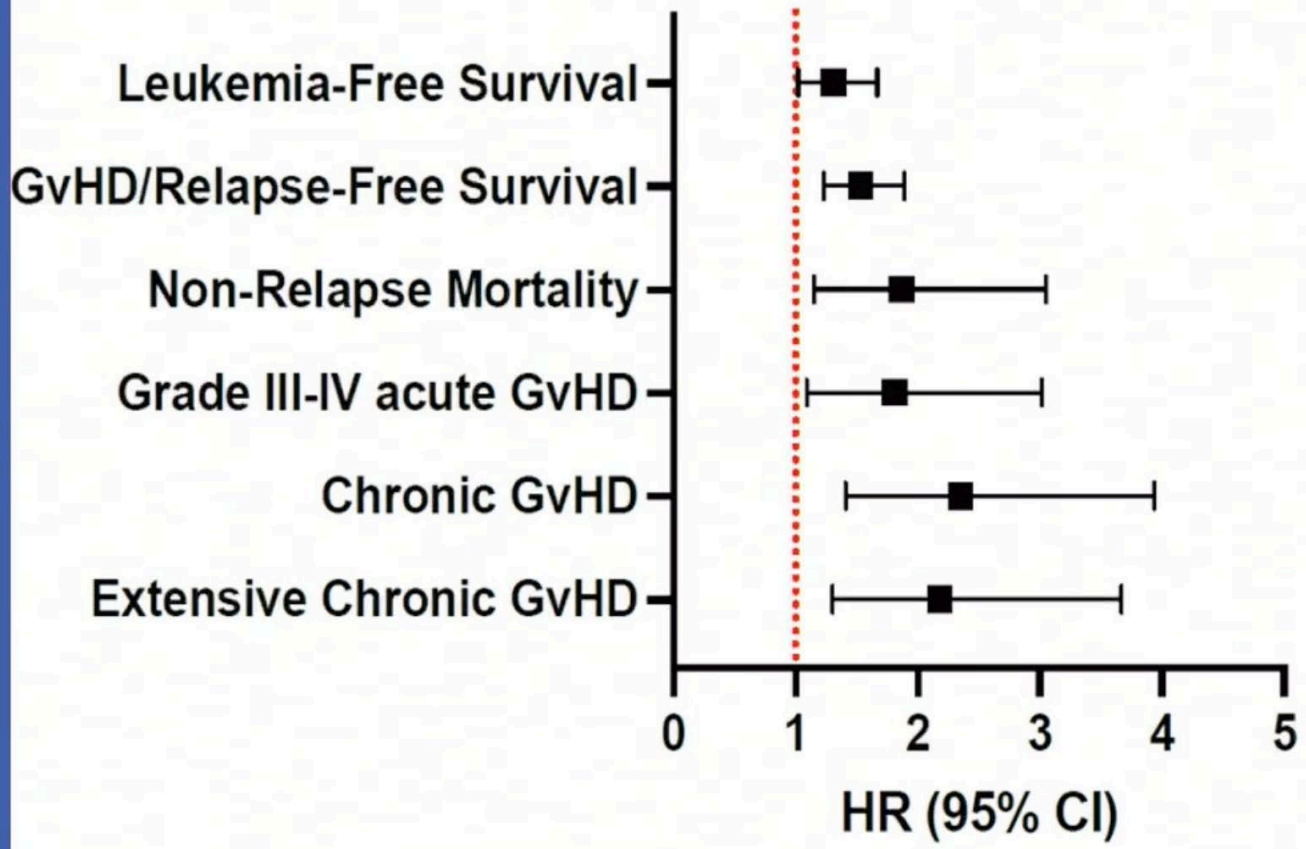
EBMT

Cause of death

	N=215	TCR αβ (N=100)	PTCY (N=115)
Relapse (%)	129 (62.9)	66 (70.2)	63 (56.8)
GvHD	12 (5.9)	3 (3.2)	9 (8.1)
Infection	29 (14.1)	10 (10.6)	19 (17,1)
Graft failure	7 (3.4)	2 (2.1)	5 (4.5)
Secondary HLH	1 (0.5)	1 (1.1)	0
TMA	7 (3.4)	6 (6.4)	1 (0.9)
VOD	7 (3.4)	2 (2.1)	5 (4.5)
Other HSCT related	13 (6.3)	4 (4.3)	9 (8.1)
missing	10	6	4

Multivariable analysis (Cox Model)

Reference: TCRαβ/CD19 depletion



	HR	(95% CI)	p-value
Leukemia-Free Survival	1.31	1.02-1.67	0.03
GvHD/Relapse-Free Survival	1.53	1.23-1.89	<0.001
Non-Relapse Mortality	1.87	1.15-3.05	0.02
Grade III-IV acute GvHD	1.81	1.09-3.02	0.02
Chronic GvHD	2.35	1.41-3.94	0.001
Extensive Chronic GvHD	2.18	1.30-3.67	0.003

Conclusions

- This is the first large retrospective comparative study between TCR αβ-and PTCY T-cell depletion platforms in children with AL who underwent haplo-HSCT;
- There are no significant differences in OS and RI between the two groups;
- However, TCR αβ-HSCT is characterized by with a lower incidence of severe acute and chronic GVHD, lower risk of NRM and better LFS and GRFS as compared to PTCY;
- The requirement of specialized cell-processing facilities could impact on large-scale applicability of TCR αβ-HSCT compared with PTCY.

COMBINED TRANSPLANTS (HEMATOPOIETIC STEM CELL AND SOLID ORGAN) TO ACHIEVE IMMUNE TOLERANCE: A EUROPEAN PEDIATRIC STUDY

Pietro Merli, Kanchan Rao, Peter Lang, Francisco Hernandez Oliveros, Robert Chiesa, Satish Meena, Mattia Algeri, Steffen Hartleif, Ane Andres, Isabella Guzzo, Juliana Silva, Tim Flaadt, Persis Amrolia, Marco Spada, Mariam Basil Abdul Aziz, Silvio Nadalin, Franco Locatelli, Krzysztof Kalwak, Antonio Perez Martinez

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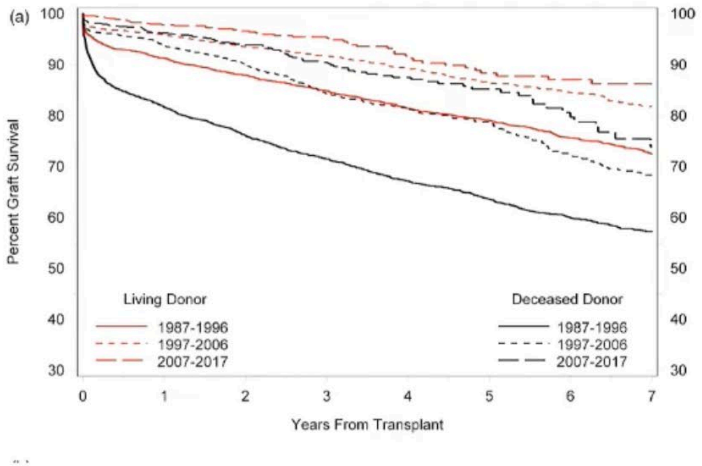
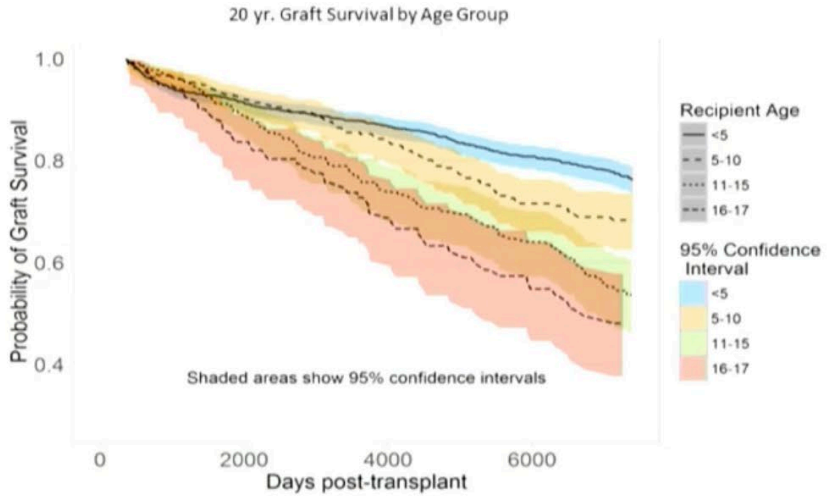
The problem – graft survival

Pediatric kidney



2018 Naprtcs report

Pediatric liver

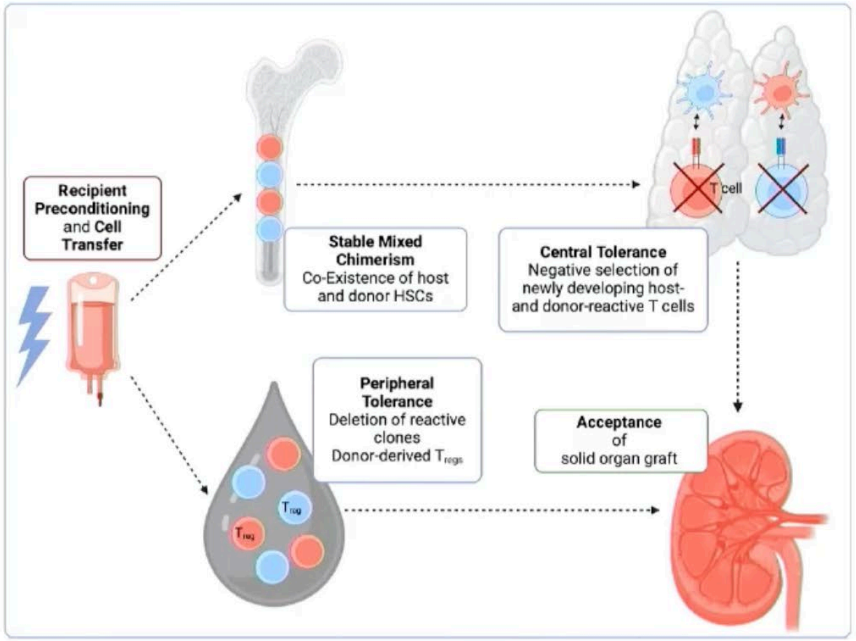


Andrews W et al., 2017

Historical perspective / the goal

Immune Tolerance:
- acceptance of the donor graft
- rejection of third-party grafts
- specific unresponsiveness of recipient immune cells to donor alloantigens without immunosuppressive treatment

Mechanisms of tolerance



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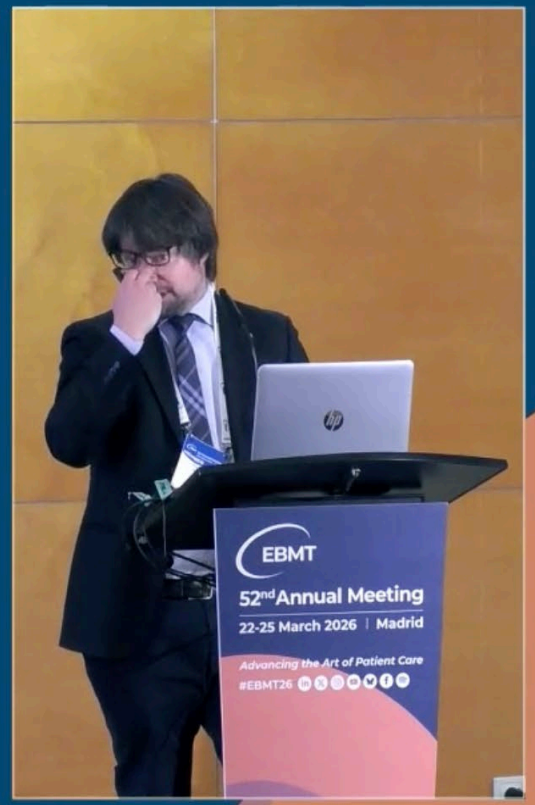

The study

- Retrospective
- Aim: what can we learn from available «real-world» data?

PDWP Organigram

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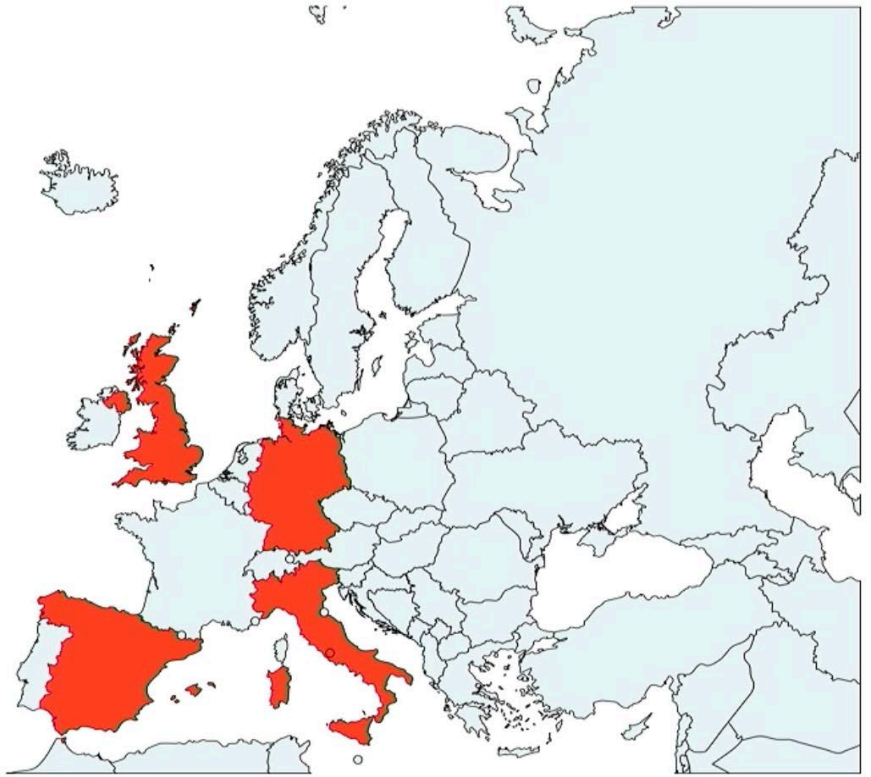


Study cohort

	N (tot=30)	% or IQR
M/F	21/9	70%/30%
Median age at first transplant (y)	6.1	4.6-11.1
Country		
Italy	6	20%
Spain	10	33.3%
UK	10	33.3%
Germany	4	13.3%
SOT		
Kidney	7	23.3%
Liver	20	66.6%
Multivisceral	3	10%

	N (tot=30)	% or IQR
Sequence		
HSCT -> SOT	9	30%
SOT -> HSCT	21	70%
Donor (HSCT:SOT)		
Same	12*	40%
Different	18	60%

* 6 kidneys and 6 liver

Indications to transplant

Indication to SOT		Number	Indication to alloHSCT	Number
Liver	hepatic failure due to nonAtoE-viral hepatitis	11	aplastic anemia	13
	hepatic failure due to adenovirus	1	acute leukemia	6
	hepatoblastoma	4	Hodgkin lymphoma	1
	autoimmune hepatitis	1	Shwachman-diamond syndrome	1
	alpha-1 antitrypsin deficiency	1	hemophagocytic lymphohistiocytosis	1
	liver failure due to secondary HLH	1	severe combined immunodeficiency	1
	iron overload	1	beta-thalassemia	1
Kidney	ESRD due to TMA	2	concomitant to favor immune tolerance	6
	interstitial nephritis	2		
	glomerular sclerosis	1		
	glomerulonephritis	1		
	SIOD	1		
Multivisceral	short bowel syndrome due to malrotation and volvulus	2		
	epithelial dysplasia	1		

Focus on donor & conditioning regimen

HSCT -> SOT	N (tot=9)	% or IQR
SOT		
Kidney	7	77.7%
Liver	2	22.2%
Median time between transplants (m)	16	11-19
HSC donor type		
Haplo	7	77.7%
MFD	2	22.2%
Conditioning intensity		
MAC	5	55.5%
RIC	3	33.3%
None	1	11.1%
Serotherapy		
Yes	7	77.7%
No	2	22.2%

SOT -> HSCT	N (tot=21)	% or IQR
SOT		
Liver	18	85.7%
Multivisceral	3	14.3%
Median time between transplants (m)	10	3-22
HSC donor type		
Haplo	7	33.3%
MFD	3	14.3%
UD (M/mm)	11 (8/3)	52.4% (38.1%/14.3%)
Conditioning intensity		
MAC	6	28.6%
RIC	15	71.4%
Serotherapy		
Yes	17	80.1%
No	4	19.9%

Rejection and IS withdrawal

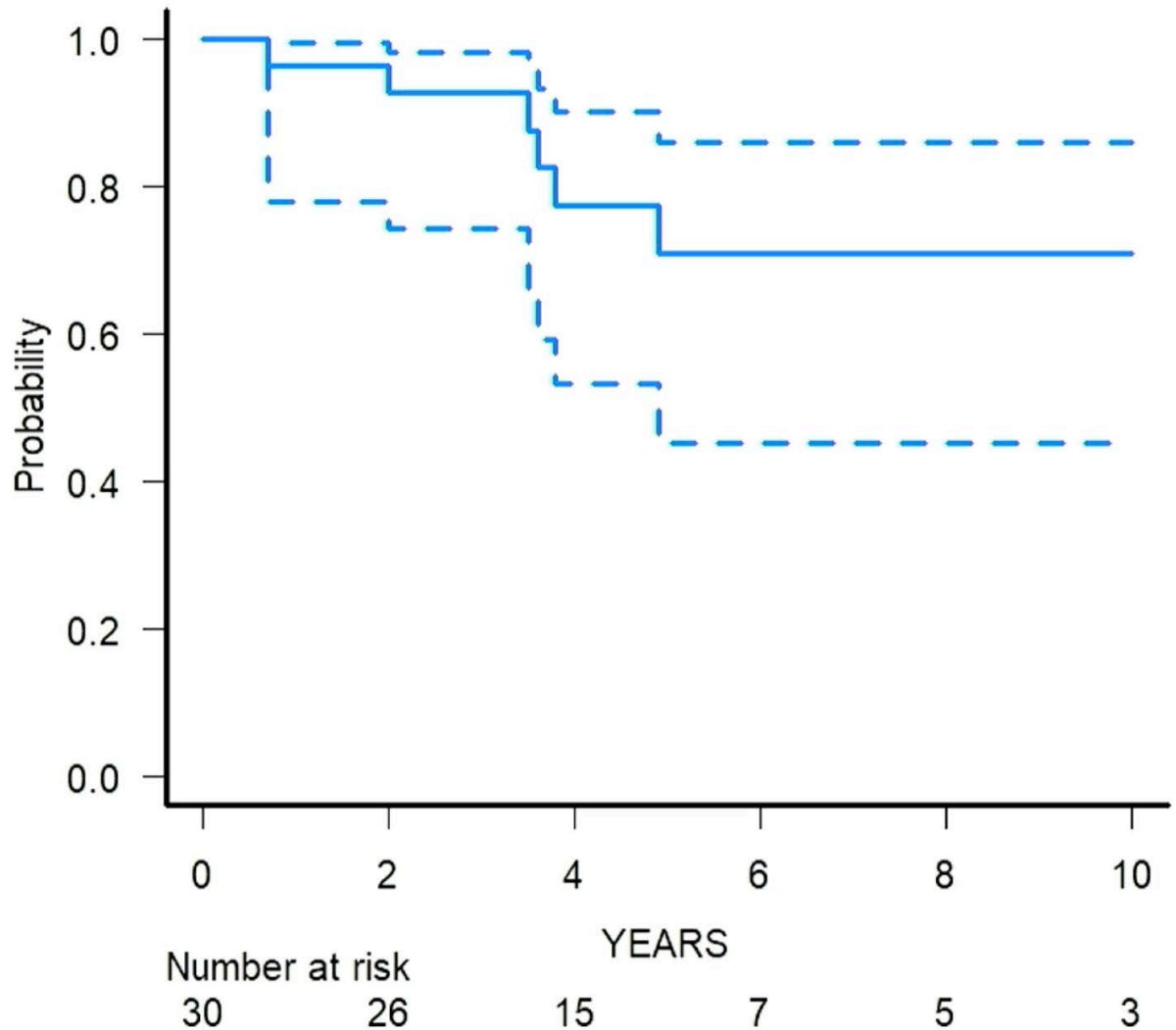
REJECTION

- 4 cases (13.3%) of rejection (humoral and cell-mediated);
- all in patients receiving SOT as first transplant; all but one cases resolved with approrpiate treatment;

IS WITHDRAWAL

- 11 patients out of 30 (36.6%), were able to safely discontinue immunosuppression;
- 6 liver transplant (who received an HSCT after SOT) and 5 kidney transplant (who received an HSCT before SOT) stopped IS after a median of 150 days after the last transplant (IQR 60-470) without occurrence of graft rejection and normal organ function at last follow-up;
- in 3 cases the donor for SOT and alloHSCT was different.

Survival


1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
2
4
6
8
10
YEARS
Number at risk
30
26
15
7
5
3

Conclusions

- In a complex scenario, with different indications, timing of transplants, donor employed and immunosuppressive regimens used, these data indicates that HSCT can induce immune tolerance also in the pediatric setting.
- Immune tolerance can be achieved performing HSCT both before and after SOT.
- Despite frail patients undergoing (at least) 2 major procedures over a long study period, survival was acceptable.
- Long-term data on organ function and chimerism/immune recovery will help in further refining this kind of interventions.
- Perspective studies and dedicated programs in children are urgently needed.

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