AIBT Associazione Italiana di Immunogenetica e Biologia dei Trapianti
XXX Congresso Nazionale
Napoli, 10/12 ottobre 2024
"The programme of this event has been approved by the EFI Education Committee"

Il Trapianto di CSE per il paziente pediatrico nel 2024

OSPEDALE PEDIATRICO SANTOBONO PAUSILIPON

Francesco Paolo Tambaro
UOC TCE e terapie cellulari
AORN Santobono Pausilipon, Napoli

Il sottoscritto ***Francesco Paolo Tambaro*** *in qualità di relatore al*

XXX CONGRESSO NAZIONALE AIBT
NAPOLI, 10/12 OTTOBRE 2024

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 dell'Accordo Stato-Regione del 19 aprile 2012, per conto di Planning Congressi srl

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- NOVARTIS

AMGEN

JAZZ

MEDAC

NEOVII

Data e firma

Napoli, 04.10.2024

Overview

- Activity
- Indications
- Cell Sources
- Donors
- Outcome

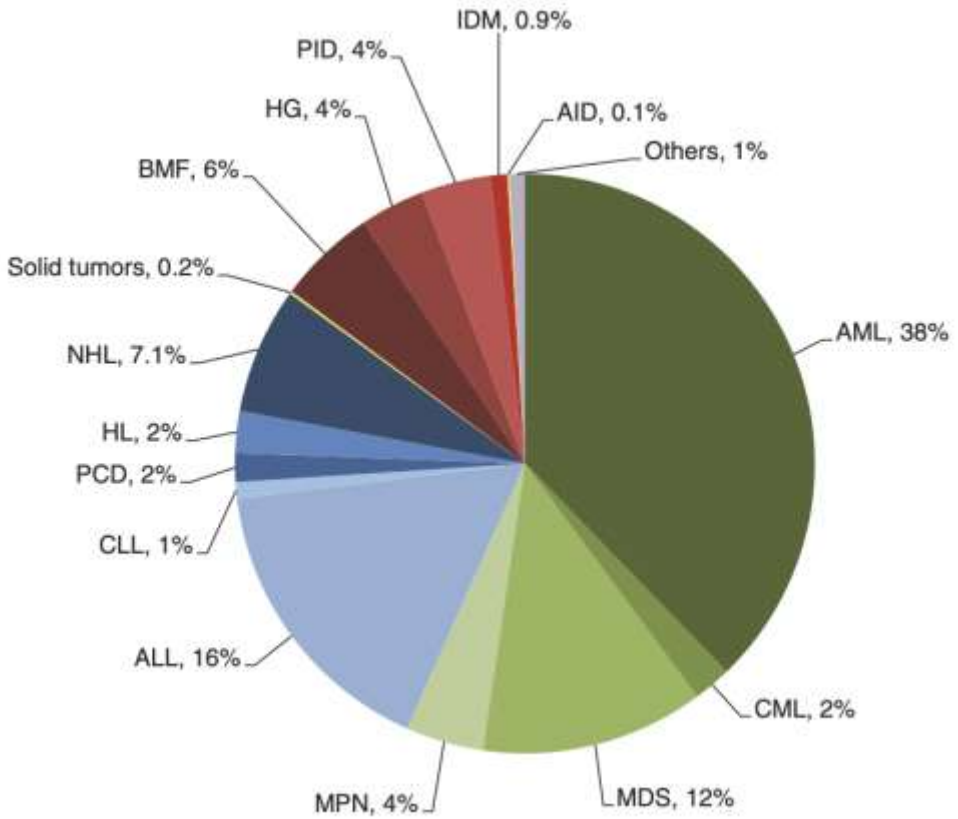
Pediatric 1st Allogeneic HSCT

- USA 2957 (CIBMTR 2020)
- Europe 4130 (EBMT 2022)
- Italy 191 (AIEOP 2021)

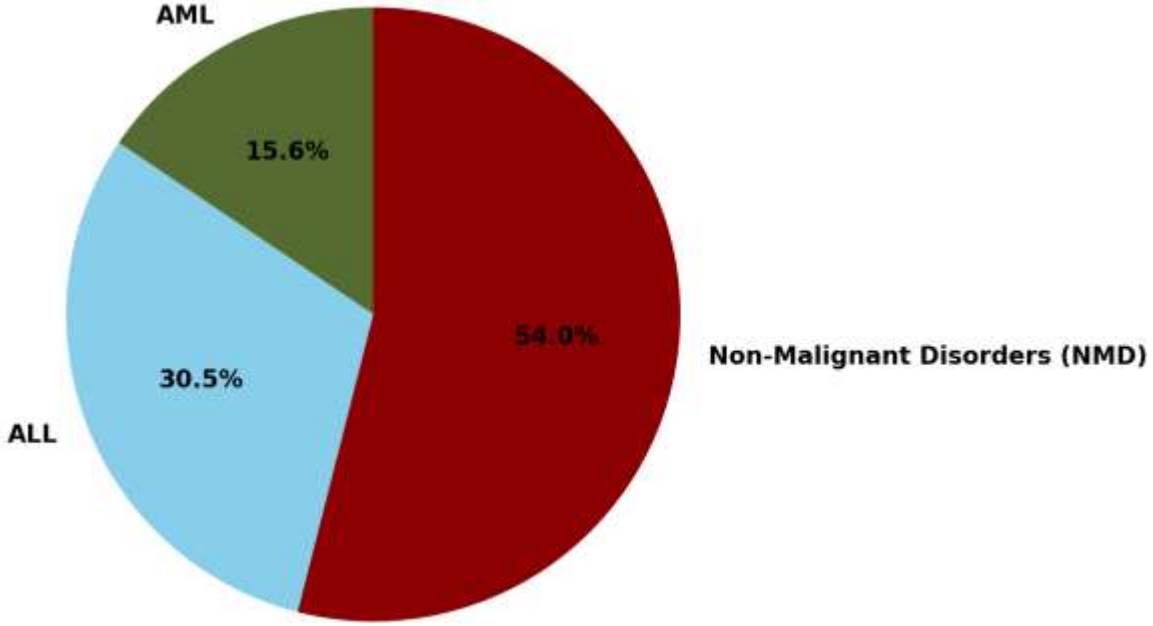
CIBMTR –EBMT- AIEOP

ALLO-SCT 2022 EBMT n=19011

a



Pediatric ALLO-SCT 2022 EBMT n(%)= 4130 (21)



Malignancies: **Adults 85% vs Pediatrics 46%**
Non Malignancies: **Adults 15% vs Pediatrics 54% (1/3 PID)**

Passweg. Bone Marrow Transplantation (2024) 59:803 – 812

Pedi/Adults ALLO-HSCT 2022: Cell Source

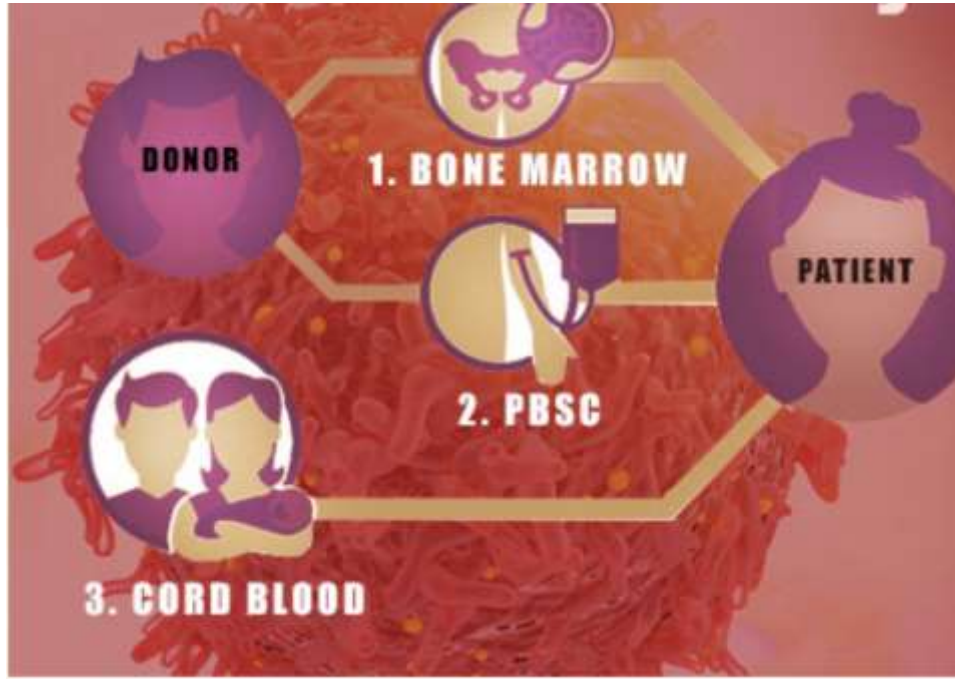
	n (%)
BONE MARROW	2083 (50.4) / 2975 (15)
PBSC	1891(45.8) / 15474 (82.8)
CORD BLOOD	156 (3.8) / 183(1.5)

Passweg. Bone Marrow Transplantation (2024) 59:803 – 812

ALLO-SCT in Pediatrics

WHO

WHEN



HOW

ALLO-HSCT in pALL

- 60% all Pediatric cancers
- 80-90% Patients Cured (Chemo/Radiation/Immune-Therapy (single or combined)
- ALLO-HSCT is one of the option to cure High Risk/Refractory/Relapsed/ patients

ALLO-SCT in ALL: Indications in CR1

RISK STRATIFICATION

- **Genetic Alteraltions**(High Risk)
- **Response to Treatment** (FCM)
- **MRD** (at different timepoints)

High Risk (HR)

- no complete remission on day 33 *or*
- positivity for *KMT2A-AFF1 or*
- positivity for *TCF3-HLF*[1] *or*
- hypodiploidy <45 chromosomes *or*
- FCM-MRD in BM on day 15 ≥ 10% *and* <u>*not*</u> *ETV6-RUNX1* positive *or*
- *IKZF1*[plus] *and* PCR-MRD at TP1 positive or inconclusive *and* <u>*not*</u> positive for *ETV6-RUNX1, TCF3-PBX1* or *KMT2A* rearr. other than *KMT2A-AFF1 or*
- PCR-MRD at TP1 ≥ $5x10^{-4}$ and positive < $5x10^{-4}$ at TP2 (PCR-MRD SER) *or*
- PCR-MRD at TP2 ≥ $5x10^{-4}$ *or*
- age < 1 year and any *KMT2A* rearrangement

Standard Risk (SR)

- no HR criteria *and*
- PCR-MRD at TP1 negative for all investigated markers with at least one marker with a quantitative range of ≤ 10^{-4} *or*
- inconclusive PCR-MRD result at TP1 *and* PCR-MRD <u>*not*</u> positive at TP2 *and* FCM-MRD in BM d15 < 0.1%

Medium Risk (MR)

- no HR criteria *and* no SR criteria

ALLO-HSCT indications according to the study AIEOP-BFM ALL 2017 except infant < 1year pBALL and KMT2A rearrangement

		PCR-MRD results				
		TP1 neg	TP1 or TP2 pos and TP2 $<5x10^{-4}$	MRD-HR		no MRD result
				MRD TP2 $\geq 5x10^{-4}$- $<5x10^{-3}$	MRD TP2 $\geq 5x10^{-3}$	
	TCF3-HLF	MMD	MMD	MMD	MMD	MMD
criteria hierarchical	no CR d33	no[b]	MD[b]	MMD	MMD	MMD
	KMT2A-AFF1	no	MD	MD	MMD	MD
	hypodiploidy < 44 chr. or DNA index < 0.8[a]	no	MD	MD	MMD	MD
	IKZF1[plus] and FCM-MRD d15 ≥ 10%	no	MD	MD	MMD	MD
	IKZF1[plus] and FCM-MRD d15 < 10%	no	no	MD	MMD	MD
	T-ALL + PPR a/o FCM-MRD d15 ≥ 10%	no	no	MD	MMD	MD
	none of the above features	no	no	MD	MMD	no

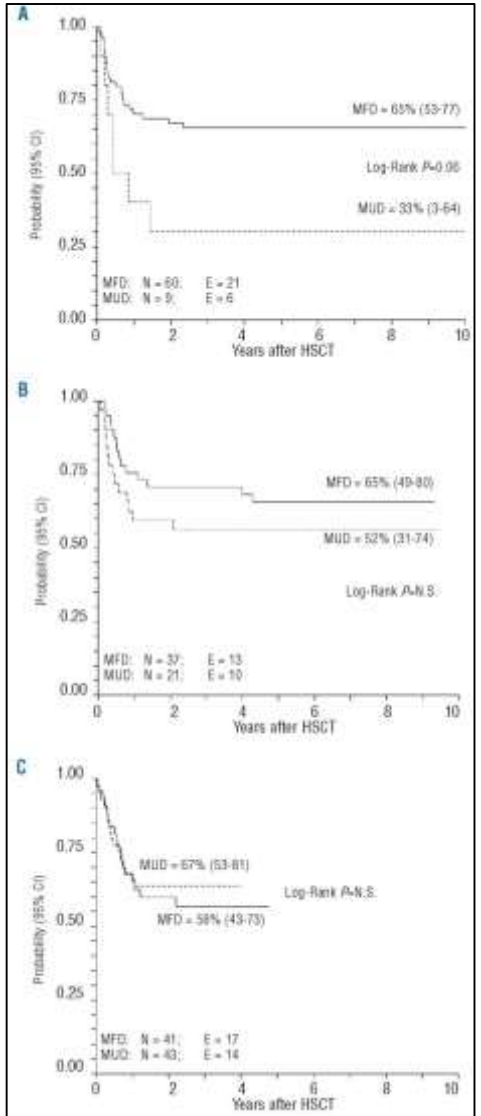
no alloHSCT not indicated
MD permitted donor: HLA-matched sibling or non-sibling donor
MMD permitted donor: HLA-matched or HLA-mismatched donor

ALLO-HSCT indications according to the study AIEOP-BFM ALL 2017 for infant < 1year pBALL KMT2A rearrangement

	PCR-MRD results			
	MRD TP2 $<5x10^{-4}$	MRD TP2 $\geq 5x10^{-4}$- $<5x10^{-3}$	MRD TP2 $\geq 5x10^{-3}$	no MRD result
no CR d33	MD	MMD	MMD	MD
age < 6 months and initial WBC > 300,000/µl	MD	MD	MMD	MD
age < 6 months and Prednisone Poor-Response	MD	MD	MMD	MD
none of the above features	no	MD	MMD	no

no alloHSCT not indicated
MD permitted donor: HLA-matched sibling or non-sibling donor
MMD permitted donor: HLA-matched or HLA-mismatched donor

ALLO-HSCT : Donor



211 pts HR -B-ALL 1stCR (1990-2008)
10 year OS and DFS for patients receing HCT in CR1 were 63.4% and 61%.

After 1999 transplant outcomes are similar from MUD and MFDs.

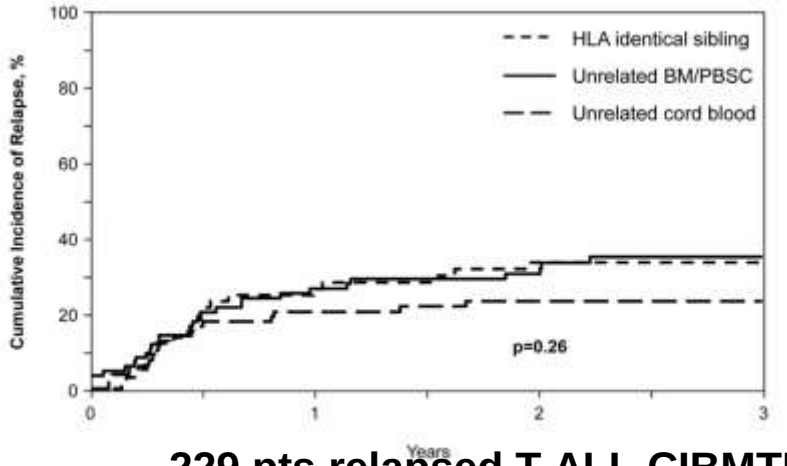
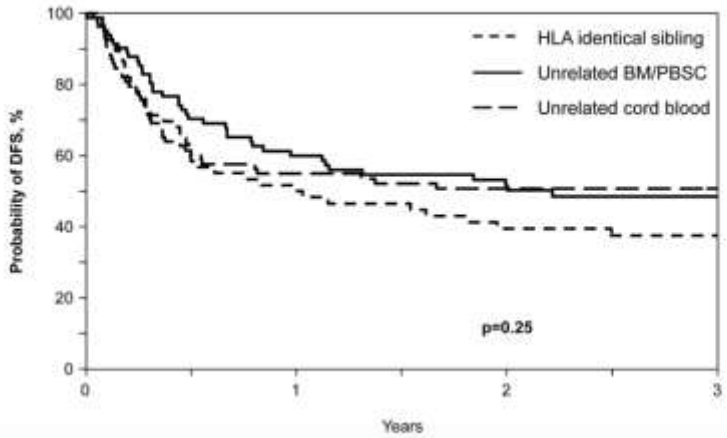


Figure 3B

229 pts relapsed T-ALL CIBMTR 2000 - 2011
3 year OS and DFS for patients with relapsed who received a HCT in CR2 were 48% and 46%.



Fagioli et al Haematologica. 2013 Aug; 98(8): 1273–1281
Burke et al.Biol Blood Marrow Transplant. 2015 December ; 21(12): 2154–2159

Allo-SCT for ALL in CR2 IntReALL SR2010

Timepoint of Relapse

Time-point	After primary diagnosis		After completion of primary therapy
Very early	< 18 months	and	< 6 months
Early	≥ 18 months	and	< 6 months
Late			≥ 6 months

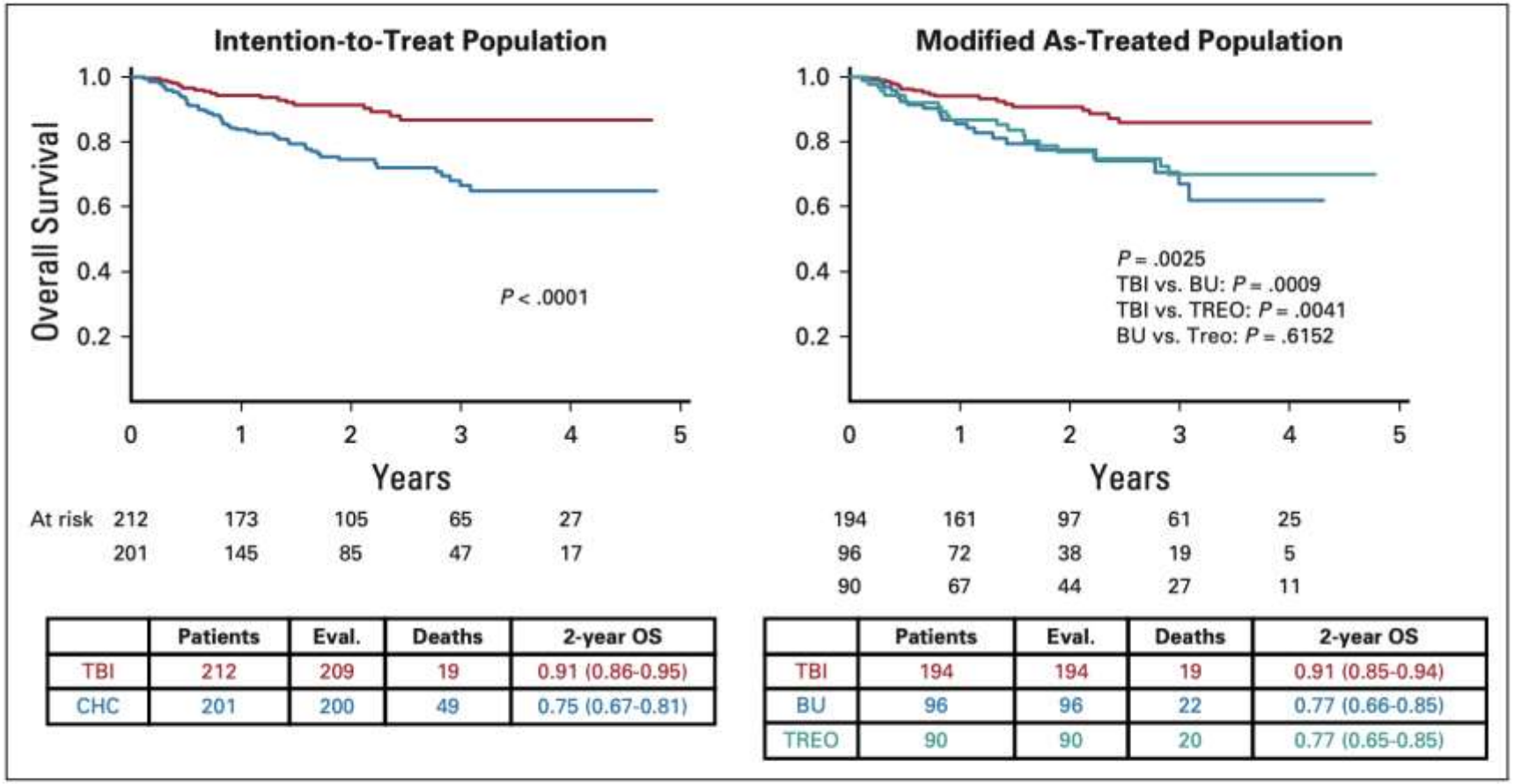
Site of Relapse

Bone marrow		M1 (< 5% blasts)	M2 (≥ 5% and < 25% blasts)	M3 (≥ 25% blasts)
extramedullary relapse	No	**No ALL relapse**	**Requires follow up control**	**Isolated bone marrow relapse**
	Yes	**Isolated extramedullary relapse**	**Combined bone marrow / extramedullary relapse**	

IntReALL SR/HR2010 risk groups

	Immunophenotype: B-cell precursor			Immunophenotype: (pre) T		
\ Site Time-point \	Extramed. Isolated	Bone marrow combined	Bone marrow isolated	Extramed. isolated	Bone marrow combined	Bone marr isolated
Very early	**HR**	**HR**	**HR**	**HR**	**HR**	**HR**
Early	**SR**	**SR**		**SR**	**HR**	**HR**
Late	**SR**	**SR**	**SR**	**SR**	**HR**	**HR**

ALLO-HSCT: Conditioning Regimen



	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

FIG 2. Primary end point: Overall survival. BU, busulfan; CHC, chemo-conditioning; CIR, cumulative incidence of relapse; EFS, event-free survival; OS, overall survival; TBI, total body irradiation; TREO, treosulfan; TRM, treatment-related mortality.

Peters et al J.Clin Oncol. 2021 Feb 1;39(4):295-307. doi: 10.1200/JCO.20.02529 .

ALLO-SCT in AML: WHO

Poor Risk: no international agreement;

- Most groups define PR disease which may benefit from HCT in CR1 through a combination of **PR cytogenetics/molecular abnormalities**, **persistence of MRD after course 1 or 2.**
- Failure to achieve CR carries a poor outcome

Intermediate Risk: The benefit of HCT in CR1 for patients with IR cytogenetics is less clear

- Patients without PR cytogenetics but with a suboptimal early response to CHT in whom:
- MRD assessment can identify those at high risk of relapse who may benefit from transplant.

Good Risk: There is no advantage for HCT in CR1 for patients with GR disease

There is no role for HCT in CR1 of acute promyelocytic leukaemia (APL) or Down syndrome myeloid leukaemia (ML-DS).

AIEOP 2013: RISK STRATIFICATION

STANDARD RISK (SR) **20-22%**	**Anomalie CBF□ (senza altre anomalie citogenetiche) e MRD < 0.1% al TP1** - *t(8;21)(q22;q22)/[inv(16)(p13q22)/t(16;16)(p13;q22)* **Pazienti con cariotipo normale e mutazioni di NPM-1 con MRD < 0.1% al TP1**	
INTERMEDIATE RISK (IR) **50-55%**	**Cariotipo normale** **t(9;11)(p22;q23) senza altre anomalie citogenetiche** **t(1;11)(p32;q23)** **t(11;19) (p13;q23)** ***t(16;21)(p11;q22)FUS-ERG, t(3;5)(q25;q34)*** **Altre anomalie citogenetiche** **M7 con t(1;22), indipendentemente dall'età del paziente** **Pazienti non altrimenti stratificabili a SR e HR** **MRD al TP1 > 0.1% ma < 1% e con MRD al TP2 < 0.1%**	

In CR1: NO HSCT

In CR1 if

- **Matched Family Donor**
- **or**
- **10/10 Unrelated Donor**

A.I.E.O.P.

AIEOP 2013: RISK STRATIFICATION

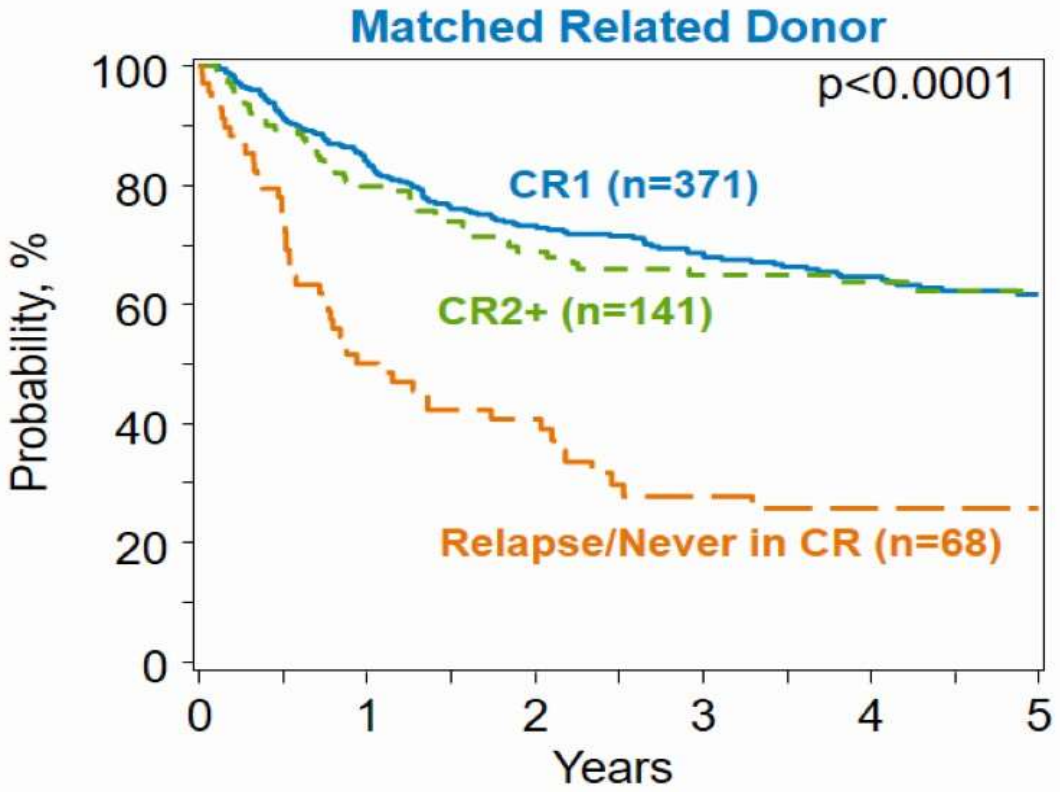
HIGH RISK (HR) 25-30%	**Anomalie citogenetiche associate ad *outcome* sfavorevole:** – *Cariotipo complesso (≥ 3 anomalie numeriche o strutturali)* – *Cariotipo monosomico, (-7, -5, altro) §* – *t(9;11)(p22;q23) associata ad altre anomalie citogenetiche* – *Anomalie citogenetiche comprendenti 11q23 non incluse nel IR: t(11;17)(q23;q21), t(10;11)(p12;q23), t(4;11)(q21;q23), t(6;11)(q27;q23), t(x;11)* - *Anomalie citogenetiche rare: t(6;9)(p23;q34), t(8-16)(p11;p13), t(9;22)(q34;q11) t(5;11)NUP98/NSD1, t(4;11)MLL/ArgBP2* **FLT3-ITD** **Pazienti con LAM citogeneticamente normale e con il trascritto di fusione CBFA2T3-GLIS2** **FAB M0, M6, M7 senza t(1;22)** ***Infants* (esclusi i pazienti con LAM M7 con t(1;22))** **Pazienti non in remissione completa morfologica al termine del primo ciclo di induzione** **MRD > 1% al TP1 o > 0.1% al TP2** **Pazienti con criteri non-SR e WBC >100.000/□L**

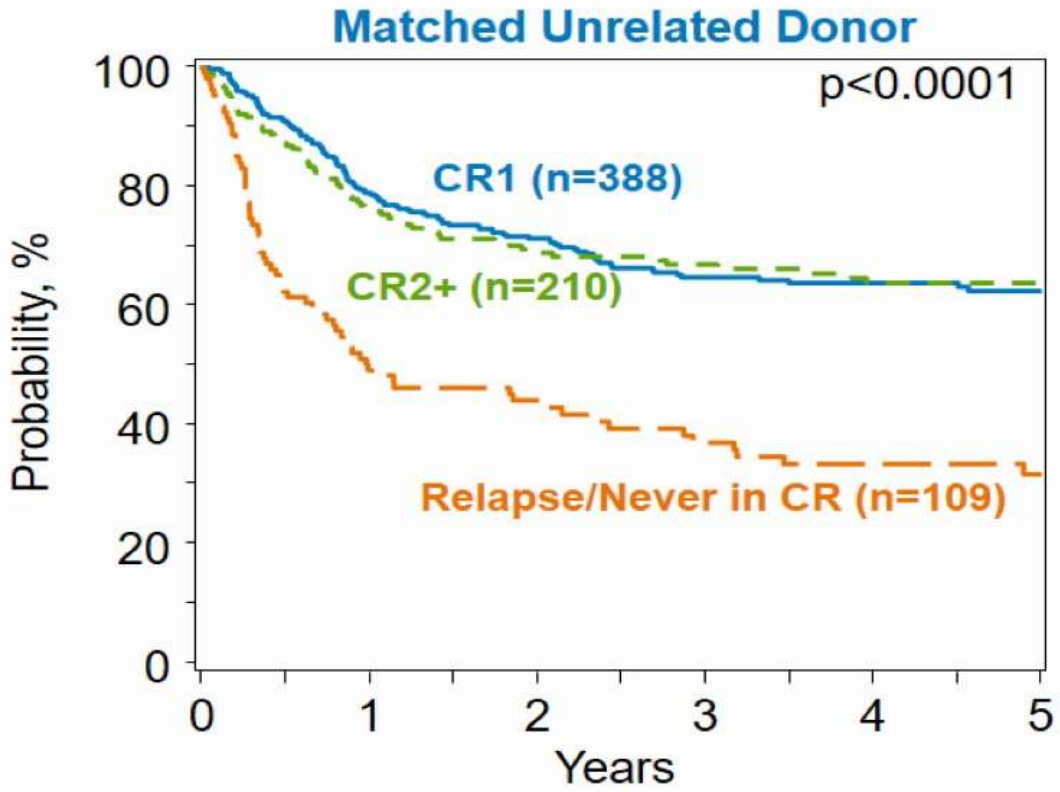
In CR1 if:

- **Matched Family Donor**
- **Unrelated Donor**
- **Haplo**

A.I.E.O.P.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia (AML), Using Matched Donors, Age <18 Years, in the U.S., 2010-2020

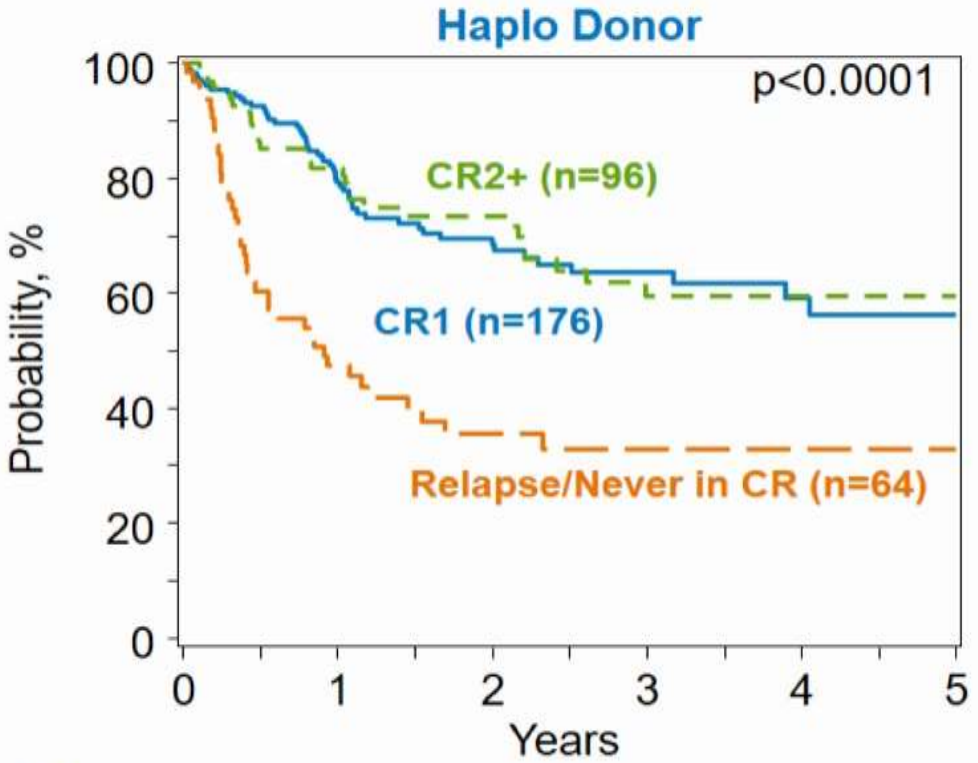


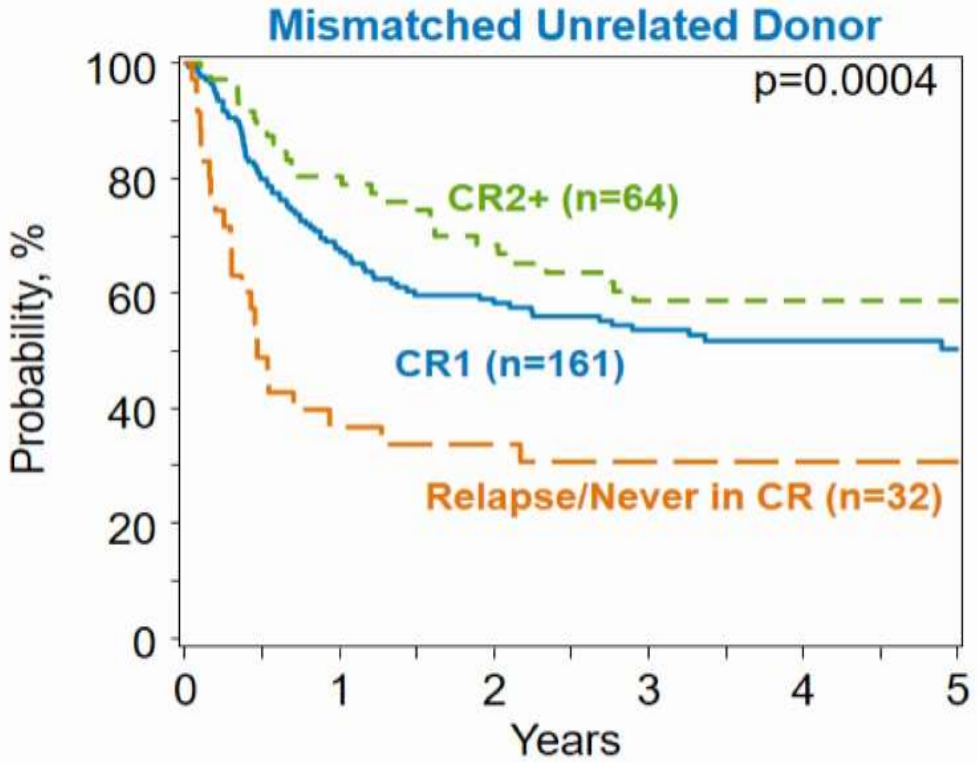


CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Abbreviation – CR: Complete remission.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia (AML), Using Mismatched Donors, Age <18 Years, in the U.S., 2010-2020





CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Abbreviation – CR: Complete remission; Haplo: ≥2 HLA antigen mismatch; MMUD: Mismatched unrelated donor ≤7/8 HLA allele match, excluding CB.

ALLO-SCT in Hemoglobinopathies

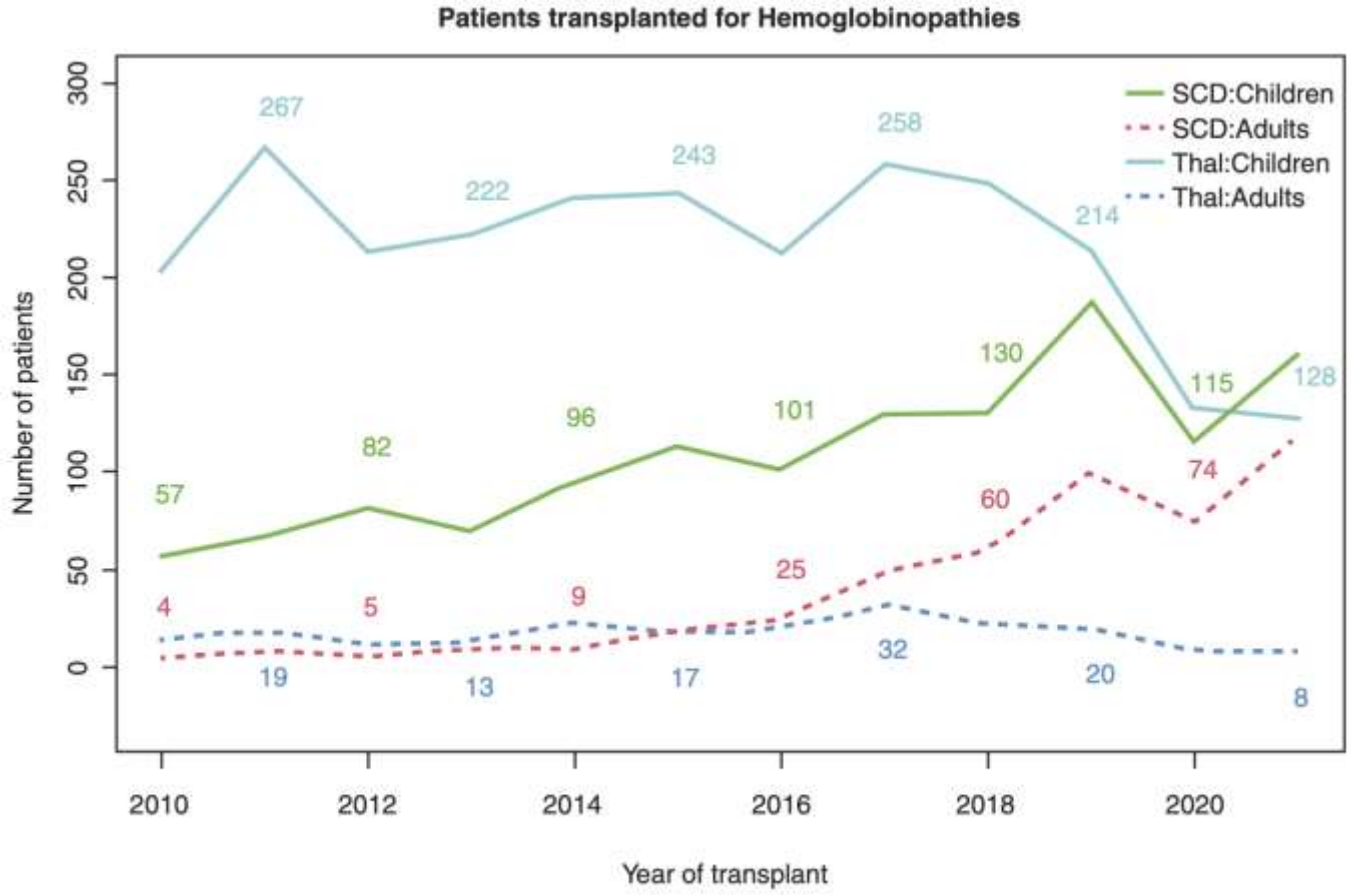


Fig. 80.1 Transplant activities in the EBMT registries for hemoglobinopathies in the last decade

Only currently available curative therapy for Hemoglobinopathies

Barriers preventing widespread application

- Lack of a suitable donor
- Lack of information
- Risk of early- and late-onset regimen-related toxicties (i.e. rejection, GVHD, and TRM)

	2 y OS
SCD: Children	95.6 (94.1–96.6)
SCD: Adults	93.5 (90.7–95.5)
Thal: Children	92.1 (90.8–93.2)
Thal: Adults	84.4 (78.1–89.0)

Major Indications for HSCT in Children with SCD

1. Recurrent severe vaso-occlusive crises (VOC)
- ≥3 painful crises per year, unresponsive to therapy.

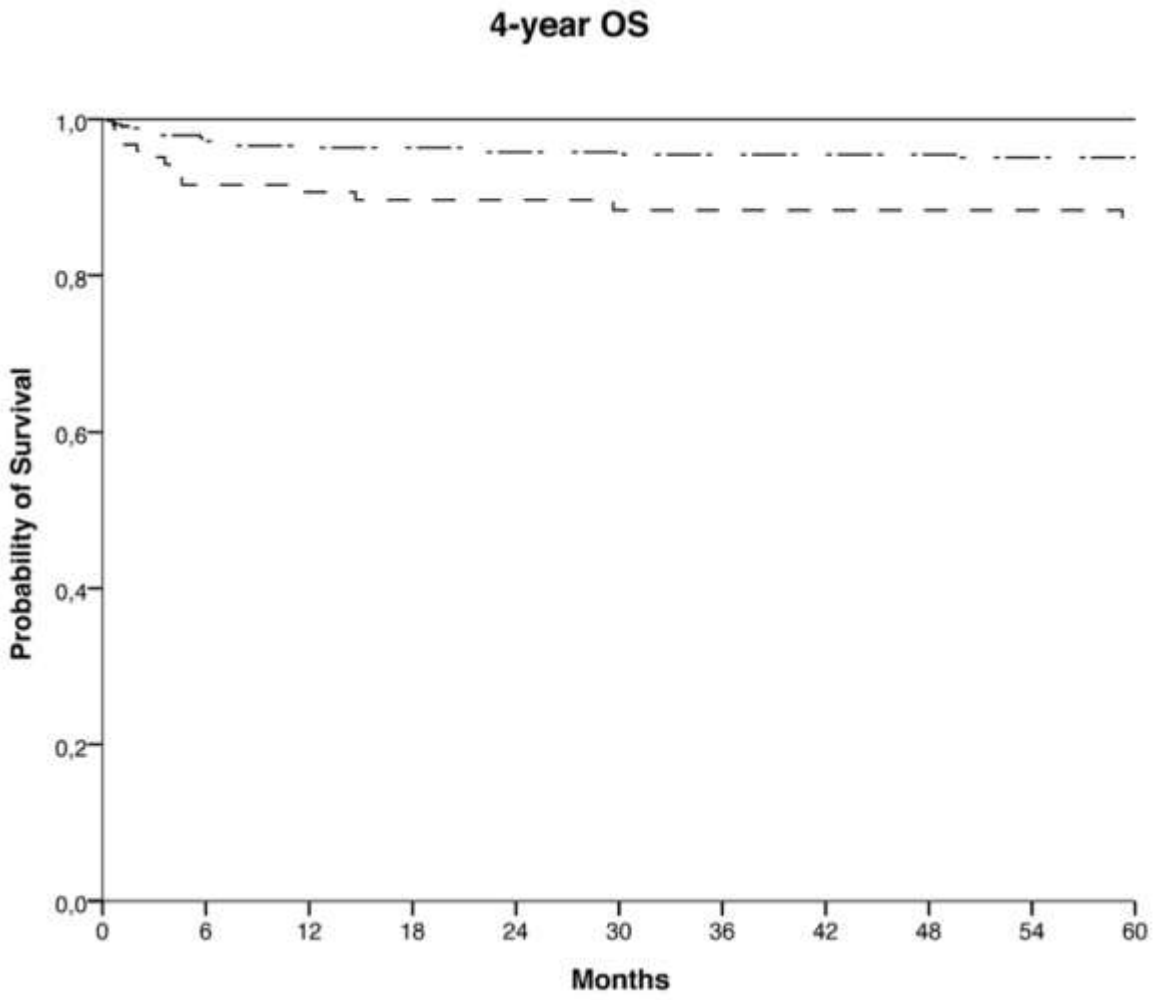
2. **Recurrent or severe acute chest syndrome (ACS)**
- Life-threatening respiratory complications.

3. **Stroke or high risk for stroke**
- Previous ischemic stroke or abnormal transcranial Doppler (TCD).

4. **Availability of a matched sibling donor (MSD)**
- Significantly improves transplant success.

Krishmahurti Hematology Am Soc Hematol Educ Program. 2021 Dec 10; 2021(1): 181-189.

HSCT in Children with SCD: AGE



N 756 pts EBMT /Eurocord MSD HSCT 1986-2017
4-year OS in according to age

Group 1 (0-5 years) (solid line): 100%,

Group 2 (5-10 years)(dash-dotted line) 95%,

Group 3 (10-15years)(dashed line) 88%, (*P*<0.001).

Cappelli et al Haematologica. 2019 Dec;104(12):e543-e546.

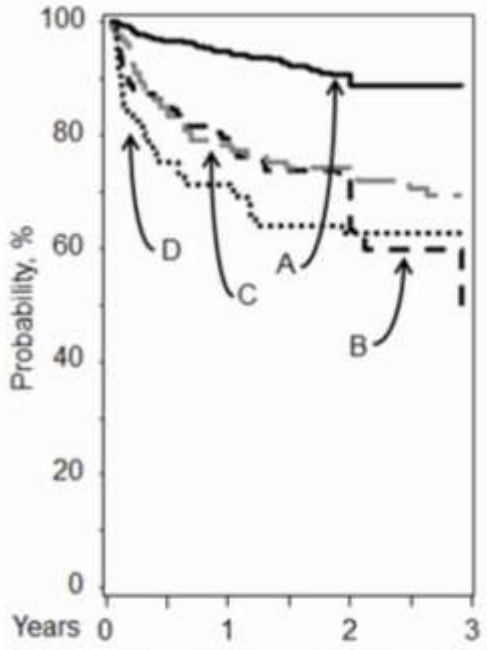
HSCT in Children with SCD: STEM CELL SOURCE

- **Bone Marrow** when available, is the preferred stem cell source, less GVHD, better engrafment
- **Umbilical Cord Blood** showed a higher rate of non engraftment (led to the premature closure of the (UCB) arm of the BMT CTN 0601
- **Peripheral blood** as a stem cell source has been associated with a higher risk of chronic GVHD (cGVHD)

Kamani NR Biol Blood Marrow Transplant. 2012;18(8):1265-1272.
Eapen M,. Lancet Haematol. 2019;6(11):e585-e596.

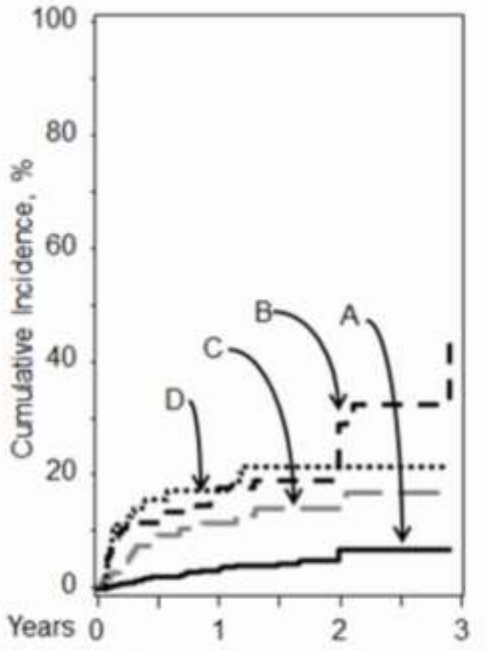
HSCT in SCD: DONOR

Event-free survival



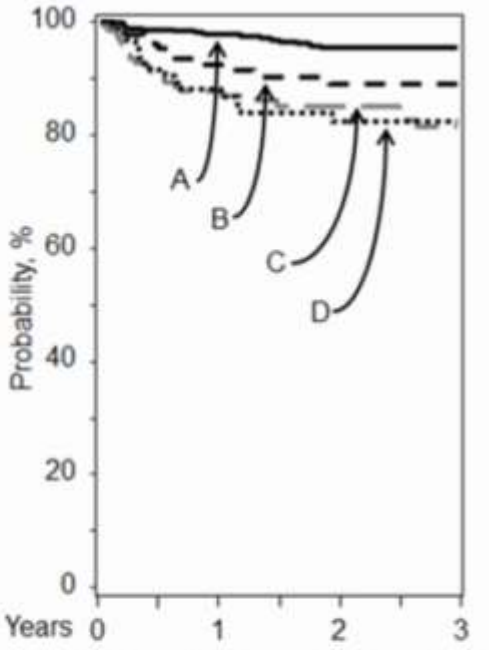
Group	Nat risk	Nat risk	Nat risk	Nat risk
A	557 (0)	444 (86)	349 (165)	261 (245)
B	137 (0)	85 (28)	61 (47)	33 (60)
C	111 (0)	72 (11)	57 (22)	40 (35)
D	104 (0)	61 (11)	42 (23)	36 (29)

Overall survival



Group	Nat risk	Nat risk	Nat risk	Nat risk
A	557 (0)	444 (97)	349 (185)	261 (265)
B	137 (0)	85 (34)	61 (56)	32 (69)
C	111 (0)	72 (27)	57 (40)	40 (55)
D	104 (0)	61 (18)	42 (33)	36 (39)

Graft failure



Group	Nat risk	Nat risk	Nat risk	Nat risk
A	557 (0)	460 (86)	362 (175)	276 (261)
B	137 (0)	97 (31)	71 (54)	50 (74)
C	111 (0)	79 (14)	63 (27)	45 (42)
D	104 (0)	82 (11)	64 (25)	52 (37)

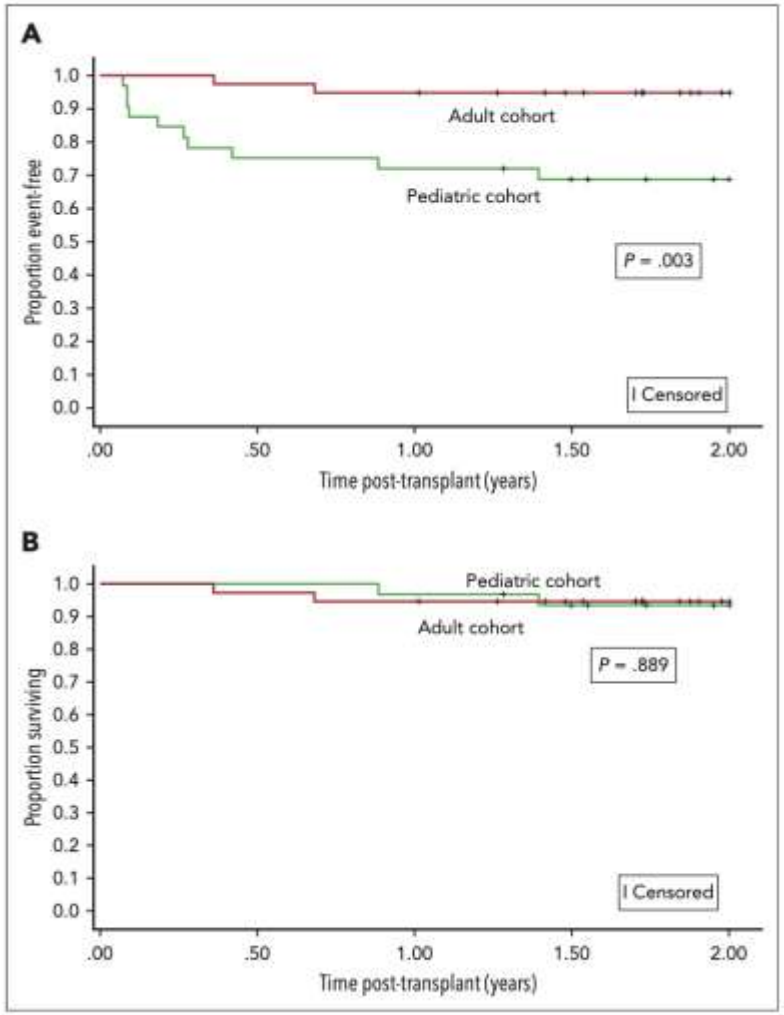
N= 910

A: HLA-matched sibling	557
B: Haploidentical relative	137
C: HLA-matched unrelated	111
D: HLA-mismatched unrelated	104

Worse Outcome in patients aged ≥13 years, RIC, no MRD

Eapen M,. Lancet Haematol. 2019;6(11):e585-e596.

Haplo-HSCT in SCD: NM-Thiotepa-PTCY



n.70 Flu Cy **Thio/PTCy**

n 32 PEDI n 38 ADULTS

2 y EFS% P 68.4 **A** 94.7

2 y OS% P 93.6 **A** 94.7

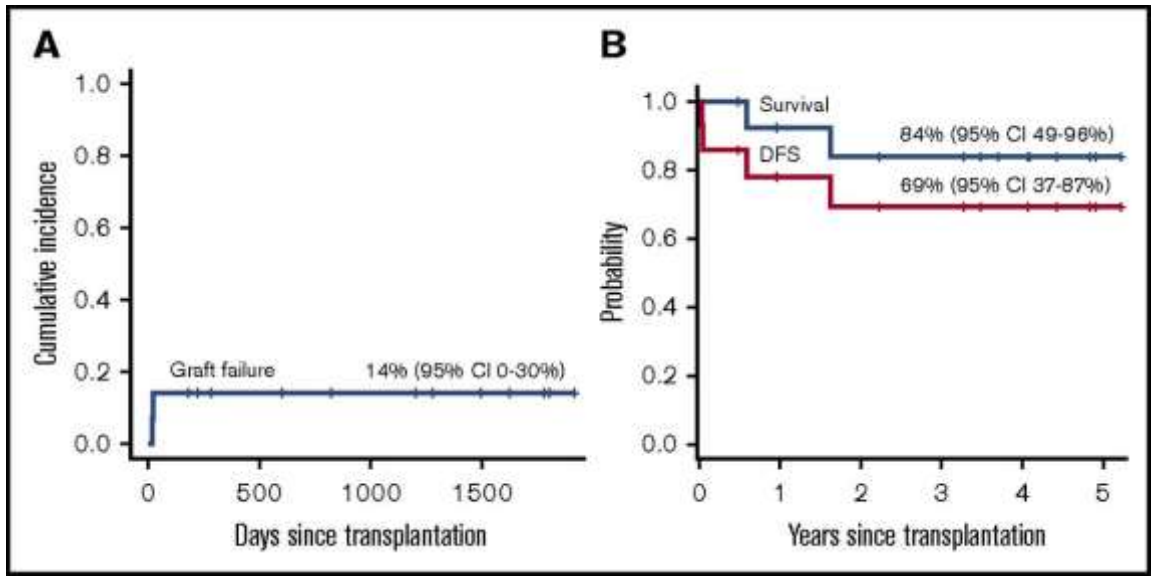
n 8 Graft failure

n 62 100% Chimerism

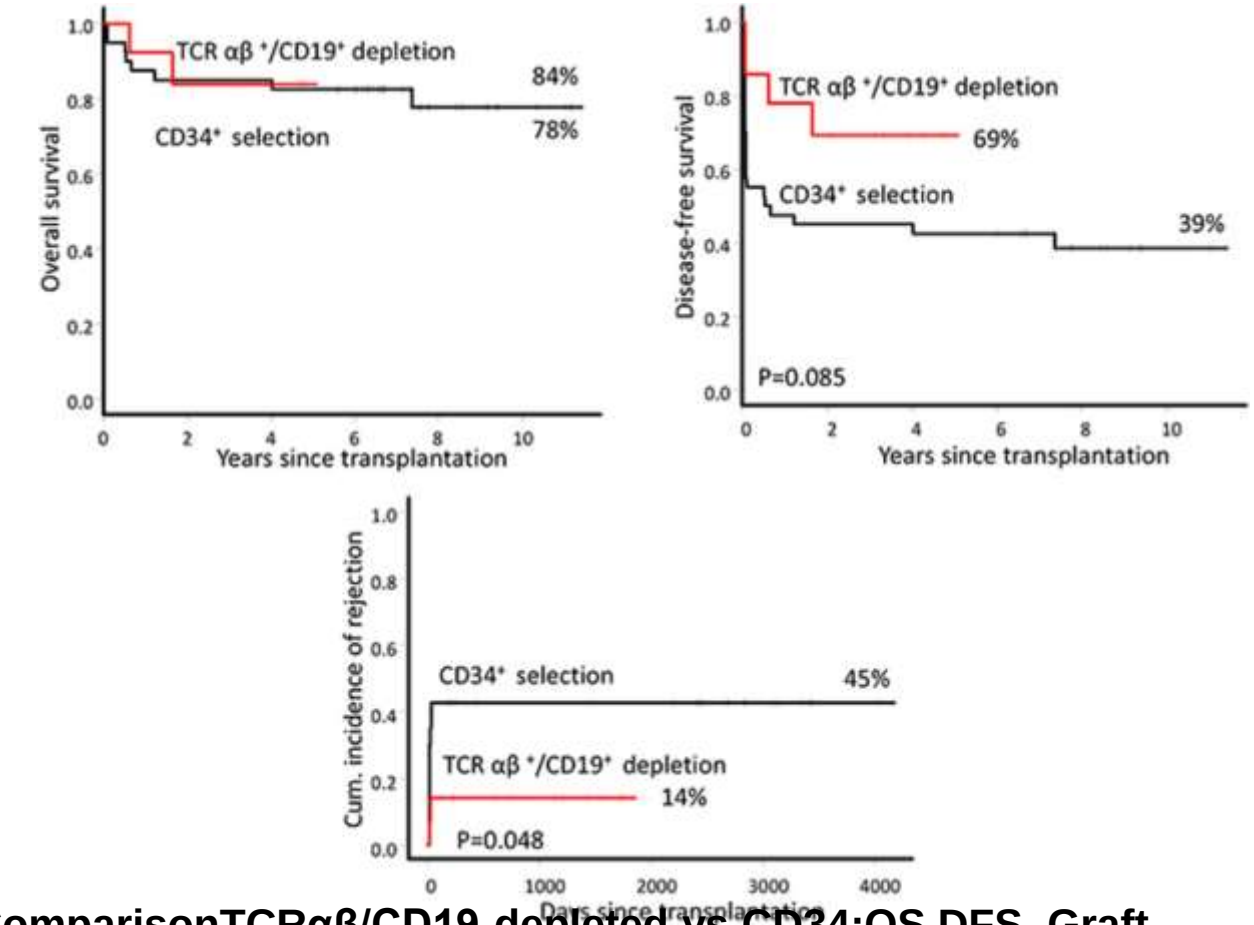
2 y mod/sev GVHD 10%

Kassim et al, Blood. 2024 Jun 20;143(25):2654-2665.

Haplo-HSCT in SCD: TCR αβ depleted



TCRαβ/CD19-depleted:Graft failure (A)OS and DFS (B)



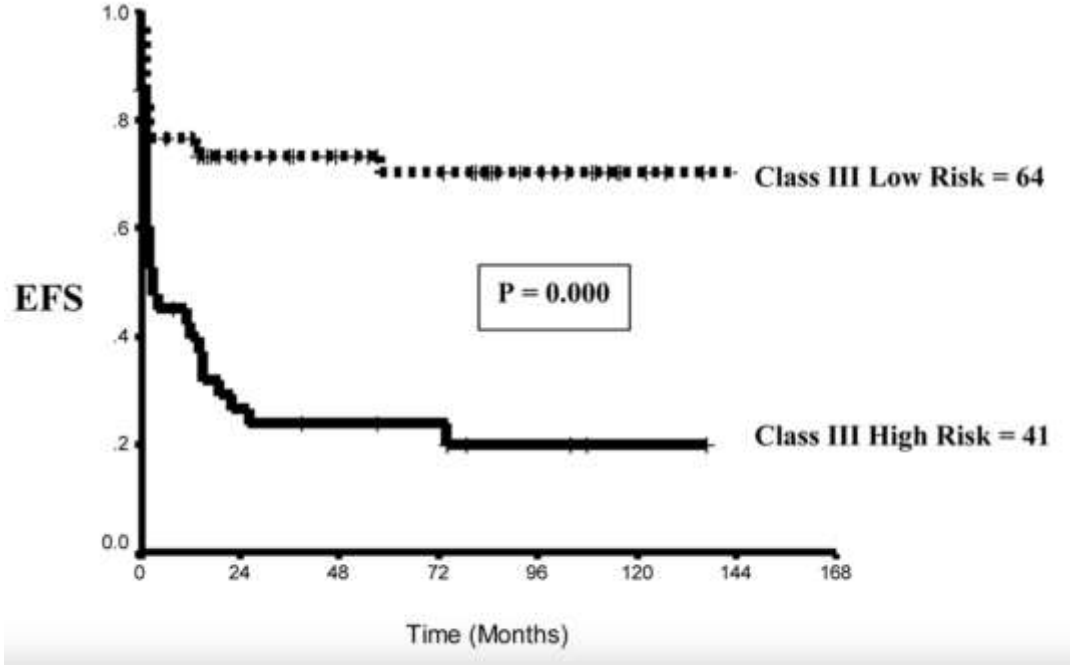
ComparisonTCRαβ/CD19-depleted vs CD34:OS,DFS, Graft failure

Gaziev et al, Blood Adv. 2018 Feb 13;2(3):263-270.

HSCT in Children with TDT: Who?

Risk factor	Class 1	Class 2 (min. 1, max. 2)	Class 3
Inadequate chelation	×	×/✓	✓
Hepatomegaly >2 cm	×	×/✓	✓
Portal fibrosis	×	×/✓	✓

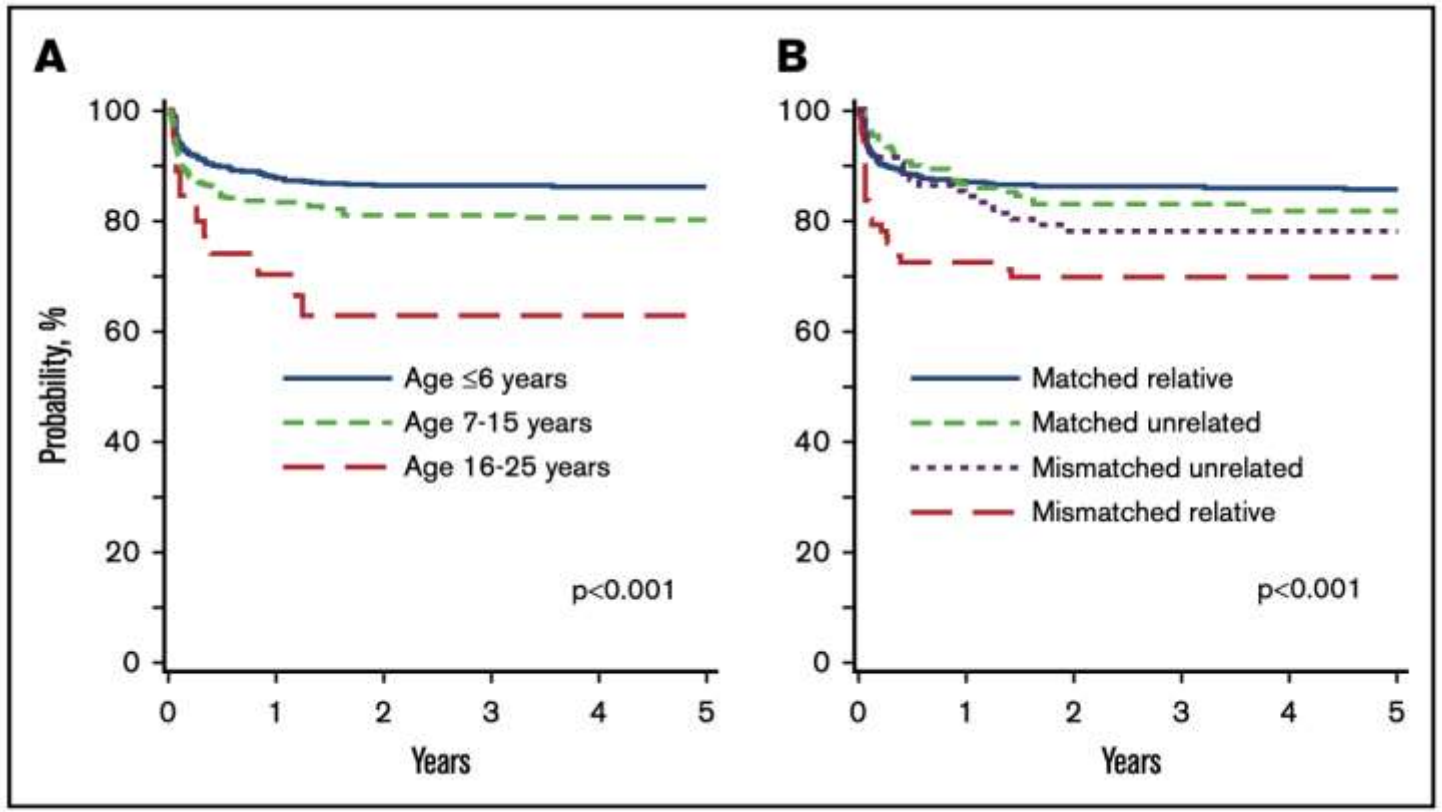
Class III High Risk vs Class III



n= 197

Angelucci E,. Am J Hematol. 2017;92:411–3
Mathews et al. Biol BMT2007, 13:889-894

HSCT in Children with TDT: Age



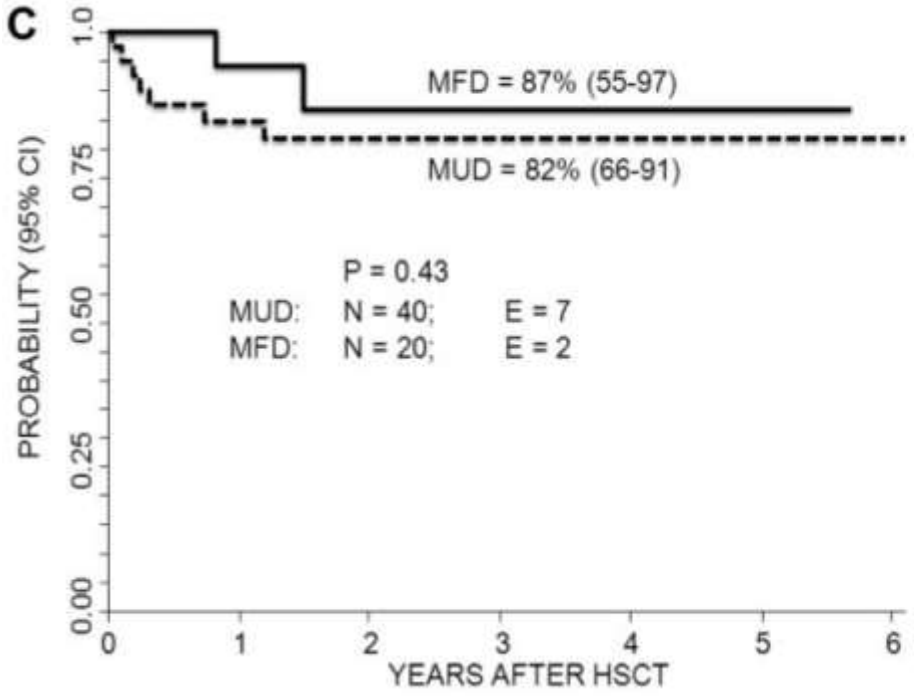
N=1110 β -thalassemia major aged≤25 y (2000-2016)

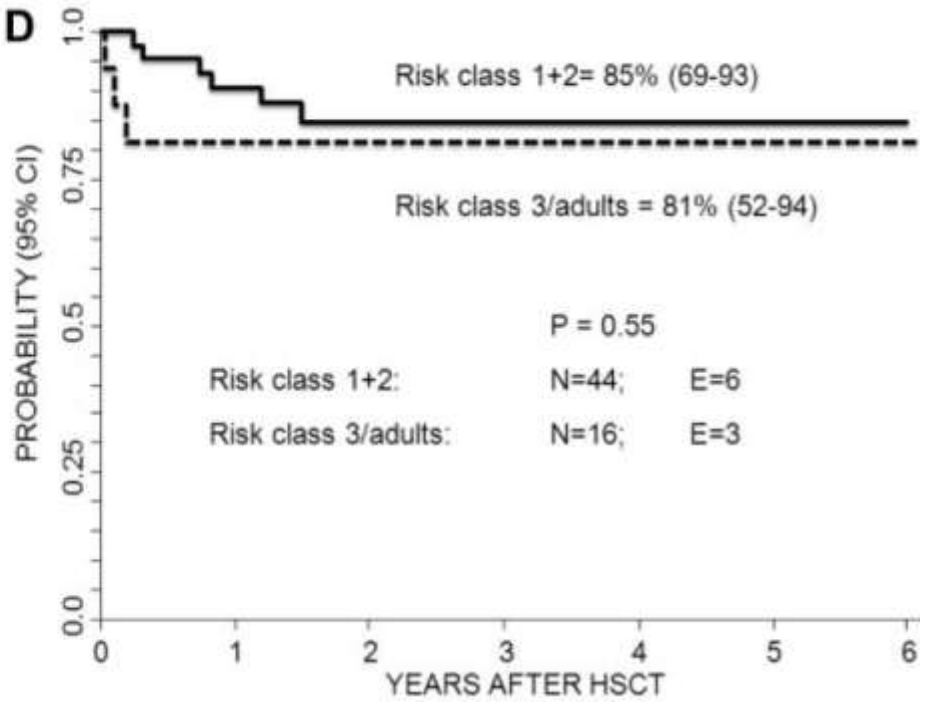
HLA-matched related	n 677	(61%)
HLA-mismatched related	n 78	(7%)
HLA-matched unrelated	n 252	(23%)
HLA-mismatched unrelated	n 103	(9%)

Overall and event- free survival did not differ between HLA-matched related and HLA-matched unrelated donor transplantation (89% vs 87% and 86% vs 82%, respectively)

Li et al.Blood Adv. 2019;3(17):2562–70.

HSCT in TDT: Treosulfan Based Conditioning Regimen

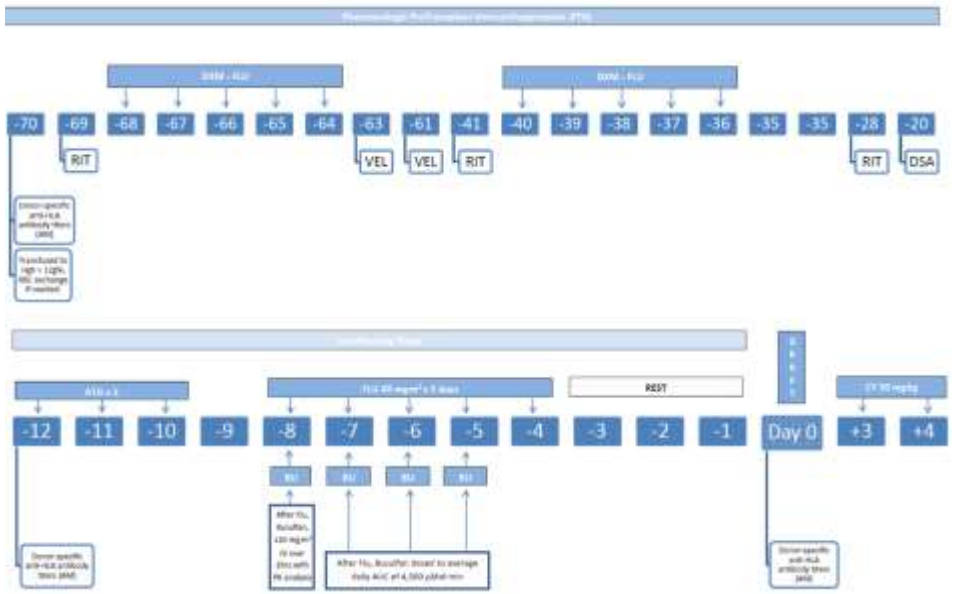




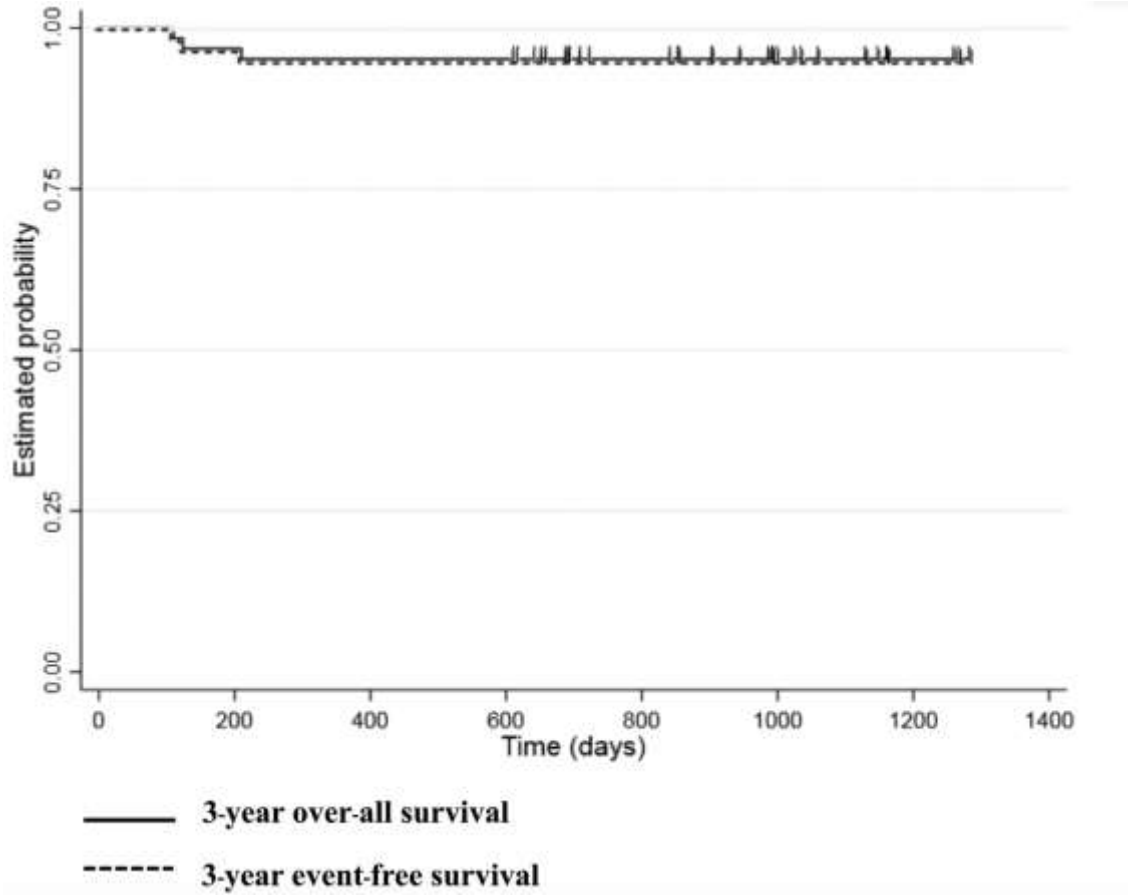
Donor	MFD	UD	TOT
Risk 1	12	15	27
Risk 2	4	13	17
Risk 3	1	3	14
Adults	3	9	12

Bernardo et al. Blood 2012 Jul 12;120(2):473-6.

HSCT in TDT: Sequential IS – RTC- Haplo



Pts=	83
Median Age=	12 (1-28)
Class 3 HR=	35
G.Failure=	3
Deaths=	4



U. Anurathapan et al. / Biol Blood Marrow Transplant 26 (2020) 11061112

Take Home Messages

Malignancy

Risk stratification: Genetic, Response to Treatment, MRD
Achievement of MRD CR predicts outcome
TBI improves outcome in pALL

Benign (Hb pathies): outcome

DONOR
Age at Transplant (and scores)
Low toxicity regimens (Treosulfan based) improve outcome

New Transplant Platforms (Haplo)/ Conditioning Regimens – GVHD prophylaxis (haplo) can overcome the lack of donors

AIBT
Associazione Italiana
di Immunogenetica
e Biologia dei Trapianti

XXX
Congresso
Nazionale

Napoli, 10/12 ottobre 2024

"The programme of this event has been approved by the EFI Education Committee"

ATTENTION

THANK YOU FOR YOUR ATTENTION