ACCADEMIA NAZIONALE DI MEDICINA

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP YOUNG PRECEPTORSHIP 2026
Nuovi approcci terapeutici in Ematologia pediatrica non oncologica

Considerazioni pratiche sull'uso del TCSE allogenico nella talassemia trasfusione-dipendente

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Disclosure

Il sottoscritto Marco Zecca

in qualità di docente/moderatore/relatore/tutor, ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

Dichiara

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

Company name	Research support	Employee	Consultant	Shareholder	Speakers' bureau	Advisory board	Other
AMGEN					X		
CLINIGEN						X	
GRIFOLS						X	
MEDAC	X				X	X	
NOVARTIS						X	
NOVO NORDISK						X	
VERTEX					X	X	

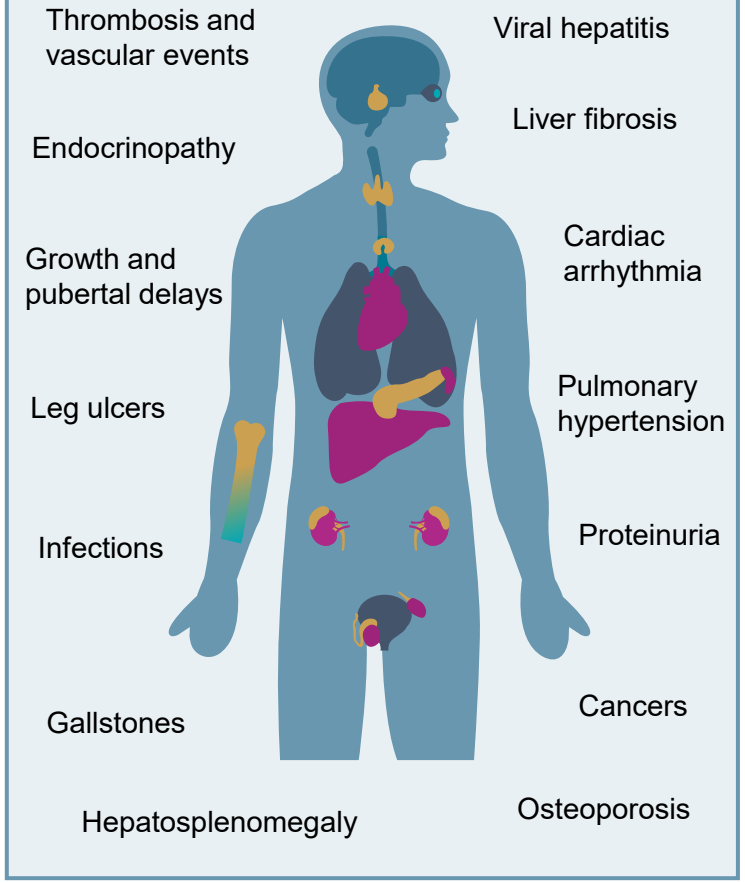
Why an MDT is essential

Haemoglobinopathies are lifelong multisystem disorders

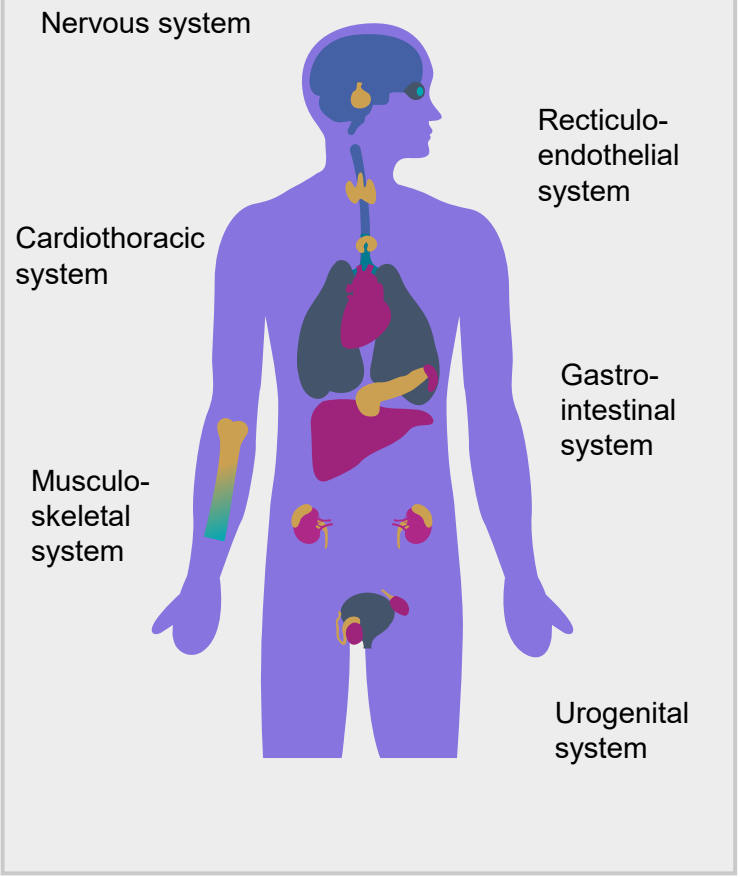
- They require comprehensive, coordinated management
- Transfusion and chelation remain essential but address only part of the disease burden
- A structured, proactive multidisciplinary approach anticipates complications
- Integration of an MDT practice improves survival, adherence, and quality of life, while ensuring equitable access to expertise[1]

Multidisciplinary care should be continuous, coordinated, and centred on the patient, rather than a sequence of isolated consultations

Thalassaemia complications[2]



Sickle cell disease complications[3]



MDT, multidisciplinary team.

1. 2025 Guidelines for the management of transfusion dependent thalassemia (5th edition). Eds.: Taher A, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Publisher: Thalassaemia International Federation;
2. Taher AT, et al. *N Engl J Med*. 2021; 384:727–743; 3. Piel FB, et al. *N Engl J Med*. 2017;376:1561–1573.

Patient baseline pre-transplant assessment

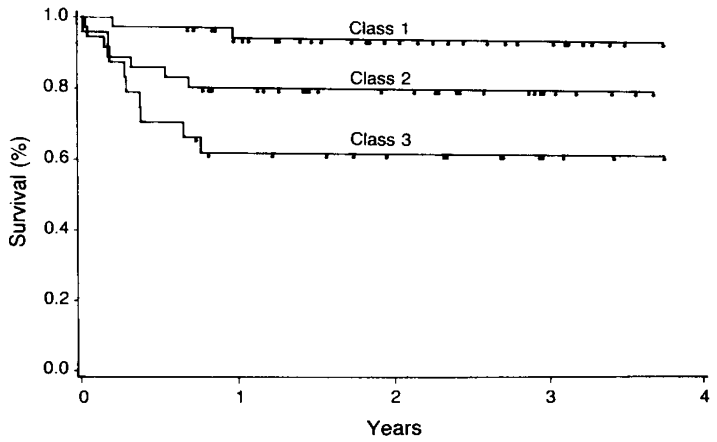
	Organ/system	Test	TDT	SCD
	Infections disease screening	• Infectious disease markers • Search for MDR colonisation	+ ++	+ ++
	Immunology	• Anti-HLA antibody screening • Extended RBC phenotyping	+++ (risk of GF if DSA+) ++	+++ (risk of GF if DSA+) ++++
	Haematology/tests for iron overload	• Quantification of RBC transfusions • Ferritin • T2* MRI of the liver • T2* MRI of the heart • % of HbS • Hypertansfusion/erythroexchange	+++ + +++ +++ No + (Hb >10g/dL)	++ + No No Yes +++ (HbS <30%)
	Lung	• Pulmonary function tests • Chest CT scan	+ No	+++ +++
	Heart	• ECG • Echocardiogram	++ ++	++ ++
	Kidney	• GFR • Urine albumin-to-creatinine ratio • Urinalysis	++ ++ ++	+++ +++ +++
	Central nervous system	• EEG • Brain MRI • Transcranial doppler (paediatric patients)	++ No No	+++ +++ +++

Information provided by speaker based on clinical experience. CT, computed tomography; DSA, donor-specific antibody; ECG, electrocardiogram; EEG, electroencephalography; GF, graft failure; GFR, glomerular filtration rate; Hb, haemoglobin; HbS, haemoglobin S; HLA, human leukocyte antigen; MDR, multi-drug resistant; MRI, magnetic resonance imaging; RBC, red blood cell; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassaemia.

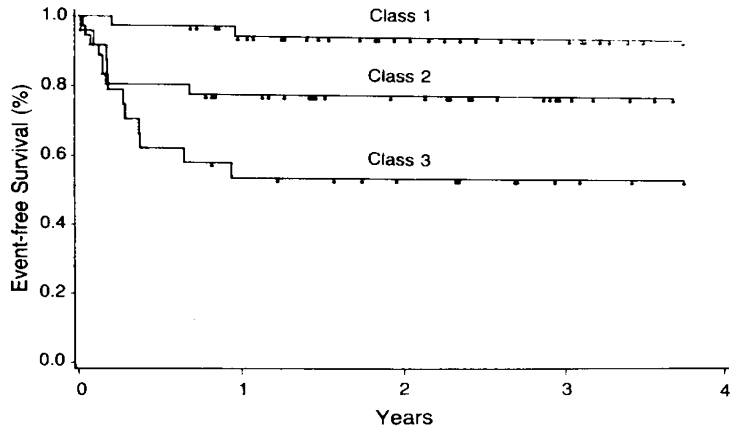
Pesaro risk classification

Risk factors[1,2]	Class 1	Class 2	Class 3
Hepatomegaly[a]	No	Yes/No	Yes
Irregular chelation[b]	No	Yes/No	Yes
Portal fibrosis	No	Yes/No	Yes
Total number of risk factors	0	1 or 2[c]	3

[a]>2 cm below costal margin.
[b]Desferoxamine initiated >18 months after the first transfusion or administered less than 8 hours continuously on at least 5 days per week.
[c]One or two of any of the three risk factors.



Outcome	Class 1	Class 2	Class 3
Survival (%)	94	84	50
Thalassaemia-free survival (%)	87	81	47
Transplant-related mortality (%)	6	15	47



1. Lucarelli G, et al. *N Engl J Med* 1990; 322:417–421. 2. Angelucci E, et al. *Am J Hematol* 2017; 92:411–413.

Key concepts in iron overload management

Implications for HCT / GT

Magnitude AND duration matter

Both the magnitude of iron overload and the duration of exposure to toxic iron are critical determinants of iron-related tissue damage[1]

Lifelong chelation is key

Regular and life-long chelation therapy is crucial to consistently suppress tissue reactive iron species and prevent tissue damage[2]

Cardiac T2* < 20 msec = early risk

In TDT, cardiac T2* below 20 msec is already associated with increased cardiac morbidity risk — long before the critical threshold of 10 msec[3,4]

Limited evidence for pre-transplant chelation

Evidence supporting benefit of intensive pre-transplant chelation in poorly chelated patients is limited; greatest potential in younger patients with sufficient time to reduce iron burden[1]

Iron impairs HSPCs function

Iron overload impairs HPSCs function through iron-induced reactive oxygen species[5] — potentially relevant for mobilisation, collection and manufacturing in GT

Risk Stratification for GT/GE — LIC and Cardiac T2* Thresholds

	✓ LOW RISK Proceed	! CAUTION Optimise first	✕ HIGH RISK Reassess / defer
LIC	≤7 mg/g dw	>7 and ≤15 mg/g dw	>15 mg/g dw
Heart T2*	≥20 msec	<20 and ≥10 msec	<10 msec

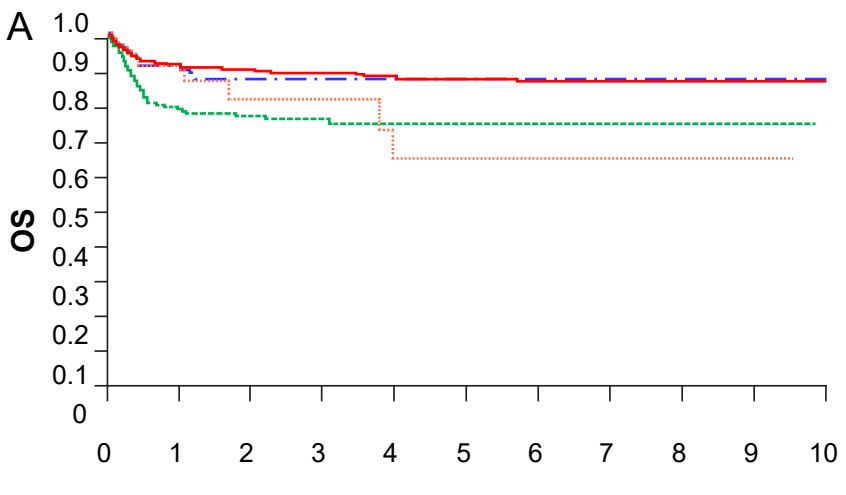
Suggested approach for LIC >7 and <15 mg/g dw and/or T2* <20 and ≥10 msec: At least 6 months of intensive chelation targeting **LIC <7 mg/g dw** and **T2* >20 msec**. If targets not achieved despite optimal efforts, consider proceeding based on clinical judgment.

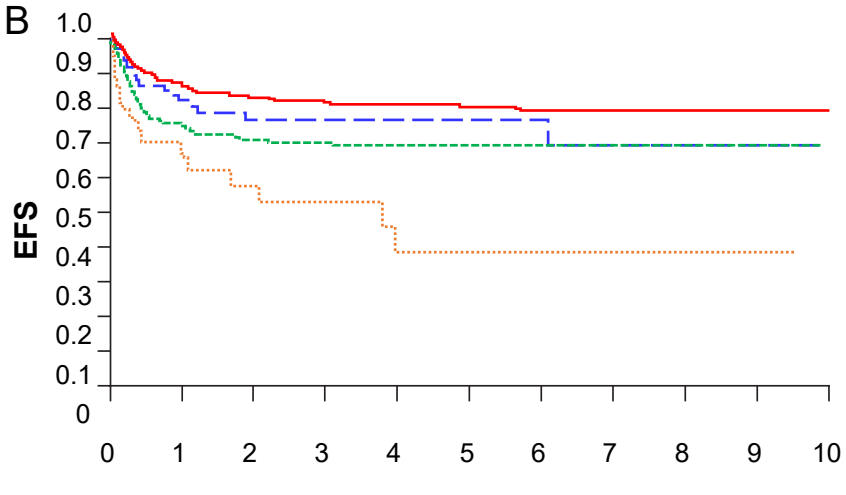
dw, dry weight; GE, gene editing; GT, gene therapy; HPSCs, haematopoietic stem and progenitor cells; LIC, liver iron concentration; TDT, transfusion-dependent β-thalassaemia.

1. Angelucci E. *Blood* 2025;145(4):372-82. 2. Coates TD, et al. *Blood* 2025;145(4):359-71. 3. Kirk P, et al. *Circulation* 2009;120(20):1961-8. 4. Pennell DJ, et al. *Circulation* 2013;128(3):281-308. 5. Jin X, et al. *Haematologica*. 2018;103(10):1627-34. Information provided by speaker based on clinical experience.

Age and type of donor determine outcomes in β-thalassaemia

Results from the EBMT Registry (2000–2010) on 1,493 patients: overall survival (a) and event-free survival (b) by donor[1]





		OS		EFS	
	Patients	Events	2-year OS	Events	2-year EFS
MSD	1061	88	0.91±0.01	151	0.83±0.01
MFD	127	11	0.88±0.04	22	0.78±0.05
MMFD	57	8	0.68±0.11	8	0.68±0.11
UD	210	43	0.77±0.03	43	0.77±0.03
P-value		<0.001		<0.001	

Donor information missing in 38 cases (2.5%)

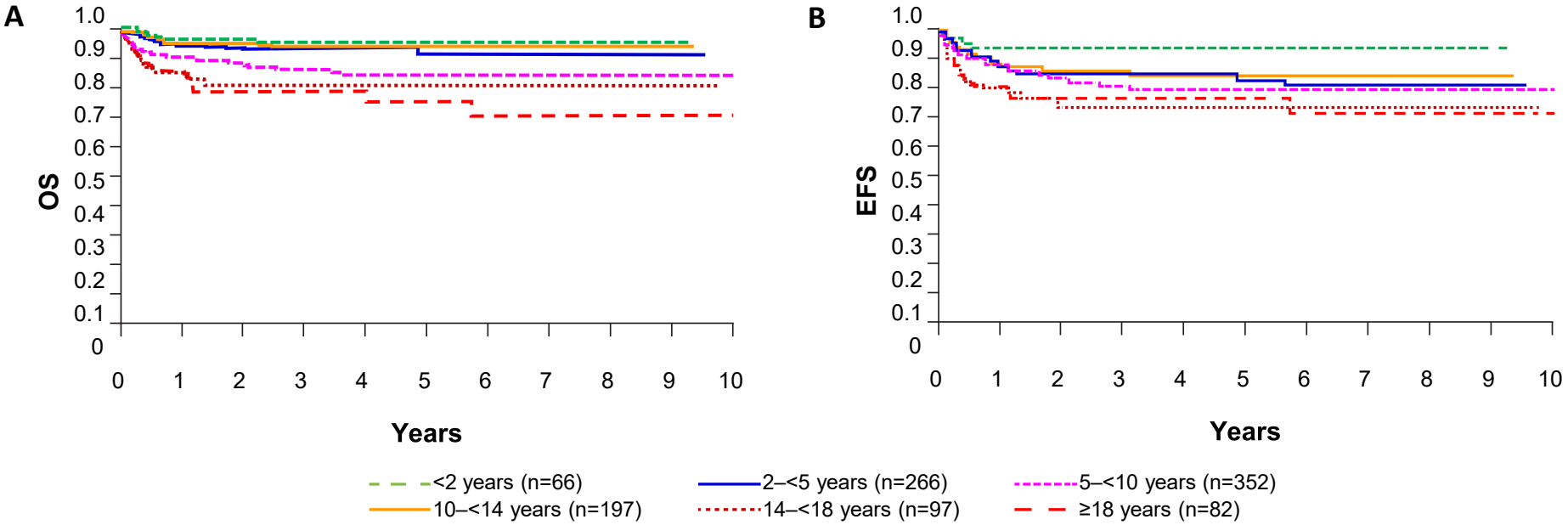
- Good outcome at 2 years after HSCT
- Outcome depends on donor type

EBMT, European Group for Blood and Marrow Transplantation; EFS, event-free survival; HSCT, haematopoietic stem cell transplantation; MFD, matched family donor other than sibling; MMFD, mismatched family donor; MSD, matched sibling donor; OS, overall survival; TDT, transfusion-dependent β-thalassaemia; UD, unrelated donor.

1. Baronciani D, et al. *Bone Marrow Transplantat* 2016;51:536–541.

HSCT for TDT: the EBMT data

Results from the EBMT Registry (2000–2010) on 1,493 patients: overall survival (a) and event-free survival (b) by donor[1]



	Patients	A) OS Events	A) OS 2-yrs. OS	B) EFS Events	B) EFS 2-yrs. pEFS
a) < 2 years	66	3	0.95±0.03	4	0.93±0.03
b) 2 - < 5 years	266	13	0.94±0.02	32	0.86±0.03
c) 5 - < 10 years	352	33	0.90±0.02	52	0.83±0.02
d) 10 - < 14 years	197	8	0.96±0.02	24	0.86±0.03
e) 14 - < 1 8 years	97	14	0.82±0.04	20	0.74±0.05
f) ≥ 18 years	82	16	0.80±0.05	18	0.76±0.05
P-value (for trend)		<0.001		<0.001	

- Good outcome at 2 years after HSCT
- Outcome depends on donor type
- Outcomes is affected by age

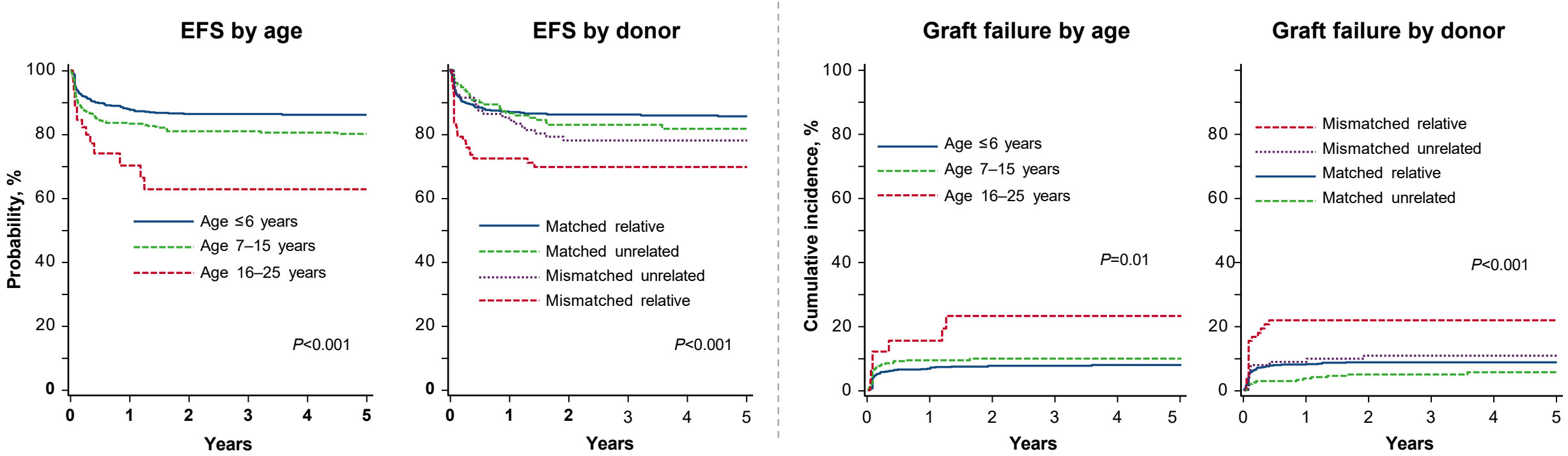
EBMT, European Group for Blood and Marrow Transplantation; EFS, event-free survival; HSCT, haematopoietic stem cell transplantation; MFD, matched family donor other than sibling; MMFD, mismatched family donor; MSD, matched sibling donor; OS, overall survival; TDT, transfusion-dependent β-thalassaemia; UD, unrelated donor.

1. Baronciani D, et al. *Bone Marrow Transplantat* 2016;51:536–541.

Age and type of donor determine outcomes in β-thalassaemia

Results from the CIBMTR (China, India and the US) between 2000–2016: 1110 patients aged ≤25 years

- 61% had matched related donor transplants



- Transplant should be offered early (≤6 years)
- No difference in outcomes between HLA-matched related and HLA-matched unrelated donors up to 15 years of age
- Graft failure is higher in mismatched donors

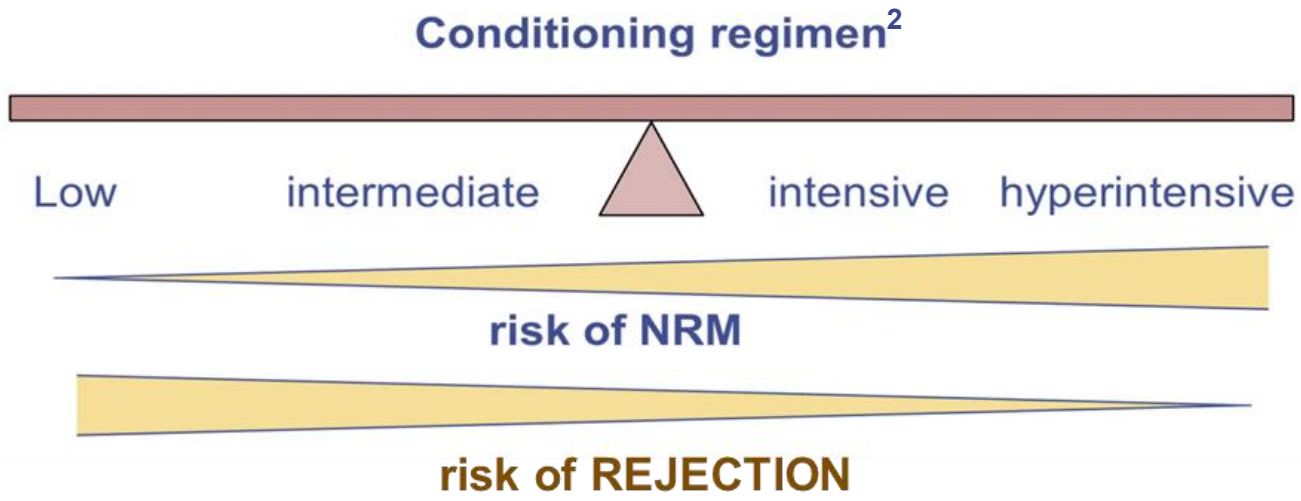
CIBMTR, Center for International Blood and Marrow Transplant Research; EFS, event-free survival; HLA, human leukocyte antigen.

Li C, et al. *Blood Adv* 2019;3:2562–2570.

The goals of the conditioning regimen

The ideal conditioning regimen should be able to:[1]

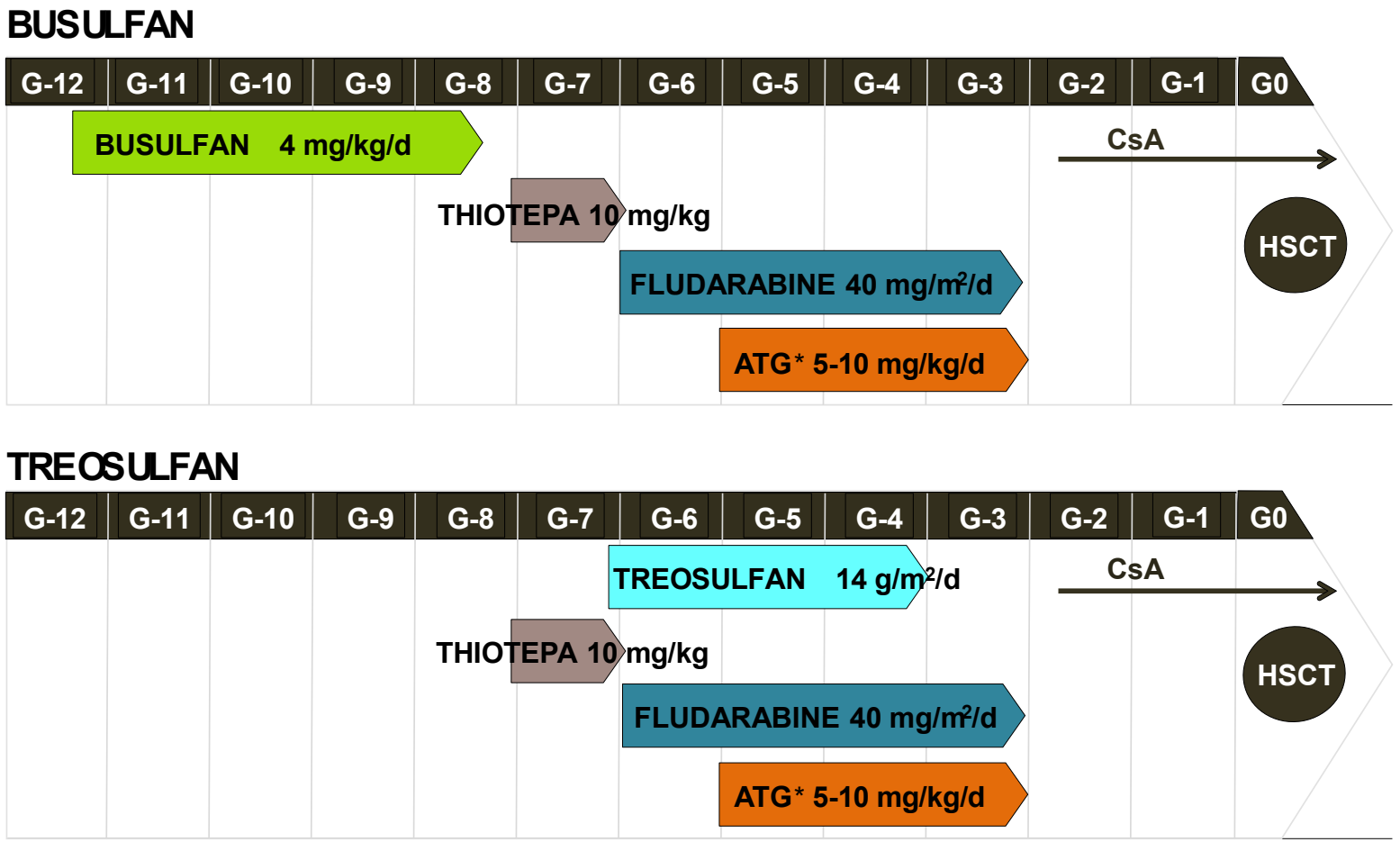
1. Eradicate an expanded bone marrow
2. Provide adequate immunosuppression to achieve sustained engraftment
3. Avoid excessive acute toxicity to chronically iron-damaged tissue
4. Avoid irreversible long-term sequelae



NRM, non-relapse mortality.

1. Information based on speaker's clinical experience; 2. Gagelmann N, et al. *Haematologica* 2021;106:1794–1804.

Conditioning regimens for haemoglobinopathies



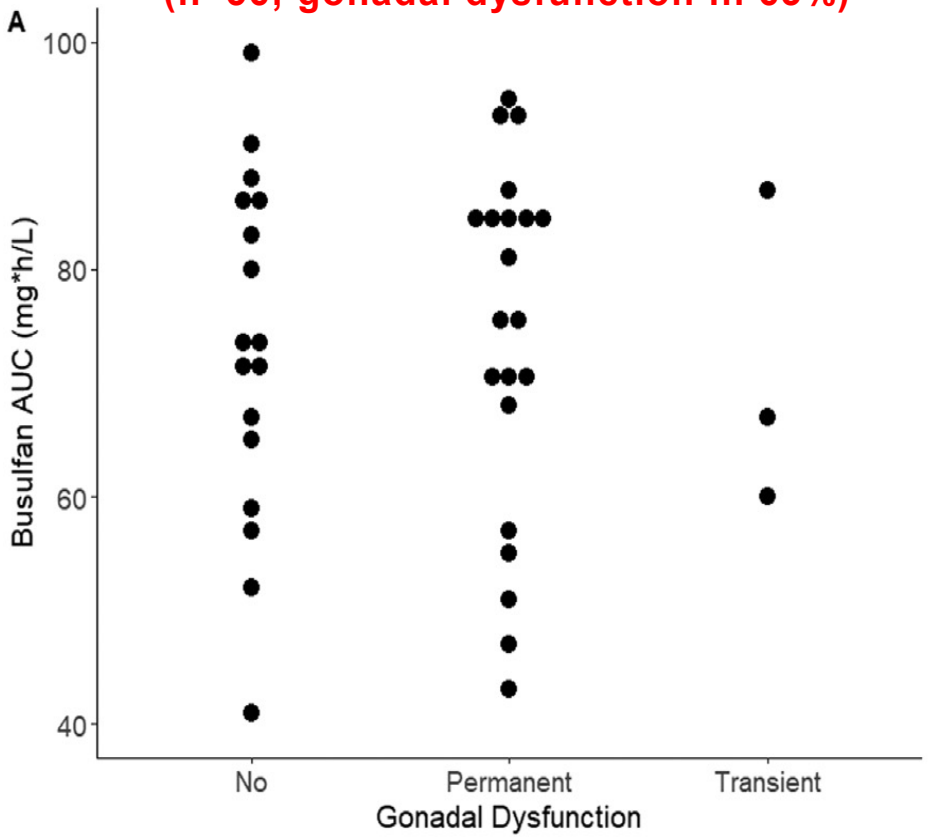
* ATG was administered to all MUD transplant recipients.
After 2010 also all MFD transplant recipients received ATG.

Strocchio L et al. Br J Haematol 2015; 169:726-736.

Busulfan and treosulfan Day 1 exposure and gonadal dysfunction

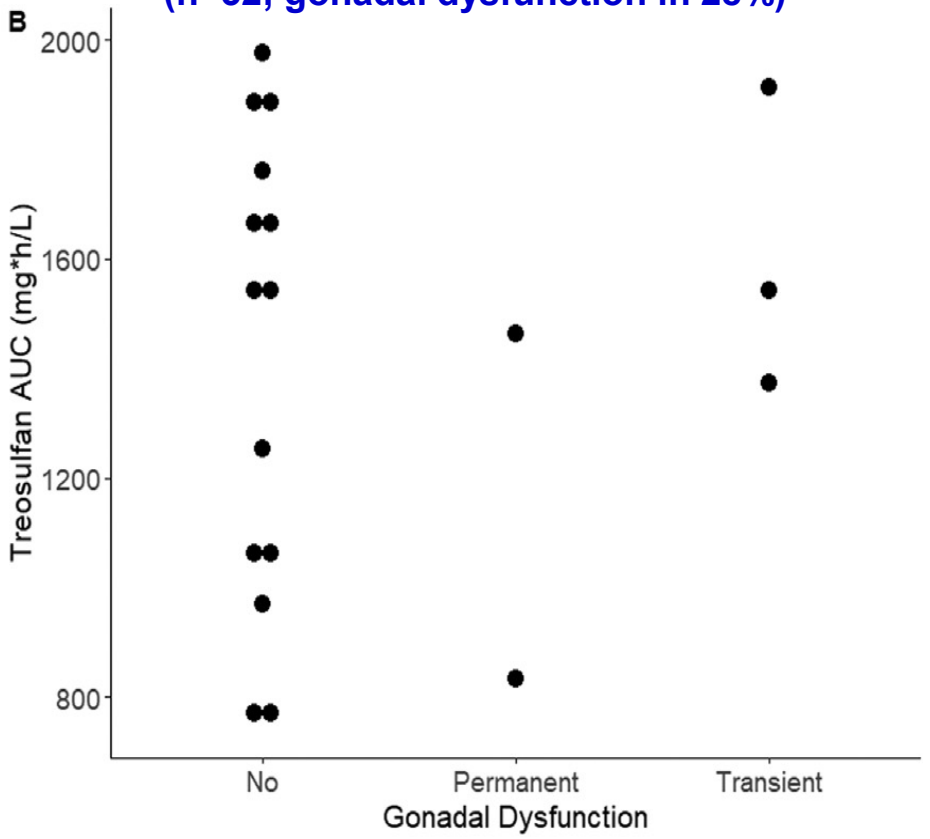
Busulfan[1]

(n=56; gonadal dysfunction in 63%)



Treosulfan[1]

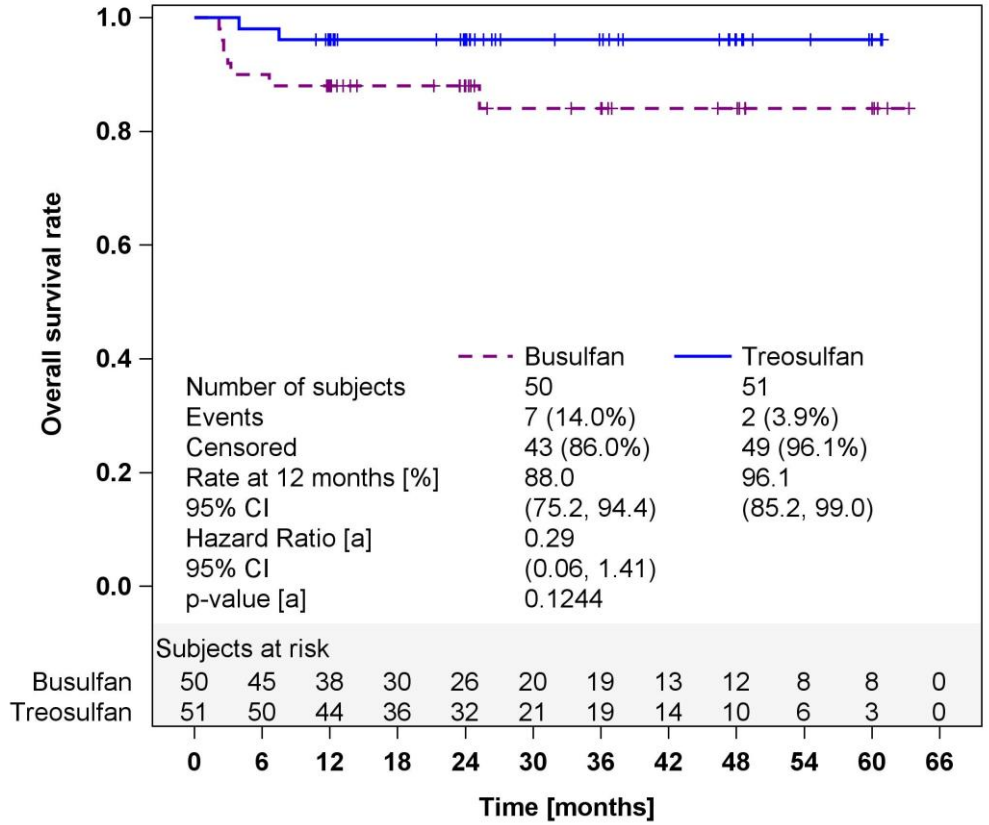
(n=32; gonadal dysfunction in 28%)



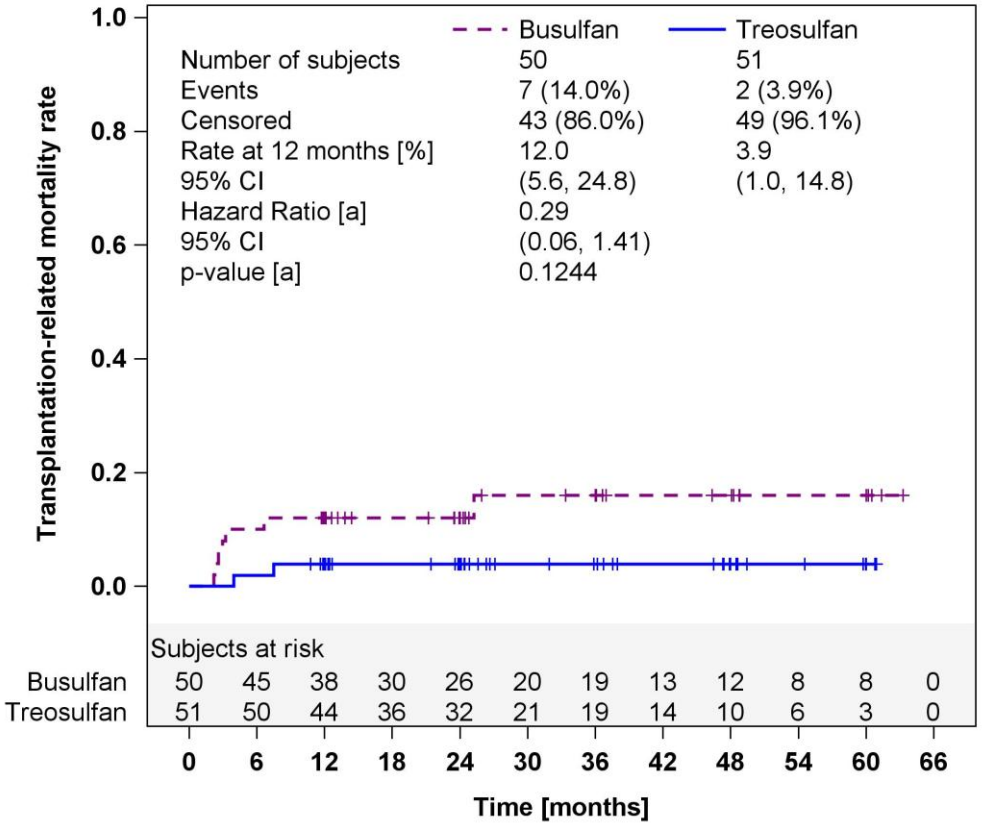
AUC, area under the curve.

1. van der Stoep MYEC, et al. *Transplant Cell Ther* 2023;29:529.e1–529.e5.

Treosulfan versus busulfan for allogeneic BMT in children with non-malignant disease: a randomised phase 2 trial[1]



[a] adjusted for Thiotepa and disease as factors using Cox regression model



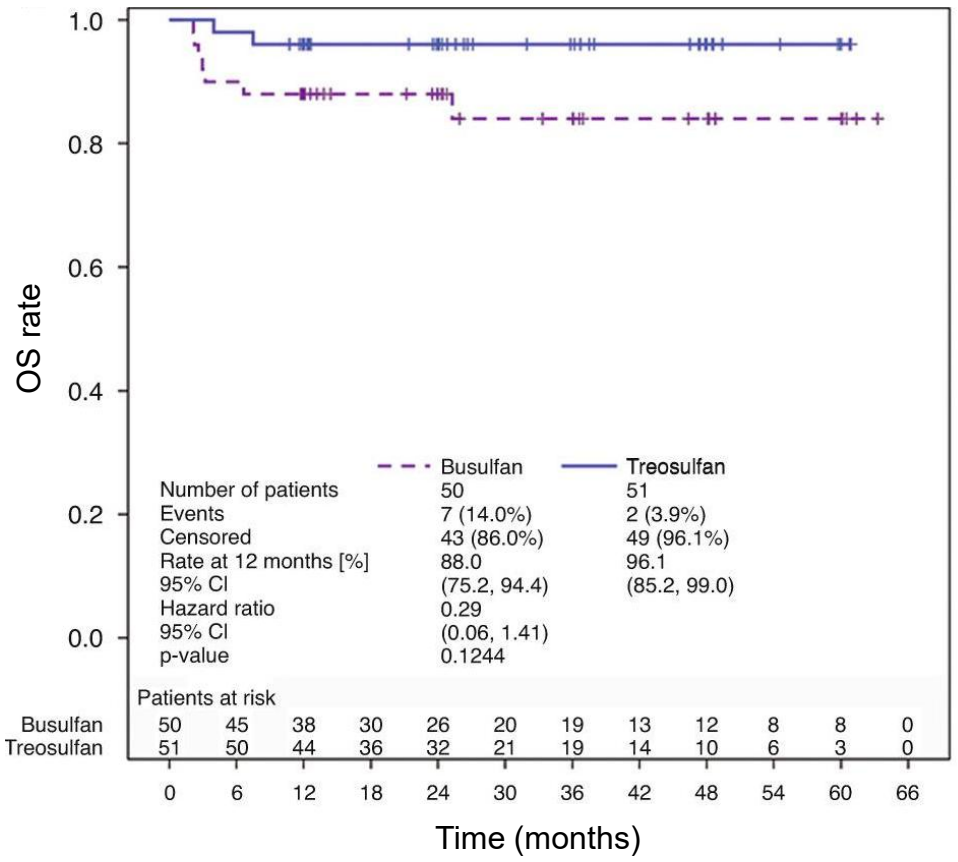
[a] adjusted for Thiotepa and disease as factors using Cox regression model

BMT, bone marrow transplant; CI, confidence interval.

1. Sykora KW, et al. *Bone Marrow Transplant* 2023. DOI: 10.1038/s41409-023-02135-9.

Treosulfan versus busulfan for allogeneic BMT in children with non-malignant disease: a randomised phase 2 trial

OS with treosulfan versus busulfan[1]



Graft failure[1]	Busulfan (n=50)	Treosulfan (n=51)
Patients with event, n (%)	2 (4.0)	11 (21.6)
Primary graft failure	2 (4.0)	2 (3.9)
Secondary graft failure	**0 (0.0)**	**9 (18.4)**
Cumulative incidence at 12 months, % (95% CI)	4.0 (0.0, 9.4)	15.8 (5.8, 25.9)
Hazard ratio (treosulfan/busulfan) (95% CI)	5.48 (1.11, 27.03)	
P-value	0.0366	

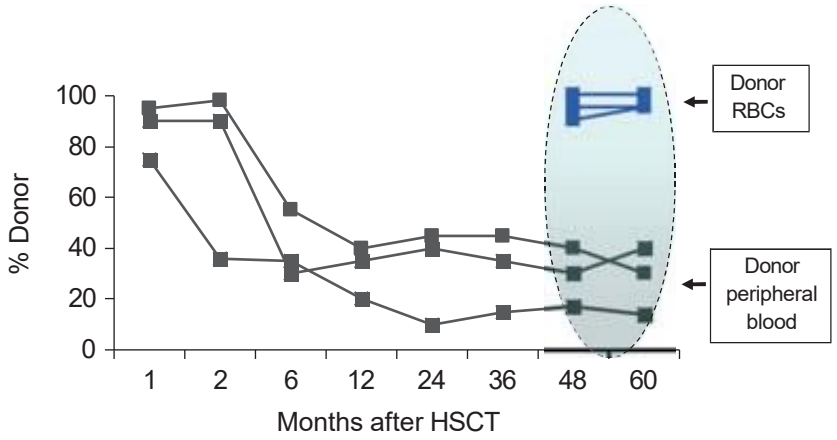
- Randomised allocation was not stratified for underlying disease and resulted in an increased number of patients with β-thalassaemia major in the treosulfan versus busulfan arm[1]
- Although secondary graft failures were more common in the treosulfan group, all of these patients were rescued by second procedures[1]
- Treating physicians may prefer treosulfan over busulfan; for example, in patients with increased risk of TRM related to concomitant infections or pre-existing organ dysfunction[2]

BMT, bone marrow transplant; CI, confidence interval; OS, overall survival; TRM, transplantation-related mortality.

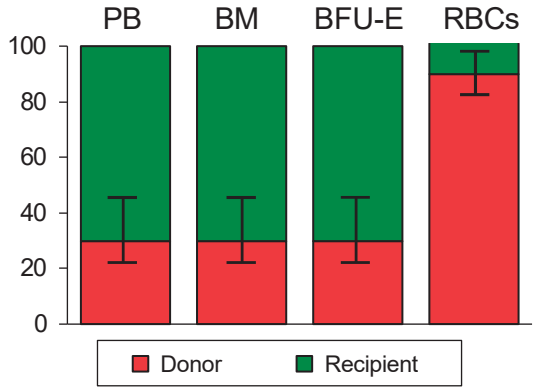
1. Sykora KW, et al. *Bone Marrow Transplant*. 2024;59(1):107–116 (table adapted); 2. Professional opinion of the speaker.

Chimerism

(A) Split chimerism between RBCs and nucleated cells[1]

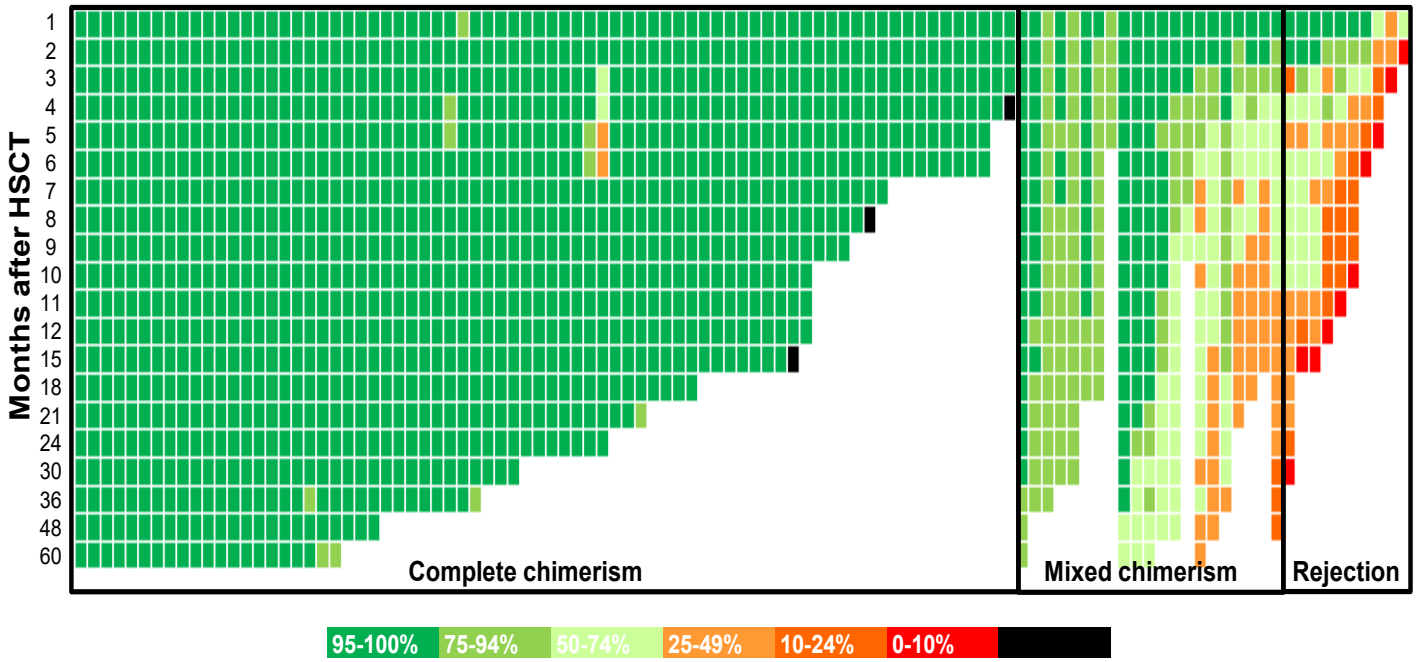


(B) Split chimerism between RBCs and peripheral blood (PB), bone marrow (BM) and erythroid precursors (BFU-E) in a patient with PMC at 60 months after HSCT[1]



Evolution of post-HSCT chimerism[2]

Patients (N = 105)
(thalassemia = 37, sickle = 33, other non malignant = 35)



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Regione Lombardia

BFU-E, erythroid precursors; BM, bone marrow; HSCT, haematopoeitic stem cell transplantation; PB, peripheral blood; PMC, persistent mixed chimerism; RBC, red blood cell.

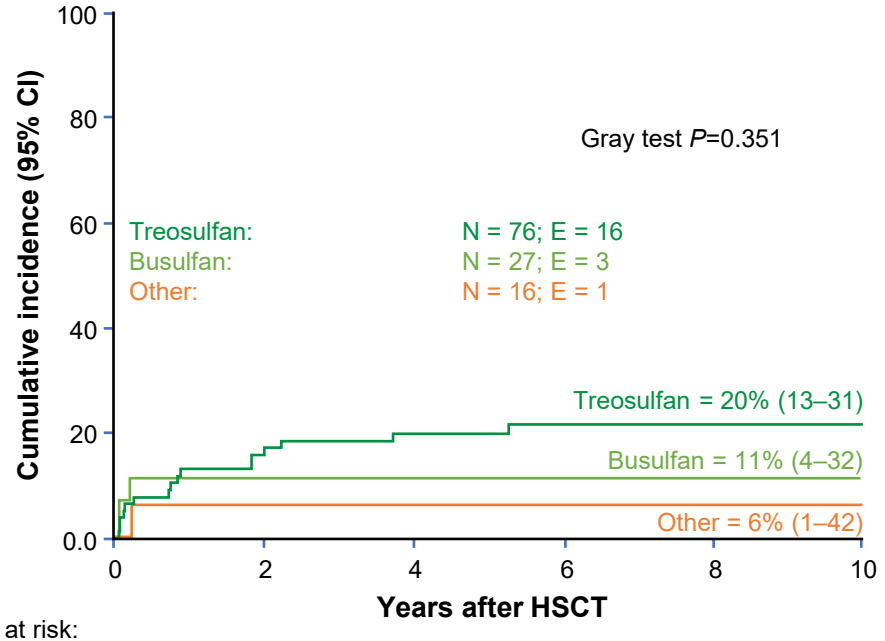
1. Andreani M et al. *Tissue Antigens* 2014;83:137–146; 2. Unpublished data provided by speaker; presented at the EBMT Paediatric Diseases Working Party midterm meeting, 8–10 July 2020.

Age, conditioning regimen and risk of rejection

163 consecutive patients with non-malignant diseases transplanted in Pavia, Italy

- Thalassaemia (n=70); sickle cell disease (n=64); other non-malignant diseases (n=29)
- Age range: 1–18 years (median 6.8 years)

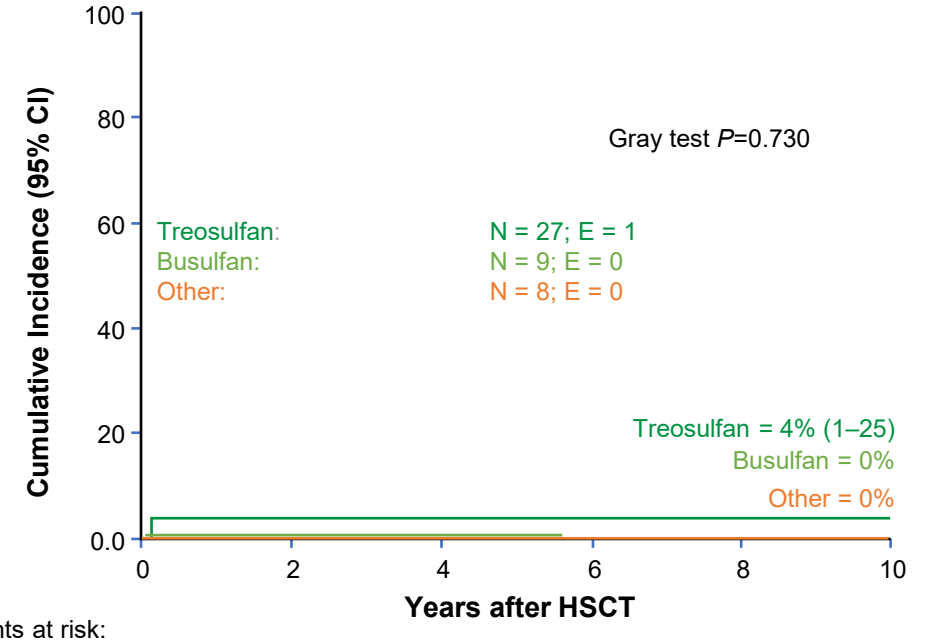
Age at HSCT <10 years



Number of patients at risk:

Treosulfan	76	61	56	42	25	12
Busulfan	27	22	3	2	2	1
Other	16	14	11	6	5	3

Age at HSCT > 10 years



Number of patients at risk:

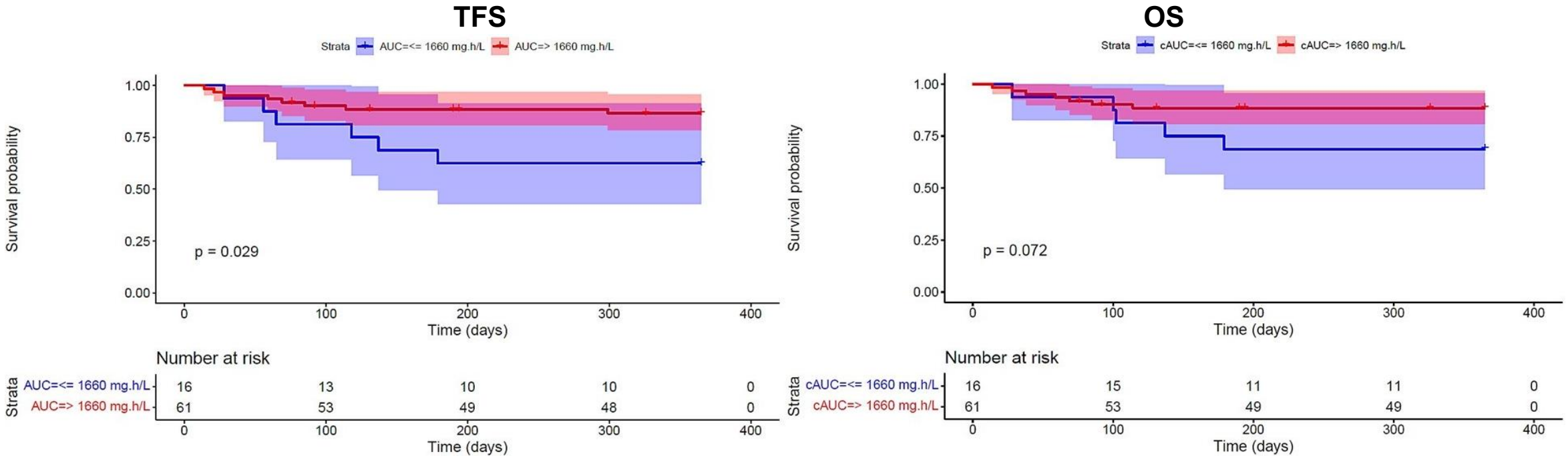
Treosulfan	27	24	22	16	10	4
Busulfan	9	7	1	0	0	0
Other	8	7	6	5	5	2

CI, confidence interval; E, event; HSCT, haematopoeitic stem cell transplantation.

Unpublished data provided by the speaker. Data were originally presented at the EBMT Midterm Focus Meeting on Non-Malignant Diseases. Virtual, 8–10 July 2020.

Eventuale sottotitolo della diapositiva

- **77 patients with TDT receiving treosulfan (14 g/m²/day for 3 days**)/fludarabine/thiotepa regimen before HSCT[1]
- **Five patients (6.5%) had graft rejection** within 1 year
- **Treosulfan AUC was lower in patients who had graft rejection** versus those who did not (1,655 vs 2,037 mg*h/L; *P*=0.07), with a trend to statistical significance
- **Treosulfan exposure ≥1660 mg*hr/L was significantly associated with better 1-year TFS** (88.5% vs 62.5%; *P*=0.029) with a trend to better 1-year OS (90.2% vs 68.8%; *P*=0.07)



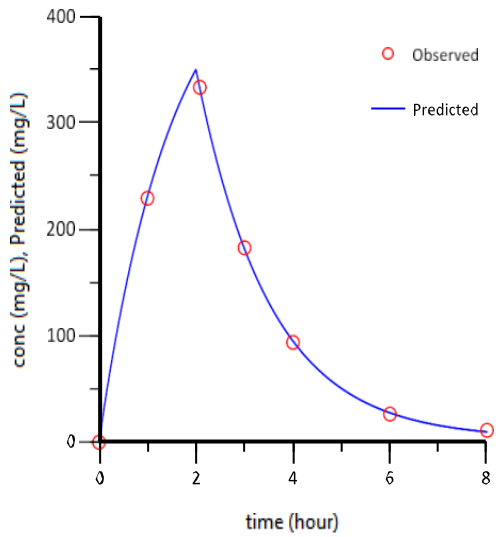
AUC, area under the curve; HSCT, haematopoietic stem cell transplantation; OS, overall survival; TDT, transfusion-dependent β-thalassaemia; TFS, thalassaemia-free survival.

Pai AA, et al. *Clin Pharmacol Therap*. 2024;115(1):116–125.

Treosulfan drug monitoring in children undergoing HSCT

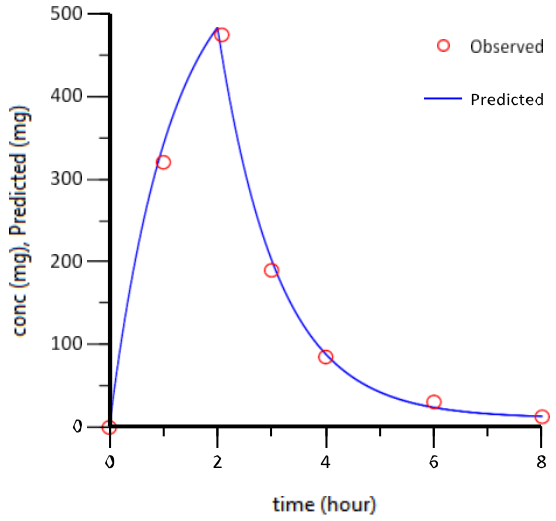
Patient E.G.
Gender: M; Age: 4 years and 3 months
Diagnosis: Sickle cell anaemia

Day 1
Initial dose treosulfan 14 g/m²/day



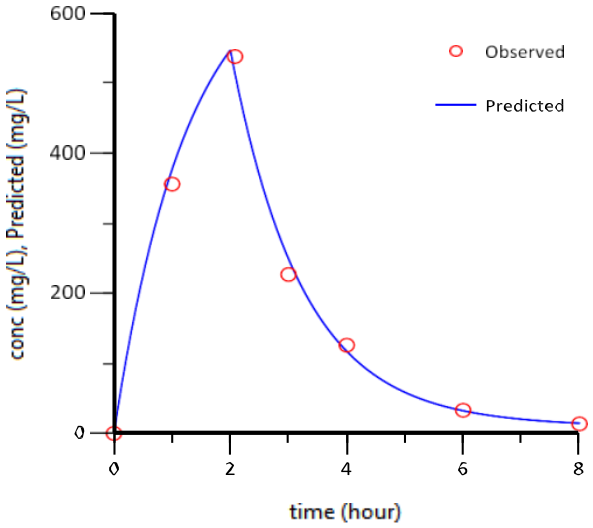
$AUC_{0\text{-}inf}$ after the first dose = 970 mg*h/L
Predicted cumulative AUC = 2,910 mg*h/L
*1,890 mg*h/L lower (-39%) than the therapeutic target*

Day 2
Treosulfan dose increased to 16 g/m²/day



$AUC_{0\text{-}inf}$ after the second dose = 1,219 mg*h/L
Predicted cumulative AUC = 3,657 mg*h/L

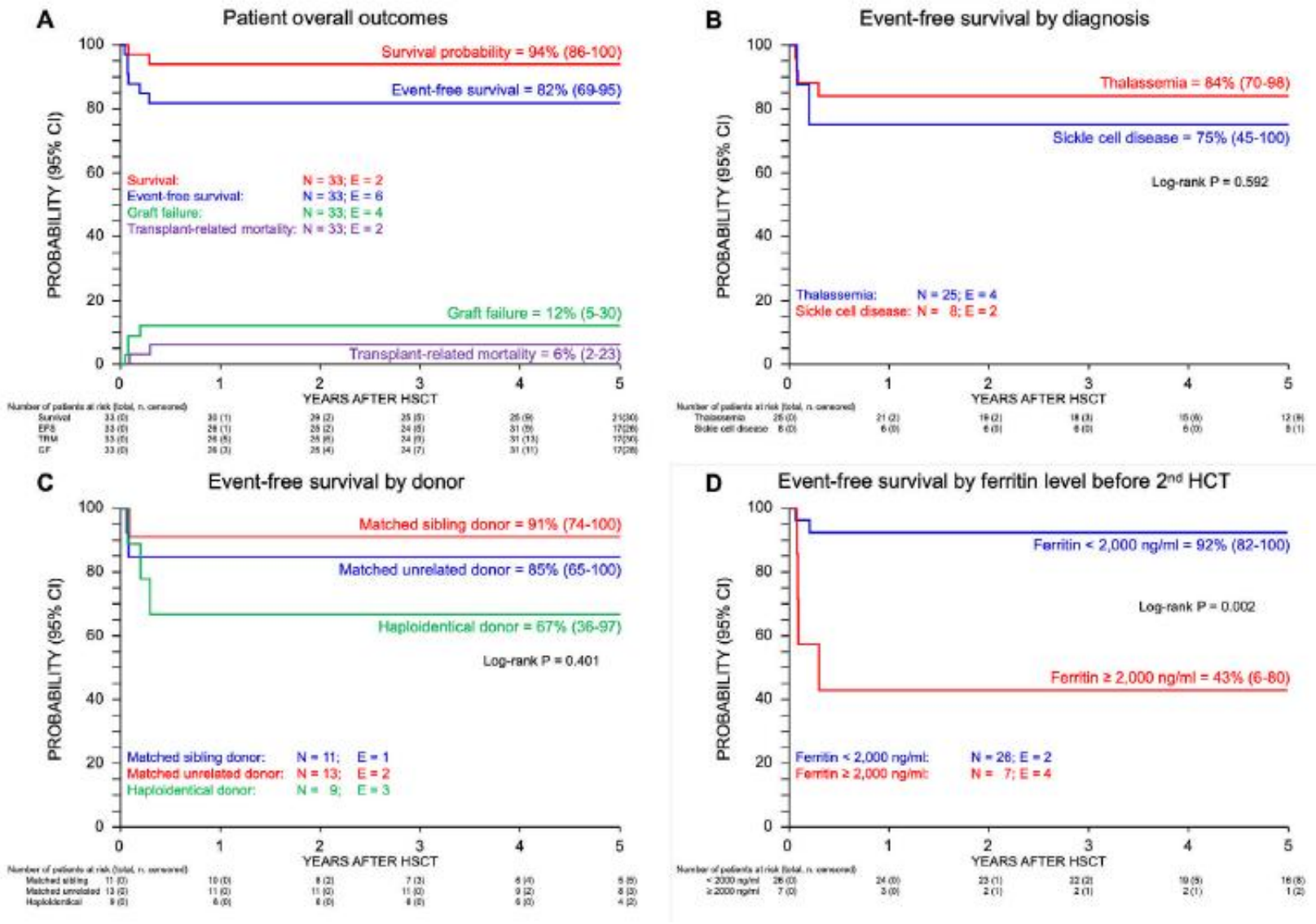
Day 3
Treosulfan dose increased to 17 g/m²/day



$AUC_{0\text{-}inf}$ after the third dose = 1,417 mg*h/L
Predicted cumulative AUC = 4,241 mg*h/L

AUC, area under the curve; HSCT, haematopoietic stem cell transplantation.
Data provided by the speaker. Data were originally presented by Delle Cave F, et al. Oral presentation at the 48th national meeting of the Italian Association of Paediatric Haematology / Oncology (AIEOP). Bologna, Italy, 2–4 October 2023.

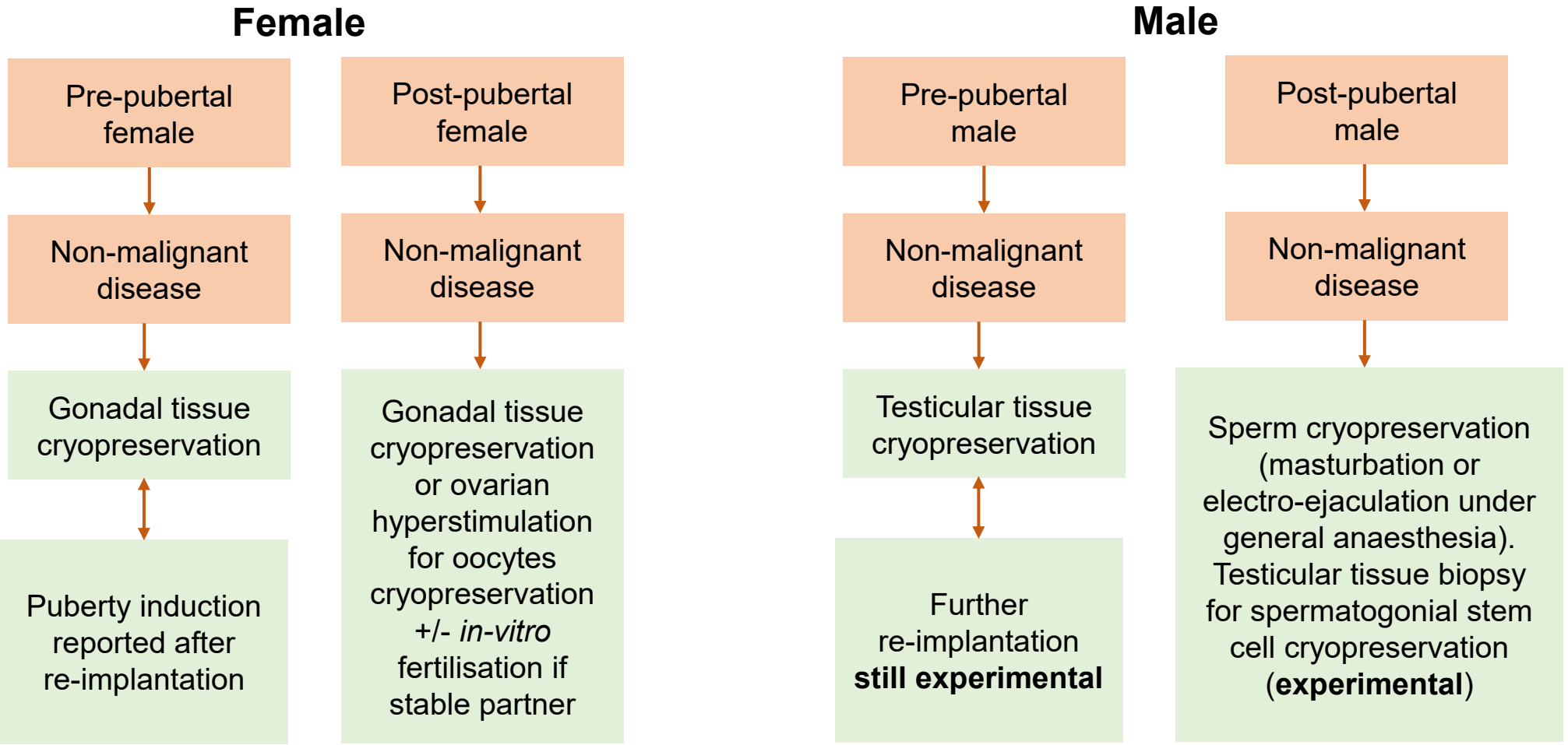
Second Allogeneic Hematopoietic Cell Transplantation After Graft Failure Is an Effective Curative Option in Children With Hemoglobinopathies



Panigari A. et al. Am J Hematol 2026; 0:1–8. https://doi.org/10.1002/ajh.70305

How to preserve fertility?

Proposed algorithm for fertility preservation in children and adolescents[1]



1. Dalle JH, et al. *Bone Marrow Transplant* 2017;52:1029–1035.