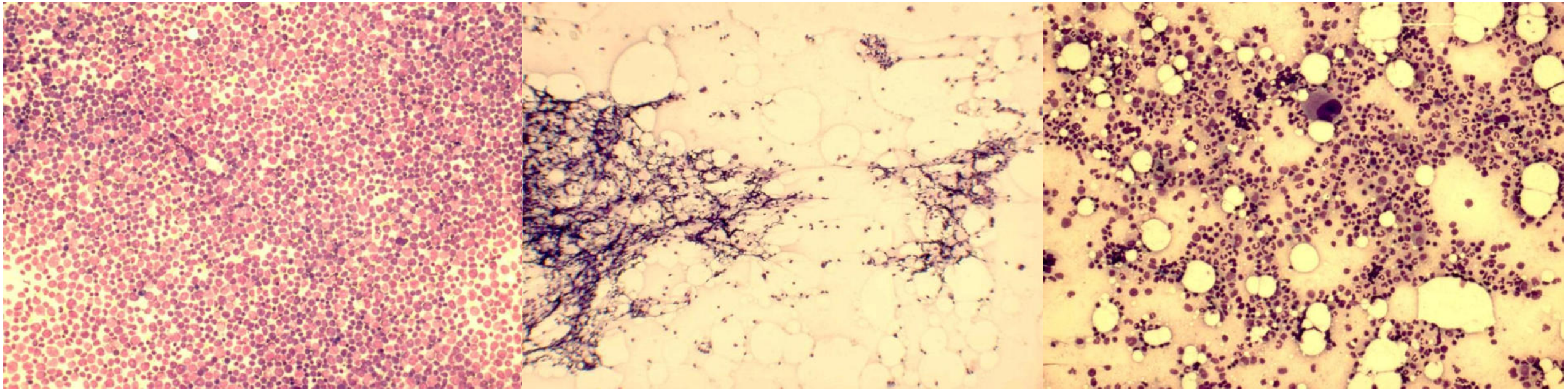
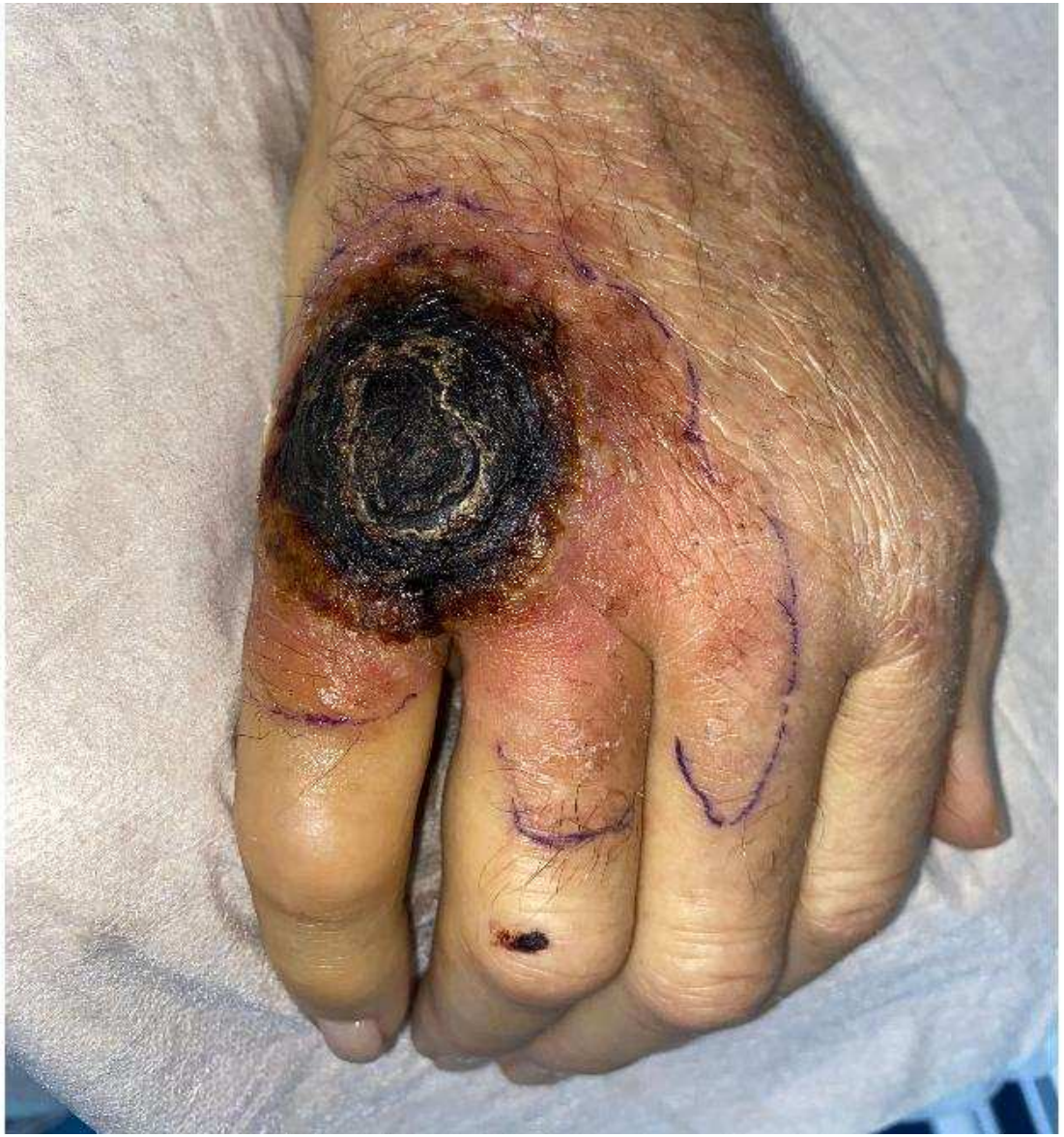
Allogene Stammzelltransplantation, nicht maligne Erkrankungen



Prof Jakob R Passweg

UNI BASEL

Universitätsspital Basel




BD
BD


W. I. LENIN
WAS TUN?
BRENNENDE FRAGEN UNSERER BEWEGUNG
VERLAG NEUER WEG BERLIN

Diagnostische Abgrenzung

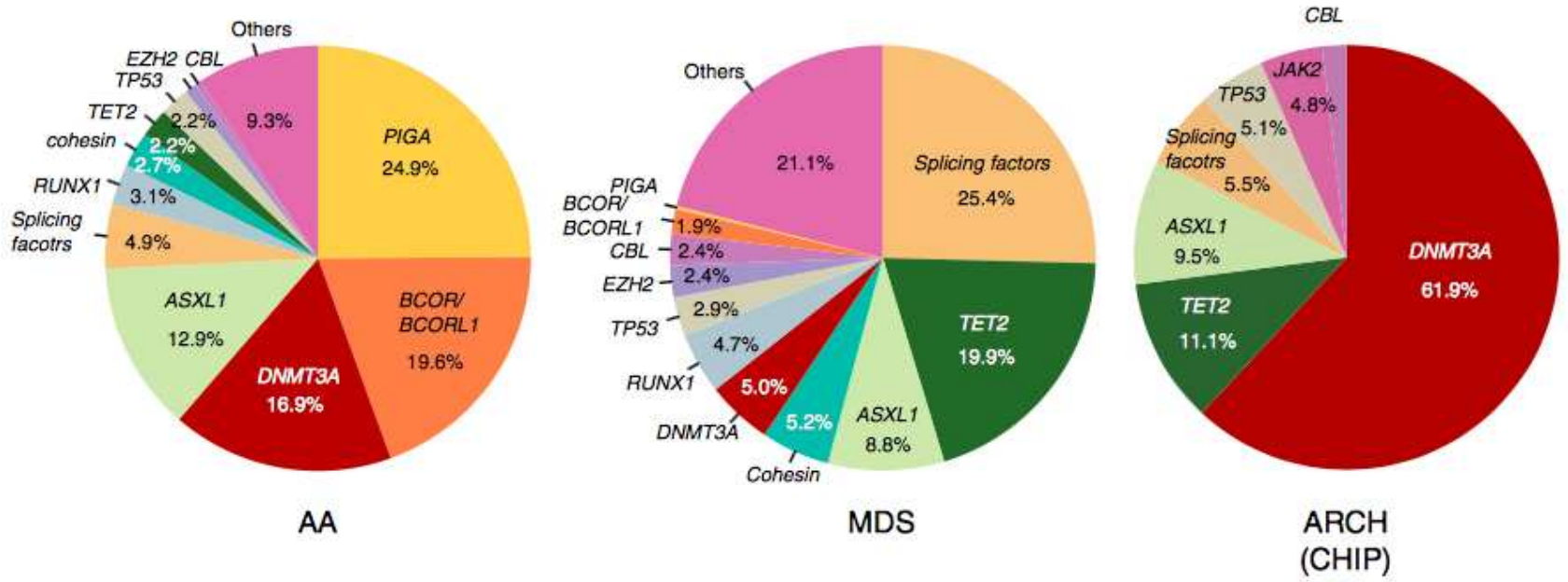
Youngerly

- DD congenital marrow failure
  - Fanconi
  - Telomeropathy
  - SDS

Elderly

- DD hypoplastic MDS

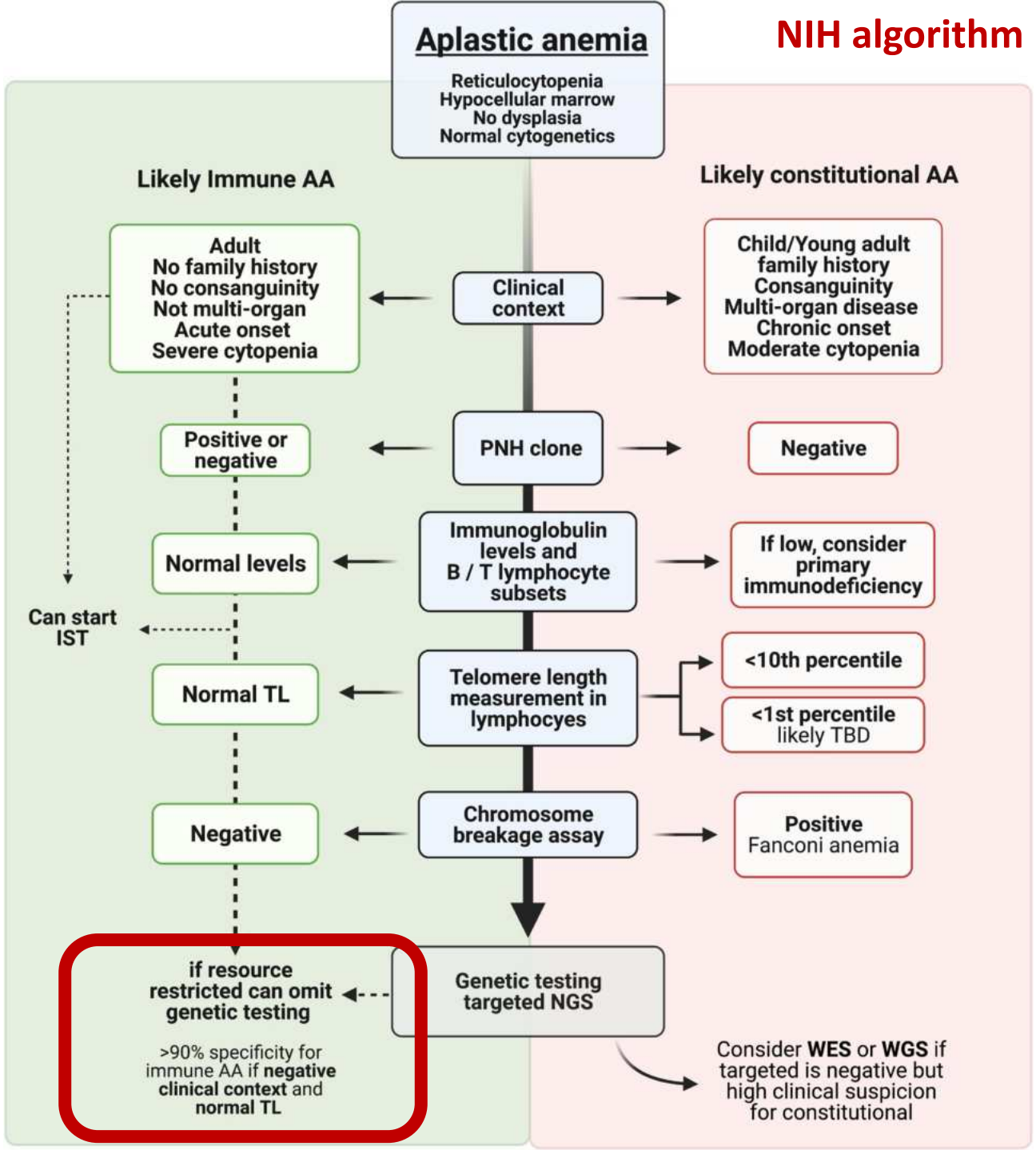
Genetischer overlap mit MDS und CHIP



Ogawa S. Blood. 2016;128(3):337-347 ; Yoshizato T et al. N Engl J Med 2015;373:35-47.;
Haferlach T, et al. Leukemia. 2014; 28(2):241-247. Jaiswal S N Engl J Med. 2014;371(26): 2488-2498

How to distuinguish BMF acquired versus congenital ?

New maschine learning algorithm by the NIH, soon available online …



Gutierrez-Rodrigues F, et al. Differential diagnosis of bone marrow failure syndromes guided by machine learning. Blood. 2022 Dec 21:blood.2022017518.

Groake E et al. Best Prac Res Clin Haematol 2021

Distinction between AA and hypoplastic MDS

Characteristics	AA	hypoplastic MDS
dyserythropoiesis	sometimes	yes
abnormal neutrophil	no	yes
dysplastic megakaryocytes	no	yes
fibrosis	no	occasional
increased blasts	no	Sometimes (ALIPS)
CD34+ cells in BM	< 1.0%	sometimes increased
clonality	possible	sometimes
splenomegaly	absent	occasional

Bennett et al. Sem Hemato 2000;37:15-29

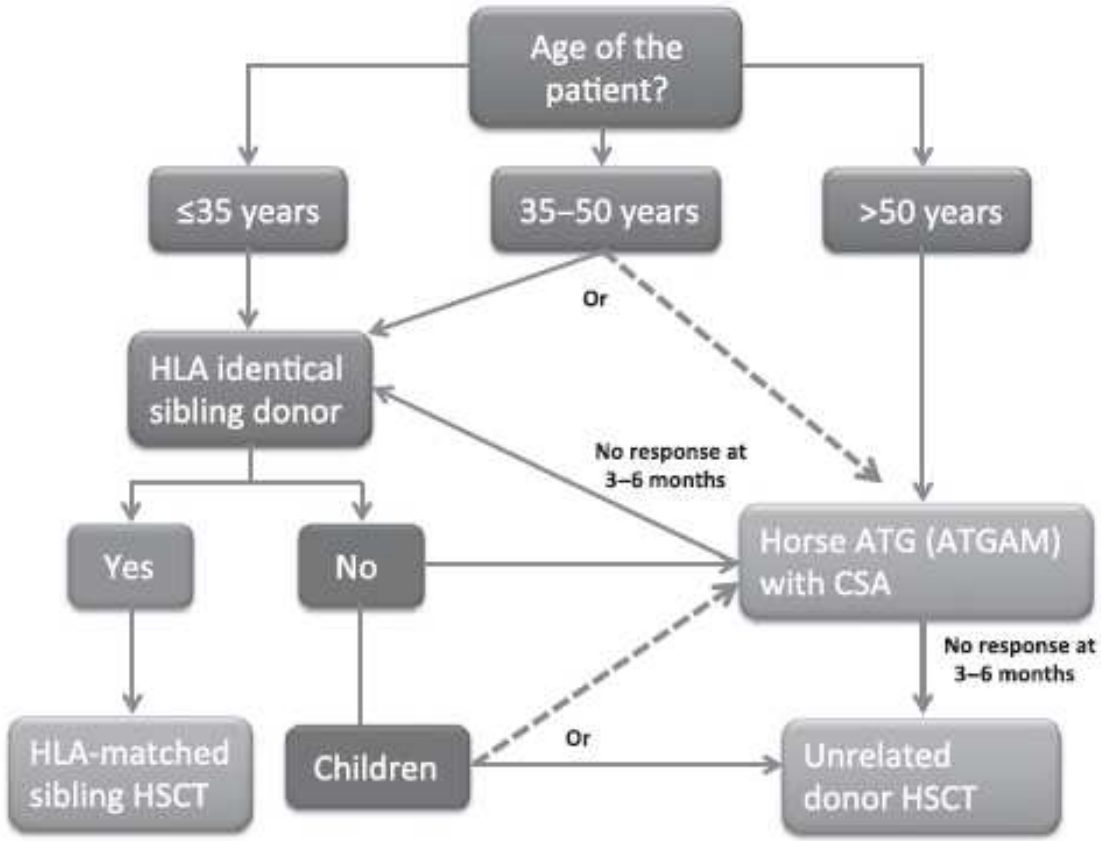
Bennett & Orazi. Haematologica 2009 Feb; 94(2):264-843-70

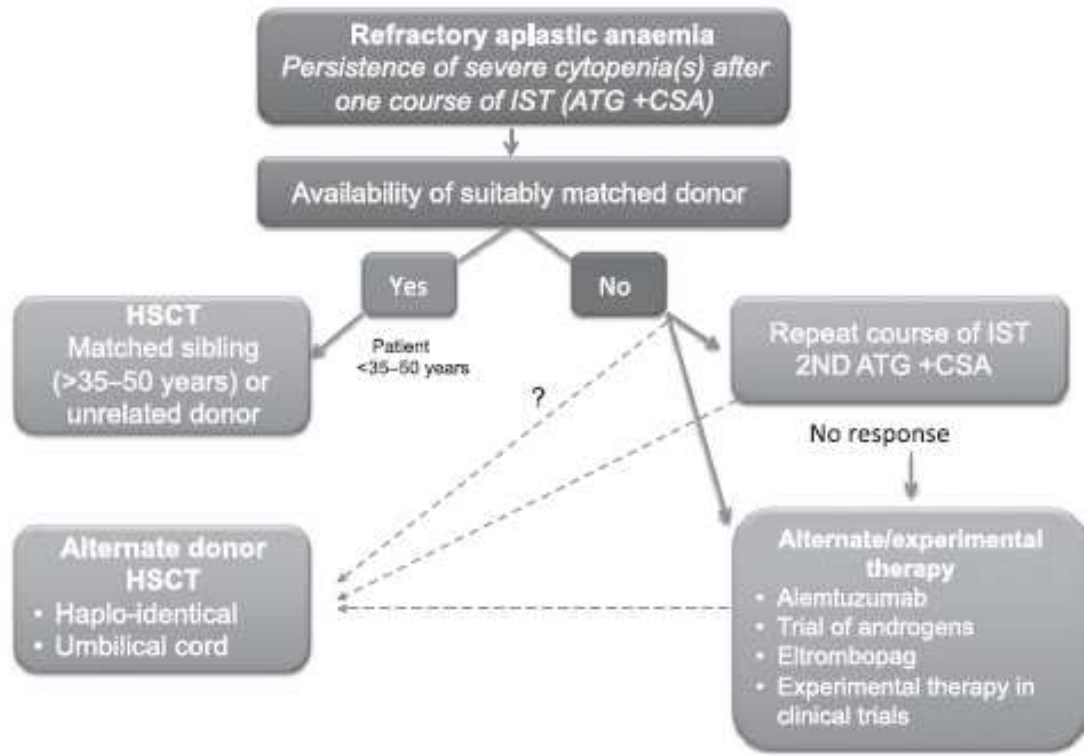
Hama A et al. Rinsho Ketsueki 2011 Aug ;52(8) :653-8

bjh guideline

Guidelines for the diagnosis and management of adult aplastic anaemia

Sally B. Killick, Writing Group Chair[1] Nick Bown,[2] Jamie Cavenagh,[3] Inderjeet Dokal,[4] Theodora Foukaneli,[5] Anita Hill,[6] Peter Hillmen,[6] Robin Ireland,[7] Austin Kulasekararaj,[7] Ghulam Mufti,[7] John A. Snowden,[8] Sujith Samarasinghe,[9] Anna Wood, BCSH Task Force Member[10] and Judith C. W. Marsh[7] on behalf of the British Society for Standards in Haematology





1. Linie Immuno-suppression

ATG+CSA for Aplastic Anemia
Standard for immune mediated marrow failure

ATG plus Cyclosporine Reduces All-Cause Mortality in Patients with Severe Aplastic Anemia – Systematic Review and Meta-Analysis

Anat Gafter-Gvili[a,c] Ron Ram[a,c] Ronit Gurion[a,c] Mical Paul[b,c]
Moshe Yeshurun[a,c] Pia Raanani[a,c] Ofer Shpilberg[a,c]

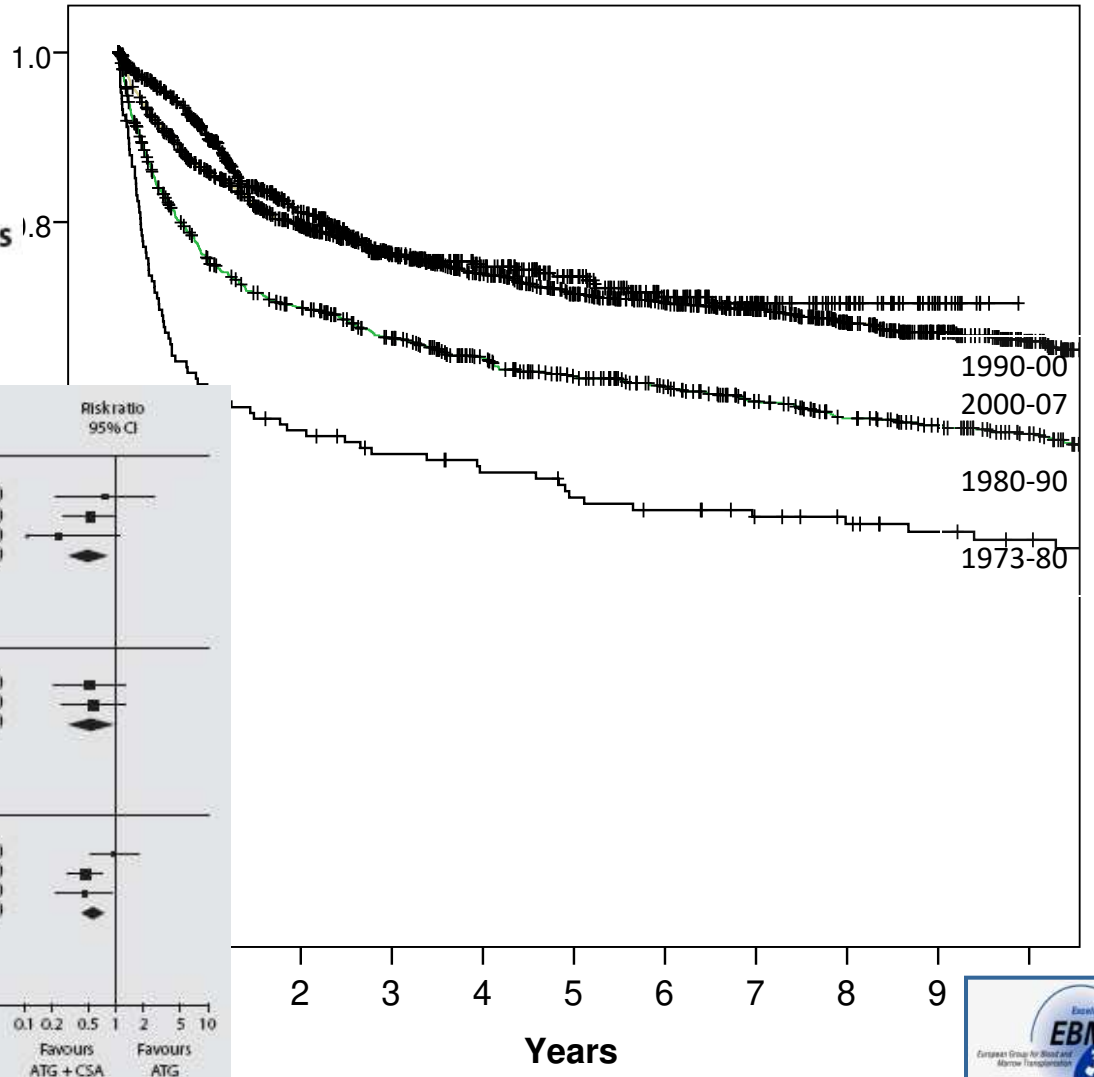
Study or subcategory	ATG+CSA events	ATG+CSA total	ATG events	ATG total	ATG weight, %	Risk ratio 95% CI
3 months						
Frickhofen, 1991, 2003	4	43	5	41	15.7	0.76 (0.22–2.64)
Miao, 2003	11	61	20	58	62.8	0.52 (0.28–0.99)
Zheng, 2006	2	47	6	33	21.6	0.23 (0.05–1.09)
Subtotal (95% CI)		151		132	100.0	0.50 (0.29–0.85)
Total events	17		31			
Heterogeneity: $\chi^2 = 1.40$, d.f. = 2 ($p = 0.50$), $I^2 = 0\%$						
Test for overall effect: $Z = 2.58$ ($p < 0.010$)						
1 year						
Frickhofen, 1991, 2003	6	43	11	41	48.9	0.52 (0.21–1.28)
Zheng, 2006	8	47	10	33	51.1	0.56 (0.25–1.27)
Subtotal (95% CI)		90		74	100.0	0.54 (0.30–0.99)
Total events	14		21			
Heterogeneity: $\chi^2 = 0.02$, d.f. = 1 ($p = 0.90$), $I^2 = 0\%$						
Test for overall effect: $Z = 1.99$ ($p < 0.05$)						
5 years						
Frickhofen, 1991, 2003	14	43	14	41	20.9	0.95 (0.52–1.75)
Miao, 2003	18	61	37	58	55.2	0.46 (0.30–0.71)
Zheng, 2006	9	47	14	33	23.9	0.45 (0.22–0.92)
Subtotal (95% CI)		151		132	100.0	0.58 (0.36–0.93)
Total events	41		65			
Heterogeneity: $\chi^2 = 4.08$, d.f. = 2 ($p = 0.13$), $I^2 = 51\%$						
Test for overall effect: $Z = 3.62$ ($p < 0.0003$)						

Risk ratio 95% CI

0.1 0.2 0.5 1 2 5 10

Favours ATG + CSA | Favours ATG

Mortality

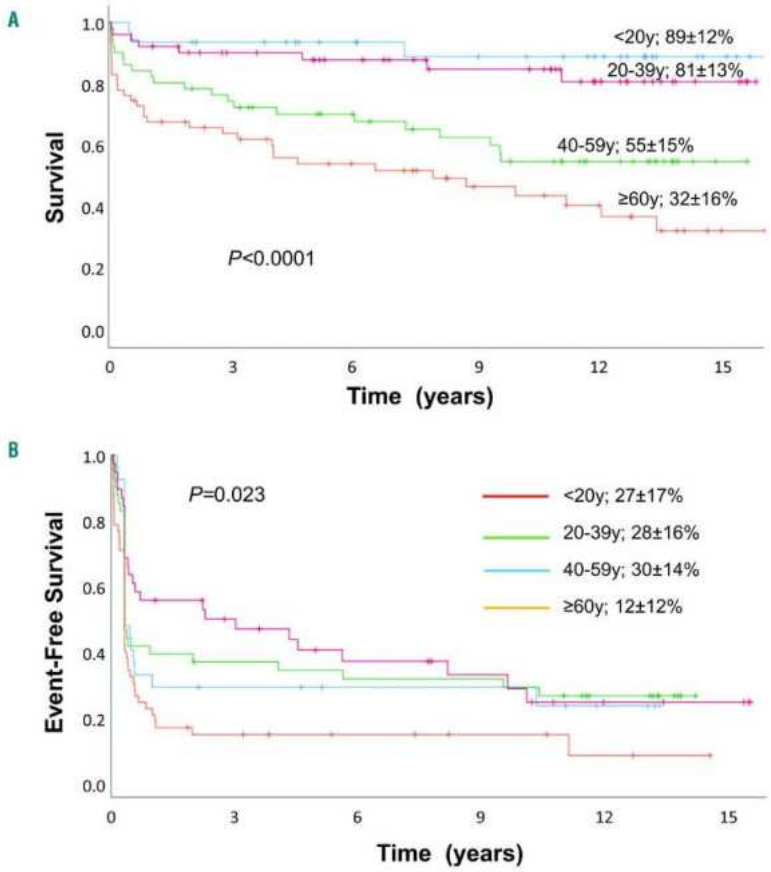


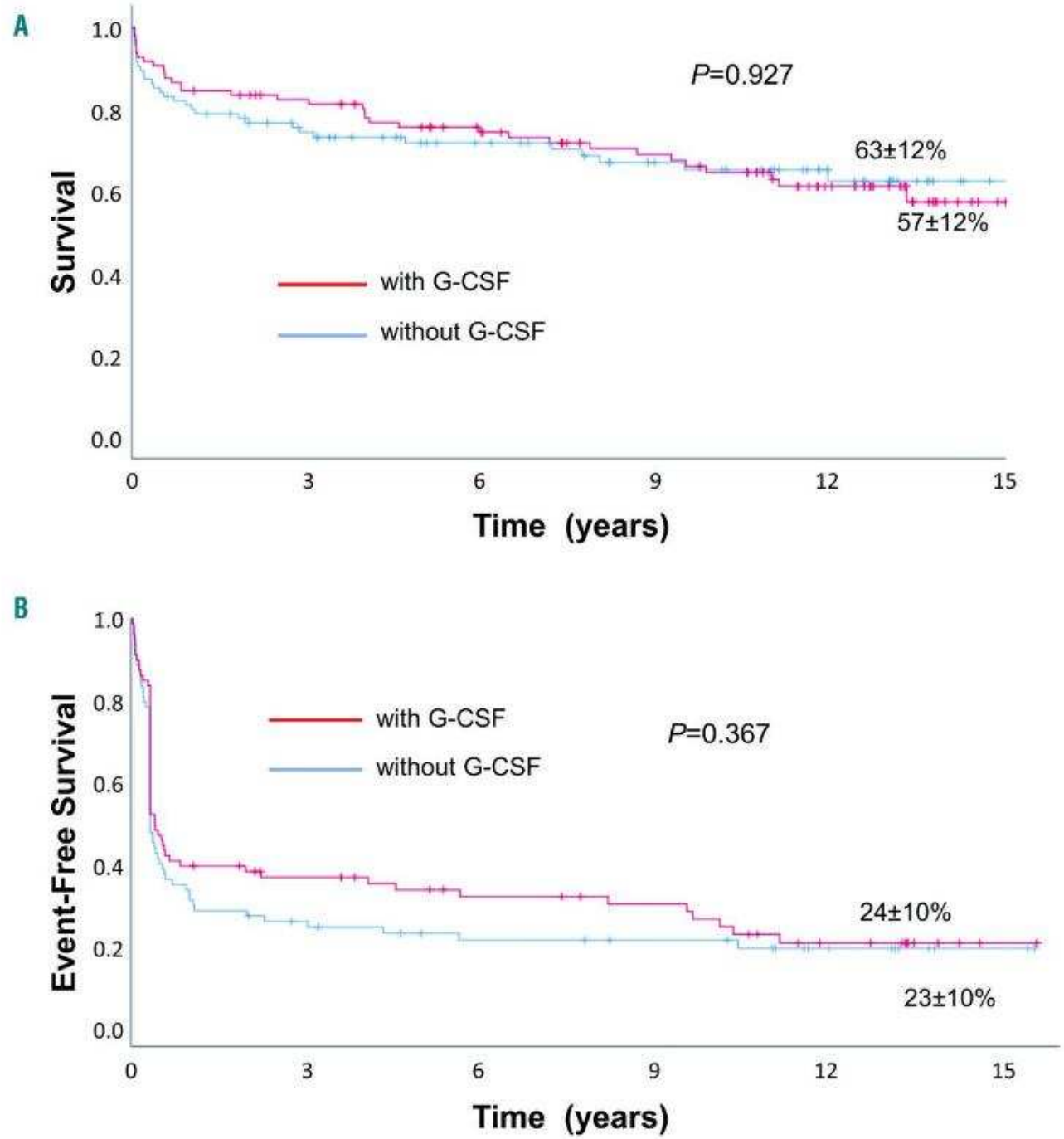
Long-term outcome of a randomized controlled study in patients with newly diagnosed severe aplastic anemia treated with antithymocyte globulin and cyclosporine, with or without granulocyte colony-stimulating factor: a Severe Aplastic Anemia Working Party Trial from the European Group of Blood and Marrow Transplantation

Ferrata Storti Foundation

Haematologica 2020
Volume 105(5):1223-1231

André Tichelli,[1] Régis Peffault de Latour,[2] Jakob Passweg,[1] Cora Knol-Bout,[3] Gérard Socié,[4] Judith Marsh,[5] Hubert Schrezenmeier,[6] Britta Höchsmann,[6] Andrea Bacigalupo,[7] Sujith Samarasinghe,[8] Alicia Rovó,[9] Austin Kulasekararaj,[10] Alexander Röth,[11] Dirk-Jan Eikema,[3] Paul Bosman,[3] Peter Bader,[12] Antonio Risitano[13] and Carlo Dufour[14] on behalf of the SAA Working Party of the EBMT

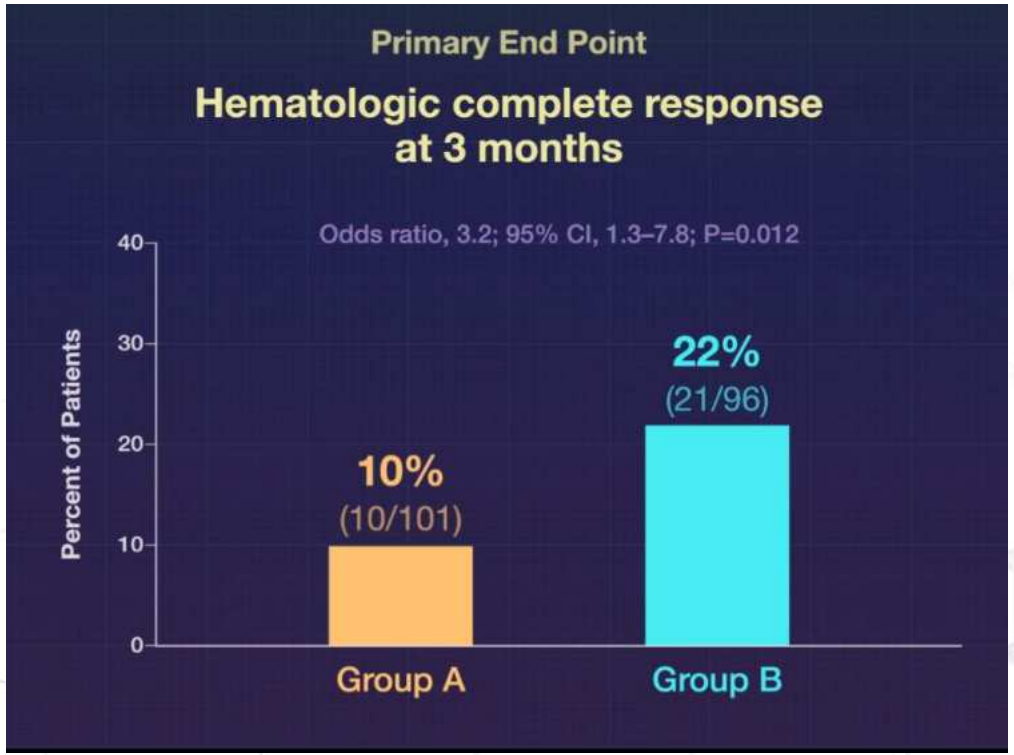


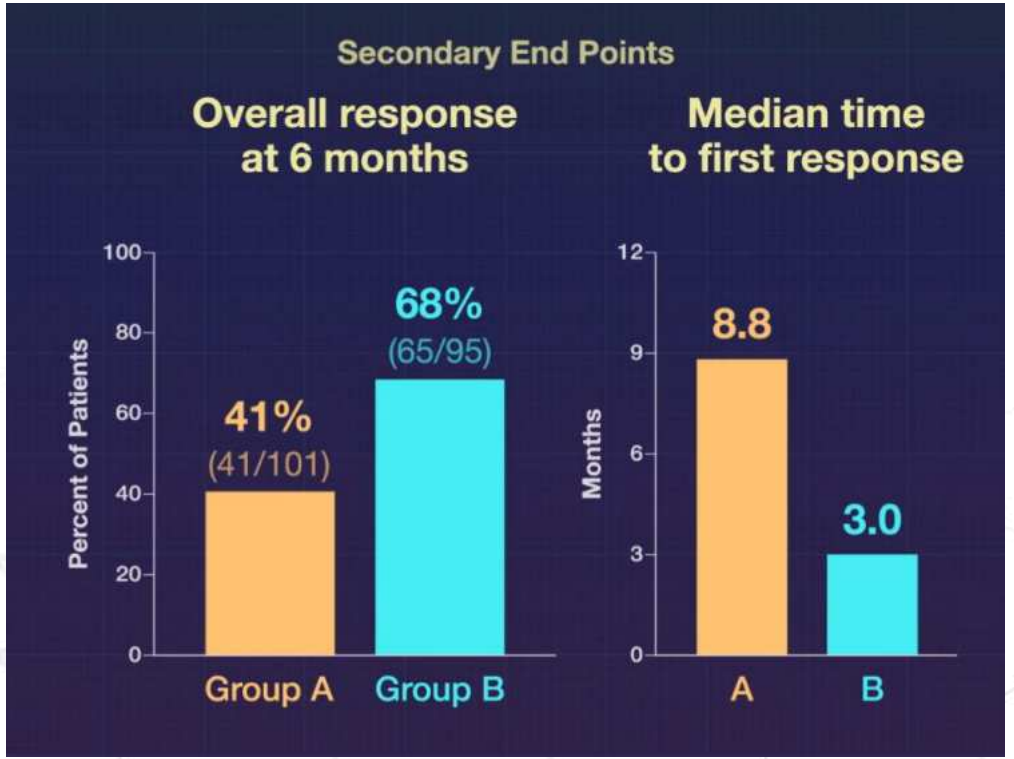


Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia

N Engl J Med 2022;386:11-23.

R. Peffault de Latour, A. Kulasekararaj, S. Iacobelli, S.R. Terwel, R. Cook, M. Griffin, C.J.M. Halkes, C. Recher, F. Barraco, E. Forcade, J.-C. Vallejo, B. Drexler, J.-B. Mear, A.E. Smith, E. Angelucci, R.A.P. Raymakers, M.R. de Groot, E. Daguindau, E. Nur, W. Barcellini, N.H. Russell, L. Terriou, A.-P. Iori, U. La Rocca, A. Sureda, I. Sánchez-Ortega, B. Xicoy, I. Jarque, J. Cavenagh, F. Sicre de Fontbrune, S. Marotta, T. Munir, J.M.L. Tjon, S. Tavitian, A. Praire, L. Clement, F. Rabian, L. Marano, A. Hill, E. Palmisani, P. Muus, F. Cacace, C. Frieri, M.-T. van Lint, J.R. Passweg, J.C.W. Marsh, G. Socié, G.J. Mufti, C. Dufour, and A.M. Risitano, for the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation*





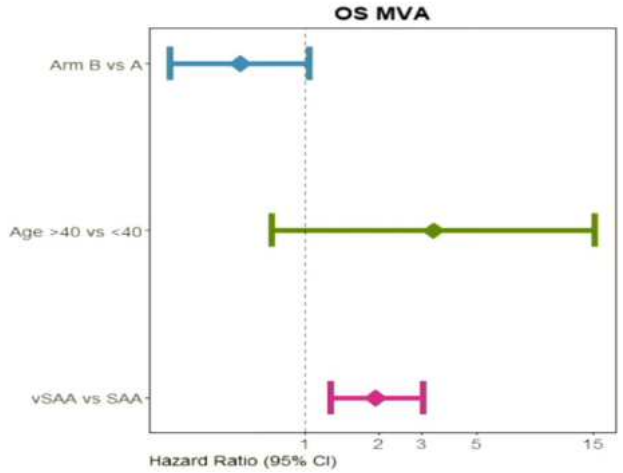
GS02-07 ELTROMBOPAG ADDED TO STANDARD IST IS SUPERIOR TO IST ALONE AS FRONT-LINE TREATMENT FOR SEVERE APLASTIC ANEMIA : FINAL 2-YEAR ANALYSIS OF EBMT-SAAWP RACE STUDY

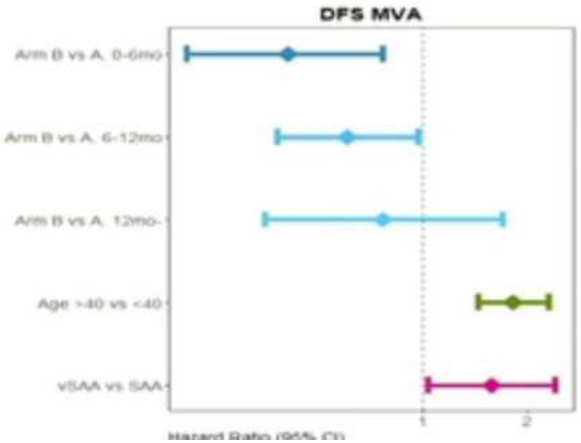
Antonio Maria Risitano[1,2,3], Austin Kulasekararaj[4], Simona Iacobelli[2,5], et al SAAWP EBMT

N=197

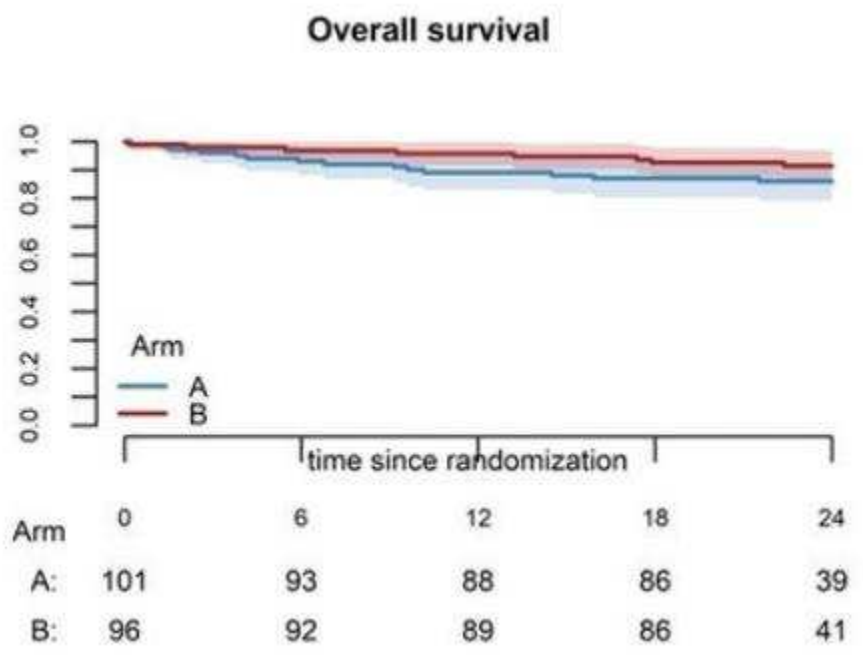
A: ATG+CSA

B: ATG + CSA + Epag

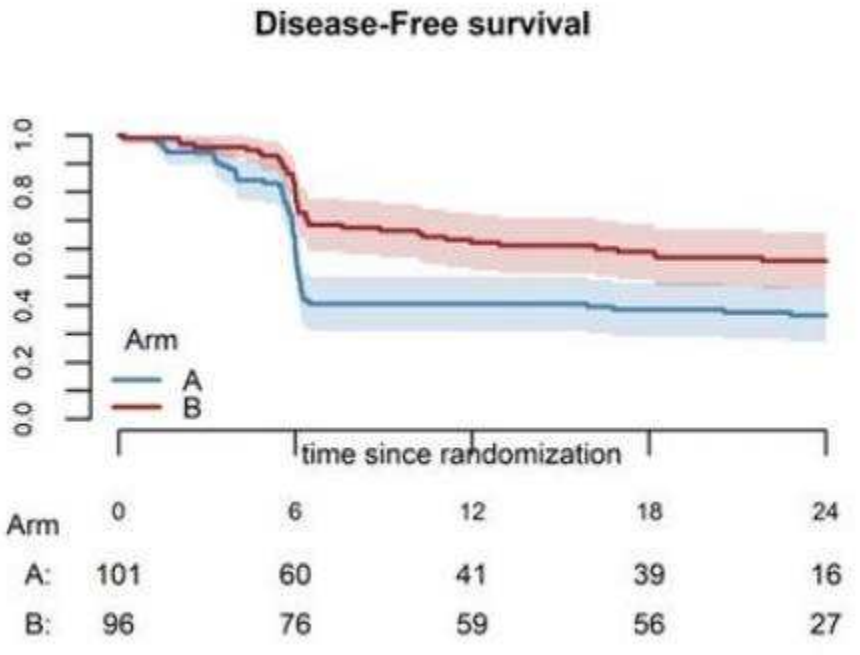




a)



b)



1. Linie
HCT

Transplant rates, Center size BMT within EBMT 2022

TR by Country Allo BMF

Country	TR BMF
Israel	31.4
Lithuania	25.0
Netherlands	21.0
Lebanon	20.0
Turkey	18.5
Sweden	18.2
United Kingdom	16.9
Portugal	15.5
Saudi Arabia	15.4
Spain	14.8
France	14.7
Macedonia	14.6
Denmark	13.6
Czech Republic	12.4
Poland	11.2
Croatia	10.4
Belgium	10.3
Ireland	9.9
Germany	9.7
Greece	9.6
Italy	9.5
Norway	9.2
Finland	9.0
Algeria	6.7
Tunisia	6.5

Top Centers Allo BMF

Year	cstate	city	hospital	dep	Indication	TotalAllo
2022	Algeria	Alger	Centre Pierre et Marie Curie	ads, peds	BM aplasia	28
2022	Saudi Arabia	Riyadh	King Faisal Specialist Hospital	peds	BM aplasia	24
2022	France	Paris	Hôpital St. Louis	ads, peds	BM aplasia	16
2022	Iran	Tehran	Shariati Hospital, SCT Research Centre	ads, peds	BM aplasia	16
2022	Iran	Tehran	Childrens Medical Centre	peds	BM aplasia	16
2022	Russian Fed.	Moscow	The Russian Children's Research Hospital	peds	BM aplasia	16
2022	Russian Fed.	Moscow	Federal Research Center for Pediatric Hematology	peds	BM aplasia	16
2022	Turkey	Istanbul	Medical Park Goztepe	peds	BM aplasia	16
2022	Netherlands	Utrecht	Princess Maxima Centre for Ped Oncology	peds	BM aplasia	14
2022	Turkey	Istanbul	Yeniyuzyil University, Gaziosmanpasa Hospital	peds	BM aplasia	14
2022	Saudi Arabia	Riyadh	King Abdul Aziz Medical City	ads, peds	BM aplasia	12
2022	United Kingdom	London	King's College Hospital	ads	BM aplasia	12
2022	Netherlands	Leiden	University Hospital	ads, peds	BM aplasia	11
2022	Poland	Wroclaw	Cape of Hope Medical University	peds	BM aplasia	11
2022	Russian Fed.	St. Petersburg	First State Pavlov Medical University of St. Petersburg	ads, peds	BM aplasia	11
2022	Turkey	Ankara	Ankara Bilkent City Hospital Pediatric Clinic	peds	BM aplasia	11
2022	United Kingdom	Bristol	Avon and Royal Hospital for Sick Children	ads, peds	BM aplasia	11
2022	Saudi Arabia	Jeddah	King Faisal Hospital	ads, peds	BM aplasia	10
2022	Saudi Arabia	Riyadh	King Faisal Specialist Hospital	ads, peds	BM aplasia	10
2022	Turkey	Antalya	Medical Park Antalya Hospital, Lara	peds	BM aplasia	10
2022	United Kingdom	London	University College Hospital	ads, peds	BM aplasia	10
2022	Italy	Rome	IRRCS Ospedale Bambino Gesu	peds	BM aplasia	9
2022	South Africa	Cape Town	Groote Schuur Hospital	ads, peds	BM aplasia	9
2022	Turkey	Adana	Cukurova University Balcali Hospital	peds	BM aplasia	9
2022	Turkey	Istanbul	Yeniyuzyil University, Gaziosmanpasa Hospital	ads	BM aplasia	9
2022	United Kingdom	Manchester	Central Manchester NHS Trust	peds	BM aplasia	9

How to decide whether initial treatment is BMT or immunosuppression?

Difference between BMT (HLA-id sibling) and Immunosuppression in 5-Year Failure Free Survival (%) after initial treatment

Neutrophil Count (x 10^9/L)	AGE (years)				
	10	20	30	40	50
0	24	20	14	6	- 2
0.1	19	14	8	1	- 7
0.2	14	9	3	- 4	- 11
0.3	10	5	- 1	- 7	- 14
0.4	6	1	- 4	- 10	- 16
0.5	3	- 2	- 7	- 12	- 17

Positive values: Advantage BMT

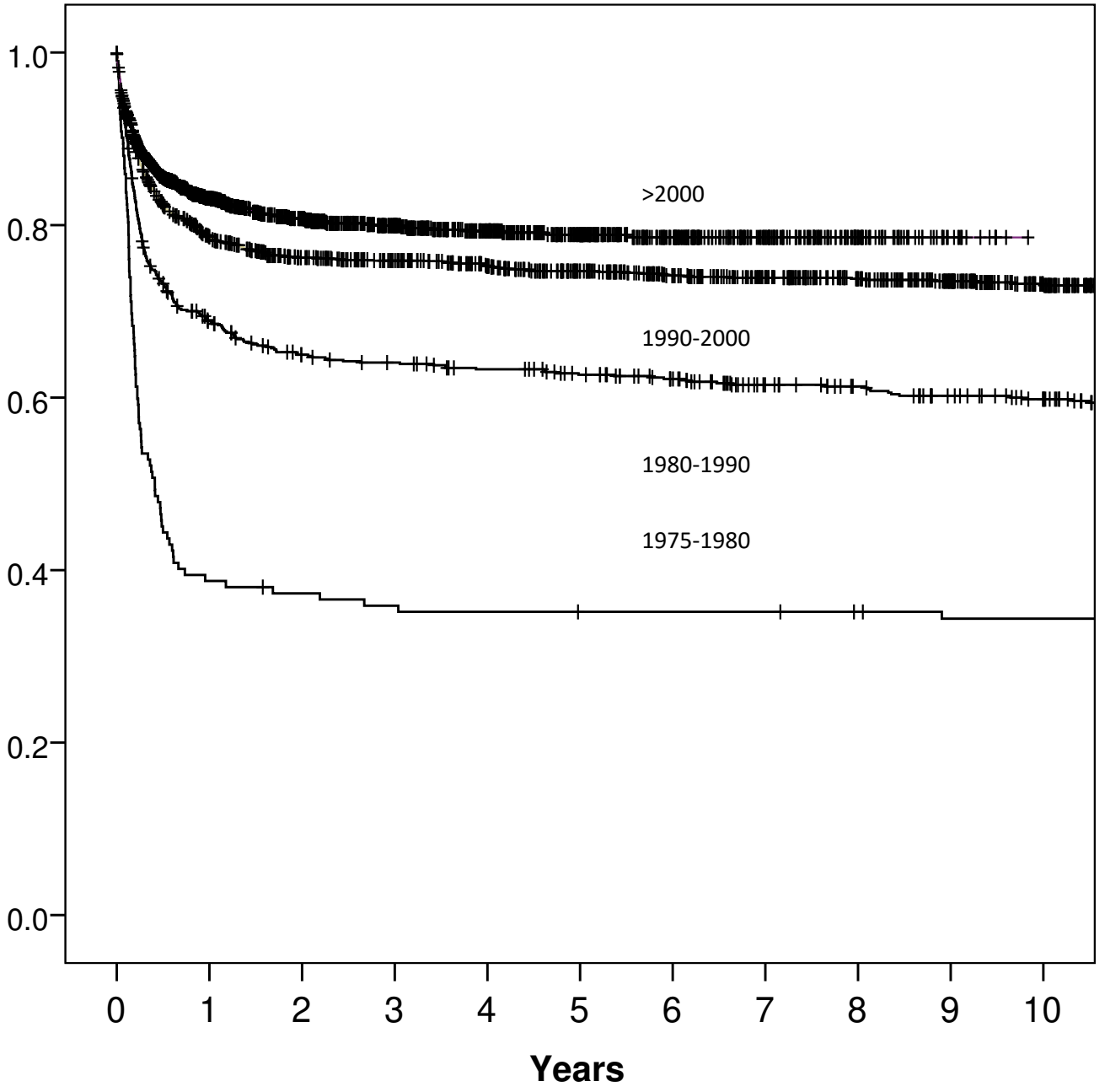
Negative values: Advantage Immunosuppresion

A.Bacigalupo et al., Seminars in Hematology.2000;37:69-80.

Acquired SAA

Transplants
From
HLA identical
Sibling Donors

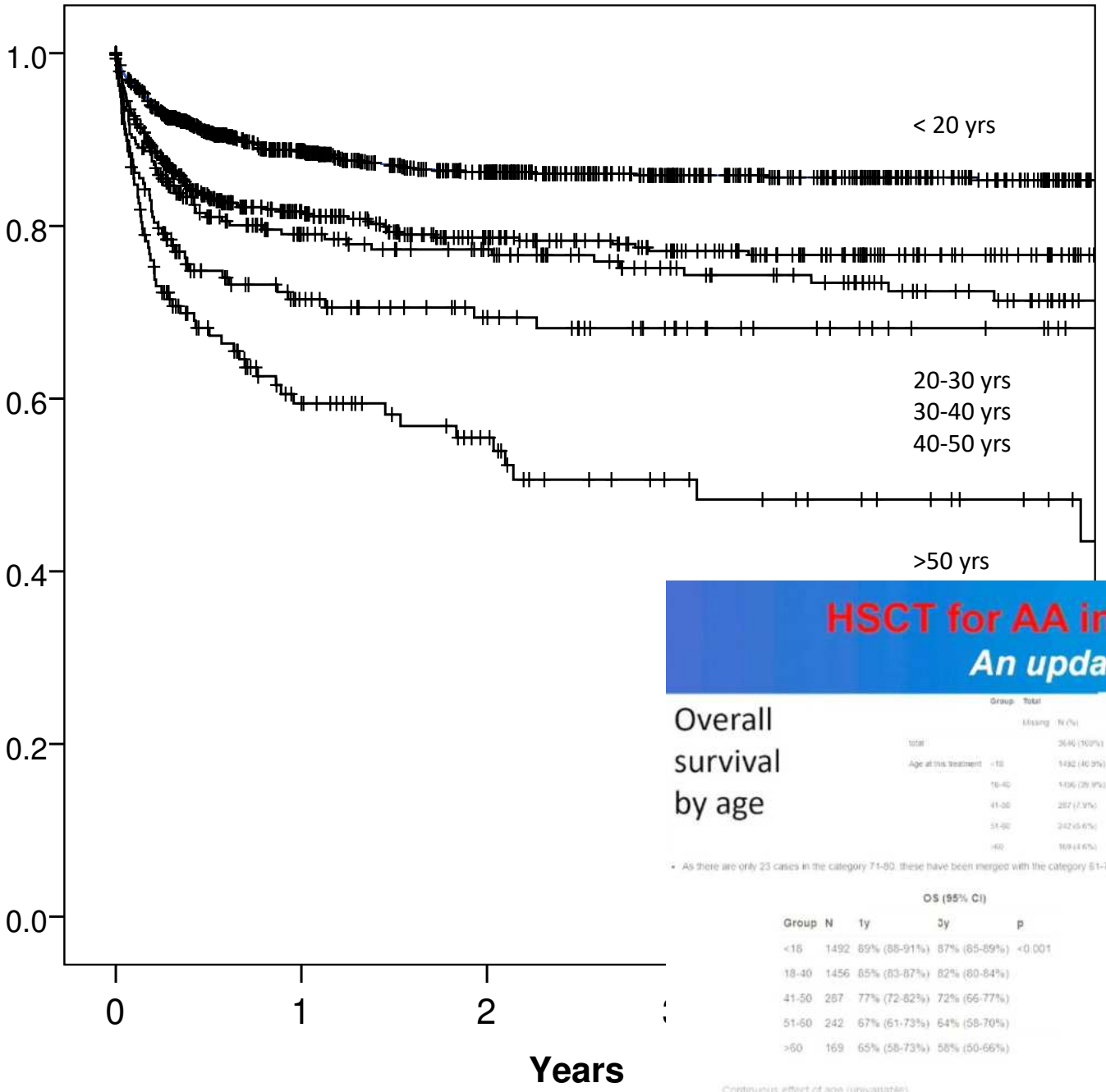
Effect of
Year of Transplant



Acquired SAA

Transplants
From
HLA identical
Sibling Donors

Effect of
Patient Age



HSCT for AA in the decade 2011-2020

An updated SAAWP study

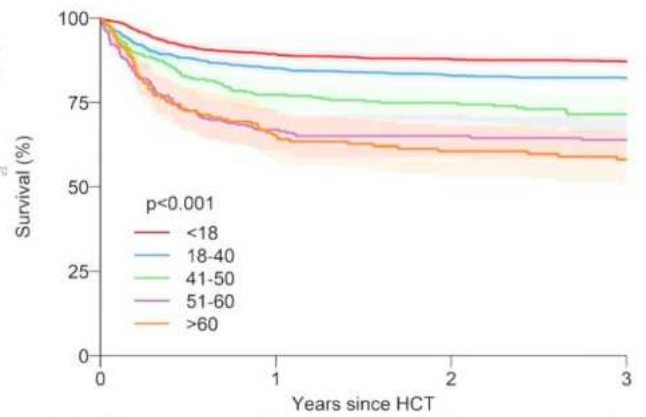
Overall survival by age

OS (95% CI)

Group	N	1y	3y	p
<18	1492	89% (88-91%)	87% (85-89%)	<0.001
18-40	1456	85% (83-87%)	82% (80-84%)	
41-50	287	77% (72-82%)	72% (66-77%)	
51-60	242	67% (61-73%)	64% (58-70%)	
>60	169	65% (58-73%)	58% (50-66%)	

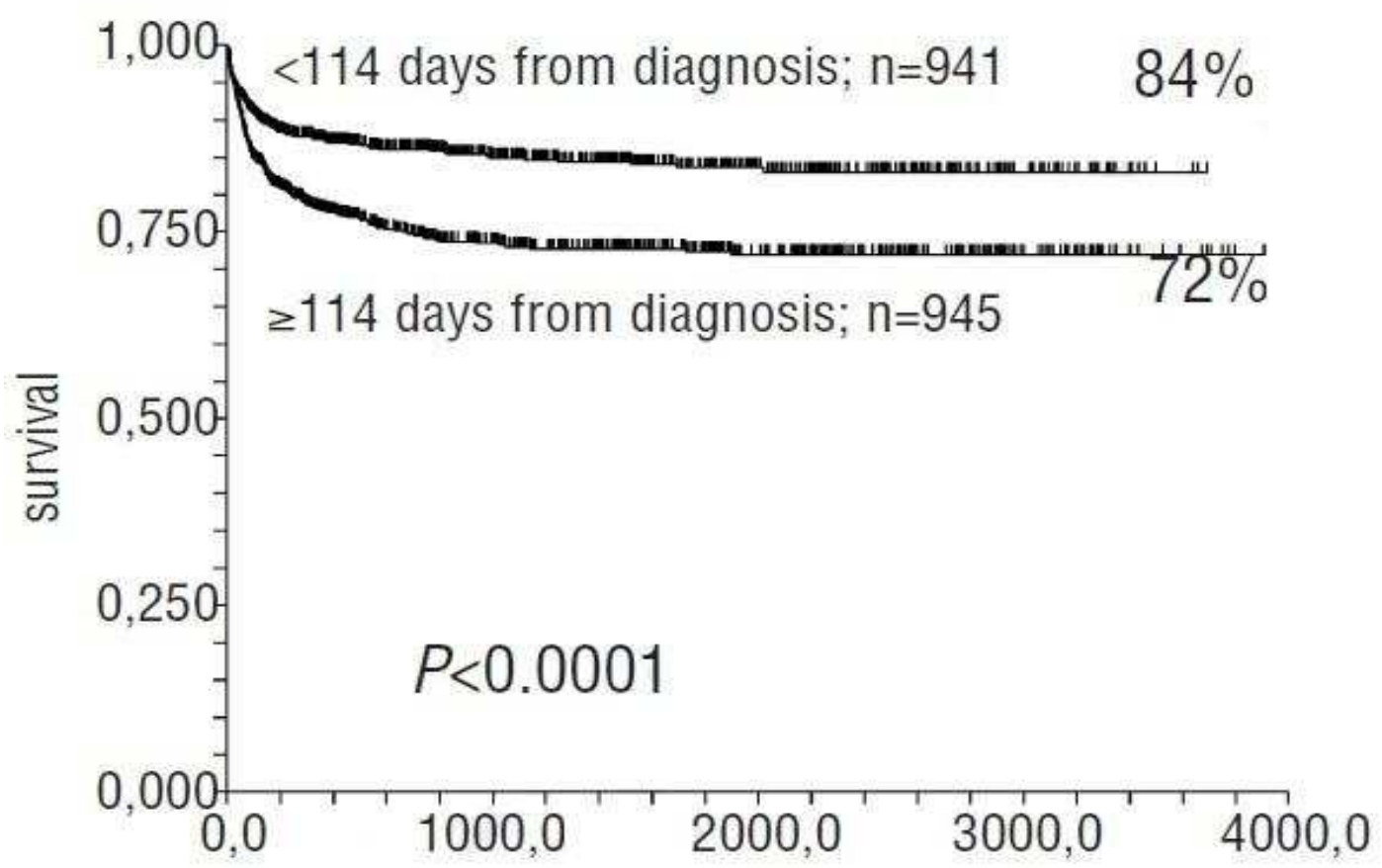
Continuous effect of age (univariable)

	n	d	HR (95% CI)	p
Age at this treatment (decades)	3646	628	1.29 (1.24-1.35)	<0.001



<18:	1492	1056	831	667
18-40:	1456	992	772	611
41-50:	287	200	165	137
51-60:	242	141	123	95
>60:	169	100	79	63

Increased time interval between diagnosis and HSCT is related with poorer outcome

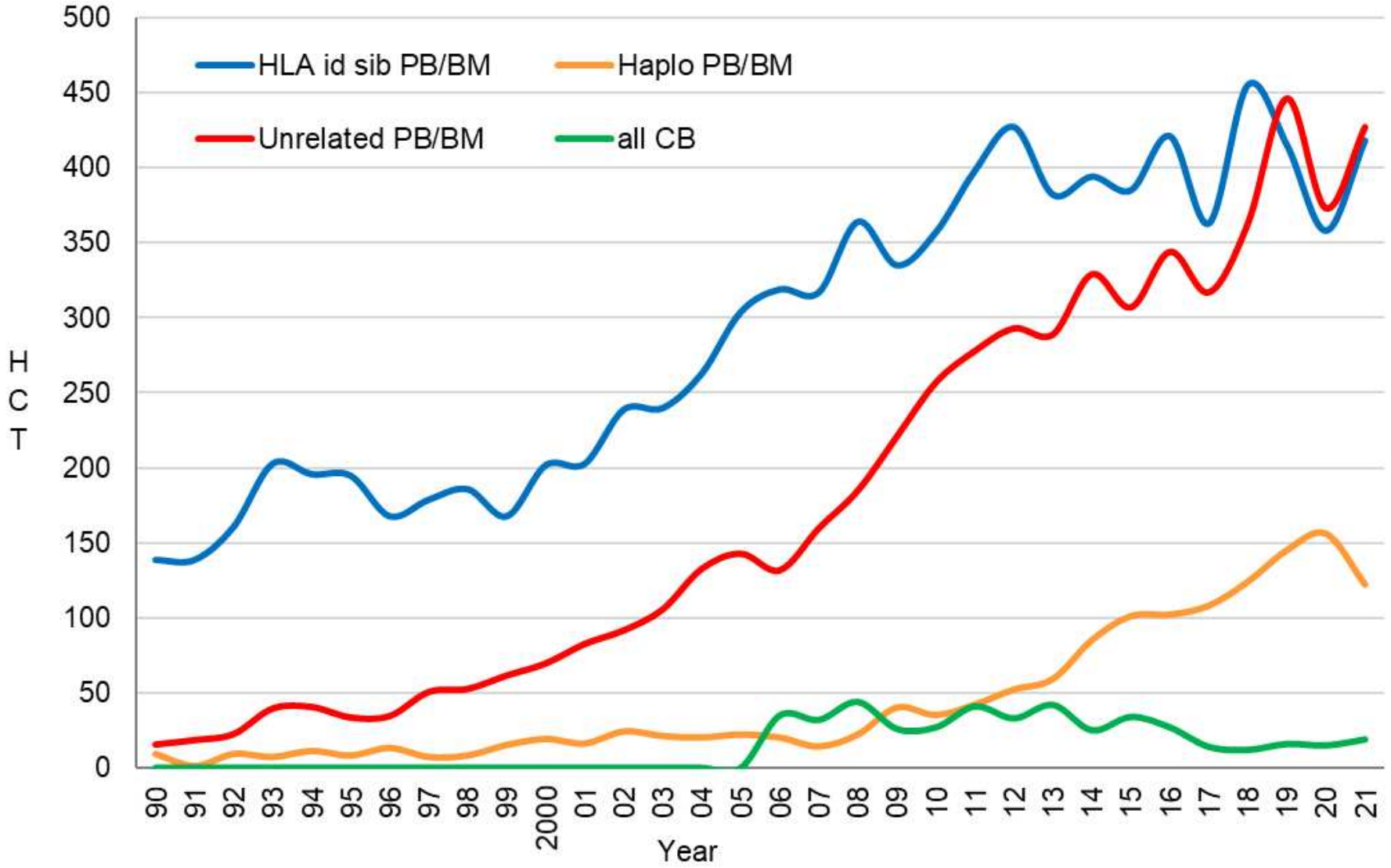


- Graft failure 3-7%
- Late graft rejection 1.3-1.4%

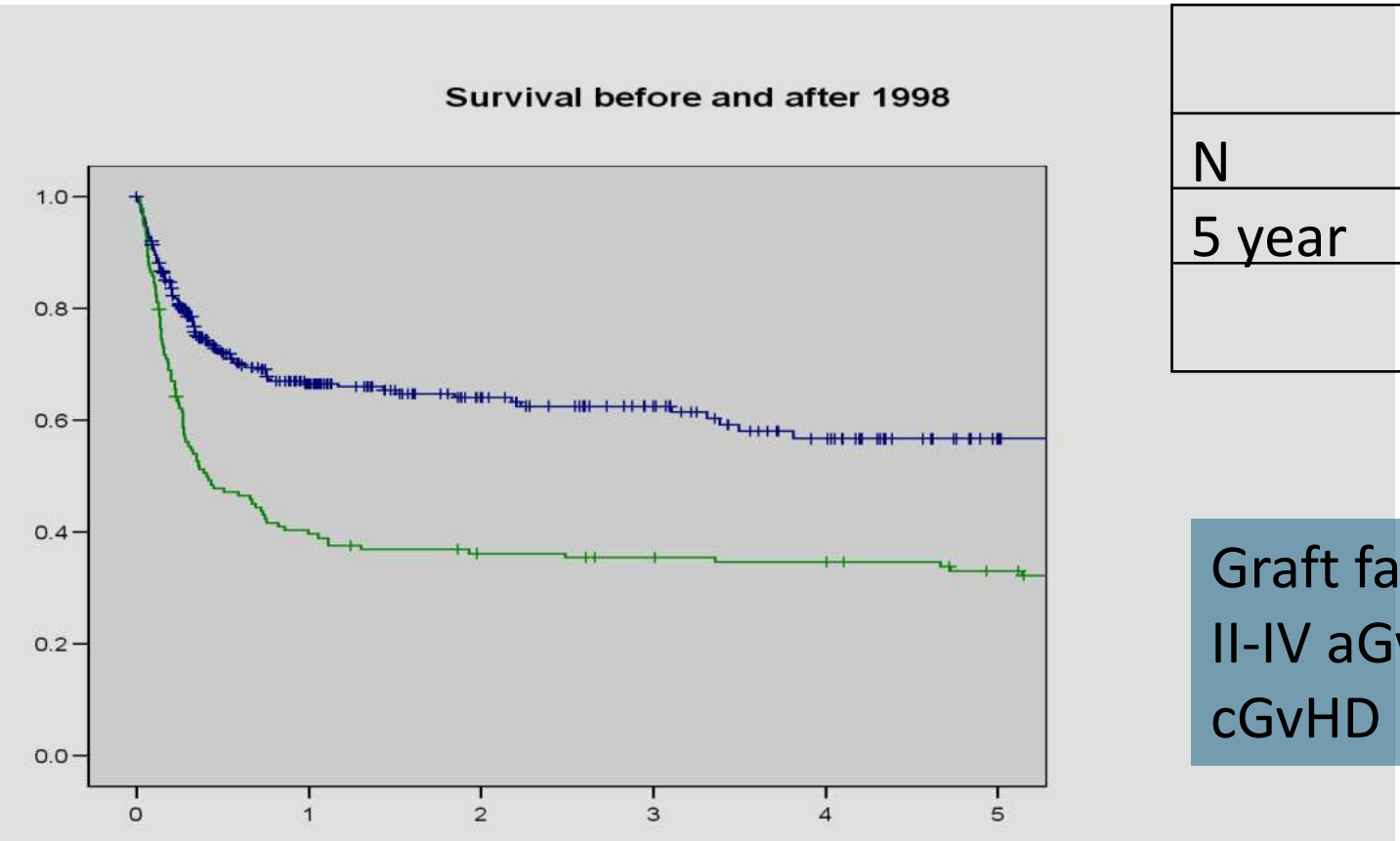
Bacigalupo A et al. Haematologica. 2012;97:1142-1148

2. Linie
HCT nach Versagen IST

HCT activity in Europe 1990-2021:
BMF by donor type



Improvements outcome MUD transplantation



	Before 1998	After 1998
N	149	349
5 year	32% (+8)	57% (+8)
		p=<0.0001

Graft failure	26%	11%
II-IV aGvHD	37%	28%
cGvHD	38%	22%

aGvHD, cGvHD and graft failure

≤1998 **>1998**

Primary or secondary graft failure

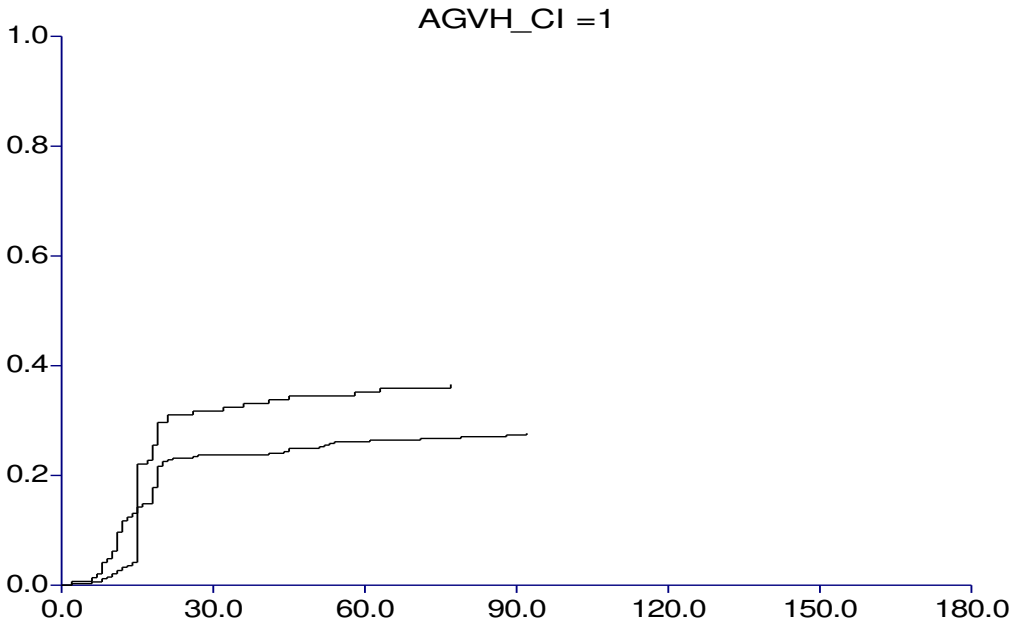
37/142 (26%) 38/338 (11%)

p<0.0001

chronic GvHD (after day 100)

32/85 (38%)53/245 (22%)

p=0.004



Cumulative incidence of grade II-IV aGvHD

0.37 0.30-0.45

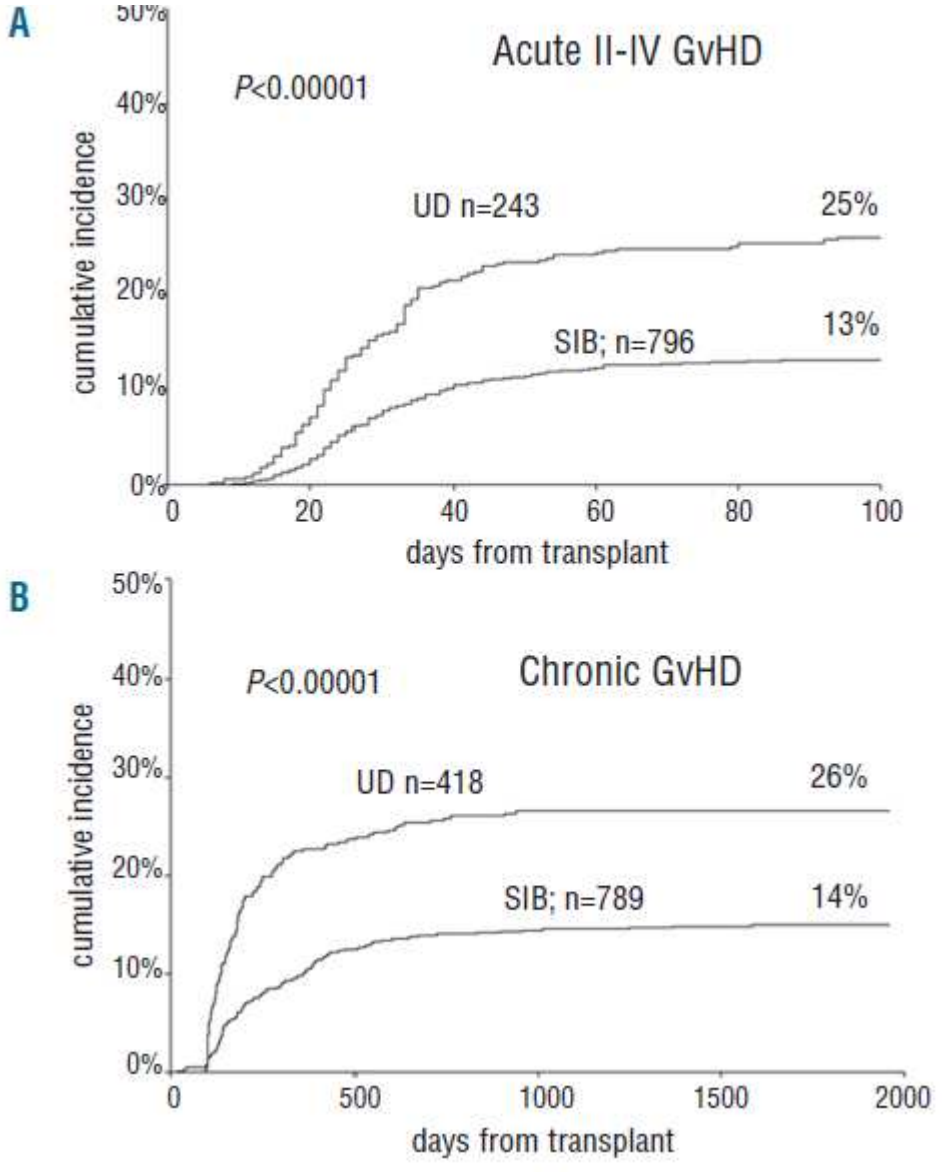
0.28 0.23-0.33

p=0.02

Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis

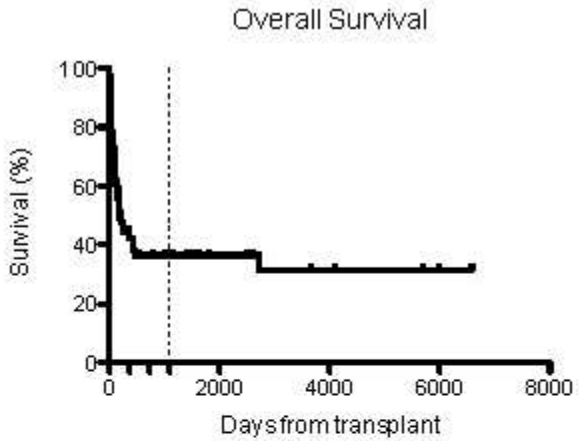
Andrea Bacigalupo,[1] Gerard Socié,[2] Rose Marie Hamladji,[3] Mahmoud Aljurf,[4] Alexei Maschan,[5] Slawomira Kyrcz-Krzemien,[6] Alicja Cybicka,[7] Henrik Sengelov,[8] Ali Unal,[9] Dietrich Beelen,[10] Anna Locasciulli,[11] Carlo Dufour,[12] Jakob R. Passweg,[13] Rosi Oneto,[1] Alessio Signori[14] and Judith C.W. Marsh;[15] for the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT)

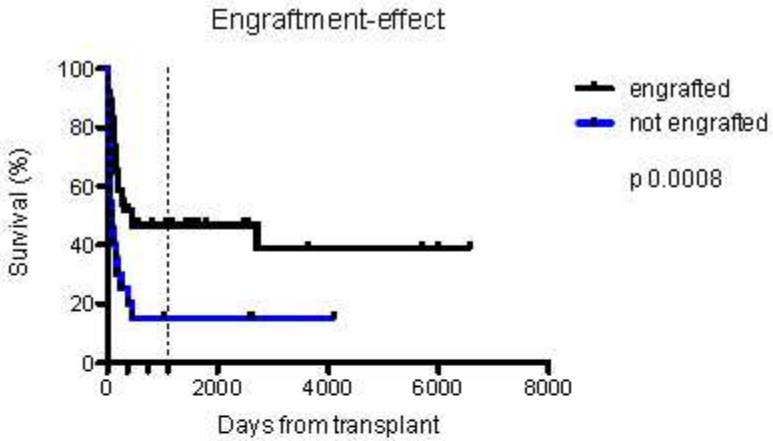
- Unrelated donor HSCT
  - More acute GvHD
  - More chronic GvHD

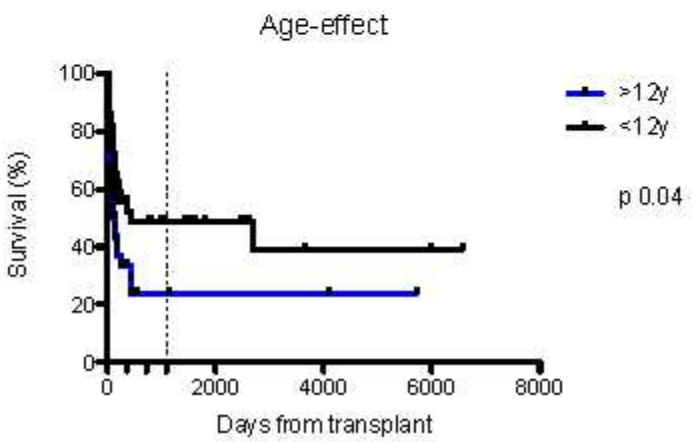


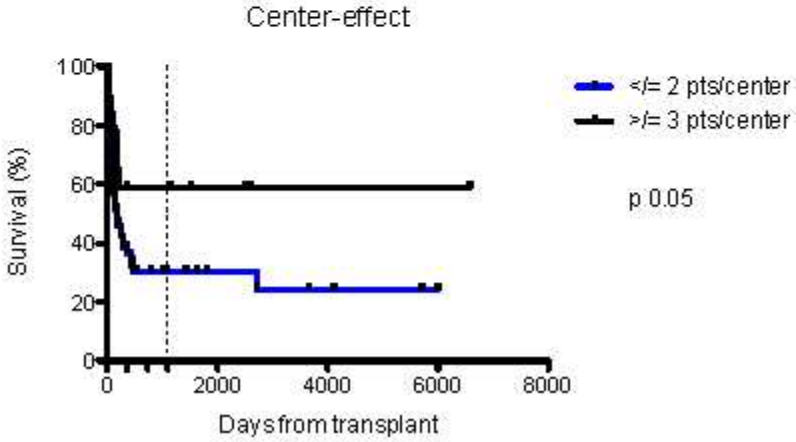
Haploidentical hematopoietic stem cell transplantation in patients with acquired severe aplastic anemia: a study by the Severe Aplastic Anemia Working Party (SAAWP) and Paediatric Diseases Working Party (PDWP) of the European Blood and Marrow Transplantation Group (EBMT).

MT Lupo-Stanghellini°, F Ciceri°, F Locatelli, A Locasciulli, Kremens B, J Dalle, Elena Guggiari°, J Passweg, C. Peters, C Dufour^, J Marsh, ET Korthof (*).









blood advances 28 APRIL 2020 • VOLUME 4, NUMBER 8

Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide

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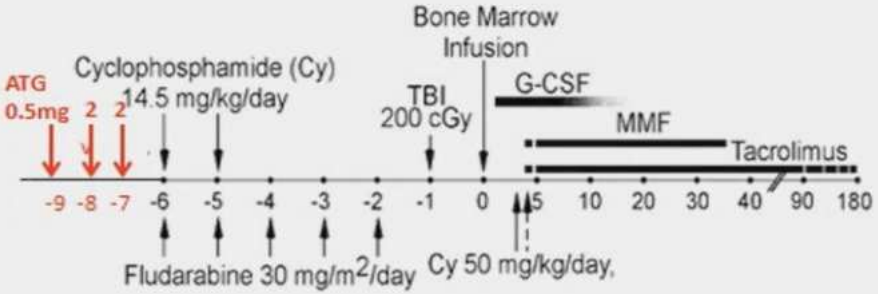
Relapse/Refr	20
Treatment naive	17

neutrophil recovery	17 days
GF	4 (2Gy)
GF	0 (4Gy)
OS	94%
III-IV aGvHD	11%
cGvHD	8%



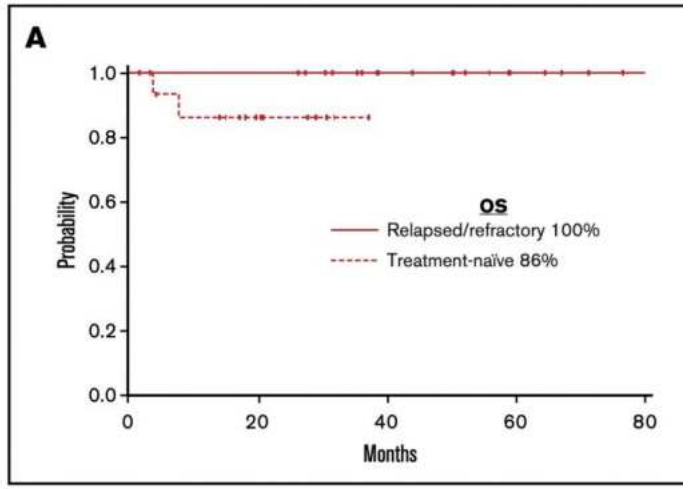
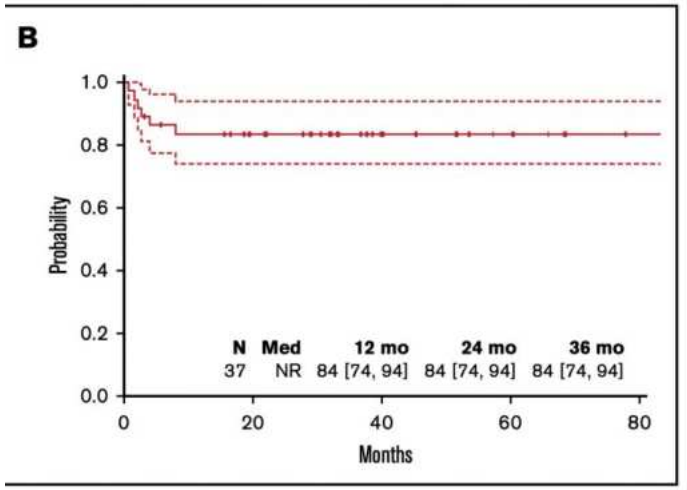


Figure 2. **Clinically meaningful endpoints for all haploid**



entical patients. (A) Overall survival. (B) GVHD-free survival.

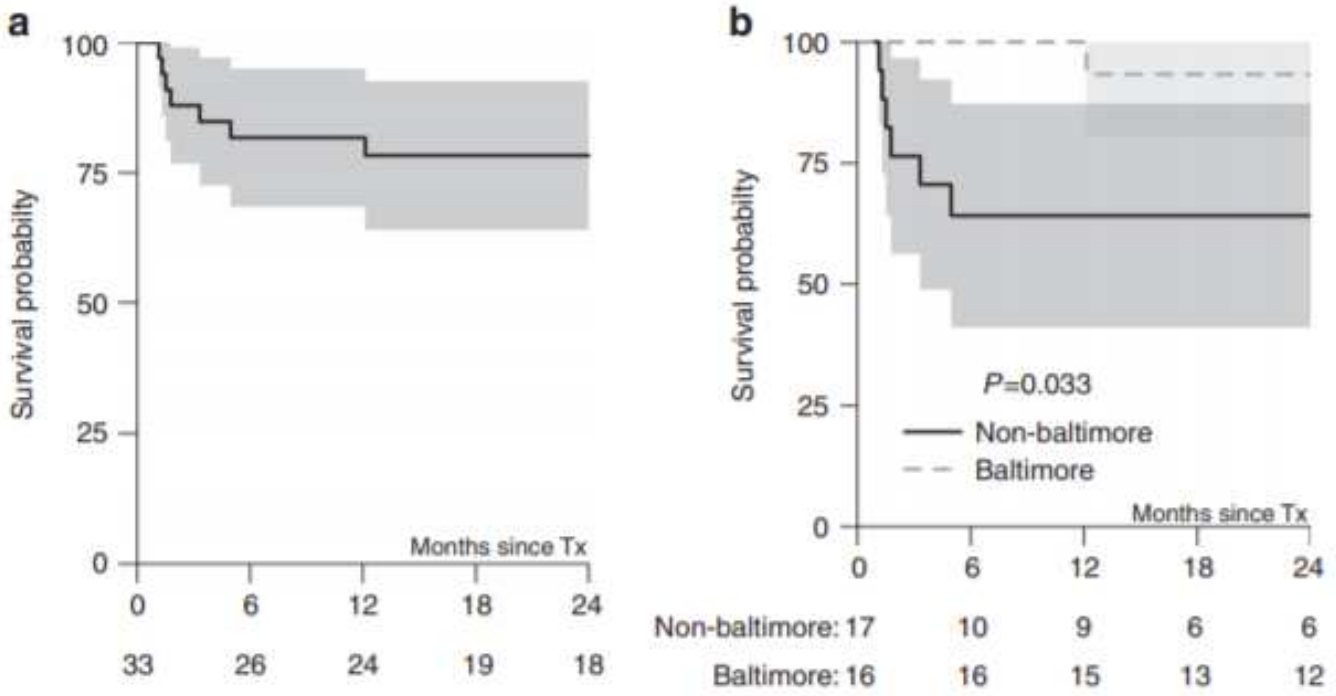
Bone Marrow Transplantation (2020) 55:1050–1058
https://doi.org/10.1038/s41409-019-0773-0

ARTICLE

Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT Severe Aplastic Anemia Working Party

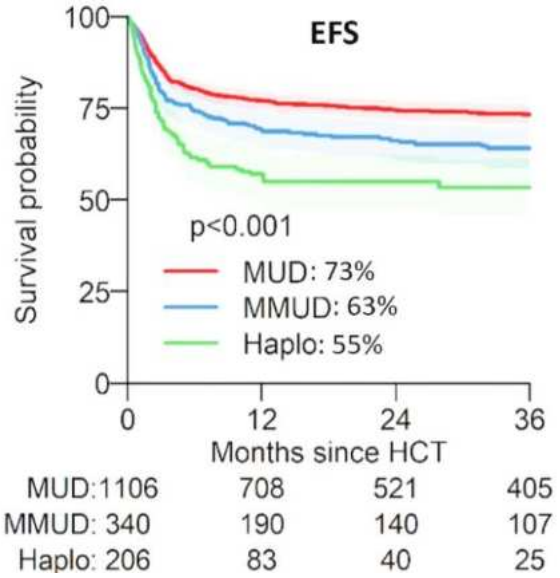
Pedro H. Prata[1] · Dirk-Jan Eikema[2] · Boris Afansyev[3] · Paul Bosman[4] · Frans Smiers[5] · José L. Diez-Martin[6] · Celso Arrais-Rodrigues[7] · Yener Koc[8] · Xavier Poiré[9] · Anne Sirvent[10] · Nicolaus Kröger[11] · Fulvio Porta[12] · Wolfgang Holter[13] · Adrian Bloor[14] · Charlotte Jubert[15] · Arnold Ganser[16] · Alina Tanase[17] · Anne-Lise Ménard[18] · Pietro Pioltelli[19] · José A. Pérez-Simón[20] · Aloysius Ho[21] · Mahmoud Aljurf[22] · Nigel Russell[23] · Helene Labussiere-Wallet[24] · Tessa Kerre[25] · Vanderson Rocha[7] · Gérard Sc[1,26] · Antonio Pisitano[27] · Carlo Dufour[28] · Régis Peffault de Latour[1] · on behalf of the SAA WP of tl

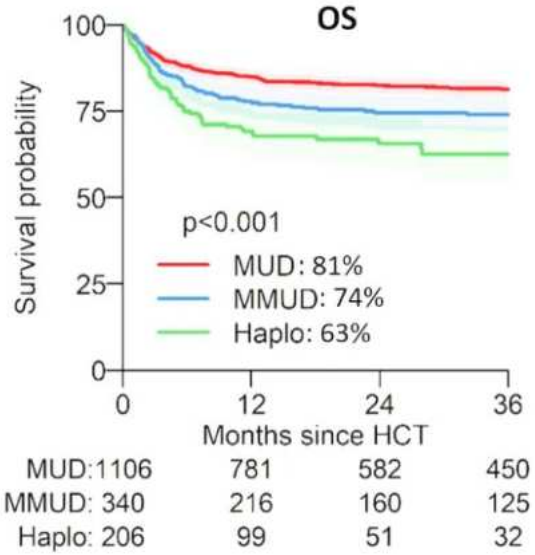
Baltimore
ATG FluCy14.5 TBI 4Gy + pTCy

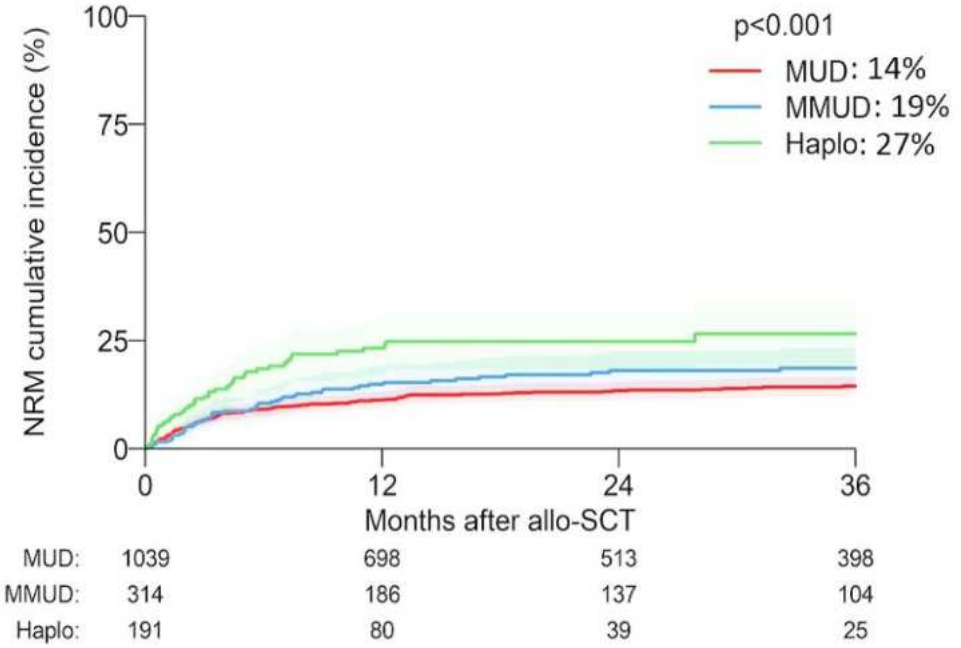


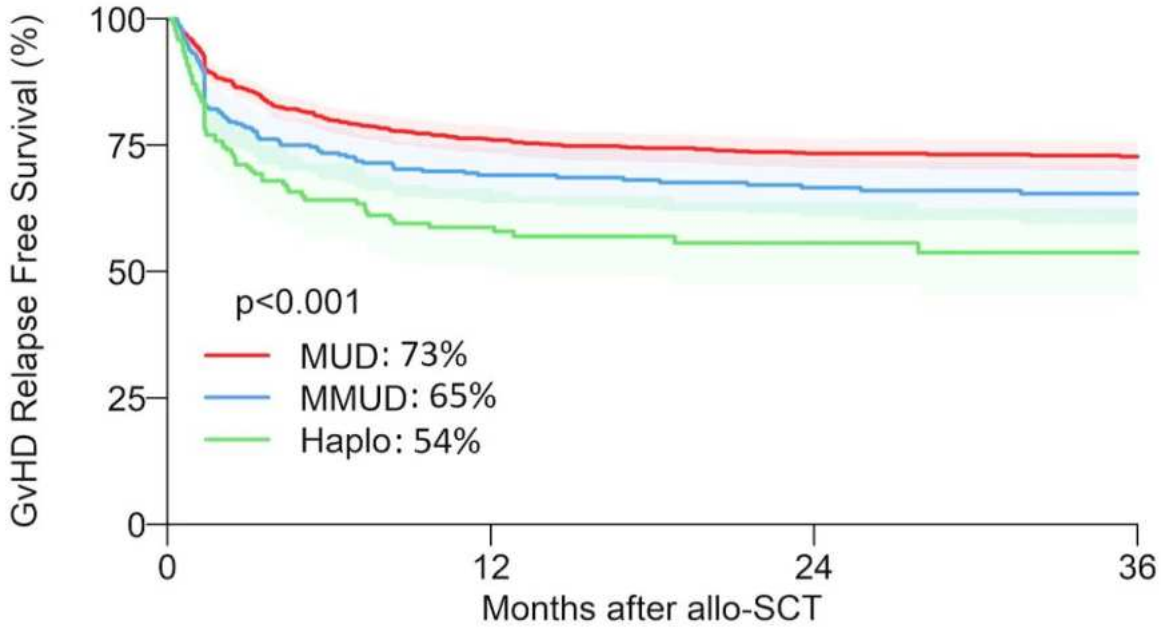
SAAWP-3 Alternative donor transplantation for severe aplastic anemia: a comparative study of the SAAWP EBMT

Juan Montoro Gómez et al









Stand heute

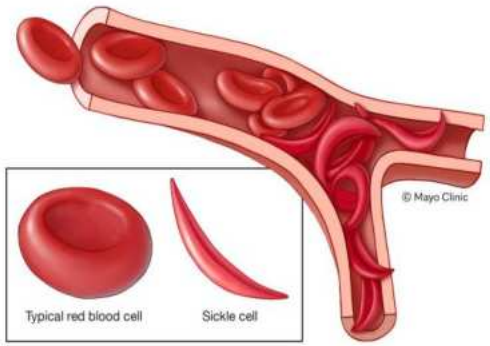
- Transplantation Option für alle Patienten, Geschwister, Unverwandt, Haploidentisch
- Strategien Konditionierung, GvHD Prophylaxe sind definiert
- Geschwister: Erstlinientherapie
- Unverwandt: Zweitlinientherapie ausser Kinder AYA
- Haploident: Zweitlinientherapie

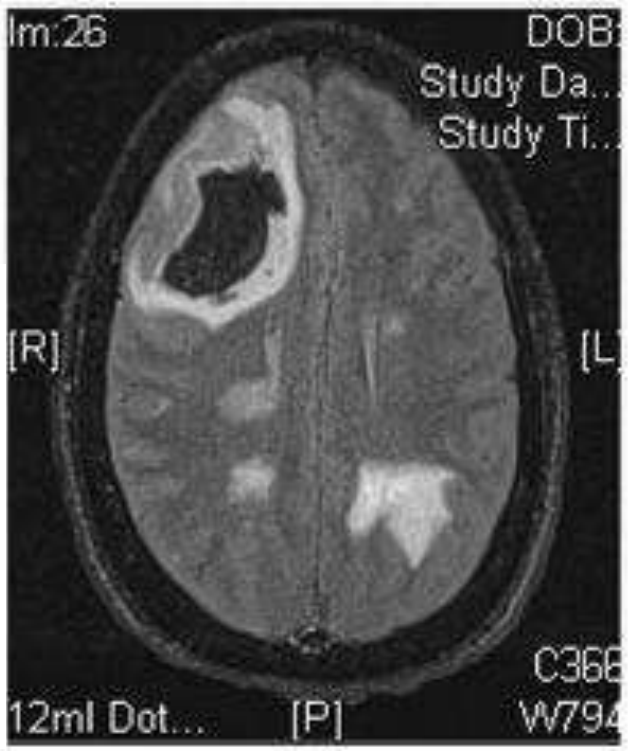
- Thema: wen und wann zur Transplantation

selten?

Sichelzellerkrankung

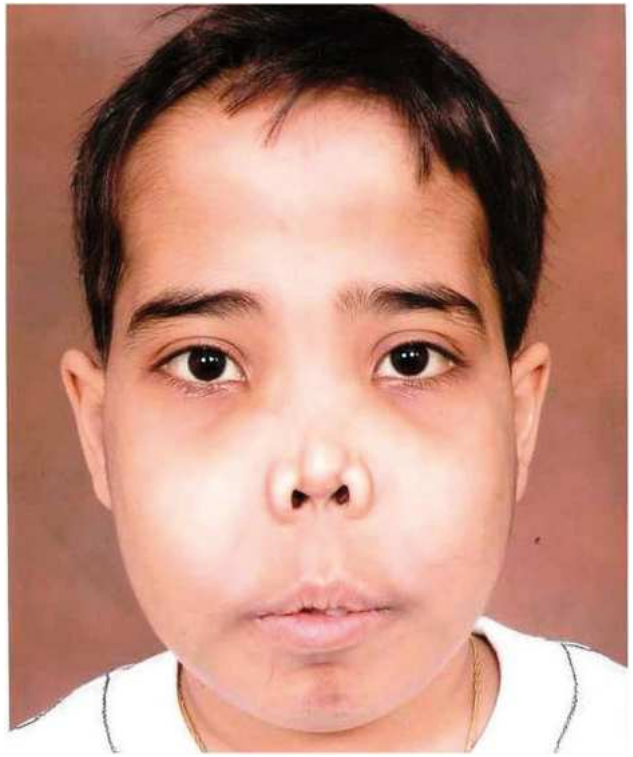
- Sichelzellträger
- Sichelzellerkrankter

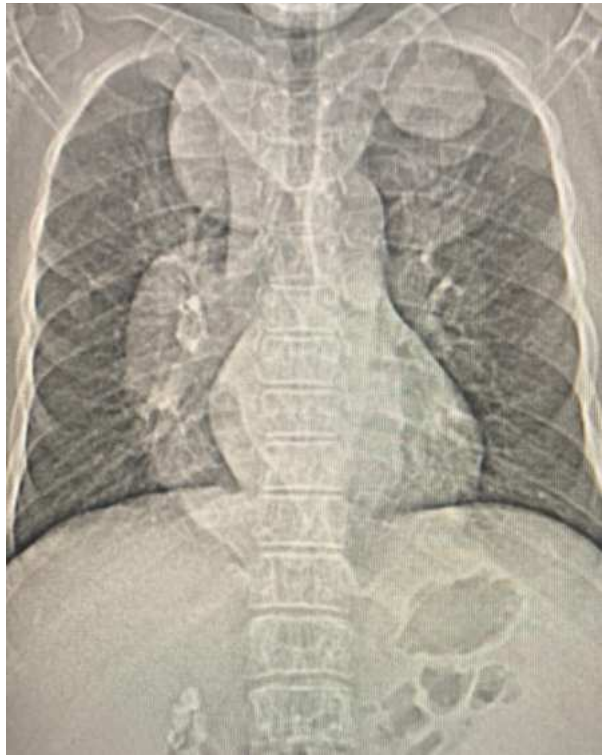


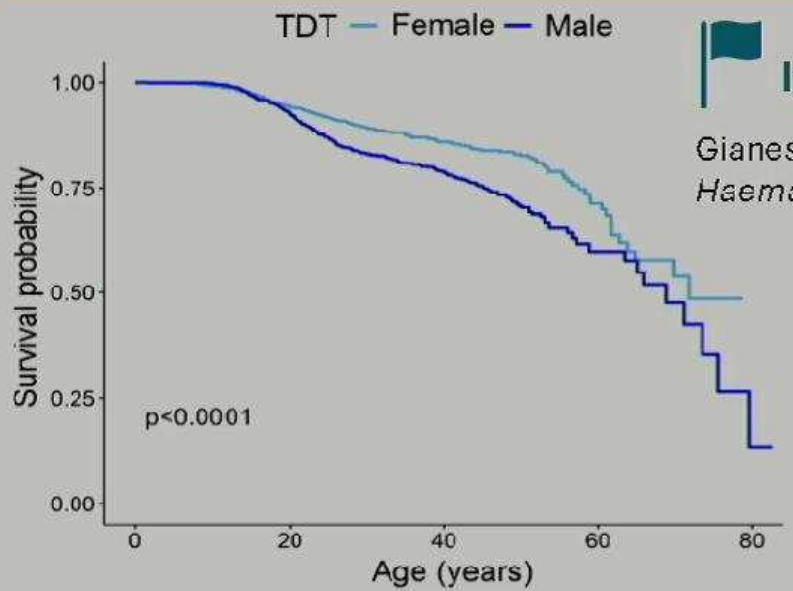


Thalassämie

- Thalassämie minor
- Thalassämie major

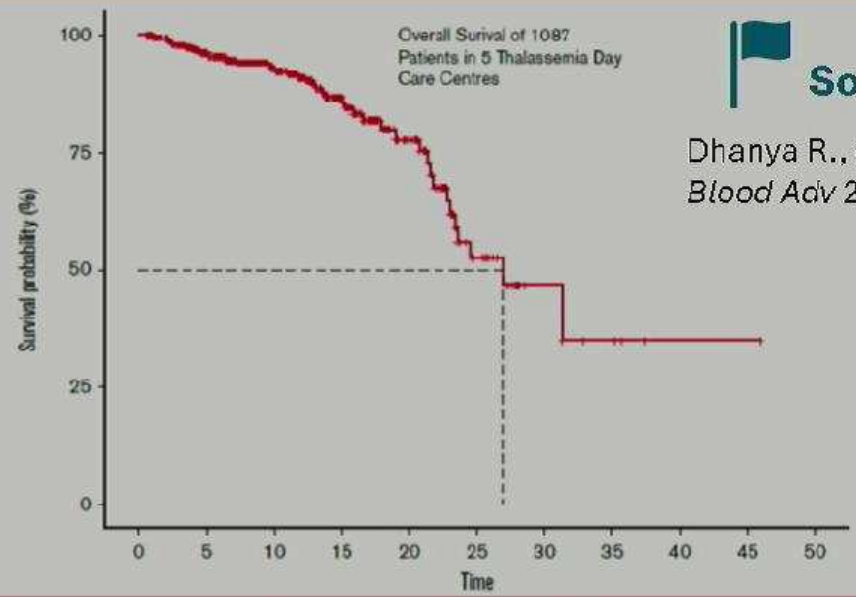






Italy

Gianesin B., et al.
Haematologica 2025



South India

Dhanya R., et al.
Blood Adv 2020;4(7):1448-1457

High-income countries[1-4]:

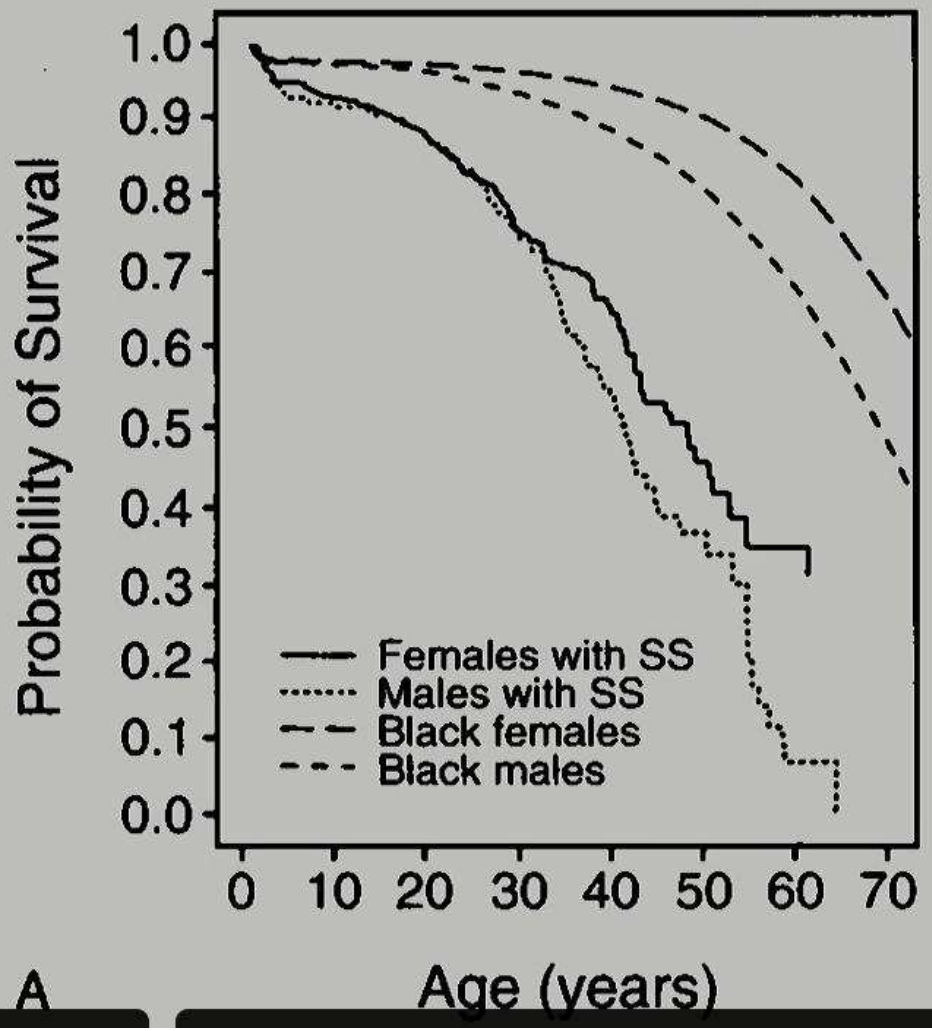
- ✅ Optimized transfusion and chelation support
- ✅ Access to disease-modifying agents
- ✅ Comprehensive management of complications
- 📈 **Median survival:** ~50-60 years (improving)
- ⚠️ Low complication-free survival and declining quality of l[illegible]m adolescence onward

Resource-limited countries[4-6]:

- ⚠️ Limited blood supply and transfusion support
- ⚠️ Irregular or inadequate iron chelation therapy
- ⚠️ No/Limited access to innovative treatments
- 📉 **Median survival:** ranging from ~20-30 to ~40-50 years
- 💔 High morbidity and impaired quality of life, often beginning in childhood

04:02

Survival in Cooperative Study of SCD



ORIGINAL ARTICLE

Mortality In Sickle Cell Disease -- Life Expectancy and Risk Factors for Early Death

Orah S. Platt, Donald J. Brambilla, Wendell F. Rosse, Paul F. Milner, Oswaldo Castro, Martin H. Steinberg, and Panpit P. Klug*et al.

June 9, 1994

In 3764 patients in the pre-hydroxyurea era
Median survival:
42 years for males
48 years for females

37:22

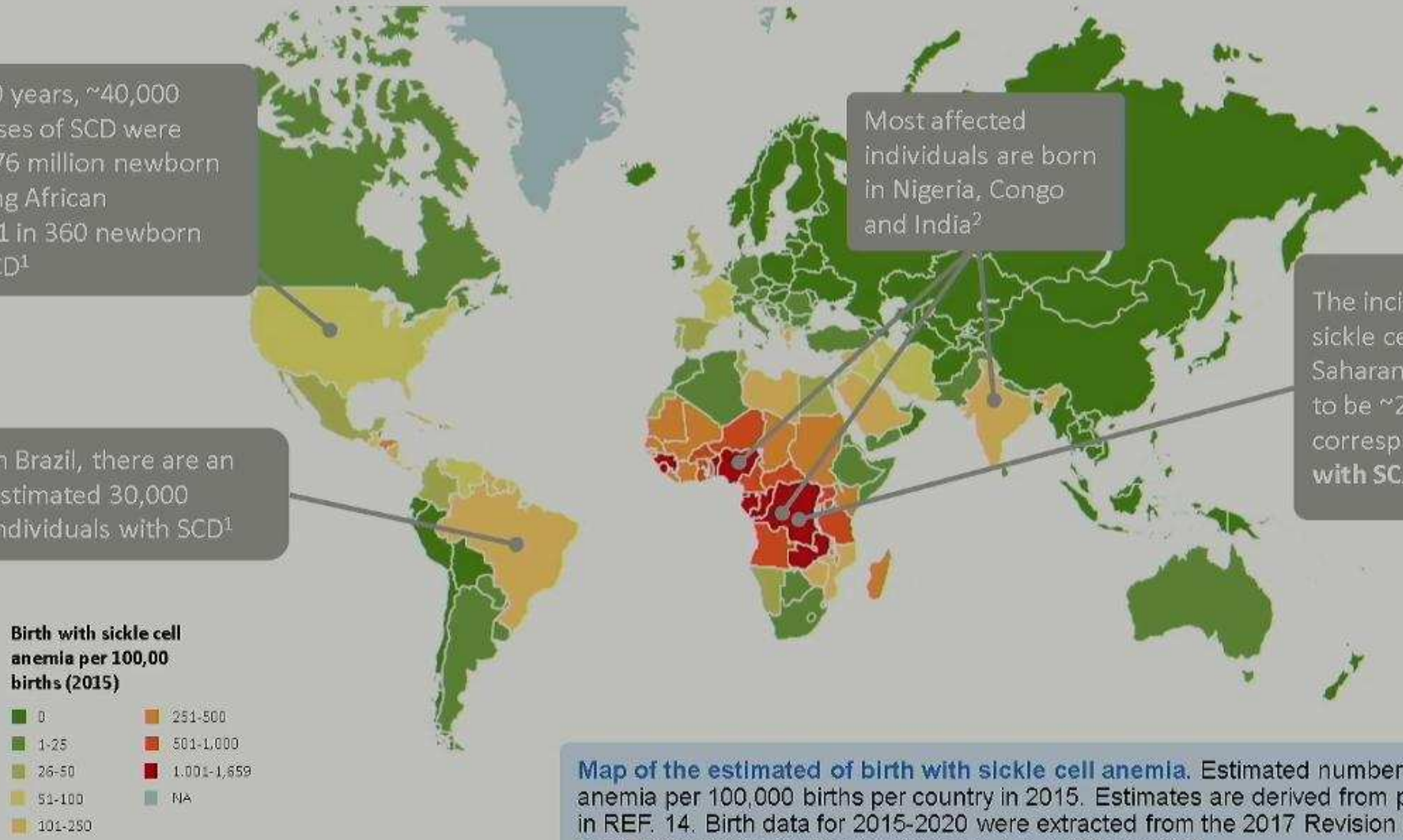
Incidence and Distribution

In the past 20 years, ~40,000 confirmed cases of SCD were identified in 76 million newborn babies. Among African Americans, ~1 in 360 newborn babies has SCD[1]

Most affected individuals are born in Nigeria, Congo and India[2]

The incidence of births with sickle cell anemia (SCA) in sub-Saharan Africa was estimated to be ~230,000 in 2010, which corresponds to **~75% of births with SCA worldwide**[1]

In Brazil, there are an estimated 30,000 individuals with SCD[1]

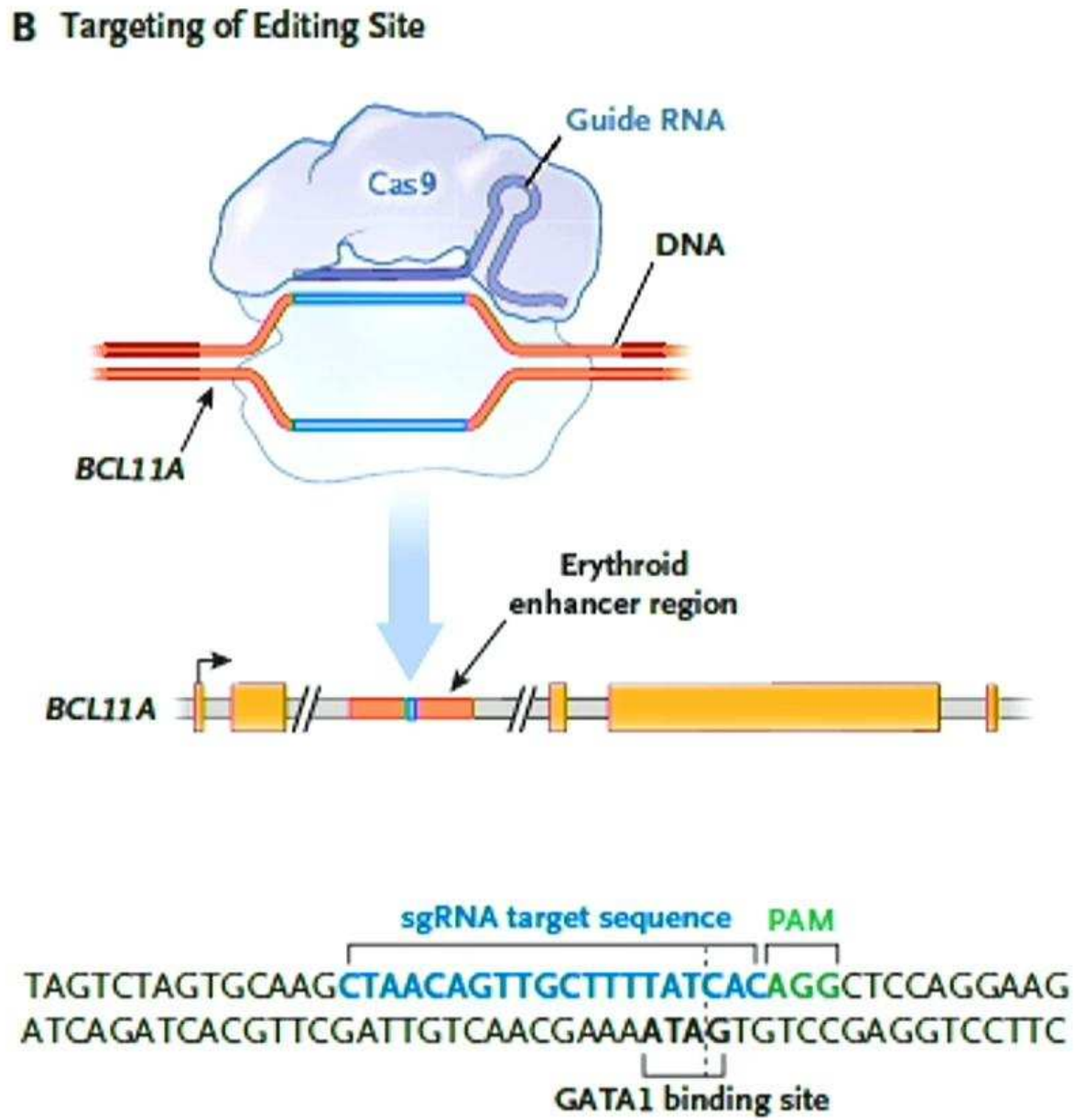


Map of the estimated of birth with sickle cell anemia. Estimated numbers of births with sickle cell anemia per 100,000 births per country in 2015. Estimates are derived from prevalence data published in REF. 14. Birth data for 2015-2020 were extracted from the 2017 Revision of the United Nations World Population Prospects database. NA, not applicable.

1. Kato GJ, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010. doi:10.1038/nrdp.2018.10. 2. Piel, FB, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010;104.

Using CRISPR-Cas9-based gene editing to target *BCL11A*

- Our goal is to edit the specific region of the *BCL11A* gene to **decrease the expression of the BCL11A protein** and increase the expression of HbF[1]



population

1,815 consecutive patients in centers across 36 countries in Europe, Asia & Africa

		children (n=1,331)	adults (n=484)
Age at HCT	median [IQR]	9.6 [6.3-13]	26.5 [21.3-32.2]
	(range)	(1.1-18)	(18-49.2)
Patient sex	Female	638 (48%)	234 (48.5%)
	Male	690 (52%)	248 (51.5%)
	missing	3	2
Year of HCT	median [IQR]	2017 [2014-2019]	2019 [2017-2020]
	(range)	(2010-2021)	(2010-2021)
Donor type	Matched relative	1,066 (80.5%)	401 (83%)
	Mismatched relative	144 (10.9%)	72 (14.9%)
	Unrelated	115 (8.7%)	10 (2.1%)
	missing	6	1

stem cell source & conditioning

- **Stem cell source:**
  - children: 80.5% received bone marrow
  - adults: 64.9% adults received PBSC

- **Conditioning regimen:**
  - children: BuCy based 43.3%
  - adults: TBI-based 68.7%
  - treosulfan based conditioning represented a quarter of all transplants in children

- **Serotherapy:**
  - only 171 children (13.1%) & 14 adults (2.9%) did not have serotherapy

outcomes

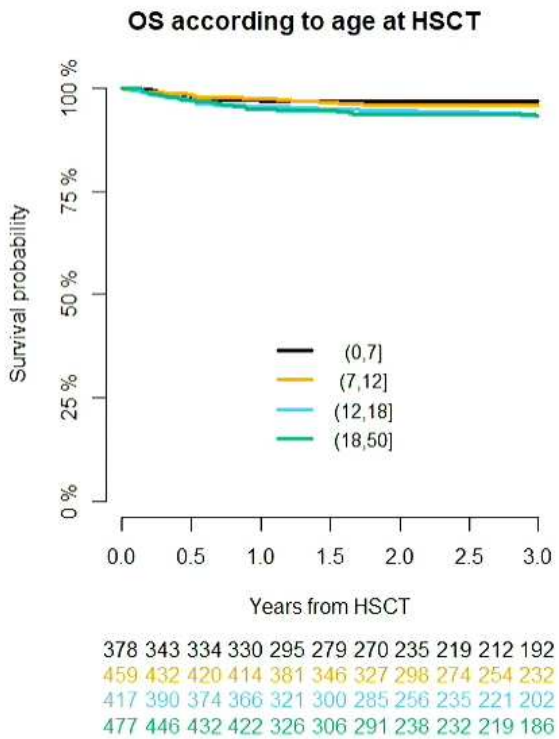
		SCD children		SCD adults
Outcomes	**N**	**Estimation (95%CI)**	**N**	**Estimation (95%CI)**
Median FU	1,254	3.1 yr (3 - 3.2)	477	2.6 yr (2.1 - 2.9)
OS (2 yr)	1,254	95.7% (94.3 - 96.7)	477	93.7% (91 - 95.7)
EFS (2 yr)	1,254	92.9% (91.3 - 94.3)	477	90.5% (87.3 - 93)
Second Tx (2 yr)	1,254	3.2% (2.3 - 4.4)	476	4.6% (2.9 - 7)
GRFS (2 yr)	1,254	86.1% (84 - 88)	477	85.5% (81.8 - 88.5)

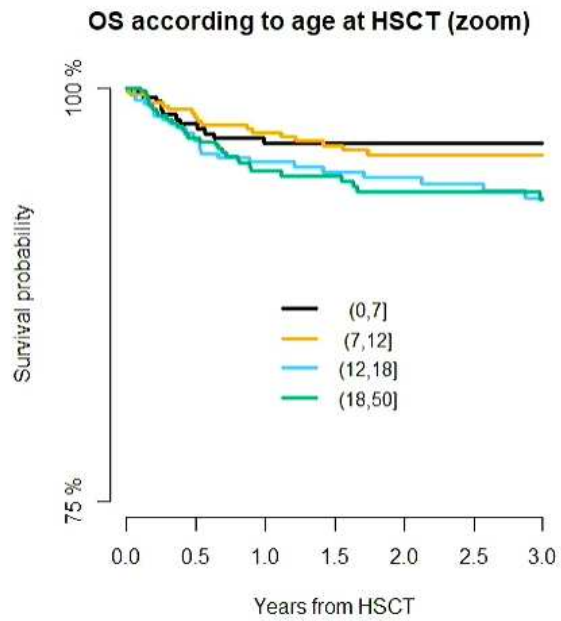
graft versus host disease

		SCD children		SCD adults
Outcomes	**N**	**Estimation (95%CI)**	**N**	**Estimation (95%CI)**
aGVH-II/IV (100 d)	1,183	13.6% (11.7 - 15.6)	461	9.4% (6.9 - 12.2)
aGVH-III/IV (100 d)	1,183	5.8% (4.5 - 7.2)*	461	3.9% (2.4 - 6)
cGVHD (2 yr)	1,130	12.7% (10.7 - 14.8)	454	11.6% (8.7 - 14.9)
cGVHD Ext (2 yr)	1,121	5.4% (4.1 - 6.9)	450	4.1% (2.5 - 6.3)

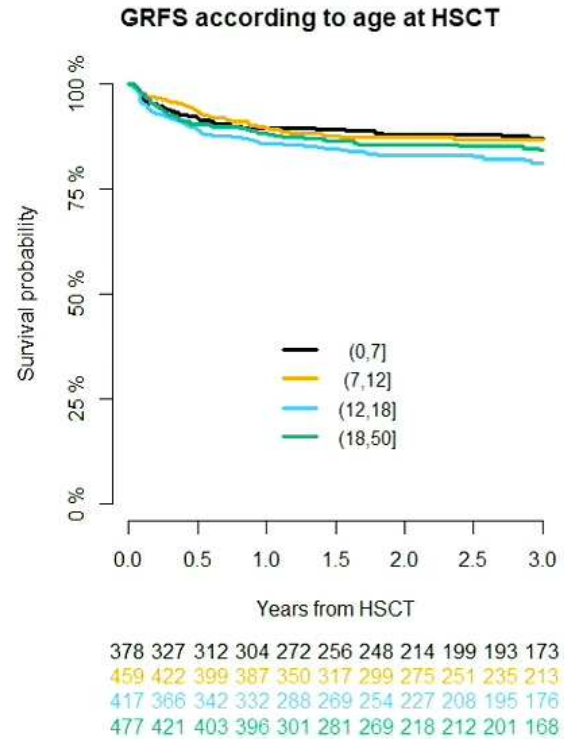
* adolescents (12-18 years) had a higher risk of grade III-IV aGVHD: HR 1.59 (1.03-2.46), p = 0.04

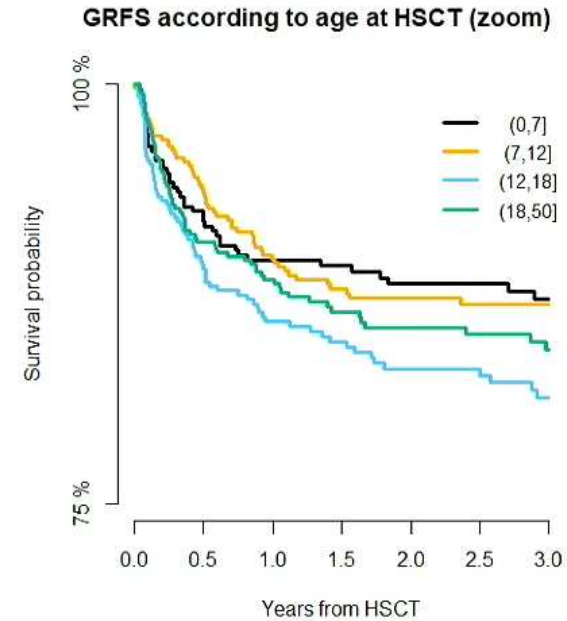
age as a factor in OS & GFRS





age	OS HR (95% CI)	p value
(0,4]	1	
(7,12]	1.27 (0.61-2.67)	0.52
(12,18]	2.01 (1.01-3.99)	0.047



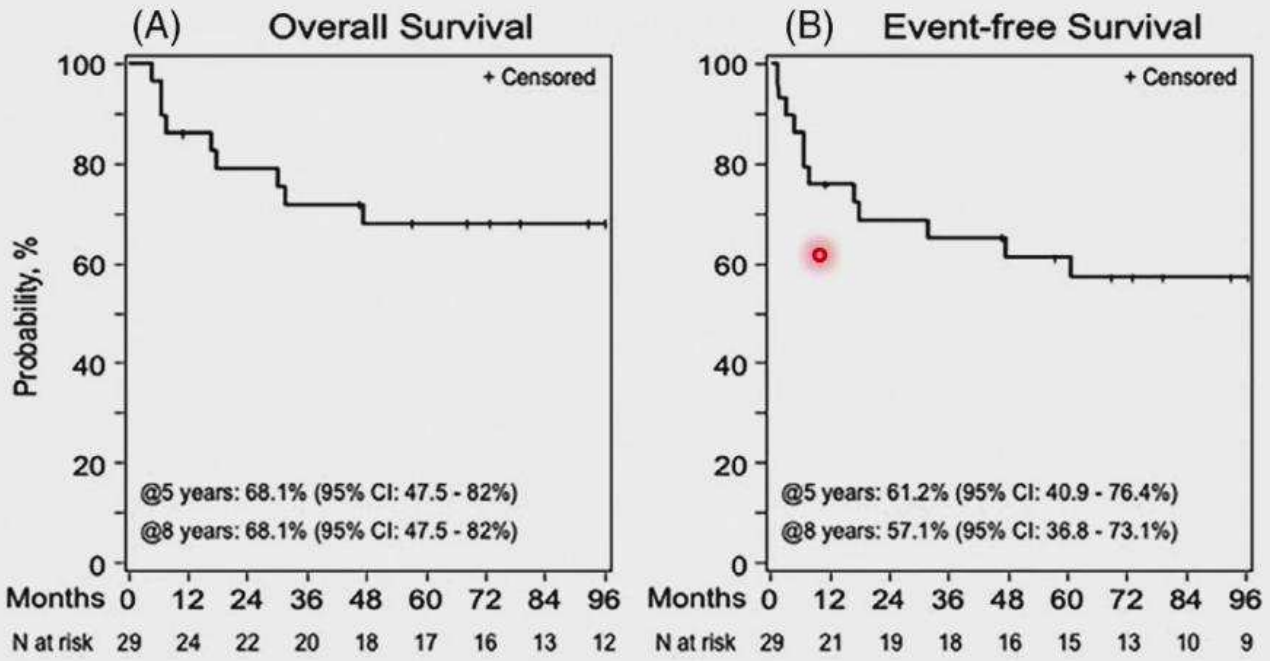


age	GRFS HR (95% CI)	p value
(0,4]	1	
(7,12]	0.6 (0.29-1.23)	0.16
(12,18]	0.72 (0.36-1.44)	0.35

MUD HCT: Sickle Cell Disease

BMTCTN 0601: 2008 – 2014; 29 of 30 MUD HCTs were evaluable

	1-year	8-years
AGVHD	28%	28%
CGVHD	**62%**	**62%**
Graft failure	10%	14%
EFS	**76%**	**57%**
Survival	**86%**	**68%**

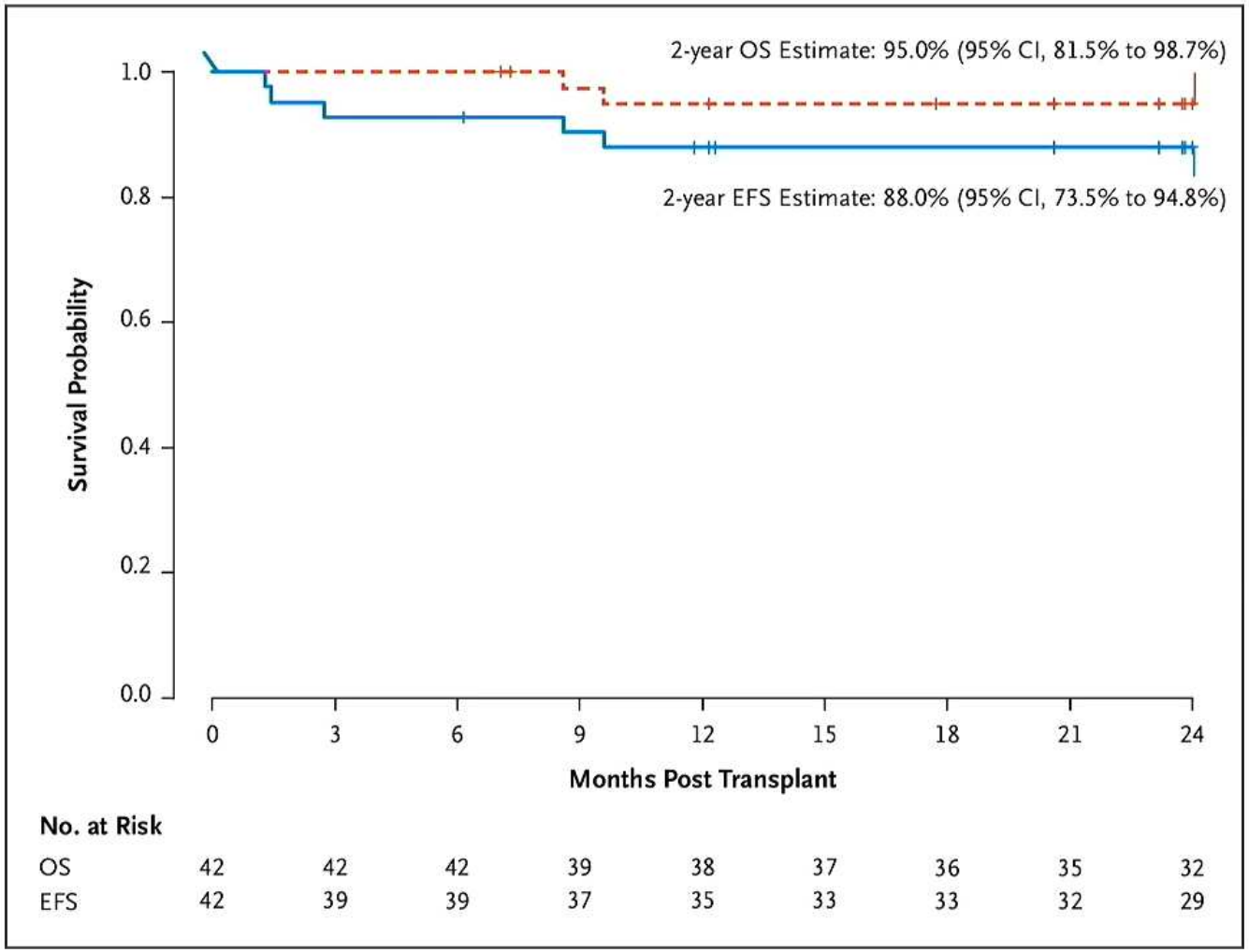


- 8 of 9 deaths were GVHD associated
  - Age 14-19 years

A high incidence of GVHD and associated mortality compromised safety of the trial

Shenoy S et al Blood 2016; Eapen M et al A J Hematol 2023

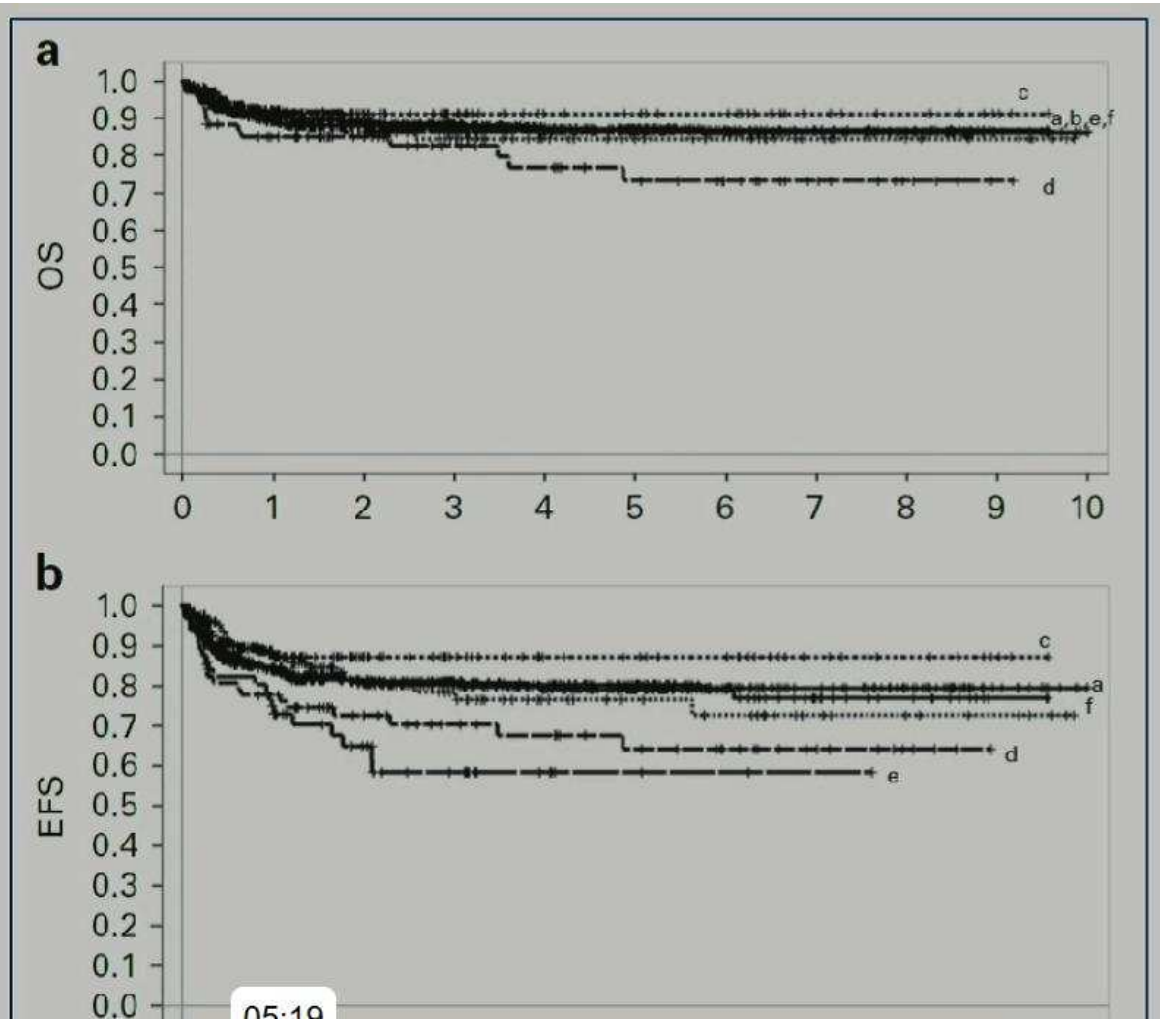
Haploidentical BMT for SCD: BMT CTN 1507



- **Total patients treated, N = 42**
- **Graft failure n = 3**
- **TRM, n = 4 (1 patient during the HU phase and 1 on day 969)**
- **24% had qualifying even at 2 years post transplant (GF, cGVHD, Death)**

- **Sickle cell related events**
  - **AVN 11.4 %**
  - **2.4% VOC (18-24 m)**
  - **2.4% CNS events**
  - **Any event 7% (0-6m) and 17% 18-24 months**

44:46



EBMT Hemoglobinopathy Registry Database:

1493 patients with thalassemia major transplanted between 1 January 2000 and 31 December 2010

		A) OS		B) EFS	
	Patients	Events	2-year OS	Events	2-year EFS
a) Italy	581	55	0.89±0.02	90	0.82±0.02
b) Turkey	216	21	0.86±0.03	32	0.80±0.04
c) UK	133	10	0.91±0.03	14	0.87±0.03
d) Iran	68	14	0.85±0.04	21	0.73±0.06
e) Saudi Arabia	64	7	0.89±0.04	21	0.65±0.07
f) Others	431	47	0.88±0.02	75	0.81±0.02
P-value		0.347		<0.001	

[a] Countries performing < 50 transplants were included in the "other" category

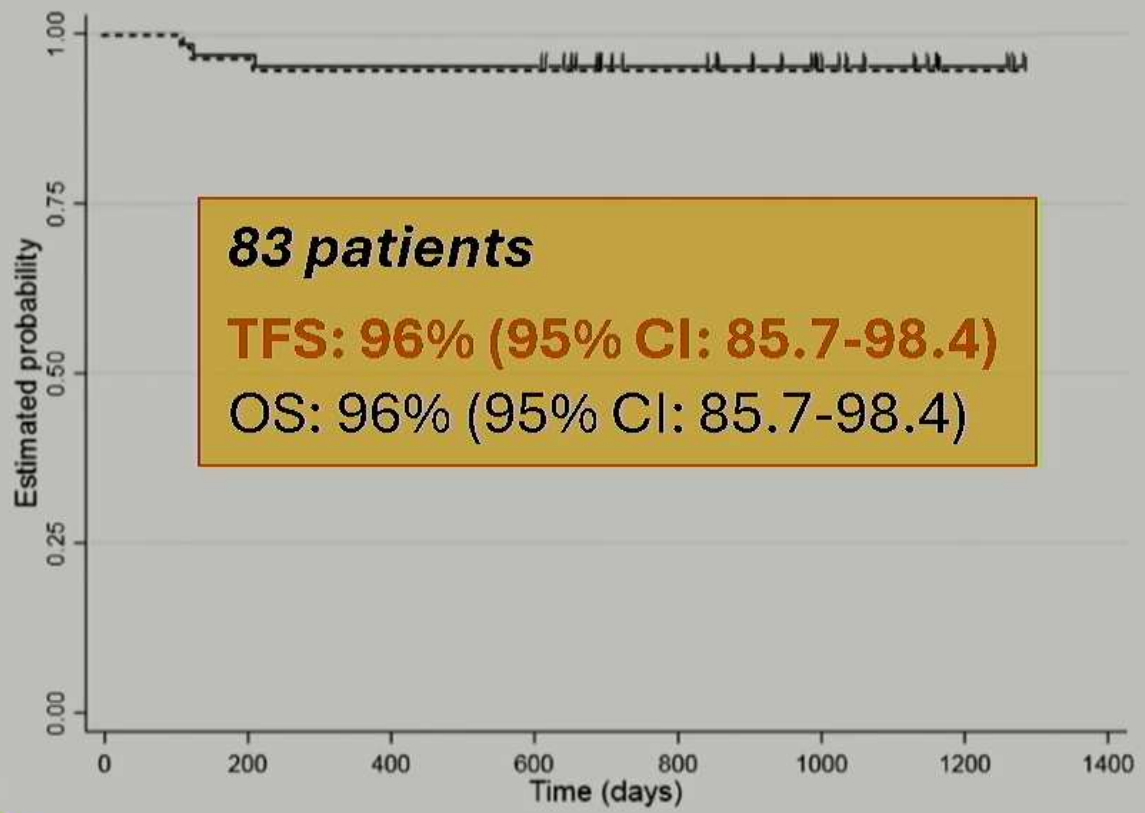
Type of Donor determines Allogeneic HSCT Outcomes in TDT

EBMT 2020 Hemoglobinopathy Registry 2,891 TDT Patients: Donor and outcome[1,2]

Donor	MSD, %	Match related, %	MM related, %	UD 10/10, %	UD < 10/10, %
OS	91.8	88.3	85.3	93.2	81.4
TFS	83	79.5	62.4	85.7	68
Rejection	8.8	8.8	22.9	7.5	13.4
NRM	8.1	11.6	14.6	6.7	18.5
aGvHD > 2	6.6	9.3	3.1	12.7	14.2
cGvHD	13.1	15.9	9.3	15	17.8

Haploidentical Transplantation for TDT

In vivo Post-Transplant Cyclophosphamide[1]

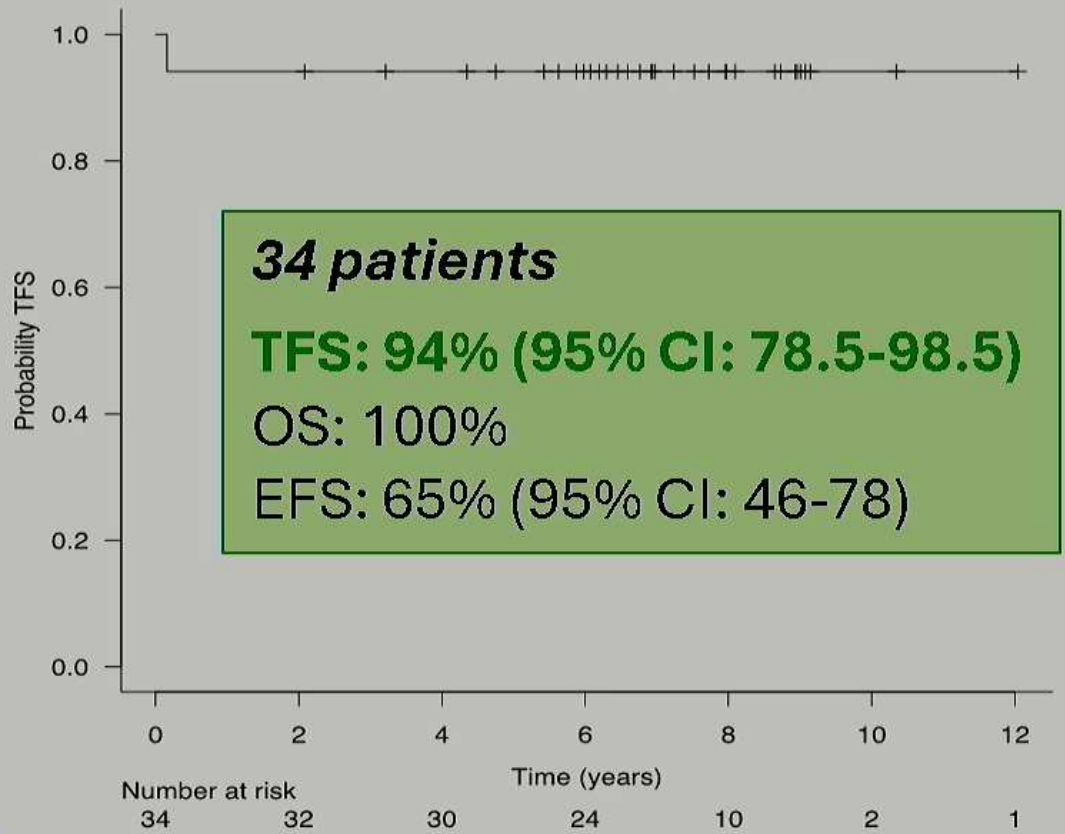


83 patients

TFS: 96% (95% CI: 85.7-98.4)

OS: 96% (95% CI: 85.7-98.4)

Ex vivo TCRαβ+/CD19+ depletion[2]



34 patients

TFS: 94% (95% CI: 78.5-98.5)

OS: 100%

EFS: 65% (95% CI: 46-78)

Idem bei Hämoglobinopathie

- Spenderwahl schwieriger
- Allosensiblisierung
- Intensive Konditionierung
- Indikationsstellung für Transplantation
- Indikationsstellung für Gentherapie

- «irreversible» Organschädigung

Nicht maligne Erkrankungen

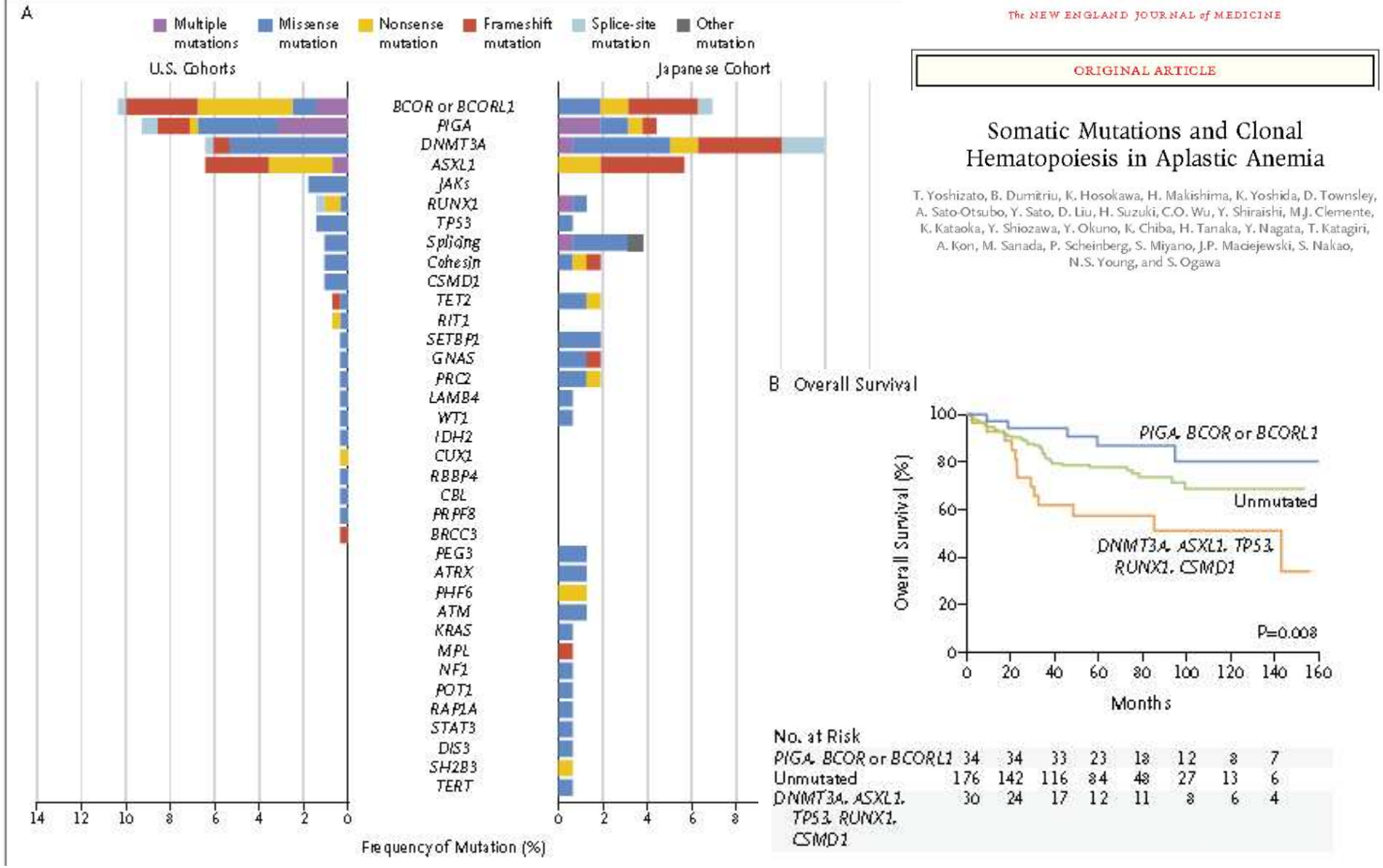
Allogene Transplantation als Option

Kein Benefit durch die Graft versus Host Erkrankung

Spenderwahl

Abwägen Therapiealternative

MERCI



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

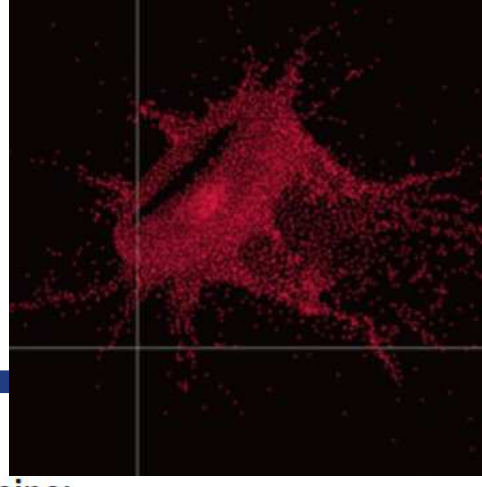
Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia

T. Yoshizato, B. Dumitriu, K. Hosokawa, H. Makishima, K. Yoshida, D. Townsley, A. Sato-Otsubo, Y. Sato, D. Liu, H. Suzuki, C.O. Wu, Y. Shiraishi, M.J. Clemente, K. Kataoka, Y. Shiozawa, Y. Okuno, K. Chiba, H. Tanaka, Y. Nagata, T. Katagiri, A. Kon, M. Sanada, P. Scheinberg, S. Miyano, J.P. Maciejewski, S. Nakao, N.S. Young, and S. Ogawa

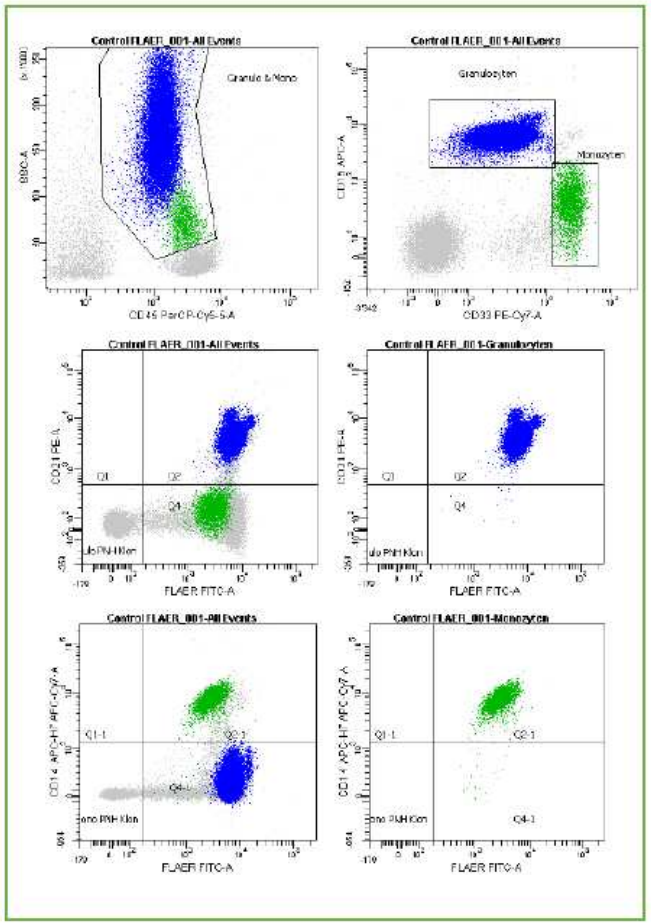
The old paradigm: AA autoimmune, MDS genetic

PNH hämolytisch thrombotisch aplastisch

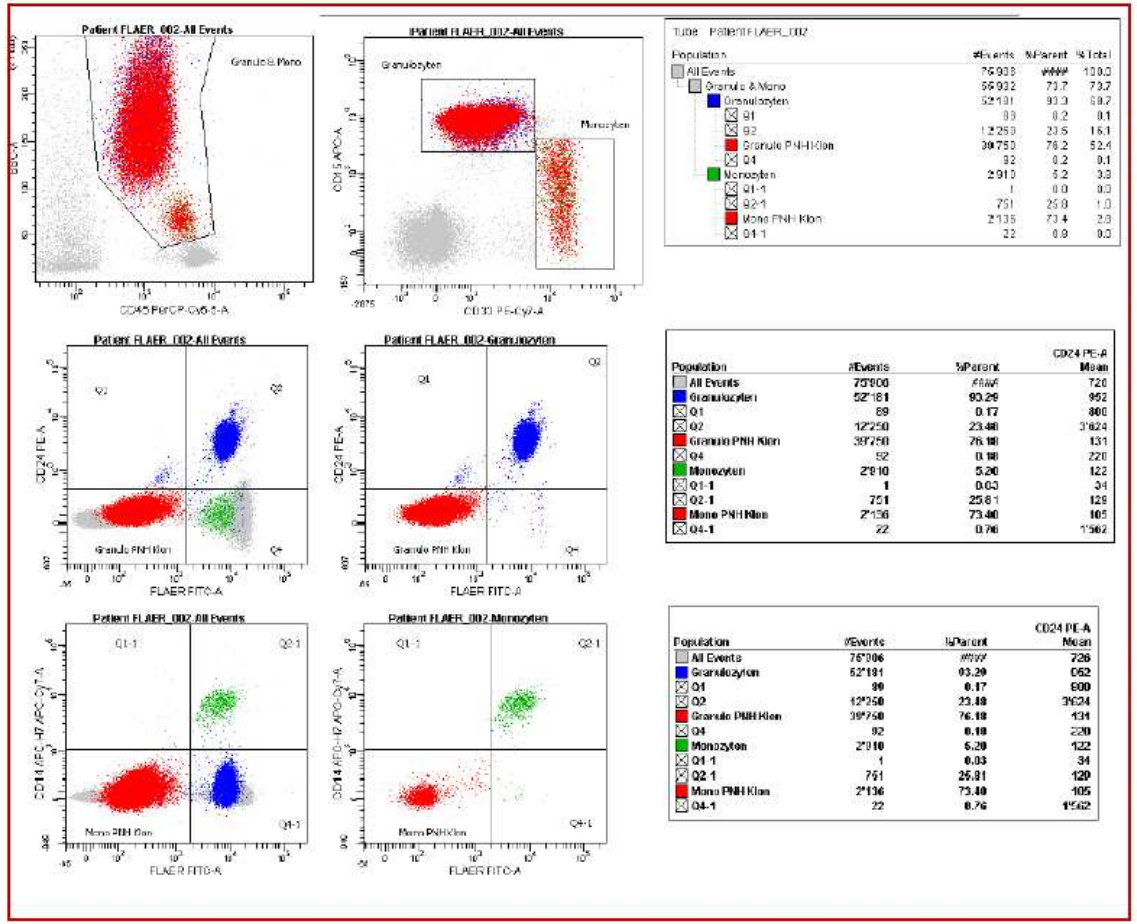
Flow



Kontrolle



Patient



- **GPI-Ankerproteine:** CD59, CD24, CD14, FLAER.
- PNH-Klon **Gran. 76%**
- PNH-Klon **Mono. 73%.**
- **Ery normal (Typ I, 83%)**
- **Ery, partiell defizient (Typ II, 2%)**
- **Ery, komplett defizient (Typ III, 16%)**

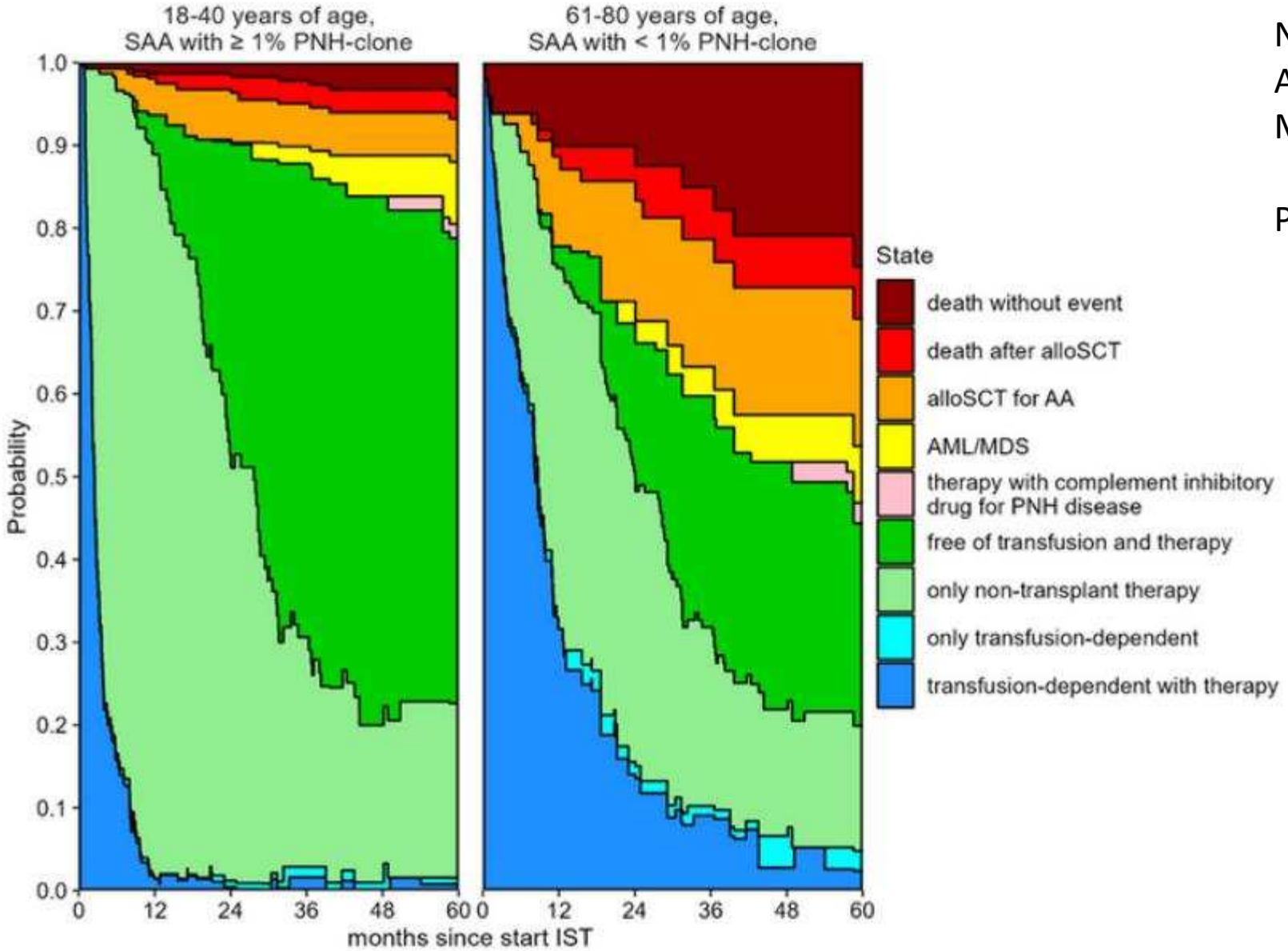
- **Sensitivitätsgrenze: 0.1%.**

Klon-Grösse Granulozyten

- **major PNH-Klon -> Klon-Grösse > 1 %**
- **minor PNH-Klon -> Klongrösse 0.1-1 %**

OS18-02 PREDICTING TRANSPLANTATION-, TRANSFUSION- AND TREATMENT-FREE SURVIVAL AFTER IMMUNE SUPPRESSIVE TREATMENT FOR ADULTS WITH ACQUIRED APLASTIC ANEMIA

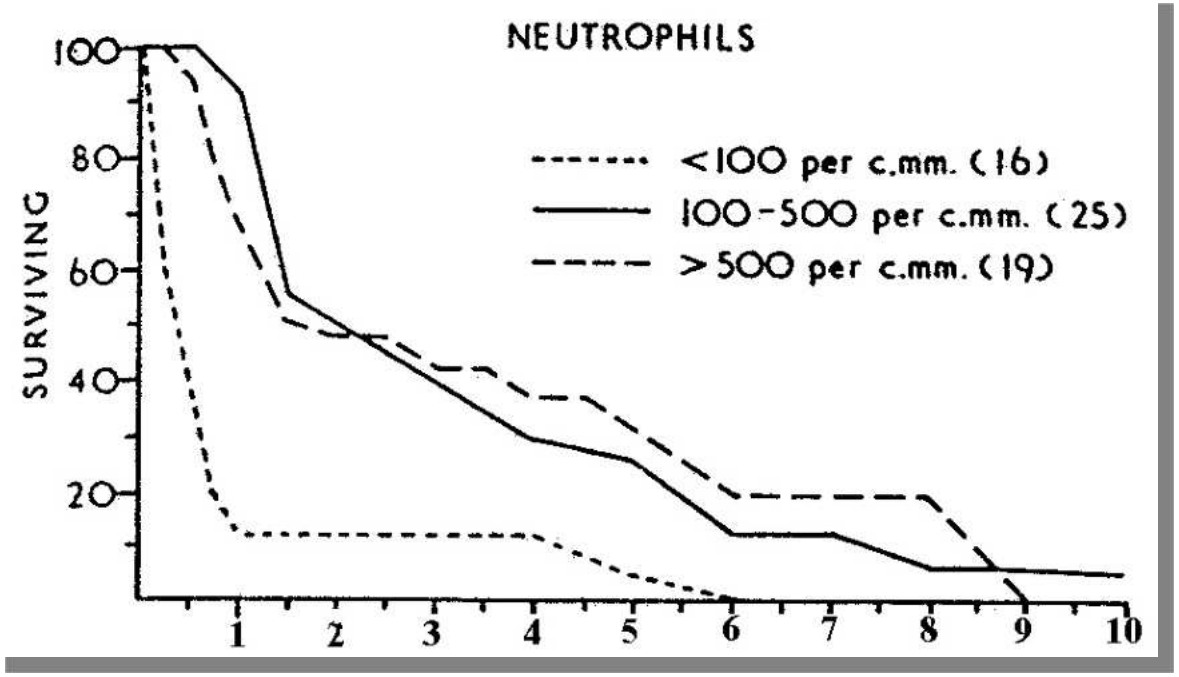
Cjm Halkes[1], Eas Koster[1], Ejm Bogers[1], Lgm Daenen[2], Sk Klein[3], Smc Langemeijer[4], F. Moenen[5], E. Nur[6,7], Mhg Raaijmakers[8], Tjf Snijders[9], Jennifer ML Tjon[1], L.C. de Wreede[1]



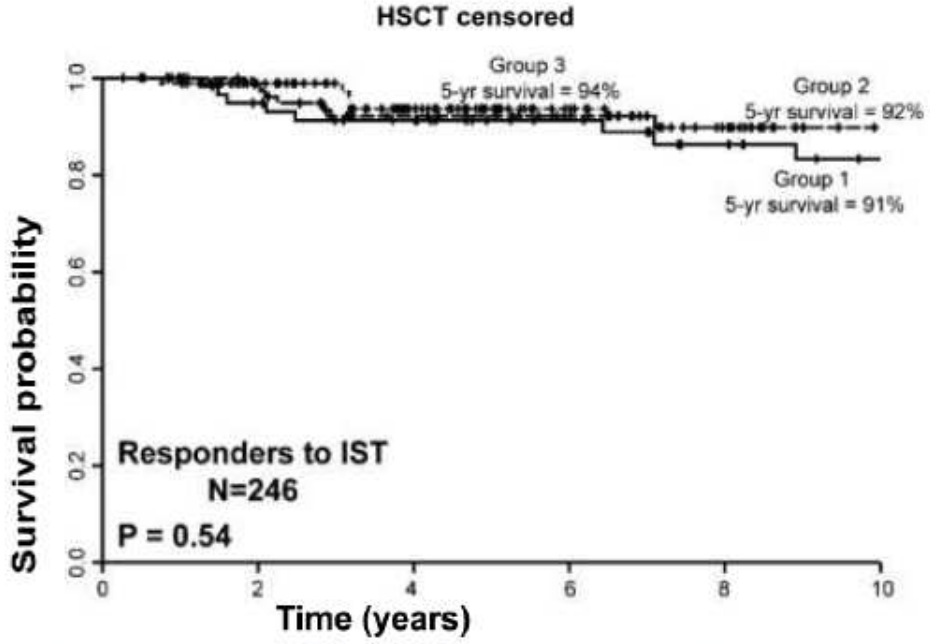
N=127
Age: 54
MultiStateModelling

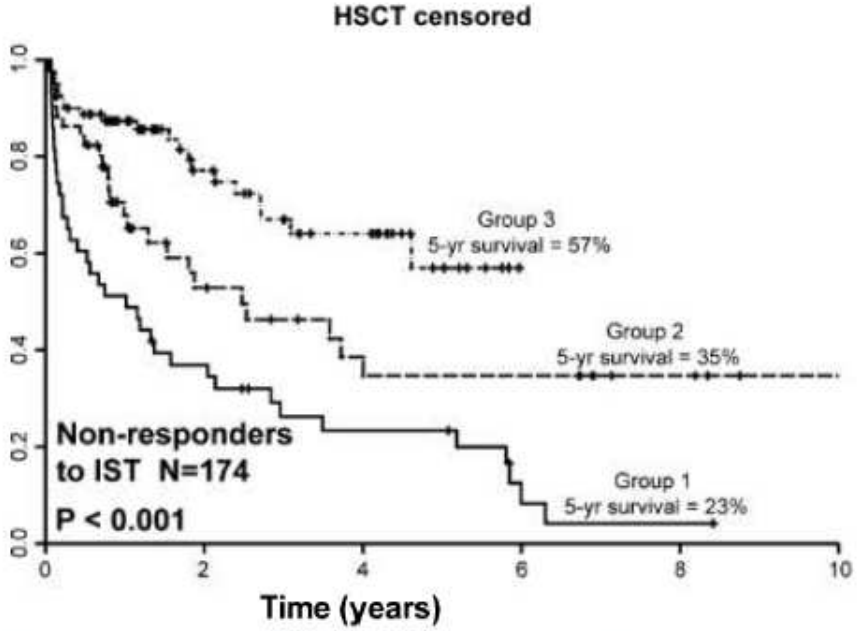
Predictors:
severity
age
pnh

Vor IST und HCT: Outcome katastrophal, abhängig von der Neutrophilenzahl



Supportive Care –the underestimated treatment





	Treatment between	Patient number	5 yr-survival responder	5-yr-survival non-responder (NR)	6 mo survival NR
Group 1	12/1989 -10/1996	43	91%	23%	61%
Group 2	11/1996 – 10/2002	51	92%	35%	82%
Group 3	11/2002 – 04/2008	80	94%	57%	89%

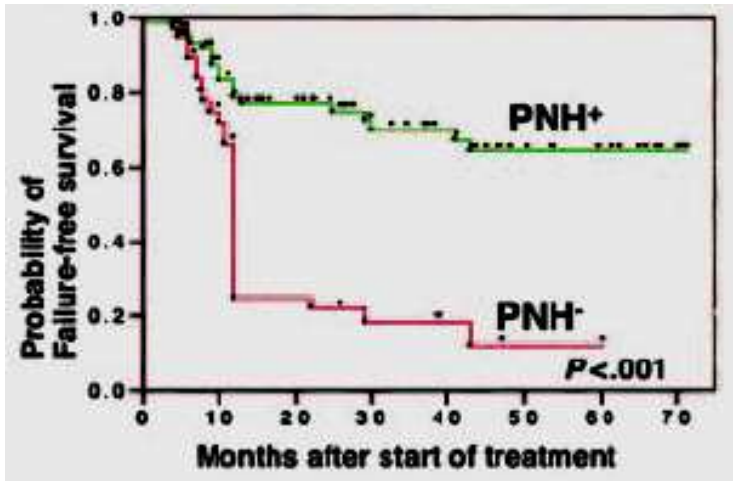
Valdez J. et al Clinical Infection Diseases 2011

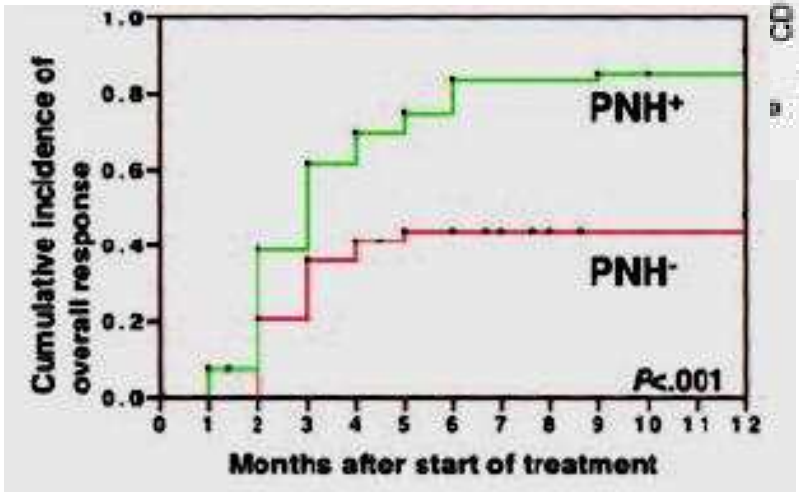
Minor population of CD55⁻CD59⁻ blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia

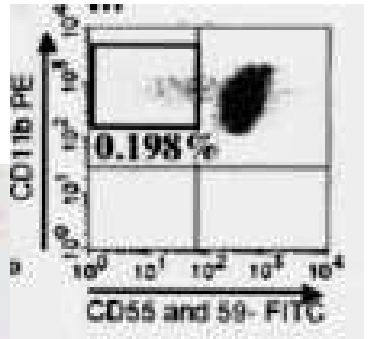
Chiharu Sugimori, Tatsuya Chuhjo, Xingmin Feng, Hirohito Yamazaki, Akiyoshi Takami, Masanao Teramura, Hideaki Mizoguchi, Mitsuhiro Omine, and Shinji Nakao

PNH clones ~ autoimmune nature of bone marrow failure?

	PNH⁺	PNH⁻
No. of patients	83	39
Median age, y (range)	57 (13-83)	54 (12-83)



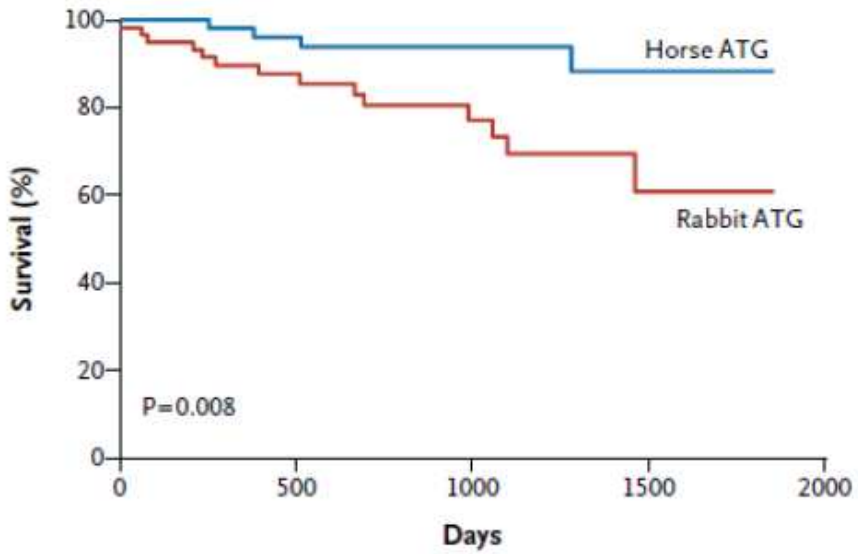




FFS **Response**

PNH in SAA: usually small clones, rarely symptomatic
Aplastic crisis in PNH vs. PNH clone in a SAA patient

Rabbit ATG as first-line IS treatment provides lower OS, response rates and higher deaths rates than horse ATG



lo. at Risk				
lorse ATG	60	44	27	12
abbit ATG	60	41	22	6

Scheinberg P.et al. NEJM. 2011; 365:430-438

- Randomized prospective trial with 120 patients
- Response at 6 months (68% vs 37%), and overall survival at 3 years (96% versus 76%) was largely in favor of horse ATG
- There were 4 death in the horse and 14 death in the rabbit ATG group

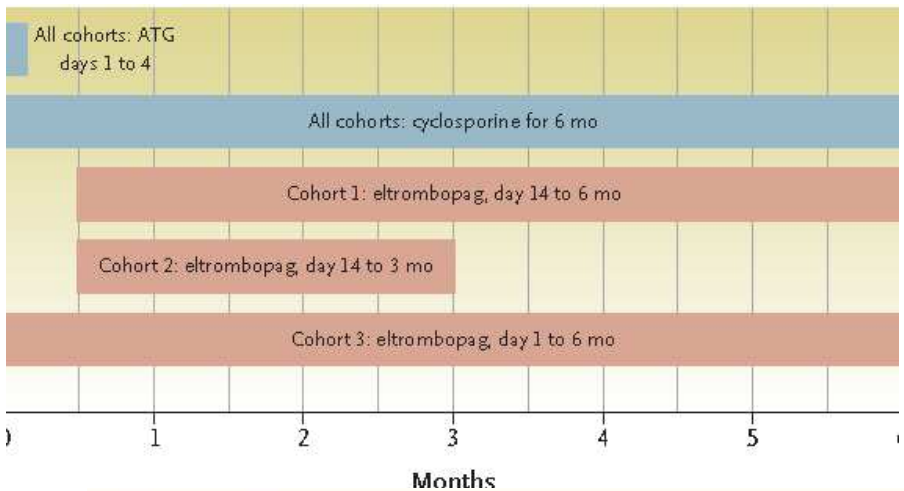
Cause of death (11/35)	Time to death
Sepsis (5)	9,210,243,326, 370
Pneumonie (2)	207; 209
Sepsis &multiorgan failure	6
Sepsis & cardiac arrest	148
Intracranial hemorrhage	288
Post-SCT fungal infection	390

Marsh J et al. Blood. 119:5391-5396

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

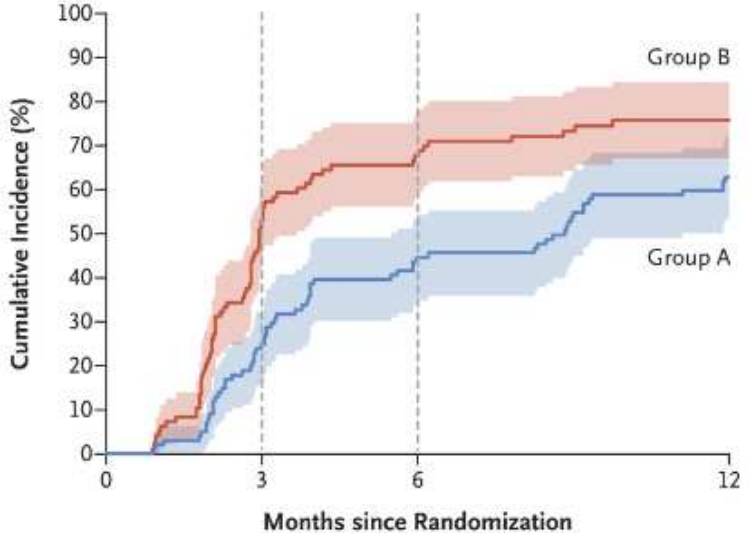
Danielle M. Townsley, M.D., Phillip Scheinberg, M.D., Thomas Winkler, M.D., Ronan Desmond, M.D., Bogdan Dumitriu, M.D., Olga Rios, R.N., Barbara Weinstein, B.S.N., Janet Valdez, P.A., Jennifer Lotter, P.A., Xingmin Feng, Ph.D., Marie Desierto, B.S., Harshraj Leuva, M.B., B.S., Margaret Bevans, Ph.D., Colin Wu, Ph.D., Andre Larochelle, M.D., Ph.D., Katherine R. Calvo, M.D., Cynthia E. Dunbar, M.D., and Neal S. Young, M.D.

N Engl J Med 2017;376:1540-50.



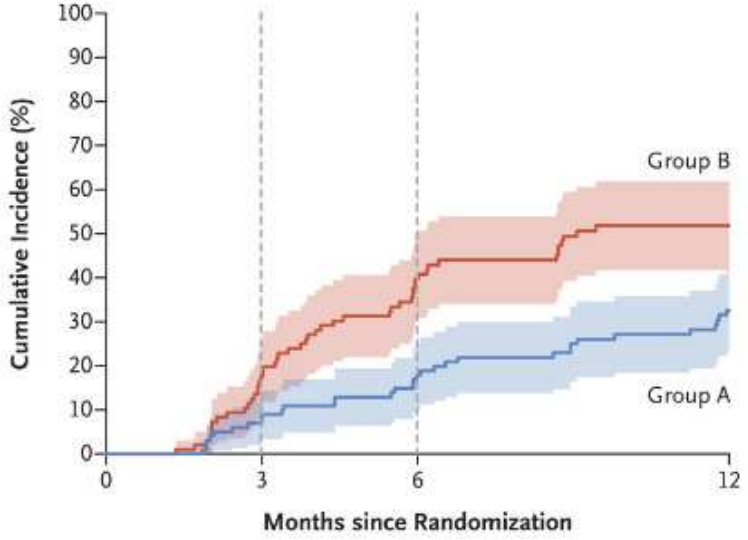
All cohorts			
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001

A First Response



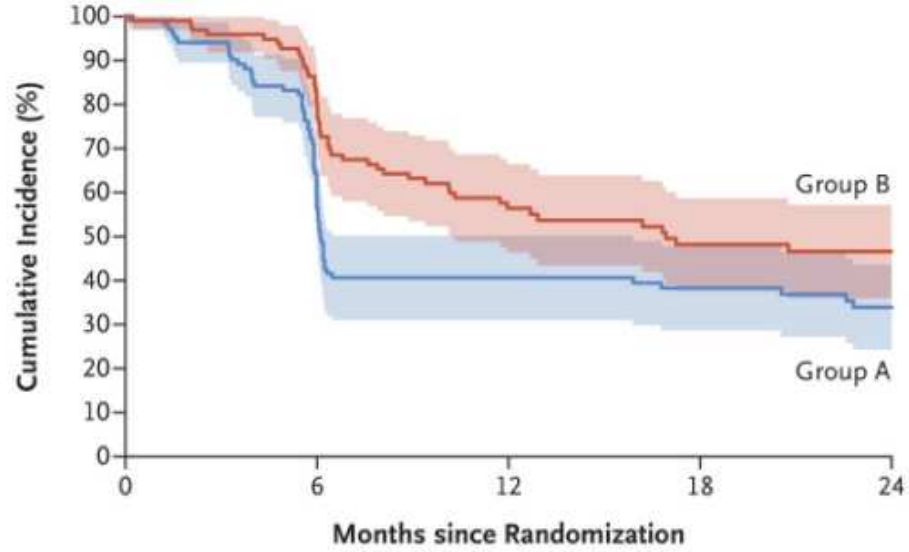
No. at Risk			
Group B	96	25	4
Group A	101	40	14

B Complete Response



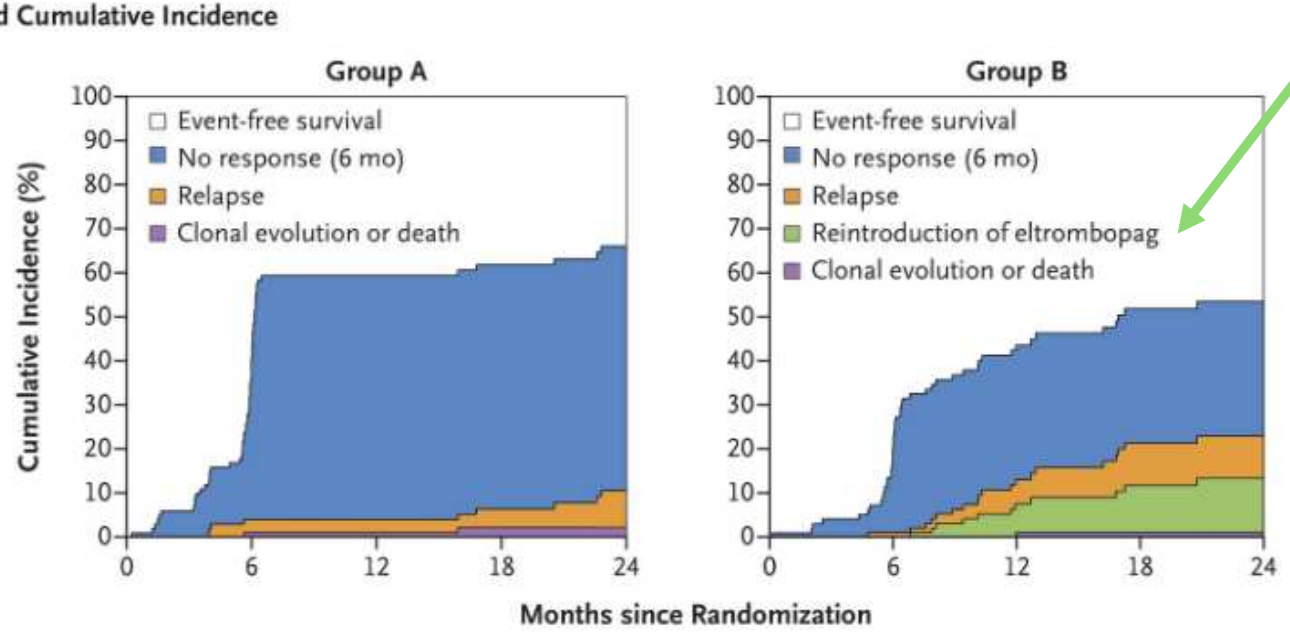
No. at Risk			
Group B	96	52	16
Group A	101	64	35

A Event-free Survival

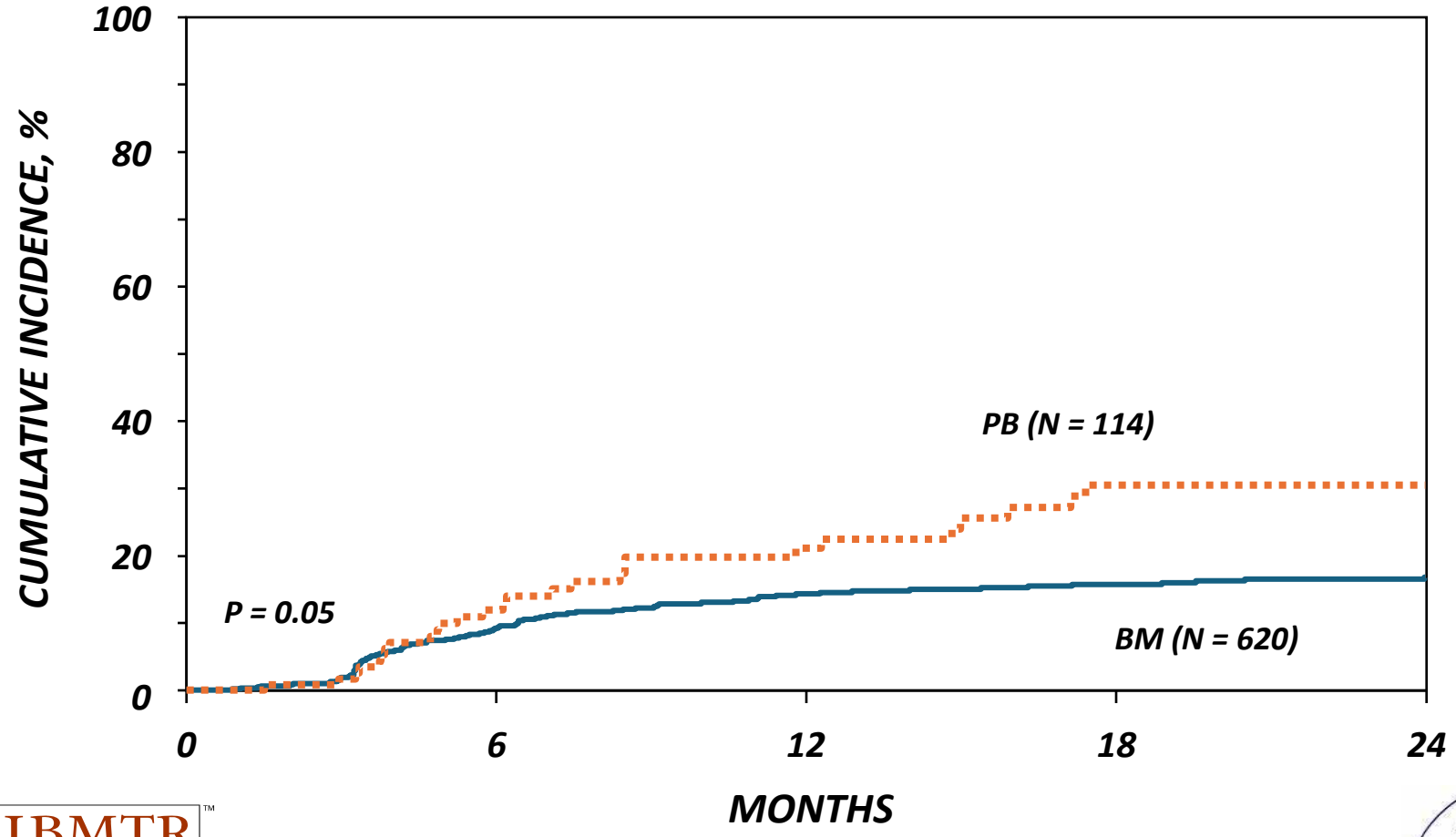


No. at Risk					
Group B	96	76	45	31	15
Group A	101	60	38	30	10

B Stacked Cumulative Incidence



Stem Cell Source
CHRONIC GVHD



CIBMTR™

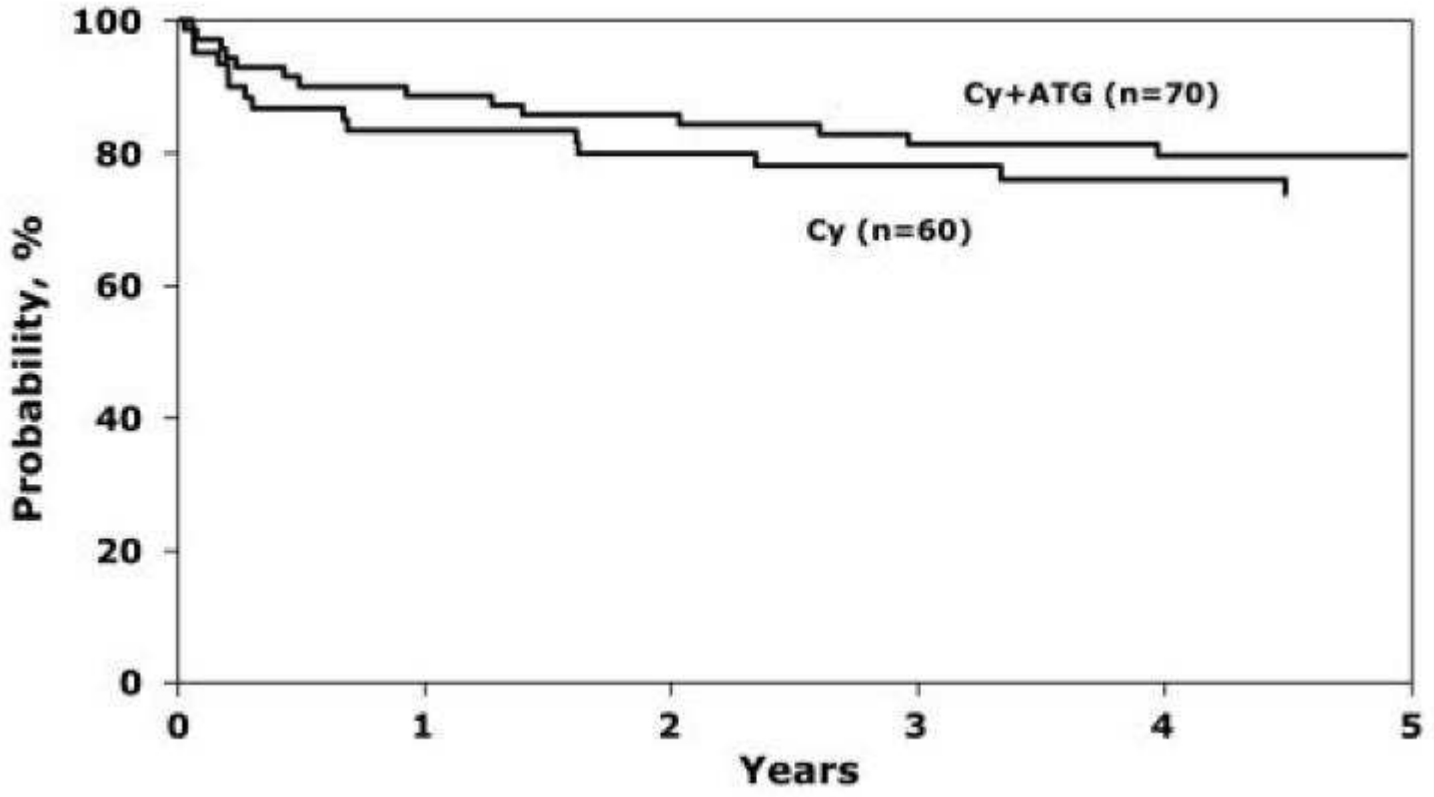
EBMT

Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens

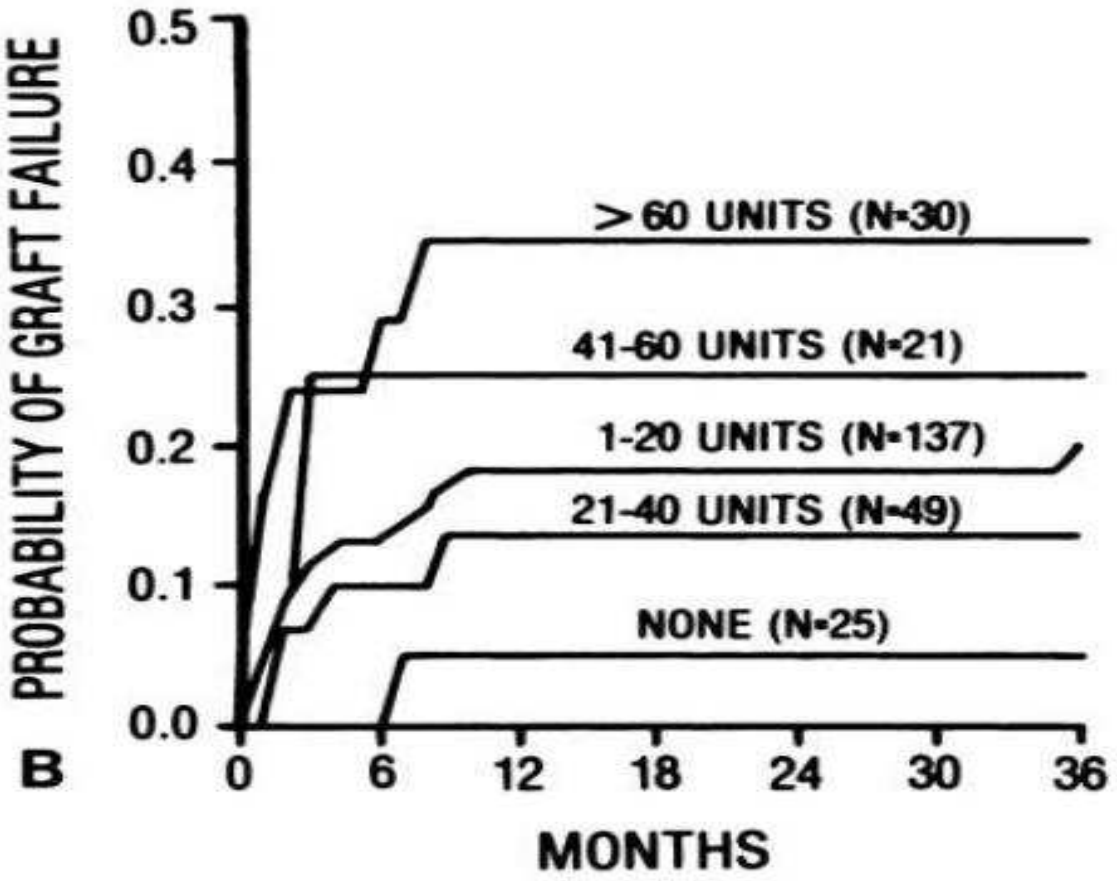
(Blood. 2007;109:4582-4585)

Richard E. Champlin,[1] Waleska S. Perez,[2] Jakob R. Passweg,[3] John P. Klein,[2] Bruce M. Camitta,[4] Eliane Gluckman,[5] Christopher N. Bredeson,[4] Mary Eapen,[2] and Mary M. Horowitz[2]

[1]M. D. Anderson Cancer Center, Houston, TX; [2]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee; [3]Hôpitaux Universitaires, Geneva, Switzerland; [4]Medical College of Wisconsin, Milwaukee; [5]Hospital St Louis, Paris, France



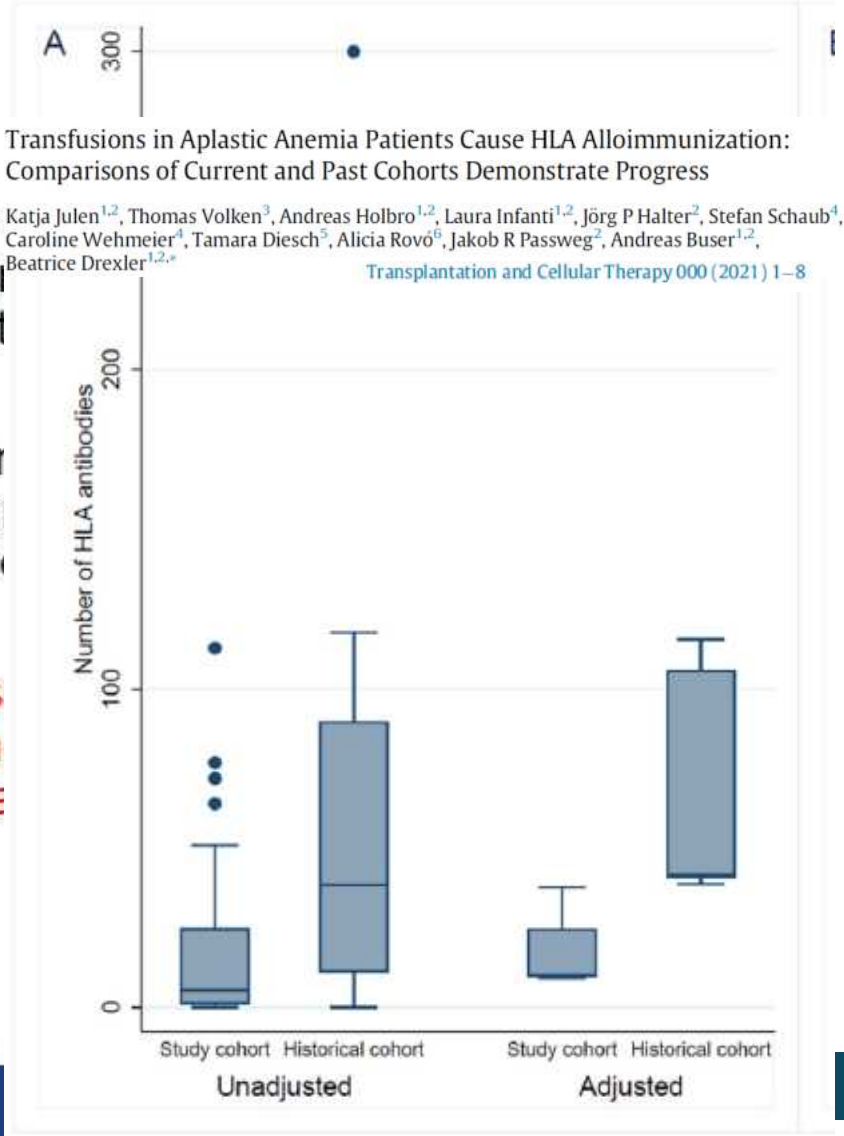
Transfusion therapy and prognosis of SCT



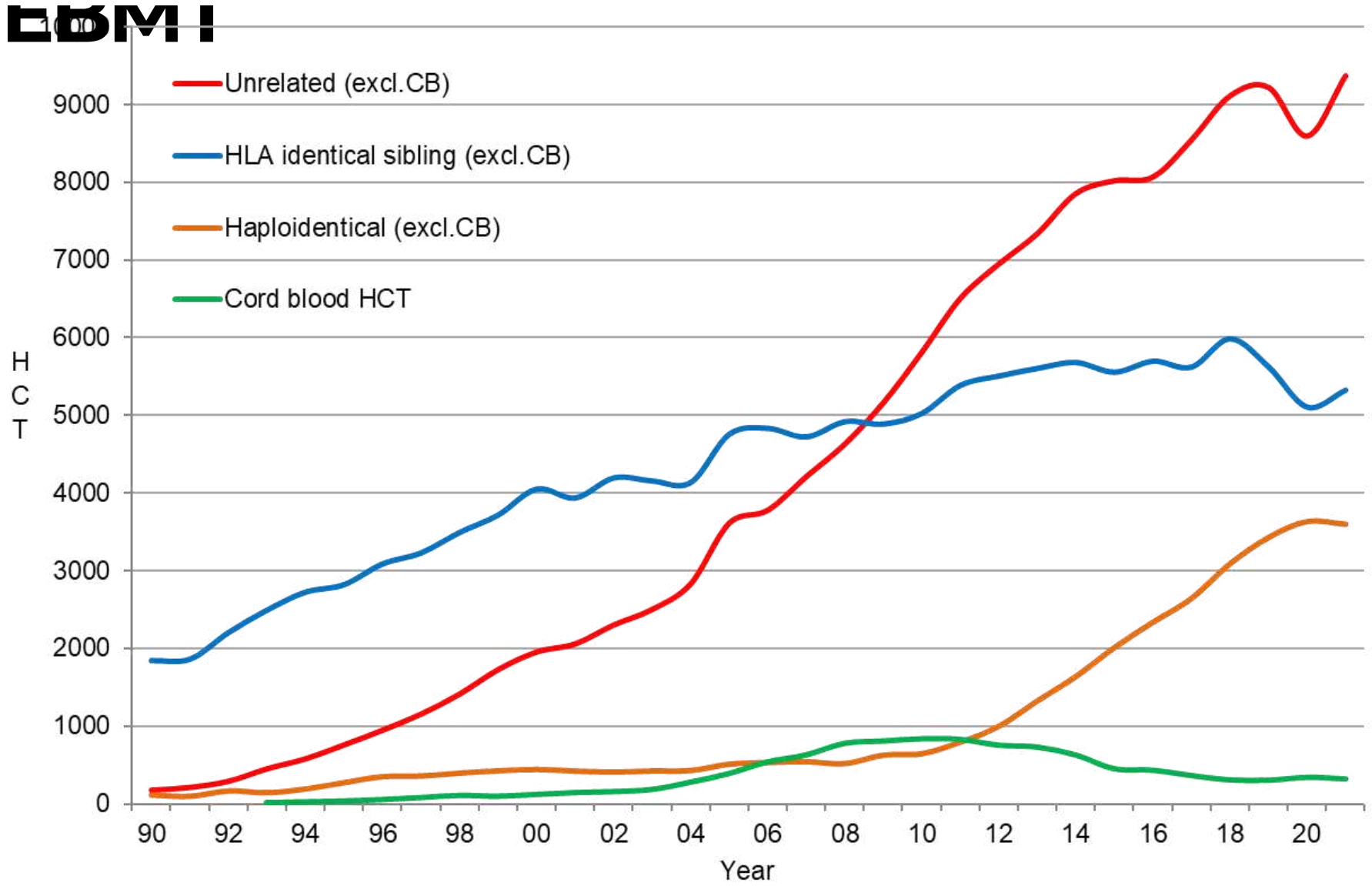
- Correlation
  Failure afte
  transplantat
- But no discr
  and PC (iro
  leucocyte d

=> neverthele
policy accordin
as necessary, a

Champlin et al Blood Vol 73, 1989:606-613



HCT activity in Europe 1990-2021:
donor origin: 1st HCT

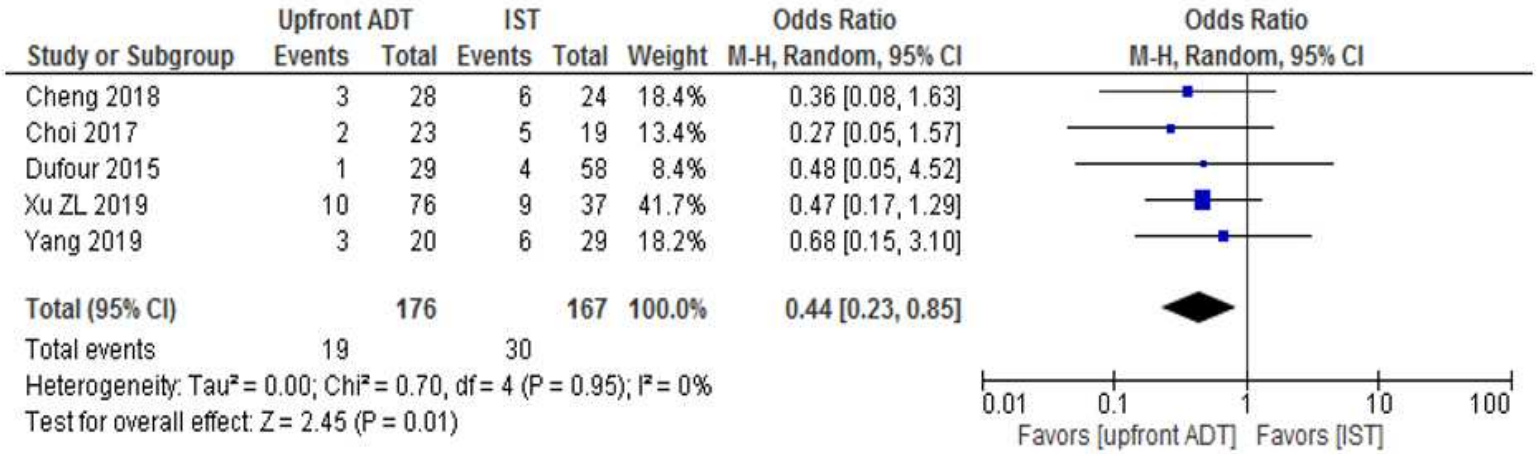


Passweg, Baldomero et al. Bone Marrow Transplant. 2023 Mar 6:1-12

"In severe aplastic anemia patients who lack fully HLA matched related donor, is upfront alternative donor transplant is a valid alternative option when compared with immunosuppressive therapy: Systematic review and meta-analysis of retrospective studies. On behalf of the Working Party of European Group for Blood and (SAAWP of EBMT)¶

Hind Alotaibi[1], Mahmoud Aljurf[2], Regis de Latour[3], M Bacigalupo[4], Riad El Fakih[2], Hubert Schrezenmeier[5], Gluckman[6], Shahid Iqbal[7], Britta Höchsmann[6], Cons Fuente[9], Nawal Alshehry[1], Simone Cesaro[10], Jakob I Antonio M. Risitano[13], John DiPersio[14], Ibraheem Mc

a¶



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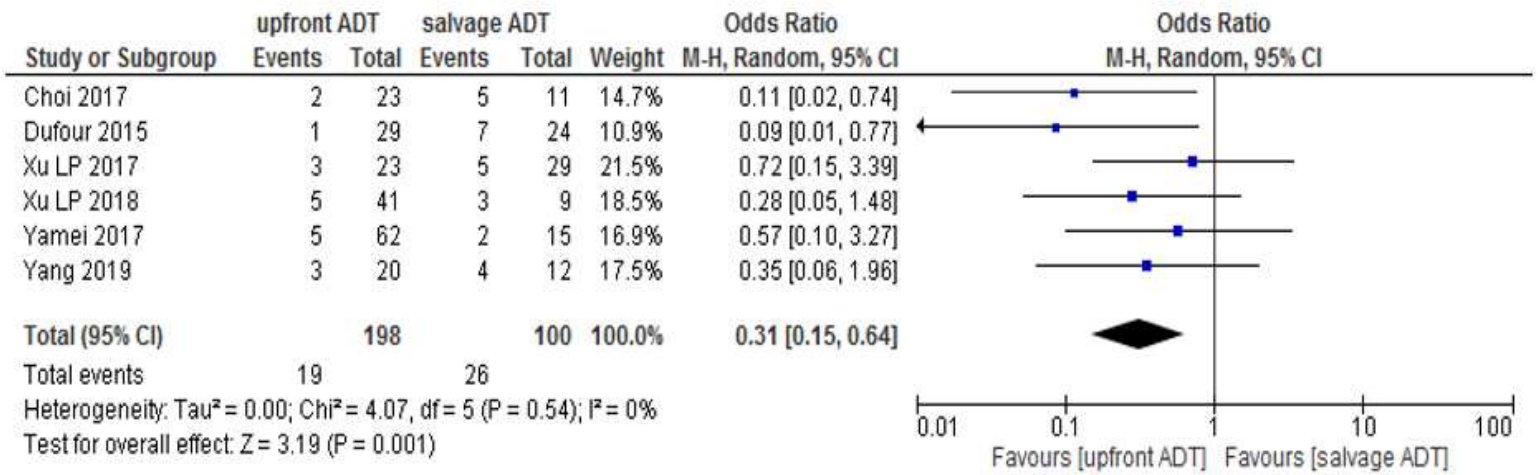
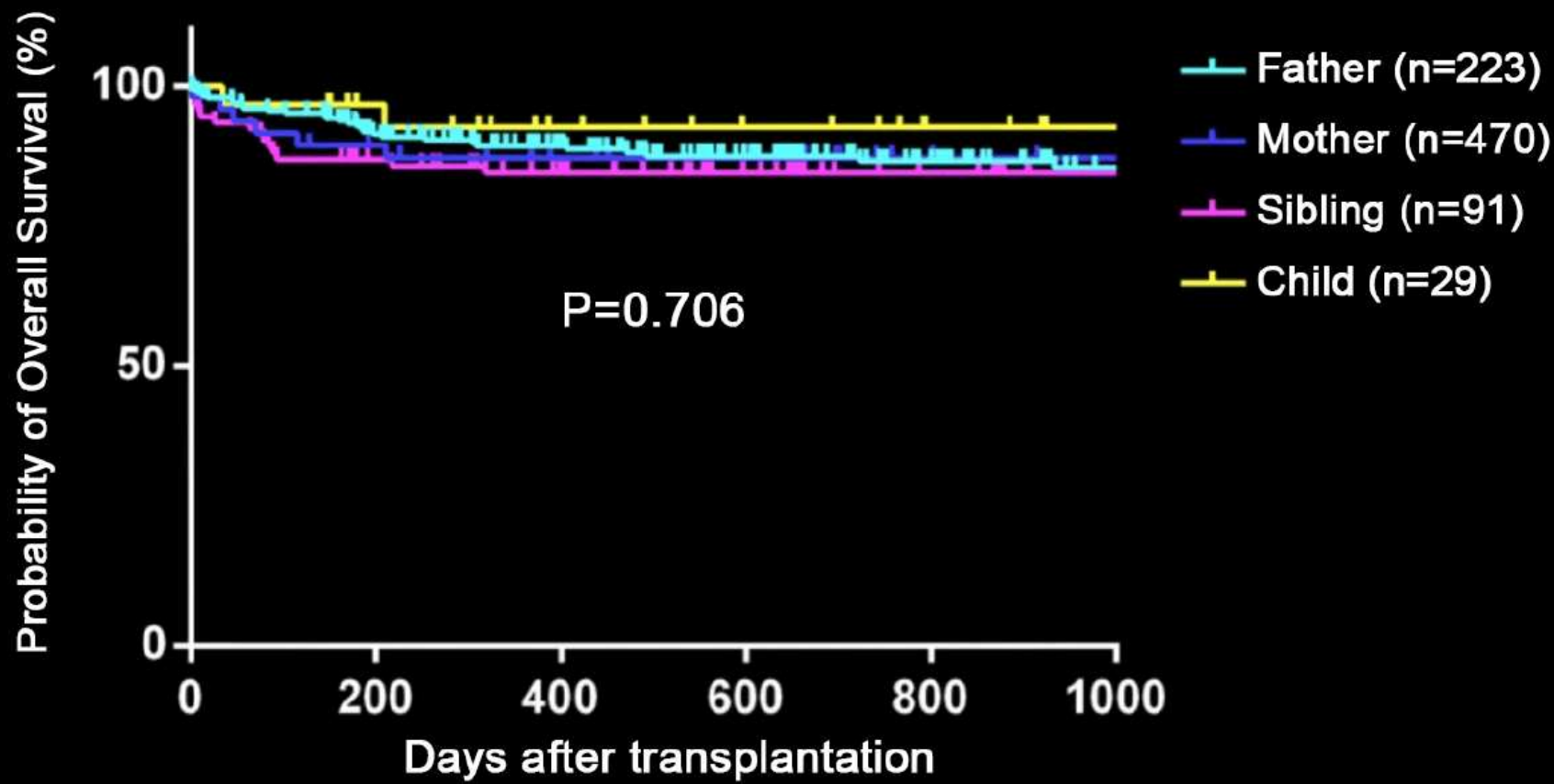


HLA-haploidentical HCT for SAA (n=813)



Xu et al. *J. Hemat. Oncol.* 12: 87, 2019

Impact of CD34 Cell Dose and Conditioning Regimen on Outcomes after Haploidentical Donor Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide for Relapsed/Refractory Severe Aplastic Anemia

Leonardo Javier Arcuri[1,*], Samir Kanaan Nabhan[2], Renato Cunha[3], Samantha Nichele[2], Andreza Alice Feitosa Ribeiro[1], Juliana Folloni Fernandes[1,4], Liane Esteves Daudt[5], Ana Luiza Melo Rodrigues[6], Celso Arrais-Rodrigues[7], Adriana Seber[8], Elias Hallack Atta[9], Jose Salvador Rodrigues de Oliveira[7], Vaneuza Araujo Moreira Funke[10], Gisele Loth[2], Luiz Guilherme Darrigo Junior[3], Alessandra Paz[5], Rodolfo Froes Calixto[11], Alessandra Araujo Gomes[12], Carlos Eduardo Sa Araujo[13], Vergilio Colturato[14], Belinda Pinto Simoes[3], Nelson Hamerschlak[1], Mary Evelyn Flowers[15], Ricardo Pasquini[2], Vanderson Rocha[4,16], Carmem Bonfim[2]

Biol Blood Marrow Transplant 26 (2020) 2311–2317

Conditioning regimen, n (%)	
Flu/Cy29/TBI200	55 (63)
Flu/Cy29/TBI300	3 (3)
Flu/Cy29/TBI400	11 (13)
Flu/Cy50/TBI200	9 (10)
Flu/Cy50/TBI400	9 (10)
r-ATG in the conditioning regimen	12 (14)
GVHD prophylaxis, n (%)	
PTCy/CSA/MMF	76 (87)
PTCy/tacrolimus/MMF	11 (13)

N= 87
Age: 14y
Marrow: 93%

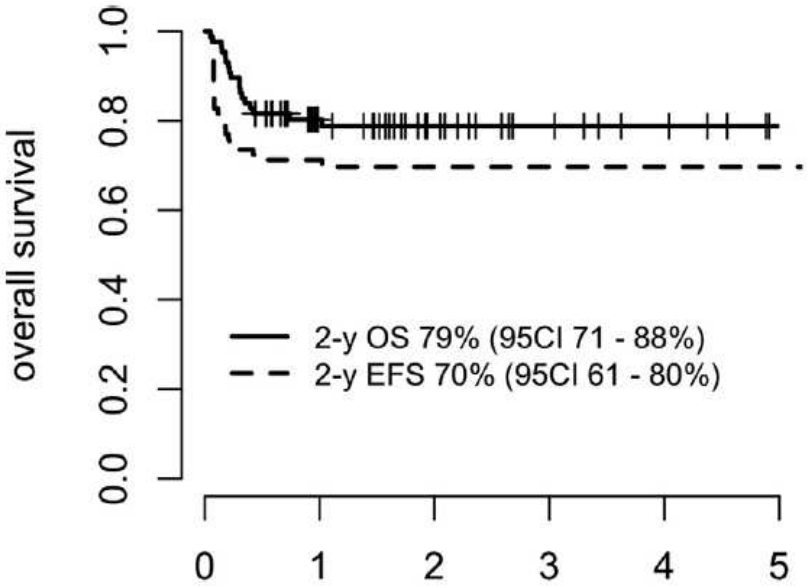
Table 2
Major Outcomes after Haploidentical HSCT for SAA (N= 87)

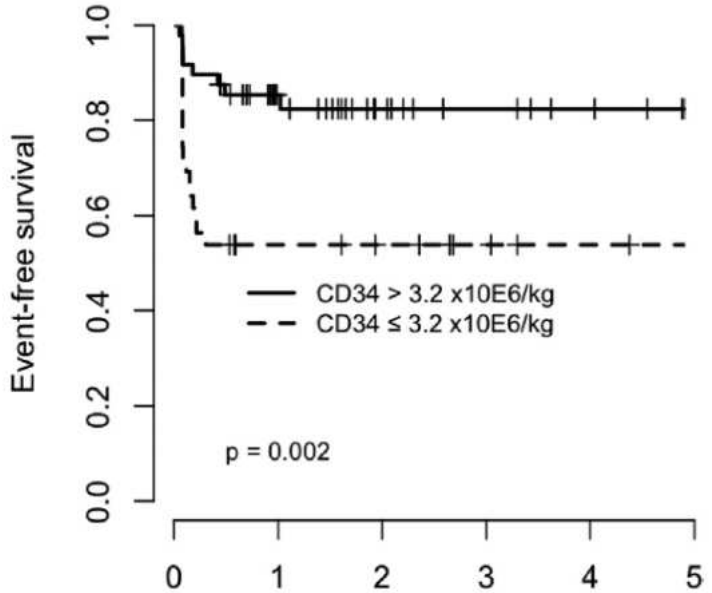
Outcome	100 Days, % (n)	1 Year, % (n)
OS	90 (9)	80 (17)
EFS	75 (22)	71 (25)
Graft failure or poor graft function	18 (16)	20 (17)
Acute GVHD grade II-IV	13 (11)	14 (12)
Acute GVHD grade III-IV	3 (3)	3 (3)
Chronic GVHD (any)	1 (1)	9 (7)
CMV reactivation	61 (53)	62 (54)

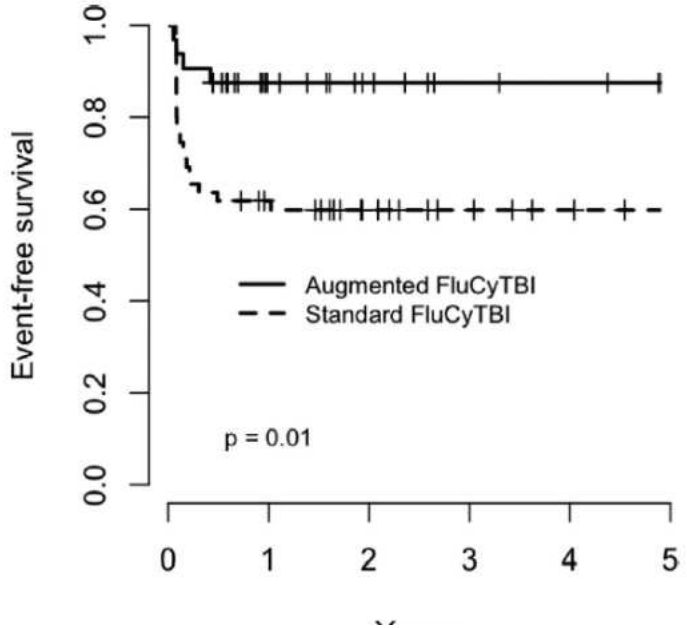
Table 4
Multivariate Analysis for Neutrophil Recovery and EFS for Patients with SAA Undergoing Haploidentical HSCT with PTCy

Variable	HR (95% CI)	*P* Value
Neutrophil recovery		
CD34 dose infused >3.2 × 10E6/kg	2.13 (1.32-3.44)	.002*
Cy 50 mg/kg and/or TBI > 200 cGy	1.72 (1.07-2.77)	.03*
EFS		
Donor-specific antibodies	3.92 (1.32-11.7)	.01*
CD34 dose infused >3.2 × 10E6/kg	.29 (.13-.68)	.004*
Cy 50 mg/kg and/or TBI >200 cGy	.28 (.09-.81)	.02*
Graft failure		
CD34 dose infused >3.2 × 10E6/kg	.27 (.09-.78)	.02*
Cy 50 mg/kg and/or TBI >200 cGy	.19 (.04-.84)	.03*
Previous ATG exposure	.28 (.11-.73)	.01*

* Statistically significant.


overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
2-y OS 79% (95CI 71 - 88%)
2-y EFS 70% (95CI 61 - 80%)


Event-free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
CD34 > 3.2 x10E6/kg
CD34 ≤ 3.2 x10E6/kg
p = 0.002


Event-free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Augmented FluCyTBI
Standard FluCyTBI
p = 0.01

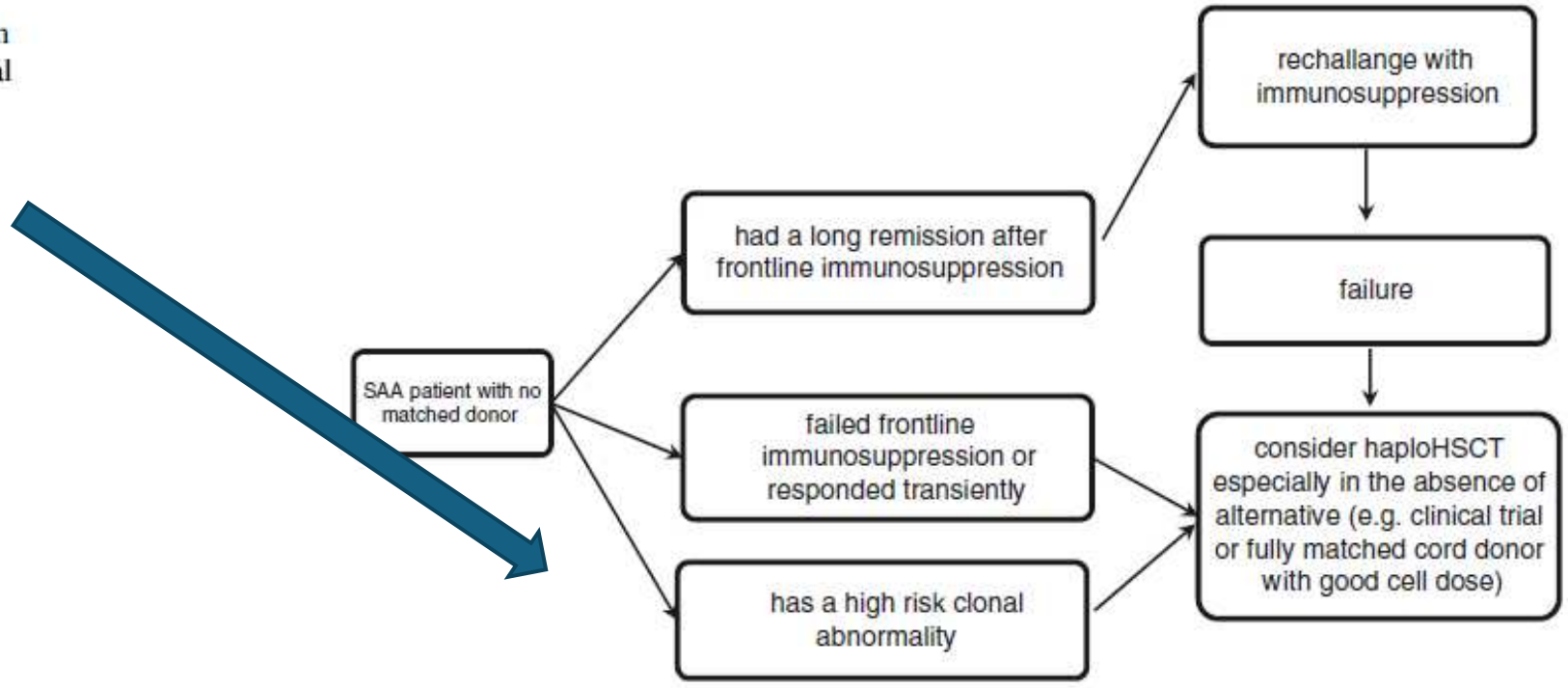
Bone Marrow Transplantation (2020) 55:1906–1917
https://doi.org/10.1038/s41409-020-0897-2

REVIEW ARTICLE

Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT)

Ghada ElGohary[1,2] · Riad El Fakih[3] · Regis de Latour[4] · Antonio Risitano[5] · Judith Marsh[6] · Hubert Schrezenmeier[7] · Eliane Gluckman[8,9] · Britta Höchsmann[7] · Filomena Pierri[10] · Constantijn Halkes[11] · Hazzaa Alzahrani[3] · Josu De la Fuente[12] · Simone Cesaro[13] · Ali Alahmari[3] · Syed Osman Ahmed[3] · Jakob Passweg[14] · Carlo Dufour[10] · Andrea Bacigalupo[15] · Mahmoud Aljurf[3]

Fig. 6 Author's opinion regarding haploidentical transplant for SAA.



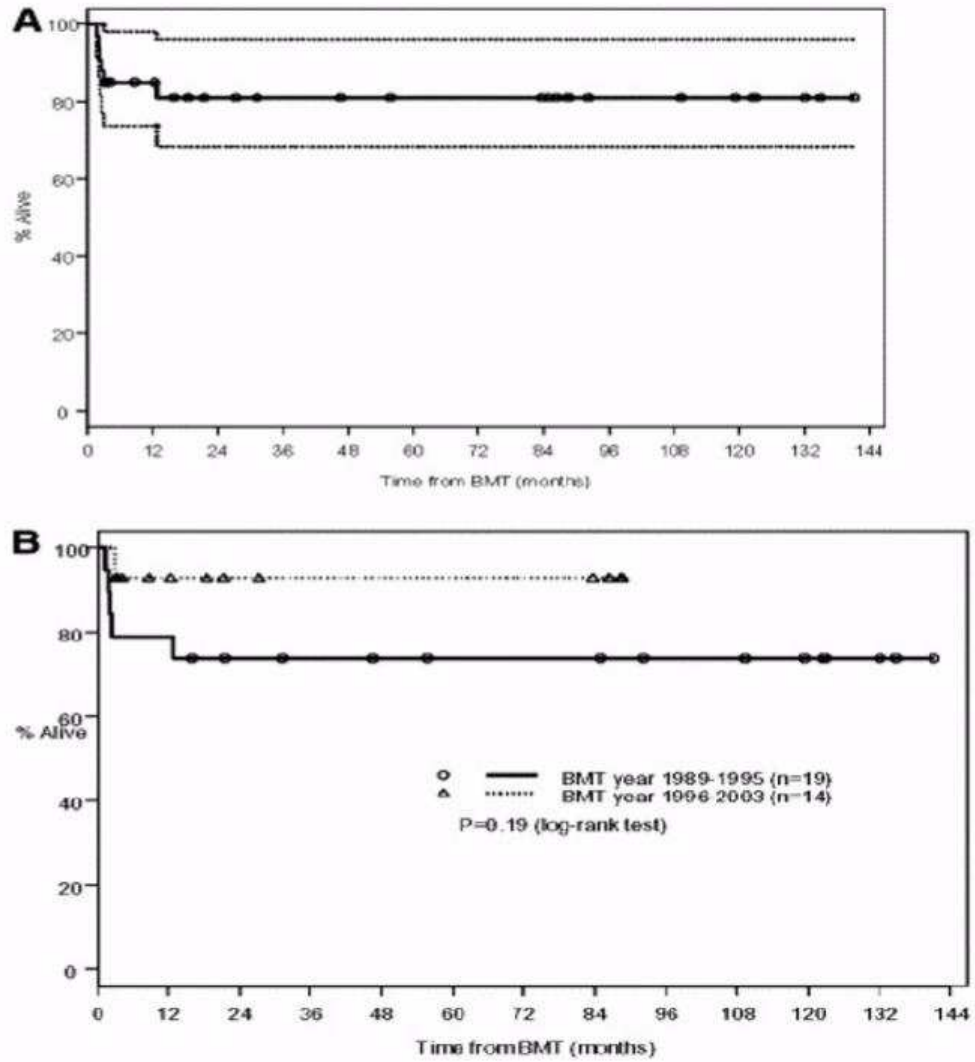
N	577
Studies	15
Engraft	97%
aGvHD	26%
cGvHD	25%
TRM	7%
pTCy	lowest rate of aGvHD

33 patients treated between 1989-2003 with acquired AA
BMT from HLA identical sibs Cyclo/Campath
Median age 17 years (range, 4–46 years)
Median follow-up 59 months
42% had previously experienced treatment failure with antithymocyte globulin-based immunosuppressive therapy

Cumulative incidence of graft failure and grade II to IV acute and chronic GVHD was 24%, 14%, and 4%, respectively.
No extensive chronic GVHD.

5-year survival was 81% (95% confidence interval, 68%-96%).
No unexpected early or late infectious or noninfectious complications were observed.

Favourable affect on GVHD should be further evaluated



FCC conditioning

Fludarabine 30mg/m^2 x 4

CY 300mg/m^2 x 4

Alemtuzumab 0.2mg/kg x 5

Ciclosporin alone; no methotrexate

Irradiation-free regimen

50 patients from 5 UK centres

Median follow-up 18.2 months (range: 2.3-118.2)

Median age 38 (8-62)

MSD = 21

MUD = 29

9/10 HLA match = 2

Stem cell source: BM in 24 (49%), G-CSF–primed BM in 7 (14%), PBSC in 14 (27%), and BM + PBSC in 5 (10%) of patients

Engraftment: neutrophil recovery was 17 days (range: 2-50) and platelet recovery was 19 days (range: 10-57

Acute GVHD

Chronic GVHD

16.5% CI at 1yr

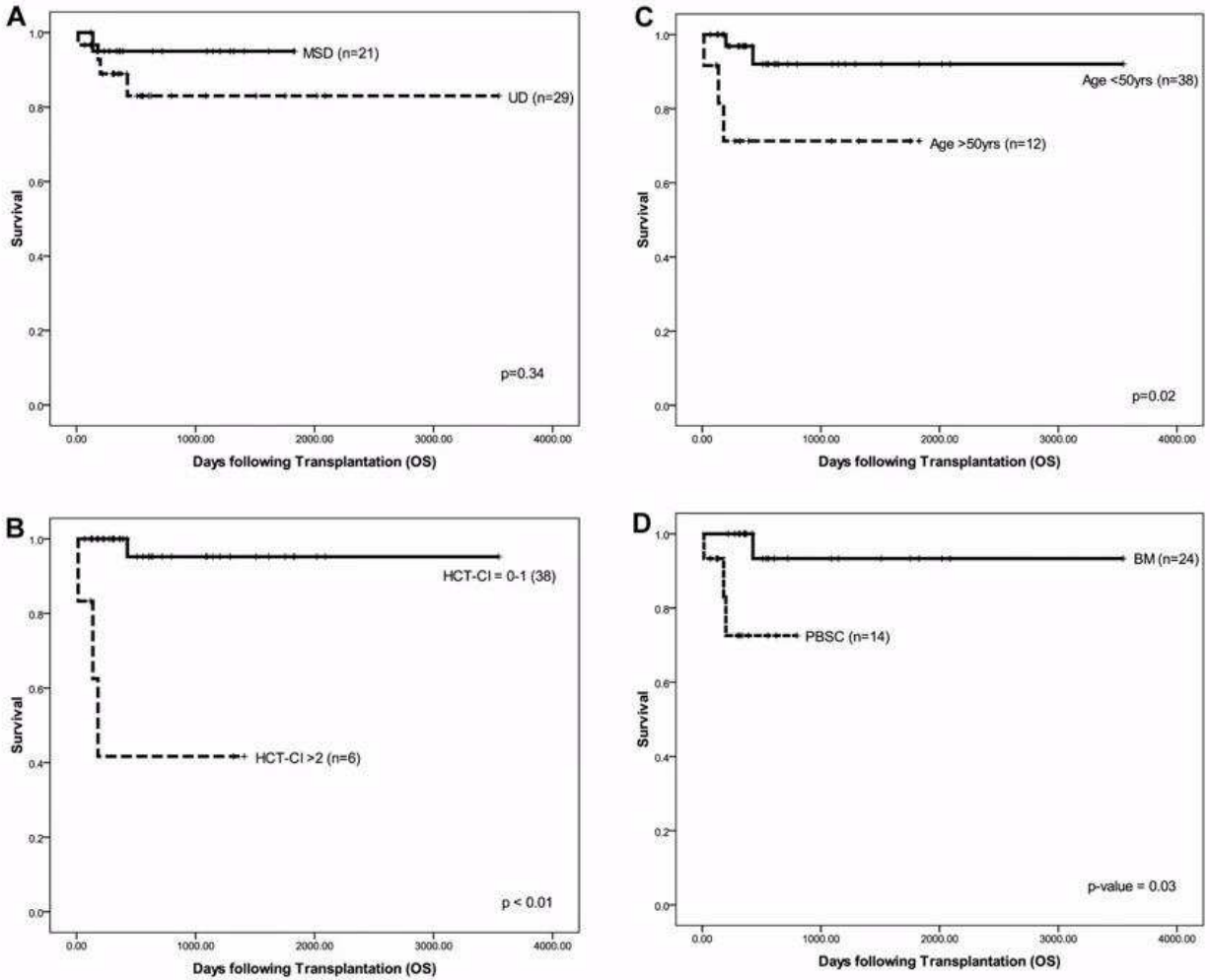
7% CI at 1yr

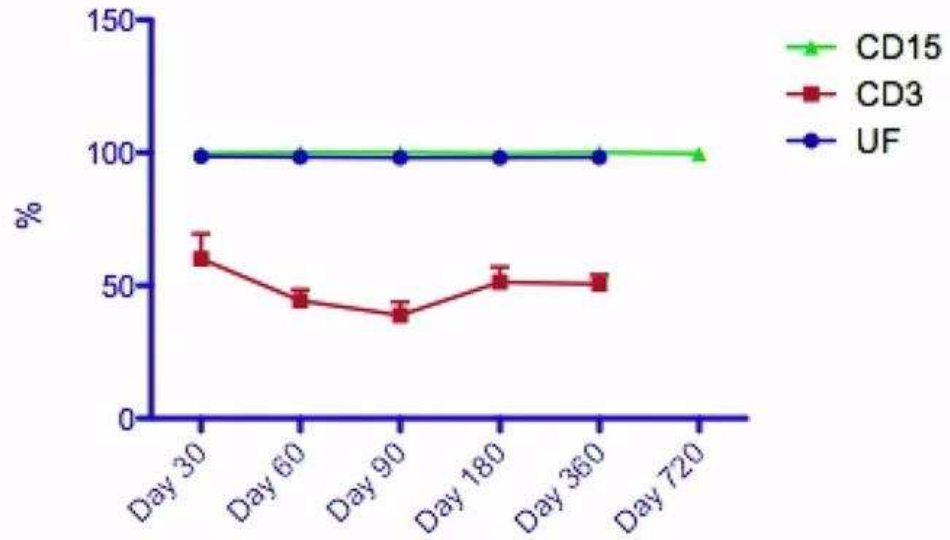
Graft failure

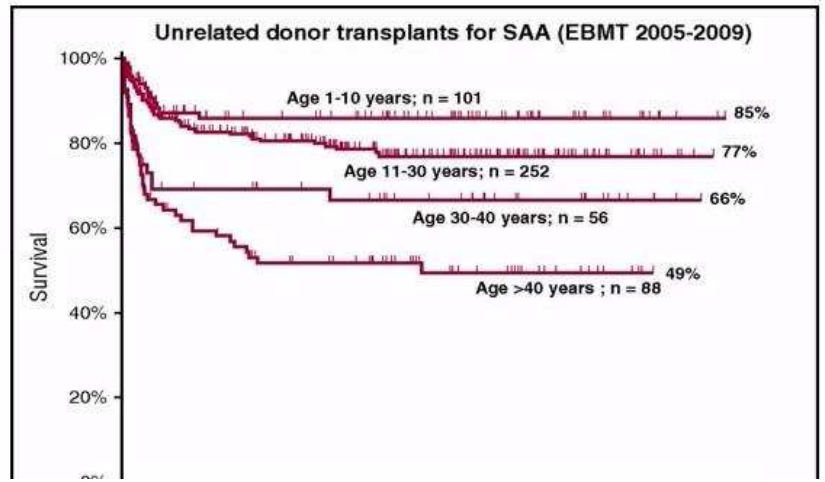
6 (12%), 3 primary, 3 secondary

9.5% MSD, 14.5% UD

Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia







FCC conditioning regimen for SAA HCT in adults

'FCC'

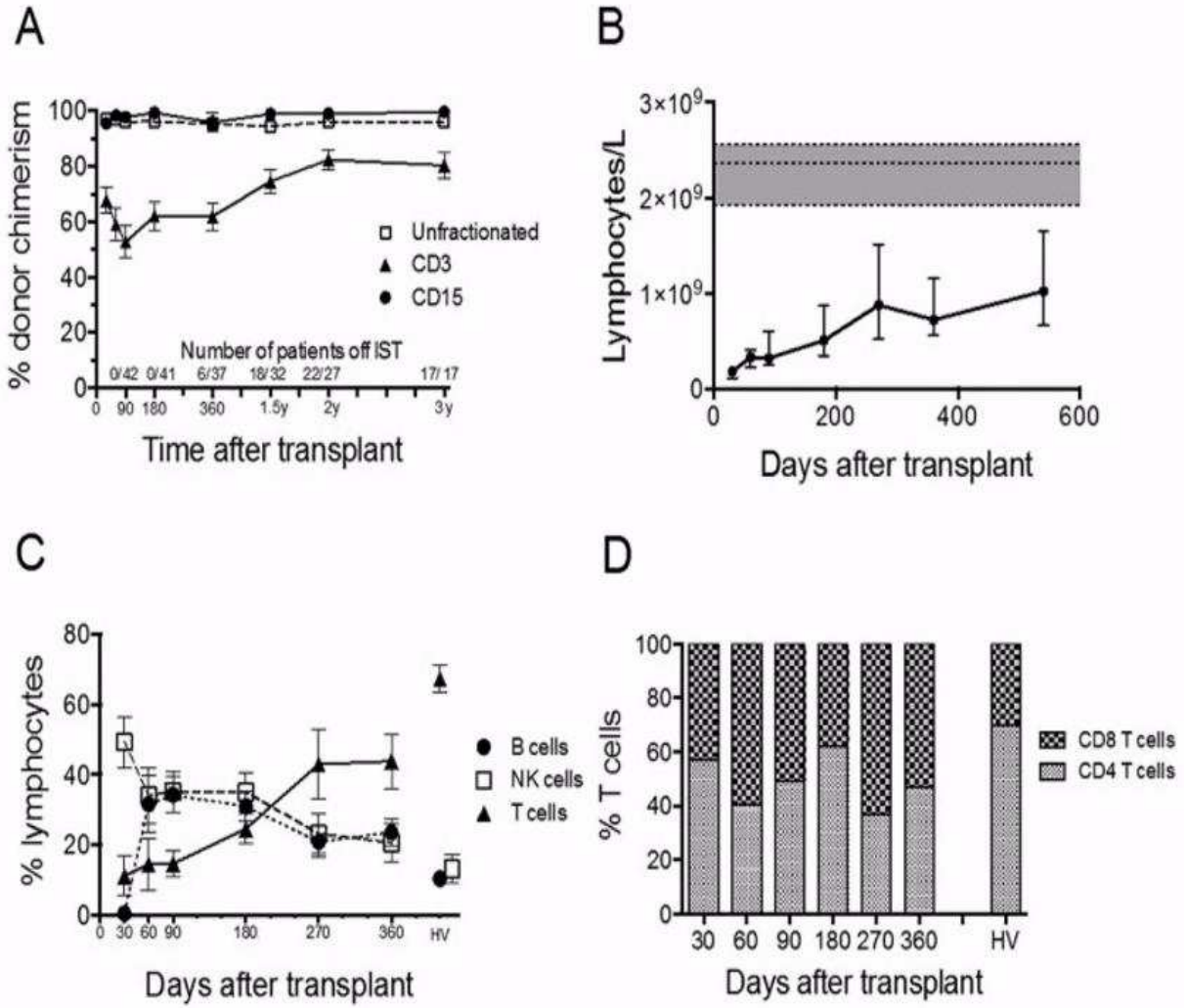
Fludarabine 30mg/m^2 x 4
CY 300mg/m^2 x 4
Alemtuzumab ('Campath') 0.2mg/kg x 5
Ciclosporin alone; no MTX
Irradiation-free regimen

Practical pointers FCC

Use PBSC
2Gy TBI for MMUD
CsA levels 250-350
Wean from 9 months
Use MMF to supplement CsA if therapeutic levels not maintained due to renal impairment

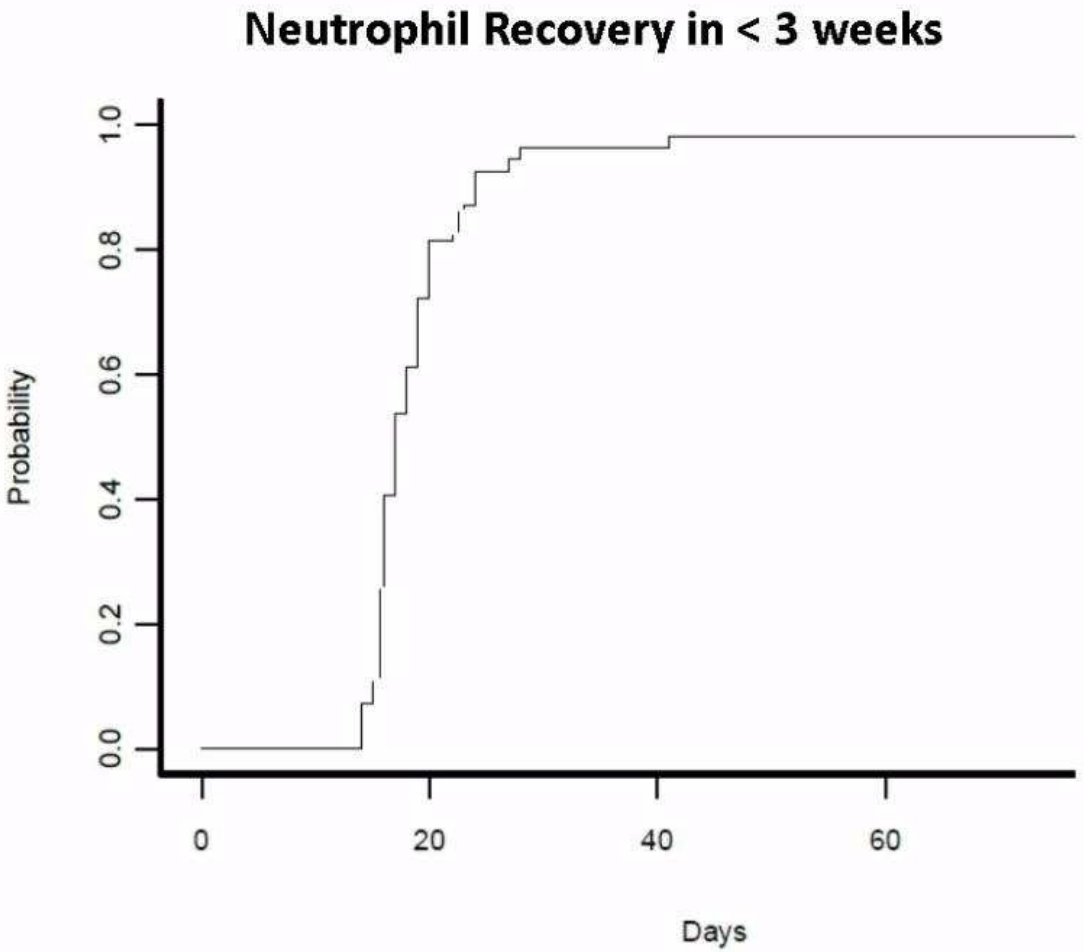
	N	Age (med,range)	Sib/UD	Graft failure	Acute GVHD	Chronic GVHD	OS
Marsh, 2011	50	35 (8-62)	42%/58%	9.5%/14.5%	13.5%	4%	95%/83% @ 2y
BSBMT, 2014	100	20 (1.5-67.5) 62% >18yr	56%/39%	9%	24% (89% Gd I-II)	11%	88% @ 5y
Hamad, 2014	41	37 (17-59) <40y:25(56%) >40y: 16 (44%)	71%/29%	10%	27% (all Gd I-II)	15%	85% @ 3y
Grimaldi, 2017	45	32 (15-63) >50y: 14 (31%)	27%/73%	2.2%	13%	13%	93% @ 5y

Mixed T Cell Chimerism After Allogeneic Hematopoietic Stem Cell Transplantation for Severe Aplastic Anemia Using an Alemtuzumab-Containing Regimen Is Shaped by Persistence of Recipient CD8 T Cells



- Lymphocyte recovery is prolonged at 1yr and beyond
- NK cells were the predominant lymphocyte population present early post-HSCT, representing 49.3% of lymphocytes at D30
- B cells not detected at D30 but rapidly recovered, representing 31.7% of lymphocytes at day 60 and remain above normal at day 360 (23.7%, compared with 10.5% for healthy volunteers; p = .002%)

- T cells were profoundly deficient; only 11.3% of lymphocytes at D30, and increasing to 43.8% at 1 year, but still significantly below normal (67.2%; P = .018)
- Rapid recovery of B cells with prolonged T cell deficiency produced abnormal dominance of B cells over T cells.



DAYS	Relapsed/ Refractory	Treatment-Naïve	Overall Median	
Neutrophil engraftment (ANC>1k x 3d)	18 (14-39)	20 (14-88)	17	90% by D30
Red cell Engraftment (Txfn Ind)	27 (6-58)	25 (14-**)	24	88% by D100
Platelet Engraftment	30	26	26	90% by D100

Acute GVHD

G2-4 at 5% at 100 days

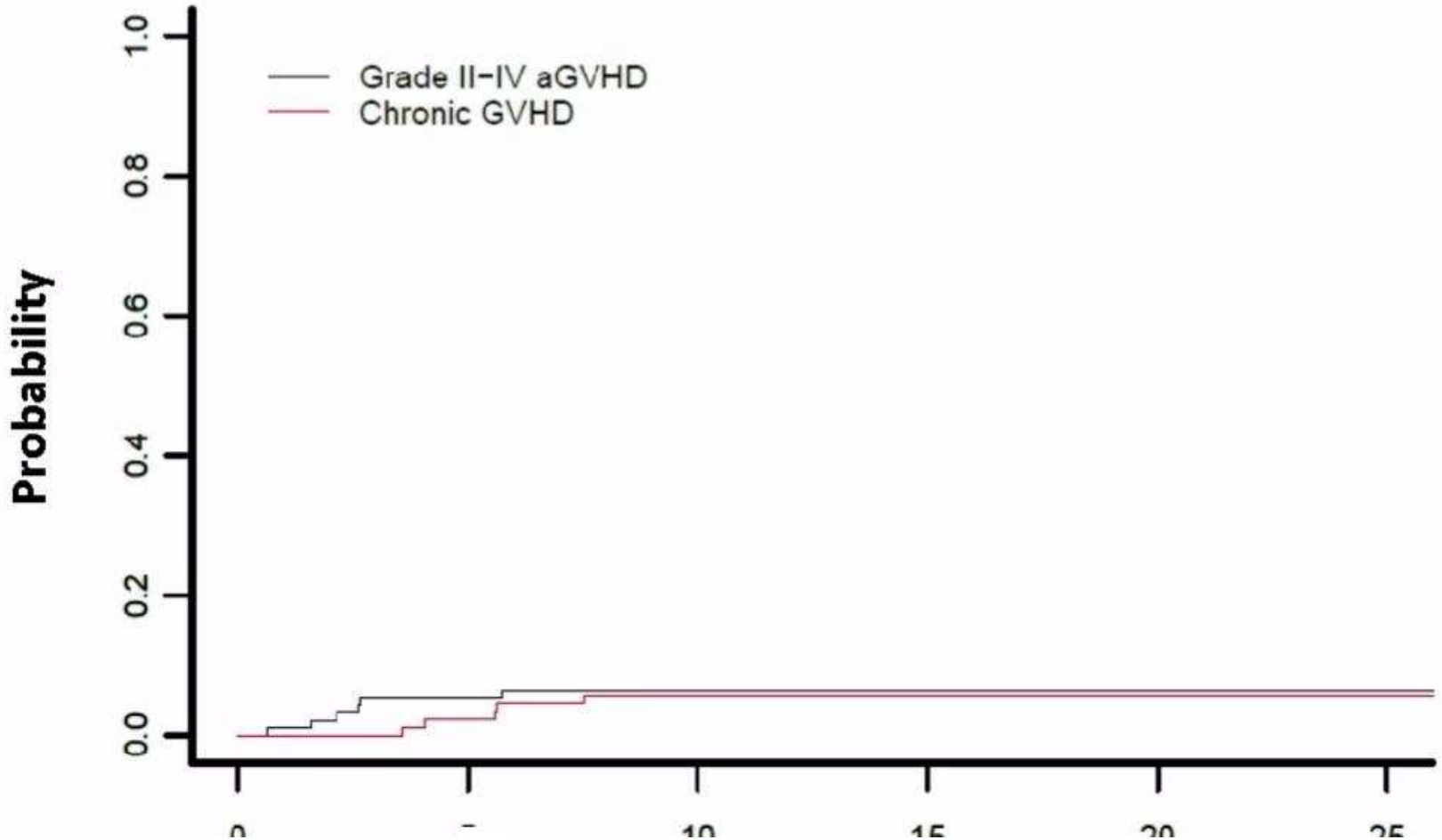
95% CI: 0.01-0.1

Chronic GVHD

6% at 24 months

95% CI: 0.01-0.1

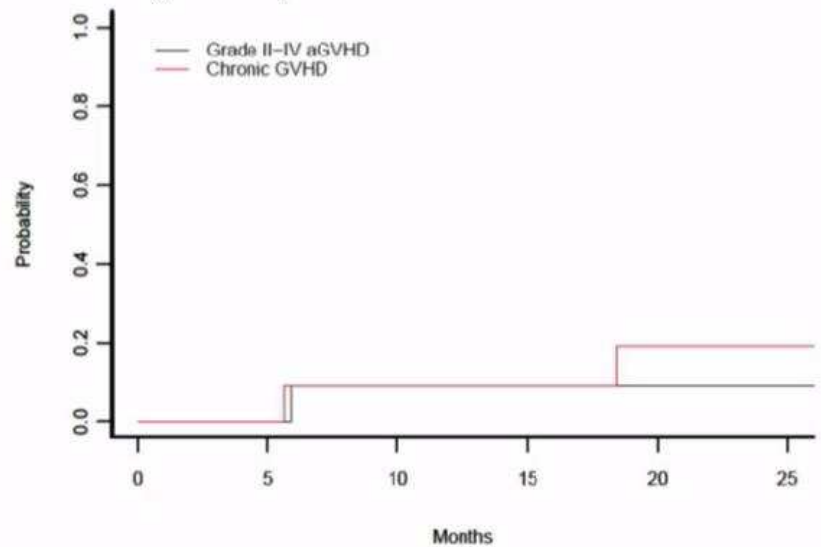
Cumulative incidences



We use same regimen in all donors with same outcomes

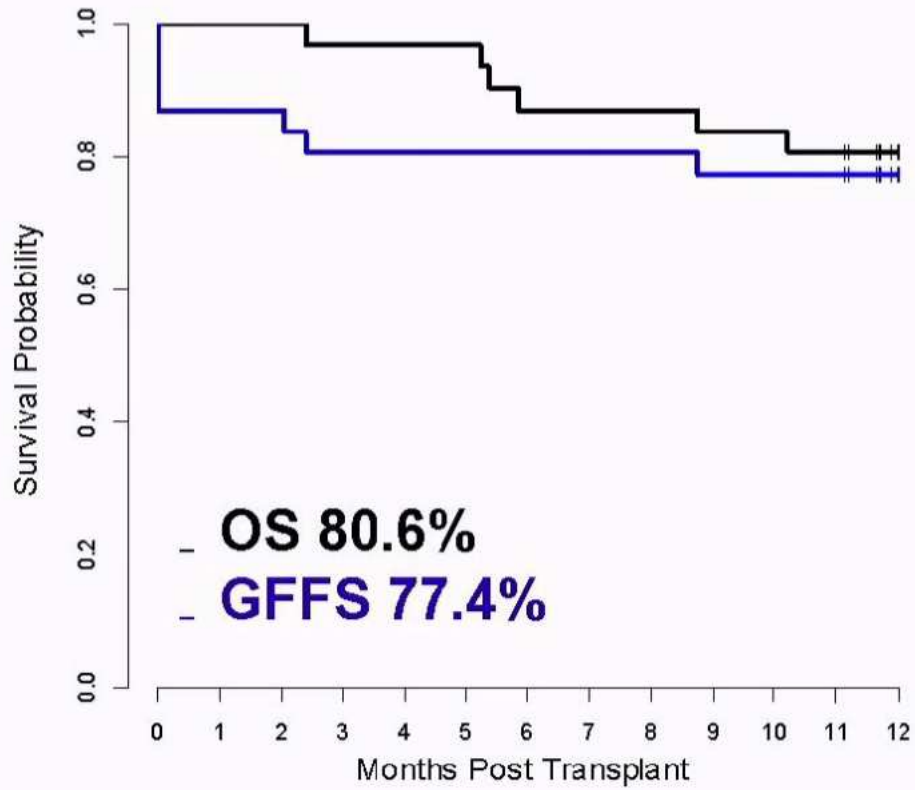
Patient recipients from 11 Fully matched donors	
Gender	
Female	5 (45%)
Age, yrs	
Mean (SD)	32 (12)
Treatment-naïve	5 (45%)
Refractory	6 (55%)
Clonality at baseline)	11 (100%)
Total Body Irradiation Dose	
200cGY	4 (36%)
400 cGy	7 (64%)
Donor Relationship	
Sibling	4 (36%)
Unrelated 10/10	4 (36%)
Unrelated 9/10	3 (27%)
Reason for use of non-haplo related donor	
Donor specific antibodies to related donors	0
No available related donors (ie: adopted, parent with illness, childlessness)	7 (64%)
Patient above age 25 years with available matched	4 (36%)

- Median follow-up 53.8 (range, 6-99) mos
- no primary graft failure
- OS 100% at 2 y
  - 90% (95% CI: 73, 100%) 3 y.
  - One patient died from complications of gastric adenocarcinoma diagnosed 2 years post BMT.



Haploidentical bone marrow transplantation in patients with relapsed or refractory severe aplastic anaemia in the USA (BMT CTN 1502): a multicentre, single-arm, phase 2 trial

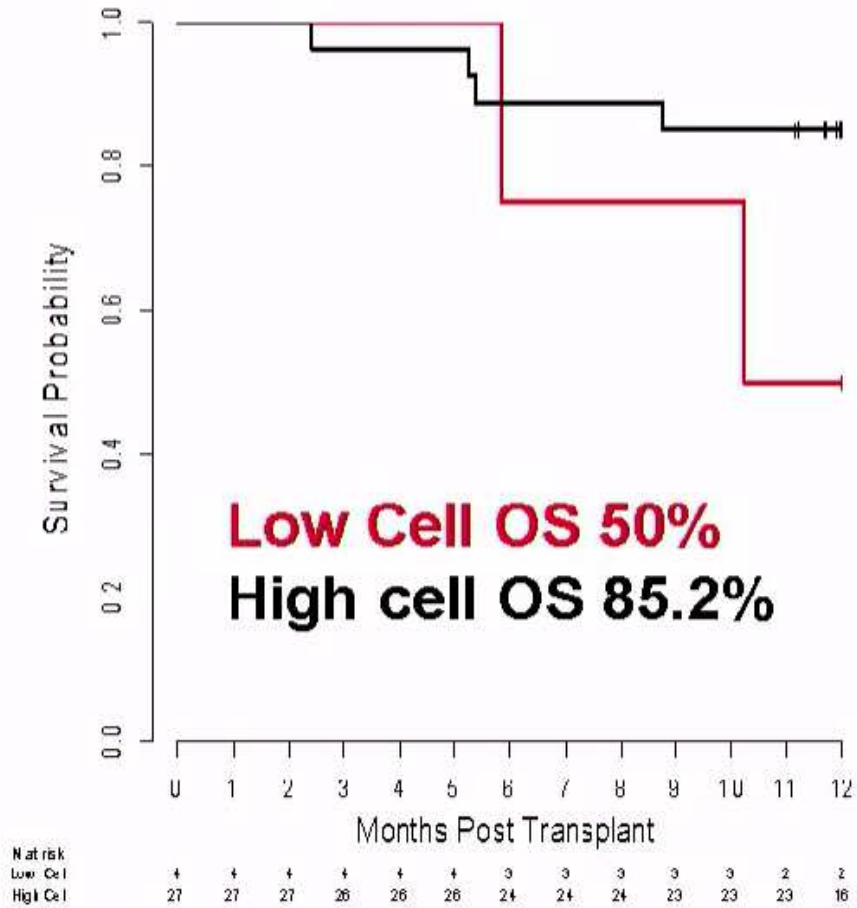
Overall Survival and Graft-Failure-Free Survival Favorable for Relapsed Population



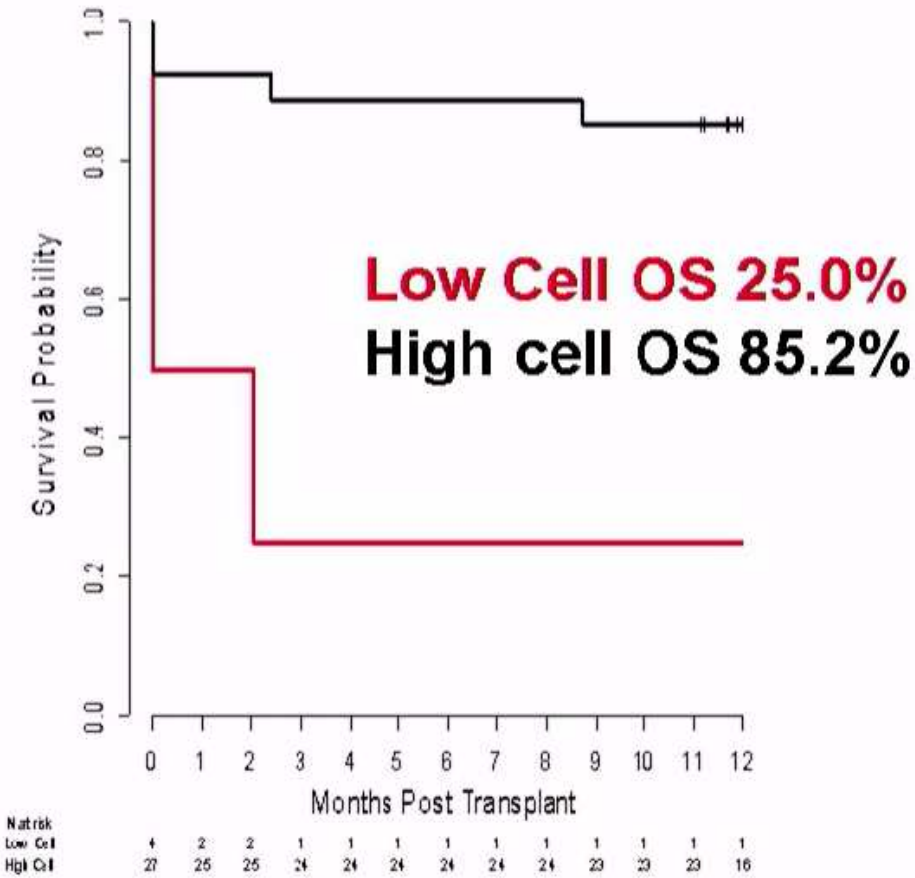
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

OS& GF FS less when cell count below the minimum of 2.5

Overall Survival



Graft Failure Free Survival



Donor Selection: Haploidentical HCT

Post-transplant Cy

- Absence of anti-donor specific HLA antibodies
  - MFI ≤1000
- Multiple donors:
  - ABO match; CMV match
  - Younger donor
  - Avoid female donors for males
- BM target TNC: 4 x 10^8/kg

TCRαβ/CD19 cell-depletion

- 1st degree relative (parent)
  - Preference for maternal donor
- CMV, Adeno seropositive
- Share 1 haplotype with alloreactivity
  - KIR/KIR ligand model
  - Presence of KIR haplotype B in donor
  - Higher B content score
  - Size of NK alloreactive subset
- Target CD34: >12 x 10^6 /kg

HLA-matching: Adult Unrelated Donor

N=663 D-R pairs; median age 10 years

	RR	Probability	P-value
Mortality			
1 MM vs. 8/8	1.29	57 vs. 65%	0.08
2 MM vs. 8/8	**1.82**	46 vs. 65%	0.0004
Graft failure			
1 MM vs. 8/8	**2.81**	28 vs. 11%	<0.0001
2 MM vs. 8/8	**2.22**	24 vs. 11%	0.006

- Higher graft failure:≥1 MM
- Lower survival: 2-loci MM
- Select HLA matched donor
  - HLA-A, B, C, DRB1
- Avoid 2-loci MM
- 1-locus MM acceptable for some diseases
- HLA DQ and DB

Horan J et al. Blood 2012

SAA

Alternative Donor HCT

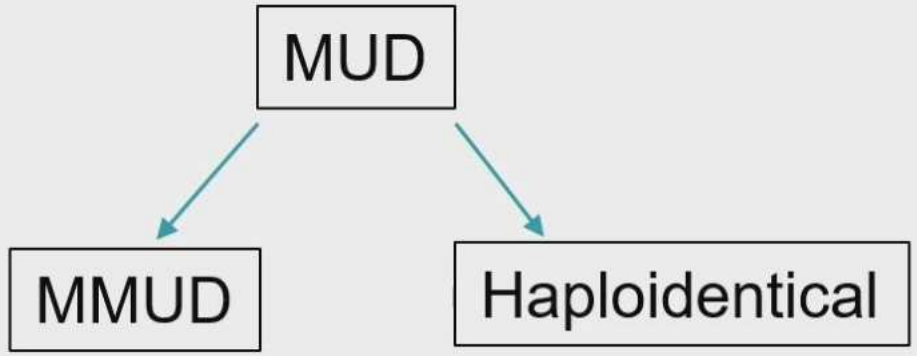
Transplant period 2012-2021

	MUD 1106	MMUD 340	Haplo 206
GF	3%	7%	**13%**
3-yr OS	**81%**	**74%**	**63%**
3-yr GRFS	73%	65%	54%

- Higher survival after MUD HCT
- Higher primary graft failure
  - MMUD, Haplo HCT

- Median age 20 years
- ~40% PB graft: all donor types
- Haplo-HCT, PTCy: ~40% no serotherapy
- Alemtuzumab: ~30%, MUD/MMUD

Donor selection algorithm



BMTCTN 0301: Beyond 1st year

Cy 50 mg/kg

- 37 of 38 patients were alive
- Median follow up 7 years
- 1 GF; 5 deaths >1 year

Cy 100 mg/kg

- 31 of 41 patients were alive
- Median follow up 8.7 years
- No GF; 1 death >1 year

	Cy 50mg/kg	Cy 100mg/kg
Chronic GVHD	42%	40%
Graft failure	15%	14%
Overall survival	**85%**	**77%**

~20% patients alive: organ dysfunction

- 12 of 15 patients aged ≥50 years died

Haplo-identical HCT: BMTCTN 1502

	1-year
Graft failure	**16%**
Grade II-IV acute GVHD	16%
Chronic GVHD	**26%**
Graft failure free survival	77%
Overall survival	**81%**

Donor

- 1st degree relative, DSA negative

Graft

- BM, TNC 4 x 10^8/kg
  - Minimum TNC 2.5 x 10^8/kg

5 graft failure

- TNC <2 x 10^8/kg (n=4)

6 deaths

- 4 associated with graft failure

HCT Outcomes: Fanconi Anaemia

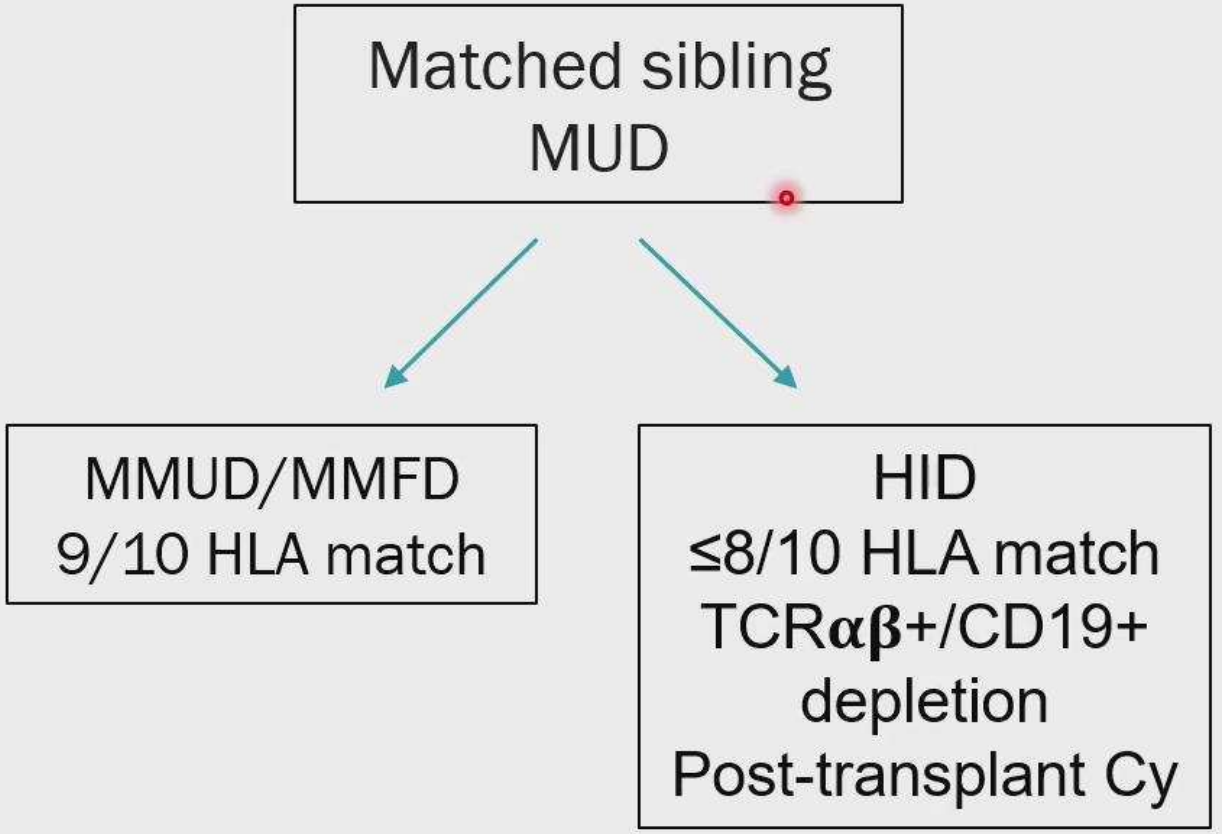
N=813 pediatric patients; 2010-2018

	Survival	EFS	AGVHD
MSD	**88%**	**85%**	17%
MUD	**86%**	**80%**	29%
MMUD	**72%**	**62%**	36%
HID	**70%**	**62%**	19%

Higher mortality

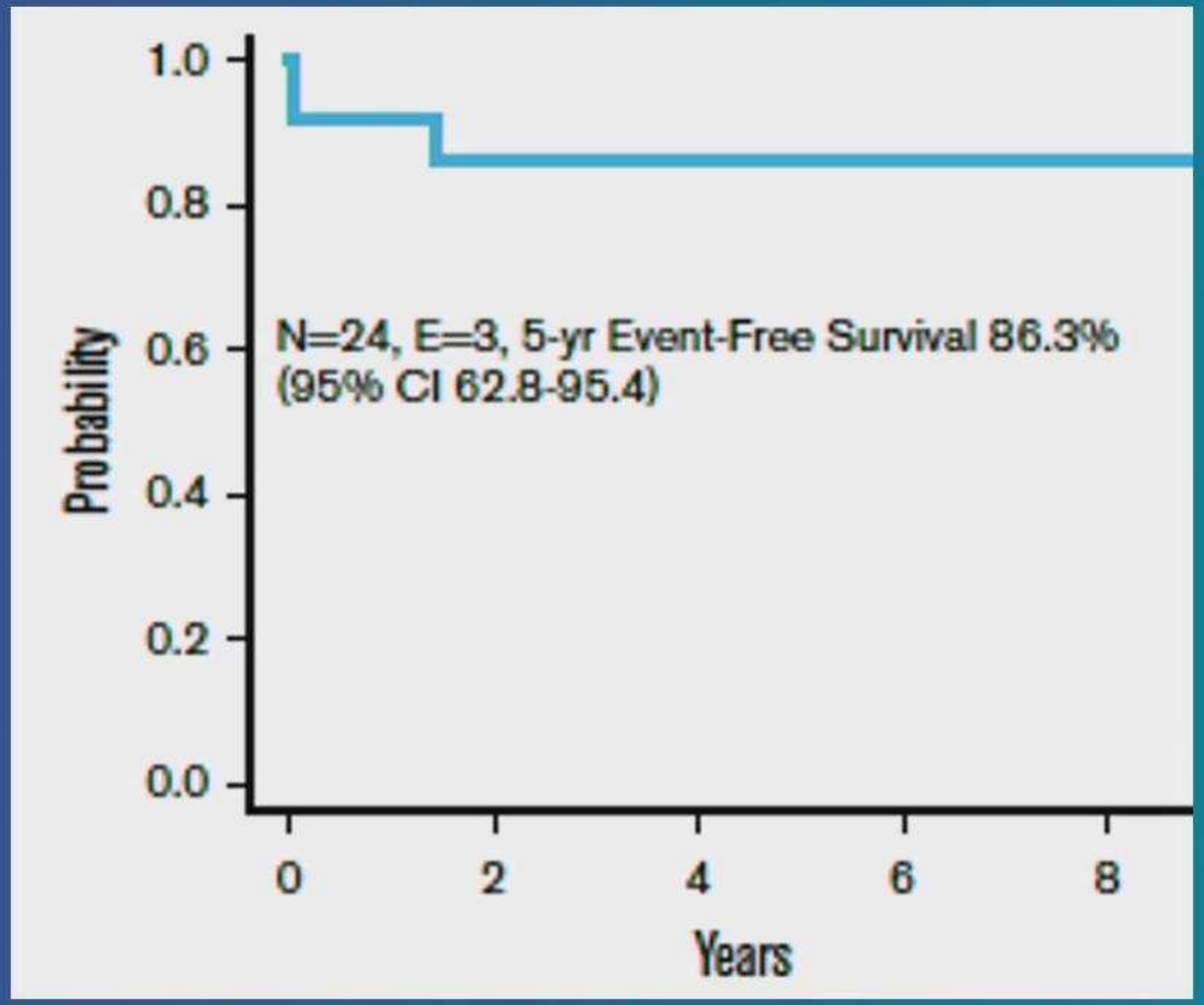
- AML/MDS vs. AA/BMF: HR 4.47; p<0001
- ATG vs. alemtuzumab: HR 3.03; p=0.01
- Flu/Cy/other vs. Flu/Cy: HR 1.81; p=0.05

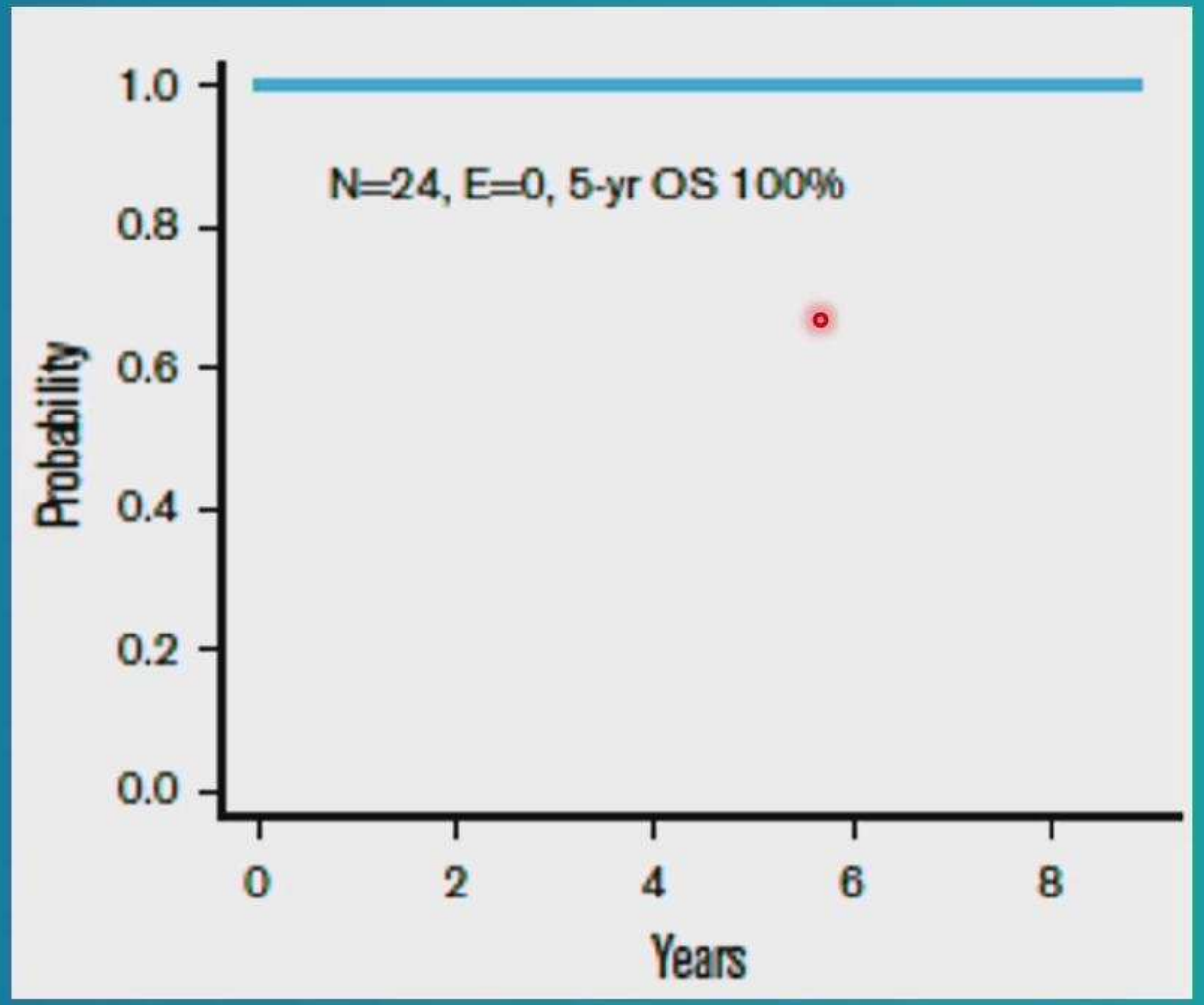
Donor selection algorithm



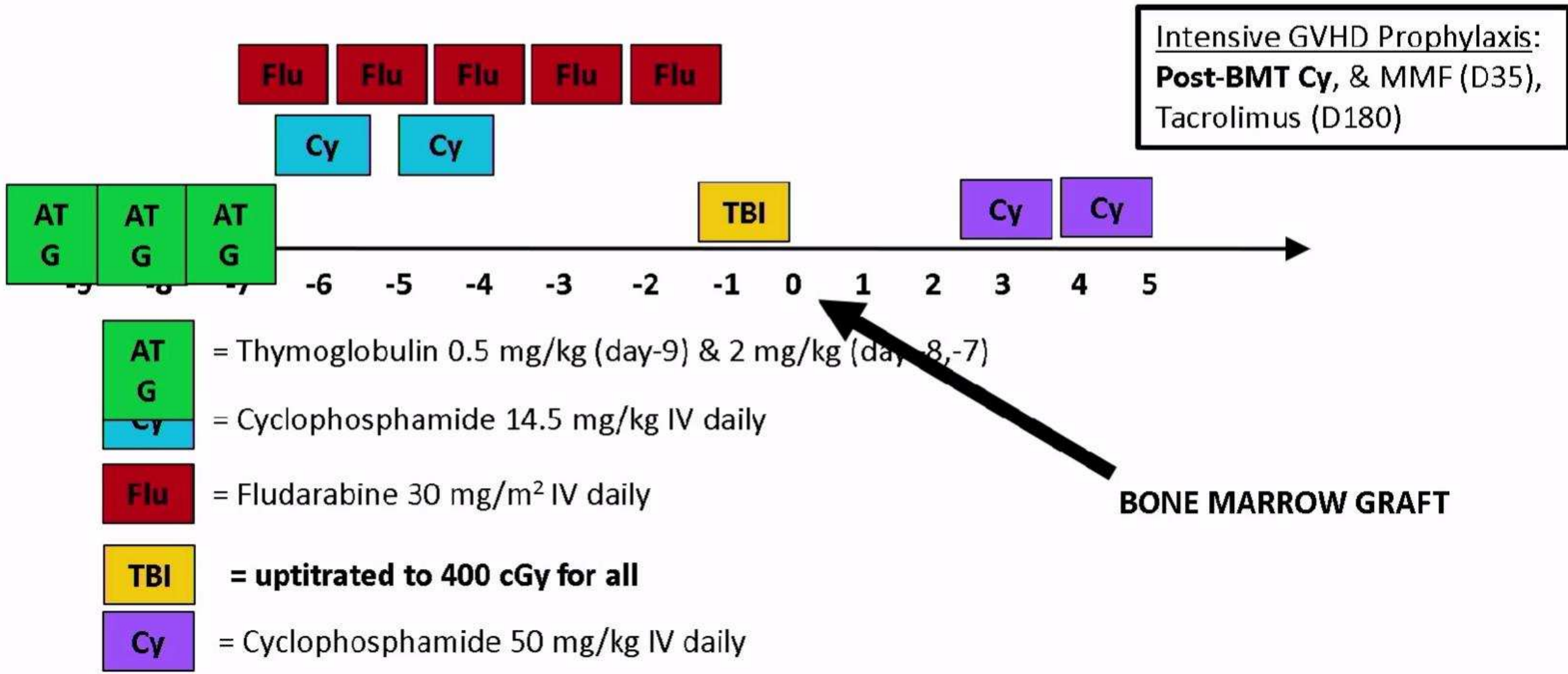
Lum SH et al. Blood 2024

TCRαβ+/CD19+ depletion: FA





Strocchio L et al Blood Adv 2021


Intensive GVHD Prophylaxis:
Post-BMT Cy, & MMF (D35),
Tacrolimus (D180)
Flu
Flu
Flu
Flu
Flu
Cy
Cy
ATG
ATG
ATG
TBI
Cy
Cy
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
ATG
= Thymoglobulin 0.5 mg/kg (day-9) & 2 mg/kg (day -8,-7)
Cy
= Cyclophosphamide 14.5 mg/kg IV daily
Flu
= Fludarabine 30 mg/m² IV daily
BONE MARROW GRAFT
TBI
= uptitrated to 400 cGy for all
Cy
= Cyclophosphamide 50 mg/kg IV daily

HLA-matching: Umbilical Cord Blood

	RR	Probability	P-value
Mortality			
1MM vs. 8/8	1.18	76 vs.79%	0.39
2 MM vs. 8/8	**1.55**	70 vs. 79%	0.018
3 MM vs. 8/8	**2.04**	62 vs. 79%	0.0001
Graft failure			
1MM vs. 8/8	1.34	21 vs. 16%	0.15
2 MM vs. 8/8	**1.50**	23 vs. 16%	0.037
3 MM vs. 8/8	**1.86**	28 vs. 16%	0.0014

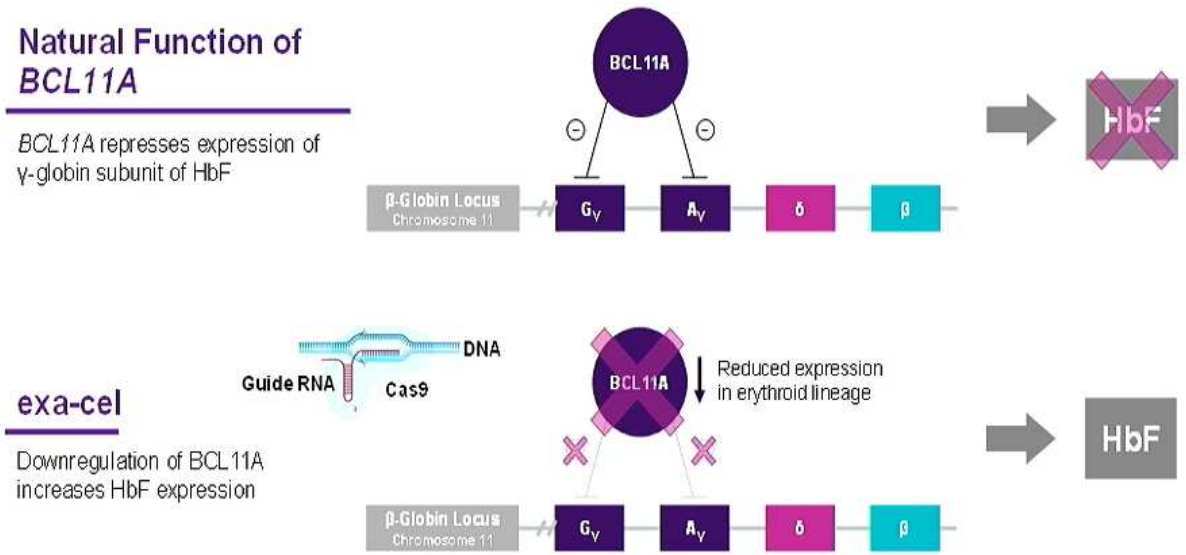
Pre-cryopreserved unit TNC

- Recommend: 4-5 x 10^7/kg

Allele-level match

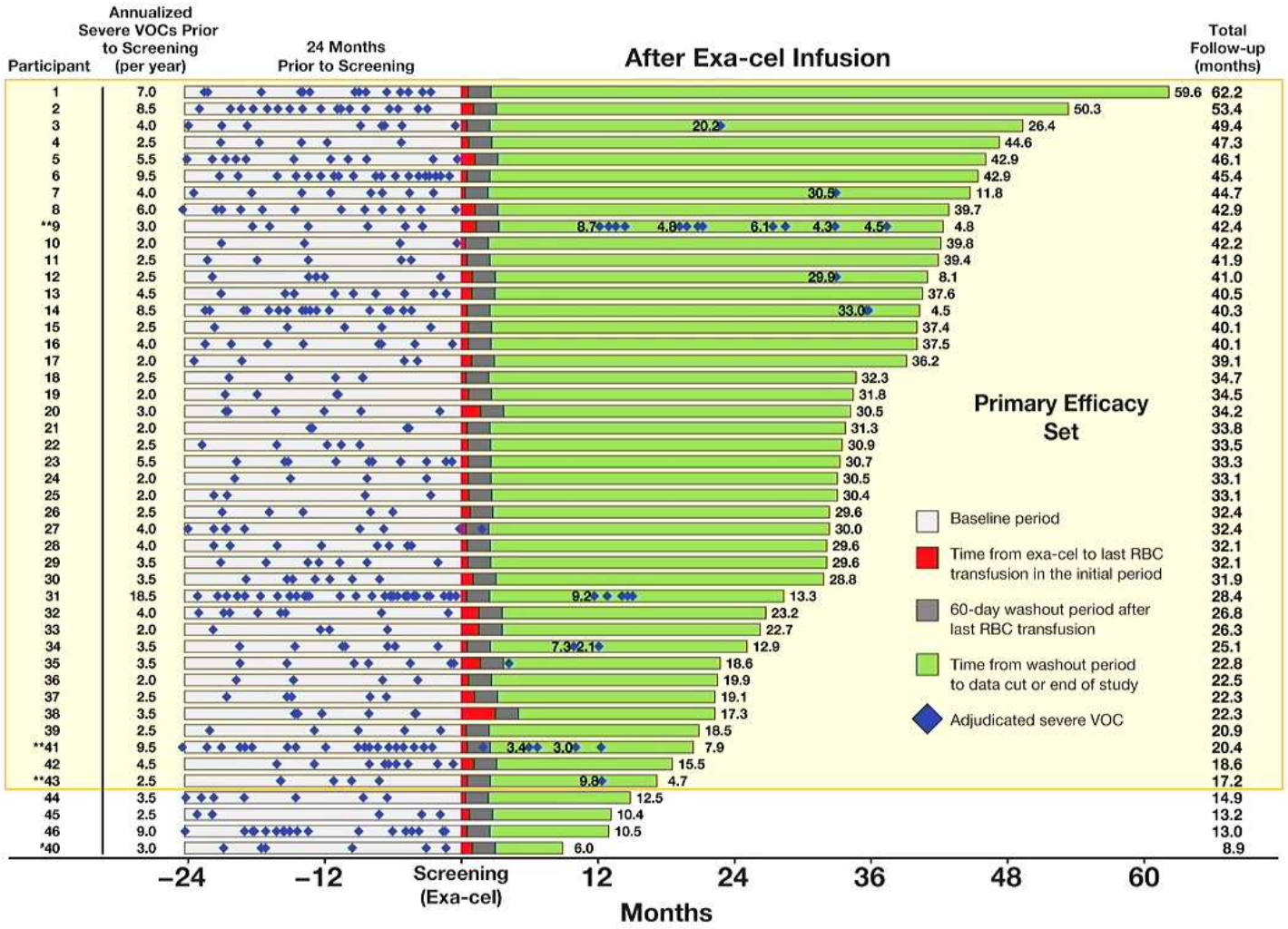
- 8/8, 7/8 HLA-match
- Avoid ≥2 MM
- Not tested
  - DQ and DP

Exa-cel is the First and Only Approved CRISPR/Cas9 Gene Editing Therapy: Autologous CD34+ HSPCs Modified Using Non-Viral *Ex-Vivo* CRISPR/Cas9



- Exa-cel (Casgevy) is the First Approved CRISPR/Cas9 Gene Editing Therapy
- Exa-cel is approved for treatment of patients aged 12 and older with[1]:
  - Transfusion- Dependent β-Thalassemia (TDT), and
  - Sickle Cell Disease (SCD) with recurrent vaso-occlusive crises (VOC)
- Exa-cel is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of *BCL11A* in CD34+ HSPCs to reduce erythroid-specific expression of *BCL11A*
- Exa-cel results in reactivation of HbF synthesis to levels known to result in reduced morbidity and mortality in patients with hemoglobinopathy and hereditary persistence of HbF[2,3]
- Exa-cel Phase 1/2/3 clinical trial data has demonstrated reactivation of HbF to levels that eliminate the need for transfusion (TDT)[4] or elimination of VOC[5]
- Updated data will be presented demonstrating durable clinical benefit with a median follow-up of over 33.2 months and longest follow-up of ~5 years

Durable VOC-Free Benefit Achieved After Exa-cel (CLIMB SCD-121 and 131)



**participants who have not yet achieved VF12; #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.

Some participants h 04:08 Cs after the washout period; numerical values before the VOC indicate the number of months a participant was VOC-free

Durable VOC-free benefit was achieved

- 93% (39/42) of evaluable participants achieved VF12 in CLIMB SCD-121 or CLIMB-131 combined (95% CI: 81%, 99%)
- Mean duration of VOC-free *30.9 months (range 12.9 to 59.6)*
- Results consistent by subgroup
  - **Age**: VF12 in 90% (27/30) of adults and 100% (12/12) of adolescents
  - **Genotype**: VF12 in 92% (36/39) of β^S/β^S and 100% (3/3) of non-β^S/β^S (includes β^s/β^0 and β^s/β^+ genotypes)

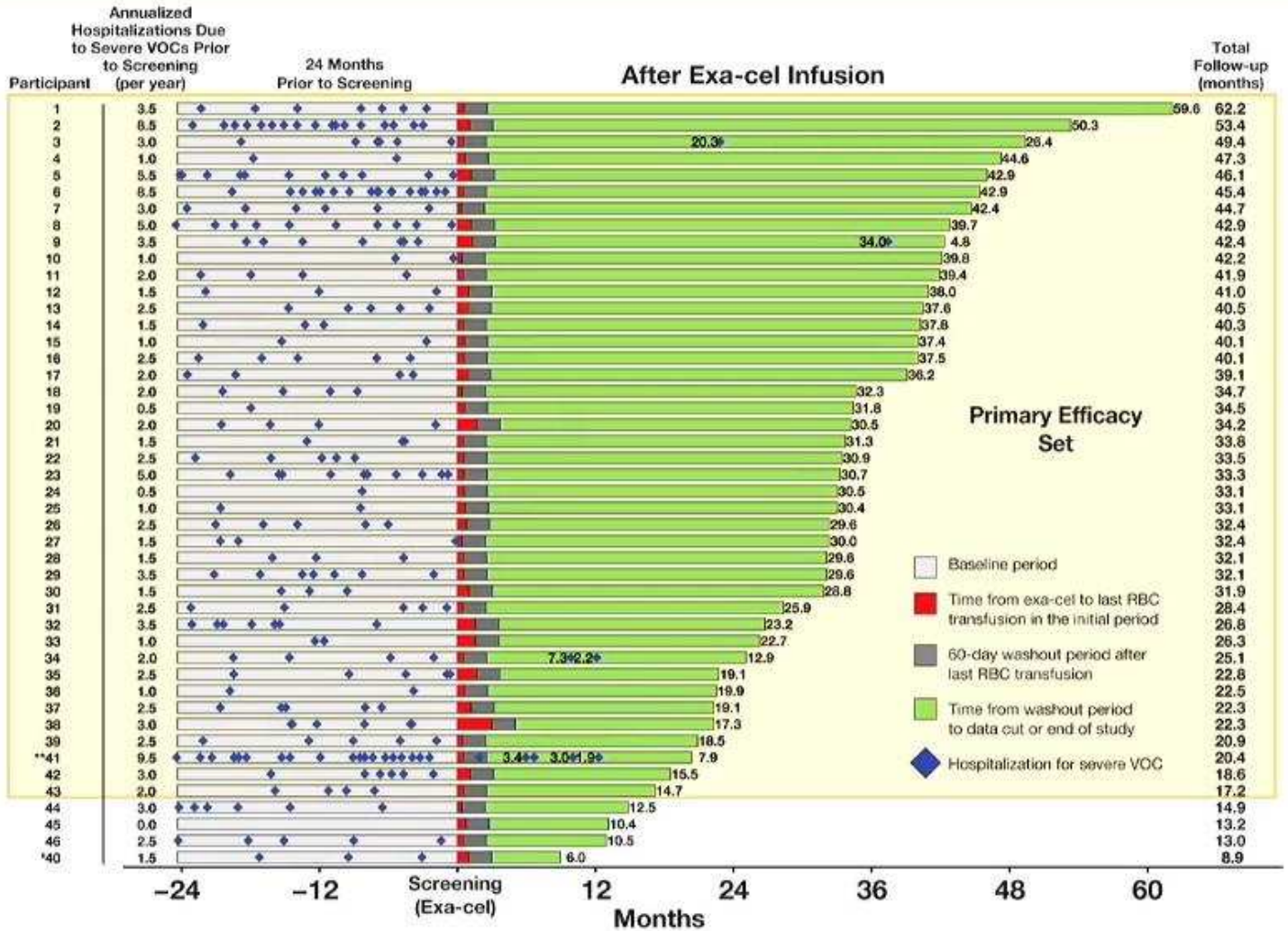
3 participants who have not yet achieved VF12 have significant clinical benefit:

- reduced hospitalization of 91%, 71%, and 100%
- no acute chest syndrome occurred post infusion

Pain events after exa-cel generally occurred in adult participants with a history of chronic pain and/or following an identifiable pain trigger such as:

- infection (e.g., parvovirus B19, influenza B, or COVID-19)
- procedure (e.g., bone marrow biopsy)
- corticosteroids

Durable Hospital-free Benefit Achieved After Exa-cel (CLIMB SCD-121 and 131)



Durable hospitalization-free benefit achieved:

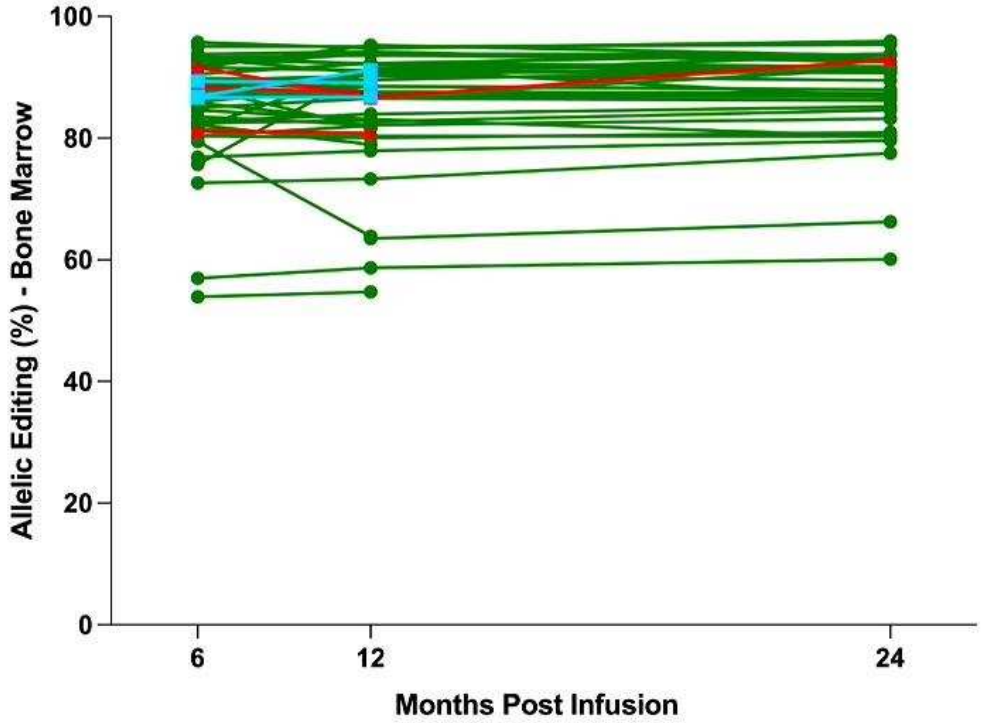
- 98% (41/42) of participants achieved HF12 in CLIMB SCD-121 and 131 (95% CI: 87%, 100%)
- Mean duration of hospitalization-free period 31.5 months (range 12.9 to 59.6)

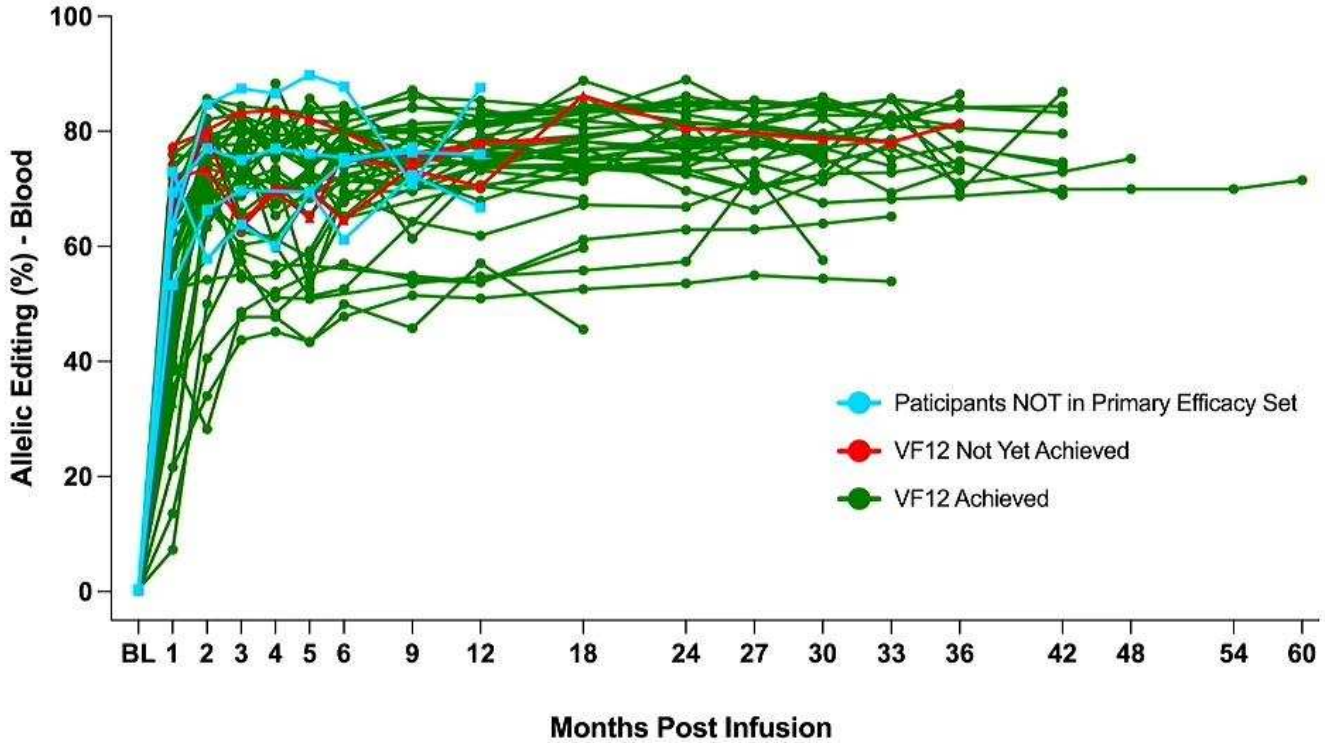
**participants who have not yet achieved HF12, #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.

Some participants had hospitalization due to severe VOCs after the washout period; numerical values before the hospitalization indicate the number of months a participant was free of hospitalizations due to VOC since the washout period/previous hospitalization due to VOC. Data shown are based on the Full Analysis Set as of Aug 2024. 34 participants have completed CLIMB SCD-121, and all 34 have enrolled in CLIMB-131.

exa-cel, exagamglogene autotemcel; **RBC,** red blood cell; ; **HF12,** free from hospitalization for severe VOCs for ≥12 consecutive months; **VOC,** vaso-occlusive crisis.

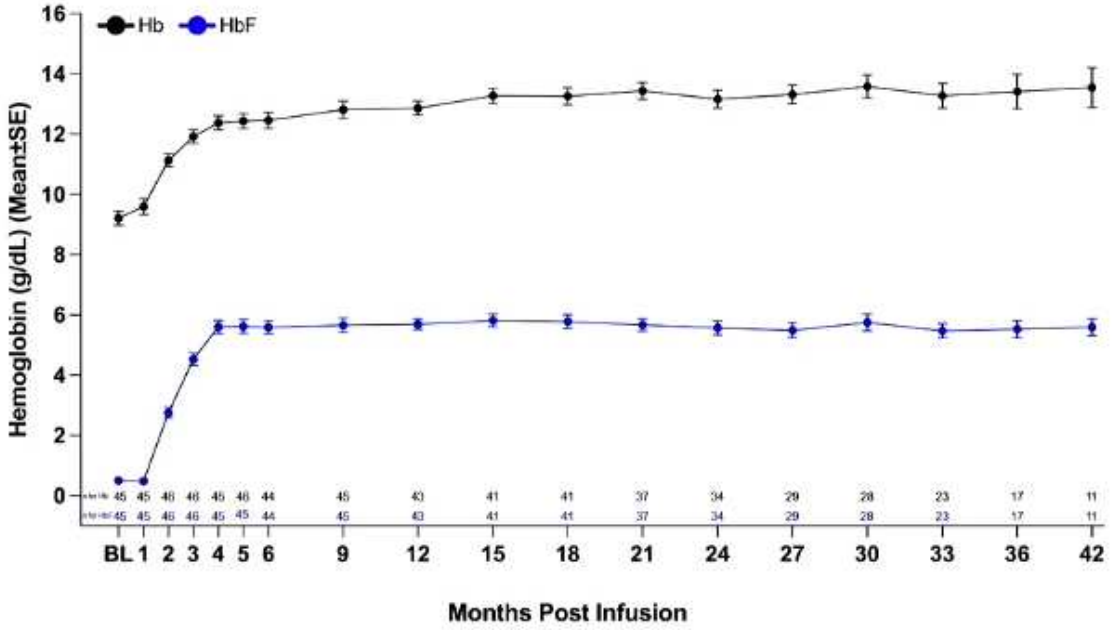
All Participants Demonstrate Durable Bone Marrow and Peripheral Blood Allelic Editing After Exa-cel



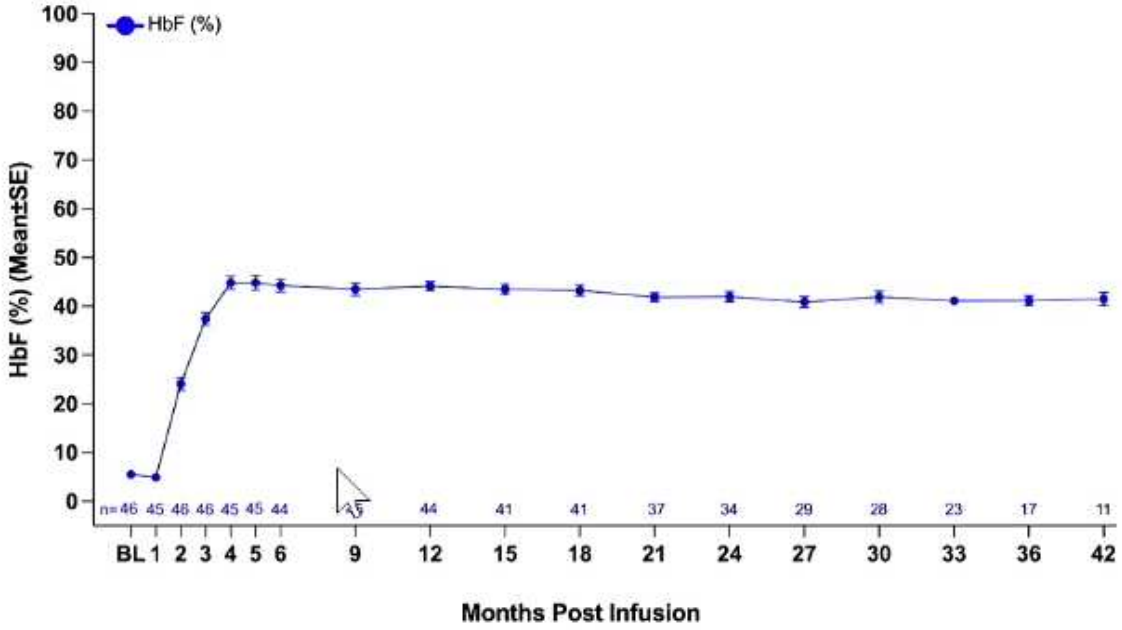


All Participants Demonstrate Durable Increase in Total Hb to Normal or Near Normal Levels and Fetal Hemoglobin to ~40% With Pancellular Distribution After Exa-Cel

Total Hb and HbF



HbF Percentage



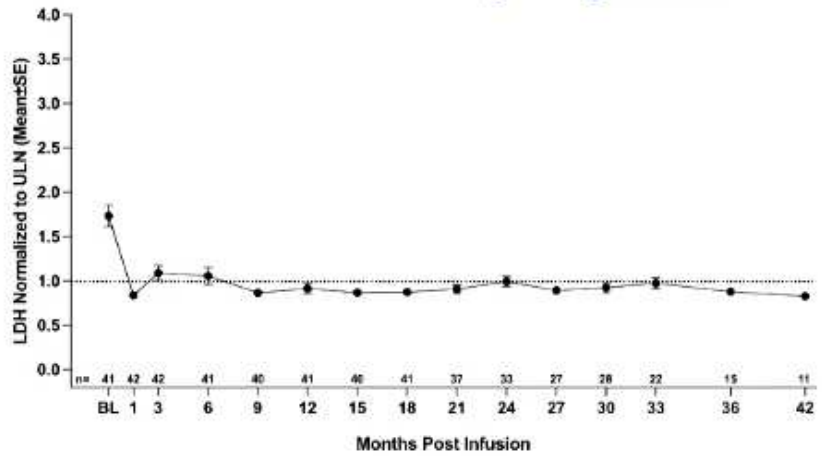
- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel

Data shown are based on the F[illegible] Analysis Set as of Aug 2024. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.
BL, baseline; **exa-cel,** exagam[illegible]one autotemcel; **Hb,** hemoglobin; **HbF,** fetal hemoglobin; **HSCs,** hematopoietic stem cells; **SE,** standard error.

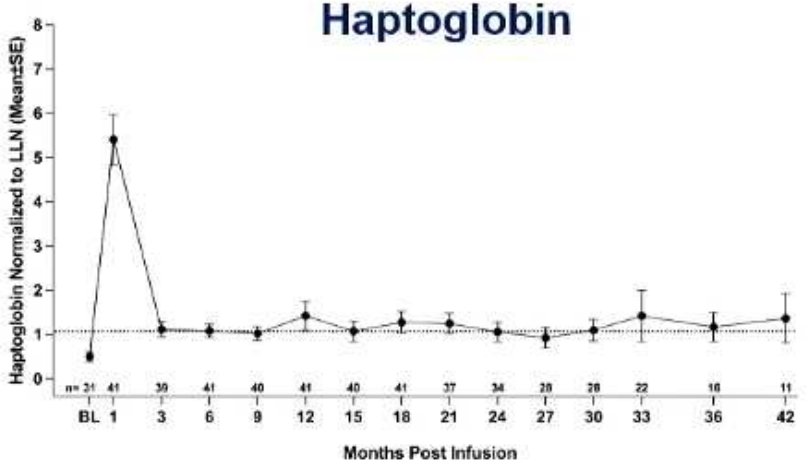
Durable Improvements in Hemolysis After Exa-cel

- Clinically meaningful improvements in hemolysis markers were observed and maintained over time.

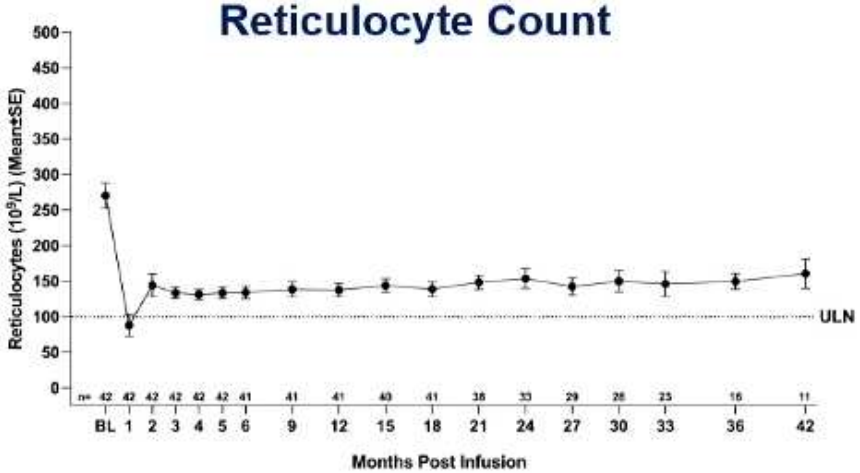
Lactate Dehydrogenase



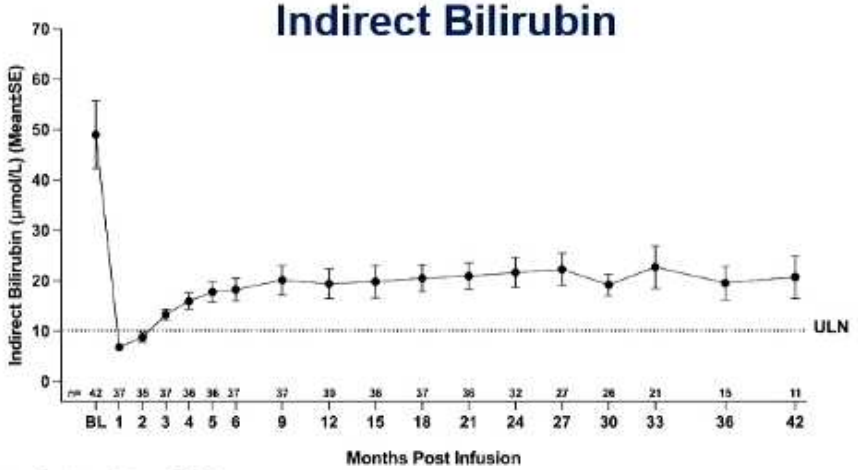
Haptoglobin



Reticulocyte Count



Indirect Bilirubin



Figures depict data for all timepoints where at least 5 participants have completed the specified visit. Data are displayed for the Primary Efficacy Set as of Aug 2024.
ULN for absolute reticulocyte count and indirect bilirubin, based on American Board of Internal Medicine (ABIM) Laboratory Test Reference Ranges – Jan 2024. ULN for LDH and LLN for haptoglobin were based on the lab normal range as collected.
BL: baseline, **exa-cel:** exagamglogene autotemcel, **LDH:** lactate dehydrogenase, **LLN:** lower limit of normal, **ULN:** upper limit of normal.

multivariate analysis

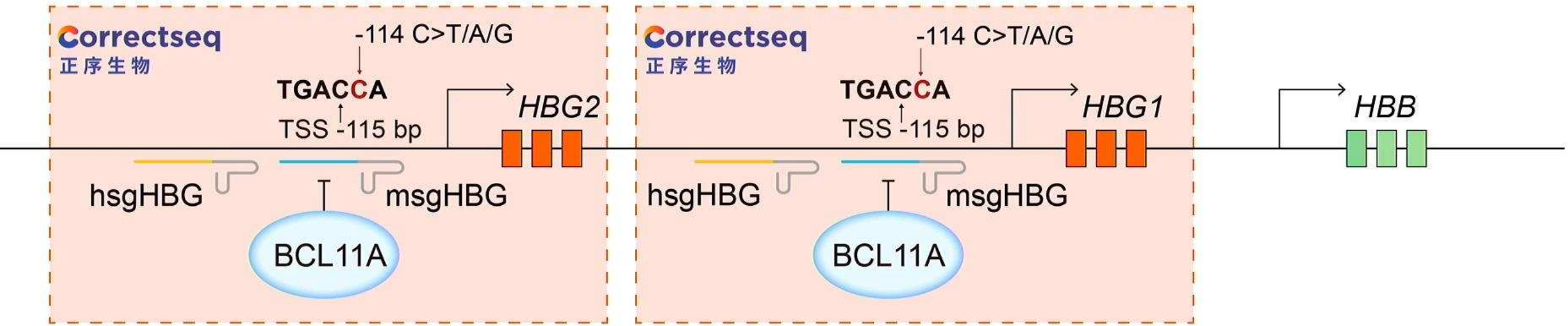
- Age of patients had a significant effect on OS [12-18 years HR 2.01 (1.01-3.99, p = 0.047) >18 years HR 2.47 (1.23-4.94, p = 0.01)].

- Age has no significant effect on the incidence of acute grade II-IV or chronic GVHD resulting in no difference in GFRS.

- The year of transplant [cut off 2015] has a significant effect on overall survival [HR 0.59 (0.37-0.93, p = 0.02):
  - a trend to lower risk of acute GVHD [HR 0.66 (0.42-1.04, p = 0.07)]
  - lower risk chronic GVHD [HR 0.54 (0.34-0.86, p = 0.01)]
  - despite a higher risk of a second transplant [HR 1.87 (01.33-2.61, p = <0.001)]

CS-101 Strategy: Reactivating Fetal Hemoglobin Expression through Precise C-to-T Base Editing

-114 C: A naturally existed SNV in hereditary persistence of fetal hemoglobin (HPFH)



BCL11A: B-cell lymphoma/leukemia 11A; **HPFH**: hereditary persistence of fetal hemoglobin;
SNV: single nucleotide variant; **HbF**: fetal hemoglobin; ***HBG***: *hemoglobin subunit gamma*

Han et al., *Cell Stem Cell*, 2023

Study design and methods

- Sept 2011 – Aug 2024
- Age 0 -18 years
- BMT for HBSS
- Fully matched sibling donors
- Hyper-transfusion pre BMT for marrow suppression
- Standard fertility cryopreservation

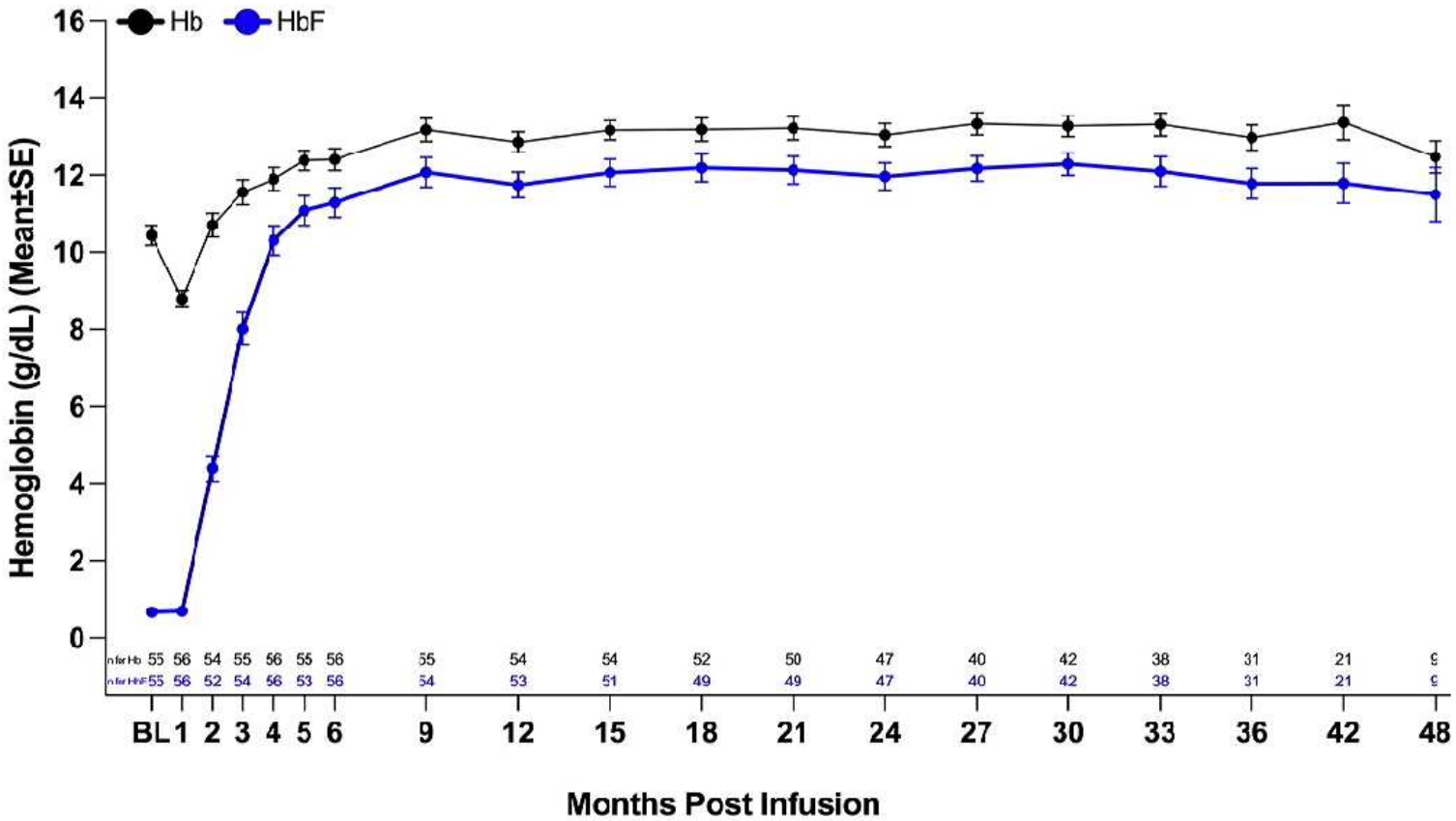
- Conditioning: fludarabine 160 mg/m^2, treosulfan 42 g/m^2, thiotepa 10 mg/kg and either ATG (Thymoglobulin) 7.5mg/kg, ATLG (Grafalon) 30mg/kg or Alemtuzumab 0.3 mg/kg.

- GVHD prophylaxis: CSA + MMF

Key Demographic Characteristics and Treatment Features

	Full Analysis Set[a] N = 56	Primary Efficacy Set[b] N = 54
Age (years) at screening, mean (SD)	21.2 (6.5)	21.3 (6.6)
≥12 and <18 years, n (%)	20 (35.7)	19 (35.2)
≥18 and ≤35 years, n (%)	36 (64.3)	35 (64.8)
Genotype, n (%)		
β^0/β^0	22 (39.3)	21 (38.9)
β^0/β^0-like (β^0/IVS-I-110; IVS-I-110/IVS-I-110)	13 (23.2)	12 (22.2)
Non-β^0/β^0-like	21 (37.5)	21 (38.9)
Neutrophil Engraftment (days)[c]		
Time to neutrophil engraftment, median (range)	29.0 (12, 56)	-
Duration of neutropenia, median (range)	20.5 (4, 48)	-
Platelet Engraftment (days)[d]		
Time to platelet engraftment, median (range)	43.5 (20, 200)	-
Splenectomized (N=16), median (range)	34.5 (20, 78)	-
Non-splenectomized (N=40), median (range)	46.0 (27, 200)	-
Time (days) to hospital discharge[e] , median (range)	39.0 (23, 110)	-
Duration (months) of follow-up after exa-cel, median (range)	38.1 (7.9, 67.1)	-

[a] Full Analysis Set includes participants who received exa-cel infusion as of Aug 2024. 48 participants have completed CLIMB THAL 111 and 7 are currently enrolled in CLIMB 131 (1 withdrew consent in 131 not due to an adverse event)
[b] Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion and ≥14 months after completion of RBC transfusions for post-transplant support or TDT management (evaluable for the primary endpoint).
[c] Defined as the first day of 3 consecutive measurement of absolute neutrophil count ≥500 cells/μL on 3 different days.
[d] Defined as the first day of 3 consecutive measurement of unsupported (no platelet transfusion in last 7 days) platelet count ≥20,000/μL on 3 different days.
[e] Defined as the number of days from exa-cel infusion to hospital discharge following neutrophil engraftment.

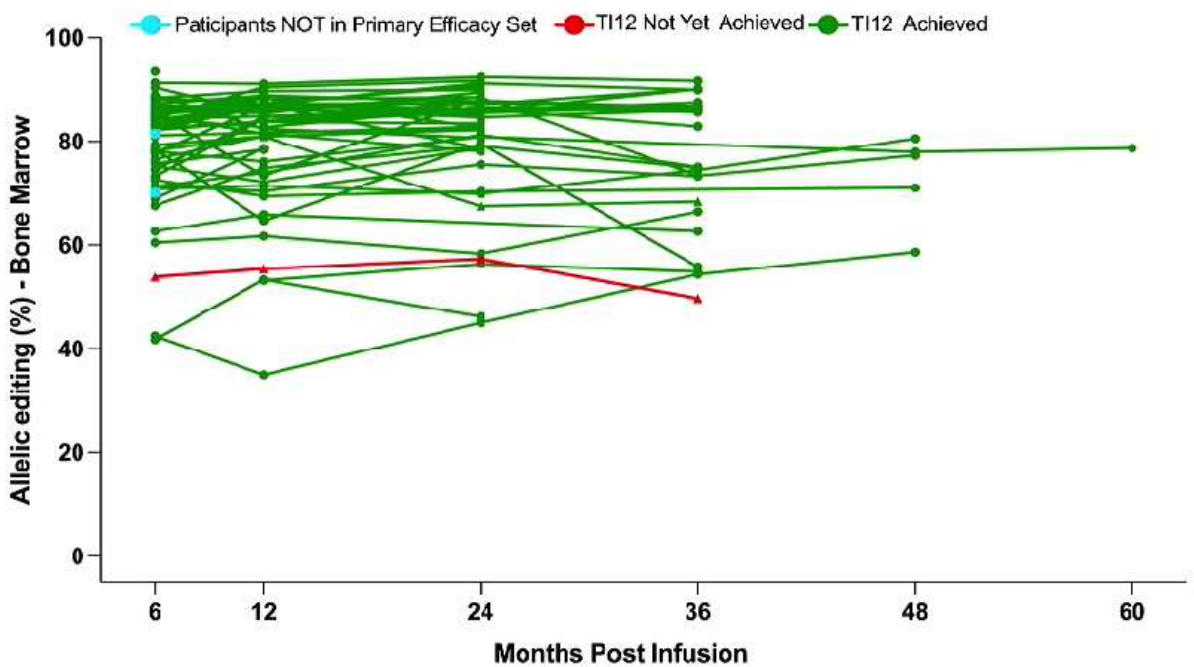


- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel

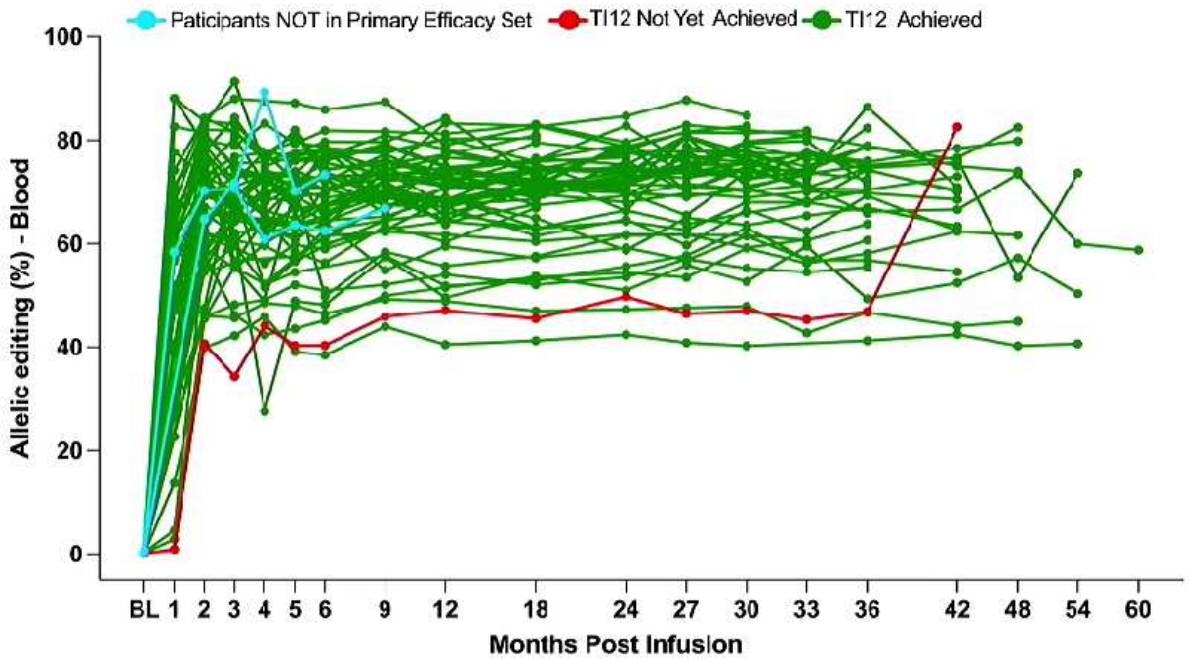
Durable Bone Marrow and Peripheral Blood Allelic Editing

Successful editing of long-term HSCs consistent with durable clinical benefit

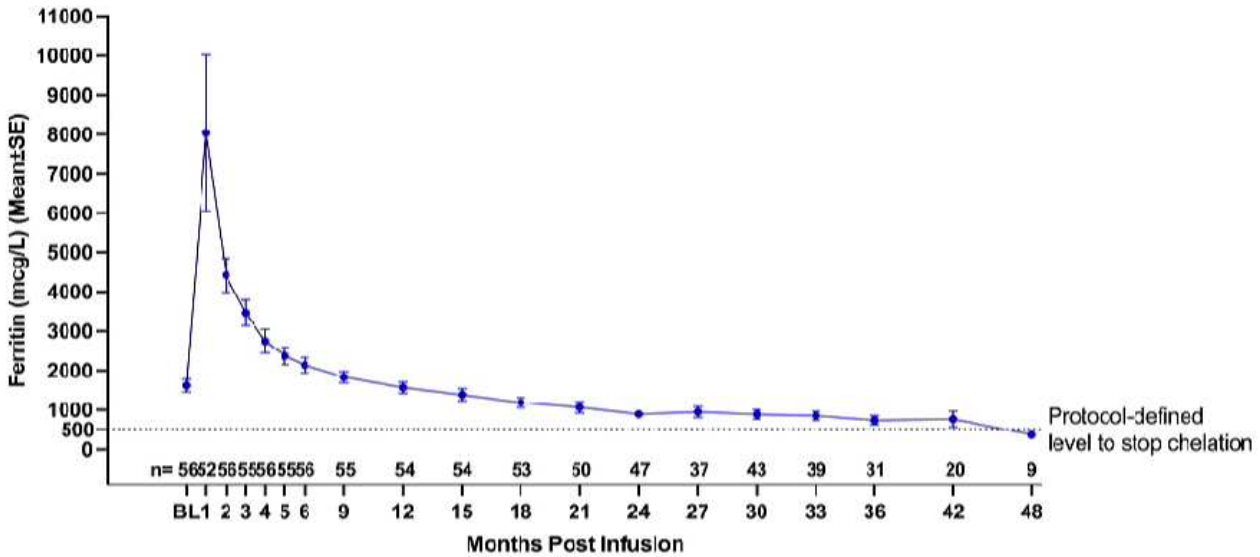
Bone Marrow

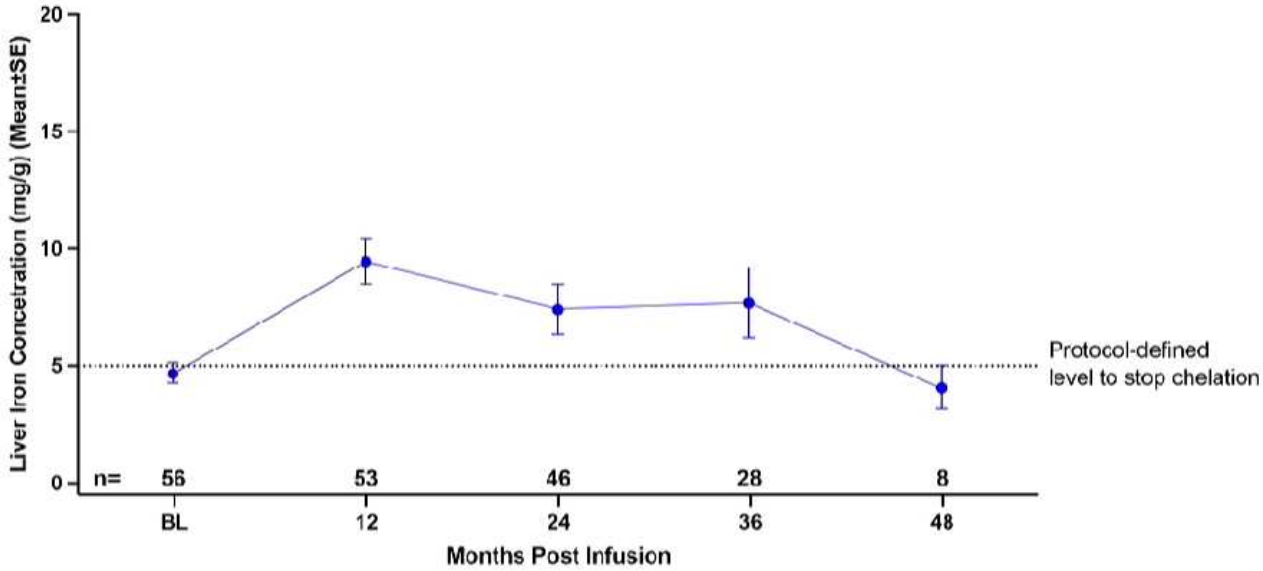


Blood



Additional Clinical Benefits: Improvement in Iron Overload Measures Over Time and Cessation of Iron Removal Therapy





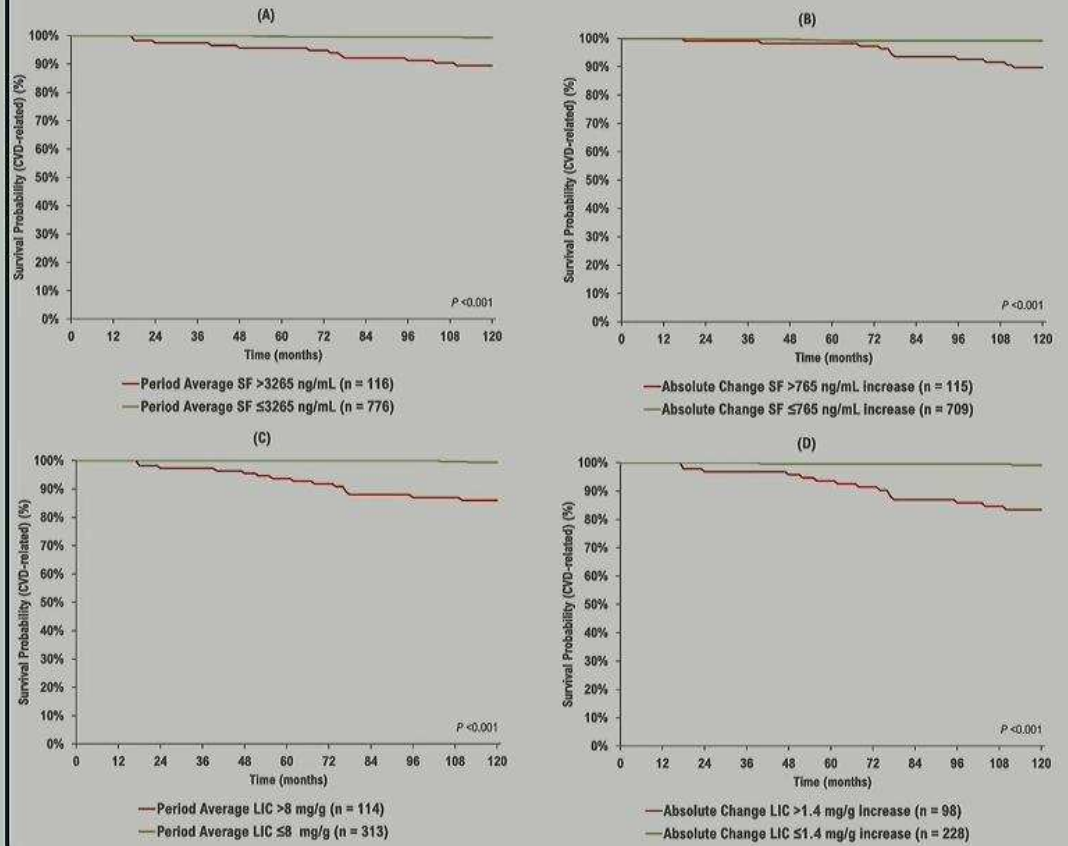
- Iron overload measures progressively improve after exa-cel, consistent with the known slow kinetics of the removal of storage iron post-HSCT [1, 2]
  - Mean **serum ferritin** decreased over time to below **baseline by Month 12**
  - Mean liver iron content (**LIC**): **decreased to below 5 mg/g [3] by Month 48**

Iron Overload Status and Gene Therapy in TDT: A Selection Paradox

Current Patient Selection Criteria:

- Priority typically given to patients with lower iron burden (e.g., LIC <7 mg/g dw).[1,2]
- These patients already have a relatively favorable prognosis with conventional treatments.[3]

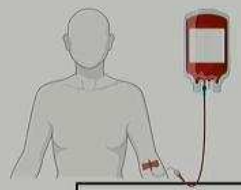
Survival probability in 912 TDT patients managed with conventional therapy over a 10 years period according to iron overload status[3]



18:14

Algorithm for the Selection of TDT Patients for Allogeneic Transplant or Gene Therapy*

*According to Speaker's own opinion and experience



Age below 14 years?
Patient is eligible for allo-HSCT?

NO

Exa-cel available and age between 12 and 35 years?
Beti-cel available and age between 4 and 35 years?

NO

Exa-cel available and age between 36 and 45 years?
Beti-cel available and age between 4 and 35 years?
Availability of a controlled experimental environment?

NO

- Continue with **conventional, high-quality medical therapy** or receive another available **experimental innovative treatment** (if patient is eligible)
- Periodically re-assess eligibility

YES

Presence of irreversible organ damage or significant cardiac, liver, lung and kidney abnormalities which can be considered temporary or permanent exclusion criteria?

YES

YES

NO

Adequate control of iron overload (LIC ≤ 7 mg/g dw and mT2* > 20ms)

YES

NO

If LIC <7 mg/g dw OR mT2* ≤20 (and >10) ms:
Perform at least 6 months of intensive chelation and re-assess

If target values (LIC ≤7 mg/g dw and mT2* >20ms) not achieved despite optimal efforts, consider to proceed based on clinical judgement

Gene Therapy

Consider prioritization of selected high-risk patients:

- *Rare erythrocyte phenotypes or a history of alloimmunization (provided that transfusion support can be ensured during treatment phases).*
- *Proven intolerance to iron-chelating drugs that would likely result in a rapidly progressive worsening of iron overload.*
- *Poor pre-transfusion hemoglobin levels (<9 g/dL)*

YES

Availability of suitable HLA-identical sibling donor?

NO

Highly motivated Family/Patient?

YES

Availability of suitable 10/10 HLA-matched unrelated donor?

NO

Heavy transfusion burden?
Low compliance or intolerance to iron chelators?
Poor quality of life with medical therapy?

NO

Consider the possibility of haploidentical HSCT in an experience center

YES

Patient is receiving regular chelation?
Iron overload is under control?

YES

NO

Encourage a period of adequate iron chelation, if feasible, and re-assess before transplant

YES

Iron overload is under control?

YES

NO

Encourage a period of adequate iron chelation, if feasible, and re-assess before transplant

YES

Iron overload is under control?

YES

NO

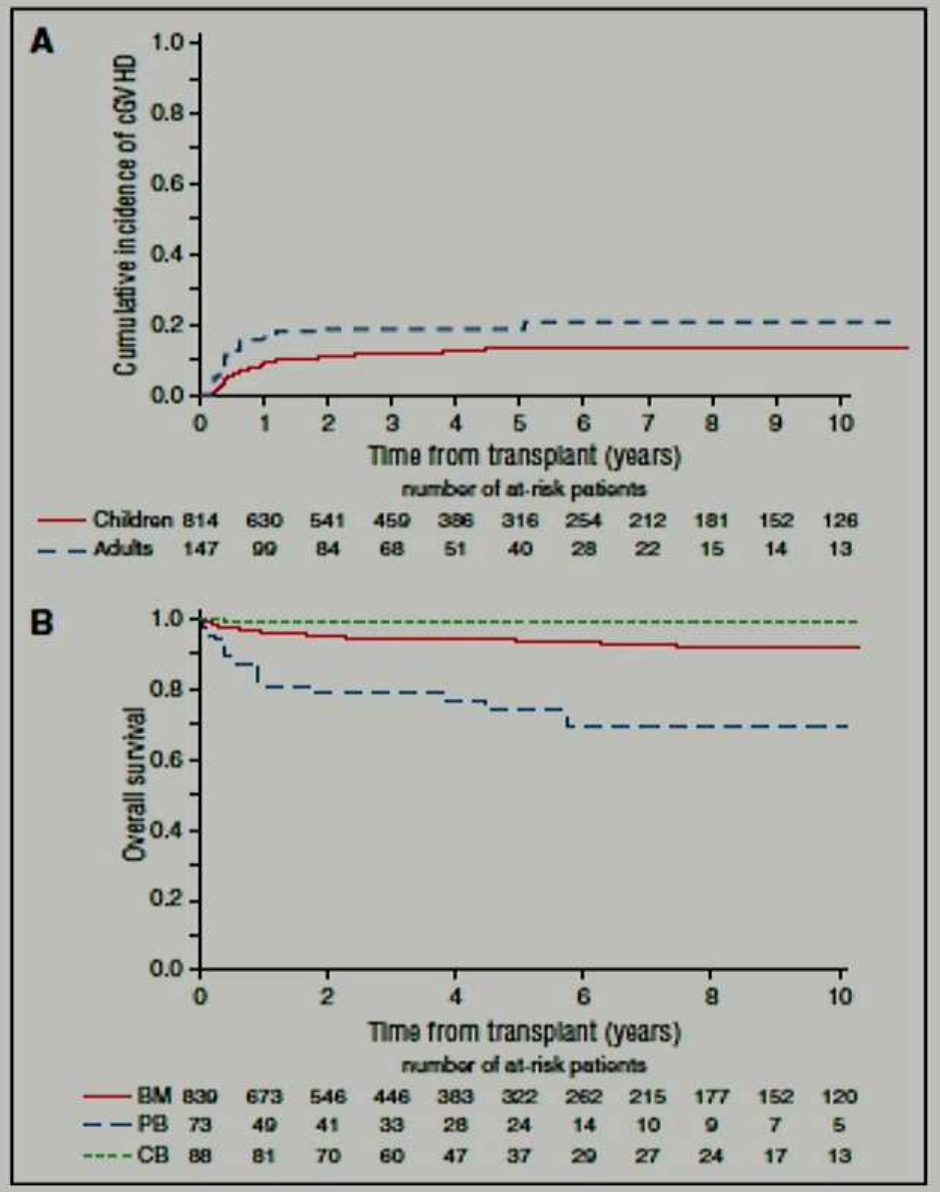
Encourage a period of adequate iron chelation, if feasible, and re-assess before transplant

Pre-conditioning and desensitization

25:56

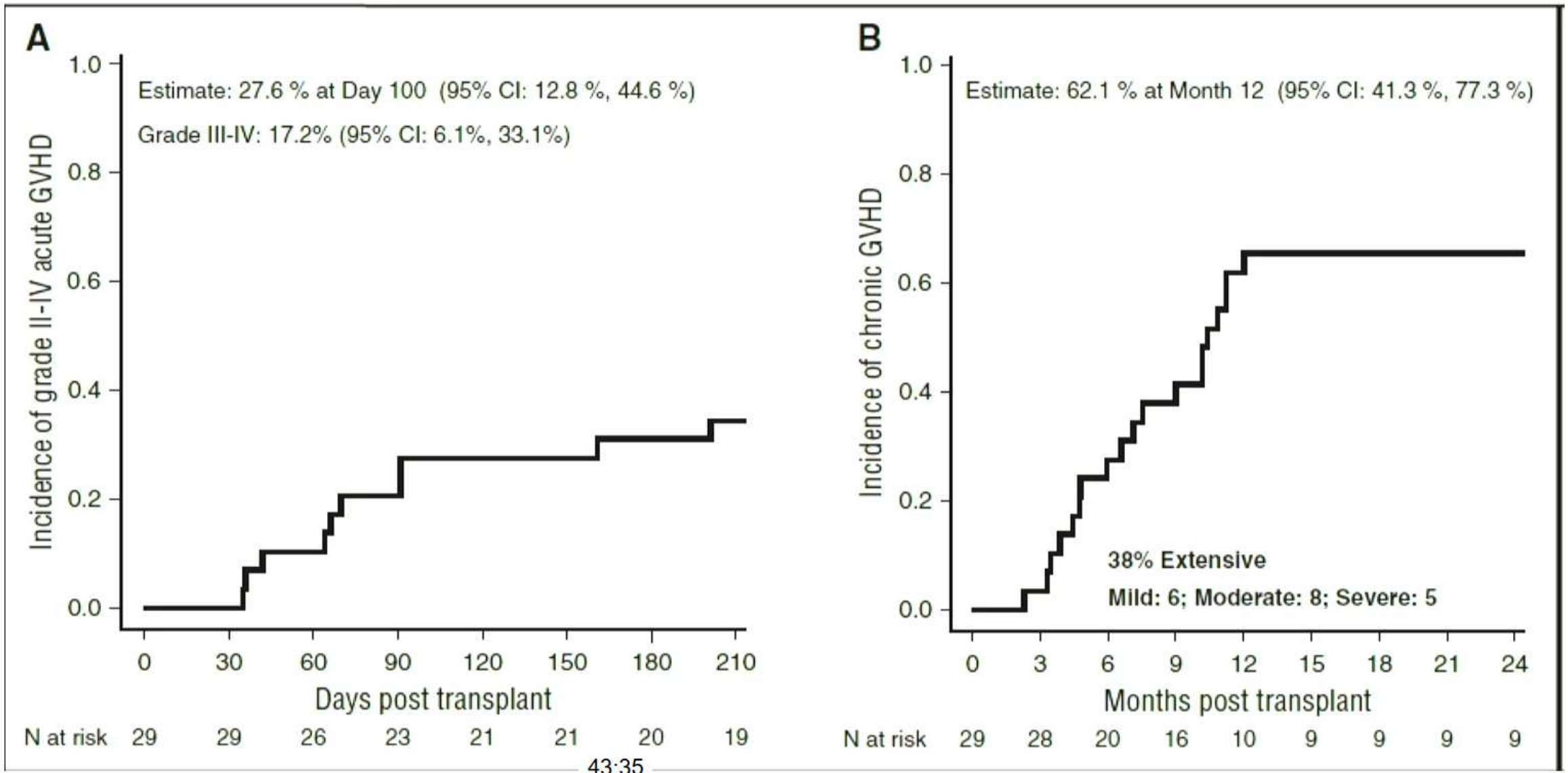
Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation (1986-2013)

- 5-year OS: 95% (95% CI, 93%-97%) and 81% (95% CI, 74%-88%) for patients younger than 16 years and those aged 16 years or older
- 5-year EFS was 93% (95% CI, 92%-95%) and 81% (95% CI, 74%-87%; $P < .001$).
- 5-year probability of GVHD-free survival was 86% and 77% for patients younger than 16 years and 16 years or older



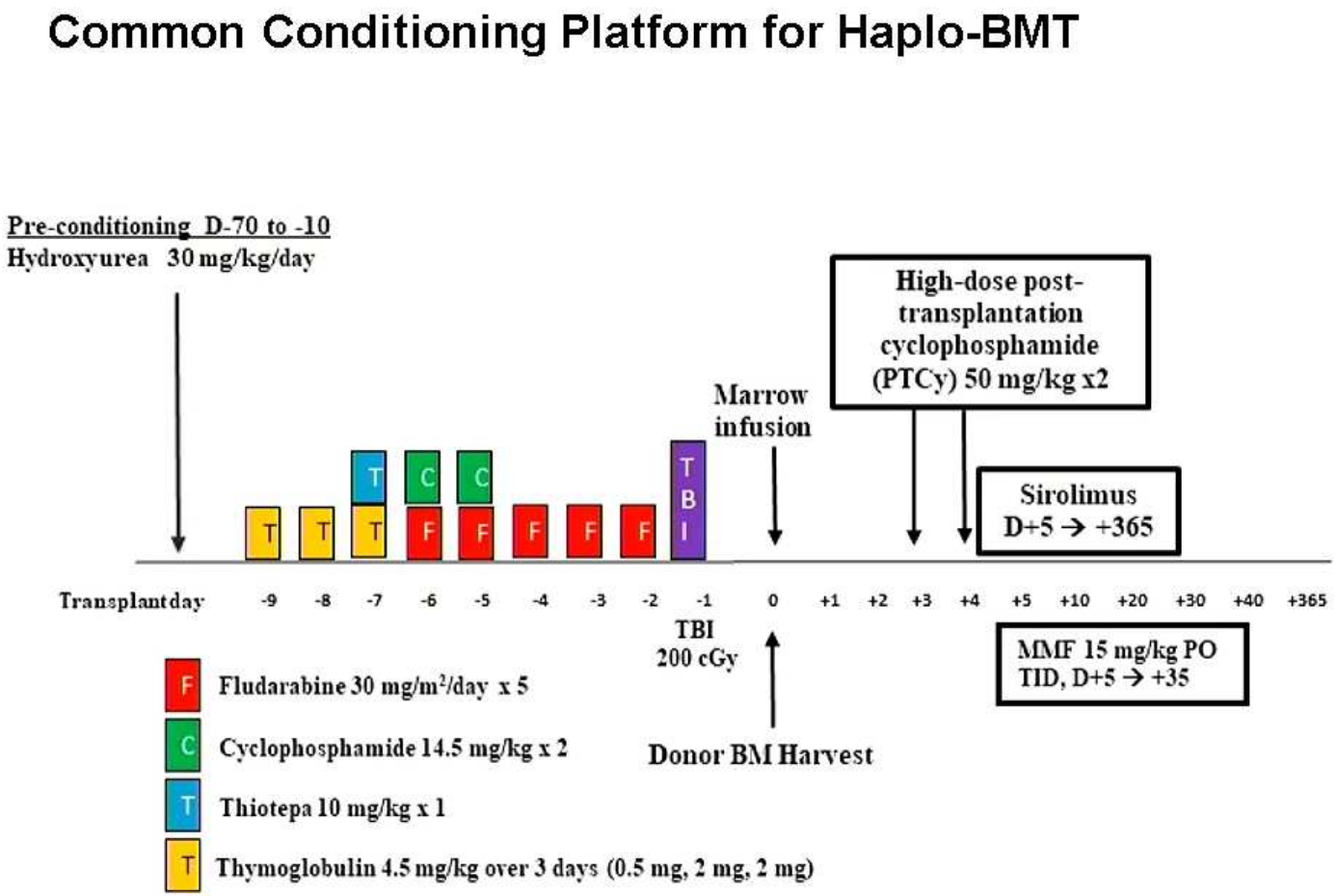
40:02

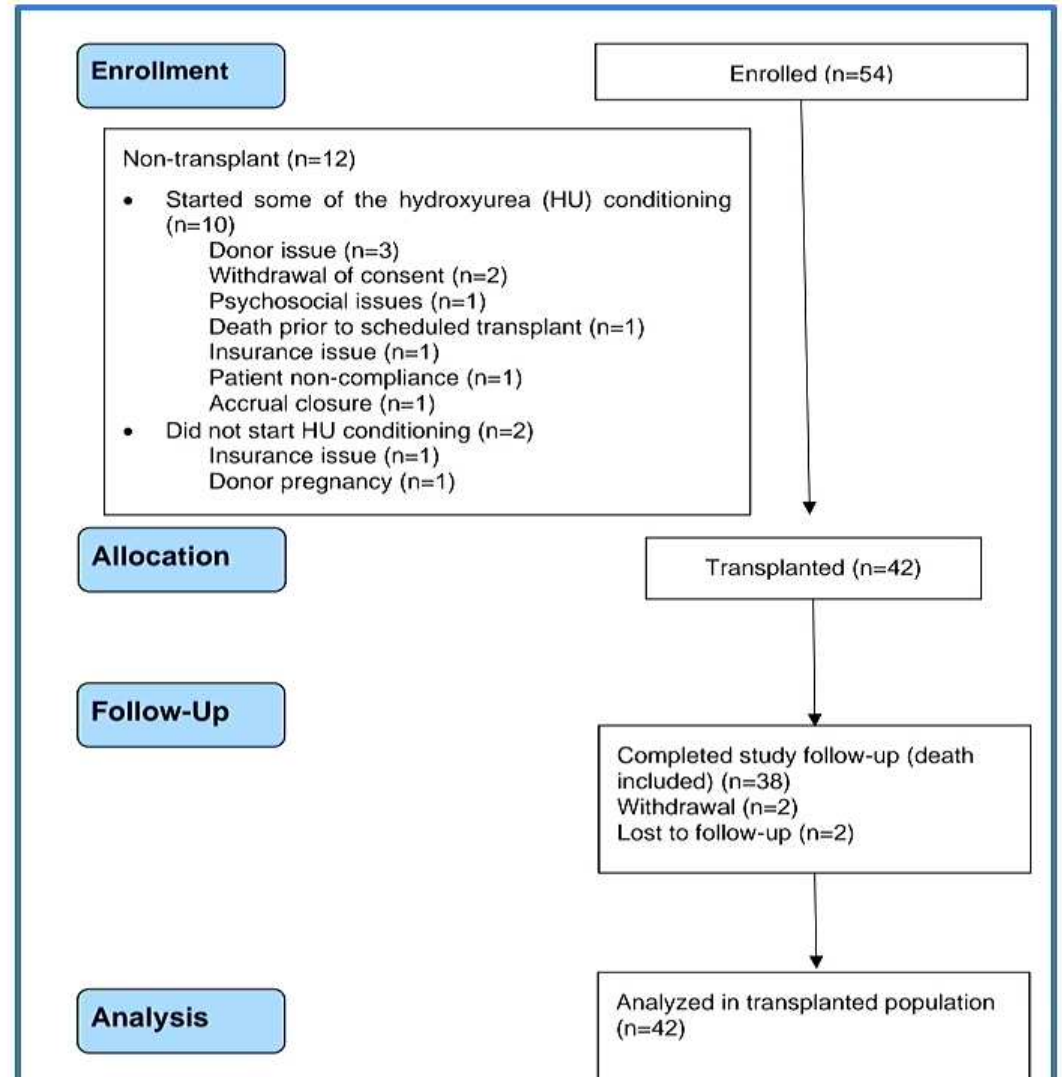
Unrelated Donor RIC HSCT for Children with Sickle Cell Disease



43:35

Haploidentical BMT for SCD: BMT CTN 1507





Haplo-HCT: Sickle Cell Disease

Vanderbilt learning collaborative; 2014-2022

	Pediatric	Adult ≥18 years
Graft failure*	**11%**	—
AGVHD	12.5%	7.9%
CGVHD*	**18.8%**	**2.6%**
EFS*	**68%**	**95%**
Survival	94%	**95%**

*Higher graft failure, mod-severe chronic GVHD
*Lower event-free survival

BMTCTN 1507; 2018-2020

	Adult (15 – 45 years)
Graft failure	**7%**
AGVHD	26% (95% CI 14-40%)
CGVHD	**22%** (95% CI 11-36%)
EFS	**88%** (95% CI 74-95%)
Survival	**93%** (95% CI 80-98%)

Absence of DSA
BM graft target TNC 4 x 10^8/kg
Minimum TNC: 2.5 x 10^8/kg

Danke für die Aufmerksamkeit

Gentechnologie verändert die Medizin

Zelluläre Krebsimmuntherapie

Zelluläre Gentherapie, veränderte Stammzellen

Gentechnisch veränderte Viren als Gentransportmittel