HLA Haploidentical Transplantation: The Journey to the "Transplantation" For All

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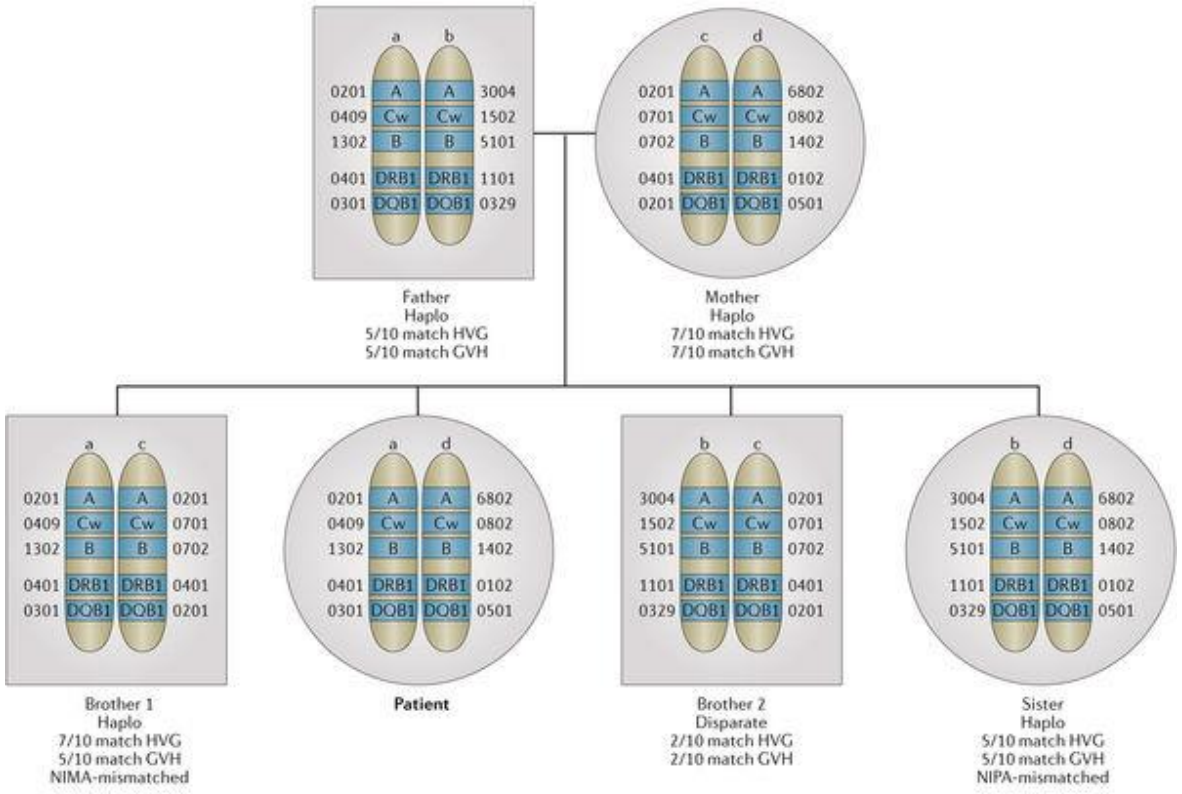
Disclosure

- No relevant conflict of interest to disclose

Outlines

- Introduction
- Major approaches of HLA haploidentical transplantation
- Selecting best donor for HLA haploidentical transplantation
- Limitation of HLA haploidentical transplantation

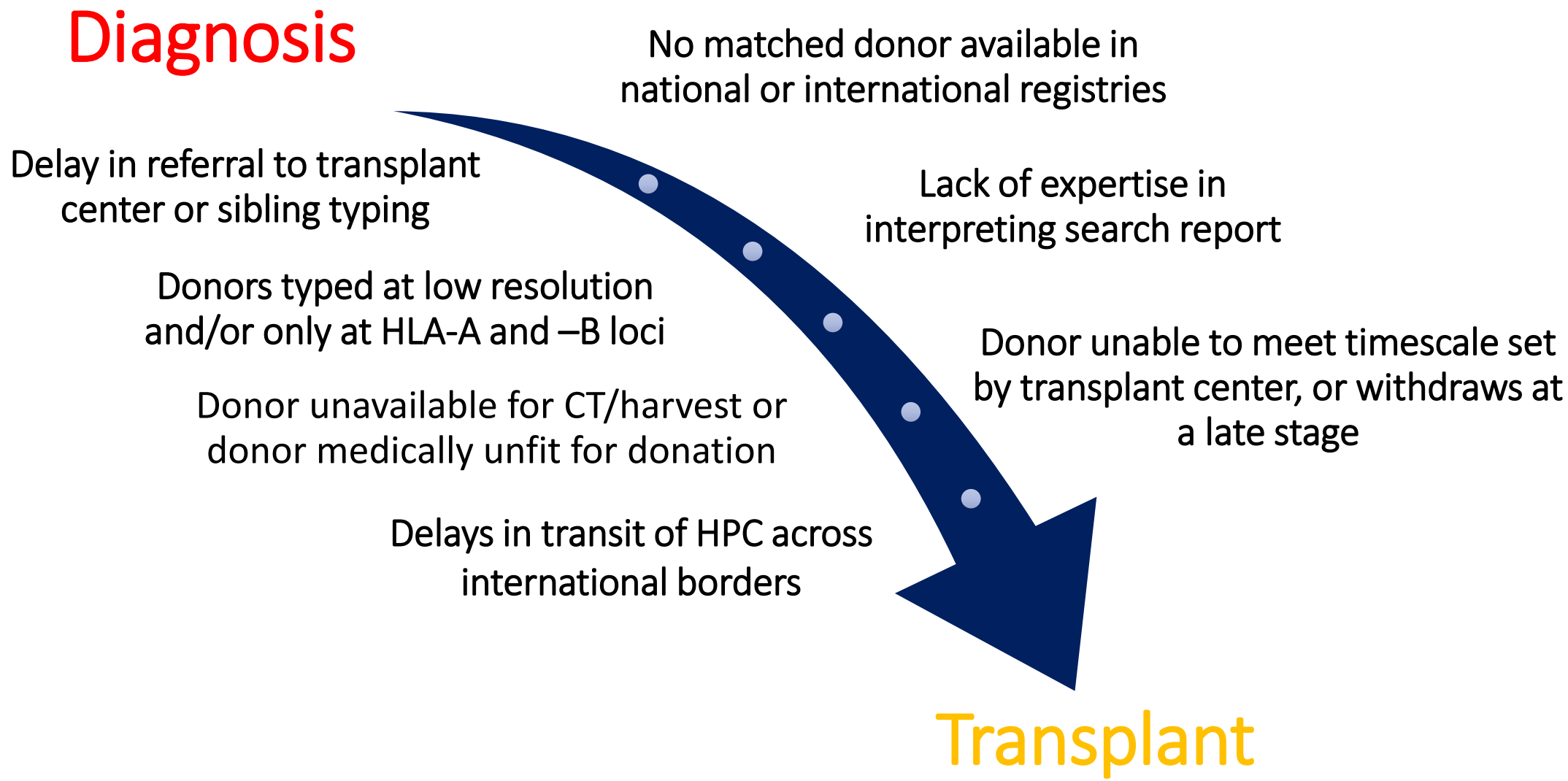
Introduction



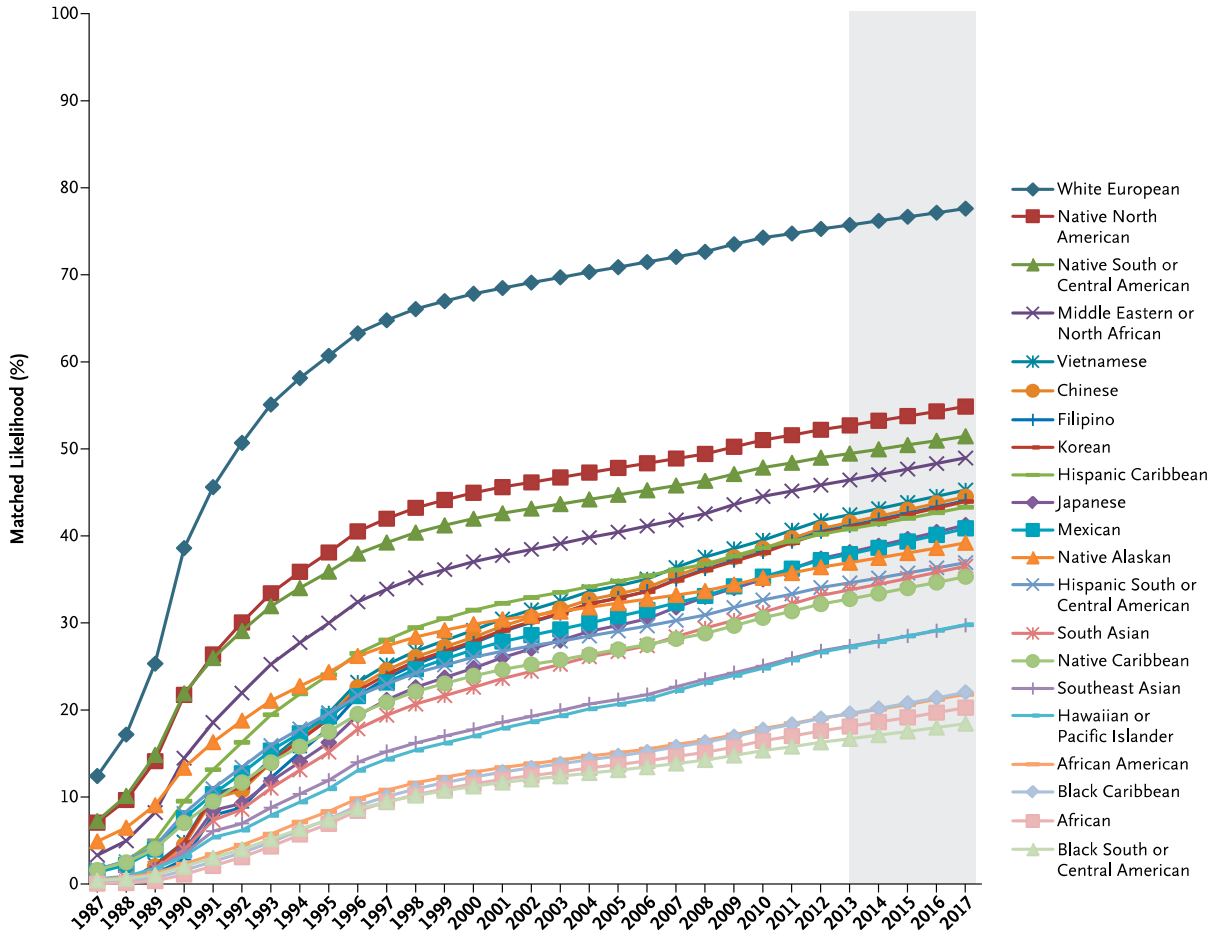
25% chance of having HLA matched sibling

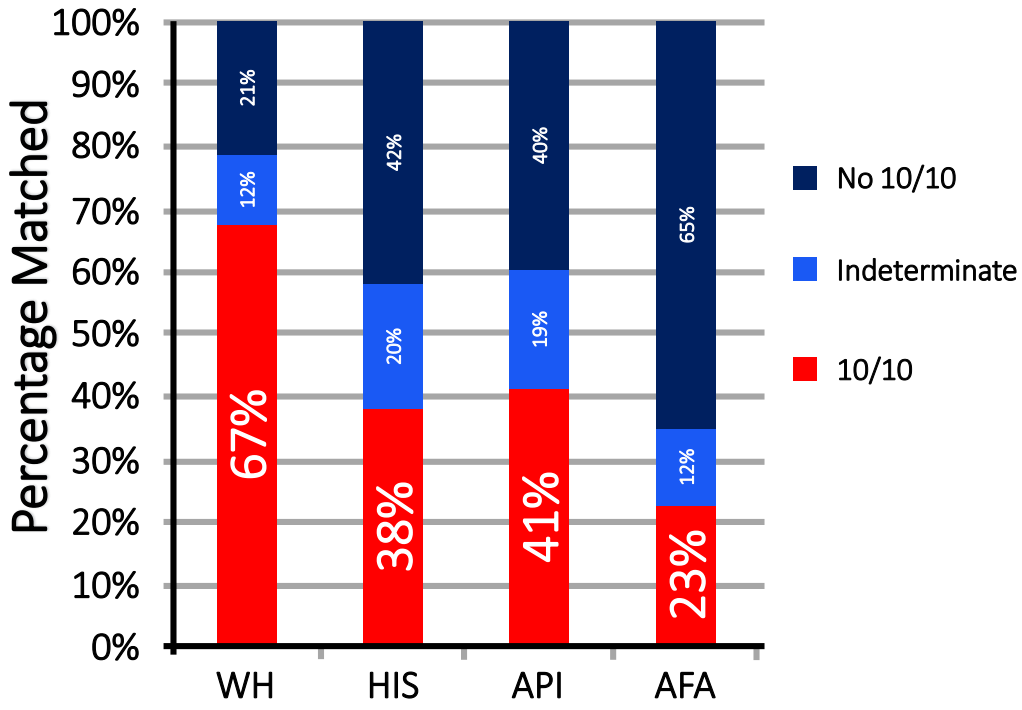
- **Only 30% chance** of available HLA matched sibling donor (MSD)
- HLA matched unrelated donor considered standard after MSD
- Availability and accessibility to HLA identical matched unrelated donor are limited

Obstacles in finding matched unrelated donor



Likelihood of HLA-matched unrelated donor availability



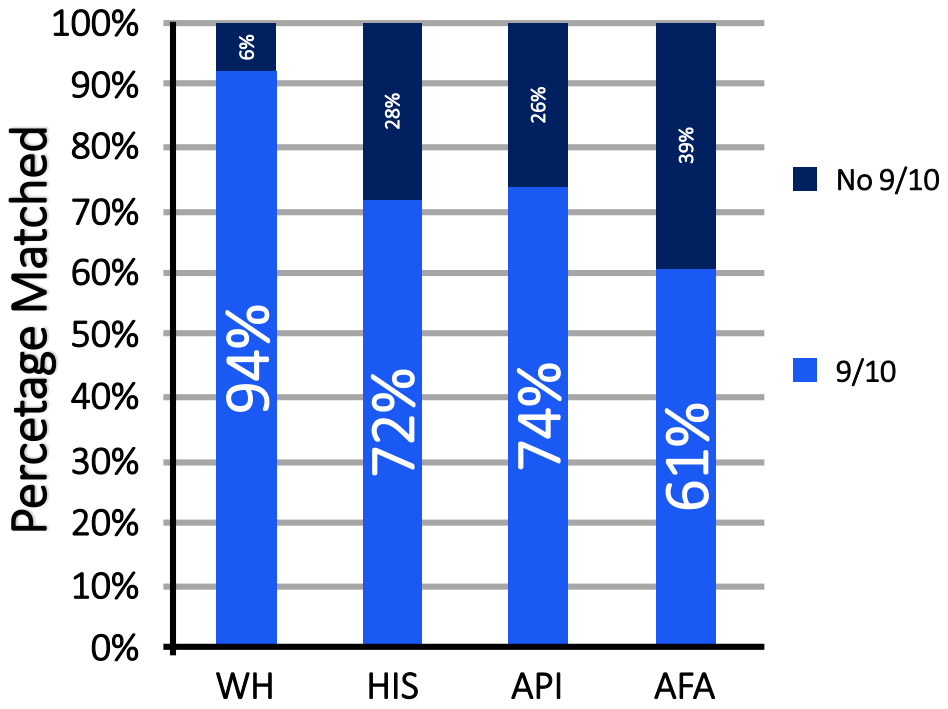


Dehn J et al. Biol Blood Marrow Transplant. 2015 Jan;21(1):137-41
Buck K et al. Biol Blood Marrow Transplant. 2016 Apr;22(4):759-763
Gragert L et al. N Engl J Med. 2014 Jul 24;371(4):339-48

Alternative hematopoietic stem cell donors

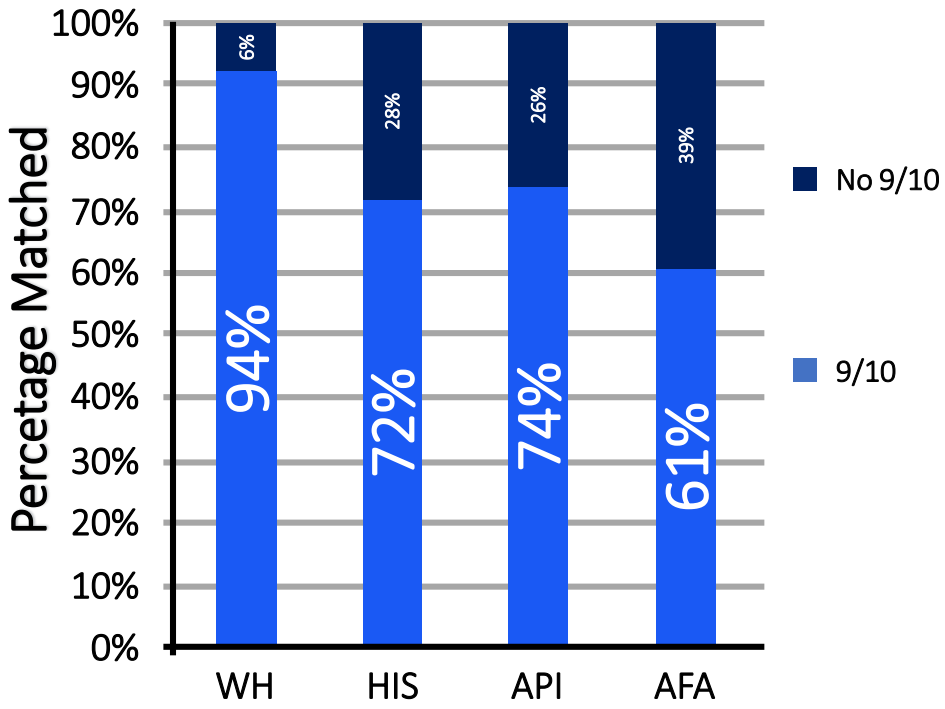
- Mismatched unrelated hematopoietic stem cell donor
  - One locus mismatch
  - ≥ two loci mismatch
- Umbilical cord blood hematopoietic stem cell
- HLA-haploidentical (related) hematopoietic stem cell donor

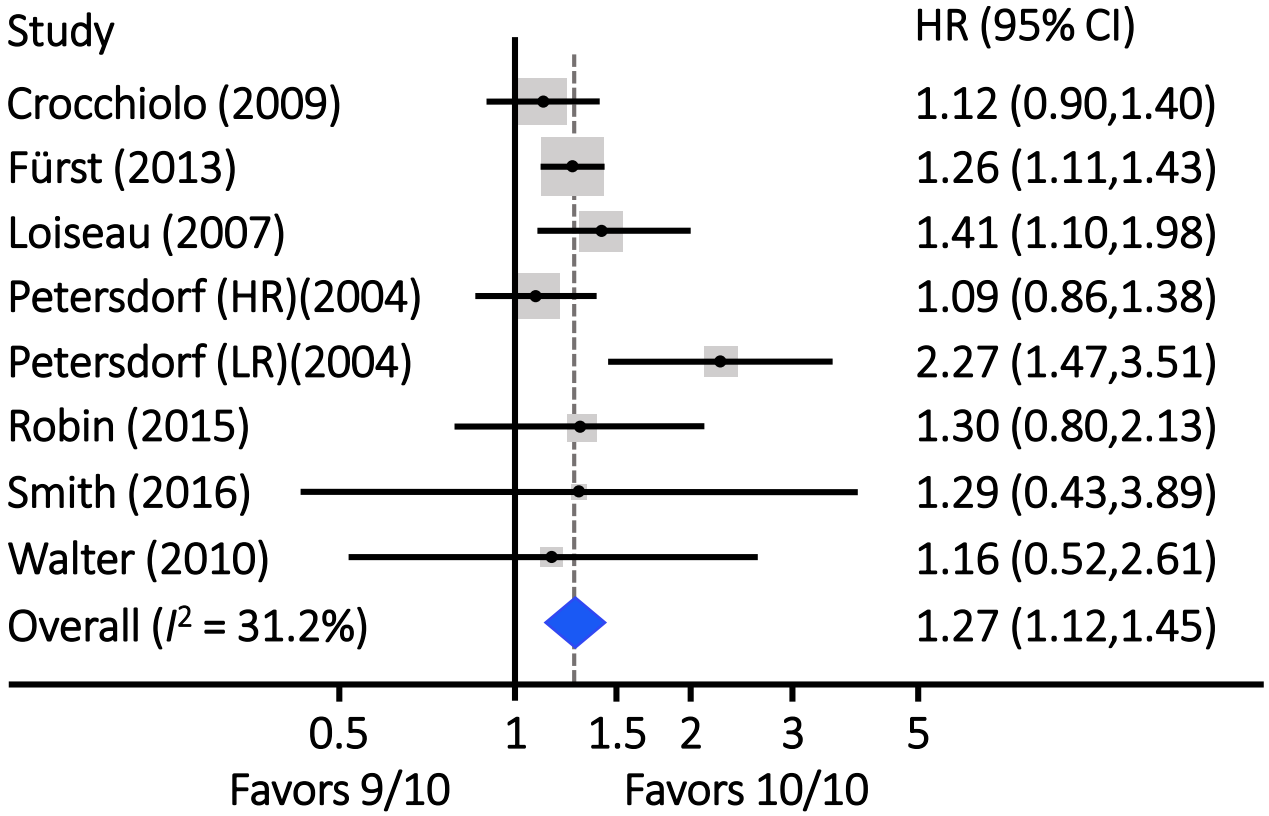
Chance and Outcome 9/10 MMUD



Kekre N et al. Am J Hematol. 2016 Jun;91(6):551-5

Chance and Outcome 9/10 MMUD



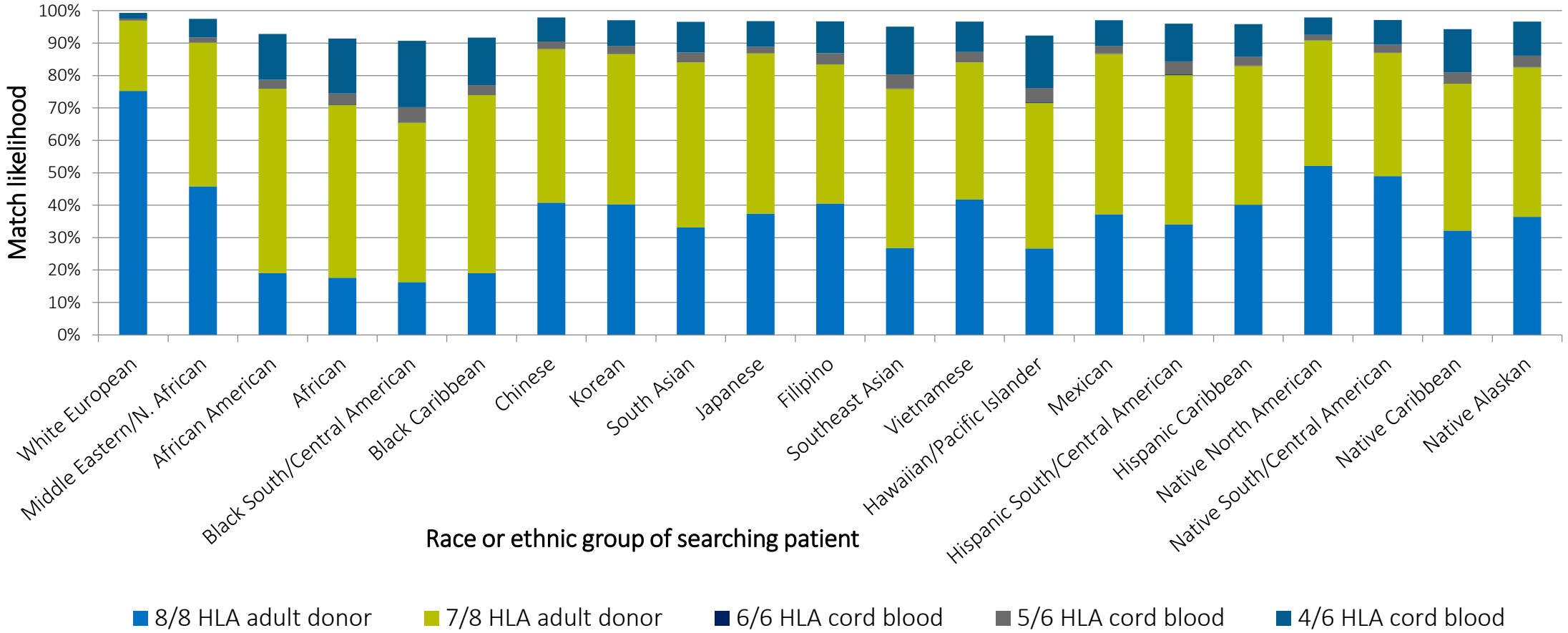


Kekre N et al. Am J Hematol. 2016 Jun;91(6):551-5

Cord blood transplantation

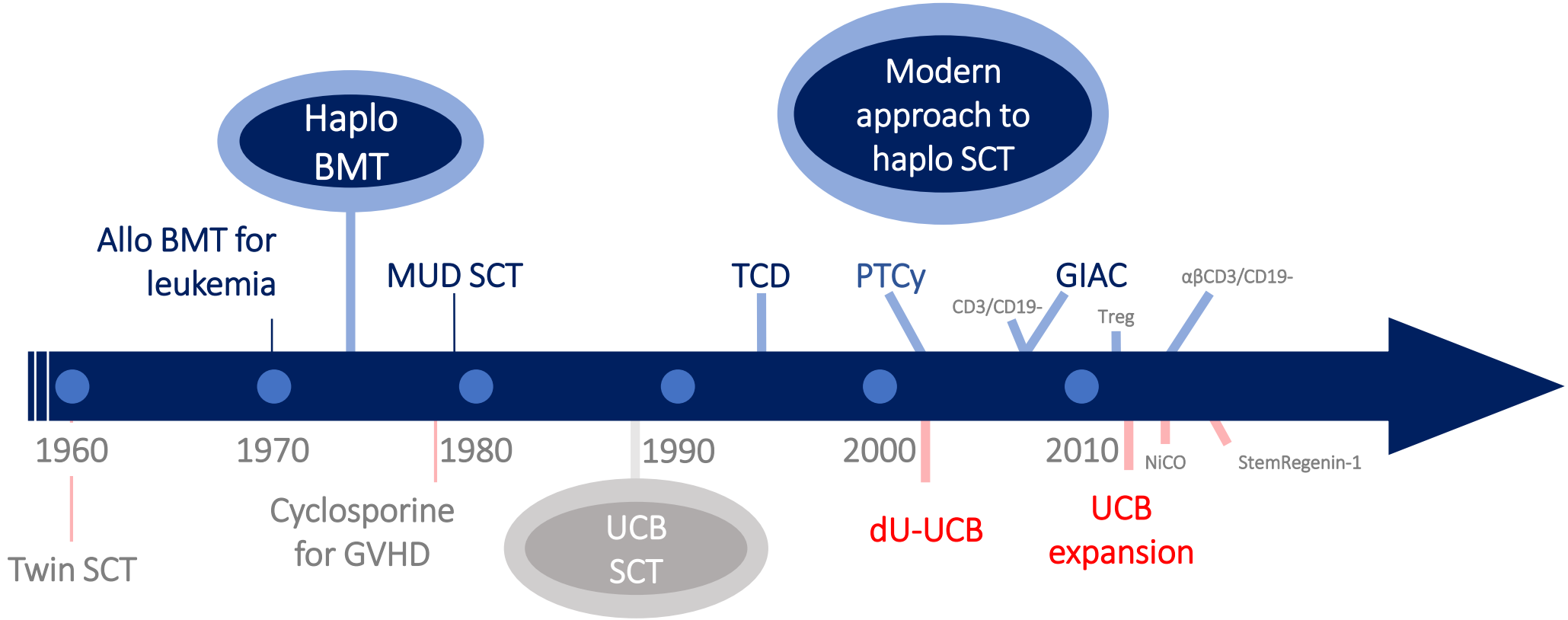
- **Advantages**
  - Readily available
  - Increased availability for minorities
  - Decreased transmission of viruses (i.e. CMV)
  - Greater degree of HLA mismatch allowed
- **Disadvantages**
  - One unit rescues one patient/no DLI
  - Theoretical risk of genetic disease transmission
  - Theoretical risk of maternal cell contamination (GVHD)
  - Slow engraftment
  - Expensive

Likelihood of Finding URD or CB when searching adult donor, then cord blood



Gragert L, et al. N Engl J Med. 2014; 371(4): 339-48

Journey of HLA haploidentical SCT



Liu JH et al. Curr Opin Hematol. 2018 Mar;25(2):103-111

Haploidentical SCT: Tug the war (Fighting of HLA disparity)

Rejection

Recipient

GVHD

Donor

Early Results

MISMATCHED FAMILY DONORS FOR BONE-MARROW TRANSPLANTATION AS TREATMENT FOR ACUTE LEUKAEMIA

R. L. POWLES
H. E. M. KAY
H. M. CLINK
A. BARRETT
M. H. DEPLEDGE
J. SLOANE
H. LUMLEY
S. D. LAWLER
G. R. MORGENSTERN
T. J. MCELWAIN
P. J. DADY
B. JAMESON
J. G. WATSON
M. LEIGH
D. HEDLEY
J. FILSHIE
B. ROBINSON

Leukaemia Unit, Royal Marsden Hospital and Institute of Cancer Research, Sutton, Surrey

Patient	TBI dose (Gy)	Metho-trexate doses	Reconsti-tution	GvHD	Survival at Nov. 9, 1982 (days)	Cause of death (where applicable)
1	9·27	0	+	A	297	Leukaemia
2	9·36	0	+R	A/C	578	Virus/GvHD)
3	9·46	0	+	A	48	PO
4	9·20	0	+	..	30	PO
5	9·22	0	+	A	1035	Alive
6	10·02	0	+	A/C	987	Alive
7	9·53	0	+	A/C	965	Alive
8	10·08	0	+	A	12	PO
9	9·92	3	+	A	860	Alive
10	10·02	3	−R	Off CS-A	556	Leukaemia
11	9·74	3	+	A	130	Virus/(GvHD)
12	10·28	3	+	A	22	PO
13	9·94	3	+	A	727	Alive
14	9·95	3	+	A	97	Pneumonitis
15	10·11	3	+	..	629	Leukaemia
16	10·38	3	+	A	53	GvHD
17	12·03	3	+	A	60	CMV/IP
18	11·79	3	−R	..	30	PO
19	11·33	3	+	A	72	PO
20	10·07	3	−R	A	168	PO
21	9·72	2	±R	A	489	Alive
22	10·41	2	±R	A	153	PO
23	10·18	1	−R	..	29	Graft failure
24	10·00	0	+	A	125	Asthma
25	10·64	0	+	A	21	PO
26	9·79	0	±	A^{co}	15	PO
27	8·72	0	+	A/C	227	Leukaemia
28	9·14	0	−R	Off CS-A	300	Alive
29	9·68	0	−	A^{co}	14	PO
30	8·88	0	±R	A	202	Alive
31	*	0	+	A	202	Alive
32	*	0	+	A	51	PO
33	9·25	0	+	A^{co}	188	Alive
34	*	0	−R	A	132	Alive
35	* 9·11	0 0	−R R	.. ..	59	Graft failure

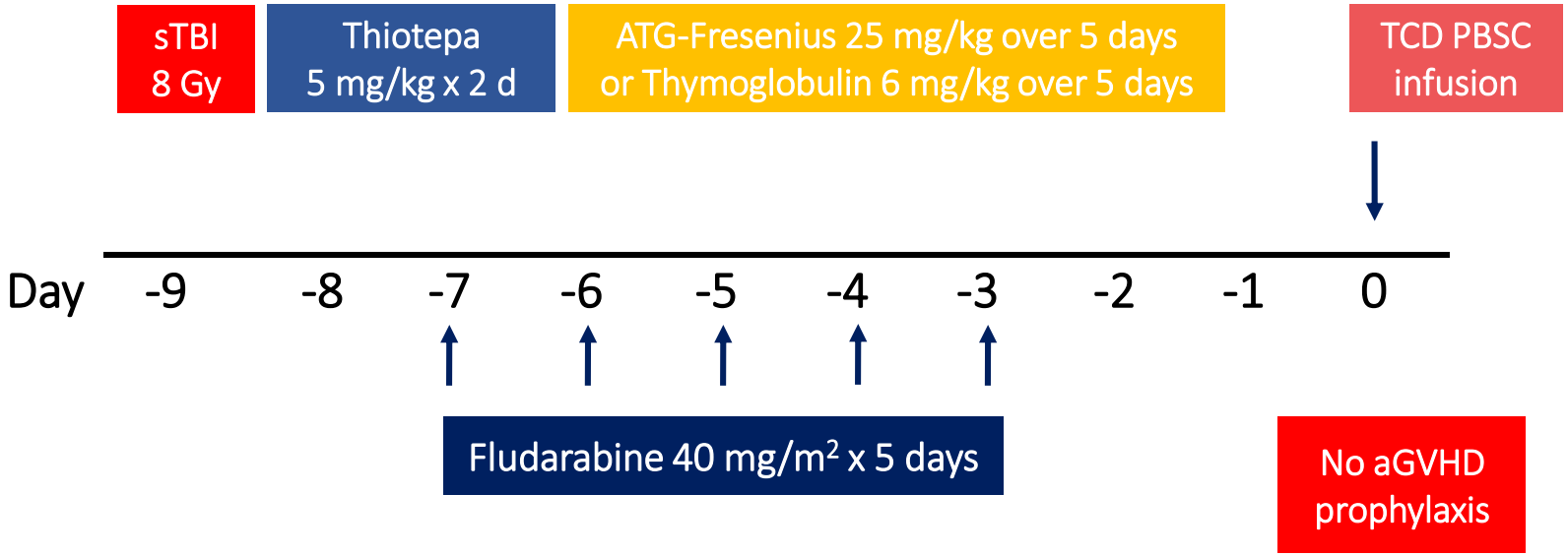
High rates of graft failure & GvHD

Powles RL et al. Lancet. 1983 Mar 19;1(8325):612-5

Approaches of modern HLA haploidentical SCT

- **T cell depleted graft**
  - Megadose HSCT approach with CD34+ selected PBSC graft **(Perugia, Italy)**
- **T cell repleted graft**
  - High-dose post-transplantation cyclophosphamide **(Hopkins)**
  - GIAC protocol **(China)**

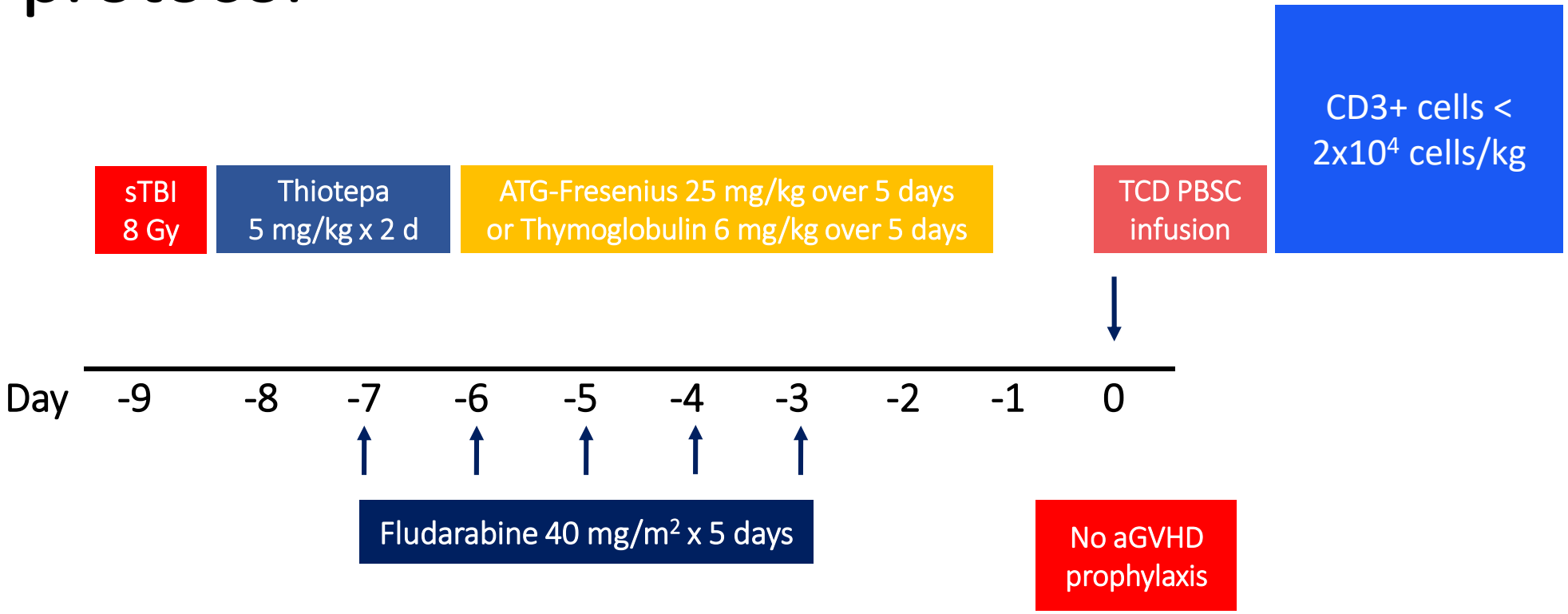
T cell Depleted Haploidentical Transplantation: Perugia protocol



- Megadose T cell depleted CD34+ cells BM + G-CSF stimulated PBSC: Ensure engraftment
- 95% achieved engraftment with minimal aGVHD & cGVHD (No GVHD prophylaxis)

Aversa F et al. Blood. 1994 Dec 1;84(11):3948-55
Aversa F et al. N Engl J Med. 1998;339:1186-93

T cell Depleted Haploidentical Transplantation: Perugia protocol



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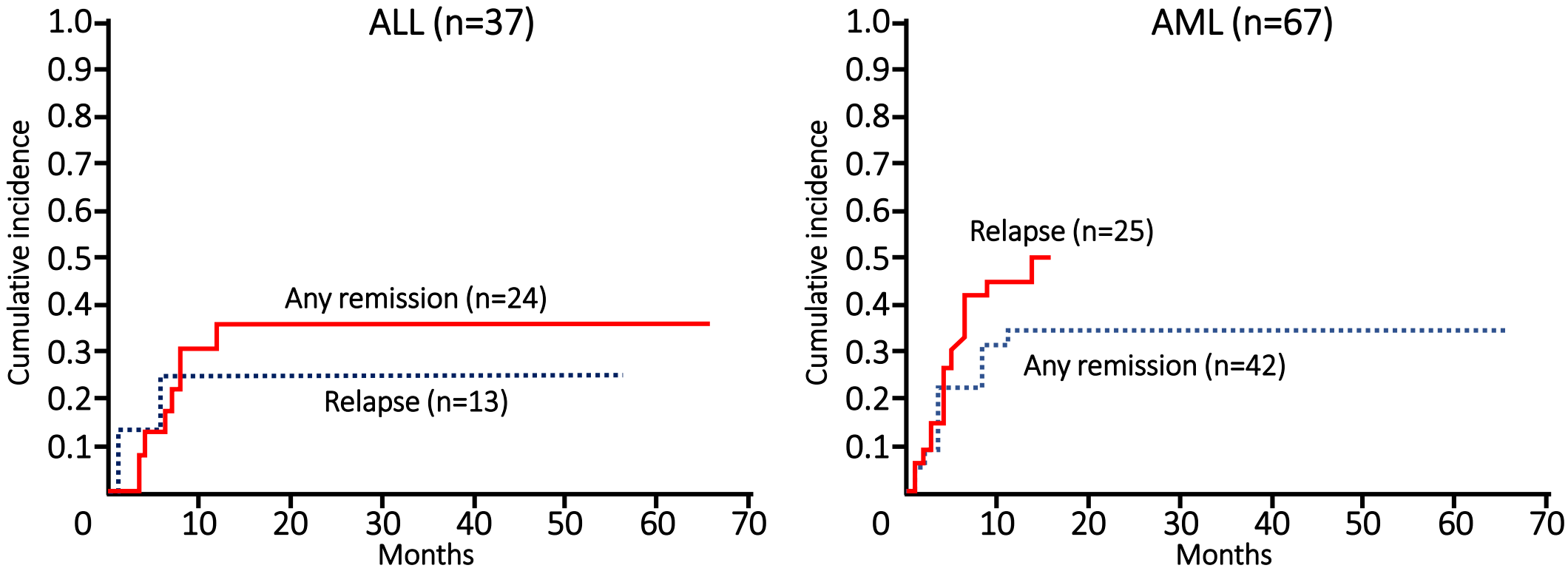
Aversa F et al. Blood. 1994 Dec 1;84(11):3948-55
Aversa F et al. N Engl J Med. 1998;339:1186-93

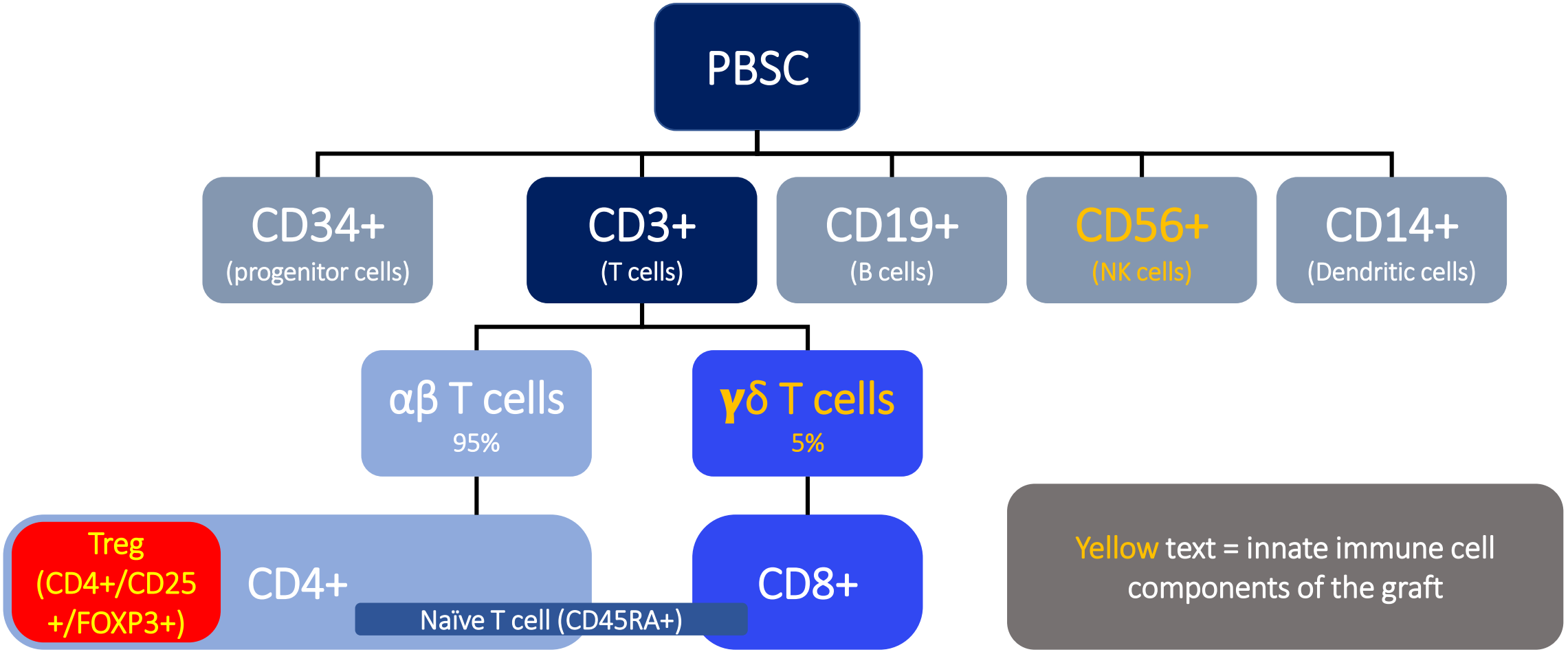
TCD haploidentical transplant: Non Relapse mortality



- 38/101 death in remission: Infection is the leading cause of death
- Low aGVHD and cGVHD but high transplant related mortality

Aversa F et al. J Clin Oncol. 2005 May 20;23(15):3447-54

Immune cell components of graft



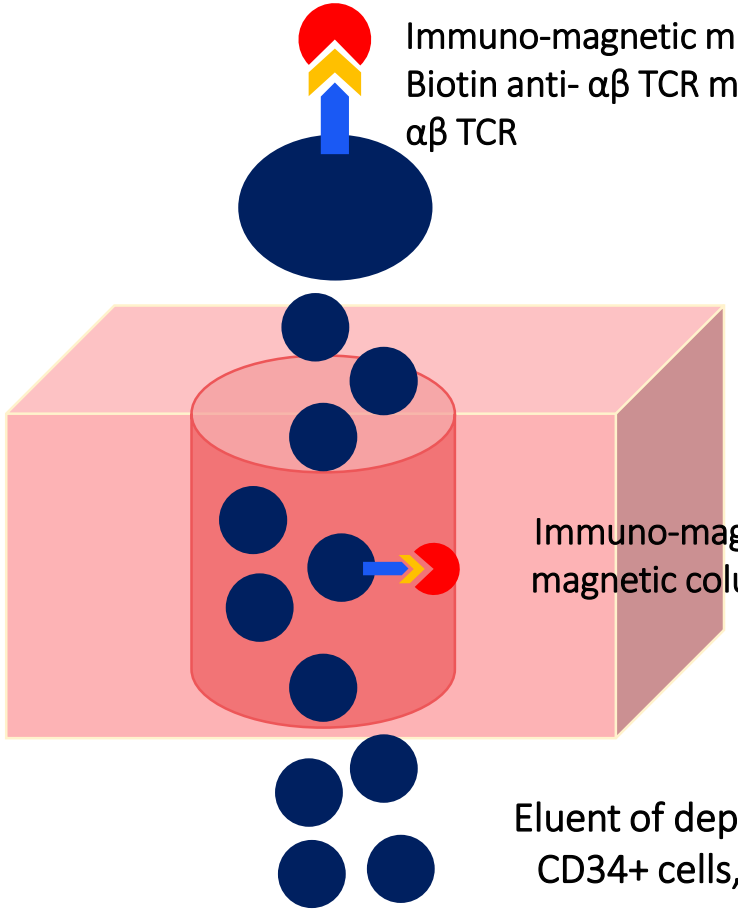
Graft manipulation strategy in TCD haplo SCT

- **Depletion (targeted negative selection)**
  - Pan T-cell depletion
  - Lymphocyte subset depletion
    - CD8+ T-cell depletion
    - CD3/CD19 cell depletion
    - αβ T-cell/CD19 cell depletion (Germany-Italy Approach)
    - Naïve T-cell depletion
- **Inclusion (positive selection/expansion → add back):** Treg cells, Tcon cells, NK cells, **γ**δ T cells

CliniMACs cell separator system

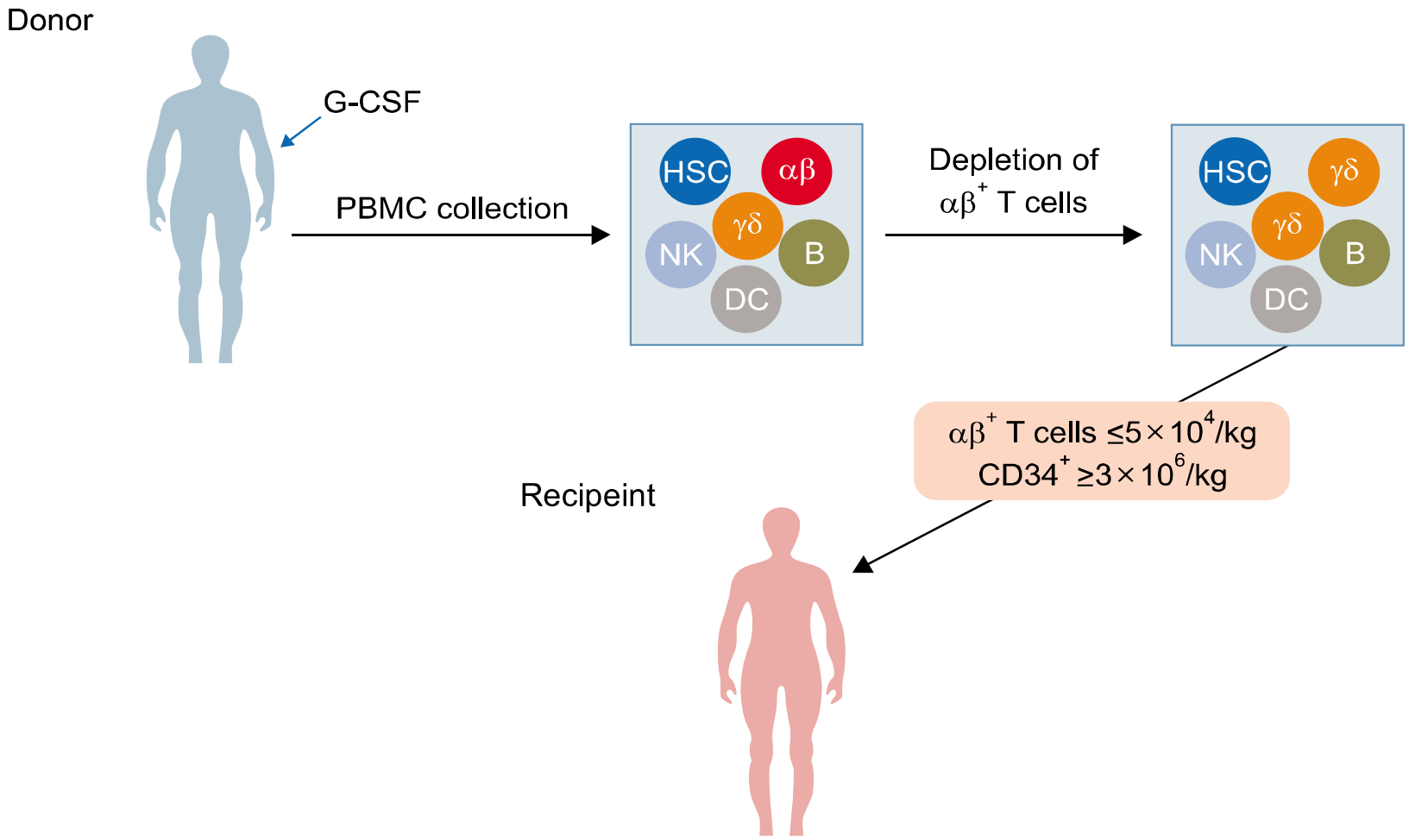
CliniMACs Plus

Magnetic column



CliniMACs cell separator system

CliniMACs Plus



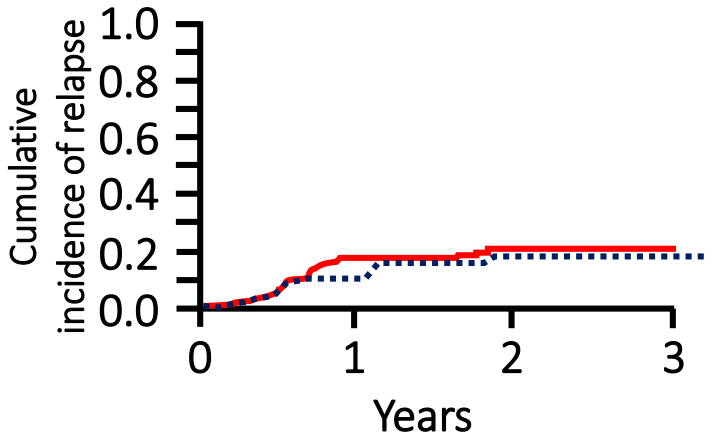
αβ T-cell/CD19 cell depleted haploidentical SCT

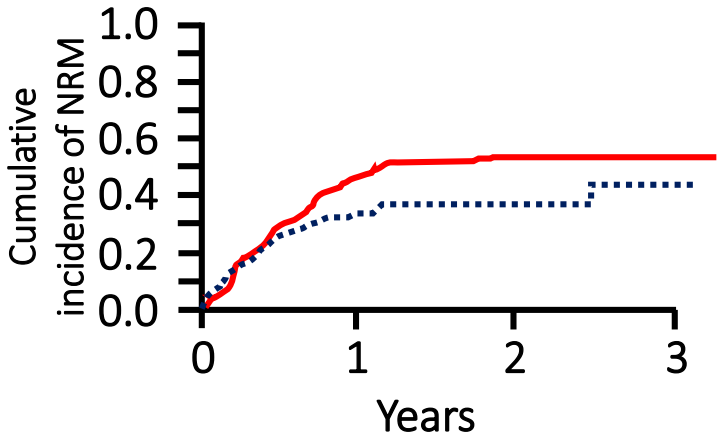
	n	Graft	Graft failure	Relapse	aGVHD	cGVHD	NRM	DFS/EFS	OS
Handgretinger (2012)	25	PBSC	12%	13	36%	28%	16%	N/A	N/A
Bertaina (2014)	23	PBSC	17%	N/A	13%	0% (18 mo)	9%	91% (2 yrs)	N/A
Balashov (2015)	37	PBSC	27%	N/A	22%	5% (15 mo)	3%	N/A	97% (1 yr)

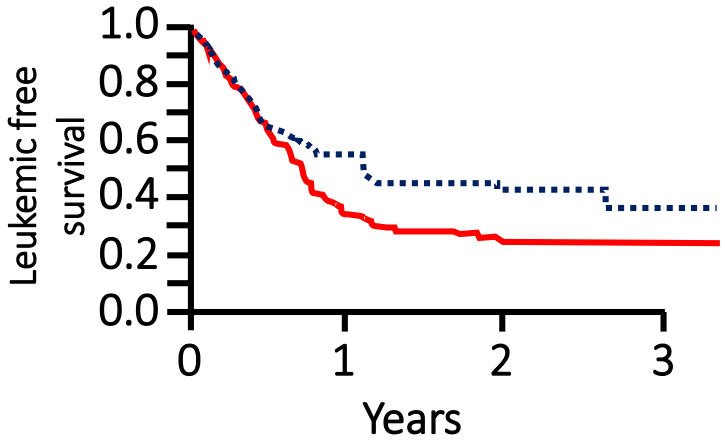
- **γ**δ T cells & NK cells exert anti-leukemic effects (GVL but less likely GVHD)
  - Decrease NRM but more GVHD
- Also use in non-malignant hematologic diseases

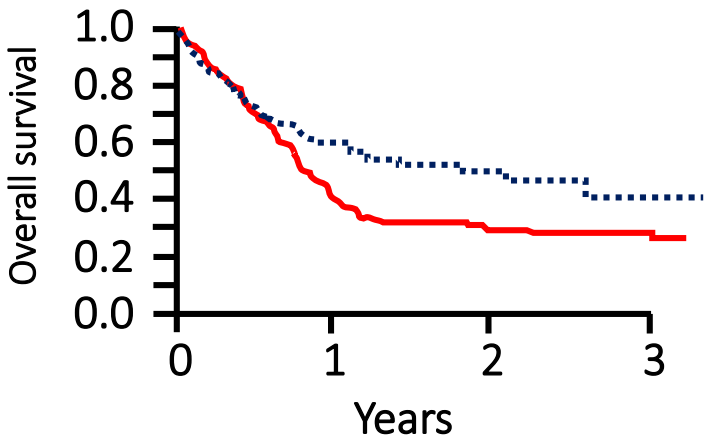
Saad A and Lamb LS. Bone Marrow Transplant. 2017 Sep;52(9):1241-48

Evolution of TCD haploidentical HSCT









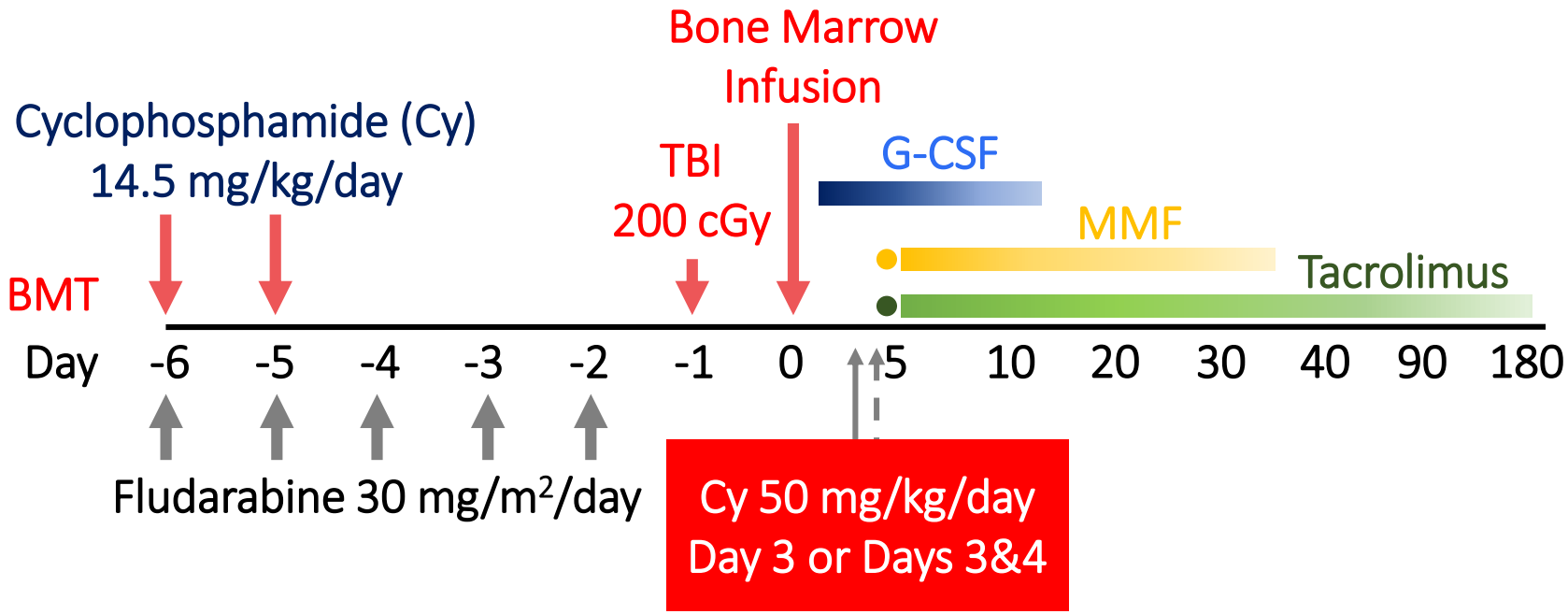
2005-2011

2012-2015

ClinicMACs Technology

Sestili S et al. Cancer. 2018 Feb 22. doi: 10.1002/cncr.31310

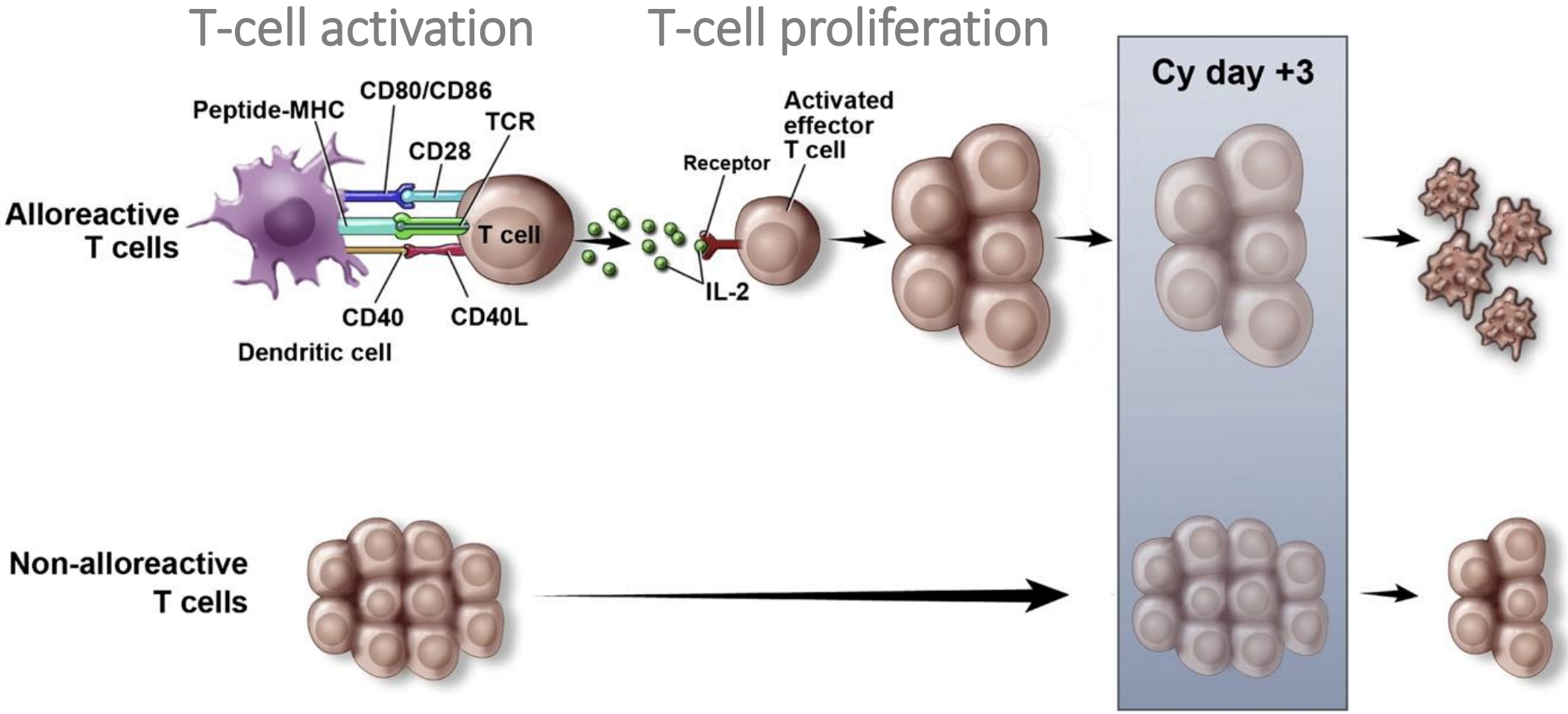
T cell Repleted Haploidentical Transplantation: Hopkins Protocol



- Mouse model data: Induced T cell tolerance
- Initial data comparing: Post-Cy Day +3 vs Day +3,+4
- More cGVHD in Day +3 cohort

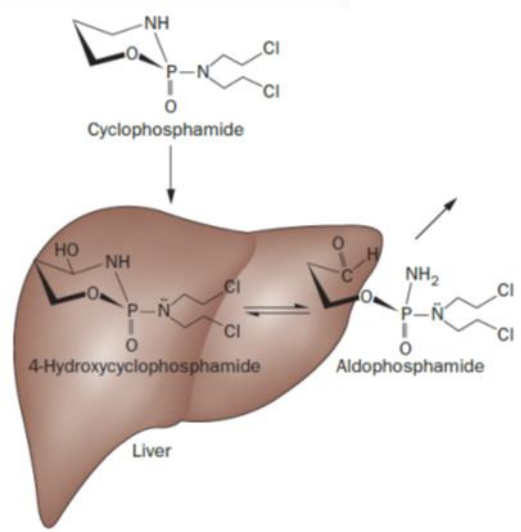
Luznik L et al. Biol Blood Marrow Transplant. 2008 Jun;14(6):641-50

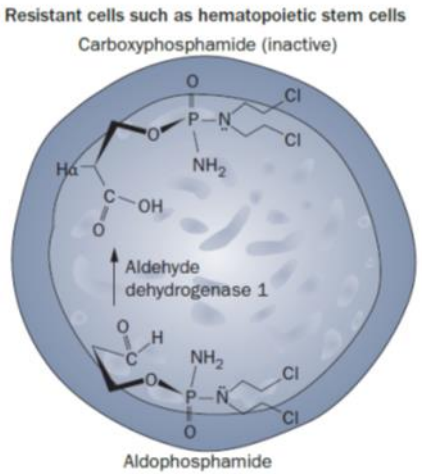
Post-Transplant Cyclophosphamide (PTCy)



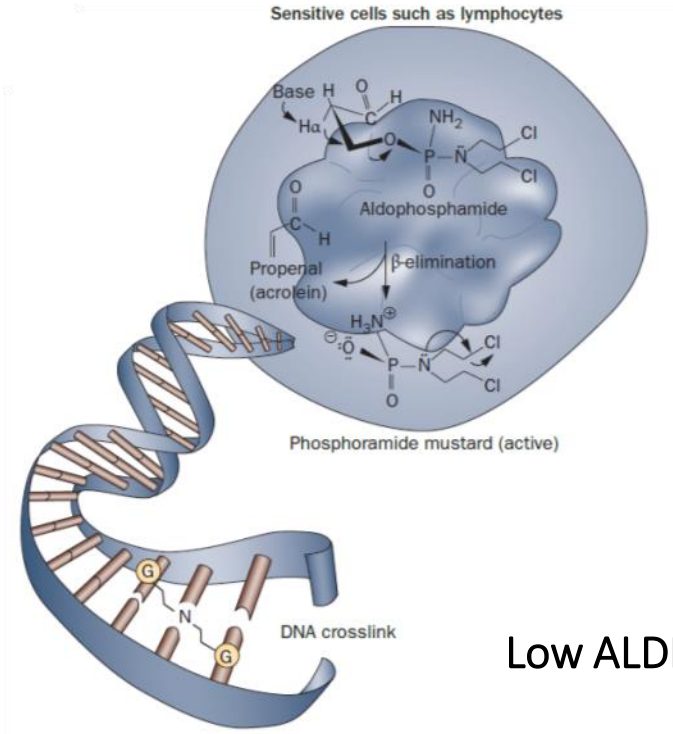
Luznik L et al. Biol Blood Marrow Transplant. 2008 Jun;14(6):641-50

Selective effect of cyclophosphamide





High ALDH

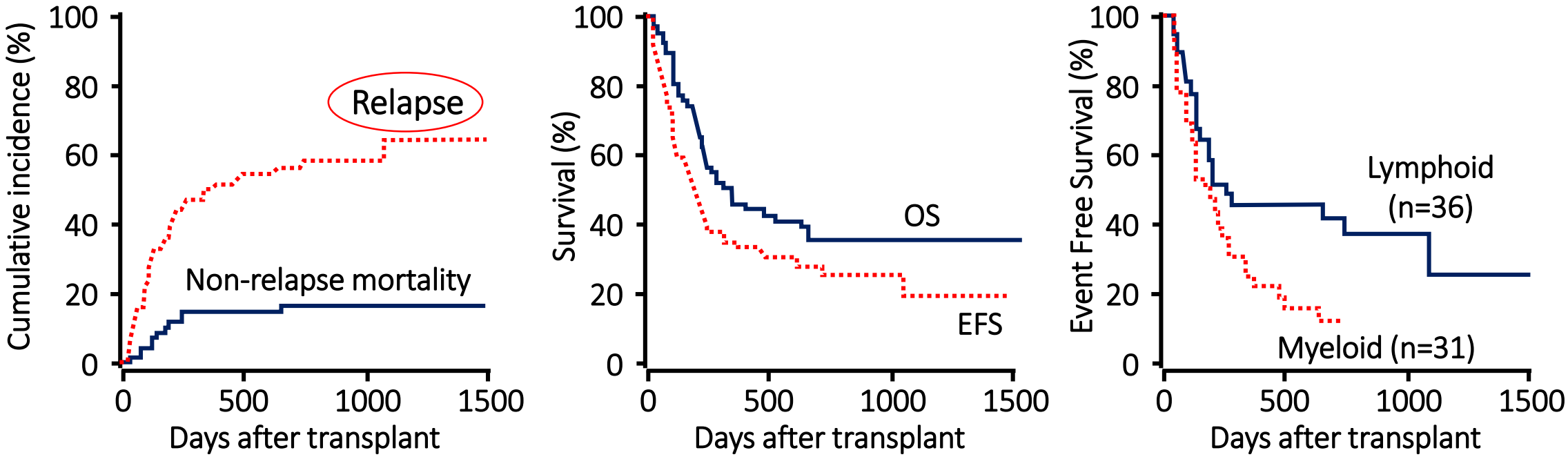


Low ALDH

- Lymphocytes show heterogeneous ALDH1 expression: Most T cells, esp. those proliferating, express low levels of ALDH1 and are sensitive to Cy
- Memory T cells, like other stem-like cells, express high levels and are resistant to Cy

- Low ALDH in alloreactive T cell
- High ALDH in Treg and naïve T cell

Outcome Post-transplant cyclophosphamide



- Very low non-relapse mortality but concerning high relapse rate
- High risk disease index patients' population: Adjusted RDI → No difference in relapse

Luznik L et al. Biol Blood Marrow Transplant. 2008 Jun;14(6):641-50

HLA haploidentical transplant with PTCY

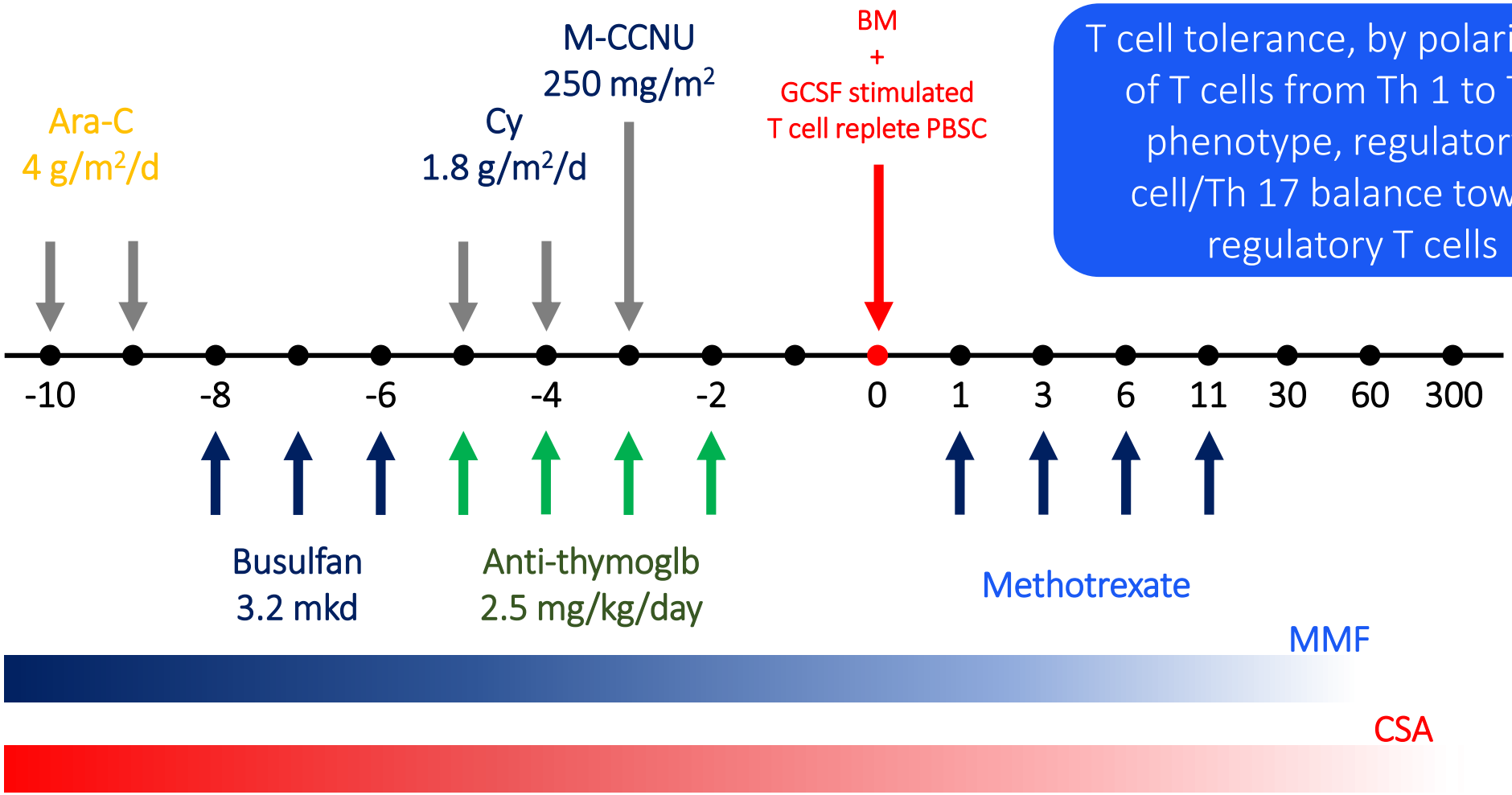
Author	Year	Size	Source	Disease	Condition	aGvHD (2-4)	aGvHD (3-4)	cGvHD	Engrafted	OS (year)	NRM (year)	Relapse (year)
Luznik *et al.*	2008	68	BM	All	RIC	34%	6%	13%	87%	36% (2)	15% (1)	51% (1)
Brunstein *et al.*	2011	50	BM	All	RIC	32%	0%	13%	98%	62% (1)	7% (1)	45% (1)
Grosso *et al.*	2011	27	PBSC	All	MA	64%	8%	16%	92%	54% (1)	22% (1)	32% (1)
Solomon *et al.*	2012	20	PBSC	All	MA	30%	10%	35%	100%	69% (1)	10% (1)	40% (1)
Ciurea *et al.*	2012	32	BM	AML	All	20%	5%	7%	94%	64% (1)	16% (1)	50% (1)
Bashey *et al.*	2013	53	All	All	MA	30%	11%	38%	98%	64% (2)	7% (2)	33% (2)
Raiola *et al.*	2014	92	BM	All	All	14%	4%	15%	99%	52% (4)	17% (4)	35% (2.5)
Castagna *et al.*	2014	69	All	All	MA	27%	6%	13%	90%	68% (2)	18% (2)	38% (2)
Di Stasi *et al.*	2014	32	BM	AML/MDS	RIC	29%	0%	11%	97%	77% (1)	24% (1)	33% (1)
Raj *et al.*	2014	55	PBSC	All	RIC	53%	8%	18%	96%	48% (2)	23% (2)	28% (2)
Sugita *et al.*	2015	31	PBSC	All	RIC	22%	3%	15%	87%	45% (1)	23% (1)	45% (1)
Ciurea *et al.*	2015	192	All	AML	All	18%	5%	32%	91%	45% (3)	9% (3)	46% (1)
Solomon *et al.*	2015	30	PBSC	All	MA	43%	23%	56%	100%	78% (2)	3% (1)	24% (2)
Kasamon *et al.*	2015	271	BM	All	RIC	32%	3%	10%	94%	46% (3)	12% (1)	46% (3)
Blaise *et al.*	2016	31	All	All	All	23%	10%	13%	97%	70% (2)	10% (2)	31% (2)
Kanate *et al.*	2015	185	All	Lymphoma	RIC	27%	8%	15%	98%	60% (3)	17% (3)	36% (3)

- Myeloablative regimens decreased relapse but increased NRM → No difference in overall survival
- Subsequent data on PBSC graft: No difference in outcome

Modified Hopkins Protocol

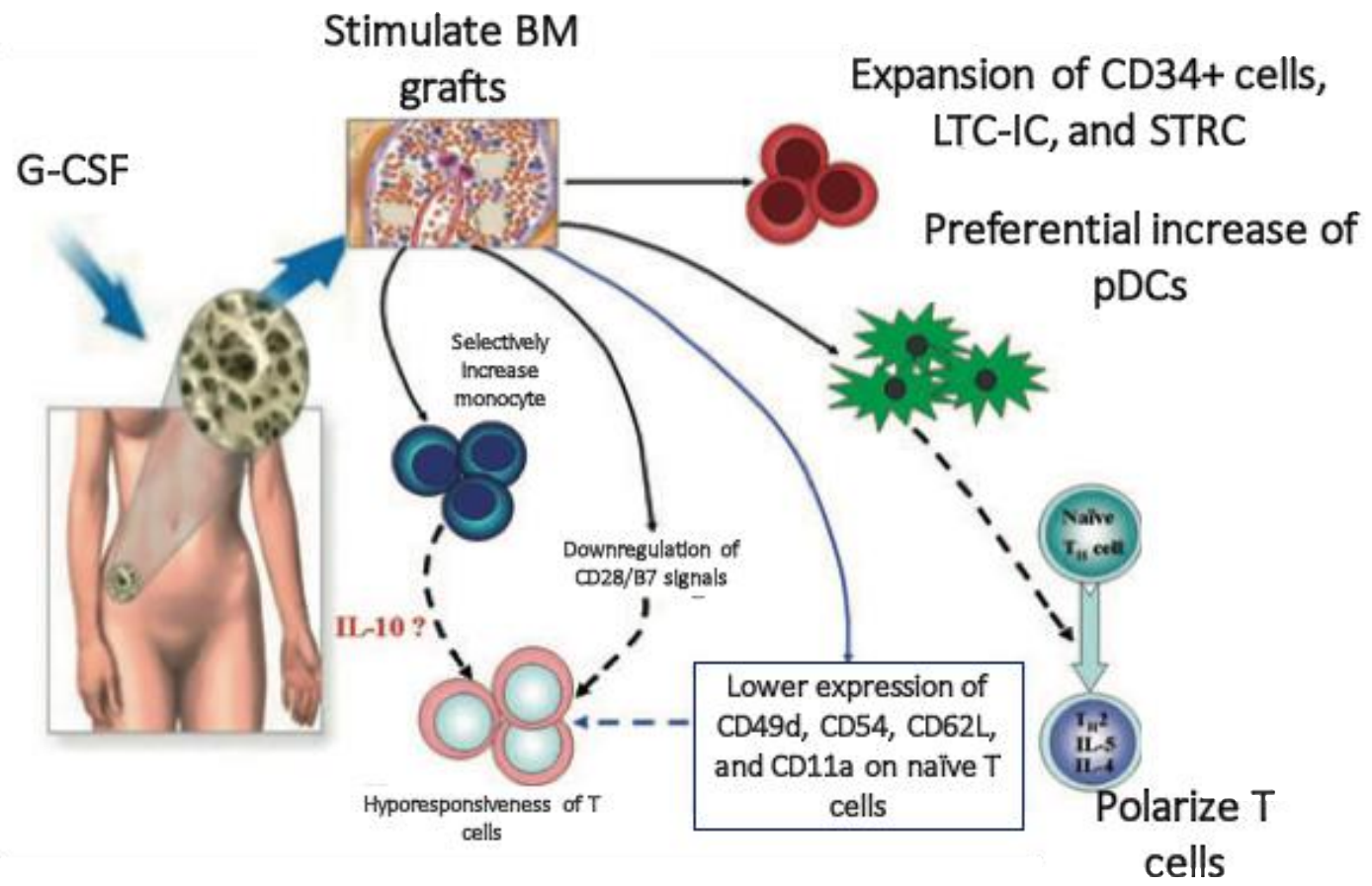
- Myeloablative regimens
  - Thiotepa-Busulfan-Fludarabine or Fludarabine-TBI with bone marrow graft
    - Prophylaxis with CSA (D-1) + MMF (D 0) Post-transplant CTX (+3, +5)
  - Treosulfan-Fludatabine with PBSC graft
    - ATG + MMF + Rapamycin + CTX

T cell Repleted Haploidentical Transplantation: GIAC Protocol



Huang XJ et al. Bone Marrow Transplant. 2006 Aug;38(4):291-7

Effects of G-CSF on Bone Marrow in Healthy Donors



- Induce immune cells alteration
- T cell polarization, from Th1 to Th2,
- Induce T cell hyporesponsive- ness
- Downregulation of adhesion molecule expression

HuangXJ, et al. Clin Transplant 2011: 25: 13–23

	# Patients	NMA/ MA	BM/PB/ Both	Engraftment (%)	aGVHD II-IV (%)	cGVHD (%)	1 yr TRM (%)	DFS (%)	Relapse (%)
Huang 2006	171	4/167	0/0/171	100	55	21	19-31	42-68 (2y)	12-39 (2y)
Huang 2009	250	0/250	0/0/250	99	45	54	19-51	24-71 (3y)	11-49 (3y)
Luo 2014	99	0/99	0/99/0	100	42	41	30	58 (3y)	14 (5y)
Fu 2014	115	0/115	0/0/115	97-100	32-40	52-61	12-16	56-58	26-32
Gao 2014	178	0/178	0/0/178	100	39-42	39-53	-	32-55 (2y)	38-60
Di Bartoloneo 2013	80	61/16	80/0/0	91	24	17	36	38 (5y)	28 (5y)
Peccatori 2015	121	0/121	0/121/0	-	35	47	31	20 (3y)	48 (3y)
Lee 2011	83	83/0	0/83/0	100	20	34	17	56 (~2y)	-

Montoro J et al. Leuk Lymphoma. 2016 Aug;57(8):1766-75

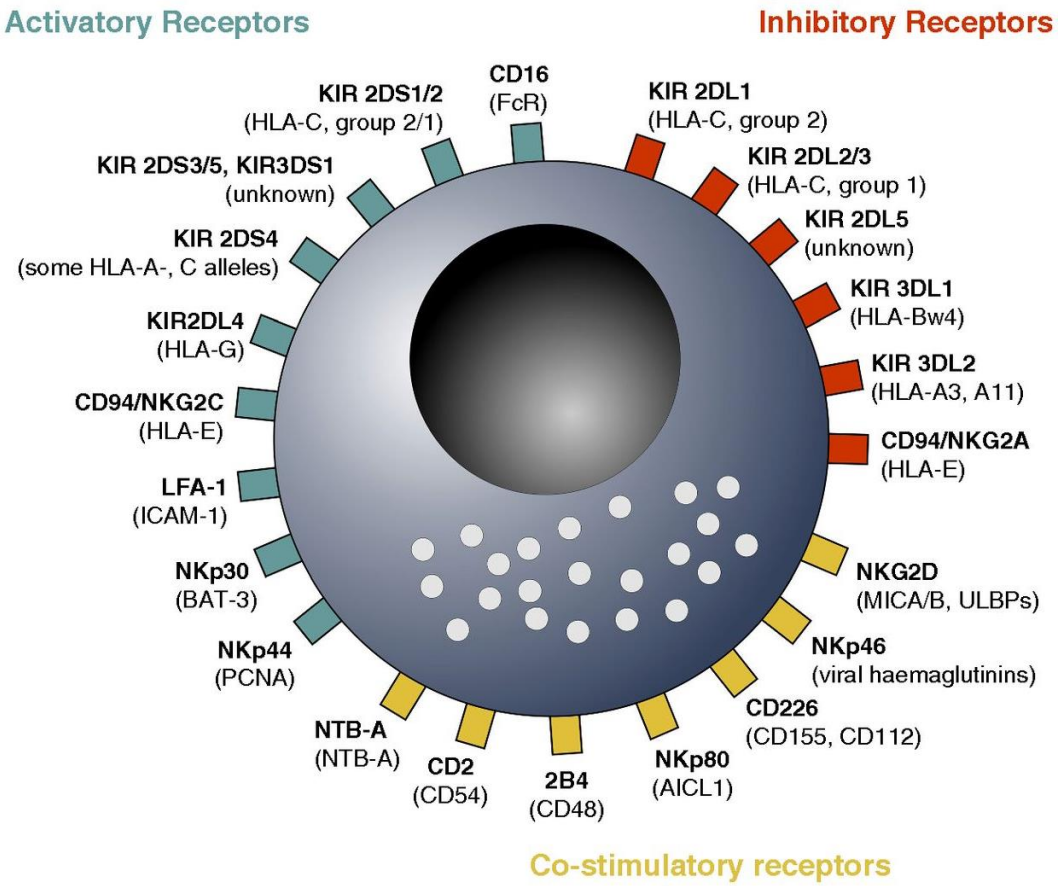
Comparison between haploidentical SCT approach

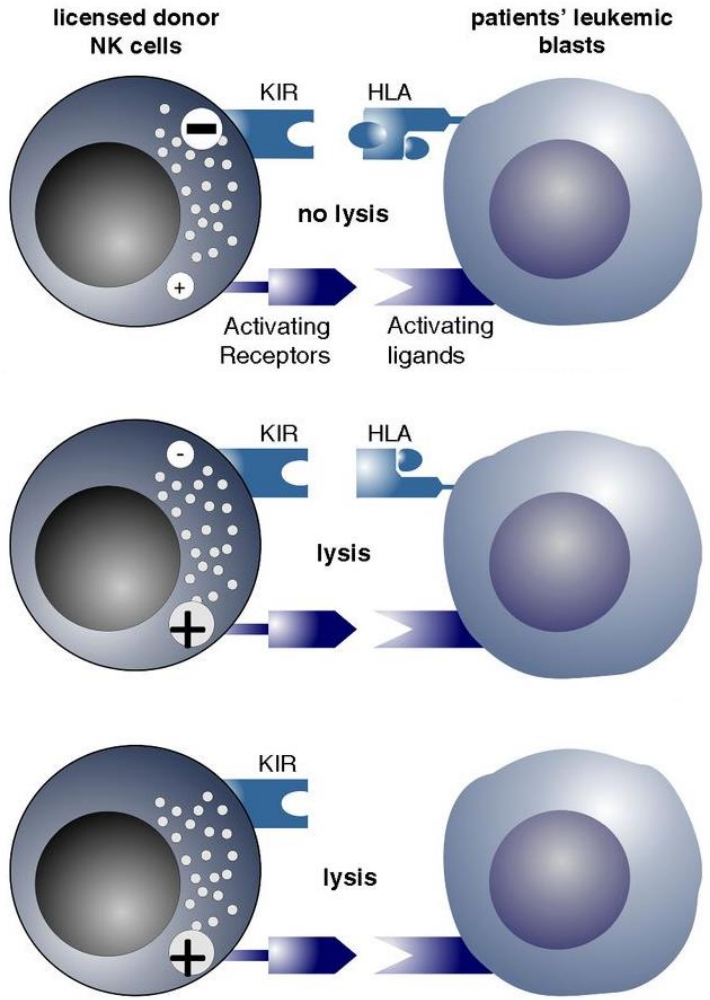
Clinical outcome	T cell depletion	GIAC protocol	PTCy
Engraftment	2-3	1	2-3
Acute GVHD	1	3	2
Chronic GVHD	1-2	3	1-2
Infection/Deaths from infection	3	2	1
Nonrelapse mortality	3	2	1
Relapse	2-3	1	2-3

Kanakry CG et al. Nat Rev Clin Oncol. 2016 Jan;13(1):10-24

Donor selection in haploidentical SCT

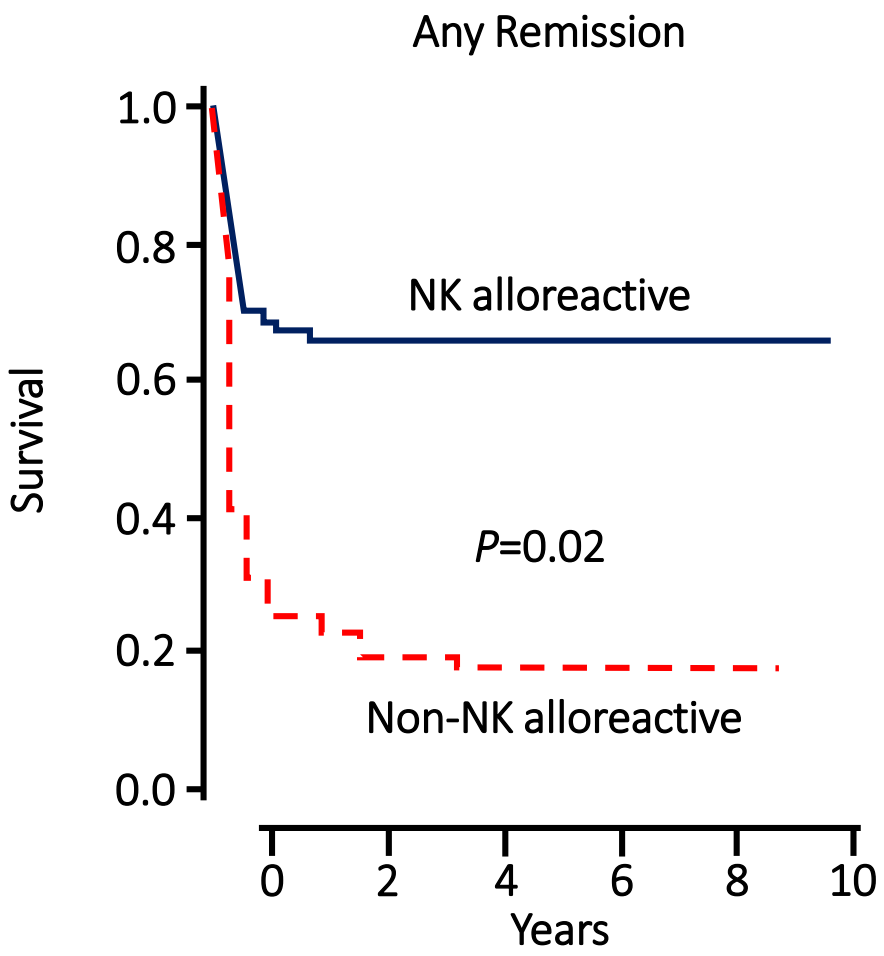
NK cell effect on anti-leukemic effect: Complex

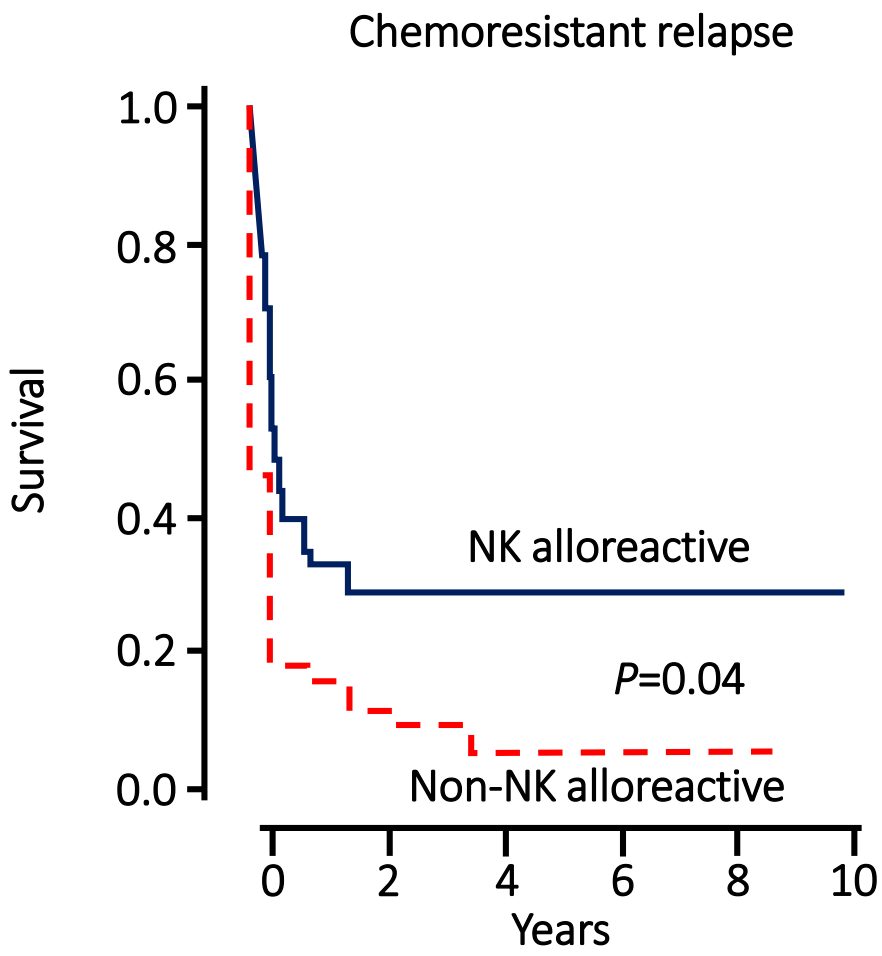




Handgretinger R, Lang P, André MC, Blood. 2016 Jun 30;127(26):3341-9

NK alloreactive effect on haploidentical SCT

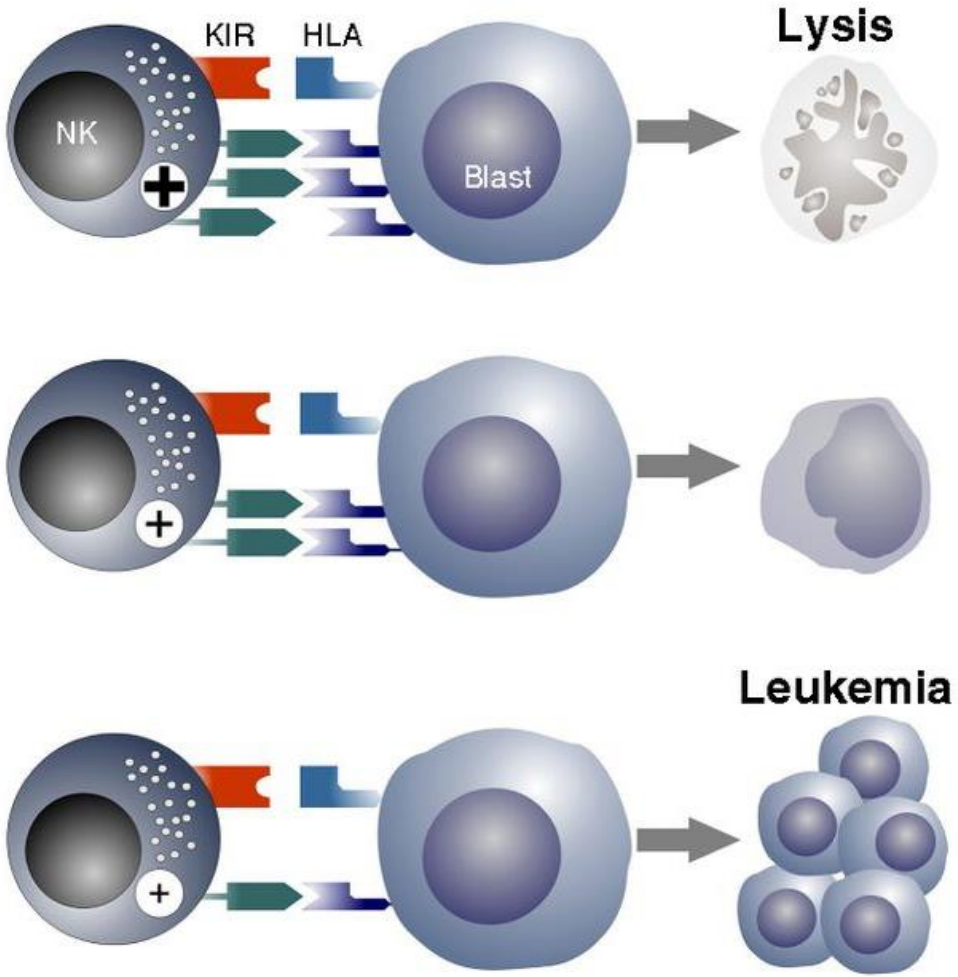


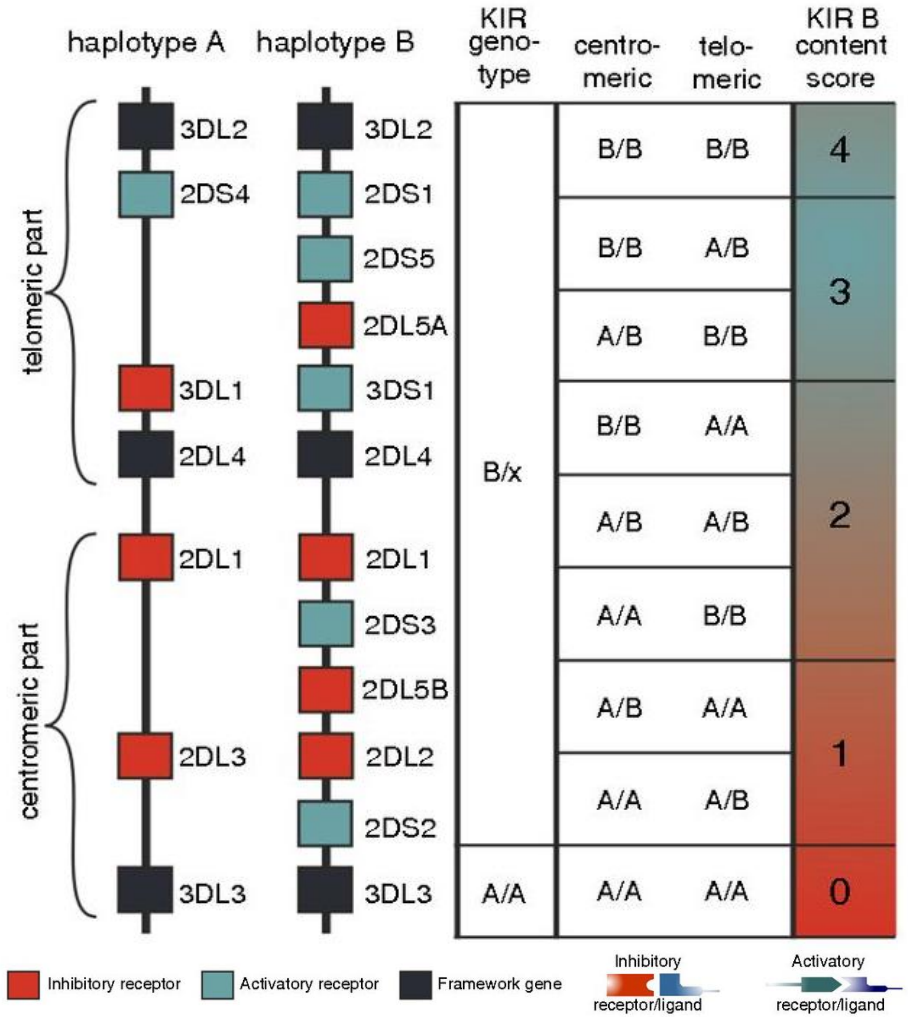


- Less relapse
- Less GvHD
- Better survival

Ruggeri L et al. Blood. 2007 Jul 1;110(1):433-40

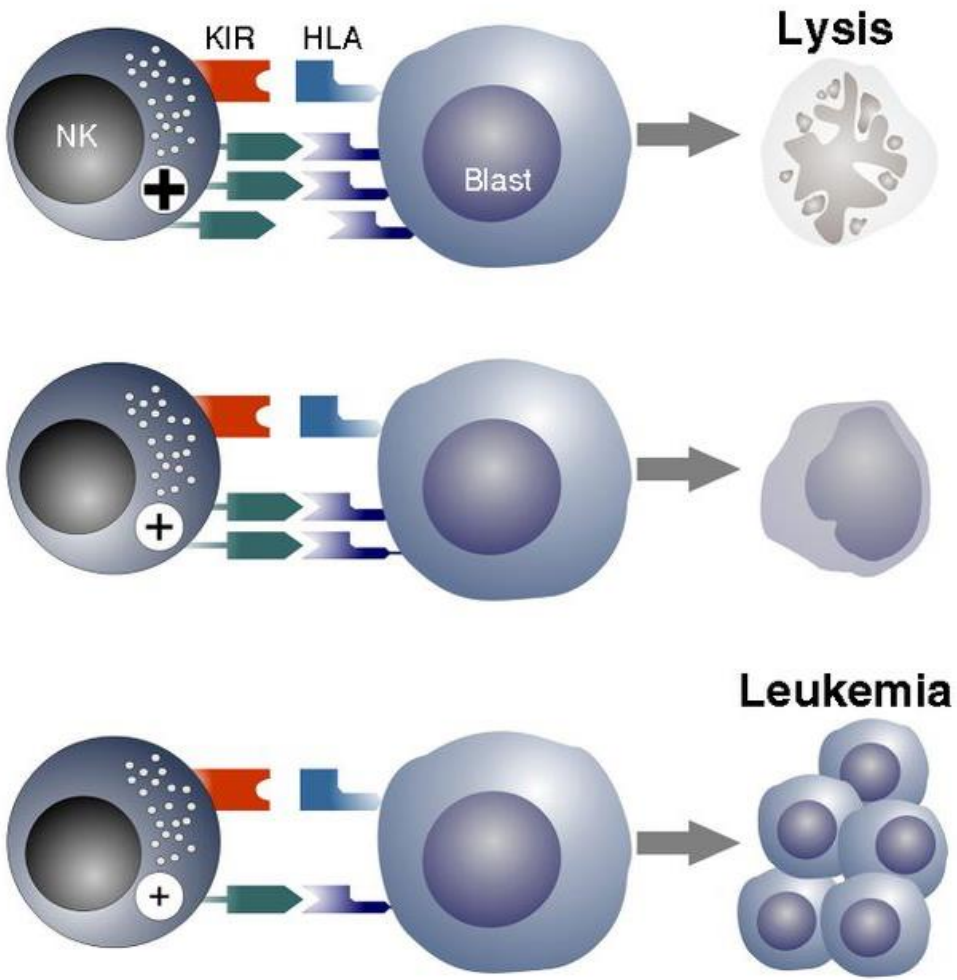
NK cell KIR phenotype in haploidentical HSCT

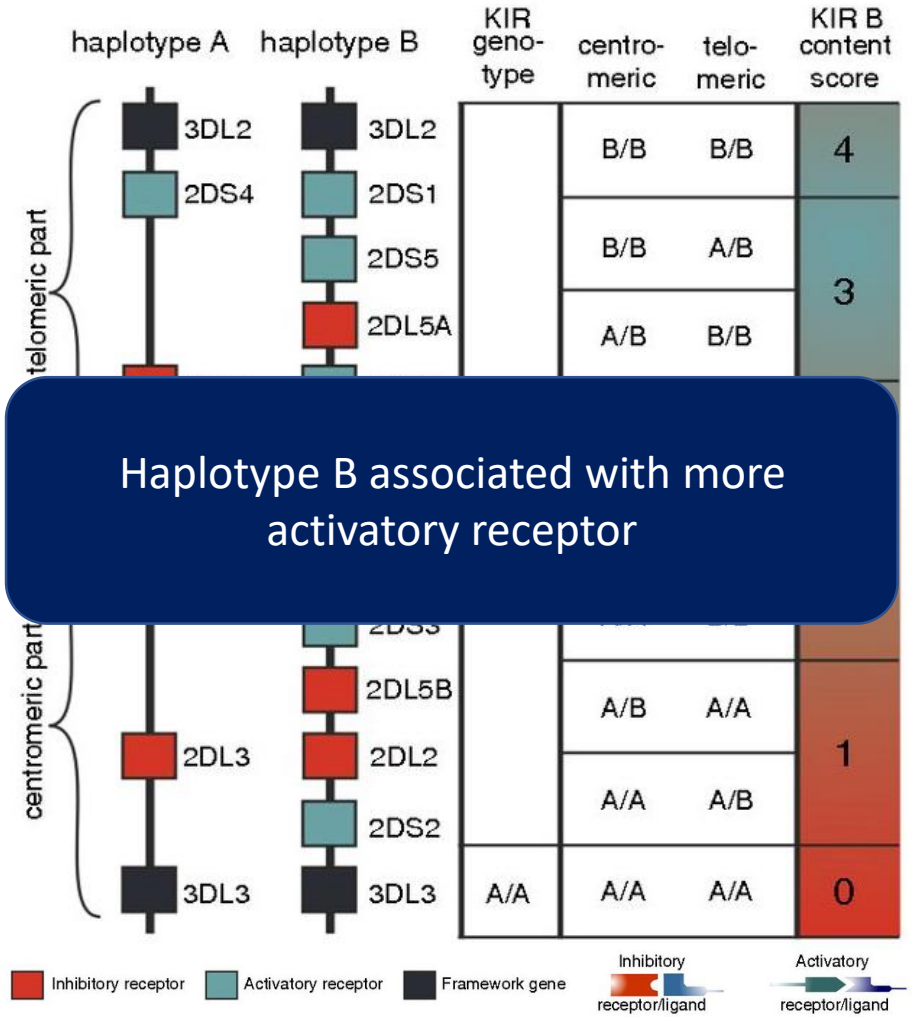




Handgretinger R, Lang P, André MC, Blood. 2016 Jun 30;127(26):3341-9

NK cell KIR phenotype in haploidentical HSCT

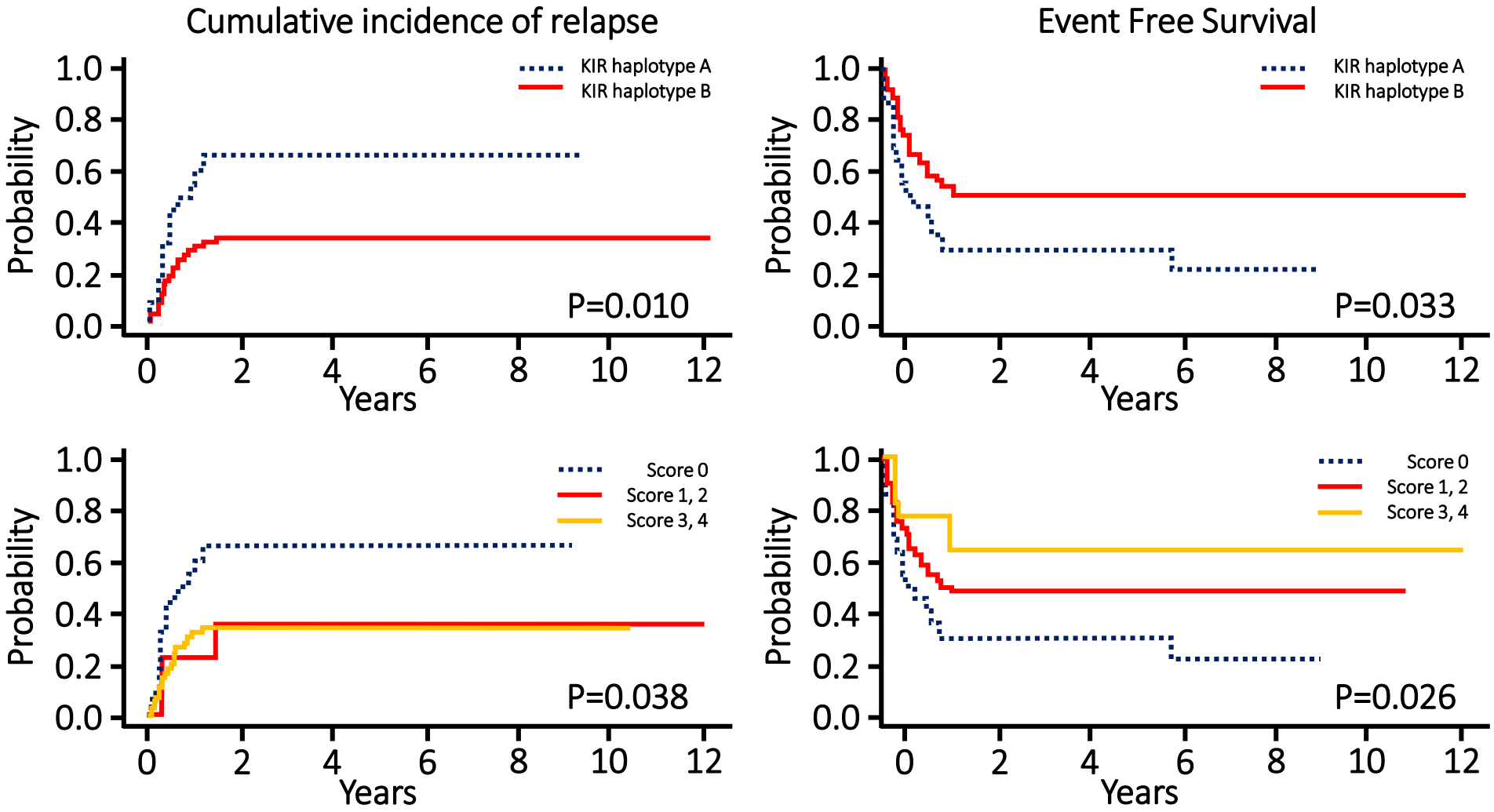




Haplotype B associated with more activatory receptor

Handgretinger R, Lang P, André MC, Blood. 2016 Jun 30;127(26):3341-9

KIR B content score in haploidentical SCT



Oevermann L et al. Blood. 2014 Oct 23;124(17):2744-7

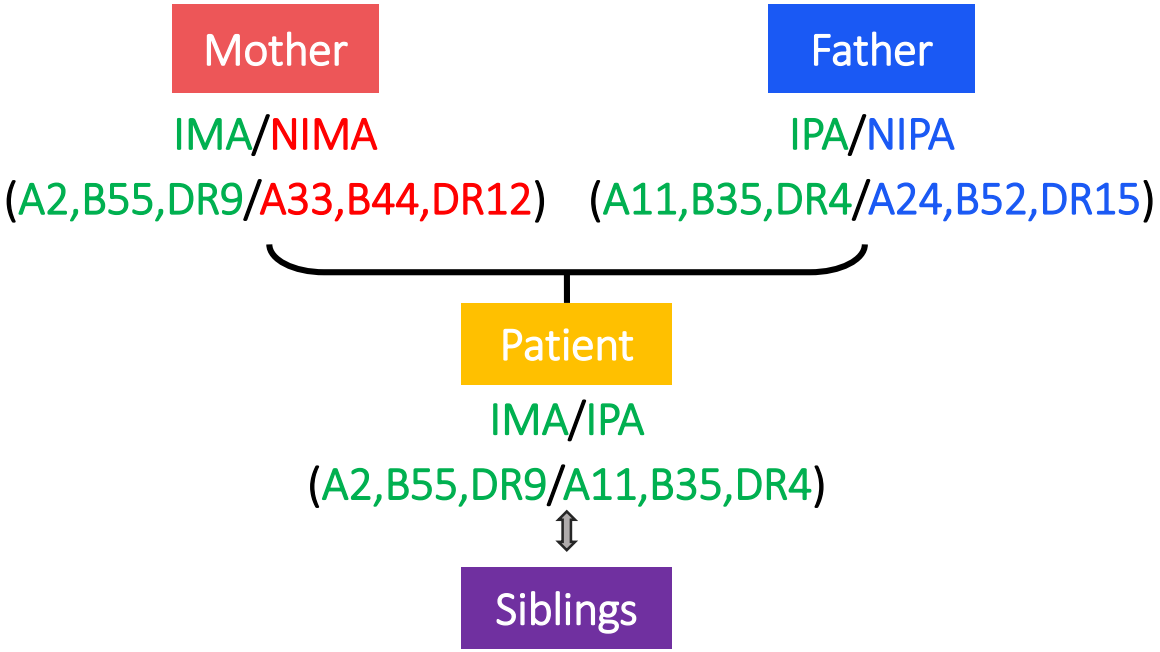
NK cell KIR phenotype in haploidentical SCT

	KIR/model	Observation	Disease	Treatment	Reference
Genetic associations	*KIR2DL2*	Increased frequency	AML/ALL	–	(Verheyden et al., 2004)
	KIR-S	Decreased frequency	ped. ALL	–	(Almalte et al., 2011)
	KIR-L / KIR-S	No association	ped ALL	–	(Babor et al., 2012)
Inhibitory KIR	Missing KIR ligand	Relapse ↓	ped. AML/ALL	Haploidentical	(Leung et al., 2004)
	Missing KIR Ligand	Survival ↑, Relapse ↓	AML/ALL	MSD HSCT	(Hsu et al., 2005)
	KIR ligand mismatch	Relapse ↓, Survival ↑	AML	Haploidentical	(Ruggeri et al., 2007)
	KIR3DL1	Survival ↓	Acute leukemia	Unrelated HSCT	(Gagne et al., 2009)
Stimulatory KIR	KIR2DS2	Survival ↓	AML (ALL)	MSD HSCT	(Cook et al., 2004)
	KIR3DS1	Survival ↓	Acute leukemia	Unrelated HSCT	(Gagne et al., 2009)
	KIR2DS1	Relapse ↓	AML	Unrelated HSCT	(Venstrom et al., 2012)
Haplotype structure	Group B	Relapse ↓ chronic GvHD ↑	Adult AML	Unrelated HSCT	(Cooley et al., 2009)
	Group B haplotype score	Relapse ↓	AML (ALL)	Unrelated HSCT	(Cooley et al., 2010)

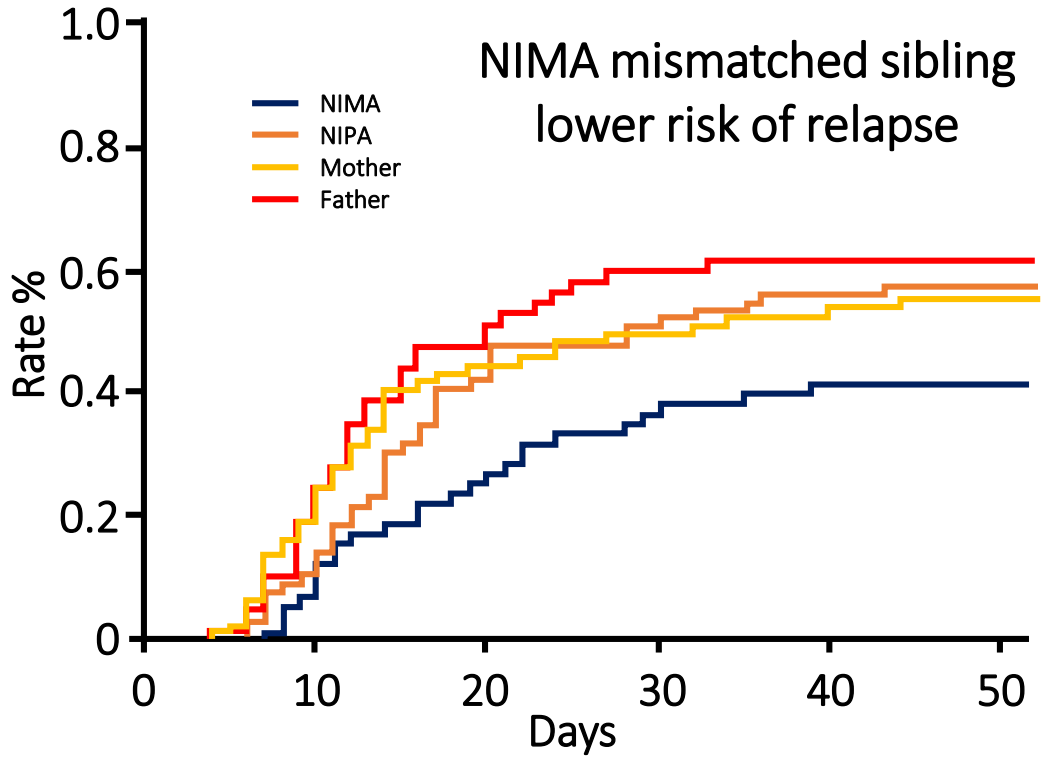
HSCT, hematopoietic stem cell transplantation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; Cen, centromeric; MSD, matched sibling donor; ped, pediatric; indiv, individuals.

Babor F, Fischer JC, Uhrberg M. Front Immunol. 2013 Feb 7;4:27

Maternal Ag Effect in transplantation: Complex & Inconsistence

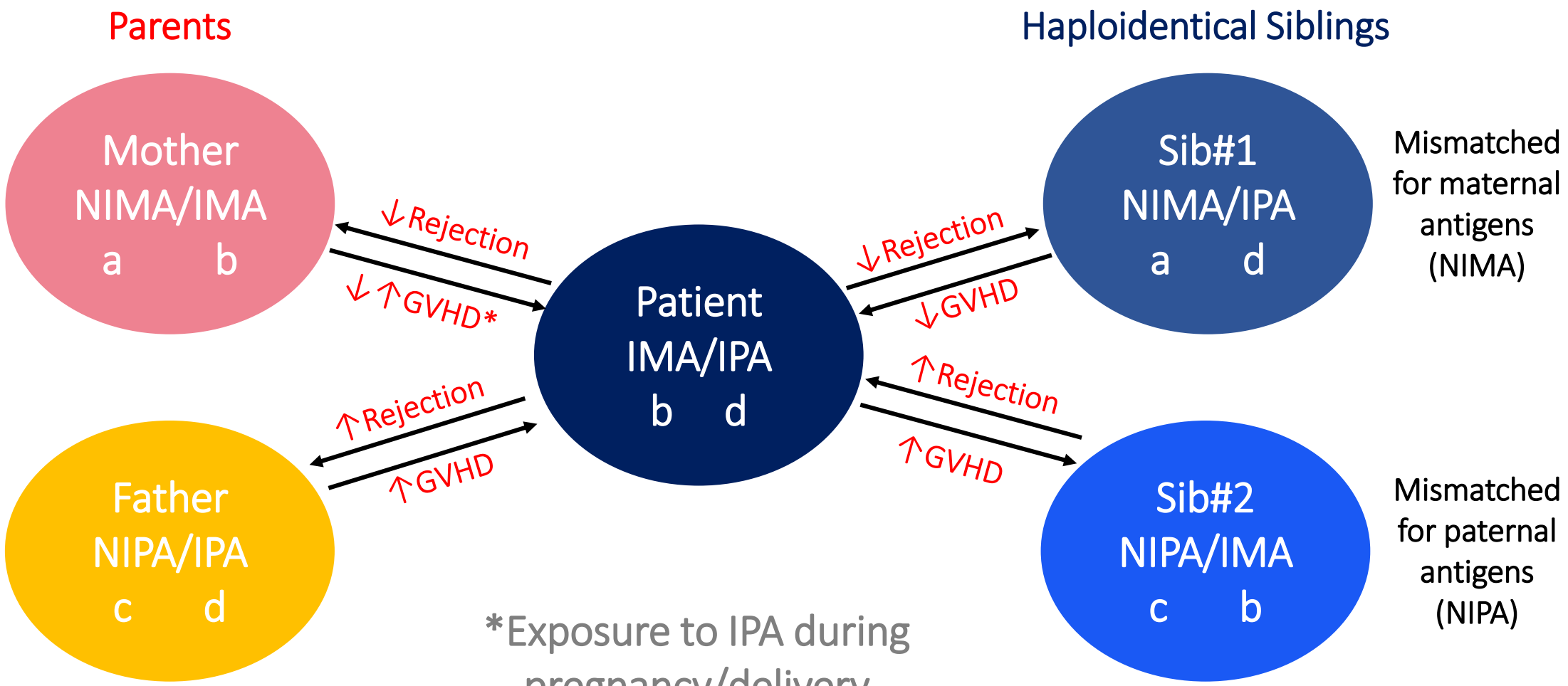


Type	HLA compatibility	Donor eligibility
IMA/IPA	HLA-identical	Suitable
NIMA/IPA	NIMA-mismatched	
IMA/NIPA	NIPA-mismatched	
NIMA/NIPA	HLA-mismatched	Unsuitable



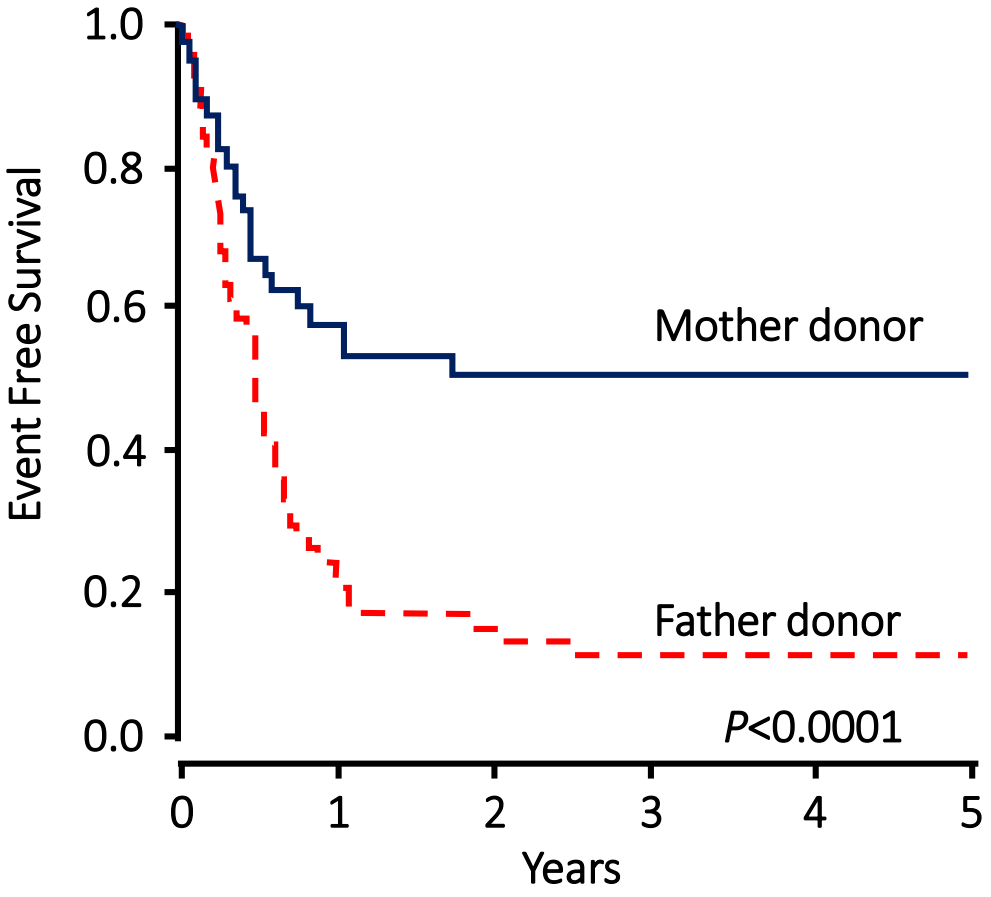
van Rood JJ et al. Blood. 2002 Mar 1;99(5):1572-7

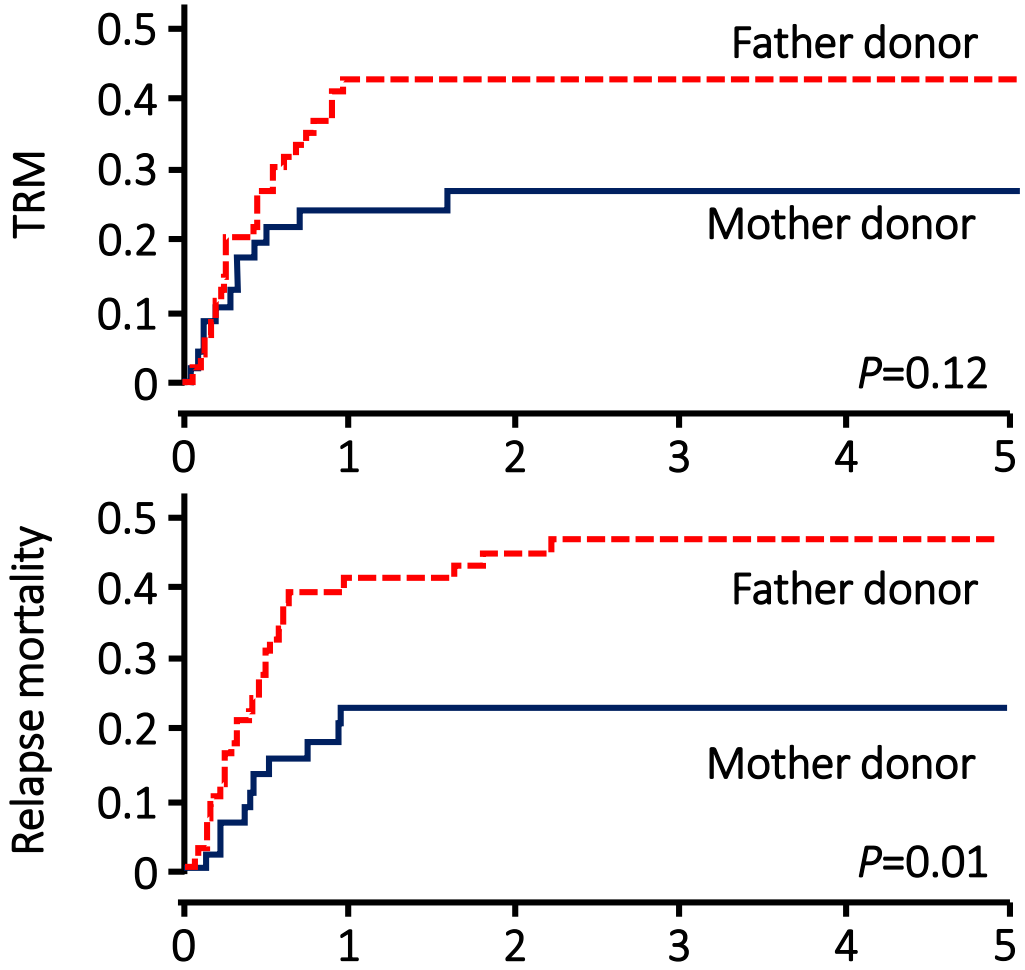
NIMA Effect on haploidentical transplantation



van Rood JJ et al. Blood. 2002 Mar 1;99(5):1572-7

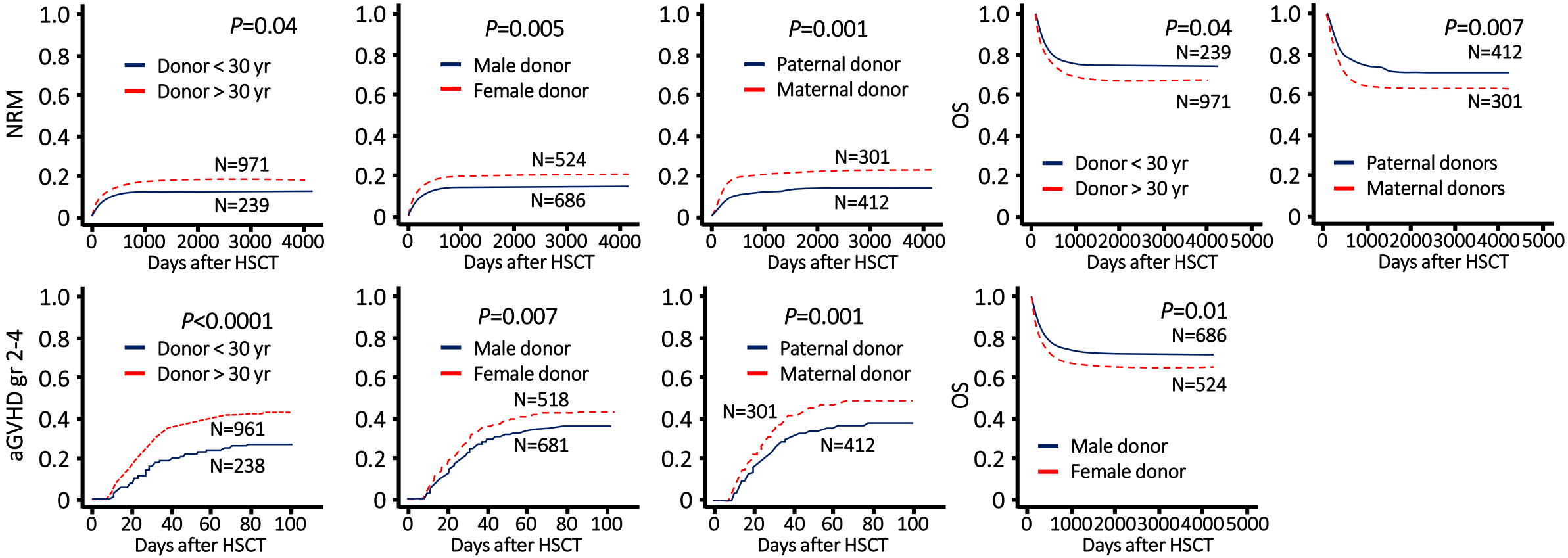
TCD Haploidentical transplant: Donor effects





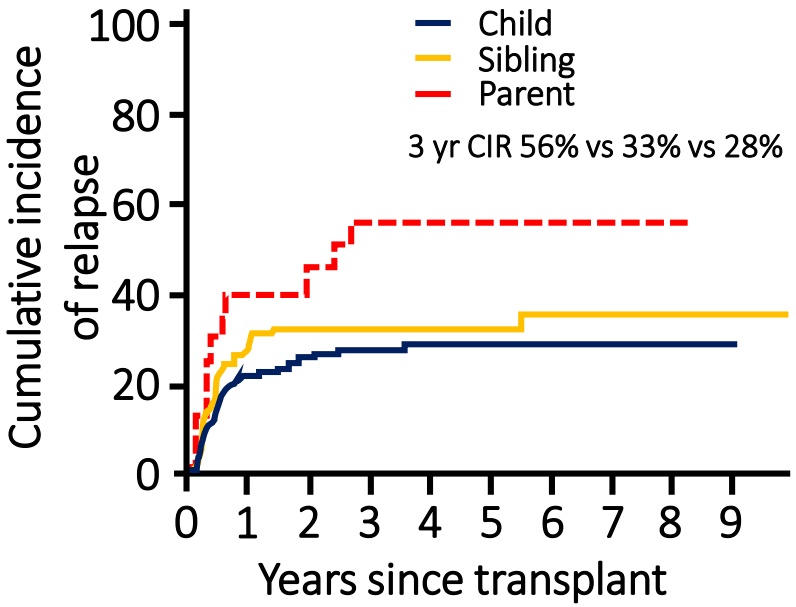
Stern M et al. Blood. 2008 Oct 1;112(7):2990-5

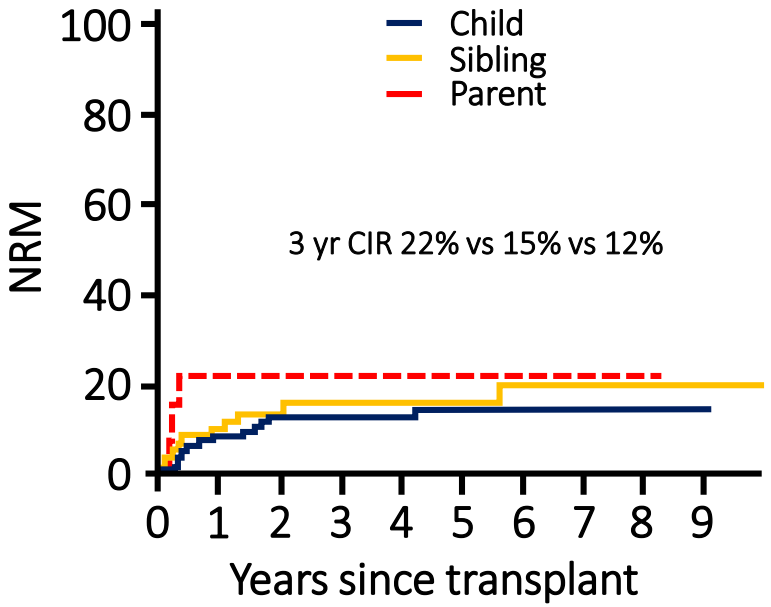
TCR Haploidentical transplant: Donor effects

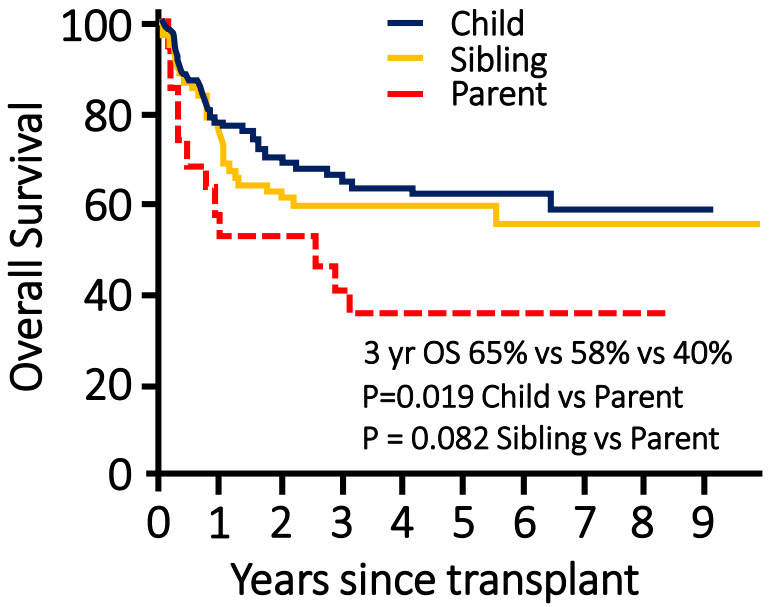


Wang Yu et al. Blood. 2014 Aug 7;124(6):843-50

TCR Haploidentical transplant: Selecting donor

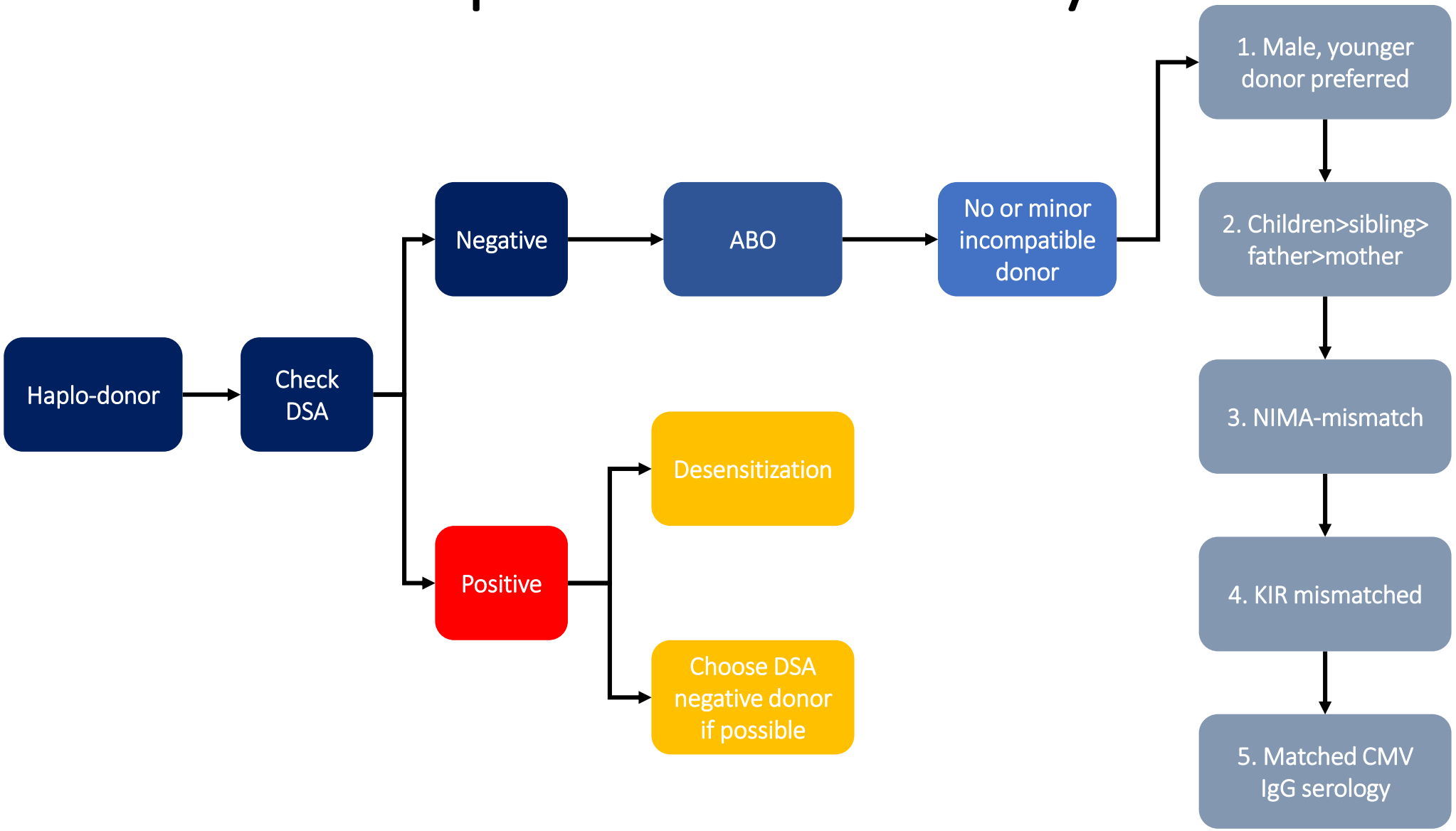






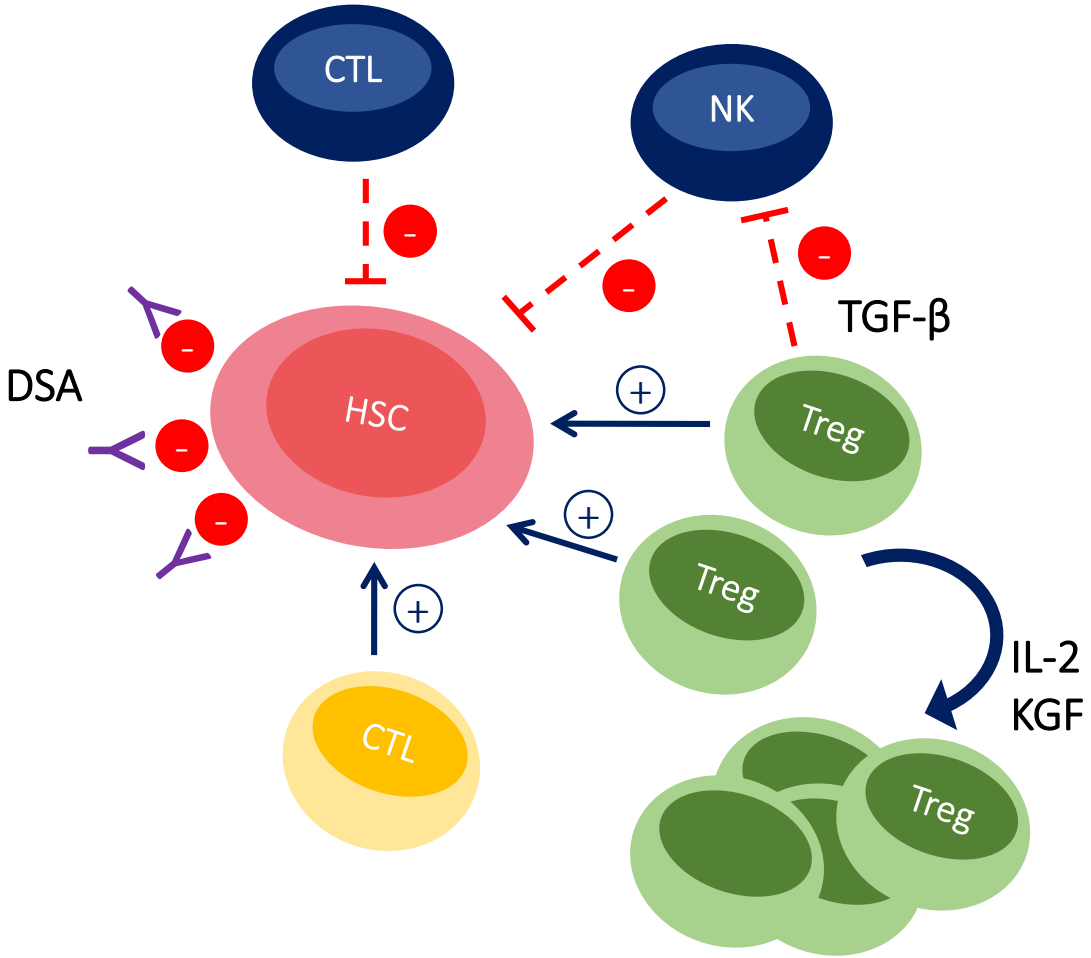
Solomon SR et al. Biol Blood Marrow Transplant. 2018 Jan 31. pii: S1083-8791(18)30028-4

Selection of Haplo-Donor: Summary



Certain limitation of haplo SCT

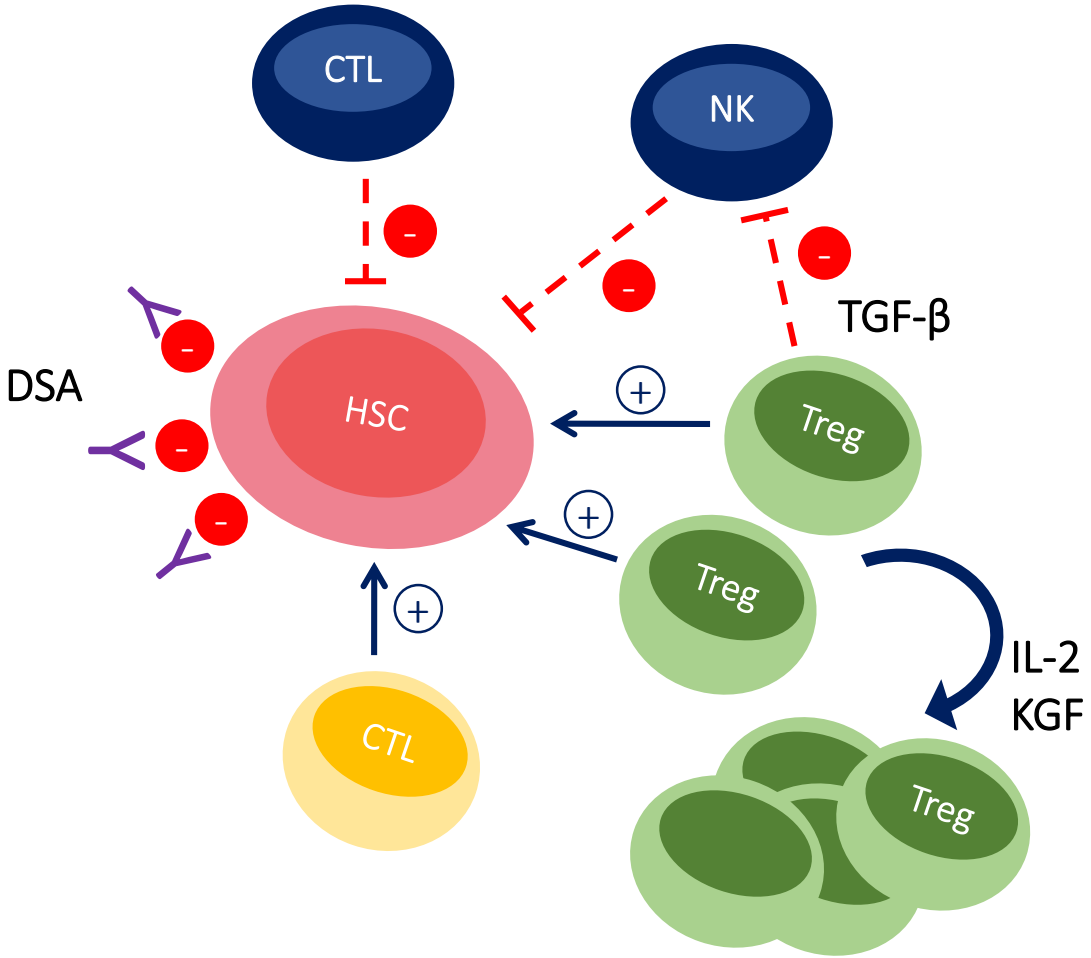
Immunologic basis of graft failure

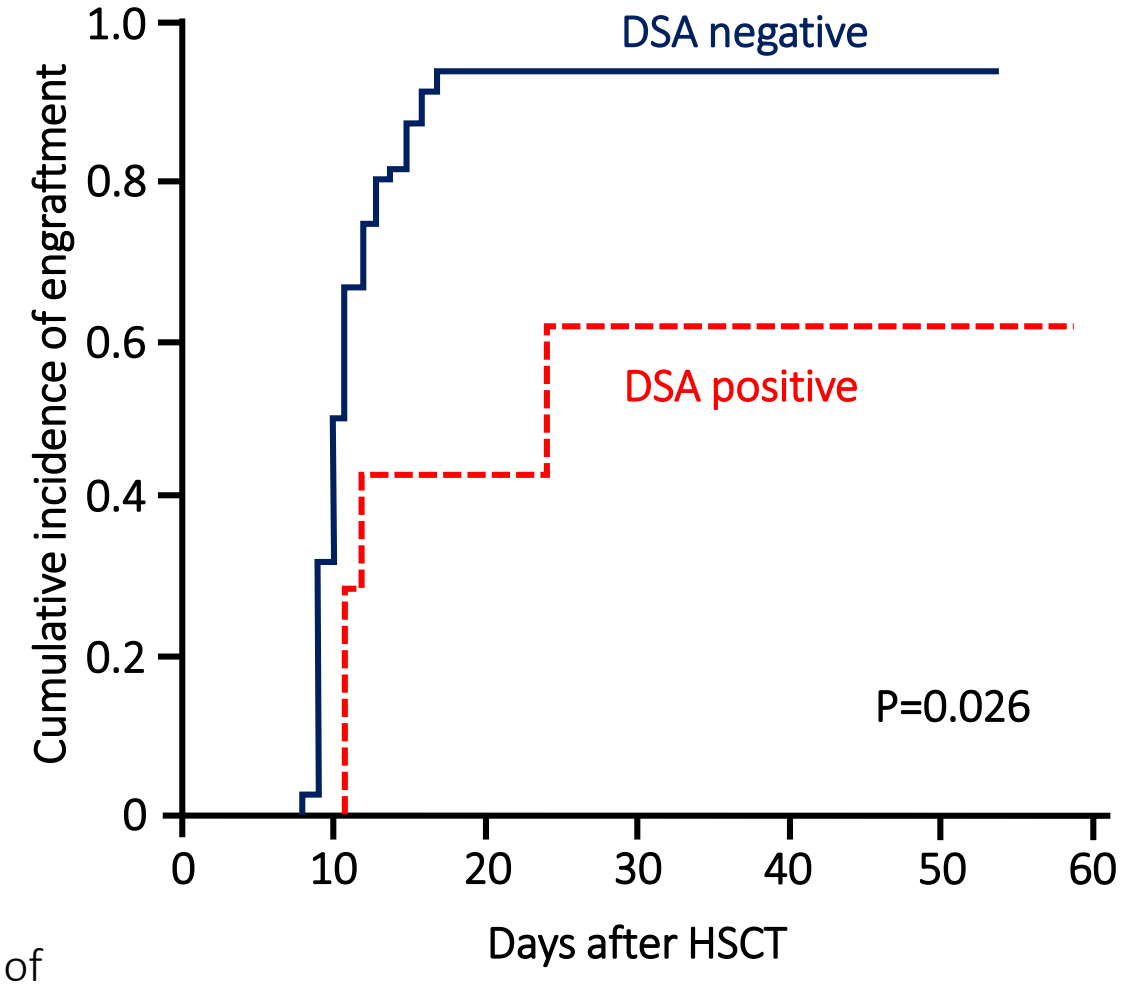


HLA-directed DSA occurred in 14.5% of all patients and 42% of women undergoing haplotransplant evaluation

Yoshihara S et al. Bone Marrow Transplant. 2012 Apr;47(4):508-15
Masouridi-Levrat S et al. Front Immunol. 2016 Sep 16;7:362

Immunologic basis of graft failure





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Yoshihara S et al. Bone Marrow Transplant. 2012 Apr;47(4):508-15
Masouridi-Levrat S et al. Front Immunol. 2016 Sep 16;7:362

Donor specific antibody in haploidentical SCT

Study	Patients #	Conditioning	Anti-HLA %	DSA %	Graft failure w or wo DSA
Yoshihara 2012	79	RIC	20.2	14	27 vs 3%
Ciurea 2009	24	RIC	ND	21	60% vs 5%
Chang 2015	345	MAC	25.2	11.3	61% vs 3.2%
Ciurea 2011	122	Non specified	ND	18	32 vs 4%

Morin-Zorman S et al. Front Immunol. 2016 Aug 12;7:307.

DSA desensitization methods

	N	Anti-HLA test	Desensitization method	MFI post treatment	Graft outcome
Barge 1989	1	CDC	Plasmapheresis	NA	Graft failure
Braun 2000	1	FCXM	Staphylococcal Protein A immunoadsorption	Negative XM	Engrafted
Ciurea 2009	4	Luminex MFI > 500	Plasmapheresis + rituximab	One neg, 1 low titer, 2 high titer	Pt w DSA neg and low titer engrafted
Yoshihara 2012	5	Luminex MFI > 500	Plasmapheresis + Rituximab (n=2), platelet transfusion (n=2), Bortezomib + Dex (n=1)	1 had temporary DSA reduction and 1 had significant DSA reduction after plasmapheresis, 2 had significant reduction post platelet transfusion, 1 had moderate DSA reduction after Bortezomib-dex	All 5 pt. engrafted
Ciurea 2015	12	Luminex MFI > 500	Plasmapheresis + Rituximab + IVIG (n=5), PE + Rituximab + IVIG + donor buffy coat (n=7)	No significant change of MFI before transplant, all patients cleared DSA after transplant	5 patients with C1q positive post treatment had GF while patients who became C1q negative engrafted
Leffell 2015	13	Luminex MFI > 1000	Plasmapheresis + IVIG + Tacrolimus	Mean reduction of DSA post Rx 64.4%	All patients engrafted by D+40

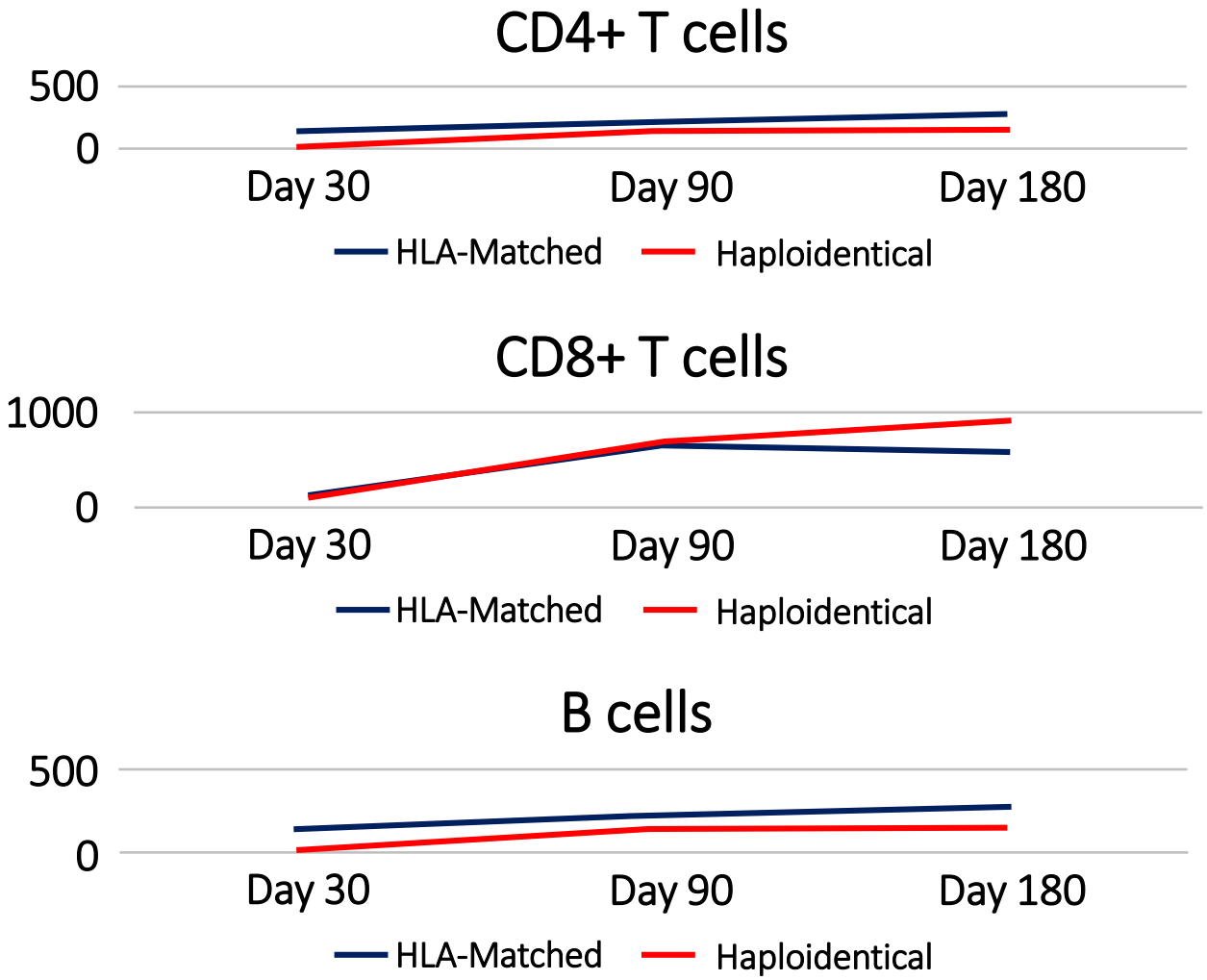
Ciurea SO et al. Bone Marrow Transplant. 2018 Jan 15. doi: 10.1038/s41409-017-0062-8

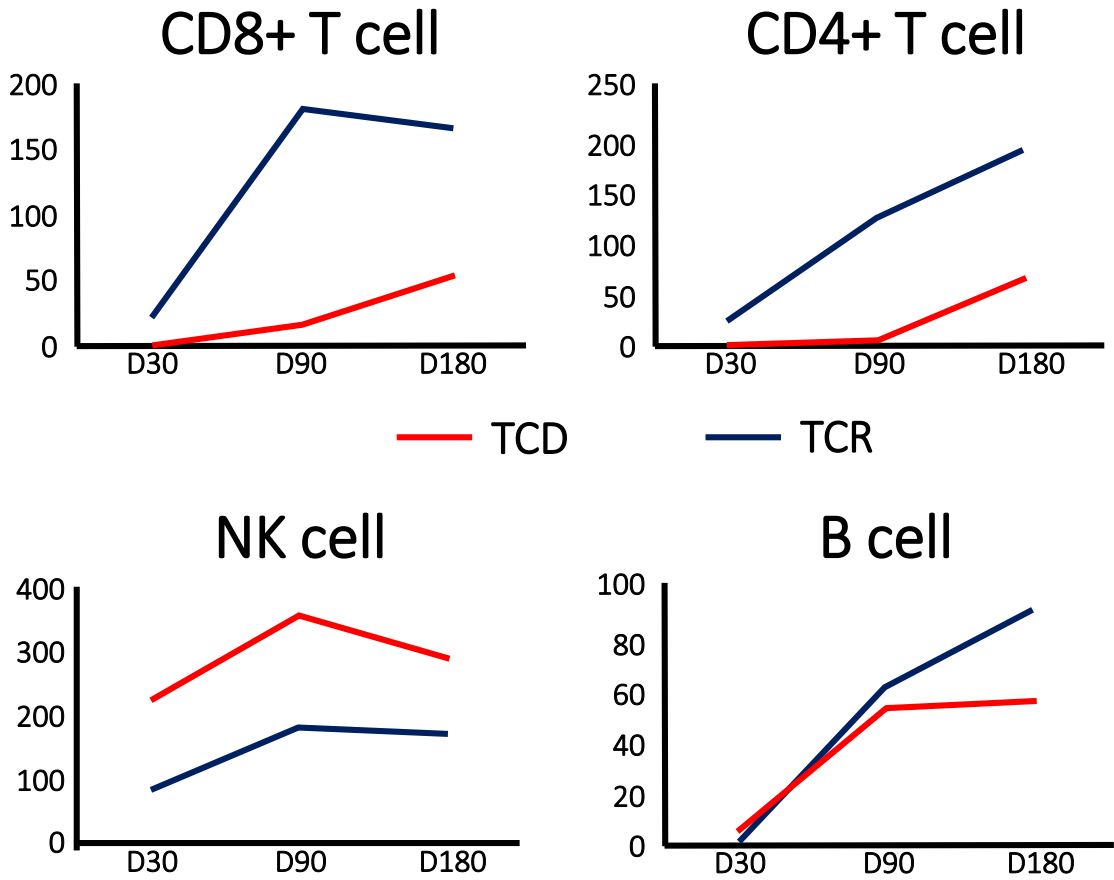
Infection in Haploidentical SCT

- Early experience → High rate of graft failure in TCD haploidentical transplant → High rate of infection and transplant related mortality
- Later experience:
  - Improved engraftment rate: Neutrophil engraftment up to 21 days so similar bacterial infection to MSD
  - T cell recovery is a prognostic determinant of infectious outcome
  - Lower T cell and dendritic cell recovery compared to MSD
  - TCD differ from TCR

Atilla E et al. Infection. 2017 Aug;45(4):403-411
Chang YJ et al. J Clin Immunol. 2012 Apr;32(2):268-80

Immune reconstitution after haploidentical SCT





Atilla E et al. Infection. 2017 Aug;45(4):403-411
Chang YJ et al. J Clin Immunol. 2012 Apr;32(2):268-80

Comparison infection rate in haploidentical SCT

	Haploidentical	MSD	MUD	UCB
Transplant related mortality	18%	24%	33%	35%
CD4+ T cell/µL at day +100	190	229	106	63
Cumulative incidence of CMV reactivation	74%	58%	60%	68%
Infection incidence at day +100: - Bacterial - Fungal	 25% 11%	 23% 4%	 36% 14%	 39% 14%
Rate of fatal infections	11%	4%	14%	17%

- CMV was the most frequent viral infection in haploidentical SCT

Raiola AM et al. Biol Blood Marrow Transplant. 2014 Oct;20(10):1573-9

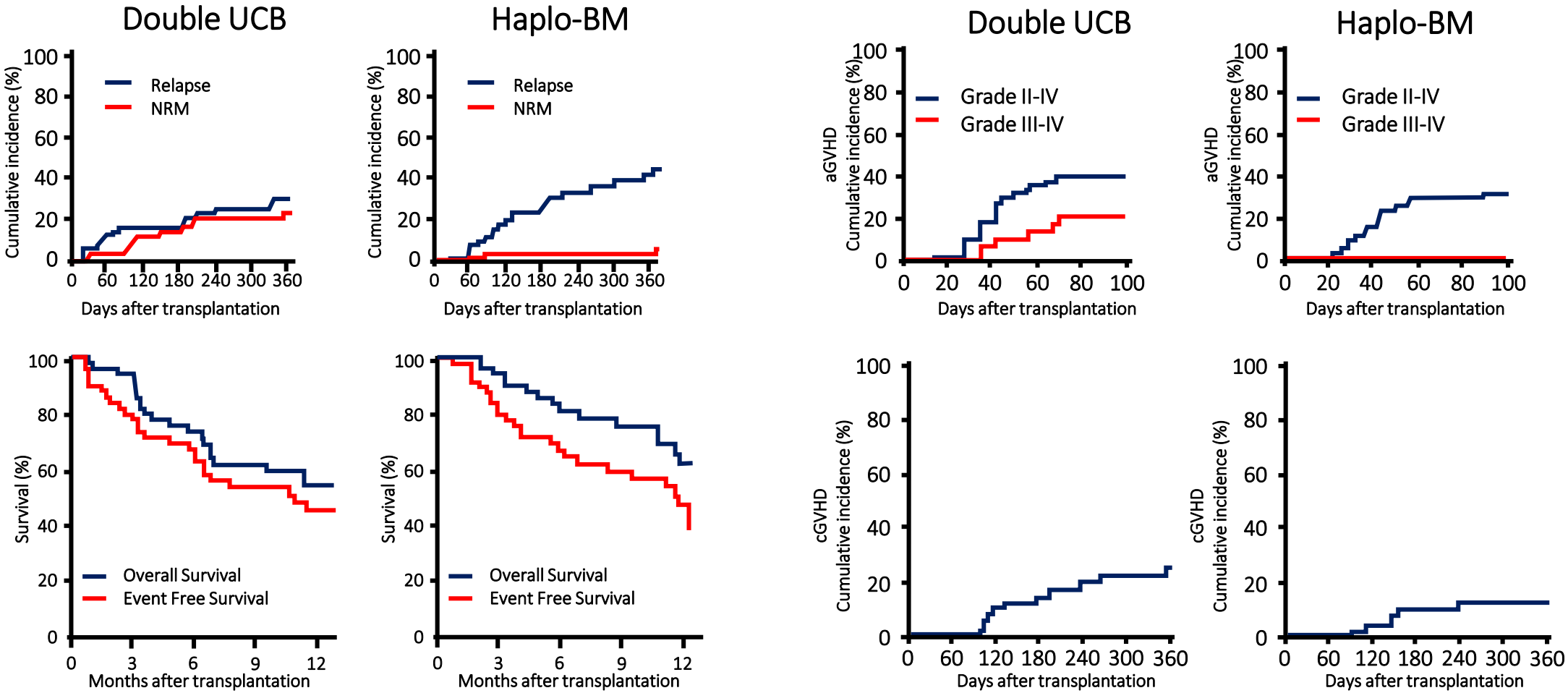
Viral infection in haploidentical SCT

	All patients (n=55)	TCD (n=28) n (%)	TCR/PTCY (n=27) n (%)
Herpesviruses			
- HSV	10	8 (29.6)	2 (7.4)
- CMV	16	12 (42.9)	4 (14.8)
- HHV-6	44	23 (82.1)	21 (77.8)
- EBV	24	19 (71.4)	5 (18.6)
- VZV	2	2 (7.1)	0 (0)
- Patients infected > 1 herpesvirus	32	26 (92.9)	6 (22.2)
Other viruses			
- Adenoviruses	9	5 (17.9)	4 (14.8)
- Polyomavirus (JC/BK)	24	11 (39.3)	13 (48.1)
- RSV	1	1 (3.6)	0 (0)
- Influenza A virus	3	2 (7.1)	1 (3.7)
- Patients infected > 1 viruses	46	27 (92.9)	19 (70.3)

Tischer J et al. Ann Hematol. 2015 Oct;94(10):1677-88

Haploidentical SCT vs other SCT approaches

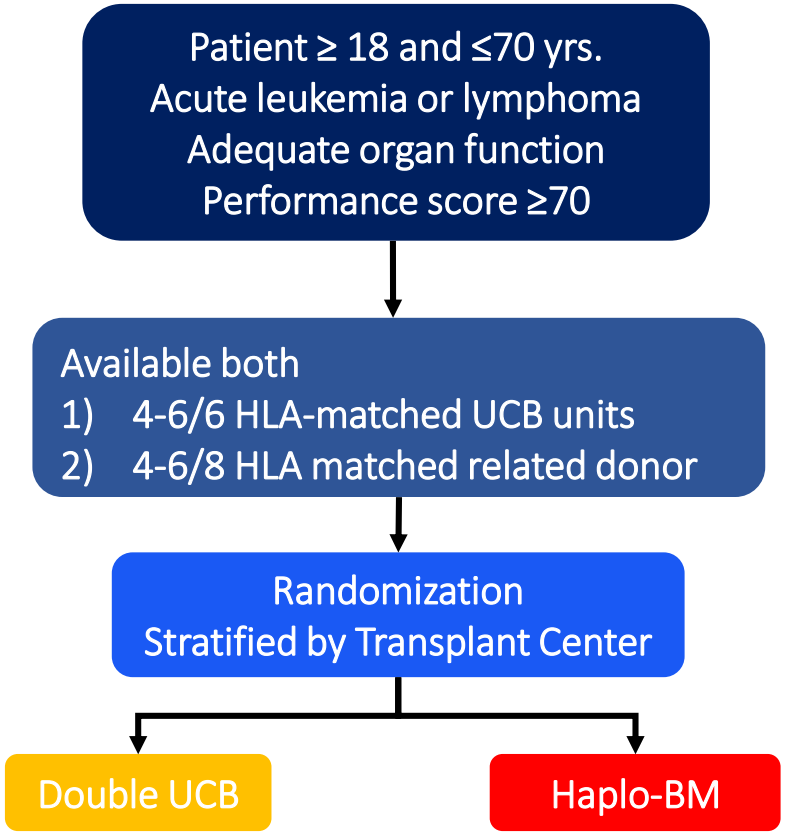
BMT CTN 0603 vs BMT CTN 0604: Parallel Study



Brunstein CG et al. Blood. 2011 Jul 14;118(2):282-8

Haploidentical BMT vs Umbilical Cord Blood SCT

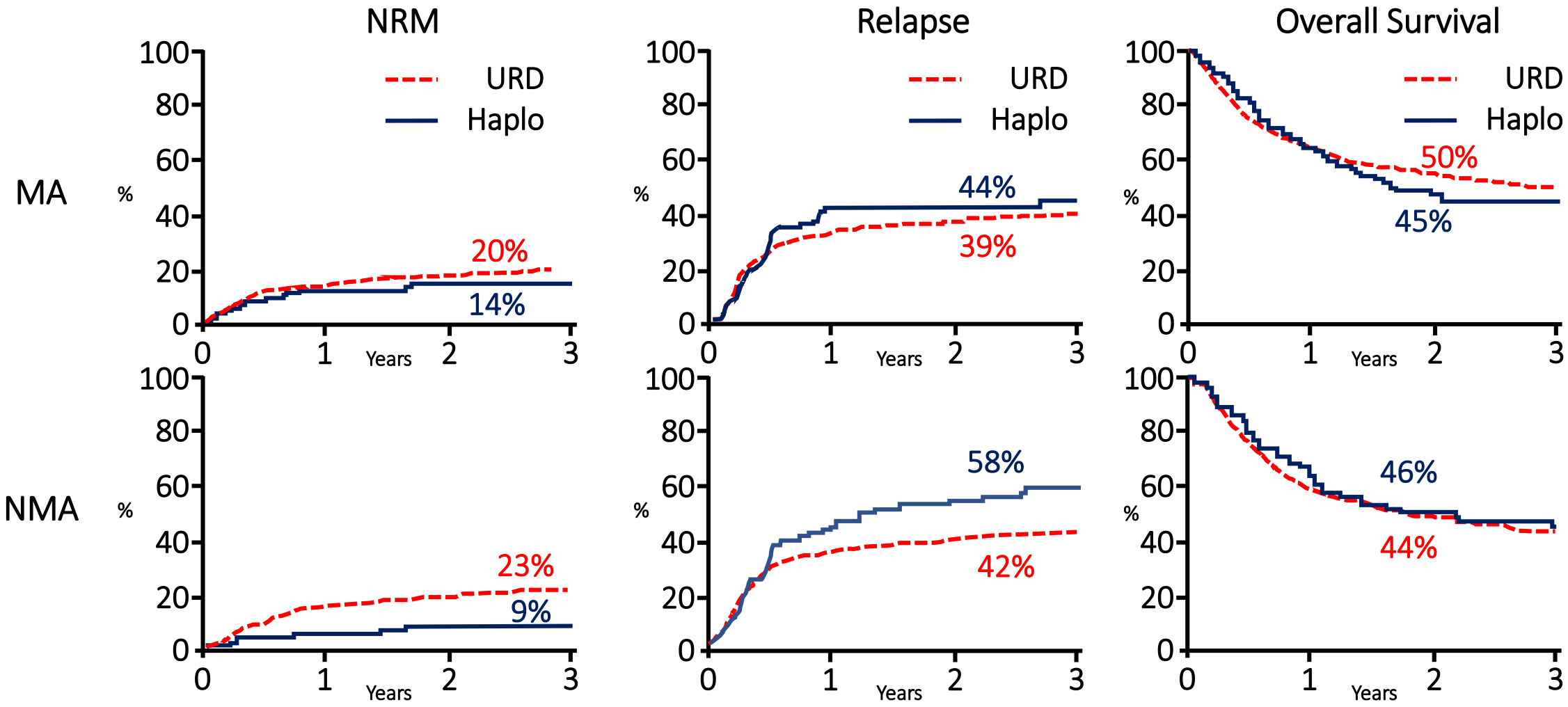
- Awaiting data from BMT CTN 1101: Estimated sample size n = 400



Haploidentical HSCT PREPARATIVE REGIMEN	
Day -6, -5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 14.5 mg/kg IV over 1-2 hours*
Day -4→ -2	Fludarabine 30 mg/m^2 IV over 30-60 minutes
Day -1	TBI 200 cGy
Day 0	Non-T-cell depleted bone marrow
Days 3, 4	Cyclophopshamide 50 mg/kg IV Mesna 40 mg/kg IV*
Day 5	Begin tacrolimus (or cyclosporine), mycophenolate mofetil, and G-CSF

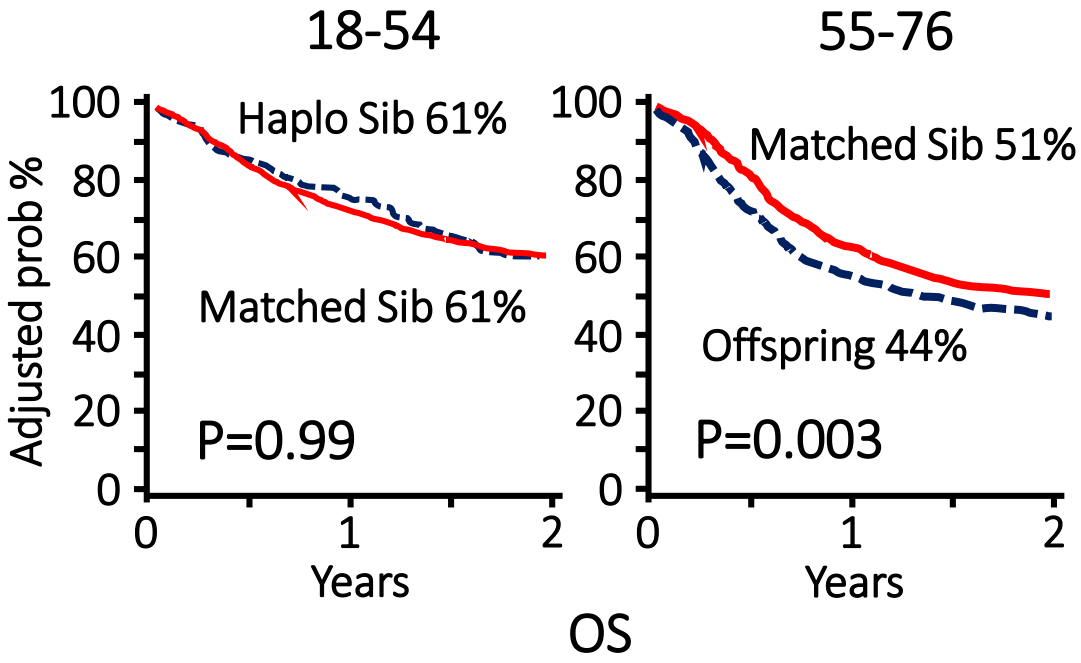
dUCB HSCT PREPARATIVE REGIMEN	
Day -6	Fludarabine 40 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 50 mg/kg IV over 2 hours
Day -5→ -2	Fludarabine 40 mg/m^2 IV over 30-60 minutes
Day -3	Begin cyclosporine (or tacrolimus) and MMF
Day -1	TBI 200 cGY
Day 0	UCB Transplant
Day 1	Begin G-CSF

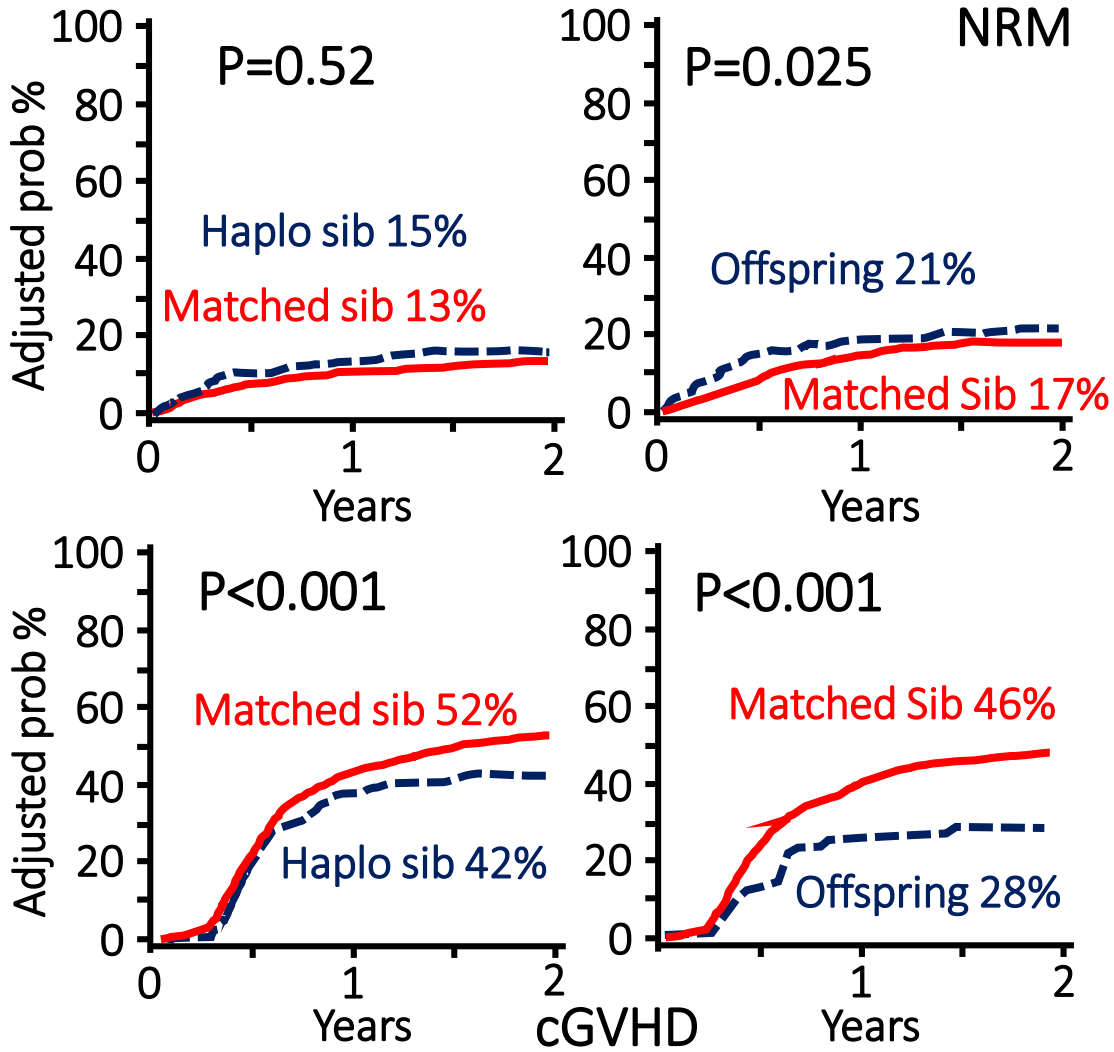
Haploidentical SCT vs Matched unrelated donor



Ciurea SO et al. Blood. 2015 Aug 20;126(8):1033-40

Haploidentical Transplant vs Matched Sibling

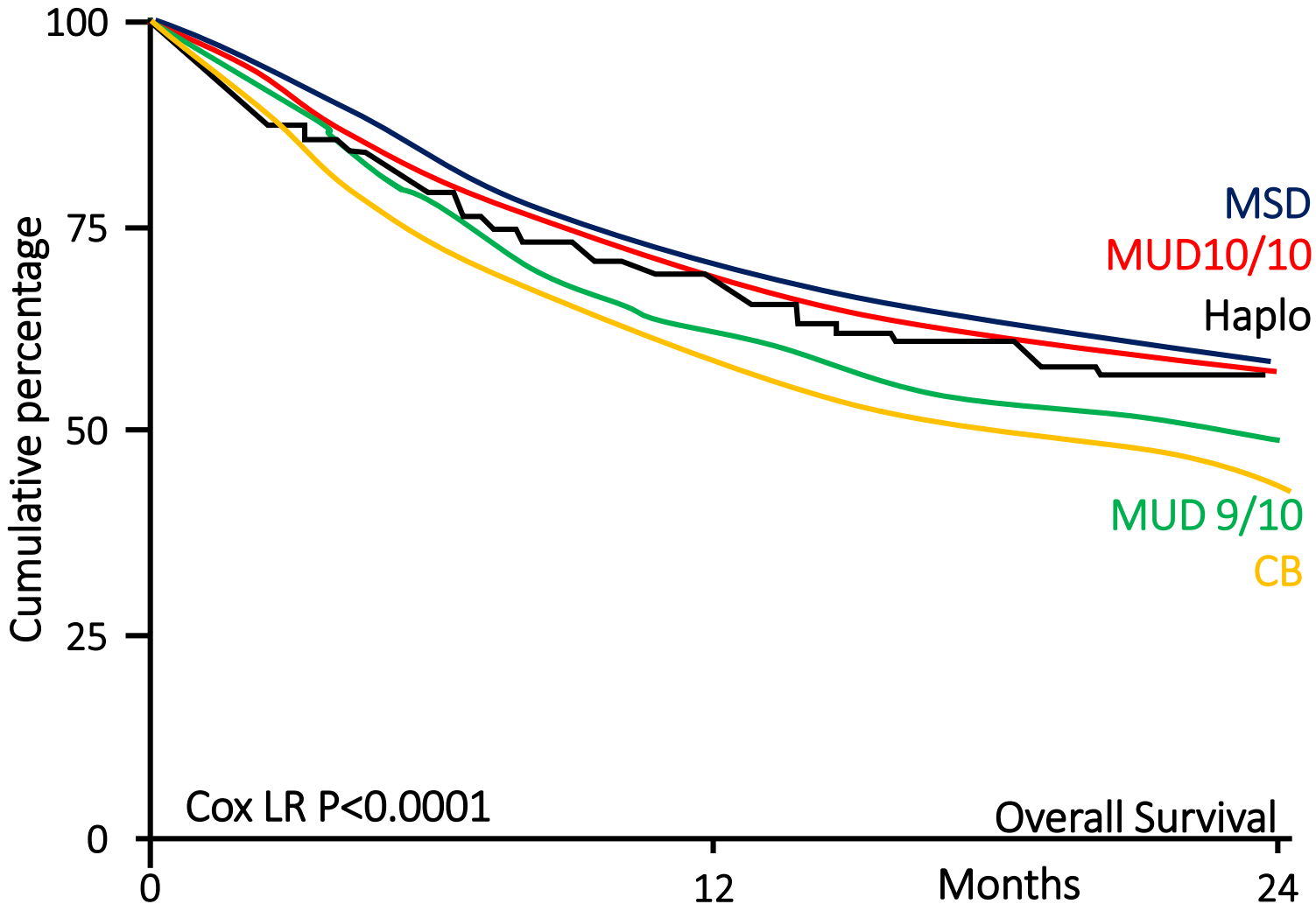




- Patient age, 18-54 years: comparable survival after transplants from an HLA matched sibling and a haploidentical sibling
- Patient age, 55-76 years: better survival after transplants from an HLA-matched sibling compared with offspring

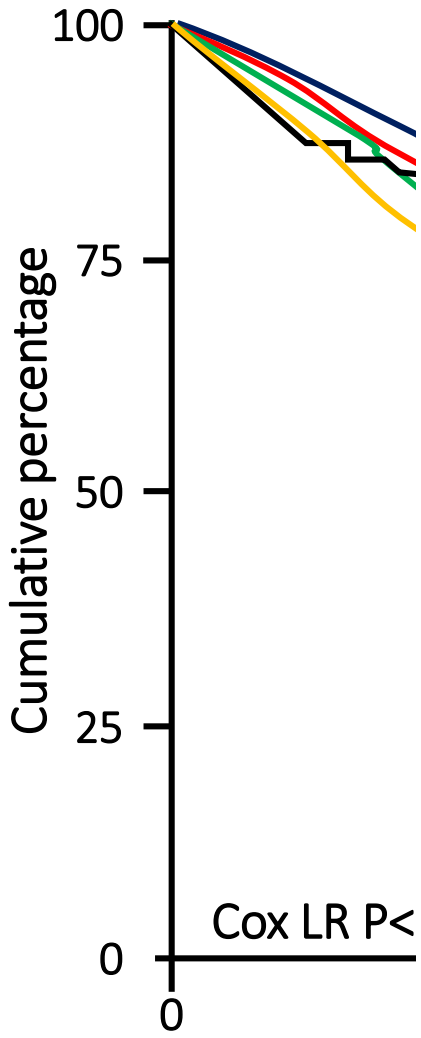
Robinson TM et al. Blood Adv. 2018 Jun 12;2(11):1180-1186

Comparison of SCT in acute myeloid leukemia



Fabricius WA. Adv Hematol. 2016;2016:5726132

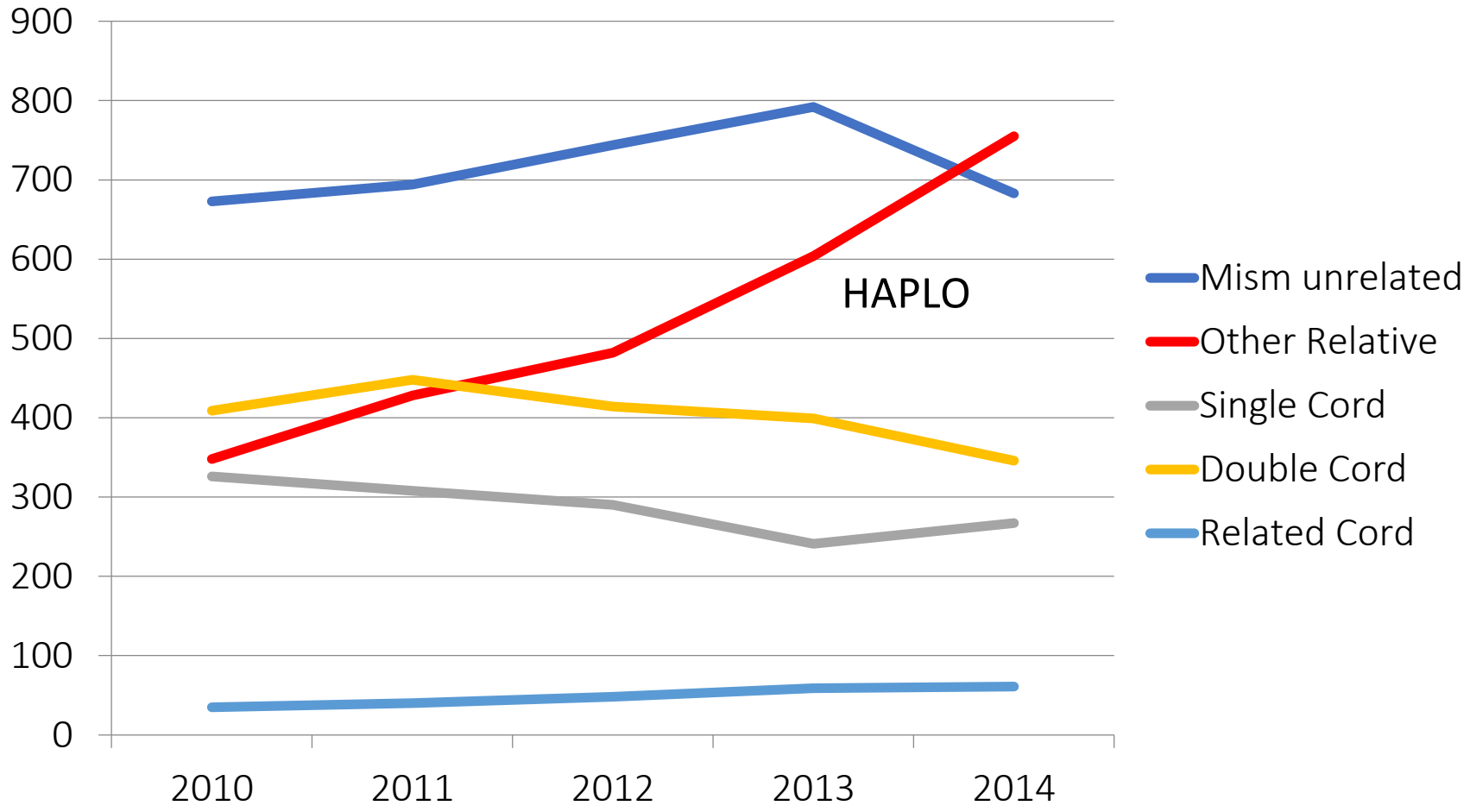
Comparis



	HAPLO	MSD	MUD	UCB
Donor availability	(~50–70%)	(~15–20%)	(~20–30%)	(~50%)
Time to transplant	(~10–20 days)	(~10–20 days)	(~2–12 months)	(~2–4 weeks)
Stem cell dose (CD34+/kg)	~6–8 × 10^6	~6–8 × 10^6	~6–8 × 10^6	~3–5 × 10^5
Days to engraftment ($p < 0.001$)	18 d	18 d	17 d	23 d
Acute GVHD, cumulative				
Grades 2–4 ($p < 0.01$)	14%	31%	21%	19%
Grades 3-4 ($p = 0.10$)	4%	7%	3%	1%
Grades 3-4 ($p = 0.004$)	10%	3%	—	—
Grades 3-4, myeloablative conditioning ($p = 0.02$)	7%	—	13%	—
Grades 3-4, reduced intensity conditioning ($p < 0.0001$)	2%	—	11%	—
Chronic GVHD				
Cumulative, moderate-severe ($p = 0.053$)	15%	29%	22%	23%
Cumulative, at 1 year, severe ($p = 0.001$)	12%	2%	—	—
Myeloablative conditioning, at 36 months ($p = 0.0001$)	30%	—	53%	—
Reduced intensity conditioning, at 36 months ($p \leq 0.002$)	34%	—	52%	—
Relapse rate				
3 y, cumulative ($p = 0.98$)	15%	15%	—	—
4 y, cumulative ($p = 0.89$)	35%	40%	23%	30%
Early disease (CR1, CR2) ($p = 0.09$)	18%	36%	20%	24%
Advanced disease (>CR2) ($p = 0.60$)	47%	47%	28%	40%
Disease-free survival				
Cumulative 3 y DFS ($p = 0.34$)	74%	78%	—	—
Cumulative 4 y DFS ($p = 0.20$)	43%	32%	36%	33%
Overall survival				
3 y OS ($p = 0.36$)	79%	82%	—	—
4 y OS ($p = 0.10$)	52%	45%	43%	34%
Relapse-related mortality	26% ($n = 24$)	26% ($n = 48$)	21% ($n = 9$)	29% ($n = 29$)
Transplantation-related mortality ($p = 0.10$)	18%	24%	33%	35%

Fabricius WA. Adv Hematol. 2016;2016:5726132

Trend in haploidentical vs other allogeneic SCT



Pasquini MC, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2015

Conclusions

- Haploidentical transplantation is an attractive transplant regimen based on the ready availability of donors
- Based on mostly retrospective data, current evidence suggests similar OS and possibly superior GVHD rate as compared with MUD or MRD transplantation
- Better understanding in immunology will result in better donor selection strategy to improve transplant outcome
- Active research in combining haploidentical transplant approach
- Extended indication of haploidentical transplant to all hematologic conditions

THANK YOU FOR YOUR ATTENTION

Any Questions?