C·H·O·R·I
Children's Hospital Oakland Research Institute

Stem cell therapies For Sickle Cell Disease

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Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014

"additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease) before HCT can become a widely used therapy"

Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. *Jama.* 2014;312:1033-1048.

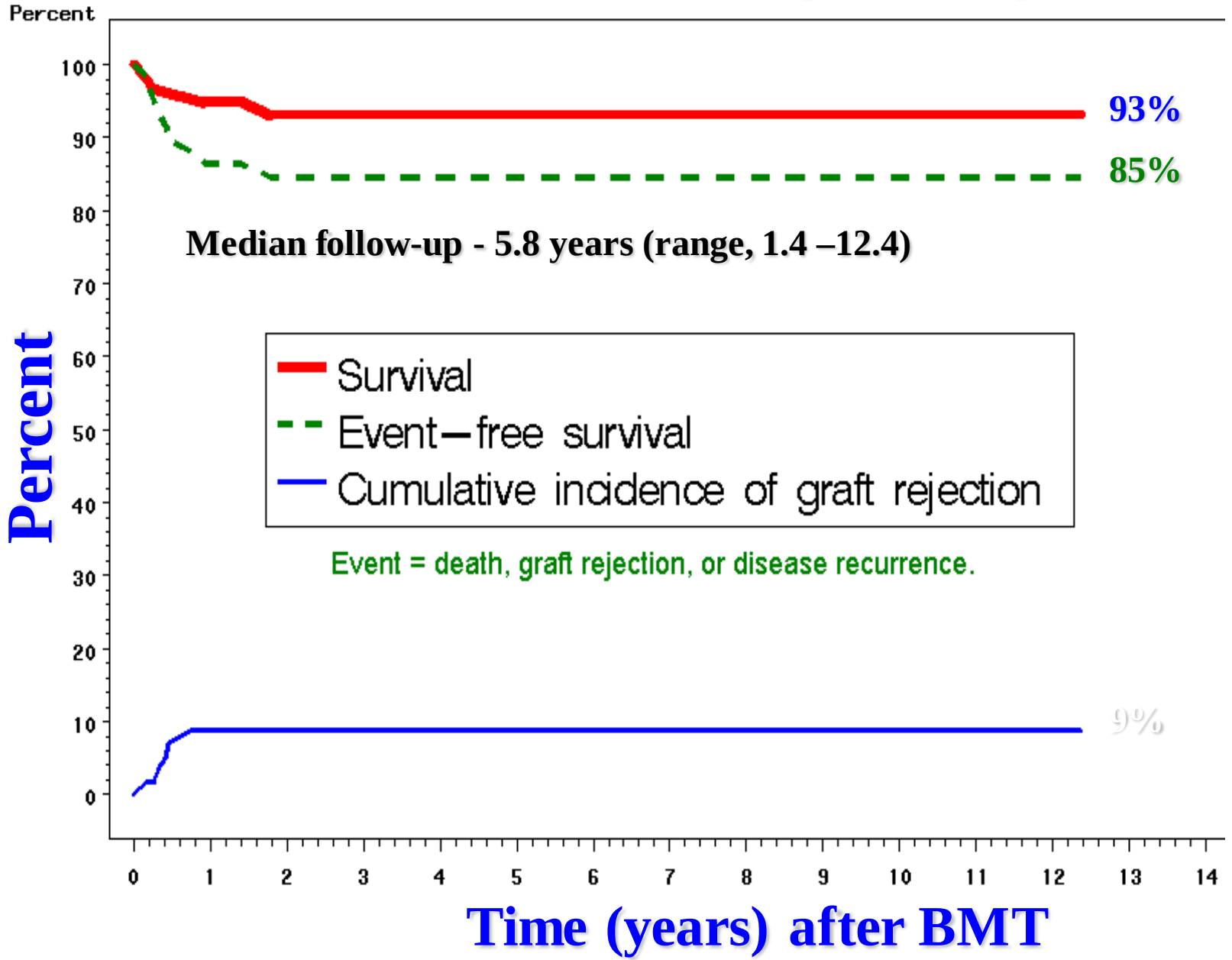
HCT in SCD: indications and management recommendations from an international expert panel

Young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at pre-school age.

Unmanipulated BM or UCB (whenever available) from matched sibling donors are the recommended stem cell source.

Angelucci E, Matthes-Martin S, Baronciani D, et al. *Haematologica.* 2014;99:811-820

BMT for SCD (N=59)



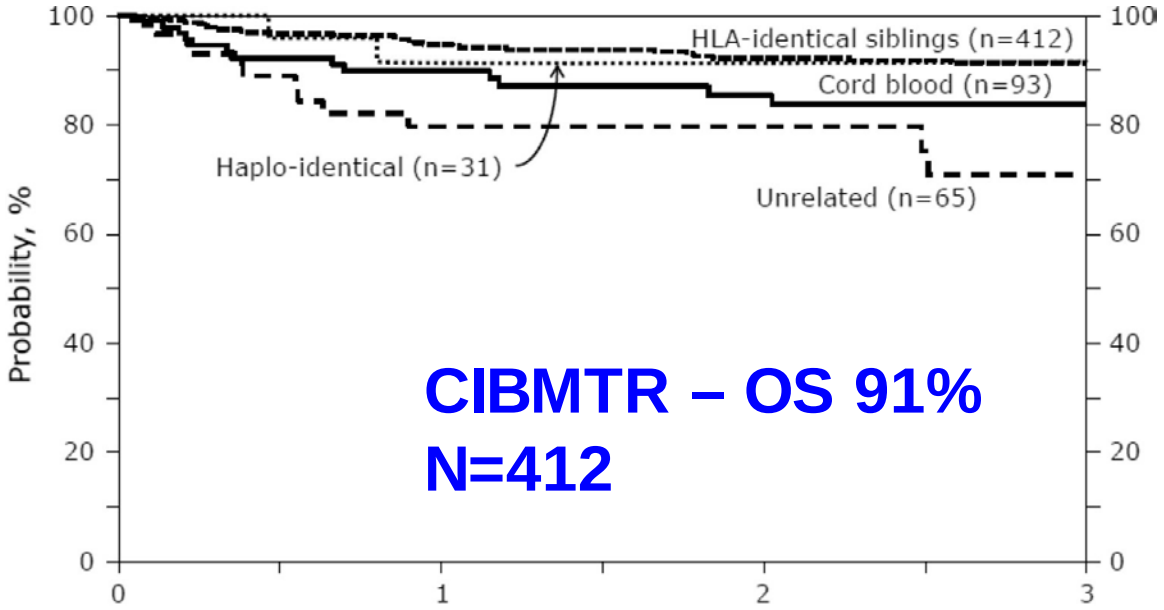
Summary of HLA-ID sib HCT for SCD

Center	Regimen	n	Age range (years)	Death (mos)	GvHD	Follow up (yrs)
Rome	BU14 mg/kg, CY 200 mg/kg/rATG 10 mg/kg, ±Flu 150 mg/m^2	40	2-17	3 (2.5, 6, 15)	17.5% acute, 5% chronic	1 - 10
Brussels	BU 13-18 mg/kg, CY 200 mg/kg, ±rATG (10 – 20 mg/kg), ±HU	50	1.7 – 15.3	2 (0.5, 6.6 yrs)	20.5% acute, 20% chronic	0.4 – 21.3
NYC	BU 12.8 – 16 mg/kg, Flu 180 mg/m^2, Alem 54 mg/m^2	18	2.3 – 20.2	none	17% acute, 11% chronic	0.4 – 7.5
Mississippi	BU 14 mg/kg, CY 200 mg/kg, ATG 90 mg/kg	10	2.8 – 16.3	1	40% acute, 10% chronic ext	2.9 – 9.9
Atlanta	BU 14 mg/kg, CY 200 mg/kg, ATG 90 mg/kg	27	3.3 – 17.4	1 (3)	12% acute, 1 death from chronic GVHD	0.1 - 10
Pavia	BU 16 mg/kg, TT 10 mg/kg, Flu 160 mg/ m^2 or Treo 14 gm/ m^2, TT 10 mg/kg, Flu 160 mg/ m^2, ATG	30	1.7 – 18.8	none	7% Gr I-II aGVHD, 7% cGVHD in BU group, none in treo group	0.5 – 14

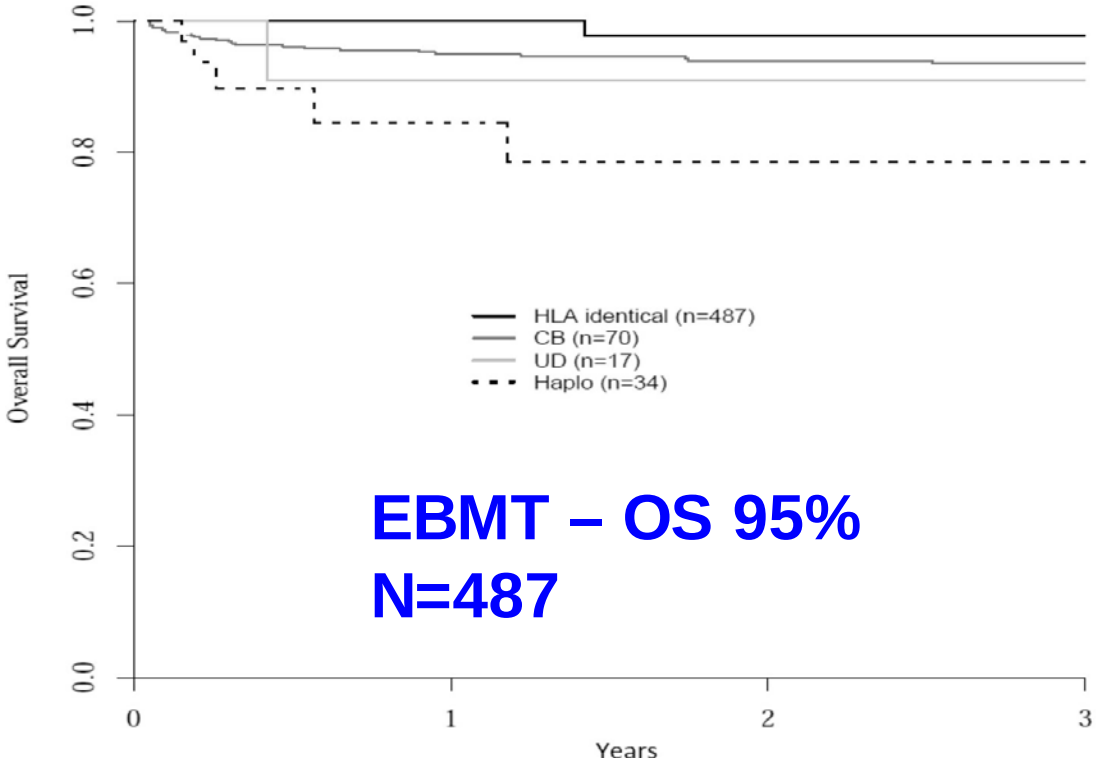
Survival summary

- **195 pediatric HLA-ID sibling allograft recipients treated at 7 US and European centers**
- **188/195 survive after HCT – 96%**
- **180/195 survive free of SCD – 92%**
- **At last follow-up, 3 of 180 survivors were receiving IST for cGVHD – 1.7%**

Lucarelli G, et al *Bone Marrow Transplant.* 2014;49:1376; Dedeken L, et al *Br J Haematol.* 2014;165:402 Bhatia M, et al *Bone Marrow Transplant.* 2014;49:913; McPherson ME, et al, *Bone Marrow Transplant.* 2011;46:27 Majumdar S, et al*Bone Marrow Transplant.* 2010;45:895; Strocchio L, et al *Br j haem.* 2015;169:726



CIBMTR – OS 91%
N=412



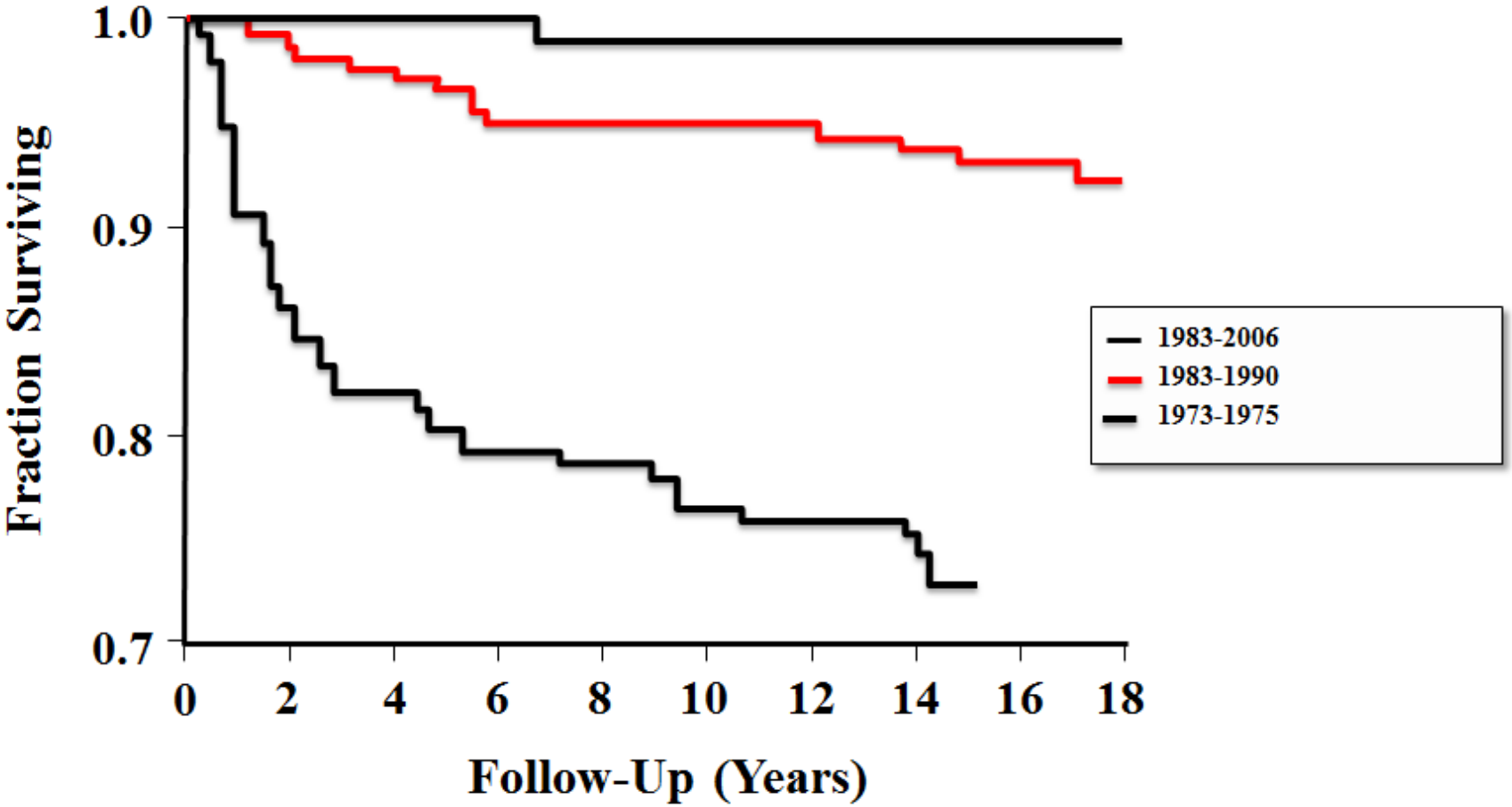
EBMT – OS 95%
N=487

Registry Data between 1994 - 2005

Gluckman E. *American Society of Hematology. Education Program.* 2013;2013:370

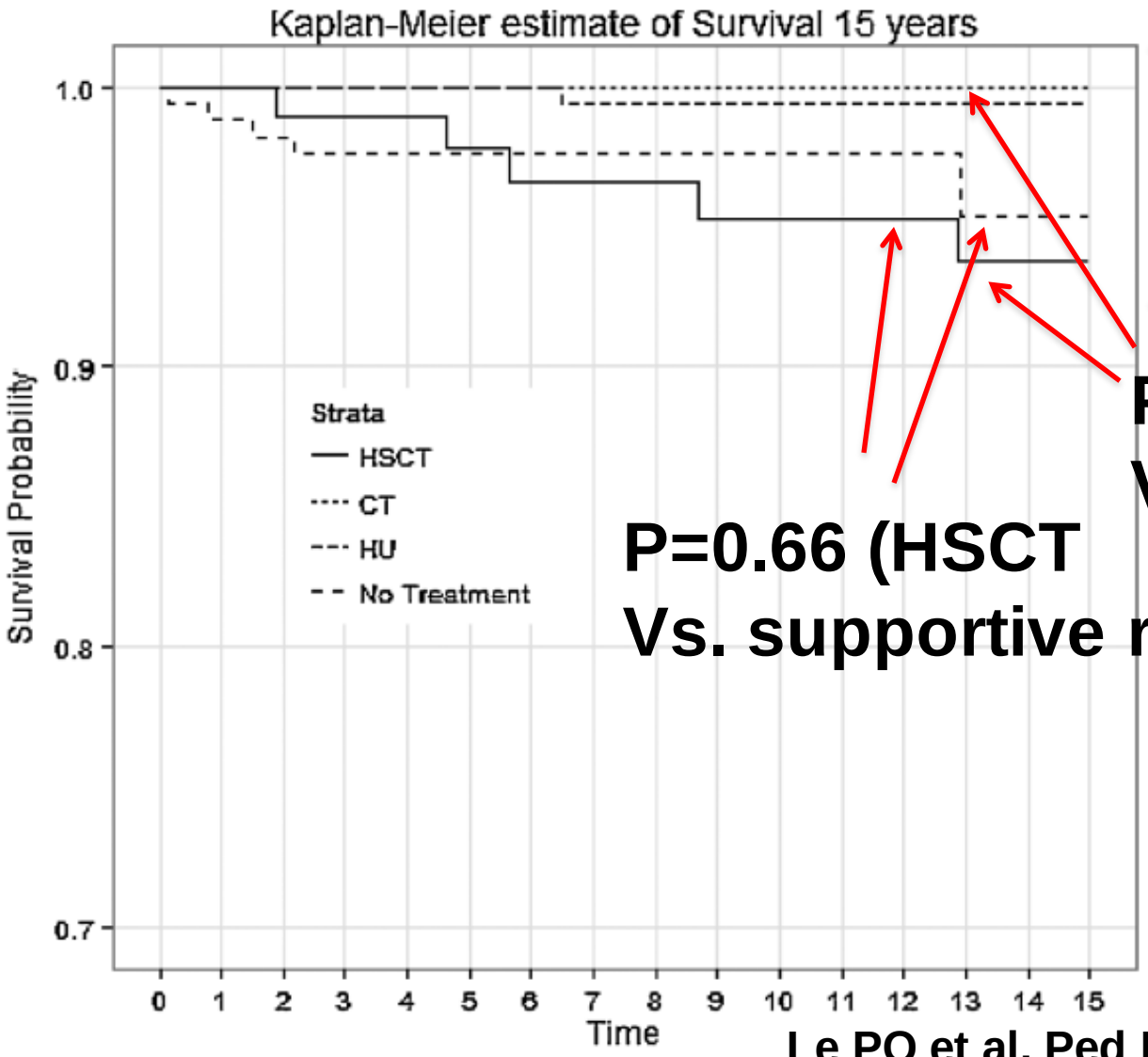
Improved Survival in Children with Sickle Cell Disease

Blood. 2010 Apr 29;115(17):3447-52



HbSS and HbSβ° patients, overall survival at 18 years of age is estimated to be 93.9% in the Dallas cohort; NB 1% mortality at 20y in East London

SCD Survival from birth in Belgium 2008 - 2012 (N=469)



P=0.07

P=0.01 (HSCT Vs. HU)

P=0.66 (HSCT Vs. supportive rx)

Le PQ et al, Ped Blood Canc, June 2015

Barriers to Transplant for SCD

- Only 14% of families have HLA-ID sibling donor
- Only 19% have well-matched unrelated donor
- Clinicians do not refer patients because of GVHD and risk of dying

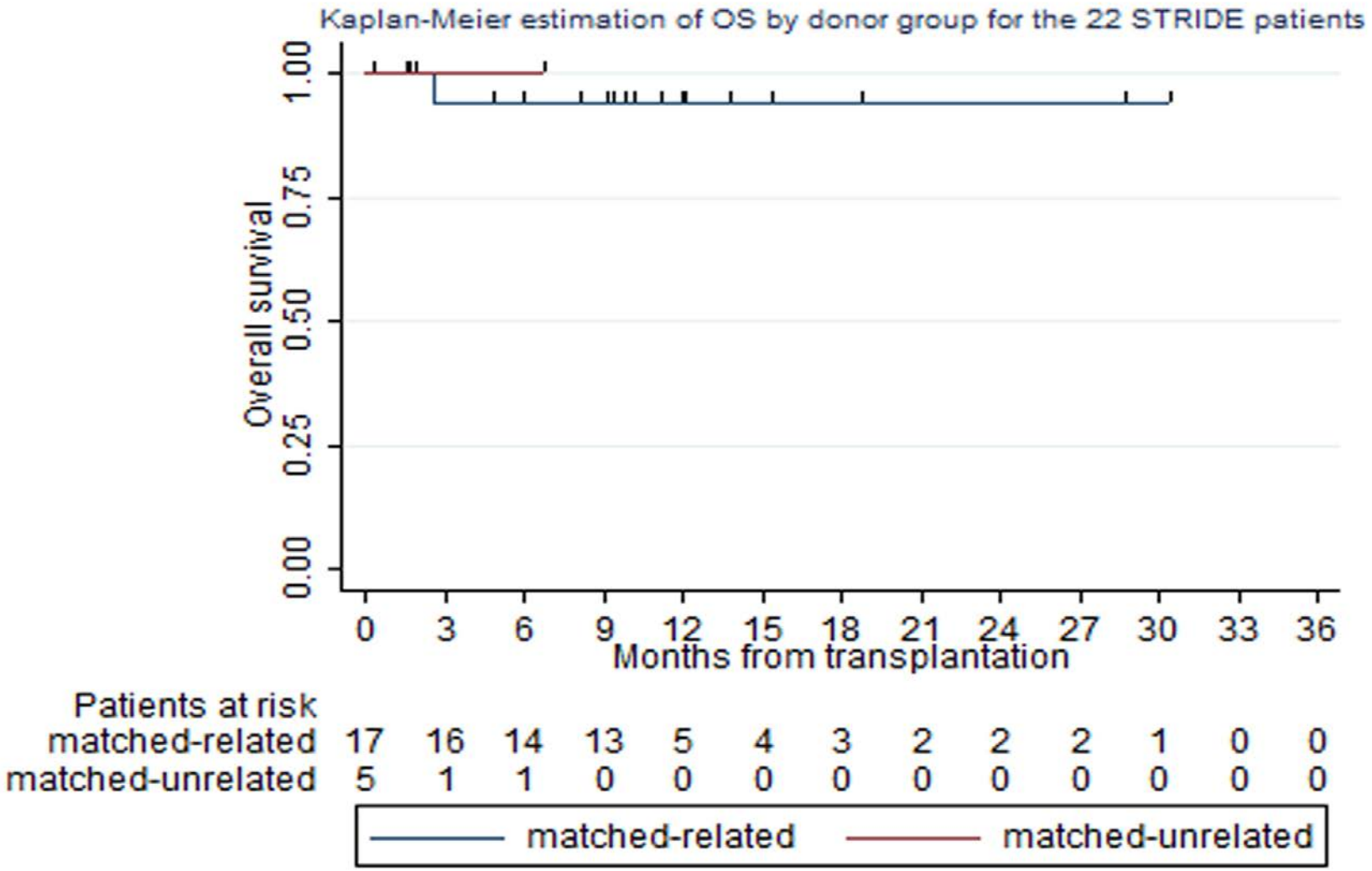
Multi-center clinical trials

- STRIDE – pilot trial of HLA-matched BMT for adults with SCD, 22 enrolled, 21 surviving free of SCD (R34 NIH funding)
- BMT-CTN 1503 (STRIDE2) comparison of HLA-matched BMT and std care in adults with SCD (U01 NIH funding)
- BMT-CTN 1507: Haplo-ID BMT in adults and children with SCD

R34 NHLBI-funded Pilot Trial (Krishnamurti)

- Objective
  - Determine the safety of HCT in patients aged 15-40 years with severe SCD defined as 1-year disease-free survival ≥75%
- Trial period: 10/2012 – 06/2015; N = 8 centers; 19 of 23 enrolled in 01/2014 – 06/2015
- N = 23 enrolled (results for N = 22)
- Median age 22 years
- Donors: 17 HLA-matched sibling; 5 HLA-matched URD
- Results
  - N = 20 alive; median follow-up: 9.7 months
  - OS and EFS 95% (90% CI 76%; 99%)

Overall and Disease-free Survival



Eligibility Criteria – BMT CTN 1503

- Age 15 – 40 years
- CNS event: stroke or deficit lasting >24 hours
- ≥ 2 episodes of acute chest syndrome (ACS) in preceding 2 years despite adequate supportive care measures
- ≥ 3 episodes of pain crisis (VOC) in preceding 2 years despite adequate supportive care measures
- ≥ 8 transfusions per year for ≥ 1 year to prevent SCD-related complications (VOC, ACS, stroke)
- Tricuspid valve regurgitant jet (TRJ) ≥ 2.7 m/sec

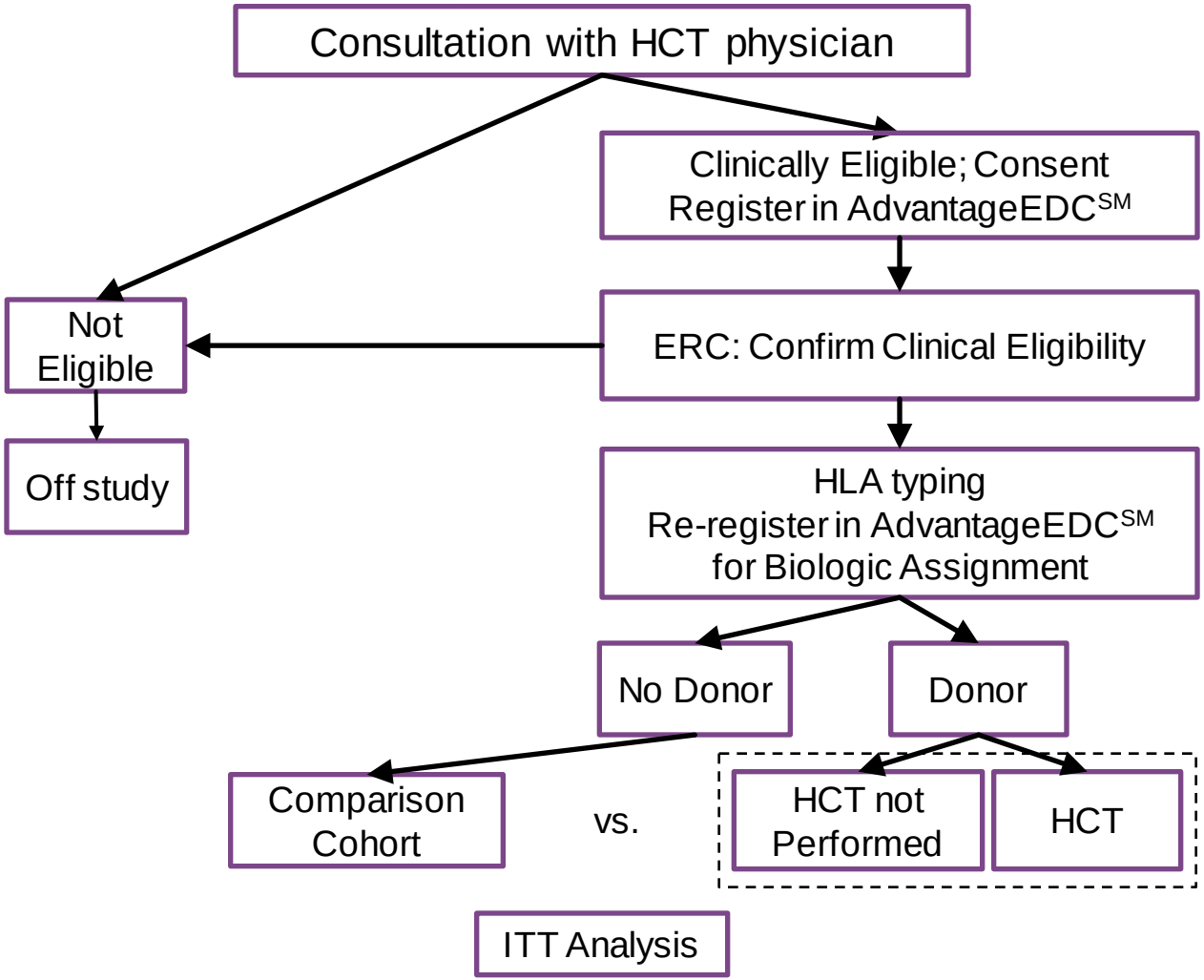
Conditioning Regimen – BMT CTN 1503

Day	Regimen
-8	IV busulfan 3.2 mg/kg
-7	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2
-6	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2, thymoglobulin 0.5 mg/kg
-5	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2, thymoglobulin 1 mg/kg
-4	IV fludarabine 35 mg/m^2, thymoglobulin 1.5 mg/kg
-3	IV fludarabine 35 mg/m^2, thymoglobulin 1.5 mg/kg
-2	IV thymoglobulin 1.5 mg/kg
-1	Rest
0	Infuse bone marrow graft

GVHD prophylaxis – BMT CTN 1503

Day	Regimen
-3	tacrolimus through day +180; taper per institutional standards; may use cyclosporine if unable to tolerate tacrolimus
0	Bone marrow infusion
+1	IV methotrexate 7.5 mg/m^2
+3	IV methotrexate 7.5 mg/m^2
+6	IV methotrexate 7.5 mg/m^2
+11	IV methotrexate 7.5 mg/m^2

Study Design - BMT CTN 1503



Reduced Intensity Conditioning before HLA-Haploidentical Bone Marrow Transplantation in Patients with Symptomatic Sickle Cell Disease

BMT CTN protocol development

Michael R. DeBaun MD MPH

Mark Walters, MD

Robert Brodsky, MD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haplo-ID BMT for SCD - Hopkins

- Conditioning regimen
  - ATG, CPM 14.5 mg/kg x 2, Flu with post-BMT CPM
- Replaced tacrolimus with sirolimus to avoid posterior reversible encephalopathy syndrome

29 consecutive patients treated
First cohort; 8/14 (57%) engrafted
Second cohort; 10/15 (67%) engrafted
Overall engraftment 62% with 97% survival

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

- Bolanos-Meade J et al, Blood 22:4285, 2012 and Brodsky R, et al. Foundation for sickle cell disease research meeting, Miami. April 2014.

Haplo-ID BMT for SCD – St. Mary's, London

- 12 patients (11 with SCD and 1 with thal major)
- Flu 150 mg/m^2, CPM 29 mg/kg, Thiotepa 10 mg/kg, rATG 4.5 mg/kg, TBI 2 Gy with HU/azathioprine 2 months before prep

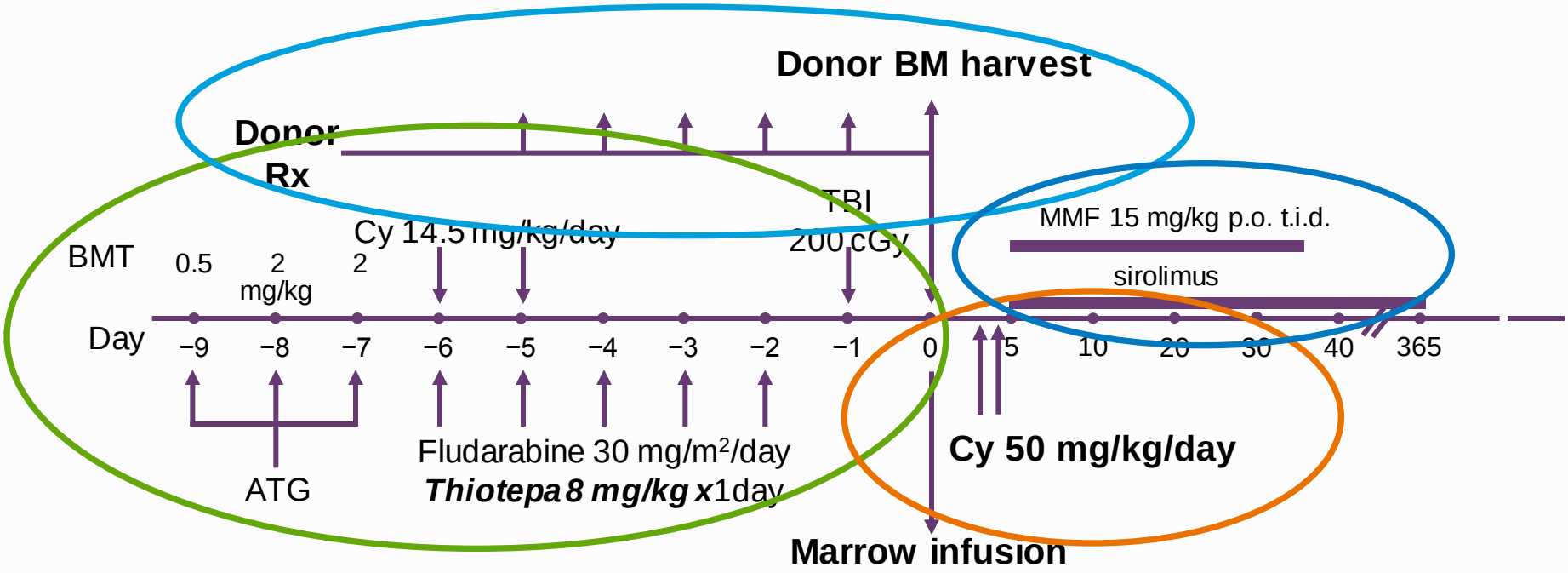
11/12 have full or partial donor chimerism (92%)
1/12 had graft rejection (8%) and also died

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Delafuente, et. al EBMT 2015.

Haplo-ID BMT for SCD – BMT CTN proposal June 2015

HU 30 mg/kg day -51 to -9



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Balaños-Meade J, et al. Blood. 2012;120:4285-91.

Primary Objective – Ph II study to define an optimal regimen for HaploID BMT

- Two co-primary end-points for power analysis: Overall survival (OS) and event-free survival (EFS) at 1 year
- Events for EFS: Death, severe GVHD, 1° or 2° GF with (or without) disease recurrence, or sickle complications by 1 year

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

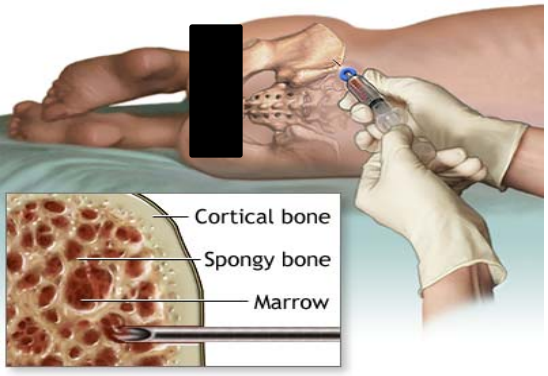
Study populations

- 2 strata
  - Children <16 years of age who have had a cerebral infarction (clinically overt or silent)
  - Adults 16-45 years of age with severe symptoms
- Analyzed together for two co-primary endpoints of OS and EFS at 1 year

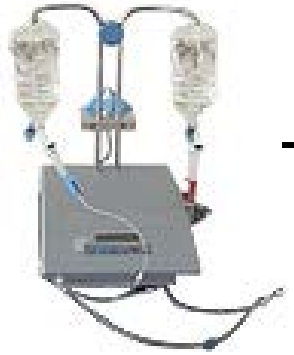
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Clinical Trial of Stem Cell Gene Therapy for Sickle Cell Disease

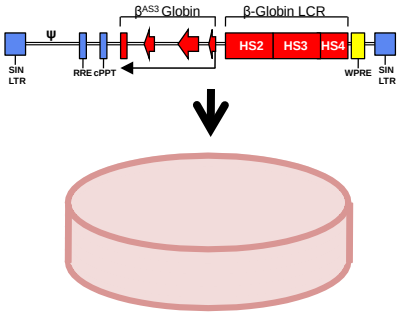
Autologous Bone Marrow Harvest



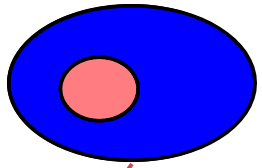
Isolate BM Stem Cells

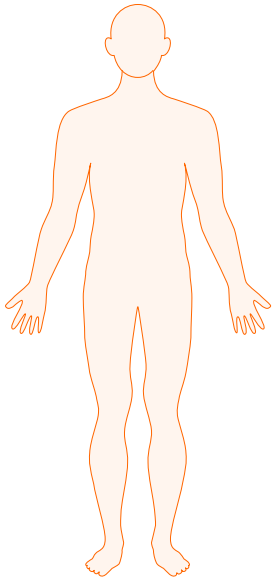


Add a Normal B-globin Gene



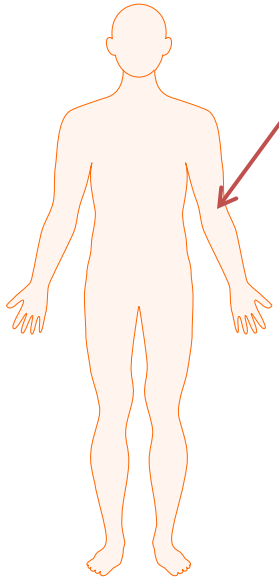
Test Cells. Freeze.





Condition with chemotherapy

Transplant BM Cells Back to Patient



Follow:
Safety
Efficacy

Gene therapy for SCD

Table 1. Demographics and Transplantation Outcomes

Subject	Age (years) /gender	Genotype	BB305 Drug Product		Day of Neutrophil Engraftment	Drug Product-related Adverse Events	Day of last pRBC transfusion	Last Study Visit	Hb amounts at last visit (g/dL)
			VCN[a]	CD34+ cell dose (x10^6 per kg)					
Subjects with β-thalassemia major									**HbA^{T87Q}/ Total Hb**
1201	18 F	β^0/β^E	1.5	8.9	Day +13	None	Day +10	12M	7.7/11.0
1202	16 M	β^0/β^E	2.1	13.6	Day +15	None	Day +12	9M	9.4/13.2
Subject with severe sickle cell disease									**HbA^{T87Q}/ HbS/HbF/Total Hb**
* 1204	13 M	β^S/β^S	1.2 / 1.0	5.6	Day +37	None	Day +88	4.5M	2.9/4.0/0.9/12.0

As of February 2015

[a] VCN, vector copy number; F=female; M= Male for gender, and months for day of last follow-up

^these authors contributed equally

*** At 4.5 mos post infusion, no sickle-related events and tapering RBC txns**

Cavazzana et al, ESH abstract, 2015

Summary

- HCT for SCD in children is performed rarely, and generally used only in children with significant complications
- However, if one chose to apply HCT more broadly in the children with a suitable sibling donor, survival after HCT and with supportive care is similar
- Studies that might expand HCT to adults and haploidentical donors are under development