The FDA

Office of Minority Health, Health Equity (OMHHE)

Presents

Update on Hematopoietic Stem Cell Transplantation for patients with Sickle Cell Disease

September 25, 2019

2:00 PM-3:00 PM

CONTINUING EDUCATION

- All attendees must sign in. These numbers are used to help determine future offering.

WORKSHOP OBJECTIVES:

Session Learning Objectives:

After completion of this activity, the participant will be able to:

- Describe the most common conditioning approach used with HLA-matched sibling transplantation for children with sickle cell disease
- List the alternative donor transplant options available for patients with sickle cell disease who lack HLA-matched sibling donors
- Compare the success and toxicity rates associated with the various alternative donor transplant options for patients with sickle cell disease.

All Faculty are expected to:

- ✓ **Use generic names**. If trade names are used, those of several companies should be used rather than only that of a single supporting company.

- ✓ **Unapproved use disclosure**: CE faculty (speakers) are required to disclose to the attendees when products or procedures being discussed are off-label/unlabeled (not FDA approved) and any limitations on the information that is presented.

DISCLOSURES

- ✓ **Courtney Fitzhugh, MD, Investigator, Cellular and Molecular Therapeutics Branch, NHLBI, NIH, *may reference off-label use***

- ✓ **Jennifer Nsenkyire, Author/Speaker/Advocate, My Pool of Bethesda has nothing to disclose**

- ✓ The faculty, planning committee, and FDA CE Consultation and Accreditation Team have nothing to disclose.

REQUIREMENTS FOR CONTINUING EDUCATION

Attend the activity, verified by Sign-in Sheet. Sign-in is required to document your attendance. Your name must be legible to receive credit. For multi-day activities, participants must sign in each day.

Requirements for Receiving CE Credit

Physicians, pharmacists, nurses, and those claiming non-physician CME: participants must attest to their attendance and complete the final activity evaluation via the CE Portal (**ceportal.fda.gov**). For multi-day activities, participants must attest to their attendance and complete the faculty evaluation each day.

Final activity evaluations must be complete within two weeks after the activity - no exceptions (October 10, 2019). Detailed instructions on how to claim credit will be sent out after the activity concludes. The claiming code for today's activity is: OMH2019RSS1

REQUIREMENTS FOR CONTINUING EDUCATION CONT'D

Pharmacy participants: partial credit cannot be awarded, therefore you must attend the entire activity to receive CPE credit. That means every day/every session. No exceptions. Pharmacists will need their NABP e-profile ID number as well as their DOB in MMDD format to claim CE credit.

Important Note regarding completion of evaluations and receiving credit Attendees have 14 days from the last day of the activity to log in, complete the required evaluation(s) and attest to your attendance to claim credit. Physicians and nurses may then view/print statement of credit. Pharmacists should log into the CPE monitor 10 weeks after the last session of the activity to obtain their CE credit.

CONTINUING EDUCATION:
ADOBE PARTICIPANTS

Continuing education credit will be available for those who attend via Adobe Connect. Pre-Registration via Adobe is required.

As a reminder to receive CE credit, participants must **“sign in”** by pre-registering in ADOBE, using your first name, last name, e-mail address, and identifying your disciplines and completing the final evaluation survey.

Update on Hematopoietic Stem Cell Transplantation for Sickle Cell Disease

Courtney D. Fitzhugh, M.D.
Investigator
Lasker Clinical Research Scholar
Laboratory of Early Sickle Mortality Prevention

Disclosures

- No financial disclosures
- The off-label use of alemtuzumab and pentostatin in nonmyeloablative peripheral blood stem cell transplantation will be discussed

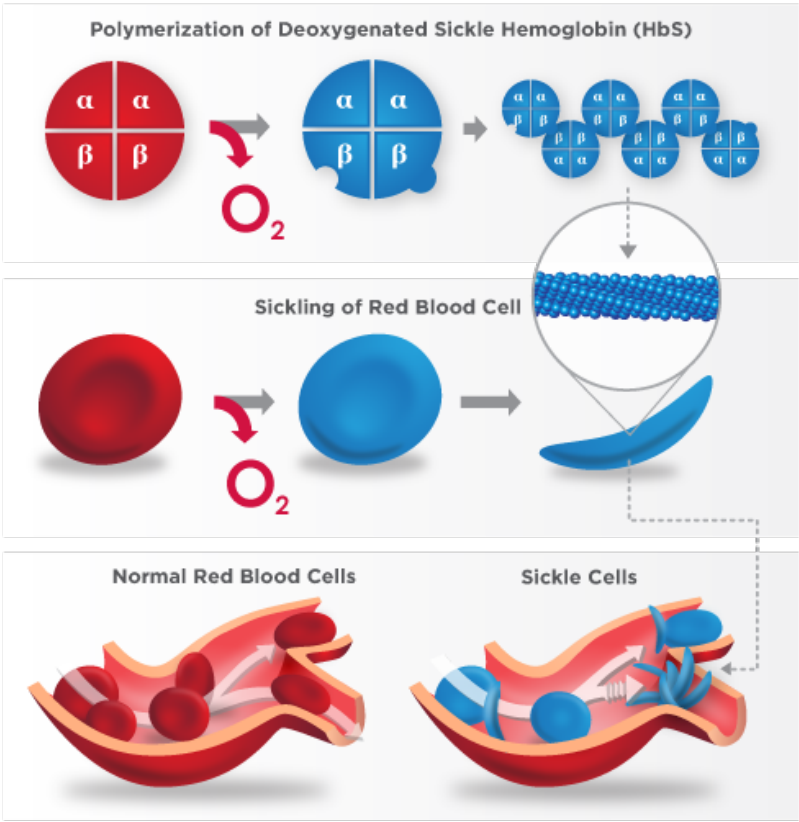
CLASSICS OF BIOLOGY AND MEDICINE

Peculiar Elongated and Sickle-shaped Red Blood Corpuscles in a Case of Severe Anemia[a]

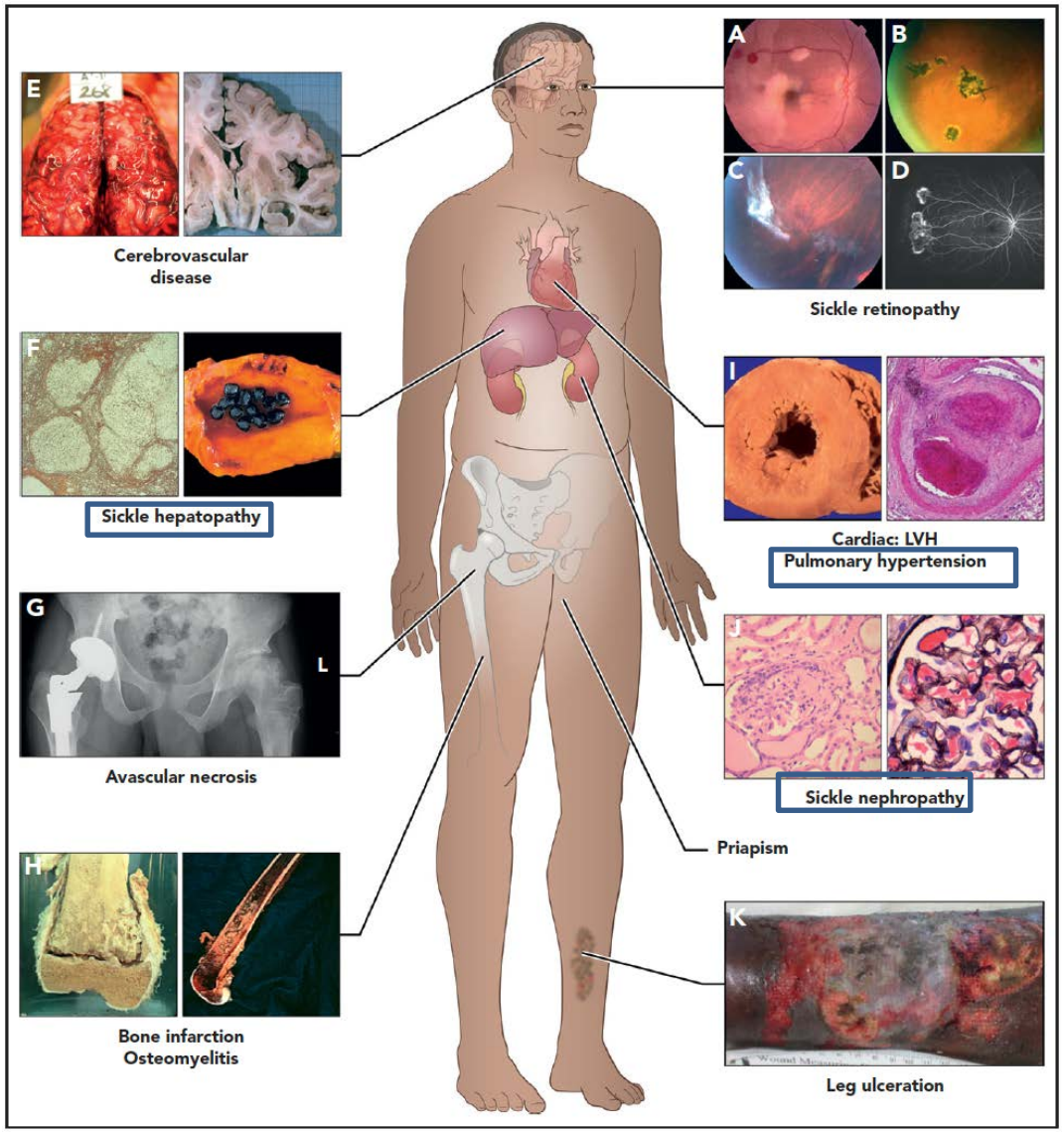
James B. Herrick, M.D.

1013 State Street, Chicago, Illinois

- Sickle cell disease was first reported in 1910
- Single substitution at position 6 of ß-globin chain
- Abnormal Hb polymerization upon deoxygenation

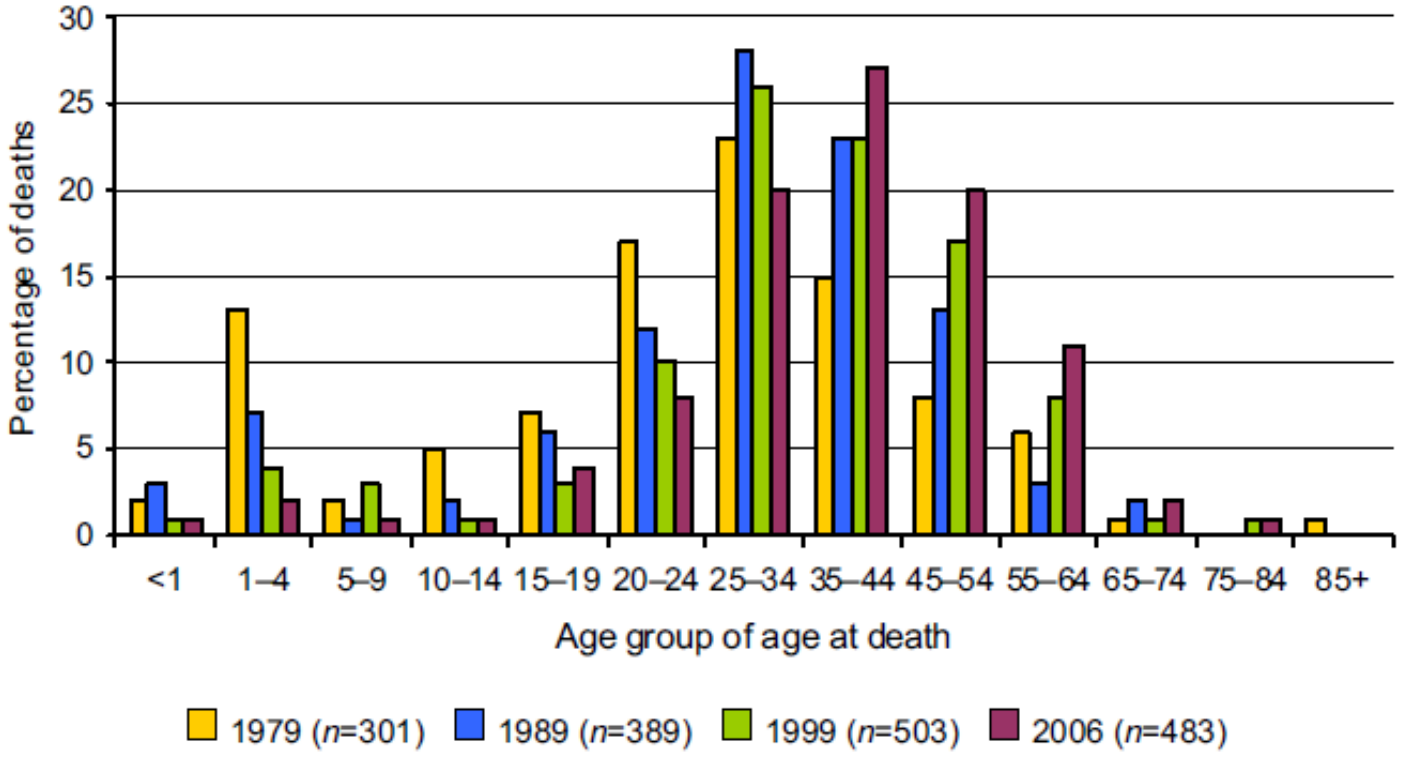


Complications of Sickle Cell Disease



Thein, SL et al. Blood, 2018. 132(17): 1750-1760.

Adults with SCD Die Prematurely

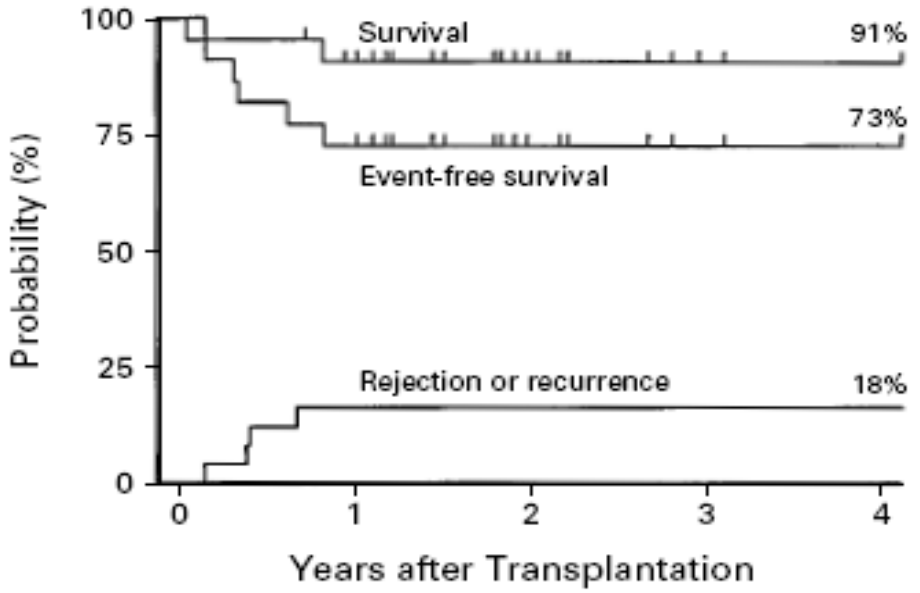


- Median age at death for adults was 39 in 2006[1] and 46 in 2015[2]
- Hematopoietic stem cell transplantation offers a potential cure which may improve quantity and quality of life

1 Hassell K. American J Preventive Medicine, 2010. 38: S512
2 Fitzhugh CD et al., PLoS One, 2015. 10(11): 1-13.

Myeloablative HLA-Matched Sibling HSCT Offers a Potential Cure for Pts with SCD

- 22 children <16 years of age underwent myeloablative (full) allogeneic HLA identical sibling marrow transplantations
- Preparative regimen included busulfan, Cytoxan, and ATG
- Patients received either MTX and CSA or CSA and prednisone for GVHD prophylaxis

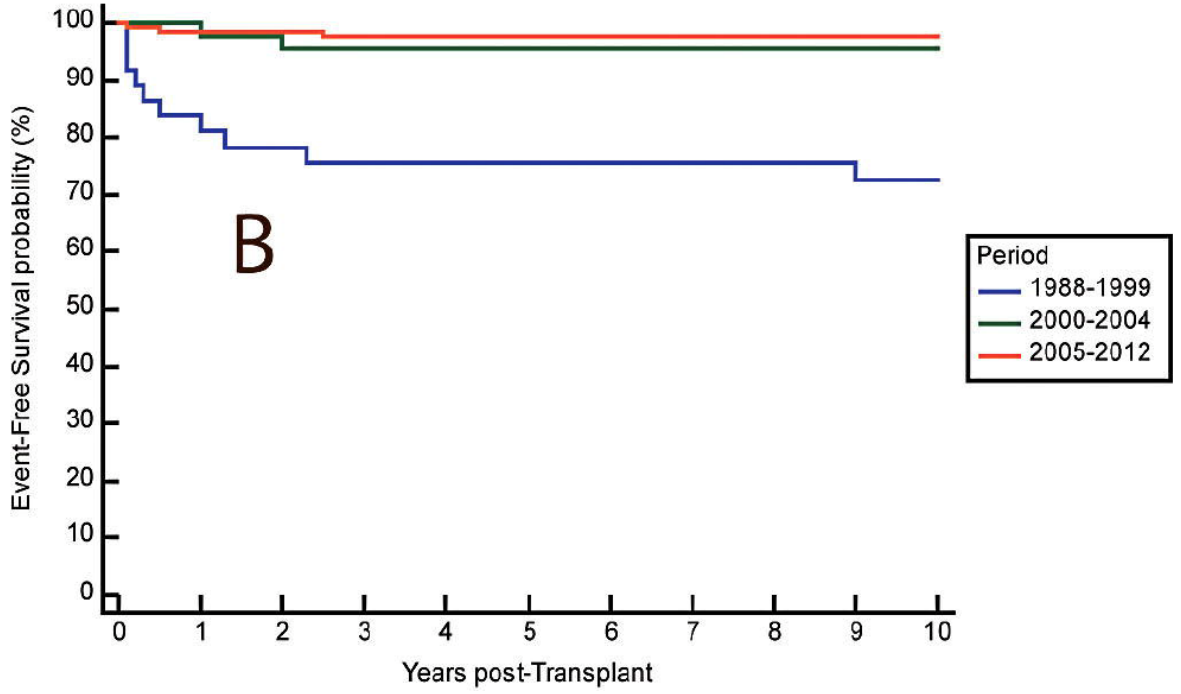


- 2 patients developed acute GVHD

Walters MC et al. The New England Journal of Medicine, 1996. 335(6): 369-376.

Improved Event-Free Survival in French Cohort

- 151 patients younger than 30 years of age received a BMT between 2005 and 2012
- Patients were conditioned with busulfan, Cytoxan, and ATG
- 5-year EFS 97.9%
- 20.1% experienced ≥grade 2 acute GVHD
- 10.5% developed chronic GVHD, 2.6% extensive



Bernaudin F et al. Haematologica, 2019. *In press*.

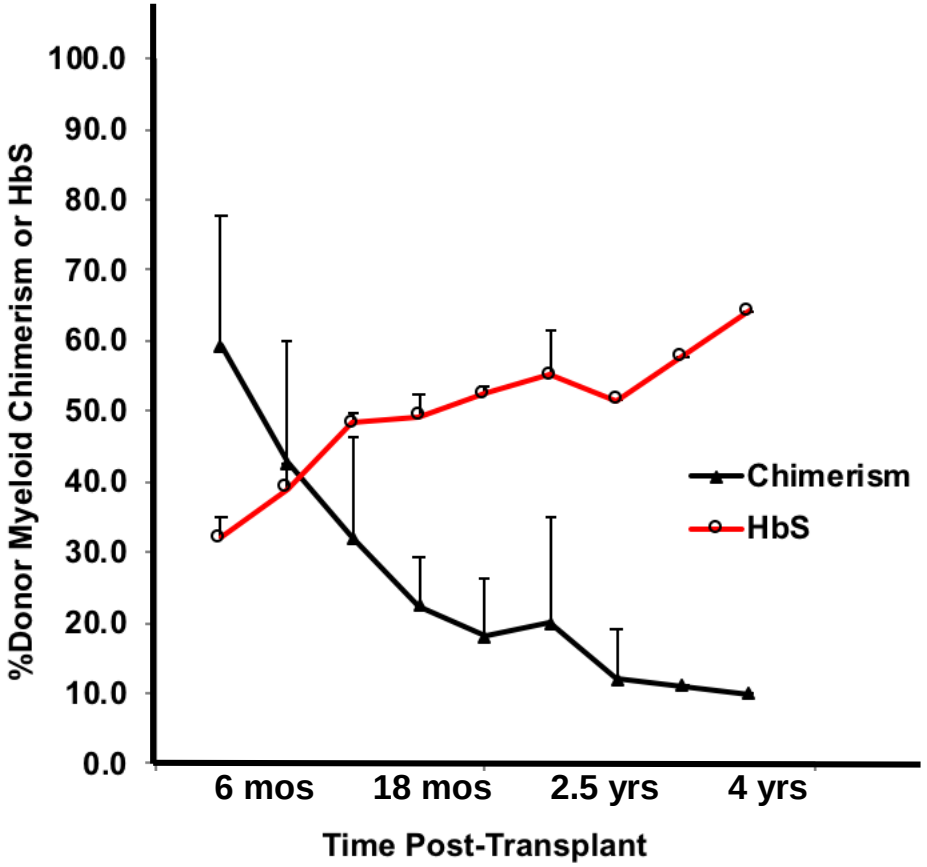
Improved Event-Free Survival in Most Recent Transplant Recipients

- 1000 patients with SCD underwent HLA-matched sibling HSCT from 1986-2013
  - 5-year overall survival 92.9%, event-free survival 91.4%
    - 5-year OS was 95% and EFS 93% for patients younger than 16 years of age
  - Cumulative incidence of grade II-IV acute GVHD was 14.8%, chronic GVHD 14.3%

Gluckman E et al. Blood, 2017. 129(11): 1548-1556.

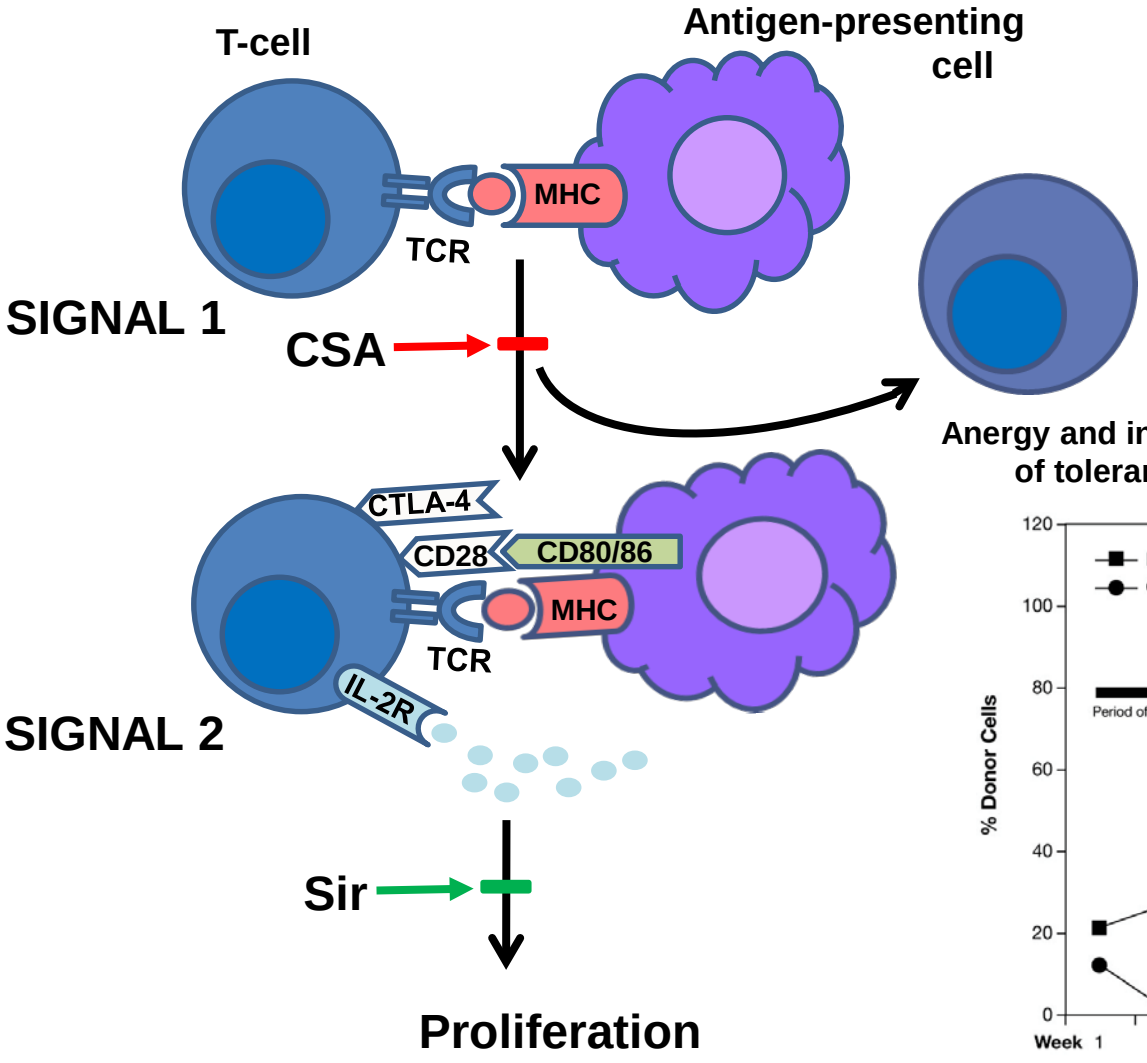
At Least 20% Donor Myeloid Chimerism is Sufficient to Reverse the Sickle Phenotype

- 67 patients who under-went nonmyeloablative HSCT at the NIH were prospectively followed
- 3 with high donor chimerism levels initially had slowly falling levels over time
- Donor myeloid chimerism level <20% was associated with return of SCD
- Our mathematical model showed that a minority of donor cells is adequate due to differences in RBC survival between donor and recipient cells



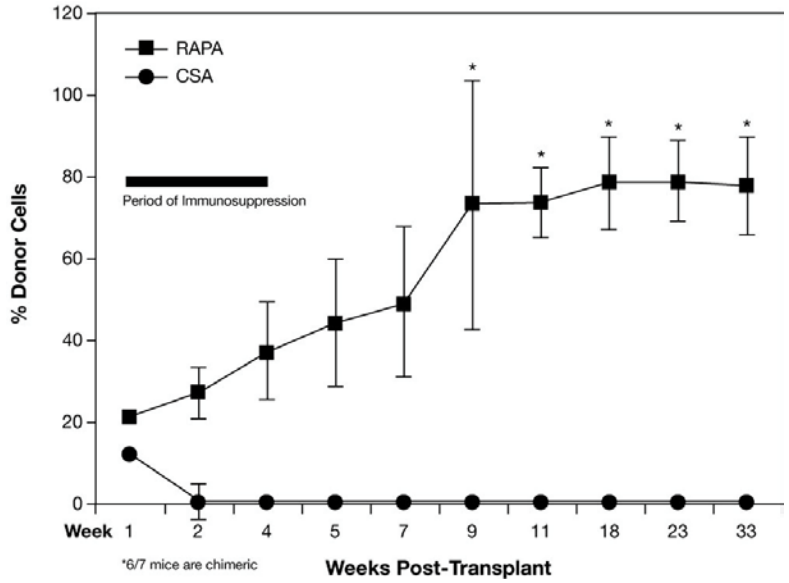
Fitzhugh CD et al. Blood, 2017. 130(17): 1946-1948.

Sirolimus, Unlike Cyclosporine, Facilitates Tolerance Induction and Stable Mixed Chimerism



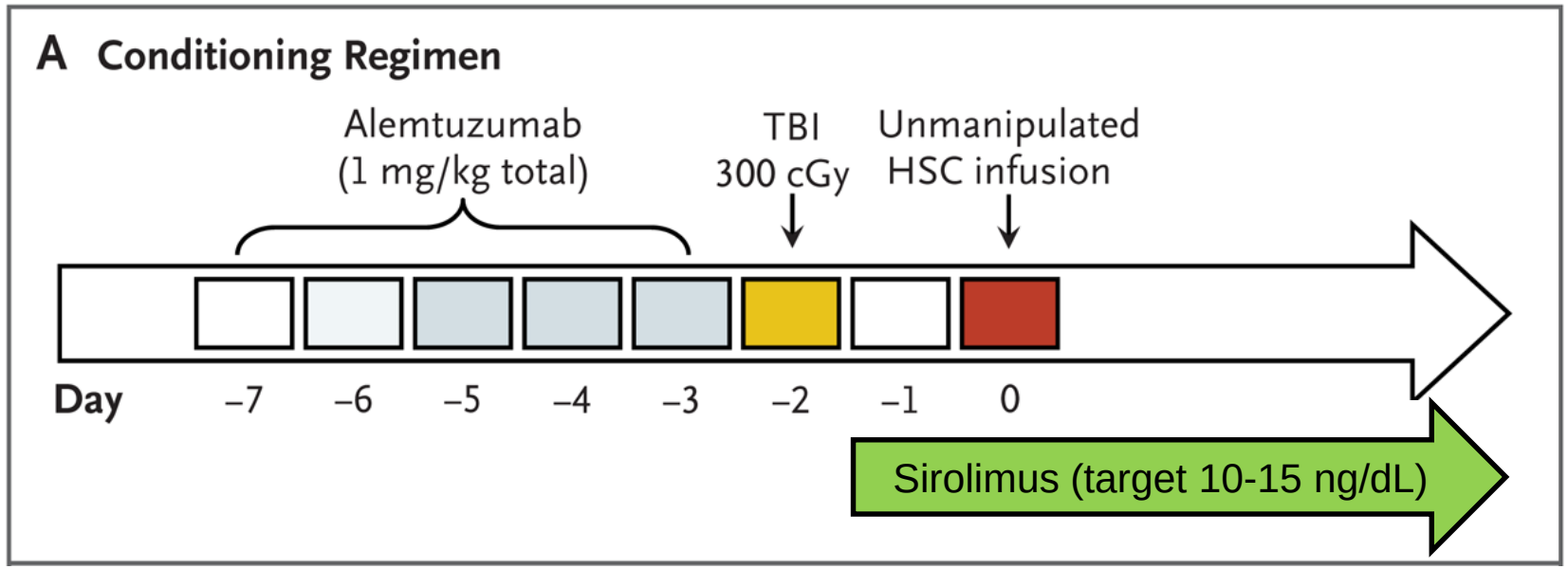
- F1 into parent model
- Sirolimus or CSA for 30 days
- 300cGy TBI
- G-CSF-mobilized splenocytes

Anergy and induction of tolerance



Powell JD, Fitzhugh CD, et al. Transplantation, 2005. 80: 1541-1545.

Non-myeloablative HLA-Matched Sibling Peripheral Blood Stem Cell Transplant for SCD

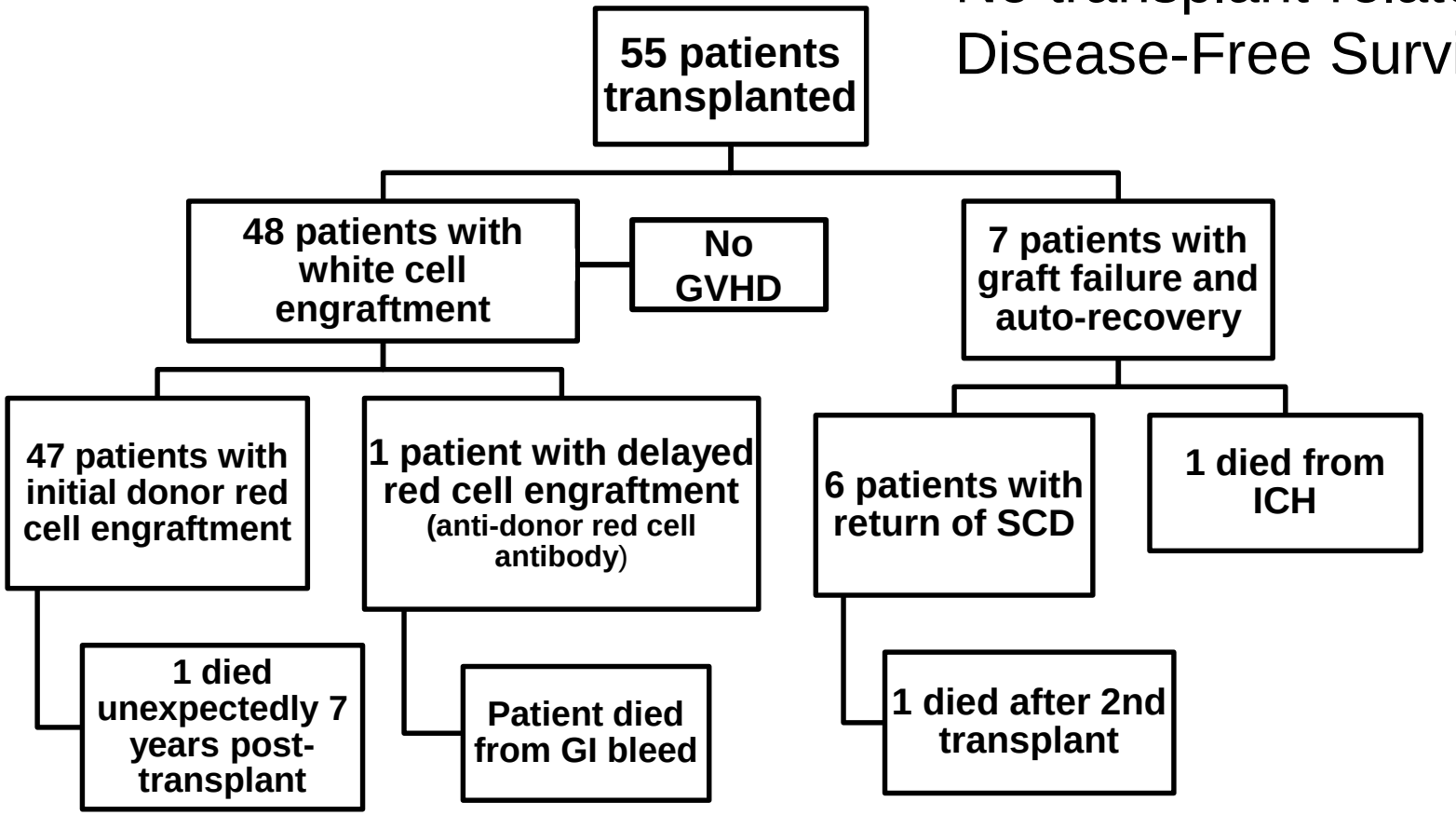


Hsieh MM, Kang E, Fitzhugh CD, et al. NEJM, 2009. 361(24): 2309-2317.

Transplant Outcome

Age range: Median 29, range 10-65 years old
Follow-up: 6.4 years (range 0.5-14.4 years)

Overall Survival: 93%
No transplant-related mortality
Disease-Free Survival: 87%



Matthew Hsieh
John Tisdale

8 patients have had 13 healthy babies post-transplant

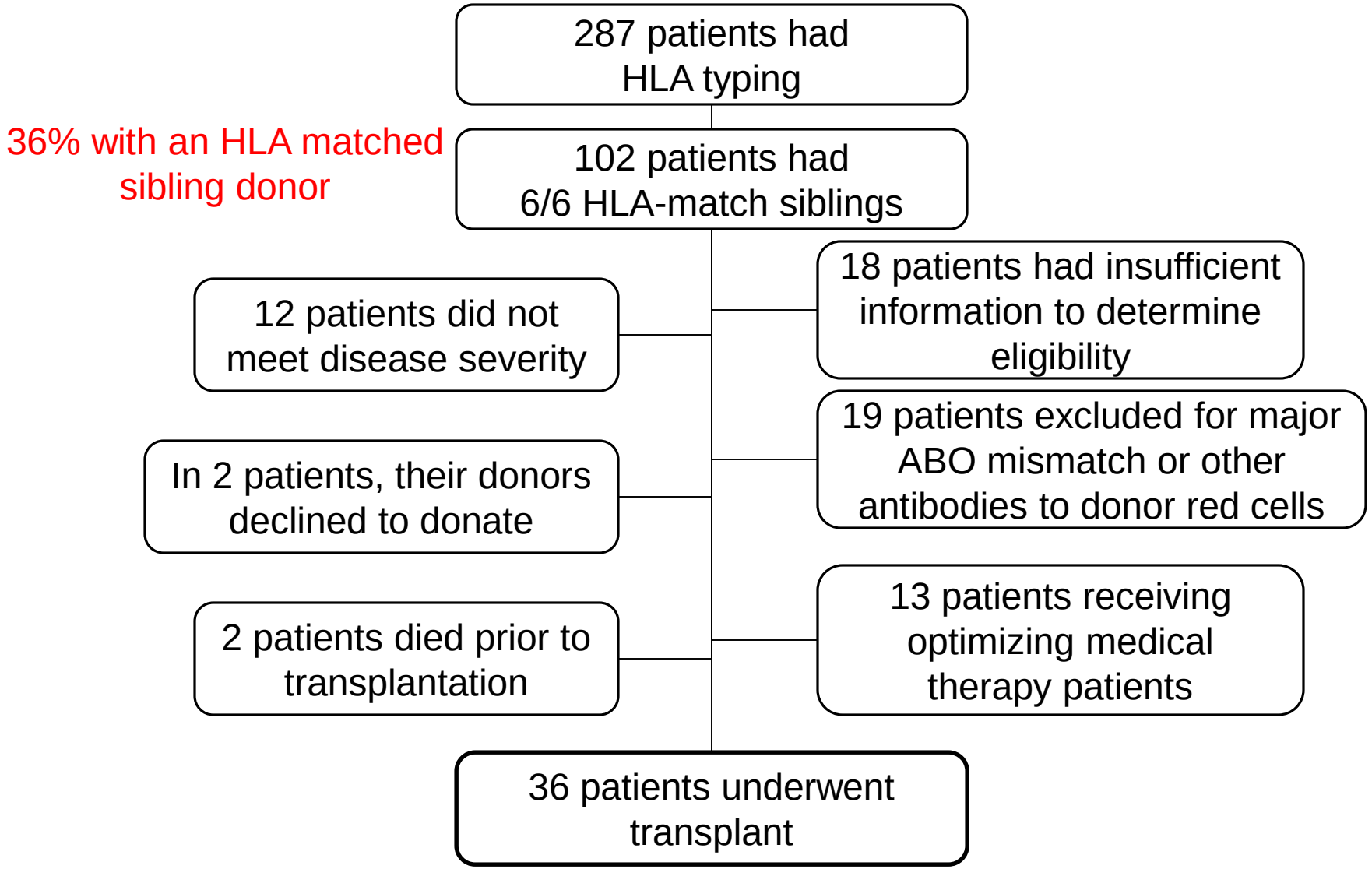
Our Results Were Duplicated at Other Institutions

- 12 of 13 adults at University of Illinois, Chicago free of SCD (=92% event-free survival)[1]
  - No GVHD
- 31 of 34 patients ≥14 years in Saudi Arabia free of SCD (=91% event-free survival)[2]
  - No GVHD
- 16 of 16 children down to 3 years of age in Alberta, Canada free of SCD (=100% event-free survival)[3]
  - No GVHD

1. Saraf SL et al. Biology of Blood and Marrow Transplantation, 2015. 22(3): 441-448.
2. Alzahrani M et al. American Society of Hematology Annual Meeting, 2018.
3. Guilcher G et al. Biology of Blood and Marrow Transplantation, 2019. 25(6): 1179-1186.

Why aren’t More Patients with Sickle Cell Disease Transplanted?

Vast Majority of Patients do not have an HLA-Matched Sibling



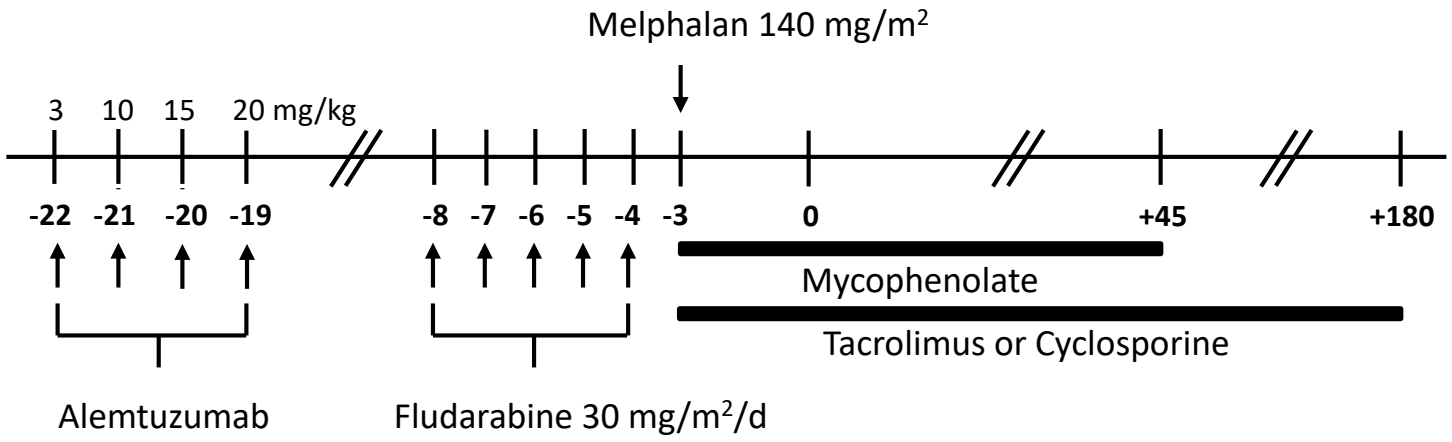
Pediatric *Related* Umbilical Cord Transplants for SCD

Reference	Transplant regimen	HLA match	Number of patients (age range)	Alive without SCD	Acute GvHD (Gr 2-4)	Chronic GvHD (extensive)	Death (cause)
Brichard, 1996	Bu 16 mg/kg, Cy 200 mg/kg, ATG, CSA	6/6	1 (5)	1	0	0	0
Miniero, 1998	Bu 16 mg/kg, Cy 200 mg/kg, CSA +/- MTX	6/6	3 (3-11)	2	0	0	0
Gore, 2000	Bu 726 mg/m^2, Cy 200 mg/kg, ATG, CSA	6/6	1 (9)	1	0	0	0
Walters, 2005	NR	6/6 42 pts, 4/6 4 pts*	8 (NR)	6	NR	NR	1 (intractable seizures)
Matthes-Martin, 2013	TLI (2 Gy), Flu 160 mg/m^2, Mel 140mg/m^2, Alem 1mg/kg, CSA, MMF	6/6	1 (11.1)	1	0	0	0
Locatelli, 2013	Bu +/- Flu +/- Cy +/- ATG/ ALG +/- TT, CSA +/- MTX	6/6	30 (2-20)*	27	11% (Gr 2-3)*	0	3 (2 hemorrhage, 1 organ failure)*
Total	-	Mostly 6/6	44	38 (86%)	11%	0	9% (of total)

*Includes patients with sickle cell disease and thalassemia

Pediatric Unrelated Cord Blood Transplant for Sickle Cell Disease

- Initial study
  - 8 children (age 7-16 years)



  - Overall survival 88%, disease-free survival 38%

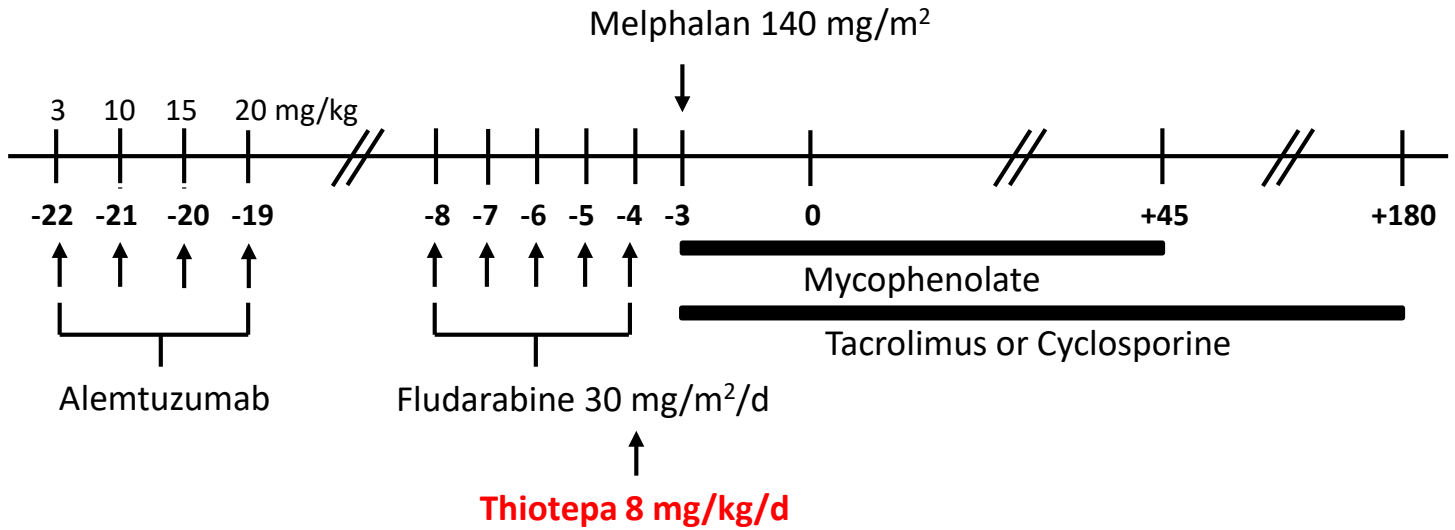
Kamani NR et al. Biol Blood Marrow Transplant, 2012. 18: 1265-1272.

Pediatric *Unrelated* Umbilical Cord Transplants for SCD

Reference	Transplant regimen	HLA match	Number of patients (age range)	Alive without SCD	Acute GvHD (Gr 2-4)	Chronic GvHD (extensive)	Death (cause)
Adamkie-wicz, 2007	Mixed, 4 pts myeloablative, 3 pts reduced-intensity	5/6 2 pts, 4/6 5 pts	7 (3.4-16.8)	3	4	1	1 (multi-organ failure)
Ruggeri, 2011	Mixed, 9 pts myeloablative, 7 pts reduced-intensity	6/6 (2) 5/6 (4) 4/6 (10)	16 (6)	8	23%	16%	1 acute GvHD
Kamani, 2012	Alem 48, Flu 150, Mel 140, CSA or tac + MMF	6/6 (1) 5/6 (7)	8 (7.4-16.2)	3	2 (Gr 2)	1 (extensive)	1 (respiratory failure)
Radhak-rishnan, 2013	Bu 12.8-16, Flu 180, Alem 54, MMF, tac	NR	8 (1-10)	4	4	0	3 (infection)
Khar-banda 2014	Flu 150, Mel 140, Alem 60, CSA, MMF	4/6	2 (8)	0	0	0	0
Total	-	Mostly mismatched	41	18 (44%)	33% (of total)	11% (of total)	15% (of total)

Pediatric Unrelated Cord Blood Transplant for Sickle Cell Disease

- Modified study
  - 9 children (age 3-10 years)



  - Overall survival 100%, disease-free survival 78%
  - 22% grade 2 acute GVHD, 11% chronic extensive GVHD

Abraham A et al. Biol Blood Marrow Transplant, 2017. 23: 1580-1596.

Matched Unrelated Donor Transplantation for Pediatric Patients with SCD

- Multicenter Phase II Trial of Unrelated Donor Reduced Intensity BMT for Children with Severe SCD (SCURT)
  - 29 patients median age 14 years (5.9-19.3)
  - Preparative regimen included alemtuzumab, fludarabine, and melphalan, and CSA/tac, methotrexate, and methylpred were given for GvHD prophylaxis
  - 1 year overall survival 86%, overall survival at time of report 76%
    - 6 patients died from GvHD
    - 1 patient died following second transplant
  - 1-year event-free survival 75%
  - 28% grade 2-4 acute GvHD (17% grade 3-4), 38% chronic extensive GvHD

Shenoy S et al. Blood, 2016. 128(21): 2561-2567.

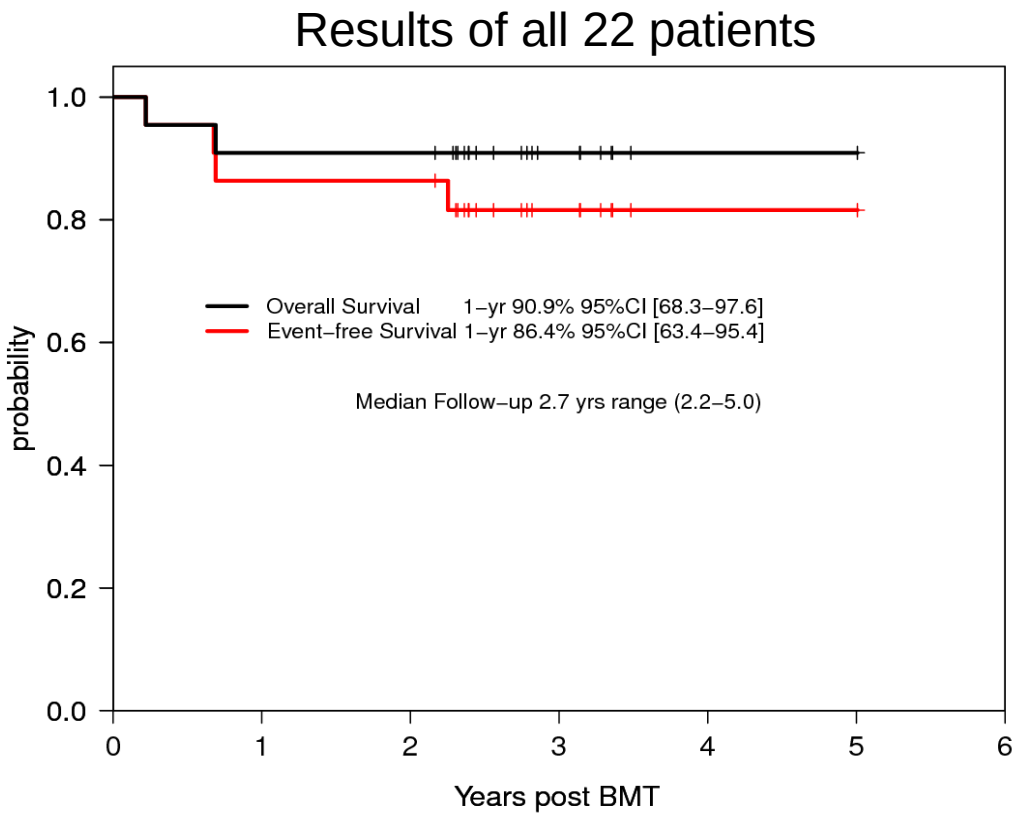
Matched Unrelated Donor Transplants for SCD

Reference	Transplant regimen	Graft Type	Number of patients (age)	Alive without SCD	Acute GvHD (Gr 2-4)	Chronic GvHD (extensive)	Death (cause)
Strocchio, 2015	Thio 10, Treo 42, Flu 160, ATG 15-30, CSA, MTX	BM (5) PBSCs (1)	6 (27-48)	5	0	0	0
Shenoy, 2016	Alem 45, Flu 150, Mel 140, CSA or tac, MTX, Methylpred	BM	29 (6-19)	20	8	11	6 (GVHD) 1 (following 2nd transplant)
Marzollo, 2017	Thio 8-10, Treo 42, Flu 160, ATG 20-60, +/- MTX, CSA	BM or T-cell depleted PBSCs*	2 (6.5-10.5)	2	2 Gr 2	0	0
Gillman, 2017	Mel 140, Thio 10, Flu 200, ATG 10 +/- Ritux 150, MTX	PBSCs	2 (5-13)	2	0	0	0
Total	Mixed	BM or PBSCs	39	29 (74%)	26% (of total)	28% (of total)	15% (of total)

*T-cell depleted PBSCs were infused for the 1 mismatched unrelated donor transplant

Matched Unrelated Donor Transplant for Adolescents and Young Adults with SCD

- 22 patients median age 22 years
  - 17 HLA-matched sibling
  - 5 MUD
- Busulfan, Fludarabine, ATG
- CSA/tac and methotrexate for GVHD prophylaxis
- MUD results
  - 4 of 5 alive
  - 3 of 5 free of SCD
    - 4th SCD-free after 2nd transplant
  - 1 patient developed grade 3 acute GVHD and 1 severe chronic GVHD



Krishnamurti L et al. American J Hematology, 2019. 94(4): 446-454.

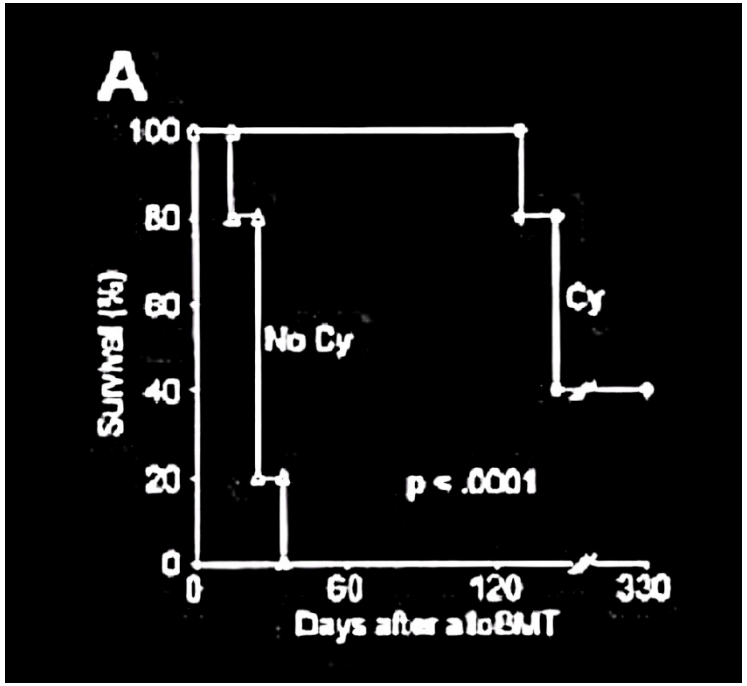
BMT CTN #1503

- Phase 2 multi-center study comparing 2-year overall survival in young adults with severe SCD who receive transplant compared to standard of care
- Age 15-40 years
- Donors:
  - HLA-matched sibling
  - Matched unrelated donor

Haploidentical PBSC Transplantation for Adults with Severe Sickle Cell Disease

- Haploidentical donors
  - Most accessible
  - Large cell doses feasible
  - Repeat collections feasible
- Immunologic barrier greater
  - Higher degree of immunomodulation
- Post-transplant cyclophosphamide
  - Generates alloreactive functional T-cell impairment[1]
  - Preserves regulatory T cells[2]
  - Reduced GvHD

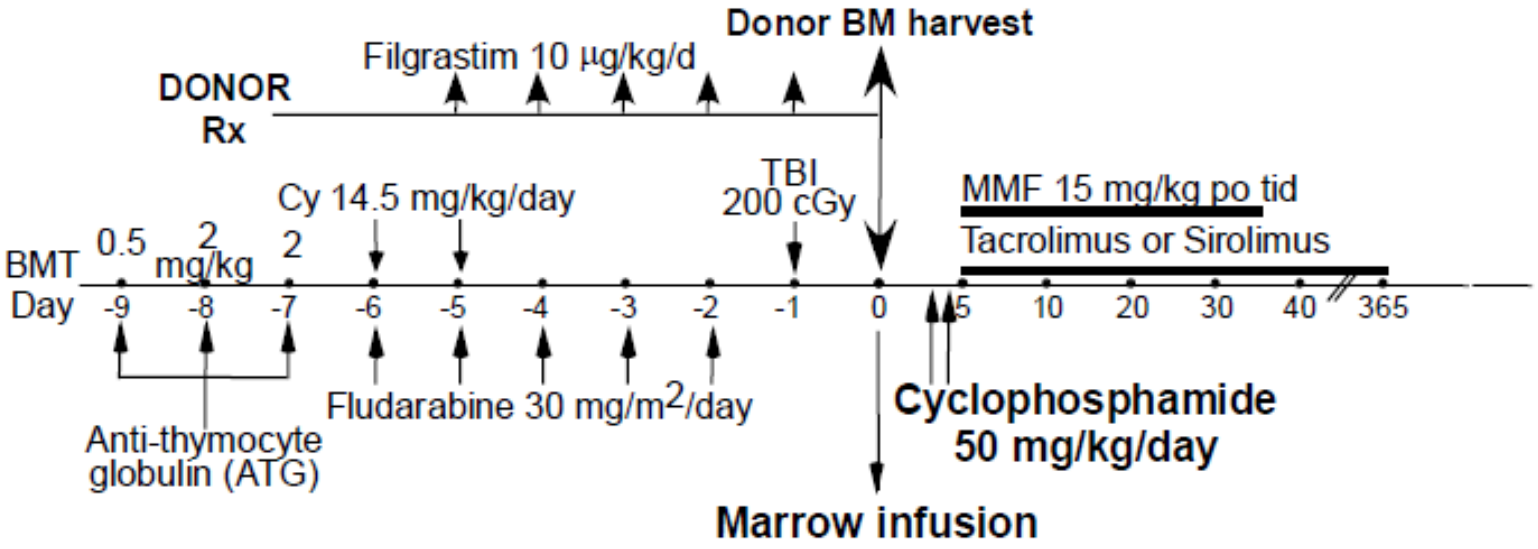
Murine GvHD Model



1 Wachsmuth LP et al. J Clin Invest, 2019. 129(6): 2357-2373.
2 Kanakry CG et al. Sci Transl Med, 2013. 5(211): 1-12.

Post-Transplant Cyclophosphamide in the Haploidentical Setting for Patients with Severe Hemoglobinopathies

- 17 patients received BMT, 14 haploidentical donors, 3 HLA-matched sib donors
- Median age 30 (15-46 years)



Balanos-Meade J et al. Blood, 2012. 120(22): 4285-4291.

ID	% Whole Blood Chimerism (most recent)	% CD3+ Chimerism (most recent)	Donor HbS (%)	6 month HbS (%)	Most recent hemoglobin (g/dL)
1	100	N/A	0	0	13.6
2	R	R	N/A	N/A	N/A
3	100	100	38.4	40.4	14.8
5	R	R	N/A	N/A	N/A
6	92	100	N/A	<5.0	11
7	100	100	38.9	39.2	9.6
8	R	R	N/A	N/A	N/A
9	5	6	39.6	60.8	6.2
10	100	100	38.2	38.7	11.1
12	R	R	N/A	N/A	N/A
14	R	R	N/A	N/A	N/A
15	R	R	N/A	N/A	N/A
16	100	>95	0	0	13
17	100	100	39.7	40.8	12

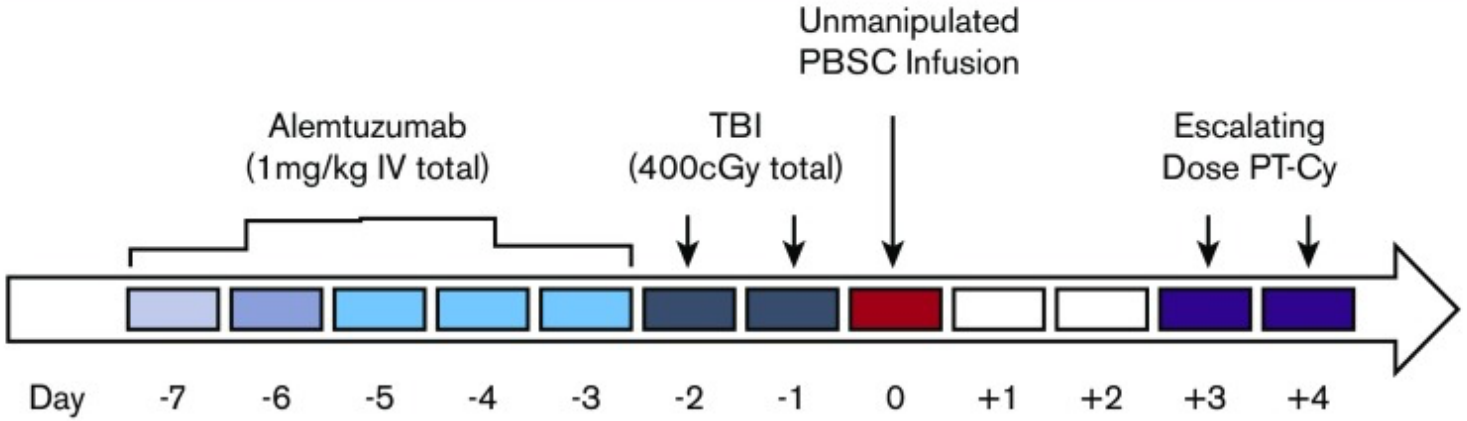
- 100% Overall Survival
- 50% Disease-Free Survival
- No acute or chronic GvHD
- 75% engrafted patients off of immunosuppressive therapy

Nonmyeloablative Haploidentical PBSC Transplantation for Adults with Severe Congenital Anemias

- Hb SS, SC, or Sβ^o-thal dz
  - Stroke
  - Sickle cell nephropathy
  - RHC-documented Pulmonary HTN
  - Sickle hepatopathy

Complication	Eligible for Hydroxyurea (HU)	Eligible for HSCT
Vaso-occlusive crises	At least 3 hospital admissions in the last year	More than 1 hospital admission per year while on HU
Acute chest syndrome (ACS)	2 prior ACS	Any ACS while on HU

Nonmyeloablative Haploidentical PBSC Transplantation for Adults with Severe Congenital Anemias

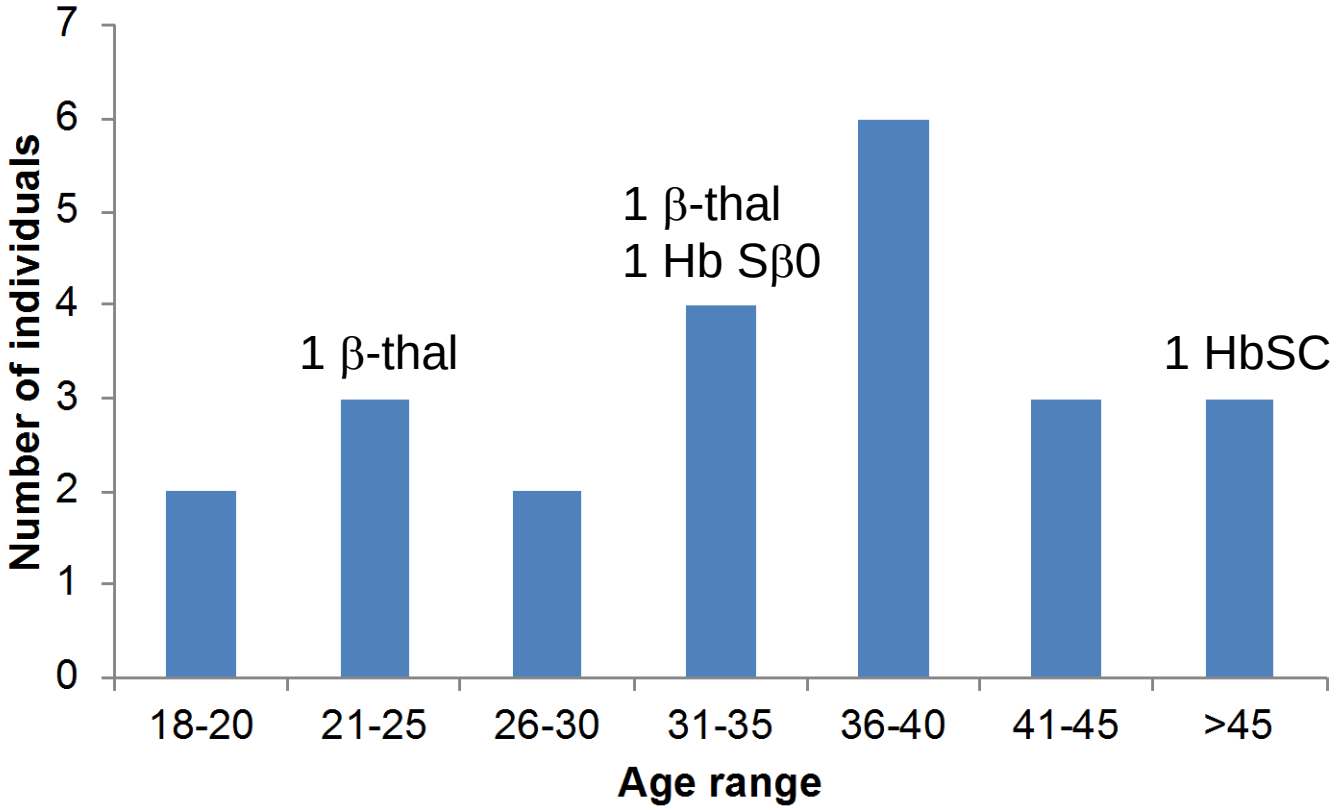


Cohort Number	Cyclophosphamide Dose (mg/kg/dose)	Day Post-Transplant	Cumulative Cyclophosphamide Dose (mg/kg)	Sirolimus Start Day Post-Transplant
1	0	N/A	0	-1
2	50	+3	50	-1 or +4
3	50 50	+3 +4	100	+5

Fitzhugh CD et al. Blood Advances, 2017. 1(11): 652-661.

Nonmyeloablative Haploidentical PBSC Transplantation for Adults with Severe Congenital Anemias

- N = 23
- Age range: Median 36, range 20-56 years old
- Follow-up: 5.9 years (range 3.4-8.6 years)
- Except where indicated, the remainder have HbSS



Haplo Patients with Severe Organ Damage Tolerate Conditioning

	N (%)
Hepatic Iron overload Cirrhosis	20 (87) 18 (78) 2 (9)
Recurrent ACS and/or VOC	19 (83)
Neurologic Stroke Moyamoya syndrome TIA	8 (35) 6 (26) 4 (17) 1 (4)
Cardiac Systolic dysfunction Diastolic dysfunction	7 (30) 5 (22) 3 (13)
Renal ESRD on PD ESRD on HD CRI with baseline Cr 2.5-5.0 mg/dL	6 (26) 3 (13) 1 (4) 2 (9)
Pulmonary hypertension	5 (22)
Autoimmune Multiple sclerosis Rheumatoid arthritis	2 (9) 1 (4) 1 (4)

Engraftment and Success Rates Improve with PT-Cy

Cohort	Cumulative Cytoxan Dose (mg/kg)	Engraftment Rate (Before Day +100)	Disease-Free Survival	GVHD
1	**0**	**1/3 (33%)**	**0/3 (0%)**	**0**

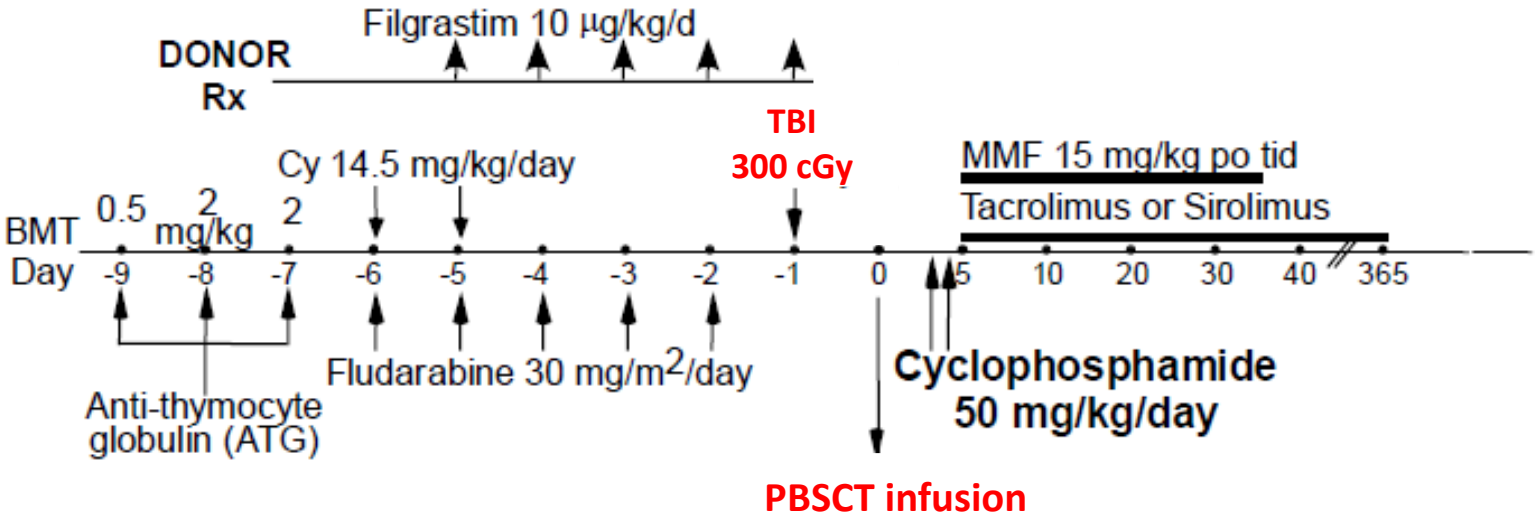
- No mortality before day 100
- 5 patients who rejected their grafts died 6 months and 3, 5, 7 and 8 years post-transplant, mostly from SCD-related complications (overall survival 78%)

Fitzhugh CD et al. Blood Advances, 2017. 1(11): 652-661.

Additional Up Front Conditioning and T cell Depletion has Improved the Outcome for Haploidentical HSCT

Modified Hopkins Regimen for Patients with SCD Undergoing Haploidentical Transplant

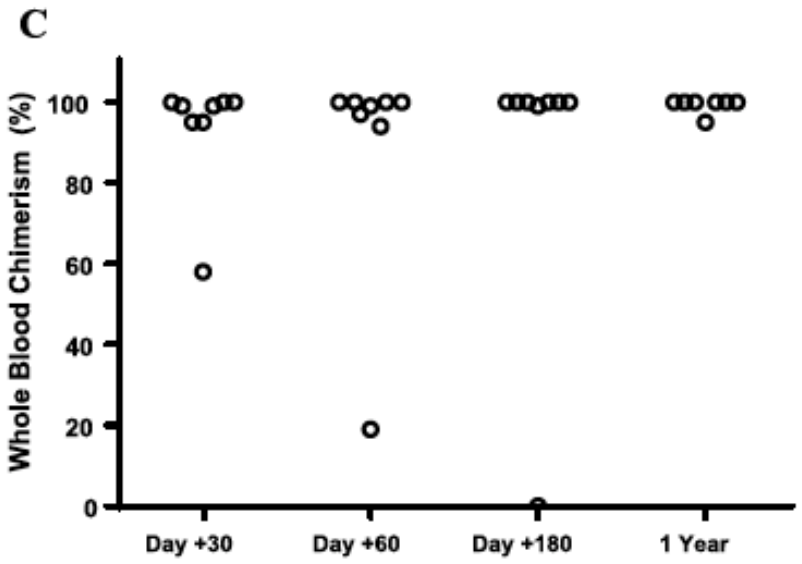
- 8 patients
- Age 20-38 years



Saraf SL et al. Biol Blood Marrow Transplant, 2018. 24: 1754-1770.

Improved Results with 300cGy TBI and Peripheral Blood Stem Cells

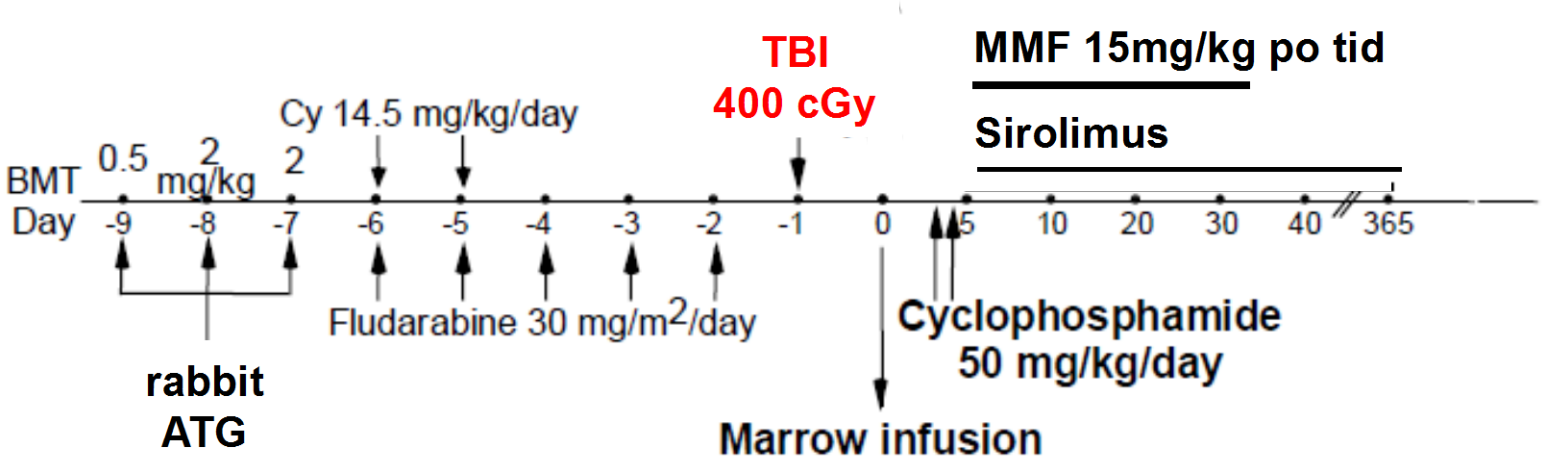
- With a median follow-up of 17 months, 6 of 8 patients are free of SCD (=Disease-free survival 75%)
  - 1 patient rejected the graft
  - 2 patients developed ≥2 acute GVHD, 1 chronic GVHD
  - 7 patients are alive (overall survival 88%)



Saraf SL et al. Biol Blood Marrow Transplant, 2018. 24: 1754-1770.

Another Modified Hopkins Regimen for Patients with SCD Undergoing Haploidentical Transplant

- 17 (12 patients with SCD, 5 patients with β-Thal)
- Age 6-31 years



Bolanos-Meade J et al. Lancet Haematology, 2019. 6(4): e183-e193.

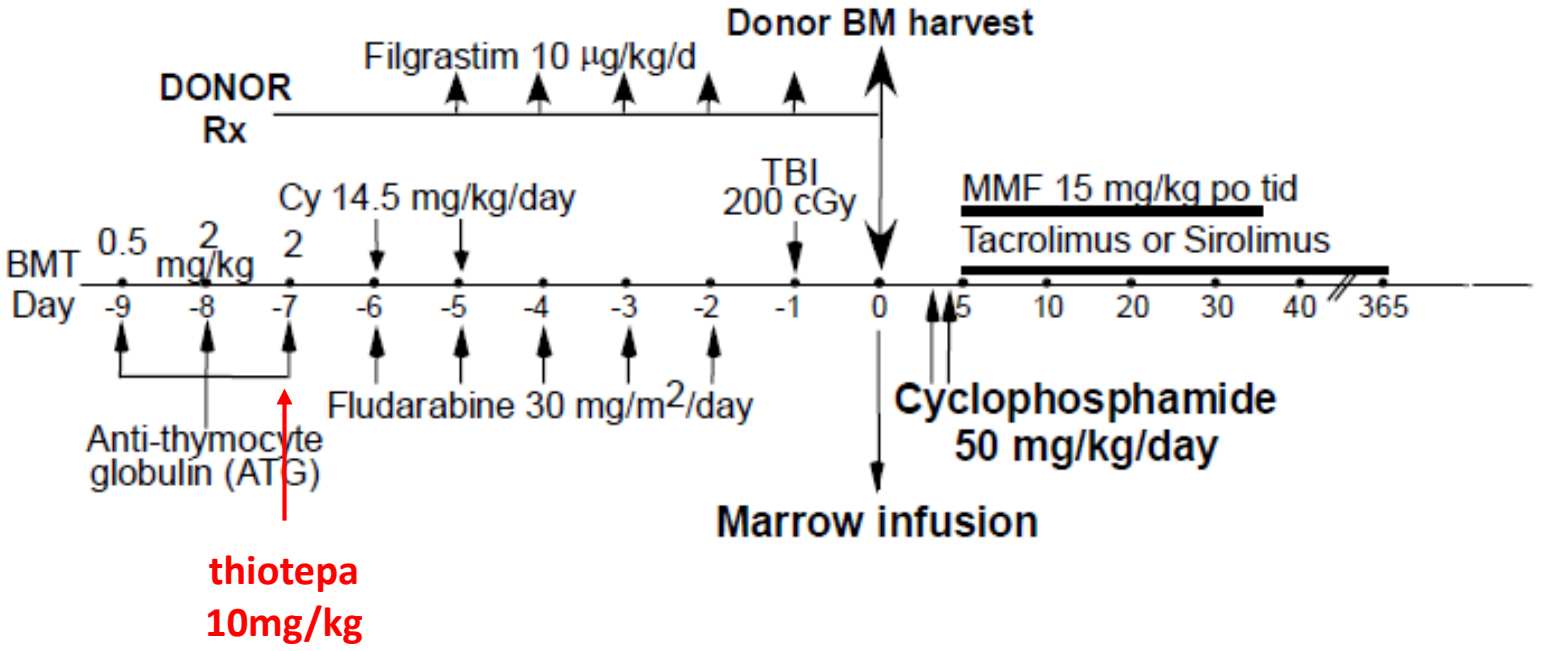
Improved Results with 300cGy TBI and Peripheral Blood Stem Cells

- 17/17 patients alive (100% overall survival)
- 83% Free of SCD
- 29% grade 2-4 acute GVHD (6% grade 3)
- 18% chronic GVHD (2 mild, 1 moderate)
- All GVHD resolved as of last follow-up with no systemic GVHD therapy
- 91% engrafted patients off of immunosuppressive therapy

Bolanos-Meade J et al. Lancet Haematology, 2019. 6(4): e183-e193.

One More Modified Hopkins Regimen for Patients with SCD Undergoing Haploidentical Transplant

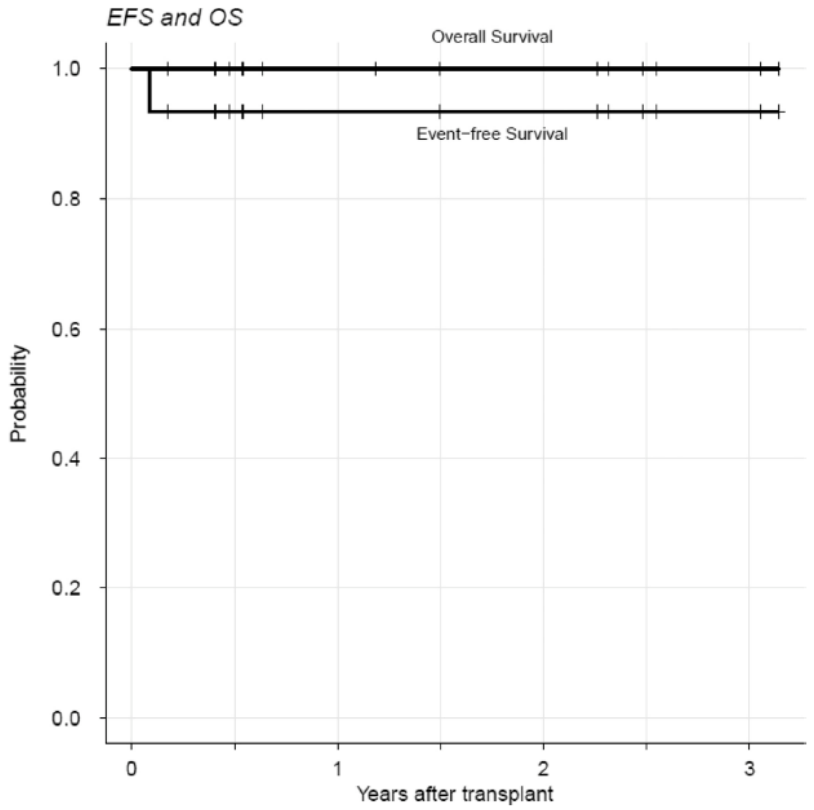
- 15 patients
- Age 12 to 26



de la Fuente J et al. Biology of Blood and Marrow Transplant, 2019. 25(6): 1197-1209.

Improved Results with Thiotepa

- With a median follow-up of 13 months
  - 15/15 patients alive (100% overall survival)
  - 14 free of SCD (=event-free survival 93%)
  - 13% grade 3-4 acute GVHD
  - 7% moderate chronic GVHD



de la Fuente J et al. Biology of Blood and Marrow Transplant, 2019. 25(6): 1197-1209.

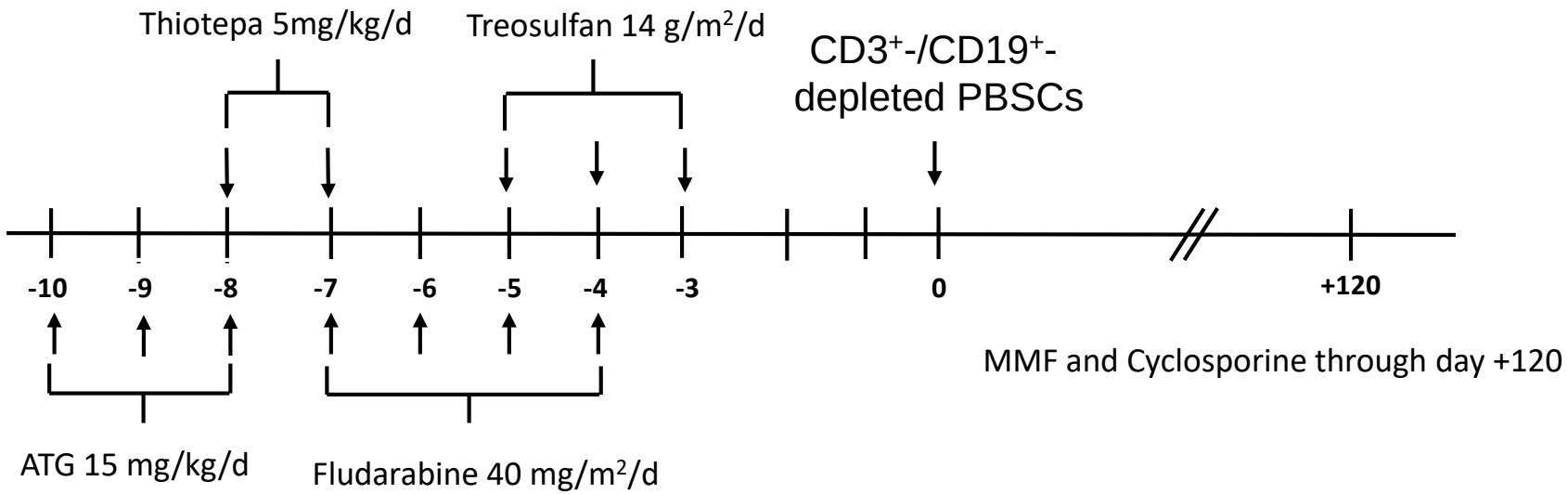
BMT CTN #1507

- Phase II, single arm, multi-center trial to estimate the efficacy and toxicity of haplo BMT in patients with sickle cell disease
- Two strata
  - Children (aged 5 – 14 years)
    - Stroke is the only indication
  - Adults (aged 15 – 45 years)
    - Stroke or neurologic event lasting >24 hours
    - ≥ 2 episodes of ACS in the 2 year period preceding enrollment
    - ≥ 3 episodes of VOC per year in the 2 year period preceding enrollment
    - Regular RBC transfusions (≥ 8 transfusions per year for ≥1 year) to prevent vaso-occlusive clinical complications (stroke, pain or ACS)
    - ECHO finding of TRJ velocity ≥2.7 m/sec (steady state)
- Sample Size
  - 40 participants per strata

Robert Brodsky, Michael DeBaun, Adetola Kassim, Mark Walters

Lymphocyte Depletion associated with High Engraftment and Low Toxicity

- 9 patients median age 16 years (range 3-31 years) underwent myeloablative haploidentical PBSCT

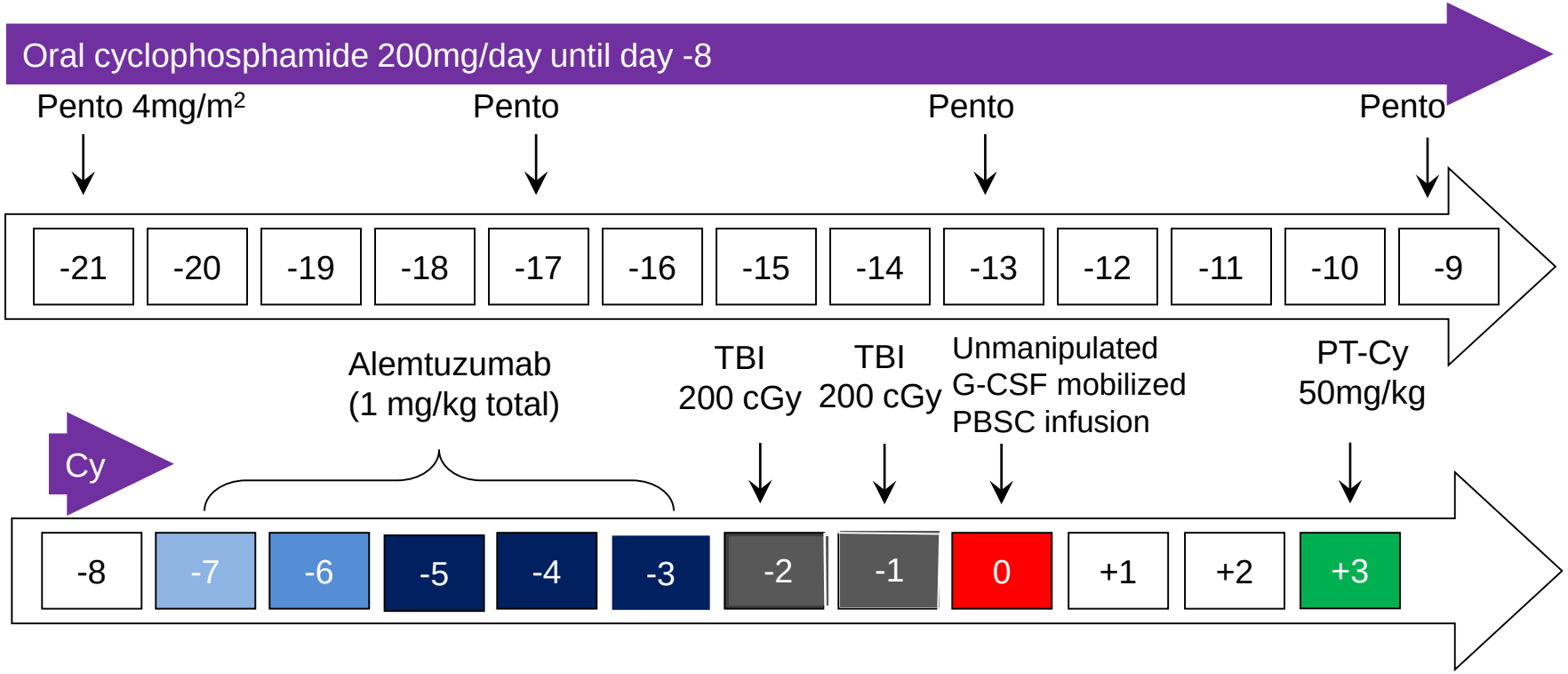


- 8 of 9 patients are free of SCD (=disease-survival 89%)
- 1 patient died from CMV pneumonitis
- 56% grade 1-2 acute GVHD, 1 moderate chronic GVHD

Foell J et al. Bone Marrow Transplant, 2017. 52(6): 938-940.

Reference	Transplant regimen	Graft Type	# of patients (age)	Alive without SCD	Acute GvHD (Gr 2-4)	Chronic GvHD (extensive)	Death (cause)
Foell, 2017	Thio 10 mg/kg, Flu 160 mg/m2, Treo 42 g/m2, ATG 45 mg/kg, CSA, MMF	CD3/ CD19 depleted PBSC	9 (3-31)	8	56% (Gr 1-2)	1 (moderate)	1 (CMV)
Marzollo, 2017	Thio 8-10 mg/kg, Treo 42 g/m2, Flu 160 mg/m2, ATG 20 mg/kg +/- Ritux 200 mg/m2,	TCRαβ/ CD19 depleted PBSC	2 (13-16)	2	1	0	0
Wiebking, 2017	Alem 0.4mg/kg, Flu 150, Treo 42, Thio 10, PT-Cy 100, MMF, tac	BM	3 (5-20)	3	0	0	0
Gilman, 2017	Mel 140, Thio 10, Flu 200, ATG 10 +/- Ritux 375, MTX	PBSC	8 (8-23)	7	2	1	1 (aspergillus)
Frangoul, 2018	Cy 29 mg/kg, Flu 150 mg/m^2, 200 cGy TBI, ATG 4.5 mg/kg, Thio 10 mg/kg, PT-Cy 100 mg/kg, sir + MMF	Primed BM or PBSC	4 (12-23)	4	4 (Gr 2)	0	0
Saraf, 2018	Cy 29 mg/kg, Flu 150 mg/m^2, 300 cGy TBI, ATG 4.5 mg/kg, PT-Cy 100 mg/kg, tac or sir + MMF	PBSC	8 (20-38)	6	2	1	1 (unknown)
Pawlowska, 2018	Flu/Dex Pre-Conditioning, ATG 4.5 mg/kg, Flu 210 mg/m2, Bu 520 mg/m2, PT-Cy 100 mg/kg, tac, MMF	BM or PBSC	4 (12-23)	4	0	0	0
Gaziev J, 2018	HU/Aza/Flu Pre-Conditioning, Bu 14 mg/kg, Thio 10 mg/kg, Cy 200 mg/kg, ATG 12.5 mg/kg, CSA, MMF or methylpred	TCRαβ/CD19 depleted PBSCs	3 (<17)	3	28% (Gr 2-3)	21%	? (thal pts included in study)
de la Fuente, 2019	Cy 29 mg/kg, Flu 150 mg/m^2, 300 cGy TBI, ATG 4.5 mg/kg, Thio 10 mg/kg PT-Cy 100 mg/kg, tac or sir + MMF	Primed BM	15 (12-26)	14	3	1	0
Bolanos-Meade, 2019	Cy 29 mg/kg, Flu 150 mg/m^2, 400 cGy TBI, ATG 4.5 mg/kg, Thio 10 mg/kg PT-Cy 100 mg/kg, tac or sir + MMF	Bone Marrow	12 (6-31)	10	29% (Gr 2-3)	1 (moderate)	0
Total	Mixed	Mixed	68	90%	31% (of total)	8% (of total)	4% of total

Protocol 17-H-0069: Haploidentical PBSC Transplantation for Patients with Severe Sickle Cell Disease



- Target ALC of <100 cells/uL prior to starting alemtuzumab
- Sirolimus starting day +4 post-transplant

Pt #	Date	% Donor chimerism	GVHD
1	6/16/17	38% myeloid 69% CD3	None
2	9/8/17	98% myeloid 99% CD3	Grade II Acute, resolved with steroids
3	10/6/17	96% myeloid 33% CD3	None
4	2/23/18	99% myeloid 78% CD3	None
5	3/2/18	58% myeloid 35% CD3	None
6	3/9/18	57% myeloid 1% CD3	None
7	10/19/18	100% myeloid 73% CD3	None
8	2/8/19	32% myeloid 21% CD3	None
9	3/29/19	70% myeloid 5% CD3	None
10	4/12/19	100% myeloid 61% CD3	None
11	5/10/19	100% myeloid 100% CD3	None
12	7/12/19	100% myeloid 46% CD3	None

Conclusions

- Conditioning regimen matters
  - HLA-matched sibling
    - Myeloablative conditioning including ATG has high efficacy
    - Nonmyeloablative conditioning aimed at tolerance induction has lower rate of GVHD, despite the use of PBSCs
  - Matched unrelated donor
    - Early alemtuzumab is associated with high rate of GVHD
      - Study ongoing to evaluate whether abatacept decreases GVHD incidence
  - Unrelated umbilical cord and Haploidentical
    - More intensive conditioning and T-cell depletion has decreased the graft rejection rate
- Longer follow-up is necessary to evaluate efficacy and to monitor for late effects
- Patients should be enrolled on clinical trials

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  - **Stephanie Housel**
  - **Adriana Byrnes**
  - **Terri Wakefield**

Case Presentation

- 30yo African-American woman with history of homozygous sickle cell disease who was evaluated for haploidentical peripheral blood stem cell transplantation on 4/18/13

History of Present Illness

- Easily fatigued
- Dyspnea on exertion after walking 2 blocks
- Intermittent palpitations about once weekly, lasting a few minutes with no associated symptoms
  - No history of syncope
- 3 pillow orthopnea
- No paroxysmal nocturnal dyspnea or lower extremity edema

- HbSS dz: not responsive to hydroxyurea or decitabine
- Transfusion-associated iron overload
  - >50 units transfused
  - Liver biopsy with mild inflammation, perisinusoidal fibrosis, and LIC 19.4mg/g
- Recurrent vaso-occlusive crises
  - 16 hospitalizations in the past year, 27 hospitalizations in the past 3 years
- Chronic back pain (6/10)
- Recurrent acute chest syndrome
- HTN
- Microalbuminuria
- Pulmonary arterial hypertension
  - RHC: PAPm 30mmHg PAWP 12mmHg
  - On ambrisentan since 8/1/2012

- Deferoxamine 3,000mg (=44mg/kg) subcutaneously over 10 hours 4 nights/week
- Oxycodone long-acting 20mg BID
- Hydromorphone 2-8mg every 4 hours prn
- Ambrisentan 10mg daily
- Lisinopril 2.5mg daily
- Nifedipine 30mg daily
- Folic acid 1mg daily
- Oxygen 2L nightly prn

Physical Examination

- General: No acute distress
- VS: HR 107 RR 18 O2 sat 95% RA
- HEENT: PERRL, EOMI, no scleral icterus, no conjunctival paleness, OP clear, no JVD
- CV: tachy, regular, II/VI early SM heard best at the left sternal border, no rubs/gallops
- Pulmonary: CTAB, no wheezes, rhonchi, rales
- Abd: +BS, soft, mild RUQ tenderness liver 2cm below right costal margin
- Extrem: no clubbing, cyanosis, edema
- MSK: full range of motion bilateral hips without pain

Laboratory Data

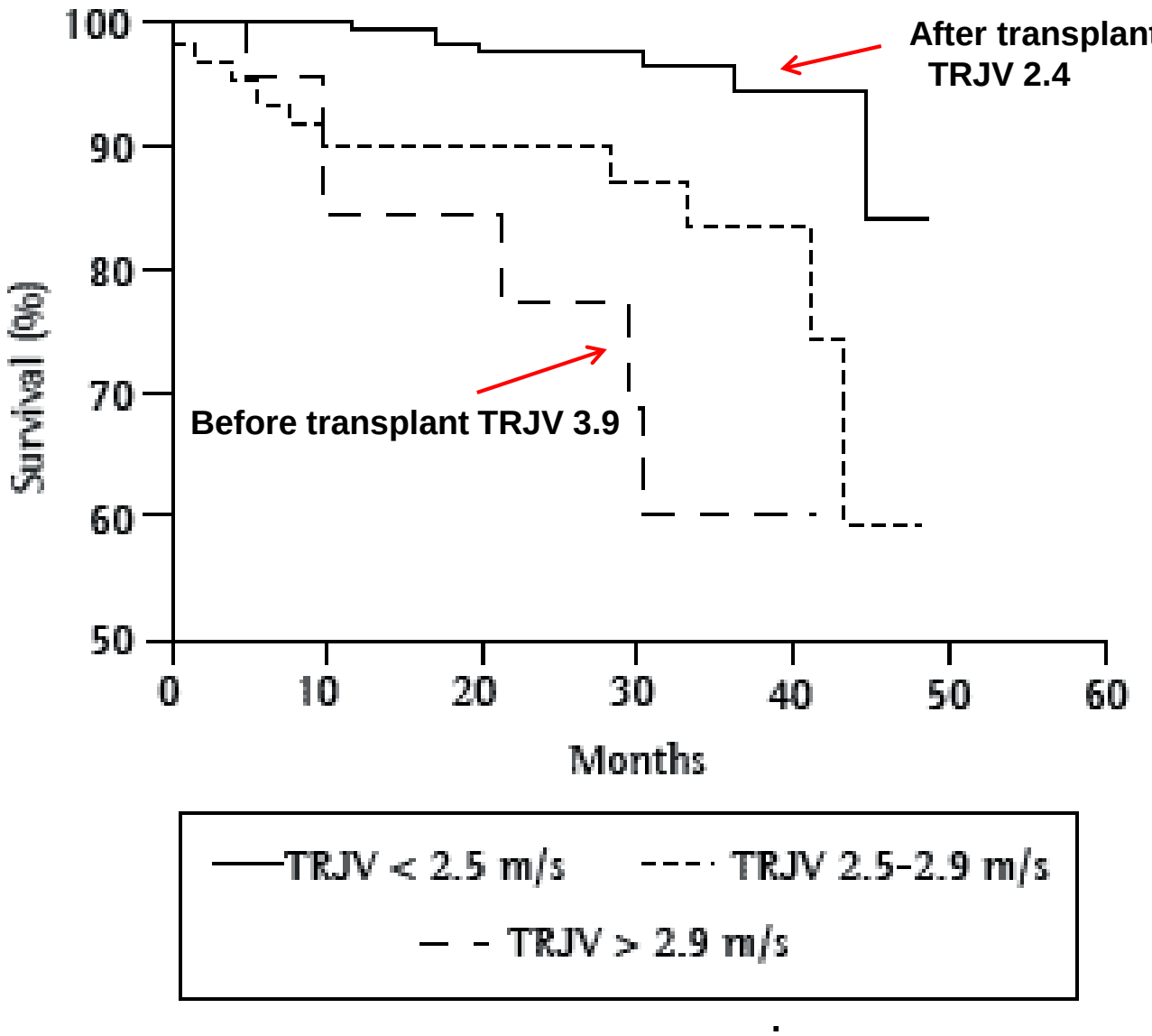
- WBC 11.05/uL Hgb 9.7g/dL Hct 27.3% Plt 482,000/uL ANC 4,640/uL ARC 441,500/uL
- BUN 7mg/dL Cr 0.67mg/dL
- AST 41U/L ALT 74U/L alk phos 85U/L
  t bili 0.9mg/dL d bili 0.4mg/dL
- LDH 281U/L NTproBNP 154pg/mL
  ferritin 2,994mcg/L

Case Presentation

- Pt underwent PBSCT on 8/9/13
- 84% donor myeloid, 42% donor CD3 6 years post-transplant
- Hgb 12.9g/dL, 56.0% HbA, 40.8% HbS
  - Completed therapeutic phlebotomy
- Off chronic narcotic therapy
- Off ambrisentan with resolution of pulmonary HTN per RHC 8/2014
  - PAPm 17mmHg, PAWP 6mmHg

Resolution of Pulmonary HTN Post-Transplant

TRV (m
RVSP (mı
EF (%
BNP (pg
6MW distar
6MW O2 (9
6MW O2 (%
mPAP (mı
PCWP (m
Cardiac O (L/mir



Pittman C et al. Bone Marrow Transplant, 2017. 52(4): 641’642.

Life Without Sickle Cell Anemia

- “Well, my son knows I’m his mother now because I’m not usually in the hospital…I can actually play with him, go to the playground, do normal things…Now, I can keep my promises- when I say I’m going to be somewhere, I can actually be there.”

Jennifer Nsenkyire

Author, Speaker, and Advocate for Chronic Disease