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LATE BREAKING ABSTRACTS

.

Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe Sickle Cell Disease: BMT CTN 1507

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Background: Allogeneic hematopoietic stem-cell transplantation has curative potential for sickle cell disease (SCD). Event-free survival (EFS) in children with SCD is >90% after a bone marrow transplant (BMT) from a myeloablative matched sibling donor (MSD). Unfortunately, <15% of patients with SCD have MSD, and myeloablative conditioning can be prohibitively toxic in adults with SCD. Reduced intensity HLA-haploidentical BMT with post-transplant cyclophosphamide (PTCy) has been shown in small studies to expand the donor pool with encouraging results. Still, concerns about graft failure and graft-versus-host disease (GVHD) persist. We present the results of a Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1507, multi-center single-arm, phase-II, prospective clinical trial (clinicaltrials.gov #NCT03263559) of haploidentical-BMT with PTCy to estimate EFS at 2-years in adults with severe SCD. Pediatric stratum data is not included in the data presentation and will be available in 2-years.

Study Design and Methods:

Eligibility: SCD patients aged 15.00-45.99 years with prior stroke, recurrent ACS or pain, chronic transfusion regimen, or tricuspid valve regurgitant jet velocity (TRJV) ≥2.7 m/sec were eligible. Participants were required to have an HLA-haploidentical first-degree relative donor, willing and able to donate bone marrow. The **primary objective** was EFS (survival without primary or secondary graft failure or second infusion of stem cells) at 2 years after haploidentical-BMT. **Secondary objectives** included determining the impact on clinical and laboratory manifestations of SCD and other transplant outcomes at 2 years post haploidentical-BMT. The protocol was opened for enrollment on 10/5/2017, completed accrual on 01/6/2021, and data are current as of 8/2023. **Preconditioning** with hydroxyurea (HU) 30mg/kg/day (Day-70 to Day-10); **Conditioning** regimen included Thymoglobulin (rATG), Thiotepa, Fludarabine, Cyclophosphamide, and Total Body Irradiation (TBI). GVHD prophylaxis included PTCy, sirolimus, and mycophenolate mofetil, figure.

Results: A total of 54 eligible participants enrolled from 19 sites; 42 (78%) proceeded to transplant. Amongst enrolled participants, 59.3% are male, 92.6% are Black, and 3.7% are Hispanic. 10 participants started HU but did not proceed to BMT, and 2 did not start HU or proceed to BMT. Reasons included donor issues (n=4), withdrawal of consent (n=2), insurance coverage (n=2), death (n=1), and other (n=3). 38/42 (90%) participants completed the study as planned; 2 participants withdrew consent, and 2 were lost to follow-up. The median age was 22.8 years at enrollment; 47/54 (87%) of enrolled participants had Hemoglobin SS disease, 40/54 (74.1%) had a Lansky/Karnofsky score of 90-100 at baseline, and 41/54 (75.9%) had an HLA match score of 4/8. Recurrent vaso-occlusive pain episodes (38.9%), acute chest syndrome (16.8%), and overt stroke (16.7%) were the most common indications for transplant. Only 13 (31%) participants achieved the intended 30 mg/kg/day dosing of HU preconditioning.

Estimated 2-year EFS is 88% (95% CI: 73.5%, 94.8%); all except one qualifying event occurred within 12 months. The 2-year overall survival (OS) post-HU was 93.0% (95% CI: 79.8%, 97.7%), and the 2-year OS post-transplant was 95.0% (95% CI: 81.5%, 98.7%); 2 (4.8%) participants had primary graft failure, and 1 (2.4%) had secondary graft failure before day +100. The cumulative incidence of grades II-IV acute GVHD at day 100 was 26.2% (95% CI: 14.0%, 40.2%), and grades III-IV acute GVHD at day 100 was 4.8% (95% CI: 0.9%, 14.4%). There were two deaths in the first year post-BMT (1 -organ failure; 1-ARDS), none in the second year; 33 (78.6%) participants reported at least one re-admission post-BMT, mainly due to either bacterial infection (n=41) or viral reactivation (n=36), table.

Conclusion: This multi-center phase-II trial of a reduced intensity haploidentical-BMT in adults with SCD shows durable donor engraftment at 2-years with low mortality. The 2-year EFS and OS are comparable to that reported after MSD myeloablative BMT. These results support haploidentical BMT with PTCy as a suitable and tolerable curative therapy for adults with SCD and severe end-organ toxicity such as stroke and pulmonary hypertension, a population typically excluded from participating in myeloablative gene therapy and gene editing trials.

Disclosures Walters: *AllCells, Inc:* Consultancy, Other: Medical Director; *BioChip Labs:* Consultancy, Other: Medical Director; *Vertex Pharmaceuticals:* Consultancy; *Ensoma, Inc:* Consultancy. **Solh:** *Bristol-Myers Squibb:* Speakers Bureau. **McKinney:** *Bluebird Bio:* Other: Advisory Board; *Horizon Therapeutics:* Other: Advisory Board. **Shaughnessy:** *Autolus Therapeutics, BMS:* Honoraria; *BMS, Sanofi:* Speakers Bureau. **Kanter:** *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *OptumRx:* Consultancy; *Beam:* Consultancy, Honoraria; *ECOR1:* Consultancy; *Fulcrum:* Consultancy; *Guidepoint Global:* Consultancy; *Watkins, Lourie, Roll&Chance:* Consultancy; *Bausch:* Honoraria; *Austin Therapeutics:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Chiesi:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Bluebird Bio:* Consultancy; *GLG:* Consultancy; *Cowen:* Consultancy. **Bollard:** *Roche:* Consultancy; *Cabaletta Bio, Catamaran Bio:* Current equity holder in private company, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: Patent applications in CAR-NKs. **Cooke:** *Jazz Pharmaceuticals:* Consultancy. **Hanna:** *Sanofi:* Speakers Bureau; *SOBI:* Speakers Bureau; *Vertex:* Honoraria; *EDITAS:* Research Funding. **Mahadeo:**

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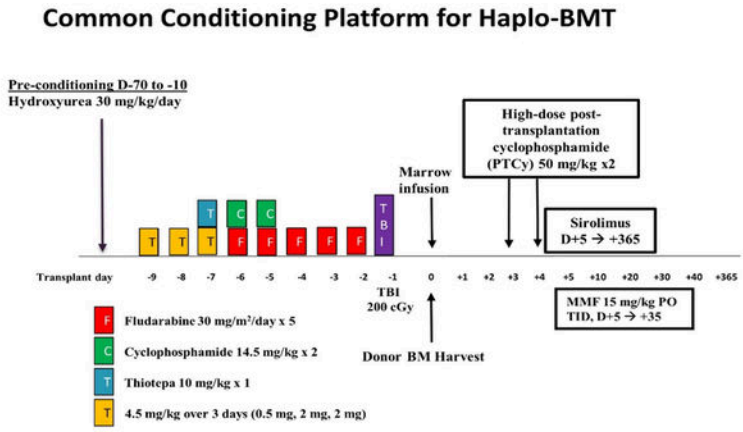

Figure Legend: PTCy (post-transplant cyclophosphamide), MMF (mycophenolate mofetil), PO (by mouth), TID (three times daily), TBI (total body irradiation)

Table: Demographic and clinical characteristics of participants. (n=42)

Variable	Adult (n=42)	Percentage (%)
Median age (years)	22.8 (15.5-43.2)	N/A
Transplanted	42	78%
Follow-up time (days), median (IQR) (n=42)	743.5 (214.0-1393)	N/A
SCD genotype (SS and Sβ⁰-thalassemia), n (%)	47	87%
TNC dose (10^8/kg), median IQR (n=37)	3.5 (2.0-5.4)	N/A
CD34⁺ cell dose (10^6/kg), median IQR (n=41)	3.6 (0.9-7.9)	N/A
Days post-transplant to neutrophil >500/mcL, median (IQR) (n=42)	25.5 (1.0-197.0)	N/A
Days post-transplant platelets >50 x 10^9/L, median (IQR) (n=42)	34.5 (19.0 – 735.0)	N/A
Primary graft failure, n (%) (n=42)	2	4.8%
Secondary graft failure, n (%) (n= 42)	1	2.4%
Death, n (%)	2	4.7%
Acute graft-versus-host-disease (grades III) (%)	2	4.8%
Chronic graft-versus-host disease, severe (%)	3	7.1%

Deaths (n=3)

Study ID	Age at Transplant (years)	Days post-transplant	Cause of Death
#1	28	Day – 63 (23 days after the start of hydroxyurea therapy, prior to transplant)	Intracranial hemorrhage from a left posterior inferior cerebellar artery aneurysm with evidence of subarachnoid hemorrhage. Progression of ischemic changes involving the left temporoparietal lobes with multifocal bilateral cerebral infarctions and vasospasm
#2	29	261	Sudden death of unclear etiology (after a febrile episode, likely cardio-respiratory failure).
#3	18	291	Acute respiratory distress syndrome

Figure 1

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