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CRISPR cas9 gene editing for sickle cell disease

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Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy that reactivates fetal hemoglobin via ex-vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem cells at the erythroid-specific enhancer region of BCL11A gene in patients with severe sickle cell disease (SCD). The pivotal CLIMB SCD-121 trial met primary and key secondary endpoints. CLIMB SCD-121 is an ongoing, 24-mo, phase 3 trial of exa-cel in pts age 12-35y with SCD and a history of ≥2 VOCs/y in 2y prior to screening. Primary efficacy endpoint is proportion of pts free of severe VOCs for ≥12 consecutive months (mos) (VF12); key secondary efficacy endpoints include proportion of pts free from inpatient hospitalization for severe VOCs for ≥12 consecutive mos (HF12). 42 pts with SCD (age 21.2 [range 12-34]y; 12[28.6%] age ≥12 to <18y; 4.2 VOCs/y at baseline) received exa-cel. Following infusion, all pts engrafted neutrophils and platelets (median 27 and 34.5 days, respectively). 19/20 (95.0%) pts evaluable for primary endpoint were free of VOCs for ≥12 consecutive mos (VF12; 95% CI, 75.1% to 99.9%; P<0.0001), 20/20 (100%) were free from hospitalizations for VOCs for ≥12 consecutive mos (HF12; 95% CI, 83.2 to 100.0; P<0.0001). Exa-cel treatment resulted in early and sustained increases in Hb and HbF leading to elimination of VOCs in 95% of pts, elimination of inpatient hospitalization for VOCs in 100% of pts and improved QOL. Safety profile of exa cel was consistent with myeloablative busulfan conditioning and autologous transplantation. Exa-cel has potential to deliver a one-time functional cure to pts with severe SCD.

Biography

Jennifer Domm, MD, MSCI is medical director of Pediatric Hematology/Oncology at Sarah Cannon Research Institute and TriStar Centennial Children's Hospital in Nashville, TN, USA. Dr. Domm completed her MD degree at Vanderbilt University followed by pediatric residency and pediatric hematology/oncology/stem cell transplant fellowship at Vanderbilt University. She was Associate Professor at Vanderbilt Children's Hospital until 2015 when she joined Sarah Cannon Research Institute to co-found the pediatric program. Dr. Domm has authored or co-authored more than 50 peer-reviewed manuscripts. She is a co-investigator for the clinical trial using CRISPR-Cas9 gene editing for patients with sickle cell disease and transfusion-dependent thalassemia.

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