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BETIBEGLOGENE AUTOTEMCEL IN PATIENTS WITH TRANSFUSION-DEPENDENT B-THALASSEMIA: UPDATED RESULTS FROM HGB-207 (NORTHSTAR-2) AND HGB-212 (NORTHSTAR-3)

Topic: 27. Thalassemias

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Background: Transfusion-dependent β-thalassemia (TDT) is a genetic disease requiring lifelong packed red blood cell (pRBC) transfusions and regular iron chelation. Betibeglogene autotemcel (beti-cel) is a one-time ex vivo gene therapy that adds functional copies of a modified *HBB* gene, $\beta^{A\text{-}T87Q}$, into patients' hematopoietic stem cells to correct the underlying genetic cause of TDT and enable lifelong, stable production of functional adult hemoglobin (Hb) sufficient for transfusion independence (TI).

Aims: To evaluate updated efficacy and safety of beti-cel in patients with TDT in ongoing, fully enrolled phase 3 studies, HGB-207 (Northstar-2; non-β^0/β^0 genotypes; NCT02906202) and HGB-212 (Northstar-3; β^0/β^0, $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$, and $\beta^0/\beta^{+IVS\text{-}I\text{-}110}$ genotypes; NCT03207009).

Methods: CD34+ cells are mobilized using granulocyte-colony stimulating factor and plerixafor, collected via apheresis, transduced with BB305 lentiviral vector, and infused back into patients after single-agent, pharmacokinetic-adjusted busulfan-based myeloablation. Primary endpoint in both studies is TI (weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 mo; the primary endpoint for HGB-212 is the result of a protocol amendment dated October 2020). Patients are followed for 2 y and, upon study completion, are eligible for a long-term follow-up study for an additional 13 y. Data are median (min–max).

Results: As of 30 November 2020, 41 patients (29 non-β^0/β^0, 12 β^0/β^0 genotype) had been treated with beti-cel and followed for 24.3 (0.9–42.2) mo. Age at informed consent was 13 (4–34) y. All patients with >1.3 mo follow-up (n=40) achieved neutrophil and platelet engraftment 25.5 (13–39) and 46.0 (13–94) d after infusion, respectively. Lymphocyte nadir within the first mo post-infusion was 0.47 x 10^9/L (0.02–1.81 x 10^9/L; n=41; reference range, 0.9–6.5 x 10^9/L [range varies by laboratory]).

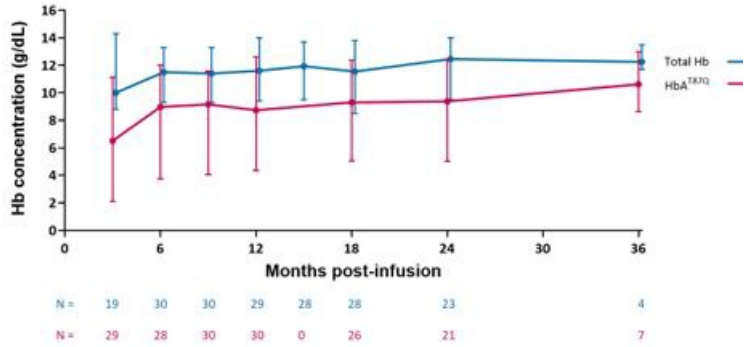
Transfusion independence was achieved by 30/34 (88.2%) evaluable patients, including 6/7 (85.7%) patients with β^0/β^0 genotypes and 24/27 (88.9%) patients with non-β^0/β^0 genotypes (including 10/11 β^+/β^0, 5/6 β^E/β^0, 3/3 β^+/β^+, 2/3 $\beta^{+\,IVS\text{-}I\text{-}110}/\beta^{+\,IVS\text{-}I\text{-}110}$, 2/2 $\beta^0/\beta^{+\,IVS\text{-}I\text{-}110}$, and 2/2 $\beta^+/\beta^{+\,IVS\text{-}I\text{-}110}$ genotypes). Weighted average Hb during TI was

11.5 (9.5–13.6) g/dL. At last follow-up, all 30 patients had maintained TI for 20.6 (12.3–39.4) mo. All patients who achieved TI had Hb ≥9 g/dL at 6 mo post-infusion. Unsupported total Hb and HbA^{T87Q} over time are shown in the **Figure**.

Adverse events in ≥2 patients considered by the investigator to be related or possibly related to beti-cel included abdominal pain (n=3) and thrombocytopenia (n=3; 1 serious event). Serious adverse events that occurred in ≥2 patients included pyrexia (n=4), thrombocytopenia (n=3), veno-occlusive liver disease (n=3), febrile neutropenia (n=2), neutropenia (n=2), and stomatitis (n=2). There were no deaths and no evidence of clonal dominance or insertional oncogenesis in these studies. Fertility preservation was performed in 30/41 (73.2%) patients. A pregnancy after in vitro fertilization was reported in the partner of a male patient who had banked sperm prior to beti-cel infusion. The pregnancy was ongoing at last follow-up.

Image:

Figure. Unsupported Total hemoglobin (Hb) and HbA^{T87Q} Levels Over Time in Patients Who Achieved Transfusion Independence. Unsupported total Hb is defined as the total Hb level without any packed red blood cell transfusions within 60 days prior. Median (min–max) depicted.



Summary/Conclusion: In this analysis, 88% of treated evaluable patients in HGB-207 and HGB-212 achieved TI and demonstrated stable HbA^{T87Q}. The safety profile was consistent with that of busulfan-based myeloablative conditioning. Beti-cel–related events were consistent with side effects of DMSO, a cryoprotectant used in the drug product.

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