CB-011, a BCMA-specific allogeneic CAR-T cell therapy, engineered with next-generation CRISPR technology to knock out B2M and express a B2M-HLA-E transgene to blunt immune cell-mediated rejection, for r/r multiple myeloma


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CB-011 off-the-shelf CAR-T cell therapy has been engineered with next-generation CRISPR technology to knock out B2M and express BCMA-HLA-E to address immune cell-mediated rejection. CB-011 therapeutics with next-generation CAR-T cells have the potential to expand and persist in vivo, and to arm and traffic allogeneic CAR-T cells for effective anti-tumor activity. CB-011 represents a next-generation allogeneic CAR-T cell therapy with potent antitumor activity and the potential to advance the treatment of r/r multiple myeloma.

**Background**

The approach and commercialization of chimeric antigen receptor (CAR) T cell therapies has opened a pathway for advanced CAR-T cell therapies with next-generation capabilities. However, the potential of CAR-T cell therapies may be limited by the broad potential of engineered cells as a leading therapeutic modality. Addressing expansion, persistence, and trafficking of allogeneic CAR-T cell therapies is critical to advancing their clinical applications. CB-011 is a genetically-engineered allogeneic anti-BCMA CAR-T cell product candidate that will be evaluated in the CamMuPhase 1 clinical trial to explore its efficacy and safety in vivo. CB-011 autologous CAR-T cells demonstrate potent antitumor activity and enhanced survival in BCMA-positive xenograft models of multiple myeloma.

**Introduction**

CB-011 is an off-the-shelf anti-BCMA CAR-T cell therapy in clinical development for the treatment of adult patients with r/r MM.

CB-011 is derived from healthy donor T cells that have been gene edited with clustered regulatory oligonucleotides (CRISPR) to knock out B2M and express a BCMA-HLA-E transgene. These allogeneic CAR-T cells demonstrate potent antitumor activity and enhanced survival in BCMA-positive xenograft models of multiple myeloma.

**CB-011 CAR-T cell manufacturing process overview**

CB-011 is engineered using Cas12a chRNDNA guides for precision genome editing.

chRNDNA guides used with Cas12a included strategically located donor DNA sites to cover high target specificity. Cas12a chRNDNA guides were designed to target the TRIM and TRIM and BCMM donors for implementation in CB-011.

(CA-ABC) The CRISPR design process began with gene editing to identify optimal CAS9 CRISPR guides. Once optimal CRISPR guides are identified, donor DNA sequence covering is equal to the target sequence.

(BD-ABC) In addition to CRISPR guides, a single donor DNA site was positioned on the Cas12a spacer and then evaluated for on-target editing efficiency of T-cells.

(CC-ABC) The positions where donor DNA sites did not encode efficient or off-target editing were confirmed by subsequent chRNDNA guide designs to identify optimal CRISPR guides using single donor DNA sites in the optimized sequence.