Autologous CD4+/CD8+ 4-1BB-CD3zeta-EGFR806-CAR-EGFRt/4-1BB-CD3zeta-CD19-CAR-HER2tG-expressing CARs T Cells

National Cancer Institute

Source

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A preparation of CD4+ and CD8+ autologous T-lymphocytes transduced with a lentiviral vector that co-expresses two different second generation chimeric antigen receptors (CARs), one composed of a short chain variable fragment (scFv) binding domain derived from depatuxizumab, a human anti-epidermal growth factor receptor (EGFR) monoclonal antibody (MAb806; ABT-806), coupled to the zeta chain of the TCR/CD3 complex (CD3-zeta) and the signaling domain of 4-1BB (CD137), and linked to a truncated form of the human epidermal growth factor receptor (EGFRt), and one composed of a short chain variable fragment (scFv) binding domain derived from an anti-CD19 monoclonal antibody, coupled to CD3-zeta) and 4-1BB, and linked to a truncated form of the human epidermal growth factor receptor 2 (HER2tG), with potential immunostimulating and antineoplastic activities. Upon intravenous administration, the autologous CD4+/CD8+ 4-1BB-CD3zeta-EGFR806-CAR-EGFRt/4-1BB-CD3zeta- CD19-CAR-HER2tG-expressing CARs T-cells are directed to, bind to, and induce selective toxicity in EGFR deletion mutation variant III (EGFRvIII)-expressing tumor cells. The binding of these T-cells to CD19 expressed on B-cells enhances their expansion and prolongs their persistence in vivo, thereby increasing the efficacy of these CAR T-cells. Devoid of both ligand binding domains and tyrosine kinase activity, the expressed EGFRt and HER2tG facilitate in vivo detection of the administered, transduced T-cells and can promote elimination of these cells through an antibody-dependent cellular cytotoxicity (ADCC) response. HER2tG allows for enhanced binding by trastuzumab. EGFRvIII, an in-frame deletion of exons 2-7 in the EGFR gene, is overexpressed by a variety of cancer cell types but absent in normal, healthy cells. It plays a key role in tumor cell proliferation, tumor angiogenesis and resistance to both radio- and chemotherapy. Depatuxizumab specifically targets abnormal conformational states

of EGFR, including EGFRvIII, and activating mutations, with lower affinity for wild-type EGFR. CD19, a transmembrane phosphoglycoprotein is expressed on the surface of cells in the B-lineage.