Autologous EGFRt/19-28z/4-1BBL CAR T-Lymphocytes

National Cancer Institute

Source

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Genetically modified autologous T-lymphocytes transduced with a replication incompetent retroviral vector expressing both tumor necrosis factor ligand superfamily (TNFSF) member 9 (TNFSF9; 4-1BBL) and a chimeric T cell antigen receptor (CAR) consisting of an anti-CD19 scFv (single chain variable fragment), fused to the extracellular, transmembrane and intracellular signaling domains of the T-cell co-stimulatory receptor CD28, the cytoplasmic signaling domain of the zeta chain of the TCR/CD3 complex (CD3-zeta) (19-28z), and a truncated form of the human epidermal growth factor receptor (EGFRt), with potential immunostimulating and antineoplastic activities. Upon intravenous administration, autologous EGFRt/19-28z/4-1BBL CAR T-lymphocytes are directed to CD19-expressing tumor cells, which induces selective toxicity in CD19-expressing tumor cells. These cells also express 4-1BBL, a secreted protein and member of the TNFSF of growth factors, that induces proliferation of T-cells and may help reverse immunosuppression in the tumor environment. CD19 antigen is a B-cell specific cell surface antigen expressed in all B-cell lineage malignancies. The CD28 co-stimulatory molecule signaling domain enhances activation and signaling after recognition of CD19. The inclusion of the CD28 signaling domain may increase proliferation of T-cells and antitumor activity compared to the inclusion of the CD3-zeta chain alone. Devoid of both ligand binding domains and tyrosine kinase activity, EGFRt both facilitates in vivo detection of the administered, transduced T-cells and can promote elimination of those cells through a cetuximab-induced antibody dependent cellular cytotoxicity (ADCC) response.