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

National Cancer Institute

Source

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A preparation of CD4+ and CD8+ autologous T-lymphocytes transduced with a lentiviral vector expressing a chimeric antigen receptor (CAR) 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), with potential immunostimulating and antineoplastic activities. Depatuxizumab specifically targets abnormal conformational states of EGFR, including the EGFR deletion mutation variant III (EGFRvIII), and activating mutations, with very low affinity for wild-type EGFR. Upon intravenous administration, the autologous CD4+/CD8+ EGFR806 specific 4-1BB-CD3zeta-EGFRt-expressing CAR T-cells are directed to and induce selective toxicity in EGFRvIII-expressing tumor cells. Devoid of both ligand binding domains and tyrosine kinase activity, the expressed EGFRt both facilitates in vivo detection of the administered, transduced T-cells and can promote elimination of these cells through an anti-EGFR antibody-dependent cellular cytotoxicity (ADCC) response. 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.