Autologous CD19CAR-CD28-CD137/CD27/CD3zeta-iCasp9-expressing T-lymphocytes

National Cancer Institute

Source

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Autologous T-lymphocytes that have been transduced with a fourth generation-lentiviral vector to express the 4SCAR19 gene composed of a chimeric antigen receptor (CAR) consisting of a single chain variable fragment (scFv) of anti-CD19 coupled to the co-stimulatory molecules CD28, 4-1BB (CD137), and CD27, and to the cytoplasmic portion of the zeta chain of the human T-cell receptor (CD3zeta), and containing the apoptosis-inducible suicide gene human caspase 9 (iCASP9 or iC9), that is linked to a drug binding domain, with potential immunostimulating and antineoplastic activities. The iCASP9 construct consists of the entire coding sequence for the human FK506-drug binding protein (FKBP12) with an F36V mutation (FKBP12-F36V) that is linked to the gene encoding iC9, which is a modified form of the CASP9 gene where the sequences encoding the endogenous caspase activation and recruitment domains have been deleted. Upon transfusion, anti-CD19-CAR-CD28/CD137/CD27/CD3zeta-iCasp9-expressing autologous T-lymphocytes target and bind to CD19-expressing neoplastic B-cells. This results in a cytotoxic T-lymphocyte (CTL) response against CD19-expressing tumor cells, and causes tumor cell lysis. If the administered T-cells cause unacceptable side effects, the chemical homodimerizer AP1903, which binds to the FKBP12-F36V drug-binding domain, can be administered; this induces caspase 9 expression, and results in apoptosis of the administered 4SCAR19 T-cells. CD19, cluster of differentiation 19, is a B-cell-specific cell surface antigen overexpressed in B-cell lineage tumors. Incorporation of the costimulatory signaling domains increases human T-cell function, expansion, and survival.