Autologous iC9-GD2CAR-CD28-CD3zeta-IL-15-expressing T-lymphocytes

National Cancer Institute

Source

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A preparation of autologous T-lymphocytes that have been transduced with the retroviral vector SFG, a Moloney murine leukemia (Mo-MuLV) virus-based vector, expressing both an extracellular domain consisting of interleukin 15 (IL-15) and a GD2-specific chimeric antigen receptor (CAR) derived from the monoclonal antibody 14G2a, linked to the CD28 and CD3zeta (TCRzeta; CD247) costimulatory signaling domains and containing the suicide gene, inducible caspase 9 (iCasp9 or iC9), with potential immunomodulating and antineoplastic activities. Upon administration, the autologous iC9-GD2CAR-CD28-CD3zeta-IL-15-expressing T-lymphocytes recognize, bind to and induce selective cytotoxicity in GD2-expressing tumor cells. IL-15 is a pro-survival cytokine that promotes T-cell persistence and potentiates the immune response against tumor cells. Incorporation of the costimulatory signaling domains increases T-cell function, expansion, and survival. The iCasp9 safety switch consists of a full-length caspase 9, including its caspase recruitment domain, linked to a human FK506 drug-binding domain with an F36V mutation (FKBP12-F36V). If the administered CAR T-cells lead to unacceptable side effects, the chemical homodimerizer AP1903, which binds to the FKBP12-F36V drug-binding domain, activates caspase 9 and results in apoptosis of the administered CAR T-cells, can be administered. GD2, a disialoganglioside and tumor-associated antigen (TAA), is overexpressed on the surface of neuroblastoma cells and other neuroectoderm-derived neoplasms and is minimally expressed on normal, healthy cells.