Ad5-yCD/mutTKSR39rep-hIL12

National Cancer Institute

Source

National Cancer Institute. Ad5-yCD/mutTKSR39rep-hIL12. NCI Thesaurus. Code C123930.

A replication-competent oncolytic adenovirus encoding the murine pro-inflammatory cytokine interleukin-12 (IL-12) gene and two suicide fusion genes, a yeast cytosine deaminase (yCD) and a mutant form of herpes simplex virus type 1 thymidine kinase (HSV-1 TKSR39), with potential immunomodulating and antineoplastic activities. Upon intratumoral administration of Ad5-yCD/mutTKSR39rep-hIL12, the adenovirus selectively infects and replicates in tumor cells, which results in direct tumor cell lysis. Synergistically, IL-12 expressed by the adenovirus may activate the immune system by promoting the activation of natural killer cells (NKs), inducing secretion of interferon-gamma (IFN-g) and inducing cytotoxic T-lymphocyte (CTL) responses against tumor cells, which may result in immune-mediated tumor cell death, inhibition of tumor cell proliferation and inhibition of tumor angiogenesis. In addition, Ad5-yCD/mutTKSR39rep-hIL12-infected cancer cells express yCD and TKSR39; upon administration of the prodrugs 5-fluorocytosine (5-FC) and valganciclovir (vGCV), the yCD and HSV-1 TKSR39 activate these prodrugs to form 5-fluorouracil (5-FU) and ganciclovir, respectively. 5-FU gets converted to 5-fluoro-uridine monophosphate (5-FUMP) and subsequently to 5-fluoro-deoxyuridine monophosphate (5-FdUMP); 5-FdUMP irreversible inhibits thymidylate synthase, inhibits deoxythymidine triphosphate (dTTP) formation and halts DNA synthesis. Once phosphorylated intracellularly, ganciclovir triphosphate competitively inhibits deoxyguanosine triphosphate (dGTP) incorporation into DNA and inhibits DNA synthesis.