Mipsagargin

National Cancer Institute

Source

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A soluble, thapsigargin prodrug containing the cytotoxic analog of thapsigargin, 8-O-(12Aminododecanoyl)-8-O debutanoylthapsigargin (12-ADT) linked, via a carboxyl group, to the targeting peptide containing aspartic acid with potential antineoplastic activity. Upon intravenous administration, mipsagargin targets prostate specific membrane antigen (PSMA), a type II membrane carboxypeptidase, which is overexpressed in prostate cancer cells and in the neovasculature of most solid tumors but not in normal blood vessels. Mipsagargin is subsequently converted, through hydrolysis, into the active cytotoxic analog of thapsigargin 12-ADT-Asp. 12-ADT binds to and blocks the Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase (SERCA) pump, thereby increasing the concentration of cytosolic calcium which leads to an induction of apoptosis. By preventing nutrient supply to tumor cells, G-202 may be able to inhibit tumor growth. Compared to thapsigargin alone, thapsigargin prodrug G-202 is able to achieve higher concentrations of the active agents at the tumor site while avoiding systemic toxicity.