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Adenosine A2A Receptor Antagonist/Phosphodiesterase 10A PBF-999

National Cancer Institute

Source

National Cancer Institute. Adenosine A2A Receptor Antagonist/Phosphodiesterase 10A PBF-999. NCI Thesaurus. Code C157489.

An orally bioavailable inhibitor of both the adenosine A2A receptor (A2AR; ADORA2A) and phosphodiesterase 10A (PDE-10A), with potential immunomodulating and antineoplastic activities. Upon administration, A2A/PDE-10A inhibitor PBF-999 selectively binds to and inhibits A2AR expressed on T-lymphocytes. This blocks tumor-released adenosine from interacting with A2AR and prevents the adenosine/A2AR-mediated inhibition of T-lymphocytes. This results in the proliferation and activation of T-lymphocytes and stimulates a T-cell-mediated immune response against tumor cells. A2AR, a G protein-coupled receptor, is highly expressed on the cell surfaces of T-cells and, upon activation by adenosine, inhibits T-cell proliferation and activation. Adenosine is often overproduced by cancer cells and plays a key role in immunosuppression. In addition, PBF-999 binds to and inhibits the activity of PDE-10A, thereby preventing the degradation of cyclic guanosine monophosphate (cGMP) and activates cGMP/cGMP-dependent protein kinase G (PKG) signaling. This induces beta-catenin degradation and thereby prevents the translocation of beta-catenin into the nucleus, and the beta-catenin-mediated induction of transcription of survival proteins, such as cyclin D1 and survivin. It also suppresses RAS/RAF/mitogen-activated protein kinase (MAPK) signaling. This induces apoptosis and inhibits the growth of tumor cells in which PDE-10A is overexpressed. PDE-10A is a cGMP-degrading PDE isozyme that is highly expressed in the brain and overexpressed in certain types of tumor cells. Elevation of intracellular cGMP is known to inhibit tumor proliferation and induce apoptosis. cGMP levels are low in cancer cells resulting from the overexpression PDE-10A.