Identification of Pan-Trk Inhibitors for the Treatment of Trk-Driven Cancers

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Abstract

The Trk family of genes, which includes trkA/NTRK1, trkB/NTRK2 and trkC/NTRK3, encode the tyrosine kinase receptors for the neurotrophin family of nerve growth factors. Deregulated kinase activity of trk family members is associated with human cancer. Oncogenic translocations involving trkC kinase domain have been identified in AML, salivary gland carcinoma, adult secretory breast cancer, congenital fibrosarcoma, and pediatric nephroma. Oncogenic trkA translocations have been reported in papillary thyroid and colorectal cancers. We have identified orally bioavailable, potent and selective ATP-competitive inhibitors of the trk family of receptor tyrosine kinases and are developing these for the treatment of Trk-driven cancers. AR523 is a pan-Trk inhibitor, inhibiting TrkA, B and C, and has similar activity against all 3 receptors in a cell based assay (IC50 ~10 nM). In a screen at 1 µM against a panel of 230 kinases, AR523 inhibited only three additional kinases more than 50% (TNK2, Bmx and Txk). In cell culture AR523 was found to exhibit selective anti-proliferative activity toward the cell line KM12, which harbors the oncogenic TPM-TrkA translocation, while exhibiting no activity toward HT29, a cell line with no trk gene rearrangements. Studies in mice engrafted with KM12 tumors revealed significant anti-tumor and pharmacodynamic activity of AR523. Administration of a single oral dose of AR523 reduced tyrosine phosphorylation of TrkA by nearly 80% at twelve hours after dosing. Parallel analysis of Akt and Erk revealed reduced phosphorylation of these downstream effectors. Administration of 100 mg AR523 daily for two weeks to mice with KM-12 xenografts produced mean tumor growth inhibition of 86% and a mean of 42% tumor regression. AR523 exhibits dose-dependent inhibition of tumor growth at 10 and 30 mg/kg in KM-12 xenografts with 54 and 72% TGI, respectively. AR523 was well-tolerated, causing no weight loss or deaths compared with vehicle control. Increasingly Trk mutations have been shown to be activating and the use of Trk inhibitors may provide a new therapeutic strategy for targeted treatment.