CP-673451 for glioblastoma recurrence

CP-673451 is a potent inhibitor of platelet-derived growth factor beta-receptor (PDGFRB) kinase- and PDGF-BB-stimulated autophosphorylation of PDGFR-beta in cells (IC(50) = 1 nmol/L) being more than 450-fold selective for PDGFR-beta versus other angiogenic receptors (e.g., VEGF receptor 2, TIE-2, and fibroblast growth factor receptor 2). Multiple models have been used to evaluate in vivo activity of CP-673,451 and to understand the pharmacology of PDGFR-beta inhibition and the effect on tumor growth. These models include an ex vivo measure of PDGFR-beta phosphorylation in glioblastoma tumors, a sponge model to measure inhibition of angiogenesis, and multiple models of tumor growth inhibition. Inhibition of PDGFR-beta phosphorylation in tumors correlates with plasma and tumor levels of CP-673,451. A dose of 33 mg/kg was adequate to provide >50% inhibition of receptor for 4 hours corresponding to an EC(50) of 120 ng/mL in plasma at C(max). In a sponge angiogenesis model, CP-673,451 inhibited 70% of PDGF-BB-stimulated angiogenesis at a dose of 3 mg/kg (q.d. x 5, p.o., corresponding to 5.5 ng/mL at C(max)). The compound did not inhibit vascular endothelial growth factor- or basic fibroblast growth factor-induced angiogenesis at concentrations that inhibited tumor growth. The antitumor efficacy of CP-673,451 was evaluated in a number of human tumor xenografts grown s.c. in athymic mice, including H460 human lung carcinoma, Colo205 and LS174T human colon carcinomas, and U87MG human glioblastoma multiforme. Once-daily p.o. x 10 days dosing routinely inhibited tumor growth (ED(50) < or = 33 mg/kg). These data show that CP-673,451 is a pharmacologically selective PDGFR inhibitor, inhibits tumor PDGFR-beta phosphorylation, selectively inhibits PDGF-BB-stimulated angiogenesis in vivo, and causes significant tumor growth inhibition in multiple human xenograft models [1].

Differentiation therapy has been proposed as an alternative for glioblastoma treatment, with the aim of bringing cancer cells into a post-mitotic/differentiated state, ultimately limiting tumor growth. As an integral component of cancer development and regulation of differentiation processes, kinases are potential targets of differentiation therapies.

Lane et al. in a study describe how the screening of a panel of kinase inhibitors (KIs) identified PDGF-Rα/β inhibitor CP-673451 as a potential differentiation agent in glioblastoma. They show that targeting PDGF-Rα/β with CP-673451 in vitro triggers the outgrowth of neurite-like processes in glioblastoma cell lines and glioblastoma stem cells (GSCs), suggesting differentiation into neural-like cells while reducing proliferation and invasion in 3D hyaluronic acid hydrogels. In addition, they report that treatment with CP-673451 improves the anti-tumor effects of temozolomide in vivo using a subcutaneous xenograft mouse model. RNA sequencing and follow-up proteomics revealed that upregulation of phosphatase DUSP1 and consecutive downregulation of phosphorylated-p38 mitogen-activated protein kinases can underlie the pro-differentiation effect of CP-673451 on Glioblastoma cells. Overall, the present study identifies a potential novel therapeutic option that could benefit Glioblastoma patients in the future, through differentiation of residual GSCs post-surgery, with the aim of glioblastoma recurrence treatment and improve quality of life [2].

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Roberts WG, Whalen PM, Soderstrom E, Moraski G, Lyssikatos JP, Wang HF, Cooper B, Baker DA, Savage D, Dalvie D, Atherton JA, Ralston S, Szewc R, Kath JC, Lin J, Soderstrom C, Tkalcevic G, Cohen BD, Pollack V, Barth W, Hungerford W, Ung E. Antiangiogenic and antitumor activity of a selective PDGFR tyrosine kinase inhibitor, CP-673,451. Cancer Res. 2005 Feb 1;65(3):957-66. PMID: 15705896.
2)
Lane R, Cilibrasi C, Chen J, Shah K, Messuti E, Mazarakis NK, Stebbing J, Critchley G, Song E, Simon T,

Giamas G. PDGF-R inhibition induces glioblastoma cell differentiation via DUSP1/p38MAPK signaling. Oncogene. 2022 Apr 7. doi: 10.1038/s41388-022-02294-x. Epub ahead of print. PMID: 35393545.