PKC 412 small-molecule tyrosine kinase inhibitor: single-compound therapy for pancreatic cancer.

BACKGROUND: PKC412 is a kinase inhibitor that blocks protein kinase C (PKC), vascular endothelial growth factor receptors, platelet-derived growth factor receptor FLT3, and other class III receptor tyrosine kinases. The enthusiasm for this compound is based on its inhibitory effect even in the case of FLT3 mutations. The aim of this study was to analyze the role of FLT3 in pancreatic cancer and to study the biological activity of combined inhibition of neovascularization and mitogenesis in this disease. METHODS: FLT3 expression was analyzed in 18 pancreatic cancer specimens by real-time quantitative polymerase chain reaction (RTQ-PCR) and immunohistochemistry. Sixteen pancreatic cancer cell lines were screened for ITD and D835 point mutations of the FLT3 gene. MTT assays and anchorage-independent growth assays were used to study cell growth. Flow cytometry was used for cell cycle analysis and apoptosis quantification. In vivo AsPC-1 and HPAF-II cells were used for orthotopic tumor modeling. Immunohistochemistry was used to quantify tumor angiogenesis. RESULTS: FLT3 expression is down-regulated in pancreatic cancer. Activating FLT3 mutations (ITD, D835) were not detectable in any of the pancreatic cancer cell lines. Cell growth was significantly inhibited as cell-cycle progression was reduced.
and programmed cell death increased. In vivo PKC412 therapy resulted in a significant inhibition of orthotopic tumor growth with abrogation of tumor angiogenesis. CONCLUSIONS: These data highlight that PKC412 may be a new compound in target therapy of inoperable pancreatic cancer patients and suggest a potential role for the combined use of broad spectrum kinase inhibitors in the management of these patients.