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SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, downregulates the Wnt signaling pathway and demonstrates antitumor activity in pancreatic cancer cell lines and *in vivo* xenograft models

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Background: Aberrant activation of the Wnt signaling pathway, a highly conserved signaling cascade implicated in multiple cancer hallmarks, is common in pancreatic cancer (PC) and may functionally support proliferation and tumor-forming capacity of PC cells as well as immune evasion. It may also promote fibrogenesis in the PC tumor microenvironment (TME), which is often characterized by a dense, fibrotic stroma that can contribute to treatment resistance. SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that has been shown to potently inhibit the Wnt signaling pathway in preclinical colorectal cancer models. The purpose of these studies was to test the *in vitro* and *in vivo* activity of SM08502 in preclinical models of PC.

Methods: SM08502 was tested against 14 PC cell lines *in vitro* and the compound's antitumor potential was analyzed in Capan-1 and HPAFII xenografts in nude mice. *In vitro* studies included cell viability (all lines), colony formation, apoptosis, and Wnt-related gene expression assays in Capan-1, Panc1, and HPAFII. Xenograft mouse model assays included assessment of tumor growth inhibition (TGI) relative to vehicle controls for both cell lines. Additionally, xenografts of Capan-1 and HPAFII with and without co-implantation of cancer-associated fibroblasts (CAFs) were performed to model tumor stroma effects.

Results: SM08502 inhibited cell viability in all 14 cell lines (regardless of *KRAS* status) (EC_{50}=0.072-0.526 µM). In Capan-1, HPAFII, and Panc1 cells, 1 µM SM08502 inhibited colony formation as well as Wnt-related gene expression by ≥50% relative to vehicle controls. In addition, SM08502 induced apoptosis as shown by elevated caspase 3/7 activity. In the HPAFII xenograft mouse model, SM08502 (25 mg/kg QD) significantly inhibited tumor growth (TGI=93%, p=0.011) and induced RECIST-defined regression in 3 of 5 mice. Notably, SM08502 administered intermittently (QOD) also significantly inhibited tumor growth (TGI=82%, p=0.011), but no regressions were observed. In the stroma modeling experiments, tumor xenografts with CAF co-implants grew larger (Capan-1, ~45%; HPAFII, ~64%) than xenografts without CAF. Despite increased tumor growth in the presence of CAFs, SM08502 (25 mg/kg QD) induced significant TGI vs. control in Capan-1 (80% and 65%; p<0.01) and HPAFII (85% and 71%; p<0.05) xenografts with or without CAF, respectively, indicating that CAFs do not affect the activity of SM08502.

Conclusion: These data demonstrate that SM08502 potently inhibits Wnt pathway-related gene expression, has strong *in vitro* and *in vivo* antitumor activity, and shows potential to overcome the

tumor-protective effects of stroma in PC. A Phase 1 study assessing safety, tolerability, and pharmacokinetics of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).