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Effects of SM08502, a novel, oral, small-molecule inhibitor of Wnt pathway signaling, on gene expression and antitumor activity in colorectal cancer (CRC) models

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Background: Aberrant activation of Wnt signaling contributing to tumorigenesis is most commonly associated with CRC (90% harbor Wnt pathway mutations). SM08502, a novel, oral Wnt signaling pathway inhibitor, was evaluated in preclinical CRC models.

Methods: ***In vitro*** **Wnt signaling:** assessed using TOPflash β-catenin/TCF reporter assay in SW480 human CRC cells. ***In vitro*** **Wnt pathway gene expression**: measured by qRT-PCR in SW480 and Wnt3a-stimulated cells (HEK-293T, IEC-6) and with the Nanostring Wnt pathway array (180 genes) across a panel of 16 CRC cell lines. ***In vitro*** **cell proliferation**: 17 CRC cell lines were used to test cell viability following treatment. ***In vivo*** **antitumor activity**: Oral SM08502 was tested in CRC mouse xenografts (SW480, HCT 116) and a PDX model over 20-21 days (QD, QOD). 24-hr pharmacodynamic (PD) analysis of Wnt pathway gene expression was done in SW480 tumor explants from mice following one 25 mg/kg dose.

Results: SM08502 inhibited Wnt pathway signaling (EC_{50} = 46 nM) in SW480 cells. Wnt pathway gene expression was inhibited by SM08502 (0.3-3 μM) in Wnt3a-stimulated cells (*AXIN2*, *LEF1*) and SW480 (*AXIN2, CTNNB1, LEF1, MYC, TCF7, TCF7L2*) at 24 hrs (P<.05 vs. vehicle). Corresponding effects on protein expression were confirmed for all genes except *CTNNB1*, suggesting that SM08502 acted independently of β-catenin. Nanostring array screening identified inhibition of *LRP5*, *DVL2*, *BTRC*, and *ERBB2* by SM08502. Cell proliferation was inhibited in all 17 lines (avg. EC_{50} =177 nM). *In vivo,* SM08502 was well tolerated and induced dose-dependent antitumor effects in xenografts and PDX models. Tumor growth inhibition for 25 mg/kg QD (max dose) was 83%, 56%, and 70% in SW480, HCT 116, and PDX, respectively. PD analysis showed significant inhibition (P<.05 vs. vehicle) of *TCF7, MYC, LRP5, DVL2,* and *BTRC* expression 8 hrs post treatment.

Conclusion: In preclinical CRC models, SM08502 was a potent inhibitor of Wnt pathway signaling and gene expression. It showed strong antitumor activity in human tumor models with activating Wnt pathway mutations. The safety, tolerability, and PK of SM08502 are being evaluated in an ongoing phase 1 study (NCT03355066).