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SM08502, a Novel, Small-Molecule CDC-like Kinase (CLK) Inhibitor, Demonstrates Strong Inhibition of the Wnt Signaling Pathway and Antitumor Effects as Monotherapy and in Combination with Chemotherapy in Triple-Negative Breast Cancer (TNBC) Models

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Background: Aberrant activation of the Wnt signaling pathway is associated with tumorigenesis, relapse/chemoresistance, and distance metastasis in TNBC. SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that has been shown to potently inhibit the Wnt signaling pathway in several preclinical cancer models. The purpose of these studies was to examine the antitumor activity of SM08502 as monotherapy and in combination with standard chemotherapy in preclinical models of TNBC.

Methods and Results: The effect of SM08502 on cell proliferation was tested 13 BC cell lines, 7 of which were TNBC derived. Cell proliferation was strongly impaired by SM08502 across all lines (average EC_{50}=0.170 μM [0.055–0.510]). SM08502 demonstrated similar potency between HR+ and TNBC cell lines with average EC_{50} values of 0.202μM (0.058–0.510) and 0.142 μM (0.055–0.240), respectively. Relative to DMSO, SM08502 (1 μM) potently inhibited Wnt pathway-related gene and protein expression (TCF7, DVL2, LRP5, and ERBB2) in TNBC cell lines. Notably, SM08502 showed little inhibitory effect on cell proliferation in normal breast cells (Hs578Bst) compared with their paired TNBC cells (Hs578T) with an EC_{50} of 1.517 μM and 0.080 μM, respectively. Wnt pathway-related proteins were also overexpressed in Hs578T cells relative to Hs578Bst, and SM08502 (1 μM) strongly reduced their expression.

In vivo antitumor effects and tolerability of oral SM08502 (25 mg/kg QD for 20 days) were assessed in mice bearing orthotopically implanted, luciferase-expressing, TNBC (MDA-MB231)-derived xenografts (n=5 mice per group). Significant tumor growth inhibition (TGI) vs. vehicle occurred in mice treated with SM08502 (80%, P<0.01). Metastasis was assessed by *ex vivo* imaging utilizing luciferase activity in bilateral lungs collected at study end. Luminescence was observed in 9/10 lungs from the vehicle-treated mice. In the SM08502-treated mice, only 3/10 lungs had measurable luminescence, suggesting that SM08502 reduced lung metastasis of TNBC tumors in this model. Additionally, SM08502 (12.5 and 25 mg/kg QD), gemcitabine (G)/Nab-paclitaxel (Nab-P) (75/30 mg/kg Q7D i.p.), and SM08502 combined with G/Nab-P were tested in MDA-MB231 xenografts. SM08502 (12.5 and 25 mg/kg) and G/Nab-P alone induced strong TGI vs. vehicle (81, 86, and 91%, respectively; P<0.0001), although no tumor regressions occurred. SM08502 (12.5 and 25 mg/kg) in combination with G/Nab-P achieved improved TGI (93% and 95%, respectively; P<0.0001 vs. vehicle) and induced tumor regression in 30% (3/10) and 60%

(6/10) of mice, respectively. SM08502 (25 mg/kg QD) was also assessed in 4 patient-derived xenograft (PDX) models of TNBC (Crown Biosciences). Inhibition of tumor growth was observed in all tested PDX models (average TGI=69% [60–81], $P<0.01$ vs. vehicle). SM08502 was well tolerated in all tested xenograft models based on bodyweight measurements.

Conclusion: In summary, SM08502 potently inhibited cell proliferation and expression of Wnt pathway-related genes in TNBC cell lines. SM08502 demonstrated strong *in vivo* antitumor effects in TNBC xenografts and PDX models and appeared to suppress lung metastasis. Additionally, SM08502 induced tumor regression in combination with G/Nab-P in TNBC xenografts, whereas G/Nab-P alone did not. These data suggest that SM08502 as a single agent or combined with standard chemotherapy has the potential to provide clinical benefit in TNBC. A Phase 1 study assessing safety, tolerability, and pharmacokinetics of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).