

Accepted as poster #6401 at the American Association for Cancer Research (AACR) Annual Meeting 2020, June 22–24, 2020

SM08502, a Novel, Small-Molecule CDC-like Kinase (CLK) Inhibitor, Demonstrates Strong Antitumor Effects and Wnt and Cyclin D-CDK4/6-RB Pathway Inhibition in Hormone-Receptor-Positive (HR+) Breast Cancer Models

Heekyung Chung, PhD, Lauren Sitts, MS, Chu-Chiao Wu, PhD, Brian Eastman, MS, Chi-Ching Mak, PhD, Sunil KC, PhD, Josh Stewart, Carine Bossard, PhD, Timothy Phalen, PhD, Steven Cha, MD

Samumed, LLC, San Diego, CA

Dysregulation of the cyclin D-CDK4/6-RB signaling axis is implicated in HR+ breast cancer (BC). While CDK4/6 inhibitors such as palbociclib (Palbo) have shown efficacy in this cancer type, overcoming resistance to these agents is an unmet need for patients. SM08502 has demonstrated strong antitumor activity in several preclinical cancer models and has been shown to inhibit the Wnt pathway via disruption of alternative splicing. We examined SM08502 activity in preclinical models of CDK4/6 inhibitor-sensitive and -resistant HR+, HER2-negative (HER2-) BC.

In vitro, SM08502 inhibited serine/arginine-rich splicing factor 6 (SRSF6) phosphorylation and suppressed Wnt-related gene and protein expression (e.g., DVL2, LRP5, TCF7L2) in MCF7 and T47D cells (HR+, HER2-). To test SM08502 activity on CDK4/6 inhibitor-resistant HR+, HER2-BC, we generated Palbo-resistant (Palbo-R) T47D cells. Resistance was confirmed by reduced RB and ER- α expression and increased cyclin E1 expression in Palbo-R versus parental cells. RB phosphorylation was not inhibited upon Palbo (1 μ M) treatment in Palbo-R versus parental cells. SM08502 impaired parental (EC₅₀=0.22 μ M) and Palbo-R (EC₅₀=0.41 μ M) T47D cell proliferation, while CDK4/6 inhibitors (Palbo, abemaciclib, ribociclib) were only effective on parental cells. Compared with DMSO, SM08502 induced apoptosis in parental and Palbo-R cells as measured by caspase 3/7 activation, PARP cleavage, and MCL-1 expression. Compared with DMSO and CDK4/6 inhibitors, SM08502 (1 μ M) inhibited RB phosphorylation and expression of ER- α , AR, and cyclins D1 and E in parental and Palbo-R cells, demonstrating potent activity against CDK4/6 pathway activation.

In vivo antitumor effects and tolerability of oral SM08502 (25mg/kg QD) alone or combined with fulvestrant (F) \pm Palbo in a CDK4/6 inhibitor-sensitive model were assessed in mice bearing orthotopic MCF7 xenografts (n=8/group). Compared with vehicle, SM08502 induced greater tumor growth inhibition (TGI) than F (75 mg/kg BIW) or Palbo (50 mg/kg QD) (70% [P <0.001], 43% [P =0.34], 48% [P =0.16], respectively). SM08502 plus F or Palbo and triplet combination induced strong TGI (75%, 78%, 86%, respectively, P <0.001) and tumor regression (6/8, 7/7, 8/8, respectively). SM08502 was reduced to 12.5 mg/kg at D12 in the triplet due to poor tolerability. In 2 patient-derived xenograft models of HR+ BC, strong TGI was observed with SM08502 (92% [P <0.001] and 71% [P <0.05]) versus vehicle. Mean bodyweight loss from baseline (tolerability assessment) was <15% in all groups over all study periods.

Together, these data suggest that SM08502 has potential antitumor activity in HR+ BC and may provide clinical benefit as a single agent or combined with standard therapy. A Phase 1 study of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).