Accepted as poster #C09 at the American Association for Cancer Research (AACR) - Pancreatic Cancer Meeting: Advances in Science and Clinical Care, Boston, Massachusetts, September 6-9, 2019

Inhibition of tumor growth and post-treatment regrowth by SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, in combination with standard of care in pancreatic cancer models

Carine Bossard[1], Igor Astsaturov[2], Nathalia Cruz[1], Brian Eastman[1], Chi-Ching Mak[1], Sunil KC[1], Betty Tam[3], Gail Bucci[1], Josh Stewart[1], Timothy Phalen[1], Steven Cha[1]

[1]Samumed, LLC, San Diego, CA
[2]Fox Chase Cancer Center, Philadelphia, PA
[3]Formerly Samumed, LLC, San Diego, CA

Background: Relapse and treatment resistance rates remain high in pancreatic cancer (PC) with standard of care (SOC) chemotherapy regimens, although combining them with targeted drug therapies holds promise for improving treatment outcomes and clinical benefits. The Wnt signaling pathway is implicated in multiple cancer hallmarks, including immune evasion, and regulation and survival of cancer stem cells. Aberrant activation of Wnt signaling is common in PC and many other cancers, making it a therapeutic target of interest. SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that potently inhibits the Wnt signaling pathway. These studies were performed to assess the tolerability and efficacy of SM08502 in combination with chemotherapy regimens including gemcitabine (G), paclitaxel (P), and Nab-paclitaxel (Nab-P) in xenograft models of PC.

Methods and Results: First, the effect of oral SM08502 in combination with G or G/P on tumor growth inhibition (TGI) relative to vehicle was assessed over 20-21 days in nude mice (n=6 per group) bearing Capan-1 or HPAFII cell-line-derived xenografts. In Capan-1 xenografts, SM08502 (12.5 mg/kg QD) + G (25 mg/kg Q7D i.p.) induced significant TGI (73%, $p=0.009$) and was more effective than either treatment alone. In HPAFII xenografts, SM08502 (6.25, 12.5, or 25 mg/kg QD) + G/P (75/30 mg/kg Q7D i.p.) induced ≥92% TGI ($p<0.001$) and tumor regressions in ≥4 of 6 mice per group at all tested doses.

Next, the effect of initial treatment of SOC (G/Nab-P) alone or combined with SM08502 (6.25, 12.5, or 25 mg/kg QD) on tumor regrowth during an observation phase was assessed in Capan-1 xenografts and a patient-derived xenograft (PDX) model. TGI was calculated both during (treatment phase) and up to 40 days after (observation phase) treatment relative to vehicle and SOC alone, respectively. In Capan-1, SM08502 + G/Nab-P (75/30 mg/kg Q7D) induced strong TGI (88-94%, $p<0.001$) and increased tumor regressions vs. G/Nab-P at the end of treatment (day 27). In the PDX model, SM08502 + G/Nab-P (50/30 mg/kg Q7D) inhibited tumor growth earlier than G/Nab-P in the treatment phase, but TGI was similar after 21 days of treatment (94-96% $p<0.0001$). At the end of observation in both the Capan-1 and PDX models, SM08502 + G/Nab-P significantly inhibited tumor regrowth (Capan-1, 25 mg/kg, 73.5%, $p=0.003$; PDX, 12.5 mg/kg, 71.4%; $p=0.01$). Additionally, survival was improved with all doses of SM08502 + G/Nab-P in Capan-1 xenografts ($p<0.05$ vs. G/Nab-P). Based on body weight measurements, all treatments

were well tolerated except for SM08502 (25 mg/kg) + G/Nab-P in the PDX model (not carried through observation phase).

Conclusion: Oral SM08502 potently inhibited tumor growth in combination with chemotherapy and extended antitumor effects in genetically distinct PC models. These data show that the combined application of SM08502 with SOC therapy has potential to provide clinical benefit in PC. A Phase 1 study assessing safety, tolerability, and pharmacokinetics of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).