Accepted as an oral presentation 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 Pathway Inhibition in Castration-Resistant Prostate Cancer (CRPC) Models

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CRPC is associated with primary and acquired chemotherapy resistance. Loss of androgen receptor (AR) signaling or development of AR splice variants (e.g., ARV7) in CRPC imparts resistance to standard of care (SOC) agents that target AR signaling (e.g., enzalutamide and abiraterone). Effective therapies are an unmet need for CRPC patients with treatment-resistant tumors. Aberrant Wnt pathway activation contributes to resistance to AR-targeted agents, and cytotoxic chemotherapies such as docetaxel have been shown to activate Wnt signaling in PC cells. SM08502 has demonstrated strong antitumor activity in several preclinical cancer models and has been shown to inhibit the Wnt signaling pathway via disruption of alternative splicing. Here, we examined the antitumor activity of SM08502 in preclinical models of CRPC.

The effect of SM08502 on cell proliferation was tested in 5 PC cell lines. Proliferation was strongly impaired by SM08502 across all cell lines (average EC_{50}=0.319 μM [0.191–0.462]) irrespective of their mutation profile or hormone sensitivity. Compared with DMSO, SM08502 inhibited serine/arginine-rich splicing factor 6 (SRSF6) phosphorylation and potently suppressed Wnt-related gene (*LRP5*, *TCF7*, *TCF7L1*) and protein expression.

In vivo antitumor effects and tolerability of QD oral SM08502 were assessed in multiple xenograft models, including mice bearing 22RV1 (ARV7+) or PC3 (AR-/-) CRPC flank xenografts (n=6/group). In 22RV1 xenografts, tumor growth inhibition (TGI) was demonstrated in mice treated with 12 and 25 mg/kg SM08502 (35%, $P<0.05$; 73%, $P<0.001$, respectively) versus vehicle at D24 of treatment. In PC3 xenografts, significant TGI was seen in mice treated with 25 mg/kg SM08502 (75%, $P=0.03$) versus vehicle. In 22RV1 xenografts, no TGI was observed with 75 mg/kg abiraterone or 30 mg/kg enzalutamide treatment (-4% and 12%, respectively) versus vehicle, which confirmed the effect of ARV7 on resistance. Similarly, no significant TGI was seen in PC3 xenografts treated with enzalutamide, abiraterone, or docetaxel (-52%, $P=0.2$; -60%, $P=0.33$; 26%, $P=0.38$, respectively). No combination effect on TGI was observed with 25 mg/kg SM08502+docetaxel (90%, $P<0.05$), but more tumor regressions occurred with combined treatment (4/6) than SM08502 alone (2/6). SM08502 was well tolerated in all tested xenograft models (<15% bodyweight loss from baseline).

In summary, SM08502 potently inhibited cell proliferation, SRSF6 phosphorylation, and Wnt-related gene expression in multiple PC cell lines. In vivo, SM08502 demonstrated strong antitumor effects in CRPC xenografts. These data suggest that SM08502 has the potential to provide clinical benefit to patients with treatment-resistant CRPC. A Phase 1 study of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).