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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 in diverse ovarian cancer models

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Background: Aberrant activation of the Wnt signaling pathway is observed in ovarian cancer (OC) and is associated with chemoresistance, immune evasion, and poor prognosis. SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that has been shown to potently inhibit the Wnt signaling pathway in preclinical colorectal cancer models. The purpose of these studies was to test the *in vitro* and *in vivo* activity of SM08502 in preclinical models of OC.

Methods: The effect of SM08502 on cell viability was tested in 10 OC cell lines of various histotypes, including high grade serous (HGS), serous, endometrioid, clear cell, and teratocarcinoma lines *in vitro*. Cell proliferation was impaired in all cell lines by SM08502 regardless of histotype and mutation profile (average EC_{50}=0.123 μM [0.034-0.275]). Relative to DMSO, SM08502 (1 μM) also potently inhibited Wnt-related gene expression (*TCF7, DVL2, LRP5,* and *ERBB2*), which correlated with inhibition of protein expression in HGSOC, endometrioid, and teratocarcinoma cell lines. Additionally, in cell lines derived from these histotypes, SM08502 strongly inhibited cyclin E1 gene and protein expression, the amplification/overexpression of which has been associated with treatment resistance and poor overall survival in HGSOC.

Results: *In vivo* antitumor effects and tolerability of oral SM08502 (6.25, 12.5, and 25 mg/kg QD for 15-22 days) were assessed in mice bearing OVCAR-3 (HGSOC; *TP53*mut), PA-1 (teratocarcinoma; N-Ras mut), and TOV-112D (endometrioid; *CTNNB1*mut) xenografts (n=5 mice per group). In OVCAR-3 xenografts, significant tumor growth inhibition (TGI) vs. vehicle occurred in mice treated with SM08502 12.5 mg/kg (66%, $p<0.01$) and 25 mg/kg (89%, $p<0.001$). SM08502 25 mg/kg also induced tumor regression in all mice. Similarly, in PA-1 xenografts, SM08502 induced TGI of 64% ($p<0.01$) at 12.5 mg/kg and 93% ($p<0.01$) with 4/5 tumors regressing at 25 mg/kg. SM08502 at 25 mg/kg also induced TGI of 64% ($p<0.01$) in TOV-112D xenografts. In addition, SM08502 (25 mg/kg QD) was assessed in 5 patient-derived xenograft (PDX) models of metastatic OC with double-hit *TP53* and *BRCA1/2* mutations (Crown Biosciences). Inhibition of tumor growth was observed in all tested PDXs (average TGI=61% [47-73], $p<0.001$). SM08502 was well tolerated in all xenograft models tested based on body weight measurements.

Conclusion: In summary, SM08502 potently inhibited cell proliferation and expression of Wnt-related genes and cyclin E1 in OC cell lines. SM08502 also demonstrated strong *in vivo* anti-tumor

effects, including tumor regressions, in different subtypes of OC xenografts and PDX models. These data suggest that SM08502 may provide clinical benefit for OC patients regardless of histotype, BRCA mutation status, or cyclin E1 expression. A Phase 1 study assessing safety, tolerability, and pharmacokinetics of SM08502 in advanced solid tumors is ongoing (NCT03355066).