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 highly conserved Wnt signaling pathway is implicated in multiple cancer hallmarks including proliferation, chemoresistance, and immune evasion
• Overexpression of cyclin E1 contributes to chemoresistance in ovarian cancer (OC)
• CDC-like kinases (CLKs) phosphorylate serine/arginine-rich splicing factors (SRFSFs), which regulate spliceosome assembly and subsequent gene expression
• 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
• These studies examined the in vitro and in vivo activity of SM08502 in preclinical models of OC

Methods

• Cell lines for further study were chosen based on their histotype and capacity for in vivo growth
• Cell viability was tested in 10 OC cell lines via Cell-ter-Blue fluorescence assay (Fig. 1)
• SM08502-mediated apoptotic activity and inhibition of gene or protein expression were assessed in OC cell cultures treated with DMSO or 1 μM SM08502 for 24 h (Figs. 2-4)
• Western blots of cleaved PARP, MCL-1, and survivin were used to assess apoptosis-related SM08502 activity (Fig. 2)
• Gene expression was determined by qRT-PCR with normalization to GAPDH via ΔΔCt (Figs. 3-4)
• Protein expression was measured by Western blot using β-actin as a control (Figs. 3-4)
• Cell line-derived xenografts – Nude mice were implanted subcutaneously in the flank with TOV-112D cells; severe combined immunodeficient (SCID) mice were implanted with OV20AR-3 or PA-1 cells (Fig. 5)
• Patient-derived xenografts (PDOX) – Tumor fragments of metastatic OC from 3 different patients were implanted subcutaneously in SCID mice (Fig. 6)
• Percent tumor growth inhibition (TGI) was calculated relative to the vehicle control group for a given time point; ΔTGI describes the change in TGI from Day 0 to study end
• Regressions were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines
• Tolerance was determined by average bodyweight change from baseline (<10% loss considered well tolerated)

Results

Figure 1. SM08502 impaired proliferation of OC cell lines regardless of histotype

Figure 2. SM08502 induced apoptosis in OC cells across different histotypes

Figure 3. SM08502 potentially inhibited SRFS6 phosphorylation and Wnt pathway gene and protein expression in OC cell lines

Figure 4. SM08502 inhibited cyclin E1 gene and protein expression in OC cell lines

Figure 5. SM08502 produced significant TGI and tumor regression in OC xenografts

Figure 6. SM08502 demonstrated strong antitumor effects in PDOX models of metastatic OC

Conclusions

• SM08502 was potent in vitro against 10 cell lines representing different OC histotypes and mutation profiles
• SM08502 significantly impaired tumor growth and induced tumor regression in xenografts of HGSOC, EOC, and TCOC cells
• SM08502 was also efficacious against 5 different patient-derived metastatic OC tumors
• SM08502 was well tolerated in all xenografts
• Inhibition of Wnt pathway gene and protein expression correlated with reduced SRFS6 phosphorylation and increased apoptosis
• Cyclin E1 expression was suppressed, suggesting SM08502 could have potential activity against chemoresistance
• Together, these data suggest that SM08502 has potential as a novel treatment for ovarian cancers
• A Phase 1 study assessing the safety, tolerability, and pharmacokinetics of SM08502 in advanced solid tumors is ongoing (NCT03355066)

References


At authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the publicly disclosed data.

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