SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, demonstrates activity against cancer stem cell (CSC)-enriched pancreatic cancer cells and suppresses stemness in vitro

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Background

- Cancer stem cells (CSCs) are a rare subpopulation of quiescent tumor cells with stemness, the ability to self-renew and form new tumors, and may contribute to chemotherapy resistance, proliferation, and relapse in pancreatic cancer (PC).1
- aberration activation of the Wnt signaling pathway is implicated in multiple cancer hallmarks including proliferation, metastasis, and immune evasion, as well as the maintenance and survival of CSCs.2
- CDC-like kinases (CLKs) phosphorylate serine/arginine-rich splicing factors (SRsFs), which regulate spliceosome assembly and subsequent gene expression.3
- SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that has been shown to potently inhibit Wnt pathway activity in preclinical colorectal cancer models.4
- These studies examined the ability of SM08502 to impair CSC viability and stemness in PC cell lines.

Methods

- Panc-1 cell cultures were enriched in CSCs (Panc1-CSC) by inducing anoikis, programmed cell death triggered by non-adherent growth conditions (Fig. 1):
  - Single cells plated in ultra-low attachment wells (20.7%; n=1)
  - Parental Panc1 cultures (69.9%; n=2)
- Cell survival and stemness of CSCs were assessed in both Panc1-CSC cultures (Fig. 3):
  - SM08502 impaired formation of Panc1-CSC spheroids
- Spheroid-forming frequency – HPAFII, Capan1, and Panc1 parent cell cultures were plated on 2D in 6-well plates and treated with SM08525 (1 µM) or vehicle per the timeline below. Spheroid-containing wells were counted around D24 (Fig. 5).

Results

- Panc1-CSC passage 11
- SM08502 impaired formation of Panc1-CSC spheroids
- Other disclosures are listed in the published abstract.

Conclusions

- CSCs were successfully enriched in Panc1-CSC parent cell cultures
- SM08502 demonstrated strong activity against CSCs in pancreatic cancer cell lines
- SM08502 anti-CSC activity was more potient than other CSC inhibitors (salinomycin and napabucasin) in vitro
- SM08502 inhibited the stemness of CSCs and parental PC cells
- SM08502 can potentially address relapse and treatment resistance in PC by depleting CSCs and reducing stemness in tumors
- A Phase 1 study assessing the safety, tolerability, and pharmacokinetics of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066)

Fig. 1. Panc1 parent cells and Panc1-CSC passage 2
Fig. 2. SM08502 impaired formation of Panc1-CSC spheroids
Fig. 3. SM08502 impaired formation of Panc1-CSC spheroids
Fig. 4. SM08502 reduced stemness-related gene expression in Panc1-CSC spheroids
Fig. 5. SM08502 dose-dependently inhibited frequency of spheroid formation in PC parental cell lines

References


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