Aberrant activity of the Hedgehog signaling pathway has been implicated in the development, progression and relapse of different cancer entities. Especially the interaction of tumor cells and the microenvironment is driven by SMO-independent Hedgehog signals and therefore Hedgehog inhibitors targeting SMO like Vismodegib were not able to demonstrate clinical benefit in SMO-independent Hedgehog driven cancer types like PDAC. 4SC-202 is an oral available epigenetic modulator exhibiting a combined inhibition of the lysine specific demethylase LSD1 (KDM1A) and histone deacetylases HDAC1, 2 and 3. Compared to HDAC inhibitors like Vorinostat and Hedgehog inhibitors targeting SMO like Vismodegib, 4SC-202 is able to inhibit canonical as well as non-canonical GLI-driven Hedgehog signaling. 4SC-202 was well tolerated in patients with advanced hematological diseases treated in the phase I TOPAS trial and demonstrated signs of efficacy. Inhibition of the HH signaling pathway could be monitored in whole blood samples of patients.

4SC-202 is to our knowledge the only clinical stage inhibitor of the non-canonical Hedgehog signaling pathway and has great potential to prolong overall survival in patients with cancer by targeting tumor-initiating cells. 4SC-202 was tested in a phase I clinical trial in patients with advanced hematological malignancies and demonstrated good tolerability along with signs of clinical efficacy with one complete response, one partial response and long-term stabilization of heavily pre-treated patients. The inhibition of HH signaling can be monitored in whole blood of patients.