Dysregulation of the cyclin D-CDK4/6-RB signaling axis is implicated in HR+ breast cancer (BC)1. While CDK4/6 inhibitors such as palbociclib (Palbo) have shown efficacy in this cancer type, overcoming resistance to these agents is an unmet need for patients.

CLks regulate activity of serine/arginine-rich splicing factors (SRSFs), which modulate spliceosome assembly, mRNA splicing, and gene expression2,3. SM08502, a pan-CLK inhibitor, has demonstrated strong antitumor activity in several preclinical cancer models and has been shown to inhibit the Wnt pathway via disruption of alternative splicing2.

We examined SM08502 activity in preclinical models of CDK4/6 inhibitor resistance. SM08502 strongly inhibited SRSF phosphorylation, an early indicator of CLK inhibition2. In addition, SM08502 inhibited proliferation and the RB pathway in Palbo-R T47D cells compared with CDK4/6 inhibitors (Fig. 2A). Figure 4 describes tumor regression in MCF7 xenografts in vivo. SM08502 strongly inhibited SRSF phosphorylation, Wnt-related gene expression, cell proliferation, and RB signaling in multiple HR+, HER2+ breast cancer cell lines. In vivo, SM08502 demonstrated strong antitumor effects in MCF7 xenografts and HR+ PDX models. Together, these data suggest that SM08502 has potential antitumor activity in HR+ BC and may provide clinical benefit to patients as a single agent or combined with standard therapy. A Phase 1 study of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).

### References


2. Heekyung Chung, PhD, Lauren Sitts, MS, Chi-Chiao Wu, PhD, Brian Eastman, MS, Sunil KC, PhD, Josh Stewart, Carine Bossard, PhD, Timothy Phalen, PhD, Steven Cha, MD. SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, demonstrates strong antitumor effects and Wnt and cyclin D-CDK4/6-RB pathway inhibition in hormone-receptor-positive (HR+) breast cancer models.