SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, demonstrates strong inhibition of the Wnt signaling pathway and antitumor effects as monotherapy and in combination with chemotherapy in triple-negative breast cancer (TNBC) models

**Background**
- Aberrant activation of the Wnt signaling pathway is associated with tumorigenesis, relapse/chemoresistance, and distance metastasis in TNBC.
- CDC-like kinases (CLKs) phosphorylate serine/arginine-rich splicing factors (SRSFs), which regulate spliceosome assembly and subsequent gene expression.1,2
- SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that has been shown to potently inhibit the Wnt signaling pathway and tumor growth in several preclinical cancer models.1,2
- These studies examined in vitro and in vivo antitumor activity of SM08502 as monotherapy and in combination with standard chemotherapy in preclinical models of TNBC.

**Conclusions**
- SM08502-mediated inhibition of SRSF6 phosphorylation was associated with potent reductions of Wnt pathway-related gene and protein expression in TNBC cell lines.
- In TNBC xenografts, oral SM08502 was well tolerated and demonstrated therapeutic potential alone or in combination with standard chemotherapy in initial treatment and as a single agent in maintenance treatment.
- SM08502 demonstrated the ability to inhibit metastasis in TNBC.
- A Phase 1 study assessing the safety, tolerability, and pharmacokinetics of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).

**Methods**
- Cell proliferation was assessed in 14 BC cell lines (7 TNBC-derived lines and 1 paired normal line) using the CellTiter-Blue® assay (Table 1).
- Inhibition of Wnt pathway-related gene and protein expression was analyzed in cells treated with DMSO or 1 μM SM08502 for 24 hours by qRT-PCR and Western blot, respectively (Fig. 1).
- In vivo antitumor activity of SM08502 (25 mg/kg QD for 19 days) was assessed in mice bearing orthotopically implanted, luciferase-expressing, TNBC (MDA-MB-231) derived xenografts (n=5 mice/group) (Fig. 2).
  - Tumor growth inhibition (TGI) was calculated relative to vehicle.
  - Metastasis was assessed ex vivo by quantifying luciferase activity in bilateral lungs collected at study end.
- MDA-MB-231 xenografts were used to assess the initial efficacy of SM08502 (12.5 and 25 mg/kg QD), nab-paclitaxel (Nab-P, 30 mg/kg QD i.p.), and gemcitabine (GEM)/Nab (75 mg/kg QD i.p.) and/or in combination. Efficacy of subsequent maintenance SM08502 (25 mg/kg QD) treatment was also assessed (Fig. 3).
  - Tumor regressions were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines: 30%-100% reduction in tumor volume relative to the start of the study.
- SM08502 (25 mg/kg QD) was assessed in 4 patient-derived xenograft (PDX) models of TNBC (Crown Biosciences) (Fig. 4).
  - ΔTGI describes the change in TGI from Day 0 to study end.
  - Tolerability was determined by average body weight change from baseline (+15% loss considered well tolerated).

**Results**
- Table 1. SM08502 impaired cellular proliferation of BC cell lines regardless of subtype
- Figure 1. SM08502 significantly inhibited SRSF6 phosphorylation and Wnt pathway-related gene and protein expression in several TNBC cell lines
- Figure 2. SM08502 greatly inhibited TNBC tumor growth and reduced lung metastasis in the MDA-MB-231/iuc orthotopic xenograft model
- Figure 3. SM08502 + GEM+Nab-P as initial treatment induced tumor regression and SM08502 as maintenance treatment induced or maintained regression in MDA-MB-231 xenografts
- Figure 4. SM08502 demonstrated strong antitumor activity in TNBC PDX models

**References**
8. Information on employees, shareholders, or consultants of samumed, LLC