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

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Poster #865

Background

- Aberrant activation of the Wnt signaling pathway is associated with tumorigenesis, relapse/chemoresistance, and distance metastasis in TNBC[1]
- CDC-like kinases (CLKs) phosphorylate serine/arginine-rich splicing factors (SRSFs), which regulate spliceosome assembly and subsequent gene expression[2,3]
- 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[4-7]
- 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

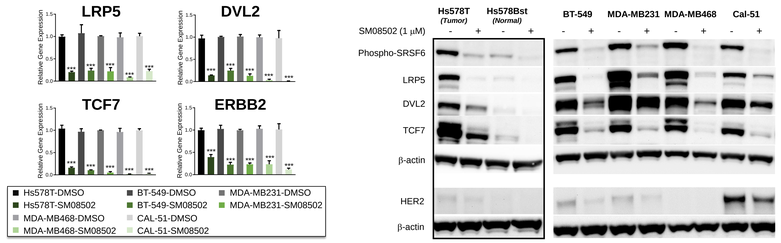
- **SM08502-mediated inhibition of SRSF6 phosphorylation was associated with potent reductions of Wnt pathway-related gene and protein expression in TNBC cell lines**
- **In TNBC xenografts, oral SM08502 was well tolerated and demonstrated therapeutic potential alone or in combination with standard chemotherapy 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)**

Results

Table 1. SM08502 impaired cellular proliferation of BC cell lines regardless of subtype

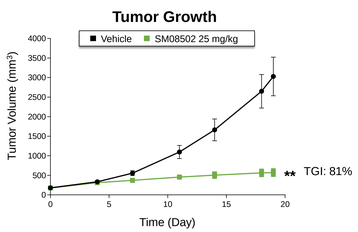
Subtype	Cell Line	EC_{50} (μM)	Average EC_{50} (μM)
Luminal A (HR+, HER2-)	MCF7	0.128	0.162
	T47D	0.147	
Luminal B (HR+, HER2+)	ZR-75-1	0.510	
	BT474	0.261	
	MDA-MB-361	0.110	
HER2 (HR-, HER2+)	SK-BR-3	0.058	
	MDA-MB-453	0.057	
TNBC	**MDA-MB-157**	**0.191**	
	MDA-MB-231	**0.143**	
	MDA-MB-468	**0.117**	
	BT-549	**0.240**	
	BT-20	**0.167**	
	CAL-51	**0.055**	
	Hs 578T	**0.080**	
Normal	Hs578Bst	1.517	N/A

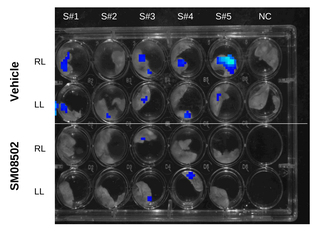
Figure 1. SM08502 significantly inhibited SRSF6 phosphorylation and Wnt pathway-related gene and protein expression in several TNBC cell lines



SM08502 25 mg/kg; Mean ± SEM; ***P*<0.001 vs. vehicle

Figure 2. SM08502 greatly inhibited TNBC tumor growth and reduced lung metastasis in the MDA-MB-231-luc orthotopic xenograft model

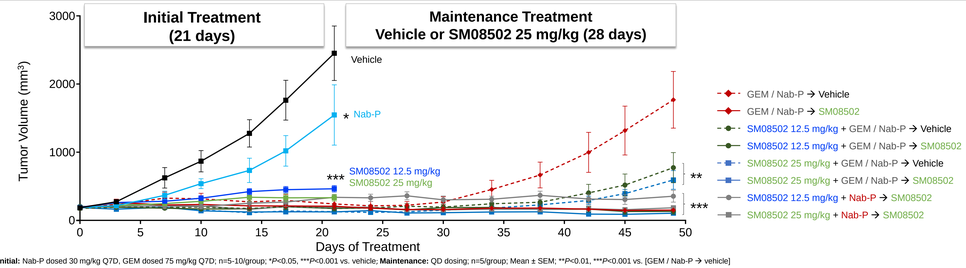




QD dosing; n=5/group; Mean ± SEM; ***P*<0.01 vs. vehicle. SM08502 was well tolerated

RL: Right lung lobe, LL: Left lung lobe
Luminescence observed in lung tissue: Vehicle (9/10) vs. SM08502 (3/10)

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

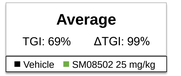


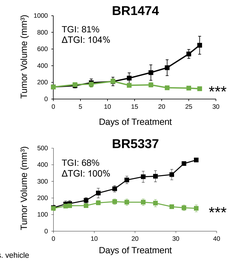
Initial: Nab-P dosed 30 mg/kg Q7D, GEM dosed 75 mg/kg Q7D; n=5-10/group; *P<0.05, ***P*<0.001 vs. vehicle; **Maintenance:** QD dosing; n=5/group; Mean ± SEM; **P<0.01, ***P*<0.001 vs. [GEM / Nab-P → vehicle]

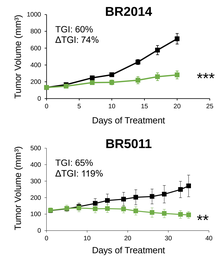
Initial Treatment	TGI *Day 21 (%)*	Regression *Day 21 (%)*	Maintenance Treatment	TGI *Day 49 (%)*	Regression *Day 49 (%)*
SM08502 12.5 mg/kg	81	0 (0/5)	N/A	N/A	N/A
SM08502 25mg/kg	86	0 (0/5)	N/A	N/A	N/A
Nab-P	37	0 (0/5)	N/A	N/A	N/A
SM08502 12.5 mg/kg + Nab-P	86	0 (0/5)	SM08502	80	20 (1/5)
SM08502 25 mg/kg + Nab-P	92	20 (1/5)	SM08502	90	60 (3/5)
GEM / Nab-P	91	0 (0/5)	Vehicle	0	0 (0/5)
		0 (0/5)	SM08502	91	40 (2/5)
SM08502 12.5 mg/kg + GEM / Nab-P	93	20 (1/5)	Vehicle	56	0 (0/5)
		40 (2/5)	SM08502	93	40 (2/5)
SM08502 25 mg/kg + GEM / Nab-P	95	60 (3/5)	Vehicle	66	20 (1/5)
		60 (3/5)	SM08502	94	80 (4/5)

SM08502 was well tolerated in all groups

Figure 4. SM08502 demonstrated strong antitumor activity in TNBC PDX models







SM08502 was well tolerated in all models
QD dosing; n=3/group; Mean ± SEM; **P<0.01, ***P*<0.001 vs. vehicle

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-MB231)-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-MB231 xenografts were used to assess the initial efficacy of SM08502 (12.5 and 25 mg/kg QD), nab-paclitaxel (Nab-P, 30 mg/kg Q7D i.p.), and gemcitabine (GEM)/Nab-P (75/30 mg/kg Q7D i.p.) separately 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 bodyweight change from baseline (<15% loss considered well tolerated)

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All authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the published abstract.

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