Inhibition of tumor growth and post-treatment regrowth by SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, in combination with standard of care in pancreatic cancer models

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Poster #C09

Background

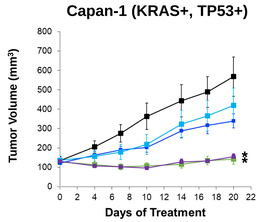
- Relapse and treatment resistance remain common in pancreatic cancer (PC) with standard of care (SOC) chemotherapy regimens
- Combining SOC with targeted drug therapies may improve treatment outcomes and clinical benefits[1, 2]
- Aberrant activation of the Wnt signaling pathway is implicated in multiple cancer hallmarks including proliferation, metastasis, and immune evasion and is common in PC[3,4,5]
- CDC-like kinases (CLKs) phosphorylate serine/arginine-rich splicing factors (SRSFs), which regulate spliceosome assembly and subsequent gene expression[6,7]
- SM08502 is a novel, oral, small-molecule pan-CLK inhibitor that has demonstrated potent Wnt signaling inhibition in preclinical colorectal and PC models[8, abstract #A02]
- These studies examined the tolerability and efficacy of SM08502 in combination with SOC chemotherapy regimens including gemcitabine (GEM), paclitaxel (P), and Nab-paclitaxel (Nab-P) in cell line- and patient-derived xenograft models of PC

Methods

- Cell line-derived xenograft – Nude mice were implanted subcutaneously in the right flank with Capan-1 or HPAFII PC-derived cell lines then randomized to treatment and vehicle (control) groups when tumors reached ~100-200 mm^3 (**Figs. 1-3**)
- Patient-derived xenograft (PDX) model – Severe combined immunodeficient (SCID) mice were implanted subcutaneously in both flanks with a patient-derived tumor (PNX0001, NexusPharma, Inc) fragment and randomized; tumor growth was calculated as percent relative to size at implantation (**Fig. 4**)
- Treatment (tumor growth) phase – Vehicle, SM08502 (QD p.o.), and/or GEM (25 or 75 mg/kg), P (15 mg/kg), and Nab-P (30 mg/kg, all Q7D i.p.) administered for 20-21 days (**Figs. 1-4**)
- Observation (tumor regrowth) phase – Mice were observed for up to 40 days after treatment discontinuation (**Figs. 3-4**)
- Tumor growth inhibition (TGI) was calculated relative to the vehicle control group (treatment phase) or the corresponding SOC group (observation phase)
- Tumor regressions were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines: 30-100% reduction in tumor volume relative to the start of the study. Safety and tolerability were assessed by bodyweight measurement

Results

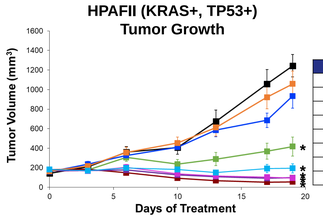
Figure 1. SM08502 + GEM inhibited tumor growth in Capan-1 xenografts



	TGI	p-value*	Regressions
Vehicle, QD	0%	1.000	0
GEM	26%	0.299	0
SM08502 25 mg/kg	**75%**	**0.007**	**1**
SM08502 12.5 mg/kg	40%	0.075	0
SM08502 12.5mg/kg + GEM	**73%**	**0.009**	**0**

SM08502 dosed PO QD, GEM/ dosed 25 mg/kg IP Q7D
n=6 mice/group; *vs. vehicle
Average bodyweight loss was <5% from baseline for all treatments

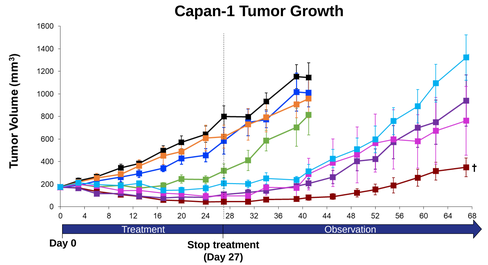
Figure 2. SM08502 + GEM/P inhibited tumor growth and induced tumor regression in HPAFII xenografts



	TGI	p-value*	Regressions
Vehicle, QD	0%	1.000	0/6
SM08502 6.25 mg/kg	15%	0.315	0/6
SM08502 12.5 mg/kg	25%	0.100	0/6
SM08502 25 mg/kg	**66%**	**0.0003**	1/6
GEM/P	**84%**	**0.0001**	2/6
SM08502 6.25 mg/kg + GEM/P	**92%**	**0.0002**	5/6
SM08502 12.5 mg/kg + GEM/P	**92%**	**0.0001**	4/6
SM08502 25 mg/kg + GEM/P	**99%†**	**0.0001**	6/6

SM08502 dosed PO QD, GEM/P dosed 75/15 mg/kg IP Q7D
n=6 mice/group; *vs. vehicle, †p<0.05 vs. GEM/P
Average bodyweight loss was <10% from baseline for all treatments

Figure 3. SM08502 + GEM/Nab-P delayed tumor regrowth and improved survival in Capan-1 xenografts



	Day 27			Day 67		
	TGI*	p-value*	Regressions	TGI†	p-value†	Regressions
Vehicle, QD	0%	1.0	0	--	--	--
SM08502 6.25 mg/kg	22%	0.233	0	--	--	--
SM08502 12.5 mg/kg	27%	0.191	0	--	--	--
SM08502 25 mg/kg	**60%**	**0.003**	**1**	--	--	--
GEM/Nab-P	**74%**	**0.0008**	**2**	0%	1.0	0
SM08502 6.25 mg/kg + GEM/Nab-P	**88%**	**0.0005**	**4**	**52%**	0.094	2
SM08502 12.5 mg/kg + GEM/Nab-P	**89%**	**0.0005**	**5**	41%	0.108	1
SM08502 25 mg/kg + GEM/Nab-P	**94%**	**0.0005**	**6**	**74%**	**0.003**	**1**

SM08502 dosed PO QD, GEM/Nab-P dosed 75 mg/kg/30 mg/kg IP Q7D
n=6 mice/group; *vs. vehicle, †vs. GEM/Nab-P
Average bodyweight loss was <10% from baseline for all treatments

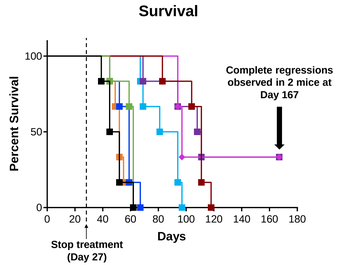
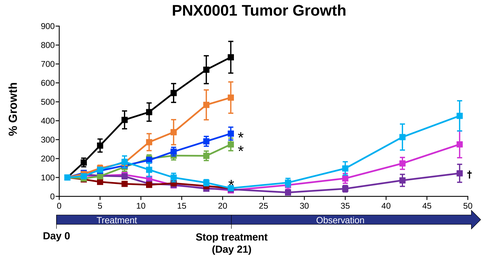


Figure 4. SM08502 + GEM/Nab-P inhibited tumor regrowth in a PDX model



		Day 21				Day 49			
	Mice	Tumors	TGI*	p-value*	Regressions	Tumors	TGI†	p-value†	Regressions
Vehicle, QD	7	12	0%	1		--	--	--	--
SM08502 6.25 mg/kg	8	15	29%	0.0877		--	--	--	--
SM08502 12.5 mg/kg	7	11	55%	**0.001**		--	--	--	--
SM08502 25 mg/kg	8	15	**63%**	**0.0004**		--	--	--	--
GEM/Nab-P	8	12	**94%**	**0.00003**	**10**	10	0%	1.0	0
SM08502 6.25 mg/kg + GEM/Nab-P	9	15	**96%**	**0.00003**	**14**	6	35%	0.18	0
SM08502 12.5 mg/kg + GEM/Nab-P	6	11	**95%**	**0.00003**	**13**	4	**71%**	**0.01**	2
SM08502 25 mg/kg + GEM/Nab-P	8	15	**94%**	**0.00003**	**10**	--	--	--	--

SM08502 dosed PO QD, GEM/Nab-P dosed 50 mg/kg/30 mg/kg IP Q7D
GEM: Gemcitabine, Nab-P: Nab-Paclitaxel; *vs. vehicle; †vs. GEM/Nab-P

Average bodyweight loss was <15% from baseline for all treatments except for SM08502 25 mg/kg + GEM/Nab-P, which was not well tolerated and thus excluded from observation

Conclusions

- **Oral SM08502 potently inhibited tumor growth both alone and in combination with chemotherapy**
- **The combination of SM08502 with GEM/P or GEM/Nab-P inhibited tumor growth more strongly than either treatment alone**
- **SM08502 extended antitumor effects into the post-treatment period when combined with SOC in genetically distinct PC models**
- **Improved survival and delay in tumor regrowth after treatment cessation suggest that SM08502 could help maintain treatment response in PC**
- **SM08502 was generally well tolerated**
- **These data showed that the combined application of SM08502 with SOC therapy has the potential to provide clinical benefit in PC**
- **A Phase 1 study assessing the safety, tolerability, and pharmacokinetics of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066)**

References

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Other disclosures are listed in the published abstract.

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