Initial results from a Phase 1 trial of a first-in-class pan-CDC2-like kinase inhibitor (SM08502) with proof of mechanism in subjects with advanced solid tumors

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Poster #CT112

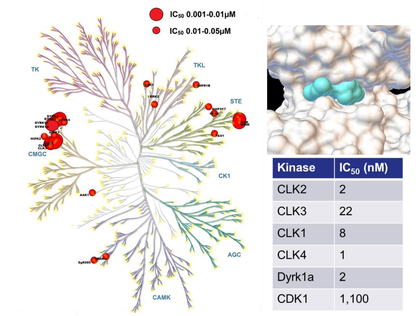
Background

- Dysregulation of alternative pre-mRNA splicing (AS) has been identified as a common mechanistic driver of tumor initiation, disease progression, and emergence of therapy resistance.[1]
- CDC2-like kinases (CLKs) regulate dynamic AS patterns by modulating pre-mRNA splice junction selection via direct phosphorylation of the serine/arginine-rich splicing factors 1–12 (SRSFs).[2,3] Therefore, CLK inhibitors offer an opportunity for therapeutic inhibition of AS.
- An iterative screening and synthetic optimization campaign identified SM08502, a potent inhibitor of CLK- and DYRK-family kinases. In preclinical studies, SM08502 inhibited growth and induced apoptosis in tumor models.[4]
- NCT03355066 is a two-part Phase 1 first-in-human study that evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of orally administered SM08502 in subjects with advanced solid tumors. Results from the dose-escalation 1A portion of the trial are presented.

Conclusions

- **In this first-in-human study, proof of mechanism for the pan-CLK inhibitor SM08502 was observed via modulation of genes associated with mRNA splicing and nonsense-mediated decay as well as through direct impact on CLK1.**
- **The most common adverse events were fatigue and GI-related events, including nausea, vomiting, and diarrhea.**
- **Tumor shrinkage was demonstrated in two subjects with endometrial cancer. One subject with prostate cancer achieved a PSA decline of 35%. Four subjects (2 each of endometrial and prostate cancer) were on study for at least 6 months.**
- **Part 1B will test SM08502 using an intermittent dosing schedule (5 days on and 2 days off).**

Figure 1. SM08502 demonstrated a selective kinase profile



Kinase	IC_{50} (nM)
CLK2	2
CLK3	22
CLK1	8
CLK4	1
Dyrk1a	2
CDK1	1,100

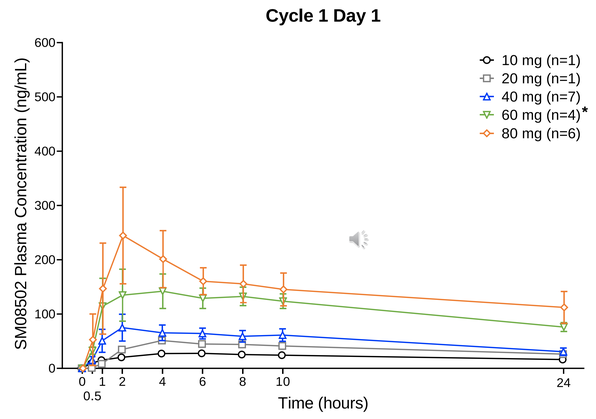
In a full kinome screen (466 kinases), SM08502 demonstrated good selectivity with CLKs (Adapted from Tam BY, et al. *Cancer Lett.* 2019).

Results

Table 1. Enrolled tumor types

Primary Cancer	Number (%) of Subjects N=19
Endometrial cancer	3 (15.8)
Ovarian cancer	3 (15.8)
Adenocarcinoma of colon	2 (10.5)
Prostate cancer	2 (10.5)
Anal cancer	1 (5.3)
Colon cancer	1 (5.3)
Hormone-refractory prostate cancer	1 (5.3)
Lip and/or oral cavity cancer	1 (5.3)
Non-small cell lung cancer	1 (5.3)
Pancreatic carcinoma	1 (5.3)
Rectal cancer	1 (5.3)
Solid pseudopapillary tumor of the pancreas	1 (5.3)
Uterine leiomyosarcoma	1 (5.3)

Figure 2. SM08502 had low-to-moderate clearance and a high volume of distribution



*Two subjects that received 60 mg SM08502 in Cycle 2 required dose interruption during Cycle 1.

Figure 3. Human pharmacodynamics demonstrated on-target pharmacology

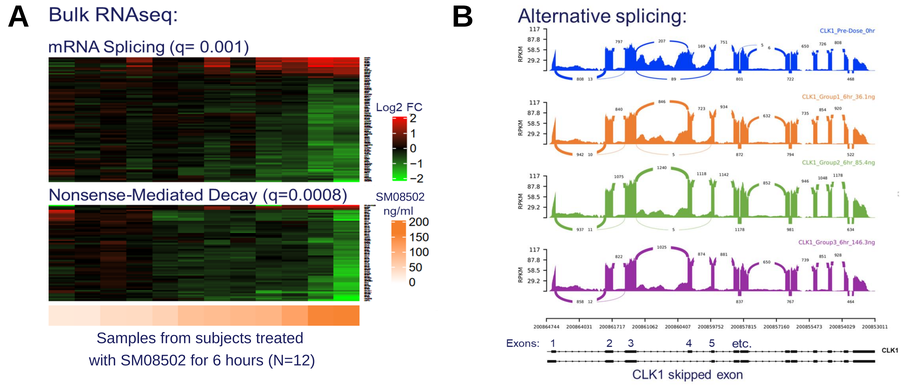
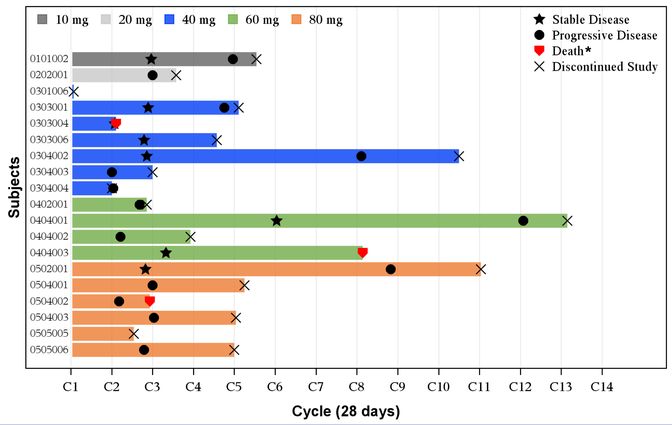


Table 2. Summary of adverse events (AEs)

	Number (%) of subjects					
	10 mg (n=1)	20 mg (n=1)	40 mg (n=7)	60 mg (n=4)	80 mg (n=6)	All Subjects (N=19)
AEs occurring in at least 15% of subjects						
Nausea	0 (0.0)	1 (100.0)	6 (85.7)	2 (50.0)	3 (50.0)	12 (63.2)
Diarrhea	0 (0.0)	1 (100.0)	3 (42.9)	3 (75.0)	3 (50.0)	10 (52.6)
Fatigue	0 (0.0)	0 (0.0)	2 (28.6)	2 (50.0)	4 (66.7)	8 (42.1)
Vomiting	0 (0.0)	1 (100.0)	3 (42.9)	2 (50.0)	1 (16.7)	7 (36.8)
Decreased appetite	0 (0.0)	0 (0.0)	3 (42.9)	2 (50.0)	1 (16.7)	6 (31.6)
Dyspnoea	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	2 (33.3)	4 (21.1)
Abdominal pain	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	1 (16.7)	3 (15.8)
Anemia	0 (0.0)	0 (0.0)	2 (28.6)	1 (25.0)	0 (0.0)	3 (15.8)
Headache	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	1 (16.7)	3 (15.8)
Hypotension	0 (0.0)	0 (0.0)	1 (14.3)	2 (50.0)	0 (0.0)	3 (15.8)
Grade 3 or higher AEs occurring in at least 10% of subjects						
Diarrhea	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	2 (33.3)	3 (15.8)
Anemia	0 (0.0)	0 (0.0)	1 (14.3)	1 (25.0)	0 (0.0)	2 (10.5)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (16.7)	2 (10.5)
Serious AEs possibly or probably related to study treatment						
Diarrhea	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (10.5)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (5.3)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (5.3)

Figure 4. Two prostate and endometrial cancer subjects were on study longer than 6 months



* The deaths of subjects 0404003 and 0504002 were due to disease progression. The death of subject 0303004 was due to an acute myocardial infraction and deemed by investigators unlikely related to the investigational product.

Methods

- For this open-label, dose-escalation, dose-finding Phase 1 study, the primary objectives were to evaluate the safety, tolerability, and PK of SM08502 administered orally in 28-day cycles to subjects with advanced solid tumors. The secondary objectives were to characterize the PD of SM08502 and evaluate preliminary efficacy.
- Part 1A utilized an accelerated-titration/3 + 3 dose-escalation design. Nineteen subjects were administered SM08502 at the following doses: 10 mg (n=1), 20 mg (n=1), 40 mg (n=7), and 60 mg (n=4) po qd. Additionally, 80 mg two days a week (n=4) and 80 mg seven days on and seven days off (n=2) were tested. Two subjects experienced dose-limiting toxicity: one at the 40 mg dose level (elevated liver function tests [ALT and AST]) and a second at the 80 mg dose level (diarrhea).
- Blood samples for measurement of SM08502 plasma concentrations were collected at various timepoints during Cycle 1 and Cycle 2 and quantified using a GLP-validated method utilizing high-pressure liquid chromatography (HPLC) coupled with mass spectrometry (LC/MS/MS) (Figure 2).
- RNA was isolated from whole blood using the Qiagen PAXgene Blood RNA Kit and Qiagene PAXgene Blood miRNA kit. The Illumina TruSeq Stranded Total RNA kit was used for RNA library construction and sequenced on the HiSeq 2500/3000 with 2x100bp read lengths at 2x60M reads per sample. GSEA analysis (v4.0.2) was performed on bulk RNAseq from patients treated with SM08502 for 6 hours and compared with pre-dose. Heatmaps (R v3.6.1; ggplot2 v3.3.2) were generated for two highly significantly enriched pathways showing fold-changes (log2) of genes in each pathway (Figure 3A).
- Patients were binned by similar exposure (n=4) at 6 hours (pre-dose, N=12) and differential alternative splicing analysis was performed using rMATS (v4.0.1) and JUM (v2.0.2). Splicing results are visualized as Sashimi plots (rmats2sashimiplot v2.03) (Figure 3B).

References

1. da Silva MR L, et al. *Biomed Res Int.* 2015.
2. Colwill K, et al. *EMBO J.* 1996.
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