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.

CCD2-like kinases (CLKs) regulate dynamic AS patterns by modulating pre-mRNA splice junction selection via direct phosphorylation of the serum/arginine-rich splicing factors 1-12 (SRFSFs). 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.

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.

**Background**

In a full-kinase screen (566 kinases), SM08502 demonstrated good selectivity with CLKs (Adapted from Kaiser ET al, Cancer cell 2016).

**Methods**

- RNA was isolated from whole blood using the Qiagen PAXgene Blood RNA Kit and sequenced on the Illumina TruSeq RNAseq 384 kit. Samples from subjects treated with SM08502 for 6 hours (N=12) and differential alternative splicing analysis was performed using rMATs (v2.0.3). Gene expression analysis was performed using the Bumera TruSeq Stranded Total RNA kit. BarSeq library construction and sequencing on the HiSeq 2500/3000 with 2x100bp read lengths at 2x60M reads per sample. GSEA analysis (v4.0.2) was performed on CDC24

**Table 1. Enrolled tumor types**

<table>
<thead>
<tr>
<th>Primary Cancer</th>
<th>Number (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Adenocarcinoma of colon</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Axial cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Cervix cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Immune-refractory prostate cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Lipo-/adenoid cyst cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Metastatic tumors of the pancreas</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Glioma/glioblastoma</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

**Table 2. Summary of adverse events (AEs)**

<table>
<thead>
<tr>
<th>AEs occurring in at least 15% of subjects</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>60 mg</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>3 (90%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>3 (90%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (60%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>

**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 demonstrated included, 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).

**Figures**

- Figure 1. SM08502 demonstrated a selective inhibitory profile (adapted from Kaiser ET al, Cancer cell 2016).
- Figure 2.SM08502 had low-to-moderate clearance and a high volume of distribution.
- Figure 3. Human pharmacodynamics demonstrated on-target pharmacology.
- Figure 4. Two prostate and endometrial cancer subjects were on study longer than 6 months.