SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, demonstrates strong antitumor effects and Wnt pathway inhibition in castration-resistant prostate cancer (CRPC) models

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Disclosure information

• Conference: 2020 American Association for Cancer Research
• Speaker: Carine Bossard, PhD
• I have the following financial relationships to disclose:
  – Employee of Samumed, LLC
• I will not discuss off-label use and/or investigational use in my presentation
Disclaimers

• This presentation is not intended to provide a comprehensive overview of all studies using SM08502

• SM08502 is an investigational compound currently in clinical trials; SM08502 has not been approved by the U.S. Food and Drug Administration (FDA) or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate

• While the complete mechanism of action (MOA) of SM08502 is unknown, further investigation is being conducted. All of the MOA information is based on nonclinical data and the relationship to clinical benefit is unknown

• This presentation is intended as a scientific exchange of medical information, is provided for educational purposes only, and is not intended for any promotional purpose or to offer medical advice
Development of therapies that overcome ARSi resistance in CRPC is an unmet medical need.

**Treatment with ARSi**

- **CRPC**
- **Response** 75%–85% patients
- **Development of resistance** 9–15 months
- **Relapse**

**ARSi resistance***

**AR-dependent mechanism**
- AR amplification
- AR splice variants (ARV7)

**AR-independent mechanism**
- Wnt activation
- PTEN, p53, Rb loss/mutation

*non-exhaustive list


ARSi: Androgen receptor signaling inhibitor

*non-exhaustive list*
Abnormal RNA splicing in cancer

Pre-mRNA

Core spliceosome

Mature mRNA

Illustration (left) adapted from Biamonti, et al. 2019.

SR: SRSF (serine/arginine-rich splicing factor)

CLK: CDC-like kinase


Illustration (right) adapted from Biamonti, et al. 2019.

Abnormal RNA splicing in cancer

Tumor progression

Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Inducing angiogenesis
Activating invasion & metastasis
Resisting cell death
Deregulating cellular energetics
Genome instability & mutation


SR: SRSF (serine/arginine-rich splicing factor)
CLK: CDC-like kinase
SM08502 is a potent CLK inhibitor that inhibits Wnt signaling in vitro

**TOPflash Wnt Reporter Assay**

- SM08502 TOPflash
- SM08502 EF1α-LucF

**Kinase Dendrogram for SM08502**

- IC$_{50}$ 0.001–0.01 µM
- IC$_{50}$ 0.01–0.05 µM

<table>
<thead>
<tr>
<th>Kinase</th>
<th>CLK2</th>
<th>CLK3</th>
<th>CLK1</th>
<th>CLK4</th>
<th>CDK1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC$_{50}$ (µM)</td>
<td>0.002</td>
<td>0.022</td>
<td>0.008</td>
<td>0.001</td>
<td>1.1</td>
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</tbody>
</table>

CLK: CDC-like kinase, CDK: Cyclin-dependent kinase
MOA of SM08502 for Wnt pathway inhibition

Transcription of Wnt target genes

β-catenin → TCF-LEF → DNA

Intron retention in TCF7

Exon skipping in LEF1

SW480 colon cancer cells
Pulse-chase RNA labeling, 6-hr SM08502 treatment; EU: 5-ethynyluridine

Tumorigenesis, stemness, and proliferation

Figure adapted from Saygin C, et al. Cell Stem Cell. 2019.
Elevated expression of CLK1/2 was associated with poorer survival in prostate cancer

**Progression-free interval of TCGA-PRAD patients expressing high and low CLK1**

![Graph showing progression-free interval for CLK1 high and low groups with p-value 0.03](image)

**Progression-free interval of TCGA-PRAD patients expressing high and low CLK2**

![Graph showing progression-free interval for CLK2 high and low groups with p-value 0.00035](image)

Cho, et al. AACR 2020; Session PO.EP01.05 - Prostate and Other Genitourinary Cancers

3521 / 18 - Transcriptome analysis of TCGA prostate cancer samples identifies an association of poorer survival and aggressive disease biology with CDC-like kinase (CLK) expression and spliceosome regulation

n=165 per high and low group
SM08502 inhibited viability of prostate cancer cell lines regardless of subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Cell lines</th>
<th>Mutations</th>
<th>EC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPC</td>
<td>PC3</td>
<td>AR-, TP53-/-, PTEN-/-</td>
<td>0.237</td>
</tr>
<tr>
<td>CRPC</td>
<td>DU145</td>
<td>AR-, PTEN+/-, TP53</td>
<td>0.377</td>
</tr>
<tr>
<td>CRPC</td>
<td>22Rv1</td>
<td>ARV7</td>
<td>0.191</td>
</tr>
<tr>
<td>Hormone-sensitive</td>
<td>LNCAP</td>
<td>PTEN -/-</td>
<td>0.329</td>
</tr>
<tr>
<td>Hormone-sensitive (partial)</td>
<td>VCaP</td>
<td>TP53</td>
<td>0.462</td>
</tr>
</tbody>
</table>

CRPC: Castration-resistant prostate cancer, AR: Androgen receptor, ARV7: Splice variant 7
SM08502 inhibited SRSF phosphorylation in CRPC cell lines
SM08502 inhibited Wnt pathway-related gene expression in CRPC cell lines

Gene expression: n=3; Mean ± SD; *P<0.05, ***P<0.001 vs. vehicle
SM08502 inhibited Wnt pathway-related protein expression in CRPC cell lines
SM08502 decreased AR and ARV7 expression in the 22Rv1 prostate cancer cell line

Gene expression: n=3; Mean ± SD; *P<0.05, ***P<0.001 vs. vehicle
SM08502 demonstrated strong antitumor activity in a SOC-resistant 22Rv1 xenograft model

22Rv1 tumor growth
PO QD dosing; Mean tumor volume ± SEM; n=6 per group; **P<0.01 vs. vehicle
All treatments were tolerated (mean bodyweight loss ≤5%)
SOC: Standard of care
SM08502 demonstrated strong antitumor activity in a SOC-resistant PTEN-/- xenograft model of CRPC.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>none</td>
</tr>
<tr>
<td>Enzalutamide 30 mg/kg</td>
<td>none</td>
</tr>
<tr>
<td>SM08502 6.25 mg/kg</td>
<td>62%</td>
</tr>
<tr>
<td>SM08502 12.5 mg/kg</td>
<td>64%</td>
</tr>
<tr>
<td>SM08502 25 mg/kg</td>
<td>78%</td>
</tr>
</tbody>
</table>

PC3 (AR-, PTEN -/-, TP53 -/-) tumor growth
PO QD dosing; Mean tumor volume ± SEM; n=6 per group, n=5 per vehicle and abiraterone group; *P<0.05 vs. vehicle
All treatments were tolerated (mean bodyweight loss ≤10%)
SOC: Standard of care, CRPC: Castration-resistant prostate cancer
SM08502 potently inhibited tumor growth and appeared more efficacious than docetaxel in a xenograft model of CRPC.

**Graph:**
- **X-axis:** Days
- **Y-axis:** Tumor Volume (mm³)
- **Legend:**
  - Black square: Vehicle
  - Orange circle: Docetaxel 10 mg/kg
  - Green square: SM08502 25 mg/kg
  - Blue diamond: SM08502 + Docetaxel

**TGI and Regression:**
- Vehicle: 26% 0/6
- Docetaxel 10 mg/kg: 90% 2/6
- SM08502 25 mg/kg: 90% 4/6
- SM08502 + Docetaxel: 90% 4/6

**PC3 (AR-, PTEN -/-, TP53 -/-) tumor growth**
- PO QD dosing for SM08502, IP Q7D dosing for docetaxel; Mean tumor volume ± SEM; n=6 per group, *P<0.05 vs. vehicle
- All treatments were tolerated (mean bodyweight loss ≤10%)

**Abbreviations:**
- CRPC: Castration-resistant prostate cancer
**Summary**

- *In vivo*, SM08502 (25 mg/kg) demonstrated strong antitumor effects in CRPC xenografts.
- SM08502 has the potential to provide clinical benefit to patients with treatment-resistant CRPC.
- A Phase 1 study of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066).

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**SM08502**

**ARSi resistance**
- AR-dependent mechanism
  - AR amplification
  - AR splice variants (ARVT)
- AR-independent mechanism
  - Wnt activation
  - PTEN, p53, Rb loss/mutation

**Tumor growth**

**CRPC**

**Response**
- 75%–85% patients

**Development of resistance**
- 9–15 months

**Relapse**

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Thank You