SDX-7320 elicits improvements in tumor-related and metabolic biomarkers: Results of a phase 1 dose-escalation study in patients with advanced refractory or late-stage solid tumors

Monica M. Mita¹, Johanna Bendell², Alain C. Mita¹, Michael Gordon³, Jasgit Sachdev³, Bradley J. Carver⁴, James Shanahan⁴, Benjamin Mayes⁴, Kris Awerkamp⁵, David Browning⁴, Neal Salomon⁴, Kimberly Sullivan⁷, Alfred Anderson-Villaluz⁸, Pierre DuFour⁴, Joe Johnson⁵, John S. Petersen⁴, David J. Turnquist¹¹, Peter Cornelius⁴.

¹Cedars-Sinai, Los Angeles, CA; ²Sarah Cannon Research Institute, Nashville, TN; ³Honor Health, Scottsdale, AZ; ⁴Syndevrx Inc., Cambridge, MA; ⁵TD2, Scottsdale, AZ; ⁶Development Insights, Beverly, MA; ⁷Radius Health, Waltham, MA; ⁸Quanterix, Billerica, MA; ¹¹Sojournix, Inc, Arlington, MA
Phase 1 Trial of SDX-7320
Polymer-conjugated inhibitor of methionine aminopeptidase 2 (MetAP2)

SDX-7320 (prodrug) Produces SDX-7539

Pleiotropic Mechanism of Action

- ↓ Insulin
  - ↓ PI3K
  - ↑ insulin sensitivity
- ↓ Leptin
  - ↓ STAT3 activation
  - ↓ Notch
  - ↓ Anti-apoptosis
- ↑ Adiponectin
  - ↑ AMPK activity
  - ↑ insulin sensitivity
- ↓ Angiogenesis
  - ↓ VEGF-C
  - ↓ bFGF/FGF2
  - ↓ IGF-1
- ↓ Immune Suppression
  - ↓ Arg-1
  - ↓ Treg
  - ↓ MSDCs

Efficacy demonstrated in preclinical oncology, metabolic disease models:
- Xenograft (A549, BT474)
- Syngeneic (B16F10, EO771)
- Diet-induced obese mice, rats

Source: SDX Internal data
Phase 1 Design, Patients
All comers, solid tumors

**Phase I Trial Design**
- Patients with advanced cancer
- Solid tumors only; no CNS tumors
- Sub-cutaneous administration, dose-escalation on a Q7D schedule (28 days/cycle) until >G2 AE, then expand to 3+3
- Switched to Q14D dosing schedule after encountering a DLT @ 49 mg/m² Q7D
- Target engagement was measured in whole blood with a custom ELISA
- Biomarkers were measured in serum using specific immunoassays
- PK for both SDX-7320 (pro-drug/polymer conjugate) as well as SDX-7539 (released active small molecule) was assessed in plasma using LC/MS

**Patient Demographics**
- 32 patients enrolled (14 male, 18 female)
- Mean age: 66 years (49 – 79)
- Mean # prior lines of therapy: 5.8 (1 – 17)
- Mean time since diagnosis: 6 years (0.6 – 24)
- Cancer types (n): lung (9), colon (6), breast (4), rectal (3), pancreatic (2), appendiceal (2), and one each of carcinoid, cholangiocarcinoma, cervical, endometrial, hepatocellular, urothelial

Source: SDX Internal data
# Phase 1 Safety Profile: TEAEs

*Relatively well-tolerated*

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>All Drug-Related TEAEs (%)</th>
<th>Drug-Related TEAEs ≥ G2 (%)</th>
<th>Drug-Related TEAEs ≥ G3 (events/patients)</th>
<th>AE Description (≥ G3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7 – 36 mg/m² (Q7D)</td>
<td>10</td>
<td>7 (70)</td>
<td>2 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>49 mg/m² (Q7D)</td>
<td>5</td>
<td>5 (100)</td>
<td>5 (100)</td>
<td>5/3</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>36 mg/m² (Q14D)</td>
<td>6</td>
<td>5 (83)</td>
<td>4 (67)</td>
<td>1/1</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>49 mg/m² (Q14D)</td>
<td>6</td>
<td>5 (83)</td>
<td>4 (67)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>65 mg/m² (Q14D)</td>
<td>5</td>
<td>4 (80)</td>
<td>3 (60)</td>
<td>1/1</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>All Patients</td>
<td>32</td>
<td>25 (78)</td>
<td>17 (53)</td>
<td>7/4</td>
<td></td>
</tr>
</tbody>
</table>

- Thrombocytopenia was reversible upon cessation of dosing
- No injection site reactions ≥ G2

Source: SDX Internal data
Phase 1: Stable Disease in 76% of Patients, Cycle 2

Target engagement in whole blood; PK data, key biomarker changes

Inhibition of MetAP2 in Whole Blood

SDX-7320 C<sub>max</sub> vs Dose (SDX-0101, Cycle 1)

SDX-7539 C<sub>max</sub> vs Dose (Cycle 1)

Exposure-Time Profile (49 mg/m<sup>2</sup>, n = 5)

Maximal Change in Biomarkers

Source: SDX Internal data
Phase 1 Summary

Ph I Safety Summary
- Most common AEs (in >10% of patients – mostly G1/2) were anemia (1 G3 event), constipation, diarrhea, nausea, vomiting, abdominal pain, decreased appetite, injection site reactions, alopecia and fatigue (1 G3 event)
- TEAEs ≥G3 possibly related to study drug were thrombocytopenia (4 patients) and vasculitis (1 patient)
- DLT was thrombocytopenia (G3, 4)
- RP2D is 49 mg/m2, Q14D

PK Summary
- Exposure of SDX-7320 (pro-drug) was proportional to dose ($r^2 = 0.47$), whereas levels of the released small molecule were more variable ($r^2 = 0.18$)
- Prolonged exposure of small molecule (SDX-7539) relative to polymer conjugate prodrug (SDX-7320)

PD Summary:
- Stable disease in 50% of patients; longest duration was 9 cycles; median = 6 cycles (95% CI = 3.8, 8.8); n = 28 patients
- Stable disease in 64% non-target lesions (n=16)
- Improvements in key biomarkers:
  - Metabolic markers: -63% insulin, -51% leptin, +74% adiponectin
  - Cancer markers: -50% bFGF, -38% VEGF-C

Ph Ib/2 Plans
- Leverage the anti-angiogenic/positive metabolic effects of SDX-7320 in a combination trial in patients with ER+/Her2- mBC
  - SDX-7320 + PI3Kα inhibitor + fulvestrant
  - Offset the negative metabolic effects of PI3Kα inhibitors (i.e., hyperglycemia, hyperinsulinemia) to extend PFS

Source: SDX Internal data
THANKS TO OUR PRESENTER

PRESENTER INFORMATION

Monica Mita, MD
Professor of Medicine
Co-Director, Experimental Therapeutics Program
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center
8700 Beverly Blvd, SCCT Mezzanine MS 35
Los Angeles, CA 90048
Office: (310) 248-6729
Fax: (310) 248-6740
E-mail: Monica.Mita@cshs.org