DS-1062

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Daiichi Sankyo., CO., LTD.

April 2, 2019
Agenda

- Overview of DXd-ADC Technology
- DS-8201 and U3-1402
- Trophoblast Cell-Surface Antigen 2: TROP-2
- DS-1062 Characteristics
- DS1062 Preclinical data
- DS1062 Phase I study
<table>
<thead>
<tr>
<th>Project (Targeted antigen)</th>
<th>Potential Indications</th>
<th>Discovery</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Pivotal study</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS-8201 (HER2)</td>
<td>Breast, Gastric, CRC, NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U3-1402 (HER3)</td>
<td>Breast, NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS-1062 (TROP2)</td>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS-7300 (B7-H3)</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS-6157 (GPR20)</td>
<td>GIST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS-6000 (undisclosed)</td>
<td>Renal, Ovarian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TA-MUC1)</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRC: colorectal cancer, NSCLC: non-small cell lung cancer, GIST: gastrointestinal stromal tumor

As of April 2019
Overview of DXd-ADC Technology
Proprietary Daiichi Sankyo ADC Technology: DXd-ADC

**DXd-ADC**

**Conjugation chemistry**
The linker is connected to cysteine residue of the antibody

**Proprietary Drug-Linker**

Payload (DXd)
Exatecan derivative

- Cysteine residue
- Drug-Linker

**High DAR**
**Stable drug-linker**
**Tumor-selective cleavable linker**

**High potency**
**Bystander effect**
**High clearance of the payload**
## DXd-ADC: High Drug to Antibody Ratio (DAR)

### High drug-to antibody ratio (DAR)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Payload</th>
<th>DAR</th>
<th><strong>Intensity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-DM1</strong></td>
<td>Trastuzumab, Tubulin inhibitor (DM1)</td>
<td>3.5</td>
<td>0 1 2 3 4 5 6 7</td>
</tr>
<tr>
<td><strong>DS-8201a</strong></td>
<td>Anti-HER2 Ab, DNA Topoisomerase I inhibitor (Exatecan derivative)</td>
<td>7-8</td>
<td>4 6 8</td>
</tr>
</tbody>
</table>

DXd-ADC: Stable Drug-linker in Plasma

Plasma conc. of DS-8201a and payload in monkey

- Total Ab (ADC + Ab)
- DS-8201a (DAR8)

Release rates of DXd from DS-8201a in plasma

- Mouse plasma
- Rat plasma
- Monkey plasma
- Human plasma
- PBS + 1% BSA

Source: Oitate-M et al., World ADC 2017 San Diego
**DXd-ADC: Mode of Action (MOA) of a Bystander Effect**

- ADC selectively targets antigen-expressing tumors
- Payload is released by lysosomal enzymes into tumors
- Membrane-permeable free drug attacks neighboring cancer cells which is effective against heterogeneous tumors

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### MOA of Bystander Effect

**HER2-positive** cancer cells

- **Internalization**
- **Drug release**
- **Degradation**
- **Arrest DNA replication**

**HER2-negative** cancer cells

- **Free payload drug penetrates neighbors**
- **Cell death**
- **DNA-Topo-1-inhibitor complex**
- **DXd**

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**Cell death**
DS-8201 and U3-1402
## Structure and Characteristics of DS-8201a Compared to T-DM1

<table>
<thead>
<tr>
<th></th>
<th>DS-8201a</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Payload</strong></td>
<td>Topoisomerase I inhibitor, Exatecan derivative</td>
<td>Tubulin inhibitor, DM1</td>
</tr>
<tr>
<td><strong>Bystander effect</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>DAR</strong></td>
<td>7-8</td>
<td>3.5</td>
</tr>
</tbody>
</table>

The linker is connected to lysine residue of the antibody via amide bond.

**DS-8201a**
- SMCC linker non-cleavable
- Digestion: ~8
- Exatecan derivative
- Payload: Topoisomerase I inhibitor, Exatecan derivative

**T-DM1**
- SMCC linker non-cleavable
- Digestion: 3.5
- Lys-SMCC-DM1
- Payload: Tubulin inhibitor, DM1

The linker is connected to lysine residue of the antibody via amide bond.
Tumor shrinkage was observed across multiple tumor types.

- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR* in the overall population is 49.3%

Source: Iwata-H et al., Abstract #2501, ASCO 2018
DS-8201a: Tumor Shrinkage Over Time by Tumor Type
ClinicalTrials.gov Identifier: NCT02564900

- Overall, 86.3% of subjects experienced tumor shrinkage
- 91.5% of these subjects experienced shrinkage at the time of first imaging assessment at 6 weeks
  Includes subjects who had ≥1 postbaseline scan. Dotted lines denote 20% increase and 30% reduction in tumor size, respectively.

Source: Iwata-H et al., Abstract #2501, ASCO 2018
**U3-1402 (Anti-HER3 ADC)**

**HER3 is an important target for ADC Smart-Chemo**

**Same ADC Technology**

- **DAR8**

**Patritumab**

Clinically validated mAb

Acceptable safety & tolerability in >300 subjects

**HER3 Expression**

In 188 screened breast cancer study patients

- HER3 1+ ~29%
- HER3 2+/3+ ~20%

**Phase 1/2 study in Breast Cancer**

ClinicalTrials.gov Identifier: NCT02980341

- HER3 positive (IHC 2+ or 3+) advanced/unresectable or metastatic breast cancer

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Escalation</td>
<td>Finding</td>
</tr>
<tr>
<td>8.0 mg/kg</td>
<td></td>
</tr>
<tr>
<td>6.4 mg/kg</td>
<td></td>
</tr>
<tr>
<td>4.8 mg/kg</td>
<td></td>
</tr>
<tr>
<td>3.2 mg/kg</td>
<td></td>
</tr>
<tr>
<td>1.6 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Efficacy of U3-1402; HER3-positive (measured by IHC [2+/3+]) Advanced / Unresectable or Metastatic Breast Cancer

ClinicalTrials.gov Identifier: NCT02980341

Potential against HER3-positive, advanced/unresectable, or metastatic breast cancer

*Analysis set: Efficacy-evaluable patients with at least 1 scan.
Baseline is defined as the last measurement taken before the first dose of study drug.
'Investigator assessment. For each patient, the best percentage change from baseline in the sum of diameters for all target lesions is represented by a vertical bar.
DCR = disease control rate; ORR = objective response rate.

Source: Kogawa-T et al., Abstract #2512, ASCO 2018
Trophoblast Cell-Surface Antigen 2: TROP2
TROP2

- A 36-kDa single pass transmembrane glycoprotein
- TROP2 is overexpressed in a variety of human carcinomas including lung, breast, pancreatic, cervical, ovarian, colorectal and gastric cancers
  - Some overlap with Irinotecan indications
  - TROP2 correlates with poor prognosis
- TROP2 is effectively internalized with binding antibody
- TROP2 is expressed in the epithelium of normal tissues including skin, esophagus and lung
  - Normal cell turnover is slower than tumor cells
  - High expression in non-target tissues requires careful determination of risk/benefit profile

TROP2 is an attractive target for ADC therapy
TROP2 and Poor Prognosis

1. High expression of TACSTD2 correlates with poor prognosis in Invasive Ductal Breast Cancer

2. TROP2 overexpression was associated with poor OS in solid tumors

3. TROP2 tended to be expressed in cases with an unfavorable outcome, and was significantly associated with an unfavorable outcome in nonlepidic-type adenocarcinomas in pulmonary adenocarcinoma
   • Virchows Arch. 2010 Jul;457(1):69-76.

4. High expression of TROP2 correlates with poor prognosis in pancreatic cancer
NSCLC is a good indication for DS-1062 because of its high TROP2 expression in both adeno and squamous cell carcinoma.

Source: Inamura K et al., Oncotarget 2017; 8:28725-28735
### TROP2-ADC Competitor: Immunomedics

<table>
<thead>
<tr>
<th>Product</th>
<th>Stage</th>
<th>Conjugated drug</th>
<th>DAR</th>
<th>Linker</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMU-132/ Sacituzumab govitecan-hziy</td>
<td>Phase 3 (TNBC)</td>
<td>SN-38 (Topo1 inhibitor)</td>
<td>7.6</td>
<td>Proteolytic &amp; PH- dependent cleavage</td>
</tr>
</tbody>
</table>

- TNBC: FDA Breakthrough Designation granted.
  - Confirmatory Phase 3 study is on-going.
  - Failed to win accelerated approval due to CMC issues.
- NSCLC & SCLC: FDA Fast Track Designation granted.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Research / Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacituzumab govitecan (IMMU-132)</td>
<td>mTNBC (3L+) (AA pending)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>mTNBC (3L) – ASCENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>Urothelial (3L) – TROPHY U-01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>HR+/HER2- mBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>CPI combo (mBC / mUC / mNSCLC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>PARPi combo (mBC / mUC / ovarian)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>Basket (mNSCLC / H&amp;N / mSCLC / endometrial / HCC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under FDA Priority Review</td>
</tr>
</tbody>
</table>

JPMorgan 2019
Sacituzumab Govitecan in TNBC

- Phase 1/2, basket design, open-label, single-group, multicenter trial involving patients with various types of advanced solid cancers who have received at least one previous therapy for metastatic disease.

- **Efficacy:**
  - ORR = 33.3%
  - mPFS = 5.5mo (n=108)

- **Safety:**
  - The most common adverse events are: nausea, diarrhea, fatigue, neutropenia, and anemia.
  - The most common adverse events of grade 3 or higher (>5% incidence): neutropenia, anemia, and a decreased white-cell count.

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**Image Description:**

A change in tumor size is shown in the graph. The x-axis represents the change from baseline in tumor size, while the y-axis shows the percentage change. The graph visualizes changes in tumor size over time, with different colors indicating progression of disease, stable disease, partial response, and complete response.
Sacituzumab Govitecan in NSCLC

FDA Fast Track Designation

Response Rate: 19%
Response Duration: 6.0 months
Median PFS: 5.2 months
Median OS: 9.5 months

Table 2. Frequency of Adverse Events Regardless of Causality

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades, No. (%)</th>
<th>Grade ≥ 3, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>8 mg/kg Dose</td>
</tr>
<tr>
<td>No. of patients</td>
<td>54 (80)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (61)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33 (61)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (46)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>21 (39)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (37)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19 (35)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (31)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (31)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>12 (22)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>10 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>10 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (19)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>9 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (15)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7 (13)</td>
<td>1 (12)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
TROP2 ADC is designed to be best in class

**Antibody**
Humanized anti-TROP2 monoclonal antibody (hIgG1)

**Payload**
Topoisomerase I inhibitor

**Selective-DAR4 to protect safety margin**

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**Non-selective DAR*4**

**Selective DAR4**

*drug-antibody ratio
DS-1062a demonstrated specific cell growth inhibitory activity to TROP2-positive cells, but not to TROP2-negative cells.
Anti-Tumor Activity of DS-1062a in Xenograft Mice Models

DS-1062a demonstrated stronger anti-tumor activity in TROP2-high tumor models compared to in TROP2-low tumor models.
## Comparison of DS-1062 and Sacituzumab Govitecan-hziy

<table>
<thead>
<tr>
<th></th>
<th>DS-1062a (Daiichi Sankyo)</th>
<th>Sacituzumab Govitecan-hziy (Immunomedics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>MAAP-9001a (humanized IgG1)</td>
<td>hRS7 (humanized IgG1)</td>
</tr>
<tr>
<td>Payload</td>
<td>DXd (TopoI inhibitor)</td>
<td>SN38 (TopoI inhibitor)</td>
</tr>
<tr>
<td>DAR</td>
<td>4</td>
<td>7.6</td>
</tr>
<tr>
<td>Linker cleavage</td>
<td>Enzymatic</td>
<td>pH-dependent and enzymatic</td>
</tr>
<tr>
<td>Human PK ($T_{1/2}$)</td>
<td>TBD</td>
<td>11.7 h at 10 mg/kg dosing*</td>
</tr>
<tr>
<td>Dosing</td>
<td>q3w regimen</td>
<td>10 mg/kg at day1 and 8 of 3 weeks</td>
</tr>
<tr>
<td>Dose Limiting Toxicity in Human</td>
<td>TBD</td>
<td>Neutropenia, MTD=12mg/kg**</td>
</tr>
<tr>
<td>Stage</td>
<td>Phase I NSCLC</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

* Reported in ASCO 2015 and AACR 2017
** Clin Cancer Res; 21(17) September 1, 2015
DS1062-A-J101 Study
DS-1062a Phase 1 Study Design

**NSCLC ≥ 3rd line**

- No selection based on TROP2 expression. TROP2 (IHC) is examined retrospectively.
- Treatment on-going in patients ≥ 1.0 mg/kg

**Dose Escalation**

- 0.27 mg/kg Q3W
- 1.0 mg/kg Q3W
- 2.0 mg/kg Q3W
- 4.0 mg/kg Q3W
- 6.0 mg/kg Q3W
- 8 mg/kg Q3W
- X mg/kg Q3W

**MTD**

- Required RDE ≥ 3mg/kg
- Assess TROP2 levels in all patients

**Dose Expansion**

- n=40 in RDE*

- Assess efficacy and safety for GO/NO-GO decision

**Following NSCLC POC**

- Open 2 other expansion cohorts for other TROP2 positive tumors

- Expansion Indication A
  - n=40

- Expansion Indication B
  - n=40

* RDE: Recommended Dose for Expansion

Safety and tolerability of DS-1062 up to 6.0mg/kg warrants further evaluation in higher dose exposures. Dose escalation data to be presented at ASCO 2019.
Phase I Study Sites

- IND/CTN approved: Dec2017
- First Patient Dosed: 07Feb2018 @ National Cancer Center Hospital

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Center Hospital (JP)</td>
<td>Toshio Shimizu, MD, PhD</td>
</tr>
<tr>
<td>National Cancer Center Hospital East (JP)</td>
<td>Kiyotaka Yoh, MD</td>
</tr>
<tr>
<td>Virginia Cancer Specialists (US)</td>
<td>Alexander Spira, MD, PhD, FACP</td>
</tr>
<tr>
<td>Dana-Farber Cancer Institute (US)</td>
<td>Jacob Sands, MD</td>
</tr>
<tr>
<td>Massachusetts General Hospital (US)</td>
<td>Rebecca Suk Heist, MD, MPH</td>
</tr>
<tr>
<td>UCLA Medical Center (US)</td>
<td>Aaron Lisberg, MD</td>
</tr>
<tr>
<td>MD Anderson Cancer Center (US)</td>
<td>Funda Meric-Berstam, MD</td>
</tr>
<tr>
<td>Sarah Cannon Research Institute (US)</td>
<td>Melissa Johnson, MD</td>
</tr>
</tbody>
</table>
Future prospects
TROP2 Expression in Various Cancers

Data from The Cancer Genome Atlas
POC in NSCLC

**NSCLC**

Fast-to-Market in Salvage line

- Monotherapy
  - Expedited pathway for accelerated approval

Earlier Lines

**Combination**
- Immunotherapy (PD-1/PD-L1)
- Antibody/Chemotherapies

Other TROP2 Positive Cancers

- TNBC
- Pancreatic cancer
- Esophageal cancer
- Cholangiocarcinoma
- Gastric cancer
- Colorectal cancer
- Bladder, Head & Neck, Ovarian cancer, Breast Cancer (HER2+, ER/PR+)

Expand development after confirming BIC potential.
TROP2 is an attractive target for DXd-ADC:
• Overexpressed in a variety of cancers
• Effectively internalized with binding antibody

DS-1062 has great potential:
• Preclinical anti-tumor efficacy and clinical evidence of Sacituzumab govitecan in TNBC
• Fulfill unmet medical needs in multiple cancers
• First-in-human study is ongoing

Phase I data will be presented at ASCO2019