Clinical & Preclinical Update of Topoisomerase I inhibitor, Exatecan Derivative based ADCs (DXd-ADC)

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Contents

Overview

DXd-ADC technology
DS-8201a Preclinical
DS-8201a Clinical
I/O combination
ADC franchise
Summary
Common obstructions in ADC technology

- **Limited payload classes**
  - Mainly tubulin inhibitors and DNA binders
  - Cross-resistance

- **Limited drug loading number**
  - Limited Drug-to-Antibody Ratio (DAR, 2-4)

- **Instable drug-linker**
  - Limited efficacy due to low ADC concentration
  - Limited safety margin due to released payload

- **Heterogeneity of drug distribution**
  - Mixture of ADC with a range of DAR
  - Difficulty in quality control of drug product and managing efficacy/safety
**Issues of existing ADC technology**
- Conflict between high DAR and efficacy/PK

**Heterogeneous conjugation (e.g. Cys)**

- **In vitro cytotoxicity**
  - Higher DAR, higher activity *In vitro*

- **PK in mice**
  - Higher DAR, lower stability *In vivo*

- **In vivo antitumor efficacy**
  - Higher DAR was not the best *In vivo*

Prior generation ADCs

- Payload related to typical chemotherapy previously received
- Limited DAR (2-4)
- Linker instability and lack of tumoral specificity result in toxicity

DXd-ADC technology

- **Novel differentiated payload**
  - Potent DNA topoisomerase I inhibitor
  - Effective in heterogeneous tumor microenvironment (bystander effect)
- High DAR (~8)
- High linker stability and cancer-cell selective drug release
DS original topoisomerase I inhibitor

- **SN-38 (Irinotecan)**
  - Topo I IC$_{50}$, 2.78 µM
  - 1990’s Launched

- **DX-8951 (Exatecan)**
  - Topo I IC$_{50}$, 0.25 µM
  - Terminated

- **DXd (DX-8951 derivative)**
  - Topo I IC$_{50}$, 0.31 µM
  - DXd-ADC
    - 2015-, Ph1
    - Ongoing

- **DE-310**
  - DX-8951
  - Terminated
Proprietary DS ADC technology: DXd-ADC

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

- **Novel payload**
- **High potency**
- **Bystander effect**
- **Short systemic half-life of the payload**

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

**Broad platform potential**

**Proprietary Drug-Linker**
Exatecan derivative

- **Payload (DXd)**
- Cys
- Cysteine residue
- Drug-Linker
Contents

Overview

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Summary
### 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>Payload</td>
<td>Topoisomerase I inhibitor, DXd</td>
<td>Tubulin inhibitor, DM1</td>
</tr>
<tr>
<td>Bystander effect</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>DAR</td>
<td>7-8</td>
<td>3.5</td>
</tr>
</tbody>
</table>

#### DS-8201a

**GGFG linker**

![DS-8201a structure](image)

**Digestion**

**DXd**

#### T-DM1

**SMCC linker**

![T-DM1 structure](image)

**Digestion**

**Lys-SMCC-DM1**
Stable drug-linker of DS-8201a

Hydrophobic Interaction Chromatography (distribution of conjugated drug)

Release rates of DXd from DS-8201a in plasma

Plasma conc. of DS-8201a at 3 mg/kg and released payload in monkeys

Stable drug-linker with DAR 7-8

- Homogeneous conjugation (DAR~8)
- Only 2% release rate of DXd in human plasma on Day 21
- No difference in plasma conc. between total mAb and ADC in monkeys
- Short systemic half-life of DXd in monkeys

DS-8201a showed potent antitumor efficacy against the HER2 low tumor due to high DAR (~8)

MOA of a bystander effect

- ADC targets antigen expressing tumors selectively
- Payloads are released in the tumors by lysosomal enzymes
- Membrane permeable free drug attacks neighboring cancer cells, which is effective against heterogenic tumors

**MOA of a bystander effect**

**HER2-positive cancer cells**
- Internalization
- Degradation
- Drug release
- DNA-Topo-1-inhibitor complex
- Arrest DNA synthesis
- Cell death

**HER2-negative cancer cells**
- Cell death
- Free payload drug penetrates neighbors
- DXd
**Bystander effect** (Preclinical, after 14 day treatment)

<table>
<thead>
<tr>
<th>Control</th>
<th>T-DM1, 10 mg/kg</th>
<th>DS-8201a, 3.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-inoculation of HER2+ and HER2- tumors in vivo</td>
<td>Activity against HER2+ tumors only</td>
<td>Activity against HER2+ and HER2- tumors</td>
</tr>
<tr>
<td>HER2+ tumors NCI-N87</td>
<td>HER2- tumors MDA-MB-468</td>
<td>HER2- tumors MDA-MB-468</td>
</tr>
</tbody>
</table>

**Tumor regression**

Source: Ogitani-Y et al., Cancer Science 2016; 107:1039–1046
## Preclinical safety profile of DS-8201a

<table>
<thead>
<tr>
<th>Species</th>
<th>Crl:CD(SD) rats</th>
<th>Cynomolgus monkeys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses</td>
<td>0, 20, 60 and 197 mg/kg</td>
<td>0, 10, 30 and 78.8 mg/kg</td>
</tr>
<tr>
<td>Regimens</td>
<td>Intravenous, every 3 weeks</td>
<td>Intravenous, every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Days 1, 22, 43 (3 times in total)</td>
<td>Days 1, 22, 43 (3 times in total)</td>
</tr>
<tr>
<td>No. of animals</td>
<td>10/sex/group (Main): all doses</td>
<td>3/sex/group (Main): all doses</td>
</tr>
<tr>
<td></td>
<td>5/sex/group (Recovery): 60 and 197 mg/kg</td>
<td>2/sex/group (Recovery): 30 and 78.8 mg/kg</td>
</tr>
<tr>
<td>Lethal dose</td>
<td>&gt;197 mg/kg</td>
<td>78.8 mg/kg (1 female died)</td>
</tr>
<tr>
<td>Body weight</td>
<td>197 mg/kg: low body weight gain</td>
<td>78.8 mg/kg: decreased in 1 male and 1 female</td>
</tr>
<tr>
<td>Hematology</td>
<td>60 mg/kg: decreased RBC and WBC parameters</td>
<td>78.8 mg/kg: decreased RBC parameters</td>
</tr>
<tr>
<td>Target organs and tissues</td>
<td>20 mg/kg: intestines, testis</td>
<td>10 mg/kg: intestines</td>
</tr>
<tr>
<td></td>
<td>60 mg/kg: bone marrow, thymus, lymph node, skin, kidney, incisor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78.8 mg/kg: bone marrow, kidney</td>
<td>30 mg/kg: lung, skin, testis</td>
</tr>
</tbody>
</table>

### STD$_{10}$/HNSTD

| STD$_{10}$/HNSTD*        | STD$_{10}$: >197 mg/kg                             | HNSTD: 30 mg/kg                              |

* STD$_{10}$, severely toxic dose of 10% in animals; HNSTD, the highest non-severely toxic dose

DS-8201a showed favorable safety profile (HNSTD, 30 mg/kg)
Contents

Overview

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I/O combination

ADC franchise

Summary
Dose escalation (Part 1)

- Breast or Gastric/GEJ adenocarcinoma:
  - 0.8 mg/kg Q3W (3 pts)
  - 1.6 mg/kg Q3W (3 pts)

- 3.2 mg/kg Q3W (3 pts)
- 6.4 mg/kg Q3W (6 pts)
- 8.0 mg/kg Q3W (3 pts)

Dose expansion (Part 2)

- Part 2a: HER2 positive T-DM1 pretreated BC
- Part 2b: HER2 positive Trastuzumab pretreated GC
- Part 2c: HER2 low BC (IHC 2+/ISH -, IHC 1+/ISH -)
- Part 2d: HER2 expressing solid tumors except BC/GC

MTD was not reached and doses of 5.4 and 6.4 mg/kg were selected for Part 2
Clinical efficacy of DS-8201a (Ph1)

Tumor size: maximum % change from baseline (5.4+6.4 mg/kg)

Data were analyzed based on the data cutoff on 11-May-2017

Potential across a broad spectrum of tumor types including not only HER2 positive BC and GC but also HER2 low and other cancers

Source: Doi-T et al., abstract 108, ASCO 2017
Clinical efficacy against breast cancer

Response and treatment duration (Breast cancer, 5.4 + 6.4 mg/kg)

Estimated median PFS: 45.4 weeks (95%CI: 32.1, NA)

Data were analyzed based on the data cutoff on 11-May-2017

Potential against T-DM1 refractory and HER2 low breast cancer

Source: Doi-T et al., abstract 108, ASCO 2017
Clinical efficacy against gastric cancer

Response and treatment duration (Gastric cancer, 5.4 + 6.4 mg/kg)

Estimated median PFS: 27.3 weeks (95%CI: 13.4, NA)

Tumor shrinkage (%)

Ongoing (22pts)
Discontinued (17pts)
• PD (11pts)
• AE (6pts)

Data were analyzed based on the data cutoff on 11-May-2017

Potential against trastuzumab refractory gastric cancer

Source: Doi-T et al., abstract 108, ASCO 2017
Pharmacokinetics profile (clinical)

**DS-8201a, Dose escalation (Phase 1)**
- 0.8 mg/kg
- 1.6 mg/kg
- 3.2 mg/kg
- 5.4 mg/kg
- 6.4 mg/kg
- 8.0 mg/kg

**DS-8201a, 6.4 mg/kg (Phase 1)**
- Total antibody
- DS-8201a
- Payload (DXd)

**DS-8201a showed high linker stability**

Source: Doi-T *et al*., abstract 108, ASCO 2017; Tamura-K *et al*., abstract 4585 (LBA17), ESMO 2016
## Favorable clinical safety profile of DS-8201a

### TEAEs by grade, >20% (No DLT observed)

<table>
<thead>
<tr>
<th>Preferred Term (N=133)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>13.5</td>
<td>9.0</td>
<td>8.3</td>
<td>3.8</td>
<td>34.6</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3.0</td>
<td>12.0</td>
<td>14.3</td>
<td>1.5</td>
<td>30.8</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0.8</td>
<td>9.8</td>
<td>12.0</td>
<td>3.0</td>
<td>25.6</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>0.8</td>
<td>12.8</td>
<td>9.0</td>
<td>1.5</td>
<td>24.1</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>51.9</td>
<td>13.5</td>
<td>1.5</td>
<td>0.0</td>
<td>66.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>33.8</td>
<td>20.3</td>
<td>3.8</td>
<td>0.0</td>
<td>57.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31.6</td>
<td>3.8</td>
<td>1.5</td>
<td>0.0</td>
<td>36.8</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>19.5</td>
<td>5.3</td>
<td>0.8</td>
<td>0.0</td>
<td>25.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>18.8</td>
<td>3.0</td>
<td>0.0</td>
<td>0.0</td>
<td>21.8</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>21.1</td>
<td>6.0</td>
<td>0.0</td>
<td>0.0</td>
<td>27.1</td>
</tr>
<tr>
<td>Malaise</td>
<td>18.0</td>
<td>4.5</td>
<td>0.8</td>
<td>0.0</td>
<td>24.1</td>
</tr>
</tbody>
</table>

Any Grade 3 or higher – 43.6%  
Data were analyzed based on the data cutoff on 11-May-2017

- No DLTs were observed and MTD was not reached.
- The most common treatment-emergent AEs were GI toxicities including nausea, decreased appetite and vomiting. Subjects rarely experienced Grade 3 or 4 toxicities.
- Grade 3 or 4 myelosuppression including thrombocytopenia and neutropenia were infrequently reported.

Source: Doi-T *et al.*, abstract 108, ASCO 2017
Overview

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Summary
### Our pipeline

<table>
<thead>
<tr>
<th>Antibody target</th>
<th>Potential indications</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase1</th>
<th>Phase2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 (DS-8201)</td>
<td>Breast, Gastric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER3 (U3-1402)</td>
<td>Breast, NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TROP2 (DS-1062)</td>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td>Best-in-class</td>
</tr>
<tr>
<td>B7-H3 (DS-7300)</td>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td>First-in-class</td>
</tr>
<tr>
<td>Project 5</td>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project 6</td>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Compounds under discussion are investigational agents and are not approved by the FDA or any other regulatory agency worldwide as a treatment for indications under investigation. Efficacy and safety have not been established in areas under investigation. There are no guarantees that these compounds will become commercially available for indications under investigation.
Strategy of HER3-ADC, U3-1402 against EGFR mutant NSCLC

**HER3 expression after EGFR TKI treatment** (in-vitro cell lines)

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Gefitinib Treatment</th>
<th>Fold</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA – 468</td>
<td>+</td>
<td>3.3</td>
</tr>
<tr>
<td>BT – 20</td>
<td>+</td>
<td>2.9</td>
</tr>
<tr>
<td>HCC1937</td>
<td>+</td>
<td>2.7</td>
</tr>
<tr>
<td>HCC1143</td>
<td>+</td>
<td>2.2</td>
</tr>
<tr>
<td>HCC38</td>
<td>+</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**HER3 is upregulated by EGFR TKI therapy**

**EGFRm NSCLC patient journey**

- **1st line TKI therapy**
- **2nd line TKI therapy for T790M+ (osimertinib)**
- **3rd line (T790M+) No approved Drug**

**HER3-ADC has potential to address unmet need of patients who progress on current therapies**

Source: Verma-N et al., Cancer Res. 2016, Adapted from NCCN Guidelines

*Note: Images and tables are not included in the natural text representation.*
## Contents

- **Overview**
- **DXd-ADC technology**
  - DS-8201a Preclinical
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  - I/O combination
  - ADC franchise
- **Summary**
A novel drug-linker technology platform with a potent DNA topoisomerase I inhibitor, DXd was created which is applicable to Best-in class (BIC) and First-in class ADCs.

- The major advantages are high DAR, bystander effect, less toxicity and wide application, showing BIC potentials against existing ADC platforms.
- DS-8201a is well tolerated in patients (MTD >8 mg/kg) and showing promising clinical responses in Phase I clinical trial.
- DS-8201a has been granted Breakthrough Therapy Designation for the treatment of patients with HER2 positive metastatic breast cancer in the US.
- DXd-ADC is a potential immune-stimulator beneficial to I/O combination.
- Several clinical and preclinical ADC projects are also ongoing.

Daiichi Sankyo actively seeking opportunities for ADC partnership to apply our ADC technology to new antibodies and targets.
Partnerships

**Immuno-Oncology partnerships** with our existing ADC assets

- HER2-ADC
- HER3-ADC
- TROP2-ADC
- B7-H3-ADC

**Partnerships to apply our ADC technology to new antibodies and targets**

- I/O mechanisms (e.g., checkpoint inhibitors)
- Our proprietary linker and novel payload
- Additional targets