R&D Day 2023
DAIICHI SANKYO CO., LTD.
December 11th, 12th 2023
Forward-Looking Statements

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Agenda

1 Opening

2 R&D Strategy

3 Research Capability

4 Clinical Progress

5 Q&A
FY2023 R&D Day presenters

Sunao Manabe  
Executive Chairperson and CEO

Ken Takeshita  
Head of Global R&D

Toshinori Agatsuma  
Head of Global Research

Mark Rutstein  
Head of Global Oncology Clinical Development
Agenda

1. Opening

2. R&D Strategy

3. Research capability

4. Clinical Progress

5. Q&A
Maximize 5DXd ADCs Values

Next Pillars

5DXd ADCs
- ENHERTU®
- Dato-DXd
- HER3-DXd
- DS-7300 (I-DXd)
- DS-6000 (R-DXd)

Oncology
- Specialty Medicine & Vaccine

Next Wave

ENHERTU®: trastuzumab deruxtecan (International Nonproprietary Name: INN), T-DXd, DS-8201 (HER2-directed ADC), Dato-DXd: datopotamab deruxtecan (INN), DS-1062 (TROP2-directed ADC), HER3-DXd: patritumab deruxtecan (INN), U3-1402 (HER3-directed ADC), DS-7300: ifinatamab deruxtecan, I-DXd (B7-H3-directed ADC), DS-6000: raludotatug deruxtecan, R-DXd (CDH6-directed ADC)
5DXd ADCs and Next Wave

Accelerate development and expand possibilities with AstraZeneca

DS-7300 (I-DXd)

DS-6000 (R-DXd)

HER3-DXd

Dato-DXd

ENHERTU®

Accelerate development & expand possibilities with Merck & Co., Inc., Rahway, NJ, USA

Develop various modalities to establish the next pillar

Oncology

Specialty Medicine & Vaccine

5DXd ADCs

ENHERTU®: trastuzumab deruxtecan (International Nonproprietary Name: INN), T-DXd, DS-8201 (HER2-directed ADC), Dato-DXd: datopotamab deruxtecan (INN), DS-1062 (TROP2-directed ADC), HER3-DXd: patritumab deruxtecan (INN), U3-1402 (HER3-directed ADC), DS-7300: ifinatamab deruxtecan, I-DXd (B7-H3-directed ADC), DS-6000: raludotatug deruxtecan, R-DXd (CDH6-directed ADC)
**EXPAND & EXTEND to deliver our technology to more patients**

- **Establish and expand DXd ADC therapies in** Breast and Lung cancers
- **Go Earlier**: explore early lines of therapy/stage of diseases; replace chemotherapy
- **Go Wider**: into new diseases beyond currently focusing areas to serve more patients in needs

- **Address unmet needs after ENHERTU® treatment**
- **Seek effective** treatment sequencing, novel combination, or formulation **to enhance efficacy and improve treatment**
- **Grow early pipeline** following 5DXd ADCs to contribute to more patients in the future
As of Apr. 2023, FY2022 Q4 earnings call

3ADCs launch plan

Active R&D investment following 3ADCs development progress exceeding the initial plan

5-Year Business Plan (FY2021-FY2025)

- FY2020
  - DESTINY-Breast01
  - DESTINY-Gastric01

- FY2021
  - DESTINY-Breast03
  - DESTINY-Breast04
  - DESTINY-Breast06
  - DESTINY-Breast09
  - DESTINY-Breast11
  - DESTINY-Gastric02
  - DESTINY-Gastric04
  - DESTINY-Lung01/02
  - DESTINY-Lung04
  - DESTINY-CRC01/02

- FY2022
  - ENHERTU
    - DESTINY-Breast05
    - TROPION-Lung01
    - TROPION-Lung08
    - TROPION-Breast01
    - TROPION-Breast02
    - HER3-DXd
      - HERTHENA-Lung01
      - HERTHENA-Lung02
  - Dato-DXd
    - TROPION-Lung07
    - TROPION-Breast03

- FY2023
  - Dato-DXd
  - HER3-DXd
  - ENHERTU
  - HERTHENA-Lung01
  - HERTHENA-Lung02

- FY2024
  - FY2025
  - FY2026
    - Combo with DS internal asset, I/O or targeted therapy in BC and NSCLC
    - Other cancer types
    - COMBO with I/O in BC and NSCLC
    - Other cancer types
    - Combo with targeted therapy in NSCLC
    - Other cancer types

Timeline indicated is based on the forecast in Apr 2023 and subject to change.
## Progress since R&D Day 2022

### Steady progress in maximizing product value of DXd ADCs

**New assets proceeded to clinical stage**

- **Data readout of pivotal studies**
  - **Dato-DXd**
    - NSCLC 2L/3L (TROPION-Lung01 study)
    - HR+/HER2 low or negative BC 2L/3L (TROPION-Breast01 study)
  - **HER3-DXd**
    - EGFR mutated NSCLC 3L (HERTHENA-Lung01 study)

- **Started New pivotal studies**
  - **Dato-DXd**
    - PD-L1<50% NSCLC, 1L (TROPION-Lung07 study)
    - Neo-adjuvant/Adjuvant, TNBC (TROPION-Breast04 study)
    - PD-L1 positive TNBC, 1L (TROPION-Breast05 study)

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### DXd ADCs in early phase

- Obtained updated data and presented at medical congresses
  - DS-7300: SCLC, CRPC, ESCC, sqNSCLC (Ph1/2 study and Ph2 study for SCLC ongoing)
  - DS-6000: OVC (Ph1 study ongoing)

- FIH study for DS-3939 has started

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### Next Wave

- Approval of quizartinib for FLT3-ITD positive AML 1L in Japan/US/EU
- FIH study for the next generation ADC, DS-9606 is ongoing
- FIH studies for new assets, DS-1103, DS-1471 have started

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Approval of COVID-19 vaccine and progress

DAICHIRONA® FOR INTRAMUSCULAR INJECTION*

- **DS original cationic lipid** is applied
  - Best lipid and lipid composition ratio are selected based on efficacy & safety perspectives
- **The first mRNA vaccine made in Japan**
- **mRNA vaccine for Omicron XBB.1.5 strain was approved in Japan** against COVID-19 in Nov 2023

Seasonal Flu/ COVID-19 combination vaccine**

Daiichi Sankyo's R&D activity on seasonal Flu/ COVID-19 combination vaccine was adopted the funding program for development of vaccines toward key infectious disease conducted by AMED

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* The research and development of DAICHIRONA® FOR INTRAMUSCULAR INJECTION is being conducted through the "Vaccine development project" promoted by the Japan Agency for Medical Research and Development (AMED) and the "Urgent improvement project for vaccine manufacturing systems" supported by the Japanese Ministry of Health, Labour and Welfare (MHLW).

** The research and development of Seasonal Flu/COVID-19 combination vaccine is being conducted through the "Vaccine development project" promoted by the Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA) for Japan Agency for Medical Research and Development (AMED).
Agenda

1. Opening
2. R&D Strategy
3. Research Capability
4. Clinical Progress
5. Q&A
Toshinori Agatsuma Career Highlights

Career

- 2023  Head of Global Research (Research Function Head of R&D Division)
- 2019  Global Oncology Research Head (Head of Oncology Research Labs. I)
- 2016  Head of Biologics & Immuno-Oncology Labs.
- 2013  Head of Biologics Pharmacology Research Labs.
- 2010  Group Leader of Biologics Research Labs.
- 2004  Group Leader of Biomedical Research Labs. in former Sankyo
- 1996  Biological Research Labs. II/ Biomedical Research Labs. in former Sankyo
- 1995  Division of Infectious Diseases in The Institute of Medical Science, The University of Tokyo
- 1994  MRC Collaborative Centre, London, UK
- 1991  Bioscience Research Labs in former Sankyo
Daiichi Sankyo created and launched innovative drugs from its own research laboratories.

- Edoxaban
- Prasugrel
- Olmesartan
- Laninamivir
- Mirogabalin
- Trastuzumab
- Valemetostat
- Deruxtecan
- Levofloxacin
- Pravastatin

Established in 2007

Shinagawa, 1908
Kasai, 1938
Shinagawa
Kasai
Long history behind the birth of DXd ADC

Several inventors of ENHERTU® have been involved in other launched products
- They have long tenure at DS, leveraged their expertise and are now research leaders growing our future talent

ADX: antibody-drug conjugate, DDS: drug delivery system, DS: Daiichi Sankyo, mAb: monoclonal antibody

Only nine years

Between DS ADC Working Team launch and ENHERTU® approval

1913
Paul Ehrlich described the concept of a "magic bullet"

1946
Nitrogen Mustards First chemotherapy in clinical trials

1975
Advent of murine mAb with hybridoma technology

1988
Advent of humanized mAb

1991
Immunogenicity of mouse mAbs a seriously limits early ADCs

1997
RITUXAN® FDA approved chimeric mAb

1998
HERCEPTIN® FDA approved humanized mAb

2000
First ADC FDA approved: MYLOTARG®

2001
GLEEVEC® FDA approved molecular-targeted drug of small-molecule

2010
MYLOTARG® withdrawn in U.S.

2010
ENHERTU® approved

2011
ADCETRIS® FDA approved

2013
KADCYLA® FDA approved

2017
BESPONSA® FDA approved

2019
MYLOTARG® FDA reapproved

NINE YEARS

History of ADCs

Source: Nakada T. et al., Chem Pharm Bull (Tokyo). 2019

ADC: antibody-drug conjugate, mAb: monoclonal antibody
Establishment of ADC Working Team

- Experience and expertise in research and production of both antibodies and small molecules are important.

- At the time, ADC technology was a new area – a trial-and-error approach was inevitable.

- In addition to pharmacological research, pharmacokinetics and safety evaluation research were also crucial.

Organized cross-functional working team specialized in the development of new ADC (Jun 2010)
Challenges that new ADCs had to overcome

- **Limited variations of payload**
  
  Limitations in treatment options for non-responsive and drug resistant tumors

- **Heterogeneity in drug binding sites**
  
  Challenges in inter-batch variability and setting formulation specification

- **Instability of linker**
  
  Decreased efficacy due to a decrease in blood concentration of ADC
  Toxicity due to an increase in free payload concentration in blood

- **Limited numbers of drugs to conjugate**
  
  Limitation in therapeutic efficacy
Daiichi Sankyo’s DXd ADC technology solved conventional challenges

Widely applicable platform

7 Key Attributes\(^a\) of DXd ADC

- Payload MOA: Topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio (DAR)
- Stable linker-payload
- Payload with short systemic half-life
- Tumor-selective cleavable linker
- Bystander antitumor effect

\(^a\)The clinical relevance of these features is under investigation.

DXd ADC Technology

Deruxtecan

Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)


ADC: antibody-drug conjugate
Strategy for ADC research in Daiichi Sankyo as of 2010

Development of original ADC technology - Generation of innovative drugs for cancer patients

**OUTCOME**
- ENHERTU®
- Dato-DXd
- HER3-DXd
- DS-7300 (I-DXd)
- DS-6000 (R-DXd)
- DS-3939

**FY2010 (APRIL)**
- Trastuzumab-ADC

**FY2011**
- Drug-Linker screening

**FY2012**
- Establishment of in-house technology (Linker-Drug)

**FY2013**
- Generation of ADC research themes (Target/Antibody)

**In-house ADC (1st wave)**
- Ab humanization
- Conjugation & Evaluation

**In-house ADC (2nd wave: New target)**
- Target identification
- Ab generation & humanization
- Conjugation & Evaluation

**Development and Generation**
- Development of original ADC technology
- Generation of innovative drugs for cancer patients

**Trastuzumab**
- Establishment of in-house technology (Linker-Drug)

**TARGET**
- HER3

**Ab generation & humanization**
- Conjugation & Evaluation

**ADC**: antibody-drug conjugate
Key point to success 1

**Discovery of potent payload**

From an **extensive in-house compound library**, candidate payloads were selected and screened, leading to the **discovery of DXd**

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**Irinotecan (CPT-11)**

- Prodrug of SN-38

**Exatecan (DX-8951)**

- 10-fold more potent than SN-38

**DE-310**

- Polymer-conjugate of exatecan

**DXd (Exatecan derivative)**

Key point to success 2

Design of drug-linker capable of demonstrating excellent efficacy

Development of unique drug-linker structure through the researchers’ imagination and creativity, utilization of past knowledge & experience to leverage the benefits and improve the drawbacks

Protease cleavable peptide: Gly-Gly-Phe-Gly

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>DAR</th>
<th>Aggregate (%)</th>
<th>KPL-4 IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>3.4</td>
<td>26</td>
<td>0.33</td>
</tr>
<tr>
<td>2</td>
<td>-NH-CH&lt;sub&gt;2&lt;/sub&gt;-(C=O)-</td>
<td>3.2</td>
<td>3</td>
<td>0.39</td>
</tr>
<tr>
<td>3</td>
<td>-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-(C=O)-</td>
<td>3.8</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>4</td>
<td>-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-(C=O)-</td>
<td>2.6</td>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td>5</td>
<td>-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-(C=O)-</td>
<td>3.4</td>
<td>4</td>
<td>0.07</td>
</tr>
<tr>
<td>6</td>
<td>-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;5&lt;/sub&gt;-(C=O)-</td>
<td>2.5</td>
<td>20</td>
<td>0.11</td>
</tr>
<tr>
<td>7</td>
<td>-NH-CH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;2&lt;/sub&gt;-C(=O)-</td>
<td>7.7</td>
<td>0.6</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Source: Abe Y et al. Drug Delivery System 34-1, pp.52-58

DAR: drug-antibody ratio
Key point to success 3

Confirmation of drug potential through animal models

Thorough drug screening utilizing a diverse range of animal models was conducted to confirm the potential of the drugs

Efficacy of ENHERTU® in 34 CDX/PDX models with varying HER2 expression level

**Tumor regression: 82% (28/34 models)**

- **T-DXd 10 mg/kg**
- **T-DM1 10 mg/kg**

| Source: Yuki Abe et al., Bioconjugate 2016 |

* Weak HER2 expression was detected in models with IHC 0, except for MDA-MB-468-Luc by another method than IHC.

CDX: cell line derived xenograft, IHC: immunohistochemistry, PDX: patient derived xenograft, T-DXd: trastuzumab deruxtecan (ENHERTU®)
The Future of ADC research and development

- Further increase in ADC products and expansion of target indications
- Investigation of drug combinations with ADC to show broader efficacy
- Develop new technologies to lessen adverse effects and seek cures
  - Establishment of new ADC technologies beyond next generation ADC through further investigation of payload, linker, DAR, etc.

Further enhance Daiichi Sankyo as a global leader in ADC technology

ADC: antibody-drug conjugate, DAR: drug-antibody ratio
Sustainable ADC Development

- **DXd ADC**
  - ENHERTU®
  - Dato-DXd
  - HER3-DXd
  - DS-7300 (I-DXd)
  - DS-6000 (R-DXd)
  - DS-3939
  - DS-XXXX

- **Next Generation ADC**
  - DS-9606
  - Multiple projects in IND enabling & discovery stage

- **New Concept ADC 1**
  - Multiple projects in IND enabling stage

- **New Concept ADC 2**
  - Multiple projects in discovery stage

- **New Concept ADC 3**
  - Multiple projects in discovery stage

ADC: antibody-drug conjugate, IND: investigational new drug application
Key success factors of Daiichi Sankyo drug discovery: Science & Technology through Craftspersonship

At DS, we

- Have an insatiable passion to pursue new science & technology
- Apply exceptional craftspersonship aiming for perfection
- Deliver unique value for patients
Crafting New Standards of Care
Data-Driven Drug Discovery (D4)

Effectively utilizing internal & external data to help deliver multiple clinical development candidates by enhancing the success rate and research speed of drug discovery research

Exploratory Hit discovery Hit to lead / Lead optimization Pre-Clinical

We will expand D4 to include various modalities and accelerate drug discovery through cutting-edge computer-driven lab automation

Source: R. Kunimoto, J. Bajorath, K. Aoki, Drug Discovery Today, 2022 (the figure is partially modified)
DMTA: Design-Make-Test-Analysis
Improvement of research efficiency and quality of compound design through Cyber DMTA

- New tools allowed us to attain higher-quality compound designs through data analysis

CADD: computer aided drug design, DMTA: Design-Make-Test-Analysis, D4: Data-Driven Drug Discovery, ML: machine learning
Further enhancement of our strengths “Science & Technology” is essential for sustainable growth

**Our Strength**

- **Human Resources**
  - Pursue cutting-edge science
  - Scientific assessment capabilities
  - Technologies originated from craftspersonship
  - A high level of engagement
  - Eagerness for innovation

- **Corporate Culture**
  - Our corporate culture: Researchers respect each other as a specialist in science and exchange opinions in a free and open-minded manner regardless of positions and tenure
  - Techniques and experiences of drug development handed down through our history

- **Core Technologies**
  - Our proprietary ADC technology platform
  - Medicinal chemistry, protein engineering, drug evaluation, computational science and translational research

**Identifying Our Next Growth Driver**
Agenda

1. Opening
2. R&D Strategy
3. Research Capability
4. Clinical Progress
5. Q&A
EXPAND & EXTEND to deliver our technology to more patients

- Establish and expand DXd ADC therapies in **Breast** and **Lung** cancers
- **Go Earlier:** explore early lines of therapy/stage of diseases; replace chemotherapy
- **Go Wider:** into new diseases beyond currently focusing areas to serve more patients in needs

- Address unmet needs after **ENHERTU®** treatment
- Seek effective **treatment sequencing, novel combination, or formulation** to enhance efficacy and improve treatment
- **Grow early pipeline** following 5DXd ADCs to contribute to more patients in the future

**Treatment Line**
- **Other cancers with remaining unmet needs**
- **Lung**
- **Breast**

**Indications**
- **Early lines Combination**

**Pipeline**
- **ENHERTU®**
  - **Dato-DXd**
  - **HER3-DXd**
  - **DS-7300 / DS-6000**
  - **DS-3939 / DS-XXXX (DXd)**

**Time**
- **Sequence Combination Replacement Formulation**
- **EXTEND**
  - Sustainable contribution

**Indications**
- **Earlier lines Combination**

**Pipeline**
- **Next-generation ADC Other new modalities**

ADC: antibody-drug conjugate
EXPAND & EXTEND to deliver our technology to more patients

Other cancers with remaining unmet needs

**Treatment Line**

- Lung
- Breast

Indications

- Earlier lines
- Combination

**EXPAND**

5DXd ADCs

**Progress and Future**

- Breast cancer
- Lung cancer
- New disease areas

ADC: antibody-drug conjugate
Our Breast Cancer Strategy

Expand on our leadership in breast cancer to deliver additional novel treatment options to improve patient outcomes for a broad set of distinct patient segments

- Establish our assets as a foundational treatment option across early to metastatic disease
- Identify novel combination and sequencing strategies to improve patient outcomes
- Enhance our knowledge of the underlying biology across the disease spectrum of breast cancer
Dato-DXd enables TROPION-Breast01 to aim to set a new standard for TROP2 ADCs in HR+/HER2 low or negative BC

**TROPION-Breast01 Study**

- **The dual primary endpoints are PFS and OS**
- **TLR was obtained in Sep 2023**
- **63% of the patients received 1L and 37% received 2L chemotherapy prior to Dato-DXd**
- **Median PFS by BICR: 6.9 months for Dato-DXd (n=365) and 4.9 months for ICC (n=367). OS data was not mature at the point of analysis**
- **Confirmed ORR: 36.4% for Dato-DXd and 22.9% for ICC.**
- **Rate of grade ≥3 TRAEs in the Dato-DXd group (21%) was less than half that in the ICC group (45%).**
- **ILD rate was low; mainly grade 1/2 events. There were one grade 3 and one grade 5 adjudicated ILD event**
- **Plan to file in the US with TROPION-Breast01 study data within FY2023**

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**BEGONIA (Arm 7)**

BEGONIA is open-label platform study to evaluate safety and efficacy of durvalumab combined with other novel therapies in 1L advanced/metastatic TNBC. Combination of durvalumab and Dato-DXd is evaluated in Arm 7 and Arm 8 (PD-L1 high).

- **Confirmed ORR**: 79%, median DOR: 15.5 months and median PFS: 13.8 months
- Antitumor responses were observed regardless of PD-L1 expression level
- The most common AEs were gastrointestinal and generally of low grade
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade 2 events, 1 grade 1 event)

**AEs**: adverse events, **CI**: confidence interval, **CR**: complete response, **DOR**: duration of response, **ILD**: interstitial lung disease, **NC**: not calculable, **ORR**: objective response rate, **PFS**: progression-free survival, **PR**: partial response, **TAP**: tumor area positivity, **TNBC**: triple-negative breast cancer
ENHERTU® is an effective treatment options for patients with HER2+ mBC with treated/stable and untreated/active brain metastasis (BM)

Pooled exploratory analysis of DESTINY-Breast01, DESTINY-Breast02 and DESTINY-Breast03 in HER2+ mBC

- Demonstrated robust intracranial (IC) responses in patients with stable BMs (IC-ORR 45.2% vs 27.6%, median IC-DoR 12.3 vs 11.0 months) and active BMs (IC-ORR 45.5% vs 12.0%, median IC-DoR 17.5 vs NA)

- Numerically longer median CNS-PFS was observed in stable BMs (12.2 vs 8.7 months) and active BMs (18.5 vs 4.0 months)

- The safety profile in patients with BMs was acceptable, generally manageable and similar to the safety profile in the overall patient population

<table>
<thead>
<tr>
<th>IC-ORR, median, months (95% CI)</th>
<th>T-DXd BM Pool</th>
<th>Comparator BM Pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated/stable BMs (n = 104)</td>
<td>12.3 (9.1-17.9)</td>
<td>17.5 (13.6-31.6)</td>
</tr>
<tr>
<td>Untreated/active BMs (n = 44)</td>
<td>11.0 (5.6-16.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Exploratory best IC response, ORR and DoR by BICR**

- **Complete response**
- **Partial response**

This table considers both target and non-target lesions at baseline. Lesions in previously irradiated areas were not considered measurable target lesions unless there was demonstrated progression in the lesion. *IC-ORR was assessed per RESIST v1.1. †IC-DoRNA due to small number of responders (n < 10).
**ENHERTU® + Endocrine Therapy** is tolerable and active in chemotherapy-naïve patients with HER2 low mBC, potentially supporting further investigation

**DESTINY-Breast08 Study**
A Ph1b study to investigate safety, tolerability, PK and preliminary anti-tumor activity of ENHERTU® in combination with other therapeutics in patients with HER2 low mBC

**Safety**

<table>
<thead>
<tr>
<th>Safety Category</th>
<th>T-DXd + ANA (N=21)</th>
<th>T-DXd + FUL (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade AEs</td>
<td>20 (95.2)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Any AEs ≥Grade 3</td>
<td>10 (47.6)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>Any AEs ≥Grade 3 possibly related to either drug</td>
<td>7 (33.3)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>AEs leading to dose interruptions/delays of T-DXd</td>
<td>12 (57.1)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>AEs leading to dose reduction of T-DXd</td>
<td>6 (28.6)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>AEs leading to discontinuation of T-DXd</td>
<td>4 (19.0)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Any SAEs</td>
<td>4 (19.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>AEs leading to death†</td>
<td>1 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>AESIs&lt;br&gt;Ejection fraction decreased‡&lt;br&gt;Pneumonitis (adjudicated as ILD related to any study drug)</td>
<td>1 (4.8)</td>
<td>0 &lt;br&gt;1 (5.0)</td>
</tr>
</tbody>
</table>

**Efficacy**

- **T-DXd + ANA (N=21)**
  - cORR 71.4% (95%CI; 47.8, 88.7)
- **T-DXd + FUL (N=20)**
  - cORR 40.0% (95%CI; 19.1, 64.0)

- For T-DXd+ ANA and T-DXd + FUL arms, 66.7% and 70.0% of patients received a prior line of treatment for mBC, respectively
- Safety profiles were generally consistent or comparable to the known safety profile
- No ILD in T-DXd + ANA arm, while 5 Grade 2 ILD/pneumonitis events in T-DXd + FUL arm
- Confirmed ORR was 71.4% in T-DXd + ANA arm and 40.0% in T-DXd + FUL arm
- mPFS was 13.4 months (95% CI; 8.5, 19.4) in T-DXd + ANA arm and NE (95% CI; 5.6, NE) in T-DXd + FUL arm
- Small datasets limit the interpretation of the efficacy results; need further research

* Reported by investigator as related to disease and drug-induced pneumonitis; however, the ILD was not considered to be drug-induced by adjudication. †Both cases Grade 2 and resolved at DCO. ‡NE signifies that DOR or PFS was not reached for these patients at the time of data cutoff.

Establish and expand DXd ADCs to address the broader spectrum of Breast Cancer

### Neoadjuvant
- **HER2+ 20%**
  - DESTINY-Breast11
- **TNBC 15%**
  - TROPION-Breast04
- **HER2 low**
- **HR+ 65%**
  - HER2 IHC >0<1+
  - HER2 IHC 0

### Adjuvant
- **DESTINY-Breast05 Non-pCR**
- **TROPION Breast03 Non-pCR**
- **TROPION Breast02 CPS<10**
- **TROPION Breast05 CPS≥10**

### 1L
- **DESTINY-Breast09**
- **DESTINY-Breast01/02/03**
- **DESTINY-Breast04 HER2 low**

### 2L+
- **DESTINY-Breast06**
- **DESTINY-Breast04**
- **TROPION-Breast01**

---

**Evaluating Potential or Preparing Study Plans**

Pivotal studies only (not exhaustive). CPS, combined positive score; HT, Hormone therapy; HR, hormone receptor; IHC: immunohistochemistry, pCR: pathological complete response, TNBC, triple-negative breast cancer.
EXPAND & EXTEND to deliver our technology to more patients

5DXd ADCs
Progress and Future

- Breast cancer
- **Lung cancer**
- New disease areas

ADC: antibody-drug conjugate
Our Lung Cancer Strategy

Deliver practice-changing medicines to meet evolving unmet needs in lung cancer for a broad set of distinct patient types by harnessing the depth of the Daiichi Sankyo portfolio

- Provide superior 2L+ treatments and differentiated combinations in metastatic NSCLC with DXd ADCs as the foundational treatment
- Leverage the innovation in DXd ADCs to move into early-stage NSCLC
- Identify novel therapeutic approaches for extensive-stage SCLC to address significant unmet need

ADC: antibody-drug conjugate, NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer
ENHERTU® 5.4mg/kg is supported as the standard of care in previously treated HER2mut NSCLC population

- ENHERTU® demonstrated deep and durable responses at both the 5.4 mg/kg and 6.4 mg/kg doses
- Responses were consistent regardless of HER2 mutation type, HER2 amplification status, and prior systemic anticancer therapy
- The safety profile was acceptable and generally manageable at both doses and favored the 5.4 mg/kg dose in terms of lower incidence of TEAEs and ILD

DESTINY-Lung02 Study
A Ph2 study assessed the efficacy and safety of ENHERTU® 5.4 mg/kg and 6.4 mg/kg in patients with HER2m metastatic NSCLC

Approval of ENHERTU® for HER2 mutant NSCLC was expanded to Japan (Aug) and EU (Oct) in 2023 based on the DESTINY-Lung02 results*

*Approved in US in Aug 2022
Dato-DXd is the first ADC to demonstrate a statistically significant improvement in PFS over docetaxel in NSCLC

### PFS for ITT

<table>
<thead>
<tr>
<th>Metric</th>
<th>Dato-DXd</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI), months*</td>
<td>4.4 (4.2-5.9)</td>
<td>3.7 (2.9-4.2)</td>
</tr>
<tr>
<td>HR</td>
<td>0.75 (0.62-0.91)</td>
<td>0.004</td>
</tr>
<tr>
<td>Prespecified boundary</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

### PFS in Key Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Events/n</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>118/162</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>95/137</td>
<td>0.63</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>136/183</td>
<td>0.79</td>
</tr>
<tr>
<td>Female</td>
<td>77/115</td>
<td>0.71</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>78/119</td>
<td>0.77</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>131/172</td>
<td>0.76</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>36/51</td>
<td>0.67</td>
</tr>
<tr>
<td>Former/current</td>
<td>177/238</td>
<td>0.77</td>
</tr>
<tr>
<td>Brain metastasis at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>33/50</td>
<td>0.64</td>
</tr>
<tr>
<td>Without</td>
<td>180/249</td>
<td>0.76</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>156/229</td>
<td>0.63</td>
</tr>
<tr>
<td>Squamous</td>
<td>57/70</td>
<td>1.38</td>
</tr>
<tr>
<td>Actionable genomic alterations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>189/252</td>
<td>0.64</td>
</tr>
<tr>
<td>Present</td>
<td>24/47</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Median PFS follow-up time was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. 4Included four CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel. 5Regardless of histology. ADC: antibody-drug conjugate, AGA: actionable genomic alteration, CI: confidence interval, DOR: duration of response, DTX: docetaxel, HR: hazard ratio, ITT: intention-to-treat, mo: months, NSCLC: non-small cell lung cancer, ORR: objective response rate, OS: overall survival, PFS: progression-free survival

- **Met dual primary endpoint of PFS**
  - Hazard Ratio: 0.75 (95% CI, 0.62-0.91)
  - ORR: Dato-DXd: 26.4%, Docetaxel: 12.8%
  - Median PFS: Dato-DXd: 4.4 months, Docetaxel: 3.7 months
  - The interim OS favors Dato-DXd, and the trial is continuing to final analysis

- **Hazard ratio for non-squamous: 0.63, and for squamous: 1.38**
- **Hazard ratio for patients without AGA: 0.84, and for patients with AGA: 0.38**
Dato-DXd is potentially practice-changing in non-squamous 2L+ NSCLC

- Longer median PFS was observed in prespecified subgroups including non-squamous histology (Nsq; 5.6 vs 3.7 months).
- Plan to amend TROPION-Lung08 study protocol to cap the squamous population
- **Plan to file in the US** with TROPION-Lung01 study data within FY2023

Squamous subset included 3 patients with AGAs.


PFS in Non-squamous (with and without AGAs)

- Median (95% CI), months: 5.6 (4.4-7.0) for Dato-DXd vs 3.7 (2.9-4.2) for Docetaxel.
- HR: 0.63 (0.51-0.78).
- ORR, %: 31.2 vs 12.8.
- DOR, months: 7.7 vs 5.6.

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

PFS in Squamous (with and without AGAs)

- Median (95% CI), months: 2.8 (1.9-4.0) for Dato-DXd vs 3.9 (2.8-4.5) for Docetaxel.
- HR: 1.38 (0.94-2.02).
- ORR, %: 9.2 vs 12.7.
- DOR, months: 5.5 vs 8.1.

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Dato-DXd</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dato-DXd</td>
<td>229</td>
<td>232</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>178</td>
<td>135</td>
</tr>
</tbody>
</table>

PFS probability % vs time since randomization, months

- Censored
Favorable tolerability against chemotherapy, careful monitoring is required for ILD management

<table>
<thead>
<tr>
<th>TRAEs, n (%)</th>
<th>Dato-DXd N=297</th>
<th>Docetaxel N=290</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>257 (87)</td>
<td>252 (87)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>73 (25)</td>
<td>120 (41)</td>
</tr>
<tr>
<td>Associated with dose reduction</td>
<td>58 (20)</td>
<td>85 (29)</td>
</tr>
<tr>
<td>Associated with dose delay</td>
<td>49 (17)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>Associated with discontinuation</td>
<td>23 (8)</td>
<td>34 (12)</td>
</tr>
<tr>
<td>Serious TRAEs</td>
<td>30 (10)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>25 (8)</td>
<td>33 (11)</td>
</tr>
</tbody>
</table>

- Fewer grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel.
- Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel.

### AESI

#### Stomatitis/oral mucositis

<table>
<thead>
<tr>
<th></th>
<th>Dato-DXd N=297</th>
<th>Docetaxel N=290</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>160 (54)</td>
<td>59 (20)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>19 (6)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

#### Ocular events

<table>
<thead>
<tr>
<th></th>
<th>Dato-DXd N=297</th>
<th>Docetaxel N=290</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>57 (19)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>5 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Adjudicated drug-related ILD

<table>
<thead>
<tr>
<th></th>
<th>Dato-DXd N=297</th>
<th>Docetaxel N=290</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>25 (8)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>10 (3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>7 (2)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

*Events included the selected PTs oral mucositis/stomatitis, oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. Ocular events included selected PTs from the corneal disorder SMQ and selected relevant PTs from the eye disorder SOC. Included 4 cases of keratitis and 1 case of ulcerative keratitis. ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). Among treated patients, histology information per the case report form.

- Seven adjudicated drug-related grade 5 ILD events:
  - Primary cause of death in 4 out of 7 was attributed to disease progression by investigator.
  - Non-squamous: 4 of 232 patients (1.7%); Squamous: 3 of 65 patients (4.6%).

**AESI**: adverse event of special interest, **ILD**: interstitial lung disease, **MedDRA**: Medical Dictionary for Regulatory Activities, **PT**: preferred term, **SMQ**: standard MedDRA queries, **TRAE**: treatment-related adverse events.
Encouraging antitumor activity was observed with Dato-DXd treatment in a heavily pretreated NSCLC population with AGAs

**Efficacy**

**TROPION-Lung05 Study**

Ph2, single-arm study evaluating Dato-DXd in patients with advanced or metastatic NSCLC with AGAs that progressed on or after targeted therapy and platinum-based chemotherapy

- Confirmed ORR and median PFS in all treated patients were **35.8%** and **5.4 months**, respectively
- Dato-DXd had a manageable safety profile, characterized by a low incidence of hematologic or drug-related grade ≥3 toxicities
- Adjudicated drug related ILD was 5 (4%) in total and 1 (1%) for grade ≥3 (as a grade 5 event)

**Response per BICR**

<table>
<thead>
<tr>
<th></th>
<th>All treated patients (N=137)</th>
<th>Patients with EGFR mutations (N=78)</th>
<th>Patients with ALK rearrangement (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR confirmed,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) [95% CI]</td>
<td>49 (35.8) [27.8-44.4]</td>
<td>34 (43.6) [32.4-55.3]</td>
<td>8 (23.5) [10.7-41.2]</td>
</tr>
<tr>
<td><strong>Median DOR,</strong></td>
<td>7.0 (4.2-9.8)</td>
<td>7.0 (4.2-10.2)</td>
<td>7.0 (2.8-8.4)</td>
</tr>
<tr>
<td>(95% CI), months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DCR confirmed,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) [95% CI]</td>
<td>108 (78.8) [71.0-85.3]</td>
<td>64 (82.1) [71.7-89.8]</td>
<td>25 (73.5) [55.6-87.1]</td>
</tr>
<tr>
<td><strong>Median PFS,</strong></td>
<td>5.4 (4.7-7.0)</td>
<td>5.8 (5.4-8.3)</td>
<td>4.3 (2.6-6.9)</td>
</tr>
<tr>
<td>(95% CI), months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff: Dec 2022


* The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method.  
  - Median PFS and PFS probabilities are based on the Kaplan-Meier method.  
  - Per BICR

Dato-DXd
TROPION-Lung05
ESMO 2023

Encouraging antitumor activity was observed with Dato-DXd treatment in a heavily pretreated NSCLC population with AGAs
HER3-DXd demonstrated **clinically meaningful and durable efficacy** in patients with EGFR-mutated NSCLC whose disease progressed after EGFR TKI and PBC

<table>
<thead>
<tr>
<th>Confirmed responses and survival</th>
<th>Prior EGFR TKI (any) and PBC (N=225)</th>
<th>Subset with prior 3G EGFR TKI and PBC (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cORR (95% CI), %</strong></td>
<td>29.8 (23.9-36.2)</td>
<td>29.2 (23.1-35.9)</td>
</tr>
<tr>
<td><strong>Best overall response (BICR), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>PR</td>
<td>66 (29.3)</td>
<td>60 (28.7)</td>
</tr>
<tr>
<td>SDa</td>
<td>99 (44.0)</td>
<td>91 (43.5)</td>
</tr>
<tr>
<td>PD</td>
<td>43 (19.1)</td>
<td>41 (19.6)</td>
</tr>
<tr>
<td>NEb</td>
<td>16 (7.1)</td>
<td>16 (7.7)</td>
</tr>
<tr>
<td><strong>DCR (95% CI), %</strong></td>
<td>73.8 (67.5-79.4)</td>
<td>72.7 (66.2-78.6)</td>
</tr>
<tr>
<td><strong>DOR, median (95% CI), mo</strong></td>
<td>6.4 (4.9-7.8)</td>
<td>6.4 (5.2-7.8)</td>
</tr>
<tr>
<td><strong>PFS, median (95% CI), mo</strong></td>
<td>5.5 (5.1-5.9)</td>
<td>5.5 (5.1-6.4)</td>
</tr>
<tr>
<td><strong>OS, median (95% CI), mo</strong></td>
<td>11.9 (11.2-13.1)</td>
<td>11.9 (10.9-13.1)</td>
</tr>
</tbody>
</table>

**HERTHENA-Lung01 Study**

Registrational Ph2 study to evaluate antitumor activities of HER3-DXd in patients with EGFR mutated NSCLC previously treated with at least one EGFR TKI and PBC

- Primary endpoint is ORR, and secondary endpoints are DOR, PFS, OS etc
- FDA granted BTD in Dec 2021
- Regulatory submission in US is planned for FY2023
- The confirmatory Ph3 study HERTHENA-Lung02 study is ongoing

- Overall population: confirmed ORR 29.8%, median DOR 6.4 months, median PFS 5.5 months, median OS 11.9 months. Efficacy was observed across diverse mechanisms of EGFR TKI resistance and across a broad range of pretreatment tumor HER3 membrane expression
- The most common TEAEs were nausea, thrombocytopenia and decreased-appetite. Incidence of ILD was 5.3% and one patient experienced grade 5 ILD. Overall safety profile was manageable and consistent with previous reports

---

**Notes:**
- a Includes non-CR/non-PD.
- b No adequate postbaseline tumor assessment (n=12); SD too early (SD <5 weeks after start of study treatment [n=4])

**HER3-DXd demonstrated clinically meaningful and durable intracranial responses in patients with no prior radiotherapy**

**Intracranial Efficacy**

<table>
<thead>
<tr>
<th>Responses by CNS BICR</th>
<th>All patients with baseline BM by CNS BICR (n=95)</th>
<th>Patients whose baseline BM had not been irradiated (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS cORR, n (%) [95% CI]</td>
<td>19 (20.0) [12.5, 29.5]</td>
<td>10 (33.3) [17.3-52.8]</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>15 (15.8)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>4 (4.2)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>SD/non-CR/non-PD, n (%)</td>
<td>57 (60.0)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>13 (13.7)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>NE, n (%)</td>
<td>6 (6.3)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>CNS DCR (95% CI), %</td>
<td>80.0 (70.5, 87.5)</td>
<td>76.7 (57.7-90.1)</td>
</tr>
<tr>
<td>CNS DOR, median (95% CI), mo</td>
<td>9.2 (8.1-11.1)</td>
<td>8.4 (5.8-9.2)</td>
</tr>
</tbody>
</table>

Snapshot data cutoff, 18 May 2023. Median study follow-up, 18.9 (range, 14.9-27.5) months.

The comparative efficacy in the CNS will be further evaluated in the randomized controlled trial HERTHENA-Lung02 study.

BICR: blinded independent central review, CNS: central nervous system, CR: complete response, DCR: disease control rate (CR+PR+SD), DOR: duration of response, MRI: magnetic resonance imaging, ORR: objective response rate, PD: progressive disease, PR: partial response, RECIST: Response Evaluation Criteria in Solid Tumors, SD: stable disease. * 7 patients had measurable target lesions; 23 patients had only nontarget lesions. † 8 patients had only nontarget lesions. ‡ Includes non-CR/non-PD.
DS-7300, a novel B7-H3-directed DXd ADC, continues to demonstrate robust and durable efficacy in patients with heavily pretreated SCLC

- Median number of prior systemic treatments: 2 (range: 1-7)
- ORR 52.4% (95% CI, 29.8-74.3), mDOR 5.9 months (2.8-7.5), mPFS 5.6 months (3.9-8.1), mOS 12.2 months (6.4-NA)
- Generally well tolerated; no new safety signals and safety profile was consistent with previous reports
- Data support further development including a Ph2 of patients with extensive stage SCLC (IDeate-1)

ADC: antibody-drug conjugate, CI: confidence interval, RECIST: response evaluation criteria in solid tumors, mDOR: median duration of response, mo: months, mOS: median overall survival, mPFS: median progression-free survival, ORR: objective response rate, SCLC: small cell lung cancer
A Ph2 dose-optimization study evaluating DS-7300 in patients with previously treated ES-SCLC is ongoing (IDeate-1)

Dose-optimization was completed, and preparing for extended enrollment

- **Study Design of Ongoing Ph2 study in ES-SCLC (IDeate-1)**

  - **ES-SCLC**
    - Treated with ≥1 prior platinum-based regimen and ≤3 previous regimens

  - **R 1:1**
    - Arm 1: DS-7300 8 mg/kg Q3W (N~40)
    - Arm 2: DS-7300 12 mg/kg Q3W (N~40)

  - **Extended enrollment at the selected dose**
    - (N=100, total 140 at RP2D)

  - **Primary Endpoints**: ORR (BICR)
  - **Secondary Endpoints**: Safety, PFS, DoR, OS etc.

- A Ph3 study will be initiated in FY2024

BICR: blinded independent central review, DOR: duration of response, ES-SCLC: extensive-stage small cell lung cancer, ORR: objective response rate, OS: overall survival, PFS: progression free survival, Q3W: every 3 weeks, RP2D: recommended Ph2 dose
Establish and expand DXd ADCs as new treatment options in Lung Cancer

NSCLC 84%
  - AGA
    - EGFRm
    - HER2m
    - Others
  - Non-AGA
    - Non-SQ
    - SQ
SCLC ~13%

Stage I - III

1L

2L+
- HERTHENA-Lung02
- HERTHENA-Lung01
- DESTINY-Lung04
- DESTINY-Lung01/02

TROPION-Lung01

Evaluating Potential or Preparing Study Plans

TROPION-Lung07
  - PD-L1 <50%

TROPION-Lung08
  - PD-L1 ≥50%

DS-7300
  (Ph2 IDEate-1 ongoing)

Launched
On-going study

Pivotal studies and major Ph2 only, not exhaustive

EXPAND & EXTEND to deliver our technology to more patients

**5DXd ADCs**

**Progress and Future**

- Breast cancer
- Lung cancer
- New disease areas

**Treatment Line**

- Lung
- Breast

**Indications**

- Earlier lines
- Combination

Other cancers with remaining unmet needs

**ADC:** antibody-drug conjugate
DXd ADCs expanding into new disease areas beyond Breast and Lung

Build upon the success of our DXd ADC platform and harness the potential of our full portfolio to extend the benefit of practice-changing medicines to more patients, including Gynecological, Genitourinary, and Gastro-Intestinal cancers

ADC: antibody-drug conjugate
ENHERTU® showed **promising efficacy** and **manageable safety** in HER2+ mCRC

- **Objective Response**
  - T-DXd 5.4 mg/kg Q3W Total (N = 82)
  - **cORR 37.8% [27.3-49.2]**
  - **mDoR 5.5 months [4.2-8.1]**

- **Promising antitumor activity** was observed at both 5.4 mg/kg and 6.4 mg/kg doses
- **Antitumor efficacy** was observed irrespective of RAS mutation status at 5.4 mg/kg dose
- The safety profile was consistent with the known profile of ENHERTU® and favored the 5.4 mg/kg
- All-grade adjudicated ILD/pneumonitis rates were 8.4% with 5.4 mg/kg and 12.8% with 6.4 mg/kg
- No grade ≥3 ILD/pneumonitis in 5.4 mg/kg arm, while 1 grade 5 case in 6.4 mg/kg arm
- The results support ENHERTU® 5.4 mg/kg as the optimal dose with positive benefit-risk profile

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**ENHERTU®** Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.

- HER2 status was assessed by central laboratory.
DESTINY-PanTumor02 demonstrated **clinically meaningful and durable responses** across a broad range of HER2 expressing advanced solid tumors

- **All patients:** ORR 37.1% and median DOR 11.3 months
- **Patients with IHC 3+:** ORR 61.3% and median DOR 22.1 months
- Durable responses led to clinically meaningful PFS & OS
- The safety profile was consistent with the known profile with grade 5 ILD 1.1%
- **Plan to file** with DESTINY-PanTumor02 study data **within FY2023** for a potential tumor agnostic therapy in previously treated patients with HER2 expressing solid tumors in the US

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Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+(n=75) or IHC 2+(n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+(n=46) or IHC 2+(n=34) status.  

* Responses in extramammary Paget’s disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer;  

  - includes patients with a confirmed objective response only.

  - **BTC:** biliary tract cancer,  
  - **CI:** confidence interval, **DOR:** duration of response, **IHC:** immunohistochemistry, **ILD:** interstitial lung disease, **NR:** not reached, **ORR:** objective response rate, **OS:** overall survival, **PFS:** progression-free survival, **T-DXd:** trastuzumab deruxtecan (ENHERTU®)
DS-7300 continued to show durable efficacy in patients with heavily pretreated solid tumors, including ESCC, mCRPC, and sqNSCLC

- Observed safety profile was manageable and tolerable
- No new safety signals were observed, and the safety profile was consistent with previous data. The most common (≥3%) Grade ≥3 TEAEs were anemia (19.0%), neutropenia (4.0%), and nausea and lymphocyte count decreased (3.4% each)
- Incidence of ILD was consistent with the previously observed data; 10 (5.7%) confirmed cases of adjudicated ILD were observed, of which two cases were Grade ≥3 (one grade 4 in 12 mg/kg cohort and one grade 5 in 16 mg/kg cohort)

DS-7300 (I-DXd)
Ph1/2 Study Data Update
ESMO 2023

DS-7300

Efficacy in selected tumor types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Best percentage change in sum of diameters from baseline to target lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCC</td>
<td>cORR: 21.4% (6/28) (95% CI 8.3–41.0) mPFS: 2.8 m (2.1-5.5) mOS: 7.0 m (4.8-12.2) No. of prior treatments, median: 4 (1-7)</td>
</tr>
<tr>
<td>mCRPC*</td>
<td>cORR: 25.4% (15/59) (95% CI 15.0–38.4) mPFS: 5.3 m (4.1-6.9) mOS: 13.0 m (10.3-16.0) No. of prior treatments, median: 6 (1-11)</td>
</tr>
<tr>
<td>sqNSCLC</td>
<td>cORR: 30.8% (4/13) (95% CI 9.1–61.4)</td>
</tr>
</tbody>
</table>

Since enrollment in this cohort is ongoing, analyses of PFS and OS are not yet mature.
No. of prior treatments, median: 3 (1-12)

* n=73, including patients with bone metastases who were not evaluable for ORR. The ORR is calculated based on 59 patients who received ≥1 dose ≥4.8 mg/kg, had measurable disease at baseline, ≥2 postbaseline scans, and/or discontinued treatment for any reason at data cutoff.
CI: confidence interval, cORR: confirmed objective response rate, ESCC: esophageal squamous cell carcinoma, ILD: interstitial lung disease, mCRPC: metastatic castration-resistant prostate cancer, mOS: median overall survival, mPFS: median progression-free survival, NE: not estimable, OS: overall survival, PFS: progression-free survival, SCLC: small cell lung cancer, sqNSCLC: squamous non-small cell lung cancer
DS-6000 (CDH6 directed DXd ADC) continued to demonstrate strong clinical activity in patients with platinum resistant ovarian cancer

Efficacy

- Confirmed ORR: 46% in the 4.8–8.0 mg/kg OVC cohort (23/50; 95% CI: 32–61)
- DCR: 98%
- Number of prior systemic regimens, median (range): 4 (1-13)

- Median time to response: 6 weeks (95% CI: 5–11)
- Median DOR: 11.2 months (95% CI: 3.0–NE)
- Median PFS: 7.9 months (95% CI: 4.4–12.4)

Confirmed ORR: 46%, median DOR: 11.2 months and median PFS: 7.9 months

Safety profile is manageable, and toxicities are consistent with those observed with other DXd ADCs

8.9% (4/45) of patients in 4.8–6.4 mg/kg cohort experienced ILD (all grade 2), of which 2 were adjudicated as treatment-related. 3.3% (2/60) of patients in 8.0 mg/kg cohort experienced grade 5 ILD

Based on the accumulated overall safety, tolerability, PK and efficacy profile, the 8.0 mg/kg cohort was closed and further assessment is ongoing at three dose levels: 4.8, 5.6 and 6.4 mg/kg

Ph2/3 study is under preparation

Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the waterfall plot and spider plot.

5DXd ADCs are making steady progress toward the vision to deliver their benefits to more patients

**Build the Foundation**
- ENHERTU®
  - Established in Breast, Gastric and HER2mut NSCLC
- Dato-DXd
  - TROPION-Lung01, TROPION-Breast01
- HER3-DXd
  - HERTHENA-Lung01/02
- DS-7300 (I-DXd)
  - Strong signal in SCLC, Ph2 IDEate-1 ongoing
- DS-6000 (R-DXd)
  - Strong signal in OVC

**Go Earlier**
- DESTINY-Breast09/05/11, DESTINY-Breast06, DESTINY-Lung04
- TROPION-Breast02/03/04/05, TROPION-Lung07/08

**Go Wider**
- DESTINY-PT02, Further planning
- TROPION-PanTumor01/02/03
- Plan in Progress
- Plan in Progress
- Plan in Progress
- Plan in Progress
- Plan in Progress

Strategic alliances further accelerate the programs

AstraZeneca

Merck & Co., Inc., Rahway, NJ, USA

Combinations further unlock the potential of DXd ADCs

- Combination is a key to realize our DXd ADC expansion strategy
- Pursuing unique combinations with our internal assets
  - Valametostat or DS-1103 combined with ENHERTU®
- Strategic alliances expand combination opportunities for DXd ADCs
  - Immune checkpoint inhibitors
  - Targeted therapies
- In addition to above, we actively work on combinations with other agents having promising new mechanisms of action

**Daiichi Sankyo Internal Assets**
- **Durvalumab**
- **Osimertinib**
- Bispecifics etc.

**AstraZeneca**
- Durvalumab
- Osimertinib
- Bispecifics etc.

**Merck & Co., Inc., Rahway, NJ, USA**
- Pembrolizumab
  - More under discussion

**Other external assets**

ADC: antibody-drug conjugate
5DXd ADCs are steadily progressing toward the vision to deliver the benefits to more patients

**Breast**
- **ENHERTU®** continues to solidify its position as standard of care in HER2+ and HER2 low BC
- **Dato-DXd** provides potential new treatment option for HR+ mBC and is expanding into TNBC in early/front line

**Lung**
- **ENHERTU®** represents a new HER2-directed therapy globally
- **HER3-DXd** and **Dato-DXd** are establishing foundation of DXd ADC therapy in various type of NSCLC
- **DS-7300** pioneers a new treatment option for ES-SCLC

**New disease areas**
- **ENHERTU®** may represent a tumor-agnostic therapy in HER2-expressing solid tumors
- **DS-7300** and all other DXd ADCs are exploring opportunities in other multiple tumor types
- **DS-6000** goes into a potential new treatment of OVC

EXPAND & EXTEND to deliver our technology to more patients

Next Wave Update

- The 6th DXd ADC in clinical stage
- Combinations with DXd ADC
- Unique and innovative assets

- ENHERTU®
- Dato-DXd
- HER3-DXd
- DS-7300 / DS-6000
- DS-3939 / DS-XXXX(DXd)

Sequence
Combination
Replacement
Formulation

Sustainable contribution

EXTEND

Pipeline

Time

ADC: antibody-drug conjugate
A Ph1/2 study is ongoing in solid tumors

**Dose Escalation Part**
DS-3939 (IV, Q3W)
Locally advanced, metastatic, or unresectable NSCLC, BC, UC, OVC, BTC, or PDAC

**Dose Expansion Part**
DS-3939 (IV, Q3W)
Multiple expansion cohorts targeting various advanced solid tumors

Evaluate safety and preliminary efficacy

- The 6th DXd ADC targeting tumor-associated mucin 1 (TA-MUC1), a transmembrane glycoprotein overexpressed in broad range of tumors including NSCLC, BC, UC, OVC, BTC, and PDAC
- Combined DXd ADC technology (DAR 8) and an anti-TA-MUC1 antibody in-licensed from Glycotope GmbH (Berlin, Germany)
- Ph1 dose escalation part is ongoing

EXPAND & EXTEND to deliver our technology to more patients

Next Wave Update

- The 6th DXd ADC in clinical stage
- Combinations with DXd ADC
- Unique and innovative assets

EXTEND

Pipeline

- Time
  - ENHERTU®
  - Dato-DXd
  - HER3-DXd
  - DS-7300 / DS-6000
  - DS-3939 / DS-XXXX(DXd)

Sequence
Combination
Replacement
Formulation

Sustainable contribution

Next-generation ADC
Other new modalities

ADC: antibody-drug conjugate
Combinations further unlock the potential of DXd ADCs

- Combination is a key to realize our DXd ADC expansion strategy
- **Pursuing unique combinations with our internal assets**
  - Valametostat or DS-1103 combined with ENHERTU®
- Strategic alliances expand combination opportunities for DXd ADCs
  - Immune checkpoint inhibitors
  - Targeted therapies
- In addition to above, we actively work on combinations with other agents having promising new mechanisms of action

**Daiichi Sankyo Internal Assets**
- Valemetostat
- DS-1103 etc.

**AstraZeneca**
- Durvalumab
- Osimertinib
- Bispecifics etc.

**Merck & Co., Inc., Rahway, NJ, USA**
- Pembrolizumab
- More under discussion

**Other external assets**

**ADC**: antibody-drug conjugate
Hypothesis: DXd ADC and valemetostat combination would increase anti-tumor activity of DXd ADC through upregulation of SLFN11

- SLFN11 is a dominant determinant of sensitivity to DNA-damaging agents
- SLFN11 expression is downregulated by EZH2 in chemoresistant tumors
- EZH2 inhibition can upregulate SLFN11 expression and sensitize to DNA-damaging agents such as Topoisomerase I inhibitor DXd
Evaluating potential of combination with DXd ADC in clinical trial

- A Ph1b study is ongoing for valemetostat combination with ENHERTU® in patients with HER2 low/ultra-low/null mBC (collaboration with MDACC)

**Key Eligibility Criteria**

- Unresectable or mBC with HER2 IHC 0, 1+, 2+/ISH-
- Received >1 line of chemo in mBC
- Progressed and no longer benefit from ET in HR+

**Dose-escalation** (n=~12) → **MTD/RDE** → **Dose-expansion** (n=~26 at RDE)

Continuous 21-days cycle until PD or unacceptable toxicities

<table>
<thead>
<tr>
<th>Dose level</th>
<th>valemetostat</th>
<th>ENHERTU®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>100 mg/day QD</td>
<td>5.4 mg/kg Q3W</td>
</tr>
<tr>
<td>Level 2</td>
<td>150 mg/day QD</td>
<td>5.4 mg/kg Q3W</td>
</tr>
<tr>
<td>Level 3</td>
<td>200 mg/day QD</td>
<td>5.4 mg/kg Q3W</td>
</tr>
</tbody>
</table>

**Primary objectives**
- Safety
- MTD
- RP2D

**Secondary objectives**
- PK
- Efficacy (ORR, DOR)
- Biomarkers

- Another combination study (company-sponsored) is under preparation to investigate valemetostat combinations with multiple DXd ADCs in multiple indications

DS-1103, an anti-SIRPα antibody, effectively blocked the "don't eat me" signal from cancer cells.

Combining DS-1103 with ENHERTU® significantly enhanced antibody-dependent cellular phagocytosis (ADCP).

The combination of an anti-mouse SIRPα surrogate antibody with ENHERTU® demonstrated a survival benefit in mice bearing HER2-expressing tumor cells.

**SITC 2022 Poster #808**

ADCP: 5 nM, Antibodies: 50 nM
Tumor: HER2+ BC cell line, Effector: Macrophage
Dunnett’s test: ENHERTU® +DS-1103 vs ENHERTU® or DS-1103
*P < 0.05 and **P < 0.01, N = 4
Evaluating potential of combination with DXd ADC in clinical trial

- A Ph1 first-in-human study of DS-1103 is ongoing in HER2-expressing solid tumors in combination with ENHERTU®

  **Dose escalation part**
  DS-1103 + ENHERTU® (5.4 mg/kg Q3W)
  HER2-expressing or HER2-mutant advanced metastatic solid tumors

  **Dose expansion part**
  DS-1103 (RDE) + ENHERTU® (5.4 mg/kg Q3W)
  HER2 low BC

- Further studies are under planning for combination with other DXd ADCs

ADC: antibody-drug conjugate, BC: breast cancer; Q3W: once every 3 weeks, RDE: recommended dose for expansion
EXPAND & EXTEND to deliver our technology to more patients

Next Wave Update

- The 6th DXd ADC in clinical stage
- Combinations with DXd ADC
- Unique and innovative assets

ADC: antibody-drug conjugate
Valemetostat monotherapy provides a clinically meaningful benefit for patients with R/R PTCL

VALENTINE-PTCL01
A Ph2 single-arm study in R/R PTCL (N=133) treated with 200 mg/day valemetostat

- Valemetostat monotherapy demonstrated a high ORR of 43.7% with CR rate 14.3%
- Responses were durable (mDoR 11.9 months)
- The safety profile was acceptable and AEs were generally manageable; 57.9% patients experienced grade ≥3 TEAEs (cytopenias were the most common)
Quizartinib + Chemotherapy now **globally approved in all three treatment phases*** for patients with newly diagnosed **FLT3-ITD (+) AML**

**QuANTUM-First Ph3 Newly Diagnosed AML**

*FLT3-ITD (+):*
- Multicenter, double-blind, randomized (1:1), placebo-controlled Ph3 trial (N=539)

**Approved:**
- Japan May 25, 2023
- US July 20, 2023
- EU November 6, 2023

*P value was calculated using a stratified log-rank test. Median follow-up time for both arms was 39.2 months*

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Erba et al. EHA Abstract 2022
QUIWI Ph2 Investigator-Initiated Study Interim Results

Preliminary evidence of efficacy of Quizartinib + Chemotherapy for patients with newly diagnosed \textit{FLT3-ITD (-)} AML (collaboration with PETHEMA)

- Roughly 70-80% of Fit AML patients will have \textit{FLT3-WT}^{1-3}
- Multicenter, double-blind, randomized (2:1), placebo-controlled Ph2 trial (N=273)
- EFS primary endpoint did not reach statistical significance:
  - HR = 0.741 (95\%CI, 0.535-1.026), \(p=0.059\) (2-sided)
- OS secondary endpoint
  - HR = 0.569 (95\%CI, 0.385-0.841), \(p=0.004\) (2-sided)
  - 2-year OS was 63.5\% with quizartinib vs 47\% with placebo

\[\text{HR, 0.569 (95\% CI, 0.385-0.841)}\]
\[P=0.004 \text{ (2-sided)}^a\]


AML: acute myeloid leukemia, CI: confidence interval, EFS: event-free survival, HR: hazard ratio, mOS: median overall survival; NR: not reached, OS: overall survival, PETHEMA: Programa para el Estudio de la Terapéutica en Hemopatía Maligna
DS-1471 is a monoclonal antibody with targeting **CD147**
A Ph1 first-in-human study is ongoing in solid tumors

- CD147 is known as a potential prognostic biomarker for various types of cancer including HCC, CRC etc.
- CD147 complex is also reported to play important roles in survival, invasion and metastasis in cancer tissues
- DS-1471 exhibits **unique mechanism of action** by downregulating CD147 complex which leads to cellular stress response and apoptotic cell death
- Ph1 dose escalation part is ongoing
Unique and innovative assets follow 5DXd ADCs to extend our contribution to future care

- Focus on combinations of selected next-wave assets with DXd ADC to maximize the potential of our assets
- Accelerate development of early clinical assets to bring new therapies to patients as quickly as possible
- Evaluating >20 candidates in IND-enabling stage in oncology, specialty medicine and vaccine areas

ADC: antibody-drug conjugate, IND: investigational new drug application
Clinical Summary

- **5DXd ADCs** establishes foundations, Go Earlier and Go Wider
- **Next Wave** pipeline continues to grow following the 5DXd ADCs

**Indications**
- Lung
- Breast
- Other cancers with remaining unmet needs

**Pipeline**
- ENHERTU®
- Dato-DXd
- HER3-DXd
- DS-7300 / DS-6000
- DS-3939 / DS-XXXX (DXd)

**Sequence**
- Combination
- Replacement
- Formulation

**Treatment Line**
- Earlier lines
- Combination

**Time**
- Sustainable contribution

ADC: antibody-drug conjugate
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