Meet AZN management: ASCO 2019
Breakout 4: trastuzumab deruxtecan

José Baselga, Executive Vice President, Oncology R&D

3 June 2019
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Trastuzumab deruxtecan
A state-of-the-art HER2\(^1\)-targeted, second-generation ADC\(^2\)

- Higher-intensity chemotherapy (more payload on each antibody)
- Membrane permeability (potential HER2-low applicability)
- Selective protease-cleavable linker
- Short half-life of free payload reduces systemic toxicities

Differentiated ADC

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

Proprietary Drug-Linker

Proprietary Payload (DXd)
DX-8951 derivative

Potential best-in-class ADC for HER2-positive breast cancer

Potential first-in-class ADC for HER2-low cancers

1. Human epidermal growth factor receptor 2.
Trastuzumab deruxtecan
Unprecedented Phase I/II data

Differentiated ADC

59.5% confirmed objective response rate

93.7% confirmed disease control rate

20.7 months median duration of response

Progression-free survival in HER2-positive breast cancer

Source: Phase I, Tamura et al., The Lancet Oncology, 2019.

Phase II primary endpoint met

Unprecedented data in advanced HER2-positive breast cancer

1. Disease control was calculated as the proportion of patients demonstrating complete response, partial response, or stable disease for a minimum of five weeks from the first dosing date

2. Not estimable.

News Release
Regulatory News Service

8 May 2019 07:00 BST
AstraZeneca demonstrates clinically-meaningful response in patients with refractory HER2-positive metastatic breast cancer, a population with high unmet need

Pivotal Phase II DESTINY-Breast01 trial met primary endpoint, supporting global regulatory submission plan to start in H2 2019

AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo) today announced positive top-line results for the pivotal Phase II DESTINY-Breast01 trial of trastuzumab deruxtecan (D9-8201). The HER2-targeting antibody drug conjugate (ADC) and potential new medicine was evaluated in patients with HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine.

The response rate in DESTINY-Breast01, as assessed by an independent review committee, confirms in a heavily-pre-treated, global patient population the unprecedented clinical activity in the recently-published Phase I trial. The safety and tolerability profile of trastuzumab deruxtecan was also consistent with previous experience. These results are expected to support planned global regulatory submissions, including a Biologics License Application with the US Food and Drug Administration (FDA) anticipated in the second half of 2019.

DESTINY-Breast01 is a pivotal Phase II, open-label, global, multicentre, two-part trial of trastuzumab deruxtecan. The optimal dose of 5.4mg/kg was previously identified in part one of the trial. Today’s results from part two evaluated the efficacy and safety of that dose in patients who have failed or discontinued previous treatment with trastuzumab emtansine.
Trastuzumab deruxtecan in breast cancer and beyond
Opportunities across treatment settings in breast cancer

**HER2-positive breast cancer**
- Post neo-adjuvant
  - Replace trastuzumab emtansine
- chemotherapy + trastuzumab + pertuzumab

**Neo-adjuvant / adjuvant**

**1st-line metastatic**
- Replace chemotherapy + trastuzumab + pertuzumab

**2nd-line metastatic**
- Replace trastuzumab emtansine

**3rd-line metastatic**
- Post trastuzumab emtansine

**HER2-low breast cancer**

**1. Hormone-receptor positive**
- HR+1: chemotherapy ± endocrine therapy

**2. Cyclin-dependent kinase 4/6 inhibitor**

**3. Triple-negative breast cancer**
- TNBC3: chemotherapy

**Beyond breast cancer**

- Expand into other cancer types: gastric, NSCLC4, CRC5 and others

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1. Hormone-receptor positive  
2. Cyclin-dependent kinase 4/6 inhibitor  
3. Triple-negative breast cancer  
4. Non-small cell lung cancer  
5. Colorectal cancer.
Trastuzumab deruxtecan
Encouraging efficacy in HER2-low breast cancer

HER2-low breast cancer efficacy

44.2% objective response rate
9.4 months DoR², 7.6 months median PFS³

HR: hormone receptor.
IHC: immunohistochemistry.
Source: poster # p6-17-02, SABCS 2018 (based on 12 October 2018 data cut off).

². Duration of response.
³. Progression-free survival.
Trastuzumab deruxtecan
Compelling efficacy in other cancer types

HER2-positive gastric cancer

Three average lines of prior treatment

43% ORR
5.6 months median PFS

Source: Phase I, Shitara et al., The Lancet Oncology.

HER2-positive and HER2-mutated NSCLC

73% ORR$^1$
14.1 months median PFS$^1$

1. HER2-mutated NSCLC only.
Trastuzumab deruxtecan
Development plans and news flow

Extensive Phase II/III programme underway

<table>
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<tr>
<th>To be communicated</th>
<th>To be communicated</th>
<th>3L+ DESTINY-Breast01 (Phase II)</th>
<th>DESTINY-Breast04 (2020+)</th>
<th>DESTINY-Gastric01 (2020)</th>
<th>Phase II</th>
<th>Phase II</th>
<th>Phase II combo with PD-1</th>
<th>To be communicated</th>
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<tr>
<td>HER2+ neoadj breast cancer</td>
<td>HER2+ adjuvant breast cancer</td>
<td>HER2+ advanced breast cancer</td>
<td>HER2 low breast cancer</td>
<td>HER2+ Gastric cancer</td>
<td>HER2+ CRC</td>
<td>HER2+ NSCLC</td>
<td>bladder cancer</td>
<td>Other cancer</td>
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News flow

- US FDA BTD² granted in Aug 2017
- DESTINY-Breast01 data presentation in H2 2019
- Regulatory decision anticipated in 2020
- Further Phase III starts anticipated in 2019-2020

US regulatory submission anticipated in H2 2019

Source: AstraZeneca data on file.

². Breakthrough Therapy Designation.
Q&A
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