

# Trastuzumab Deruxtecan: A Quantum Leap in HER2-Positive Breast Cancer

## Abstract

Docetaxel, trastuzumab, and pertuzumab, known as THP, is the preferred first-line treatment for HER2-positive advanced breast cancer, and the second-line drug of choice is trastuzumab emtansine. Most patients eventually develop resistance to systemic therapy. Trastuzumab deruxtecan, a novel HER2-targeted antibody drug conjugate, has shown to be promising in this subset. It is a HER2-targeted antibody drug conjugate structurally composed of humanized anti-HER2 monoclonal antibody, cleavable tetra-peptide-based linker, and a potent payload (topoisomerase 1 inhibitor: Exatecan). A phase 2 trial of heavily pretreated advanced HER2-positive breast cancer (median of six lines of prior therapy) showed an overall response of 61% and a median progression-free survival of 16 months. In December 2019, the Food and Drug Administration announced accelerated approval of trastuzumab deruxtecan for HER2-positive advanced breast cancer patients who were prior exposed to two or more lines of anti-HER2 therapy in a metastatic setting.

**Keywords:** Advanced breast cancer, HER2 positive, trastuzumab deruxtecan

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## Introduction

Docetaxel, trastuzumab, and pertuzumab, known as THP, is the preferred first-line treatment for HER2-positive advanced breast cancer and has shown a median overall survival (OS) of 4½ years.<sup>[1]</sup> The second-line drug of choice is trastuzumab emtansine (TDM1).<sup>[2]</sup> Resistance to anti-HER2 therapy develops due to various factors including loss of HER2 expression, downregulation of HER2 expression, heterogeneous HER2 expression, and receptor mutation.<sup>[3]</sup>

There is no standard third-line therapy for patients who progress after exposure to TDM1. Recently, tucatinib<sup>[4]</sup> in combination with trastuzumab and capecitabine has shown to be promising in this subset, especially in those with brain metastasis. Trastuzumab deruxtecan, a novel HER2-targeted antibody drug conjugate, has shown to be promising in patients with heavily pretreated HER2-positive advanced breast cancer.

## Mechanism of Action

Trastuzumab deruxtecan is a HER2-targeted antibody drug conjugate structurally

composed of humanized anti-HER2 monoclonal antibody, cleavable tetra-peptide-based linker, and a potent payload (topoisomerase 1 inhibitor: Exatecan).<sup>[5]</sup> The monoclonal antibody targets HER2-expressing tumor cells and internalizes the payload. The lysosomes cleave the linker, causing the payload to inhibit topoisomerase 1, and cause tumor cell death.

## Landmark Trials

### Preclinical

Trastuzumab deruxtecan (DS-8201a) significantly suppressed tumor growth in immunocompetent mouse models with human HER2-expressing cell lines. It enhanced antitumor immunity by increased expression of dendritic cell markers, augmenting the expression of major histocompatibility complex Class I in tumor cells, and rejection of rechallenged tumor cells by adaptive immune cells.<sup>[6]</sup>

### Phase 1

This dose-expansion study<sup>[7]</sup> included 115 patients with heavily pretreated (seven prior lines) HER2-positive advanced breast cancer. The overall response rate was

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60%, the median time to response was 1.5 months, and the median progression-free survival (PFS) and OS were 22 months and not reached, respectively. The recommended phase 2 dose was 5.4 mg/kg or 6.4 mg/kg.<sup>[8]</sup>

### Phase 2

The Destiny-Breast01 trial<sup>[9]</sup> included 184 patients with a median age of 55 years, 38% of Asian ethnicity with a median tumor size of 5.5 cm. This cohort included a heavily pretreated subset with a median of six lines of prior therapy (range: 2–27). All patients were prior exposed to trastuzumab and TDM1 and 66% had received pertuzumab. The overall response rate was 61%, with a median PFS of 16 months.

### Phase 3

The Destiny-Breast02 trial will assess the efficacy and safety of trastuzumab deruxtecan versus investigators' choice in patients who progress on TDM1. The Destiny-Breast03 trial will assess the efficacy and safety of trastuzumab deruxtecan versus TDM1.

### Advantages

The remarkable response of trastuzumab deruxtecan is due to the highly potent payload (topoisomerase 1 inhibitor: Exatecan), high drug-to-antibody ratio (8 with trastuzumab deruxtecan and 3.5 with TDM1), stable linker payload in circulation, tumor-selective cleavable linker, and payload-induced bystander effect.<sup>[10]</sup>

### Novelty

Trastuzumab deruxtecan has also shown activity in patients with low HER2-expressing (immunohistochemistry <3+ and negative *in situ* hybridization)<sup>[11]</sup> breast cancer.

### Approval

#### Breakthrough therapy

In August 2017, the Food and Drug Administration (FDA) granted breakthrough therapy designation to trastuzumab deruxtecan for the treatment of patients with advanced HER2-positive breast cancer previously treated with trastuzumab and pertuzumab and whose disease progressed after TDM1.

#### Accelerated approval

In December 2019, the FDA granted accelerated approval for trastuzumab deruxtecan for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who had received two or more lines of anti-HER2-based regimen in a metastatic setting.

### Dose

The recommended dose is 5.4 mg/kg every 3 weeks until disease progression/unacceptable toxicity.

### Side Effects

The grade 3 or 4 adverse effects are neutropenia (20%), anemia (9%), and nausea (8%). The potential serious adverse effect is interstitial lung disease (ILD) (Grade 1–2: 11%; Grade 3–4: 0.5%; and Grade 5: 2%).

### Monitoring

Patients need to be monitored closely for fever, cough, or dyspnea for early detection of ILD. Patients who develop ILD should be managed with steroids, dose reductions, or discontinuation.

### Other HER2-Positive Cancers

Trastuzumab deruxtecan is also being evaluated in HER2-positive gastro-esophageal cancer, gastric cancer, colon cancer, and HER2 mutated non-small cell lung cancer.

### Newer Anti-HER2 Drugs in Pipeline

- Tucatinib in combination with trastuzumab and capecitabine has shown a survival advantage in pretreated HER2-positive breast cancer, especially those with brain metastasis<sup>[4]</sup>
- Neratinib in combination with capecitabine has shown improved PFS as compared to lapatinib with capecitabine in pretreated HER2-positive advanced breast cancer<sup>[12]</sup>
- Margetuximab and chemotherapy improves PFS as compared to trastuzumab and chemotherapy in pretreated HER2-positive advanced breast cancer.<sup>[13]</sup>

### Conclusion

Trastuzumab deruxtecan is a novel antibody drug conjugate with impressive and durable response in heavily pretreated HER2-positive advanced breast cancer.

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### Conflicts of interest

There are no conflicts of interest.

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