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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 liker, 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.[1] The second-line drug of choice is trastuzumab emtansine (TDM1).[2] 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.[3]

There is no standard third-line therapy for patients who progress after exposure to TDM1. Recently, tucatinib[4] 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 liker, and a potent payload (topoisomerase 1 inhibitor: Exatecan).[5] 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.[6]

Phase 1

This dose-expansion study[7] 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.[8]

Phase 2

The Destiny-Breast01 trial[9] 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.[10]

Novelty

Trastuzumab deruxtecan has also shown activity in patients with low HER2-expressing (immunohistochemistry <3+ and negative *in situ* hybridization)[11] 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[4]
- Neratinib in combination with capecitabine has shown improved PFS as compared to lapatinib with capecitabine in pretreated HER2-positive advanced breast cancer[12]
- Margetuximab and chemotherapy improves PFS as compared to trastuzumab and chemotherapy in pretreated HER2-positive advanced breast cancer.[13]

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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