NEW DRUGS

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Trastuzumab deruxtecan

Approved indication: breast cancer

Enhertu (Astra Zeneca)
vials containing 100 mg powder for reconstitution

Since it first became available over 20 years ago, the monoclonal antibody trastuzumab has become a standard part of the management of HER2-positive breast cancer. For patients with metastatic cancer that has progressed despite treatment, trastuzumab has been combined with a cytotoxin. Although this combination, trastuzumab emtansine, can improve progression-free survival, the cancer is likely to progress again. There is then uncertainty about the best option for third-line therapy.

A possible option is trastuzumab deruxtecan. In this product the anti-HER antibody is conjugated with deruxtecan, a topoisomerase inhibitor. This conjugate is reconstituted with sterile water then diluted with 5% dextrose and given as a slow intravenous infusion. It is incompatible with sodium chloride solution. The conjugate is stable in plasma, but after binding to HER2 it is cleaved by lysosomal enzymes within the cancer cells. Release of cytotoxic deruxtecan causes apoptosis. The drug:antibody ratio of trastuzumab deruxtecan is greater than that of trastuzumab emtansine. While trastuzumab is cleared like other antibodies, deruxtecan is metabolised by cytochrome P450 (CYP) 3A4 but no dose adjustment is recommended for patients taking inhibitors of CYP3A. Most of the deruxtecan is thought to be excreted in the faeces. Data are insufficient to make dose recommendations for patients with moderate and severe hepatic impairment or severe renal impairment. The half-life of trastuzumab deruxtecan is approximately six days.

Trastuzumab deruxtecan and trastuzumab emtansine have been compared in a phase III trial. This randomised 524 patients with HER2-positive breast cancer that had progressed despite treatment with trastuzumab and a taxane. After a median duration of treatment of 14.3 months there was a response in 79.7% of the 261 women given trastuzumab deruxtecan and in 34.2% of the 263 women given trastuzumab emtansine. A median progression-free survival was not reached with trastuzumab deruxtecan, but it was 6.8 months with trastuzumab emtansine. At 12 months the survival rates were 94.1% and 85.9%.[1]

An open-label phase II trial has studied trastuzumab deruxtecan as third-line therapy for unresectable or metastatic HER2-positive breast cancer. These cancers had progressed after treatment with trastuzumab emtansine, or the patients had needed to discontinue trastuzumab emtansine. After the dose-finding part of the trial, 184 women were given an infusion of trastuzumab deruxtecan 5.4 mg/kg. This was repeated every three weeks. After a median follow-up of 11.1 months approximately 61% of the patients had a response, such as a reduction in tumour size. The median duration of the response was 14.8 months with a median progression-free survival of 16.4 months. The estimated overall survival at 12 months was 86.2%.[2]

Adverse effects are generally more frequent with trastuzumab deruxtecan than with trastuzumab emtansine.[1] In the phase II trial approximately 15% of the women stopped trastuzumab deruxtecan because of adverse events. The most frequent adverse effects were nausea, fatigue, alopecia, vomiting and constipation. Blood counts were reduced, with approximately 35% of the patients having a decreased neutrophil count.[2] There is a risk of febrile neutropenia and neutropenia is one reason for interrupting treatment. Another reason is a reduction in left ventricular ejection fraction. During the phase II trial 13.6% of the women developed interstitial lung disease, including some fatal cases.[2] While asymptomatic cases may respond to an interruption of therapy, symptomatic interstitial lung disease is an indication for stopping trastuzumab deruxtecan. As the conjugate has cytotoxic effects, pregnancy should be avoided. Reflecting the results of the phase II trial, trastuzumab deruxtecan has been provisionally approved for use in patients with unresectable or metastatic HER2-positive breast cancer that has already been treated with two or more anti-HER2 regimens. As evidence is limited, its benefits need to be confirmed in a phase III trial.

T manufacturer provided the product information

REFERENCES

1. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 2022;386:1143-54. https://doi.org/10.1056/NEJMoa2115022
2. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382:610-21. https://doi.org/10.1056/nejmoa1914510

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.