NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2023

Trastuzumab deruxtecan neoadjuvant therapy for high-risk HER2-positive early stage breast cancer

Company/Developer	Daiichi Sankyo UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33919	NICE ID: Not available	UKPS ID: 668897

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Trastuzumab deruxtecan is in clinical development for the neoadjuvant treatment of high-risk HER2-positive early-stage breast cancer. Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Breast cancer that has not spread beyond the breast or the axillary lymph nodes is known as early-stage. There are different subtypes of breast cancer. Among them, is HER2-positive disease, characterised by overexpression of HER2, a receptor protein associated with a more aggressive form of the disease. Neoadjuvant therapy refers to any treatment that is given for cancer before surgery. There are limited neoadjuvant treatment options for patients with early stage HER2-postitive breast cancer and patients often relapse. Therefore, there is need for more effective therapies.

Trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate (ADC) that binds to HER2 expressed on the surface of certain tumour cells to result in DNA damage and cell death. It has been demonstrated to show robust activities and efficacy in previous studies. It is administered as an intravenous infusion. If approved, trastuzumab deruxtecan will offer a novel neoadjuvant treatment option for high-risk HER2-positive early stage breast cancer.

Proposed Indication

Neoadjuvant treatment in adult patients with high-risk Human Epidermal Growth Factor Receptor 2 (HER2)-positive early stage breast cancer.[1]

Technology

Description

Trastuzumab deruxtecan (Enhertu, DS-8201a, T-DXd) is a HER2-targeted antibody-drug conjugate.[2,3] The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd) bound by a tetrapeptide-based cleavable linker. The antibody-drug conjugate is stable in plasma. The function of the antibody portion is to bind to HER2 expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan complex then undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane permeable DXd causes DNA damage and apoptotic cell death.[2]

Trastuzumab deruxtecan is in clinical development for the neoadjuvant treatment of high-risk HER2-positive early stage breast cancer. In the phase III clinical trial (DESTINY-Breast11; NCT05113251), patients will be administered 5.4 mg/kg of trastuzumab deruxtecan via intravenous (IV) infusion for 8 cycles.[1,4]

Key Innovation

Trastuzumab deruxtecan is a novel antibody–drug conjugate for the treatment of advanced solid tumours, including breast cancer, which overexpress or have amplification of the HER2. The novel structure of trastuzumab deruxtecan means that it can deliver a highly potent cytotoxic agent to HER2-expressing tissues resulting in selective killing of cancer cells. In phase I and II trials, trastuzumab deruxtecan showed response rates in heavily pre-treated populations, including patients who had received prior treatment with another highly active antibody–drug conjugate.[5] Also, the efficacy of T-DXd has been demonstrated in phase III trials in the HER2-positive metastatic setting.[6]

If licensed, trastuzumab deruxtecan will offer a novel neoadjuvant treatment option for high-risk HER2-positive early stage breast cancer.

Regulatory & Development Status

Trastuzumab deruxtecan as monotherapy has Marketing Authorisation in the UK for the following indications:[2]

- treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2 based regimens.
- treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Trastuzumab deruxtecan is also currently in phase II and III clinical trials for the treatment of several indications including:[7]

- Non-small cell lung cancer
- Oesophageal cancer
- Gastric cancer
- Gastroesophageal cancer and GEJ cancers

- Bladder cancer

Trastuzumab deruxtecan has the following regulatory designations:[8]

- a UK Innovative Licensing and Access Pathway (ILAP) Innovation Passport in May 2022.[a]

Patient Group

Disease Area and Clinical Need

Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Breast cancer most commonly starts in the cells that line the milk ducts of the breast.[9] Early stage breast cancer is defined as disease that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA breast cancers.[10,11] There are different pathological subtypes of breast cancer. Among them is HER2-positive disease, characterised by overexpression of HER2 (a transmembrane receptor protein), which accounts for approximately 20% of breast cancers and is associated with more aggressive disease in the absence of HER2 directed therapy. HER2 plays a role in cell growth and differentiation.[6] The causes of breast cancer are not completely understood, however several factors are known to increase its likelihood, such as exposure to radiation, age, increased alcohol consumption, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors.[12] One of the first noticeable symptom of breast cancer amongst women is a lump or an area of thickened tissue in their breast. Other common signs and symptoms include a change in the size or shape of one or both breasts, nipple discharge, dimpling on the skin of your breasts, and a rash on or around the nipple.[13,14]

In the UK, breast cancer is the most common cancer accounting for 15% of all new cancer cases (2016-2018).[15] In England, in 2017, there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the directly age-standardised rates per 100,000 population of newly diagnosed cases were 166.7 among females and 1.3 among males.[16] In 2021-22, there were 244,374 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 240,790 admissions resulting in 60,220 bed days and 218,006 day cases.[17] In England (2017), there were 9,569 deaths due to malignant neoplasm of the breast; the directly age-standardised rates per 100,000 population of registrations of death from malignant neoplasm of the breast were 33.3 and 0.3 for females and males respectively.[16] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5- year age-standardised survival rates for all stages of breast cancer were 95.8% and 85% respectively.[18]

Recommended Treatment Options

National Institute for Health and Care Excellence currently recommends pertuzumab in combination with tastuzumab and chemotherapy for the neoadjuvant treatment of HER2-positive breast cancer that is locally advanced, inflammatory, or early stage with a high-risk of recurrence in adults.[19]

Clinical Trial Information

Trial	**DESTINY-Breast11**, NCT05113251, EudraCT-2021-000603-21; A phase 3 open-label trial of neoadjuvant trastuzumab deruxtecan (T-DXd) monotherapy or

[a] Information provided by Daiichi Sankyo UK Ltd.

	T-DXd followed by THP compared to ddAC-THP in participants with high-risk HER2-positive early-stage breast cancer. **Phase III**- Active, not recruiting. **Location (s)**: Five EU countries, Canada, USA, and other countries **Primary completion date**: December 2023
Trial Design	Randomised, parallel assignment, open label
Population	N= 644 (actual); all sexes; aged 18 years and older; subjects with histologically documented HER2-positive early breast cancer
Intervention(s)	• Trastuzumab deruxtecan (IV) 5.4 mg/kg (8 cycles).[4] • Trastuzumab deruxtecan (IV) (4 cycles) followed by 4 cycles of paclitaxel (IV), trastuzumab (IV) and pertuzumab (IV).[4]
Comparator(s)	Doxorubicin and cyclophosphamide (IV) (4 cycles), followed by 4 cycles of paclitaxel (IV), trastuzumab (IV) and pertuzumab (IV).[4]
Outcome(s)	Primary outcome measure: Rate of pathologic complete response (pCR) [Time frame: Up to 32 months after study start] Proportion of participants who have no evidence by H&E staining of residual invasive disease. See trial records for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Trastuzumab deruxtecan is already marketed in the UK; a 100mg vial costs £1,455.00.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Palbociclib for treating high-risk early breast cancer after neoadjuvant chemotherapy (ID3846). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). March 2018.
- NICE technology appraisal guidance. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424). December 2016.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- NICE quality standard. Breast cancer (QS12). June 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard contract for Cancer: Chemotherapy (Adult). B15/S/a.

- NHS England. 2013/14 NHS standard contract for Cancer: Radiotherapy (All ages). B01/S/a.

Other Guidance

- European Society for Medical Oncology. Early Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. October 2019.[21]
- American Society of Clinical Oncology. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. August 2018.[22]
- Healthcare Improvement Scotland. SIGN 134: Treatment of primary breast cancer. A national clinical guideline. September 2013.[23]

Additional Information

References

1 Clinicaltrials.gov. *A Phase 3 Open-label Trial of Neoadjuvant Trastuzumab Deruxtecan (T-DXd) Monotherapy or T-DXd Followed by THP Compared to ddAC-THP in Participants With High-risk HER2-positive Early-stage Breast Cancer (DESTINY-Breast11).* Available from: https://clinicaltrials.gov/ct2/show/NCT05113251 [Accessed 13 June 2023].

2 Electronic Medicine Compendium (emc). *Enhertu 100 mg powder for concentrate for solution for infusion: Pharmacolgical properties*. Available from: https://www.medicines.org.uk/emc/product/12135/smpc [Accessed 13 June 2023].

3 Narayan P, Osgood CL, Singh H, Chiu HJ, Ricks TK, Chiu Yuen Chow E, et al. FDA Approval Summary: Fam-Trastuzumab Deruxtecan-Nxki for the Treatment of Unresectable or Metastatic HER2-Positive Breast Cancer. *Clin Cancer Res*. 2021;27(16):4478-85. Available from: https://doi.org/10.1158/1078-0432.Ccr-20-4557.

4 OncLive. *Neoadjuvant Trastuzumab Deruxtecan Dosed in First Patient With Early-Stage HER2+ Breast Cancer*. 2021. Available from: https://www.onclive.com/view/neoadjuvant-trastuzumab-deruxtecan-dosed-in-first-patient-with-early-stage-her2-breast-cancer [Accessed 22 June 2023].

5 Linehan AS, Fitzpatrick OM, Morris PG. Profile of Trastuzumab Deruxtecan in the Management of Patients with HER2-Positive Unresectable or Metastatic Breast Cancer: An Evidence-Based Review. *Breast Cancer (Dove Med Press)*. 2021;13:151-9. Available from: https://doi.org/10.2147/bctt.S245024.

6 Ahmed S, Sami A, Xiang J. HER2-directed therapy: current treatment options for HER2-positive breast cancer. *Breast Cancer*. 2015;22(2):101-16. Available from: https://doi.org/10.1007/s12282-015-0587-x.

7 Clinicaltrials.gov. *Current Phase II/III trials indications for Trastuzumab deruxtecan*. Available from: https://www.clinicaltrials.gov/ct2/results?term=Trastuzumab+deruxtecan&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 13 June 2023].

8 Healthcare Improvement Scotland. *Trastuzumab deruxtecan, 100mg powder for concentrate for solution for infusion (Enhertu®)*. 2023. Available from: https://www.scottishmedicines.org.uk/media/7509/trastuzumab-deruxtecan-enhertu-final-march-amended-030423-for-website.pdf [Accessed 22 June 2023].

9 Cancer Research UK. *What is breast cancer?* Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 13 June 2023].

10 MedicalNewsToday. *Early stage breast cancer: A guide*. Available from: https://www.medicalnewstoday.com/articles/early-stage-breast-cancer#definition [Accessed 13 June 2023].

11 National cancer Institute (NIH). *Early-stage breast cancer*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer [Accessed 13 June 2023].

12 National Health Service (NHS). Breast cancer in women: causes. 2019. https://www.nhs.uk/conditions/breast-cancer/causes/.

13 National Health Service (NHS). *Breast cancer in women: symptoms*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/symptoms/ [Accessed 13 June 2023].

14 American Cancer Society. *Breast Cancer Signs and Symptoms*. 2022. Available from: https://www.cancer.org/cancer/types/breast-cancer/screening-tests-and-early-detection/breast-cancer-signs-and-symptoms.html [Accessed 13 June 2023].

15 Cancer Research UK. *Breast cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero [Accessed 13 June 2023].

16 Office for National Statistics. *Cancer registration statistics, England*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 13 June 2023].

17 NHS Digital. *Hopsital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 15 June 2023].

18 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 15 June 2023].

19 National Institute for Health and Care Excellence (NICE). *Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer*. Available from: https://www.nice.org.uk/guidance/ta424 [Accessed 22 June 2023].

20 British National Formulary (BNF). *Trastuzumab deruxtecan: medicinal form*. Available from: https://bnf.nice.org.uk/drugs/trastuzumab-deruxtecan-specialist-drug/medicinal-forms/ [Accessed 15 June 2023].

21 Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2019;30(8):1194-220. https://www.sciencedirect.com/science/article/pii/S0923753419312876.

22 Denduluri N, Chavez-MacGregor M, Telli ML, Eisen A, Graff SL, Hassett MJ, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. *Journal of Clinical Oncology*. 2018;36(23):2433-43. Available from: https://doi.org/10.1200/jco.2018.78.8604.

23 Healthcare Improvement Scotland. *Treatment of primary breast cancer*. Available from: https://associationofbreastsurgery.org.uk/media/64109/sign134.pdf [Accessed 15 June 2023].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.