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Trastuzumab deruxtecan adjuvant treatment of high-risk HER2-positive, residual invasive breast cancer after neoadjuvant therapy

Company/Developer	Daiichi Sankyo UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30805	NICE ID: N/A	UKPS ID: 672098

Licensing and Market Availability Plans

Currently in phase III clinical trial

Summary

Breast cancer occurs when abnormal cells in the breast grow and divide uncontrollably, forming a tumour. Cancers that have high levels of a protein called human epidermal growth factor receptor 2 (HER2) on the cell surface are called HER2-positive cancers, making them more aggressive and prone to rapid spread and growth compared to HER2-negative cancers. Neoadjuvant therapies, such as chemotherapy combined with trastuzumab and pertuzumab, are used before surgery to shrink tumours and improve surgical outcomes for patients. If cancerous cells remain in the breast or surrounding lymph nodes after neoadjuvant treatment, they are called 'residual invasive disease'. The presence of residual invasive disease increases the risk of cancer recurrence, spread to other parts of the body (metastasis) or death. However, additional adjuvant therapies post-surgery can reduce this risk in early-stage breast cancer.

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) designed to deliver chemotherapy directly to HER2-postive cancer cells. It links trastuzumab, a tumour specific antibody, with deruxtecan, a cytotoxic drug, improving efficacy and minimising harm to nearby healthy cells. Administered intravenously trastuzumab deruxtecan offers a potential new treatment option for patients with HER2-positive breast cancer and residual invasive disease of the breast or axillary lymph nodes post-neoadjuvant therapy.

Proposed Indication

High-risk human epidermal growth factor receptor 2 (HER2) positive participants with residual invasive breast cancer following neoadjuvant therapy.[1]

Technology

Description

Trastuzumab deruxtecan (Enhertu) is a HER2-targeted antibody-drug conjugate (ADC). 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 patients with high-risk HER2-positive early breast cancer who have residual invasive disease following neoadjuvant therapy. In the ongoing phase III clinical trial (DESTINY-Breast05, NCT04622319), trastuzumab deruxtecan is administered as an intravenous (IV) infusion at a starting dose of 5.4mg/kg on Day 1 of each 21-day treatment cycle with 14 cycles in total.[1]

Key Innovation

Studies have indicated that the lower the level of residual disease, the lower the risk of disease recurrence and death.[3] HER2-positive breast cancers are characterised as being more aggressive and having higher rates of cell proliferation, lymph node metastases and being chemotherapy resistant compared with HER2-negative breast cancers.[4] Consequently, there is a need for additional treatment strategies for the clinical management of residual invasive HER2-positive breast cancer.

Trastuzumab deruxtecan is an ADC that links a tumour-specific antibody to a cytotoxic drug for targeted delivery of a cytotoxic substance to tumour cells, thus it limits off target toxicity in systemic circulation as it is attached to an antibody. Once internalised there may be a bystander effect on non-HER2 expressing cells and has the potential to improve therapeutic index.[3] If licensed, trastuzumab deruxtecan will offer an additional treatment option for patients with HER2-positive primary breast cancer who have residual invasive disease in the breast or axillary lymph nodes.

Regulatory & Development Status

Trastuzumab deruxtecan currently has Marketing Authorisation in the EU/UK for the treatment of adult patients with:[2]

- Unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens
- Unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy
- Advanced non-small cell lung cancer whose tumours have an activating HER2 mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.
- Advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

Trastuzumab deruxtecan is in phase II/III clinical development for:[5]

- Advanced solid tumors
- Brain cancer
- Oesophageal cancer
- Gastroesophageal cancer
- Biliary tract cancer
- Triple negative breast cancer

Patient Group

Disease Area and Clinical Need

Primary breast cancer occurs when abnormal cells in the breast or surrounding axillary lymph nodes grow and divide uncontrollably, forming a tumour that has not metastasised.[6] Some breast cancers have higher than normal amounts of a protein called HER2 on the cell surface, and these are known as HER2-positive cancers. The HER2 protein can stimulate cancer cells to grow, making HER2-positive cancers more aggressive compared to HER2-negative ones.[3] After undergoing neoadjuvant therapy (treatment given before surgery), the presence of residual invasive cancer cells in the breast or axillary lymph nodes is associated with poorer prognostic outcomes and survival rates compared to those who experience a pathological complete response, where no invasive cancer is found at surgery.[4] Symptoms of breast cancer include lumps in the breast, skin changes in the breast such as a rash, fluid leaking from the nipple in woman who are not breastfeeding or pregnant, as well as changes in the position of the nipple.[7] Risk factors for developing breast cancer include being female, ageing, being overweight or obese, using contraceptive pills, family history of breast cancer, inherited genes, higher levels of sex hormones such as oestrogen, progesterone, testosterone, and having benign breast tissue.[8]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2017-2019).[9] Approximately 15% of breast cancers are HER2 positive.[10] The age-standardised incidence rate of breast cancer in England is 1.4 and 170.3 per 100,000 amongst males and females, respectively.[11] In England (2022-23), there were 259,866 finished consultant episodes (FCEs) and 256,441 admissions for malignant neoplasm of the breast (ICD 10 code C50) which resulted in 61,787 FCE bed days and 233,521 day cases.[12] In England (2017), there were 46,109 patients diagnosed with malignant neoplasm of the breast and 9,569 deaths registered where malignant neoplasm of the breast was the cause.[13] For women diagnosed with stage 1 cancer between 2013 and 2017, followed up to 2018, the age standardised 1-year and 5-year net survival rates were 100% and 97.9% respectively.[14]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommended treatment for the adjuvant treatment of HER2-positive early breast cancer in adults with residual invasive disease in breast or lymph nodes following neoadjuvant therapy is trastuzumab emtansine.[15]

Clinical Trial Information

Trial	**DESTINY-Breast05; NCT04622319, EudraCT 2020-003982-20;** A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in Participants With High-Risk HER2-Positive Primary Breast Cancer Who Have

	Residual Invasive Disease in Breast or Axillary Lymph Nodes Following Neoadjuvant Therapy. **Phase III** – Active, not recruiting **Location(s)** – Twelve EU countries, UK, USA, Canada and other countries **Primary completion date**: Dec 2025
Trial Design	Randomised, parallel-assignment, open-label
Population	N=1,600 (planned); adults with residual invasive HER2-positive breast cancer following completion of neoadjuvant treatment
Intervention(s)	Trastuzumab deruxtecan IV infusion at a starting dose of 5.4mg/kg on Day 1 of each 21-day cycle with 14 cycles in total
Comparator(s)	Trastuzumab emtansine IV infusion at a starting dose of 3.6mg/kg on Day 1 of each 21-day cycle with 14 cycles in total
Outcome(s)	Primary outcome: invasive disease-free survival See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price of one vial of trastuzumab deruxtecan (100mg) is £1,455.00.[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer (TA632). June 2020.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- NICE quality standard. Breast cancer (QS12). September 2011.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Proton beam therapy for breast cancer (all ages) [210402P] (URN: 1787). June 2021.
- NHS England. Clinical Commissioning Policy: Radiotherapy after primary cancer for breast cancer. 16038/P. July 2016.
- NHS England's West Midlands Expert Advisory Group for Breast Cancer. Clinical Guidelines for the Management of Breast Cancer. December 2016.

Other Guidance

- European Society for Medical Oncology. Early Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. August 2019.[17]

- Healthcare Improvement Scotland. SIGN 134: Treatment of primary breast cancer. A national clinical guideline. September 2013.[18]

Additional Information

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