NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Trastuzumab deruxtecan for treating HER2-low, HR-positive, metastatic breast cancer

Company/Developer	Daiichi Sankyo

☐ New Active Substance ☒ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Trastuzumab deruxtecan is in clinical development for the treatment of human epidermal growth factor receptor (HER)2-low, hormone receptor positive (HR+), advanced or metastatic breast cancer in people whose disease has progressed after previous endocrine therapy. Breast cancer occurs when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Cancers that have receptors for the hormones oestrogen or progesterone are HR+, and HER2-low tumours are those whose cells contain lower levels of the HER2 protein on their surface. Metastatic cancers have spread from where they started to other parts of the body. Currently available HER2-directed therapies have been ineffective in people with HER2-low cancers. There are no therapies available in the UK specifically for HER2-low breast cancer.

Trastuzumab deruxtecan is a HER2-targeted drug complex. The trastuzumab portion of the drug binds to HER2 expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan complex then internalises inside tumour cells, and gets released by enzymes that upregulate in the cancer cells. Upon release, the deruxtecan component causes DNA damage and cell death. It is administered as an intravenous infusion. If approved, it will provide a novel treatment option for HER2-low, HR+, advanced or metastatic breast cancer that have progressed on endocrine therapy.

Proposed Indication

Treatment of human epidermal growth factor receptor (HER)2-low, hormone receptor positive (HR+), advanced or metastatic breast cancer in people whose disease has progressed on first line treatment with an endocrine therapy combined with a cyclin dependent kinase 4 and 6 (CDK4/6) inhibitor, or progressed on at least 2 previous lines of endocrine therapy with or without a targeted therapy in the metastatic setting.[1]

Technology

Description

Trastuzumab deruxtecan (Enhertu, DS-8201a; T-DXd) is a HER2-targeted antibody-drug conjugate.[1,2] 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. DXd, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.[2]

Trastuzumab deruxtecan is in clinical development for the treatment of HER2-low, HR+, advanced or metastatic breast cancer in people who have progressed after previous endocrine therapy. In the phase III trial (NCT04494425), trastuzumab deruxtecan will be administered via intravenous (IV) infusion.[1]

Key Innovation

Only people with breast cancers whose tumour cells produce high levels of HER2, known as HER2-positive breast cancer, had been shown to benefit from drugs that target HER2, but only about 15%–20% of people with breast cancer have HER2-positive tumours. The rest have no detectable HER2 or low levels.[3] Currently available HER2-directed therapies have been ineffective in people with these "HER2-low" cancers.[4] Trastuzumab deruxtecan is the first HER2-targeted therapy shown to provide clinically meaningful improvement in progression-free and overall survival compared with standard chemotherapy in people with HER2-low metastatic breast cancer.[3] If licensed, trastuzumab deruxtecan will offer a novel treatment option for HER2-low, HR+, advanced or metastatic breast cancer who have progressed on endocrine therapy.

Regulatory & Development Status

Trastuzumab deruxtecan has a Marketing Authorisation in the UK as monotherapy for the treatment of unresectable or metastatic HER2-positive breast cancer in adults who have received one or more prior anti-HER2-based regimens.[2]

Trastuzumab deruxtecan is also currently in phase II and III clinical trials for the treatment of several indications including:[5]

- Non-small cell lung cancer (NSCLC)
- Oesophageal cancer
- Gastric cancer
- Gastroesophageal cancer and gastroesophageal junction cancers
- Bladder Cancer
- Biliary Tract Cancer

- Cervical Cancer
- Endometrial Cancer
- Ovarian Cancer
- Pancreatic Cancer
- Rare Tumors
- Colorectal cancer
- HER2 solid tumours

Trastuzumab deruxtecan has the following regulatory designation:

- A Breakthrough Therapy by the US FDA for treatment of adults with unresectable or metastatic HER2-low breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy in April 2022.[6]
- A UK Innovative Licensing and Access Pathway (ILAP) Innovation Passport in May 2022.[a]

Patient Group

Disease Area and Clinical Need

Breast cancer occurs when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour).[7] HER2-low tumours are defined as those whose cells contain lower levels of the HER2 protein on their surface.[3] HR+ means that tumour cells have receptors for the hormones oestrogen or progesterone, which can promote the growth of HR+ tumours.[8] Metastatic cancers have spread from where they started to other parts of the body. Cancers that have spread are often thought of as advanced when they can't be cured or controlled with treatment. Not all metastatic cancers are advanced cancers.[9] Breast cancer symptoms include a breast lump, a lump or swelling in the armpit, change in size, shape or feel of the breast, skin changes of the breast, change in position of nipple and breast pain.[10] Risk factors for developing breast cancer include being overweight, alcohol consumption, use of the contraception pill or hormone replacement therapy, being inactive, ageing, genetics, radiation and diabetes.[11]

Breast cancer is the most common cancer in the UK. It mainly affects women, but men can get it too. Around 55,500 women and around 370 men are diagnosed in the UK each year. 1 in 7 women in the UK develop breast cancer during their lifetime. It is more common in older women.[7] Incidence rates for breast cancer in the UK are highest in people aged 90+ (2016-2018). Almost 9 in 10 (85%) of women diagnosed with breast cancer in England survive their disease for five years or more (2013-2017).[12] HER2-low tumours account for about 50%–60% of all breast cancers.[3] Applying this statistic to yearly estimates for breast cancer in women and men, it can be estimated that around 27,750-33,300 women and 185-222 men have HER2—low breast cancer every year in the UK. There are an estimated 35,000 people living with secondary (metastatic) breast cancer in the UK.[13] In England (2021-22) there were 244,374 finished consultant episodes (FCEs) and 240,790 admissions for malignant neoplasm of breast (ICD-10 code C50), which resulted in 218,006 day cases and 60,220 FCE bed days.[14] The specific population likely to be eligible to receive trastuzumab deruxtecan could not be estimated from available published sources.

Recommended Treatment Options

HER2-positive breast cancers, which meet a certain high threshold of HER2 molecules, can be treated with HER2-targeted therapies such as trastuzumab. Conversely, breast cancers with HER2 levels below the threshold are considered HER2-negative and are not treatable with these therapies.[15] HER2-low is a new

[a] Information provided by Daiichi Sankyo.

classification of the HER2 subtype. It describes a new subtype of breast cancer that has some HER2 proteins on the cell surface, but not enough to be classified as HER2-positive.[16] There are currently no treatment options offered specifically for HER2-low breast cancers.[17]

Clinical Trial Information

Trial	**DESTINY-Breast06; NCT04494425; EudraCT- 2019-004493-26;** A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-Low, Hormone Receptor Positive Breast Cancer Patients Whose Disease Has Progressed on Endocrine Therapy in the Metastatic Setting **Phase III –** Recruiting **Location(s) –** 12 countries in EU, UK, USA, Canada and other countries **Primary completion date** – July 2023
Trial Design	Randomised, parallel assignment, open label
Population	N = 850 (estimated); 18 years to 105 years; advanced or metastatic breast cancer; HER2-low, HR+; no prior chemotherapy
Intervention(s)	Trastuzumab deruxtecan, IV infusion
Comparator(s)	Investigators choice of oral capecitabine, IV paclitaxel or IV nab-paclitaxel
Outcome(s)	**Primary outcomes** • Progression Free Survival (PFS) in HR+, HER2-low population [Time Frame: Until progression or death, assessed up to approximately 60 months] See trial records for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Trastuzumab deruxtecan is already marketed in the UK; The NHS indicative price (hospital only) of trastuzumab deruxtecan is £1,455.00 for 1 vial of 100mg powder for concentrate for solution for infusion.[18]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA836). October 2022.
- NICE technology appraisal guidance. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725). September 2021.
- NICE technology appraisal guidance. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA687). March 2021.

- NICE technology appraisal guidance. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA619). January 2020.
- NICE technology appraisal guidance. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017.
- NICE guideline. Suspected cancer: recognition and referral (NG12). December 2021.
- NICE quality standard. Suspected cancer (QS124). December 2017.
- 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

- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. June 2022.[19]
- European Society for Medical Oncology. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). December 2020.[20]
- NHS England. Clinical Guidelines for the Management of Breast Cancer. 2019.[21]

Additional Information

References

1 ClinicalTrials.gov. *Study of Trastuzumab Deruxtecan (T-DXd) vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer (DB-06). Trial ID: NCT04494425*. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04494425 [Accessed 7th November 2022].

2 Electronic Medicines Compendium. *Enhertu 100 mg powder for concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/12135/smpc [Accessed 7th November 2022].

3 National Cancer Institute. *Enhertu Improves Survival for Metastatic "HER2-Low" Breast Cancer.* 2022. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2022/enhertu-her2-low-breast-cancer [Accessed 7th November 2022].

4 Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med.* 2022 Jul 7;387(1):9-20. Available from: https://doi.org/10.1056/NEJMoa2203690.

5 ClinicalTrials.gov. *Trastuzumab deruxtecan | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* 2022. 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 7th November 2022].

6 OncLive. *FDA Grants Breakthrough Therapy Designation to Trastuzumab Deruxtecan for HER2-Low Metastatic Breast Cancer.* 2022. Available from: https://www.onclive.com/view/fda-grants-breakthrough-therapy-designation-to-

trastuzumab-deruxtecan-for-her2-low-metastatic-breast-cancer [Accessed 7th November 2022].
7 Cancer Research UK. *What is breast cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 7th November 2022].
8 National Cancer Institute. *Cancer Stat Facts: Female Breast Cancer Subtypes.* 2022. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html [Accessed 7th November 2022].
9 American Cancer Society. *Understanding Advanced and Metastatic Cancer.* 2020. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html [Accessed 7th November 2022].
10 Cancer Research UK. *Breast cancer symptoms.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms [Accessed 7th November 2022].
11 Cancer Research UK. *Risk factors.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/risks-causes/risk-factors [Accessed 7th November 2022].
12 Cancer Research UK. *Breast cancer statistics.* 2022. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Three [Accessed 7th November 2022].
13 Breast Cancer Now. *Facts and statistics 2021.* 2021. Available from: https://breastcancernow.org/about-us/media/facts-statistics [Accessed 7th November 2022].
14 NHS Digital. *Hospital Admitted Patient Care Activity 2021-22: Diagnosis.* 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 7th November 2022].
15 Breast Cancer Research Foundation. *HER2-Low Breast Cancer Explained.* 2022. Available from: https://www.bcrf.org/blog/her2-low-breast-cancer-explained/ [Accessed 7th November 2022].
16 US Food and Drug Administration. *FDA Approves First Targeted Therapy for HER2-Low Breast Cancer.* 2022. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-her2-low-breast-cancer [Accessed 7th November 2022].
17 National Institute for Health and Care Excellence. *Breast cancer - Products.* 2022. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/breast-cancer/products?Status=Published&ProductType=Guidance&ProductType=QualityStandards [Accessed 7th November 2022].
18 British National Formulary. *Trastuzumab deruxtecan - Medicinal forms.* 2022. Available from: https://bnf.nice.org.uk/drugs/trastuzumab-deruxtecan/medicinal-forms/ [Accessed 7th November 2022].
19 Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2022;20(6):691-722. Available from: https://doi.org/10.6004/jnccn.2022.0030.
20 Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology.* 2020;31(12):1623-49. Available from: https://doi.org/10.1016/j.annonc.2020.09.010.
21 NHS England. *Clinical Guidelines for the Management of Breast Cancer.* 2018. Available from: https://www.england.nhs.uk/mids-east/wp-

content/uploads/sites/7/2018/02/guidelines-for-the-management-of-breast-cancer-v1.pdf [Accessed 18th October 2022].

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