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HEALTH TECHNOLOGY BRIEFING
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Trastuzumab deruxtecan for unresectable or metastatic HER2-low (HR+/-) breast cancer – after chemotherapy

NIHRIO ID	28897	**NICE ID**	10441
Developer/Company	Daiichi Sankyo Ltd	**UKPS ID**	655939

Licensing and market availability plans	Currently in phase III clinical trials.

***COMMERCIAL IN CONFIDENCE**

SUMMARY

Trastuzumab deruxtecan is in clinical development for the treatment of adults with HER2-low, hormone receptor (HR) positive or HR negative (HR+/-), unresectable and/or metastatic breast cancer (BC) who have previously been treated with chemotherapy. Metastatic BC (stage IV) is when the cancer has spread beyond the breast and nearby lymph nodes, whilst unresectable refers to cancer that cannot be treated by surgery. HER2 receptors help control how a healthy breast cell grows, divides, and repairs itself. In the case of IHC 0 and 1+ results or IHC+ with a negative ISH assay, BC is considered HER2-low (or HER2-negative). Breast tumours are tested for both oestrogen receptors (ER) and progesterone receptors (PR). About 74 % of all BCs are both HR-positive (HR+) and HER2-negative. In England, adults with stage 4 breast cancer, that were diagnosed between 2012-2016 and followed up to 2017, had a 66% survival rate one year after diagnosis.

Trastuzumab deruxtecan is a HER2 directed antibody drug conjugate (ADC). ADCs are targeted cancer medicines that deliver cytotoxic agents to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Other HER2-targeted therapies which are clinically effective in HER2-positive breast cancer, have, thus far, failed to show activity in the context of HER2-low disease. If licensed, trastuzumab deruxtecan will offer an additional treatment option for patients with HER2-low (HR+/-), unresectable or metastatic BC previously treated with chemotherapy.

PROPOSED INDICATION

Treatment of patients with HER2-low, unresectable and/or metastatic breast cancer that has been treated before.[1]

TECHNOLOGY

DESCRIPTION

Trastuzumab deruxtecan (DS-8201a, Enhertu) is a novel, human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate (ADC) with humanised anti-HER2 antibody, cleavable peptide-based linker and potent topoisomerase I inhibitor payload.[2] HER2 is a member of the epidermal growth factor transmembrane receptor family that is overexpressed in breast cancer and contributes to tumour cell proliferation, adhesion, migration, differentiation, and apoptosis.[2,3] ADCs are targeted cancer medicines that deliver cytotoxic agents to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Trastuzumab deruxtecan works as an ADC which targets and delivers the cytotoxic agents (deruxtecan) to the cancer cells via a linker attached to a monoclonal antibody (trastuzumab) that binds to a specific target HER2 expressed on cancer cells.[4]

Trastuzumab deruxtecan is currently in phase III clinical development for patients with HER2-low, unresectable, and/or metastatic breast cancer that were previously treated with chemotherapy.[1] In the phase III clinical trial (NCT037340290), 577 subjects will be randomized 2:1 to T-DXd (5.4 mg/kg intravenous every 3 weeks) or physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel).[5]

INNOVATION AND/OR ADVANTAGES

Most patients with metastatic breast cancer have HER2-negative breast cancer. If HER2-negative breast cancer is also hormone receptor positive, the most common treatment is hormonal therapy, but chemotherapy or targeted therapy may also be given.[6]

The novel feature of trastuzumab deruxtecan is that the released payload is highly membrane permeable and able to exert anti-tumour activity on neighbouring cells including cells with no HER2 expression, through the bystander effect; this effect does not extend to distant sites.[7] This feature is designed for efficient delivery of the payload to tumour cells while reducing the potential for systemic toxicities.[2]

For the patient population with HR-positive, HER2-negative breast cancer, the current standard of care after exhaustion of hormonal therapies consists of single-agent chemotherapies. These agents provide limited benefit in this setting, with a median progression free survival (PFS) of about 3 to 5 months in many studies. Although limited in sample size, the PFS of trastuzumab deruxtecan in this study of heavily pretreated patients compares favourably (has a PFS of 11.1 months) with these previous reports and is encouraging for patients with breast cancer with few or no remaining treatment options.[8]

Other HER2-targeted therapies, including trastuzumab and ado-trastuzumab emtansine (T-DM1), which are clinically effective in HER2-positive breast cancer, have, thus far, failed to show activity in the context of HER2-low disease. Preclinical in vitro and in vivo studies demonstrated that the released payload of trastuzumab deruxtecan, unlike T-DM1, is cell membrane permeable and that trastuzumab deruxtecan induces a bystander cytotoxic effect on cells in close proximity to targeted HER2-expressing tumour cells, regardless of their HER2 status.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

On 10 December 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product trastuzumab deruxtecan, intended for the treatment of metastatic HER2-positive breast cancer. Trastuzumab deruxtecan was reviewed under EMA's accelerated assessment programme.[9]

Trastuzumab deruxtecan will be available as 100 mg powder for concentrate for solution for infusion.[9]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer (BC) is the most common type of cancer in the UK. About 1 in 8 women are diagnosed with BC during their lifetime. Most women diagnosed with BC are over the age of 50, but younger women can also get BC.[10]
Symptoms include:[10]

- a change in the size or shape of one or both breasts
- discharge from either of the nipples, which may be streaked with blood
- a lump or swelling in either of the armpits
- dimpling on the skin of the breasts
- a rash on or around the nipple
- a change in the appearance of the nipple, such as becoming sunken into the breast

Unresectable means the cancer cannot be removed with surgery. Metastatic BC is cancer that has spread to parts of the body away from the breast, such as the bones or liver. Metastatic BC is considered to be stage 4 or advanced cancer.[11,12]

The HER2 gene makes HER2 proteins (also sometimes referred to as HER2/neu proteins). HER2 proteins are receptors on breast cells. Normally, HER2 receptors help control how a healthy breast cell grows, divides, and repairs itself.[13] HER2 positive BC has an immunohistochemistry (IHC) assay score of 3+ or a gene amplification on an in-situ hybridization (ISH) assay on at least one tumour sample. In the case of IHC 0 and 1+ results or IHC+ with a negative ISH assay, BC is considered HER2-low. In clinical practice, these tumours are reported as HER2 negative.[14] In about 50% of BC a low-level expression of HER2 without HER2 amplification can be observed.[15]

HR is short for hormone receptor. Breast tumours are tested for both oestrogen receptors (ER) and progesterone receptors (PR). Approximately 80% of BCs test positive for ER. About 65% of those are also positive for PR. About 74 % of all BCs are both HR-positive (HR+) and HER2-negative.[16]

The exact causes of BC are not fully understood. However, there are certain factors known to increase the risk of BC. These include:[10]

- age (the risk increases as the person gets older)
- a family history of breast cancer
- a previous diagnosis of breast cancer
- a previous non-cancerous (benign) breast lump
- being tall, overweight, or obese
- drinking alcohol

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2017 there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the direct age-standardised rate per 100,000 population was 166.7 among females.[17] Incidence rates are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[18]

In 2019-20 there were 230,944 finished consultant episodes (FCEs) and 74,647 FCE bed days with a primary diagnosis of malignant neoplasm of breast (C50). There were 226,544 hospital admissions, of which 193,849 were day cases.[19]

In England, adults with stage 4 breast cancer, that were diagnosed between 2012-2016 and followed up to 2017, had a 66% survival rate one year after diagnosis. Whilst those diagnosed at stage one have a survival rate of 100% one year after diagnosis.[20]

Breast cancer is the 4th most common cause of cancer death in the UK, accounting for 7% of all cancer deaths in 2017.[21] In England, in 2017, there were 10,219 registrations of death from malignant neoplasm of breast, and the directly age standardised death rate per 100,000 population was 33.3 among females and 0.3 among males.[17,22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The management of BC requires different approaches and involves the use of different therapies. Patients are assigned to a multidisciplinary team to provide the best treatment and care. The main treatments for BC include surgery, radiotherapy, chemotherapy, hormone therapy, and targeted therapy. Patients may have one of these treatments or a combination. The type or combination of treatments will depend on how the cancer was diagnosed and the stage it is at.[23]

For advanced/metastatic HER2-negative BC, NICE pathways recommend a sequence of first-line, second-line and third-line treatment options that combines biological therapies with chemotherapy.[24,25]

CURRENT TREATMENT OPTIONS

Depending on if the BC is HR+ or HR-, there are some therapeutic approaches for the treatment of advanced HER2-negative BC after chemotherapy which include:

HR+:[24]

- Treatment options after chemotherapy
    - Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen
    - Eribulin for treating locally advanced or metastatic BC after 2 or more chemotherapy regimens. Eribulin is recommended as an option for treating locally advanced or metastatic BC in adults, only when:
        - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).
        - the company provides eribulin with the discount agreed in the patient access scheme.

HR-:[25]

- Second-line treatment
    - Eribulin for treating locally advanced or metastatic BC after 1 chemotherapy regimen. Eribulin is not recommended for treating locally advanced or metastatic BC in adults who have had only 1 chemotherapy regimen.
- Third-line treatment
    - Eribulin for treating locally advanced or metastatic BC after 2 or more chemotherapy regimens. Eribulin is recommended as an option for treating locally advanced or metastatic BC in adults, only when:
        - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).
        - the company provides eribulin with the discount agreed in the patient access scheme.

PLACE OF TECHNOLOGY

If licenced, trastuzumab deruxtecan will offer an additional treatment option for patients with HER2-low, unresectable and/or metastatic breast cancer.

CLINICAL TRIAL INFORMATION

Trial	**DESTINY-Breast04. NCT03734029, 2018-003069-33; A Phase 3, Multicentre, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects** **Phase III** - Active, not recruiting **Location(s): EU (including the UK), Canada, United States and other countries** **Primary completion date: January 2023**
Trial design	Randomised, parallel assignment, quadruple-blind, open-label, active controlled
Population	N = 557; aged 18 years and older; subjects with documented unresectable, metastatic, HER2-low breast cancer who have been previously treated with chemotherapy; is HR-positive or HR-negative
Intervention(s)	Trastuzumab deruxtecan (DS-8201a) • 5.4mg/kg administered intravenously every 3 weeks[5]
Comparator(s)	Randomized to Physician's choice from the following options: • Capecitabine • Eribulin • Gemcitabine • Paclitaxel • Nab-paclitaxel
Outcome(s)	Primary outcome: Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) [Time Frame: within approximately 3 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of trastuzumab deruxtecan is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab in combination with chemotherapy for neoadjuvant treatment of triple negative breast cancer. (GIDTA10399). Expected publication date TBC.
- NICE technology appraisal guidance. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens. (TA423). December 2016.
- NICE technology appraisal guidance. Guidance on the use of trastuzumab for the treatment of advanced breast cancer. (TA34). March 2002.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment. (CG81). August 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

- European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5). 2020.[26]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[27]

ADDITIONAL INFORMATION

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