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HEALTH TECHNOLOGY BRIEFING
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Trastuzumab deruxtecan for metastatic HER2 - positive breast cancer – second line

NIHRIO ID	24202	**NICE ID**	10444
Developer/Company	Daiichi Sankyo Ltd	**UKPS ID**	655938

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

SUMMARY

Trastuzumab deruxtecan is in clinical development for the treatment of adults with HER2-positive, unresectable and/or metastatic breast cancer who have previously been treated with trastuzumab and taxane. HER2-positive breast cancer is when the cancer tests positive for HER2 protein, which promotes the growth of cancer cells and tend to be more aggressive than other types of breast cancer. Metastatic breast cancer (stage IV) is when the cancer has spread beyond the breast and nearby lymph nodes to other organs in the body, while unresectable means that the cancer cannot be treated by surgery. Treatment of the disease often involves the use of anti-HER2 therapies, chemotherapy, or a combination of both.

Trastuzumab deruxtecan consists of an anti-HER2 therapy (trastuzumab) and a chemotherapy agent (deruxtecan) combined as an antibody-drug conjugate. Trastuzumab deruxtecan is administered intravenously. It has been developed such that the trastuzumab specifically binds to cancer cells that are HER2-positive which provides a targeted delivery of deruxtecan inside cancer cells, which then acts to kill the cancer cells. This reduces systemic exposure to the chemotherapy with the potential to reduce associated toxicities and adverse effects. If licenced, trastuzumab deruxtecan could provide an additional second line treatment option for HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane.

PROPOSED INDICATION

Second line treatment of adults with HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane.[1]

TECHNOLOGY

DESCRIPTION

Trastuzumab deruxtecan (DS-8201a) 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]

In the phase III clinical trial (NCT03529110) participants will receive trastuzumab deruxtecan in form of a sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) at a dose of 5.4mg/kg, administered intravenously once every 3 weeks.[1,5]

INNOVATION AND/OR ADVANTAGES

Trastuzumab deruxtecan, was designed to improve on the critical attributes of currently available antibody-drug conjugates. It has a high drug-to-antibody ratio while retaining a favourable pharmacokinetic profile.[5,6] The proprietary tetrapeptide-based linker is stable in plasma and is selectively cleaved by cathepsins that are up-regulated in tumour cells. Trastuzumab deruxtecan has a released payload that easily crosses the cell membrane, which potentially allows for a potent cytotoxic effect on neighbouring tumour cells regardless of target expression.[6] This feature is designed for efficient delivery of the payload to tumour cells while reducing the potential for systemic toxicities.[2] In addition, the released payload has a short half-life, which is designed to minimise systemic exposure.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Trastuzumab deruxtecan does not currently have Marketing Authorization in the EU/UK for any indication.

In July 2020, the European Medicines Agency (EMA) validated the Marketing Authorisation Application (MAA) for trastuzumab deruxtecan, for the treatment of adults with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2 based regimens. Trastuzumab deruxtecan was granted accelerated assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP).[7]

Trastuzumab deruxtecan has been granted breakthrough therapy by the U.S. FDA in 2017.[4,8]

Trastuzumab deruxtecan is in phase II clinical development for non-small cell lung cancer, gastric cancer, osteosarcoma and advanced solid tumours with HER2 mutations.[9]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is cancer that starts in the breast tissue, most commonly in the cells that line the milk ducts of the breast. Metastatic breast cancer (also called stage IV or advanced breast cancer) is breast cancer that has spread to another part of the body, most commonly the liver, brain, bones, or lungs. Cancer cells can break away from the original tumour in the breast and travel to other parts of the body through the bloodstream or the lymphatic system. Breast cancer can come back in another part of the body months or years after the original diagnosis and treatment.[10]

There are different immune/pathological subtypes of breast cancer. Among them, is the HER2, a transmembrane receptor protein that is overexpressed in about 20% of breast cancers and associated with more aggressive disease in the absence of HER2 directed therapy. HER2 plays a role in cell growth and differentiation.[11]

The exact aetiology of breast cancer is unknown, but family history is a strong risk factor (hereditary factors).[12] Other risk factors for breast cancer include increased age, reproductive history and hormone exposure, lifestyle factors, medical history, and radiation exposure.[13] The first symptom of breast cancer most women notice 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 the breasts, and rash on or around the nipple.[14,15]

CLINICAL NEED AND BURDEN OF DISEASE

Breast cancer is the most common malignancy in women, and one of the three most common cancers worldwide, along with lung and colon cancer.[16]

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 and 1.3 among males.[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 2017 the National Cancer Registration and Analysis Service (NCRAS) had registered 2,372 cases of breast cancer in stage IV in the England.[19]

HER2 gene amplification and/or overexpression occurs in about 20% of breast cancers.[11] This would be approximate to 9,221 of the newly diagnosed breast cancer cases in England in 2017.

In England 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 (ICD-10; C50). There were

226,544 hospital admissions, of which 193,849 were day cases.[20] In England and Wales in 2019, there were 10,147 registrations of death from malignant neoplasm of breast.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The management of breast cancer 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 breast cancer include surgery, radiotherapy, chemotherapy, hormone therapy, and biological therapy (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.[22]

CURRENT TREATMENT OPTIONS

Trastuzumab emtansine is recommended, as an option for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.[23]

PLACE OF TECHNOLOGY

If licenced, trastuzumab deruxtecan could provide an additional second line treatment of HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane.

CLINICAL TRIAL INFORMATION

Trial	**DESTINY-B03, NCT03529110, EudraCT 2018-000222-61;** A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of DS-8201a (Trastuzumab Deruxtecan), an Anti-HER2 Antibody Drug Conjugate (ADC), Versus Ado Trastuzumab Emtansine (T-DM1) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With Trastuzumab and Taxane **Phase III** - Active, not recruiting **Location(s):** EU (including the UK), Canada, United States and other countries **Primary completion date:** February 2022
Trial design	Randomised, Parallel Assignment, Open Label
Population	N = 500 (planned), HER-positive unresectable and/or metastatic breast cancer, previously treated with trastuzumab and taxane; adults aged 18 years and older

Intervention(s)	Trastuzumab deruxtecan (DS-8201a) is sterile lyophilised powder reconstituted into a sterile aqueous solution (100 mg/5 mL) to be administered intravenously
Comparator(s)	Ado-trastuzumab emtansine (T-DM1) treatment in accordance with the approved label
Outcome(s)	Primary Outcome Measures: • Progression-free survival (PFS) based on blinded independent central review (BICR) [Time Frame: Baseline up to 43 months post dose] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of trastuzumab deruxtecan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). November 2017.
- 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.[24]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[25]

ADDITIONAL INFORMATION

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