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HEALTH TECHNOLOGY BRIEFING
AUGUST 2019

Trastuzumab deruxtecan for HER2-positive metastatic or unresectable breast cancer

NIHRIO ID	23835	**NICE ID**	10157
Developer/Company	Daiichi Sankyo Ltd	**UKPS ID**	652993

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Trastuzumab deruxtecan is in clinical development for the treatment of adults with HER2-positive, unresectable and/or metastatic breast cancer who have previously received anti-HER2 therapies. 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 involve 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 together as an antibody-drug conjugate. It has been developed such that the trastuzumab specifically binds to cancer cells that are HER2-positive which provides a targeted delivery of the cytotoxic deruxtecan inside cancer cells. This reduces systemic exposure to the chemotherapy with the potential to reduce associated toxicities and adverse effects. If licensed, trastuzumab deruxtecan will offer an additional treatment option for patients whose disease progressed despite previous treatment with other anti-HER2 therapies.

PROPOSED INDICATION

Adults with HER2-positive, unresectable and/or metastatic breast cancer who have previously received anti-HER2 therapies.[1,2]

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.[3] 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.[3,4] 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.[5]

Trastuzumab deruxtecan is currently in phase III clinical development for the treatment of adults with HER2-positive, unresectable and/or metastatic breast cancer previously treated with anti-HER2 therapies. In phase III clinical trials (NCT03523585; DESTINY-Breast02 and NCT03529110; DESTINY-Breast03), participants will receive trastuzumab deruxtecan in form of a sterile lyophilized powder reconstituted into a sterile aqueous solution (100 mg/5 mL) and administered intravenously.[1,2] There have been phase I studies conducted to establish treatment dosage and duration. Doses of 5.4 mg/kg and 6.4 mg/kg administered intravenously every 3 weeks were selected as the recommended doses for expansion on the basis of the observed preliminary anti-tumour activity and safety results. The lower dose of 5.4mg/kg has been selected for ongoing phase 3 studies.[4,6]

INNOVATION AND/OR ADVANTAGES

Recommended first-line therapy for patients with metastatic HER2-positive breast cancer is dual blockade with anti-HER2 humanised monoclonal antibody therapies trastuzumab and pertuzumab, in combination with chemotherapy. At the time of disease progression, the recommended treatment is trastuzumab emtansine, a HER2-targeted antibody-drug conjugate with a tubulin inhibitor payload. However, no standard of care has been established for HER2-targeted therapy in patients with metastatic HER2-positive breast cancer whose disease has progressed on or after trastuzumab emtansine. Thus, a substantial need remains unmet in this patient population. The result from a pre-clinical trial suggested that trastuzumab deruxtecan was very potent in inhibiting tumour growth.[3]

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.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Trastuzumab deruxtecan has been granted breakthrough therapy by the U.S. FDA in 2017.[5,8]

Trastuzumab deruxtecan has received SAKIGAKE designation for the treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer by the Japan Ministry of Health, Labour and Welfare.[8]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common malignancy diagnosed in women worldwide.[9] The exact etiology is unknown, but family history is a strong risk factor (hereditary factors).[10] Other risk factors for breast cancer include genetic causes, increased age, reproductive history and hormone exposure, lifestyle factors, medical history, and radiation exposure.[11] 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.[12,13]

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.[14]

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.[15]

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.[16] 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).[17] The National Cancer Registration and Analysis Service (NCRAS) has registered 2,309 cases of breast cancer in stage IV in the UK.[18]

Between 15 and 25 of every 100 women with breast cancer (15 to 25%) have HER2 positive cancers.[19] This would be approximate to 6,916 and 11,587 of the newly diagnosed breast cancer cases in England in 2017.

In 2017-18 there were 212,840 finished consultant episodes (FCEs) and 80,769 FCE bed days with a primary diagnosis of malignant neoplasm of breast (ICD-10; C50). There were 209,061 hospital admissions, of which 177,174 were day cases.[20] In England in 2017, there were 10,219 registrations of death from malignant neoplasm of breast,[21] and the directly age-standardised death rate per 100,000 population was 33.6.[16]

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]

For advanced/metastatic HER2-positive breast cancer, NICE pathways recommends a sequence of first-line, second-line and third-line treatment options that combines biological therapies with chemotherapy.[23]

CURRENT TREATMENT OPTIONS

There are some therapeutic approaches for the treatment of advanced HER2-positive breast cancer which include:[23]

First-line treatment

- Pertuzumab, in combination with trastuzumab and docetaxel
- Trastuzumab in combination with paclitaxel
- Trastuzumab monotherapy for people who have received at least two chemotherapy regimens for metastatic breast cancer

Second-line treatment

- 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.

Third-line treatment

- Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:
    - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).

PLACE OF TECHNOLOGY

If licensed, trastuzumab deruxtecan will offer an additional treatment option for patients with HER2-positive, unresectable and/or metastatic breast cancer who have previously received anti-HER2 therapies.

CLINICAL TRIAL INFORMATION

Trial	DESTINY-Breast02, NCT03523585, DS8201-A-U301, EudraCT 2018-000221-31; trastuzumab deruxtecan (DS 8201a) vs trastuzumab or lapatinib both in addition to capecitabine; ≥18 years old; phase III
Sponsor	Daiichi Sankyo, Inc
Status	Ongoing
Source of Information	Trial registry; [1,24] Journal article[25]
Location	EU countries (inc the UK) and the USA
Design	Randomised, active comparator-controlled, open label study
Participants	N=600; aged ≥ 18 years older; patients should have a pathologically diagnosed HER2-positive, unresectable or metastatic breast cancer; previously treated with trastuzumab emtansine (T-DM1), and documented radiologic progression (during or after most recent treatment or within 6 months after completing adjuvant therapy).
Schedule	Subjects will be randomised among 2 arms (2:1) to receive trastuzumab deruxtecan 5.4 mg/kg dose or receiving the treatment of investigator's choice, administered intravenous (IV) once every 3 weeks.
Follow-up	A follow-up to 45 months.
Primary Outcomes	Progression-free survival (PFS) based on blinded independent central review (BICR) [time frame: within 45 months]
Secondary Outcomes	• Overall survival (OS) [time frame: at 45 months] • Objective response rate (ORR) based on BICR and investigator assessment [time frame: within 45 months] • Duration of response (DoR) based on BICR and investigator's assessment [time frame: within 45 months] • Clinical benefit rate (CBR) based on BICR and investigator assessment [time frame: within 45 months] • Progression-free survival (PFS) based on investigator's assessment [time frame: within 45 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in February 2022.

Trial	DESTINY-Breast03, NCT03529110, DS8201-A-U302, EudraCT 2018-000222-61; trastuzumab deruxtecan (DS 8201a) vs T-DM1; ≥18 years old; phase III
Sponsor	Daiichi Sankyo, Inc
Status	Ongoing
Source of Information	Trial registry;[2,26] Journal article[27]
Location	EU countries (inc the UK), the USA, Canada, and other countries
Design	Randomised, active comparator-controlled, open label study

Participants	N=500; aged ≥ 18 years older; patients should have a pathologically diagnosed HER2-positive, unresectable or metastatic breast cancer; previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane; and documented radiologic progression (during or after most recent treatment or within 6 months after completing adjuvant therapy).
Schedule	Subjects will be randomized (1:1) to receive trastuzumab deruxtecan 5.4 mg/kg or T-DM1 (3.6 mg/kg) IV once every 3 weeks.
Follow-up	A follow-up to 45 months.
Primary Outcomes	Progression-free survival (PFS) based on blinded independent central review (BICR) [Time frame: within 45 months]
Secondary Outcomes	• Overall survival (OS) [time frame: at 45 months] • Objective response rate (ORR) based on BICR and investigator assessment [time frame: within 45 months] • Duration of response (DoR) based on BICR and investigator's assessment [time frame: within 45 months] • Clinical benefit rate (CBR) based on BICR and investigator assessment [time frame: within 45 months] • Progression-free survival (PFS) based on investigator's assessment [time frame: within 45 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in February 2022.

Trial	DESTINY-Breast01, NCT03248492, DS8201-A-U201, EudraCT 2016-004986-18; aged ≥18 years old; phase II
Sponsor	Daiichi Sankyo, Inc
Status	Ongoing
Source of Information	Trial registry[28,29] Company
Location	EU countries (inc the UK) and the USA
Design	Randomised, sequential assignment, open label study
Participants	N=230; aged ≥ 18 years older; patients should have a pathologically diagnosed HER2-positive, unresectable or metastatic breast cancer; an adequate tumour sample and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
Schedule	This study includes 2 parts and patients will be randomised among 4 arms. The three treatment groups will be divided into 20 patients each receiving 5.4mg/kg, 6.4mg/kg and 7.4mg/kg respectively to establish the pharmacokinetics of trastuzumab deruxtecan in this patient population. 60 patients will be further randomised into low (5.4mg/kg) or high (7.4mg/kg) treatment group to determine the recommended dose which will be used to treat 110 patients in part 2 of the study.
Follow-up	A follow-up to 22 months.
Primary Outcomes	Objective response rate (ORR) per imaging assessment [time frame: within 22 months]

Secondary Outcomes	• Duration of response [time frame: within 22 months] • Best per cent change in the sum of the longest diameters (SLD) of measurable tumours [time frame: within 22 months] • Disease control rate (DCR) [time frame: within 22 months] • Clinical benefit rate (CBR) [time frame: within 22 months] • Progression-free survival [time frame: within 22 months] • Overall survival (OS) [time frame: at 22 months] • ORR assessed by the investigator based on RECIST version 1.1 [time frame: within 22 months] • Maximum plasma/serum concentration (Cmax) [time frame: within 21 days] • Time to Cmax (Tmax) [time frame: within 21 days] • Area under the concentration-time curve (AUC) from dosing until the last quantifiable concentration (AUClast) [time frame: within 21 days] • AUC from the time of dosing until day 21 (AUC0-21d) [time frame: at day 21]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in February 2020.

ESTIMATED COST

The cost of trastuzumab deruxtecan is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in developement. Trastuzumab emtansine for adjuvant treatment of HER2-positive breast cancer (ID1516). Expected publication date: TBC.
- NICE technology appraisal guidance in developement. Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab (ID981). Expected publication date: October 2019.
- NICE technology appraisal guidance. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). March 2018.
- NICE technology appraisal guidance. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). November 2017.
- NICE technology appraisal guidance. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424). December 2016.
- NICE technology appraisal guidance. Breast cancer (locally advanced, metastatic) - eribulin (after chemotherapy) (ID964). December 2016.
- NICE technology appraisal guidance. Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane (TA371). December 2015.
- NICE technology appraisal guidance. Guidance on the use of trastuzumab for the treatment of advanced breast cancer (TA34). March 2002.
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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). 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[30]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[31]

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