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Newcastle University

Health Technology Briefing
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Datopotamab deruxtecan for previously treated unresectable or metastatic HR+ HER2- breast cancer

Company/Developer	Daiichi Sankyo Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34380	NICE TSID: Not available	UKPS ID: 668866

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Datopotamab deruxtecan is in clinical development for the treatment of inoperable or metastatic HR-positive HER2-negative breast cancer after one or two lines of systemic chemotherapy. Breast cancer is the growth of abnormal cells in the breast which divide uncontrollably to eventually form a tumour. Breast cancers can also be hormone receptor positive (HR+), meaning that hormones such as oestrogen or progesterone can bind to the cancer cells and promote cell growth. HER2 is 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. The exact cause of breast cancer is unknown. However, risk factors include increased age, lifestyle factors, medical history, and radiation exposure. Current chemotherapy options have limited efficacy and substantial toxicities, therefore there is a need for safer and more effective treatment options.

Datopotamab deruxtecan is a type of drug called an antibody-drug conjugate (ADC) and is administered via intravenous infusion. Datopotamab deruxtecan is designed to enter cancer cells and release chemicals to cause cell death. As a rapidly growing therapeutic class, it is suggested that ADCs yield greater safety and efficacy. If licensed, datopotamab deruxtecan will provide an additional treatment option for patients with inoperable or metastatic HR-positive HER2-negative breast cancer.

Proposed Indication

Treatment of adults with inoperable or metastatic Hormone Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2-Negative (HER2-) breast cancer who have received one or two prior lines of systemic chemotherapy.[1]

Technology

Description

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is an antibody-drug conjugate (ADC) that binds specifically to trophoblast cell surface antigen 2 (TROP2) to prevent the growth of cancer cells. Datopotamab deruxtecan is comprised of a humanized anti-TROP2 IgG1[3] monoclonal antibody, attached to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker.[2] ADC is an antibody conjugated with cytotoxic drugs through a chemical linker. ADC in cancer therapy is designed to bind to cancer-associated cell-surface antigens and internalise into cancer cells, and then release cytotoxic drugs into the cytoplasm to cause cell death. TROP2 is highly expressed on different epithelial tumours and is associated with poor prognosis.[2] TROP 2 expression has been detected in a wide range of breast cancer subtypes, including the HR+, HER2- subtype.[3]

Datopotamab deruxtecan is in clinical development for the treatment of inoperable or metastatic HR+ HER2- breast cancer in adult patients who have received one or two prior lines of systemic chemotherapy. In the phase III clinical trial (TROPION-Breast01, NCT05104866), patients received 6 mg/kg datopotamab deruxtecan intravenous (IV) infusion every three weeks.[1,4]

Key Innovation

ADCs are a rapidly growing therapeutic class and have a broader therapeutic window compared to conventional chemotherapeutic cancer drugs.[2] Current chemotherapy options have limited efficacy and substantial toxicities.[4] Datopotamab deruxtecan has greater antitumour efficacy via TROP2-directed deruxtecan delivery into tumour cells than conventional chemotherapy in a broad range of TROP2-expressing tumours. In addition to the efficiency of deruxtecan delivery into cancer cells, the sensitivity of cancer cells to deruxtecan can be another key factor which defines the potency of datopotamab deruxtecan. Deruxtecan showed potent cell growth inhibitory activity against all of the cancer cell lines across various tumour types in preclinical settings.[2]

If licensed, datopotamab deruxtecan will provide an additional treatment option for patients with inoperable or metastatic HR+ HER2- breast cancer who have been treated with at least one prior line of systemic chemotherapy.

Regulatory & Development Status

Datopotamab deruxtecan does not currently have Marketing Authorisation in the EU/UK for any indication.

Datopotamab deruxtecan is currently in phase II and III clinical development for the following indications:[5]

- Non-small cell lung cancer
- Breast cancer
- Endometrial cancer
- Prostate cancer

- Gastric cancer

Patient Group

Disease Area and Clinical Need

Breast cancer is the growth of abnormal cells in the breast which divide uncontrollably to eventually form a tumour. Although men can also have the condition, it mainly affects women and commonly starts in the cells lining the milk ducts of the breast.[6] The exact cause of breast cancer is unknown. However, risk factors include increased age, reproductive history and hormone exposure, lifestyle factors (obesity, alcohol consumption), medical history and radiation exposure.[7] One of the first noticeable symptoms of breast cancer amongst women 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 a rash on or around the nipple.[8] Metastatic cancer occurs when the cancer has spread to other areas of the body and may or may not be advanced.[9] HER2 is 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.[10] The remaining 80% of patients with breast cancer are HER2-negative. Breast cancers can also be hormone receptor positive (HR+), which means that hormones such as oestrogen or progesterone can bind to the cancer cells and promote cell growth. Approximately 70% of breast cancers are oestrogen receptor positive (ER+).[11]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018). In England, 2013-17, the breast cancer survival rate for women was 76% for 10 or more years.[12] Between 2017 and 2019, there were 11,499 deaths from breast cancer. The age standardised mortality rate per 100,000 population in the UK was 33 and 0.3 for females and males respectively.[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]

Recommended Treatment Options

Chemotherapy is the main treatment option for breast cancer and NICE currently recommends eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens.[15]

Clinical Trial Information

Trial	**TROPION-Breast01**; NCT05104866; A Phase-3, Open-Label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy (ICC) in Participants With Inoperable or Metastatic HR-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy **Phase III:** Active, not recruiting **Location(s):** Eight EU countries, UK, Canada, USA and other countries **Primary completion date:** August 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=733 (actual); aged 18 years and older; all sexes; subjects with inoperable or metastatic HR+, HER2- breast cancer and treated with 1 or 2 lines of prior chemotherapy

Intervention(s)	Datopotamab deruxtecan 6 mg/kg IV every 3 weeks.[4]
Comparator(s)	• Capecitabine (oral) • Gemcitabine (IV) • Eribulin mesylate (IV) • Vinorelbine (IV)
Outcome(s)	Primary outcome measures: • Progression Free Survival [Time frame: from randomisation until progression as assessed by BICR or death due to any cause (anticipated to be 21 months after the first participant has been randomised)] • Overall Survival [Time frame: approximately 44 months after the first participant has been randomised] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of datopotamab deruxtecan is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy (ID3935). Expected November 2023.
- NICE technology appraisal. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423). December 2016.
- NICE technology appraisal. Gemcitabine for the treatment of metastatic breast cancer (TA116). January 2007.
- NICE Clinical Guideline . Advanced breast cancer: diagnosis and treatment (CG81). February 2009. Last updated August 2017.
- NICE quality standard. Breast cancer (QS12). September 2011. Last updated 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 Society for Medical Oncology. Metastatic Breast Cancer: ESMO Clinical Practice Guidelines for the Diagnosis, Staging and Treatment of Patients with Metastatic Breast Cancer. October 2019.[16]
- American Society of Clinical Oncology. Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2 Negative Metastatic Breast Cancer: ASCO Guideline Update. July 2021.[17]

Additional Information

References

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