Health Technology Briefing
February 2024

Datopotamab deruxtecan for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer

Company/Developer	Daiichi Sankyo Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35138	NICE TSID: Not Available	UKPS ID: 668900

Licensing and Market Availability Plans

Currently in phase III clinical trial

Summary

Datopotamab deruxtecan is in development for the treatment of patients with previously untreated, locally recurrent inoperable or metastatic triple negative breast cancer (TNBC), who are not suitable candidates for PD-1/PD-L1 inhibitor therapy. TNBC is a subtype of breast cancer which lacks hormone receptor expression. The risk factors for TNBC include a history of breast disease and radiation therapy, family history of TNBC, alcohol intake, smoking, exposure to carcinogenic chemicals, and the intake of processed food. TNBC signs and symptoms include lump or thickening in the breast or armpit, changes in the position of the nipple such as an inverted nipple, and changes in the skin of the breast such as redness, rash, puckering or dimpling of the skin. Chemotherapy is the main form of treatment for patients with TNBC, however, the effectiveness of chemotherapy for TNBC remains limited.

Datopotamab deruxtecan is a new treatment that consist of two drugs. Datopotamab is a monoclonal antibody that attaches to a protein called trophoblast cell-surface antigen 2 (TROP2) on cancer cells. It then releases deruxtecan into the cancer cell. Deruxtecan is the chemotherapy part of the drug. It kills or damages the cancer cells. Datopotamab deruxtecan is administered intravenously (through the vein). If licenced, datopotamab deruxtecan may provide a new treatment option for patients with previously untreated, locally recurrent inoperable or metastatic TNBC, who are not candidates for PD-1/PD-L1 inhibitor therapy.

Proposed Indication

Patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC), who are not candidates for PD-1/PD-L1 inhibitor therapy.[1,2]

Technology

Description

Datopotamab deruxtecan (Dato-DXd) is an investigational trophoblast cell-surface antigen 2 (TROP2) directed antibody-drug conjugate (ADC) being developed for the treatment of metastatic Triple-negative breast cancer (TNBC).[3] TROP2 expression is an unfavourable prognostic factor for overall survival in all types of breast cancer.[4] Datopotamab deruxtecan is comprised of a humanised anti-TROP2 immunoglobulin G1 (IgG1) monoclonal antibody, attached to a number of topoisomerase I inhibitor payloads, an exatecan derivative, via tetrapeptide-based cleavable linkers.[3] Datopotamab deruxtecan consists of two parts: datopotamab (an antibody) and DXd (the cancer-cell-killing toxic component), which are joined via a stable linker. Datopotamab binds to the TROP2 protein found on TNBC tumours and is taken into the cell. The linker is then broken and releases DXd, which kills the tumour cell. By binding to cancer cells before releasing the payload, treatment is directed to the tumour, minimizing side effects in the rest of the body.[2]

In a phase III clinical trial (TROPION-Breast02; NCT05374512), participants aged 18 years and above with previously untreated, locally recurrent inoperable or metastatic TNBC, who are not candidates for PD-1/PD-L1 inhibitor therapy, received an intravenous (IV) infusion of datopotamab deruxtecan 6 mg/kg every 3 weeks.[1,2]

Key Innovation

Chemotherapy is the main form of treatment for patients with TNBC, however, the effectiveness of chemotherapy for TNBC is still limited.[5] TNBC is a subtype of breast cancer that is hard to treat. Tumours lack receptors for oestrogen and progesterone, which means that standard endocrine therapy is ineffective, and it does not express HER2, so HER2 therapies are also not appropriate.[2] Patients with metastatic TNBC who are not able to receive PD-1/PD-L1 inhibitor treatment often experience recurrence following chemotherapy, so additional options in the first-line treatment setting are needed.[3] However, the majority of TNBC tumours do possess a cell surface protein called TROP2 which provides a way of directing treatment inside tumour cells that is more selective than traditional chemotherapy.[2] TROP2 is a transmembrane glycoprotein overexpressed in several solid tumours, including breast cancer.[3,6] TROP2 expression has been detected in a wide range of breast cancer subtypes, including approximately 80% of patients with TNBC.[3,7-9] ADCs utilise target-specific antibodies as vehicles to deliver a potent cytotoxic to tumour cells while sparing healthy cells, thus limiting toxicity.[10] DCs combine the potent cytotoxicity of chemotherapy with the antigen-specific targeted approach of antibodies into one single molecule.[10] Datopotamab deruxtecan is one of the leading ADCs in development.[3] In a phase I trial (TROPION-PanTumor01; NCT03401385), datopotamab deruxtecan demonstrated median progression-free survival (PFS) of 4.4 months (95% confidence interval [CI], 3.0-7.3) and median overall survival (OS) of 13.5 months (95% CI, 10.1-16.3) amongst advanced solid tumours.[11] In the TNBC cohort of the trial (N=44), the overall response rate was 34% at a median follow-up of 7.6 months.[12] If licenced, datopotamab deruxtecan may provide a new treatment option for patients with previously untreated, locally recurrent inoperable or metastatic TNBC, who are not candidates for PD-1/PD-L1 inhibitor therapy.

Regulatory & Development Status

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

Datopotamab deruxtecan is also in phase II/III development for the following indications:[13]

- Non-small cell lung cancer
- Endometrial cancer
- Gastric cancer
- Prostate cancer
- Ovarian cancer
- Colorectal cancer
- Biliary tract cancer
- Urothelial cancer

Patient Group

Disease Area and Clinical Need

Breast cancer is a cancer that starts in the breast tissue.[14] Breast cancer can be grouped according to types, stages and grades.[15,16] A metastatic breast cancer is a stage IV breast cancer where the cancer has spread to other parts of the body.[17] TNBC is a specific subtype of breast cancer, representing approximately 15% of breast cancer cases. It is characterised by the lack of expression of the oestrogen receptor, progesterone receptor, and HER2 receptor on the cell surface.[18,19] TNBC is the most aggressive subtype of breast cancer, characterised by shorter overall survival in the inoperable (stage IV) setting.[20-22] The risk factors for TNBC include, history of breast disease and radiation therapy, family history of TNBC, alcohol intake, smoking, exposure to carcinogenic chemicals, and the intake of processed food.[23] TNBC signs and symptoms include lump or thickening in the breast or armpit, changes in the position of the nipple such as an inverted nipple, and changes in the skin of the breast such as redness, rash, puckering or dimpling of the skin.[24]

Breast cancer is the most common type of cancer in the UK, accounting for 15% of all new cancer cases (2016-2018), with about 1 in 7 women diagnosed with breast cancer during their lifetime, and in rare cases, men can also be diagnosed.[25,26] The age standardised incidence rate of breast cancer in England is 1.3 and 169.2 per 100,000 amongst males and females respectively.[27] In England (2022-23) there were 259,866 finished consultant episodes (FCEs) and 256,441 admissions for malignant neoplasm of the breast (ICD-10 code C50), which resulted in 233,521 day cases and 61,787 FCE bed days.[28] In England (2017), there were 46,109 patients diagnosed with breast cancer (ICD-10 code C50) and 9,569 deaths registered where breast cancer was the underlying cause.[29] For patients diagnosed between 2013 and 2017, and followed up to 2018, the 1-year and 5-year age-standardised survival rates for stage IV (metastatic) breast cancer were 66.0% and 26.2% respectively.[30]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for previously untreated metastatic TNBC.

- First-line pembrolizumab plus chemotherapy (paclitaxel or nab-paclitaxel) for patients whose tumours express PD-L1.[31]
- First-line atezolizumab with nab-paclitaxel for patients whose tumours express PD-L1.[32]

Clinical Trial Information

Trial	**TROPION-Breast02; NCT05374512, EudraCT 2021-005223-21;** A Phase 3, Open-label, Randomised Study of Datopotamab Deruxtecan (Dato-DXd) Versus Investigator's Choice of Chemotherapy in Patients Who Are Not Candidates for PD-1/PD-L1 Inhibitor Therapy in First-line Locally Recurrent Inoperable or Metastatic Triple-negative Breast Cancer. **Phase III** – Recruiting **Location(s)**: Seven EU countries, UK, US, Canada, and other countries **Primary Completion Date**: December 2025
Trial Design	Randomised, open-label, parallel assignment
Population	N=600 (estimated); adults aged 18 years and above with previously untreated, locally recurrent inoperable or metastatic TNBC, who are not candidates for PD-1/PD-L1 inhibitor therapy.
Intervention(s)	Datopotamab deruxtecan administered as 6 mg/kg iv. every 3 weeks
Comparator(s)	Intravenous infusion of investigator's choice of chemotherapy as active comparator
Outcome(s)	Primary outcome measures: - Progression Free Survival (PFS) [Time frame: from randomisation until progression as assessed by blinded independent central review or death due to any cause (anticipated to be up to 26 months)] - Overall Survival (OS) [Time frame: from randomisation until the date of death due to any cause (approximately 42 months)] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of datopotamab deruxtecan is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Capivasertib with paclitaxel for untreated metastatic triple-negative breast cancer (GID-TA11411). Expected publication date to be confirmed.
- NICE technology appraisal awaiting development. Sacituzumab govitecan for untreated PD-L1-negative triple-negative advanced breast cancer (GID-TA11489). Expected publication date to be confirmed.
- NICE technology appraisal guidance. Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer (TA801). June 2022.

- NICE technology appraisal guidance. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer (TA639). July 2020.
- NICE guideline in development. Breast cancer guidelines (GID-HUB10003). Expected date of publication to be confirmed.
- NICE quality standard. Breast cancer (QS12). September 2011. Last updated June 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England's West Midlands Expert Advisory Group for Breast Cancer. Clinical Guidelines for the Management of Breast Cancer. December 2016
- 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

- Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, Blair SL, Burstein HJ, et al. Breast Cancer Version 3. 2020.[33]
- Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[34]

Additional Information

References

1 ClinicalTrials.gov. *A Study of Dato-DXd Versus Investigator's Choice Chemotherapy in Patients With Locally Recurrent Inoperable or Metastatic Triple-negative Breast Cancer, Who Are Not Candidates for PD-1/PD-L1 Inhibitor Therapy (TROPION-Breast02). Trial ID: NCT05374512*. 2022. Status: Recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05374512 [Accessed 21 February 2024].

2 Dent RA, Cescon DW, Bachelot T, Jung KH, Shao Z-M, Saji S, et al. TROPION-Breast02: Datopotamab deruxtecan for locally recurrent inoperable or metastatic triple-negative breast cancer. *Future Oncology*. 2023;19(35):2349-59. Available from: https://doi.org/10.2217/fon-2023-0228.

3 Daiichi Sankyo. *TROPION-Breast02 Phase 3 Trial of Datopotamab Deruxtecan Initiated in Patients with Previously Untreated Metastatic Triple Negative Breast Cancer*. 2022. Available from: https://daiichisankyo.us/documents/364091/12104058/Dato-DXd+TROPION-Breast02+Initiation+Press+Release_FINAL.pdf/7f074465-4e35-a19f-9d60-620ddd282f09 [Accessed 21 February 2024].

4 Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. *Oncotarget*. 2018;9(48). https://www.oncotarget.com/article/25615/text/.

5 Zhu S, Wu Y, Song B, Yi M, Yan Y, Mei Q, Wu K. Recent advances in targeted strategies for triple-negative breast cancer. *Journal of Hematology & Oncology*. 2023;16(1):100. Available from: https://doi.org/10.1186/s13045-023-01497-3.

6 Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. *Oncotarget*. 2018;9(48):28989-9006. Available from: https://doi.org/10.18632/oncotarget.25615.

7 Zaman S, Jadid H, Denson AC, Gray JE. Targeting Trop-2 in solid tumors: future prospects. *OncoTargets and Therapy*. 2019;12:1781-90. Available from: https://doi.org/10.2147/ott.S162447.

8 Ambrogi F, Fornili M, Boracchi P, Trerotola M, Relli V, Simeone P, et al. Trop-2 is a determinant of breast cancer survival. *PloS One*. 2014;9(5):e96993. Available from: https://doi.org/10.1371/journal.pone.0096993.

9 Vidula N, Yau C, Rugo HS. Trop2 gene expression (Trop2e) in primary breast cancer (BC): Correlations with clinical and tumor characteristics. *Journal of Clinical Oncology*. 2017;35(15_suppl):1075-. Available from: https://doi.org/10.1200/JCO.2017.35.15_suppl.1075.

10 Shastry M, Jacob S, Rugo HS, Hamilton E. Antibody-drug conjugates targeting TROP-2: Clinical development in metastatic breast cancer. *Breast*. 2022;66:169-77. Available from: https://doi.org/10.1016/j.breast.2022.10.007.

11 AstraZeneca. *Datopotamab deruxtecan showed promising responses as monotherapy and in combination with Imfinzi in patients with metastatic triple-negative breast cancer in two early trials*. 2022. Available from: https://www.astrazeneca.com/media-centre/press-releases/2022/datopotamab-deruxtecan-showed-promising-responses-as-monotherapy-and-in-combination-with-imfinzi-in-patients.html [Accessed 21 February 2024].

12 The American Society of Clinical Oncology (ASCO) Post. *Datopotamab Deruxtecan Shows Activity in Advanced Triple-Negative Breast Cancer*. 2022. Available from: https://ascopost.com/issues/october-10-2022-supplement-breast-cancer-almanac/datopotamab-deruxtecan-shows-activity-in-advanced-triple-negative-breast-cancer/ [Accessed 21 February 2024].

13 ClinicalTrials.gov. *Datopotamab deruxtecan (Dato-DXd) | Phase 2, 3*. 2023. Available from: https://classic.clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=Datopotamab+deruxtecan+%28Dato-DXd%29&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 22 January 2024].

14 Cancer Research UK. *Breast cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer [Accessed 24 January 2024].

15 Cancer Research UK. *Breast cancer stages, types and grades*. 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades [Accessed 27 April 2023].

16 Li CH, Karantza V, Aktan G, Lala M. Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. *Breast Cancer Research*. 2019;21(1):143. Available from: https://doi.org/10.1186/s13058-019-1210-4.

17 Cancer Research UK. *Stage 4 breast cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-grades/stage-4 [Accessed 21 February 2024].

18 Zagami P, Carey LA. Triple negative breast cancer: Pitfalls and progress. *npj Breast Cancer*. 2022;8(1):95. Available from: https://doi.org/10.1038/s41523-022-00468-0.

19 National institute for Health and Care Excellence (NICE). *Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]*.

2020. Available from: https://www.nice.org.uk/guidance/ta801/documents/final-scope [Accessed 21 February 2024].

20 Cortes J, Rugo HS, Cescon DW, Im S-A, Yusof MM, Gallardo C, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *New England Journal of Medicine*. 2022;387(3):217-26. Available from: https://doi.org/10.1056/NEJMoa2202809.

21 Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *New England Journal of Medicine*. 2021;384(16):1529-41. Available from: https://doi.org/10.1056/NEJMoa2028485.

22 Leon-Ferre RA, Goetz MP. Advances in systemic therapies for triple negative breast cancer. *BMJ*. 2023;381:e071674. Available from: https://doi.org/10.1136/bmj-2022-071674.

23 Almansour NM. Triple-Negative Breast Cancer: A Brief Review About Epidemiology, Risk Factors, Signaling Pathways, Treatment and Role of Artificial Intelligence. *Front Mol Biosci*. 2022;9:836417. Available from: https://doi.org/10.3389/fmolb.2022.836417.

24 Cancer Research UK. *Triple negative breast cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/types/triple-negative-breast-cancer [Accessed 21 January 2024].

25 Nation Health Service (NHS). *Breast cancer in women*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/ [Accessed 27 April 2023].

26 Cancer Research UK. *Breast cancer statistics: Breast cancer incidence (invasive)* 2023. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero [Accessed 24 January 2024].

27 Cancer Research UK. *Breast cancer incidence (invasive) statistics: Breast cancer incidence by sex and UK country*. 2023. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero [Accessed 24 January 2024].

28 National Health Service (NHS) 75 Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F34%2FC4E943%2Fhosp-epis-stat-admi-diag-2022-23-tab.xlsx&wdOrigin=BROWSELINK [Accessed 11 Oct 2023].

29 Office for National Statistics. *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 24 January 2024].

30 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 24 January 2024].

31 National Institute for Health and Care Excellence (NICE). *Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer*. 2022. Available from: https://www.nice.org.uk/guidance/ta801/chapter/1-Recommendations [Accessed 21 January 2024].

32 National institute for Health and Care Excellence (NICE). *Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer*. 2020. Available from: https://www.nice.org.uk/guidance/ta639/chapter/1-Recommendations [Accessed 21 January 2024].

33 Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2020;18(4):452-78. Available from: https://doi.org/10.6004/jnccn.2020.0016.

34 Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Annals of Oncology*. 2018;29(8):1634-57. Available from: https://doi.org/10.1093/annonc/mdy192.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.