NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2024

Pertuzumab biosimilar with trastuzumab and chemotherapy neoadjuvant and adjuvant therapy for early stage and locally advanced HER2-positive breast cancer

Company/Developer	Organon Pharma UK

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36177	NICE ID: Not Available	UKPS ID: 667713

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pertuzumab biosimilar is in clinical development for the adjuvant and neoadjuvant treatment of invasive early stage or locally advanced breast cancer (BC) that is human epidermal growth factor 2 (HER2) positive (+). HER2 is a protein found on some cancer cells. Neoadjuvant therapy comes before primary treatment. Adjuvant therapy follows the primary treatment. BC is experienced when abnormal cells in the breast begin to grow and divide in an uncontrolled way and form a tumour. Early-stage BC means the cancer has not spread beyond the breast or lymph nodes. Locally advanced means the cancer has spread from the breast to the lymph nodes close to the breast, to the skin of the breast or to the chest wall. HER2-targeted drugs such as pertuzumab have contributed to greater survival outcome in HER2 + BC patients. However, such therapies can be costly. Biosimilars are medicines that are very close in structure and function to an existing medicine but are usually at substantially lower cost.

Pertuzumab biosimilar administered intravenously (IV) is a monoclonal antibody (a protein which can bind to other specific proteins). Pertuzumab biosimilar binds to HER2 protein on BC cells to prevent further tumour growth. Pertuzumab biosimilar in combination with chemotherapy will provide an additional neoadjuvant and adjuvant treatment option for patients with invasive early stage or locally advanced BC that is HER2+.

Proposed Indication

Neoadjuvant and adjuvant treatment for adult patients with early stage and locally advanced HER2-positive breast cancer.[1]

Technology

Description

Pertuzumab biosimilar (HLX11) an anti-human epidermal growth factor receptor 2 (HER2) domain II humanized monoclonal antibody injection and is a biosimilar candidate of pertuzumab.[2] Pertuzumab biosimilar composed of the variable region of a humanized murine-derived anti-HER2 antibody and the constant region of a human IgG1 antibody, and it is a glycosylated monoclonal antibody containing two 448-amino-acid heavy chains and two 214-amino-acid light chains.[3] Pertuzumab biosimilar can specifically bind with the subdomain II of HER2 extracellular domain and inhibit the heterodimerisation of HER2 and other HER family receptors, i.e., EGFR, HER3, and HER4. This will inhibit signal transduction of relevant pathways and lead to the stop of growth and apoptosis of tumour cells. In the meantime, Pertuzumab biosimilar can also enhance the tumour-killing activity of immune cells via antibody-dependent cell cytotoxicity.[4]

Pertuzumab biosimilar with chemotherapy is currently in clinical development for the treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage BC. In the phase III clinical trial (NCT05346224), during the neoadjuvant treatment phase, patients will be intravenously (IV) administered, a loading dose of 840 mg Pertuzumab biosimilar followed by 420 mg IV in combination with chemotherapy every three weeks (q3w). In the adjuvant treatment phase, pertuzumab biosimilar will be IV administered combined with trastuzumab.[1]

Key Innovation

Pertuzumab binds to a different epitope than trastuzumab, therefore, combination therapy with pertuzumab and trastuzumab results in a more complete blockade of HER2 signalling than trastuzumab monotherapy. Clinical studies have shown that the combination of these two HER2 inhibitors has a good synergistic effect that significantly improves clinical efficacy and prognosis.[5] Although pertuzumab and other biological therapies offer substantial clinical benefits, they are costly, which can limit their availability. Evidence suggests that pertuzumab and trastuzumab are underused worldwide.[6] Compared to the original drugs, the development of biosimilars provides more cost-effective alternatives to the originator due to lower costs and improved treatment access, thus alleviating unmet clinical needs.[7] In preclinical and toxicity studies, pertuzumab biosimilar has shown similar efficacy and safety to its brand originator.[3] If licensed, pertuzumab biosimilar will offer an additional, more affordable treatment option for patients with HER2-positive, locally advanced, inflammatory, or early-stage BC.

Regulatory & Development Status

Pertuzumab biosimilar does not currently have Marketing Authorisation in the EU/UK for any indication.

Pertuzumab biosimilar is not in any late clinical trials for any other indication.

Patient Group

Disease Area and Clinical Need

BC is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a tumour. BC can start in different parts of the breast. Most commonly it starts in the cells that line the ducts of the breast. Invasive means the cancer cells have spread outside the ducts where they started and into the surrounding breast tissue.[8] Early stage BC means the cancer has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA BCs.[9] Stage 3 means that the cancer has spread from the breast to the lymph nodes close to the breast, to the skin of the breast or to the chest wall. It is also called locally advanced BC.[10] Some BCs have large amounts of HER2 protein. BCs that have large amounts of HER2 are called HER2-positive BCs. About 15 out of every 100 BCs are HER2-positive.[11] Symptoms of BC include: a new lump or thickening in the breast or armpit, a change in size, shape or feel of the breast, skin changes in the breast such as puckering, dimpling, a rash or redness of the skin, fluid leaking from the nipple in a woman who isn't pregnant or breastfeeding and changes in the position of the nipple.[12] Environmental risk factors of BC include: obesity, alcohol, contraceptive pill and hormone replacement therapy. Some unchangeable risk factors include: age, family history, radiation, and diabetes.[13]

BC 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 BC during their lifetime, and in rare cases, men can also be diagnosed with BC.[14,15] The age standardised incidence rate of BC in England is 1.3 and 169.2 per 100,000 amongst males and females respectively.[16] In England (2022-23) there were 25,9866 finished consultant episodes (FCE) and 25,6441 admissions for malignant neoplasm of breast (ICD-10 code C50), which resulted in 23,3521 day cases and 61,787 FCE bed days.[17] In England (2017) there were 9,569 deaths due to malignant neoplasm of the breast; the directly age-standardised rates per 100,000 population of registrations of death from malignant neoplasm of the breast were 33.3 and 0.3 for females and males respectively.[18] Around 3 in 4 (75.9%) women diagnosed with breast cancer in England survive their disease for ten years or more, it is predicted (2013-2017). Around 8 in 10 (80.6%) women in England diagnosed with breast cancer between ages 15-44 survive their disease for ten years or more, compared with almost 6 in 10 (57.1%) women diagnosed aged 75-99 (2013-2017); ten-year survival is highest in women aged 55-64 (87.2%) (2013-2017).[15]

Recommended Treatment Options

NICE guidelines recommend the following neoadjuvant treatment options of HER2 positive BC: [19]

- Pertuzumab, in combination with trastuzumab and chemotherapy

NICE guidelines recommend the following adjuvant treatment options of HER2 positive BC:[20-22]

- Trastuzumab emtansine
- Pertuzumab
- Neratinib (extended use)

NICE guidelines recommend the following combination treatment options of HER2 positive BC: [23]

- Pertuzumab with trastuzumab and docetaxel

Clinical Trial Information

Trial	NCT05346224; A Multicenter, Randomized, Double-Blind, Parallel-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Pertuzumab Biosimilar HLX11 vs. EU-Perjeta in the Neoadjuvant Therapy of HER2-Positive

	and HR-Negative Early-stage or Locally Advanced Breast Cancer **Phase III** – Active, not recruiting **Location(s):** China **Primary completion date:** November 2024
Trial Design	Randomised parallel assignment, quadruple masking.
Population	N = 900 (estimated); adults aged 18 years and older with HER2-positive and HR-negative early-stage or locally advanced breast cancer with a primary tumour > 2 cm.
Intervention(s)	Neoadjuvant phase: pertuzumab biosimilar (loading dose of 840 mg IV, followed by 420 mg IV q3w) + trastuzumab (loading dose of 8 mg/kg IV, followed by 6mg/kg IV q3w) + docetaxel (75mg/m2 IV q3w) Adjuvant phase: doxorubicin (60 mg/m2 IV q3w) + cyclophosphamide (600 mg/m2 IV q3w), total four cycles; trastuzumab (loading dose of 8mg/m2 IV, followed by 6 mg/m2 IV q3w) + HLX11(loading dose of 840 mg IV, followed by 420 mg IV q3w), 13 cycles.
Comparator(s)	Neoadjuvant phase: (q3w/cycle, total four cycles): Perjeta (loading dose of 840 mg IV, followed by 420 mg IV q3w) + trastuzumab (loading dose of 8 mg/kg IV, followed by 6mg/kg IV q3w) + docetaxel (75mg/m2 IV q3w). Adjuvant phase: doxorubicin (60 mg/m2 IV q3w) + cyclophosphamide (600 mg/m2 IV q3w), total four cycles; trastuzumab (loading dose of 8mg/m2 IV, followed by 6 mg/m2 IV q3w)+ HLX11 or Perjeta (loading dose of 840 mg IV , followed by 420 mg IV q3w), 13 cycles
Outcome(s)	Primary outcome: the total pathological complete response rate assessed by the Independent Review Committee [Time frame: immediately after the surgery] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of pertuzumab biosimilar is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer (TA632). June 2020.
- NICE technology appraisal. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early-stage breast cancer after adjuvant trastuzumab (TA612). November 2019.
- NICE technology appraisal. Pertuzumab for adjuvant treatment of HER2-positive early-stage

breast cancer (TA569). March 2019.
- NICE technology appraisal. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424). December 2016.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). January 2024.

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

Other Guidance

European Society for Medical Oncology (ESMO). International Consensus Guidelines for Advanced Breast Cancer. 2018.[24]
ESMO. Early breast cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. October 2019.[25]

Additional Information

References

1 ClinicalTrials.gov. *A Multicenter, Randomized, Double-Blind, Parallel-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Pertuzumab Biosimilar HLX11 vs. EU-Perjeta® in the Neoadjuvant Therapy of HER2-Positive and HR-Negative Early-stage or Locally Advanced Breast Cancer*. *Trial ID: NCT05346224*. Available from: https://clinicaltrials.gov/study/NCT05346224?term=NCT05346224&rank=1 [Accessed 29th April 2024].

2 Organon. *Organon Enters into Global License Agreement to Commercialize Henlius' Investigational Perjeta® (Pertuzumab) and Prolia®/Xgeva® (Denosumab) Biosimilar Candidates*. 2022. Available from: https://www.organon.com/canada-en/news-release-organon-enters-into-global-license-agreement-to-commercialize-henlius-investigational-perjeta-pertuzumab-and-prolia-xgeva-denosumab-biosimilar-candidates/ [Accessed 02 May 2024].

3 Yang J, Lin L, Long Q, Zhang Q, Sun G, Zhou L, et al. HLX11, a Proposed Pertuzumab Biosimilar: Pharmacokinetics, Immunogenicity, and Safety Profiles Compared to Three Reference Biologic Products (US-, EU-, and CN-Approved Pertuzumab) Administered to Healthy Male Subjects. *BioDrugs*. 2022;36(3):393-409. Available from: https://doi.org/10.1007/s40259-022-00534-w.

4 Biosimilar Development. *First Subject Dosed In Phase 3 Clinical Trial Of Pertuzumab Biosimilar HLX11*. 2022. Available from: https://www.biosimilardevelopment.com/doc/first-subject-dosed-in-phase-clinical-trial-of-pertuzumab-biosimilar-hlx-0001 [Accessed 19th July 2024].

5 Aboudaram A, Loap P, Loirat D, Dhia SB, Cao K, Fourquet A, et al. Pertuzumab and Trastuzumab Combination with Concomitant Locoregional Radiotherapy for the Treatment of Breast Cancers with HER2 Receptor Overexpression. *Cancers*. 2021.
6 Jackisch C, Lammers P, Jacobs I. Evolving landscape of human epidermal growth factor receptor 2-positive breast cancer treatment and the future of biosimilars. *Breast*. 2017;32:199-216. Available from: https://doi.org/10.1016/j.breast.2017.01.010.
7 Huizinga TWJ, Torii Y, Muniz R. Adalimumab Biosimilars in the Treatment of Rheumatoid Arthritis: A Systematic Review of the Evidence for Biosimilarity. *Rheumatology and Therapy*. 2021;8(1):41-61. Available from: https://doi.org/10.1007/s40744-020-00259-8.
8 Cancer Research UK. *What is breast cancer?* 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 19th July 2024].
9 National Cancer Institute. *Early-stage breast cancer*. 2024. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer [Accessed 02 May 2024].
10 Cancer Research UK. *Stage 3 breast cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-grades/stage-3 [Accessed 02 May 2024].
11 Cancer Research UK. *Tests on your breast cancer cells*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/tests-breast-cancer-cells [Accessed 02 May 2024].
12 Cancer Research UK. *Symptoms of breast cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms [Accessed 02 May 2024].
13 Cancer Research UK. *Risk factors for breast cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/risks-causes/risk-factors [Accessed 02 May 2024].
14 National Health Service (NHS). *Breast cancer in women*. 2024. Available from: https://www.nhs.uk/conditions/breast-cancer-in-women/ [Accessed 02 May 2024].
15 Cancer Research UK. *Breast cancer statistics*. 2024. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Three [Accessed 19th July 2024].
16 Cancer Research UK. *Breast cancer incidence (invasive) statistics*. 2024. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero [Accessed 02 May 2024].
17 National Health Service (NHS). *Primary diagnosis: 3 character*. 2023. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F7A%2FDB1B00%2Fhosp-epis-stat-admi-diag-2022-23-tab_V2.xlsx&wdOrigin=BROWSELINK [Accessed 02 May 2024].
18 Office for National Statistics. *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 02 May 2024].
19 National Institute for Health and Care Excellence (NICE). *Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer*. 2016. Available from: https://www.nice.org.uk/guidance/ta424 [Accessed 02 May 2024].
20 National Institute for Health and Care Excellence (NICE). *Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer*. 2020. Available from: https://www.nice.org.uk/guidance/ta632 [Accessed 02 May 2024].
21 National Institute for Health and Care Excellence (NICE). *Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after*

adjuvant trastuzumab. 2019. Available from: https://www.nice.org.uk/guidance/ta612 [Accessed 02 May 2024].

22 National Institute for Health and Care Excellence (NICE). *Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer*. 2019. Available from: https://www.nice.org.uk/guidance/ta569 [Accessed 02 May 2024].

23 National Institute for Health and Care Excellence (NICE). *Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer*. 2018. Available from: https://www.nice.org.uk/guidance/ta509 [Accessed 02 May 2024].

24 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)†. *Ann Oncol*. 2018;29(8):1634-57. Available from: https://doi.org/10.1093/annonc/mdy192.

25 The European Society for Medical Oncology. *Clinical Practice Guideline – Early Breast Cancer*. 2024. Available from: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-breast-cancer/early-breast-cancer#:~:text=Early%20breast%20cancer%3A%20ESMO%20Clinical%20Practice%20Guideline%20for,representing%20a%20range%20of%20institutions%20worldwide.%20More%20items [Accessed 19th July 2024].

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.