NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2023

Pembrolizumab with chemotherapy for HR+/HER2- locally recurrent inoperable or metastatic breast cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33370	NICE ID: 11858	UKPS ID: 665571

Licensing and Market Availability Plans

Pembrolizumab with chemotherapy for HR+/HER2- locally recurrent inoperable or metastatic breast cancer is currently in Phase III trials.

Summary

Pembrolizumab in combination with chemotherapy is currently in clinical development for metastatic or locally recurrent, inoperable breast cancer. Symptoms of breast cancer can include a lump or a thickened area of breast tissue, changes in the size of the breasts, discharge from the nipples, and lumps or swelling underneath the armpits. When breast cancer becomes metastatic, this means it has spread to other parts of the body. If a cancer is locally recurrent, it means that it has come back into the breast, armpit, or chest wall after already being treated. Currently, breast cancer is the second most common form of cancer death among women but there are few recommended treatments for people with metastatic or locally advanced, inoperable breast cancer.

Pembrolizumab alongside chemotherapy is being proposed as a new treatment option for people with either metastatic or locally recurrent, inoperable breast cancer. Pembrolizumab is administered intravenously and works by binding to specific receptors, blocking their interaction with ligands. In turn, this enhances the responses of specific cells in the body, including anti-tumour cells. If licensed, the use of pembrolizumab alongside chemotherapy could provide another treatment option for people with the condition.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Proposed Indication

Pembrolizumab with chemotherapy is indicated for treating hormone receptor positive (HR+)/ human epidermal growth factor receptor 2 negative (HER2-) locally recurrent inoperable or metastatic breast cancer.[1]

Technology

Description

Pembrolizumab (KEYTRUDA) is a humanised monoclonal antibody that binds to programmed cell death-1 receptors, blocking their interactions with programmed death ligand (PD-L)-1 and PD-L2. As the programmed death 1 (PD-1) receptor has been shown to be involved in the control of T-cell immune responses, pembrolizumab is designed to enhance T-cell responses, including anti-tumour responses, by blocking PD-1 that binds to PD-L1 and PD-L2, which may both be expressed in tumours.[2]

Pembrolizumab in combination with chemotherapy is in clinical development for locally recurrent inoperable or metastatic breast cancer. A phase III trial is assessing the effectiveness of pembrolizumab (200 mg administered by intravenous infusion on day one of each 21-day cycle) and an investigator's choice of one of four chemotherapy regimens in people with locally recurrent inoperable or metastatic breast cancer (KEYNOTE-B49/MK-2475; NCT04895358).[1]

Key Innovation

Currently, options for treating advanced cancer are limited,[3] and it has been noted that new treatment strategies to treat endocrine-resistant, HR+, HER2-negative metastatic breast cancer are needed.[4] Additionally, treatments can be associated with side-effects like fluid build-up, changes to menstruation in women, nausea and vomiting and vaginal changes.[5] Pembrolizumab is already licensed in the EU/UK for many different cancer indications.[2] If licensed, the combination of pembrolizumab and chemotherapy would offer people with locally recurrent inoperable or metastatic breast cancer another potential treatment option.

Regulatory & Development Status

Pembrolizumab currently has Marketing Authorisation in the EU/UK as a combination therapy for:[2]

- non-small cell lung carcinoma (NSCLC)
- urothelial carcinoma
- head and neck squamous cell carcinoma (HNSCC)
- renal cell carcinoma (RCC)
- oesophageal carcinoma
- triple-negative breast cancer (TNBC)
- endometrial carcinoma
- cervical cancer

Pembrolizumab currently has Marketing Authorisation in the EU/UK as a monotherapy for:[2]

- melanoma
- NSCLC
- classical Hodgkin Lymphoma (cHL)
- urothelial carcinoma

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

- HNSCC
- RCC
- microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers (including colorectal cancer, advanced or recurrent endometrial carcinoma and unresectable or metastatic gastric, small intestine or biliary cancer)
- TNBC (as adjuvant treatment after surgery)

Pembrolizumab is in phase II and III clinical trials for multiple indications, including but not limited to:[6]

- hepatocellular carcinoma (HCC)
- muscle-invasive bladder cancer
- stage III melanoma
- cutaneous squamous cell carcinoma
- non-small-cell lung cancer
- RCC

Patient Group

Disease Area and Clinical Need

Breast cancer is cancer that starts in the breast tissue. Breast cancer is commonly diagnosed in women, but men can also be diagnosed, particularly those over 60 years old.[7,8] Metastatic (Stage 4) breast cancer means that the cancer has spread to other parts of the body, while locally recurrent breast cancer is when the cancer has come back into the breast, armpit or chest wall following prior treatment.[9] If the breast cancer cells either have oestrogen or progesterone receptors (or both), this is known as hormone receptor-positive (HR+) breast cancer.[10] HER2 is a protein that causes breast cancer cells to grow more quickly; having small amount or a lack of these proteins means the cancer is HER2-negative (HER2-).[11] Symptoms of breast cancer include a lump or thickened area of breast tissue, changes in the size of one or both breasts, discharge from the nipples, lumps or swelling underneath the armpits, changes in the look or feel of the skin of the breast, and changes in the overall appearance of the nipple (e.g. becoming sunken into the breast).[8,12] The exact causes of breast cancer are unknown but factors such as age, family history, previous diagnoses of the condition and drinking alcohol may increase the risk of it developing.[7]

It is estimated that between 2016 and 2018 there were around 55,900 new cases of breast cancer in the UK each year, with rates in women increasing by 5% over the past decade and rates in men remaining stable. Approximately 11,500 people die from breast cancer in the UK each year (2017-2019); it is the second most common form of cancer death in women in the UK.[13] In 2021-22, malignant neoplasm of the breast (ICD-10 code C50) lead to 244,374 finished consultant episodes (FCEs), of which 243,116 were female and 1,196 were male.[14] This resulted in 240,790 hospital admissions, 218,006 day cases and 60,220 FCE bed days.[14] In England in 2020, 5.6% of breast cancers were diagnosed at Stage 4.[15]

Recommended Treatment Options

Currently, the National Institute for Health and Care Excellence (NICE) recommends palbociclib plus fulvestrant, abemaciclib plus fulvestrant, and ribociclib plus fulvestrant for use in adults who have had endocrine therapy if exemestane plus everolimus is the most appropriate alternative to a CDK4/6 inhibitor.[16-18]

In premenopausal and perimenopausal women, NICE recommend ovarian suppression if they have previously been treated with tamoxifen and then experience disease progression. For those who are not

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

suitable for treatment with anthracyclines, systemic chemotherapy is offered in the form of single-agent vinorelbine or capecitabine (second line) and then whichever of vinorelbine or capecitabine was not used as second line treatment (third line).[3]

The European Society for Medical Oncology (ESMO) notes that, in ER-positive, HER2- metastatic breast cancer following progression on a CDK4/6 inhibitor, the optimal sequence of endocrine-based therapy is dependent on which agents were used previously, duration of response to endocrine therapy (for use of second-line, single-agent endocrine therapy), disease burden, treatment availability and patient preference. ESMO state that second-line therapies may include fulvestrant-alpelisib (for PIK3CA-mutated tumours), exemestane-everolimus, tamoxifen-everolimus, chemotherapy or ploy (ADP-ribose) polymerase (PARP) inhibitors (for tumours harbouring gBRCAm). In the third-line setting, ESMO recommends continuation of endocrine therapy agents not previously used for patients who are endocrine-sensitive, while chemotherapy should be considered for those who are endocrine-resistant. Single-agent chemotherapy regimens are generally preferred in this setting due to quality of life considerations.[19]

Clinical Trial Information

Trial	**KEYNOTE-B49/MK-3475, NCT04895358, EudraCT-2020-005407-38**; A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer (KEYNOTE-B49) **Phase III** – Recruiting **Location(s):** the UK, 11 EU countries, the USA and other countries **Primary completion date**: July 2028
Trial Design	Randomised, parallel assignment, placebo-controlled, double-blind
Population	N = 800 (estimated); adults with locally recurrent inoperable or metastatic HR+/HER2- breast cancer that has not previously been treated with cytotoxic chemotherapy in the non-curative setting. Has progressed on prior endocrine therapy and is now a chemotherapy candidate.
Intervention(s)	Pembrolizumab (IV administration, 200 mg) on day 1 of each 21-day cycle + one of four chemotherapy regimens: • paclitaxel 90 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle (Q4W); • nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, and 15 Q4W; • liposomal doxorubicin 50 mg/m^2 IV on Day 1 Q4W; or • capecitabine 1000 mg/m^2 by oral administration (PO) twice a day (BID) on Days 1-14 Q3W for up to 35 administrations.
Comparator(s)	Placebo (normal saline or dextrose, IV administration) on day 1 of each 21-day cycle + one of four chemotherapy regimens: • paclitaxel 90 mg/m^2 IV on Days 1, 8, and 15 (Q4W); • nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, and 15 Q4W; • liposomal doxorubicin 50 mg/m^2 IV on Day 1 Q4W; or • capecitabine 1000 mg/m^2 by oral administration (PO) twice a day (BID) on Days 1-14 Q3W for up to 35 administrations.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Outcome(s)	1. Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) by blinded independent central review (BICR) in participants with combined positive score (CPS) ≥ 10 [up to approximately 33 months] 2. PFS per RECIST 1.1 by BICR in participants with CPS ≥ 1 [up to approximately 33 months] 3. Overall survival (OS) in participants with CPS ≥ 10 [up to approximately 75 months] 4. OS in participants with CPS ≥ 1 [up to approximately 75 months] See trial record for full list of all outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of pembrolizumab 100mg/4ml (25 mg per 1 ml) solution for infusion vial is £2,630 (hospital only).[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA836). October 2022.
- NICE technology appraisal. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (TA816). August 2022.
- NICE technology appraisal. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725). September 2021.
- NICE technology appraisal. Ribociclib with fulvestrant for treating hormone-receptor positive, HER2-negative advanced breast cancer after endocrine therapy (TA687). March 2021.
- NICE technology appraisal. Fulvestrant for the treatment of locally advanced or metastatic breast cancer (TA239). December 2011.
- NICE guideline. Suspected cancer: recognition and referral (NG12). December 2021.
- NICE guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- NICE clinical guideline. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). November 2019.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017.
- NICE quality standard. Suspected cancer (QS124). December 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

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

- Gennari, A., André, F., Barrios, C. H., Cortés, J., de Azambuja, E., DeMichele, A., et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. December 2021.[19]
- Gradishar, W. J., Anderson, B. O., Abraham, J., Aft, R., Agnese, D., Allison, K. H., et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. April 2020.[21]
- Chacón López-Muñiz, J. I., de la Cruz Merino, L., Gavilá Gregori, J., Martínez Dueñas, E., Oliveira, M., Seguí Palmer, M. A., et al. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). Clinical and Translational Oncology. 2019.[22]

Additional Information

References

1 ClinicalTrials.gov. *A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer (KEYNOTE-B49). Trial ID: NCT04895358*. 2021. Status: Recruting. Available from: https://clinicaltrials.gov/ct2/show/NCT04895358 [Accessed 13 January 2023].

2 electronic medicines compendium (emc). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/2498#ORIGINAL [Accessed 10 March 2023].

3 National Institute for Health and Care Excellence. *Advanced breast cancer: diagnosis and treatment (CG81)*. Last Update Date: 16 August 2017. Available from: https://www.nice.org.uk/guidance/cg81 [Accessed 16 January 2023].

4 Pérez-García JM, Llombart-Cussac A, Gion M, Curigliano G, López-Miranda E, Alonso JL, et al. Pembrolizumab plus eribulin in hormone-receptor–positive, HER2-negative, locally recurrent or metastatic breast cancer (KELLY): An open-label, multicentre, single-arm, phase Ⅱ trial. *European Journal of Cancer*. 2021;148:382-94. Available from: https://doi.org/10.1016/j.ejca.2021.02.028.

5 Cancer Research UK. *Tamoxifen*. 2019. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/treatment/drugs/tamoxifen [Accessed 16 January 2023].

6 ClinicalTrials.gov. *Search for: Pembrolizumab | Merck | Phase 2, 3*. 2022. Available from: https://clinicaltrials.gov/ct2/results?intr=Pembrolizumab&spons=Merck&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 18 January 2023].

7 National Health Service. *Causes: Breast cancer in women*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/causes/ [Accessed 13 January 2023].

8 National Health Service. *Overview: Breast cancer in men*. 2020. Available from: https://www.nhs.uk/conditions/breast-cancer-in-men/ [Accessed 13 January 2023].

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

9 Cancer Research UK. *About breast cancer staging and grades*. 2020. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/about-breast-cancer-staging-grades [Accessed 13 January 2023].
10 American Cancer Society. *Breast Cancer Hormone Receptor Status*. 2021. Available from: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html [Accessed 13 January 2023].
11 American Cancer Society. *Breast Cancer HER2 Status*. 2022. Available from: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html [Accessed 13 January 2023].
12 National Health Service. *Symptoms: Breast cancer in women*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/symptoms/ [Accessed 13 January 2023].
13 Cancer Research UK. *Breast cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Two [Accessed 13 January 2023].
14 NHS Digital. *Hospital Admitted Patient Care Activity 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 13 January 2023].
15 Cancer Research UK. *Early Diagnosis Data Hub*. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ [Accessed 24 February 2023].
16 National Institute for Health and Care Excellence. *Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA836)*. Available from: https://www.nice.org.uk/guidance/ta836/chapter/1-Recommendations [Accessed 9 March 2023].
17 National Institute for Health and Care Excellence. *Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725)*. Available from: https://www.nice.org.uk/guidance/ta725/chapter/1-Recommendations [Accessed 9 March 2023].
18 National Institute for Health and Care Excellence. *Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA687)*. Available from: https://www.nice.org.uk/guidance/ta687/chapter/1-Recommendations [Accessed 9 March 2023].
19 Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Annals of Oncology*. 2021;32(12):1475-95. Available from: https://doi.org/10.1016/j.annonc.2021.09.019.
20 National Institute for Health and Care Excellence. *Pembrolizumab: Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/pembrolizumab/medicinal-forms/ [Accessed 16 January 2023].
21 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*. 2020;18(4):452-78. https://jnccn.org/view/journals/jnccn/18/4/article-p452.xml?rskey=j8Zjsn&result=598&utm_source=TrendMD&utm_medium=cpc&utm_campaign=JNCCN_TrendMD_1.
22 Chacón López-Muñiz JI, de la Cruz Merino L, Gavilá Gregori J, Martínez Dueñas E, Oliveira M, Seguí Palmer MA, et al. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). *Clinical and Translational Oncology*. 2019;21:31-45. https://link.springer.com/article/10.1007/s12094-018-02010-w#Sec7.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

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.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.