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Health Technology Briefing
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Pembrolizumab adjuvant therapy for treating Triple-Negative breast cancer

Company/Developer	Merck Sharp & Dohme Ltd.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID:23993	NICE ID: Not Available	UKPS ID: 663970

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Pembrolizumab is in clinical development as an adjuvant treatment for triple-negative breast cancer (TNBC). In this type of cancer, the cells don't have receptors for oestrogen, progesterone, and a protein called human epidermal growth factor receptor 2 (HER-2), therefore cannot be treated with hormonal or targeted therapy. TNBC is usually more aggressive, harder to treat, and more likely to come back. Adjuvant therapy is a type of cancer treatment given after the initial treatment to reduce the risk of the cancer returning. The likely outcome or chance of recovery for these patients is typically extremely poor, so there is a need to develop additional treatment options.

Pembrolizumab is a monoclonal antibody, a protein that has been designed to recognise and block a receptor ('target') called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system (the body's natural defences), preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licensed, pembrolizumab may provide an additional adjuvant treatment option for the treatment of early-stage TNBC.

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.

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Proposed Indication

Adjuvant therapy for triple receptor-negative breast cancer with >/= 1 CM residual invasive cancer or positive lymph nodes (ypN1mi, ypN1-3) after neoadjuvant chemotherapy.[1]

Technology

Description

Pembrolizumab (Keytruda, MK-347)[1] is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity involved in controlling T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through the blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[2]

In the phase III clinical trial (KEYNOTE-242, NCT02954874), participants will receive pembrolizumab intravenous (IV) infusion as an adjuvant therapy over 30 minutes on days 1 and 22. Cycles will be repeated every 42 days for 52 weeks in the absence of disease progression or unacceptable toxicity.[1]

Key Innovation

Triple-negative breast cancer (TNBC) is the most malignant subtype of breast cancer, characterised by its highly aggressive behaviour, early recurrence, and poor prognosis.[3,4] Due to a lack of receptor markers, patients with TNBC respond poorly to endocrine or human epidermal growth factor receptor 2 (HER2)-targeted medications and, therefore, have more limited options. Anthracycline/taxane-based regimens are the standard of care chemotherapy in adjuvant settings.[4]

Despite treatment with multiagent chemotherapy in the neoadjuvant and/or adjuvant setting, the burden of the disease remains high, demonstrating the continued need for therapies to improve long-term outcomes.[5] Pembrolizumab has been found to be effective in the early stage and is well tolerated with an acceptable safety profile in TNBC patients.[6] If licensed, pembrolizumab may provide an additional treatment option as an adjuvant monotherapy treatment in TNBC after neoadjuvant therapy.

Regulatory & Development Status

Pembrolizumab currently has Marketing Authorisation in the UK for the following indications as monotherapy:[2]

- Melanoma
- Non-small cell lung carcinoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers

Pembrolizumab is currently in phase II and III clinical trials as an adjuvant therapy for various types of cancer, including: [7]

- Oesophageal squamous cell carcinoma
- Non-small cell lung cancer
- Renal cell carcinoma

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- Hepatocellular carcinoma
- Head and neck cancer
- Bladder urothelial carcinoma
- Melanoma.

Patient Group

Disease Area and Clinical Need

Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Breast cancer most commonly starts in the cells that line the milk ducts or the lobules of the breast.[8] Breast cancer can be invasive or non-invasive (in situ). Invasive breast cancer is when cancer cells have spread outside the milk ducts or lobules, where they start spreading into surrounding breast tissue.[9]Triple-negative breast cancers are cancers whose cells don't have receptors for the hormones oestrogen, progesterone, and a protein called HER2.[10] Around 15% of breast cancers are TNBC, which is characterised by its aggressiveness, early relapse, and a greater tendency to present in advanced stages.[11] Risk factors include age (women under 40 years), gender, ethnicity/race, prior history of breast cancer, positive family history, BReast CAncer gene 1 (BRCA 1) or BReast CAncer gene 2 (BRCA 2) mutation, obesity, tall stature, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity, radiotherapy to the chest at a young age, dense breast tissue and hormone replacement therapy.[10,12,13] One of the first noticeable symptoms of breast cancer in women is a lump or an area of thickened tissue in the 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.[14,15]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases. There are around 56,800 new breast cancer cases every year, of which about 99% are in females and 1% in males (2017-2019). The age-standardised incidence rate of breast cancer in England is 1.4 and 170.3 per 100,000 among males and females, respectively.[16] In England, in 2023-2024, there were 265,571 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 261,890 admissions resulting in 64,821 FCE bed days and 240,356 day cases.[17] In England (2017), there were 46,109 patients diagnosed with breast cancer and 9,569 deaths registered where breast cancer was the underlying cause.[18] The latest published survival statistics for breast cancer for women in England (patients diagnosed between 2013 and 2017, followed up to 2018) reported a 1-year survival rate of 95.8% and a 5-year survival rate of 85% (age-standardised).[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommended treatment options for treating TNBC stage 1-3 are:

- Surgery and radiotherapy. Surgery may be mastectomy or breast-conserving surgery, with or without radiotherapy, to reduce local recurrence rates.[20,21]
- Chemotherapy may be given before surgery (neoadjuvant chemotherapy) to shrink a large tumour or after surgery (adjuvant chemotherapy) to reduce the chances of TNBC recurrence.[20,21]
- Adjuvant anthracycline–taxane combination chemotherapy is recommended in patients with invasive breast cancer who are at sufficient risk of disease recurrence to require chemotherapy.[20,21]
- Olaparib (alone or with endocrine therapy) for adjuvant treatment of HER2-negative high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy in adults with germline BRCA1 or 2 mutations.[22]

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- Pembrolizumab with chemotherapy as an option for neoadjuvant treatment and then continued alone as an adjuvant treatment after surgery for adults with triple-negative early breast cancer at high risk of recurrence or locally advanced breast cancer.[23]

Clinical Trial Information

Trial	**KEYNOTE-242**, NCT02954874; A randomised, phase III trial to evaluate the efficacy and safety of pembrolizumab (MK-3475) as adjuvant therapy for triple receptor-negative breast cancer with >/= 1 CM residual invasive cancer or positive lymph nodes (ypN1mi, ypN1-3) after neoadjuvant chemotherapy. **Phase III** – Active, not recruiting. **Location(s)**: United States (including Puerto Rico) and Canada **Primary completion date**: May 2026
Trial Design	Randomised, open-label, parallel assignment
Population	N= 1155 (planned); adult participants with non-metastatic, non-recurrent breast cancer after neoadjuvant chemotherapy; confirmed oestrogen receptor (ER)-, progesterone receptor (PR)- and HER2-negative (triple-negative, TNBC) or ER-, PR- weakly positive and/or HER2- equivocal status.
Intervention(s)	Pembrolizumab IV
Comparator(s)	Standard of care
Outcome(s)	Primary outcome measures: • Invasive disease-free survival [Time frame: from the date of randomization to date of first invasive recurrence, second invasive primary cancer (breast or not), or death due to any cause, assessed up to 10 years] • Severity of fatigue [Time frame: 55 weeks after randomisation] • Physical function [Time frame: 55 weeks after randomisation] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK. The NHS indicative price is £2,630 for a 100 mg/4 ml concentrate for solution for infusion vial.[24]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy (TA886). Published: May 2023

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- NICE technology appraisal guidance. Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer (TA851). Published: December 2022
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- NICE quality standard. Breast cancer (QS12). June 2016
- NICE diagnostics guidance. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (DG34). December 2018

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

- NHS England. Clinical guidelines for the management of breast cancer.[25]
- European Society of Medical Oncology. Clinical Practice Guidelines: Breast Cancer.[26]
- Early Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. October 2019.[27]
- Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. August 2018.[28]

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