NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of locally advanced non-metastatic triple-negative breast cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for the neoadjuvant and adjuvant treatment of locally advanced non-metastatic triple-negative breast cancer.

Background

Breast cancer arises from the tissues of the ducts or lobules of the breast. It is described as invasive when the cancer cells have grown through the lining of the ducts into the surrounding tissue. Breast cancer is described as 'locally advanced' if the cancer has spread from the breast to lymph nodes close to the breast, to the skin of the breast, or to the chest wall but has not spread to other parts of the body (clinical stage 3).[1]

Over 46,100 people were diagnosed with breast cancer in England in 2017[2] and there were approximately 9,600 deaths from breast cancer in England in 2018.[3] Around 15% of breast cancers are triple-negative breast cancers whereby the cancer cells test negative for oestrogen receptors and progesterone receptors (hormone-receptor-negative cancer) and human epidermal growth factor receptor 2 (HER2-negative cancer).[4]

Triple-negative breast cancer is associated with poor prognosis with high risk of relapse and short progression-free survival and overall survival. As many as 50% of patients diagnosed with stage 1 to 3 triple-negative breast cancer experience disease recurrence, and 37% die in the first 5 years after surgery.[5] Depending on the stage of its diagnosis, triple-negative breast cancer can be particularly aggressive, is more likely to recur than other subtypes of breast cancer and is associated with poorer survival. It is diagnosed more frequently in younger people, black people, and in people with BRCA1 mutations (a gene on chromosome 17 that normally helps to supress cell growth, which is an inherited gene mutation that may increase the risk of breast cancer).[6]

NICE guideline 101 (NG101) recommends neoadjuvant chemotherapy for people with oestrogen receptor-negative invasive breast cancer as an option to reduce tumour size before surgery. It further recommends consideration of adding a platinum to an anthracycline-containing neoadjuvant chemotherapy regimen for triple-negative invasive breast cancer. For adjuvant treatment after surgery, NG101 recommends offering a regimen that contains both a taxane and an anthracycline. Standard chemotherapy options used for

neoadjuvant and adjuvant treatment of triple negative breast cancer include doxorubicin, epirubicin, docetaxel, paclitaxel and carboplatin.

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, anti-programmed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Pembrolizumab does not currently have a marketing authorisation in the UK for the neoadjuvant and adjuvant treatment of locally advanced triple-negative breast cancer. It has been studied in a clinical trial as a neoadjuvant treatment in combination with chemotherapy, compared with placebo plus chemotherapy, in people with previously untreated locally advanced non-metastatic triple-negative breast cancer. After neoadjuvant treatment, people in the trial underwent surgery and then had adjuvant treatment with pembrolizumab, or placebo.

Intervention	Pembrolizumab in combination with standard neoadjuvant and adjuvant chemotherapy
Population	Adults with previously untreated locally advanced, non-metastatic triple-negative breast cancer
Comparators	Standard neoadjuvant and adjuvant chemotherapy without pembrolizumab
Outcomes	The outcome measures to be considered include: • overall survival • disease free survival • surgical outcomes • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: • Early and locally advanced breast cancer: diagnosis and management (2018) NICE clinical guideline NG101 • Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. (2013, updated 2019) NICE clinical guideline CG164 Related Quality Standards: • Breast cancer (2011, updated 2016) NICE quality standard QS12 Related NICE Pathways: • Early and locally advanced breast cancer NICE pathway • Familial breast cancer NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care, NHS Outcomes

	Framework 2016-2017: Domains 1 and 3 to 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for pembrolizumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for neoadjuvant and adjuvant treatment of locally-advanced, non-metastatic triple-negative breast cancer?

What neoadjuvant and adjuvant chemotherapies are given when treating locally advanced, non-metastatic triple negative breast cancer?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider pembrolizumab will fit into the existing NICE pathway, Early and locally advanced breast cancer?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Cancer Research UK (2020) Number stages of breast cancer. Accessed July 2021.

2 Office for National Statistics (2019) Cancer registration statistics, England, 2017. Accessed July 2021.

3 Cancer research UK (2018) Breast cancer mortality statistics. Accessed July 2021.

4 The Institute of Cancer Research (2016) Promising drug target for aggressive 'triple negative' breast cancers identified. Accessed July 2021.

5 Costa RLB and Gradishar WJ. Triple-negative breast cancer: current practice and future directions. Journal of Oncology Practice 13, no. 5 (May 1 2017) 301-303.

6 Couch FJ, Hart SN, Sharma P et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. Journal of Clinical Oncology 2015;33(4):304-311