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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy for early-strage breast cancer

NIHRIO ID	26985	**NICE ID**	10462
Developer/Company	Merck Sharp & Dohme (UK) Ltd	**UKPS ID**	656481

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Pembrolizumab in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy is in clinical development for the treatment of early-stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) breast cancer. Early breast cancer is where the disease is limited to the breast region and has not spread to other parts of the body. Treatment of early-stage breast cancer usually involves surgery. Most patients will often receive some treatment after ('adjuvant') the surgery to improve the success rate of the treatment. Treatment with medicines prior to surgery (neoadjuvant) may provide better long-term survival prospects for patients with early-stage operable breast cancer.

Pembrolizumab is a drug administered intravenously (IV) that binds to the programmed cell death-1 (PD-1) receptor and improves the activity of the immune system to kill cancer cells. If licenced, pembrolizumab in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy would provide an additional treatment option for ER+/HER2- breast cancer.

PROPOSED INDICATION

Combination with neoadjuvant chemotherapy and adjuvant endocrine therapy for the treatment of high-risk early-stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) breast cancer.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab is a humanised monoclonal antibody which 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 that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through 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 (NCT03725059), pembrolizumab 200mg was administered in the neoadjuvant setting to patients via IV infusion once every 3 weeks alongside paclitaxel 80mg/m2 via IV infusion once weekly for 4 cycles. This was followed by pembrolizumab 200mg administered to patients via IV infusion, doxorubicin 60mg/m2 or epirubicin 100mg/m2 via IV infusion and cyclophosphamide 600mg/m2 via IV infusion once every 3 weeks for 4 cycles. At 3 to 6 weeks after the final cycle of neoadjuvant treatment, patients undergo definitive surgery. Following surgery and in the adjuvant setting, patients are administered pembrolizumab 200mg via IV infusion once every 3 weeks for 9 cycles alongside variable endocrine therapy for up to 10 years. All cycles are 21 days long.[1]

INNOVATION AND/OR ADVANTAGES

Approximately 25% of patients with early-stage breast cancer who receive neoadjuvant chemotherapy experience a recurrence within 5 years. Previous studies have demonstrated an improved outcome by the addition of pembrolizumab to standard neoadjuvant chemotherapy in early stage, HER2- breast cancer. If approved for this indication, pembrolizumab added to both neoadjuvant chemotherapy and adjuvant endocrine therapy would offer a potentially improved therapeutic regimen for this patient group.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licensed for a number of cancer indications, both as a monotherapy and as a combination. It is not currently licensed to treat early stage breast cancer.[2]

Pembrolizumab is currently licenced as a monotherapy for:[2]

- advanced (unresectable or metastatic) melanoma in adults
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a $\geqslant$ 1% tumour proportion score (TPS) and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

- first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ⩾ 50% TPS with no EGFR or ALK positive tumour mutations
- adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ⩾ 10
- recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ⩾ 50% TPS and progressing on or after platinum containing chemotherapy.
- the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1
- the first line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

Pembrolizumab is currently licenced in combination with:[2]

- axitinib, for the first-line treatment of advanced renal cell carcinoma in adults
- pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations
- carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults
- platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 1.

Very common adverse events (frequency ≥ 1/10) of pembrolizumab in combination with chemotherapy include: anaemia, neutropenia, thrombocytopenia, hypokalaemia, decreased appetite, dizziness, headache, peripheral neuropathy, dysgeusia, dyspnoea, cough, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, alopecia, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, pyrexia, oedema and blood creatinine increased.[2]

Pembrolizumab is in clinical trials for various cancer indications as a neoadjuvant and as an adjuvant therapy, including: non-small cell lung cancer, oesophageal and gastric cancers, head and neck cancer, melanoma, prostate and bladder cancer.[4,5]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common cancer in the UK, and mainly affects women, although men can also have the condition. It usually starts in the cells that line the ducts of the breast.[6] Early stage breast cancer is defined as disease confined to the breast with or without regional lymph node involvement and the absence of distant metastatic disease.[7]

There are different immune/pathological subtypes of breast cancer, among which is human epidermal growth receptor 2 (HER2) and oestrogen receptor (ER). HER2 is a transmembrane receptor protein that is overexpressed in about 20% of breast cancers and associated with

more aggressive disease in the absence of HER2 directed therapy. HER2 plays a role in cell growth and differentiation. Those with cancer cells with HER2 are HER2+ diagnosed, whereas those without are diagnosed HER2-.[8,9] ER positive (ER+) cells have a protein that binds to the hormone estrogen. Cancer cells that are ER+ may need estrogen to grow and hormonal therapies work well for ER+ breast cancer. Approximately 70% of breast cancers are ER+.[9]

The exact aetiology is unknown, but family history is a strong risk factor (hereditary factors).[10] Other risk factors for breast cancer include increased age, reproductive history and hormone exposure, lifestyle factors, medical history and radiation exposure.[11]

One of the first noticeable symptom of breast cancer amongst women is a lump or an area of thickened tissue in their 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.[12,13]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2017, breast cancer was the most common cancer accounting for 15% of all new cancer cases.[14] In England, in 2017 there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the direct age-standardised rate per 100,000 population was 166.7 among females and 1.3 among males.[15] Incidence rates among females are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[16]

In England, in 2019-20 there were 230,944 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 226,544 admissions resulting in 74,647 bed days and 193,849 day cases.[17]

In England in 2020, there were 10,385 registrations of death from malignant neoplasm of breast,[18] and in 2017 the direct age-standardised death rate per 100,000 population was 0.3 and 33.3 among males and females respectively.[15]

The latest published survival statistics for breast cancer for women in England (patients diagnoses 2013-2017) reported a 1-year survival rate of 95.8% and a 5-year survival rate of 85% (age-standardised).[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of breast cancer should be carried out in specialised breast units/centres and provided by a multidisciplinary team specialised in breast cancer, consisting of at least medical oncologists, breast surgeons, radiation oncologists, breast radiologists, breast pathologists and breast nurses (or similarly trained and specialised health care practitioners).[19]

The management of breast cancer requires different approaches and involves the use of different therapies. The main treatments for breast cancer include surgery, radiotherapy, chemotherapy, hormone therapy, biological therapy (targeted therapy). Patients may have one of these treatments or a combination. The type or combination of treatments will depend on how the cancer was diagnosed and the stage of the disease.[20]

Adjuvant systemic therapy should be started without undue delays, as data show an important decrease in efficacy when it is administered >12 weeks after surgery. The decision on adjuvant

systemic therapies should be based on an individual's risk of relapse (which depends on tumour burden and tumour biology), the predicted sensitivity to particular types of treatment, the benefit from their use and their associated short- and long-term toxicities, the patient's biological age, general health status, comorbidities and preferences.[19] In some cases, the therapy may be given before surgery, to shrink a large tumour (neo-adjuvant).[20]

CURRENT TREATMENT OPTIONS

The following are recommended in the treatment of early breast cancer:[21]

Chemotherapy[22]

- Neoadjuvant chemotherapy for people with ER+ invasive breast cancer as an option to reduce tumour size if chemotherapy is indicated.

Bisphosphonate therapy[20]

- Zoledronic acid or sodium clodronate as adjuvant therapy for postmenopausal women with node positive invasive breast cancer or node-negative invasive breast cancer and a high risk of recurrence.

Hormone therapy[20]

- Tamoxifen as a treatment for ER+ breast cancer
- Aromatase inhibitors, such as anastrozole, exemestane and letrozole for postmenopausal women with ER+ breast cancer
- Ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer may also be considered.
- Neoadjuvant endocrine therapy should be considered for postmenopausal women with ER-positive invasive breast cancer as an option to reduce tumour size if there is no definite indication for chemotherapy.

PLACE OF TECHNOLOGY

If licenced, pembrolizumab in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy would provide an additional treatment option for ER+/HER2- breast cancer.

CLINICAL TRIAL INFORMATION

Trial	**MK-3475-756/KEYNOTE-756;** NCT03725059, 2017-004869-27; A Randomized, Double-Blind, Phase III Study of Pembrolizumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy for the Treatment of High-Risk Early-Stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) Breast Cancer (KEYNOTE-756) **Phase III** - Recruiting **Locations:** 8 EU countries, United Kingdom, United States, Canada and other countries **Primary completion date:** January 2031
Trial design	Randomized, parallel assignment, triple masked
Population	N = 1140 (estimated), localized invasive breast ductal adenocarcinoma, centrally confirmed ER+/HER2-, grade 3 breast cancer of ductal histology, aged 18 years and older

Intervention(s)	- Neoadjuvant: participants receive pembrolizumab (K) 200 mg via IV infusion once every 3 weeks (Q3W) + paclitaxel 80 mg/m^2 via IV infusion once weekly (QW) for 4 cycles, followed by pembrolizumab 200 mg via IV infusion + doxorubicin or epirubicin (A or E; 60 mg/m^2 or 100 mg/m^2) via IV infusion Q3W + cyclophosphamide 600 mg/m^2 via IV infusion Q3W or Q2W (dose-dense) for 4 cycles. At 3 to 6 weeks after last cycle of neoadjuvant treatment, participants will undergo surgery for their breast cancer - Adjuvant: participants receive pembrolizumab 200 mg via IV infusion Q3W for 9 cycles + variable endocrine therapy for up to 10 years. Each cycle is 21 days long.
Comparator(s)	- Neoadjuvant: IV placebo and chemotherapy - Adjuvant: IV placebo
Outcome(s)	Primary outcomes; - Pathological Complete Response (pCR) Rate Using the Definition of ypT0/Tis ypN0 [Time Frame: Up to approximately 7 months (Time of surgery)] - Event-Free Survival (EFS) [Time Frame: Up to approximately 12 years] 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.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Taselisib for previously treated ER-positive, HER2-negative, PIK3CA-positive breast cancer in postmenopausal women (ID 1401). Expected publication date: To be confirmed.
- NICE technology appraisal guidance in development. Amcenestrant for treating ER-positive, HER2-negative advanced breast cancer after hormonal therapy (ID3857). Expected publication date: To be confirmed.
- NICE technology appraisal guidance in development. Abemaciclib for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer (ID3919). Expected publication date: To be confirmed.
- NICE technology appraisal guidance. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer (TA501). January 2018
- 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

- Early Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. October 2019[19]
- Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. August 2018[24]
- Healthcare Improvement Scotland. SIGN 134 – Treatment of primary breast cancer – A national clinical guideline. September 2013[25]

ADDITIONAL INFORMATION

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