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Pembrolizumab in addition to chemotherapy for locally advanced, non-metastatic triple negative breast cancer – neoadjuvant, first line

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LAY SUMMARY

Breast cancer is cancer that develops from breast tissue. Triple negative breast cancer (TNBC) is an uncommon type of breast cancer, whose cells don't have receptors for the hormones oestrogen and progesterone and HER2 protein. Many breast cancers have receptors for one or more of these substances. But TNBC do not have any of them. When certain substances in the body attach to the receptors, they trigger a reaction in the cancer cells that tell them to grow. Therefore hormone treatment and targeted cancer drugs do not work for people with TNBC. Symptoms of this type of breast cancer may include a lump or thickening in an area of the breast, a change in the size, shape or feel of the breast, dimpling of the skin, a change in the shape of the nipple, a blood stained discharge from the nipple, a rash on a nipple or surrounding area, or a swelling lump in the armpit.

Pembrolizumab is a drug that is already used for other types of cancer, given as intravenous infusion. Pembrolizumab is a type of immunotherapy, which works by targeting specific proteins that stimulate an immune response attacking the cancer cells. It increases the body's natural ability to identify and kill cancer cells. Pembrolizumab is being developed to be given in combination with chemotherapy as a neo-adjuvant (given before the main treatment), first line treatment for locally advanced, non-metastatic TNBC. If licensed, pembrolizumab in combination with chemotherapy will therefore offer an additional treatment option for patients with locally advanced, non-metastatic, triple negative breast cancer.

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TARGET GROUP

Breast cancer (locally advanced, non-metastatic, triple negative) – neo adjuvant, first line; in combination with chemotherapy

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) 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. [1]

In the phase III trial (NCT03036488/KEYNOTE-522) Participants receive pembrolizumab every 3 weeks + paclitaxel weekly + carboplatin (weekly or every 3 weeks) in 4 cycles, followed by pembrolizumab every 3 weeks + doxorubicin OR epirubicin + cyclophosphamide every 3 weeks in 4 cycles as neoadjuvant therapy prior to surgery, followed by 9 cycles of pembrolizumab every 3 weeks as adjuvant therapy post-surgery. Each cycle is 21 days.[2]

Pembrolizumab is currently licensed in the EU as a monotherapy under its commercial name Keytruda for the following indications:[1]

- advanced (unresectable or metastatic) melanoma in adults
- metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK) positive tumour mutations – first line
- locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% 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
- adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1)
- 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.[a, 3]

The most common side effects with pembrolizumab (which may affect more than 1 in 10 people) are diarrhoea, nausea (feeling sick), itching, rash and tiredness, most of which are mild to moderate in severity. Other common side effects of pembrolizumab related to the activity of the immune system

[a] A conditional restriction has been placed by the EMA on the use of Keytruda after early data from this clinical trial showed reduced survival when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. EMA, 1 June 2018, EMA/364553/2018

causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping pembrolizumab.[4]

Phase II clinical trials of pembrolizumab are ongoing for advanced solid tumours, cutaneous squamous cell carcinoma, ovarian and prostate cancer. Phase III clinical trials of pembrolizumab are ongoing for breast, colorectal, esophageal, gastric, head and neck, liver, nasopharyngeal, renal and small cell lung cancer.[5]

INNOVATION and/or ADVANTAGES

Endogenous anticancer immunity may be enhanced with immune checkpoint inhibition by increased tumour-specific antigen release after chemotherapy. Combining the anti–PD-1 inhibitor pembrolizumab with chemotherapy may be an effective treatment strategy for triple negative breast cancer (TNBC) in neoadjuvant and adjuvant settings.[6] If licensed, pembrolizumab in combination with chemotherapy will offer an additional neoadjuvant, first line treatment option for patients with locally advanced, non-metastatic, TNBC

DEVELOPER

Merck Sharp & Dohme Ltd

PATIENT GROUP

BACKGROUND

Breast cancer is cancer that develops from breast tissue. Breast cancer is not a single disease, but rather a group of several different tumour subtypes.[7] Triple negative breast cancer (TNBC) is an uncommon type of breast cancer, whose cells do not have receptors for the hormones oestrogen and progesterone and human epidermal growth factor receptor 2 (HER2) protein.[8] Testing negative for all three, oestrogen receptors (ER-), progesterone receptors (PR-) and HER2 (HER2-), means that the cancer is triple negative. TNBC does not respond to hormonal therapy or therapies targeted at HER2 receptors. Approximately 10-20% of breast cancers are found to be triple negative. TNBC is most likely to occur before age 40 or 50, unlike other breast cancer types which more commonly occur in people aged 60 and older.[9,10] Some women with TNBC have the faulty BRCA1 gene, which is inherited from a parent and can cause breast cancer to run in families. Most breast cancers caused by BRCA1 are triple negative.[11]

Locally advanced cancer means that the cancer has spread into the tissues around the breast but has not spread to other organs.[12] Locally advanced cancer can be defined as the most advanced breast tumours in the absence of distant metastasis.[13] Non-metastatic refers to a cancer that has not spread from the primary site (place where it started) to other places in the body.[14]

The causes of breast cancer are not completely understood. However, a number of factors are known to increase its likelihood, such as exposure to radiation, increased alcohol consumption, being taller, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors.[15] Breast cancer in adults can occur at any age, with an increased risk in postmenopausal women. Moreover, a previous benign breast lump, or a prior diagnosis of early breast cancer further increases the risk.[16]

Patients diagnosed with early stage breast cancer can live for many years without their quality of life being dramatically impacted by the disease. Advanced breast cancers that require complete removal of the breast, known as mastectomy, can be very distressing for a woman, affecting sexuality and body image.[17]

Symptoms of TNBC are similar to other breast cancer types and may include a lump or thickening in an area of the breast, a change in the size, shape or feel of the breast, dimpling of the skin, a change in the shape of the nipple, a blood stained discharge from the nipple, a rash on a nipple or surrounding area, or a swelling lump in the armpit.[8]

CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancers. Around 55,200 people are diagnosed with breast cancer in the UK each year. That is around 150 people a day.[18] In females in the UK, breast cancer is the most common cancer, with around 54,800 new cases (an incidence rate of 90 per 100,000 people) in 2015. The lifetime risk of developing breast cancer is 1 in 8 women in 2012 in the UK. Incidence rates for breast cancer are projected to rise by 2% in the UK between 2014 and 2035, to 210 cases per 100,000 females by 2035. [19]

In England in 2016 there were 45,960 registrations of newly diagnosed cancer of the breast (ICD-10 code C50) of which 45,656 among females. The directly age-standardised rate per 100,000 population was 1.3 for males and 167.9 for females. There were 9,626 registrations of death from neoplasm of the breast, and the directly age-standardised rate per 100,000 population was 0.3 for males and 34.3 for females.[20]

In England in 2016/17 there were 207,043 finished consultant episodes (FCEs) and 85,801 FCE bed days with primary diagnosis of ICD-10 code C50 (malignant neoplasm of breast). There were 203,454 hospital admissions, of which 169,800 were day cases.[21]

Breast cancer risk is strongly related to age, with a quarter of new breast cancer cases diagnosed in people aged 75 years and older in the UK from 2013-2015.[22] An estimated 23% of female breast cancers in the UK are linked to lifestyle factors including overweight and obesity (8%), alcohol (8%), and certain occupational exposures (5%).[19]

Approximately 15% of breast cancers are triple negative[8] (around 7,500 women in the UK being diagnosed each year[23]). TNBC tends to be more aggressive than other types of breast cancer. Five-year survival rates tend to be lower than for other breast cancer types.[10] TNBC present with a varied natural history but are collectively associated with poor diagnosis with high risk of relapse and short progression-free survival (PFS) and overall survival (OS). As many of 50% of patients diagnosed with early-stage TNBC (stages I-III) experience disease recurrence, and 37% die in the first 5 years after surgery.[24]

There were around 11,400 breast cancer deaths in the UK in 2014, that's 31 deaths every day. Breast cancer is the fourth most common cause of cancer death in the UK, accounting for 7% of all cancer deaths in 2016. Breast cancer deaths in England are more common in females living in the most deprived areas.[22]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pembrolizumab for previously treated metastatic triple negative breast cancer (ID1246). Expected publication date TBC.
- NICE technology appraisal guidance in development. Ribociclib in combination with endocrine therapy and goserelin for previously untreated hormone receptor-positive, HER2-negative advanced breast cancer in premenopausal women (ID1307). Expected publication date TBC.
- NICE technology appraisal guidance in development. Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer (ID1318). Expected publication date TBC.
- NICE technology appraisal guidance in development. Veliparib for treating HER2-negative, BRCA-positive breast cancer (ID1404). Expected publication date TBC.
- NICE technology appraisal guidance in development. Abemaciclib monotherapy for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy and chemotherapy (ID1347). Expected publication date TBC.
- NICE technology appraisal guidance in development. Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (ID1339). Expected publication date TBC.
- NICE technology appraisal guidance in development. Olaparib for treating BRCA 1 or 2 mutated metastatic breast cancer after prior chemotherapy (ID1382). Expected publication date TBC.
- NICE technology appraisal guidance in development. Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer (ID1227). Expected publication date February 2019.
- NICE technology appraisal guidance. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer (TA501). January 2018.
- NICE technology appraisal guidance. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA495). December 2017.
- NICE technology appraisal guidance. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA496). December 2017.
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- NICE quality standard. Suspected cancer (QS124). Published June 2016, updated December 2017.
- NICE quality standard. Breast cancer (QS12). September 2011.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). Published February 2009, updates August 2017.
- NICE clinical guideline. Familial breast cancer: classification, care, managing breast cancer and related risks in people with a family history of breast cancer (CG164). June 2013.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and treatment (CG80). February 2009.
- NICE clinical guideline. Improving outcomes in breast cancer (CSG1). August 2002.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.

NHS ENGLAND and POLICY 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

- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer (2017).[25]
- Primary breast cancer: ESMO clinical Practice Guidelines for diagnosis, treatment and follow-up (2015).[26]

CURRENT TREATMENT OPTIONS

Management of TNBC is challenging because of a lack of targeted therapy, aggressive behaviour and relatively poor prognosis. There are no specific treatment guidelines for TNBCs and they are managed with standard treatment.[27] The main treatments for triple negative breast cancer in the UK are surgery and chemotherapy.[28]

NICE recommend mastectomy (or in exceptional cases breast conserving surgery) followed by radiotherapy to patients with locally advanced breast cancer who have been treated with chemotherapy. However there are no treatments currently recommended specifically for the neoadjuvant treatment of triple negative breast cancer.[29]

Chemotherapy is recommended for the vast majority of triple negative breast cancers. The benefit of chemotherapy tends to be more pronounces in ER- breast cancers. The most frequently used regimes contain anthracyclines and/or taxanes, although CMF (Cyclophosphamide, Methotrexate and Fluorouracil) regimes may be used in selected patients. Four cycles of doxorubicin and cyclophosphamide (AC) are considered equal to six cycles of CMF. The added value of six cycles of three-drug anthracycline-based regimens is controversial. The addition of taxanes improves the efficacy of chemotherapy independently of age, nodal status, tumour size or grade, steroid receptor expression or tamoxifen use, but at the cost of increased non-cardiac toxicity. Overall, chemotherapy regimens based on anthracyclines and taxanes reduce breast cancer mortality by about one-third [89, 98]. Non-anthracycline, taxane-based regimens, such as four cycles of docetaxel and cyclophosphamide (TC), may be used as an alternative to four cycles of anthracycline- based chemotherapy in selected patients (i.e. those at risk of cardiac complications). No robust, prospective randomised data exist on the use of platinum compounds in the adjuvant setting, either in unselected triple-negative tumours or BRCA 1/2 mutation carriers. Therefore, its use cannot be recommended for routine use. Chemotherapy is usually administered for 12–24 weeks (four to eight cycles), depending on the individual recurrence risk and the selected regimen.[26] Chemotherapy is commonly given after surgery and usually include a combination of chemotherapy drugs including doxorubicin, epirubicin, paclitaxel, docetaxel, carboplatin and cisplatin. A chemotherapy combination called FEC-T (Flurouracil (5FU), Epirubicin, Cyclophosphamide and T-Docetaxel (Taxotere) may also be given.[28]

Cancer Research UK suggests chemotherapy with a combination of drugs that might include: doxorubicin, epirubicin, paclitaxel, docetaxel, carboplatin, cisplatin. It is reported that patients might be given a combination called FCE-T (Fluorouracil (5FU), Epirubicin, Cyclophosphamide, Docetaxel (Taxotere)).[8]

EFFICACY and SAFETY

Trial	KEYNOTE-522, NCT03036488, 2016-004740-11; Pembrolizumab neoadjuvant therapy vs placebo in neoadjuvant therapy, both in combination with chemotherapy, vs pembrolizumab vs placebo as adjuvant therapy; phase III
Sponsor	Merck Sharp & Dohme Ltd
Status	Ongoing
Source of Information	Trial Registry[2]
Location	EU (incl UK) USA, Canada, and other countries
Design	Randomised, parallel assignment, double-blind
Participants	N= 1150 (planned); aged 18 years and older; males and females; newly diagnosed, locally advanced, non-metastatic ,centrally confirmed TNBC; previously untreated
Schedule	Randomised to: Pembrolizumab every 3 weeks (Q3W) + paclitaxel weekly + carboplatin (weekly or every three weeks) x 4 cycles, followed by pembrolizumab Q3W + (doxorubicin OR epirubicin) + cyclophosphamide Q3W x 4 cycles as neoadjuvant therapy prior to surgery; followed by 9 cycles of pembrolizumab Q3W as adjuvant therapy post-surgery. Each cycle is 21 days. Or Placebo (normal saline solution) Q3W + paclitaxel weekly + carboplatin (weekly or Q3W) x 4 cycles, followed by placebo + (doxorubicin OR epirubicin) + cyclophosphamide Q3W x 4 cycles as neoadjuvant therapy prior to surgery; followed by 9 cycles of placebo Q3W as adjuvant therapy post-surgery. Each cycle is 21 days.
Follow-up	Active treatment period: approximately 24 weeks Follow up period: 8 years
Primary Outcomes	• Pathological complete response (pCR) rate using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; non-invasive breast residuals allowed) at the time of definitive surgery [Time Frame: Up to approximately 27-30 weeks] • Event-free Survival (EFS) as assessed by Investigator [Time Frame: Up to approximately 8 years]
Secondary Outcomes	• pCR rate using an alternative definition, ypT0 ypN0 (i.e., no invasive or non-invasive residual in breast or nodes) at the time of definitive surgery [Time Frame: Up to approximately 27-30 weeks] • pCR rate using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; non-invasive breast residuals allowed) at the time of definitive surgery in participants with tumours expressing programmed cell death - ligand 1 (PD-L1) [Time Frame: Up to approximately 27-30 weeks] • EFS in participants with tumours expressing PD-L1 [Time Frame: Up to approximately 8 years] • pCR rate using an alternative definition, ypT0 ypN0 (i.e., no invasive or non-invasive residual in breast or nodes) at the time of definitive surgery in participants with tumours expressing PD-L1 [Time Frame: Up to approximately 27-30 weeks] • pCR rate using an alternative definition, ypT0/Tis (i.e., absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal

	involvement) at the time of definitive surgery [Time Frame: Up to approximately 27-30 weeks] • Overall survival (OS) [Time Frame: Up to approximately 8 years] • Percentage of participants who experience an adverse event (AE) [Time Frame: Up to approximately 61 weeks] • Percentage of participants who discontinue study treatment due to an AE [Time Frame: Up to approximately 57 weeks] • European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 Questionnaire (QLQ-C30) score [Time Frame: Up to approximately 27-30 weeks] • EORTC Breast Cancer-Specific QoL Questionnaire (QLQ-BR23) score [Time Frame: Up to approximately 27-30 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date November 2018. Estimated study completion date March 2025.

ESTIMATED COST and IMPACT

COST

The NHS indicative price for a vial of pembrolizumab (100mg per 4ml vial) is £2630 (hospital only).[30]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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