Innovation Observatory

NHS National Institute for Health Research

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Pembrolizumab in addition to chemotherapy for locally recurrent, inoperable or metastatic triple-negative breast cancer - first line

NIHRIO ID	24236	**NICE ID**	10032
Developer/Company	Merck Sharp & Dohme Ltd (MSD)	**UKPS ID**	647713

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

SUMMARY

Pembrolizumab, in addition to chemotherapy, is in clinical development for adults with triple-negative breast cancer (TNBC) that is locally recurrent, inoperable or metastatic. TNBC is an uncommon type of breast cancer whose cells do not have receptors for the hormones oestrogen and progesterone or HER2 protein. This means that many cancer treatments do not work for people with TNBC. Patients with TNBC have worse clinical outcomes and a unique pattern of recurrence compared with the other major subtypes of breast cancer. Patients with TNBC have been shown to have the highest rate of recurrence within the first 5 years after diagnosis.

Pembrolizumab is a drug administered by intravenous infusion which stimulates the body's own immune system to fight cancer cells. If licensed, pembrolizumab in addition to chemotherapy could provide an alternative first line treatment option to patients who currently have limited treatment options for locally recurrent or metastatic TNBC not previously treated with chemotherapy.

PROPOSED INDICATION

Locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) in adults - first line therapy. [1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda) 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]

Pembrolizumab is in clinical development for patients with previously untreated locally recurrent inoperable or metastatic triple negative breast cancer. In the phase III trial (MK-3475-355/KEYNOTE-355; NCT02819518), pembrolizumab is administered by intravenous infusion (IV) at 200mg on day 1 of each 21-day cycle in addition to one of three chemotherapy regimens: 1) nab-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 of each 28-day cycle, 2) paclitaxel 90 mg/m^2 IV on days 1, 8 and 15 of each 28-day cycle, or 3) gemcitabine/carboplatin 1000 mg/m^2 (gemcitabine) and an Area Under the Curve 2 (carboplatin) on days 1 and 8 of each 21-day cycle. Duration of treatment is not reported.[1]

INNOVATION AND/OR ADVANTAGES

Chemotherapy is the only available non-investigational systemic treatment option for non-BRCA-mutated advanced TNBC, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds.[3] Trials have shown that immunotherapy (including checkpoint inhibitors such as pembrolizumab) administered with chemotherapy works better than immunotherapy alone, as chemotherapy may make the checkpoint blockade more effective.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is licensed in the EU/UK as a monotherapy for the treatment of:[2]

- 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 EGFR or ALK positive tumour mutations – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen
- adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant 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

- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy

The most common side effects of pembrolizumab (affecting more than one in ten people) include diarrhoea, nausea, rash, pruritus and fatigue.[2]

The combination of pembrolizumab and chemotherapy is also in development for:

- Non-small-cell lung cancer (squamous and non-squamous)
- Head and neck cancer
- Sarcoma
- Oesophageal cancer
- Urothelial cancer
- Gastric cancer and gastro-oesophageal junction cancer
- Cervical cancer

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.[5] Locally recurrent breast cancer occurs when the cancer affects the area of the breast after treatment. Metastatic breast cancer occurs when the cancer has spread to other parts of the body, such as the liver or bones.[6]

Triple-negative breast cancer (TNBC) is an uncommon type of breast cancer where the cells do not have receptors for the hormones oestrogen and progesterone or HER2 protein. Consequently, patients with TNBC do not respond to hormone treatment therapies targeted at HER2 receptors. Some women with TNBC also have a BRCA1 gene fault, which can increase the risk of breast cancer within families.[7] TNBC is more common in women under 40 years of age and black women.[8]

Patients with TNBC have worse clinical outcomes and a unique pattern of recurrence compared with the other major subtypes of breast cancer (HR+ and HER2+). Patients with TNBC have been shown to have the highest rate of recurrence within the first 5 years after diagnosis, with a significant decrease and plateauing of the recurrence rate afterwards. Post-recurrence survival is also decreased compared to patients with HR+ tumours.[9]

Symptoms of TNBC are similar to other breast cancer types, and can include a lump or thickening in an area of the breast, changes in the size, shape or feel of the breast or nipple, or a swelling in the armpit.

Breast cancer patients experience physical symptoms and psychosocial distress that adversely affect their quality of life (QOL). Treatment, including chemotherapy, can cause physical and psychological problems that adversely affect patient QOL, and cancer can have other effects including anger, grief, suffering and pain.[10]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that round 15% of breast cancers are triple-negative.[7]

In England in 2016 there were 45,960 registrations of newly-diagnosed breast cancer (ICD-10 C50).[11] Using the above estimate, this would equate to 6,894 cases of TNBC. Statistics from Cancer Research UK report that in UK in 2014 there were 54,833 observed cases of breast cancer, an age-standardised rate of 204.93 per 100,000, and predict that this will increase to 71,022 cases in 2035, with an age-standardised rate of 209.51 per 100,000.[12]

In England and Wales in 2017, there were 10,219 deaths with malignant neoplasm of breast (ICD-10 code C50) recorded as the underlying cause.[13] The latest published survival statistics for breast cancer for women in England (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 95.6% and 5-year survival rate of 86.0% (age-standardised).[14]

In England in 2016/2017 there were 203,454 hospital admissions with a primary diagnosis of malignant neoplasm of breast (ICD-10 code C50), resulting in 85,801 bed days and 169,800 day cases.[15]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

The main treatments for TNBC are surgery and chemotherapy, depending on where the cancer is, the stage and grade of the cancer confirmed by pathology, and the patient's general health. Surgery may be a lumpectomy (usually followed by radiotherapy to the rest of the breast tissue) or a mastectomy. Chemotherapy may be given before surgery, and is also usually given following surgery.[7]

Systemic sequential therapy should be offered to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. Combination chemotherapy should be considered to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.[16]

CURRENT TREATMENT OPTIONS

NICE recommends for patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), single-agent docetaxel should be offered as first line.[16]

NICE recommends gemcitabine in combination with paclitaxel, within its licensed indication, as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[17]

European guidelines recommend that in advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.[3]

PLACE OF TECHNOLOGY

If licenced, pembrolizumab in addition to chemotherapy may offer an additional first line treatment option for patients with locally recurrent inoperable or metastatic triple-negative breast cancer.

CLINICAL TRIAL INFORMATION

Trial	MK-3475-355/KEYNOTE-355, NCT02819518, EudraCT 2016-001432-35; pembrolizumab vs placebo, both in addition to chemotherapy; phase III
Sponsor	Merck Sharp & Dohme Ltd (MSD)
Status	Ongoing
Source of Information	Trial registry[1], search portal[18]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled
Participants	n=858 (planned); aged 18 yrs and older; breast cancer; triple-negative; locally recurrent inoperable or metastatic; first line
Schedule	Part 1: Randomised to pembrolizumab 200 mg intravenously (IV) on Day 1 of each 21-day cycle plus nab-paclitaxel 100 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle; or pembrolizumab 200 mg IV on Day 1 of each 21-day cycle plus paclitaxel 90 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle; or pembrolizumab 200 mg IV on Day 1 of each 21-day cycle plus gemcitabine/carboplatin 1000 mg/m^2 (gemcitabine) and an Area Under the Curve (AUC) 2 (carboplatin) on Days 1 and 8 of each 21-day cycle. Part 2: Randomised to pembrolizumab 200 mg IV on Day 1 of each 21-day cycle plus one of three chemotherapy regimens: 1) nab-paclitaxel 100 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle, 2) paclitaxel 90 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle, or 3) gemcitabine/carboplatin 1000 mg/m^2 (gemcitabine) and an AUC 2 (carboplatin) on Days 1 and 8 of each 21-day cycle; or placebo (normal saline) IV on Day 1 of each 21-day cycle plus one of three chemotherapy regimens: 1) nab-paclitaxel 100 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle, 2) paclitaxel 90 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle, or 3) gemcitabine/carboplatin 1000 mg/m^2 (gemcitabine) and an AUC 2 (carboplatin) on Days 1 and 8 of each 21-day cycle
Follow-up	Response will be assessed at wk 8, 16, 24, then at 9-wk intervals up to 1 y, and at 12-wk intervals thereafter
Primary Outcomes	Part 1: % of participants who experience an adverse event (AE) [Time Frame: up to 44 mths] % of participants who discontinue study due to an AE [Time Frame: up to 41 mths] Part 2: Progression-free survival - all participants and participants with PD-L1 positive tumours [Time Frame: up to 41 mths]

	Part 2: Overall survival - all participants and participants with PD-L1 positive tumours [Time Frame: up to 41 mths]
Secondary Outcomes	All Part 2, Time Frame up to 41 mths unless otherwise stated Objective response rate - all participants and participants with PD-L1 positive tumours Duration of response - all participants and participants with PD-L1 positive tumours Disease control rate - all participants and participants with PD-L1 positive tumours % of participants who experience an AE [Time Frame: up to 44 mths] % of participants who discontinue study due to an AE
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Dec 2019

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs £2,630, and 50mg powder for concentrate for solution for infusion vial costs £1,315.[19]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (TA263). August 2012.
- NICE technology appraisal guidance. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (TA214). February 2011.
- NICE technology appraisal guidance. Gemcitabine for the treatment of metastatic breast cancer (TA116). January 2007.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 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.

OTHER GUIDANCE

- European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[3]

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[11] Office for National Statistics. *Cancer Registration Statistics, England, 2016*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Downloaded 24 August 2018] [Accessed 28 August 2018]

[12] Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four . [Downloaded 9 March 2018] [Accessed 28 August 2018]

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