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Pembroluzimab (Keytruda®) for triple negative breast cancer

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LAY SUMMARY

Breast cancer is the most common cancer in the UK. Triple negative breast cancer is an uncommon type of breast cancer. These types of cancer do not have receptors for the hormones oestrogen and progesterone, or Her2 protein. This characteristic rules out the option of hormone based treatments.

Pembrolizumab is a type of immunotherapy. It stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein triggers the T-cells to find and kill cancer cells. It is administered as a drip into a vein for 30 minutes every three weeks for up to 35 cycles.

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TARGET GROUP

Breast cancer: metastatic; triple negative – second/third line

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda® ; MK-3475; MK3475; SCH900475; SCH-900475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation and plays a key role in in tumour evasion from host immunity.[1] Keytruda® is the branded name for this drug.

In the ongoing Phase III trial NCT02555657/KEYNOTE-119 due for completion in May 2017 participants receive pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations.

Pembrolizumab is currently licensed in the EU under its commercial name Keytruda for the following indications:

- Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- Keytruda as monotherapy is indicated for the first-line treatment of 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.
- Keytruda as monotherapy is indicated for the treatment of 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 Keytruda.
- Keytruda as monotherapy is indicated for the treatment of 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.

The most common side effects with Keytruda (which may affect more than 1 in 10 people) are diarrhoea, nausea (feeling sick), itching, rash, joint pain and tiredness, most of which are mild to moderate in severity. Other common side effects of Keytruda related to the activity of the immune system causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping Keytruda.[2]

Additional Phase III trials of pembrolizumab are registered for the following indications:

- Head/Neck 1L: NCT02358031
- Head/Neck 2L: NCT02252042
- Gastroesophageal /Gastric 1L: NCT02678572

- Colorectal 1L: NCT02563002
- Esophageal/Esophagogastric 2L: NCT02564263
- 2L Gastric/Gastroesophageal NCT02370498
- Multiple Myeloma 1L: NCT02579863
- Multiple Myeloma 3L or beyond: NCT02576977
- Bladder/Renal 1L: NCT02853305
- Bladder/Renal 2L: NCT02256436
- Mesothelioma 2L: NCT02991482
- Liver 2L: NCT03062358
- Non-Small Cell Lung Cancer 1L: NCT02220894
- Small Cell Lung Cancer 1L: NCT03066778

INNOVATION and/or ADVANTAGES

Pembrolizumab has the potential to extend progression free and/or overall survival compared to common treatment with chemotherapy agents Trastuzumab, Paclitaxel and Carboplatin (TPC).

DEVELOPER

Merck Sharp & Dohme Corp.

AVAILABILITY, LAUNCH or MARKETING

PATIENT GROUP

BACKGROUND

Breast cancer arises from the tissues of the breast and most commonly originates in the cells that line the ducts. There are several types of breast cancer described according to the receptors expressed on the surface of tumour cells, stage of diagnosis, and rate of growth.[3] Hormone-receptor positive (HR+) breast cancer includes disease in which tumour cells express either oestrogen receptors (ER+) or progesterone receptors (PR+).[4] Approximately 80% of breast cancers in postmenopausal women are HR+3 and around two-thirds of breast cancers are ER+. Human epidermal growth factor receptors (HER2) are overexpressed in around 15-25% of women with breast cancer and promote tumour growth.[5] HER2-negative breast cancer refers to disease that does not overexpress HER24.[4] Both HR+ and HER2- negative breast cancers are associated with a better prognosis than HR-negative and HER2-positive disease.

Advanced or metastatic (stage IV) breast cancer refers to disease that has spread to other parts of the body. Common sites for metastases include the bones, liver, lung and brain. 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.[6] The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes (e.g. BRCA2, BRCA1 and TP53).

Breast cancer in adults can occur at any age, though there is an increased risk in postmenopausal women, and a previous benign breast lump or diagnosis of early breast cancer further increases the risk.[6] Breast cancer is normally characterised by a lump or thickened tissue in the breast area, however not all lumps will be cancerous. Other features include a change in breast size or shape, discharge from the nipple (which may include blood), lumps/swelling in armpits, dimples on the skin of the breast and a rash around the nipple area. Symptoms include pain in the breast or axilla and signs and symptoms can occur in one or both breasts.[6]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, breast cancer is the most common cancer; 15 per cent of all newly diagnosed cancers are breast cancer. One in eight women and one in 870 men develop breast cancer during their lifetime. Most of the women who get breast cancer have had their menopause, but about two out of every 10 (20%) are under 50 years old.[7] Breast cancer risk is strongly related to age, and while the incidence of breast cancer is highest in those from higher socioeconomic groups, survival is lowest in those from lower socioeconomic groups. Family history and lifestyle factors such as obesity and smoking are additional risk factors.

Breast cancer that is negative for ER, PR and HER2 are referred to as triple negative and account for about 12-15% of all breast cancers.[8]

Ten year survival rates in women with breast cancer in the UK is 78 per cent.[9] Five-year survival rates tend to be lower for TNBC than for other forms of breast cancer.[10]

Relative survival rates for breast cancer in England are below the average for Europe (82%). Scotland (79%) and Wales (78%) are also below the European average with Northern Ireland similar to the average for Europe (82%).[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (TA263). Aug 2012
- NICE Technology Appraisal. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (TA214). Feb 2011

- NICE guidelines. Early and locally advanced breast cancer: diagnosis and treatment (CG80) Feb 2009 last updated Mar 2017

- NICE Quality Standard. Breast cancer (QS12). Sep 2011 last updated Jun 2016

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 Mutations. NHS England E01/P/b. July 2015
- 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

- European Society for Medical Oncology. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). 2014.[11]
- American Society of Clinical Oncology. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women with Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. 2015.[12]
- European Society for Medical Oncology. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2013.[13]
- Scottish Intercollegiate Guidelines Network. Treatment of primary breast cancer (134). 2013.[14]
- European Society for Medical Oncology. BRCA in Breast Cancer: ESMO Clinical Practice Guidelines. 2011[15]

CURRENT TREATMENT OPTIONS

Hormone therapy is not usually an effective treatment for TNBC. Treatment often involves a combination of surgery, radiotherapy and chemotherapy.

Emerging treatments such as poly polymerase (PARP) enzyme inhibitors are promising.[16] In England, the main chemotherapy treatment for triple negative breast cancer is usually a combination of chemotherapy drugs. The combination should include a type of chemotherapy drug called an anthracycline, such as doxorubicin or epirubicin.[17,18]

EFFICACY and SAFETY

Trial	NCT02555657; KEYNOTE-119	NCT02447003; KEYNOTE-086
Sponsor	Merck Sharp & Dohme Corp.	Merck Sharp & Dohme Corp.
Status	Ongoing, but not recruiting participants	Ongoing, but not recruiting participants
Source of Information	Trial registry[19]	Trial registry[20]

Location	Countries in SE Asia and Latin America.	Australia, New Zealand and USA, Belgium, France, Germany, Italy, Puerto Rico, United Kingdom
Design	Randomised and controlled.	Non-randomised
Participants	N=600; aged 18 years and older; Metastatic Triple Negative Breast Cancer	N=285; aged 18 years and older; Breast Cancer
Schedule	Participants receive pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations; Participants receive capecitabine, eribulin, gemcitabine, or vinorelbine as TPC in accordance with local regulations and guidelines.	Participants receive pembrolizumab, 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 24 months
Follow-up	Active treatment period for up to 28 months, follow-up period 28 months.	Follow-up period 24 months.
Primary Outcomes	Progression Free Survival (PFS); Overall Survival (OS)	Overall Response Rate; Number of Participants Experiencing at Least One Adverse Event (AE); Number of Participants Discontinuing Study Drug Due to AEs
Secondary Outcomes	Overall Response Rate (ORR); Disease Control Rate (DCR); progression free survival	Not reported
Key Results	-	Among 111 patients with TNBC whose tumour samples were screened for PD-L1 expression, 58.6% had PD-L1-positive tumours. Thirty-two women (median age, 50.5 years; range, 29 to 72 years) were enrolled and assessed for safety and antitumor activity. The median number of doses administered was five (range, 1 to 36 doses). Common toxicities were mild and similar to those observed in other tumour cohorts (e.g. arthralgia, fatigue, myalgia, and nausea), and included five (15.6%) patients with grade

		≥ 3 toxicity and one treatment-related death. Among the 27 patients who were evaluable for antitumor activity, the overall response rate was 18.5%, the median time to response was 17.9 weeks (range, 7.3 to 32.4 weeks), and the median duration of response was not yet reached (range, 15.0 to ≥ 47.3 weeks)[16, 21]. Bets overall response; complete response (3.7%); partial response (14.8%), stable disease (25.9%), and progressive disease (48.1%) was also reported. [21] Overall, 37.5% of patients experienced a decrease from baseline in tumour burden. The disease control rate (ie, percentage of patients with best response of CR, PR, or SD for >= 24 weeks) was 25.9% (95% CI, 11.1% to 46.3%).[21] Twenty-two PFS events were observed, and the median PFS was 1.9 months (95% CI, 1.7 to 5.5), with a 6-month PFS rate of 24.4%. The median OS was 11.2 months (95% CI, 5.3 to [not reached]), with 6-month and 12-month OS rates of 66.7% and 43.1%, respectively. [21]
Adverse effects (AEs)	-	Number of Participants Experiencing at Least One Adverse Event (AE); Number of Participants Discontinuing Study Drug Due to AEs
Expected reporting date	Study completion date reported as November 2017	Study completion date reported as December 2018

ESTIMATED COST and IMPACT

COST

The cost of pembrolizumab for this indication is not yet known. However, pembrolizumab is approved for use in the UK for the treatment of advanced melanoma.

The current medicinal product price registered in the NHS is for Keytruda 100mg/4ml concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial at £2,630.00[22] and for Keytruda 50mg powder for concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial is £1,315.00.[22,23]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other: *specify, e.g. improved quality of life for carers, improved patient convenience, wider societal benefits (e.g. earlier return to normal activities, including employment) etc.*

☐ 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: *specify, e.g. new staff training requirements, requirement for new facilities, specialist laboratory testing, etc.*

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs: *specify, e.g. new specialist clinics required, capital investment required, additional staff training required, additional costs for IV administration in clinic, more patients eligible for treatment, etc.*

☐ Other reduction in costs: *specify, e.g. reduced use of secondary care/specialist services, reduced need for interventional procedures, reduced social care costs, etc.*

☒ Other: *specify, e.g. uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*

☒ None identified

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