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Pembrolizumab (KEYTRUDA®) for advanced, metastatic oesophageal cancer – second line

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LAY SUMMARY

Oesophageal cancer is the fourteenth most common cancer in the UK. This type of cancer affects the oesophagus (gullet), which is the long muscular tube that carries food from the throat to the stomach as part of the digestive process. However, advanced or metastatic cancers mean the cancer has spread to other parts of the body. The most common types of oesophageal cancer are squamous cell carcinoma and adenocarcinoma. Symptoms of these types of oesophageal cancer include swallowing difficulty, persistent acid indigestion or heartburn, weight loss and regurgitation of food. The main risk factors for oesophageal cancer are excessive alcohol consumption, smoking, being overweight or obese, unhealthy diet, increasing age, and having certain other medical conditions.

The most common treatment options for oesophageal cancer in the UK is surgery; alternative treatments are radiotherapy and chemotherapy. Pembrolizumab is a type of immunotherapy, which works targeting specific proteins that stimulates an immune response that targets the cancer cells. It increases the body's natural ability to identify and attack cancer cells. If licenced, pembrolizumab will offer an additional treatment option for patients with oesophageal cancer and prolong the time without cancer progression.

TARGET GROUP

Oesophageal cancer (advanced/metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert Type I adenocarcinoma of the esophagogastric junction) – second line

TECHNOLOGY

DESCRIPTION

Pembrolizumab (KEYTRUDA®, lambrolizumab, MK-3475) [1, 2, 3] 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 adenomatous polyposis coli (APCs). Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity.[4]

Pembrolizumab is currently licensed in the EU for the following indications: [5,6]

Pembrolizumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Pembrolizumab 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.

Pembrolizumab 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.

Pembrolizumab 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.

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

Pembrolizumab is also globally in Phase III clinical trials or preregistration for the following indications:

- Bladder cancer
- Head and neck cancer
- Laryngeal cancer

- Oropharyngeal cancer
- Gastric cancer
- Breast cancer
- Small-cell lung cancer
- Hepatocellular carcinoma
- Hypopharyngeal cancer
- Colorectal cancer
- Renal cell carcinoma
- Urothelial cancer
- Oral cavity cancer
- Ureter cancer
- Urethral cancer.[3]

In the phase III clinical trial participants receive pembrolizumab 200mg intravenously (IV) on Day 1 of every 21-day (3-week) cycle (Q3W) for up to 35 administrations (approximately 2 years).[7]

INNOVATION and/or ADVANTAGES

Drugs targeting the PD-1 pathway may provide antitumor immunity, especially in PD-L1 positive tumours. Various cancers, such as melanoma, hepatocellular carcinoma, glioblastoma, lung, kidney, breast, ovarian, pancreatic, and oesophageal cancers, as well as haematological malignancies, have positive PD-L1 expression, and this expression has been correlated with poor prognosis.[8]

If licenced, pembrolizumab will offer an additional treatment option and prolong progression free survival for patients with second line, advanced, metastatic oesophageal cancer.

DEVELOPER

Merck Sharp & Dohme Ltd

AVAILABILITY, LAUNCH or MARKETING

Pembrolizumab for oesophageal cancer received orphan drug designation by the FDA in June 2017.[9]

PATIENT GROUP

BACKGROUND

Oesophageal cancer affects the oesophagus, which is part of the digestive system. However, if the cancer is advanced it means it has spread to another part of the body. The most common types of oesophageal cancer, accounting for over 95% of cases, are squamous cell carcinoma (SCC) and adenocarcinoma (AC).[10] The type of oesophageal cancer defines the location and type of cells involved in the cancer development. Squamous cell cancers develop from the cells that make up the inner lining of the oesophagus. They tend to develop in the upper and middle part of the oesophagus. Adenocarcinoma are cancers that develop in the glands within the oesophagus. These cells make mucus in the lining of the oesophagus and usually start in the lower part of the oesophagus.[11] Defined by Siewert and Stein, adenocarcinomas of the oesophagogastric junction (AEG) are classified into three subtypes: type I, adenocarcinoma of the distal oesophagus with the centre located within 1-5 cm above the anatomic oesophagogastric junction (EGJ); type II, true carcinoma of the cardia with the

tumour centre within 1 cm above and 2 cm below the EGJ; type III, subcardial carcinoma with the tumour centre between 2-5 cm below EGJ, which infiltrates the EGJ and distal oesophagus from below.[12]

Symptoms of oesophageal cancer include difficulty swallowing, persistent acid indigestion or heartburn, weight loss, regurgitation of food; pain in the throat or behind the breastbone, hoarseness, chronic cough, coughing up blood, and dark stool.[13]

Ninety percent of oesophageal cancer cases are attributed to lifestyle factors, such as being overweight or obese, smoking or using tobacco, alcohol consumption and not eating enough fruit and vegetables. Oesophageal cancer occurs most commonly amongst older people, with 80% of occurrences being in people aged 60 years or older.[14]

CLINICAL NEED and BURDEN OF DISEASE

Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cases. In 2014 there were 8,919 new cases of oesophageal cancer in the UK, whereby 6,019 (67%) occurred in men and 2,900 (33%) in women. The crude incidence rate shows that there are 19 new oesophageal cancer cases for every 100,000 males in the UK, and 9 for every 100,000 females. This cancer is strongly related to age, with the highest incidence rates being in older men and women. On average oesophageal cancer is diagnosed in people aged 70 and over. Age specific incidence rates rise sharply from around age 45-49, with the highest rates in the 90+ age group.[15]

SCC (ICD-O M805-M808) accounted for more than a quarter (28%) of all oesophageal cancer cases, while AC (ICD-O M814-M838) accounted for more than half (55%) in England in 2008-2010.[15]

Oesophageal cancer accounted for 7,790 deaths in 2014 in the UK. 44% of men survive oesophageal cancer for at least one year, and this is predicted to fall to 16% surviving for five years or more. For women the survival is slightly lower at one year (38%) but similar at five years (15%). Most people with advanced cancer live for between 3 to 12 months after their cancer is diagnosed. Around 4 out of 100 people live for 5 years or more.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer (ID1096). Expected October 2018.
- NICE technology appraisal guidance in development. Nivolumab for previously treated gastric or gastro-oesophageal junction cancer (ID1118). Expected February 2018.
- NICE technology appraisal guidance. Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy (TA378). January 2016.
- NICE interventional procedures guidance. Palliative photodynamic therapy for advanced oesophageal cancer (IPG206). January 2007.
- NICE interventional procedures guidance. Photodynamic therapy for early-stage oesophageal cancer (IPG200). December 2006.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/S/a.
- NHS England. Clinical Commissioning Policy: Robotic assisted surgery for oesophagus-gastric cancers. 16006/P. July 2016.

OTHER GUIDANCE

No other guidance identified.

CURRENT TREATMENT OPTIONS

Treatment options for oesophageal cancer depend on how far the cancer has spread. In earlier stages (I-III) oesophageal cancer is usually treated with surgery in order to remove the affected section of oesophagus. To make surgery more effective, chemotherapy or radiotherapy may be given before removal of the tumour in order to reduce its size. Stage IV cancers usually spread too far to get it removed with surgery. Hence, chemotherapy and radiotherapy may be used to slow the spread of disease and relieve symptoms.[17]

Three different types of surgery can be conducted: Oesophagectomy, whereby the tumour containing section of the oesophagus is removed and, if necessary, the nearby lymph nodes; Endoscopie mucosal resection (EMR), it involves cutting out the tumour using a loop of wire at the end of an endoscope, which is passed down the throat; stents, expands and holds the oesophagus open in case swallowing difficulties arise.[17]

Neo-adjuvant chemotherapy aims to improve operability by shrinking the tumour. Cisplatin, 5-flourouracil, epirubicin and capecitabine showed significant improvements in progression free survival. Paclitaxel, irinotecan, gemcitabine and nedaplatin may be used in combination with others to treat oesophageal cancer.[18] Carboplatin and oxaliplatin are used in regimens for either preoperative chemoradiation or definite chemoradiation.[19]

Advanced metastatic oesophageal cancer is cancer that has spread to other distant sites in the body, such as lungs or liver. It can therefore not be removed completely with surgery. The majority of patients with advanced, recurrent or metastatic disease are not treated with curative intent. A number of palliative treatment options are available for this group of patients to relief the symptoms and prolong and maximise their quality of life. Hereby, in addition to other treatment options mentioned above, palliative radiotherapy, dysphagia, laser-thermal endoluminal tumour destruction or photodynamic therapy might be used.[18]

EFFICACY and SAFETY

Trial	MK-3475-181/KEYNOTE-181, NCT02564263, EudraCT-2015-002782-32, Phase III
Sponsor	Merck Sharp & Dohme Ltd
Status	Ongoing, recruiting participants.
Source of Information	Trial registry[20]
Location	EU (incl UK), USA, countries in Asia and Latin America

Design	Randomized, active-controlled
Participants	N=600 (planned); >= 18 years old; Histologically- or cytological-confirmed diagnosis of adenocarcinoma or squamous cell carcinoma of the oesophagus or Siewert type I adenocarcinoma of the EGJ, Metastatic disease or locally advanced, unresectable disease; Life expectancy of greater than 3 months; Measurable disease based on Response Evaluation Criteria In Solid Tumours (RECIST) 1.1; Documented radiographic or clinical disease progression on no more or less than one previous line of standard therapy; Can provide either a newly obtained or archival tumour tissue sample for intra-tumoral immune-related testing and for anti-programmed cell death (PD)-1; Participants of reproductive potential must be willing to use adequate contraception for the course of the study through 120 days after the last dose of pembrolizumab or through 180 days after the last dose of paclitaxel, docetaxel or irinotecan; Adequate organ function;
Schedule	Participants receive pembrolizumab 200 mg, intravenously (IV) on Day 1 of every 21-day (3-week) cycle (Q3W) for up to 35 administrations (approximately 2 years) Active comparator. Standard therapy: Participants receive Investigator's choice of paclitaxel 80-100 mg/m^2 IV on Days 1, 8, and 15 of every 28-day (4-week) cycle, OR docetaxel 75 mg/m^2 IV on Day 1 of every 21-day (3-week) cycle, OR irinotecan 180 mg/m^2 IV on Day 1 of every 14-day (2-week) cycle.
Follow-up	Not reported
Primary Outcomes	Progression-free Survival (PFS) Overall Survival (OS)
Secondary Outcomes	Objective Response Rate (ORR)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date May 2018. Estimated study completion date August 2018.

ESTIMATED COST and IMPACT

COST

Pembrolizumab is already marketed in the UK for other indications. The list price per 50mg vial is £1,315.[21] The company has a signed commercial access agreement (CAA) with the Department of Health and NHS England, and this scheme provides a discount to the list price of pembrolizumab. The level of the discount is commercial in confidence.[22]

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

INFORMATION FROM

Merck Sharp & Dohme Ltd

UK PharmaScan ID number 642402

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