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HEALTH TECHNOLOGY BRIEFING DECEMBER 2019

Pembrolizumab in addition to cisplatin and fluorouracil for recurrent locally advanced or metastatic oesophageal cancer – First-line

NIHRIO ID	23790	**NICE ID**	10209
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	649921

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

SUMMARY

Pembrolizumab in addition to cisplatin and fluorouracil is being developed for patients with recurrent locally advanced or metastatic oesophageal cancer. Advanced or metastatic oesophageal cancer begins in the food pipe and spreads to other parts of the body. Symptoms include difficulty swallowing, persistent acid indigestion or heartburn, weight loss, pain in the throat, and chronic cough. Lifestyle factors are attributed to most oesophageal cancers, including smoking and being overweight. Advanced or metastatic cancer cannot usually be cured and current treatment with chemotherapy aim to control the disease, relieve symptoms, and give patients a better quality of life.

Pembrolizumab is administered by intravenous infusion and works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Cisplatin and fluorouracil are both standard chemotherapies that are used in treating many different types of advanced or metastatic cancers. If licensed, pembrolizumab in combination with cisplatin and fluorouracil may offer an additional treatment option for patients with recurrent locally advanced or metastatic oesophageal cancer.

PROPOSED INDICATION

First-line treatment of recurrent locally advanced or metastatic oesophageal cancer in adults.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody (mAb) 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 in addition to cisplatin and fluorouracil is in clinical development for the first-line treatment of recurrent locally advanced or metastatic oesophageal cancer in adults. In the phase III clinical trials (NCT03189719; MK-3475-590/KEYNOTE-590), participants will receive pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W), cisplatin 80 mg/m^2 IV Q3W, and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours).[1]

INNOVATION AND/OR ADVANTAGES

Treatment options for patients with unresectable advanced or metastatic oesophageal or oesophagogastric junction cancer are limited. Current guidelines for the first-line treatment of advanced or metastatic disease recommend platinum-based chemotherapy in combination with fluoropyrimidine.[3]

The addition of pembrolizumab to standard chemotherapy may translate to superior effectiveness and improved patient outcomes. It is known that platinum salts can have an iatrogenic impact on cancer evolution via the generation of neoantigens when tumour cells are destroyed, and, in oesophageal cancers, these may be added to de novo mutations caused by common carcinogens, such as tobacco smoke and alcohol toxins. Because the mutational landscape can determine sensitivity to PD-1 blockade, the presence of these neoantigens may increase pembrolizumab effectiveness and influence tumour regression.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[4]

- advanced (unresectable or metastatic) melanoma in adults.
- adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- 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.
- 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.
- 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.
- as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.
- recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.

Pembrolizumab is also licensed in the UK in combination with:[4]

- pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

The most common adverse events of pembrolizumab as monotherapy and in combination with chemotherapy (affecting more than one in ten people) include anaemia, neutropenia, thrombocytopenia, hypothyroidism, hyperthyroidism, decreased appetite, hypokalaemia, headache, dizziness, neuropathy peripheral, dysgeusia, hypertension, dyspnoea, cough, dysphonia, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, alopecia, palmar-plantar, erythrodysaesthesia syndrome, musculoskeletal pain, arthralgia, pain in extremity, fatigue, asthenia, oedema, pyrexia, blood creatinine increased, alanine aminotransferase increased, and aspartate aminotransferase increased.[2]

Pembrolizumab is currently in phase II and III clinical trials for the treatment of multiple malignant conditions such as breast cancer, colorectal cancer, prostate cancer etc.[5]

PATIENT GROUP

DISEASE BACKGROUND

Oesophageal cancer is a type of cancer affecting the food pipe (oesophagus), the long tube that carries food from the throat to the stomach.[6] Most oesophageal cancers can be categorised into two main histologic subtypes: squamous cell carcinoma (SCC) and adenocarcinoma.[3] Cancer can develop in any part of the oesophagus: upper and middle part, lower part, and gastro oesophageal junction.[7]

The exact cause of oesophageal cancer is unknown, but the risk of developing oesophageal cancer depends on many things including: age, lifestyle (smoking, drinking too much alcohol over many years), being overweight or obese, having an unhealthy diet that is low in fruit and vegetables, and other medical conditions.[6,8]

The most common symptoms of oesophageal cancer include: difficulty swallowing (dysphagia), indigestion or heartburn that do not go away, weight loss, pain in the throat or behind the breastbone, and a cough that does not go away.[9]

Unfortunately advanced cancer cannot usually be cured. Treatments can control the disease, relieve symptoms, and give patients a better quality of life for a period of time. Sometimes cancer is advanced when it is first diagnosed or the cancer has come back and spread after treatment(s) for the original cancer. Cancers that have spread to another part of the body are called secondary cancer, metastases or metastatic cancer. Locally advanced cancer means that the cancer has spread into the tissues around the oesophagus. It has not spread to other organs.[10]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016, oesophageal cancer was the 14th most common cancer in the UK. There were approximately 9,100 new cases of oesophageal cancer in the UK in 2014-2016.[11] The age-standardised incidence rate in England for oesophageal cancer, in 2016, was 22.6 per 100,000 in males and 8.3 per 100,000 in females.[12]

Oesophageal cancer patients with a known stage are diagnosed at a late stage (70-80% are diagnosed at stage III or IV), than an early stage (21-30% are diagnosed at stage I or II). Between 37% and 42% of patients have metastases at diagnosis (stage IV).[13] In the UK, 31% of oesophageal cancer cases are in females, and 69% are in males.[12] According to 2010-2012 data in the UK, the largest proportion of oesophageal cancer cases occur in the lower third of the oesophagus, with much smaller proportions in the middle and upper thirds.[14]

In England, in 2018-2019, there were 40,807 finished consultant episodes (FCE) for malignant neoplasm of oesophagus (ICD 10: C15), resulting in 32,088 hospital admissions and 85,230 FCE bed days.[15]

According to 2010-2011 data, 15% of people diagnosed with oesophageal cancer in England and Wales survive their disease for five years or more.[16] Most people with advanced oesophageal cancer live for between 3 to 12 months after their cancer is diagnosed. Around 4 out of 100 people (4%) live for 5 years or more.[17]

Oesophageal cancer was the 7th most common cause of cancer death in the UK in 2017. Crude mortality rate in England was 11.6 per 100,000 in 2017.[18] Oesophageal cancer mortality is strongly related to age, with the highest mortality rates being in older people.[19] In the 2017 death registration in England and Wales, there were 6,905 deaths (4,812 males, 2,093 females) due to malignant neoplasm of oesophagus (C15) with the higher proportions in aged 65 and above.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment depends on several factors. These include the type of oesophageal cancer, how big it is and whether it has spread (the stage), and what the cancer cells look like under the microscope (grade). It also depends on patient general health. A team of health professional should discuss the best treatment and care for each individual patient.[21]

The main treatments for oesophageal cancer are surgery, radiotherapy, and chemotherapy. The patient may have one of these treatments or a combination. Chemotherapy combined with radiotherapy is called chemoradiotherapy. Patients might have it on its own as the main treatment, or before surgery.[21]

Chemotherapy uses anti-cancer (cytotoxic) drugs to destroy cancer cells. The chemotherapy might be delivered before or after surgery for oesophageal cancer. Common chemotherapy drugs for oesophageal cancer are fluorouracil, capecitabine, cisplatin and epirubicin.[22]

CURRENT TREATMENT OPTIONS

NICE recommendation about first-line palliative chemotherapy for locally advanced or metastatic oesophago-gastric cancer treatment include:[23]

- Trastuzumab (in combination with cisplatin and capecitabine or 5-fluorouracil) as a treatment option to people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:
  - have not received prior treatment for their metastatic disease and
  - have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

- First-line palliative combination chemotherapy to people with advanced oesophago-gastric cancer who have a performance status 0 to 2 and no significant comorbidities. Possible drug combinations include:
  - doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
  - triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in addition to cisplatin and fluorouracil will offer an additional option for the first-line treatment of recurrent locally advanced or metastatic oesophageal cancer in adults.

CLINICAL TRIAL INFORMATION

Trial	MK-3475-590/KEYNOTE-590, NCT03189719, 3475-590, EudraCT 2017-000958-19; adults aged ≥18 years; pembrolizumab vs. placebo, both arms in combination with cisplatin and 5-fluorouracil; phase III
Sponsor	Merck Sharp & Dohme Corp.
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (including the UK), Canada, United States and other countries
Design	Randomised, placebo-controlled, double-blind
Participants	n= 700 (planned); aged ≥18 years old; has histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the oesophago-gastric junction; has measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment; Eastern Cooperative Group (ECOG) performance status of 0 to 1; and adequate organ function
Schedule	Participants were randomised to receive: - Pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W), cisplatin 80 mg/m^2 IV Q3W, and 5-FU 800 mg/m^2/day continuous IV

	infusion on Days 1 to 5 (120 hours). All treatments will be administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle. - Placebo to pembrolizumab (saline) IV Q3W, cisplatin 80 mg/m^2 IV Q3W, and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours). All treatments will be administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.
Follow-up	Up to 2 years
Primary Outcomes	• Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in all participants [Time frame: up to 2 years] • PFS per RECIST Version 1.1 in PD-L1 biomarker-positive participants [Time frame: up to 2 years] • Overall Survival (OS) in all participants [Time frame: up to 2 years] • OS in PD-L1 biomarker-positive participants [Time frame: up to 2 years]
Secondary Outcomes	• Objective Response Rate (ORR) per RECIST 1.1 in all participants [Time frame: up to 2 years] • ORR per RECIST 1.1 in PD-L1 biomarker-positive participants [Time frame: up to 2 years] • Duration of Response (DOR) per RECIST 1.1 in all participants [Time frame: up to 2 years] • DOR per RECIST 1.1 in PD-L1 biomarker-positive participants [Time frame: up to 2 years] • Number of participants with an adverse event (AE) [Time frame: up to 27 months] • Number of participants with an adverse event (AE) [Time frame: up to 27 months] • Change from baseline in the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) Score [Time frame: baseline, end of treatment (~1 year)] • Change from baseline in the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18) Score [Time frame: baseline, end of treatment (~1 year)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as August 2021.

ESTIMATED COST

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[24]

- A 1 x 100 mg/4 ml concentrate for solution for infusion vial costs £2630.00
- A 1 x 50 mg powder for concentrate for solution for infusion vial costs £1315.00

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer (ID1096). Expected publication: TBC
- NICE technology appraisal guidance in development. Pembrolizumab for previously treated metastatic gastric or gastro-oesophageal junction cancer (ID1168). Expected publication: TBC
- NICE clinical guidelines. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.
- NICE quality standards. Oesophago-gastric cancer (QS176). December 2018.
- NICE interventional procedure guidance. Minimally invasive oesophagectomy (IPG407). September 2011.
- NICE interventional procedure guidance. Palliative photodynamic therapy for advanced oesophageal cancer (IPG206). January 2007.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy Proposition: 18F-flourodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) as part of radical radiotherapy treatment planning for oesophageal cancer (all ages). Published date to be confirmed.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/S/a.
- 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 of Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[25]

ADDITIONAL INFORMATION

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