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Newcastle University

Health Technology Briefing
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Pembrolizumab with radiotherapy and chemotherapy for treating unresectable oesophageal cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29275	NICE TSID: 11852	UKPS ID: 656641

Licensing and Market Availability Plans

Currently in phase 3 clinical development.

Summary

Pembrolizumab in combination with chemotherapy and radiotherapy is in clinical development for the treatment of unresectable, programmed death-ligand 1 positive (PD-L1+), squamous cell oesophageal cancer. This is a type of cancer that begins in the thin, flat cells lining the food pipe (oesophagus) and may spread to other parts of the body and is untreatable by surgery. Symptoms include difficulty swallowing, persistent indigestion or heartburn, weight loss, pain in the throat, and chronic cough. In the UK it is more common in older people (≥75 years old) and males. There is a need for new treatment options, including immunotherapies, as oesophageal cancer progresses rapidly and is associated with a high mortality.

Pembrolizumab is a drug administered intravenously and comprises a protein that has been designed to recognise and block a receptor ('target') called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system (the body's natural defences), preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licensed in combination with definitive chemoradiotherapy, pembrolizumab will offer an additional treatment option for patients with unresectable, PD-L1+, squamous cell oesophageal cancer who currently have few well tolerated and effective therapies available.

Proposed Indication

Treatment of oesophageal cancer patients receiving definitive chemotherapy and radiotherapy.[1]

Technology

Description

Pembrolizumab (MK-3475[1], 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]

In the phase III trial (NCT04210115, KEYNOTE-975), the safety and efficacy of treatment with definitive chemoradiotherapy and pembrolizumab will be evaluated in patients with oesophageal carcinoma who are ineligible for curative surgery. Participants will be intravenously (IV) administered with 200mg of pembrolizumab on day 1 of each 3-week cycle for 8 cycles followed by 400mg of pembrolizumab IV administered on day one of each 6-week cycle for 5 cycles. This will be given in combination with either FP therapy or FOLFOX therapy (types of chemotherapies) and radiotherapy.[1]

Key Innovation

Despite curative-intent treatment, most patients with locally advanced oesophageal cancer will experience disease recurrence or locoregional progression, highlighting the need for new therapies.[3] Current guidelines recommend definitive chemoradiotherapy in patients ineligible for surgical resection, but survival outcomes are poor. Pembrolizumab is well tolerated and provides promising antitumour activity in patients with previously treated, advanced, unresectable oesophageal cancer. Combining pembrolizumab with chemoradiotherapy, is a new combination and may further improve outcomes in the first-line setting.[3] If licensed, pembrolizumab in combination with chemotherapy and radiotherapy will provide an additional treatment option for patients oesophageal cancer.

Regulatory & Development Status

Pembrolizumab has a Marketing Authorisation in the EU/UK for the following indications:[2]

- Non-small cell lung cancer (NSCLC)
- Classical hodgkin lymphoma
- Melanoma
- Head and neck squamous cell carcinoma (HNSCC)
- Renal cell carcinoma
- Oesophageal cancer
- Triple-negative breast cancer
- Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers (colorectal and non-colorectal)
- Cervical cancer

Pembrolizumab is also in phase III clinical development for the treatment many indications, including but not limited to:[4]

- Hepatocellular carcinoma
- Bladder cancer

[a]Information provided by UKPS

- Prostate cancer
- Ovarian cancer
- NSCLC
- Melanoma
- Endometrial cancer
- Colorectal cancer
- Breast cancer
- Merkel cell carcinoma

Patient Group

Disease Area and Clinical Need

Oesophageal cancer is cancer that is found anywhere within the oesophagus, which connects the mouth to the stomach.[5] Most oesophageal cancers can be categorised into two main histologic subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC is one of the most common oesophageal cancer subtypes and develops from the squamous cells that make up the inner lining of the oesophagus.[6,7] Cancers that have grown into nearby structures or that have spread to distant lymph nodes or to other organs are considered unresectable.[8] The most common symptoms of oesophageal cancer include; difficulty swallowing, persistent indigestion or heartburn, unexplained weight loss and pain in the throat or behind the breastbone.[9] Some of the risk factors for oesophageal cancer are age; with 41% of new cases in people over 75 years of age, being overweight/obese, smoking or using tobacco, drinking alcohol, having Barrett's oesophagus, having gastro-oesophageal reflux disease, having radiotherapy and drinking very hot drinks.[10,11]

Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-18).[11] The age standardised incidence rate of malignant neoplasm of the oesophageal in England (2017) is 22.2 and 8.1 per 100,000 amongst males and females respectively.[12] In England, 2021-22, there were 43,451 finished consultant episodes (FCE) and 34,765 admissions for malignant neoplasms of the oesophagus (ICD-10 code C15) which resulted in 79,373 FCE bed days and 27,178 day cases.[13] In England (2017), there were 7,569 patients diagnosed with oesophageal cancer and 6,458 deaths registered where neoplasms of the oesophagus was the underlying cause.[12] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 46.5% and 17.0% respectively.[14]

Recommended Treatment Options

NICE recommends nivolumab within its marketing authorisation, for treating unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults after fluoropyrimidine and platinum based therapy.[15]

For previously untreated advanced oesophageal cancer, pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended in patients.[16]

Clinical Trial Information

Trial	**KEYNOTE-975,** NCT04210115, EudraCT2019-002006-51; A Randomised, Double-blind, Placebo controlled Phase 3 Trial of Pembrolizumab (MK-3475) Versus Placebo in Participants With Esophageal Carcinoma Receiving Concurrent Definitive Chemoradiotheraphy (KEYNOTE975) **Phase III:** Recruiting

[a]Information provided by UKPS

	Locations: 9 EU countries, UK, USA, Canada and other countries. **Primary Completion date:** February 2027
Trial Design	Randomised, parallel assignment, triple masked
Population	N=700 (estimated); 18 years or older; has histologically confirmed diagnosis of upper thoracic oesophageal carcinoma, is deemed suitable for definitive chemoradiotherapy, is inedible for curative surgery based on the documented opinion of a qualified medical/surgical/radiation oncologist.
Intervention(s)	Pembrolizumab (IV infusion, 200mg or 400mg) Cisplatin (IV infusion) 5-FU (IV infusion) Radiotherapy (external radiation) Leucovorin (IV infusion) Levoleucovorin (IV infusion) Oxaliplatin (IV infusion)
Comparator(s)	Placebo (matched to pembrolizumab)
Outcome(s)	The primary outcome measures are: • Event-free survival (EFS) [Time frame: up to 60 months] • Overall survival (OS) [Time frame: up to 72 months] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100 mg/4 ml concentrate for solution for infusion costs £2,630 for.[17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma (ID2712). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tislelizumab with chemotherapy for untreated advanced oesophageal squamous cell cancer (ID5113). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tislelizumab with chemoradiation for treating localised oesophageal squamous cell cancer (ID5077). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable metastatic oesophageal squamous cell carcinoma (ID1629). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tislelizumab for previously treated advanced oesophageal squamous cell cancer. Expected January 2024.
- NICE technology appraisal. Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma. [TA865]. Published February 2023.

[a]Information provided by UKPS

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). Publishing 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

- Jaffer A. A., Thomas A. D., David J. B. et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. 2019.[18]
- European Society of Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[19]
- Allum W.H., Blazeby J.M., Griffin S.M. et al. Guidelines for the management of oesophageal and gastric cancer. 2011.[20]

Additional Information

References

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[a]Information provided by UKPS

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[a]Information provided by UKPS