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Newcastle University

Health Technology Briefing
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Pembrolizumab with lenvatinib and chemotherapy for the treatment of metastatic squamous cell oesophageal carcinoma

Company/Developer	Merck Sharp & Dohme LLC

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33617	NICE ID: Not Available	UKPS ID: 674945

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Lenvatinib in combination with pembrolizumab and chemotherapy is in clinical development as a first line therapy for metastatic squamous cell oesophageal carcinoma (SCOC). SCOC is a type of cancer that originates in the squamous cells that line the oesophagus (sometimes referred to as the food pipe or gullet). Metastatic cancer means the cancer has spread to other parts of the body. SCOC can be ultimately fatal and symptoms can include difficulty swallowing or eating, weight loss, and pain in the throat or chest that can be very detrimental to patient's quality of life.

Pembrolizumab is a monoclonal antibody (protein) that stimulates the body's immune system by triggering T-cells (a type of white blood cells) to find and kill cancer cells. Lenvatinib selectively blocks receptors involved in several chemical pathways that lead to cell division, this reduces the replication of cancerous cells which slows the growth of tumours. Pembrolizumab is administered intravenously (into a vein), and lenvatinib can be swallowed as an oral capsule. If licensed, lenvatinib in combination with pembrolizumab and chemotherapy would provide another option for the first line treatment of metastatic SCOC.

Proposed Indication

For the first line treatment of metastatic squamous cell oesophageal carcinoma (SCOC).[1]

Technology

Description

Pembrolizumab (Keytruda; MK-3475) 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]

Lenvatinib (Lenvima; Kisplyx; MK-7902) is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα , KIT, and RET.[3]

A combination of pembrolizumab and lenvatinib, alongside standard of care chemotherapy, is currently in clinical development for the treatment of metastatic SCOC. In the phase III clinical trial (NCT04949256) 400mg of pembrolizumab is administered intravenously once every 6-week-cycle, along with daily 8mg (induction) or 20mg (consolidation) lenvatinib oral capsules plus chemotherapy.[1]

Key Innovation

Combination immunotherapies that modulate different aspects of tumour immunobiology may help to overcome primary and acquired resistance to immunotherapy and may offer improved efficacy across a broad range of cancers.[4] Combining immune checkpoint inhibitors, such as with pembrolizumab, with lenvatinib has been reported to demonstrate more potent antitumor activity than either respective monotherapy in preclinical trials.[5] The anti-angiogenic effect of lenvatinib in combination with the immune-stimulatory effect of pembrolizumab also more promising antitumour activity and resulted in higher survival rates in the several cancers during phase I/II clinical trials.[6] If licenced, the combination of lenvatinib and pembrolizumab with chemotherapy will offer an additional treatment option in the first line treatment of metastatic SCOC.

Regulatory & Development Status

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

- Melanoma
- Non-small cell lung carcinoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Colorectal cancer
- Oesophageal carcinoma
- Triple-negative breast cancer
- Endometrial carcinoma
- Cervical cancer
- Gastric or gastro-oesophageal junction adenocarcinoma

- Biliary tract carcinoma

Lenvatinib (Kisplyx) has Marketing Authorisation in the EU/UK for the following indications:[3]

- The treatment of adults with advanced renal cell carcinoma (in combination with pembrolizumab as first-line treatment, and in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy)

Lenvatinib (Lenvima) has Marketing Authorisation in the EU/UK for the following indications:[7]

- As monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)
- As monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy

Lenvatinib (Lenvima) in combination with pembrolizumab has Marketing Authorisation in the EU/UK for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.[7]

Pembrolizumab in combination with lenvatinib is also in phase II and/or III clinical development for the treatment of various types of cancer, including:[8]

- Solid tumours
- Gastric cancer
- Hepatocellular carcinoma
- Renal cell carcinoma
- Thymic carcinomas
- Biliary tract cancers
- Colorectal cancer
- Melanoma

Patient Group

Disease Area and Clinical Need

Oesophageal cancer is a cancer that starts in the oesophagus, sometimes called the food pipe or gullet. The lining of the oesophagus in made of two cell types, adenomatous cells and squamous cells, SCOC is when the cancer originates in the squamous cells lining the oesophagus.[9] Metastatic cancer means that some of the cancerous cells have broken away from the primary tumour and spread to other parts of the body.[10] The most common symptoms of oesophageal cancer include, difficulty swallowing (dysphagia), unexplained weight loss, indigestion or heartburn that doesn't go away and pains in the throat or behind the breastbone.[11] It is not known exactly what causes oesophageal cancer but there are several risk factors associated with SCOC, including smoking or chewing tobacco, being overweight or obese and drinking more than 11 units of alcohol a week.[12]

Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cancer cases (2017-2019).[13] The age standardised incidence rate of oesophageal cancer in England is 22.3 and 8.2 per 100,000 amongst males and females respectively.[14] In England (2022-23) there were 45,092 finished consultant episodes (FCEs) and 36,834 admissions for malignant neoplasm of oesophagus (ICD-10 code C15), which resulted in 29,550 day cases and 83,355 FCE bed days.[15] In England (2017), there

were 7,569 patients diagnosed with malignant neoplasm of oesophagus and 6,458 deaths registered where malignant neoplasm of oesophagus was the underlying cause.[16] For patients diagnosed with stage IV oesophageal cancer between 2013 and 2017, followed up to 2018, the 1-year survival rate was 21.1%.[17]

Recommended Treatment Options
NICE currently recommends the following therapies for the first line treatment of metastatic squamous cell oesophageal carcinoma:[18] • Pembrolizumab plus chemotherapy • Nivolumab with fluoropyrimidine-based and platinum-based combination chemotherapy (only recommended if pembrolizumab plus chemotherapy is not suitable)

Clinical Trial Information

Trial	NCT04949256; 2020-001911-26; A Phase 3, Randomized Study to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) + Lenvatinib (E7080/MK-7902) + Chemotherapy Compared With Standard of Care as First-line Intervention in Participants With Metastatic Esophageal Carcinoma **Phase III -** Active, recruiting **Location(s) -** 6 EU countries, UK, USA, Canada, Japan and other countries **Primary completion date:** December 2025
Trial Design	Randomised, open label, parallel assignment
Population	N=862 (estimated); 18 years or older; histologically or cytologically confirmed diagnosis of metastatic squamous cell carcinoma of the oesophagus with adequate organ function; no prior treatment for locally advanced unresectable or metastatic oesophageal cancer
Intervention(s)	Pembrolizumab 400mg IV once every 6 weeks + lenvatinib 8mg (induction) or 20mg (consolidation) oral once daily and chemotherapy
Comparator(s)	Standard of care pembrolizumab (IV) and chemotherapy
Outcome(s)	• Primary outcome measures: • Number of participants with dose limiting toxicities [Time frame: up to 21 days] • Number of participants with adverse events [Time frame: up to 51 months] • Number of participants who discontinued study treatment due to an AE [Time frame: up to 51 months] • Overall survival (OS) in all participants [Time frame: up to 49 months] • Progression-free survival (PFS) per response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR) [Time frame: up to 41 months] • See trial record for full list of other outcomes.
Results (efficacy)	-

Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4ml vial costs £2,630.[19]
Lenvatinib is already marketed in the UK; 30 capsules of 4mg or 10mg costs £1,437.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable metastatic oesophageal squamous cell carcinoma (GID-TA10841). Expected date of issue to be confirmed.
- Technology appraisal guidance. Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (TA865). February 2023.
- Technology appraisal guidance. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021.
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). Last updated July 2023.
- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018.

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). March 2019.
- 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

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- European Society of Medical Oncology (ESMO). Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[22]
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Additional Information

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