NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Pembrolizumab with Lenvatinib and chemotherapy for previously untreated advanced or metastatic gastroesophageal adenocarcinoma

Company/Developer	Merck Sharp & Dohme Ltd; Eisai Inc.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34532	NICE TSID: 11861	UKPS ID: 662147, 665570

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab in combination with lenvatinib and chemotherapy is in clinical development for patients with advanced or metastatic gastroesophageal adenocarcinoma. Gastric cancer (GC) also called stomach cancer, is cancer that starts in any part of the stomach or the stomach wall. Gastro-oesophageal junction cancer (GEJC) starts at the gastro-oesophageal junction, where the food pipe (oesophagus) joins the stomach. Advanced GC is cancer that started in the stomach and has spread to another part of the body. Some cancers do not respond or become unresponsive to treatment over time when a given drug is used as the sole treatment, hence the need for combinations of drugs that attack the tumour in different ways.

Pembrolizumab is a type of protein (monoclonal antibody) that is administered intravenously and has been designed to increase the immune system's ability to kill cancer cells. Lenvatinib administered orally, works by blocking the activity of enzymes in cancer cells. Through the blocking of these enzymes, lenvatinib can block the formation of new blood vessels and hence cut off the blood supply that allows cancer cells to grow. If licensed, pembrolizumab in combination with lenvatinib and chemotherapy will offer an additional treatment option for adults with advanced or metastatic gastroesophageal adenocarcinoma.

Proposed Indication

First-line treatment of adult patients with advanced or metastatic gastroesophageal adenocarcinoma.[1]

Technology

Description

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody which binds to the programmed cell death1 (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.[2,3]

Lenvatinib (Lenvima; Kisplyx; MK-7902) is a multi-targeted tyrosine kinase inhibitor (TKI) 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 tyrosine kinases including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET that are involved in tumour proliferation.[4,5]

Pembrolizumab with lenvatinib and chemotherapy is in clinical development for the first-line treatment of patients with advanced or metastatic gastroesophageal adenocarcinoma. In the phase III trial (LEAP-015; NCT04662710), patients will be administered pembrolizumab 400mg every six weeks (Q6W) via intravenous (IV) infusion in combination with lenvatinib 8mg induction/20 mg consolidation by oral administration every day, plus chemotherapy.[1]

Key Innovation

Lenvatinib and pembrolizumab are both antineoplastic agents approved as monotherapies and in combination for several cancer indications in the UK.[2,4,6] 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.[7] In a recent phase II trial in patients with advanced gastric cancer (NCT03797326), lenvatinib in combination with the anti–PD-1 antibody pembrolizumab demonstrated promising antitumor activity with manageable safety for both first- and second-line treatments.[8]

This novel combination of lenvatinib and pembrolizumab with chemotherapy for the treatment of advanced or metastatic gastroesophageal adenocarcinoma could provide patients with an additional effective treatment option due to its promising antitumour profile.

Regulatory & Development Status

Lenvatinib (Lenvima) in combination with pembrolizumab is currently licensed in the UK for the treatment of adult patients with advanced or recurrent endometrial carcinoma 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.[4] Lenvatinib (Kisplyx) in combination with pembrolizumab is also licensed for the first-line treatment of adults with advanced renal cell carcinoma.[6]

Pembrolizumab in combination lenvatinib is currently in phase II and III clinical development for the treatment of various types of cancer, some of which include:[9]

- Advanced kidney cancer
- Head and Neck Squamous Cell carcinoma
- Urothelial carcinoma
- Salivary gland cancer
- Advanced biliary tract carcinoma

Patient Group

Disease Area and Clinical Need

Gastric cancer (GC), also called stomach cancer, is cancer that starts in any part of the stomach or the stomach wall. Most stomach cancers start in the gland cells in the inner stomach lining. These are called adenocarcinomas.[10] Gastro-oesophageal junction cancer (GEJC) starts at the gastro-oesophageal junction, where the food pipe (oesophagus) joins the stomach. There are three different types of GEJC: Type 1 is the most similar to oesophageal cancer and has spread down into the gastro-oesophageal junction from above; Type 2 is centred at the actual junction; and Type 3, being most similar to GC, has spread up into the junction from below.[11] Advanced cancer is cancer that has spread to at least one other part of the body, such as the liver or lungs.[12,13] GC is more common in men, and older people over the age of 50.[14] GC or GEJC can also be linked to certain medical conditions such as gastro-oesophageal reflux disease, long-term helicobacter pylori infection, Barrett's oesophagus, or gastritis.[14,15] Symptoms of gastro-oesophageal cancers can include difficulty and pain when swallowing, nausea or vomiting, heartburn, indigestion, loss of appetite, fatigue, unexplained weight loss, or a lump in the upper abdomen.[16,17]

GEJC is staged according to either oesophagus or GC guidelines depending on how far the centre of the cancer is into the stomach, but most commonly is referred to as GC in literature and statistics.[11,18] GC is the 17th most common cancer in the UK, accounting for 3% of all cancer deaths (2018). Each year in the UK there are approximately 6,500 new cases of GC (2016-18), and the five years or more survival rate in England is 21.6% (2013-17).[19] In England (2021-22), there were 7,446 finished consultant episodes (FCE) for malignant neoplasms of the stomach unspecified (ICD-10 code: C16.9), with 5,830 hospital admissions that resulted in 14,744 FCE bed days and 4,400 day cases.[20] For malignant neoplasms of the lower third of the oesophagus (ICD-10 code: 15.5) in England (2021-22), there were 23,013 FCE, with 18,788 hospital admissions that resulted in 39,228 bed days and 15,134 day cases.[20]

Recommended Treatment Options

NICE guidelines recommend the following first-line palliative chemotherapy options for advanced or metastatic oesophago-gastric adenocarcinoma:[21,22]

- 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
- Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy

NICE guidelines also recommend capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer.[23]

Clinical Trial Information	
Trial	NCT04662710; EudraCT2020-001990-53; **LEAP-015;** Phase 3, Randomized Study to Evaluate the Efficacy and Safety of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) Plus Chemotherapy Compared With Standard of Care Therapy as First-line Intervention in Participants With Advanced/Metastatic Gastroesophageal Adenocarcinoma **Phase III-** Recruiting **Location(s):** 7 EU countries, UK, USA, Canada and other countries **Primary completion date:** February 2026
Trial Design	Randomised, open label, parallel assignment
Population	N=890 (estimated); Subjects aged 18 and older with histologically and/or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic gastroesophageal adenocarcinoma
Intervention(s)	Lenvatinib 8mg induction/20mg consolidation (oral) every day + pembrolizumab 400 mg (IV) every 6 weeks + chemotherapy
Comparator(s)	Chemotherapy
Outcome(s)	Primary outcome measures: • Number of Participants with Dose Limiting Toxicities (DLTs) [Time Frame: Up to ~21 days] • Number of Participants with Adverse Events (AEs) [Time Frame: Up to ~28 months] • Number of Participants who Discontinued Study Treatment Due to an AE [Time Frame: Up to ~25 months] • Overall Survival (OS) in Participants with Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) ≥1 [Time Frame: Up to ~44 months] • OS in All Participants [Time Frame: Up to ~44 months] • Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants with PD-L1 CPS ≥1 [Time Frame: Up to ~34 months] • PFS Per RECIST 1.1 as Assessed by BICR in All Participants [Time Frame: Up to ~34 months] See trial for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4 ml concentrate of solution for infusion vial costs £2,630.[24]

Lenvatinib is already marketed in the UK; a pack of 30 x 4mg and 30 x 10mg capsules each cost £1,437.[25]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (GID-TA10352). Expected January 2023.
- NICE technology appraisal. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021.
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018.
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.

NHS England (Policy/Commissioning) Guidance

- 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

Other Guidance

- National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. July 2019.[26]
- European Society of Medical Oncology (ESMO). Oesophageal cancer: ESMO clinical practice guidelines. 2016.[27]
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Additional Information

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