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Newcastle University

Health Technology Briefing
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Lenvatinib with pembrolizumab for previously treated metastatic non-small cell lung cancer

Company/Developer	Merck Sharp & Dohme Ltd, Eisai Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27373	NICE ID: 10524	UKPS ID: 653346, 656034

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Lenvatinib with pembrolizumab is in development for the treatment of metastatic non-small cell lung cancer (NSCLC). NSCLC is the most common form of lung cancer. Metastatic NSCLC describes tumours that have spread from the lungs to other parts of the body. Smoking tobacco is the cause of most lung cancers and the biggest risk factor. Other risk factors include second-hand smoke, exposure to workplace carcinogens, radiation exposure, environmental pollution, and family history of lung cancer. Current standard of care treatment can help to control the cancer for some time and reduce symptoms, however, sometimes NSCLC can continue to grow despite chemotherapy and immunotherapy.

Lenvatinib is a targeted therapy which prevents the formation of new blood vessels that support tumour growth. Pembrolizumab is a type of therapy that stimulates the body's immune system (immunotherapy) by triggering immune cells called T-cells to find and kill cancer cells. These therapies modulate different aspects of tumour biology and combining them may result in improved efficacy and help overcome resistance to immunotherapy. Lenvatinib is administered as an oral capsule and pembrolizumab is administered into the vein (intravenously, IV). If licensed, lenvatinib with pembrolizumab could provide an additional effective antitumour therapy for previously treated NSCLC.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Lenvatinib in combination with pembrolizumab is indicated for the treatment of metastatic non-small cell lung cancer in patients who have received platinum doublet chemotherapy and immunotherapy.[1]

Technology

Description

Lenvatinib (Lenvima) is a multiple receptor tyrosine kinase inhibitor (TKI) with a binding mode that selectively inhibits the kinase activities of all vascular endothelial growth factor receptors (VEGFR), in addition to other proangiogenic and oncogenic pathway-related kinases including all fibroblast growth factor receptors (FGFR), the platelet-derived growth factor (PDGF) receptor PDGFRα, KIT and RET that are involved in tumour proliferation.[2]

In the phase III trial, LEAP-008 (NCT03976375), pembrolizumab 200mg will be administered every three weeks (Q3W) via intravenous (IV) infusion in combination with lenvatinib at 20mg, once daily (QD) via oral capsule.[1]

Key Innovation

Lenvatinib and pembrolizumab are both anti-tumour biological drugs with different mechanisms of action and are approved as monotherapies and in combination for several cancer indications in the UK.[2-4]

For metastatic NSCLC, chemotherapy and immunotherapy is the standard of care. This treatment can help to control the cancer for some time and reduce symptoms, however, sometimes NSCLC can continue to grow despite chemotherapy and immunotherapy.[5] Evidence shows that pembrolizumab plus lenvatinib demonstrates promising efficacy in advanced tumours and greater antitumour activity has been seen with this combination than with either agent alone in the treatment of lung cancer.[6,7] This novel combination for the treatment of NSCLC could provide patients with an additional effective treatment option due to its promising antitumour profile.[8]

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.[9] Lenvatinib (Kisplyx) in combination with pembrolizumab is also licensed for the first line treatment of adults with advanced renal cell carcinoma.[4] The combination is currently undergoing appraisal from the National Institute for Health and Care Excellence (NICE) for both indications.[10,11]

Lenvatinib (Lenvima) is currently licensed as a monotherapy for differentiated thyroid carcinoma and hepatocellular carcinoma. Lenvatinib (Kisplyx) is also licensed in combination with everolimus for advanced renal cell carcinoma following one prior endothelial growth factor-targeted therapy.[12]

Lenvatinib in combination with pembrolizumab is in phase II/III clinical development for the following indications:[13,14]

- Melanoma
- Head and neck squamous cell carcinoma
- Gastric cancer
- Oesophageal cancer

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- Colorectal cancer
- Biliary tract cancer
- Glioblastoma
- Pancreatic cancer
- Prostate cancer
- Small cell lung cancer

Patient Group

Disease Area and Clinical Need

NSCLC is the most common form of lung cancer. Around 80 to 85% of lung cancer cases in the UK are NSCLC. The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[15] Smoking tobacco is the cause of most lung cancers and the biggest risk factor. Other risk factors include second-hand smoke, exposure to workplace chemicals, radiation exposure, air pollution and family history of lung cancer.[16] Symptoms of lung cancer include a cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness. However, lung cancer may not always have symptoms early on. Sometimes it is found by chance when a person is having tests for another condition.[17]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases.[18] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days and 62,688 day cases.[19] There are around 35,100 lung cancer deaths in the UK every year and in England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV was 19.3% at one year and 2.9% at five years.[18,20]

Recommended Treatment Options

Treatment for lung cancer includes surgery, chemotherapy, radiotherapy, immunotherapy, and other targeted therapy drugs. People may be offered one or more different treatments depending on the stage, histology and type of lung cancer as well as their general health.[21]

For previously treated advanced non-squamous cell NSCLC with PD L1 > 50%, NICE recommends:[22]

- Nintedanib in combination with docetaxel or docetaxel monotherapy if there has been treatment progression after first-line chemotherapy with pembrolizumab combination
- On progression after pembrolizumab monotherapy, pemetrexed with carboplatin or other platinum doublet chemotherapy
- Pemetrexed when patient's disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their ECOG performance status is 0 or 1 at the start of maintenance treatment or following platinum-based chemotherapy

For previously treated advanced non-squamous cell NSCLC with PD L1 < 50%, NICE recommends:[22]

- Nintedanib in combination with docetaxel or docetaxel monotherapy if there has been treatment progression after first-line chemotherapy with pembrolizumab combination or atezolizumab combination
- Pemetrexed when patient's disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their ECOG performance status is 0 or 1 at the start of maintenance treatment or following platinum-based chemotherapy

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- Atezolizumab for PD L1 negative tumours in adults who have had chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour) if atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses
- Nivolumab for PD-L1 positive tumours after chemotherapy if it is stopped at 2 years of uninterrupted treatment, or earlier if their disease progresses, and the patient has not had a PD-1 or PD-L1 inhibitor before
- Pembrolizumab for PD-L1-positive tumours in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour) if it is stopped at 2 years of uninterrupted treatment and no documented disease progression

For previously treated advanced squamous cell NSCLC, NICE recommends:[22]

- Gemcitabine or vinorelbine and cisplatin or carboplatin if there has been progression after treatment with pembrolizumab (PD L1 > 50%)
- Atezolizumab, nivolumab or pembrolizumab if there has been progression after first-line chemotherapy (PD L1 < 50%)
- Docetaxel monotherapy if there has been progression after first-line chemotherapy

Clinical Trial Information

Trial	**LEAP-008; NCT03976375; 2018-003791-12;** A Phase 3, Multicenter, Randomized, Open-label Trial to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Lenvatinib (E7080/MK-7902) Versus Docetaxel in Previously Treated Participants With Metastatic Non-small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (LEAP-008) **Phase III–** Recruiting **Location(s):** 7 EU countries, UK, USA, Canada, and other countries **Primary completion date:** August 2023
Trial Design	Randomised, parallel assignment, open label
Population	N=405 (planned); subjects with confirmed diagnosis of metastatic squamous or non-squamous NSCLC; has progressive disease on treatment with one prior anti-PD-1/PD-L1 monoclonal antibody and during/after platinum doublet chemotherapy; aged 18 years and older
Intervention(s)	Pembrolizumab IV and lenvatinib (oral capsules) or lenvatinib monotherapy
Comparator(s)	IV infusion of docetaxel
Outcome(s)	Primary outcomes: • Overall Survival (OS) [Time frame: up to ~48 months] • Progression-free Survival (PFS) per response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) [Time frame: up to ~36 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

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Estimated Cost

Lenvatinib is already marketed in the UK. The NHS indicative price for 4mg and 10mg capsules (30 units) is £1,437.[23]

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

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy (TA713). July 2021.
- NICE technology appraisal. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy (TA655). October 2020.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). September 2017.
- NICE technology appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). August 2016.
- NICE technology appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). December 2015.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE technology appraisal guidance. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.
- NICE interventional procedures guidance. Percutaneous radiofrequency ablation for primary or secondary lung cancers (IPG372). December 2010.

NHS England (Policy/Commissioning) Guidance

- 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

- NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[25]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.[26]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[27]

Additional Information

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