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Newcastle University

Health Technology Briefing
February 2022

Lenvatinib with pembrolizumab for the treatment of squamous cell carcinoma of the head and neck

Company/Developer	Eisai Ltd, Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27748	NICE ID: 10502	UKPS ID: 656001, 656289

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Lenvatinib in combination with pembrolizumab is being developed as a first-line therapy for adults with programmed death-ligand 1 (PD-L1) expressing recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). HNSCC is a cancer of the mouth, nose or throat that develops in the squamous cells found in the outer layer of skin and the mucous membranes that line body cavities. About a half of the patients with HNSCC have it return after treatment (recurrent) or it spread to other parts of the body (metastatic). Recurrent/metastatic HNSCC is a difficult disease to treat, with poor prognosis and survival rates.

Pembrolizumab is an immunotherapy, administered intravenously, that stimulates the body's immune system by triggering T-cells (a type of white blood cells) to find and kill cancer cells. Lenvatinib is a targeted therapy drug, administered orally, that inhibits cancer growth by preventing the formation of new blood vessels. Combining these drugs, with their different methods of fighting the cancer, may result in improved efficacy and help overcome resistance to therapy. If licenced, lenvatinib in combination with pembrolizumab will provide an additional first-line therapy for adults with PD-L1 expressing recurrent or metastatic HNSCC.

Proposed Indication

First-line treatment in adult patients with PD-L1 expressing recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).[1]

Technology

Description

Lenvatinib (Lenvima) is a 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 kinases including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.[2]

Pembrolizumab (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.[3]

Lenvatinib in combination with pembrolizumab is currently in phase III clinical development for the first-line treatment of adults with PD-L1 expressing and recurrent or metastatic HNSCC. In the phase III trial (NCT04199104), lenvatinib 20mg is administered orally once daily, in combination with pembrolizumab 200mg IV infusion once every 3 weeks for up to 35 3-week cycles.[1]

Key Innovation

Recurrent/metastatic HNSCC have poor prognosis with a median survival of about 12 months despite current treatments.[4]

Combination immunotherapies that modulate different aspects of tumor immunobiology may help to overcome primary and acquired resistance to immunotherapy and may offer improved efficacy across a broad range of cancers. The combined blockade of VEGF and inhibitory immune checkpoint signaling has been shown to enhance immune activation and tumor destruction in preclinical models such as the combination of lenvatinib and pembrolizumab.[5]

Pembrolizumab is licensed, as monotherapy and with chemotherapy, for HNSSC.[5]Lenvatinib is not licensed (as monotherapy nor in any combination) for HNSCC. In a phase 1b/2 trial (NCT02501096) of pembrolizumab plus lenvatinib in solid tumors, the combination demonstrated promising antitumor activity and a manageable safety profile in patients with HNSCC.[6]

If licenced, lenvatinib in combination with pembrolizumab would provide additional first-line treatment for PD-L1 expressing recurrent or metastatic HNSCC.

Regulatory & Development Status

Lenvatinib (Lenvima) in combination with pembrolizumab has a Marketing Authorisation in the 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.[2]

Lenvatinib (Lenvima) has a Marketing Authorisation in the UK as monotherapy in adults for progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine, and advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy.[2]

Lenvatinib (Kisplyx) has a Marketing Authorisation in the UK for the treatment of adults with advanced renal cell carcinoma; in combination with pembrolizumab as first-line treatment, and with everolimus following one prior VEGF-targeted therapy.[7]

Pembrolizumab (Keytruda) has a Marketing Authorisation in the UK, as monotherapy and in combination, for a range of cancer indications, including:[3]

- as monotherapy or with platinum-containing chemotherapy, as first-line treatment for metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a combined positive score ≥ 1
- as monotherapy for recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score and have progressed on or after platinum-containing chemotherapy.

The combination of lenvatinib with pembrolizumab is in phase III trials for several cancer indications:[8]

- Non-small cell lung cancer
- Hepatocellular carcinoma
- Malignant melanoma
- Urothelial cancer
- Colorectal cancer
- Gastroesophageal adenocarcinoma
- Oesophageal squamous cell carcinoma

Lenvatinib with pembrolizumab is also in phase II trials for several other cancer indications.[8]

Patient Group

Disease Area and Clinical Need

Head and neck cancer is a general term that covers many different types of cancer, including the oral cavity, pharynx (throat – includes nasopharynx, oropharynx and hypopharynx) and larynx (voice box).[9] HNSCC is a cancer that arises from particular cells called squamous cells. Squamous cells are found in the outer layer of skin and in the mucous membranes, which are the moist tissues that line body cavities such as the airways and intestines. HNSCC typically develops in the mucous membranes of the mouth, nose and throat.[10] The strongest risk factors for developing this form of cancer are tobacco use and heavy alcohol consumption. In addition, studies have shown that infection with certain strains of human papillomavirus (HPV) is linked to the development of HNSCC. HPV infection accounts for the increasing incidence of HNSCC in younger people.[10] The symptoms of head and neck cancers may include a lump or a sore that does not heal, a sore throat that does not go away, difficulty or pain in swallowing and a change or hoarseness in the voice.[11] Quality of life may also be affected as the head and the neck are anatomical sites of basic functions, including speech, swallowing, hearing and breathing, which are necessary for social interaction.[12]

In England in 2017, there were a total of 7,587 registrations of malignant neoplasm of the lip, oral cavity and pharynx (ICD-10 codes C00-C14). Overall, malignant neoplasm of the lip, oral cavity or pharynx accounted for roughly 2.5% of cancer registrations for that year.[13] In England in 2020-21, there were 23,738 finished consultant episodes (FCE), and 21,555 admissions with a primary diagnosis of malignant

neoplasm of the lip, oral cavity or pharynx (ICD-10 codes C00-C14), resulting in 12,368 day cases and 58,030 FCE bed days.[14] In the UK in 2020, there were 2,851 deaths from head and neck cancer.[15] Over 83.9% of people diagnosed with cancer of the larynx in England survive their disease for 1 year or more (2013-2017) and over half (63.9%) survive their disease for 5 years or more (2013-2017).[16]

Recommended Treatment Options

Current NICE recommended treatment options for untreated, metastatic HNSCC include:[17]

- Pembrolizumab
- Cetuximab

Clinical Trial Information

Trial	**MK-7902-010, LEAP-10, NCT04199104, EudraCT2019-003717-34;** A Phase 3, Randomized, Placebo-controlled, Double-blind Clinical Study of Pembrolizumab (MK-3475) With or Without Lenvatinib (E7080/MK-7902) to Evaluate the Safety and Efficacy of Pembrolizumab and Lenvatinib as 1L Intervention in a PD-L1 Selected Population of Participants With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) (LEAP-010). **Phase III -** Recruiting **Location(s):** 6 EU countries, United Kingdom, Canada, United States and other countries **Primary completion date:** November 2023
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 500 (estimated), diagnosis of recurrent or metastatic HNSCC that is considered incurable by local therapies, aged 18 years and older
Intervention(s)	Lenvatinib 20 mg orally once a day (QD) plus pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W)
Comparator(s)	Pembrolizumab with placebo
Outcome(s)	**Primary outcomes;** • Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR). [Time Frame: Up to approximately 24 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). [Time Frame: Up to approximately 30 months] • Overall Survival (OS) [Time Frame: Up to approximately 44 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT02501096; EudraCT2017-000300-26; A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors **Phase I/II -** Active, not recruiting **Location(s):** United States, Spain, Norway **Study completion date:** September 2023
Trial Design	Single group assignment, open label
Population	N=357; metastatic selected solid tumour types with 0-2 prior lines of systemic therapy, aged 18 years and older
Intervention(s)	Lenvatinib administered orally once daily continuously in a 21-day treatment cycle + Pembrolizumab 200mg Q3W via IV infusion in a 21-day treatment cycle
Comparator(s)	None
Outcome(s)	**Primary outcomes;** • MTD (Phase 1b) [Time Frame: Cycle 1 (21 Days)] • Objective response rate (ORR) at Week 24 [Time Frame: Week 24] • Dose Limiting Toxicity (DLT) (Phase 1b) [Time Frame: Cycle 1 (21 Days)] See trial record for full list of other outcomes.
Results (efficacy)	Patients with squamous cell carcinoma of the head and neck achieved an objective response rate (ORR) at week 24 of 36% (8/22; 95% CI, 17.2% to 59.3%) and an overall ORR of 46% (10/22; 95% CI, 24.4% to 67.8%) . The median duration of response was 8.2 months (95% CI, 2.2 to 12.6 months), and the median progression-free survival was 4.7 months (95% CI, 4.0 to 9.8 months). In total, treatment was ongoing for 14% (3/22) of patients with squamous cell carcinoma of the head and neck at the time of data cutoff.[18]
Results (safety)	The most common treatment-related adverse events were fatigue (58%), diarrhea (52%), hypertension (47%), and hypothyroidism (42%).[18]

Estimated Cost

Lenvatinib is already marketed in the UK. The NHS indicative price for 4 mg and 10 mg capsules (30 units) is £1,437.[19]
Pembrolizumab is already marketed in the UK. The NHS indicative price for 100 mg/4 ml concentrate for solution for infusion vial is £2,630:[20]

Relevant Guidance

NICE Guidance

- NICE Technology appraisal guidance. Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma (TA661). November 2020.
- NICE Technology appraisal guidance. Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA473). August 2017.
- NICE clinical guideline. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36). June 2018.

- NICE quality standard. Head and neck cancer (QS146). March 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/13 NHS Standard Contract for Cancer: Head and Neck (Adult).
- B16/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

- The Journal of Laryngology and Otology. Head and Neck Cancer: United Kingdom Multidisciplinary Guidelines. 2016.[21]
- European Society for Medical Oncology (ESMO). Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2010.[22]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 90. Diagnosis and Management of Head and Neck Cancer. 2006.[23]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.