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Newcastle University

Health Technology Briefing
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Lenvatinib and pembrolizumab with transarterial chemoembolisation for treating hepatocellular carcinoma

Company/Developer	Eisai Co Ltd, Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29291	NICE ID: 10503	UKPS ID: 656033, 656291

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Lenvatinib and pembrolizumab with transarterial chemoembolization (TACE) is being developed as a first-line treatment for incurable/non-metastatic hepatocellular carcinoma (HCC). HCC is the most common type of liver cancer. This type of cancer develops from the main form of liver cells, called hepatocytes. Treatment and survival depends on the stage at which the cancer is diagnosed, non-metastatic means the cancer has not spread from the liver to other parts of the body. HCC is more common in people who have long-term damage to the liver (cirrhosis) due to hepatitis B or C or excessive alcohol intake and metabolic causes such as obesity. It is also more likely to develop in men than in women and it becomes more common as people get older.

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 multi-targeted tyrosine kinase inhibitor, administered orally, that inhibits cancer growth by preventing the formation of new blood vessels. TACE involves giving chemotherapy directly to the tumour through an injection. The combined effect of the two products and TACE may produce a stronger, more targeted response of longer duration against the cancer cells when compared to current treatments. If licenced, lenvatinib and pembrolizumab with TACE will provide an additional treatment option for treating HCC.

Proposed Indication

Treatment of participants with incurable/non-metastatic hepatocellular carcinoma (HCC).[1]

Technology

Description

Lenvatinib (Lenvima) 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 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 potent humanised IgG4 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 and TACE is currently in phase III clinical development for the treatment of participants with incurable/non-metastatic HCC. In the phase III trial (NCT04246177), lenvatinib patients will receive a dose of 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) via oral capsules once a day during each 21-day cycle. Pembrolizumab will be administered via IV infusion at a dose of 400 mg once every 6 weeks. The first transarterial chemoembolisation (TACE) procedure must take place between 2 and 4 weeks after start of study intervention. For participants who require split-TACE (a second procedure to target the remaining, previously untreated lesions), the second TACE must be ≥1 month after the initial procedure and must be completed prior to the first evaluation scan. If residual disease is seen on the first disease evaluation scan, a second (series of) TACE procedure(s) may be performed to target any remaining viable lesions ≥1 month after the previous TACE.[1]

Key Innovation

The current standard of care for patients with intermediate Barcelona Clinic Liver Cancer (BCLC) B disease who are ineligible for curative treatment is locoregional therapy with chemoembolization (TACE).[4] Lenvatinib is indicated as a monotherapy for the treatment of adult patients with advanced or unresectable HCC, with no prior systemic therapy.[2] Pembrolizumab is not currently indicated as a monotherapy for HCC.

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] Data from a phase 1b trial of lenvatinib plus pembrolizumab demonstrated that the combination has promising antitumor activity and manageable safety in patients with unresectable, intermediate-stage HCC not amenable to TACE.[4]

If licenced, lenvatinib in combination with pembrolizumab with TACE will provide an additional treatment option for incurable/non-metastatic hepatocellular carcinoma.

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 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 in combination with everolimus following one prior VEGF-targeted therapy.[6]

Pembrolizumab has a Marketing Authorisation in the UK as monotherapy and in combination, for a range of cancer indications, including melanoma, head and neck cancer and non-small cell lung cancer.[3]

The combination of lenvatinib with pembrolizumab is in phase III trials for several cancer indications:[7]

- Head and neck cancer
- Non-small cell lung cancer
- 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.[7]

Patient Group

Disease Area and Clinical Need

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, which develops from the main liver cells, called hepatocytes.[8] Most patients with HCC have liver cirrhosis, which develops following long periods of chronic liver disease. Cirrhosis is characterised by a decrease in hepatocyte proliferation, indicating an exhaustion of the regenerative capacity of the liver, and results in an increase in fibrous tissue and a destruction of liver cells.[9] HCC is the most rapidly increasing cause of cancer death, with hepatitis C virus as the major etiology affecting generally more than half of HCC patients in developed countries.[10] Other risk factors for developing HCC include: hepatitis B infection, alcoholic liver disease, non-alcoholic steatohepatitis, intake of aflatoxin-contaminated food, diabetes and obesity.[9] HCC patients are frequently asymptomatic, and the appearance of symptoms can signal the development of severe disease.[11] The main symptoms of liver cancer may include: weight loss, a swollen abdomen, jaundice, loss of appetite over a period of a few weeks, being sick, feeling full or bloated after eating (even after a small meal), itching, a sudden worsening of health in somebody with known chronic hepatitis or cirrhosis, high temperature and sweating.[12] The symptoms of HCC in addition to the side-effects of treatment may

significantly impact the quality of life of individuals with the condition. Nine out of ten patients reported experiencing pain over their HCC treatment course in a qualitative analysis.[13]

In England, HCC accounts for up to 55% of all primary liver cancer diagnoses in men and up to 28% of diagnoses in women.[14] In England in 2017 there were a total of 4,975 registrations of newly diagnosed malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C.22).[15] Hospital Episodes Statistics for England for the period 2020-21 recorded 18,583 finished consultant episodes (FCEs), 12,887 admissions of which 6,443 were days cases and 48,483 FCE bed days for primary diagnosis malignant neoplasm of the liver and intrahepatic bile ducts.[16] In England and Wales in 2020 there were 5,445 deaths recorded for malignant neoplasm of the liver and intrahepatic bile ducts as the underlying cause.[17] Survival statistics (patients diagnosed between 2013-2017) report a 1-year ages-standardised net survival rate of 38.2% and a 5-year age-standardised net survival rate of 12.9% for patients with liver cancer.[18]

Recommended Treatment Options

Treatment options for HCC include interventional procedures such as TACE (using doxorubicin or cisplatin) or selective internal radiation therapy, and external beam radiotherapy.[19]

Current NICE recommended treatment options for untreated, advanced HCC include:[20]

- Atezolizumab with bevacizumab
- Lenvatinib
- Sorafenib

Clinical Trial Information

Trial	**MK-7902-012/LEAP-012,** NCT04246177, **EudraCT**2019-002345-37**;** A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) With Pembrolizumab (MK-3475) in Combination With Transarterial Chemoembolization (TACE) Versus TACE in Participants With Incurable/Non-metastatic Hepatocellular Carcinoma (LEAP-012) **Phase III -** Recruiting **Location(s):** 8 EU countries, United Kingdom, United States and other countries **Primary completion date:** April 2025
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 950 (estimated), HCC localized to the liver and not amenable to curative treatment, aged 18 years and older.
Intervention(s)	Lenvatinib will be administered at a dose of 12 mg or 8 mg orally once a day and pembrolizumab will be administered via IV infusion at a dose of 400 mg once every 6 weeks. Participants will undergo TACE as a background procedure of chemotherapeutic and embolic agent(s)
Comparator(s)	Oral placebo plus IV placebo plus TACE
Outcome(s)	**Primary outcomes;** • Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) assessed by blinded independent central review (BICR) [Time Frame: Up to ~5 years]

	• Overall Survival (OS) [Time Frame: Up to ~5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

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.[21]
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:[22]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab with bevacizumab and transarterial chemoembolisation for treating locally advanced hepatocellular carcinoma (ID3944). Expected publication date: To be confirmed.
- NICE technology appraisal in development. Lenvatinib with pembrolizumab for untreated advanced or unresectable hepatocellular carcinoma (ID3930). Expected publication date: To be confirmed.
- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated unresectable hepatocellular carcinoma (ID2725). Expected publication date: August 2021.
- NICE technology appraisal. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma (TA666). December 2020.
- NICE technology appraisal. Lenvatinib for untreated advanced hepatocellular carcinoma (TA551). December 2018.
- NICE technology appraisal. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for hepatobiliary and pancreas (Adult). A02/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.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma. 16022/P. July 2016.
- NHS England. Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma. B01/PS/a. June 2013.

Other Guidance

- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018.[23]
- European Society for Medical Oncology (ESMO). Hepatocellular Carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2018.[24]

- American Association for the Study of Liver Diseases. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018. Practice Guidance by the American Association for the Study of Liver Diseases. 2018.[25]

Additional Information

References

1 ClinicalTrials.gov. Safety and Efficacy of Lenvatinib (E7080/MK-7902) With Pembrolizumab (MK-3475) in Combination With Transarterial Chemoembolization (TACE) in Participants With Incurable/Non-metastatic Hepatocellular Carcinoma (MK-7902-012/E7080-G000-318/LEAP-012). *Trial ID: NCT04246177*. 2020;Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04246177.

2 electronic Medicines Compendium (eMC). *LENVIMA 10 mg hard capsules.* 2021. Available from: https://www.medicines.org.uk/emc/product/7880/smpc [Accessed 28 January 2022].

3 electronic Medicines Compendium (eMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/2498 [Accessed 28 January 2022].

4 Ogasawara S, Llovet J, El-Khoueiry A, Vogel A, Madoff D, Finn R, et al. P-107 LEAP-012: A randomized, double-blind, phase 3 study of pembrolizumab plus lenvatinib in combination with transarterial chemoembolization (TACE) in patients with intermediate-stage hepatocellular carcinoma not amenable to curative treatment. *Annals of Oncology*. 2020;31:S124-S5. Available from: https://doi.org/10.1016/j.annonc.2020.04.189.

5 Taylor MH, Schmidt EV, Dutcus C, Pinheiro EM, Funahashi Y, Lubiniecki G, et al. The LEAP program: lenvatinib plus pembrolizumab for the treatment of advanced solid tumors. *Future Oncology*. 2021;17(6):637-48. Available from: https://doi.org/10.2217/fon-2020-0937.

6 electronic Medicines Compendium. Kisplyx 10 mg hard capsules. 2022. Available from: https://www.medicines.org.uk/emc/product/7881/smpc.

7 ClinicalTrials.gov. *lenvatinib AND pembrolizumab | Phase 2, 3.* 2022. Available from: https://clinicaltrials.gov/ct2/results?term=lenvatinib+AND+pembrolizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 28 January 2022].

8 Cancer Research UK. *Types of liver cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/types [Accessed 28 January 2022].

9 Sanyal A, Yoon S, Lencioni R. The Etiology of Hepatocellular Carcinoma and Consequences for Treatment. *The Oncologist*. 2010;15:14-22. Available from: https://doi.org/10.1634/theoncologist.2010-S4-14

10 Baumert TF, Jühling F, Ono A, Hoshida Y. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. *BMC medicine*. 2017;15(1):52-. Available from: https://doi.org/10.1186/s12916-017-0815-7.

11 Charach L, Zusmanovitch L, Charach G. Hepatocellular Carcinoma. Part 2: Clinical Presentation and Diagnosis. *EMJ Hepatol*. 2017;5(1):81-8. Available from: https://emj.emg-health.com/wp-content/uploads/sites/2/2017/11/Hepatocellular-Carcinoma-Part-2.pdf

12 Cancer Research UK. *Symptoms.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/symptoms [Accessed 28 January 2022].

13 Butt Z, Mallick R, Mulcahy M, Benson A, Cella D, Kaiser K. Pain and other symptoms in patients with hepatocellular carcinoma (HCC): A qualitative analysis. *Journal of Clinical Oncology*.31. Available from: https://doi.org/10.1200/jco.2013.31.15_suppl.e15187

14 National Cancer Registration and Analysis Service (ncras). *Trends in incidence of primary liver cancer subtype.* Available from: http://www.ncin.org.uk/publications/data_briefings/trends_in_incidence_of_primary_liver_cancer_subtypes [Accessed 28 January 2022].

15 Office for National Statistics (ONS). *Cancer registration statistics, England: 2017.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 28 January 2022].

16 NHS Digital. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Downloaded 28 January 2022].

17 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality.* 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 28 January 2022].

18 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed: 2013 - 2017 edition of this dataset.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 28 January 2022].

19 National Insititute for Health and Care Excellence (NICE). *Nivolumab for untreated advanced hepatocellular carcinoma.* 2018. Available from: https://www.nice.org.uk/guidance/gid-ta10221/documents/draft-scope-post-referral [Accessed 28 January 2022].

20 National Insititute for Health and Care Excellence (NICE). *Liver cancers overview.* 2021. Available from: https://pathways.nice.org.uk/pathways/liver-cancers#content=view-node%3Anodes-hepatocellular-carcinoma [Accessed 28 January 2022].

21 British National Formulary (BNF). *LENVATINIB.* 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/lenvatinib.html [Accessed 18 Nov 2019].

22 National Institute for Health and Care Excellence (NICE). *Pembrolizumab.* Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 28 January 2022].

23 European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology*. 2018;69:182-236. Available from: https://www.journal-of-hepatology.eu/article/S0168-8278(18)30215-0/pdf

24 Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular Carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29:iv238-iv55. Available from: https://www.esmo.org/guidelines/gastrointestinal-cancers/hepatocellular-carcinoma

25 Marrero J, Kulik L, Sirlin C, Zhu A, Finn R, Abecassis M, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68(2):723-50. Available from: https://www.aasld.org/sites/default/files/2019-06/AASLD_2018_HCC_Guidance_on_Diagnosis%2C_Staging_and_Management_hep_29913%20%281%29.pdf

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