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HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Lenvatinib in combination with pembrolizumab for advanced/unresectable hepatocellular carcinoma – first-line

NIHRIO ID	26982	**NICE ID**	10279
Developer/Company	Eisai Co Ltd and Merck Sharpe and Dohme	**UKPS ID**	655491, 655873

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Lenvatinib in combination with pembrolizumab is in clinical development for the treatment of hepatocellular carcinoma (HCC), which is cancer that originally develops in the liver and accounts for nine in ten primary liver cancer cases. Advanced or unresectable HCC occurs when the cancer has spread to lymph nodes or to other organs and cannot be treated by surgery alone. It is often diagnosed late in life and has a poor prognosis. It is a debilitating condition with many distressing symptoms, including pain, digestive problems and weight loss. There are currently limited treatment options, yet research has suggested combining different drugs may improve survival for HCC patients.

Lenvatinib is an orally administered tyrosine kinase inhibitor that targets several different growth factor receptors. By blocking these receptors, lenvatinib can reduce tumour growth. Pembrolizumab is an intravenously administered drug that improves the activity of the immune system to kill cancer cells. If licensed pembrolizumab in combination with lenvatinib, could provide an additional first-line treatment option for patients with advanced or unresectable HCC.

PROPOSED INDICATION

First-line treatment of advanced or unresectable hepatocellular carcinoma (HCC) in adults.[1]

TECHNOLOGY

DESCRIPTION

Lenvatinib 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.[2]

Pembrolizumab 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]

In the phase III trial (NCT03713593, LEAP-002), participants receive lenvatinib 12 mg (for participants with screening body weight ⩾60 kg) or 8 mg (for participants with screening body weight <60 kg) orally once a day plus pembrolizumab 200 mg by IV infusion on day 1 of each 21-day cycle. Pembrolizumab will be administered for up to 35 cycles (approximately 24 months). Lenvatinib will be administered until progressive disease or unacceptable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

Immune checkpoint inhibitors are expected to exert synergistic effects when combined with chemotherapeutic agents or molecular targeted agents. Because several antiangiogenic inhibitors have been shown to be useful for the treatment of HCC, the combination of immune checkpoint inhibitors with these antiangiogenic inhibitors is now very much anticipated.[4]

In preclinical studies, lenvatinib has been shown to enhance the activity of anti-PD-1 antibodies, and clinical studies examining lenvatinib plus pembrolizumab combination therapy for various types of cancer have been started. Preliminary data of a phase Ib study testing pembrolizumab plus lenvatinib for first-line treatment of unresectable HCC indicated an acceptable safety profile, with an objective response rate of 42.3% and a median progression-free survival of 9.69 months (95% CI =5.55–not evaluable).[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lenvatinib is currently licenced as a monotherapy for the treatment of adult patients with advanced or unresectable HCC who have received no prior systemic therapy.[6]

Pembrolizumab is currently licenced as a monotherapy for:[3]

- advanced (unresectable or metastatic) melanoma in adults
- adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection

- locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ⩾ 1% TPS and who have received at least one prior chemotherapy regimen
- first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ⩾ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ⩾ 10
- recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ⩾ 50% TPS and progressing on or after platinum containing chemotherapy.

Pembrolizumab is currently licenced in combination with:[3]
- axitinib, for the first-line treatment of advanced RCC in adults
- pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations
- carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults
- as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 1.

Very common adverse events (frequency ⩾ 1/10) of pembrolizumab as monotherapy include: anaemia, hypothyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.[3]

Lenvatinib in combination with pembrolizumab is in phase III clinical development for NSCLC, malignant melanoma, RCC, head and neck squamous cell carcinoma, endometrial neoplasms and urothelial carcinoma. This combination is also in phase II clinical development for advanced solid tumours like gastric, thyroid and breast cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

Hepatocellular carcinoma (HCC) is a type of primary liver cancer that is seen in nine out of ten cases. Primary liver cancer starts in the liver and develops in hepatocytes (liver cells), whereas secondary liver cancer develops in other areas of the body and spreads to the liver, this can also be called metastatic or advanced cancer.[8,9]

HCC can be caused by a number of factors including age, genetics, smoking and having other medical conditions such as previous scarring of the liver tissue (cirrhosis), alcoholism, non-alcoholic fatty liver disease, diabetes, hepatitis viruses and HIV. Most patients are over the age of 60, with it being most common in those over the age of 85 years. Additionally, men are more likely to develop HCC than women though the exact reasons why are unknown.[10,11]

Symptoms of liver cancer include unintentional loss of weight, jaundice (yellowing skin), lethargy and generally feeling unwell. Liver cancer can be difficult to notice as the organ is resilient to damage and symptoms may only develop as disease severity progresses.[8,12]

CLINICAL NEED AND BURDEN OF DISEASE

HCC incidence and mortality has been found to have tripled over the last twenty years (1997 onwards) in England.[13] In 2014 in the UK 5,520 people were diagnosed with liver cancer and that number is predicted to increase to over 11,000 in 2035.[14] 5,087 people in the UK died from liver cancer in 2014 and this is predicted to increase to over 12,000 in 2035.[15]

In 2017 in England alone there were 4,975 new cases of malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C22).[16] In England (2019-20) there were 14,287 hospital admissions related to HCC (ICD-10 C22) and a total of 21,495 finished consultant episodes (FCE) and 66,989 FCE bed days.[17]

From data gathered between 2013-17 in England (for all liver cancers) one year survival was 40.0% for men and 34.6% for women after diagnosis, with a five year survival of 13.7% for men and 10.7% for women.[18] In England and Wales (2019) 3,144 men and 2,132 women died with HCC as the underlying cause of death.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of liver cancer is dependent on a number of factors including:[20,21]

- If the cancer is primary or secondary, though treatments are similar
- The size and type of cancer
- Location of cancer, for example if it is close to gallbladder or blood vessels
- Health of the liver
- General health of the patient

The management of liver cancer requires different approaches and involves the use of different therapies. A multidisciplinary team of specialists, including doctors and other professionals, help explain treatment options, side effect management and work with the patient to find the most suitable treatment. The main treatments for liver cancer include surgery such as a liver resection, lobectomy or transplant, radiotherapy (in the case of metastatic cancer), chemotherapy, thermal ablation and biological therapy (targeted therapy). Patients may have one of these treatments or a combination. The type or combination of treatments will depend on where cancer was diagnosed and the stage of the disease.[20,21]

CURRENT TREATMENT OPTIONS

In England, NICE recommends the following treatment options for advanced (stage B not eligible for locoregional therapy or stage C) HCC:[22]

- Atezolizumab plus bevacizumab is recommended as an option for treating advanced or unresectable HCC in adults who have not had previous systemic treatment
- Lenvatinib is recommended as an option for untreated, advanced, unresectable HCC in adults
- Sorafenib is recommended as an option for treating advanced HCC.

PLACE OF TECHNOLOGY

If licensed lenvatinib in combination with pembrolizumab, could provide an additional efficacious and safe treatment option for patients with advanced or unresectable HCC.

CLINICAL TRIAL INFORMATION

Trial	LEAP-002; NCT03713593; 2018-002983-26; A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) in Combination With Pembrolizumab (MK-3475) Versus Lenvatinib in First-line Therapy of Participants With Advanced Hepatocellular Carcinoma (LEAP-002) **Trial phase** – Phase III **Location(s):** EU countries (incl UK), USA, Canada and other countries **Primary completion date:** May 2022
Trial design	Randomised, parallel assignment, double masked.
Population	N=750 participants, diagnosis of HCC, BCLC Stage C disease (advanced) or BCLC Stage B disease, not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach, aged 18 years and older.
Intervention(s)	Lenvatinib 12mg or 8 mg administered orally once a day during each 21-day cycle and pembrolizumab 200 mg by intravenous infusion on day 1 of each 21-day cycle.
Comparator(s)	Lenvatinib administered orally once a day during each 21-day cycle and saline placebo.
Outcome(s)	Primary outcome(s); - Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) [Time frame: up to approximately 44 months] - Overall Survival (OS) [Time frame: up to approximately 44 months] 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 is for 4 mg and 10 mg capsules (30 units) is £1,437.[23]

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[24]

- A 100 mg/4 ml concentrate for solution for infusion vial costs £2630.00.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Selective internal radiation therapies for treating hepatocellular carcinoma (TA10381). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Doxorubicin nanoparticles for previously treated advanced hepatocellular carcinoma (TA10251). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for untreated advanced hepatocellular carcinoma. (TA10221). Expected date of issue to be confirmed.
- 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.
- NICE guideline. Cirrhosis in over 16s: assessment and management (NG50). July 2016.
- NICE interventional procedures guidance. Irreversible electroporation for primary liver cancer (IPG664). November 2019.
- NICE interventional procedures guidance. Selective internal radiation therapy for primary hepatocellular carcinoma (IPG460). July 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a.

OTHER GUIDANCE

- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018.[25]
- European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2018.[26]
- 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.[27]
- British Society of Gastroenterology. BSG guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. 2003.[28]

ADDITIONAL INFORMATION

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