NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
AUGUST 2021

Pembrolizumab for Hepatocellular Carcinoma – Adjuvant

NIHRIO ID	27206	**NICE ID**	10406
Developer/Company	Merck Sharp & Dohme (UK) Limited	**UKPS ID**	655495

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pembrolizumab is in clinical development as an adjuvant treatment for hepatocellular carcinoma (HCC). HCC is the most common type of liver cancer. This type of cancer develops from the main liver cells, called hepatocytes. Treatment and survival depends on the stage at which the cancer is diagnosed. HCC is more common in people who have long-term damage to the liver (cirrhosis) due to a viral infection or excessive alcohol intake. It is also more likely to develop in men than in women and it becomes more common as people get older. Surgical resection or local ablation are the primary treatments for HCC although this may require adjuvant treatments to lower the risk of the cancer coming back. There are currently limited adjuvant treatment options for HCC.

Pembrolizumab, administered by intravenous infusion (injection into the vein), is a type of immunotherapy that stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein allows the T-cells to find and kill the cancer cells. Pembrolizumab is already widely approved and in use in a range cancer types (melanoma, non-small-cell lung cancer, squamous cell carcinoma, etc) and in various

settings (e.g. first line, adjuvant etc). Therefore, if licensed, pembrolizumab would offer an adjuvant treatment option for the treatment of HCC.

PROPOSED INDICATION

Adjuvant treatment of adult patients with hepatocellular carcinoma (HCC) and complete radiological response after surgical resection or local ablation.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) 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.[2]

Pembrolizumab is currently in development as adjuvant therapy in patients with hepatocellular carcinoma (HCC) and complete radiological response after surgical resection or local ablation. In the phase III clinical trial, NCT03867084, patients will be given an intravenous (IV) infusion of pembrolizumab 200 mg on day 1 of each 21-day cycle for up to 17 cycles.[1]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab is a strong, selective, IgG4/κ isotype humanised monoclonal antibody that directly inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2. The administration of PD-1 antibodies such as pembrolizumab can unlock the immune "brake" mechanism, restoring the ability of the immune system to attack tumor cells. Unlike conventional chemotherapies and molecular-targeted therapies, PD-1 antibodies act on tumor cells by restoring the potent and accurate host immune system.[3]

Pembrolizumab is already widely in use as a monotherapy and in combination in a range cancer types (melanoma, non-small-cell lung cancer, squamous cell carcinoma, etc) and in various settings (e.g. first line, adjuvant etc). However, no PD-1 receptor blockers are currently recommended by NICE for HCC.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab, administered as a solution for infusion, is currently licenced in the UK for the following indications:[2]

- Melanoma

- Non-small cell lung carcinoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Colorectal cancer
- Oesophageal carcinoma

Very common (≥ 1/10) adverse reactions for pembrolizumab as monotherapy includes anaemia, hypothyroidism, decreased appetite, headache, dyspnoea, diarrhoea, cough, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema, and pyrexia.[2]

Pembrolizumab is in phase II clinical development for: [5]

- Hodgkin's Lymphoma
- Primary mediastinal large B-cell lymphoma (PMBCL)
- Renal cell carcinoma
- Colorectal cancer
- Urothelial
- Lung cancer
- Oesophagus cancer
- Anal cancer

Pembrolizumab is in phase III clinical development for:[6]

- Lung cancer
- Merkel cell carcinoma
- Head and neck squamous cell carcinoma
- Bladder cancer
- Skin cancer
- Oesophagus cancer

PATIENT GROUP

DISEASE BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, which develops from the main liver cells, called hepatocytes.[7] 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, which may ultimately lead to the development of cancerous nodules. Half of all cases of HCC are associated with hepatitis B virus infection, with a further 25% associated with hepatitis C virus. Other risk factors for developing HCC include: alcoholic liver disease, non-alcoholic steatohepatitis, and intake of aflatoxin-contaminated food, diabetes and obesity.[8]

HCC patients are frequently asymptomatic, and the appearance of symptoms can signal the development of severe disease. However, symptoms can appear early in patients with HCC due to chronic liver cancer.[9] The main symptoms of liver cancer may include: weight loss, a swollen abdomen, jaundice, loss of appetite, itching, pain in abdomen or right shoulder, and a lump in the right side of the abdomen.[10] HCC is usually diagnosed using a combination of blood tests (liver function tests, urea and electrolytes, tumour markers – particularly alpha fetoprotein), ultrasound, CT or MRI scans, biopsy (of liver tumour tissue) and laparoscopic investigation.[11]

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.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In England, HCC accounts for up to 55% of all primary liver cancer diagnoses in men and up to 28% of diagnoses in women.[13] 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).[14]

For the UK, the European age-standardised incidence rate of liver cancer is projected to increase by 38% in the UK between 2014 and 2035, to 15 cases per 100,000 in 2035.[15] Meanwhile, the European age-standardised mortality rate for males is projected to rise by 58% between 2014 and 2035, to 16 deaths per 100,000 by 2035.[16]

Hospital Episodes Statistics for England for the period 2019-2020 recorded 21,495 finished consultant episodes (FCEs), 14,287 admissions of which 6,747 were days cases and 66,989 FCE bed days for primary diagnosis malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22.0).[17] In England and Wales in 2017 there were 4,967 deaths recorded for malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22.0) as the underlying cause.[18]

The Barcelona Clinic Liver Cancer (BCLC) staging system is used to aid healthcare professionals in decision-making regarding treatment with stage 0 meaning the patient's tumour is less than 2cm and their liver is working normally (Child-Pugh A, which is a score of 5-6). Stage A means the patient has a single tumour of any size, or up to three tumours less than 3cm and their liver is working well (Child-Pugh A or B, which includes scores of 5-6).[19] For patients at stages 0 and A, where treatment options are ablation, resection or liver transplant, the median survival is 3 years or more without treatment. At stage 0 patients who receive treatment are between 70-90% likely to live 5 years or more, and at stage A 50-70% are predicted to live 5 years or more.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for HCC depends on the location and stage of cancer and how well the liver function is preserved. Commonly the Barcelona Clinic Liver Cancer (BCLC) staging system (stages 0, A, B, C and D) are used to assess the number and size of tumours in the liver as well as performance status and liver function.[19]

Patients with very early HCC (stage 0) are candidates for tumour resection or radiofrequency ablation. Early-stage HCC (stage A) can be treated with curative-intent radical therapies such as resection, liver transplantation, percutaneous ethanol injection, or radiofrequency ablation.[21]

CURRENT TREATMENT OPTIONS

There are no current NICE recommended adjuvant pharmacological treatment options for HCC patients with complete radiological response after surgical resection or local ablation.[4]

PLACE OF TECHNOLOGY

If licensed, pembrolizumab will offer an adjuvant treatment option for patients with HCC and complete radiological response after surgical resection or local ablation.

CLINICAL TRIAL INFORMATION

Trial	**KEYNOTE-937; NCT03867084; 2018-004800-20;** A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) Versus Placebo as Adjuvant Therapy in Participants With Hepatocellular Carcinoma and Complete Radiological Response After Surgical Resection or Local Ablation (KEYNOTE-937) **Phase III** - Recruiting **Location(s):** 11 EU countries, UK, USA, Canada and other countries **Primary completion date:** June 2025
Trial design	Double-blind, two-arm, randomised, parallel assignment, double-masking
Population	N = 950, patients aged 18 years and older, patients with a diagnosis of HCC by radiological criteria and/or pathological confirmation, patients with an eligibility scan (CT of the chest, triphasic CT scan or MRI of the abdomen, and CT or MRI of the pelvis) confirming complete radiological response ≥4 weeks after complete surgical resection or local ablation.

Intervention(s)	Pembrolizumab • Participants receive IV pembrolizumab at 200 mg on Day 1 of each 21-day cycle for up to 17 cycles.
Comparator(s)	Placebo • IV infusion of 0.9% normal saline at 200 mg on Day 1 of each 21-day cycle for up to 17 cycles.
Outcome(s)	Primary outcome(s); • Recurrence-Free Survival (RFS) [Time Frame: Up to ~4 years] • Overall Survival (OS) [Time Frame: Up to ~6 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs £2,630.00.[22]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab for adjuvant treatment of high-risk hepatocellular carcinoma after liver resection or ablation (GID-TA10745). Expected publication date: TBC.

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 live liver transplantation service. A02/S(HSS)/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. 2021.[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 Pembrolizumab (MK-3475) Versus Placebo as Adjuvant Therapy in Participants With Hepatocellular Carcinoma (HCC) and Complete Radiological Response After Surgical Resection or Local Ablation (MK-3475-937 / KEYNOTE-937). Trial ID: NCT03867084.* 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03867084 [Accessed 22 Jun 2021]

2 Electronic Medicines Compendium (emc). *Keytruda 25 mg/mL concentrate for solution for infusion.* Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 22 Jun 2021]

3 Kudo M. Pembrolizumab for the Treatment of Hepatocellular Carcinoma. *Liver Cancer*. 2019;8:143-54. Available from: https://doi.org/10.1159/000500143

4 National Institute for Health and Care Excellence (NICE). *Hepatocellular carcinoma.* Available from: https://pathways.nice.org.uk/pathways/liver-cancers#content=view-node%3Anodes-hepatocellular-carcinoma [Accessed 12 Jul 2021]

5 ClinicalTrials.gov. *Pembrolizumab | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Merck | Phase 2.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=pembrolizumab&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=Merck&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 12 Jul 2021]

6 ClinicalTrials.gov. *Pembrolizumab | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Merck | Phase 3.* Available from: https://clinicaltrials.gov/ct2/results?term=pembrolizumab&spons=Merck&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 12 Jul 2021]

7 Cancer Research UK. *Types of liver cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/types [Accessed 08 Jul 2021]

8 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

9 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

10 Cancer Research UK. *Symptoms.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/symptoms [Accessed 08 Jul 2021]
11 Cancer Research UK. *Tests to diagnose.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/getting-diagnosed/tests-diagnose [Accessed 08 Jul 2021]
12 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
13 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 08 Jul 2021]
14 Office for National Statistics (ONS). *Cancer registration statistics, England: 2017.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 12 Jul 2021]
15 Cancer Research UK. *Liver cancer incidence statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence#heading-Three [Accessed 12 Jul 2021]
16 Cancer Research UK. *Liver cancer mortality statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/mortality#heading-Three [Accessed 12 Jul 2021]
17 National Health Service (NHS). *Hospital Admitted Patient Care Activity 2019-20: Diagnosis.* 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 12 Jul 2021]
18 Office for National Statistics (ONS). *Death Registrations Summary Statistics, England and Wales: 2017 edition of this dataset.* 2018. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 12 Jul 2021]
19 Cancer Research UK. *BCLC staging system and the Child-Pugh system.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/stages/bclc-staging-system-child-pugh-system [Accessed 12 Jul 2021]
20 Cancer Research UK. *Liver Cancer - Survival.* Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/survival [Accessed 11 Aug 2021]
21 Bteich F, Bisceglie A. Current and Future Systemic Therapies for Hepatocellular Carcinoma. *Gastroenterol Hepatol (N Y)*. 2019;15(5):266-72. Available from: https://pubmed.ncbi.nlm.nih.gov/31360140/
22 National Institute for Health and Care Excellence (NICE). *Pembrolizumab.* Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 12 Jul 2021]
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, Martinelli E. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Ann Oncol*. 2021;32(6):801-5. Available from: https://doi.org/10.1016/j.annonc.2021.02.014
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

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.