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Health Technology Briefing
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Durvalumab for previously untreated, hepatocellular carcinoma

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance: ✖ Significant Licence Extension (SLE):

NIHRIO ID: 30627	NICE ID: 10572	UKPS ID: 659873

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Durvalumab is in clinical development for previously untreated patients with hepatocellular carcinoma (HCC), the most common type of liver cancer that develops in liver cells known as hepatocytes. Typically, this type of cancer occurs in patients with underlying chronic liver disease and scarring of the liver caused by long-term liver damage (cirrhosis), as a result of viral infection or lifestyle factors such as high alcohol intake and obesity. Currently, there are a limited number of effective therapies available to treat patients with HCC, and their overall survival prognosis is poor due to rapid disease progression. Therefore, there is a need to develop more effective medicinal products for these patients.

Durvalumab is given by intravenous (IV) infusion into the vein and works by blocking an immune protein called programmed cell death ligand-1 (PD-L1). Normally, the immune system recognises and kills cancer cells. However, cancer cells can develop PD-L1 on their surface, allowing the cancer cells to avoid recognition by the immune system. By blocking PD-L1, durvalumab allows the immune system to recognise and target the cancer cells. If licensed, durvalumab will offer an additional treatment option for patients with unresectable HCC who currently have very poor survival outcomes.

Proposed Indication

First-line treatment of HCC.[1]

Technology

Description

Durvalumab (Imfinzi, MEDI4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80. Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (e.g., IFNgamma) and can be expressed on both tumour cells and tumour associated immune cell in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80. By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD1 and PD-L1/CD80 interactions enhances anti-tumour immune responses and increases T-cell activation.[2]

Durvalumab is in clinical development for previously untreated patients with HCC. In the phase III clinical trial (HIMALAYA, NCT03298451) patients received durvalumab by IV infusion.[1]

Key Innovation

Patients with HCC have few approved systemic treatment options resulting in a poor prognosis with rapid disease progression and short overall survival.[3] Currently, for patients with advanced HCC there are no immunotherapies approved as a first-line monotherapy treatment option.[4,5]

Durvalumab demonstrated non-inferior overall survival and an improved tolerability profile when compared to the standard of care for first-line systemic therapy in patients with advanced HCC. If approved, it would provide an additional treatment option for patients HCC who currently have very poor survival outcomes.[6]

Regulatory & Development Status

Durvalumab currently has Marketing Authorisation in the EU/UK as a monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy, and in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer.[2]

Durvalumab is also currently in phase II and/or III clinical development for the treatment of a number of different cancer indications including bladder cancer, cervical cancer and non-small cell lung cancer.[7]

Durvalumab in combination with tremelimumab was granted orphan drug designation in the USA in January 2020 for the treatment of patients with advanced hepatocellular carcinoma.[6]

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, 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, intake of aflatoxin-contaminated food, diabetes and obesity.[9] Most patients do not have any noticeable symptoms associated with hepatocellular carcinoma.[10]. In the advanced stages of the disease some patients will experience mild to moderate pain in the upper abdomen and may feel full despite eating less food than usual (early satiety). Some may experience fatigue, unintended weight loss or have a mass that can be felt (palpable) in the upper abdomen. Less commonly, fever or diarrhoea may be present.[10]

HCC is the 18th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-18).The age standardised incidence rate of HCC in England is 14.3 and 6.2 per 100,000 amongst males and females respectively.[11] In England, in 2020-21 there were 7,736 finished consultant episodes (FCEs) and 4,995 admissions for liver cell carcinoma (ICD-10 code C22.0), which resulted in 1,530 day cases and 18,483 FCE bed days.[12] In England in 2017, there were 2,704 deaths registered in England and Wales where liver cell carcinoma was the underlying cause. For people diagnosed in 2013, followed up to 2017, the 1-year and 5-year survival rates were 38.1% and 12.7% respectively.[13]

Recommended Treatment Options

Treatment for liver cancer depends on the size and type of cancer the patient has; where the cancer is located, if the cancer has metastasised; and the general health of the patient.[14,15] For patients who are unable to have surgery (unresectable HCC) treatment options include chemotherapy, thermal ablation and targeted medicines.[14]

NICE currently recommends the following first-line systemic treatment options for patients with advanced HCC:[16]

- Atezolizumab with bevacizumab
- Lenvatinib
- Sorafenib

Clinical Trial Information

Trial	**HIMALAYA;** NCT03298451; A Randomized, Open-label, Multi-Centre Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma **Phase III** – Recruiting **Locations:** 4 EU, United States, Canada and other countries. **Actual primary completion date:** 27 August 2021
Trial Design	Randomised, parallel assignment, open-label
Population	N=1504; aged 18 to 100 years; HCC based on histopathological confirmation; no prior systemic therapy for HCC

Intervention(s)	• Durvalumab (IV) • Durvalumab (IV) plus tremelimumab (IV)
Comparator(s)	Sorafenib
Outcome(s)	Primary outcome measure: • Overall survival (OS) [Time Frame: From the date of randomisation until death due to any cause, assessed up to 4 years] See trial record for full list of outcome measures
Results (efficacy)	Durvalumab monotherapy demonstrated a non-inferior OS compared to sorafenib with a numerical trend in favour of durvalumab.[6]
Results (safety)	Durvalumab demonstrated an improved tolerability profile compared to sorafenib.[6]

Estimated Cost

The NHS indicative price for durvalumab is £592 for a 120mg/2.4ml concentrate for solution for infusion vial and £2466 for a 500mg/10ml concentrate for solution for infusion vial.[17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Lenvatinib with pembrolizumab for untreated advanced or unresectable hepatocellular carcinoma (TA10811). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for untreated advanced hepatocellular carcinoma (TA10830). Expected date of issue to be confirmed.
- NICE technology appraisal. Selective internal radiation therapies for treating hepatocellular carcinoma (TA688). March 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. 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 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.[18]
- British Society of Gastroenterology (BSG). BSG guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. 2003.[19]

Additional Information

References

1 Clinicaltrials.gov. *A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma*. *Trial ID: NCT03298451*. 2017. Status: Recruiting. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03298451 [Accessed 02 November 2021].

2 Electronic Medicines Compendium (EMC). *Imfinzi 50 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/9495#gref [Accessed 02 November 2021].

3 National Institute for Health and Care Excellence (NICE). *Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma* (*TA666)*. Last Update Date: December 2020. Available from: https://www.nice.org.uk/guidance/ta666/resources/atezolizumab-with-bevacizumab-for-treating-advanced-or-unresectable-hepatocellular-carcinoma-pdf-82609262480581 [Accessed 03 November 2021].

4 Guardascione M, Toffoli G. Immune Checkpoint Inhibitors as Monotherapy or Within a Combinatorial Strategy in Advanced Hepatocellular Carcinoma. *International Journal of Molecular Sciences*. 2020;21(17). Available from: https://doi.org/10.3390/ijms21176302.

5 Huppert LA, Gordan JD, Kelley RK. Checkpoint Inhibitors for the Treatment of Advanced Hepatocellular Carcinoma. *Clinical Liver Disease*. 2020;15(2):53-8. Available from: https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/cld.879.

6 AstraZeneca. *Imfinzi plus tremelimumab significantly improved overall survival in HIMALAYA Phase III trial in 1st-line unresectable liver cancer.* 2021. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-and-tremelimumab-improved-os-in-liver-cancer.html [Accessed 18 November 2021].

7 Clinicaltrials.gov. *Search for durvalumab clinical studies: phase II and III.* 2021. Available from: https://clinicaltrials.gov/ct2/results?cond=durvalumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 03 November 2021].

8 Cancer Research UK. *Types of Liver Cancer.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/types [Accessed 03 November 2021].

9 Sanyal AJ, Yoon SK, Lencioni R. The Etiology of Hepatocellular Carcinoma and Consequences for Treatment. *The Oncologist*. 2010;15(S4):14-22. Available from: https://pubmed.ncbi.nlm.nih.gov/21115577/.

10 National Organisation of Rare Disorders (NORD). *Hepatocellular Carcinoma.* 2017. Available from: https://rarediseases.org/rare-diseases/hepatocellular-carcinoma/ [Accessed 03 November 2021].

11 Cancer Research UK. *Liver cancer incidence statistics.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence#heading-Zero [Accessed 03 November 2021].

12 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Downloaded 16 September 2021].

13 Office For National Statistics (ONS). *Cancer survival in England - adults diagnosed*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded 12 August 2019].

14 National Health Service (NHS). *Liver Cancer Treatment.* 2020. Available from: https://www.nhs.uk/conditions/liver-cancer/treatment/ [Accessed 03 November 2021].

15 Zhang J-f, Shu Z-j, Xie C-y, Li Q, Jin X-h, Gu W, et al. Prognosis of unresectable hepatocellular carcinoma: comparison of seven staging systems (TNM, Okuda, BCLC, CLIP, CUPI, JIS, CIS) in a Chinese cohort. *PloS one*. 2014;9(3):e88182-e. Available from: https://doi.org/10.1371/journal.pone.0088182.

16 National Institute for Health and Care Excellence (NICE). *Liver cancers - everything NICE says in an interactive flowchart.* 2021. Available from: https://pathways.nice.org.uk/pathways/liver-cancers#content=view-node%3Anodes-hepatocellular-carcinoma [Accessed 03 November 2021].

17 National Institute for Health and Care Excellence (NICE). *Durvalumab solution for infusion.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/durvalumab.html [Accessed 03 November 2021].

18 European Association for the Study of the Liver (EASL). *EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma.* 2018. Available from: https://www.sciencedirect.com/science/article/pii/S0168827818302150 [Accessed 03 November 2021].

19 British Society of Gastroenterology (BSG). *BSG guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults.* 2003. Available from: https://www.bsg.org.uk/clinical-resource/bsg-guidelines-for-the-diagnosis-and-treatment-of-hepatocellular-carcinoma-hcc-in-adults/ [Accessed 03 November 2021].

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