NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# March 2022

# Durvalumab with transarterial chemoembolisation for hepatocellular carcinoma

| Company/Developer | AstraZeneca UK Ltd |
|---|---|

☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 33505 | NICE ID: 10757 | UKPS ID: 663169 |
|---|---|---|

## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Durvalumab with transarterial chemoembolization (TACE) is in clinical development for treating patients with locoregional hepatocellular carcinoma (HCC). HCC is the most common type of primary liver cancer, which affects men more than women, and is more likely to develop the older a person gets. Symptoms include weight loss, jaundice (yellowing of skin), itching, nausea (feeling sick), bloating of the abdomen, loss of appetite, feeling full after eating small amounts, abdomen pain and a lump on the right side of the abdomen.

Durvalumab is given through intravenous infusion and blocks interaction between programmed cell death ligand 1 (PD-L1) and CD80. This enhances immune response against cancerous cells. 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 immune response against the cancer cells when compared to current treatments. If licensed durvalumab in combination with TACE could provide an additional efficacious and safe treatment option for patients with locoregional HCC.

## Proposed Indication

Treatment for patients with locoregional hepatocellular carcinoma (HCC) not amenable to curative therapy.[1]

## Technology

### Description

Durvalumab (Imfinzi, MEDI4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand 1 (PD-L1) with PD-1 and CD80 (B7.1).[1] Durvalumab does not induce antibody dependent cell mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances anti-tumour immune responses and increases T-cell activation. Expression of 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., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in the tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.[2]

Durvalumab and TACE (+/- bevacizumab) is in clinical development for the treatment of patients with locoregional HCC. In the phase III clinical trial (EMERALD-1, NCT03778957) patients will receive either:[1,3]

- Intravenous (IV) durvalumab (1500 mg Q4W) in combination with TACE followed by 1120 mg durvalumab plus placebo Q3W
- IV durvalumab (1500 mg Q4W) in combination with TACE followed by 1120 mg durvalumab plus 15 mg/kg bevacizumab Q3W
- TACE in combination with placebo followed by placebos

### Key Innovation

Local therapy for cancer is expected to affect the tumour microenvironment and to reinforce the efficacy of immune checkpoint inhibitors. In addition, it is expected to enhance therapeutic efficacy by stimulating the release of tumour-associated antigens and neoantigens from cancer cells into the blood. In patients with HCC, local therapy such as radiofrequency ablation (RFA) and TACE has often been used as a standard therapy. Clinical studies have been started with the expectation of synergistic effects when immune checkpoint inhibitors are combined with such local therapeutic approaches.[4]

A phase I/II trial reviewing the safety of second line durvalumab monotherapy in treating solid tumours showed durvalumab to have an acceptable safety profile and to be promising, with a 10% response rate and a median survival time of 13.2 months for the advanced HCC cohort.[5,6]

### Regulatory & Development Status

Durvalumab in combination with TACE +/- bevacizumab does not currently have Marketing Authorisation in the EU/UK for any indication. However, durvalumab is recommended 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 (ES-SCLC).[2]

The most common side effects of durvalumab (>10%) are cough/productive cough, diarrhoea, rash, pyrexia, upper respiratory tract infections, abdominal pain, pruritus, and hypothyroidism.[2]

In addition to HCC, durvalumab is in clinical development for:[7]

- Biliary tract neoplasms
- Bile duct cancers
- Bladder cancers

## Patient Group

### Disease Area and Clinical Need

HCC is the commonest type of primary liver cancer, affecting the main liver cells called hepatocytes.[8] Symptoms include weight loss, jaundice, itching, nausea, bloating of the abdomen, loss of appetite, feeling full after eating small amounts, abdomen pain and a lump on the right side of the abdomen.[9] It is more likely to develop in men than in women and becomes more common as a person ages.[8] Other risk factors of developing HCC include liver cirrhosis, smoking, being overweight or obese, excessive alcohol, non-alcoholic fatty liver disease, and infection with hepatitis viruses.[10]

In England, 2020-21, there were 18,583 finished consultant episodes (FCE) of malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C22) resulting in 48,483 FCE bed days and 6,443 day cases.[11] In the UK, 2016-18, there were 5,635 deaths every year from liver cancer.[12]

There are no UK-wide statistics for liver cancer, however the following survival statistics (with treatment) are taken from the 2012 European Clinical Practice Guidelines for HCC:[13,14]

- Barcelona Clinic Liver Cancer (BCLC) stage 0 (very early stage; Child-Pugh A) – 70-90% will survive ≥5 years
- BCLC stage A (early stage; Child-Pugh A-B) – 50-70% will survive ≥5 years
- BCLC stage B (intermediate stage; Child-Pugh A-B) – Median survival 20 months
- BCLC stage C (advanced stage; Child-Pugh A-B) – Median survival 6-11 months

### Recommended Treatment Options

In England, NICE recommends the following treatment options for untreated HCC:[15]

- Selective internal radiation therapy (SIRT)
- Atezolizumab plus bevacizumab
- Lenvatinib
- Sorafenib

## Clinical Trial Information

| | |
|---|---|
| Trial | **EMERALD-1**, NCT03778957, 2018-002134-20; A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Transarterial Chemoembolization (TACE) in Combination With Either Durvalumab Monotherapy or Durvalumab Plus Bevacizumab Therapy in Patients With Locoregional Hepatocellular Carcinoma<br>**Phase III –** Active, not recruiting<br>**Location(s):** 3 EU countries, US, Canada, and other countries<br>**Primary completion date:** September 2022 |
| Trial Design | Randomised, quadruple-masked, parallel assignment |

| | |
|---|---|
| Population | N=710 (estimated); ages 18 to 110 years; locoregional HCC; no evidence of extrahepatic disease; disease not amenable to curative surgery or transplantation, or curative ablation, but amenable to TACE |
| Intervention(s) | • Experimental Arm A: TACE in combination with 1500 mg Q4W durvalumab followed by 1120 mg durvalumab plus placebo Q3W.[3]<br>• Experimental Arm B: TACE in combination with 1500 mg Q4W durvalumab followed by 1120 mg durvalumab plus 15 mg/kg bevacizumab Q3W.[3] |
| Comparator(s) | Placebo comparator (Arm C): Matched placebos and TACE |
| Outcome(s) | Progression Free Survival (PFS) for Arm B vs Arm C [Time frame: approximately 5 years]<br><br>See trial record for full list of outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

Durvalumab is available as 120mg/2.4ml concentrate for solution for infusion vial that costs £592, and a 500mg/10ml concentrate for solution for infusion vial costs £2,466.[16]

## Relevant Guidance

### NICE Guidance

- NICE Technology appraisal guidance. Regorafenib for previously treated advanced hepatocellular carcinoma (TA555). January 2019.
- NICE Technology appraisal guidance. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma (TA551). December 2018.
- NICE Technology appraisal guidance. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.
- NICE MedTech innovation briefing. SIR-Spheres for treating inoperable hepatocellular carcinoma (MIB63). March 2016.
- NICE MedTech innovation briefing. TheraSphere for treating operable and inoperable hepatocellular carcinoma (MIB62). March 2016.
- NICE Interventional procedures guidance (IPG460). Selective internal radiation therapy for primary hepatocellular carcinoma. July 2013.

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/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. 2016.

### Other Guidance

- The American Association for the Study of Liver Diseases. AASLD guidelines for the treatment of hepatocellular carcinoma. 2018.[17]
- Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. 2017.[18]
- The European Society of Medical Oncology. Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012.[19]
- The European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC). Management of hepatocellular carcinoma, EASL EORTC clinical practice guidelines. 2012.[20]

## Additional Information

## References

1 Clinicaltrials.gov. *A Global Study to Evaluate Transarterial Chemoembolization (TACE) in Combination With Durvalumab and Bevacizumab Therapy in Patients With Locoregional Hepatocellular Carcinoma (EMERALD-1)*. *Trial ID: NCT03778957*. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03778957 [Accessed 18 Mar 2022].

2 European Medicines Compendium (emc). *Imfinzi 50 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/9495 [Accessed 14 Feb 2022].

3 Kudo M. Immuno-Oncology Therapy for Hepatocellular Carcinoma: Current Status and Ongoing Trials. *Liver Cancer*. 2019;8(4):221-38. Available from: https://doi.org/10.1159/000501501.

4 Okusaka T, Ikeda M. Immunotherapy for hepatocellular carcinoma: current status and future perspectives. *ESMO Open*. 2018;3(Suppl 1):e000455. Available from: https://doi.org/10.1136/esmoopen-2018-000455.

5 Ghavimi S, Apfel T, Azimi H, Persaud A, Pyrsopoulos NT. Management and Treatment of Hepatocellular Carcinoma with Immunotherapy: A Review of Current and Future Options. *Journal of clinical and translational hepatology*. 2020;8(2):168-76. Available from: https://doi.org/10.14218/JCTH.2020.00001.

6 Wainberg ZA, Segal NH, Jaeger D, Lee K-H, Marshall J, Antonia SJ, et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). *Journal of Clinical Oncology*. 2017;35(15_suppl):4071-. Available from: https://doi.org/10.1200/JCO.2017.35.15_suppl.4071.

7 Clinicaltrials.gov. *Phase II and III clinical development for durvalumab.* Available from: https://clinicaltrials.gov/ct2/results?term=Durvalumab&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 15 Mar 2022].

8 Cancer Research UK. *Types of liver cancer.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/types [Accessed 14 Feb 2022].

9 Cancer Research UK. *Symptoms of liver cancer.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/symptoms [Accessed 14 Feb 2022].

10 Cancer Research UK. *Liver cancer - Risks and causes.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/risks-causes [Accessed 14 Feb 2022].
11 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 [Accessed 09 Dec 2021].
12 Cancer Research UK. *Liver cancer mortality.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#heading-One [Accessed 14 Feb 2022].
13 Cancer Research UK. *Liver cancer - Survival.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/survival [Accessed 14 Feb 2022].
14 Cancer Research UK. *BCLC staging system and the Child-Pugh system.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/stages/bclc-staging-system-child-pugh-system [Accessed 14 Feb 2022].
15 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 14 Feb 2022].
16 British National Formulary. *Durvalumab* Available from: https://bnf.nice.org.uk/medicinal-forms/durvalumab.html [Accessed 14 Feb 2022].
17 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358-80. Available from: https://doi.org/https://doi.org/10.1002/hep.29086.
18 Kudo M, Trevisani F, Abou-Alfa GK, Rimassa L. Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. *Liver Cancer*. 2017;6(1):16-26. Available from: https://doi.org/10.1159/000449343.
19 Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23 Suppl 7:vii41-8. Available from: https://doi.org/10.1093/annonc/mds225.
20 EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908-43. Available from: https://doi.org/10.1016/j.jhep.2011.12.001.

***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.***