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HEALTH TECHNOLOGY BRIEFING
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Durvalumab and bevacizumab in addition to transarterial chemoembolisation for locoregional hepatocellular carcinoma

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Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not Available

Licensing and market availability plans	In phase III clinical trials

***COMMERCIAL IN CONFIDENCE**

SUMMARY

Durvalumab and bevacizumab in addition to transarterial chemoembolisation (TACE) is in clinical development for treating patients with locoregional hepatocellular carcinoma (HCC). HCC is the most common type of primary liver cancer in adults and the most common cause of death in people with cirrhosis (scarring of the liver). It usually presents at an advanced stage and has a poor prognosis. The current standard of care can only slow the progression of the cancer and extend survival.

Durvalumab and bevacizumab are drugs given through intravenous infusion that act through different pathways to stimulate the body's immune system to fight 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 bevacizumab and TACE could provide an additional efficacious and safe treatment option for patients with locoregional HCC.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

For treating 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). 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]

Bevacizumab (Avastin) binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.[5]

Durvalumab and bevacizumab in addition to transarterial chemoembolisation (TACE) is in clinical development for the treatment of patients with locoregional HCC. In the phase III trial (EMERALD-1; NCT03778957), patients will receive intravenous infusion of durvalumab once every month (Q4W), with TACE. After completion of the last TACE procedure, they will receive durvalumab with or without bevacizumab 15 mg/kg (Q3W) given intravenously (full dosing schedule unavailable).[1,6]

INNOVATION AND/OR ADVANTAGES

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, in particular, 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.[7]

Checkpoint inhibitors, such as durvalumab, are currently the most successful immunotherapy treatment for HCC. Cancer cells can avoid immune surveillance by overexpressing PD-L1 and activating PD-L1/PD-1 signaling, which is observed in HCC tissues. Inhibition of PD-L1 and

DNA methyltransferase 1 significantly suppresses the growth of sorafenib-resistant HCC cells *in vitro*. This points to checkpoint inhibitors being a possible novel treatment option for sorafenib-resistant HCC.[8] The combination of checkpoint inhibitors and VEGF or VEGFR inhibitors may cause a greater net activation of the immune system than checkpoint inhibitors alone due to the added effect of VEGF inhibition.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab and bevacizumab are recommended as monotherapy and in combination with other chemotherapies for several indications, however, durvalumab and bevacizumab in addition to TACE does not currently have Marketing Authorisation in the EU/UK for any indication.

The most common side effects with durvalumab are cough, upper respiratory tract infections, rash and diarrhoea. It is also associated with immune-related adverse reactions including pneumonitis, hepatitis, colitis, hypothyroidism or hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, hypophysitis or hypopituitarism, nephritis and rash.[10]

The most common side effects with bevacizumab are hypertension (high blood pressure), tiredness or asthenia, diarrhoea and abdominal pain. The most serious side effects are gastrointestinal perforation, haemorrhage and arterial thromboembolism.[5,14]

Durvalumab in combination with bevacizumab is in phase II and phase III trials for other indications such as:[12]

- Ovarian cancer
- Glioblastoma
- High risk of recurrence of HCC
- Biliary tract carcinoma
- Colorectal 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.[15] Most patients with HCC have liver cirrhosis, which develops following long periods of chronic liver disease. 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.[16]

The symptoms of liver cancer may include: weight loss, a swollen abdomen, jaundice, loss of appetite, feeling sick, feeling full or bloated after eating small amounts, itching, pain in the abdomen or right shoulder, lump in the right side of the abdomen.[17] 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.[18]

CLINICAL NEED AND BURDEN OF DISEASE

HCC is the most common type of primary liver cancer and more likely to develop in men than in women.[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).[21] The Hospital Episodes Statistics for England 2019-20 recorded a total of 21,495 finished consultant episodes (FCE) that resulted in 14,287 admissions and 66,989 FCE bed days (ICD-10 code C22).[22]

Incidence rates for liver cancer in the UK are highest in people aged 85 to 89 years (2015-2017). Each year more than 4 in 10 (43%) of all new liver cancer cases in the UK are diagnosed in people aged 75 and over (2015-2017). Since the early 1990s, liver cancer incidence rates have increased by more than two-and-a-half times (166%) in the UK. Rates in females have increased by around two-and-a-half times (145%) and rates in males have increased by more than two-and-a-half times (166%) (2015-2017). Incidence rates for liver cancer are projected to rise by 38% in the UK between 2014 and 2035, to 15 cases per 100,000 people by 2035.[23]

In England, in 2017, there were 4,967 deaths where the underlying cause was recorded as malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22).[24] Five year survival for liver cancer in England is one of the lowest of any forms of cancer with 10.7% of women surviving more than 5 years following diagnosis and 13.7% of men between 2013 and 2018.[25]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for HCC depends on the location and stage of the cancer, and how well the liver function is preserved. For people with more advanced disease, treatment is palliative rather than curative. Treatment options include interventional procedures such as TACE (using doxorubicin or cisplatin) or selective internal radiation therapy, and external beam radiotherapy. People for whom these treatments are not suitable, or those with metastatic disease, are treated with sorafenib or lenvatinib in the first-line setting. Some people with HCC are treated with best supportive care.[26,27]

HCC can be treated with surgical resection, liver transplantation, trans-catheter arterial chemo-embolisation, percutaneous ablation, systemic drug treatment, and external beam or stereotactic radiotherapy.[28]

CURRENT TREATMENT OPTIONS

In England, NICE recommends the following treatment options for advanced hepatocellular carcinoma:[27]

- Atezolizumab plus bevacizumab for treating advanced or unresectable HCC in adults who have not had previous systemic treatment, only if they have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1.
- Lenvatinib for untreated, advanced, unresectable hepatocellular carcinoma in adults, only if they have Child–Pugh grade A liver impairment and an ECOG performance status of 0 or 1.

- Sorafenib for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment.
- Regorafenib for treating advanced unresectable hepatocellular carcinoma in adults who have had sorafenib, only if they have Child–Pugh grade A liver impairment and an ECOG performance status of 0 or 1.

PLACE OF TECHNOLOGY

If licenced, durvalumab and bevacizumab in addition to TACE will offer an additional treatment option for people with locoregional HCC not amenable to curative therapy, and may potentially improve quality of life and survival outcomes.

CLINICAL TRIAL INFORMATION

Trial	**EMERALD-1;** NCT03778957**,** EudraCT-2018-002134-20**,** D933GC00001**;** 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 **Phase III –** ongoing **Locations – EU countries (not incl UK),** Canada, United States and other countries **Primary completion date -** August 31, 2021
Trial design	Randomised, parallel assignment, quadruple masking, placebo-controlled
Population	N=600; subjects with Hepatocellular carcinoma not amenable to curative surgery or transplantation or curative ablation but disease amenable to TACE; aged 18 to 110 years
Intervention(s)	Experimental Arm A: Durvalumab IV (intravenous) + TACE Experimental Arm B: Durvalumab IV + Bevacizumab IV 15mg/kg + TACE
Comparator(s)	Experimental Arm C: Matched placebo + TACE
Outcome(s)	Primary outcome: Progression Free Survival (PFS) for Arm B vs Arm C [Time Frame: Approximately 5 years]
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.[29]

Bevacizumab is available as:[30]

- Bevacizumab100mg/4ml solution for infusion vials that costs £242.66 and 400mg/16ml solution for infusion vials costs £924.40.
- Bevacizumab100mg/4ml solution for infusion vials at a cost of £218.39 and 400mg/16ml solution for infusion vials at £831.96.
- Bevacizumab 100mg/4ml solution for infusion vials at a cost of £225.67 and 400mg/16ml solution for infusion vials at £902.70.

RELEVANT GUIDANCE

NICE GUIDANCE

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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

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ADDITIONAL INFORMATION

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