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Health Technology Briefing
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Durvalumab with bevacizumab adjuvant therapy for treating newly diagnosed hepatocellular carcinoma at high risk of recurrence after curative therapy

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27181	NICE ID: 10736	UKPS ID: 665477

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Durvalumab with bevacizumab is intended to treat hepatocellular carcinoma (HCC), the most common type of liver cancer, where there is a high risk of the cancer returning after curative treatment. It is common that people with HCC are asymptomatic (do not show symptoms related to the cancer). There is increased risk of developing HCC if you have underlying liver disease (e.g., hepatitis B/C or non-alcoholic fatty liver disease), or cirrhosis (scarring of the liver). There is an unmet need in this setting as no effective treatments have been identified for cancer that is at risk of returning after surgery.

Durvalumab is a type of monoclonal antibody administered by intravenous (IV) infusion, which works by blocking a protein called programmed death ligand 1 (PD-L1). This helps the immune system to kill cancer cells. Bevacizumab binds to vascular endothelial growth factor (VEGF) and limits tumour growth. An effective treatment to reduce the risk of cancer returning after surgery in HCC patients has not been identified. The combination of durvalumab and bevacizumab may enhance anti-tumour activity and would offer a new treatment approach for HCC patients at high risk of disease recurrence.

Proposed Indication

Adjuvant treatment of adults with newly diagnosed HCC at high risk of recurrence after curative therapy.[1]

Technology

Description

Durvalumab (Imfinzi) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed death ligand 1 (PD-L1) with PD-1 and CD80(B7.1). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). [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.[3]

Durvalumab with bevacizumab is currently in phase III clinical development for the adjuvant treatment of adults with newly diagnosed HCC at high risk of recurrence after curative therapy. In the phase III clinical trial (EMERALD-2, NCT03847428) participants received either intravenous (IV) infusion of durvalumab monotherapy at a dosage of 1120mg once every three weeks (Q3W), or 1120mg durvalumab IV infusion and 15mg/kg bevacizumab IV infusion once every 3 weeks.[1]

Key Innovation

An effective adjuvant therapy for HCC patients has not been demonstrated to date and the prevention and/or delay of recurrence of HCC after curative treatment presents a high unmet medical need. There is encouraging evidence that adjuvant therapy involving agents that engage the immune response, including immunotherapy such as durvalumab, can prolong recurrence-free survival (RFS) in some patients with HCC. Other evidence shows that inhibiting the VEGF pathway may enhance the activity of PD-L1 blockade in some patients with HCC.[4]

Regulatory & Development Status

Durvalumab as a monotherapy has a Marketing Authorisation in the UK 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. It is also licensed 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]

Bevacizumab has a Marketing Authorisation in the UK for the following indications:[3]

- With fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum
- With paclitaxel for the first-line treatment of adult patients with metastatic breast cancer
- With capecitabine for the first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate

- In addition to platinum-based chemotherapy for the first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC
- In combination with interferon alfa-2a for the first line treatment of adult patients with advanced and/or metastatic renal cell cancer
- In combination with carboplatin and paclitaxel for the first-line treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer
- In combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents
- In combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents
- In combination with paclitaxel and cisplatin or alternatively paclitaxel and topotecan in patients who cannot receive platinum therapy for the treatment of adult patients with persistent, recurrent or metastatic carcinoma of the cervix

Durvalumab and bevacizumab in combination are in phase III/II clinical trials for ovarian cancer, breast cancer, small cell lung cancer (SCLC), and gastric cancers.[5]

Durvalumab has US Orphan Drug Designation for the treatment of HCC.[6]

Patient Group

Disease Area and Clinical Need

HCC is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide.[7] Most patients diagnosed with HCC have an underlying liver disease such as an infection with the hepatitis B or C virus, or non-alcoholic fatty liver disease (NAFLD). Most people also have cirrhosis, which is scarring of the liver that can occur as a result of chronic liver diseases. It is common for people to not have any noticeable symptoms associated with HCC.[8] Many factors affect the risk of post-operative HCC recurrence, including tumour size, tumour encapsulation, microvascular invasion, liver cirrhosis, serum α-fetoprotein (AFP) level >400µg/L and use of antiviral drugs.[9]

In 2019, a total of 5,741 patients in England were diagnosed with malignant neoplasm of liver and intrahepatic bile ducts (ICD10 C22).[10] HCC accounts for approximately 90% of primary liver cancers, however most patients are in the advanced stages at diagnosis and therefore ineligible for surgery[11,12] The annual recurrence rate of HCC after 1 year after surgical resection is >20%, and reaches 70-80% after 5 years.[11,13] In England, between 2013-17, the average 5-year overall survival rate for liver cancer was 13%.[14]

Recommended Treatment Options

NICE currently does not recommend any adjuvant therapies for HCC at high risk of recurrence following curative treatment.[15]

Clinical Trial Information

Trial	**EMERALD-2**; NCT03847428; 2018-004105-85; A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multi Center Study of Durvalumab Monotherapy or in Combination With Bevacizumab as Adjuvant Therapy in Patients With Hepatocellular Carcinoma Who Are at High Risk of Recurrence After Curative Hepatic Resection or Ablation **Phase III** – Active, not recruiting **Locations:** 5 EU countries, USA, Canada and other countries **Primary completion date:** May 2023
Trial Design	Randomised, double-blind, placebo-controlled.
Population	N=887; Adults with histologically or cytologically (or radiologically for patients undergoing curative ablation), newly diagnosed, confirmed HCC who have successfully completed curative therapy (resection or ablation)
Intervention(s)	Durvalumab IV 1120mg Q3W and bevacizumab placebo or durvalumab 1120mg IV Q3W and bevacizumab 15mg/kg IV Q3W
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measures:** Recurrence free survival (RFS) [Time frame: up to 49 months after first patient randomised] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of durvalumab concentrate for solution for infusion vial, NHS indicative price (hospital only), is:[16]

- 120mg/2.4ml £592
- 500mg/10ml £2,466

The cost of bevacizumab 100mg/4ml concentrate for solution for infusion vial, NHS indicative price (hospital only), is between £205.55 and £242.66.[17]

Relevant Guidance

NICE Guidance

- NICE guidance in development. Pembrolizumab for adjuvant treatment of hepatocellular carcinoma [ID3994]. Expected date of issue to be confirmed.
- NICE guidance in development. Nivolumab for adjuvant treatment of high-risk hepatocellular carcinoma after liver resection or ablation [ID3858]. Expected February 2024.

NHS England (Policy/Commissioning) Guidance

No relevant guidance found.

Other Guidance

- European Society for Medical Oncology (ESMO). Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2018.[18]
- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. July 2018.[19]

Additional Information

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