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Newcastle University

Health Technology Briefing
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Durvalumab adjuvant therapy for treating hepatocellular carcinoma at high risk of recurrence after curative treatment

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34479	NICE ID: 11797	UKPS ID: 665478

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Durvalumab as an adjuvant therapy is in clinical development for treating 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 HCC that is at risk of returning after surgery.

Durvalumab is a type of monoclonal antibody (a type of protein that is made in the laboratory) 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. An effective treatment to reduce the risk of cancer returning after surgery in HCC patients has not been identified. Durvalumab as an adjuvant therapy may enhance anti-tumour activity and would offer a new treatment approach for HCC patients at high risk of disease recurrence.

Proposed Indication

Adjuvant therapy for patients with HCC who are at high risk of recurrence after curative hepatic resection or ablation.[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]

Durvalumab is currently in phase III clinical development for the adjuvant treatment of adults with HCC who are at high risk of recurrence after curative hepatic resection or ablation. In the phase III clinical trial (EMERALD-2, NCT03847428) participants received durvalumab 1120mg intravenously (IV) once every 3 weeks along with a bevacizumab placebo.[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 an 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.[3]

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]

Durvalumab as a monotherapy is in phase II and III clinical development for several indications including papillary renal cell carcinoma, advanced solid malignancies, head and neck squamous cell carcinoma, amongst others.[4]

Durvalumab has US Orphan Drug Designation for the treatment of HCC.[5]

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.[6] 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.[7] 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.[8]

In 2019, a total of 5,741 patients in England were diagnosed with malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 C22).[9] In 2020-21 there were 18,583 finished consultant episodes (FCE) for patients with ICD-10 C22, accounting for 48,483 FCE bed days and 6,443 day cases.[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] In England, between 2013-17, the average 5-year overall survival rate for liver cancer was 13%.[13]

Recommended Treatment Options

NICE currently does not recommend any adjuvant therapies for HCC at high risk of recurrence following curative treatment.[14]

Clinical Trial Information

Trial	**EMERALD-2; NCT03847428; EudraCT 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 **Location(s):** 5 EU countries, USA, Canada and other countries **Primary completion date:** June 2023
Trial Design	Randomised, quadruple-masked (participant, care provider, investigator, outcomes assessor) parallel assignment
Population	N= 877 (actual); diagnosed with HCC; successfully completed curative therapy (resection or ablation)
Intervention(s)	Experimental: Arm B – Durvalumab intravenously (IV) 1120mg (Q3W) and bevacizumab placebo
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Recurrence-free survival (RFS) for Arm A (experimental durvalumab and bevacizumab) vs Arm C (placebo comparator) [Time Frame: Up to 49 months after first patient randomized] 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:[15]

- 120mg/2.4ml £592

- 500mg/10ml £2,466

Relevant Guidance

NICE Guidance

- NICE guidance in development. Atezolizumab with bevacizumab for adjuvant treatment of resected or ablated hepatocellular carcinoma at high risk of recurrence [ID10650]. Expected date of issue to be confirmed.
- 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.[16]
- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. July 2018.[17]

Additional Information

References

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