Health Technology Briefing
September 2024

Durvalumab and tremelimumab with or without lenvatinib in combination with concurrent transarterial chemoembolisation in patients with locoregional hepatocellular carcinoma

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34847	NICE ID: Not available	UKPS ID: 670212

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Durvalumab and tremelimumab with or without lenvatinib in combination with concurrent transarterial chemoembolisation are in clinical development for the treatment of adults with hepatocellular carcinoma (HCC). HCC is a primary cancer arising from hepatocytes in predominantly cirrhotic liver. However, some patients may not have cirrhosis before developing HCC, especially those with chronic hepatitis B virus. A significant number of patients may be asymptomatic and are diagnosed following screening. Symptoms of HCC can include: the whites of eyes turning yellow or skin turning yellow, loss of appetite or losing weight without trying to, feeling tired, feeling generally unwell or having symptoms like flu, a lump in the right side of tummy, and symptoms of indigestion. Current treatment options may include surgery, chemotherapy, using heat to destroy the cancer (thermal ablation), targeted medicines, and radiotherapy. There is need for more treatment options with more efficacy because the current treatment options are limited.

The combination of durvalumab and tremelimumab, is currently under investigation for the treatment of adult patients with HCC, the most common type of liver cancer. Durvalumab and tremelimumab are drugs both given through intravenous infusion that act through different pathways to stimulate the body's immune system to fight cancerous cells. If licensed durvalumab in combination with tremelimumab could provide an additional efficacious and safe treatment option for patients with unresectable HCC and may produce a stronger more targeted immune response against the cancer cells.

Proposed Indication

Treatment of locoregional hepatocellular carcinoma (HCC) in adults aged 18 years and older.[1]

Technology

Description

The combination of durvalumab (Imfinzi, MEDI4736) and tremelimumab (MEDI1123) is [1] a novel combination immunotherapy for unresectable HCC.[2] Durvalumab is a highly selective human IgG1 monoclonal inhibitor that blocks interaction with PD-1 and CD80 to overcome blockage of primary human T-cell activation.[3] 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.[4] Tremelimumab has a high affinity to human IgG2 monoclonal antibody of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[5] Tremelimumab binds to CTLA4 on activated T-lymphocytes and blocks the binding of the antigen presenting cell ligands CD80 and CD86 to CTLA4, resulting in inhibition of CTLA4-mediated downregulation of T-cell activation. This leads to a cytotoxic T-lymphocyte mediated immune response against cancer cells.[6]

The combination of durvalumab and tremelimumab is currently in clinical development for the treatment of HCC in adults. In the phase III clinical trial (NCT05301842), participants were randomly assigned to Arm A (durvalumab, tremelimumab, TACE and lenvatinib), Arm B (durvalumab, tremelimumab, and TACE), or Arm C (TACE alone).[7]

Key Innovation

The current durvalumab plus tremelimumab regimen is the first combination immunotherapy with anti-PD-L1 and anti-CTLA-4 antibodies that have reportedly been successful in the phase 3 setting.[2] This combination, through its mechanism of action consisting of simultaneous inhibition of two independent pathways that acts to supress T-cell responses to tumours had a response rate of 25%, suggesting that this combined therapy might be more effective than durvalumab monotherapy.[8] Furthermore, pre-clinical data suggests that targeting both pathways could have an additive or synergistic effect providing the potential for increased effectiveness when compared with current therapies for HCC.[3] Combining a single priming dose of the anti–CTLA-4 agent tremelimumab with durvalumab has shown significant promise in the treatment of patients with unresectable HCC.[9]

If licensed, the combination of durvalumab plus tremelimumab will offer an additional treatment option for patients with locoregional HCC.

Regulatory & Development Status

Durvalumab in combination with tremelimumab is licensed in the EU/UK as a first line treatment for adults with advanced or unresectable HCC.[10]

Durvalumab as a monotherapy is licensed in the EU/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.[4]
Tremelimumab as a monotherapy does not currently have marketing authorisation for any indication in the EU/UK.
Durvalumab in combination with tremelimumab is also in the phase II/III clinical development for the following indications:[11]

- advanced rare solid tumours
- unresectable urothelial cancer
- muscle invasive bladder cancer
- metastatic HER2 negative breast cancer
- squamous cell carcinoma of the head and neck
- colorectal cancer
- NSCLC
- progressive, refractory advanced thyroid carcinoma
- advanced gastric or gastro-oesophageal junction adenocarcinoma
- ovarian cancer

Patient Group

Disease Area and Clinical Need

HCC is the most common type of primary liver cancer.[14] It develops from the main liver cells known as hepatocytes. The major risk factor for HCC is liver cirrhosis, which is scarring of the liver due to previous damage, although not all patients will have cirrhosis prior to developing HCC.[12,13] Other risk factors include smoking, obesity, hepatitis B or C and non-alcoholic fatty liver disease.[12] Symptoms of liver cancer often do not appear until the cancer is at an advanced stage, with the majority of patients (80%) not diagnosed until an advanced stage of the HCC when it is usually not amenable to surgery (i.e. unresectable).[14] Symptoms include, unintentional weight loss, loss of appetite, feeling nauseous, pain or swelling in the abdomen, jaundice, itchy skin and feeling very tired or weak.[14]

Approximately 3,600 people are diagnosed with HCC each year in the UK. While HCC is the third most common cancer worldwide, it remains relatively rare in the UK.[15] HCC affects 3.4 times as many men as women, with a mean age at diagnosis of approximately 68.4 years.[16] Approximately 1 in 10 (8.0%) people diagnosed with liver cancer in England survive their disease for ten years or more. Additionally, liver cancer five-year survival in England is higher in males than females. Around a third (34.3%) of people in England diagnosed with liver cancer aged 15-44 survive their disease for five years or more, compared with around 5 in 100 (6.0%) people diagnosed aged 75-99.[17] In England in 2022-2023, there were 22,679 finished consultant episodes (FCE) and 16,440 hospital admissions for malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C22.0) which resulted in 59,485 FCE bed days and 9,636 day cases.[18]

Recommended Treatment Options
The National Institute for Health and Care Excellence (NICE) recommends the following regimen for the treatment of HCC: • Sorafenib for treating advanced HCC only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement.[19] • Lenvatinib for untreated, advanced, unresectable HCC in adults, only if they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and the company provides according to the commercial agreement.[20] • Cabozantinib for advanced HCC 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 and the company provides it according to the commercial agreement.[21] • Regorafenib for treating advanced unresectable HCC in adults who have had sorafenib, only if they have Child-Pugh grade A liver impairment and ECOG performance status of 0 or 1 and the company provides according to the commercial agreement.[22] • 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 ECOG performance status of 0 or 1 and the company provides according to the commercial agreement.[22]

Clinical Trial Information	
Trial	NCT05301842, 2021-003822-54; A phase III, randomized, open-label, sponsor-blinded, multicentre study of durvalumab in combination with tremelimumab ± lenvatinib given concurrently with TACE compared to TACE alone in patients with locoregional hepatocellular carcinoma (EMERALD-3) **Phase III –** Active, recruiting **Location(s):** Six EU countries, USA, Canada, and other countries **Primary completion date:** December 2025
Trial Design	Randomised, multicentre, open label, single-blinded (outcomes assessor), parallel assignment
Population	N=725 (estimated); subjects with locoregional HCC not amenable to curative therapy (e.g., surgical resection, transplantation, or ablation); aged 18 years to 120 years (adult, older adult)
Intervention(s)	Experimental arm A includes tremelimumab, durvalumab and lenvatinib in combination with TACE Experimental arm B includes tremelimumab and durvalumab in combination with TACE
Comparator(s)	Active Comparator TACE alone
Outcome(s)	Primary outcome measure:

	• Progression Free Survival (PFS) for Arm A vs Arm C [Time Frame: Approximately 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The list price of durvalumab is £2,466 per 500 mg per 10 ml infusion vial.
The cost of tremelimumab is not yet known.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab (Imfinzi) with bevacizumab (Avastin) for high-risk adjuvant hepatocellular carcinoma (ID6146). TBC.
- NICE technology appraisal in development. Durvalumab with transarterial chemoembolization for treating incurable locally advanced hepatocellular carcinoma (ID5124). TBC.
- NICE technology appraisal in development. Durvalumab with bevacizumab and transarterial chemoembolization for treating locally advanced hepatocellular carcinoma (ID3944). TBC.
- NICE technology appraisal in development. Durvalumab for untreated unresectable hepatocellular carcinoma (ID4068).
- NICE technology appraisal in development. Atezolizumab with bevacizumab for adjuvant treatment of resected or ablated hepatocellular carcinoma at high risk of recurrence (ID6148). TBC.
- NICE technology appraisal in development. Hepatocellular carcinoma (unresectable, untreated) – tislelizumab (ID6129). TBC.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated advanced hepatocellular carcinoma (ID10345). TBC.
- NICE technology appraisal in development. Lenvatinib with pembrolizumab and transarterial chemoembolization for untreated localised hepatocellular carcinoma (ID5117). TBC.
- NICE technology appraisal guidance. Cabozantinib for previously treated advanced hepatocellular carcinoma (TA849). December 2022.
- NICE technology appraisal guidance. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma (TA666). December 2020.

- NICE technology appraisal guidance. Regorafenib for previously treated advanced hepatocellular carcinoma (TA555). January 2019.
- NICE technology appraisal guidance. Lenvatinib for untreated advanced hepatocellular carcinoma (TA551). December 2018.
- NICE technology appraisal guidance. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.
- NICE Quality Standard. Liver disease (QS152). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS Wales. 2021 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a
- NHS England. Clinical commissioning policy: Stereotactic ablative radiotherapy (SABR) for hepatocellular carcinoma (adults) (URN: 1913) [200206P]. March 2020.
- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a

Other Guidance

- European Society for Medical Oncology. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. 2021. [24]
- Benson AB, D'Angelica MI, Abbott DE, Anaya DA, Anders R, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Journal of The National Comprehensive Cancer Network. 2021. [25]

Additional Information

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