

## HEALTH TECHNOLOGY BRIEFING OCTOBER 2019

### Durvalumab in combination with tremelimumab for unresectable hepatocellular carcinoma – first line

<b>NIHRIO ID</b>	20506	<b>NICE ID</b>	10254
<b>Developer/Company</b>	AstraZeneca	<b>UKPS ID</b>	654273

<b>Licensing and market availability plans</b>	Currently in phase III trials
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### SUMMARY

Durvalumab in combination with tremelimumab is in clinical development for patients with unresectable hepatocellular carcinoma (HCC), the most common type of liver cancer that occurs mainly in patients with underlying chronic liver disease and cirrhosis. Unresectable HCC occurs when the cancer has spread to lymph nodes or to other organs and cannot be treated by surgery. Unresectable HCC is often diagnosed late in life and has a poor prognosis. It is a debilitating condition with many distressing symptoms, including pain, digestive problems and weight loss. The current standard of care can only slow the progression of the cancer and extend survival.

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. The combined effect of the two products may produce a stronger more targeted immune response against the cancer cells when compared to current treatments. If licensed durvalumab in combination with tremelimumab could provide an additional efficacious and safe treatment option for patients with unresectable hepatocellular carcinoma.

*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

Advanced unresectable Hepatocellular Carcinoma (HCC)- first line.<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Durvalumab (Imfinzi, MEDI4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of 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 programmed cell death ligand-1 (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 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.<sup>2</sup>

Tremelimumab (CP-675,206) is a human immunoglobulin (Ig)G2 monoclonal antibody which binds to cytotoxic T-lymphocyte-associated protein 4 (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.<sup>3</sup>

Durvalumab in combination with tremelimumab is in clinical development for the first line treatment of patients with advanced unresectable HCC.<sup>1</sup> In the phase III study of durvalumab with or without tremelimumab versus sorafenib (HIMALAYA; NCT03298451), subjects in the combination therapy arms receive durvalumab and tremelimumab intravenously. Patients in all arms will continue therapy until disease progresses.<sup>4</sup>

### INNOVATION AND/OR ADVANTAGES

Recently, sorafenib and several other molecular-targeted agents have demonstrated survival advantages in patients with advanced HCC. Therapy with sorafenib (the current standard of care in HCC), can only extend the overall survival of patients with advanced HCC by 3 months and is associated with significant adverse effects. Therefore, the prognosis of patients with HCC is still quite poor, and further efforts to develop new treatment methods are needed.<sup>5,6</sup>

The combination of durvalumab and tremelimumab, through its mechanism of action consisting of simultaneous inhibition of two independent pathways that acts to suppress T-cell responses to tumours has been assessed in a phase I/II study that enrolled 40 patients and had a response rate of 25%, suggesting that this combined therapy might be more effective than durvalumab monotherapy.<sup>7</sup> 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 hepatocellular carcinoma.<sup>8</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab in combination with tremelimumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Durvalumab monotherapy is indicated 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. The most common side effects with durvalumab (which may affect more than 1 in 5 people) are cough, nose and throat infections, and rash. The most common serious side effect (which may affect up to 1 in 10 people) is pneumonia (infection of the lungs).<sup>9</sup>

Durvalumab in combination with tremelimumab is in phase II clinical trials for the treatment of biliary tract, oesophageal and gastric cancer, and in phase III clinical trials for the treatment of bladder cancer, non-small-cell lung cancer and head and neck squamous cell carcinoma.<sup>10</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

Hepatocellular carcinoma (HCC) 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.<sup>11,12</sup> Other risk factors include smoking, obesity, hepatitis B or C and non-alcoholic fatty liver disease.<sup>11</sup>

Symptoms of liver cancer often do not appear until the cancer is at an advanced stage so most patients (80%) with HCC are not diagnosed until an advanced stage of the disease when it is usually not amenable to surgery (i.e. unresectable). 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.<sup>13</sup>

HCC cannot be diagnosed by routine blood tests. The only specific blood test that can be used towards the diagnosis of HCC is a test to measure the levels of the protein alfa-fetoprotein in serum (AFP). However, only around half of all tumours will have a raised reading of AFP and people with cirrhosis without HCC will have raised AFP so it can't be used on its own to accurately diagnose HCC. Ultrasound and biopsy are also carried out if HCC is suspected.<sup>14</sup>

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.<sup>15</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

HCC is the most common type of primary liver cancer accounting for 75% of all liver cancers.<sup>11,14</sup> In 2017 in England alone there were 4,975 new cases of malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C22).<sup>16</sup> The Hospital Episodes Statistics for England 2017-18 recorded a total of 18,973 finished consultant episodes (FCE) that resulted in 12,812 admissions and 61,043 FCE bed days (ICD-10 code C22).<sup>17</sup>

The European Age-Standardised incidence rate was 9.7 for 100,000 population in 2016.<sup>18</sup> The risk of developing HCC increases with age. The overall incidence of HCC has increased by 162% in the UK between 1993-1995 and 2014-2016. Liver cancer incidence rates are projected to rise by 38% in the UK from 5,520 observed cases (equating to 11.16 per 100,000) in 2014 to 11,133 projected cases (equating to 15.39 per 100,000) in 2035.<sup>19</sup>

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).<sup>20</sup> 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.<sup>21</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Since most diagnosis of HCC are often made in the advanced stage of the disease after patients have become symptomatic there is often no effective treatment to improve survival rates.<sup>22</sup>

Most hospitals use multi-disciplinary teams to treat liver cancer. The treatment for liver cancer depends on the stage of the condition and how well liver function is maintained.<sup>12</sup> Treatment can include surgery resection, liver transplant, chemotherapy, radiotherapy, thermal ablation and medication.<sup>11,22</sup>

### CURRENT TREATMENT OPTIONS

In England, NICE recommends the following treatment options for advanced (stage B not eligible for locoregional therapy or stage C) hepatocellular carcinoma:<sup>23</sup>

- Lenvatinib is recommended as an option for untreated, advanced, unresectable hepatocellular carcinoma in adults
- Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment

### PLACE OF TECHNOLOGY

If licenced, durvalumab in combination with tremelimumab will offer an additional treatment option for people with advanced hepatocellular carcinoma and may potentially improve quality of life and survival outcomes.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	HIMALAYA, <a href="#">NCT03298451</a> , <a href="#">EudraCT-2016-005126-11</a> , D419CC00002; adults aged 18 years and older; durvalumab and tremelimumab vs sorafenib; phase III
<b>Sponsor</b>	AstraZeneca
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial Registry <sup>1,24</sup>
<b>Location</b>	4 EU countries (not incl UK), USA, Canada and other countries
<b>Design</b>	Randomized, open-labelled, parallel assigned, active controlled study
<b>Participants</b>	n=1,310 (planned); aged 18 to 100 years; HCC based on histopathological confirmation; no prior systemic therapy for HCC; Barcelona Clinic Liver Cancer stage B or stage C; Child-Pugh Score class A; ECOG performance status of 0 or 1 at enrolment.

<b>Schedule</b>	Patients will be randomized in a 1:1:1:1 ratio to durvalumab (arm1), combination therapy with durvalumab plus tremelimumab (arm 2 – regimen 1), combination therapy with durvalumab plus tremelimumab (arm 3 – regimen 2) and sorafenib (arm 4).
<b>Follow-up</b>	Active treatment until disease progression, follow-up 4 years.
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Overall survival [Time frame: up to 4 years].</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Time to Progression (TTP) [ Time Frame: From randomization until objective tumor progression, assessed up to 4 years. ]</li> <li>• Progression-free survival (PFS) [ Time Frame: From date of randomization until the date of objective disease progression or death, assessed up to 4 years. ]</li> <li>• Objective response rate (ORR) [ Time Frame: Until progression, assessed up to 4 years. ]</li> <li>• Disease control rate (DCR) [ Time Frame: Until progression, assessed up to 4 years. ]</li> <li>• Duration of response (DoR) [ Time Frame: From the date of first documented response (RECIST 1.1.) until the first date of documented progression or death in the absence of disease progression, assessed up to 4 years. ]</li> <li>• Health status/quality of life measured by European Organization for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30) [ Time Frame: From randomization up to approximately 3 months from the treatment discontinuation, assessed up to 4 years. ]</li> <li>• Presence of ADA for durvalumab and tremelimumab [ Time Frame: Starting prior to the first dose of the treatment up to approximately 3 months from the treatment discontinuation, assessed up to 4 years. ]</li> <li>• The pharmacokinetics (PK) of durvalumab and tremelimumab as determined by trough concentration [ Time Frame: Starting prior to the first dose of the treatment up to approximately 3 months from the treatment discontinuation, assessed up to 4 years. ]</li> <li>• Disease-related symptoms measured by EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18) [ Time Frame: From randomization up to approximately 3 months from the treatment discontinuation, assessed up to 4 years. ]</li> <li>• The pharmacokinetics (PK) of durvalumab and tremelimumab as determined by peak concentration [ Time Frame: Starting prior to the first dose of the treatment up to approximately 3 months from the treatment discontinuation, assessed up to 4 years. ]</li> <li>•</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Study completion date reported as June 2021

## ESTIMATED COST

Durvalumab is already marketed in the UK for the treatment of non-small-cell lung cancer; a 120mg/2.4ml concentrate for solution for infusion vial costs £592 and a 500mg/10ml concentrate for solution for infusion vial costs £2,466.<sup>25</sup>

The cost of durvalumab in combination with tremelimumab is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal in development. Selective internal radiation therapies for treating hepatocellular carcinoma (TA10381). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for untreated advanced hepatocellular carcinoma. (TA10221). Expected August 2020.
- NICE technology appraisal. Lenvatinib for untreated advanced hepatocellular carcinoma (TA551). December 2018.
- NICE technology appraisal. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.
- NICE interventional procedures guidance. Selective internal radiation therapy for primary hepatocellular carcinoma (IPG460). July 2013.
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### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for specialist liver disease service (children). E03/S(HSS)/d
- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a

### OTHER GUIDANCE

- European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO Clinical practice Guidelines for diagnosis, treatment and follow-up. 2018.<sup>26</sup>
- European Association for the Study of Liver. Management of Hepatocellular Carcinoma guideline. 2018.<sup>27</sup>

## ADDITIONAL INFORMATION

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