Health Technology Briefing
July 2022

Nivolumab-ipilimumab for previously untreated advanced hepatocellular carcinoma

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28189	NICE ID: 10345	UKPS ID: 653698

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Nivolumab and ipilimumab is in development for the first-line treatment of advanced hepatocellular carcinoma (HCC). HCC is the most common type of primary liver cancer, which affects men more than women, and is more likely to develop the older a person gets. Advanced HCC means the cancer is incurable. Symptoms include weight loss, jaundice (yellowing of skin), itching, nausea (feeling sick), bloating of the abdomen, loss of appetite, feeling full after eating small amounts, abdomen pain and a lump on the right side of the abdomen. There is a need for treatment options for advanced HCC, as there are currently limited first-line options.

Nivolumab is a human monoclonal antibody, a type of protein that has been designed to attach to a receptor called PD-1 found on cells of the immune system called T cells. Cancer cells can produce proteins (PD-L1 and PD-L2) on their surface that attach to this receptor and switch off the activity of the T cells, preventing them from attacking the cancer. By attaching to the receptor, nivolumab prevents PD-L1 and PD-L2 from switching off the T cells, thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab is an immune checkpoint inhibitor, it acts by interfering with a protein on T-cells and molecules which bind to it, this stops the T-cells from being inhibited. If licensed nivolumab in combination with ipilimumab, administered via intravenous (into the vein) injection, would offer an additional first-line treatment option for patients with advanced HCC.

Proposed Indication

For the first-line treatment of patients with advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy.[1]

Technology

Description

Nivolumab (Opdivo) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment which results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2,3]

Ipilimumab (Yervoy) is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intra-tumoural T-effector/ T-regulatory cell ratio which drives tumour cell death.[4,5]

Nivolumab in combination with ipilimumab is currently in clinical development for the first-line treatment of advanced HCC. In the phase III clinical trial (CheckMate 9DW, NCT04039607) participants receive the combination therapy as intravenous (IV) infusion.[1]

Key Innovation

This is a new combination for this indication and neither technology is currently licensed for HCC in the UK.

In a phase I/II trial, the combination of nivolumab and ipilimumab demonstrated clinically meaningful antitumour activity, durable responses, encouraging long-term overall survival, and a manageable safety profile in patients with chemotherapy-refractory esophagogastric cancer.[6]

Regulatory & Development Status

In the UK, nivolumab is currently licensed in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma, in combination with chemotherapy for the first-line treatment of metastatic non-small cell lung cancer and first-line treatment of intermediate/poor-risk advanced renal cell carcinoma in adults.[2,4]

Nivolumab in combination with ipilimumab is currently in phase III clinical development for the treatment of various types of cancers including lung, renal, esophageal, head and neck.[7]

Patient Group

Disease Area and Clinical Need

HCC is the commonest type of primary liver cancer, affecting the main liver cells called hepatocytes.[8] Symptoms include weight loss, jaundice, itching, nausea, bloating of the abdomen, loss of appetite, feeling full after eating small amounts, abdomen pain and a lump on the right side of the abdomen.[9] It is more likely to develop in men than in women and becomes more common as a person ages.[8] Other risk factors of developing HCC include liver cirrhosis, smoking, being overweight or obese, excessive alcohol, non-alcoholic fatty liver disease, and infection with hepatitis viruses.[10] Advanced cancer means that it is incurable.[11]

In England, 2020-21, there were 7,736 finished consultant episodes (FCE) of malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C22.0) resulting in 18,483 FCE bed days and 1,530 day cases.[12] In the UK, 2017-19, there were 5,830 deaths every year from liver cancer.[13]

There are no UK-wide statistics for liver cancer survival, however the following survival statistics (with treatment) are taken from the 2012 European Clinical Practice Guidelines for HCC:[14,15]
- Barcelona Clinic Liver Cancer (BCLC) stage 0 (very early stage; Child-Pugh A) – 70-90% will survive ≥5 years
- BCLC stage A (early stage; Child-Pugh A-B) – 50-70% will survive ≥5 years
- BCLC stage B (intermediate stage; Child-Pugh A-B) – Median survival 20 months
- BCLC stage C (advanced stage; Child-Pugh A-B) – Median survival 6-11 months

Recommended Treatment Options

NICE recommends the following treatment options as first-line for patients with advanced HCC:[16-18]
- Lenvatinib
- Sorafenib
- Atezolizumab with bevacizumab

Clinical Trial Information

Trial	**CheckMate 9DW; NCT04039607;** A Randomized, Multi-center, Phase 3 Study of Nivolumab in Combination With Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants With Advanced Hepatocellular Carcinoma **Phase III –** Recruiting **Location(s):** 9 EU countries, UK, USA, Canada and other countries **Primary completion date:** May 2024
Trial Design	Randomised, open label, parallel assignment
Population	Aged 18 years and older; advanced HCC; untreated
Intervention(s)	Nivolumab in combination with ipilimumab as an intravenous (IV) infusion.
Comparator(s)	Active comparator of sorafenib (oral tablet) or lenvatinib (oral capsule).
Outcome(s)	Overall Survival (OS) [Time frame: Up to 4 years]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Nivolumab is already marketed in the UK. The NHS indicative prices for nivolumab solution for infusion vials are as follows:[3]

- Nivolumab Opdivo 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1097.00 (Hospital only)
- Nivolumab Opdivo 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £2633.00 (Hospital only)
- Nivolumab Opdivo 40mg/4ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £439.00 (Hospital only)

Ipilimumab is already marketed in the UK. The NHS indicative prices for ipilimumab solution for infusion vials are as follows:[5]

- Ipilimumab Yervoy 200mg/40ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £15000.00 (Hospital only)
- Ipilimumab Yervoy 50mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £3750.00 (Hospital only)

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab with bevacizumab and transarterial chemoembolisation for treating locally advanced hepatocellular carcinoma (ID3944). Expected publication date: TBC.
- NICE technology appraisal in development. Cabozantinib with atezolizumab for untreated advanced hepatocellular carcinoma (ID3940). Expected publication date: TBC.
- NICE technology appraisal in development. Lenvatinib with pembrolizumab for untreated advanced or unresectable hepatocellular carcinoma (ID3930). Expected publication date: TBC.
- NICE technology appraisal in development. Durvalumab with transarterial chemoembolisation for treating incurable locally advanced hepatocellular carcinoma (TS ID 10757). Expected publication date: TBC.
- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated unresectable hepatocellular carcinoma (ID2725). Expected publication date: August 2021.
- NICE technology appraisal guidance. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma (TA666). December 2020.
- 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.

NHS England (Policy/Commissioning) Guidance

- 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.
- NHS England. 2013/14 NHS Standard Contract for hepatobiliary and pancreas (Adult). A02/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- The European Society of Medical Oncology (ESMO). Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. 2021.[19]
- The European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018.[20]
- The American Association for the Study of Liver Diseases (AASLD). AASLD guidelines for the treatment of hepatocellular carcinoma. 2018.[21]

Additional Information

References

1 Clinicaltrials.gov. *A Study of Nivolumab in Combination With Ipilimumab in Participants With Advanced Hepatocellular Carcinoma (CheckMate 9DW)*. *Trial ID: NCT04039607*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04039607 [Accessed 09 Jun 2022].

2 European Medicines Compendium (emc). *OPDIVO 10 mg/mL concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/6888 [Accessed 09 Jun 2022].

3 National Institute for Health and Care Excellence (NICE). *Nivolumab.* Available from: https://bnf.nice.org.uk/drugs/nivolumab/medicinal-forms/ [Accessed 09 Jun 2022].

4 European Medicines Compendium (emc). *YERVOY 5 mg/ml concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/4683 [Accessed 09 Jun 2022].

5 National Institute for Health and Care Excellence (NICE). *Ipilimumab.* Available from: https://bnf.nice.org.uk/drugs/ipilimumab/medicinal-forms/ [Accessed 09 Jun 2022].

6 Janjigian YY, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, et al. CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. *J Clin Oncol*. 2018 Oct 1;36(28):2836-44. Available from: https://doi.org/10.1200/jco.2017.76.6212.

7 Clinicaltrials.gov. *Phase II and III Clinical Trials for Nivolumab in Combination Ipilimumab* Available from: https://clinicaltrials.gov/ct2/results?term=nivolumab+and+ipilimumab&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 09 Jun 2022].

8 Cancer Research UK. *Types of liver cancer.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/types [Accessed 09 Jun 2022].

9 Cancer Research UK. *Symptoms of liver cancer.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/symptoms [Accessed 09 Jun 2022].

10 Cancer Research UK. *Risks and causes of liver cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/risks-causes [Accessed 09 Jun 2022].

11 Macmillan. *Advanced Cancer.* 2019. Available from: https://www.macmillan.org.uk/cancer-information-and-support/advanced-cancer [Accessed 09 Jun 2022].
12 NHS Digital. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 09 Jun 2022].
13 Cancer Research UK. *Liver cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer [Accessed 09 Jun 2022].
14 Cancer Research UK. *Liver cancer - Survival.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/survival [Accessed 13 Jun 2022].
15 Cancer Research UK. *BCLC staging system and the Child-Pugh system.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/stages/bclc-staging-system-child-pugh-system [Accessed 09 Jun 2022].
16 National Institute for Health and Care Excellence (NICE). *Sorafenib for treating advanced hepatocellular carcinoma* (*TA474)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta474 [Accessed 09 Jun 2022].
17 National Institute for Health and Care Excellence (NICE). *Lenvatinib for untreated advanced hepatocellular carcinoma* (*TA551)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta551 [Accessed 09 Jun 2022].
18 National Institute for Health and Care Excellence (NICE). *Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma* (*TA666)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta666 [Accessed 09 Jun 2022].
19 Vogel A, Martinelli E. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Ann Oncol*. 2021 Jun;32(6):801-5. Available from: https://doi.org/10.1016/j.annonc.2021.02.014.
20 EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018 Jul;69(1):182-236. Available from: https://doi.org/10.1016/j.jhep.2018.03.019.
21 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358-80. Available from: https://doi.org/10.1002/hep.29086.

NB: This briefing presents independent research funded by the National Institute for Heath and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.