

**NIHR Innovation Observatory
Evidence Briefing: April 2017**

Nivolumab (Opdivo) for the treatment of Hepatocellular Carcinoma

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LAY SUMMARY

Hepatocellular Carcinoma (HCC) is the most common type of liver cancer, with approximately 15 new cases diagnosed every day. Treatment and survival depends on the stage at which the cancer is diagnosed. Treatment of late stage HCC with chemotherapy and the drug sorafenib can only slow the progression of the cancer and extend survival. However if the cancer is not responsive to these treatments there are no further treatment options available.

Nivolumab is a drug which blocks a protein, called the programmed death-1 (PD-1) receptor, on the surface of certain immune cells (called T-cells). By blocking the PD-1 receptor this triggers the T-cells to find and kill cancer cells. Nivolumab is given as a drip directly into a vein in the hand or arm. Studies of nivolumab in HCC patients are currently being conducted to determine if it may extend survival or slow the progression of the disease.

If nivolumab is licenced in the UK, it could provide a new treatment option for patients with late stage HCC.

This briefing is based on information available at the time of research 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.

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TARGET GROUP

Hepatocellular Carcinoma: first line

TECHNOLOGY

DESCRIPTION

Nivolumab [anti-PD-1 MAb, Medarex; anti-PD-1 MAb, Ono; BMS-936558; MDX-1106; nivolumab; NSC-748726; ONO-4538; Opdivo] is a fully-human IgG4 monoclonal antibody which targets and blocks the PD-1 (programmed death-1) receptor on the surface of T-cells. This action triggers a T-cell mediated immune response against cancer cells.^{1,2} Nivolumab is administered by intravenous (IV) infusion at 3mg/kg over 60 minutes every 2 weeks for its currently approved indications.

Nivolumab has been approved/licensed for use in the EU for the following indications:³

- Advanced or metastatic (squamous and non-squamous) non-small cell lung cancer
- First and second line advanced unresectable or metastatic melanoma.
- Advanced renal cell carcinoma after prior therapy in adults
- Relapsed or refractory classical Hodgkin's lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin

Recognised common adverse events (>10%) of nivolumab in the currently licenced indications include: fatigue (32%), rash (18%), pruritus (13%), diarrhoea (13%), and nausea (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).⁴

Nivolumab is currently in registration for urogenital cancer and in preregistration for colorectal and gastric cancer.

Nivolumab is currently in phase III trials for:

- Glioblastoma
- Hepatocellular carcinoma
- Mesothelioma
- Multiple Myeloma
- Oesophageal Cancer
- Ovarian Cancer
- Small Cell Lung Cancer

Nivolumab is currently in phase II trials for the following indications:

- Acute Myeloid Leukaemia
- Breast Cancer
- Carcinomatous Meningitis
- Cervical Cancer
- Chronic Lymphocytic Leukaemia
- Diffuse Large B-cell Lymphoma
- Follicular Lymphoma
- Myelodysplastic Syndromes
- Prostate Cancer

- Soft Tissue Sarcoma
- Testicular Cancer
- Uterine Cancer
- Uveal Melanoma

INNOVATION and/or ADVANTAGES

If licensed, nivolumab will offer an additional treatment option for adults with advanced HCC who currently have few effective therapies available.

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

AVAILABILITY, LAUNCH or MARKETING

Nivolumab was designated orphan drug status in USA, awarded PIM status by MHRA and designated Breakthrough Therapy, priority review status, accelerated approval status and Fast Track status by the FDA.

PATIENT GROUP

BACKGROUND

Hepatocellular Carcinoma (HCC) is the fifth most common type of cancer worldwide and the third leading cause of cancer mortality.⁵ In the UK it is the 7th most common cause of cancer death, accounting for 3% total cancer deaths.⁶ HCC is the most common type of primary liver cancer which occurs in the most prevalent liver cells (hepatocytes).⁷ The main symptoms of HCC are significant appetite and weight loss (>10% body weight), pain and swelling of the abdomen, jaundice, nausea, bloating and itching.⁸ The origin of HCC is usually related to previous liver disease, injury and infection, however there are many risk factors which increase the likelihood of developing HCC. These risk factors include cirrhosis (scarring of the liver), heavy alcohol consumption, non-alcoholic fatty liver disease (NAFLD), hepatitis infection, smoking, impaired immunity (HIV/AIDS, immunosuppressive medication), systemic lupus erythematosus (SLE), family history, diabetes, previous gallbladder removal, previous radiation exposure and obesity.⁹

HCC is usually diagnosed using a combination of blood tests (Liver Function tests, urea and electrolytes, tumour markers – particularly alpha fetoprotein), ultrasound, CT or MRI scans, biopsy (of liver tumour tissue) and laparoscopic investigation.¹⁰ Treatment and survival rates depend on the cancer stage at diagnosis and are discussed further in ‘current treatment options’ section.

CLINICAL NEED and BURDEN OF DISEASE

For England, the incidence of liver cancer was 8.4 per 100,000 population in 2014 and for the UK the incidence of liver cancer was 8.6 per 100,000 in 2014.¹¹

For UK, the prevalence of liver cancer 1, 5 and 10 years after diagnosis (as of 2006) was 1113, 2108 and 2626 people respectively.¹²

In adults in England diagnosed with liver cancer, 35% will survive >1 year after diagnosis and 10% will survive >5 years after diagnosis.¹³

The European Clinical Practice Guidelines have estimated survival based on liver cancer stage, as follows:¹³

- Stage 0 – Median survival without treatment is > 3 years and median survival with treatment for 70-90% patients will be >5 years
- Stage A – Median survival without treatment is 3 years and median survival with treatment for 50-70% patients will be >5 years
- Stage B – Median survival without treatment is 16 months and median survival with treatment is 20 months
- Stage C – Median survival without treatment is 4-8 months and median survival with treatment is 6-11 months
- Stage D – Median survival without treatment is <4 months. There are currently no approved treatments for this stage of liver cancer

Liver cancer (C22) deaths were 7.9 per 100,000 (total 5091 people) in the UK in 2014 at a male: female ratio of 15:10.¹⁴

In 2015/2016, there were 11,256 admissions for Malignant neoplasms of the liver and intrahepatic bile ducts (C22) in England, resulting in 60, 804 bed days and 16,730 finished consultant episodes.¹⁵

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Nivolumab for previously treated advanced hepatocellular carcinoma [ID1141]. Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Regorafenib for previously treated unresectable hepatocellular carcinoma (ID991). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma (ID1089). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Hepatocellular carcinoma (advanced and metastatic) – sorafenib (first line) (review of TA189)[ID1012] – CDF rapid reconsideration process. Expected date of issue to be confirmed.
- NICE Technology appraisal. Sorafenib for the treatment of advanced hepatocellular carcinoma (TA189). May 2010
- NICE MedTech innovation briefing. SIR-Spheres for treating inoperable hepatocellular carcinoma (MIB63). March 2016
- NICE MedTech innovation briefing. TheraSphere for treating operable and inoperable hepatocellular carcinoma (MIB62). March 2016
- NICE Interventional procedures guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary and metastatic liver cancer (IPG488). May 2014.
- NICE Interventional procedures guidance. Selective internal radiation therapy for primary hepatocellular carcinoma (IPG460). July 2013

- NICE Interventional procedures guidance. Irreversible electroporation for treating primary liver cancer (IPG444). February 2013
- NICE Interventional procedures guidance. Ex-vivo hepatic resection and reimplantation for liver cancer (IPG298). April 2009
- NICE Interventional procedures guidance. Microwave ablation of hepatocellular carcinoma (IPG214). March 2007
- NICE Interventional procedures guidance. Laparoscopic liver resection (IPG135)
- NICE Interventional procedures guidance. Radiofrequency ablation of hepatocellular carcinoma (IPG2). July 2003
- Do not do recommendation. Do not offer surveillance for HCC for people who are receiving end of life care. December 2016
- Do not do recommendation. Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are not suitable. June 2015.

NHS ENGLAND and POLICY 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. July 2016
- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a
- 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 cancer: pancreatic (adult). A02/S/b
- NHS England. Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT). B01/PS/a. June 2013

CURRENT TREATMENT OPTIONS

The treatment of HCC depends on the stage of cancer at diagnosis. The NHS uses the BCLC staging system to define liver cancer stages, as follows:¹⁶

- Stage 0: single tumour <2cms, patient feels well and liver is functioning normally
- Stage A: single tumour <5cms or up to 3 tumours all <3cms, patient feels well and liver is functioning well
- Stage B: multiple tumours, patient feels well and liver is functioning well
- Stage C: cancer spread to the blood vessels, lymph nodes or other organs, patient does not feel well, and liver is functioning
- Stage D: severe liver damage or patient does not feel well and liver is functioning poorly

Curative treatment is possible for HCC diagnosed at Stage A. Treatments available for Stage A HCC are:^{17, 18}

- Surgical liver resection – removal of a section of the liver recommended for those with minimal liver damage and localised cancer
- Liver transplant – recommended for those with a single tumour <5cms or less than 3 tumours each <3cms or a good response to other treatments with no tumour growth in the last 6 months

- Microwave/Radiofrequency ablation – targeting tumours with microwaves or radio waves (via small electrodes introduced percutaneously, laparoscopically or surgically) with the aim of shrinking the tumour. This is recommended for treatment of early cancer in tumours <5cm, and can be carried out in 3 ways

Treatments available for Stage B and C aim to slow the progression of the cancer, relieve symptoms and prolong life, they are not curative. These treatments include:^{17, 18}

- Chemotherapy – specifically the TACE procedure where chemotherapy medication and small plastic beads are injected into the hepatic artery via a catheter inserted into the femoral artery (in the groin), with the aim of slowing cancer growth
- Alcohol injections – recommended for small tumours as alcohol dehydrates the cells
- Sorafenib – oral medication which disrupts blood supply to liver tumours and slows their growth (not available in the NHS)

Treatments available for Stage D focus solely on relieving symptoms and discomfort. These treatments include:^{17, 18}

- Painkillers – e.g. codeine, morphine
- Anti-sickness and Laxative medications

EFFICACY and SAFETY		
Trial	Checkmate 040; NCT01658878; CA209-040; CDR738406; 2012-001514-42; JapicCTI-152941; NCI-2013-00864; EudraCT-2012-001514-42; Nivolumab alone and in combination with Ipilimumab ; phase I/II trial	CheckMate 459; NCT02576509; CA209-459; 2015-002740-13; EudraCT-2015-002740-13; NCI-2015-01952; CDR777139; U1111-1171-2590; JapicCTI-153109; IRAS-192888; CA209459; HKUCTR-2023; Nivolumab vs Sorafenib (active comparator); phase III trial
Sponsor	Bristol-Myers Squibb Company and Ono Pharmaceutical Co Ltd	Bristol-Myers Squibb Company and Ono Pharmaceutical Co Ltd
Status	Ongoing	Ongoing
Source of Information	trial registry ¹⁹	trial registry ²⁰
Location	EU (incl UK), USA and countries in Asia-Pacific	EU (incl UK), Canada, USA and countries in Asia-Pacific
Design	Non-randomised followed by subgroup randomisation, active controlled	Randomised, active-controlled
Participants	n=570 (planned); >18 years; histologically confirmed advanced HCC; not eligible or progression after surgical therapies;	N=726; >18 years; histologically confirmed HCC; not eligible or progression after surgical therapies; no prior systemic therapy
Schedule	Part 1 (Dose escalation stage): HCC cohort without HBV/HCV infection receive Nivolumab IV, ranging from 0.1	Randomised to Nivolumab 10mg/ml IV on specified days until disease progression or 200mg sorafenib (film coated tablets) taken orally on

	<p>to 10mg/ml, every 2 weeks for up to 2 years.</p> <p>Part 2 (dose expansion stage): HCC cohort are randomised to 1 of 4 experimental arms. All receive 3mg/kg Nivolumab every 2 weeks:</p> <p>Arm 1: Nivolumab IV (dose as specified)</p> <p>Arm 2: Sorafenib (active comparator): taken orally on specified days</p> <p>Arm 3: Nivolumab IV (dose as specified) plus ipilimumab IV (on specific days)</p> <p>Arm 4: Patients with Child-Pugh B stage HCC receiving Nivolumab (dose as specified).</p>	specified days until disease progression.
Follow-up	Up to 9 years	Not reported
Primary Outcomes	Adverse events (AEs) and serious adverse events (SAEs) for each dose expansion phase experimental arm, Objective response rate (ORR) for each dose expansion phase experimental arm	Overall Survival (OS), Time To Progression (TTP)
Secondary Outcomes	Complete response (CR) Rate, Disease control rate (DCR), Duration of response (DOR), Time to response (TTR), Time to progression (TTP), TTP Rate, Progression free survival (PFS), Overall survival (OS), Overall survival rate (OSR), PD-L1 expression, Maximum observed serum concentration (C_{max}) of nivolumab, Time of maximum observed serum concentration (T_{max}) of nivolumab, Area under the serum concentration time curve in the dosing interval AUC(TAU) of nivolumab, Serum concentration achieved at the end of the infusion (C_{eoinf}) of nivolumab, C_{max} at Cycle 3/ C_{max} at Cycle 1 ($AI_{C_{max}}$) of nivolumab, AUC (TAU) at Cycle 3/ AUC(TAU) at Cycle 1 (AI_{AUC}) of nivolumab, Effective T-Half of nivolumab	Overall Response Rate (ORR), Progression-Free Survival (PFS), Programmed death (PD)-L1 expression, Exploratory patient-reported measures, (including effects of treatment on health status and quality of life), Duration of Response (DOR), Time to Response (TTR)
Key Results	Interim results (pooled results from HCC participants enrolled in the dose expansion and dose escalation cohorts) from the company based on 262 participants. The overall response rate was 20% (95% CI 15–26) in 214 patients treated in the dose expansion	-

	phase with a median duration of response of 9.9 months; disease control rate was 64% (95% CI 58–71). The 9-month overall survival rate in the expansion phase was 74% (95% CI 67–79). ²¹	
Adverse effects (AEs)	Interim results (pooled results from HCC participants enrolled in the dose expansion and dose escalation cohorts) from the study showed AEs were mostly mild-moderate in intensity. AEs included: abnormal AST level (19% participants), abnormal ALT levels (15% participants), rash (17% participants), elevation of Amylase (15% participants) and elevation of lipase (17% participants) ²² . Interim results from 2017 based on 262 participants reported Grade 3/4 treatment-related adverse events occurred in 20% participants. ²¹	-
Expected reporting date	01-12-2017	16-07-2017

ESTIMATED COST and IMPACT

COST

Nivolumab is already marketed in the UK; a 100mg vial (10mg/mL) costs £1097 and a 40mg vial (10mg/ml) costs £439.²³

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

- | | |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |

Other

None identified

IMPACT ON COSTS and OTHER RESOURCE USE

Increased drug treatment costs

Reduced drug treatment costs

Other increase in costs: Administration of IV medication

Other reduction in costs

Other

None identified

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

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