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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Nivolumab for hepatocellular carcinoma - adjuvant

NIHRIO ID	20554	**NICE ID**	10206
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	646338

Licensing and market availability plans	Currently in Phase III clinical trials.

SUMMARY

Nivolumab is in clinical development for the treatment of a primary liver cancer (hepatocellular carcinoma), which is cancer that originally develops in the liver and accounts for nine in ten primary liver cancer cases. Current treatment options commonly include surgical intervention such as liver transplants, as such there is a gap in treatment for minimally invasive pharmacological options.

Nivolumab, administered by intravenous infusion (injection into the vein), will be used as a secondary treatment for people who have already had cancerous tissue removed through surgery or other methods, but have had disease reoccurrence. Current recommended medical treatments target enzyme pathways, whereas nivolumab uses an alternative treatment pathway by targeting the immune system. Cancer cells commonly have receptor-blockers that make themselves invulnerable to the body's immune cells, such as T-cells. Ordinarily T-cells bind to harmful, disease-causing cells or faulty cells via receptors and cause the cell to burst and die. Nivolumab works by activating T-cells, which can then kill cancer cells. Therefore, if licensed, nivolumab would offer an additional secondary treatment option for the treatment of liver cancer.

PROPOSED INDICATION

Adjuvant nivolumab in patients who are at high risk of recurrence after curative hepatic resection or ablation for hepatocellular carcinoma (HCC).[a]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo, BMS-936558, ONO-4538) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 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, 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.[1]

Nivolumab is currently in phase III clinical development for the adjuvant treatment of hepatocellular carcinoma for patients who are at high risk of recurrence after curative hepatic resection or ablation.

INNOVATION AND/OR ADVANTAGES

Nivolumab is included in a class of cancer treatments known as anti-cancer immune checkpoint inhibitors (ICIs). These immunotherapies target proteins that prevent the body's immune system from attacking cancer cells. By blocking PD-1 on cancer cells, this allows the body's T-cells to bind and kill cancer cells, subsequently reducing tumour growth.[2] This represents an alternative to current recommended medical treatments which target enzyme pathways.[3] Studies have shown that nivolumab, as monotherapy or in combination with other treatments, is successful amongst patients diagnosed with many types of cancers.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab is not currently licenced in the UK as a monotherapy or as an adjunct for the treatment of HCC.[5]

Nivolumab is currently licenced in the EU/UK for the following conditions:[5]

- Advanced renal cell carcinoma (as a monotherapy or in combination with ipilimumab)
- Melanoma (as a monotherapy or in combination with ipilimumab)
- Adjuvant treatment of melanoma (as a monotherapy)
- Non-small cell lung cancer (as a monotherapy)
- Urothelial carcinoma (as a monotherapy)
- Squamous cell cancer of the head and neck (as a monotherapy)
- Classical Hodgkin lymphoma (as a monotherapy)

The most common side effects (affecting more than 1 in 10 people), from information pooled across all tumour types where nivolumab was used as a monotherapy, include fatigue, rash, pruritus, diarrhoea and nausea.[4] Other examples of common or very common side effects

[a] Information provided by Bristol-Myers Squibb

include abdominal pain, cough, decreased leucocytes, hypertension and increased risk of infection.[6]

Nivolumab is in phase II and phase III clinical development, as a monotherapy or in combination therapy, for multiple indications including metastatic pancreatic cancer, lung cancer, bladder cancer, gliomas, brain cancer and prostate cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

Hepatocellular carcinoma (HCC) is a type of primary liver cancer that is seen in nine out of ten cases. Primary liver cancer starts in the liver and develops in hepatocytes (liver cells), whereas secondary liver cancer develops in other areas of the body and spreads to the liver, this can also be called metastatic cancer.[8,9]

There a number of risk factors for HCC including increased age, genetics, smoking and having other medical conditions such as previous scarring of the liver tissue (cirrhosis), alcoholism, non-alcoholic fatty liver disease, diabetes, hepatitis viruses and HIV. Most patients are over the age of 60, with it being most common in those over the age of 85. Additionally, men are more likely to develop HCC than women though the exact reasons why are unknown.[10,11]

Symptoms of liver cancer include unintentional loss of weight, jaundice (yellowing skin), lethargy and generally feeling unwell. Liver cancer can be difficult to notice as the organ is resilient to a lot of damage and symptoms may only develop as disease severity progresses.[8,12]

CLINICAL NEED AND BURDEN OF DISEASE

HCC incidence and mortality has been found to have tripled over the last twenty years (1997 onwards) in England.[13] In 2014 in the UK 5,520 people were diagnosed with liver cancer and that number is predicted to increase to over 11,000 in 2035.[14] 5,087 people in the UK died from liver cancer in 2014 and this is predicted to increase to over 12,000 in 2035.[15]

From data gathered between 2013-17 in England (for all liver cancers) one year survival was 40.0% for men and 34.6% for women after diagnosis, with a five year survival of 13.7% for men and 10.7% for women.[16] In England (2018-19) 36,942 patients with HCC (ICD-10 C22) were admitted to hospital, with a total of 20,385 finished consultant episodes (FCE) specifically related to HCC.[17] In England and Wales (2017) 3,029 men and 1,938 women died with HCC as the underlying cause of death.[18]

The Barcelona Clinic Liver Cancer (BCLC) staging system is used to aid healthcare professionals in decision-making regarding treatment with stage 0 meaning the patient's tumour is less than 2cm and their liver is working normally (Child-Pugh A, which is a score of 5-6). Stage A means the patient has a single tumour of any size, or up to three tumours less than 3cm and their liver is working well (Child-Pugh A or B, which includes scores of 5-6).[19] For patients at stages 0 and A, where treatment options are ablation, resection or liver transplant, the median survival is 3 years or more without treatment. At stage 0 patients who receive treatment are between 70-90% likely to live 5 years or more, and at stage A 50-70% are predicted to live 5 years or more.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of liver cancer is dependent on a number of factors including:[21,22]

- If the cancer is primary or secondary, though treatments are similar
- The size and type of cancer
- Location of cancer, for example if it is close to gallbladder or blood vessels
- Health of the liver
- General health of the patient

The management of liver cancer requires different approaches and involves the use of different therapies. A multidisciplinary team of specialists, including doctors and other professionals, help explain treatment options, side effect management and work with the patient to find the most suitable treatment. The main treatments for liver cancer include surgery such as a liver resection, lobectomy or transplant, radiotherapy (in the case of metastatic cancer), chemotherapy, thermal ablation and biological therapy (targeted therapy). Patients may have one of these treatments or a combination. The type or combination of treatments will depend on where cancer was diagnosed and the stage of the disease.[21,22]

CURRENT TREATMENT OPTIONS

The following are recommended for the pharmacological treatment of HCC:[21,22]

Chemotherapy

- Trans arterial chemoembolization (TACE) – chemotherapy into blood vessels that supply the cancerous tumour to kill the cancer cells and reduce growth using medication like doxorubicin and cisplatin

Biological therapy

- Sorafenib – tyrosine kinase inhibitor (TKI) that prevents cancer cell growth
- Levatinib – newer kind of cancer growth blocker
- Regorafenib - used as an adjuvant alongside sorafenib to prevent cancer cell growth

PLACE OF TECHNOLOGY

If licensed, nivolumab could be given as an option to delay disease progression and movement to advanced HCC.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 9DX; NCT03383458; A Phase 3, Randomized, Double-blind Study of Adjuvant Nivolumab Versus Placebo for Participants With Hepatocellular Carcinoma Who Are at High Risk of Recurrence After Curative Hepatic Resection or Ablation** **Phase III – Recruiting** **Location(s): EU (including UK), USA, Canada and other countries** **Primary completion date: 17th April 2022**
Trial design	Randomised, quadruple-blinded parallel assignment.

Population	N= 530 (planned); adults aged 18 and over; participants with a first diagnosis of hepatocellular carcinoma (HCC) who have undergone a curative resection or ablation
Intervention(s)	Nivolumab at a specified dose.
Comparator(s)	Matched placebo.
Outcome(s)	Recurrence-free Survival (RFS) [Time Frame: Up to 49 months] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab injections are as follows:[23]

- Nivolumab 100mg/10ml concentrate for solution for infusion vials (prescription only medicine) cost £1097.00 (Hospital only)
- Nivolumab 240mg/24ml concentrate for solution for infusion vials (prescription only medicine) cost £2633.00 (Hospital only)
- Nivolumab 40mg/4ml concentrate for solution for infusion vials (prescription only medicine) cost £439.00 (Hospital only)

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Doxorubicin nanoparticles for previously treated advanced hepatocellular carcinoma (ID1314). Publication date: TBC
- NICE technology appraisal guidance. Regorafenib for previously treated advanced hepatocellular carcinoma (TA555). January 2019
- NICE technology appraisal guidance. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017
- NICE guideline. Cirrhosis in over 16s: assessment and management (NG50). July 2016
- NICE interventional procedures guidance. Irreversible electroporation for primary liver cancer (IPG664). November 2019
- NICE interventional procedures guidance. Selective internal radiation therapy for primary hepatocellular carcinoma (IPG460). July 2013

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma. B01/PS/a. June 2013

OTHER GUIDANCE

- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018[24]

- European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2018[25]
- American Association for the Study of Liver Diseases. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. 2018[26]
- British Society of Gastroenterology. BSG guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. 2003[27]

ADDITIONAL INFORMATION

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