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Pembrolizumab for advanced hepatocellular carcinoma – second line onwards

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LAY SUMMARY

Hepatocellular Carcinoma (HCC) is the most common type of liver cancer. This type of cancer develops from the main liver cells, called hepatocytes. Treatment and survival depends on the stage at which the cancer is diagnosed. HCC is more common in people who have long-term damage to the liver (cirrhosis) due to a viral infection or excessive alcohol intake. It is also more likely to develop in men than in women and it becomes more common as people get older. The advanced stage of HCC occurs when the cancer has spread to other parts of the body and there often are limited curative treatment options at this stage.

Pembrolizumab is a type of immunotherapy that stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein allows the T-cells to find and kill the cancer cells. It is administered as a drip into a vein every three weeks for up to 35 cycles. If approved, the addition of pembrolizumab to other standard treatments will offer an alternative treatment option for patients with advanced HCC that have received previous chemotherapy. This treatment option has the potential to improve survival in this patient group.

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TARGET GROUP

Hepatocellular carcinoma (advanced) – second line; in addition to best supportive care (BSC).

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda®, MK-3475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T-cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen-presenting cells. Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity.[1]

In the phase III trial (KEYNOTE-240; NCT02702401), participants with previously systemically treated advanced hepatocellular carcinoma receive a pembrolizumab 200 mg intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment in addition to best supportive care. According to the trial protocol, best supportive care include pain management and management of other potential complications including ascites per local standards of care.[2]

Pembrolizumab is currently licensed in the EU under its commercial name Keytruda for the following indications[3]:

- Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- Keytruda as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda.
- Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.
- Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

The most common side effects with Keytruda (which may affect more than 1 in 10 people) are diarrhoea, nausea (feeling sick), itching, rash, joint pain and tiredness, most of which are mild to moderate in severity. Other common side effects of Keytruda related to the activity of the immune

system causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping Keytruda.[4]

Additional Phase III clinical trials of pembrolizumab are registered for the following indications:

- Head/Neck
- Gastric/Gastroesophageal
- Colorectal
- Oesophageal/Oesophagogastric
- Breast
- Bladder/Renal
- Mesothelioma
- Small Cell Lung Cancer
- Non-Small Cell Lung Cancer
- Melanoma

INNOVATION and/or ADVANTAGES

Patients with advanced hepatocellular carcinoma who have progressed after previous systemic treatment currently have limited treatment options available, and are often managed with best supportive (palliative) care. The addition of pembrolizumab to best supportive care has the potential to improve overall and progression-free survival in this group of patients.

DEVELOPER

Merck Sharp & Dohme Ltd

PATIENT GROUP

BACKGROUND

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver.[5] Chronic liver disease and cirrhosis are the most important risk factors for the development of HCC of which viral hepatitis and excessive alcohol intake are the leading risk factors worldwide.[6] The cell(s) of origin are believed to be the hepatic stem cells, although this remains the subject of investigation. Tumours progress with local expansion, intrahepatic spread, and distant metastases. HCC is now the third leading cause of cancer deaths worldwide, with over 500,000 people affected.[5]

The presentation of HCC has evolved significantly over the past few decades. Whereas in the past, HCC generally presented at an advanced stage with right-upper-quadrant pain, weight loss, and signs of decompensated liver disease, it is now increasingly recognized at a much earlier stage as a consequence of the routine screening which includes both radiologic tests, such as ultrasound, computerized tomography, and magnetic resonance imaging, and serological markers such as α-fetoprotein at 6-month intervals of patients with known cirrhosis.[5,6]

Symptoms of liver cancer may include any of the following:[7]

- Abdominal pain or tenderness, especially in the upper-right part

- Easy bruising or bleeding
- Enlarged abdomen (ascites)
- Yellow skin or eyes (jaundice)
- Unexplained weight loss

Hepatocellular carcinoma (HCC) is a complex condition associated with poor prognosis. Treatment outcomes are affected by multiple variables, including liver function, performance status of the patient, and tumour stage, making a multidisciplinary approach to treatment essential for optimal patient management. Only ~30% of patients are eligible for curative therapies (surgery or ablation).[8] The symptoms of HCC in addition to the side-effects of treatment may significantly impact the quality of life of individuals with the condition, who may experience pain, fatigue, diarrhoea and loss of appetite. Nine out of ten patients reported experiencing pain over their HCC treatment course in a qualitative analysis.[9]

CLINICAL NEED and BURDEN OF DISEASE

The incidence of HCC is highest in Asia and Africa, where the endemic high prevalence of hepatitis B and hepatitis C strongly predisposes to the development of chronic liver disease and subsequent development of HCC.[5]

Over the last decade, liver cancer incidence rates have increased by almost two-thirds (63%) in the UK. Rates in males have increased by around two-thirds (65%), and rates in females have increased by more than half (53%).[10]

In 2016 in England there were a total of 3,235 newly diagnosed male and 1,690 newly diagnosed female cases of malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C.22).[11]

For males, incidence rates for liver cancer are projected to rise from 16.21 per 100,000 (EASR) in 2014 to 23.23 per 100,000 (EASR) in 2035 (approximately 7,770 cases). For females, incidence rates for liver cancer are projected to rise from 6.87 per 100,000 (EASR) in 2014 to 8.32 per 100,000 (EASR) in 2035 (approximately 3,364 cases).[12]

In England in 2016/2017 there were a total of 12,569 hospital admissions resulting in 59,608 FCE bed days. Of these admissions 5,599 were day cases (primary diagnosis ICD-10 code C.22).[13]

In general, liver cancer has poor prognosis. Five year survival for patients diagnosed between 2011 and 2015 and followed up in 2016 in England range between 13% in men and 10% in women.[14] Prognosis and survival will depend mainly on how advanced is the cancer at the time of diagnosis.

There are a number of different staging systems for liver cancer, one well-known is the Barcelona Clinic Liver Cancer (BCLC).[15] There are five different stages according to the BCLC and patient population being targeted in this briefing are those classed as BCLC Stage C disease, or BCLC Stage B disease, not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach.[2] Survival at those two stages range between 20 months and 16 months with or without treatment at Stage B and between 4 and 11 months with or without treatment at Stage C respectively.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. ADI-PEG 20 for previously treated hepatocellular carcinoma (GID-TA10259). Expected publication date: TBC
- NICE technology appraisal in development. Doxorubicin nanoparticles for previously treated advanced hepatocellular carcinoma (GID-TA10251). Expected publication date: TBC
- NICE technology appraisal in development. Cabozantinib for treating advanced hepatocellular carcinoma after prior therapy (GID-TA10287). Expected publication date: TBC
- NICE technology appraisal in development. Regorafenib for previously treated unresectable hepatocellular carcinoma (GID-TA10112). Expected publication date: 21 March 2018.
- NICE technology appraisal. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for hepatobiliary and pancreas (Adult). A02/S/a
- NHS England. 2013/14 NHS Standard Contract for live liver transplantation service. A02/S(HSS)/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- 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. Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT). B01/PS/a. June 2013.

OTHER GUIDANCE

- EASL Clinical Practice Guidelines. Management of hepatocellular carcinoma, EASL-EIRTC clinical practice guidelines.[17]

CURRENT TREATMENT OPTIONS

The treatment for liver cancer depends on the stage of the condition. Treatment can include surgery and medication.[18] At stage B or C (advanced according to the Barcelona Clinic Liver Cancer staging system), HCC treatment will aim to slow the progression of the cancer, relieve the symptoms and prolong life for months, or in some cases, years.[18]

Current NICE guidelines recommend the use of sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment, this is, when the liver is still working normally.[19] Sorafenib is a medication given in tablet form that can disrupt the blood supply to liver tumours and slow down their growth.[18] Currently there are no other medicinal products approved for the treatment of this type of cancer at advanced stage.

EFFICACY and SAFETY

Trial	NCT02702401, KEYNOTE-240, EudraCT 2015-004567-36, MK-3475-240; pembrolizumab in addition to Best Supportive Care (BSC) versus placebo in addition to BSC
Sponsor	Merck Sharp & Dohme Ltd.
Status	Ongoing
Source of Information	Trial registry[2]
Location	Not provided
Design	Randomised, placebo-controlled
Participants	N= 408 (planned); aged 18 and older; HCC diagnosis confirmed by radiology, histology or cytology; Barcelona Clinic Liver Cancer (BCLC) Stage C disease, or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach.
Schedule	Randomised to pembrolizumab 200 mg intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment in addition to BSC; or placebo (0.90% w/v sodium chloride) IV infusion on Day 1 of each 3-week cycle for up to 35 cycles of treatment in addition to BSC.
Follow-up	Active treatment for 35 cycles, follow-up for two years
Primary Outcomes	• Progression-free survival • Overall survival
Secondary Outcomes	• Objective response rate • Disease control rate • Time to progression • Duration of response
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as 1st February 2019

ESTIMATED COST and IMPACT

COST

The current medicinal product price registered in the NHS is for Keytruda 100mg/4ml concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial at £2,630[20] and for Keytruda 50mg powder for concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial at £1,315.[20]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ 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

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *trial results not published yet*

☐ None identified

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