NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab for previously treated advanced hepatocellular carcinoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for previously treated advanced hepatocellular carcinoma.

Background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer in England, accounting for 55% of primary liver cancer diagnoses in men and 28% of diagnoses in women[1]. HCC is commonly associated with cirrhosis (scarring of the liver), which can be caused by excessive alcohol intake, viral infections such as hepatitis B or C, or other diseases that result in chronic inflammation of the liver[2]. There were 2,456 people diagnosed with HCC in England in 2015[3]. The risk of developing HCC increases with age, with the average age at diagnosis being 66 years[2].

Treatment for HCC depends on the location and stage of the cancer, and how well the liver function is preserved. Early stage hepatocellular carcinoma may be treated with potentially curative surgery (hepatic resection or liver transplantation), or percutaneous radiofrequency/thermal ablation in patients with well-preserved liver function, or liver transplantation for those with impaired liver function.

However, treatment is palliative rather than curative for people with more advanced disease. Treatment options include interventional procedures such as transarterial chemoembolisation (using doxorubicin or cisplatin) or selective internal radiation therapy, and external beam radiotherapy. People for whom these treatments are not suitable, or those with metastatic disease, are treated with sorafenib (a multi-kinase inhibitor). NICE Guidance TA474 (Cancer Drugs Fund reconsideration of TA189) recommends sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment. However, some people may not respond or may be intolerant to this therapy, these people are treated with best supportive care.

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, anti-programmed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Pembrolizumab does not currently have a marketing authorisation in the UK for treating advanced hepatocellular carcinoma. It has been studied in two phase III randomised controlled trials in adults with advanced hepatocellular carcinoma who have progressed after prior treatment or were intolerant to sorafenib.

Intervention(s)	Pembrolizumab
Population(s)	Adults with advanced hepatocellular carcinoma (HCC) after prior systemic therapy.
Comparators	• Cabozantinib (subject to ongoing NICE appraisal) • Regorafenib (subject to ongoing NICE appraisal) • Ramucirumab (subject to ongoing NICE appraisal) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • time-to-treatment discontinuation • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Hepatocellular carcinoma (advanced and metastatic) - sorafenib (first line) (review of TA189) - CDF rapid reconsideration process (2017) NICE technology appraisal 474. Next review August 2020. Regorafenib for previously treated unresectable hepatocellular carcinoma (2018) NICE technology appraisal 514. Next review March 2021 **Appraisals in development (including suspended appraisals):** Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma. NICE technology appraisal guidance [ID1089] Publication expected October 2018 Cabozantinib for treating advanced hepatocellular carcinoma after prior therapy. NICE technology appraisal guidance [ID1243] Publication date to be confirmed Nivolumab for untreated advanced hepatocellular carcinoma NICE technology appraisal guidance [ID1248] Publication date to be confirmed Ramucirumab for previously treated advanced hepatocellular carcinoma NICE technology appraisal guidance [ID860] Publication date to be confirmed **Suspended/discontinued**: Nivolumab for previously treated advanced hepatocellular carcinoma. NICE technology appraisals guidance [ID1141]. Suspended Sept 2017– company advised that they would not be seeking regulatory approval from the European Medicines Authority for this indication **Related NICE Pathways:** Liver cancers (2018) NICE pathway

Related National Policy	**NHS England:** NHS England (May 2017) Manual for prescribed specialised services 2017/18, chapter 131 (page 308): Specialist services for complex liver, biliary and pancreatic diseases in adults. **Department of Health:** Department of Health (2011) Improving Outcomes: A Strategy for Cancer Department of Health (2016) NHS Outcomes Framework 2016-2017. Domains 1 and 2.

Questions for consultation

Have all relevant comparators for pembrolizumab been included in the scope? Is best supportive care a comparator for the populations described above? If so, how should best supportive care be defined?

Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider pembrolizumab will fit into the existing NICE pathway, liver cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic.

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. National Cancer Registration and Analysis Service (2010) Trends in incidences in primary liver cancer subtypes. Accessed June 2018

2. Patient (2015) Hepatocellular carcinoma. Accessed June 2018
3. Office for National Statistics (2016) Cancer registration statistics. Accessed June 2018