

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**Health Technology Appraisal****Nivolumab for untreated advanced hepatocellular carcinoma****Draft scope****Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for untreated 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 women¹. 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 liver². There were 2,456 people diagnosed with HCC in England in 2015³.

Treatment for HCC depends on the location, stage of the cancer and how well the liver function is preserved. Early stage hepatocellular carcinoma may be treated with surgery (hepatic resection or liver transplantation), percutaneous radiofrequency or thermal ablation to cure the disease. However, many people are diagnosed with advanced unresectable disease, when treatment is palliative rather than curative. Treatment options for unresectable disease include interventional procedures such as transarterial chemoembolisation (TACE) (using doxorubicin or cisplatin) or selective internal radiation therapy and external beam radiotherapy. People for whom these treatments are unsuitable, or those with metastatic disease are treated with sorafenib (a multi-kinase inhibitor) or best supportive care (BSC). NICE technology appraisal guidance [TA474](#) (Cancer Drugs Fund reconsideration of TA189) recommended sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a monoclonal antibody that targets a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Nivolumab is administered intravenously.

Nivolumab does not currently have a marketing authorisation in the UK for hepatocellular carcinoma. It has been studied in a clinical trial as first-line treatment in adults with advanced hepatocellular carcinoma with Child-Pugh grade A liver impairment and ECOG status of 0 or 1 in whom surgical or loco-regional therapies had failed or were not suitable.

Intervention(s)	Nivolumab
Population(s)	Adults with advanced hepatocellular carcinoma whose disease is unsuitable for surgical or loco-regional therapy or has progressed after those types of therapy
Comparators	<ul style="list-style-type: none"> • Sorafenib • Lenvatinib (subject to ongoing NICE appraisal) • best supportive care
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression free survival • time to disease progression • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access scheme and commercial access agreements for the intervention or comparator technologies should be taken into account</p>

<p>Other considerations</p>	<p>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.</p> <p>If the evidence allows, consideration will be given to subgroups based on Child-Pugh score and ECOG score.</p>
<p>Related NICE recommendations and NICE Pathways</p>	<p>Related Technology Appraisals:</p> <p>Hepatocellular carcinoma (advanced and metastatic) - sorafenib (first line) (review of TA189) - CDF rapid reconsideration process (2017) NICE Technology Appraisal 474. Next review August 2020.</p> <p>Appraisals in development (including suspended appraisals)</p> <p>Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma. NICE Technology Appraisal Guidance [ID1089] Publication expected October 2018</p> <p>Related NICE Pathways:</p> <p>Liver cancers (2018) NICE pathway.</p>
<p>Related National Policy</p>	<p>NHS England:</p> <p>NHS England (May 2016) Manual for prescribed specialised services 2016/17, chapter 131 (page 300): Specialist services for complex liver, biliary and pancreatic diseases in adults.</p> <p>Department of Health:</p> <p>Department of Health (2011) Improving Outcomes: A Strategy for Cancer</p> <p>Department of Health (2016) NHS Outcomes Framework 2016-2017. Domains 1 and 2.</p>

References

1. National Cancer Registration and Analysis Service (2010) [Trends in incidences in primary liver cancer subtypes](#). Accessed March 2018
2. Patient (2015) [Hepatocellular carcinoma](#). Accessed March 2018
3. [Office for National Statistics \(2015\) Cancer registration statistics](#). Accessed March 2018.

4. [Cancer Drug Fund](#) (2018) [National Cancer Drug Fund List. ver1.71](#). Accessed March 2018.

Questions for consultation

Have all relevant comparators for nivolumab 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 advanced hepatocellular carcinoma? What is considered to be first-line therapy for people with Child-Pugh Class B liver function?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Would you consider outcomes for people with Child-Pugh Class B liver function and those with ECOG score >1 to be clinically equivalent to those in the trial population?

Where do you consider nivolumab 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 nivolumab 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 nivolumab 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 nivolumab 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?