NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of atezolizumab with bevacizumab within its marketing authorisation for treating unresectable or advanced hepatocellular carcinoma.

Background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer developing from the main liver cells, called hepatocytes. HCC accounts for up to 55% of primary liver cancer diagnoses in men and up to 28% of diagnoses in women in England.[1] Most people with HCC will have liver cirrhosis (scarring of the liver), which can develop following long periods of chronic liver disease. In 2017 there were a total of 4,975 registrations of newly diagnosed malignant neoplasm of liver and intrahepatic bile ducts. Based on the percentages of HCC diagnoses above, this is equal to 2,736 newly diagnosed cases of HCC in men and up to 1,393 in women in England.[2] The average age at diagnosis is 66 years.[3]

Treatment depends on the location and stage of the cancer, and how well the liver function is preserved. For people with more advanced disease treatment is palliative rather than curative. Treatment options include interventional procedures such as trans arterial chemoembolisation (using doxorubicin or cisplatin) or selective internal radiation therapy, and external beam radiotherapy. People who do not respond to these therapies or have metastatic disease, are treated with sorafenib or lenvatinib in the first line setting. Some people with HCC are treated with best supportive care.

For people with advanced HCC that have not received previous treatment, the NICE technology appraisal guidance 474 recommends sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment. NICE technology appraisal guidance 551 recommends treatment with lenvatinib only for people with Child-Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The technologies

Atelozolizumab (Tecentriq; Roche) is a humanised, anti-programmed cell death ligand-1 (PD-L1) monoclonal antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. Atezolizumab, increases the ability of the immune system to attack the cancer cells and slows down disease progression and is administered by intravenous infusion.

Bevacizumab (Avastin, Roche) is a humanised immunoglobin (IgG10) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) preventing tumour growth. Bevacizumab decreases tumour growth by stopping the development of tumour blood vessels and is administered via intravenous infusion.

Atezolizumab with bevacizumab does not currently have a marketing authorisation in the UK for treating hepatocellular carcinoma. It is being studied in a phase III randomised open-label trial compared with sorafenib in adults with locally advanced or metastatic and/or unresectable hepatocellular carcinoma who have not received prior systemic therapy.

Intervention(s)	Atezolizumab with bevacizumab
Population(s)	People with untreated unresectable or advanced hepatocellular carcinoma who have had no previous treatment
Comparators	• Sorafenib • Lenvatinib • Best supportive care (BSC)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • 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. 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:** Lenvatinib for untreated advanced hepatocellular carcinoma (2018) NICE Technology appraisal guidance 551. Sorafenib for treating advanced hepatocellular carcinoma

	(2017) NICE Technology appraisal guidance 474. **Terminated appraisals:** Cabozantinib for previously treated advanced hepatocellular carcinoma (terminated appraisal) (2019). NICE Technology Appraisal 582 **Appraisals in development (including suspended appraisals):** Hepatocellular carcinoma (advanced and metastatic) - sorafenib (first line) (2017) NICE technology appraisal 474. Next review August 2020. Nivolumab for untreated advanced hepatocellular carcinoma NICE technology appraisal guidance [ID1248] Publication date to be confirmed **Related Interventional Procedures:** Irreversible electroporation for treating primary liver cancer (2013) NICE interventional procedures guidance 444. Microwave ablation of hepatocellular carcinoma (2007) NICE interventional procedures guidance 214. Laparoscopic liver resection (2005) NICE interventional procedures guidance135. Radiofrequency-assisted liver resection (2007) NICE interventional procedures guidance 211. Radiofrequency ablation of Hepatocellular carcinoma (2003) NICE interventional procedures guidance 2. Ex-vivo hepatic resection and reimplantation for liver cancer (2009) NICE interventional procedures guidance 298. Selective internal radiation therapy for primary hepatocellular carcinoma (2013) NICE interventional procedures guidance 460. **Related NICE Pathways:** Liver cancers (2018) NICE pathway
Related National Policy	**NHS England:** The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) chapter 131 (page 357): Specialist services for complex liver, biliary and pancreatic diseases in adults. NHS England (2016) The use of stereotactic ablative radiotherapy (SABR) as a treatment option for patients with

	hepatocellular carcinoma or cholangiocarcinoma. Clinical commissioning policy. Reference: NHS England: 16022/P **Department of Health and Social Care:** Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy

Questions for consultation

Have all relevant comparators for ateloizumab with bevacizumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma?

Would people with untreated HCC ever be treated with best supportive care rather than an active systemic therapy? If so, how should best supportive care be defined?'

Are the outcomes listed appropriate?

Are there any subgroups of people in whom ateloizumab with bevacizumab is expected to be more clinically effective and cost effective?

Where do you consider ateloizumab with bevacizumab 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 ateloizumab with bevacizumab 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 ateloizumab with bevacizumab 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 ateloizumab with bevacizumab 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 http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

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.

- Would it be appropriate to use the cost comparison methodology for 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 August 2019

2 Office for National Statistics ((2017) Cancer Registration Statistics, England Accessed August 2019

Patient (2015) Hepatocellular carcinoma. Accessed August 2019

