National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Atezolizumab with bevacizumab for untreated hepatocellular carcinoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Roche	The anticipated licence is as follows: [redacted] We recommend the remit is updated to reflect this. Further, we recommend that the technology appraisal and scope titles are updated to reflect this for transparency to the clinical and patient community. We suggest it is updated to: [redacted]	Thank you for your comments. The remit and titles have been amended.

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	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	Wording OK	Thank you for your comment.
Timing Issues	Roche	Liver cancer is globally the most frequent cause of cancer-related death with hepatocellular carcinoma (HCC) representing about 90% of the primary liver cancers.[1] There is high unmet medical need for patients with advanced unresectable HCC, who require new, more efficacious, and less toxic treatments that can improve their clinical outcomes and quality of life. Atezolizumab in combination with bevacizumab has demonstrated considerable improvement in outcomes versus sorafenib in the IMbrave150 trial, with Marketing Authorisation anticipated in [redacted]. In addition, atezolizumab in combination with bevacizumab has been designated PIM status, [redacted], therefore, it is critical this appraisal continues without delay to prevent patients missing an opportunity of treatment with a significant advance over current standard of care. [1] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice	Thank you for your comments. The prevalence and impact of HCC have been noted in the scope. No changes have been made. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal. No changes have been made.

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		Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236	
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	Urgent. New data has already been published indicating atezolizumab/bevacizumab (atezo/bev) offers significant overall survival (OS) benefit compared to the current UK standard of care therapy.	Thank you, your comment has been noted. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal. No changes have been made.
Additional comments on the draft remit	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	Please note; there are instances within the draft remit document where atezolizumab is spelt incorrectly.	Thank you for your comments. Instances of incorrect spelling have been amended in the documents.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	No comments.	Thank you for your response.
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	It would be worth noting that the UK incidence of HCC has shown a significant increase in the past 10 years due to increasing alcohol misuse, diabetes, and obesity. This increase is expected to continue.	Thank you for your comments. The prevalence and impact of HCC have been noted in the scope. No changes have been made.
	Royal College of Pathologists	Consideration should be given to whether histological confirmation of HCC is required prior to commencing treatment with Atezolizumab with Bevacizumab	Thank you for your comment. The appraisal committee will discuss the requirements for commencing treatment with atezolizumab and bevacizumab. No changes have been made.
The technology/ intervention	Roche	Yes, the description of the technology is accurate	Thank you for your comment. No changes have been made.

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	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	Yes	Thank you for your comment. No changes have been made.
Population	Roche	Yes, the definition of the population is accurate	Thank you for your comment. No changes have been made.
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	I think the population needs to be better defined; People with untreated unresectable or advanced hepatocellular carcinoma who have had no previous treatment and have performance status (PS) 0 or 1, and are Child-Pugh (CP) class A. This is because the clinical trial supporting the use of atezo/bev restricted recruitment to patients with PS 0/1 and CP class A.	Thank you for your comment. The committee will consider the evidence base submitted by the company and will appraise to technology in line with the marketing authorisation. No changes have been made.
Comparators	Roche	The draft scope includes the following comparators: • Sorafenib	Thank you for your comments. Best supportive care has

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		• Lenvatinib • Best supportive care (BSC) The comparators listed on the draft scope are representative of the NICE treatment pathway for untreated HCC. However, with regards to BSC, given the availability of other treatments, it is assumed BSC alone is not an established treatment option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who can tolerate, or are willing to have pharmacological intervention will be eligible for atezolizumab in combination with bevacizumab. Therefore, BSC is not an appropriate comparator for atezolizumab + bevacizumab and should be removed from the final scope.	been included because some people may choose not to have a systemic therapy such as sorafenib or lenvatinib, or may be contraindicated. Consultees can submit further information as part of their evidence submissions which will be considered by the appraisal committee. No changes have been made.
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	The best comparators are sorafenib and lenvatinib. I don't think BSC should be a comparator as patients who have advanced HCC with PS 0/1 and CP A should be considered for systemic therapy rather than BSC	Thank you for your comments. Best supportive care has been included because some people may choose not to have a systemic therapy such as sorafenib or lenvatinib, or may be contraindicated. Consultees can submit further information as part of their evidence submissions which will

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			be considered by the appraisal committee No changes have been made.
Outcomes	Roche	Yes, the listed outcomes capture the most important health-related benefits and harms.	Thank you for your comment. No changes have been made.
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	Yes, outcomes are appropriate.	Thank you for your comment. No changes have been made.
Economic analysis	Roche	Atezolizumab with bevacizumab has demonstrated considerable benefit over sorafenib, thus a cost-effectiveness analysis is the most appropriate economic analysis. This will be expressed in terms of incremental cost per quality-adjusted life-year. The time horizon should be sufficient to capture all health related benefits and costs of treatment. A lifetime horizon that captures the full expected overall survival of patients is the appropriate time horizon.	Thank you, your comment has been noted.
	1) British Association for	No comment.	Thank you for your response.

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	the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology		
Equality and Diversity	Roche	No equality issues have been identified.	Thank you, your comment has been noted.
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	No concerns.	Thank you, your comment has been noted.
Other considerations	Roche	No additional issues will be covered by the appraisal.	Thank you, your comment has been noted.

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	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	None to add.	Thank you, your comment has been noted.
Innovation	Roche	Promising Innovative Medicine (PIM) Designation was issued on 16 July 2019 for atezolizumab in combination with bevacizumab for the treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy, and [redacted]. The PIM status indicates that atezolizumab represents a significant advance in a disease with a high unmet clinical need, [redacted]. [redacted]	Thank you, your comment has been noted. During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with bevacizumab is an innovative technology when making its recommendations. No changes have been made.

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		[redacted] Atezolizumab in combination with bevacizumab is likely to provide a step-change for the management of this condition.	
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	Yes, innovative. This is the first systemic therapy monotherapy or combination therapy for patients with advanced HCC to show a [redacted] compared to sorafenib, which has been the standard of care for approximately 10 years. [redacted]. [redacted] of patients receiving atezo/bev were free from disease progression after 6 months of therapy compared to [redacted] of patient receiving sorafenib. There is also a proportion of patients who achieve durable responses, with approximately [redacted] of patients remaining free of progression at 1-year after commencing atezo/bev. Atezo-bev is well tolerated with a safety profile similar to sorafenib in the IMBrave 150 clinical trial. Atezo/bev [redacted] the time to deterioration of patient-reported quality of life compared with sorafenib. Relevant data is from the IMBrave 150 clinical trial presented in oral abstract form at the ESMO Asia conference in Nov 2019 by Dr A-L Cheng and co-authors.	Thank you, your comment has been noted. During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with bevacizumab is an innovative technology when making its recommendations. No changes have been made.
	Roche	• Have all relevant comparators for atezolizumab been included in the scope?	Thank you for your responses to the

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Questions for consultation		Please see comment on comparators above. • Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma? Please see comment on comparators above. In clinical practice, Sorafenib and Lenvatinib are established treatments for HCC. Given Lenvatinib's recent MA and approval by NICE, Sorafenib is the global and UK standard of care for the first-line treatment of patients with advanced HCC. • 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?' No comment – see comment in the comparators section for rationale on why BSC not considered appropriate in this treatment setting • Are the outcomes listed appropriate? Yes. Please see comments on outcomes above. • Are there any subgroups of people in whom atezolizumab with bevacizumab is expected to be more clinically effective and cost effective? Atezolizumab in combination with bevacizumab has demonstrated superior clinical effectiveness across the ITT population. As such, no further subgroups have been identified as relevant. • Where do you consider atezolizumab with bevacizumab will fit into the existing NICE pathway, **Liver cancers**?	questions for consultation. Best supportive care has been included because some people may choose not to have a systemic therapy such as sorafenib or lenvatinib, or may be contraindicated. Consultees can submit further information as part of their evidence submissions which will be considered by the appraisal committee. No changes have been made to the outcomes listed in the scope. The scope has been amended to include the consideration of

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		Atezolizumab in combination with bevacizumab will be used in the first line for adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy • 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 atezolizumab 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. No equality issues have been identified • Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Clinical trial results from Phase III IMbrave150 trial. • Do you consider atezolizumab with bevacizumab to be innovative in its potential to make a significant and substantial impact on health-related	relevant subgroups if evidence allows. No changes have been made to the pathway for HCC. Thank you, your comment on equalities issues has been noted. The appraisal committee will consider the clinical and cost effectiveness evidence

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		benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, atezolizumab in combination with bevacizumab has demonstrated considerable improvement in outcomes in this setting, thus is considered a step change in the management of this condition. As detailed above, PIM designation has been given for atezolizumab in combination with bevacizumab for the treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy. Following the PIM designation, [redacted] • Do you consider that the use of atezolizumab with bevacizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No comment • Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Phase III randomised clinical trial: IMbrave150 trial providing robust progression free survival and overall survival data. • 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. No barriers to adoption are expected	during the development of the appraisal. During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with bevacizumab is an innovative technology when making its recommendations. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal.

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		• 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). This process is appropriate. • 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? A cost-effectiveness analysis is the most appropriate method for this appraisal • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? As outlined above in the innovation section, atezolizumab in combination with bevacizumab is clinically superior to the comparator which represents the current primary standard of care. An indirect comparison will be provided to assess clinical efficacy versus lenvatinib. Any differences in resource use will be accounted for within the CEA. • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?	Thank you for your response. Thank you for your response. Thank you for your response. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal.

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		Yes • 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? A further event-driven analysis is estimated to become available during the second half of the year; however, this will be descriptive only.	Thank you for your response. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal.
	Eisai Limited	• Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma? Both sorafenib and lenvatinib are currently considered to be established clinical practice in the UK for advanced/unresectable hepatocellular carcinoma (HCC). • Where do you consider atezolizumab with bevacizumab will fit into the existing NICE pathway, Liver cancers? Eisai consider that atezolizumab with bevacizumab will be used as an alternative option to lenvatinib or sorafenib in those patients with unresectable hepatocellular carcinoma who have not previously received systemic treatment.	Thank you for your responses to the questions for consultation. No changes have been made to the pathway for HCC.

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		In addition, we would like to highlight that the atezolizumab + bevacizumab combination has a different mode of action to the currently approved tyrosine kinase inhibitors (TKIs), lenvatinib and sorafenib. Therefore, feedback from UK clinicians is that, once patients progress on the combination, if possible, they would then consider using either lenvatinib or sorafenib. This change to the current treatment pathway would be consistent with the NHS England reimbursement criteria in place for renal cell carcinoma.	During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with bevacizumab is an innovative technology when making its recommendations.
	1) British Association for the Study of the Liver (BASL), 2) HCC-UK, 3) Association of Cancer Physicians, 4) British Society of Gastroenterology	• Have all relevant comparators for ateloizumab with bevacizumab been included in the scope? Yes, all relevant comparators have been considered. • Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma? For patients with advanced disease who have not received systemic therapy the established therapies in the UK are sorafenib and lenvatinib. • 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?' Yes, patients may be managed with BSC, but only if their PS or liver dysfunction secondary to background cirrhosis or disease burden makes then ineligible for systemic therapies as above (CP class B or C).	Thank you for your responses to the questions for consultation. Best supportive care has been included because some people may choose not to have a systemic therapy such as sorafenib or lenvatinib, or may be contraindicated. Consultees can submit further information as part of their evidence submissions which will

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			be considered by the appraisal committee.
		• Are the outcomes listed appropriate? Yes.	Thank you for your response.
		• Are there any subgroups of people in whom ateloizumab with bevacizumab is expected to be more clinically effective and cost effective? No, there are currently no available biomarkers to accurately predict patients who might benefit from atezo/bev more (or less) than others.	The scope has been amended to include the consideration of relevant subgroups if evidence allows.
		• Where do you consider ateloizumab with bevacizumab will fit into the existing NICE pathway, Liver cancers? Patients with advanced HCC not amenable to surgery/ablation, liver transplantation, or loco-regional therapy with TACE.	No changes have been made to the pathway for HCC.
		• 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:	

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		○ 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; No concerns. ○ 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; No concerns. ○ could have any adverse impact on people with a particular disability or disabilities. No concerns. • 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)? Yes. See 'Innovation' section above.	Thank you, your comments on equalities issues have been noted. During the development of the appraisal, the committee will consider the degree to which atezolizumab in combination with bevacizumab is an innovative technology when making its recommendations. The appraisal committee will consider

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		• 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? Yes. Atezo/bev [redacted] the time to deterioration of patient-reported quality of life compared with sorafenib. • Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Relevant data is from the IMBrave 150 clinical trial presented in oral abstract form at the ESMO Asia conference in Nov 2019 by Dr A-L Cheng and co-authors. • 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. Yes. There may be some barriers to adoption of this technology since some physicians treating HCC may not be familiar with immunotherapy and the management of the uncommon but potentially serious immune-related side effects of this class of agent. Some patient will not be suitable for atezo/bev due to auto-immune conditions (such as ulcerative colitis) which can be severely exacerbated by immunotherapy agents. • 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	the clinical and cost effectiveness evidence during the development of the appraisal. The appraisal committee will discuss any potential barriers to adoption of this technology. Comment noted.

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		available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). Appropriate for STA process. • 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. o Would it be appropriate to use the cost comparison methodology for this topic? I am not suitably qualified to comment here. o Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Similar resource use. Improved clinical efficacy. o Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes, still relevant. o 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? There is an ongoing clinical trial of another combination involving an immunotherapy agent in patients with advanced HCC (LEAP-002 trial; pembrolizumab+lenvatinib vs lenvatinib), but this trial is still	Comment noted. Comment noted. Comment noted. The appraisal committee will consider the clinical and cost effectiveness evidence during the development of the appraisal.

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		recruiting patients so I don't think it will report within the next 12 months (more likely in at least 18months). A further trial (COSMIC-312) is investigating atezolizumab+cabozantinib vs sorafenib vs cabozantinib, but again this trial won't report for at least 18months.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

none