National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma [ID2725]
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	It is appropriate to evaluate this topic via the Single Technology Appraisal route.	Comment noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	Yes it is appropriate and timely to evaluate this drug combination as a single technology appraisal.	Comment noted. No action needed.
Wording	AstraZeneca	Yes	Comment noted. No action needed.
	British Association for the Study of the	Yes	Comment noted. No action needed.

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	Liver (BASL) / HCC UK		
Timing issues	AstraZeneca	There is a remaining unmet need for a safe and efficacious first-line treatment option for patients with advanced or unresectable hepatocellular carcinoma (HCC). Durvalumab in combination with tremelimumab (henceforth referred to as STRIDE [Single Tremelimumab Regular Interval Durvalumab]) received MHRA marketing authorisation in June 2023, based on data from HIMALAYA, an open-label pivotal phase 3 trial. HIMALAYA reported that STRIDE is associated with statistically significantly improved overall survival compared to sorafenib.[1] STRIDE fulfils an unmet need for a well-tolerated and effective treatment alternative for advanced HCC patients in the UK, with unprecedented, highly mature evidence supporting the prolongation of survival in this patient population.[1,2] **References** 1. Abou-Alfa G.K. et al (2022) Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma NEJM Evid 2022; 1 (8) 2. Sangro B. et al (2024) Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma Ann Oncol. 2024 Feb 19:S0923-7534(24)00049-8. doi: 10.1016/j.annonc.2024.02.005	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10571. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	This drug combinations offers an important therapeutic option for patients with advanced HCC and is associated with the best long-term outcomes reported to date. Given the poor prognosis for those with advanced HCC, this evaluation should be considered urgently.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website:

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			https://www.nice.org.uk/guidance/indevelopment/gid-ta10571. No action needed.
Additional comments on the draft remit	AstraZeneca	None	Comment noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	No other comments	Comment noted. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	**STRIDE** Since the publication of the draft scope, the British Society of Gastroenterology (BSG) guidelines for the management of hepatocellular carcinoma in adults have been published and require inclusion in the final scope.[3] The BSG guidelines list the combination of durvalumab and tremelimumab as an effective alternative first- line combination therapy despite the fact that the regimen has not yet been approved by NICE. The guidelines highlight the risk of variceal bleeding appears reduced compared with atezolizumab plus bevacizumab (evidence high; recommendation strong).[3]	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the evaluation. No action needed.

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		SIRT (selective internal radiation therapy) and transarterial chemoembolization (TACE) for advanced HCC Whilst NICE TA688 recommends SIRTs (SIR-Spheres and TheraSphere) as an option for treating unresectable advanced HCC for people with Child–Pugh grade A liver impairment when conventional transarterial therapies are inappropriate, AstraZeneca would like to propose that the 'Background' be expanded to reflect the recent BSG guidelines. According to the BSG guidelines, the subgroup of patients who will benefit from SIRT has yet to be clearly defined. Patients in whom SIRT may be considered include those with large solitary tumours, and patients with tumours associated with local macrovascular tumour invasion in whom tolerance to systemic therapy is, or is likely to be, a concern.[3] This is in alignment with UK clinician feedback who highlight that eligible patients are most likely to be referred for systemic treatment, due to the uncertainty around the evidence and optimal protocols associated with TACE and SIRT. **References** 3. Suddle A. et al (2024) British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. Gut 2024;0:1–34. doi:10.1136/gutjnl-2023-331695	
	British Association for the Study of the Liver (BASL) / HCC UK	Please note that BASL has just published UK guidelines on HCC (Suddle A et al GUT 2024 doi: 10.1136/gutjnl-2023-331695) and these provide up to date reference material. BCLC is a staging system for HCC but Child Pugh and ECOG performance status are factors used to assign BCLC stage rather than staging systems in their own right. ALBI is just used to assess liver function and not used for staging at present.	Comments noted. The background section has been updated to reflect the suggested changes.

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		Transarterial bland embolization (TAE) is also used as an alternative to chemoembolization (TACE). Systemic therapy is usually indicated in those who are refractory to locoregional therapy like TAE/TACE or SIRT, or are **not suitable due to extent of cancer within the liver** or metastatic disease.	
Population	AstraZeneca	The target population defined is aligned with the MHRA marketing authorisation for durvalumab in combination with tremelimumab	Comment noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	As mentioned above, the technology is not only relevant to those that have progressed after local therapy or those with metastatic disease but also includes those who have liver confined diseases which is not felt suitable for local therapy due to the extent of disease.	Comment noted. NICE will evaluate the technology within its marketing authorisation. No action needed.
Subgroups	AstraZeneca	None	Comment noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	Within the context of patients with Child-Pugh score A and ECOG PS 0 or 1, there are no subgroups that that have been proven to derive greater or less benefit.	Comment noted. No action needed.
Comparators	AstraZeneca	**Selective internal radiation therapies (SIRT) including SIR-Spheres and TheraSphere** SIRT (with SIR-Spheres, TheraSphere or QuirumSphere) is not a relevant comparator for this appraisal, as the target patient population for this interventional procedure is different to the target patient population for durvalumab in combination with tremelimumab.[3]	Comments noted. To keep the scope broad at this early stage, all comparators have been retained. The company will have the opportunity

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		SIRT is a complex multidisciplinary treatment that requires close coordination between nuclear medicine, interventional radiology and oncology. It is a highly specialised procedure, with only 11 NHS centres providing SIRT.[9] Requiring specific equipment and expertise, SIRT is used very infrequently (0.45% of first and 0.47% of 2nd locoregional treatments).[5] ***Guidance on SIRT from BSG*** According to the BSG guidelines, the subgroup of patients who will benefit from SIRT has yet to be clearly defined. Patients in whom SIRT may be considered include those with large solitary tumours, and patients with tumours associated with local macrovascular tumour invasion in whom tolerance to systemic therapy is, or is likely to be, a concern.[3] As such, these patients would not be suitable candidates for STRIDE. ***Guidance on SIRT from ESMO*** According to the ESMO Clinical Practice Guidelines for HCC, SIRT may be considered only in exceptional circumstances for patients with liver-confined disease and good liver function in which neither TACE nor systemic therapy is possible. It is listed as an alternative treatment rather than a standard of care option.[4] ***Guidance on SIRT according to clinician feedback*** According to UK clinician feedback, SIRT is a treatment option only for a very small proportion of patients due to the paucity of supporting data. It is not anticipated to replace TACE or systemic treatment for HCC, with the latter favoured over embolisation protocols where eligibility allows. **Best supportive care** Palliative/best supportive care is offered to patients with end-stage liver disease to alleviate symptom burden and is employed when no treatment	during the full evaluation to outline which comparators it considers to be most relevant. No action needed.

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		options are deemed to bring benefit.[7] Therefore, best supportive care is not deemed a relevant comparator in this appraisal. **In conclusion, SIRT is not a relevant comparator for this appraisal. Since the NICE recommendation of SIRT for HCC, UK clinicians have had differing opinions as to its applicability for advanced HCC. Some clinicians use SIRT in intermediate HCC, others believe the evidence is limited and favour other more established modalities such as TACE.[3] BSC is also not a relevant comparator for this appraisal, as in most cases it is a palliative approach for patients not anticipated to benefit from interventional or systemic treatment.** **The relevant comparators for this appraisal are:** • **Atezolizumab in combination with bevacizumab** • **Sorafenib** • **Lenvatinib** **References** 3. Suddle A. et al (2024) British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. Gut 2024;0:1–34. doi:10.1136/gutjnl-2023-331695 4. Vogel A. et al. (2018) Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2018) 29 (Suppl 4): iv238–iv255. 5. Zalin-Miller A et al (2023) P47 Treatment pathways of patients diagnosed with hepatocellular carcinoma (HCC) after initial locoregional treatment in England. Gut 2023;72:A42-A43. 7. NHS England (2016) ENHANCED SUPPORTIVE CARE Integrating supportive care in oncology (Phase I: Treatment with palliative	

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		intent). Available at: https://www.england.nhs.uk/wp-content/uploads/2016/03/ca1-enhncd-supprtv-care-guid.pdf 9. SIRT Approved for Routine Commissioning on the NHS. Available at: https://www.mysirtstory.org.uk/how/nhs.htm	
	British Association for the Study of the Liver (BASL) / HCC UK	The main comparator is the combination of atezolizumab and bevacizumab which, like the combination in question, has been shown to be superior to sorafenib. Lenvatinib has been shown to be non-inferior to sorafenib. So, the current recommended first line therapy is atezolizumab and bevacizumab unless there are contraindications to either drug in which case sorafenib or lenvatinib are used.	Comments noted. To keep the scope broad at this early stage, all comparators have been retained. The company will have the opportunity during the full evaluation to outline which comparators it considers to be most relevant. No action needed.
Outcomes	AstraZeneca	AstraZeneca considers the outcome measures listed in the draft scope are appropriate and comprise the important outcomes for the assessment of efficacy, health-related benefits and harms associated with durvalumab in combination with tremelimumab.	Comments noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	Disease control rate can be helpful too.	Comment noted. More specific outcomes relevant to the broader outcome headings included in the scope can be considered as part of the evaluation process. Disease

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			control rate is captured under “response rates”. No action needed.
Equality	AstraZeneca	AstraZeneca are not aware of any issues of inequality in the management of unresectable or metastatic HCC in England and Wales.	Comment noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	I do not see any issues relating to equality of access.	Comment noted. No action needed.
Other considerations	AstraZeneca	None	Comment noted. No action needed.
Questions for consultation	AstraZeneca	**Are selective internal radiation therapies and best supportive care relevant comparators? If relevant, how should best supportive care be defined?** Selective internal radiation therapies and BSC are not relevant comparators for this appraisal as the target treatment population for these treatment options is not the anticipated target population for durvalumab in combination with tremelimumab. Please refer to the Comparators section for detailed rationale.	Comments noted. To keep the scope broad at this early stage, all comparators have been retained. The company will have the opportunity during the full evaluation to outline which comparators it considers to be most relevant. No action needed.

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		Where do you consider durvalumab with tremelimumab will fit into the existing care pathway for advanced or unresectable hepatocellular carcinoma? Durvalumab in combination with tremelimumab is anticipated to be positioned as a first-line treatment option for patients with advanced or unresectable HCC. These patients may have either intermediate (BCLC B) or advanced (BCLC C) HCC which is unresectable, and not amenable to locoregional treatment (such as TACE or SIRT). Durvalumab with tremelimumab is anticipated to provide prescribing clinicians an alternative option in the first-line setting, in addition to the currently available systemic treatment options (sorafenib, lenvatinib and atezolizumab + bevacizumab).	NICE will evaluate the technology within its marketing authorisation. The company will have an opportunity to outline the technology's proposed positioning and relevant comparators. No action needed.
		Would durvalumab with tremelimumab be a candidate for managed access? Considering the maturity of data from the HIMALAYA trial, durvalumab + tremelimumab is not expected to be a candidate for managed access.	No action needed.
		Do you consider that the use of durvalumab with tremelimumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? With the STRIDE regimen, there is no requirement for an endoscopy prior to receiving the regimen, unlike atezolizumab + bevacizumab. This leads to faster treatment initiation.	No action needed.

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Additional comments on the draft scope	AstraZeneca	None	Comment noted. No action needed.
	British Association for the Study of the Liver (BASL) / HCC UK	Any additional comments on the draft scope • Are selective internal radiation therapies and best supportive care relevant comparators? If relevant, how should best supportive care be defined? As mentioned, the main comparator is atezolizumab and bevacizumab. SIRT has not been shown to be superior to systemic therapy and in randomised trials, the survival outcomes are similar to sorafenib which is inferior to atezolizumab and bevacizumab. Best supportive care is reserved for those who do not meet the eligibility criteria for systemic therapy and represent a different patient population from that proposed here. • Where do you consider durvalumab with tremelimumab will fit into the existing care pathway for advanced or unresectable hepatocellular carcinoma? Durvalumab with tremelimumab will be considered as a first line option for patients with advanced disease in preference to sorafenib or lenvatinib providing there are no contraindications to either drug.	Comments noted. To keep the scope broad at this early stage, all comparators have been retained. The company will have the opportunity during the full evaluation to outline which comparators it considers to be most relevant. No action needed. NICE will evaluate the technology within its marketing authorisation. The company will have an opportunity to outline the technology's proposed positioning and relevant comparators. No action needed.

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		• Would durvalumab with tremelimumab be a candidate for managed access? I think the randomised phase three data and the subsequent published analysis provide compelling evidence of efficacy. Therefore, I do not see that managed access has a role. • Do you consider that the use of durvalumab with tremelimumab can result in any potential 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 committee to take account of these benefits. The pivotal global phase three trial was published in New England Journal Evidence in June 2022 (DOI: 10.1056/EVIDoa2100070) and demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of overall survival for durvalumab with tremelimumab in comparison with standard of care sorafenib. In addition, durvalumab with tremelimumab was associated with an improved response rate, and delay in deterioration of quality of life. The rate of grade 3/4 treatment emergent adverse events was similar across both arms suggesting that the clinical benefit was not at the expense of increased toxicity. More recently in May 2024, the extended follow-up for survival has been reported (10.1016/j.annonc.2024.02.005) and this has demonstrated a four-year survival of 25.2% for durvalumab with tremelimumab versus 15.1% for sorafenib. This means that a quarter of patients with advanced HCC can expect a durable response and a survival rate that has not so far been achieved with any therapy in this patient population. • **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and**	No action needed. No action needed.

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		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 durvalumab with tremelimumab are licensed;** **No** • **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** • **could have any adverse impact on people with a particular disability or disabilities.** **No**	No action needed.

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

Roche

Sirtex Medical United Kingdom