National Institute for Health and Care Excellence

Health Technology Evaluation

Nivolumab with ipilimumab for untreated advanced or unresectable hepatocellular carcinoma ID6239
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	BMS (company)	It is appropriate to evaluate this topic via the Single Technology Appraisal route.	Thank you for your comment. No action.
	British Association for the Study of the Liver (BASL)/ HCC-UK	It is appropriate to evaluate this topic now on the basis of the recent positive data from the Phase 3 Checkmate 9DW study. This was a global study which is a fair representation of the UK patient population - including 44% of patients from Europe/North and over a third of patients with a non-viral aetiology of chronic liver disease as is increasingly observed in the UK HCC patient population. Single technology appraisal is the most appropriate evaluation route.	Thank you for your comments. No action.
Wording	BMS (company)	Yes [Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.]	Thank you for your comment. No action.

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	British Association for the Study of the Liver (BASL)/ HCC-UK	Should be re-worded as per below to clarify that patients are naïve to systemic therapy but may have been previously treated e.g. with loco-regional therapy. "To appraise the clinical and cost effectiveness of nivolumab with ipilimumab within its marketing authorisation for advanced or unresectable hepatocellular carcinoma that has not previously been treated with systemic therapy."	Thank you for your comment. We have updated the remit wording.
Timing issues	BMS (company)	There remains unmet clinical need for safe and efficacious treatment in the first line setting of unresectable or advanced hepatocellular carcinoma (uHCC). Nivolumab in combination with ipilimumab received MHRA marketing authorisation for uHCC on 7th July 2025, based on data from the open-label randomised Phase 3 trial CheckMate 9DW (Yau et al., 2025). This trial demonstrated that treatment with nivolumab plus ipilimumab resulted in a significant overall survival benefit versus investigators' choice of lenvatinib or sorafenib, and manageable safety in patients with previously untreated unresectable hepatocellular carcinoma. **Reference** Yau T. et al. (2025). *Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial*. Lancet 405; 1851-1864.	Thank you for your comments. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.
	British Association for	As a result of the CheckMate 9DW study, international guidelines on the management of HCC have been amended to include ipi/nivo as a potential	Thank you for your comments. This topic

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	the Study of the Liver (BASL)/ HCC-UK	first line therapy and this has already been implemented elsewhere in the world.	has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BMS (company)	No comments	No action
	British Association for the Study of the Liver (BASL)/ HCC-UK	• The term MASLD (metabolic dysfunction-associated steatotic liver disease) should be clearly listed as a major risk factor for cirrhosis, rather than referring to cirrhosis being more common in older people or those with diabetes. • BCLC staging explanation is incomplete. Suggest amending to "The BCLC system combines tumour characteristics with the Child-Pugh score and performance status (measured on ECOG scale) to classify patients into 5 stages (0,A,B,C, and D), which can be used to determine prognosis and define treatment options. • Paragraph 3 should come after paragraph 1 and before discussion of staging. • The sentence "for people with more advanced disease, treatment options include interventional procedures…" "more advanced disease" should be replaced with "intermediate stage disease".	Thank you, we have amended the background section as suggested.
Population	BMS (company)	The population is consistent with the wording for the MHRA Licence for nivolumab plus ipilimumab in uHCC.	Thank you for your comment. No action.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Association for the Study of the Liver (BASL)/ HCC-UK	Should be re-worded to clarify that patients with prior locoregional treatment are still eligible, i.e. adults with advanced or unresectable hepatocellular carcinoma **who have not previously received systemic therapy**	Thank you for your comment. We have updated the population wording.
Subgroups	BMS (company)	No subgroups have been identified for separate consideration.	Thank you for your comment. No action.
	British Association for the Study of the Liver (BASL)/ HCC-UK	No particular subgroups with improved benefit identified in the checkmate 9DW study	Thank you for your comment. No action.
Comparators	BMS (company)	BMS believes that best supportive care (BSC) is not a relevant comparator. BSC is offered to patients with end-stage liver disease to alleviate symptom burden and is employed when no treatment options are considered to bring benefit. It is therefore proposed to remove BSC as a comparator. 1. BSG HCC Guidelines state that atezolizumab plus bevacizumab is considered as a first-choice standard of care in untreated uHCC (Suddle et al., 2024). Durvalumab with tremelimumab has subsequently been approved by NICE (TA1090). Sorafenib and lenvatinib are considered by the guidelines as second-choice systemic therapies in untreated uHCC. 2. BMS would therefore propose the primary comparators of nivolumab plus ipilimumab to be durvalumab plus tremelimumab, and atezolizumab and	Thank you for your comment. Best supportive care has been removed from the comparators list.

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		bevacizumab. Sorafenib and lenvatinib would be considered secondary comparators. **Reference** 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	We now have more than one first line therapy with proven efficacy in first line, I would therefore argue that best supportive care is no longer an appropriate comparator and in this study there is no BSC arm.	Thank you for your comment. Best supportive care has been removed from the comparators list.
Outcomes	BMS (company)	BMS considers the outcomes listed to appropriately capture the benefits and harms of the technologies considered.	Thank you for your comment. No action.
	British Association for the Study of the Liver (BASL)/ HCC-UK	Yes [Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?]	Thank you for your comment. No action.
Equality	BMS (company)	BMS is not aware of any issues relating to equality of opportunity.	Thank you for your comment. No action.
	British Association for the Study of the	No comments	Thank you for your comment. No action.

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	Liver (BASL)/ HCC-UK		
Questions for consultation	BMS (company)	**Where do you consider nivolumab with ipilimumab will fit into the existing care pathway for untreated advanced HCC?** Nivolumab with ipilimumab will be prescribed in secondary care with routine follow-up in secondary care. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** The setting for prescribing and routine follow-up will be the same for the comparators and subsequent treatments as for nivolumab plus ipilimumab. **Are selective internal radiation therapies and best supportive care relevant comparators? If relevant, how should best supportive care be defined?** As stated above, BSC is not considered an appropriate comparator. Selective internal radiation therapy (SIRT; SIR-Spheres, TheraSphere or QuiremSpheres) 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 nivolumab plus ipilimumab. The BSG HCC guidelines state it is difficult, on the basis of current scientific data, to make clear recommendations about the subgroup of patients who will benefit most from SIRT. (Suddle et al., 2024) They make a 'weak' recommendation for use of SIRT in patients with tumours associated with local macrovascular tumour invasion in whom tolerance to systemic therapy is, or is likely to be, a concern. Current usage of SIRT is very low, with registry data suggest SIRT	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comments. Best supportive care has been removed from the comparators list.

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		is used in less than 0.5% of loco-regional cases of untreated uHCC (Zalin-Miller et al., 2023). **Have all relevant comparators for nivolumab with ipilimumab been included in the scope?** The relevant comparators are as follows: 1. Durvalumab with tremelimumab 2. Atezolizumab with bevacizumab 3. Lenvatinib 4. Sorafenib As stated above, BSC is not considered an appropriate comparator. **Which treatments are considered to be established clinical practice in the NHS for untreated advanced HCC?** BSG HCC Guidelines state that atezolizumab plus bevacizumab is considered as a first-choice standard of care in untreated uHCC (Suddle et al., 2024). Durvalumab with tremelimumab has subsequently been approved by NICE (TA1090). Sorafenib and lenvatinib are considered by the guidelines as second-choice systemic therapies in untreated uHCC. **Are there any subgroups of people in whom nivolumab with ipilimumab is expected to be more clinically effective and cost effective? Are there other groups that should be examined separately?**	Thank you for your comments. Thank you for your comments. Thank you for your comments.

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		In line with the trial population and license, BMS expects nivolumab in combination with ipilimumab to be efficacious as a first line treatment option across all subgroups. **Would nivolumab with ipilimumab be a candidate for managed access?** No. **Do you consider that the use of nivolumab with ipilimumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The risk of variceal bleeding with nivolumab plus ipilimumab is reduced compared with atezolizumab plus bevacizumab, therefore there is no requirement for endoscopy or active management of varices prior to treatment initiation. This leads to reduced patient and carer burden and faster treatment initiation. The availability of nivolumab for administration subcutaneously rather than intravenously ([redacted]) would reduce the patient burden in receiving treatment, as well as free up NHS resources in administering treatment. **References** 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	Thank you for your comment. Thank you for your comments. The appraisal committee may consider any factors that relate to uncaptured benefits.

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		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.	

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

Eisai Ltd