National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Nivolumab for previously treated 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	Bristol-Myers Squibb	We recommend that the wording of the remit is amended to 'To appraise the clinical and cost-effectiveness of nivolumab within its marketing authorisation for treating hepatocellular carcinoma after prior systemic therapy'.	Comment noted.
Timing Issues	Bristol-Myers Squibb	The appraisal should be prioritised as there are currently no treatments that have a marketing authorisation or NICE approval for patients with hepatocellular carcinoma after prior systemic therapy has failed or in whom systemic therapy is not tolerated. This represents a significant area of unmet need in the care of these patients. Furthermore, priority scheduling of this appraisal will facilitate NICE's aim to publish guidance within 90 days of marketing authorisation.	Comment noted. NICE aims, where possible, to produce timely guidance in line with health technologies receiving their marketing authorisations.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol-Myers Squibb	We were unable to find the primary source of the statement that "Hepatocellular carcinoma accounts for about 90% of all liver cancers" at the reference provided. The literature we have reviewed suggests that the 90% figure may be relevant in some countries (Zhang et al. 2015) but that in the UK the proportion of liver cancers that are hepatocellular carcinoma is closer to 35-45% (NCIN 2012; West et al. 2006)	Comments noted. The background section has been updated. Please provide any further details of expected prevalence in the UK during the appraisal.
	Royal College of Pathologists	As the proposed study involves the assessment of a novel treatment for HCC, the final study design should consider histological confirmation of HCC as an entry criterion.	Comment noted. No further action required.
The technology/ intervention	Bristol-Myers Squibb	The description of the technology is accurate.	Comment noted. No further action required.
Population	Bristol-Myers Squibb	[redacted]	Comments noted. The population in the scope has been amended to 'Adults with previously treated advanced hepatocellular carcinoma'. Guidance will be issued in line with marketing authorisation.
Comparators	Bristol-Myers Squibb	Best supportive care (as listed in the NICE draft-scope) is the only relevant comparator as there are currently no approved second-line treatments for patients with hepatocellular carcinoma.	Comment noted. No further action required.

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Outcomes	Bristol-Myers Squibb	The outcome measures listed in the NICE draft scope are relevant: • objective response rate (ORR) • progression-free survival • overall survival • adverse effects of treatment • health-related quality of life. There is evidence of early and sustained response in patients responding to treatment with nivolumab. Therefore, in addition to the outcomes listed above, it will be important for the appraisal to consider the following outcomes: • duration of response • time to response • time to progression.	Comments noted. Duration of response, time to response, and time to disease progression have been added to the list of outcomes in the scope.
Economic analysis	Bristol-Myers Squibb	The economic analysis will estimate the cost-effectiveness of nivolumab compared to BSC and will be expressed in terms of incremental cost per quality-adjusted life year. The analysis will have a lifetime horizon. Costs will be considered from an NHS and Personal Social Services perspective.	Comment noted. No further action required.
Equality and Diversity	Bristol-Myers Squibb	We believe the draft scope is in line with NICE's commitment to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.	Comment noted. No further action required.

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Innovation	Bristol-Myers Squibb	BMS consider nivolumab to be innovative in the treatment of HCC due to its novel mechanism of action in this therapeutic area, and the potential for it to make a significant impact on the substantial unmet need. The innovative nature of nivolumab for the treatment of HCC has recently been recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) in their designation of it as a Promising Innovative Medicine (PIM 2017/0001). Nivolumab is a novel immunotherapy agent for the treatment of cancer, with a new mechanism of action as a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. It specifically binds to PD-1 receptor on the surface of immune cells and restores T-cell activity by blocking the binding of the PD-L1 and PD-L2 ligands found at the tumour site to PD-1 receptors on immune cells. This approach, enabling the body's own immune system to target cancer, is novel in HCC. Despite being a rare form of cancer in the UK, HCC is among the leading causes of cancer-related deaths. Effective treatment options are limited for patients with HCC after prior systemic therapy; there is no option available to patients who progress on sorafenib, or are intolerant to it. Evidence shows that nivolumab monotherapy leads to: • Objective responses which are durable irrespective of infection status (uninfected or infected with HCV or HBV). • Early responses and longer survival than observed historically for best supportive care.	Comments noted. No further action required.

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		• Maintenance of good quality of life following treatment with nivolumab, compared to baseline measures. • A tolerable safety profile that is similar to that observed in other tumour types without any new safety signals. The above nivolumab data are presented in the pivotal study (CheckMate040) clinical study report (CSR) and data describing historic survival for patients treated with BSC is available from the literature.(Llovet et al. 2013; Bruix et al. 2016)	
Other considerations	Bristol-Myers Squibb	[redacted]	Comment noted. No further action required.
Questions for consultation	Bristol-Myers Squibb	*The clinical trial includes a cohort including nivolumab in combination with ipilimumab. Is this combination treatment likely to be used in clinical practice?* Nivolumab is not expected to be used in combination with ipilimumab under this indication. CheckMate 040 has several cohorts, one of which evaluates the safety of a nivolumab and ipilumumab combination in patients with HCC. [redacted] The marketing authorisation will therefore specify the use of nivolumab as monotherapy. *Have all relevant comparators for nivolumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for previously treated advanced hepatocellular carcinoma?* Best supportive care is the relevant comparator as previously stated. There are no other NICE/EMA approved treatments following sorafenib progression or intolerance.	Comments noted.

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		We note that there are ongoing or scheduled NICE appraisals for other treatments of HCC; however none of these are currently licenced or in routine use in the UK. *Should best supportive care be included as a comparator, and if so how should it be defined?* As stated above, best supportive care is the only appropriate comparator for this patient population. Medical treatments and palliative care will both constitute best supportive care in this patient population (patients with HCC after progression on, or intolerance to sorafenib). Patients typically receive a range of drug treatment for HCC-related symptoms. For example: • diurtetics (e.g. spironolactone) • antiemetics (e.g. metoclopramide) • pain relief (e.g. morphine sulfate and other opioids) • corticosteroids (e.g. dexamethasone). Patients will typically undergo haematological and liver function monitoring. In addition patients will receive in- and out-patient care to treat specific HCC-related symptoms (such as ascites, abdominal pain, anaemia, hyperbilirubinemia, asthenia/fatigue) Treatment of HCC and management of the underlying liver disease may fall under the care of a hepatologist as well as the oncology and palliative care teams. *Are the outcomes listed appropriate?* As stated above, the outcomes listed are appropriate. In addition to these the duration of response, time to response, and time to progression are also important outcome measures.	

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		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? There is currently no evidence to identify subgroups of patients within the second-line indication for whom the technology is expected to be more effective or cost-effective. No subgroups were pre-specified in the 2L-EXP cohort of the key clinical study (CheckMate040). *Where do you consider nivolumab will fit into the existing NICE pathway?* *http://pathways.nice.org.uk/liver-cancers* In the existing NICE pathway for the treatment of liver cancer, we expect nivolumab to be placed under the heading of 'treatments for hepatocellular carcinoma'. [redacted] *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)* Appraisal of nivolumab through the STA process is appropriate. It is important that patients with HCC are able to access this innovative medicine as soon as possible, given that there are currently no other approved treatments available to them.	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	None		

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

Department of health