National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma
ID2712
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
Please note: NICE consulted on assessing nivolumab in combination with ipilimumab (ID1629) and nivolumab in combination with platinum-based chemotherapy (ID2712) in the same technology appraisal. Following the consultation for ID1629, the remit for ID2712 has been updated to also include nivolumab with ipilimumab: **Final remit:** To appraise the clinical and cost effectiveness of nivolumab with fluoropyrimidine- and platinum-based combination chemotherapy, and nivolumab in combination with ipilimumab within their marketing authorisations for untreated advanced unresectable, recurrent or metastatic oesophageal cancer			
Wording	BMS	No comments on the remit.	-
	Roche	If the study did not allow investigators to choose different chemotherapy regimens, please only include cisplatin plus fluorouracil as chemotherapy option.	Thank you for your comment. No action needed. Please note that intervention is specified in the PICO table, and that the remit was updated to specify squamous cell carcinoma.

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Timing Issues	BMS	It is important for NICE to provide a recommendation for the use of nivolumab within the NHS as close to marketing authorisation as possible, given the limited effective treatment options currently available to these patients, thus demonstrating an unmet need in this area. The majority of oesophageal cancer patients in the UK are diagnosed at advanced age and disease stage, so that options for curative treatment (such as surgery) may no longer be viable and the aim of treatment is palliative.1 Consequently, clinical outcomes at this advanced stage may also be poor, as noted in the draft scope. There are limited therapeutic regimens available and those that are available have poor efficacy and poor safety profiles. Further, oesophageal cancer often exhibits or develops resistance to chemotherapeutic agents within a relatively short period. For those patients who are not eligible for currently approved first-line targeted therapy, due to age or comorbidities, treatment options are limited. These factors translate to very poor clinical outcomes. Nivolumab has the potential to significantly improve outcomes in this patient population, so a timely appraisal is crucial. [1] Cancer Research UK. Oesophageal cancer statistics. 2017 21 April 2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer.	Thank you for your comments. NICE has scheduled this topic into its work programme. No action needed.
	Roche	No comment.	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BMS	No comments	-
	Roche	Consider adding information related to the efficacy of immunotherapy in squamous cell carcinoma vs adenocarcinoma. It is well known and reported that the two histological types respond differently to immunotherapy treatments.	Thank you for your comments. The background section provides a brief summary of the disease and current treatment pathway. Further details can be given at the submission stage. No action needed.
The technology/ intervention	BMS	No comments	-
	Roche	Indicate the use of cisplatin plus fluorouracil instead of chemotherapy if the trial did not include other chemotherapy types.	Thank you for your comment. The intervention was updated to “nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy”.
Population	BMS	The population is in squamous cell carcinoma of the oesophagus only (CM648) and therefore should not include adenocarcinoma of the oesophagus. Suggest rewriting as:	Thank you for your comments. The population was updated as suggested.

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		People with advanced unresectable, recurrent or metastatic previously untreated oesophageal squamous cancer	
	Roche	PD-L1 status and tumour histology can be predictive or prognostic of treatment response.	Thank you for your comment. If the evidence allows subgroups by degree of PD-L1 expression and cancer histology will be considered.
Comparators	BMS	BMS broadly agree with the comparators listed in the draft scope. However, given that this is solely in the squamous population, the triplet treatments are no longer relevant comparators. Pembrolizumab with platinum-based chemotherapy [ID3741] and Nivolumab in combination with cisplatin plus fluorouracil [ID2712] are not currently available in baseline commissioning and should not be considered relevant comparators	Thank you for your comment. The comparators are based on NG83. No action needed. In order to keep the scope broad at this stage, pembrolizumab with platinum-based chemotherapy (subject to ongoing appraisal [ID3741]) was added to the list of comparators.
	Roche	No comment	-
Outcomes	BMS	The outcomes listed in the scope are appropriate.	Thank you for your comment. If the

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		To note: The co-primary endpoints of the CheckMate 648 trial were OS and PFS in patients expressing PDL1 >1%. Outcomes in all enrolled patients were assessed as secondary endpoints.	evidence allows subgroups by degree of PD-L1 expression and cancer histology will be considered.
	Roche	Yes	Thank you for your comment. No action needed.
Economic analysis	BMS	No comments	-
	Roche	No comment	-
Equality and Diversity	BMS	No equality issues have been identified	Thank you for your comment. No action needed.
	Roche	No comment	-
Other considerations	BMS	Subgroups by degree of PD-L1 can be explored. Subgroups by histology are not appropriate given that only a small percentage of patients [redacted] are adenosquamous and the rest are squamous.	Thank you for your comment. If the evidence allows subgroups by degree of PD-L1 expression will be considered.
	Roche	No additional comment	Thank you. No action needed.

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Innovation	BMS	BMS clinical trials have demonstrated that nivolumab is an innovative medicine that has proven its efficacy across multiple indications. Nivolumab can also be considered innovative in the treatment of advanced oesophageal cancer, due to its novel mechanism of action in this therapeutic area. 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 gastro-oesophageal cancer and is viewed by physicians and patient interest groups as a 'step-change' in its management. In patients with advanced unresectable, recurrent or metastatic previously untreated oesophageal cancer, outcomes are poor; characterised by a very short survival and few recommended treatment options, so that there is significant unmet need in this patient population. Based on available data relating to nivolumab, this treatment is of major interest to public health, in particular from the view point of therapeutic innovation, as it has the potential to offer an alternative therapeutic option with an expected significant benefit over management of patients in the absence of nivolumab, including significantly improved long-term survival in a proportion of patients.	Thank you for your comments. A case for innovation can be made in your submission. No action needed.
	Roche	No comment	-
Questions for consultation	BMS	***Have all relevant comparators for nivolumab with platinum-based chemotherapy or ipilimumab been included in the scope?*** They key comparators [for nivolumab in combination with ipilimumab] are platinum-based chemotherapies such as doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin.	Thank you for your comments. The comparators are based on NG83. In order to keep the scope broad at

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		Triplet treatments with fluorouracil or capecitabine plus cisplatin or oxaliplatin plus epirubicin as epirubicin are rarely used in ESCC and should not be considered as a comparator. Pembrolizumab with platinum-based chemotherapy and Nivolumab in combination with cisplatin plus fluorouracil are not currently available in baseline commissioning and should not be considered as relevant comparators. ***Which treatments are considered to be established clinical practice in the NHS for advanced unresectable, recurrent or metastatic oesophageal cancer that has not been previously treated?*** Platinum-based chemotherapy including doublet (cisplatin or oxaliplatin with fluorouracil or capecitabine) ***Are the outcomes listed appropriate?*** No further comments ***Are there any subgroups of people in whom nivolumab with platinum-based chemotherapy is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** Subgroups by degree of PD-L1 can be explored ***If evidence allows, should squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma be considered separately?*** The pivotal clinical trial only has patients with squamous cell carcinoma.	this stage, pembrolizumab with platinum-based chemotherapy (subject to ongoing appraisal [ID3741]) was added to the list of comparators. If the evidence allows subgroups by degree of PD-L1 expression will be considered. Please note that the remit and population was updated to specify squamous cell carcinoma. Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy and nivolumab in combination with ipilimumab will be

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		Subgroups by histology are not appropriate given that only a small percentage of patients [redacted] are adenosquamous. ***Where do you consider nivolumab will fit into the existing NICE pathway, Oesophageal and gastric cancer overview?*** Nivolumab plus chemotherapy will be used to treat previously untreated patients with advanced, unresectable, recurrent or metastatic squamous oesophageal cancer. ***Would it be appropriate to assess nivolumab in combination with ipilimumab and nivolumab in combination with cisplatin plus fluorouracil (ID2712) in the same technology appraisal; that is, as a multiple technology appraisal (MTA)?*** An MTA would not be appropriate as these are considered as two separate license applications and so should be treated as two separate STAs in case of any differences in regulatory timelines or outcomes. Furthermore, MTAs are known to be more resource intensive than STAs. For efficiency we propose this could be sent to the same ERG and committee. The MTA process also means the appraisal group would run the process not the company, who will have better access to the required data. ***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***	assessed as a single technology appraisal.

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		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 the treatment 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.*** No further comments ***Do you consider nivolumab 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)?*** No further comments ***Do you consider that the use of nivolumab 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.***	

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		Patients with oesophageal cancer have significant unmet need: there are few effective therapies, short survival and poor prognosis. Nivolumab plus platinum-based chemotherapy has the potential to significantly improve outcomes. Although these effects will be demonstrated in the cost-effectiveness modelling, it should be noted that improving outcomes helps improve quality of life in ways that may not be identified through standard elicitation methods. In particular, delayed progression helps maintain patient dignity for longer. Further, it avoids hospital visits, due to reduced treatment appointments and improved progression, allowing patients to spend more time with family, promoting independence and avoiding reliance on carers. As an additional benefit, during the Covid-19 pandemic, delaying progression and reducing treatment visits helps patients avoid hospital stays and appointments, preventing possible Covid-19 transmission and alleviating pressure on the NHS. ***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 anticipated	
	Roche	No additional comments	Thank you. No action needed.
Additional comments on the draft scope	BMS	None	Thank you. No action needed.

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

British Society of Gastroenterology

Pfizer