National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465]

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 Pharmaceuticals Ltd.	No comments on the remit.	Thank you for your comment. The remit has been updated to include oesophageal adenocarcinoma, in line with patients included in the trial.
Timing Issues	Bristol-Myers Squibb Pharmaceuticals Ltd.	It is important for NICE to provide a recommendation for the use of nivolumab combination therapy within the NHS as close to marketing authorisation as possible, given the poor prognosis for patients and limited effective treatment options. The majority of gastric 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. Consequently, clinical outcomes at this advanced stage may also be poor, as noted in the draft scope.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled

Section	Consultee/ Commentator	Comments [sic]	Action
		There are limited therapeutic regimens available and those that are available have poor efficacy and poor safety profiles. Further, gastric 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 therapy, due to age or comorbidities, treatment options are limited. These factors translate to very poor clinical outcomes. Nivolumab combination therapy has the potential to significantly improve outcomes in this patient population, so a timely appraisal is crucial.	this topic into its work programme. No changes to the remit required.
Additional comments on the draft remit	Bristol-Myers Squibb Pharmaceuticals Ltd.	None.	Thank you for your comment. No further action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comments	Thank you for your comment. The background section has been updated to include oesophageal adenocarcinoma. No further action required.

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comments	Thank you for your comment. No further action required.
Population	Bristol-Myers Squibb Pharmaceuticals Ltd.	Oesophageal adenocarcinoma (EAC) is not included in the population section of scope. Patients with EAC are typically treated similarly to gastric adenocarcinomas, as opposed to oesophageal squamous cell carcinoma. Patients with EAC comprised approximately 12-13% of patients in CheckMate 649.	Thank you for your comment. The population section of the scope has been updated to include oesophageal adenocarcinoma. No further action required.
Comparators	Bristol-Myers Squibb Pharmaceuticals Ltd.	BMS broadly agree with the comparators listed in the draft scope. However, it should be noted that clinical advice indicates that epirubicin use is extremely limited in the first-line treatment of gastro-oesophageal cancers, due to toxicity. Hence, this should not be considered a comparator.	Thank you for your comment. NICE clinical guideline (NG83) recommends that patients who have a performance status 0 to 2 and no significant comorbidities may have chemotherapy combination regimens. Possible combinations may include epirubicin. No further action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	Bristol-Myers Squibb Pharmaceuticals Ltd.	The outcomes listed in the scope are appropriate.	Thank you for your comment. No further action required.
Economic analysis	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comments	Thank you for your comment. No further action required.
Equality and Diversity	Bristol-Myers Squibb Pharmaceuticals Ltd.	No equality issues have been identified	Thank you for your comment. No further action required.
Other considerations	Bristol-Myers Squibb Pharmaceuticals Ltd.	Subgroup analysis by HER2 status will be provided. However, it should be noted that the majority of patients included in CheckMate 649 were HER2 negative. This limits the potential conclusions that could be drawn on HER2 status. Efficacy of nivolumab is not anticipated to vary by HER2 status.	Thank you for your comment. This will be considered by the NICE appraisal committee during the appraisal. Subgroup analyses by HER2 status have been removed and replaced by analyses by PD-L1 status, in line with the clinical trial population. No further action required.
Innovation	Bristol-Myers Squibb	BMS clinical trials have demonstrated that nivolumab is an innovative medicine that has proven its efficacy across multiple indications. Nivolumab	Thank you for your comment. The

Section	Consultee/ Commentator	Comments [sic]	Action
	Pharmaceuticals Ltd.	can also be considered innovative in the treatment of advanced gastric cancer, due to its novel mechanism of action in this therapeutic area. It also offers the potential to make a significant impact on the substantial unmet need, including a long-term survival impact in a proportion of the target population. Nivolumab is an immunotherapy agent for the treatment of cancer and acts as a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. It specifically binds to the 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 gastric 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.	innovative nature of nivolumab will be considered by the NICE appraisal committee during the appraisal. No further action required.
Questions for consultation	Bristol-Myers Squibb	**Have all relevant comparators for nivolumab been included in the scope?** No further comments	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pharmaceuticals Ltd.	**Should trastuzumab be included as a comparator?** Trastuzumab should be considered a relevant comparator in HER2+ patients only, which comprise 6-30% of the gastric cancer population, dependent on tumour location. **Which treatments are considered established clinical practice in the NHS for untreated locally advanced or metastatic gastric or gastro-oesophageal junction cancer?** No further comments. **Are the outcomes listed appropriate?** No further comments **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?** The pivotal clinical trial was not powered to detect statistically significant differences in subgroups. This is of particular importance given the low prevalence of some subgroups. Hence, pre-specified subgroup analysis of clinical outcomes will be presented but cost-effectiveness outcomes will be presented by overall trial population. **Are gastro-oesophageal junction cancer and oesophageal adenocarcinoma expected to respond similarly to treatment?** Clinical expert opinion indicates that gastro-oesophageal adenocarcinomas are treated comparably within NHS England. Outcomes may vary slightly, according to prognosis, but treatment effect may be expected to be comparable.	The scope specifies that trastuzumab is a relevant comparator only in people with HER2- positive gastric or gastro-oesophageal cancer. Additional benefits of nivolumab that are unlikely to be included in the QALY calculation will be considered by the NICE appraisal committee during the appraisal. No further action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Where do you consider nivolumab will fit into the existing oesophageal and gastric cancer NICE pathway? Nivolumab plus chemotherapy will be used to treat previously untreated patients with advanced, unresectable, recurrent or metastatic gastric cancer. **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 nivolumab 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	

Section	Consultee/ Commentator	Comments [sic]	Action
		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.** Patients with gastric cancer have significant unmet need: there are few effective therapies, short survival and poor prognosis. Nivolumab plus 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	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Bristol-Myers Squibb Pharmaceuticals Ltd.	None.	Thank you for your comment. No further action required.

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

Amgen Ltd