National Institute for Health and Care Excellence

Health Technology Evaluation

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

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	Association of Respiratory Nurses	There are no current treatments for adjuvant therapy post surgery where neoadjuvant treatment has been given. Excellent to see further assessment of treatment options for this group of patients.	Thank you for your comment.
	AstraZeneca	N/A	Thank you for your comment.
	British Thoracic Oncology Group	No concerns	Thank you for your comment.
	Bristol Myers Squibb	The proposed evaluation, via single technology appraisal, is appropriate.	Thank you for your comment.
Wording	Association of Respiratory Nurses	yes	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
	AstraZeneca	N/A	Thank you for your comment.
	British Thoracic Oncology Group	Yes	Thank you for your comment.
	Bristol Myers Squibb	Wording is appropriate.	Thank you for your comment.
Timing Issues	Association of Respiratory Nurses	Important to provide this treatment option at the earliest available date.	Thank you for your comment.
	AstraZeneca	N/A	Thank you for your comment.
	British Thoracic Oncology Group	Currently effective peri-operative strategies exist. However this is still clinical unmet need to improve outcomes. Therefore this should be considered within a reasonable time frame	Thank you for your comment.
	Bristol Myers Squibb	BMS considers that the current appraisal should be carried out in line with current NICE scheduling timelines.	Thank you for your comment.
Additional comments on the draft remit	AstraZeneca	N/A	Thank you for your comment.
	Bristol Myers Squibb	No	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of Respiratory Nurses	Significant background information provided.	Thank you for your comment.
	British Thoracic Oncology Group	Accurate and complete	Thank you for your comment.
	Bristol Myers Squibb	Pembrolizumab (TA1017[1]) and durvalumab (TA1030[2]), used before and after surgery for resectable non-small cell lung cancer (NSCLC), have been included as comparators in the scope but are not described in the background information. It would be clearer if the background was rewritten to reflect the new standard of care (SOC) in this setting. BMS suggests removing other treatments because these are not widely used or are irrelevant to the decision problem. See “comparators” for further information.	Thank you for your comment. The background information is considered accurate at the time of writing. NICE’s preference is to remain inclusive of comparators at the scope stage.
Population	Association of Respiratory Nurses	Yes	Thank you for your comment.
	AstraZeneca	The defined population is in line with previous relevant appraisals (TA ID 6220 and TA ID 1017)	Thank you for your comment.
	British Thoracic Oncology Group	Yes	Thank you for your comment.
	Bristol Myers Squibb	Yes	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
Subgroups	Association of Respiratory Nurses	The subgroups listed are appropriate	Thank you for your comment.
	British Thoracic Oncology Group	Potentially higher stage, higher PDL1 (greater than 50%) and non-squamous histology patients will confer greater benefit	Thank you for your comment.
	Bristol Myers Squibb	BMS does not intend to explore subgroup analyses for this appraisal. BMS intends to seek reimbursement for the intention-to-treat population of the CheckMate 77T trial in line with the anticipated MHRA licence wording, and in line with TA1017[1] and TA1030[2] reimbursement.	Thank you for your comment.
Comparators	Association of Respiratory Nurses	Yes	Thank you for your comment.
	AstraZeneca	The listed comparators are in line with previous relevant appraisals (TA ID 6220 and TA ID 1017)	Thank you for your comment.
	British Thoracic Oncology Group	All relevant comparators have been listed. The below are either not available on the NHS or not appropriate as a comparator • Pembrolizumab (subject to NICE appraisal) • Durvalumab (subject to NICE appraisal) • Alectinib (for people with ALK-positive NSCLC and subject to NICE appraisal)	Thank you for your comment. Some of these treatments have recently been recommended by NICE (durvalumab, TA1030; alectinib, TA1014)..

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	Bristol Myers Squibb	BMS believes that the relevant comparators for this appraisal are pembrolizumab (TA1017[1]) and durvalumab (TA1030[2]). In the NICE appraisal committee meetings (ACMs) for TA1017 and TA1030, nivolumab as neoadjuvant therapy (TA876[3]) was agreed by the NICE committees as representing the SOC in this setting. Pembrolizumab and durvalumab were both considered cost-effective versus neoadjuvant nivolumab and have recently been recommended by NICE. Pembrolizumab and durvalumab have now replaced neoadjuvant nivolumab as the new SOC in this setting, as confirmed by 5 clinical experts consulted by BMS. To further support the above, rationale for the exclusion of other comparators was accepted by the EAG and NICE committees in the pembrolizumab and durvalumab ACMs[1,2]. In the pembrolizumab recommendation and/or EAG report[1]: ▪ Neoadjuvant chemoradiotherapy (CRT) was agreed to not be a relevant comparator. In NG122,[4] CRT with surgery is only recommended for patients with operable stage III (N2) disease. Clinical advice was that, for this small group of patients, CRT has been displaced by neoadjuvant nivolumab with chemotherapy.[5] ▪ The committee agreed it is not appropriate to compare outcomes from studies evaluating adjuvant treatments with outcomes from studies including perioperative or neoadjuvant treatments because the populations, and timepoints for decisions, differ.[6] Specifically, studies reviewing adjuvant treatments include patients who have undergone resection, whilst studies reviewing perioperative and neoadjuvant treatments include patients who have not yet undergone resection. o Therefore, adjuvant chemotherapy, adjuvant osimertinib, and atezolizumab after adjuvant cisplatin-based chemotherapy are not considered relevant to this appraisal.	Thank you for your comment. NICE's preference is to remain inclusive of comparators at the scope stage.

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		○ Further, adjuvant osimertinib is only recommended by NICE as a treatment option for patients with EGFR-positive tumours who have undergone complete resection.[7] Patients with EGFR-positive mutations were excluded from the CheckMate-77T trial.[8] Osimertinib is therefore not an appropriate comparator for this appraisal. ○ Atezolizumab is used after adjuvant chemotherapy and is currently in the Cancer Drugs Fund[9] and, therefore, not a relevant comparator for this appraisal. ▪ Clinical advice to the EAG in TA10175 was that neoadjuvant chemotherapy is rarely used in NHS practice, and the NG122 guideline[4] recommended against the use of neoadjuvant chemotherapy for stage I and stage II disease. As noted above, it is not appropriate to compare outcomes from studies evaluating adjuvant treatments with outcomes from studies including periadjuvant or neoadjuvant treatments[6] because the populations, and timepoints for decision, differ, and therefore, adjuvant chemotherapy is not a valid comparator. Finally, alectinib is also not an appropriate comparator for this appraisal. Alectinib is "recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC in adults" (TA536).[10] People with known ALK translocations were excluded from the CheckMate 77T trial and are directly excluded in the anticipated MHRA label.	
Outcomes	Association of Respiratory Nurses	Should assess PROMS	Thank you for your comment. The relevance of PROMs will be considered by the committee following

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			evidence submissions and critiques.
	AstraZeneca	The outcomes listed are appropriate and in line with previous relevant appraisals. In particular: • EFS measures the success/failure of neoadjuvant followed by adjuvant therapy. It considers the occurrence of multiple patient-relevant events. • DFS is most appropriate following adjuvant therapy, as it often includes time to recurrence or death events measured from the date of surgery. ○ This would be the subset of patients receiving adjuvant therapy after surgery and does not including events leading up to surgery ○ DFS should be considered in conjunction with other outcomes	Thank you for your comment. The committee will consider both EFS and DFS as it is considering the treatment both in the neoadjuvant and adjuvant setting. The committee will consider the relative importance of outcome measures in their decision making.
	British Thoracic Oncology Group	Yes	Thank you for your comment.
	Bristol Myers Squibb	All key outcomes are listed. ▪ 'DFS' may be removed as 'EFS' is the appropriate outcome for perioperative indications and is the primary outcome of the CheckMate 77T trial.	Thank you for your comment. The committee will consider both EFS and DFS as it is considering the treatment both in the neoadjuvant and adjuvant setting. The committee will consider the relative importance

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			of outcome measures in their decision making.
Equality	Association of Respiratory Nurses	No concerns	Thank you for your comment.
	British Thoracic Oncology Group	n/a	Thank you for your comment.
	Bristol Myers Squibb	No equality issues are anticipated.	Thank you for your comment.
Other considerations	British Thoracic Oncology Group	n/a	Thank you for your comment.
	Bristol Myers Squibb	No comments.	Thank you for your comment.
Questions for consultation	British Thoracic Oncology Group	Where do you consider nivolumab with chemotherapy (as neo-adjuvant) and then nivolumab monotherapy (as adjuvant) will fit into the existing care pathway for locally advanced NSCLC? **Difficult to say on the current available data. Nivolumab plus chemotherapy neoadjuvantly (Checkmate 816) is logistically and resource wise a much more attractive treatment option. Hence using peri-operative SACT will need to be significantly superior in terms of end points. Alternatively we need to be able to identify a subgroup of patients who would benefit from the adjuvant component (eg patient that does not achieve cPR or mPR). However the 2 strategies have different numbers of neo-adjuvant cycles administered – hence a clinician would need to know from the outset whether they are**	Thank you for your comment. The committee will consider these insights during the evaluation process.

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		considering neo-adjuvant only or neoadjuvant and adjuvant (but pathological response would only be known at the time of surgery) Are the subgroups suggested appropriate? **Yes – although would add histology to this (squamous versus non-squamous)** Are there any other subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? **See above** Would nivolumab with chemotherapy (as neo-adjuvant) and then nivolumab monotherapy (as adjuvant) be a candidate for managed access? **Yes** Do you consider that the use of nivolumab with chemotherapy (as neo-adjuvant) and then nivolumab monotherapy (as adjuvant) can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? - Would nivolumab with chemotherapy (as neo-adjuvant) and then nivolumab monotherapy (as adjuvant) only be used in people whose NSCLC was PD-L1 positive? **Not necessarily – although the benefit will likely be greater in this population**	

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		Would all patients with resectable NSCLC that receive neoadjuvant treatment with nivolumab continue to receive adjuvant treatment? Are there any clinical features post-surgery that may make patients less likely to benefit from adjuvant treatment? **No not all patient would. Some patients may not recover post surgery to receive it or may have had a toxicity in the neo-adjuvant setting that would preclude adjuvant treatment.** **Patient achieving a mPR or cPR may not benefit from further adjuvant treatment – although this is not certain** Are there any patients with resectable NSCLC who would not have a neo-adjuvant treatment but who would have an adjuvant treatment after surgery? If so, what might the reasons be for this and which treatments would they have? **Yes – lower stage patients where surgery can proceed quickly may proceed with resection upfront. Especially those with low / negative PDL1 expression where the benefit in CM816 was not as pronounced. Also patient may have a contraindication to immunotherapy or SACT in general** **These patient will have either surgery alone, surgery followed by platinum doublet chemotherapy or surgery followed by platinum doublet chemotherapy and Atezolizumab**	

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		If a patient in current practice had nivolumab with chemotherapy as a neo-adjuvant treatment, would they have any chemotherapy regimens as an adjuvant treatment? **This is clinicians discretion – but it is difficult to think of a scenario where this would be appropriate (unless treatment had to be suspended prematurely in the neoadjuvant setting, there was still significant viable tumour cells seen at resection and the patient was deemed suitable / fit to receive adjuvant platinum doublet)** Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **CheckMate 77T**	
	Bristol Myers Squibb	No comments.	Thank you for your comment.
Additional comments on the draft scope	Roche	Alectinib has been mentioned as a comparator, but associated guidance has not been included in the list- https://www.nice.org.uk/guidance/ta1014	Thank you for your comment.
	Bristol Myers Squibb	No comments.	Thank you for your comment.

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

N/A