National Institute for Health and Care Excellence

Health Technology Evaluation

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]
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	MSD	MSD consider it appropriate to refer this topic to NICE for evaluation through the Single Technology Appraisal route.	Thank you for your comment. No action required.
	BTOG	The evaluation and route seem appropriate	Thank you for your comment. No action required.
Wording	MSD	MSD consider the suggested wording appropriate.	Thank you for your comment. No action required.
	BTOG	No comments	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
Timing issues	MSD	Despite the availability of treatments with curative intent (e.g., surgery), there is a high unmet need for the defined population, which would benefit from new treatments that reduce the risk of recurrence and improve survival outcomes. For the reasons outlined, MSD consider that the current appraisal should be carried out in line with current NICE scheduling, to allow timely patient access after the intervention has obtained regulatory approval for use in the indicated population.	Thank you for your comment. No action required.
	BTOG	This is an active issue in patient management	Thank you for your comment. No action required.
Additional comments on the draft remit	MSD	None.	Thank you for your comment. No action required.
	BTOG	None.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD	The background information is accurate and comprehensive.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	BTOG	No comment	Thank you for your comment. No action required.
Population	MSD	MSD suggest amending the description of the population to (amendment in italics): "People with untreated resectable NSCLC, irrespective of PD-L1 status". MSD suggest the change to ensure the population of interest aligns with the pivotal trial from which evidence on clinical effectiveness will be derived. PD-L1 positivity was not an inclusion criterion in KEYNOTE-671, and a proportion of people with PD-L1 expression of <1% are likely to have been enrolled into the study.	Thank you for your comment. The population wording has been updated to reflect the clinical trial inclusion criteria.
	BTOG	Should stipulate resectable IIA-IIIB NSCLC. There is data supporting activity in PDL1 negative in terms of pCR rates but it seems that is being excluded from this review	Thank you for your comment. The population wording has been updated.
Subgroups	MSD	Three subgroups were specified in the NICE scope: 1. Whether pembrolizumab is used before and after surgery; 2. PD-L1 tumour proportion score; 3. Disease stage. MSD consider the three subgroups listed to be of interest to the decision problem, with the caveat that KEYNOTE-671 was not powered to detect a difference in clinical effectiveness between the treatment groups in any subgroup. Thus, the results of subgroup analyses will be hypothesis generating and should be interpreted with caution. However, of the three	Thank you for your comment. The subgroups have been kept inclusive to allow committee to consider any subgroups it considers relevant. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		subgroups listed, disease stage at baseline and PD-L1 tumour proportion score were both stratification factors at randomisation in KEYNOTE-671 and are pre-specified subgroup analysis within the protocol.	
	BTOG	A subgroup to consider are patient who get a major path response and should these receive post operative component	Thank you for your comment. The draft scope included a subgroup to allow the consider the evidence in people who may or may not have the post-operative component.
Comparators	MSD	MSD request that the introductory text in the Comparator section be amended to: "Established CM without ***pembrolizumab***, which may include…". MSD note that only cisplatin-based chemotherapy was administered in KEYNOTE-671. MSD consider the comparators to be predominantly appropriate. MSD suggest that, with the recommendation of neoadjuvant nivolumab as a treatment option for resectable NSCLC (TA876) in March 2023, the comparison with active monitoring is potentially no longer a relevant comparator to the decision problem. MSD suggest that the comparison with atezolizumab (for those with PD-L1 ≥50%) after adjuvant cisplatin is not relevant to the decision problem. MSD consider the population enrolled in the study evaluating adjuvant atezolizumab to be a clinically distinct patient group from those eligible for KEYNOTE-671, in which patients received treatment in the neoadjuvant setting with no adjuvant chemotherapy. By contrast, those receiving adjuvant	Thank you for your comments. The introductory text has been amended. The comparators have been kept inclusive to allow committee to consider comparisons with any alternative treatments considered to be relevant to clinical practice.

Section	Consultee/ Commentator	Comments [sic]	Action
		atezolizumab had undergone complete resection of their tumours and had completed 1-4 cycles of cisplatin-based adjuvant chemotherapy without disease recurrence. MSD consider the adjuvant setting to represent a different phase of care to the periadjuvant setting. MSD has another study evaluating pembrolizumab in the adjuvant setting – KEYNOTE-091 – and consider atezolizumab (subject to NICE appraisal) to be a more relevant comparator in that technology appraisal.	
	BTOG	The appropriate comparators are 1. surgery followed by adjuvant chemo followed by adjuvant atezolizumab (the latter only in PDL1 >50%) 2. The other comparator is neoadjuvant chemo+nivolumab for 3 cycles preoperatively. The comparator statement mentioned durvalumab which does not make sense as its role in lung cancer is only after radical chemoRT (which is for unresectable patients)	Thank you for your comments. The introductory text has been amended.
Outcomes	MSD	MSD consider the outcomes to be predominantly appropriate. MSD suggest that response rate might not be clinically relevant outcome in the early stage setting for lung cancer when the goal of neoadjuvant treatment is surgery rather than response. MSD note that response rate was not collected in the KEYNOTE-671 study, and therefore will not be reported in MSD's submission. Additionally, disease-free survival (DFS) was not captured as a separate outcome in KEYNOTE-671, which had co-primary endpoints of event-free survival (EFS) overall survival (OS). EFS was defined as the time from randomization to the first of the following events: disease or local progression, inability to resect tumor, local or distant recurrence, or death.	Thank you for your comment. Thank you for your comment. The outcomes have been kept broad to allow committee to consider the relevant outcomes.

Section	Consultee/ Commentator	Comments [sic]	Action
	BTOG	yes	Thank you for your comment.
Equality	MSD	MSD consider that the proposed remit and scope do not impact Equality, as described in the Notes section.	Thank you for your comment.
	BTOG	No issues	Thank you for your comment.
Other considerations	MSD	MSD do not have additional comments.	Thank you for your comment.
	BTOG	No issues	Thank you for your comment.
Questions for consultation	MSD	**Have all relevant comparators for pembrolizumab for neoadjuvant and adjuvant treatment of resectable non-small-cell lung cancer been included in the scope?** Please see MSD's response in the "Comparator" section above. **Which treatments are considered to be established clinical practice in the NHS for resectable NSCLC? How does this differ by stage?** Until NICE recommended nivolumab as a neoadjuvant treatment option in the management of resectable NSCLC (TA876), standard of care for resectable lung cancer was as outlined in NICE guideline NG122 – Diagnosis and management of lung cancer. NICE guidance recommended that postoperative chemotherapy be:	Thank you for your responses to the consultation questions.

Section	Consultee/ Commentator	Comments [sic]	Action
		• offered as an option for those with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC; • considered for those with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter; • cisplatin-based combination chemotherapy regimen as adjuvant chemotherapy. For people with stage I–II NSCLC that are suitable for surgery, use of neoadjuvant treatment is not advised, unless the patient in in a clinical trial. **Would all patients with resectable NSCLC that receive neoadjuvant treatment with pembrolizumab continue to receive adjuvant treatment? Are there any clinical features post-surgery that may make patients less likely to benefit from adjuvant treatment?** KEYNOTE-671 was designed such that patients could receive up to 4 cycles of neoadjuvant treatment and surgical resection followed by up to 13 cycles of pembrolizumab. Clinicians in England have fed back to MSD that pathologic complete response might be a key factor in their decision to proceed with adjuvant treatment. **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?** Until NICE recommended nivolumab as a neoadjuvant treatment option in the management of resectable NSCLC (TA876), neoadjuvant treatment in resectable NSCLC was not standard of care (in line with NICE guideline NG122) and, therefore, implementation of the neoadjuvant treatment pathway is a work in progress at centres in the UK. Surgeons consulted by MSD	

Section	Consultee/ Commentator	Comments [sic]	Action
		highlighted that there may be instances in which they would prefer to move to immediate resection of the tumour, such as Stage II N0 tumours (AJCC 8th ed), instead of proceeding with neoadjuvant treatment. Another example where surgery may be preferable is upstaging of the tumour after resection. Delays in biomarker results, particularly EGFR mutation, may be another factor determining whether a patient does not receive neoadjuvant treatment. **If a patient had nivolumab with chemotherapy as a neo-adjuvant treatment, would they have any chemotherapy regimens as an adjuvant treatment?** MSD note that in the pivotal trial evaluating the clinical effectiveness and safety profile of neoadjuvant nivolumab (CheckMate-816) patients in both groups could receive up to four cycles of adjuvant chemotherapy, radiotherapy, or both. Adjuvant chemotherapy was received by 11.9% of the patients in the nivolumab-plus-chemotherapy group and 22.2% of those in the chemotherapy-alone group. **What considerations are made in determining whether pembrolizumab is used before or after neoadjuvant chemoradiotherapy or adjuvant chemotherapy?** MSD note that in the design of KEYNOTE-671 adjuvant chemotherapy was not a treatment option. The clinical effectiveness of pembrolizumab in the adjuvant setting after complete resection is evaluated in KEYNOTE-091, in a population that is aligned with the cohort in the study evaluating atezolizumab in the adjuvant setting. In KEYNOTE-091, adjuvant chemotherapy was permitted. **Is there a routine test to detect the biomarker PD-L1 in resectable samples?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		Yes, by means of the PD-L1 IHC 22C3 pharmDx assay. **Are the outcomes listed appropriate?** Please see MSD's response in the "Outcomes" section. Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? As noted earlier, MSD consider subgroup analyses to be hypothesis generating and results should be interpreted with caution. In its submission, MSD will present results on co-primary outcomes of clinical effectiveness for prespecified subgroups.	
	BTOG	None submitted.	None.
Additional comments on the draft scope	MSD	Please find below a list of additional comments/suggestions on the draft scope: • Page 1; For clarity, suggest amending the wording "… interconnected decision points based on the number staging system …" to "…interconnected decision points based on disease stage…". • Page 1; Typographical error: "… NSCLC. People…". • Page 2 and Decision Problem Table: Description of the Technology/Intervention: MSD suggest amending the description of the intervention to clarify the regimen given in the neoadjuvant phase and in the adjuvant phase. – MSD suggest making it clear that participants in both groups received neoadjuvant chemotherapy in addition to either pembrolizumab or placebo, then had surgery and moved onto	Thank you for your comments. These have been taken into consideration whilst preparing the final scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		adjuvant pembrolizumab or placebo as per allocated treatment group. – For the description on Page 2, perhaps something like: “It is currently being studied in a clinical trial compared with a placebo for pembrolizumab in people with previously untreated and pathologically confirmed resectable stage 2, 3A, or 3B NSCLC. In the neoadjuvant phase of the trial, in addition to pembrolizumab or placebo, participants received neoadjuvant cisplatin-based chemotherapy. Patients then underwent surgery, after which they received pembrolizumab or placebo as an adjuvant treatment”. And in Table 1: Pembrolizumab with chemotherapy for neoadjuvant treatment followed by pembrolizumab monotherapy as an adjuvant treatment.	
	BTOG	None submitted.	None.

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