National Institute for Health and Care Excellence

Health Technology Evaluation

Pembrolizumab before surgery (neoadjuvant) then with radiotherapy after surgery (adjuvant) for newly diagnosed, resectable, locally advanced, squamous cell head and neck cancer [ID6477]
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	Merck Sharp & Dohme (UK)	MSD agrees that it is appropriate for NICE to evaluate this topic and that the appropriate route is a single technology appraisal	Thank you for your comment. No action needed.
Wording	Merck Sharp & Dohme (UK)	The wording of the remit reflects the issue of clinical and cost-effectiveness about this technology.	Thank you for your comment. No action needed.
Timing	Merck Sharp & Dohme (UK)	The current standard of care (SOC) for patients with resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC) is surgery followed by adjuvant radiotherapy (RT) with or without platinum-based chemotherapy. Since the addition of cisplatin to RT in 2004 for patients with high-risk pathological features post-surgery, there have been no changes to SOC in over 20 years. Currently, approximately a third of LA HNSCC patients treated with SOC have disease recurrence within 1 year, the majority within the first two years, and fewer than 50% of patients are expected to live past 5 years. Consequently, there remains a high unmet need for innovative	Thank you for your comment. No action needed.

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		treatment options in this population to reduce the risk of recurrence and improve survival outcomes. Perioperative pembrolizumab, in combination with SOC, is the first treatment in two decades to demonstrate a statistically significant and clinically meaningful improvement in event-free survival (EFS) for patients with resectable LA HNSCC, and will be the first immunotherapy to be appraised by NICE in this population. In addition, it is the first indication offering a perioperative treatment option for HNSCC patients. **MSD urge NICE to prioritise the scheduling of this appraisal, ensuring that final guidance can be issued as soon as possible and close to regulatory approval so that patients can benefit from this paradigm shifting technology for resectable LA HNSCC.**	
Additional comments on the draft remit	Merck Sharp & Dohme (UK)	No additional comments	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Merck Sharp & Dohme (UK)	MSD considers the background information to be appropriate.	Thank you for your comment. No action needed.
Population	Merck Sharp & Dohme (UK)	MSD considers the population to be appropriately defined.	Thank you for your comment. No action needed.
Subgroups	Merck Sharp & Dohme (UK)	MSD request the following amendments to the subgroups listed in the draft scope: **“Whether pembrolizumab is used before and after surgery”:**	Thank you for your comment. The scope has been amended.

Section	Consultee/ Commentator	Comments [sic]	Action
		The KEYNOTE-689 trial was designed to compare the efficacy of pembrolizumab **as a perioperative treatment regimen** (i.e. both neoadjuvant and adjuvant) in addition to adjuvant radiotherapy (with or without chemotherapy) versus adjuvant radiotherapy (with or without chemotherapy). The KEYNOTE-689 trial does not allow for stratification by whether pembrolizumab was used before and after surgery, and was not designed to evaluate the efficacy of neoadjuvant or adjuvant pembrolizumab separately. Therefore, MSD will not be able to provide this information and do not consider this to be an appropriate subgroup for consideration. **MSD therefore request the removal of this subgroup from the draft scope.** **"PD-L1 tumour proportion score":** In the KEYNOTE-689 trial, stratification was performed for PD-L1 status according to centrally determined tumour proportion score (TPS; ≥50% vs. <50%) to inform the trial randomisation. However, the analyses of the primary and secondary endpoints were assessed in participants whose tumours expressed PD-L1 with a combined positive score (CPS) of 10 or more, 1 or more, and all participants irrespective of the CPS score. As such, CPS score is the appropriate subgroup for consideration in this appraisal and therefore MSD request this subgroup to be changed to: "PD-L1 combined positive score (CPS)" to ensure consistency with the clinical trial statistical analysis plan and the evidence informing the regulatory submissions.	
Comparators	Merck Sharp & Dohme (UK)	The KEYNOTE-689 study recruited patients with resectable newly diagnosed, locally advanced nonmetastatic HNSCC. Pembrolizumab was given as a perioperative intervention. **To be eligible for perioperative pembrolizumab (in the trial and in clinical practice), key criteria are that patients must have a resectable tumour, be planned for surgery, and be fit enough to undergo this surgery followed by adjuvant radiotherapy (RT) ± chemotherapy**. As such, any treatments which are intended for patients not	Thank you for your comment. The Comparators are kept inclusive at this stage to allow the committee to consider any comparator

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		undergoing surgery are not appropriate comparators for the population under consideration. Further details are provided below. **Established clinical management without pembrolizumab:** • Current standard of care (SOC) for patients with untreated, **resectable**, LA HNSCC is **surgery followed by adjuvant RT with or without platinum-based chemotherapy**. It should also be noted that radiotherapy (with or without chemotherapy) in either the *neoadjuvant* setting or *as definitive treatment* (i.e. as the primary treatment, without surgery) would not be an appropriate comparator, as neoadjuvant RT is not used in clinical practice, and definitive RT is not relevant to a resectable population. • 'Platinum-based chemotherapy regimens' alone, without RT, are not recommended in the neoadjuvant or adjuvant setting. Induction chemotherapy is sometimes used to treat patients with aggressive disease who are due to receive definitive RT; however, as this is a non-surgical treatment approach, this is not an appropriate comparator for this appraisal. • In the locally advanced setting, best supportive care (BSC) would only be an option for patients who are unfit for, or refuse treatment with, current SOC (surgery followed by adjuvant RT with or without chemotherapy). As such, these patients would not meet the remit requiring patients to have 'resectable' disease and thus would not be considered eligible for treatment with perioperative pembrolizumab administered in addition to current SOC. Therefore, MSD do not consider best supportive care to be an appropriate comparator for this appraisal. **Cetuximab in combination with radiotherapy for locally advanced head and neck cancer:** • Cetuximab in combination with radiotherapy (NICE TA145) was based on a ***trial that excluded patients*** **who had previously undergone**	technologies for which evidence might be identified. Best supportive care has been removed from the scope. As noted, the population in this appraisal is eligible to receive surgery followed by adjuvant radiotherapy with or without chemotherapy and therefore would not receive best supportive care. Platinum-based chemotherapy regimens' alone, without RT have been removed from the scope. As noted, induction chemotherapy can be used in some people prior to receiving radiotherapy but this would not be used in combination with surgery.

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		surgery for HNSCC, positioning cetuximab plus RT as a definitive treatment option (i.e. as the primary treatment, without surgery) rather than in the adjuvant setting for resected patients. Additionally, the NICE recommendation restricts reimbursement to patients for whom all forms of platinum-based chemoradiotherapy are contraindicated, whereas eligibility for radiotherapy, with or without platinum-based chemotherapy, is a prerequisite for eligibility for perioperative pembrolizumab. Clinical expert feedback to MSD has indicated that cetuximab plus radiotherapy is very rarely used in the locally advanced setting, in practice reserved only for patients with renal impairment. **Therefore, cetuximab in combination with RT is not an appropriate comparator for this appraisal. MSD therefore requests the removal of cetuximab from the final scope.** MSD therefore propose that appropriate wording for the comparator be as follows: • "Surgery followed by adjuvant radiotherapy with or without platinum-based chemotherapy" Based on clinical expert opinion sought by MSD, the KEYNOTE-689 study comparator arm is fully reflective of UK clinical practice.	
Outcomes	Merck Sharp & Dohme (UK)	**The KEYNOTE-689 study recruited patients with resectable newly diagnosed, locally advanced nonmetastatic HNSCC. Pembrolizumab was given as a perioperative intervention.** The primary endpoint of the study was event-free survival (EFS), and overall survival (OS) was a key secondary endpoint. MSD does not consider the following outcomes to be relevant in this setting:	Thank you for your comment. The outcomes are kept inclusive at this stage therefore progression-free survival, disease-free survival and response times will remain as an outcome

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		Progression-free survival: This was not an endpoint measured in the KEYNOTE-689 trial as it is not relevant outcome for cancer in the early-stage (neoadjuvant/adjuvant) setting. It is therefore not an appropriate outcome for this appraisal and should be removed from consideration. **Disease-free survival:** This was not an endpoint measured in the KEYNOTE-689 trial. In the perioperative setting, event-free survival (EFS) is the appropriate endpoint for assessing efficacy versus the comparator. Therefore, disease-free survival is an inappropriate endpoint and should be removed from consideration. **Response times:** This was not an endpoint measured in the KEYNOTE-689 trial as it is not relevant outcome for cancer in the early-stage (neoadjuvant/adjuvant) setting. It is therefore an inappropriate outcome for this appraisal and should be removed from consideration. MSD propose the following secondary endpoints from the KEYNOTE-689 trial to be added as outcomes that may be considered of relevance for the appraisal: • Major pathological response • Pathological complete response	of interest. Major pathological response and pathological complete response have been added as outcomes to the scope.
Equality	Merck Sharp & Dohme (UK)	MSD has no additional comments.	Thank you for your comment. No action needed.
Other considerations	Merck Sharp & Dohme (UK)	MSD has no additional comments	Thank you for your comment. No action needed

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Questions for consultation	Merck Sharp & Dohme (UK)	Question: Would pembrolizumab be given as both neoadjuvant and adjuvant treatment? Response: Pembrolizumab would be given as per the KEYNOTE-689 trial and anticipated market authorisation as a neoadjuvant treatment, then continued as adjuvant treatment in combination with radiation with or without cisplatin followed by pembrolizumab as single agent. Question: Are there situations where pembrolizumab would be given either only as neoadjuvant or only as an adjuvant treatment? Response: As stated in response to the previous question, the anticipated marketing authorisation is for pembrolizumab as a neoadjuvant treatment, then continued as adjuvant in combination with radiation with or without platinum-containing chemotherapy followed by pembrolizumab as a single agent. The KEYNOTE-689 trial was not designed, nor powered, to evaluate pembrolizumab as a neoadjuvant-only or adjuvant-only treatment. MSD is not able to comment on any use of pembrolizumab outside of the anticipated label in the perioperative setting. Question: Are there any clinical features post-surgery that may make patients less likely to benefit from adjuvant treatment? Response: As per the KEYNOTE-689 trial, patients are assessed for the presence of high-risk pathological features, defined by extranodal extension and/or positive surgical margins, post-surgery to determine eligibility for adjuvant chemotherapy (cisplatin) in addition to radiotherapy. Question: Where do you consider pembrolizumab will fit into the existing care pathway for head and neck cancer? Response: In line with its anticipated marketing authorisation, pembrolizumab would be offered as a neoadjuvant treatment pre-surgery, and then in addition to adjuvant SOC post-surgery for patients with resectable LA HNSCC.	Thank you for your comments. No action required.

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		Question: Are the subgroups suggested appropriate? Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Response: Please see response to subgroup section above. Question: Are the comparators suggested appropriate? Response: Please see responses to comparator section above. Question: Please select from the following, will pembrolizumab be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): Response: *C. Prescribed in secondary care with routine follow-up in secondary care.* Question: For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Response: The setting for prescribing and routine follow-up of comparators and subsequent treatments is not expected to differ from the intervention. Question: Would pembrolizumab be a candidate for managed access? Response: Should the technology appraisal committee be unable to recommend pembrolizumab for routine commissioning, then MSD believes that this indication would be a potential candidate for managed access.	

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		Question: Do you consider that the use of pembrolizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Response: MSD considers relevant health benefits will be captured in the QALY calculation.	
Additional comments on the draft scope	Merck Sharp & Dohme (UK)	MSD propose that 'ORACLE Head & Neck Cancer UK' be added to the stakeholder list for this appraisal.	Thank you for your comment. ORACLE Head & Neck Cancer UK have been added to the stakeholder list.

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